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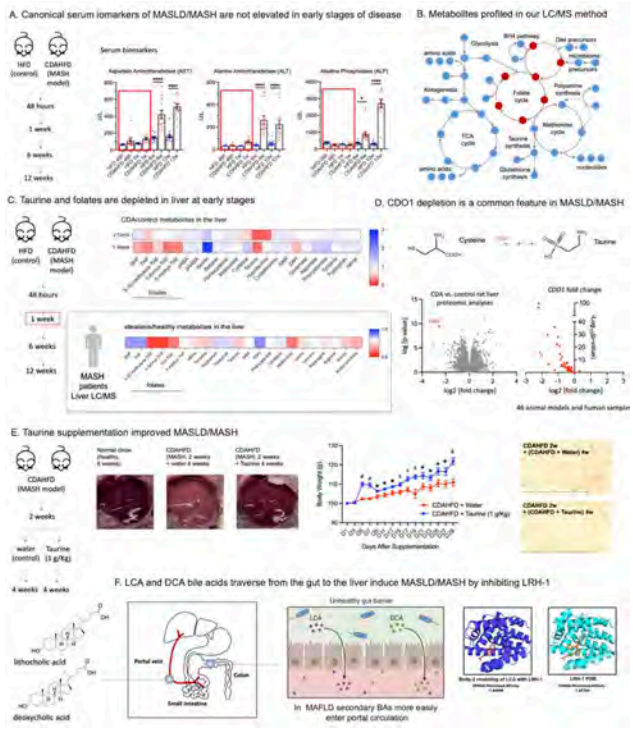
ABSTRACTS

The Liver Meeting: 2026 Abstracts

0001 | CROSSTALK BETWEEN ONE-CARBON METABOLISM AND BILE ACID SIGNALING DRIVES THE ONSET OF METABOLIC LIVER DISEASE

Snehal Chaudhari[1] Jonathan Williams[1] Yongtao Wang[2] Raymond Chung[3], [1]University of Wisconsin - Madison, [2]Harvard/MGH, [3]Massachusetts General Hospital

Background: The onset of metabolic dysfunction-associated steatotic liver disease (MASLD) is largely asymptomatic, delaying diagnosis until irreversible damage occurs. Identifying early metabolic aberrations is critical to discover driver pathways and develop timely interventions. We previously demonstrated that alterations in the intestinal bile acid (BA) repertoire precede liver damage (***Science Advances, 2022*** , PMID: 36026454). However, the downstream hepatic pathways triggered by these shifted BAs at MASLD onset remain poorly defined. Concurrently, one-carbon metabolism (OCM) deficiencies —folates in particular—strongly correlate with MASLD and MASH severity , but their precise mechanistic roles and regulation by BA signaling remain unknown. **Methods:** We utilized a novel LC/MS metabolomics platform profiling over 150 OCM-associated metabolites to map the first tissue-specific OCM atlas in conventional and germ-free mice (***Nature Metabolism, 2026***, PMID: 41888596). Novel aspects of the platform include an extraction protocol that allows stable isolation of metabolites from all organs, and a custom LC system that leverages physicochemical properties of metabolites for MS detection. We have built an interactive website (https://chaudharilab.com/folate-atlas/) for the science community to have free access to this foundational dataset.Applying this platform to multiple rodent models (choline-deficient [CDA] and Gubra-Amylin [GAN] diets) and human MASLD/MASH biopsies, we tracked early metabolic shifts. Mechanistic validation incorporated transcriptomics, proteomics, 16S rRNA microbiome sequencing, and *in vitro/in vivo* assays. **Results:** We identified profound deficiencies in hepatic folate and its downstream metabolite, taurine, strictly preceding histological liver damage. Bioinformatic analysis across 46 rodent models and longitudinal human studies confirmed taurine depletion as a universal MASLD/MASH feature. Proteomic profiling revealed this depletion stems from the downregulation of cysteine dioxygenase 1 (CDO1), the rate-limiting enzyme in taurine synthesis. Interventional administration of taurine in drinking water significantly rescued MASLD/MASH phenotypes in CDA rats. Enterohepatic BA profiling via LC/MS revealed that the secondary bile acids lithocholic acid (LCA) and deoxycholic acid (DCA) act as potent inhibitors of hepatic OCM and taurine synthesis. Notably, LCA/DCA-mediated OCM suppression does not signal through canonical BA receptors, but rather operates through the nuclear receptor LRH-1. **Conclusion:** This study defines a novel gut microbiome–BA–OCM–MASLD axis. We demonstrate that secondary BA-mediated inhibition of hepatic CDO1 drives early taurine depletion and metabolic dysfunction via LRH-1. These early OCM alterations offer highly promising biomarkers for early detection and novel therapeutic targets to halt MASLD progression.



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0002 | SINGLE-CELL SPATIAL TRANSCRIPTOMIC ANALYSIS OF THE UNFOLDED PROTEIN RESPONSE IN PRIMARY SCLEROSING CHOLANGITIS AND PRIMARY BILIARY CHOLANGITIS

Xiaoying Liu[1] Connor Lantz[1] Michael Mihalov[1] Richard Green[1], [1]Northwestern University Feinberg School of Medicine

Background: Primary sclerosing cholangitis (PSC) and primary biliary cholangitis (PBC) are chronic cholestatic liver diseases characterized by biliary injury that can progress to liver fibrosis, cirrhosis and need for liver transplantation. The etiology and pathogenesis of both diseases are complex and remain incompletely understood. The unfolded protein response (UPR) is a protective cellular response activated in response to endoplasmic reticulum stress and has been implicated in cholestatic liver disorders. In this study, we characterized UPR signaling pathway activation in PSC and PBC at a spatially resolved single-cell level to better understand their molecular pathogenesis. **Methods:** Formalin-fixed paraffin-embedded patient liver biopsy specimens were identified through Northwestern Medicine Enterprise Data Warehouse and obtained from Northwestern University Pathology Core facility. Specimens were classified into three groups: (1) control with normal liver morphology and normal liver function test (n = 2); (2) PSC (n = 5); and (3) antimitochondrial antibody positive PBC (n = 3). Single-cell spatial transcriptomic analysis was performed using the Xenium In Situ platform (10x Genomics) with the Xenium Prime 5K Human Pan Tissue & Pathways Panel supplemented by 50 custom probes targeting bile acid metabolism and UPR-related genes. Initial analyses, including cell segmentation and clustering, were performed on the Xenium instrument and visualized with Xenium Explorer. Cell types were manually annotated based on enriched expression of canonical marker genes. This study was approved by NU Institutional Review Board. **Results:** In PBC samples, clusters of plasma cells were identified in periportal regions surrounding bile ducts based on the expression of marker genes *MZB1*, *IRF4*, *CD38* and *PRDM1*. UPR pathway gene expression was significantly higher in these plasma cells compared with the other cell types, including *XBP1* ($log_2FC = 2.9$), *XBP1* spliced ($log_2FC = 3.5$), the XBP1 downstream targets *ERdj4* ($log_2FC = 2.6$) and *EDEM1* ($log_2FC = 2$), as well as *ERN1* ($log_2FC = 2$), *EIF2AK3* ($log_2FC = 3.2$), and *ATF4* ($log_2FC = 1.7$) ($P_{adj} < 0.00001$ for all genes). Across all groups, *XBP1* expression was moderate in hepatocytes, but minimal in cholangiocytes, hepatic stellate cells and Kupffer cells. In one PSC case, two distinct cholangiocyte clusters were identified: one lining bile ducts within portal tracts and another diffusely distributed in periportal regions. *TRAF2* gene expression was enriched in cholangiocytes in control and PSC samples, but not in PBC. **Conclusion:** These findings demonstrate that UPR gene expression and activation are cell-type specific and appear to differ across cholestatic liver diseases. Single-cell spatial transcriptomics provides novel insights into the molecular pathogenesis of PSC and PBC. Furthermore, the enhanced expression of UPR-related genes in plasma cells suggests potential therapeutic targets in PBC.

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★ 0003 | SHARED AND ISOFORM-SPECIFIC ROLES OF PPAR-α, -δ, AND -γ SIGNALING IN MITIGATING CHOLESTATIC HEPATOCYTE INJURY IN PRIMARY BILIARY CHOLANGITIS

Garnik Arustamyan[1] Masashi Okawa[1] Yein Woo[1] Daniel Pinski[1] Meng Li[1] Takeshi Saito[2], [1]University of Southern California, Keck School of Medicine, [2]University of Southern California

Background: PBC is a chronic cholestatic liver disease in which autoimmune-mediated bile duct injury impairs bile flow, leading to intrahepatic accumulation of toxic bile acids and consequent hepatocyte stress and injury. UDCA remains the first-line therapy; however, a substantial proportion of patients have an incomplete response and remain at risk for disease progression. PPAR agonists have emerged as effective second-line PBC therapies; however, the isoform-specific mechanisms by which PPAR activation protects hepatocytes from cholestatic bile acid injury remain poorly defined. We therefore aimed to define the shared and distinct roles of PPAR-α, -δ, and -γ signaling in regulating bile acid homeostasis and mitigating cholestatic injury in primary human hepatocytes (HHs). **Methods:** HHs were benchmarked against normal human liver tissue to confirm PPAR isoform expression and intracellular localization. HHs were then treated with PPAR isoform-selective and multi-isoform agonists, including fenofibrate, seladelpar, elafibranor, and lanifibranor. Effects on bile acid homeostasis and canalicular bile secretory machinery were assessed by RNA-seq profiling, fluorescence microscopy with CDFDA and fluorescent bile acids, and LC-MS quantification of intracellular and extracellular bile acid species. PPAR isoform dependence was tested using solid-phase reverse-transfection–based siRNA knockdown of PPAR isoforms, individually and in combination. Parallel studies with

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UDCA and obeticholic acid assessed additive or synergistic interactions between PPAR pathways and FXR signaling. Therapeutic efficacy of PPAR isoform-specific agonists alone or in combination with UDCA was evaluated in a CDCA-induced in vitro model of cholestatic HH injury by assessing reductions in bile acid–induced cellular stress and injury and modulation of canalicular bile secretory function. **Results:** Gain- and loss-of-function studies using PPAR agonists and siRNA-mediated silencing revealed isoform-specific regulation of bile acid homeostasis. Dual PPAR-α/δ agonism most effectively reduced the intracellular toxic bile acid pool in HHs, whereas PPAR-γ signaling had minimal effect. The anticholestatic effect of PPAR-α/δ agonist was mediated primarily through enhanced canalicular bile acid export. Dual PPAR-α/δ agonism, particularly when combined with UDCA, exhibited the strongest anticholestatic and cytoprotective effects in the CDCA-induced cholestatic hepatocyte injury model. **Conclusion:** Dual PPAR-α/δ agonism, exemplified by elafibranor, enhanced canalicular bile acid export in primary HHs, thereby reducing the intracellular toxic bile acid pool that drives CDCA-induced cholestatic stress and injury. The additional protection observed with UDCA co-treatment further supports enhanced hepatocellular bile acid disposal as a central mechanism for mitigating cholestatic injury in PBC.

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0005 | DECOUPLING OF DISEASE ACTIVITY AND FIBROSIS IN MASH: INSIGHTS FROM CONTEMPORARY BIOPSY COHORTS IN THE GLP-1 RECEPTOR AGONIST ERA

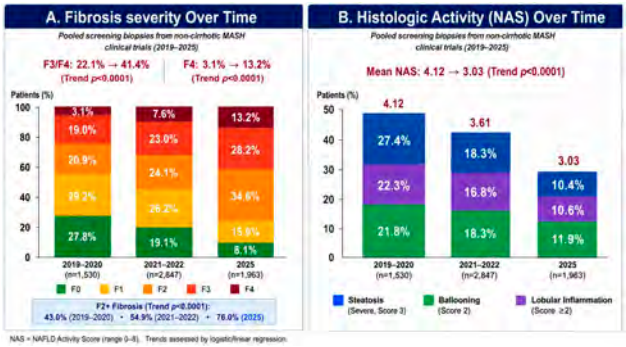
Winston Dunn[1] Gražina Binkauskiene[2] Elizabeth Brombosz[2] Rashmee Patil[3] Rohit Puskoor[4] David Huang[5] Nirupama Esther Jerome[4] John Poulos[6] Alaa Abousaif[7] Aasim Sheikh[8] Alma Laura Ladrón de Guevara[9] Marcelo Kugelmas[10] Mousab Tabbaa[11] Sam Moussa[12] Vlad Ratziu[13] Meena Bansal[14] Jörn Schattenberg[15] Mazen Noureddin[16] Naim Alkhouri[17], [1]University of Kansas Medical Center, [2]Summit Clinical Research Solutions, [3]Pinnacle at San Antonio, Summit Clinical Research Solutions, [4]Pinnacle at Austin, Summit Clinical Research Solutions, [5]Houston Research Institute – Main, [6]Coastal Research Institute, [7]Providence St. Joseph Hospital-Orange, [8]GI Specialists of Georgia, [9]Centro De Investigacion Y Gastroenterologia, [10]South Denver Gastroenterology, [11]Clinical Research Institute of Ohio, [12]Adobe Clinical Research, [13]Service D' Hepatogastroenterologie (FR), [14]Icahn School of Medicine at Mount Sinai (ISMMS), [15]Saarland University Medical Center, [16]Houston Methodist Hospital, Houston Research Institute, Summit Clinical Research Solutions, [17]Summit Clinical Research

Background: GLP-1 receptor agonists (RAs) are increasingly used in MASH, yet their association with liver histology in real-world biopsy cohorts remains incompletely characterized. We evaluated temporal trends in fibrosis severity and histologic activity among patients enrolled in contemporary MASH clinical trials and assessed the relationship between GLP-1RA use and biopsy findings. **Methods:** We analyzed pooled biopsy data from patients screened for non-cirrhotic MASH clinical trials between 2019 and 2025. Cirrhosis-focused trials were excluded to reduce selection bias. Histologic outcomes included NAS and its individual components. Temporal trends were assessed using logistic and linear regression models. GLP-1RA exposure, ongoing GLP-1RA use, diabetes, BMI, and biopsy year were evaluated in adjusted models examining associations with fibrosis and NAS. **Results:** Among 7,819 patients with available biopsy date and fibrosis staging, advanced fibrosis increased substantially over time. F4 increased from 3.1% in 2019–2020 to 13.2% in 2025, while F3/F4 increased from 22.1% to 41.4%, and F2+ from 43.0% to 76.0% (all $p < 0.0001$). In contrast, histologic activity improved over time: mean NAS decreased from 4.12 to 3.03 (estimate −0.259/year, $p < 0.0001$). Severe steatosis declined from 27.4% to 10.4%, ballooning decreased from 21.8% to 11.9%, and higher lobular inflammation scores also declined over time. GLP-1RA use increased from 7.8% in 2023 to 10.3% in 2025 (total $n = 553$). During the same period, F4 prevalence increased from 7.7% to 31.4%, while F3/F4 fibrosis increased from 28.6% to 55.2%. Logistic models confirmed increasing odds of F4 fibrosis over time (OR 2.07/year, $p < 0.0001$). GLP-1RA users had greater unadjusted fibrosis severity than non-users (F3/F4: 69.8% vs 41.6%; F4: 32.5% vs 21.0%; both $p < 0.0001$). However, after adjustment for biopsy year, BMI, and diabetes, GLP-1RA use was associated with lower NAS (estimate −0.186, $p = 0.01$), with similar findings for ongoing GLP-1RA use (estimate −0.222, $p = 0.005$). Diabetes was more common among GLP-1RA users (57.7% vs 37.3%). **Conclusion:** In contemporary MASH clinical trial populations, fibrosis severity increased markedly over time despite improvement in inflammatory and steatotic histologic features. Increasing GLP-1RA use was associated with lower adjusted NAS, suggesting improved necroinflammatory activity, but not with reduced fibrosis severity. The higher fibrosis burden observed among GLP-1RA

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users likely reflects confounding by diabetes, metabolic risk, referral patterns, and insufficient duration for fibrosis regression. These findings highlight a potential divergence between short-term improvements in disease activity and longer-term fibrosis outcomes in modern MASH populations.



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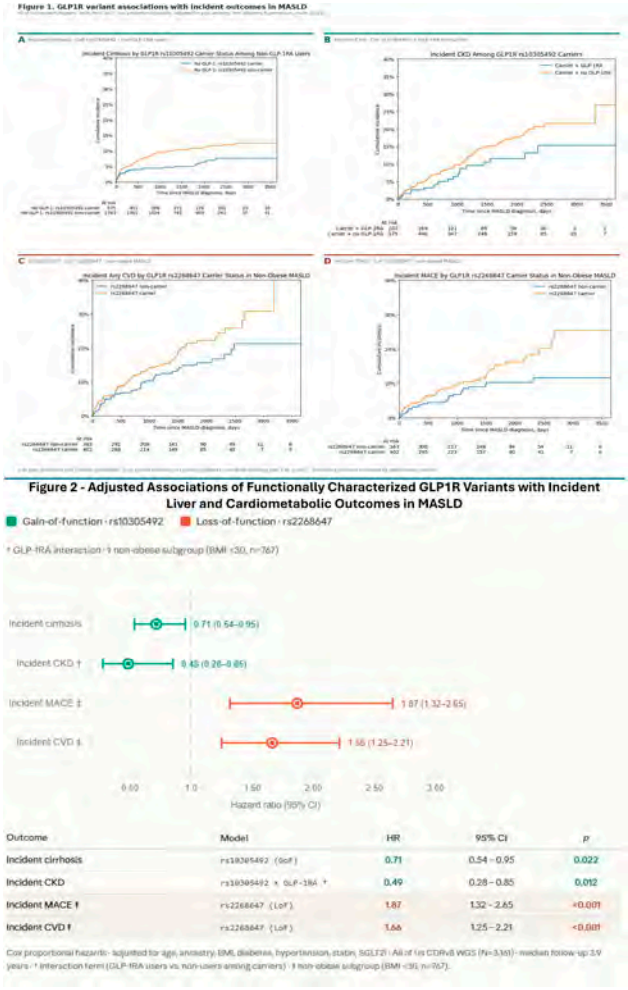
★ 0006 | *GLP1R* GENE VARIANTS MODIFY LONGITUDINAL OUTCOMES AND GLP1 RECEPTOR AGONIST RESPONSE IN MASLD: A WHOLE-GENOME SEQUENCING PHARMACOGENOMIC STUDY

Sarpong Boateng[1] Guy Nguefang[2] Yazan Al-ajlouni[3] Chimezirim Ezeano[4] Nkengeh Tazinkeng[5] Ihunanya Kanu[6] Basile Njei[7], [1]Yale New Haven Health, Bridgeport Hospital, [2]Guy Loic Nguefang, [3]Montefiore School of Medicine, [4]Advocate Aurora Healthcare, [5]Rutgers/Newark Beth Israel Medical Center, [6]Baptist Memorial Hospital- Golden Triangle, [7]Yale University

Background: GLP-1 receptor agonists (GLP-1RAs) improve metabolic and hepatic outcomes in MASLD, yet substantial variability in treatment response persists. Inherited variation in the GLP1R gene may contribute to heterogeneity in MASLD progression and treatment-associated outcomes, but longitudinal data are limited. We thus evaluated whether functionally characterized GLP1R variants are associated with differential longitudinal outcomes whether these variants modify therapeutic response to GLP-1RA therapy. **Methods:** We identified 3,161 adults with MASLD and whole-genome sequencing data in the All of Us Research Program (2016–2023). Four previously characterized GLP1R variants were evaluated: gain-of-function (GoF) variants rs10305492 and rs75151020, and loss-of-function (LoF) variants rs10305420 and rs2268647. Incident outcomes included cirrhosis, CKD, major adverse cardiovascular events (MACE; MI, heart failure, or stroke), any cardiovascular disease (CVD), HCC, and all-cause mortality. Baseline was defined as MASLD diagnosis; prevalent cases were excluded from each outcome analysis. GLP-1RA use was defined as post-MASLD ever-use based on EHR records. Follow-up continued until outcome, death, or censoring (October 1, 2023). Cox models adjusted for age, ancestry, BMI, diabetes, hypertension, statin, and SGLT2 inhibitor use. Interaction analyses evaluated GLP1R variant×GLP-1RA therapy effects. Prespecified analyses were performed in non-obese individuals (BMI < 30 kg/m²). **Results:** Mean age at MASLD diagnosis was 55.5 ± 13.4 years; 58.2% were White and 7.4% Black/African American. Mean BMI was 35.4 ± 8.4 kg/m², and 25.3% received GLP-1RA therapy. Median follow-up was 3.5–4.0 years.In adjusted analyses, the GoF variant rs10305492 was associated with lower risk of incident cirrhosis (HR 0.71, 95% CI 0.54–0.95; $p = 0.022$). Interaction analyses demonstrated treatment-associated heterogeneity for incident CKD by rs10305492 carrier status and GLP-1RA use (interaction HR 0.49, 95% CI 0.28–0.85; $p = 0.012$). Among non-obese individuals with MASLD, the loss-of-function variant rs2268647 was associated with higher risk of incident MACE (HR 1.87, 95% CI 1.32–2.65; $p < 0.001$) and incident CVD (HR 1.66, 95% CI 1.25–2.21; $p < 0.001$). No significant associations were observed for HCC or all-cause mortality. **Conclusion:** Functionally characterized GLP1R variants were differentially associated with longitudinal hepatic and cardiometabolic outcomes in adults with MASLD. A GoF variant was associated with lower incident cirrhosis risk and modified the association between GLP-1RA therapy and CKD risk, whereas a LoF variant identified non-obese individuals at elevated cardiovascular risk. These findings suggest that inherited GLP1R variation may contribute to MASLD heterogeneity and support further investigation of pharmacogenomic approaches to risk stratification and GLP-1RA treatment-response prediction.

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0007 | BULEVIRTIDE MONOTHERAPY PREVENTS LIVER DECOMPENSATION IN HDV-RELATED CIRRHOSIS: 3-YEAR RESULTS FROM A EUROPEAN, RETROSPECTIVE, CONTROLLED COHORT STUDY

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Background: Bulevirtide (BLV) monotherapy yields high rates of virological and biochemical responses in chronic hepatitis delta (CHD); however, the impact of BLV treatment on hard clinical outcomes has not been established. **Methods:** Consecutive CHD patients with cirrhosis receiving BLV monotherapy for up to 3 years in a retrospective European cohort study were compared with pooled data from two BLV-untreated cohorts. The primary endpoint was the incidence of de novo liver-related events ([LREs]: decompensation and hepatocellular carcinoma [HCC]); deaths, and liver transplantation occurring over 3 years were compared for treated and untreated patients, including risk adjustment by inverse probability of treatment weighting (IPTW) and Cox regression analysis. **Results:** A total of 642 patients were included: 344 BLV-treated and 298 untreated controls. Treated patients were older (50 *vs.* 40 years, $p < 0.0001$), more frequently women (males 62% *vs.* 78%, $p = 0.001$), Caucasian (84% *vs.* 62%, $p < 0.0001$), on NUC (91% vs. 40%, $p < 0.0001$) and with higher HDV RNA (5.4 *vs.* 4.9 Log_{10}IU/mL, $p = 0.002$). By contrast, the proportion of patients with previous decompensation, HCC or CSPH was similar. The 3-year cumulative incidence of LREs was lower in BLV-treated patients *vs.* untreated: 8.9% (95%CI 4-12%) *vs.* 16.2% (95% CI 11-22%), respectively ($p = 0.03$). The corresponding figures for decompensation were 2.7% (95%CI 1-4%) *vs.* 11.3% (95%CI 7-16%) ($p = 0.001$) and for HCC 6.1% (95% CI 3-8%) *vs.* 6.6% (95% CI 3-11%) ($p = 0.49$), respectively. In IPTW-adjusted Cox regression analysis, BLV-treated *vs.* untreated controls had significantly lower risk of developing LREs (HR 0.44, 95% CI 0.27-0.72, $p = 0.001$) or decompensation (HR 0.16, 95% CI 0.07-0.36, $p < 0.0001$). These results were confirmed by IPTW-adjusted competing risks regression model (SHR 0.16, 95%CI 0.06-0.40, $p < 0.0001$). Conversely, the HCC risk was similar across all cohorts. Lower baseline albumin values independently predicted LREs, both in the BLV-treated cohort (HR 0.22, 95% CI 0.08-0.64, $p = 0.006$) and untreated controls (HR 0.38, 95% CI 0.20-0.72, $p = 0.002$). Mild pruritus (10%) and injection site reactions (3%) were the most reported adverse events during BLV treatment. **Conclusion:** In CHD patients with cirrhosis, a 3-year course of BLV monotherapy reduced the risk of LREs and decompensation, but not HCC, compared to an untreated IPTW-matched population.

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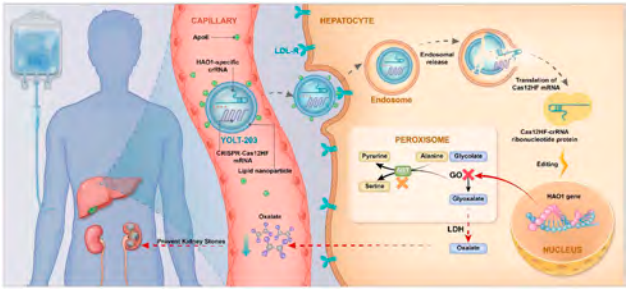
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★ 0008 | CRISPR-CAS12 BASED GENE EDITING THERAPY FOR PRIMARY HYPEROXALURIA TYPE 1: A PHASE 1 CLINICAL TRIAL

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Background: Primary hyperoxaluria type 1 (PH1) is a rare inherited metabolic disorder caused by hepatic oxalate overproduction, leading to recurrent kidney stones, nephrocalcinosis and progressive kidney failure. Targeting key enzymes in hepatic oxalate metabolism can reduce oxalate production and provides a therapeutic strategy for PH1. **Methods:** Here we report results from an open-label, first-in-human phase 1 clinical trial (ClinicalTrials.gov identifier: NCT06511349) of YOLT-203, a lipid nanoparticle-delivered in vivo gene-editing therapy using an engineered CRISPR–Cas12 nuclease to disrupt HAO1. Seven patients with PH1 aged 8–25 years received a single intravenous infusion of YOLT-203 at 0.3 mg kg^{-1} (n = 2) or 0.45 mg kg^{-1} (n = 5) and were followed for 52 weeks. **Results:** No serious treatment-related adverse events or dose-limiting toxic effects were observed. All adverse events were mild to moderate, with infusion-related reactions in four patients (57.1%) and transient elevations in alanine aminotransferase and aspartate aminotransferase in one patient (14.3%). Mean 24-hour urinary oxalate excretion was reduced from baseline by day 14 and remained suppressed throughout follow-up, with reductions of 45.7% in the 0.3 mg kg^{-1} group and 64.9% in the 0.45 mg kg^{-1} group at week 52. **Conclusion:** These findings support further clinical evaluation of YOLT-203 as a potential treatment for PH1.



Disclosures: Taihua Yang:Nothing to Disclose.

★ 0009 | TWELVE-MONTH BIOCHEMICAL RESPONSE TO UDCA PREDICTS FIVE-YEAR DECOMPENSATION AND MORTALITY IN PRIMARY BILIARY CHOLANGITIS: A PROPENSITY-MATCHED LANDMARK COHORT STUDY

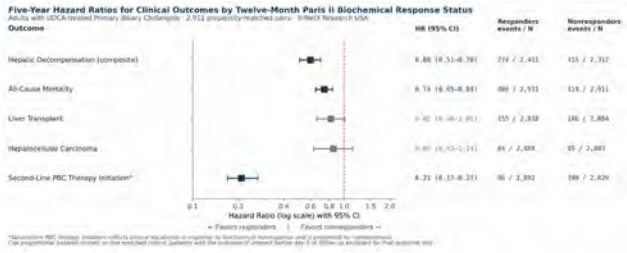
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Background: Primary biliary cholangitis (PBC) is a chronic immune-mediated cholestatic liver disease for which ursodeoxycholic acid (UDCA) is first-line therapy. Biochemical response at 12 months, assessed by criteria such as Paris II, anchors treatment-escalation decisions in registry cohorts (UK-PBC, GLOBE), but real-world multi-center EHR validation against hard 5-year clinical endpoints remains limited. **Methods:** Retrospective propensity-matched landmark cohort using TriNetX Research USA (147M adults, 112 healthcare organizations). Adults ≥18 with PBC (≥2 ICD-10 K74.3 codes ≥30 days apart, 2013–2024) initiating UDCA were classified at a 12-month landmark using ALP and total bilirubin measured 9–15 months after the index diagnosis: responders met modified Paris II criteria (ALP ≤130 U/L and bilirubin ≤1.0 mg/dL); nonresponders failed one or both. AST was not included due to EHR data limitations; absolute thresholds were used as a proxy for ULN-based cutoffs. Pre-index HCC, liver transplant, HIV, HBV, and prior second-line PBC therapy were excluded. 1:1 propensity matching on 29 covariates (demographics, liver and behavioral comorbidities, baseline labs, encounter types) achieved all categorical SMDs <0.05. Outcomes ascertained days 1–1825 post-landmark: composite hepatic decompensation, liver transplant, HCC, all-cause mortality, and second-line PBC therapy initiation; patients with the outcome before the window were excluded for that outcome only (incident-event analysis). Cox proportional hazards models estimated hazard ratios (HR) from the landmark date forward, eliminating immortal-time bias. **Results:** 2,911 matched pairs (mean age 61, 87% female, 77% White) were analyzed. Over 5 years, biochemical responders had lower composite hepatic decompensation (HR 0.60, 95% CI 0.51–0.70; 5-year event-free survival 75.9% vs 67.7%; p<0.001) and lower all-cause mortality (HR 0.74, 95% CI 0.65–0.84; p<0.001). Liver transplant (HR 0.82, 95% CI 0.66–1.01; p=0.06) and hepatocellular carcinoma (HR 0.85, 95% CI 0.63–1.14; p=0.28) trended favorably without reaching statistical

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significance, likely reflecting limited 5-year event accrual. Second-line PBC therapy initiation was substantially lower among responders (HR 0.21, 95% CI 0.17–0.27), consistent with clinical practice escalating therapy in nonresponders. Absolute 5-year differences in the responder arm: 6.6 percentage-point lower decompensation incid **Conclusion:** In a large real-world EHR cohort, modified Paris II response at 12 months was associated with lower 5-year hepatic decompensation and mortality, supporting its use as a prognostic anchor for treatment escalation.



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0010 | EARLY AND WEEK 52 BIOMARKER (MRI-PDFF, ALT, MRE AND PRO-C3) RESPONSES TO RESMETIROM PREDICT IMPROVEMENTS IN MASH AND LIVER FIBROSIS

Rohit Loomba[1] Rebecca Taub[2] Krishna Padmanabhan[2] Dominic Labriola[2] Mazen Noureddin[3] Naim Alkhouri[4], [1]San Diego School of Medicine, [2]Madrigal Pharmaceuticals, [3]Houston Methodist Hospital, [4]Summit Clinical Research

Background: MAESTRO-NASH (NCT03900429) is an ongoing 54-month, randomized, double-blind, placebo (PBO)-controlled Phase 3 trial evaluating the efficacy of resmetirom (RES) in patients with MASH and F2/F3 fibrosis. The 52-week histologic endpoints demonstrated resolution of MASH (MR) and fibrosis improvement (FI) with RES 80 mg and 100 mg leading to approval. We report early non-invasive biomarkers of change and their correlation with Week (W) 52 biopsy responses, as well as the odds of achieving an early biomarker response with treatment. **Methods:** To assess relationships between early biomarker responses and W52 liver biopsy outcomes, changes in ALT, MRE, MRI-PDFF, at W12,24 52 following initiation of RES or PBO were analyzed for correlation with biopsy-defined MR and FI. Odds of achieving early improvement in these biomarkers were evaluated as a function of treatment. PRO-C3 change was a measure of response. **Results:** $\geq$20% reduction in ALT at w12, 24, 52 was associated with higher odds (OR) of W52 MR/FI. With RES, ALT response showed an OR of 2.0, 2.2, 2.6 repectively at W12, 24, 52; $p < 0.002$). RES OR of achieving an FI response at w12, 24 and 52, compared to PBO: ORs of 2.2, 2.7, 3.6 respectively. All $p < 0.001$. MR was similar. $\geq$15% reduction in MRE at W16, 52 was associated with higher OR of Week 52 FI/MR. With RES, MRE response ORs FI, 2.6 and 2.3 at W16, 52, respectively, $p \leq 0.02$, less association in PBO. MR was similar. RES compared with PBO stat sig. odds of achieving an MRE response, at W52 (OR = 1.71) but not at (W16 OR = 1.31). A $\geq$30% reduction in MRI-PDFF from baseline at W16 and 52 was strongly associated with higher odds of FI and MR. With RES, MRI-PDFF response was associated with increased odds of FI (ORs 1.9 and 2.95 at w16 and 52, respectively; $p \leq 0.02$) and MR at Week 52 (OR ~ 6.5). RES was associated with significantly higher odds of achieving an PDFF response compared with PBO at W16, 52 (ORs 12.4 and 6.7; both $p < 0.0001$). For Pro-C3, change and % change n PRO-C3 at Weeks 24 and 52 in F3 showed a relationship to FI in all treatment groups, w52: 80 mg, -7%, -23%; 100 mg, -14%, -20%; PBO, 0%, -20% FI nonresponders and responders, respectively with far more responders in RES, regression currve $p = 0.0017$ RES, $p = 0.04$ PBO. **Conclusion:** Early and W52 responses to RES, particularly reduction in PDFF at W16 and W52, correlate with FI and MR responses on liver biopsy. Reduction in ALT, MRE and PRO-C3 ($\leq$W24 and W52) showed a significant correlation with FI on biopsy with RES treatment.

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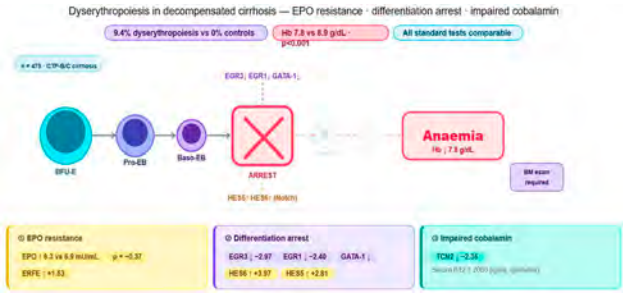
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0011 | DYSERYTHROPOIESIS UNDERLIES SEVERE REFRACTORY ANAEMIA IN DECOMPENSATED CIRRHOSIS THROUGH ERYTHROPOIETIN RESISTANCE, ERYTHROID DIFFERENTIATION ARREST, AND IMPAIRED CELLULAR COBALAMIN UPTAKE

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Background: Severe anemia (Hb < 8 g/dL) affects > 1/3 decompensated cirrhosis patients, more so in CTP-B/C. Standard haematological investigations fail to identify its cause in a substantial subgroup. We examined whether disordered erythroid maturation (dyserythropoiesis) in the bone-marrow (BM) underlies this refractory phenotype and its mechanistic basis. **Methods:** Cirrhosis patients (n = 475) undergoing BM examination (2010-2025) for clinical indications were enrolled alongside non-liver-disease controls (n = 196) and CKD patients (n = 170) as comparators. Dyserythropoiesis was graded (> 5% abnormal erythroid precursors; mild 5–10%, moderate 10–15%, marked > 15%). Serum erythropoietin (EPO), erythroferrone (ERFE), hepcidin, vitamin B12, iron panel, reticulocyte count, lactate dehydrogenase (LDH), and thyroid stimulating harmone (TSH) were compared between dyserythropoietic and non-dyserythropoietic patients. Erythroid cell biomarkers and RNA sequencing was performed. **Results:** Severe anaemia occurred in 36.2% of cirrhosis patients, highest in CTP-C. Dyserythropoiesis was seen in 9.4% of cirrhosis patients, 2.4% in CKD, and none in controls, clustering in CTP-B/C (p = 0.003), with grade 3 limited to CTP-C. Dyserythropoietic patients had lower haemoglobin [7.8 (6.8–8.9) vs 8.9 (7.5–10.8) g/dL; p < 0.001].Conventional markers did not distinguish dyserythropoietic patients: serum iron, transferrin saturation, ERFE, hepcidin, reticulocyte count, LDH, and TSH were similar. Serum EPO was higher in cases with dyserythropoiesis (8.3 vs 6.9 mU/mL; p = 0.052), elevated overall in cirrhosis vs controls/CKD, and inversely correlated with haemoglobin (rho = −0.37; p < 0.001), suggesting EPO resistance. Serum B12 was paradoxically higher in dyserythropoietic patients (2,000 vs 1,413 pg/mL; p = 0.006), indicating impaired cellular cobalamin uptake.Erythroid TFs: *EGR3* (log2FC−2.9) and *EGR1* (−2.4), which drive terminal differentiation, were downregulated, with reduced GATA-1 and nonnuclear HSP70 protein levels. Notch effectors *HES6* (+3.9) and *HES5* (+2.8) were upregulated, maintaining progenitors in an undifferentiated state and promoting erythroid hyperplasia with ineffective output. *TCN2* (−2.3), which mediates cobalamin uptake into erythroblasts, was downregulated, explaining elevated serum B12 despite impaired maturation. *ERFE* (+1.53) was upregulated, confirming intense but ineffective erythropoiesis. **Conclusion:** In decompensated cirrhosis, dyserythropoiesis is the BM correlate of severe treatment-refractory anaemia, concentrated in CTP-B/C and invisible to all standard laboratory parameters. Coraborative evidence points to erythroid transcription factor collapse, Notch pathway gene upregulation, and impaired cellular cobalamin transport as the mechanistic substrate. Bone marrow examination is required for identification of this entity.



Disclosures: Chhagan Bihari:Nothing to Disclose, Sukriti Baweja:Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose.

0012 | ALCOHOL-RELATED PLASMA PROTEOMIC SIGNATURE AND RISK OF CANCER AND MORTALITY: A PROSPECTIVE STUDY IN THE UK BIOBANK

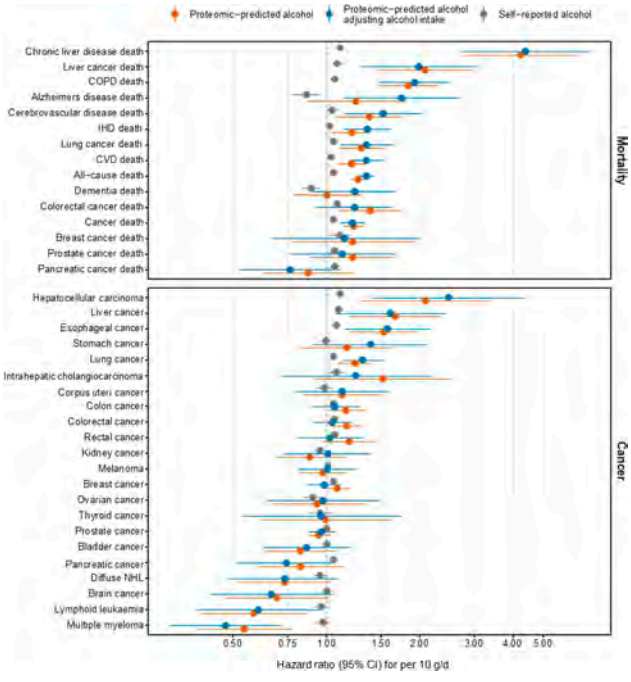
Loggang Zhao[1] Xuehong Zhang[2], [1]Yale School of Nursing, [2]Yale University

Background: Alcohol intake is an established risk factor for liver disease, cancer, and mortality, but risk assessment based on self-reported intake is limited by measurement error and may not capture alcohol-related biological injury. Plasma proteomics may provide a molecular signature of alcohol exposure and its downstream effects, but its relevance to liver-related, cancer, and mortality outcomes remains unclear. We developed a proteomic signature of alcohol intake in the UK Biobank and examined its associations with cancer incidence and cause-specific mortality beyond self-reported alcohol intake. **Methods:** We conducted a prospective analysis of UK Biobank participants with baseline Olink Explore plasma proteomic data and self-reported alcohol intake, excluding participants with baseline cancer or liver disease (N = 35,519). Proteomic-predicted alcohol intake was derived using elastic net regression with 10-fold cross-validation. Incident cancers and deaths were ascertained through cancer and death registries. Cox

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models estimated hazard ratios (HRs) and 95% CIs for cancer incidence and mortality per 10 g/day increment in proteomic-predicted alcohol intake, adjusting for sociodemographic, lifestyle, and clinical factors, including self-reported alcohol intake. **Results:** The elastic net model selected 74 proteins to derive the proteomic-predicted alcohol intake. Enrichment analyses suggested inflammatory, cytokine-response, immune-cell trafficking, and cell-adhesion pathways. During a median follow-up of 10.9 years, 3,270 cancers and 2,131 total deaths were documented. After adjustment for self-reported alcohol intake, higher proteomic-predicted alcohol intake was associated with increased risks of multiple cancer and mortality outcomes, with the strongest associations observed for liver-related outcomes. Each 10 g/day increment in proteomic-predicted alcohol intake was associated with higher risks of chronic liver disease mortality (HR [95% CI]: 4.36 [2.70–7.04]), hepatocellular carcinoma (2.47 [1.40–4.35]), liver cancer incidence (1.60 [1.06–2.42]) and mortality (1.98 [1.29–3.03]). Positive associations were also observed for selected cancers, respiratory and neurovascular mortality, cardiovascular mortality, all-cause mortality, and cancer mortality, with HRs ranging from 1.21 to 1.92. **Conclusion:** Alcohol-related proteomic signatures were associated with risks of cancer and mortality outcomes beyond self-reported alcohol intake, especially for liver-related outcomes. Plasma proteomics may provide molecular insight into alcohol-related biological risk and improve identification of high-risk individuals.



Disclosures: Loggang Zhao:Nothing to Disclose, Xuehong Zhang:Nothing to Disclose.

0013 | QEL-001, AN ENGINEERED TREG CELL THERAPY TARGETING HLA-A2, DEMONSTRATES SAFETY, PHENOTYPIC STABILITY, DURABILITY AND FACILITATES MINIMIZATION OF IMMUNOSUPPRESSION IN LIVER TRANSPLANT PATIENTS (LIBERATE)

Alberto Sanchez-Fueyo[1] Kourosh Saeb-Parsy[2] Jacques Pirenne[3] Jordi Colmenero[4] Manuel Rodriguez-Peralvarez[5] Anthony Demetris[6] Andrew Lesniak[6] Gareth Wright[7] Annie Woodburne[7] Sarah-Jayne Reilly[7] Chris Sharpe[7] Nikola Novcic[7] Rupert Kenefect[7] Anna Fettiplace[7] Laurie Baylor Curtis[8] Marc Martinez-Llordella[7] Alan Magovern[7] Nathalie Belmonte[7] Kasia Averall[7] Luke Devey[7], [1]RW Institute of Liver Studies, Kings College London, [2]University of Cambridge and NIHR Biomedical Research Centre, Cambridge, UK, [3]University Hospitals Leuven, [4]Liver Unit, Hospital Clinic Barcelona, Spain, [5]Hospital Reina Sofia, Universidad de Cordoba, Spain, [6]University of Pittsburgh, [7]Quell Therapeutics Ltd, [8]Quell Therapeutics

Background: Regulatory T cells (Tregs) are essential for maintaining immune tolerance & pre-clinical data supports their ability to promote allograft tolerance. LIBERATE (NCT05234190) was a first-in-human Phase I/II trial evaluating QEL-001, an autologous HLA-A2-specific CAR-Treg therapy, in liver transplantation. Here we report the clinical, cellular kinetic, pharmacodynamic & immunosuppression (IS) modulation data from LIBERATE. **Methods:** LIBERATE was an open-label, dose-escalation Phase I/II study in HLA-A2-negative adult recipients of HLA-A2-positive liver allografts with QEL-001 CAR-Tregs targeting HLA-A2 to promote liver allograft tolerance. The primary objective of LIBERATE was to evaluate safety & tolerability of a single dose of QEL-001. Secondary and exploratory endpoints included clinical activity, CAR-Treg cellular kinetics, pharmacodynamic effects on peripheral and graft-associated immune populations, and feasibility of immunosuppression minimisation. Patients in the expansion cohort received ATG prior to QEL-001 dosing. **Results:** A total of 9 participants were dosed with QEL-001 during the LIBERATE study (n = 3, safety cohort; n = 6, expansion cohort). Overall, QEL-001 was well-tolerated, with no acute peri-/post-infusion toxicities & no safety signals observed (up to 2.5 years follow-up). Most adverse events (AEs) were Grade 1–2 and no AEs were related to QEL-001; 2 participants experienced serious AEs (rejection AEs; resolved). No CAR-positive cellular impurities (i.e., CD8+ effector cells) were detected in blood or liver tissue in any participants, including those

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who experienced rejection episodes. In the expansion cohort, IS weaning was evaluated in 5 participants. All 5 discontinued calcineurin inhibitors (CNI [tacrolimus]) at a median of 28 days post-infusion & remained stable on mTOR inhibitor monotherapy (everolimus [EVR]) for at least 6 months. On weaning beyond low dose EVR, 3 experienced T cell mediated rejection episodes, which resolved with re-introduction of IS. Longitudinal analysis showed that QEL-001 persists in peripheral blood for ≥12 months & maintains lineage stability and canonical Treg phenotype in blood and liver tissue. In liver biopsies, the magnitude of CAR-Treg accumulation was strongly correlated with the overall degree of T-cell infiltration. CAR-Tregs preferentially co-localized to portal regions containing other immune cell infiltrates, indicating targeted homing to sites of alloimmune activity. **Conclusion:** These results from LIBERATE demonstrate that QEL-001 is safe & well-tolerated with durable persistence & preferential enrichment in the liver, providing a foundation for CAR-Tregs to potentially facilitate weaning of long-term immunosuppression in liver transplantation.

Disclosures: Alberto Sanchez-Fueyo:Quell Therapeutics Ltd: Consultant, Kourosh Saeb-Parsy:Nothing to Disclose, Jacques Pirenne:Nothing to Disclose, Jordi Colmenero:Nothing to Disclose, Manuel Rodriguez-Peralvarez:Nothing to Disclose, Anthony Demetris:Nothing to Disclose, Andrew Lesniak:Nothing to Disclose, Gareth Wright:Quell Therapeutics: Employee, Annie Woodburne:Nothing to Disclose, Sarah-Jayne Reilly:Quell Therapeutics: Employee, Chris Sharpe:Nothing to Disclose, Nikola Novcic: Nothing to Disclose, Rupert Kenefect:Nothing to Disclose, Anna Fettiplace:Nothing to Disclose, Laurie Baylor Curtis:Nothing to Disclose, Marc Martinez-Llordella:Nothing to Disclose, Alan Magovern:Nothing to Disclose, Nathalie Belmonte:Nothing to Disclose, Kasia Averall:Nothing to Disclose, Luke Devey:Nothing to Disclose.

0014 | EXTRACORPOREAL LIVER SUPPORT USING A BIOENGINEERED LIVER FOR THE TREATMENT OF ACUTE LIVER FAILURE, ALCOHOL ASSOCIATED HEPATITIS OR ACUTE-ON-CHRONIC LIVER FAILURE: RESULTS FOR A FIRST-OF-ITS-KIND PHASE I CLINICAL TRIAL

Christopher Danford[1] Aanchal Kapoor[2] Sander Florman[3] Jody Olson[4] John Lake[5] M Mason Macenski[6] Christopher Fecteau[6] Joshua Carlson[6] Jeff Ross[6],

[1]Intermountain Health, [2]Cleveland Clinic, [3]Mount Sinai Medical, [4]Mayo Clinic Rochester, [5]University of Minnesota, [6]Miromatrix Medical

Background: Currently, there is no effective treatment for acute liver failure other than liver transplantation. We performed a Phase 1 study of extracorporeal Liver Support (miroliver*ELAP*®) using a bioengineered liver (MIRO-001) to treat acute liver failure. Herein, we report the safety profile of treatment and identified early effectiveness signals. **Methods:** The miroliver*ELAP* system consists of a MIRO-001 inserted into an extracorporeal blood circuit. MIRO-001 is manufactured using a decellularized porcine liver matrix seeded with human umbilical vein endothelial cells and primary human liver cells. Seven critically ill patients (mean MELD = 39; see Table 1) presenting with acute liver failure, acute-on-chronic liver failure or alcohol associated hepatitis were recruited from 4 study sites. Inclusion criteria included MELD ≥ 20, INR ≥ 2.0, and West Haven HE grade I – III. Subjects were liver transplantation ineligible. Subjects or legal representative granted informed consent and the study conformed to the ethical guidelines of the 1975 Declaration of Helsinki. Subjects were monitored every 4 hours during treatment and followed on days 3, 4, 14, 21, and 32 post-treatment. All adverse events (AE) were recorded and assessed for severity and relatedness. **Results:** Seven subjects received from 9 to 60 hours of continuous miroliver*ELAP* therapy. Across all subjects, with alcohol associated hepatitis or acute-on-chronic liver failure, there were 42 total AEs. Of these, 29% were possibly or probably related to the miroliver*ELAP* treatment or system. No subjects experienced a serious AE while on treatment. Clinically insignificant thrombocytopenia occurred in 4 of 7 treated subjects. Three deaths occurred in 5 subjects that completed treatment (≥44 hrs) and none were related to the miroliver*ELAP* treatment. Two of 3 deaths were due to multi-organ failure, secondary to the underlying disease and occurred well after treatment completion. The third death was attributed to aspiration. Four of 5 subjects who completed treatment experienced improved HE grade. Of the 3 patients on vasopressors at baseline who completed treatment, vasopressors were discontinued in 2 and the dose markedly reduced in the other. **Conclusion:** Extracorporeal liver support using miroliver*ELAP* with a MIRO-001 was associated with a very favorable safety profile. There were no deaths or unanticipated serious AEs attributed to miroliver*ELAP* treatment. Promising efficacy signals (improved HE grade and lower vasopressor requirements) were observed. The very favorable Phase 1

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experience with miroliver*ELAP* in this first-of-its-kind clinical trial establishes the framework to proceed with a Phase 2-3 clinical trial.

Table 1: Subject Characteristics and Medically Significant Adverse Events

Subject	Screening				Treatment Time (hour)	West Haven (Hepatic Encephalopathy) Grade			Vasopressors	Medically Significant Adverse Events (Grade ≥ 3) during 48-hour Treatment
	INR	MELD	Lactate (mg/dL)	Bilirubin (mg/dL)		Screening	ELAP Baseline	Hour 48	Norepinephrine Equivalents	D
1	3.9	49	1.2*	65.2	59.8	2	2	NR**	Baseline: 0.88 µg/kg/min Hour 48: 0.22 µg/kg/min Hour 60: 0.15 µg/kg/min	Fungal peritonitis Unlikely related to MIRO-001 or treatment Expected
2	2.2	26	1.1	9.7	46.3	3	3	1	None	None reported
3	1.9	32	1.6	38.5	48.2	2	3	1	None	None reported
4	2.7	43	4.7	36.6	48.0	2	2	2	Baseline: 0.10 µg/kg/min Hour 48: None	None reported
5	2.3	42	1.1	33.9	48.1	1	1	0	Baseline: 0.11 µg/kg/min Hour 48: 0.05 µg/kg/min	None reported
6	2.1	31	1.1	29.2	9.0	3	3	N/A	None	None reported
7	3.1	52	3.0	38.4	17.2	3	3	N/A	None	1 - Worsening anemia Possibly related to MIRO-001 or treatment Expected 2 - Worsening lactic acidosis Possibly related to MIRO-001 or treatment Expected

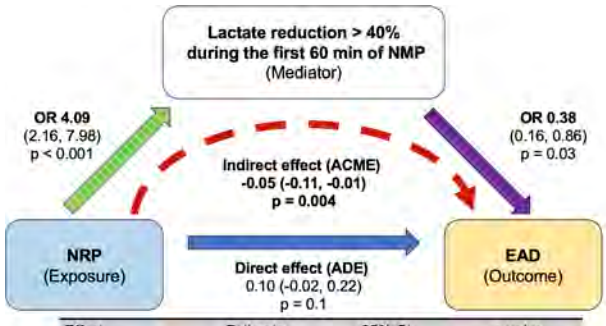
* Taken at Baseline **Not reported N/A Unplanned treatment discontinuation prior to this time point

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0015 | ADDING NORMOTHERMIC REGIONAL PERFUSION BEFORE NORMOTHERMIC MACHINE PERFUSION ENHANCES EARLY LACTATE REDUCTION AND INDIRECTLY REDUCES EARLY ALLOGRAFT DYSFUNCTION IN DCD LIVER TRANSPLANTATION

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Background: Normothermic machine perfusion (NMP) and normothermic regional perfusion (NRP) are increasingly used in liver transplantation (LT) from DCD donors. However, the clinical benefit of adding NRP before NMP remains unclear. The aim of this study was to investigate the effects of adding NRP on early metabolic recovery. **Methods:** This retrospective single-center study included adult recipients who underwent isolated DCD LT with NMP between January 2022 and February 2026. Patients were divided into NMP alone and NMP with NRP groups according to NRP use. Lactate levels during NMP were assessed at 60, 120, and 180 minutes using the closest available measurement to each target time point. Lactate reduction was calculated for each interval using the actual elapsed time between measurements. The primary clinical outcome was early allograft dysfunction (EAD). Multivariable logistic regression adjusted for donor BMI and donor sex, along with mediation analysis, was used to evaluate the association among NRP use, early lactate reduction, and EAD. **Results:** A total of 215 DCD LT recipients were included, of whom 145 underwent NMP alone and 70 underwent NMP with NRP. Donor age was significantly higher in the NMP with NRP group than in the NMP alone group (61 vs. 53 years, $p < 0.001$). EAD incidence did not differ between groups (16.0% vs. 18.6%, $p = 0.63$). There was no significant difference in lactate levels at the start of NMP. The 0–60 minute lactate reduction was greater in the NMP with NRP group than in the NMP alone group (47.8% vs. 30.5%, $p < 0.001$), while no significant differences were observed during 60–120 or 120–180 minutes. Lactate reduction during the first 60 minutes of NMP was categorized as < 0%, 0–40%, or > 40%, with the 40% cutoff selected based on the median value of early lactate reduction. A lactate reduction > 40% within 60 minutes occurred more frequently in the NMP with NRP group than in the NMP alone group (71.6% vs. 37.5%, $p < 0.001$). EAD incidence decreased across lactate reduction categories, from 33.3% in patients with < 0% reduction to 22.6% in those with 0–40% reduction and 9.4% in those with > 40% reduction ($p = 0.01$). In multivariable logistic regression adjusted for donor BMI and donor sex, lactate reduction > 40% during the first 60 minutes of NMP was an independent protective factor against EAD (OR 0.30, 95% CI 0.12–0.75, $p = 0.01$), whereas NRP use itself was not directly associated with EAD. Mediation analysis demonstrated a significant indirect effect of NRP on EAD through lactate reduction > 40% during the first 60 minutes of NMP (ACME −0.05, 95% CI −0.11 to −0.01, $p = 0.004$), whereas the direct effect was not significant (ADE 0.10, 95% CI −0.02 to 0.22, $p = 0.10$). **Conclusion:** Although NRP was used in older donors, adding NRP before NMP was associated with improved early lactate reduction during the first 60 minutes of NMP. Mediation analysis further suggested that NRP may indirectly reduce the risk of EAD through enhanced early lactate reduction.



Effect	Estimate	95% CI	*p-value*
ACME average	-0.05	-0.11, -0.01	0.004
ADE average	0.10	-0.02, 0.22	0.10
Total effect	0.05	-0.07, 0.17	0.49

Adjusted: Donor BMI, Donor Sex Values in parentheses indicate 95% CIs.

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0016 | WAITLIST RECOMPENSATION ACROSS STEATOTIC LIVER DISEASE PHENOTYPES: ALD, METALD, AND MASLD IN 43,410 UNOS CANDIDATES (2017–2023)

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Background: The 2023 Delphi consensus established MetALD metabolic dysfunction superimposed on intermediate alcohol use as a distinct steatotic liver disease (SLD) phenotype. Whether MetALD confers a recompensation trajectory on the liver transplant waitlist distinct from ALD or MASLD is unknown. We conducted the first national competing-risk analysis of waitlist recompensation stratified by 2023 SLD nomenclature. **Methods:** Using OPTN/UNOS STAR data (2017–2023), we classified 43,410 adult waitlist candidates across 120 centers as ALD, MetALD, or MASLD via the validated UNOS algorithm (MELD-Na ≥ 10; first-time liver-only listing). The primary outcome was waitlist recompensation. Fine-Gray subdistribution hazard models estimated adjusted subdistribution hazard ratios (aSHR; transplant + death as competing events), adjusted for age, sex, race, MELD-Na, BMI, diabetes, ascites, encephalopathy, HCC, calendar year, insurance, and UNOS region. Durability among 1,590 recompensated patients was assessed by Kaplan-Meier and Cox proportional hazards for time-to-re-listing. Recompensation defined as >5 points decrease in MELD score since lisitng or removal from the waitlist due to improvement. **Results:** At 24 months, cumulative recompensation incidence was 8.4% (ALD), 5.1% (MetALD), and 2.1% (MASLD). In adjusted Fine-Gray models (reference: ALD), MetALD carried equivalent recompensation hazard (aSHR 1.00, $p = 0.98$), while MASLD was associated with 57% lower recompensation hazard (aSHR 0.43, $p < 0.001$). Among recompensated patients, 24-month freedom from re-listing was 98.0% (ALD), 93.4% (MetALD), and 89.4% (MASLD), $p < 0.001$. Cox regression confirmed MetALD (HR 3.00, $p = 0.001$) and MASLD (HR 4.41, $p < 0.001$) carried significantly higher re-listing hazard than ALD. Phenotype-stratified analyses identified albumin as the dominant recompensation predictor in ALD and BMI with diabetes in MASLD (Figures 1&2). In phenotype-stratified multivariate analyses, albumin and lack of encephalopathy were the dominant predictors of recompensation in ALD and MetALD, whereas lower BMI and absence of diabetes predicted recompensation in MASLD. Notably, metabolic risk factors explicitly drove the higher re-listing hazard observed in the MetALD cohort. **Conclusion:** We identify a phenotype-specific dissociation: the alcoholic component drives recompensation equally in ALD and MetALD, while the metabolic substrate predicts recompensation failure in both MetALD and MASLD (3–4× higher re-listing hazard). These data support phenotype-specific listing observation periods and post-recompensation surveillance protocols across SLD.

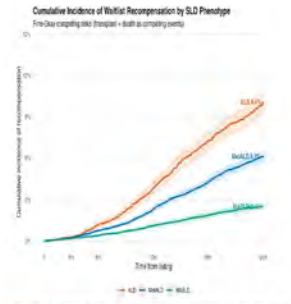


Figure 1. Cumulative incidence of recompensation by SLD phenotype. ALD 8.4%, MetALD 5.1%, MASLD 2.1% at 24 months.

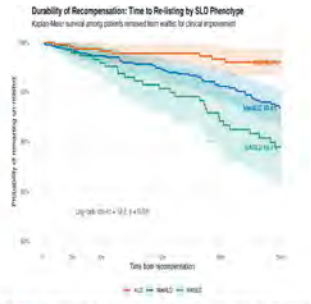


Figure 2. Durability of recompensation: freedom from re-listing at 24 months. ALD 98.0%, MetALD 93.4%, MASLD 89.4%.

Disclosures: Islam Mohamed:Nothing to Disclose, Mohamed Nadeem:Nothing to Disclose, Basil Jalamneh:Nothing to Disclose, Mohamad Ali Ibrahim:Nothing to Disclose, Prasun Jalal:Mallinckrodt Pharmaceuticals: Advisor, Madrigal: Grant/Research Support, Ipsen: Grant/Research Support, mirum: Advisor.

0017 | LOW-DOSE CONTINUOUS TERLIPRESSIN: COMPARABLE EFFICACY, LOWER TOXICITY IN ACLF VARICEAL BLEEDING

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Background: Acute oesophageal variceal bleeding (AVB) in patients with acute-on-chronic liver failure (ACLF) carries a high 28-day mortality. Recent data in cirrhosis suggest that continuous infusion (CI) of terlipressin is as effective as bolus injections (BOL)

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and is preferred owing to fewer adverse events; however, data in ACLF patients with AVB are lacking. We compared efficacy and safety of CI versus BOL terlipressin in ACLF patients presenting with AVB. **Methods:** This single-centre, prospective, open-label, randomized controlled trial (NCT06815770) was conducted at ILBS, New Delhi. ACLF patients (18–70 years), with esophageal variceal bleed were randomized to CI terlipressin (2 mg/24 h IV; escalated to 4 mg/24 h if required) or BOL terlipressin (1 mg IV every 4 h for 48 h, followed by every 6 h for 72 h). All patients underwent endoscopic variceal ligation and standard medical therapy. Primary endpoint was 28-day all-cause mortality. Secondary endpoints included rebleeding, transfusion requirement, renal outcomes, hemodynamic response, and terlipressin-related adverse events at 24 hours, Day 5, and Day 28 **Results:** Of 104 ACLF patients present with AVB, 60 were randomized (n = 30 per arm). Exclusions were due to gastric/non-variceal bleed, severe hyponatremia, cardiac contraindications, and lack of consent. Baseline characteristics were comparable [MELD score: 30.8 ± 7.2 vs 31.7 ± 7.2, p = 0.618; AARC Grade III: 53.3% vs 63.3%, p = 0.60].28-day survival was comparable (CI 46.7% vs BOL 43.3%; p = 0.79). There was no significant difference in 5-day rebleeding (16.7% vs 13.3%; p = 0.45) or PRBC transfusion requirements (3.7 vs 3.6 units; p = 0.54). Mean daily terlipressin dose was approximately half in the CI arm (1.84 vs 3.70 mg/day; p < 0.001). CI group showed significantly fewer adverse events (23.3% vs 73.3%; p < 0.001) and fewer drug discontinuations (10.0% vs 30.0%).Although HVPG could not be assessed in all patients due to the critically ill nature of the cohort, in the evaluable subset (HVPG subset, n = 4 per arm), CI demonstrated a trend towards superior portal pressure reduction — relative HVPG reduction at 48 hours: 12.1 ± 5.4% (CI) vs 9.6 ± 6.1% (BOL); p = 0.080; absolute reduction: 2.8 ± 1.2 vs 2.2 ± 1.5 mmHg; p = 0.070. The CI was associated with a 66% reduction in the odds of post-bleed AKI within 5 days (16.7% vs 36.7%; OR 0.34; 95% CI 0.10–1.16) and a reduced need for RRT (3.3% vs 13.3% p = 0.36). **Conclusion:** In ACLF-AVB subset, continuous terlipressin infusion achieves equivalent hemostatic efficacy to standard bolus dosing with half the cumulative drug exposure, a three-fold reduction in adverse events, renal-protective effects, and a trend towards better portal pressure control. Continuous terlipressin infusion should be recommended in ACLF patients presenting with acute variceal bleed.

Disclosures: Khushboo Yadav:Nothing to Disclose, Vinod Arora:Nothing to Disclose, Chitranshu Vashishtha:Nothing to Disclose, Manoj Sharma:Nothing to Disclose, Rakhi Maiwall:Nothing to Disclose, Ashok Kumar Choudhury:Nothing to Disclose, Rajan Vijayaraghavan:Nothing to Disclose, Ankur Jindal:Nothing to Disclose, Harsh Tevethia:Nothing to Disclose, Kavitha Jonnalagadda:Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose.

0018 | EARLY DEEP SEDATION IS ASSOCIATED WITH INCREASED MORTALITY IN MECHANICALLY VENTILATED PATIENTS WITH CIRRHOSIS

Benjamin Rosenthal[1] Douglas Schaubel[1] Marina Serper[1], [1]University of Pennsylvania

Background: Patients with cirrhosis who require mechanical ventilation (MV) experience high mortality, yet optimal sedation strategies are poorly defined. Cirrhosis alters sedative and analgesic pharmacokinetics and increases vulnerability to prolonged coma, hepatic encephalopathy (HE), delirium and organ failure. We evaluated whether early deep sedation was associated with mortality among mechanically ventilated adults with cirrhosis. **Methods:** This was a retrospective cohort study of adults with cirrhosis who underwent mechanical ventilation across 6 hospitals in the University of Pennsylvania Health System between 2017-2025 using the Complete Inpatient Record Using Comprehensive Electronic Data. Sedation depth was quantified using the observed Richmond Agitation-Sedation Scale (RASS). Deep sedation was defined as RASS -5 to -3 ("unarousable" to "moderate sedation") within the first 48 hours after MV initiation. We evaluated time-weighted deep sedation as the proportion spent in deep sedation, modeled per 10% increase. The primary outcome was time to 14-day in hospital mortality after the first 48-hours. Large language models identified HE and other patient characteristics. Cox proportional hazards models were adjusted for age, PaO_2/FiO_2, laboratory values, vasopressor use, renal replacement therapy, HE and hospital. **Results:** Among n = 859 MV patients with cirrhosis, the median percentage of time in deep sedation was 52% (IQR 19-83%). 82% and 74% of patients were deeply sedated $\geq$ 10% and $\geq$ 20% of the time. Patients with sedation $\geq$ 10% had higher median MELD-Na score (26 vs 23, p < 0.001), bilirubin (3.6 vs 2.0 mg/dL, p < 0.001), INR (1.8 vs 1.6, p < 0.001), lactate (3.6 vs 2.4 mmol/L, p < 0.001), were more likely to be located at a non-transplant center (67% vs 53%, p = 0.001), and more likely to be on vasopressors (84% vs 71%, p < 0.001). Deeply sedated patients received more midazolam (57% vs 36%, p < 0.001) and less dexmedetomidine (18% vs 26%, p = 0.021). Fourteen-day mortality was 30%. In a multivariable model, time in deep sedation was independently associated with mortality (adjusted hazard ratio 1.07 per 10% increase of time, 95% CI 1.02-1.12, p = 0.004). Older age, bilirubin, INR, creatinine, lactate, and history of HE were also associated with mortality. Kaplan-Meier analyses demonstrated lower survival probability among patients with $\geq$ 10% deep sedation (Figure). **Conclusion:** In this multi-hospital cohort of

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mechanically ventilated patients with cirrhosis, greater time spent in deep sedation was associated with increased 14-day mortality. Early sedation depth is an important and potentially modifiable risk factor in critically ill patients with cirrhosis and support future studies evaluating liver-specific sedation strategies.

Covariate	Adjusted Hazard Ratio (95% CI)	p-value
Primary exposure		
Time-weighted deep sedation, per 10% increase	1.07 (1.02–1.12)	0.004
Demographics		
Age, per year	1.04 (1.03–1.05)	<0.001
PF ratio category		
200–300 vs >300	0.64 (0.38–1.06)	0.086
<200 vs >300	0.86 (0.60–1.24)	0.419
Laboratory values, first 48 hours		
Sodium minimum	0.98 (0.96–1.01)	0.067
Bilirubin maximum	1.02 (1.01–1.04)	0.005
INR maximum	1.19 (1.06–1.34)	0.005
Creatinine maximum	1.11 (1.04–1.18)	0.001
Albumin minimum	1.03 (0.80–1.33)	0.807
Lactate maximum	1.08 (1.05–1.11)	<0.001
WBC maximum	1.01 0.99–1.02)	0.353
Clinical severity markers		
Any vasopressor: Yes vs No	1.39 (0.79–2.43)	0.250
RRT exposure: Yes vs No	0.89 (0.66–1.21)	0.473
Hepatic Encephalopathy History	1.39 (1.00–1.92)	0.049
Transplant Center vs Non-Transplant Center	0.81 (0.56–1.19)	0.294

Description: Multivariable Cox proportional hazards model evaluating factors associated with hazards of 14-day landmark mortality after the 48-hour mechanical ventilation exposure period among mechanically ventilated patients with cirrhosis. The primary exposure was time-weighted deep sedation during the first 48 hours after mechanical ventilation initiation, modeled per 10% increase in time spent deeply sedated. The model included 689 patients and 211 mortality events. Hazard ratios greater than 1 indicate a higher hazard of mortality, while hazard ratios less than 1 indicate a lower hazard.

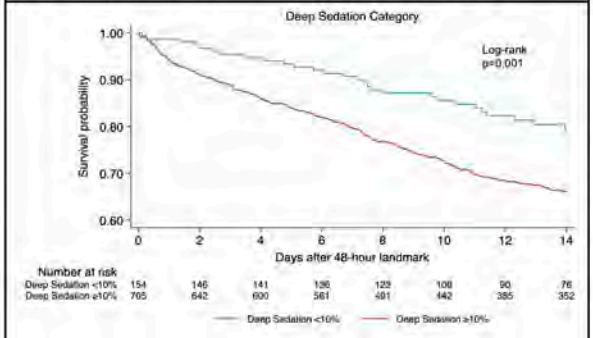


Figure: Kaplan–Meier survival after the 48-hour landmark by early deep sedation exposure.
Kaplan–Meier curves show lower 14-day survival among patients who spent ≥10% of the first 48 hours of mechanical ventilation in deep sedation compared with those who spent <10% of time in deep sedation. The number at risk is shown below the plot.

Disclosures: Benjamin Rosenthal:Nothing to Disclose, Douglas Schaubel:Nothing to Disclose, Marina Serper: Transplant Genomics: Grant/Research Support, Grifols: Grant/Research Support.

0019 | CHRONIC KIDNEY DISEASE AND MORTALITY IN CRITICALLY ILL PATIENTS WITH DECOMPENSATED CIRRHOSIS

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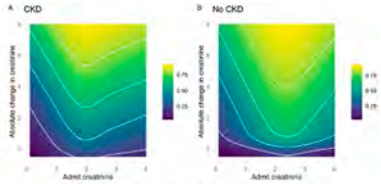
Background: Background: Kidney dysfunction is a major driver of mortality in critically ill patients with acute-on-chronic liver failure. International Club of Ascites (ICA) and global liver societies (including AASLD) use serum creatinine (sCr)-based definitions to classify AKI stages irrespective of baseline chronic kidney disease (CKD) status. We aimed to determine whether current definitions adequately capture the impact of kidney dysfunction given the evolving population of critically ill patients with decompensated cirrhosis. **Methods:** Methods: We examined critically ill adult patients with decompensated cirrhosis admitted to intensive care units across a large integrated healthcare system comprising 20 hospitals between 2019–2022. The primary outcome was 30-day all-cause mortality. Key exposures included admission sCr and maximum absolute change in sCr during hospitalization (ΔsCr). Mortality contour mapping was performed to identify admission sCr and ΔsCr thresholds associated with predefined mortality probabilities of 20%, 30%, 40%, and 50% by presence of CKD. **Results:** Results: Among 3,913 critically ill patients, 14% had CKD. Across CKD and non-CKD, higher admission sCr and greater ΔsCr were associated with progressively higher 30-day mortality; however, equivalent sCr trajectories carried markedly **different** prognostic effects according to baseline CKD status. The greatest divergence was observed at admission sCr levels between 2–3 mg/dL, where relatively small increases in sCr among non-CKD patients were associated with sharp increases in mortality. For example, a ΔCr of 1.0 mg/dL (2.5–3.5mg/dL) carried a predicted 30-day mortality of 62% in non-CKD patients compared to 40.2% in CKD patients. A lower KDIGO stage thus carried **higher** mortality than a higher stage when admission sCr was elevated. (**Figure 1A**) Mortality contour mapping further demonstrated that non-CKD patients crossed predefined 20%, 30%, 40%, and 50% mortality thresholds at substantially smaller ΔsCr values than CKD patients (**Figure 1B**). **Conclusion:** In critically ill patients with decompensated cirrhosis, the prognostic significance of kidney dysfunction differs substantially according to baseline CKD status. We propose that mortality-based creatinine thresholds may better characterize clinically meaningful renal dysfunction than current creatinine staging systems (e.g. KDIGO or AKIN) and have important implications for organ failure definitions for renal failure, endpoint selection in ACLF clinical trials and organ transplantation.

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30-day mortality and AKI stage in CKD versus non CKD



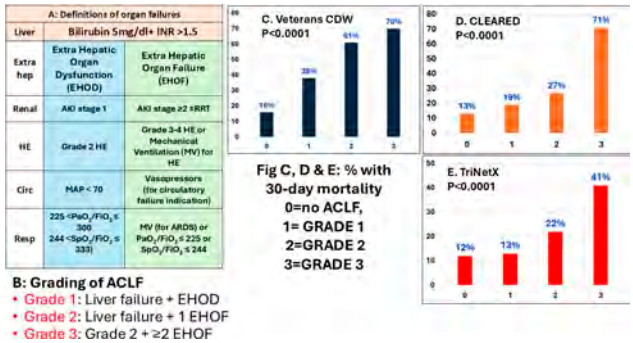
Delta Creatinine and 30-day mortality in CKD versus non-CKD

Disclosures: Rahul Thakkar:Nothing to Disclose, Sumeet Asrani:Nothing to Disclose, Gerald Ogola: Nothing to Disclose, Lauren Hall:Nothing to Disclose, Kavish Patidar:Madrigal Pharmaceuticals: Medical Advisory Board, Mallincrodt Pharmaceuticals: Consultant, HepQaunt: Consultant, Mallinckrodt Pharmaceuticals: Medical Advisory Board, OrganOx: Advisor, Madrigal Pharmaceuticals: Advisor, Keenova Therapeutics: Advisor and Consultant., Keenova Therapeuatics: Advisor and Consultant, Novo Nordisk: Advisor, HepQaunt: Consultant, Keenova Therapeutics: Advisor and Consultant, HepQuant: Consultant.

0020 | PRAGMATIC DEFINITION OF ACLF USING GLOBAL HARMONIZATION PREDICTS MORTALITY WITH INCREASING GRADES ACROSS THREE LARGE PATIENT COHORTS

Jasmohan Bajaj[1] Scott Silvey[2] Ohm Patel[2] Florence Wong[3] Jacob George[4] Wai-Kay Seto[5] Qing Xie[6] Mário Alvares-da-Silva[7] Peter Hayes[8] Mark Topazian[9] Brian Bush[2] Ramazan Idilman[10] Aldo Torre[11] Patrick Kamath[12] Nilang Patel[2], [1]Virginia Commonwealth University, [2]VCU, [3]University of Toronto, [4]The University of Sydney, [5]The University of Hong Kong, [6]Ruijin Hospital, [7]Porto Alegre, [8]U Edinburgh, [9]St Paul Millennium College Addis Ababa, [10]Ankara University School of Medicine, [11]Gastroenterology Department Centro Médico ABC, [12]Mayo Clinic

Background: Acute on Chronic Liver failure is associated with higher death and need for transplant but definitions vary. A consensus is building towards getting an equitable, data-driven definition that has worldwide representation and is benchmarked to mortality. The definition, created using a harmonization process, focuses on ensuring that the definition is easy to remember and apply in the hands of all clinicians and not just liver or ICU specialists. This defintion involves pragmatic combinations of liver and extrahepatic organ dysfunction (EHOD) and failures (EHOFs) but needs validation. **Methods:** Three large datasets were evaluated for the diagnosis and grading of ACLF based on consensus EHOD/F definitions. The definition (Fig A) includes user-friendly definitions of liver failure (bilirubin 5mg/dl+INR > 1.5) , EHOD (HE grade 2, AKI stage 1 per KDIGO criteria, MAP < 70, respiratory compromise per ARDS criteria) & EHOF (HE 3-4 or mechanical ventilation (MV) for that , AKI ≥ stage 2, vasopressor use (per SOFA-2) or severe respiratory compromise/ MV for ARDS) with ACLF grading (Fig B). The datasets used were: (a) **CLEARED**, a global consortium of inpatients with cirrhosis , (b) **Veterans Corporate Data Warehouse** (US Veterans with cirrhosis with MELD3.0 > 15 on admission between 2020-24), and (c) **TriNetX database** (US-based insured patients with cirrhosis admitted between 2020-24). In each cohort, definitions and grades of ACLF were extracted and their impact on 30D mortality was evaluated. We also did a sensitivity analysis using bilirubin 7.5mg/dl+INR > 1.5 for all liver failure variables. **Results: CLEARED** : 6206 patients from 125 centers from 37countries (36% high, 44% upper-middle & 20% low-income) were included. 50% of the patients were from Asia, 20% from North America, 9% Africa, 8% Oceania, S America & Europe each. Median age was 57 yrs, 64% men, with MELD-Na 21. 18% died at 1 month. Prevalence of Grade 1ACLF was 6.7%, Grade 2, 9.3%, & Grade 3 was 6.6%. **TriNetX:** 117,437 patients were included. The median age was 61 yrs, 59% were men, and median MELD-Na was 22. Prevalence of ACLF-1: 7.2%, Grade 2:4.7% and Grade 3 was 6.5% . 14.5% died at 1 month. Death rate increased with higher ACLF grades **.VA-CDW:** 18,781 patients, median age 69 yrs, 97% men as expected due to military service, with a median of MELD-Na 20. 17.8% died at 1 month. ACLF-1 was seen in 2.9%, Grade 2:1.5%, and Grade 3 : 1%. For all 3 cohorts, the death rate significantly increased with increasing ACLF grades (Fig C-E). Similar patterns but relatively lower prevalence was seen for the 7.5mg/dl bilirubin threshold. **Conclusion:** The new pragmatic definition of ACLF and grading shows higher 30-day mortality with increasing grades in three large unrelated cohorts of inpatients with cirrhosis, despite differences in demographics. These have global and North American representation and could improve harmonization of ACLF diagnosis worldwide.



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0021 | SOLUBLE PROGRAMMED DEATH LIGAND 1 OUTPERFORMS INTERLEUKIN 6, URINARY NEUTROPHIL GELATINASE-ASSOCIATED LIPOCALIN, AND NEUTROPHIL-TO-LYMPHOCYTE RATIO FOR ACLF PREDICTION IN PATIENTS WITH CIRRHOSIS: THE LIVERHOPE BIOMARKER STUDY

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Background: Acute-on-chronic liver failure (ACLF) is the most severe form of decompensated cirrhosis, characterized by systemic inflammation and immune dysfunction. Identification of patients at high risk of ACLF remains challenging. Previous studies identified Interleukin-6 (IL-6), urinary Neutrophil Gelatinase-Associated Lipocalin (uNGAL) and Neutrophil-to-Lymphocyte ratio (NLR) as promising prognostic biomarkers in cirrhosis. However, their ability to predict ACLF remains inconsistent. Soluble programmed death ligand-1 (sPD-L1) has recently emerged as a marker of immune dysregulation and bacterial infection development in cirrhosis. The current study aimed to evaluate the prognostic value of sPD-L1, IL-6, uNGAL, and NLR for ACLF development in patients with decompensated cirrhosis. **Methods:** Prospective multicohort study including 562 patients with decompensated cirrhosis from two European cohorts. The derivation cohort included 222 patients from the LiverHope Efficacy Trial, while the validation cohort included 340 patients from two European University Hospitals. Patients were followed for 1 year. Time-to-event analyses were performed using Cox and Fine-Gray competing risk models. **Results:** In the Liverhope Trial cohort, patients were predominantly male (74%) with alcohol-related liver disease as the main etiology (71%). During follow-up, 28 patients (12%) in the derivation cohort developed ACLF. Among all biomarkers, only sPD-L1 was associated with ACLF development. Baseline sPD-L1 levels were higher in patients developing ACLF (116 vs 92 pg/mL; $p = 0.017$), and each 10 pg/mL increase was associated with increased ACLF risk (HR 1.045; 95%CI 1.008–1.084). In multivariable analyses, sPD-L1 and MELD-Na remained independent predictors of ACLF. Patients with sPD-L1 ≥ 147 pg/mL showed higher cumulative ACLF incidence ($p = 0.0075$) compared to those with sPD-L1 < 147 pg/mL. There was a relationship between sPD-L1, bacterial infection, and ACLF. Among 35 patients who developed bacterial infection during follow-up, 11 (31%) progressed to ACLF. These patients had higher baseline sPD-L1 and MELD-Na values. In the validation cohort, 47 (14%) patients developed ACLF during follow-up. Soluble PD-L1 levels were higher in patients developing ACLF (155 vs 119 pg/mL; $p < 0.001$), and multivariate analysis confirmed sPD-L1, MELD-Na, and previous bacterial infection as independent predictors, whereas NLR showed no prognostic value. **Conclusion:** The sPD-L1 is a reproducible and independent predictor of ACLF in decompensated cirrhosis. It outperformed IL-6, uNGAL, and NLR across two international cohorts and provided prognostic information beyond MELD-Na. Its association with bacterial infection and ACLF highlights the central role of immune dysfunction in cirrhosis progression and supports sPD-L1 as a biomarker for risk stratification of ACLF.

Disclosures: María Moreta:Nothing to Disclose, Adrià Juanola:Grifols: Speaking and Teaching.

0022 | BLOODSTREAM INFECTION PHENOTYPES AND RESISTANCE PATTERNS AMONG PATIENTS WITH CIRRHOSIS HOSPITALIZED WITH ACUTE-ON-CHRONIC LIVER FAILURE

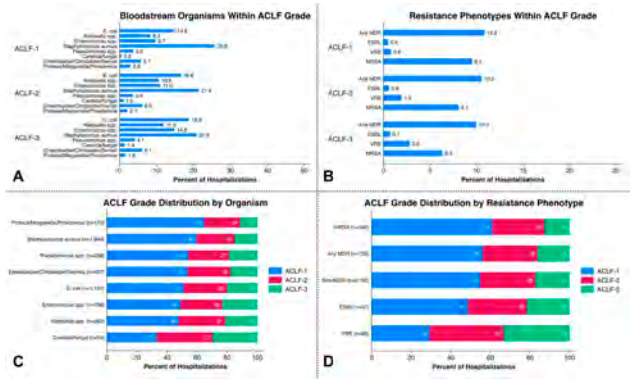
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Background: Acute-on-chronic liver failure (ACLF) is a syndrome of acute decompensation in patients with chronic liver disease (CLD) characterized by organ failure and high short-term mortality. Patients with CLD are at elevated risk for infections, which are common precipitants of acute decompensations and hospitalizations. Given growing concern for multidrug-resistant organisms, we aimed to better characterize bloodstream infection organisms among patients hospitalized with ACLF. **Methods:** We conducted a retrospective cross-sectional study of patients with cirrhosis in the VOCAL cohort (Veterans Health Administration, 128 centers, 2008-2025). ACLF hospitalizations were graded using EASL-CLIF criteria and evaluated for associated positive blood cultures. Bloodstream organisms were grouped into categories and resistance phenotypes. Patient characteristics and organism distributions were compared using chi-square and Wilcoxon rank-sum tests. **Results:** The analytic cohort comprised 7,888 ACLF hospitalizations; the most common CLD etiologies were MASLD (35.1%), HCV (28.6%), and ALD (12.1%). ACLF grades 1, 2, and 3 comprised 54.3%, 28.1%, and 17.6% of hospitalizations, respectively. ACLF-3 patients were younger, more likely to have ALD, and had higher rates of organ failures ($p < 0.001$). Across ACLF grades, bloodstream organism distribution varied significantly ($p < 0.001$). *Candida*/fungal organisms were identified in 0.5% of ACLF-1 hospitalizations versus 1.4% in ACLF-3 hospitalizations (**Figure 1A**). VRE phenotypes were identified in 0.8% of ACLF-1 hospitalizations versus 2.8% of ACLF-3 hospitalizations (**Figure 1B**). Conversely, MRSA bloodstream infections were less likely in ACLF-3 hospitalizations (6.3%) compared to ACLF-1 hospitalizations (9.5%) (**Figure 1B**). *Proteus/Morganella/Providencia* organisms were less common in ACLF-3 hospitalizations (1.6%) compared to ACLF-1 hospitalizations (2.9%) (**Figure 1A**). *Candida*/fungal organisms and VRE phenotypes showed a greater concentration of higher ACLF grades compared with other infection categories (**Figure 1C/D**). **Conclusion:** Greater ACLF severity was associated with distinct bloodstream infection and resistance phenotypes, including higher frequencies of Candida/fungal organisms, VRE, and polymicrobial infections. These findings improve understanding of infectious precipitants of ACLF and may inform diagnostic evaluation, empiric antibiotic selection, and future management for patients with ACLF. Additionally, resistant and fungal bloodstream infection phenotypes were associated with greater ACLF severity distributions, suggesting potential relationships between organism profile and severity of critical illness in ACLF.



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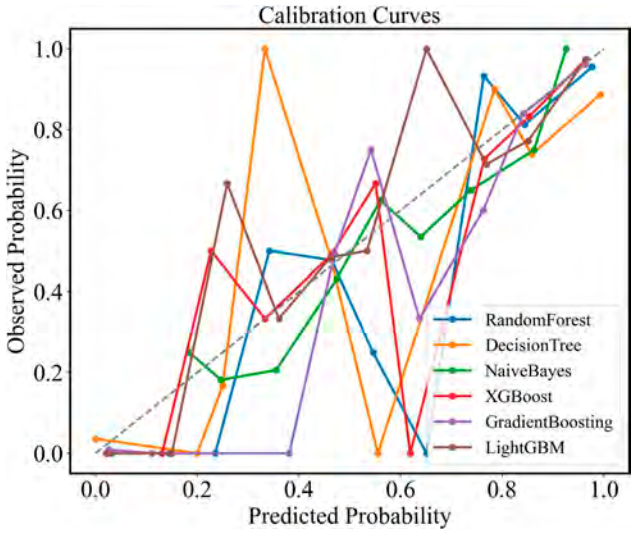
0023 | USING INTERPRETABLE MACHINE LEARNING MODEL TO PREDICT HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH MASLD

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Background: Metabolic dysfunction–associated steatotic liver disease (MASLD) is a common chronic liver condition that can impair health-related quality of life (HRQoL). Identifying patients at risk of low HRQoL is challenging due to multifactorial influences. Interpretable machine learning (ML) can predict risk and clarify key contributors. **Methods:** HRQoL was assessed in 821 MASLD patients using the Chronic Liver Disease Questionnaire (CLDQ). Six predictors—alcohol use, exercise habits, smoking history, age, education, and arthritis—were selected via combined univariate, random forest, and LASSO feature selection. Six ML algorithms were trained and evaluated using ROC, calibration, and decision curve analyses; SHapley Additive exPlanations (SHAP) provided interpretability. **Results:** Among 821 patients, 205 (25%) were classified as having low HRQoL (CLDQ < 25th

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percentile). Gradient Boosting achieved the highest performance with AUC = 0.942, accuracy = 84.5%, sensitivity = 76.4%, specificity = 91.5%, and F1-score = 0.82. SHAP analysis identified alcohol use (mean |SHAP| = 0.91) and exercise habits (mean |SHAP| = 0.89) as the dominant predictors, followed by smoking history (0.70), age (0.45), education (0.32), and arthritis (0.28). Age modified the effects of lifestyle behaviors, while other predictors contributed consistently across subgroups. **Conclusion:** Interpretable ML models accurately identify MASLD patients at risk of low HRQoL using six routinely obtainable variables. Lifestyle behaviors—especially alcohol consumption and exercise—are the primary drivers, supporting targeted risk screening and actionable interventions in clinical practice.



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★ 0024 | LITEMEDSAM AND MEDNET: A SEGMENTATION-ASSISTED, ATTENTION-GUIDED LIGHTWEIGHT FRAMEWORK FOR EDGE-DEPLOYABLE SONOGRAPHIC CLASSIFICATION OF HEPATOCELLULAR CARCINOMA

Jansi Sethuraj[1] Elangovan Krishnan[2] Kavin Elangovan[3] Nayanika Tummala[4] Ramya Elangovan[5], [1]The University of Texas Health Science Center at Houston, [2]Indian Institute of Technology Bombay, [3]AIM, [4]NYMC St Marys St Clares, [5]Johns Hopkins University

Background: Accurate sonographic differentiation of hepatocellular carcinoma (HCC) from benign hepatic hemangioma, critical given HCC's global burden exceeding 800,000 deaths annually, remains one of the most consequential unresolved challenges in liver imaging. B-mode ultrasound, the dominant surveillance modality across most health systems, yields diagnostically equivocal findings in a substantial proportion of cases. Existing deep learning solutions achieve high benchmark accuracy through architecturally complex, GPU-dependent models that are structurally ill-suited for resource-limited or point-of-care deployment. **Methods:** We developed LiteMedSAM-MedNet: LiteMedSAM, operating from bounding-box prompts, segmented focal liver lesions and extracted perilesional crops (10–20% margin), which were then classified by MedNet — a purpose-designed lightweight architecture integrating depthwise separable convolutions, residual connections, and convolutional block attention module (CBAM) spatial-channel attention. Training and internal validation used SMC-LUD — 5,385 B-mode images from 1,021 patients, all HCC cases histopathologically confirmed and hemangioma cases independently verified by two board-certified abdominal radiologists, patient-level split 70:20:10. External validation used the TCIA liver dataset; prespecified outcomes included AUROC, sensitivity, specificity, F1-score, F2-score, and Dice Similarity Coefficient (DSC). **Results:** LiteMedSAM yielded a DSC of 0·85 (zero-shot) and 0·86 (fine-tuned). MedNet on standard lesion crops achieved 92·0% accuracy and F1-score; perilesional-margin cropping improved performance to 93·0%. AUROC was 0·97, HCC sensitivity 97%, and hemangioma specificity 98%. Full pipeline inference completed under 1 second on consumer-grade CPU hardware without GPU acceleration. **Conclusion:** LiteMedSAM-MedNet demonstrates that domain-adapted, attention-guided lightweight architectures can approach the diagnostic accuracy of computationally intensive classifiers in liver lesion characterisation. The convergence of CBAM-based attention with efficient convolutional design offers a translatable blueprint for edge-deployable hepatology AI. Validation across heterogeneous ultrasound platforms and geographically diverse patient cohorts is required before clinical implementation.

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0025 | MENOPAUSE IN WOMEN WITH LIVER DISEASE: SYMPTOM BURDEN, METABOLIC CHANGES, AND HORMONAL REPLACEMENT THERAPY USE

Lorrinda Gray-Davis[1] Mustafa Behan[2] Jutta Kurz[2] Karen Hoyt[1] Tresha Elaine Ramonal[2] Rachma

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Purnama[3] Michael Tunkelrott[3] Emmanuel Gorospe[4] Tarek Hassanein[5], [1]None, [2]Amsety, [3]Amsety LLC, [4]Burrell College of Osteopathic Medicine, [5]Southern California Liver Centers

Background: Menopause is a key physiological transition in women associated with hormonal changes that can have wide-ranging effects on metabolic and systemic health. In the context of liver disease, these changes may influence liver fat accumulation, cholesterol, and inflammation. There is a need to better understand the relationship between menopause and liver disease in clinical practice. Aim: to examine differences in symptom burden, metabolic and clinical changes, and real-world use of hormonal and non-hormonal therapies across menopausal stages in women with liver disease. **Methods:** We conducted an exploratory survey of 71 women with liver disease across menopausal stages, drawn from the Amsety database of 650,000 Americans living with liver disease. It examined menopause status, symptoms, perceived changes in metabolic and clinical markers, and the use of hormone replacement therapy (HRT) and non-hormonal treatments. **Results:** Average age of respondents was 48 years and an average BMI of 30. 49% were pre- and peri-menopausal, while 51% were post-menopausal and surgical menopausal. The majority had MASLD (69%) as the etiology for liver disease. 8% had cirrhosis. Liver disease diagnosis varied by menopausal stage: MASLD was higher in the post-menopausal stage (72%) compared with the pre- and peri-menopausal stages (66%), while MASH was also higher in the post-menopausal stage (11%) compared with the pre- and peri-menopausal stages (8%). Early-stage disease was more common among pre- and peri-menopausal patients (74%) than post-menopausal patients (42%). Common symptoms for pre- and peri-menopausal patients include hot flashes (76%), fatigue (74%), and joint pain (68%), while for post-menopausal patients, fatigue is highest (89%), followed by joint pain (86%) and mood changes (72%). For HRT use, 54% have never used it, 21% are currently using it, and 14% have previously used it. Reported benefits after HRT use include improved hot flashes (39%), mood (19%), and fatigue (13%). 50% experience side effects after HRT use such as elevated liver enzymes. Respondents also use alternatives to HRT, including dietary changes/supplements (18%), SSRIs/SNRIs (15%), and gabapentin/pregabalin (15%). **Conclusion:** Menopause is an important but often under-recognized factor in women with liver disease, with differences observed across stages in disease presentation, symptom burden, and metabolic changes. Hormonal and non-hormonal treatments are used across groups with varying perceived effects. This analysis highlights the importance of considering menopausal stage in assessment and management to support more individualized care in liver patients. There's a need for further research and clearer guidance on the use of HRT in women with liver disease, including its potential benefits and risks.

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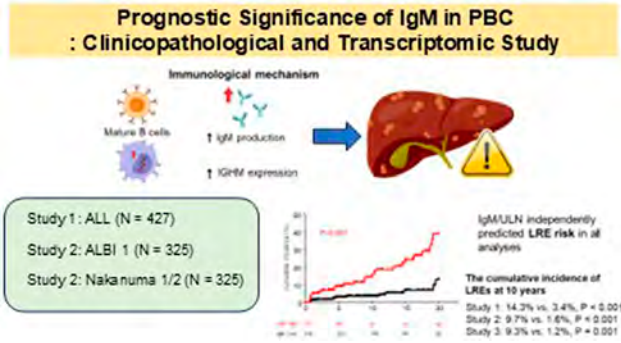
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0026 | SERUM IGM AS A PROGNOSTIC BIOMARKER LINKED TO INTRAHEPATIC IMMUNE ACTIVATION IN PRIMARY BILIARY CHOLANGITIS: INSIGHTS FROM HISTOPATHOLOGY

Taiki Okumura[1] Kaede Fujita[1] Yuma Kamijo[1] Shun-Ichi Wakabayashi[2] Hiroyuki Kobayashi[1] Tomoo Yamazaki[1] Takefumi Kimura[1], [1]Shinshu University Hospital, [2]Shinshu University School of Medicine

Background: Elevated serum immunoglobulin M (IgM) is a hallmark of primary biliary cholangitis (PBC), yet its prognostic significance and biological basis remain incompletely understood. We investigated whether serum IgM normalized to the upper limit of normal (IgM/ULN) predicts liver-related events (LREs) in PBC and explored the pathological and molecular mechanisms underlying IgM elevation. **Methods:** A total of 427 treatment-naïve patients with PBC from four Japanese centers were retrospectively analyzed. Associations between baseline IgM/ULN and LREs were evaluated using Cox proportional hazards models. LREs were defined as ascites, gastroesophageal varices, hepatic encephalopathy, or hepatocellular carcinoma. Additional integrative analyses, including histopathology, immunohistochemistry, bulk mRNA expression profiling, single-cell transcriptomics, and network analyses, were performed to investigate intrahepatic sources and mechanistic pathways associated with IgM elevation. **Results:** The median age at diagnosis was 58 years, and the cohort included 70 males and 357 females, with a median follow-up of 9.0 years. During follow-up, 39 LREs occurred, and the cumulative incidence of LREs at 20 years was 22.7%. In multivariate Cox analysis, low serum albumin (hazard ratio [HR] 0.18, $P < 0.001$) and elevated IgM/ULN (HR 1.53, $P < 0.001$) were independently associated with LREs. An optimal cutoff of IgM/ULN ≥ 1.6 identified patients with significantly higher cumulative incidence of LREs compared with IgM/ULN < 1.6 ($P < 0.001$), and this prognostic significance was retained in clinically and pathologically early-stage disease. Higher IgM/ULN levels were associated with histological progression, particularly bile duct loss. Hepatic IGHM expression correlated with both serum IgM/ULN levels and bile duct injury. Immunohistochemistry demonstrated intrahepatic IgM-producing plasma cells and mature B cells, while single-cell transcriptomic analysis identified plasma cells, mature B cells, and plasmacytoid dendritic cells as potential contributors to local IgM production. Network analyses implicated NF-κB– and cytokine-related inflammatory pathways associated with cholangiocyte injury and IgM elevation. **Conclusion:** Serum IgM/ULN is a simple, standardized, and widely available biomarker that independently predicts liver-related events in PBC, including in early-stage disease. Integrative molecular analyses suggest that elevated IgM reflects intrahepatic immune activation and bile duct injury, supporting its utility as both a prognostic and pathobiological biomarker in PBC.



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0027 | IMPROVED MODULATION OF PRURITIC AND PHARMACODYNAMIC BIOMARKERS WITH LINERIXIBAT ADDED TO A STABLE BACKGROUND OF BILE ACID BINDING RESINS OR PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR AGONISTS IN GLISTEN

Janelle Lennie[1] Brandon Swift[2] Bishoy Hanna[3] Linda Casillas[1] Ivana Lazic[4] Brooke Currie[1] Zsofia Kiss[5] Alexander Cobitz[1] Megan McLaughlin[6] Christopher Bowlus[7] Andreas Kremer[8], [1]GSK, Collegeville, PA, US,

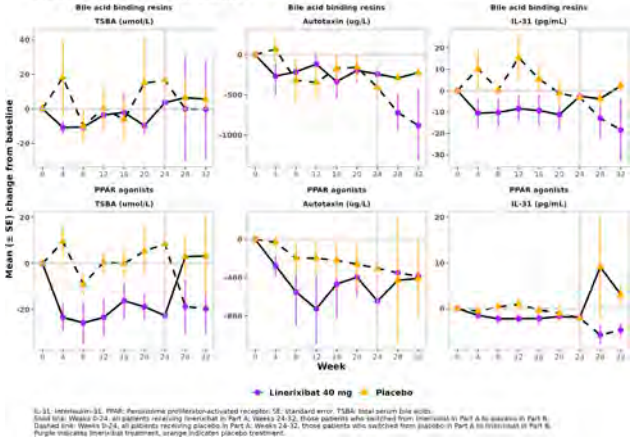
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Background: Bile acid binding resins (BABRs) and fibrates/peroxisome proliferator-activated receptor (PPAR) agonists have been recommended in treatment guidelines for cholestatic pruritus in primary biliary cholangitis (PBC). Linerixibat (ileal bile acid transporter inhibitor) was approved in the US for the treatment of cholestatic pruritus in PBC, following positive results from the GLISTEN study (NCT04950127). This post hoc analysis assessed the effect of linerixibat on mediators of pruritus (total serum bile acids [TSBA]; autotaxin [ATX]; a surrogate for lysophosphatidic acid; interleukin-31 [IL-31]) and pharmacodynamic markers of bile acid synthesis/reabsorption (7-alpha-hydroxy-4-cholesten-3-one [C4]; fibroblast growth factor-19 [FGF-19]) in a subset of patients (pts) receiving a stable dose of BABRs and/or PPAR agonists. **Methods:** GLISTEN was a Phase 3, randomized, double-blind, placebo-controlled study of adults with PBC and moderate-to-severe pruritus. In Part A, patients received linerixibat 40 mg twice daily or placebo for 24 weeks; this was followed by Part B, an 8-week crossover period where patients either switched or maintained treatment. Biomarker concentrations were measured at baseline and every 4 weeks through Week 32; change from baseline was assessed in pts on a stable background (no initiation/discontinuation/dose changes 8 weeks before screening through treatment end) of BABRs and/or PPAR agonists. **Results:** Of 238 randomized pts, 8% were receiving concomitant BABRs at baseline (linerixibat n = 10; placebo n = 10) and 22% were receiving PPAR agonists (linerixibat n = 23; placebo n = 30). Overall, linerixibat produced greater (generally sustained) reductions in TSBA, ATX, and IL-31 than placebo when added to stable BABR or PPAR agonist therapy over 24 weeks (Part A). At Week 32, after switching between linerixibat and placebo pts had rapid, directional biomarker changes across cohorts. Decreases in TSBA, ATX, and IL-31 were greater with linerixibat plus stable PPAR agonists than with placebo plus PPAR agonists in Part A; switching treatments led to corresponding increases or decreases despite stable PPAR agonist therapy (**Figure, bottom**). Similar trends were observed for IL-31 with linerixibat added to BABR regimens compared to placebo with BABR regimens; TSBA and ATX showed greater variability across cohorts in Part A. However, following treatment switch, biomarker reductions were rapid in pts switching to linerixibat, while concentrations increased in pts switching to placebo despite stable BABR therapy (**Figure, top**). C4 increased and FGF-19 decreased when adding linerixibat to stable concomitant BABR or PPAR agonist therapy. **Conclusion:** Reduction of systemic markers of cholestatic pruritus are detectable following addition of linerixibat in patients entering GLISTEN on stable guideline therapies for itch. **Funding:** GSK (212620)

Figure: Mean change from baseline in pruritus mediators by treatment group in GLISTEN participants entering the study and remaining on stable background BABR (top row) or PPAR agonist (bottom row) therapy



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0028 | FIRST-IN-DISEASE OBJECTIVE ASSESSMENT OF SCRATCH AND SLEEP PATTERNS USING A WEARABLE DIGITAL HEALTH TOOL IN PRIMARY BILIARY CHOLANGITIS: THE LUMINARIA STUDY

Cynthia Levy[1] Anita Kohli[2] Marlyn Mayo[3] Andreas Kremer[4] Mark Swain[5] Seema Meloni[6] Christelle Pommie[7] Marwan Sleiman[7] Joanna Harton[8] Yu Hong[8] Marlene Smurzynski[8] David Jones[9], [1]Schiff Center for Liver Diseases, University of Miami, Miami, FL, USA, [2]Arizona Liver Health, Chandler, AZ, USA, [3]University of Texas Southwestern Medical Center, Dallas, TX, USA, [4]Department of Gastroenterology and Hepatology, University Hospital Zürich, Zürich, Switzerland, [5]Department of Medicine, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada, [6]Ipsen, Cambridge, MA, USA, [7]Ipsen, Paris, France, [8]Genesis Research Group, Hoboken, NJ, USA, [9]NIHR Newcastle Biomedical Research Centre, Newcastle University, Newcastle Upon Tyne, UK

Background: While patient-reported outcome (PRO) instruments are valuable for assessing symptoms in primary biliary cholangitis (PBC), their subjective nature introduces potential bias and measurement variability. LUMINARIA (NCT07049887) is the first study to utilize a wearable sensor to objectively measure nocturnal scratch and sleep patterns in patients (pts) with PBC. **Methods:** In LUMINARIA, a multicenter, non-interventional, prospective, longitudinal US study, pts with PBC received standard clinical care and wore the ADvanced Acousto Mechanic (ADAM) sensor on the dominant hand during sleep across four 7-day wear periods (Weeks 0, 4, 8, and 12). Pts also completed validated PRO measures of pruritus, sleep disturbance, and fatigue at baseline (BL) and during each wear period. Analyses are descriptive; pts were stratified by BL pruritus severity using Worst-Itch Numeric Rating Scale (WI NRS), with no formal hypothesis testing. **Results:** Of 30 pts enrolled, 28 met inclusion criteria for analysis. Of these, 26 (93%) were female, mean age was 59.7 (SD: 11.7) years, and median time since diagnosis was 3.8 (IQR: 1.7−13.8) years. For 17 pts with BL data, median ALP was 150 (IQR: 109−184) U/L. At BL, 10 (36%) pts had mild/no pruritus (WI NRS < 4, “low itch”) and 18 (64%) had moderate-to-severe pruritus (WI NRS ≥ 4, “high itch”). Most ($n = 24$; 86%) pts wore the sensor for all wear periods. Median total wear duration during the study was 27 days. At Weeks 4, 8, and 12, median hourly nocturnal scratch events ranged from 0.1–0.4 in pts with low itch and 0.4–0.6 with high itch (**Table**). Median hourly scratch duration appeared slightly higher in pts with high versus low itch; there was no difference in scratch duration per night or scratch intensity. While total sleep time per night as well as proportions of wakefulness time during either overall sleep or scratch periods were consistent for all pts, median duration of sleep between scratch periods ranged from 110−200 mins in pts with low itch and 82 −115 mins with high itch. Median scores across WI NRS, PBC-40 Itch domain, and 5-D Itch were generally consistent within each group over 12 weeks (**Table**). For other PBC-40 domains (General Symptoms, Fatigue, Cognitive Function, Social Function, Emotional Function); PROMIS Fatigue SF-7a; and Sleep Disturbance NRS, IQRs were broad and overlapping with no differences between the low and high itch groups. All 19 pts who completed a usability survey rated their experience using the sensor as “good” or “excellent.” **Conclusion:** The integration of wearable sensor technology provides unprecedented, objective insights into novel dimensions of itch in PBC, including the interplay between nocturnal scratching behavior and

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sleep disturbance. This innovative approach generates clinically meaningful new evidence and advances understanding of symptom burden in this population.

Table. ADAM sensor measurements and PRO measure results for each 7-day wear period

	Low Itch (WI NRS <4) n=10				High Itch (WI NRS ≥4) n=18			
	W0	W4	W8	W12	W0	W4	W8	W12
ADAM Sensor Measurements – median [n] (IQR)								
Nocturnal scratch events per hour – n/hour	0.2 [10] (0.1–1.4)	0.4 [9] (0.2–0.6)	0.1 [10] (0.0–0.2)	0.2 [9] (0.1–0.5)	0.6 [17] (0.2–1.1)	0.6 [18] (0.2–1.9)	0.4 [16] (0.2–0.9)	0.5 [16] (0.2–1.2)
Duration of scratch per night – seconds	8.1 [10] (5.9–28.4)	7.4 [9] (5.6–9.8)	6.3 [9] (5.8–8.4)	6.9 [9] (5.8–10.3)	7.6 [16] (6.1–10.7)	7.8 [18] (5.7–9.8)	7.1 [16] (6.3–8.0)	8.5 [15] (6.8–11.1)
Hourly duration of scratch events per night – seconds/hour[a]	6.1 [10] (0.5–20.3)	2.2 [9] (1.6–7.4)	0.7 [10] (0.1–1.7)	1.5 [9] (0.9–4.1)	4.0 [17] (1.1–12.6)	4.7 [18] (1.2–18.0)	2.6 [16] (1.4–6.0)	5.8 [16] (1.4–20.2)
Scratch intensity per night – g^2/Hz^a	0.08 [10] (0.06–0.15)	0.14 [9] (0.10–0.20)	0.08 [9] (0.07–0.15)	0.10 [9] (0.04–0.15)	0.09 [16] (0.05–0.15)	0.07 [18] (0.04–0.11)	0.07 [16] (0.05–0.11)	0.07 [15] (0.05–0.11)
Sleep time per night – hours	7.1 [10] (6.9–7.5)	7.1 [9] (6.6–7.5)	6.9 [10] (6.4–7.6)	6.2 [9] (5.9–7.2)	6.9 [17] (6.3–7.7)	7.1 [18] (5.9–8.4)	7.7 [16] (6.7–9.0)	7.5 [16] (6.6–8.4)
Wakefulness after sleep onset during sleep period – % time	3.7 [10] (1.7–5.1)	3.5 [9] (2.4–5.1)	3.1 [10] (1.6–5.6)	4.5 [9] (2.8–6.1)	5.4 [17] (3.9–7.4)	4.1 [18] (1.9–7.0)	4.9 [16] (1.9–6.6)	4.2 [16] (1.9–6.1)
Wakefulness during scratch periods – % time	18.9 [10] (0.0–38.0)	0.0 [9] (0.0–73.6)	0.0 [9] (0.0–59.7)	48.4 [9] (0.0–78.4)	52.8 [16] (30.5–66.4)	9.5 [18] (0.0–40.0)	12.1 [16] (0.0–93.1)	27.2 [15] (6.4–100.0)
Sleep period duration between scratch events – minutes	165.2 [10] (38.1–245.7)	110.2 [9] (78.6–175.0)	200.2 [10] (97.1–289.5)	167.6 [9] (93.3–251.1)	86.1 [17] (48.8–160.6)	82.1 [18] (30.3–182.6)	114.6 [16] (59.6–159.1)	88.0 [16] (45.0–162.2)
PRO Measures[b] – median [n] (IQR)								
WI NRS	2.0 [10] (1.0–3.0)	3.0 [7] (1.0–6.0)	2.0 [9] (1.0–5.0)	2.0 [8] (0.5–5.5)	5.5 [18] (4.0–7.0)	5.5 [16] (4.5–7.5)	5.0 [17] (3.0–7.0)	6.0 [17] (3.0–8.0)
PBC-40 Domain Score	[10]	[7]	[9]	[8]	[18]	[16]	[16]	[16]
Symptoms	15.0 (14.0–20.0)	15.0 (12.0–15.0)	14.0 (13.0–15.0)	15.5 (13.0–19.0)	18.5 (15.0–20.0)	16.5 (14.0–22.0)	18.0 (15.0–19.0)	18.0 (16.5–21.5)
Itch	4.0 (3.0–6.0)	3.0 (3.0–6.0)	4.0 (3.0–5.0)	4.0 (2.5–6.5)	7.0 (4.0–11.0)	6.0 (4.5–7.5)	5.5 (4.0–8.5)	5.5 (4.0–8.0)
Fatigue	23.0 (14.0–33.0)	15.0 (12.0–27.0)	18.0 (13.0–30.0)	16.0 (11.5–34.0)	31.0 (27.0–35.0)	26.5 (24.0–34.5)	29.5 (26.5–35.5)	28.5 (26.0–34.5)
Cognitive	12.0 (6.0–14.0)	9.0 (6.0–14.0)	7.0 (6.0–12.0)	6.0 (6.0–15.0)	14.0 (12.0–15.0)	14.0 (11.0–16.5)	14.5 (10.0–16.5)	11.5 (10.0–15.5)
Social	29.0 (27.0–30.0)	29.0 (26.0–32.0)	29.0 (26.0–30.0)	30.0 (29.5–32.0)	27.5 (24.0–29.0)	27.0 (25.5–29.5)	27.5 (26.0–30.0)	28.0 (22.0–29.0)
Emotional	7.0 (6.0–9.0)	8.0 (5.0–8.0)	7.0 (6.0–8.0)	7.0 (5.5–8.5)	7.0 (5.0–12.0)	8.0 (6.0–10.5)	7.0 (5.5–10.0)	6.5 (5.5–10.0)
5-D Itch Total Score	10.0 [10] (5.0–12.0)	11.0 [7] (9.0–14.0)	9.0 [9] (6.0–12.0)	9.0 [8] (3.0–12.5)	14.5 [18] (12.0–16.0)	14.5 [16] (12.5–15.5)	12.5 [16] (11.0–15.0)	13.0 [15] (9.0–16.0)
PROMIS Fatigue SF-7a T-Score	51.5 [10] (39.5–57.8)	47.6 [7] (39.6–53.7)	50.8 [9] (41.9–57.6)	42.9 [8] (36.3–59.9)	56.4 [17] (55.1–59.2)	56.5 [16] (53.0–60.6)	54.4 [16] (50.8–59.9)	53.7 [17] (49.2–57.8)
Sleep Disturbance NRS	0.5 [10] (0.0–2.0)	0.0 [7] (0.0–1.0)	0.0 [9] (0.0–1.0)	0.0 [8] (0.0–4.0)	4.5 [18] (2.0–5.0)	3.0 [16] (0.5–4.5)	3.0 [17] (2.0–4.0)	1.0 [17] (0.0–4.0)

[a] Excludes patients who had 0 total scratch events during the time window; [b] PRO response completed closest to the end of each wear period. ADAM: ADvanced Acousto Mechanic; IQR: interquartile range (Q1–Q3); NRS: Numeric Rating Scale; PBC: primary biliary cholangitis; PRO: patient-reported outcome; PROMIS: Patient-Reported Outcomes Measurement Information System; SF: Short-Form; W: Week; WI NRS: Worst-Itch NRS.

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0029 | REAL-WORLD EFFICACY OF ELAFIBRANOR IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS: EXPERIENCE FROM A COMMUNITY-BASED HEPATOLOGY PRACTICE

Rida Nadeem[1] Anita Kohli[1] Richard Manch[1] Justin Reynolds[1] Cody Chen[1] Jessica Omana Castaneda[1] Ann Moore[1] Erfan Asadipour[1] Rayan Ahmed[1] Phuong Nguyen[1], [1]Arizona Liver Health

Background: Primary biliary cholangitis (PBC) is a chronic cholestatic liver disease associated with progressive fibrosis, cirrhosis, and liver-related morbidity. Despite standard therapy with ursodeoxycholic acid (UDCA), a substantial proportion of patients fail to achieve adequate biochemical response. Elafibranor, a dual peroxisome proliferator-activated receptor (PPAR)-α/δ agonist, has emerged as a novel therapeutic option for patients with inadequate response or intolerance to UDCA. Real-world data evaluating the effectiveness of elafibranor in routine clinical practice remain limited. **Methods:** We conducted a retrospective real-world analysis of adult patients with PBC treated with elafibranor at a single outpatient hepatology center for at least 12 months. Patients with available baseline and follow-up laboratory data were included. Primary efficacy outcomes included changes in alkaline phosphatase (ALP), total bilirubin normalization, improvement in liver transaminases, and patient reported outcomes following initiation of therapy. **Results:** A total of 10 patients with PBC were included in the final analysis (mean age 66 years; 83.3% females; mean BMI 28.9). Average time on ursodiol before starting a second-line agent was about 4.3 years. Following initiation of elafibranor therapy, patients demonstrated clinically meaningful reductions in ALP levels compared with baseline (mean reduction of 84 IU/L). Mean reduction in total bilirubin of 0.16 mg/dL. Improvements were also observed in cholestatic and hepatic biochemical parameters, including reductions in AST and GGT of 2.9 IU/L and 96.1 IU/L respectively. 17% reported improvement in pruritis. Elafibranor was generally well tolerated in this real-world cohort, with a 26.67% discontinuation rate overall. **Conclusion:** In this real-world community hepatology cohort, elafibranor treatment was associated with improvements in cholestatic liver biochemistries and fibrosis-related markers among patients with PBC. These findings support the effectiveness of elafibranor in routine clinical practice and reinforce its role as a promising therapeutic option for patients with inadequate biochemical response to standard therapy. Larger longitudinal studies are warranted to further evaluate long-term clinical outcomes and treatment durability.

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0030 | ELAFIBRANOR VERSUS SELADELPAR IN UDCA-TREATED PRIMARY BILIARY CHOLANGITIS: A 111-HEALTH-SYSTEM PROPENSITY-MATCHED COMPARATIVE EFFECTIVENESS STUDY

Mohammad Alabbas[1] Barish Eren[1] Omar Sims[1] Dian Chiang[2], [1]Cleveland Clinic Foundation, [2]Cleveland Clinic

Background: Elafibranor and seladelpar have expanded second-line options for primary biliary cholangitis (PBC) with inadequate response to ursodeoxycholic acid (UDCA), but head-to-head real-world comparative data are limited. Because both agents received accelerated approval based on alkaline phosphatase (ALP) reduction rather than proven prevention of liver decompensation, comparative effectiveness and safety data are clinically important. **Methods:** We used the TriNetX Research Network (111 healthcare organizations) to emulate an active-comparator cohort study

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of adults with PBC receiving UDCA who initiated elafibranor or seladelpar. Index date was first qualifying drug exposure after documented UDCA plus PBC. Patients with competing liver diseases, including PSC, autoimmune hepatitis, alcohol-related liver disease, viral hepatitis, hemochromatosis, Wilson disease, or alpha-1-antitrypsin deficiency, were excluded. Outcomes were assessed from day 1 through 365 days after index. Cohorts were 1:1 propensity-score matched on available demographics, diagnoses, medications, and laboratory values. The primary outcome was a major adverse liver outcome (MALO) composite including hepatic encephalopathy, variceal bleeding, ascites, portal hypertension, hepatorenal syndrome, cirrhosis codes, hepatocellular carcinoma, or death. Secondary outcomes included all-cause hospitalization, MACE, ALP distribution, albumin ≤ 3.5 g/dL, and spontaneous bacterial peritonitis. **Results:** After matching, 238 elafibranor and 238 seladelpar users were analyzed. At 1 year, MALO occurred in 12.6% versus 15.5% (RR 0.81, 95% CI 0.52–1.27; HR 0.82, 95% CI 0.51–1.33; log-rank $p = 0.417$). All-cause hospitalization was similar (5.5% vs 5.0%; RR 1.08, 95% CI 0.51–2.33; HR 1.11, 95% CI 0.50–2.42; $p = 0.803$). MACE was numerically lower with elafibranor but not significant (6.3% vs 8.0%; RR 0.79, 95% CI 0.41–1.52; HR 0.81, 95% CI 0.41–1.59; $p = 0.538$). Among patients with available follow-up ALP, mean ALP was 162.7 ± 110.6 U/L with elafibranor versus 175.1 ± 103.8 U/L with seladelpar (median 135 vs 142 U/L; $p = 0.324$). Albumin ≤ 3.5 g/dL occurred in 8.4% versus 9.2% (RR 0.91, 95% CI 0.51–1.62; HR 0.92, 95% CI 0.50–1.68; $p = 0.784$). No spontaneous bacterial peritonitis events occurred in either group. **Conclusion:** In this propensity-matched real-world cohort of UDCA-treated PBC patients, elafibranor and seladelpar showed comparable 1-year liver, hospitalization, cardiovascular, ALP, albumin, and SBP outcomes. Although event rates were numerically favorable for elafibranor for MALO, MACE, ALP, and hypoalbuminemia, confidence intervals crossed the null. These early data support clinical equipoise and underscore the need for larger comparative studies with longer follow-up and validated biochemical-response definitions.

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0031 | EFFICACY AND MECHANISM OF VITAMIN E COMBINED WITH URSODEOXYCHOLIC ACID (UDCA) IN THE TREATMENT OF CHOLESTATIC LIVER DISEASE VIA MODULATING LIPID-ASSOCIATED MACROPHAGES

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Background: Ursodeoxycholic acid (UDCA) serves as the primary first-line clinical treatment for cholestatic liver diseases, such as primary biliary cholangitis (PBC); however, a subset of patients exhibits an insufficient response, presenting a significant clinical challenge. This study aims to investigate the therapeutic efficacy of vitamin E (VitE) combined with UDCA in the treatment of cholestatic liver disease and to elucidate the underlying mechanisms from the interactive perspective of macrophage lipid metabolism. Ultimately, this research seeks to provide a novel combination therapy strategy for patients with an insufficient response to UDCA. **Methods:** Plasma samples were collected from PBC patients with sufficient and insufficient responses to UDCA treatment. Untargeted metabolomics analyses were performed to evaluate the association between metabolite abundance and clinical parameters. Two murine models of cholestatic liver disease were established using 0.1% DDC diet induction and ANIT induction. Mice were subsequently treated with UDCA or VitE monotherapy, as well as their combination. Single-cell RNA sequencing (scRNA-seq) was utilized to analyze alterations in the hepatic immune microenvironment. Finally, in vivo flow cytometry was applied for the phenotypic validation of critical cell subpopulations, notably lipid-associated macrophages (LAMs). **Results:** Metabolomic analysis revealed that the relative abundance of α-tocopherol (the active form of vitamin E) in the plasma of patients with a sufficient response to UDCA was significantly higher than that in the insufficient response group. Furthermore, the abundance of α-tocopherol was significantly and negatively correlated with multiple clinical indicators of liver function and lipid metabolism. In both DDC and ANIT murine models, UDCA and VitE, either alone or in combination, effectively ameliorated liver injury. scRNA-seq data indicated a substantial increase in the proportion of lipid-associated macrophages (LAMs) exhibiting a pro-inflammatory phenotype in the livers of DDC model mice. Following VitE treatment, the proportion of these pro-inflammatory LAMs decreased significantly. Transcriptomic results demonstrated that VitE primarily enriched and modulated lipidmetabolism-related pathways **Conclusion:** During the treatment of cholestatic liver disease, UDCA functions primarily by targeting hepatocytes to regulate bile acid metabolism, whereas vitamin E specifically acts on the lipid metabolism pathways of macrophages, improving the hepatic immune microenvironment by suppressing the expansion of pro-inflammatory LAMs. The combined application of these two agents establishes a synergistic complementarity in metabolic mechanisms, providing a robust theoretical foundation and translational prospect for enhancing the clinical response rate of PBC patients to UDCA.

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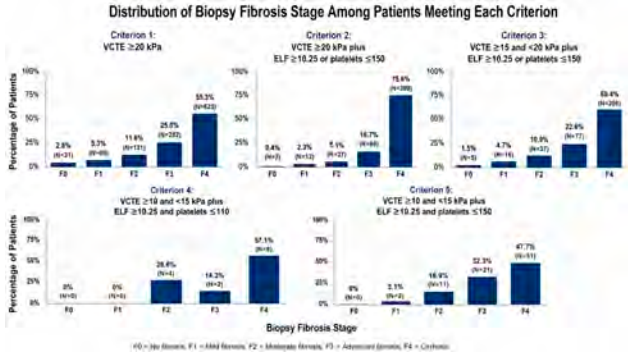
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0032 | UTILITY OF NONINVASIVE CRITERIA IN IDENTIFYING PATIENTS WITH MASH CIRRHOSIS FOR CLINICAL TRIALS

Naim Alkhouri[1] Gražina Binkauskiene[2] Winston Dunn[3] Elizabeth Brombosz[2] Rohit Puskoor[4] Rashmee Patil[3] John Poulos[5] Alma Laura Ladrón de Guevara[6] Marcelo Kugelmas[7] Sudha Kodali[8] Meena Bansal[9] Jörn Schattenberg[10] Mazen Noureddin[11], [1]Summit Clinical Research Solutions, Clinical Research Institute of Ohio, [2]Summit Clinical Research Solutions, [3]Pinnacle at San Antonio, Summit Clinical Research Solutions, [4]Pinnacle at Austin, Summit Clinical Research Solutions, [5]Coastal Research Institute, [6]Centro De Investigacion Y Gastroenterologia, [7]South Denver Gastroenterology, [8]Houston Methodist Hospital, [9]Icahn School of Medicine at Mount Sinai (ISMMS), [10]Saarland University Medical Center, [11]Houston Methodist Hospital, Houston Research Institute, Summit Clinical Research Solutions

Background: New criteria based on noninvasive tests (NITs) have been recently approved by regulatory authorities to enroll patients in MASH cirrhosis trials without the need for liver biopsy. These criteria are based on meeting certain thresholds based on VCTE liver stiffness measurement (LSM), enhanced liver fibrosis (ELF) test, and platelet count. However, given the known limitations of NITs, there is an inherent risk of enrolling patients with lower fibrosis stages which will impact the expected number of clinical outcomes. This study aimed to evaluate the efficacy of these criteria in identifying subjects with MASH cirrhosis in a multicenter database using fibrosis stage on biopsy as the gold standard. **Methods:** Patients with LSM, ELF, platelet count, and available biopsy data were identified from a multicenter database of screening and baseline data from 12 MASH clinical trials. Performance of the following NIT criteria for MASH cirrhosis were evaluated: Criterion 1: VCTE $\geq$20 kPa, Criterion 2: VCTE $\geq$20 kPa plus ELF $\geq$10.25 or platelets $\leq$150, Criterion 3: VCTE $\geq$15 and $<$20 kPa plus ELF $\geq$10.25 or platelets $\leq$150, Criterion 4: VCTE $\geq$10 and $<$15 kPa plus ELF $\geq$10.25 and platelets $\leq$110, and Criterion 5: VCTE $\geq$10 and $<$15 kPa plus ELF $\geq$10.25 and platelets $\leq$150. **Results:** Our cohort consisted of 10,386 patients with biopsy proven MASLD including 1,880 patients with cirrhosis (F4) (18.1%). The mean age was 55.4 years, 43.8% were male, median BMI of 36.5 kg/m2, and 38.3% with type 2 diabetes. The mean LSM for the entire cohort was 13.9 8.3 kPa and the mean LSM for the cirrhosis group was 20.3 $\pm$ 10.8. The mean ELF for the entire cohort was 9.82 and for the cirrhosis group was 10.52. The percentage of patients with cirrhosis on biopsy that met each criterion was as follows: Criterion 1: 55.3%, Criterion 2: 75.6%, Criterion 3: 60.4%, Criterion 4: 57.1%, and Criterion 5: 47.7%. The breakdown of other fibrosis stages on biopsy in patients meeting different criteria is shown in the figure. **Conclusion:** Using different NIT-based criteria to diagnose MASH cirrhosis may overestimate the likelihood of MALO in patients with no evidence of significant fibrosis on liver biopsy. More strict criteria based on combination NITs are needed.



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0033 | SMART-MASH (*SEQUENTIAL MACHINE-LEARNING ASSESSMENT FOR RISK TRIAGE IN MASH CIRRHOSIS*): AN ADAPTIVE SEQUENTIAL MACHINE LEARNING STRATEGY USING POINT-OF-CARE LABORATORIES, SELECTIVE VCTE, AND SELECTIVE ELF TESTING FOR CIRRHOSIS PRESCREENING IN MASLD CLINICAL TRIALS

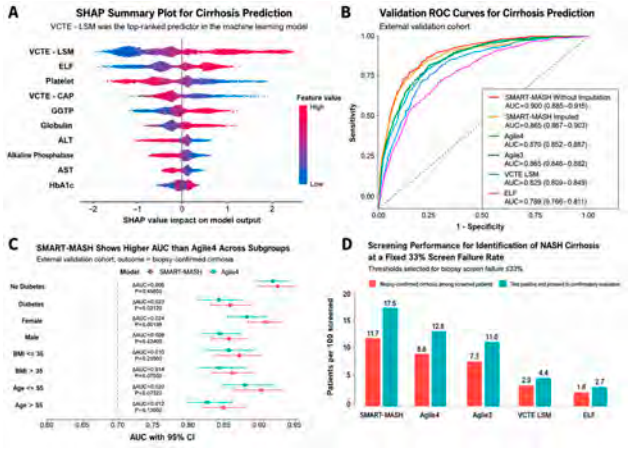
Winston Dunn[1] Mazen Noureddin[2] Elizabeth Brombosz[3] Gražina Binkauskiene[3] Rashmee Patil[4] Rohit Puskoor[5] David Huang[6] Nirupama Esther Jerome[5] John Poulos[7] Alaa Abousaif[8] Aasim Sheikh[9] Alma Laura Ladrón de Guevara[10] Marcelo Kugelmas[11] Mousab Tabbaa[12] Sam Moussa[13] Vlad Ratziu[14] Meena Bansal[15] Jörn Schattenberg[16] Naim Alkhouri[17],

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Background: Efficient identification of cirrhosis is critical for MASLD clinical trial enrollment. Current prescreening strategies rely on VCTE LSM and ELF testing, but VCTE has limited accessibility and ELF is costly with prolonged turnaround time. We aimed to develop an adaptive machine learning (ML) strategy integrating point-of-care laboratory parameters, selective VCTE, and selective ELF testing to improve cirrhosis prescreening. **Methods:** A total of 2,909 patients with MASLD from a multi-center cohort, including 743 with cirrhosis, were used for model training, with external validation in 2,383 patients (455 with cirrhosis) from network sites. XGBoost ML models predicted cirrhosis probability. A sequential strategy was used in which point-of-care laboratories (AST, ALT, platelets, HbA1c, GGT, globulin) were first used to impute LSM. Patients with imputed LSM $\geq$11 kPa underwent measured VCTE. ELF was then imputed using laboratories and LSM, unless the imputed ELF was $\geq$9.8; in these cases, ELF was measured directly. The final prediction used hybrid measured and imputed LSM and ELF values. **Results:** SHAP analysis identified the top-performing variables used to create the SMART-MASH model (Panel A). SMART-MASH achieved AUC 0.90 without imputation. Imputed LSM and ELF correlated with measured values (r = 0.42 and r = 0.60). SMART-MASH using imputed LSM >11 kPa and imputed ELF >9.8 to trigger measured VCTE and ELF achieved AUC 0.885, outperforming Agile 3 (0.865, p = 0.0075) and Agile 4 (0.870, p = 0.0195) (Panel B). Measured VCTE and ELF were required in 72.4% and 36.6% of patients, respectively. Performance remained superior to Agile 4, particularly in female and diabetic patients (Panel C). At a fixed 33% biopsy screen failure rate, 18 of 100 screened patients would proceed to confirmatory biopsy, 12 of whom would have biopsy-confirmed cirrhosis, representing >36% improvement over Agile 4 (Panel D). **Conclusion:** SMART-MASH, a novel adaptive sequential ML strategy integrating POC laboratory parameters, selective VCTE, and selective ELF testing, substantially improved cirrhosis prescreening efficiency compared with Agile 3 and Agile 4. By dynamically escalating testing intensity only in higher-risk patients, the strategy reduced reliance on universal VCTE and ELF testing while maintaining high discrimination and improving clinical trial enrollment efficiency. The web-based calculator is publicly available at https://aihepatology.shinyapps.io/SMART-MASH/



Disclosures: Winston Dunn:Nothing to Disclose, Mazen Noureddin:Nothing to Disclose, Elizabeth Brombosz:Nothing to Disclose, Gražina Binkauskiene:Nothing to Disclose, Rashmee Patil:Akero Therapeutics: Grant/Research Support, Akero Therapeutics: Grant/Research Support, Altimmune: Grant/Research Support, Altimmune: Grant/Research Support, 89Bio: Grant/Research Support, 89Bio: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Boston Pharmaceuticals: Grant/Research Support, Boston Pharmaceuticals: Grant/Research Support, Eli Lilly: Grant/Research Support, Eli Lilly: Grant/Research Support, Helio Health: Grant/Research Support, Helio Health: Grant/Research Support, Inventiva: Grant/Research Support, Inventiva: Grant/Research Support, Madrigal Pharmaceuticals: Grant/Research Support, Madrigal Pharmaceuticals: Grant/Research Support, Madrigal Pharmaceuticals: Speaking and Teaching, Madrigal Pharmaceuticals: Speaking and Teaching, Merck: Grant/Research Support, Merck: Grant/Research Support, Novo Nordisk: Grant/Research Support, Novo Nordisk: Grant/Research Support, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Galectin Therapeutics: Grant/Research Support, Galectin Therapeutics: Grant/Research Support, Hepion Pharmaceuticals: Grant/Research Support, Hepion Pharmaceuticals: Grant/Research Support, GlaxoSmithKline: Grant/Research Support, GlaxoSmithKline: Grant/Research Support, Corcept Therapeutics: Grant/Research Support, Corcept Therapeutics: Grant/Research Support, Boehringer Ingelheim: Consultant, Boehringer Ingelheim: Consultant, Novo Nordisk: Speaking and Teaching, Novo Nordisk: Speaking and Teaching, Genentech Roche: Grant/Research Support, LiverRight: Advisor, Hinova Pharmaceuticals: Consultant, Akero Therapeutics: Grant/Research Support, Akero Therapeutics: Grant/Research Support, Altimmune: Grant/Research Support, Altimmune: Grant/Research Support,

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0034 | BEYOND ALCOHOL SELF-REPORT: PHOSPHATIDYLETHANOL (PETH) ASSESSMENT UNCOVERS CLINICALLY SIGNIFICANT ALCOHOL EXPOSURE IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD)

Zobair Younossi[1] Nikolaj Torp[2] Fatema Nader[3] Mads Israelsen[2] Camilla Dalby Hansen[4] Markos Kalligeros[1] Johanne Hansen[2] Linda Henry[1] Helle Schnefeld[4] Andrei Racila[1] Katrine Bech[4] Shira Zelber-Sagi[5] Marianne Bergmann[6] Maria Stepanova[1] Aleksander Krag[7], [1]The Global NASH/MASH Council, [2]Odense University Hospital, [3]Center for Outcomes Research in Liver Diseases, CORLD, [4]Liver Research Centre, Department of Gastroenterology and Hepatology, Odense University Hospital, Od, [5]Global NASH/MASH Council, [6]Department of Biochemistry and Immunology, Lillebaelt Hospital - University Hospital of Southern De, [7]University of Southern Denmark

Background: MASLD is defined by the absence or minimal alcohol use; however, self-reported alcohol intake underestimates actual exposure. PEth, a direct metabolite of ethanol, is an objective biomarker of alcohol consumption. We evaluated PEth in two MASLD cohorts. **Methods:** MASLD subjects (hepatic

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steatosis and at least one cardiometabolic risk) with available PEth were included. The cases comprised 1,065 MASLD patients enrolled from US hepatology setting (age 48.0 ± 12.9 years, 38.3% male, BMI 41.1 ± 10.6 kg/m²; 32.3% type 2 diabetes [T2D], 55.6% hypertension, 54.2% hyperlipidemia, 18.3% current smokers). Controls consisted of 1,152 MASLD subjects from Denmark hepatology setting (age 55.3 ± 9.1 years, BMI 34.9 ± 5.6 kg/m²; 62.6% T2D, 84.9% hypertension, 70.1% dyslipidemia, 9.1% smokers). Alcohol use was assessed by self-report, and PEth was measured in stored blood. PEth cutoffs were ≥ 20 ng/mL (any alcohol exposure), < 20 ng/Md (MASLD), 20– < 200 ng/mL (MetALD), and ≥ 200 ng/mL (ALD). Clinical characteristics were stratified by PEth status within each group. **Results:** Combined analysis of 2,217 subjects revealed substantial discordance between self-report and objective assessment. In the U.S., 89.8% reported no alcohol use and only 0.4% reported ≥ 15 drinks/week; however, PEth ≥ 20 ng/mL was detected in 13.4% (n = 143), with 11.3% meeting MetALD and 2.2% ALD criteria. The control group from Denmark showed PEth ≥ 20 ng/mL in 33.9% (n = 391), with 28.9% MetALD and 5.0% ALD. Across both groups, patients with elevated PEth were predominantly male (U.S.: 56.6% vs. 35.5%; controls: 54.0% vs. 28.8%; both $p < 0.001$) and had lower BMI (U.S.: 36.1 ± 9.2 vs. 41.9 ± 10.6; controls: 33.1 ± 4.5 vs. 35.8 ± 5.9; both $p < 0.001$). U.S. patients with PEth ≥ 20 ng/mL were more likely smokers (41.0% vs. 14.5%, $p < 0.0001$) but had lower T2D prevalence (19.5% vs. 34.2%, $p = 0.0007$), while controls with PEth ≥ 20 ng/mL showed the opposite pattern: T2D 67.8% vs. 59.9%, $p = 0.009$; smoking 10.2% vs. 8.5%, $p = 0.35$. Self-report concordance with PEth differed substantially between cohorts. In the U.S., among patients with PEth ≥ 20 ng/mL, 59.4% reported no alcohol use and only 6.3% reported ≥ 15 drinks/week, demonstrating weak correlation and concordance (Spearman's $r = 0.28$, Cohen's $\kappa = 0.24$, $p < 0.0001$). Controls exhibited better correlation and concordance: 84.8% with PEth ≥ 20 ng/mL reported any alcohol use and 14.4% reported ≥ 15 drinks/week, with Spearman's $r = 0.66$, $p < 0.005$, Cohen's $\kappa = 0.42$. **Conclusion:** Self-reported alcohol assessment underestimates actual alcohol exposure among MASLD patients. Our findings demonstrate that objective PEth testing reclassified over 13% of U.S. cases initially attributed to MASLD as MetALD or ALD, highlighting a critical diagnostic gap. Objective biomarker assessment via PEth is essential for accurately distinguishing true MASLD from occult alcohol-related disease and enabling appropriate patient stratification and treatment.

Disclosures: Zobair Younossi:Zobair M. Younossi is a consultant or has received research: Consultant, madrigal: Grant/Research Support, Siemens: Research funding, GSK: Consultant, BI: Consultant, Sanofi: Research funding, Nikolaj Torp:Nothing to Disclose, Fatema Nader:Nothing to Disclose, Mads Israelsen:Nothing to Disclose, Camilla Dalby Hansen: Novo Nordisk: Speaking and Teaching, Markos Kalligeros:Nothing to Disclose, Johanne Hansen: Nothing to Disclose, Linda Henry:Nothing to Disclose, Helle Schnefeld:Nothing to Disclose, Andrei Racila: Nothing to Disclose, Katrine Bech:Nothing to Disclose, Shira Zelber-Sagi:Nothing to Disclose, Marianne Bergmann:Nothing to Disclose, Maria Stepanova: Nothing to Disclose, Aleksander Krag:Nothing to Disclose.

★ 0035 | IDENTIFYING SILENT PROGRESSORS: MACHINE LEARNING PREDICTION OF MAJOR ADVERSE LIVER OUTCOMES IN AN EARLY AT-RISK SLD POPULATION

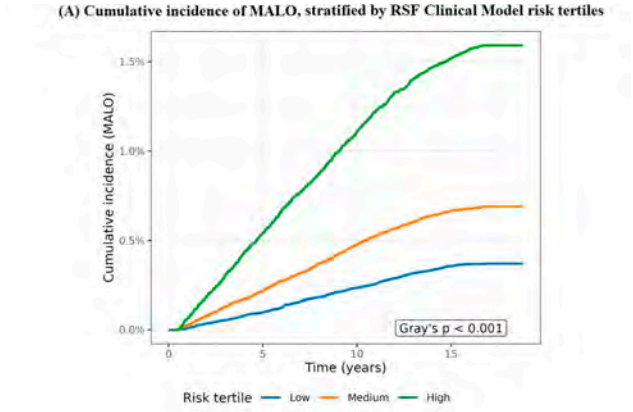
Butros Fakhoury[1] Ronnie Li[1] Vinay Jahagirdar[1] Leandro Sierra[2] Krishan Patel[1] Stephen Hoang[1] Richard Sterling[1] Luis Díaz[3] Juan Pablo Arab[1],
[1]Virginia Commonwealth University, [2]Cleveland Clinic Foundation, [3]Pontificia Universidad Católica de Chile

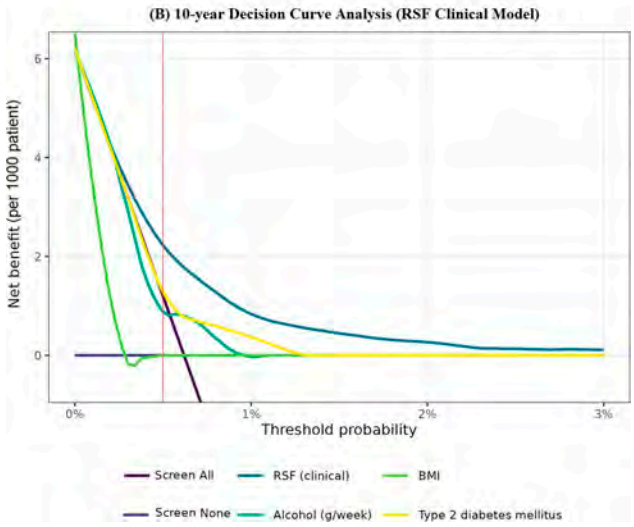
Background: Among early at-risk steatotic liver disease (SLD) patients with low FIB-4, current guidelines assign surveillance intervals based on the presence of type 2 diabetes or ≥ 2 cardiometabolic risk factors. These categorical rules do not integrate alcohol dose-response, adiposity thresholds, or risk factor interactions. We developed a Random Survival Forest (RSF) model to predict major adverse liver outcomes (MALOs) and individualize surveillance intensity in this population. **Methods:** We included 205,541 UK Biobank participants meeting early at-risk SLD criteria: type 2 diabetes, medically complicated obesity, metabolic syndrome, or alcohol intake exceeding MASLD thresholds (> 140 g/week for women, > 210 g/week for men). We excluded prevalent advanced liver disease (baseline FIB-4 > 2.67 or prior MALO). The primary outcome was incident MALO (cirrhosis, decompensation, HCC, transplant, or liver-related mortality), with non-liver death modeled as a competing event within a cause-specific hazard framework. After validating non-linear risk trajectories via natural cubic splines, we trained an RSF Clinical Model (age, sex, BMI, diabetes, smoking, alcohol intake) and a Precision Model (adding waist circumference, PNPLA3, TM6SF2, and HSD17B13 variants). Global feature importance was extracted via Monte Carlo-approximated SHAP values. Performance was validated across 5 cross-validation folds using time-dependent AUC, Harrell's C-index, and Decision Curve Analysis (utilizing inverse-probability-of-censoring weighting) against Fine-Gray regression, CLivD, and FIB-4. **Results:** Over a median 16.9-year follow-up, 1,807 MALOs occurred (0.88%). Alcohol consumption was the dominant prognostic

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driver, exhibiting a non-linear risk trajectory captured by the RSF framework. The RSF Clinical Model achieved a 5-year td-AUC of 0.706 and 10-year td-AUC of 0.700, with C-index of 0.692; the Precision Model achieved 0.721, 0.714, and 0.706, respectively. Both models outperformed the laboratory-based CLivD score (C-index 0.678) and FIB-4 (0.613). Risk tertiles derived from the Clinical Model revealed a greater than four-fold gradient in 10-year MALO incidence (0.25% vs. 0.5% vs. 1.1%). Decision Curve Analysis confirmed superior net clinical benefit across relevant thresholds compared to individual risk factor-based strategies at both 5- and 10-year horizons. **Conclusion:** An RSF model using routine primary care variables identifies silent progressors within the early at-risk SLD population, enabling individualized fibrosis surveillance within the existing guideline framework. Patients with predicted 10-year MALO incidence $\geq$0.5% may warrant intensified FIB-4 reassessment (every 1–2 years), while lower-risk individuals may be appropriately managed with standard surveillance. External validation in diverse cohorts is warranted.





Disclosures: Butros Fakhoury:Nothing to Disclose, Ronnie Li:Nothing to Disclose, Vinay Jahagirdar: Nothing to Disclose, Leandro Sierra:Nothing to Disclose, Krishan Patel:Nothing to Disclose, Stephen Hoang:PS Fertility: Consultant, Remedy Plan Inc.: Consultant, Richard Sterling:ABIM: GI Specialty Board, Abbott: Grant/Research Support, GSK: Grant/Research Support, HCV Vax: Grant/Research Support, Gilead: Grant/Research Support, Zydus: Grant/Research Support, Vertex: Consultant, Madrigal: Advisor, Gigagen: Grant/Research Support, Atea: Grant/Research Support, Cima Science: Consultant, Celaris: Consultant, GSK: Advisor, Luis Díaz:Nothing to Disclose, Juan Pablo Arab:Nothing to Disclose.

0036 | ELEVATED LIPOPROTEIN (A) LEVELS CHARACTERIZE A DISCORDANT MASLD PHENOTYPE

Álvaro Raya Marín[1] Alain Ibañez de Opakua[1] Rubén Gil-Redondo[1] Maider Bizkarguenaga[1] Ángela de Diego[1] Mikel Azkargorta[1] Nieves Embade[1] David Fernández Ramos[2] Fernando Lopitz-Otsoa[1] Ángela Domínguez-Gil[1] Felix Elortza[1] Serena Pelusi[3] Sara Margarita[3] Francesco Malvestiti[3] Massimiliano Ruscica[4] Shelly Lu[5] Urko Marigorta[1] Luca Valenti[3] Óscar Millet[1] José Mato[1], [1]CIC bioGUNE, BRTA, [2]CIBERehd, ISCIII, [3]Fondazione Ca' Granda OMP Milano, [4]Università degli Studi di Milano, [5]Cedars-Sinai Medical Center

Background: Metabolic dysfunction–associated steatotic liver disease (MASLD) is a heterogeneous condition with variable lipid and cardiovascular risk profiles. We investigated whether lipoprotein(a) [Lp(a)] identifies biologically distinct MASLD subtypes with divergent metabolic, genetic, and cardiovascular characteristics. **Methods:** Lipoproteins, metabolites, and clinical parameters were analyzed in 337 individuals at high risk of MASLD (Liver Bible cohort). Findings were validated in 5,068 participants with metabolic syndrome and/or MASLD from the UK Biobank (UKBB), integrating lipoprotein profiling, metabolomics, clinical outcomes, and polygenic scores (PGSs). **Results:** Two MASLD phenotypes were identified. A concordant phenotype exhibited more pronounced liver involvement, a triglyceride-rich, pro-atherogenic lipoprotein profile, and was associated with low Lp(a). In contrast, a discordant phenotype displayed reduced triglyceride-rich lipoproteins, higher HDL-cholesterol, and elevated Lp(a), together with a distinct metabolic signature.In UKBB, MASLD was associated with lower circulating Lp(a) levels compared with controls despite similar *LPA* PGS. Within MASLD, higher Lp(a) levels were associated with higher *LPA* PGS, lower triglyceride content in VLDL and chylomicrons, and increased prevalence of atherosclerotic heart disease, whereas lower Lp(a) was linked to a dysmetabolic phenotype, including higher

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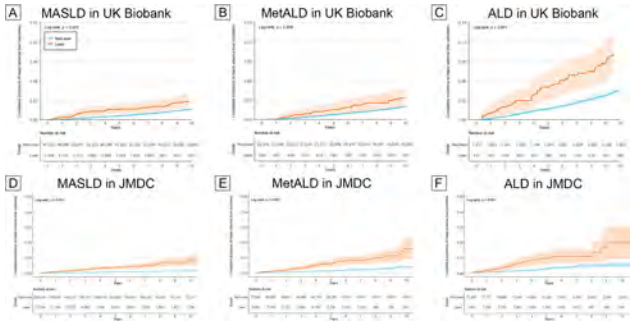
glucose, branched-chain amino acids, and type 2 diabetes prevalence. MASLD PGS did not differ across Lp(a) strata. **Conclusion:** These findings support a two-axis model of MASLD heterogeneity: hepatic steatosis is primarily driven by genetic susceptibility and metabolic factors, whereas genetically determined Lp(a) modulates cardiovascular risk. Thus, once MASLD is established, individuals may diverge into distinct cardiometabolic trajectories –one dominated by dysmetabolic, triglyceride-rich lipoproteins, and another characterized by elevated Lp(a) and atherothrombotic risk– despite similar overall polygenic burden for MASLD, potentially reflecting distinct underlying genetic and metabolic architectures.

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★ 0037 | LEAN PHENOTYPE IDENTIFIES A HIGH-RISK GROUP FOR MAJOR LIVER-RELATED OUTCOMES ACROSS STEATOTIC LIVER DISEASE SUBTYPES

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Background: The clinical implications of the lean phenotype across steatotic liver disease (SLD) subtypes, including metabolic dysfunction-associated SLD (MASLD), metabolic dysfunction and alcohol-associated liver disease (MetALD), and alcohol-associated liver disease (ALD), remain incompletely understood, particularly in MetALD and ALD. We aimed to evaluate the impact of the lean phenotype on the incidence of clinical endpoints across SLD subtypes. **Methods:** This population-based cohort study included participants with SLD from the UK Biobank and Japan Medical Data Center (JMDC) cohorts. We evaluated the associations of lean phenotype with major adverse liver outcomes (MALOs), major adverse cardiovascular events (MACEs), and all-cause mortality across SLD subtypes. **Results:** A total of 79,709 participants from the UK Biobank and 720,951 from the JMDC cohort were included. Lean phenotype was consistently associated with increased risk of MALOs in MASLD, MetALD, and ALD in both UK Biobank **(Figure 1A–1C)** and JMDC cohort **(Figure 1D–1F)** . Adjusted hazard ratios (95% confidence intervals) for MALOs in MASLD, MetALD, and ALD were 1.64 (1.22–2.22), 1.45 (1.01–2.10), and 1.99 (1.50–2.64), respectively, in the UK Biobank and 3.98 (2.90–5.44), 4.13 (2.89–5.89), and 3.12 (1.99–4.90), respectively, in the JMDC cohort. In contrast, lean phenotype was associated with lower MACE risk in MASLD, whereas MetALD and ALD showed no significant association. For all-cause mortality, lean phenotype was associated with increased risk in MetALD, whereas no significant association was observed in MASLD. These findings remained consistent across sensitivity analyses. **Conclusion:** The lean phenotype was associated with increased risk of MALOs across all SLD subtypes and mortality in MetALD, while MACE risk was lower in MASLD. In particular, lean individuals with MetALD may constitute a particularly high-risk group requiring clinical attention.



Disclosures: Takao Miwa:Nothing to Disclose, Shun-Ichi Wakabayashi:Nothing to Disclose, Takefumi Kimura:Nothing to Disclose, Nobuharu Tamaki:Nothing to Disclose, Luis Antonio Díaz:Nothing to Disclose, Burcin Özdirik: Nothing to Disclose, Xinyi Wang:Nothing to Disclose, Hongzhong Zhou:Nothing to Disclose, Xinlian Zhang: Nothing to Disclose, Naoki Tanaka:Nothing to Disclose, Masayuki Kurosaki:Gilead: Speaking and Teaching, AbbVie: Speaking and Teaching, Chugai: Speaking and Teaching, Eisai: Speaking and Teaching, GSK: Speaking and Teaching, AstraZeneca: Speaking and Teaching, Bristol-Myers Squibb: Speaking and Teaching, Ono: Speaking and Teaching, Rohit Loomba:Eli Lilly and Company: Consultant, 89bio: Consultant, Aardvark Therapeutics: Consultant, Altimmune: Consultant, Alnylam/ Regeneron: Consultant, Amgen: Consultant, Arrowhead Pharmaceuticals: Consultant, AstraZeneca: Consultant,

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0038 | AIM-AH: A MINISTRY SUPPORTED MULTICENTRE INDIAN EXPLAINABLE AI DECISION SUPPORT TOOL FOR RISK STRATIFICATION, REFERRAL, AND EARLY MORTALITY PREDICTION IN ALCOHOL-ASSOCIATED HEPATITIS

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Background: Alcohol-associated hepatitis (AH) is associated with high short-term mortality, yet early bedside risk stratification remains suboptimal. Conventional prognostic scores were not designed as real-time clinical decision support systems for triage, referral, ICU escalation, or transplant-related decision-making across heterogeneous and resource-variable healthcare settings. We developed and externally validated AIM-AH, a Ministry-supported multicentre Indian explainable artificial intelligence (AI)-based clinical decision support tool for early mortality prediction and clinically actionable risk stratification in AH **Methods:** Data from 2,396 patients with AH across 15 tertiary care centres in India were analysed. Following quality control and missingness filtering, 2,227 patients constituted the derivation cohort, while 169 patients from PGI Chandigarh served as the external validation cohort. Multiple machine learning and survival-analysis approaches, including logistic regression (LR), random forest, XGBoost, Cox proportional hazards, and XGBoost survival-embedding models, were systematically evaluated. Feature selection was performed using RFECV and Boruta algorithms. Model performance was assessed using AUROC, calibration, decision-curve analysis (DCA), and clinically actionable operating thresholds. The final model was developed as a web-based decision support tool enabling low-, intermediate-, and high-risk stratification to facilitate referral from primary and secondary care settings and escalation decisions at tertiary centres. **Results:** The most generalizable model was an interpretable six-variable LR model incorporating hepatic encephalopathy (HE),

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infection status, oxygen saturation, bilirubin, INR, and creatinine. On external validation, AIM-AH achieved an AUROC of 0.884 (95% CI, 0.832–0.932), outperforming MELD (0.769), MDF (0.748), and ABIC (0.727). At a low-risk threshold of <0.40, AIM-AH demonstrated 80.0% sensitivity, while at a high-risk threshold of >0.50, the specificity was 92%, significantly better than MELD ($p<0.001$). DCA demonstrated superior net clinical benefit over conventional prognostic scores. A compact and interpretable web tool with a guideline-grounded decision support application was developed and successfully tested in a TRL-5 clinical environment **Conclusion:** AIM-AH represents the first multicentre Indian explainable AI-based decision support tool for AH. Using six routinely available bedside variables, AIM-AH improves early mortality prediction beyond conventional prognostic scores and enables clinically actionable low-, intermediate-, and high-risk stratification to support referral pathways, treatment-intensity decisions, ICU escalation, and early transplant evaluation across resource-variable healthcare systems



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0039 | BEYOND MELD: METABOLIC RISK FACTOR BURDEN AND QUANTITATIVE FIBROSIS IDENTIFY DISTINCT HISTOPHENOTYPES AND PREDICT DOSE-RESPONSE MORTALITY IN ALCOHOL-ASSOCIATED LIVER CIRRHOSIS (QFM-ALD STUDY)

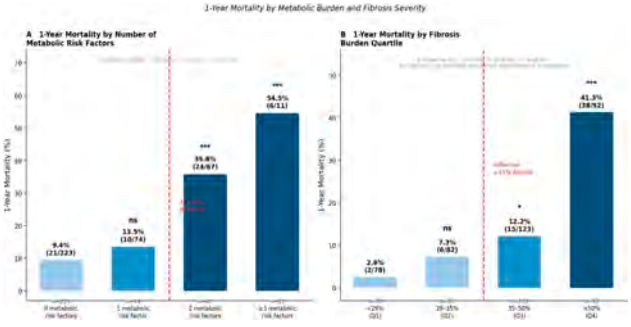
Mohit Kumar Varshney[1] Chhagan Bihari[1] Ravi Nishad[1] Zeenat Naz[1] Shiv Kumar Sarin[1], [1]Institute of Liver and Biliary sciences

Background: The 2023 SLD nomenclature classifies alcohol-associated liver disease into MetALD (alcohol 210–420 g/week [men] or 140–350 g/week [women] with ≥ 1 metabolic risk factor [MRF]) and ALD (>420/>350 g/week men/women), stratified by MRF count. How MRF burden shapes histology and outcomes across subtypes remains undefined. We aimed to characterise their histophenotypic features and identify predictors of short-term mortality. **Methods:** We prospectively enrolled adults with biopsy-proven alcohol-associated SLD cirrhosis; categorized them into MetALD and ALD with varying number of MRFs (ALD-0, ALD-1, or ALD-hm (≥ 2 MRFs)). All biopsies were reviewed by two blinded hepatopathologists; quantitative fibrosis burden was measured as collagen proportionate area (CPA) by digital morphometry. Immunohistochemistry for p21 and CDK2 characterised hepatic cell senescence. The primary outcome was death or liver transplantation at one year. Dose-response relationships between MRF count, histological parameters, and one-year outcome were assessed by Fisher's exact test; independent predictors were identified by multivariable logistic regression **Results:** Of 409 patients enrolled (375/409, 91.7% follow-up), 249 (60.9%) were ALD-0, 27 (6.6%) ALD-1, 106 (25.9%) MetALD, and 27 (6.6%) ALD-hm. Fibrosis rose stepwise: ALD-0 33.8% (IQR 28.9–46.0%), ALD-1 35.0% (IQR 29.6–41.3%), MetALD 45.0% (IQR 32.4–53.7%), ALD-hm 60.0% (IQR 49.0–63.5%); all inter-subtype $p<0.001$; ALD-0 vs ALD-1 $p=0.955$. Conventional injury markers were comparable (all $p>0.05$). A p21-high/CDK2-low senescence signature was present in MetALD and ALD-hm vs ALD ($p<0.001$). One-year mortality showed a clear MRF dose-response: 9.4% (0 MRF, $n=223$), 13.5% (1 MRF, $n=74$; ns), 35.8% (2 MRF, $n=67$; OR 4.56, 95% CI 2.18–9.55; $p<0.001$), and 54.5% (≥ 3 MRF, $n=11$; OR 8.71, 95% CI 1.75–43.30; $p<0.001$). Mortality at 0 vs 1 MRF was equivalent ($p=0.379$), rising steeply at ≥ 2 MRFs, confirming the ALD-hm designation. By subtype: 9.4% (ALD), 23.3% (MetALD), 51.9% (ALD-hm; $p<0.001$); a five-fold gradient. On multivariable analysis, fibrosis burden (aOR 1.08/1%, 95% CI 1.05–1.11; $p<0.001$) and MRF count (aOR 1.77, 95% CI 1.29–2.42;

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$p < 0.001$) independently predicted mortality; MELD was non-significant ($p = 0.219$). A five-variable score achieved AUROC 0.824 vs 0.492 for MELD ($p < 0.001$). ALD-hm had selectively higher jaundice (62.1% vs 33.8–34.1%; $p = 0.012$) and AKI (27.6% vs 8.8–22.8%; $p = 0.016$); portal hypertensive complications did not differ. **Conclusion:** Our data document for the first time that MetALD, ALD (0–1 MRF), and ALD-hm (≥ 2 MRF) are histologically and prognostically distinct phenotypes. Quantitative fibrosis burden is the strongest short-term mortality predictor across all subtypes and warrants incorporation into prognostic algorithms. A p21/CDK2 senescence signature implicates regenerative exhaustion as a mechanistic substrate for the fibrosis-mortality gradient.

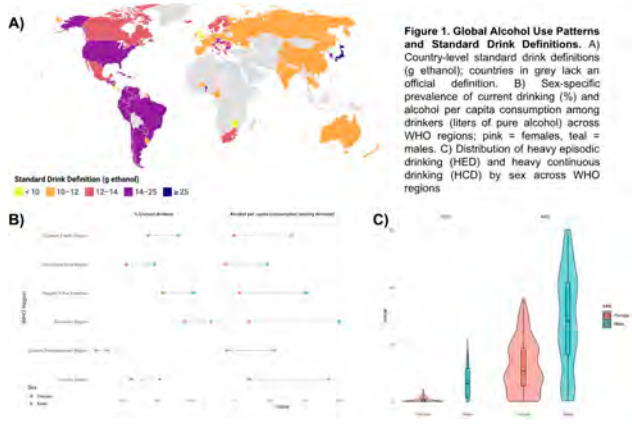


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0040 | SEX DIFFERENCES IN ALCOHOL CONSUMPTION: A GLOBAL ANALYSIS OF PREVALENCE ESTIMATES AND DRINK DEFINITION HETEROGENEITY

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Background: Alcohol is a major global health burden with marked sex differences in harm and consumption. How the differences vary by region and relate to national alcohol metrics remains unclear. Despite the WHO 10 g ethanol standard, global adherence is inconsistent. We examined global variation in standard drink definitions and their relationship with sex-specific alcohol consumption and heavy drinking patterns. **Methods:** We analyzed policy and epidemiologic data from 185 countries (WHO 2024, World Bank, national guidelines) to assess variation in standard drink definitions and their relation with alcohol per capita consumption (APC). Sex-specific studies for heavy episodic drinking (HED) and heavy continuous drinking (HCD) were also evaluated. Regional summaries and sex-stratified violin plots were performed to visualize data. **Results:** Across all regions, males demonstrated higher alcohol exposure than females. These disparities were most marked in the European, Americas, and Western Pacific Regions, where alcohol consumption among male drinkers was approximately 2–3-fold higher than among females and exceeded the WHO-recommended benchmark of 10 g/day. Regional differences in alcohol consumption were statistically significant for both sexes (males: Kruskal–Wallis $\chi^2 = 78.73$, $p < 0.001$; females: $\chi^2 = 85.78$, $p < 0.001$). Global sex-specific HED and HCD distributions differed significantly (Kruskal–Wallis $\chi^2 = 283.15$, $p < 0.001$), with greater density and variability observed in HED compared with HCD for both sexes, particularly among males. Among females, consumption patterns showed greater regional variability, potentially reflecting the differential influence of sociocultural and policy factors across settings. **Conclusion:** Global alcohol use shows marked regional and sex-specific variation, driven largely by male-female differences in consumption. These disparities coincide with wide variation in standard drink definitions, with misalignment from WHO recommendations in high-exposure regions. Given evidence that females experience greater harm per unit of alcohol consumed and that sex-specific consumption gaps are narrowing in several regions, sex-disaggregated metrics and risk thresholds warrant particular attention in future guidelines. Aligning standard drink definitions with regional and sex-specific risk profiles could strengthen global approaches to alcohol risk assessment and public health policy.



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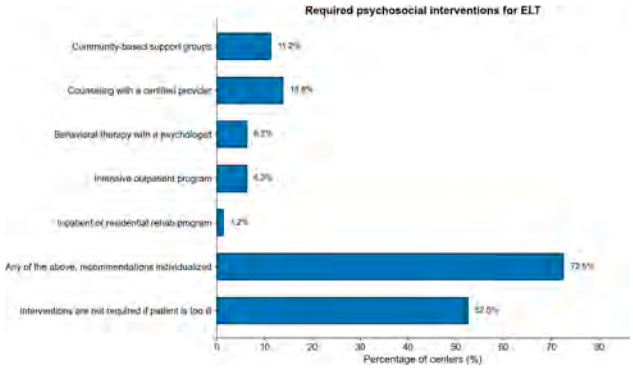
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Rhoads:Nothing to Disclose, Vinay Jahagirdar:Nothing to Disclose, Kavin Parmar:Nothing to Disclose, Krishan Patel:Nothing to Disclose, Stephen Hoang:PS Fertility: Consultant, Remedy Plan Inc.: Consultant, Luis Díaz: Nothing to Disclose, Juan Pablo Arab:Nothing to Disclose.

0041 | EARLY LIVER TRANSPLANTATION IS UNIVERSALLY ADOPTED BUT PRE-TRANSPLANT PSYCHOSOCIAL PROTOCOLS REMAIN HETEROGENEOUS IN THE UNITED STATES

Holly Huang[1] Debra Yen[2] Po-Hung (Victor) Chen[3] FNU Baimaji[3] Nicholas Lim[4] Allison Kwong[5] Alexander Yang[6] Neil Mehta[1] Gene Im[7] Courtney Sherman[1], [1]University of California, San Francisco, [2]California Pacific Medical Center, [3]Johns Hopkins University, [4]University of Rochester, [5]Stanford University Medical Center, [6]University of California San Diego, [7]Center for Liver Disease and Transplantation, Division of Digestive and Liver Diseases Columbia Univ

Background: Alcohol-related liver disease (ALD) remains the top indication for liver transplantation (LT) in the United States. Early liver transplantation (ELT) improves survival of vulnerable patients with severe ALD and less than 6 months of alcohol abstinence. However, pre-transplant psychosocial practices vary across U.S. LT centers. We conducted a national survey to characterize psychosocial resources, practices, and protocols in AUD and ALD management before ELT. **Methods:** We developed and disseminated a web-based survey via email from November 13, 2025 to April 20, 2026 to one hepatologist per adult LT center in the United States, selecting medical directors or transplant hepatologists knowledgeable in their center's practices. We stratified centers by ELT adoption (High ELT: ≥ 5 years and ≥ 20 patients/year [n = 15]; Low ELT: ≤ 5 years and ≤ 5 patients/year [n = 10]) and assessed differences with Fisher's exact test. **Results:** Eighty of 117 centers (68%) completed the survey. All (100%) had adopted ELT, and nearly all (99%) required no minimum abstinence period. Half (51%) had performed ELT for 5+ years, and 58% transplanted 11+ ELT patients annually. Although psychosocial resources were broadly accessible, with social workers (99%), mental health providers (95%), and substance use specialists (84%) available across all centers, only 40% felt resources were fully adequate. Three-quarters (76%) had a formal psychosocial AUD protocol. Most (73%) individualized interventions per patient and over half (53%) waived requirements for patients too ill to participate, suggesting a trend towards medical necessity superseding psychosocial risk in candidate selection (Figure 1). Minimum psychosocial intervention duration was rarely fixed, depending instead on clinical status (51%) or psychosocial risk (19%). Key drivers of intervention intensity included transplant social work assessment (77%) and post-transplant alcohol use risk tool scores (62%). Most centers accepted partial adherence to interventions assessed by the treating team (38%) or selection committee (32%). For patients needing LT during their index admission, 35% of centers imposed no psychosocial requirements, while 29% required virtual support group initiation and 24% in-person addiction counseling. ELT adoption level was not associated with resource adequacy, protocol use, inpatient requirements, or adherence expectations. **Conclusion:** ELT has been universally adopted across U.S. LT centers, but heterogeneity persists in psychosocial resource adequacy, formal protocol structure, and inpatient requirements. AUD management remains largely individualized, reflecting the complexity of balancing transplant urgency with variable psychosocial risk and intervention options. These findings provide a national baseline and underscore the need for studies linking these practices to post-transplant outcomes to optimize future ELT protocols.



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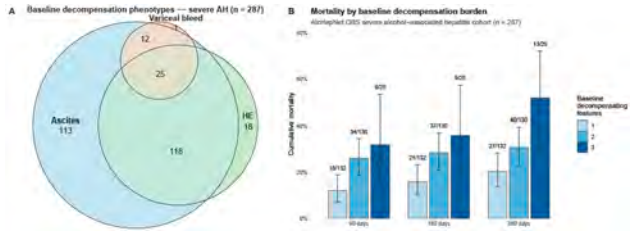
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0042 | DECOMPENSATION BURDEN, MORTALITY, AND RECOMPENSATION IN ALCOHOL-ASSOCIATED HEPATITIS

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Background: Alcohol-associated hepatitis (AH) presents with hepatic decompensation and high short-term mortality. The distribution of decompensating events, incidence of recompensation, and mortality in this population are poorly defined. **Methods:** We analyzed data from 287 hospitalized patients with AH enrolled in the AlcHepNet prospective observational cohort. Baseline decompensating events, including ascites, hepatic encephalopathy (HE), and variceal bleeding (VB), were characterized individually and by combination. Mortality at 90, 180, and 360 days was compared across one, two, or three concurrent baseline features. Recompensation, defined per Baveno VII criteria as sustained resolution of decompensating events and off medical therapy, was assessed at 3, 6, and 12 months using cumulative incidence functions with death as the competing event. Factors associated with recompensation were examined by Fine-Gray subdistribution hazards regression. **Results:** Mean age was 45 years, 42% female, 84% severe AH, mean MELD 28.3 (SD 8.9) and Maddrey's discriminant function 63.3 (SD 35.0). Ascites was present in 268/287 patients (93.4%); HE in 161 (56.5%), and VB in 38 (13.6%) (**Figure 1A**). Baseline decompensation burden was associated with mortality 90, 180, and 360 days. Among patients with one, two, and three concurrent features at enrollment, mortality was 12.1%, 26.2%, and 32.0% at 90 days ($p = 0.006$); 15.9%, 28.5%, and 36.0% at 180 days ($p = 0.016$); and 20.5%, 30.8%, and 52.0% at 360 days ($p = 0.003$) (**Figure 1B**). Recompensation was uncommon: 28 patients (9.8%) at 3 months, 45 (15.7%) at 6 months, and 52 (18.1%) at 12 months. However, among patients alive at 3 months with available alcohol intake data, those who remained abstinent from alcohol (94/121) had increasing rates of recompensation over time: 19.1% at 3 months, 34.0% at 6 months, and 37.2% at 12 months. **None of the 80 patients who died within a year had recompensated** . On Fine-Gray regression, lower baseline MELD (sHR = 0.95, 95% CI [0.91, 0.99]; $p = 0.009$) and higher educational attainment (sHR = 2.62, 95% CI: [1.12, 6.12]; $p = 0.026$) were independently associated with recompensation. **Conclusion:** In AH, the baseline decompensation phenotype is dominated by ascites, and the number of concurrent decompensating features at admission predicts mortality at 90, 180, and 360 days. Recompensation is uncommon, occurring in 18.1% of patients at 12 months, but is more frequent among patients who are abstinent from alcohol at 3 months, reaching 37.2% by 12 months. Recompensation was not observed among patients who died within the first year. Enumerating decompensating events helps identify patients at the highest risk and least likely to recover.



Disclosures: Kavish Patidar:Madrigal Pharmaceuticals: Medical Advisory Board, Mallincrodt Pharmaceuticals: Consultant, HepQaunt: Consultant, Mallinckrodt Pharmaceuticals: Medical Advisory Board, OrganOx: Advisor, Madrigal Pharmaceuticals: Advisor, Keenova Therapeutics: Advisor and Consultant., Keenova Therapeuatics: Advisor and Consultant, Novo Nordisk: Advisor, HepQaunt: Consultant, Keenova Therapeutics: Advisor and Consultant, HepQuant: Consultant, Wanzhu Tu:Nothing to Disclose, Douglas Simonetto: Mallinckrodt: Consultant, BioVie: Consultant, Resolution Therapeutics: Consultant, Evive: Consultant, Iota: Consultant, Novo Nordisk: Consultant, Astra Zeneca: Consultant, Yunpeng Yu:Nothing to Disclose, Juan Pablo Arab:Nothing to Disclose, Amon Asgharpour: Nothing to Disclose, Vatsalya Vatsalya:Nothing to Disclose, Ashwani Singal:Madrigal: Speaking and Teaching, Pleiogenix: Stock – privately held company, Pleiogenix: Consultant, CLD Foundation: Advisor, Medical Speaker's Network: Speaking and Teaching, Up-to-Date: Royalties or patent beneficiary, Medscape: Speaking and Teaching, University of Louisville School of Medicine: Employee, NIAAA: Grant/Research Support, Gastro Endo News: Executive role, Durect: Advisor, University of Louisville Health: Other, Jacqueline O'Leary:Genfit: Consultant, CVS: Stock - publicly traded company, Mallinckrodt: Advisor, PharmaIn: Advisor, PharmaIn: Consultant, Genfit: Consultant, PharmaIn: Consultant, Genfit: Consultant, Patrick

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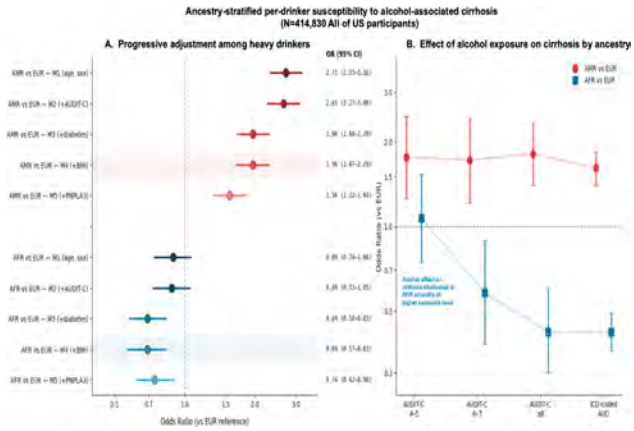
★ 0043 | GENETIC ANCESTRY, *PNPLA3*, AND PER-DRINKER SUSCEPTIBILITY TO ALCOHOL-ASSOCIATED CIRRHOSIS: A MULTI-ANCESTRY ANALYSIS OF 414,830 ALL OF US PARTICIPANTS

Hyunseok Kim[1] Walid Ayoub[1] Alexander Kuo[2] Paul Martin[2] Aarshi Vipani[2] Yun Wang[2] Stephen Pandol[2] Yee Hui Yeo[2] Debiao Li[2] Suthat Liangpunsakul[3] Shelly Lu[2] Juan Pablo Arab[4] JuDong Yang[2], [1]Cedars-Sinai Medical Center, [2]Cedars Sinai Medical Center, [3]Indiana University Medical Center, [4]Virginia Commonwealth University Medical Center

Background: Alcohol-associated liver disease (ALD) shows U.S. racial/ethnic disparities, with lower prevalence in Black and higher prevalence in Hispanic populations. The contribution of genetic ancestry to per-drinker susceptibility, independent of alcohol exposure, metabolic comorbidities, and *PNPLA3* rs738409, has not been jointly quantified in a contemporary U.S. cohort using whole-genome sequencing (WGS). We estimated ancestry-stratified per-drinker cirrhosis risk and assessed *PNPLA3* mediation. **Methods:** We analyzed 414,830 All of Us participants with WGS (median age 60, 60.9% female; 52.4% Non-Hispanic White, 19.2% Hispanic/Latino, 17.7% Non-Hispanic Black), assigned to gnomAD ancestry groups: European (EUR; n = 234,353; reference), African (AFR; n = 84,148), Admixed American (AMR; n = 79,106; 89.8% self-reported Hispanic/Latino). Heavy alcohol exposure required AUDIT-C $\geq$ 4 (women)/$\geq$ 5 (men) or ICD-coded AUD. Alcohol-associated cirrhosis (n = 1,941) required ICD cirrhosis, heavy exposure without viral hepatitis. *PNPLA3* rs738409 dosage was extracted from short-read WGS. Logistic regression compared AMR and AFR to EUR with progressive adjustment: M1 age+sex; M2 +AUDIT-C; M3 +diabetes; M4 +BMI; M5 +*PNPLA3*, plus ancestry×alcohol and ancestry×PNPLA3 interactions. Sensitivity analyses included strict (ICD+FIB-4) and decompensated cirrhosis, AUDIT-C-tier-stratified, and AUD-diagnosed subsets. **Results:** Among heavy drinkers, alcohol-associated cirrhosis per 100,000 was 1,543 (EUR), 3,019 (AMR), 1,242 (AFR). *PNPLA3* G allele frequency was 0.23 (EUR), 0.14 (AFR), 0.45 (AMR). AMR ancestry remained strongly associated with cirrhosis versus EUR after alcohol adjustment (M2 OR 2.65), attenuating after diabetes and BMI adjustment (M4 OR 1.96, 95% CI 1.67-2.29). *PNPLA3* adjustment attenuated AMR risk by ~42% but a substantial association remained (M5 OR 1.56, 1.32-1.84, p < 0.001); the AMR effect strengthened for decompensated cirrhosis (OR 3.01, 2.43-3.74). Compared to EUR, alcohol's impact on cirrhosis was attenuated in AFR: risk did not increase proportionally with exposure intensity (M4 OR 0.69 overall; OR 0.42 in AUDIT-C $\geq$ 8 and ICD-AUD subsets; ancestry×alcohol p < 0.001), and this was *PNPLA3*-independent (M5 OR 0.74). Ancestry×*PNPLA3* interactions were null (p > 0.2), indicating conserved per-allele effects (OR 1.49 AFR, 1.59 AMR; both p < 0.001). **Conclusion:** In the largest WGS-based multi-ancestry ALD analysis to date, AMR ancestry conferred substantially higher per-drinker cirrhosis risk versus EUR, only partially explained by *PNPLA3*. In contrast, the effect of alcohol exposure on cirrhosis risk was substantially weaker in AFR ancestry independent of *PNPLA3*, suggesting that additional ancestry-linked modifiers beyond established risk variants influence alcohol susceptibility. These findings indicate that *PNPLA3* alone does not explain ancestry-related disparities in ALD susceptibility.

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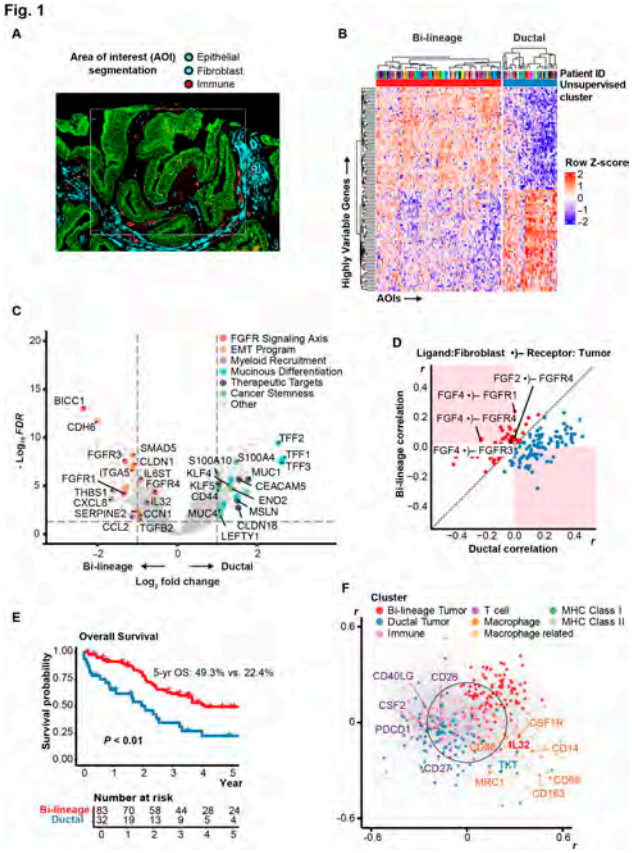
★ 0044 | SPATIALLY RESOLVED LINEAGE PROGRAMS DEFINE PROGNOSIS, THERAPEUTIC VULNERABILITIES, AND STROMAL CROSSTALK IN INTRAHEPATIC CHOLANGIOCARCINOMA

Kenta Makino[1] Peter Richieri[1] Vindhya Vijay[1] Lei Zhao[2] Deepa Patil[2] Sahar Hosseini[3] Richard Dunne[4] Maria McGreevy[4] Diana Agostini-Vulaj[4] Haley Ellis[1] Brandon Huffman[3] Joy Awosika[3] Alison Hannigan[3] Elizabeth Andrews[3] Linda Nieman[1] Katherine Xu[1] Yuhui Song[1] Andrew Aguirre[3] William Lotter[3] Jonathan Nowak[2] Brian Wolpin[3] Cristina Ferrone[5] Vikram Deshpande[6] Srivatsan Raghavan[3] Bidish Patel[1] Nabeel Bardeesy[1] James Cleary[3] David Ting[1], [1]Massachusetts General Hospital, [2]Brigham and Women's Hospital, [3]Dana-Farber Cancer Institute, [4]University of Rochester Medical Center, [5]Cedars-Sinai Medical Center, [6]Beth Israel Deaconess Medical Center

Background: Intrahepatic cholangiocarcinoma (iCCA) is a heterogeneous malignancy with variable outcomes, underscoring the need for biology-based molecular classification. Multi-omics profiling and CRISPR screening of cell lines previously identified two transcriptional states—Bi-lineage (BL) and Ductal—with distinct genetic dependencies. We applied spatial transcriptomics on human iCCA tumors to characterize these transcriptional states in the context of the microenvironment. **Methods:** 124 primary, treatment-naïve iCCAs were profiled on tissue microarrays by GeoMx Digital Spatial Profiler (~19,000 genes). PanCK, α-SMA, and CD45 staining segmented tumor epithelium, cancer-associated fibroblast (CAF), and immune compartments (Fig. 1A). After quality control and Q3 normalization, 703 areas of interest were analyzed, encompassing 162,546 epithelial, 13,008 fibroblast, and 31,957 immune cells. **Results:** Unsupervised clustering of highly variable genes in tumor epithelium resolved two primary transcriptional states that recapitulated the BL and Ductal subtypes defined in cell lines (Fig. 1B). ssGSEA metascores confirmed lineage distinctions: Ductal AOIs exhibited a bile duct-restricted program, whereas BL AOIs co-expressed hepatocyte and biliary markers. Differential expression nominated subtype-specific targets: FGFR genes in BL; CLDN18/MSLN in Ductal (Fig. 1C). Consistently, ligand-receptor analysis revealed FGF–FGFR signaling enrichment in BL, with FGF ligands from fibroblasts engaging FGFRs on tumor cells (Fig. 1D). Transcription factor inference identified elevated HNF1A/1B activity in BL tumors and MYC-driven programs in Ductal tumors. Ductal tumors conferred significantly poorer 5-year overall survival (22.4% vs 49.3%; log-rank $P < 0.01$) (Fig. 1E). Although immune and CAF compositions were broadly similar, BL tumors exhibited selective coupling of tumor-derived IL32 with M2 macrophage abundance (Fig. 1F) and myCAFs, cooperatively forming an immunosuppressive niche. **Conclusion:** Spatial transcriptomics has refined our understanding of lineage-encoded subtypes of iCCA linked with different clinical outcomes. Their conservation in cell line models suggests that these states are hard-wired, supporting further exploration of the regulation of these lineage programs and their links to iCCA behavior. Subtype-specific differences, notably IL32–M2 macrophage–myCAF crosstalk in BL-iCCA, suggest potential therapeutic opportunities and provide a framework for patient selection.

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0045 | HUMAN LIVER STEM CELL-DERIVED EXOSOMAL MIR-4492 PROTECTS FROM ACUTE LIVER FAILURE BY INHIBITING IQGAP1-MEDIATED DISULFIDPTOSIS

Qi Yang[1] Xiaoxuan Liu[2] yu chen[2] Li Bai[2], [1]Beijing You'an Hospital ,Capital Medical University, [2]Beijing You'an Hospital, Capital Medical University

Background: Acute liver failure (ALF) is a life-threatening clinical syndrome, unfortunately, its pathogenesis remains to be elucidated and novel effective therapy is urgently needed. Our previous work confirmed that human liver stem cell line HYX1 protects mice from ALF. However, the underlying mechanism still needs to be explored. Herein, we attempted to dissect the molecular basics of hepatoprotection conferred by HYX1-derived exosomes (HYX1-Exos), and focused on disulfidptosis, a newly identified mode of programmed cell death. **Methods:** Disulfidptosis levels were assessed in vitro and in vivo ALF models. The protective role of HYX1-Exos against ALF was evaluated, and disulfidptosis signaling was analyzed. miRNA sequencing was performed, and specific miRNAs which can inhibit disulfidptosis signaling were screened. LDH and disulfidptosis levels were assessed in ALF cells treated with selected miRNA mimics. Then, the crucial disulfidptosis molecules in ALF were screened by bioinformatics analysis. Next, the target relationship between target molecule and specific miRNA was verified. Subsequently, the gain-of-function (recombinant protein) and loss-of-function (siRNA) experiments of target molecule were conducted, and LDH and disulfidptosis levels were assessed. Finally, ALF cells were treated with mimics plus recombinant protein, and hepatocyte damage and disulfidptosis levels were analyzed. **Results:** Disulfidptosis signaling was significantly activated in ALF cells, as manifested by elevated LDH and NADP+/NADPH, reduced levels of cysteine and NAPDH, increased mRNA expression of disulfidptosis molecules, and contracted F-actin. The administration of TCEP, a specific disulfidptosis inhibitor, reversed these changes. In parallel, disulfidptosis critically involved in the pathogenesis of ALF mice, as shown by reduced survival rate and ALT/AST levels as well as improved pathology upon TCEP treatment. Similarly, disulfidptosis levels were remarkably inhibited in TCEP-treated ALF mice. Hepatic damage assessed by H&E staining and ALT/AST levels was obviously mitigated in ALF mice upon Exos treatment. Correspondingly, disulfidptosis levels were evidently suppressed. miR-4492 and miR-4508 were screened out as the protective cargoes carried by HYX1-Exos. The

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administration of miR-4492 mimics resulted in reduced LDH and disulfidptosis levels in ALF cells. IQGAP1 could be targeted and inhibited by miR-4492. Recombinant IQGAP1 aggravated hepatocyte damage and disulfidptosis levels in ALF cells, conversely, IQGAP1 knockdown brought about the decreased LDH and disulfidptosis levels. Recombinant IQGAP1 destroyed the protective effects of miR-4492 mimics on ALF cells. **Conclusion:** HYX1-derived exosomal miR-4492 protects from ALF by inhibiting IQGAP1-mediated disulfidptosis. Our work provides novel insights into the pathogenesis and therapy of ALF.

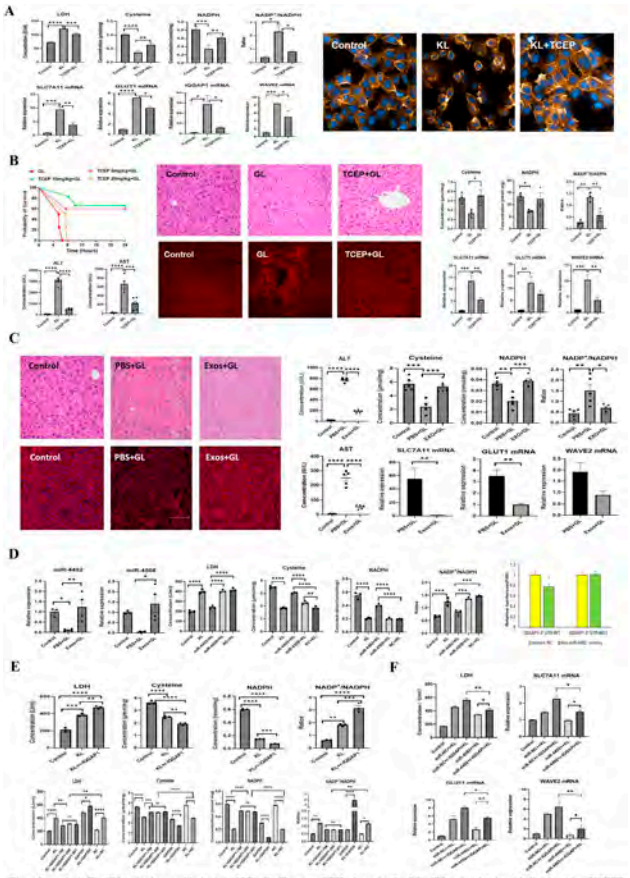


Figure Legend: **A**. Disulfidptosis plays a critical role in ALF cells. Shown are LDH release, levels of disulfidptosis-related metabolites (cysteine, NADPH, NADP+/NADPH), expression of disulfidptosis-related genes, and immunofluorescence staining of F-actin, along with changes in these parameters upon TCEP treatment; **B**. Disulfidptosis plays a critical role in ALF mice. Shown are survival rate, serum ALT/AST levels, liver H&E staining, F-actin staining, disulfidptosis-related metabolites, and expression of disulfidptosis-related genes, along with changes in these parameters upon TCEP treatment; **C**. Therapeutic effect of HYX1-Exos on ALF mice. Shown are serum ALT/AST levels, liver H&E staining, F-actin staining, disulfidptosis-related metabolites, and expression of disulfidptosis-related genes; **D**. Therapeutic effects of miR-4492 and validation of its target; **E**. Functional investigation of IQGAP1 in ALF; **F**. miR-4492 alleviates ALF by targeting IQGAP1 and inhibiting disulfidptosis.

Disclosures: Qi Yang:Nothing to Disclose, Xiaoxuan Liu:Nothing to Disclose, yu chen:Nothing to Disclose, Li Bai:Nothing to Disclose.

0046 | WIDE PRACTICE VARIATION IN PLASMA EXCHANGE FOR ACUTE LIVER FAILURE HIGHLIGHTS NEED FOR EVIDENCE-BASED GUIDANCE

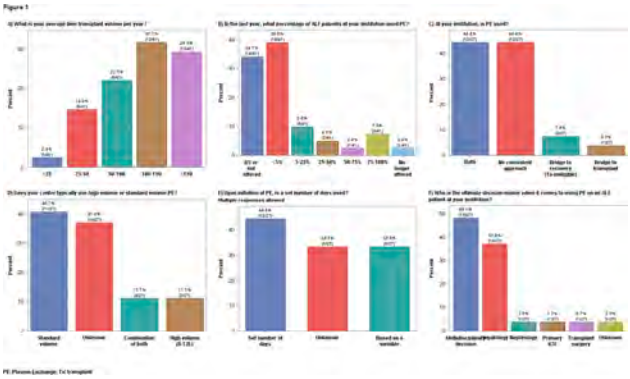
Paige Hammis[1] Whitney Jackson[2] Rocio Lopez Moscoso[1] Jesse Schold[1] Susana Arrigain[1] Deena Brosi[1] Ryan Lavanchy[1] JP Norvell[3], [1]University of Colorado, [2]University of Colorado Denver, [3]University of Colorado School of Medicine

Background: Acute liver failure (ALF) is associated with high mortality requiring prompt management. Plasma exchange (PE) has emerged as a potential treatment to address the underlying inflammatory response seen in ALF and has been associated with increased transplant-free survival. Currently, the American societies do not provide guidance on the role of PE in ALF, while European societies provide limited direction regarding patient selection and protocol. The primary objective of this study was to obtain data from liver transplant (LT) centers across the United States to better understand how PE is used in ALF and to examine the extent of variation in clinical practice. **Methods:** We conducted a national cross-sectional survey of United States LT centers. An electronic questionnaire assessing PE utilization in ALF was emailed to transplant hepatology medical directors of all LT programs (n = 117). Responses were summarized using frequencies and percentages. **Results:** A total of 41 survey responses were received, yielding a 35% response rate. All but one were academic centers. One center reported that it did not have PE capabilities. Approximately 60% (n = 25) of respondents reported performing more than 100 LTs annually (Figure 1A). Only 24% (n = 10) reported utilizing PE in more than 5% of ALF cases during the preceding year (Figure 1B). Among centers utilizing PE for ALF (n = 27), 44.4% (n = 12) reported using PE both as a bridge to transplantation and for transplant-ineligible patients, while an equal proportion reported no consistent approach to patient selection (Figure 1C). Standard-volume PE was the most reported modality (40.7%, n = 11), compared with exclusive use of high-volume PE (11.1%, n = 3). An additional 11.1% (n = 3) reported utilizing both approaches, while 37.0% (n = 10) were unaware of the volume strategy used at their institution (Figure 1D). Upon initiation of PE, 44.4% (n = 12) of centers reported using a predetermined treatment duration, whereas 33.3% (n = 9) based treatment duration on clinical variables and 33.3%

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(n = 9) were unaware of their institution's approach (Figure 1E). Decisions regarding PE use were most commonly made by a multidisciplinary team (48.1%, n = 13), followed by hepatology alone (37.0%, n = 10) (Figure 1F). **Conclusion:** These survey results demonstrate wide variation in the practice patterns of PE use among large volume academic LT programs nationally. PE is generally decided on a case-by-case basis instead of as part of a standardized protocol. Many institutions utilize PE sparingly or not at all, which may be a result of the lack of published guidelines surrounding candidate selection for PE in ALF. Most notably there is discordance in use of PE for transplant ineligible patients or as a bridge to transplant. Lack of institutional protocols and perceived limitations highlight the need for high volume centers to pool data to help facilitate evidence-based guidance.

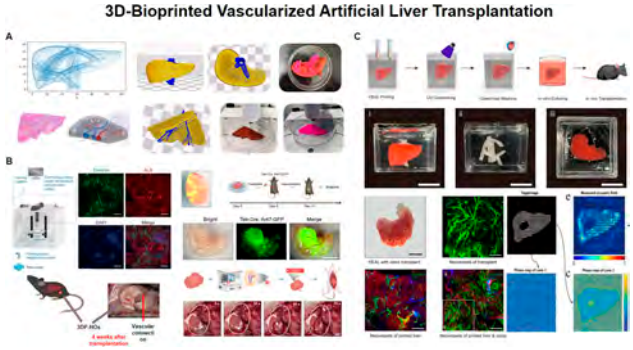


Disclosures: Paige Hammis:Nothing to Disclose, Whitney Jackson:Nothing to Disclose, Rocio Lopez Moscoso:Nothing to Disclose, Jesse Schold:Nothing to Disclose, Susana Arrigain:Nothing to Disclose, Deena Brosi:Nothing to Disclose, Ryan Lavanchy:Nothing to Disclose, JP Norvell:Nothing to Disclose.

0047 | DEVELOPMENT OF A VOLUMETRIC 3D-BIOPRINTED VASCULARIZED ARTIFICIAL LIVER FOR TRANSPLANTABLE SUPPORT IN LIVER FAILURE

Liwei Du[1] Huayu Yang[1] Yilei Mao[1], [1]Peking Union Medical College Hospital

Background: Liver failure remains a lethal condition for which transplantation is limited by donor shortage and immune rejection. Existing bioartificial liver systems provide transient detoxification but lack implantable vascular and biliary architecture. We developed a volumetric 3D-bioprinting strategy to fabricate a perfusable multicellular artificial liver for transplantable support in liver failure. **Methods:** Human iPSCs were differentiated into hepatic, vascular and bile duct organoids and assessed by morphology, lineage staining and functional assays. An ECM-mimetic bioink was optimized for printability and compatibility. Volumetric bioprinting was combined with extrusion patterning, suspended printing, acoustic assembly and sacrificial templating to fabricate 7×5×5-mm constructs with hepatocyte-rich, vascular and biliary-like compartments. Constructs were evaluated by viability, ALB/HNF4A, CD31/PDGFRβ, CK19/CK7 staining, hepatic function, biliary transport and perfusion. **Results:** We established three hiPSC-derived organoid modules. Hepatic organoids formed ALB/HNF4A-positive structures. Vascular organoids generated sprouting CD31-positive networks with mural support. Bile duct organoids acquired CK19/CK7-positive biliary epithelial features and early polarization. These modules were incorporated into 7×5×5-mm volumetric bioprinted artificial liver constructs. Our prior 3D-bioprinted liver platform showed > 99% viability at day 5 in 3–5% decellularized liver scaffold gel and 23.3 ± 2.4% Ki67-positive cells in 5% gel. Expanded hepatocytes retained ALBUMIN positivity in 96.9 ± 1.5% of cells. A 3DP-liver containing 2.7×10^7 functional hepatocytes, about 18% of mouse liver hepatocyte mass, improved liver function and survival in Fah-deficient tyrosinemia and 90% hepatectomy models. Neovascularization appeared within 1 day after transplantation, with functional GFP-positive networks by day 7. Embedded HEAL constructs with venous structures maintained > 90% viability at day 10 and > 80% at day 21; endothelialized veins increased vascular density by about 10% and total vessel length by 1.6-fold. Acoustic holography enabled patterned hepatocyte spheroid assembly within 3–6 days and improved hepatic readouts versus conventional culture. **Conclusion:** We developed a modular volumetric 3D-bioprinting strategy that integrates hiPSC-derived hepatic, vascular and biliary organoids into a multicellular artificial liver construct. This platform provides a scalable framework for generating vascularized and biliary-patterned artificial liver tissue and supports further optimization toward perfusable graft maturation, large-animal transplantation and regenerative therapy for liver failure.



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0048 | DOES CONTINUOUS RENAL REPLACEMENT THERAPY IMPROVE SURVIVAL IN ACUTE LIVER FAILURE AND ACUTE-ON-CHRONIC LIVER FAILURE: A TIME-VARYING ANALYSIS OF 8,734 ICU PATIENTS

Mohamed Nadeem[1] Jingyi Huang[2] John McMichael[2] Shilpa Junna[2], [1]Cleveland Clinic Foundation, [2]Cleveland Clinic

Background: Acute liver failure (ALF) and ACLF (Acute-on-Chronic Liver Failure) are frequently complicated by acute kidney injury and hyperammonemia, and continuous renal replacement therapy (CRRT) is increasingly used in these settings. Although prior data suggest a short-term transplant-free survival (TFS) benefit, the association of CRRT with overall survival (OS) and TFS in routine practice is not well characterized, and CRRT is preferentially initiated in the most critically ill patients. **Methods:** Adults with ALF and ACLF admitted to the ICU within a single health system (2014–2024; N=8,734) were identified using ICD-10 codes, and required a new diagnosis of renal failure at the time of ICU admission to be included in the cohort. CRRT was modeled as a time-varying exposure, with follow-up split at initiation so that patients were defined as having unexposed person-time before CRRT and exposed person-time after initiation of CRRT. The CRRT hazard ratio compares event risk during follow-up after CRRT has started against event risk during follow-up when patients are not on CRRT (including pre-CRRT time and never-CRRT patients). Baseline characteristics are reported by ever-CRRT status (Table 1) to illustrate confounding by indication; these groups are descriptive and are not the units of analysis. From ICU admission and liver failure onset we assessed OS and TFS at 21 and 370 days. Cox proportional-hazards models were adjusted for age, sex, race, BMI, baseline chronic kidney disease, and MELD at ALF/ACLF diagnosis. Missing covariates (MELD missing in 24.8%) were handled with multiple imputation by chained equations; a complete-case analysis served as a sensitivity check. **Results:** Of 8,734 patients, 7,573 (86.7%) received CRRT. Baseline groups were balanced for MELD (standardized mean difference [SMD] 0.28) and race (SMD 0.40). By day 21, there were 1,337 deaths and 1,696 death-or-transplant events; by day 370, 2,928 and 3,763 events, respectively. The post-CRRT state was associated with higher adjusted hazards across all endpoints: OS-21 hazard ratio (HR) 5.34 (95% CI 4.48–6.38), TFS-21 HR 3.70 (3.21–4.26), OS-370 HR 4.36 (3.85–4.93), and TFS-370 HR 3.44 (3.12–3.81); all $p < 0.001$. Complete-case estimates were consistent and similar or larger (e.g., OS-21 HR 7.15, (5.65–9.05)). **Conclusion:** In this large ALF and ACLF mixed cohort, CRRT was associated with substantially higher short- and long-term mortality and death-or-transplant hazard rates. These findings likely reflect the severity of illness among patients requiring CRRT rather than a harmful effect of CRRT itself. Modeling CRRT as a time-varying exposure improves temporal validity, but residual confounding by dynamic clinical deterioration remains likely. Prospective studies incorporating time-updated markers of renal failure, ammonia burden, and timing of CRRT initiation are needed to identify ALF and ACLF patients most likely to benefit from CRRT.

Table 1. Baseline characteristics of the ALF/ACLF cohort by ever-CRRT status

Variable	Ever CRRT	No CRRT	SMD	Missing (%)
N	7,573	1,161		
MELD at ALF, mean (SD)	19.06 (5.80)	17.49 (5.26)	**0.283**	24.8
Age, mean (SD)	59.02 (14.45)	59.89 (15.34)	0.058	0.0
Sex, n (%)			0.026	0.0
Female	3,314 (43.8)	520 (44.8)		
Male	4,258 (56.2)	641 (55.2)		
Missing	1 (0.0)	0 (0.0)		
Race, n (%)			**0.402**	3.6
Asian	64 (0.8)	11 (0.9)		
Black	1,088 (14.4)	79 (6.8)		
Other	335 (4.4)	38 (3.3)		
White	5,891 (77.8)	910 (78.4)		
Missing	195 (2.6)	123 (10.6)		
BMI, mean (SD)	29.06 (7.32)	28.80 (6.79)	0.036	0.6
Baseline CKD, n (%)	1,480 (19.5)	159 (13.7)	**0.158**	0.0

SMD: standardized mean difference. [SRSI 2.0.1] (see) compared, non-zero imbalance. MELD missing in 24.8% was handled with m-type imputation by chained equations in the primary analysis. Groups are descriptive (confounding by indication) and are not the units of analysis.

Table 2. Adjusted hazard ratios for CRRT across survival endpoints (time-varying Cox models)

Endpoint	Events	Primary HR (MICE) 95% CI	Sensitivity HR (complete case), 95% CI
Death ≤ 21 d (OS-21)	1,337	5.34 (4.48–6.38)	7.15 (5.65–9.05)
Death or transplant ≤ 21 d (TFS-21)	1,696	3.70 (3.21–4.26)	4.30 (3.61–5.13)
Death ≤ 370 d (OS-370)	2,928	4.36 (3.85–4.93)	4.94 (4.25–5.75)
Death or transplant ≤ 370 d (TFS-370)	3,763	3.44 (3.12–3.81)	3.65 (3.24–4.10)

HR > 1 indicates higher hazard in the post-CRRT state. All p < 0.001. Cox proportional-hazards models with CRRT as a time-varying exposure, adjusted for age, sex, race, BMI, baseline CKD, and MELD at ALF. MICE, multiple imputation by chained equations.

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0049 | FXR AND PPAR LIGANDS REVEAL POTENTIAL PHARMACOLOGICAL CROSSTALK WITH MRGPRX4 IN HEPATOBILIARY PRURITUS

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Background: The MAS-related G protein-coupled receptor X4 (MRGPRX4) is a bile acid and heme metabolite-sensing receptor predominantly expressed in small-diameter non-peptidergic sensory neurons of dorsal root and trigeminal ganglia. MRGPRX4 has emerged as a key mediator of hepatobiliary pruritus. Despite its pathophysiological relevance, the receptor

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remains insufficiently characterized, and selective pharmacological antagonists are lacking, hindering biological investigation and therapeutic advancement. As nuclear receptor ligands have been widely explored in the context of hepatobiliary liver disease, potential crosstalk with MRGPRX4 may represent a clinically relevant interface between metabolic signalling, sensory neuron activation and pruritus. **Methods:** Pharmacological compounds (n = 4,356) were screened for activity at hMRGPRX4 using β-arrestin recruitment assays at a final concentration of 10 μM (PathHunter, DiscoverX). Selected ligands were further characterised by concentration–response curves to determine their EC_{50} or IC_{50} values. Calcium mobilisation assays (Flexstation 3, Molecular Devices) were used as an orthogonal functional readout. **Results:** FXR agonists activated hMRGPRX4 in β-arrestin recruitment assays, including obeticholic acid (EC_{50}: 23.1 μM), cilofexor (EC_{50}: 52.1 μM) and tropifexor (EC_{50}: 19.4 μM). Conversely, selected PPAR agonists inhibited agonist-induced hMRGPRX4 activation, including seladelpar (IC_{50}: 2.25 μM), fenofibrate (IC_{50}: 2.89 μM), elafibranor (IC_{50}: 3.26 μM) and, with lower potency, bezafibrate (IC_{50}: 83.2 μM). Calcium mobilisation assays revealed comparable activity profiles for these selected FXR and PPAR ligands. Specificity profiling further demonstrated that FXR agonist-mediated activation was not recapitulated at hMRGPRX2, an itch-relevant MRGPR family member, or at hGPR35, supporting selective hMRGPRX4 engagement. Among the PPAR agonists, seladelpar displayed the most favourable hMRGPRX4-selective inhibitory profile, while the broader activity of additional PPAR ligands suggests a wider pharmacological interaction landscape relevant to itch modulation. **Conclusion:** This study identified clinically relevant nuclear receptor ligands as modulators of MRGPRX4. FXR agonist engagement of MRGPRX4 may contribute to hepatobiliary itch, while PPAR agonist-mediated MRGPRX4 inhibition could explain antipruritic effects and suggest repurposing opportunities for other itch-entities. Functional interplay between MRGPRX4, FXR and PPAR pathways in hepatobiliary pruritus warrants further investigation. The identified compounds may serve as lead structures for developing targeted antipruritic therapies.

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0050 | APALUTAMIDE AND ENZALUTAMIDE PROMOTE LIVER REGENERATION AND ATTENUATE CHOLESTATIC INJURY THROUGH CAR/PXR ACTIVATION

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Background: Liver failure remains major causes of mortality after liver resection and partial liver transplantation, yet no pharmacologic therapy is widely used to enhance hepatic regenerative capacity. We identified the FDA-approved androgen receptor antagonists apalutamide (APAL) and enzalutamide (ENZA) as unexpected inducers of liver growth in mice. Preliminary data suggest this effect is mediated by off-target activation of constitutive androstane

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receptor/pregnane X receptor (CAR/PXR), rather than androgen receptor blockade. Since CAR/PXR signaling also regulates bile acid homeostasis, we further examined whether APAL may benefit cholestatic liver disease. **Methods:** Mice were treated with APAL, ENZA, or darolutamide (DARO) and evaluated for liver-to-body weight ratio, hepatocyte Ki67 labeling, plasma ALT, qPCR, and bulk RNA-seq. Regenerative efficacy was assessed in a 70% partial hepatectomy (PHx) model using perioperative ENZA treatment, followed by serial analysis of liver mass recovery and hepatocyte proliferation. To assess therapeutic potential in cholestatic liver disease, Mdr2 knockout mice were treated with APAL for 2 weeks, followed by measurement of bile acid levels and bulk RNA sequencing. **Results:** Short-course APAL or ENZA increased liver-to-body weight ratio and hepatocyte Ki67 positivity without biochemical evidence of hepatotoxicity, whereas DARO had no effect. Bulk RNA-seq of APAL-treated livers demonstrated enrichment of xenobiotic metabolism and cell-cycle programs, including E2F targets and G2/M checkpoint signatures. APAL-induced transcriptional changes showed strong overlap with a published TCPOBOP-induced CAR gene program, supporting CAR/PXR pathway activation. qPCR confirmed induction of proliferation-associated genes and canonical CAR/PXR targets. In the 70% PHx model, perioperative ENZA accelerated liver mass recovery and increased early hepatocyte proliferation after surgery. Notably, in Mdr2 knockout mice, 2-week APAL treatment reduced blood bile acid levels and decreased expression of biliary fibrosis-related genes, supporting a beneficial effect in cholestatic liver injury. **Conclusion:** APAL and ENZA induce a regenerative liver program characterized by CAR/PXR-associated transcriptional activation and hepatocyte cell-cycle entry, with perioperative benefit in experimental hepatectomy. In addition, longer-term APAL treatment ameliorates cholestatic disease features in Mdr2-deficient mice. These findings support APAL/ENZA as a promising repurposing candidate for both liver regeneration and cholestatic liver disease.

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0051 | GEOMETRY-TUNED PRIMARY HUMAN HEPATOCYTE CULTURE DEFINES A MECHANOTRANSDUCTION SET POINT FOR HEPATOCYTE IDENTITY LOSS

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Background: Maintenance of mature human hepatocyte (HH) identity depends in part on preservation of native cellular architecture. In normal human liver, hepatocytes display constrained lateral dimensions (20–25 μm), whereas cirrhotic hepatocytes show marked geometric heterogeneity (18–40 μm), with enlargement associated with identity loss. Primary HH culture models this geometry–identity relationship, in which loss of tissue-imposed constraints renders hepatocytes susceptible to seeding density–dependent distortion and lateral spreading. This study aimed to define the cellular geometry–mechanotransduction set point that preserves hepatocyte identity by integrating liver tissue benchmarking with density-tuned primary HH culture. **Methods:** HHs were seeded as 2D monolayers at graded densities on substrates of varying stiffness to modulate lateral cell geometry and cell–matrix tension. Low-density culture permitted aberrant lateral spreading, whereas high-density culture imposed spatial confinement approximating normal liver dimensions. Cell geometry was quantified by projected area, equivalent circular diameter, and major/minor lateral axes, while cellular mechanics were measured by atomic force microscopy. Hepatocyte architecture and polarity were assessed by confocal microscopy, including bile canaliculi formation. These readouts were integrated with single-cell RNA sequencing to link geometric and mechanical states with mature hepatocyte identity and YAP/TAZ-associated mechanotransduction. In vitro geometry–identity states were benchmarked against normal and cirrhotic human liver tissue. **Results:** Density- and stiffness-tuned HH cultures generated distinct geometry states ranging from spatially confined cells within the normal liver size range to laterally enlarged cells resembling cirrhosis-associated geometric heterogeneity. Lateral enlargement >28 μm correlated with altered mechanics, disrupted canalicular architecture, YAP/TAZ-associated mechanotransduction, and loss of mature hepatocyte identity. Single-cell RNA sequencing identified a 16-gene identity-loss signature enriched in enlarged HHs and upregulated in cirrhotic hepatocytes. Signature-positive cells segregated into four subpopulations: residual mature hepatocyte, cholangiocyte-like, hepatic progenitor-like, and mesenchymal-like states. **Conclusion:** Expansion beyond an equivalent lateral diameter of 28 μm marked the emergence of hepatocyte identity-loss programs, with maladaptive mechanotransduction and canalicular disorganization mirroring cirrhosis. These findings refine cirrhosis as a hepatocyte identity-loss state, not solely hepatocyte loss, and support geometry-tuned primary HH culture as an in vitro platform to model cirrhosis-associated hepatocyte failure and identify therapeutic targets.

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0052 | HEPATIC X-BOX BINDING PROTEIN 1 (XBP1) REGULATES THE BILE ACID SYNTHETIC ENZYME CHOLESTEROL 7 ALPHA-HYDROXYLASE (CYP7A1) IN THE LIVER

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Background: The unfolded protein response (UPR) is an adaptive cellular response to endoplasmic reticulum (ER) stress that occurs in multiple liver disorders including cholestatic liver diseases. X-box binding protein 1 (XBP1), an important component of the UPR, is activated through a splicing mechanism to produce the active spliced form of XBP1 (XBP1s). Our previous work has demonstrated that hepatic deletion of XBP1 impairs bile acid metabolism and reduced the synthetic activity of cholesterol 7 alpha-hydroxylase (CYP7A1), the rate-limiting enzyme in the classic pathway of bile acid synthesis. Despite lower activity, the hepatic gene and protein expression of CYP7A1 were higher in liver-specific XBP1 knockout mice compared with control mice. In this study, we investigated the potential regulatory mechanisms of CYP7A1 by XBP1. **Methods:** Liver-specific doxycycline-inducible XBP1s transgenic (TG) mice and their WT littermate control mice were fed chow supplemented with doxycycline (200 mg/kg) for 48 hr to induce hepatic XBP1s overexpression. Liver tissues were collected for RNA and protein expression analysis. WT C57BL/6 mice were also treated with the selective XBP1 activator IXA4 (50 mg/kg, ip) or vehicle for 2 hr. XBP1 ChIP-seq and ATAC-seq were performed on whole liver tissues and analyzed with HOMER. Mouse liver cell lines AML12 and Hepa 1-6 cells were co-transfected with a mouse *Cyp7a1* promoter luciferase reporter construct and a plasmid overexpressing mouse XBP1s. A reporter assay was performed to examine m*Cyp7a1* promoter activity. **Results:** In TG mice, hepatic overexpression of XBP1s with doxycycline-feeding significantly reduced the gene expression of *Cyp7a1* in the liver of both female and male mice compared to WT littermate controls (female: 84% reduction, $P < 0.05$; male: 82% reduction, $P < 0.01$). Hepatic CYP7A1 protein expression was also decreased in female XBP1s TG mice after doxycycline feeding (37% reduction, $P < 0.05$). The hepatic gene expression of small heterodimer partner (SHP), a transcriptional repressor of *Cyp7a1*, did not change in female XBP1s TG mice while slightly increased in male XBP1s TG mice after doxycycline feeding (0.7-fold increase, $P < 0.05$). XBP1 ChIP-seq analysis revealed putative binding of XBP1s protein to the promoter region of mouse *Cyp7a1* in IXA4-treated mice. ATAC-seq analysis demonstrated similar chromatin accessibility at the *Cyp7a1* promoter region in both IXA4 and vehicle-treated groups. In vitro, overexpression of mouse XBP1s decreased *Cyp7a1* promoter activity in both AML12 (30% reduction, $P < 0.01$) and Hepa 1-6 cells (29% reduction, $P < 0.001$). **Conclusion:** Our data indicates that the UPR protein XBP1s negatively regulates the expression of the key bile acid synthetic enzyme CYP7A1, at least in part, through a SHP-independent transcriptional mechanism. This study demonstrates a novel regulatory mechanism of bile acid metabolism by ER stress and UPR.

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0053 | DFNA5-MEDIATED SECONDARY NECROSIS PROMOTES TNF/NF-κB SIGNALING DURING HEPATOCARCINOGENESIS

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Background: Hepatocyte death plays a central role in the progression of chronic liver disease. We previously demonstrated that persistent hepatocyte apoptosis promotes hepatocarcinogenesis. However, the contribution of non-apoptotic cell death to chronic liver disease-associated hepatocarcinogenesis remains unclear. Dfna5, also known as GSDME or Gasdermin E is a key mediator of secondary necrosis. Nevertheless, its role in hepatocarcinogenesis has not been fully elucidated. **Methods:** Alb-Cre Mcl-1 fl/fl mice, which exhibit persistent hepatocyte apoptosis and spontaneous HCC development, were used as a chronic liver disease-associated hepatocarcinogenesis model. DFNA5 was silenced in AML12, murine hepatocytes, using siRNA, and apoptosis was induced with the Bcl-xL inhibitor ABT-737. Cell death was assessed by LDH release assay and Annexin V/propidium iodide

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(PI) flow cytometry. Co-culture experiments were performed using AML12 and RAW264.7, murine macrophages. Clinical relevance was evaluated using TCGA-LIHC datasets. **Results:** Hepatocyte-specific Mcl-1 knockout mice showed increased hepatic *Tnf* expression. Depletion of Kupffer cells with clodronate liposomes abolished this *Tnf* upregulation, suggesting that Kupffer cells are the major source of TNF in this model. Hepatocyte-specific deletion of Dfna5 in Mcl-1 knockout mice did not alter liver-to-body weight ratio, serum ALT levels, or TUNEL-positive cells. However, bulk RNA-seq analysis demonstrated suppression of TNF/NF-κB signaling and inflammatory cytokine-related pathway pathways.In AML12 cells, ABT-737 induced caspase-3/7 activation and Dfna5 cleavage. *Dfna5* knockdown significantly reduced LDH release and decreased the Annexin V/PI double-positive population, suggesting that DFNA5 promotes secondary necrosis. Furthermore, co-culture of ABT-737-treated AML12 cells with RAW264.7 cells induced Tnf expression in RAW264.7 cells, which was attenuated by Dfna5 knockdown in AML12 cells.HCC developed in 100% of Mcl-1 knockout mice, whereas tumor incidence was significantly reduced in Mcl-1/Tnf double-knockout mice (47.8%, 17/17 vs 11/23; $p = 0.0008$). High DFNA5 expression was positively correlated with *TNF* and *CCL2* expression and was associated with poor prognosis in TCGA-LIHC cohorts. **Conclusion:** DFNA5 mediates secondary necrosis in hepatocytes and amplifies macrophage-derived TNF/NF-κB inflammatory signaling. These findings suggest that DFNA5-TNF/NF-κB axis might promote chronic inflammation-associated hepatocarcinogenesis.

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0054 | CONSTITUTIVE C-MAF EXPRESSION VIA ADENOVIRAL DELIVERY ENABLES THREE-DIMENSIONAL CULTURE OF LSEC LIKE CELLS IN VITRO

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Background: Chronic liver disease claims over 2 million lives annually worldwide; in the United States alone, 4.5 million adults are diagnosed and 50,000 die each year. Liver transplantation remains the only curative option for end-stage liver failure, yet fewer than 20% of patients in need receive a transplant due to organ scarcity, making new therapeutic strategies urgently needed. In a healthy liver, liver sinusoidal endothelial cells (LSECs) maintain organ homeostasis through paracrine signaling coordinating hepatocyte function, immune surveillance, and tissue repair. Dysregulation of the endothelial-hepatocyte axis underlies the progression from steatosis to fibrosis and liver failure. **Methods:** Our laboratory recently defined the transcriptional identity of LSECs and identified the transcription factor c-Maf as the master orchestrator of their sinusoidal program (Gomez-Salinero et al., Cell Stem Cell 2022). Doxycycline-inducible overexpression of c-Maf in naïve endothelial cells in vitro recapitulates sinusoidal gene expression and supports stable long-term hepatocyte co-culture. However, these studies relied on two-dimensional monolayer cultures, or spheroids, that don't capture the three-dimensional structure of the hepatic sinusoids, limiting our capacity to accurately model liver disease. **Results:** To overcome this limitation, we developed an adenoviral vector strategy for constitutive c-Maf expression that enables LSEC engineering under three-dimensional conditions. Compared to control ECs, c-Maf LSECs in 3D culture adopt a distinct morphology forming large, open intercellular spaces that recapitulate the hepatic sinusoidal architecture. Building on this technology, we have established co-cultures of c-Maf LSECs with hepatocyte organoids under healthy conditions, as well as exposed to free fatty acids modeling lipotoxic stress during liver disease. **Conclusion:** This platform enables the study of the crosstalk of endothelial cells and hepatocytes during the progression of liver disease, allowing the study to drug response and analysis of defined immune cell populations deliver under pathological conditions. Long-term, we envision transplanting c-Maf LSEC vascularized hepatocyte organoids as a

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cell therapy strategy to achieve rapid revascularization of the hepatocytes during acute liver failure. Together, this vascularized liver platform provides both a mechanistic tool for studying liver disease progression in a physiologically context, and the foundation for the development of vascular therapies for chronic liver disease.

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0056 | DISTRIBUTION OF NATURAL HISTORY STAGES IN CHILDREN AGED 1–12 YEARS WITH CHRONIC HEPATITIS B VIRUS INFECTION: A REAL-WORLD MULTICENTER RETROSPECTIVE STUDY

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Background: Real-world epidemiological data regarding the natural history of chronic hepatitis B virus (HBV) infection in children aged 1–12 years remain limited. This study aimed to investigate the distribution of disease stages and virological characteristics among untreated children with chronic HBV infection, and to provide evidence to inform clinical management strategies. **Methods:** We retrospectively collected data from untreated children aged 1–12 years with chronic HBV infection who had consecutive follow-up data at four teaching hospitals in Henan Province, China, between 2022 and 2026. Natural history staging was performed according to the *AASLD IDSA Practice Guideline on treatment of chronic hepatitis B (2025 Edition)*. **Results:** A total of 340 children with chronic HBV infection were identified across the four participating hospitals during the study period, and all were screened for eligibility, and 232 untreated children with chronic HBV infection who had consecutive data were ultimately included (Table 1). Among them, 99 (42.67%) were classified as being in the immune-tolerant phase, 107 (46.12%) in the immune clearance (HBeAg-positive immune active) phase, 1 (0.43%) in the inactive (HBeAg-negative) phase, 4 (1.72%) in the reactivation (HBeAg-negative immune active) phase, and 21 (9.05%) in the indeterminate phase. Due to the limited sample sizes in the inactive and reactivation phases, these groups were excluded from intergroup analyses. Median HBV DNA levels in the immune tolerance, immune clearance, and indeterminate groups were 8.20 (8.07–8.45), 7.85 (7.36–8.21), and 6.45 (3.85–7.41) $\log_{10}$ IU/mL, respectively, while median HBsAg levels were 4.70 (4.50–4.86), 4.19 (3.83–4.40), and 3.68 (3.37–3.87) $\log_{10}$ IU/mL, respectively. Significant differences in HBV DNA and HBsAg levels were observed among the three groups (all $P < 0.001$). **Conclusion:** A substantial proportion of untreated children aged 1–12 years with chronic HBV infection were already in the immune clearance phase rather than the immune-tolerant phase. These findings challenge the traditional view that most children remain in immune-tolerant phase and may not require antiviral therapy. Large-scale prospective studies are warranted for further validation.

Table 1 Distribution of natural history stages and virological characteristics in children with chronic hepatitis B virus infection

Parameters	Immune tolerance phase	Immune clearance phase	Inactive phase	Reactivation phase	Indeterminate phase
n, %	99 (42.67%)	107 (46.12%)	1 (0.43%)	4 (1.72%)	21 (9.05%)
Age, years	7.0 (5.0, 10.0)	7.5 (5.0, 10.0)	11.0 (11.0, 11.0)	8.0 (3.5, 11.0)	7.0 (4.0, 11.0)
Male, n (%)	57 (57.6%)	60 (61.7%)	1 (100.0%)	2 (50%)	7 (33.3%)
HBV DNA, log10 IU/mL	8.20 (8.07, 8.45)	7.85 (7.36, 8.21)	8.00 (8.00, 8.00)	8.03 (7.78, 8.18)	6.45 (3.85, 7.41)
HBsAg, log10 IU/mL	4.70 (4.50, 4.86)	4.19 (3.83, 4.40)	2.96 (2.96, 2.96)	4.80 (4.50, 4.97)	3.68 (3.37, 3.87)
ALT, U/L	19.00 (15.00, 23.00)	62.00 (41.25, 101.75)	15.00 (15.00, 15.00)	152.85 (130.75, 695.02)	20.00 (15.50, 25.00)

Disclosures: Xue-Jing Yu:Nothing to Disclose, Shi-Xi Zhang:Nothing to Disclose, Yu-Fu Wang:Nothing to Disclose, Yan-Qin Ai:Nothing to Disclose, Qing-Lei Zeng:Nothing to Disclose.

★ 0057 | INTEGRATING HEPATITIS B SCREENING INTO PRIMARY CARE IN A HIGH-BURDEN LMIC: A MIXED-METHODS IMPLEMENTATION STUDY FROM VIET NA

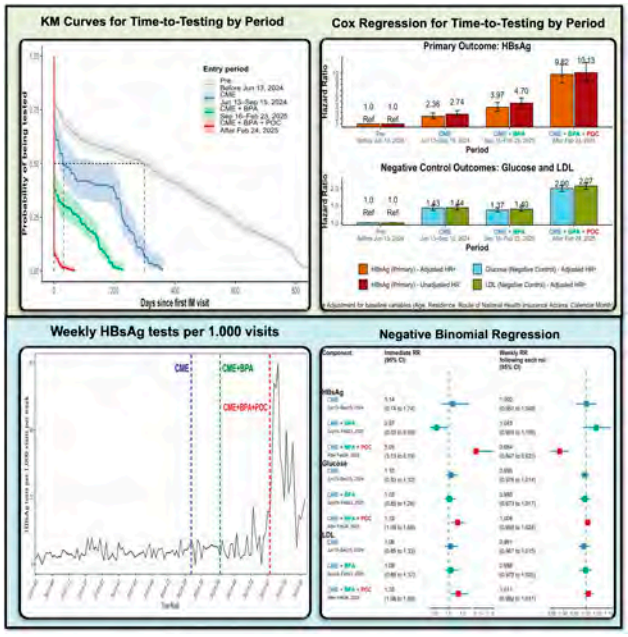
Thanh Kim[1] Trang Ngoc Doan Pham[2] Doan Dao[3] Diem Dao[4] Loc Phan[5] Linh Le[1] Toan Le[6] Thuy Tran[6] Vu Dang[6] Trang Nguyen[7] Khanh Tran[6] Anh Le[8] Cong Ly[6] Hung Vo[6] Tung Do[6], [1]Pham Ngoc Thach University of Medicine, [2]Harvard Medical University, [3]Mass General Hospital, [4]Vietnam Viral Hepatitis Alliance, [5]Vietnam Viral Hepatiits Alliance, [6]Le Van Thinh Hospital, Viet Nam, [7]Le Van Thinh Hospital, [8]Viet Nam Viral Hepatitis Alliance

Background: Globally, 290 million people live with chronic hepatitis B (CHB), yet only 13% are diagnosed and <3% receive treatment. HBsAg screening is the essential first step in the care cascade. Viet Nam represents a high-burden LMIC where 70% of individuals with CHB remain unaware of their infection. In routine primary care, HBsAg testing is typically symptom-driven, resulting in major gaps in diagnosis and linkage to care. Scalable strategies to integrate HBV screening into routine primary care are urgently needed. **Methods:** We conducted a quasi-experimental, mixed methods implementation trial at a large public

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primary care hospital in Ho Chi Minh City, Viet Nam. A three-component strategy, guided by the Consolidated Framework for Implementation Research (CFIR), was introduced sequentially over 12 months: continuing medical education (CME), an electronic best practice advisory (BPA), and point-of-care (POC) HBsAg rapid testing. Implementation outcomes (adoption, reach) and service outcomes (weekly HBsAg testing per 1,000 visits) were assessed using electronic medical records. Time-to-testing was analyzed using Kaplan–Meier and Cox regression models, and trends were evaluated using segmented negative binomial interrupted time-series. LDL and glucose testing served as netative controls. Qualitative data were analyzed using a CFIR-guided framework to delineate mechanisms and contextual factors. **Results:** Among 225,209 outpatient visits and 46,857 patients, CME improved provider knowledge but led to minimal increases in screening. BPA reminders were frequently bypassed during high-volume work flows. In contrast, introduction of free POC HBsAg rapid testing resulted in a rapid and sustained increase in testing rates and significantly reduced time-to-testing. These effects were substantially greater than negative control outcomes. Qualitative findings demonstrated that removal of financial and procedural barriers was the primary driver of uptake, while workflow integration and task-sharing influenced implementation success. **Conclusion:** In a high-burden LMIC setting, integrating HBV screening into primary care is feasible but requires addressing structural barriers. Point-of-care testing, rather than education or electronic prompts alone, was the dominant driver of screening uptake. This model provides a scalable, real-world strategy to expand HBV diagnosis and accelerate progress toward global elimination targets.



Disclosures: Thanh Kim:Nothing to Disclose, Trang Ngoc Doan Pham:Nothing to Disclose, Doan Dao: Roche: Grant/Research Support, Gilead Sciences: Grant/Research Support, IVQIA: Consultant, BMJ: Independent Contractor, Fujifilm Medical System: Grant/Research Support, DELFI Diagnostics Inc.: Grant/Research Support, Ludwig Institute for Cancer Research: Grant/Research Support, Abbott Diagnostics: Grant/Research Support, Diem Dao:Nothing to Disclose, Loc Phan:Nothing to Disclose, Linh Le: Nothing to Disclose, Toan Le:Nothing to Disclose, Thuy Tran:Nothing to Disclose, Vu Dang:Nothing to Disclose, Trang Nguyen:Nothing to Disclose, Khanh Tran:Nothing to Disclose, Anh Le:Nothing to Disclose, Cong Ly: Nothing to Disclose, Hung Vo:Nothing to Disclose, Tung Do:Nothing to Disclose.

0058 | HEPATITIS B VIRUS PREVALENCE AMONG US-BOUND REFUGEES, 2018–2023

Erin Mann[1] Kelly Searle[1] Jose Debes[1], [1]University of Minnesota

Background: Hepatitis B virus (HBV) prevalence is highly heterogeneous globally. Refugees originating from regions such as Asia or sub-Saharan Africa are thought to be at high risk, but recent prevalence estimates among US-bound refugees are limited, making successful care assignment and cascade decisions difficult. **Methods:** We analyzed HBV screening data from refugees undergoing overseas health assessments through the United States Refugee Admissions Program between October 2018 and September 2023. Prevalence was estimated by region, nationality, age (0–5y, 6–17y, ≥18 y), sex, and year. Log-binomial regression estimated adjusted risk ratios. For the two largest nationalities, we compared adjusted prevalence among adults by country of evaluation, a proxy for ethnic group and migration pathway. Among minors aged 11–17, we compared HBV prevalence between unaccompanied minors and accompanied minors, adjusting for nationality, age, sex, and year using conditional logistic regression. **Results:** Of 190,247 refugees screened, 3,545 (1.86%) tested HBsAg-positive. Prevalence declined from 3.13% in 2018 to 1.46% in 2023, persisting after adjustment for region, age, and sex (aRR 0.66, 95% CI 0.58–0.76). Prevalence rose with age (0–5y: 0.10%; 6–17y: 0.54%; ≥18y: 3.15%) and varied by region (Asia 3.62%, Africa 2.56%, Eastern Mediterranean 1.08%, Europe 0.91%, Americas 0.21%) and nationality (range 0%–13.8%). Adjusting for sex and year, adult prevalence was highest in Asia and Africa: 5.94% and 4.47% (95% CI 5.51–6.37 and 4.26–4.67 respectively); among children this reversed, with Africa exceeding Asia at ages 0–5y:

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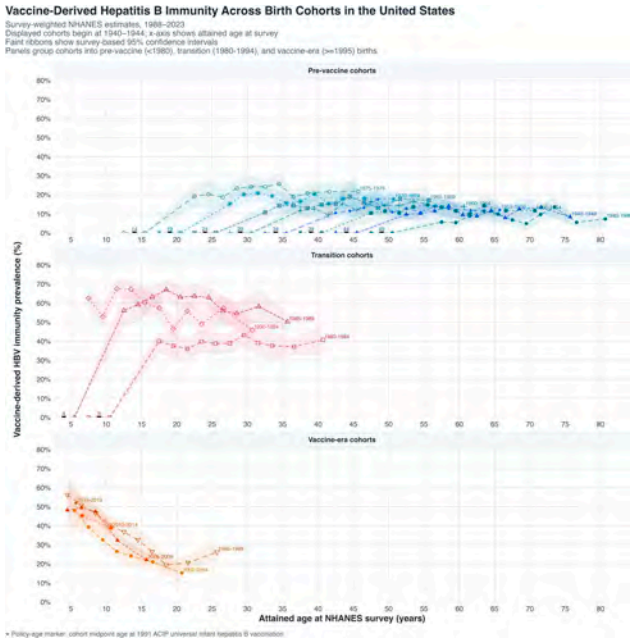
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0.15% vs 0.10% (95% CI 0.09–0.21 and 0.00–0.19, respectively) and 6–17y: 0.95% vs 0.61% (95% CI 0.83–1.07 and 0.40–0.82, respectively). Interestingly, predicted adult prevalence varied by country of evaluation (despite the same country of origin): Myanmar nationals in Thailand (8.5%, 95% CI 7.6–9.5) vs. Malaysia (5.4%, 95% CI 4.8–5.9); Democratic Republic of the Congo nationals in Tanzania (5.7%, 95% CI 5.2–6.1) vs. Zambia (3.2%, 95% CI 2.3–4.1). Of 1,673 unaccompanied minors, 21 (1.3%) tested positive, with over twice the odds of accompanied peers (OR 2.05, 95% CI 1.24–3.41). **Conclusion:** HBV prevalence among refugees has declined but remains substantial and heterogeneous. The adult-to-child reversal between Asia and Africa may reflect differing transmission dynamics and progress in pediatric vaccination. Our findings can inform screening, vaccination, and linkage to care for displaced populations worldwide helping in elimination strategies.
Disclosures: Erin Mann:Nothing to Disclose, Kelly Searle:Nothing to Disclose, Jose Debes:Nothing to Disclose.

★ 0059 | GENERATIONAL SHIFTS IN U.S. HEPATITIS B VACCINE-DERIVED IMMUNITY AFTER UNIVERSAL INFANT VACCINATION

Giovanni Roldan[1] Eva Enns[1] John Lake[1] Jesse Fletcher[1] Timothy Davie[1] Kartik Dapke[2] Serena Brosten[1] Anna Strauss[1] Prowpanga Udompap[3], [1]University of Minnesota, [2]Saint Vincent Hospital, [3]Minneapolis VA Medical Center

Background: The licensure of the hepatitis B (HBV) vaccine in 1982 and the subsequent 1991 U.S. ACIP recommendation for universal infant vaccination reshaped HBV epidemiology. However, how vaccine-derived serologic immunity evolves across birth cohorts has not been directly characterized at the population level. We analyzed NHANES serologic data using birth-cohort trajectories to both quantify generational shifts in HBV vaccine-derived serologic immunity and to characterize changes in detectable anti-HBs positivity over time. **Methods:** We analyzed thirteen National Health and Nutrition Examination Survey (NHANES) waves spanning from 1988 to 2023 (N = 84,996). Survey-weighted prevalence of vaccine-derived HBV immunity (anti-HBs positive/anti-HBc negative) was estimated within 23 five-year birth cohorts born from 1905–1909 to 2015–2019 and mapped to attained age, estimated as survey midpoint year minus birth-cohort midpoint year. Weighted linear models assessed age-related change within pre-vaccination (born 1940-1979), transitional (1980–1994), and universal-vaccination (born 1995 and later) strata. Anti-HBc trajectories were analyzed in parallel to assess HBV exposure across eras. **Results:** Pre-1980 cohorts had persistently low vaccine-derived immunity throughout adulthood (weighted mean prevalence, 12.7%; +1.1 percentage points per decade of attained age). Transitional cohorts born 1980–1994, reflecting infant and catch-up adolescent vaccination, reached the highest observed prevalence, peaking at 67.0–67.5% — more than five-fold higher than pre-vaccination cohorts — and showed only modest decline (−2.6 points/decade), with prevalence of 50.2% at age 35.7 years in the 1985–1989 cohort and 45.8% at age 30.7 years in the 1990–1994 cohort. Universal-vaccination-era cohorts born after 1995 achieved high initial rates of vaccine-derived immunity (48.0–56.2% in early childhood), confirming strong population-level vaccine uptake. Detectable anti-HBs positivity in these cohorts declined by 20.1 percentage points per decade of attained age (95% CI, 16.3–23.8; $P < 0.001$). Anti-HBc prevalence declined across eras, from 5.44% in pre-vaccination cohorts to 1.07% in transitional and 0.31% in universal-vaccination cohorts, confirming a marked generational reduction in HBV exposure. **Conclusion:** Birth-cohort trajectory mapping demonstrates that universal HBV vaccination produced a transformative, more than five-fold generational increase in U.S. vaccine-derived HBV serologic immunity and a marked reduction in HBV exposure. Detectable anti-HBs positivity declines substantially with attained age in universal-vaccination-era cohorts, yet anti-HBc prevalence remains very low, consistent with durable clinical protection despite serologic waning. Population-level surveillance of prior vaccination policies can guide future changes in HBV vaccine recommendations.



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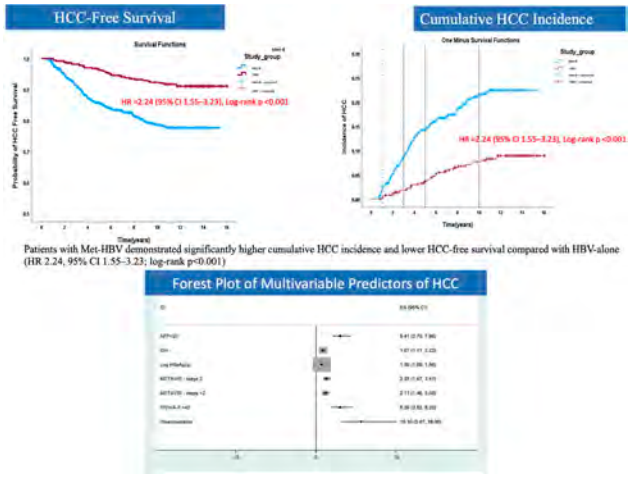
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Disclosures: Giovanni Roldan:Nothing to Disclose, Eva Enns:Nothing to Disclose, John Lake:Miromatrix: Receive salary, Scientific Registry of TR: Senior staff, for which the U of Minn receives compensation, Jesse Fletcher:Nothing to Disclose, Timothy Davie:Nothing to Disclose, Kartik Dapke:Nothing to Disclose, Serena Brosten:Nothing to Disclose, Anna Strauss:Nothing to Disclose, Prowpanga Udompap:Nothing to Disclose.

★ 0060 | "METABOLIC HEPATITIS B" (MET-B): A DISTINCT CLINICAL PHENOTYPE CARRIES A HIGHER RISK OF HEPATOCELLULAR CARCINOMA DEVELOPMENT DESPITE EFFECTIVE ANTIVIRAL THERAPY - A LARGE HISTOLOGY BASED LONGITUDINAL COHORT STUDY

Phool Chand[1] Shiv Kumar Sarin[2] Manoj Sharma[3] Vinod Arora[2] Varsha Shasthry[2] Ankit Bhardwaj[4] Ravi Nishad[2] Jaifrin Daniel[2] Satender Singh[2] Ankur Jindal[2] Chhagan Bihari[2] Archana Rastogi[4] Guresh Kumar[4] Mahima Chaudhary[2], [1]Institute of Liver and Biliary Sciences (ILBS), New Delhi, [2]Institute of Liver and Biliary Sciences, New Delhi, [3]Institute of Liver and Biliary Sciences, [4]Institute of Liver and Biliary Sciences, New Delhi.

Background: The impact of metabolic dysfunction–associated steatotic liver disease (MASLD) on hepatocellular carcinoma (HCC) risk in chronic hepatitis B (CHB) remains controversial. Histology-driven longitudinal data evaluating the interaction between metabolic dysfunction, antiviral response, and hepatocarcinogenesis are limited. We evaluated the impact of metabolic dysfunction on virologic outcomes, liver histology, and long-term HCC risk in a biopsy-characterized CHB cohort. **Methods:** We conducted a retrospective longitudinal cohort study of HBsAg-positive CHB patients who underwent liver biopsy between 2010 and 2024. Met-B was defined as presence of CHB with ≥ 1 cardiometabolic risk factor. Patients with coinfection, baseline HCC, significant alcohol intake, prior transplantation, or inadequate follow-up were excluded. Among 1,920 screened patients, 1,333 comprised the final analytic cohort: 833 Met-B and 500 HBV-alone patients. **Results:** Median follow-up was 8.0 ± 4.2 years in Met-B and 10.6 ± 4.5 years in HBV-alone ($p < 0.001$). Met-B patients had higher prevalence of diabetes (57.7%), hypertension (42.9%), dyslipidemia (75.4%), and cirrhosis (31.5%) (all $p < 0.001$). Liver biopsy demonstrated significantly greater fibrosis, steatohepatitis, perisinusoidal fibrosis, inflammatory activity, ductular reaction, and cholestatic injury in Met-B (all $p < 0.001$). Met-B patients also demonstrated inferior virologic response (50.1% vs 68.2%), biochemical response (55.5% vs 77.6%), HBeAg seroconversion (10.0% vs 16.2%), HBsAg clearance (3.5% vs 7.2%), and functional cure (2.0% vs 5.8%) (all $p \leq 0.002$). During follow-up, incident HCC occurred in (143/833)17.2% of Met-B patients versus (36/500)7.2% in HBV-alone (HR 2.24, 95% CI 1.55–3.23; $p < 0.001$).Independent predictors of HCC development included AFP ≥ 20 ng/mL (aHR 5.41), PIVKA-II ≥ 40 mAU/mL (aHR 5.39), steatohepatitis (aHR 10.11), METAVIR F2 fibrosis (aHR 2.35), METAVIR F3/F4 fibrosis (aHR 2.11), diabetes mellitus (aHR 1.57), and elevated quantitative HBsAg (aHR 1.30) (all $p < 0.05$). **Conclusion:** Metabolic dysfunction identifies a biologically aggressive CHB phenotype characterized by impaired antiviral response, delayed serologic clearance, advanced steatohepatitis, and substantially increased HCC risk despite antiviral therapy. These findings support incorporation of metabolic and histologic profiling into HCC risk stratification frameworks for chronic hepatitis B.



Disclosures: Phool Chand:Nothing to Disclose, Shiv Kumar Sarin:Nothing to Disclose, Manoj Sharma: Nothing to Disclose, Vinod Arora:Nothing to Disclose, Varsha Shasthry:Nothing to Disclose, Ankit Bhardwaj: Nothing to Disclose, Ravi Nishad:Nothing to Disclose, Jaifrin Daniel:Nothing to Disclose, Satender Singh: Nothing to Disclose, Ankur Jindal:Nothing to Disclose, Chhagan Bihari:Nothing to Disclose, Archana Rastogi: Nothing to Disclose, Guresh Kumar:Nothing to Disclose, Mahima Chaudhary:Nothing to Disclose.

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0061 | LIVER STIFFNESS PREDICTS HCC IN NON-CIRRHOTIC HBEAG NEGATIVE PATIENTS WHO DO NOT MEET TREATMENT CRITERIA BASED ON HBV DNA AND ALT – RESULTS FROM THE GLOBAL RADICAL CONSORTIUM

Lisa van Velsen[1] Gabriele Ricco[2] Norah Terrault[3] Karen Cheuk Ying Ho[4] Zillah Cargill[5] Marc Ghany[6] Elena Vargas-Accarino[7] Mai Kilany[8] Sara Battistella[9] Özgür Muhammet Koc[10] Stéphanie Narguet[11] Bettina Hansen[12] Jef Verbeek[13] Frederik Nevens[13] Tarik Asselah[14] Dirk Posthouwer[10] Yao-Chun Hsu[15] Sabela Lens[9] Jordan Feld[16] Maria Buti[17] Kosh Agarwal[5] Maud Lemoine[18] Wai-Kay Seto[19] Man-Fung Yuen[19] Maurizia Brunetto[20] Harry Janssen[21] Milan Sonneveld[1],
[1]Erasmus University Medical Center, [2]University Hospital of Pisa, [3]University of Southern California, [4]The University of Hong Kong, Hong Kong, [5]King's College Hospital, [6]NIH/NIDDK, [7]Hospital Universitari Vall d'Hebron, [8]Toronto Centre for Liver Disease, [9]Hospital Clinic Barcelona, [10]Maastricht University Medical Center, [11]AP-HP Hôpital Beaujon, [12]Erasmus MC Rotterdam, [13]KU Leuven University Hospital Leuven, [14]Hôpital Beaujon, [15]I-Shou University, [16]Toronto General Hospital, [17]Hospital Valle Hebron, [18]Imperial college London, [19]The University of Hong Kong, [20]University of Pisa, [21]Erasmus MC

Background: HBeAg negative patients who do not meet treatment criteria based on HBV DNA and ALT levels remain at risk of hepatocellular carcinoma (HCC), requiring long-term follow-up for accurate disease staging and phase classification. We hypothesized that a single liver stiffness measurement (LSM) could be helpful in HCC risk stratification. **Methods:** The current study utilized data collected for the global RADICAL study, which examines long-term outcomes in CHB patients who do not meet treatment criteria. We extracted data from HBeAg negative patients without cirrhosis who did not meet criteria for antiviral therapy according to HBV DNA and ALT criteria set forth in the 2025 EASL guideline. We then assessed HCC risk stratified for baseline LSM in the overall population, and in the subset of patients who were classified as being in the 'grey-zone' (GZ) based on laboratory data obtained during the first year of follow-up. For this analysis, the GZ was defined as not meeting criteria for HBeAg negative chronic infection (previously known as inactive carrier, defined as persistently HBeAg negative, without significant fibrosis (LSM $\leq$7 kPa, or F0-1 on biopsy), and maintained ALT $\leq$40 U/L with HBV DNA $<$2000 IU/mL). **Results:** In total, 2542 patients were included. Median age was 43 years (IQR 34-53), 48% were male, 45% were Asian and 29% were Caucasian. Baseline ALT was 25 U/L (IQR 19-34), HBV DNA was 2.8 log10 IU/mL (IQR 2.0-3.5), and LSM was 4.8 kPa (IQR 4.1-5.8). Patients were followed for a median of 7.8 (IQR 5.3-9.2) years. In the overall cohort, the 10-year cumulative incidence of HCC was 0.3%. Baseline LSM $>$7 kPa was highly predictive of HCC (HR: 14.8, 95% CI 3.5-62, $p<0.001$). Amongst patients with an LSM $\leq$7 kPa, the 10-year cumulative incidence of HCC was 0.1%, compared to 2.4% in patients with an LSM $>$7 kPa ($p<0.001$) (Figure 1). Based on laboratory assessments obtained in the first year after inclusion, 50% of patients were categorized as GZ, and 50% as HBeAg negative chronic infection. Amongst 1262 GZ patients, 48% were male, and 45% were Asian, 28% were Caucasian, with median baseline ALT of 29 U/L and HBV DNA of 3.5 log10 IU/mL. Amongst GZ patients, 64% had HBV DNA $\geq$2000 IU/mL with ALT $\leq$40 U/L and 24% had HBV DNA $<$2000 IU/mL but ALT $>$40 U/L, and 13% had fluctuating HBV DNA or ALT levels. In line with the observations in the overall cohort, GZ patients with an LSM $>$7 kPa (n=149) had a higher risk of HCC compared to patients with an LSM $\leq$7 kPa (0.2% vs 3.4% at 10 years, $p<0.001$). **Conclusion:** In HBeAg negative patients not meeting EASL treatment criteria based on ALT and HBV DNA levels, LSM $>$7 kPa identifies those at increased risk of HCC. LSM can therefore be used to select patients who could benefit from antiviral therapy and who are in need of HCC surveillance.

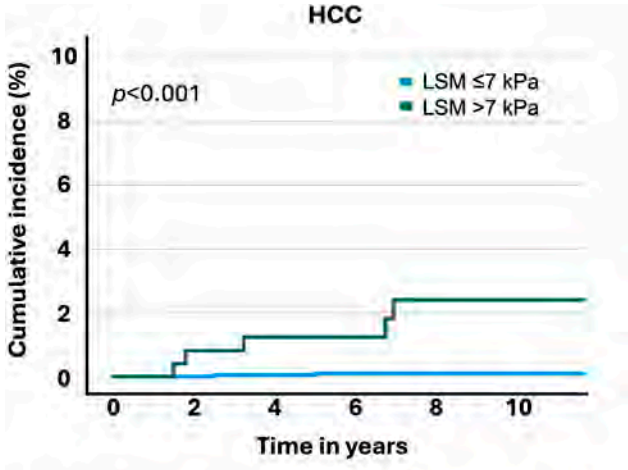


Figure 1. Cumulative incidence of HCC stratified for baseline liver stiffness measurement (LSM) ≤7 kPa and >7 kPa.

Disclosures: Lisa van Velsen:Gilead Sciences: Research Support, Gabriele Ricco:Nothing to Disclose, Norah Terrault:Nothing to Disclose, Karen Cheuk Ying Ho:Nothing to Disclose, Zillah Cargill:Nothing to Disclose, Marc Ghany:Vir Bio: Grant is to NIDDK, NIH not to Investigator, Elena Vargas-Accarino:Nothing to Disclose, Mai Kilany:Nothing to Disclose, Sara Battistella:Nothing to Disclose, Özgür Muhammet Koc:Nothing to Disclose, Stéphanie Narguet:Nothing to Disclose,

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0062 | HRS-4729, A NOVEL GLP-1/GIP/GLUCAGON TRIPLE-RECEPTOR AGONIST, REDUCES LIVER FAT IN PARTICIPANTS LIVING WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) AND OBESITY: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE 1B STUDY

Qing Wen[1] Kun He[1] Cuigang Li[1] Lei Diao[2] Hong Chen[2] Lin Wang[2] Mengshan Ni[2] Pingan Yao[2] Hui Liu[2] Hui Dong[2], [1]Central Hospital Affiliated to Shandong First Medical University, [2]Jiangsu Hengrui Pharmaceuticals

Background: HRS-4729, a novel long-acting triple agonist of GLP-1, GIP, and glucagon receptors, has shown therapeutic potential in animal models of MASLD and obesity. Here, we present data on liver fat, weight, lipid profiles, and safety of HRS-4729 in participants living with MASLD and obesity, from a randomized, double-blind, placebo-controlled, multiple ascending dose study. **Methods:** Adults aged 18–55 years with a BMI of 28–40 kg/m2 were randomized (5:1 per dose cohort) to receive weekly SC HRS-4729 (1 mg fixed; 4, 8, or 12 mg titration) or placebo for 12 weeks. The MASLD subgroup included participants with a liver fat content of $\geq$5%, measured by MRI-PDFF. Efficacy outcomes included percentage change from baseline (CFB) in liver fat; proportion of participants achieving liver fat reduction targets;

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percentage CFB in body weight, waist circumference, and lipid profiles at week 12. **Results:** Of the 48 randomized participants, 34 had MASLD (30 treated with HRS-4729, and 4 with placebo). Of those with MASLD, 58.8% participants were male; the mean weight was 87.75 kg (SD, 8.02); and the mean liver fat content was 13.4% (SD, 8.8%). The mean percentage CFB in liver fat was -63.9% with HRS-4729 (1, 4, 8, and 12 mg cohorts: -41.0%, -67.2%, -81.0%, and -55.4%, respectively), compared with -41.0% with placebo. A higher proportion of HRS-4729–treated participants achieved ≥30%, ≥50%, and ≥70% reductions in liver fat (83.3%, 70.0%, and 46.7%, respectively) versus placebo (50.0%, 50.0%, and 25.0%). Liver fat <5% was achieved by 83.3% of participants treated with HRS-4729, compared with 25.0% with placebo. Of those with baseline liver fat ≥8% (n=17) and ≥10% (n=12), a greater degree of liver fat reduction following HRS-4729 was observed, with a maximum reduction of 89.8% (Table); and 100% of participants in 8 and 12 mg cohorts achieved liver fat <5%. Among all MASLD participants, mean percentage CFB in body weight was greater with HRS-4729 compared with placebo (-13.6% vs. -4.8%), and a dose-dependent trend was observed with HRS-4729 (Table). The mean percentage CFB in waist circumference was also larger with HRS-4729 (-11.1% vs. -6.4%). Reductions in lipids (such as LDL-C, triglycerides, and cholesterol) generally favored HRS-4729. Treatment-emergent adverse events (TEAEs) following HRS-4729 were mostly mild gastrointestinal events, consistent with incretin-based therapies. No severe or serious TEAEs occurred, and no TEAEs led to treatment discontinuation. **Conclusion:** HRS-4729 reduced liver fat, body weight, and waist circumference in participants with liver fat ≥5%, and was safe and well tolerated, supporting further development of HRS-4729 for MASLD.

Table. Effects of HRS-4729 on liver fat, body weight, and waist circumference in participants with baseline liver fat ≥5%, ≥8%, and ≥10%.

	Placebo	HRS-4729				
		1 mg	4 mg	8 mg	12 mg	All
Participants with baseline liver fat ≥5%						
No. of participants enrolled	4	5	10	8	7	30
Baseline liver fat content (%)	14.8 (10.9)	13.9 (9.3)	12.7 (9.0)	17.6 (10.1)	8.5 (3.9)	13.2 (8.7)
Percentage CFB in liver fat (%)	-41.0 (32.8)	-41.0 (29.1)	-67.2 (14.5)	-81.0 (11.4)	-55.4 (24.0)	-64.0 (23.1)
Proportion of participants achieving liver fat reduction targets, n (%)						
≥30% reduction	2 (50.0)	3 (60.0)	9 (90.0)	8 (100.0)	5 (71.4)	25 (83.3)
≥50% reduction	2 (50.0)	2 (40.0)	7 (70.0)	8 (100.0)	4 (57.1)	21 (70.0)
≥70% reduction	1 (25.0)	1 (20.0)	5 (50.0)	6 (75.0)	2 (28.6)	14 (46.7)
Percentage CFB in body weight (%)	-4.8 (3.5)	-9.7 (4.9)	-12.8 (5.6)	-14.9 (3.6)	-16.6 (3.7)	-13.6 (4.9)
Percentage CFB in waist circumference (%)	-6.4 (2.6)	-8.3 (4.3)	-10.3 (3.4)	-13.7 (5.0)	-11.2 (6.4)	-11.1 (4.9)
Participants with baseline liver fat ≥8%						
No. of participants enrolled	3	3	5	7	2	17
Baseline liver fat content (%)	17.6 (11.5)	19.0 (8.5)	18.3 (10.1)	19.2 (9.8)	14.2 (0.2)	18.3 (8.6)
Percentage CFB in liver fat (%)	-27.1 (21.4)	-51.4 (34.5)	-78.1 (7.8)	-82.6 (11.3)	-78.8 (2.8)	-75.2 (19.1)
Proportion of participants achieving liver fat reduction targets, n (%)						
≥30% reduction	1 (33.3)	2 (66.7)	4 (80.0)	7 (100.0)	2 (100.0)	15 (88.2)
≥50% reduction	1 (33.3)	2 (66.7)	4 (80.0)	7 (100.0)	2 (100.0)	15 (88.2)
≥70% reduction	0	1 (33.3)	4 (80.0)	6 (85.7)	2 (100.0)	13 (76.5)
Participants with baseline liver fat ≥10%						
No. of participants enrolled	2	2	4	4	2	12

Data are mean (SD), unless otherwise specified.
CFB, change from baseline.

Disclosures: Qing Wen:Nothing to Disclose, Kun He:Nothing to Disclose, Cuigang Li:Nothing to Disclose, Lei Diao:Nothing to Disclose, Hong Chen:Nothing to Disclose, Lin Wang:Nothing to Disclose, Mengshan Ni:Nothing to Disclose, Pingan Yao:Nothing to Disclose, Hui Liu:Nothing to Disclose.

0063 | PEMVIDUTIDE TREATMENT RESULTS IN CONCURRENT REDUCTIONS IN MULTIPLE NON-INVASIVE TESTS FOR HEPATIC INFLAMMATION AND FIBROSIS: 48-WEEK RESPONDER ANALYSES OF THE IMPACT PHASE 2B TRIAL IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS

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Background: Pemvidutide is a balanced 1:1 glucagon/GLP-1 dual receptor agonist in development for the treatment of metabolic dysfunction-associated steatohepatitis (MASH). IMPACT was a phase 2b, randomized, placebo-controlled, double-blind trial in patients with biopsy-confirmed MASH and fibrosis stage F2 or F3 (NCT05989711). Histologically, pemvidutide treatment yielded statistically significant MASH resolution and high rates of fibrosis improvement within 24 weeks. Pemvidutide also resulted in statistically significant reductions in individual non-invasive tests (NITs) of hepatic inflammation and fibrosis that continued to improve over time. A reduction of ≥30% in liver fat content (LFC) is associated with improvements in MASH and a reduction of ≥17 IU/L in alanine aminotransferase (ALT) is predictive of histologic response. Similarly, reductions of ≥0.5 in enhanced liver fibrosis (ELF) score or ≥30% in liver stiffness measurement (LSM) are associated with fibrosis regression. While individual NITs may be indicators of therapeutic effect, composite analyses using multiple overlapping NITs may provide a more rigorous assessment of therapeutic improvement as they increase diagnostic accuracy and stringency. Here we present 48-week responder analyses of composite NITs from the IMPACT trial. **Methods:** 212 patients were randomized 1:2:2 to receive once-weekly subcutaneous pemvidutide (1.2 mg or 1.8 mg) administered without dose titration, or placebo. Secondary endpoints included the NITs for LFC, ELF score, LSM, and ALT. **Results:** The mean age was 53 yrs, the mean BMI was 39 kg/m^2, 58% were female, and 43% had type 2 diabetes. With respect to MASH improvement, a greater percentage of patients receiving either dose of pemvidutide achieved concurrent responses in LFC (≥30% reduction), ALT (≥17 U/L reduction), and LSM (≥30% reduction) compared to placebo [1.2 mg

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(34.3%; p = 0.0001); 1.8 mg (42.9%; p < 0.0001); placebo (3.3%)]. Similarly, a greater percentage of patients receiving either dose of pemvidutide achieved concurrent responses in two markers of fibrosis improvement, ELF score (≥ 0.5 reduction) and LSM (≥ 30% reduction) compared to placebo [1.2 mg (27.8%; p = 0.0003); 1.8 mg (32.4%; p < 0.0001); placebo (3.2%)]. In a more stringent analysis of concurrent responses in LFC (≥ 50% reduction), ELF score (≥ 0.5 reduction), and LSM (≥ 30% reduction), pemvidutide also resulted in a higher percentage of patients achieving a response compared to placebo [1.2 mg (17.1%; p = 0.0018); 1.8 mg (25.8%; p < 0.0001); placebo (0.0%)]. **Conclusion:** Pemvidutide treatment led to statistically significant increases in the percentage of patients achieving concurrent responses in multiple NITs of MASH improvement and hepatic fibrosis at 48 weeks.

Composite Endpoint	1.2 mg pemvidutide	1.8 mg pemvidutide	placebo
Reductions ≥30% LFC + ≥17 IU/L ALT + ≥30% LSM	12/35 (34.3%)	30/70 (42.9%)	2/60 (3.3%)
p-value vs. placebo	0.0001	<0.0001	--
Reductions ≥0.5 ELF + ≥30% LSM	10/36 (27.8%)	22/68 (32.4%)	2/63 (3.2%)
p-value vs. placebo	0.0003	<0.0001	--
Reductions ≥30% LFC + ≥0.5 ELF + ≥30% LSM	6/35 (17.1%)	17/66 (25.8%)	0/59 (0.0%)
p-value vs. placebo	0.0018	<0.0001	--

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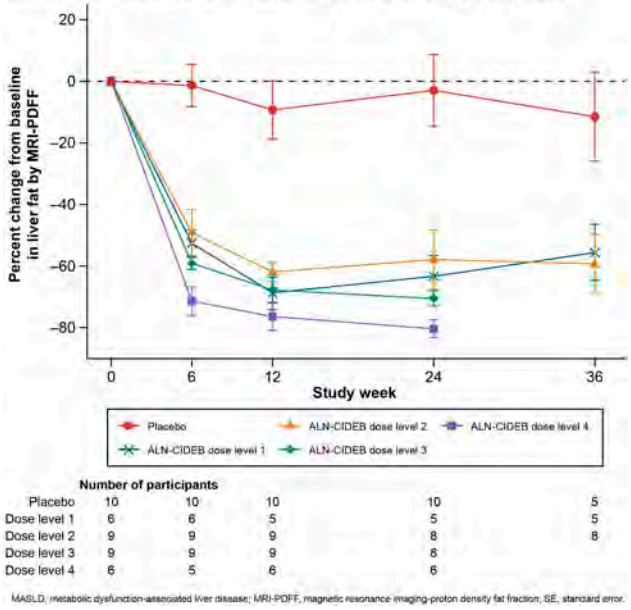
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0064 | LIVER-DIRECTED RNA INTERFERENCE TARGETING CELL DEATH-INDUCING DFFA-LIKE EFFECTOR B (*CIDEB*) NORMALIZES LIVER FAT AND LOWERS SERUM TRANSAMINASE LEVELS IN METABOLIC DYSFUNCTION-ASSOCIATED LIVER DISEASE (MASLD)

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Background: The Regeneron Genetics Center discovered that loss-of-function variants in *CIDEB*, which encodes a structural protein of hepatic lipid droplets, are associated with a profound reduction in the risk of steatotic liver disease and cirrhosis. Nonclinical models corroborate these findings, with *CIDEB* knockdown reducing hepatic steatosis, inflammation, and fibrosis in murine metabolic dysfunction-associated steatohepatitis (MASH). We hypothesized that therapeutic suppression of hepatic *CIDEB* expression would reduce liver fat and improve markers of liver disease in people with MASLD. **Methods:** In the phase 1 portion of an ongoing randomized, double-blind, placebo-controlled, phase 1/2a trial (NCT06836609), adults with MASLD and baseline liver fat content $\geq$8.5% by magnetic resonance imaging-proton density fat fraction (MRI-PDFF) were randomized (3:1) to receive single ascending doses of ALN-CIDEB—a subcutaneously administered, liver-targeted small interfering RNA (siRNA) designed to reduce hepatic *CIDEB* messenger RNA expression—or placebo. The primary endpoint was incidence and severity of treatment-emergent adverse events (TEAEs). Key pharmacodynamic endpoints included change from baseline in liver fat content by MRI-PDFF and serum transaminase levels. **Results:** Interim data from 47 participants are reported. ALN-CIDEB was well tolerated at all dose levels. All TEAEs were mild or moderate in severity except for one serious TEAE of hyperglycemia that was graded severe but not attributed to the study drug by the investigator. Across all dose levels, ALN-CIDEB resulted in rapid, profound, and durable reductions in liver fat vs placebo. At Week 12, mean reductions from baseline reached approximately 70% (Figure), with mean liver fat content near or below the upper limit of normal (5%) for all dose levels. Treatment effects were sustained through 24 weeks of follow-up. At Week 12, mean serum alanine aminotransferase levels declined from baseline by 18–35% across ALN-CIDEB dose levels, consistent with attenuation of hepatocellular injury. **Conclusion:** In this first-in-human trial of a first-in-class liver-specific siRNA targeting *CIDEB*, a single dose of ALN-CIDEB was well tolerated and rapidly and sustainably normalized liver fat, accompanied by improvements in serum transaminases. Concordant with human genetics data and nonclinical MASH models, these findings support the continued clinical development of hepatic *CIDEB* knockdown as a therapeutic strategy for MASH.

Figure. Mean percent change (+/−SE) from baseline in liver fat by MRI-PDFF over time in participants with MASLD after a single dose of ALN-CIDEB or placebo



Number of participants

Placebo	10	10	10	10	5
Dose level 1	6	6	5	5	5
Dose level 2	9	9	9	8	8
Dose level 3	9	9	9	8	
Dose level 4	6	5	6	6	

MASLD, metabolic dysfunction-associated liver disease; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; SE, standard error.

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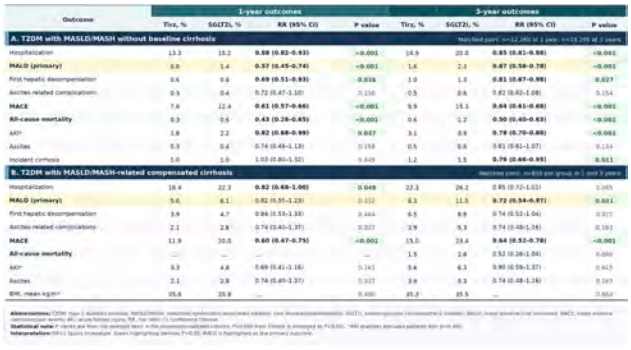
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0065 | STAGE-STRATIFIED COMPARATIVE EFFECTIVENESS OF TIRZEPATIDE VERSUS SGLT2 INHIBITORS IN TYPE 2 DIABETES (T2DM) ON MAJOR ADVERSE LIVER OUTCOMES (MALO) AND MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE) WITH MASLD/MASH

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Background: Tirzepatide and SGLT2 inhibitors (SGLT2i) are increasingly used in T2DM with MASLD/MASH, but comparative outcomes across liver-disease stage remain uncertain. We compared 1- and 3-year hepatic, cardiovascular, hospitalization, kidney, and mortality outcomes after tirzepatide versus SGLT2i initiation in noncirrhotic MASLD/MASH and MASLD/MASH-related compensated cirrhosis. **Methods:** TriNetX Research Network data from 110 health care organizations were used to identify adults with T2DM and MASLD/MASH initiating tirzepatide or SGLT2i on/after June 1, 2022. Mutually exclusive cohorts were noncirrhotic disease and compensated cirrhosis, defined by cirrhosis codes without prior ascites, variceal bleeding, encephalopathy, jaundice/hepatic failure, hepatorenal syndrome, spontaneous bacterial peritonitis, or malignant ascites. Exclusions included prior comparator exposure, competing liver disease, malignancy, transplant, ESRD/dialysis, HIV, and baseline decompensation; baseline cirrhosis was excluded from the noncirrhotic cohort. Groups were 1:1 propensity-score matched on demographics, comorbidities, medications, and labs. Primary outcome was MALO (decompensation-related events, HCC, transplant, or death); secondary outcomes included hospitalization, first decompensation, ascites-related complications, MACE, mortality, AKI, and incident cirrhosis. **Results:** In noncirrhotic MASLD/MASH, 12,260 pairs were matched at 1 year and 18,291 at 3 years. Tirzepatide was associated with lower 1-year MALO (0.8% vs 1.4%; RR 0.57; $P < 0.001$), hospitalization (13.3% vs 15.2%; RR 0.88; $P < 0.001$), MACE (7.6% vs 12.4%; RR 0.61; $P < 0.001$), mortality (0.3% vs 0.6%; RR 0.43; $P < 0.001$), and AKI (1.8% vs 2.2%; RR 0.82; $P = 0.037$). At 3 years, lower MALO (1.6% vs 2.3%; RR 0.67; $P < 0.001$), MACE (9.9% vs 15.3%; RR 0.64; $P < 0.001$), mortality (0.6% vs 1.2%; RR 0.50; $P < 0.001$), AKI (3.1% vs 3.9%; RR 0.78; $P < 0.001$), and incident cirrhosis (1.2% vs 1.5%; RR 0.79; $P = 0.011$) persisted, without increased ascites. In compensated cirrhosis (816 pairs), tirzepatide was associated with lower 1-year hospitalization (18.4% vs 22.3%; RR 0.82; $P = 0.049$) and MACE (11.9% vs 20.0%; RR 0.60; $P < 0.001$). At 3 years, tirzepatide was associated with lower MALO (8.3% vs 11.5%; RR 0.72; $P = 0.031$) and MACE (15.0% vs 23.4%; RR 0.64; $P < 0.001$), with no excess AKI or ascites-related outcomes. **Conclusion:** In this large stage-stratified active-comparator study of T2DM with MASLD/MASH, tirzepatide initiation was associated with lower hepatic and cardiometabolic events in noncirrhotic disease and lower MACE plus 3-year MALO in compensated cirrhosis, without ascites-related harm. Prospective studies should confirm integrated liver and cardiometabolic risk reduction across MASLD/MASH severity.



Outcome	1-year outcomes				3-year outcomes			
	Tirz, %	SGLT2i, %	RR (95% CI)	P value	Tirz, %	SGLT2i, %	RR (95% CI)	P value
A. T2DM with MASLD/MASH without baseline cirrhosis								
Hospitalization	13.3	15.2	**0.88 (0.82–0.93)**	<0.001	18.9	20.8	**0.85 (0.81–0.88)**	<0.001
MALO (primary)	0.8	1.4	**0.57 (0.45–0.74)**	<0.001	1.6	2.3	**0.67 (0.58–0.78)**	<0.001
First hepatic decompensation	0.6	0.8	**0.69 (0.51–0.93)**	0.016	1.0	1.3	**0.81 (0.67–0.98)**	0.027
Ascites-related complications	0.5	0.4	0.72 (0.47–1.10)	0.130	0.5	0.6	0.82 (0.62–1.08)	0.154
MACE	7.6	12.4	**0.61 (0.57–0.66)**	<0.001	9.9	15.3	**0.64 (0.61–0.68)**	<0.001
All-cause mortality	0.3	0.6	**0.43 (0.28–0.65)**	<0.001	0.6	1.2	**0.50 (0.40–0.63)**	<0.001
AKI*	1.8	2.2	**0.82 (0.68–0.99)**	0.037	3.1	3.9	**0.78 (0.70–0.88)**	<0.001
Ascites	0.3	0.4	0.74 (0.48–1.13)	0.158	0.5	0.6	0.81 (0.61–1.07)	0.134
Incident cirrhosis	1.0	1.5	1.03 (0.80–1.32)	0.849	1.2	1.5	**0.79 (0.66–0.95)**	0.011
B. T2DM with MASLD/MASH-related compensated cirrhosis								
Hospitalization	18.4	22.3	**0.82 (0.68–1.00)**	0.049	22.3	26.2	0.85 (0.72–1.01)	0.065
MALO (primary)	5.6	8.1	0.82 (0.55–1.23)	0.332	8.3	11.5	**0.72 (0.54–0.97)**	0.031
First hepatic decompensation	3.9	4.7	0.84 (0.53–1.33)	0.464	6.5	8.9	0.74 (0.52–1.04)	0.077
Ascites-related complications	2.1	2.8	0.74 (0.40–1.37)	0.327	2.9	5.3	0.54 (0.30–1.00)	0.047
MACE	11.9	20.0	**0.60 (0.47–0.75)**	<0.001	15.0	23.4	**0.64 (0.52–0.78)**	<0.001
All-cause mortality	—	—	—	—	1.9	2.8	0.52 (0.26–1.04)	0.060
AKI*	3.3	4.8	0.69 (0.41–1.16)	0.161	5.6	8.3	0.80 (0.59–1.07)	0.123
Ascites	2.1	2.8	0.74 (0.40–1.37)	0.337	3.9	5.3	0.74 (0.48–1.14)	0.167
BMI, mean kg/m²	35.8	35.9	—	0.880	35.2	35.5	—	0.864

Abbreviations: T2DM, type 2 diabetes mellitus; MASLD/MASH, steatotic dysfunctional associated liver disease/steatohepatitis associated liver disease; MALO, major adverse liver outcomes; MACE, major adverse cardiovascular events; AKI, acute kidney injury; RR, risk ratio; CI, confidence interval.
Statistical note: P values are from risk-ratio tests in the propensity-matched cohorts. Pairs were formed 1:1 unweighted by PS (0.02). *AKI analyses excluded patients with prior AKI.
Interpretation: Of 11 figures (1 primary, 10 secondary), 7 were significant at P < 0.05; MALO is highlighted as the primary outcome.

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Cima Science: Consultant, Celaris: Consultant, GSK: Advisor.

0066 | EFRUXIFERMIN DRIVES MULTIDIMENSIONAL HISTOLOGIC IMPROVEMENT IN COMPENSATED CIRRHOSIS: AN AI-BASED ANALYSIS FROM THE SYMMETRY RANDOMIZED CONTROLLED TRIAL

Mazen Noureddin[1] Jörn Schattenberg[2] Vlad Ratziu[3] Ylaine Gerardin[4] Alyson Warr[4] Jacqueline Brosnan-Cashman[4] Doreen Chan[5] Erik Tillman[5] Reshma Shringarpure[5] Mary Rinella[6], [1]Houston Methodist Hospital, [2]Saarland University Medical Center, Saarland University, Homburg, Germany, [3]Service D' Hepatogastroenterologie (FR), [4]PathAI, [5]Akero Therapeutics, a Novo Nordisk Company, [6]The University of Chicago

Background: In the Phase 2b SYMMETRY trial (NCT05039450) in participants with compensated cirrhosis (F4c) due to MASH, efruxifermin (EFX) significantly improved fibrosis by conventional pathology at 96 weeks. To further explore EFX- and time-dependent changes in liver histopathology in F4c MASH beyond categorical, semi-quantitative CRN scores, we conducted a retrospective analysis of SYMMETRY utilizing two AI-powered tools, LiverExplore* and AIM-MASH+*. **Methods:** The analysis comprised N = 154 SYMMETRY participants with available baseline, week 36 (w36) and week 96 (w96) liver biopsies from the placebo (Pbo), 28 mg EFX (EFX28), or 50 mg EFX (EFX50) study arms. Paired H&E- and trichrome-stained slides were analyzed with AIM-MASH+, which provides sub-ordinal, continuous NAS (cNAS) and fibrosis (cFib) scores. H&E slides were also analyzed with LiverExplore to quantify liver histology features, such as fibrosis and cell type proportions. For each EFX arm and timepoint, changes in cNAS and cFib scores and feature fold-changes were compared to Pbo using ANCOVA. **Results:** AIM-MASH+ revealed EFX effects on continuous NAS and fibrosis scores (Fig. 1A). At w36, cNAS decreased by 1.7 points from baseline in EFX28 and 1.6 in EFX50 compared to -0.3 in Pbo ($p < 0.001$). Early (w36) trends towards improvement in cFib (-0.2 in EFX28 and -0.1 in EFX50, vs 0.01 in Pbo) expanded at w96 to significant reductions of 0.4 in both EFX28 and EFX50, compared to 0.1 in Pbo ($p = 0.01$ and $p = 0.002$, respectively). The expansion of antifibrotic effects was further corroborated by LiverExplore: reductions in total fibrosis and component patterns increased in magnitude from w36 to w96 for EFX28 and EFX50 (Fig. 1B). Notably, at w96, advanced (complete septal and nodular) fibrosis decreased from baseline by 42% in EFX28 and 48% in EFX50, compared to -16% in Pbo ($p = 0.02$ and $p = 0.003$, respectively). Steatotic and ballooned hepatocytes were also significantly decreased across EFX doses at both timepoints, accompanied by increased normal hepatocytes. **Conclusion:** AI-powered histology analyses of SYMMETRY revealed significant reductions in subordinal, continuous histopathologic scores, as well as decreased prevalence of specific fibrosis subtypes. Combined with reduced steatotic and ballooned hepatocytes and increased normal hepatocytes, these results support the improvements in histology and non-invasive metrics of fibrosis and liver injury observed with EFX treatment in F4c MASH. *For Research Use Only. Not for use in diagnostic procedures.

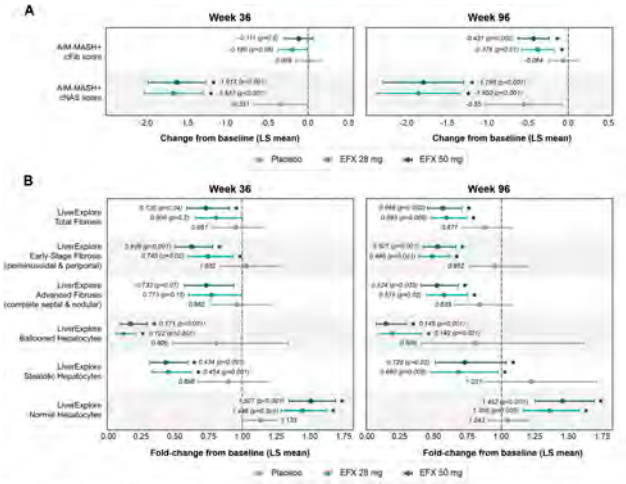


Figure 1. ANCOVA results for AIM-MASH+ continuous scores (A) and LiverExplore features (B). Point estimates and 95% confidence intervals are shown. In (B), fibrosis features represent the fraction of total evaluable tissue area belonging to each fibrosis class, and hepatocyte features represent the proportion of total cells belonging to each cell class. All p-values are for nominal difference between treatment arm and placebo; stars indicate $p<0.05$. EFX: efruxifermin; LS: least squares; cFib: continuous fibrosis score; cNAS: continuous NAS score.

Disclosures: Mazen Noureddin:Akero: Advisor, Alligos: Advisor, Altimmune: Advisor, AstraZeneca: Advisor, Boehringer Ingelheim: Advisor, Boston Pharma: Advisor, Cytodyn: Advisor, GSK: Advisor, Lilly: Advisor, Madrigal: Advisor, Merck: Advisor, Novo Nordisk: Advisor, Sagimet: Advisor, Terns: Advisor, Takeda: Advisor, Akero: Principal Investigator, Allergan: Principal Investigator, Altimmune: Principal Investigator, Boehringer Ingelheim: Principal Investigator, Bristol Myers Squibb: Principal Investigator, Boston Pharma: Principal Investigator, Conatus: Principal Investigator, Corcept: Principal Investigator, Galectin: Principal Investigator, Genfit: Principal Investigator, GSK: Principal Investigator, Kowa: Principal Investigator, Enanta: Principal Investigator, Madrigal: Principal Investigator, Lilly: Principal Investigator, Merck: Principal Investigator, Novartis: Principal Investigator, Novo Nordisk: Principal Investigator, Rivus: Principal Investigator, Shire: Principal Investigator, Takeda: Principal Investigator, Terns: Principal Investigator, Viking: Principal Investigator, Zydus: Principal Investigator, Rivus: Stock – privately held company, Cytodyn: Stock - publicly traded company, ChronWell: Stock – privately held

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★ 0067 | GLP-1 RECEPTOR AGONIST USE AFTER LIVER TRANSPLANTATION IN MASH OR METABOLIC-RISK RECIPIENTS IS ASSOCIATED WITH IMPROVED SURVIVAL AND RENAL PROTECTION: A THREE-CENTER COHORT STUDY

Zhihao Li[1] Kai-Philipp Seeger[1] Jie Na[1] Randi Ryan[1] Alexander Cortez[1] Tayyab Diwan[1] Timucin Taner[2] Kymberly Watt[1] Amit Mathur[3] Blanca Lizaola-Mayo[1] David Chascsa[3] Dana Perry[4] Liu Yang[1] Julie Heimbach[2], [1]Mayo Clinic, [2]Mayo Clinic Rochester, [3]Mayo Clinic Arizona, [4]Mayo Clinic Florida

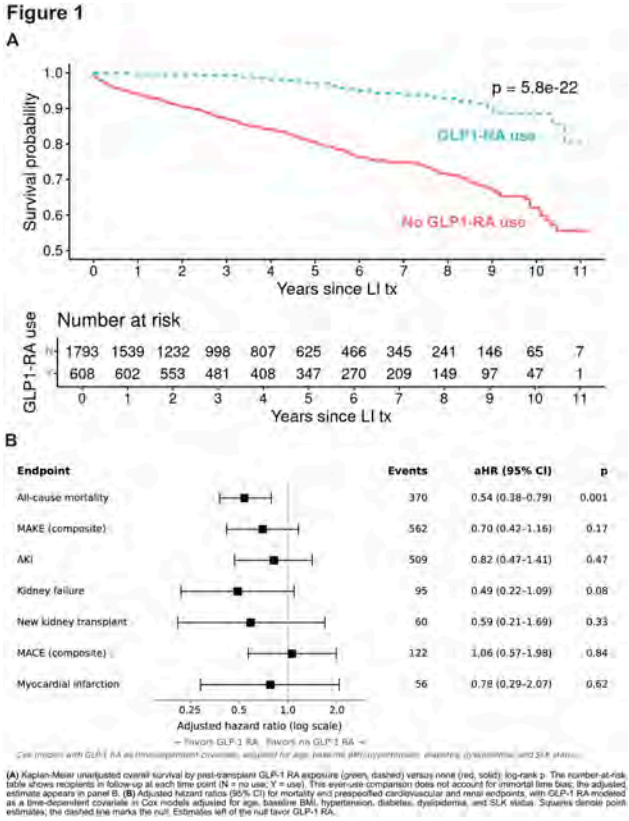
Background: Metabolic dysfunction-associated steatohepatitis (MASH) is now a leading indication for liver

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transplantation in the United States, and recipients with MASH or cardiometabolic comorbidities remain at substantial risk for cardiovascular events and chronic kidney disease driven by persistent cardiometabolic dysfunction and calcineurin inhibitor exposure. GLP-1 receptor agonists (RA) improve glycemic control, weight, and cardiorenal outcomes in non-transplant populations. However, whether posttransplant GLP-1 RA use confers survival or renal benefit in this transplant population remains undefined. **Methods:** We conducted a retrospective cohort study of adult liver transplant recipients across three Mayo Clinic sites (2015–2025) with MASH or cirrhosis with diabetes or BMI > 30. Simultaneous liver-kidney (SLK) recipients were retained; peri-operative deaths were excluded. GLP-1 RA exposure was modeled as a time-dependent covariate, with separate terms for pre- and post-transplant initiation to address immortal time bias. The primary endpoint was overall survival; secondary endpoints were major adverse kidney events (MAKE; ≥ 40% eGFR decline, CKD G5, dialysis, or kidney transplant) and major adverse cardiovascular events (MACE; myocardial infarction or stroke). Multivariable Cox models adjusted for age, baseline BMI, hypertension, diabetes, dyslipidemia, and SLK status. Longitudinal lipid and HbA1c trajectories were modeled with linear mixed-effects regression on log-transformed values, separating effects of treatment initiation from cumulative exposure. **Results:** Among 2,401 MASH or metabolic-risk liver transplant recipients (median age 61, 66% male, MELD 20), 608 (25%) initiated GLP-1 RA post-transplant at a median 2.5 years after transplantation; baseline BMI was higher in initiators (32.9 vs 31.7, p < 0.001). Over a median follow-up of 4.0 years, 370 deaths, 562 MAKE, and 122 MACE events occurred. Kaplan-Meier analysis demonstrated superior unadjusted survival among GLP-1 RA users (log-rank p < 0.001, Fig.1A). In time-dependent Cox models, post-transplant GLP-1 RA exposure was associated with a 46% reduction in all-cause mortality (aHR 0.54, 95% CI 0.38–0.79, p = 0.001). A trend toward protection was observed for kidney failure (aHR 0.49, 95% CI 0.22–1.09, p = 0.08) and overall MAKE (aHR 0.70, 95% CI 0.42–1.16, p = 0.17), while no association was seen with MACE (aHR 1.06, 95% CI 0.57–1.98, p = 0.84) or AKI (aHR 0.82, p = 0.47, Fig.1B). LDL was 8% lower on treatment (p < 0.001), and HbA1c showed progressive improvement with longer exposure (interaction p = 0.008). **Conclusion:** In MASH or metabolic-risk liver transplant recipients, post-transplant GLP-1 RA use was associated with substantially improved survival, a trend toward renal protection, and favorable lipid and glycemic trajectories. Validation of these results with external health system data will be a valuable next step.

Figure 1



(A) Kaplan-Meier unadjusted overall survival by post-transplant GLP-1 RA exposure (green, dashed) versus none (red, solid); log-rank p. The number-at-risk table shows recipients in follow-up at each time point (N = no use; Y = use). This ever-use comparison does not account for immortal time bias; the adjusted estimate appears in panel B. (B) Adjusted hazard ratios (95% CI) for mortality and prespecified cardiovascular and renal endpoints, with GLP-1 RA modeled as a time-dependent covariate in Cox models adjusted for age, baseline BMI, hypertension, diabetes, dyslipidemia, and SLK status. Squares denote point estimates; the dashed line marks the null. Estimates left of the null favor GLP-1 RA.

Disclosures: Zhihao Li:Nothing to Disclose, Kai-Philipp Seeger:Nothing to Disclose, Jie Na:Nothing to Disclose, Randi Ryan:Nothing to Disclose, Alexander Cortez:Nothing to Disclose, Tayyab Diwan:Nothing to Disclose, Timucin Taner:Nothing to Disclose, Kymberly Watt:Madrigal: Stock - publicly traded company, Viking: Stock - publicly traded company, Novo Nordisk: Speaking and Teaching, Amit Mathur:Nothing to Disclose, Blanca Lizaola-Mayo:Nothing to Disclose, David Chascsa:Nothing to Disclose, Dana Perry:Nothing to Disclose, Liu Yang:Nothing to Disclose, Julie Heimbach:Nothing to Disclose.

0068 | BUTTERMILK SUPPLEMENTATION AMELIORATES HEPATIC STEATOSIS IN METABOLIC DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE

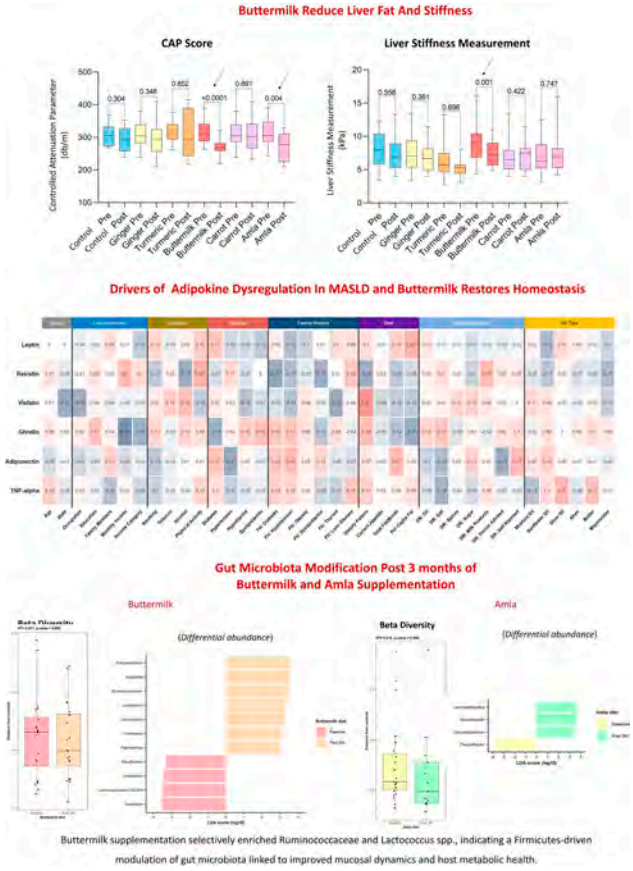
Vibhuti Jakhmola[1] Sukriti Baweja[2] Aduonuo Ziephru[1] Ashmit Mittal[2] Shiv Kumar Sarin[2], [1]Institute of Liver and Biliary Sciences, [2]Institute of Liver and Biliary Sciences, New Delhi, India

Background: MASLD is a rapidly progressive metabolic disorder with limited effective therapeutics. Known

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to be driven by hepatic steatosis, adipokine dysregulation, and gut-liver axis dysfunction. Although dietary modification is central to MASLD management, the therapeutic potential of specific food items remains unclear. We evaluated the potential of specific functional foods in management of MASLD. **Methods:** Patients with clinically confirmed MASLD n = 216 {CAP > 250; LSM < 10}; were enrolled and randomized into five dietary supplementation groups (n = 32 each group); buttermilk, amla, turmeric, carrot and ginger. Twentyone placebo served as controls. All subjects underwent pre- and post-intervention laboratory tests, serum adipokine measurements, anthropometry and Fibroscan for estimation of hepatic fat by controlled attenuation parameter (CAP) and liver fibrosis by liver stiffness measurement (LSM). They were advised exercise and lifestyle alterations. Gut microbiome profiling via 16S rRNA sequencing was performed. **Results:** At baseline, MASLD patients exhibited significantly impaired hepatic, metabolic, and anthropometric parameters($p < 0.0001$) compared to controls. Among the dietary interventions after 3 months, buttermilk supplementation produced the most comprehensive therapeutic effects, improving CAP score($p = 0.0004$), transaminases($p < 0.05$), triglycerides and cholesterol ($p < 0.05$). Buttermilk was the only intervention to suppress leptin, resistin, visfatin(all $p < 0.001$), and TNF-α ($p = 0.0002$), while significantly increasing adiponectin($p < 0.0001$) and ghrelin($p = 0.0002$), reflecting broad adipokine axis restoration. Amla supplementation also showed significant reduction in CAP ($p = 0.0001$), and liver enzymes ($p < 0.05$), with increase in ghrelin levels ($p = 0.037$). Ginger and carrot interventions produced selective reductions in leptin and visfatin ($p < 0.05$), whereas turmeric lowered serum triglyceride levels ($p = 0.035$). Post buttermilk and amla microbiome profiling revealed significant inter-group beta diversity divergence($p = 0.001$). Buttermilk selectively enriched short-chain fatty acid–producing taxa, including Ruminococcaceae and Lactococcus spp., while depleting dysbiosis-associated genera such as Clostridium and Desulfovibrio ($p < 0.001$). PICRUSt functional annotation revealed enrichment of N-glycan biosynthesis pathways. Similarly, amla enriched Lacticaseibacillus and reduced Flavonifractor abundance than controls. **Conclusion:** This is the first study to reveal the functional benefits of natural food products in MASLD. Our data provides a catalogue from which specific food items singularly or in combination can be used in MASLD patients. Buttermilk supplementation, enriched in probiotics, acts through N-glycan biosynthesis mediated gut microbial restoration, positioning it as a promising dietary intervention for MASLD management.



Disclosures: Vibhuti Jakhmola:Nothing to Disclose, Sukriti Baweja:Nothing to Disclose, Aduonuo Ziephru: Nothing to Disclose, Ashmit Mittal:Nothing to Disclose, Shiv Kumar Sarin:Nothing to Disclose.

0069 | STRUCTURED LIFESTYLE INTERVENTION BASED ON COGNITIVE-BEHAVIORAL THERAPY PRINCIPLES REDUCES HEPATIC STEATOSIS AND IMPROVES METABOLIC PARAMETERS IN PATIENTS WITH MASLD: PRELIMINARY RESULTS OF A RANDOMIZED CONTROLLED STUDY

Vaclav Smid[1] Jakub Klevar[1] Frantisek Novak[1] Marie Rysankova[1] Lukas Lambert[1] Iva Malkova[2] Libor Vitek[3] Radan Bruha[4], [1]General University Hospital and First Faculty of Medicine, [2]STOB Prague, [3]General University Hospital in Prague, [4]Charles University in Prague, 1st Faculty of Medicine

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Background: Although new pharmacological therapies for MASLD are becoming available, lifestyle modification remains a necessary component of treatment and a prerequisite for optimal therapeutic outcomes. Therefore, it is essential to identify effective and sustainable ways to implement these changes in clinical practice. We hypothesize that individualized counselling focused on lifestyle modification, based on cognitive-behavioral therapy (CBT) principles and expert nutritional intervention, will reduce hepatic steatosis and improve non-invasive markers of liver disease in patients with metabolic syndrome and MASLD. **Methods:** During the 12-month study, patients were randomized to either a standard-of-care group or an intensive lifestyle intervention group. Fifty patients were enrolled in a specialized program based on CBT principles, including mindfulness-based approaches. Under expert supervision, participants were encouraged to modify their dietary and physical activity habits, both of which were assessed before and after the intervention. The control group consisted of fifty patients receiving standard hepatological care, including regular outpatient follow-up and standard recommendations regarding weight loss and lifestyle modification. During the one-year follow-up, all patients underwent repeated assessments including anthropometric measurements, bioimpedance analysis, biochemical testing, transient elastography for liver stiffness measurement, and nuclear magnetic resonance spectroscopy. The study is registered at ClinicalTrials.gov (NCT05816915). **Results:** In patients who have already completed the 12-month intervention (n = 37), a statistically significant reduction in hepatic fat content was observed in the intervention group compared with the control group (6.1% vs. 1.4%, $p < 0.05$). The reduction in hepatic fat was accompanied by a significant decrease in the FAST score, reaching values below the 0.35 cutoff. Significant improvements were also observed in liver enzyme levels (ALT decreased from 45.2 ± 16 to 35.2 ± 10 U/L, $p < 0.05$) and glucose metabolism parameters (glucose decreased from 6.52 ± 1.8 to 5.29 ± 0.45 mmol/L, $p < 0.05$; insulin decreased from 21.54 ± 6.3 to 14.74 ± 4.5 mIU/L, $p < 0.01$). In contrast, no significant changes in ALT, glucose metabolism parameters, hepatic fat content, or FAST score were observed in the control group (n = 28). **Conclusion:** Our preliminary results suggest that an intensive lifestyle intervention based on CBT principles and nutritional counselling may significantly improve hepatic steatosis, liver enzyme levels, and glucose metabolism in patients with MASLD and metabolic syndrome. These findings further support structured lifestyle modification as a key component of MASLD management. Supported by: MH CZ – DRO – VFN00064165 and by AZV MHCZ NU23-01-00288.

Disclosures: Vaclav Smid:Nothing to Disclose, Jakub Klevar:Nothing to Disclose, Frantisek Novak:Nothing to Disclose, Marie Rysankova:Nothing to Disclose, Lukas Lambert:Nothing to Disclose, Nothing to Disclose, Iva Malkova:Nothing to Disclose, Libor Vitek:Nothing to Disclose, Radan Bruha:Nothing to Disclose.

0070 | SEMAGLUTIDE AND FIBROSIS PROGRESSION IN MASLD: A TARGET TRIAL EMULATION COMPARING SEMAGLUTIDE VERSUS DPP-4 INHIBITORS IN A NATIONAL COHORT

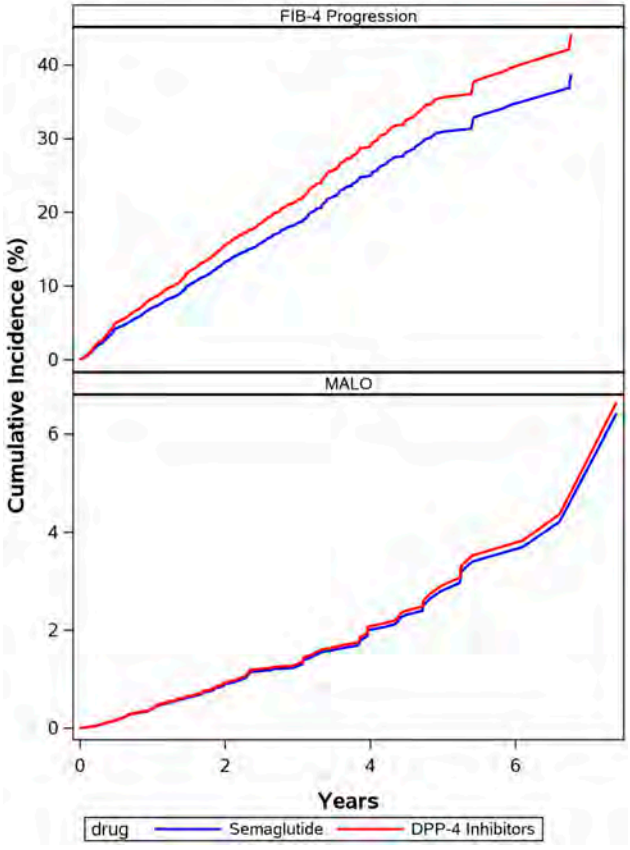
Binu John[1] Samuel Soon[2] Bassam Dahman[2], [1]University of Miami and Miami VA, [2]Virginia Commonwealth University

Background: Semaglutide is approved for the treatment of metabolic dysfunction-associated steatohepatitis (MASH) with stage 2-3 fibrosis; However, its effect on liver fibrosis progression across the broader spectrum of metabolic dysfunction-associated steatotic liver disease (MASLD) without established advanced fibrosis remains poorly defined. remains unclear. We aimed to examine the association between semaglutide and the risk of fibrosis progression and major adverse liver outcomes (MALO) relative to DPP-4 inhibitors (DPP4i) in a large national Veterans cohort. **Methods:** This was an active comparator, new-user target trial emulation study of adults from Veteran's Health Administration comparing new users of Semaglutide and DPP4i in patients with MASLD between 9/5/17 and 10/14/25. Adults with MASLD, identified by steatosis on imaging via validated natural language processing combined with at least one cardiometabolic risk factor and absence of harmful alcohol use, who initiated semaglutide or a DPP4i with baseline FIB-4 < 2.67 were eligible. Groups were balanced on baseline characteristics using inverse probability of treatment weighting (IPTW). The primary outcome was fibrosis progression, defined as transition from low or intermediate (FIB-4 < 2.67) to high fibrosis risk (FIB-4 > 2.67), confirmed on two separate measurements obtained 3-12 months apart. The secondary outcome was MALO, defined as the composite of hepatocellular carcinoma, decompensation, liver transplantation, or liver-related death. Progression-free survival was modeled using multivariable Fine and Gray competing risk incorporating IPTW adjustment. Patients were followed from treatment initiation until discontinuation, treatment switching, death, or loss to follow-up; FIB-4 progression analyses were additionally censored at the last available measurement. **Results:** A total of 14,182 semaglutide and 7,678 DPP4i initiators were identified (median age 64.2 years [IQR 17.2]; 86.1%

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male). Median treatment duration was 1.2 years (IQR 1.4) for semaglutide versus 1.1 years (IQR 1.6) for DPP4i. Fibrosis progression occurred in 1,715 participants (7.0%) and MALO in 228 (1.0%). Semaglutide was associated with a significantly reduced hazard of FIB-4 progression compared to DPP4i (aHR 0.84 [95% CI 0.78–0.90]; $p < 0.0001$). No statistically significant differences in MALO was observed. **Conclusion:** In this large national target trial emulation, semaglutide was associated with a 16% reduction in fibrosis progression risk compared to DPP4i among MASLD patients without advanced fibrosis at baseline. The absence of a significant MALO difference likely reflects insufficient follow-up duration and low event rates rather than a true null effect. Longer-term real-world studies are needed to determine whether semaglutide-mediated fibrosis attenuation translates into reduced liver-related morbidity and mortality in MASLD.



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★ 0071 | IMPACT OF MULTIDISCIPLINARY CARE ON LONGITUDINAL ALT OUTCOMES IN CHILDREN WITH MASLD

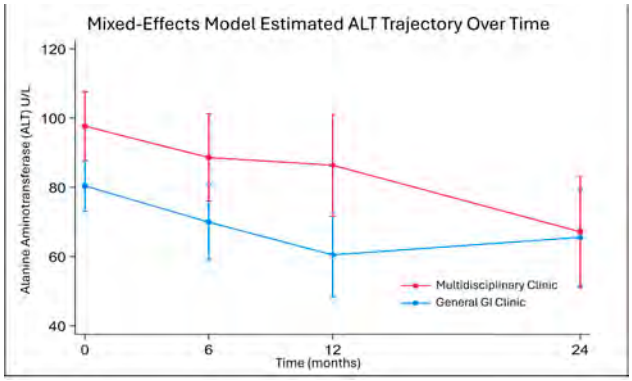
Brandon Perumpail[1] Sarah Abu-Alreesh[2] Andrea Tou[3] Jennifer Panganiban[4], [1]Children's Hospital of Philadelphia, [2]Al Jalila Children's Hospital, [3]Children's Hospital of Philadelphia, [4]The Children's Hospital of Philadelphia

Background: Lifestyle intervention remains the cornerstone of pediatric metabolic dysfunction-associated steatotic liver disease (MASLD) therapy. In children receiving standard of care (SOC) lifestyle advice only 22% of patients at 1 year and 31% after 2 years had improved. Multidisciplinary care models for MASLD have been strongly endorsed by expert opinion and guidelines, yet there are no pediatric studies directly comparing multidisciplinary care to SOC and long-term outcomes remain unclear. **Methods:** Retrospective longitudinal cohort study of children in a tertiary care center, aged 3-20 years with serial alanine aminotransferase (ALT) measurements who were managed in either a multidisciplinary (MM) clinic lead by a gastroenterologist, dietician, and activity specialist with obesity expertise versus a general gastroenterology (GG) clinic from 2016-2026. Baseline and longitudinal ALT trends were evaluated including usage of mixed-effects models adjusting for age, sex, and race/ethnicity at 6, 9, 12, and 24 months after first visit. **Results:** A total of 209 patients were included in the MM cohort (mean age 13.2 years; 73% male; 38% Hispanic) and 378 in the GG cohort (mean age 12.2 years; 61% male; 22% Hispanic). Baseline ALT was significantly higher in the MM cohort compared with the GG cohort (101.6 vs 78.5 U/L, $p = 0.003$), and a greater proportion of MM patients had ALT > 80 U/L (47.9% vs 31.7%, $p < 0.001$). In mixed-effects models adjusting for demographic variables, ALT improvement over time was similar between cohorts, although there was a trend toward greater ALT reduction in the MM cohort at 24 months ($p = 0.15$). Adjusted mean ALT change from baseline at 24 months in the MM cohort was −30.5 U/L ($p < 0.01$) vs −12.9 U/L ($p < 0.01$) in the GG cohort; however, between-group differences were not statistically significant. In a restricted adjusted analysis of the 12- to 24-month interval, the MM cohort demonstrated a 22.3% greater ALT reduction compared with the GG cohort ($p = 0.028$), whereas ALT improvement in the GG cohort plateaued during this period.In secondary unadjusted exploratory analyses at 24 months, ALT change from baseline was -41.4 U/L ($p < 0.01$) in MM vs

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-16.5 U/L ($p < 0.01$) in GG. In both cohorts 50% achieved an ALT reduction of ≥ 17 U/L and 45% achieved a ≥ 40% reduction in ALT at 24 months (inter-group $p > 0.05$). **Conclusion:** This is the first real-world study comparing a dedicated multidisciplinary clinic to standalone general GI care in the management of pediatric MASLD. Both models improve ALT outcomes compared to baseline over 24 months. Despite higher baseline ALT levels, patients in the MM clinic demonstrated ALT reduction comparable to those in a GG clinic, with continued improvement beyond 12 months, while ALT trajectories plateaued in the GG cohort. These findings suggest multidisciplinary care models as a strategy to promote sustained biochemical improvement in the management of pediatric MASLD and warrant prospective evaluation.



Disclosures: Brandon Perumpail:Nothing to Disclose, Sarah Abu-Alreesh:Nothing to Disclose, Andrea Tou: Nothing to Disclose, Jennifer Panganiban:Madrigal: Served on a one time ad board meeting, Novo Nordisk: We have not yet met and I have not received any payment.

0072 | SEMAGLUTIDE IMPROVES LIVER HEALTH IN NON-OBESE PARTICIPANTS WITH MASH: A POST HOC ANALYSIS FROM THE PHASE 3 ESSENCE TRIAL

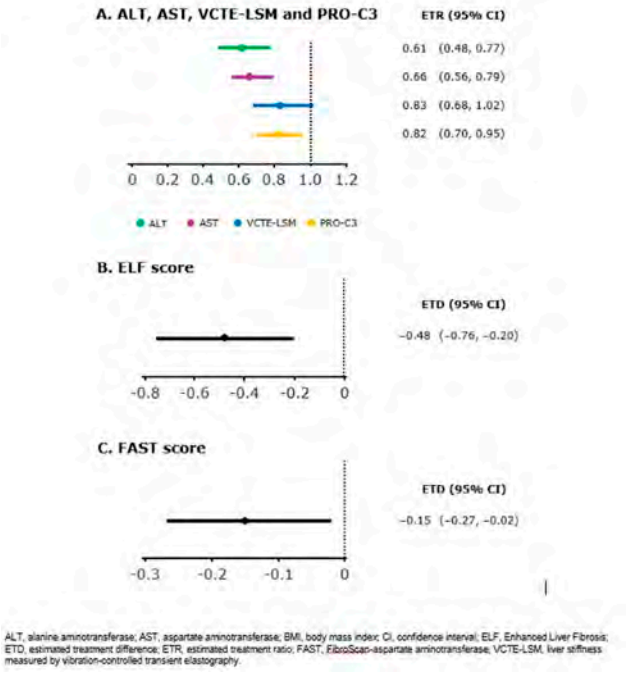
Jörn Schattenberg[1] Matthew Armstrong[2] Igor Bakulin[3] Anja Geerts[4] Jacob George[5] Ewa Janczewska[6] Niels Krarup[7] Chun-Jen Liu[8] Håvard Midgard[9] Ahsan Shoeb[7] Thea Vestergaard[7] Michael Roden[10], [1]Department of Internal Medicine II, Saarland University Medical Center, Homburg, Germany, [2]University of Birmingham, Birmingham, UK, [3]North-Western State Medical University, St Petersburgh, Moscow, Russia, [4]Department of Gastroenterology & Hepatology, University Hospital Ghent, Ghent, Belgium, [5]Westmead Hospital New South Wales, Sydney, Australia, [6]Hepatology Outpatient Clinic, ID Clinic, Mysłowice, Poland, [7]Novo Nordisk A/S, Copenhagen, Denmark, [8]Department of Internal Medicine, National Taiwan University College of Medicine, Taipei, Taiwan, [9]Department of Gastroenterology, Oslo University Hospital, Oslo, Norway, [10]Heinrich Heine University of Düsseldorf, Düsseldorf, Germany

Background: In the 72-week interim analysis of part 1 of the ongoing phase 3 ESSENCE trial (NCT04822181), once-weekly subcutaneous semaglutide 2.4 mg improved both primary histological endpoints—resolution of steatohepatitis without worsening of liver fibrosis, and improvement in liver fibrosis without worsening of steatohepatitis—in non-obese (body mass index [BMI] < 27 kg/m^2) participants with metabolic dysfunction-associated steatohepatitis (MASH) and liver fibrosis. We aimed to further explore the effects of semaglutide on liver health-related parameters in this population. **Methods:** This *post hoc* analysis evaluated changes in liver-related parameters from baseline to week 72 in the subgroup of participants with a baseline BMI of < 27 kg/m². The analysis was conducted using the same predefined endpoints and statistical methods as in the primary trial analyses. Assessments included alanine aminotransferase (ALT), aspartate aminotransferase (AST), liver stiffness measured by vibration-controlled transient elastography (VCTE-LSM), Enhanced Liver Fibrosis (ELF) score, FibroScan-AST (FAST) score, and the fibrogenesis biomarker PRO-C3. Treatment effects were reported as estimated treatment ratios (ETRs) or estimated treatment differences (ETDs) for semaglutide versus placebo. **Results:** Out of 800 randomized participants included in the interim analysis, 106 had a BMI of < 27 kg/m²: 67.9% were female, 68.9% were of Asian race, and 52.8% had type 2 diabetes, highlighting the metabolic and ethnic heterogeneity of non-obese MASH. At week 72, semaglutide treatment was associated with improvements in ALT (ETR 0.61; 95% confidence interval [CI] 0.48, 0.77), AST (ETR 0.66; 95% CI 0.56, 0.79), FAST score (ETD −0.15; 95% CI −0.27, −0.02), and VCTE-LSM (ETR 0.83; 95% CI 0.68, 1.02), compared with placebo (**Figure**). Improvements in non-invasive fibrosis biomarkers favored semaglutide over placebo for both ELF score (ETD −0.48; 95% CI −0.76, −0.20) and PRO-C3 (ETR 0.82; 95% CI 0.70, 0.95) (**Figure**), with additional improvement in cardiometabolic risk factors. **Conclusion:** In non-obese individuals with MASH and liver fibrosis, once-weekly semaglutide 2.4 mg resulted in meaningful improvements across multiple liver health-related measures after 72 weeks of treatment. These findings complement the observed histological benefits and support the potential role of semaglutide in improving disease activity and fibrosis in individuals with MASH and a BMI below 27 kg/m².

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Figure. Effects of semaglutide versus placebo on liver-related parameters at week 72 in participants with a BMI of <27 kg/m²



ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; ELF, Enhanced Liver Fibrosis; ETD, estimated treatment difference; ETR, estimated treatment ratio; FAST, FibroScan-aspartate aminotransferase; VCTE-LSM, liver stiffness measured by vibration-controlled transient elastography.

Disclosures: Jörn Schattenberg:Akero: Consultant, 89Bio: Consultant, Boehringer Ingelheim: Consultant, Ipsen: Consultant, Inventiva Pharma: Consultant, Madrigal: Consultant, Northsea Therapeutics: Consultant, Novo Nordisk: Consultant, Roche: Consultant, Siemens Healthineers: Consultant, Boehringer Ingelheim: Advisor, AGED diagnostics: Stock – privately held company, Hepta Bio: Stock – privately held company, Novo Nordisk: Speaking and Teaching, Madrigal: Stock - publicly traded company, MedPublico GmbH: Speaking and Teaching, Eli Lilly: Advisor, Altimmune: Consultant, Astra Zeneca: Consultant, Gilead Science: Consultant, Merck: Consultant, MSD Sharp & Dohme GmbH: Consultant, AbbVie: Advisor, Matthew Armstrong:Nothing to Disclose, Igor Bakulin:Nothing to Disclose, Anja Geerts:Nothing to Disclose, Jacob George:Novo Nordisk: Speaking and Teaching, novo Nordisk: Advisor, Boehringer Ingleheim: Advisor, Boehringer Ingleheim: Speaking and Teaching, Roche: Advisor, Astra Zeneca: Advisor, Gilead: Advisor, Eisai: Advisor, Ewa Janczewska:Roche: Grant/Research Support, CymaBay: Grant/Research Support, Dr. Falk: Grant/Research Support, Astrazeneca: Grant/Research Support, MSD: Grant/Research Support, Novo Nordisk: Grant/Research Support, GSK: Grant/Research Support, Janssen-Cilag: Grant/Research Support, Inventiva: Grant/Research Support, Galectin: Grant/Research Support, Caliiditas: Grant/Research Support, Niels Krarup:Novo Nordisk: Employee, Chun-Jen Liu:Nothing to Disclose, Håvard Midgard:Nothing to Disclose, Ahsan Shoeb:Novo Nordisk: Employee, Novo Nordisk: Stock - publicly traded company, Thea Vestergaard:Novo Nordisk: Employee, Michael Roden:Astra Zeneca: Speaking and Teaching, Echosens: Advisor, Boehringer Ingelheim: Grant/Research Support, Madrigal: Speaking and Teaching, MSD: Speaking and Teaching, Lilly: Advisor, Novo Nordisk: Advisor, Synlab: Speaking and Teaching.

0073 | HIGH SALT SUPPLEMENTATION OF A MASH-INDUCING DIET CAUSES LEAN MASH PHENOTYPE WITH INCREASED HEPATIC UREA CYCLE ACTIVITY AND EIF5A HYPUSINATION

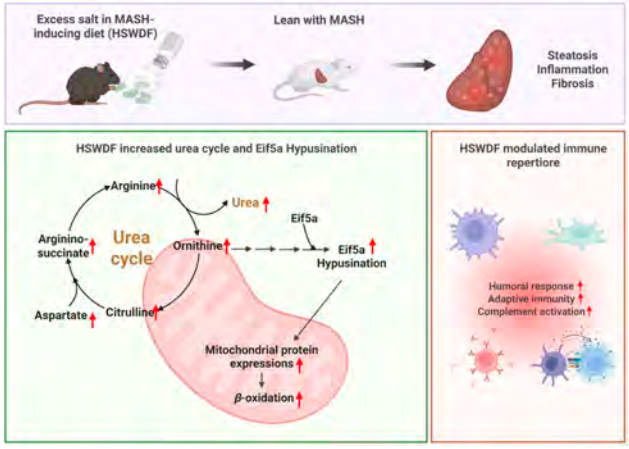
Shaopeiwen Luo[1] Norihiko Morisawa[1] anissa anindya widjaja[1] Brijesh Kumar Singh[1] Derek Hausenloy[2] Paul Yen[3] Jin Zhou[1], [1]Duke-NUS Medical School, [2]Duke-NUS Medical School; National Heart Research Institute Singapore; University College London, [3]Duke-NUS Medical School; Duke University School of Medicine; National Heart Centre Singapore

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most prevalent chronic liver disease worldwide. Metabolic dysfunction-associated steatohepatitis (MASH) is the more aggressive form of MASLD. Approximately 19% of individuals with MASLD/MASH are lean, challenging the traditional view that MASLD/MASH occurs only in obesity. Lean patients with MASLD/MASH are at higher risk for all-cause mortality and liver-related events than obese patients; however, little is known about the pathogenesis of lean MASH. Several epidemiological studies have suggested that there may be an association between high salt intake and the prevalence of lean MASH. Excess salt consumption also increases the risk of hepatic fibrosis and cirrhosis. Therefore, it is intriguing to speculate that increased high salt consumption could be an environmental factor contributing to the higher prevalence of lean MASH. **Methods:** Mouse models, biochemical assays, liver histology, qRT-PCR, Western blotting, cell cultures, targeted metabolomics, and single-cell RNA-sequencing were performed. **Results:** We previously showed that mice fed Western diet plus fructose (WDF) for 16 weeks, compared to mice fed normal chow diet (NCD), developed obesity and hepatic steatosis, inflammation and fibrosis, and decreased hypusination of the translation factor, Eif5a ($Eif5a^{H}$), which is essential for the efficient synthesis of several mitochondrial proteins that regulate mitochondrial activity and β-oxidation capacity. Here, we demonstrated these mice also decreased hepatic urea cycle activity, mitochondrial biogenesis, and β-oxidation, and increased pro-inflammatory responses than mice fed NCD. Surprisingly, high salt supplementation of WDF (HSWDF) generated mice with lean MASH phenotype

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with decreased adiposity, reduced hepatosteasis, and similar hepatic inflammation and fibrosis as mice fed WDF. Mice fed HSWDF also had improved urea cycle activity, hypusination of translation factor Eif5a (Eif5a^{H}), and β-oxidation of fatty acids than mice fed WDF which may account for the reduced hepatosteatosis seen in mice fed HSWDF.Single-cell RNA sequencing (scRNA-seq) of hepatic immune cells showed major changes in the immune profiles of mice fed HSWDF compared to WDF. We observed coordinated changes of gene expression in pathways relating to humoral immune response, adaptive immunity, and complement activation in both innate and adaptive immune cells from the liver of mice fed HSWDF compared to WDF . These additional effects were likely due to high salt intake. Treatment of RAW264.7 macrophages with additional salt with or without fat also showed increases in fibrotic and inflammatory gene expression. **Conclusion:** Our study showed for the first time that high salt intake can play a causal role in the development of lean MASH in mice . We believe that we have also generated the first model of lean MASH that is dependent upon only dietary factors.



Disclosures: Shaopeiwen Luo:Nothing to Disclose, Norihiko Morisawa:Nothing to Disclose, anissa anindya widjaja:Nothing to Disclose, Brijesh Kumar Singh:Nothing to Disclose, Derek Hausenloy:Nothing to Disclose, Paul Yen:Nothing to Disclose, Jin Zhou:Nothing to Disclose.

0074 | LONG-ACTING FGF21 ANALOGUE PEGOZAFERMIN INDUCES FIBROSIS REVERSAL AND PREVENTS HEPATOCELLULAR CARCINOMA IN A MURINE MASH CIRRHOSIS MODEL

Zaur Abilov[1] Chandra S Shankar[1] Pinzhu Huang[1] Zhensheng Zhang[1] Yoshiko Nanki[1] Andrew Farag[1] Arvo Justice[1] Ayushi Maity[1] Victor Turkowski[1] Kristin Lichti-Kaiser[2] Cynthia Hartsfield[2] Jorge Alfonso Ross Terres[3] Leo Tseng[2] Yury Popov[1], [1]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, United States, [2]89bio Inc, a member of the Roche Group, San Francisco, CA, United States, [3]Genentech, Inc, San Francisco, CA, United States

Background: There are currently no therapeutic options available for metabolic dysfunction-associated steatohepatitis (MASH) in late-stage (F4) disease. Treatments to reverse cirrhosis or prevent progression to decompensation in MASH are a critical unmet need to prevent liver transplant. Here, we investigated the efficacy of pegozafermin (PGZ), an FGF21 analogue, in advanced stages of a murine model of MASH cirrhosis and hepatocellular carcinoma (HCC). **Methods:** Cirrhotic MASH was induced in male C57BL/6J mice by HF-CDAA feeding as previously described[1] . PGZ treatment was initiated for 12 weeks at three doses (0.1, 1.0 and 6 mg/kg every 3 days s/c) after induction of 1) established fibrosis, stage F3 (12 weeks on diet) or 2) compensated cirrhosis, stage F4 (20 weeks on diet). Animals (10-12 per group) were kept on HF-CDAA diet throughout and liver fibrosis and HCC burden were analyzed at the end of the study. **Results:** In both study arms, 12 weeks of PGZ therapy resulted in significant improvement of hepato- and splenomegaly and robust reduction in serum ALT levels. A dose dependent moderate weight loss was observed in both arms. In animals with F3 fibrosis, PGZ therapy prevented the development of histological cirrhosis signs (bridging fibrosis, regenerative nodules) and reduced hepatic collagen content well below control levels. Additionally, 42% of the animals in the placebo arm (5/12) developed HCC at the 24-week study endpoint. Development of HCC was highly suppressed by PGZ 1.0 mg/kg (9.1%, 1/11) and completely prevented in 6.0 mg/kg group (0/11). In mice with compensated cirrhosis (F4), PGZ therapy resulted in robust improvement in ALT levels and reduction in hepatic collagen content below pre-treatment levels. Histologically, PGZ treated groups demonstrated marked slowing of fibrosis progression in 1.0 mg/kg dose and clear signs of cirrhosis reversal in 6.0 mg/kg dose with fibrotic septa fragmentation and disappearance of regenerative nodules compared to placebo. In the late-treatment group, 100% of mice (11/11) in the placebo arm developed HCC, which was reduced by PGZ to 67% in the 1.0 mg/kg arm (8/12) and to 33% in the 6.0 mg/kg arm (4/12). **Conclusion:** In this mouse model of cirrhotic MASH, pegozafermin demonstrated robust antifibrotic activity with strong evidence of fibrosis reversal, even when treatment started after development of compensated cirrhosis. These data also suggest that pegozafermin may have the potential to suppress cirrhosis-associated HCC.1. Wei et al, Am J Physiol G&L 2019

Disclosures: Zaur Abilov:Nothing to Disclose, Chandra S Shankar:Nothing to Disclose, Pinzhu Huang:

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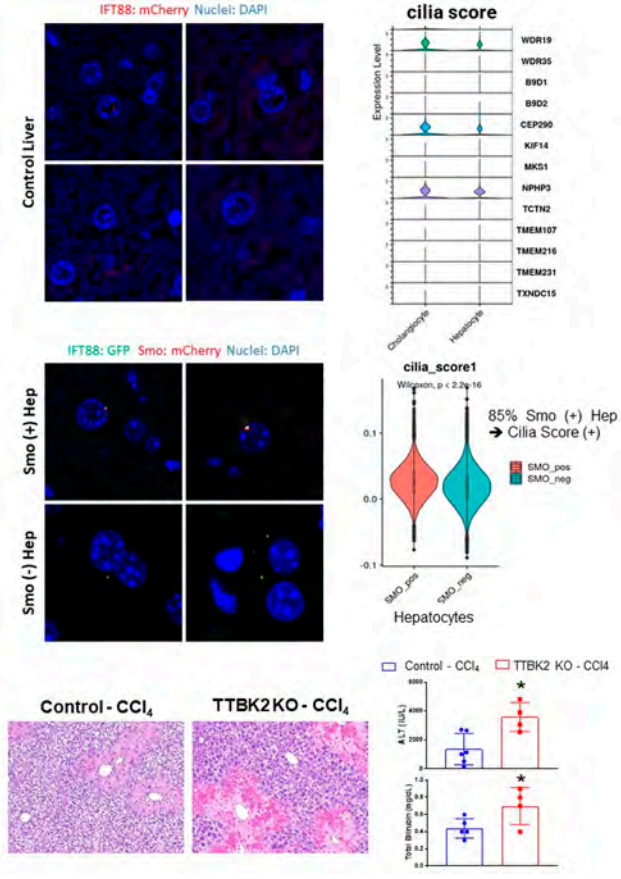
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Nothing to Disclose, Zhensheng Zhang:Nothing to Disclose, Yoshiko Nanki:Nothing to Disclose, Andrew Farag:Nothing to Disclose, Arvo Justice:Nothing to Disclose, Ayushi Maity:Nothing to Disclose, Victor Turkowski:Nothing to Disclose, Kristin Lichti-Kaiser: Nothing to Disclose, Cynthia Hartsfield:89bio Inc, A member of the Roche group: Employee, Jorge Alfonso Ross Terres:Nothing to Disclose, Leo Tseng:Nothing to Disclose, Yury Popov:Nothing to Disclose.

0076 | PRIMARY CILIA–HEDGEHOG SIGNALING REGULATES HEPATOCYTE PLASTICITY

Anna Mae Diehl[1] Raquel Maeso-Diaz[1] Rajesh Dutta[1] Seh-Hoon Oh[1] Sarah Goetz[1], [1]Duke University

Background: Primary cilia (PC) are signaling organelles that regulate metabolism and tissue repair. Human ciliopathies, including Alström syndrome, are associated with insulin resistance, steatosis, and fibrosis. Hedgehog signaling requires Smoothened (SMO) trafficking to primary cilia for activation. We previously demonstrated that hepatocyte-specific Smo deletion induces insulin resistance, steatotic liver disease, and fibrosis in mice, despite the prevailing view that unlike cholangiocytes, adult hepatocytes do not possess primary cilia, creating a paradox. **Methods:** High-resolution confocal microscopy was performed to detect ciliary markers (IFT88+, Arl13b, TTBK2) and SMO in adult mouse liver and primary hepatocytes. Single-nucleus RNA sequencing of 48,059 hepatocytes from healthy and MASLD human livers was analyzed using Seurat v5. SMO+ hepatocytes were defined by detectable normalized Smo transcripts. A composite cilia score was generated from 303 SYSCILIA Gold Standard genes. Independent RNA-seq datasets from regenerating mouse livers after partial hepatectomy were analyzed for ciliogenesis-associated pathways. Hepatocyte-specific TTBK2-deficient mice were generated to disrupt ciliogenesis and evaluated following acute CCl4 liver injury. **Results:** A distinct hepatocyte subpopulation expressed primary cilia markers and ciliary transcriptional signatures. In human liver, ~35% of hepatocytes were SMO+, and 85% of these cells were enriched for ciliary gene programs. SMO co-localized with IFT88 in hepatocytes, supporting hepatocyte ciliary signaling machinery. Compared with SMO− hepatocytes, SMO + hepatocytes exhibited significantly higher cilia scores and increased expression of genes that, when dysregulated, cause Alström syndrome and related ciliopathies that lead to steatotic liver disease and fibrosis. Mice with SMO- hepatocytes developed worse MASH and liver fibrosis than control mice when fed MASH-inducing diets. To determine whether ciliogenesis is dynamically regulated during tissue repair, we analyzed two independent mouse hepatocyte RNA-seq datasets following partial hepatectomy and observed induction of ciliogenesis pathways 48 hours after liver resection. Functionally, hepatocyte-specific TTBK2 deletion impaired ciliogenesis and suppressed recovery from CCl4 liver injury, increasing AST, bilirubin, and liver-to-body weight ratio. **Conclusion:** Adult human hepatocytes contain ciliary signaling machinery linked to distinct ciliary transcriptional programs. Hepatocyte ciliogenesis is induced during liver regeneration and is required for appropriate injury responses. Loss of primary cilia–Hedgehog signaling exacerbates liver damage by disrupting regenerative adaptation, establishing primary cilia as critical regulators of hepatic homeostasis.



Disclosures: Anna Mae Diehl:Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Raquel Maeso-Diaz:Nothing to Disclose, Rajesh Dutta:Nothing

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to Disclose, Seh-Hoon Oh:Nothing to Disclose, Sarah Goetz:Nothing to Disclose.

0077 | CD74+ EFFEROCYTIC MACROPHAGES SUPPRESS CATHEPSIN C EXPRESSION THROUGH METHIONINE METABOLIC REPROGRAMMING IN MASLD AND LIVER FIBROSIS

Yang Xiao[1] Tian Lan[1] Jinhang Gao[1] Yuanshui Long[1] Zhiyin Huang[1] Chengwei Tang[1], [1]West China hospital

Background: In metabolic dysfunction-associated steatohepatitis (MASH) and liver fibrosis, the persistence of dead hepatocytes suggests that macrophages are unable to clear these cells efficiently via efferocytosis. Given the heterogeneity among macrophage populations, it is critical to identify those subsets that possess a superior capacity to efferocytose dead hepatocytes, and explore targeted therapies for MASH and fibrosis. **Methods:** To characterize macrophage phenotypes following efferocytosis, RNA-sequencing (RNA-seq) and metabolomics analyses were conducted. Macrophage-specific *Cd74* knockout mice, macrophage-specific cathepsin C (*Ctsc*) knockout mice and littermate control mice were fed a CDAHFD diet for 12 weeks to establish a MASH model. Single-cell RNA-sequencing (scRNA-seq), spatial transcriptomics, and multiplex immunofluorescence *in vivo*, and fluorescence-activated cell sorting and live-cell imaging *in vitro* were performed to assess CD74+ macrophages-mediated efferocytosis. Mechanistically, the histone modification compounds library and immunoprecipitation-mass spectrometry were employed to explore how CD74+ macrophages-mediated efferocytosis influences CTSC expression. DOT1L inhibitor, WDR5 inhibitor, and CTSC inhibitor were used in MASH and liver fibrosis models to conduct pharmacological intervention. **Results:** Based on RNA-seq and metabolomics, we found that macrophages exhibited distinct response patterns after efferocytosis of hepatocytes undergoing different forms of programmed cell death. Furthermore, we identified CD74+ macrophages as a potential subset with high efferocytic capacity, which can approach and efferocytose dead hepatocytes through MIF and GAS6. ScRNA-seq and spatial transcriptomics revealed that macrophage-specific *Cd74* knockout impaired efferocytosis and exacerbated MASLD and liver fibrosis, whereas overexpression of CD74 alleviated liver fibrosis by enhancing efferocytosis. Metabolomics showed that CD74-mediated efferocytic macrophages reduced the expression of CTSC through methionine metabolism reprogramming. Moreover, the metabolic reprogramming of efferocytic macrophages suppressed CTSC via blocking the histone methyltransferase DOT1L/WDR5-STAT1 axis. Macrophage-specific *Ctsc* knockout ameliorated fibrosis by reducing activated TGFβ. In pharmacological intervention, we found that the inhibitor of CTSC, DOT1L or WDR5 significantly alleviated MASH and liver fibrosis. **Conclusion:** CD74+ macrophage-mediated efferocytosis suppresses expression of DOT1L/WDR5-STAT1 axis-induced CTSC via methionine metabolism reprogramming, thereby providing novel therapeutic targets for treating MASH and liver fibrosis. **Disclosures:** Yang Xiao:Nothing to Disclose, Tian Lan:Nothing to Disclose, Jinhang Gao:Nothing to Disclose, Yuanshui Long:Nothing to Disclose, Zhiyin Huang:Nothing to Disclose, Chengwei Tang:Nothing to Disclose.

0078 | AGING-IMPAIRED RXRα ACETYLATION DRIVES GCH1 LOSS AND FERROPTOSIS-PROMOTED SENESCENCE IN MASH

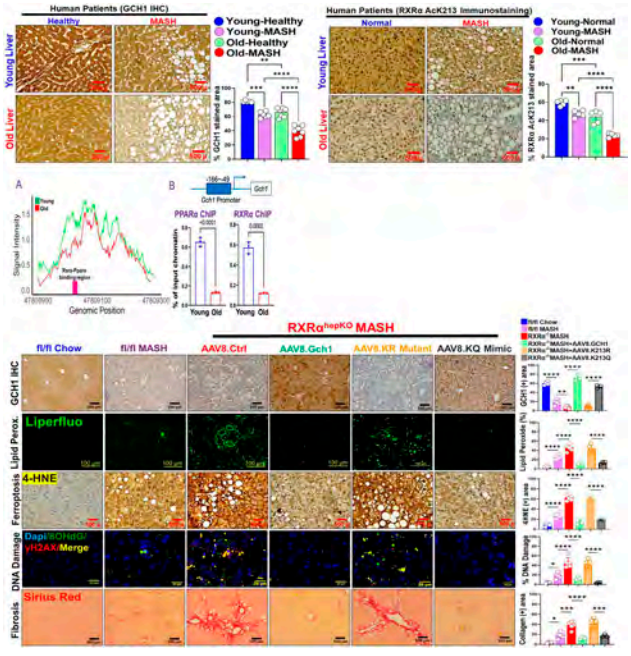
Mayank Choubey[1] Munichandra Tirumalasetty[1] Rashu Barua[1] Md Wahiduzzaman[1] Mohammad Sarif Mohiuddin[1] Qing Miao[1], [1]NYU Grossman Long Island School of Medicine

Background: Elderly patients with MASLD progress more rapidly to MASH with severe fibrosis, suggesting aging compromises hepatic resilience. Ferroptosis, an iron-dependent, lipid peroxidation–driven cell death, triggers inflammation, mitochondrial damage, and fibrosis in MASH, but the mechanisms governing its susceptibility in the aged liver are unclear. Reanalysis of human liver snRNA-seq data identified GTP cyclohydrolase 1 (GCH1), a key anti-ferroptotic regulator, as the predominant ferroptosis gene lost in aged hepatocytes. We hypothesized that acetylation of Retinoid X Receptor alpha (RXRα) preserves RXRα–PPARα-mediated GCH1 transcription, and that its impairment in the aged liver causes GCH1 loss, ferroptosis, and mitochondrial dysfunction. **Methods:** Publicly available human liver snRNA-seq (GSE210077, GSE189600) and ATAC-seq (GSE243630) datasets were re-analyzed for ferroptosis and senescence signatures and nuclear receptor occupancy. Human patient liver tissue arrays were stained for GCH1 and acetylated RXRα-K*. Hepatocyte-specific RXRα knockout (hepKO) and aged (24-month) mice were studied by ChIP-qPCR and RNA-seq. RXRα acetylation was characterized by mass spectrometry, CRISPR/Cas9 knockout, and co-immunoprecipitation. Mitochondrial function was assessed by Seahorse XF, TMRE, and mitochondrial 8-OHdG. AAV8-TBG delivered liver-specific GCH1 and RXRα-K* mutants. **Results:** GCH1 transcript and protein declined with aging and were further

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suppressed in MASH; GCH1-negative hepatocytes were enriched for both ferroptosis and senescence signatures. ATAC-seq and ChIP-qPCR showed reduced RXRα/PPARα occupancy at the GCH1 promoter in aged liver. We identified a novel acetylation site on RXRα, K*, acetylated by CBP and required for heterodimerization with PPARα; this acetylation was selectively impaired by TNFα via CBP phosphorylation. GCH1 knockdown impaired mitochondrial membrane potential, spare respiratory capacity, and ATP production, with mitochondrial 8-OHdG accumulation. RXRα hepKO mice on a MASH diet developed GCH1 loss, ferroptosis, mitochondrial damage, and fibrosis. AAV8-GCH1 or the acetylation-mimic RXRα-K*Q (but not K*R* Ac mutant) restored GCH1, reduced lipid peroxidation by ~80% and Sirius Red fibrosis by ~70%, and attenuated mitochondrial DNA damage. Acetylated RXRα-K* was reduced ~3-fold in livers of elderly MASH patients versus young healthy controls ($P < 0.05$). **Conclusion:** RXRα acetylation at K* is an aging-regulated resilience factor that preserves PPARα-mediated GCH1 transcription, anti-ferroptotic capacity, and mitochondrial integrity. Inflammation-driven loss of RXRα acetylation in the aged liver causes GCH1 deficiency, ferroptosis-promoted mitochondrial damage, and fibrosis. Targeting RXRα acetylation or restoring GCH1 represents a novel therapeutic strategy for age-related MASH and fibrosis, a major unmet need in elderly patients.



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0079 | MULTI-OMIC AND FUNCTIONAL CHARACTERIZATION OF FIBROSIS-ASSOCIATED HEPATOCYTE PROGRAMS IN MASLD

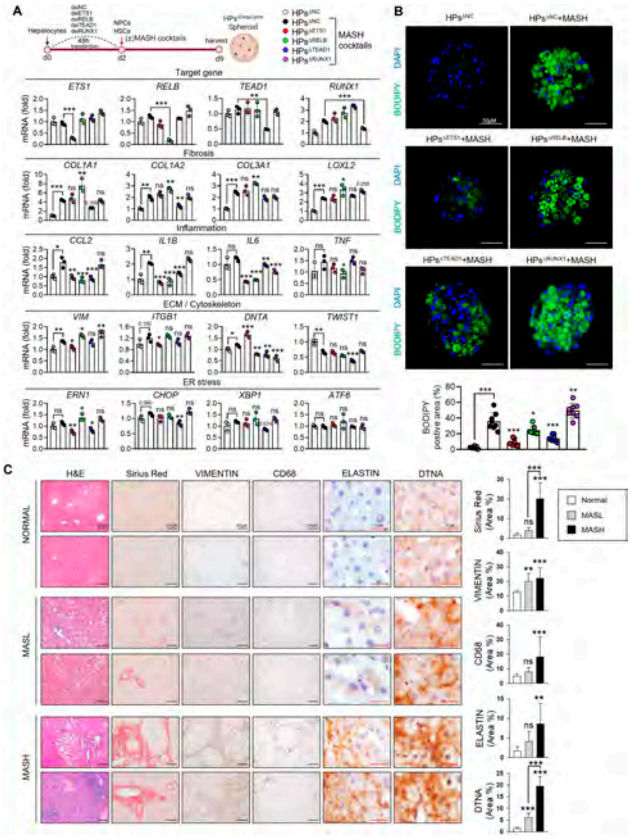
JeongSu Park[1] Xiao Liu[1] Karin Diggle[1] Charlene Miciano[1] Allen Wang[1] David Brenner[2] Tatiana Kisseleva[1], [1]University of California San Diego, [2]Sanford Burnham Prebys Medical Discovery Institute

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) progresses from steatosis to metabolic dysfunction-associated steatohepatitis (MASH) with fibrosis; however, the hepatocyte-specific regulatory mechanisms driving disease progression remain incompletely understood. We leveraged a human liver multi-omic atlas to define fibrosis-associated hepatocyte (Fib-a) programs during MASLD progression. **Methods:** Integrated single-cell, spatial transcriptomic, and epigenomic datasets across MASLD stages were analyzed to identify Fib-a regulatory networks. To functionally validate candidate transcription factors (TFs), primary human hepatocytes were transfected with dsiRNAs targeting ETS1, RELB, TEAD1, or RUNX1 and incorporated into multicellular human liver spheroids under MASH-like conditions. Expression of inflammatory, extracellular matrix (ECM), fibrogenic, and ER stress-related genes was analyzed by qRT-PCR, and lipid accumulation was assessed by BODIPY staining. Human liver tissues were analyzed by western blotting and histology. **Results:** Multi-omic profiling identified Fib-a hepatocytes enriched for inflammatory, cytoskeletal remodeling, ECM, and stress-response pathways, with increased activity of ETS1, RELB, TEAD1, and RUNX1 regulatory networks. Spatial analyses localized Fib-a hepatocytes adjacent to fibrotic regions, supporting their association with active tissue remodeling during MASLD progression. Fib-a-associated injury signatures were validated in human liver tissues. Keratin-associated stress programs were enriched in Fib-a hepatocytes, and KRT8/18 protein expression was significantly increased in MASLD and MASH livers compared to normal controls. Histological analyses demonstrated progressive increases in fibrosis and inflammatory features, including enhanced Sirius Red, Vimentin, and CD68 staining. DTNA expression was also increased in parenchymal regions of MASLD and MASH livers, consistent with hepatocyte structural remodeling. Functional perturbation studies demonstrated distinct TF-specific roles under MASH-like conditions. ETS1 knockdown suppressed inflammatory and ER stress-associated pathways. RELB knockdown reduced inflammatory signaling but enhanced fibrogenic programs. TEAD1 perturbation broadly suppressed inflammatory, mesenchymal remodeling, and ER stress pathways, whereas

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RUNX1 knockdown selectively altered cytoskeletal remodeling and increased lipid accumulation. **Conclusion:** These findings identify fibrosis-associated hepatocyte regulatory programs and provide functional validation of key Fib-a TF networks. Integration of human multi-omic analyses with spheroid modeling highlights hepatocyte-intrinsic pathways as potential therapeutic targets for MASH and liver fibrosis.



Disclosures: JeongSu Park:Nothing to Disclose, Xiao Liu:Nothing to Disclose, Karin Diggle:Nothing to Disclose, Charlene Miciano:Nothing to Disclose, Allen Wang:Nothing to Disclose, David Brenner:Nothing to Disclose, Tatiana Kisseleva:Nothing to Disclose.

0080 | EFFICACY AND SAFETY OF BELAPECTIN FOR THE PREVENTION OF ESOPHAGEAL VARICES IN MASH CIRRHOSIS: A MULTI-DOSE META-ANALYSIS

Rahul Falodia[1] Ehsanullah Alokozay[2] Farhan Murtaza[3] Muhammad Junaid Azhar[4] Rameen Khalid[5] Waqas Anwar[6] Muhammad Hammad ul Hassan[7] Ahmed Ibrahim[8] Abdul Wahab Ali[5] Muhammad Ikram[9] Bacel Nseir[10] Miriam Michael[4], [1]All India Institute of Medical Sciences, Jodhpur, [2]Faculty of Medicine, Kandahar University, Kandahar, Afghanistan, [3]Program Director, HCA Houston healthcare/ University of Houston Program, [4]Howard University Hospital, [5]Rawalpindi Medical University, [6]Wyckoff heights medical center, [7]South Brooklyn Health NY, [8]University at Buffalo, Catholic Health System, [9]Allama Iqbal Memorial Teaching Hospital Sialkot, [10]HCA Houston healthcare/ University of Houston Program

Background: Preventing esophageal varices development in metabolic dysfunction-associated steatohepatitis (MASH) cirrhosis remains an unfulfilled clinical priority. Belapectin (GR-MD-02), a galectin-3 inhibitor, has shown preclinical and clinical promise in reducing portal hypertension, but its non-linear exposure-response profile requires robust validation. This meta-analysis systematically synthesizes multi-dose clinical trial data across phases to define its therapeutic window, efficacy, and safety profile. **Methods:** Randomized, double-blind, placebo-controlled trials assessing Belapectin in advanced chronic liver disease were included. Multi-dose subgroup models evaluated the incidence of new varices in baseline-free patients and severe toxicities (CTCAE Grade > 3 treatment-emergent adverse events [TEAEs]) using Risk Ratios (RRs) and 95% confidence intervals (CIs). Continuous trajectories of Liver Stiffness Measurements (LSM) were pooled using Standardized Mean Differences (SMDs). **Results:** Across all consolidated doses, Belapectin significantly protected against variceal progression (Overall RR = 0.59; 95% CI: 0.38–0.91). Stratified by dose tiers, the optimal therapeutic window was confirmed at 2 mg/kg, which achieved a significant reduction in new esophageal varices (RR = 0.52; 95% CI: 0.27–0.99). Reflecting target-mediated drug disposition, higher concentrations failed to demonstrate traditional dose-response scaling (4 mg/kg RR = 0.71; 95% CI: 0.39–1.32; 8 mg/kg RR = 0.24; 95% CI: 0.03–1.86). Continuous LSM changes similarly favored active treatment over placebo across cohorts (Overall SMD = -0.14; 95% CI: -0.29 to 0.01). Safety pooling revealed that Grade > 3 TEAE risks were not significantly elevated at 2 mg/kg (RR = 1.32; 95% CI: 0.91–1.92), with highly balanced cross-arm safety distributions overall (Overall Safety RR = 1.30; 95% CI: 1.00–1.69) showing absolute trial homogeneity (I^2 = 0%, p = 0.84). No adjudicated drug-induced liver injury or anaphylactic events were observed. **Conclusion:** Belapectin at 2 mg/kg safely and reproducibly mitigates new esophageal varices development in compensated MASH cirrhosis and portal hypertension. Its non-monotonic exposure-response profile highlights that maintaining dosing parameters strictly within the targeted macrophage-saturation window is essential for maximizing clinical benefit in future trial designs.

Disclosures: Rahul Falodia:Nothing to Disclose, Ehsanullah Alokozay:Nothing to Disclose, Farhan Murtaza:

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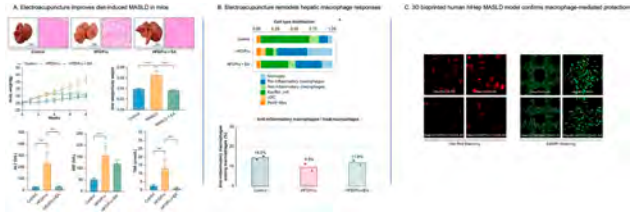
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Nothing to Disclose, Muhammad Junaid Azhar:Nothing to Disclose, Rameen Khalid:Nothing to Disclose, Waqas Anwar:Nothing to Disclose, Muhammad Hammad ul Hassan:Nothing to Disclose, Ahmed Ibrahim: Nothing to Disclose, Abdul Wahab Ali:Nothing to Disclose, Muhammad Ikram:Nothing to Disclose, Bacel Nseir:Nothing to Disclose, Miriam Michael:Nothing to Disclose.

0081 | ELECTROACUPUNCTURE ATTENUATES EXPERIMENTAL MASLD VIA NEUROIMMUNE REMODELING OF HEPATIC MACROPHAGE RESPONSES

Shangze Jiang[1] Huayu Yang[1] Yilei Mao[1], [1]Peking Union Medical College Hospital

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is driven by metabolic stress, lipotoxic injury, and chronic hepatic inflammation. Lifestyle modification remains the cornerstone of management, but safe and mechanism-informed adjunctive strategies are limited. Electroacupuncture has been implicated in autonomic and immune regulation; however, whether it attenuates MASLD through coordinated neuroimmune remodeling remains unclear. **Methods:** A diet-induced murine MASLD model was established and treated with electroacupuncture. Liver phenotype was assessed by body and liver indices, serum biochemical markers, histology, lipid staining, and inflammatory/metabolic gene analyses. Neural pathway engagement and hepatic immune remodeling were evaluated using tracing-related approaches, immunostaining, and single-cell profiling. To enhance human relevance, a 3D bioprinted human hiHep MASLD model was generated under lipid-overload conditions to test macrophage-associated anti-inflammatory protection against hepatocellular injury. **Results:** Electroacupuncture improved experimental MASLD phenotypes, including liver-to-body weight changes, serum injury/metabolic indices, hepatic steatosis, and inflammatory activation. Histology and lipid staining showed reduced lipid deposition after treatment, accompanied by attenuation of injury-associated inflammatory features. Mechanistic profiling suggested engagement of an autonomic neuroimmune pathway and remodeling of the hepatic immune landscape. Among immune populations, macrophages represented the most treatment-responsive compartment. Single-cell analysis showed a shift away from inflammatory activation and toward reparative, lipid-handling, and tissue-restorative programs. In the 3D bioprinted human hiHep MASLD model, macrophage-associated anti-inflammatory modulation reduced lipid accumulation, improved cell viability, and partially normalized transcriptomic patterns related to lipid transport, extracellular remodeling, and immune repair. These concordant in vivo and human bioprinted findings support macrophage remodeling as a central effector process linking electroacupuncture to MASLD improvement. **Conclusion:** Electroacupuncture attenuates experimental MASLD and is associated with neuroimmune remodeling of hepatic macrophage responses. By integrating animal phenotyping, single-cell immune profiling, and 3D bioprinted human hiHep validation, this study provides translational evidence supporting electroacupuncture as a potential non-pharmacological strategy for MASLD and highlights hepatic macrophage remodeling as a key direction for further investigation.



Disclosures: Shangze Jiang:Nothing to Disclose, Huayu Yang:Nothing to Disclose, Yilei Mao:Nothing to Disclose.

0082 | DR10624, A NOVEL FIBROBLAST GROWTH FACTOR 21 (FGF21)

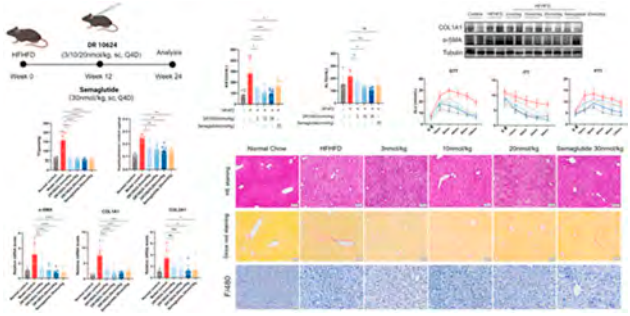
Yixuan Zhu[1] Jie Li[2], [1]Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University, Nanjing, [2]Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University

Background: DR10624 is a novel triple agonist targeting FGF21R, GCGR, and GLP-1R. This study aimed to evaluate the therapeutic effects of DR10624 on MASH-related liver fibrosis both in vivo and in vitro, and to further elucidate the underlying molecular mechanisms. **Methods:** Two murine models of MASH-associated liver fibrosis were established: an 8-week choline-deficient, L-amino acid-defined, high-fat diet (CDA-HFD) model and a 24-week high-fat/high-fructose diet (HFHFD) model. Mice were treated with DR10624 at doses of 3, 10, and 20 nmol/kg, while semaglutide (at dose of 30 nmol/kg) was used as a positive control. Histopathological analyses were performed to assess hepatic steatosis, inflammation,

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ballooning, and fibrosis. In addition, body weight, liver function, and glucose and lipid metabolic parameters were also evaluated. RNA sequencing of liver tissues was conducted to explore the potential mechanisms underlying the therapeutic effects of DR10624, followed by mechanistic validation in LX-2 cells. **Results:** DR10624 exerted significant therapeutic effects in both models of MASH-associated liver fibrosis. Treatment with DR10624 reduced body weight and serum ALT and AST levels, improved dyslipidaemia, enhanced glucose tolerance and insulin sensitivity, and alleviated metabolic dysfunction. Histopathological analyses further demonstrated that DR10624 markedly attenuated hepatic steatosis, inflammatory infiltration, and collagen deposition. At the molecular level, DR10624 dose-dependently reduced the mRNA and protein expression of α-SMA, Col1a1, and Col3a1 in liver tissues and TGF-β-stimulated LX-2 cells. Moreover, DR10624 also inhibited LX-2 cell migration, proliferation, and collagen contraction capacity, thereby suppressing hepatic stellate cell activation. RNA sequencing analysis revealed that DR10624 primarily regulated pathways associated with glucose, lipid, and cholesterol metabolism, with the most pronounced effects observed in glycolytic pathways. Further investigation demonstrated that DR10624 significantly inhibited pyruvate kinase activity. Lentiviral overexpression of PKM2 partially reversed the inhibitory effects of DR10624 on fibrosis-related markers in TGF-β-stimulated LX-2 cells. In addition, DR10624 enhanced K48-linked ubiquitination of PKM2, suggesting that its anti-fibrotic effects may be mediated through promotion of PKM2 degradation. **Conclusion:** This study is the first to demonstrate that DR10624, a novel FGF21R/GCGR/GLP-1R tri-agonist, exerts potent anti-fibrotic effects against MASH-associated liver fibrosis both in vivo and in vitro, with superior efficacy compared with the GLP-1R mono-agonist semaglutide. Mechanistically, these effects may be associated with enhanced K48-linked ubiquitination of PKM2, suppression of glycolysis, and inhibition of hepatic stellate cell activation.



Disclosures: Yixuan Zhu:Nothing to Disclose, Jie Li: Nothing to Disclose.

0083 | EFFICACY OF SURVODUTIDE TREATMENT ASSESSED BY LIVER ENDPOINTS ACROSS WEIGHT-REDUCTION CATEGORY AT END OF TREATMENT: RESULTS FROM A PHASE 2 TRIAL OF SURVODUTIDE IN PEOPLE WITH METABOLIC DYSFUNCTION–ASSOCIATED STEATOHEPATITIS AND FIBROSIS

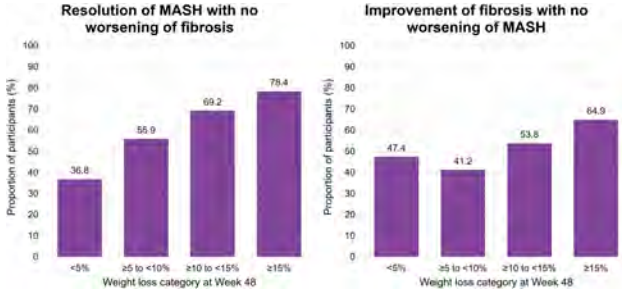
Elisabetta Bugianesi[1] Quentin Anstee[2] Eric Lawitz[3] Mazen Noureddin[4] Naim Alkhouri[5] Jörn Schattenberg[6] Mandy Fraessdorf[7] Ahmad Alhussein[8] Corinna Schoelch[7] Luiza Borowska[8] Arun Sanyal[9], [1]University of Turin, [2]Newcastle upon Tyne Hospitals NHS Trust, [3]University of Texas Health San Antonio, [4]Houston Methodist Hospital, [5]Arizona Liver Health, [6]Saarland University Medical Center, [7]Boehringer Ingelheim Pharma GmbH & Co. KG, [8]Boehringer Ingelheim International GmbH, [9]Virginia Commonwealth University

Background: Survodutide is a glucagon receptor/glucagon-like peptide-1 receptor dual agonist being investigated in phase 3 trials for metabolic dysfunction–associated steatohepatitis (MASH), and obesity. In a phase 2 trial in people with biopsy-confirmed MASH and F1–F3 liver fibrosis, survodutide improved both steatohepatitis and liver fibrosis. We evaluated the efficacy of survodutide treatment assessed by liver endpoints by weight reduction categories at Week 48. **Methods:** Among 295 people aged 18–80 years randomized to once-weekly s.c. survodutide 2.4, 4.8, or 6.0 mg, or placebo (PBO) for 48 weeks, 170 participants who had F2–F3 fibrosis stage at baseline and paired liver biopsy results at baseline and end of trial were included in this analysis. Weight reduction categories at Week 48 included $<5\%$, ≥ 5 to $<10\%$, ≥ 10 to $<15\%$, and $\geq 15\%$. Liver endpoints included resolution of MASH (absence of ballooning [score of 0], no or mild inflammation [score of 0 or 1], and any value of steatosis [score of 0 to 3]) with no worsening of fibrosis, improvement in fibrosis (≥ 1 stage decrease) with no worsening of MASH, ≥ 0.5 reduction in enhanced liver fibrosis (ELF™) score, $\geq 20\%$ reduction in propeptide of type III collagen (PRO-C3), $\geq 30\%$ reduction in liver fat content (LFC; magnetic resonance imaging proton density fat fraction assessed), $>30\%$ reduction in liver stiffness measurement (LSM; FibroScan®), and relative change in alanine aminotransferase (ALT) and aspartate aminotransferase (AST). **Results:** Among 54 participants treated with placebo, 85.2% (46) had a weight reduction of $<5\%$ at Week 48. Among 116 survodutide-treated participants, 16.4% (19) had a weight reduction of $<5\%$, 29.3% (34) had ≥ 5 to $<10\%$, 22.4% (26) had ≥ 10 to $<15\%$, and 31.9% (37) had $\geq 15\%$; 36.8, 55.9, 69.2, and 78.4%

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had resolution of MASH without worsening of fibrosis (figure); 47.4, 41.2, 53.8, and 64.9% had an improvement in fibrosis without worsening of MASH (figure); 41.2, 56.3, 64.0, and 70.6% had a ≥0.5 reduction in ELF™; 18.8, 50.0, 76.0, and 58.8% had a ≥20% reduction in PRO-C3, 31.6, 72.7, 100, and 100% had a >30% reduction in LFC; and 36.8, 52.9, 53.8, and 78.4% had a ≥30% reduction in LSM, per weight reduction category. The relative change in ALT was −22.5, −50.5, −59.4, and −42.0%, and AST were −21.5, −45.9, −49.2, and −27.6%, per weight reduction category. **Conclusion:** Liver endpoints were improved with survodutide treatment at Week 48, even at the <5% weight reduction category. Liver improvements increased with increased weight reduction, although the magnitude was more pronounced in steatohepatitis-related endpoints than fibrosis-related endpoints, suggesting improvements in steatohepatitis-related endpoints were largely associated with weight reduction, consistent with the metabolic drivers of the disease, whereas fibrosis-related endpoints could be attributed to a direct hepatic effect of survodutide.



Disclosures: Elisabetta Bugianesi:Nothing to Disclose, Quentin Anstee:AstraZeneca, Boehringer Ingelheim, Intercept.: Grant/Research Support, Alimentiv, Akero, AstraZeneca, Axcella, 89Bio: Consultant, Boehringer Ingelheim, Bristol Myers Squibb, Corcept: Consultant, Enyo Pharma, Galmed, Genfit, Genentech, Gilead, GlaxoSmithKl: Consultant, Hanmi, HistoIndex, Intercept, Inventiva, Ionis, IQVIA, Janss: Consultant, Madrigal, Medpace, Merck, Metadeq, NGMBio, North Sea T: Consultant, Novartis, Novo Nordisk, PathAI, Pfizer, Pharmanest: Consultant, Poxel, Prosciento, Resolution Therapeutics, Roche,: Consultant, Ridgeline Therapeutics, RTI, Shionogi, Terns: Consultant, Fishawack, Integritas Communications, Kenes,: Speaking and Teaching, Novo Nordisk, Madrigal, Medscape, Springer Healthcare: Speaking and Teaching, Elsevier Ltd: Royalties or patent beneficiary, Eric Lawitz:89Bio: Grant/Research Support, Akero Therapeutics: Grant/Research Support, Astrazeneca: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Bristol-Myers Squibb: Grant/Research Support, Cour Pharmaceuticals: Grant/Research Support, Cymabay Therapeutics: Grant/Research Support, Eli Lilly and Company: Grant/Research Support, Galectin Therapeutics: Grant/Research Support, Gilead Sciences: Grant/Research Support, GlaxoSmithKline: Grant/Research Support, Hanmi Pharmaceuticals: Grant/Research Support, Hightide Biopharma: Grant/Research Support, Intercept Pharmaceuticals: Grant/Research Support, Inventiva: Grant/Research Support, Ipsen: Grant/Research Support, Madrigal Pharmaceuticals: Grant/Research Support, Merck & Co: Grant/Research Support, NGM Biopharmaceuticals: Grant/Research Support, Novartis: Grant/Research Support, Novo Nordisk Inc: Grant/Research Support, Regeneron: Grant/Research Support, Sagimet Biosciences: Grant/Research Support, Takeda: Grant/Research Support, Terns Pharmaceuticals: Grant/Research Support, Viking Therapeutics: Grant/Research Support, Zydus Pharmaceuticals: Grant/Research Support, Gilead Sciences: Speaking and Teaching, Abbvie: Speaking and Teaching, Intercept: Speaking and Teaching, Madrigal Pharmaceuticals: Speaking and Teaching, 89Bio: Consultant, Boehringer Ingelheim: Consultant, Merck & Co: Consultant, Novo Nordisk Inc: Consultant, Organovo: Consultant, Regeneron: Grant/Research Support, Sagimet Biosciences: Consultant, Corcept Therapeutics: Consultant, Corcept Therapeutics: Grant/Research Support, Astrazeneca: Consultant, inventiva: Consultant, Mazen Noureddin:Akero: Advisor, Alligos: Advisor, Altimmune: Advisor, AstraZeneca: Advisor, Boehringer Ingelheim: Advisor, Boston Pharma: Advisor, Cytodyn: Advisor, GSK: Advisor, Lilly: Advisor, Madrigal: Advisor, Merck: Advisor, Novo Nordisk: Advisor, Sagimet: Advisor, Terns: Advisor, Takeda: Advisor, Akero: Principal Investigator, Allergan: Principal Investigator, Altimmune: Principal Investigator, Boehringer Ingelheim: Principal Investigator, Bristol Myers Squibb: Principal Investigator, Boston Pharma: Principal Investigator, Conatus: Principal Investigator, Corcept: Principal Investigator, Galectin: Principal Investigator, Genfit: Principal Investigator, GSK: Principal Investigator, Kowa: Principal Investigator, Enanta: Principal Investigator, Madrigal: Principal Investigator, Lilly: Principal Investigator, Merck: Principal Investigator, Novartis: Principal Investigator, Novo Nordisk: Principal Investigator, Rivus: Principal Investigator, Shire: Principal Investigator, Takeda: Principal Investigator, Terns: Principal Investigator, Viking: Principal Investigator, Zydus: Principal Investigator, Rivus: Stock – privately held company, Cytodyn: Stock - publicly traded company, ChronWell: Stock – privately held company, Madrigal: Speakers bureau, Gilead Sciences: Principal Investigator, Akero: Consultant, Altimmune: Consultant, Alligos: Consultant, AstraZeneca: Consultant, BI: Consultant, Boston Pharma: Consultant, Curve bioscience: Consultant, Cytodyn: Consultant, GSK: Consultant, Histoindex: Consultant, Lilly: Consultant, Madrigal: Consultant, Merck: Consultant, Novo Nordisk: Consultant, Sagimet: Consultant, Terns: Consultant, Allergan: Grant/Research Support,

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0084 | POSITIVE PHASE 2B CLINICAL RESULTS OF NOVEL FIRST-IN-CLASS PAN-PDE INHIBITOR ZSP1601: SAFETY, ANTIFIBROTIC AND METABOLIC IMPROVEMENT IN MASH PARTICIPANTS WITH F2/F3 FIBROSIS

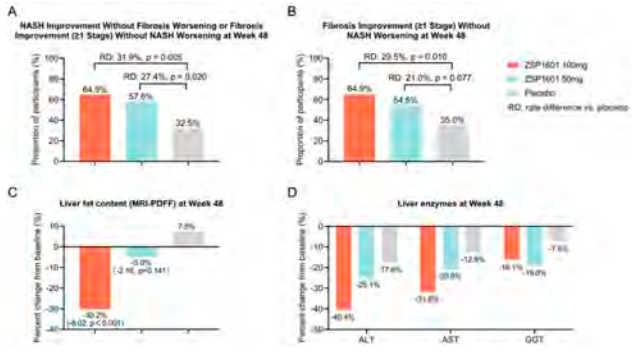
Jinlin Hou[1] Junqi Niu[2] Jinjun Chen[1] Xieer Liang[1] Qiya Huang[3] Qianguo Mao[4] Yongning Xin[5] Shenghong Zhang[6] Xiaoping Wu[7] Jing Li[8] Yun Peng[8] Haijun Li[8] Xiaoxin Chen[8], [1]Nanfang Hospital, Southern Medical University, [2]The First Hospital of Jilin University, [3]The Affiliated Qingyuan Hospital(Qingyuan People's Hospital), Guangzhou Medical University, [4]Xiamen Hospital of Traditional Chinese Medicine, [5]Qingdao Municipal Hospital, [6]The First Affiliated Hospital, Sun Yat-sen University, [7]The First Affiliated Hospital of Nanchang University, [8]Guangdong Raynovent Biotech Co., Ltd

Background: ZSP1601, a first-in-class pan-phosphodiesterase (Pan-PDE) inhibitor targeting multiple PDE subtypes, has previously demonstrated improvements in non-invasive liver markers of inflammation, steatosis, and fibrosis in MASH. This phase 2b trial aimed to assess the safety and efficacy of ZSP1601 in patients with non-cirrhotic MASH and F2–F3 stage fibrosis. **Methods:** This multi-center, randomized, double-blind, placebo-controlled phase 2b trial enrolled adults with biopsy-confirmed MASH and F2/F3 fibrosis (using the NASH-CRN scoring system). Eligible participants were randomized in a 1:1:1 ratio to receive oral ZSP1601 twice daily (BID) at a dose of 50 mg or 100 mg or placebo for 48 weeks. The primary endpoint was the proportion of participants achieving either NASH improvement (NAFLD activity score reduction ≥ 2

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points, ballooning decrease ≥1 point, no steatosis increase) without worsening of fibrosis, or fibrosis improvement (decreased ≥1 stage) without worsening of NASH at week 48. Key secondary outcomes included change in liver fat content by MRI-PDFF, changes in serum biomarkers (ALT, AST, GGT), and the overall safety profile. **Results:** Of 181 randomized patients, 110 with baseline biopsy-proven F2-F3 MASH and evaluable paired biopsies formed the primary analysis population. Baseline characteristics were balanced across groups: mean age 37.0 yrs, 74.5% male, mean BMI 29.78 kg/m^2, 30.0% with diabetes, ALT 86.9 U/L, AST 47.6 U/L. At week 48, the proportion of participants achieving the primary endpoint was 64.9% in the ZSP1601 100 mg group ($p = 0.005$ vs. placebo), 57.6% in the ZSP1601 50 mg group ($p = 0.02$ vs. placebo), and 32.5% in the placebo group. For fibrosis improvement (≥1 stage) without NASH worsening, the placebo-adjusted rate differences were 29.50% (100 mg; $p = 0.01$) and 21.00% (50 mg; $p = 0.077$); for improvement of ≥2 stages , the differences were 10.60% (100 mg; $p = 0.036$) and 2.58% (50 mg; $p = 0.358$). ZSP1601 reduced liver fat content, with mean percent changes from baseline of -30% (100 mg) and -5% (50 mg) vs. +7% (placebo). Reductions in ALT and AST were dose-dependent, while GGT reductions were similar between the two active treatment groups. The incidence of treatment-emergent adverse events (TEAEs) was similar across groups, with no deaths reported. Grade ≥3 TEAEs occurred in 9.8% (50 mg), 13.3% (100 mg), and 18.3% (placebo). No dose-related safety signal was observed. **Conclusion:** In MASH patients with F2/F3 fibrosis, 48 weeks of ZSP1601 (50 mg or 100 mg BID) treatment significantly improved histological endpoints, including fibrosis, compared with placebo, with a favorable safety profile. These findings support the further development of ZSP1601 for MASH.



Disclosures: Jinlin Hou:Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Junqi Niu:Nothing to Disclose, Jinjun Chen:Nothing to Disclose, Xieer Liang:Nothing to Disclose, Qiya Huang:Nothing to Disclose, Qianguo Mao:Nothing to Disclose, Yongning Xin:Nothing to Disclose, Shenghong Zhang:Nothing to Disclose, Xiaoping Wu:Nothing to Disclose, Jing Li:Nothing to Disclose, Yun Peng:Nothing to Disclose, Haijun Li: Nothing to Disclose, Xiaoxin Chen:Nothing to Disclose.

★ 0085 | IMPACT OF GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS (GLP-1 RA) ON METABOLIC DYSFUNCTION ASSOCIATED STEATOHEPATITIS (MASH) CIRRHOSIS

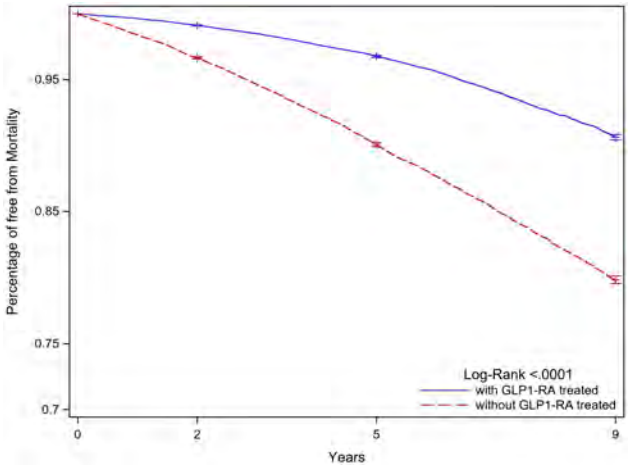
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Background: Glucagon-like peptide-1 receptor agonists (GLP-1 RA) improve metabolic risk factors, have been shown to improve steatohepatitis, and may improve fibrosis in metabolic dysfunction-associated steatohepatitis (MASH). However, their impact on major adverse liver outcomes (MALO) in patients with MASH cirrhosis remains incompletely characterized. We aimed to evaluate the association between GLP-1 RA exposure and MALO among veterans with MASH cirrhosis. **Methods:** We performed a retrospective cohort study using Veterans Health Administration data from 1/1/2016 to 12/31/2025. Veterans with MASH cirrhosis were identified. We excluded patients with non-MASH liver diagnoses, baseline hepatic decompensation and hepatobiliary malignancy, extra-hepatic malignancy, transplantation, or missing body mass index. GLP-1 RA-treated and untreated patients were propensity score matched in a 1:1 ratio based on age, race, and sex. Cox regression models evaluated associations between GLP-1 RA exposure and outcomes, adjusting for age, sex, race, obesity, diabetes, dyslipidemia, hypertension, cardiovascular disease, and pulmonary disease. We defined MALO as incident hepatic decompensation, hepatobiliary malignancy, or death. Hepatic decompensation was defined as ascites, encephalopathy, or variceal hemorrhage. Follow up time was from cirrhosis diagnosis to development of MALO, censoring for liver transplant, loss to follow up, and end of the study. **Results:** The matched cohort included 104,120 veterans with MASH cirrhosis. The median age was 56 years, 87% were male, and 16.5% were Black. Compared with untreated patients, GLP-1 RA-treated patients had higher rates of obesity (88% vs 67%), diabetes (81% vs 40%), dyslipidemia (90% vs 79%), hypertension (85% vs 71%), cardiovascular disease (49% vs 38%), and chronic pulmonary disease (18% vs 17%; all with $p < 0.001$). GLP-1 RA use was associated with lower risk of hepatic decompensation in both univariable (HR 0.70, 95% CI

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0.64–0.76; p < 0.001) and multivariable (adjusted HR [aHR] 0.53, 95% CI 0.49–0.58; p < 0.001) analyses, though this relationship exhibited non-proportional hazards over time. GLP-1 RA was associated with lower risk of hepatobiliary malignancy in univariable (HR 0.78, 95% CI 0.70–0.86; p < 0.001) and multivariable (aHR 0.62, 95% CI 0.55–0.70; p < 0.001) analyses. GLP-1 RA was also associated with lower risk of death in univariable analysis (HR 0.39, 95% CI 0.37–0.40; p < 0.001). **Conclusion:** In this national cohort of veterans with MASH cirrhosis, GLP-1 RA treatment was associated with lower risk of hepatic decompensation, hepatobiliary malignancy, and death. These findings support a potential liver-protective association of GLP-1 RA therapy in MASH cirrhosis and warrant prospective validation.

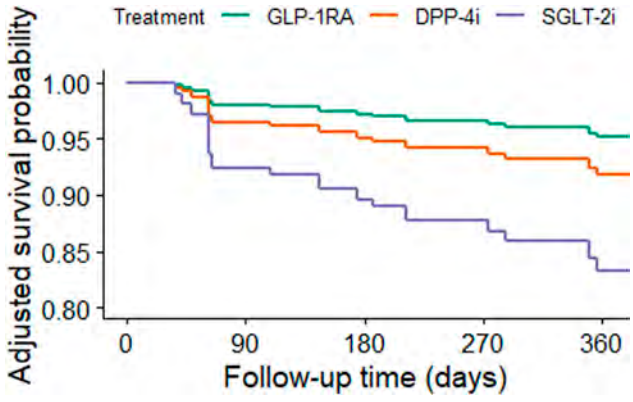


Disclosures: Olufunso Agbalajobi:Nothing to Disclose, Peng Yan:Nothing to Disclose, Claire Durkin:Nothing to Disclose, Adeel Butt:Nothing to Disclose, Obaid Shaikh:Nothing to Disclose.

0086 | INITIATING GLP-1 RECEPTOR AGONISTS IN PATIENTS WITH DECOMPENSATED ALCOHOL-ASSOCIATED CIRRHOSIS IS RELATED TO BETTER PROGNOSIS: AN INVERSE PROBABILITY WEIGHTING TARGET TRIAL EMULATION

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Background: Disease-modifying management options for decompensated cirrhosis remain limited outside of liver transplantation. Although GLP-1 receptor agonists (GLP-1RA) and SGLT-2 inhibitors (SGLT2i) have been demonstrated to improve metabolic dysfunction-associated steatohepatitis, their role in alcohol-related liver disease is unclear. We aimed to explore the association of GLP-1RA, DPP-4 inhibitors (DPP4i), and SGLT2i with hepatic outcomes among patients with decompensated alcohol-associated cirrhosis. **Methods:** We queried structured health records data at our institute to identify patients with decompensated alcohol-associated cirrhosis and first-time medication orders for GLP-1RAs (reference group), SGLT2is, or DPP4is between 1/1/2012 and 4/30/2026. Hepatic decompensation, ascertained by ICD codes, was defined as ascites, variceal hemorrhage, hepatic encephalopathy, jaundice, or hepatic renal syndrome. Patients who received initiated medications prior to the diagnosis of decompensated cirrhosis or underwent liver transplantation prior to medication initiation were excluded. Patients who underwent liver transplantation, deceased, or lost to follow-up within 30 days of medication initiation were also excluded. Our outcome was the time to the first occurrence of liver transplant, hepatic decompensation, or death. Inverse probability weighting Cox proportional hazards model with intention-to-treat analysis was performed and 95% confidence intervals (95% CI) were estimated by bootstrapping with 1,000 replications. **Results:** Among 184 patients contributing 389 person-years of follow-up (median follow-up: 1.38 years), 71 (38.6%), 66 (35.9%), and 47 (25.5%) patients were initiated with GLP-1RA, SGLT2i, and DPP-4i after diagnosis of decompensated cirrhosis, respectively. The median baseline MELD 3.0 score was 12.0 ([Q1, Q3]: [9.4, 17.3]) and was a predictor in inverse probability. Twenty-seven (14.7%) patients experienced the outcome. After weighting (standardized mean differences < 0.1), the respective effective sample size for the groups were 66, 62, and 44. Compared with GLP-1RA initiation, SGLT2i initiation was associated with a higher hazard of the outcome (weighted HR 4.12, 95% CI 1.10–45.7, Figure). No significant difference was observed between DPP4i and GLP-1RA. Nine patients (4.9%) developed acute pancreatitis (3 patients each group), but no significant difference was present between groups (p = 0.85). **Conclusion:** Among patients with decompensated alcohol-associated cirrhosis, GLP-1RA initiation was associated with a lower risk of hepatic complications compared with SGLT-2i initiation. Given the limited sample size and potential survivorship bias related to the exclusion criteria, the findings are interpreted as hypothesis-generating. Prospective randomized controlled trials are required to determine the efficacy and safety of GLP-1RA.



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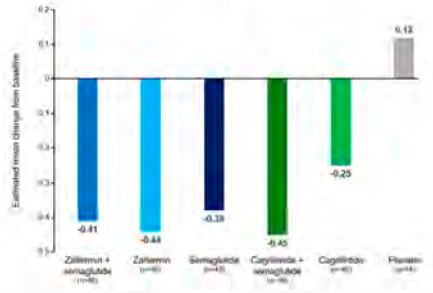
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0087 | EFFECTS OF ZALFERMIN, CAGRILINTIDE, AND SEMAGLUTIDE ON NON-INVASIVE FIBROSIS BIOMARKERS IN ALCOHOL-RELATED LIVER DISEASE: A PHASE 2 RANDOMIZED TRIAL

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Background: Alcohol-related liver disease (ALD) is a leading cause of cirrhosis, hepatocellular carcinoma, liver transplantation, and liver-related mortality. Sustained alcohol abstinence is central to management but difficult to achieve, and no approved therapies target the underlying fibrogenic process. ALD and metabolic dysfunction-associated steatohepatitis (MASH) share overlapping liver-injury pathways and so therapies effective in MASH may also benefit ALD. We evaluated agonists of the FGF-21 (zalfermin), GLP-1 (semaglutide), and amylin (cagrilintide) receptors to assess their potential to improve fibrosis in ALD. **Methods:** This was a phase 2, multinational (13 countries, 87 sites), randomized, double-blinded, placebo-controlled trial (RCT) evaluating the effect of once-weekly subcutaneous zalfermin 30 mg, cagrilintide 2.4 mg, and semaglutide 2.4 mg alone or in combinations vs placebo on markers of liver fibrosis and alcohol use (NCT06409130). Eligible participants were aged ≥18 years, with a ≥5-year history of unhealthy alcohol consumption (mean of ≥50 grams/day [g/d] for males and ≥40 g/d for females in the preceding year), and an Enhanced Liver Fibrosis (ELF) score of ≥9.0. The primary endpoint was change in ELF score from baseline to week 28. Secondary endpoints evaluated after 28 weeks of treatment included change in liver stiffness measured by vibration-controlled transient elastography (VCTE-LSM), PRO-C3, alcohol use assessed by Timeline Follow-Back (TLFB), safety, and tolerability. **Results:** A total of 270 participants were randomized (Zalfermin + semaglutide [n = 46], Zalfermin [n = 45], semaglutide [n = 43], cagrilintide + semaglutide [n = 46], cagrilintide [n = 46], placebo [n = 44]): 25.9% were female, had a mean age of 59.7 years, mean BMI of 32.4 kg/m^2, and 26.3% had type 2 diabetes. Baseline alcohol use was high (TLFB 81 g/d); 59.3% had an Alcohol Use Disorders Identification Test score of ≥15. Liver disease was advanced (mean ELF score 10.2; geometric mean VCTE-LSM 10.1 kPa). The primary endpoint of change in ELF score was met for all active treatments with greater reductions vs placebo (+0.12), including −0.41 for zalfermin + semaglutide, −0.44 for zalfermin, −0.38 for semaglutide, −0.45 for cagrilintide + semaglutide, and −0.25 for cagrilintide (**Figure**), and accompanied by consistent improvements in both VCTE-LSM and PRO-C3. Although a trend for decreased alcohol consumption was observed in all treatment groups, no significant differences vs placebo were observed for TLFB. No unexpected safety concerns were identified for the active treatments, with safety profiles consistent with prior studies in other indications. **Conclusion:** This is the first RCT to show that pharmacological treatment can drive improvements in fibrosis biomarkers in people with ALD, with effects evident across the study population and independent of changes in alcohol consumption.

Figure. Estimated mean change in ELF score from baseline to week 28.



ELF score was analyzed using a linear model with treatment group as the categorical factor, adjusted for type 2 diabetes status (yes/no) at screening and baseline ELF score. Missing data were handled by unconditional reference-based multiple imputation, i.e., imputation of missing data was informed by participants assigned to placebo.
ELF, Enhanced Liver Fibrosis.

Disclosures: Vijay Shah:Boehringer Ingelheim: Consultant, GSK: Consultant, GENFIT SA: Consultant, Intercept Pharmaceuticals, Inc.: Advisor, Korro Bio, Inc.: Consultant, Novo Nordisk A/S: Consultant, Resolution Therapeutics, Ltd.: Advisor, Seal Rock Therapeutics, Ltd.: Consultant, Surrozen: Advisor, Dexcel Pharma Technologies, Ltd.: Consultant, Dimension Inx.: Advisor, Enveda: Consultant, Ochre Bio: Consultant, Satellite Biosciences, Inc.: Consultant, Juan Pablo Arab:Nothing to Disclose, Ramon Bataller:Nothing to Disclose, Jerome Boursier:echosens: Consultant, Inventiva: Consultant, Siemens: Consultant, Pfizer: Advisor, Novonordisk: Consultant, Gilead: Royalties

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0088 | ALCOHOL-ASSOCIATED HEPATITIS DOES NOT INDEPENDENTLY AFFECT RESPONSE OR MORTALITY IN TERLIPRESSIN-TREATED PATIENTS WITH HEPATORENAL SYNDROME-ACUTE KIDNEY INJURY: RESULTS FROM THE HRS-HARMONY CONSORTIUM

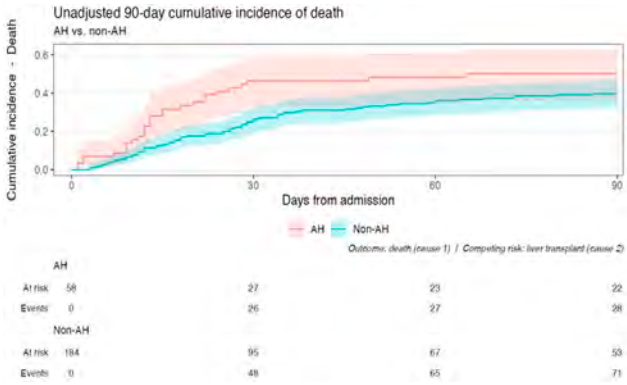
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Background: Hepatorenal syndrome-acute kidney injury (HRS-AKI) is a serious complication of advanced liver disease, frequently occurring in alcohol-associated hepatitis (AH), a population with high inflammatory burden and multi-organ failure. Terlipressin is the only FDA-approved therapy for HRS-AKI, but whether treatment response, safety, and short-term outcomes differ in patients with AH is not well defined. **Methods:** We analyzed consecutive adults with HRS-AKI treated with terlipressin at 16 U.S. academic centers. AH was defined per NIAAA criteria. Primary outcome was overall response (complete or partial) and secondary outcome was 90-day mortality. Multivariable logistic regression models were used to evaluate the association between AH and overall response. Fine-Gray competing risk models were used to evaluate the association between AH and mortality, treating liver transplantation (LT) as a competing event. **Results:** Among 242 patients, 58 (24%) had AH. Patients with AH were younger (53 vs 58 yrs, $p < 0.01$), more often male (74% vs 60%, $p = 0.04$), and had greater illness severity, including higher MELD 3.0 (34 vs 31; $p < 0.01$) and more ACLF grade 3 (62% vs 39%; $p < 0.01$) compared to patients without AH. Overall response was 47% in AH vs 58% in non-AH patients ($p = 0.19$) and was similar among patients with ACLF grade 3 (44% vs 46%, $p = 0.90$). After adjustment for age, sex, and ACLF grade, AH was not associated with overall response (OR 0.81, 95%CI 0.42-1.54; $p = 0.50$). Renal replacement therapy was identical (31% vs 31%) and discontinuation for respiratory failure was similar (12% vs 9%; $p = 0.61$). Overall at 90 days, 42% died and 27% underwent LT, with significantly lower LT rates in AH (12% vs. 32%, $p = 0.01$). The cumulative incidence of death was numerically higher in patients with AH [50% (95% CI 36-62)] compared to those without AH [40% (95%CI 32-47)] (**Figure)** . However, this difference was not statistically significant [sHR 1.54 (95%CI 0.98-2.43), $p = 0.06$]. AH was not associated with death after adjustment for age and MELD 3.0 [sHR 1.58 (95%CI 0.97-2.56) $p = 0.07$) or age, sex, and ACLF grade [sHR 1.39 (95%CI 0.86-2.24) $p = 0.20$]. **Conclusion:** In this multicenter cohort, terlipressin-treated patients with HRS-AKI and AH had similar treatment response and 90-day mortality compared to those without AH. These findings suggest that AH alone should not deter terlipressin use and highlight the importance of early transplant evaluation in this high-risk population.



Disclosures: Christina Lee:Nothing to Disclose, Andrew Allegretti:Nothing to Disclose, Ann Ma:Nothing to Disclose, R. Todd Frederick:Nothing to Disclose, Nneka Ufere:Nothing to Disclose, Sydney Whittaker: Nothing to Disclose, Tianqi Ouyang:Nothing to Disclose, Raffi Karagozian:Nothing to Disclose, Stevan Gonzalez:Mallinckrodt Pharmaceuticals: Speaking and Teaching, Mallinckrodt Pharmaceuticals: Consultant, Madrigal Pharmaceuticals: Advisor, HEPQuant: Advisor, Xing Li:Nothing to Disclose, Justin Belcher:Mallinckrodt Pharmaceuticals: Advisor, Giuseppe Cullaro: Ocelot Bio: Consultant, Retro Sciences: Consultant, Ipsen: Consultant, J. Pedro Teixiera:Vantive: Consultant, Mallinckrodt: Consultant, Talphera: Consultant, Eli Lilly: Stock - publicly traded company, Novo Nordisk: Stock - publicly traded company, Pfizer: Stock - publicly traded company, Deidre Sawinski:Nothing to Disclose, Michael Granda:Nothing to Disclose, Luma Succar: Nothing to Disclose, Eric Orman:Sitero: Consultant, Biovie: Advisor, Bausch Health: Consultant, Vertex: Consultant, Zydus: Consultant, Eccogene: Consultant, Zealand: Consultant, Javier Neyra:Nothing to Disclose, Justin Boike:W. L. Gore and Associates: Grant/Research Support, Echosens: Consultant, W. L. Gore and Associates, Inc.: Consultant, Novo Nordisk: Speaking and Teaching, Andres Duarte-Rojo:Echosens: Grant/Research Support, Echosens: Grant/Research Support, CIMA Sciences: Consultant, HepQuant: Advisor, Merz: Advisor, CIMA Sciences: Grant/Research Support, Merz Therapeutics: Advisor, Robert Wilechansky:Nothing to Disclose, Hugo Vargas: Sequana Medical: Consultant, Mallinckrodt: Consultant, Ocelot: Grant/Research Support, Arrowhead Phama: Grant/Research Support, Takeda: Grant/

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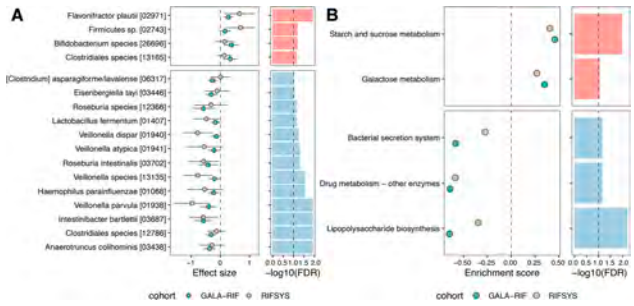
0089 | RIFAXIMIN-α AFFECTS GUT MICROBIOME FUNCTION AND REDUCES CIRCULATING CCL-20 IN PATIENTS WITH ALCOHOL-RELATED LIVER DISEASE

Nikolaj Torp[1] Evelina Stankevic[2] Suguru Nishijima[3] Julie Dubourg[4] Marisa Keller[3] Diënty Hazenbrink[3] Stine Johansen[5] Laura Pikkupeura[6] Johanne Hansen[1] Camilla Dalby Hansen[5] Ida Villesen[1] Sönke Detlefsen[1] Helene Bæk Juel[7] Maximilian Joseph Brol[8] Robert Schierwagen[9] Dennis Pohl[3] Anthony Fullam[3] Christian Schudoma[3] Diana Leeming[10] Morten Karsdal[10] Mary Rinella[11] Maja Thiele[12] Mani arumugam[7] Jonel Trebicka[13] Michael Kuhn[3] Peer Bork[3] Torben Hensen[7] Aleksander Krag[14] Mads Israelsen[1], [1]Odense University Hospital, [2]University of Copenhagen, [3]Molecular Systems Biology Unit, European Molecular Biology Laboratory, Heidelberg, Germany, [4]Eccogene Inc., Boston, Massachusetts, USA, [5]Department of Gastroenterology & Hepatology, Odense University Hospital, Odense, Denmark, [6]Novo Nordisk Foundation Center for Basic Metabolic Research University of Copenhagen, [7]Novo Nordisk Foundation Center for Basic Metabolic Research, University of Copenhagen, Copenhagen, D, [8]University Hospital Münster, [9]University Hospital Muenster, [10]Nordic Bioscience, [11]The University of Chicago, [12]Evido.health, [13]Department of Internal Medicine B, University of Münster, Munster, Germany, [14]University of Southern Denmark

Background: Fibrosis progression in alcohol-related liver disease (ALD) is driven in part by gut dysbiosis, increased microbial translocation, and epithelial immune activation. These early gut–liver axis disturbances provide a rationale for microbiome-targeted therapy. Rifaximin-α, a widely used gut-restricted antibiotic and pregnane X receptor agonist, has demonstrated anti-inflammatory activity in advanced liver disease, but its mechanistic effects remain unclear. We therefore examined whether rifaximin-α alters microbial functional pathways and systemic inflammatory signaling in the randomized GALA-RIF trial with comprehensive validation in independent cohorts and in vitro and ex vivo models. **Methods:** This prespecified mechanistic study analyzed samples from the randomized, double-blind, placebo-controlled GALA-RIF trial, testing the effects of rifaximin-α in ALD (n = 136). Stool metagenomics (n = 134) and plasma proteomics (n = 131) were obtained at baseline, 1 month, and 18 months. Outcomes included rifaximin-associated changes in microbial composition and function, circulating proteins, and their clinical correlations. Findings were validated *in vitro*, in the RIFSYS trial, and through population-scale proteomic–phenomic associations in the UK Biobank. **Results:** Rifaximin-α preserved overall microbial diversity and load but produced selective shifts in microbial guilds implicated in barrier disruption, including reductions in oral-derived and mucin-degrading taxa (e.g., *Veillonella*, *Haemophilus*, *Roseburia*) and enrichment of short-chain fatty acid-associated species such as *Flavonifractor plautii* (**Figure**). In both the derivation and validation cohorts, microbial functional analysis showed that rifaximin-α induced a significant shift towards lower lipopolysaccharide (LPS) synthesis and increased starch, sucrose, and galactose metabolism (**Figure**). Rifaximin-α significantly reduced circulating CCL20 (FDR < 0.05). CCL20 levels correlated strongly with biochemical and histological markers of liver injury and fibrosis and predicted incident liver disease in the UK Biobank. In vitro and ex vivo experiments validated rifaximin sensitivity of affected taxa. **Conclusion:** Rifaximin-α selectively reprograms gut microbial function and attenuates LPS-linked epithelial chemokine signaling, notably CCL20, a candidate mediator of gut–liver immune crosstalk. These findings provide a mechanistic rationale for targeting the gut-liver axis in ALD to reduce liver fibrosis progression.

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0090 | NALTREXONE AND BACLOFEN ARE ASSOCIATED WITH LOWER INCIDENT OF LIVER DISEASE COMPARED TO ACAMPROSATE IN ALCOHOL USE DISORDER: A PROPENSITY-WEIGHTED COHORT STUDY OF A LONGITUDINAL BIOBANK REPOSITORY

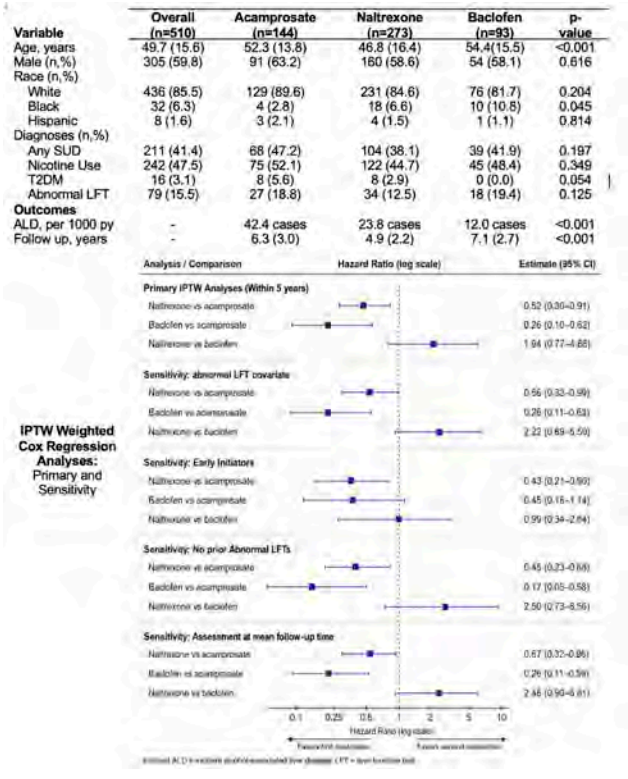
Katherine Cooper[1] Rachael Mahle[1] Sanjana Rane[1] Russell Goodman[2] Esperance Schaefer[3] Wei Zhang[2] Eric Przybyszewski[2] Jay Luther[2], [1]Massachusetts General Hospital, Harvard Medical School, [2]Massachusetts General Hospital, [3]Brigham and Women's Hospital

Background: Pharmacotherapy for alcohol use disorder (AUD) is associated with improved alcohol-related outcomes, but comparative data on liver outcomes in patients initiating medications for AUD (mAUD) remain limited. **Methods:** We performed a target trial emulation (TTE) among patients diagnosed with AUD between 2005-2020 without viral hepatitis or pre-existing alcohol associated liver disease (ALD) who newly initiated a mAUD within 5 years of AUD diagnosis. Time zero was defined as the date of medication initiation. The primary outcome was incident ALD, assessed over 10-year follow-up. Unadjusted incidence rates were calculated up to 10 years. Target trials were then conducted with pairwise comparisons between naltrexone, acamprosate, and baclofen. Stabilized inverse probability of treatment weights (IPTW) were estimated using age, sex, race, ethnicity, tobacco use, other substance use disorder, and type 2 diabetes mellitus. Weighted Cox proportional hazards models were used to estimate hazard ratios. Sensitivity analyses were performed in patients with early initiation of mAUD, defined as within 2 years of AUD diagnosis, and after excluding patients with any history of abnormal baseline liver function test (LFT). **Results:** Among 510 eligible patients with mean age 50.5 years were included (273 naltrexone, 144 acamprosate, 93 baclofen). Prior to weighting, demographics varied by

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group (Table 1). Crude incidence of ALD was higher among acamprosate initiators (42.4 per 1000 py) than naltrexone (23.8 per 1000 py) and baclofen (12.0 per 1000 py). In independent target trials, both naltrexone (HR 0.52, 95% CI 0.30-0.91; p = 0.021), and baclofen (HR 0.26, 95% CI 0.10–0.62; p = 0.003) were associated with lower incident ALD compared to acamprosate. The association was attenuated but remained significant when evaluating ALD or death among baclofen compared to acamprosate initiators (HR 0.46, 95% CI 0.24-0.87, p = 0.017). Adding abnormal LFTs to the IPTW-model did not change results, and findings were directionally consistent in sensitivity analyses restricted to treatment initiation within 2 years and after excluding patients with abnormal LFTs (Figure 1). In exploratory stratified analyses, findings were similar in males and females, and in those with BMI < 30 and BMI ≥ 30 (*not shown*). **Conclusion:** In this TTE of patients diagnosed with AUD without pre-existing liver disease, incident ALD rates differed by mAUD type. Compared with acamprosate, naltrexone and baclofen were associated with lower risk of incident ALD, with findings generally consistent across sensitivity analyses that consider both time to initiation and baseline risk. These results suggest that mAUD selection may have implications for downstream liver disease risk, although prospective studies are needed to confirm these findings.



Disclosures: Katherine Cooper:Nothing to Disclose, Rachael Mahle:Nothing to Disclose, Sanjana Rane: Nothing to Disclose, Russell Goodman:Nothing to Disclose, Esperance Schaefer:Nothing to Disclose, Wei zhang:Nothing to Disclose, Eric Przybyszewski: Nothing to Disclose, Jay Luther:Nothing to Disclose.

0092 | FDA APPROVED PDE4-SPECIFIC INHIBITOR ROFLUMILAST DEMONSTRATES REMARKABLE THERAPEUTIC EFFICACY IN MOUSE MODEL OF ALD

Diego Montoya-Durango[1] Mary Nancy Walter[1] Yali Wang[1] Jingwen Zhang[1] Jing Feng[1] Dibson Gondim[1] Mercia Gondim[1] Xiang Zhang[1] Shirish Barve[2] Craig McClain[1] Leila Gobejishvili[1], [1]University of Louisville, [2]University of Louisville and Norton Neuroscience Institute Cressman Parkinson's Research Team

Background: Alcohol-associated liver disease (ALD) is a major health problem with no FDA-approved therapy. Preclinical studies identified phosphodiesterase 4 (PDE4) as a therapeutic target for ALD. Importantly, our group showed that patients with ALD have higher hepatic levels of PDE4 enzymes. We also showed that the first FDA-approved PDE4 inhibitor for COPD, Roflumilast, significantly attenuated endotoxin-inducible inflammatory cytokine production in *ex vivo* whole blood of patients with ALD. To date three PDE4 inhibitors have been approved by FDA for various inflammatory and fibrotic diseases, however the studies evaluating their efficacy in ALD are lacking. **Methods:** C57Bl/6J mice were subjected to a 16-week ALD model (Western diet with alcohol in drinking water). The control group had access to drinking water, while the alcohol group drank alcohol (alternating 10%/20% weekly). 10 weeks after alcohol, one group of mice received Roflumilast (PDE4i) (3 mg/kg body weight) three times a week, while another received placebo for the remaining six weeks of alcohol drinking. Plasma levels of liver injury markers (ALT, ALP, keratin 18), total bile acids, cholesterol, soluble CD14 (sCD14, a marker of systemic inflammation) were measured at 10 and 16 weeks. Liver sections were evaluated for steatosis; real time qPCR and Western blot analyses were performed. Liver lipid composition and functional lipidomic analysis were carried out using mass spectrometry and visualized using R language and LipidOne. One-Way ANOVA statistical testing using GraphPad Prism was performed. **Results:** Roflumilast prevented alcohol-induced increases in liver injury markers, bile acids, cholesterol and sCD14 compared to placebo. Liver/white adipose tissue-to-body weight ratios were also significantly lower. PDE4i prevented alcohol-induced steatosis, lowered both liver triglyceride levels and the expression of lipogenic genes (*CD36*, *Plin2*, and *Fasn*) while increasing CPT1a levels.

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PDE4i decreased pro-apoptotic (*Bim*, *Bak*, *Bax),* and ER stress genes (*Chop, Aft3, Atf4, Gadd45b*), genes involved in oxidative stress (*Gst1a*, *Gpx2*, *Gpx4)* and inflammation (*Ccl2*, *Ccr2*) compared to placebo. Functional lipidomic analysis revealed that 10-week alcohol lowered antioxidant protection and membrane fluidity, elevated mitochondrial/lysosomal activity and altered endosomal trafficking. Prolonged alcohol drinking for 16 weeks increased oxidized phospholipids, lipid storage and accumulation, reduced cardiolipins and lipolysis, indicating increased oxidative stress, mitochondrial dysfunction and membrane destabilization. In comparison, PDE4i treatment increased cardiolipin and polar lipids, and lipid turnover/mobilization compared to placebo. **Conclusion:** Roflumilast effectively prevented ALD progression by modulating multiple pathogenic pathways, including beneficial hepatic lipid remodeling, strongly supporting its use in ALD patients.

Disclosures: Diego Montoya-Durango:Nothing to Disclose, Mary Nancy Walter:Nothing to Disclose, Yali Wang:Nothing to Disclose, Jingwen Zhang:Nothing to Disclose, Jing Feng:Nothing to Disclose, Dibson Gondim:AstraZeneca: Advisor, Mercia Gondim:Nothing to Disclose, Xiang Zhang:Nothing to Disclose, Shirish Barve:Nothing to Disclose, Craig McClain:Novo Nordisk: Speaking and Teaching, Intercept Pharmaceuticals: Grant/Research Support, Altimmune: Grant/Research Support, Target Pharma Solutions: Grant/Research Support, NIH: Grant/Research Support, VAMC: Grant/Research Support, VAMC: Employee, National Institutes of Health: Grant/Research Support, NovoNordisk: Speaking and Teaching, VAMC: Employee, VAMC: Grant/Research Support, Intercept Pharmaceuticals: Grant/Research Support, Target PharmaSolutions: Grant/Research Support, Leila Gobejishvili:Nothing to Disclose.

0093 | THE THBS2–SPP1 AXIS IN HSC-DRIVEN LIVER FIBROGENESIS: A SYNERGISTIC TARGET FOR ANTIFIBROTIC THERAPY

Hong Li[1] Ning Zhang[1] Wen Zhang[1] Wenyue Wu[1] Ziyan Pan[1] Haodong Ma[1] Caihong Wang[1] Ruoyu Gao[1] Zhi Chen[1] Qiushuang Ji[1] Xunzhen Yan[1] Aiting Yang[1] Aiting Yang[1] Wei Chen[1] Hong You[1], [1]Beijing Friendship Hospital, Capital Medical University

Background: Thrombospondin-2 (THBS2) is markedly upregulated in fibrotic livers and correlates with fibrosis stage independently of etiology. This study aimed to elucidate the role and underlying mechanisms of hepatic stellate cell (HSC)-derived THBS2 in the progression of liver fibrosis. **Methods:** HSC-specific *Thbs2* knockout (*Thbs2*$^{\Delta HSC}$) and human *THBS2* knock-in (h*THBS2*$^{KI\ HSC}$) mice were generated. Liver fibrosis was induced by carbon tetrachloride (CCl_4) injection or bile duct ligation (BDL). The functional role of the THBS2–SPP1 axis was investigated using a dual targeting strategy: extracellular SPP1 was neutralized by intraperitoneal administration of an anti-mouse SPP1 antibody (inVivoMAb), while intracellular SPP1 was suppressed via AAV6-GFAP-sh*Spp1*. Additionally, a THBS2-specific inhibitor was identified and combined with an SPP1-targeting small molecule to evaluate the therapeutic potential of dual THBS2–SPP1 inhibition in liver fibrosis **Results:** *Thbs2*$^{\Delta HSC}$ mice exhibited markedly attenuated hepatic inflammation and fibrosis in both CCl_4- and BDL-induced models. Conversely, h*THBS2*$^{KI\ HSC}$ mice showed significantly aggravated inflammation and fibrotic progression. Mechanistically, *Thbs2* knockdown in HSCs markedly suppressed the expression of the pro-fibrotic mediator SPP1, whereas THBS2 overexpression robustly increased both SPP1 expression and secretion—findings consistently validated in vitro. Moreover, molecular interaction analyses revealed that THBS2 directly interacts with SPP1. Importantly, both anti-SPP1 neutralizing antibody administration and AAV6-GFAP-sh*Spp1*-mediated gene silencing significantly attenuated fibrotic progression in CCl_4treated h*THBS2*$^{KI\ HSC}$ mice, indicating that SPP1 plays an essential role in THBS2-mediated liver fibrogenesis. Furthermore, a novel THBS2 inhibitor was identified through integrated virtual drug screening combined with surface plasmon resonance (SPR) validation. Pharmacodynamic analyses demonstrated that this compound exerted significant antifibrotic effects in both CCl_4- and 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC)-induced liver fibrosis models, accompanied by marked histopathological improvement. Notably, combined targeting of the THBS2–SPP1 axis produced synergistic anti-fibrotic effects in CCl_4treated h*THBS2*$^{KI\ HSC}$ mice. **Conclusion:** Our findings demonstrate that HSC-derived THBS2 drives liver fibrogenesis through regulation of SPP1. Coordinated targeting of the THBS2–SPP1 axis represents a promising therapeutic strategy to substantially mitigate liver fibrosis.

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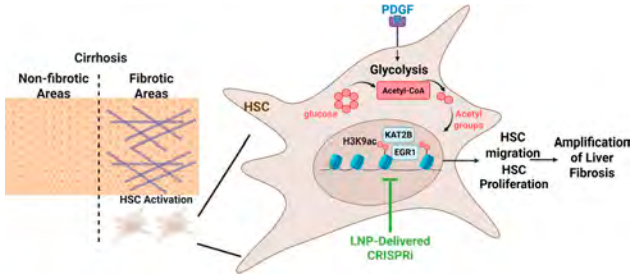
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Nothing to Disclose, Nothing to Disclose, Wei Chen: Nothing to Disclose, Hong You:Nothing to Disclose.

0094 | SPATIAL EPIGENOMICS, *IN VIVO* CRISPRI, AND $^{13}C_6$-GLUCOSE TRACING REVEAL GLYCOLYSIS-TO-HISTONE ACETYLATION TO DRIVE HEPATIC STELLATE CELL ACTIVATION AND SUBSEQUENT MURINE AND HUMAN LIVER FIBROSIS

Alexander Washington[1] Zeba Firdaus[1] Jeff Meridew[1] Ya Li[1] Chunmiao Cai[1] Patrick Starlinger[1] Timucin Taner[2] Julie Heimbach[2] Vijay Shah[2] Petra Hirsova[2] Kirk Wangensteen[1] Saigopalakrishna Yerneni[1] Alexandre Maia[1] Taro Hitosugi[1] Enis Kostallari[2], [1]Mayo Clinic, [2]Mayo Clinic Rochester

Background: Activated hepatic stellate cells (HSCs) in fibrotic regions drive liver fibrosis through enhanced glycolysis. Glycolysis-derived pyruvate may generate acetyl-coenzyme A (Ac-CoA) through pyruvate dehydrogenase (PDH). Ac-CoA, which may be generated through several metabolic pathways, fuels histone acetylation. Nonetheless, how glycolysis directly regulates the epigenomic landscape of activated HSCs and liver fibrosis remains unknown and is the focus of this study. **Methods:** Patient-derived healthy or cirrhotic liver tissues were analyzed by spatial epigenomics (CUT&TAG) and precision-cut liver slices (PCLS). *In vitro*, primary human HSCs were activated by platelet-derived growth factor B (PDGF) and analyzed by western blot (WB), transwell assay, 5-ethynyl-2′-deoxyuridine (EdU) uptake, liquid chromatography mass spectrometry (LC/MS), and chromatin immunoprecipitation sequencing (ChIP-seq). *In vivo*, dCas9-Krab^{HSC} mice expressing *dCas9-Krab* selectively in HSCs were injected retro-orbitally with lipid nanoparticle (LNP) carrying single guide RNAs (sgRNA) to repress lysine acetyltransferase 2B (Kat2b). Liver fibrosis was induced by carbon tetrachloride (CCl_4). **Results:** We previously showed that PDGF specifically increased histone 3 lysine 9 acetylation (H3K9ac) (TLM2025), an epigenetic mark associated with active gene promoter regions. To understand whether glycolysis is directly involved in H3K9ac, $^{13}C_6$-glucose carbons were traced by LC/MS. PDGF increased 2.5-fold glucose-derived carbons in Ac-CoA compared to vehicle (incorporation of 2 heavy isotopes: M+2, $p < 0.05$). Inhibiting glycolysis-derived Ac-CoA through PDH1 inhibitor Devimistat reduced 3-fold PDGF-mediated H3K9ac (WB $p < 0.05$), suggesting that glycolysis directly promotes H3K9ac. To determine the H3K9ac-dependent gene program regulator in the human fibrotic niche, we integrated spatial epigenomics H3K9ac CUT&TAG from healthy and cirrhotic human livers, and ChIP-seq from primary human HSCs. Motif analysis of H3K9ac CUT&TAG demonstrated that compared to non-fibrotic regions and healthy control, H3K9ac in fibrotic regions was associated with gene programs that were upregulated by early growth response 1 (EGR1). ChIP-seq revealed EGR1 as one of the top regulators of PDGF-mediated pro-migratory and pro-proliferative genes in primary human HSCs. EGR1 knockdown reduced 2.7-fold PDGF-mediated HSC proliferation (EdU, $n = 6$, $p < 0.05$) and 3.1-fold migration (transwell, $n = 6$, $p < 0.05$). In dCas9-Krab^{HSC} mice, CCl_4-induced collagen deposition (19.1-fold by Sirius Red, 20.1-fold by IF, $p < 0.05$) was reduced by LNP-delivered sgKat2b specifically to HSCs (2.1-fold by Sirius Red, 3.2-fold by IF, $p < 0.05$, 5 mice/group). Ex vivo, H3K9ac-selective inhibitor CPTH6 reduced 4.5-fold collagen deposition in cirrhotic human PCLS (WB, $n = 5$, $p < 0.05$). **Conclusion:** Glycolysis-derived H3K9ac upregulates an EGR1-dependent fibrogenic gene program leading to HSC activation and subsequent liver fibrosis.



Disclosures: Alexander Washington:Nothing to Disclose, Zeba Firdaus:Nothing to Disclose, Jeff Meridew: Nothing to Disclose, Ya Li:Nothing to Disclose, Chunmiao Cai:Nothing to Disclose, Patrick Starlinger:Nothing to Disclose, Timucin Taner:Nothing to Disclose, Julie Heimbach:Nothing to Disclose, Vijay Shah:Boehringer Ingelheim: Consultant, GSK: Consultant, GENFIT SA: Consultant, Intercept Pharmaceuticals, Inc.: Advisor, Korro Bio, Inc.: Consultant, Novo Nordisk A/S: Consultant, Resolution Therapeutics, Ltd.: Advisor, Seal Rock Therapeutics, Ltd.: Consultant, Surrozen: Advisor, Dexcel Pharma Technologies, Ltd.: Consultant, Dimension Inx.: Advisor, Enveda: Consultant, Ochre Bio: Consultant, Satellite Biosciences, Inc.: Consultant, Petra Hirsova:Nothing to Disclose, Kirk Wangensteen:Nothing to Disclose, Saigopalakrishna Yerneni:Nothing to Disclose, Alexandre Maia:Nothing to Disclose, Taro Hitosugi:Nothing to Disclose, Enis Kostallari:Nothing to Disclose.

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0097 | ITPR1-DEPENDENT MITOCHONDRIA–ER CONTACT REMODELING PROMOTES HEPATIC STELLATE CELL ACTIVATION AND LIVER FIBROSIS.

Rui Zhang[1] Hui Han[1], [1]China Pharmaceutical University

Background: Hepatic stellate cell (HSC) activation leads to extracellular matrix deposition. Mitochondria-endoplasmic reticulum contact sites (MERCs) coordinate inter-organelle Ca^{2+} transfer and regulate mitochondrial metabolism. However, whether profibrogenic signaling is coupled with structural remodeling of MERCs and whether this process contributes to liver fibrosis remains unclear. We hypothesized that MERC remodeling enhances Ca^{2+} transfer to support HSC activation, thereby promoting liver fibrosis. **Methods:** Human and mouse single-cell datasets were analyzed to assess the expression of MERC-related genes in HSCs during liver fibrosis. MERCs were quantified in vivo using a split-GFP MERC reporter and proximity ligation assay (PLA). Tamoxifen-inducible HSC-specific *Itpr1* knockout mice (*Itpr1*$^{\Delta HSC\text{-}ERT2}$) were generated and subjected to the CDAA-HFD MASH-induced fibrosis model. LX-2 human HSCs were used for functional and mechanistic studies *in vitro*. **Results:** The MERC-localized Ca^{2+} channel ITPR1 (or *Itpr1*) was upregulated in HSCs from fibrotic human (or mouse) livers. Both split-GFP MERC reporter imaging and PLA demonstrated increased MERCs in HSCs during MASH-induced fibrosis. *Itpr1*$^{\Delta HSC\text{-}ERT2}$ mice showed attenuated liver fibrosis compared to controls, as evidenced by reduced Sirius Red-positive area, HSC activation markers (*Col1a1*, *Acta2*), and collagen deposition, with relatively limited effects on steatohepatitis. In LX-2 cells, TGFB stimulation recapitulated the increase in MERCs observed *in vivo*. TGFB increased expression of HSC activation markers (*COL1A1*, *ACTA2*, *FN1*, *COL3A1*), as well as mitochondrial Ca^{2+} levels, while these effects were suppressed by *ITPR1* siRNA. Pharmacological inhibition of the mitochondrial Ca^{2+} uniporter (MCU) that receives Ca^{2+} transferred from ITPR1, using MCU-i4, recapitulated the effects of ITPR1 siRNA. Conversely, forced enhancement of MERCs by transfection of a mitochondria-ER linker facilitated TGFB-induced activation, whereas this effect was attenuated by ITPR1 silencing. **Conclusion:** HSCs undergo MERC remodeling during activation, which contributes to liver fibrosis progression. This process is at least partly mediated by ITPR1-dependent mitochondrial Ca^{2+} transfer. Future studies will investigate the upstream mechanisms driving MERC remodeling.
Disclosures: Rui Zhang:Nothing to Disclose, Hui Han: Nothing to Disclose.

0098 | HUMAN LIVER PROGENITOR CELL-DERIVED EXTRACELLULAR VESICLES DRIVE CONVERGENT ANTIFIBROTIC RESPONSES THROUGH MODEL-DISTINCT IMMUNE REMODELING IN MURINE MASH

Kiminori Kimura[1] Noriyo Okamoto[1] Juntaro Matsuzaki[2] Kenichi Harada[3] Takahiro Ochiya[4], [1]Tokyo Metropolitan Komagome Hospital, [2]Keio University Faculty of Pharmacy, [3]Kanazawa University Graduate School of Medical Sciences, [4]Tokyo Medical University

Background: Stem/progenitor cell-derived extracellular vesicles (EVs) are emerging as cell-free therapeutics for chronic liver disease, yet their antifibrotic mechanisms are typically defined in a single model, leaving unclear whether they act through a shared or context-specific program. Using human chemically induced liver progenitor cell-derived EVs (hCLiP-EV) in two distinct murine MASH models (CDAHFD and GAN diet), we tested whether hCLiP-EV converge on a common antifibrotic endpoint while engaging model-dominant fibrogenic and immune programs. **Methods:** In CDAHFD, mice were fed a CDAHFD for 16 weeks and received hCLiP-EV (1×10^9 or 1×10^{10} particles, tail vein) weekly for four weeks from week 12, after fibrosis was established. In the GAN diet model, the same regimen began at week 20 or 28, with livers harvested at week 24 or 32. Fibrosis and hepatic stellate cell (HSC) activation were assessed by Sirius Red, hydroxyproline, and fibrogenic markers (αSMA/Acta2, Col1a1, Ccn2/CTGF), with serum ALT and hepatic triglyceride. Mechanisms were examined by bulk RNA-seq with GSEA, immunostaining, flow cytometry, and spatial transcriptomics. **Results:** hCLiP-EV attenuated fibrosis in both models. In CDAHFD, it reduced Sirius Red-positive area ($P = 0.0039$) and hydroxyproline at both doses ($P = 0.0095$, $P = 0.002$), with direct HSC deactivation (reduced αSMA, Col1a1). Transcriptomic responses were dose-dependent: low-dose EVs induced regenerative programs (cell cycle; NES = +1.97) while suppressing ECM/TGF-β signaling (NES = −1.87), whereas high-dose EVs restored hepatocyte metabolism (NES = +2.03; Cyp2c54, Ces1d) with sustained ECM suppression (NES = −1.60). These accompanied reduced Clec4f/F4/80-positive populations and LCN2, indicating attenuated Kupffer cell/macrophage inflammation; spatial transcriptomics confirmed reduced fibro-enriched niches. In the GAN diet model, hCLiP-EV reduced hydroxyproline at 24 and 32 weeks ($P = 0.0318$, $P = 0.0022$), whereas serum ALT was unchanged. In contrast to CDAHFD, regenerative programs and collagen genes (Col1a1/Col1a2/Col3a1) were unchanged; instead, fibrosis attenuation

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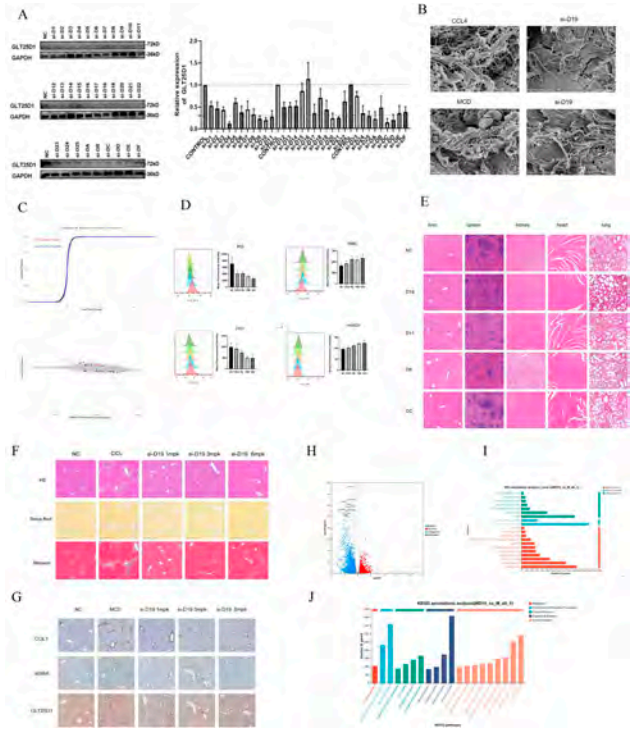
was driven by selective suppression of the fibrogenic master regulator Ccn2/CTGF and B-cell/immunoglobulin-associated programs (Cd19, Cd79a/b, Ig genes), with reduced hepatic B-cell accumulation. **Conclusion:** hCLiP-EV exerted antifibrotic effects across two MASH models, converging on reduced hepatic fibrosis through divergent, model-dominant mechanisms: in CDAHFD, direct HSC deactivation with attenuated Kupffer cell/macrophage inflammation; in GAN-diet MASH, selective CTGF suppression and reduced B-cell activation. These findings support hCLiP-EV as a cell-free therapeutic engaging context-specific fibrogenic and immune niches across distinct MASH microenvironments.

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0099 | SIRNA-MEDIATED GLT25D1 SILENCING ATTENUATES LIVER FIBROSIS VIA IMPAIRMENT OF COLLAGEN O-GLYCOSYLATION, ER RETENTION, AND DEGRADATION OF MISFOLDED PROCOLLAGEN

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Background: Effective antifibrotic therapies remain limited because signaling-directed interventions are often compensated by redundant inflammatory and TGF-β pathways. Collagen export and fibril stability depend on hydroxylysine O-glycosylation during procollagen maturation. GLT25D1 catalyzes this modification, but its role in liver fibrosis remains unclear. **Methods:** More than 100 chemically modified GLT25D1 siRNAs were screened in LX-2 cells and primary hepatic stellate cells (HSCs) for silencing efficiency, specificity, cytotoxicity, and innate immune activation. Lead liver-directed siRNAs were evaluated in CCl_4- and methionine/choline-deficient (MCD) diet-induced murine fibrosis models. Therapeutic efficacy was assessed using histology, Ishak scoring, immunostaining, serum biochemistry, hematology, and scanning electron microscopy (SEM). Mechanistic studies included glycosylation assays, mass spectrometry, immunofluorescence confocal imaging, ubiquitination analysis, RNA sequencing, and ER-associated degradation (ERAD) evaluation. **Results:** Nine siRNAs reduced GLT25D1 expression by ≥70% in HSCs, and four optimized candidates demonstrated improved serum stability without cytotoxicity or interferon-like responses. In both CCl_4 and MCD fibrosis models, siD19 dose-dependently reduced collagen deposition, fibrotic septa formation, and Ishak fibrosis scores, accompanied by decreased COL1 and α-SMA expression. SEM revealed remodeling of dense collagen networks into thinner and loosely organized fibrils. Mechanistically, GLT25D1 inhibition reduced procollagen hydroxylysine O-glycosylation, resulting in defective procollagen folding and impaired triple-helix maturation. Mass spectrometry confirmed reduced collagen glycosylation and accumulation of immature collagen intermediates. Immunofluorescence confocal imaging demonstrated procollagen retention within the endoplasmic reticulum together with increased co-localization with GRP78, indicating activation of ER stress responses. Ubiquitination assays further showed enhanced targeting of misfolded procollagen toward ER-associated degradation, leading to accelerated intracellular clearance and reduced secretion of mature collagen. These changes were accompanied by extracellular matrix remodeling and attenuation of mechanosensitive FAK/YAP/TAZ profibrotic signaling. Transcriptomic profiling revealed broad remodeling of pathways involved in cellular stress adaptation, extracellular matrix regulation, and profibrotic signaling. **Conclusion:** Targeting GLT25D1 with siRNA suppresses fibrosis by disrupting collagen structural maturation and promoting clearance of misfolded procollagen, representing a structure-oriented antifibrotic strategy beyond conventional signaling inhibition.



Disclosures: Ziteng Wang:Nothing to Disclose, Hongshan Wei:Nothing to Disclose.

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0100 | CIRRHOTIC LIVER EXTRACELLULAR MATRIX REVEALS MATRISOME REMODELING AND SERVES AS A SCAFFOLD FOR ADVANCED HUMAN *IN VITRO* MODELS

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Background: The liver extracellular matrix (ECM) is a dynamic regulator of cellular behavior and is extensively remodeled during chronic liver disease. In cirrhosis, ECM remodeling involves changes in matrix composition and organization that reshape the hepatic microenvironment. However, comprehensive characterization of the cirrhotic liver matrisome remains limited. Here, we aimed to characterize ECM protein composition in cirrhotic liver and assess whether human liver-derived decellularized ECM (dECM) supports repopulation by cholangiocyte organoid-derived cells and their differentiation towards hepatocytes. **Methods:** Human control and cirrhotic liver tissues were decellularized and analyzed by LC–MS/MS-based proteomics. Protein group data were log2-transformed, median-scale normalized, and analyzed for differential expression using limma with Benjamini–Hochberg correction. Ultrastructural organization of control and cirrhotic dECM was assessed by scanning electron microscopy (SEM). dECM samples were repopulated with dissociated human cholangiocyte organoids, cultured for 15 days in hepatocyte differentiation media, and evaluated by H&E staining and immunostaining for cholangiocyte-associated markers (SOX9, CK17, CK19) and albumin (ALB). **Results:** Decellularization enriched ECM components, increasing matrisome abundance from 3.2% in native tissue to 45.7% in dECM. Proteomic analysis of dECM identified 1,907 protein groups, including 157 matrisome-associated protein groups across multiple ECM functional classes. Principal component analysis showed clear separation between control and cirrhotic dECM. Differential analysis identified 20 matrisome protein groups significantly upregulated in cirrhosis, including collagens and glycoproteins associated with fibrosis-related processes. SEM revealed altered matrix architecture in cirrhotic dECM compared with control dECM. Following repopulation, nuclei were detected on H&E staining in both control and cirrhotic dECM. Successful repopulation of dECM control and cirrhotic livers was confirmed by the presence of nuclei on H&E staining. Immunostaining demonstrated expression of cholangiocyte-associated markers (SOX9, CK17, and CK19). ALB expression was detected in differentiated hepatocyte-like cells seeded onto both control and cirrhotic dECM, confirming hepatocyte-lineage differentiation. **Conclusion:** Human liver-derived dECM from control and cirrhotic tissues supports engraftment of organoid-derived cells. Cirrhotic dECM displays distinct ultrastructural organization, altered matrisome protein composition, and favors hepatocyte differentiation compared to control dECM. Our findings establish human cirrhotic dECM as a disease-specific matrix platform that captures cirrhosis-associated matrisome remodeling and serves as a scaffold for human *in vitro* cirrhotic modeling and drug screening.

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0101 | IDENTIFYING AN OUTCOME-BASED LIVER FRAILTY INDEX CUTOFF TO DEFINE ROBUSTNESS AS A TARGET FOR FRAILTY INTERVENTION

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Background: The Liver Frailty Index (LFI) predicts waitlist mortality (WLM) in cirrhosis, with an established cut-point ($\geq$4.4) identifying "frail" patients at increased risk. No corresponding threshold defines "robust"—the LFI below which patients are no longer at increased risk. The robust cut-point of 3.2 currently in use was derived distributionally, designated as the 20th percentile of LFI scores in the derivation cohort, rather than from clinical outcomes data. An outcomes-based threshold of "robust" is essential to identify a specific target for frailty-directed interventions. We aimed to address this gap. **Methods:** We analyzed data from ambulatory adults with cirrhosis without HCC listed for liver transplant (LT) at 11 centers in the Functional Assessment in Liver Transplantation (FrAILT) Study from 2012-24. Fine-Gray models, with competing risk deceased donor LT and adjusted for MELD 3.0, age, and sex, evaluated dichotomous LFI cut-points from 3.0 to 4.3 in 0.1 increments for association with WLM at 3 mos. Replacing LFI cut-points with continuous LFI, the same adjusted models with restricted cubic splines models visualized inflection points. Considering significance and effect size from the cut-point models and inflection points from the spline models, we determined an LFI cut-point for "robust". Using adjusted Fine-Gray models stratified by the derived robust cut-point, we assessed the association between continuous LFI and 3-mo WLM; 6- and 12-mo WLM were evaluated as secondary endpoints. **Results:** Among 3,017 LT candidates, 42% women; median (Q1-Q3) age 58y (49.7-64.0), MELD 3.0 18 (14-22), LFI 4.0 (3.5-4.4); 26% were frail (LFI $\geq$ 4.4). WLM at 3, 6, and 12 mos was 3%, 6%, and 10%. Spline modeling revealed an inflection point near LFI 3.6, above which 3-mo WLM rose more steeply. Dichotomous cut-point analysis identified LFI 3.6 as the threshold below which patients experienced meaningfully lower 3-month mortality. Each 0.1-unit LFI increase was significantly and positively associated with 3-, 6-, and 12-month WLM among patients with LFI $\geq$ 3.6 (SHR 1.07-1.10) but not among those with LFI $<$ 3.6 (SHR 0.98-1.04; Table). **Conclusion:** An LFI of 3.6 identified a threshold of "robust" below which LFI was no longer significantly associated with 3-, 6-, and 12-mo WLM. This outcome-based cutoff offers a clinically meaningful target for interventions aimed at optimizing frailty status in patients with cirrhosis awaiting LT.

Table. Association Between Continuous LFI and WL Mortality by LFI Subgroup

WL Mortality	LFI Subgroup	N (Events)	SHR for continuous LFI per 0.1 unit (95% CI)	p-value
3-month	<3.6	895 (8)	0.98 (0.88-1.09)	0.73
	≥3.6	2122 (71)	1.10 (1.07-1.13)	<0.001
6-month	<3.6	895 (20)	1.04 (0.95-1.15)	0.39
	≥3.6	2122 (138)	1.08 (1.06-1.11)	<0.001
12-month	<3.6	895 (41)	1.01 (0.93-1.10)	0.81
	≥3.6	2122 (216)	1.07 (1.05-1.09)	<0.001

Abbreviations: LFI = Liver Frailty Index; SHR = subdistribution hazard ratio; CI = confidence interval.
Notes: Models are adjusted for MELD 3.0, age, and sex.

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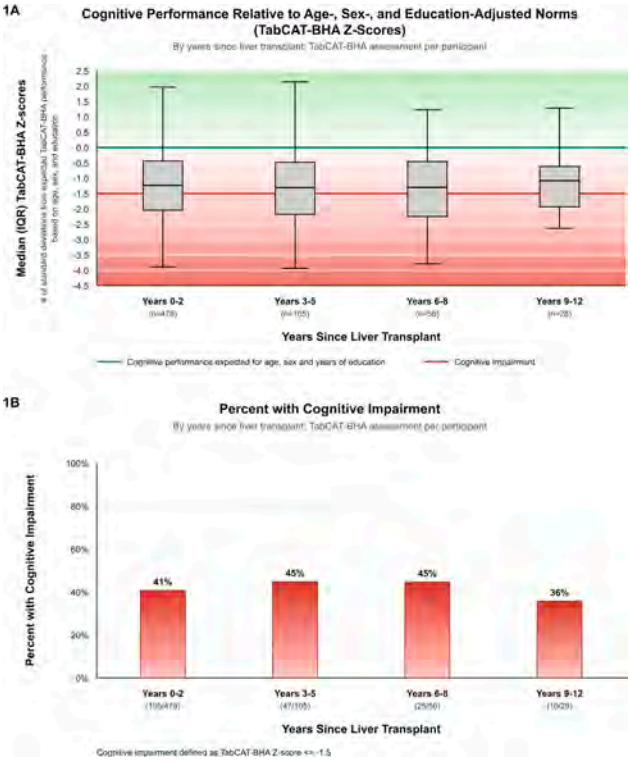
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Research Support, Novo Nordisk: Consultant, Genfit: Consultant, Boehringer Ingelheim: Advisor, Lipocine: Site PI, Gilead: Site PI, Insmed: Consultant, Cosmo: Advisor.

0102 | COGNITIVE IMPAIRMENT IS HIGHLY PREVALENT AFTER LIVER TRANSPLANTATION AND ASSOCIATED WITH PRE-TRANSPLANT FRAILTY

Kacey Berry[1] Fawzy Barry[1] Matthew Kappus[2] Andres Duarte-Rojo[3] Daniel Ganger[4] Daniela Ladner[5] Avesh Thuluvath[6] Elizabeth Verna[7] Marwan Ghabril[8] Elizabeth King[9] Amit Tevar[10] Amy Shui[1] Robert Rahimi[11] Meredith Pearson[12] Katherine Possin[1] Elena Tsoy[1] Lawren VandeVrede[1] Jennifer Lai[1], [1]University of California, San Francisco, [2]Duke University, [3]Northwestern Medicine, [4]Northwestern Memorial Hospital, [5]Northwestern University, [6]Columbia University Irving Medical Center, [7]Columbia University Medical Center, [8]Indiana University, [9]Johns Hopkins Medicine, [10]University of Pittsburgh, [11]Baylor University Medical Center, [12]University of Washington Medicine

Background: Liver transplantation (LT) is widely understood to reverse neurocognitive sequelae of cirrhosis, namely, hepatic encephalopathy (HE). Emerging evidence suggests that a significant subset of LT recipients experience cognitive impairment (CI) that persists beyond the post-operative period—yet prevalence estimates have been hampered by small sample sizes, insensitive instruments, and lack of long-term testing. The prevalence of CI years after LT and associated factors remain undefined. **Methods:** To assess prevalence of post-LT CI and its associated factors, we enrolled ambulatory English-fluent adult LT recipients at 8 U.S. sites. CI was assessed at a post-LT visit via the Tablet-based Cognitive Assessment Tool-Brain Health Assessment (TabCAT-BHA), a validated 10-minute digital screener used worldwide for detecting neurodegenerative cognitive decline. Cognitive impairment (CI) was defined as a TabCAT-BHA z-score $\leq$ -1.5 (in other words, cognitive performance that was 1.5 or more standard deviations below age-, sex- and education-adjusted regression-based norms). Pre-LT and peri/post-LT factors were investigated. Linear regression associated pre- and post-LT factors with CI. **Results:** Of 690 post-LT participants, median age was 61y (IQR 54-69), 38% were female, and median years of education was 14y (IQR 12-16). Median months since LT was 18 (IQR 12-40). Median TabCAT-BHA z-score was -1.3 (IQR -2.2 – (-0.47)); **43% met criteria for CI**. Notably, neither median TabCAT-BHA z-score nor rates of CI differed by post-LT year (Figure 1A and 1B). Pts with vs. without CI were younger (60 v 62y), more likely non-white non-Hispanic (35% v 23%), had fewer median years of education (14 v 15y), higher rates of pre-LT HE (63% v 53%), and increased LT length of stay (9 v 8d). Median pre-LT LFI was higher for those with vs. without CI (4.0 v 3.8). In univariable linear regression, increased pre-LT frailty was associated with worse post-LT cognitive performance: every 0.1 unit increase in LFI was associated with 0.03-unit lower TabCAT-BHA z-score [coeff -0.027, 95% CI -0.040- (-0.015); $p < 0.001$], which persisted after adjusting for age, sex, education, race/ethnicity, pre-LT HE, and post-LT length of stay [coeff -0.026, 95% CI -0.030 – (-0.013); $p < 0.001$]. **Conclusion:** In this multicenter cohort of 690 LT recipients, cognitive impairment was present in over 40%. This rate approximates the prevalence of cognitive impairment in 80-84-year-old community dwelling adults, roughly 20 years older than the median age of our study participants, suggesting accelerated cognitive aging in this population. Pre-LT frailty emerged as a risk factor, including after controlling for co-variates, pointing to a potentially modifiable upstream contributor. Our study provides motivation for routine screening for cognitive impairment after liver transplantation and demonstrates a need to reduce the burden of cognitive impairment in liver transplant recipients.



Disclosures: Kacey Berry: Nothing to Disclose, Fawzy Barry: Nothing to Disclose, Matthew Kappus: Mallinckrodt: Short term engagement advising, Andres Duarte-

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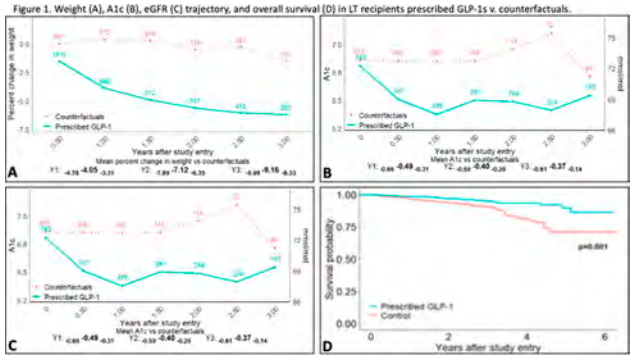
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0103 | OUTCOMES OF GLP-1 USE IN LIVER TRANSPLANT RECIPIENTS WITH DIABETES AND OBESITY: A NATIONAL TARGET TRIAL EMULATION STUDY

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Background: Liver transplant (LT) recipients with diabetes and obesity are at greater risk of graft failure and mortality. GLP-1s may improve outcomes, though LT recipients have been excluded from phase III clinical trials of GLP-1s. We sought to characterize the outcomes of GLP-1s in LT recipients with obesity and diabetes. **Methods:** Using Epic Cosmos, a national electronic health record (EHR) database, we identified adult deceased donor LT recipients 2019-June 2024 with BMI 30+ who were diagnosed with type 2 diabetes prior to LT. Exposed patients included cases prescribed GLP-1 medications approved for weight loss (tirzepatide, liraglutide, semaglutide). Using a target trial emulation framework, we selected one counterfactual control without replacement for each case in which age at transplant was +/-5 y, imputed index date post-LT was +/-30 days, and most recent BMI measurement was +/-5 units of the matched case. We calculated recipients' mean weight in 3-month windows and used inverse probability of treatment weighting (IPTW) to account for potential reporting bias. We plotted weight, A1c, and eGFR trajectories for those with eGFR < 60 at study initiation, as well as survival post-GLP-1 initiation or index date and obtained p-values from linear regression. We also examined safety outcomes. **Results:** 1,038 LT recipients with obesity and diabetes prescribed a GLP-1 were matched to 1,038 counterfactuals. Both groups were comparable in terms of age at LT (mean 60.0 for both groups; p = 0.9), race (72.6% vs 71.6% White, 2.3% vs 3.8% Black; p = 0.2), Hispanic ethnicity (17.2% vs 17.7%; p = 0.8), BMI (34.2 vs 33.8; p = 0.54), and baseline eGFR (55.8 vs 55.9; p = 0.5). GLP-1 recipients were more likely to be female (39.1% vs 33.3%; p = 0.006), have MASH as the etiology of their liver disease (47.9% vs 43.2%; p = 0.042), to have a higher baseline A1c (6.6 vs 6.1%; p < 0.001), and to be on insulin at baseline (85.7% vs 70.6%; p < 0.001). Mean adjusted total body weight loss (Fig 1A), change in A1c (Fig 1B), and eGFR (Fig 1C) at 3 years were -9.16% (95%CI: -9.99 to -8.33), -0.37% (95%CI: -0.61 to -0.14), 2.08 mL/min/1.73 m² (95%CI: 0.68 to 3.49) in GLP-1 recipients vs counterfactuals, respectively. Mortality was 53% lower in the GLP-1 group (Fig 1D; aHR: 0.47; 95%CI: 0.30-0.75), but at an increased risk of developing cholangitis (aHR: 2.42; 95%CI: 1.07-5.48). **Conclusion:** GLP-1 medications lead to greater weight loss, improved A1c, and better eGFR in LT recipients with type 2 diabetes and obesity compared to those who do not take them. They also were associated with improved survival but at the increased risk of developing cholangitis.



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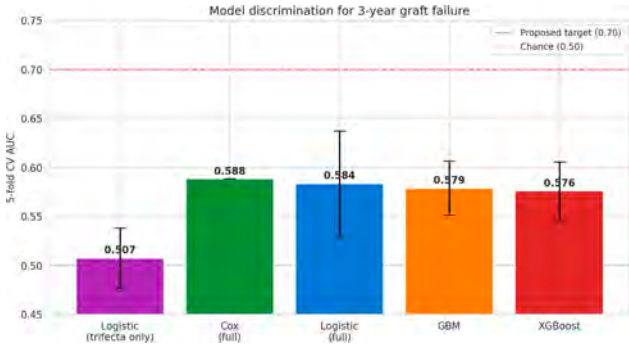
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0104 | METABOLIC FRAILTY PHENOTYPING AND MACHINE LEARNING FOR PREDICTING GRAFT FAILURE AFTER LIVER TRANSPLANTATION FOR MASH

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Background: Metabolic dysfunction-associated steatohepatitis (MASH) is a growing indication for liver transplantation (LT), yet the prognostic value of a pre-LT metabolic frailty phenotype remains uncertain. We evaluated whether a "metabolic trifecta" consisting of class II obesity, diabetes, and functional dependence improves prediction of post-LT graft failure in adult MASH recipients. **Methods:** We performed a retrospective cohort study of adult, single-organ, first LT recipients transplanted for MASH from 2014-2024 who survived ≥30 days post-LT. The trifecta was defined as body mass index ≥35 kg/m2, diabetes, and functional dependence at transplant; patients were classified by component count. Outcomes were graft failure at 90 days, 1 year, and 3 years. Multivariable Cox models adjusted for recipient, donor, operative, and waitlist factors. Five-fold cross-validation compared full logistic regression, trifecta-only logistic regression, gradient boosting, and XGBoost for 3-year graft failure prediction. **Results:** Among 2,787 recipients, median age was 59 years; 1,644 (59.0%) were male. Class II obesity, diabetes, and functional dependence were present in 375 (13.5%), 812 (29.1%), and 1,521 (54.6%), respectively; 76 (2.7%) had the full trifecta. Three-year graft failure occurred in 542 recipients. Three-year graft failure increased incrementally with greater phenotype burden. Each additional trifecta component was associated with higher 3-year graft failure risk (HR 1.21, 95% CI 1.08-1.36; p = 0.001). In component models, diabetes (HR 1.28, 95% CI 1.07-1.53; p = 0.007) and functional dependence (HR 1.21, 95% CI 1.02-1.45; p = 0.034) predicted 3-year graft failure, whereas body mass index ≥35 did not. Diabetes remained associated with 1-year graft failure (HR 1.32, 95% CI 1.01-1.73; p = 0.045) but not 90-day graft failure. Model discrimination was limited: Cox C-index 0.588; cross-validated AUCs were 0.584 for full logistic regression, 0.507 for trifecta-only logistic regression, 0.579 for gradient boosting, and 0.576 for XGBoost. Top XGBoost predictors included diabetes, donation after circulatory death, male sex, donor age, and waitlist time. (Figure 1) **Conclusion:** In contemporary MASH LT recipients, diabetes and functional dependence—not severe obesity alone—drive the association between metabolic phenotype and 3-year graft failure. Advanced ML models did not achieve strong discrimination underscoring the challenge that pre-transplant variables alone are insufficient to predicant graft outcomes in MASH recipients.



Disclosures: Sri Harsha Boppana: Nothing to Disclose, Subash Gurappa: Nothing to Disclose, Sachin Sravan Kumar Komati: Nothing to Disclose, Gautam Maddineni: Nothing to Disclose, Raja Chandra Chakinala: Nothing to Disclose, Venkata Sunkesula: Nothing to Disclose, Pradeep Yarra: Nothing to Disclose, Christina Awad: Nothing to Disclose.

0105 | GLP-1 RECEPTOR AGONISTS ARE ASSOCIATED WITH IMPROVED SURVIVAL AND CARDIO-KIDNEY OUTCOMES WITHOUT INCREASED REJECTION IN LIVER TRANSPLANT RECIPIENTS WITH DIABETES: A NATIONWIDE TARGET TRIAL EMULATION

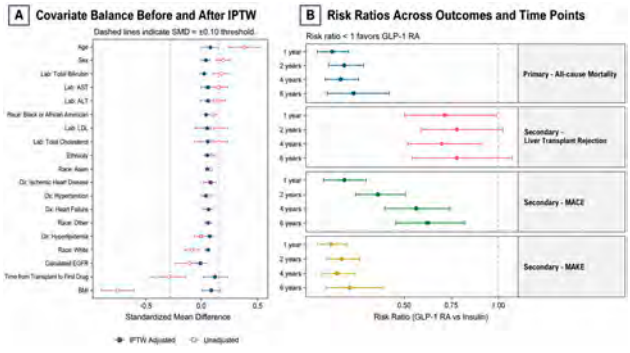
Kavish Patidar[1] Corneilius Rosenbaum[1] Sudha Kodali[1] Tamneet Basra[1] Michele Pauley-Jones[1] Mazen Noureddin[1] Stephen Jones[1] Luma Succar[1] Constance Mobley[1] Ashish Saharia[1] Caroline Simon[1] Yee Lee Cheah[2] Ashton Connor[1] Urmi Sengupta[1] Linda Moore[1] Mohammad Siddiqui[3] Sumeet Asrani[4] Andrew Allegretti[5] Giuseppe Cullaro[6] R. Mark Ghobrial[7] David Victor III[1], [1]Houston Methodist Hospital, [2]Houston Methodist, [3]University of Virginia, [4]Liver Consultants of Texas, [5]Massachusetts General Hospital, [6]Columbia University, [7]Houston Methodist JC Walter Transplant Center

Background: Liver transplant (LT) recipients with diabetes have high risk of cardiovascular disease, advanced chronic kidney disease, and premature mortality. Although GLP-1 receptor agonists (GLP-1RAs) improve cardiometabolic and kidney outcomes in the general diabetes population, their effectiveness and immunologic safety after LT remain poorly defined. **Methods:** Using Epic Cosmos data from >250 U.S. health systems, we performed an active-comparator, new-user cohort study emulating a target trial

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of GLP-1RA versus long-acting insulin (LAI). We included adult LT recipients who were ≥1 yr post-LT and newly initiated GLP-1RA or LAI between 1/1/2007 and 12/31/2025. Treatment groups were mutually exclusive, and the index date was the first prescription date. Patients were followed for up to 6 years, until outcome occurrence, or study end (5/5/2026), whichever occurred first. The primary outcome was all-cause mortality. Secondary outcomes included major adverse cardiovascular events (MACE; composite of incident myocardial infarction, stroke, or death), major adverse kidney events (MAKE; composite of incident CKD stage 4/5, renal replacement therapy, or death), and LT rejection. Inverse probability of treatment weighting (IPTW) balanced baseline covariates, including time from LT to index date. Weighted Cox proportional hazards models with delayed entry estimated all-cause mortality; time-specific risk ratios at 1, 2, 4, and 6 years, derived from weighted survival estimates, summarized treatment effects across outcomes. **Results:** Among 1,697 LT recipients, 809 initiated GLP-1RA and 888 initiated LAI. Before IPTW, GLP-1RA initiators were younger (median age, 60 vs. 62 yrs), more often female (40% vs. 30%), and more frequently White (86% vs. 79%) compared with LAI initiators. GLP-1RA initiators also had higher median BMI (32 vs 28), longer median interval from LT to treatment initiation (668 vs. 547 days) and lower median HbA1c (5.8% vs. 6.3%) Cardiovascular comorbidities were similar between groups. After IPTW, all measured covariates were well balanced, with standardized mean differences <0.1 (**Figure A**). Over a median follow-up of 4.1 yrs (IQR 2.5–5.9), GLP-1RA initiation was associated with substantially lower all-cause mortality versus LAI (HR 0.12, 95% CI 0.08–0.20). Risk ratio estimates consistently favored GLP-1RA for all-cause mortality, MACE, and MAKE at 1, 2, 4, and 6 yrs (**Figure B**). GLP-1RA initiation was not associated with increased LT rejection, with risk estimates favoring GLP-1RA early and attenuating toward the null over time. **Conclusion:** In this nationwide target trial emulation of LT recipients with diabetes, GLP-1RA initiation was associated with improved survival and favorable cardiovascular and kidney outcomes compared with LAI, without an increased rejection signal. These findings support prospective evaluation of GLP-1RAs as a cardiometabolic risk-reduction strategy after LT.



Disclosures: Kavish Patidar: Madrigal Pharmaceuticals: Medical Advisory Board, Mallincrodt Pharmaceuticals: Consultant, HepQaunt: Consultant, Mallinckrodt Pharmaceuticals: Medical Advisory Board, OrganOx: Advisor, Madrigal Pharmaceuticals: Advisor, Keenova Therapeutics: Advisor and Consultant., Keenova Therapeuatics: Advisor and Consultant, Novo Nordisk: Advisor, HepQaunt: Consultant, Keenova Therapeutics: Advisor and Consultant, HepQuant: Consultant, Corneilius Rosenbaum: Nothing to Disclose, Sudha Kodali: SIRTEX: Advisor, Astrazeneca: Advisor, Gilead: Speaking and Teaching, Gilead: Speaking and Teaching, SIRTEX: Advisor, Astrazeneca: Consultant, Tamneet Basra: Nothing to Disclose, Michele Pauley-Jones: Nothing to Disclose, Mazen Noureddin: Nothing to Disclose, Stephen Jones: Nothing to Disclose, Luma Succar: Nothing to Disclose, Constance Mobley: Nothing to Disclose, Ashish Saharia: Nothing to Disclose, Caroline Simon: Nothing to Disclose, Yee Lee Cheah: Nothing to Disclose, Ashton Connor: Nothing to Disclose, Urmi Sengupta: Nothing to Disclose, Linda Moore: Nothing to Disclose, Mohammad Siddiqui: NovoNordisk: Grant/Research Support, 89Bio: Consultant, Sagimet: DSMB, Sumeet Asrani: Nothing to Disclose, Andrew Allegretti: Nothing to Disclose, Giuseppe Cullaro: Ocelot Bio: Consultant, Retro Sciences: Consultant, Ipsen: Consultant, R. Mark Ghobrial: Nothing to Disclose, David Victor III: Nothing to Disclose.

0106 | CARDIOVASCULAR-KIDNEY-METABOLIC SYNDROME STAGE AT ONE YEAR PREDICTS CARDIOVASCULAR, RENAL, AND TRANSPLANT OUTCOMES AFTER LIVER TRANSPLANTATION

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Background: Cardiovascular disease (CVD) is the leading cause of non-graft-related death after liver transplantation (LT), yet tools to integrate cardiometabolic risk in this population are limited. The American Heart Association cardiovascular-kidney-metabolic (CKM) syndrome staging framework defines a continuum of risk from ideal health (stage 0), excess adiposity (Stage 1), metabolic risk factors or chronic kidney disease (Stage 2), subclinical or high CVD risk (Stage 3), to clinical CVD (Stage 4) and predicts cardiovascular events (CVEs) in the general population. However, its relevance in LT recipients (LTRs) is unknown. We aimed to define CKM burden after LT, assess outcomes, and identify modifiable drivers of progression.

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Methods: We conducted a retrospective cohort study using the TriNetX Global Collaborative Network, a federated research network of 171 healthcare organizations, including adult LTRs (2009-2026) surviving to one-year post-LT; multi-organ recipients were excluded. CKM stage at one year was categorized as non-advanced (Stages 1-2) or advanced (Stages 3-4) using diagnosis (ICD-10-CM), laboratory (LOINC), and procedural (CPT) codes. The primary outcome was three-year incident CVEs (myocardial infarction, stroke, or revascularization). Secondary outcomes included all-cause mortality, graft failure, and new dialysis. Time-to-event outcomes were analyzed using Cox proportional hazards models in cohorts balanced via 1: 1 propensity score matching for demographics, comorbidities, and medication exposures. Among LTRs with non-advanced CKM, we evaluated associations between immunosuppression strategy (steroid-free vs. steroid-containing; tacrolimus vs. cyclosporine) and progression to advanced CKM. **Results:** Among 69,630 LT recipients (mean age 61.8 years, 61.9% male, 64.2% White), CKM staging at one year demonstrated substantial cardiometabolic burden (Stage 1: 4.8%, Stage 2: 29.2%, Stage 3: 16.0%, Stage 4: 9.3%).After 1: 1 propensity matching non-advanced (Stages 1-2) and advanced (Stages 3-4) cohorts ($n = 22,724$), advanced CKM was associated with three-year risk of CVEs (2.5% vs. 0.6%; HR 4.46, 95% CI 3.39-5.86), all-cause mortality (HR 1.75, 1.55-1.99), graft failure (HR 1.97, 1.76-2.21), and incident dialysis (HR 11.60, 7.05-19.08).Among LTRs with non-advanced CKM, corticosteroid-containing immunosuppression at one year was associated with increased progression to advanced CKM (5.5% vs. 3.7%, HR 1.49, 1.28-1.75), whereas calcineurin inhibitor choice (tacrolimus vs. cyclosporine was not associated with progression (HR 0.71, 0.46-1.09). **Conclusion:** Advanced CKM stage at one-year post-LT is strongly associated with adverse cardiovascular, renal, and transplant outcomes. These findings support CKM staging as a clinically relevant risk stratification tool in LTRs and identify corticosteroid exposure as a potentially modifiable factor associated with CKM progression.

Table. Relationship Between Advanced CKM stage on Adverse outcomes post-LT

Outcome	Advanced CKM (Stages 3-4)**	Non-Advanced CKM (Stages 1-2)**	HR	95% CI	*P*-value
CVE*	237 (2.5%)	65 (0.6%)	4.46	3.39-5.86	<0.001
All-cause mortality	657 (5.8%)	400 (3.5%)	1.75	1.55-1.99	<0.001
Graft failure	831 (7.3%)	460 (4.0%)	1.97	1.76-2.21	<0.001
New-onset dialysis	176 (1.7%)	17 (0.2%)	11.60	7.05-19.08	<0.001

*Defined as myocardial infarction, stroke, or revascularization

**Cohort sizes given after propensity matching for age, sex, race, ethnicity, liver disease etiologies, behavioral history (alcohol use, tobacco use), hepatocellular carcinoma, body mass index, serum laboratory tests (cholesterol, hemoglobin A1c, estimated glomerular filtration), medications (antihypertensives, lipid lowering therapies, glucagon-like-peptide-1 receptor agonists, sodium-glucose cotransporter 2 inhibitors, mineralocorticoid receptor antagonists, antiplatelets), immune suppression, family history of cardiovascular disease. (total cohort size: $n = 22,724$)

Disclosures: Joseph Gunderson: Nothing to Disclose, Ludovic Saba: Nothing to Disclose, Saket Girotra: Nothing to Disclose, Sarah Lieber: Nothing to Disclose, Arjmand Mufti: Nothing to Disclose, Madhukar Patel: Nothing to Disclose, Lisa VanWagner: W.L. Gore & Associates: Grant/Research Support, Akero: Grant/Research Support, Madrigal: Grant/Research Support, Gerson Lehrman Group: Consultant, Madrigal: Advisor, Slingshot Insights: Consultant, Antheneum Partners: Consultant, Gerson Lehrman Group: Consultant, Alpha Insights: Consultant, Slingshot Insights: Consultant, Madrigal Pharmaceuticals: Grant/Research Support, W.L. Gore & Associates: Grant/Research Support, BD: Grant/Research Support, Medicolegal consulting: Consultant.

0107 | META-ANALYSIS OF ALCOHOL-ASSOCIATED LIVER CIRRHOSIS IDENTIFIED NEW RISK LOCI

Callie Zaborenko[1] Marco Abreu[1] Samer Gawrieh[1] Marijana Vujkovic[2] Kyong-Mi Chang[2] Devanshi Seth[3] Timothy Morgan[4] Tae-Hwi Schwantes-An[1], [1]Indiana University School of Medicine, [2]University of Pennsylvania, [3]University of Sydney, [4]VA Long Beach Healthcare System

Background: Alcohol-associated liver cirrhosis (ALC) and metabolic dysfunction-associated steatotic liver disease (MASLD) cirrhosis share remarkably similar genetic architectures, with the strongest GWAS loci consistently overlapping across both conditions. These findings raise the question of whether ALC represents a genetically distinct disease entity or a phenotypic manifestation along a shared biological spectrum of progressive liver injury. However, genetic discovery in ALC has been limited by substantially smaller cohort sizes compared with MASLD cirrhosis studies, reducing statistical power for locus discovery and fine-mapping. Here, we present the largest meta-analysis GWAS of ALC to date to define its genetic architecture and compare it with MASLD cirrhosis. **Methods:** In total, three new and three previously published cohorts are included in this meta-analysis. Million Veterans Project, Indiana Biobank, and GenomALC retrospective cohort were newly analyzed and GenomALC prospective cohort, UK Biobank, and Buch et al. represent three previously published cohorts. Cases were defined as having clinician confirmed diagnosis of ALC or having at least one instance of ICD-9/10 codes for ALC. Controls were defined as problematic drinkers without any known liver diagnoses. All analyses were conducted in participants who clustered with EUR reference samples. Individual site analyses were conducted using logistic regression models while adjusting for age, sex, and two principal components of genetic ancestry. Meta-analysis of variants available in at least 4 cohorts

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was conducted using *METAL* with genomic control option to adjust for study heterogeneity. **Results:** In total, 13,739 cases and 57,828 controls were included in the meta-analysis. Rs4248168, an intergenic variant upstream of *HLA-DQB1* was genome-wide associated with the risk of ALC (OR = 1.10; 95% CI 1.07-1.13; $p = 2.74x10^{-9}$. There were six additional suggestive ($p = 5x10^{-6}$ to $5x10^{-8}$) associated loci. Also, we replicated previously reported associations in *PNPLA3*, *TM6SF2*, *SERPINA1*, *HSD17B13*, and *MARC1* genes. **Conclusion:** We report an association between *HLA* locus and risk for developing ALC in the largest up-to-date meta-GWAS. In addition to the genome-wide associated locus, we identified 6 suggestive associations that are in or nearby genes that have been implicated glucose dysregulation and lipid metabolism changes due to alcohol. Our findings suggest additional genetic factor drive risk for ALC.

Genome-wide associations							
CHR	POS	MarkerName	Gene	Effect	Other	OR (95%C.I.)	Pvalue
1	220970028	1:220970028:A:G	MTARC1	a	g	0.90 (0.87-0.93)	1.56E-09
4	88186441	4:88186441:G:A	HSD17B13	a	g	0.86 (0.84-0.89)	7.16E-19
6	32659743	6:32659743:G:C	HLA-DQB1	c	g	0.91 (0.88-0.94)	2.74E-09
14	94844947	14:94844947:C:T	SERPINA1	t	c	1.49 (1.35-1.65)	8.76E-15
19	19379549	19:19379549:C:T	TM6SF2	t	c	1.26 (1.20-1.33)	3.18E-18
22	44340904	22:44340904:C:T	PNPLA3	t	c	1.57 (1.52-1.63)	5.02E-152
Suggestive Associations							
CHR	POS	MarkerName	Gene	Effect	Other	OR (95%C.I.)	Pvalue
2	238485481	2:238485481:G:A	RAB17	a	g	1.12 (1.07-1.18)	4.55E-06
4	88066259	4:88066259:G:A	AFF1	a	g	0.91 (0.87-0.94)	7.94E-07
10	115069858	10:115069858:T:C	TCF7L2	t	c	1.13 (1.07-1.19)	1.78E-06
11	28982849	11:28982849:C:T	METTL15	t	c	1.08 (1.05-1.11)	1.05E-06
12	58166403	12:58166403:T:G	AVIL	t	g	1.08 (1.05-1.12)	9.75E-07
20	17111967	20:17111967:G:A	PCSK2	a	g	1.11 (1.06-1.16)	2.50E-06

Table1. Summary table of genome-wide associations and suggestive associations. CHR = Chromosome, POS = base position in hg19, Effect = coded/effect allele, Other = non-tested allele, OR (95% C.I.) = odds ratio and 95% confidence interval for each copy of effect allele

Disclosures: Callie Zaborenko: Eli Lilly: Stock - publicly traded company, Marco Abreu: Nothing to Disclose, Samer Gawrieh: Transmedics: Consultant, pfizer: Consultant, kowa: Consultant, spruce: Consultant, viking: Grant/Research Support, zydus: Grant/Research Support, dsm: Grant/Research Support, Sonicincytes: Grant/Research Support, Novo Nordisk: Consultant, GSK: Consultant, Marijana Vujkovic: Nothing to Disclose, Kyong-Mi Chang: Nothing to Disclose, Nothing to Disclose, Devanshi Seth: Nothing to Disclose, Timothy Morgan: Nothing to Disclose, Tae-Hwi Schwantes-An: Nothing to Disclose.

★ 0108 | LOSS OF Y CHROMOSOME IS A NOVEL SOMATIC ANEUPLOIDY AND POTENTIAL BIOMARKER IN HEPATOCELLULAR CARCINOMA

Gopanandan Parthasarathy[1] Renumathy Dhanasekaran[1] Siddhartha Jaiswal[1], [1]Stanford University

Background: Loss of Y chromosome (LOY) is the most common somatic aneuploidy in males and affects proliferative cell types such as hematopoietic cells. Mosaic LOY has been described in several solid cancers and associated with poor outcomes. However, its prevalence, cell-type specificity, and mechanistic consequences in hepatocellular carcinoma (HCC) are undefined. **Methods:** LOY was identified in 1026 male HCC patients across three orthogonal platforms: single-cell RNA-seq (n = 81, 7 cohorts), bulk microarray (n = 731, 7 cohorts), and whole-exome sequencing (n = 214, The Cancer Genome Atlas Program, TCGA). Per-cell LOY was scored using a 9-gene Y-signature to cohort-reference and LOY defined as tumor/reference ratio < 0.5. To characterize mechanistic implications downstream of LOY genes, cancer-testis antigen (CTA) and senescence-associated secretory phenotype (SASP) signatures were co-quantified at single-cell and pseudobulk resolution. Population-level hematopoietic LOY was assessed in the UK Biobank (UKB; n = 214,915 males) and All of Us (AoU; n = 172,711) using array-based bioinformatic pipelines and correlated with liver disease prevalence with age-adjusted Cox regression. **Results:** LOY was present at a concordant rate of 21–26% of all male patients with HCC across platforms (Fig 1A). Among LOY+ tumors, a median of 66% of malignant cells have LOY suggesting clonality. Within tumors, hepatocyte LOY was not correlated with hematopoietic LOY, and neither was correlated with age. LOY+ tumors showed higher TP53 mutation rates (OR = 2.41, $P < 0.05$), greater genomic instability and macrophage enrichment. In TCGA, mosaic LOY was associated worse overall survival (median 11.7 vs 20.7 months, log-rank $P < 0.01$) (Fig 1B). Given loss of KDM5D (an H3K4me3 demethylase), LOY+ tumors exhibited 4-fold greater CTA upregulation in tumor versus matched normal liver ($P < 0.001$) (Fig 1C). Pretreatment CTA expression was predictive of immunotherapy response across two independent cohorts (n = 38; $P < 0.05$) (Fig 1D). Separately, at the patient level, LOY was correlated with reduced SASP expression, particularly the profibrotic signature driven by MMP9, IGFBP3, and SERPINE1 (r = 0.583, FDR Q < 0.05). In UKB and AoU (n = 387,626 combined), hematopoietic LOY in peripheral blood was correlated with age (r = -0.25, $P < 0.01$) and overall mortality, but showed no association with MASLD, cirrhosis, or HCC after age adjustment (all $P > 0.05$). **Conclusion:** We describe for the first time that LOY occurs in 25% of HCC across multi-platform methods and is correlated with poorer outcomes. Mechanistically, LOY leads to CTA de-repression and profibrotic SASP with potential therapeutic implications. Large-scale population data confirm hematopoietic LOY is correlated with age but not liver disease progression. Tumor-compartment LOY represents a novel, orthogonally validated biomarker axis warranting prospective evaluation in HCC and immunotherapy response.

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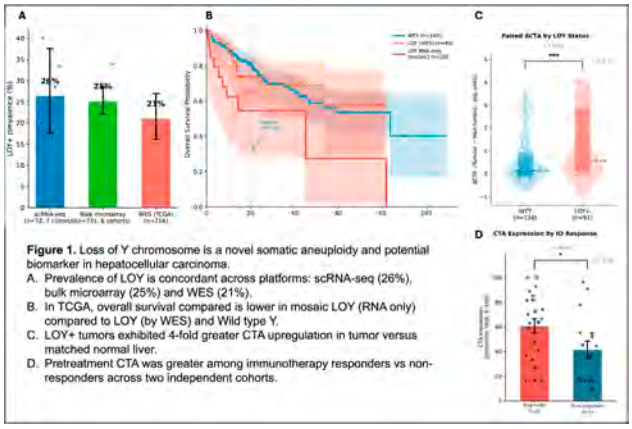


Figure 1. Loss of Y chromosome is a novel somatic aneuploidy and potential biomarker in hepatocellular carcinoma.
A. Prevalence of LOY is concordant across platforms: scRNA-seq (26%), bulk microarray (25%) and WES (21%).
B. In TCGA, overall survival compared is lower in mosaic LOY (RNA only) compared to LOY (by WES) and Wild type Y.
C. LOY+ tumors exhibited 4-fold greater CTA upregulation in tumor versus matched normal liver.
D. Pretreatment CTA was greater among immunotherapy responders vs non-responders across two independent cohorts.

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0109 | SINGLE-CELL, SINGLE-NUCLEI, AND SPATIAL TRANSCRIPTOMICS REVEALS SIGNATURE-SPECIFIC MICROENVIRONMENTS IN HEPATOBLASTOMA

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Background: Hepatoblastoma (HB), the most common pediatric liver cancer, exhibits intra- and inter-tumoral heterogeneity that challenges clinical risk stratification. Current prognostic tools rely primarily on histology and serum alpha-fetoprotein (AFP), leaving a gap in molecular biomarkers for precision oncology. We previously identified five tumor transcriptomic signatures across 9 patients using single-cell RNA sequencing (scRNA-seq), but were limited by small cohort size, absence of high-risk cases, and reliance on scarce fresh tissue. **Methods:** We developed an integrated multimodal framework across three platforms. First, we expanded scRNA-seq profiling to 12 patients, including the first high-risk case. Second, to overcome constraints imposed by fresh tissue, we established a single-nuclei RNA sequencing (snRNA-seq) pipeline for frozen biobank specimens, using SNP-based genetic demultiplexing of multiplexed lanes. Rigorous QC, including ambient RNA removal and doublet filtering, ensured high-quality nuclear transcriptomes. Third, we applied Xenium spatial transcriptomics to 17 HB samples using a custom 480-gene panel derived from our single-cell atlas, and developed a graph-based algorithm leveraging spatial connectivity and gene expression to assign tissue regions to tumor interior, interface, or exterior. **Results:** Single-cell profiling revealed six distinct tumor signatures shared across patients: Hepatoblast I-III, fibroblast, erythroid, and neuroendocrine. A newly identified Hepatoblast_III signature, enriched in AFP and aggressive-disease genes, was linked to the high-risk patient. Cross-platform validation confirmed that snRNA-seq from frozen specimens reproduced identical signatures, with cells clustering by biological identity rather than platform, enabling a 40% cohort expansion via nine additional biobanked samples. Spatial transcriptomics revealed that distinct tumor signatures create fundamentally different microenvironments: Hepatoblast signatures were enriched for vascular endothelial cells and tumor-associated fibroblasts at the tumor-stroma interface, with HGF-MET and EGF-family signaling identified by ligand-receptor analysis, while neuroendocrine signatures exhibited somatostatin autocrine signaling and SLIT-mediated fibroblast crosstalk. **Conclusion:** Integrating single-cell, single-nuclei, and spatial transcriptomics across 17 patients and over one million cells, we established a comprehensive molecular atlas of HB heterogeneity. Our multimodal approach uncovered clinically relevant tumor signatures with potential for improved risk stratification and identified signature-specific microenvironmental interactions as candidate therapeutic targets. The computational tools developed—including the graph-based spatial region algorithm and cost-effective demultiplexing pipeline—are broadly applicable across tumor types.

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0110 | EPIGENETIC-METABOLIC PHOSPHOLIPID REPROGRAMMING BY BAP1 LOSS CONFERS CHOLANGIOCARCINOMA RESISTANCE TO FERROPTOSIS

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Background: BAP1 loss-of-function mutations occur in 26-32% of cholangiocarcinoma (CCA) cases,

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conferring chemotherapy resistance and poor prognosis. We hypothesized that BAP1 loss rewires membrane phospholipid composition to evade ferroptosis, defining a targetable vulnerability. **Methods:** Isogenic BAP1-deficient models were generated by shRNA/siRNA and CRISPR/Cas9 in CCLP1, HuCCT1, TFK-1 human and FAC, SB1, KPPC murine CCA cells. Ferroptosis was quantified by CellTiter-Glo (dose-response to RSL3/IKE/Erastin/JKE-1674), C11-BODIPY, MitoPeDPP, MitoCLox, and MitoFerroGreen. Lipid remodeling was profiled by species-resolved LC-MS/MS phospholipidomics and TMT proteomics (n = 3/arm). Syngeneic orthotopic SB1/FAC (C57BL/6J, n = 7-20/group) and BAP1-mutant PDX were used to assess ferroptosis *in vivo*. EpCAM-aptamer coated siRNA-packaged lactosomes (siGPX4, 2×10^{12} particles, 3×/week i.v.) were used to induce tumor-selective ferroptosis in syngeneic orthotopic models (n = 15-20/group). TCGA-CHOL, GSE308455 organoids, Mayo Clinic Tempus CCA cohort (n = 191; 12% BAP1-altered) were used for translational studies. **Results:** LC-MS/MS phospholipidomics in isogenic shBAP1 vs shControl CCLP1 revealed depletion of ferroptosis-promoting PUFA-PLs (PUFA-PE log2FC -0.369, $p < 0.01$; PUFA-PC -0.420, $p < 0.01$; PUFA-PI -0.798, $p < 0.05$) and enrichment of ferroptosis-blocking lipids (sphingomyelin +0.425, $p < 0.01$; non-PUFA PE +0.130, $p < 0.05$). TMT proteomics identified TLCD1 (phosphatidylethanolamine acyltransferase, log2FC +0.41) and LPCAT1 (log2FC +0.66, q = 0.0017) as top candidates. Cross-cohort REML meta-analysis confirmed TLCD1 elevation in BAP1-mutant CCA: pooled log2FC +0.41 [95% CI +0.13, +0.68], p = 0.004, $I^2 = 44\%$; TCGA-CHOL log2FC +0.82, FDR = 0.045; GSE308455 organoids log2FC +0.44, FDR = 0.001. TLCD1 amplification correlated with BAP1 loss in TCGA (p = 0.03, n = 51). ChIP-PCR analysis showed that BAP1 loss increased H2A ubiquitination at the TLCD1 promoter. TLCD1 knockdown in BAP1-deficient CCLP1 and TFK-1 significantly restored sensitivity to RSL3 and IKE. IKE (30 mg/kg/day i.p.) reduced SB1 orthotopic tumor burden by 57% vs vehicle (n = 7/group). JKE-1674 alone and combined with gemcitabine/cisplatin reduced PAX103 PDX burden by 29% and 68%, separately. EpCAM-aptamer lactosomes reduced Gpx4 mRNA 60%, suppressed tumor growth by 43%, elevated Ptgs2, reduced Ki67, with no systemic toxicity. **Conclusion:** BAP1 loss drives ferroptosis evasion through TLCD1-mediated MUFA-PL enrichment and PUFA-PL depletion, validated across isogenic lines, organoids, and two human cohorts. siRNA-based nanotherapeutics siGPX4 delivery suppresses CCA *in vivo*, establishing a biomarker-stratified therapeutic strategy for BAP1-mutant cholangiocarcinoma.

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0111 | MULTI-ANCESTRY WHOLE-GENOME STUDY IDENTIFIES POPULATION-SPECIFIC EFFECTS OF *PNPLA3*, *TM6SF2*, *MBOAT7*, *HSD17B13*, AND *MARC1* ON CIRRHOSIS, MASLD, AND HEPATOCELLULAR CARCINOMA IN 414,830 ALL OF US PARTICIPANTS

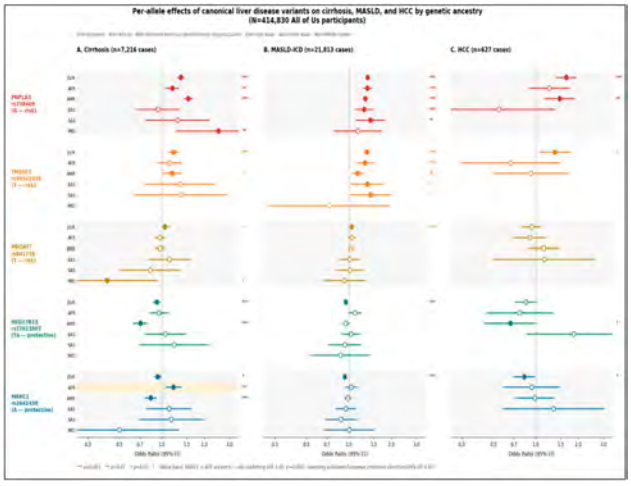
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Background: Five variants (*PNPLA3* rs738409, *TM6SF2* rs58542926, *MBOAT7* rs641738, *HSD17B13* rs72613567, and *MARC1* rs2642438) shape risk of cirrhosis, metabolic dysfunction-associated steatotic liver disease (MASLD), and hepatocellular carcinoma (HCC). Per-allele effects derive predominantly from European-ancestry cohorts (UK Biobank, GenomALC); generalizability to U.S. admixed and African-ancestry populations is unclear. We characterized variant frequencies, U.S. population burden, and ancestry-specific liver disease associations in the largest multi-ancestry whole-genome sequencing (WGS) cohort to date. **Methods:** We analyzed 414,830 All of Us participants with short-read WGS (CDR v8; median age 60, 61% female; 52% Non-Hispanic White, 19% Hispanics, 18% Non-Hispanic Black, 3% Asian). Participants were assigned to gnomAD-derived ancestry groups: European (EUR; n = 234,353, reference), African (AFR; n = 84,148), Admixed American (AMR; n = 79,106, predominantly Hispanics), East Asian (n = 10,099), South Asian (n = 5,579), and Middle Eastern (n = 1,545). Outcomes: cirrhosis (n = 7,216), ICD-coded MASLD (n = 21,813), HSI ≥ 36-based MASLD (as a sensitivity definition, n = 124,074), and HCC (n = 627). Per-allele logistic regression adjusted for age, sex, BMI, diabetes, heavy alcohol exposure, and 5 ancestry PCs. U.S. burden estimates used AoU allele frequencies × Census 2024 adult distributions. **Results:** Allele frequencies matched gnomAD v4 (e.g., PNPLA3 G: EUR 0.23, AFR 0.14, AMR 0.45). Projected U.S. burden: ~114M carry the PNPLA3 G risk allele,

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95M the HSD17B13 TA protective allele, and 107M the MARC1 A protective allele. PNPLA3 showed substantial ancestry variation for cirrhosis (EUR OR 1.36, 95% CI 1.30-1.43; AFR 1.18, 1.06-1.31; AMR 1.54, 1.44-1.65), with similar pattern for MASLD-ICD; HCC effect was 1.64 in EUR ($p < 0.0001$) and 1.48 in AMR ($p < 0.01$) but null in AFR (1.24, $p = 0.20$). TM6SF2 was risk-conferring overall (cirrhosis OR 1.18, 1.10-1.26). MBOAT7 showed minimal cirrhosis association (OR 1.01, $p = 0.67$) despite high allele frequency, challenging European-derived estimates. MARC1 showed directional heterogeneity: protective in EUR (OR 0.94, 0.89-0.99) and AMR (0.83, 0.76-0.91) but risk-conferring in AFR (1.20, 1.06-1.37, $p < 0.01$), reversing the protective direction reported in UK Biobank European estimates (OR 0.87). HSD17B13 was broadly protective for cirrhosis (overall OR 0.87, $p < 0.0001$), with markedly stronger protection in AMR (OR 0.70, $p < 0.0001$). **Conclusion:** In a multi-ancestry U.S. population, canonical liver disease variants demonstrated substantial ancestry-specific heterogeneity in effect size and direction. European-ancestry estimates replicated in EUR but diverged in AMR and AFR, most strikingly for MARC1, which reversed direction. European-derived risk estimates may not uniformly generalize across diverse U.S. populations and support ancestry-aware genetic risk stratification.



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★ 0112 | FECAL VIROME IS ASSOCIATED WITH CLINICAL OUTCOMES IN PRIMARY SCLEROSING CHOLANGITIS

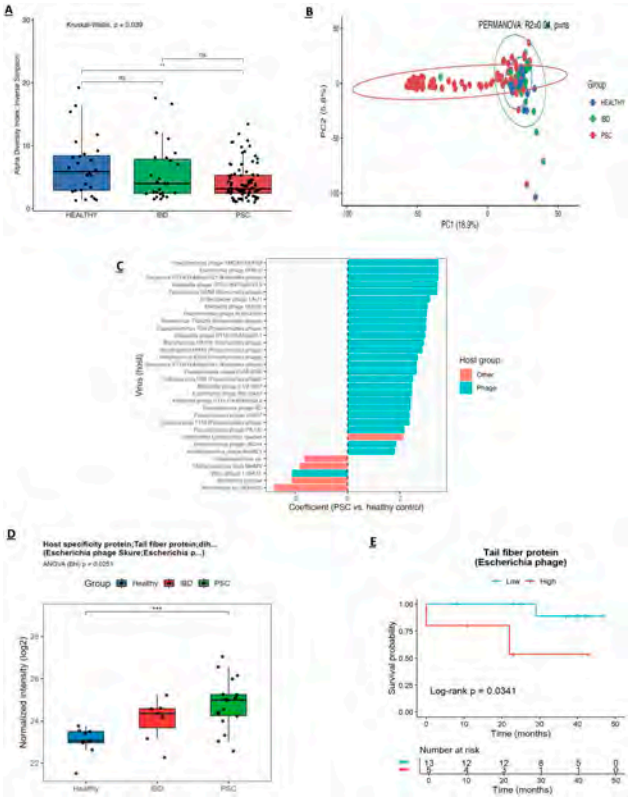
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Background: Growing evidence supports a role of the gut microbiome in primary sclerosing cholangitis (PSC), however, there are no studies exploring the virome. In this single-center study, we comprehensively studied the fecal virome in PSC and its link with clinical outcomes. **Methods:** Individuals with PSC, inflammatory bowel disease (IBD) and healthy controls (HC) were recruited from Charité-Universitätsmedizin Berlin, Germany. Fecal viruses were extracted using sequential filtration, concentration, nuclease treatment. Illumina NovaSeq X Plus (7 million 150bp paired end reads), hecatomb pipeline were used for viral read processing. For 16S, StrainID kit (spanning full 16S and partial 23S rRNA genes), SBanalyzer 2.4 (Shoreline Biome) were used for read mapping and annotation using PacBio-compatible barcoded primers with DADA2 for amplicon sequence variant inference. Proteomics was done on Thermo Scientific Orbitrap Astral mass spectrometer, analyzed with a custom UniProt-based database of identified viral species. Primary outcome was transplantation-free survival (survival free of transplantation and/or liver-related death). **Results:** The study included 141 participants (PSC = 86, IBD = 27, HC = 28). Viral alpha diversity was lower in PSC *vs* HC ($p = 0.04$, **Fig 1A**) and correlated with MELD (rho = 0.3, $p = 0.007$) and Mayo Risk Score (MRS; rho = 0.3, $p = 0.02$). Beta diversity was similar amongst the three groups (**Fig 1B**). Several viruses eg. *Pseudomonas*, *Escherichia*, *Klebsiella* phages, were enriched in PSC (**Fig 1C**). There was an inverse correlation between viral and bacterial alpha diversity (rho = -1.8, $p = 0.05$), though no concordance in their community structures (Procrustes $r = 0.11$, $p = 0.44$). Distance-based redundancy analysis revealed that the bacteriome composition significantly explained variation in the virome in HC, but not in PSC or IBD. Fecal proteomics revealed 150 viral proteins; those in PSC patients differed from HC ($p = 0.009$). Specifically, tail fiber protein of an *Escherichia* phage ($p = 0.025$) and TCP-1/cpn60 chaperonin family protein of a *Vibrio* phage ($p = 0.025$) were enriched in PSC (Tukey HSD

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p < 0.001; **Fig 1D**). Survival analysis showed that high abundance of *Escherichia* phage tail fiber protein correlated with poorer transplant-free survival (p = 0.034; **Fig. 1E**), cirrhosis (p = 0.0025), higher MELD (p = 0.005) and higher MRS (p = 0.04). **Conclusion:** Fecal virome in PSC is enriched in phages infecting pathogenic gram-negative bacteria and healthy phage-bacteria coupling is lost in PSC. Viral alpha diversity, and fecal viral proteins-specifically an *Escherichia* phage tail fiber protein-correlate with disease severity and clinical outcomes.



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0113 | LONG-READ METAGENOMICS REVEALS DISTINCT TRANSKINGDOM MICROBIAL SIGNATURES AND PHAGE-BACTERIA INTERACTIONS ACROSS THE CHOLESTATIC LIVER DISEASE SPECTRUM

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Background: Primary sclerosing cholangitis (PSC) is a progressive cholestatic liver disease with no approved therapy. Its association with inflammatory bowel disease (IBD) implicates the gut-liver axis. However, prior 16S rRNA studies produced inconsistent bacterial signatures and ignored the gut virome, which may drive disease through phage-mediated bacterial shifts. No prior PSC microbiome study has employed long-read metagenomic sequencing, which enables strain-level bacterial and high-confidence viral profiling. Here, we leverage these advantages to define microbial signatures and phage-bacteria interactions in cholestatic liver disease. **Methods:** We prospectively enrolled 44 patients at Massachusetts General Hospital (2024 to 2026) with primary biliary cholangitis (PBC), PSC with IBD (PSC-IBD), or PSC without IBD (PSC-only). Stool underwent PacBio HiFi long-read metagenomic sequencing. Microbial species-level genome bins (SGBs) were profiled with MetaPhlAn v4. Viral genome bins (VGBs) were profiled with BAQLaVa v0.5, a high-resolution reference-based, assembly-free viral profiler for bulk metagenomes. Phage-bacterial host pairs were predicted with iPHoP and tested for covariation. Between-group differences used α/β diversity and linear discriminant analysis effect size. **Results:** Among 44 patients (21 PBC, 10 PSC-IBD, 13 PSC-only), PSC patients were younger (median 51 vs. 67 years) and more often male. Microbial and viral diversity trended highest in PSC-only (Fig. 1a). Microbial composition differed significantly across groups (PERMANOVA R2 = 5.8%, p = 0.038) with viral trending similarly (Fig. 1b). Pairwise comparisons revealed both overlapping and disease-specific signals, supporting our study's ability to disentangle PSC-specific features from those attributable to cholestasis or IBD comorbidity (Fig. 1c). PSC-only was enriched for Enterobacter hormaechei, a pro-inflammatory Proteobacterium (Fig. 1d). PSC-only emerged as the most ecologically distinctive subgroup, harboring 14 uniquely enriched SGBs (Fig. 1e), including Streptococcus

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raffinosi, an oral-typical microbe. Among iPHoP-predicted phage-host pairs, Caudoviricetes and Oscillospiraceae, among several others, were strongly correlated in PSC-only (R = 0.77, p = 0.0089; Fig. 1f), consistent with network-structured, disease-specific multi-kingdom dysbiosis. **Conclusion:** Long-read transkingdom metagenomics reveals distinct microbial and viral signatures of cholestatic liver disease, particularly those attributable to PSC rather than cholestasis or concomitant IBD. Multicenter expansion, untargeted metabolomics, and strain-resolved genomics are underway to nominate bioactive microbial determinants and prioritize novel targets.

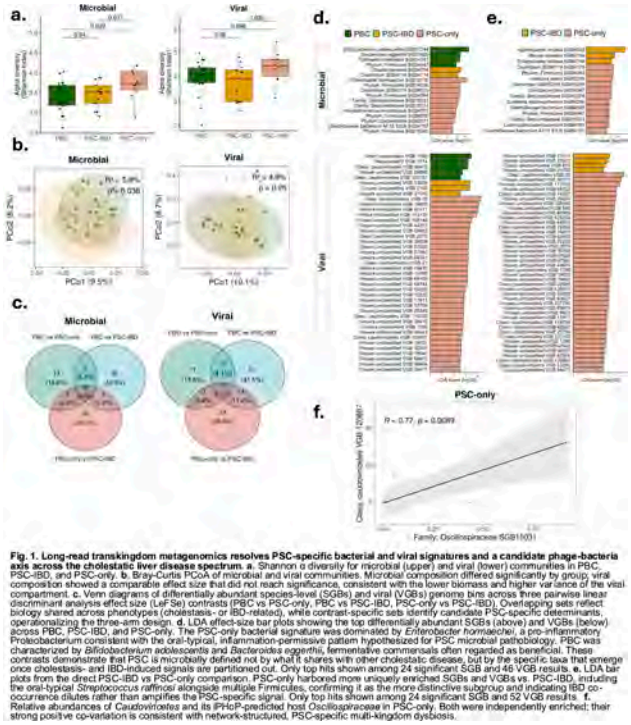


Fig. 1. Long-read transkingdom metagenomics resolves PSC-specific bacterial and viral signatures and a candidate phage-bacteria axis across the cholestatic liver disease spectrum. a. Shannon α diversity for microbial (upper) and viral (lower) communities in PBC, PSC-IBD, and PSC-only. **b.** Bray-Curtis PCoA of microbial and viral communities. Microbial composition differed significantly by group; viral composition showed a comparable effect size that did not reach significance, consistent with the lower biomass and higher variance of the viral compartment. **c.** Venn diagrams of differentially abundant species-level (SGBs) and viral (VGBs) genome bins across three pairwise linear discriminant analysis effect size (LeFSe) contrasts (PBC vs PSC-only, PBC vs PSC-IBD, PSC-only vs PSC-IBD). Overlapping sets reflect biology shared across phenotypes (cholestasis- or IBD-related), while contrast-specific sets identify candidate PSC-specific determinants, operationalizing the three-arm design. **d.** LDA effect-size bar plots showing the top differentially abundant SGBs (above) and VGBs (below) across PBC, PSC-IBD, and PSC-only. The PSC-only bacterial signature was dominated by *Enterobacter hormaechei*, a pro-inflammatory Proteobacterium consistent with the oral-typical, inflammation-permissive pattern hypothesized for PSC microbial pathobiology. PBC was characterized by *Bifidobacterium adolescentis* and *Bacteroides eggerthii*, fermentative commensals often regarded as beneficial. These contrasts demonstrate that PSC is microbially defined not by what it shares with other cholestatic disease, but by the specific taxa that emerge once cholestasis- and IBD-induced signals are partitioned out. Only top hits shown among 24 significant SGB and 46 VGB results. **e.** LDA bar plots from the direct PSC-IBD vs PSC-only comparison. PSC-only harbored more uniquely enriched SGBs and VGBs vs. PSC-IBD, including the oral-typical *Streptococcus raffinosi* alongside multiple Firmicutes, confirming it as the more distinctive subgroup and indicating IBD co-occurrence dilutes rather than amplifies the PSC-specific signal. Only top hits shown among 24 significant SGB and 52 VGB results. **f.** Relative abundances of Caudoviricetes and its iPHoP-predicted host *Oscillospiraceae* in PSC-only. Both were independently enriched; their strong positive co-variation is consistent with network-structured, PSC-specific multi-kingdom dysbiosis.

Disclosures: Prooksa Ananchuensook: Nothing to Disclose, Jiaxian Shen: Nothing to Disclose, Shruti Patel: Nothing to Disclose, Yael Nobel: Mirum Pharmaceuticals: Consultant, Etienne Nzabarushimana: Nothing to Disclose, Jordan S. L. Jensen: Nothing to Disclose, Daniel Sikavi: Nothing to Disclose, Jeremy Wilkinson: Nothing to Disclose, Gregory Gores: Nothing to Disclose, Andrew Chan: Nothing to Disclose, Curtis Huttenhower: Nothing to Disclose, Kelsey Thompson: Nothing to Disclose, Daniel Pratt: Ipsen: Advisor, Gilead: Advisor, RegCell: Advisor, Zydus: Advisor, Mirum: Advisor, Long Nguyen: Nothing to Disclose.

0114 | BUTYRATE-PRODUCING *ROSEBURIA* SPECIES RESTORATION ATTENUATES LIVER FIBROSIS BY GUT-LIVER LPS/TLR4/SMAD AXIS.

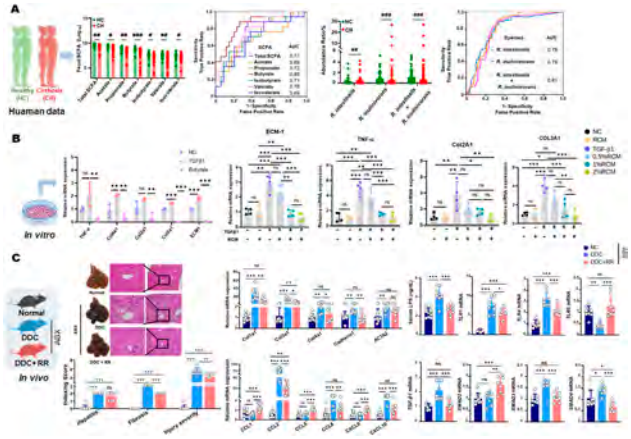
Satya Priya Sharma[1] HoYeong Yoon[2] Jeong Min Kim[2] Su A Kim[2] Hee-Jin Park[2] Goo Hyun Kwon[2] Kyeong Jin Lee[2] Jung A Eom[2] In Gyu Park[2] Sang Jun Yoon[2] Sung-Min Won[2] Ki-Kwang Oh[2] Gwang Ho Baik[2] Dong Joon Kim[2] Ki Tae Suk[2], [1]Institute for Liver and Digestive Diseases, [2]Institute for Liver and Digestive Diseases, Hallym University, Chuncheon, Republic of Korea

Background: Gut dysbiosis–mediated metabolic reprogramming critically influence cirrhosis progression thus health-promoting metabolite producing microbes become key regulators in cirrhosis. Here, we demonstrate that loss of butyrate-producing *Roseburia* functionally contributes to liver fibrosis. **Methods:** Fecal SCFAs (HC n = 17, cirrhosis n = 34) and microbiome abundance (HC n = 52, cirrhosis n = 142) were compared and evaluated by ROC analysis. Series of *in vitro* and *in vivo* experiments were conducted to define the functional role of butyrate-producing *Roseburia* in liver fibrosis. **Results:** In human cirrhosis data analysis, fecal microbial-metabolite profiling revealed broad depletion of SCFAs, and butyrate-producing *Roseburia* species. Total SCFAs and individual SCFAs were reduced, with butyrate showing the strongest diagnostic performance among SCFAs (AUC 0.85), while total SCFA yielded an AUC of 0.77. Consistently, *R. intestinalis* and *R. inulinivorans* were significantly decreased in cirrhosis, with individual AUCs of 0.78 and 0.79 and a combined *Roseburia* AUC of 0.81. *Roseburia* abundance positively correlated with SCFAs, albumin and platelets, and inversely correlated with MELD score, AST/ALT, bilirubin, INR and GGT, linking *Roseburia* species loss to impaired hepatic function and disease severity and identified a cirrhosis-associated loss of the *Roseburia*-butyrate axis. *In vitro*, this microbiome-metabolite axis showed direct antifibrotic activity. In LX-2 cells, butyrate and *Roseburia*-inoculated medium attenuated TGF-β1-driven stellate-cell activation, significantly suppressing ***TNF-***α, ***ECM1*** and collagen gene expression, with maximal inhibition at 1–2% RCM ($p < 0.05$–0.001). In antibiotic-depleted DDC mice, oral *R. intestinalis* + *R. inulinivorans* (RR) improved terminal body weight, reduced histologic fibrosis and injury severity scores (DDC vs RR: fibrosis 3 to 2; injury severity ~5 to ~4; $p < 0.01$–0.001), and improved AST, ALT, ALP, bilirubin and cholesterol. RR also suppressed hepatic extracellular-matrix and inflammatory markers, including ***Col1a1***, ***Col3a1***, ***Col4a1***, ***TGF-β1***, ***TNF-***α, ***IL-1beta***, ***CCL2***, ***CCL8*** and ***CXCL10***. Mechanistically, RR reduced serum LPS (~4.3 to ~2.7 ng/dL), ***TLR1*** (~7.5 to ~5.5), ***TLR4*** (~3.0 to ~2.0), *SMAD3* (~1.7 to ~1.1) and ***SMAD4*** (~1.4 to ~0.6), while ***TLR5*** increased toward normal and ***SMAD2*** showed a divergent increase. In non-antibiotic DDC mice, RR retained antifibrotic activity by reducing ALP, bilirubin, histologic hepatitis/fibrosis/injury scores and ***Col1a1*** / ***Col3a1*** expression, although AST, ALT and cholesterol were not significantly changed. **Conclusion:** Depletion of *Roseburia* and butyrate defines a

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cirrhosis-associated microbiome-metabolite signature. Repletion with *R. intestinalis* + *R. inulinivorans* limited liver injury, fibrosis, endotoxemia, TLR4 and SMAD3/4 signaling, supporting *Roseburia*-based gut-liver axis restoration as a candidate antifibrotic approach.



Disclosures: Satya Priya Sharma: Nothing to Disclose, HoYeong Yoon: Nothing to Disclose, Jeong Min Kim: Nothing to Disclose, Su A Kim: Nothing to Disclose, Hee-Jin Park: Nothing to Disclose, Goo Hyun Kwon: Nothing to Disclose, Kyeong Jin Lee: Nothing to Disclose, Jung A Eom: Nothing to Disclose, In Gyu Park: Nothing to Disclose, Sang Jun Yoon: Nothing to Disclose, Sung-Min Won: Nothing to Disclose, Ki-Kwang Oh: Nothing to Disclose, Gwang Ho Baik: Nothing to Disclose, Dong Joon Kim: Nothing to Disclose, Ki Tae Suk: Nothing to Disclose.

★ 0115 | HUMORAL IMMUNE DYSFUNCTION DEFINES HIGH-RISK CIRRHOTIC ASCITES

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Background: Among patients with cirrhosis, infection is a leading driver of acute decompensation and mortality. Spontaneous bacterial peritonitis (SBP), one of most common infections, occurs predominantly in the ascites fluid of patients with cirrhosis. However, the host and microbial determinants of SBP and mortality in cirrhosis remain incompletely defined. **Methods:** To identify ascites-associated factors linked to mortality in cirrhosis, we collected ascitic fluid from 111 patients: 61 patients with cirrhosis and 50 non-cirrhotic controls (primarily malignancy or heart failure). RNA-based metagenomic next-generation sequencing (mNGS) was used to simultaneously profile host and microbial transcriptomic signatures. Host cell subtypes in ascites were classified using spectral flow cytometry, cell sorting, and single-cell RNA sequencing. Humoral effector responses were measured directly in ascites, including B cell receptor sequencing, Ig subclass measurement, and IgA dimerization state. **Results:** Among patients with cirrhosis, host transcriptomic analysis revealed a marked downregulation of B cell and plasma cell genes, emerging as one of the predominant differences relative to non-cirrhotic ascites. In parallel, microbial mNGS demonstrated an absolute increase in oropharyngeal taxa known to be associated with cirrhosis: Viridans group streptococcus species (e.g. S. mitis) and anaerobes (e.g. F. nucleatum). We hypothesized that patients with cirrhosis would have reduced plasma cell numbers associated with the observed microbial changes. To measure immune cell populations in ascites, we performed flow cytometry in 8 patients (4 with cirrhosis, 4 without). Patients with cirrhosis demonstrated a marked reduction in the ratio of memory B cells (CD19+/CD27+) to naïve B cells (CD19+/IgD+; $p < 0.029$). We sorted CD19+ B cells from 4 patients (2 with cirrhosis, 2 without) and performed single-cell RNA sequencing. We observed a >10-fold reduction in plasma cells in cirrhosis, particularly IgG producing plasma cells. We measured ascites immunoglobulin levels in 81 patients (45 with cirrhosis, 36 without). Patients with cirrhosis had lower ascites IgG, which was associated with increased S. mitis abundance ($p < 0.05$). We also measured the fraction of monomeric versus dimeric IgA in ascites, revealing that a reduced fraction of dimeric IgA was associated with a significant increase in 90-day mortality in cirrhosis. **Conclusion:** We identified defining features of cirrhotic ascites: a marked reduction in the number of plasma cells and a commensurate decrease in the amount of IgG and dimeric IgA. Loss of dimeric IgA is known to impair mucosal IgA secretion and promote microbial translocation and inflammation in murine models. Our findings in human ascites parallel these observations, supporting a model in which impaired humoral immunity is a central determinant of microbial translocation and poor outcomes in cirrhosis.

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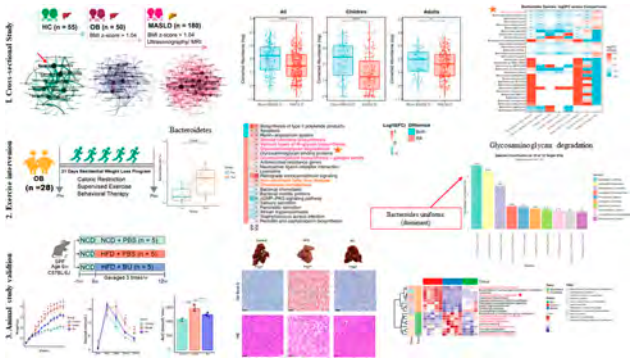
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Institute: Grant/Research Support, Novo Nordisk: Consultant, Genfit: Consultant, Boehringer Ingelheim: Advisor, Lipocine: Site PI, Gilead: Site PI, Insmed: Consultant, Cosmo: Advisor, Joseph DeRisi: Nothing to Disclose.

0116 | EXERCISE REPROGRAMS A *BACTEROIDES UNIFORMIS*-CENTRIC MICROBIAL NETWORK TO ACTIVATE GLYCOSAMINOGLYCAN DEGRADATION IN PEDIATRIC MASLD

Yan Ni[1], [1]Zhejiang University School of Medicine Affiliated Children's Hospital

Background: Childhood obesity is strongly associated with MASLD progression, yet exercise-responsive microbial mediators that directly link physical activity to hepatic improvement remain undefined. We hypothesized that exercise acts through a discrete responder species capable of reprogramming the gut–liver metabolic axis. **Methods:** Two pediatric cohorts and a preclinical model were integrated. *Cohort 1 (n = 285):* Children with MASLD *(n = 180)*, obese controls *(n = 50)*, and healthy controls *(n = 55)* underwent fecal metagenomic sequencing with network reconstruction, metabolomic profiling, and correlation with liver injury markers ALT/AST.*Cohort 2 (n = 28):* Overweight/obese children (aged 8–17) completed a structured 3-week exercise program; paired pre/post metagenomics and metabolic profiling were performed.*Preclinical: Bacteroides uniformis* (BU) from healthy donors was administered to HFD-obese mice (2×10^9 CFU/mL, 3×/week, 12 weeks) with multi-omics analysis. **Results:** In Cohort 1, pediatric MASLD was characterized by depletion of *B. uniformis*, *Phocaeicola vulgatus*, and *Parabacteroides distasonis*. BU was the strongest negative correlate of ALT and AST ($p < 0.05$), identifying it as a central hub linking microbial community structure to hepatic injury. In Cohort 2, exercise significantly improved BMI Z-score, TC, TG, and LDL. Metagenomics demonstrated consistent enrichment of BU as the dominant exercise-responsive species. Functionally, exercise induced coordinated activation of glycosaminoglycan (GAG) degradation—a distinct post-exercise metabolic signature absent at baseline and orthogonal to the carbohydrate dysregulation defining MASLD. In HFD mice, BU supplementation recapitulated the human responder phenotype, reducing weight gain, improving glucose tolerance, and decreasing ALT/AST. Integrated metagenomics and transcriptomics confirmed BU-driven GAG degradation in gut microbiome and hepatic tissue, with downstream improvement in lipid metabolic homeostasis. **Conclusion:** *Bacteroides uniformis* is a keystone exercise-responsive species linking physical activity to hepatic improvement in pediatric MASLD. Exercise rewires the gut–liver axis through a BU-driven GAG degradation program—a previously unrecognized hepatoprotective mechanism. BU-associated GAG metabolism represents a novel biomarker of exercise response and therapeutic target for microbiome-based intervention in pediatric MASLD.



Disclosures: Yan Ni: Nothing to Disclose.

0117 | A MACHINE LEARNING-DERIVED GUT METABOLOMIC SIGNATURE PREDICTS REVERSAL OF LIVER FIBROSIS IN PATIENTS WITH CHRONIC HEPATITIS B

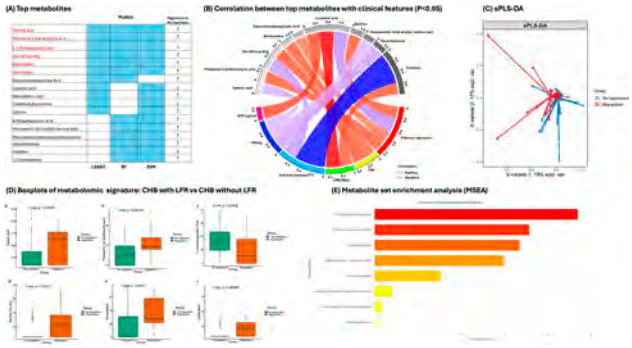
Lu Li[1] Saisai Zhang[1] Zhe Zhang[1] Ning Ma[1] Wenyi Tan[1] Wenjie Li[1] Lung-Yi Mak[1] Man-Fung Yuen[1] Wai-Kay Seto[1], [1]The university of Hong Kong

Background: Gut bacterial metabolites mediate host-microbe interactions via the gut-liver axis and influence disease progression, their contribution to liver fibrosis regression (LFR) in chronic hepatitis B (CHB) remains unknown. Here, we aimed to identify gut microbiota-derived metabolic signatures for predicting LFR in CHB. **Methods:** We enrolled CHB patients who had received nucleos(t)ide analogue therapy (serum HBV DNA < 10 U/mL for ≥ 12 months), a baseline liver stiffness measurement (LSM) ≥ 7 kPa recorded at least 3 years prior, and a follow-up LSM at enrollment. LFR was defined as an absolute LSM decrease > 30% from baseline, and fecal samples were collected for untargeted metabolomic profiling. Three machine learning (ML) models, including least absolute shrinkage and selection operator (LASSO), support vector machine (SVM), and random forest (RF), were applied to identify metabolic biomarkers for predicting LFR. Metabolite set enrichment analysis (MSEA) was performed to characterize pathway alterations between patients with and without LFR. **Results:** A total of 124 CHB patients (72.5% male, 61.3% liver steatosis, 63.7% type 2 diabetes) were included and all three models successfully differentiated patients with LFR (n = 36) from those

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without LFR (n = 88), with the highest accuracy of 0.84. To identify key metabolites for LFR, we selected the top 20 from each of three models and defined those identified by all three models as 'metabolomic signatures', which included testolic acid, phenazine-1,6-dicarboxylic acid, L-2-Hydroxyglutaric acid, Glu-Gln-Lys-Arg, strictosidine, and telmisartan. Among these, five showed significantly higher levels in LFR samples (t-test, P < 0.05). Sparse partial least squares discriminant analysis (sPLS-DA) constructed from the 'metabolomic signatures' revealed a clear separation between samples with and without LFR. Correlation analysis between metabolites identified by at least two models and clinical features shows that phenazine-1,6-dicarboxylic acid (p = 0.017), glycochenodeoxycholic acid (p = 0.039),quinine (p = 0.017) were all significantly positively correlated with LFR, whereas levullinic acid shows negative correlation with LFR (p = 0.002) and positive correlation with higher LSM (p = 0.003). Metabolite set enrichment analysis (MSEA) revealed the significant enrichment of pentose phosphate pathway in the patients with LFR (ER = 23.53,p = 0.042). **Conclusion:** This study identified a metabolomic signature for LFR by ML models, offering new insights into gut bacterial metabolites in CHB patients. Our findings provide a scientific basis for further exploration of non-invasive biomarkers and therapeutic targets for CHB. This study was supported by Shenzhen Natural Science Foundation Basic Research Fund-General Program (JCYJ20250604180826035).



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0118 | DISPARITIES IN ELECTRONIC HEALTH RECORD PATIENT PORTAL ENGAGEMENT AMONG ADULTS WITH CIRRHOSIS: AN EPIC COSMOS STUDY

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Background: Electronic health record (EHR) patient portals are increasingly central to communication and care coordination in hepatology. However, because of the digital divide, portal-based care may worsen inequities if access is uneven. We evaluated demographic and socioeconomic differences in EHR patient portal engagement among adults with cirrhosis. **Methods:** We conducted a retrospective, cross-sectional analysis using aggregate data from March 2020-May 2026 in Epic Cosmos, a dataset created in collaboration with a community of Epic health systems representing over 300 million patient records. The cohort included adults ≥ 18 years residing in the United States with billed ICD-10 codes for cirrhosis (K70.3, K70.31, K70.30, K74.6, K74.69, or K74.60). Outcomes were current active patient portal (MyChart, Epic Systems, Verona, WI) status and patient portal access within the preceding 90 days. Portal engagement was compared across age, sex, race, ethnicity, language, primary payer, Rural-Urban Commuting Area (RUCA), Area Deprivation Index (ADI), and Social Vulnerability Index (SVI). Analyses used aggregate counts with chi-square tests, unadjusted odds ratios (ORs), and trend tests for

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ordered variables. **Results:** Among 1,713,212 adults with cirrhosis, 1,010,251 (59.0%) had active MyChart status and 618,435 (36.1%) had portal access within 90 days (see Table). Active portal status declined from 80.4% among patients aged 18-24 years to 56.0% among those aged ≥65 (OR 0.31, 95% CI 0.29-0.33). Compared with White patients (37.7%), Black/African American (27.9%; OR 0.64, 95% CI 0.63-0.65) and American Indian/Alaskan Native patients (28.5%; OR 0.66, 95% CI 0.64-0.67) demonstrated lower engagement as measured by recent portal access. Lower portal engagement was also observed with male sex, Hispanic ethnicity, non-English language preference, non-commercial insurance, micropolitan/small town/rural residence, and higher ADI and SVI. All comparisons and trend analyses were statistically significant ($p < 0.001$). **Conclusion:** In this large Epic Cosmos cohort of adults with cirrhosis, substantial disparities in EHR patient portal engagement were observed across sociodemographic variables. Given the large cohort size, statistical significance was expected for many comparisons; however, the observed absolute differences and effect sizes support clinically meaningful inequities in portal engagement. Recent portal access may more accurately reflect active patient engagement than activation status alone because many health systems automatically activate MyChart accounts during routine clinical workflows. These findings suggest that increasing reliance on portal-based healthcare delivery may risk amplifying existing inequities in hepatology care without targeted digital inclusion strategies and nonportal communication pathways.

Table: Variables associated with EHR patient portal engagement among adults with cirrhosis

	N	Active Portal Status N (%)	Active Portal Status OR (95% CI)	Recent Portal Access N (%)	Recent Portal Access OR (95% CI)
Total Cohort	1,713,212	1,010,251 (59.0%)	-	618,435 (36.1%)	-
Age					
18-24	4,428	3,559 (80.4%)	Reference	2,710 (61.2%)	Reference
25-64	148,243	99,924 (69.3%)	0.53 (0.49-0.57)	61,371 (42.0%)	0.46 (0.43-0.49)
45-64	634,361	387,283 (61.1%)	0.36 (0.36-0.41)	240,345 (37.9%)	0.39 (0.36-0.41)
≥65	928,180	519,480 (56%)	0.31 (0.29-0.33)	314,009 (33.8%)	0.32 (0.31-0.34)
Sex					
Male	978,794	542,593 (55.4%)	Reference	319,417 (32.6%)	Reference
Female	721,628	459,279 (63.6%)	1.41 (1.40-1.42)	293,948 (40.7%)	1.42 (1.41-1.43)
Race					
White	1,248,000	780,950 (61.0%)	Reference	470,624 (37.7%)	Reference
Black/African American	184,744	92,617 (50.1%)	0.64 (0.64-0.65)	51,625 (27.9%)	0.64 (0.63-0.65)
Asian/Pacific Islander	53,032	34,428 (64.9%)	1.18 (1.16-1.21)	20,776 (39.2%)	1.06 (1.05-1.08)
American Indian/Alaskan Native	38,342	19,283 (50.3%)	0.65 (0.63-0.66)	10,910 (28.5%)	0.66 (0.64-0.67)
Ethnicity					
Non-Hispanic/Latino	1,317,526	786,923 (59.7%)	Reference	484,947 (36.8%)	Reference
Hispanic/Latino	191,556	101,200 (52.8%)	0.76 (0.75-0.76)	57,668 (30.1%)	0.74 (0.73-0.75)
Language					
English	1,459,919	871,716 (59.7%)	Reference	535,561 (36.7%)	Reference
Other language	253,293	138,533 (54.7%)	0.81 (0.81-0.82)	82,874 (32.7%)	0.84 (0.83-0.85)
Primary Payer					
Commercial	660,265	485,537 (73.2%)	Reference	327,649 (49.4%)	Reference
Medicare	990,552	575,798 (58.1%)	0.51 (0.50-0.51)	356,301 (36.0%)	0.56 (0.57-0.58)
Medicaid	510,749	293,073 (57.4%)	0.49 (0.48-0.50)	168,272 (32.9%)	0.50 (0.50-0.51)
VA/Tricare	57,917	31,889 (55.0%)	0.45 (0.44-0.46)	17,758 (30.7%)	0.45 (0.44-0.46)
RUCA					
Metropolitan	1,408,979	854,350 (60.6%)	Reference	524,449 (37.2%)	Reference
Micropolitan	172,102	94,318 (54.8%)	0.79 (0.78-0.80)	57,566 (33.4%)	0.85 (0.84-0.86)
Small town/Rural	140,513	73,603 (52.4%)	0.71 (0.71-0.72)	44,779 (31.9%)	0.79 (0.78-0.80)
ADI					
<10	40,432	26,703 (66.0%)	Reference	16,604 (41.1%)	Reference
10-19	74,931	49,486 (66.0%)	1.00 (0.97-1.03)	31,415 (41.9%)	1.04 (1.01-1.06)
20-29	96,437	64,429 (66.8%)	1.03 (1.01-1.06)	41,285 (42.8%)	1.07 (1.05-1.10)
30-39	112,912	74,851 (66.1%)	1.00 (0.98-1.03)	48,419 (42.9%)	1.06 (1.05-1.10)
40-49	123,306	79,929 (64.8%)	0.95 (0.93-0.97)	51,592 (41.8%)	1.03 (1.01-1.06)
50-59	129,407	81,088 (62.7%)	0.86 (0.84-0.88)	51,895 (40.1%)	0.96 (0.94-0.99)
60-69	130,867	79,344 (60.7%)	0.79 (0.78-0.81)	50,894 (38.8%)	0.90 (0.88-0.92)
70-79	129,056	74,895 (58.0%)	0.71 (0.69-0.73)	46,361 (35.9%)	0.80 (0.79-0.82)
80-89	127,527	70,677 (55.4%)	0.64 (0.62-0.65)	42,739 (33.5%)	0.72 (0.71-0.74)
≥90	126,456	64,099 (50.7%)	0.53 (0.52-0.54)	37,035 (29.3%)	0.59 (0.58-0.61)
SVI					
<25	225,731	151,671 (67.2%)	Reference	101,347 (44.9%)	Reference
25-49	335,780	214,969 (64.0%)	0.87 (0.86-0.88)	138,144 (41.1%)	0.86 (0.85-0.87)
50-74	435,681	262,307 (60.2%)	0.74 (0.73-0.75)	162,150 (37.2%)	0.73 (0.72-0.74)
≥75	705,541	376,578 (53.4%)	0.56 (0.55-0.57)	214,983 (30.4%)	0.54 (0.53-0.54)

Abbreviations: OR: odds ratio; CI: confidence interval; EHR: electronic health record; VA: Veterans Administration; RUCA: rural-urban commuting area; ADI: area deprivation index; SVI: social vulnerability index

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0119 | SOCIAL DETERMINANTS OF HEALTH, RATHER THAN DISEASE SEVERITY, DRIVE SECOND-LINE THERAPY ESCALATION IN PRIMARY BILIARY CHOLANGITIS

Liliana Vittini-Hernandez[1] Lital Aliasi-Sinai[1] Christopher Kim[1] Jihae Jeon[1] Francina Collado[1] Douglas Dieterich[1] Anna Mageras[1] Frances Lee[1], [1]Icahn School of Medicine at Mount Sinai

Background: Patients with primary biliary cholangitis (PBC) and inadequate biochemical response to ursodeoxycholic acid (UDCA) are candidates for second-line (2L) therapy. Prior work in our cohort showed race and insurance status resulted in differences in 2L escalation. Here, we sought to determine whether laboratory markers of disease severity or hepatic fibrosis stage were associated with prescription of 2L therapy. **Methods:** This was a single-center retrospective cohort study from 2000-2025. Adults with PBC (ICD-10 code), ALP >200 IU/L, and active UDCA for ≥12 months were considered eligible for 2L therapy. The primary outcome was 2L therapy prescription. Covariates included age, sex, race, preferred language, marital status, insurance type, laboratory values (bilirubin, albumin, platelets, INR), and transient elastography (TE) results. Firth penalized logistic regression was used for univariable and multivariable analyses using R. A separate multivariable model incorporating lab variables was constructed. Hepatic fibrosis stage or liver stiffness measurements (LSM) on TE were assessed in 88 patients using Fisher's exact test and Cochran-Armitage trend test. **Results:** Among 262 eligible patients, the mean age was 64 years; 88% were female, 51% White, 12% Hispanic, 7% Black, and 8% uninsured. Overall, 76 patients (29%) received 2L therapy. 73.7% had no documented discussion of escalation, and no Black patients received 2L therapy (0/19). Only 1 of 22 uninsured patients (4.5%) received 2L therapy. In the demographics-only multivariable model, Black race (aOR 0.051, 95% CI 0.000–0.404, $p = 0.001$) and uninsured status (aOR 0.147, 95% CI 0.016–0.639, $p = 0.008$) were the only independent negative predictors of escalation. After incorporation of laboratory values ($n = 248$), these associations persisted for Black race (aOR 0.051, 95% CI 0.000–0.423, $p = 0.002$) and uninsured status (aOR 0.166, 95% CI 0.018–0.724, $p = 0.014$), while no laboratory variable was independently associated with 2L therapy initiation. Among 88 patients with TE data, escalation rates were similar across LSM (Fisher's exact test (OR 0.84, 95% CI 0.31–2.25, $p = 0.821$), Cochran-Armitage trend test ($Z = -0.23$, $p = 0.821$)). **Conclusion:** Black race and

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uninsured status remain the sole predictors of failure to escalate treatment, even after accounting for laboratory markers of disease severity and hepatic fibrosis stage. These findings suggest that social determinants of health, rather than clinical disease burden, may be the primary drivers of 2L treatment disparity. Targeted interventions addressing racial and insurance-based barriers are needed to promote equitable escalation of PBC therapy. Future studies should evaluate physician-, system-, and patient-level barriers to 2L initiation to better understand missed opportunities for treatment escalation.

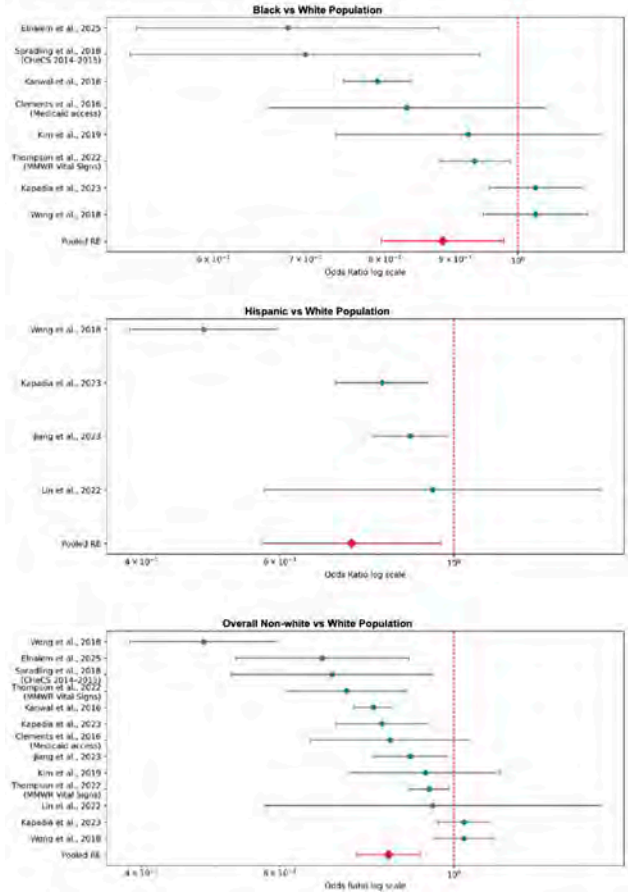
Disclosures: Liliana Vittini-Hernandez: Nothing to Disclose, Lital Aliasi-Sinai: Nothing to Disclose, Christopher Kim: Nothing to Disclose, Jihae Jeon: Nothing to Disclose, Francina Collado: Nothing to Disclose, Douglas Dieterich: Nothing to Disclose, Anna Mageras: The Kinetix Group: Advisor, Novo Nordisk: Advisor, Gilead Sciences: Grant/Research Support, Gilead Sciences: Advisor, Frances Lee: Nothing to Disclose.

0120 | UNEQUAL ACCESS TO CURATIVE THERAPY: RACIAL AND ETHNIC DISPARITIES IN DIRECT-ACTING ANTIVIRAL TREATMENT FOR CHRONIC HEPATITIS C IN THE UNITED STATES

Abbas Syed[1] Mohammad Dawar Zahid[2] Victor Akinditan[1] Syed Hasan[1] Khurram Bari[3], [1]University of Cincinnati, [2]AGA KHAN UNIVERSITY, [3]University of Cincinnati, University Hospital Inc Program

Background: Direct-acting antivirals (DAAs) have transformed the treatment of chronic hepatitis C virus (HCV) infection and offer the potential for cure in most treated patients. However, equitable access to DAA therapy remains essential to achieving HCV elimination goals. We performed a systematic review and meta-analysis evaluating racial and ethnic disparities in DAA treatment initiation among adults with chronic HCV infection in the United States. **Methods:** A systematic review of PubMed and Scopus identified U.S based studies published from 2014 onward evaluating racial and ethnic disparities in DAA treatment initiation among adults with chronic HCV infection. Of 685 identified studies, 70 duplicates were removed and 46 studies underwent full text review following title and abstract screening. Twelve observational studies met inclusion criteria, comprising 660,513 patients. Two reviewers independently screened studies and extracted data, with disagreements resolved by consensus. As most included studies utilized multivariable analyses to reduce confounding, adjusted odds ratios (aORs) were preferentially used for pooled analysis. Random-effects meta-analyses were performed to calculate pooled odds ratios (ORs) with 95% confidence intervals (CIs), and heterogeneity was assessed using the I^2 statistic. **Results:** Twelve observational studies comprising 660,513 patients with chronic HCV infection were included. Black patients demonstrated lower odds of receiving DAA therapy compared with White patients (pooled OR 0.88, 95% CI 0.80–0.98; $I^2 = 86.1\%$). Hispanic patients similarly demonstrated lower odds of DAA treatment initiation (pooled OR 0.74, 95% CI 0.57–0.96; $I^2 = 88.0\%$). In the overall comparison of non-White versus White patients, minority populations had lower odds of receiving DAA therapy (pooled OR 0.83, 95% CI 0.75–0.91; $I^2 = 86.4\%$). Although substantial heterogeneity was observed across analyses, the direction of effect was largely consistent across studies (as seen in forest plot in Image 1), with most demonstrating lower treatment uptake among racial and ethnic minority populations despite differences in study populations and healthcare settings. **Conclusion:** Racial and ethnic disparities in access to curative HCV therapy persist in the DAA era in the United States, with lower odds of DAA treatment initiation among Black, Hispanic, and overall non-White patients compared with White patients. Future research should focus on identifying the underlying drivers of these disparities and developing targeted interventions to ensure equitable access to curative HCV therapy.

IMAGE 1. FOREST PLOTS VISUALIZING POOLED ANALYSIS RESULTS



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0121 | SOCIAL DETERMINANTS OF HEALTH AND HCC SURVEILLANCE RECEIPT IN PATIENTS WITH CIRRHOSIS: A MULTICENTER COHORT STUDY

Mohammed Al-Hasan[1] Nicole Rich[1] Lisa Quirk[1] Juana Campos[2] Yan Liu[2] Mohammad Jarrah[1] Eunice Amador[1] Samantha Rangel Silos[1] Kayleen Sorto[1] Jahna Anyanwu[2] Amanda Gibbons[2] Valeria Londono[2] Gabriela Morales Pielago[2] Aaron Nguyen[2] Dalal Youssef[2] Jennifer Kramer[2] Fasiha Kanwal[3] Amit Singal[1], [1]University of Texas Southwestern Medical Center, [2]Baylor College of Medicine, [3]Michael E. DeBakey VA Medical Center

Background: Social determinants of health (SDOH) contribute to failures across the cancer care continuum for several cancer types; however, their association with hepatocellular carcinoma (HCC) surveillance receipt among patients with cirrhosis remains understudied. **Methods:** We prospectively enrolled patients with cirrhosis from four large health systems in the U.S. All patients were required to have at least one outpatient visit in the previous year, demonstrating connectedness to clinical care. Patient completed validated surveys to capture SDOH factors including education, income, insurance, health literacy, housing stability, and barriers to liver care. We collected clinical and HCC surveillance data from electronic medical records. Surveillance was defined as receipt of either abdominal ultrasound, contrast-enhanced MRI, or multiphase CT at semi-annual or annual intervals during the year before and after survey administration. We also defined proportion of time covered (PTC) over an 18-month window (6 months prior and 12 months after survey), with 6 months of coverage provided for each imaging study. Multivariable ordinal logistic and Tobit regression models were used to examine factors associated with surveillance. **Results:** Of 1,326 eligible patients (median age 62 years, 59.3% men, 42.0% non-Hispanic White), 29.6% had HCV-, 26.9% alcohol-, and 27.3% had MASLD-related cirrhosis; 60.0% had Child Pugh A cirrhosis. Although most patients (61.4%) completed annual surveillance, only 25.9% completed semi-annual surveillance. The median PTC was 65.5% (IQR 33.5-85.2%). Factors associated with surveillance are detailed in **Table 1**. In multivariable analysis, semi-annual surveillance was positively associated with higher educational attainment (college vs. high school or less: OR 1.50, 95% CI 1.15-1.96), alcohol-associated liver disease (OR 1.60, 95% CI 1.16-2.21), and Child-Pugh C cirrhosis (vs. Child Pugh A: OR 1.80, 95% CI 1.19-2.73), while it was inversely associated with female gender (OR 0.73, 95% CI 0.58-0.93), Spanish language (OR 0.64, 95% CI 0.42-0.98), Medicaid insurance (OR 0.55, 95%CI 0.34-0.86), and self-reported barriers to liver care (4th vs. 1st quartile: OR 0.60, 95% CI 0.44-0.82). Results were similar for factors associated with annual surveillance and PTC (**Table 1**). **Conclusion:** Only a few patients with cirrhosis completed semi-annual HCC surveillance. Beyond traditional demographic and clinical factors, several SDOH including educational attainment, insurance coverage, and patient-reported barriers to care are associated with surveillance receipt. Addressing barriers to liver care and a focus on underinsured patients belonging to high-risk subgroups may improve surveillance utilization and early-stage HCC detection.

Table 1: Multivariable Analysis of Factors Associated with Semi-Annual and Annual HCC Surveillance and Proportion of Time Covered (PTC)

	Semi-Annual OR (95% CI)	Annual OR (95% CI)	Proportion of Time Covered	
			Median (%)	β Coefficient (95% CI)
Age				
Age <65	Reference	Reference	61.06	Reference
Age ≥65	0.99 (0.74-1.34)	1.17 (0.86-1.59)	68.74	1.77 (−3.60 to 7.14)
Gender				
Men	Reference	Reference	67.28	Reference
Women	**0.73 (0.58-0.93)**	**0.67 (0.53-0.85)**	55.30	**-8.22 (-12.48 to -3.95)**
Race/Ethnicity				
White	Reference	Reference	66.91	Reference
Black	0.80 (0.58−1.09)	0.77 (0.56-1.05)	63.53	-3.31 (-8.98 to 2.36)
Hispanic	1.01 (0.73-1.40)	0.95 (0.68-1.34)	61.70	0.95 (-4.88 to 6.78)
Others	0.47 (0.22-1.00)	0.80 (0.38-1.70)	59.41	-6.04 (-19.51 to 7.42)
Language Preference				
English	Reference	Reference	66.91	Reference
Spanish	**0.64 (0.42-0.98)**	0.75 (0.49-1.15)	55.12	-5.81 (-13.49 to 1.87)
Education				
High school or less	Reference	Reference	53.75	Reference
Some college or above	**1.50 (1.15-1.96)**	**1.45 (1.10-1.89)**	69.29	**8.42 (3.64 to 13.20)**
Household Income				
<$50K	Reference	Reference	61.61	Reference
≥$50K	0.85 (0.64-1.14)	0.99 (0.73-1.34)	69.38	-0.23 (-5.47 to 5.02)
Etiology				
HCV	Reference	Reference	58.14	Reference

Disclosures: Mohammed Al-Hasan: Nothing to Disclose, Nicole Rich: AstraZeneca: Advisor, AstraZeneca: Advisor, Genentech: Consulting, Genentech: Consulting, Exelixis: Advisor, Exelixis: Advisor, Eisai: Advisor, Eisai: Advisor, Madrigal: Advisor, Madrigal: Advisor, AstraZeneca: Advisor, AstraZeneca: Advisor, Genentech: Consulting, Genentech: Consulting, Exelixis: Advisor, Exelixis: Advisor, Eisai: Advisor, Eisai:

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Advisor, Madrigal: Advisor, Madrigal: Advisor, Lisa Quirk: Nothing to Disclose, Juana Campos: Nothing to Disclose, Yan Liu: Nothing to Disclose, Mohammad Jarrah: Nothing to Disclose, Eunice Amador: Nothing to Disclose, Samantha Rangel Silos: Nothing to Disclose, Kayleen Sorto: Nothing to Disclose, Jahna Anyanwu: Nothing to Disclose, Amanda Gibbons: Nothing to Disclose, Valeria Londono: Nothing to Disclose, Gabriela Morales Pielago: Nothing to Disclose, Aaron Nguyen: Nothing to Disclose, Dalal Youssef: Nothing to Disclose, Jennifer Kramer: Nothing to Disclose, Fasiha Kanwal: Nothing to Disclose, Amit Singal: Genentech: Consultant, AstraZeneca: Consultant, Bayer: Consultant, Eisai: Consultant, Exelixis: Consultant, Merck: Consultant, Elevar: Consultant, FujiFilm Medical Sciences: Consultant, Exact Sciences: Consultant, Glycotest: Consultant, Boston Scientific: Consultant, Sirtex: Consultant, HelioGenomics: Consultant, ImCare: Consultant, DELFI: Consultant, Curve Biosciences: Consultant, Catalym: Consultant, Verve: Consultant.

0122 | SAME DISEASE, DIFFERENT HOSPITAL: RURAL VS. URBAN OUTCOMES IN ALCOHOL-ASSOCIATED HEPATITIS

Het Patel[1] Daniel Guirguis[1] Erik Dehkes[1] Hammad Liaquat[1], [1]St. Luke's University Healthcare Network

Background: Alcohol-associated hepatitis is a severe form of liver disease associated with high inpatient morbidity and mortality. Differences in healthcare access and hospital resources between rural and urban settings may influence management and outcomes. This study evaluated differences in patient characteristics and clinical outcomes between rural and urban hospitalizations using a nationally representative database. **Methods:** We conducted a retrospective cohort study using the National Inpatient Sample (NIS) database, identifying adults hospitalized between 2019 and 2022 with alcohol-associated hepatitis without cirrhosis and comparing demographics, comorbidities, hospital characteristics, and inpatient complications in rural versus urban hospitals. Univariate analyses were performed using STATA software. **Results:** Of the 47,295 patients who met inclusion criteria, the majority (57%) were male, with a mean age of 44 years in both rural and urban groups ($p \geq 0.05$). White (OR 1.670 95% CI 1.439-1.938) and Native American patients (OR 4.436 95% CI 3.319-5.929), as well as patients with COPD (OR 1.447 95% CI 1.133-1.846), were more likely to receive care at rural hospitals, whereas Black (OR 0.380 95% CI 0.288-0.501), Hispanic (OR 0.352 95% CI 0.259-0.477), and Asian (OR 0.192 95% CI 0.071-0.518) patients were less likely. No significant differences were observed in gender distribution or Charlson Comorbidity Index (CCI) between groups ($pP \geq 0.05$). Rural hospitals had higher odds of ascites (OR 1.270 95% CI 1.107-1.457) and spontaneous bacterial peritonitis (OR 1.786 95% CI 1.107-2.882), but lower odds of sepsis (OR 0.753 95% CI 0.577-0.984). Hospital mortality did not differ between groups (≥ 0.05). No differences were observed in variceal bleeding, paracentesis, acute kidney injury, hepatic encephalopathy, vasopressor use, acute liver failure, liver transplantation, ICU admission, mechanical ventilation, length of stay and total hospitalization charges ($p \geq 0.05$). **Conclusion:** Despite prior population-level studies demonstrating higher alcohol-associated liver disease mortality in rural populations, inpatient mortality and major clinical outcomes were similar between rural and urban hospitals in our cohort. These findings suggest comparable inpatient management and outcomes for alcohol-associated hepatitis across both settings, potentially reflecting effective triage and transfer systems with improved treatment protocols in rural settings. Further prospective studies could help investigate this further.

Table 1: Demographics

	Rural Hospital (n = 5,845)	Urban Hospital (n = 41,450)	p value	Odds Ratio (95% Confidence Interval)
Mean Age, years	44.7	44.3	0.365	-
Gender, n				
Male	3365 (57.6%)	23580 (56.9%)	0.653	1.028(0.910-1.161)
Female	2480 (42.4%)	17870 (43.1%)	0.653	0.972(0.861-1.098)
Race, n				
White	4485 (76.7%)	27515 (66.4%)	<0.001	1.670(1.439-1.938)
Black	285 (4.9%)	4925 (11.9%)	<0.001	0.380(0.288-0.501)
Hispanic	285 (4.9%)	5275 (12.7%)	<0.001	0.352(0.259-0.477)
Asian	20 (0.3%)	730 (1.8%)	0.001	0.192(0.071-0.518)
Native	425 (7.3%)	720 (1.7%)	<0.001	4.436(3.319-5.929)
Other	80 (1.4%)	1245 (3.0%)	0.002	0.448(0.269-0.747)
Cancer, n	35 (0.6%)	290 (0.7%)	0.697	0.855(0.389-1.882)
Hypertension, n	2125 (36.4%)	14845 (35.8%)	0.713	1.024(0.903-1.160)
COPD, n	415 (7.1%)	2080 (5.0%)	0.003	1.447(1.133-1.846)
Diabetes, n	515 (8.8%)	3690 (8.9%)	0.918	0.989(0.797-1.227)
Smoking History, n	3285 (56.2%)	22405 (54.1%)	0.179	1.091(0.961-1.238)
Malnutrition, n	500 (8.6%)	4050 (9.8%)	0.186	0.864(0.695-1.073)
Charlson Comorbidity Index, n				
3 or less	5210 (89.1%)	37510 (90.5%)	0.139	0.862(0.708-1.049)
4	425 (7.3%)	2465 (5.9%)	0.075	1.240(0.979-1.571)
5	150 (2.6%)	860 (2.1%)	0.280	1.243(0.838-1.845)
6	35 (0.6%)	315 (0.8%)	0.548	0.787(0.360-1.720)
7 or more	25 (0.4%)	300 (0.7%)	0.257	0.589(0.236-1.472)

Table 2: Hospitalization Co-illnesses

	Rural Hospital (n = 5,845)	Urban Hospital (n = 41,450)	p value	Odds Ratio (95% Confidence Interval)
Variceal Bleed, n	125 (2.1%)	675 (1.6%)	0.195	1.320(0.867-2.010)
Ascites, n	1685 (28.8%)	10025 (24.2%)	0.001	1.270(1.107-1.457)
Paracentesis, n	210 (3.6%)	1225 (3.0%)	0.231	1.224(0.879-1.703)
Spontaneous Bacterial Peritonitis (SBP), n	100 (1.7%)	400 (1.0%)	0.017	1.786(1.107-2.882)
Acute Kidney Injury (AKI), n	1075 (18.4%)	7300 (17.6%)	0.516	1.054(0900-1.237)
Hepatic Encephalopathy (HE), n	20 (0.3%)	260 (0.6%)	0.242	0.544(0.196-1.508)
Sepsis, n	320 (5.5%)	2960 (7.1%)	0.038	0.753(0.577-0.984)
Vasopressors, n	30 (0.5%)	420 (1.0%)	0.106	0.504(0.220-1.157)
Acute Liver Failure (ALF), n	455 (7.8%)	2970 (7.2%)	0.453	1.094(0.865-1.382)
Liver Transplant, n	40 (0.7%)	500 (1.2%)	0.122	0.564(0.273-1.165)
Intensive Care Unit (ICU) Admission, n	135 (2.3%)	1175 (2.8%)	0.303	0.810(0.543-1.209)
Mechanical Ventilation, n	125 (2.1%)	10005 (2.4%)	0.987	0.879(0.580-1.334)
Mortality, n	130 (2.2%)	925 (2.2%)	0.987	0.997(0.651-1.527)
Length of Stay, days	5.3	5.3	0.960	-
Total Charge, dollars	$113,220.30	$114,853.90	0.613	-

Disclosures: Het Patel: Nothing to Disclose, Daniel Guirguis: Nothing to Disclose, Erik Dehkes: Nothing to Disclose, Hammad Liaquat: Nothing to Disclose.

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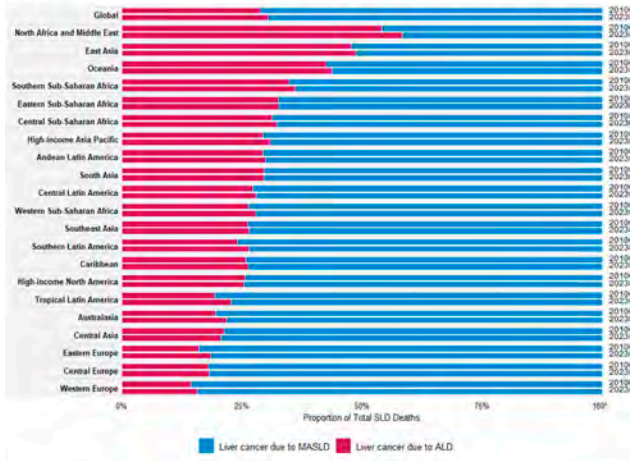
0123 | METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH) OUTPACING ALCOHOL-ASSOCIATED LIVER DISEASE (ALD) AS THE PRINCIPAL DRIVER OF RISING STEATOTIC LIVER DISEASE-ASSOCIATED LIVER CANCER

Eliabe Abreu[1] James Paik[1] Manal Abdelmalek[2] Robert Wong[3] Khalid AlNaamani[1] Saleh Alqahtani[4] Zobair Younossi[5], [1]Global NASH/MASH Council, [2]Mayo Clinic Rochester, [3]Stanford/VA Palo Alto Healthcare System, [4]King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia, [5]The Global NASH/MASH Council

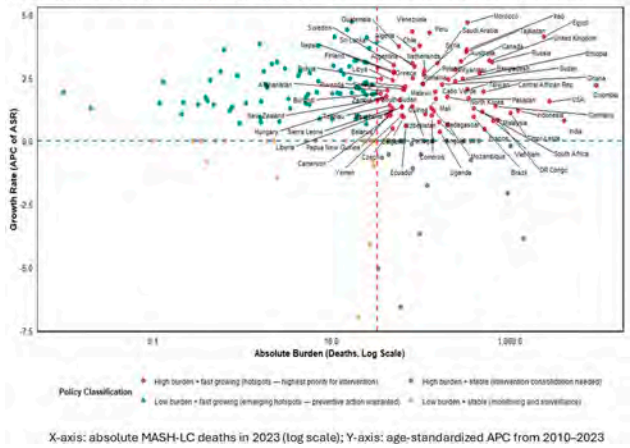
Background: Steatotic liver disease (SLD), fueled by rising epidemics of obesity, diabetes, and hazardous alcohol use, has been recently incorporated into the WHO global noncommunicable disease agenda. We evaluated global trends in SLD-associated liver cancer (SLD-LC) from 2010 to 2023, characterizing the burden and growth of MASH versus ALD. **Methods:** SLD-LC was defined by combining MASH- and ALD-attributable LC from GBD 2023 per multi-society nomenclature. Annual percent change (APC) in age-standardized rates was estimated using Joinpoint Regression for 2010–2023, 2010–2019, and 2019–2023. Countries were classified into four policy-relevant quadrants based on median absolute MASH-LC deaths in 2023 and APC > 0 as thresholds to identify nations where high disease burden coincides with rising trends, requiring urgent intervention: high burden + fast growing (hotspots), high burden + stable, low burden + fast growing, and low burden + stable. **Results:** Between 2010 and 2023, prevalent SLD-LC cases increased from 147,686 to 216,947 (+46.9%). In 2023, SLD-LC accounted for 24.0% of all LC deaths globally, with an estimated 136,789 deaths. SLD-LC was the only major etiology group with a consistently positive age-standardized APC across all four burden measures: deaths (+0.36%), incidence (+0.35%), prevalence (+0.33%), and DALYs (+0.42%), while HBV [range: -0.57% to -0.37%], HCV [-0.88% to -0.48%], and overall LC [-0.32% to -0.26%] all declined after age adjustment. MASH accounted for 28.9% of SLD-LC deaths in 2010, increasing to 30.5% by 2023 (Figure A). Despite this modest proportional shift, the APC for MASH-LC deaths (+0.85%) was six-times that of ALD (+0.15%), as MASH-LC never declined across any timeframe or burden measure, in contrast to ALD which decreased from 2010 to 2019 before accelerating post-2019. A marked inflection was observed after 2019: MASH-LC APC accelerated from +0.22% (2010–2019) to +2.30% (2019–2023), with the sharpest acceleration seen in DALYs (+2.69% post-2019). MASH-LC APC exceeded ALD-LC in 17 of 21 GBD regions, with the highest growth in Southern Latin America (+3.59%), North Africa and Middle East (+2.95%), and Australasia (+2.92%). Notably, 27 countries had MASH comprising more than 50% of SLD-LC deaths, predominantly in North Africa and the Middle East, including Saudi Arabia (79.9%), Iran (65.2%), and Egypt (61.8%). Policy classification identified 84 (41%) countries as MASH-LC hotspots, with the highest APC observed in Morocco, Venezuela, and Peru (Figure B) **Conclusion:** SLD-LC burden increased globally from 2010 to 2023, driven principally by MASH-LC, which never declined across any burden measure and accelerated markedly after 2019. Policy classification identified nations requiring immediate public health prioritization, underscoring the urgent need for metabolic disease management and targeted LC surveillance strategies worldwide.

Figure. Global Burden and Policy Classification of MASH-Associated Liver Cancer, 2010–2023.

(A) Proportion of MASH versus ALD within SLD-associated liver cancer deaths by GBD region for 2010 and 2023, sorted by 2023 MASH proportion in descending order.



(B) Country-level policy classification matrix of MASH-associated liver cancer mortality.



X-axis: absolute MASH-LC deaths in 2023 (log scale); Y-axis: age-standardized APC from 2010–2023

Disclosures: Eliabe Abreu: Nothing to Disclose, James Paik: Nothing to Disclose, Manal Abdelmalek: 89Bio, Akero, Madrigal, Inventiva, Novo Nordisk,

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0124 | HISPANIC/LATINO LIVER TRANSPLANT CANDIDATES HAVE LOWER ACCESS TO LIVING DONOR LIVER TRANSPLANTATION IN THE UNITED STATES: A NATIONAL COMPETING-RISK ANALYSIS

Tulio L Correa[1] Leandro Sierra[2] Ximena Parraga[3] Luiz A Díaz[4] Douglas Simonetto[5] Juan Pablo Arab[6],
[1]University of Pittsburgh, [2]Cleveland Clinic Foundation, [3]Virginia Commonwealth University School of Medicine, [4]Departamento de Gastroenterologia, Escuela de Medicina, Pontificia Universidad Catolica de Chile, [5]Mayo Clinic Rochester, [6]Virginia Commonwealth University

Background: Living donor liver transplantation (LDLT) expands access to liver transplantation, yet Hispanic/Latino patients remain underrepresented among transplant recipients despite a high burden of chronic liver disease. We aimed to evaluate disparities in access to LDLT between Hispanic/Latino and non-Hispanic White candidates using a national competing-risk analysis. **Methods:** We performed a retrospective cohort study using the OPTN/UNOS STAR registry of adult candidates listed for first-time, single-organ liver transplantation between 2014 and 2024. The primary exposure was Hispanic/Latino ethnicity. The primary outcome was receipt of LDLT. Fine-Gray competing-risk models were used to estimate subdistribution hazard ratios (sHRs) for LDLT, adjusting for age, sex, body mass index, MELD at listing, diabetes mellitus, liver disease etiology, insurance type, educational attainment, employment status, and citizenship/residency status. Deceased donor liver transplantation (DDLT) and waitlist death/removal were treated as competing events. **Results:** Among 118,385 candidates, 23,915 (20.2%) were Hispanic/Latino and 94,470 (79.8%) were non-Hispanic White. Hispanic/Latino candidates were younger (54.1 vs 55.2 years), more frequently female (40.1% vs 36.7%), and had higher rates of type 2 diabetes (35.1% vs 27.1%) and renal replacement therapy requirement (8.9% vs 6.1%) (all $P < 0.001$). They also had lower educational attainment, lower employment (21.2% vs 27.1%), greater Medicaid/public insurance use (54.3% vs 42.7%), and lower U.S. citizenship rates (80.6% vs 98.4%) (all $P < 0.001$). In addition, they spent longer on the waiting list (309.2 vs 281 days) and had higher final MELD-Na scores at transplant/removal (22.5 vs 21.6; both $P < 0.001$). LDLT receipt was significantly lower among Hispanic/Latino candidates (2.7% vs 3.8%, $P < 0.001$), as was DDLT receipt (51.3% vs 56.0%, $P < 0.001$). In adjusted competing-risk analysis, Hispanic/Latino ethnicity remained independently associated with lower likelihood of LDLT (sHR 0.86, 95% CI 0.76–0.96, $P = 0.009$) (Figure). **Conclusion:** Hispanic/Latino liver transplant candidates experienced significantly lower access to LDLT compared with non-Hispanic White candidates, even after adjustment for clinical and socioeconomic factors and competing events. Our findings may inform tailored strategies to improve access to LDLT among Hispanic/Latino candidates.

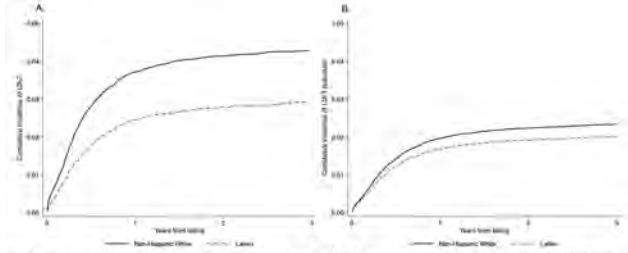


Figure. *Cumulative incidence of living donor liver transplantation among adult liver transplant candidates, by Latino ethnicity, OPTN/UNOS registry, 2014–2024.* ***Figure A.*** *Unadjusted cumulative incidence of living donor liver transplantation (LDLT) estimated using nonparametric competing-risk methods, treating deceased donor liver transplantation and waitlist death or removal as competing events. Three years after listing, the cumulative incidence of LDLT was 4.3% in non-Hispanic White candidates and 2.9% in Latino candidates.* ***Figure B.*** *Adjusted cumulative incidence of LDLT predicted from the Fine-Gray subdistribution hazard model (Table 3). After adjustment, Latino candidates had a 14% lower subdistribution hazard of LDLT receipt than non-Hispanic White candidates (subdistribution hazard ratio 0.86, 95% confidence interval 0.76–0.96, P=0.009). Abbreviations: LDLT, living donor liver transplantation; MELD-Na, Model for End-Stage Liver Disease–Sodium score; OPTN, Organ Procurement and Transplantation Network; UNOS, United Network for Organ Sharing.*

Disclosures: Tulio L Correa: Nothing to Disclose, Leandro Sierra: Nothing to Disclose, Ximena Parraga: Nothing to Disclose, Luiz A Díaz: Nothing to Disclose, Douglas Simonetto: Mallinckrodt: Consultant, BioVie: Consultant, Resolution Therapeutics: Consultant, Evive: Consultant, Iota: Consultant, Novo Nordisk: Consultant, Astra Zeneca: Consultant, Juan Pablo Arab: Nothing to Disclose.

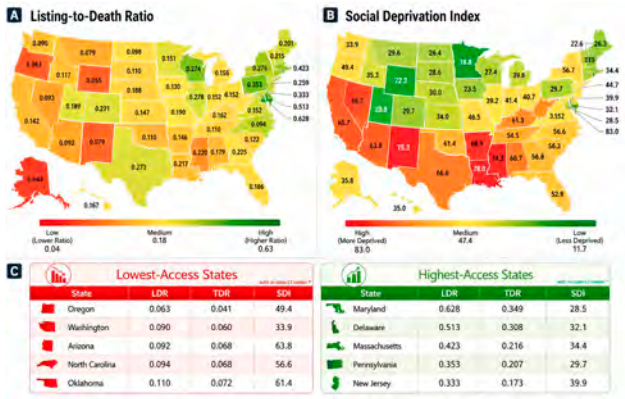
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0125 | GEOGRAPHIC DISPARITIES LEAVE PATIENTS IN THE WESTERN US WITH UNEQUAL ACCESS TO LIVER TRANSPLANT FOR ALCOHOL-ASSOCIATED LIVER DISEASE

Sharmitha Yerneni[1] Russell Rosenblatt[2] Eytan Palte[1] Giuseppe Cullaro[1] Elizabeth Verna[1] Gene Im[1], [1]NYP - Columbia University Irving Medical Center, [2]Weill Cornell Medicine

Background: Alcohol-associated liver disease (ALD) is the leading indication for liver transplantation (LT) in the United States, however access to LT continues to vary across geographic regions. Examining population-based access to LT using disease-attributable mortality can identify barriers to equitable access to life-saving care. **Methods:** We conducted a retrospective study using data from the UNOS and CDC WONDER databases from 2011 to 2024. Adults aged 18 and older waitlisted for LT for either alcohol-associated cirrhosis or alcohol-associated hepatitis, and deaths attributed to these conditions, were included. The primary outcome was the listing-to-death ratio (LDR), defined as the ratio of LT waitlist registrations to ALD-related deaths. LDR provides a population-based measure of access to LT. Secondary outcomes included transplant-to-death ratio (TDR) and state-level Social Deprivation Index (SDI). Pearson correlation analysis was performed to evaluate associations between LDR, TDR, and SDI. **Results:** A total of 48,820 LT listings for ALD and 262,909 ALD-related deaths over 13 years were analyzed. At the state and UNOS region-levels, the LDR for ALD ranged from the lowest in Alaska and its UNOS region 6 (0.04, 0.06, respectively) to the highest in Maryland and its UNOS region 2 (0.63, 0.29, respectively), a greater than 15- and 4-fold difference, respectively (Figure A). There was significant interstate heterogeneity in LDR for ALD, with states in the highest quartile having LDRs 2-5 times greater than those in the lowest quartile; median 0.18 (IQR 0.12-0.23; Figure B). At the US census regional level, the West demonstrated a significantly lower LDR compared with the South (0.12 vs. 0.21, $p < 0.001$) and Midwest (0.12 vs. 0.19, $p < 0.001$), with the largest disparity observed relative to the Northeast (0.12 vs. 0.31, $p < 0.001$). Similar associations were observed for TDR. LDR was moderately inversely associated with state-level SDI ($r = -0.386$, $p = 0.005$), indicating lower LT access in states with greater socioeconomic deprivation (Figure C). **Conclusion:** Substantial geographic variation in access to LT for ALD was observed across the US, leaving patients in the Western US with unequal access compared to the Northeast. Causes of these disparities to access are complex, but specific to ALD, may include center-level variations in candidate selection and patient-level socioeconomic status factors.



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0126 | HEPATORENAL SYNDROME MORTALITY IN THE UNITED STATES, 2018–2024: PRE-COVID, COVID-ERA, AND POST-COVID NATIONAL TRENDS AND DISPARITIES

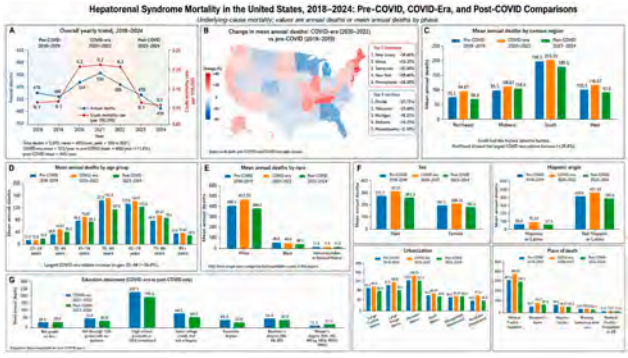
Naga Anvesh Kodali[1] Sri Ram Charan Gundapaneni[1] Pragathi Munnangi[2] Serene Sara John[3] Mounika Kotte[4] Jagadish Koyi[5] Hardik Dineshbhai Desai[6] Izuchukwu Nwakoby[1], [1]UCF/HCA Florida Ocala Hospital, Ocala, Florida, United States, 34471, [2]BronxCare Health System, Bronx, New York - 10457, [3]Detroit medical center, Detroit, Michigan, 48201, [4]Prime south consortium, Weslaco, Texas, USA,78596, [5]Integris Health, Oklahoma City, Oklahoma. USA. 73112, [6]AB Plus Multispecialty Hospital

Background: Hepatorenal syndrome (HRS) is a severe complication of advanced liver disease with high short-term mortality, but U.S. population-level mortality patterns across the COVID-19 period are poorly characterized. We evaluated national HRS mortality before, during, and after the COVID-19 era. **Methods:** We analyzed U.S. underlying-cause-of-death data for HRS from 2018–2024. Annual deaths, crude mortality rates, and age-adjusted mortality rates were assessed overall and by census region, state, urbanization, age, sex, race, Hispanic origin, education attainment, and place of death. Pre-COVID (2018–2019), COVID-era

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(2020–2022), and post-COVID (2023–2024) periods were compared using mean annual deaths. Annual percent change (APC) was estimated using log-linear regression. **Results:** From 2018–2024, 3,395 HRS deaths occurred in the United States (mean 485/year). Annual deaths rose from 476 in 2018 and 460 in 2019 to 514 in 2020 and peaked at 550 in 2021, then declined to 506 in 2022, 470 in 2023, and 419 in 2024. Mean annual deaths increased from 468/year pre-COVID to 523/year during COVID-era (+11.8%), then fell to 445/year post-COVID (-5.0% vs pre-COVID). The South had the highest absolute burden (1,368 total deaths; mean 198.5, 203.3, and 180.5 across pre-, COVID-, and post-COVID phases), while the Northeast showed the largest COVID-era relative increase (73.5 to 94.7/year; +28.8%). States with the greatest COVID-era increases versus pre-COVID were New Jersey (+38.5%), Illinois (+33.3%), Tennessee (+30.0%), New York (+28.5%), and Pennsylvania (+26.5%); the largest declines were in Florida (-27.7%), Wisconsin (-23.1%), Michigan (-18.5%), Alabama (-14.3%), and Massachusetts (-12.5%). Males consistently exceeded females (273.5 vs 194.5 pre-COVID; 317.0 vs 206.3 during COVID-era; 262.5 vs 182.0 post-COVID). The largest COVID-era relative increase by age occurred in 35–44 years (26.0 to 40.7/year; +56.4%), while the highest absolute counts were in 55–64 years (137.5 to 142.0) and 65–74 years (127.0 to 133.0). By race, mean annual deaths increased among White individuals (398.5 to 453.3; +13.8%) and slightly among American Indian/Alaska Native individuals (11.0 to 11.5; +4.5%), but decreased among Black individuals (48.0 to 46.0; -4.2%). Among Hispanic groups, deaths increased from 52.0 to 70.3/year (+35.3%) in Hispanic/Latino persons and from 415.0 to 451.3/year (+8.8%) in non-Hispanic/Latino persons. **Conclusion:** HRS mortality in the United States demonstrated a clear COVID-era surge followed by post-COVID decline, despite relatively stable population-level mortality rates. The burden remained concentrated in the South, men, and middle-to-older adults, with disproportionately large COVID-era relative increases in the Northeast, rural noncore areas, younger adults aged 35–44 years, and deaths occurring at home.



Disclosures: Naga Anvesh Kodali: Nothing to Disclose, Sri Ram Charan Gundapaneni: Nothing to Disclose, Pragathi Munnangi: Nothing to Disclose, Serene Sara John: Nothing to Disclose, Mounika Kotte: Nothing to Disclose, Jagadish Koyi: Nothing to Disclose, Hardik Dineshbhai Desai: Nothing to Disclose, Izuchukwu Nwakoby: Nothing to Disclose.

0127 | HAVING INSURANCE IS NOT ENOUGH: MEDICAID INSURED PATIENTS STILL LACK EQUITABLE ACCESS TO LISTING FOR LIVER TRANSPLANT

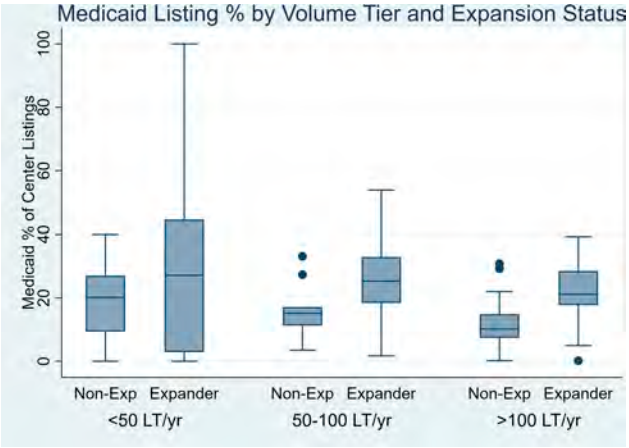
Russell Rosenblatt[1] David Goldberg[2], [1]Weill Cornell Medicine, [2]University of Miami

Background: Medicaid expansion increased insurance access to millions of Americans starting in 2014. This in turn has resulted in increased listings in patients listed for liver transplant (LT) in expansion states. However, it remains unclear if Medicaid patients have equitable access to all LT centers within each state. Therefore, we performed a state-level analysis to compare Medicaid patient listing rates in centers, stratified by Medicaid expansion status. **Methods:** Adults at time of listing from the UNOS STAR file from 2014-2024 were included. We compared states that expanded Medicaid in 2014 or never expanded. States with ≥ 3 centers were included. LT centers were assigned to states if $\geq 50\%$ of listed patients were from a single state. The primary outcome was the percentage of patients listed having Medicaid insurance. Outcomes were also stratified by center annual volume - low (<50), medium (50–100), or high (>100). Outcomes and distributional differences were compared using Wilcoxon rank-sum and two-sided Kolmogorov-Smirnov test, respectively. Finally, waitlist mortality by insurance type was assessed by multivariable competing risk regression, with covariates selected *a priori*. **Results:** This study included 114,778 patients listed in 33 states (21 expander, 12 non-expander) in 142 centers. 60.4% of patients in 93 centers were in expander states. More patients were listed with Medicaid insurance in expander states (23.6% vs 10.0%, $p<0.001$), with all non-expander centers $<40\%$ of listing being Medicaid-insured. There were significant differences in center-level distribution of Medicaid patients ($p<0.001$). As center volume increased, Medicaid listing proportion decreased among both cohorts and was most pronounced among highest volume (>100 LTs/year) centers – 23.2% vs 9.8%, $p<0.001$. As an example, in one non-expander state, two larger centers with a combined 2,800 listings during the study period each had 0.2% of patients with Medicaid insurance, while a center with 222 listings had 26.6% of patients with Medicaid insurance. Notably, LT volume alone did not

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account for Medicaid proportion (p = 0.15). Transplant rates were not significantly different among expander status (p > 0.05). Finally, waitlist mortality was significantly lower in privately insured patients in both expander (sHR 0.82, 95% CI 0.76-0.89) and non-expander states (sHR 0.83, 95% CI 0.74-0.93), but Medicare was not significantly different in either cohort. **Conclusion:** Listing for LT in patients with Medicaid varies significantly among both centers and states. Understandably, Medicaid non-expanding states have worse access to LT listing for patients with Medicaid. This gap is even more pronounced in the highest-volume LT centers, further exacerbating disparities. Further research is needed to investigate why Medicaid patients continue to face disparities in access to the LT waitlist.

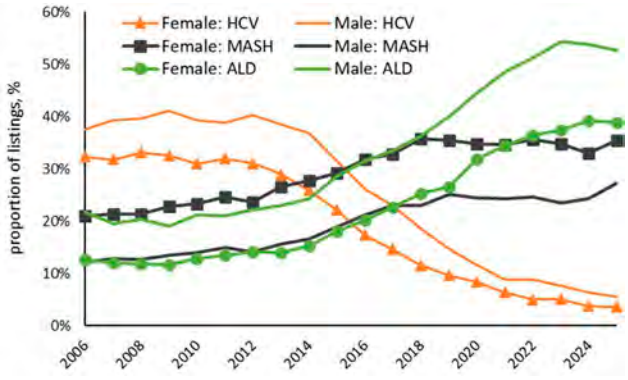


Disclosures: Russell Rosenblatt: Gilead: Grant/Research Support, David Goldberg: Nothing to Disclose.

0128 | SEX DISPARITIES IN THE LIVER TRANSPLANT JOURNEY: FROM CANDIDACY TO LONG-TERM OUTCOMES IN A 20-YEAR US COHORT

Linda Henry[1] Maria Stepanova[1] Giacomo Germani[1] Adrian Gadano[1] Patrizia Burra[1] Rohit Satoskar[2] Khalid AlNaamani[1] Saleh Alqahtani[1] Zobair Younossi[1], [1]The Global NASH/MASH Council, [2]Georgetown University Hospital

Background: Sex-related differences in chronic liver disease (CLD) epidemiology may influence liver transplantation (LT) listing and outcomes. We assessed sex-specific trends in CLD etiologies among LT candidates and recipients in the US. **Methods:** Adult LT candidates and recipients with CLD were identified from the Scientific Registry of Transplant Recipients (SRTR, 2006–2025). Etiologies included hepatitis B (HBV), hepatitis C (HCV), metabolic-dysfunction associated steatohepatitis (MASH), autoimmune hepatitis (AIH), alcohol-related liver disease (ALD), ALD+HCV, primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), and other CLD. Sex-specific outcomes were compared. **Results:** Among 214,827 LT candidates, 78,610 (36.6%) were female. Males more likely to have ALD (34.5% vs. 24.4%), HCV (24.5% vs. 17.1%), HBV (3.0% vs. 1.3%), ALD+HCV (5.5% vs. 2.0%), and PSC (4.8% vs. 4.1%), whereas females more commonly had MASH (30.3% vs. 19.8%), AIH (6.3% vs. 1.4%), and PBC (6.9% vs. 0.7%) (all p < 0.0001).HCV listings declined in both sexes: 32.3% to 3.6% (females) and 37.6% to 5.6% (males). Steatotic liver disease increased with divergent patterns. Females: MASH 21.0%→35.5%, ALD 12.6%→38.8%. Males: ALD 21.7%→52.7%, MASH 12.2%→27.2%. By 2025, ALD and MASH represented the first and second most common etiologies in both sexes. The third and fourth etiologies differed by sex: PBC (5.4%) and AIH (5.0%) in females versus HCV (5.6%) and PSC (4.2%) in males.Males had lower MELD (20.8 ± 10.1 vs. 21.5 ± 10.4) and higher transplantation rates (64.8% vs. 61.1%). Females had higher crude waitlist mortality (10.8% vs. 9.2%), deterioration (9.4% vs. 8.9%) (p < 0.01). Multivariable competing-risk analyses showed female sex was not independently associated with waitlist mortality in any etiology group (all p > 0.05). Common predictors of waitlist mortality included advanced age, elevated MELD, poor functional status, life support, ascites, encephalopathy, and HCC.Five-year post-LT mortality was higher in males (21.9% vs. 20.1%). Male sex was independently associated with higher post-LT mortality in HBV (aHR = 1.31, 95% CI 1.07–1.62), HCV (aHR = 1.09, 1.04–1.14), MASH (aHR = 1.17, 1.12–1.23), PBC (aHR = 1.55, 1.31–1.83), and PSC (aHR = 1.26, 1.11–1.42), but not AIH, ALD, or ALD+HCV (p > 0.05). Post-LT mortality predictors included advanced age, diabetes, public insurance, reduced functional status, life support, and prior transplantation (p < 0.01). **Conclusion:** CLD epidemiology requiring liver transplantation has substantially changed with pronounced sex-specific trends. Waitlist mortality showed no independent sex differences within etiology groups, while male sex was an independent risk factor for higher post-transplant mortality across most CLD etiologies.



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0129 | BURDEN OF HEALTH-RELATED SOCIAL NEEDS ARE INDEPENDENTLY ASSOCIATED WITH FRAILTY AND MINIMAL HEPATIC ENCEPHALOPATHY IN COMPENSATED CIRRHOSIS: A LIVER CIRRHOSIS NETWORK STUDY

Ani Kardashian[1] Abigail Smith[2] Ann Kan[2] Elliot Tapper[3] Mandana Khalili[4] Srinivasan Dasarathy[5] Nicole Welch[5] Elizabeth Verna[6] Robert Brown[7] Matthew Kappus[8] Cynthia Moylan[8] Douglas Simonetto[9] Vijay Shah[9] Patricia Denise Jones[10] Andrew Scheinberg[10] Neehar Parikh[3] Rohit Loomba[11] Monica Tincopa[11] Bilal Hameed[4] Jasmohan Bajaj[12] Arun Sanyal[12] Norah Terrault[1], [1]University of Southern California, [2]Northwestern University, [3]University of Michigan Medical Center, [4]University of California, San Francisco, [5]Cleveland Clinic, [6]Columbia University Medical Center, [7]Weill Cornell Medicine, [8]Duke University, [9]Mayo Clinic Rochester, [10]University of Miami, [11]University of California, San Diego, [12]Virginia Commonwealth University

Background: Health-related social needs (HRSNs) are understudied in compensated cirrhosis, with prior data limited to a single domain (e.g. food insecurity) and a comprehensive evaluation of social risk lacking. We hypothesize that HRSNs influence frailty and minimal hepatic encephalopathy (MHE), often the earliest signs of decompensation and reduced quality of life, through competing demands, poor nutrition, financial stress, and limited access to care. In turn, frailty and MHE limit patients' capacity to address their social needs, fueling a self-reinforcing cycle. This study evaluated the association of individual and cumulative HRSN burden with frailty and MHE in a well-characterized multicenter cohort of adults with compensated cirrhosis. **Methods:** The Liver Cirrhosis Network Cohort Study includes adults from 10 US sites with compensated cirrhosis. Four core (housing instability, utility needs, food insecurity, transportation insecurity) and two supplemental (social support, financial strain) HRSNs were assessed at baseline by the Accountable Health Communities HRSN and USDA Household Food Security Surveys. Frailty was measured by Liver Frailty Index (LFI) and MHE by Stroop test using age-adjusted validated cutoffs. Multivariable linear and logistic regression models adjusted for age, race-ethnicity, sex, cirrhosis etiology, MELD 3.0, alcohol use, Charlson Comorbidity Index, and BMI examined associations of individual and cumulative HRSN burden (0, 1, ≥ 2) with frailty and MHE. **Results:** Among 859 participants, 234 (27%) had ≥ 1 core HRSN, 12% were frail (LFI > 4.5), and 56% had MHE. Among HRSN ≥ 1 vs HRSN = 0, median [IQR] LFI was higher (3.97 [3.60-4.34] vs 3.73 [3.26-4.11]) and MHE prevalence was greater (63% vs 54%). In multivariable analysis, all six HRSNs were independently associated with greater frailty: housing (b = 0.27, 95%CI [0.15-0.38]), food (b = 0.29 [0.15-0.44]), utility (b = 0.32 [0.12-0.52]), transportation (0.29 [0.12-0.47]), social (b = 0.40 [0.26-0.54]) and financial (b = 0.29 [0.18-0.39]) (**Figure**). For MHE, food (OR = 1.88, 1.16-3.13), social (OR = 1.85, 1.15-3.05), and financial (OR = 1.78, 1.26-2.53) insecurities were associated with greater odds. Incremental increase in core HRSN burden was associated with progressively greater frailty (b = 0.19 [0.08-0.30] for HRSN = 1, b = 0.43 [0.27-0.59] for HRSN ≥ 2) and MHE (OR = 1.82 [1.07-3.20] for HRSN ≥ 2) in multivariable models. **Conclusion:** In this large multicenter study of compensated cirrhosis, 1 in 4 adults reported ≥ 1 HRSN, highlighting the need for routine HRSN screening. A strong, graded association was observed between HRSNs and both frailty and MHE. While this cross-sectional analysis cannot establish directionality, these findings suggest that HRSNs may represent a modifiable barrier to the clinical management of frailty and MHE, particularly in compensated cirrhosis when disease trajectory may still be amenable to intervention.

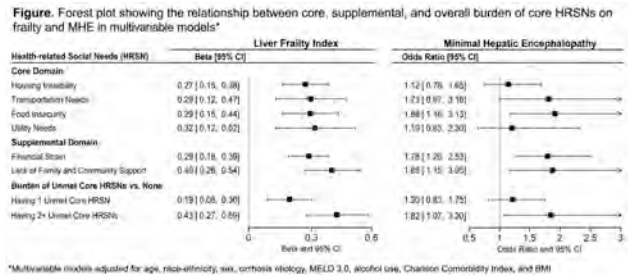


Figure. Forest plot showing the relationship between core, supplemental, and overall burden of core HRSNs on frailty and MHE in multivariable models*

*Multivariable models adjusted for age, race-ethnicity, sex, cirrhosis etiology, MELD 3.0, alcohol use, Charlson Comorbidity Index, and BMI

Disclosures: Ani Kardashian: Nothing to Disclose, Abigail Smith: Boehringer Ingelheim: Consultant, Boehringer Ingelheim: Grant/Research Support, Dimerix: Grant/Research Support, Ann Kan: Nothing to Disclose, Elliot Tapper: Madrigal: Grant/Research Support, Gilead: Consultant, Ipsen: Consultant, Merz: Consultant, Mandana Khalili: gilead sciences: Grant/Research Support, GSK pharmaceuticals: Consultant, Intercept

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0130 | MACHINE LEARNING-BASED PHENOTYPING OF CRYPTOGENIC HEPATOCELLULAR INJURY IN THE US ADULT POPULATION

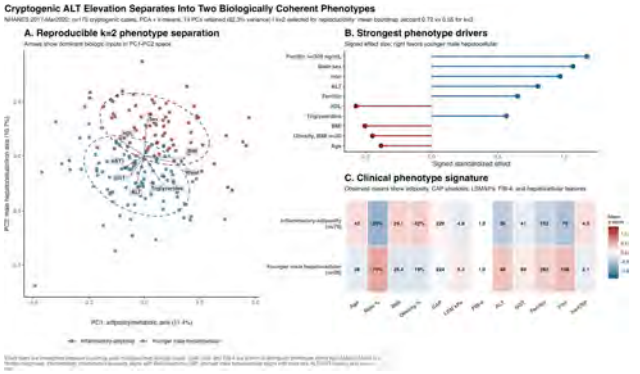
Kartik Dapke[1] Timothy Davie[2] Jesse Fletcher[2] Serena Brosten[2] Anna Strauss[2] Giovanni Roldan[3] Prowpanga Udompap[4], [1]Department of Medicine, Saint Vincent Hospital, Worcester, MA, [2]Department of Medicine, University of Minnesota, [3]Division of Gastroenterology, Hepatology and Nutrition, University of Minnesota, [4]Division of Gastroenterology, Minneapolis VA Medical Center

Background: Alanine aminotransferase (ALT) is the primary serum marker of hepatocellular injury. Despite a structured diagnostic workup, a significant proportion of ALT elevations have no identifiable etiology. Defined as a diagnosis of exclusion, the prevalence and clinical characteristics of this cryptogenic subset remain unknown. **Methods:** This cross-sectional study analyzed NHANES 2017–March 2020 data from adults aged ≥20 years with measured ALT. Elevated ALT was defined as >33 U/L in men and >25 U/L in women. To identify cryptogenic cases, we applied rigorous, prespecified adjudication rules using vibration controlled transient elastography (VCTE), laboratory, medications, and survey data to exclude individuals with Metabolic Dysfunction Steatotic Liver disease (MASLD), MASLD with increased alcohol intake (MetALD), alcohol-associated liver disease, viral hepatitis (B or C), iron overload, suspected autoimmune hepatitis, or drug-induced liver injury. National prevalence estimates were calculated using NHANES sample survey weights. For the cryptogenic population, distinct phenotypes were identified using principal component analysis followed by k-means clustering, validated by silhouette width and bootstrap Jaccard coefficients. **Results:** Among 7,880 adults with ALT measured, representing 225.7 million (M) U.S. adults, 1,501 had elevated ALT, corresponding to a weighted prevalence of 18.1% (95% CI 16.5–19.8) or 40.8M U.S. adults. Of these, 884 elevated ALT adults with complete etiologic adjudication, 175 had cryptogenic hepatocellular injury, corresponding to a weighted prevalence of 21.1% (95% CI 17.1–25.9) or an estimated of 6.2M U.S. adults. Internal validation supported a 2-cluster solution over 3 clusters (silhouette 0.093 vs 0.089; minimum bootstrap Jaccard 0.706 vs 0.491). Cluster 1 (n = 96) was younger, male-predominant (79%), and had higher ALT (47.9 vs 35.9 U/L) and ferritin (261.6 vs 101.5 ng/mL). Cluster 2 (n = 79) was older, less often male (20%), and showed greater adiposity (BMI 29.1 vs 26.4 kg/m²) and inflammatory burden (CRP 3.98 vs 2.13 mg/L). (Figure 1) **Conclusion:** Cryptogenic hepatocellular injury affects an

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estimated 6.2 million U.S. adults and comprises two clear phenotypes: a younger, male-predominant cohort with suspected iron-mediated injury, and an older, female-predominant cohort with an adiposity and inflammatory profile highly consistent with MASLD. This second cluster exposes a critical systemic vulnerability, where true metabolic liver disease is likely missed due to the inherent diagnostic limitations of VCTE. These results underscore that a "cryptogenic" designation should not lead to clinical watch-and-wait approaches. Instead, when unexplained transaminitis mirrors a patient's metabolic and inflammatory risk profile, clinicians must look past negative elastography scores and aggressively pursue secondary screening and early metabolic management.



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0131 | SOCIODEMOGRAPHIC AND STRUCTURAL BARRIERS AMONG INDIVIDUALS WITH HEPATITIS B IN THE US: ANALYSIS OF THE ALL OF US DATABASE

Xiaohan Ying[1] Jacky Choi[2] Himel Mallick[2] Tatyana Kushner[2], [1]NewYork Presbyterian/Weill Cornell, [2]Weill Cornell Medicine

Background: Chronic hepatitis B (HBV) remains a leading cause of cirrhosis and hepatocellular carcinoma worldwide. In the United States its burden is increasingly concentrated among socially and economically marginalized populations. The extent to which structural inequities in socioeconomic status, insurance coverage, and healthcare access contribute to barriers to care is not clearly defined. We aimed to further evaluate sociodemographic characteristics and structural barriers using the All of Us Database as well as to examine whether HBV status is independently associated with poor health status. **Methods:** We performed a cross-sectional analysis of all patients enrolled in the All of Us Research Database, a National Institute of Health funded database focused on recruiting those historically underrepresented in biomedical research. Individuals with HBV were identified through ICD-10 codes or positive HBV surface antigen and/or HBV DNA. Sociodemographic characteristics, insurance coverage, healthcare access, and patient-reported overall health were compared between HBV and non-HBV populations. Chi-square tests were used for categorical and Wilcoxon rank-sum tests were used for continuous variables. Multivariable logistic regression examining self-reported health was adjusted for age, sex, race, ethnicity, and income. **Results:** Of 626,383 participants, 2,323 (0.4%) individuals had a diagnosis of HBV. Individuals with HBV were older (median 64 vs 57 years), more likely to be male (52% vs 36%), foreign born (24% vs 15%), and more likely to be Black (37% vs 19%) or Asian (11% vs 4.2%) compared to participants without HBV, all $p < 0.001$. Patients with HBV were more likely to have income $\leq$\$50K (70% vs 47%) and lower educational attainment (college or above: 30% vs 47%). They were less likely to have employer-sponsored insurance (17% vs 36%) and more likely to be covered by Medicaid (31% vs 19%) or Medicare (16% vs 13%), with all comparisons $p < 0.001$. Patients with HBV were more likely to experience greater barriers to care, including higher rates of delayed care due to transportation (12% vs 8.6%, $p < 0.001$), and difficulty affording prescription medications (15% vs 13%, $p = 0.025$). Patients with HBV were more likely to self-report poor/fair health (40% vs 23%, $p < 0.001$). In adjusted analysis, positive HBV status was independently associated with worse self-reported health (OR 1.90, 95% CI 1.7-2.1, $p < 0.001$) after adjusting for age, race/ethnicity, and income (Table 1). **Conclusion:** In a large, nationally diverse cohort, HBV status was associated with substantial structural and socioeconomic disadvantages as well as worse self-reported health. These findings highlight structural inequities that require policy and health system interventions addressing affordability, access barriers, and equitable delivery of care to ensure optimal care for patients with HBV.

Characteristics	OR	95% CI	p-Value
HBV Status	1.9	1.70, 2.11	**<0.001**
Age	1	1.00, 1.00	**<0.001**
Sex			
Female	-	-	
Male	0.91	0.89, 0.92	**<0.001**
Race			
White	-	-	
Black	1.22	1.20, 1.25	**<0.001**
Multi-Race	1.3	1.26, 1.35	**<0.001**
Asian	0.72	0.68, 0.75	**<0.001**
Ethnicity			
Not Hispanic	-	-	
Hispanic	1.08	1.04, 1.12	**<0.001**
Income			
Up to $50K	-	-	
$50K - $100K	0.44	0.43, 0.45	**<0.001**
$100K - $150K	0.31	0.30, 0.32	**<0.001**
$150K - $200K	0.24	0.23, 0.25	**<0.001**
More than $200K	0.19	0.18, 0.20	**<0.001**

Table 1. Multivariable analysis of impact of Hepatitis B status on self-reported health, adjusted for age, sex, race, ethnicity, and income.
Abbreviations: OR = Odds Ratio, CI = Confidence Interval

Symbols: ♦, Poster of Distinction; ★, Foundation Award Recipient

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0132 | SEQUENTIAL ALGORITHMS USING FIB-4, FOLLOWED BY VCTE OR ELF TO DETECT ADVANCED FIBROSIS: VALIDATION OF RISK STRATIFICATION STRATEGY IN THE UNITED STATES (U.S.) PRIMARY CARE SETTING

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Background: In the U.S., MASLD risk stratification algorithms endorse sequential non-invasive tests (NITs) with FIB-4 followed by VCTE or ELF. Performance of these algorithms in primary care, where prevalence of AF is lower than the referral centers, remains unquantified. We report three-zone evaluation of sequential NITs performance with guideline-based clinical action, anchoring registry-based NITs performance to NHANES-derived prevalence of AF which is closer to population seen at primary care. **Methods:** NHANES 2017–2020 data (N = 5,969) were used to estimate AF prevalence (LSM ≥ 12 kPa) among adults with type 2 diabetes (T2D) and medically complicated obesity without T2D (MCOB) in primary care. Other causes of chronic liver diseases and excessive alcohol use were excluded. Sensitivity and specificity of NITs were derived from our biopsy-confirmed MASLD registry patients (n = 17,978) with available FIB-4 (T2D n = 8,370 [AF 50.8%]; MCOB n = 6,540 [25.0%]) and adjusted for fibrosis stage distribution differences expected between the registry and primary care. Based on algorithms, VCTE or ELF were performed only in patients with FIB-4 ≥ 1.3 (FIB-4+VCTE: T2D n = 5,285 [53.6%], MCOB n = 3,216 [29.4%]; FIB-4+ELF: T2D n = 3,354 [74.2%], MCOB n = 1,488 [50.2%]). Adjusted performance was applied using Bayesian correction at age-specific NHANES AF prevalence (Table), classifying patients into Rule-Out (FIB-4 < 1.3), Indeterminate (FIB-4 ≥ 1.3 but 2nd line NIT below threshold), or Rule-In zones (FIB-4 ≥ 1.3 and 2nd NIT above threshold) and further stratified into MASH F2–F3, AF without cirrhosis, and cirrhosis according to 2026 consensus thresholds (Table). **Results:** In primary care, FIB-4 followed by VCTE or ELF classified 67% of T2D and 78% MCOB patients as Rule-Out for AF (NPV 95% and 97%, respectively). In contrast, 15% of T2D and 8% of MCOB were Rule-In (PPV 83% and 71%, respectively). Of all patients tested, 9% of T2D and 5% of MCOB were identified as MASH F2–F3, 3% and 1% had AF without cirrhosis, both eligible for pharmacotherapy, and 3% and 2% had probable cirrhosis and not candidates for pharmacotherapy (Table). The remaining patients fell into the Indeterminate zone, subdivided into low-risk followed by primary care and at-risk after 2nd NIT which required clinical decision about pharmacotherapy (Table).Age-stratified analysis showed that 2nd NITs added greatest value in patients ≥ 65 years, where FIB-4 specificity was lowest (68% in T2D; 61% in MCOB) and FIB-4-alone had inadequate PPV (17% in T2D; 4% in MCOB). VCTE raised Rule-In PPV in this group to 88% and 80% and Rule-Out NPV reached 95% and 99%. **Conclusion:** The recommended two-NIT sequential algorithm excludes AF for most high-risk patients (T2D and MCOB) in primary care. Confirmatory 2nd line NITs (VCTE or ELF) improved PPV. This approach was most valuable in patients aged ≥ 65 years, where initial FIB-4 step was inadequate for rule-in decisions.

Table. Performance of the Sequential Risk Stratification Algorithm at Primary Care Advanced Fibrosis Prevalence

Cohort/Age Group	Prevalence Advanced fibrosis	Rule-Out	Intermediate low risk	Intermediate at risk	Rule-In MASH F2–F3	Rule-In Adv Fibrosis	Rule-In Probable Cirrhosis	Rule-out NPV, %	Rule-in PPV, %
First line NIT		FIB-4 <1.3	FIB-4 ≥1.3						
Second Line VCTE			VCTE <8	VCTE 8–10	VCTE 10–15	VCTE 15–20	VCTE ≥20	Rule-out NPV, %	Rule-in PPV, %
T2D Overall	9.7%	67%	11%	7%	9%	3%	3%	95%	83%
T2D 35–64	10.4%	66%	12%	7%	9%	3%	3%	94%	82%
T2D ≥65	9.0%	65%	10%	8%	10%	3%	3%	95%	88%
OB Overall	6.0%	78%	10%	4%	5%	1%	2%	97%	71%
OB 35–64	8.0%	73%	12%	5%	6%	2%	2%	97%	70%
OB ≥65	2.4%	60%	16%	9%	10%	3%	2%	99%	80%
Second Line: ELF			ELF <9.2	ELF 9.2-9.8	ELF 9.8-10.5	ELF 10.5-11.3	ELF ≥11.3	Rule-out NPV, %	Rule-in PPV, %
T2D Overall	9.7%	67%	11%	9%	8%	4%	2%	95%	90%
T2D 35–64	10.4%	66%	12%	10%	7%	3%	2%	94%	91%
T2D ≥65	9.0%	65%	10%	9%	8%	6%	2%	95%	88%
OB Overall	6.0%	78%	11%	5%	4%	2%	1%	97%	81%
OB 35–64	8.0%	73%	13%	6%	5%	2%	1%	97%	80%
OB ≥65	2.4%	60%	18%	7%	8%	4%	3%	99%	87%

Zone proportions estimated at age-specific NHANES advanced fibrosis prevalence among adults with T2D and medically complicated obesity (OB) using a conditional independence approximation applied to registry-derived sensitivity and specificity.

"Rule-Out"-Low risk; maintain primary care management; lifestyle intervention; retest in 1–3 years based on cardiometabolic risk factors.
Indeterminate-Low risk: Primary care management; lifestyle intervention; retest in 1–3 years.
Indeterminate-At risk: Clinical judgment based on cardiometabolic risk factors; may treat as MASH F2–F3.
"Rule-In"- MASH F2–F3: Refer to specialist; lifestyle intervention; eligible for resmetirom or semaglutide.
"Rule-In"- Advanced fibrosis excluding cirrhosis: Use second-line NIT to exclude cirrhosis; if excluded, treat as MASH F2–F3.
"Rule-In"- Probable cirrhosis : Specialist referral for cirrhosis care; resmetirom and semaglutide not recommended.

T2D, type 2 diabetes; OB, medically complicated obesity without T2D; VCTE, vibration-controlled transient elastography; ELF, Enhanced Liver Fibrosis score; NPV, negative predictive value; PPV, positive predictive value; NHANES, National Health and Nutrition Examination Survey; LSM, liver stiffness measurement; CMR, cardiometabolic risk factor; MASH, metabolic dysfunction-associated steatohepatitis

Disclosures: Zobair Younossi: Zobair M. Younossi is a consultant or has received research: Consultant, madrigal: Grant/Research Support, Siemens: Research funding, GSK: Consultant, BI: Consultant, Sanofi: Research funding, James Paik: Nothing to Disclose, Leyla de Avila: Nothing to Disclose, Maria Stepanova: Nothing to Disclose, Markos Kalligeros: Nothing to Disclose, Annette Paik: Nothing to Disclose, Khalid AlNaamani: Nothing to Disclose, Saleh Alqahtani: Nothing to Disclose, Linda Henry: Nothing to Disclose.

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★ 0133 | LIVER TRANSPLANT QUALITY MEASURES AFFECT HEALTH OUTCOMES: A MULTICENTER ANALYSIS OF THE CONSORTIUM FOR THE HOLISTIC ASSESSMENT OF RISK IN TRANSPLANT

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Background: The American Association for the Study of Liver Diseases (AASLD) recently published pre-transplant quality measures; however, their feasibility and clinical relevance in real-world practice remain uncertain. We used electronic health record (EHR) data from a multicenter transplant consortium to evaluate the feasibility of operationalizing these measures, variation across centers, and associations with outcomes. **Methods:** Among 18,657 referred patients, we analyzed 9,888 who underwent outpatient LT evaluation (2016-2022) across seven centers in the Consortium for the Holistic Assessment of Risk in Transplant. We assessed the feasibility of operationalizing 32 post-referral AASLD pre-transplant quality measures and quantified center-level variation. Associations between evaluation timing measures and downstream outcomes were evaluated using Fine-Gray competing risk models adjusted for patient sociodemographic and clinical characteristics and center. **Results:** Of 32 post-referral measures, 13 (41%) were operationalized. Most non-operationalized measures relied on documentation not captured in structured EHR fields. Among evaluated patients, 4,694 (50%) were waitlisted and 2,927 (30%) underwent LT. Median times from referral to evaluation initiation and completion were 21 days (IQR 10-35) and 85 days (IQR 39-168), with substantial variation across centers (medians ranging from 7-33 days and 37-112 days, respectively). Among waitlisted patients, 13% experienced dropout due to death or clinical deterioration (center range 8-17%) and 62% underwent transplantation (center range 52-77%). Center-level variation in evaluation and waitlist outcomes persisted after adjustment. Earlier evaluation initiation ($\leq$30 days vs. >30 days) was associated with increased likelihood of waitlist placement (sHR 1.24, 95% CI 1.16-1.32) and higher pre-transplant mortality (sHR 1.20, 95% CI 1.04-1.38), though the latter was attenuated in sensitivity analyses limited to patients with available MELD-Na data (**Figure**). Longer time to evaluation completion, particularly beyond 90 days (vs. 46-90 days), was associated with increased waitlist dropout due to death or being too sick (91-120 days: sHR 1.32, 95% CI 1.02-1.71; >120 days: sHR 1.23, 95% CI 1.00-1.51) and reduced likelihood of transplantation (91-120 days: sHR 0.88, 95% CI 0.78-1.00; >120 days: sHR 0.76, 95% CI 0.68-0.84; **Figure**). **Conclusion:** Nearly half of AASLD post-referral pre-transplant quality measures could be operationalized using real-world EHR data. Among feasible measures, evaluation timing demonstrated substantial inter-center variation and was associated with clinically meaningful transplant outcomes. These findings support the use of measurable, EHR-based process metrics such as time to evaluation initiation and completion as potential benchmarks for quality improvement in pre-transplant care.

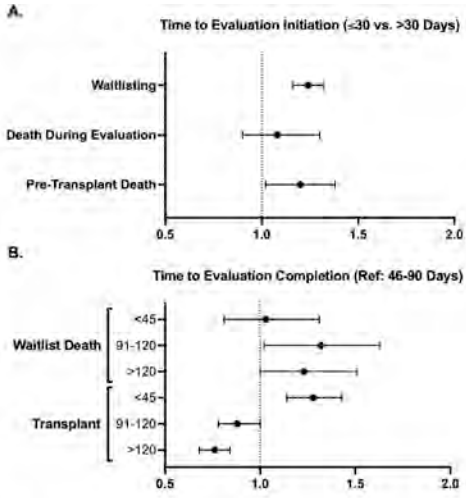


Figure. Association between evaluation timing and transplant outcomes. Multivariable Fine-Gray competing risk models evaluating associations of (A) time to evaluation initiation (≤30 vs. >30 days) and (B) time to evaluation completion (reference: 46-90 days) with downstream outcomes. Points represent subdistribution hazard ratios; error bars represent 95% confidence intervals. Pre-transplant mortality represents death at any time after evaluation initiation. Waitlist death includes removal for clinical deterioration.

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0134 | HEPATOCELLULAR CARCINOMA IN INCARCERATED INDIVIDUALS: PREVALENCE, RISK FACTORS, AND TRENDS IN A LARGE U.S. CORRECTIONAL COHORT, 2015–2023

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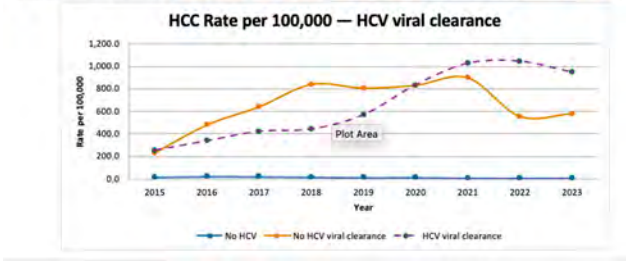
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Background: The epidemiology of hepatocellular carcinoma (HCC) among incarcerated individuals remains poorly defined despite the high burden of risk factors, particularly chronic hepatitis C virus (HCV). We aimed to describe the burden of HCC within the Texas Department of Criminal Justice (TDCJ) prison system. **Methods:** Individuals ≥ 18 years incarcerated in TDCJ facilities for any duration between January 1, 2015, and December 31, 2023, were included. HCC was identified using ICD-9/10 codes and verified with chart review. Demographics, incarceration duration, HCV status and hepatitis B infection were extracted from the electronic medical record. Prevalence was calculated annually per 100,000 individuals and stratified by key variables. **Results:** Among 519,964 incarcerated individuals (mean incarceration 3.5 years, SD 2.5), 408 HCC cases were identified. The overall prevalence of HCV was 8.1% (8096.3 per 100,000). Among those with HCC, mean incarceration was of 4.7 years (SD 2.4); 97.8% were male, 38.5% White, 37.0% Hispanic, and 47.6% ≥60 years old. HCC prevalence rose from 27.8 per 100,000 in 2015 to highest in 2021 (71.7 per 100,000). Prevalence was consistently higher in males (peak 76.4 per 100,000 in 2021) than females (peak 25.2 per 100,000 in 2021). Prevalence was highest among those ≥60 years, peaking at 640.0 per 100,000 in 2021, versus 80.6 per 100,000 in the 50–59 age group and less than 25 per 100,000 in younger groups. Hispanics had the highest early prevalence (40.3 per 100,000 in 2015), while Whites increased overtime with highest in 2021 - 85.3 per 100,000. Blacks had consistently lower prevalence (38.1–56.1 per 100,000). Those with HCV had substantially higher HCC prevalence than those without HCV (647.8 vs. 7.2 per 100,000 in 2021). Individuals with HCV viral clearance showed a paradoxical rise in HCC prevalence, reaching 1,044 per 100,000 by 2022 versus 898 per 100,000 among those without clearance. HBV infection was associated with elevated HCC prevalence (peak 1,176 per 100,000 in 2022), though interpretation is limited by small case counts. **Conclusion:** This is the largest characterization of HCC prevalence in a U.S. correctional system, revealing a substantial and growing burden driven by chronic HCV. The paradoxical rise in HCC prevalence among individuals achieving HCV viral clearance may be explained by persistent risk even after HCV eradication, survivor bias, or increased detection through closer follow-up. A better understanding of HCC epidemiology in this high-risk population is essential for improving outcomes and for guiding strategies to identify, treat, and ultimately eliminating HCV. Successful antiviral treatment programs within the prison system offer an opportunity to reduce HCC incidence, eliminate HCV, and prevent ongoing transmission within and outside the prison population.

HCC Prevalence Heatmap — TDCJ 2015–2023

Prevalence per 100,000 persons · Color scale applied independently within each category · Darker = higher prevalence

Category	Subgroup	2015	2016	2017	2018	2019	2020	2021	2022	2023
Race	White	19.5	37.7	45.7	63.4	71.2	71.6	85.3	69.1	66.6
	Black	24.3	41.8	44.2	52.3	46.6	56.1	54.6	38.3	38.1
	Hispanic	40.3	64.4	75.6	73.1	67.7	89.8	72.8	56.2	51.6
Sex	Male	31.2	53.0	60.6	69.5	68.1	78.0	76.4	61.4	56.9
	Female		4.1	8.3	8.3	12.8	22.2	25.2		10.8
Age	18–39 yrs	0.7	0.8	0.8	0.8	0.8	1.0	2.2	1.1	
	40–49 yrs	4.1	14.9	23.4	23.0	14.7	14.1	17.3	16.1	6.4
	50–59 yrs	103.4	184.6	177.4	181.4	169.6	126.5	92.6	95.1	80.6
	60+ yrs	235.7	328.3	421.3	508.9	505.9	620.2	640.0	439.5	447.8
Overall	All persons	27.8	47.6	54.8	62.8	62.0	70.7	71.7	55.4	52.3



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0135 | TELEHEALTH VS IN-PERSON EARLY PALLIATIVE CARE FOR PATIENTS WITH CIRRHOSIS: RESULTS FROM THE PAL-LIVER MULTI-CENTER TRIAL

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Background: Patients with cirrhosis experience substantial symptom burden, impaired quality of life (QoL), and limited access to palliative care (PC). Telehealth may improve access to PC, but comparative data

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evaluating telehealth versus in-person delivery in cirrhosis are limited. We compared outcomes of telehealth and in-person early PC delivery among patients with cirrhosis enrolled in the PAL LIVER trial. **Methods:** This is an ancillary analysis of the PAL-LIVER comparative effectiveness cluster RCT conducted at 19 U.S. centers. All enrolled patients received PC either from PC specialist or trained hepatologist, according to their assigned site model by randomization. Of the 935 enrolled, 816 patients were included (modified ITT population who had at least one intervention visit). Participants received 4 structured PC visits over 3 months and were categorized by delivery modality: in-person only, telehealth only, or mixed.The primary outcome was change in QoL at 3 months measured by the Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep). Secondary outcomes included symptom burden (ESAS), depression (PHQ-9) and satisfaction (FAMCARE-P). Adjusted analyses used mixed linear models accounting for differences in baseline characteristics, intervention arms and clinical setting. **Results:** The mean [SD] age was 62.9 [10.3] years; 29% were female. 37% received in-person PC, 31% telehealth-only, and 32% mixed. Mean MELD 3.0 score was 14.4 (5.2). Participants who self-reported as Hispanic, Black, with high-school or less, and without insurance were more likely to receive in-person only visits. The mean FACT-Hep total score significantly increased for each intervention modality: 6.28 points for in-person, 6.79 points for telehealth, and 8.59 points for mixed. The increase in scores for the mixed modality reached the MCID threshold (8-9 points) for clinical significance. There was no significant difference in the change in FACT-Hep scores from baseline to 3 months by intervention modality ($p = 0.40$). Among those in mixed modality, patients who had their initial visit in-person had a clinically significant improvement in FACT-Hep (+9 points, $p < 0.001$) when compared to those with initial telehealth.Symptom burden decreased similarly across modalities (−5.09, −6.42, and −6.98). Depression also improved in all groups (-1.14, -1.16 and -0.72) without any difference between groups. Satisfaction improved in the in-person and mixed groups but not significantly in the telehealth-only group; between-group differences were not significant. Intervention fidelity was high and comparable across modalities. **Conclusion:** Telehealth delivery of PC for cirrhosis was associated with improvements in QoL, depression and symptom burden comparable to in-person care, supporting telehealth as a scalable model to expand access without compromising outcomes. Mixed modality with initial in-person visit can be a feasible strategy.

Table 1: **Adjusted mean change in primary and secondary outcomes at 3 months**

Outcome (change from baseline to 3 months)	In-person (N=305) Adjusted mean (95% CI)	P-value	Telehealth (N=250) Adjusted mean (95% CI)	P-value	Mixed (N=261) Adjusted mean (95% CI)	P-value	overall P-value between group difference
FACT-Hep total score	6.28 (3.76, 8.80)	<0.001	6.79 (3.96, 9.63)	<0.001	8.59 (6.08, 11.09)	<0.001	0.40
FACT-Hep subscales							
Physical Well Being (PWB)	1.02 (0.30, 1.75)	0.005	1.55 (0.76, 2.34)	<0.001	1.16 (0.44, 1.87)	0.002	0.58
Social Well-Being (SWB)	0.43 (-0.27, 1.12)	0.23	0.39 (-0.38, 1.16)	0.32	1.17 (0.48, 1.85)	<0.001	0.17
Emotional Well-Being (EWB)	1.11 (0.54, 1.68)	<0.001	0.48 (-0.16, 1.13)	0.14	1.20 (0.63, 1.76)	<0.001	0.22
Functional Well-being (FWB)	1.01 (0.27, 1.75)	0.008	1.05 (0.22, 1.88)	0.013	1.17 (0.43, 1.90)	0.002	0.95
Modified ESAS Total score (13 items)	-5.09 (-7.52, -2.66)	<0.001	-6.42 (-9.12, -3.71)	<0.001	-6.98 (-9.37, -4.59)	<0.001	0.53
PHQ-9 (Depression)	-1.14 (-1.77, -0.51)	<0.001	-1.16 (-1.87, -0.45)	0.001	-0.72 (-1.33, -0.10)	0.022	0.57
DT (Distress)	-0.14 (-0.48, 0.20)	0.42	-0.30 (-0.68, 0.08)	0.13	-0.48 (-0.82, -0.15)	0.005	0.38
FAMCARE-P13 (Satisfaction)	2.97 (1.77, 4.16)	<0.001	1.04 (-0.33, 2.41)	0.14	1.74 (0.52, 2.95)	0.005	0.092

Higher scores reflect better QoL (FACT-hep total score and all subscales). Higher ESAS means higher symptom burden, PHQ-9 -higher depression, FAMCARE P13- better patient satisfaction.

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0136 | EFFICACY OF ELEBSIRAN (VIR-2218) + TOBEVIBART (VIR-3434) IN PARTICIPANTS WITH CHRONIC HEPATITIS DELTA INFECTION: PATTERNS OF HDV RNA RESPONSES THROUGH WEEK 96

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Background: Hepatitis delta virus (HDV) infection causes the most severe form of chronic viral hepatitis with limited treatment options. The ongoing phase 2 SOLSTICE study is investigating the antiviral activity and

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safety of the monoclonal antibody tobevibart and an interfering RNA (siRNA) elebsiran in combination in participants with chronic HDV infection, with or without compensated cirrhosis, on NRTI therapy (NCT05461170). **Methods:** Antiviral efficacy, including patterns of HDV RNA responses, was assessed in participants receiving combination therapy with elebsiran 200 mg plus tobevibart 300 mg subcutaneously (SC) every 4 weeks (elebsiran+tobevibart Q4W) through 96 weeks. **Results:** At week 96, 88% (28/32) of participants receiving elebsiran+tobevibart Q4W achieved undetectable HDV RNA (target not detected [TND], no amplification by PCR) and 53% (17/32) achieved ALT normalization (missing equals failure analysis). More participants reached undetectable HDV RNA over time: 66% (21 out of 32) achieved it after 48 weeks of treatment, and 88% achieved it after 96 weeks. After achieving undetectable HDV RNA, no confirmed virologic rebound >LLOQ was observed through week 96. Participants receiving elebsiran+tobevibart Q4W had substantial reduction in HBsAg, with ~91% achieving HBsAg <10 IU/mL by week 48 and these reductions were maintained through week 96. Treatment-emergent adverse events were primarily Grade 1-2 and transient, with influenza-like syndrome (ILS) being the most common reported AE. Ninety-seven percent of ILS was associated with first dose administration and generally resolved within the first 24-48 hours. No treatment-related serious adverse events occurred. We will present detailed summaries of HDV RNA response patterns, including the time to achieving undetectable HDV RNA after treatment initiation and durability of this response, as well as correlation with measures of liver disease, through 96 weeks of elebsiran+tobevibart Q4W therapy. **Conclusion:** Elebsiran+tobevibart Q4W combination therapy resulted in rapid and maintained HDV RNA suppression, with 88% achieving undetectable HDV RNA by week 96. Robust HBsAg reductions and ALT normalization were also observed. Adverse events were generally mild to moderate and transient. These results support further development of elebsiran+tobevibart Q4W, which is now being evaluated in the registrational ECLIPSE program for chronic HDV infection.

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0137 | BRELOVITUG MONOTHERAPY FOR THE TREATMENT OF CHRONIC HEPATITIS D: RESULTS FROM BEYOND WEEK 24 TREATMENT IN THE AZURE-1 PHASE 2B STUDY

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Background: Chronic Hepatitis D (CHD) is the most severe form of viral hepatitis, and current treatments are limited. Brelovitug (BJT-778) is a fully human monoclonal antibody against Hepatitis B surface antigen. Brelovitug is currently being evaluated in AZURE-1(NCT06907290), a global, randomized, Phase 2b/3 trial versus delayed treatment (DT) in adults with CHD. Brelovitug was shown to be safe and effective through 24 weeks of treatment for CHD with and without cirrhosis in the phase 2b portion of AZURE-1. Here we report on data beyond 24 weeks from AZURE-1 phase 2b. **Methods:** Participants were randomized 2: 2: 1 to receive brelovitug 300mg subcutaneous (SC) weekly (QW) self-administered at home, 900mg SC every 4 weeks (Q4W) administered in the clinic, or delayed treatment (DT) for 24 weeks followed by brelovitug 300mg QW. Key inclusion criteria included hepatitis D virus (HDV) RNA > 500 IU/mL, ALT > upper limit of normal (ULN), and Child-Pugh Score < 7; HIV co-infection and compensated cirrhosis with or without portal hypertension were allowed. There were no exclusion criteria for liver stiffness, bilirubin, albumin, INR or maximum ALT. The primary endpoint (PE) was a composite of virologic response (HDV RNA $\geq$ 2 log10 IU/mL decrease or < LLOQ/TND) and ALT normalization at W24. **Results:** 53 participants were enrolled; 21 to 300mg QW, 20 to 900mg Q4W, and 12 to DT groups. The mean (SD) age overall was 46 (8.2) years, 49 (92%) were White, 37 (70%) were male, and 28 (53%) had cirrhosis. Mean (SD) baseline HDV RNA was 5.5 (0.83) log10 IU/mL and ALT was 124 (95.3) U/L, including 11 (21%) with ALT $\geq$ 5xULN, 8 (15%) with liver stiffness > 25kpa, and 4 (14%) with CTP score of 6.At W24, PE was achieved in 45% (9/20) p = 0.003, 35% (7/20) p = 0.024, and 0% (0/12) for the 300mg QW, 900mg Q4W, and DT groups, respectively. A virologic response was observed in 100% (20/20), 75% (15/20), and 0% (0/12) for the 300mg QW, 900mg Q4W, and DT groups, respectively. ALT normalization occurred in 45% (9/20), 40% (8/20), and 8% (1/12) of patients, respectively. 7 participants (17%) reported mild injection site reactions in both 300 mg QW and 900 mg Q4W groups and 1 (5%) reported mild flu-like symptoms in the 900 mg Q4W groups. There were no treatment-related SAEs, Grade $\geq$ 3 AEs, or AEs leading to study discontinuation. After W24, additional ALT normalization and virologic suppression were observed. Among those with data at W36, a 100% virologic response was observed in both 300 mg (6/6) and 900 mg (6/6) groups. ALT normalization occurred in 67% of patients in both the 300 mg (4/6) and 900 mg (4/6) groups. Complete W48 results will be shared at the time of presentation as the trial is ongoing. **Conclusion:** In individuals with CHD, brelovitug demonstrated continued improvements in both HDV RNA and ALT and was well-tolerated with continued treatment beyond 24 weeks. The AZURE-1 Phase 3 trial and other phase 3 trials in CHD patients are ongoing.

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0138 | PREVALENCE AND OUTCOMES OF VIROLOGICAL BREAKTRHOUGHS DURING BULEVIRTIDE MONOTHERAPY IN CHD PATIENTS: A POOLED ANALYSIS FROM THE SAVE-D AND D-SHIELD MULTICENTER STUDIES

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Background: Bulevirtide (BLV) 2 mg/day is approved for the treatment of chronic hepatitis Delta (CHD), but real-world data on virological breakthroughs (VBK) during long-term BLV monotherapy remain limited. We evaluated the incidence and timing of VBK during BLV 2 mg/day monotherapy in two multicenter real-life cohorts (SAVE D and D SHIELD). **Methods:** CHD patients treated with BLV 2 mg/day monotherapy from the retrospective/prospective multicenter, observational, real-world SAVE-D and D-SHIELD studies with available paired baseline-week 24-48-72 or 96 data were included. VBK was defined as ≥ 1 Log_{10} HDV RNA increase compared to a previous timepoint (nadir). Virological (HDV-RNA undetectable or ≥ 2 Log_{10} decline *vs.* baseline), biochemical (BR, ALT < 40 U/L), combined response (CR, biochemical+virological), HDV RNA undetectability and liver-related events were also assessed. **Results:** Among a total of 900 CHD patients enrolled in the SAVE-D and D-SHIELD studies, a total of 276 patients with available paired baseline-W72 data (111 with available week 96 data) were included: at baseline (BLV start), median age was 52 (IQR 42-60) years, 55% males, 73% with cirrhosis, median ALT 81 (45-144), liver stiffness measurement (LSM) 14.0 (6.1-25.0) kPa, HBsAg 3.7 (3.2-4.2) Log_{10}IU/mL, HDV RNA 5.3 (3.9-6.4) Log_{10}IU/mL. Overall, rates of response at week 48 were 68% (VR), 67% (BR), 52% (CR) and 28% (HDV RNA undetectable), while the corresponding figures at week 96 were 68% (VR), 65% (BR), 50% (CR) and 38% (HDV RNA undetectable), respectively. During BLV monotherapy, a VBK occurred in 15 (5%) patients at week 48, 24 (9%) at week 72 and 8 (3%) at week 96. At VBK, a BR was maintained in 7/15 (47%) patients at week 48, 10/24 (42%) at week 72, and 7/8 (87%) at week 96. Occurrence of VBK was independent of baseline ALT levels ($p = 0.08$), HDV RNA ($p = 0.72$) and cirrhosis status ($p = 0.15$). VBK was stable at two consecutive timepoints in 7 (15%) patients, while in the remnants VBK was only transient and resolved at the following treatment timepoint. None of the patients with

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VBK developed a de novo liver-related event. **Conclusion:** During BLV 2 mg/day monotherapy up to 96 weeks, 17% of the patients experienced a VBK. Nevertheless, most cases of VBK were transient and not associated with increased ALT levels.

Disclosures: Elisabetta Degasperi: Gilead: Speaking and Teaching, Roche: Advisor, Abbvie: Speaking and Teaching, IPSEN: Speaking and Teaching, MIRUM: Advisory Board, Maria Paola Anolli: Nothing to Disclose, Dana Sambarino: Nothing to Disclose, Marta Borghi: Nothing to Disclose, Riccardo Perbellini: Nothing to Disclose, Liliana-Simona Gheorghe: Nothing to Disclose, Alessandro Loglio: Nothing to Disclose, Alessia Ciancio: Nothing to Disclose, GIANPIERO D'Offizi: Nothing to Disclose, Christoph Schramm: Nothing to Disclose, Thomas Reiberger: Nothing to Disclose, Maurizia Brunetto: Nothing to Disclose, Kosh Agarwal: Nothing to Disclose, Maria Buti: Roche Pharma/Diagnostics: Consultant, Gilead Sciences: Consultant, GSK: Consultant, Abbvie: Consultant, Janssen: Consultant, Roche Pharma/Diagnostics: Speaking and Teaching, Gilead Sciences: Speaking and Teaching, GSK: Speaking and Teaching, Abbvie: Speaking and Teaching, Janssen: Speaking and Teaching, Bepirovirsen – GSK: Referral to unlabelled/unapproved products, Serena Zaltron: Nothing to Disclose, Frank Tacke: Gilead: Grant/Research Support, MSD: Grant/Research Support, AstraZeneca: Grant/Research Support, Agomab: Grant/Research Support, NovoNordisk, Boehringer, Gilead, MSD, GSK: Consultant, Pfizer, Sanofi: Advisor, Madrigal, Mirum, Ipsen: Consultant, Sanofi: Advisor, Falk: Speaking and Teaching, Heiner Wedemeyer: Gilead Sciences GmbH & Gilead Sciences Ltd.: Grant/Research Support, Madrigal Pharmaceuticals, Inc.: Grant/Research Support, Biotest AG: Grant/Research Support, Gilead Sciences GmbH & Gilead Sciences Ltd.: Clinical Trials / Investigator, Madrigal Pharmaceuticals, Inc.: Clinical Trials / Investigator, Dr. Falk Pharma GmbH: Clinical Trials / Investigator, IPSEN Pharma S.A.S.: Clinical Trials / Investigator, AstraZeneca GmbH: Clinical Trials / Investigator, Bluejay Therapeutics: Clinical Trials / Investigator, GlaxoSmithKline Services Unlimted: Clinical Trials / Investigator, Lilly Deutschland GmbH: Clinical Trials / Investigator, Mirum Pharmaceuticals Germany GmbH: Clinical Trials / Investigator, Takeda Pharma Vertrieb GmbH & Co. KG: Clinical Trials / Investigator, BioMarin Pharmaceuticals Inc.: Clinical Trials / Investigator, Vir Biotechnology: Clinical Trials / Investigator, Gilead Sciences GmbH & Gilead Sciences Ltd.: Consultant, Madrigal Pharmaceuticals, Inc.: Consultant, Dr. Falk Pharma GmbH: Consultant, IPSEN Pharma S.A.S.: Consultant, AstraZeneca GmbH: Consultant, Bluejay Therapeutics: Consultant, Bluejay Therapeutics: Consultant, GlaxoSmithKline Services Unlimited: Consultant, Lilly Deutschland GmbH: Consultant, Mirum Pharmaceuticals Germany GmbH: Consultant, Takeda Pharma Vertrieb GmbH & Co. KG: Consultant, Vir Biotechnology, Inc.: Consultant, MSD Sharp & Dohme GmbH: Consultant, Novo Nordisk Pharma GmbH: Consultant, Abbott Laboratories & Abbott Molecular Inc.: Consultant, Alfasigma GmbH: Consultant, Aligos Therapeutics, Inc.: Consultant, Atea Pharmaceuticals, Inc.: Consultant, Bristol-Myers-Squibb: Consultant, EIT Pharma, Inc.: Consultant, F. Hoffmann-La Roche Ltd.: Consultant, IntergerBio, Inc.: Consultant, Orphalan GmbH: Consultant, Pfizer Pharma GmbH: Consultant, Primmune Therapeutics, Inc.: Consultant, Ribocure Pharmaceuticals AB: Consultant, Gilead Sciences GmbH & Gilead Sciences Ltd.: Speaking and Teaching, Dr. Falk Pharma GmbH: Speaking and Teaching, IPSEN Pharma S.A.S.: Speaking and Teaching, MSD Sharp & Dohme GmbH: Speaking and Teaching, Novo Nordisk Pharma GmbH: Speaking and Teaching, BioMarin Pharmaceuticals Inc.: Speaking and Teaching, Biotest AG: Speaking and Teaching, CSL Behring: Speaking and Teaching, SANOFI Aventis Deutschland GmbH: Speaking and Teaching, Verein Falk Foundation e.V.: Speaking and Teaching, Margarita Papatheodoridi: Nothing to Disclose, Florian van Bömmel: Nothing to Disclose, Sabela Lens: Nothing to Disclose, Alessandro Federico: Nothing to Disclose, Elena Rosselli del Turco: Nothing to Disclose, Magdalena Meszaros: Nothing to Disclose, Álvaro Giráldez-Gallego: Nothing to Disclose, Filipe Calinas: Nothing to Disclose, michele milella: Nothing to Disclose, Laura Turco: Nothing to Disclose, Andrea Di Lorenzo: Nothing to Disclose, Mariarosa Tamè: Nothing to Disclose, Pierluigi Toniutto: Nothing to Disclose, Antonio Gasbarrini: Nothing to Disclose, Letizia Marinaro: Nothing to Disclose, Francesco Paolo Russo: Nothing to Disclose, Andrea Gori: Nothing to Disclose, Ivana Maida: Nothing to Disclose, teresa santantonio: Nothing to Disclose, Raffaele Bruno: Nothing to Disclose, Edoardo Giannini: Nothing to Disclose, IRENE CACCIOLA: Nothing to Disclose, Filomena Morisco: Nothing to Disclose, Alessandra Mangia: Nothing to Disclose, Stella De Nicola: Nothing to Disclose, Antonietta Romano: Nothing to Disclose, Monia Maracci: Nothing to Disclose, Biagio Pinchera: Nothing to Disclose, Saveria Lory Crocè: Nothing to Disclose.

0139 | FINAL RESULTS OF THE DDR SPAIN PROJECT: CONTEMPORARY EPIDEMIOLOGY AND CLINICAL PROFILE OF HEPATITIS DELTA VIRUS INFECTION IN SPAIN

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Symbols: ♦, Poster of Distinction; ★, Foundation Award Recipient

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Background: Hepatitis delta virus (HDV) infection is the most severe form of chronic viral hepatitis and is associated with accelerated fibrosis progression and early hepatic decompensation. Despite its clinical relevance, HDV remains underdiagnosed due to inconsistent screening strategies among HBsAg-positive individuals. We aimed to evaluate the epidemiology, diagnostic cascade and clinical profile of HDV infection in Spain. **Methods:** We conducted a nationwide multicenter observational study including a retrospective evaluation of HDV prevalence and diagnostic cascade among HBsAg-positive individuals (2022–2024) and a prospective cohort launched in 2024 as part of the DDR Spain project. Demographic, clinical and virological variables were systematically collected in a centralized REDCap database. Multivariable logistic regression analyses identified factors independently associated with active HDV infection and advanced fibrosis. **Results:** Between 2022 and 2024, 65,763 HBsAg-positive individuals were evaluated in 80 centers from 16 Spanish Autonomous Communities. Anti-HDV prevalence remained stable over time (5.6% in 2022, 4.9% in 2023 and 5.3% in 2024). However, only 40.1%, 31.6% and 31.0% of anti-HDV-positive individuals had confirmatory HDV-RNA testing in 2022, 2023 and 2024, respectively, highlighting important gaps in the diagnostic cascade.By March 2026, 1,112 anti-HDV-positive individuals had been prospectively enrolled. Median age was 54 years (IQR 43–61), 60% were male and 49% were born in Spain. HIV and HCV coinfection were present in 20% and 21% of patients, respectively. Active HDV infection was detected in 42%, with a median HDV viral load of 4.1 log IU/mL. HDV

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genotype 1 predominated (90%). Advanced liver disease was frequent: 41% presented METAVIR F3–F4 fibrosis, median liver stiffness was 7.8 kPa and 18% had previous hepatic decompensation. HIV and HCV coinfection were associated with higher rates of active infection and advanced fibrosis. In multivariable analysis, HBV treatment and active HDV infection were independently associated with advanced fibrosis, while younger age, higher platelet count and higher albumin levels were associated with lower probability of active HDV replication. **Conclusion:** This nationwide study provides updated epidemiological and clinical data on HDV infection in Spain and identifies persistent deficiencies in the diagnostic cascade. The high burden of advanced liver disease and active viral replication reinforces the need for systematic HDV screening and optimized clinical management strategies.
Disclosures: Ana Alberola: Nothing to Disclose, Lucía Pérez Rodríguez: Nothing to Disclose, Adolfo De Salazar: Nothing to Disclose, Raquel Carracedo: Nothing to Disclose, Waldo Sánchez-Yebra: Nothing to Disclose, carolina freyre carrillo: Nothing to Disclose, Berta Becerril Carral: Nothing to Disclose, Isabel Viciana: Nothing to Disclose, Inmaculada López Rodríguez: Nothing to Disclose, Teresa Trujillo Soto: Nothing to Disclose, Ana María Domínguez Castaño: Nothing to Disclose, Jaime Borrego: Nothing to Disclose, Encarnación Ramírez Arellano: Nothing to Disclose, Carmen Liébana: Nothing to Disclose, Francisco Franco Álvarez de Luna: Nothing to Disclose, María Carmen Lozano: Nothing to Disclose, Begoña Palop: Nothing to Disclose, Antonio Sampedro: Nothing to Disclose, Ana Belén Pérez: Nothing to Disclose, Sonia Algarate: Nothing to Disclose, Pablo Fraile: Nothing to Disclose, Mª Dolores Ocete: Nothing to Disclose, María Victoria Domínguez Márquez: Nothing to Disclose, María Gil Fortuño: Nothing to Disclose, Estefanía Aguirre: Nothing to Disclose, Laura Navarro: Nothing to Disclose, Nieves Orta Mira: Nothing to Disclose, Olalla Martínez Macias: Nothing to Disclose, Josefina Magraner Egea: Nothing to Disclose, María Beatriz Castro Hernández: Nothing to Disclose, Aldara Vallejo: Nothing to Disclose, María José Pena: Nothing to Disclose, María Aroca: Nothing to Disclose, Magdalena Lara: Nothing to Disclose, Ana Rodríguez-Fernández: Nothing to Disclose, Julio García Díez: Nothing to Disclose, Jose Joaquín Blas: Nothing to Disclose, Alicia Beteta: Nothing to Disclose, César Gómez: Nothing to Disclose, Alejandro González Praetorius: Nothing to Disclose, Antonio Puerta: Nothing to Disclose, Ana María Blázquez: Nothing to Disclose, Ruth Sáez: Nothing to Disclose, Sonsoles Garcinuño: Nothing to Disclose, Helena Miriam Lorenzo Juanes: Nothing to Disclose, Pilar Tajada Alegre: Nothing to Disclose, Susana García-De Cruz: Nothing to Disclose, Marta Sandoval Torrientes: Nothing to Disclose, Belén Lorenzo: Nothing to Disclose, María Teresa García Valero: Nothing to Disclose, María Reyes Vidal-Acuña: Nothing to Disclose, Luz María Moldes: Nothing to Disclose, Noelia Calvo: Nothing to Disclose, María José Gude: Nothing to Disclose, Patricia Ordóñez: Nothing to Disclose, Sandra Cortizo: Nothing to Disclose, Miriam Blasco: Nothing to Disclose, Ana Arribi: Nothing to Disclose, Roberto Alonso Fernández: Nothing to Disclose, Iker Falces: Nothing to Disclose, Laura Martínez: Nothing to Disclose, Asunción Iborra: Nothing to Disclose, Margarita Cámara: Nothing to Disclose, María Jesús Del Amor Espín: Nothing to Disclose, Eva Cascales: Nothing to Disclose, María Luz Núñez: Nothing to Disclose, Ana Miqueleiz: Nothing to Disclose, Luis Elorduy: Nothing to Disclose, Mikele Macho: Nothing to Disclose, Carmen Gómez: Nothing to Disclose, Paloma Liendo: Nothing to Disclose, Milagrosa Montes Ros: Nothing to Disclose, Antonio Aguilera: Nothing to Disclose, Federico Garcia: Gilead: Speaking and Teaching, ViiV: Speaking and Teaching.

0140 | HEPATIC RECOMPENSATION, SAFETY AND VIRAL SUPPRESSION IN PATIENTS WITH ADVANCED DECOMPENSATED CHRONIC HEPATITIS DELTA TREATED WITH BULEVIRTIDE:

Magdalena Meszaros[1] Georges-Philippe Pageaux[2] Mauro Viganò[3] Elisa Farina[3] Filomena Conti[4] Sébastien Dharancy[5] Teresa Antonini[6] Stefano Fagiuoli[3] Alessandro Loglio[3], [1]Liver Transplantation and Hepatogastroenterology Unit, CHU Montpellier, CHU Montpellier, Montpellier, [2]Liver Transplantation and Hepatogastroenterology Unit, CHU Montpellier, Montpellier, France, [3]Gastroenterology, Hepatology and Transplantation Division, ASST Papa Giovanni XXIII, Bergamo, Italy, [4]Hepatology Unit, Pitié Salpêtrière, Assistance Publique-Hôpitaux de Paris, Paris, France, [5]Hepatology Unit, Claude Huriez Hospital, CHU Lille, Lille, France, [6]Hepatology Unit, Hôpital de la Croix- Rousse, Lyon, France

Background: Bulevirtide (BLV) is currently approved only for patients with compensated Chronic Hepatitis D (CHD). However, its potential to induce hepatic recompensation, as defined by the Baveno VII criteria, in decompensated CHD patients has not yet been established. **Methods:** This retrospective multicentre longitudinal study included all CHD patients under evaluation or listed for liver transplantation (LT) due to decompensated [Child-Pugh (CP) score B/C with ascites or variceal bleeding or hepatic encephalopathy) disease treated with BLV 2 mg/day in Italy and France. Hepatic recompensation was defined as achievement of all the following criteria: undetectable HDV-RNA, absence of new decompensation events for $\geq$12 months, and improvement to a MELD score $<$10

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and/or CP A score, sustained for at least 6 months. **Results:** Eleven coinfected (HBV/HDV) patients were included: 64% male, 44 (32-68) years, CP C score 55% [median 10 (7-12)], MELD 15 (7-32), ALT 79 (32-1,345) U/L, albumin 3.0 (2.0-3.9) g/dL, bilirubin 43 (24-444) µmol/L; HDV-RNA 3.7 (1.4-7.4) Log_{10} IU/mL, 100% HBeAg and HBV-DNA negative; all had severe portal hypertension [platelets 35 (26-275)*10^3 /mmc, spleen 19 (15-26) cm, esophageal varices (large in 45%)] while one had also an HCC BCLC B. During 22 (2-67) months of treatment, BLV induced a significant reduction in HDV-RNA, with 7/9 evaluable patients having undetectable HDV-RNA at week 48, and 7/9 with normal ALT [median 32 (22-114) U/L]. Marked liver function improvement was observed at week 48: MELD decreased to 13 (8-17), while CP A5 score was achieved in 5/9 [median 5 (5-8), with an improvement of 2 (1-7) points]. Four patients (36%) were delisted following clinical improvement. Six patients (55%) underwent LT (after 2, 9, 12, 21, 22 and 34 months on BLV), one for ESLD and two for HCC during the first year, while for a virological breaktrought in the remaining 3 patients. Among the 3 patients eligible for the 1-year recompensation assessment (alive, no LT within 12 months, ≥12 months follow-up), achieved full Baveno VII recompensation only a female patient still HDV-RNA undetectable after 67 months. Overall, fully recompensation rate was 1/11 (9%). **Conclusion:** In decompensated CHD patients treated with BLV, significant improvements in MELD and CP scores were observed, leading to LT delisting in 36% of patients, while hepatic recompensation according to the Baveno VII criteria was achieved in 9%. Overall BLV, in this setting of young patients with severe liver disease, is safe and may postpone LT although close clinical management at expert Centers remains essential.

Disclosures: Magdalena Meszaros: Nothing to Disclose, Georges-Philippe Pageaux: Nothing to Disclose, Mauro Viganò: Nothing to Disclose, Elisa Farina: Nothing to Disclose, Filomena Conti: Nothing to Disclose, Sébastien Dharancy: Nothing to Disclose, Teresa Antonini: Nothing to Disclose, Stefano Fagiuoli: Nothing to Disclose, Alessandro Loglio: Nothing to Disclose.

0141 | DURABLE AND NEWLY EMERGENT TREATMENT RESPONSE DURING A 24-WEEK FOLLOW-UP IN A FINITE LONAFARNIB TREATMENT REGIMEN: EXTENDED ANALYSES FROM THE PHASE 3 D-LIVR TRIAL

Robert Taylor[1] Ohad Etzion[2] Saeed Hamid[3] Tarik Asselah[4] George Gherlan[5] Maria Buti[6] Pietro Lampertico[7] Turcanu Adela[8] George Stancu[9] Liliana-Simona Gheorghe[9] Natalia Voronkova[10] Natalia Barsukova[11] Soo Aleman[12] Jordan Feld[13] Jean-Karl Sirois[14] Armaan Hirani[15] Hebaalla Agha[15] Leen Kawas[16] Nancy Reau[17] Christopher Koh[18] Theo Heller[19] Cihan Yurdaydin[20] Xue Hua[15] Jeffrey Glenn[21], [1]EIT Pharma, Inc, [2]Soroka University Medical Center, Beersheba, Israel, [3]Aga Khan University, Karachi, Pakistan, [4]Hôpital Beaujon, [5]Carol Davila University of Medicine and Pharmacy/Dr. Victor Babes Foundation, Bucharest, Romania, [6]Hospital Valle Hebron, [7]University of Milan, [8]The State University of Medicine and Pharmacy, Republic of Moldova, [9]Institutul Clinic Fundeni, Bucharest, Romania, [10]H-Clinic, LLC, Moscow, Russia, [11]Center for Targeted Therapy, LLC, Moscow, Russia, [12]Karolinska Universitetssjukhuset, Huddinge, Sweden, [13]Toronto General Hospital, [14]YBR Analytics, Inc., [15]EIT Pharma, Inc., [16]EIT Pharma Inc., [17]Rush University Medical Center, [18]Liver Disease Branch, NIDDK, NIH, Bethesda MD, USA, [19]NIH/NIDDK, [20]Koc University School of Medicine, Istanbul, Turkey, [21]Stanford University School of Medicine

Background: Lonafarnib (LNF) boosted with ritonavir (LNF/RTV) is the only oral therapeutic under development for the treatment of chronic hepatitis D (CHD). LNF inhibits host farnesyltransferase to both disrupt HDV virion assembly and promote immune response in infected hepatocytes. LNF/RTV either with or without peg-interferon alfa-2a is being developed as a finite therapy for patients living with CHD. **Methods:** D-LIVR was a Phase 3 randomized placebo-controlled HDV study (N = 407) evaluating LNF/RTV with or without peginterferon alfa-2a (PEG) and is the largest placebo-controlled clinical trial in CHD patients to date. Both LNF-containing finite regimens met the primary composite efficacy endpoint compared to placebo (LNF/RTV: p = 0.004, LNF/RTV + PEG: p < 0.0001), defined as a ≥ 2 log reduction in HDV RNA and ALT normalization compared to baseline at 48-weeks on-treatment (end of treatment [EOT]). D-LIVR also included a 24-week off-treatment follow-up period to evaluate durability of treatment response after a finite regimen (end of study [EOS]). **Results:** The composite response rate improved up to 40% after 24 weeks off treatment in both the LNF/RTV treatment arm (EOS composite response rate of 14.2% compared to 10.1% at EOT) and in the LNF/RTV + PEG treatment arm (EOS composite response rate of 26.4% compared to 19.2% at EOT). There were no EOS composite responses in the placebo group. EOT composite responses were durable through EOS in 44.4% and 41.7% of EOT composite responders in the LNF/RTV and LNF/RTV + PEG treatment arms, respectively. In addition, among patients who were not composite responders at EOT, newly emergent composite response was observed in 10% of the LNF/RTV treatment group and 22.8% of the LNF/RTV + PEG treatment group.Transient mild ALT elevations (ALT measurement > 2X reference or > 3X ULN) were common among LNF/RTV and LNF/RTV + PEG

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patients in the post-treatment follow-up period (LNF/RTV: 47.3% [70 of 148], LNF/RTV + PEG: 40.9% [45 of 110]) and these elevations were typically followed by rapid decline in HDV RNA viral load, ALT normalization, and were not associated with any decompensation events. **Conclusion:** Oral LNF/RTV is a first-in-class CHD therapy with efficacy and safety in patients with CHD and substantial benefit after treatment cessation. Durability of response and newly emergent composite responders in a 24-week off-treatment follow-up period supports the continued development of lonafarnib-based therapy as a finite treatment regimen for CHD either with or without PEG.

Disclosures: Robert Taylor: EIT Pharma, Inc: Employee, Ohad Etzion: Nothing to Disclose, Saeed Hamid: Nothing to Disclose, Tarik Asselah: Nothing to Disclose, George Gherlan: Nothing to Disclose, Maria Buti: Roche Pharma/Diagnostics: Consultant, Gilead Sciences: Consultant, GSK: Consultant, Abbvie: Consultant, Janssen: Consultant, Roche Pharma/Diagnostics: Speaking and Teaching, Gilead Sciences: Speaking and Teaching, GSK: Speaking and Teaching, Abbvie: Speaking and Teaching, Janssen: Speaking and Teaching, Bepirovirsen – GSK: Referral to unlabelled/unapproved products, Pietro Lampertico: ROCHE PHARMA/DIAGNOSTICS, GILEAD SCIENCES, GSK, ABBVIE, JANS: Advisor, Turcanu Adela: Nothing to Disclose, George Stancu: Nothing to Disclose, Liliana-Simona Gheorghe: Nothing to Disclose, Natalia Voronkova: Nothing to Disclose, Natalia Barsukova: Nothing to Disclose, Soo Aleman: Nothing to Disclose, Jordan Feld: AbbVie: Advisor, Bluejay: Advisor, Gilead: Advisor, GlaxoSmithKline: Advisor, Precision Biosciences: Advisor, Arbutus: Advisor, Astra Zeneca: Advisor, Roche: Advisor, Vir: Advisor, Orphalan: Advisor, Pfizer: Advisor, Abbvie: Grant/Research Support, Gilead: Grant/Research Support, GlaxoSmithKline: Grant/Research Support, Atea: Advisor, Atea: Grant/Research Support, Roche: Grant/Research Support, Vir: Grant/Research Support, Mirum: Grant/Research Support, Mirum: Advisor, AusperBio: Advisor, Jean-Karl Sirois: Nothing to Disclose, Armaan Hirani: Nothing to Disclose, Hebaalla Agha: EIT Pharma, Inc.: Employee, Leen Kawas: EIT Pharma, Inc.: Executive role, Nancy Reau: Gilead: Grant/Research Support, Gilead: Grant/Research Support, Arbutus: Consultant, Arbutus: Consultant, Gilead: Consultant, Gilead: Consultant, VIR: Consultant, VIR: Consultant, Salix: Consultant, Salix: Consultant, Salix: Grant/Research Support, Salix: Grant/Research Support, AbbVie: Grant/Research Support, AbbVie: Grant/Research Support, VIR: Grant/Research Support, VIR: Grant/Research Support, mirum: Grant/Research Support, mirum: Consultant, GSK: Consultant, IPSEN: Consultant, Gilead: Grant/Research Support, Gilead: Grant/Research Support, Arbutus: Consultant, Arbutus: Consultant, Gilead: Consultant, Gilead: Consultant, VIR: Consultant, VIR: Consultant, Salix: Consultant, Salix: Consultant, Salix: Grant/Research Support, Salix: Grant/Research Support, AbbVie: Grant/Research Support, AbbVie: Grant/Research Support, VIR: Grant/Research Support, VIR: Grant/Research Support, mirum: Grant/Research Support, mirum: Consultant, GSK: Consultant, IPSEN: Consultant, Christopher Koh: Nothing to Disclose, Theo Heller: Nothing to Disclose, Cihan Yurdaydin: Nothing to Disclose, Xue Hua: Nothing to Disclose, Jeffrey Glenn: Nothing to Disclose.

★ 0142 | A NOVEL POINT OF CARE TEST FOR DETECTION OF HCV ANTIGENS USING SMART POLYMER TECHNOLOGY: A PROSPECTIVE MULTINATIONAL STUDY

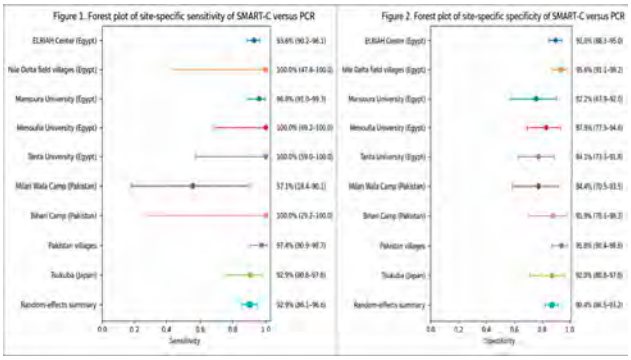
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Background: There is an unmet need for a rapid, affordable, highly sensitive point-of-care HCV antigen test suitable for decentralised settings. We developed a thermo-responsive smart polymer–based platform for the extraction and enrichment of HCV antigens. This platform was coupled to colloidal gold nanoparticles and integrated into a lateral-flow format (SMART-C). Here, we report the first large multicentre prospective clinical validation of SMART-C against PCR. **Methods:** We conducted a multinational, multicentre, prospective diagnostic accuracy study (2022–2026) at hospital and field sites in Egypt, Pakistan, and Japan. Paired samples were tested blindly using SMART-C and quantitative HCV RNA PCR as the reference standard. Sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) were calculated following the STARD guidelines. In addition, prospectively-collected samples from 20 patients initiating direct-acting antiviral (DAA) therapy were tested

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with SMART-C and PCR to assess the performance of SMART-C during treatment and after cure. **Results:** Among 1,353 paired samples, sensitivity was 94.6% (474/501, 95% CI 92.3–96.3) and specificity 91.3% (778/852, 89.2–93.0), with accuracy 92.5%, positive predictive value 86.5%, and negative predictive value 96.6%. Agreement with PCR was high ($\kappa = 0.843$). In the bivariate model, summary sensitivity was 92.9% (86.1–96.6; prediction interval 73.7–98.4) and specificity 90.4% (86.5–93.2; 79.0–95.9). SMART-C paralleled PCR-defined viral decline during therapy. **Conclusion:** SMART-C demonstrates robust performance with high sensitivity and specificity and detection at very low viral levels. Delivered as a rapid, single-step assay suitable for decentralised use, and could support progress towards WHO hepatitis C elimination targets.



Disclosures: Riham Soliman: Nothing to Disclose, Mitsuhiro Ebara: Nothing to Disclose, Ayman Hassan: Nothing to Disclose, Hidenori Toyoda: Nothing to Disclose, Mohammed Abdelsameea: Nothing to Disclose, Yosra Khalifa: Nothing to Disclose, Eman Abbdelsameea: Nothing to Disclose, Ahmed Farahat: Nothing to Disclose, Nothing to Disclose, Dina Ziada: Nothing to Disclose, Asad Choudhry: Nothing to Disclose, Auj Chaudhry: Nothing to Disclose, Hafsa Asad: Nothing to Disclose, Hossam Galbt: Nothing to Disclose, Nothing to Disclose, Ahmed Nabil: Nothing to Disclose, Gaston Picchio: Nothing to Disclose, Gamal Shiha: Nothing to Disclose.

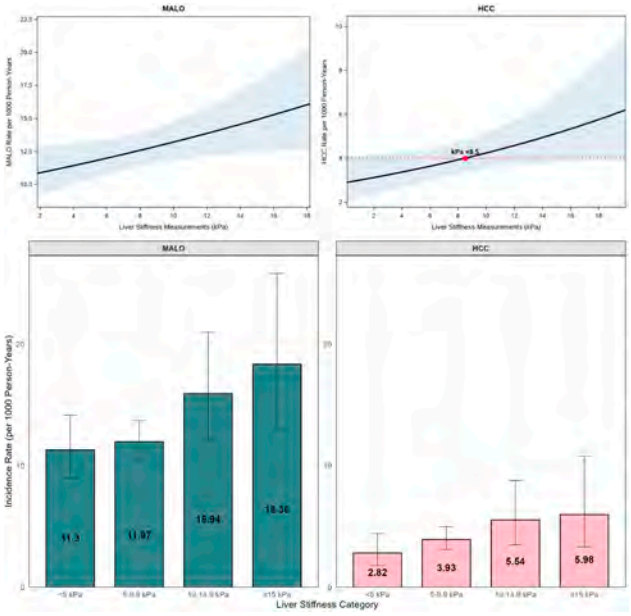
0143 | POST-SVR LIVER STIFFNESS MEASUREMENT AND RISK OF MAJOR ADVERSE LIVER OUTCOMES AND HEPATOCELLULAR CARCINOMA IN VETERANS WITH CHRONIC HEPATITIS C AND WITHOUT CIRRHOSIS

Binu John[1] Samuel Soon[2] Dustin Bastaich[2] Bassam Dahman[2], [1]University of Miami and Miami VA, [2]Virginia Commonwealth University

Background: While patients with HCV cirrhosis are recommended to continue ongoing HCC surveillance even after SVR, residual risk of hepatocellular carcinoma (HCC) and major adverse liver outcomes (MALO) persist after SVR even in the absence of cirrhosis. While Liver stiffness measurement cut-offs for HCV were derived from viremic patients, there is limited data on LSM cut-offs in patients after SVR. We evaluated the association of post-SVR liver stiffness measurement (LSM) with major adverse liver outcomes (MALO) and HCC among Veterans with HCV without cirrhosis to identify patients who may benefit from HCC surveillance. **Methods:** This was a retrospective cohort study using Veteran Health Administration data of individuals with HCV without cirrhosis who achieved SVR after 03/09/2000 and underwent a Vibration controlled transient elastography after SVR, with follow-up until 9/24/2025. The baseline assessment was the first eligible post-SVR VCTE; invalid measurements (IQR% >30%, or <10 valid acquisitions) were excluded. Follow-up began 6 months after the first post-SVR LSM to mitigate reverse causation. LSM was categorized as <5, 5–9.9, 10–14.9, and ≥15 kPa and evaluated continuously per 5-kPa increase. MALO was defined as a composite of HCC, liver decompensation, liver transplantation, or liver-related death. Multivariable time-dependent Cox models adjusted for age, sex, race/ethnicity, BMI, diabetes, time-updated AUDIT-C and platelet count, treatment type, and time from SVR to VCTE. Incidence rates were estimated per 1,000 person-years using Poisson regression. **Results:** The cohort included 6,269 Veterans (median age 64.9 years [IQR 8.0]; 96.0% male; 44.3% Black). LSM was distributed as: <5 kPa (n = 1,556), 5-9.9 kPa (n = 3,703), 10-14.9 kPa (n = 668), and ≥15 kPa (n = 342). During follow-up, 366 participants (5.8%) experienced a MALO - most commonly decompensation (3.9%), and 112 (1.8%) developed HCC. MALO incidence increased across LSM strata: 11.30, 11.97, 15.94, and 18.36 per 1,000 person-years. HCC incidence followed the same graded pattern: 2.82, 3.93, 5.54, and 5.98 per 1,000 person-years. HCC incidence was above the cost-effectiveness threshold for HCC surveillance at LSM of ≥8.5 kPa. Compared with LSM <5 kPa, LSM ≥15 kPa was independently associated with higher risk of MALO (aHR 1.65, 95% CI 1.08–2.52) and HCC (aHR 2.34, 1.10–4.98). Each 5-kPa increase was associated with 11% higher MALO risk (aHR 1.11, 1.05–1.17) and 15% higher HCC risk (aHR 1.15, 1.06–1.24). Diabetes (aHR 1.97) and older age (aHR 1.26 per 5 years) (both $p < 0.0001$) were the strongest independent predictors of MALO. **Conclusion:** Among Veterans with HCV and without cirrhosis who achieved SVR, higher post-SVR LSM was independently associated with increased risk of MALO and HCC with a post-SVR LSM of ≥8.5 kPa having a HCC risk high enough for cost-effective HCC surveillance.

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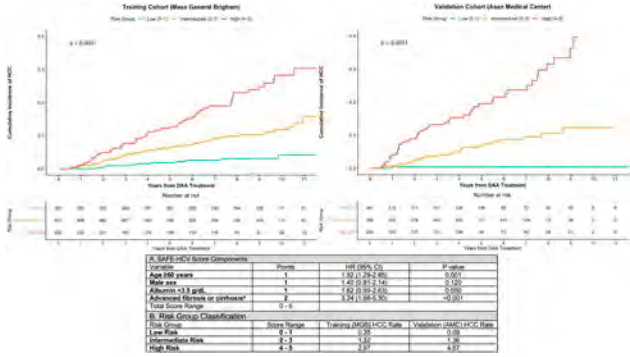


Disclosures: Binu John: Exact Sciences: Grant/Research Support, Genentech: Grant/Research Support, Glycotest, Inc: Grant/Research Support, Gilead: Grant/Research Support, Takeda: Grant/Research Support, Exelixis: Consultant, Exact Sciences: Received institutional research funding, Genentech: Received institutional research funding, Takeda: Received institutional research funding, Madrigal: Advisor, Ipsen: Advisor, Samuel Soon: Nothing to Disclose, Dustin Bastaich: Nothing to Disclose, Bassam Dahman: Nothing to Disclose.

0144 | SAFE-HCV SCORE FOR HEPATOCELLULAR CARCINOMA SURVEILLANCE

Doan Dao[1] Jonggi Choi[2] Megan Michta[3] Raymond Chung[3] Ji won Yang[4], [1]Mass General Hospital, [2]University of Ulsan, Asan Medical Center, [3]Massachusetts General Hospital, [4]Asan Medical Center

Background: Patients with chronic hepatitis C achieving sustained virologic response (SVR) after direct-acting antivirals (DAAs) remain at risk for hepatocellular carcinoma (HCC), but optimal surveillance strategies are unclear. We developed the SAFE-HCV (Surveillance After Fibrosis Evaluation in Hepatitis C Virus) score to guide risk-stratified HCC surveillance in post-SVR patients with significant fibrosis. **Methods:** We included 1,183 SVR patients with significant fibrosis (FIB-4 ≥1.45 or transient elastography ≥8 kPa) from Mass General Brigham (2010-2024), excluding those with HIV or HBV co-infection. Using Fine-Gray competing-risk regression accounting for death and liver transplantation as competing events, we developed a simple clinical score incorporating age ≥60 years (1 point), male sex (1 point), albumin <3.5 g/dL (1 point), and advanced fibrosis or cirrhosis (2 points), yielding scores from 0-5. Advanced fibrosis or cirrhosis was defined as FIB-4 ≥3.25, liver stiffness ≥12 kPa, or radiologic evidence of cirrhosis. External validation was performed in 808 SVR patients from Asan Medical Center, South Korea. **Results:** During median follow-up of 7.4 years (training) and 4.4 years (validation), 107 (9.0%) and 70 (8.7%) HCC events occurred. The SAFE-HCV score achieved C-index of 0.789 (95% CI: 0.730-0.841) in validation. Risk stratification identified low-risk patients (score 0-1, 30.9% of cohort) with very low HCC incidence (0.09-0.35 per 100 person-years), intermediate-risk (score 2-3, 44.3%) with moderate incidence (1.32-1.36), and high-risk (score 4-5, 24.8%) requiring intensive surveillance (2.97-4.67). Performance was superior to PAGE-B, FIB-4, THRI and aMAP score. **Conclusion:** The SAFE-HCV score enables personalized HCC surveillance strategies in post-SVR patients, identifying low-risk individuals who may benefit from de-escalated surveillance and high-risk patients requiring intensive monitoring.



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0145 | NMR-BASED SERUM METABOLOMICS IDENTIFIES A 7-METABOLITE PANEL THAT DISCRIMINATES HCV-RELATED CIRRHOSIS FROM CHRONIC HEPATITIS C

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Background: Non-invasive tools to stage fibrosis in chronic hepatitis C (CHC) remain imperfect, while biopsy is invasive and prone to sampling variability. We evaluated whether proton NMR-based serum metabolomics can discriminate HCV-related liver cirrhosis (CHC-LC) from non-cirrhotic CHC and define candidate metabolic biomarkers and pathways of disease progression. **Methods:** Serum from well-annotated adults with CHC (n = 57 total enrolled; analyzable cohort as per protocol) was collected after overnight fast and profiled on an 800-MHz spectrometer using 1H CPMG acquisition. Spectra were processed with Chenomx for metabolite identification/quantification and analyzed in MetaboAnalyst 5.0. Multivariate models (PCA, PLS-DA with permutation testing), univariate statistics (Student's t test), and ROC analyses (including SVM-based multivariate ROC and MCCV) were applied. Pathway impact and enrichment were assessed using MetPA. **Results:** PCA showed partial overlap between CHC and CHC-LC, whereas supervised PLS-DA achieved satisfactory separation ($R2 = 0.66$, $Q2 = 0.55$; permutation $p = 0.01$). Twenty metabolites differed between groups (VIP ≥ 1.0, $p < 0.05$), predominantly amino acids and intermediates linked to energy/protein metabolism (e.g., alanine, glutamine, serine, valine, citrate, urea), with consistent decreases in cirrhosis. A 7-metabolite panel—glutamine, asparagine, threonine, valine, creatine, serine, and citrate—demonstrated strong diagnostic performance (AUC 0.95). An SVM model using the top two features (glutamine, serine) yielded AUC 0.93 (95% CI 0.83–0.99); inclusion of broader features increased AUC to 0.97 (95% CI 0.90–1.00). Pathway analysis highlighted significant perturbations in glycine/ serine/ threonine metabolism, aminoacyl-tRNA biosynthesis, alanine/aspartate/glutamate metabolism, glyoxylate/dicarboxylate metabolism, arginine biosynthesis, and ammonia recycling, consistent with impaired TCA cycle fueling, nitrogen handling, and altered protein turnover in cirrhosis. **Conclusion:** High-field 1H NMR serum metabolomics delineates a reproducible metabolic signature distinguishing HCV-related cirrhosis from non-cirrhotic CHC. A concise 7-metabolite panel achieves high accuracy and maps to biologically plausible pathways of energetic and amino acid dysregulation. These findings support metabolomics as a scalable, non-invasive adjunct for cirrhosis detection and monitoring in CHC. Validation in larger, multi-center cohorts with external calibration and assessment of antiviral treatment effects is warranted.

Disclosures: SUMIT RUNGTA: Nothing to Disclose, Amar Deep: Nothing to Disclose, Shweta Kumari: Nothing to Disclose.

0146 | AN OPPORTUNISTIC LIS-BASED STRATEGY TO RECAPTURE PATIENTS WITH ACTIVE HCV: EFFICACY AND COST-EFFECTIVENESS OF PROLINK-C IN SPAIN

Alberto Vázquez Blanquiño[1] Ana Fuentes[1] Raquel Domínguez Hernández[2] Ana Belén Pérez Jiménez[3] Francisco Franco Álvarez de Luna[4] Carolina Freyre[5] Teresa Trujillo[6] Natalia Montiel[6] Carmen Rodríguez Baños[7] Inmaculada López[8] Jesús Machuca[9] Carmen Lozano[10] Antonio Sampedro[11] Isabel Viciana[12] Jaime Borrego[13] Juan Carlos Galán[14] Alejandro Gonzalez-Praetorius[15] Federico Garcia[1], [1]Hospital Universitario Clínico San Cecilio, [2]PORIB - Pharmacoeconomics & Outcomes Research Iberia, [3]Hospital Universitario Reina Sofía, [4]Hospital Universitario Juan Ramón Jiménez, [5]Hospital Universitario de Puerto Real, [6]Hospital Universitario Puerta del Mar, [7]Hospital Universitario Torrecárdenas, [8]Hospital Universitario Costa del Sol, [9]Hospital Universitario Infanta Elena, [10]Hospital Universitario Virgen del Rocío, [11]Hospital Universitario Virgen de las Nieves, [12]Hospital Universitario Virgen de la Victoria, [13]Hospital Universitario Poniente, [14]Hospital Universitario Ramón y Cajal, [15]Hospital Universitario de Guadalajara

Background: Chronic hepatitis C virus infection remains a major public health concern despite the widespread availability of direct-acting antivirals (DAA). Identifying individuals previously diagnosed with HCV but never treated, or without documented sustained virological response (SVR), remains a key challenge in the final stages of HCV elimination. Retrospective searches based on historical records have shown limited efficiency. ProLINK-C is a multicentre project implementing an opportunistic, fully automated, LIS-based strategy to re-engage such patients during routine healthcare encounters. We present data on the effectiveness of this strategy, together with a cost-effectiveness analysis (CEA). **Methods:** A daily automated process was implemented in the Laboratory Information System (LIS) across participating centres in Spain. The system generated lists of patients with a previous positive anti-HCV antibody result and a currently available serum sample submitted to the laboratory for any reason. Laboratory records and electronic medical records were reviewed to identify evidence of DAA and/or documented SVR. When no such evidence was found, HCV-RNA testing was reflexively performed using the available serum sample. A validated lifetime Markov model of the natural history of chronic HCV infection was adapted to compare ProLINK-C with no intervention. The model incorporated Spanish epidemiological data, SVR rates, and healthcare costs obtained of the study data. The analysis was conducted from the perspective of the Spanish National Health System. An annual discount rate of 3% was applied to healthcare costs and outcomes. **Results:** Between May 2023 and

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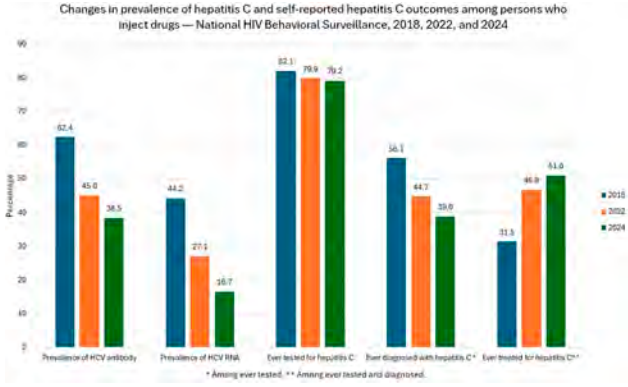
March 2026, reflex HCV-RNA quantification was performed on 696 patients. Of these, 212 patients had detectable HCV-RNA, confirming active HCV infection and constituting the study cohort. Among the 169 patients eligible for DAA, 116 initiated therapies, corresponding to 68.6% of eligible patients, and 64 have achieved SVR to date.Compared with no intervention, ProLINK-C increased short-term diagnostic costs by €68,406 but reduced lifetime costs associated with advanced liver disease by €2,546,640. The strategy was associated with reductions in decompensated cirrhosis, hepatocellular carcinoma, liver transplantation, and liver-related mortality, by 64%, 56%, 61%, and 59%, respectively. The results of the CEA showed that ProLINK-C was a dominant strategy (low costs and better health outcomes. **Conclusion:** ProLINK-C provides a scalable, reproducible, and efficient opportunistic strategy to re-engage untreated patients with chronic HCV infection who are already in contact with the healthcare system. In addition to its clinical impact, ProLINK-C is cost-effective in Spain, maximizing health benefits while reducing costs. These findings provide strong evidence to support the national implementation of ProLINK-C as part of HCV elimination policies.

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0147 | CHANGES IN PREVALENCE OF HEPATITIS C AND SELF-REPORTED HEPATITIS C TESTING, DIAGNOSIS, AND TREATMENT AMONG PERSONS WHO INJECT DRUGS — NATIONAL HIV BEHAVIORAL SURVEILLANCE, 2018, 2022, AND 2024

Megan Hofmeister[1] Lauren Peretz[1] Hasan Symum[1] Brooke Hoots[1] Dita Broz[1] Eyasu Teshale[1] Cyprian Wejnert[1] Kathryn Lee[1] Johanna Chapin-Bardales[1], [1]Centers for Disease Control and Prevention

Background: In the United States, persons who inject drugs (PWID) are disproportionately affected by hepatitis C virus (HCV) infection. Hepatitis C prevalence estimates and longitudinal data assessing changes in prevalence over time among PWID are limited in the United States. **Methods:** We sought to characterize changes in prevalence of HCV antibody, HCV RNA, and self-reported hepatitis C outcomes among PWID in select U.S. cities (10 in 2018, 9 in 2022, and 10 in 2024), using data from the Centers for Disease Control and Prevention's National HIV Behavioral Surveillance (NHBS). HCV antibody and HCV RNA tests were performed among eligible participants who consented to hepatitis testing; HCV RNA testing was performed regardless of HCV antibody result. We assessed temporal changes by calculating relative percent change between survey cycles (2018, 2022, and 2024) and conducting t-tests or Fisher exact tests for each pair-wise comparison. Statistical significance was defined as $P < .05$. **Results:** Among 12,300 eligible participants (5,200 in 2018; 2,477 in 2022; 4,623 in 2024) who met inclusion criteria, 12,152 (98.8%) received an HCV antibody test with a valid result and 9,290 (75.5%) received HCV RNA testing with a valid test result. Overall, prevalence of HCV antibody was 62.4% in 2018, 45.0% in 2022, and 38.5% in 2024 (-38.3% relative decrease from 2018 to 2024; $P < .05$), while prevalence of HCV RNA was 44.2% in 2018, 27.1% in 2022, and 16.7% in 2024 (-62.1% relative decrease from 2018 to 2024; $P < .05$). From 2018 to 2024, the percentage of PWID self-reporting ever tested for hepatitis C decreased slightly (-3.5% relative decrease, $P < .05$; 2018: 82.1%; 2022: 79.9%; 2024: 79.2%), the percentage ever diagnosed with hepatitis C among those tested decreased (-30.5% relative decrease, $P < .05$; 2018: 56.1%; 2022: 44.7%; 2024: 39.0%), and the percentage that reported ever being treated for hepatitis C among those ever tested and diagnosed increased (62.2% relative increase, $P < .05$; 2018: 31.5%; 2022: 46.8%; 2024: 51.0%). **Conclusion:** These data show that the prevalence of HCV antibody and RNA among PWID in select U.S. cities decreased significantly from 2018 to 2024. To ensure that this progress towards HCV elimination endures, continued efforts are needed to provide access to testing, treatment, and preventive services among PWID.



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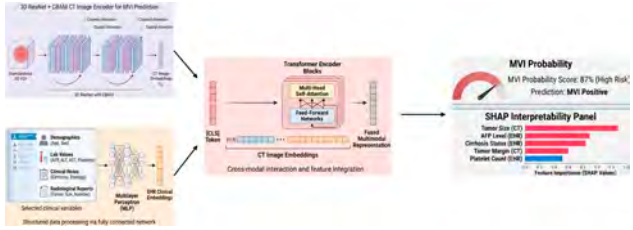
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0148 | MULTIMODAL IMAGE-BASED DEEP LEARNING FOR PREOPERATIVE PREDICTION OF MICROVASCULAR INVASION IN HEPATOCELLULAR CARCINOMA

Rex Wan-Hin Hui[1] Yan Miao[1] Keith Chiu[2] Ho-Ming Cheng[1] Chenlu Wang[1] Lung Yi Mak[1] Man-Fung Yuen[1] Philip Leung-Ho Yu[3] Wai-Kay Seto[1], [1]The University of Hong Kong, [2]Queen Elizabeth Hospital, [3]The Education University of Hong Kong

Background: Histological microvascular invasion (MVI) is a risk factor for recurrence after curative resection of hepatocellular carcinoma (HCC). Preoperative MVI prediction may improve risk stratification and guide patient selection for neoadjuvant treatment. **Methods:** The MATCH (M ultimodal A ttention T ransformer for C haracterizing H CC) model integrates preoperative triphasic CT scans and clinical parameters to predict histological MVI. The architecture utilizes a 3D ResNet with a Convolutional Block Attention Module for CT data, and a multilayer perceptron for clinical parameters. The imaging and clinical data were integrated by a transformer-based multimodal fusion module to enable binary MVI prediction. The preoperative CT scans were obtained from a multicenter patient cohort who had surgical resection for HCC. MVI was ascertained from the resected HCC specimens by expert pathologists. The MATCH model was evaluated on a 15% testing holdout against a CT-only deep learning model and an IBSI-compliant radiomics random forest baseline. **Results:** Among 1231 patients with resected HCC (age 62.4 years, 83.1% male, 30.6% steatosis, 40.7% cirrhosis), 591 patients (48.0%) had histological MVI. The MATCH model achieved AUC of 0.809 (95%CI 0.775-0.839) in predicting MVI (Sensitivity 0.777, specificity 0.726, positive predictive value 0.790, negative predictive value 0.711), significantly outperforming the radiomics model (AUC 0.750, 95%CI 0.715-0.787) and the CT-only deep learning model (AUC 0.712, 95%CI 0.673-0.751) (both $p < 0.001$). The MATCH model had robust performance across steatosis and cirrhosis subgroups (AUC $\geq$ 0.78), consistently outperforming the CT-only deep learning model (all $p < 0.05$). When assessing model explainability, the dominant HCC lesion size and tumor shape (elongation and sphericity) were the most important radiological features in predicting MVI, whereas the most important clinical feature was serum alpha-fetoprotein level. **Conclusion:** The MATCH model enabled accurate and non-invasive prediction of MVI in HCC. Multimodal image-based deep learning may improve preoperative prognostication and clinical care pathways in potentially resectable HCC.



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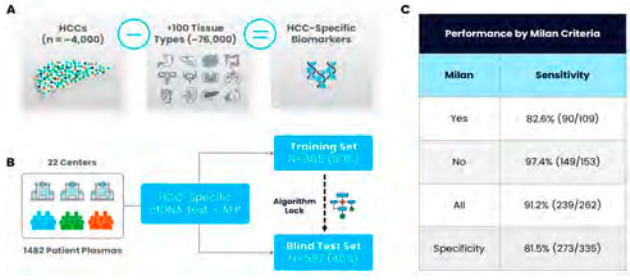
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0149 | A PLASMA DNA METHYLATION BIOMARKER PANEL FROM THE WHOLE-BODY ATLAS™ ENABLES ACCURATE DETECTION OF EARLY-STAGE HCC

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Background: Ultrasound plus alpha fetoprotein (AFP), the current standard hepatocellular carcinoma (HCC) surveillance strategy, is limited by poor adherence, operator dependency, and suboptimal sensitivity for early-stage detection. Blood-based biomarkers may improve surveillance effectiveness; however, prior biomarker discovery efforts have been limited by small sample sizes and restricted diversity of tissues, resulting in residual background noise from non-hepatic tissues. **Methods:** We used 80,000 tissue specimens from >100 healthy and diseased tissue types within the Whole-Body Atlas to identify methylation biomarkers specific to HCC among patients with chronic liver disease. Candidate biomarkers were incorporated into a next-generation sequencing assay with AFP, and an HCC classifier was trained using plasma samples from 885 patients with cirrhosis or chronic HBV infection (373 HCC cases; 512 controls) enrolled across 22 centers in the United States and Asia. A locked classifier was subsequently tested in a blinded, independent test set of 597 patients (262 HCC cases; 335 controls). HCC cases were defined by characteristic imaging (LI-RADS 5) or histology. Controls had no evidence of HCC on imaging at time of blood draw. The primary outcome was sensitivity for early-stage HCC detection and specificity was a secondary outcome. **Results:** The independent test set included 93.1% individuals from the U.S. and 6.9% from Asia, with a median age of 63 years; 60.3% were men. Most participants (57.3%) had Child Pugh A cirrhosis. Liver disease etiologies included 34.7% MASLD, 28.1% ALD, 25.6% HCV, and 10.1% HBV. Sensitivity for early-stage HCC was 82.6% (90/109) for tumors within Milan criteria and 85.3% (110/129) for BCLC stage 0/A disease. Sensitivity increased with greater tumor burden, reaching 97.4% (149/153) for tumors beyond Milan criteria and 98.0% (96/98) for BCLC stage B/C disease. Overall sensitivity was 91.2% (239/262) with 81.5% (272/335) specificity. The test detected 77.8% (21/27) of 1-2 cm HCC, 88.4% (107/121) for >2-5 cm HCC and 97.3% (107/110) of those >5cm. Test performance was consistent across age, gender, BMI, and liver disease etiology subgroups. Among detected HCC cases, 53.6% were identified by both methylation markers and AFP, 43.9% by methylation markers alone, and 2.5% by AFP alone. Methylation scores correlated with tumor size (Spearman $r = 0.71$, $p < 0.0001$). Among 11 controls with high false positive results and follow-up imaging, 4 (36%) were diagnosed with HCC within 2-8 months. **Conclusion:** A novel plasma DNA methylation biomarker panel demonstrated high sensitivity and specificity for early-stage HCC detection in a multicenter case-control validation study. These findings support efforts to further prospectively evaluate this approach for HCC surveillance.



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0150 | PREDIAGNOSTIC CIRCULATING BILE ACID PROFILES AND LIVER CANCER RISK ACROSS THE CHRONIC LIVER DISEASE SPECTRUM

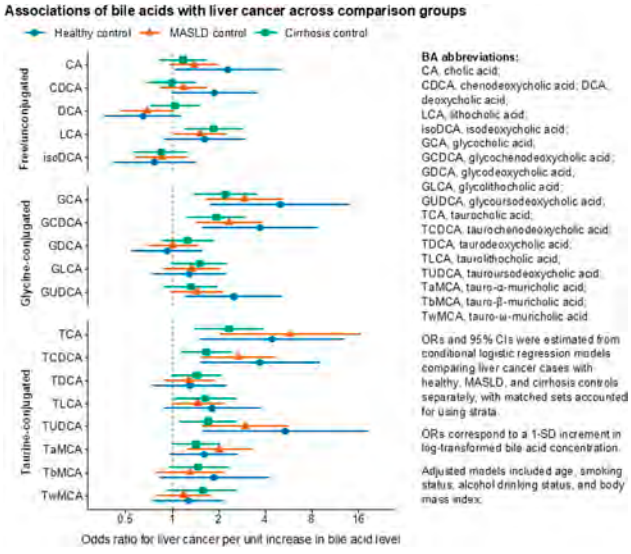
Loggang Zhao[1] Xinyuan Zhang[2] Tamar Taddei[3] Katherine McGlynn[4] Huiping Zhou[5] Xuehong Zhang[3], [1]Yale School of Nursing, [2]Brigham and Women's Hospital, [3]Yale University, [4]National Cancer Institute, [5]Virginia Commonwealth University

Background: Bile acids regulate hepatic metabolism, inflammation, and gut–liver axis signaling and have been implicated in hepatocarcinogenesis. Prior studies linked circulating bile acids to liver cancer risk, but most used general controls, leaving unclear whether bile acid alterations distinguish liver cancer from MASLD or cirrhosis. We evaluated associations between prediagnostic bile acids and liver cancer in the Mass General Brigham Biobank (MGBB) using disease-spectrum controls (healthy, MASLD, and cirrhosis), and synthesized prospective evidence through meta-analysis. **Methods:** We conducted a nested case-control study of 59 incident liver cancer cases with plasma collected $\geq$6 months before diagnosis, 111 cirrhosis controls, 113 MASLD controls, and 59 healthy controls. Controls were matched on age, sex, race, and blood collection year; cirrhosis/MASLD controls were additionally matched on time from blood collection to event, and healthy controls on Charlson comorbidity index group. Bile acids were assayed by LC-MS/MS. Conditional logistic regression accounting for matched sets and adjusted for age, smoking, alcohol use, and BMI estimated ORs and 95% CIs per 1-SD increment in log-transformed levels. Random-effects meta-analysis pooled high-versus-low estimates from seven published prospective studies plus MGBB, comprising 2,136 cases and 2,916 controls. **Results:** In MGBB, conjugated bile acids were higher in liver cancer cases than healthy and MASLD controls. Per 1-SD increment in log-transformed levels, GCA, TUDCA, TCA, TCDCA, and GCDCA were associated with greater odds of liver cancer versus healthy controls (ORs 3.72 to 5.40);

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similar associations were observed versus MASLD controls (ORs 2.34 to 5.80). Associations were attenuated but persisted versus cirrhosis controls for the same bile acids (ORs 1.67 to 2.35). In meta-analysis, conjugated primary bile acids showed the strongest pooled associations, including GCA, GCDCA, TCA, and TCDCA (ORs 2.90 to 6.01). **Conclusion:** Higher prediagnostic levels of circulating conjugated bile acids were associated with liver cancer in MGBB and supported by meta-analysis. Associations persisted, although attenuated, among cirrhosis controls, suggesting that bile acid dysregulation may capture hepatobiliary dysfunction relevant to hepatocarcinogenesis beyond advanced liver disease alone. These findings support further evaluation of bile acid profiling to refine liver cancer risk stratification across the chronic liver disease spectrum.



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0151 | EFFECTIVENESS OF A STRUCTURED SURVEILLANCE PROGRAM FOR EARLY DETECTION OF HEPATOCELLULAR CARCINOMA IN CONTEMPORARY PATIENTS WITH ADVANCED CHRONIC LIVER DISEASE

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Background: Hepatocellular carcinoma (HCC) surveillance is recommended for patients with advanced chronic liver disease (ACLD), but real-world adherence is variable and often measured using binary or semi-quantitative approaches. We aimed to quantify surveillance adherence longitudinally using a continuous time-based metric and to assess its association with clinical outcomes. We additionally evaluated the diagnostic yield of a structured re-linkage initiative for patients overdue for routine surveillance. **Methods:** We analyzed 639 ACLD patients enrolled in the prospective Vienna Cirrhosis Study (VICIS; NCT03267615) between 2017 and 2024 who received regular care in our center. Surveillance adherence was assessed using the proportion of time covered (PTC), assigning six months of coverage to each imaging examination. Associations between PTC and outcomes were analyzed using adjusted Cox regression and internally validated in a propensity score-matched cohort balanced for age, sex, etiology, and Child-Pugh score (CPS), using Fine-Gray competing-risk models. Overdue patients were prospectively identified and re-linked to imaging through a structured program. **Results:** Median imaging-based PTC was 83% (IQR 60-98%). During a median follow-up of 43 months, 47 patients (7.4%) developed HCC, of whom 47% were diagnosed at an early stage (Barcelona Clinic Liver Cancer 0/A). PTC showed a non-linear association with early HCC detection, with a marked increase above 85% surveillance coverage. Biannual imaging was associated with a 6.6-fold higher likelihood of early HCC detection compared with annual imaging (HR 6.57; 95% CI 2.38-18.11). After propensity score matching, high adherence (PTC $\geq$85%) was independently associated with early HCC detection (adjusted SHR 2.44; $p = 0.015$) and curative treatment option (adjusted SHR 2.60; $p = 0.024$), with a trend toward improved post-HCC survival (SHR 0.37; $p = 0.087$). Among 52 overdue patients actively re-linked to imaging, 8 (15%) had newly detected suspicious hepatic lesions, including one biopsy-confirmed HCC. **Conclusion:** In this contemporary ACLD cohort, sustained high adherence to HCC surveillance was associated with earlier tumor detection and option for curative treatment. Continuous time-based metrics such as PTC may provide a more precise assessment of surveillance quality, while structured re-linkage of overdue patients represents a simple strategy to strengthen HCC surveillance in routine care.

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0152 | CHANGING CLINICAL PATTERNS AND OUTCOMES OF HEPATOCELLULAR CARCINOMA ACROSS TREATMENT ERAS: A MULTICENTER COHORT STUDY

Karim Seif El Dahan[1] Nicole Rich[2] Patrick Hazelrigg[3] Andrew Moon[3] Naomy Kim[4] Ju Dong Yang[4] Reena Salgia[5] Madeline Smith[6] Rashmita Raghunathan[6] Neehar Parikh[6] Prasun Jalal[7] Anjana Pillai[8] Lisa Quirk[1] Amit Singal[1], [1]UT Southwestern Medical Center, [2]University of Texas Southwestern Medical Center, [3]University of North Carolina, [4]Cedars-Sinai Medical Center, [5]Henry Ford Health, [6]University of Michigan Medical Center, [7]Baylor College of Medicine, [8]University of Chicago

Background: Advances in antiviral therapy, surveillance strategies, and expanded eligibility for curative treatments may have influenced patterns of hepatocellular carcinoma (HCC) presentation, management, and outcomes over time. We characterized temporal trends in clinical characteristics, treatment patterns and outcomes of patients with HCC in a large multicenter U.S. cohort. **Methods:** We conducted a retrospective cohort study across nine large health systems from the HCC-Live Consortium including patients diagnosed with HCC between 2008 and 2023. We defined three eras based on major changes in HCC management: group 1 (2008–2012, sorafenib/pre-direct-acting antiviral [DAA] era); group 2 (2013–2017, DAA era); and group 3 (2018–2023, expanded downstaging and immunotherapy era). Multivariable logistic regression was used to assess associations between era and early-stage HCC detection (BCLC stage 0/A), surveillance receipt, and curative treatment (liver transplant, surgical resection, or local ablation). Multivariable Cox regression was used to evaluate associations with overall survival. **Results:** Among 5,428 patients with HCC (group 1: n = 621; group 2: n = 2,442; group 3: n = 2,365), median age was 63.3 years, and 26.4% were women. The cohort was racially and ethnically diverse (48.3% White, 21.9% Hispanic, 20.0% Black). Over time, the median age at diagnosis increased (58.2, 62.8, and 65.0 years), as did the proportion of women (22.7%, 26.3%, and 27.5%). HCV-related HCC decreased over time (66.2%, 63.2%, and 51.5%; $p < 0.001$), whereas MASLD (7.2%, 12.4%, and 18.8%; $p < 0.001$) and ALD-related HCC (11.8%, 11.8%, and 16.9%; $p < 0.001$) increased. Surveillance receipt remained low across eras (37.0%, 52.2%, and 41.5%; group 3 vs. group 1: OR 1.05, 95%CI 0.87–1.28). Early-stage HCC detection increased modestly over time (36.7%, 39.1%, and 40.3%) with higher odds in group 3 vs. group 1, although this did not reach statistical significance (OR 1.17, 95%CI 0.96–1.41). Compared with group 1, patients in group 2 (OR 2.23, 95%CI 1.79–2.78) and group 3 (OR 1.88, 95%CI 1.51–2.35) were more likely to receive curative treatment. Median overall survival improved over time (12 (95%CI, 9.8–15), 26 (95%CI, 24–28), and 20 (95%CI 18–22) months, respectively). In adjusted analyses groups 2 (HR 0.65, 95%CI 0.58–0.72) and 3 (HR 0.78, 95%CI 0.70–0.87) had lower mortality than group 1. **Conclusion:** Overall survival among patients with HCC has improved substantially over time, coinciding with advances in antiviral therapy and curative treatment approaches. However, surveillance receipt and early-stage detection remained suboptimal, highlighting persistent gaps in HCC surveillance and early detection.

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0153 | CIRCULATING TUMOR DNA FOR EARLY RECURRENCE DETECTION AND MOLECULAR RESIDUAL DISEASE MONITORING IN HEPATOCELLULAR CARCINOMA AND BILIARY TRACT CANCER: A REAL-WORLD MULTICENTER ANALYSIS

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Background: Hepatocellular carcinoma (HCC) and biliary tract cancer (BTC) carry high recurrence rates following curative-intent resection or liver transplantation (LT), and existing biomarkers such as AFP and CA19-9 have limited postoperative prognostic utility. Circulating tumor DNA (ctDNA) has emerged as a promising tool for molecular residual disease (MRD) assessment and recurrence detection across gastrointestinal malignancies. We evaluated the clinical utility of a personalized, tumor-informed ctDNA assay across both HCC and BTC in real-world practice. **Methods:** This retrospective, multicenter real-world study analyzed 1,472 plasma samples from 292 patients, 125 with HCC and 167 with Stage I–III resected BTC, who underwent serial ctDNA testing using a personalized 16-plex mPCR-NGS assay (Signatera™, Natera, Inc.). In HCC, patients were monitored post-LT or post-resection across four cohorts. In BTC, samples were collected pre-operatively, in the MRD window (2–12 weeks post-resection), and during longitudinal post-definitive treatment surveillance. ctDNA results were correlated with relapse-free survival (RFS), overall survival (OS), and radiographic recurrence, and compared to concurrent standard biomarkers (AFP for HCC; CA19-9 and CEA for BTC). Multivariable analyses identified independent predictors of recurrence in both tumor types. **Results:** Median follow-up was 40 months (range 1.5–60) for HCC and 21 months (range 2–97) for BTC. In HCC, ctDNA positivity in the MRD window strongly predicted clinical recurrence (HR 7.2, 95% CI 2.6–20.0; $p < 0.0001$), and ctDNA positivity during surveillance was even more strongly associated

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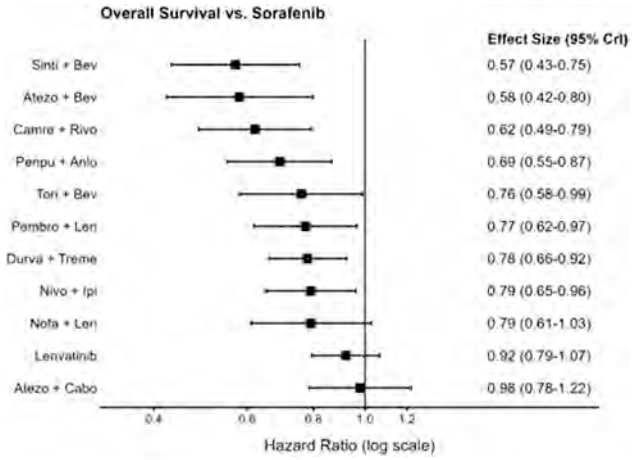
with recurrence (HR 18.0, 95% CI 3.9–85.0; $p < 0.0001$). ctDNA demonstrated a significantly longer lead time over AFP for recurrence detection (7.9 vs. 2.2 months). In BTC, ctDNA positivity was the strongest independent predictor of inferior RFS during the MRD window (HR 15.86, 95% CI 4.69–53.6; $p < 0.001$) and surveillance (HR 14.93, 95% CI 5.33–41.9; $p < 0.001$) on multivariable analysis, outperforming both CA19-9 and CEA, which were not independently prognostic in either setting. ctDNA identified radiographic recurrence a median of 3.7 months before imaging in BTC. Across both tumor types, longitudinal ctDNA dynamics correlated with treatment response and helped resolve equivocal imaging findings. **Conclusion:** In this combined real-world analysis of 292 patients across HCC and BTC, serial personalized ctDNA testing was the strongest independent predictor of recurrence and survival, consistently outperforming standard biomarkers with clinically meaningful imaging lead times. These findings establish ctDNA-based MRD monitoring as a superior postoperative surveillance strategy across primary liver and biliary cancers, warranting prospective validation and integration into adjuvant therapy decision-making frameworks.

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0154 | COMPARATIVE EFFICACY AND SAFETY OF FIRST-LINE SYSTEMIC COMBINATIONS IN UNRESECTABLE HEPATOCELLULAR CARCINOMA (UHCC): A BAYESIAN NETWORK META-ANALYSIS OF 11 PHASE III TRIALS

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Background: The treatment landscape for uHCC has rapidly evolved with the introduction of immune checkpoint inhibitors (ICI) combined with anti-VEGF therapy, tyrosine kinase inhibitors (TKI), or a second ICI (CTLA-4). In the absence of head-to-head randomized controlled trials, optimal first-line regimen selection remains uncertain. This network meta-analysis evaluates the comparative efficacy and safety of modern first-line combinations to guide treatment sequencing. **Methods:** A systematic review identified Phase III trials of first-line systemic therapies for uHCC. Risk of bias was assessed using Cochrane RoB 2. A Bayesian network meta-analysis (fixed-effects model) was performed using gemtc in R. Primary endpoints were overall survival (OS) and progression-free survival (PFS). Secondary endpoints included objective response rate (ORR) and class-specific grade ≥ 3 adverse events (hypertension, hemorrhage/variceal bleeding, hepatitis, and colitis). Certainty of evidence was assessed using the GRADE framework. Sorafenib served as the common reference node. **Results:** Eleven Phase III RCTs comprising 7,495 patients were included. Overall risk of bias was generally low. For OS, ICI–anti-VEGF and ICI–TKI combinations demonstrated the highest efficacy (moderate GRADE certainty). Sintilimab plus bevacizumab (HR 0.57, 95% CrI 0.44–0.75), atezolizumab plus bevacizumab (HR 0.58, 0.43–0.79), and camrelizumab plus rivoceranib (HR 0.62, 0.49–0.80) showed the most significant OS improvements compared with sorafenib. Dual immune checkpoint blockade (ICI–ICI) regimens, including nivolumab plus ipilimumab (HR 0.79, 0.65–0.96) and durvalumab plus tremelimumab (HR 0.78, 0.65–0.93), also improved OS but ranked lower than ICI–anti-VEGF/ICI–TKI strategies.For PFS (low-to-moderate GRADE certainty), ICI–TKI regimens such as penpulimab plus anlotinib (HR 0.52, 0.41–0.66) showed the highest probability of being the best treatment.Regarding safety, distinct toxicity profiles emerged. ICI–anti-VEGF and ICI–TKI regimens were associated with higher odds of grade ≥ 3 hypertension and hemorrhage compared with sorafenib. Conversely, ICI–ICI regimens had the lowest risk of vascular toxicities but showed increased odds of severe immune-mediated adverse events, specifically grade ≥ 3 hepatitis and colitis. **Conclusion:** This network meta-analysis shows that multiple combination strategies significantly outperform standard-of-care TKIs in first-line uHCC, with distinct efficacy and safety profiles. ICI–anti-VEGF and selected ICI–TKI combinations provide the greatest survival benefit but increase vascular toxicity. In contrast, ICI–ICI combinations achieve higher objective response rates with lower bleeding risk, despite inferior progression control. These results provide quantitative evidence to support treatment selection based on efficacy–toxicity trade-offs.



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Disclosures: Rahul Falodia: Nothing to Disclose, Maheen Afzal: Nothing to Disclose, Ubaid Ahmed: Nothing to Disclose.

0155 | AUGMENTING THE TUMOR BOARD: A MULTI-AGENT AI PIPELINE FOR LIVER CANCER TREATMENT RECOMMENDATIONS

Richie Manikat[1] Vetri Elango[2] Renumathy Dhanasekaran[1], [1]Stanford University School of Medicine, [2]Arithmedics, Inc.

Background: Multidisciplinary tumor boards are essential to hepatocellular carcinoma (HCC) management, yet preparing each case requires significant physician time to extract and synthesize unstructured clinical, laboratory, and imaging data, stage tumors, and formulate personalized treatment plans. We developed a custom multi-agent AI tool, anchored in our institution's tumor board protocols and powered by a Retrieval-Augmented Generation (RAG) framework, to automate this workflow end-to-end. **Methods:** We built a three-agent workflow: (1) an Extraction Agent that converts unstructured clinical notes, radiology reports, and pathology reports into structured formats; (2) a Synthesis and Staging Agent that extracted parameters to generate summaries, assign BCLC stage, and provide Stanford-specific treatment recommendations as a starting point; and (3) a Tumor Board Report Agent that produces presentation-ready reports for use in live multidisciplinary tumor boards. In Phase 1, we validated the tool on 25 simulated cases spanning all four BCLC stages, benchmarking performance against GPT-4.0 and an expert hepatologist. In Phase 2, the tool was applied to de-identified real-world data extracted from the Stanford Research Repository (STARR) to test feasibility at scale on unstructured EHR data. **Results:** In Phase 1, the HCC-AI Tool accurately generated narrative summaries and BCLC staging from unstructured clinical notes across all 45 cases, achieving 100% concordance with the expert hepatologist and outperforming GPT-4.0 (80%). The Tumor Board Report Agent produced presentation-ready outputs that have been used in actual case presentations at our institutional tumor board. In Phase 2, STARR retrieved raw unstructured EHR data for 93 HCC patients. The Extraction Agent successfully identified and structured key staging parameters (AFP, MELD, tumor size and number, vascular invasion, extrahepatic spread, performance status) across clinical notes, lab results, and radiology reports. The Synthesis and Staging Agent assigned BCLC classification for 58% of patients, identifying 19 who met Milan criteria for liver transplant evaluation and 35 who did not. The remaining 39 patients had incomplete data due to missing laboratory values (n = 9), incomplete tumor characterization from outside-institution imaging (n = 20), or indeterminate findings requiring clinical correlation (n = 10). **Conclusion:** The HCC-AI Tumor Board Tool demonstrates strong performance in automating HCC tumor board preparation, achieving expert-level staging accuracy and presentation-ready reports. Real-world deployment confirmed feasibility at scale within a PHI-compliant institutional framework. These findings underscore the importance of institution-specific customization in clinical AI and highlight the potential to extend expert-level HCC decision-making to centers without dedicated multidisciplinary tumor boards.

Disclosures: Richie Manikat: Nothing to Disclose, Vetri Elango: Nothing to Disclose, Renumathy Dhanasekaran: Nothing to Disclose.

★ 0156 | SEQUENTIAL TRANSARTERIAL RADIOEMBOLIZATION AND ATEZOLIZUMAB PLUS BEVACIZUMAB IMPROVES SURVIVAL IN ADVANCED HEPATOCELLULAR CARCINOMA: A PROPENSITY SCORE-MATCHED ANALYSIS

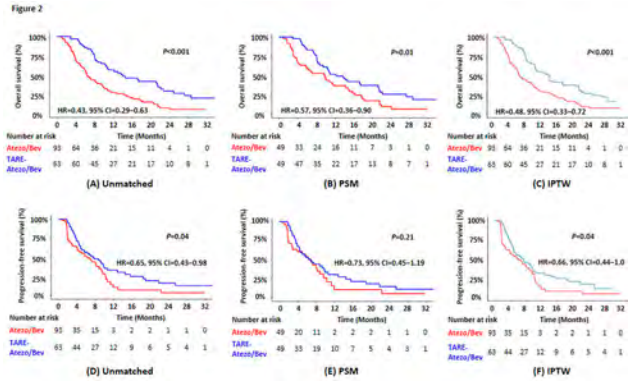
Yunmi Ko[1] Yoon Jun Kim[2], [1]Inha University Hospital, [2]Seoul National University Hospital

Background: Yttrium-90 transarterial radioembolization (TARE) combined with immune checkpoint inhibitors has been investigated as a potential therapeutic strategy for advanced hepatocellular carcinoma (HCC); however, evidence supporting its addition to current standard systemic therapy remains limited. We aimed to compare clinical outcomes in patients with advanced HCC treated with TARE followed by atezolizumab plus bevacizumab (TARE–Atezo/Bev) and Atezo/Bev alone. **Methods:** This retrospective cohort study included systemic therapy-naïve patients with advanced HCC treated with Atezo/Bev alone or TARE–Atezo/Bev at a single tertiary hospital between 2018 and 2025. Baseline characteristics were adjusted using propensity score matching (PSM) and inverse probability of treatment weighting (IPTW). The primary outcome was overall survival (OS), and the secondary outcome was progression-free survival (PFS). **Results:** A total of 156 eligible patients were enrolled, including 93 in the Atezo/Bev group and 63 in the TARE–Atezo/Bev group. In the unmatched cohort, median OS was significantly longer in the TARE–Atezo/Bev group than in the Atezo/Bev group (14.1 vs. 6.4 months; hazard ratio = 0.43, 95% confidence interval = 0.29–0.63; $P < 0.001$), with consistent results after PSM ($P = 0.01$) and IPTW ($P < 0.001$). Although PFS was comparable between groups in the overall cohort, patients with Child-Pugh

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class A (OS: 14.6 vs. 7.1 months; PFS: 7.7 vs. 6.3 months) or ALBI grade 1 (OS: 21.4 vs. 8.3 months; PFS: 8.1 vs. 5.7 months) had significantly longer OS and PFS in the TARE–Atezo/Bev group, with similar results after adjustment. **Conclusion:** Sequential TARE–Atezo/Bev may improve survival compared with Atezo/Bev alone in patients with advanced HCC and well-preserved liver function.

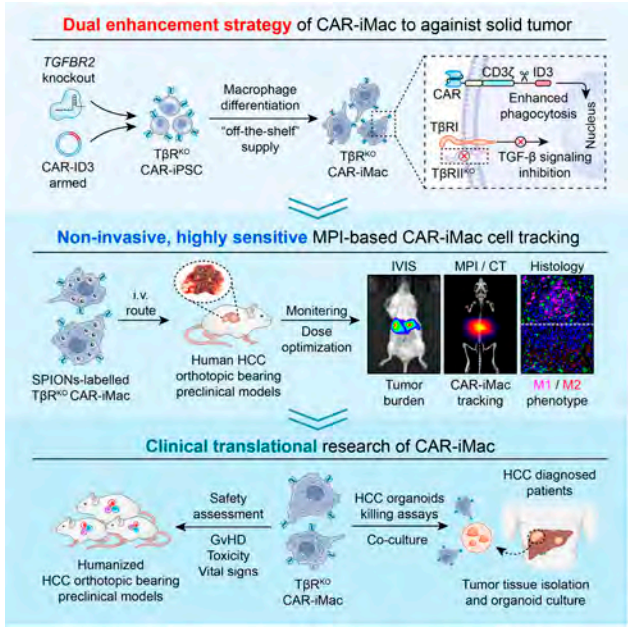


Disclosures: Yunmi Ko: Nothing to Disclose, Yoon Jun Kim: Nothing to Disclose.

0157 | MAGNETIC PARTICLE IMAGING GUIDES DOSING OF ID3-ENHANCED, TGFBR2-DELETED IPSC-DERIVED CAR MACROPHAGES FOR HEPATOCELLULAR CARCINOMA

Tuo Shao[1] Chao Tang[1] Xin Feng[2] Hui Hui[2] Raymond Chung[3] Jie Tian[2], [1]The First Affiliated Hospital of Soochow University, [2]CAS Key Laboratory of Molecular Imaging, Institute of Automation, Chinese Academy of Sciences, [3]Division of Gastroenterology and Hepatology, Mass General Brigham

Background: Hepatocellular carcinoma (HCC) remains resistant to cellular immunotherapy because of poor effector-cell infiltration and a strongly immunosuppressive tumor microenvironment. Induced pluripotent stem cell (iPSC)-derived chimeric antigen receptor macrophages (CAR-iMac) may offer an off-the-shelf myeloid platform, but their antitumor state, resistance to transforming growth factor-β (TGF-β), and in vivo exposure remain difficult to control. We developed an ID3-enhanced, TGFBR2-deleted, glypican-3 (GPC3)-targeted CAR-iMac and used magnetic particle imaging (MPI) to guide dosing in preclinical HCC. **Methods:** Human cord blood CD34+ cells were reprogrammed into iPSCs, engineered with an anti-GPC3 CAR containing ID3, and further edited by CRISPR-Cas9 to delete TGFBR2. Differentiated CAR-iMac were assessed by flow cytometry, transcriptomics, tumor-cell killing/phagocytosis assays, orthotopic HCC mouse models, SPION-based MPI/CT tracking, PBMC-humanized safety/efficacy models, and patient-derived HCC organoids co-cultured with autologous CD3+ T cells. **Results:** ID3-endowed CAR-iMac retained pluripotency before differentiation, maintained CAR expression during myeloid differentiation, and showed stronger GPC3-dependent clearance of HepG2 and Huh7 cells than truncated CAR-iMac, with limited activity against GPC3-negative SK-Hep-1 cells. TGFBR2 deletion further enhanced antitumor function, increased CD80/CD86, reduced CD163/CD206, enriched inflammatory and chemotaxis programs, and produced the greatest suppression of orthotopic HCC growth. SPION labeling preserved viability and macrophage-marker profiles, and MPI signals were linearly related to cell number. Longitudinal MPI showed hepatic localization and dose-dependent persistence: 1×10^6 cells decayed rapidly, 5×10^6 persisted to day 30 but did not improve efficacy, whereas 2.5×10^6 cells plus pro-inflammatory support achieved better early-to-mid tumor suppression and a higher M1-associated fraction. In PBMC-humanized HCC mice, split dosing (2.5×10^6 cells on days 0 and 15) reduced high-dose inflammatory toxicity, maintained lower tumor burden, and prolonged survival. In patient-derived HCC organoids, TGFBR2-deleted CAR-iMac cooperated with autologous T cells to reduce organoid size, increase IL-2, IL-6, IL-1β, IL-8, and TNF-α, and enhance LDH-defined cytotoxicity. **Conclusion:** Dual ID3 enhancement and TGFBR2 deletion generates a potent, scalable, and monitorable GPC3-targeted CAR-iMac platform for HCC. MPI-defined exposure reveals that intermediate, fractionated dosing may be superior to maximal single dosing by preserving antitumor activity while limiting inflammatory toxicity and M2-like reprogramming.



Disclosures: TUO SHAO: Nothing to Disclose, Chao Tang: Nothing to Disclose, Xin Feng: Nothing to

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Disclose, Hui Hui: Nothing to Disclose, Raymond Chung: Nothing to Disclose, Jie Tian: Nothing to Disclose.

0158 | ETIOLOGY DISSOCIATES THE CAUSES OF DEATH AFTER LIVER TRANSPLANT FOR HEPATOCELLULAR CARCINOMA: A COMPETING-RISKS ANALYSIS OF 12,001 DAA-ERA RECIPIENTS

Mohamed Nadeem[1] Islam Mohamed[2] Basil Jalamneh[1] Sobia Laique[3] Shilpa Junna[3], [1]Cleveland Clinic Foundation, [2]The Cleveland Clinic Foundation-Fairview hospital, [3]Cleveland Clinic

Background: The etiology of cirrhosis and associated hepatocellular carcinoma has been gradually evolving, with the increasing global incidence of MASH-related liver disease. The role of cirrhosis etiology in predicting post-LT HCC recurrence is not well known. **Methods:** We analyzed 12,001 adult HCC-exception first-time liver-only transplants with etiology-classifiable cirrhosis in OPTN/UNOS STAR (2014–2023, direct-acting-antiviral era), linked to explant pathology, post-LT malignancy follow-up, and exception files. Etiology of cirrhosis (HCV/HBV/MASLD/MetALD/ALD) was assigned via a viral-dominant hierarchy on primary and secondary diagnoses, with ALD plus ≥ 1 cardiometabolic risk factor reclassified as MetALD. Cardiometabolic risk factors included Type 2 diabetes mellitus and obesity. Additional information regarding the cohort can be found in Table 1.Composite recurrence of malignancy, recurrence-attributed graft failure, and recurrence-attributed cause of death were collected. Fine-Gray subdistribution hazards modeled recurrence of HCC (reference MASLD); a second Fine-Gray model, with non-recurrence death as the primary event, tested whether differences in patient characteristics and medical comorbidities accounted for the etiology-related differences in mortality. **Results:** Composite recurrence of HCC occurred in 1,445 recipients (12.0%); with a median follow-up of 5.0–6.4 years. Adjusted recurrence sHR versus MASLD: HCV 1.39 (1.18–1.64, $p < 0.001$), ALD 1.67 (1.12–2.48, $p = 0.011$), HBV 1.25 (NS), MetALD 1.14 (NS). Five-year recurrence cumulative incidence: ALD 13.0%, HCV 11.7%, HBV 9.9%, MetALD 8.0%, MASLD 7.4% (Gray's $p < 0.001$). Recurrence was the principal late-mortality driver (time-dependent HR 13.4, 11.9–15.0). Five-year recurrence-related versus non-recurrence death ratios diverged by etiology: HBV 1.34 and ALD 1.07 (recurrence-dominant), HCV 0.85, MetALD 0.56, MASLD 0.42 (non-recurrence dominant). MASLD recipients were older (mean 63.7 years) and more often diabetic (68.8%) than HCV recipients (27.0% diabetic). An adjusted Fine-Gray for non-recurrence death attenuated HCV versus MASLD from sHR 0.71 ($p < 0.001$) to 0.89 ($p = 0.040$), with diabetes sHR 1.40 ($p < 0.001$) consistent with the case mix rather than a distinct metabolic-liver effect. **Conclusion:** Patients with a component of viral or alcohol related liver disease and associated HCC had higher rates of recurrence, compared to their counterparts with MASLD-associated HCC after LT in the DAA era, with ALD showing the highest cumulative incidence. The post-LT mortality of MASH-related HCC patients is instead driven by cardiometabolic events. Etiology-specific surveillance and cardiometabolic risk reduction merit integration into post-LT care of HCC patients.

Table 1. Baseline recipient, tumor, and donor characteristics by etiology

Variable	HCV	HBV	MASLD	MetALD	ALD
N	6,962	811	2,465	1,542	221
Recipient age (mean, SD)	61.6 (5.5)	58.7 (8.8)	63.7 (6.6)	61.1 (7.3)	59.0 (9.0)
Sex, n (%)					
Female	1456 (21%)	126 (16%)	860 (35%)	139 (9%)	70 (32%)
Male	5506 (79%)	685 (84%)	1605 (65%)	1403 (91%)	151 (68%)
Race/Ethnicity, n (%)					
Asian	236 (3%)	493 (61%)	88 (4%)	19 (1%)	7 (3%)
Black	836 (12%)	87 (11%)	29 (1%)	42 (3%)	8 (4%)
Hispanic	1104 (16%)	32 (4%)	556 (23%)	433 (28%)	31 (14%)
Other	106 (2%)	13 (2%)	28 (1%)	17 (1%)	0 (0%)
White	4680 (67%)	186 (23%)	1764 (72%)	1031 (67%)	175 (79%)
BMI (mean, SD)	28.9 (5.1)	26.4 (4.5)	32.3 (5.5)	30.5 (4.4)	22.8 (1.9)
MELD-Na at TX (mean, SD)	12.9 (7.0)	11.2 (6.2)	15.7 (8.0)	15.8 (7.9)	15.1 (7.5)
Albumin at TX (mean, SD)	3.4 (0.7)	3.7 (0.7)	3.2 (0.6)	3.3 (0.6)	3.4 (0.6)
Diabetes, n (%)					
No	5083 (73%)	588 (73%)	770 (31%)	912 (59%)	221 (100%)
Yes	1879 (27%)	223 (27%)	1695 (69%)	630 (41%)	0 (0%)
AFP pre-TX (mean, SD)	38.5 (228.0)	34.8 (177.8)	19.3 (70.8)	20.7 (87.7)	27.4 (97.0)
AFP category, n (%)					
<20	5315 (76%)	669 (82%)	2149 (87%)	1349 (87%)	185 (84%)
20–999	1624 (23%)	137 (17%)	314 (13%)	190 (12%)	36 (16%)
≥1000	23 (0%)	5 (1%)	2 (0%)	3 (0%)	0 (0%)
Within-Milan on explant, n (%)					
Beyond Milan	1650 (31%)	194 (30%)	543 (34%)	331 (33%)	41 (30%)
Within Milan	3660 (69%)	443 (70%)	1034 (66%)	685 (67%)	94 (70%)
Vascular invasion, n (%)					
Absent	4763 (85%)	581 (87%)	1437 (86%)	917 (86%)	122 (85%)
Present	838 (15%)	84 (13%)	238 (14%)	154 (14%)	21 (15%)
Poor differentiation, n (%)					
Poor	410 (10%)	45 (10%)	121 (9%)	83 (10%)	10 (10%)
Well/Moderate	3857 (90%)	419 (90%)	1192 (91%)	733 (90%)	95 (90%)
Donor age (mean, SD)	42.9 (15.9)	44.2 (16.8)	44.9 (16.6)	44.5 (16.1)	43.1 (17.1)
Donor type (DCD vs DBD), n (%)					
DBD	6188 (91%)	707 (89%)	2095 (88%)	1309 (87%)	182 (85%)
DCD	643 (9%)	83 (11%)	288 (12%)	203 (13%)	32 (15%)
Allocation era, n (%)					
DAA / pre-AC (2014–19)	5848 (84%)	616 (76%)	1610 (65%)	1053 (68%)	162 (73%)
Post-AC (2020–23)	1114 (16%)	195 (24%)	855 (35%)	489 (32%)	59 (27%)

Disclosures: Mohamed Nadeem: Nothing to Disclose, Islam Mohamed: Nothing to Disclose, Basil Jalamneh: Nothing to Disclose, Sobia Laique: Madrigal Pharmaceuticals Inc: Advisor, Madrigal Pharmaceutical: Consultant, Novo Nordisk: MASH Curriculum Steering Committee, Shilpa Junna: Nothing to Disclose.

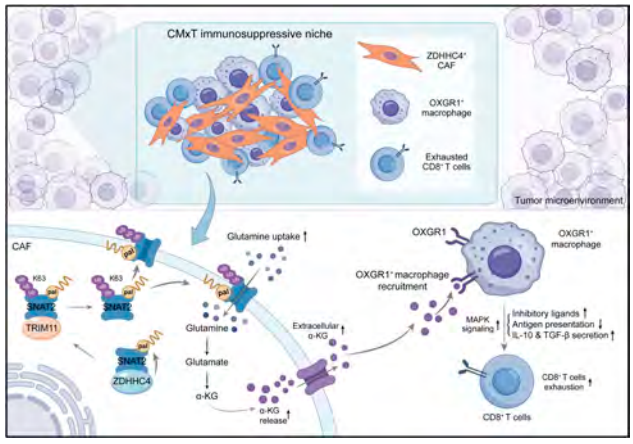
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0159 | ZDHHC4+ CAFS ESTABLISH AN IMMUNOSUPPRESSIVE CMXT NICHE IN HEPATOCELLULAR CARCINOMA

Suiqing Zhou[1] Chunyao Fang[1] Xuehao Wang[1], [1]Nanjing Medical University

Background: The immune microenvironment of hepatocellular carcinoma is organized into spatially coordinated niches rather than random cellular aggregates. Immunotherapy response depends not only on immune cell abundance, but also on their spatial localization, functional state, and interactions with stromal cells. However, the key spatial niches and molecular drivers of immune suppression in hepatocellular carcinoma remain unclear. **Methods:** We integrated CODEX imaging, Visium HD spatial transcriptomics, spatial metabolomics, single-cell RNA sequencing, metabolomics, RNA-seq, IP/MS, and palmitoyl-proteomics to map cellular interactions in hepatocellular carcinoma. Fibroblast-specific Zdhhc4 knockout mice, DEN/CCL4-induced liver cancer models, orthotopic tumor models, primary CAF-macrophage co-culture, isotope tracing, multiplex immunofluorescence, Co-IP, PLA, GST pull-down, and anti-PD-1 treatment assays were used for validation. **Results:** Spatial analysis identified a tricellular niche composed of CAFs, macrophages, and exhausted CD8+ T cells, termed the CMxT niche. High CMxT abundance was associated with poor overall survival independently of total immune infiltration. ZDHHC4 expression in CAFs negatively correlated with the distance to neighboring macrophages and exhausted CD8+ T cells, suggesting a niche-driving role. Fibroblast-specific Zdhhc4 deletion reduced tumor burden and impaired local enrichment of OXGR1+ macrophages and exhausted CD8+ T cells. Mechanistically, ZDHHC4 palmitoylated the glutamine transporter SNAT2, enhanced SNAT2-TRIM11 interaction, promoted K63-linked ubiquitination and membrane localization of SNAT2, and increased glutamine flux and α-ketoglutarate release from CAFs. α-Ketoglutarate acted as an endogenous OXGR1 ligand to recruit OXGR1+ macrophages and promote CD8+ T-cell exhaustion. In clinical samples, ZDHHC4+ CAFs, OXGR1+ macrophages, exhausted CD8+ T cells, and local α-ketoglutarate levels were spatially correlated. Targeting ZDHHC4 in CAFs disrupted this niche axis and enhanced anti-PD-1 efficacy. **Conclusion:** This study defines a ZDHHC4+ CAF/OXGR1+ macrophage/exhausted CD8+ T-cell CMxT niche in hepatocellular carcinoma and reveals a ZDHHC4-SNAT2-α-ketoglutarate-OXGR1 axis driving spatial immune suppression. CAF-intrinsic ZDHHC4 may represent a therapeutic target to remodel the tumor immune microenvironment and improve anti-PD-1 therapy.



Disclosures: Suiqing Zhou: Nothing to Disclose, Chunyao Fang: Nothing to Disclose, Xuehao Wang: Nothing to Disclose.

0160 | LIPID-ASSOCIATED SPP1+MACROPHAGES DRIVE ATTENUATED RESPONSES TO IMMUNE CHECKPOINT INHIBITORS IN MASLD-ASSOCIATED HEPATOCELLULAR CARCINOMA

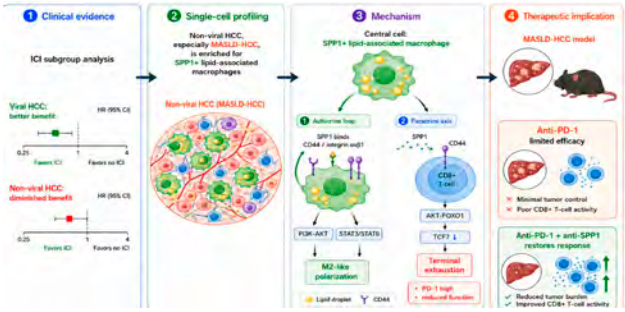
Enrui Xie[1] Xinyuan He[1] Xu Gao[1] Taotao Yan[1] Yue Zhang[1] Siyuan Wang[2] Xiao Yuan[1] Xindi Huang[1] Jiaxuan Hou[3] Yidi Zhao[1] Qian Wang[1] Xiaofan Song[4] Baohua Li[4] Ting La[4] Wen Kang[5] Pengfei Liu[4] Shuo Jin[2] Taotao Huo[4] Fanpu Ji[4], [1]The Second Affiliated Hospital of Xi'an Jiaotong University, [2]Beijing Tsinghua Changgung Hospital, [3]The First Affiliated Hospital of Xi'an Jiaotong University, [4]The Second Affiliated Hospital of Xi'an Jiaotong University, [5]Fourth Military Medical University

Background: The efficacy of immune checkpoint inhibitor (ICI)-based therapy varies across hepatocellular carcinoma (HCC) etiologies, but the mechanisms underlying poor responses in non-viral HCC remain unclear. **Methods:** We performed a meta-analysis of 16 phase III RCTs and integrated publicly available scRNA-seq datasets from viral and non-viral HCC. Findings were validated using a methionine- and choline-deficient (MCD) diet–induced orthotopic MASLD-HCC mouse model and mechanistic in vitro assays targeting SPP1-mediated macrophage–T cell crosstalk. **Results:** ICI-based therapy improved overall survival in advanced HCC, but its benefit was attenuated in non-viral HCC. Public scRNA-seq analyses revealed enrichment of SPP1+ lipid-associated macrophage(LAM)-like cells in non-viral and steatotic HCC, accompanied by increased CD8+ T-cell terminal

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exhaustion. In MASLD-HCC mice, reduced anti-PD-1 efficacy was associated with elevated macrophage SPP1 expression. Mechanistically, SPP1 promoted immunosuppression via macrophage autocrine CD44/integrin αvβ1–PI3K/AKT–STAT3/STAT6 signaling and $CD8^+$ T-cell paracrine CD44–AKT–FOXO1 signaling, thereby driving macrophage immunosuppressive polarization and T-cell exhaustion. Dual SPP1 and PD-1 blockade synergistically suppressed MASLD-HCC progression and enhanced antitumor immunity. **Conclusion:** Non-viral HCC shows an attenuated response to ICI-based therapy associated with $SPP1^+$ LAM-like macrophage. Combined SPP1 and PD-1 blockade may offer an immunotherapy strategy for MASLD-associated HCC.



Disclosures: Enrui Xie: Nothing to Disclose, Xinyuan He: Nothing to Disclose, Xu Gao: Nothing to Disclose, Taotao Yan: Nothing to Disclose, Yue Zhang: Nothing to Disclose, Siyuan Wang: Nothing to Disclose, Xiao Yuan: Nothing to Disclose, Xindi Huang: Nothing to Disclose, Jiaxuan Hou: Nothing to Disclose, Yidi Zhao: Nothing to Disclose, Qian Wang: Nothing to Disclose, Xiaofan Song: Nothing to Disclose, Baohua Li: Nothing to Disclose, Ting La: Nothing to Disclose, Wen Kang: Nothing to Disclose, Pengfei Liu: Nothing to Disclose, Shuo Jin: Nothing to Disclose, Taotao Huo: Nothing to Disclose, Fanpu Ji: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose.

0161 | BILIARY LOSS OF PRIMARY CILIA AND PTEN DRIVE INTRAHEPATIC CHOLANGIOCARCINOMA RESEMBLING A HUMAN SUBTYPE WITH A POOR PROGNOSIS

Jinbiao Chen[1] Fan Zhang[2] Ngan Cheng[3] Jade Boland[4] Paul Coleman[3] Jessamy Tiffen[5] Tomas Gershevitch[6] Stuart Forbes[7] James Kench[8] Emad El-omar[9] Jennifer Gamble[3] Ken Liu[10] Geoffrey McCaughan[1]

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Background: Intrahepatic cholangiocarcinoma (iCCA) is an aggressive liver cancer with a poor prognosis and limited therapies. PI3K/PTEN/AKT activation and loss of primary cilia (PC) are common features of iCCA. However, their mechanistic relationship remains poorly understood. This study investigated how biliary Pten loss and PC dysfunction drive iCCA development. It also elucidated the underlying molecular mechanisms and identified potential therapeutic targets. **Methods:** Biliary epithelial cell (BEC)-specific knockout of Pten, Kif3a (PC loss), or both was achieved using CK19CreERT-driven recombination in adult mice. Thioacetamide (TAA) was used to induce chronic liver injury and fibrosis. Experimental treatments were administered from week 17 to 20 post-TAA. Liver tissues were analysed by histopathology and RNA-sequencing. **Results:** Under conditions of chronic liver injury, BEC-specific Pten deletion induced iCCA with cystic biliary lesions and marked PC loss in adult mice, highlighting the critical role of inflammation in tumour initiation. PC loss accelerated tumour progression, supporting its role as a tumour suppressor in iCCA. Mechanistically, Pten loss triggered PC disassembly via the CK1ε–Dvl2–AurKA axis. Activation of this pathway promoted ciliary loss and tumour progression, whereas CK1ε inhibition reduced tumour progression and immune cell infiltration in a PC-dependent manner.Transcriptomic analyses revealed that the Pten/PC-deficient (PKO) iCCAs recapitulated key features of poor-prognosis inflammatory human iCCA subtype, including enrichment of integrins, matrix remodelling genes, innate immune signatures, and immune checkpoint-associated genes. Furthermore, membrane-associated carbonic anhydrases (CA4, CA9, and CA12) were markedly upregulated, particularly in PC-deficient tumours. CA inhibition with acetazolamide significantly reduced tumour progression and altered the immune microenvironment (Fig. 1). **Conclusion:** Pten loss and PC dysfunction synergistically drive iCCA progression during chronic injury. Targeting the CK1ε–Dvl2–AurKA pathway and membrane-associated carbonic anhydrases offers potential therapeutic targets. The PKO mouse model closely recapitulates aggressive, inflammatory human iCCA.

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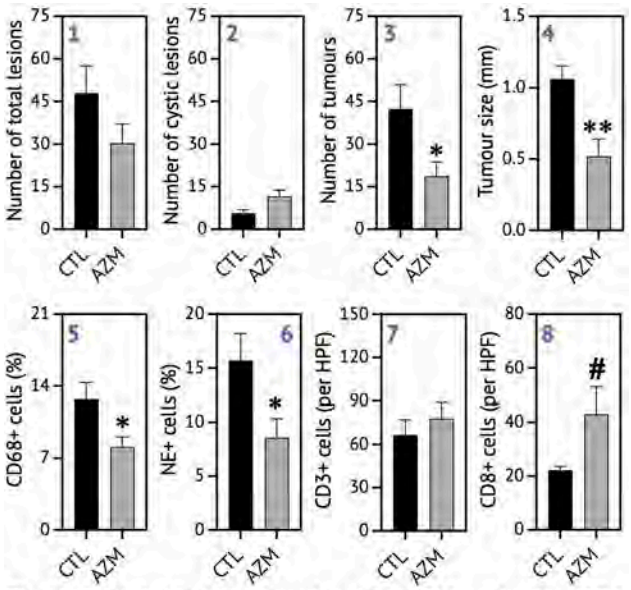


Fig. 1. CA inhibitor acetazolamide (AZM) reduces iCCA progression in vivo. (1) total lesions, (2) cystic lesions, (3) tumors, (4) the size of tumors, (5) CD68+ cells, (6) neutrophils, (7) CD3+ cells, (8) CD8+ cells. Statistical significance - unpaired student's t- test, * p<0.05, ** p<0.01; Welch's t-test, # p<0.05.

Disclosures: Jinbiao Chen: Nothing to Disclose, Fan Zhang: Nothing to Disclose, Ngan Cheng: Nothing to Disclose, Jade Boland: Nothing to Disclose, Paul Coleman: Nothing to Disclose, Jessamy Tiffen: Nothing to Disclose, Tomas Gershevitch: Nothing to Disclose, Stuart Forbes: Nothing to Disclose, James Kench: Nothing to Disclose, Emad El-omar: Nothing to Disclose, Jennifer Gamble: Nothing to Disclose, Ken Liu: Nothing to Disclose, Geoffrey McCaughan: Nothing to Disclose.

0162 | DONOR HBV EXPOSURE STATUS IS ASSOCIATED WITH INCREASED RECURRENCE OF HEPATOCELLULAR CARCINOMA AFTER LIVER TRANSPLANTATION: A NATIONAL REGISTRY ANALYSIS WITH PROPENSITY-SCORE AND WEIGHTING-BASED COMPETING-RISKS MODELS

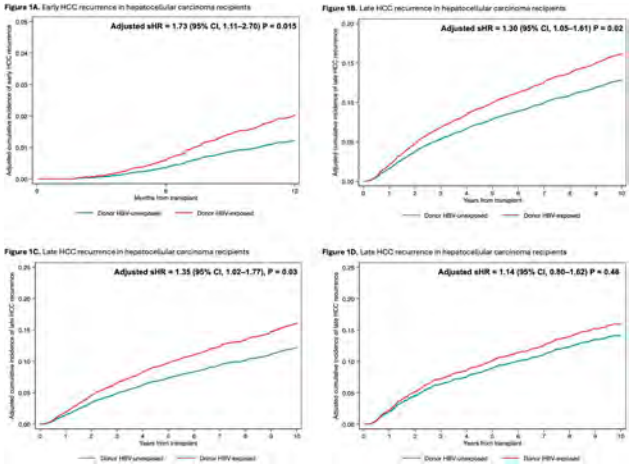
Leandro Sierra[1] Rachael Mahle[2] Katherine Cooper[2] Abigail Scherrer[2] Teresa Rice[2] Irun Bhan[2] Eric Przybyszewski[2] Amit Singal[3] Emily Bethea[2],
[1]Cleveland Clinic Foundation, [2]Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA, [3]The University of Texas Southwestern Medical Center, Dallas, TX, USA

Background: Use of donor grafts with hepatitis B virus (HBV) exposure has expanded in liver transplantation (LT) for hepatocellular carcinoma (HCC). HBV-exposed grafts may harbor covalently closed circular DNA and integrated viral sequences capable of reactivation under immunosuppression. Prior U.S. studies show comparable survival with HBV-exposed grafts, but the association with HCC recurrence and whether it differs by recipient HBV serostatus, remains unexplored. **Methods:** We conducted a retrospective study using the Scientific Registry of Transplant Recipients from 2013 to 2025. Adults receiving first deceased-donor LT for HCC with explant pathology were compared by donor HBV exposure: unexposed (all serology negative) versus exposed (anti-HBc, HBsAg, or HBV NAT positive). Recipients were classified as HBV-naïve (negative anti-HBc, HBsAg, and HBV DNA) or HBV-exposed (any marker positive). Primary outcome was HCC recurrence, modeled with Fine-Gray competing-risks regression at 1-year (early recurrence) and 10-year (late recurrence), with death without recurrence as the competing event. Robustness was confirmed by two parallel study designs: 1: 1 propensity-score matching and inverse probability of treatment weighting. Additional sensitivity analyses excluded HBV/HDV coinfection, restricted to within-Milan recipients, applied a 30-day landmark, and adjusted for transplant year and region. All models were adjusted by recipient demographics, MELD, tumor burden and differentiation, AFP, locoregional therapy, donor risk index (DRI), and satellite lesions. **Results:** Of 16,426 LT recipients with HCC, 1,078 (6.6%) received HBV-exposed grafts. HBV-related HCC was overrepresented among recipients of HBV-exposed grafts (8.7% vs 5.0%, $p < 0.001$), and DRI was higher (2.0 vs 1.3, $p < 0.001$). At 10 years, cumulative HCC recurrence was higher among HBV-exposed versus non-exposed grafts (16.2% vs 12.9%, $p < 0.001$). Donor HBV exposure was independently associated with increased early recurrence (sHR 1.73, 95% CI 1.11–2.70, $p = 0.015$) and late recurrence (sHR 1.30, 95% CI 1.05–1.61, $p = 0.02$). The association with late recurrence was moderated by recipient HBV serostatus, with increased risk among HBV-naïve recipients (sHR 1.35, 95% CI 1.02–1.77, $p = 0.03$) but not HBV-exposed recipients (sHR 1.14, 95% CI 0.80–1.62, $p = 0.46$). Early recurrence did not differ by recipient HBV status. Donor HBV exposure was not associated with mortality (10-year HR 1.06, 95% CI 0.90–1.23, $p = 0.46$). Findings were robust across all sensitivity analyses (early sHR range 1.71–2.25; late sHR range 1.29–1.42). **Conclusion:** Donor HBV exposure is associated with increased post-LT HCC recurrence, particularly among HBV-naïve recipients. This may reflect impaired tumor surveillance by donor-derived HBV antigens in the absence of pre-existing HBV immunity. Findings support enhanced HCC surveillance in HBV-naïve

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recipients of HBV-exposed grafts.

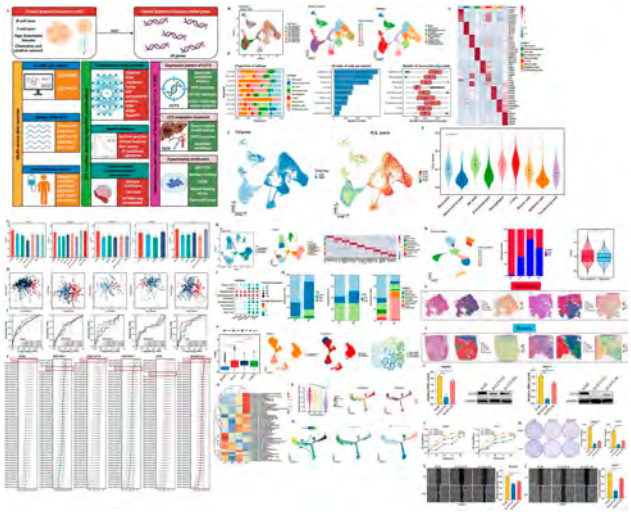


Disclosures: Leandro Sierra: Nothing to Disclose, Rachael Mahle: Nothing to Disclose, Katherine Cooper: Nothing to Disclose, Abigail Scherrer: Nothing to Disclose, Teresa Rice: Nothing to Disclose, Irun Bhan: Nothing to Disclose, Eric Przybyszewski: Nothing to Disclose, Amit Singal: Genentech: Consultant, AstraZeneca: Consultant, Bayer: Consultant, Eisai: Consultant, Exelixis: Consultant, Merck: Consultant, Elevar: Consultant, FujiFilm Medical Sciences: Consultant, Exact Sciences: Consultant, Glycotest: Consultant, Boston Scientific: Consultant, Sirtex: Consultant, HelioGenomics: Consultant, ImCare: Consultant, DELFI: Consultant, Curve Biosciences: Consultant, Catalym: Consultant, Verve: Consultant, Emily Bethea: Nothing to Disclose.

0163 | INTEGRATING BULK, SINGLE-CELL, AND SPATIAL TRANSCRIPTOMICS REVEALS POTENTIAL BIOMARKERS OF TERTIARY LYMPHOID STRUCTURE-RELATED GENES IN PROGNOSIS AND IMMUNOTHERAPY RESPONSE IN HEPATOCELLULAR CARCINOMA

Yuexi Yu[1] Huiru Liu[1] Fengmei Wang[1], [1]Tianjin First Central Hospital

Background: Tertiary lymphoid structures (TLS) are closely associated with the efficacy of anti-tumor immunotherapy; however, their value and significance in hepatocellular carcinoma (HCC) remain unclear. **Methods:** TLS-related genes were identified through AUCell analysis based on integrated single-cell RNA sequencing (scRNA-seq) and bulk transcriptomic data. Data from five HCC cohorts were analyzed to develop a tertiary lymphoid structure-related signature (TLSRS) using 10 machine-learning algorithms and their 101 combinations. Validation was performed using six immunotherapy cohorts (IMvigor210 and melanoma cohorts) as well as spatial transcriptomics datasets. Finally, Spearman correlation analysis identified the key gene **CCT3**, and loss-of-function experiments were conducted to explore the biological function of CCT3 in HCC. **Results:** The TLSRS, composed of 10 genes, demonstrated high accuracy in predicting the prognosis of patients with HCC. TLSRS effectively predicted outcomes in patients receiving immunotherapy and was positively associated with immunotherapy resistance. Patients with different TLSRS scores showed distinct patterns of immune cell infiltration, immune cell gene markers, and immune checkpoint–related marker expression. **CCT3** was identified as a key gene in the TLSRS (correlation = 0.7, $p < 0.001$). In vitro experiments showed that knockdown of **CCT3** significantly inhibited the proliferation and migration of HCC cells. **Conclusion:** TLSRS provides a precise risk stratification tool and guidance for immunotherapy in patients with hepatocellular carcinoma. **CCT3**, as a key gene within TLSRS, may serve as a potential therapeutic target for HCC.



Disclosures: Yuexi Yu: Nothing to Disclose, Huiru Liu: Nothing to Disclose, Fengmei Wang: Nothing to Disclose.

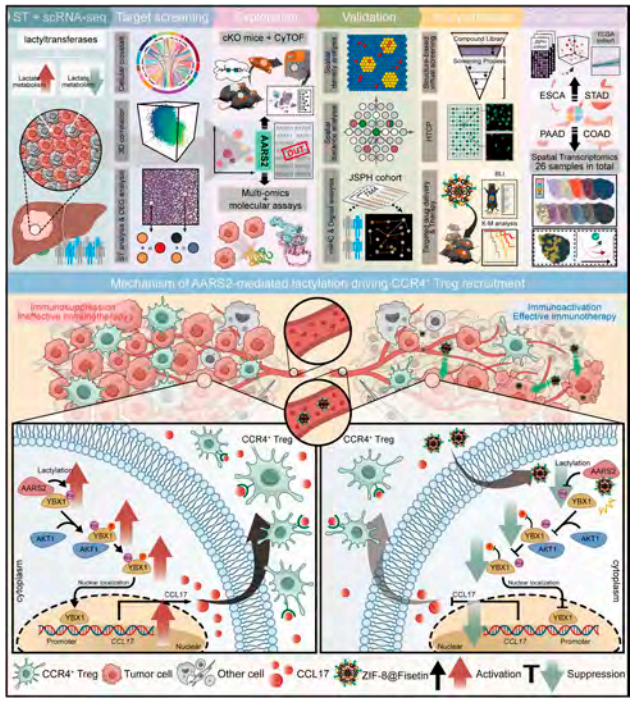
0164 | AARS2-MEDIATED LACTYLATION DRIVES CCR4⁺ TREG RECRUITMENT AND IMMUNOTHERAPY RESISTANCE IN HEPATOCELLULAR CARCINOMA

Chunyao Fang[1] Suiqing Zhou[1] Xuehao Wang[1], [1]Nanjing Medical University

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Background: Hepatocellular carcinoma exhibits extensive metabolic reprogramming and an immunosuppressive tumor microenvironment, limiting the efficacy of immune checkpoint blockade. Although lactate metabolism and protein lactylation are increasingly recognized as regulators of tumor immunity, we observed that not all patients with high lactate metabolism display immunosuppressive features, suggesting the existence of key molecular mediators that determine lactate-driven immune escape. **Methods:** We integrated single-cell RNA sequencing, spatial transcriptomics, multiplex immunofluorescence, CyTOF, and HCC patient cohorts to define lactate-associated immune programs. Hepatocyte-specific Aars2 knockout mice, primary hepatocarcinogenesis models, and orthotopic HCC models were used to assess AARS2 function. Mechanistic studies included IP-MS, lactylome profiling, Co-IP, GST pull-down, PLA, ChIP-qPCR, luciferase assays, phosphorylation analysis, and rescue experiments. Structure-based screening identified inhibitors of the AARS2–YBX1 interaction, followed by SPR validation and therapeutic testing. A Fisetin-loaded ZIF-8 nanoplatform was developed and combined with anti-PD-1 therapy. **Results:** Lactate-associated metabolism was enriched in malignant HCC cells and spatially aligned with immunosuppressive tumor regions. AARS2 was identified as a key lactylation-related regulator enriched in lactate-high niches, and high AARS2 expression predicted poor prognosis and poor response to PD-1 blockade. Aars2 deficiency significantly reduced tumor burden and decreased intratumoral CCR4$^+$ regulatory T cell infiltration. Spatial analyses showed that AARS2-high malignant regions preferentially recruited CCR4$^+$ Tregs. Mechanistically, AARS2 directly interacted with YBX1 and catalyzed its lactylation at K296, enhancing YBX1–AKT1 interaction, YBX1 phosphorylation, and nuclear translocation. Nuclear YBX1 transcriptionally activated CCL17, thereby promoting CCR4$^+$ Treg recruitment and immune evasion. Fisetin disrupted the AARS2–YBX1 interaction, inhibited YBX1 nuclear translocation, reduced CCR4$^+$ Treg infiltration, and improved anti-PD-1 efficacy. ZIF-8-based nanodelivery enhanced tumor targeting of Fisetin and synergized with PD-1 blockade in orthotopic HCC models. Pan-cancer spatial analyses further showed that AARS2 is upregulated in digestive malignancies and associated with CCR4$^+$ Treg enrichment. **Conclusion:** This study reveals an AARS2–YBX1–AKT1–CCL17–CCR4$^+$ Treg axis linking lactate-driven lactylation to immune evasion and immunotherapy resistance in HCC. Targeting AARS2 with Fisetin nanodelivery may provide a promising strategy to overcome Treg-mediated resistance to PD-1 blockade.



Disclosures: Chunyao Fang: Nothing to Disclose, Suiqing Zhou: Nothing to Disclose, xuehao Wang: Nothing to Disclose.

0165 | LIVER FUNCTION STABILITY FOLLOWING YTTRIUM-90 RESIN MICROSPHERE RADIOEMBOLIZATION IN HEPATOCELLULAR CARCINOMA: RESULTS FROM THE DOORWAY90 STUDY (NCT04736121)

Sudha Kodali[1] Armeen Mahvash[2] Ammar Sarwar[3] Gregory Nadolski[4] Eric Wehrenberg-Klee[5] Nima Kokabi[6] S Kappadath[7], [1]Houston Methodist, [2]UT MD Anderson Cancer Center, [3]Beth Israel Deaconess Medical Center, [4]University of Pennsylvania, [5]Massachusetts General Hospital, [6]University of North Carolina, [7]University of Texas MD Anderson Cancer Center

Background: DOORwaY90 is a prospective, multicenter, open-label, single-arm study that evaluated the safety and efficacy of radioembolization with yttrium-90 (Y-90) resin microspheres as first-line treatment for local tumor control in unresectable hepatocellular carcinoma (HCC). Maintaining hepatic functional reserve is critical in the setting of underlying cirrhosis and disease progression. This analysis of prospectively collected data from a large patient cohort focuses on

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the safety outcomes and stability of liver-related laboratory values following treatment. **Methods:** All patients enrolled in DOORwaY90 (N = 100) completed a minimum of 12 months of safety follow-up. Inclusion criteria: confirmed HCC ineligible for resection or ablation, maximal single lesion size ≤ 8 cm, sum of diameters ≤ 12 cm, and preserved baseline organ function. Other key inclusion criteria: platelet count > 50,000/μL (without transfusion or growth factor support); hemoglobin > 8.5 g/dL; AST and ALT < 5x upper limit of normal (ULN); total bilirubin ≤ 2.0 mg/dL; albumin > 3.0 g/dL; INR ≤ 2.0; and GFR > 50 mL/min. Laboratory tests were performed at screening/baseline, at the time of the radioembolization procedure, and at follow-up visits at 1, 2, 4, 6, 9, and 12 months. **Results:** Laboratory findings for liver biomarkers remained stable throughout the 12-month follow-up period. Analysis of liver function indicators, including AST, ALT, total bilirubin, and albumin, demonstrated less than 3% deviation from normal limits at each recorded visit. Over 95% of patients maintained stable liver function after radioembolization, with biomarkers remaining within the normal range across all follow-up timepoints. No hepatic decompensation (as measured by albumin, bilirubin, or INR) or severe hematologic toxicity (hemoglobin or platelet count) were observed. **Conclusion:** The DOORwaY90 study demonstrates that radioembolization with Y-90 resin microspheres for HCC is associated with a high degree of safety and preservation of hepatic function. The high rate of biomarker stability (> 95%) through 12 months suggests that radioembolization can be delivered with minimal impact on liver reserve, even in a population at risk for disease-related functional decline.

Disclosures: Sudha Kodali: SIRTEX: Advisor, Astrazeneca: Advisor, Gilead: Speaking and Teaching, Gilead: Speaking and Teaching, SIRTEX: Advisor, Astrazeneca: Consultant, Armeen Mahvash: Nothing to Disclose, Ammar Sarwar: Nothing to Disclose, Gregory Nadolski: Nothing to Disclose, Eric Wehrenberg-Klee: Sirtex: Consultant, Boston Scientific: Consultant, Delcath: Consultant, Embolx: Consultant, Nima Kokabi: Nothing to Disclose, S Kappadath: Nothing to Disclose.

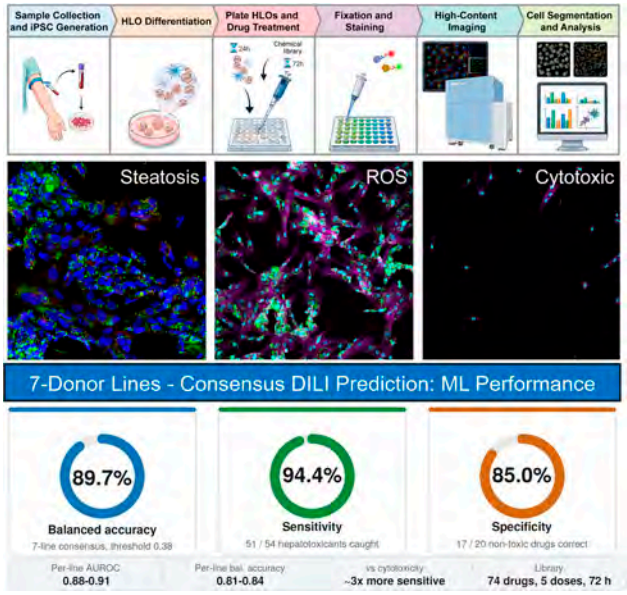
0166 | HIGH-THROUGHPUT DRUG-INDUCED LIVER INJURY RISK PREDICTION USING MORPHOLOGICAL PROFILING AND MACHINE LEARNING IN PATIENT-DERIVED HUMAN LIVER ORGANOIDS

Jonathan Sexton[1] Robert Fontana[2] Max Garcia[3] Neil Zhao[3] Sophia Meyer[3] Matthew McConnachie[3] Jesse Wotring[3] Joel Yates[3] Diana Flores-Diaz[3] Charles Zhang[3], [1]University of Michigan Medical Center, [2]University of Michigan Hospitals and Health Centers, [3]University of Michigan

Background: Drug-induced liver injury (DILI) is a leading cause of clinical trial failure for new agents and post-marketing withdrawal. Existing in vitro models miss human-specific liabilities, cytotoxicity-based screening misses sublethal perturbations, and single-donor systems fail to capture inter-individual susceptibility. We hypothesized that patient-derived human liver organoids (HLOs) coupled with high-content imaging and machine learning (ML) can predict hepatotoxicity with high sensitivity and specificity while preserving donor-specific responses. **Methods:** Six iPSC lines from DILIN-enrolled patients with high single-drug causality scores and one healthy donor (72.3) were differentiated into HLOs, dissociated, seeded into collagen-coated 384-well plates, and exposed for 72 h to 74 compounds (54 hepatotoxicants, 20 non-hepatotoxic) across 5 concentrations in triplicate. Cells were stained for nuclei, lipids, mitochondria, HNF4α, and cytoplasm, imaged on the Yokogawa CV8000, and segmented in CellProfiler. Well-aggregated, MAD-robustized features trained AutoGluon classifiers with compound-grouped 5-fold cross-validation. Benchmark dose (BMD) modeling used BMDExpress3, and TNFα co-treatment was tested with sulindac. **Results:** Per-donor classifiers achieved AUROC 0.88-0.91 and balanced accuracy 0.81-0.84. Cross-donor consensus yielded 94.4% sensitivity, 85.0% specificity, and 89.7% balanced accuracy, outperforming cytotoxicity (84.6% vs 43.8% in HLOs) and the same ML pipeline in immortalized cell lines (73.3%). BMD modeling showed significant inter-donor variability for all 54 hepatotoxicants, with up to 13-fold differences (tamoxifen) and non-overlapping confidence intervals. Unsupervised Leiden clustering identified four mechanism-associated clusters: mitochondrial toxicity, phospholipidosis, apoptotic/nuclear stress, and lipid accumulation. Sulindac, a persistent false negative under basal conditions (ML probability 0.30), was reclassified as true positive (0.71-0.78) with TNFα co-treatment, demonstrating detection of inflammation-potentiated hepatotoxicity. **Conclusion:** Multi-donor patient-derived HLOs combined with high-content morphological profiling and ML provide a scalable, human-relevant NAM platform for DILI risk prediction that outperforms cytotoxicity and immortalized cell lines, captures inter-individual variability, supports mechanism-driven hypothesis generation, and detects inflammation-dependent idiosyncratic DILI with cytokine priming.

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0167 | NOVEL GENETIC VARIANTS ASSOCIATED WITH IMMUNE-MEDIATED LIVER INJURY FROM CHECKPOINT INHIBITORS: RESULTS FROM THE DILIN REGISTRY AND AN INDEPENDENT COHORT

Linnea Swanson[1] Yi-Ju Li[2] Andrew Dellinger[2] Andrew Tucker[1] LaVana Greene-Higgs[1] Venkata Sai Jasty[1] Jessica Sheehan[1] Vincent Chen[1] Robert Fontana[3], [1]University of Michigan, [2]Duke University, [3]University of Michigan Hospitals and Health Centers

Background: Immune-mediated liver injury from checkpoint inhibitors (ILICI) arises in 10 -15% of oncology patients receiving immune checkpoint inhibitors (ICIs) and can result in therapy interruption, discontinuation and need for corticosteroids. The aim of our study was to identify novel genetic variants for ILICI using a cohort of high causality ILICI cases compared to ICI exposed and unexposed controls. **Methods:** Patients with high causality ILICI and genetic data were identified in the Michigan Genomics Institute (MGI; n = 67, 2010-2024) and the Drug-Induced Liver injury Network database (DILIN; n = 65, 2012-2023). Liver injury was defined as AST or ALT $\geq$ 5x ULN, ALP $\geq$ 2x ULN, bilirubin $\geq$ 2.5, or INR $\geq$ 1.5. Causality assessment was based on DILIN expert opinion. Two sets of controls were compared: 1) ICI-exposed controls (patients exposed to ICI but not develop ILICI, n = 741); and 2) unexposed controls (n = 2440). Genome-wide association studies (GWAS) were conducted for ILICI cases in Non-Hispanic Whites (NHW) with SNPs meeting $p < 5x10^{-8}$ considered genome-wide significant. **Results:** The median age (65.6 vs 61.3; p = 0.14), proportion male (53.7% vs 63.1%; p = 0.36), prevalence of melanoma (59.7% vs 44.6%; p = 0.15), and proportion of hepatocellular injury (34.3 vs 50%; p = 0.13) were similar in MGI and DILIN cohorts. Ipilimumab, nivolumab, and pembrolizumab were the most frequently implicated agents in both cohorts. Rates of corticosteroid use (70.1% vs 86.2%, p = 0.67) and 6-month survival (14.1 vs 25.9%; p = 0.24) were also comparable between cohorts. Compared to those without liver injury, patients with ILICI from MGI had lower rates of cancer progression (40.3% vs 52.1%; p < 0.001) and death (37.3% vs 51.2%; p < 0.001). Compared with MGI cases, DILIN cases demonstrated more severe liver injury with higher AST, ALT and total bilirubin at onset and peak as well as greater need for mycophenolate (44.6% vs 7.5%, p < 0.001) compared to MGI. In the GWAS analysis of the combined 111 NHW ILICI cases, three SNPs reached genome-wide significance ($p < 5x10^{-8}$) (**Table 1**): rs991262 in SLCO1B1, rs164752 in CHMP1A, and rs258322 in CDK10. Among them, CDK10 rs258322 ranked at the top with OR of 3.44 (CI 2.27, 5.2; $p = 4.73 \times 10^{-9}$) against non-exposed controls and OR 1.7 (CI 1.17, 2.48; p = 0.006) against ICI-exposed controls. As this CDK10 SNP was previously associated with melanoma, a secondary analysis by tumor type was undertaken that showed CDK10 rs258322 remained significant in both melanoma and non-melanoma cases. **Conclusion:** Three novel SNPs associated with ILICI were identified in a large cohort of adjudicated ILICI cases compared to ICI exposed controls and unexposed controls. The variant in CDK10 is of particular interest as the gene has previously been identified as suppressor of tumor immune surveillance and warrants further validation.

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Table 1: Top list of genes with a variant meeting $p < 10^{-6}$ in at least one analysis of the 111 ILICI cases.

			Combined MGI and DILIN cases (n=111)			
			vs. ICI-Exposed Controls		vs. Non-Exposed Controls	
Chr:BP:A1:A2	SNP	Gene	OR (95% CI)	P	OR (95% CI)	P
5:22991467:T:C	rs12514225	CDH12	2.07(1.32, 3.26)	0.002	3.29(2.05,5.3)	8.08E-07
12:21181280:G:A	rs991262	**SLCO1B1**	1.91(1.2,3.03)	0.006	3.8(2.42,5.96)	**6.12E-09**
12:21333648:A:C	rs61927805	SLCO1A2	1.71(1.13,2.59)	0.012	3.06(1.98,4.74)	5.54E-07
16:89641629:G:A	rs12921177	DPEP1	1.78(1.18,2.67)	0.006	3.27(2.1,5.08)	1.42E-07
16:89655982:G:A	rs164752	**CHMP1A**	1.83(1.23,2.72)	0.003	3.5(2.29,5.36)	**7.22E-09**
16:89657860:C:T	rs35415928	SPATA33	1.8(1.2,2.7)	0.005	3.28(2.13,5.06)	6.92E-08
16:89669495:A:G	rs258322	**CDK10**	1.7(1.17,2.48)	0.006	3.44(2.27,5.2)	**4.73E-09**
16:89703317:C:A	rs342655416	SPATA2L	1.65(1.12,2.42)	0.011	3.09(2.03,4.69)	1.23E-07
16:89715348:T:A	rs34714188	VPS9D1-AS1*	1.65(1.09,2.48)	0.017	3.19(2.04,4.99)	3.8E-07
16:89729609:G:A	rs34659644	ZNF276	1.74(1.15,2.64)	0.008	3.35(2.14,5.25)	1.35E-07
16:89780269:G:C	rs75570604	FANCA	1.67(1.11,2.50)	0.014	3.11(1.99,4.87)	6.68E-07
16:89967283:C:G	rs77606435	AFG3L1P	1.53(1.01,2.31)	0.043	3.2(2.06,4.97)	2.32E-07
16:90011614:T:C	rs77381714	DBNDD1	1.47(0.97,2.23)	0.067	3.09(1.98,4.84)	7.76E-07
16:90044390:C:T	rs74583214	GAS8*	1.47(0.97,2.23)	0.066	3.29(2.1,5.15)	1.91E-07

*rs34714188 is located in both VPS9D1 and VPS9D1-AS1; rs74583214 is located in GAS8 and URAHP.

Disclosures: Linnea Swanson: Nothing to Disclose, Yi-Ju Li: Nothing to Disclose, Andrew Dellinger: Nothing to Disclose, Andrew Tucker: Nothing to Disclose, LaVana Greene-Higgs: Nothing to Disclose, Venkata Sai Jasty: Nothing to Disclose, Jessica Sheehan: Nothing to Disclose, Vincent Chen: AstraZeneca: site PI on industry-sponsored trial, Ipsen: site co-I on industry-sponsored trial, Kowa: site co-I on industry-sponsored trial, Madrigal: Grant/Research Support, GSK: Site PI for clinical trial, CSL: Site PI for clinical trial, Robert Fontana: kezar pharmaceuticals: Grant/Research Support, Takeda Pharmaceuticals: Grant/Research Support, moderna: Consultant, MasterSwitch Bio: Stock ownership, Fractyl: Grant/Research Support, MiroMatrix: Grant/Research Support, Roche: Consultant, roche: Consultant, egenesis: Advisor, intellius: Consultant.

0168 | ADDITIONAL SAFETY AND EFFICACY RESULTS FROM HELIOS: A PHASE 2, OPEN-LABEL, LONG-TERM EXTENSION STUDY OF BITOPERTIN IN ERYTHROPOIETIC PROTOPORPHYRIA

Amy Yeung[1] Gayle Ross[2] Sioban Keel[3] Herbert Bonkovsky[4] Peter Stewart[5] Karl Anderson[6] Manisha Balwani[7] Cynthia Levy[8] Manish Thapar[9] Bruce Wang[10] Brendan McGuire[11] Will Savage[12], [1]Harvard Medical School and Massachusetts General Hospital, [2]Royal Melbourne Hospital, [3]University of Washington, [4]Wake Forest University School of Medicine and Atrium Health Wake Forest Baptist, [5]Royal Prince Alfred Hospital, [6]University of Texas Medical Branch, [7]Icahn School of Medicine at Mount Sinai, [8]University of Miami, [9]Temple University, [10]University of California San Francisco Porphyria Center, [11]University of Alabama at Birmingham, [12]Disc Medicine

Background: Erythropoietic protoporphyria (EPP) and X-linked protoporphyria (XLP) are characterized by accumulation of photoreactive protoporphyrin IX (PPIX) in the skin and liver. PPIX accumulation causes phototoxic skin reactions upon sunlight exposure and, in some cases, life-threatening protoporphyric hepatopathy. Bitopertin is a selective, orally bioavailable inhibitor of glycine transporter 1 (GlyT1), which imports extracellular glycine into erythroid precursor cells for heme biosynthesis. In prior EPP/XLP studies, treatment with bitopertin resulted in significant reductions in PPIX levels associated with improved light tolerance.[1,2] **Methods:** HELIOS (NCT05883748) is a multi-center, open-label, long-term extension study of bitopertin in participants who completed prior studies. The aims of the study are to evaluate the long-term safety, tolerability, and efficacy of bitopertin in participants with EPP or XLP. The study is being conducted in the US and Australia, with additional sites opening in the UK and EU, and includes participants $\geq$12 years of age with confirmed EPP or XLP. Participants receive once-daily oral bitopertin 60 mg. Primary endpoints are safety and tolerability. Secondary endpoints include changes in whole-blood metal-free PPIX and light tolerance. Additional endpoints include patient-reported outcomes measures. **Results:** As of 01 Nov 2025, 86 participants (including 3 adolescents) were enrolled. Median total exposure was 25.3 months (range: 13.8-32.7). To date, 61 of 86 (71%) participants reported adverse events (AEs). One adult participant involved in a motor vehicle accident reported multiple serious AEs, not related to study drug. The only other Grade 3 event was a nonserious unrelated AE of hypertransaminasaemia. All other AEs were mild or moderate. The most common AEs (>5 participants) were COVID-19 (12%), nasopharyngitis (9%), and headache (7%). Participants initially randomized to placebo had significant reductions in whole blood metal-free PPIX at Week 24 (-32.8%; $p < 0.001$). Participants treated with bitopertin in AURORA/BEACON and HELIOS had sustained reductions through 1 year. Light tolerance also improved through Week 24, with significant increases vs baseline in total hours in light (+4.9 hours; $p < 0.001$) and time to prodrome (+101.8 minutes; $p < 0.001$). Data from patient-reported outcomes measures will be presented. **Conclusion:** By reducing PPIX levels, bitopertin targets the underlying pathophysiology of EPP and XLP. HELIOS results, including >2.5 years of exposure, support longer-term efficacy and safety in adult and adolescent patients.References 1. Ross G, et al. Clin Exp Dermatol. Published online 13 Jan 2026. doi: 10.1093/ced/llag002 2. Yeung AK, et al. J Am Acad Dermatol. 2026;94(4): 1167-1176.

Disclosures: Amy Yeung: Nothing to Disclose, Gayle Ross: Sanofi: Honoraria for speaking, Medison: Paid focus group, Abbvie: Medical Advisor, Sioban Keel: Nothing to Disclose, Herbert Bonkovsky: Nothing to Disclose, Peter Stewart: Nothing to Disclose, Karl Anderson: Nothing to Disclose, Manisha Balwani: Alnylam Pharmaceuticals: Consulting/Advisory Board/Speaker's Bureau, Mitsubishi Tanabe: Grant/Research

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★ 0169 | NOVEL ACETAMINOPHEN FORMULATION AT SUPRATHERAPEUTIC DOSES WITH A FAVORABLE HUMAN LIVER SAFETY PROFILE: PREVENTING TOXIC METABOLITE FORMATION

Yuhan Lin[1] Te-Yu Lin[2] Ting-Yi Chiang[1] Yung-Chih Wang[2] Chi-Chi Chou[1] Cheng-Huei Hsiong[1] Hsin-Tien Ho[1] Kai-Min Chu[1] Yoa-Pu Hu[3], [1]Sinew Pharma Inc., [2]Tri-Service General Hospital, [3]Taipei Medical University

Background: Acetaminophen (APAP) overdose causes severe hepatotoxicity primarily via CYP-mediated formation of the reactive metabolite NAPQI. Furthermore, contrary to previous reports, our preclinical data demonstrates APAP-Cys protein adducts formation within the brain tissue of mice and rats. Given the potentially underestimated scope of APAP toxicity, we developed SafeTynadol®, a novel APAP formulation that co-delivers safe modulators of key CYP enzymes to suppress NAPQI generation. When administered within the therapeutic range, the modulator concentration remains very low, resulting in no significant inhibitory effect. Consequently, no drug–drug interactions occur. In practice, the safe modulators accumulate to inhibit enzyme activities, thereby suppressing NAPQI formation under overdose conditions and clinically preventing hepatotoxicity. Preclinical safety success motivated this clinical evaluation at supratherapeutic doses. **Methods:** We performed a multiple-dose clinical trial in 48 healthy adults. Participants received Panadol® 4 g/d or SafeTynadol® 4–12 g/d as four doses within 24 h, with pharmacokinetic (PK) and safety assessments through 168 h. The primary endpoint was alanine aminotransferase (ALT), with systemic APAP-Cys protein adduct quantification and a hepatic-failure composite as key secondary measures. **Results:** ALT levels were within the reference range in all cohorts, with no predefined hepatotoxicity occurring. The highest mean APAP-Cys protein adduct levels were 12.3 ± 8.64 ng/mL at 12 g/d (~4.1% of the toxicity threshold). Adverse events were mild and transient (14.6%), consistent with high-dose APAP exposure. **Conclusion:** Inhibiting NAPQI formation with SafeTynadol® preserved hepatic safety up to 12 g/d, supporting further development as a safer APAP option, including settings at risk for overdose.

Disclosures: Yuhan Lin: SINEW PHARMA INC.: Employee, Te-Yu Lin: Nothing to Disclose, Ting-Yi Chiang: Nothing to Disclose, Yung-Chih Wang: Nothing to Disclose, Chi-Chi Chou: Nothing to Disclose, Cheng-Huei Hsiong: Nothing to Disclose, Hsin-Tien Ho: Nothing to Disclose, Kai-Min Chu: Nothing to Disclose, Yoa-Pu Hu: Nothing to Disclose.

0170 | A SEMI-AUTOMATED ARTIFICIAL INTELLIGENCE (AI) BASED ALGORITHM TO PRIORITIZE POTENTIAL DRUG INDUCED LIVER INJURY (DILI) CASES FROM CLINICAL TRIALS FOR HUMAN CLINICAL REVIEW

Aaron Waddell[1] Mark Gordon[1] Jasmine Amirzadegan[1] Mark Avigan[2] Paul Hayashi[1], [1]Food and Drug Administration, [2]Food and Drug Adminstration

Background: Drug applications may have 50-100 liver injury cases needing review, but most cases will not be DILI. Drug exposure-to-injury course (EIC) is the foundation of a DILI diagnosis, so DILI Team reviewers (DT-r) prioritize cases for review using EIC line graphs showing liver blood tests by study day & drug exposure. We hypothesized that an AI-based program (AI-p) could assist DT-r prioritization, thereby increasing efficiency & providing early insights into overall DILI risk. Our aim was to create an AI-p to prioritize liver injury cases for human review using EIC data. **Methods:** We used RStudio and FDA's AI tool, Elsa (Gemini 2.5), to create an AI-p using 154 cases from 5 drug applications. All cases were in eDISH Temple's Corollary (TC) quadrant with ALT >5x ULN or in Hy's law (HL) quadrant. We created training and validation sets. Using only EIC graphs, a DT-r (PHH) categorized cases into A (high), B (moderate), and C (low) priority. DT-r categorization was the standard. AI-p categorized each training set case into A, B, and C categories based on EIC data. With iterative DT-r input, AI-p was refined to maximize performance with a conservative bias, favoring higher AI-p priority compared to DT-r in marginal cases. AI-p then prioritized validation set cases. **Results:** Of 91 training set cases, DT-r assigned 23 As (25%), 40 Bs (44%), & 28 Cs (31%)

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vs AI-p's 31 As (34%), 35 Bs (38%), & 25 Cs (27%). A1-p & DT-r agreed in 80 (88%; kappa 0.82). Of 63 validation cases, DT-r had 29 As (46%), 30 Bs (48%), & 4 Cs (6%) vs AI-Ps 42 As (67%), 19 Bs (30), & 2 Cs (3%). There was agreement on 46 (73%; kappa 0.51). AI-p accurately identified all 52 DT-r high priority (A) cases from both sets (Figure). A1-p prioritization was never off by more than one category from DT-r in both sets. Under conservative programming (over prioritization on marginal cases), AI-p had minimal under-prioritization error of 1-2%. AI-p categorized as a lower priority than DT-r once in training and once in validation, both were AI-p C vs. DT-r B. **Conclusion:** AI-p may be able to rapidly prioritize liver injury cases for in-depth human assessment. This proof-of-concept AI-p tool correctly identified all DT-r high priority cases. Using conservative programming (favoring higher priority on marginal cases), A1-p agreed with or gave a higher priority than DT-r in 99% and 98% of training and validation sets respectively. Ultimately, AI-p prioritization labels (A, B, or C) could be added next to plotted points in eDISH HL and TC quadrants providing another layer of case categorization that may correlate with a later DILI diagnosis made by humans, thereby increasing efficiency of DILI risk assessment. This abstract's content is the responsibility of the authors and does not necessarily represent the official views of the Food and Drug Administration.

Training Set

DT-r \ AI-p	A	B	C	Totals
A	23	0	0	23
B	6	33	1	40
C	2	2	24	28
Totals	31	35	25	91

Kappa = 0.82

Complete agreement rate: 88% (black boxes)

Complete agreement or AI-p with higher rating than DT-r: 99% (black + grey boxes)

Validation Set

DT-r \ AI-p	A	B	C	Totals
A	29	0	0	29
B	13	16	1	30
C	0	3	1	4
Totals	42	19	2	63

Kappa = 0.51

Complete agreement rate: 73% (black boxes)

Complete agreement or AI-p with higher rating than DT-r: 98% (black + gray boxes)

Figure DT-r (DILI Team reviewer) versus AI-p (Artificial intelligence-based program) categorization of 154 liver injury cases from five different drug applications split into Training and Validation Sets. DT-r and AI-p categorized cases based on drug exposure-to-injury course (EIC) data including line graphs (liver blood tests by study day and drug exposure). Categories were high (A), moderate (B), and low (C) concern for potential DILI. AI-p aligned with DT-r on all cases in the black boxes. Those in gray boxes were over-calls by AI-p (i.e., higher priority than DT-r) and those in white boxes were under-calls by AI-p (i.e. lower priority than DT-r).

Disclosures: Aaron Waddell: Nothing to Disclose, Mark Gordon: Nothing to Disclose, Jasmine Amirzadegan: Nothing to Disclose, Mark Avigan: Nothing to Disclose, Paul Hayashi: Nothing to Disclose.

0171 | ART4, A TRANSLATION-ENHANCING ANTISENSE OLIGONUCLEOTIDE, RESTORES JAG1 EXPRESSION AND IMPROVES LIVER DISEASE IN PRECLINICAL MODELS OF ALAGILLE SYNDROME

Lingdi Zhang[1] Nima Niknejad[1] Jian Li[1] Lansha Peng[1] Surendra Jain[1] Rich Thai[1] Xing Xian Yu[1] Yanfeng Wang[1] Xuehai Liang[2], [1]ARNATAR THERAPEUTICS INC, [2]Arnatar Therapeutics, Inc

Background: Alagille syndrome (ALGS) is a rare autosomal dominant disorder caused primarily by JAG1 haploinsufficiency, resulting in impaired Notch signaling, bile duct paucity, cholestasis, and progressive liver disease. Current therapies are largely supportive and do not address the underlying genetic defect. ART4 is a novel antisense oligonucleotide (ASO) developed using Arnatar's ACT-UP1™ platform to selectively enhance endogenous JAG1 translation. **Methods:** ART4 was evaluated in human, rodent, and non-human primate cells for its ability to increase JAG1 protein expression by Western blot. Pharmacodynamic studies were performed in wild-type mice, and efficacy studies were conducted in Jag1+/– ALGS mouse models following subcutaneous administration. ART4 was tested across multiple dose levels (1, 3, and 6 mg/kg) and dosing paradigms initiated at postnatal day 1, 7, or 14, including repeat dosing. Endpoints included hepatic JAG1 expression, bile duct morphology, liver histopathology, serum biomarkers, necrotic lesion assessment, and body weight. Downstream Notch pathway RNA markers were analyzed by qRT-PCR. Safety and tolerability were evaluated in rodent and non-human primate toxicology studies. **Results:** ART4 increased JAG1 protein expression by 40–80% across multiple cell types, including ALGS patient-derived cells. In vivo, subcutaneous administration increased hepatic Jag1 protein levels by up to 2-fold, with sustained activity observed for up to four weeks after dosing. In Jag1+/– ALGS mice, ART4 treatment improved bile duct development and reduced cholestatic and liver injury biomarkers, including bile acids, total bilirubin, ALT, and AST, across multiple dose levels and dosing schedules. ART4-treated animals also demonstrated improved body weight gain and reduced hepatic necrotic lesions. Downstream Notch pathway RNA markers showed modest and transient activation during the early post-dose period. Similar pharmacologic activity was observed in non-human primates, supporting translational relevance and the potential feasibility of monthly clinical dosing. ART4 was well tolerated in juvenile rodent and non-human primate studies, supporting a projected therapeutic index greater than 30-fold relative to the proposed clinical

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starting dose. **Conclusion:** ART4 is a first-in-class ASO therapeutic designed to selectively enhance endogenous JAG1 translation. In preclinical ALGS models, ART4 restored JAG1 expression, improved bile duct development, and ameliorated liver disease phenotypes, supporting its continued development as a potential disease-modifying therapy for ALGS. Currently, ART4 is being evaluated in ALGS patients in an investigator-initiated clinical trial.
Disclosures: Lingdi Zhang: Nothing to Disclose, Nima Niknejad: Nothing to Disclose, Jian Li: Nothing to Disclose, Lansha Peng: Nothing to Disclose, Surendra Jain: Nothing to Disclose, Rich Thai: Nothing to Disclose, Xing Xian Yu: Nothing to Disclose, Yanfeng Wang: Nothing to Disclose, Xuehai Liang: Nothing to Disclose.

0172 | CLOSING THE MATURATION GAP: MACHINE LEARNING-DRIVEN OPTIMIZATION OF HPSC-DERIVED HEPATOCYTE FUNCTION

Christian Elabd[1] Yaniv Ovadia[1] Sherry Li Zheng[1] Vandya Juneja Shah[1] Frank Li[1], [1]Stately Bio, Inc.

Background: Hepatocyte transplantation is an intriguing clinical approach for treating liver failure, but it is limited by the availability of high-quality primary cells. Differentiating human pluripotent stem cells (hPSCs) into hepatocytes offers a promising solution; however, existing differentiation protocols yield immature, fetal-like cells lacking the function of primary human hepatocytes (PHHs).We developed machine learning (ML) models capable of predicting hepatocyte maturation directly from live, label-free phase contrast images. This enabled non-destructive, real-time monitoring of differentiation status in high-throughput protocol screens to improve hepatocyte maturation. **Methods:** Baseline hPSC differentiation was established using a published protocol. ML models were trained on paired phase contrast and immunofluorescence images of 8 markers related to hepatic metabolism, detoxification, and protein synthesis, collected at various stages of differentiation. These models were then used to predict cell count, marker expression, and functional readouts – directly from phase contrast imaging. Validated ML models were used to score maturation in phenotypic screening experiments, where differentiating hPSC-derived hepatocytes were exposed to small molecules and biologics at varying concentrations, durations, and combinations in iterative cycles to improve maturation. To quantify maturation against a meaningful benchmark, we established a panel of in vitro assays of clinically-relevant liver functions (albumin secretion, ammonia detoxification, coagulation factor secretion, and phase II metabolism) and characterized cellular function head-to-head against PHHs. **Results:** ML predictions from phase contrast images showed strong correlations with immunofluorescence data, achieving < 15% mean absolute error in percent-positivity for each of the 8 markers. Leveraging these predictions for screening, we identified novel differentiation protocols showcasing significantly enhanced maturation. Albumin secretion, urea secretion, factor VII secretion, and UDP-glucuronosyltransferase activity reached median per-cell performance of 201%, 57%, 51%, and 71% that of adult PHH on direct comparison. **Conclusion:** Our approach highlights a significant improvement in hPSC-derived hepatocyte maturation, with immediate clinical implications. It also showcases the utility of ML-driven imaging as a platform technology for optimizing differentiation protocols broadly.
Disclosures: Christian Elabd: Nothing to Disclose, Yaniv Ovadia: Nothing to Disclose, Sherry Li Zheng: Stately Bio: Employee, Vandya Juneja Shah: Nothing to Disclose, Frank Li: Stately Bio, Inc.: Executive role.

0173 | PEMVIDUTIDE TREATMENT REDUCES ALCOHOL INTAKE IN A LEAN GOLDEN SYRIAN HAMSTER MODEL

Maynara Lucca Andrade[1] John Suschak[1] Francois Briand[2] Scot Roberts[3], [1]Altimmune, Inc, [2]Physiogenex, [3]Altimmune, Inc.

Background: There are an estimated 28.1 million patients in the United States with alcohol use disorder (AUD). Left untreated, chronic, excessive alcohol use can result in alcohol-related liver disease (ALD), characterized by liver inflammation and hepatic fibrosis. Approximately 2.0% of AUD patients are treated with medication, and the currently available treatments are limited by undesirable side effects or lack of efficacy. Pemvidutide is a balanced 1: 1 glucagon/GLP-1 dual receptor agonist in development for the treatment of AUD and ALD. Recent data suggests that GLP-1 receptor agonists can reduce alcohol intake, but GLP-1 agonists do not have direct effects on the liver. Preclinical and clinical studies evaluated pemvidutide's effects on hepatic steatosis, inflammation, and fibrosis, potentially important attributes in the treatment of AUD and ALD. Here we present data demonstrating the effects of pemvidutide on alcohol intake in a golden Syrian hamster model of AUD. **Methods:** During a 4-week induction period, golden Syrian hamsters were allowed free access to a

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standard chow diet and either normal tap water or 15% alcohol-enriched water. After a 4-week induction period with free-choice access to alcohol, hamsters were randomized into two treatment groups (n = 12 per group) and were treated once daily with vehicle or pemvidutide 10 nmol/kg subcutaneously for three weeks while maintaining the same diet. Fluid intake was monitored throughout the study. **Results:** Following the free-choice induction period, hamsters showed a strong preference for 15% alcohol-enriched water compared to normal tap water, with a mean percent alcohol intake [mL 15% alcohol-enriched water / (mL 15% alcohol-enriched water + mL tap water)] of 66%. After three weeks of treatment with pemvidutide, a maximal reduction in mean percent alcohol intake of approximately 80% from treatment initiation was achieved. The reduced alcohol intake remained consistent throughout the remainder of the study and coincided with an increase in tap water consumption. Conversely, the mean percent of alcohol intake increased by approximately 5% by the end of the study in vehicle-treated hamsters. Additionally, the mean cumulative 15% alcohol-enriched water intake during the 3-week treatment period was significantly reduced in the pemvidutide group (55.7 mL, $p < 0.0001$) compared to vehicle (143.1 mL). **Conclusion:** Pemvidutide treatment resulted in a rapid reduction in alcohol intake in a golden Syrian hamster model of AUD. These data suggest that pemvidutide may decrease alcohol-craving and alcohol intake, providing evidence for further investigation in a clinical setting.

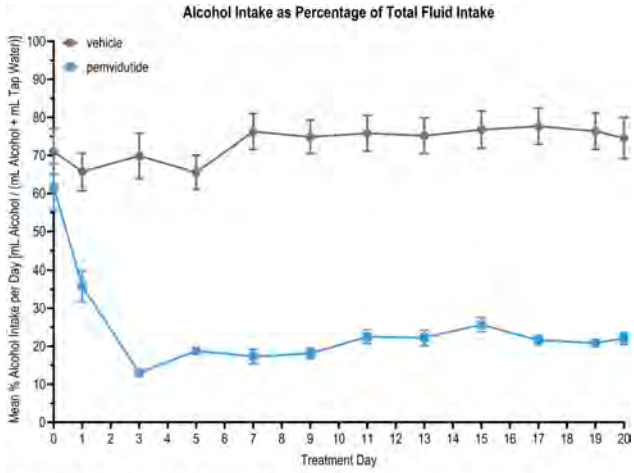


Figure 1. Mean percent alcohol intake during 3-week treatment period.

Disclosures: Maynara Lucca Andrade: Altimmune Inc.: Employee, Altimmune Inc.: Employee, John Suschak: Altimmune: Employee, Francois Briand: Physiogenex: Employee, Physiogenex: Stock – privately held company, Scot Roberts: Nothing to Disclose.

0174 | CIRCULATING PROTEIN BIOMARKERS ASSOCIATED WITH REDUCTIONS IN LIVER FAT AND VISCERAL AND SUBCUTANEOUS ADIPOSITY IN ADULTS WITH OBESITY AND MASLD WITH RETATRUTIDE TREATMENT

YoSon Park[1] Matthew Coghlan[1] James Trevaskis[1] Colm O'Dushlaine[1] Paul Titchenell[1] Melissa Thomas[1], [1]Eli Lilly

Background: Retatrutide (Reta) is a triple GIP/GLP-1/glucagon receptor agonist. In a phase 2 trial, adults with obesity showed dose-dependent weight loss up to 24.2% at 48 weeks with substantial reductions in MRI-assessed liver fat (MHFF, PCBL = -86%), visceral adipose tissue (VAT, PCBL = -44.5%), and abdominal subcutaneous adipose tissue (ASAT, PCBL = -43.5%) with Reta treatment. **Methods:** Fasting serum samples were collected at baseline, 24 weeks, and 48 weeks in the phase 2 MASLD substudy (NCT04881706). Participants with ≥ 10% MHFF at baseline received once-weekly subcutaneous Reta (1/4/8/12 mg; n = 14/16/14/14) or placebo (n = 10) for 48 weeks. Liver fat content was measured by MRI-PDFF, and VAT and ASAT measured by MRI. Circulating proteins were measured via Olink ExploreHT in 229 subjects from the full trial cohort. PCBL of protein abundance was estimated using MMRM at 24 and 48 weeks per treatment group. Spearman correlations and multivariable regression, with FDR corrections for multiple comparisons, were used to estimate proteomics changes with MHFF, ASAT and VAT for pooled Reta-treated completers (n = 58). **Results:** Reta treatment produced dose-dependent changes for biomarkers associated with MASH pathologies, MHFF, ASAT and VAT. Among 38 proteins significantly associated with MHFF PCBL at week 24, MSTN ($\rho = 0.58$, FDR = 9.35×10^{-6}) and TLR3 ($\rho = 0.56$, FDR = 2.89×10^{-5}) were positively correlated, and STC2 ($\rho = -0.50$, FDR = 0.002) was negatively correlated with reductions in MHFF. At 48 weeks, STC2 and TGFBR3 continued to show strong negative correlation with reductions in MHFF ($\rho = -0.45$, FDR = 2.0×10^{-3}; $\rho = -0.49$, FDR = 9.0×10^{-3}). A total of 49 proteins were significantly correlated with VAT reduction at week 48 (FDR < 0.05). LEP ($\rho = 0.70$, FDR = 2.95×10^{-8}), GHR ($\rho = 0.69$, FDR = 6.47×10^{-8}), and MSTN ($\rho = 0.63$, FDR = $2.02 \times^{-6}$) showed positive correlation to VAT reduction. IGFBP1 ($\rho = -0.73$, FDR = $2.06 \times^{-9}$) and COL4A1 ($\rho = -0.69$, FDR = 3.45×10^{-8}) were negatively correlated with VAT reduction. 41 of 49 VAT-correlated proteins also significantly correlated with ASAT changes. Biomarkers independently associated with lobular inflammation (ACY1, TXNRD1 and FCGR3B_FCGR3A) and steatosis (PTGR1 and GUSB) were significantly reduced in Reta 4, 8, and 12 mg

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groups. **Conclusion:** In the MASLD substudy, Reta treatment was associated with significant changes in MHFF, VAT and ASAT. Additionally, changes in MHFF with Reta were associated with changes in proinflammatory biomarkers and multiple intracellular signaling pathways. Changes in proteins correlated with VAT and ASAT changes with Reta were associated with insulin resistance, adipose stores and tissue remodeling. Consistent with our observations from liver fat and body composition, biomarkers independently associated with MASH/MASLD pathology including steatosis, lobular inflammation and fibrosis showed significant reduction at 24 and 48 weeks across all dose groups in the obesity trial subjects.
Disclosures: YoSon Park: Eli Lilly: Employee, Eli Lilly: Stock - publicly traded company, Pfizer: Employee, Pfizer: Stock - publicly traded company, Matthew Coghlan: Nothing to Disclose, James Trevaskis: Nothing to Disclose, Colm O'Dushlaine: Nothing to Disclose, Paul Titchenell: Eli Lilly and Company: Employee, Melissa Thomas: Eli Lilly and Company: Shareholder, Eli Lilly and Company: Employee.

0175 | TARGETING BILE COMPOSITION IN PSC: RTY-406, A DUAL-ACTING ABCB4/BSEP POSITIVE FUNCTIONAL MODULATOR REDUCES DISEASE-RELEVANT MARKERS IN A MOUSE MODEL AND NON-HUMAN PRIMATE

Eric Bell[1] Nathan Fuller[2] Youhwa Jo[1] Jennifer Truong[1] John Miller[1] Pol Boudes[1] Robert Hughes[1], [1]Rectify Pharmaceuticals, [2]Rectify Pharmacueticals

Background: Primary Sclerosing Cholangitis (PSC) is a progressive bile duct disease characterized by changes in bile composition, biliary inflammation, ductular reaction, cholestasis, and fibrosis, with no approved therapy. The canalicular transporters ABCB4/MDR3 and ABCB11/BSEP transport phospholipid (PL) and bile acids (BA) from hepatocytes to bile ducts, respectively, and are important for maintaining bile composition and bile flow. RTY-406 is a first-in-class dual-acting ABCB4/BSEP positive functional modulator (PFM) that increases transporter proteins levels to increase biliary PL secretion and enhance BA efflux. Selected preclinical endpoints included markers with established clinical relevance for PSC. **Methods:** RTY-406 was dosed orally twice daily for 6 weeks in a mouse model of PSC[1] . Serum BA, alkaline phosphatase (ALP), biliary PL, and gallbladder cholesterol crystal formation were monitored for proof of mechanism of increased ABCB4/BSEP action. Liver gene expression, chemokines, and histology were assessed for ductular reaction, cholangitis, and fibrosis endpoints associated with PSC to determine efficacy. RTY-406 was also evaluated in naïve Cynomolgus monkeys dosed orally once daily for 28 days to determine impact on ALP, gamma-glutamyl transferase (GGT) and total cholesterol. **Results:** In the PSC mouse model, RTY-406 increased biliary PL and reduced liver BA levels, demonstrating target modulation. Gallbladder crystal formation, serum BA and ALP were all reduced by RTY-406. Dose-dependent reductions were observed in clinically relevant markers: Cxcl-1 (murine equivalent of IL-8), which is associated with native liver survival in PSC[2], Spp1/osteopontin, a marker correlated with PSC fibrosis severity and transplant-free survival[3], and Timp-1, an ELF test component and validated predictor of transplant-free survival[4]. Histology confirmed reductions in ductular reaction, biliary immune cell infiltration, and fibrosis. In the non-human primate repeat-dose study, RTY-406 reduced total cholesterol, ALP, and GGT, markers consistent with target modulation. **Conclusion:** RTY-406, a first-in-class orally active dual PFM for ABCB4/BSEP, reduced clinically relevant markers of cholestasis, cholangitis, and fibrosis in a PSC mouse model, and demonstrated translational evidence of target modulation and proof of mechanism in non-human primates. These data support the advancement of RTY-406 into the clinic as a disease modifying therapy for PSC and related hepatobiliary diseases.1. Bell et al, Liver Int Comm 2026 DOI: 10.1002/lci2.700402. Vesterhus et al., *J Hepatol* 2017 DOI: 10.1016/j.jhep.2017.01.0193. De Muynck et al., Hepatology 2024 DOI: 10.1097/HEP.0000000000005574. de Vries et al., *Liver Int* 2017 DOI: 10.1111/liv.13402
Disclosures: Eric Bell: Rectify Pharmaceuticals: Employee, Nathan Fuller: Nothing to Disclose, Youhwa Jo: Nothing to Disclose, Jennifer Truong: Nothing to Disclose, John Miller: Rectify Pharmaceuticals, Inc.: Employee, Pol Boudes: Nothing to Disclose, Robert Hughes: Nothing to Disclose.

0176 | SUITABILITY OF INTRAVENOUS ADMINISTRATION OF REGENERATIVE MACROPHAGE THERAPY FOR THE TREATMENT OF DECOMPENSATED CIRRHOSIS

Jessica Llewellyn[1] Joanna Sweetman[1] Philip Starkey Lewis[1] Anna Hoy[1] Lara Campana[1], [1]Resolution Therapeutics Ltd

Background: There are no approved medical therapies for the treatment of decompensated cirrhosis, beyond clinical symptoms management. The sole curative solution is liver transplantation, a surgery hampered by its complexity, shortage of organs, and

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need for lifelong immunosuppression. Regenerative Macrophage Therapy (RMT) has shown significant promise for the treatment of advanced cirrhosis in the clinic, with non-engineered RMT showed statistically significant increase in transplant free survival at 4 years post-treatment. Key to the mechanism of action of these cells are their anti-inflammatory and anti-fibrotic properties. Further development led to engineer IL10 and MMP9 to bolster the anti-inflammatory and anti-fibrotic mechanisms of action (lead candidate RTX001), opening the opportunity to treat patients shortly after an acute decompensation to improve transplant free survival. RMTs need in-depth biodistribution studies post-intravenous administration to support their regulatory journey. In this project, we robustly assess biodistribution of RTX001 and non-engineered RMT with various methods and in distinct models of disease. **Methods:** We utilised non-injured, immunocompromised mouse models to test BD of non-engineered and RTX001 RMT. We then performed BD studies as part of our GLP-Toxicology and in-house safety studies to support Phase 1/2 initiation utilising Alu-qPCR. Further, we developed surrogate mouse (m) RMTs to perform BD studies in immunocompetent backgrounds, including (i) pilot studies using *in vivo* imaging of non-engineered RMT in healthy mice; (ii) in-depth studies of mRTX001 biodistribution in distinct models of liver disease. Finally, surrogate mRTX001 was utilised for BD studies in embryos and placenta. **Results:** Once injected intravenously, RMTs exit the circulation within minutes, and within hours distribute to the lung. RMT then localises to the liver from 24h where, according to PCR-based methods, it remains for up to two weeks. A small signal is detected in spleen and kidney in the early stages. No presence of RMT in organs other than in the liver was found beyond one week. These data confirm that the therapy efficiently reaches its target organ, the liver, after a transient passage in the lung. The well-tolerated nature of RMT upon injection, and the lack of notable histological finding highlights that the passage through the lung is largely safe. Interestingly, surrogate mRTX001 shows a slightly distinct pattern of distribution in CDAA-HFD models in comparison with TAA models. Finally, lack of distribution to the embryo and placenta negated the need for dedicated repro-Tox studies. **Conclusion:** Post-i.v. administration, RMT distributes primarily to the liver, with little persistence in other organs past 72h. Lack of distribution to gonads, embryos and placentas further corroborates its tolerability profile and suitability for treatment of patients with advanced cirrhosis.

Disclosures: Jessica Llewellyn: Nothing to Disclose, Joanna Sweetman: Nothing to Disclose, Philip Starkey Lewis: Nothing to Disclose, Anna Hoy: Nothing to Disclose, Lara Campana: Resolution Therapeutics: Employee.

0177 | THE PD-L1 INTRACELLULAR DOMAIN LIMITS MYELOID CELL ACTIVATION AND FIBROSIS IN METABOLIC-DYSFUNCTION ASSOCIATED STEATOHEPATITIS

Jessica Olivas-Corral[1] Lucy Fry[1] Uma Kantheti[1] David Orlicky[1] Beth Tamburini[1], [1]University of Colorado Anschutz

Background: Programmed death ligand-1 (PD-L1) binds to programmed cell death protein-1 (PD-1) leading to downregulation of the T cell receptor, decreased T cell proliferation and thus dampening of the T cell response. PD-L1 also binds to CD80 in cis on myeloid cells, PD-L1: CD80 interactions prevent PD-L1: PD-1 inhibitory interactions without impeding CD80: CD28 activating interactions. Thus, an intricate interplay between these immune checkpoint activators and inhibitors can tune the magnitude of the immune response. To build upon these findings we recently demonstrated the importance of PD-L1 for DC migration via cis CD80: PD-L1 interactions, rather than PD-1: PD-L1 interactions, in myeloid dendritic cells for initiating signaling through the PD-L1 intracellular domain. Three amino acid residues, TSS, within the PD-L1 intracellular domain have proven critical for cellular movement and responses to innate cytokines. Therefore, we investigated the consequences of mutation of the intracellular PD-L1 TSS residues to alanine in the liver during liver injury. We implemented both a carbon tetrachloride (CCl_4) injury model, and an established high fat and high cholesterol diet-based model of Metabolic-dysfunction Associated Steatohepatitis (MASH). **Methods:** For analysis of the contribution of the PD-L1 intracellular domain to liver injury, WT and *Pdl1*^{CyMt} mice were fed a high fat (40% kcal fat) and high cholesterol (2%) diet (HFHC) for 15 (N = 10 mice/group) or 22 (N = 15 mice/group) weeks or intraperitoneally administered carbon tetrachloride in corn oil for 4 weeks. Samples were taken for histology, immunofluorescence, RNA isolation, and flow cytometry. Mice were perfused after euthanasia and prior to removal of liver tissue for histology and staining. The remainder of the liver tissue was used for flow cytometric analysis of isolated non-parenchymal cells. Bulk RNA sequence analysis was performed on isolated RNA from FACs sorted CD11c +MHCII+ cells from the above indicated mice using an Illumina Nova Seq X platform with paired-end reads (N = 5mice/group). For in vitro evaluation of myeloid cell cytokine secretion, metabolism and function, we used bone marrow derived dendritic cells (BMDC) or macrophages (BMDM) from WT and *Pdl1*^{CyMt} mice, bred in-house. Myeloid cells were activated for 4-48 hours with 200ng/lipopolysaccharide (LPS) at 37C followed by cytokine quantification of the supernatants and metabolite analysis of the cell lysate. **Results:** Here, we demonstrate that *Pdl1*^{CyMt} -expressing mice displayed

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increased liver pathology during diet induced MASH, but not CCl_4, characterized as increased tissue scarring and inflammation scoring compared to WT mice. CD11c +MHCII$^+$ frequencies of CD45+ cells were similar between *Pdl1^{CyMt}* and WT MASH livers as assessed by immunofluorescence and flow cytometric analysis of the immune compartment isolated from liver parenchyma. We observed increased collagen gene *Col1a1*, *Ccr2*, and *Tgfb* transcripts suggesting that in the diet induced MASH model the disease is accelerated and may result from increased myeloid cell recruitment, as shown with CCR2 expression. In late stages of disease (fibrosis), analysis of FACs sorted myeloid cells followed by RNA sequencing of WT and *Pdl1^{CyMt}* livers revealed pathways of myeloid cell activation were upregulated in *Pdl1^{CyMt}* myeloid APCs. Furthermore, glycolysis and redox systems were also upregulated in *Pdl1^{CyMt}* sorted myeloid cells with increased gene expression of *Pgam1* and *Prdx1*. These data were corroborated by metabolite analysis of LPS-stimulated *Pdl1^{CyMt}* compared to WT BMDCs, which showed a reduction of the metabolite a-ketoglutarate and increase in glycerone phosphate. While T cell activation and effector functions were similar between WT and *Pdl1^{CyMt}* mice early on in disease (~15 weeks on diet), T cells displayed increased production of effector cytokines during the fibrotic stage of the disease (22 weeks on diet) as assessed by both immunofluorescence and flow cytometry. **Conclusion:** Together, these data establish the importance of PD-L1 intrinsic signals for myeloid cell activation and regulation of metabolism in a diet-induced murine model of MASH. Our observations demonstrate that the intracellular domain of PD-L1 is important for restraining immunopathology. Overall, these data support a previously unknown mechanism that limits myeloid cell activation and guides downstream T cell responses. Thus, the PD-L1 intracellular domain provides an important immune regulatory mechanism within myeloid cells that limits pathological outcomes in chronic liver disease.

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0178 | GM-CSF TREATMENT PROMOTES IMMUNE REGULATORY MACROPHAGE POLARIZATION AND REDUCES HEPATIC INJURY IN OBSTRUCTIVE CHOLESTASIS

Kathryn Kilpatrick[1] Eric Katz[1] Ioannis Ziogas[2] William Janssen[3] Ronald Sokol[4] Katherine Hisert[3] Sarah Taylor[5], [1]University of Colorado Anschutz Medical Campus, Children's Hospital Colorado, [2]University of Colorado, [3]National Jewish Health, [4]University of Colorado School of Medicine, [5]Children's Hospital Colorado

Background: Obstructive cholangiopathies carry a high burden across the lifespan with limited medical therapies. GM-CSF (granulocyte-macrophage colony-stimulating factor) has been associated with improved outcomes in biliary atresia but its therapeutic role has not been explored. We aimed to define the mechanism by which GM-CSF modulates macrophage function and liver injury in the mouse model of bile duct ligation (BDL). **Methods:** BDL or sham surgery (control) was performed in adult wild-type (WT) C57BL/6 or whole body GM-CSF knock-out (KO) mice. WT BDL mice were treated with daily intra-peritoneal GM-CSF (0.09µg/g) vs saline starting at post-operative day 0 (POD0). POD3 outcome analyses included single-cell RNA-sequencing (scRNA-seq) analysis (KO experiments only), biochemical markers of liver injury, histologic evaluation of inflammatory liver injury (modified Ishak score), and flow cytometry of macrophage subsets. **Results:** Compared to WT BDL mice, GM-CSF KO BDL mice at POD3 exhibited increased alkaline phosphatase, direct bilirubin, and Ishak score (ANOVA $p < 0.05$ for all) with no differences for sham surgery by genotype. Flow cytometry analysis showed reduced frequency of recruited macrophages (RM) in KO BDL ($p = 0.002$, **Fig 1A**) with MHCII+ RM proportion of total macrophages decreased by 41% compared to WT BDL. Tissue-resident macrophages (i.e. Kupffer Cells) were similarly decreased in both BDL groups compared to their sham controls. scRNA-seq analysis of KO BDL RMs showed enrichment for pro-inflammatory pathways while pathways associated with phagocytosis and antigen presentation were decreased. Ligand–receptor analysis (CellChat R package) demonstrated a shift in KO RMs from reparative Mif-Cd74 and Cd45-Mrc1 signaling toward maladaptive Sirp-Cd47 and Tgfb signaling (**Fig 1B-C**). WT BDL mice treated with GM-CSF exhibited reduced Ishak liver injury scores at POD3 and greater proportion of RMs by flow cytometry (**Fig 1A**) with MHCII+ RM proportion of total macrophages increased by 55% compared to WT BDL mice treated with saline. **Conclusion:** Our data support a critical role for GM-CSF in maintaining a coordinated immune response among RMs characterized by active antigen presentation and debris removal (Cd74/ Mrc1 pathways). In contrast, GM-CSF insufficiency may result in impaired Sirp-associated clearance of apoptotic cells by RMs and increased Tgfb signaling. These findings align with the emerging appreciation of an anti-inflammatory role for GM-CSF in specific disease states and highlight it's potential as an immune-regulatory therapy in early stages of obstructive cholestasis.

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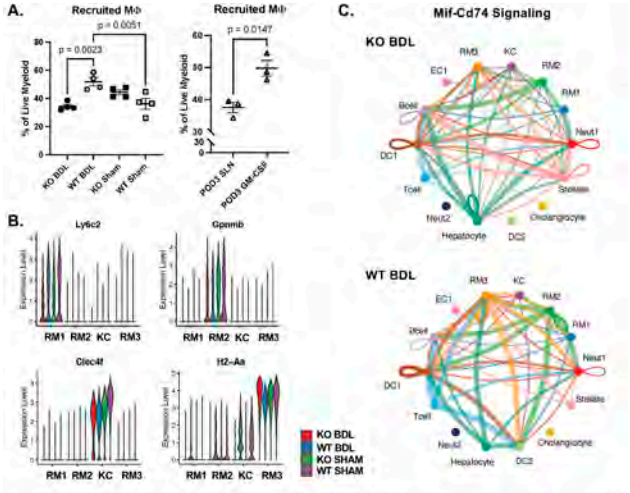


Figure 1. A. Flow cytometry analysis of macrophages (MΦs) demonstrated decreased proportion of recruited macrophages (RM) in GM-CSF knock-out (KO) mice at post-operative day (POD) 3 after bile duct ligation (BDL). GM-CSF treatment in wild-type BDL mice increased the proportion of RMs at POD 3. ANOVA with Šidák correction and two-tailed t-test was used for statistical comparisons. **B.** scRNA-seq analysis identified 3 subsets of RMs of which RM3 exhibited high expression for MHCII genes. **C.** CellChat ligand-receptor analysis identified increased MΦ migration inhibitory factor (Mif) signaling with Cd47 (MHCII invariant chain) in WT BDL mice particularly in RM3. RM - recruited MΦ, KC - Kupffer cell, Neut - neutrophil, DC - dendritic cell, EC - endothelial cell.

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0179 | FROM INFLAMMATION TO SURVEILLANCE: INTRAHEPATIC NK CELL REMODELLING WITH TOBEVIBART AND ELEBSIRAN IN CHRONIC HEPATITIS D - A TRANSLATIONAL SUB-STUDY OF THE SOLSTICE TRIAL

Upkar Gill[1] Jantarika Arora[1] Chanelle Fernandes[1] Akhilesh Mulay[1] Gerard Hernandez-Mir[1] Andrew Watson[1] Almuthana Mohamed[1] Apostolos Koffas[1] Michael Chattergoon[2] Patrick Kennedy[1], [1]Blizard Institute, Barts and The London, School of Medicine, QMUL, London, [2]Michael Chattergoon

Background: Chronic HDV infection is the most severe form of viral hepatitis. Although immune-mediated, antigen-specific adaptive responses are weak, placing NK cells at the centre of immunopathogenesis and viral control. In chronic HDV, NK cells are functionally compromised, skewed towards CD56bright subsets producing excess IFNγ and TNFα. Despite evidence that NK cells eliminate HDV-infected hepatocytes via a TRAIL/TRAIL-R2 axis and that bulevirtide restores NK immune checkpoint expression (TIGIT), the intrahepatic NK transcriptional landscape and its remodelling by HBsAg-targeting therapy remains uncharacterised. **Methods:** Five chronic HDV patients (n = 3 tobevibart monotherapy; n = 2 tobevibart + elebsiran) underwent paired PBMC and fine-needle aspiration (FNA) liver sampling at baseline and 6 months within the SOLSTICE study. Median baseline HDV RNA was 26,273 IU/mL (range 599–4,640,855) and HBsAg 4,780 IU/mL (range 1,504–20,928). Single-cell RNA sequencing of 197,191 cells identified 7,518 NK cells (FNA: 3,263; PBMC: 4,255), annotated into seven subsets. Differential gene expression (DEG) (FindMarkers; $|avg\_log_2FC| \geq 0.5$, $p < 0.05$) and KEGG pathway enrichment (gprofiler2) were performed per subset, pre- vs. post-treatment. **Results:** At 6 months, all patients achieved undetectable HDV RNA, with mean HBsAg decline of 2.91 log_{10}IU/mL (range 2.01–3.99). Pre-treatment, intrahepatic NK cells showed broad metabolic activation (ACADM, NAMPT, CPT1A) and cytokine-receptor upregulation (XCL1, FASLG, IL2RB), with IFN-activated NK cells dominated by IRF9 and OAS1. Following therapy, adaptive NK cells increased towards a surveillance phenotype (NFKB1, STAT2, KLRB1, FOXO1, CXCR6). IFN-activated NK cells showed reduced interferon dominance with post-treatment IL10RA and MTOR, suggesting immunomodulatory reprogramming. Proliferating NK cells expanded, upregulating cell cycle (CDK1, BIRC5) and PI3K-Akt genes (MTOR, FOXO3), indicating intrahepatic renewal. CXCR4 was upregulated across FNA NK subsets. Peripheral blood showed limited remodelling, with IFIT1 as the leading DEG. **Conclusion:** HBsAg-targeting therapy induces coordinated intrahepatic NK cell remodelling in chronic HDV, largely absent from peripheral blood. The shift from IFN-driven inflammation towards adaptive NK enrichment, proliferative renewal, and immunomodulatory reprogramming suggests a transition to a more controlled intrahepatic immune state, providing novel mechanistic insight into regimens effectively targeting HBsAg.

Disclosures: Upkar Gill: Nothing to Disclose, Jantarika Arora: Nothing to Disclose, Chanelle Fernandes: Nothing to Disclose, Akhilesh Mulay: Nothing to Disclose, Gerard Hernandez-Mir: Nothing to Disclose, Andrew Watson: Nothing to Disclose, Almuthana Mohamed: Nothing to Disclose, Apostolos Koffas: Gilead Sciences UK&I: Advisor, Michael Chattergoon:

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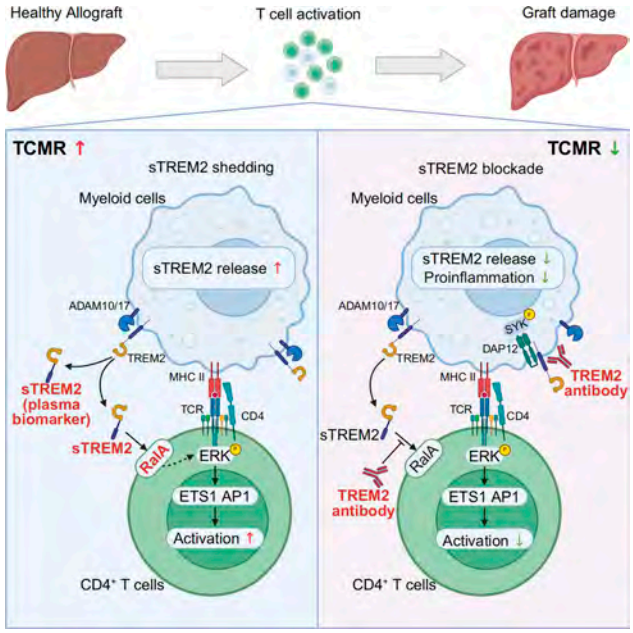
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Nothing to Disclose, Patrick Kennedy: Nothing to Disclose.

0180 | STREM2 ENHANCES CD4+ T CELL ACTIVATION AND DRIVES T CELL-MEDIATED REJECTION FOLLOWING LIVER TRANSPLANTATION

Aiwei Zhou[1] Qi Pan[1] Hongyuan Liu[1] Bingran Wang[1] Yongbo Liu[1] Yuan Liu[1] Qiang Xia[1], [1]Renji Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Background: T cell-mediated rejection (TCMR) remains a major clinical challenge following liver transplantation (LT), lacking reliable non-invasive biomarkers and mechanistic clarity. This study investigated soluble triggering receptor expressed on myeloid cells 2 (sTREM2) as both a diagnostic biomarker and pathogenic driver of TCMR. **Methods:** We enrolled 63 pediatric LT recipients classified by biopsy as normal (n = 38), TCMR (n = 17), or antibody-mediated rejection (AMR, n = 8). Plasma sTREM2 was measured by ELISA and evaluated for diagnostic performance. Single-cell RNA sequencing (scRNA-seq) was performed on liver allografts and peripheral blood to identify cellular sources of TREM2. A fully MHC-mismatched murine LT model (C57BL/6→C3H/He) evaluated sTREM2 function in vivo. In vitro, CD4+ T cells were activated with anti-CD3/CD28 in the presence or absence of sTREM2, and the status of activation, proliferation, and signaling were assessed. Affinity purification-mass spectrometry (AP-MS) and Co-IP mapped the sTREM2 receptor. A TREM2-specific monoclonal antibody (4D9) was evaluated for therapeutic potential. **Results:** Plasma sTREM2 was significantly elevated in TCMR patients compared to normal allografts (AUROC = 0.7477, p = 0.0036), with specificity against AMR. scRNA-seq revealed that TREM2 upregulation was predominantly localized to intrahepatic macrophages. In the murine LT model, sTREM2 administration significantly exacerbated TCMR severity and enhanced CD4+ T cell effector function. Mechanistically, sTREM2 directly promoted CD4+ T cell activation, evidenced by upregulated activation marker (CD69 and CD25) and enhanced ERK-MAPK signaling. RNA-seq analysis showed that sTREM2 upregulated T cell activation genes (IL2, CXCR3, CCR4, and ETS1), and GSEA revealed significant enrichment of the AP-1 signaling pathway. AP-MS and Co-IP identified RalA as the sTREM2-interacting protein and RalA knockdown abolished sTREM2-enhanced ERK phosphorylation downstream of the T cell receptor (TCR). Therapeutically, a TREM2-specific antibody (4D9) significantly ameliorated TCMR in LT mice by inhibiting sTREM2 shedding, neutralizing its pathogenic function and enhancing TREM2-dependent anti-inflammatory signaling. **Conclusion:** sTREM2 is a non-invasive biomarker and pathogenic mediator of TCMR. The sTREM2-RalA-ERK axis defines a myeloid-T cell crosstalk mechanism driving alloreactive CD4+ T cell activation.Targeting TREM2 with therapeutic antibodies may offer a precision immunotherapy strategy for TCMR management.



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0181 | T CELL RECEPTOR SEQUENCING REVEALS A UNIQUE T CELL IMMUNE REPERTOIRE SHARED BETWEEN BLOOD AND LIVER IN DECOMPENSATED CIRRHOSIS

Elsa Solà[1] Pari Waghela[2] Chunlin Wang[3] Ana Jimena Pavlovitch-Bedzyk[3] Deeksha Lahori[3] Jie Zhang[3] Adrià Juanola[4] Allison Kwong[5] Natalie Torok[6] Paul Kwo[5] Pere Gines[7] Carlos Esquivel[5] Mark Davis[3], [1]Division of Gastroenterology and Hepatology, Stanford University, [2]Department of Abdominal Transplantation, Stanford University, [3]Institute for Immunity, Transplantation and Infection, Stanford University, [4]Hospital Clinic i Provincial de Barcelona, [5]Stanford University Medical Center, [6]Division of Gastroenterology and Hepatoloy, Stanford University, [7]Liver Unit, Hospital Clinic Barcelona

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Background: T cell activation contributes to cirrhosis-associated immune dysfunction. Data regarding the specific drivers of T cell activation remain limited. We aimed to investigate the T cell receptor (TCR) repertoire in cirrhosis to determine whether there are shared specificities and to identify potential differences between circulating blood and intrahepatic T cells. **Methods:** Peripheral blood mononuclear cells and intrahepatic lymphocytes were isolated from paired blood and liver tissue samples from patients with decompensated cirrhosis undergoing liver transplantation. We performed combined single-cell and bulk TCR sequencing. TCR clustering was performed using the GLIPH2 algorithm, which clusters together TCRs with a high probability of sharing antigen specificities. To determine whether TCR clusters are unique to cirrhosis or common in the general population, we combined the cirrhosis data with data from healthy controls and public sequences with known antigen specificities (i.e., CMV, EBV). **Results:** We obtained 14,786 unique TCR sequences derived from paired liver and blood samples from patients with alcohol-related decompensated cirrhosis (n = 3). Cirrhosis data was combined with 9,970 TCR sequences from healthy controls and controls with known antigen specificities. Clustering analysis revealed 2,278 clusters including only sequences from patients with cirrhosis out of a total of 16,876 clusters. Interestingly, 704 out of the 2,278 cirrhosis-specific clusters included TCR sequences derived from all 3 patients, suggesting that T cells from different patients with cirrhosis respond to the same antigens. Notably, among the cirrhosis-specific clusters we identified 11 clusters that included TCR sequences present in both blood and liver across all 3 patients, suggesting that T cell clones with same antigen specificity are shared between different patients with cirrhosis and present in both blood and liver. Comparison with public data showed that the sequences from these 11 clusters do not present any overlap with sequences from healthy controls with known antigen specificities and therefore do not correspond to T cells responding to common antigens seen in the general population. **Conclusion:** Our findings demonstrate a distinct T cell repertoire in patients with decompensated cirrhosis. The same T cell clones are present in the peripheral blood and the intrahepatic compartment. The presence of shared clones with no overlap with healthy individuals suggests that liver-disease specific antigens drive T cell activation in cirrhosis and shape the immune response both at the peripheral blood and the intrahepatic compartments. This offers new insights into the drivers of cirrhosis-associated immune dysfunction and helps investigate novel preventive or therapeutic approaches.

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0182 | SCHEDULED PREOPERATIVE EXERCISE THERAPY MODULATES CIRCADIAN-DEPENDENT ITACONATE METABOLISM IN KUPFFER CELLS TO PROTECT AGAINST LIVER ISCHEMIA-REPERFUSION INJURY

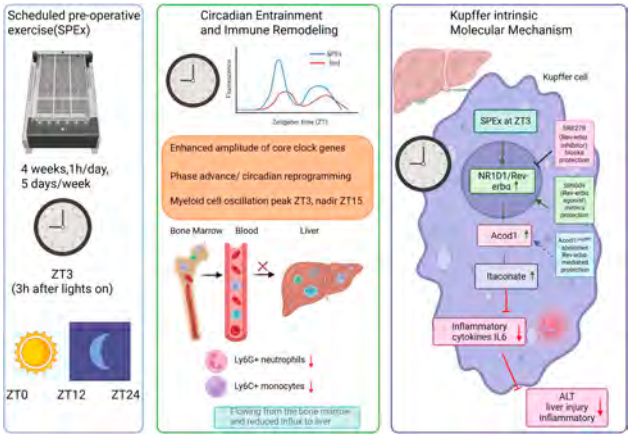
Ti Yang[1] Yi Jiang[1] Jiannan Hu[1] Xingping Huang[1] Grace Wu[1] Ameilia Solan[1] Meihong Deng[1] Hai Huang[2], [1]Feinstein Institute for Medical Research, [2]Feinstein Institutes for Medical Research

Background: Hepatic ischemia/reperfusion (I/R) injury remains a major cause of morbidity following liver surgeries and transplantation, driven by immune and metabolic dysregulation. We recently demonstrated that pre-operative exercise therapy (PEx) triggers anti-inflammatory trained immunity in Kupffer cells (KCs) and reshapes bone marrow hematopoiesis. Given that exercise is a potent modulator of circadian rhythms, and that nuclear receptor NR subfamily 1 group D member 1 (NR1D1 gene, encodes Rev-erbα) regulates both circadian biology and inflammation, we hypothesized that scheduled PEx confers hepatic protection by entraining circadian-dependent immunometabolic reprogramming in Kupffer cells. **Methods:** Circadian profiling of bone marrow, blood, liver tissue, and nonparenchymal cells was performed across

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multiple time points (ZT3, ZT6, ZT9, ZT12, ZT15, and ZT21) after exercise at ZT3. 70% patrial hepatic I/R was induced at ZT3. Pharmacologic modulation of Rev-erbα was achieved using the antagonist SR8278 and agonist SR9009. Hepatic damage, inflammation, circadian genes, and immune cell subpopulations were assessed. KC-specific metabolic responses were evaluated by qPCR and immunoblotting following *in vivo* and *in vitro* manipulation, and Kupffer cell-specific ACOD1 knockout (*Acod1*$^{\Delta Kupffer}$) mice were used to assess functional dependency on itaconate metabolism. **Results:** Myeloid cell populations exhibited circadian oscillations, peaking at ZT3 and reaching a nadir at ZT15. SPEx significantly reduced Ly6C^{high} monocytes and Ly6G^{+} neutrophils in bone marrow at ZT3 and in the liver at ZT12, indicating time-dependent suppression of inflammatory cell mobilization. PEx enhanced the amplitude of core clock gene expression and alter the phase or period to advance. Notably, *Nr1d1* expression was significantly upregulated in KCs and liver tissue at ZT3 following PEx. Pharmacologic inhibition of Rev-erbα abrogated PEx-mediated hepatoprotection, as evidenced by elevated ALT and IL-6 levels and exacerbated liver injury, whereas Rev-erbα activation recapitulated protective effects. Mechanistically, Rev-erbα modulated expression of *Acod1*, a key enzyme that generates the anti-inflammatory metabolite itaconate, thereby linking circadian signaling to KC immunometabolism. Importantly, the protective effects of Rev-erbα activation were lost in *Acod1*$^{\Delta Kupffer}$ mice, demonstrating a KC-intrinsic NR1D1-ACOD1 axis. **Conclusion:** In summary, our findings provide compelling evidence that scheduled preoperative exercise therapy entrains circadian immunity to protect against liver I/R injury through an Rev-erbα -ACOD1-itaconate metabolic axis in Kupffer cells. These findings establish a mechanistic link between circadian regulation, exercise, and immunometabolic reprogramming, and suggest that targeting this pathway may enable chronotherapy-based strategies for perioperative liver protection.



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0183 | STATINS BEYOND CHOLESTEROL: REDUCED DECOMPENSATION AND OVERALL MORTALITY IN 18,560 ADULTS WITH COMPENSATED CIRRHOSIS

Monica Tincopa[1] Xinlian Zhang[2] Lars Eckmann[2] Rohit Loomba[1] Bernd Schnabl[2], [1]University of California, San Diego, [2]UCSD

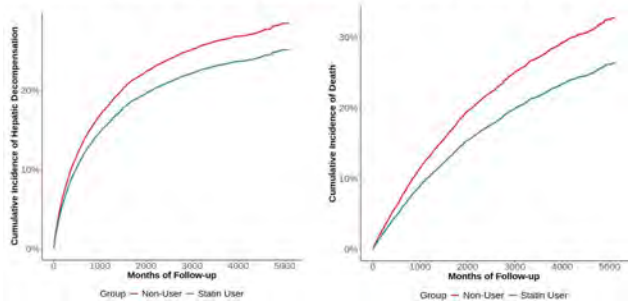
Background: Statins have demonstrated pleiotropic antinflammatory and antifibrotic properties, making them of particular interest in cirrhosis. However, large-scale data evaluating statin therapy in compensated cirrhosis are lacking. The aim of this study was to assess the association of between statin use and risk of hepatic decompensation overall mortality in a large, population-based, multi-site cohort of adults with compensated cirrhosis. **Methods:** Using the University of California (UC) Health Data Warehouse comprised of patients seen at UC health facilities 2012-present, we identified patients with cirrhosis and no prior history of hepatic decompensation using validated ICD-10 algorithms. A new-user design was employed, requiring ≥90-day period following cirrhosis diagnosis with no statin exposure or outcome attainment. Statin users were defined as those with a new statin prescription after cirrhosis diagnosis with continuous statin exposure ≥ 90 days. The primary outcome was composite hepatic decompensation [ascites, SBP, variceal bleeding, hepatic encephalopathy, or hepatorenal syndrome (HRS)] and the secondary outcome was overall mortality. Liver transplant and death were considered competing events. Inverse probability of treatment weighting (IPTW)-adjusted Cox proportional hazards regression models were used to estimate cumulative incidence and adjusted subhazard ratios (aSHR). Propensity score calculation included demographics, alcohol and tobacco use, cirrhosis etiology, medical comorbidities (diabetes, CKD, CAD, dyslipidemia, malignancy), and labs (MELD, platelets, AST, ALT). **Results:** A total of 18560 subjects were included in the analysis. The median age of the overall cohort was 58 at diagnosis, 44% female and 51% White with a median follow-up time of 7.9 years after diagnosis of cirrhosis. Cumulative incidence of decompensation and mortality was 18.2% and 14.6% in the statin and 22.7% and 21.2% in the non-statin users over the entire study period. After adjusting for baseline (index date) confounding via IPTW and accounting for competing risks, statin initiation was associated with a statistically

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significant reduction in the risk of composite hepatic decompensation (aSHR = 0.86, 95%CI: 0.78-0.96, p = 0.008) and overall mortality (aSHR = 0.77, 95% CI: 0.68–0.87, p < 0.001). **Conclusion:** In a large population-based IPTW-adjusted cohort of adults with compensated cirrhosis, statin therapy was associated with significantly lower rates of hepatic decompensation and overall mortality over 8 years of follow-up. These data suggest potential preventive benefit of statin therapy in adults with compensated cirrhosis that should be further assessed in randomized clinical trials.

Figure. Cumulative Incidence of A) Hepatic Decompensation and B) Overall Mortality by Statin use



Disclosures: Monica Tincopa: Nothing to Disclose, Nothing to Disclose, Xinlian Zhang: Nothing to Disclose, Lars Eckmann: Nothing to Disclose, Rohit Loomba: Eli Lilly and Company: Consultant, 89bio: Consultant, Aardvark Therapeutics: Consultant, Altimmune: Consultant, Alnylam/Regeneron: Consultant, Amgen: Consultant, Arrowhead Pharmaceuticals: Consultant, AstraZeneca: Consultant, Bristol Myers Squibb: Consultant, CohBar: Consultant, Eli Lilly: Consultant, Galmed Pharmaceuticals: Consultant, Gilead: Consultant, Glympse Bio: Consultant, Hightide: Consultant, Inipharma: Consultant, Intercept: Consultant, Inventiva: Consultant, Ionis: Consultant, Janssen, Inc.: Consultant, Madrigal Pharmaceuticals: Consultant, Merck, Metacrine, Inc.: Consultant, NGM Biopharmaceuticals: Consultant, Novartis: Consultant, Novo Nordisk: Consultant, Pfizer: Consultant, Sagimet Biosciences: Consultant, Terns Pharmaceuticals: Consultant, Theratechnologies and Viking Therapeutics: Consultant, 89bio: Stock options, Sagimet Biosciences: Stock options, Arrowhead Pharmaceuticals: Research grant, AstraZeneca: Research grant, Boehringer Ingelheim: Research grant, Bristol Myers Squibb: Research grant, Eli Lilly: Research grant, Galectin Therapeutics: Research grant, Galmed Pharmaceuticals: Research grant, Gilead: Research grant, Hanmi: Research grant, Intercept: Research grant, Inventiva: Research grant, Ionis: Research grant, Janssen, Inc.: Research grant, Madrigal Pharmaceuticals: Research grant, Merck: Research grant, NGM Biopharmaceuticals: Research grant, Novo Nordisk: Research grant, Pfizer: Research grant, Sonic Incytes: Research grant, Terns Pharmaceuticals: Research grant, LipoNexus, Inc.: Co-founder, Cascade Pharmaceuticals: Consultant, Eccogene: Consultant, HeptaBio: Consultant, Metavi: Consultant, Neurobo: Consultant, Novo Nordisk: Consultant, Sourcebio: Consultant, Roche: Consultant, Roche: Consultant, Takeda: Consultant, GSK: Grant/Research Support, Roche: Grant/Research Support, TensorBio: Grant/Research Support, Aarrowhead Pharmaceuticals: Consultant, Boehringer-Ingelheim: Consultant, Altimmune: Grant/Research Support, Eccogene: Grant/Research Support, Heptabio: Grant/Research Support, 89 bio: Grant/Research Support, Takeda: Grant/Research Support, Bernd Schnabl: Nothing to Disclose.

0184 | TOWARDS A DIGITAL-TWIN-INSPIRED FRAMEWORK FOR PERSONALIZED 5-YEAR LIVER DISEASE RISK PREDICTION AND PREVENTION IN INDIVIDUALS WITH ELEVATED FIB-4

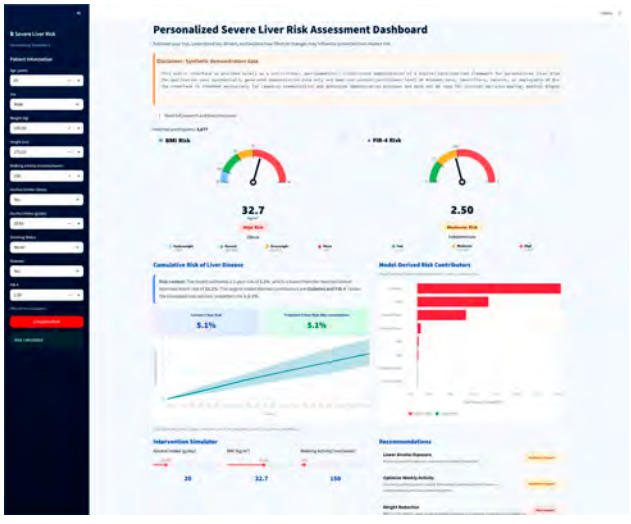
Thriveni Basavanapura Raju[1] Benjamin Laevens[2] Corinna Meeβen[2] Tobias Seibel[1] Jan Clusmann[3] Saleh Alqahtani[4] Kai Markus Schneider[5] Sandra Geisler[6] Carolin Schneider[1], [1]University Hospital RWTH Aachen, Department of Internal Medicine III, Aachen, Germany, [2]University Hospital RWTH Aachen, Department of Internal Medicine III, Gastroenterology, Germany, [3]Else Kroener Fresenius Center for Digital Health, Medical Faculty Carl Gustav Carus, Dresden, Germany, [4]King Faisal Hospital and Research Centre Riyadh, Saudi Arabia, [5]University Hospital Carl Gustav Carus Dresden, Department of Medicine1, Dresden, Germany, [6]Data Stream Management and Analysis, RWTH Aachen University, Aachen, Germany

Background: Individuals with elevated FIB-4 scores are at increased risk for major adverse liver outcomes (MALO), yet current risk stratification tools remain static and provide limited support for individualized prevention. We developed a digital-twin-inspired prototype with an interactive website that identifies clinically similar individuals, estimates individualized 5-year MALO risk and explores scenario-based risk changes under alternative lifestyle profiles. **Methods:** Baseline UK Biobank individuals with elevated fibrosis risk (FIB-4 $\geq$ 1.3) (n = 137709) were included. The outcome was incident MALO, defined using linked hospital episode statistics (HESIN) records and ICD-10 codes: K74, C22, K72, K76.6, I85, R18. Clinically similar individuals were identified by shared sex, age group ($\geq$ 50 years) and same BMI group (BMI $\geq$ 18.5), while demographic, clinical, biochemical, and lifestyle predictors were incorporated to predict MALO risk. A 5-year risk was estimated using a penalized Cox proportional hazards

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model. Risk estimation was restricted to clinically similar subgroups with at least 150 observed MALO events, which was chosen to reduce sparse-data bias and unstable subgroup-specific risk estimates, corresponding to approximately ≥10 outcome events per effective predictor parameter, while penalization and bootstrap resampling were used to further mitigate overfitting. Scenario-based risk estimates were generated by modifying selected potentially modifiable predictors, including alcohol use, BMI, and physical activity, while keeping all other covariates constant and applying the coefficients from the multivariable penalized Cox model within the same matched risk set. Internal validation of the model was performed using bootstrap resampling (1000 iterations), where the model was repeatedly trained and tested using randomly sampled participants from the cohort. **Results:** Among 137709 UK Biobank participants with elevated FIB-4, 1760 developed incident MALO over a median follow-up of 8.7 years. Internal validation of the model demonstrated good discrimination in identifying individuals at higher risk of developing MALO with those at lower risk, with an optimism-corrected C-index of 0.70 (95% CI 0.69-0.71) and a 5-year AUROC of 0.73 (95% CI 0.70-0.76). Calibration was acceptable, with a calibration slope of 0.87 and calibration-in-the-large of 0.03. An interactive web-based prototype interface, accessible via https: //liver-digital-twin-prototype.streamlit.app/, was developed for demonstration using synthetic data designed to reflect the training cohort without including participant-level UKB records. No UK Biobank data can be accessed, calculated or displayed through the public interface. **Conclusion:** The framework provides a foundation for personalized liver risk assessment. Current limitations include the use of baseline-only covariates without longitudinal updating.



Disclosures: Thriveni Basavanapura Raju: Nothing to Disclose, Benjamin Laevens: Nothing to Disclose, Corinna Meeßen: Nothing to Disclose, Tobias Seibel: Nothing to Disclose, Jan Clusmann: Nothing to Disclose, Saleh Alqahtani: Nothing to Disclose, Kai Markus Schneider: IPSEN: Advisor, AstraZeneca: Advisor, Abbvie: Speaking and Teaching, Sandra Geisler: Nothing to Disclose, Carolin Schneider: Nothing to Disclose.

0185 | COMBINING LIVER STIFFNESS WITH FIB-4 CATEGORIES TO STRATIFY RISK OF MAJOR ADVERSE LIVER OUTCOMES ACROSS MASLD, METALD, ALD AND CURED HCV

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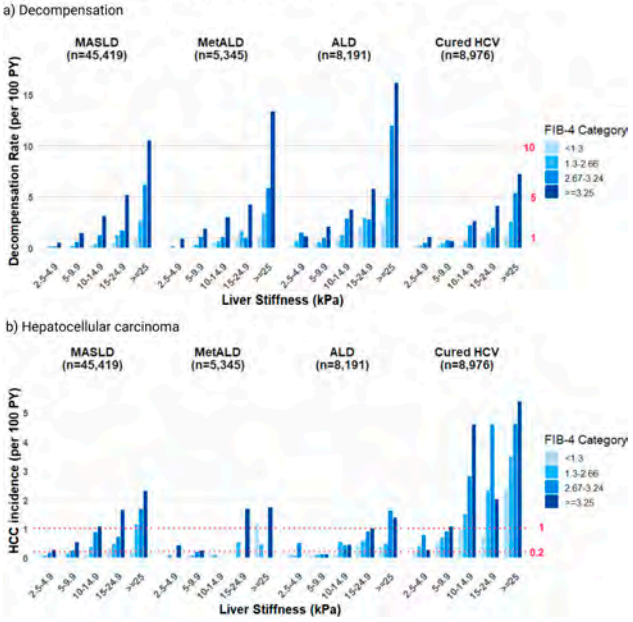
Background: The prognostic value of jointly interpreting liver stiffness (LS) and Fibrosis-4 (FIB-4) across chronic liver diseases is uncertain. We evaluated how the risk of hepatic decompensation, hepatocellular carcinoma (HCC), and mortality vary across combined LS/FIB-4 categories in metabolic dysfunction-associated steatotic liver disease (MASLD), metabolic and alcohol-associated liver disease (MetALD), alcohol-associated liver disease (ALD) and cured hepatitis C virus (HCV). **Methods:** We identified 67,931 patients (67% MASLD, 8% MetALD, 12% ALD, and 13% cured HCV) who underwent LS measurement by transient elastography from 2014-2024, excluding those with prior decompensation, HCC, or liver transplantation. Patients were classified into five LS strata (2.5–4.9, 5–9.9, 10–14.9, 15–24.9, ≥25 kPa) and further subclassified into four FIB-4 strata (<1.3, 1.3–2.66, 2.67–3.24, ≥3.25). Follow-up extended from date of LS measurement through 9/2025 for hepatic decompensation, HCC, and all-cause mortality. **Results:** Median age was 61 years and 92% were male. Across all etiologies, incidence of hepatic decompensation, HCC, and mortality increased stepwise with higher LS and was further stratified by FIB-4

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in a near-monotonic dose–response pattern (Figure). In patients with MASLD, HCC incidence ranged more than 100-fold from 0.02 to 2.3 per 100 person-years (PYs) and risk of decompensation from 0.06 to 10.5 per 100 PYs across LS/FIB-4 strata. Marked heterogeneity in risk, often exceeding ten-fold, was observed within LS strata by FIB-4 (e.g., decompensation in MASLD at LS 15–24.9 kPa was 0.45 per 100 PYs for FIB-4 <1.3 vs. 5.13 per 100 PYs for FIB-4 ≥ 3.25). All-cause mortality followed a similar stepwise pattern, ranging from 0.7 to 11.4 per 100 PYs in MASLD across LS/FIB-4 strata, with comparable gradients observed across other etiologies. For decompensation, MetALD consistently demonstrated intermediate risk between MASLD and ALD (e.g., at LS ≥ 25 kPa and FIB-4 ≥ 3.25: 10.5, 13.3, and 16.1 per 100 PYs, respectively). MetALD also exhibited the highest mortality at the highest LS/FIB-4 stratum (14.2 per 100 PYs vs. 11.4 for MASLD and 11.6 for ALD). At comparable LS/FIB-4 levels, cured HCV consistently exhibited the highest HCC risk (up to 5.38 per 100 PYs), whereas ALD showed the highest risk of hepatic decompensation (up to 16.1 per 100 PYs). **Conclusion:** Combined LS/FIB-4 categorization provides a pragmatic framework for stratifying risks of decompensation, HCC, and death. Distinct etiology-specific patterns—highest HCC risk in cured HCV and highest decompensation risk in ALD—highlight the value of interpreting LS and FIB-4 by liver disease etiology.

Figure. Incidence of (a) hepatocellular carcinoma and (b) hepatic decompensation across liver stiffness and FIB-4 strata, stratified by liver disease etiology



Disclosures: Philip Vutien: Nothing to Disclose, Nicole Kim: Madrigal: Grant/Research Support, Madrigal Pharmaceuticals: Clinical trial (to institution), Madrigal: Grant/Research Support, Abbey Barnard Giustini: Nothing to Disclose, Andrew Moon: TARGET RWE: Consultant, DCN Diagnostics: Grant/Research Support, Intercept Pharmaceuticals: DSMB, IDEOlogy: Consultant, Eisai: Consultant, AstraZeneca: Consultant, Sirtex: Consultant, Madrigal: Grant/Research Support, Chunnan Hsu: Nothing to Disclose, Kay Johnson: Nothing to Disclose, Trang VoPham: Nothing to Disclose, Bret Mecham: Nothing to Disclose, Vyshnika Sriskantharajah: Nothing to Disclose, George Ioannou: Nothing to Disclose.

★ 0186 | PARADOXICALLY ELEVATED SLEEP-STAGE HEART RATE VARIABILITY IS ASSOCIATED WITH COGNITIVE IMPAIRMENT IN CIRRHOSIS INDEPENDENT OF LIVER DISEASE SEVERITY

Adam Buckholz[1] Himel Mallick[2] Alec Chang[2] Avesh Thuluvath[3] Lara Phipps[2] Edwin Kan[4] Ana Krieger[2] Robert Brown[5], [1]New York Presbyterian Hospital Program, [2]NewYork-Presbyterian/Weill Cornell Medical Center, [3]Columbia University Irving Medical Center, [4]Cornell University, [5]Weill Cornell Medicine

Background: Autonomic dysfunction and sleep disturbance are common in cirrhosis and hepatic encephalopathy (HE), yet biomarkers capable of identifying covert cognitive impairment remain limited. Heart rate variability (HRV), a noninvasive marker of autonomic function associated with cirrhosis severity and outcomes, may be particularly informative during sleep because it can be measured passively and longitudinally under stable physiologic conditions. We evaluated whether nocturnal HRV measured using wearable devices discriminates cognitive status in patients with cirrhosis. **Methods:** We analyzed longitudinal nocturnal HRV recordings from 102 patients with cirrhosis wearing a commercial wearable device. Participants included had ≥ 14 valid wear days with $\geq 80\%$ wear time and analyzable sleep-stage HRV. HRV was measured as root mean square of successive differences (RMSSD, ms) across 30-second epochs of scored sleep and averaged across overall nocturnal sleep as well as deep, light, and REM sleep stages. Cognitive status was assessed using the Psychometric Hepatic Encephalopathy Score (PHES), with covert HE (CHE) defined as PHES $\leq$ -4. Mixed-effects models with subject-level random intercepts evaluated associations between HRV and both continuous PHES performance and CHE status. Adjusted models included age, MELD 3.0, and beta-blocker use. **Results:** Contrary to the expected reduction in HRV observed with worsening cirrhosis severity, cognitive impairment was associated with paradoxically elevated nocturnal RMSSD across sleep stages. In the full cohort, CHE patients demonstrated significantly higher adjusted RMSSD compared to non-CHE patients during overall sleep (+5.50 ms, $p = 0.014$), deep sleep (+5.16 ms,

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p = 0.030), light sleep (+5.83 ms, p = 0.010), and REM sleep (+5.65 ms, p = 0.013). Among HE-treated patients, associations were most pronounced during REM sleep, where CHE was associated with 7.28 ms higher adjusted RMSSD (p = 0.023). Importantly, similar findings persisted among untreated patients without prior overt HE, where untreated CHE was associated with significantly higher nocturnal RMSSD across overall, deep, and light sleep stages after adjustment for age, with similar effect sizes observed following additional adjustment for MELD 3.0 and beta-blocker use (overall +7.44 ms, p = 0.045; deep +8.06 ms, p = 0.038; light +8.13 ms, p = 0.029). **Conclusion:** Paradoxically elevated nocturnal HRV was observed in cognitive impairment across sleep stages independent of age, beta-blocker use, and partially independent of liver disease severity. The consistency of these findings, including among untreated patients without prior overt HE suggests that altered nocturnal autonomic regulation may represent an early physiologic manifestation of HE. Wearable-derived sleep-stage HRV may represent a novel digital biomarker for longitudinal assessment of covert cognitive dysfunction in cirrhosis.

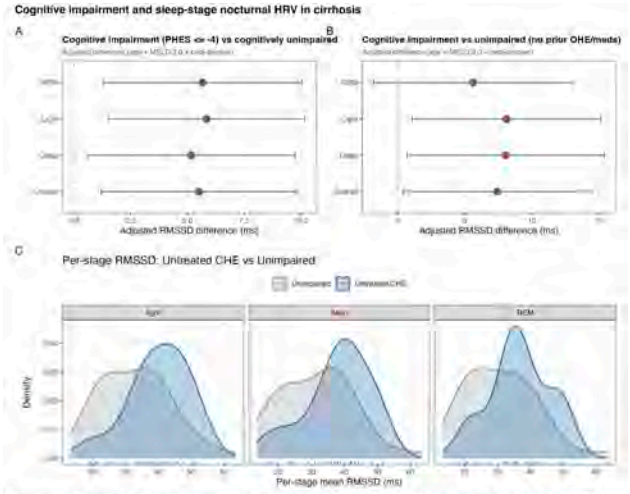


Figure 1. Cognitive impairment and sleep-stage nocturnal heart rate variability (HRV) in cirrhosis. Cognitive status was defined by the Psychometric Hepatic Encephalopathy Score (PHES), with cognitive impairment defined as PHES ≤ -4. HRV was quantified as the root mean square of successive differences (RMSSD, ms) from Oura ring inter-beat intervals on 30-second sleep-staged epochs, summarized per subject within each sleep stage (deep, light, REM) and as a per-night nocturnal average across stages ("Overall"). Wake epochs were excluded. (A) Adjusted difference in RMSSD between cognitively impaired (PHES ≤ -4) and cognitively unimpaired patients by sleep stage, from linear mixed-effects models with a subject-level random intercept, adjusted for age, MELD 3.0, and beta-blocker use. Points are the estimated mean difference (ms), horizontal bars are 95% Wald confidence intervals, and the dashed line marks no difference; values to its right indicate higher RMSSD in the cognitively impaired group. (B) Restricted to patients with no prior overt hepatic encephalopathy (OHE) and no hepatic encephalopathy medication use, reference = cognitively unimpaired. Model structure and adjustment (age, MELD 3.0, beta-blocker use) are identical to panel A. This panel tests whether the association in A persists in patients whose impairment is not attributable to prior OHE or to ongoing treatment. (C) Subject-level per-stage RMSSD distributions for the same no-prior-OHE, untreated subgroup, shown as kernel densities for cognitively unimpaired versus untreated covert hepatic encephalopathy (CHE) patients across light, deep, and REM sleep. Tick marks (rug) denote individual subjects.

Disclosures: Adam Buckholz: Tortugas Neurosciences: Consultant, Himel Mallick: Nothing to Disclose, Alec Chang: Nothing to Disclose, Avesh Thuluvath: Nothing to Disclose, Lara Phipps: Nothing to Disclose, Edwin Kan: Nothing to Disclose, Ana Krieger: Nothing to Disclose, Robert Brown: Gilead: Consultant, Intercept: Consultant, Abbvie: Consultant, Madrigal: Consultant, GSK: Consultant, eGenesis: Consultant, mirum: Consultant, mallinckrodt: Consultant.

0187 | COST-EFFECTIVENESS OF ADHERENCE TO SPONTANEOUS BACTERIAL PERITONITIS QUALITY METRICS IN CIRRHOSIS HOSPITALIZATIONS: A DECISION-ANALYTIC MODEL

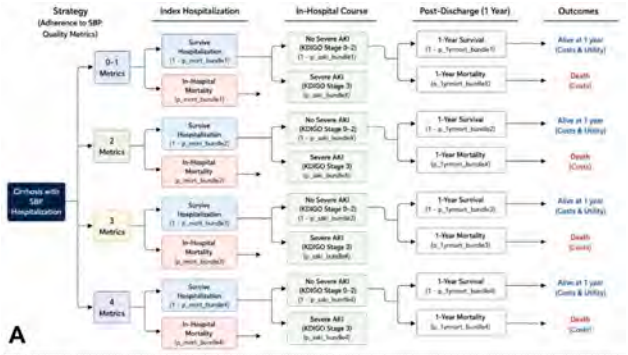
Claudio Salinas[1] Marina Serper[2] David Kaplan[3] Siqi Zhang[3] Nadim Mahmud[1], [1]Hospital of the University of Pennsylvania, [2]University of Pennsylvania Health System, [3]University of Pennsylvania

Background: Spontaneous bacterial peritonitis (SBP) is associated with substantial morbidity, mortality, and healthcare utilization in patients with cirrhosis. Although guideline-recommended quality metrics for SBP management have been established and recently shown to be associated with clinical outcomes, the economic and clinical value of achieving higher adherence to these metrics remains poorly defined. We aimed to evaluate the cost-effectiveness of increasing adherence to SBP quality metrics during cirrhosis hospitalizations. **Methods:** We developed a decision-analytic model using TreeAge Pro to evaluate strategies based on achievement of 0-1, 2, 3, or 4 SBP quality metrics during hospitalization (antibiotics within 48 hours, albumin per guidelines, SBP discharge code, repeat paracentesis at 48 hours; Figure Panel A). Model pathways incorporated in-hospital mortality, severe acute kidney injury (AKI; KDIGO stage 3), and 1-year post-discharge mortality; utilities were derived from published health utility literature. Transition probabilities were derived from granular Veterans Health Administration cohort data stratified by quality metric adherence level. Costs were estimated from observed healthcare expenditures and stratified by hospitalization survival and severe AKI status. Health outcomes were expressed as quality-adjusted life years (QALYs) over a 1-year horizon. Incremental cost-effectiveness ratios (ICERs) were calculated from a healthcare system perspective using a willingness-to-pay threshold of $100,000/QALY. Deterministic one-way sensitivity analyses and probabilistic sensitivity analyses were performed. **Results:** Strategies achieving 0-1 and 2 quality metrics were absolutely dominated, demonstrating higher costs and lower effectiveness compared with higher-adherence strategies. Achieving 3 quality metrics was associated with the lowest expected cost ($59,194) and an effectiveness of 0.34 QALYs. Achieving 4 quality metrics increased effectiveness to 0.40 QALYs at an incremental cost of $2,837, corresponding to an ICER of $49,896/QALY gained (Figure Panel B). One-way sensitivity analyses demonstrated that results were most sensitive to post-hospitalization costs among survivors without severe AKI,

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baseline utility estimates, and in-hospital mortality probability. Across plausible parameter ranges, the 4-metric strategy remained cost-effective at a willingness-to-pay threshold of $100,000/QALY. **Conclusion:** Greater adherence to SBP quality metrics during cirrhosis hospitalization was associated with improved clinical outcomes and favorable cost-effectiveness. Achieving all 4 quality metrics was cost-effective compared with lower-adherence strategies, supporting efforts to improve implementation of evidence-based SBP care.



B

Strategy	Dominance Status	Expected Cost ($)	Expected QALYs	Incremental Cost ($)	Incremental QALYs	ICER ($/QALY)	Net Monetary Benefit ($)*
0–1 Metrics	Absolutely Dominated	68,293.31	0.28	6,262.37	-0.12	-52,745.74	-40,515.29
2 Metrics	Absolutely Dominated	69,062.09	0.30	7,031.15	-0.09	-74,691.63	-38,824.89
3 Metrics	Undominated (Reference)	59,194.32	0.34	Reference	Reference	Reference	-25,228.57
4 Metrics	Undominated	62,030.94	0.40	2,836.62	0.06	49,896.49	-22,380.18

*Net monetary benefit calculated at a willingness-to-pay threshold of $100,000/QALY.

Disclosures: Claudio Salinas: Nothing to Disclose, Marina Serper: Transplant Genomics: Grant/Research Support, Grifols: Grant/Research Support, David Kaplan: AstraZeneca Inc: Grant/Research Support, Roche Genentech: Independent Contractor, Exact Sciences: Grant/Research Support, Glycotest: Grant/Research Support, Exelixis: Advisor, AstraZeneca: Advisor, Gilead: Grant/Research Support, Bausch Healthcare: Grant/Research Support, Mirumn: Grant/Research Support, Bausch: Grant/Research Support, Exact Sciences: Grant/Research Support, AstraZeneca: Grant/Research Support, Mirum: Grant/Research Support, Siqi Zhang: Nothing to Disclose, Nadim Mahmud: Nothing to Disclose.

0188 | A BLOOD-TEST-FREE LSM–SSM FUSION SCORE FOR POINT-OF-CARE DIAGNOSIS OF CLINICALLY SIGNIFICANT PORTAL HYPERTENSION (CSPH): A MULTICENTRE STUDY

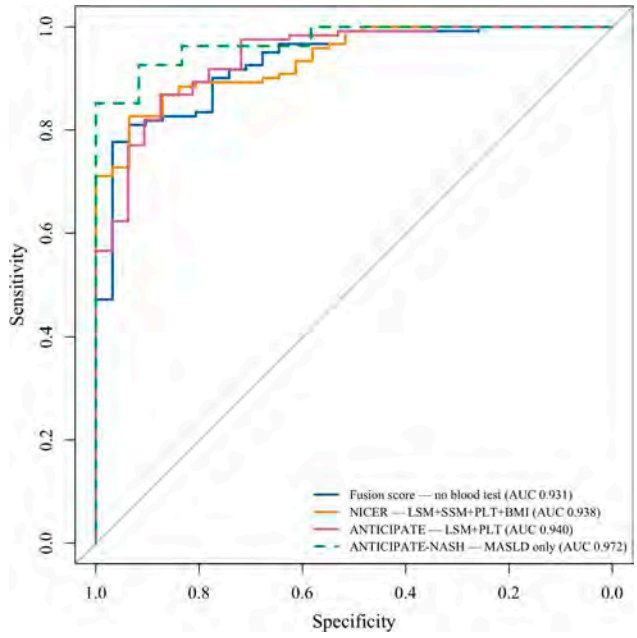
Lucia Parlati[1] Lucile Moga[2] Alexis Dupre[1] Pierre-Emmanuel Rautou[2] Vincent Mallet[1], [1]AP-HP.Centre Université Paris Centre, Groupe Hospitalier Cochin Port Royal, [2]AP-HP.Nord Université Paris Centre, Hôpital Beaujon

Background: Non-invasive evaluation of CSPH fails up to half of compensated advanced chronic liver disease (cACLD) patients, leaving them in a grey zone that requires invasive hepatic venous pressure gradient (HVPG) measurement. Existing models improve reclassification but depend on blood tests. We derived and locked a fully blood-test-free fusion score combining liver stiffness measurement (LSM) and spleen stiffness measurement (SSM) for point-of-care CSPH classification, with a primary focus on grey zone reclassification. **Methods:** Consecutive patients with cACLD (LSM $\geq$10 kPa) from three French tertiary hepatology centres underwent same-session LSM and SSM using FibroScan® (Echosens) or Hepatus® (Mindray). CSPH was defined by oesophageal varices, prior hepatic decompensation, or HVPG $\geq$10 mmHg. The fusion score $s = \alpha \cdot z(\text{LSM}) + (1-\alpha) \cdot z(\text{SSM})$ was derived by grid search on the FibroScan® cohort; all parameters (α, μ and σ for LSM and SSM, Youden threshold) were locked in a version-controlled package and applied without recalibration in every downstream analysis. The score was tested cross-platform, and against ANTICIPATE and NICER with a pre-specified non-inferiority margin of $\Delta\text{AUC} \geq -0.03$, and across pre-specified sensitivity analyses [HVPG-confirmed CSPH, non-alcohol-related liver disease (ALD), non-censored measurements, Child-Pugh A]. **Results:** Between 2022 and 2025, 156 patients with cACLD were included (median age 58 years, 66% male, 63% ALD, 26% MASLD; CSPH prevalence 79%). On the derivation cohort (N = 115, CSPH 80%), the optimal fusion weight was α = 0.86 (median; IQR 0.76–0.94; 95% CI 0.43–0.98), with AUC 0.937 [95% CI 0.887–0.987]. Cross-platform evaluation on Hepatus® (N = 41, CSPH 78%) yielded AUC 0.935 [95% CI 0.857–1], equivalent after propensity-score matching (p = 0.97). Against HVPG-confirmed CSPH (N = 126), non-inferiority to both ANTICIPATE (ΔAUC +0.004 [95% CI -0.023, +0.031]) and NICER (ΔAUC +0.015 [95% CI -0.025, +0.052]) was formally demonstrated on the −0.03 margin, without any blood test. On the broader composite-CSPH cohort, the point estimate against both comparators remained negligible (ΔAUC -0.007 and -0.007). In the combined Baveno VII/VIII grey zone (N = 37, CSPH 35%) — patients unclassifiable by both LSM-based and SSM-based blood-test-free criteria — the fusion score achieved NPV 100% (14/14 true negatives, zero CSPH missed) and reclassified 73% of patients. Sensitivity analyses confirmed stable AUC across HVPG-only (0.91), non-ALD (0.88), non-censored (0.9), and Child-Pugh A scenarios. **Conclusion:** A two-measurement, blood-test-free LSM–SSM fusion score was formally non-inferior to ANTICIPATE and NICER against HVPG-confirmed CSPH and achieved NPV 100% in the combined Baveno VII/VIII grey zone where current blood-test-free criteria fail (NPV 12.5%). These findings

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support prospective multicentre external validation as a point-of-care tool to reduce the diagnostic grey zone in cACLD.



Disclosures: Lucia Parlati: AbbVie: Speaking and Teaching, Gilead: Speaking and Teaching, NovoNordisk: Speaking and Teaching, Ipsen: Speaking and Teaching, Madrigal: Speaking and Teaching, GSK: Consultant, Lucile Moga: Nothing to Disclose, Alexis Dupre: Nothing to Disclose, Pierre-Emmanuel Rautou: Genfit: Consultant, Jazz: Speaking and Teaching, Cook: Consultant, AstraZeneca: Consultant, Vincent MALLET: Nothing to Disclose.

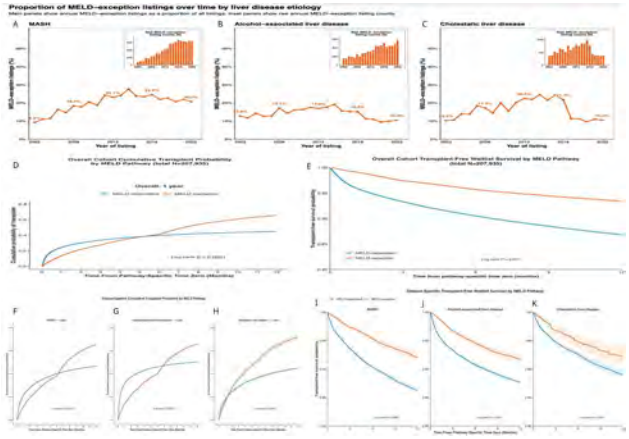
0189 | INCREASING DEPENDENCE ON MELD-EXCEPTION ALLOCATION IN CONTEMPORARY LIVER TRANSPLANTATION: DISEASE-SPECIFIC DIFFERENCES AND WAITLIST OUTCOMES

Shiv Patel[1] Jonathan Smith[1] Brian Wentworth[1] Zachary Henry[1] Curtis Argo[1] Nicolas Intagliata[1] Neeral Shah[1] Stephen Caldwell[1] Anya Mezina[1] Yazan Al-Adwan[1] Shawn Pelletier[1] Stephanie Silpe[1] Juan Guerra[1] Mohammad Siddiqui[1] Anh Bui[2], [1]University of Virginia, [2]Virginia Commonwealth University

Background: MELD exception (eMELD) pathways allow liver transplant (LT) prioritization for disease processes inadequately captured by laboratory MELD. Despite major allocation policy changes and evolving waitlist composition, contemporary data evaluating trends in eMELD utilization and their impact on waitlist outcomes remain limited. We evaluated national trends in eMELD dependence and comparative waitlist outcomes between eMELD and conventional MELD-dependent (cMELD) pathways, with emphasis on metabolic dysfunction-associated steatohepatitis (MASH). **Methods:** Using SRTR/UNOS data, we performed a retrospective cohort study of adult LT candidates listed between 2003-2023. Candidates were classified as cMELD or eMELD according to approved exception status. 1-year transplant probability and transplant-free waitlist survival were assessed using Kaplan-Meier and multivariate Cox proportional hazard models. Disease-specific analysis focused on MASH, alcohol, and cholestatic liver diseases. **Results:** Among the 207,935 waitlist candidates included in the overall cohort, 49,992 (19.6%) were listed via eMELD pathway. The eMELD utilization increased progressively over the study period, with the largest increase among MASH candidates (9.2% to 20.8%, **Fig. 1A-C**). The most common indication for eMELD was HCC/cholangiocarcinoma followed by pulmonary complications including hepatopulmonary syndrome and portopulmonary hypertension. Although cMELD candidates demonstrated greater early transplant probability, eMELD candidates had significantly higher 1-year transplant probability (log-rank $p < 0.0001$, **Fig. 1D, F-H**). eMELD candidates also had better 1-year transplant-free waitlist survival (log-rank $p < 0.001$, **Fig. 1E**), with the largest survival differential observed in MASH (**Fig. 1I-K**). In adjusted multivariate analysis, eMELD was independently associated with lower waitlist mortality (aHR 0.39, 95% CI 0.38-0.41, $p < 0.001$) and greater transplant likelihood (aHR 1.61, 95% CI 1.59-1.63, $p < 0.001$). These associations were observed across etiologies, with greater benefits observed in MASH candidates. **Conclusion:** Contemporary LT increasingly depends on exception-based allocation. MASH cirrhosis has emerged as one of the populations most dependent on exception-based allocation, suggesting the laboratory MELD may incompletely capture transplant urgency in this patient population. The striking outcome differential between eMELD and cMELD candidates exposes a critical gap in the current allocation policy, underscoring the need to reassess how transplant urgency is measured.

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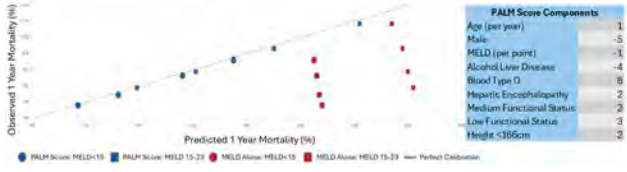
Disclosures: Shiv Patel: Nothing to Disclose, Jonathan Smith: Nothing to Disclose, Brian Wentworth: Ipsen: Consultant, Ipsen: Speaking and Teaching, GSK: Consultant, Luna Labs USA: Consultant, Zachary Henry: Nothing to Disclose, Curtis Argo: Nothing to Disclose, Nicolas Intagliata: Nothing to Disclose, Neeral Shah: McGraw Hill Publishing: Royalties or patent beneficiary, UptoDate: Royalties or patent beneficiary, Stephen Caldwell: Nothing to Disclose, Anya Mezina: Nothing to Disclose, Yazan Al-Adwan: Nothing to Disclose, Shawn Pelletier: Nothing to Disclose, Stephanie Silpe: Nothing to Disclose, Juan Guerra: Nothing to Disclose, Mohammad Siddiqui: NovoNordisk: Grant/Research Support, 89Bio: Consultant, Sagimet: DSMB, Anh Bui: Zydus: Consultant.

0191 | THE PALM (PREDICTING ACCESS IN LOW MELD) SCORE: A NEW METHOD TO IDENTIFY HIGH MORTALITY RISK WITH LOW TRANSPLANT ACCESS AMONG LOW MELD WAITLIST CANDIDATES

Xiaohan Ying[1] Brett Fortune[2] Russell Rosenblatt[3], [1]NewYork Presbyterian/Weill Cornell, [2]Miami Transplant Institute/Jackson Health, [3]Weill Cornell Medicine

Background: The MELD score is the foundation of liver allocation in the United States and prioritizes candidates based on short-term mortality risk. However, low MELD patients often experience a discordance between clinical urgency and access to liver transplant (LT). We aimed to identify high-risk low-access (HRLA) candidates with high waitlist (WL) mortality and low probability of LT by creating and validating the PALM score. **Methods:** We used the UNOS STAR file and included adult LT candidates listed from 2/4/20-12/31/25. We excluded candidates listed with status 1A, multiorgan, exception points, prior LT, and MELD > 23 (median MELD of our cohort). The cohort was split randomly 50: 50 into derivation and validation groups. Competing-risk regression including *a priori* covariates estimated WL mortality and LT. Candidates were stratified into 3x3 risk categories based on predicted WL mortality and LT probability. HRLA candidates were defined by having the highest WL mortality risk and lowest LT probability within 1 year of listing.Multivariable logistic regression was performed using *a priori* covariates present at listing to identify those who are more likely to be HRLA. These covariates were used to create the PALM score and were applied to the validation cohort. Discrimination was assessed using the area under the curve. We then compared PALM vs MELD estimation of 1-year mortality within MELD < 15 and 16-23 cohorts. **Results:** Among 14,311 derivation cohort candidates, 595 (4.2%) met HRLA criteria. HRLA candidates were more likely to be older (aOR 1.3), have blood type O (aOR 11.9), and grade 3/4 hepatic encephalopathy (HE) (aOR 3.3) **,** medium functional status (aOR 1.21), and poor functional status (aOR 1.49). Male sex (aOR 0.2), higher MELD (aOR 0.7), and alcohol liver disease (ALD) (aOR 0.2) were inversely associated with HRLA status. HRLA candidates have higher WL mortality (11.3% vs 6.8%) and lower LT rates (36.1% vs 49.4%), $p < 0.001$. The PALM score incorporated eight variables above along with height, due to its association with decreased organ access: Age (+1 per year), Male (-5), MELD (-1 per point), ALD (-4), Blood Type O (+8), Grade 3/4 HE (+2), Medium Functional Status (+2), Low Functional Status (+3), Height (+2 if < 166cm). The median score was 42, with the highest quartile cutoff (≥ 51) capturing every HRLA patient. In the validation cohort, the PALM score improved discrimination for WL mortality compared to MELD alone (AUC 0.60 vs 0.55, $p = 0.001$). Critically, the PALM score estimated mortality more accurately in patients with MELD < 15 and 15-23 (mean absolute error 0.3% vs 6.4%) **Figure 1**. **Conclusion:** In the post–acuity circles era, low MELD adult LT candidates can have discordance between risk of WL death and LT access. The PALM score outperforms MELD in informing patients and providers about prognosis and LT access, thereby empowering them to consider alternative strategies such as living donation or expanded donor acceptance.

Figure 1. Comparison of PALM Score and MELD in prediction of 1-year mortality in WL patients with MELD < 15 and MELD 15-23



Disclosures: Xiaohan Ying: Nothing to Disclose, Brett Fortune: WL Gore and Associates: Consultant, BD

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Medical: Consultant, Madrigal Pharm: Consultant, Gilead Sciences: Consultant, Madrigal Pharma: Consultant, WL Gore and Associates: Consultant, BD medical: Consultant, Novo Nordisk: Consultant, Ipsen Pharmaceuticals: Consultant, Russell Rosenblatt: Gilead: Grant/Research Support.

0192 | HEPATIC ENCEPHALOPATHY INDEPENDENTLY PREDICTS WAITLIST MORTALITY AND REDUCES TRANSPLANT PROBABILITY IN CIRRHOTIC PATIENTS: EVIDENCE FOR MELD-BASED ALLOCATION REFORM

Neev Mehta[1] Hisham Habib[1] Marwa Elmahi[1] Dafallah Miqdad[2] Raza Malik[3], [1]Lahey Clinic, [2]BWH, [3]Lahey Hospital & Medical Center

Background: Overt hepatic encephalopathy (HE) develops in up to 40% of patients with cirrhosis and carries a 1-year mortality of nearly 60% without liver transplantation (LT). Despite this prognosis, HE receives no formal weight in the Model for End-Stage Liver Disease (MELD) score, which governs deceased donor organ allocation in the United States. Patients with HE may therefore be systematically disadvantaged, dying on the waitlist before an organ is available, yet not prioritized by the current scoring. **Methods:** We analyzed data from a published retrospective cohort study (Lee et al., *Transplantation Direct*, 2024) examining **39,025 adult liver transplant candidates** listed in the OPTN database between January 2016 and December 2021. Candidates were grouped by complication status at listing: neither moderate HE nor ascites, moderate ascites alone (mAscites), moderate HE alone (mHE), or both. Supplementary data on national transplant volume and rates were drawn from the OPTN/SRTR 2022 Annual Data Report (Kwong et al., *Am J Transplant*, 2024). The primary outcome was **one-year waitlist mortality** (death or delisting for being too sick to transplant). We examined **cumulative transplant probability** at 3, 6, and 12 months, which accounts for the competing risk of waitlist death. Adjusted hazard ratios (HRs) were obtained from multivariable Cox models reported in Lee et al., controlling for MELD 3.0, age, sex, race/ethnicity, and primary liver diagnosis. All data derived from published literature; no primary patient-level data or SRTR Standard Analysis Files used. **Results:** Waitlist mortality increased with complication burden. Patients listed with HE had more than twice the 1-year waitlist mortality of those without complications (38% vs. 17%), with an adjusted HR of 2.24 (95% CI 1.88–2.67), a risk that exceeded that of ascites alone (HR 1.76) and was independent of MELD 3.0 score. The combination of HE and ascites was the highest-risk subgroup, with nearly half of patients dying or becoming too ill for transplant within 12 months. Patients with HE are far less likely to reach transplantation. At 12 months, cumulative transplant probability fell from 46.1% in patients without complications to 29.3% in those with HE alone and 22.5% in those with both HE and ascites, reductions of 37% and 51%, respectively. **Conclusion:** HE independently predicts waitlist mortality and reduces the probability of achieving liver transplantation, even after adjustment for MELD 3.0 score. The current allocation system does not account for HE, leaving a clinically vulnerable group at disproportionate risk of dying before transplant. These findings add to the growing evidence supporting the incorporation of objectively documented HE for example, via hospitalization records for grade 2 or higher episodes, into MELD. We are currently pursuing a primary analysis to validate these findings at the patient level and examine outcomes by HE grade and etiology of cirrhosis.

Table 1. *One-year waitlist mortality by complication status (OPTN 2016–2021; Lee et al., 2024)*

Complication group	N (%)	1-yr waitlist mortality	Adjusted HR (vs. neither)	95% CI
Neither HE nor ascites	~23,415 (60%)	17%	Reference	—
Moderate ascites only	~11,318 (29%)	30%	1.76	1.55–2.00
Moderate HE only	~1,171 (3%)	38%	2.24†	1.88–2.67
Both moderate ascites + HE	~3,122 (8%)	47%	3.12†	2.71–3.59

†P < 0.001 vs. reference. HR adjusted for MELD 3.0, age, sex, race/ethnicity, and primary diagnosis. Source: Lee BT et al., Transplantation Direct 2024. doi:10.1097/TXD.0000000000001625.

Table 2. *Cumulative probability of achieving liver transplant at 3, 6, and 12 months, by complication group*

Complication group	3 months	6 months	12 months
Neither HE nor ascites	13.8%	26.2%	46.1%
Moderate ascites only	11.0%	20.7%	35.8%
Moderate HE only	9.0%	17.0%	29.3%
Both moderate ascites + HE	6.8%	12.9%	22.5%

Estimates derived from competing risk analyses in Lee et al. 2024 and overall transplant probability data from the OPTN/SRTR 2022 Annual Data Report. Accounts for competing risks of waitlist death and non-transplant removal.

Disclosures: Neev Mehta: Nothing to Disclose, Hisham Habib: Nothing to Disclose, Marwa Elmahi: Nothing to Disclose, Dafallah Miqdad: Nothing to Disclose, Raza Malik: Nothing to Disclose.

0193 | EXPLORING THE EFFECT OF NEGATIVE PRESS ON DECEASED DONOR LIVER DONATION

Chelsea Pan[1] Nicole Kim[2] Elizabeth Aby[3] Howard (Tzu-Hao) Lee[4] Hersh Shroff[5] Jin Ge[1], [1]University of California, San Francisco, [2]University of Washington Medical Center, [3]University of Minnesota, [4]Baylor College of Medicine, [5]UNC Chapel Hill

Background: Organ donation and transplantation rely on sustained public trust. Recent negative media

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coverage of the U.S. organ transplantation system in major outlets, including the New York Times (NYT), Washington Post, and Associated Press, may influence confidence in organ allocation systems. This study evaluated whether intensified negative media coverage was associated with changes in deceased liver donation rates. We hypothesized that negative media attention may temporarily reduce donor registration, family authorization, and hospital referral, ultimately decreasing liver donation. **Methods:** We performed a retrospective interrupted time series analysis using negative binomial regression of the UNOS STAR database. Adult deceased liver donors from Jan 1, 2024 to Mar 31, 2026 were included. The pre-intervention period was Jan 1, 2024 to Feb 25, 2025. Assuming gradual media exposure, two one-month intervention periods were defined using peaks in media intensity identified via ProQuest U.S. Major Dailies and Google Trends searches for “organ donation” and “organ transplant". The first intervention period (Feb 26 to Mar 26, 2025) corresponded to NYT investigative reports published on Feb 26 and Feb 27, 2025 that alleged ignored transplant waitlists and the second intervention period (July 21 to Aug 21, 2025) corresponded to U.S. Department of Health and Human Services announcements on July 21, 2025 to reform organ procurement policies. Immediate change was defined as the difference between observed and predicted donations at intervention onset; sustained change was defined as the change in slope before versus after each intervention period. We adjusted for day of week and month to control for cyclical variation. Subgroup analyses assessed variation across 11 UNOS regions. **Results:** There was a significant pre-intervention upward trend in liver donations of 0.12% per day (~55% annually; IRR 1.00, p = 0.04). Intervention period 1 showed a significant immediate increase in donations (+12.4%, IRR 1.12, p = 0.04) without sustained change. Intervention period 2 showed a non-significant immediate decrease (−9.5%, IRR 0.91, p = 0.09) without sustained change. Region 6 (Pacific Northwest) demonstrated a significantly greater immediate decline in donation counts relative to Region 1 (New England) after intervention period 2, without sustained change (interaction IRR 0.57, p = 0.002). Overall trends remained stable. **Conclusion:** Intensified negative media coverage was not associated with significant short- or long-term declines in deceased liver donation, suggesting sustained public trust. A non-significant reduction between intervention periods may reflect temporary hesitation, though this did not reach statistical significance. The lack of effect may reflect the complexity of donation decision-making, inability to directly assess donor registration, and concurrent policy changes.

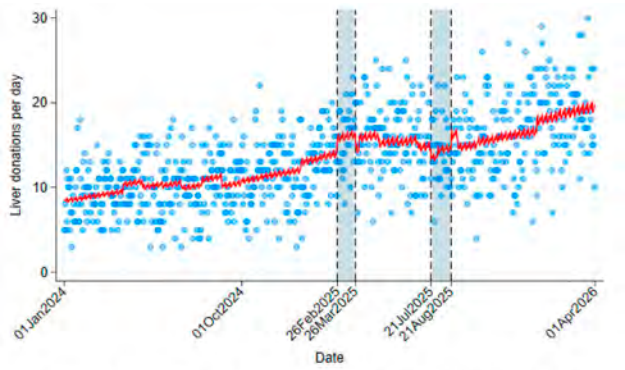


Figure 1. Daily deceased donor liver donation rates between Jan 1, 2024 and to Mar 31, 2026 with intervention periods 1 and 2 highlighted in blue.

Disclosures: Chelsea Pan: Nothing to Disclose, Nicole Kim: Madrigal: Grant/Research Support, Madrigal Pharmaceuticals: Clinical trial (to institution), Madrigal: Grant/Research Support, Elizabeth Aby: United Health Care Group: Stock - publicly traded company, Medtronic: Stock - publicly traded company, Howard (Tzu-Hao) Lee: Abbvie: Consultant, Hersh Shroff: Glaxo-Smith-Kline: Grant/Research Support, Jin Ge: Merck and Co: Grant/Research Support, Iota Biosciences/ Astellas Pharmaceuticals: Consultant, Madrigal Pharamaceuticals: Consultant, Gilead Sciences: Consultant.

0194 | SEX-BASED DISPARITIES IN LIVER TRANSPLANT ALLOCATION AMID MELD 3.0 AND THE EMERGENCE OF MACHINE PERFUSION

Tomohiro Tanaka[1] David Axelrod[2] Jennifer Lai[3], [1]University of Iowa, [2]University Hospitals Cleveland Medical Center, [3]University of California, San Francisco

Background: Despite MELD 3.0, sex-based disparities in liver transplant (LT) access persist. Normothermic machine perfusion (NMP) has expanded the donor pool, potentially altering size-mismatch-driven access gaps. We examined sex disparities in LT access, waitlist mortality, and offer acceptance, stratified by center-level NMP utilization and MELD 3.0 era, testing whether alternative body-size metrics better capture residual disparity. **Methods:** Using OPTN data, we identified adult candidates listed pre-MELD 3.0 (1/2022-6/2023) and post-MELD 3.0 (10/2023-9/2025). LT centers were classified as High or Low NMP by upper-tertile NMP utilization (NMP livers / total LTs per center). Fine-Gray models estimated subdistribution hazard ratios (sHR) for LT access and WL mortality,

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sequentially adjusting for confounders and body size. Offer-level multilevel models assessed top-5 acceptance with attenuation by recipient height and estimated liver volume ratio (eLVr); NMP vs. non-NMP LT characteristics were also compared. **Results:** Among 43,636 candidates (17,645 female), females had lower 90-day LT access across all strata (adjusted sHR 0.71-0.89, all 95% CI < 1) while WL mortality was low (1.4-2.6%) with no sex difference (sHR 0.92-1.27, all CI crossing 1). Height attenuated LT access disparity at Low NMP centers (sHR 0.89→0.96 [0.90-1.03]; 69% mediated) but not High NMP (0.85→0.88 [0.81-0.95]; 22%). In offer-level analysis (206,825 offers) at High NMP centers post-MELD 3.0, eLVr attenuated the sex gap (OR 0.78→0.91 [0.83-1.001]; 67% mediated) beyond recipient height; center random effects showed no variation in sex-based acceptance. Among 30,359 large-for-size offers (eLVr > 1.2), female acceptance was lower at High NMP (OR 0.71 [0.57-0.88]) but not Low NMP centers (0.84 [0.70-1.01]). Sensitivity analyses (top-40% NMP threshold, top-3/10 offers, donor-recipient weight ratio replacing eLVr) corroborated these findings. Among 29,599 LTs (7,335 NMP), recipient sex was similar, while NMP LTs had lower MELD, higher eLVr, yet shorter recipients (all p < .01). Adjusted mean eLVr for males was higher with NMP (0.962) vs non-NMP (0.942, p < .001) grafts, whereas females remained equivalently oversized (1.038 vs 1.039, p = .84); the adjusted estimate of the sex-by-NMP interaction (β = −0.021 for female vs male NMP differential, p = .002) indicated that NMP's eLVr gain did not extend to females. **Conclusion:** Sex disparities in LT access persist post-MELD 3.0 despite WL mortality convergence, challenging mortality as the sole equity benchmark. At Low NMP centers, candidate body size largely attenuated the disparity, but at High NMP centers, donor-recipient size ratios contributed to the disparity due to limited acceptance of larger livers for female candidates. Match-based size compatibility in allocation, rather than candidate-side adjustments alone, may better address sex-based disparities amid NMP expansion.

Table: Key Estimates of Sex-Based Disparity by NMP Tier and MELD 3.0 Era

LT access rate	sHR (95%CI)	P	*Offer acceptance*	OR (95%CI)	P
High-NMP			**High-NMP**		
Pre-MELD 3.0			*Pre-MELD 3.0*		
Base model	0.72 (0.66-0.78)	<.001	Base model	0.70 (0.63-0.78)	<.001
with Height	0.77 (0.68-0.86)	<.001	with Height	0.74 (0.63-0.86)	<.001
			with eLV ratio	0.84 (0.75-0.95)	.005
Post-MELD 3.0					
Base model	0.85 (0.80-0.90)	<.001			
with Height	0.88 (0.81-0.95)	.001	*Post-MELD 3.0*		
			Base model	0.78 (0.72-0.84)	<.001
Low-NMP			with Height	0.86 (0.76-0.96)	.013
Pre-MELD 3.0			with eLV ratio	0.91 (0.83-1.001)	.051
Base model	0.82 (0.77-0.88)	<.001			
with Height	0.92 (0.85-1.01)	.074			
Post-MELD 3.0					
Base model	0.89 (0.85-0.94)	<.001			
with Height	0.97 (0.90-1.03)	.313			

Disclosures: Tomohiro Tanaka: Nothing to Disclose, David Axelrod: Nothing to Disclose, Jennifer Lai: Nestle Nutrition Institute: Grant/Research Support, Novo Nordisk: Consultant, Genfit: Consultant, Boehringer Ingelheim: Advisor, Lipocine: Site PI, Gilead: Site PI, Insmed: Consultant, Cosmo: Advisor.

★ 0195 | CENTER-LEVEL VARIATION IN DONATION AFTER CIRCULATORY DEATH LIVER TRANSPLANTATION AND ITS ASSOCIATION WITH ACCESS AND OUTCOMES

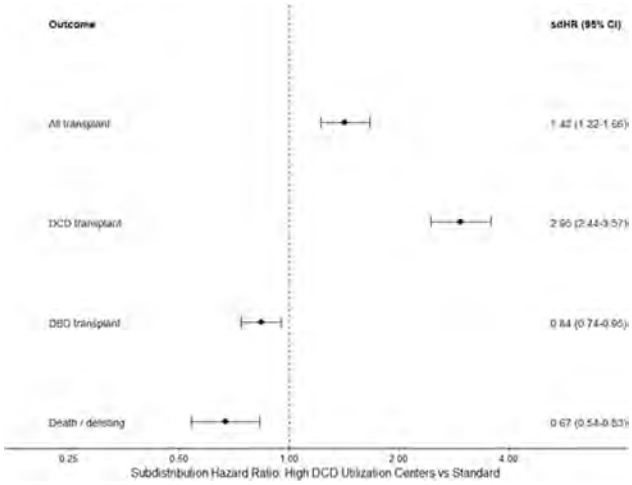
Katie Ross-Driscoll[1] Casey Woods[1] Sarah Huber[1] James Butler[1] Chandrashekhar Kubal[1] Lauren Nephew[1], [1]Indiana University

Background: Donation after circulatory death (DCD) grafts now comprise an increasingly important source of donor livers in the United States, yet adoption of DCD transplantation remains highly variable across centers. We evaluated whether center-level DCD utilization influences access to liver transplantation and post-transplant outcomes. **Methods:** Using Scientific Registry of Transplant Recipients data, we identified adult liver transplant candidates listed and recipients transplanted between 1/1/2022 and 12/31/2025. Centers in the highest quartile of DCD utilization (> 29.2% of recipients receiving DCD grafts) were classified as high utilizers. We estimated time to transplant using Fine-Grey regression, accounting for competing risks of death and delisting. **Results:** Among 52,925 waitlisted candidates across 118 centers, 30 centers were classified as high DCD utilizers (n = 15,415 candidates). Candidates listed at high-utilization centers were less likely to be Hispanic (13.8% vs 21.6%), more likely privately insured (52.7% vs 49.4%), and from less socioeconomically deprived communities (all p < 0.001). Median time to transplant was substantially shorter at high-utilization centers (62 vs 149 days). After adjustment, listing at a high-utilization center was associated with increased cumulative incidence of transplant (sdHR 1.42, 95%CI 1.22-1.66), driven specifically by increased DCD transplantation (sdHR 2.95, 95%CI 2.44-3.57) (**Figure 1**). Among 37,547 recipients, 9,657 (25.7%) received DCD grafts; patients transplanted at high-utilization centers were twice as likely to receive DCD (RR 2.02, 95%CI 1.94-2.14). Post-transplant graft failure, death, or re-listing did not differ between DCD and DBD recipients. **Conclusion:** In the contemporary era, transplant center utilization of DCD grafts is a major determinant of transplant opportunity. Centers with greater DCD expertise and infrastructure achieve substantially higher transplant rates without compromised short-term outcomes. Broader dissemination of the technical expertise, clinical workflows, and

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technologies supporting DCD transplantation may represent an important strategy to expand equitable access to liver transplant.

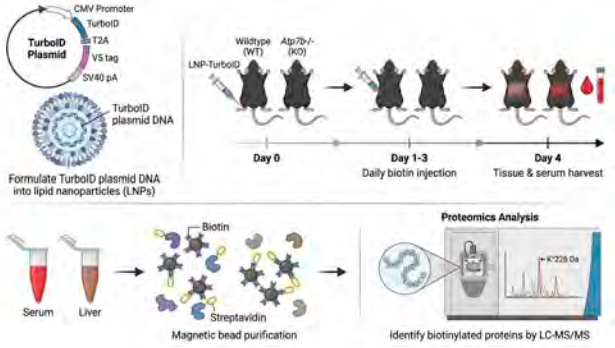


Disclosures: Katie Ross-Driscoll: Nothing to Disclose, Casey Woods: Nothing to Disclose, Sarah Huber: Nothing to Disclose, James Butler: Nothing to Disclose, Chandrashekhar Kubal: Nothing to Disclose, Lauren Nephew: NovoNordisk: Consultant, NovoNordisk: Consultant, NovoNordisk: Consultant, NovoNordisk: Consultant.

0196 | DEFINING THE HEPATIC SECRETOME IN WILSON DISEASE USING A LIPID NANOPARTICLE GENE DELIVERY SYSTEM FOR PROXIMITY BIOTINYLATION OF SECRETED PROTEINS

Robert Hughes[1] James Hamilton[1] Svetlana Lutsenko[1],
[1]Johns Hopkins University

Background: Wilson Disease is an autosomal recessive disorder caused by mutations in ATP7B, a copper-transporting ATPase localized to the trans-Golgi network and essential for hepatobiliary copper excretion. Inactivation of ATP7B results in copper accumulation in various tissues including the liver, but clinical presentation and disease severity do not necessarily correlate with hepatic copper content. While the genetic cause of Wilson Disease is clear, the mechanism of disease remains only coarsely defined. Copper-dependent enzymes such as ceruloplasmin, lysyl oxidase, and peptidylglycine α-amidating monooxygenase (PAM) are essential for post-translational processing of secretory proteins. Therefore, we hypothesized that ATP7B deficiency disrupts these copper-dependent pathways and alters the hepatocyte secretome to favor chronic inflammation and injury independent of hepatic copper accumulation. **Methods:** We utilized a Sec61b-TurboID proximity biotinylation system to label endoplasmic reticulum-transiting proteins in *Atp7b*knockout murine hepatocytes as well as *ATP7B*$^{-/-}$ induced pluripotent stem cell (iPSC)-derived human hepatocytes. For targeted gene delivery to the liver in our *in vivo* model system, we used a lipid nanoparticle formulation optimized by collaborators at the Johns Hopkins Institute for Nanobiotechnology. Mass spectrometry was then employed to profile differentially secreted proteins in serum and liver lysates (*in vivo* model) or conditioned media (human iPSC model) from ATP7B knockout versus wild-type samples. **Results:** Initial analysis suggests that copper imbalance in ATP7B knockout systems substantially affects protein secretion, as shown by reduced abundance of secreted proteins, including ceruloplasmin, compared with wild-type controls. However, a subset of proteins is significantly increased in ATP7B knockout models and may be functionally relevant to disease pathogenesis. Pathway enrichment analysis reveals that these candidates are primarily associated with extracellular matrix turnover, cytokine signaling, and vitamin D metabolism. These candidates will be tested further using neutralization or knockdown assays to determine whether and how they modify the Wilson Disease phenotype. **Conclusion:** By studying secreted proteins from the liver in a model of Wilson Disease, we hope to better understand the intercellular communication pathways involved in its pathophysiology. In addition, the Wilson Disease hepatic secretome may reveal novel biomarkers to aid in early diagnosis and better predict clinical outcomes. Lastly, the lipid nanoparticle gene delivery system is a powerful tool currently being used in clinical trials for gene therapy, and we highlight its utility here as a discovery platform.



Disclosures: Robert Hughes: Nothing to Disclose, James Hamilton: orphalan pharmaceuticals: Advisor, mirum pharmacueticals: Advisor, Svetlana Lutsenko: Nothing to Disclose.

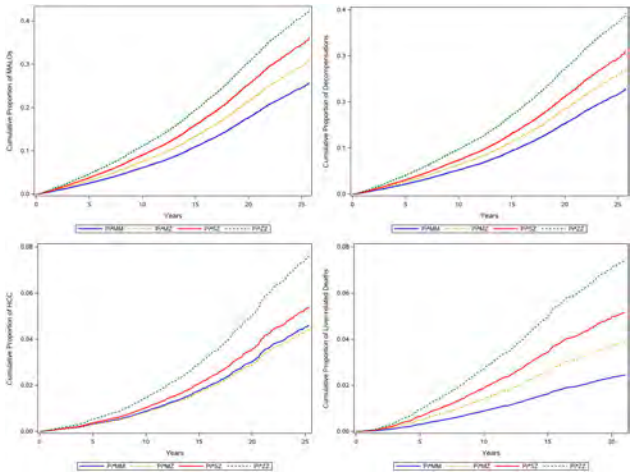
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0197 | BEYOND CIRRHOSIS: MAJOR ADVERSE LIVER OUTCOMES ACROSS PIMZ, PISZ, AND PIZZ GENOTYPES IN ALPHA-1 ANTITRYPSIN DEFICIENCY

Dustin Bastaich[1] Bassam Dahman[2] Austen Hentschel[3] Andres Samos[4] Chitra Karki[5] Tami Nussbaum[5] Suna Park[5] Seth Spector[6] Gregory Bigford[7] Brian Garnet[6] Michael Campos[6] Binu John[6], [1]Virginia Commonwealth University, [2]Virginia Commonwealth University and Miami VA, [3]Florida International University and Miami VA, [4]Washington University and Miami VA, [5]Takeda, [6]University of Miami and Miami VA, [7]Miami VA

Background: Alpha-1 antitrypsin deficiency (AATD) increases susceptibility to chronic liver disease, yet data on major adverse liver outcomes (MALO) across heterozygous and homozygous Z-allele genotypes remains limited, due to the abence of large populatkion based cohorts with longitudinal follow up and fibrosis staging. We assessed the risk of MALO-encompassing decompensation, hepatocellular carcinoma (HCC), liver transplantation (LT), and liver-related death (LRD), across AATD protease inhibitor MZ (PiMZ), PiSZ, and PiZZ genotypes compared to PiMM. **Methods:** This retrospective cohort study utilized the Veterans Analysis of Liver Disease (VALID) cohort (January 2000-April 2025). Veterans with classifiable AATD genotypes and a baseline fibrosis stage (via biopsy, elastography, FIB-4, or APRI) were included. Those under 18 or with MALO within 90 days of baseline were excluded. Genotypes were identified using validated natural language processing, shown previously to have a high agreement with manual chart review ($\kappa = 0.89$). Multivariable Cox proportional hazards models (with censoring at non-liver-related death or the end of study period) estimated the hazard of MALO, adjusting for fibrosis stage, age, BMI, sex, race, and co-existing liver disease etiologies. **Results:** Of 22,537 participants with genotype testing, 19,665 were PiMM, 1,656 PiMZ, 281 PiSZ, and 935 PiZZ with 352,612 person years of follow up and a median follow up per patient of >16 years. Median age was 50 years (IQR = 15); 92.5% were male. MALO risk increased sequentially with allele burden: PiMZ (aHR 1.24, 95% CI 1.11-1.39), PiSZ (aHR 1.50, 1.17-1.94), and PiZZ (aHR 1.87, 1.65-2.12), versus PiMM. MALO incidence rates for PiMM, PiMZ, PiSZ, and PiZZ, respectively were 11.3 (ref), 13.0 ($p < 0.01$ vs. ref), 14.6 ($p = 0.05$ vs. ref), and 19.2 ($p < 0.0001$ vs. ref) per 1,000 person-years respectively, while five-year MALO probability was 3.5%, 5.5%, 5.4%, and 8.1% respectively. PiZZ was associated with significantly increased risk of all individual MALO components: decompensation (aHR 1.91, 95% CI 1.67- 2.19), HCC (aHR 1.68, 95% CI 1.27-2.21), LT (aHR 5.29, 95% CI 3.84-7.27), and LRD (aHR 3.12, 95% CI 2.46-3.94). PiSZ and PiMZ were associated with higher risk of decompensation, LT, and LRD, but not HCC. Findings were consistent in a sensitivity analysis restricted to participants with MASLD. **Conclusion:** In this large cohort, MALO risk increased in a stepwise fashion across AAT genotypes carrying a Z allele, from PiMZ to PiSZ to PiZZ. Although prior studies have examined progression to cirrhosis, we believe this is the first study sufficiently powered to examine MALO in homozygous and heterozygous Z-allele carriers in a longitudinal cohort including patients across all stages of fibrosis. Notably, even heterozygous carriers demonstrated elevated MALO risk, underscoring the need for timely diagnosis, genetic counseling, and enhanced clinical surveillance.



Disclosures: Dustin Bastaich: Nothing to Disclose, Bassam Dahman: Nothing to Disclose, Austen Hentschel: Nothing to Disclose, Andres Samos: Nothing to Disclose, Chitra Karki: Nothing to Disclose, Tami Nussbaum: Takeda: Employee, Suna Park: Nothing to Disclose, Seth Spector: Nothing to Disclose, Gregory Bigford: Nothing to Disclose, Brian Garnet: Nothing to Disclose, Michael Campos: Nothing to Disclose, Binu John: Exact Sciences: Grant/Research Support, Genentech: Grant/Research Support, Glycotest, Inc: Grant/Research Support, Gilead: Grant/Research Support, Takeda: Grant/Research Support, Exelixis: Consultant, Exact Sciences: Received institutional research funding, Genentech: Received institutional research funding, Takeda: Received institutional research funding, Madrigal: Advisor, Ipsen: Advisor.

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0198 | RESIDUAL HEPATIC, NEUROLOGIC, AND PSYCHIATRIC DISEASE BURDEN IN TREATMENT-EXPERIENCED PATIENTS WITH WILSON DISEASE: BASELINE FINDINGS FROM THE FOCUS PHASE 3 TRIAL

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Background: Wilson disease (WD) is a rare, progressive, autosomal-recessive disorder of copper accumulation that drives hepatic, neurologic, and psychiatric morbidity. Real-world cohorts have documented persistent disease across these domains despite long-term treatment with penicillamine, trientine, and/or zinc, the current standard-of-care (SoC) therapies. To characterize the residual disease burden among patients receiving SoC, we analyzed baseline data from the FoCus trial (NCT03403205), the largest randomized controlled WD trial conducted to date. **Methods:** The FoCus trial was a multicenter Phase 3 randomized controlled trial evaluating tiomolibdate choline (TMC; ALXN1840) head-to-head against SoC. Patients aged ≥ 12 years with a confirmed diagnosis of WD (Leipzig score ≥ 4) were eligible for enrollment at clinical centers in 22 countries, including North America, Europe, and Asia. Exclusion criteria included severe hepatic (MELD > 13), neurologic (inpatient care required), and renal (ESRD) comorbidities. Patients were categorized based on prior WD treatment history as t reatment-naïve (TN, ≤ 28 days) or -experienced (TE, > 28 days). Baseline disease burden was characterized using cirrhosis status, Unified WD Rating Scale (UWDRS), Brief Psychiatric Rating Scale (BPRS-24), 24-hour urine copper excretion (UCE), and non-ceruloplasmin-bound copper (NCC). **Results:** Of 207 patients (189 adult, 18 adolescent) enrolled in the FoCus trial, 77% were TE with a median 9.3 yrs of prior WD treatment. Cirrhosis was present at baseline in 39% of TE patients and 30% of TN patients. Neurologic symptoms were frequent, with UWDRS Part II or Part III score > 0 in 79% of TE and 83% of TN patients. UWDRS Part III scores were greater than the minimum clinically important difference (4.67 points) in 55% of TE and 51% of TN patients. Psychiatric symptoms were present in 75% of TE and 70% of TN patients. In the TE group, 47% had NCC within the target range per treatment guidelines (5–15 µg/dL). Among patients on SoC > 12 months, 31% had a baseline 24-hour UCE above guideline-directed targets for maintenance treatment. **Conclusion:** After a median of nearly 10 years on SoC, TE patients with WD continued to exhibit substantial multi-system disease, including cirrhosis in nearly 40%, persistent neurologic or psychiatric symptoms in the majority, fewer than half within the guideline-recommended NCC target range, and approximately one-third with 24-hour UCE above guideline-directed maintenance targets. These data underscore the inability of existing WD therapies (penicillamine, trientine, and/or zinc) to fully address the disease burden of WD and the high unmet need for novel therapeutic approaches.

Disclosures: Frederick Askari: Alexion: Advisor, Ultragenyx Pharmaceutical, Inc.: Advisor, Vivet: Advisor, Deep Genomics: Advisor, Intercept: Advisor, Valentina Medici: Orphalan: Advisor, Arbormed: Research Grant, Ultragenix: Grant/Research Support, Vivet: Grant/Research Support, Eton Pharmaceuticals: Consultant, Mars Inc.: Advisor, Prime Medicine: Grant/Research Support, Thomas Sandahl: Nothing to Disclose, Chandler Robinson: Nothing to Disclose, Andrew Cittadine: Monopar Therapeutics: Executive role, Monopar Therapeutics: Stock - publicly traded company, Declan Tuffy: Monopar Therapeutics: Employee, Karl Heinz Weiss: Nothing to Disclose, Aftab Ala: Nothing to Disclose.

0199 | ANALYSIS OF ACUTE HEPATIC PORPHYRIA METABOLITE (ALA/PBG) FLUCTUATIONS AND ATTACK RATE WITH GIVOSIRAN TREATMENT IN THE PHASE 3 ENVISION STUDY

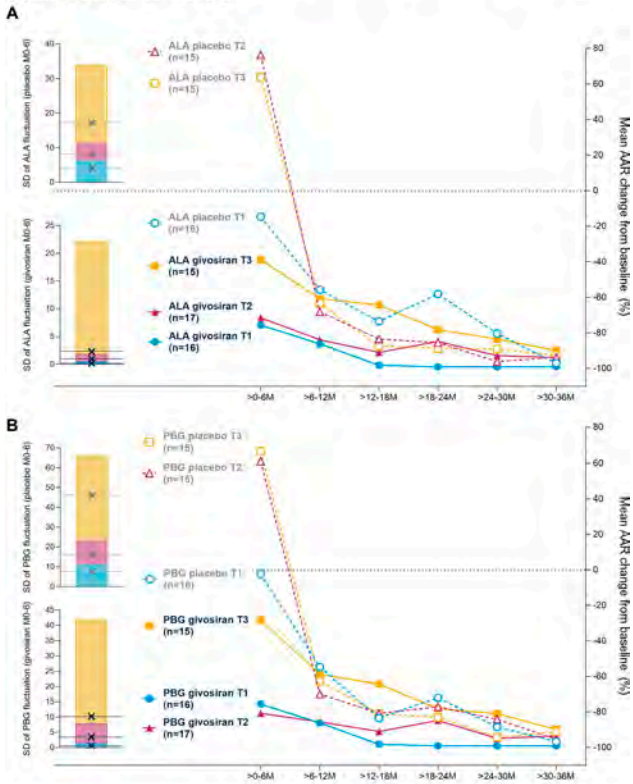
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Background: Acute hepatic porphyrias (AHPs) are rare disorders of hepatic heme synthesis resulting in elevated levels of the toxic metabolites δ-aminolevulinic acid (ALA) and porphobilinogen (PBG). Patients may present to hepatologists with recurring acute attacks characterized by severe abdominal pain, nausea, and neuropsychiatric symptoms, and may also experience chronic symptoms and low health-related quality of life (HRQoL). In the phase 3 ENVISION trial (NCT03338816), givosiran, an RNA interference therapeutic approved for AHP treatment, led to reduction of ALA/PBG levels, sustained reductions in annualized attack rate (AAR), and improved HRQoL. This *post hoc* analysis investigated how early fluctuations in ALA/PBG influenced AAR and HRQoL with givosiran treatment. **Methods:** Patients with AHP ≥12 years old with ≥2 attacks requiring hospitalization, urgent care, or intravenous hemin at home in the 6 months (M) before randomization entered a placebo (PBO)-controlled 6M double-blind (DB) period followed by a 30M open-label extension, in which all patients received givosiran (givo). Patients within each treatment sequence arm (PBO/givo and givo/givo) were split into tertiles (T) by standard deviation (SD) in ALA or PBG levels recorded between 0.5M and 6M of the DB period. **Results:** The analysis included 94 patients. Most patients (n = 89) had acute intermittent porphyria, among whom the most common *HMBS* variant was c.517C > T (n = 12 patients); 2 patients had AIP without an identified variant. Variant distribution was similar across tertiles. During the DB period (> 0-6M), patients in the PBO/givo group with low ALA/PBG fluctuation (T1) had a lower mean (SD) AAR than those in the medium (T2) and high (T3) fluctuation tertiles (ALA, 6.1 [6.1] vs 20.3 [16.4] and 16.4 [12.7], respectively; PBG, 8.7 [9.2] vs 17.4 [16.2] and 16.5 [13.7], respectively). AAR decreased with givosiran initiation in all tertiles of both treatment sequences and continued to decrease with each 6M interval (**Figure**). Mean percentage reductions from baseline in AAR were similar across treatment sequences and ALA tertiles by > 30-36M of treatment (PBO/givo, −97%, −94%, and −93%; givo/givo, −99%, −94%, and −90%; for T1, T2, and T3, respectively). Similar findings were observed in the analysis of PBG (**Figure**). An increase from baseline in EQ-VAS scores was observed in all groups at 36M. Apart from ALA T3 and PBG T2 in the PBO/givo group, all groups achieved a clinically meaningful increase of ≥7-8 points on the EQ-VAS at 36M (mean change from baseline between 11.2 [PBO/givo PBG T3] and 22.1 [givo/givo ALA T3] points). **Conclusion:** Patients with higher ALA/PBG fluctuation during the first 6M had greater attack burden. However, AAR decreased with continued givosiran treatment and converged across all tertiles by 36M. HRQoL improvements were also observed. The results support that long-term benefits of givosiran extend even to patients with early fluctuations in AHP metabolites.

Tertile Thresholds and Mean AAR Change From Baseline by ALA Fluctuation (A) and PBG Fluctuation (B)



Tertiles were defined separately within each treatment sequence and biomarker using the SD of ALA or PBG during the DB period (excluding baseline). Inset figure panels show tertile thresholds for each biomarker and treatment sequence; median values for SD in ALA/PBG within each tertile are shown by horizontal lines and crosses.
AAR, annualized attack rate; ALA, δ-aminolevulinic acid; DB, double-blind; M, month; PBG, porphobilinogen; SD, standard deviation; T, tertile.

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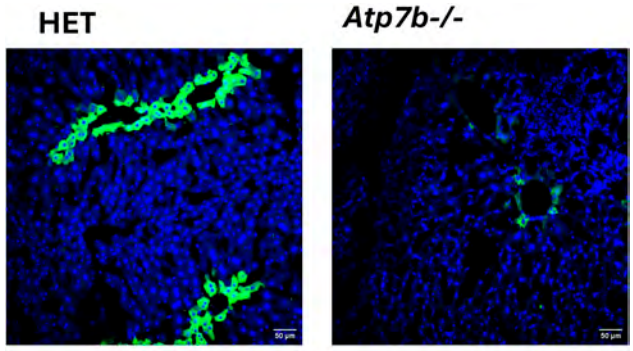
0200 | ATP7B INACTIVATION DISRUPTS HEPATIC METABOLIC ZONATION AND DRIVES DIET-DEPENDENT STEATOHEPATITIS IN A MOUSE MODEL OF WILSON DISEASE.

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Background: Wilson disease (WD) is caused by inactivating mutations in ATP7B, the hepatic copper (Cu) transporter, resulting in progressive Cu accumulation and liver injury. Hepatic steatosis is an early and clinically significant manifestation of WD; however, its mechanistic basis remains poorly defined. Critically, hepatic Cu burden does not correlate with the severity of steatosis, suggesting secondary pathogenic determinants. The liver executes metabolic functions in a spatially segregated manner along the periportal-to-pericentral axis, with copper handling and fatty acid oxidation concentrated in the peri-portal area and lipogenesis in the peri-central area. How Atp7b deficiency affects this zonation remains unknown. **Methods:** snRNAseq was conducted on the livers of our established in vivo model of WD, of Atp7b -/- mice, and het controls. Transcription factor regulon activity was inferred by SCENIC. Findings were validated by immunofluorescence (IF) and RNAscope. LXR agonist treatment was administered to Atp7b$^{-/-}$ mice to assess pathway rescue. Atp7b$^{-/-}$ mice were subjected to a high-calorie diet to model WD-related steatohepatitis. **Results:** Atp7b inactivation induced significant hepatocyte depletion with reciprocal expansion of non-parenchymal cells, including stellate cells, endothelial cells, and cholangiocytes, confirmed by IF. The decrease in hepatocytes was accompanied by a loss of periportal-to-pericentral metabolic zonation, with SCENIC analysis implicating downregulation of the Tcf7l2 regulon as a candidate transcriptional mechanism. IF also revealed a pan-hepatocyte increase in β-catenin alongside disruption of its pericentral compartmentalization, pointing to a broad dysregulation of the zonation program. Intercellular communication analysis identified suppression of LXR multicellular signaling in Atp7b$^{-/-}$ livers. LXR agonist treatment restored the Tcf7l2 regulon, rescued hepatic zonation, and normalized non-parenchymal cell composition, thereby implicating the LXR pathway as a potential therapeutic target for WD. These findings prompted investigations into whether a lipogenic high-carbohydrate diet deficient in LXR agonists exacerbates hepatic pathology during copper overload. This dietary regimen stimulated steatohepatitis in the Atp7b mice, generating a long-sought-after animal model for studying the prevalent dysregulated hepatic fat accumulation in WD. **Conclusion:** These findings show that Atp7b inactivation in WD promotes hepatic pathology by altering metabolic periportal-pericentral zonation through the downregulation of the Tcf7l2 regulon. LXR pathway activation represents a candidate therapeutic strategy warranting further investigation. A high-calorie diet devoid of LXR agonists triggers steatohepatitis in the context of copper overload, establishing nutritional status as a secondary determinant of excessive hepatic lipid accumulation in WD.



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0201 | REAL WORLD EVIDENCE OF THERAPY IMPACT IN UNSTABLE WILSON DISEASE USING NON-CERULOPLASMIN BOUND COPPER BY SPECIATION AS A NOVEL MONITORING TOOL

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Background: Monitoring of efficacy and adherence in Wilson disease (WD) remains challenging, underscoring a substantial unmet need for accurate and clinically practical biomarkers to tailor treatment. Non-ceruloplasmin bound copper by speciation (NCC-Sp) measures circulating bioavailable copper and as a monitoring tool has been associated with better biochemical outcomes in treated WD patients (Ott P. et al JHEP Rep 2024). **Aim:** To describe changes in NCC-Sp in a real-world setting of biochemically unstable WD patients on standard of care over 12 months by different treatment modalities. **Methods:** REASON (NCT05783687) was a prospective, non-interventional study conducted across 9 U.S. sites from

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June 2023 to October 2025. Adult biochemically unstable (determined by AST, ALT or urinary copper excretion [UCE]) WD patients (n = 42) on treatment > 1 year were enrolled. Serum samples were collected and NCC-Sp measurements performed after study completion, with treating physicians blinded to results at the time of clinical decision-making. Changes from baseline (BL) to end of study (EOS) in NCC-Sp, 24-hour UCE, AST and ALT were evaluated for patients receiving chelators, zinc, or combination therapy. Only patients with both BL and EOS values were included. **Results:** NCC-Sp (ng/ml), mean (SD) declined from BL to EOS across all three treatment groups: chelators -26.0 (57.73), zinc -14.1 (19.72), and combination -40.6 (54.42), though high standard deviations reflect considerable inter-individual variability. UCE (mcg/d) decreased at EOS by -62.7 with chelators and -53 in combination therapy, while zinc patients most often were changed to chelators or combination zinc + chelator with an increase (+90.0). Chelators demonstrated the most consistent liver enzyme improvements with reductions in both ALT (-18.2 IU/L) and AST (-16.5 IU/L). Zinc revealed modest reductions in both enzymes. Combination therapy showed minimal changes in AST and ALT (see table). **Conclusion:** The fact that NCC-Sp declined across all therapy groups in biochemically unstable WD patients suggests NCC-Sp can be used to track treatment responses. In patients on combination therapy, NCC-Sp may be the most useful biomarker to follow given the variability and unknown targets for UCE. NCC-Sp as a measure of bioavailable copper has the potential to improve current recommended monitoring, including personalizing therapy. Larger studies are needed to validate these findings.

Unstable patients with both BL and EOS results	Chelators (n=30)	Zinc (n=6)	Combination (Zinc + Chelator) (n=6)
NCC-Sp (ng/ml) BL, mean (SD)*	100.5 (73.41)	95.2 (29.32)	102.6 (38.58)
Change from BL	- 26.0 (57.73)	-14.1 (19.72)	-40.6 (54.42)
24h UCE (mcg/d) BL, mean (SD)**	375.1 (275.78)	91.7 (23.73)[†]	278.4 (227.84)
Change from BL	- 62.7 (250.63)	90.0 (209.07)	- 53.0 (148.08)
ALT (IU/L) BL, mean (SD)***	89.3 (72.11)	77.5 (39.13)	72 (33.83)
Change from BL	-18.2 (61.42)	-13.5 (31.55)	3.8 (20.11)
AST (IU/L) BL, mean (SD)***	56.7 (53.96)	42.0 (21.40)	67.5 (42.19)
Change from BL	-16.5 (52.42)	-5.0 (13.59)	-15.8 (38.78)

*All patients had both BL and EOS results
** Numbers with results at both time periods: 15/30 on chelators, 5/6 on zinc, and 3/6 on combination
*** Numbers of patients with results at both time periods: 22/30 on chelators, 4/6 on zinc, and 4/6 on combination
All patients were on chelators or combination zinc + chelator by EOS

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0202 | SPLEEN SIZE CORRELATES WITH INCREASED LIVER STIFFNESS MEASUREMENT ON MRI BUT HAS LOW POSITIVE PREDICTIVE VALUE FOR CIRRHOSIS IN MASLD

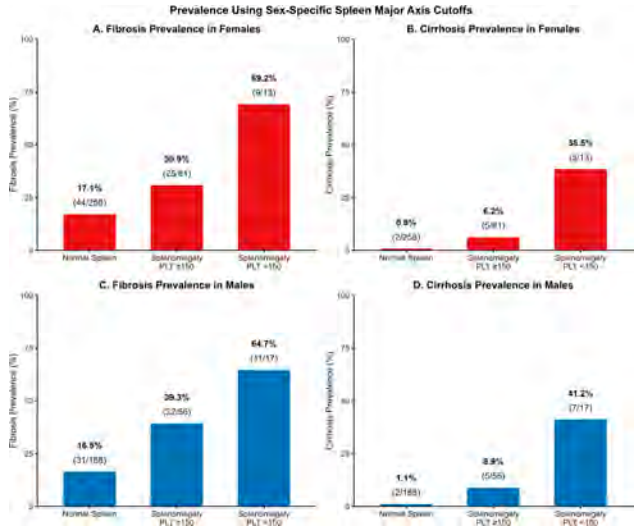
Kyle Rodrigues[1] Brian Derstine[1] Grace Su[2] Vincent Chen[1], [1]University of Michigan, [2]University of Michigan Medical Center

Background: The presence of splenomegaly is often a trigger for portal hypertension concern and cirrhosis. However, data are limited about the association between spleen size and liver disease severity, especially in non-cirrhotic conditions like Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD). In this study of MASLD patients, we aim to better characterize the relationship between spleen size parameters and liver stiffness measurements (LSM) to elucidate the extent to which spleen size predicts fibrosis and cirrhosis. **Methods:** We included 693 adult patients with MASLD who underwent an abdominal MRI with liver elastography in the University of Michigan Health System. MRI scans were processed using TotalSegmentator for spleen measurements. Cutoffs of LSM $\geq$ 3.1 kPa were used for significant fibrosis (SF) and LSM $\geq$ 5 kPa for cirrhosis. Splenomegaly was defined as spleen major axis or spleen volume $\geq$ 2 standard deviations above a normal population mean. **Results:** The median age of the of the cohort was 53 years old; 58% were female and

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83% were Caucasian. Median BMI was 34.8 kg/m^2 and prevalence of diabetes, hypertension, and dyslipidemia was 42%, 62%, and 59% respectively. 24% of patients had SF and 5% had cirrhosis. Male sex (Spearman r = 0.23), height (Pearson r = 0.28), weight (Pearson r = 0.39), BMI (Pearson r = 0.27), and diabetes (Spearman r = 0.13) were associated with increased spleen major axis length (all p < 0.001). Spleen volume and spleen major axis length had an r $\asymp$ 0.2 correlation with LSM, and patients with SF had larger mean spleen volume and major axis length than those without. After adjusting for weight, height, age, and diabetes, each 1 cm increase in spleen major axis was associated with increased odds of SF in women (OR: 1.40, 95% CI 1.24-1.60, p < 0.001) and men (OR: 1.31, 95% CI 1.16-1.49, p < 0.001). Similar findings were seen with each 1 cm increase in spleen major axis length for cirrhosis in women (OR: 2.25, 95% CI 1.70-3.23, p < 0.001) and men (OR: 1.41, 95% CI 1.17-1.72, p < 0.001). In women, the prevalence of SF was 17.1%, 30.9%, and 69.2% in patients with spleen major axis < ULN, ≥ ULN with platelets ≥ 150x10^9 /L, ≥ ULN with platelets < 150x10^9 /L, respectively (p < 0.001). The corresponding values in men were 16.5%, 39.3%, and 64.7% (p < 0.001). A similar trend was seen for cirrhosis (Figure) and when spleen volume was used. Within each sex, spleen size, and platelet count category, obesity or diabetes were only weakly associated with higher prevalence of SF (< 25%) or cirrhosis (< 15%) after excluding comparisons of < 10 patients. **Conclusion:** Larger spleen size is associated with higher prevalence of fibrosis and cirrhosis in MASLD patients undergoing MR elastography, especially those with thrombocytopenia. However, most MASLD patients with splenomegaly and normal platelet counts did not have MR elastography evidence of SF let alone cirrhosis. Isolated splenomegaly should not be considered an indicator of cirrhosis in MASLD.



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0203 | MRI-PDFF PLUS AST IDENTIFIES PEDIATRIC MASH, AND LONGITUDINAL MRI-PDFF REDUCTION PREDICTS HISTOLOGIC RESPONSE

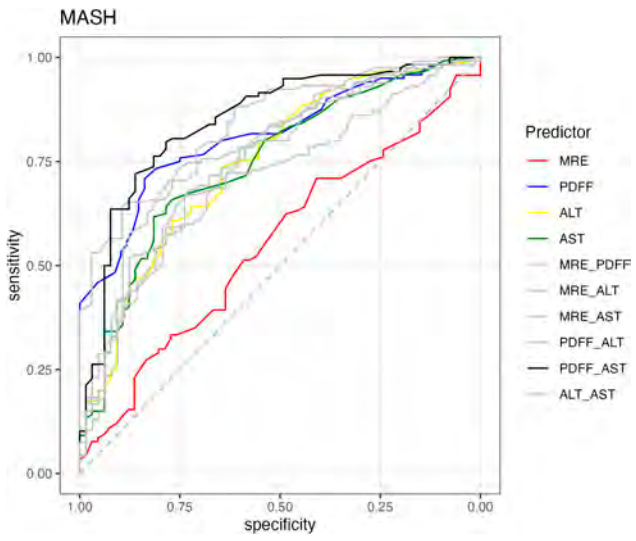
Laurin Koenke[1] Xinlian Zhang[1] Andrea Schreck[1] Raphael Yoo[1] Rush Chewning[1] Jerry Dwek[1] Denise Malicki[1] Phillipp Hartmann[1], [1]University of California San Diego

Background: Pediatric metabolic dysfunction-associated steatotic liver disease (MASLD), particularly metabolic dysfunction-associated steatohepatitis (MASH), is associated with fibrosis, morbidity, and long-term mortality. Reliable biomarkers beyond ALT/AST to detect pediatric MASH and fibrosis are lacking. We compared MRI-based modalities, alone or combined with routine biochemical markers, for detecting MASH and fibrosis stages in children. **Methods:** We prospectively enrolled 190 children with biopsy-confirmed MASLD who underwent MR elastography (MRE) and MRI-proton density fat fraction (PDFF) within 100 days of biopsy, plus 30 healthy controls. Alanine and aspartate aminotransferases (ALT and AST) were assessed. Analyses included t-tests, logistic regression, areas under the curve (AUCs), and Pearson correlations. **Results:** Children with MASLD had mean age 13.0 years, 76.8% were boys, mean body mass index was 33.3, mean NAFLD activity score (NAS) was 3.98, and fibrosis stages were F0 n = 47, F1 n = 82, F2 n = 39, F3 n = 21, and F4 n = 1. MRI-PDFF, MRE, ALT, and AST were higher in patients with MASLD than controls. Among children with MASLD, MRE correlated with fibrosis stage (R = 0.28, p < 0.001) but not NAS, whereas MRI-PDFF correlated with fibrosis stage (R = 0.22, p = 0.002) and NAS (R = 0.5, p < 0.001). AUCs for MRE vs MRI-PDFF were 0.55 vs 0.81 for MASH, 0.56 vs 0.65 for F2-F4, and 0.73 vs 0.69 for F3-F4, respectively. Logistic regression using up to all four biomarkers achieved AUCs of 0.88 for MASH and 0.87 for F3-F4. A simplified, clinically applicable two-parameter model, the sum of PDFF and AST, detected MASH with AUC 0.85 (Figure) and F3-F4 with AUC 0.86. Of note, MRI-PDFF > 30% ruled in MASH (100% specificity/PPV), and PDFF+AST < 70 ruled out advanced fibrosis (100% sensitivity/NPV).Longitudinally, over a mean 1 year 7.5 months between biopsies, ≥ 30% relative MRI-PDFF improvement predicted MASH

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resolution (odds ratio [OR] 18.33, p = 0.02; AUC 0.77; sensitivity 0.92; specificity 0.63), while ≥ 60% improvement had AUC 0.88 (sensitivity 0.75; specificity 1.00). In the important MASH F2-F3 subgroup, relative MRI-PDFF change correlated with NAS change (R = 0.76, p = 0.004) and fibrosis stage change (R = 0.7, p = 0.012), whereas MRE change did not correlate with NAS or fibrosis stage change. In this subgroup, ≥ 30% MRI-PDFF improvement had AUC 0.83 for fibrosis improvement (sensitivity 1.00; specificity 0.67), and ≥ 60% improvement had AUC 0.75 (sensitivity 0.67; specificity 0.83). For MASH resolution, ≥ 30% MRI-PDFF improvement had AUC 0.83 (sensitivity 1.00; specificity 0.67), and ≥ 60% improvement had AUC 0.92 (sensitivity 0.83; specificity 1.00). **Conclusion:** PDFF+AST detects MASH and rules out advanced fibrosis with high certainty in children. Relative PDFF improvement predicts histologic response on repeat biopsy, including in MASH with F2-F3, supporting MRI-PDFF as a pediatric MASH trial endpoint.



Disclosures: Laurin Koenke: Nothing to Disclose, Xinlian Zhang: Nothing to Disclose, Andrea Schreck: Nothing to Disclose, Raphael Yoo: Nothing to Disclose, Rush Chewning: Nothing to Disclose, Jerry Dwek: Nothing to Disclose, Denise Malicki: Nothing to Disclose, Phillipp Hartmann: Nothing to Disclose.

0204 | MAPS: A NEW NON-INVASIVE SCORE FOR IDENTIFYING MASH AND PREDICTING DISEASE PROGRESSION

Yousif Alyousifi[1] Chinmay Raut[1] Lishi Yin[1] Antonino Oliveri[2] Emma Ulrich[1] Vincent Chen[1] Yanhua Chen[1] Elizabeth Speliotes[3], [1]University of Michigan, [2]Univerity of Michigan, [3]University of Michigan Medical Center

Background: Metabolic dysfunction-associated steatohepatitis (MASH) affects up to 14% of adults and can progress to cirrhosis and hepatocellular carcinoma; however, diagnosis often requires liver biopsy or MRI, which are invasive, expensive, and not widely accessible. Current non-invasive scores are designed primarily for fibrosis detection; they may miss early MASH and have limited performance in predicting long-term progression risk. We developed MAPS (**M** ASH- **A** ssociated **P** rogression **S** core), a non-invasive score model integrating routine clinical and genetic predictors to identify MASH and predict disease progression. **Methods:** A total of 33,966 UK Biobank (UKBB) participants with MRI-derived liver phenotyping were used to develop MAPS, where MASH was defined as proton density fat fraction (PDFF) ≥ 5% and iron-corrected T1 (cT1) > 800. From 338 candidate variables, we selected seven predictors using BorutaSHAP algorithm. Six machine learning models were evaluated using 10-fold stratified cross-validation; the best model with the highest discrimination was selected as a final model. MAPS was internally and externally validated in a held-out UKBB test set and Michigan Genomics Initiative (MGI) cohort (*n* = 7,521). MAPS' prognostic performance for incident cirrhosis was evaluated and compared with existing fibrosis scores, FIB-4, SAFE, and NFS, in an independent UKBB sub-cohort with ICD-defined MASH (*n* = 11,272). **Results:** MAPS showed strong discrimination in identifying MASH, achieving an AUC of 0.88 (95% CI 0.87–0.89) in the UKBB held-out test set and 0.79 (95% CI 0.75 - 0.82) in MGI. MAPS outperformed MASH-specific scores (AUC 0.76 - 0.83), and fibrosis scores (AUC 0.56 - 0.66) in the UKBB held-out test set. Cirrhosis event rates increased across MAPS risk strata (0.12%, 0.24%, 0.83%). MAPS uniquely detected more true cirrhosis cases (198 vs 47 SAFE, 8 FIB-4, 7 NFS), and cases identified only by MAPS had a longer median time to incident cirrhosis (11.1 vs 6.5–9.3 years), consistent with earlier detection, while maintaining a rule-out negative predictive value of 0.99. **Conclusion:** MAPS accurately identifies MASH and predicts future cirrhosis earlier than other scores using seven key variables, demonstrating improved risk stratification and long-term prediction compared with these other scores across independent cohorts. Our model may help identify high-risk individuals earlier and guide timely preventive or therapeutic interventions before liver disease complications develop and become hard to treat.

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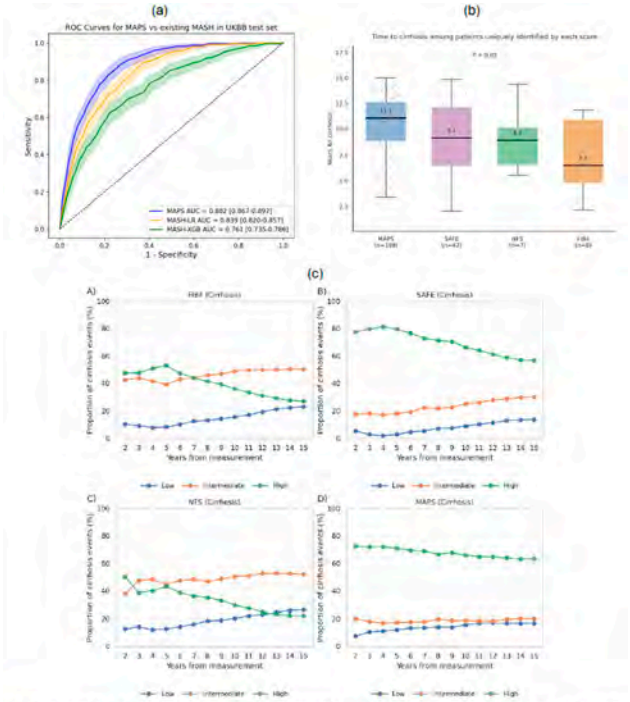


Figure 1. (a) Discrimination performance of MAPS compared with the current MASH-specific scores: MASH-LR by Huang et al.(2025) and MASH-XGB by Njei et al.(2024) using UKBB (Test set) (b) Time to cirrhosis among patients uniquely identified as high-risk by each score. (c) Proportion of cirrhosis events occurring within each risk stratum (low, intermediate, high) over 2–15 years of follow-up for FIB-4, SAFE, NFS, and MAPS.

Disclosures: Yousif Alyousifi: Nothing to Disclose, Chinmay Raut: Nothing to Disclose, Lishi Yin: Nothing to Disclose, Antonino Oliveri: Nothing to Disclose, Emma Ulrich: Nothing to Disclose, Vincent Chen: AstraZeneca: site PI on industry-sponsored trial, Ipsen: site co-I on industry-sponsored trial, Kowa: site co-I on industry-sponsored trial, Madrigal: Grant/Research Support, GSK: Site PI for clinical trial, CSL: Site PI for clinical trial, Yanhua Chen: Nothing to Disclose, Elizabeth Speliotes: University of Michigan: Pending patent on use systems for MASLD/insulin resistance.

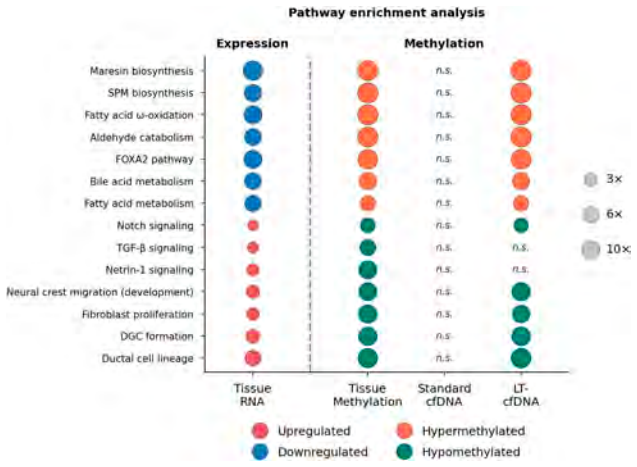
0205 | PLASMA CFDNA METHYLATION ENABLES NON-INVASIVE SNAPSHOT OF LIVER PATHWAY ACTIVITY, CELL COMPOSITION, AND FIBROSIS STAGE

Anna Mae Diehl[1] Pourya Naderi Yeganeh[2] Amin Naghdloo[3] Leila Bazargan[3] Chong Lu[3] Rajesh Dutta[1] Kuo Du[1] Liuyang Wang[1] Hamed Amini[3] Rohit Loomba[4] Manal Abdelmalek[5] Soheil Damangir[3], [1]Duke University, [2]Harvard Medical School, [3]Hepta Bio, Inc., [4]University of California, San Diego, [5]Mayo Clinic Rochester

Background: Liver biopsy remains the reference for MASH histopathology but is invasive, sampling-limited, and unsuited to large-scale or longitudinal studies. Plasma cfDNA methylation carries liver-derived information, but in chronic disease the signal is distributed across millions of fragments with subtle quantitative shifts that conventional locus-by-locus analyses cannot resolve. We aimed to build an AI system purpose-built for liquid biopsy that can recover tissue-level pathway biology non-invasively from cfDNA alone. **Methods:** Using plasma samples from the Duke University Biobank, we generated whole-methylome sequencing of plasma cfDNA from 59 controls and 217 biopsy-confirmed MASLD patients. On all patients with biopsy, bulk liver RNA-seq was performed. Whole methylomes were also generated on a subset of the liver tissues ($n = 50$). Biological ground truth was first established on the data from liver tissue, and then LiquidTransformer (LT) was used to recover the established tissue biology from cfDNA. LT is a novel attention-based AI architecture that treats each of hundreds of millions of cfDNA fragments as a molecular token and learns which fragments carry disease-relevant methylation. Analyses compared F0-F1 with F3-F4 group, adjusting for age, sex, BMI, and type 2 diabetes. **Results:** In tissue, 16,699 differentially methylated CpGs and 2,183 differentially expressed genes converged at the pathway level on coordinated silencing of hepatocyte identity (HNF4A, FXR, PPARα targets) and activation of biliary lineage and developmental signaling. Permutation-based GSEA test identified FOXA2-cascade silencing as the dominant program responsible for repressing the majority of the top transcription factors ($p < 0.001$). We then looked into the recovery of those biological changes non-invasively. Conventional cfDNA analysis recovered little of this signal (Spearman $\rho = 0.07$ plasma vs tissue). LT cfDNA on the other hand recovered most of the signal (Spearman $\rho = 0.54$ LT plasma vs tissue) leading to a 87% pathway-level agreement between plasma cfDNA LT and tissue signal from RNA and methylation. Cell-type deconvolution using LT also revealed graded hepatocyte loss and biliary cell expansion with advancing fibrosis indicating that change in cell composition can also be measured non-invasively. **Conclusion:** Plasma cfDNA methylation, interpreted through purpose-built AI, provides a non-invasive virtual pathology axis of MASH that recovers pathway activity, cell composition, and fibrosis severity from a routine blood draw. LiquidTransformer has previously been shown to outperform current non-invasive tests for identifying patients with significant fibrosis. This study shows that it can read the biology underlying disease progression, supporting risk stratification, mechanistic phenotyping, and treatment selection in the rapidly evolving MASH therapeutic landscape.

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Disclosures: Anna Mae Diehl: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Pourya Naderi Yeganeh: Nothing to Disclose, Amin Naghdloo: Hepta Bio: Employee, Leila Bazargan: Nothing to Disclose, Chong Lu: Nothing to Disclose, Rajesh Dutta: Nothing to Disclose, Kuo Du: Nothing to Disclose, Liuyang Wang: Nothing to Disclose, Hamed Amini: Nothing to Disclose, Rohit Loomba: Eli Lilly and Company: Consultant, 89bio: Consultant, Aardvark Therapeutics: Consultant, Altimmune: Consultant, Alnylam/Regeneron: Consultant, Amgen: Consultant, Arrowhead Pharmaceuticals: Consultant, AstraZeneca: Consultant, Bristol Myers Squibb: Consultant, CohBar: Consultant, Eli Lilly: Consultant, Galmed Pharmaceuticals: Consultant, Gilead: Consultant, Glympse Bio: Consultant, Hightide: Consultant, Inipharma: Consultant, Intercept: Consultant, Inventiva: Consultant, Ionis: Consultant, Janssen, Inc.: Consultant, Madrigal Pharmaceuticals: Consultant, Merck, Metacrine, Inc.: Consultant, NGM Biopharmaceuticals: Consultant, Novartis: Consultant, Novo Nordisk: Consultant, Pfizer: Consultant, Sagimet Biosciences: Consultant, Terns Pharmaceuticals: Consultant, Theratechnologies and Viking Therapeutics: Consultant, 89bio: Stock options, Sagimet Biosciences: Stock options, Arrowhead Pharmaceuticals: Research grant, AstraZeneca: Research grant, Boehringer Ingelheim: Research grant, Bristol Myers Squibb: Research grant, Eli Lilly: Research grant, Galectin Therapeutics: Research grant, Galmed Pharmaceuticals: Research grant, Gilead: Research grant, Hanmi: Research grant, Intercept: Research grant, Inventiva: Research grant, Ionis: Research grant, Janssen, Inc.: Research grant, Madrigal Pharmaceuticals: Research grant, Merck: Research grant, NGM Biopharmaceuticals: Research grant, Novo Nordisk: Research grant, Pfizer: Research grant, Sonic Incytes: Research grant, Terns Pharmaceuticals: Research grant, LipoNexus, Inc.: Co-founder, Cascade Pharmaceuticals: Consultant, Eccogene: Consultant, HeptaBio: Consultant, Metavi: Consultant, Neurobo: Consultant, Novo Nordisk: Consultant, Sourcebio: Consultant, Roche: Consultant, Roche: Consultant, Takeda: Consultant, GSK: Grant/Research Support, Roche: Grant/Research Support, TensorBio: Grant/Research Support, Aarrowhead Pharmaceuticals: Consultant, Boehringer-Ingelheim: Consultant, Altimmune: Grant/Research Support, Eccogene: Grant/Research Support, Heptabio: Grant/Research Support, 89 bio: Grant/Research Support, Takeda: Grant/Research Support, Manal Abdelmalek: 89Bio, Akero, Madrigal, Inventiva, Novo Nordisk, Intercept, Merck,: Advisor, Hanmi, Novo Nordisk: Consultant, Madrigal, Gilead, Inventiva, 89Bio, Akero, Hanmi: Grant/Research Support, Medscape; Clinical Care Options; Fishawack Inc, LLC; CLDF: Speaking and Teaching, Up-to-Date: Royalties or patent beneficiary, Prometheus: Advisor, Novo Nordisk: Consultant, Boehringer-Ingelheim: Grant/Research Support, Soheil Damangir: Nothing to Disclose.

0206 | HERITABILITY OF THE SERUM PROTEOME AND SHARED GENETIC ARCHITECTURE WITH STEATOSIS AND FIBROSIS: A TWIN STUDY

Maria Mironova[1] Igor Wierzbicki[1] Chi-Hua Chen[1] Veeral Ajmera[2] Kaleb Tesfai[1] Seema Singh[1] Egbert Madamba[1] Mary Dalupang[1] Shailja Shah[1] Tatiana Kisseleva[3] Amit Majithia[1] Claude Sirlin[1] David Gonzalez[1] Rohit Loomba[3], [1]UCSD, [2]University of California San Diego, [3]University of California, San Diego

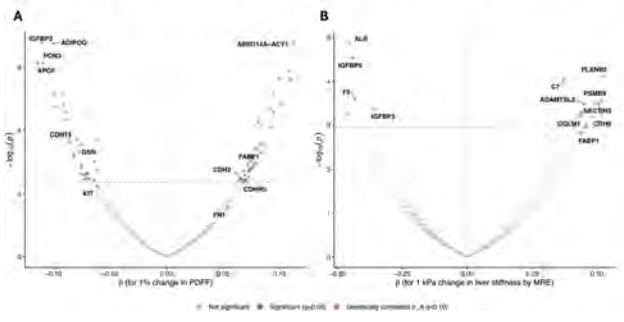
Background: We previously showed that hepatic steatosis and fibrosis in MASLD are heritable. Whether the serum proteome shares genetic determinants with these traits is unknown. Our aim was to estimate serum proteome heritability and its genetic correlation with imaging-quantified steatosis and fibrosis in a well-phenotyped twin cohort. **Methods:** From a prospective twin cohort, we identified 136 twins (46 monozygotic and 22 dizygotic pairs) for serum proteomics; 118 twins also had quantified steatosis by MRI-PDFF and fibrosis by MRE, respectively (24 twins with MASLD and 94 non-MASLD). Untargeted analysis of serum proteome was performed using Orbitrap Astral MS (~850 proteins). Univariate and bivariate AE models, which partition phenotypic variance into additive genetic (A) and unique environmental (E) components, were used to estimate heritability (h^2) and genetic correlation (rA), with age, sex, and race as covariates. A descriptive ACE check classified proteins as stable (shared environment component $c^2 < 10\%$). Differential expression was analyzed using mixed-effects models. Benjamini-Hochberg FDR was used to adjust for multiplicity: significance was defined as $q < 0.10$ (rA) and $q < 0.05$

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(differential expression). **Results:** The serum proteome was highly heritable: 552 proteins were significantly heritable with median $h^2 = 0.48$ (range 0.24-0.86); among those 190 showed no detectable shared environment contribution. Eight proteins were genetically correlated with steatosis - negatively for CDH13, GSN, APOF, KIT, and positively for FABP1, CDH2, FN1, CDHR5. FABP1 was the only protein genetically correlated with fibrosis. Differential abundance was consistent with known MASLD pathophysiology: among proteins upregulated in steatosis were ADH4, ADH1A, SELE, AFM, ADAMTSL2, and downregulated – ADIPOQ, APOF, IGFBP2, SHBG. Among proteins upregulated in fibrosis were C7, PSMB9, CDH6, and downregulated – ALB, IGFBP3, IGFBP5, F5.(Fig 1A-B) Pathway analysis showed suppressed adaptive-immune signaling in steatosis, and upregulated gluconeogenesis/glycolysis and downregulated immune response and lipid transport in fibrosis. Six proteins met all three criteria – heritable, genetically correlated with steatosis, and differentially abundant: APOF, GSN, CDH13, CDH2, CDHR5, and FABP1. (Fig 1A) **Conclusion:** The serum proteome is highly heritable, and a set of proteins shares genetic architecture with hepatic steatosis and fibrosis, indicating that part of inherited risk for MASLD is reflected in measurable circulating proteins. Two liver-enriched proteins stand out: APOF, a lipid-handling apolipoprotein that is heritable, genetically correlated and downregulated in steatosis, and FABP1, the only protein genetically correlated with both steatosis and fibrosis. Both are candidates for genetically informed MASLD risk stratification and warrant testing by Mendelian randomization.

Figure 1. A. Differential expression on continuous MRI-PDFF (β for a 1% change in PDFF from a linear mixed-effects model with twin-pair random effects, adjusted for age, sex, and self-reported race)
B. The same model against continuous MR elastography (β for a 1 kPa change in liver stiffness).



Disclosures: Maria Mironova: Nothing to Disclose, Igor Wierzbicki: Nothing to Disclose, Chi-Hua Chen: Nothing to Disclose, Veeral Ajmera: Nothing to Disclose, Kaleb Tesfai: Nothing to Disclose, Seema Singh: Nothing to Disclose, Egbert Madamba: Nothing to Disclose, Mary Dalupang: Nothing to Disclose, Shailja Shah: Nothing to Disclose, Tatiana Kisseleva: Nothing to Disclose, Amit Majithia: Nothing to Disclose, Claude Sirlin: Bayer: Grant/Research Support, GE Healthcare: Grant/Research Support, Pfizer: Grant/Research Support, Siemens: Grant/Research Support, Butterfly: Grant/Research Support, AMRA: Grant/Research Support, Perspectum: Grant/Research Support, OrsoBio: Independent Contractor, Prosciento: Independent Contractor, Velocity: Independent Contractor, Bayer: Consultant, Boehringer-Ingelheim: Consultant, Ascelia: Consultant, Livivos: Advisor, Livivos: Executive role, Wolters Kluwer: Royalties or patent beneficiary, HealthPro Match: Speaking and Teaching, Foundation for Care Management: Speaking and Teaching, David Gonzalez: Nothing to Disclose, Rohit Loomba: Eli Lilly and Company: Consultant, 89bio: Consultant, Aardvark Therapeutics: Consultant, Altimmune: Consultant, Alnylam/Regeneron: Consultant, Amgen: Consultant, Arrowhead Pharmaceuticals: Consultant, AstraZeneca: Consultant, Bristol Myers Squibb: Consultant, CohBar: Consultant, Eli Lilly: Consultant, Galmed Pharmaceuticals: Consultant, Gilead: Consultant, Glympse Bio: Consultant, Hightide: Consultant, Inipharma: Consultant, Intercept: Consultant, Inventiva: Consultant, Ionis: Consultant, Janssen, Inc.: Consultant, Madrigal Pharmaceuticals: Consultant, Merck, Metacrine, Inc.: Consultant, NGM Biopharmaceuticals: Consultant, Novartis: Consultant, Novo Nordisk: Consultant, Pfizer: Consultant, Sagimet Biosciences: Consultant, Terns Pharmaceuticals: Consultant, Theratechnologies and Viking Therapeutics: Consultant, 89bio: Stock options, Sagimet Biosciences: Stock options, Arrowhead Pharmaceuticals: Research grant, AstraZeneca: Research grant, Boehringer Ingelheim: Research grant, Bristol Myers Squibb: Research grant, Eli Lilly: Research grant, Galectin Therapeutics: Research grant, Galmed Pharmaceuticals: Research grant, Gilead: Research grant, Hanmi: Research grant, Intercept: Research grant, Inventiva: Research grant, Ionis: Research grant, Janssen, Inc.: Research grant, Madrigal Pharmaceuticals: Research grant, Merck: Research grant, NGM Biopharmaceuticals: Research grant, Novo Nordisk: Research grant, Pfizer: Research grant, Sonic Incytes: Research grant, Terns Pharmaceuticals: Research grant, LipoNexus, Inc.: Co-founder, Cascade Pharmaceuticals: Consultant, Eccogene: Consultant, HeptaBio: Consultant, Metavi: Consultant, Neurobo: Consultant, Novo Nordisk: Consultant, Sourcebio: Consultant, Roche: Consultant, Roche: Consultant, Takeda: Consultant, GSK: Grant/Research Support, Roche: Grant/Research Support, TensorBio: Grant/Research Support, Aarrowhead Pharmaceuticals: Consultant, Boehringer-Ingelheim: Consultant, Altimmune: Grant/Research Support, Eccogene: Grant/Research Support, Heptabio: Grant/Research Support, 89 bio: Grant/Research Support, Takeda: Grant/Research Support.

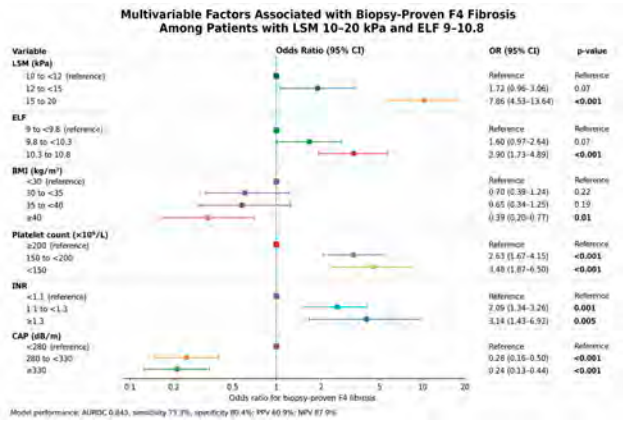
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0207 | RULING OUT CIRRHOSIS IN PATIENTS WITH ELF TEST 9–10.8 AND VCTE LSM 10–20 KPA (HIGH-RISK MASLD)

Mazen Noureddin[1] Winston Dunn[2] Elizabeth Brombosz[3] Gražina Binkauskiene[3] Rashmee Patil[2] Dimple Desai[4] Rohit Puskoor[5] David Huang[6] Nirupama Esther Jerome[5] John Poulos[7] Alaa Abousait[8] Aasim Sheikh[9] Alma Laura Ladrón de Guevara[10] Marcelo Kugelmas[11] Vlad Ratziu[12] Jörn Schattenberg[13] Naim Alkhouri[14], [1]Houston Methodist Hospital, Houston Research Institute, Summit Clinical Research Solutions, [2]Pinnacle at San Antonio, Summit Clinical Research Solutions, [3]Summit Clinical Research Solutions, [4]Pinnacle at Brownsville, Summit Clinical Research Solutions, [5]Pinnacle at Austin, Summit Clinical Research Solutions, [6]Houston Research Institute, [7]Coastal Research Institute, [8]Providence St. Joseph Hospital-Orange, [9]GI Specialists of Georgia, [10]CENTRO DE INVESTIGACION Y GASTROENTEROLOGIA, [11]South Denver Gastroenterology, [12]Service D' Hepatogastroenterologie (FR), [13]Saarland University Medical Center, [14]Summit Clinical Research

Background: There is a growing need for accurate non-invasive tests (NITs) to identify patients with MASH at the highest risk of disease progression while simultaneously ruling out cirrhosis. A combination of ELF 9-10.8 and LSM (VCTE) 10-20 kPa has been suggested to identify such patients with high-risk MASLD. However, the utility of these thresholds in ruling out F4 is unclear. This study aims to identify patients with LSM 10-20 kPa in whom cirrhosis can be accurately ruled out. This is particularly relevant, as recent FDA discussions emphasize combining high-sensitivity and high-specificity NITs when replacing biopsy for ruling out cirrhosis in clinical trials. **Methods:** A multicenter database of patients screened for enrollment in at-risk MASH and MASH cirrhosis trials was reviewed retrospectively. The analysis included patients with biopsy-proven F2-F4 MASH with LSM 10-20 kPa and ELF 9-10.8. Binary logistic regression was used to identify factors associated with biopsy-proven F4 vs F2/F3. Variables associated with F4 with $p < 0.10$ in univariable analysis were considered for inclusion in multivariable candidate models. Separate analyses were performed using predictors modeled as continuous or categorical variables. Model performance was assessed using AUROC, AIC, and likelihood ratio testing. **Results:** A total of 1316 patients were included in the analysis, of whom 29% were F4 and 71% were F2/F3. Demographically, patients with F4 were older (median, IQR: 61 [54-67] vs 58 [51-64] years; $p < 0.001$). Race ($p = 0.007$) and ethnicity ($p = 0.050$) differed between groups, with patients with F4 less likely to be Hispanic/Latino (28.4% vs 34.8%) and less likely to identify as American Indian or Alaska Native (4.1% vs 8.0%). In the multivariable analysis using continuous variables, the top-performing model incorporated LSM, ELF, BMI, MELD, and platelet count, with an AUROC of 0.840. The best-performing multivariable formula model using categorical variables included LSM, ELF, BMI, platelet count, INR, and CAP, with an AUROC of 0.845, sensitivity of 73.3%, specificity of 80.4%, PPV of 60.9%, and NPV of 87.9%. This model also had the highest observed AUROC of all models tested. **Conclusion:** A combination of LSM, ELF, platelet count, and INR can effectively distinguish patients with cirrhosis from those with high-risk MASLD. Adding platelet count and INR to existing screening algorithms can more accurately identify patients likely to have cirrhosis. This approach may enable fully biopsy-free trial designs and have broader clinical implications for ruling out cirrhosis and guiding initiation of NIT-indicated therapies.



Disclosures: Mazen Noureddin: Nothing to Disclose, Winston Dunn: Nothing to Disclose, Elizabeth Brombosz: Nothing to Disclose, Gražina Binkauskiene: Nothing to Disclose, Rashmee Patil: Akero Therapeutics: Grant/Research Support, Akero Therapeutics: Grant/Research Support, Altimmune: Grant/Research Support, Altimmune: Grant/Research Support, 89Bio: Grant/Research Support, 89Bio: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Boston Pharmaceuticals: Grant/Research Support, Boston Pharmaceuticals: Grant/Research Support, Eli Lilly: Grant/Research Support, Eli Lilly: Grant/Research Support, Helio Health: Grant/Research Support, Helio Health: Grant/Research Support, Inventiva: Grant/Research Support, Inventiva: Grant/Research Support, Madrigal Pharmaceuticals: Grant/Research Support, Madrigal Pharmaceuticals: Grant/Research Support, Madrigal Pharmaceuticals: Speaking and Teaching, Madrigal Pharmaceuticals: Speaking and Teaching, Merck: Grant/Research Support, Merck: Grant/Research Support, Novo Nordisk: Grant/Research Support, Novo Nordisk: Grant/Research Support, Novo Nordisk: Consultant, Novo Nordisk: Consultant,

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0208 | CLINICALLY SILENT ADVANCED LIVER FIBROSIS IN U.S. ADULTS WITH NORMAL AMINOTRANSFERASES: AN EXPLAINABLE ARTIFICIAL INTELLIGENCE ANALYSIS OF NHANES 2017–2018

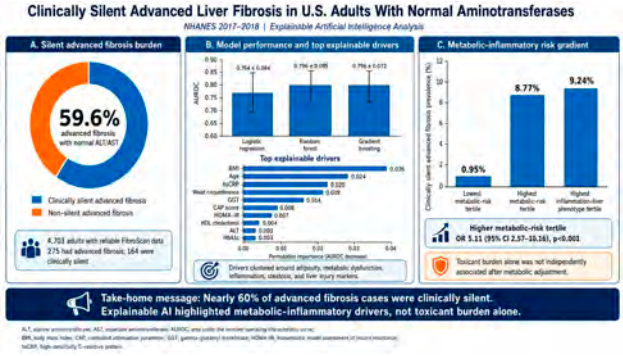
Nayanika Tummala[1] Sri Ram Charan Gundapaneni[2] Serene John[3] Jagadish Koyi[4] Pragathi Munnangi[5]

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Mounika Kotte[6] Digantkumar Patel[7] Hardik Dineshbhai Desai[8] Vinod Nookala[9], [1]NYMC ST Mary's General Hospital St Clares, [2]UCF/HCA Florida Ocala Hospital, Ocala, Florida, United States, 34471, [3]Detroit medical center, Detroit, Michigan, 48201, [4]Integris Health, Oklahoma City, Oklahoma. USA. 73112, [5]BronxCare Health System, Bronx, New York - 10457, [6]Prime south consortium, Weslaco, Texas, USA,78596, [7]Springfield Clinic, Springfield, IL, USA, [8]AB Plus Multispecialty Hospital, Ahmedabad, Gujarat, India, [9]NYMC ST Marys ST Clares

Background: Advanced liver fibrosis may remain clinically unrecognized when aminotransferases are normal. Weevaluated the burden of clinically silent advanced fibrosis and used explainable artificial intelligence toidentify metabolic, inflammatory, liver-related, and environmental predictors among U.S. adults. **Methods:** We analyzed adults from NHANES 2017–2018 with reliable transient elastography data. Hepatitis Cvirus–positive participants were excluded. Advanced fibrosis was defined as liver stiffnessmeasurement ≥ 9.7 kPa. Clinically silent advanced fibrosis was defined as advanced fibrosis withnormal alanine aminotransferase and aspartate aminotransferase. Environmental exposures includedblood lead, cadmium, mercury, and per- and polyfluoroalkyl substance markers. Machine-learningmodels included logistic regression, random forest, and gradient boosting, with permutation-basedexplainability to identify dominant predictors. **Results:** Among 4,703 adults with reliable FibroScan data, 275 had advanced fibrosis, of whom 164 hadnormal aminotransferases. Overall, 59.6% of adults with advanced fibrosis had clinically silentdisease. In the environmental-exposure analytic subset, 1,265 adults were included, with 50 clinicallysilent advanced fibrosis cases. Gradient boosting showed the highest model discrimination, with areaunder the receiver operating characteristic curve 0.796 ± 0.072, similar to random forest, 0.796 ± 0.085, and higher than logistic regression, 0.764 ± 0.084. The strongest explainable predictors werebody mass index, age, high-sensitivity C-reactive protein, waist circumference, gamma-glutamyltransferase, controlled attenuation parameter score, homeostatic model assessment of insulinresistance, high-density lipoprotein cholesterol, alanine aminotransferase, and hemoglobin A1c.Clinically silent advanced fibrosis prevalence increased from 0.95% in the lowest metabolic-risk tertileto 8.77% in the highest tertile. The highest inflammation–liver phenotype tertile showed 9.24%prevalence. High metabolic-risk tertile was independently associated with clinically silent advancedfibrosis, odds ratio 5.11, 95% confidence interval 2.57–10.16, $p < 0.001$. Toxicant burden alone was notindependently associated after metabolic adjustment. **Conclusion:** In NHANES 2017–2018, nearly 60% of adults with advanced fibrosis had normal aminotransferases,highlighting the clinical importance of silent fibrosis detection beyond routine liver enzymes.Explainable artificial intelligence identified adiposity, metabolic dysfunction, inflammation, steatosis,and liver injury markers as the dominant predictors of clinically silent advanced fibrosis, whereastoxicant burden alone was not independently associated after metabolic adjustment.



Disclosures: Nayanika Tummala: Nothing to Disclose, Sri Ram Charan Gundapaneni: Nothing to Disclose, Serene John: Nothing to Disclose, Jagadish Koyi: Nothing to Disclose, Pragathi Munnangi: Nothing to Disclose, Mounika Kotte: Nothing to Disclose, Digantkumar Patel: Nothing to Disclose, Hardik Dineshbhai Desai: Nothing to Disclose, Vinod Nookala: Nothing to Disclose.

★ 0209 | CONTEMPORARY TRENDS IN HEALTHCARE AND ECONOMIC BURDEN OF MASLD, MASH CIRRHOSIS, AND ACLF AMONG HOSPITALIZED PATIENTS IN THE UNITED STATES: A NATIONWIDE ANALYSIS (2016-2023)

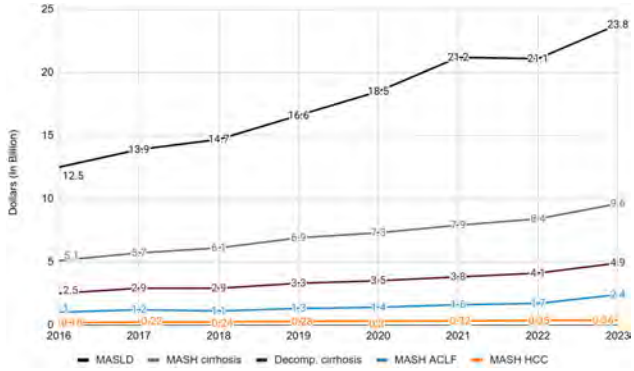
Aalam Sohal[1] Mariam Alamgir[1] Carol Singh[2] Kris Kowdley[1], [1]Liver Institute Northwest, [2]Dayanand Medical College and Hospital

Background: Metabolic-dysfunction associated steatotic liver disease (MASLD) has now emerged as the most common cause of chronic liver disease in the United States. Our study aims to assess the in-hospital healthcare and economic burden of MASLD and its complications among hospitalized patients in the United States between 2016 and 2023. **Methods:** Adult hospitalizations with MASLD were identified using the National Inpatient Sample from 2016 to 2023. Cirrhosis, decompensated cirrhosis, HCC, and ACLF hospitalizations were identified among patients with MASLD. The total healthcare cost was estimated using the cost-to-charge ratio and adjusted for inflation to 2023 dollars. Total hospitalization costs among patients with MASLD,

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stratified by year and by liver-related complications, were also calculated. **Results:** A total of 6.4 million hospitalizations with MASLD were identified. MASLD hospitalizations increased from 618,345 in 2016 to 1.04 million in 2023, reflecting a 68% increase. Total hospitalization costs of MASLD hospitalizations were $142.3 billion between 2016 and 2023. Total hospitalization costs among patients with MASLD nearly doubled from $12.5 billion in 2016 to $23.7 billion in 2023. MASH cirrhosis-associated hospitalizations and decompensated cirrhosis hospitalizations increased from 247,180 patients in 2016 to 411,520 in 2023 (66% increase) and from 99,405 in 2016 to 188,770 in 2023 (89% increase). MASH-related ACLF hospitalizations and HCC increased from 16,355 in 2016 to 54,595 in 2023 (233% increase) and from 7,490 in 2016 to 14,340 in 2023 (91% increase). The proportion of MASLD hospitalizations with cirrhosis remained stable, while the proportion with ACLF nearly doubled during the study period. Total hospitalization costs secondary to MASH cirrhosis, decompensated cirrhosis, ACLF, and HCC were $57 billion, $27.9 billion, $11.7 billion, and $2.3 billion, respectively. Liver transplantation (LT) increased from 2,145 in 2016 to 2,970 in 2023, a 27% increase. Total hospitalization costs increased across the spectrum of MASH, with MASH-related ACLF showing the steepest increase from $1 billion in 2016 to $2.4 billion in 2023. For LT, total hospitalization costs increased from $438 million to $606 million. The proportion of patients requiring LT decreased from 0.35% to 0.28% during the study period. In-hospital mortality decreased from 4.6% in 2016 to 4% in 2023 (with a transient spike during the COVID-19 pandemic) **Conclusion:** Our study reports a striking increase in MASLD hospitalizations and economic burden driven by rising rates of MASH cirrhosis, decompensated cirrhosis, ACLF, and HCC in the United States. Despite an alarming increase in MASLD patients, the rates of liver transplantation and in-hospital mortality have declined, suggesting better management and improved outcomes of MASH. Lifestyle modifications and new pharmacologic therapies are critical to curb this rising healthcare burden.



Disclosures: Aalam Sohal: Nothing to Disclose, Mariam Alamgir: Nothing to Disclose, Carol Singh: Nothing to Disclose, Kris Kowdley: Nothing to Disclose.

0210 | STEATOSIS IS COMMON, FIBROSIS IS SELECTIVE: PREVALENCE AND METABOLIC PHENOTYPING OF MASLD IN A PROSPECTIVE COMMUNITY SCREENING COHORT

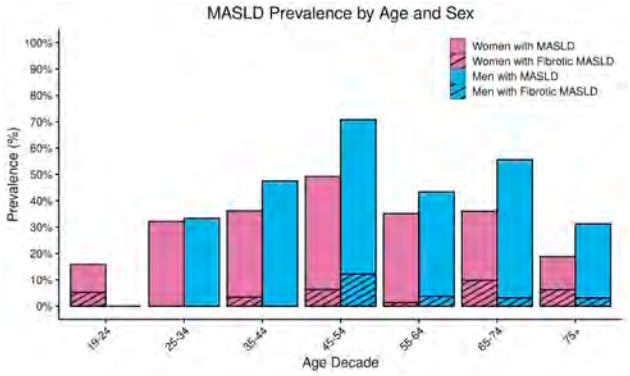
Alina Allen[1] Olivia Bobek[2] Rachel Canning[2] Maysa Eslami[2] Joanne Benson[2] Sudhakar Venkatesh[1] Meng Yin[2] Richard Ehman[1] Graham Rondell[2] Fang-Shu Ou[2], [1]Mayo Clinic Rochester, [2]Mayo Clinic

Background: MASLD is the most common chronic liver disease globally, yet imaging-confirmed community prevalence data stratified by age, sex, and metabolic risk remain scarce. Understanding the true burden and phenotypic spectrum of previously undiagnosed MASLD, including fibrotic disease, is foundational for population-level care planning. **Methods:** The Olmsted NAFLD Epidemiology Study (TONES) is an on-going, prospective, cross-sectional community screening cohort (Olmsted County, MN; NCT04365855). All participants underwent MRI-PDFF and MRE for screening, irrespective of metabolic burden or age; liver biopsy was performed in participants with abnormal MRE findings and interpreted by one study pathologist blinded to imaging results. MASLD was defined as MRI-PDFF $>5\%$ or LSM ≥ 5 kPa irrespective of PDFF to capture burned-out cirrhosis. Fibrotic MASLD was defined by histologic fibrosis stage ≥ 2 or MRE LSM ≥ 3.1 kPa. MetSyn2 was defined as ≥ 2 metabolic syndrome components. Disease prevalence was estimated by sex, age decade, and comorbidity status. **Results:** Between January 2018 and April 2026, 621 adults with no prior history of MASLD were enrolled (mean age 53 years; 56% women; 90.0% White; mean BMI 29.2 kg/m²; 10.5% diabetes). MASLD prevalence was 254/621 (40.9%), peaking in the 45-54 decade (60/104, 57.7%) (Figure). Men had consistently higher MASLD prevalence in older (35+) age group (Figure). MetALD was present in 23/621 (3.7%). Fibrotic MASLD was identified in 25/621 (4.0%), concentrated in high-risk strata: 13/65 (20.0%) in diabetes and 24/211 (11.4%) in MetSyn2. All 25 fibrotic MASLD cases had ≥ 1 metabolic syndrome component; 24/25 (96%) met MetSyn2. A burned-out phenotype (PDFF $\leq 5\%$) was present in 6/25 (24%) of fibrotic MASLD cases. Among individuals with diabetes and fibrotic MASLD, 8/13 (62%) had normal AST and ALT. **Conclusion:** In a prospective community screening cohort with gold-standard liver imaging, undiagnosed MASLD was present in 4 of 10 adults,

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far exceeding clinically coding estimates. Fibrotic MASLD was concentrated in diabetes (20%) and metabolic syndrome (11.4%), was invisible to steatosis-based screening in one-quarter of cases and was undetectable by liver enzymes in the majority of affected individuals with diabetes. These data establish the contemporary epidemiologic foundation for metabolic risk-stratified MASLD screening.



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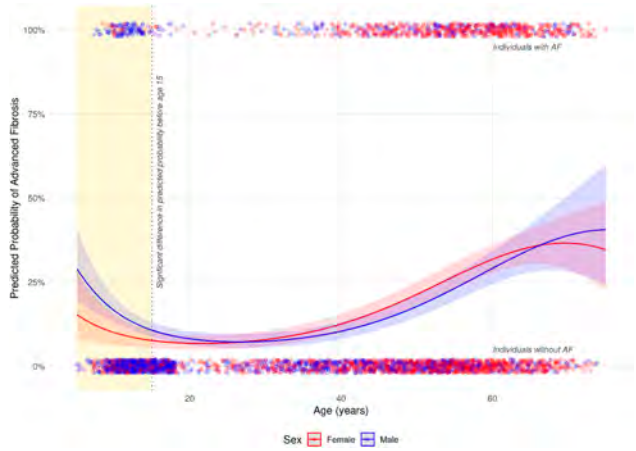
0211 | ADVANCED FIBROSIS IN MASLD SHOWS EARLY MALE PREDOMINANCE BUT NO POSTMENOPAUSAL FEMALE SURGE

Callie Zaborenko[1] Marco Abreu[1] Samer Gawrieh[1] Jingyi Tan[2] Jie Yao[2] Xiuqing Guo[2] Jean Molleston[1] Aaron Hakim[3] Jerome Rotter[2] Naga Chalasani[4] Tae-Hwi Schwantes-An[1], [1]Indiana University School of Medicine, [2]Lundquist, [3]Beth Israel Deaconess Medical Center, [4]Indiana University Medical Center

Background: Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) affects individuals across the lifespan, yet the extent to which sex modifies the relationship between age and fibrosis severity remains poorly understood. We examined (a) sex differences in the proportion of advanced fibrosis (AF, fibrosis stage $\geq$ 3) across the lifespan of MASLD patients and (b) age intervals in which these differences are most pronounced. **Methods:** We conducted a cross-sectional analysis of patients with biopsy-proven MASLD aged 5-75 years in the NASH CRN. Multivariable logistic regressions were conducted to examine the associations between age and AF by sex, adjusting for genetic ancestry, BMI, T2D and a 16 SNP weighted, MASLD polygenic risk score (PMIDR), via doubly robust inverse probability weighted (IPW) models. Sex-by-age interaction terms were tested, and goodness-of-fit indicators guided final models. Predicted probabilities of AF by sex across 5-year age groups were estimated. **Results:** Among 3,322 patients with MASLD (mean age 44.1 years; 53% female, 28% children), 25% had AF. There was a significant interaction between sex and age (Wald test: χ^2 = 54.5, df = 4, p = 4.1e-11) in the risk for AF. The relationship between age and the proportion of patients with AF was U-shaped, with a high prevalence in early childhood, a steep decrease until age 25, then a slow increase until age 70 for both sexes (Figure). In unweighted models, the proportion of AF was higher in boys than girls aged 5-15 and higher in women than men aged 45-55, with no significant difference between sexes at other ages. However, in IPW models, the proportion of AF was higher in boys than girls aged 5-15 (age 5-10: OR = 2.00, 95% CI 1.11-3.61, p = 0.022, age 10-15: OR = 1.60, 95% CI 1.02-2.50, p = 0.039), but there was no longer a difference at age 45-55. There were differences in the rate of change, with the proportion of AF decreasing faster for males aged 5-25, then increasing more slowly for males aged 25-40 (all p < 0.05). We did not observe an inflection point for AF among women around menopausal age. **Conclusion:** Sex differences in AF among MASLD patients are age-dependent, with males bearing a disproportionately higher frequency of AF in childhood. Notably, we did not observe an acceleration in the risk for AF in postmenopausal women. These findings highlight the importance of considering age-specific biologic mechanisms when evaluating fibrosis risk in MASLD.

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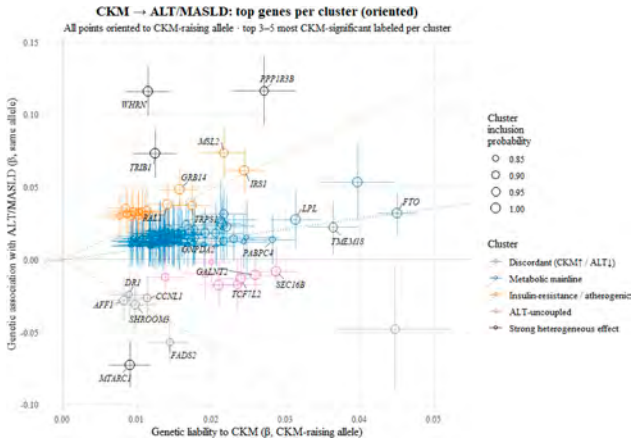
0212 | IS MASLD PART OF CARDIOVASCULAR-KIDNEY-METABOLIC SYNDROME? GENETIC EVIDENCE FOR A CAUSAL, METABOLICALLY-MEDIATED CKM-TO-ALT EFFECT

Eleonora Scorletti[1] Guoyi Yang[2] Daniel Rader[2] Marijana Vujkovic[3], [1]Johns Hopkins University, [2]University of Pennsylvania, [3]Univerrsity of Pennsylvania

Background: The 2023 AHA cardiovascular-kidney-metabolic (CKM) statement placed metabolic dysfunction-associated steatotic liver disease (MASLD) within CKM pathophysiology but not stage definitions. MASLD is increasingly recognized as part of a broader, multi-organ syndrome of metabolic dysfunction, and recent cardiometabolic consensus literature has argued it should be a defining CKM component. Genetic adjudication will require multiple complementary tests. As a first step, we used a European-ancestry CKM construct from 10 metabolic and kidney GWAS to test whether genetic CKM liability is associated with ALT, what biology drives the effect, and to characterize the overlap between CKM lead variants and known liver-specific MASLD loci. **Methods:** We used genomic structural equation modeling (SEM) to model the shared genetic architecture of CKM components, leveraging ten European-ancestry genome-wide association study (GWAS) summary statistics for adiposity, metabolic risk factors, and kidney function. We conducted a multivariate CKM GWAS (Neff = 1,135,862). We performed clustered Mendelian randomization (MR) analyses to identify variant clusters with distinct causal effects of CKM syndrome on MASLD proxied by chronic elevation of alanine aminotransferase (cALT, N = 90,408 cases and 128,187 controls). Variant clusters were mapped to KEGG/Reactome pathways. **Results:** We identified 544 independent variants genome-wide significant for shared CKM components. Because the CKM construct included no liver or ALT input, canonical liver-specific MASLD lead loci were largely absent from the CKM lead set by construction (except PPP1R3B and MTARC1), which does not indicate that MASLD is genetically distinct from CKM. Each 1-SD higher genetic liability to CKM was associated with higher odds of cALT [OR = 1.86 (95% CI 1.68–2.07), p = 3×10^{-30}]. Clustered MR identified three substantive variant clusters with heterogeneous effects on cALT. Most CKM variants showed a moderate effect (metabolic-mainline pattern; Fig.1). However, a smaller insulin-resistance and atherogenic-dyslipidemia cluster, including IRS1, GRB14, MSL2, and SH2B3, showed a stronger effect on cALT. In contrast, a discordant cluster including SHROOM3 and FADS2 indicated an inverse association with cALT. Pathway enrichment supported this biology: the metabolic-mainline cluster was enriched for Maturity-Onset Diabetes of the Young (KEGG), and the insulin-resistance cluster for Receptor Tyrosine Kinase signaling (Reactome). **Conclusion:** Genetically predicted CKM is associated with higher ALT, consistent with a causal effect driven primarily by insulin-resistance/atherogenic-dyslipidemia variants, with a discordant cluster showing an inverse effect. These data establish a strong, metabolically mediated CKM-to-ALT genetic signal; analyses formally testing MASLD's inclusion in CKM are ongoing.

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Disclosures: Eleonora Scorletti: Nothing to Disclose, Guoyi Yang: Nothing to Disclose, Daniel Rader: Nothing to Disclose, Marijana Vujkovic: Nothing to Disclose.

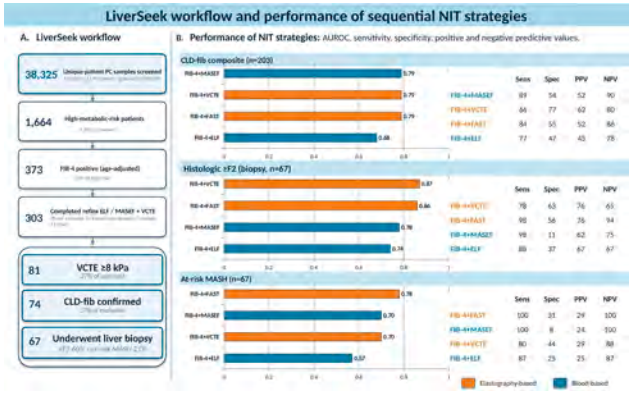
0214 | SEQUENTIAL BLOOD- AND ELASTOGRAPHY-BASED STRATEGIES FOR MASLD FIBROSIS CASE-FINDING IN PRIMARY CARE: PROSPECTIVE VALIDATION OF ELF AND MASEF IN THE LIVERSEEK PROGRAM

Luis Ibáñez Samaniego[1] Susana Sanchez Berdial[1] Laura Suárez[1] Carmen Corps[1] María Sasía[1] Eduardo Montenegro[1] Sonia Irisarri Vega[1] Zhanhui Wang Jiang[1] Andres Conthe[1] Jacobo Caride[1] Francisco Antonio Bernabeu-Andreu[2] Isabel Peligros[1] Luis Menchen[3] Carmen Lorenzo[1] Rafael Bañares[4] Rodolfo Romero[1] Magdalena Salcedo[1], [1]Hospital General Universitario Gregorio Marañón, [2]Hospital Universitario Puerta de Hierro, [3]Hospital General Universitario Gregorio Marañón. Universidad Complutense de Madrid, [4]Universidad Complutense de Madrid, CIBEREHD

Background: Scalable primary care (PC) case-finding for MASLD with significant fibrosis (~1.6% of European adults) is lacking, and ELF and MASEF lack prospective validation in PC. LiverSeek is a laboratory-information-system-driven, passive reflex-testing program for MASLD-related fibrosis case-finding in PC. We aimed to: 1) quantify the yield of LiverSeek for previously undiagnosed MASLD-related fibrosis; 2) prospectively validate ELF and MASEF in PC for significant fibrosis (≥F2); 3) compare sequential NIT strategies combining FIB-4 with ELF, MASEF, VCTE or FAST for hepatology referral in high-metabolic-risk PC patients. **Methods:** Over 6 months, blood samples from individual patients were screened at 11 PC centres in Madrid serving approximately 350,000 residents. Patients aged 50-75y meeting any cardiometabolic criterion — BMI > 30 + HbA1c > 6.5%, HbA1c > 6.5% + ALT > ULN, or BMI > 30 + ALT > ULN — triggered automatic FIB-4 with age-adjusted cutoffs (≥1.30 if <65y; ≥2.00 if ≥65y). When positive, reflex ELF and MASEF were measured and a nurse-led FibroScan scheduled; any positive NIT prompted hepatology referral. Four sequential strategies (FIB-4 + VCTE, FAST, ELF or MASEF) were assessed against: i) histologic ≥F2; ii) chronic liver disease with fibrosis (CLD-fib) defined using LiverScreen-consistent criteria: biopsy F1-F4 or ultrasound with ≥2 CLD/portal-hypertension signs or two consecutive VCTE ≥10 kPa. AUROCs with 95% CIs were compared with DeLong's test; sens, spec, PPV and NPV were computed at prespecified cutoffs (VCTE ≥8 kPa, FAST ≥0.35, ELF ≥9.8, MASEF ≥0.33). **Results:** 38,325 unique-patient samples were screened; 1,664 (4.3%) were high-metabolic-risk. FIB-4 was elevated in 373 (22%); 303 completed reflex testing and elastography (age 61.5 ± 5.7y, 41% female, BMI 31.5 ± 5.1, T2D 62%); 81/303 (27%) had VCTE ≥8 kPa. Biopsied and non-biopsied patients had similar demographic, metabolic and baseline NIT profiles. Yield of previously undiagnosed MASLD-related fibrosis: CLD-fib confirmed in 37%; 67 biopsied (≥F2 60%, at-risk MASH 21%). For ≥F2 (biopsy), AUROCs were FIB-4+VCTE 0.87 (0.77–0.94), FIB-4+FAST 0.86 (0.76–0.95), FIB-4 +MASEF 0.78 (0.65–0.88) and FIB-4+ELF 0.74 (0.60–0.86). For CLD-fib, FIB-4+MASEF (0.79; 0.72–0.85) outperformed FIB-4+ELF (0.68; 0.60–0.75; $p < 0.05$) and showed similar AUROC to FIB-4+VCTE (0.79); FIB-4+MASEF reached sens 89% and NPV 90%. **Conclusion:** (1) The LiverSeek program identifies previously undiagnosed MASLD-related fibrosis at high yield (37% CLD-fib among evaluable; 60% ≥F2 among biopsied).(2) FIB-4+MASEF outperforms FIB-4 +ELF for CLD-fib and performs comparably to FibroScan-based strategies, supporting MASEF as the most informative blood-based reflex test within this PC pathway.(3) For histologic ≥F2, FibroScan-based strategies (FIB-4+VCTE/FAST) remain most accurate; FIB-4+MASEF is a viable one-step blood-based alternative when elastography is unavailable.

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0215 | ENGINEERING INJURY-RESISTANT FUNCTIONAL BILIARY TREES WITH ENHANCED DRUG EFFLUX CAPACITY

Jun Li[1] Shiwen Ma[1] Jiaxian Chen[1] Meiqian Hu[1] Jiaojiao Xin[1] Jing Jiang[1] Dongyan Shi[1], [1]The First Affiliated Hospital, Zhejiang University School of Medicine

Background: The reconstruction of functional biliary trees (FBTs) is crucial in the development of bioengineered liver. However, the decellularized liver scaffolds (DLS) as the scaffold of FBTs exhibit mechanical instability that leads to luminal collapse and subsequent hypoxic stress, severely compromising FBT functions. Furthermore, existing engineered biliary structures lack sufficient injury resistance to withstand toxic stress. **Methods:** This work aimed to generate macro-scale FBTs with drug efflux capacity and injury resistance using DLS as templates and mouse primary cholangiocytes as the cellular source. FBTs were assessed using functional assays, transcriptomic profiling, and hepatotoxic injury testing to validate their structural stability and injury resistance. **Results:** The FBTs generated with genipin-crosslinked DLS exhibited improved structural stability and fluid mechanical properties, which facilitated cholangiocyte adhesion and alleviated hypoxic stress, as supported by downregulation of the HIF pathway. By day 7, FBTs formed relatively stable biliary tree-like structures with greater biliary tree continuity and cell viability than non-crosslinked controls, accompanied by preserved mitochondrial membrane potential as confirmed by JC-1 staining. Morphological evaluation revealed that FBTs recapitulated key features of native biliary networks, including multilevel branching architecture, organized luminal epithelial lining, and proper apical-basal polarity. Scanning electron microscopy further revealed elongated primary cilia projecting toward the biliary lumen and organized epithelial cell-cell junctions. Functionally, compared with conventional Matrigel-cultured cholangiocyte organoids, FBTs showed a more mature biliary epithelial phenotype, characterized by strengthened polarity and barrier integrity together with enhanced biliary transport and P-glycoprotein (P-gp)-mediated drug efflux capacity. Notably, these functional advantages translated into superior resistance to toxic stress, as FBTs better maintained cellular homeostasis and biliary function than organoids following chlorpromazine (CPZ)-induced injury. Verapamil-mediated inhibition of P-gp activity partially compromised this protection, suggesting that P-gp-mediated efflux contributes in part to FBT injury resistance. **Conclusion:** These injury-resistant FBTs with enhanced drug efflux capacity provide a promising functional biliary network for bioengineered liver construction and future translational applications.

Disclosures: Jun Li: Nothing to Disclose, Shiwen Ma: Nothing to Disclose, Jiaxian Chen: Nothing to Disclose, Meiqian Hu: Nothing to Disclose, Jiaojiao Xin: Nothing to Disclose, Jing Jiang: Nothing to Disclose, Dongyan Shi: Nothing to Disclose.

0216 | BILIARY GENE THERAPY

Pervin Choksi[1], [1]UCSF

Background: Delivery of therapeutic genetic cargo to biliary epithelial cells (BECs) is an unmet need for cholangiopathies and cholangiocarcinoma (CCA). The characteristic liver tropism of adenoassociated viral (AAV) capsids applies to hepatocytes, but not BECs. Here, we sought to identify an AAV capsid capable of efficient and specific BEC targeting in healthy and diseased livers. **Methods:** Using next-generation sequencing of the principal liver cell populations we screened a library of 82 barcoded AAV capsids in mice. We validated a lead candidate, AAV-BEC, in mouse models of liver homeostasis, cholestasis and CCA using single-cell RNA sequencing, flow cytometry and 3D imaging. We investigated the translational potential in mice in which mouse BECs were replaced by human

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BECs. All mice were intravenously injected with the same AAV-BEC vector dose of 4×10^{11} viral genomes. **Results:** An AAV-BEC vector expressing Cre recombinase from the ubiquitous CMV promoter achieved 78% transduction of naive BECs, accompanied by off-targeting of hepatocytes (53.6%) and macrophages (10.7%), in fluorescent reporter mice. Equipping the vector with a Prom1 promoter and binding sites for miR-122 and miR-142 reduced off-targeting ($<0.5\%$) while achieving 45% transduction of BECs. In a mouse model of cholangiopathy due to *Abcc12* gene knockout, AAV-BEC-mediated ABCC12 delivery restored biliary function as evidenced by improved bile-duct morphology and reduced blood levels of ALP. In mice with cholestasis due to DDC diet, AAV-BEC-mediated CRISPR knockout of the Notch signaling effector gene *Rbpj* reduced the number of reactive BECs but worsened blood markers of liver injury, consistent with the ductular reaction affording bile drainage. In mice with CCAs induced by the oncogenes NICD and AKT, an AAV-BEC vector achieved 40% transduction of malignant BECs. Moreover, using AAV-BEC for diphtheria toxin-mediated cell ablation in diphtheria toxin receptor-transgenic mice with CCAs efficiently reduced tumor burden as evidenced by the total number of BECs decreasing from 10.8% to 0.35% of non-hepatocyte liver cells. In mice in which the biliary system was partially humanized an EYFP-expressing AAV-BEC vector achieved 40% transduction of human BECs. **Conclusion:** AAV-BEC facilitates efficient and specific in vivo gene delivery to naive, reactive and malignant BECs, providing an opportunity for development of gene therapies for a broad range of biliary diseases.

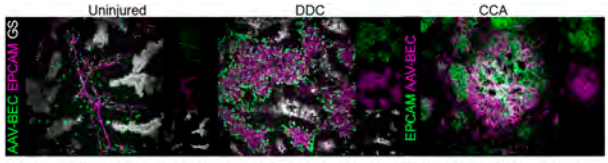


Figure. 3D imaging of uninjured (left) and DDC-injured (middle) livers transduced with an AAV-BEC vector detargeted from hepatocytes and macrophages, and of a CCA in a liver (right) transduced with an AAV-BEC vector with unaltered tropism.
EPCAM labels BECs, GS pericentral hepatocytes.

Disclosures: Pervin Choksi: Nothing to Disclose.

0217 | LIVER-SPECIFIC TJP2 DEFICIENCY IN A HUMANIZED BILE ACID MOUSE MODEL DRIVES CHOLESTATIC INJURY VIA IMMUNE ACTIVATION AND METABOLIC SUPPRESSION

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Background: Progressive familial intrahepatic cholestasis type 4 (PFIC4) is caused by mutations in tight junction protein 2 (TJP2) gene, leading to paracellular bile leakage and progressive liver injury. Conventional *Tjp2*-deficient mice exhibit only mild phenotypes, likely due to the predominance of hydrophilic murine bile acids. We aimed to establish a physiologically relevant PFIC4 model by utilizing a humanized bile acid background. **Methods:** We utilized Cyp2a12/Cyp2c70 double-knockout (CYPDKO) mice to mimic a human-like hydrophobic bile acid profile. Liver-specific Tjp2 deletion was induced via AAV8-mediated CRISPR/Cas9 genome editing. Phenotypic changes were evaluated through serum biochemistry, histology (Sirius Red, IHC for F4/80 and CK19), and transmission electron microscopy. Comprehensive transcriptomic analysis (RNA-seq) and bioinformatic modeling were performed to identify key differentially expressed genes and altered signaling pathways **Results:** Liver-specific *Tjp2* deletion was induced in Cyp2a12/Cyp2c70 double-knockout (CYPDKO) mice using AAV-mediated CRISPR/Cas9 genome editing. Compared to controls, TJP2-deficient CYPDKO mice developed severe liver injury, with elevated serum transaminases and alkaline phosphatase, periportal fibrosis, ductular reaction, and macrophage infiltration. Electron microscopy revealed disrupted tight junction architecture with significantly reduced junctional width.Transcriptomic analysis identified 594 differentially expressed genes (DEGs), characterized by the robust induction of interferon-stimulated genes, innate immune activation, extracellular matrix remodelling, and epithelial stress pathways. Conversely, key metabolic pathways were markedly suppressed, including PPARα signalling, fatty acid oxidation, bile acid transport, and xenobiotic metabolism. These findings suggest that TJP2 deficiency under hydrophobic bile acid conditions triggers a coordinated response involving barrier disruption, interferon-driven inflammation, and metabolic reprogramming. **Conclusion:** Liver-specific *Tjp2* deficiency in a humanized bile acid background recapitulates the key structural, inflammatory, and metabolic features of PFIC4. This model supports a “two-hit” mechanism in which junctional instability and bile acid hydrophobicity synergistically drive liver injury. Our findings establish a physiologically relevant platform for PFIC4 research and highlight nuclear receptor–mediated metabolic pathways as potential therapeutic targets

Disclosures: Thi Hao Vu: Nothing to Disclose, Kota Tsuruya: Eisai Co., Ltd.: Speaking and Teaching, Kowa Company, Ltd.: Speaking and Teaching, Chugai Pharmaceutical Co., Ltd.: Speaking and Teaching, AbbVie GK: Speaking and Teaching, Boehringer Ingelheim: Speaking and Teaching, Yusuke Mishima:

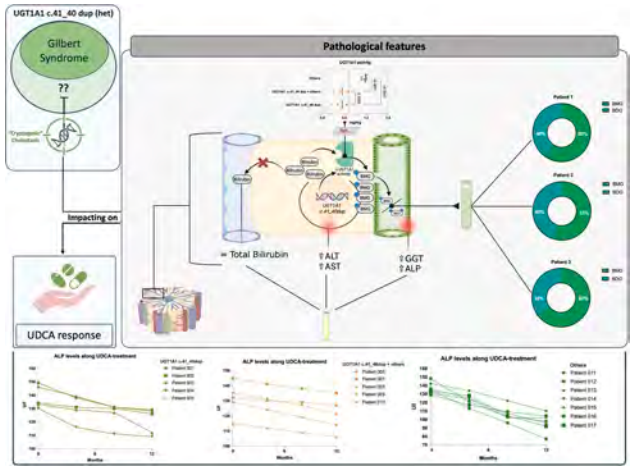
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0218 | BEYOND GILBERT SYNDROME: HETEROZYGOUS UGT1A1 C.41_40DUP DEFINES A DISTINCT CHOLANGIOPATHIC PHENOTYPE IN YOUNG ADULTS WITH UNEXPLAINED CHRONIC CHOLESTASIS

Mario Romeo[1] Fiammetta Di Nardo[1] Carmine Napolitano[1] Paolo Vaia[1] Claudio Basile[1] Giusy Senese[1] Marco Niosi[1] Marcello Dallio[1] Alessandro Federico[1], [1]University Hospital Luigi Vanvitelli, Piazza Miraglia 2, 80138, Naples, Italy

Background: Unexplained chronic cholestasis (UCC) in young adults is traditionally viewed as a disorder of hepatocellular secretion or canalicular transport. However, in a subset of patients, the underlying process may be better explained by a cholangiopathy driven by alterations in bile composition. Uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) is a key enzyme involved in bilirubin conjugation. The heterozygous UGT1A1 c.41_40dup variant, commonly linked to Gilbert syndrome (GS), is frequently detected in individuals without overt manifestations of GS. Even in this context, reduced UGT1A1 activity may shift bilirubin conjugation toward a higher proportion of bilirubin monoglucuronide (BMG) and a lower proportion of bilirubin diglucuronide (BDG). We therefore investigated whether this variant may contribute to a bile composition–driven cholangiopathic phenotype associated with chronic biliary epithelial injury. **Methods:** In this prospective proof-of-concept study, 34 UDCA-naïve young adults with UCC and normal serum bilirubin were enrolled. Patients were stratified as: Group A, isolated heterozygous UGT1A1 c.41_40dup (n = 10); Group B, UGT1A1 c.41_40dup plus additional cholestasis-related variants (n = 11); and Group C, non-carriers with other variants only (n = 13). All underwent targeted next-generation sequencing, liver biopsy, and assessment of hepatic UGT1A1 activity and bilirubin conjugate composition by HPLC. Patients received UDCA (15 mg/kg/day) and were followed for 12 months. At 12 months, biochemical evolution was assessed using ALP levels (> 1.9× ULN) as a pragmatic benchmark. **Results:** Patients harboring the UGT1A1 c.41_40dup variant showed markedly lower hepatic UGT1A1 activity and a significantly higher BMG/BDG ratio than non-carriers (both p < 0.0001), together with a greater prevalence of gallstone-related manifestations. Despite normal serum bilirubin levels, variant carriers displayed persistent elevation of ALP and GGT and a higher prevalence of advanced fibrosis (p = 0.0022). Overall, this constellation of clinical, biochemical, and histological findings was consistent with a cholangiopathy-like phenotype suggestive of ascending cholestatic injury. After 12 months, ALP levels > 1.9× ULN were observed more frequently in variant carriers than in non-carriers (70% vs 28%; p < 0.0001). In exploratory analyses, reduced UGT1A1 activity was associated with this outcome. **Conclusion:** The heterozygous UGT1A1 c.41_40dup variant may act as a non-canonical modifier of bile composition, contributing to a bile composition-driven cholangiopathic phenotype characterized by gallstone disease, hepatocellular injury, fibrosis progression, and reduced UDCA responsiveness. These hypothesis-generating findings support the potential role of UGT1A1 testing in refining phenotypic stratification of young adults with UCC.



Disclosures: Mario Romeo: Nothing to Disclose, Fiammetta Di Nardo: Nothing to Disclose, Carmine Napolitano: Nothing to Disclose, Paolo Vaia: Nothing to Disclose, Claudio Basile: Nothing to Disclose, Giusy Senese: Nothing to Disclose, Marco Niosi: Nothing to Disclose, Marcello Dallio: Nothing to Disclose, Alessandro Federico: Nothing to Disclose.

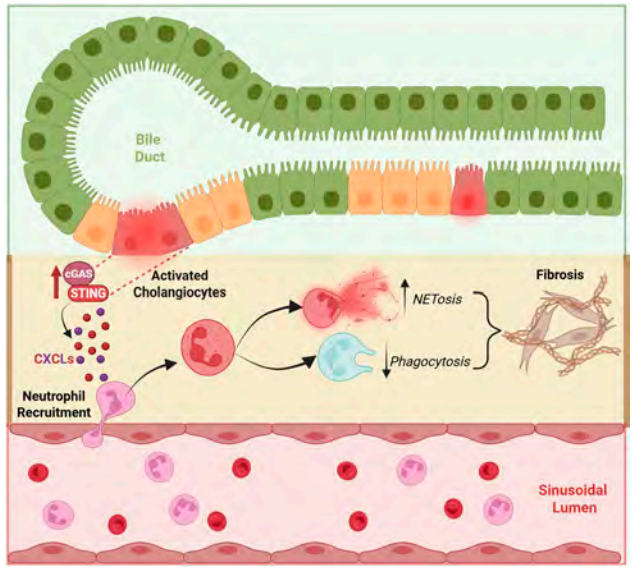
0219 | BILIARY CGAS-STING SIGNALING MEDIATES NEUTROPHILIC INFLAMMATION AND FIBROSIS IN CHOLESTATIC LIVER DISEASE

Mobin Ibne Mokbul[1] Abid Anwar[1] Maleeha Farheen Kalaiger[1] Sofia Jerez[1] Papawee Sutthirat[1] Zhensheng Zhang[1] Usman Yaqoob[1] Purnima Tyagi[1] Jose M. de Hoyos-Vega[1] Alexander Revzin[1] Moira Hilscher[1] Robert Huebert[1] Nidhi Jalan-Sakrikar[1], [1]Mayo Clinic Rochester

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Background: Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease characterized by progressive bile duct inflammation and fibrosis. Although diverse immune cells, including neutrophils, infiltrate the periportal region in PSC, the mechanisms and consequences of their liver recruitment are unknown. The cyclic GMP–AMP synthase–stimulator of interferon genes (cGAS-STING) signaling pathway is a key mediator of inflammatory gene expression in response to cellular stress, but its role in cholestatic disease is undefined. Here, we investigated the role of biliary cGAS-STING signaling in homing neutrophils to the bile duct and modulating their function to promote inflammation and fibrosis in PSC. **Methods:** Human PSC liver tissues were interrogated by GeoMx DSP, Phenocycler, and immunofluorescence (IF) and enzyme linked immune assay (ELISA). Murine models of PSC (Mdr2-/- and DDC-diet) were used for neutrophil directed treatment (anti-Ly6G or Cl-Amidine). Mice with cholangiocyte-selective STING deletion were fed a DDC diet to investigate immune cell infiltration using mass cytometry (CyTOF). Liver enzymes and histology were also assessed. Human cholangiocytes with TNFα stimulus and STING intervention were used for RNA sequencing. Human neutrophil migration was assessed using microfluidic devices. Neutrophil phenotypes (i.e., phagocytosis, NETosis) were measured by flow cytometry. **Results:** Human and mouse PSC livers showed significant periportal neutrophil accumulation by IF and enhanced neutrophil extracellular traps (NETs) deposition by IF and ELISA. Both neutrophil depletion with anti-Ly6G or pharmacological inhibition of NETs formation with Cl-amidine in the $Mdr2^{-/-}$ mouse model significantly reduced liver damage markers including ALT (p = 0.0017), AST (p = 0.0024), and ALP (p = 0.0114) and fibrosis (8.954 vs 3.931; p = 0.0255). RNA sequencing revealed that STING knockdown in human cholangiocytes significantly reduced TNFα-induced chemokine expression and signaling. Healthy human neutrophils exposed to an inflammatory cholangiocyte milieu depicted enhanced migration, NET formation (p = 0.001), and reduced phagocytosis (p = 0.0192). Consistently, both pharmacological inhibition and genetic deletion of STING in DDC-diet model of PSC reduced neutrophil infiltration, as assessed by IF and CyTOF analysis (17.65 vs 0.04000; p = 0.0064). Congruently, DDC- induced liver fibrosis, measured by picrosirius red, was also significantly reduced with cholangiocyte-selective STING deletion (9.797 vs 3.009; p = 0.0188). **Conclusion:** Neutrophil recruitment and inflammatory amplification in PSC are driven by cholangiocyte-intrinsic cGAS–STING signaling. By producing NETs, neutrophils actively contribute to biliary damage and fibrosis. Targeting STING signaling and NETs may be a promising therapeutic approach to reduce inflammation and slow the progression of biliary fibrosis in PSC.



Disclosures: Mobin Ibne Mokbul: Nothing to Disclose, Abid Anwar: Nothing to Disclose, Maleeha Farheen Kalaiger: Nothing to Disclose, Sofia Jerez: Nothing to Disclose, Papawee Sutthirat: Nothing to Disclose, Zhensheng Zhang: Nothing to Disclose, Usman Yaqoob: Nothing to Disclose, Purnima Tyagi: Nothing to Disclose, Jose M. de Hoyos-Vega: Nothing to Disclose, Alexander Revzin: Nothing to Disclose, Moira Hilscher: Orphalan: Consultant, Robert Huebert: Nothing to Disclose, Nidhi Jalan-Sakrikar: Nothing to Disclose.

0220 | LOSS OF BILIARY ADHERENS JUNCTIONS RESULTS IN PRIMARY SCLEROSING CHOLANGITIS-LIKE CHOLESTATIC INJURY

Vik Meadows[1] Yekaterina Krutsenko[1] Chang Kyung Kim[1] Zachary Cannova[1] Hiroki Inada[1] Jia-Jun Liu[1] Shuchang Liu[1] Minakshi Poddar[1] Sucha Singh[1] Satdarshan (Paul) Monga[1], [1]University of Pittsburgh

Background: Loss of β-catenin in adherens junctions (AJ) is compensated by γ-catenin, a homologous desmosomal protein. We have shown dual loss of β- and γ-catenin in all liver epithelial cells leads to progressive intrahepatic cholestasis and high mortality indicated by cytoplasmic instead of membranous E-cadherin followed by E-cadherin degradation and loss. Here, we investigate the impact of dual catenin loss from cholangiocytes. **Methods:** We utilized Ctnnb fl/fl; Jup fl/fl mice with Opn-iCreERT2+/- to delete both β-catenin (*Ctnnb1*) and γ-catenin (*Jup*) from cholangiocytes in both male and female mice. Littermate control

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with no Opn-iCreERT2+/+ were used as controls. Mice received four (DKO4) intraperitoneal injections of tamoxifen (100 mg/kg) dissolved in corn oil. DKO4 mice were sacrificed at various time points within two weeks of the first injection, with >30% body weight loss as the endpoint for serum analysis, histology, and RNA sequencing. PSC patient livers were also examined for β-catenin and E-cadherin histology. **Results:** DKO4 mice showed significant mortality associated with severe weight loss, visible jaundice, and elevated liver enzyme levels (ALT, AST, ALP) as early as 11 days after first injection compared to controls. Histologically, the earliest changes were visible at 11 days after first injection in the form of inflammation, loss of membranous E-cadherin, and increased onion skin portal fibrosis. At 14 days, DKO4 mice displayed extensive biliary infarcts and worsening inflammation and fibrosis. There was negligible bile flow through extrahepatic bile duct and india ink injection revealed bile duct paucity and interstitial leakage from intrahepatic ducts. Due to histological resemblance, we queried DKO4 for any molecular overlap with primary sclerosing cholangitis (PSC). Bulk RNAseq of DKO4 livers showed significant overlap with end-stage PSC patients, especially in the fibrotic gene signature. snRNA sequencing and transcriptional factor enrichment analysis showed DKO4 cholangiocytes and PSC patients displaying common transcriptional programs. Biopsies and explanted PSC livers showed a significant subset of cases to have decreased membranous b-catenin and E-cadherin (+/-cytoplasmic staining). **Conclusion:** The simultaneous loss of β- and γ-catenin from cholangiocytes is evident in notable subset of patients with PSC and their dual loss in cholangiocytes in mice mimic PSC like disease thus providing novel insights into the pathogenesis of this heterogenous and complex disease.

Disclosures: Vik Meadows: Nothing to Disclose, Yekaterina Krutsenko: Nothing to Disclose, Chang Kyung Kim: Nothing to Disclose, Zachary Cannova: Nothing to Disclose, Hiroki Inada: Nothing to Disclose, Jia-Jun Liu: Nothing to Disclose, Shuchang Liu: Nothing to Disclose, Minakshi Poddar: Nothing to Disclose, Sucha Singh: Nothing to Disclose, Satdarshan (Paul) Monga: Vicero Inc.: Advisor, Alnylam: Grant/Research Support, Alnylam: Consultant, Vicero: Advisor, UbiquiTx: Consultant, Alnylam: Grant/Research Support, Alnylam: Consultant, UbiquiTx: Consultant, Revolution Medicines: Grant/Research Support, Antlera: Advisor, Vicero Inc.: Advisor, Alnylam: Grant/Research Support, Alnylam: Consultant, Vicero: Advisor, UbiquiTx: Consultant, Alnylam: Grant/Research Support, Alnylam: Consultant, UbiquiTx: Consultant, Revolution Medicines: Grant/Research Support, Antlera: Advisor.

★ 0221 | MULTI-COMPARTMENT DNA METHYLATION ANALYSIS REVEALS IMMUNE AND INFLAMMATORY EPIGENETIC REMODELING IN ALCOHOL-ASSOCIATED HEPATITIS

Brandon Peiffer[1] Yongchun Wang[1] Chris Umbricht[1] Maria Parra[1] Francisco Lopez[1] Jamal Masri[1] Zhe Deng[1] Niket Harsh[1] Leslie Cope[1] Zhaoli Sun[1], [1]The Johns Hopkins School of Medicine

Background: Dysregulation of DNA methylation (DnaM) has been implicated in many human diseases; however, the role of epigenetic alterations in alcohol-associated liver disease (ALD) remains poorly understood. Although genome-wide methylation studies in alcohol use disorder (AUD) have identified clear alcohol-related changes, the role of the epigenome in the development of ALD has not been systematically studied to date. To address this gap, we analyzed DnaM profiles in alcohol-associated hepatitis (AH), alcohol-associated cirrhosis (AC), and metabolic dysfunction-associated steatohepatitis (MASH), a non-alcohol–associated chronic liver disease comparator included to distinguish alcohol-specific epigenetic alterations from shared inflammatory and fibrotic pathways. **Methods:** Liver tissue samples were collected from explanted livers obtained during transplantation from patients with AH, AC, or MASH. Tissues were either snap-frozen or enzymatically digested with collagenase to isolate non-parenchymal cells (NPCs). Peripheral blood was collected prior to transplantation, and leukocytes were isolated following red blood cell lysis. Neutrophil subsets with high or low IL8 expression were further isolated by flow cytometric sorting. Differential methylation (diffM) analyses were performed across hepatic and peripheral immune compartments. All human samples were collected from consented patients under Johns Hopkins IRB protocol IRB00107893. **Results:** Distinct DnaM signatures clearly separated AH from both AC and MASH in bulk liver and NPCs. The resulting differential methylation was disproportionately concentrated in gene enhancer regions. indicating extensive epigenetic remodeling in severe alcohol-associated liver injury. Cellular deconvolution analysis further revealed enrichment of neutrophils within the NPC compartment of AH livers relative to other disease groups. KEGG pathway analysis of transcription factors predicted to bind differentially methylated regions in AH demonstrated enrichment of pathways associated with cytokine signaling, infection, and addiction-related processes. In peripheral blood, IL8-high and IL8-low neutrophil populations exhibited markedly distinct DnaM profiles,

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including differential methylation at key CpG loci commonly used for epigenetic neutrophil identification. **Conclusion:** ALD, particularly AH, is associated with distinct and compartment-specific DNA methylation alterations characterized by enhancer hypomethylation and inflammatory epigenetic remodeling. The identification of epigenetically distinct neutrophil subsets further highlights immune heterogeneity in AH. These findings suggest that DNA methylation profiling may provide mechanistic insights into ALD pathogenesis and support development of novel biomarkers and epigenetic-targeted therapies for severe ALD.

Disclosures: Brandon Peiffer: Nothing to Disclose, Yongchun Wang: Nothing to Disclose, Chris Umbricht: Nothing to Disclose, Maria Parra: Nothing to Disclose, Francisco Lopez: Nothing to Disclose, Jamal Masri: Nothing to Disclose, Zhe Deng: Nothing to Disclose, Niket Harsh: Nothing to Disclose, Leslie Cope: Nothing to Disclose, Zhaoli Sun: Nothing to Disclose.

0222 | UBC9 PHOSPHORYLATION REPROGRAMS SRC EXPRESSION THROUGH JUNB/AP-1 FEEDBACK AXIS DURING MACROPHAGE INFLAMMATORY ACTIVATION IN ALCOHOL-ASSOCIATED LIVER DISEASE

Manisha Dagar[1] Swati Chandla[1] Youngyi Lim[1] Joshua Martinez[1] Komal Ramani[2] Maria Lauda Tomasi[1], [1]Cedars Sinai Medical Center, [2]Cedars-Sinai Medical Center

Background: Alcohol-associated liver disease (ALD) is driven in part by gut-derived endotoxin, which activates Kupffer cells (KCs) and promotes inflammatory signaling via SRC kinase and NF-κB pathways. Ubiquitin-conjugating enzyme 9 (UBC9), the sole E2 enzyme for SUMOylation, regulates transcription by modifying the DNA-binding activity of nuclear factors. We previously reported that LPS decreases UBC9 levels but induces SRC-mediated phosphorylation of UBC9 at Y68, possibly compensating for UBC9 reduction and altering SUMOylation-dependent transcription. Here, we examined if UBC9 phosphorylation regulates SRC expression via a SUMO-sensitive promoter feedback mechanism. **Methods:** RAW 264.7 and THP-1 cells were used for in vitro studies, and KCs from NIAAA-fed and pair-fed mice were used to assess ALD relevance. UBC9 phosphorylation status was modeled using unphosphorylated and phosphomimetic UBC9 Y68 peptides and disrupted by CRISPR/Cas9-mediated editing. SRC expression/promoter activity, UBC9 stability, and pUBC9 interactors were assessed by RT-qPCR, western blotting, luciferase assay, cycloheximide (CHX) chase, and co-IP/mass spectrometry. **Results:** Unphosphorylated UBC9 Y68 mimetic peptide decreased SRC expression in LPS-treated RAW 264.7 and THP-1 cells, whereas the Y68 phosphomimetic peptide increased SRC expression. These opposing effects suggest that UBC9 phosphorylation status differentially regulates SRC transcription, with phosphorylated UBC9 promoting SRC upregulation. Importantly, in vivo and in vitro CRISPR/Cas9-CD68 editing of UBC9 Y68 prevented SRC induction in KCs and RAW 264.7 cells, supporting a requirement of pUBC9 in this response. CHX chase assays showed that pUBC9 remained detectable in the time course despite LPS-associated reduction of total UBC9, suggesting that the pUBC9 pool may be preferentially maintained and less susceptible to degradation. To identify transcriptional mediators linking pUBC9 to SRC regulation, we analyzed the UBC9 interactome in NIAAA KCs. JunB, an AP-1 family transcription factor and regulator of macrophage activation, strongly interacted with pUBC9, showing a 9-fold higher association in alcohol-fed compared with pair-fed control KCs. Because JunB/AP-1 promotes SRC promoter activity through an AP-1 site and JunB SUMOylation at K237 supports DNA binding, these findings identify JunB as a strong SUMO-sensitive candidate mediator linking pUBC9 to SRC promoter activation. **Conclusion:** These findings suggest that UBC9 Y68 phosphorylation acts as a switch that promotes SRC expression and stabilizes pUBC9 in macrophages. The strong pUBC9-JunB interaction supports a SRC–pUBC9–JunB/AP-1 feedback axis that may sustain macrophage inflammatory activation in ALD.

Disclosures: Manisha Dagar: Nothing to Disclose, Swati Chandla: Nothing to Disclose, Youngyi Lim: Nothing to Disclose, Joshua Martinez: Nothing to Disclose, Komal Ramani: Nothing to Disclose, Maria Lauda Tomasi: Nothing to Disclose.

0223 | ETHANOL INDUCED HEPATOCELLULAR STEATOSIS IS A CATABOLIC LIPOPHAGY DEFECT RESULTING FROM LYSOSOME DAMAGE.

Sandhya Sen[1] Eugene Krueger[1] Carol Casey[2] Mark McNiven[3], [1]Mayo Clinic, [2]University of Nebraska Medical Center, [3]Mayo Foundation for Medical

Background: Hepatocytes accumulate lipid droplets (LDs) markedly in response to EtOH exposure by unknown mechanisms. We have recently described a process utilized by hepatocytes to degrade and catabolize their lipid stores via direct action of the lysosome (lipophagy, PNAS 2020). Thus, the functional and structural integrity of the lysosome is essential for reducing lipid stores. Our IHC staining of human AFLD/ASH patient tissues revealed an elevation of known

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lysosome-damage/repair proteins. Therefore, the **Goal of this study** was to determine if this LD accumulation from EtOH exposure represents a catabolic defect due to lysosome damage vs increased lipid synthesis. **Methods:** Primary mouse hepatocytes (PMHs) were isolated from mice fed on a 5% ethanol diet for 10 days, along with a single ethanol binge of 5g/kg orally or control mice that were pair-fed a calorically equivalent diet. Lysosomal damage and repair were induced by either EtOH and/or the lysosome-damaging agent LLOMe. Levels of damage and repair were measured by several criteria including: a reduction of the lysosomal pH gradient, or recruitment of several known lysosome repair proteins including Galectin-3 or Alix, (Gal3-mCherry or Alix-mCherry). **Results:** PMH isolated from the ethanol-fed group exhibited a 2.5 fold LD accumulation. Cells were treated with DGAT inhibitors to attenuate nascent LD synthesis, along with incubation in low nutrient media to induce catabolism. Surprisingly, EtOH damaged cells retained 64% of their LDs under these starvation conditions compared to just 22% retained by control cells; indicating a substantial lipophagic defect. To assess whether EtOH treatment induces an accumulation of damaged lysosomes that are unable to repair, PMH from control or EtOH-fed mice were treated with LLOMe for 15 mins then allowed to recover over time. Importantly, Gal3-mCh puncta accumulation on lysosomes from the ethanol-damaged cells was 2.5 fold that of control cells. Further, these EtOH-damaged lysosomes recruited 80% less of the ESCRT protein Chmp2a than control, indicating a defective lysosomal repair process. Western blot analysis of purified lysosomes from control vs EtOH-damaged hepatocytes supported these morphological findings and revealed a more than 50% reduction of these repair proteins associated with lysosomes. **Conclusion:** Taken together, these findings indicate EtOH-induced hepatocellular steatosis is a result of defective LD catabolism and provide some of the first insights into structural damage of hepatocellular lysosomes by EtOH. This study was supported by NIAAA grant RO1AA020735 to MM and CC.

Disclosures: Sandhya Sen: Nothing to Disclose, Eugene Krueger: Nothing to Disclose, Carol Casey: Nothing to Disclose, Mark McNiven: Nothing to Disclose.

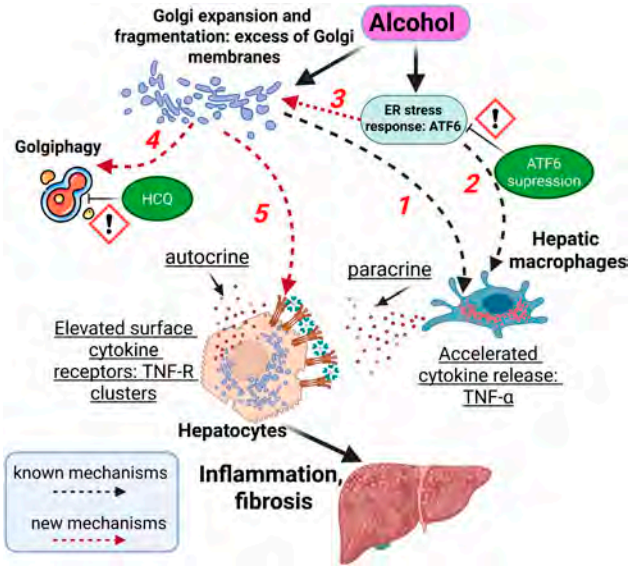
0224 | TARGETING PATHOLOGIC TNF-α SIGNALING IN ALD WITHOUT SYSTEMIC CYTOKINE BLOCKADE

Armen Petrosyan[1] Carol Casey[1] Tania Kamal[1],
[1]University of Nebraska Medical Center

Background: Clinical trials targeting TNF-α in alcohol-associated liver disease (ALD), including the TNF-α inhibitor Etanercept, failed due to severe immunosuppression and increased mortality, highlighting the need for alternative approaches. We hypothesized that alcohol exposure amplifies TNF-α signaling through two coordinated mechanisms: enhanced ATF6-dependent TNF-α production by liver macrophages and MGAT5/Galectin-3 (Gal-3)–mediated clustering of TNF-α receptor 1 (TNFR1) at the hepatocyte plasma membrane (PM). We further examined whether hydroxychloroquine (HCQ), an autophagy inhibitor that restores Golgi integrity, suppresses this pathway. **Methods:** WT and ATF6 knockout (KO) mice were subjected to chronic or chronic-plus-binge ethanol (EtOH) feeding with or without HCQ treatment. Liver tissues, Kupffer cells, and hepatocytes were analyzed by IHC, IF, lectin staining, high-resolution microscopy, Sirius Red staining, and serum cytokine/aminotransferase analysis. Also, we use human ASH samples and EtOH-treated VA-13 hepatocytes. **Results:** Both chronic and chronic-plus-binge EtOH exposure induced severe Golgi disorganization accompanied by ATF6 activation, WIPI2 and LC3B-II accumulation, MGAT5 upregulation, high-molecular-weight Gal-3 complexes, and enhanced TNFR1 stabilization at the PM (two-way ANOVA, $p < 0.01$–0.0001). Human ASH liver samples similarly demonstrated Golgi fragmentation, elevated nuclear ATF6, and increased MGAT5 expression versus normal liver (unpaired t test/Kruskal-Wallis, $p < 0.05$–-0.01). In hepatocytes, EtOH-induced MGAT5-mediated glycosylation promoted Gal-3–dependent TNFR1 retention at the PM, correlating with NF-κB activation, whereas Kupffer cells exhibited ATF6-dependent TNF-α upregulation. Consistently, serum TNF-α, IL-6, and KC/GRO levels were reduced in ATF6-deficient mice, supporting attenuation of inflammatory signaling. EtOH also induced marked Perilipin-2 accumulation and collagen deposition in WT mice, both significantly reduced in ATF6-deficient and HCQ-treated animals (two-way ANOVA, $p < 0.01$–0.0001). Combined ATF6 deficiency and HCQ produced the lowest steatotic burden, indicating cooperative roles of ATF6-dependent ER–Golgi stress and autophagy in alcohol-induced steatotic remodeling and collagen accumulation. HCQ restored compact Golgi morphology and attenuated TNFR1 stabilization and downstream inflammatory signaling without suppressing YAP1-dependent regenerative signaling in hepatocytes. Unlike Etanercept, HCQ attenuated ER/Golgi stress while avoiding intracellular TNF-α accumulation and macrophage apoptosis. **Conclusion:** Alcohol amplifies TNF-α signaling through an ATF6–Golgi stress pathway linking macrophage TNF-α overproduction with TNFR1 clustering. Targeting this pathway suppresses inflammatory and steatotic signaling while preserving regenerative pathways in ALD.

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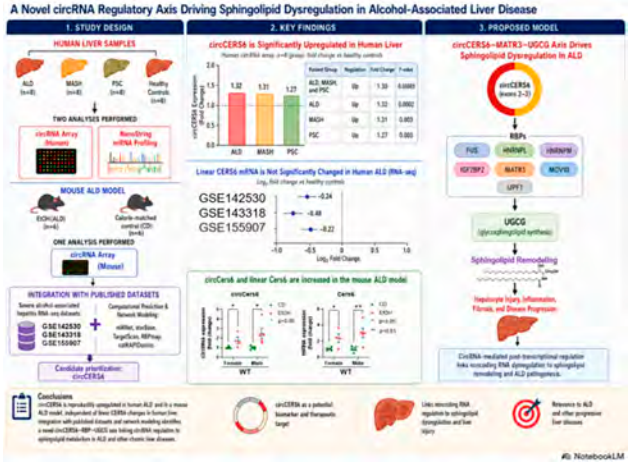


Disclosures: Armen Petrosyan: Nothing to Disclose, Carol Casey: Nothing to Disclose, Tania Kamal: Nothing to Disclose.

0225 | A NOVEL CIRCRNA REGULATORY AXIS DRIVING SPHINGOLIPID DYSREGULATION IN ALCOHOL-ASSOCIATED LIVER DISEASE

Hongkun Lu[1] Nan Wu[1] Grayson Way[1] Meiyi Song[1] Chen Chen[1] Derrick Zhao[1] Hui Li[1] Sareh Bayatpour[1] Lianyong Su[1] Yun-Ling Tai[1] Xuan Wang[1] Emily Gurley[1] Phillip Hylemon[2] Huiping Zhou[2], [1]Virginia Commonwealth University, [2]Virginia Commonwealth University, Stravitz-Sanyal Institute for Liver Disease and Metabolic Health

Background: Alcohol-associated liver disease (ALD) remains a leading cause of preventable liver-related mortality, yet the noncoding RNA mechanisms driving progression are incompletely defined. Circular RNAs (circRNAs) are stable regulators that shape gene networks through RNA-binding protein (RBP) and miRNA interactions. Although sphingolipid dysregulation is a feature of ALD, whether circRNAs regulate sphingolipid remodeling is unknown. **Methods:** We performed circRNA array profiling of human liver samples from patients with ALD, MASH, PSC, and healthy controls (n = 8), and parallel circRNA array profiling in the NIAAA chronic-plus-binge mouse ALD model (n = 6). These original human and mouse circRNA datasets were integrated with published transcriptomic datasets from patients with severe alcohol-associated hepatitis (GSE155907, GSE143318, GSE142530) to identify conserved circRNA-associated regulatory networks. Human liver samples were also profiled by NanoString miRNA analysis to support integrated noncoding RNA network assessment. **Results:** Human circRNA array identified hsa_circ_0056939 (circCERS6), generated from CERS6 exons 2-3, as upregulated in ALD (1.32-fold, P = 0.0002). circCERS6 was also increased in MASH (1.31-fold, P = 0.003) and PSC (1.27-fold, P = 0.003), suggesting a shared chronic liver disease response. In contrast, linear CERS6 mRNA was not significantly altered across three human ALD RNA-seq cohorts, supporting circRNA-selective regulation. Mouse circRNA array and validation confirmed alcohol-responsive upregulation of hepatic circCers6, with parallel induction of Cers6 mRNA. Integration of circRNA, miRNA, mRNA, and RBP resources prioritized a circCERS6-centered network. Seven convergent candidate circCERS6-associated RBPs were identified: FUS, HNRNPL, HNRNPM, IGF2BP2, MATR3, MOV10, and UPF1. Overlay with 32 dysregulated sphingolipid genes revealed a connected network in which MATR3, FUS, and UGCG emerged as central nodes, nominating a circCERS6-RBP-sphingolipid axis. **Conclusion:** circCERS6 is dysregulated in human ALD and alcohol-exposed mice and may act independently of host-gene transcription in severe human disease. Integrated noncoding RNA and transcriptomic modeling identifies a previously unrecognized circCERS6-MATR3-UGCG axis linking circRNA regulation to sphingolipid remodeling. These findings suggest circCERS6 as a novel candidate biomarker and mechanistic regulator of progressive liver injury in ALD and other chronic liver diseases.



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Ling Tai: Nothing to Disclose, Xuan Wang: Nothing to Disclose, Emily Gurley: Nothing to Disclose, Phillip Hylemon: Nothing to Disclose, Huiping Zhou: Nothing to Disclose.

0226 | AN ALCOHOL-INDUCED BILE ACID INTERMEDIATE REGULATES INTESTINAL FXR-FGF15/19 SIGNALING

Weiran Wang[1] Yantao Zhao[1] Carolina Hogerty[1] Steven Weinman[1] Wei Zhong[1], [1]University of Kansas Medical Center

Background: Bile acid homeostasis is tightly regulated through gut-liver signaling pathways. Under physiological conditions, mature bile acids activate intestinal Farnesoid X receptor (FXR), inducing FGF15/19 signaling to suppress hepatic bile acid synthesis. We previously found that alcohol-associated hepatic peroxisomal dysfunction leads to accumulation of the C27 bile acid intermediate 3a,7a,12a-trihydroxycholestanoic acid (THCA) in the intestine. In the present study, we investigated the effects of THCA on intestinal FXR-FGF15/19 signaling and bile acid homeostasis. **Methods:** Male C57BL/6J mice were administered THCA (50 mg/kg) by oral gavage for 5 days. Intestinal epithelial cells and small intestinal organoids were used to evaluate the effect of THCA on FXR-FGF15/19 signaling. FXR binding and transcriptional activity were assessed using molecular docking and FXR reporter assays. **Results:** THCA treatment significantly altered serum and hepatic bile acid compositions in mice. Hepatic expression of bile acid synthesis genes, such as *Cyp7a1*, was suppressed following THCA administration. THCA-treated mice had significantly increased ileal FGF15 at both mRNA and protein levels compared with controls. This FGF15 inducing effect was recapitulated using *in vitro* models. In mouse small intestinal organoids, THCA directly stimulated FGF15 expression. Similarly, treating human-derived Caco-2 cells with THCA for 6 and 24 h significantly increased FGF19 expression. Mechanistically, we found that FXR expression in both mouse ileal tissue and Caco-2 cells was increased after THCA exposure. Molecular docking analysis demonstrated that THCA bound FXR with binding affinity comparable to the canonical FXR agonist chenodeoxycholic acid (CDCA). FXR reporter assays further demonstrated that THCA activated FXR transcriptional activity to a degree comparable to CDCA at same concentrations. **Conclusion:** These findings identify THCA as a biologically active bile acid intermediate that functions as a potent intestinal FXR agonist and regulator of enterohepatic bile acid signaling. Our study suggests that pathological bile acid interactions generated during alcohol-induced peroxisomal dysfunction and intestinal accumulation of THCA can engage physiological bile acid sensing pathways and alter gut-liver metabolic communication. This may feedback on the liver to exacerbate ALD.

Disclosures: Weiran Wang: Nothing to Disclose, Yantao Zhao: Nothing to Disclose, Carolina Hogerty: Nothing to Disclose, Steven Weinman: Nothing to Disclose, Wei Zhong: Nothing to Disclose.

0227 | OPTIMIZING DCD PROCUREMENT INITIATION WITH INTERPRETABLE MACHINE LEARNING PREDICTION OF 60-MINUTE MORTALITY AFTER WLST

Alexander Huang[1] Julie Heimbach[1] Jenny Lam[2] Umesh Goswami[3] Travis Geraci[3] Ray Kim[3] Joseph Ahn[1], [1]Mayo Clinic Rochester, [2]Scripps Health, [3]Mayo Clinic Arizona

Background: Accurate prediction of timely progression to circulatory death after withdrawal of life-sustaining therapy (WLST) in donation after circulatory death (DCD) donors is crucial to reduce extensive resources required for donor organ recoveries and may reduce donor family distress. Prior models rely heavily on neurological examinations (brainstem reflexes and GCS score) which may not be well-documented and have examiner variability. In this study, we leverage universally available electronic health record (EHR) data to develop an interpretable machine-learning model. **Methods:** Demographic and clinical data on DCD candidates from January 2019 to August 2023 were retrospectively analyzed from our local OPO (LifeSource) prospective database. Mortality within 60 minutes of WLST was the outcome. Covariates included laboratory values, patient medications, vital signs, and patient demographics. Model development utilized gradient boost methods (GBM) as a binary mortality classifier and continuous time-to-mortality predictor, Shapely additive values for interpretation, and Denoising Diffusion Probabilistic Models for variance reduction. AUROC and Kaplan-Meier (KM) curves were utilized to assess efficacy of model predictions. **Results:** A total of 356 consecutive DCD candidates were included; with 251 (72%) having 60-minute mortality. Using laboratory values, vital signs, and medications, the final GBM model achieved AUROC = 0.75 (95% CI: [0.72-0.78]). At a high-sensitivity threshold, the model achieved NPV 96% for 60-minute mortality, identifying candidates unlikely to progress within the procurement window; at a high-specificity threshold, PPV was 84% for identifying candidates highly likely to progress. SHAP analysis identified hyperchloremia, thrombocytopenia, rising BUN, and hyponatremia as dominant predictors. Patients in the

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highest-risk model quintile had 4.3% 60-minute survival vs 84% in the lowest-risk quintile (log-rank $p < 0.001$; Figure). **Conclusion:** This interpretable, EHR-based machine-learning model accurately stratifies DCD candidates for 60-minute mortality after WLST using universally available HER data, overcoming the reliance on subjective neurological examination that has limited prior models. High NPV at low-risk thresholds and high PPV at high-risk thresholds support its use as a decision-support tool to reduce futile procurement attempts. Prospective multi-OPO validation is the next step toward clinical integration.

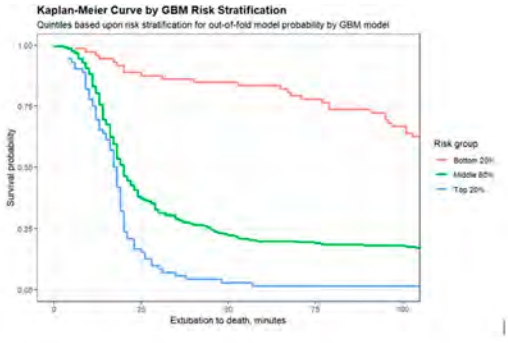


Figure: Kaplan Meier Curve of patients most likely (top 20%) vs least likely (bottom 20%) to have Mortality within 60 minutes of WLST (P<0.001)

Disclosures: Alexander Huang: Nothing to Disclose, Julie Heimbach: Nothing to Disclose, Jenny Lam: Nothing to Disclose, Umesh Goswami: Nothing to Disclose, Travis Geraci: Nothing to Disclose, Ray Kim: Novo Nordisk: Consultant, Gilead: Consultant, Grifols: Consultant, GSK: Consultant, Joseph Ahn: Nothing to Disclose.

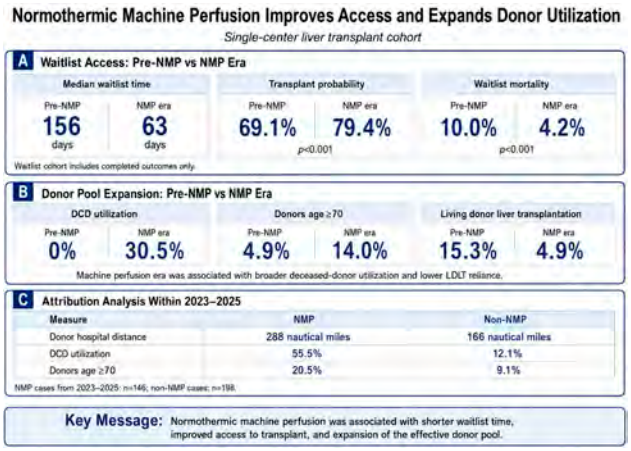
0228 | IMPACT OF NORMOTHERMIC MACHINE PERFUSION ON TRANSPLANT ACCESS, DONOR UTILIZATION, AND THE EVOLVING ROLE OF LIVING DONOR LIVER TRANSPLANTATION: A SINGLE-CENTER EXPERIENCE

Yusuf Yalcin[1] Marwa Elmahi[1] Sarah Meade[1] Raza Malik[1] Mohamed Akoad[1], [1]Lahey Hospital and Medical Center

Background: Normothermic machine perfusion has expanded use of extended-criteria donor livers, but its broader effects on transplant access, donor utilization, and the relevance of living donor liver transplantation remain incompletely defined. We evaluated its association with waitlist outcomes, donor pool expansion, and changes in living donor liver transplantation at a single center. **Methods:** We performed a retrospective single-center study using Lahey-specific United Network for Organ Sharing waitlist and transplant data from 2016–2025, supplemented by institutional normothermic machine perfusion records. Adult liver transplant recipients ($n = 938$) and waitlisted patients with completed outcomes ($n = 1293$) were grouped into pre–normothermic machine perfusion (2016–2022) and normothermic machine perfusion era (2023–2025) for program-level era comparison. To assess direct attribution of normothermic machine perfusion, transplants performed in 2023–2025 were further analyzed by comparing recipients who received normothermic machine perfusion grafts ($n = 146$) with those who did not ($n = 198$). Living donor liver transplantation rates were examined by MELD group and primary diagnosis. **Results:** Normothermic machine perfusion adoption increased from 17.4% of transplants in 2023 to 40.6% in 2024 and 70.1% in 2025. Median waitlist time decreased from 156 days (interquartile range 33–393) to 63 days (13–285). Transplant probability increased from 69.1% to 79.4% ($p < 0.001$), while waitlist mortality decreased from 10.0% to 4.2% ($p < 0.001$). Donation after circulatory death utilization increased from 0% to 30.5%, and donors aged 70 years or older from 4.9% to 14.0%. Within the normothermic machine perfusion era, normothermic machine perfusion grafts were associated with greater donor hospital distance (288 vs 166 nautical miles) and higher donation after circulatory death utilization (55.5% vs 12.1%), consistent with expanded acceptance of marginal donors. Overall living donor liver transplantation declined from 15.3% to 4.9%, with decreases observed across all diagnosis groups and MELD strata. **Conclusion:** In this single-center experience, normothermic machine perfusion adoption was associated with substantially improved waitlist outcomes and expanded utilization of marginal donors, including donation after circulatory death, older, and more geographically distant grafts. Coinciding with these changes, living donor liver transplantation declined broadly across diagnoses and MELD groups. Whether this decline reflects a true substitution effect, and whether living donor liver transplantation retains a selective role in patients with low MELD scores and high disease burden such as primary sclerosing cholangitis and polycystic liver disease, warrants further investigation in national cohort data.

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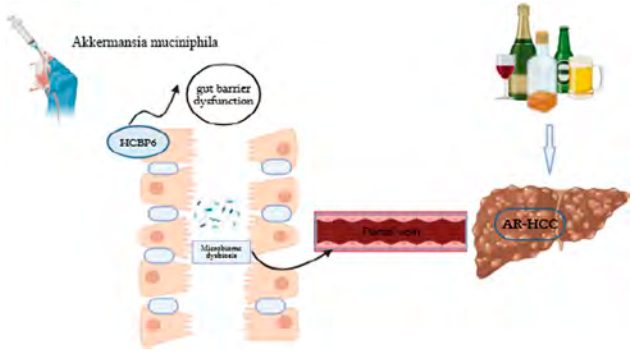


Disclosures: Yusuf Yalcin: Nothing to Disclose, Marwa Elmahi: Nothing to Disclose, Sarah Meade: Nothing to Disclose, Raza Malik: Nothing to Disclose, Mohamed Akoad: Nothing to Disclose.

0229 | PRE-PERFUSION RISK PREDICTION MODEL FOR EARLY ALLOGRAFT DYSFUNCTION IN DCD LIVER TRANSPLANTATION WITH NORMOTHERMIC MACHINE PERFUSION

Atsushi Nishimagi[1] Almokdad Mohammad[1] Jack Avedikian[1] Adhnan Mohamed[1] Ahmed Nassar[1] Abbas Al-Kurd[1] Atsushi Yoshida[1] Marwan Abouljoud[1] Shunji Nagai[1], [1]Henry Ford Hospital

Background: Normothermic machine perfusion (NMP) has reduced the incidence of early allograft dysfunction (EAD). However, the current definition of EAD was established and validated primarily in static cold storage (SCS) cohorts, and its prognostic impact and risk profile in DCD liver transplantation (LT) using NMP remain unclear. Therefore, this study aimed to evaluate the prognostic significance of EAD in DCD LT with NMP and to develop a pre-perfusion risk prediction model for EAD. **Methods:** We conducted a single-center retrospective cohort study of adult recipients who underwent DCD LT alone between January 2016 and August 2025. Patients were divided into two groups based on the use of NMP. The primary outcome was 180-day patient survival. Logistic regression analyses were performed to identify factors associated with EAD. EAD was defined according to the standard Olthoff criteria. All NMP procedures were initiated at donor hospitals as on-site NMP. In NMP cases, cold ischemia time (CIT) was defined as the interval from aortic cross-clamp to initiation of NMP. **Results:** A total of 257 DCD LT recipients were included, of whom 164 underwent LT with NMP and 93 underwent LT without NMP. The incidence of EAD was significantly lower in the NMP group than in the non-NMP group (17.1% vs. 60.2%, $p < 0.001$). EAD was associated with significantly worse 180-day survival in the NMP group ($p = 0.003$), but not in the non-NMP group ($p = 0.53$). In multivariable logistic regression analyses stratified by NMP use, older donor age was an independent predictor of EAD in the non-NMP group, but not in the NMP group. In the NMP group, older recipient age, male donor sex, higher donor BMI, and CIT ≥ 150 minutes were identified as independent predictors of EAD. The risk prediction model incorporating these factors demonstrated good discrimination, with an area under the receiver operating characteristic curve of 0.77 (95% confidence interval, 0.67–0.87). A two-dimensional risk map incorporating recipient age and a donor risk score derived from donor BMI, donor sex, and CIT ≥ 150 minutes stratified recipients into low-risk ($< 10\%$), intermediate-risk (10–30%), and high-risk ($> 30\%$) groups based on the predicted probability of EAD. The corresponding observed EAD incidences were 4.3%, 16.9%, and 40.7%, respectively ($p < 0.001$). **Conclusion:** This study demonstrates that EAD remains an important prognostic marker in DCD LT in the NMP era and suggests that its risk profile differs from that in conventional SCS cohorts. To our knowledge, this is the first pre-perfusion risk prediction model specifically developed for EAD in DCD LT with NMP. This model may help identify high-risk cases before perfusion and support more careful postoperative graft assessment and clinical follow-up.



Disclosures: ATSUSHI NISHIMAGI: Nothing to Disclose, Almokdad Mohammad: Nothing to Disclose, Jack Avedikian: Nothing to Disclose, Adhnan Mohamed: Nothing to Disclose, Ahmed Nassar: Nothing to Disclose, Abbas Al-Kurd: Nothing to Disclose, Atsushi Yoshida: Nothing to Disclose, Marwan Abouljoud: Nothing to Disclose, Shunji Nagai: Nothing to Disclose.

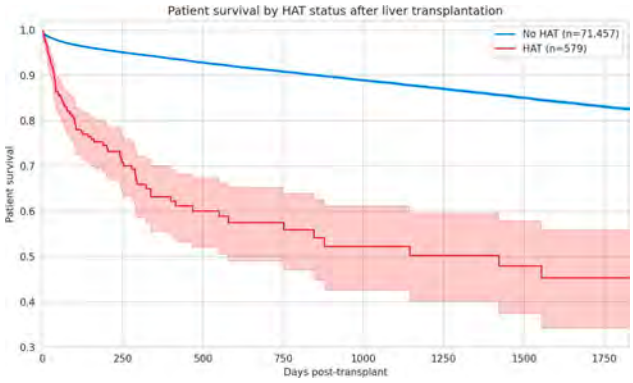
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0230 | HEPATIC ARTERIAL THROMBOSIS AFTER LIVER TRANSPLANTATION: NATIONAL INCIDENCE, HIGH-RISK PHENOTYPES, AND NEAR-UNIVERSAL EARLY GRAFT FAILURE IN 72,037 RECIPIENTS

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Background: Hepatic arterial thrombosis (HAT) is an uncommon but catastrophic vascular complication after liver transplantation (LT), with potential for rapid graft loss, retransplantation, and death. Contemporary national data defining high-risk phenotypes and post-HAT outcomes remain limited. We aimed to identify independent predictors of HAT after adult LT and quantify its association with early graft failure, retransplantation, and mortality. **Methods:** We performed a retrospective cohort study of adult primary liver-only transplant recipients in the OPTN/UNOS STAR file from March 31, 2015 to December 31, 2024, the era in which post-transplant HAT was reliably captured. HAT was defined using post-transplant follow-up reporting and/or HAT listed as a contributing cause of graft failure. Multivariable logistic regression identified independent predictors of HAT. Clinical consequences were assessed by 30-day graft failure, retransplantation, and mortality after HAT. Patient survival was visualized using Kaplan-Meier analysis stratified by HAT status. **Results:** Among 72,037 adult LT recipients, 579 developed HAT, yielding a national incidence of 0.80%. HAT was predominantly an early event, occurring at a median of 21 days post-LT; 58.0% occurred within 30 days and 71.7% within 90 days. Incidence was highest after living-donor LT (1.94%) and partial/split graft transplantation (1.86%). Independent predictors included living-donor LT (adjusted OR 2.45, 95% CI 1.68–3.59; $p < 0.001$), pre-transplant portal vein thrombosis (OR 1.54, 95% CI 1.24–1.93; $p = 0.0001$), older donor age (OR 1.01 per year; $p = 0.0009$), lower donor BMI (OR 0.97 per kg/m²; $p = 0.0001$), younger recipient age (OR 0.99 per year; $p = 0.0008$), and Asian race versus White race (OR 1.57, 95% CI 1.14–2.17; $p = 0.006$). Within 30 days of HAT, graft failure occurred in 95.9%, retransplantation in 79.8%, and death in 17.4%. Thirty-day mortality was nearly ten-fold higher after HAT compared with non-HAT recipients (17.4% vs 1.8%; RR 9.5). Kaplan-Meier analysis demonstrated marked early and sustained separation in patient survival by HAT status. (Figure 1) **Conclusion:** In this contemporary national LT cohort, HAT occurred in fewer than 1% of adult recipients but was associated with near-universal early graft failure, frequent retransplantation, and substantially higher mortality. Living-donor LT, partial/split graft use, pre-transplant portal vein thrombosis, and donor-recipient factors define a clinically recognizable high-risk phenotype. These findings support targeted perioperative risk stratification and intensified early arterial surveillance in high-risk LT recipients.



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0231 | BALANCING ICI WASHOUT AND EXPOSURE DURATION IS ASSOCIATED WITH PATHOLOGIC DOWNSTAGING WITHIN MILAN CRITERIA AND POST-TRANSPLANT OUTCOMES IN HCC: RESULTS FROM THE LIFT-HCC CONSORTIUM

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Background: Immune checkpoint inhibitors (ICIs) are emerging as a downstaging strategy for liver transplantation (LT) in patients with hepatocellular carcinoma (HCC). While a long ICI washout period reduces the risk of rejection, recent studies suggested that it may also reduce antitumor efficacy and prolonged ICI exposure may increase the risk of resistance. Herein, we aimed to evaluate factors associated with successful pathologic downstaging to Milan criteria (MC), with particular attention to ICI-related variables. **Methods:** In the International Consortium on Leveraging Immunotherapy for LT in HCC (LIFT-HCC), we included patients who received ICIs and underwent LT. To assess the combined effect of ICI washout period and exposure duration, patients were stratified into six groups based on a composite variable: $\leq$30 days/ $\leq$6 months (n = 55), $\leq$30 days/ > 6 months (n = 19), 31-90 days/ $\leq$6 months (n = 95), 31-90 days/ > 6 months (n = 50), > 90 days/ $\leq$6 months (n = 106), and > 90 days/ > 6 months (n = 73). Among patients beyond MC at ICI initiation, logistic regression was performed to identify factors associated with successful pathologic downstaging to MC. **Results:** A total of 412 patients from 15 countries were included (mean age [SD], 54 [10] years; 91% male; 75% Child-Pugh A at ICI start). Median (IQR) ICI washout duration was 74 (38-169) days, and 36% had ICI exposure > 6 months. Locoregional therapy (LRT) was used in 91%, with 36% receiving LRT only before ICI. Overall, 23% were within MC on imaging at ICI start, increasing to 45% on explant pathology. During a median follow-up of 20.8 months (95% CI, 18.4-25.2), 19% experienced rejection, 26% recurrence, and 20% died. The $\leq$30 days washout and > 6 months ICI exposure group had the highest pathologic complete response rate (36.8%), with low recurrence (5.3%) but the highest rejection rate (31.6%). ICI treatment for 6 months or longer is associated with a higher likelihood of pathologic downstaging with minimal increase in the risk of rejection while ICI washout periods of > 90 days provided the best balance between low rejection and low recurrence rates (**Figure**). In multivariable analysis, with $\leq$30 days/ < 6 months as a reference group, both $\leq$30 days/ > 6 months (OR: 5.05; 95%CI: 1.02-25.04) and 31-90 days/ > 6 months (6.9; 1.68-28.40) were significantly associated with successful pathologic downstaging to MC, while > 90 days/ $\leq$6 months (3.03; 0.94-9.77) showed a borderline association. Treatment in China (0.19; 0.08-0.44), number of lesions (0.80; 0.66-0.97), Child-Pugh class B/C (0.38; 0.17-0.85), and concurrent or post-ICI LRT (2.12; 1.04-4.33) were independent predictors of downstaging to MC on explant. **Conclusion:** Balancing ICI washout period and exposure duration may help optimize the tradeoff between antitumor activity and rejection risk. Preserved liver function and concurrent or post-ICI LRT improve the chance of pathologic downstaging on explant.

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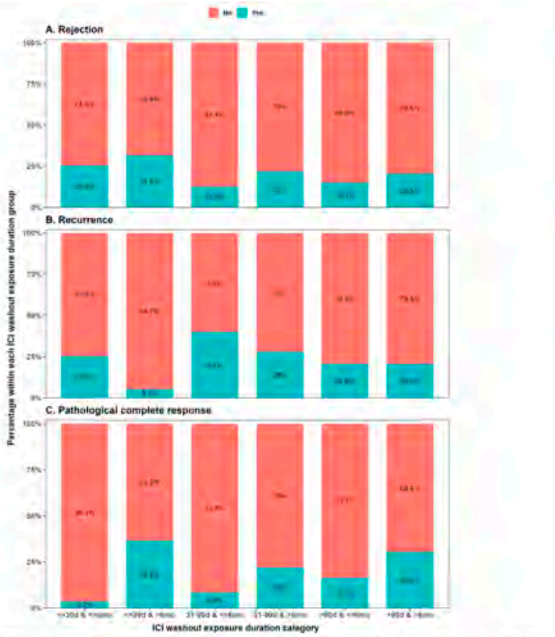


Figure. Association of Immune Checkpoint Inhibitor Washout Period and Exposure Duration with Rejection (Panel A), Recurrence (Panel B), and Pathological Complete Response (Panel C) Rates
Patients were categorized into six groups according to ICI washout period (≤30 days, 31-90 days, and >90 days) and ICI exposure duration (≤6 months vs >6 months). Stacked bar plots show the percentage of outcomes within each washout-exposure category.

The category with ≤30 days of washout and >6 months of ICI exposure had the highest rejection rate, but also the highest pathological complete response rate, along with a low recurrence rate. Washout periods of ≤30 days were associated with the highest rejection rates (>25%) regardless of ICI exposure duration. Washout periods of 31-90 days showed the highest recurrence rates. Overall, ICI washout periods of >90 days provided the best balance between low rejection and low recurrence rates (both around 20%). Within the >90-day washout group, ICI exposure duration >6 months was associated with a higher pathological complete response rate, although with a slightly higher rejection rate.

Abbreviations: ICI, immune checkpoint inhibitor; d, day; mo, month

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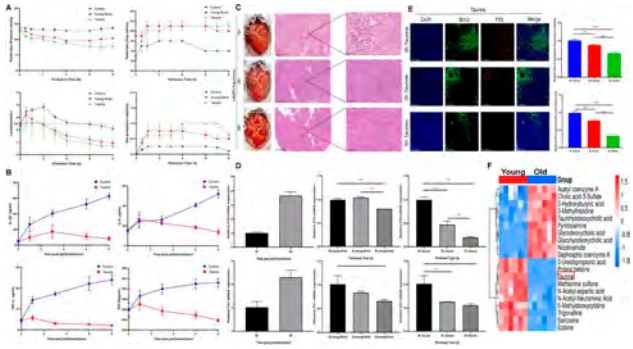
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★ 0232 | TAURINE ATTENUATES SENESCENCE IN AGED LIVERS DURING NORMOTHERMIC MACHINE PERFUSION

Jianjun Zhu[1] Zhicong Zhao[1] Mingxi Zhang[1] Lei Xia[1] Qiang Xia[1], [1]Renji Hospital, Shanghai Jiaotong University

Background: Aged donor livers are increasingly used in transplantation but remain highly susceptible to steatosis, metabolic dysfunction, and ischemia-reperfusion injury. We investigated whether taurine supplementation during normothermic machine perfusion (NMP) could improve ex vivo functional recovery and attenuate senescence-associated injury in aged rat livers. **Methods:** Metabolomic profiling was performed in young and aged rat blood and liver tissues. Livers from 24-month-old rats were procured and subjected to ex vivo perfusion under three conditions: control perfusion, young-blood perfusion, and taurine-supplemented perfusion. Functional assessment included bile production, lactate clearance, perfusion pressure, perfusion flow, and perfusate injury markers. Histologic and senescence-related changes were evaluated by hematoxylin-eosin staining, RT-qPCR, western blotting, immunofluorescence, and SA-β-gal staining. A doxorubicin-induced senescent HepG2 model was used for in vitro validation. RNA sequencing and KEGG pathway enrichment analysis were performed to explore potential mechanisms. **Results:** Compared with young livers, aged livers showed reduced taurine-associated metabolism. During NMP, taurine supplementation increased bile production, accelerated lactate clearance to below 2.5 mmol/L within 2 hours, lowered perfusion pressure, and increased perfusion flow, indicating improved metabolic recovery and more stable microcirculation. Taurine-treated livers also showed lower perfusate liver enzyme levels than control and young-blood groups, together with histologic improvement in age-related fatty change. Senescence markers were markedly reduced after taurine treatment. At 6 hours of perfusion, p16INK4a expression decreased by approximately 70% and p21 by approximately 50%, whereas the corresponding reductions in the young-blood group were approximately 30%. Western blot findings were concordant. Immunofluorescence demonstrated decreased Bcl-2 and p53 expression, and SA-β-gal positivity declined over time. In senescent HepG2 cells, taurine similarly reversed p16INK4a and p21 upregulation. Transcriptomic analysis further suggested enrichment of autophagy, FOXO, and apoptosis-related pathways after taurine treatment. **Conclusion:** Taurine supplementation during NMP improves ex vivo functional recovery and attenuates senescence-associated injury in aged rat livers. These protective effects may be related to metabolic remodeling and activation of autophagy- and stress-response pathways. Taurine may represent a feasible strategy to improve the quality of aged donor livers.



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0234 | EVALUATION OF THE BAVENO VIII CRITERIA FOR CLINICALLY SIGNIFICANT PORTAL HYPERTENSION IN COMPENSATED ADVANCED CHRONIC LIVER DISEASE: A CONTEMPORARY MULTICENTER COHORT STUDY

Paula Höfinger[1] Jose Ignacio Fortea[2] Fanny Turon[3] Lucile Moga[4] Luis Tellez[5] Petra Fischer[6] Dario Saltini[7] Wilhelmus Kwanten[8] Maria Grasso[9] Elba Llop Herrera[10] Yuly Mendoza[11] Angelo Armandi[12] Carlos Pardo[3] Antonio Colecchia[13] Federico Ravaioli[14] Benjamin Maasoumy[15] Wim Laleman[16] Jose Presa[17] Jörn Schattenberg[18] Annalisa Berzigotti[11] Jose Luis Calleja[10] Vincenza Calvaruso[9] Sven Francque[19] Filippo

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Schepis[7] Bogdan Procopet[6] Agustin Albillos[5] Pierre-Emmanuel Rautou[4] Juan Carlos Garcia-Pagan[3] Ángela Puente[2] Aitor Odriozola[20] Thomas Reiberger[21] Mattias Mandorfer[21] Mathias Jachs[21], [1]Medical University of Vienna, Vienna, Austria, [2]Marqués de Valdecilla University Hospital, Santander, Spain, [3]Universitat de Barcelona, Barcelona, Spain, [4]Université Paris-Cité, Unité Mixte de Recherche 1149, Paris, France, [5]Hospital Universitario Ramón y Cajal, Madrid, Spain, [6]Iuliu Hatieganu University of Medicine and Pharmacy, Cluj- Napoca, Romania, [7]University of Modena, Reggio Emilia, and Azienda Ospedaliero-Universitaria di Modena, Italy, [8]University Hospital Antwerp, [9]University of Palermo, Palermo, Italy, [10]Universidad Autonoma de Madrid, Madrid, Spain, [11]University of Bern, Bern, Switzerland, [12]University of Turin, Turin, Italy; University Medical Center Mainz, Mainz, Germany, [13]University of Modena, Reggio Emilia, and Azienda Ospedaliero-Universitaria di Modena, Modena, Italy, [14]Universitaria di Bologna, European Reference Network on Hepatological Diseases, Bologna, Italy, [15]Hannover Medical School, Hannover, Germany, [16]University Hospitals Leuven, Katholieke Universiteit Leuven, Leuven, Belgium, [17]Hospital Center of Trás-os-Montes and Alto Douro, Vila Real, Portugal, [18]University Medical Center Mainz, Mainz, Germany, [19]University of Antwerp, Antwerp, Belgium, [20]Hospital General Universitario Sierrallana, Torrelavega, Spain., [21]Medical University of Vienna

Background: Clinically significant portal hypertension (CSPH) defines the hemodynamic threshold for hepatic decompensation in patients with compensated advanced chronic liver disease (cACLD). While the gold standard remains the hepatic venous pressure gradient (HVPG) measurement, noninvasive tests (NITs) are increasingly used for the diagnosis of CSPH. The VCTE-based models ANTICIPATE ± NASH (liver stiffness, platelet count ± BMI) and NICER (liver & spleen stiffness, platelet count, BMI) offer well-calibrated individual CSPH risk estimates. Baveno VIII recommends an ANTICIPATE ± NASH or NICER threshold of 75% for ruling-in CSPH. The present study provides the evidence supporting the NICER 75%-threshold and a comparison to other diagnostic criteria for CSPH. **Methods:** Four hundred and forty-seven patients were included in this retrospective multicenter study from 16 European expert centers. Paired HVPG measurement, laboratory testing and NITs were performed between 2020 and 2024. Diagnostic performance of CSPH probability was evaluated by sensitivity, specificity, NPV, PPV, LR+ and LR-. Reduction of the Baveno VII grey/indeterminate zone was assessed by sequential application of the $\geq$75% CSPH probability cutoff of the NICER model in patients who remained unclassified after evaluation according to the Baveno VII criteria (rule out: LSM $\leq$15kPa, PLT $\geq 150 \times 10^9$/L; rule in: LSM $\geq$25kPa). **Results:** The prevalence of CSPH according to the HVPG was 60.6%, the median age was 60 years, 67.8% were male and 37.8% were obese. Using the cutoff of $\geq$75%, the NICER model classified more patients as positive than the ANTICIPATE ± NASH model (47.7% vs. 37.6%). In addition, NICER achieved greater sensitivity (69.4% vs. 53.1%) with a similar level of specificity (85.8% vs. 86.4%), resulting in a lower false-negative rate for missed CSPH cases. Sequential application of Baveno VII criteria followed by NICER $\geq$75% reduced the proportion of unclassified patients from 49.0% to 32.4%. **Conclusion:** The inclusion of spleen stiffness enables NICER $\geq$75% to correctly classify more patients with CSPH than ANTICIPATE ± NASH $\geq$75%, while further decreasing the intermediate-risk area following sequential application of the Baveno VII criteria.

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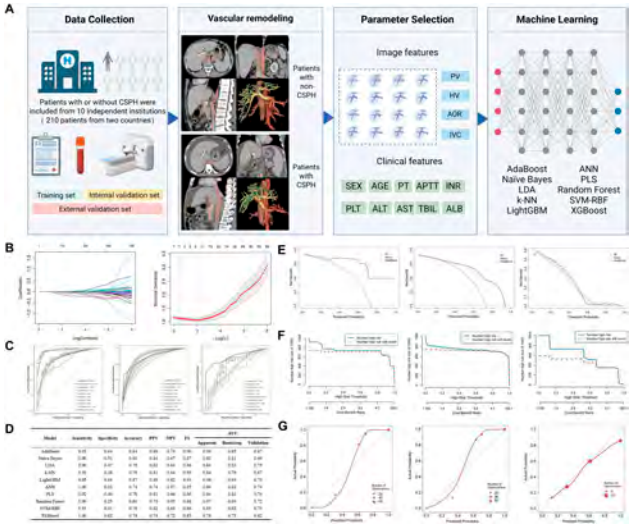
0235 | NON-INVASIVE DIAGNOSIS OF CLINICALLY SIGNIFICANT PORTAL HYPERTENSION USING MACHINE LEARNING MODEL BASED ON VASOMICS PLATFORM: A DEVELOPMENT AND VALIDATION STUDY

Ling Yang[1] Jiang Bai[1] Yi Xiang[2] Xiaolin Wang[2] Jiawei Zhang[2] Deqiang Ma[3] Zhenyu Dai[4] Dazhi Chen[5] Halim Bou Daher[6] Yanna Liu[7] Chuan Liu[2] Shanghao Liu[2] Yueming Lu[2] Yechong Huang[8] Tianyu Liu[9] He Zhu[10] Huiling Xiang[11] Deping Ding[3] Jie Liu[9] Chunlong Li[4] Wei Chen[12] Wei Wang[10] Sen Luo[3] Qianlong Li[4] Shoufang Dai[12] Lijun Peng[13] Haijian Guo[14] Wenjing Liu[15] Muqing Lin[16] Huajie Yu[16] Rui Hu[16] Juan Yuan[16] Wei Zhang[17] Haiyu Wang[18] Shaoting Zhang[8] Chengyan Wang[19] Don Rockey[20] Xiaolong Qi[2], [1]Zhongda Hospital, Medical School, Southeast University, [2]Zhongda Hospital, School of Medicine, Southeast University, [3]Taihe Hospital, Hubei University of Medicine, [4]Yancheng Third People's Hospital, [5]People's Hospital of Ningxia Hui Autonomous Region, [6]Saint Louis University School of Medicine, [7]Beijing Youan Hospital, Capital Medical University, [8]SenseTime Research, [9]Suining Central Hospital, [10]The Sixth People's Hospital of Shenyang, [11]Tianjin Third Central Hospital, [12]Xingtai People's Hospital, [13]Peking University People's Hospital Qingdao Hospital, [14]Jiangsu Provincial Center for Diseases Control and Prevention, [15]MEI Medical Technologies Co., Ltd., [16]Shenzhen Mindray Bio-medical Electronics Co., Ltd., [17]The Third Affiliated Hospital of Sun Yat-sen University, [18]Nanfang Hospital, Southern Medical University, [19]Shanghai Pudong Hospital and Human Phenome Institute, Fudan University, [20]Digestive Disease Research Center, Medical University of South Carolina

Background: Clinically significant portal hypertension (CSPH) is a critical prognostic determinant in chronic liver disease, yet its gold standard diagnosis via hepatic venous pressure gradient (HVPG) measurement remains invasive and limited in availability. This study aimed to develop and validate an interpretable machine learning model for non-invasive CSPH diagnosis using computed tomography (CT)-derived vasomics features. **Methods:** This multicenter retrospective study enrolled adults who underwent HVPG measurement and contrast-enhanced abdominal CT within two weeks from ten hospitals in China and the United States between November 2018 and September 2023. An automated platform extracted 64 quantitative geometric features from four key vessels (portal vein, hepatic vein, aorta, and inferior vena cava) based on vasomics three-dimensional segmentation. Routine blood biomarkers were also collected and analyzed. Feature selection was performed using least absolute shrinkage and selection operator (LASSO) regression, and multiple machine learning algorithms were evaluated. Model performance was assessed via internal bootstrap validation and external validation on a temporally and geographically independent cohort. **Results:** Among 210 included patients (median age 54 years, 64% male), 148 (70.5%) had CSPH. LASSO regression identified seven vascular geometric features reflecting distinct aspects of portal hypertensive remodeling, while all blood biomarkers were eliminated due to coefficient shrinkage. Among ten machine learning algorithms, the Adaptive Boosting (AdaBoost) model performed best for CSPH prediction, with training AUC of 0.963 (95% CI: 0.935–0.991), bootstrap-corrected AUC of 0.847 (95% CI: 0.780–0.900), and external validation AUC of 0.867 (95% CI: 0.771–0.962). At the optimal threshold, the model achieved sensitivity of 0.92 and accuracy of 0.84. Decision curve analysis and clinical impact curves confirmed clinical utility and favorable risk stratification, with well-calibrated predictions (Figure 1). Shapley Additive exPlanations (SHAP) analysis identified venous remodeling features, particularly main branch length of the inferior vena cava and portal vein, as the strongest predictors. A web application was developed using the R Shiny framework to enable CSPH risk prediction based on user-input vascular characteristics: https: //csph-prediction.shinyapps.io/publish/. **Conclusion:** We developed and validated a machine learning model based on vasomics platform that accurately diagnoses CSPH from routine CT imaging. With robust performance and good generalizability, this interpretable non-invasive approach has the potential to improve clinical decision-making and reduce reliance on invasive measurement.

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0236 | UPPER ENDOSCOPY, NSBB USE, AND VARICEAL HEMORRHAGE ACROSS BAVENO ERAS IN ALBERTA: A POPULATION-BASED STUDY

Abdel-Aziz Shaheen[1] Mark Swain[1] Jason Jiang[2] Juan Abraldes[3], [1]University of Calgary, [2]Alberta Health Services, [3]University of Alberta

Background: Baveno VI/VII recommendations have encouraged selective endoscopic screening and broader nonselective beta-blocker (NSBB) use in compensated cirrhosis with suspected clinically significant portal hypertension (CSPH). Their effect on real-world upper endoscopy (EGD), endoscopic therapy, NSBB uptake, and variceal hemorrhage is unknown. **Methods:** We performed a population-based Alberta cohort study of adults with compensated cirrhosis identified from administrative data from 2012-2025. Full-cohort rates of EGD, banding/sclerotherapy and active NSBB use were calculated per 1,000 person-years and as annual proportions of alive at-risk patients. A compensated inception cohort excluded patients with decompensation within 365 days of index diagnosis and those with EGD within 7 days. Patients were assigned to Pre-Baveno VI (2012-2014), Baveno VI (2015-2020), or Baveno VII (2021-2023). Joinpoint regression evaluated temporal changes in 1-year EGD, 1-year NSBB initiation, and 3-year variceal hemorrhage. Cox models estimated hemorrhage risk by era, adjusted for sex, Charlson comorbidity, and alcohol etiology. Platelet-stratified analyses at PLT $<150\times 10^9$/L as a Baveno VI surrogate. **Results:** The full cohort included 32,570 patients. EGD and banding/sclerotherapy rates decreased markedly from 2013-2024, while NSBB use increased in contemporary years. The inception cohort included 7,507 patients: 2,280 Pre-Baveno VI, 3,953 Baveno VI, and 1,274 Baveno VII; 4,558 (60.7%) had alcohol-related cirrhosis. EGD use declined gradually without a significant joinpoint ($p=0.26$). NSBB initiation had a significant joinpoint at 2017 ($p=0.003$), changing from -2.4% annually before the joinpoint (95% CI -16.9% to 14.6%) to +39.6% annually after it (24.3% to 56.7%). Variceal hemorrhage had a joinpoint at 2015 ($p=0.001$), changing from -31.1% annually (-48.5% to -7.9%) to +12.6% annually (3.9% to 22.0%). EGD rates remained stable in alcohol-related cirrhosis (24.4% to 23.2%; $p=0.52$) but had a non-statistically significant decline in non-alcohol cirrhosis (25.1% to 18.8%; $p=0.07$). In the Baveno VII era, among patients with PLT ≥ 150, EGD use was 20.3% in alcohol vs 15.8% in non-alcohol related cirrhosis ($p=0.13$). Alcohol etiology independently predicted variceal hemorrhage (HR 1.71, 1.45–2.02; $p<0.001$). **Conclusion:** Across Baveno eras, Alberta shifted from endoscopic toward NSBB-based portal hypertension care. Our findings highlights incomplete risk-concordant implementation for EGD and NSBB delivery, especially in alcohol-related cirrhosis.

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★ 0237 | UPDATED SURGICAL RISK ASSESSMENT IN PATIENTS WITH CIRRHOSIS

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Background: Postoperative mortality trends in patients with cirrhosis have not been thoroughly assessed following the optimization and implementation of minimally invasive surgical techniques. We aimed to 1) determine the postoperative mortality rates in cirrhotic patients using updated data and 2) generate a prediction model for postoperative mortality risk that best stratifies cirrhotic patients as low- and high-risk surgical candidates. **Methods:** We conducted a single-center retrospective cohort study identifying 3,559 patients ($\geq$18 years old) with cirrhosis who underwent surgery at Mayo Clinic in Rochester, MN, between 2008 and 2023. Cirrhosis was defined by a combination of laboratory tests, imaging, and portal hypertension, or by histology. Pre-operative and operative variables with P values < 0.2 in univariate analysis were included in a forward stepwise multivariate Cox proportional hazards regression model to identify independent predictors of 30-, 90-, and 180-day postoperative mortality. These predictors were used to generate the predictive model, and subsequently, internal validation was performed. The model's discriminatory capacity was compared to the Mayo Risk Score (MRS), Veterans Outcomes and Costs Associated with Liver Disease (VOCAL)-Penn, MELD, MELD-Na, and MELD 3.0 scores. **Results:** Among the enrolled cirrhotic patients, the majority were males (56.9%) with a median age of 62 (18-97) years. The most prevalent cirrhosis etiology was alcohol-related liver disease (39%). Based on the type of surgery, the median MELD score values differed significantly [upper abdominal: 10 (6-43); neurosurgery: 7 (6-43); trauma: 12 (6-36); orthopedic: 9 (6-40); cardiovascular: 12 (6-34); head/neck/skin: 9 (6-34); and lower abdominal: 7 (6-27), $P < 0.001$]. Over half of the underweight or normal-weight patients had ascites (63.2%). At 30, 90, and 180 days, the mortality rates were 5.8%, 9.4%, and 12.3%, respectively. A predictive model that included age, underweight/normal weight, diuretic treatment, serum albumin levels, platelet count, MELD score, American Society of Anesthesiologists (ASA) classification, emergency status, and surgery type demonstrated excellent discrimination and was significantly superior to the other scores ($P < 0.005$, Figure 1A-C). On internal validation, the model exhibited excellent performance and was significantly superior to the other scores at 30 and 90 days ($P < 0.005$), while at 180 days it maintained its superiority over MRS, MELD 3.0, MELD, and MELD-Na ($P < 0.005$) and was slightly different from the VOCAL-Penn score ($P = 0.069$, Figure 1D-F). **Conclusion:** A model utilizing 8 independent clinical characteristics may be used to stratify cirrhotic patients as low- and high-risk surgical candidates. Cirrhotic patients with a predicted mortality of $\geq$ 5% at 30 days, $\geq$ 10% at 90 days, and $\geq$ 14.7% at 180 days were classified as high-risk with a sensitivity of 84-85% and specificity of 60-65%.

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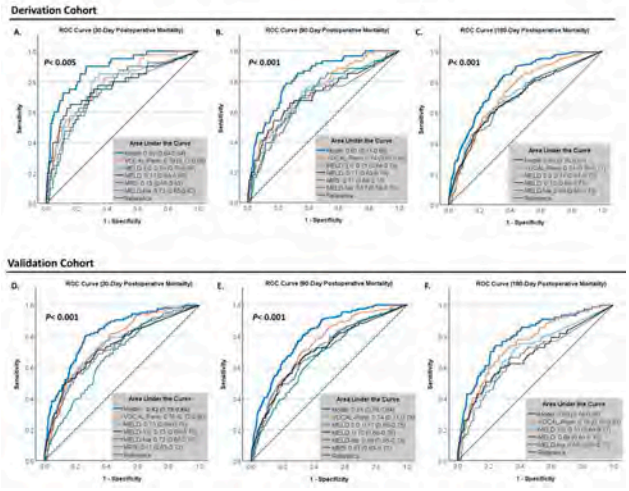


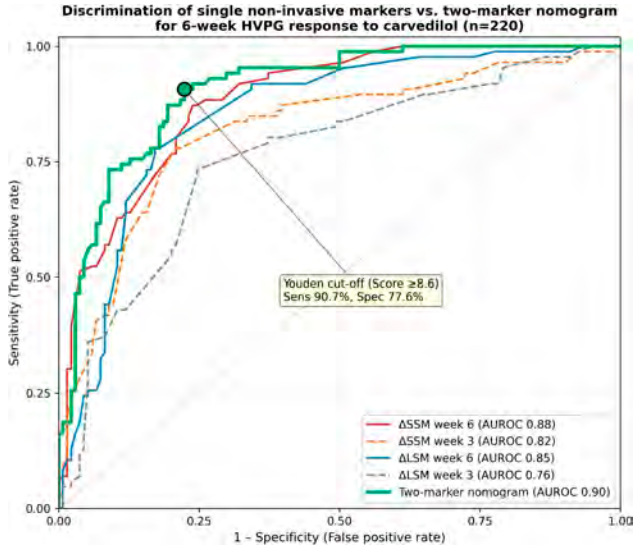
Figure 1. Receiver Operating Characteristics Curves for (**A**) 30-Day, (**B**) 90-Day, and (**C**) 180-Day Postoperative Mortality in the Derivation Cohort as well as for (**D**) 30-Day, (**E**) 90-Day, and (**F**) 180-Day Postoperative Mortality in the Validation Cohort.

Disclosures: Christina Liava: Nothing to Disclose, Toby Weingarten: Nothing to Disclose, Moira Hilscher: Orphalan: Consultant, Patrick Kamath: Sequana: Advisor, NovoNordisk: Advisor, GSK: Advisor.

0238 | HAEMODYNAMIC RESPONSE TO CARVEDILOL AFTER ACUTE VARICEAL BLEED : THE "STOP BLEED STUDY" - A PROSPECTIVE DERIVATION STUDY

Harsh Tevethia[1] Aditya Chaturvedi[2] Akhil Deshmukh[3] Ibrar Ahmed[2] Ankur Jindal[2] Manoj Sharma[4] Esha Baidiya Kayal[2] Guresh Kumar[2] Shiv Kumar Sarin[2], [1]INSTITUTE OF LIVER AND BILIARY SCIENCES (ILBS),NEW DELHI, [2]ILBS, [3]Aster hospitals, [4]Institute of Liver and Biliary Sciences

Background: Hepatic venous pressure gradient (HVPG) is the gold standard to assess beta-blocker response after acute variceal bleeding (AVB), but is invasive and requires to be repeated at six weeks. Whether spleen and liver stiffness measurements (SSM, LSM) can serve as non-invasive surrogates for HVPG as well as classify responders early, is not well studied. **Methods:** This was a prospective single-centre derivation study conducted between.Altogether 244 Child-Pugh A/B patients were enrolled after index AVB and treated with carvedilol. 220 patients completed paired HVPG, SSM and LSM assessment at baseline and week 3 and 6. The primary outcome was diagnostic accuracy of serial SSM/LSM for 6-week HVPG response ($\geq$20% reduction from baseline or HVPG $\leq$12 mmHg) at 6 weeks whereas secondary objectives included 90-day rebleeding, liver-related events,. A two-marker nomogram(Score = 2×ΔSSM_6 + ΔLSM_6, in kPa) was built by multivariable logistic regression and validated by 1,000-resample bootstrap with optimism correction. **Results:** Overall 220 cirrhosis patients [mean age 50.2 ± 11.1 years, males (91.8%), mean baseline HVPG 18.8 ± 2.3 mmHg, mean MELD 15.1 ± 2.7] with predominant etiology being alcohol (41.4%) and MASLD (39.3%), completed per protocol analysis and were analysed.. HVPG response was seen in 86/220 (39.1%) patients. ΔSSM reduction correlated with ΔHVPG reduction (week 6 $r = 0.50$, week 3 $r = 0.38$; both $p < 0.001$). In multivariable regression, both ΔSSM_6 [OR 1.25 (95% CI 1.18–1.33), $p < 0.001$]and ΔLSM_6 (OR 1.11 (95% CI 1.07–1.15), $p < 0.001$) were independent predictors of HVPG response.For individual markers at week 6, ΔSSM AUROC was 0.88 (95% CI 0.84–0.93) and ΔLSM AUROC was 0.85 (0.80–0.90) and at week 3, ΔSSM AUROC was 0.82 (0.75–0.87) and ΔLSM AUROC was 0.76 (0.69–0.82). ΔSSM predicted response at both time points: $\geq$3 kPa at week 3 (sensitivity 77.9%, specificity 79.1%) and $\geq$5 kPa at week 6 (sensitivity 87.2%, specificity 76.1%) whereas ΔLSM change of $\geq$1 kPa at week 6 (sensitivity 76.7%, specificity 82.8%) predicted response. The two-marker nomogram combining week-6 ΔSSM and ΔLSM achieved bootstrap-corrected AUROC 0.90 (95% CI 0.86–0.94). A Score $\geq$10 at week 6 identified responders with sensitivity 87.2% and specificity 79.1% with PPV 72.8% and NPV 90.6%. At 90 days, ITT rebleeding was seen in 48/ 244 (19.7%) (8.0% responders vs 26.3% non-responders, $p < 0.001$) and liver-related events were seen in 36/ 244 (14.8%) (4.5% responders vs 20.5% non-responders, $p < 0.001$) patients. **Conclusion:** A simple two-marker nomogram score of $\geq$10 combining week-6 ΔSSM and ΔLSM is highly sensitive and specific for predicting carvedilol-induced HVPG response after AVB. The score non-invasively and reliably segregates carvedilol non-responders for alternative interventions to prevent rebleed.



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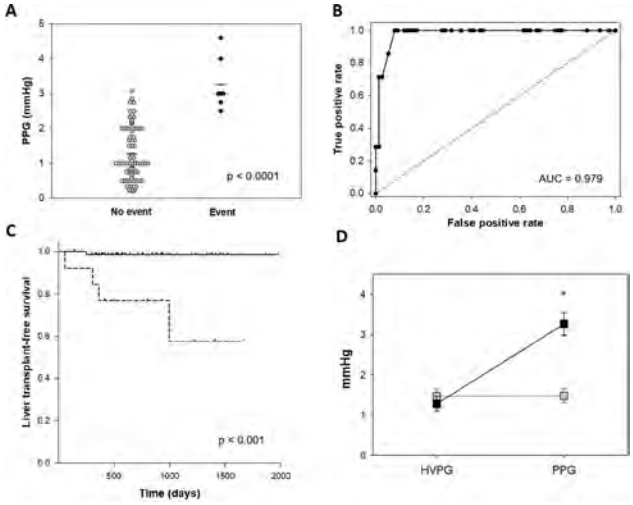
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0239 | UTILITY OF ENDOSCOPIC ULTRASOUND GUIDED PRESSURE MEASUREMENT IN ASSESSING FONTAN-ASSOCIATED LIVER DISEASE SEVERITY

Jordan Sack[1] Marvin Ryou[1] Thomas Wang[1] David Papke[1] Michelle Gurvitz[2] Fred Wu[2] Stephen Zucker[1], [1]Brigham and Women's Hospital, [2]Boston Children's Hospital

Background: There presently are no tests that reliably predict the severity of Fontan-associated liver disease (FALD). We explored whether the portal pressure gradient (PPG) measured using an endoscopic ultrasound (EUS)-guided transgastric approach correlates with liver events in patients with FALD. **Methods:** We directly measured hepatic and portal vein pressures in a cohort of 83 adult patients with Fontan circulation using an EUS-guided approach. The correlation of the PPG with liver events (ascites, hepatic encephalopathy, variceal hemorrhage, hepatocellular carcinoma) was assessed and compared with other standard measures of liver disease severity, including esophageal varices, vibration-controlled transient elastography, imaging, histology, and balloon occlusion transvenous hepatic venous pressure gradient (HVPG). **Results:** The majority of patients (89.2%) underwent EUS as an outpatient, with two mild adverse events. The mean PPG was 1.4 ± 0.9 mmHg. Liver events occurred in 7 (8.4%) patients (ascites: 4, hepatic encephalopathy: 2, and hepatocellular carcinoma: 1. PPG was significantly higher in patients who experienced a liver event (3.3 ± 0.8 v 1.3 ± 0.8 mmHg, $p < 0.0001$), **Figure A**. The odds of a liver event increased 5.6-fold for every 1 mmHg increase in PPG (95% CI 1.8-16.8, $p = 0.002$). PPG had a strong ability to discriminate liver events (AUC 0.979; $p < 0.001$), **Figure B**. Liver transplant free survival was significantly higher among patients with PPG less than 2.5 mmHg (log rank $p < 0.001$), **Figure C**. No other liver assessment tool provided independent predictive value beyond the PPG. While there was no association of esophageal varices with liver events ($p = 0.48$) or PPG ($p = 0.09$), those with distal esophageal varices had higher PPG ($p = 0.006$). There was no correlation of liver imaging or liver stiffness with liver events ($p = 0.28$, $p = 0.57$) or PPG ($p = 0.57$, $p = 0.39$), respectively. In the sub-set of patients with available liver histology, the presence of advanced hepatic fibrosis was not significantly associated with a liver event ($p = 0.11$). When all stages of hepatic fibrosis were considered, there was a linear correlation ($p = 0.049$) between higher PPG and increasing liver fibrosis; however, hepatic fibrosis stage had modest discriminatory ability for liver events. While there was generally good correlation between HVPG and PPG, HVPG significantly underestimated PPG in patients who experienced liver events (1.3 v 3.3 mmHg, $p = 0.02$), **Figure D**. **Conclusion:** PPG outperforms HVPG and other standard measures of liver disease severity in identifying adult Fontan patients experiencing liver events.



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★ 0240 | INTEGRATED IMAGING AND PLASMA BIOMARKERS FOR DETECTION OF DUCTAL DISEASE AND FIBROSIS IN PEDIATRIC AUTOIMMUNE LIVER DISEASE

Alexander Miethke[1] Tamar Ogard[2] Cyd Castro-Rojas[3] Rebekah Karns[3] Mosab Alquraish[3] Wujuan Zhang[4] Annika Yang Vom Hofe[1] Michelle Damen[3] Jonathan Dillman[5] Andrew Trout[5] Carlos Ferreira[6], [1]Cincinnati Children's Hospital Medical Center, [2]Pediatric Gastroenterology, Hadassah-Hebrew University Medical Center, Jerusalem, Israel, [3]Pediatric Gastroenterology, Cincinnati Children's Hospital, Cincinnati, OH, [4]The Wistar Institute, Philadelphia, PA, [5]Pediatric Radiology, Cincinnati Children's Hospital, Cincinnati, OH, [6]Perspectum Ltd, Oxford, UK

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Background: Bile duct injury frequently coexists with, or evolves, in pediatric autoimmune hepatitis and is associated with worse prognosis. MRCP-based diagnosis of cholangiopathy is limited by interreader variability. We evaluated non-invasive tests for detection of large-duct disease, fibrosis progression, and prediction of liver outcomes in pediatric-onset autoimmune liver disease (AILD). **Methods:** Fifty-seven patients with AILD (median age 16 [IQR 14–18], disease duration 1 [0–3] year, 54% male, clinical diagnosis: 46% with AIH, 54% with PSC or PSC/AIH overlap syndrome) underwent multi-modal MRI including MRCP and MR elastography (MRE). Two blinded radiologists assessed PSC features, severity of intra- (grade 0–3) and extrahepatic (0–4) large duct disease (Majoie classification), and fibrosis signs (cirrhotic dysmorphology, varices, ascites, splenomegaly. MRCP+ (25 quantitative measures) and corrected (c) T1 mapping as readout for liver heterogeneity were obtained. Plasma bile acids (BA) were measured by mass spectrometry; 80 cytokines/chemokines were quantified by Luminex. **Results:** Radiologists identified PSC features in 27/57 (47%), advanced duct disease (Majoie sum score > 2) in 20/57 (35%), and advanced fibrosis in 12/57 (21%); 10 (17%) experienced endpoints of hepatic decompensation (liver transplant, variceal bleeding, ascites, or hepatic encephalopathy). Compared with age-matched, healthy controls (n = 10), most primary and secondary BA species were elevated in AILD. BA differences between PSC and non-duct AILD were limited; however, advanced duct disease showed higher total cholic acid and glycocholic acid. Highest plasma BA levels occurred prior to decompensation. Cytokines/chemokines were reduced in PSC vs AIH, notably the potent chemokine MCP1 (CCL2), and cleaved cytokine receptors, TNFRII and IL2R, whereas advanced fibrosis associated with broader immune activation. No plasma BA or routine laboratory tests (GGT, ALP) specifically identified PSC; decreased CD30 and MCP1 yielded AUC > 0.7. Quantitative MRCP+ metrics (e.g., maximal duct dilation, total duct length, biliary tree volume) achieved AUC > 0.8 for PSC diagnosis. Total taurine-conjugated (T)BA, TCDCA, APRI, cT1 IQR, and liver stiffness by MRE predicted future liver events (AUC > 0.91). LASSO regression analysis showed best PSC discrimination using plasma TDCA and G-T ratio with SCF cytokine and MRCP+ metrics; adding circulating markers did not improve imaging-based prediction of hepatic decompensation. **Conclusion:** Quantitative MRCP+ measures outperform circulating biomarkers for detecting PSC cholangiopathy in pediatric AILD. APRI, TBA, and MRE/ cT1 IQR accurately predict fibrosis progression and clinical outcomes. Most cytokines reflect fibrosis rather than ductal disease.

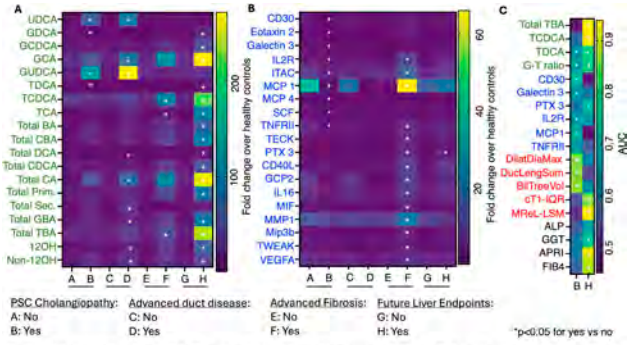


Fig 1. Fold change in plasma BA (**A**) and cytokine/chemokine concentrations (**B**) in patients with AILD relative to the mean of 10 healthy controls. Significant differences by presence of PSC cholangiopathy, advanced duct disease, advanced radiographic fibrosis, or future liver endpoints are indicated (*). (C) Area under the curve (AUC) for plasma BA, cytokines/chemokines, quantitative MRCP+ metrics, cT1 IQR, MRE–derived liver stiffness, and standard laboratory tests in discriminating large duct disease and predicting liver endpoints.

Disclosures: Alexander Miethke: Mirum Pharmaceutical Inc: Grant/Research Support, Mirum Pharmaceutical Inc: Consultant, Ipsen: Speaking and Teaching, Perspectum Ltd.: Grant/Research Support, Esperion: Advisor, Tamar Ogard: Nothing to Disclose, Cyd Castro-Rojas: Nothing to Disclose, Rebekah Karns: Nothing to Disclose, Mosab Alquraish: Nothing to Disclose, Wujuan Zhang: Nothing to Disclose, Annika Yang Vom Hofe: Nothing to Disclose, Michelle Damen: Nothing to Disclose, Jonathan Dillman: Nothing to Disclose, Andrew Trout: Siemens Healthineers: Funding to institution, GE Healthcare: Funding to institution, GE Healthcare: Expert review of images, Perspectum Inc: Funding to institution, Carlos Ferreira: Perspectum: Employee.

0241 | *UCA1* LONG NONCODING RNA IN CISPLATIN RESISTANT HEPATOBLASTOMA

Maryam Shaikh[1] Morgan Brown[1] Mehreen Aftab[2] Nazia Nazam[1] Pranava Nande[1] Ali Eakes[1] Abdulraheem Kaimari[1] Joel Opara[1] Elizabeth Beierle[1], [1]University of Alabama at Birmingham, [2]Jamia Hamdard

Background: Hepatoblastoma is the most common primary liver cancer in children. Surgery and platin-based chemotherapy are the mainstays of treatment, but children with recurrent disease are challenging to treat due to chemoresistance. Treatment regimens for these children are ineffective, and often result in severe long-term effects including deafness, nephrotoxicity, and cardiotoxicity, making this cohort of children the one most in need of innovative and novel therapeutics. Long noncoding RNAs (lncRNAs), have been identified as indispensable regulators in a variety of oncogenic or tumor suppressor functions, and may offer enhanced therapeutic potential compared to protein coding genes. Urothelial carcinoma associated 1 (*UCA1)*

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lncRNA has been implicated in chemoresistance and metastasis in other malignancies, but its contribution to these processes in hepatoblastoma has not been investigated. This study investigates the role of lncRNA, *UCA1*, in chemotherapy resistance of hepatoblastoma tumor cells. **Methods:** A cisplatin resistant human hepatoblastoma cell line, HLM_2, was established by serial tail vein injections of HuH6 hepatoblastoma cell line in mice, followed by dissociation of metastatic pulmonary lesions. Murine tumor models were established by orthotopic injection of HuH6 or HLM_2 cells in the liver of NOD-SCID mice. Patient derived xenograft (PDX) models established from a metastatic hepatoblastoma patient were propagated in athymic nude mice. RNA sequencing and analysis of HLM_2 and HuH6 cells was performed. Real-time quantitative PCR confirmed the expression of *UCA1* in tumor cells and tissues. siRNA silencing of *UCA1* was performed to investigate the role of *UCA1* regulated chemoresistance mechanisms in HLM_2 cells by clonogenic assays, flow cytometry, and immunoblotting. **Results:** RNA sequence data of cisplatin resistant HLM_2 compared to parent HuH6 cells revealed significant upregulation of lncRNA *UCA1* in the HLM_2 cells. *UCA1* was also significantly upregulated in patient derived xenografts relative to normal liver controls. siRNA silencing of *UCA1* reduced clonogenicity and promoted cisplatin-induced apoptosis in HLM_2 cells. Immunoblotting revealed that siRNA mediated silencing of *UCA1* decreased Akt phosphorylation, while increasing PTEN expression, both in the presence and absence of cisplatin treatment. **Conclusion:** This study shows that upregulated transcript levels of *UCA1* is associated with cisplatin resistance in hepatoblastoma cells potentially through the activation of the Akt pathway, indicating treatments targeting *UCA1* may provide meaningful therapeutic strategies for cisplatin resistance hepatoblastoma patients.

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0242 | BLOOD CD8 TISSUE RESIDENT MEMORY-LIKE ENDOTYPES PERSIST THROUGHOUT DISEASE COURSE IN PATIENTS WITH ACTIVATED T-CELL PEDIATRIC ACUTE LIVER FAILURE

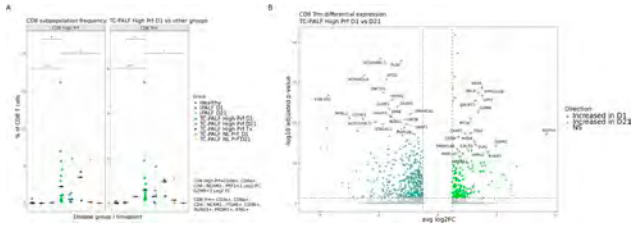
Tamir Diamond[1] Alyssa Baccarella[2] Catherine Chapin[3] David Smith[2] Portia Kreiger[2] Sarah Henrickson[2] Niansheng Chu[2] Ezuka Ogbolu[2] Anna Banc-Husu[4] Daniel Leung[5] Amrita Narang[6] Beth Carter[7] Scott Elisofon[8] Ryan Fischer[9] Amber Hildreth[10] Mike Leonis[11] Steven Lobritto[12] Saeed Mohammad[13] Anna Peters[14] Norberto Rodriguez-Baez[15] Rene Romero[16] David Rudnick[17] James Squires[18] Shikha Sundaram[19] Kyla Tolliver[20] Pamela Valentino[21] Zemin Su[22] Valerie Durkalski-Mauldin[22] Katie Neighbors[23] Simon Horslen[24] Kathleen Loomes[1] Estella Alonso[3] Edward Behrens[2], [1]The Children's Hospital of Philadelphia, [2]Children's Hospital of Philadelphia, [3]Ann and Robert H. Lurie Children's Hospital of Chicago, [4]Baylor College of Medicine, Texas Children's Hospital, [5]Texas Children's Hospital, [6]Stanford, [7]Children's Hospital Los Angeles, [8]Boston Childrens Hospital, [9]Children's Mercy Kansas City, [10]University of California San Diego, [11]Cleveland Clinic Children's Outpatient Center (R3), [12]NY Presbyterian Hospital - Columbia University, [13]Monroe Carell Jr. Children's Hospital at Vanderbilt, [14]Cincinnati Children's Hospital Medical Center, [15]University of Texas Southwestern Medical Center, [16]Emory University School of Medicine, [17]Washington University Medical Center, [18]Children's Hospital of Pittsburgh, [19]Children's Hospital Colorado, [20]Indiana University School of Medicine, [21]University of Washington, [22]Medical University of South Carolina, [23]Ann & Robert H. Lurie Children's Hospital of Chicago, [24]UPMC Children's Hospital of Pittsburgh

Background: Activated T-cell pediatric acute liver failure (TC-PALF) is the most common cause of liver failure in children in North America. Work from the PALF Immune Response Network (PALF-IRN) described two distinct disease endotypes that differ by their CD8+ T-cell Perforin1 (Prf) expression: TC-PALF High Prf and TC-PALF Normal Prf (TC-PALF NL Prf). TC-PALF High Prf patients have a unique CD8 T-cell population with a transcriptional program similar to tissue effector resident memory cell (CD8 Trm) despite being in peripheral blood. However, how these endotypes evolve longitudinally is unknown. We hypothesized that CD8Trms differentiate stable TC-PALF endotypes that persist over time. **Methods:** Peripheral blood mononuclear cells samples from day 1, 21 (transplant free survival patients), and liver transplant (Tx) from patients enrolled in the PALF-IRN clinical trial, TReatment for ImmUne Mediated PathopHysiology (TRIUMPH) (NCT04862221) were utilized. Standard 10x GEM-Ex 5' single cell RNA sequencing was performed and analyzed using standard pipelines included in Seurat. Healthy control samples were integrated from a local database. Investigators remain blinded to patient study treatment arm, which included 3 arms: equine anti-thymocyte globulin, methylprednisolone or supportive care. Statistical analysis was performed using R studio 4.4.0. **Results:** Healthy controls (n = 5), indeterminate-PALF (iPALF) (n = 3), TC-PALF High Prf (n = 13), and TC-PALF NL Prf (n = 4) were compared. CD8 High Prf cells (*CD3e+,*

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CD8a+, CD4-, NCAM1-, PRF1 > 3 Log_2 FC, *GZMB* > 3 Log_2 FC) and CD8 Trm cells (*CD3e+ CD8+ CD4- NCAM1- ITGAE+ CD38+ RUNX3+ PRDM1+IFNG+*) persisted at day 21 (D21) and at Tx in the High Prf group and remained absent over time in Healthy, iPALF and TC-PALF NL Prf except for one patient (Fig. 1A). To determine if CD8Trms change functionally over time, we compared differentially expressed Trm genes between D1 and D21 in High Prf patients. D21 Trms demonstrate a transcriptional program of exhaustion, including upregulation of SMARCA2, KLRG1 and NR4A2, and downregulation of GZMB, RUNX2 and CXCR3 (Fig. 1B). **Conclusion:** A CD8 Trm population persists in peripheral blood of patients with TC-PALF High Prf during recovery (D21) and at Tx. This supports the hypothesis that CD8 Trm cells in peripheral blood are a marker of a distinct endotype, rather than simply reflecting where a patient is in the disease's natural course. CD8 Trms appear transcriptionally more exhausted at D21 consistent with a model of excessive antigen stimulation in High Prf patients. Validation of these markers by flow cytometry could provide a useful minimally invasive tool to diagnose these different endotypes clinically for precision medicine approaches for these patients.



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0243 | OUTCOMES BENCHMARKS IN PEDIATRIC AUTOIMMUNE LIVER DISEASE: A FOUNDATION AND A CHALLENGE FOR IMPROVEMENT FROM THE AUTOIMMUNE LIVER DISEASE NETWORK FOR KIDS (A-LINK)

Amy Taylor[1] Cyd Castro-Rojas[1] Karan Mudaliar[1] Mary Bauer[1] Catharine Whitacre[1] Mosab Alquraish[1] Mary Ayers[2] Nanda Kerkar[3] Sakil Kulkarni[4] Sindhu Pandurangi[5] Katelyn Saarela[6] Kyla Tolliver[7] Alexander Weymann[8] Shehzad Saeed[9] Christine Browner[10] Nicole Horton[10] Fionna Kopp[10] Jane Weyer[10] Lorrie Williams[10] James Squires[11] Alexander Miethke[1], [1]Cincinnati Children's Hospital Medical Center, [2]UPMC Children's Hospital of Pittsburgh, [3]Massachusetts General Brigham for Children, [4]Washington University in St. Louis, [5]UT Southwestern, Children's Medical Center Dallas, [6]Seattle Children's Hospital, [7]Indiana University, [8]Nationwide Children's Hospital, [9]Dayton Children's Hospital, [10]A-LiNK Connections, [11]Children's Hospital of Pittsburgh

Background: There is no standardized mechanism to prospectively track outcomes in children with autoimmune liver disease (AILD), hindering clinical care. Here, we define key outcome measures and establish baseline metrics for children with AILD. **Methods:** Children 1+ years old with a new or established diagnosis of AILD from 8 A-LiNK sites were prospectively enrolled. Demographics, laboratory values, medications, steroid-associated side effects, and disease complications were documented at

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each clinical visit. U charts were constructed with a defined centerline after 12 consecutive months with ≥ 30 patients. Remission was defined as transaminases below the upper limit of normal (ULN) for age/sex. Flare was defined as 2 consecutive transaminase values above the ULN in those previously in remission. GGT normalization was defined as < 50 IU/L. **Results:** 266 participants were enrolled (Figure 1A): 152 with autoimmune hepatitis (AIH), 62 with autoimmune sclerosing cholangitis (ASC), and 52 with primary sclerosing cholangitis (PSC). 54% were female, 77% White, 10% Black/African American, and 86% non-Hispanic. Median age at enrollment was 15.9 yrs and median disease duration was 3.9 yrs. The remission centerline was 63.6% for those 12+ months from AIH/ASC diagnosis (Fig 1B). Steroid-free treatment was more common in those in remission (46/71, 65%) vs those not in remission (26/61, 43%). Those in remission prescribed prednisone were on lower doses than those not in remission (5.6mg/day vs 16.6mg/day, $p < 0.0001$). 21% (44/213) with AIH/ASC experienced steroid-associated side effects: 15% obesity, 3% steroid-associated diabetes, and 2% hypertension, cataract/glaucoma, and/or low bone mineral density. Flare rates were 3% per 100 patient-months, with an average of 862 patient-days between flare events (Fig 1C). GGT normalization centerline 6 months after PSC diagnosis was 54.1% (Fig 1D). The cohort complication rate was low: 4/132 (3%) experienced cholangitis; 8/266 (3%) experienced cirrhosis-associated complications; and 1 patient had a liver transplant. **Conclusion:** A-LiNK represents the largest prospective cohort of children with AILD, providing follow-up and monthly performance feedback on key outcome measures. AIH remission rates are lower than reported, and GGT normalization occurs in approximately half of PSC cases, highlighting the need to improve therapy and implement quality-improvement strategies to enhance care and long-term outcomes for children with AILD.

Figure 1

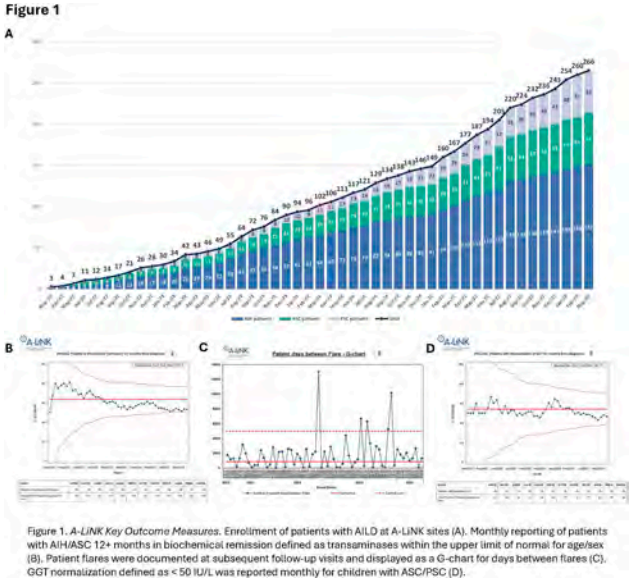


Figure 1. *A-LiNK Key Outcome Measures.* Enrollment of patients with AILD at A-LiNK sites (A). Monthly reporting of patients with AIH/ASC 12+ months in biochemical remission defined as transaminases within the upper limit of normal for age/sex (B). Patient flares were documented at subsequent follow-up visits and displayed as a G-chart for days between flares (C). GGT normalization defined as < 50 IU/L was reported monthly for children with ASC/PSC (D).

Disclosures: Amy Taylor: Nothing to Disclose, Cyd Castro-Rojas: Nothing to Disclose, Karan Mudaliar: Nothing to Disclose, Mary Bauer: Nothing to Disclose, Catharine Whitacre: Nothing to Disclose, Mosab Alquraish: Nothing to Disclose, Mary Ayers: Nothing to Disclose, Nanda Kerkar: Mirum: Advisor, Elsevier: Royalties or patent beneficiary, Ipsen: Advisor, Orphalan: Advisor, Sakil Kulkarni: Nothing to Disclose, Sindhu Pandurangi: Nothing to Disclose, Katelyn Saarela: Nothing to Disclose, Kyla Tolliver: Nothing to Disclose, Alexander Weymann: Nothing to Disclose, Shehzad Saeed: Nestle Health Sciences: Advisor, Christine Browner: Nothing to Disclose, Nicole Horton: Nothing to Disclose, Fionna Kopp: Nothing to Disclose, Jane Weyer: Nothing to Disclose, Lorrie Williams: Nothing to Disclose, James Squires: Sanofi: Data Safety Committee, Mirum: Advisor, Ipsen: Advisor, Sanofi: Data Safety Committee, Sanofi: Data Safety Committee, Mirum: Advisor, Mirum: Advisor, Ipsen: Advisor, Ipsen: Advisor, Sanofi: Data Safety Committee, Mirum: Advisor, Ipsen: Advisor, Sanofi: Data Safety Committee, Sanofi: Data Safety Committee, Mirum: Advisor, Mirum: Advisor, Ipsen: Advisor, Ipsen: Advisor, Sanofi: Data Safety Committee, Mirum: Advisor, Ipsen: Advisor, Sanofi: Data Safety Committee, Sanofi: Data Safety Committee, Mirum: Advisor, Mirum: Advisor, Ipsen: Advisor, Ipsen: Advisor, Alexander Miethke: Mirum Pharmaceutical Inc: Grant/Research Support, Mirum Pharmaceutical Inc: Consultant, Ipsen: Speaking and Teaching, Perspectum Ltd.: Grant/Research Support, Esperion: Advisor.

★ 0244 | THE NATURAL HISTORY, CLINICAL AND LABORATORY PREDICTORS OF SURVIVAL AND PORTAL HYPERTENSION IN PEDIATRIC FONTAN-ASSOCIATED LIVER DISEASE (FALD): A MULTICENTER PED FALD NETWORK

Chaowapong Jarasvaraparn Henry Lin [1]Dieudonne Nonga[2] John Kelly[2] Omar Khalid[2] Deepti Bhat[3] Pinar Bulut[3] Alyssa Kriegermeier[4] Steven Lobritto[5] Manjari Madhusudanan[5] Sindhu Pandurangi[6] Amal Aqul[7] Stephanie Segura[8] Kim Liss[9] Ryan Himes[10] Christopher Chu[11] Amber Hildreth[12] Ruba Azzam[13] Adebowale Adeyemi[14] Alexis Gumm[15] Michael Nowicki[16] Megan Butler[17] Alisa Muniz Crim[18] Shilpa Sood[19] Debora Kogan-Liberman[20] Victoria Shakhin[21] Jessica Hochberg[22] Anita Pai[23] Anthony Perkins[24] R. Mark Payne[25] Katryn Furuya[26] Wikrom Karnsakul[27] Jean Molleston[25], [1]Doernbecher Children's Hospital, [2]Nationwide Children's Hospital, [3]Phoenix Children's Hospital, [4]Ann and Robert H. Lurie Children's Hospital of Chicago, [5]Columbia University, [6]UT Southwestern,

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Background: Fontan procedure is the standard of care for patients with a single ventricle physiology, but over time results in development of Fontan associated liver disease (FALD). FALD is a near-universal consequence of the Fontan circulation, yet reliable predictors of adverse outcomes in children remain poorly defined. We aimed to characterize the natural history of pediatric FALD and identify non-invasive laboratory markers associated with survival and portal hypertension in a large multicenter cohort. Laboratory tests and clinical data were collected during routine visits. **Methods:** A retrospective 24 multicenter study was conducted across the Pediatric FALD (PED FALD) Network, including 1,031 children ($\leq$ 18 years old) post-Fontan. Primary outcomes were overall survival (OS), native heart survival (NHS), and event-free survival (EFS). Event-free survival was defined as the absence of a failing Fontan, heart transplant, or death. Features of portal hypertension were reported using the VAST score, which was calculated by the sum of clinical findings (Varices, Ascites, Splenomegaly, and Thrombocytopenia). A VAST score $\geq$ 2 indicated portal hypertension. Survival was analyzed using Kaplan-Meier curves and Cox proportional hazards models, including a frailty model to account for center effects. Non-invasive fibrosis scores (APRI, FIB-4) at the first available were evaluated as predictors of mortality. **Results:** The cohort (n = 1,031) had a mean age at Fontan of 3.4 ± 1.7 years. During follow-up (mean 12 ± 5 years), failing Fontan was observed in 11.8% of patients, while 5.2% required isolated heart transplants and 2.4% died. Portal hypertension-related complications, including GI bleeding and encephalopathy, occurred in 2.7% and 0.6% of patients, respectively. OS was 99.1% at 10 years, 97.2% at 15 years, 93.1% at 20 years. The proportion of patients remaining free of portal hypertension was 96.9% at 10 years, 91.2% at 15 years, and 87.5% at 20 years. Older age at Fontan was a significant independent predictor of worse OS (HR 1.47, $p < 0.001$), NHS (HR 1.32, $p < 0.001$), and EFS (HR 1.19, $p < 0.001$) after adjusting for center effects. Notably, African American race was associated with significantly lower EFS (HR 1.94, $p = 0.008$) in the fixed-effects model. Higher liver fibrosis scores were strongly associated with mortality. An APRI > 0.43 was associated with a 3.44-fold increase in mortality risk ($p = 0.031$). Similarly, a FIB-4 > 0.43 was associated with a 4.28-fold increase in mortality risk compared to the lowest tier ($p = 0.015$). **Conclusion:** In the largest pediatric FALD cohort to date, age at Fontan procedure and non-invasive fibrosis markers (APRI and FIB-4) serve as critical prognostic indicators for long-term survival. These findings suggest that higher APRI and FIB-4 levels may identify high-risk patients who require intensified surveillance or early intervention.

Table 1 Survival Analysis Results – no Center Effect

	Overall Survival		Native Liver Survival		Event Free Survival	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Male	2.47 (0.94, 6.50)	0.066	1.52 (0.92, 2.50)	0.101	1.09 (0.77, 1.53)	0.632
Asian	3.56 (0.81, 15.66)	0.093	1.98 (0.72, 5.44)	0.186	1.27 (0.56, 2.87)	0.568
Black	2.18 (0.57, 8.34)	0.257	1.60 (0.73, 3.49)	0.237	1.94 (1.19, 3.15)	0.008
Other	1.81 (0.08, 39.52)	0.705	2.19 (0.59, 8.12)	0.243	0.85 (0.24, 3.02)	0.795
Unknown	0.99 (0.24, 4.15)	0.995	1.50 (0.78, 2.88)	0.220	0.90 (0.54, 1.50)	0.672
White (ref)	1.00				1.00	
Font Age	1.38 (1.18, 1.61)	<0.001	1.25 (1.12, 1.39)	<0.001	1.24 (1.15, 1.34)	<0.001

Table 2 Survival Analysis Results – Center entered as random effect into a frailty model

	Overall Survival		Native Liver Survival		Event Free Survival	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Male	2.54 (0.95, 6.75)	0.062	1.29 (0.78, 2.13)	0.328	0.94 (0.67, 1.32)	0.727
Asian	2.21 (0.45, 10.83)	0.327	1.64 (0.56, 4.82)	0.366	1.59 (0.67, 3.78)	0.296
Black	1.52 (0.37, 6.13)	0.560	1.32 (0.59, 2.97)	0.497	1.62 (0.96, 2.74)	0.067
Other			0.76 (0.18, 3.20)	0.707	0.37 (0.09, 1.51)	0.165
Unknown	0.92 (0.15, 5.58)	0.25	1.08 (0.49, 2.36)	0.854	0.99 (0.53, 1.83)	0.962
White (ref)	1.00		1.00		1.00	
Font Age	1.47 (1.22, 1.76)	<0.001	1.32 (1.16, 1.49)	<0.001	1.19 (1.10, 1.30)	<0.001

Disclosures: Chaowapong Jarasvaraparn: Nothing to Disclose, Henry Lin: Ipsen: Advisory Board, Mirum: Advisory Board, Ipsen: Advisory Board, Dieudonne Nonga: Nothing to Disclose, John Kelly: Nothing to Disclose, Omar Khalid: Nothing to Disclose, Deepti Bhat: Nothing to Disclose, Pinar Bulut: Nothing to Disclose, Alyssa Kriegermeier: Mirum Pharmaceuticals: Advisor, Steven Lobritto: Nothing to Disclose, Manjari Madhusudanan: Nothing to Disclose, Sindhu Pandurangi: Nothing to Disclose, Amal Aqul: Mirum Pharmaceuticals: Consultant, Ipsen: Consultant, Sarepta Therapeutics: Consultant, Stephanie Segura: Nothing to Disclose, Kim Liss: Nothing to Disclose, Ryan Himes: Mirum: Consultant, Ipsen: Consultant, Christopher Chu: Mirum Pharmaceuticals: Consultant, Amber Hildreth: Nothing to Disclose, Ruba Azzam: Nothing to Disclose, Adebowale Adeyemi: Nothing to Disclose, Alexis Gumm: Mirum Pharmaceuticals: Consultant, Michael Nowicki: Nothing to Disclose, Megan Butler: Ipsen pharmaceuticals: Consultant, Alisa Muniz Crim: Nothing to Disclose, Shilpa Sood: Nothing to Disclose, Debora Kogan-Liberman: Nothing to Disclose, Victoria Shakhin: Nothing to Disclose, Jessica

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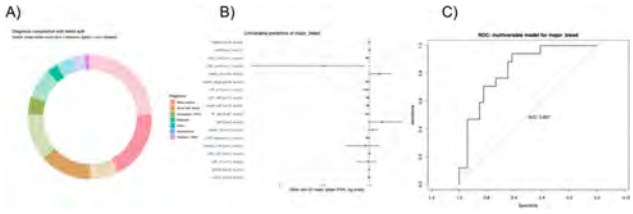
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0245 | UTILISATION OF THROMBOELASTOGRAPHY AND AND VON WILLEBRAND FACTOR ANTIGEN PROFILE IN CHILDREN WITH BLEEDING IN LIVER TRANSPLANT

Harry Sutton[1] Akshat Goel[2] Michael Avery[2] Bethany Tucker[2] Miriam Cortescerisuelo@nhs.net[3] lara Roberts[4] Eirini Kyrana[2] Anish Gupta[5] Robert Hegarty[2] Tassos Grammatikopoulos[6], [1]Toronto Hospital for Sick Children, [2]Paediatric Liver, GI & Nutrition Centre and MowatLabs, King's College Hospital, London, UK, [3]Liver Transplant Surgery, Institute of Liver Studies, King's College Hospital, London, [4]Department of Haematological Medicine, King's Thrombosis Centre, King's College Hospital NHS Foundat, [5]Division of Liver Transplant, Anaesthetic Department, King's College Hospital NHS Foundation Trust, [6]King's College Hospital

Background: Bleeding is a common perioperative complication associated with portal hypertension and liver transplantation (LT). Thromboelastography (TEG), reflecting hemostatic status, and von Willebrand Factor Antigen (vWFAg), a vascular endothelial activation marker, can independently predict bleeding and death in liver disease with limited data in children undergoing LT. We investigated whether preoperative TEG parameters and vWFAg predict perioperative bleeding, intraoperative transfusion, and intensive care stay in children undergoing LT. **Methods:** We carried out an observational cohort study in children listed for LT at King's College Hospital between June 2021–Nov 2024, recording all TEG parameters (Citrated Rapid TEG, Kaolin, Functional Fibrinogen), vWFAg, GPIbR, and clinical and laboratory data including bleeding outcomes per departmental protocol. **Results:** 75 (m = 38, median age = 3.6yr) children with Chronic Liver Disease (CLD, n = 58) (n = 58) or Acute Liver Failure (ALF, n = 17) were included (Figure 1A). Major bleeding (defined as >/= 40ml/kg red blood cell transfusion or >/= 80ml/kg total blood products intra- or post-op) occurred in 28 (37%) children and 9 (12%) developed thrombosis peri-operatively. Lower platelet count (OR 0.99, p = 0.012), higher vWFAg (OR 1.02, p = 0.004), and weaker/slower clot formation on TEG (Kaolin Angle, Kaolin/CRT maximum amplitude and amplitude-at-10-minutes; all $p < 0.05$) predicted major bleeding, whereas clot-initiation parameters (TEG-ACT, TEG-R) did not (p = 0.60) (Figure 1B). A multivariable model (vWFAg, platelets) discriminated major bleeding well (bootstrap-corrected AUC 0.82) (Figure 1C). Clot-strength parameters predicted ICU stay ($R^2 \asymp 0.45$, $p < 10^{-5}$, aetiology-adjusted). No parameter predicted thrombosis. ALF patients experienced a significantly longer PICU stay post-transplant than the CLD patients (median 25 vs 2 days, $p < 0.0001$) and had slower clot-initiation parameters. **Conclusion:** To our knowledge, this is the first paediatric study correlating comprehensive TEG and vWFAg with LT bleeding outcomes. Preoperative platelet count, vWFAg, and TEG clot-strength parameters independently predict perioperative bleeding. ALF patients had prolonged clot initiation compared with those with CLD and had a tenfold increase in PICU length of stay. These exploratory findings highlight the complex coagulopathy present in children prior to transplant and suggest that these variables may be useful in predicting peri-transplant bleeding.



Disclosures: Harry Sutton: Mirium: Consultant, Akshat Goel: Nothing to Disclose, Michael Avery: Nothing to Disclose, Bethany Tucker: Nothing to Disclose, Miriam Cortescerisuelo@nhs.net: Nothing to Disclose, lara Roberts: Nothing to Disclose, Eirini Kyrana: Nothing to Disclose, Anish Gupta: Nothing to Disclose, Robert Hegarty: Nothing to Disclose, Tassos Grammatikopoulos: Nothing to Disclose.

0247 | ALCOHOL EXPOSURE AND SURVIVAL IN PRIMARY SCLEROSING CHOLANGITIS: A PROPENSITY SCORE-MATCHED COHORT STUDY

Muyiwa Awoniyi[1] Jingyi Huang[1] Mariana Campuzano[1] Nicole Jordan[1] Li Tang[1] John McMichael[1], [1]Cleveland Clinic

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Background: Primary sclerosing cholangitis (PSC) is a progressive cholestatic liver disease without effective medical therapy, where liver transplantation is the only life-extending option. Despite established genetic predisposition, susceptibility loci explain less than 10% of disease liability, implicating environmental exposures as dominant, poorly characterized drivers of progression. Alcohol is a compelling candidate: a hepatotoxin disrupting bile acid homeostasis and intestinal dysbiosis through the gut-liver axis central to PSC. Evidence-based guidance is absent; prior evidence is limited to two conflicting studies with methodologic constraints. We hypothesized that alcohol independently impairs PSC survival and designed a propensity score-matched cohort study to test this. **Methods:** We performed a retrospective cohort study of PSC patients at a quaternary referral center (2015-2025), using delayed entry to account for left truncation of patients diagnosed before the observational window. Alcohol exposure was ascertained as a time-fixed binary variable via a composite algorithm of phosphatidylethanol (PEth) levels, AUDIT-C scores (sex-specific thresholds), ICD-coded alcohol use disorder diagnoses, and self-reported consumption. Primary endpoints were overall survival (OS; all-cause death) and transplant-free survival (TFS; composite of all-cause death or liver transplantation). Separate endpoint-specific 1: 4 nearest-neighbor propensity score matching was performed using age, sex, race, delayed-entry status, and baseline cirrhosis. Associations were estimated using Cox models with time-updated 3-month-interval data, adjusting for time-varying diabetes, hypertension, hyperlipidemia, and IBD; robust standard errors were clustered by patient. **Results:** Among 1,030 patients (OS) and 882 (TFS), propensity score matching yielded cohorts of 25 alcohol-exposed vs. 100 unexposed (OS) and 20 vs. 78 (TFS). All post-matching standardized mean differences (SMDs) were below 0.2, confirming adequate balance. Alcohol exposure was independently associated with significantly higher hazard of all-cause death (OS: HR 4.58, 95% CI 1.75–12.00; p = 0.002) and death or transplantation (TFS: HR 5.40, 95% CI 1.95–14.91; p = 0.001). **Conclusion:** This first propensity score-matched analysis demonstrates that alcohol exposure independently and markedly impairs both overall and transplant-free survival in PSC. These findings address the key methodologic limitations of prior conflicting studies and provide the strongest available evidence supporting formal alcohol abstinence counseling as a core component of PSC management. Cautious interpretation is warranted, given the limited absolute number of events; prospective validation in larger multicenter cohorts is needed.

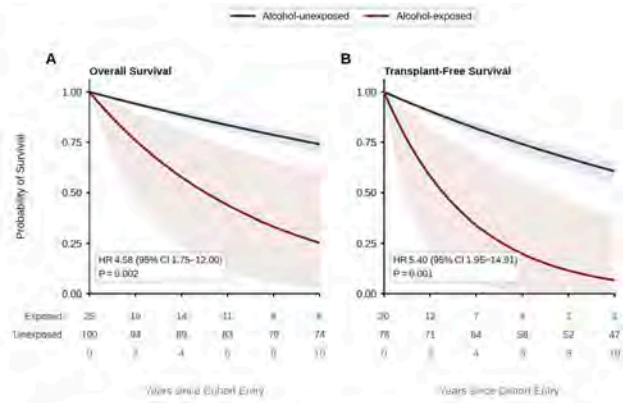


Figure 1. *Kaplan–Meier survival estimates by alcohol exposure status in propensity score–matched primary sclerosing cholangitis cohorts.*

Panel A, overall survival (OS; 25 alcohol-exposed vs. 100 unexposed); Panel B, transplant-free survival (TFS; 20 vs. 78). Cohorts matched 1:4 on age, sex, race, delayed-entry status, and baseline cirrhosis; all post-matching standardized mean differences <0.20. Hazard ratios from Cox models with time-updated 3-month interval data adjusted for time-varying diabetes, hypertension, hyperlipidemia, and IBD; robust standard errors clustered by patient. Shaded bands, 95% CI. Numbers below panels, patients at risk. CI denotes confidence interval; HR denotes hazard ratio; IBD denotes inflammatory bowel disease; OS denotes overall survival; PSC denotes primary sclerosing cholangitis; TFS denotes transplant-free survival.

Disclosures: Muyiwa Awoniyi: Nothing to Disclose, Jingyi Huang: Nothing to Disclose, Mariana Campuzano: Nothing to Disclose, Nicole Jordan: Nothing to Disclose, Li Tang: Nothing to Disclose, John McMichael: Nothing to Disclose.

★ 0248 | VITAMIN C REPROGRAMS THE HEPATIC IMMUNE LANDSCAPE TO ALLEVIATE CONA-INDUCED LIVER INJURY

Juan Lu[1], [1]The First Affiliated Hospital, Zhejiang University

Background: Autoimmune hepatitis (AIH) is a progressive liver disease with limited treatment options. Notably, vitamin C has been widely studied in metabolic liver diseases, but its role in immune-mediated liver injury remains largely unexplored. **Methods:** We first analyzed a human cohort of 48 proven AIH patients to find that serum L-ascorbic acid (vitamin C, Vit C) levels in patients with moderate-to-severe necroinflammation performance compared to healthy controls. Consistently, using an untargeted metabolomics approach in a concanavalin A (ConA)-induced mouse model of acute AIH, we identified marked depletion of Vit C, an essential micronutrient derived exclusively from dietary sources, in injured livers. To dissect the underlying mechanisms, CyTOF and scRNA-seq were employed to profile the hepatic immune microenvironment. **Results:** We found that serum L-ascorbic acid (vitamin C, Vit C) levels were significantly lower in patients with moderate-to-severe necroinflammation performance

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compared to healthy controls, and inversely correlated with serum ALT and AST levels. We identified exogenous Vit C supplementation dose-dependently alleviated ConA-induced liver injury, as evidenced by reduced serum aminotransferases and ameliorated histopathology. Vit C treatment profoundly reprogramed the hepatic immune landscape, reducing proinflammatory neutrophils while expanding regulatory B cells, cDCs, and CD4+ T cells. CellChat analysis revealed that Vit C suppressed pro-inflammatory signaling while inducing immunomodulatory pathways. High-resolution subset analysis demonstrated that Vit C reprogrammed neutrophils from a hyper-inflammatory S100a6+ Neu-dominant state toward a regulatory Ccl2 + Neu phenotype. Similarly, Vit C reshaped macrophage subsets, upregulating MHC II and costimulatory molecules while downregulating stress/repair genes, indicating a shift toward immune-activated status. **Conclusion:** These findings reveal that vitamin C acts as a key immune regulator that orchestrates immune cell subset remodeling and intercellular communication networks, providing a mechanistic basis for Vit C as a potential safe adjunct therapy for AIH, further supported by our human cohort observation that lower Vit C levels predict higher inflammatory activity.

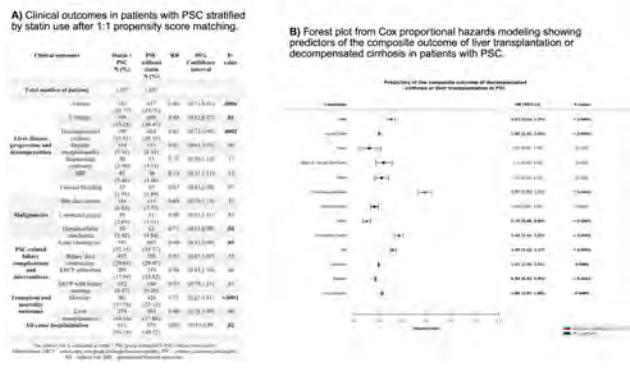
Disclosures: JUAN LU: Nothing to Disclose.

0249 | STATIN EXPOSURE IS ASSOCIATED WITH REDUCED HEPATIC DECOMPENSATION AND MORTALITY IN PRIMARY SCLEROSING CHOLANGITIS

Sameer Rao[1] Rohan Karkra[1] Kranthi Mandava[1] Ethan Shamsian[2] Raquel Olivo-Salcedo[3] Shivani Patel[1] Ahmed Al-Khazraji[1] Paul Gaglio[4] Nikki Duong[5], [1]Rutgers New Jersey Medical School, [2]Rutgerse New Jersey Medical School, [3]Rutgers University - New Jersey Medical School, [4]Rutgers NJ Medical School, [5]Stanford University

Background: Primary sclerosing cholangitis (PSC) is a progressive cholestatic liver disease without an established disease-modifying therapy. Statins have pleiotropic anti-inflammatory, antifibrotic, endothelial-modulating, and potential chemopreventive effects, but their association with clinical outcomes in PSC remains incompletely understood. **Methods:** We conducted a retrospective cohort study using the TriNetX United States Collaborative Network from 2015 to 2024. Adults with PSC were identified and stratified by statin exposure. Patients with prior liver transplantation, cholangiocarcinoma, hepatocellular carcinoma, or primary biliary cholangitis were excluded. Statin-treated and non-statin cohorts were matched 1: 1 using propensity scores based on demographics, comorbidities, medications, and liver disease–related laboratory parameters. Outcomes included liver disease progression, hepatic decompensation, hepatobiliary malignancies, biliary complications, liver transplantation, hospitalization, and all-cause mortality. A subgroup analysis was performed among patients with concomitant inflammatory bowel disease (IBD). Cox proportional hazards modeling was performed to evaluate predictors of the composite outcome of decompensated cirrhosis or liver transplantation. **Results:** After matching, 1,695 statin-treated patients with PSC were compared with 1,695 non-statin users. Statin use was associated with lower rates of ascites (20.77% vs 25.78%; P = .0006), cirrhosis (35.28% vs 39.47%; P = .01), decompensated cirrhosis (23.01% vs 28.55%; P = .0002), acute cholangitis (32.15% vs 35.57%; P = .03), hepatocellular carcinoma (HCC) (3.42% vs 4.84%; P = .04), all-cause hospitalization (36.54% vs 40.37%; P = .02), and all-cause mortality (17.76% vs 25.13%; P < .0001). Rates of liver transplantation were similar between groups. In patients with concomitant IBD, statin use was associated with lower rates of acute cholangitis and mortality, however, associations with cirrhosis, decompensated cirrhosis, and ascites were attenuated. In Cox proportional hazards analysis, statin use was independently associated with lower hazard of decompensated cirrhosis or liver transplantation (hazard ratio 0.76; 95% confidence interval 0.68–0.84). Immunosuppressant use, UDCA use, male sex, older age, higher INR, higher creatinine, and higher bilirubin were associated with increased hazard, while higher sodium levels were associated with lower hazard. **Conclusion:** Statin use was associated with improved liver-related and clinical outcomes in PSC, including lower risks of decompensation, acute cholangitis, HCC, hospitalization, and mortality. These associations were attenuated among patients with concomitant IBD. While causality cannot be inferred, these findings support prospective evaluation of statin exposure as a potential modifier of PSC outcomes.

Figure - Outcomes and predictors in primary sclerosing cholangitis (PSC) by statin use



Disclosures: Sameer Rao: Nothing to Disclose, Rohan Karkra: Nothing to Disclose, Kranthi Mandava: Nothing

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to Disclose, Ethan Shamsian: Nothing to Disclose, Raquel Olivo-Salcedo: Nothing to Disclose, Shivani Patel: Nothing to Disclose, Ahmed Al-Khazraji: Nothing to Disclose, Paul Gaglio: Nothing to Disclose, Nikki Duong: Nothing to Disclose.

0250 | VOLIXIBAT IMPROVES PRURITUS WITHOUT WORSENING IBD ACTIVITY IN PATIENTS WITH PSC: RESULTS FROM THE VISTAS STUDY IBD SUBGROUP

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Background: Primary sclerosing cholangitis (PSC) is a chronic cholangiopathy often causing severe cholestatic pruritus and associated with inflammatory bowel disease (IBD) in up to 80% of patients. Volixibat (VLX) is a minimally absorbed ileal bile acid transporter inhibitor (IBATi) that disrupts enterohepatic recirculation of bile acids and increases fecal bile acid excretion. In the Phase 2b VISTAS study, a 28-week multicenter, randomized, double blind (DB), placebo (PBO)-controlled study, VLX demonstrated statistically significant improvements in cholestatic pruritus with a safety profile consistent with IBAT inhibition. Here we report the efficacy and safety of VLX in the subgroup of patients with IBD. **Methods:** Details of the VISTAS trial design and primary endpoint have been previously reported. Descriptive subgroup analyses were

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conducted on patients with concomitant IBD. IBD activity was assessed using Partial Mayo Index Score (PMIS) sub-scores and Crohn's Disease Activity Index (CDAI); all patients were in remission or had mild IBD activity on stable therapy. **Results:** 74% (82/111) of the VISTAS primary cohort had concomitant IBD with 71% of these patients having ulcerative colitis (UC); rates of Crohn's disease (CD) and UC were balanced across treatment arms. In the primary cohort IBD subgroup (VLX: n = 40; PBO: n = 42), VLX treatment resulted in significant reductions in cholestatic pruritus compared with PBO (LS Mean CFB in Adult ItchRO: -2.88 vs -1.39; Δ-1.50, P = 0.0018). Baseline IBD activity scores by PMIS/CDAI were assessed in all participants (i.e., includes those with mild pruritus; VLX: n = 48; PBO: n = 54): VLX remission 85% (41), mild 13% (6) and moderate 2% (1); PBO remission 96% (52), mild 4% (2). Maximum postbaseline IBD activity scores by PMIS/CDAI were: VLX remission 60% (29), mild 40% (19); PBO remission 74% (40); mild 24% (13) and moderate or severe 2% (1). In patients with UC (VLX: n = 37; PBO: n = 41), change in PMIS was driven by increased stool frequency scores (SFS). Mild increase in stool frequency (SFS 1 or 1-2 more stools/day) was reported in 38% (14) of VLX patients and 24% (10) of PBO patients. Rates of SFS of 2 (3-4 more stools/day) and 3 (>5 more stools/day) were low and similar across treatment arms. No stool frequency change was reported in 41% (15) of VLX and 59% (24) of PBO patients. Most UC patients had a maximum rectal bleeding score of 0 (89% [33] VLX, 90% [37] PBO). **Conclusion:** In the VISTAS IBD subgroup, VLX demonstrated a significant and clinically meaningful reduction in cholestatic pruritus compared with PBO. Rates of IBD activity were low across both treatment arms. Although VLX-treated UC patients had higher rates of increased SFS, there was no increase in rectal bleeding, suggesting these changes reflect the mechanism of action of IBATi rather than worsening IBD activity. These findings support VLX as a well-tolerated and effective option for cholestatic pruritus in patients with PSC and concomitant IBD.

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0251 | PRIMARY SCLEROSING CHOLANGITIS IS ASSOCIATED TO THE HIGHEST RISK OF RECURRENCE-RELATED GRAFT FAILURE AFTER LIVER TRANSPLANTATION: A PROPENSITY-MATCHED UNOS ANALYSIS IN THE POST-DAA ERA

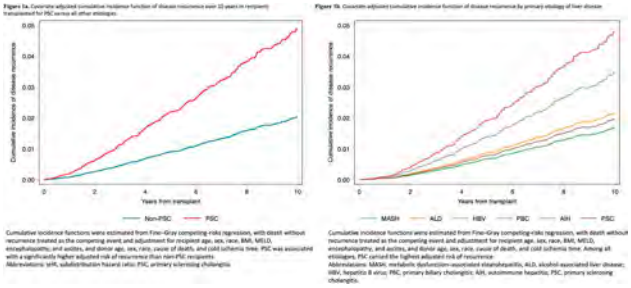
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Background: Recurrent liver disease is an increasingly recognized cause of late allograft loss after liver transplantation (LT), yet contemporary estimates of recurrence-related graft failure across LT era are lacking. PSC is clinically understood to recur and threaten the allograft, but the associated risk recurrence brings has not been evaluated in large scale populations. We aimed to quantify this risk in the national transplant registry. **Methods:** Using the UNOS/SRTR registry, we identified adults who underwent LT from 2014 to 2025. The outcome was graft failure attributed to recurrent disease, with death or graft failure from other causes treated as the competing events. PSC recipients were 1: 1 matched to non-PSC recipients by nearest-neighbor propensity matching on recipient age, sex, race, BMI, MELD, comorbidities, and key donor-related risk factors. Cumulative incidence was estimated by the Aalen–Johansen method; associations were modeled with Fine–Gray competing-risks regression and Cox regression at 1, 5, and 10 years. A secondary analysis compared PSC against each individual etiology using the same statistical approach. **Results:** Of 46,319 adult LT recipients, 1: 1 matching yielded 6,145 pairs (n = 12,290) with excellent balance (recipient age 47.0 vs 47.4 yr; MELD 22.7 vs 22.8; cold ischemia 7.2 vs 7.2 h; all $P > 0.7$). Despite matching, PSC recipients had a significantly shorter post-transplant length of stay (14.4 vs 18.2 days, $P < 0.001$). Over

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10 years, 302 recurrence-related graft failures occurred (218 in PSC vs 84 in non-PSC), at a median of 4.8 years (IQR 3.1–7.2) in PSC versus 2.9 years (IQR 1.4–5.3) in non-PSC recipients. The risk was strongly time-dependent: no difference between groups at 1 year (sHR 0.61, 95% CI 0.24–1.56), with a difference emerging by 5 years (sHR 1.69, 1.24–2.31; P = 0.001), and highest at 10 years (sHR 2.44, 1.88–3.17; P < 0.001) (**Figure 1a**); Cox estimates were concordant (10-yr HR 2.46, 1.91–3.17). The 10-year cumulative incidence of recurrence-related graft failure was approximately 4.8% in PSC vs 2.0% in non-PSC recipients. Among all transplant indications (**Figure 1b**), PSC carried the highest adjusted risk of recurrence related graft failure at 10 years (sHR 2.91, 95% CI 1.06–7.96; P = 0.038). **Conclusion:** PSC confers the highest risk of recurrence-related graft failure among LT indications, a risk that is negligible early but accumulates progressively, reaching a nearly three-fold increased risk in 10 years. These findings support intensified post-transplant surveillance in PSC recipients.



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0252 | DIAGNOSTIC LATENCY AND MAJOR ADVERSE HEPATIC EVENTS IN PRIMARY SCLEROSING CHOLANGITIS: A MULTICENTER REGISTRY ANALYSIS

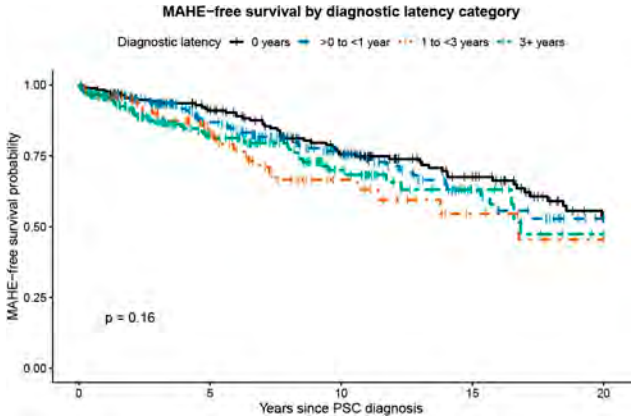
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Background: Primary sclerosing cholangitis (PSC) is a progressive fibroinflammatory cholangiopathy that confers substantial risk of hepatic decompensation, liver transplantation, and hepatobiliary malignancy. Early disease may be asymptomatic, and cholestatic abnormalities may be overlooked, delaying diagnosis. Whether diagnostic latency — the interval from earliest objective evidence to formal diagnosis — independently predicts adverse hepatic outcomes has not been rigorously evaluated in a date-validated multicenter cohort. **Methods:** We analyzed patients with PSC from the North American Consortium for Autoimmune Liver Diseases (CALiD). Earliest objective evidence was defined as the first date of abnormal cholestatic biochemistry, PSC-compatible imaging, or PSC-consistent histology. Patients with unverifiable diagnosis dates or insufficient follow-up were excluded. The primary outcome was time to first major adverse hepatic event (MAHE), defined as hepatic decompensation, liver transplantation, hepatobiliary malignancy, or death. Diagnosis-anchored cox models evaluated latency continuously, per 5 years, log-transformed, and categorically, adjusting for age, sex, IBD, cirrhosis, and large-duct PSC (LD-PSC) classification. **Results:** Of 1,101 patients with PSC, 690 met inclusion criteria. Median age at diagnosis was 46 years (IQR, 34-60), 435 (63.0%) were male, 669 (97.0%) had concomitant IBD, and 558 (80.9%) had LD-PSC. Median post-diagnosis follow-up was 6.6 years and median diagnostic latency was 0.53 years (range, 0-31.0). Earliest objective evidence was abnormal cholestatic biochemistry in 562 patients (81.4%), PSC-compatible imaging in 79 (11.4%), and PSC histology in 49 (7.1%). MAHE occurred in 187 patients (27.1%); time-to-event analyses counted only the first MAHE per patient. MAHE components included liver transplantation in 104 patients (15.1%), hepatic decompensation in 95 (13.8%), hepatobiliary malignancy in 44 (6.4%), and death in 5 (0.7%). Latency was not associated with MAHE per 1-year increment (HR, 1.01; 95% CI, 0.97-1.04; P = 0.75), per 5-year increment (HR, 1.03; 95% CI, 0.87-1.22; P = 0.75), or log-transformed (HR, 1.08; 95% CI, 0.92-1.27; P = 0.34). No diagnostic latency stratum reached statistical significance after adjustment for age, sex, IBD, known cirrhosis at baseline, and LD-PSC. **Conclusion:** In this cohort, these findings suggest that the interval from earliest objective evidence to formal diagnosis does not, by itself, stratify risk of adverse hepatic outcomes. Rather, baseline disease phenotype and fibrosis burden may be more prognostically important than

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elapsed time to formal diagnosis, supporting future analyses incorporating disease-stage biomarkers and evidence-source phenotype.



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0253 | ANTICIPATE-NASH RISK STRATIFICATION PREDICTS VARICEAL DEVELOPMENT IN COMPENSATED MASH CIRRHOSIS: RESULTS FROM THE NAVIGATE TRIAL

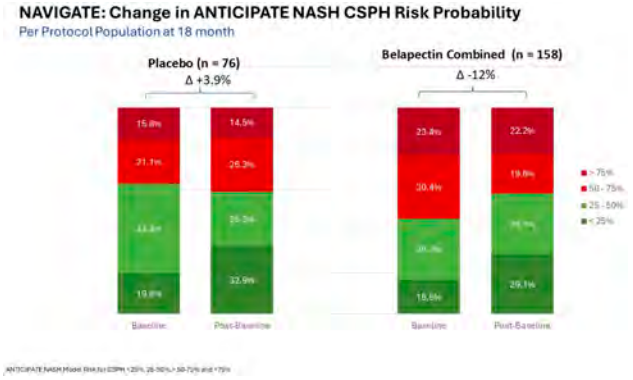
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Background: The ANTICIPATE-NASH model is a validated noninvasive tool to predict clinically significant portal hypertension (CSPH; hepatic venous pressure gradient $\geq$10 mmHg) and stratify risk of liver-related events in MASH cirrhosis. NAVIGATE is a global, randomized, placebo-controlled trial evaluating belapectin, a galectin-3 inhibitor, in patients with compensated MASH cirrhosis and portal hypertension without baseline varices. Belapectin at 2 and 4 mg/kg previously demonstrated a reduction in incident varices versus placebo in the per-protocol population. Here, we evaluated the utility of ANTICIPATE-NASH risk stratification to predict variceal development and assess treatment effects **Methods:** The ANTICIPATE-NASH model incorporates liver stiffness, platelet count, and body mass index to estimate CSPH probability. Predefined thresholds of $\geq$75% probability were used to rule-in CSPH, while $\geq$50% probability identified an enrichment population for clinical trials. Subjects were categorized at baseline into probability groups (<25%, 25–50%, 50–75%, $\geq$75%) and reassessed at 18 months. Incidence of new varices was evaluated via blinded central review of endoscopy videos according to baseline risk category and changes in risk category over time in subjects receiving pooled belapectin (2 and 4 mg/kg) or placebo. **Results:** At baseline, distribution across ANTICIPATE-NASH probability categories (<25%, 25–50%, 50–75%, $\geq$75%) was 19.7%, 43.4%, 21.1%, and 15.8% in the placebo group, and 16.5%, 29.7%, 30.4%, and 23.4% in the belapectin group. A higher proportion of subjects in the belapectin arm had $\geq$50% CSPH probability at

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baseline; however, this difference was not statistically significant.At 18 months a net category shift favored belapectin, as placebo subjects had a 3.9% net worsening to >50% CSPH probability, whereas belapectin subjects had a 12% net improvement to <50%, yielding a placebo-adjusted difference of 15.9% (p = 0.04).Incidence of varices increased across higher CSPH probability categories, with the highest rates observed in subjects with ≥75% probability. Overall incidence across categories (<25%, 25–50%, 50–75%, ≥75%) was 2.4%, 17.5%, 15.6%, and 18.4%, respectively. Across all baseline risk strata, belapectin-treated subjects demonstrated lower incidence of varices compared with placebo (0% vs 6.7%, 14.9%vs 21.2%, 12.5% vs 25%, and 16.2% vs 25%, respectively). **Conclusion:** Belapectin treatment was associated with a reduction in CSPH risk, as reflected by shifts to lower ANTICIPATE-NASH probability categories. Lower variceal incidence was observed with belapectin across all ANTICIPATE-NASH risk strata. These findings suggest that belapectin treatment is associated with favorable changes in noninvasively predicted CSPH risk, which may translate into a reduced risk of hepatic decompensation in future studies.



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★ 0254 | A MULTICENTER, RANDOMIZED CONTROLLED TRIAL COMPARING ENDOSCOPIC ULTRASOUND-GUIDED COIL AND GLUE EMBOLIZATION WITH BALLOON-OCCLUDED RETROGRADE TRANSVENOUS OBLITERATION FOR PREVENTION OF REBLEEDING FROM GASTRIC VARICES

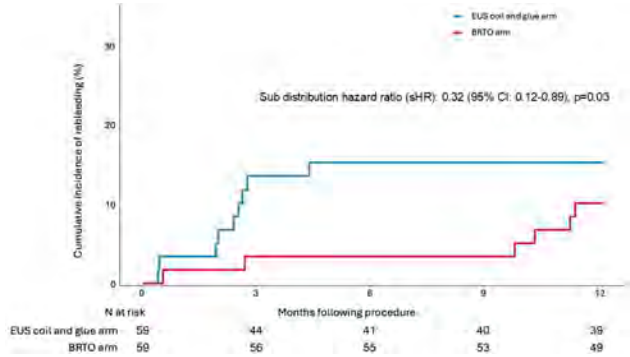
Sagnik Biswas[1] Santhosh Kumar[2] Sanchita Gupta[3] Asisha Janeela[2] Arun Valsan[4] Shubham Mehta[5] Shekhar Swaroop[3] Arnav Aggarwal[3] Ayush Agarwal[3] Manish Saini[3] Vignesh Dwarakanathan[3] Samagra

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Agarwal[3] Ajay Kumar[6] Siddharth Srivastava[6] Rajesh Puri[5] Srikant Moorthy[4] Ravi Chaudhary[5] Sanjay Baijal[5] Shyamkumar Keshava[2] Raju Sharma[3] Ashish Goel[2] Deepak Gunjan[3] Soumya Jagannath[3] Pramod Garg[3] Shivanand Gamanagatti[3]. Shalimar[3], [1]All India Institute of Medical Sciences New Delhi, [2]Christian Medical College, Vellore, [3]All India Institute of Medical Sciences, New Delhi, [4]Amrita Institute of Medical Sciences, Kochi, [5]Medanta-The Medicity, [6]Govind Ballabh Pant Institute of Post Graduate Medical Education and Research

Background: There is no consensus on the optimal modality for secondary prophylaxis of gastric varices (GV) in patients with cirrhosis. We compared the efficacy and safety of endoscopic ultrasound-guided coil and glue embolization (EUS-CG) with balloon-occluded retrograde transvenous obliteration (BRTO) for prevention of rebleeding in patients with cirrhosis and GV hemorrhage. **Methods:** In this randomized controlled trial conducted at five tertiary care centres in India (November 2022 - May 2025), 118 patients with cirrhosis and bleeding from GV (GOV-2 and IGV-1) were randomly assigned (1: 1) to BRTO or EUS-CG for secondary prophylaxis. The primary outcome was GV-related rebleeding at 1-year. Secondary outcomes included all-cause mortality, further decompensation, change in liver function and worsening of esophageal varices at 1-year. Competing risk analysis was performed for rebleeding and further decompensation, with death as the competing event. **Results:** Baseline characteristics were similar between groups. Alcohol was the most common etiology of cirrhosis (47/118, 39.8%). The median Child-Pugh and MELD score of the cohort was 7 (6-8) and 14 (11-17) respectively, with a male predominance (90/118, 76.3%). Technical success was 100% in both groups. Complete GV obliteration rates at 4-weeks were higher with BRTO (55/57, 96.5%) than EUS-CG (47/55, 85.5%, p = 0.04). At 1-year, BRTO was associated with significantly lower rates of GV-related rebleeding (1/59, 1.7% vs 8/59, 13.6%; p = 0.03) and all-cause rebleeding (4/59, 6.8% vs 12/59, 20.3%) compared with EUS-CG; sHR for rebleeding: 0.32 (95% CI: 0.12-0.89); p = 0.03. Most GV rebleeding events after EUS-CG were related to coil extrusion ulcers. Further decompensation was comparable between groups (EUS-CG: 27/59, 45.8% vs BRTO: 20/59, 33.9%; p = 0.19) with new-onset/worsening of ascites being the most common decompensating event (EUS-CG: 27.1% vs BRTO: 28.8%; p = 0.84). Aggravation of esophageal varices occurred more frequently after BRTO than after EUS-CG (15/59, 25.4% vs 7/59, 11.9%, p = 0.05). The median change in Child-Pugh and MELD scores between both groups were similar. The 6-week mortality (EUS-CG: 4/59, 6.8% vs BRTO: 2/59, 3.4%; p = 1.0) and 1-year mortality (EUS-CG: 13/59, 22.0% versus BRTO: 8/59, 13.6%; p = 0.33) were comparable between groups. **Conclusion:** BRTO was associated with significantly lower 1-year GV-related rebleeding rates compared with EUS-CG in patients with cirrhosis and GV hemorrhage, although all-cause mortality and further decompensation at 1-year were similar between groups. [CTRI/2022/10/046363]



Disclosures: Sagnik Biswas: Nothing to Disclose, Santhosh Kumar: Nothing to Disclose, Sanchita Gupta: Nothing to Disclose, Asisha Janeela: Nothing to Disclose, Arun Valsan: Nothing to Disclose, Shubham Mehta: Nothing to Disclose, Shekhar Swaroop: Nothing to Disclose, Arnav Aggarwal: Nothing to Disclose, Ayush Agarwal: Nothing to Disclose, Manish Saini: Nothing to Disclose, Vignesh Dwarakanathan: Nothing to Disclose, Samagra Agarwal: Nothing to Disclose, Ajay Kumar: Nothing to Disclose, Siddharth Srivastava: Nothing to Disclose, Rajesh Puri: Nothing to Disclose, Srikant Moorthy: Nothing to Disclose, Ravi Chaudhary: Nothing to Disclose, Sanjay Baijal: Nothing to Disclose, Shyamkumar Keshava: Nothing to Disclose, Raju Sharma: Nothing to Disclose, Ashish Goel: Nothing to Disclose, Deepak Gunjan: Nothing to Disclose, Soumya Jagannath: Nothing to Disclose, Pramod Garg: Nothing to Disclose, Shivanand Gamanagatti: Nothing to Disclose, Shalimar: Nothing to Disclose.

0255 | SAFETY AND EFFICACY OF SGLT-2 INHIBITORS IN LIVER CIRRHOSIS PATIENTS WITH REFRACTORY ASCITES: A RANDOMISED CLINICAL CONTROL TRIAL

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Background: Refractory ascites in cirrhosis is associated with poor quality of life, frequent hospitalizations, repeated large-volume paracentesis (LVP), and high mortality. Sodium-glucose cotransporter-2 (SGLT2) inhibitors have natriuretic and diuretic properties that may provide therapeutic benefit in refractory ascites; however, data regarding their efficacy and safety in cirrhosis remain limited. This study evaluated the efficacy and safety of dapagliflozin in cirrhosis patients

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with refractory ascites. **Methods:** In this prospective randomized controlled trial (CTRI/2025/12/098898), 73 patients with liver cirrhosis and refractory ascites were enrolled. 37 patients received dapagliflozin plus standard medical therapy, while 36 received standard medical therapy alone. The primary outcome was ascites control at 6 months, categorized as complete response, partial response, or non-response. Secondary outcomes included changes in urine sodium, urine output, body weight, abdominal girth, renal function, CTP and MELD-Na scores, LVP requirement, adverse events, and survival. Survival analysis was performed using Kaplan-Meier curves and log-rank testing. **Results:** Baseline demographic, clinical, and laboratory characteristics were comparable between groups. At 6 months, ascites control was significantly better in the dapagliflozin group compared with controls ($p = 0.036$). Complete response occurred in 8.1% (3/37) versus 0% (0/36), while partial response occurred in 27.0% (10/37) versus 13.9% (5/36) in the dapagliflozin and control groups, respectively. Dapagliflozin therapy was associated with greater improvement in urine sodium (+32.84 vs +11.28 mEq/day; $p = 0.001$), urine output (+648.65 vs +271.11 mL/day; $p = 0.002$), body weight (−5.41 vs −2.08 kg; $p = 0.028$), abdominal girth (−1.92 vs +1.27 cm; $p = 0.034$), CTP score (−1.14 vs −0.39; $p = 0.021$), and MELD-Na score (−2.35 vs −0.83; $p = 0.048$). Patients receiving dapagliflozin had lower need for paracentesis (64.9% vs 86.1%; $p = 0.036$), fewer LVP sessions (1.84 vs 3.11; $p = 0.002$), and lower cumulative albumin requirement (128.65 vs 214.72 g; $p = 0.001$). Rates of AKI, infections, hepatic encephalopathy, electrolyte disturbances, and mortality were comparable between groups. Kaplan–Meier analysis showed no significant difference in survival (log-rank $p = 0.679$). **Conclusion:** Dapagliflozin therapy in cirrhosis patients with refractory ascites was associated with improved ascites control, enhanced natriuresis and diuresis, reduced paracentesis requirement, and improvement in liver disease severity scores without significant increase in adverse events. SGLT2 inhibitors may represent a promising adjunctive therapy for refractory ascites in cirrhosis.

Response category	Dapagliflozin Group (n=37)	Control Group (n=36)	p value
Complete response	3 (8.1%)	0 (0.0%)	
Partial response	10 (27.0%)	5 (13.9%)	
No response*	24 (64.9%)	31 (86.1%)	
Overall p value			**0.036**
Variable (Δ = 6 month − baseline)	**Dapagliflozin Group (n=37)**	**Control Group (n=36)**	**p value**
Δ Urine sodium (mEq/day)	+32.84 ± 24.16	+11.28 ± 19.47	**0.001**
Δ Urine output (mL/day)	+648.65 ± 522.41	+271.11 ± 438.26	**0.002**
Δ CTP score	−1.14 ± 1.38	−0.39 ± 1.21	**0.021**
Δ MELD-Na score	−2.35 ± 3.84	−0.83 ± 3.27	**0.048**
Δ Mean arterial pressure (mmHg)	+3.19 ± 7.12	+1.06 ± 6.84	0.214
Δ Serum creatinine (mg/dL)	+0.08 ± 0.31	+0.03 ± 0.28	0.487
Δ Serum sodium (mEq/L)	+2.14 ± 4.88	+0.72 ± 4.27	0.191
Δ Weight (kg)	−5.41 ± 6.72	−2.08 ± 5.84	**0.028**
Δ Abdominal girth (cm)	−1.92 ± 6.66	+1.27 ± 5.15	**0.034**

Table showing comparison of ascites control and change in clinical and laboratory parameters at 6 months between study groups

*No response included persistent/recurrent refractory ascites requiring paracentesis and death before 6 months.
Values are expressed as n (%), mean ± standard deviation

Disclosures: Sunil Dadhich: Nothing to Disclose, Arihant Seth: Nothing to Disclose, Surender Kumar: Nothing to Disclose.

0256 | EARLY RESULTS OF A PROSPECTIVE MULTICENTER TRIAL OF THE LIVERTY™ TIPS STENT GRAFT WITH TAILORED EXPANSION FOR PORTAL HYPERTENSION COMPLICATIONS

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Background: Transjugular intrahepatic portosystemic shunt (TIPS) is an established treatment for complications of portal hypertension; however, hepatic encephalopathy (HE) remains a major limitation, particularly with larger diameter shunts. This study evaluated the safety and effectiveness of the Liverty™ TIPS Stent Graft and assessed a tailored expansion procedure (TEP) enabling stepwise diameter optimization (6–10 mm) to reduce HE while maintaining clinical efficacy. **Methods:** In this prospective, multicenter study, 177 patients (mean age 58.5 years; 59.3% male) underwent successful TIPS creation across 26 centers in the United States, France, and Germany. Indications included refractory ascites (68.4%), esophageal (24.3%) or gastric (2.8%) variceal bleeding, and hepatic hydrothorax (4.5%). Final shunt diameters were ≤ 7 mm in 40.7% of patients (if TEP performed). Final shunt diameters ≤ 8 mm in the overall cohort was 83.1%, reflecting usage of a small-caliber strategy in this study. **Results:** Technical success was 100%. Mean portosystemic gradient decreased from 17.8 mmHg to 7.8 mmHg. At 6 months, 90.4% of TIPS remained patent and free of dysfunction (primary endpoint; $p = 0.0002$). No device-related major complications were observed through 30 days. Freedom from major complications through 30 days was 85.8% ($p = 0.4341$) (primary endpoint). West Haven Grade 1 and 2 HE events resolved with medical therapy and proportion of patients free from major complications was 94.3% ($p < 0.0001$), and probability of freedom from $\geq$ grade 3 HE was 95%, with no high-grade HE observed in 6–7 mm shunts.Clinical success rates (defined as freedom from occurrence of) were 78.8% for ascites, 96.7% for variceal bleeding, and 71.4% for hydrothorax. Among patients with 6–7 mm shunts, clinical success outcomes (as defined above) remained favorable (ascites 84.8%; variceal bleeding 91.7%), with 80% free from HE-related impairment at 6 months compared with 69.2% in larger (8–10 mm) shunts. Transplant-free survival at 6 months was 81.4%. Health-related quality of life remained stable with modest improvements in selected domains. **Conclusion:** The Liverty™ TIPS Stent Graft demonstrated favorable safety and efficacy

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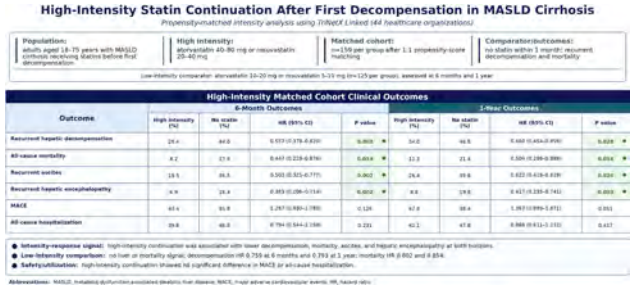
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for treatment of portal hypertension complications. Use of smaller initial shunt diameters (6–7 mm) with a tailored expansion approach was associated with reduced incidence and severity of HE while preserving clinical effectiveness. These findings support a step-up strategy as a potential new standard for TIPS creation. **Disclosures:** K. Rajender Reddy: BD (Becton, Dickinson and Company): Consultant.

0257 | HIGH-INTENSITY STATIN CONTINUATION AFTER FIRST HEPATIC DECOMPENSATION IN MASLD CIRRHOSIS: A PROPENSITY-MATCHED SIGNAL CHALLENGING LOW-DOSE PARADIGMS

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Background: Low-dose statins are commonly favored in cirrhosis because of safety concerns, yet whether statin intensity modifies post-decompensation outcomes is unknown. We evaluated low- and high-intensity statin continuation after first hepatic decompensation in MASLD cirrhosis. **Methods:** Using TriNetX Linked (44 healthcare organizations), we identified adults aged 18–75 years with MASLD cirrhosis receiving statins before first hepatic decompensation hospitalization. Patients with competing liver diseases, ESRD/dialysis, end-stage heart failure, pregnancy, transplant, HCC, rhabdomyolysis, INR $\geq$2.50, or bilirubin $\geq$5.10 mg/dL were excluded. Continuation was any statin prescription within 1 month after decompensation. Low-intensity continuation was atorvastatin 10–20 mg or rosuvastatin 5–10 mg; high-intensity continuation was atorvastatin 40–80 mg or rosuvastatin 20–40 mg. Each intensity group was 1: 1 propensity-score matched to no statin. Co-primary outcomes were recurrent hepatic decompensation and all-cause mortality at 6 months and 1 year; secondary outcomes included recurrent ascites, recurrent hepatic encephalopathy, MACE, and hospitalization. **Results:** Low-intensity continuation included 125 matched pairs and did not reduce liver outcomes at 6 months or 1 year: recurrent decompensation was 36.8% vs 43.2% (HR 0.76; p = 0.182) at 6 months and 43.2% vs 47.2% (HR 0.79; p = 0.252) at 1 year; mortality was 12.0% vs 14.4% (HR 0.80; p = 0.546) and 16.8% vs 18.4% (HR 0.85; p = 0.641), respectively. MACE was lower with low-intensity therapy at 6 months (24.8% vs 37.6%; HR 0.56; p = 0.007) and 1 year (27.2% vs 40.8%; HR 0.60; p = 0.011). High-intensity continuation included 159 matched pairs and showed lower 6-month recurrent decompensation (26.4% vs 44.0%; HR 0.56, 95% CI 0.38–0.82; p = 0.003), mortality (8.2% vs 17.6%; HR 0.45, 95% CI 0.23–0.88; p = 0.019), recurrent ascites (19.5% vs 36.5%; HR 0.50; p = 0.002), and recurrent encephalopathy (6.9% vs 16.4%; HR 0.38; p = 0.002). At 1 year, high-intensity continuation remained associated with lower decompensation (34.0% vs 46.5%; HR 0.66; p = 0.028), mortality (11.3% vs 21.4%; HR 0.50; p = 0.018), ascites (26.4% vs 39.6%; HR 0.62; p = 0.020), and encephalopathy (8.8% vs 19.5%; HR 0.42; p = 0.003). Hospitalization did not differ. **Conclusion:** In selected MASLD cirrhosis patients already receiving statins before first decompensation, high-intensity continuation—not low-intensity continuation—was associated with lower recurrent decompensation, mortality, ascites, and encephalopathy. This intensity-response signal is hypothesis-generating but clinically provocative and warrants prospective evaluation.



Disclosures: Mohammad Alabbas: Nothing to Disclose, Akram Alnounou: Nothing to Disclose, Riddhi Machchhar: Nothing to Disclose, Omar Sims: Nothing to Disclose, William Carey: Nothing to Disclose.

0258 | ASSOCIATION BETWEEN DIRECT ORAL ANTICOAGULANT INITIATION AND HEPATIC DECOMPENSATION IN COMPENSATED CIRRHOSIS AND ATRIAL FIBRILLATION: A PROPENSITY SCORE-MATCHED LANDMARK COHORT STUDY

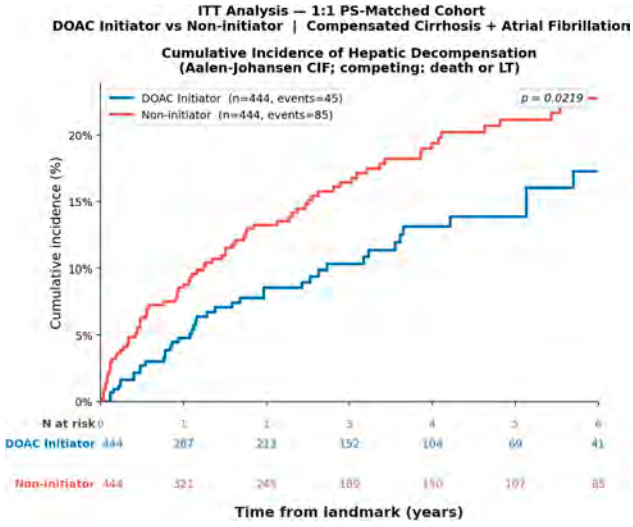
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Background: Patients with compensated liver cirrhosis and atrial fibrillation (AF) face both thromboembolic risk and cirrhosis progression. Whether direct oral anticoagulant (DOAC) initiation influences hepatic decompensation risk remains unclear. We evaluated the association between DOAC initiation and hepatic decompensation in patients with compensated cirrhosis and AF. **Methods:** We conducted a landmark cohort study using the Mass General Brigham Research Patient Data Registry. Patients with compensated cirrhosis and AF aged ≥18 years were identified using ICD-9/10 codes with radiologic confirmation. The index date was the first AF diagnosis. Patients with prior hepatic decompensation, hepatocellular carcinoma, liver transplantation, low CHA_2DS_2-VASc score, valvular heart disease, valve surgery, early decompensation within 90 days, recent warfarin exposure, warfarin-to-DOAC switching, or concurrent warfarin/DOAC use were excluded. Under an intent-to-treat framework, patients were classified as DOAC initiators or non-initiators based on new DOAC prescription within 90 days of the index date. A 90-day landmark was applied to reduce immortal time bias. The primary outcome was confirmed hepatic decompensation verified by chart review. The secondary outcome was confirmed non-portal hypertensive major bleeding. Death and liver transplantation were treated as competing events. Primary analysis used 1: 1 propensity score matching (PSM), with inverse probability of treatment weighting (IPTW) as sensitivity analysis. Cumulative incidence was estimated using the Aalen-Johansen method and compared using Gray's test. **Results:** Among 5,112 patients with compensated cirrhosis and AF, 1,986 met eligibility criteria (DOAC initiators n = 521; non-initiators n = 1,465). After landmark restriction, 1: 1 PSM yielded 444 matched pairs with balanced baseline characteristics. DOAC initiators had significantly lower 5-year cumulative incidence of hepatic decompensation compared with non-initiators (14.1% vs 21.8%; Gray's test p = 0.022). Absolute risk reduction at 5 years was 7.7%. In IPTW analysis (n = 1,676), weighted hazard ratio was 0.75 (95% CI 0.53–1.08), with 5-year cumulative incidence of 14.6% versus 20.0% (Gray's test p = 0.074), showing consistent directionality. There was no significant difference in confirmed non-portal hypertensive major bleeding between groups in the PS-matched cohort (5-year cumulative incidence 25.2% vs 20.7%; Gray's test p = 0.484). **Conclusion:** DOAC initiation in patients with compensated cirrhosis and AF was associated with lower risk of hepatic decompensation without increased non-portal hypertensive major bleeding. These findings suggest a potential hepatoprotective role of DOACs and warrant external validation in larger cohort



Disclosures: Jonggi Choi: Nothing to Disclose, Nothing to Disclose, Erik Almazan: Nothing to Disclose, Megan Michta: Nothing to Disclose, Raymond Chung: GSK: Grant/Research Support, Salix: Grant/Research Support, GSK: Consultant, Precision Biosciences: Consultant, Boehringer: Grant/Research Support, BMS: Grant/Research Support, Aligos: Grant/Research Support, Curve: Grant/Research Support.

0259 | SINGLE-CELL TRANSCRIPTIONAL LANDSCAPE OF HBV IN CHRONIC HEPATITIS B INFECTION UNCOVERS LOWER CCCDNA TRANSCRIPTION DURING TREATMENT AND IN HBEAG-NEGATIVE INFECTION

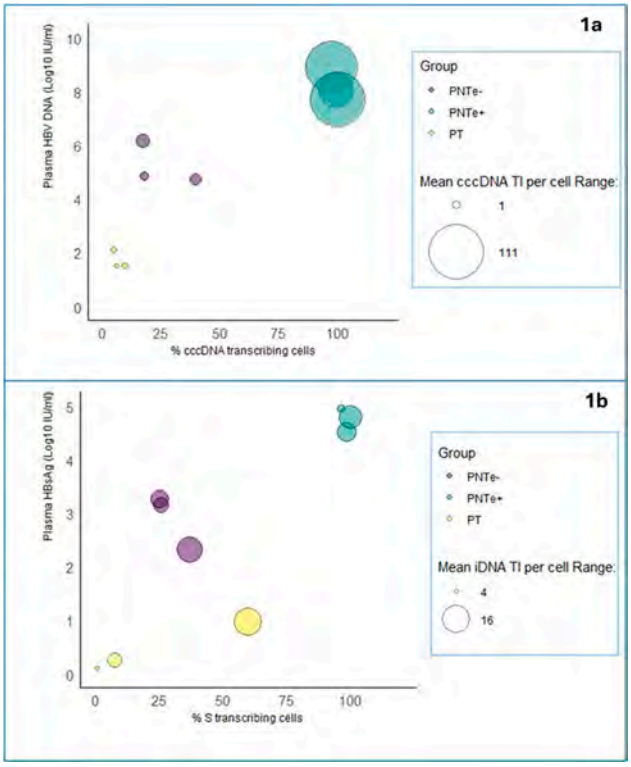
Prakriti Sinha[1] Paola Sorto Quijano[1] Naomi Esrig[1] Jasneet Aneja[2] Georg Lauer[2] Scott Fung[3] Chloe Thio[1] Ashwin Balagopal[1], [1]Johns Hopkins University, [2]Massachusetts General Hospital, [3]University Health Network

Background: In chronic hepatitis B (CHB), HBV RNAs are transcribed from covalently closed circular DNA (cccDNA) and HBV DNA integrated into host genome (iDNA). Both produce hepatitis B surface antigen (HBsAg). To understand HBV transcription in people with CHB with various degrees of HBV replication and nucleos(t)ide analogue (NUC) treatment, we performed single-cell studies of liver tissue. **Methods:** We dissected 150-300 single-cell equivalents (SCE) from liver tissues of nine people with CHB: 3 people on treatment (PT), and 6 people not on treatment of which 3 were HBeAg-ve (PNTe-) and 3 were HBeAg+ve (PNTe+). From each SCE, total HBV DNA, cccDNA, and RNA transcripts at the 5'-, mid-, and 3'-HBV positions were quantified using digital PCR platforms.

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Cells were considered infected with cccDNA if they were positive for any target except for mid-HBV, which can derive from cccDNA or iDNA. An iDNA transcriptional index (iDNA TI; mid-HBV: 3'-HBV ratio) was used to distinguish cells with S transcripts that encode HBsAg that derive from cccDNA vs iDNA. **Results:** Plasma HBV DNA was $\leq$2 log10IU/ml in PT, 4 to 6 log10IU/ml in PNTe-, and 7 to 9 log10IU/ml in PNTe+. The proportion of infected cells ranged from 14-28% in PT, 37-60% in PNTe-, and 97-100% in PNTe+ and correlated with plasma HBV DNA (r = 0.915, P = 0.0005). Plasma HBV DNA also correlated with the proportion of cells transcribing from cccDNA (r = 0.884; P = 0.001) as well as with the mean cccDNA transcriptional index (cccDNA TI; 5'-HBV RNA: cccDNA per cell) (r = 0.772; P = 0.01) (Fig. 1a). Per cell, the copies of HBV DNA and RNA transcripts and cccDNA TI were significantly higher in PNTe+ than in PT and PNTe- (P = 0.0001); while there were some cells with higher copies of these targets in PNTe-, these were not significantly different from PT. Lastly, while the proportion of S-transcribing cells correlated with the plasma HBsAg levels (r = 0.824; p = 0.01), mean iDNA TI per cell did not (Fig. 1b). **Conclusion:** We applied single-cell approaches to liver tissues from people with CHB and found that HBV control as observed in plasma DNA levels are reflected in the proportion of infected cells and in the cccDNA transcription per cell. In contrast, plasma HBsAg levels appear to reflect the proportion of cells that transcribe S specifically, irrespective of their DNA source.



Disclosures: Prakriti Sinha: Nothing to Disclose, Paola Sorto Quijano: Nothing to Disclose, Naomi Esrig: Nothing to Disclose, Jasneet Aneja: Nothing to Disclose, Georg Lauer: GSK: Grant/Research Support, GSK: Consultant, Scott Fung: Gilead Sciences: Advisor, Gilead Sciences: Speaking and Teaching, Abbvie: Speaking and Teaching, Abbvie: Advisor, Novo Nordisk: Speaking and Teaching, Novo Nordisk: Advisor, Novo Nordisk: Grant/Research Support, GSK: Advisor, GSK: Speaking and Teaching, Lupin: Speaking and Teaching, AstraZeneca: Speaking and Teaching, AstraZeneca: Advisor, Chloe Thio: Nothing to Disclose, Ashwin Balagopal: Nothing to Disclose.

0260 | BEPIROVIRSEN B-WELL PHASE 3 TRIALS: PREDICTING FUNCTIONAL CURE RATES BASED UPON HEPATITIS B SURFACE ANTIGEN AT WEEK 12

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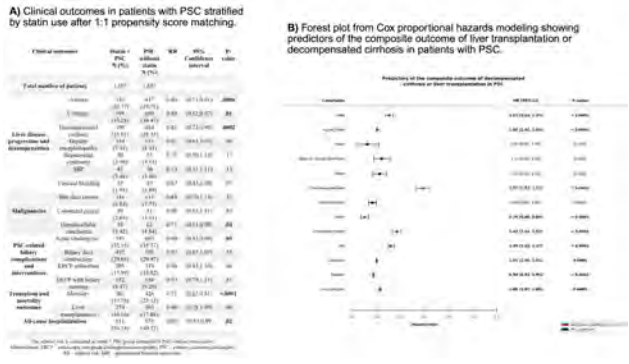
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Background: In the B-Well Phase 3 trials, a 24-week (wk) course of bepirovirsen (BPV), an antisense oligonucleotide, resulted in 19% functional cure (FC) rate in participants (pts) with chronic hepatitis B virus (HBV) infection and baseline hepatitis B surface antigen (HBsAg) level $\leq$3000 IU/mL. Higher FC rates (26%) were observed among those with HBsAg levels $\leq$1000 IU/mL. Here, we evaluated the relationship between on-treatment HBsAg levels and the likelihood of FC response to support informed early treatment-stopping discussions. **Methods:** The B-Well 1 and 2 global double-blind trials enrolled adults receiving nucleos(t)ide analog therapy for chronic HBV infection (HBV DNA $<$90 IU/mL) who had HBsAg concentrations ranging from $>$100 to $\leq$3000 IU/mL. A pre-specified net benefit (NB) analysis was conducted using combined trial data to assess HBsAg as an on-treatment predictor of FC response. Response criteria based on absolute HBsAg values or log changes from baseline at Wks 8 to 14 were evaluated across the entire cohort, as well as stratified by baseline HBsAg levels. The NB analysis facilitated comparison between response criteria to optimize early identification of individuals unlikely to achieve FC with continued treatment, while minimizing the incorrect predictions for those who ultimately attained FC. **Results:** Based on NB findings for pts with baseline HBsAg $>$1000 and $\leq$3000 IU/mL, an HBsAg value of $<$0.05 IU/mL at Wk 12 was deemed the optimal on-treatment predictor of FC response. Among those failing to meet this Wk 12 HBsAg criterion (i.e. $\geq$0.05 IU/mL), only 4/287 (1.4%; 95% confidence interval [CI]: 0.3%, 3.1%) achieved FC, whereas 22/106 (20.8%; 95% CI: 13.3%, 28.9%) who met the criteria (i.e. $<$0.05 IU/mL) achieved FC. For pts with baseline HBsAg $\leq$1000 IU/mL, an HBsAg value $<$1 IU/mL at Wk 12 was identified as the optimal on-treatment predictor of FC response. Among those failing to meet this criterion (i.e. $\geq$1 IU/mL), only 7/280 (2.5%; 95% CI: 0.8%, 4.6%) achieved FC, whereas 179/426 (42.0%; 95% CI: 37.2%, 47.0%) who met the criteria (i.e. $<$1 IU/mL) achieved FC (**Table**). **Conclusion:** A HBsAg level at Wk 12 of $\geq$0.05 IU/mL for pts with baseline HBsAg $>$1000 and $\leq$3000 IU/mL, and $\geq$1 IU/mL for those with baseline HBsAg $\leq$1000 IU/mL, predicts a low probability of achieving FC (1.4–2.5%). In contrast, a higher probability of achieving FC was predicted for those that meet the HBsAg criteria at Wk 12 and complete the treatment regimen (20.8–42%). These findings can facilitate discussions concerning the anticipated outcome of continued BPV therapy. **Funding:** GSK (202009/NCT05630807; 219288/NCT05630820).[for the B-Well Study Group]

Figure - Outcomes and predictors in primary sclerosing cholangitis (PSC) by statin use



Disclosures: Pietro Lampertico: Roche Pharma/Diagnostics: Consultant, Roche Pharma/Diagnostics: Speaking and Teaching, Gilead Sciences: Consultant, Gilead Sciences: Speaking and Teaching, GSK: Consultant, GSK: Speaking and Teaching, Abbvie: Consultant, Abbvie: Speaking and Teaching, Janssen: Consultant, Janssen: Speaking and Teaching, MYR: Consultant, MYR: Speaking and Teaching, Eiger: Consultant, Eiger: Speaking and Teaching, Antios: Consultant, Antios: Speaking and Teaching, Aligos: Consultant, Aligos: Speaking and Teaching, Vir: Consultant, Vir: Speaking and Teaching, Grifols: Consultant, Grifols: Speaking and Teaching, Altona: Consultant, Altona: Speaking and Teaching, Roboscreen: Consultant, Roboscreen: Speaking and Teaching, Bluejay: Consultant, Bluejay: Speaking and Teaching, Jinlin Hou: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose,

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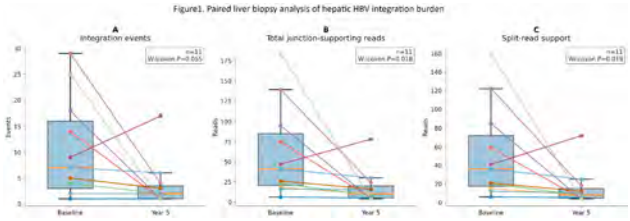
0261 | PAIRED LIVER BIOPSY ANALYSIS OF HBV INTEGRATION DURING FIVE YEARS OF NUCLEOS (T)IDE ANALOGUE THERAPY: DECLINING EVIDENCE BURDEN AND DELAYED HBV DNA SUPPRESSION

Xinyue Meng[1] Jing Zhao[2] Pengxuan Wu[1] Jianxia Dong[1] Shan Ren[1] Xinyue Chen[1] Sujun Zheng[1], [1]First Department of Hepatology, Beijing YouAn Hospital, Capital Medical University, Beijing, China, [2]First Department of Hepatology, Beijing YouAn Hospital, Capital Medical University, Beijing,China

Background: HBV DNA integration is a durable viral-host genomic event in chronic hepatitis B (CHB), but paired-liver evidence during nucleos(t)ide analogue (NA) therapy is limited. We examined five-year changes in hepatic HBV integration burden and its viral and immune-inflammatory correlates. **Methods:** Baseline liver tissues from 22 NA-treated CHB patients were analyzed; 11 had paired biopsies after five years. HBV integration was detected by capture-based sequencing with liquid-phase probe enrichment and paired-end sequencing. Integration burden was defined by integration events, total junction-supporting reads, and split-read support. Paired changes were tested by Wilcoxon signed-rank test and correlations by Spearman analysis. **Results:** In 11 paired samples, integration evidence burden decreased after five years. Integration events declined from 7.00 to 2.00 ($P = 0.055$), total junction-supporting reads from 41.00 to 10.00 ($P = 0.018$), and split-read support from 36.00 to 8.00 ($P = 0.019$); both read-support metrics decreased in 10/11 patients. HBV DNA, HBV RNA, HBcrAg, qHBsAg, intrahepatic total HBV DNA, cccDNA, Ishak fibrosis score, and Knodell score also decreased. However, changes in integration burden were not significantly correlated with changes in HBsAg, HBsAg isoforms, HBcrAg, HBV DNA, HBV RNA, cccDNA, total intrahepatic HBV DNA, or histological scores. In the 22-patient baseline analysis, integration burden was not consistently associated with HBV DNA, HBV RNA, HBsAg, HBcrAg, or cccDNA. In contrast, baseline integration burden correlated positively with baseline RANTES levels, including integration events (rho = 0.547, $P = 0.008$), total junction-supporting reads (rho = 0.506, $P = 0.016$), and split-read support (rho = 0.520, $P = 0.013$). Baseline integration burden also correlated with higher five-year HBV DNA levels (rho = 0.584, 0.564, and 0.544 for the three integration metrics; all $P < 0.01$) and longer time to HBV DNA undetectability (rho = 0.523, 0.548, and 0.515; all $P < 0.05$). No significant differences in integration burden reduction or residual five-year integration burden were observed between ETV- and ADV-treated patients. **Conclusion:** Five years of NA therapy was associated with reduced hepatic HBV integration evidence burden. Integration changes were not synchronized with HBsAg, HBcrAg, cccDNA, or histology. Baseline serum viral markers did not reliably reflect hepatic integration burden, whereas higher baseline integration burden was associated with RANTES-related immune activity, delayed HBV DNA suppression, and higher residual HBV DNA after five years.

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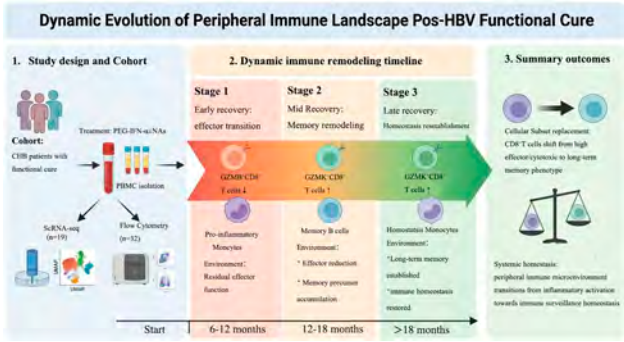


Disclosures: Xinyue Meng: Nothing to Disclose, Jing Zhao: Nothing to Disclose, Pengxuan Wu: Nothing to Disclose, Jianxia Dong: Nothing to Disclose, Shan Ren: Nothing to Disclose, Xinyue Chen: Nothing to Disclose, Sujun Zheng: Nothing to Disclose.

0262 | IMMUNE REMODELING AFTER HBV FUNCTIONAL CURE FEATURES COORDINATED ENRICHMENT OF GZMK⁺ CD8⁺ T CELLS AND ACTIVATED MEMORY B CELLS

Qi Zheng[1] Zhen Xun[1], [1]Fujian Medical University

Background: Interferon-α (IFN-α)-induced functional cure of chronic hepatitis B (CHB) offers an opportunity to examine immune changes following HBV clearance. We aimed to characterize the longitudinal dynamics of peripheral T and B cell subsets and their temporal coordination after cure. **Methods:** Peripheral blood mononuclear cells from CHB patients with PEG-IFN-α-induced HBsAg loss (n = 51) were collected. A cohort of 19 patients was analyzed by droplet-based single-cell RNA-seq. An independent cohort of 32 patients was assessed by multicolor flow cytometry. A third longitudinal cohort (n = 8) was sampled at baseline, weeks 24, 36, and 48 of PEG-IFN-α therapy. Post-cure patients were stratified by time since HBsAg loss: 6–12, 12–18, and > 18 months. CellChat was used to infer cell-cell communication. **Results:** During IFN-α treatment, peripheral GZMK⁺ CD8⁺ T cells progressively declined while GZMB⁺ CD8⁺ T cells gradually increased. After therapy discontinuation, this pattern reversed: GZMK⁺CD8⁺ cells expanded over time (> 18 months vs. 6–12 months, p = 0.038) and GZMB⁺CD8⁺ cells continued to contract. In parallel, the IgG⁺ fraction within classical memory B cells (cMBC) was significantly higher at > 18 months compared with both 6–12 months (p = 0.047) and 12–18 months (p = 0.013). The proportion of activated memory B cells (actMBC) tended to increase at > 18 months versus 6–12 months (p = 0.050), but was comparable between 12–18 months and > 18 months (p = 0.28). The increase in GZMK⁺ CD8⁺ T cells and memory B cell subsets was temporally coordinated. Phenotypically, post-cure GZMK⁺ CD8⁺cells displayed a memory precursor profile (IL7R, CD27), whereas GZMB⁺CD8⁺T cells exhibited a terminal effector signature (CX3CR1, GNLY). To investigate potential interactions between the coordinately expanding populations, CellChat analysis revealed that the MIF-CD74-CXCR4 signaling axis between GZMK⁺CD8⁺ T cells and B cells was progressively strengthened with time after cure, suggesting an evolving T-B crosstalk underlying their synchronous dynamics. While this T-B communication signal strengthened, antigen presentation pathways in B cells and monocytes declined over time after cure. **Conclusion:** In patients with IFN-α-induced HBV functional cure, GZMK⁺ CD8⁺ T cells and activated memory B cells coordinately increase over time after cure, while GZMB⁺ CD8⁺ T cells decline, indicating a shift from an effector-dominated to a memory-biased immune profile.



Disclosures: Qi Zheng: Nothing to Disclose, Zhen Xun: Nothing to Disclose.

0263 | ISRIB AS A PROMISING SAVIOR FOR ACUTE LIVER FAILURE: MODULATING THE GUT MICROBIOTA-TRYPTOPHAN METABOLISM-IMMUNE AXIS

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Background: Acute liver failure (ALF) is a rapidly progressive, life-threatening syndrome with limited effective medical therapy beyond liver transplantation and artificial liver. Increasing evidence highlights the critical role of the gut-liver axis in ALF progression. ISRIB, a selective integrated stress response inhibitor,

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has demonstrated anti-inflammatory and cytoprotective effects in multiple disease models, but its therapeutic potential and mechanistic basis in ALF remain unknown. We investigated whether ISRIB alleviates ALF by reshaping the gut microbiota, regulating tryptophan metabolism, and modulating hepatic immune responses. **Methods:** Male C57BL/6 mice were used to establish an LPS/D-galactosamine-induced ALF model. ISRIB was administered intraperitoneally 12 hours before and during ALF induction. Mice were sacrificed 6 hours after modeling. Liver injury, inflammatory cytokines, intestinal barrier integrity, and endotoxemia were evaluated by biochemical assays, histopathology, ELISA, and RT-qPCR. Gut microbial composition was profiled by 16S rRNA sequencing, fecal metabolites were analyzed by untargeted metabolomics, and hepatic immunity-related transcriptional profiles were assessed by RNA sequencing. Antibiotic depletion, fecal microbiota transplantation, probiotic intervention and metabolite supplementation were further conducted to validate microbiota-dependent mechanisms. **Results:** ISRIB significantly attenuated ALF-associated liver injury, as demonstrated by reduced serum ALT/AST levels, decreased hepatic necroinflammation and suppression of systemic inflammatory cytokines. ISRIB also partially restored gut microbial diversity and shifted the abundance of key taxa, including *Akkermansia*, *Alistipes*, and *Lactobacillus*. Metabolomic profiling identified multiple tryptophan-related and redox-associated metabolites, including 5-methoxytryptophan, together with additional lipid and oxidative stress-linked candidates. Transcriptomic analysis indicated that ISRIB reversed inflammatory and innate immune activation signatures associated with ALF, particularly pathways linked to cytokine signaling, immune remodeling, and metabolic stress responses. Integrated multi-omics analysis suggested a coordinated interaction among ISRIB-responsive gut microbes, tryptophan metabolites and hepatic immune pathways. **Conclusion:** ISRIB exerts a protective effect against experimental ALF and may represent a promising therapeutic strategy for acute liver injury. Mechanistically, ISRIB appears to ameliorate ALF through modulation of the gut microbiota-tryptophan metabolism-immune axis, highlighting a previously unrecognized gut-liver immunometabolic mechanism underlying ISRIB-mediated hepatoprotection.

Disclosures: Qi Jiang: Nothing to Disclose, Haonan Zhang: Nothing to Disclose, Yuxi Zhao: Nothing to Disclose, Lingxiao Zhu: Nothing to Disclose, Yan Lv: Nothing to Disclose, Yan Jin: Nothing to Disclose, Wei Wang: Nothing to Disclose, Lanjuan Li: Nothing to Disclose.

0264 | MACHINE LEARNING MODEL ACCURATELY PREDICTS SPONTANEOUS SURVIVAL OF PHOSPHORUS RELATED HEPATOTOXICITY PATIENTS TREATED WITH PLASMA EXCHANGE.

Ashish Goel[1] Santhosh Kumar[1] Amirthalingam Mangaiyarkarasi[2] Kshitij Jadhav[3] S Akilesh[1] Kamya Gupta[3] Vijay Alexander[1] Gayathiri Chellaiya[1] Dolly Daniel[1] Vinoi David[1] A Nirmala[2] P Kalidas[2] Krishnasamy Narayanasamy[4] E Senthil[2] Bhavik Kanekar[5] Hannah Thomas[1] Uday Zachariah[1] C Eapen[1], [1]Christian Medical College, Vellore, [2]Coimbatore Medical College, [3]Koita Centre for Digital Health, Indian Institute of Technology Bombay, [4]The Tamil Nadu Dr MGR Medical University, [5]Koita Centre for Digital Health, Indian Institute of Technology Bombay, Mumbai

Background: Rodenticide (yellow phosphorus) induced hepatotoxicity (RH) is an hyperendemic cause of acute liver failure in India (PMID: 38638507). Plasma exchange (PLEX) has shown to improve outcomes in these patients. King's College Hospital (KCH) criteria have not been validated for RH-related acute liver failure (ALF), and the 'Kochi' criteria have not been evaluated in RH patients undergoing PLEX. The study aimed to develop and validate a machine learning (ML) model to predict in-hospital spontaneous survival in patients with RH treated with PLEX. **Methods:** In this multicenter retrospective study, clinical data were collected from RH patients treated with low-volume PLEX and low-dose steroids. The primary outcome was prediction of in-hospital survival. Predictions were evaluated at five distinct time points: admission (T1), pre-PLEX (T2), and following the first (T3), second (T4), and third (T5) PLEX sessions. Several tree-based ML models were developed, with the XGBoost model demonstrating the most consistent performance. Feature selection was guided by Shapley Additive Explanations (SHAP) values. To ensure model explainability, sigmoid curves were fitted to individual features to identify inflection points, which served as objective cutoff values for differentiating survival from mortality. **Results:** The cohort included 360 patients: 65 (18%) with uncomplicated hepatitis, 128 (35.6%) with acute liver injury, and 167 (46.4%) with ALF. Of these, 239 were discharged alive, 116 died, and 5 were excluded due to transfer. None of the patients had liver transplantation. Table 1 shows the performance of the model at the five time points for the entire cohort and among ALF subgroup with top SHAP features (with its cut-off) listed at each time point. The resulting RHPLEX model significantly outperformed the Kochi criteria. At admission (T1), the RHPLEX model achieved higher

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accuracy compared to Kochi (80.6% vs. 59.7%), specifically demonstrating a much higher recall for mortality (76.7% vs. 24.1%). At the pre-PLEX (T2) stage, RHPLEX maintained superior accuracy (77.8% vs. 66.3%) and mortality recall (74.1% vs. 37.9%).The model demonstrated sustained accuracy at subsequent time points: T3 (80.2%), T4 (74.6%), and T5 (79.4%). SHAP analysis identified traditional markers of liver severity (bilirubin, INR, and creatinine) as key predictors, but also highlighted the prognostic importance of hematological indices, including neutrophil and lymphocyte counts and the lymphocyte-monocyte ratio. In the ALF subgroup, the RHPLEX model remained superior to KCH criteria (accuracy 76.1% vs. 60.4%). **Conclusion:** The RHPLEX model provides a robust, explainable, and early prediction of survival in patients with phosphorus-induced hepatotoxicity treated with PLEX. By outperforming established criteria, this model offers a potential clinical tool for early risk stratification, though further external validation is warranted.

Table 1: The performance of the model for the entire data set and among ALF patients and top features on Shapley and their cut-offs with arrow indicating the direction of the value to have a favourable outcome

Time point	All Patients (Accuracy)	Parameter's Range	Patients with ALF (Accuracy)	Parameter's Range
Baseline (T1)	80.60%	Creatinine: 1.2 mg%	70.23%	INR 1.87
		Bilirubin: 8.7 mg%		Platelets 183000/cumm (till 50,000)
		Monocytes: 8.1 %		TC 4754.42 /cumm
		INR: 2.93		Hb 14.31 gm% (till 10)
		LMR: 2.38		Lymphocytes 21.71%
				Bilirubin 6.40 mg%
				Creatinine 0.33 mg%
Preplex (T2)	77.77%	Lymphocytes: 30.29%	76.10%	TC 4410.48 /cumm
		INR: 8.02		Bilirubin 3.64 mg%
		LMR: 2.37		Platelets 167000/cumm
		Creatinine: 1.26 mg%		Neutrophil 50.42%
				Creatinine 1.01 mg%
				INR 1.88
Post 1 plex (T3)	80.22%	INR: 2.97	76.20%	INR 3.914
		Creatinine: 1.24 mg%		Bilirubin 3.75 mg%
				Creatinine 0.93 mg%
Post 2 plex (T4)	74.60%	Bilirubin: 5.96 mg%	69.80%	INR 2.65
		INR: 2.06		Creatinine 0.67 mg%
Post 3 plex (T5)	79.40%	INR 2.43	79.05%	INR 2.77
		Bilirubin 5.93 mg%		Bilirubin 8.52 mg%
		NLR 3.56		
		Platelets 115000/cumm		
		Lymphocytes 19.91%		

Disclosures: Ashish Goel: Nothing to Disclose, Santhosh Kumar: Nothing to Disclose, Amirthalingam Mangaiyarkarasi: Nothing to Disclose, Kshitij Jadhav: Nothing to Disclose, S Akilesh: Nothing to Disclose, Kamya Gupta: Nothing to Disclose, Vijay Alexander: Nothing to Disclose, Gayathiri Chellaiya: Nothing to Disclose, Dolly Daniel: Nothing to Disclose, Vinoi David: Nothing to Disclose, A Nirmala: Nothing to Disclose, P Kalidas: Nothing to Disclose, Krishnasamy Narayanasamy: Nothing to Disclose, E Senthil: Nothing to Disclose, Bhavik Kanekar: Nothing to Disclose, Hannah Thomas: Nothing to Disclose, Uday Zachariah: Nothing to Disclose, C Eapen: Nothing to Disclose.

0265 | MONOTHERAPY WITH SIRNA HRS-5635 INDUCES AN HBSAG LOSS IN CHRONIC HBV INFECTION: A MULTICENTER, RANDOMIZED, PHASE II STUDY

Xieer Liang[1] Yingli He[2] Yongning Xin[3] Xingxiang Yang[4] Sikui Wang[5] Zhihong Liu[1] Rui Hua[6] Shuqiang Ou[7] Hainv Gao[8] Dachuan Cai[9] Jun Ye[10] Shuangsuo Dang[11] Minghua Su[12] Xuebing Yan[13] Chuanmiao Liu[14] Guang-Ming Li[15] Zuxiong Huang[16] Xiaopeng Wang[17] Ying Wang[17] Lingling Xu[17] Jinlin Hou[1], [1]Nanfang Hospital, Southern Medical University, [2]The First Affiliated Hospital of Xi'an Jiaotong University, [3]Qingdao Municipal Hospital, [4]Sichuan Provincial People's Hospital, [5]Liaocheng People's Hospital, [6]The First Hospital of Jilin University, [7]Pingxiang NO.2 People's Hospital, [8]Shulan (Hangzhou) Hospital, [9]The Second Affiliated Hospital of Chongqing Medical University, [10]The Second Affiliated Hospital of Anhui Medical University, [11]The Second Affiliated Hospital of Xi'an Jiaotong University, [12]The First Affiliated Hospital of Guangxi Medical University, [13]The Affiliated Hospital of Xuzhou Medical University, [14]The First Affiliated Hospital of Bengbu Medical University, [15]The Sixth People's Hospital of Zhengzhou, [16]Mengchao Hepatobiliary Hospital of Fujian Medical University, [17]Fujian Shengdi Pharmaceutical Co., Ltd.

Background: Loss of HBsAg is the optimal but rarely achieved goal for chronic HBV infection. HRS-5635 is the first N-acetylgalactosamine (GalNAc)-conjugated siRNA advancing into phase III registrational trials, which targets all HBV mRNAs and suppresses the synthesis of viral proteins, thereby inducing HBsAg loss and ultimately achieving a functional cure of chronic HBV infection. **Methods:** Here, we present the Part A results of the multicenter phase II trial of HRS-5635. Patients with HBsAg 100-3000 IU/mL and suppressed HBV DNA while on stable nucleos(t)ide analogue (NA) therapy were randomized (1: 2: 2: 2) to receive 48 weeks of subcutaneous HRS-5635: 50 mg every 4 weeks (Arm 1), 200 mg every 4 weeks (Arm 2), 400 mg every 4 weeks (Arm 3), or 100 mg weekly (Arm 4), followed by a 24-week off-treatment follow-up. NA therapy was discontinued for eligible participants. Primary endpoint was HBsAg reduction from baseline at Week 12. Secondary endpoints included HBsAg loss, HBeAg loss, and safety. **Results:** The full analysis set comprised 15, 32, 32, and 30 participants in Arms 1 to 4, respectively. Overall, 68% of participants were male with a mean age of 43 yrs, 30% being HBeAg-positive. Mean (SD) baseline HBsAg ranged from 1058 (960) to 1200 (898) IU/mL, and 42% of participants had baseline HBsAg $\geq$1000 IU/mL. The mean (SD)HBsAg reductions (log10 IU/mL) from baseline at Week 12 were 1.3 (0.4), 2.0 (0.5), 2.1 (0.8), and 1.9 (0.5) in Arms

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1 to 4, respectively. At treatment completion (Week 48), HBsAg loss was achieved in 7% (1/15), 6% (2/32), 16% (5/32), and 7% (2/30) of participants in Arms 1 to 4, respectively. The corresponding rates at Week 72 (24 weeks off treatment) were 7% (1/15), 6% (2/32), 19% (6/32), and 7% (2/30), respectively. Furthermore, in HBeAg-negative patients receiving 400 mg HRS-5635, the Week 72 HBsAg loss rate was 24% (5/21); this rate reached 33% (5/15) in those with baseline HBsAg <1000 IU/mL, whereas no HBsAg loss (0%) was observed in participants with baseline HBsAg ≥ 1000 IU/mL. The two participants with baseline HBsAg ≥ 1000 IU/mL who achieved HBsAg loss were both in Arm 4. Additionally, HBeAg loss occurred in 0%, 11% (1/9), 27% (3/11), and 11% (1/9) of participants in Arms 1 to 4, respectively, at Week 72. Treatment-emergent adverse events were generally grade 1 or 2, with no dose-dependent pattern. No treatment-related adverse events led to study discontinuation. **Conclusion:** A finite duration of 400 mg HRS-5635 therapy was well-tolerated and achieved higher HBsAg loss rates at 24 weeks post-treatment cessation. These findings warrant further clinical assessment of this regimen for pursuing functional cure of chronic HBV infection.

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0266 | RATES OF FUNCTIONAL CURE IN PARTICIPANTS WITH CHRONIC HEPATITIS B VIRUS (HBV) INFECTION TREATED WITH BEPIROVIRSEN: B-WELL PHASE 3 TRIALS END OF STUDY RESULTS

Jinlin Hou[1] Man-Fung Yuen[2] Seng Gee Lim[3] Maria Buti[4] Edward Gane[5] Pietro Lampertico[6] Norah Terrault[7] Huy Nguyen[8] Hyung Joon Yim[9] Qing Xie[10] Jianmei Lin[11] Yunqing Qiu[12] Rachel Wen-Juei Jeng[13] Jeong Heo[14] Cheng-Yuan Peng[15] Chien Hung Chen[16] Wan Long Chuang[16] Yao Xie[17] Maria Hlebowicz[18] Nevin Idriz[19] Kosh Agarwal[20] Monica Gomes da Silva[21] Alex Franca[22] Roxana Cernat[23] Apinya Leerapun[24] Carla Coffin[25] Adrián Gadano[26] Pietro Andreone[27] Shigetoshi Fujiyama[28] Vasileios Sevastianos[29] Yuichiro Suzuki[30] Tien Huey Lim[31] Tarik Asselah[32] Yasuhito Tanaka[33] Xieer Liang[1] Jennifer Cremer[34] Tamara Lukic[35] Lin-Ming Shen[36] Helene Plein[37] Geoffrey Quinn[38] Yu Tao[39] Melanie Paff[39] Dickens Theodore[34] Robert Elston[38],
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Background: Functional cure (FC) – defined as ≥24 weeks (wks) of sustained HBV DNA < lower limit of quantification (LLOQ) and hepatitis B surface antigen (HBsAg) loss after finite therapy, with or without hepatitis B surface antibody – is the treatment goal in chronic HBV infection. Bepirovirsen (BPV), an antisense oligonucleotide, is the first anti-HBV therapy in global Ph3 trials with FC as the primary outcome. **Methods:** B-Well 1 and 2 are global double-blind Ph3 trials. Non-cirrhotic adults with nucleos(t)ide analog (NA)-suppressed chronic HBV infection (HBV DNA <90 IU/mL) and HBsAg >100–≤3000 IU/mL were randomized 2: 1 to BPV 300 mg or placebo (PBO) weekly for 24 wks. Participants (pts) discontinued NAs at Wk48, if eligible. The primary outcome was FC response rate at Wk72 for all pts. Key secondary outcomes included FC response rate for pts with baseline (BL) HBsAg ≤1000 IU/mL. Pts who discontinued NAs entered the durability stage after Wk72 and were monitored for safety and durability of FC response to Wk96. **Results:** Among BPV pts, 20% (127/650) in B-Well 1 and 19% (106/570) in B-Well 2 achieved FC at Wk72. No PBO pts achieved FC. A total of 24% pts on BPV (B-Well 1, 159/650; B-Well 2, 136/570) entered the NA cessation stage at Wk48 and 24% (B-Well 1, 155/650; B-Well 2, 136/570) entered the durability stage after Wk72; no PBO pts were eligible for NA cessation. Among BPV pts with BL HBsAg ≤3000 IU/mL who stopped NAs, achieved FC at Wk72, and completed Wk96, 90% (114/127; B-Well 1) and 92% (97/105; B-Well 2) had a durable FC response at Wk96; a similar proportion of durable response was observed in BPV pts with BL HBsAg ≤1000 IU/mL who achieved FC at Wk72. Among BPV pts with BL HBsAg ≤3000 IU/mL who achieved DNA. Among pts who stopped NAs at Wk48, 5 had HBV DNA replication at Wk72, of which 1 had viral relapse and reinitiated NAs post Wk72. For pts who achieved DNA suppression at Wk72, 6 had HBV DNA replication (3 confirmed/3 unconfirmed) at Wk96. Most common AEs for BPV pts in Wks 73–96 were upper respiratory tract infection (4% [12/291]), creatinine renal clearance decreased (2% [5/291]), and nasopharyngitis (2% [5/291]). AEs related to study treatment reported in Wks 73–96 (after BPV cessation) occurred in 2% (5/291) of pts, and these were single events. **Conclusion:** FC induced by 24-wk BPV treatment was durable through to Wk96 (48 wks post-cessation of all HBV treatment, including NAs) in virologically suppressed pts with chronic HBV infection. BPV had an acceptable safety profile without any evidence of latent safety concerns associated with prior BPV treatment. These data demonstrate the potential for BPV to be a first-in-class therapy for FC. **Funding:** GSK (202009/NCT05630807; 219288/NCT05630820)[For the B-Well Study Group]

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0267 | GENETIC ANALYSES OF 1,732 BILIARY ATRESIA CASES IDENTIFY NOVEL ETIOLOGIC RISK GENES IN DEVELOPMENTAL, CILIARY, AND CHOLESTATIC INJURY PATHWAYS

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Background: Biliary atresia (BA) is the most clinically relevant developmental cholangiopathy of children yet has poorly understood genetic contributors. A limited number of genes have been linked to the etiology of BA, including *PKD1L1*, *ADD3*, *CFC1* and CPLANE genes; however, large-scale analyses have been constrained by small cohort sizes and a lack of matched controls. To fill this gap, we analyzed whole-exome sequencing (WES) results from the large NIDDK-supported ChiLDReN consortium and matched multi-ethnic controls to identify novel BA-associated candidate etiologic loci. **Methods:** Variants were jointly called using Illumina DRAGEN in 1,732 BA cases (187 identified as BA with splenic malformation [BASM]) from the ChiLDReN consortium and 4,853 matched controls, while 1,697 were genotyped using the Illumina 650K SNP array. Genetic ancestry was inferred via K-nearest neighbors on 1000 Genomes-projected principal components. Multiple analytical approaches were applied, including gene-based rare variant burden testing (SKAT-O, SAIGE-GENE+), variant-level association analysis (GCTA), and biallelic carrier enrichment testing. Correlations with select post-Kasai portoenterostomy (KPE) outcomes proceeded via QTL analyses. Case-only AI-based variant prioritization was performed with GEM to derive gene candidates based on variant pathogenicity, phenotype, and Mendelian disease associations. **Results:** *PKD1L1* was confirmed as a BASM risk gene (OR = 17.7, p-adj = 0.034) from WES variants. SNP array analysis confirmed enrichment of the *ADD3* lead SNP (rs17095355), particularly in inferred East Asian ancestry. Gene-based analysis identified excess variants in the PIDDosome gene *PIDD1* (a determinant of hepatocyte ploidy during development) in cases vs controls. SAIGE-GENE+ revealed *HBEGF*, an EGFR ligand suppressing cholestatic injury, as a potential candidate. Biallelic carrier analysis identified *TTLL5*, a known ciliopathy gene, as enriched in cases vs. controls. QTL analysis nominally linked rs6431625 (*UGT1A3*) and rs7665271 (*BBS12*) to elevated post-KPE 3-month total serum bilirubin (TB) levels. Using GEM, candidate genes were significantly enriched in ciliopathy-related gene sets, highlighting Mendelian candidates like *PKD1L1*, *JAG1*, *PKD2* and *DCDC2*. **Conclusion:** Application of multiple WES and SNP array analytical methodologies to a large BA case-control cohort identified new BA candidate genes including *PIDD1*, *HBEGF*, and *TTLL5*, and corroborated *PKD1L1* and *ADD3* gene variants in specific clinical and genetic ancestry groups. *UGT1A3* and *BBS12* variants were associated with elevated TB levels at 3 months post-KPE. Taken together, multiple analytical approaches of the largest BA genetic case-control cohort reported to date worldwide reveal various genetic contributions to the complex etiopathogenesis of BA from ciliary, developmental and adaptive processes.



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0268 | A PHASE 2-READY ASK1 INHIBITOR SUPPRESSES POST-OBSTRUCTIVE CHOLESTATIC INFLAMMATION AND FIBROSIS IN EXPERIMENTAL BILIARY ATRESIA

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Background: Biliary atresia (BA) progresses rapidly from cholangiopathy to fibro-inflammatory liver injury, yet no post-Kasai pharmacotherapy prevents progression to transplant. Apoptosis signal-regulating kinase 1 (ASK1/MAP3K5), an oxidative stress-responsive MAP kinase, is activated in human BA and its inhibition restores bile duct patency in experimental BA. Here, we tested whether SRT-015, a phase 2-ready ASK1 inhibitor, attenuates progressive liver fibrosis. **Methods:** ASK1-linked pathways were evaluated in RNA-seq/proteomic datasets from normal control (NC) and BA liver/serum, and transplant-stage patient cholangiocyte organoids (BACO-Tx). Post-Kasai cholangiopathy was modeled using a murine pseudo-Kasai BA liver fibrosis (BALF) model with patent extrahepatic duct. Newborn WT mice received i.p. saline or $1.75x10^6$ ffu RRV to induce BALF, followed by daily vehicle or SRT-015 (10 or 20 mg/kg). Outcomes at day 19 post-RRV included phenotype, survival, ALT/AST/ALP, H&E and Sirius Red histology scored by Ishak modified HAI and Fibrosis Staging, immunofluorescence for ASK1, p-ASK1, p38, and p-p38 and quantified as mean fluorescence intensity (MFI) in BA-Tx and BALF livers, hepatic qPCR of MAPK/apoptotic/inflammatory/fibrotic genes, and hepatic immune cell profiling by flow cytometry. **Results:** Transcriptomic and serum proteomics analyses of BACO-Tx and livers revealed upregulated ASK1-regulated molecules, with sustained p38 (MAPK11/12), CASP1, CCL2, CXCL8, CTGF, and SPP1 from diagnosis and de novo appearance of MAP2K4/6/7, TGFβ1/β2, FN1, LCN2, ACTA2, and CCL20/28 at transplant. BA-Tx livers showed increased cholangiocyte and immune-cell MFI for ASK1, p-ASK1, p38, and p-p38 (BA 444 ± 87 vs NC 83 ± 23; $P \leq 0.0001$). At day 19, vehicle-treated BALF mice showed jaundice and growth failure, while SRT-015 resolved jaundice, restored growth, and improved survival ($P \leq 0.001$). ASK1/p-ASK1 localized to injured cholangiocytes and reduced with SRT-015. SRT-015 reduced ALT (89 ± 11 vs 130 ± 33), AST (172 ± 38 vs 245 ± 78), and ALP (242 ± 72 vs 522 ± 325), attenuated portal/bridging inflammation (Ishak HAI: 0.3 ± 0.6 vs 2.3 ± 0.6), and periportal/bridging collagen deposition (Ishak fibrosis: 0.3 ± 0.6 vs 3.6 ± 0.5). Hepatic *Map3k5*, *Map2k4/6/7*, *Casp1/3/4*, *Il1β*, *Tnfα*, and profibrotic *Ctgf*, *Acta2*, *Tgfβ1*, *Thbs1*, and *Loxl2/4* were reduced 3-8-fold ($P \leq 0.01$). Flow cytometry showed fewer $CD45^+$ $COL1A1^+$ fibrocytes, MHCII/$CCR2^+$ $CD11b^+$ $F4/80^+$ macrophages/$CD11b^+$ $Gr1^+$ neutrophils, and $CD11c^+$ $CD11b^+$ mDCs (all $P \leq 0.01$), indicating suppression of the fibro-inflammatory niche. **Conclusion:** ASK1 signaling persists during the fibrotic phase of BA. SRT-015 improved survival, attenuated MAPK activation, cholestatic injury, inflammation, collagen deposition, fibro-inflammatory immune remodeling, and preserved bile flow. These findings support clinical evaluation of post-Kasai ASK1 inhibition as a long-term antifibrotic strategy for BA.

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0269 | FIBRONECTIN&NDASH; INTEGRIN α5β1 CROSSTALK IS A THERAPEUTIC EPITHELIAL-IMMUNE AXIS IN BILIARY ATRESIA

Wenqi Li[1] Nithyananthan Subramaniyam[1] Reena Mourya[1] Jorge Bezerra[1] Pranavkumar Shivakumar[1], [1]University of Texas Southwestern Medical Center

Background: Biliary atresia (BA) is driven in part by epithelial-immune crosstalk that amplifies cholangiocyte injury and obstruction. Macrophage-mediated inflammation is central to bile duct damage. Prior cholangiocyte organoid-macrophage cocultures identified fibronectin (Fn)-integrin α5β1 signaling as a candidate pathway by which cholangiocytes activate macrophages. BA cholangiocytes showed increased Fn production and enhanced macrophage-activating capacity; however, the functional contribution of the Fn-integrin α5β1 axis to BA has not been defined. **Methods:** To test patient-derived epithelial-immune mechanism across complementary platforms, we combined human BA cholangiocyte organoids (BACO), human embryonic stem cell-derived macrophages, pathway-selective perturbation, and in vivo antibody blockade. Macrophages were exposed to conditioned medium from normal control cholangiocyte organoid (NCO) or BACO. Fn-dependent signaling was inhibited

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with RGDS, whereas integrin α5β1 signaling was blocked with volociximab to distinguish ligand-level from receptor-level regulation; IL-1β and IL-8 were quantified by flow cytometry. For in vivo validation, newborn BALB/c mice received $1.5x10^6$ ffu rhesus rotavirus (RRV) i.p. to induce BA and were treated every other day through day 11 with combined anti-ITGA5/anti-ITGB1 blocking antibodies or isotype control. Weight, jaundice score (0-4), and survival were measured daily, and liver and bile duct histology were assessed at day 12. This strategy links patient signals to mechanistic and anatomic rescue endpoints. **Results:** BACO conditioned medium induced macrophage inflammatory activation, increasing IL-8 and IL-1β by 1.7-1.8-fold, ($P < 0.01$). Fn inhibition with RGDS selectively reduced BACO-induced IL-1β (45.8 ± 2.3% vs 51.5 ± 0.6% in untreated control; $P = 0.02$), but not IL-8 (56.6 ± 1.3% vs 54.9 ± 0.8%; $P = 0.35$), suggesting partial Fn dependence. In contrast, direct integrin α5β1 blockade with volociximab suppressed both IL-1β (42.8 ± 0.5 vs 47.5 ± 2.0%; $P < 0.01$) and IL-8 (39.5 ± 1.6 vs 51.5 ± 1.9%; $P < 0.01$), identifying integrin α5β1 as a functional macrophage response node downstream of BA cholangiocyte-derived Fn signals. In vivo, combined ITGA5/ITGB1 blockade improved the RRV-induced BA phenotype. At day 12, antibody-treated mice had higher body weight than isotype-treated controls (5.6 ± 0.7 vs 4.5 ± 0.3 g, $P < 0.01$), markedly lower jaundice scores (0.4 ± 0.5 vs 4.0 ± 0.0, $P < 0.01$), and >80% reduction in anatomic extrahepatic bile duct atresia (16.7% vs 100%). Treated mice maintained luminal continuity and bile flow, indicating reduced clinical disease severity. **Conclusion:** BA cholangiocytes activate macrophages through Fn-integrin α5β1 signaling. Blocking this epithelial-immune axis reduced macrophage cytokine production and bile duct obstruction, identifying integrin α5β1 signaling as a translational strategy to reduce immune-mediated injury in BA.

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0270 | EARLY TIMEPOINTS ARE CRITICAL IN BILIARY ATRESIA: RESULTS FROM PROSPECTIVELY FOLLOWING 831 INFANTS RECEIVING THE KASAI PORTOENTEROSTOMY

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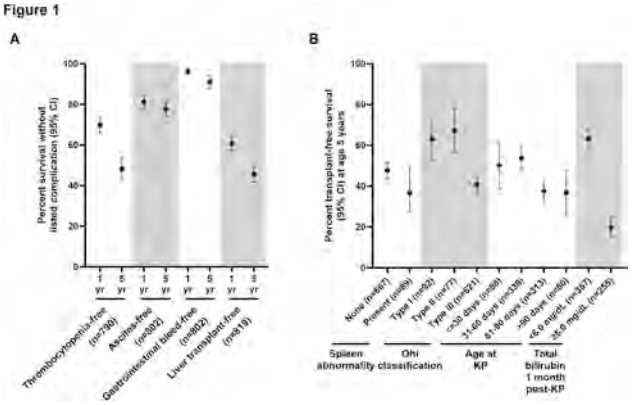
Background: Infants with biliary atresia are treated with the Kasai portoenterostomy (KP), with the goal of relieving bile retention and ultimately improving outcomes. In this study, we analyzed the largest multicenter prospective study of biliary atresia to (i) better understand the disease's natural history after KP and (ii) identify early factors that predict long-term liver transplant-free survival. **Methods:** Patients with biliary atresia, treated with the KP, and enrolled in the Childhood Liver Disease Research Network's (ChiLDReN) Prospective Database of Infants with Cholestasis (PROBE; NCT00061828) from 2004-2025 were studied. Clinical endpoints such as thrombocytopenia, ascites, and gastrointestinal bleeding were defined a priori and collected during annual follow-up visits. Cox Proportional Hazards and Kaplan-Meier analyses were used for survival estimates and analysis of prognostic factors, respectively. **Results:** There were 831 infants from the United States and Canada included, who were 54% female (n = 446), 62% white (n = 492), and 23% Hispanic (n = 189). One-year estimated survival without thrombocytopenia was 69.8%, without ascites 81.2%, and without gastrointestinal bleeding was 96.3% (Figure 1A). One-year survival with native liver was 60.7%. Between ages 1-5 years, estimates for survival without ascites and gastrointestinal bleeding dropped minimally, indicating that disease progression is less rapid in infants surviving with their native liver beyond the first year. Early non-modifiable factors that predicted better native liver survival at age 5 years included absence of splenic abnormalities ($p = 0.04$) and Ohi antomical type I and II ($p < 0.0001$) (Figure 1B). In comparison, early modifiable factors that predicted better native liver survival at age 5 years included performing the KP at ≤30 days of life or 30-60 days of life ($p = 0.0003$). Another early factor that may or may not be modifiable was improvement of bile flow immediately

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after KP, as indicated by better native liver survival at age 5 years in those who achieved total bilirubin < 6.0 mg/dL within 1 month after KP ($p < 0.0001$). **Conclusion:** In the largest propspective study of infants with biliary atresia, signs of disease progression appeared rapidly in the first year of life but slower after the first year of life. In addition, early non-modifiable, modifiable, and possibly modifiable factors were associated with long-term outcomes. Our findings highlight the importance of the first year of life and the peri-KP period specifically in biliary atresia, and raise the possibility that interventions in a narrow early window—such as screening to accelerate the age at KP and treating immediately after KP with adjunctive therapies that promote bile flow—may be especially efficacious in improving long-term outcomes.

Figure 1



Disclosures: Sanjiv Harpavat: Syneos Health: I sit on a Data Safety Monitoring Board, Sindhu Pandurangi: Nothing to Disclose, Steve Guthery: Nothing to Disclose, Saul Karpen: Albireo/Ipsen: Consultant, Mirum: Consultant, Intercept: Consultant, Kathleen Loomes: Nothing to Disclose, Estella Alonso: Nothing to Disclose, Simon Horslen: Mirum: Grant/Research Support, Albireo/Ipsen: Consultant, Mallinckrodt Pharma: Consultant, Rohit Kohli: Mirum: Consultant, Ipsen: Consultant, Epigen: Grant/Research Support, Sanofi Rare Disease: Consultant, iECURE: Consultant, Solid Biosciences: Consultant, John Magee: Nothing to Disclose, Alexander Miethke: Mirum Pharmaceutical Inc: Grant/Research Support, Mirum Pharmaceutical Inc: Consultant, Ipsen: Speaking and Teaching, Perspectum Ltd.: Grant/Research Support, Esperion: Advisor, Jean Molleston: Gillead: Grant/Research Support, Albireo: Grant/Research Support, Abbvie: Grant/Research Support, Mirum/Shire: Grant/Research Support, Philip Rosenthal: Nothing to Disclose, Pamela Valentino: Nothing to Disclose, Kasper Wang: Nothing to Disclose, Ronald Sokol: Mirum: Advisor, Ipsen/Albireo: Advisor, Malinkrodt: Consultant, Alexion: Consultant, ProQR: Consultant, Benjamin Shneider: Nothing to Disclose, the Childhood Liver Disease Research Network (ChiLDReN): Nothing to Disclose.

0271 | GENOTYPIC SPECTRUM AND CLINICAL OUTCOMES OF GENETIC LIVER DISEASES ACROSS ASIA-PACIFIC COUNTRIES: THE ANGELD STUDY

Huey-Ling Chen[1] Ayano Inui[2] Anupam Sibal[3] Ruey Terng Ng[4] Chatmanee Lertudomphonwanit[5] Jae Sung Ko[6] Byung-Ho Choe[7] Voranush Chongsrisawat[8] Winita Hardikar[9] Chia-Ray Lin[10] Bang-Yu Liou[10] Mei-Hwei Chang[1] Way-Seah Lee[4] Suporn Treepongkaruna[5] Yen-Hsuan Ni[10], [1]National Taiwan University, [2]Saiseikai Yokohamashi Tobu Hospital, Kanagawa, Japan, [3]Indraprastha Apollo Hospital, New Delhi, India, [4]University of Malaya, Malaysia, [5]Ramathibodi Hospital, Mahidol University, Bangkok, Thailand, [6]Seoul National University College of Medicine, Seoul National University Children's Hospital, Seoul, [7]Kyungpook National University School of Medicine, Korea, [8]Chulalongkorn University, Thailand, [9]Royal Children's Hospital, Melbourne, Australia, [10]National Taiwan University College of Medicine and Children's Hospital, Taipei, Taiwan

Background: Pediatric genetic liver diseases comprise a heterogeneous group of disorders, with disease spectrum and prevalence varying across geographic regions. However, the disease burden and genetic landscape in the Asia-Pacific region remain less characterized. This study aimed to investigate the causative genes and disease spectrum of pediatric genetic liver diseases in the Asia-Pacific region. **Methods:** The ANGELD study, conducted by the Asia-Pacific Network of Genetic Liver Diseases, is a multicenter collaborative consortium study. A case registry was established to collect clinical information, serum biochemical profiles, genetic testing results, and prognostic outcomes. Patients with disease onset between 0 and 18 years of age and a diagnosis of genetic liver disease between 2000 and 2023 were included. Patients with suspected genetic liver disease but without access to genetic testing were also recruited. **Results:** The registry included 718 patients, comprising 370 patients with a confirmed genetic diagnosis and 348 patients with suspected genetic liver disease but without genetic testing. Among the 370 genetically confirmed cases, 64 distinct genetic liver diseases were identified. The most common disease-associated genes were *SLC25A13*, *JAG1*, and progressive familial intrahepatic cholestasis (PFIC)-associated genes, including *ATP8B1*, *ABCB11*, and *ABCB4*. These genes, together with *ATP7B*, *TJP2*, and *HSD3B7*, were identified across more than three countries in the Asia-Pacific region. Approximately 70% of genetically confirmed cases were attributable to the eight most common genetic liver diseases, whereas the remaining 30% were distributed across

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56 rare genetic liver diseases. Most patients with neonatal intrahepatic cholestasis caused by citrin deficiency (NICCD) demonstrated favorable long-term outcomes. Apart from NICCD, the 10-year native liver survival rates were 59.48% among patients with genetically confirmed liver diseases other than NICCD and 61.19% among patients without a genetic diagnosis. The 20-year overall survival rates were 79.89% and 66.75%, respectively. Kaplan–Meier analysis revealed that both native liver survival and overall survival were significantly better in patients with NICCD than in those with other genetic liver diseases or without a genetic diagnosis. (Figure) **Conclusion:** This multicenter collaborative consortium study characterized the genetic etiologies and prognostic outcomes of pediatric genetic liver diseases across Asia-Pacific countries. The findings revealed substantial etiologic diversity and disease-specific differences in prognosis. These results highlight the need for regionally coordinated strategies to improve genetic diagnosis, risk stratification, and management of children with genetic liver diseases.

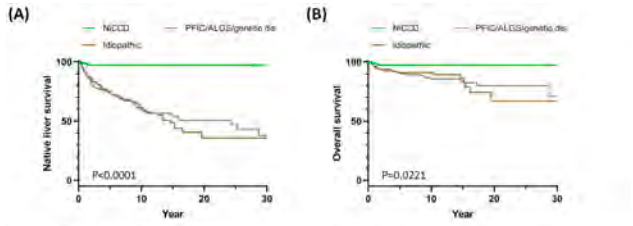


Figure (A) The native liver survival and (B) overall survival of genetic diagnostic NICCD cases (green line), case with PFIC, ALGS or other genetic defects (gray line) and idiopathic cases (brown line) (Native liver survival: NICCD vs PFIC/ALGS/other genetic disease, p < 0.0001, NICCD vs idiopathic p-value < 0.0001; Overall survival: NICCD vs PFIC/ALGS/other genetic disease, p = 0.0071, NICCD vs idiopathic, p = 0.0064)

Disclosures: Huey-Ling Chen: Nothing to Disclose, Ayano Inui: Nothing to Disclose, Anupam Sibal: Nothing to Disclose, Ruey Terng Ng: Nothing to Disclose, Chatmanee Lertudomphonwanit: Nothing to Disclose, Jae Sung Ko: Nothing to Disclose, Byung-Ho Choe: Nothing to Disclose, Voranush Chongsrisawat: Nothing to Disclose, Winita Hardikar: Nothing to Disclose, Chia-Ray Lin: Nothing to Disclose, Bang-Yu Liou: Nothing to Disclose, Mei-Hwei Chang: Nothing to Disclose, Way-Seah Lee: Nothing to Disclose, Suporn Treepongkaruna: Nothing to Disclose, Yen-Hsuan Ni: Nothing to Disclose.

0273 | ADJUVANT GRANULOCYTE COLONY-STIMULATING FACTOR AFTER KASAI PORTOENTEROSTOMY FOR BILIARY ATRESIA: A PHASE 2 RANDOMIZED CONTROLLED TRIAL

Anh - Hoa Pham Nguyen[1] Aixuan Holterman[2],
[1]National Children 's Hospital, [2]University of Illinois

Background: Post operative outcome for Kasai portoenterostomy (KPE) is limited from recurrent cholangitis, progressive liver failure despite a technically successful surgery., Granulocyte colony-stimulating factor (G-CSF) has been demonstrated in animal models of cholestasis to have both regenerative and immunomodulatory properties through mobilization of bone marrow–derived stem cells, enhancement of hepatocyte proliferation, activation of hepatic progenitor cells, and attenuation of intrahepatic inflammatory signaling. Experimental and clinical studies further suggest that G-CSF may reduce fibrogenesis, improve hepatic microcirculation, and preserve residual liver function. **Objective:** To evaluate the efficacy and safety of granulocyte colony-stimulating factor (G-CSF) as adjuvant therapy in patients with biliary atresia (BA) following Kasai portoenterostomy (KPE). **Methods:** In this open-label, randomized, controlled Phase 2 trial (ClinicalTrials.gov NCT04373941), 80 infants with type III BA undergoing KPE at Vietnam National Children's Hospital between November 2023 and April 2026 were randomized to standard postoperative care alone (KSt; n = 46) or standard care plus G-CSF (KG; filgrastim 10 μg/kg/day subcutaneously for 3 consecutive days starting on postoperative day 4 ± 1; n = 34). Mean follow-up was 11.3 ± 6.3 months overall (KSt 10.5 ± 5.7; KG 12.3 ± 7.1). The primary endpoint was successful biliary drainage defined as total bilirubin < 34.2 μmol/L at 3 months, analyzed by Fisher's exact test in the 75 infants who had reached the 3-month assessment by data cutoff. Two secondary endpoints (cholangitis-free transplant-free survival and transplant-free native liver survival) were analyzed by Kaplan–Meier with log-rank tests and Cox proportional hazards regression on the full intention-to-treat cohort: (composite of first cholangitis, transplant, or death). Other outcomes were reported descriptively as exploratory. **Results:** G-CSF therapy was well tolerated, with no treatment-related serious adverse events. The primary endpoint of bile drainage at 3 months, did not differ between the arms (KG 13/31 [41.9%] vs KSt 15/44 [34.1%]; Fisher p = 0.63). The proportion of subjects with Cholangitis-free transplant-free survival at 12 months was 35% in the KG group and 10% in the KSt group (10%), with log-rank p = 0.0002 and Cox HR 0.36 (95% CI 0.20–0.64); composite events occurred in 18/34 KG vs 39/46 KSt. Native liver survival at 12 months 90% (95% CI 77.8–100%) in the KG group and 59.5%, 95% CI 42.2–83.8% in the KSt group, with log-rank p = 0.014 and Cox HR 0.23 (95% CI 0.06–0.82); death or liver transplantation occurred in 3/34 KG (1 death, 2 transplants) vs 12/46 KSt (9 deaths, 3 transplants). Exploratory outcomes (longitudinal GGT trajectories, gastrointestinal bleeding, and liver-disease severity scores) all favored G-CSF **Conclusions:** Adjuvant G-CSF after Kasai portoenterostomy was safe. The primary endpoint of successful

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biliary drainge did not differ between arms; while secondary endpoints of cholangitis and transplant-free survival significantly favored the G-CSF treatment group. Confirmation in larger multicenter trials with longer follow-up is warranted.
Disclosures: Anh - Hoa Pham Nguyen: Nothing to Disclose, Aixuan Holterman: Nothing to Disclose.

0274 | A MULTI-AGENT AI SYSTEM FOR MAINTAINING LIVER DISEASE GUIDELINES: EVIDENCE SYNTHESIS, CONSENSUS BUILDING, AND CLINICAL IMPACT

Wang Zixing[1], [1]Peking University People's Hospital

Background: The rapid expansion of hepatology evidence outpaces the updating of liver disease guidelines. Manual processes cannot match this pace, leaving clinicians with potentially outdated recommendations. To our knowledge, this is the first evaluation of a multi-agent AI system specifically benchmarked against current liver disease guidelines. **Methods:** We developed MARG (Multi-Agent Retrieval-Augmented Generation), a system where multiple AI agents independently review evidence, debate disagreements through structured rounds, and reach consensus. The system was tested on seven 2025 EASL Clinical Practice Guidelines spanning six major hepatological domains: HBV infection, HCC, autoimmune hepatitis, Wilson's disease, extrahepatic cholangiocarcinoma, TIPS, and cirrhosis with extrahepatic surgery – totaling 137 clinical decision scenarios across diagnosis, prevention, and treatment. We evaluated MARG across three dimensions: (1) evidence synthesis quality (recency, reproducibility, and Level I evidence capture, benchmarked against expert review); (2) consensus strength through structured inter-agent debate; and (3) clinical impact on hepatologists across training levels. **Results:** MARG showed 77.4% overall agreement with liver disease guidelines. Guideline-consistent rates increased stepwise with agent consensus: 45.8% under weak consensus (50-60% agreement) to 87.8% at full consensus (p-trend < 0.001). Performance varied by task: 65.5% (diagnosis), 75.0% (prevention), and 81.0% (treatment). Compared to manual review, MARG delivered superior recency (6.3% vs 0.9%), reproducibility (25.5% vs 7.5%), and Level I evidence capture (24.2% vs 8.0%). Through four structured debate rounds, the system resolved 95.8% of initial agent conflicts, achieving strong consensus (> 85% agreement) in 74.5% of final outputs – with consensus degree correlating with independent hepatology expert panels ($\kappa = 0.239$, comparable to inter-expert agreement in complex liver disease). MARG corrected 40-60% of guideline-inconsistent decisions across all experience levels, with the largest gain among early-career clinicians. **Conclusion:** Multi-agent AI offers a scalable, transparent, and training-level-adaptive solution to maintain liver disease guidelines. By resolving disagreements through structured debate, this approach addresses three unmet needs in evidence-based hepatology: keeping pace with evidence growth, surfacing disagreement hotspots across AI agents, human experts, and AI-human pairs, and supporting fellowship training.
Disclosures: Wang Zixing: Nothing to Disclose.

★ 0275 | LIVERRISK SCORE FOR EARLY DETECTION OF LIVER FIBROSIS IN THE GENERAL POPULATION: THE LIVERSCREEN IMPLEMENTATION STUDY

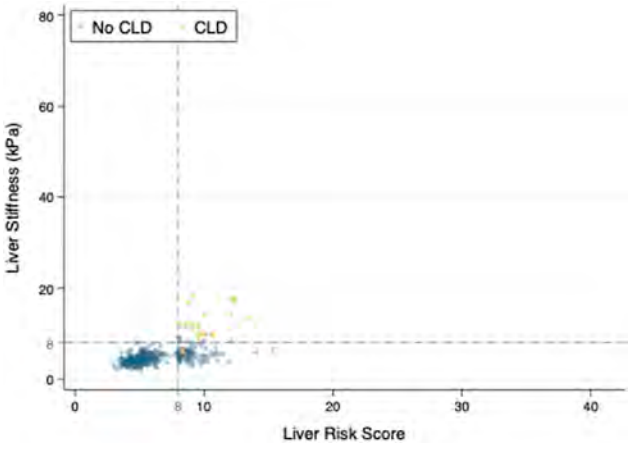
Adrià Juanola[1] Sandro Kukic[2] Julia Kahlhöfer[3] Ruth Nadal[4] Anita Madir[2] Petra Kujundzic[2] Anita Arslanow[3] Marina Vélez[5] Heiner Wedemeyer[3] Albert Albrecht[6] Kathrin Schuchardt[6] Lars Nachbar[6] Roser Ferrer[7] Albert Blanco[8] Antonio Torrejon[9] Patricia Such[9] José Mª Navarrete[9] Ana Maria de la Arada[10] Gemma Sáez-Rubio[10] Ricard Riel[11] Maria José Pardo[11] Elisa Pose[5] Isabel Graupera[5] Nuria Fabrellas[12] Miquel Serra-Burriel[13] Ivica Grgurevic[2] Frank Lammert[3] Pere Gines[5], [1]Hospital Clinic i Provincial de Barcelona, [2]Dpt. of Gastroenterology, Hepatology and Clinical Nutrition, University Hospital Dubrava, Croatia, [3]Hannover Medical School (MHH), Hannover, Germany, [4]FCRB-IDIBAPS, Barcelona, Spain, [5]Liver Unit, Hospital Clínic of Barcelona, Barcelona, Spain, [6]Volkswagen AG. Wolfsburg, Germany, [7]Biochemistry Department, Clinical Laboratories, Vall d'Hebron University Hospital, Barcelona, Spain, [8]Biochemistry Department, Clinical Laboratories, Vall d'Hebron University Hospital, Barcelona, Spain., [9]Health, Safety and Emergencies of SEAT, CUPRA and the Volkswagen Group Companies in Spain, Martorell, [10]Centre d'Atenció Primària (CAP) La Marina, Barcelona, Spain, [11]Institut Catala de la Salut (ICS), Ambit d'Atenció Primària, Barcelona, Spain, [12]Faculty of Medicine and Health Sciences, University of Barcelona, Barcelona, Spain, [13]Epidemiology, Statistics, and Prevention Institute, University of Zurich, Zurich, Switzerland

Background: LiverRisk score (LRS) is a non-invasive method for the detection of liver fibrosis based on the combination of 8 variables (age, sex, and six routinely available laboratory variables), which has been reported to outperform classical non-invasive tests such as FIB-4. The LiverScreen implementation study was a prospective cohort study in three European countries (Croatia, Germany, Spain) investigating the

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feasibility of LiverRisk score for liver fibrosis screening in routine health care. **Methods:** In this multinational, prospective cohort study performed in primary care centers and two car-making companies, participants undergoing blood tests as part of routine healthcare assessment were invited to participate. People with known chronic liver disease were excluded. The LRS value was automatically calculated by central laboratory facilities. Participants with LRS $\geq$ 8 were referred to an academic liver center for a visit that included a complete hepatology evaluation. In addition, a randomly selected subset of participants with LRS < 8 also underwent this visit as control. **Results:** Between December 2024 and January 2026, we recruited 8,708 participants, 5,559 (64%) men, most of them caucasian, with a mean age of 52 ± 9 years. An increased LRS ($\geq$ 8) was found in 176 (2%) participants, of whom 123 (70%) attended the hepatology visit. Thirty-three of the 123 participants (27%) had liver stiffness measurement (LSM), as measured by vibration-controlled transient elastography (VCTE, $\geq$ 8 kPa suggestive of liver fibrosis), whereas only 1 of the 280 participants from the control group presented with LSM $\geq$ 8 kPa. LSM was >10 kPa in 19 participants. Metabolic risk factors were more prevalent among individuals with LRS $\geq$ 8: more than 60% had two or more risk factors, compared with 20% of those with LRS < 8 (p-value < 0.001). After hepatology evaluation, 23 participants (19%) had confirmed diagnosis of chronic liver disease, with the most common etiologies being MASLD, ALD, and MetALD (56%, 13% and 9%, respectively). The AUROC of LRS for chronic liver disease diagnosis was 0.934 (0.902 - 0.966). **Conclusion:** These results demonstrate that a targeted intervention with measurement of LiverRisk score followed by VCTE and hepatology assessment can detect people with undiagnosed chronic liver disease with fibrosis. They also underscore the need for further research investigating whether screening for liver fibrosis reduces morbidity and mortality due to chronic liver diseases and liver cancer.



Disclosures: Adrià Juanola: Grifols: Speaking and Teaching, Sandro Kukic: Nothing to Disclose, Julia Kahlhöfer: Nothing to Disclose, Ruth Nadal: Nothing to Disclose, Anita Madir: Nothing to Disclose, Nothing to Disclose, Petra Kujundzic: Nothing to Disclose, Anita Arslanow: Nothing to Disclose, Marina Vélez: Nothing to Disclose, Heiner Wedemeyer: Gilead Sciences GmbH & Gilead Sciences Ltd.: Grant/Research Support, Madrigal Pharmaceuticals, Inc.: Grant/Research Support, Biotest AG: Grant/Research Support, Gilead Sciences GmbH & Gilead Sciences Ltd.: Clinical Trials / Investigator, Madrigal Pharmaceuticals, Inc.: Clinical Trials / Investigator, Dr. Falk Pharma GmbH: Clinical Trials / Investigator, IPSEN Pharma S.A.S.: Clinical Trials / Investigator, AstraZeneca GmbH: Clinical Trials / Investigator, Bluejay Therapeutics: Clinical Trials / Investigator, GlaxoSmithKline Services Unlimted: Clinical Trials / Investigator, Lilly Deutschland GmbH: Clinical Trials / Investigator, Mirum Pharmaceuticals Germany GmbH: Clinical Trials / Investigator, Takeda Pharma Vertrieb GmbH & Co. KG: Clinical Trials / Investigator, BioMarin Pharmaceuticals Inc.: Clinical Trials / Investigator, Vir Biotechnology: Clinical Trials / Investigator, Gilead Sciences GmbH & Gilead Sciences Ltd.: Consultant, Madrigal Pharmaceuticals, Inc.: Consultant, Dr. Falk Pharma GmbH: Consultant, IPSEN Pharma S.A.S.: Consultant, AstraZeneca GmbH: Consultant, Bluejay Therapeutics: Consultant, Bluejay Therapeutics: Consultant, GlaxoSmithKline Services Unlimited: Consultant, Lilly Deutschland GmbH: Consultant, Mirum Pharmaceuticals Germany GmbH: Consultant, Takeda Pharma Vertrieb GmbH & Co. KG: Consultant, Vir Biotechnology, Inc.: Consultant, MSD Sharp & Dohme GmbH: Consultant, Novo Nordisk Pharma GmbH: Consultant, Abbott Laboratories & Abbott Molecular Inc.: Consultant, Alfasigma GmbH: Consultant, Aligos Therapeutics, Inc.: Consultant, Atea Pharmaceuticals, Inc.: Consultant, Bristol-Myers-Squibb: Consultant, EIT Pharma, Inc.: Consultant, F. Hoffmann-La Roche Ltd.: Consultant, IntergerBio, Inc.: Consultant, Orphalan GmbH: Consultant, Pfizer Pharma GmbH: Consultant, Primmune Therapeutics, Inc.: Consultant, Ribocure Pharmaceuticals AB: Consultant, Gilead Sciences GmbH & Gilead Sciences Ltd.: Speaking and Teaching, Dr. Falk Pharma GmbH: Speaking and Teaching, IPSEN Pharma S.A.S.: Speaking and Teaching, MSD Sharp & Dohme GmbH: Speaking and Teaching, Novo Nordisk Pharma GmbH: Speaking and Teaching, BioMarin Pharmaceuticals Inc.: Speaking and Teaching, Biotest AG: Speaking and Teaching, CSL Behring: Speaking and Teaching, SANOFI Aventis Deutschland GmbH: Speaking and Teaching, Verein Falk Foundation e.V.: Speaking and Teaching, Albert Albrecht: Nothing to Disclose, Kathrin Schuchardt: Nothing to Disclose, Lars Nachbar: Nothing to Disclose, Roser Ferrer: Nothing to Disclose, Albert Blanco: Nothing to

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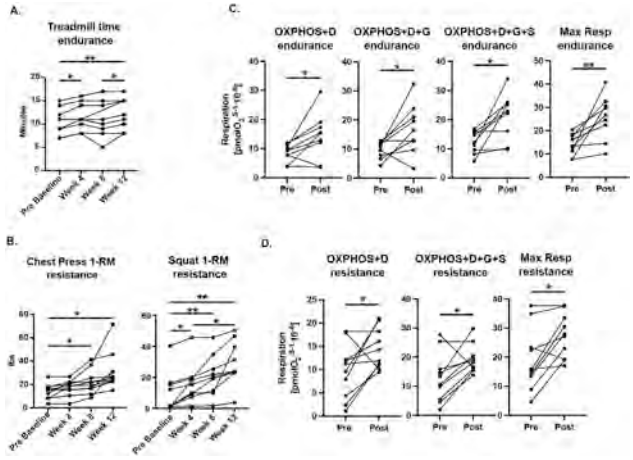
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0276 | SUPERVISED EXERCISE TRAINING IMPROVES SKELETAL MUSCLE MITOCHONDRIAL FUNCTION AND PHYSICAL PERFORMANCE IN CIRRHOSIS: A PROSPECTIVE RANDOMIZED CONTROLLED TRIAL

Annette Bellar[1] Nicole Welch[1] Pugazhendhi Kannan,[1] Seshu Vardhan Pothabathula[1] Vandana Agrawal[1] Jasmin Cunningham[1] Saurabh Mishra[1] Srinivasan Dasarathy[1], [1]Cleveland Clinic

Background: Sarcopenia, contractile dysfunction, and skeletal muscle mitochondrial oxidative dysfunction contribute significantly to physical frailty, reduced exercise capacity, and poor outcomes in cirrhosis. Exercise has demonstrated benefits in healthy individuals with distinct functional, molecular, and mechanistic responses being different in endurance exercise (EE) and resistance exercise (RE) training. Though benefits with EE or RE have been reported in cirrhosis, data are confounded by low adherence rates and there are no reports of direct comparisons of responses to EE vs. RE in cirrhosis. **Methods:** Patients with compensated cirrhosis were randomized to supervised, structured, EE, RE, or no intervention for 12 weeks (NCT05982769). Patients had a MELD score <21, Child score 5-10, and were eligible to recieve muscle biology (INR ≤ 1.7, platelets $\geq 60{,}000$, and not on blood thinners) without recent GI bleeding or hepatic encephalopathy. Home-based cycling three times weekly for 60 minutes of physical activity at 60–70% heart rate reserve RE consisted of supervised whole-body resistance band training twice weekly. Aerobic fitness (VO_2max, duration/distance run on a treadmill, time to reach anerobic threshold), and muscular fitness by 1-repetition maximum (1RM), body composition by DEXA, patient reported outcome measures information system (PROMIS) of physical function, alcohol use. Fatigue and meaning and purpose. We also measured mitochondrial oxidative function using substrate-uncoupler-inhibitor titration protocols on muscle biopsies were determined at baseline (BL) and end of 12 weeks study (EOS). **Results:** There were 10 subjects in the EE and 9 in the RE arm, mean age (EE age 62 $\pm$ 8, range 45-74; RE age 63 $\pm$ 7, range 48-75), with 2 males and 7 females in the EE group and 5 males and 5 females in the RE group. Etiology of cirrhosis in the EE group was 67% MASLD and 33% alcohol related. In the RE group the etiology was 60% MASLD, 30% alcohol related, and 10% other etiologies of cirrhosis. All subjects achieved predefined adherence to protocol criteria (<6 missed visits over the course of 12 weeks). Body composition at baseline was similar in the 2 groups and changes from BL to EOS were not different. EE training improved treadmill exercise duration and VO_2max-related performance measures ($p<0.05$) but not strength measures of legs, arms, or core body ($p>0.05$) from BL to EOS **(Fig.1A)**. RE training improved strength measures **(Fig. 1B)** including squat, chest press, and bicep curl 1RM testing ($p<0.05$) with no change in VO_2max, VO_2 time, or exercise time ($p>0.05$). Both EE and RE improved mitochondrial respiration parameters **(Fig. 1C,D)** including ADP-supported respiration, succinate-supported respiration, and maximal respiration ($p<0.05$ for all). **Conclusion:** Supervised exercise home-based training in compensated cirrhosis achieved complete adherence with modality specific improvement in aerobic fitness and muscle strength.



Disclosures: Annette Bellar: Nothing to Disclose, Nicole Welch: Nothing to Disclose, Pugazhendhi Kannan,: Nothing to Disclose, Seshu Vardhan Pothabathula: Nothing to Disclose, Vandana Agrawal: Nothing to Disclose, Jasmin Cunningham: Nothing to Disclose, saurabh mishra: Nothing to Disclose, Srinivasan Dasarathy: Nothing to Disclose.

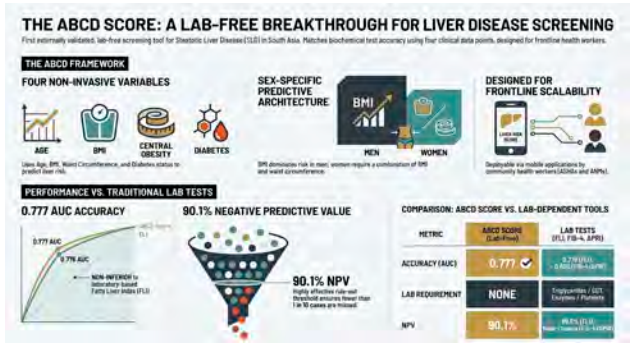
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0277 | THE ABCD SCORE: A LABORATORY-FREE, SEX-SPECIFIC PREDICTION MODEL FOR COMMUNITY-LEVEL STEATOTIC LIVER DISEASE SCREENING — DEVELOPMENT AND EXTERNAL VALIDATION IN INDIA

Kanica Kaushal[1] Harsh Tevethia[1] Manoj Sharma[1] Aditya Chaturvedi[1] Guresh Kumar[1] Shiv Kumar Sarin[1], [1]Institute of Liver and Biliary Sciences, New Delhi

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) affects nearly one in three adults globally, with the highest burden in low- and middle-income countries (LMICs). All existing non-invasive prediction tools for steatotic liver disease (SLD) require laboratory investigations unavailable at frontline primary care across most LMIC settings. No externally validated, fully laboratory-free, sex-specific SLD prediction model exists. We developed and externally validated the ABCD score — Age, BMI, Central obesity (waist circumference), and Diabetes status — for community-level MASLD screening, deployable by frontline community health workers without any biomarker requirement. **Methods:** A cross-sectional, community-based study enrolled 3,130 adults by probability-proportional-to-size cluster sampling across three tehsils of Jaipur, Rajasthan, India (February–July 2023). SLD was defined as controlled attenuation parameter (CAP) ≥248 dB/m on vibration-controlled transient elastography. Sex-specific logistic regression with 5-fold cross-validation was used; eight classifier families were compared, and the score was benchmarked against six established non-invasive scores (FLI, HSI, FIB-4, APRI, BARD, FAST). External validation was performed in an independent urban community cohort in Delhi, India (n = 3,325). **Results:** SLD prevalence was 29.5% (women 35.2%, men 26.0%). ABCD achieved AUC 0.777 (95% CI 0.763–0.791) — non-inferior to the laboratory-based Fatty Liver Index (AUC 0.776; DeLong p = 0.948) — and substantially superior to all fibrosis-optimised scores (APRI 0.535, FIB-4 0.550, BARD 0.567; all p < 0.001) and HSI (0.747; p < 0.001). BMI was the dominant predictor (70.6% of Gini impurity reduction), with a clear threshold effect at the Asian overweight cut-point (23.0 kg/m²), particularly in women. Combined BMI and waist circumference elevation conferred 8.51-fold increased odds of SLD (95% CI 6.67–10.87). At the rule-out threshold (probability < 0.20), sensitivity was 85.9% with NPV 90.1%. In external validation (Delhi SLD prevalence 54.9%), AUC was 0.769 (0.751–0.783) — ΔAUC −0.008 — with calibration slope 0.96. Sex-stratified discrimination was preserved (women 0.790, men 0.749). **Conclusion:** The ABCD score is the first fully laboratory-free, sex-specific SLD prediction model externally validated in South Asia. Discrimination matches laboratory-based steatosis tools and substantially outperforms fibrosis-focused alternatives misapplied for steatosis screening. The model provides a transferable framework for MASLD screening across LMIC primary care, deployable by frontline health workers (e.g., India's Auxiliary Nurse Midwives and ASHAs) via mobile application. It offers a scalable pathway to identifying an estimated 300 million Indians with undiagnosed SLD, extensible to other LMIC settings facing similar laboratory-access constraints.



Disclosures: Kanica Kaushal: Nothing to Disclose, Harsh Tevethia: Nothing to Disclose, Manoj Sharma: Nothing to Disclose, Aditya Chaturvedi: Nothing to Disclose, GURESH KUMAR: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose.

★ 0278 | COMPARISON OF ENDOSCOPIC ULTRASOUND-GUIDED VERSUS PERCUTANEOUS LIVER BIOPSY: A SYSTEMATIC REVIEW AND META-ANALYSIS

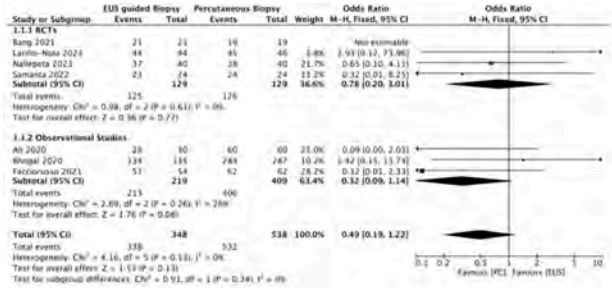
Ramsha Khan[1] Sunil Samnani[1] Moneer mohammed[1] Abdulrahman Bassam[1] Muhammad Anas Fazal[2] Matthew Collins[1] Rhea Thomas[1], [1]McMaster University, [2]University of Alberta

Background: Liver biopsy is critical for diagnosing, staging, and managing liver diseases such as fibrosis, cirrhosis, and malignancy. The traditional

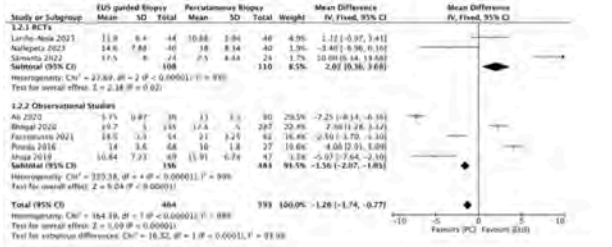
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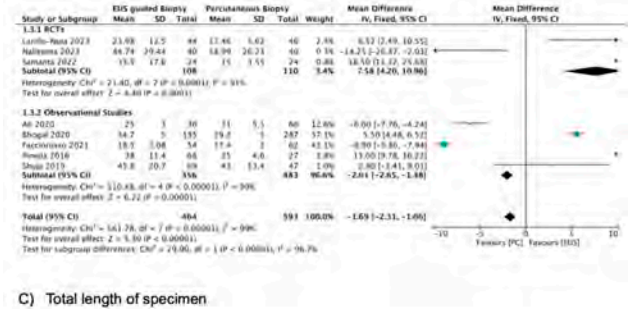
percutaneous (PC) approach is common but may cause pain, complications, and variable specimen quality. Endoscopic ultrasound-guided (EUS) liver biopsy has emerged as a minimally invasive alternative. **Aim:** To compare EUS-guided and PC liver biopsies regarding diagnostic adequacy, complete portal tracts, total specimen length, adverse events, and post-procedure pain. **Methods:** A systematic review and meta-analysis was conducted following PRISMA guidelines. Databases including Medline, Embase, and CENTRAL were searched from inception to November 2025. Randomized controlled trials (RCTs) and observational studies directly comparing EUS and PC liver biopsies were included. Primary outcomes were diagnostic adequacy. Secondary outcomes included number of complete portal tracts, total biopsy specimen length, and pain score at 1 hour post-procedure. Data were pooled using fixed- or random-effects models based on heterogeneity (I2), with subgroup analyses by study design. **Results:** Nine studies were included (4 RCTs, 5 observational), encompassing 1097 procedures (485 EUS, 612 PC). Overall, diagnostic adequacy was comparable (OR 0.49, 95% CI 0.19-1.22, P = 0.13, I2 = 0%). In sensitivity analysis by study design, observational studies showed favoritism toward PC (OR 0.12, 95% CI 0.03-0.43), while RCTs showed no significant difference (OR 0.78, 95% CI 0.20-3.01), with a significant test for subgroup differences (P = 0.04). Adverse events were similar overall (OR 0.57, 95% CI 0.14-2.36, P = 0.44, I2 = 68%), with few events reported. EUS significantly reduced pain scores at 1-hour post-procedure overall (MD -2.01, 95% CI -2.47 to -1.55, P < 0.00001, I2 = 88%). Sensitivity analysis revealed a smaller reduction in RCTs (MD -1.00, 95% CI -1.82 to -0.18, P = 0.02) compared to observational studies (MD -2.75, 95% CI -3.07 to -2.43, P < 0.00001), with a significant subgroup difference (P = 0.003). PC provided more complete portal tracts overall (MD -1.49, 95% CI -2.31 to -0.67, P = 0.0004, I2 = 99%). Similarly, PC yielded longer biopsy specimens overall (MD -1.26, 95% CI -1.74 to -0.77, P < 0.00001, I2 = 98%). **Conclusion:** EUS-guided liver biopsy demonstrates similar diagnostic adequacy and adverse event rates to PC, with superior post-procedure pain control. While PC may yield higher-quality specimens overall, sensitivity analyses highlight discrepancies by study design, with observational studies favoring PC and RCTs showing neutral or EUS-favoring results, suggesting potential selection bias in observational data. EUS may be preferable for patients prioritizing comfort, but further high-quality RCTs are needed to resolve discrepancies.



A) Diagnostic adequacy



B) Number of Complete Portal Tracts



C) Total length of specimen

Disclosures: Ramsha Khan: Nothing to Disclose, Sunil Samnani: Nothing to Disclose, Moneer mohammed: Nothing to Disclose, Abdulrahman Bassam: Nothing to Disclose, Muhammad Anas Fazal: Nothing to Disclose, Matthew Collins: Nothing to Disclose, Rhea Thomas: Nothing to Disclose.

0279 | PREVALENCE AND PREDICTORS OF RECURRENT HELLP SYNDROME: A MULTICENTER RETROSPECTIVE STUDY ACROSS THREE HOSPITAL SYSTEMS

Jacqueline Slobin[1] Elina Stoffel[2] Clara McNatt[3] Nina Rodriguez[1] Lauren Alpert[1] Rhoda Sperling[1] Keith Sigel[1] Tatyana Kushner[3], [1]Icahn School of Medicine at Mount Sinai, [2]Vagelos College of Physicians and Surgeons, Columbia University, and New York-Presbyterian Hospital, [3]Weill Cornell Medicine

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Background: Hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome is a life-threatening obstetric complication. Despite its clinical significance, the risk of HELLP syndrome recurrence in subsequent pregnancies remains incompletely understood. Identifying reliable predictors of recurrent HELLP syndrome is critical for preconception counseling, antenatal surveillance planning, and risk stratification in subsequent pregnancies. **Methods:** We conducted a retrospective cohort study at three large academic medical centers in New York City. We included patients diagnosed with HELLP syndrome in their index pregnancy who subsequently had another pregnancy. Index cases of HELLP were identified by diagnosis codes and were verified by clinical notes and laboratory values in the electronic health record; recurrence was determined based on clinical notes. Data on demographics, medical history, laboratory results, and pregnancy outcomes were extracted via chart review. Wilcoxon rank sum tests, Fisher's exact tests, and Firth's penalized logistic regression were performed. **Results:** Of 853 patients identified with a HELLP diagnosis code, 91 delivered a subsequent singleton pregnancy. Mean age of 32.5 years (SD 5.6) at their index pregnancy and 35.3 years (SD 5.4) at the subsequent pregnancy; mean pre-pregnancy BMI was 24.4 kg/m2. The cohort was 63% White, 18% Hispanic, 6.7% Black and 4.4% Asian. Twelve patients (13.2%) received a clinical diagnosis of HELLP recurrence in a subsequent pregnancy. Among these patients, mean age was 31 at index pregnancy and 33 at subsequent pregnancy; 8 (67%) were White, 2 (17%) were Hispanic, and 2 (17%) were Black. Three (25%) had chronic hypertension. Of 6 patients with a pregnancy prior to their index pregnancy, 3 (50%) had a history of preeclampsia. In univariate analyses, peak ALT ($p = 0.014$) and peak AST ($p = 0.030$) during the index pregnancy were higher among patients with recurrence, whereas peak LDH and minimum platelet count did not significantly differ (Table). In Firth's penalized logistic regression adjusting for chronic hypertension and inter-pregnancy interval, higher peak ALT during the index pregnancy was associated with increased odds of recurrence (OR 1.67 per doubling of ALT; 95% CI 1.04-2.98; $p = 0.035$; AUC 0.79). **Conclusion:** In this multicenter cohort, HELLP recurred in approximately 13% of subsequent pregnancies, and higher peak ALT and AST during the index pregnancy was associated with recurrence. These preliminary findings suggest that index-pregnancy transaminase levels may warrant further investigation as a potential marker of recurrence risk. These findings should be validated in larger cohorts to help clinicians risk-stratify patients with a history of HELLP syndrome and provide more individualized preconception counseling.

Table 1. Summary of Patient Cohort

Characteristic	Overall N = 90¹	No Recurrence N = 78¹	HELLP Recurrence N = 12¹	p-value²
DEMOGRAPHICS				
Age, index pregnancy	32.5 (5.6)	32.8 (5.6)	30.5 (5.2)	0.220
Age, subsequent pregnancy	35.0 (32.0, 39.0)	35.5 (33.0, 39.0)	33.5 (27.5, 37.5)	0.155
Race				0.382
White	57 (63%)	49 (63%)	8 (67%)	
Black	6 (6.7%)	4 (5.1%)	2 (17%)	
Asian	4 (4.4%)	4 (5.1%)	0 (0%)	
Other	23 (26%)	21 (27%)	2 (17%)	
Ethnicity				0.851
Non-Hispanic	69 (77%)	60 (77%)	9 (75%)	
Hispanic	16 (18%)	14 (18%)	2 (17%)	
Other	5 (5.6%)	4 (5.1%)	1 (8.3%)	
Pre-pregnancy BMI	23.5 (4.2)	23.5 (4.2)	23.6 (4.9)	0.978
Inter-pregnancy interval (months)	30 (22, 41)	30 (24, 44)	24 (17, 33)	0.108
PAST MEDICAL HISTORY				
Hypertension	8 (8.9%)	5 (6.4%)	3 (25%)	0.070
Autoimmune disease	3 (3.3%)	3 (3.8%)	0 (0%)	>0.999
Hypercoagulable Condition*	6 (6.7%)	4 (5.1%)	2 (17%)	0.181
Smoking history	11 (12%)	8 (10%)	3 (25%)	0.161
PREGNANCY HISTORY PRIOR TO INDEX PREGNANCY				
Pregnancy prior to HELLP diagnosis	29 (32%)	23 (29%)	6 (50%)	0.190
Gestational hypertension	2 (8.3%)	1 (5.6%)	1 (17%)	0.446
Preeclampsia	4 (17%)	1 (5.6%)	3 (50%)	**0.035**
Gestational diabetes	1 (4.2%)	0 (0%)	1 (17%)	0.250
INDEX PREGNANCY CHARACTERISTICS				
Gestational age at delivery (days)	260 (234, 276)	265 (235, 276)	252 (219, 260)	0.095
Timing of HELLP diagnosis				0.151
Very preterm (< 34 weeks)	24 (27%)	20 (26%)	4 (33%)	
Preterm (34-37 weeks)	18 (20%)	14 (18%)	4 (33%)	
Term (> 37 weeks)	45 (50%)	42 (54%)	3 (25%)	
Postpartum	3 (3.3%)	2 (2.6%)	1 (8.3%)	
Mississippi criteria fulfilled	27 (33%)	21 (30%)	6 (55%)	0.165
Peak ALT	237 (102, 385)	207 (95, 339)	366 (239, 620)	**0.014**
Peak AST	183 (92, 355)	175 (90, 335)	379 (198, 418)	**0.030**
Peak LDH	446 (336, 688)	445 (336, 660)	688 (326, 727)	0.554
Minimum platelets	82 (58, 106)	79 (58, 104)	100 (54, 120)	0.491
Preeclampsia or eclampsia	66 (73%)	59 (76%)	7 (58%)	0.291
Gestational diabetes mellitus	5 (5.6%)	5 (6.4%)	0 (0%)	>0.999
Gestational hypertension	15 (17%)	14 (18%)	1 (8.3%)	0.682
In vitro fertilization	14 (16%)	12 (15%)	2 (17%)	>0.999
Delivery mode				0.750
Vaginal	32 (36%)	27 (35%)	5 (42%)	
Cesarean	57 (64%)	50 (65%)	7 (58%)	
NICU admission	39 (44%)	32 (42%)	7 (58%)	0.356
Stillbirth	3 (3.4%)	3 (3.9%)	0 (0%)	>0.999
Neonatal death	2 (2.3%)	2 (2.6%)	0 (0%)	>0.999
ICU admission	7 (7.9%)	6 (7.8%)	1 (8.3%)	>0.999
Acute kidney injury	9 (10%)	7 (9.0%)	2 (17%)	0.343
Disseminated intravascular coagulation	5 (5.6%)	4 (5.1%)	1 (8.3%)	0.520
Capsule rupture	2 (2.2%)	2 (2.6%)	0 (0%)	>0.999

¹Values are mean (SD), median (Q1, Q3), or n (%). Bold p-values indicate statistical significance ($p < 0.05$)
²Mean (SD): Median (Q1, Q3): n (%).
³Wilcoxon rank-sum test, Fisher's exact test.
*Includes antiphospholipid syndrome (APLS), Factor V Leiden, and deep vein thrombosis (DVT)

Disclosures: Jacqueline Slobin: Nothing to Disclose, Elina Stoffel: Nothing to Disclose, Clara McNatt: Nothing to Disclose, Nina Rodriguez: Nothing to Disclose, Lauren Alpert: Nothing to Disclose, Rhoda Sperling: Nothing to Disclose, Keith Sigel: Nothing to Disclose, Tatyana Kushner: Gilead: Grant/Research Support, Gilead: Advisor, GSK: Advisor, Eiger: Advisor, GSK: Consultant, Madrigal: Advisor, Ipsen: Advisor, Mirum: Advisor, Mirum: Grant/Research Support, Ipsen: Grant/Research Support.

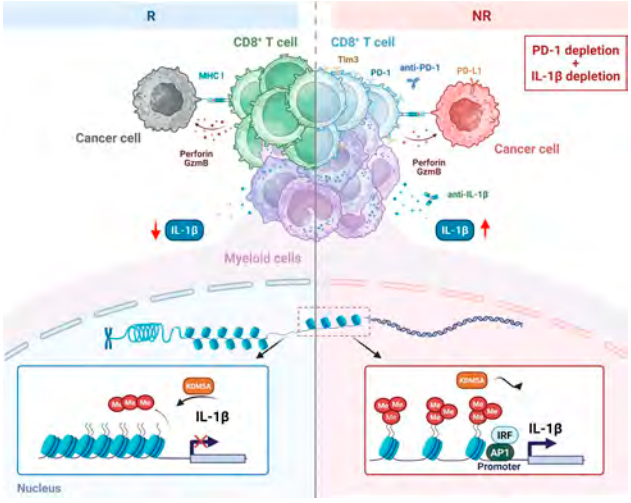
0280 | TARGETABLE IL1B-DRIVEN MYELOID INFLAMMATION MEDIATES RESISTANCE TO ANTI–PD-1 THERAPY IN HEPATOCELLULAR CARCINOMA

Wenying Qiao[1] Xiaoyan Ding[1] Xi Wang[1] Ronghua Jin[1],
[1]Beijing Ditan Hospital, Capital Medical University

Background: Although immune checkpoint inhibitors have reshaped the treatment landscape of advanced hepatocellular carcinoma (HCC), most patients fail to achieve durable benefit from programmed cell death protein 1 (PD-1) blockade. HCC is frequently sustained by chronic inflammation, yet how inflammatory myeloid programs are epigenetically activated and contribute to immunotherapy resistance remains poorly defined. We hypothesized that dysregulated IL1B-driven myeloid inflammation limits antitumor T-cell immunity and promotes resistance to PD-1 blockade. **Methods:** Baseline peripheral blood mononuclear cells from

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patients with advanced hepatitis B virus-related HCC receiving anti–PD-1 therapy were analyzed by single-cell and bulk RNA sequencing. Spatial transcriptomics and multiplex immunofluorescence were used to define the tissue distribution and immune context of IL1B-expressing myeloid cells. ATAC-seq and H3K4me3 ChIP-seq characterized chromatin accessibility and histone modification landscapes. Therapeutic relevance was evaluated in subcutaneous and orthotopic HCC models treated with anti–IL-1β, anti–PD-1, or their combination. **Results:** Integrated transcriptomic analyses identified a distinct IL1B$^+$ CD14$^+$ monocyte population enriched in non-responders to anti–PD-1 therapy and associated with heightened inflammatory activity. Spatial and multiplex immunofluorescence analyses confirmed accumulation of IL1B$^+$ myeloid cells within an immunosuppressive tumor microenvironment marked by impaired cytotoxic T-cell activity. Epigenomic profiling revealed increased chromatin accessibility and active H3K4me3 modification at the IL1B locus in non-responders. Mechanistically, KDM5A acted as an epigenetic brake on IL1B transcription by limiting H3K4me3 deposition and AP-1 recruitment at the IL1B promoter; this restraint was preserved in responders but disrupted in non-responders. Functionally, IL-1β promoted CD8$^+$ T-cell exhaustion, with increased PD-1 and TIM-3 expression and reduced cytotoxic activity. In both HCC models, combined IL-1β and PD-1 blockade suppressed tumor growth, reduced tumor-associated macrophage infiltration, and restored cytotoxic T-cell function more effectively than either monotherapy. **Conclusion:** Our findings reveal that anti–PD-1 resistance in HCC is not solely driven by T-cell exhaustion, but is actively shaped by epigenetically programmed IL1B$^+$ myeloid inflammation. Targeting IL-1β reprograms the immunosuppressive tumor microenvironment and restores sensitivity to PD-1 blockade, supporting dual IL-1β/PD-1 inhibition as a mechanistically grounded strategy for resistant HCC.



Disclosures: Wenying Qiao: Nothing to Disclose, Xiaoyan Ding: Nothing to Disclose, Xi Wang: Nothing to Disclose, Ronghua Jin: Nothing to Disclose.

0281 | PRACTICE CHALLENGES FACING ADVANCED PRACTICE PROVIDERS IN MANAGING MASLD PATIENTS ON RESMETIROM: EXPERIENCE OF A SINGLE NON-ACADEMIC, COMMUNITY-BASED LIVER CENTER

Anna Hefner[1] Ismael Hernandez[1] Noha Abdelgelil[1] Eric Storey[1] Maryam Yasso[1] Fatma Barakat[2] Tarek Hassanein[1], [1]Southern California Liver Centers, [2]SCTI Research Foundation

Background: Fatty liver is on the rise. It is accompanied with metabolic syndrome and patients (pts) are at risk for increased fibrosis and steatosis. Resmetirom is approved to improve fibrosis in MASLD pts with a fibrosis stage 2 or 3. GLP-1 prescribed to control diabetes or weight loss might lead to decreasing steatosis in the liver. Despite these advancements, there are several challenges clinical practices. Aim: describe practice challenges a single non-academic community-based liver center faces in managing predominantly Hispanic pts with MASLD. **Methods:** This is a retrospective analysis of MASLD pts who initiated resmetirom between December 2024 and May 2026. Management plan was set in consultation with hepatologists while follow up was done primarily by Advanced Practice Providers (APP). Pts were managed according to standardized and individualized management protocols. **Results:** APPs focused on working with the pt as a team and managing medication, adherence, clinical visits, nutrition, and exercise. The plan was adjusted as needed. Initial emphasis was on educating pts about MASLD being a silent disease, its progression, establishing/maintaining a healthy lifestyle utilizing diagrams and a liver model. The approach was kept simple. Reminders were sent to the pt about completing tasks. Clinic Visits: Pts were seen every 3 months. Reviewing how the pt perceived their health and felt, going over each medication and detailed review of results (e.g. labs, elastography, ELF, and iliac crest measurement) was critical to motivating the pt to continue with the care plan. Exercise: Having an attainable goal that did not cost anything e.g. walking continuously for 5 minutes and gradually increasing it over time, showing pts chair exercises, helping them find time during the day to exercise were useful in improving adherence to exercising. Nutrition: was culturally sensitive and material provided was mainly pictorial e.g. to show the kinds of foods to eat/try to avoid. Pts found them helpful to making healthy food

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choices. Medications: In addition to resmetirom, pts were typically prescribed GLP-1. However, health insurance denial was a major barrier in continuing these medications. Outcomes: 64% female. Mean age 60.7 years. 45.5% Hispanic. Refer to table for analysis of 1-year analysis data for 22 out of 161 pts. **Conclusion:** Real-world experience of a single non-academic community-based liver center confirmed that APPs are integral members of a liver pt's care team taking resmetirom. The cheer leading provided at visits and the simplicity of the education to build upon were assets. Pts who were able to see changes in their bodies or aren't as fatigued were more motivated to continue with the management plan. MASLD is a harmful silent disease but breaking it into doable lifestyle change pieces does encourage sustainable change. More individualized management is needed, especially in underserved population.

N=22	Baseline	1-year follow-up
FibroScan® kPa	9.7	6.7
FibroScan® CAP	277	273
AST	38.2	27.1
ALT	54.1	35.5
Alk Phosphate	97.5	99.4
T. Bili	0.67	0.62

Disclosures: Anna Hefner: Nothing to Disclose, Ismael Hernandez: Nothing to Disclose, Noha Abdelgelil: Nothing to Disclose, Eric Storey: Nothing to Disclose, Maryam Yasso: Nothing to Disclose, Fatma Barakat: Nothing to Disclose, Tarek Hassanein: AbbVie: Speaker and Research Support, Gilead: Speaker and Research Support, HepQuant Shunt: Advisor, Madrigal: Advisor and Research Support, Amgen: Grant/Research Support, Astra Zeneca: Grant/Research Support, Boehringer- Ingelheim: Grant/Research Support, COUR: Grant/Research Support, Escient: Grant/Research Support, Galectin: Grant/Research Support, Grifols: Grant/Research Support, Intercept: Grant/Research Support, Janssen: Grant/Research Support, Merck: Grant/Research Support, Mirum: Grant/Research Support, NeuroBo: Grant/Research Support, Novartis: Grant/Research Support, Novo Nordisk: Grant/Research Support, Pfizer: Grant/Research Support, Regeneron: Grant/Research Support, Salix Pharmaceuticals: Grant/Research Support, Takeda: Grant/Research Support, Akero: Grant/Research Support, Ipsen: Grant/Research Support, Kowa: Grant/Research Support, Bristol-Myers Squibb: Grant/Research Support, DURECT: Grant/Research Support, HepQuant: Grant/Research Support, Terns Pharmaceuticals: Grant/Research Support, Mallinckrodt: Speaker and Research Support, Eli Lilly: Grant/Research Support, PharmaIn: Grant/Research Support, Sonic incytes: Grant/Research Support, Tensor Bio: Grant/Research Support, 89Bio: Grant/Research Support, Terns Pharmaceuticals: Grant/Research Support, Nterica: Consultant, Atea: Grant/Research Support, Harbinger: Grant/Research Support, Sanofi-Aventis: Grant/Research Support, CurveBio: Grant/Research Support, AbbVie: Speaker and Research Support, Gilead: Speaker and Research Support, HepQuant Shunt: Advisor, Madrigal: Advisor and Research Support, Amgen: Grant/Research Support, Astra Zeneca: Grant/Research Support, Boehringer-Ingelheim: Grant/Research Support, COUR: Grant/Research Support, Escient: Grant/Research Support, Galectin: Grant/Research Support, Grifols: Grant/Research Support, Intercept: Grant/Research Support, Janssen: Grant/Research Support, Merck: Grant/Research Support, Mirum: Grant/Research Support, NeuroBo: Grant/Research Support, Novartis: Grant/Research Support, Novo Nordisk: Grant/Research Support, Pfizer: Grant/Research Support, Regeneron: Grant/Research Support, Salix Pharmaceuticals: Grant/Research Support, Takeda: Grant/Research Support, Akero: Grant/Research Support, Ipsen: Grant/Research Support, Kowa: Grant/Research Support, Bristol-Myers Squibb: Grant/Research Support, DURECT: Grant/Research Support, HepQuant: Grant/Research Support, Terns Pharmaceuticals: Grant/Research Support, Mallinckrodt: Speaker and Research Support, Eli Lilly: Grant/Research Support, PharmaIn: Grant/Research Support, Sonic incytes: Grant/Research Support, Tensor Bio: Grant/Research Support, 89Bio: Grant/Research Support, Terns Pharmaceuticals: Grant/Research Support, Nterica: Consultant, Atea: Grant/Research Support, Harbinger: Grant/Research Support, Sanofi-Aventis: Grant/Research Support, CurveBio: Grant/Research Support.

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1001 | ◆ A STABILIZED FORM OF β-CATENIN FACILITATES HEPATOCYTE-TO-CHOLANGIOCYTE TRANSDIFFERENTIATION IN AN ORGANOID MODEL AND IMPROVES INJURY IN A MOUSE MODEL OF CHOLESTATIC LIVER DISEASE

Tony (Chun-Cheng) Chiang[1] Pamela Cornuet[1] Kari Nejak-Bowen[1], [1]University of Pittsburgh

Background: Cholestatic liver diseases are characterized by impaired bile flow or bile acid-mediated damage to liver parenchyma. Hepatocyte-to-cholangiocyte transdifferentiation occurs in response to biliary injury and may repair damaged bile ducts. Our preliminary data showed that canonical Wnt/β-catenin signaling is increased during hepatocyte-to-cholangiocyte transdifferentiation. Therefore, we hypothesize that overexpression of β-catenin may augment hepatocyte-to-cholangiocyte transdifferentiation, alleviate biliary injury, and restore liver function. To test this, we used a 3D organoid derived from isolated primary hepatocytes to mimic bile duct paucity, as well as a transgenic mouse overexpressing β-catenin in a biliary injury model. **Methods:** For the organoid model, transgenic (TG) serine-45-aspartate-mutated (S45D) β-catenin and wild-type (WT) mice were crossed with Rosa26-stopf/f-EYFP mice, respectively. After AAV8-TBG-Cre injection, these hepatocytes were labeled with EYFP. Mouse livers were perfused to isolate hepatocytes, which were then seeded in a collagen-precoated pleated bottle. Each bottle contains medium with specific growth factors essential for transdifferentiation. Organoids were harvested on day 21 of culture for downstream analysis.For the mouse model, TG S45D β-catenin mice bred to an mdr2 knockout, mdr2 knockout alone (KO), and their wildtype littermates, all carrying Rosa26-stopf/f-EYFP alleles, were injected with AAV8-TBG-Cre to label hepatocytes and sacrificed at various timepoints. Serum biochemical markers of liver injury were assessed. Livers were studied for histopathology, and ductular proliferation was quantified by CK19 immunohistochemistry. Hepatocyte-to-cholangiocyte transdifferentiation was traced by Sox9 and EYFP immunofluorescence staining. **Results:** Cholangiocyte-like cells and ductular structures were seen in hepatocyte organoids. Lineage tracing demonstrated that these cholangiocyte-like cells originated from hepatocytes, confirming transdifferentiation. TG organoids had a greater number of mature, HNF4a-negative cholangiocyte-like cells than WT organoids. Serum biochemistry showed that TG β-catenin reduces liver injury in KO mice. Histopathology revealed inflammation, fibrosis, and ductular reaction in KO mice, which were ameliorated in TG mice. Immunofluorescence staining showed more EYFP+ cholangiocytes and Sox9+ hepatocytes in the periportal zone of TG mice with a KO background than in KO alone mice, indicating that transdifferentiation increased when β-catenin was overexpressed in hepatocytes. **Conclusion:** S45D β-catenin enhanced hepatocyte-to-cholangiocyte transdifferentiation in organoids. TG S45D β-catenin slowed injury progression and increased transdifferentiation in mdr2 KO mice. Based on these findings, we plan to use both biased and unbiased approaches in the future to elucidate further mechanisms.

Disclosures: Tony (Chun-Cheng) Chiang:Nothing to Disclose, Pamela Cornuet:Nothing to Disclose, Kari Nejak-Bowen:Surrozen, Inc.: Consultant.

1002 | ◆ ENDOTHELIAL-SPECIFIC ARYL HYDROCARBON RECEPTOR (AHR) DELETION DRIVES A FULLY PENETRANT MURINE MODEL OF PORTOSYSTEMIC SHUNT AND HEPATOCARCINOGENESIS

Sadhana Sah[1] Piu Saha[1] Matam Vijay-Kumar[1] Beng San Yeoh[1], [1]University of Toledo

Background: Portosystemic shunt (PSS) is a vascular abnormality that diverts portal blood away from the liver into the systemic circulation, impairing hepatic clearance of gut-derived metabolites. In humans, PSS is associated with hepatic encephalopathy, metabolic dysfunction, and hepatocellular carcinoma (HCC). Our prior studies showed that spontaneous congenital PSS in C57BL/6J mice predisposes to cholestatic liver injury and HCC when fed on a purified diet supplemented with inulin (a fermentable fiber). However, the low penetrance of spontaneous PSS limits mechanistic investigation. Here, we assessed PSS incidence in an endothelial-specific aryl hydrocarbon receptor knockout mouse model (*Ahr*fl/fl;*Cdh5*-Cre) and assess its susceptibility to diet-induced liver injury and HCC.

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Methods: Male *Ahr*fl/fl;*Cdh5*-Cre mice and *Ahr*fl/fl littermate controls were evaluated for biochemical, metabolic, and histopathologic features of PSS. Serum bile acids, lipid profiles, glucose tolerance, and insulin sensitivity were measured. To induce liver injury and HCC, mice were fed an inulin-containing purified diet (ICD; 7.5% w/w) for 7 days or 6 months. A separate cohort was fed a high-fat diet (HFD) for 6 months. In addition, another group of ICD-fed mice was treated with D-galactosamine (20 mg/mouse, intraperitoneally) to assess susceptibility to acute liver injury. **Results:** *Ahr*fl/fl;*Cdh5*-Cre mice exhibited 100% penetrance of congenital PSS and demonstrated hallmark features including severe cholemia, hypolipidemia, enhanced glucose and insulin tolerance, and liver atrophy. When compared to non-PSS *Ahr*fl/fl controls, *Ahr*fl/fl;*Cdh5*-Cre mice exhibited hepatic inflammation, ductular reaction, and arteriole thickening consistent with chronic cholestatic injury. Short-term ICD feeding induced cholestatic hepatitis characterized by elevated serum transaminases, bilirubin, and bile acids, whereas prolonged ICD feeding for 6 months resulted in multifocal HCC exclusively in *Ahr*fl/fl;*Cdh5*-Cre mice and not *Ahr*fl/fl controls. *Ahr*fl/fl;*Cdh5*-Cre mice fed HFD for 6 months, however, did not develop HCC despite developing hepatic steatosis. D-galactosamine treatment, on the other hand, induced markedly more severe fulminant hepatic failure in *Ahr*fl/fl;*Cdh5*-Cre mice compared with *Ahr*fl/fl controls. **Conclusion:** Endothelial AHR deletion in mice engenders a fully penetrant congenital PSS that recapitulates key features of PSS-associated liver disease. Chronic exposure to dietary fermentable fiber, but not a high-fat diet, induced cholestatic injury and HCC development in this model. Together, these findings identify disrupted portal circulation and diet-dependent metabolic stress as drivers of HCC pathogenesis, and establish *Ahr*fl/fl;*Cdh5*-Cre mice as a tractable preclinical model for studying PSS-associated liver disease.

Disclosures: Sadhana Sah:Nothing to Disclose, Piu Saha:Nothing to Disclose, Matam vijay-kumar:Nothing to Disclose, Beng San Yeoh:Nothing to Disclose.

★ 1003 | ◆ TOLEROGENIC KLF2-EXPRESSING T CELLS CONFER PROTECTION IN A PRECLINICAL MODEL OF PRIMARY SCLEROSING CHOLANGITIS

Abigail Russi[1] Abigail Detloff[1] Dena Acton[1] Brian DeBosch[1], [1]Indiana University School of Medicine

Background: Commensal tolerance is critical to restraining aberrant inflammation in the intestines and requires a population of suppressive IL-10-producing CD4 T cells defined by Küppel-like transcription factor 2 (KLF2) and CD44 expression. This population of "Tk cells" functions independently from FOXP3+ T regulatory cells and KLF2-mediated sphingosine-1-phosphate receptor 1 (S1PR1) trafficking to selectively avert Th17-driven intestinal inflammation. Questions remain as to how Tk cells alter susceptibility and tolerance throughout the gut-liver axis. **Methods:** These experiments utilize established mouse immunology tools (flow cytometry analysis and sorting, histology, ELISA, qRT-PCR, magnetic T cell isolation and adoptive transfer) while simultaneously employing preclinical modeling of PSC using 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC). DDC induces an ascending cholangitis with biliary fibrosis and associated low-level intestinal inflammation, recapitulating the key aspects of human PSC. Comparison and figure generation of *KLF2*, *CD44*, *IL10*, and *S1PR1* gene expression in liver biopsies from patients with PSC compared to healthy (NDD) controls was obtained from the publicly available dataset from *Andrews et al.* (PMID: 38199298). **Results:** *In vitro* co-culture assays demonstrate that Tk cells maintain robust suppression of responder CD4 T cell proliferation and cytokine production under both Th17 and Th1 conditions (**Fig. 1A,B**). Notably, congenic adoptive transfer experiments confirm that Tk cells *selectively* avert aberrant Th17 inflammation *in vivo* (**Fig. 1C,D**). Importantly, IL-10 production by Tk cells is maintained under Th17 conditions (**Fig. 1E**) and Tk-derived IL-10 is critical for IL-17 suppression (**Fig. 1F**). In DDC-induced PSC, mice exhibit pathognomonic "onion-skinning" biliary fibrosis (**Fig. 2A)** and accumulate Tk cells in the livers (**Fig. 2B**). *KLF2* and *CD44* signatures significantly increase in the T cell population within the livers of patients with PSC compared to control patients, as does *IL10*. Importantly, *SIPR1* does not significantly change suggesting that this change is independent of KLF2-mediated S1PR1-dependent T cell trafficking (**Fig. 2C**). Tk-deficient mice (CD4CreKLF2FF) exhibit more severe weight loss, increased direct bilirubin, and increased alkaline phosphatase compared to their DDC-treated Cre-negative littermate controls (**Fig. 2D-F**). **Conclusion:** KLF2 identifies a new suppressive lineage of IL10-producing CD4 T (Tk) cells that selectively regulates Th17-driven aberrant inflammation in the gut-liver axis. We propose that Tk cells maintain tolerance throughout the gut-liver as their absence exacerbates cholestatic liver disease. Immediate next steps will utilize adoptive transfer, inducible Cre-mediated Tk cell depletion, and microbiota-dependent disease models to interrogate the protective mechanisms of Tk cells in the immunopathogenesis of PSC.

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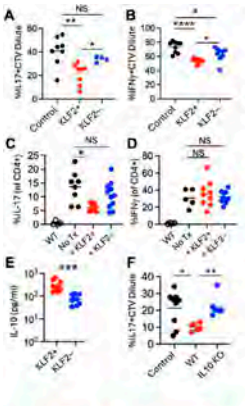


Fig. 1: Tk cells selectively suppress Th17 inflammation via IL-10. **(A,B)** Percent of responder CD4 T cells expressing canonical cytokine or cell-trace violet (CTV) dilution (indicating proliferation) after 4 day co-culture with KLF2+CD44+ Tk cells or KLF2-CD44+ T cells compared to control responder splenocytes alone under Th17 (A) or Th1 (B) polarizing conditions. **(C,D)** Percent of endogenous recipient CD4 T cells in secondary lymphoid organs expressing IL-17 **(C)** or IFNg **(D)** after adoptive transfer (Tx). **(E)** IL-10 concentration measured by ELISA after 2 day activation with αCD3/αCD28. **(F)** *In vitro* suppression assay as in (A,B) comparing wildtype (WT) Tk cells to IL10 KO Tk cells. (A-B, E-F) n= 3 independent experiment with duplicate wells show. (C,D) n=3 exps with individual mice shown. *p<0.05, **p<0.01, ***p<0.001,****p<0.0001 by unpaired Student's t test.

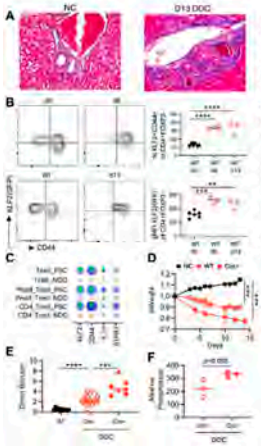


Fig. 2: Tk cells confer protection in DDC-induced primary sclerosing cholangitis (PSC). Mice were fed chow supplemented with 0.05% DDC for 6 or 13 days as noted. **(A)** Liver histology with trichrome stain in WT mice +/- DDC. **(B)** Representative flow cytometry plots and quantification of Tk cells in the livers of DDC-treated dual reporter mice. **(C)** Analysis of publicly available single cell sequencing dataset for genes of interest (Andrews et al). Size of dot indicative of proportion of positive cells, green asterisk indicative of statistically differs from control liver (NDD). **(D)** Weight loss, **(E)** serum direct bilirubin, and **(F)** serum alkaline phosphatase of Tk-deficient ($CD4^{Cre}KLF2^{f/f}$) mice fed 0.05% DDC compared to their Cre-negative littermate controls. For (A-B), n=2 experiments with individual mice shown. For (D-F), n= 1 experiment with error bars representing SEM (D) or individual mice shown (E,F). Serum alkaline phosphatase ran on a cohort with sufficient serum remaining after direct bilirubin assay. **p<0.01, ***p<0.05, ****p<0.0001 by unpaired Student's t test (B, E) or ***p<0.001 by one-way Anova (D).

Disclosures: Abigail Russi:Nothing to Disclose, Abigail Detloff:Nothing to Disclose, Dena Acton:Nothing to Disclose, Brian DeBosch:Nothing to Disclose.

1004 | DECREASED YAP/TAZ COPY NUMBER LEADS TO TARGETED SMALL BILE DUCT LOSS

Laura Molina[1] Jia-Jun Liu[2] Shuchang Liu[3] Adelya Gabdulkhakova[4] Sungjin Ko[3] Satdarshan (Paul) Monga[3] Kari Nejak-Bowen[3], [1]University of Pittsburgh Medical Center, [2]University of Pittsburgh School of Medicine, [3]University of Pittsburgh, [4]University of Heidelberg

Background: We showed that deleting Yes-associated protein 1 (Yap) in early liver development leads to failure of intrahepatic bile duct development, and that its paralog TAZ could not compensate in the formation of ducts but influenced the inflammatory response in these livers. We next determined that reduced copy numbers of YAP and TAZ result in a gradual loss of small bile ducts reminiscent of vanishing bile duct injury or primary biliary cirrhosis. **Methods:** We deleted Yap and Taz during early liver development using the Foxa3 promoter to drive Cre expression. We examined male and female mice with the range of 0-4 functional copies of Yap and Taz combined, using microscopy, serum biochemistry, and single-nucleus RNA sequencing. **Results:** Our data shows that if there are two functional alleles of Yap, regardless of the status of Taz, the bile ducts will be formed properly. If there is only one functional allele of Yap, bile ducts will still be formed properly if there is at least one functional allele of Taz. However, if there is only one functional allele of Yap and no functional alleles of Taz (TKYH mice), the bile ducts will mostly form during prenatal development but will be gradually lost over the first 1-3 months of the mouse's life. These mice develop severe cholestasis over the first 3-4 months of life. This loss begins with the smallest ducts and spreads toward the hilum of the liver, accompanied by a largely lymphocytic immune reaction. The large bile ducts, hilum, and extrahepatic biliary tree are preserved, and there is some expansion of large bile ducts which preserves the overall ratio of bile ducts per portal vein despite the geographic loss of peripheral bile ducts. Single-nucleus RNA-sequencing demonstrates significant changes in cholangiocyte signaling and communication with endothelial cells, Kupffer cells, hepatic stellate cells and T cells, especially through extracellular matrix components, integrin signaling, and angiogenetic cytokine production. **Conclusion:** We show that Taz is essential for the stability and survival of murine bile duct when the function of Yap is hampered. The phenotype of TKYH mice shows features of diseases like vanishing bile duct syndrome, intrahepatic biliary atresia, primary biliary cirrhosis, and other conditions where small bile ducts are preferentially injured, such as drug-induced liver injury or ischemic injury to transplanted livers. This model illustrates molecular mechanisms that may drive the loss of small bile ducts and can be targeted to prevent or slow progression of human disease.

Disclosures: Laura Molina:Nothing to Disclose, Jia-Jun Liu:Nothing to Disclose, Shuchang Liu:Nothing to Disclose, Adelya Gabdulkhakova:Nothing to Disclose, Sungjin Ko:Nothing to Disclose, Satdarshan (Paul) Monga:Vicero Inc.: Advisor, Alnylam: Grant/Research Support, Alnylam: Consultant, Vicero: Advisor, UbiquiTx: Consultant, Alnylam: Grant/Research Support, Alnylam: Consultant, UbiquiTx: Consultant, Revolution Medicines: Grant/Research Support, Antlera: Advisor, Vicero Inc.: Advisor, Alnylam: Grant/Research Support, Alnylam: Consultant, Vicero: Advisor, UbiquiTx: Consultant, Alnylam: Grant/Research Support, Alnylam: Consultant, UbiquiTx: Consultant, Revolution

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Medicines: Grant/Research Support, Antlera: Advisor, Kari Nejak-Bowen:Surrozen, Inc.: Consultant.

1005 | CHOLECYSTECTOMY BLUNTS THE RESPONSE TO GLP1 RECEPTOR AGONISTS IN TYPE 2 DIABETES: A PROPENSITY MATCHED REAL WORLD ANALYSIS

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Background: GLP1 receptor agonists (GLP1 RAs) transformed type 2 diabetes mellitus (T2DM) management but continues to elevate biliary risk, often necessitating cholecystectomy. Whether prior cholecystectomy alters GLP1 RA effectiveness remains unknown, despite plausible disruption of bile acid signaling through FXR/TGR5 pathways. As such, we aimed to determine whether prior cholecystectomy modifies metabolic, hepatobiliary, and cardiovascular outcomes during GLP1 RA therapy **Methods:** Within the TriNetX US Collaborative Network (65 HCOs), adults with Type 2 Diabetes Mellitus on any GLP1 RA were stratified by prior cholecystectomy (performed ≥ 1 month before GLP1 initiation) versus none. After 1:1 propensity score matching on demographics, comorbidities (hypertension, hyperlipidemia, CKD, ASCVD, HF, MASLD, NASH, obesity), and concomitant medications (insulin, metformin, statins), **29,087 cholecystectomy-exposed patients were matched 1:1 to 29,087 unexposed patients** drawn from a pre-matching pool of 1,299,852. All baseline standardized differences fell below 0.05 after matching. Risk and Cox hazard ratios were also computed. **Results:** Cholecystectomy significantly blunted metabolic response: HbA1c $<7\%$ attainment fell from 37.4% to 35.9% (RR 0.96; $p=0.043$) and BMI <30 from 14.7% to 13.4% (RR 0.91; $p<0.001$). Hepatobiliary risk rose sharply: choledocholithiasis nearly doubled (HR 2.13, 1.36 to 3.33) and expectedly, postcholecystectomy syndrome rose fourfold (HR 4.18, 2.48 to 7.03; both $p<0.001$); acute cholecystitis collapsed (HR 0.21). Strikingly, cholecystectomy patients showed a 30% reduction in all cause mortality (HR 0.84; $p<0.001$), 18% lower stroke (RR 0.82; $p<0.001$), and 10% lower myocardial infarction (RR 0.90; $p=0.016$). Earlier signals for pancreatitis and bariatric surgery vanished after matching, exposing baseline metabolic burden as their true driver. **Conclusion:** Prior cholecystectomy alters GLP1 outcomes, revealing a 'cholecystectomy paradox', attenuated metabolic efficacy alongside amplified hepatopancreatic risk, likely reflecting disrupted bile acid mediated FXR/TGR5 signaling. It also confers substantial mortality and cardiovascular benefit, establishing cholecystectomy as a meaningful pharmacotherapy modifier in T2D that mandates routine surgical history elicitation before GLP1 initiation, recalibrated counseling on glycemic and weight targets, and heightened biliary vigilance. Future studies should evaluate bile acid sequestrants and FXR/TGR5 modulators as adjuncts to restore GLP1 efficacy, and validate these findings in independent EHR networks with longer follow up. Interpretation is tempered by the retrospective EHR design, which limits causal inference; residual confounding and medication adherence cannot be fully excluded.

Disclosures: Emeka Stanley Obi:Nothing to Disclose, chimezirim ezeano:Nothing to Disclose, IFELUNWA OSANAKPO:Nothing to Disclose, Gedion Amdetsion: Nothing to Disclose, Joshua Kalu:Nothing to Disclose, Nothing to Disclose, Adedeji Adenusi:Nothing to Disclose, Bright Nwatamole:Nothing to Disclose, Abdulrahman Atasi:Nothing to Disclose, Anthony Martinez: Gilead: Consultant, Gilead: Speaking and Teaching, Abbvie: Consultant, Abbvie: Speaking and Teaching, Arbutus: Consultant, Braeburn: Speaking and Teaching, Sirtex: Consultant, Roche: Consultant, Syneos/VBI: Consultant, Madrigal: Speaking and Teaching, Altimune: Consultant, Madrigal: Consultant, Ipsen: Consultant, novo: Speaking and Teaching, atea: Consultant, cepheid: Consultant.

★ 1006 | CHOLANGIOCYTE STEAROYL-COA DESATURASE (SCD) ISOFORMS HAVE PARADOXICAL ROLES IN BILIARY INFLAMMATION

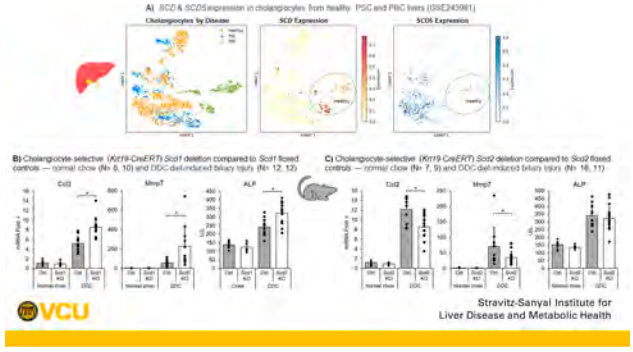
Sayed Obaidullah Aseem[1] Ahmed Younis[1] Grayson Way[1] Derrick Zhao[1] Yunling Tai[1] Xuan Wang[1] Emily Gurley[1] Phillip Hylemon[1] Nidhi Jalan-Sakrikar[2] Robert Huebert[2] Saul Karpen[3] Arun Sanyal[1] Huiping Zhou[1], [1]Virginia Commonwealth University, [2]Mayo Clinic

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Rochester, [3]VCU Stravitz-Sanyal Institute for Liver Disease and Metabolic Health

Background: Cholangiocytes orchestrate signaling that drives biliary inflammation in cholangiopathies including primary sclerosing cholangitis (PSC) and primary biliary cholangitis (PBC). These inflammatory signals require metabolomic remodeling, mediated in part by stearoyl-CoA desaturase (SCD), the rate-limiting Δ9-desaturase and central hub of lipid metabolism with a critical role in fibroinflammatory signaling. Here, we investigated distinct *SCD* isoforms (human: *SCD1*, *SCD5*; mouse *Scd1*, *Scd2*) in cholangiocytes to elucidate the molecular and metabolomic mechanisms of biliary inflammation. **Methods:** PSC and PBC transcriptomic databases (GSE243981) were interrogated using the Biomni Lab AI tool and independently verified in R (v4.3.3) with Seurat (v5.1.0). *In vitro*, human H69 cholangiocytes underwent siRNA knockdown of *SCD1* or *SCD5*. *In vivo*, cholangiocyte-selective *Scd1* and *Scd2* knockout (KO) mice were generated by crossing floxed strains with *Krt19*-Cre*ERT* mice. KO mice and respective floxed controls were challenged with an intermittent 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC) diet for 24 days; hepatic markers of inflammation, serum injury enzymes, and lipid profiles were evaluated. **Results:** Transcriptomic analysis revealed a 3.2- and 4.6-log fold decrease in *SCD1* expression in PSC and PBC cholangiocytes, respectively, compared to healthy controls (FDR <0.05). Conversely, *SCD5* transcript detection increased from 4% in controls to 27% and 48% in PSC/PBC cholangiocytes, correlating significantly with *MMP7*, *CCL2*, epithelial-mesenchymal transition, and WNT/β-catenin signaling. Mdr2$^{-/-}$ and DDC-fed mouse cholangiocytes showed analogous *Scd1* downregulation and *Scd2* upregulation. In H69 cells, *SCD1* knockdown ($\geq$95%) significantly amplified TNFa-stimulated *CCL2* expression by 2.3-fold, whereas *SCD5* knockdown ($\geq$92%) significantly attenuated basal and LPS-induced *CCL2* expression. Consistently, *Scd1* KO mice on the DDC diet exhibited significantly elevated hepatic *Ccl2*, *Mmp7* and *Tnfa* compared to controls, with significantly increased serum ALP, but not ALT (N = 12 KO, 12 control). Conversely, *Scd2* KO mice showed significantly reduced expression of these inflammatory genes, without a significant change in serum ALP or ALT (N = 18 KO, 11 control). Serum total cholesterol significantly increased in both DDC-fed KO models; only *Scd1* deficiency significantly reduced serum triglycerides, consistent with known Scd1 function. **Conclusion:** These findings support divergent, paradoxical roles for cholangiocyte *SCD* isoforms in regulating biliary inflammation and lipid metabolism. Further investigation of the isoform-specific molecular and lipidomic mechanisms will provide critical insights into the pathogenesis and therapeutic targeting of cholestatic liver diseases.



Disclosures: Sayed Obaidullah Aseem:Galmed Pharmaceuticals: Grant/Research Support, Gilead pharma: Consultant, Ahmed Younis:Nothing to Disclose, Grayson Way:Nothing to Disclose, Derrick Zhao:Nothing to Disclose, Yunling Tai:Nothing to Disclose, Xuan Wang: Nothing to Disclose, Emily Gurley:Nothing to Disclose, Phillip Hylemon:Nothing to Disclose, Nidhi Jalan-Sakrikar:Nothing to Disclose, Robert Huebert:Nothing to Disclose, Saul Karpen:Albireo/Ipsen: Consultant, Mirum: Consultant, Intercept: Consultant, Arun Sanyal:Nothing to Disclose.

1007 | FGFR SIGNALING IN PROM1-EXPRESSING LIVER PROGENITORS ACCELERATES FIBROINFLAMMATORY DUCTULAR REACTION AND LIVER FIBROSIS DURING CHRONIC CHOLESTATIC LIVER INJURY

Mallikarjuna Siraganahalli Eshwaraiah[1] Jiaohong Wang[1] Ying Li[1] Ashley Chrissan[1] August Sriwattnanon[1] Maria Lauda Tomasi[2] Akil Merchant[2] Komal Ramani[2] Nirmala Mavila[2], [1]Cedars Sinai Medical Center, [2]Cedars-Sinai Medical Center

Background: Ductular reaction (DR), chronic inflammation, and bridging fibrosis are key features of chronic cholestatic liver diseases. However, the molecular mechanisms regulating DR and its contribution to fibrosis remain unclear. This study aimed to define the role of the fibroblast growth factor receptor 1/2 (FGFR1/2) signaling axis in PROMININ1 (PROM1)$^{+}$ liver progenitor-like cells (LPCs) in driving DR and liver fibrosis. **Methods:** Human liver specimens from biliary atresia (BA) and primary sclerosing cholangitis (PSC), along with cholestatic mouse models with PROM1-cell type targeted Fgfr1/2 knockdown, were used to investigate FGFR1/2 function in fibrogenesis. GeoMX spatial transcriptomic profiling was performed on BA liver tissues to identify DR-associated molecular drivers of bridging liver fibrosis. **Results:** FGFR1/2 signaling was markedly

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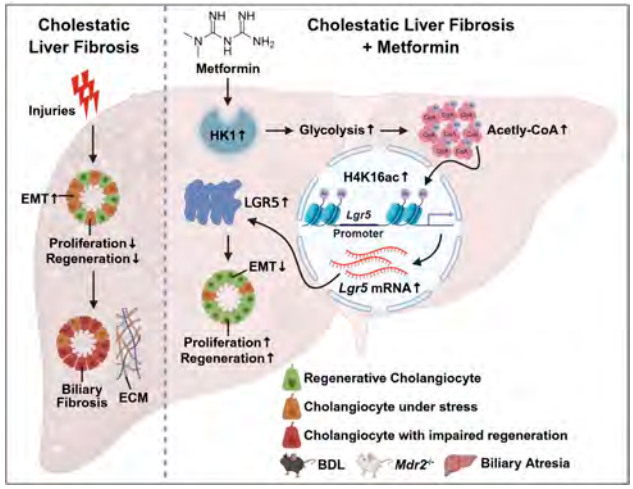
activated in liver tissues from patients with BA and PSC, as well as in multiple models of liver fibrosis. FGFR1/2 expression co-localized with PROM1^{+} LPCs, and PROM1 enhanced FGFR activation in cholangiocytes. Conditional deletion of *Fgfr1/2* in PROM1^{+} cells significantly reduced LPC expansion, inflammatory responses, and fibrosis progression in mouse models. Mechanistically, in cholangiocytes, PROM1 facilitates constitutive activation of FGFRs via a Focal Adhesion Kinase-dependent mechanism. Spatial transcriptomic analysis revealed that PROM1+ reactive cholangiocytes serve as a major source of fibro-inflammatory mediators in human BA livers. **Conclusion:** FGFR1/2 signaling in PROM1+ LPC promotes the expansion of fibroinflammatory DR during chronic liver injury. Targeting the FGFR pathway in fibroinflammatory PROM+ LPCs may represent a promising therapeutic strategy to alleviate pathological DR and limit fibrosis progression in chronic cholestatic liver diseases.

Disclosures: MALLIKARJUNA SIRAGANAHALLI ESH WARAIAH:Nothing to Disclose, Jiaohong Wang:Nothing to Disclose, Ying Li:Nothing to Disclose, Ashley Chrissan:Nothing to Disclose, August Sriwattnanon:Nothing to Disclose, Maria Lauda Tomasi:Nothing to Disclose, Akil Merchant:Nothing to Disclose, Komal Ramani: Nothing to Disclose, Nirmala Mavila:Nothing to Disclose.

1008 | METFORMIN PROMOTES CHOLANGIOCYTE REGENERATION IN CHOLESTATIC FIBROSIS VIA HK1-GLYCOLYSIS-DEPENDENT EPIGENETIC ACTIVATION OF LGR5

Yingyu Liang[1] Paul Kwong Hang Tam[1] Yan Chen[1], [1]Macau university of Science and Technology

Background: Cholestatic liver fibrosis, characterized by impaired cholangiocyte regeneration and elevated epithelial-mesenchymal transition (EMT), lacks novel therapeutics. We adopted an alternative therapeutic strategy by exploring the repurposing of existing clinically approved drugs. Among potential candidates, metformin emerged as a particularly promising agent, yet its therapeutic properties remain unelucidated in cholestasis. **Methods:** The therapeutic effects of metformin were validated using bile duct ligation (BDL) and *Mdr2*$^{-/-}$ mouse models. Bulk RNA-seq was conducted to identify gene changes, focusing on cholangiocyte regeneration and EMT pathways. Krt19CreERT2*Hk1*$^{fl/fl}$ mice were subjected to BDL to investigate the role of HK1 in cholangiocyte regeneration and the therapeutic effects of metformin. The binding of acetylated histone H4 lysine 16 (H4K16ac) to the *Lgr5* promoter was investigated using CUT&Tag and ChIP-qPCR. **Results:** Metformin ameliorated cholestatic fibrosis in both BDL and *Mdr2*$^{-/-}$ models, with consistent results showing reduced fibrosis and enhanced cholangiocyte regeneration. Metformin also enhanced stemness and cell proliferation in cholangiocyte organoids (Cho-Orgs). Transcriptomics identified HK1-glycolysis as a key downstream pathway upregulated by metformin in BDL, *Mdr2*$^{-/-}$ mice-derived Cho-Orgs. Findings in Krt19CreERT2*Hk1*$^{fl/fl}$ mice with cholestasis revealed a promising role of HK1 in improving liver fibrosis and cholangiocyte regeneration, as well as mediating the therapeutic effects of metformin. Mechanistically, metformin promoted HK1-glycolysis in Cho-Orgs, which upregulated acetyl-CoA (acCoA), leading to increased H4K16ac at the *Lgr5* promoter and elevated LGR5 expression. These findings were corroborated in human cholestatic patient-derived organoids (PDOs). **Conclusion:** Our findings reveal HK1 as a novel therapeutic target mediating the hepatoprotective effects of metformin in cholestatic fibrosis. Metformin enhances the HK1-glycolysis-acCoA axis, upregulating the interaction of H4K16ac with the *Lgr5* promoter, thereby promoting LGR5-mediated regeneration and dampening EMT in Cho-Orgs. These findings position metformin as a promising, safe, and cost-effective candidate for drug repurposing in cholestatic fibrosis.



Disclosures: Yingyu Liang:Nothing to Disclose, Paul Kwong Hang Tam:Nothing to Disclose, Yan Chen: Nothing to Disclose.

1009 | THE IMPLICATION OF TRIMETHYLAMINE *N*-OXIDE IN THE DEVELOPMENT OF PRIMARY SCLEROSING CHOLANGITIS IN *CYP2C70*$^{-/-}$/*CYP2A12*$^{-/-}$ MICE WITH HUMAN-LIKE BILE ACID COMPOSITION

Teruo Miyazaki[1] Hajime Ueda[1] Tadashi Ikegami[1] Akira Honda[1], [1]Tokyo Medical University Ibaraki Medical Center

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Background: Primary sclerosing cholangitis (PSC) is characterized by extensive fibrosis around the large bile ducts (onion-skin fibrosis) and is frequently complicated by inflammatory bowel disease. Although its pathogenesis remains unclear, its development may be associated with hydrophobic (Hbic) bile acids (BAs). Trimethylamine *N*-oxide (TMAO)—an oxidized form of the gut bacteria product trimethylamine (TMA) generated via flavin-containing monooxygenase 1 (FMO1) in the liver—is implicated in atherosclerosis and cardiovascular disease, and may contribute to liver inflammation and fibrosis through BA metabolism. We previously established a PSC mouse model by orally administering low-dose lithocholic acid (LCA) to *Cyp2c70* $^{-/-}$ */Cyp2a12*$^{-/-}$ mice (HuBA) with human-like Hbic BAs. This study aimed to evaluate the role of TMAO in the pathogenesis of PSC using this mouse model and cultured human cholangiocytes (MMNK1). **Methods:** Male wild-type (Wt) and HuBA mice (5 weeks of age) were treated with LCA (75 mg/L) via drinking water for 15 weeks. TMAO and BAs levels in bile and liver, as well as expression of genes related to TMAO and BA metabolism and transport, were evaluated. MMNK1 was treated with 50 μM TMAO and/or 100 μM Hbic BAs (LCA, chenodeoxycholic acid [CDCA], or deoxycholic acid [DCA]) in media containing 5 mM (pH 6.8), 20 mM (pH 7.4), or 44 mM (pH 7.8) bicarbonate. Cell proliferation and gene expression were analyzed. **Results:** The onion-skin fibrosis area in the HuBA mice was significantly increased by LCA treatment. TMAO level and the mRNA expression of its biliary efflux transporter *Mdr1*, as well as *Fmo1*, in liver were significantly higher in the HuBA mice than in the Wt mice, and were further increased by LCA treatment in both mouse strains. In contrast, hepatic mRNA expression of the basolateral efflux transporter *Mrp4* was also significantly higher in HuBA mice but was reduced by LCA treatment. No significant difference was observed in TMAO level in bile among the groups, presumably due to individual variation of bile concentration. In MMNK1 cells, TMAO treatment did not affect cell proliferation under any pH condition. However, the mRNA expression of cell adhesion/binding factors (*Vcam1*, *Cldn1*, *Itgb6*) was increased by the Hbic BAs and was further enhanced by co-treatment with TMAO, only in 5 mM (pH 6.8) bicarbonate condition. **Conclusion:** These results suggested that TMAO oxidation and biliary excretion are promoted through the upregulation of FXR-target Fmo1 and PXR-target Mdr1 in PSC liver. In addition, increased biliary excretion of TMAO may contribute to cholangiosclerosis and inflammation in distal cholangiocytes, where the epithelial barrier by bicarbonate umbrella is weaker, thereby enhancing the effects of epithelial adhesion and fibrosis-related factors. In the bile ducts of PSC, the increased excretion of TMAO into the bile, in combination with Hibc BAs, may trigger the development of cholangiosclerosis and inflammation.

Disclosures: Teruo Miyazaki:Nothing to Disclose, Hajime Ueda:Nothing to Disclose, Tadashi Ikegami: Nothing to Disclose, Akira Honda:Nothing to Disclose.

★ 1010 | BATTED REVEALS CYP7A1 AS A TARGETABLE PATHWAY IN BILIARY ATRESIA

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Background: Biliary atresia (BA) is a leading cause of neonatal cholestasis and progressive fibrosis. Few large-animal studies reproduce BA-like cholangiopathy. CYP7A1 regulates the rate-limiting step in primary bile acid synthesis and may amplify cholestatic injury. We tested whether CYP7A1 is increased in vivo and targetable by siRNA in vitro using our patent-pending BATTED (Biliary Atresia Through Targeted Endothelial Destruction) piglet system. **Methods:** Twelve 7-day-old piglets were randomized to sham or BATTED (n = 6/group). BATTED involved cholecystectomy, 95% ethanol ductal injection, and ethanol-retainer placement. Blood and liver were collected at baseline and 6 weeks. Serum chemistries, histology, IHC, and hepatic bile acid regulatory genes were assessed. HepG2 cells were transfected with CYP7A1 or control siRNA, with expression measured at ~50 hours. Student's t-test was used; $p < 0.05$ was significant. **Results:** Six weeks after BATTED, piglets developed cholestasis and liver injury. Conjugated bilirubin rose in BATTED animals, mean Δ0.39 to 3.88 mg/dL, versus sham, Δ0.39 to 0.98 mg/dL. GGT increased Δ16.3 to 89.5 IU/L after BATTED, while sham showed minimal change, Δ9.2 to 10.4 IU/L. ALT, ALP, and bile acids were also elevated. Histology showed periportal expansion, ductular reaction, inflammatory infiltrates, and diffuse collagen deposition. Sirius Red showed periportal/bridging fibrosis with a 16-fold increase in collagen-positive area versus sham. CK7 increased 9-fold, confirming bile duct proliferation. CD3 increased 7-fold, indicating T-cell-rich portal inflammation consistent with cholangitis. Fibrogenic markers increased, including alpha-SMA, 8.85-fold, and COL1A1, 11.7-fold. CYP7A1 increased 7-fold in BATTED liver versus sham, with expanded hepatocyte CYP7A1 immunoreactivity, supporting enhanced primary bile acid synthesis as a candidate injury mechanism. FXR and SHP also increased, indicating bile acid regulatory signaling. To assess targetability, HepG2 cells were transfected with CYP7A1 siRNA. CYP7A1 expression decreased from ~1.0 in untreated cells to 0.069 and 0.028 after siRNA

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transfection, whereas negative-control siRNA did not show comparable target suppression. These data demonstrate robust CYP7A1 knockdown and support CYP7A1 silencing as a feasible strategy for future in vivo testing. **Conclusion:** BATTED piglets reproduced key BA features. CYP7A1 activation identifies enhanced bile acid synthesis as a candidate driver of hepatocellular injury. Effective CYP7A1 knockdown in HepG2 cells supports evaluation of CYP7A1 siRNA silencing in BATTED as a potential adjunctive therapeutic strategy for BA.

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1011 | A HUMAN HEPATOCYTE CHIMERIC MOUSE MODEL REVEALS CONSERVED HEPATOCYTE UPR ACTIVATION AND BILE ACID METABOLISM RESPONSES TO ER STRESS AND IBAT INHIBITION

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Background: Cholestatic liver diseases are driven by an accumulation of toxic bile acids (BAs) that cause hepatocyte injury, ER stress, and unfolded protein response (UPR) activation, yet effective therapies remain limited. A key barrier to translation is the hydrophilic, muricholic acid–rich murine BA pool, which is less cytotoxic than the hydrophobic human pool. Enterohepatic feedback also differs across species: ileal BAs induce FGF15 in mice and FGF19 in humans. Mouse-ileal FGF15 represses hepatic BA synthesis via FGF Receptor-4 (FGFR4), but cannot activate human FGFR4. We used FRG mice with the majority of mouse hepatocytes replaced by human hepatocytes (FRGh) as a translationally relevant model of human hepatocyte ER stress and BA homeostasis. **Methods:** FRGh mice received the pharmacologic ER stress-inducer tunicamycin (TUN; 0.5 mg/kg ip, 4 h) or vehicle (DMSO), or chow with the IBAT inhibitor maralixibat (MIBAT; 150 mg/kg/day) or normal chow (n = 2 per arm) for one week. Serum LFTs and bile acids were measured. Hepatic BA metabolism and UPR gene expression were assessed by qPCR with species-specific primers. Engrafted human hepatocyte transcriptomes were determined by bulk RNA-seq (all mice) and snRNA-seq (TUN, DMSO; n = 1) with Hallmark Gene Set Enrichment Analysis (GSEA) of TUN vs DMSO and MIBAT vs chow following alignment to a combined human–mouse reference genome. **Results:** In human hepatocytes, MIBAT vs chow GSEA showed significant induction of TNFα signaling and cholesterol homeostasis, with downward trends in UPR, fatty acid metabolism, and ROS pathways. Hepatic qPCR revealed a species-divergent BA-synthesis response: murine Cyp7a1 was fully suppressed at baseline and strongly induced by MIBAT, while human CYP7A1, lacking baseline FGFR4 repression, did not change. A parallel trend was seen for Cyp8b1/CYP8B1. Serum BAs were markedly lower in MIBAT- than chow-fed animals (24.5 vs 241.5 µmol/L). GSEA of TUN vs DMSO induced UPR, PI3K-AKT, and p53 signaling in human hepatocytes, with concordant qPCR induction of XBP1, CHOP, and ERDJ4 in human and murine hepatocytes; snRNA-seq confirmed UPR induction in human hepatocytes. **Conclusion:** In FRGh mice, MIBAT lowered serum BAs and exposed a species-divergent BA-synthesis response: murine Cyp7a1 was strongly de-repressed, while human CYP7A1 was minimally induced from its elevated baseline, though MIBAT induced broader pathway changes in human hepatocyte cholesterol and BA metabolism. This is consistent with ileal FGF15/liver FGFR4 feedback occurring only in mice, leaving human BA synthesis under cell-autonomous FXR rather than FGF19 control. TUN activated a robust UPR in engrafted human hepatocytes with concordant murine induction, demonstrating that human hepatocytes mount an ER-stress response similar to mice. These findings establish the FRGh mouse as a platform to study human hepatocyte UPR modulation and develop UPR-based therapies for cholestatic disease.

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1012 | METHYLDOPA ALLEVIATES BILE ACID ACCUMULATION IN A MURINE MODEL OF INTRAHEPATIC CHOLESTASIS OF PREGNANC

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Background: Intrahepatic cholestasis of pregnancy (ICP) is the most prevalent pregnancy-associated liver disease and is defined by elevated serum bile acid (BA) concentrations, which increase placental

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permeability and are associated with adverse fetal outcomes including preterm delivery and meconium-stained amniotic fluid. ICP frequently co-occurs with hypertensive disorders of pregnancy, including pre-eclampsia, for which methyldopa is a commonly used antihypertensive agent. Despite this clinical overlap, the effects of methyldopa on BA homeostasis have not been characterized. **Methods:** We investigated the effects of methyldopa in a well characterized murine model of estrogen-induced cholestasis. Female C57BL/6J mice were treated with ethinylestradiol (EE; 10 mg/kg, s.c.) alone or in combination with methyldopa (250 mg/kg, p.o.) for 7 days. BA profiles were quantified by LC-MS in plasma, bile, liver, urine, intestine, and feces. Total and free cholesterol were quantified in liver tissue by GC-MS. Hepatic expression of BA-regulatory enzymes and transporters was evaluated by RT-qPCR and Western blot. **Results:** Methyldopa significantly reduced total BA concentrations in plasma and liver of EE-treated mice without a compensatory increase in fecal or urinary BA excretion, indicating a reduction in BA load rather than rerouted elimination. This was accompanied by transcriptional upregulation of phase I/II biotransformation enzymes (Cyp2b10, Ugt1a1, Sult2a1) and BA transporters (Abcb11, Slc10a1, Abcc3/4) — a gene expression signature consistent with constitutive androstane receptor (CAR) activation, mediated indirectly through p-ERK downregulation. Methyldopa also reduced hepatic free cholesterol in cholestatic mice, with concurrent downregulation of Hmgcr and upregulation of Acat2, suggesting that decreased cholesterol substrate availability contributes to attenuated BA synthesis. **Conclusion:** Methyldopa attenuates estrogen-induced BA accumulation through a dual mechanism: suppression of BA synthesis and enhanced hepatic detoxification, likely via indirect CAR activation. These findings raise the clinically relevant hypothesis that methyldopa, when prescribed for hypertensive disorders of pregnancy, may simultaneously reduce BA burden and delay the progression of cholestatic injury in patients with ICP. Prospective clinical studies are needed to evaluate this potential benefit.

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1013 | ASSOCIATIONS OF FIRST-TRIMESTER ALKALINE PHOSPHATASE LEVELS, URSODIOL USAGE, AND ADVERSE PREGNANCY OUTCOMES AMONG PRIMARY BILIARY CHOLANGITIS AND PRIMARY SCLEROSIS CHOLANGITIS PATIENTS

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Background: Primary sclerosing cholangitis (PSC) and primary biliary cholangitis (PBC) are rare cholestatic liver diseases with limited pregnancy-specific data to guide counseling and management. We evaluated whether first-trimester alkaline phosphatase (ALP) levels and ursodiol use were associated with adverse pregnancy outcomes (APOs) among pregnant persons with PBC and PSC. **Methods:** We performed a retrospective cohort study using the TriNetX research network. Pregnant persons with PBC or PSC were identified using electronic health record data extracted through 2025. Primary exposures were elevated first-trimester ALP (> 100 U/L) and any ursodiol use within the first 20 weeks of pregnancy. APOs were assessed from 20 weeks onward and included preterm birth, preeclampsia or gestational hypertension, gestational diabetes, cesarean delivery, fetal growth restriction, and postpartum hemorrhage. Multivariable logistic regression models adjusted for age, race, chronic hypertension, and pregestational diabetes. Sensitivity analyses restricted exposure ascertainment to 94.5 days after pregnancy onset to reduce potential reverse causation. Pre-planned subgroup analyses compared PBC versus PSC cohorts and alternative ALP thresholds (> 167 U/L and > 200 U/L). **Results:** The ALP and ursodiol analyses included 341 and 408 pregnant persons with PBC and PSC, respectively; 97 patients had elevated ALP levels. Among those with elevated ALP, 70 (77%) received ursodiol compared with 21 (23%) with normal ALP levels ($p < 0.001$). Median maternal age was 37 years (IQR 33-41), 70% were non-Hispanic White, and 5% had chronic hypertension or pregestational diabetes. Baseline demographic and clinical characteristics did not differ by ALP status. In both unadjusted and adjusted analyses, neither elevated ALP levels nor ursodiol use were significantly associated with APOs. Sensitivity and subgroup analyses yielded similar findings across exposure

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definitions and disease subtypes. **Conclusion:** Among pregnant persons with PBC and PSC, neither elevated first-trimester ALP levels nor ursodiol use were independently associated with adverse pregnancy outcomes. However, the rarity of PBC and PSC in pregnancy and low event counts limited statistical power; therefore, findings should be considered hypothesis-generating. Larger prospective studies are needed to better define predictors of maternal and fetal risk in this population and inform multidisciplinary counseling and management strategies.

Table 1. Unadjusted and Adjusted Models Examining Elevated ALP (> 100 U/L), Ursodiol Usage, and Adverse Pregnancy Outcomes Among PBC/PSC Patients[a]

Model 1: Elevated ALP Levels as Primary Exposure (n=341)		
Adverse Pregnancy Outcomes	OR (95% CI)	aOR (95% CI)[b]
Preterm birth	1.16 (0.61-2.27)	1.24 (0.63-2.47)
Preeclampsia or gestational hypertension	0.562 (0.27-1.14)	0.516 (0.24-1.07)
Gestational diabetes	0.567 (0.26-1.21)	0.555 (0.23-1.27)
Postpartum hemorrhage	1.24 (0.60-2.60)	1.23 (0.59-2.64)
Cesarean section	0.582 (0.19-1.65)	0.587 (0.19-1.69)
Fetal growth restriction	0.960 (0.44-2.13)	0.987 (0.44-2.21)
Model 2: Any Ursodiol Usage as Primary Exposure (n=408)		
Adverse Pregnancy Outcomes	OR (95% CI)	aOR (95% CI)
Preterm birth	1.51 (0.70-3.13)	1.60 (0.73-3.37)
Preeclampsia or gestational hypertension	0.968 (0.39-2.17)	1.02 (0.43-2.39)
Gestational diabetes	1.12 (0.49-2.37)	1.13 (0.48-2.48)
Postpartum hemorrhage	1.83 (0.74-4.37)	1.76 (0.67-4.39)
Cesarean section	0.842 (0.27-2.23)	0.90 (0.28-2.44)
Fetal growth restriction	0.841 (0.30-2.07)	0.86 (0.30-2.12)

[a]Models adjusted for age, race, diabetes, and hypertension.
[b]Abbreviations: OR = unadjusted odds ratio; aOR = adjusted odds ratio.

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1014 | ETHANOL EXPOSURE ATTENUATES CHOLESTATIC LIVER INJURY IN THE HUMANIZED BILE ACID *CYP2C70*$^{-/-}$ MOUSE MODEL

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Background: Bile acids (BAs) play important roles in intestinal fat absorption and initiate signaling processes that maintain lipid homeostasis throughout the body. Therefore, BA-focused therapeutic strategies have been leveraged for several diseases including diverse liver diseases. Unfortunately, differences in BA metabolism between mice and humans hamper translation of preclinical outcomes. *Cyp2c70* knockout (*Cyp2c70*$^{-/-}$) mice represent a "humanized" BA mouse model lacking the liver enzyme responsible for synthesis of 6-hydroxylated muricholate BA species that predominate in rodents. *Cyp2c70*$^{-/-}$ mice possess a more hydrophobic "human-like" bile acid composition, and as a result are prone to female-dominant progressive hepatobiliary injury and portal fibrosis. Here, we hypothesized that *Cyp2c70*$^{-/-}$ mice would have accelerated liver injury in response to alcohol consumption, given excessive alcohol exposure promotes liver damage and fibrosis. **Methods:** Age-matched cohorts of male and female *Cyp2c70*$^{+/+}$ and *Cyp2c70*$^{-/-}$ mice were subjected to 10 days of ethanol exposure, while controls were pair-fed. At necropsy, histological and biochemical markers of liver injury were quantified, hepatic bile acid composition and gut microbiome composition were analyzed. **Results:** After only 10 days of ethanol exposure, the cholestatic liver injury known to occur in *Cyp2c70*$^{-/-}$ mice was attenuated when compared to *Cyp2c70*$^{-/-}$ mice not consuming ethanol. Acute ethanol exposure unexpectedly reduced circulating markers of liver injury (ALT/AST) and improved histological and gene expression markers of fibrosis, liver inflammation, and ductular reaction normally seen in *Cyp2c70*$^{-/-}$ mice. Furthermore, ethanol-induced alterations of the gut microbiome were strikingly different in *Cyp2c70*$^{+/+}$ and *Cyp2c70*$^{-/-}$ mice. Interestingly, ethanol exposure stimulates the gene and protein expression of other related enzymes within the *Cyp2c* genetic locus, which may further shape metabolism to improve liver function. **Conclusion:** Although alcohol consumption is a predominant risk factor for liver fibrosis in humans, ethanol exposure in the fibrotic *Cyp2c70*$^{-/-}$ mouse model paradoxically improves liver injury. Results from this study provide insights into novel species-specific interactions between alcohol intake, metaorganismal (i.e. microbe and host) BA metabolism, and liver fibrosis.

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1015 | COMPLEX CONTEXT-DEPENDENT CONSEQUENCES OF CONCURRENT FGF19 AND FXR SIGNALING IN A HUMANIZED MOUSE MODEL OF CHOLESTASIS: FOCUS ON FIBROTIC AND THROMBOTIC PATHWAYS

Stephen Hoang[1] Leslie Wakefield[2] Anne Vonada[2] Allison MacMillan[2] Ronnie Li[1] Thomas Andl[1] Andrew Pryor[1] Huiping Zhou[1] Paul Dawson[3] Markus Grompe[2] Saul Karpen[1], [1]VCU Stravitz-Sanyal Institute for Liver Disease and Metabolic Health, [2]Oregon Health and Science University, [3]Emory University

Background: Cholestatic human conditions incorporate retained bile acids, liver cell damage and inflammation resulting in fibrosis and alterations of liver function. Given the complexity and often unpredictable nature of the cholestatic response, along with some contradictory findings of mouse models to the human condition, we sought to address this knowledge gap by focusing upon the two principal drivers and responders of ongoing cholestasis—hepatic FGF19 and FXR signaling—in a well-established human hepatocyte-engrafted murine model undergoing bile duct ligation (BDL). **Methods:** Human hepatocytes were engrafted for 130 days in FRGN mice followed by treatments with the FXR agonist cilofexor and/or adenoviral FGF19, in sham-operated mice or after 2 days of BDL. Serum/plasma proteomics and liver tissue transcriptomics, biochemical analyses and histology were assessed. Treatment effects were assessed on curated FXR-activated and FXR-repressed datasets with cross-layer concordance. **Results:** Mouse livers were engrafted to > 80% with human hepatocytes and showed expected as well as unanticipated responses to FGF19 and FXR signaling. Serum liver chemistries and liver bile acid analyses trended as predicted. Depending upon the treatments, fibrogenesis and fibrinolysis and well as thrombosis and thrombolysis pathways were all activated as revealed by transcriptomic and serum proteomic analyses. One example of the combinatorial contradictory responses in cholestasis, was upregulation of the FXR-repressed gene *SERPINE1/PAI-1* in both the non-BDL and BDL mice (protein > 5-fold, non-BDL; > 2-fold, BDL). *SERPINE1* RNA and protein expression was unchanged by cilofexor in non-BDL hepatocytes, minimally repressed after BDL. The directionality of gene expression regulation by cilofexor in the BDL context generally lacked coherence with reported FXR activation, consistent with contributing endogenous bile acid saturation of FXR signaling in cholestasis. However, the canonical signature of FXR agonism was restored when cilofexor was given with FGF19. **Conclusion:** The interaction of FGF19 and FXR pathways in cholestatic human livers leads to complex consequences modeled in part in our novel human hepatocyte-engrafted mouse model. Focusing on FXR-regulated thrombotic pathways mimics the contradictory nature of predicting coagulation status in human cholestasis. Studies like these help expand our understanding of the interwoven set of signals from the membrane (FGF19) to the nucleus (FXR) in cholestasis and may also help explain some features of humans exposed to FGF19 analogs and FXR agonists in clinical trials. Ongoing analyses of cell signaling and chromatin-based consequences in this model will likely reveal the molecular consequences of FGF19 and FXR mediated pathways and therapeutics in human cholestasis.

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1016 | LOSS OF PRIMARY CILIA PROMOTES AUTOPHAGIC DEGRADATION OF CBL AND SUSTAINS EGFR SIGNALING IN CHOLANGIOCYTES

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Background: Primary cilia are sensory organelles that regulate signaling pathways involved in cholangiocyte homeostasis, proliferation, and differentiation. Loss of primary cilia is a hallmark of cholangiociliopathies and cholangiocarcinoma (CCA), yet the molecular mechanisms linking ciliary dysfunction to sustained oncogenic signaling remain incompletely understood. Casitas B-lineage lymphoma (CBL), an E3 ubiquitin ligase that mediates epidermal growth factor receptor (EGFR) ubiquitination and degrada-

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tion, is frequently dysregulated in cancer. We investigated whether loss of primary cilia promotes autophagy-dependent degradation of CBL, leading to sustained EGFR signaling in cholangiocytes and CCA. **Methods:** Primary cilia dysfunction was induced in normal human cholangiocytes through deletion or knockdown of IFT88, IFT20, and KIF3A. CBL and EGFR expression and localization were evaluated by immunoblotting and immunofluorescence. Autophagy-dependent degradation pathways were assessed using chloroquine, mefloquine, and siRNA targeting ATG5 and the selective autophagy receptor NBR1. CBL expression and ciliary status were also examined in human CCA cell lines. Restoration of ciliogenesis was induced using the HDAC6 inhibitor ACY1215 or HDAC6-shRNA in HuCCT1 cells and an orthotopic rat model of CCA. **Results:** Loss of primary cilia resulted in reduced CBL protein expression accompanied by sustained EGFR activation and downstream proliferative signaling. Similarly, cilia-deficient human CCA cells exhibited significantly lower CBL levels compared to normal cholangiocytes. Pharmacologic inhibition of autophagy or genetic suppression of ATG5 and NBR1 restored CBL protein expression, demonstrating that ciliary loss promotes selective autophagic degradation of CBL. Increased CBL expression was also observed in orthotopic rat CCA tissues following chloroquine treatment, supporting the in vivo relevance of this pathway. Restoration of primary cilia through ACY1215 treatment or HDAC6-shRNA increased ciliary localization and stabilization of CBL, enhanced EGFR degradation, reduced EGFR signaling, and suppressed CCA growth in vitro and in vivo. **Conclusion:** This study identifies a novel mechanism linking primary cilia dysfunction to sustained EGFR signaling through autophagy-dependent degradation of CBL in cholangiocytes and cholangiocarcinoma. Loss of cilia promotes selective autophagic clearance of CBL, impairing EGFR degradation and prolonging oncogenic signaling. Restoration of ciliogenesis through HDAC6 inhibition, or blockade of autophagy, rescues CBL-mediated EGFR regulation and suppresses tumor growth. These findings establish a novel cilium–CBL–EGFR signaling axis and support the therapeutic potential of ciliotherapy and autophagy-targeted approaches for cholangiocarcinoma.

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1017 | HEPATIC STELLATE CELL ACTIVATION THROUGH THE SNAI1-GREM1 AXIS ENABLES MOLECULAR DIAGNOSIS OF BILIARY ATRESIA

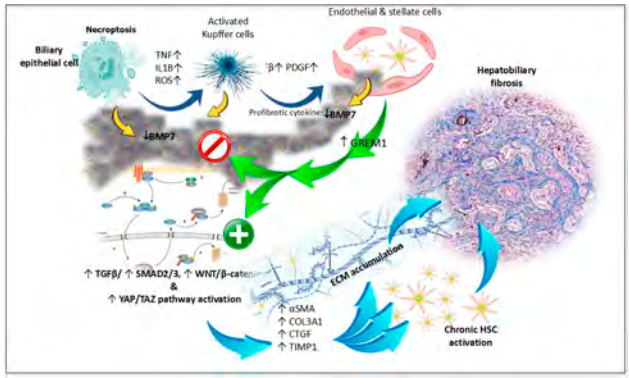
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Background: Biliary atresia (BA) is a life-threatening pediatric cholangiopathy characterized by progressive fibrosis and biliary injury leading to liver failure. Aberrant molecular signaling disrupts the balance between tissue repair and cellular clearance, resulting in pathological remodeling and persistent fibrogenesis. Early differentiation of BA from other neonatal cholestatic (NC) disorders remains clinically challenging; therefore, identifying dysregulated molecular pathways may aid in the discovery of reliable diagnostic biomarkers and therapeutic targets. **Methods:** Peripheral blood and extrahepatic biliary tissue samples from BA patients and healthy controls (HC) were analyzed using customized RT² Profiler PCR arrays targeting fibrosis and apoptosis related genes. Gene expression data underwent PCA, hierarchical clustering, and WGCNA to identify dysregulated molecular networks. Feature selection and biomarker prioritization were performed using multi-model machine learning with cross-validation. Candidate genes were validated by qPCR and IHC in an independent cohort comprising HC, NC, and BA patients. Functional enrichment and molecular interaction analyses were conducted using IPA, while correlation and ROC analyses were performed to evaluate clinical and diagnostic utility. **Results:** Publicly available BA datasets (GSE122340 and GSE46960) revealed significant enrichment of apoptosis- and fibrosis-related pathways in BA. Gene expression profiling identified a molecular signature comprising GREM1, SNAI1, IL-10, FASLG, TNF-α, and COL1A1 with strong discriminatory power between BA and controls. IPA demonstrated co-activation of the TGF-β/SMAD2/3 pathway. GREM1 and SNAI1 were significantly upregulated in BA compared with NC and HC ($p < 0.001$) and showed strong positive correlation with serum γ-GT levels ($r = 0.73$, $p < 0.001$). IHC confirmed distinct differential expression patterns with high diagnostic utility. ROC analysis demonstrated excellent performance, with SNAI1 showing an AUC of 0.818 and the combined TNF-α + SNAI1 panel achieving superior diagnostic accuracy (AUC = 0.975, sensitivity = 95.1%, specificity = 91.4%). **Conclusion:** This study establishes an apoptosis–fibrosis molecular framework underlying

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progressive biliary injury in BA. GREM1, SNAI1, and TNF-α emerged as key regulatory hubs associated with fibrogenesis and hepatic injury. The combined TNF-α + SNAI1 panel demonstrated excellent diagnostic performance, highlighting its potential as a minimally invasive biomarker signature for differentiating BA from other neonatal cholestatic disorders. Targeting SNAI1-mediated signaling may further represent a promising therapeutic strategy to limit hepatic stellate cell activation and fibrotic remodeling in BA.



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1018 | MRP9 MAINTAINS CHOLANGIOCYTE INTEGRITY THROUGH REGULATION OF PORPHYRIN HOMEOSTASIS AND MITOCHONDRIAL FUNCTION

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Background: Cholangiopathies are chronic progressive disorders that target cholangiocytes and can cause significant morbidity and mortality due to a lack of effective therapies. We previously identified biallelic frameshift variants in *ABCC12*, encoding the multidrug resistance-associated protein MRP9, in a patient with cholangiopathic cholestasis. Studies in human liver tissue and zebrafish and mouse models demonstrated that MRP9 is expressed in cholangiocytes and that its loss increases susceptibility to bile acid-induced cholangiocyte death. We further observed mitochondrial localization of MRP9 and found that MRP9 deficiency causes mitochondrial injury and ectopic accumulation of the heme intermediate protoporphyrin IX (PPIX) in cholangiocytes. This study tested the hypothesis that MRP9 regulates porphyrin homeostasis to maintain mitochondrial function and cholangiocyte integrity. **Methods:** H69 human cholangiocyte cell line homozygous for the index patient *ABCC12* variant and *abcc12-/-* zebrafish were used as *in vitro* and *in vivo* models. Chemical and genetic approaches were employed to reduce porphyrin biosynthesis or enhance mitochondrial biogenesis and quality, and their effects on cholangiocyte survival were evaluated. Untargeted metabolomic profiling was performed on wild-type and *ABCC12-/-* H69 cells. Pharmacologic inhibitors were used to define the cell death mechanism responsible for cholangiocyte injury. **Results:** Inhibition of porphyrin biosynthesis with succinylacetone, an ALAD inhibitor, significantly reduced aminolevulinic acid-induced cell death in *ABCC12-/-* H69 cells. *In vivo*, hemin treatment rescued cholangiocyte loss in *abcc12-/-* zebrafish. Genetic suppression of the porphyrin transporter ABCG2 reduced PPIX accumulation and attenuated cholangiocyte death in *abcc12-/-* zebrafish. To determine whether mitochondrial dysfunction contributes to cholangiocyte injury, we generated transgenic zebrafish overexpressing human PGC1α, a master regulator of mitochondrial biogenesis, specifically in cholangiocytes. PGC1α overexpression reduced cholangiocyte loss in *abcc12* mutants. Untargeted metabolomics revealed tricarboxylic acid cycle dysfunction and a metabolic shift toward glycolysis in *ABCC12-/-* H69 cells. Finally, ferrostatin-1 treatment of H69 cells indicated that ferroptosis is a major driver of cholangiocyte death caused by MRP9 deficiency. **Conclusion:** These novel findings identify MRP9 as a critical regulator of porphyrin homeostasis in cholangiocytes and demonstrate that MRP9 loss leads to PPIX accumulation, mitochondrial dysfunction, and ferroptotic cell death of cholangiocytes. Importantly, targeting porphyrin metabolism or enhancing mitochondrial function mitigated cholangiocyte loss, highlighting potential therapeutic strategies for MRP9-associated cholangiopathies.

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1019 | HEPATOBILIARY OUTCOMES IN ADULTS WITH CYSTIC FIBROSIS: A PROPENSITY-MATCHED TRINETX ANALYSIS

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Background: Cystic fibrosis (CF) is increasingly recognized as a multisystem disease with significant hepatobiliary manifestations in adults. However, large-scale real-world data evaluating the risk of advanced liver-related outcomes in adults with CF remain limited. Therefore, this study aimed to evaluate the risk of primary biliary cirrhosis (PBC), portal hypertension, liver transplantation, and mortality among adults with CF compared with matched non-CF controls. **Methods:** We performed a retrospective cohort study using the TriNetX US Collaborative Network including adults aged $\geq$18 years from January 2015 onward. Patients with CF were identified using ICD-10 code E84 and compared with adults without CF. Propensity score matching (1:1) was performed for age, sex, race, viral hepatitis, primary sclerosing cholangitis, alcohol dependence, and nonalcoholic steatohepatitis. Outcomes included PBC, portal hypertension, liver transplantation, and all-cause mortality. Risk ratios (RR) and hazard ratios (HR) with 95% confidence intervals (CI) were calculated. **Results:** After propensity score matching, 29,786 patients were included in each cohort. Adults with CF had significantly higher risks of hepatobiliary complications compared with matched controls. The risk of PBC was markedly increased in the CF cohort (0.5% vs 0.1%; RR 8.24, 95% CI 5.06–13.44; HR 8.45, 95% CI 5.18–13.78; $p < 0.001$). Portal hypertension was also more common among patients with CF (1.7% vs 0.3%; RR 5.45, 95% CI 4.36–6.80; $p < 0.001$). Additionally, liver transplantation occurred more frequently in the CF cohort (0.8% vs 0.1%; RR 11.50, 95% CI 7.36–17.96; $p < 0.001$). Mortality risk was significantly higher in adults with CF compared with controls (12.7% vs 3.5%; RR 3.64, 95% CI 3.41–3.90; HR 3.75, 95% CI 3.50–4.02; $p < 0.001$). **Conclusion:** Adults with cystic fibrosis are at substantially increased risk of advanced hepatobiliary disease, liver transplantation, and mortality compared with matched non-CF controls. These findings highlight the importance of longitudinal hepatology surveillance and early multidisciplinary management in the growing adult CF population.

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1020 | ALTERNATIVELY SPLICED TISSUE FACTOR IS INTEGRAL TO NORMAL HEPATIC FUNCTION: LESSONS FROM THE ASTF^{NULL} MOUSE.

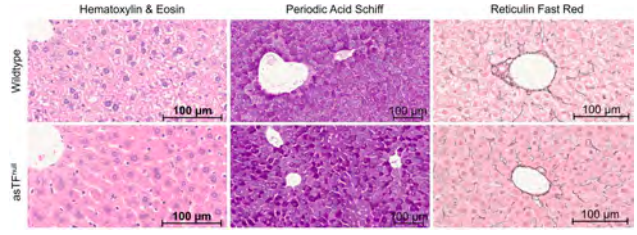
Clayton Lewis[1] Hailey Doerflein[2] Sabahat Ahsan[2], [1]University of Cincinnati College of Medicine, [2]University of Cincinnati IM Gastro Hep

Background: The tissue factor gene encodes two proteins with different biological functions. Full-length tissue factor is membrane-bound and serves as a scaffold for the activation of the extrinsic pathway of coagulation. In contrast, the alternatively spliced isoform (asTF) is a soluble protein that is dispensable for normal coagulation – instead it serves as a potentiator of integrin activity. Previously, we reported histological findings demonstrating that in normal human liver asTF expression is zonally and spatially regulated – asTF is expressed by zone 3 hepatocytes and held in exocysts polarized toward their biliary canaliculi. In specimens from patients with varying degrees of MASH-related fibrosis, we found asTF levels rise with worsening disease and begins to be expressed by all hepatocytes, not just zone 3. To set the foundation for understanding the role asTF may play in disease progression, we sought to determine the native biologic function of asTF in the liver. **Methods:** Utilizing CRISPR/Cas9, we generated a novel mouse lacking intron 4 in the tissue factor gene, which precludes alternative mRNA splicing and production of asTF. Mice homozygous for this deletion – termed asTF^{null} – were characterized via clotting assays and histological assessment of the liver in comparison to heterozygous and wildtype litter mate controls. These three genotypes were subjected to dietary challenge using diet high in fat, fructose, and cholesterol for 24 weeks and compared to kcal matched chow diet controls. **Results:** Immunohistochemical evaluation of wildtype mice revealed asTF expression is confined to pericentral hepatocytes adjacent to canalicular membranes, as observed in humans. No difference was found in clotting times between adult asTF^{null} mice and littermate controls in a tail clipping assay. Histochemical analysis of asTF^{null} livers revealed a distinct pathological phenotype characterized by i) enhanced sinusoidal dilation, ii) hypergranular hepatocytes, iii) altered glycogen storage pattern, and iv) active zone 1 regeneration. Immunohistochemical analysis of male and female adult mice revealed 50% more cholangiocytes in asTF^{null} mice

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than their littermates. In dietary challenge studies, we found male asTF^{null} mice gained weight more rapidly than littermate controls. asTF^{null} mice had a significantly higher liver weight to body weight ratio and developed more severe liver pathologies than littermate controls including cholangiocarcinoma. **Conclusion:** Here we demonstrate asTF serves an integral function in normal liver biology. When compared to wildtype controls, asTF^{null} mice have distinct pathologic features, supporting the ongoing hypothesis that asTF supports biliary canaliculi architecture by facilitating integrin binding.



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1021 | ORAL CANNABIDIOL ATTENUATES EXPERIMENTAL CHOLANGIOPATHY BY MODULATING INTESTINAL ENDOCANNABINOID SYSTEM AND BARRIER-DEFENSE SIGNALING

Lixian Chen[1] Chunbao Sun[1] Panpan Huang[1] Guihua Pan[1] Xing Gao[1] Rahul Pushparaj[1] Lihua Zhang[1] Wenke Feng[1], [1]Tulane University

Background: Primary sclerosing cholangitis (PSC) is a progressive cholangiopathy with no approved drug therapy to halt progression. Gut barrier dysfunction and gut-derived inflammation are increasingly implicated in PSC pathogenesis. The endocannabinoid system (ECS) regulates intestinal barrier integrity, mucosal inflammation, and hepatic injury, but whether ECS-targeted modulation attenuates cholangiopathic injury remains unclear. Cannabidiol (CBD), a non-intoxicating cannabinoid, modulates ECS tone and intestinal homeostasis. We hypothesized that oral CBD protects against PSC-relevant cholangiopathy through a gut-engaged mechanism via intestinal ECS/barrier-defense restoration. **Methods:** Ten-week-old male C57BL/6 mice were fed a 0.1% 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC) diet for 4 weeks to induce cholangiopathic liver injury. CBD was administered at 2 mg/kg/day by oral gavage in sesame oil beginning on the first day of DDC feeding. A separate DDC-fed cohort was also treated with intraperitoneal CBD at 2 mg/kg/day. Serum liver injury and cholestasis markers, including AST, ALT, ALP, and total bilirubin, were measured. Liver ductular reaction, hepatic inflammation, apoptosis, and fibrosis were assessed by CK19, CD68, TUNEL, and Sirius Red staining, respectively. Hepatic and ileal CB1/CB2 expression and intestinal barrier-defense markers, including Claudin-1, IgA, and Reg3γ, were evaluated by molecular and histologic approaches. Bacterial translocation to the liver was assessed by 16S rRNA gene qPCR in liver tissue and portal vein blood. **Results:** Oral CBD significantly attenuated DDC-induced elevations in serum liver injury and cholestasis markers and reduced ductular reaction, hepatic macrophage accumulation, apoptosis and fibrosis. Compared with oral CBD, intraperitoneal CBD showed only limited effect, with reducing ALT but not broadly improving AST, ALP, or total bilirubin. DDC feeding decreased CB1 and CB2 expression in both liver and ileum. Oral CBD did not restore hepatic CB1/CB2 expression but partially restored ileal CB1/CB2 expression, supporting selective intestinal ECS modulation. DDC-induced cholangiopathy was also associated with impaired intestinal barrier-defense signatures, including reduced ileal Claudin-1 and IgA staining and decreased Reg3γ expression. Oral CBD improved intestinal barrier-associated responses. Oral CBD also reduced bacterial translocation, as indicated by decreased 16S rRNA gene levels in liver tissue and portal vein blood. **Conclusion:** Oral CBD attenuates DDC-induced cholangiopathic injury and associates with selective restoration of ileal but not hepatic CB1/CB2 expression. Together with improved intestinal barrier-defense markers, these findings support a gut-engaged mechanism of CBD action and nominate intestinal ECS-associated barrier-defense signaling as a potential therapeutic axis for PSC-relevant cholangiopathy.

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1022 | THE MDR2-/- MICE MODEL FEATURES OF PRIMARY SCLEROSING CHOLANGITIS IN THE LIVER AND INTRAHEPATIC BILE DUCTS, BUT NOT IN THE EXTRAHEPATIC BILE DUCTS

Takuki Sakaguchi[1] Ashley Calder[2] John Tobias[3] Nataliya Razumilava[1], [1]University of Michigan, [2]University of Michigan Medical Center, [3]University of Pennsylvania

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Background: Primary sclerosing cholangitis (PSC) targeting epithelial cells of the biliary tree is characterized by inflammation with biliary hyperproliferation, fibrosis and cholestasis. PSC affecting the large intra- and extra- hepatic bile ducts (IHBDs and EHBDs) carries a high risk of developing cirrhosis and biliary tract cancer. Treatment options for patients with large duct PSC are limited by a poor understanding of PSC pathophysiology and limited pre-clinical models. Mice deficient in Mdr2(Abcb4) lack phosphatidylcholine in bile and are widely used to model PSC with liver and intrahepatic bile duct inflammation and fibrosis. Whether Mdr2-/- mouse model recapitulates PSC in the perihilar and extrahepatic biliary tree, the important targets of PSC in humans, is currently unknown. Aim: to investigate the utility of Mdr2-/- mice as a model of large duct PSC in the extrahepatic bile duct. **Methods:** Mdr2-/- mice were maintained on a C57BL/6 background. Liver and EHBD tissues were isolated and examined with immunohistochemistry, morphometrics and transcriptomics as bulk RNA-seq and gene ontology analyses. Mouse serum was tested for liver function tests. **Results:** As anticipated, Mdr2-/- mice showed liver fibrosis at 3 months of age as assessed by Sirius red histologic examination and had increased Col1a1 expression as compared to wild-type (WT) livers. Mdr2-/- mice had increased expression of cholangiocyte marker genes Krt19 and Krt7 within the liver suggestive of cholangiocyte expansion and ductular reaction. However, the EHBD of Mdr2-/- mice showed no overt histologic changes by H&E and had decreased KI67+ (proliferation marker) expression as compared with WT mice. There were limited transcriptional changes in the EHBD of Mdr2-/- mice with less than 100 differentially expressed genes with + >0.5 Log2FC and no changes in genes encoding collagens or cholangiocyte markers Krt7 or Krt19 as compared with WT EHBDs. **Conclusion:** The Mdr2-/- mouse model of inflammatory fibrotic cholangiopathy models PSC features in the liver and intrahepatic bile ducts with limited to no phenotype in EHBDs, which are often affected in PSC. This highlights the model limitations and difference in intra- and extra- hepatic bile duct pathology with a remaining need for models recapitulating features of PSC in large EHBDs.

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1023 | ACTIVATION OF CANNABINOID RECEPTOR 2 REGULATES MACROPHAGE CYTOKINE SECRETION TO IMPROVE CHOLESTATIC LIVER FIBROSIS

Suxian Zhao[1], [1]Hebei Medical University Third Hospital

Background: Cirrhosis is the progression of various chronic liver diseases to a pathological stage characterized by diffuse fibrosis of the liver, pseudo follicular formation, and proliferation of intra- and extrahepatic blood vessels. Cirrhosis of the liver has a variety of causes, of which cholestasis is an important one. Herein, we explored the therapeutic potential of targeting the cannabinoid-2 receptor (CB2-R) utilizing a commonly used mouse model of liver fibrosis, induced by bile duct ligation (BDL). **Methods:** Liver perforated paraffin tissues were collected from 50 patients with primary biliary cholangitis hospitalized in the Department of Traditional and Western Medical Hepatology of the Hebei Medical University Third Hospital from 2021 to 2024, and the patients were classified into early and late stages based on histological diagnostic criteria, and immunohistochemical staining for CD68 and CD163 was performed on the patients with early and late stages, respectively. 12-16 week-old C57BL/6J male mice were used and BDL was performed as described earlier. Following surgery, the animals were randomly assigned to one of six groups: Sham, Sham (AM-1241-treated), Sham (vehicle-treated), BDL, BDL(AM-1241-treated), and BDL, (vehicle-treated). The protein levels of YAP, TAZ, CTGF, α-SMA, ARG1、INOS、CD11b、F4/80 and TGF-βwere detected by Western blotting, while the mRNA levels of IL-6、IL-10、TNF-α、TGF-β、INOS、ARG1、MCP1、MIP1α、MIP2、CD68、CD163、CB2 and α-SMA were examined by real-time polymerase chain reaction (RT-PCR). **Results:** In advanced PBC patients, the expression of CD68 and CD163 is significantly higher compared to that in early-stage patients. The CB2-R agonist AM1241 is capable of modulating macrophage phenotypes, significantly reducing the expression of pro-inflammatory cytokines in the liver and alleviating the inflammatory response in the liver. Furthermore, AM1241 notably decreases the protein expression levels of YAP, TAZ, CTGF, and α-SMA. Histologically, AM1241 restricts the extension of fibroplasia and breaks the course of bridging fibrosis. **Conclusion:** Our results suggest that macrophages play a role in the development and progression of cholestatic liver disease. Additionally, CB2 receptor

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agonists significantly alleviate the inflammatory response to cholestatic liver fibrosis and ameliorate hepatic fibrosis through the YAP/TAZ signaling pathway.

Disclosures: suxian Zhao:Nothing to Disclose.

1024 | LOW PHOSPHOLIPID-ASSOCIATED CHOLELITHIASIS (LPAC) SYNDROME: A FOUR-GENERATION FAMILIAL CLUSTER ASSOCIATED WITH CIRRHOSIS AND HEPATOCELLULAR CARCINOMA

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Background: Low Phospholipid-Associated Cholelithiasis (LPAC) is a rare genetic form of cholelithiasis linked to pathogenic variants in **ABCB4** (MDR3), resulting in reduced biliary phosphatidylcholine, cholesterol supersaturation, and bile-mediated hepatocellular injury. We report a multigenerational family in which LPAC phenotype co-segregates with advanced liver disease, including cirrhosis and hepatocellular carcinoma (HCC). **Methods:** The proband is a 47-year-old man with a first attack of pancreatitis at age 19, followed by a second episode later that year. At that time, gallstones were detected in the absence of cholecystitis. He subsequently underwent cholecystectomy. However, despite the cholecystectomy, he went on to develop recurrent intra- and extrahepatic bile duct stones and multiple episodes of cholangitis, managed with repeated ERCPs. Most recently, in April 2026, he underwent another ERCP for cholangitis, with extraction of stones and biliary sludge. The early onset of symptomatic cholelithiasis, post-cholecystectomy recurrence, and a striking family history prompted evaluation for LPAC. Pedigree analysis, spanning four generations and including 13 relatives, was conducted. The patient was initiated on ursodeoxycholic acid (UDCA). **Results:** Pedigree review identified 10 first-degree relatives with available clinical data: five developed cirrhosis, and three of these progressed to HCC, two requiring orthotopic liver transplantation. Multiple relatives underwent cholecystectomy at young ages or had documented gallstone disease. No cases of cholangiocarcinoma were identified in this family. The clinical pattern—early symptomatic gallstones, recurrent biliary lithiasis after cholecystectomy, and clustering of advanced hepatobiliary disease—supports an inherited ABCB4-related disorder with a high penetrance for progressive liver injury in affected members. **Conclusion:** LPAC should be suspected in patients with gallstone disease presenting at a young age (< 40 years), with recurrent biliary lithiasis after cholecystectomy. Familial ABCB4/MDR3 deficiency may predispose to chronic hepatocellular injury, cirrhosis, and HCC. Early recognition, targeted genetic testing, cascade family screening, genetic counseling, and consideration of medical management with UDCA may reduce progression to advanced liver disease and inform surveillance strategies for at-risk relatives.



Disclosures: Gerond Lake-Bakaar:Nothing to Disclose.

1025 | REAL-WORLD TREATMENT RESPONSE AND HISTOLOGICAL CHARACTERISTICS OF PRIMARY BILIARY CHOLANGITIS IN A LARGE CHINESE COHORT

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Background: Primary biliary cholangitis (PBC) is a chronic autoimmune cholestatic liver disease that may progress to cirrhosis and liver failure. Ursodeoxycholic acid (UDCA) is the standard first-line therapy; however, a substantial proportion of patients exhibit inadequate biochemical response. Real-world data integrating demographics, histology, and treatment response in non-Western PBC populations remain limited. **Methods:** We conducted a retrospective cohort study of patients diagnosed with PBC at Mengchao Hepatobiliary Hospital of Fujian Medical University in China from January 2017 to March 2026. Demographic characteristics, liver biopsy findings, and treatment data were collected. Histological inflammation and fibrosis stages were evaluated in patients undergoing liver biopsy. Biochemical response was assessed after ≥ 12 months of UDCA monotherapy or UDCA plus fenofibrate using standard criteria. **Results:** A total of 1,974 patients with PBC were included, with a female predominance (71%). Most patients were middle-aged, with the

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highest proportion between 51–60 years; patients aged ≤30 or >70 years accounted for smaller proportions. Liver biopsy were performed on 317 patients, revealing heterogeneous disease stages. Most patients diagnosed at a non-cirrhotic stage, while 10.74%(33/317) patients had established cirrhosis.Among 1,646 patients with follow-up data, 1,623 received UDCA therapy. The biochemical response rate to UDCA monotherapy was 62.3% (1,011/1,623). A total of 612 patients showed inadequate response to UDCA; among them, 125 received add-on fenofibrate therapy, with a response rate of 28.7% (36/125). Inadequate responders were more frequently observed among patients with advanced histological stages and cirrhosis. **Conclusion:** In this large real-world Chinese PBC cohort, patients were predominantly middle-aged women but demonstrated substantial heterogeneity in histological stage at diagnosis. More than one-third of patients had an inadequate biochemical response to UDCA, and response to add-on fenofibrate therapy remained limited. These findings highlight persistent unmet therapeutic needs in PBC, particularly among patients with advanced fibrosis, and support the need for more effective second-line treatment strategies.
Disclosures: Zuxiong Huang:Nothing to Disclose, Qiaorong Gan:Nothing to Disclose, Qiuxiang Lin:Nothing to Disclose, Zhechang Chen:Nothing to Disclose, Aifang Lin:Nothing to Disclose, Xuwei Wu:Nothing to Disclose.

1026 | ◆ SE-1 ANTIBODY-CONJUGATED MSC EXOSOMES ENHANCE LSEC-TARGETED DELIVERY FOR LIVER FIBROSIS THERAPY

Hyung Tark Lee[1] Seul Ki Han[2] Moon Young Kim[2], [1]Department of Internal Medicine, Yonsei University Wonju, [2]Department of Internal Medicine, Yonsei University Wonju College of Medicine, Korea

Background: Liver sinusoidal endothelial cell dysfunction is a critical event in liver fibrogenesis. Loss of LSEC fenestration and subsequent capillarization impair hepatic microcirculation, facilitate hepatic stellate cell activation, and accelerate extracellular matrix deposition. We reported that MSC-derived exosomes have shown anti-inflammatory, anti-fibrotic, and regenerative potential. We aimed to develop an LSEC-targeted MSC exosome platform by combining PEGylation for prolonged circulation with SE-1 antibody conjugation for active sinusoidal endothelial targeting. **Methods:** Human MSC-derived exosomes were isolated using tangential flow filtration. Exosomes were surface-modified with polyethylene glycol and subsequently conjugated with anti-SE-1 antibodies. Particle size distribution and stability were assessed by nanoparticle tracking analysis, and cellular toxicity was evaluated using a CCK-8 assay. Targeting specificity was examined in vitro using primary LSECs. In vivo biodistribution and liver accumulation were analyzed after systemic administration in mice to compare SE-1 antibody-conjugated exosomes with unmodified control exosomes. **Results:** Engineered SE-1 antibody-conjugated exosomes demonstrated a stable and uniform particle profile after surface modification. PEGylation improved physicochemical stability without inducing significant cytotoxicity. Compared with unmodified exosomes, SE-1 antibody-conjugated exosomes showed significantly greater binding affinity to primary LSECs in vitro, supporting cell-specific targeting through SE-1 recognition. After intravenous administration, engineered exosomes showed improved systemic persistence and enhanced hepatic accumulation compared with native exosomes. These findings suggest that PEGylation and SE-1 antibody conjugation can cooperatively improve circulation stability and active delivery to the hepatic sinusoidal endothelium. **Conclusion:** SE-1 antibody-conjugated MSC exosomes achieved enhanced LSEC-specific binding and hepatic accumulation, addressing major delivery limitations of native exosomes. This engineered exosome platform represents a promising strategy for precision delivery of regenerative and anti-fibrotic signals and may provide a foundation for future LSEC-targeted therapy in liver fibrosis.
Disclosures: Hyung Tark Lee:Nothing to Disclose, Seul Ki Han:Nothing to Disclose, Moon Young Kim:Nothing to Disclose.

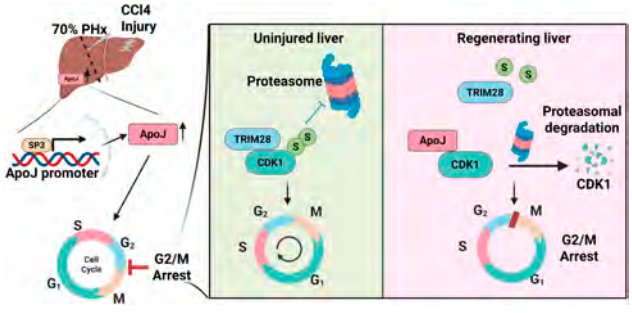
1027 | ◆ APOLIPOPROTEIN J RESTRAINS LIVER REGENERATION BY DESTABILIZING CDK1 THROUGH A TRIM28-LINKED SUMO-UBIQUITIN AXIS

Zhaohong Mo[1] Kai Ke[1] Shanyu Zhao[1] Guandou Yuan[1] Songqing He[1] Shuangdi Duan[1], [1]The First Affiliated Hospital of Guangxi Medical University

Background: Liver regeneration requires precise cell-cycle re-entry and progression, with tightly controlled protein homeostasis (proteostasis) as an essential prerequisite. However, the chaperone network, a central arm of the proteostasis machinery, remains poorly defined during liver regeneration. Apolipoprotein J (ApoJ/clusterin) is a stress-responsive molecular chaperone implicated in several liver disorders, but its role in regenerative growth is unknown. Here we sought to define the function and mechanism of ApoJ during liver regeneration and to

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assess whether this pathway is therapeutically tractable. **Methods:** We performed integrative transcriptomic screening, single-cell analyses, and in vivo validation to identify regeneration-associated chaperone after 70% partial hepatectomy. Hepatocyte-specific ApoJ knockout mice, AAV-mediated ApoJ overexpression, 70% partial hepatectomy, and CCl4-induced liver injury models were used to evaluate the functional role of ApoJ in liver regeneration. Mechanistic studies were conducted to examine the interaction among ApoJ, CDK1, and TRIM28, as well as the effects of ApoJ on CDK1 SUMOylation, ubiquitination, proteasomal degradation, and G2/M cell-cycle progression. Based on these findings, a CDK1-derived competitive peptide was designed to disrupt the ApoJ-CDK1 interaction and tested in hepatectomized mice. **Results:** ApoJ was identified as a hepatocyte-enriched chaperone induced during liver regeneration after 70% partial hepatectomy, and its induction was driven, at least in part, by the stress-responsive transcription factor Sp3. Hepatocyte-specific deletion of ApoJ accelerated regenerative proliferation, whereas AAV-mediated ApoJ overexpression impaired liver regeneration after partial hepatectomy and CCl4-induced injury. Mechanistically, ApoJ bound the C-lobe of CDK1, disrupted the TRIM28-CDK1 interaction, reduced protective SUMOylation of CDK1, and promoted ubiquitin-dependent proteasomal degradation, resulting in decreased CDK1 abundance and delayed G2/M progression. The CDK1-derived competitive peptide disrupted the ApoJ-CDK1 interaction, preserved CDK1 protein abundance, and enhanced liver regeneration in hepatectomized mice. **Conclusion:** ApoJ acts as a stress-induced brake on liver regeneration by destabilizing CDK1 through a TRIM28-linked SUMO-ubiquitin proteostatic pathway. Targeting the ApoJ-CDK1 interaction may therefore represent a potential strategy to improve delayed or insufficient hepatic regeneration.



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1028 | ◆ UNDERSTANDING LIVER COMMUNICATION: MOLECULAR CROSSTALK BETWEEN HEPATOCYTES AND NONPARENCHYMAL CELLS IN A HEPACTOCYTE-SPECIFIC *FUT8* DELETED MODEL

Andrew Bauer[1] Hongyan Liang[1] Mengjun Wang[1] Shaaron Ochoa-Rios[2] Anand Mehta[1], [1]Medical University of South Carolina, [2]Moffitt Cancer Center

Background: Over the last decade, MASLD prevalence has climbed to an estimated 30% of the global population, with industrialized countries often being affected disproportionately. Likewise, HCC has become much more widespread, causing approximately 800,000 deaths a year. We have previously shown changes in N-linked glycosylation in both MASLD and HCC in tissue and on individual cells. Of the changes, core fucosylation, a post-translational modification also found on the cancer biomarker AFP-L3, is one of the most common alterations associated with both MASLD progression and HCC. Little is known about the role of hepatic core fucosylation, and thus, this was tested through a hepatocyte-specific deletion of the only involved gene, fucosyltransferase 8 (*FUT8).* **Methods:** Female FUT8 flox/flox ($FUT8^{f/f}$) mice were bred with male mice positive for Albumin Cre in the liver, generating mice that had a hepatocyte-specific *FUT8* deletion. For data analysis, both $FUT8^{f/f}$ and $FUT8^{-/-}$ mice were sacrificed using standard procedures, perfusing their livers before isolating either primary hepatocytes or nonparenchymal cells. Each isolated cell type was then individually spotted on amine-reactive slides and MALDI-MSI was used to obtain the m/z values and the intensity level of expressed lipids and N-linked glycans. **Results:** Initial results indicate that deletion of *FUT8* in primary hepatocytes significantly decreases surface level lipids and N-linked glycans, excluding a small subgroup in the N-linked glycans and lipids. For the N-linked glycans, two nonfucosylated glycans are elevated in the $FUT8^{f/f}$ hepatocytes. Similarly, a subgroup of twenty-seven lipids consisting of ten PEs, six PSs, six SMs, three Hex2Cers, and two PCs had higher expression in the $FUT8^{f/f}$ hepatocytes. In nonparenchymal cells, almost all observed N-linked glycans and lipids found in stellate cells isolated from hepatocyte-specific $FUT8^{f/f}$

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deleted livers showing an increase in expression. In endothelial cells, N-linked glycans showed a slight decrease in expression while lipid signals were split into two groups of higher and lower presence. Of note is the significant increase in four core fucosylated N-linked glycans in stellate cells that share the same basal structure with differences only existing in small post-translation modifications. **Conclusion:** Based on the results, core fucosylation may be a necessary component in expression of specific lipid structures along with impacting N-linked glycosylation. Furthermore, the increase of N-linked glycans in FUT8$^{f/f}$ associated stellate cells, including ones of high fucosylation and similar structure, suggests that the nonparenchymal cells are attempting to compensate for the decreased levels in hepatocytes. It is also likely that the specific glycans in the stellate cells represent a specialized stress signal to communicate the issues that are occurring within the liver both to other local cells and the rest of the body.

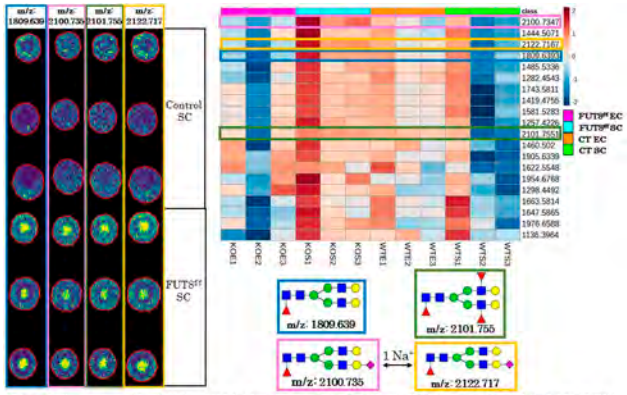


Figure 1. The top twenty N-linked glycans of the four nonparenchymal cell types (FUT8$^{f/f}$-associated endothelial cells, FUT8$^{f/f}$-associated stellate cells, control endothelial cells, and control stellate cells) and their intensity in a heatmap along with Bruker SCiLS images showing the intensity of m/z 1809.639, 2100.735, 2101.755, and 2122.717 in each stellate cell type. Each highlighted m/z corresponds in color to a proposed structure. Multiple of these structures share the same basal structure with minor post-translation modification or ionic changes, suggesting a coordinated response by the cell type to communicate with surrounding cells and potentially compensate for deficiencies. Heatmap is transformed by Log10 and auto scaled.

Disclosures: Andrew Bauer:Nothing to Disclose, Hongyan Liang:Nothing to Disclose, Mengjun Wang:Nothing to Disclose, Shaaron Ochoa-Rios:Nothing to Disclose, Anand Mehta:N-Zyme Scientific: Stock – privately held company, GlycoTest, INC: Stock – privately held company.

1030 | SINGLE-CELL PROFILING OF CHOLESTATIC LIVER INJURY REVEALS AN NLRP3+ INFLAMMASOME-ASSOCIATED NEUTROPHIL SUBPOPULATION DRIVING RECIPROCAL BILIARY CROSSTALK

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Background: Primary sclerosing cholangitis (PSC) is a cholestatic liver disease in which cholangiocytes acquire a pro-inflammatory phenotype recruiting immune cells, including neutrophils, to periportal bile ducts. Although neutrophils are enriched within this biliary immune niche, their transcriptional diversity and contribution to cholangiocyte–immune crosstalk during PSC progression remain poorly defined. **Methods:** Fixed single-cell RNA sequencing (FLEX) was performed on liver tissue, intrahepatic leukocytes, and bone marrow cells from wild-type (Chow-fed), and two murine models of PSC, DDC-fed (2 or 10 days) and Mdr2-/-mice. Bioinformatic analyses included clustering, differential gene-expression, pseudotime trajectory, and pathway-enrichment. Cell populations were annotated using canonical marker genes, followed by neutrophil-focused sub-clustering. Ligand–receptor interaction was analyzed using CellChat between cholangiocytes and different neutrophil subsets. **Results:** Neutrophil sub-clustering identified seven transcriptionally distinct subsets: myeloid progenitor, proliferative (Mki67+), reactive oxygen species-associated (Cybb+), matrix-remodeling (Mmp8+), interferon-responsive (Ifit3+), chemotactic/inflammatory (Retnlg+), and inflammasome-associated (Nlrp3+). Pseudotime trajectory analysis revealed a maturation continuum, with progenitor/proliferative in early states to chemotactic/inflammatory and inflammasome-associated as terminally differentiated. Nlrp3+ was the predominant intrahepatic subset in injury models, exhibiting the strongest NETosis-associated program and high immunoregulatory signatures, suggesting a disease-associated inflammatory neutrophil state. Ligand–receptor analysis shows enhanced bidirectional communication during disease. Cholangiocytes signaled to disease-associated neutrophil subsets through adhesion, chemokine, and immune-recruitment pathways (Spp1–Cd44, Jam1–Itgal/Itgb2, App–Sorl1, C3–Itgam/Itgb2, and Fn1–Cd44). Mature neutrophil subsets signaled back to cholangiocytes through Sema4a/Sema4d–Plxnb1/Plxnb2, Tgm2–Adgrg1, Osm–Osmr/Il6st, and Tgfb1-associated receptor complexes. Network-level analysis identified the Nlrp3+ subset cholangiocytes axis as a major hub, suggesting that this reciprocal signaling may amplify the biliary immune niche during cholestatic liver injury. **Conclusion:** Single-cell profiling identifies Inflammasome-associated neutrophils as a dominant disease-associated neutrophil subset in cholestatic liver injury. Bidirectional cholangiocyte–neutrophil signaling suggests that injured cholangiocytes and mature neutrophil subsets reciprocally reinforce the biliary immune niche, potentially promoting inflammation and fibrosis. Targeting pathogenic neutrophil states or specific crosstalk axes may represent a novel therapeutic strategy for PSC.

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Disclosures: Sofia Jerez:Nothing to Disclose, Papawee Sutthirat:Nothing to Disclose, Zhang Zhensheng:Nothing to Disclose, Abid Anwar:Nothing to Disclose, Alexander Wixom:Nothing to Disclose, Vijay Shah:Boehringer Ingelheim: Consultant, GSK: Consultant, GENFIT SA: Consultant, Intercept Pharmaceuticals, Inc.: Advisor, Korro Bio, Inc.: Consultant, Novo Nordisk A/S: Consultant, Resolution Therapeutics, Ltd.: Advisor, Seal Rock Therapeutics, Ltd.: Consultant, Surrozen: Advisor, Dexcel Pharma Technologies, Ltd.: Consultant, Dimension Inx.: Advisor, Enveda: Consultant, Ochre Bio: Consultant, Satellite Biosciences, Inc.: Consultant, Robert Huebert:Nothing to Disclose, Moira Hilscher:Orphalan: Consultant, Nidhi Jalan-Sakrikar:Nothing to Disclose.

1031 | FORMATION OF FIBROSIS RESOLUTION MACROPHAGES IS INDUCED BY OXYSTEROLS VIA ACTIVATION OF THE INTEGRIN–FOCAL ADHESION KINASE PATHWAY

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Background: Resolution of liver fibrosis following cessation of chronic injury requires active extracellular matrix (ECM) remodeling mediated in part by fibrolytic macrophages (Mφ). Previously published scRNAseq analysis in a mouse model of alcohol-associated liver disease identified a population of fibrolytic Mφ, enriched for matrix metalloproteinases (MMPs). These represent a subpopulation of monocyte-derived Kupffer cells. Studies have shown that the Notch, BMP, and LXR signaling pathways are critical for Kupffer cells formation. We have previously shown that oxysterols play an important role in the acquisition of the fibrosis resolution phenotype, however, the signaling mechanisms responsible for fibrolytic Mφ development are not understood. This study aimed to determine the signaling pathways responsible for the transformation of monocyte-derived cells into fibrolytic Mφ. **Methods:** Bone marrow-derived macrophages (BMDMs) were incubated with 25-hydroxycholesterol (25-HC) in vitro. MMP12 and MMP13 were measured by RT-qPCR. Inhibition studies were performed with Notch/LXR inhibitors, myeloid-specific $RBPJ^{-/-}$ cells, and integrin/focal adhesion kinase (FAK) inhibitors. These pathways were further evaluated using LXR agonists, and immobilized DLL4 and fibronectin. Ingenuity Pathway Analysis (IPA) was performed on transcriptional datasets from 25-HC-treated Mφs. FAK phosphorylation was determined by western blot, and collagen degradation activity was measured by DQ collagen assay. **Results:** 25-HC induced a fibrolytic phenotype in BMDM characterized by increased MMP12 and MMP13 expression and enhanced collagen degradation activity. The effect of 25-HC was partially inhibited by LXR antagonists and Notch inhibition, suggesting that both LXR and Notch activation were important. However, agonist treatment to selectively activate LXR or Notch had no effect, suggesting that these were necessary but not sufficient. IPA analysis showed that 25-HC robustly activated the FAK pathway and 25-HC caused FAK phosphorylation in vitro, suggesting Integrin-FAK as a possible mediator of 25-HC effects. FAK inhibitor completely blocked both basal and 25-HC-stimulated MMP12 expression and collagenase activity. scRNAseq data showed that fibrolytic KCs selectively express Itga5 and also express Itgb1, the components of integrin α5β1 (fibronectin receptor). A peptide integrin α5β1 inhibitor reduced MMP expression, while direct exposure of BMDM to a fibronectin matrix caused an increase in mRNA expression of MMP12 and MMP13. **Conclusion:** These findings reveal a previously unrecognized role for integrin–FAK signaling in regulating oxysterol-induced macrophage-mediated ECM degradation. Although oxysterols are LXR agonists, LXR activation only modulates this integrin-FAK effect and is not sufficient, by itself, to induce the fibrolytic phenotype.

Disclosures: Ayobami Dare:Nothing to Disclose, Kyle Yuquimpo:Nothing to Disclose, Isabel Aranzazu Pulido Ruiz:Nothing to Disclose, Sheetal Rooge:Nothing to Disclose, Madhulika Sharma:Nothing to Disclose, Ann Wozniak:Nothing to Disclose, Irina Tikhanovich:Nothing to Disclose, Steven Weinman:Nothing to Disclose.

1032 | INVESTIGATING HEPATOCYTE PLOIDY IN MURINE AND HUMAN LIVER

Dale Brokaw[1] Sydney Shaffer[1], [1]The University of Pennsylvania

Background: Hepatocytes are unique variably in genome copy number per cell, or ploidy, ranging from two genome copies per cell to as many as 16 copies per cell divided between one or two nuclei. The function of polyploid hepatocytes in the liver remains unknown. Diploid hepatocytes have been observed be more proliferative and more resistant to acetaminophen injury relative to polyploid hepatocytes; polyploid hepatocytes are more robust to loss of function mutations but are associated with higher levels of oxidative damage and Metabolic Associated Fatty Liver Disease (MAFLD). Difficulty capturing polyploid cell states has limited the investigation of polyploidy in the liver. Here, we use spatial transcriptomics to describe the gene expression and localization of polyploid hepatocytes in

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the mouse and human liver. **Methods:** Mouse data: A custom 215-gene seqFISH panel was applied to wildtype, low-ploidy (E2F7-/- E2F8-/-), and aging C57BL/6J mice (3, 10, and 20 months). Data was generated on the Spatial Genomics GenePS platform and processed in Scanpy (Python). Human data: Liver biopsies from seven patients (ages 26–64) were profiled using the 10x Genomics Xenium 5K panel across tumor, adjacent, and distant regions, then processed in Scanpy. PloidyXPress: Nuclear ploidy was inferred from nuclear area and intron counts in mice, and nuclear area alone in humans, classifying nuclei as 2n, 4n, or 8n+. Binuclear cells were identified by nearest-neighbor pairing, and paired nuclei expression profiles were summed. **Results:** Expression: Total transcripts per cell scaled with cell area and sublinearly with genome copy number, limiting the dosage response of individual genes. Multiple metabolic (Mlxipl, Angptl4, Gckr, Usp40) and cell-cycle related genes (Ccnl2, Zbtb16, Rfx7) showed ploidy-dependent expression independent of zonation. These dosage responses were conserved across aging. Localization: Using cholangiocytes and the pericentral Glul+ hepatocytes to define bile ducts and central veins, we found that genome copy number increased from periportal (zone 1) to pericentral (zone 3) regions in mouse liver. This gradient was driven largely by enrichment of hyperpolyploid 8N+ hepatocytes, persisted with aging, and colocalized with cycling hepatocytes. Translation: Human Xenium liver data revealed conserved ploidy-dependent expression of several genes, including Mlxipl and Zbtb16. However, unlike mouse liver, human samples did not display a clear periportal-to-pericentral ploidy gradient. **Conclusion:** This study provides a spatial characterization of gene expression changes in polyploid hepatocytes. We identify conserved dosage regulation of ploidy-associated genes across mouse and human liver. In mice, but not humans, hepatocyte ploidy forms a stable periportal-to-pericentral gradient, suggesting species-specific mechanisms of polyploidization.

Disclosures: Dale Brokaw:Nothing to Disclose, Sydney Shaffer:Nothing to Disclose.

1033 | TRANSCRIPTIONAL PROFILING OF THE MATERNAL LIVER ACROSS THE REPRODUCTIVE CYCLE REVEALS COORDINATED PROGRAMS OF GESTATIONAL GROWTH AND POSTPARTUM INVOLUTION

Anisha Jain[1] Satdarshan (Paul) Monga[1] Jia-Jun Liu[1] Silvia Hu[1], [1]University of Pittsburgh

Background: Pregnancy requires substantial hepatic adaptation to meet fetal metabolic demands, including organ growth during gestation and postpartum regression. Lactation sustains continued hepatic adaptation, while weaning triggers acute regression toward the prepartum state. The molecular programs coordinating these transitions and the mechanisms by which the liver restores homeostasis postpartum remain poorly defined. We aimed to characterize the temporal dynamics and molecular architecture of hepatic adaptation across the full reproductive cycle in mice. **Methods:** Liver RNA was collected from age-matched nulliparous (NP) controls and mice at gestational days 6, 12, 14, 16, and 18, and postpartum days 1, 10, 20, 22, 25, 27, and 31 (n = 3 per timepoint). Weaning occurred at day 21; day 22 was the first post-weaning timepoint. Bulk RNA-seq was performed and unsupervised hierarchical clustering identified co-expressed gene modules across the reproductive timeline. Gene Ontology Molecular Function (GO-MF) enrichment was performed per cluster, and targeted analysis of key gene families was conducted within involution-associated clusters. **Results:** Clustering identified five transcriptionally distinct modules with temporally coordinated expression. Early gestation featured upregulation of ATP hydrolysis, GTPase binding, ubiquitin ligase binding, and protein-folding chaperone activity. Peak gestation was associated with extracellular matrix structural constituents, glycosaminoglycan binding, lipid transporter activity, and growth factor binding, consistent with active scaffold remodeling to accommodate hepatic expansion. Post-weaning involution was characterized by ribosomal constituent activity, RNA polymerase II transcription factor binding, and immunoglobulin binding. Concurrently, post-weaning involution engaged proteostatic clearance machinery, including proteasomal shuttle proteins (Rad23b) and selective autophagy receptors (Calcoco1), showing progressive induction through PP27–PP31 and indicating parallel engagement of proteasomal and autophagic degradation. Global gene expression returned to NP baseline by postpartum day 31, confirming a complete and reversible transcriptional cycle. **Conclusion:** The maternal liver executes a coordinated, reversible transcriptional program across reproduction, comprising ECM-driven gestational expansion followed by post-weaning involution marked by proliferative shutdown and engagement of proteostatic degradation machinery. This temporal architecture is previously undescribed and establishes a framework for hepatic plasticity that may illuminate mechanisms disrupted in pregnancy-associated liver disease.

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1034 | TARGETING TEAD1 ALTERNATIVE SPLICING IN HEPATIC MYOFIBROBLASTS SUPPRESSES CHOLESTATIC FIBROSIS AND BILIARY REACTIVITY

Roi Isaac[1] Jinyue Wang[1] Jerrold Olefsky[1] John Youhanna[1] Theresa Rohm[1] Ludovic Vallier[2] Carla Frau[2] Tatiana Kisseleva[1], [1]University of California, San Diego, [2]Berlin Institute of Health Center for Regenerative Therapies, BIH@Charite, Berlin, Germany

Background: Primary sclerosing cholangitis (PSC) is a cholestatic liver disease characterized by biliary inflammation and periductal fibrosis, for which effective treatments are lacking. Portal fibroblasts (PFs) and hepatic stellate cells (HSCs) are key fibrogenic myofibroblasts. We showed that active TEAD1 (TEAD1$^{\Delta Ex5}$), generated by hnRNPU-mediated skipping of exon 5, drives HSC activation. Here, we tested whether targeting this TEAD1 alternative splicing axis with a splicing-modulating antisense oligonucleotide (TEAD1-Ex5-ASO) deactivates both PFs and HSCs, thereby alleviating cholestatic injury and paracrine biliary and inflammatory pathology. **Methods:** Human PSC liver RNA-seq was analyzed for TEAD target expression. Primary human and mouse PFs and LX-2 HSCs were transfected with TEAD1-Ex5-ASO, and bulk RNA-seq was performed on treated LX-2 cells. *In vivo* ASO efficacy was assessed in sorted GFP+ myofibroblasts from ColGFP/Mdr2KO mice. Male Mdr2KO mice received weekly intraperitoneal injections of TEAD1-Ex5-ASO (10 mg/kg) or control ASO for 4 weeks (ages 6–10 weeks). Paracrine effects of HSC-conditioned media (CM) were evaluated on H69 cholangiocytes, human intrahepatic cholangiocyte organoids (ICOs), and macrophages. **Results:** The TEAD1 target gene, CYR61, was elevated in PSC liver and correlated with fibrosis stage, supporting the relevance of TEAD1/YAP in disease. TEAD1-Ex5-ASO reduced levels of the active TEAD1$^{\Delta Ex5}$ isoform and suppressed pro-fibrotic and inflammatory targets CTGF, ACTA2, and IL6 in PFs and HSCs. RNA-seq further revealed broad suppression of the TEAD1/YAP transcriptional program, TGFβ-induced genes, and ECM organization pathways, as well as a defined secretome including PDGFB, CCN2, FGF1, and MMP7. Isoform-specific suppression was confirmed in sorted ColGFP/Mdr2KO myofibroblasts, accompanied by downregulation of *Col1a1*/*Msln* and upregulation of *Bambi*. ASO-treated Mdr2KO mice exhibited 30-50% reductions in ALT/AST and marked attenuation of periductal and periportal fibrosis, as assessed by hydroxyproline and Sirius red staining. Although cholangiocytes express >90% TEAD1$^{\Delta Ex5}$, the ASO failed to reduce the active isoform. However, HSC-CM deactivated H69 cholangiocytes by attenuating TGFβ signaling, reducing PAI1, FN1, and IL6. HSC-CM also suppressed expansion and increased apoptotic markers in ICOs, and attenuated pro-inflammatory macrophage gene expression, downregulating *Nos2* and *Il6*. **Conclusion:** Targeting the hnRNPU-TEAD1 splicing axis deactivates both PFs and HSCs, markedly reducing cholestatic injury and periductal fibrosis through direct myofibroblast deactivation and paracrine suppression of biliary reactivity and inflammation.

Disclosures: Roi Isaac:Nothing to Disclose, Jinyue Wang:Nothing to Disclose, Jerrold Olefsky:Nothing to Disclose, John Youhanna:Nothing to Disclose, Theresa Rohm:Nothing to Disclose, Ludovic Vallier:Nothing to Disclose, Carla Frau:Nothing to Disclose, Tatiana Kisseleva:Nothing to Disclose.

1035 | HYPERAMMONEMIA STABILIZES MUSCLE HYPOXIA INDUCIBLE FACTOR (HIF)-1A BY DECREASED HYDROXYLATION AND INCREASED ACETYLATION

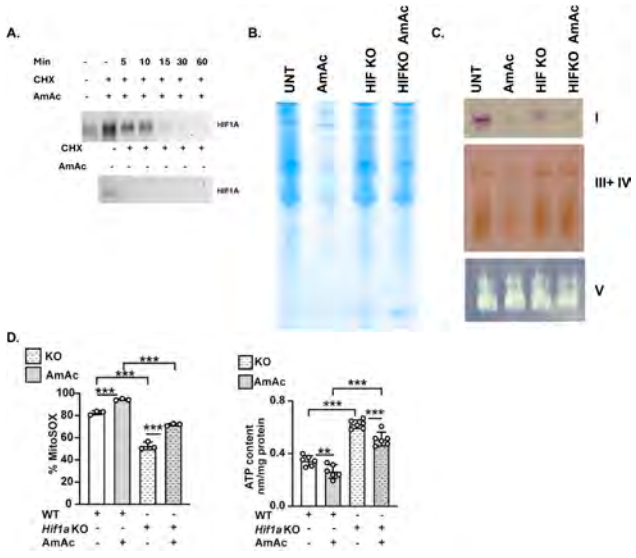
Nicole Welch[1] Pugazhendhi Kannan[1] Seshu Pothabathula[1] Saurabh Mishra[1] Annette Bellar[1] Vandana Agrawal[1] Jasmin Cunningham[1] Srinivasan Dasarathy[1], [1]Cleveland Clinic

Background: HASR causes sarcopenia in cirrhosis and stabilizes skeletal muscle HIF1a, but the post-translational mechanisms of HIF1a stabilization are unknown. Since normoxic HIF1a turnover requires hydroxylation, Von Hippel-Lindau protein (pVHL) recognition, and proteasomal degradation, we tested whether hyperammonemia stabilizes HIF1a by decreasing hydroxylation and degradation while increasing acetylation. **Methods:** C2C12 myotubes, hiPSC-derived myotubes were untreated/treated with 10mM ammonium acetate (AmAc) and skeletal muscle from mice with/without muscle specific HIF1a deletion (KO) were implanted with osmotic pumps containing either vehicle (phosphate buffered saline) or 2.5 mmol/kg/d AmAc infused over 28 days, and human skeletal muscle biopsies from the vastus lateralis of subjects with cirrhosis were studied. HIF1a protein, mRNA and target genes, nuclear/cytoplasmic localization, hydroxylated(OH-)HIF1a, pVHL, p300, GCN5, and Ac-HIF1a were quantified by immunoblotting(IB). In vivo imaging luciferase assay, immunoprecipitation of HIF1a/IB for acetyl-lysine, and MG132 protease inhibitor and

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cycloheximide chase (CXH) were used to determine HIF1a stability. Dimethyl alpha keto glutarate (dmaKG) rescue was studied. Protein synthesis and senescence signaling and mitochondrial supercomplex assembly/in-gel activity quantified in HASR with HIF KO. **Results:** AmAc increased HIF1a protein in C2C12 myotubes, hiPSC-derived myotubes, mouse muscle, and human muscle without increasing HIF1a mRNA. HIF1a accumulated in nuclear and cytoplasmic fractions and increased HIF-dependent transcriptional activity. AmAc prolonged HIF1a stability by CHX(**1A**). Although AmAc decreased aKG, dm-aKG did not reverse HIF1a stabilization in myotubes, and EGLN/PHD expression was not increased. AmAc decreased OH-HIF1a while total HIF1a increased, and pVHL-dependent studies in RCC VHL-/- and transfected RCC expressing pVHL-plasmid showed stabilization of HIF1a with AmAc was equivalent in control/AmAc treatment and restored with pVHL exogenous expression. In parallel, in myotubes, AmAc increased p300, GCN5, and acetyl-HIF1a, and HIF1a immunoprecipitation followed by acetyl-lysine immunoblotting confirmed increased HIF1a acetylation. HIF1a KO reversed AmAc-mediated suppression of p-P70S6K and p-eIF2a signaling, partially restored mitochondrial in-gel activity(**1B**), supercomplex assembly(**1C**), reactive oxygen species, ATP(**1D**) and reduced post-mitotic senescence signaling, including p21 and p-p53 (not shown). **Conclusion:** Hyperammonemia stabilizes HIF1a through decreased hydroxylation, impaired pVHL-dependent degradation, and increased p300/GCN5-associated acetylation. HIF1a mediates impaired protein synthesis, mitochondrial dysfunction, and post-mitotic senescence during HASR identifying acetylation-dependent HIF1a stabilization as a mechanism of sarcopenia in cirrhosis.



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1036 | OXIDIZED LOW-DENSITY LIPOPROTEIN (OXLDL)-DEPENDENT CD36 SIGNALING DECREASES LYMPHATIC ENDOTHELIAL PERMEABILITY IN CHRONIC LIVER DISEASE

Destiny DeNicola[1] Abbigayl Burtis[1] Nathaly Limon de la Rosa[1] Matthew Burchill[2], [1]University of Colorado Anschutz Medical Campus, [2]University of Colorado - Anschutz

Background: Lymphatic drainage is critical for maintaining liver homeostasis, and impaired lymphatic function contributes to progression of chronic liver disease. Previous studies demonstrated that oxidized low-density lipoprotein (oxLDL) drives lymphatic dysfunction through increased VE-cadherin (V-Cad) expression in liver lymphatic endothelial cells (LECs), while restoration of lymphatic drainage improves liver injury in mouse models of metabolic dysfunction-associated steatohepatitis. However, the signaling mechanisms by which oxLDL regulates V-Cad and lymphatic permeability remain unknown. Here, we sought to define the signaling pathways mediating oxLDL-induced lymphatic dysfunction. **Methods:** Primary human LECs or vascular endothelial cells (VECs) were treated with oxLDL, LDL, or HDL in the presence or absence of blocking antibodies targeting CD36, LDLR, and LOX-1 or specific inhibitors of AKT and SRC signaling. V-Cad expression, oxLDL uptake, and downstream signaling were assessed by western blot, immunofluorescence, and flow cytometry. Proteins that interact with V-Cad in LECs were identified by immunoprecipitation and mass spectrometry. In vivo confirmations of in vitro findings were performed using oxLDL injection, lymphatic drainage assays, and lymphatic-specific CD36 knockout mice. **Results:** Primary human LECs increased surface V-Cad in response to oxLDL through CD36-dependent signaling, while LOX-1 and LDLR were dispensable. Inhibition of oxLDL interactions with CD36 did not prevent oxLDL uptake in LECs, indicating that ligand internalization alone is insufficient to drive junctional remodeling. Treatment with LDL or HDL did not alter V-Cad levels, demonstrating ligand specificity. This response was specific to LECs, as oxLDL treatment did not increase V-Cad expression in VECs. Further, we found that both AKT and SRC are phosphorylated in a CD36 dependent manner in LECs following oxLDL treatment and inhibition of AKT, but not SRC, partially attenuated

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V-Cad accumulation. Additionally, co-immunoprecipitation results showed that oxLDL treatment reduced V-Cad association with p47 and VCP, consistent with altered AKT-dependent cadherin trafficking. Finally, in vivo studies confirmed that CD36 is required on LECs for oxLDL-induced V-Cad increase and lymphatic drainage dysfunction. **Conclusion:** These studies conclude that the interaction between oxLDL and CD36 alters lymphatic permeability *in vitro* and *in vivo* through promoting the retention of V-Cad on the surface of LECs and identifies AKT signaling as the primary driver of this response downstream of CD36. These findings provide mechanistic insight into lymphatic dysfunction in chronic liver disease and identify potential therapeutic targets for restoring lymphatic function in MASH and related inflammatory liver diseases.

Disclosures: Destiny DeNicola:Nothing to Disclose, Abbigayl Burtis:Nothing to Disclose, Nathaly Limon de la Rosa:Nothing to Disclose, Matthew Burchill:Nothing to Disclose.

1037 | *ALCOHOL-ASSOCIATED LIVER DISEASE DRIVES DUCTULAR REACTION IN HUMAN PRECISION CUT LIVER SLICES.*

Sehrish Naz[1] Susmita Bhattarai[2] Shanshan Su[2] Hua Xu[2] Sofia Izunza Barba[2] Denisse Rubio Cruz[2] Imad Nasser[3] Z. Gordon Jiang[3] Gyongyi Szabo[3], [1]Beth Israel Deaconess Medical Centre, Harvard medical school, [2]BIDMC, Harvard medical school, [3]Beth Israel Deaconess Medical Center

Background: Precision cut liver slice (PCLS) is a human tissue derived 3D culture that captures the native architecture of the donor liver. We have recently established an extended PCLS culture model, thus enabling the study of tissue remodeling during extended human PCLS culture. In this study, we compared differential tissue remodeling in PCLS derived from explant livers of alcohol-associated liver diseases (ALD) and control livers, which potentially recapitulates human pathologies of alcohol-associated hepatitis (AH). **Methods:** We procured liver tissue from explants of patients enrolled in the End-Stage Liver Disease Registry. ALD patients included those with alcohol-associated cirrhosis (AC) and AH, while control tissues were obtained from patients with metastatic cancer or polycystic liver diseases. PCLS preparation, culture and quality assessment was performed using an optimized protocol as previously published. We evaluated tissue remodeling using histology and gene expression analyses. **Results:** PCLS from explant liver can be cultured for up to 14 days as visualized by whole mount imaging of tissue with simultaneous staining of live and dead cells by different probes. In PCLS with normal liver microarchitecture, progressive fibrosis occurred spontaneously with increasing number of cells expressing alpha smooth muscle actin (ASMA) driven by stellate cell activation. By day 7, there was evidence of hepatocellular regeneration characterized by clusters of cells with homogenous morphology and lacking basement membrane, which was universally seen surrounding native hepatocytes. These findings supporting hepatocellular regeneration were not seen in PCLS derived from ALD patients. In contrast, ALD-derived PCLS exhibited progressive expansion of CK19+ cells representing cholangiocytes(Fig.1). These ductular reactions were most prominent around the periphery of hepatic lobule and circumference of the PCLS where oxygen availability was highest. A significant subset of CK19+ cells also expressed EPCAM and SOX9, markers of hepatic progenitor cells and Ki67, markers of active proliferation. **Conclusion:** During extended culture, PCLS remodels itself in response to the stress of a new *in vitro* environment. Our observation suggests that this intrinsic capability is shaped by the donor liver state, and to a significant extent, reflects the biology or pathology of the donor liver. PCLS with normal liver microarchitecture exhibits hepatocyte regeneration, restoring the tissue through proliferation. In ALD, the diseased microenvironment triggers a robust hepatocyte-to-biliary transition in PCLS, replacing the normal regenerative route, a finding that may recapitulate the pathophysiology of AH. PCLS preserves complex cell-to-cell interactions in the liver tissue *in vitro* and enables studies of cellular plasticity, ductular reaction, and fibrogenesis.

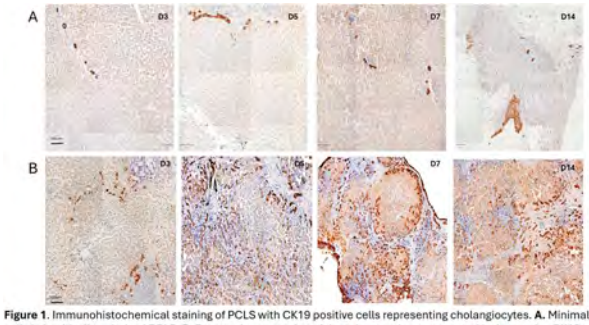


Figure 1. Immunohistochemical staining of PCLS with CK19 positive cells representing cholangiocytes. **A.** Minimal CK19+ cells in healthy liver derived PCLS. **B.** Progressive expansion of ductular reaction represented by increasing CK19+ cells in ALD-derived PCLS.

Disclosures: SEHRISH NAZ:Nothing to Disclose, Susmita Bhattarai:Nothing to Disclose, Shanshan Su:Nothing to Disclose, Hua Xu:Nothing to Disclose, Sofia Izunza Barba:Nothing to Disclose, Denisse Rubio Cruz:Nothing to Disclose, Imad Nasser:Nothing to Disclose, Z. Gordon Jiang:Olix Pharmaceutical: Consultant, Gyongyi Szabo:CYTA Therapeutics: Consultant, Durect Corporation: Consultant, Pandion

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1038 | MYELOID FOCAL ADHESION KINASE PROMOTES MACROPHAGE ACCUMULATION BUT IS DISPENSABLE FOR TUMOR PROGRESSION IN HEPATOCELLULAR CARCINOMA

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Background: Hepatocellular carcinoma (HCC) develops within an immunologically complex tumor microenvironment heavily shaped by infiltrating myeloid cells. Despite immune-based regimens like atezolizumab plus bevacizumab, durable responses remain uncommon, motivating efforts to identify signaling programs that sustain pro-tumor myeloid states. Focal adhesion kinase (FAK, encoded by *PTK2*) integrates adhesion, growth factor, proliferative, and inflammatory signaling, but the contribution of FAK in myeloid cells to HCC has not been tested. **Methods:** In this study, human HCC transcriptomic datasets were analyzed to characterize *PTK2* expression and associated transcriptional changes in myeloid cells. Single-cell analyses were performed using the PRHCCdb and NCI-CLARITY datasets. To test the functional role of FAK in myeloid cells, we generated myeloid-specific FAK knockout (LysMCre; $FAK^{f/f}$) mice and evaluated baseline conditions and after induction of MET/ß-catenin-driven HCC via hydrodynamic tail vein injection. **Results:** Analysis of the PRHCCdb single-cell database showed that *PTK2* expression was enriched in myeloid populations. Higher *PTK2* expression in myeloid-rich TCGA-LIHC tumors was associated with a significantly worse overall survival. Further analysis of the NCI-CLARITY single-cell dataset localized the strongest FAK-associated transcriptional programs to a monocyte-derived macrophage state marked by *VCAN* and *COLEC12*. This population demonstrated an enriched transcriptional signature for hypoxia-associated, inflammatory, and angiogenic programs. Deletion of myeloid-specific FAK in mice did not alter baseline liver morphology, liver-to-body weight ratio, or proliferation. When challenged with the MET/ß-catenin-driven HCC model, myeloid-specific FAK deletion did not significantly affect survival, gross tumor burden, or tumor proliferation. However, tumors from the LysMCre;$FAK^{f/f}$ mice showed significantly reduced $F4/80^{+}$ macrophage accumulation compared with $FAK^{f/f}$ controls. **Conclusion:** These findings identify a *PTK2*-associated transcriptional program within specific myeloid populations in human HCC and suggest that myeloid-specific FAK supports macrophage accumulation but is dispensable for tumor progression in this oncogene-driven HCC model.
Disclosures: Eugene Ham:Nothing to Disclose, Claudia Rose Keating:Nothing to Disclose, Kyle Boedeker:Nothing to Disclose, Ruisong Ye:Nothing to Disclose, Xianzhong Ding:Nothing to Disclose, Jonathan Rennhack:Nothing to Disclose, Wei Qiu: Nothing to Disclose.

1039 | SKELETAL MUSCLE REMODELING FOLLOWING LEUCINE-ENRICHED ESSENTIAL AMINO ACID SUPPLEMENTATION

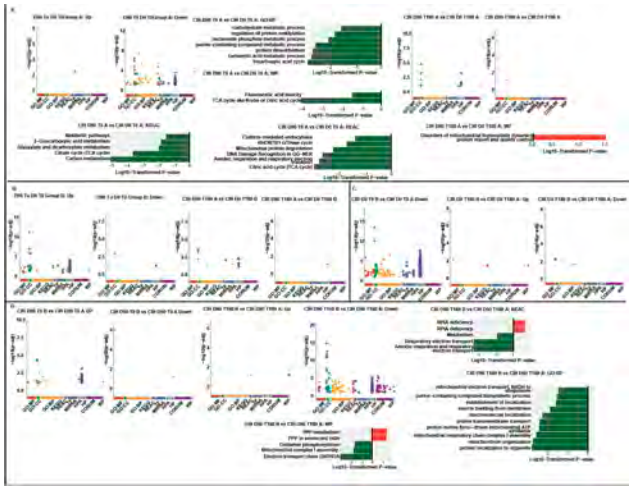
Annette Bellar[1] Nicole Welch[1] Ryan Musich[1] Pugazhendhi Kannan[1] Saurabh Mishra[1] John Kirwan[2] Marielle Engelen[3] Nicolass Deutz[4] Srinivasan Dasarathy[1], [1]Cleveland Clinic, [2]Pennington Biomedical Research Center, [3]Texas A&M University, [4]Texas A & M University

Background Sarcopenia and impaired skeletal muscle metabolism are common complications of cirrhosis and contribute to reduced functional status and poor clinical outcomes. The molecular responses to long-term leucine-enriched amino acid supplementation in cirrhosis are not known. **Methods:** Patients with compensated cirrhosis were prospectively randomized to receive either a leucine-enriched essential amino acid (LEAA; n = 11, age 53 $\pm$ 11 range 33-66, 100% alcohol related liver disease) or an isonitrogenous balanced amino acid (BAA; n = 11 age 57 $\pm$ 11 range 46-71, 54% alcohol related liver disease, 37% Hep-C, 9% MASH) supplement twice daily for 90 days (NCT03208868). Body composition and vastus lateralis muscle biopsies were obtained at baseline and end of study. Plasma and muscle tissue untargeted proteomics and metabolomics, and targeted amino acid profile analyses were performed baseline and Day 90 **Results:** Patients on LEAA had greater increases in plasma leucine, isoleucine, and valine compared with subjects receiving BAA with both acute and long term supplementation (all $p < 0.05$). Longitudinal skeletal muscle proteomic

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analyses demonstrated distinct remodeling patterns between groups (**Fig.1A-D**). Within-group analyses identified differential protein expression following 90 days of supplementation in both groups. Integrated pathway enrichment analyses further demonstrated significant coordinated alterations in mitochondrial and oxidative metabolic pathways following leucine-enriched supplementation ($p < 0.05$; **Fig. 1A-D**). In the LEAA group, enriched pathways included tricarboxylic acid cycle metabolism, carbon metabolism, aerobic respiration, respiratory electron transport, oxidative phosphorylation, mitochondrial ATP synthesis, and mitochondrial organization. BAA subjects showed weaker and less coordinated pathway enrichment patterns (**Fig.1B,C**). Comparative analyses between groups identified significant divergence in pathways related to mitochondrial organization, respiratory chain assembly, proton motive force-driven ATP synthesis, and electron transport chain activity following intervention ($p < 0.05$; **Fig.1D**). Our multiomics analyses in serial and longitudinal muscle biopsies in compensated cirrhosis identify a distinct pattern of metabolic remodeling of skeletal muscle mitochondria following LEAA vs BAA. **Conclusion:** Our data provide a unique skeletal muscle metabolic signature of mitochondrial oxidative responses with LEAA acutely which persisted over 90 days of use, supporting a long-term supplementation program to restore muscle responses in cirrhosis.



Disclosures: Annette Bellar:Nothing to Disclose, Nicole Welch:Nothing to Disclose, Ryan Musich: Nothing to Disclose, Pugazhendhi Kannan: Nothing to Disclose, saurabh mishra:Nothing to Disclose, John Kirwan:Nothing to Disclose, Marielle Engelen:Nothing to Disclose, Nicolass Deutz:Nothing to Disclose, Srinivasan Dasarathy:Nothing to Disclose.

1040 | UNBIASED IN VIVO CRISPRI SCREENING IDENTIFIES ACMSD AS A CANDIDATE MODULATOR OF HEPATIC NAD⁺ FOR LIVER REGENERATION

Salah Adlat[1] Lance Cai[2] Dingzi Yin[2] Markus Lee[2] David Frederick[3] Joseph Baur[3] Kirk Wangensteen[2], [1]Mayo Clinic, Rochester, [2]Mayo Clinic, [3]University of Pennsylvania

Background: Liver regeneration after acute injury or major resection lacks approved pharmacologic therapies that directly enhance hepatocyte repair. NAD^+ supports mitochondrial respiration, redox balance, and cell-cycle entry, but mechanisms controlling hepatic NAD^+ availability during regeneration remain incompletely defined. ACMSD is a liver-enriched kynurenine-pathway enzyme that diverts tryptophan-derived intermediates away from quinolinate, the obligate precursor for *de novo* NAD^+ synthesis. We hypothesized that ACMSD limits regenerative NAD^+ availability and represents a candidate metabolic target to support liver repopulation. **Methods:** To identify regulators of NAD^+ turnover during hepatocyte repopulation, *in vivo* CRISPRi screens were performed using a CRISPRi gRNA library targeting 143 NAD^+-pathway genes with 715 gRNAs and 100 non-targeting controls. Screens were conducted in *Fah*$^{-/-}$; *dCas9*$^+$ and *Nampt*$^{-/-}$;*Fah*$^{-/-}$;*dCas9*$^+$ mice, the latter modeling regeneration under impaired NAD^+ production. Transposon plasmids encoding *Fah* and the gRNA library were delivered to hepatocytes by hydrodynamic tail vein injection, followed by NTBC withdrawal to induce clonal expansion. gRNA enrichment was quantified by high-throughput sequencing and MAGeCK. ACMSD knockdown was further evaluated using CRISPRi in a cell line. For human validation, de-identified precision-cut liver slices (PCLS) were treated with TES-1025, a selective ACMSD inhibitor, and assessed by H&E, LDH release, and LC-MS/MS quantification of NAD^+-related metabolites normalized to protein. **Results:** The CRISPRi platform was highly reproducible, with strong concordance between replicate gRNA readouts in both models ($R^2 > 0.987$). ACMSD emerged among the top positively selected candidates in both the NAD-wildtype and the NAD-deficient screening background, with multiple independent sgRNAs enriched during repopulation, suggesting that ACMSD suppression may confer a selective advantage under regenerative and low-NAD^+ stress. Acmsd knockdown was confirmed by RT-qPCR, with ~70% reduction in expression ($p < 0.01$). In human PCLS,

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targeting ACMSD with TES-1025 preserved tissue architecture by H&E and did not show evidence of toxicity by LDH measurement. Targeted LC-MS showed variable changes in NAD^+-related metabolites, with trends toward higher levels of several pathway metabolites that require validation in additional donor tissues. **Conclusion:** *In vivo* CRISPRi screening identified hepatic ACMSD as a candidate regulator of NAD^+-linked hepatocyte repopulation. Initial human PCLS studies support the feasibility of testing TES-1025 in intact liver tissue, while its metabolic effects remain preliminary. Expanded donor cohorts, ^{13}C-flux tracing, and PHx studies are ongoing to define ACMSD's role in hepatic NAD^+ metabolism and regeneration.

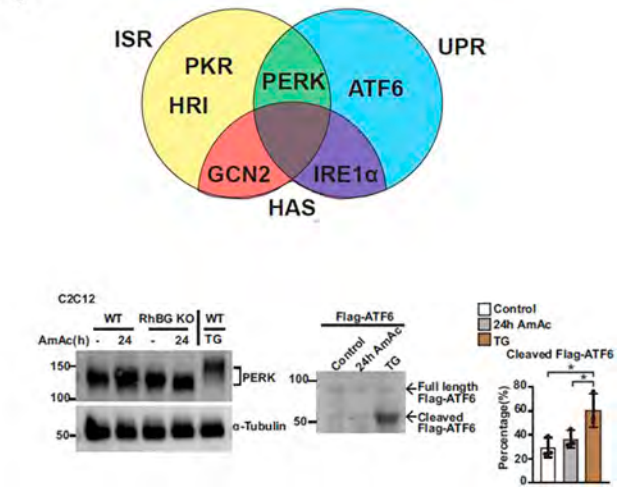
Disclosures: Salah Adlat:Nothing to Disclose, Lance Cai:Nothing to Disclose, Dingzi Yin:Nothing to Disclose, Markcus Lee:Nothing to Disclose, David Frederick: Nothing to Disclose, Joseph Baur:Nothing to Disclose, Kirk Wangensteen:Nothing to Disclose.

1041 | HYPERAMMONEMIC STRESS TRIGGERS A CONTEXT SPECIFIC MALADAPTIVE PARTIAL STRESS RESPONSE IN SKELETAL MUSCLE

Pugazhendhi Kannan[1] Nicole Welch[1] Saurabh Mishra[1] Annette Bellar[1] Jasmin Cunningham,[1] Seshu Vardhan Pothabathula,[1] Shashi Shekhar Singh[2] Vandana Agrawal[1] Maria Hatzoglou[2] Srinivasan Dasarathy[1],
[1]Cleveland Clinic, [2]Case Western Reserve University

Background: Hyperammonemia is a major metabolic complication of liver disease that induces a cytotoxic hyperammonemic stress response (HAS) in skeletal muscle and contributes to muscle wasting. Cellular adaptation to stress is regulated through the integrated stress response (ISR), mediated by the GCN2/PERK/PKR/HRI kinases, and the unfolded protein response (UPR) consisting of the IRE1α, PERK, and ATF6 arms. However, whether HAS globally activates these pathways or selectively regulates specific ISR and UPR signaling arms remains unclear. We investigated if hyperammonemia activates the GCN2 arm of the ISR together with the IRE1α arm of the UPR independent of PERK and ATF6, resulting in a context specific maladaptive partial stress response during HAS. **Methods:** Studies were performed in differentiated C2C12 myotubes and skeletal muscle tissues from hyperammonemic mice. Hyperammonemic stress response (HASR) was induced using 10 mM ammonium acetate in myotubes and continuous ammonium acetate infusion (2.5 $mmol \cdot kg^{-1} \cdot day^{-1}$ for 28 days) or saline in mice. Activation of integrated ISR kinases, including GCN2 and PERK, together with canonical UPR branches involving IRE1α-XBP1s, PERK, and ATF6 signaling, was evaluated by immunoblotting across multiple experimental models. To distinguish selective hyperammonemic stress signaling from canonical ER stress, PERK mobility shift were performed to assess PERK phosphorylation and activation status during HASR. **Results:** Hyperammonemic stress activated the GCN2 arm of the ISR and selectively activated IRE1α branch of the unfolded protein response UPR in both C2C12 myotubes and skeletal muscle tissues from hyperammonemic mice. Hyperammonemia significantly increased pGCN2 ($p < 0.01$), peIF2α ($p < 0.05$), and pIRE1α expression ($p < 0.05$), accompanied by enhanced XBP1 splicing, demonstrating activation of IRE1α endonuclease signaling during HASR. In contrast, other ISR kinases, including PERK, remained unchanged during hyperammonemic stress, as confirmed by immunoblotting and PERK mobility shift. Similarly, the canonical UPR branches mediated by PERK and ATF6 were not activated under HAS **(Fig.1)** . Collectively, these findings demonstrate that hyperammonemia induces a context-specific maladaptive partial stress response characterized by activation of the GCN2 and selective activation IRE1α-XBP1s axis pathways independent of canonical PERK and ATF6 mediated ER stress signaling. **Conclusion:** These findings demonstrated that hyperammonemic stress activated the GCN2 arm of the ISR and the IRE1α-XBP1 arm of the UPR without activation of PERK or ATF6 signaling. Unlike canonical ER stress, hyperammonemia induced a context specific maladaptive partial stress response, identifying selective GCN2 and IRE1α/XBP1s as a key mechanism underlying hyperammonemia associated skeletal muscle stress pathology.

Fig 1



Disclosures: Pugazhendhi Kannan:Nothing to Disclose, Nicole Welch:Nothing to Disclose, Saurabh Mishra:Nothing to Disclose, Annette Bellar:Nothing to

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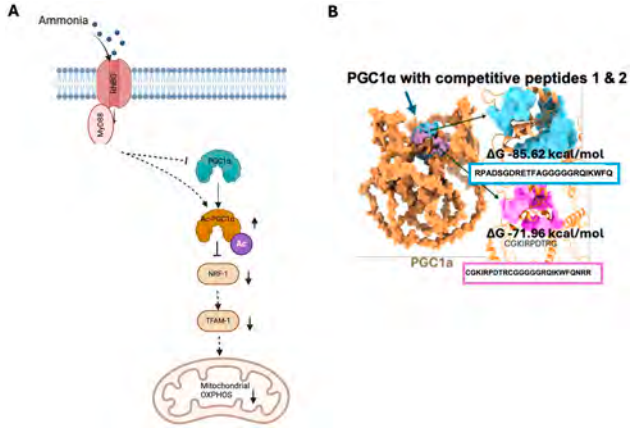
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1042 | GCN5/KAT2A DEPENDENT ACETYLATION OF PGC1A CAUSE STRUCTURAL AND FUNCTIONAL DEFECTS DURING HYPERAMMONEMIA

Saurabh Mishra[1] Seshu Vardhan Pothabathula[1] Pugazhendhi Kannan[1] Vandana Agrawal[1] Jasmin Cunningham[1] Annette Bellar[1] Dhanachandra Singh Khuraijam[1] Nicole Welch[1] Srinivasan Dasarathy[1], [1]Cleveland Clinic

Background: PGC-1α is a master transcriptional coactivator that orchestrates mitochondrial biogenesis and cellular energy homeostasis. Under hyperammonemic stress, GCN5-mediated acetylation of PGC-1α attenuates its transcriptional activity, promotes nuclear export, and contributes to mitochondrial dysfunction. The present study aimed to characterize the structural basis of the GCN5–PGC-1α interaction and evaluate the therapeutic potential of competitive inhibitory peptides targeting this axis. **Methods:** Three dimensional structures of GCN5/KAT2A (Q9JHD2) and PGC-1α (O70343) were retrieved from the AlphaFold database. Protein–protein docking was performed using HDOCK2.4 to evaluate binding affinity and conformational stability, followed by cluster RMSD analysis. Structural refinement and interaction profiling were conducted using GROMACS (GROMOS96 43a1 force field) and ChimeraX, respectively. Degron motifs were identified using DEGRON OPEDIA. Based on the predicted interaction interface, three cell penetrating peptides were rationally designed: a scrambled peptide (RPADSGDRETFAGGGGGRQIKWFQNRRMKW), a cyclic peptide (LPLPFLASPALGGGGGRQIKWFQNRRMKW), and a linear peptide (CGKIRPDTRCGGGGGRQIKWFQNRRMKW). Peptides were synthesized commercially, and cellular uptake of the FITC-conjugated linear peptide was validated by fluorescence microscopy. **Results:** Docking analysis demonstrated a highly favorable interaction between GCN5 and PGC-1α, with a minimum binding energy of −82 kcal/mol. Critical interaction residues, including Ser738–Lys253 and Asn408–Lys412, were identified as key contributors to complex stabilization and acetylation-associated conformational regulation. A. Fluorescence imaging confirmed efficient intracellular penetration of the designed peptides within 30 minutes of treatment. Among the tested constructs, the linear peptide exhibited superior efficacy in disrupting the GCN5–PGC-1α interaction, as determined by pulldown and immunoblot analyses. Hyperammonemic stress significantly suppressed the expression of downstream mitochondrial regulatory proteins, including NRF1, NRF2, TFAM, and OXPHOS complexes. Notably, inhibition of the GCN5:PGC-1α interaction restored the expression of these mitochondrial targets, indicating functional recovery of mitochondrial oxidative pathways. **Conclusion:** Collectively, these findings establish the GCN5–PGC-1α interaction as a structurally stable and functionally critical regulatory mechanism during hyperammonemia. Competitive inhibition of this interaction, particularly using rationally designed linear peptides, represents a promising therapeutic strategy for restoring mitochondrial bioenergetics and oxidative metabolism under hyperammonemic conditions.



Disclosures: Saurabh Mishra:Nothing to Disclose, Seshu Vardhan Pothabathula:Nothing to Disclose, Pugazhendhi Kannan:Nothing to Disclose, Vandana Agrawal:Nothing to Disclose, Jasmin Cunningham:Nothing to Disclose, Annette Bellar:Nothing to Disclose, Dhanachandra Singh Khuraijam:Nothing to Disclose, Nicole Welch:Nothing to Disclose, Srinivasan Dasarathy:Nothing to Disclose.

1043 | PROS1-MERTK MEDIATED CELL-CELL COMMUNICATION MODULATES HCC TUMOR MICROENVIRONMENT AND IMMUNE THERAPY EFFICACY

Zhengxin Liu[1] Jianfeng Xing[1] Xiang Lin[1] Yannan Peng[1] Buyang Zhai[1] Zhuan Li[1], [1]Hunan Normal University

Background: Hepatocellular carcinoma (HCC) remains a leading cause of cancer related mortality worldwide. Although immune checkpoint inhibitors (ICIs) have shown promise effects in advanced

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HCC, clinical efficacy is limited by low response rates and frequent acquired resistance. MerTK macrophage is subpopulation of tumor-associated macrophages (TAMs) frequently restrict $CD8^+$ T cell infiltration and establish a "cold tumor" phenotype. Mediators and mechanism underlying its polarization remain elusive. **Methods:** PROS1 and MerTK expression profiles were analyzed using GEO and single-cell RNA-sequencing datasets, and differentially expressed genes in MerTK-high macrophages were identified. Expression of PROS1 and MerTK was further confirmed using clinical samples. Crosstalk between cells was evaluated by co-culture systems. Western Blot and qRT-PCR were used for protein and mRNA measurement. Tumor-suppressive efficacy were analyzed through cell counting kit-8 (CCK-8), and orthotopic HCC mouse models, respectively. **Results:** MerTK-high macrophages exhibited 151 differentially expressed genes enriched in immune regulation and proliferation pathways. Single-cell sequencing and IHC revealed that PROS1 was predominantly expressed in tumor cells and expression level of PROS1 was positively correlated with MerTK macrophages infiltration in human HCC. Knockdown or neutralizing PROS1 in vivo significantly impaired MerTK macrophage and TAM formation, tumor growth but increased CD8+T cell infiltration and immune therapy efficacy. In addition, we found that PROS1 served as MerTK ligand which was essential for maintaining tumor promoting phenotype in macrophage. **Conclusion:** PROS1-MerTK axis drives TAM polarization, contributing to immunosuppressive tumor microenvironment. Therapeutic targeting PROS1-MerTK axis might potentiate novel options against human HCC.

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1044 | CELL DIFFERENTIATION INCREASES HEPATOCELLULAR SENSITIVITY TO ENDOPLASMIC RETICULUM STRESS

Zewei Zhang[1] Theo Velarde[1] Thomas Rutkowski[1], [1]University of Iowa Carver College of Medicine

Background: Hepatocellular identity is established through the differentiation from stem cells through definitive endoderm toward hepatic lineage. This liver identity is disrupted by unfolded protein response (UPR) when misfolded proteins are accumulated in the endoplasmic reticulum, also known as endoplasmic reticulum stress. Both hepatic identity disruption and endoplasmic reticulum stress are implicated in liver injury and disease. We have previously reported that loss of hepatic identity protects liver cells from endoplasmic reticulum stress. However, it remains unclear how differentiation states affect hepatocellular responses to endoplasmic reticulum stress. **Methods:** Human induced pluripotent stem cells (iPSCs) were differentiated into endoderm cells or iPSC-derived hepatocytes (iHeps) through a stepwise treatment of small-molecule cocktails. Cells at individual differentiation states were challenged with endoplasmic reticulum stress inducers, tunicamycin or thapsigargin. Cells were then assessed for endoplasmic reticulum stress readouts, including UPR gene expression and cell death. **Results:** In response to tunicamycin or thapsigargin, iPSCs, endoderm cells, and iHeps showed mild, moderate, and strong increases in UPR target gene expression, respectively. The greatest increase occurred during the differentiation from iPSCs to endoderm. Also, upon exposure to tunicamycin or thapsigargin, iPSCs exhibited minimal cell death, while endoderm cells underwent greater loss of viability. At the molecular level, compared with iPSCs, endoderm cells demonstrated higher expression of IRE1α protein and more active splicing of XBP1 mRNA. **Conclusion:** These findings suggest that differentiation along the hepatic lineage enhances cellular sensitivity to endoplasmic reticulum stress, providing insights into how impaired cell identity and stress response contribute together to liver injury and disease.

Disclosures: Zewei Zhang:Nothing to Disclose, Theo Velarde:Nothing to Disclose, Thomas Rutkowski:Nothing to Disclose.

1045 | MITOCHONDRIAL PEROXISOMAL CROSSTALK AS A MECHANISTIC DRIVER IN FONTAN-ASSOCIATED LIVER DISEASE

Moumita Chakraborty[1] Zulfeqhar Syed[2] Valentina Baena Echeverri[2] Rownock Afruza[1] Nivedha Vaidy[1] Mary Winnicki[1] Anjali Rai[1] Theo Heller[1], [1]NIH/NIDDK, [2]NIH/NHLBI

Background: Fontan-Associated liver disease (FALD) is an inevitable consequence of the Fontan circulation and a major cause of progressive liver failure in young congenital heart disease survivors. Chronic elevation of central venous pressure and reduced cardiac output impose sustained hepatic congestion and hypoxia, leading to fibrosis, cirrhosis, and hepatocellular carcinoma often in the absence of reliable biochemical predictors. The cellular mechanisms initiating this progression remain undefined. Because oxygen tension governs zonated hepatic metabolism, we hypothesized that coordinated mitochondrial peroxisomal dysfunction represents a central, yet unexplored, driver of FALD pathogenesis.

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Aim: To test that congestion driven hypoxia induces coupled mitochondrial injury and peroxisomal depletion, establishing an organelle failure axis that amplifies oxidative stress and fibrogenesis in FALD. **Methods:** We conducted high-resolution transmission electron microscopy of liver tissues from FALD patients (n = 5) and controls (n = 14) to systematically characterize mitochondrial morphology, cristae architecture, organelle clustering, peroxisome abundance, and extracellular matrix deposition. **Results:** FALD hepatocytes demonstrated coordinated and progressive organelle remodeling. Compared to controls, FALD samples exhibited marked collagen deposition within the space of Disse, pronounced mitochondrial clustering, solitary grossly swollen mitochondria with lucent matrix and disrupted cristae, megamitochondria formation, and significant mitochondrial ($p = 0.022$) and peroxisomal depletion ($p = 0.003$). Moreover, a significance increase of mitochondrial area ($p = 0.006$) was found in FALD samples as compared to controls. These findings reveal a synchronized breakdown of mitochondrial peroxisomal integrity consistent with impaired metabolic flux and redox disequilibrium, supporting a mechanistic model of hypoxia driven organelle failure preceding advanced fibrosis. **Conclusion:** This study reframes FALD as an active hepatocellular organelle failure model rather than passive congestion model, establishing mitochondrial-peroxisomal crosstalk as a novel and actionable mechanistic axis. By defining early ultrastructural biomarkers of organelle failure, this work lays the foundation for mechanistically targeted interventions that could transform risk stratification and therapeutic development for FALD an urgent need in congenital heart disease patients.

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1046 | GPC3 CAR ARMORED WITH DOMINANT NEGATIVE APOPTOSIS MEDIATING SURFACE ANTIGEN FAS/ TGF-BETA RECEPTOR II AND PROLIFERATION ELEMENT IL-7R DEMONSTRATE ENHANCED EFFICACY IN HEPATOCELLULAR CARCINOMA

Yuling Zhang[1] Ji Liu[1] Qi Cao[1] Haihua Gu[1] Shaun Cordoba[1], [1]JW Therapeutics R&D (Shanghai)

Background: Glypican-3 (GPC3) is a glycosylphosphatidylinositol-anchored protein overexpressed in hepatocellular carcinoma (HCC) but absent in normal adult liver, making it an attractive immunotherapy target. However, clinical GPC3 CAR-T therapies have shown limited durability due to the immunosuppressive tumor microenvironment (TME), which induces apoptosis and limits T cell persistence. We developed a fully human GPC3 CAR-T ("GPC3 turbo") armored with dominant-negative FAS (dnFAS), dominant-negative TGF-β receptor II (dnTGFβRII), and IL-7 receptor (IL-7R) to counteract FASL/TGF-β–mediated suppression and enhance persistence. **Methods:** Primary $CD4^+$ and $CD8^+$ T cells were lentivirally transduced to generate CAR-T cells. Cytotoxicity was assessed using xCELLigence RTCA in co-culture with HepG2 cells. Proliferation was measured by cell counting. Armor function was evaluated under soluble FASL and/or TGF-β1 conditions. In vivo efficacy was tested in an NCG xenograft HCC model. Tumor growth and CAR-T persistence were assessed by tumor volume and flow cytometry. **Results:** GPC3 turbo CAR-T cells showed enhanced cytotoxicity and proliferation versus non-armored CAR-T under FASL and TGF-β1 exposure. dnFAS and dnTGFβRII reduced apoptosis and TME-mediated suppression, while IL-7R improved survival under cytokine deprivation. In vivo, GPC3 turbo demonstrated superior tumor clearance and increased persistence. **Conclusion:** Armoring GPC3 CAR-T cells with dnFAS, dnTGFβRII, and IL-7R enhances resistance to TME suppression, reduces apoptosis, and improves persistence. GPC3 turbo shows improved antitumor activity and supports further clinical development for advanced $GPC3^+$ HCC.

Disclosures: Yuling Zhang:Nothing to Disclose, Ji Liu:Nothing to Disclose, Qi Cao:Nothing to Disclose, Haihua Gu:Nothing to Disclose, Shaun Cordoba:Nothing to Disclose.

1047 | DISTINCT TRANSCRIPTOMIC AND LIPIDOMIC PATTERNS IN HUMAN INDUCED PLURIPOTENT STEM CELLS (IPSCS) FROM MASH/CIRRHOSIS AND NORMAL PATIENTS

Moloud Aflaki Sooreshjani[1] Xiaoying Liu[1] Ryan Shaw[1] Nate Schmidt[2] Noah Greenberg[1] Ekta Minocha[2] John G Purdy[2] Jason A Wertheim[2] Richard Green[1], [1]Northwestern University Feinberg School of Medicine, [2]University of Arizona

Background: MASLD is the leading cause of abnormal liver function tests in the United States and a major driver of cirrhosis, liver failure, and hepatocellular carcinoma. Genetic factors contribute

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substantially to disease susceptibility, with heritability estimates ranging from 25–50%. Although only 20% of patients with fatty liver develop MASH, robust molecular and lipid biomarkers to identify patients at risk of MASH and disease progression to cirrhosis are lacking. We used human iPSCs as a platform for modeling disease mechanisms and to test whether iPSCs can be used to identify gene expression and lipidomic signatures differences between patients who develop MASH/Cirrhosis (MASH/CIR) and healthy controls (CON). iPSC-based models have applications for precision medicine and tailoring patients directed therapies. **Methods:** iPSCs reprogrammed from PBMCs isolated from patients with MASLD/Cirrhosis listed for liver transplantation were compared to normal healthy controls. iPSCs were treated with either fatty acid free bovine serum albumin (BSA) vehicle or 125 μM oleic acid/25 μM palmitic acid (OA/PA) for 48 hours. Cells were harvested and analyzed for gene expression using RNA-Seq or RT-PCR and for lipid analysis using liquid chromatography–tandem mass spectrometry. Gene set enrichment analysis (GSEA) with Hallmark gene sets was used with RNA-seq and comparison between groups used T-tests with the Benjamin–Hochberg procedure to control for the false discovery rate. **Results:** Human iPSC pluripotency was verified and similar in both groups. After OA/PA treatment in MASH/CIR group, GSEA revealed significant upregulation of pathways for unfolded protein response, oxidative phosphorylation, TNFα signaling via NF-κB and mTOR signaling ($p < 0.05$). In contrast, OA/PA treatment in CON iPSCs did not increase any inflammatory or UPR pathways. Lipidomic analysis demonstrated that BSA-treated MASH/CIR iPSCs had ~ 50% higher total triglyceride (TG) content compared to BSA-treated CON iPSCs ($p < 0.003$). Treatment with OA/PA induced a 3–4-fold increase in iPSC TG content in both groups, with no statistically significant differences between groups. In response to OA/PA treatment, 62 TGs were increased with 53 being increased in both groups and 9 unique to the CON group (TG: 66:8, 64:5, 62:4, 68:8, 66:7, 64:10, 66:6, 58:2, 68:9). **Conclusion:** These data indicate that iPSCs can serve as a model to distinguish transcriptomic and lipidomic signatures that differ between MASH/CIR and healthy patients. This may have important applications to determine the pathogenesis of MASH progression and for the development of biomarkers.

Disclosures: Moloud Aflaki Sooreshjani:Nothing to Disclose, Xiaoying Liu:Nothing to Disclose, Ryan Shaw:Nothing to Disclose, Nate Schmidt:Nothing to Disclose, Noah Greenberg:Nothing to Disclose, Ekta Minocha:Nothing to Disclose, John G Purdy:Nothing to Disclose, Jason A Wertheim:Nothing to Disclose, Richard Green:Mirum Pharmaceuticals: Advisor.

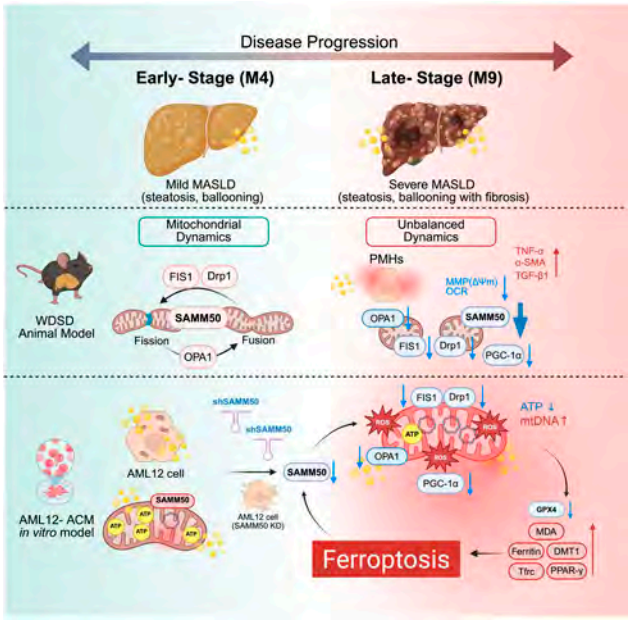
1048 | THE SAMM50 REGULATES MITOCHONDRIAL REDOX HOMEOSTASIS AND FERROPTOSIS DURING MASLD PROGRESSION

Shu-Chi Wang[1] Chi-Sheng Chen[1] Chia-Yang Li[1] Hui-Kuan Lin[2] Mohammed Eslam[3], [1]Kaohsiung Medical University., [2]Duke University, [3]The University of Sydney

Background: Mitochondrial dysfunction is a central feature of metabolic dysfunction–associated steatotic liver disease (MASLD). Sorting and Assembly Machinery Component 50 (SAMM50), a critical outer membrane protein, maintains mitochondrial architecture, yet its role in regulating metabolic stress-induced cell death remains poorly understood. This study investigates the SAMM50-GPX4 axis as a key determinant of ferroptosis sensitivity and disease severity in MASLD. **Methods:** We employed a long-term Western diet and sugar-drinking (WDSD) murine model to induce progressive MASLD. Hepatic transcriptomics and pathway analyses were used to identify core regulatory nodes. Functional assays in SAMM50-knockdown hepatocytes evaluated mitochondrial dynamics, ATP production, and ROS generation. The therapeutic potential of targeting this axis was assessed using the ferroptosis inhibitor UAMC-3203. Clinical relevance was validated by analyzing SAMM50 expression in human datasets across the spectrum of NAS scores and fibrosis stages. **Results:** In the progressive MASLD model induced by WDSD, classic steatosis and fibrosis were accompanied by a significant loss of mitochondrial SAMM50 inside the hepatocytes of liver tissues. Whole liver transcriptomic analysis indicated reduced oxidative phosphorylation, disrupted mitochondrial homeostasis, and enrichment of ferroptosis-related pathways. Mechanistically, SAMM50 deficiency enhances hepatocyte sensitivity to ferroptosis via decreased GPX4, upregulation of Transferrin Receptor (TFRC) and ferritin, and promoting lipid peroxidation. This sensitivity is further exacerbated by iron overload but pharmacologically mitigated by UAMC-3203. *In vivo* treatment with the ferroptosis inhibitor UAMC-3203 robustly alleviated hepatic steatosis and fibrotic progression, while concurrently blunting the aberrant activation of the cGAS-STING axis and its downstream inflammatory mediators, p-IRF3 and p-NF-κB. Multiple-database analysis shows that diminished SAMM50 expression strongly correlates with advancing fibrosis and elevated NAFLD Activity Scores (NAS) in patients. **Conclusion:** Our findings identify the SAMM50-GPX4 axis as a pivotal regulator of mitochondrial redox homeostasis. The metabolism-driven suppression of this axis reveals a latent vulnerability to ferroptosis, driving the transition from simple steatosis to advanced fibrosis. Targeting the SAMM50-GPX4 axis or inhibiting the downstream ferroptotic response offers a promising translational strategy for MASLD treatment.

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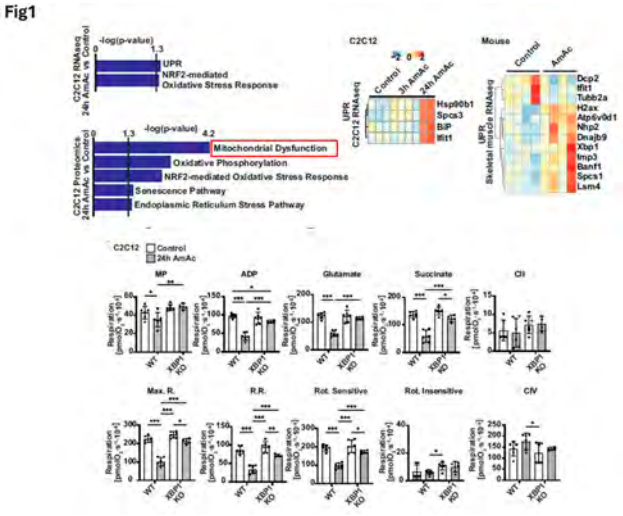
Disclosures: Shu-Chi Wang:Nothing to Disclose, Chi-Sheng Chen:Nothing to Disclose, Chia-Yang Li:Nothing to Disclose, Hui-Kuan Lin:Nothing to Disclose, Mohammed Eslam:Nothing to Disclose.

1049 | MALADAPTIVE IRE1α-XBP1S AXIS DISRUPTS MITOCHONDRIAL DYNAMICS DURING HYPERAMMONEMIC STRESS IN SKELETAL MUSCLE

Pugazhendhi Kannan[1] Nicole Welch[1] Annette Bellar[1] Saurabh Mishra[1] Shashi Singh[2] Jasmin Cunningham[1] Seshu Vardhan Pothabathula[1] Vandana Agrawal[1] Maria Hatzoglou[2] Srinivasan Dasarathy[1], [1]Cleveland Clinic, [2]Case Western Reserve University

Background: Hyperammonemia resulting from impaired ammonia metabolism in cirrhosis induces a cytotoxic hyperammonemic stress response (HASR) in skeletal muscle that contributes to sarcopenia through disrupted mitochondrial homeostasis. Mitochondrial dysfunction during HASR is characterized by impaired oxidative phosphorylation, altered mitochondrial dynamics, excessive mitochondrial fission, defective fusion, and accumulation of dysfunctional mitochondria. Since hyperammonemic stress selectively activates inositol-requiring enzyme-1 alpha (IRE1α), a conserved arm of the unfolded protein response (UPR), we investigated if the activation of the IRE1α-XBP1s signaling axis mediates mitochondrial fission–fusion imbalance and mitochondrial oxidative dysfunction during HASR-induced skeletal muscle sarcopenia. **Methods:** Studies were performed in differentiated C2C12 myotubes and in male and female C57BL6 mice with/without muscle-specific deletion (msd) of XBP1. HASR was induced using 10 mM ammonium acetate (AmAc) in myotubes and continuous AmAc infusion (2.5 mmol·kg^{-1}·day^{-1} for 28 days) or saline in mice. Integrated multiomics analyses, including RNA seq, and proteomics were performed in myotubes and skeletal muscle tissue to define the role of IRE1α-XBP1 signaling in mitochondrial remodeling during HASR. Mitochondrial oxidative function, mitochondrial dynamics, and signaling proteins regulating mitochondrial fission and fusion were quantified by immunoblotting and mitochondrial respiration using high resolution respirometry by substrate uncoupler inhibitor titration protocols. Mito and ER dynamics were evaluated by live cell fluorescence imaging using MitoTracker and ER Tracker to assess mitochondrial morphology, ER remodeling, and mito-ER interactions during HAS. **Results:** Hyperammonemic stress disrupted mitochondrial dynamics in skeletal muscle by increasing mitochondrial fission, as evidenced by elevated p-DRP1^{Ser616} ($p < 0.05$), DRP1, FIS1 ($p < 0.01$), and MFF expression, while suppressing mitochondrial fusion p-DRP1^{Ser637}, MFN1, MFN2, and OPA1 markers ($p < 0.05$), resulting in pathological mitochondrial fragmentation. Based on multiomics (Fig. 1) and experimental validation, deletion of XBP1 reversed these maladaptive alterations by attenuating mitochondrial dysfunction restoring dynamics (fission/fusion) and biogenesis, thereby preserving mitochondrial integrity and mitochondrial homeostasis during HAS. **Conclusion:** Hyperammonemic stress activates the IRE1α-XBP1s signaling axis to drive maladaptive mitochondrial dynamics (fision/fusion) and biogenesis in skeletal muscle. Deletion of XBP1 restored mitochondrial integrity and preserved mitochondrial homeostasis during HASR, identifying the IRE1α-XBP1s pathway as a central regulator of mitochondrial dynamics and a potential therapeutic target for hyperammonemia induced skeletal muscle sarcopenia.

Fig1



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1050 | ALYREF DRIVES HEPATOCELLULAR CARCINOMA PROGRESSION VIA LIQUID–LIQUID PHASE SEPARATION–MEDIATED ENHANCEMENT OF MRNA NUCLEAR EXPORT

Chun-Ming Wong[1] Xiaodan Zhang[1] Qidong Li[1] Carmen Wong[1] Irene Oi-Lin Ng[1], [1]The University of Hong Kong

Background: Efficient mRNA transport from the nucleus to the cytoplasm is essential for protein synthesis and cellular function. While transcriptional regulation has been extensively studied in hepatocellular carcinoma (HCC), the role of mRNA nuclear export in HCC progression remains largely unexplored. The transcription–export (TREX) complex is a conserved nuclear assembly that couples mRNA processing to export through the nuclear pore complex (NPC), with ALYREF serving as a critical RNA export adaptor that directly binds mRNAs. **Methods:** RNA sequencing (RNA-Seq) was employed to profile the expression of TREX complex components in primary HCC and matched non-tumorous liver tissues. Additionally, RNA-Seq was used to separately analyze nuclear and cytoplasmic mRNA pools to assess the impact of ALYREF on mRNA nuclear export. ALYREF knockdown HCC cell lines were generated using shRNA. Data-independent acquisition (DIA) proteomic analysis was performed to evaluate downstream protein changes. Immunofluorescence staining, in vitro phase separation assays, and fluorescence recovery after photobleaching (FRAP) assays were conducted to characterize ALYREF-mediated liquid–liquid phase separation (LLPS) and condensate formation. Nude mice subcutaneous orthotopic xenograft models were used to study tumor formation in vivo. GalNAc-conjugated siRNA (GalNAc-siRNA) targeting ALYREF was administered to evaluate therapeutic potential in mouse models. **Results:** Multiple TREX complex components, including ALYREF, were significantly upregulated in human HCC tissues and correlated with poor patient prognosis. ALYREF contains an intrinsically disordered region (IDR) that mediates LLPS to form nuclear condensates, facilitating nuclear export of cell cycle–related mRNAs. This mechanism promotes proliferation and migration of HCC cells. ALYREF knockdown markedly suppressed tumor cell growth in vitro and in vivo, effects rescued by wild-type but not IDR-mutant ALYREF. Targeted delivery of GalNAc-siRNA against ALYREF significantly inhibited HCC tumor growth in mice. **Conclusion:** Our findings establish ALYREF as a key LLPS-dependent RNA export adaptor that drives oncogenic gene expression programs in hepatocellular carcinoma. ALYREF represents a promising therapeutic target for intervention in HCC progression.

Disclosures: Chun-Ming Wong:Nothing to Disclose, Xiaodan Zhang:Nothing to Disclose, Qidong Li:Nothing to Disclose, Carmen Wong:Merck: Independent Contractor, Irene Oi-Lin Ng:Nothing to Disclose.

1051 | TARGETING ALK5 ATTENUATES HYPERAMMONEMIA INDUCED AMPK ACTIVATION AND DOWNSTREAM METABOLIC DYSFUNCTION

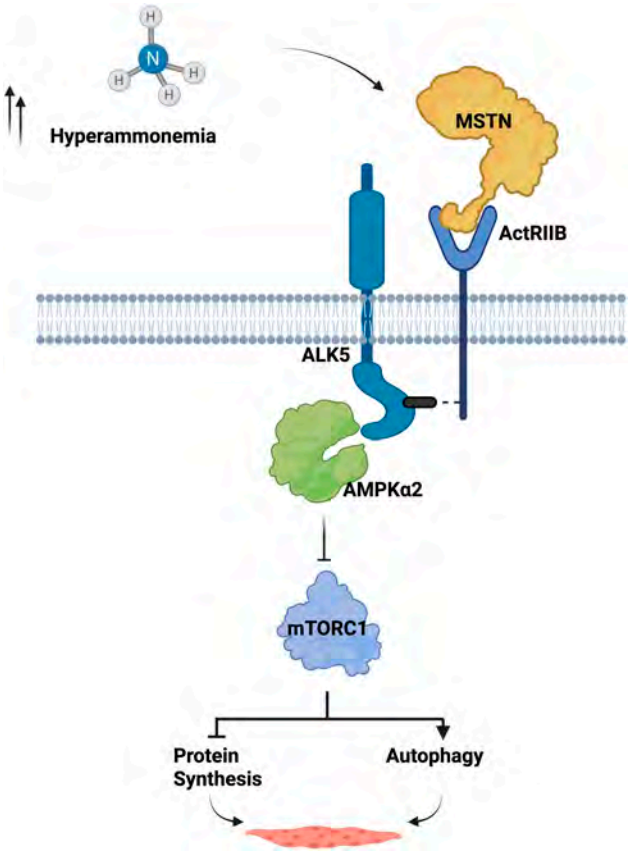
Saurabh Mishra[1] Muaz Alsabbagh Alchirazi Alchirazi[1] Annette Bellar[1] Seshu Vardhan Pothabathula[1] Pugazhendhi Kannan[1] Mohan Maradumane[1] Dhanachandra Khuraijam[1] Yuxin Wang[1] Nicole Welch[1] Srinivasan Dasarathy[1], [1]Cleveland Clinic

Background: We have previously reported that TGF-β superfamily member myostatin to cause sarcopenia during hyperammonemic stress response (HASR), a multicomponent response to perturbed ammonia metabolism, in cirrhosis. HASR also induces phosphorylation and activation of AMP-activated protein kinase (AMPK), with dysregulated protein homeostasis and sarcopenia. Canonical, myostatin signaling occurs via TGF-β receptor type I kinases ALK4/5-dependent activation of the transcription factor SMAD2/3 to cause muscle loss. Here we identified that AMPK to be an ALK5 target during HASR. **Methods:** Differentiated murine C2C12 myotubes with shRNA-mediated knockdown (KD) of canonical AMPK kinases (CaMKIIβ, TAK1, LKB1), and ALK4, ALK5, and both ALK4/5 were treated with 10 mM ammonium acetate (AmAc) for 24 h to induce HASR. Phosphorylated AMPKThr172 and canonical target ACCSer79 were quantified by immunoblotting. Functional rescue studies were performed by overexpressing ALK4, wild-type ALK5 (WT-ALK5), constitutively active ALK5 (ALK5-TD), and kinase-dead ALK5 (ALK5-KR) in myotubes with ALK4 or ALK5 KD. In vitro kinase assays using purified ALK4, ALK5, and active/inactive AMPK proteins. Myotubes were treated with ALK4 inhibitor SB-431542 and selective ALK5 inhibitor SB-525334 to determine non-canonical activation of AMPK during HASR. Mice with HASR induced by infusion of 2.5mmo.kg-1.-d for 28 days

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were treated with vehicle or ALK5 inhibitor for 14 days. **Results:** In vitro kinase assays demonstrated that both ALK4 and ALK5 phosphorylated AMPK, and this phosphorylation was inhibited by ALK4/5 inhibitors. In cellular experiments during HASR, KD of only ALK5 or double KD of ALK4/5 but not ALK4 alone or other canonical AMPK kinases CaMKIIβ, TAK1, LKB1, reversed AMPK phosphorylation/activation. Overexpression of wild type, full length ALK5 but not ALK4 restored HASR-induced AMPK phosphorylation/activation in KD myotubes. Expression of AMPK^{Thr172Ala} mutant in AMPK knockout C2C12 myotubes reversed ACC^{Ser79} phosphorylation, showing canonical AMPK^{Thr172} phosphorylation during HASR. Pharmacological inhibition of ALK5, but not ALK4, significantly inhibited phosphorylation of both AMPK and ACC. Muscle mass was restored with ALK5 inhibitor in mice with HASR. **Conclusion:** ALK5 is the principal kinase mediating HASR-dependent AMPK activation in skeletal muscle. Pharmacological inhibition of ALK5 attenuates downstream AMPK and ACC signaling, providing the rationale to target ALK5 to treat sarcopenia in cirrhosis.



Disclosures: Saurabh Mishra:Nothing to Disclose, Muaz Alsabbagh Alchirazi Alchirazi:Nothing to Disclose, Annette Bellar:Nothing to Disclose, Seshu Vardhan Pothabathula:Nothing to Disclose, Pugazhendhi Kannan:Nothing to Disclose, Mohan Maradumane: Nothing to Disclose, Dhanachandra Khuraijam:Nothing to Disclose, Yuxin Wang:Nothing to Disclose, Nicole Welch:Nothing to Disclose, Srinivasan Dasarathy:Nothing to Disclose.

1052 | COORDINATED METHYLATION ACROSS PPAR ISOFORMS IN PLASMA CELL-FREE DNA REFLECTS PATHWAY-WIDE EPIGENETIC DYSREGULATION IN MASLD AND SUPPORTS A PAN-PPAR THERAPEUTIC RATIONALE

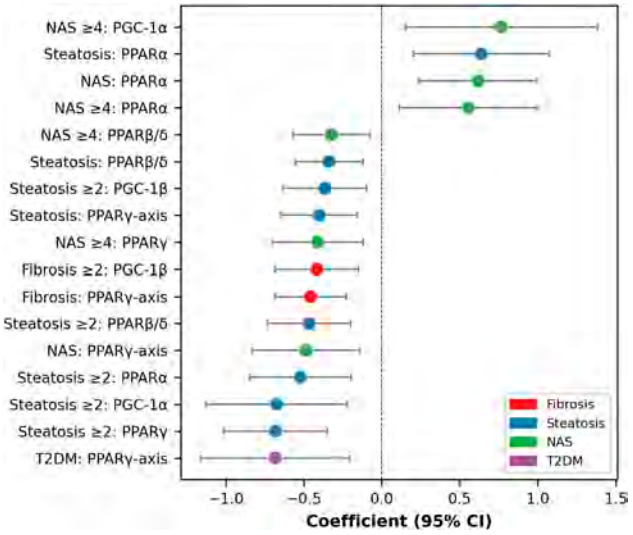
Manal Abdelmalek[1] Soheil Damangir[2] Guillaume Wettstein[3] Amin Naghdloo[2] Chong Lu[2] Leila Bazargan[2] Hamed Amini[2] Anna Mae Diehl[4], [1]Mayo Clinic Rochester, [2]Hepta Bio, Inc., [3]Inventiva, [4]Duke University

Background: PPARα, PPARβ/δ, PPARγ, and the PPARγ coactivators PGC-1α and PGC-1β jointly govern hepatic lipid metabolism, inflammation, and fibrogenesis. Pan-PPAR therapeutic strategies engage all three isoforms on the premise that their complementary activities address distinct aspects of MASLD pathophysiology. While methylation changes occur at many genes in MASLD, whether the PPAR family stands apart as a coordinated pathway, beyond what would be expected from genome-wide variation, has not been established. Prior methylation studies have used small targeted panels at single isoforms without comparison to the broader genome. We used whole-methylome plasma cfDNA to test whether the PPAR family, as a group, shows MASLD-associated methylation changes beyond what is seen across other genes in the genome. **Methods:** 278 plasma samples (59 controls; 219 biopsy-confirmed MASLD, F0–F4) from the Duke Biobank underwent whole-methylome cfDNA sequencing. For PPARα, PPARβ/δ, PPARγ, and the PPARγ coactivators PGC-1α and PGC-1β, co-methylated blocks in promoter, CpG island, and gene body regions were tested against fibrosis, steatosis, NAS (ordinal logistic; age, sex, T2DM-adjusted) and T2DM status (binary logistic; age, sex-adjusted), at pathway-group and individual-gene levels. The same pipeline was applied to other gene groups across the protein-coding genome; permutation testing evaluated whether PPAR's MASLD association exceeded this genome-wide reference. p-value < 0.05 was reported. When appropriate p-values were corrected for multiple hypothesis testing using Benjamini Hochberg. **Results:** Promoter regions of PPARγ was hypermethylated. All five PPAR family genes showed coordinated gene body hypomethylation in moderate-to-severe steatosis (OR 0.51–0.69). The PPARγ-axis was associated with

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fibrosis (p = 0.0008; via PGC-1β), steatosis (p = 0.011), NAS (p = 0.027), and T2DM (p = 0.046); PPARα with steatosis and NAS (both p = 0.012); PPARβ/δ with steatosis (p = 0.011). Effect directions at PPAR gene body loci were concordant across outcome pairs (steatosis vs NAS 100%, steatosis vs fibrosis 83%, fibrosis vs NAS 83%). PPAR family genes were more consistently associated with MASLD severity across all four outcomes than 99.9% of other gene groups in the protein-coding genome (permutation p < 0.001). **Conclusion:** Plasma cfDNA reveals coordinated gene body methylation change across the PPAR family in MASLD, with overlapping but distinct isoform contributions (PGC-1β to fibrosis, PPARα to disease activity, pan-PPAR involvement in steatosis) mirroring their complementary biological roles. This pathway-wide epigenetic signature supports the biological rationale for engaging multiple PPAR isoforms rather than targeting a single isoform. Detectability in cfDNA further suggests potential utility as a non-invasive readout of pan-PPAR pathway engagement and treatment response, to be explored in on-treatment cohorts.



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1053 | COMPREHENSIVE MAPPING OF BILE ACID METABOLISM, TRANSPORT, AND SIGNALLING GENES IN THE MOUSE WHOLE BRAIN: A SINGLE-CELL ATLAS BRIDGING THE LIVER-BRAIN AXIS

Emmanuel Dixon[1], [1]Medical University of Vienna

Background: Emerging evidence identifies BAs as signalling molecules that cross the blood-brain barrier and modulate neurological function via receptors, including the FXR and TGR5, contributing to the growing recognition of the liver-brain axis. Disruptions in BA signalling have been implicated in several neurological and psychiatric disorders, including Alzheimer's disease, Parkinson's disease, depression, and metabolic-associated cognitive impairment. However, our understanding of how BA metabolism and signalling machinery are distributed across the mammalian brain remains remarkably limited. Most studies have focused on targeted regions like hypothalamus or hippocampus, and a systematic, cell-type-resolved map of BA-related gene expression across the entire brain has never been generated, representing a critical gap between hepatology and neuroscience. **Methods:** We leveraged the Allen Brain Cell Atlas Mouse Whole Brain 10Xv3 single-cell RNA sequencing dataset comprising 2,341,350 cells across 26 anatomically defined brain regions, processed using Seurat v5 with BPCells on-disk matrix storage. Following quality control, normalisation, dimensionality reduction, and Louvain clustering (103 clusters), we systematically mapped expression of genes spanning BA synthesis, transport, nuclear and membrane receptors across all annotated neuronal subtypes and glial populations. **Results:** Our findings reveal striking regional and cellular heterogeneity in the expression of BA-related genes. Notably, key nuclear receptor such as *Nr1h2* (LXRβ) was ubiquitously expressed across virtually all brain regions, while *Nr1h4* (FXR) was enriched in specific GABAergic and glutamatergic subtypes. *Gpbar1* (TGR5) showed selective enrichment in cerebellar regions, midbrain, and hypothalamus. These patterns suggest that discrete neuronal circuits may be particularly sensitive to circulating or locally produced BAs. *Fgf15, Fgfr4,* and *Klb,* showed widespread neuronal expression, with the highest enrichment in the hypothalamus, thalamus, and hippocampus, consistent with a neuroendocrine signalling role. The observation of region-specific enrichment of *Cyp7b1, Cyp27a1,* and transporters *Slc10a2, Abcb11* further supports the possibility of localized BA production and transport within the CNS. Transport genes, including *Slc51a/b* (OSTα/β), were detected in glial populations. **Conclusion:** This preliminary analysis presents the

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first comprehensive single-cell atlas of BA-related gene expression across the mouse brain, establishing a molecular foundation for the liver-brain axis. On-going analysis is underway to integrate MERFISH spatial transcriptomics, which will enable 3D anatomical mapping and identification of BA-sensing neuronal circuits.

Disclosures: Emmanuel Dixon:Nothing to Disclose.

1054 | MZB1 LOSS DISRUPTS EARLY TRANSCRIPTIONAL REPROGRAMMING OF METABOLIC, PROLIFERATIVE, AND STRESS-RESPONSE GENE NETWORKS DURING LIVER REGENERATION

Jiang Li[1] Noriko Kitano[1] Lorien Walker[1] Sudrishti Chaudhary[1] Jia-Jun Liu[1] Silvia Liu[1] Juliane Beier[1] Oliver Eickelberg[1] Marta Bueno[1] Gavin Arteel[1], [1]University of Pittsburgh

Background: We previously reported that MZB1 expression is elevated in human fibrotic liver disease and that MZB1 knockout (KO) mice develop more severe CCl4-induced liver injury and fail to regenerate normally following 70% partial hepatectomy (PHx), with hepatocytes blocked at the G0-G1 transition at 24 hours. Those findings established MZB1 as a regulator of hepatocyte proliferation, but the upstream mechanism remains unknown. The early post-PHx period represents a critical priming phase during which transcriptional programs governing metabolic adaptation and growth factor signaling are established prior to cell cycle entry. The present study examined 6-hour transcriptional events following PHx to determine how MZB1 loss disrupts this program. **Methods:** Wild type and MZB1 KO mice underwent 70% PHx, with liver tissues harvested at 6 and 24 hours. RNA sequencing (RNAseq) was performed on both time-points and analyzed by Ingenuity Pathway Analysis (IPA), Gene Ontology and KEGG pathway enrichment, and STRING/Cytoscape protein network analysis. **Results:** At 6 hours post-PHx, MZB1 KO livers showed 2,000 differentially expressed genes (DEGs) relative to WT controls (872 uniquely dysregulated in KO, 1,128 shared), with 1,015 DEGs persisting at 24 hours. Both whole-body and inducible conditional KO models showed concordant results, supporting a cell-autonomous transcriptional phenotype rather than a developmental compensation effect. IPA identified dysregulation of pathways governing connective tissue cell proliferation and tumor cell growth, with transcriptional regulators STAT1, STAT6, MEK3, and TP73 among the most significantly altered. GO and KEGG enrichment analyses identified impairment of steroid and lipid metabolic processes, xenobiotic and retinol metabolism, bile secretion, and steroid hormone biosynthesis. STRING and Cytoscape network analyses confirmed disruption of protein interaction hubs central to regenerative signaling, including HGF/c-Met, STAT3, and mTOR pathway components. In WT mice, 6-hour PHx samples showed expected enrichment in metabolic pathways, TNF and MAPK signaling, insulin resistance pathways, and stress-response processes, demonstrating that WT livers mount the expected early transcriptional response, which is substantially attenuated in KO animals. **Conclusion:** The early transcriptional disruption observed here precedes the G0-G1 cell cycle block reported previously and clarifies the mechanism by which MZB1 supports hepatocyte proliferation. The exacerbated injury phenotype in KO mice reflects a proliferative rather than antifibrotic role for MZB1 in the liver, contrasting with its profibrotic function in lung and skin. These data strengthen the rationale for targeting MZB1 as a strategy to improve liver regeneration in clinical settings.

Disclosures: Jiang Li:Nothing to Disclose, Noriko Kitano:Nothing to Disclose, Lorien Walker:Nothing to Disclose, Sudrishti Chaudhary:Nothing to Disclose, Jia-Jun Liu:Nothing to Disclose, Silvia Liu:Nothing to Disclose, Juliane Beier:Nothing to Disclose, Oliver Eickelberg:Nothing to Disclose, Marta Bueno:Nothing to Disclose, Gavin Arteel:Nothing to Disclose.

1055 | TERRESTRIAL–COSMIC COMPARISON: LIVER COMPENSATORY MECHANISMS IN HUMAN DISEASE AND SPACEFLIGHT-EXPOSED MICE

Mary Winnicki[1] Nivedha Vaidy[1] Rownock Afruza[1] Moumita Chakraborty[1] Anjali Rai[1] Theo Heller[1], [1]National Institutes of Health

Background: Mitochondrial stress is a central and reproducible biological response to spaceflight. Because mitochondrial dysfunction is implicated in hepatic injury and liver disease progression, spaceflight-exposed liver may provide a useful model for studying mitochondrial-associated mechanisms of hepatic vulnerability. Prior studies have shown that spaceflight-exposed mouse liver develops disease-like metabolic remodeling. However, whether these changes involve broader conserved stress-response programs shared with liver disease is not well defined. By comparing mouse spaceflight-exposed liver with human liver disease datasets, this project seeks to identify conserved pathways that may represent mitochondrial-associated mechanisms of hepatic dysfunction. **Methods:** Mouse liver transcriptomic datasets were acquired from the NASA Open Science

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Data Repository (OSDR). Compared cohorts included basal controls, ground controls, spaceflight mice sacrificed onboard the International Space Station (ISS), and live animal return (LAR) mice that returned to Earth before tissue collection. Raw count data were analyzed for differential expression, and resulting gene-level statistics were used for gene set enrichment analysis to identify pathways altered by spaceflight exposure. Network-based integration of enriched pathways, leading-edge genes, and WGCNA-derived co-expression modules was then used to define coordinated stress-response signatures. Mouse-derived pathway and module signatures were mapped to human orthologs and compared with human liver disease datasets to identify conserved stress-response programs shared between liver disease and spaceflight-exposed liver. Exploratory feature-prioritization analyses were used to assess whether conserved signatures distinguished spaceflight-exposed liver from controls and aligned with human disease patterns. **Results:** Spaceflight-exposed liver showed recurrent enrichment of mitochondrial, metabolic, immune, and cytoskeletal stress-response programs across mouse datasets. The relative contribution of these programs varied by strain, flight duration, and dissection location, but conserved stress signatures were still observed across spaceflight models. Notably, immune-associated pathways appeared to be partially decoupled from metabolic and cytoskeletal features, suggesting distinct adaptive stress-response axes during spaceflight exposure. **Conclusion:** Spaceflight-exposed liver demonstrates conserved stress-response signatures despite model-specific variation in mitochondrial, metabolic, immune, and cytoskeletal remodeling. These findings support its use as both a comparative model for liver disease vulnerability and a unique system for identifying spaceflight-associated mechanisms of hepatic stress remodeling.

Disclosures: Mary Winnicki:Nothing to Disclose, Nivedha Vaidy:Nothing to Disclose, Rownock Afruza: Nothing to Disclose, Moumita Chakraborty:Nothing to Disclose, Anjali Rai:Nothing to Disclose, Theo Heller: Nothing to Disclose.

1056 | *METABOLIC REMODELING INDUCED BY GERANYLGERANYL COMPOUNDS IN HEPATOCELLULAR CARCINOMA CELLS*

Ignasi Bofill verdaguer[1] Damelia Echevarria[2] Carmen Garcia-Ruiz[2] Jose Carlos Fernandez-Checa[2], [1]Institute of Biomedical Research of University of Sao Paulo, [2]Spanish National Research Council

Background: Geranylgeraniol (GGOH) is a diterpene obtained from dietary sources and also synthesized endogenously from geranylgeranyl diphosphate (GGPP), a key end-product of the mevalonate (MVA) pathway. GGOHcan either be oxidized into bioactive metabolites such as geranylgeranoic acid (GGA), or phosphorylated back into GGPP. Beyond this metabolic role, GGOH has been reported to downregulate the MVA pathway and to exert pleiotropic biological effects, including anticancer activity. Given these dual roles, identifying non-metabolizable analogues that retain its regulatory and anticancer properties could provide new tools to modulate the MVA pathway without being rapidly metabolized. **Methods:** To address this, we investigated the metabolic and functional effects of GGOH and teprenone (geranylgeranylacetone), a synthetic diterpene analogue, in human hepatocellular carcinoma HepG2 cells. We performed in vitro radiolabeling experiments to assess GGOH metabolism, its incorporation into cellular components, and the impact of teprenone on these processes. Lipid extraction and lipidomics analyses were conducted to evaluate changes in lipid composition and acetate incorporation into lipid species. Additionally, transcriptional profiling was used to examine the regulation of genes involved in mitochondrial function and key metabolic pathways, including lipid and carbohydrate metabolism. **Results:** Radiolabeling experiments revealed that teprenone interferes with GGOH metabolism, reducing its incorporation into cellular proteins and enhancing its cytotoxic effects. Teprenone alone, and more prominently in combination with GGOH, disrupted the MVA pathway. Both diterpenes altered cellular lipid composition and reduced acetate incorporation into lipids, with the strongest effects observed under co-treatment conditions. At the mechanistic level, both compounds induced an anti-Warburg effect, shifting cellular metabolism away from glycolysis and toward mitochondrial respiration. This was accompanied by broad transcriptional changes affecting genes involved in mitochondrial function, lipid and carbohydrate metabolism. **Conclusion:** Together, these findings establish GGOH as both an endogenous lipid precursor and a regulator of cellular bioenergetics, with significant effects on lipid metabolism and mitochondrial function. Teprenone emerges as a non-metabolizable analogue that preserves many of GGOH's biological activities, including MVA pathway modulation and anticancer effects, while avoiding its metabolic conversion. These results highlight the potential of both GGOH and teprenone as valuable tools for studying metabolic regulation and as promising candidates for therapeutic strategies targeting cancer and metabolic diseases.

Disclosures: Ignasi Bofill verdaguer:Nothing to Disclose, Damelia Echevarria:Nothing to Disclose,

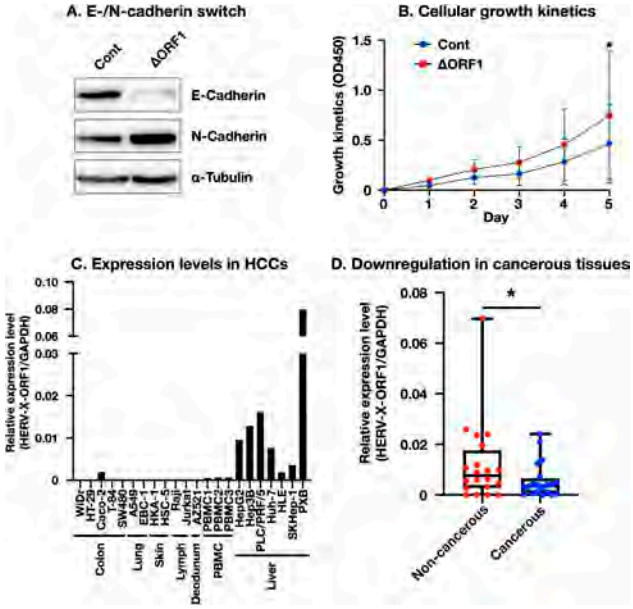
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Carmen Garcia-Ruiz:Nothing to Disclose, Jose Carlos Fernandez-Checa:Nothing to Disclose.

1057 | AN ENDOGENOUS RETROVIRUS-DERIVED GENE MAINTAINS THE EPITHELIAL STATE OF HUMAN HEPATOCYTES

Yuki Nakaya[1] Kazuhisa Murai[2] Daichi Onomura[1] Tomoko Yamagata[1] Masao Honda[3] Kazumoto Murata[1], [1]Jichi Medical University, [2]Kanazawa University Graduate School of Medical Sciences, [3]Kanazawa University Graduate School of Medical Science

Background: Endogenous retroviruses (ERVs) are remnants of ancestral retroviral infections in the germline and are increasingly recognized to play physiological roles in humans. Recent studies have suggested that a human ERV-derived transcript (HERV-X) is preferentially expressed in normal liver tissues, although its precise function remains unclear. Here, we characterized its molecular functions and detailed expression profile in hepatocytes. **Methods:** The protein encoded by the HERV-X transcript was characterized. Loss- and gain-of-function studies assessing gene expression, cell growth, and migration were performed in HepG2 cells. HERV-X transcription levels in primary human hepatocytes (PHHs), hepatocellular carcinoma (HCC) cell lines, and paired non-cancerous and cancerous liver tissues from identical patients (n = 20) were analyzed by HERV-X-specific RT-qPCR. **Results:** Although the HERV-X transcript contained three open reading frames (ORFs), only ORF1, derived from the envelope region, efficiently produced a detectable protein localized predominantly in the nucleoli of HCC cells. ORF1 exhibited RNA nuclear export activity, likely mediated by its nuclear export signal and nuclear localization signal, similar to HERV-K Rec. Depletion of ORF1 in HepG2 cells (HepG2ΔORF1) induced epithelial–mesenchymal transition (EMT)-related genes, including β-catenin, TGF-β2, and SNAI2, resulting in E-/N-cadherin switching and enhanced cellular growth and migration. Transient re-expression of ORF1 in HepG2ΔORF1 cells partially reversed the E-/N-cadherin switch. ORF1 transcription levels were significantly higher in non-cancerous liver tissues than in cancerous tissues, consistent with the findings in PHHs and HCC cell lines. Moreover, ORF1 expression was associated with the EMT status of HCC cells. **Conclusion:** HERV-X ORF1 is required for maintaining the epithelial state of human hepatocytes and may contribute to the suppression of tumorigenesis. Our findings provide new insights into the physiological functions of ERVs in previously underexplored biological contexts.



Disclosures: Yuki Nakaya:Nothing to Disclose, Kazuhisa Murai:Nothing to Disclose, Daichi Onomura:Nothing to Disclose, Tomoko Yamagata:Nothing to Disclose, Masao Honda:Nothing to Disclose, Kazumoto Murata:Nothing to Disclose.

1058 | OXIDATIVE STRESS SUPPRESSES NNMT VIA MIR-182-5P TO IMPAIR HEPATOCELLULAR ENERGY HOMEOSTASIS: IMPLICATIONS FOR ISCHEMIA–REPERFUSION INJURY

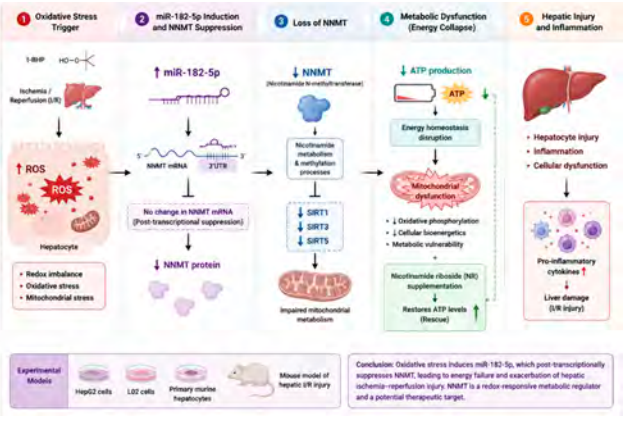
Yun Gyeong Kim[1] Haneul Kim[1] Eun Jin Shin[1] Kyu Min Kim[1], [1]Department of Biomedical Science, Chosun University, Gwangju, Korea

Background: Oxidative stress is a major driver of hepatic ischemia–reperfusion (I/R) injury, yet how redox imbalance is mechanistically coupled to hepatocellular metabolic dysfunction remains poorly defined. Nicotinamide N-methyltransferase (NNMT) consumes nicotinamide via methyl-group transfer and influences NAD^+ availability and cellular energy homeostasis. We investigated how oxidative stress regulates NNMT expression in hepatocytes and whether NNMT modulates energy metabolism under oxidative stress. **Methods:** Oxidative stress was induced with tert-butyl hydroperoxide (t-BHP) in HepG2 cells, L02 cells, and primary murine hepatocytes. NNMT was assessed at the mRNA and protein levels, with antioxidant treatment and protein degradation assays used to define the mode of regulation. Candidate microRNAs were identified by screening,

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and miR-182-5p was evaluated using luciferase reporter assays and mimic/inhibitor experiments. Functional effects were examined by measuring ROS generation, cytotoxicity, and intracellular ATP, including after nicotinamide riboside supplementation and NNMT overexpression. NNMT expression was also assessed in a murine hepatic I/R injury model. **Results:** t-BHP markedly reduced NNMT protein expression across all hepatocyte models, whereas antioxidant treatment restored NNMT expression, indicating redox-dependent regulation. NNMT downregulation occurred without changes in mRNA levels or protein degradation, implicating post-transcriptional control. miR-182-5p was significantly upregulated by oxidative stress; luciferase reporter assays confirmed direct binding to the 3′-untranslated region of NNMT, and mimic and inhibitor experiments demonstrated reciprocal regulation of NNMT expression. NNMT modulation did not significantly alter ROS generation or cytotoxicity; however, NNMT inhibition aggravated ATP depletion under oxidative stress, whereas nicotinamide riboside supplementation restored intracellular ATP levels. NNMT overexpression increased expression of the NAD^+-dependent regulators SIRT1, SIRT3, and SIRT5, linking NNMT to NAD^+-dependent metabolic signaling. Consistently, hepatic NNMT expression was significantly decreased in the murine hepatic I/R injury model. **Conclusion:** NNMT is a redox-responsive metabolic regulator that is post-transcriptionally suppressed by miR-182-5p during oxidative stress. By supporting NAD^+-linked energy metabolism and sirtuin expression, NNMT contributes to hepatocellular energy homeostasis and may represent a potential therapeutic target for hepatic I/R injury.



Disclosures: Yun Gyeong Kim:Nothing to Disclose, Haneul Kim:Nothing to Disclose, Eun Jin Shin:Nothing to Disclose, Kyu Min Kim:Nothing to Disclose.

1059 | AGING DISRUPTS HEPATOCYTE ZONATION HOMEOSTASIS IN MICE AND HUMANS

Saloni Sinha[1] Tuo Zhang[1] Jason Sethiadi[1] Robert Schwartz[1], [1]Weill Cornell Medicine

Background: Aging-induced changes in the liver increase the risk of chronic liver disease, yet underlying mechanisms remain poorly defined. Hepatocyte zonation, the spatial segregation of metabolic functions across periportal (zone 1), intermediate (zone 2), and pericentral (zone 3) regions is essential to liver function. We investigated how aging alters liver architecture, intercellular communication, and hepatocyte zonation in mice and humans. **Methods:** Livers from young (2-mo) and aged (>24-mo) C57BL/6J mice were analyzed by histology and single-nucleus RNA sequencing (snRNA-seq). Differentially expressed genes (DEGs) were identified by pseudobulk analysis; intercellular signaling was inferred with CellChat; transcription factor (TF) activity was profiled by SCENIC. Zonation was assessed by immunostaining for ASS1 (zone 1), CYP2E1 (zones 2/3), and GS (zone 3). For translational validation, biopsies from healthy young (≤25YO) and aged (>60YO) human donors without obesity, liver disease, or abnormal liver enzymes underwent parallel analyses. **Results:** Aged mouse livers showed no fibrosis but marked hepatocyte enlargement, lipofuscin accumulation, and immune infiltration. snRNA-seq of 41,568 nuclei resolved 21 clusters across hepatocytes, HSCs, LSECs, KPCs, BECs, and fibroblasts, with altered cell-type proportions and zone-specific changes (663 DEGs in zone 1; 267 in zone 2; 231 in zone 3). CellChat revealed a ~4-fold increase in intercellular interactions (410 vs. 110), enriched in VEGFA–VEGFR2, IGF1–IGF1R, FGF1–FGFR, and F2–Pard3 signaling. Immunostaining confirmed expansion of ASS1+, CYP2E1+, and GS+ zones with discontinuous marker expression around veins. Strikingly, aged livers harbored "bi-zonal" hepatocytes co-expressing ASS1 and GS near central veins. SCENIC identified downregulation of key zonation TFs (Ctnnb1, Foxo1, Tcf7l2, Cebpb, Clock), with compensatory Rspo3/Wnt2 upregulation from HSCs and LSECs. IL-6 and TNF-α were elevated. Aged human livers recapitulated these findings: enlarged hepatocytes, expanded ASS1+/CYP2E1+/GS+ zones, and bi-zonal hepatocytes without fibrosis. **Conclusion:** Aging disrupts hepatic zonation homeostasis via widespread transcriptional remodeling, altered Wnt/Rspo3 signaling, and emergence of bi-zonal hepatocytes are hallmarks

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of aging that is conserved across mice and humans. Zonation breakdown represents a fundamental mechanism of liver aging and a potential therapeutic target for age-associated liver disease.

Disclosures: Saloni Sinha:Nothing to Disclose, Tuo Zhang:Nothing to Disclose, Jason Sethiadi:Nothing to Disclose, Robert Schwartz:Miromatrix Inc: Advisor, Miromatrix Inc: Advisor, Lime Therapeutics: Advisor, Miromatrix Inc: Advisor, Otsuka Inc.: Grant/Research Support, Lime Therapeutics: Advisor, Lime Therapeutics: Advisor, Alnylam Pharmaceuticals: Speaking and Teaching, Otsuka Inc.: Grant/Research Support, Otsuka Inc.: Grant/Research Support, Alnylam Pharmaceuticals: Consultant, Alnylam Pharmaceuticals: Speaking and Teaching, Alnylam Pharmaceuticals: Speaking and Teaching, Alnylam Pharmaceuticals: Consultant, Alnylam Pharmaceuticals: Consultant, Miromatrix Inc: Advisor, Miromatrix Inc: Advisor, Lime Therapeutics: Advisor, Miromatrix Inc: Advisor, Otsuka Inc.: Grant/Research Support, Lime Therapeutics: Advisor, Lime Therapeutics: Advisor, Alnylam Pharmaceuticals: Speaking and Teaching, Otsuka Inc.: Grant/Research Support, Otsuka Inc.: Grant/Research Support, Alnylam Pharmaceuticals: Consultant, Alnylam Pharmaceuticals: Speaking and Teaching, Alnylam Pharmaceuticals: Speaking and Teaching, Alnylam Pharmaceuticals: Consultant, Alnylam Pharmaceuticals: Consultant, Miromatrix Inc: Advisor, Miromatrix Inc: Advisor, Lime Therapeutics: Advisor, Miromatrix Inc: Advisor, Otsuka Inc.: Grant/Research Support, Lime Therapeutics: Advisor, Lime Therapeutics: Advisor, Alnylam Pharmaceuticals: Speaking and Teaching, Otsuka Inc.: Grant/Research Support, Otsuka Inc.: Grant/Research Support, Alnylam Pharmaceuticals: Consultant, Alnylam Pharmaceuticals: Speaking and Teaching, Alnylam Pharmaceuticals: Speaking and Teaching, Alnylam Pharmaceuticals: Consultant, Alnylam Pharmaceuticals: Consultant.

1060 | CELL-FREE DNA PROFILING IDENTIFIES DISTINCT MOLECULAR SUBTYPES OF HEPATOCELLULAR CARCINOMA

Paola Cruz Rivera[1] Gopanandan Parthasarathy[2] Renumathy Dhanasekaran[1], [1]Stanford Healthcare, [2]Stanford University

Background: The molecular relationship between hepatocellular carcinoma (HCC) and cholangiocarcinoma (CCA) remains poorly characterized in liquid biopsy. We applied unsupervised clustering to cfDNA profiles to define HCC molecular subtypes and determine whether HCC and CCA occupy distinct or shared molecular space. **Methods:** HCC (n = 59; median age: 69 years, 7% male; etiology: alcohol-associated liver disease 30%, MASLD 28%, HCV 24%, HBV 24%) and CCA (n = 63; median age: 66 years; 52% female) cases seen at Stanford Hospital Center were analyzed using the Guardant360 panel. A binary somatic gene mutation matrix was constructed from non-CHIP alterations. Principal component analysis (PCA) followed by k-means clustering was performed on HCC samples alone (using genes present in $\geq$5% of HCC samples) and on combined HCC+CCA samples (using tumor-type discriminating genes). Optimal cluster number was selected by silhouette analysis. Gene enrichment was assessed by Fisher's exact test with Benjamini-Hochberg correction. **Results:** HCC harbored significantly more somatic alterations than CCA (median 17 vs 4 per sample; $p < 0.0001$). HCC molecular subtypes: Silhouette analysis identified four HCC subtypes ($k = 4$). Cluster 1 (16% of cohort) was defined by near-universal CTNNB1 mutation (93% vs 14% in other clusters; $p < 0.0001$), with co-enrichment of ARID1A (64% vs 15%; adj $p = 0.002$) and NOTCH1 (36% vs 8%; adj $p = 0.03$), higher median tumor fraction (20% vs 10%), and a median age of 73 years representing a Wnt/CTNNB1-activated, epigenetically disrupted subtype. Cluster 2 (80% of cohort) was enriched for TERT promoter mutations (39%), representing canonical TERT-driven HCC. Clusters 3 ($n = 2$) and 4 ($n = 2$) were small subgroups with distinct co-alteration patterns: TP53/POLE with highest tumor fraction (30%), and TERT/PDGFRA with the highest median AFP (64 ng/mL), respectively. Overall survival did not differ significantly between clusters (median 11.9–16.7 months; all pairwise comparisons $p > 0.4$). HCC and CCA showed markedly different genomic profiles: TERT (47% vs 1%; $p < 0.0001$) and CTNNB1 (28% vs 1%; $p < 0.0001$) were virtually exclusive to HCC, while PIK3CA (6% vs 19%; $p = 0.025$), PTEN (0% vs 11%; $p = 0.002$), and RET (0% vs 9%; $p = 0.005$) were CCA-enriched. Unsupervised clustering of 153 combined samples identified two molecular groups ($k = 2$; $\chi^2 = 26.19$; $p = 3.1\times10^{-7}$). Cluster 1 ($n = 27$, 96% HCC) was defined by TERT and CTNNB1 alterations, an HCC-specific molecular signature. Cluster 2 ($n = 126$) was molecularly ambiguous: TP53-driven HCC co-clustered with CCA, sharing oncogenic space despite distinct histologies. **Conclusion:** ctDNA profiling reveals a biologically and clinically relevant convergence between a subset of HCC and CCA. These findings open new avenues for subtype-informed therapeutic strategies. This advances the case for cfDNA-based molecular profiling as a clinically meaningful tool in the management of liver cancers.

Disclosures: Paola Cruz Rivera:Nothing to Disclose, Gopanandan Parthasarathy:Nothing to Disclose, Renumathy Dhanasekaran:Nothing to Disclose.

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1061 | ◆ LIVER-DIRECTED PRIME EDITING CORRECTS *ATP7B* P. H1069Q AND RESTORES COPPER HANDLING IN WILSON DISEASE MODELS

David Waterman[1] Tiernan O'Malley[1] Michelle O'Connor[1] Andrew Taylor[1] Alan Wilhelm[1] XiChun Zhang[1] Shivangi Modi[1] Celia Chang[1] Weiyi Li[1] Caroline Focht[1] Tyler Harvey[1] Luis Santos[1] Rowshon Alam[1] Jacob Stewart-Ornstein[1] Seth Alexander[1] Jon Winnay[1] Andrea De Erkenez[1] Jon Levy[1] Andrew Anzalone[1] Vivian Choi[1], [1]Prime Medicine

Background: Wilson disease (WD) is caused by *ATP7B* loss-of-function mutations that disrupt copper homeostasis and cause toxic copper accumulation in the liver and other organs. Current therapies are lifelong, burdensome, and do not correct the underlying genetic defects. Prime Editing enables precise correction of pathogenic *ATP7B* mutations to wild-type sequence without requiring DNA double-strand breaks or installing bystander edits. PM577a is a liver-directed lipid nanoparticle-formulated Prime Editor (PE) designed to precisely correct *ATP7B* p.H1069Q. We describe studies evaluating PM577a-mediated *ATP7B* p.H1069Q mutation correction and copper homeostasis across multiple humanized WD mouse models. We are also advancing a second PE that corrects *ATP7B* p.R778L. These two mutations account for >40% of WD alleles in the US, EU, and East Asia and Pacific regions. **Methods:** PM577a activity was evaluated in hepatocyte models containing *ATP7B* p.H1069Q and in humanized *ATP7B* p.H1069Q mice, including adult homozygous mutant mice with advanced liver disease. Pharmacodynamic endpoints included hepatic *ATP7B* precise editing, corrected *ATP7B* transcript, ATP7B protein expression, and hepatic copper content. Copper handling was assessed using ^{64}Cu challenge followed by positron emission tomography (PET) imaging. Additional studies evaluated Prime Editing in *ATP7B*$^{H1069Q/R778L}$ compound heterozygous mice, durability in non-human primates using an *ATP7B* surrogate PE, and unintended editing in human hepatocytes and patient-derived cells. **Results:** PM577a achieved efficient *ATP7B* p.H1069Q mutation correction in hepatocyte models and dose-dependent precise editing in humanized *ATP7B* p.H1069Q mice. Precise editing leads to *ATP7B* transcript correction, restoration of wild type ATP7B protein expression, and reduced hepatic copper. At sub-saturating doses, PM577a restored copper homeostasis as determined by ^{64}Cu PET imaging and reduced hepatic copper accumulation. Editing and copper-lowering activity were also observed in *ATP7B*$^{H1069Q/R778L}$ compound heterozygous mice. Durability was supported in non-human primates, with hepatic editing maintained >1.5 years after infusion of an *ATP7B* surrogate PE. No detectable off-target edits were observed in human hepatocytes or WD patient-derived cells. Learnings from PM577a were applied to rapidly develop a second PE using the same liver LNP platform to correct a second pathogenic mutation, R778L, achieving >90% hepatocytes gene correction *in vivo.* **Conclusion:** PM577a precisely corrects the *ATP7B* p.H1069Q mutation and restores copper homeostasis across multiple WD models. Preclinical ^{64}Cu PET data support restoration of copper handling and provide a translational pharmacodynamic approach for clinical evaluation. PRIME-0211, an observational study in Wilson disease patients, has been initiated to identify individuals who could be eligible for PM577a clinical evaluation.

Disclosures: David Waterman:Nothing to Disclose, Tiernan O'Malley:Prime Medicine: Employee, Michelle O'Connor:Nothing to Disclose, Andrew Taylor:Nothing to Disclose, Alan Wilhelm:Prime Medicine: Employee, XiChun Zhang:Nothing to Disclose, Shivangi Modi: Nothing to Disclose, Celia Chang:Nothing to Disclose, Weiyi Li:Nothing to Disclose, Caroline Focht:Nothing to Disclose, Tyler Harvey:Nothing to Disclose, Luis Santos:Nothing to Disclose, Rowshon Alam:Nothing to Disclose, Jacob Stewart-Ornstein:Nothing to Disclose, Seth Alexander:Nothing to Disclose, Jon Winnay:Nothing to Disclose, Andrea De Erkenez:Nothing to Disclose, Jon Levy:Nothing to Disclose, Andrew Anzalone:Nothing to Disclose, Vivian Choi:Prime Medicine: Employee.

1062 | ◆ DIAGNOSTIC PERFORMANCE OF A PLASMA CFDNA METHYLATION PANEL TARGETING GNB4 AND RIPLET FOR LIVER CANCER DETECTION

Lianglu Zhang[1] Dihan Zhou[1] Lanlan Dong[1] Jun Zhou[1] Hong Guo[1], [1]Wuhan Ammunition Life-Tech Co., Ltd.

Background: Primary liver cancer is a leading cause of cancer-related death worldwide, with poor prognosis mainly due to late diagnosis. Circulating cell-free DNA (cfDNA) methylation-based liquid biopsy is a promising non-invasive method for early liver cancer detection, overcoming limitations of invasive biopsy and suboptimal performance of conventional biomarkers such as alpha-fetoprotein (AFP). We developed a dual-gene cfDNA methylation assay targeting GNB4 and Riplet and evaluated its diagnostic performance for liver cancer. **Methods:** A total of 1182 plasma samples were prospectively collected from three hospitals, including 430 liver cancer

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patients and 752 controls. Cases covered all TNM stages (I–IV) and main pathological subtypes: hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma (ICC), and combined hepatocellular-cholangiocarcinoma (cHCC-CCA). Controls included benign liver diseases and non-hepatic malignancies. Methylation levels of GNB4 and Riplet were quantified by methylation-specific PCR (MSP). Diagnostic accuracy was assessed against the clinical reference standard. **Results:** The dual-gene assay achieved an overall sensitivity of 92.3% (95% confidence interval [CI]: 89.3%–94.6%) for liver cancer. Sensitivities for HCC, ICC, and cHCC-CCA were 91.9% (95% CI: 87.4%–94.9%), 93.3% (95% CI: 85.4%–97.2%), and 90.0% (95% CI: 66.9%–98.2%), respectively. Stage-specific sensitivities for TNM stages I–IV were 84.4% (95% CI: 76.5%–90.1%), 93.6% (95% CI: 86.8%–97.2%), 98.1% (95% CI: 92.8%–99.7%), and 100.0% (95% CI: 91.6%–100.0%). Overall specificity in controls was 93.4% (95% CI: 91.3%–95.0%), with 97.6% (95% CI: 95.7%–98.7%) in benign liver diseases and 85.3% (95% CI: 80.2%–89.2%) in non-hepatic malignancies. **Conclusion:** Plasma cfDNA methylation analysis of GNB4 and Riplet shows high sensitivity and specificity for liver cancer. It effectively detects early-stage (TNM I) cancers and maintains high specificity in benign liver diseases. This accurate, convenient, non-invasive test holds great potential for auxiliary diagnosis of liver cancer and screening of high-risk populations.

Disclosures: Lianglu Zhang:Wuhan Ammunition Life-Tech Co., Ltd.: Employee, Dihan Zhou:Nothing to Disclose, Lanlan Dong:Nothing to Disclose, Jun Zhou: Nothing to Disclose, Hong Guo:Nothing to Disclose.

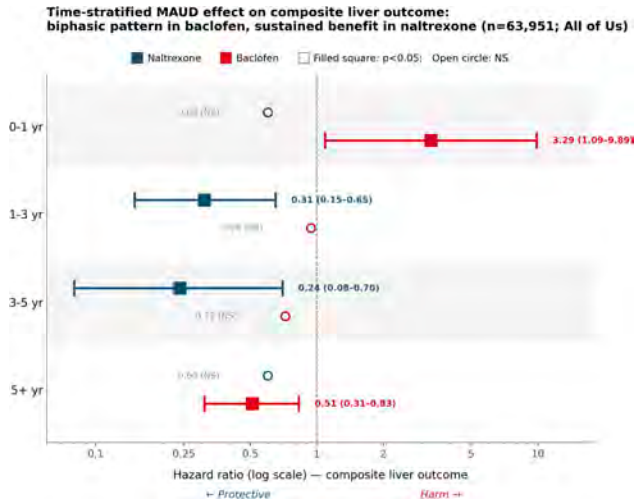
1063 | ◆ HSD17B13 LOSS-OF-FUNCTION ATTENUATES THE BENEFIT OF MEDICATIONS FOR ALCOHOL USE DISORDER (MAUD) ON LIVER OUTCOMES: A PHARMACOGENOMIC TARGET TRIAL EMULATION IN 63,951 HEAVY DRINKERS FROM ALL OF US COHORT

Hyunseok Kim[1] Derin Celtik[1] Walid Ayoub[1] Alexander Kuo[2] Paul Martin[2] Aarshi Vipani[2] Yun Wang[2] Stephen Pandol[2] Debiao Li[2] Yee Hui Yeo[2] Suthat Liangpunsakul[3] David Cohen[2] Shelly Lu[2] JuDong Yang[2], [1]Cedars-Sinai Medical Center, [2]Cedars Sinai Medical Center, [3]Indiana University Medical Center

Background: Recent observational studies suggest naltrexone reduces hepatic complications in alcohol-associated cirrhosis, while comparative effectiveness data for acamprosate and baclofen remain mixed. Whether benefits of medications for alcohol use disorder (MAUD) extend to prevention populations before cirrhosis develops, and whether they are modified by established liver-disease variants, is unknown. **Methods:** We conducted a prespecified target trial emulation among 63,951 heavy drinkers (AUDIT-C ≥ 4 [women] or ≥ 5 [men], or ICD-coded alcohol use disorder [AUD]) from the All of US data with whole-genome sequencing (1.0% baseline cirrhosis; AMR, EUR, and AFR ancestries; median follow-up 4.9 years [exposed] and 3.6 years [unexposed]). MAUD exposure required ≥ 3 prescriptions per ingredient. The composite outcome included hepatic decompensation, hepatocellular carcinoma, liver transplant, and liver-related death. Confounding by indication was addressed using ancestry-stratified gradient-boosted propensity scores, weight truncation, and empirical-overlap trimming in the AMR stratum. Cox proportional hazards models tested a prespecified PNPLA3 rs738409 × MAUD and an exploratory HSD17B13 rs72613567 × MAUD interactions. **Results:** Across 1,209 composite events, naltrexone ($n = 968$) was the only protective agent (HR 0.41, 95% CI 0.28-0.62, $p < 0.0001$), with the greatest benefit in years 1-3 (HR 0.31, 95% CI 0.15-0.65) and effects sustained through 5 years. Acamprosate ($n = 164$) showed no significant benefit. Baclofen ($n = 1,252$) demonstrated early harm attributed to channeling (HR 3.29 at 0-1 year) followed by a late liver benefit (HR 0.51 at 5+ years, $p = 0.007$); however, only 59% had AUD diagnostic codes despite all meeting heavy-drinking criteria, limiting causal interpretation. Naltrexone's protective effect persisted when analyses were restricted to participants without baseline liver disease (HR 0.38; peak 1-3 year HR 0.15), extending prior findings to a pre-cirrhotic prevention population. The prespecified PNPLA3 × MAUD interaction was null (HR 1.04, 95% CI 0.39-2.82, $p = 0.94$). By contrast, HSD17B13 loss-of-function (LOF) carriage attenuated MAUD benefit (interaction HR 3.99, 95% CI 1.53-10.44, $p < 0.01$), an effect that was strongest in years 0-3, and remained significant across sensitivity analyses. **Conclusion:** We report the first pharmacogenomic interaction between MAUD and an established liver-disease locus: HSD17B13 LOF attenuates MAUD benefit through a plausible ceiling-effect mechanism, while PNPLA3 had no effect. Naltrexone was associated with early and sustained reductions in liver-related outcomes, with effects persisting in pre-cirrhotic populations. These hypothesis-generating findings warrant external validation and may inform precision-medicine strategies for ALD prevention and progression.

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1065 | CLONAL HEMATOPOIESIS IS ENRICHED IN LIVER CANCERS AND ASSOCIATED WITH GREATER SOMATIC TUMOR COMPLEXITY

Gopanandan Parthasarathy[1] Paola Cruz Rivera[2] Renumathy Dhanasekaran[1], [1]Stanford University, [2]Stanford Healthcare

Background: Clonal hematopoiesis of indeterminate potential (CHIP) are somatically mutated, clonally expanded hematopoietic stem cells, associated with chronic liver disease and could modulate the hepatic tumor microenvironment. Ultra-sensitive cell-free DNA platforms enable CH mutation detection in nontumor cells from peripheral blood across a wide variant allele frequency (VAF) range, though the biologically relevant threshold remains undefined. We examined CH prevalence and clinical associations in a contemprorary cohort of primary liver cancer patients. **Methods:** Plasma cfDNA from patients with liver cancers (n = 122) HCC (n = 59; median age 69 y, 71% male; alcohol-associated liver disease 30%, MASLD 28%, HCV 24%, HBV 24%; 74% with cirrhosis) and cholangiocarcinoma (CCA; n = 63; median age 66 y; 52% female) profiled at our center using the Guardant360 panel were analyzed. CH variants were identified across 39 genes and reported at two thresholds: VAF $\geq$2% (CHIP, standard threshold) and VAF $\geq$0.5% (CH, exploratory analysis). CH prevalence was compared between tumor types by Fisher's exact test; continuous outcomes by Mann-Whitney U test; gene associations by Fisher's exact test with Benjamini-Hochberg correction. Overall survival (OS) was compared between CH+ and CH– HCC patients. **Results:** At VAF $\geq$2% threshold, CHIP was prevalent in 12% of HCC and 10% of CCA (P = 0.77). At VAF $\geq$0.5%, CH mutations were detected in 51% of HCC (30/59) and 16% of CCA (10/63; $P < .01$, despite similar age (69 vs 66 y; P = .18). DNMT3A was the predominant CH mutation, enriched in HCC versus CCA (36% vs 11%; adj $P < 0.05$), with PPM1D trending higher in HCC (8% vs 2%). HCC patients with CH mutations were significantly older than those without (median 71 vs 65 years; $P < 0.05$), consistent with age-driven somatic mutagenesis. Despite higher CH mutational burden, OS did not differ significantly between CH+ and CH– HCC patients (median 14.0 vs 13.4 months; $P = 0.39$). Among HCC, CH+ patients had greater somatic mutational burden than CH– samples (median 22 vs 10 alterations; P < .001), suggesting co-occurrence of hematopoietic and tumor genomic instability. In CCA, somatic BAP1 mutations were enriched in CH+ patients (30% [3/10] vs 6% [3/53]; P < .05), identifying a subgroup with convergent disruption of DNA damage response pathways across hematopoietic and epithelial compartments. **Conclusion:** CH mutations are common in HCC and CCA, driven by DNMT3A and PPM1D variants, associated with greater somatic tumor complexity, but without impact on OS in this cohort. A cfDNA-appropriate VAF threshold for CH mutation detection in peripheral blood remains undefined but CH mutations are 3-fold more common in HCC compared to CCA. These findings support a model of parallel genomic disruption across hematopoietic and tumor compartments in HCC and CCA. The high prevalence of CH detection by cfDNA has important implications for liquid biopsy interpretation in primary liver cancers.

Disclosures: Gopanandan Parthasarathy:Nothing to Disclose, Paola Cruz Rivera:Nothing to Disclose, Renumathy Dhanasekaran:Nothing to Disclose.

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1066 | SINGLE-NUCLEUS RNA SEQUENCING OF FFPE HUMAN LIVER TISSUE IDENTIFIES ZONE-SPECIFIC EXPRESSION PATTERNS OF MASLD-ASSOCIATED GENES

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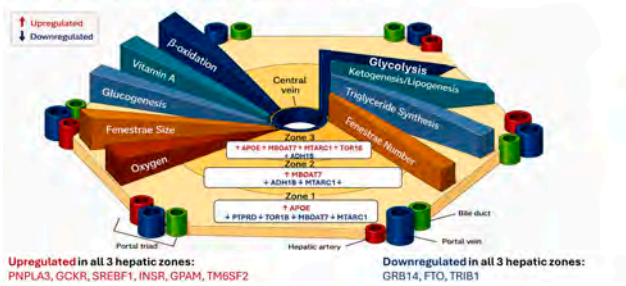
Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a leading cause of chronic liver disease worldwide. Our previous genome-wide association studies (GWAS) identified 17 MASLD loci; however, the hepatic zones in which these genes act are unclear. Recent advances in single-nucleus RNA sequencing (snRNA-seq) now enable transcriptomic profiling of archived formalin-fixed paraffin-embedded (FFPE) liver tissue. **Methods:** We carried out single cell and spatial transcriptomic analyses on 16 FFPE samples spanning the MASLD spectrum from the Michigan Genomics Initiative. Quality control, normalization, integration, clustering, cell marker identification (using FindAllMarkers) was done using Seurat v5. We identified periportal (zone 1), interzonal (zone 2), and pericentral (zone 3) hepatocytes using published markers and subcluster analysis. We performed differential expression analysis using Model-based Analysis of Single-cell Transcriptomics (MAST) to evaluate expression patterns of genes previously implicated by MASLD GWAS. Significance was determined after Bonferroni correction for 18,129 genes expressed (P adjusted < 0.05). **Results:** Our FFPE snRNA-seq dataset identified expected hepatic cell populations and hepatocyte zonation patterns across MASLD stages. Fifteen among the 17 MASLD-associated loci demonstrated significant differential expression in hepatocyte populations, with distinct zone-specific transcriptional signatures. PNPLA3, GCKR, GPAM, INSR, SREBF1, and TM6SF2 were broadly upregulated, whereas FTO, GRB14, and TRIB1 were consistently downregulated across hepatocyte zones. Other genes, including ADH1B, APOE, MBOAT7, MTARC1, and TOR1B, exhibited heterogeneous zonal expression patterns. PTPRD is only down regulated in zone 1 hepatocytes. ADH1B was downregulated in zone 3 and zone 2 hepatocytes only; APOE was upregulated in zone1 and zone3 hepatocytes; MBOAT7 was upregulated in zone 2 and zone 3 hepatocytes but downregulated in zone 1 hepatocytes. MTARC1 was upregulated in zone 3 hepatocyte and downregulated in zone 2 and zone 1 hepatocytes; TOR1B was upregulated in zone 3 hepatocytes and downregulated in zone 1 hepatocytes. **Conclusion:** We established a human liver FFPE snRNA-seq cohort spanning MASLD stages and mapped the cell-type and zone-specific expression patterns of MASLD GWAS genes. Our findings suggest spatially distinct roles for GWAS identified MASLD genes. Our future work will integrate a spatial transcriptomics cohort to interpret the local biology of these genes.

Table 1. Average log2 fold change of GWAS identified MASLD genes

Gene	Periportal hepatocyte (Zone 1)	interzonal hepatocyte (Zone 2)	pericentral hepatocyte (Zone 3)
PNPLA3	1.06 (P = 5.7e-188)	1.25 (P = 4.2e-120)	1.07 (P = 2.5e-44)
GCKR	0.54 (P = 9.4e-193)	0.71 (P = 4.8e-84)	0.18 (P = 8.1e-48)
SREBF1	1.06 (P = 1.3e-127)	1.16 (P = 2.8e-68)	1.03 (P = 4.9e-66)
INSR	0.59 (P = 1.8e-66)	0.41 (P = 1.3e-31)	0.27 (P = 3.4e-40)
GPAM	0.54 (P = 5.3e-61)	0.56 (P = 6.3e-29)	0.48 (P = 2.1e-24)
TM6SF2	0.77 (P = 1.7e-55)	0.93 (P = 1.4e-24)	0.41 (P = 6.7e-21)
GRB14	-0.57 (P = 1.1e-106)	-0.39 (P = 3.5e-28)	-0.35 (P = 8.2e-10)
FTO	-0.22 (P = 1.8e-22)	-0.28 (P = 5.1e-06)	-0.20 (P = 7.7e-03)
TRIB1	-0.48 (P = 1.4e-96)	-0.14 (P = 2.2e-23)	-0.25 (P = 3.1e-60)
MTARC1	-0.68 (P = 7.4e-117)	-0.40 (P = 2.5e-32)	0.25 (P = 8.6e-39)
ADH1B	NS	-0.13 (P = 8.8e-41)	-0.10 (P = 1.0e-54)
MBOAT7	-0.16 (P = 6.5e-25)	0.48 (P = 2.3e-12)	0.65 (P = 2.6e-13)
APOE	0.51 (P = 3.5e-252)	NS	0.12 (P = 1.3e-237)
TOR1B	-0.33 (P = 1.6e-16)	NS	0.23 (P = 2.1e-08)
PTPRD	-0.48 (P = 1.7e-09)	NS	NS

Values represent average log2 fold change from differential expression analysis.
P values shown in parentheses are Bonferroni-corrected adjusted P values.
"NS" indicates not statistically significant after Bonferroni correction.

Figure 1. Zonal expression patterns of GWAS identified MASLD loci



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1067 | BLOOD DNA METHYLATION SIGNATURES PREDICT INCIDENT ALL-CAUSE LIVER CIRRHOSIS IN THE MILLION VETERAN PROGRAM

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Background: Liver cirrhosis is a major complication of chronic liver disease predominantly caused by alcohol use, viral hepatitis, and metabolic dysfunction-associated steatotic liver disease (MASLD), often manifesting silently over decades. Current biomarkers for early

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detection are limited, making it difficult to identify individuals at risk before irreversible liver damage occurs. Because DNA methylation reflects both genetic susceptibility and environmental exposures, it may serve as a minimally invasive, blood-based marker of early disease risk and progression. **Methods:** We conducted an epigenome-wide association study (EWAS) in European ancestry participants from the Million Veteran Program, analyzing 768,569 CpG sites among 45,460 individuals on the Illumina EPIC array. Cases were individuals who developed cirrhosis at least two years after enrollment and blood draw (177 cases; 26,689 population controls), analyzed via logistic regression with genomic inflation correction using BACON. **Results:** We identified 46 CpG sites significantly associated with incident cirrhosis risk after adjustment for demographic factors, technical covariates, and clinical risk factors including alcohol use disorder, viral hepatitis, MASLD, HIV, smoking, and medication history. Signals were predominantly hypomethylated, consistent with global epigenetic dysregulation in chronic liver disease. Notably, 41 of the 46 incident CpG sites were also associated with Horvath epigenetic age acceleration, suggesting faster biological aging in at-risk individuals prior to disease onset.To characterize the cellular and genetic architecture of the cirrhosis signals, we performed cell-type interaction analyses using cellDMC and cis-mQTL analyses. CD8 T-cells were the primary immune cell type driving incident CpG associations, contributing to eight CpGs signals, with a smaller contribution from eosinophils at two CpG sites. Cis-mQTL analysis identified 285 independent genetic variants regulating cirrhosis-associated CpG sites (FDR < 5%). Gene-environment interaction analyses between top cis-mQTL variants and major etiologies revealed that viral hepatitis and HIV amplified genetic effects on methylation at nominal significance ($P < 0.05$). Cross-compartment validation in an independent liver tissue dataset supported *HIVEP3* promoter methylation as a marker of disease progression. **Conclusion:** These findings demonstrate that blood DNA methylation signatures can identify individuals at increased cirrhosis risk and capture immune-mediated, aging-related, and exposure-specific pathways, highlighting the potential of methylation-based biomarkers for early risk stratification.



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1068 | METHYLOME-WIDE ANALYSIS OF ALCOHOL ASSOCIATED CIRRHOSIS RISK IN MILLION VETERANS PROJECT

Marco Abreu[1] Callie Zaborenko[1] Josephine Johnson[2] Marijana Vujkovic[2] Kyong-Mi Chang[2] Timothy Morgan[3] Tae-Hwi Schwantes-An[1], [1]Indiana University School of Medicine, [2]University of Pennsylvania, [3]VA Long Beach Healthcare System

Background: Alcohol-associated liver cirrhosis (ALC) is a major contributor to liver-related mortality and transplant worldwide. Although genome-wide association studies have identified risk loci, including *PNPLA3*, *TM6SF2*, and *HSD17B13*, these only explain a modest proportion of heritability. Chronic alcohol exposure also induces widespread DNA methylation changes through oxidative stress, inflammation, and disrupted one-carbon metabolism, suggesting epigenetic mechanisms may contribute to ALC susceptibility. Using an methylation cohort from the Million Veteran Program, we conducted an epigenome-wide association study (EWAS) of ALC. **Methods:** Cases were participants with at least one ICD-9/10 diagnosis code for alcohol-associated liver cirrhosis. Controls had ICD-9/10 diagnoses related to heavy alcohol use but no history of MASLD or alcohol-associated liver disease. Genome-wide methylation across >751,000 CpG sites was assessed using the EPIC v1 array. Linear regression models were fitted using *limma* in R to evaluate methylation differences at each CpG site while adjusting for age, sex, 5 technical PCs, 5 genomic PCs, sample storage duration, estimated cell-type proportions, and scanner batch effects. **Results:** The discovery cohort included 550 cases and 3,173 controls clustering with EUR reference samples; the replication cohort included 215 cases and 1,867 controls from AFR samples. We identified 32 differentially methylated regions (DMRs; ≥5 CpGs) associated with ALC at genome-wide significance (adjusted $p < 5x10^{-08}$) in the

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EUR cohort. Of these, 20 DMRs replicated in AFR cohort (adjusted $p < 0.05$). Replicated DMRs mapped to genes involved in interferon/antiviral response, innate immune and cytokine signaling, and inflammatory remodeling. **Conclusion:** In the largest EWAS of alcohol-associated cirrhosis to date, we identified 20 replicated DMRs implicating coordinated immune and inflammatory epigenetic dysregulation in ALC susceptibility among heavy drinkers. Enrichment for interferon-responsive and innate immune pathways suggests that chronic immune activation may be a central feature of ALC biology beyond known genetic risk loci. Because of the cross-sectional nature of the study, we cannot determine whether these methylation changes precede disease development or arise because of cirrhosis. Further longitudinal and functional studies are needed to clarify the directionality and biological significance of these epigenetic alterations.

Chromosome	start	end	width	no.cpgs	min_smoothed_fdr	Stouffer	HMFDR	Fisher	maxdiff	meandiff	overlapping.genes
chr1	41918802	41920269	1468	10	3.62E-51	7.71E-27	1.03E-10	5.81E-32	0.25	0.13	HIVEP3
chr1	202161215	202162055	841	5	6.16E-29	1.20E-16	3.64E-09	3.77E-18	-0.12	-0.09	PTPN7
chr5	132073465	132073943	479	8	1.92E-45	3.28E-24	2.66E-14	6.20E-27	-0.11	-0.07	CSF2
chr6	30730866	30731585	780	12	1.82E-32	2.66E-15	3.08E-05	2.23E-16	-0.12	0.07	FLOT1
chr6	31792567	31793284	718	11	5.59E-25	4.30E-10	3.53E-03	1.67E-10	0.15	0.06	VARS1
chr6	32841879	32843475	1597	11	4.07E-51	6.68E-26	2.87E-08	7.12E-29	-0.10	-0.07	PSMB8
chr6	32555514	32556163	650	5	6.17E-26	1.75E-13	1.75E-06	3.72E-14	-0.12	-0.09	PSMB9
chr10	30435090	30435444	355	5	4.97E-26	9.64E-15	2.98E-05	1.61E-13	-0.10	-0.07	MAP3K8
chr10	72297946	72298333	388	5	1.61E-37	2.89E-13	2.55E-13	1.32E-28	-0.16	-0.07	<NA>
chr11	312559	315750	3192	13	2.30E-52	2.33E-43	7.35E-14	6.65E-56	-0.22	-0.08	IFITM2, IFITM1
chr14	73760727	73761680	953	5	2.37E-48	5.70E-31	4.01E-14	2.42E-31	-0.10	-0.08	MIDEAS
chr15	44735884	44736396	513	5	1.78E-33	5.65E-22	6.26E-09	3.13E-22	-0.12	-0.09	TRIM69
chr16	56989109	56989442	334	5	5.73E-31	3.07E-05	2.43E-15	1.39E-19	-0.27	-0.09	<NA>
chr16	57638488	57640080	1593	10	9.65E-63	5.69E-27	1.95E-11	4.23E-36	0.13	0.08	ADORA1
chr17	58038303	58039281	979	5	5.04E-93	8.77E-66	4.89E-22	5.20E-84	-0.31	-0.23	VMP1
chr17	78278058	78278774	717	5	3.92E-48	4.77E-35	7.31E-16	2.86E-36	-0.17	-0.11	LINC01993
chr17	78358539	78359592	1054	7	2.20E-63	1.61E-29	5.86E-14	2.41E-40	-0.25	-0.11	SOCS5
chr19	17404676	17406658	1983	12	9.41E-55	1.36E-35	1.50E-10	2.51E-41	-0.13	-0.09	BISPR, MVB12A, BST2
chr19	46784520	46785657	1138	9	2.31E-49	7.20E-28	3.89E-08	1.89E-29	0.16	0.09	SLC1A6

Table1. Summary table of genome-wide associated DMRs. Start = staring base position in hg19, end = ending base position in hg19, width = length of DMR, no.cpgs = number of CpG in the DMR, min_smoothed_fdr = smallest adjusted pvalue among CpGs in the DMR. Stouffer = Region pvalue for DMR using Stouffer's method, HMFDR = Region based adjusted pvalue using harmonic mean FDR method, Fisher = Region pvalue using Fisher's method, maxdiff = maximum log2-fold change value in methylation among the included CpGs, negative value shows reduced methylation among cases and a positive value indicates increased methylation among cases compared to the controls, meandiff = mean log2-fold chang values among CpGs in the DMR. Overlapping.genes= genes in or near each DMR.

Disclosures: Marco Abreu:Nothing to Disclose, Callie Zaborenko:Eli Lilly: Stock - publicly traded company, Josephine Johnson:Nothing to Disclose, Marijana Vujkovic:Nothing to Disclose, Kyong-Mi Chang:Nothing to Disclose, Nothing to Disclose, Timothy Morgan: Nothing to Disclose, Tae-Hwi Schwantes-An:Nothing to Disclose.

1069 | UNDERSTANDING HEPATOBLASTOMA HETEROGENEITY AND TUMOR MICROENVIRONMENT FOR PRECISION MEDICINE: FOCUS ON HIGH-RISK HEPATOBLASTOMA-ASSOCIATED NEUROENDOCRINE TUMOR CELLS

Elise Lelou[1] Abhishek Murti[1] Saphia Nguyen[1] Matthew Choi[1] Cindy Ament[1] Nikita Sajai[1] Phoebe Miller[1] Soo-Jin Cho[1] E. Alejandro Sweet-Cordero[1] Amar Nijagal[1] Bruce Wang[1], [1]University of California, San Francisco, United States of America

Background: Hepatoblastoma (HB) is the most common primary pediatric liver cancer. Among childhood tumors, it has one of the highest mortality rates, with 20% of cases resulting in death or liver transplantation. We previously used single-cell RNA sequencing (scRNA-seq) to identify 5 tumor cell types shared across patients. We now expand this analysis, using scRNA-seq, single-nuclei RNA sequencing (snRNA-seq), and spatial transcriptomics to further characterize tumor cells and their microenvironments. **Methods:** scRNA-seq was performed using microwell capture on 12 freshly dissociated tumors, and snRNA-seq was performed using droplet capture on 18 banked frozen tumors. Data was analyzed using Scanpy. Tissue microarrays of FFPE-Hepatoblastoma from 17 patients were prepared for Xenium spatial transcriptomics using a custom liver 480-gene panel based on our scRNA-seq dataset and analyzed with Scanpy and Squidpy. **Results:** We confirmed the reproducibility of tumor cell populations across techniques using matched sc/snRNA-seq patient samples. Our expanded sc/snRNA-seq datasets validated the previously identified 5 tumor cell populations, and identified 4 new populations (Hepatoblast-III, Wnt-I, Wnt-II, and Neuroendocrine-II (*CHGB*+)). Surprisingly, neuroendocrine tumor cell types, rarely reported in the literature for HB, were identified in 4 of 21 patients, with Neuroendocrine-I (*CHGA*+, *CHGB*+) being specific to the high-risk HB patient 8. Spatial transcriptomics revealed that distinct tumor cell types occupied discrete spatial regions within the tumor. Furthermore, using neighborhood analysis, we found that each tumor cell type had a distinct microenvironment. Neuroendocrine-I and II tumor cells form tumor nests. While Neuroendocrine-I nests have no other cell types enriched within and are enriched with fibroblasts at their interface, Neuroendocrine-II nests contain Wnt-I/II tumor cells and fibroblasts inside, and have cholangiocytes (BEC) at their interface. Using cell-cell interaction analysis, we found that Neuroendocrine-I, which may be associated with high-risk, exhibited somatostatin autocrine signaling and *SLIT*--mediated fibroblast crosstalk. **Conclusion:** We established a molecular and spatial single-cell-resolution atlas of HB. We identified clinically relevant shared tumor cell types with distinct microenvironments, including 2 neuroendocrine tumor cell types. These results could improve risk stratification and identify tumor cell type-specific microenvironmental interactions representing therapeutic target candidates, like the high-risk HB-associated Neuroendocrine-I somatostatin signaling pathway. This can be tested using patient-derived organoids from freshly resected tumors that maintain patient features and that we developed in our lab.

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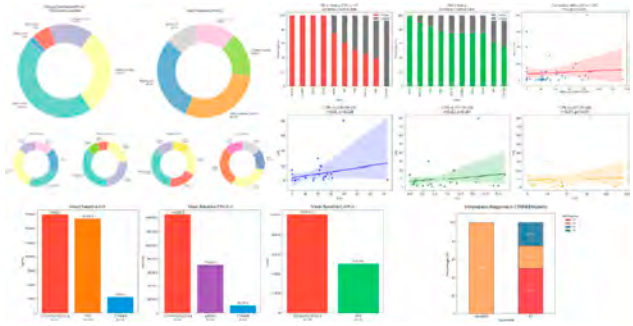
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Nothing to Disclose, Matthew Choi:Nothing to Disclose, Cindy Ament:Nothing to Disclose, Nikita Sajai:Nothing to Disclose, Phoebe Miller:Nothing to Disclose, Soo-Jin Cho:Nothing to Disclose, E. Alejandro Sweet-Cordero: Nothing to Disclose, Amar Nijagal:Nothing to Disclose, Bruce Wang:Nothing to Disclose.

1070 | GENOMIC PROFILES AS DETERMINANTS OF THERAPEUTIC EFFICACY IN HEPATOCELLULAR CARCINOMA: TOWARDS PRECISION MEDICINE

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Background: As therapeutic options for hepatocellular carcinoma (HCC) expand, optimizing treatment selection based on individualized genomic profiles remains a clinical challenge. We hypothesized that patient-specific mutational landscapes and associated biological characteristics significantly influence treatment efficacy and tumor burden. **Methods:** We analyzed 42 patients treated for HCC between January 2025 and February 2026 who had available tumor biopsy samples. Targeted Next-Generation Sequencing (NGS) was performed to identify genomic alterations. These profiles were correlated with etiology, pathological features (CK19, GPC3, PD-L1 CPS), initial tumor markers, and therapeutic responses across systemic and localized modalities. PD-L1 expression was specifically analyzed using a threshold of CPS $\geq$ 10. Genomic instability was assessed using the HRD sum score. **Results:** In the overall cohort (N = 42), the most frequent genomic alterations were mutations in TP53 (45.2%), TERT promoter (45.2%), and CTNNB1 (23.8%). In HBV-related HCC, the top alterations were TP53 (42.9%), TERT promoter (33.3%), and RIT1 (23.8%) whereas in MASLD-related HCC was TERT promoter (69.2%), CTNNB1 (46.2%), and TP53 (38.5%). Regarding tumor burden, baseline markers were notably high in cases with FGF-family amplifications (Median AFP 4,601) or AXIN1 mutations (Median AFP 2,324), whereas CTNNB1 mutations were associated with a significantly lower baseline tumor burden (Median AFP 40.8). TP53 mutations and FGF-family amplifications were strongly associated with PD-L1 expression (CPS > = 10: 52.6% and 75.0%, respectively) and GPC3 positivity (78.9% and 75.0%, respectively). AXIN1 mutations and RIT1 amplifications were consistently associated with refractory disease, with AXIN1 mutants and RIT1 amplification showing rapid progression and AFP/PIVKA-II surge under ICI (AFP +2,658.6, +1,939.6 ng/mL respectively). ARID1A mutants exhibited response dissociation, showing better extrahepatic control under ICI despite intrahepatic progression. CTNNB1 mutants showed poor response to ICI (PD-Ref 25.0%) but showed stable response under Lenvatinib (100% SD, Mean Delta AFP +0.27). ARID1A alterations are favorable for ICI, while CTNNB1 is best managed with Lenvatinib or HAIC. Conversely, TP53 and AXIN1 mutations had high resistance to ICI but remain sensitive to HAIC, with significant marker reduction (TP53: Mean AFP -2,912.1 ng/mL). **Conclusion:** Genomic profiling via targeted NGS provides critical insights into HCC tumor burden and treatment-specific outcomes. The dominance of CTNNB1 in NBNC HCC, its association with lower tumor burden, and the clinical stability of Lenvatinib and HAIC highlight the importance of genotype-directed strategies. Integration of mutational data into clinical decision-making enables optimized, personalized treatment in HCC.



Disclosures: Pil Soo Sung:Nothing to Disclose.

1071 | COMPUTATIONAL PATHOLOGY OUTPERFORMS CLINICAL AND MOLECULAR PROGNOSTIC MARKERS AND REVEALS TARGETABLE MORPHOLOGIC PHENOTYPES IN HEPATOCELLULAR CARCINOMA

Tyler Yasaka[1] Shaila Afrin[2] Junyan Tao[1] Po-Yuan Chen[1] Chang Kyung Kim[1] Anisha Jain[1] Laura Molina[3] Rebekah Dadey[1] Riyue Bao[1] Satdarshan (Paul) Monga[3] Yu-Chiao Chiu[1], [1]University of Pittsburgh School of Medicine, [2]University of Pittsburgh School of Medicine, [3]University of Pittsburgh

Background: Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality, and outcomes remain poor despite well-characterized transcriptomic subtypes that have not translated into routine clinical care. By utilizing routine hematoxylin and eosin (H&E) staining, computational pathology may bridge this gap by extracting molecular-grade biological and prognostic information from morphologic features, enabling scalable precision medicine for HCC. **Methods:** We developed a computational

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pathology framework (Tissue Encoded Subtype Elucidation and Risk Assessment or TESERA) that generates morphology-based embeddings from routine H&E whole-slide images. Embeddings from The Cancer Genome Atlas Liver Hepatocellular Carcinoma (TCGA-LIHC; $n = 336$) cohort were analyzed by unsupervised clustering, with subtype-defining biology characterized via pathway and mutational enrichment analyses; a candidate target was tested by pharmacologic inhibition in a corresponding murine model. For patient-level prognostication, a Cox model trained on histologic embeddings was benchmarked head-to-head against clinical variables, bulk transcriptomic principal components, and published HCC prognostic signatures, then evaluated in an independent in-house cohort ($n = 48$). **Results:** Unsupervised clustering of histologic embeddings using TESERA yielded two transcriptionally coherent subtypes—TES1 and TES2—that recovered the metabolism-versus-proliferation axis of HCC biology directly from morphology and stratified overall survival (OS; $p < 0.0001$). TES1 (favorable) was enriched for fatty acid β-oxidation, PPARα target genes, and *CTNNB1* mutations; TES2 (poor prognosis) was enriched for proliferative programs and *TP53* mutations. In a murine model recapitulating TES1 transcriptional features, pharmacologic PPARα inhibition—nominated by subtype-enriched fatty acid β-oxidation—significantly reduced tumor burden ($p < 0.05$), validating a morphology-derived therapeutic vulnerability in vivo. In head-to-head benchmarking, the supervised risk model outperformed all comparators (C-index 0.731; 1-, 3-, 5-year AUCs 0.82, 0.80, 0.79), remained independently prognostic after multivariable adjustment (HR 2.97, 95% CI 1.62–5.40, $p < 0.001$), and stratified OS in external validation (C-index 0.655; AUCs 0.80, 0.79, 0.70). **Conclusion:** By recovering metabolism- and proliferation-based HCC subtypes from routine H&E alone, TESERA shows that morphology encodes clinically actionable molecular biology. It outperformed established clinical and transcriptomic prognostic benchmarks, generalized to an external cohort, and identified a therapeutic vulnerability validated in vivo. Released as a publicly accessible pipeline, TESERA offers a scalable foundation for HCC precision medicine and demonstrates that routine histology can deliver molecular-grade insights.

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1072 | GENETIC DETERMINANTS OF THE CHOLESTATIC BIOCHEMICAL PHENOTYPE IN MASLD: INSIGHTS FROM THE SPANISH HEPAMET REGISTRY

Antonio Gil-Gómez[1] Rocio Aller[2] Douglas Maya-Miles[1] Juan Pericàs[3] David Marti-Aguado[4] Águeda González-Rodríguez[5] Jose Luis Calleja[6] Jesus Rivera-Esteban[7] Judith Gomez-Camarero[8] Manuel Romero-Gómez[9] Javier Ampuero Herrojo[10], [1]Departamento de Fisiología, Facultad de Biología, Universidad de Sevilla, [2]Centro de Investigación de Endocrinología y Nutrición, Hospital Clínico Universitario de Valladolid, [3]Liver Unit, Vall d'Hebron University Hospital Campus, Vall d'Hebron Institut de Recerca, Universitat, [4]Clinic University Hospital, INCLIVA Health Research Institute, Valencia, Spain., [5]Instituto de Investigaciones Biomédicas Sols-Morreale (IIBM), CSIC-UAM, Madrid 28029, Spain., [6]Digestive Department, Hospital Universitario Puerta de Hierro, Madrid, Spain., [7]Gastroenterology and Hepatology, Puerta de Hierro University Hospital of Majadahonda, Spain, [8]Digestive Department, Hospital Universitario de Burgos, Burgos, Spain., [9]Virgen del Rocio University Hospital, [10]Digestive Department, Hospital Universitario Virgen del Rocío, Sevilla, Spain

Background: Recent studies have highlighted not only the existence but also the clinical relevance of a cholestatic biochemical pattern in patients with MASLD. This phenotype has been associated with differences in liver histology and prognosis, independently of other disease-related features. Considering the role of genetic burden in the development and progression of MASLD, this study aimed to assess the impact of genetic background on MASLD phenotypes defined by the biochemical pattern of liver injury. **Methods:** A total of 879 patients from different centers included in the Spanish HEPAMET Registry with a diagnosis of MASLD were included. Patients were classified according to the SAF score into steatosis or steatohepatitis, and according to fibrosis stage. In addition, patients were categorized based on the presence of a cholestatic biochemical pattern, defined by the formula: (ALT/ALT ULN)/(ALP/ALP ULN) < 2. Patients were genotyped for 60 genetic

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variants previously associated with MASLD or theoretically involved in pathways related to hepatocellular or cholestatic liver injury. **Results:** Overall, 56% of patients (490/879) showed a cholestatic biochemical pattern. In multivariate analysis adjusted for demographic, clinical and biochemical variables, four genetic variants were independently associated with the cholestatic phenotype, located within or near genes including *PTPRD* [OR 0.10 (0.06-0.18); p = 0.001], *ABCA1* [1.65 (1.07-2.53); p = 0.022], *ASGR1* [1.63 (1.03-2.06); p = 0.039] and *NR1H4* [0.75 (0.53-0.99); p = 0.048]. Moreover, the impact of genetic background differed according to the biochemical phenotype. Among patients with a cholestatic pattern, five SNPs were independently associated with advanced fibrosis. In contrast, among patients with a non-cholestatic phenotype, six different SNPs were associated with advanced fibrosis (Table 1). **Conclusion:** MASLD patients with a cholestatic biochemical pattern display a distinct clinical and genetic profile. Beyond differences in age, sex, metabolic features and liver enzymes, specific genetic variants were independently associated with the cholestatic phenotype, suggesting a potential genetic contribution to this form of disease presentation. Besides, the different SNPs associated with advanced fibrosis across cholestatic and non-cholestatic phenotypes suggest partially divergent genetic determinants of disease progression. These findings reinforce the heterogeneity of MASLD and highlight the potential value of integrating biochemical phenotyping and genetic profiling for refined patient stratification.

	Advanced Fibrosis OR (CI95%); p-value		
	Total cohort	*Non- Cholestatic n=389*	*Cholestatic n=490*
Age	1.04 (1.02-1.06); 0.001	1.06 (1.03-1.09); 0.001	1.03 (1.00-1.0); 0.008
DM	4.24 (2.82-6.38); 0.001	3.78 (1.97-7.26); 0.001	4.20 (2.35-7.49); 0.001
Platelets	0.99 (0.98-0.99); 0.001	0.99 (0.99-0.99); 0.001	0.99 (0.98-0.99); 0.001
GGT			1.00 (1.00-1.01); 0.001
PNPLA3	2.25 (1.45-3.51); 0.001	2.91 (1.46-5.80); 0.002	
AC007652.1	2.17 (1.47-3.21); 0.001	2.37 (1.30-4.32); 0.005	2.38 (1.35-4.16); 0.002
GPBAR1	1.53 (1.02-2.39); 0.042		2.32 (1.15-4.66); 0.018
MERTK	1.50 (1.01-2.24); 0.048	2.32 (1.18-4.61); 0.015	
ABCB11	0.46 (0.25-0.83); 0.010	0.24 (0.09-0.59); 0.002	
HSD17B13	0.70 (0.47-1.00); 0.052		0.56 (0.31-0.99); 0.047
VDR		1.82 (1.00-3.32); 0.050	
TJP2		0.46 (0.25-0.84); 0.011	
TM6SF2			1.94 (0.99-3.85); 0.054
MTARC1			1.89 (1.09-3.29); 0.024

Disclosures: Antonio Gil-Gómez:Nothing to Disclose, rocio aller:Nothing to Disclose, Douglas Maya-Miles: Nothing to Disclose, Juan Pericàs:Nothing to Disclose, David Marti-Aguado:Nothing to Disclose, Águeda González-Rodríguez:Nothing to Disclose, Jose Luis Calleja: Nothing to Disclose, Jesus Rivera-Esteban:Nothing to Disclose, Nothing to Disclose, Judith Gomez-Camarero:Nothing to Disclose, Manuel Romero-Gómez:Nothing to Disclose, Javier Ampuero Herrojo:Nothing to Disclose.

1074 | IDENTIFICATION OF TISSUE-OF-ORIGIN RESOLVED BIOMARKER CANDIDATES FOR STEATOSIS, STEATOHEPATITIS, AND FIBROSIS USING AN INTEGRATIVE MULTI-OMICS APPROACH

Yash Bhagat[1], [1]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA

Background: With advancements in medications targeting reversal of liver steatosis and fibrosis, the lack of an accurate and economical non-invasive diagnostic test to identify patients with these conditions remains the biggest hurdle in preventing progression to cirrhosis. While FIB-4, liver elastography, and magnetic resonance imaging aid in diagnosis of liver disease, they suffer from a low specificity. Fortunately, advancements in omics have allowed multiplexed screening of serum biomarkers. **Methods:** As such, our study utilizes shotgun proteomics and RNA-sequencing (RNA-seq) in tissues that contribute to steatosis, steatohepatitis and fibrosis, including the liver and adipose, to nominate disease-specific tissue-resolved biomarkers for future diagnostic modelling. **Results:** We first performed ultracentrifugation on cultured monolayers of hepatocellular carcinoma cells (HepG2), primary human preadipocytes (PAd), and in vitro differentiated adipocytes (Ad) individually to obtain their secreted exosomes. Shotgun mass spectrometry on the exosome isolates identified 1,438, 389, and 349 secreted proteins from HepG2, PAd, and Ad, respectively. The 2,176 proteins were enriched in cellular compartment gene ontology annotations of secretory vesicle (p = 2.86x10-95), thus validating their secretion by the tissues of interest. Next, we leveraged cohorts with histologically graded liver biopsies for steatosis, lobular inflammation, hepatocellular ballooning, and fibrosis to define steatosis, steatohepatitis and fibrosis. We first used bulk subcutaneous adipose tissue (SAT) and liver RNA-seq data (nLiver = 267, nAdipose = 217) from the KOBS cohort to find that the transcripts of 890 exosome hepatokines and 28 exosome adipokines significantly correlate with steatosis, steatohepatitis or fibrosis (adjusted p < 0.01). Then, we performed Wilcoxon testing on counts derived from single nucleus RNA-seq data in independent replication cohorts with SAT (KOBS) and liver biopsies (Kim et al., Journal of Hepatology, 2024) (nLiver = 17, nAdipose = 59) and liver histology graded phenotypes to find cell-type-specific correlations for the disease states. Our analysis identified 122, 199, and 135 proteins as potential biomarkers, originating from HepG2, Ad, or Pad, the transcripts of which associated with steatosis, steatohepatitis and fibrosis in a cell-type-specific manner (adjusted p < 0.01). **Conclusion:** Altogether, we combined histologically determined liver phenotypes in cohorts with adipose and liver RNA-seq

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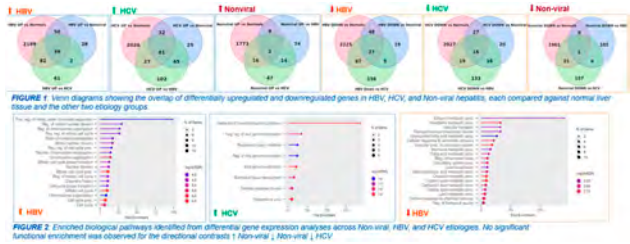
data and mass spectrometry-based secreted exosome proteins, which nominated tissue-of-origin resolved biomarkers for our machine learning models targeted to design a non-invasive diagnostic model for steatosis, steatohepatitis and fibrosis.

Disclosures: Yash Bhagat:Nothing to Disclose.

1075 | ETIOLOGY-SPECIFIC TRANSCRIPTIONAL AND EPIGENETIC PROGRAMS IN HBV-, HCV-, AND NON-VIRAL HEPATOCELLULAR CARCINOMA REVEALED BY ANCESTRY-ADJUSTED MULTI-OMIC PROFILING

Amerti Guta[1] Aditya Bhagwate[1] Daniel O'Brien[2] Lewis Roberts[1] Jean-Pierre Kocher[1], [1]Mayo Clinic, [2]Ambry Genetics

Background: Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death worldwide, yet responses to immune checkpoint inhibitor therapy remain variable and poorly predicted across principal etiologic subtypes: hepatitis B virus (HBV), hepatitis C virus (HCV), and non-viral disease. Each etiology drives hepatocarcinogenesis through distinct biological mechanisms, but the extent to which these differences produce unique transcriptional and epigenetic tumor landscapes, independent of ancestry-related confounding, has not been systematically characterized. **Methods:** We analyzed 325 HCC tumors from the TCGA-LIHC cohort (113 HBV, 48 HCV, 164 non-viral) classified by viral status using Exogene viral read detection. Differential expression analysis was performed using edgeR on TCGA RNA-seq data. Tumor versus normal comparisons were conducted by integrating TCGA tumor RNA-seq data processed through the MAPRSeq pipeline with GTEx normal liver samples. Batch effects were corrected using ComBat. Ancestry-associated genes were excluded to reduce population stratification confounding. Pathway enrichment analysis was performed using ShinyGO and DNA methylation data from TCGA were integrated to assess epigenetic regulation of etiology-specific gene sets. **Results:** The three groups differed significantly in age (HBV mean 53.9 years versus HCV 62.1 years versus non-viral 63.0 years; $p < 0.001$), sex (HBV 78.8% male; $p < 0.001$), racial composition (HBV 92.9% Asian versus HCV and non-viral predominantly White; $p < 0.001$), histologic grade, and fibrosis burden. HBV-associated HCC showed 39 consensus upregulated genes enriched for cell cycle processes (BIRC5, CDC20, TERT, E2F1, MYBL2, UBE2C) and 27 consensus downregulated genes reflecting loss of hepatic detoxification (ADH4, CYP2A6, SULT1B1). HCV-associated HCC showed a dominant immune signature with 81 consensus upregulated genes enriched for interferon-stimulated genes and immunoglobulin loci reflecting intratumoral immune infiltration, and 16 consensus downregulated genes with no pathway enrichment. Non-viral HCC yielded only 2 consensus upregulated genes including CYP17A1, suggesting altered steroidogenic metabolism. A shared pan-tumoral program of cell cycle activation and hepatic metabolic suppression was identified across all subtypes relative to normal liver(fig1&2). DNA methylation analysis revealed group-level epigenetic differences consistent with etiology-specific transcriptional regulation. **Conclusion:** HBV, HCV, and non-viral HCC harbor molecularly distinct transcriptional and epigenetic landscapes. The predominance of immune and interferon signaling in HCV-HCC, cell cycle dysregulation in HBV-HCC, and CYP17A1-associated steroidogenic pathway dysregulation in non-viral HCC define etiology-specific molecular features with implications for biomarker development and therapeutic stratification



Disclosures: AMERTI GUTA:Nothing to Disclose, Aditya Bhagwate:Nothing to Disclose, Daniel O'Brien:Nothing to Disclose, Lewis Roberts:Nothing to Disclose, Jean-Pierre Kocher:Nothing to Disclose.

1076 | THE IFNL4-PRODUCING GENOTYPE IS ASSOCIATED WITH AN INCREASED RISK OF CIRRHOSIS AND LIVER CANCER IN PATIENTS WITH CHRONIC HEPATITIS C

Alexis Moore[1] Bennett Waxse[2] Keisuke Fukutomi[3] Joshua Denny[2] Barbara Rehermann[4], [1]NIDDK, National Institutes of Health, [2]NHGRI, National Institutes of Health, DHHS, [3]National Institutes of Health, [4]NIH/NIDDK

Background: The interferon lambda 4 protein (IFNL4) is produced by the ancestral rs368234815-ΔG allele. Conversely, the rs368234815-TT/TT genotype causes a frameshift mutation that abrogates IFNL4 production. The rs368234815-TT/TT genotype is only found in humans and was positively selected for after the out-of-Africa migration. As a result, around 70% of people with African ancestry have the IFNL4-producing genotype, compared to around 10-20% of people with Asian ancestry. Paradoxically, the IFNL4-producing genotype impairs spontaneous clearance of hepatitis C virus but

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has been associated with reduced liver inflammation in those with chronic hepatitis C. **Methods:** We utilized the *All of Us* Research Program to investigate in a large cohort the effect of *IFNL4* genotype on the long-term outcome of chronic liver disease. We identified 17,543 subjects with ICD codes for chronic liver disease (encompassing viral, metabolic, alcohol-associated, autoimmune, and cholestatic etiologies) and 4,189 subjects with ICD codes for chronic hepatitis C. A control cohort consisted of 163,066 subjects without chronic liver disease ICD codes. For all cohorts, time-to-event analyses were performed over a follow-up period exceeding 25 years using a Cox proportional hazards model with liver cirrhosis and liver cancer as separate outcomes. Results were adjusted for age, sex, and inferred genetic ancestry based on principal component analysis. **Results:** In the chronic liver disease cohort, subjects who produce IFNL4 had a 13% higher hazard of liver cirrhosis (HR 1.13, 95% CI 1.01-1.26, $p = 0.033$) and a 64% higher hazard of liver cancer (HR 1.64, 95% CI 1.24-2.17, $p < 0.001$) compared to subjects who do not produce IFNL4. Similar associations were observed in the chronic hepatitis C cohort (cirrhosis: HR 1.20 95% CI 1.003-1.44, $p = 0.046$; liver cancer: HR 1.71, 95% CI 1.18-2.49, $p = 0.005$), but not in the control cohort (cirrhosis: HR 0.97, 95% CI 0.82-1.14, $p = 0.705$; liver cancer: HR 1.34, 95% CI 0.88-2.03, $p = 0.174$). Other chronic liver diseases, including MASLD, MASH, and hepatitis B, showed directionally consistent, but non-significant, hazard ratios when looking at the outcome of liver cancer. This may suggest a broader effect of the IFNL4 genotype on liver cancer risk. **Conclusion:** The IFNL4-producing genotype is associated with a higher risk of liver cirrhosis and liver cancer in patients with chronic hepatitis C, despite previous literature reporting reduced liver inflammation.

Disclosures: Alexis Moore:Nothing to Disclose, Bennett Waxse:Nothing to Disclose, Keisuke Fukutomi: Nothing to Disclose, Joshua Denny:Nothing to Disclose, Barbara Rehermann:Nothing to Disclose.

1077 | ITGB4 PROMOTES INTRAHEPATIC CHOLANGIOCARCINOMA PROGRESSION BY REGULATING PURINE METABOLISM AND IMMUNE EVASION VIA MEDIATING LACTYLATION MODIFICATION OF IMPDH2.ITGB4通过介导IMPDH2的乳酸化修饰,调节嘌呤代谢和免疫逃避,促进肝内胆管癌的进展

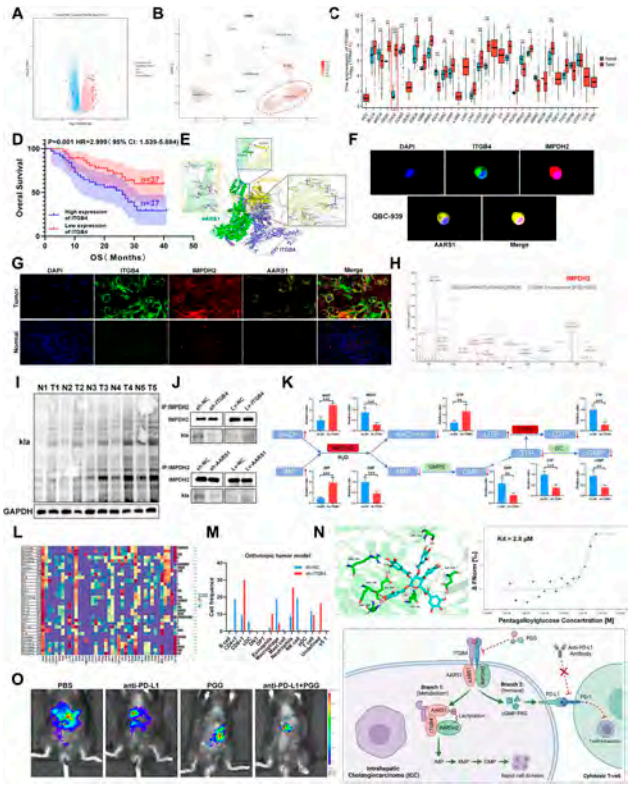
Taiyang Chen[1] HaiBo Yu[1], [1]People's Hospital of Zhengzhou University

Background: Intrahepatic cholangiocarcinoma (ICC) ranks as the second most prevalent primary liver cancer with steadily rising incidence. Characterized by insidious early symptoms and the absence of specific diagnostic biomarkers, approximately 60%–70% of patients are diagnosed at advanced stages unresectable for radical surgery. Conventional radiotherapy and chemotherapy yield limited therapeutic efficacy. Although immunotherapy has achieved preliminary breakthroughs, low overall response rates and elusive drug resistance mechanisms render ICC a clinically intractable malignancy. Elucidating the unique molecular regulatory mechanisms and immune microenvironment of ICC, is critical to breaking therapeutic barriers and improving patient prognosis.肝内胆管癌(ICC)是第二大流行的原发性肝癌,发病率稳步上升. 其特点是早期症状隐匿,缺乏特异性的诊断性生物标志物,大约60% - 70%的患者被诊断为晚期,无法进行根治性手术. 传统的放化疗治疗效果有限. 尽管免疫治疗已经取得了初步突破,但低总体反应率和难以捉摸的耐药机制使ICC成为临床难治性恶性肿瘤. 阐明ICC独特的分子调控机制和免疫微环境,对打破治疗障碍、改善患者预后至关重要. **Methods:** ICC clinical samples were applied for candidate biomarker screening using single-cell and high-throughput sequencing. Clinical specimens, cell lines and mouse xenograft models were utilized for functional validation combined with clinical prognostic analysis. Transcriptomics, co-IP, mass spectrometry, targeted and untargeted metabolomics were adopted to explore molecular interaction and metabolic pathways. Lactylation modification mechanism was verified via mass spectrometry, molecular docking and site-directed mutagenesis. Immune microenvironment alterations were evaluated by mass cytometry. ITGB4 targeted small molecule inhibitor PGG was identified by virtual screening and MST, and its synergistic anti-tumor efficacy with anti-PD-L1 antibody was validated in preclinical models.ICC临床样本应用单细胞和高通量测序进行候选生物标志物筛选. 利用临床标本、细胞系和小鼠异种移植模型进行功能验证并结合临床预后分析. 采用转录组学、协同ip、质谱、靶向和非靶向代谢组学来探索分子相互作用和代谢途径. 通过质谱分析、分子对接和定点诱变验证了乳酸化修饰机理. 免疫微环境改变用细胞计数法测定. 通过虚拟筛选和MST鉴定ITGB4靶向小分子抑制剂PGG,并通过临床前模型验证其与抗pd - l1抗体的协同抗肿瘤效果. **Results:** ITGB4 is specifically upregulated in ICC and serves as an adverse prognostic indicator. Rather than activating classic signaling pathways, ITGB4 acts as a scaffold protein to recruit AARS1 and bind IMPDH2, inducing K205 lactylation of IMPDH2. This modification triggers purine metabolic reprogramming and activates the cGMP-PKG-PD-L1 axis, ultimately resulting in $CD8^+$ T cell exhaustion and tumor immune evasion. PGG specifically targets ITGB4, and combination treatment with anti-PD-L1 antibody presents potent

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synergistic anti-tumor activity, providing an innovative metabolism-immune combination regimen for ICC treatment.ITGB4在ICC中特异性上调,并作为不良预后指标. ITGB4不是激活经典的信号通路,而是作为支架蛋白招募AARS1并结合IMPDH2,诱导IMPDH2的K205乳酸化 这种修饰触发嘌呤代谢重编程,激活cGMP-PKG-PD-L1轴,最终导致CD8 + T细胞衰竭和肿瘤免疫逃逸PGG特异性靶向ITGB4,与抗pd - l1抗体联合治疗具有强大的协同抗肿瘤活性,为ICC治疗提供了一种创新的代谢-免疫联合治疗方案. **Conclusion:** This study first reveals that ITGB4 acts as a core driver of progression and immune evasion in ICC. By recruiting AARS1 to mediate K205 lactylation of IMPDH2, ITGB4 directly links purine metabolic reprogramming to the cGMP-PKG-PD-L1 signaling axis, ultimately inducing $CD8^+$ T cell exhaustion. Combined administration of the ITGB4 targeted small molecule PGG and anti-PD-L1 antibody exerts synergistic anti-tumor activity in preclinical models, offering an innovative strategy combining metabolic intervention and immunotherapy.这项研究首次揭示了ITGB4是ICC进展和免疫逃避的核心驱动因素. ITGB4通过募集AARS1介导IMPDH2的K205乳酸化,将嘌呤代谢重编程直接连接到cGMP-PKG-PD-L1信号轴,最终诱导CD8 + T细胞衰竭.在临床前模型中,ITGB4靶向小分子PGG和抗pd - l1抗体联合给药具有协同抗肿瘤活性,提供了代谢干预和免疫治疗相结合的创新策略.



Disclosures: Taiyang Chen:Nothing to Disclose, HaiBo Yu:Nothing to Disclose.

1078 | MRI DERIVED LIVER AGE GAP IS ASSOCIATED WITH PREVALENT OR INCIDENT LIVER DISEASE, MORTALITY, AND LIFESTYLE IN 67,130 UK BIOBANK PARTICIPANTS

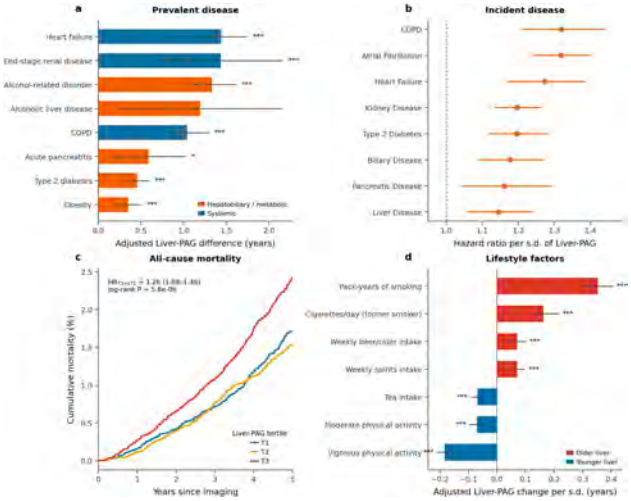
Yufeng Wang[1] Zengtian Deng[1] Lixia Wang[1] Abdelrahman Attia[1] Minsun Kwak[2] Saeid Rezaee-Zavareh[3] Stephen Pandol[1] Yibin Xie[1] Hyunseok Kim[1] Debiao Li[1] Ju Dong Yang[4], [1]Cedars Sinai Medical Center, [2]Seoul National University Hospital, [3]Middle East Liver Diseases (MELD) Center, [4]Cedars-Sinai Medical Center

Background: Chronological age incompletely reflects liver health. We developed a deep-learning liver MRI age clock and evaluated whether the resulting liver-predicted age gap, Liver-PAG, captures accelerated liver aging associated with prevalent/incident liver disease, all-cause mortality, and modifiable lifestyle factors. **Methods:** Four-channel abdominal Dixon MRI from 67,130 UK Biobank participants underwent automated liver segmentation. A MedNeXt model was trained to predict chronological age in a strictly healthy reference subset. Liver-PAG was defined as bias-corrected predicted liver age minus chronological age, with positive values indicating an older-appearing liver. Cross-sectional associations with prevalent disease were assessed using covariate-adjusted linear models. Prospective associations with incident disease and all-cause mortality over 5 years were evaluated using Cox models among participants free of the corresponding outcome at baseline, adjusted for age, sex, BMI, smoking, and alcohol use. A Healthy Lifestyle Score, or HLS, was derived by summarizing 108 lifestyle variables across five domains: diet, physical activity, sleep, alcohol use, and smoking. Associations of Liver-PAG with HLS and individual lifestyle factors were tested in adjusted models. **Results:** The model predicted chronological age accurately (mean absolute error 2.75 years; $R^2 = 0.776$). Higher Liver-PAG was observed in alcohol-related disorders (+1.33 years; FDR < 0.001), alcohol-associated liver disease (+1.19 years), type 2 diabetes (+0.46 years; FDR < 0.001), heart failure (+1.44 years), and COPD (+1.04 years) (Panel A). Each SD increase in Liver-PAG was associated with a higher risk of incident liver disease (HR 1.14, 95% CI 1.06–1.24), biliary disease (HR 1.18, 1.09–1.27), type 2 diabetes (HR 1.20, 1.12–1.28), and all-cause mortality (HR 1.15, 1.08–1.22) (Panel B). Compared with the lowest Liver-PAG tertile, the highest tertile was associated with higher 5-year all-cause mortality risk (HR 1.26, 1.08–1.46; log-rank P < 0.001) (Panel C). Higher HLS was associated with lower Liver-PAG (−0.14 years per one-point increase in HLS). Among individual lifestyle factors, greater smoking burden was associated with older-appearing liver age (+0.35 years per SD of pack-years), whereas

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vigorous physical activity was associated with younger-appearing liver age (−0.18 years per SD) (Panel D). **Conclusion:** A deep-learning derived liver age clock quantifies an organ-specific imaging biomarker of accelerated liver aging. Liver-PAG is associated with prevalent hepatic and systemic disease, incident hepatobiliary and cardiometabolic outcomes, all-cause mortality, and modifiable lifestyle exposures. These findings support Liver-PAG as a scalable, non-invasive imaging biomarker for liver and systemic health risk stratification.



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1079 | PNPLA3 GENOTYPE IS ASSOCIATED WITH INCREASED PROGRESSION TO CIRRHOSIS INDEPENDENT OF LIVER STIFFNESS MEASUREMENT BY VIBRATION-CONTROLLED TRANSIENT ELASTOGRAPHY IN STEATOTIC LIVER DISEASE

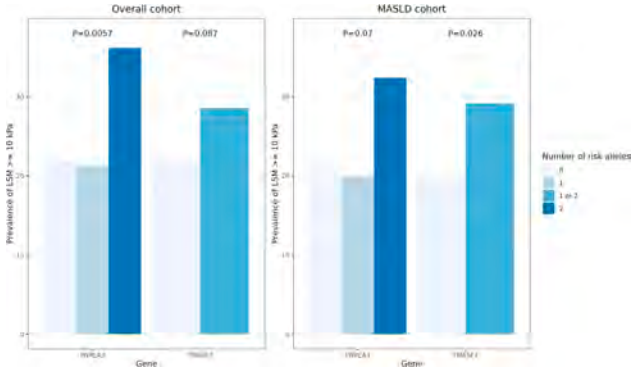
Kira Zhao[1] Vincent Chen[1], [1]University of Michigan

Background: *PNPLA3*-rs738409 and *TM6SF2*-rs58542926 genotypes are associated with increased risk of cirrhosis/fibrosis and major adverse liver outcomes (MALO) in steatotic liver disease (SLD). Genetics provides prognostic information beyond FIB4 and histologic fibrosis stage for MALO risk. However, whether genetics improves upon vibration-controlled transient elastography (VCTE) for development of advanced liver disease is not known. **Methods:** This was a single-center study of patients with SLD at Michigan Medicine who underwent VCTE and genotyping. The primary predictors were *PNPLA3*-rs738409 and *TM6SF2*-rs58542926 genotype. The primary outcomes were new diagnosis of cirrhosis, and MALO defined as hepatic decompensation, hepatocellular carcinoma, or liver-related death. Associations were modeled as Cox proportional hazards models with effects shown as hazard ratios (HR). Models were unadjusted or adjusted for age, sex, body mass index, diabetes status, and principal components 1-5 to account for genetic ancestry. **Results:** The cohort included 875 patients, of whom 753 had MASLD and 122 had ALD. The median age was 57 years; 49% were female and 84% were white. Median follow-up was 47 months (IQR 16-77 months). The mean body mass index was 31.5 kg/m^2 and 47%, 75%, and 72% had type 2 diabetes, dyslipidemia, and hypertension, respectively. Median liver stiffness measurement (LSM) was 6.1 kPa, with 201 (23%) having LSM >= 10 kPa and 93 (11%) having LSM >= 15 kPa. The *PNPLA3*-rs738409-G allele was associated with a higher proportion of LSM >= 10 kPa (36% vs. 22% for GG vs. CC alleles, p = 0.0057); this remained significant in multivariable models. *TM6SF2*-rs58542926-T carriage had a borderline significant association with LSM >= 10 kPa (29% vs. 22% for CC vs. CT/TT alleles, p = 0.087). After exclusion of patients with alcohol-associated liver disease (ALD), the association between *PNPLA3* genotype and LSM >= 10 kPa lost significance (p = 0.07) while that between *TM6SF2* genotype and LSM >= 10 kPa became significant (29% vs. 20% for CC vs. CT/TT alleles, p = 0.026). *PNPLA3*-rs738409-GG was associated with greater incidence of cirrhosis diagnosis (HR 2.04 [95% CI 1.18-3.51] vs. CC genotype, p = 0.010); this association remained significant in a multivariable model. After additional adjustment for baseline LSM, the association was attenuated but remained significant (HR 1.78 [95% CI 1.01-3.15], p = 0.048). *PNPLA3* genotype was not associated with incident cirrhosis in patients with baseline LSM < 10 kPa or after excluding ALD patients. *TM6SF2* genotype was not associated with incident cirrhosis. Neither *PNPLA3* nor *TM6SF2* genotype was associated with MALO. **Conclusion:** In patients with SLD, *PNPLA3* genotype associated with higher baseline LSM by VCTE, and increased risk of progression to cirrhosis independent of baseline LSM.

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Neither *PNPLA3* nor *TM6SF2* genotype was associated with MALO in this cohort.



Disclosures: Kira Zhao:Nothing to Disclose, Vincent Chen:AstraZeneca: site PI on industry-sponsored trial, Ipsen: site co-I on industry-sponsored trial, Kowa: site co-I on industry-sponsored trial, Madrigal: Grant/Research Support, GSK: Site PI for clinical trial, CSL: Site PI for clinical trial.

1080 | DIVERGENT EFFECTS ON HISPANIC (AMERINDIAN) ANCESTRY ON DISEASE SUSCEPTIBILITY AND HISTOLOGIC SEVERITY IN MASLD

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Background: Hispanic individuals exhibit a higher prevalence of metabolic dysfunction–associated steatotic liver disease (MASLD), a phenomenon largely attributed to genetic factors such as *PNPLA3* variants. However, whether Hispanic (Amerindian [AMR]) ancestry influences disease risk and histologic severity or phenotype is not fully understood. We interrogated AMR ancestry– MASLD prevalence and severity associations across population-based and biopsy-confirmed cohorts. **Methods:** We analyzed the association between genetically inferred proportion of AMR ancestry and MASLD phenotypes in two complementary datasets: (1) the Multi-Ethnic Study of Atherosclerosis (MESA), a population-based cohort, and (2) the NASH CRN, liver biopsy-confirmed cohort of MASLD patients. Multivariable logistic regression models adjusting for age, sex, body mass index, and diabetes were used to assess associations between AMR ancestry (continuous proportion) and MASLD presence (MESA) or histologic features (NASH CRN), including steatosis, lobular inflammation, ballooning, NAS ≥ 4, and advanced fibrosis. Mediation by *PNPLA3* genotype was evaluated. **Results:** In MESA, AMR ancestry was strongly associated with MASLD (OR 7.33 [5.15–10.4] in all participants; OR 4.47 [2.45–8.13] and within Hispanic individuals (both $P < 0.001$). Adjustment for *PNPLA3 G-allele* attenuated the ancestry effect by >50% (OR falls from 4.47 to 2.17 for AMR ancestry), indicating partial mediation via *PNPLA3* .In contrast, in the NASH CRN cohort, increasing AMR ancestry was associated with **lower odds of steatosis** in the entire cohort (OR 0.5 [0.3–0.8], $P = 0.003$) and within Hispanic individuals (OR 0.3 [0.1–0.9], $P = 0.04$), but **higher odds of lobular inflammation** in the entire cohort (OR 1.8 [1.1–2.8], $P = 0.01$) and within Hispanic individuals (OR 3.1 [1.0–9.1], $P = 0.04$). No significant associations were observed for advanced fibrosis, NAS ≥ 4, ballooning, or portal inflammation. **Conclusion:** These findings suggest a **cohort-dependent divergence** in ancestry–MASLD associations. While AMR ancestry confers increased susceptibility to MASLD at the population level, with significant contribution from *PNPLA3* variation, a biopsy-based cohort reveals a different phenotype characterized by lower steatosis but higher inflammation.

Table 1: Relationship with AMR Ancestry and the risk for MASLD susceptibility and histological severity

		All ancestry groups		Self-reported Hispanic group	
Study	Phenotypes	OR (95% C.I.)	Pvalue	OR (95% C.I.)	Pvalue
MESA	MASLD	7.33 (5.15-10.4)	<0.001	4.47 (2.45-8.13)	<0.001
NASH CRN	Advanced Fibrosis within MASLD	0.6 (0.3-1.0)	0.06	1.2 (0.5-2.8)	0.68
NASH CRN	NAS ≥ 4 within MASLD	1.0 (0.6-1.6)	0.97	1.1 (0.4-3.4)	0.88
NASH CRN	Steatosis within MASLD	0.5 (0.3-0.8)	2.67E-03	0.3 (0.1-0.9)	0.04
NASH CRN	Lobular Inflammation within MASLD	1.8 (1.1-2.8)	0.01	3.1 (1.0-9.1)	0.04
NASH CRN	Portal Inflammation within MASLD	0.8 (0.4-1.4)	0.39	2.7 (0.5-13.3)	0.23
NASH CRN	Ballooning within MASLD	1.3 (0.8-2.1)	0.32	2.1 (0.7-6.5)	0.2

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1081 | CLINICAL CHARACTERISTICS AND REAL-WORLD OUTCOMES OF ENZYME REPLACEMENT THERAPY IN PATIENTS FROM THE US WITH LYSOSOMAL ACID LIPASE DEFICIENCY: DATA FROM THE INTERNATIONAL LAL-D REGISTRY

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Background: Lysosomal acid lipase deficiency (LAL-D) is a rare, progressive autosomal recessive lysosomal storage disease, leading to progressive liver disease and atherogenic dyslipidemia. Enzyme replacement therapy (ERT) with sebelipase alfa is available since 2015, but US-specific real-world data are limited. We aimed to characterize the disease burden, diagnostic delay, and outcomes of US patients with LAL-D enrolled in the International LAL-D Registry. **Methods:** We conducted a retrospective analysis of data from US patients who were not included in a clinical trial with sebelipase alfa enrolled in the International LAL-D Registry (NCT01633489) as of March 2, 2026. Descriptive analyses assessed demographics, diagnostic delay, longitudinal liver and lipid parameters and liver histology. **Results:** Of 64 US registry patients, 38 met the inclusion criteria. Median age at diagnosis and first reported symptom was 13.38 years and 7.5 years, respectively (n = 34), the median time from symptom onset to diagnostic testing was 4.27 years (n = 27). Hepatomegaly and splenomegaly raised the suspicion of LAL-D in 13/38 and 7/38 patients, respectively.20 patients had baseline liver biopsy results; mixed macro- and microvesicular steatosis and microvesicular steatosis only were most frequent (7/20, 35% and 6/20, 30%, respectively). Fibrosis stage was reported for 7/20 patients, with 43% showing stage ≥ 3 fibrosis, including cirrhosis (1/7).Overall, 36/38 (94.7%) participants received sebelipase alfa.Among treated patients with paired alanine aminotransferases (ALT) data (n = 24), mean ALT decreased from 2.90×ULN at baseline to 1.21×ULN at last follow-up, with normalization increasing from 4.2% to 54.2% and ALT ≥ 3×ULN decreasing from 37.5% to 4.2%. AST showed similar improvement. All patients with paired biopsies (4/4) had decreased fibrosis stage, and among those with paired abdominal imaging (n = 12), 7/12 (58.3%) had hepatomegaly at baseline that resolved by last follow-up.Dyslipidemia was frequent, with elevated LDL in 34.2% (12/38), and elevated triglycerides in 31.6% (12/38) of patients. In patients not receiving lipid-modifying therapy (N = 10), dyslipidemia was more pronounced, with 90% exhibiting elevated LDL-C (> 130 mg/dL), including 60% with levels > 160 mg/dL; mean LDL-C was 187.7 mg/dL and mean HDL-C was 34.0 mg/dL. Mean LDL-C decreased from 187.7 mg/dL to 140.2 mg/dL, mean HDL-C increased from 34.0 mg/dL at baseline to 48.1 mg/dL at last follow-up. **Conclusion:** US patients with LAL-D commonly present with liver involvement and dyslipidemia and experience a clinically meaningful diagnostic delay. Sebelipase alfa ERT is associated with sustained improvements in liver and lipid parameters.

Disclosures: Thomas Kerr:Madrigal: Consultant, GSK: Grant/Research Support, Alnylam: Consultant, Salix: Consultant, Alexion: Grant/Research Support, Lorenzo D'Antiga:Alexion: Advisor, Mirum: Advisor, IPSEN: Advisor, Daniel Staub:Alexion Pharma GmbH: Salary by employment, Sophie Kitchen:Nothing to Disclose, Florian Abel:Alexion AstraZeneca Rare Disease: Employee, AstraZeneca: Stock - publicly traded company, Gilead Sciences: Stock - publicly traded company, Novartis: Stock - publicly traded company, Sandoz: Stock - publicly traded company, William Balistreri:Otsuka: Consultant, Mirum: Consultant, Alexion, AstraZeneca Rare Disease: International LAL-D Registry Scientific Advisory Board.

1082 | GENETIC SUSCEPTIBILITY TO HEPATITIS C–ASSOCIATED HEPATOCELLULAR CARCINOMA ACROSS DIVERSE ANCESTRIES: A GWAS FROM THE MILLION VETERAN PROGRAM

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Background: Host genetic factors contributing to progression from chronic hepatitis C virus (HCV) infection to hepatocellular carcinoma (HCC) remain

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incompletely understood. We performed a multi-ancestry genome-wide association study (GWAS) to identify susceptibility loci associated with HCV-related HCC (HCV-HCC) within the Million Veterans Program (MVP). **Methods:** We analyzed 2,628 HCV-HCC, 11,761 HCV-only, and 2,091 HCC-only participants from the MVP. GWAS analyses were performed using Scalable and Accurate Implementation of GEneralized mixed model (SAIGE) with adjustment for age, sex and genetic ancestry. Analyses included Cosmopolitan and ancestry-stratified Harmonized Ancestry and Race/Ethnicity (HARE) cohorts including African American (AFR), European (EUR), and Hispanic (HIS) groups. Fine mapping, credible set construction, pathway enrichment, overrepresentation analyses, and linkage disequilibrium (LD)-based trait clustering were subsequently performed. **Results:** The strongest associations localized to immune-related loci within the major histocompatibility complex (MHC) region. Variants in HLA-DQB1/DQB2 differentiated HCV-HCC from both HCV-only and HCC-only cohorts at genome-wide significance. In the Cosmopolitan cohort, rs3519547 (HLA-DQB1) differentiated HCV-HCC from all controls (P = 3.08×10^-19, OR 0.67 [0.62–0.73]). Variants in interferon signaling genes, including IFNL4/IFNL3P1, were also significantly associated with HCV-HCC. rs1418044546 demonstrated genome-wide significance in the comparison of HCV-HCC versus all controls (P = 1.34×10^-9, OR 1.22 [1.14–1.30]). Additional significant associations involved CD81-AS1, MTCO3P1, DMD, SAMD5, PTPRD, KLHL8, and TERT. Previously reported MASLD-associated variant rs3747207 in PNPLA3 differentiated HCV-HCC from HCC-only cohorts in both Cosmopolitan and EUR analyses. Fine mapping resolved several loci into small or single-variant credible sets with high posterior inclusion probabilities, supporting potential causal signals. Pathway analyses demonstrated modest enrichment of interferon signaling, IL2-STAT5 signaling, p53-related pathways, and metabolic pathways, although none reached predefined significance thresholds. Trait clustering identified overlapping viral, inflammatory, and metabolic phenotypes. **Conclusion:** HCV-related hepatocarcinogenesis demonstrates a complex multi-ancestry genetic architecture enriched for immune-regulatory, interferon-signaling, and metabolic susceptibility loci. These findings support interactions between antiviral immunity and metabolic-inflammatory pathways in HCV-HCC progression and identify candidate loci for future mechanistic and translational investigation.

Disclosures: Theodore Feldman:Gilead Sciences: Stock - publicly traded company, Astrazeneca PLC: Stock - publicly traded company, Moderna: Stock - publicly traded company, Merck: Stock - publicly traded company, AbbVie: Stock - publicly traded company, Lauren Carter:Nothing to Disclose, Kaelyn Nannini:Nothing to Disclose, Chunlei Zhang:Nothing to Disclose, Karlynn Dulberger:Nothing to Disclose, Meghana Yellanki:Nothing to Disclose, David Kaplan: AstraZeneca Inc: Grant/Research Support, Roche Genentech: Independent Contractor, Exact Sciences: Grant/Research Support, Glycotest: Grant/Research Support, Exelixis: Advisor, AstraZeneca: Advisor, Gilead: Grant/Research Support, Bausch Healthcare: Grant/Research Support, Mirumn: Grant/Research Support, Bausch: Grant/Research Support, Exact Sciences: Grant/Research Support, AstraZeneca: Grant/Research Support, Mirum: Grant/Research Support, Gyorgy Baffy:Astellas Pharma, Inc: Consultant, Novo Nordisk, Inc: Consultant, Timothy Morgan: Nothing to Disclose, Daniel Dochtermann:Nothing to Disclose, Saiju Pyarajan:Nothing to Disclose, Mary Brophy:Nothing to Disclose, Nathanael Fillmore:Nothing to Disclose, Nhan Do:Nothing to Disclose.

1083 | *PNPLA3 I148M* RNA EDITING OUTPERFORMS *PNPLA3* SILENCING IN IMPROVING HEPATOCYTE LIPID METABOLISM *IN VITRO* AND *EX VIVO*

Ginnie Yang[1] Yuan Yin[1] Chikdu Shivalila[1] Genliang Lu[1] Stearne Briem[1] Michael Byrne[1] Alyse Faraone[1] Naoki Iwamoto[1] Tomomi Kawamoto[1] Richard Looby[1] Frank Favaloro[1] Stephany Standley[1] Suma Veeramachineni[1] Hailin Yang[1] Hui Yu[1] Pachamuthu Kandasamy[1] Chandra Vargeese[1] Erik Ingelsson[1], [1]Wave Life Sciences

Background: *PNPLA3 I148M* is both a gain- and loss-of-function variant that disrupts hepatic lipid homeostasis and retinol metabolism and is associated with substantially increased risk of liver-related deaths, including from MASH. We developed RNA editing oligonucleotides, or AIMers, to edit the base sequence of *PNPLA3 I148M* transcripts to restore functional protein. Emerging evidence shows that PNPLA3 plays an important role in hepatic lipid metabolism. For the treatment of *PNPLA3 I148M* liver disease, an RNA editing approach that restores PNPLA3 enzymatic function may be preferable to silencing *PNPLA3,* which causes a loss of function. **Methods:** We synthesized GalNAc-conjugated AIMers to edit the I148M variant in hepatocytes and compared their impact to silencing PNPLA3 by GalNAc-siRNA. GalNAc-AIMer editing efficiency was quantified by Sanger sequencing in human homozygous *PNPLA3 I148M* primary hepatocytes. The impact of editing or silencing on intracellular lipid droplet density was evaluated using the human homozygous I148M hepatocytes in a HEPATOPAC system and in long-term primary human hepatocyte monolayer cultures. Using an *ex vivo* human *PNPLA3 I148M* model, we compared the impact of PNPLA3

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AIMers to PNPLA3 siRNA on lipid metabolism, fibrosis, mitochondrial function, and inflammation. Lipid metabolic pathway flux was also compared between M/M, I/M, and I/I human hepatocytes. Mice were also dosed subcutaneously with GalNAc-AIMers, and tissue concentrations of PNPLA3 AIMers in liver were quantified by ELISA after one week. **Results:** The most effective AIMers directed potent (EC_{50} 12 nM) and efficient (~70%) editing of *PNPLA3* transcripts. In the HEPATOPAC system, PNPLA3 GalNAc-AIMers significantly decreased lipid droplet density compared to mock treatment ($p < 0.0001$), whereas PNPLA3 GalNAc-siRNA did not have a significant effect. In long-term cultures of human primary hepatocytes, ~50% PNPLA3 RNA editing corresponded with a substantial lowering of lipid droplet density. The impact of PNPLA3 AIMer on lipid metabolism, inflammation, and fibrosis pathways will be presented. In mice expressing only wild-type mouse *Pnpla3*, GalNAc-AIMers dosed subcutaneously reached up to ~1,000 µg/g in liver. **Conclusion:** These data demonstrate that AIMers supporting *PNPLA3 I148M* editing restore functional PNPLA3 protein, decrease fat content in hepatocytes, and outperform *PNPLA3* silencing in lowering lipid density. PNPLA3 GalNAc-AIMers dosed in mice reached concentrations expected to yield substantial RNA editing based on in vitro experiments in hepatocytes. Overall, these data support continued advancement of AIMers for the treatment of *PNPLA3 I148M* liver disease, and we expect to file a CTA to advance this program in 2026.
Disclosures: Ginnie Yang:Nothing to Disclose, Yuan Yin:Nothing to Disclose, Chikdu Shivalila:Nothing to Disclose, Genliang Lu:Nothing to Disclose, Stearne Briem:Nothing to Disclose, Michael Byrne:Nothing to Disclose, Alyse Faraone:Nothing to Disclose, Naoki Iwamoto:Nothing to Disclose, Tomomi Kawamoto: Nothing to Disclose, Richard Looby:Nothing to Disclose, Frank Favaloro:Nothing to Disclose, Stephany Standley:Nothing to Disclose, Suma Veeramachineni: Nothing to Disclose, Hailin Yang:Wave Life Sciences: Employee, Hui Yu:Nothing to Disclose, Pachamuthu Kandasamy:Nothing to Disclose, Chandra Vargeese: Nothing to Disclose, Erik Ingelsson:Nothing to Disclose.

1084 | EXTERNAL VALIDATION OF THE SIMPLE MACHINE LEARNING MODEL (FAET SCORE) FOR PREDICTION OF ADVANCED FIBROSIS IN A LARGE BIOPSY-PROVEN MASLD PATIENT COHORT

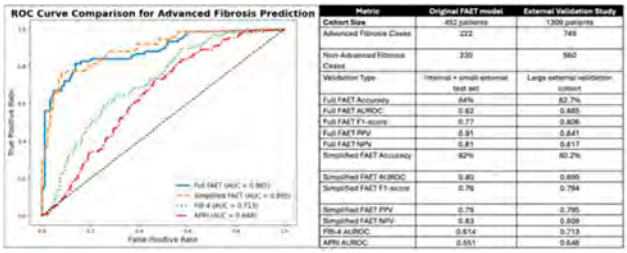
Ashok Kumar Choudhury Radhika Sharma[1] Shobha Sharma[2] Archana Rastogi[1] Sandip Kumar[1] Tapan Gandhi[2] Manoj Kumar[1] Shiv Kumar Sarin[1] Bishnupriya Sahoo[3], , [1]Institute of Liver and Biliary Sciences, [2]Indian Institute of Technology Delhi, [3]SGT University, Faculty of Medicine

Background: MASLD with fibrosis associated with disease progression, liver related events and mortality. Commonly used non-invasive FIB-4 and APRI limited by accuracy and our previous study showed a simple Fibrosis Assessment using Extra Trees (FAET) score has a better accuracy for prediction of advanced fibrosis non-invasively from simple parameters using AI. We performed external validation of both the FAET model and the simplified score in a large biopsy-proven MASLD cohort. **Methods:** This retrospective medical records of biopsy proven 1309 MASLD patients were analyzed. Patients were classified into non-advanced fibrosis (F0-F2, NAF) and advanced fibrosis (F3-F4, AF) groups. External validation of the original 13-feature FAET model and the simplified 5-feature FAET simple model was performed for prediction of advanced fibrosis. A comparative ROC analysis with FIB-4, APRI and LSM from VCTE was performed. Calibration analysis, SHAP explainability analysis, decision curve analysis, and repeated stratified cross-validation were used to evaluate model reliability and clinical applicability. **Results:** A total of 1309 biopsy-proven MASLD patients [F0-325, F1-117, F2-118, F3-118 and F4-631 patients] with analysis cohort as AF-749 (57.2%) and NAF-560 (42.8%). Patients with advanced fibrosis were older and had significantly lower hemoglobin and platelet counts, along with higher AST, ALP, GGT, and bilirubin levels. The externally validated full 13-feature FAET model showed strong predictive performance with an AUROC of 0.885, accuracy of 82.7%, F1-score of 0.806, sensitivity of 77.3%, specificity of 87.4%, PPV of 84.1%, and NPV of 81.7%. The simplified 5-feature FAET model, which included age, presence of diabetes mellitus, platelet count, AST, and total cholesterol demonstrated a discrimination with AUROC of 0.895, accuracy of 80.2%, and F1-score of 0.784. The simplified FAET models performed better than conventional fibrosis scores i.e. FIB-4 (AUROC 0.713) and APRI (AUROC 0.648). Calibration analysis demonstrated good agreement between predicted and observed probabilities, while decision curve analysis showed favorable clinical utility across clinically relevant threshold probabilities. Cross-validation further confirmed stable and reproducible model performance. **Conclusion:** External validation demonstrated excellent performance of the FAET framework consisting simple parameters (age, DM, platelet count, AST, and total cholesterol) hold valid and accurate. Simple and routinely available clinical and biochemical parameters in this FAET model with excellent discriminatory ability may be better tool for screening high-risk MASLD patients over and above the existing

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standard models.



Metric	Original FAST model	External Validation Study
Cohort Size	452 patients	1306 patients
Advanced Fibrosis Cases	222	748
Non-Advanced Fibrosis Cases	230	562
Validation Type	Internal + small external test set	Large external validation cohort
Full FAST Accuracy	84%	82.7%
Full FAST AUROC	0.92	0.885
Full FAST F1-score	0.77	0.806
Full FAST PPV	0.91	0.841
Full FAST NPV	0.81	0.817
Simplified FAST Accuracy	82%	80.2%
Simplified FAST AUROC	0.89	0.866
Simplified FAST F1-score	0.76	0.784
Simplified FAST PPV	0.79	0.795
Simplified FAST NPV	0.83	0.809
FIB-4 AUROC	0.614	0.713
APRI AUROC	0.551	0.648

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1085 | ENDOTHELIAL IDENTITY COLLAPSE AND RNA STRUCTURAL REPROGRAMMING IN HEPATOCELLULAR CARCINOMA: A TCGA-LIHC TRANSCRIPTOMIC AND RNAFOLD-BASED DISCOVERY OF DRUGGABLE RNA TARGETS

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Background: Hepatocellular carcinoma (HCC) is the most common primary liver malignancy and remains a major cause of cancer-related mortality worldwide. Although transcriptomic profiling has identified widespread gene dysregulation in HCC, expression changes alone do not fully explain post-transcriptional mechanisms that contribute to tumor progression. This study integrated transcriptomic analysis with RNA secondary structure prediction to identify endothelial-associated, structurally distinctive RNA targets in HCC. **Methods:** Publicly available RNA-sequencing data and clinical annotations from the TCGA Liver Hepatocellular Carcinoma (TCGA-LIHC) cohort were obtained through UCSC Xena. Primary Tumor samples (n = 371) were compared with Solid Tissue Normal samples (n = 50). Differential expression analysis was performed in R using the limma empirical Bayes framework with Benjamini-Hochberg false discovery rate correction. Genes with false discovery rate < 0.05 and absolute log2 fold change ≥ 1 were considered significant. Candidate genes were prioritized based on statistical significance and endothelial relevance. The 3′ untranslated region sequences of the top five targets were retrieved using Ensembl BioMart and analyzed with ViennaRNA RNAfold to evaluate minimum free energy and ensemble diversity. **Results:** A total of 3,690 genes were significantly dysregulated in HCC. Endothelial-associated genes CLEC4M, CLEC4G, STAB2, and BMPER were strongly downregulated, with log2 fold changes of -8.38, -8.17, -7.18, and -5.79, respectively, consistent with loss of normal sinusoidal endothelial identity. GABRD was markedly upregulated (log2 fold change +4.33). RNA secondary structure analysis showed substantial heterogeneity across candidate 3′-UTRs. BMPER demonstrated the most extreme structural profile, with minimum free energy of -1255.1 kcal/mol and ensemble diversity of 923.19, suggesting a highly stable yet structurally plastic regulatory region. STAB2 and CLEC4M also displayed pronounced structural complexity, whereas GABRD exhibited the lowest conformational diversity. **Conclusion:** HCC is characterized not only by extensive transcriptomic dysregulation but also by marked RNA structural remodeling in selected vascular- and microenvironment-associated transcripts. These findings identify BMPER, STAB2, CLEC4M, CLEC4G, and GABRD as candidate RNA-based biomarkers and potential druggable RNA targets in HCC, supporting future structural validation and RNA-directed therapeutic investigation.

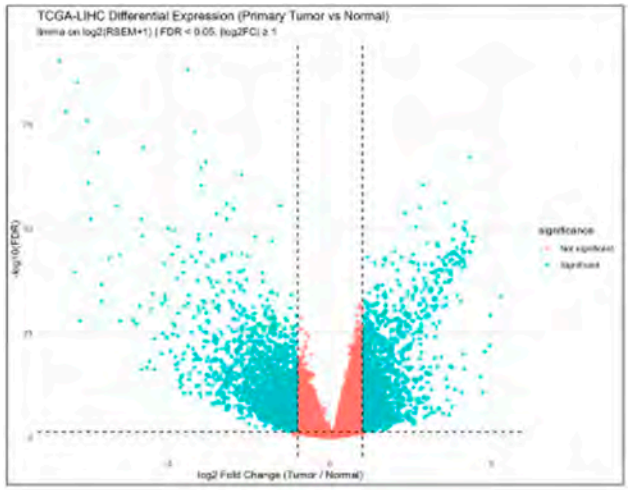


Fig. 2: Volcano Plot of TCGA-LIHC Normal v/s HCC Cells showing Dys-regulated Genes (Up & Down Regulated).

Disclosures: Yana Joshi:Nothing to Disclose, Ayanjeet Chowdhury:Nothing to Disclose, Sharvari Kulkarni: Nothing to Disclose.

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1086 | SPATIAL TRANSCRIPTOMICS REVEALS SEX-SPECIFIC MOLECULAR ZONATION SIGNATURES IN F2 MASLD FIBROTIC LIVERS

Mohamed Abdelnabi[1] Aydin Herik[1] Wagdi Almishri[2] Konstantin Koro[1] Erika Prando-Munhoz[1] Mark Swain[1] Henry Nguyen[3], [1]University of Calgary, [2]Cumming School of Medicine | University of Calgary, [3]University of Calgary Cumming School of Medicine

Background: Metabolic dysfunction–associated steatotic liver disease (MASLD) is a growing global health issue, affecting approximately 30% of adults worldwide and projected to impact one in three Canadians within five years. The disease includes a spectrum of liver pathology including steatosis, inflammation, fibrosis, and tumor development, with fibrosis being the main determinant of progression and adverse outcomes. MASLD pathogenesis is complex and multifactorial, with limited therapies, highlighting the need to better understand its mechanisms. Sexual dimorphism contributes to MASLD pathogenesis and fibrosis progression but is often overlooked in clinical and translational studies. Using the Calgary Liver Unit biobank, we sought to investigate sex-specific signatures in MASLD patients with F2-stage fibrosis, a transition stage linked to higher progression risk. **Methods:** We profiled >18,000 protein-coding genes using the GeoMx Digital Spatial Profiler on FFPE liver biopsies from 14 MASLD patients all with F2 liver fibrosis (7 males, 7 females). Inclusion criteria included histological confirmation based on the NAFLD Activity Score (NAS) assessed on FFPE liver biopsy specimens and independently reviewed by a pathologist, patient age between 46 and 70 years, and absence of other chronic liver diseases (e.g., viral hepatitis, autoimmune hepatitis, or inherited/metabolic liver disorders). Exclusion criteria included alcohol misuse, insulin therapy, use of oral hypoglycemic agents, and weight-loss medications (including GLP-1 receptor agonists). Two patients (one male and one female) were excluded due to inadequate biopsy quality, resulting in a final cohort of 14 patients. Regions of interest were selected and annotated as Portal and Non-Portal. Data were analyzed in R (v4.4.2), including quality control, normalization, batch correction, differential expression, enrichment, and clinical association analysis. **Results:** We identified significant sex-associated transcriptomic differences in MASLD across both non-zonal and zone-specific analysis. Global or non-zonal signatures (174 genes, FDR <0.05) were enriched for pathways related to antigen processing and presentation, mineral absorption, and fatty acid metabolism. Sex-specific zonal signatures in portal zones included neutrophil degranulation, phagocytic activity, and cytoskeletal remodeling (54 genes, FDR < 0.05), while in Non-Portal zones they comprised cholesterol metabolism, oxidative phosphorylation, and glycolysis (468 genes, FDR < 0.05). Notably, the global sex signature correlated positively with peripheral lymphocytes, and neutrophils in women, but negatively in men. **Conclusion:** Our findings suggest sexual dimorphism at both global and zonation-specific levels in MASLD liver biopsies, potentially influencing disease progression differently in men and women.

Disclosures: mohamed Abdelnabi:Nothing to Disclose, Aydin Herik:Nothing to Disclose, Wagdi Almishri:Nothing to Disclose, Konstantin Koro:Nothing to Disclose, Erika Prando-Munhoz:Nothing to Disclose, Mark Swain:Gilead, Ipsen, Novo Nordisk, Advanz, Abbott, GSK, Mirum, Boehringer Ingelheim, Moderna.: Advisor, GSK, Mirum, Boehringer Ingelheim: Advisor, Gilead, GSK, Kowa, Novo Nordisk, Pfizer, Ancella, Merck, Galectin, Ipsen, Madrigal, Roche, Altimmune: Grant/Research Support, Novo Nordisk, Pfizer, Ancella, Merck, Galectin: Grant/Research Support, Calliditas, Ipsen, Madrigal, Roche, Altimmune: Grant/Research Support, 89Bio, Inventiva, Boehringer Ingelheim: Grant/Research Support, : Ipsen, Gilead, Umecrine, Abbott, Novo Nordisk, Mirum: Speaking and Teaching, Ipsen: Speaking and Teaching, Henry Nguyen:Nothing to Disclose.

1087 | A MISSENSE VARIANT IN *DNAJC22* REDUCES HEPATOCYTE LIPID ACCUMULATION AND PROTECTS AGAINST STEATOTIC LIVER DISEASE

Aaron Hakim[1] James Park[2] Brian Hobbs[3] Niek Verweij[3] Michael Cho[2] Naga Chalasani[4] Tae-Hwi Schwantes-An[5] Jerome Rotter[6] John Doench[7] Rajat Gupta[2], [1]Beth Israel Deaconess Medical Center, [2]Brigham and Women's Hospital, [3]Regeneron Genetics Center, [4]Indiana University Medical Center, [5]Indiana University School of Medicine, [6]The Lundquist Institute for Biomedical Innovation at Harbor-UCLA Medical Center, [7]Broad Institute

Background: The accumulation of lipid droplets within hepatocytes plays a causal role in the pathogenesis of steatotic liver disease. We previously identified that CRISPR Cas9-mediated knockout of *DNAJC22* reduced lipid droplet accumulation in hepatocytes. Additionally, a rare (allele frequency ~1%) missense variant in *DNAJC22* (rs146774114, p.A163T) protected against chronic liver disease in UK Biobank, FinnGen, and Million Veteran Program. It remains unknown whether the p.A163T variant reduces lipid droplet accumulation in hepatocytes. Here, we used pooled cytosine base editing to compare the effect of the p.A163T variant in *DNAJC22* versus complete knockout of *DNAJC22* on hepatic lipid

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accumulation. We also explored whether *DNAJC22* p.A163T protected against chronic liver disease in the Indiana University (IU) Biobank and the Geisinger Health System (GHS) MyCode cohort. **Methods:** We optimized a base editing protocol to introduce the *DNAJC22* p.A163T mutation into HuH7 cells using mRNA nucleofection of the cytosine base editor BE4max. The pool of mutant and wildtype cells was incubated with oleic acid to stimulate lipid droplet accumulation; lipid droplets were stained with BODIPY$^{493/503}$, and cells were sorted into five equal bins using FACS based on degree of lipid droplet accumulation. Next-generation sequencing was used to determine the fraction of variant-edited cells relative to wildtype in each bin. We performed similar experiments to introduce a premature stop codon (p.Q164X) or synonymous control mutation (p.L172L) in *DNAJC22*. In the IU and GHS biobanks, we evaluated the association of *DNAJC22* p.A163T with chronic liver disease by ICD-10 codes using Firth penalized logistic regression. **Results:** We achieved a >25% editing rate of the p.A163T variant with a low rate of off-target mutations. There was a dose-dependent enrichment of p.A163T-edited cells in bins with successively lower lipid droplet accumulation (log_2fold change -0.55, p = 1.2x10^{-09}). The premature stop codon in *DNAJC22* had a larger impact on reducing lipid droplet accumulation compared to the p.A163T missense variant (log_2fold change -1.29, p = 2.57x10^{-10}). The synonymous control mutation did not impact lipid droplet accumulation (log_2fold change = -0.05, p = 0.165). *DNAJC22* p.A163T reduced risk of chronic liver disease in IU Biobank (OR = 0.57, p = 2.3x10^{-02} , n = 1,033 cases, n = 3,239 controls) and in the GHS cohort (OR = 0.89, p = 5.1x10^{-03}, n = 22,185 cases, n = 103,006 controls). **Conclusion:** Complete loss-of-function of *DNAJC22* had a larger cellular phenotypic effect on lipid droplet accumulation than the p.A163T variant. This suggests that p.A163T is a partial loss-of-function mutation. Given that the *DNAJC22* p.A163T variant is associated with reduced liver disease risk across multiple human genetic biobanks, complete therapeutic silencing of *DNAJC22* may have even stronger protective effects.

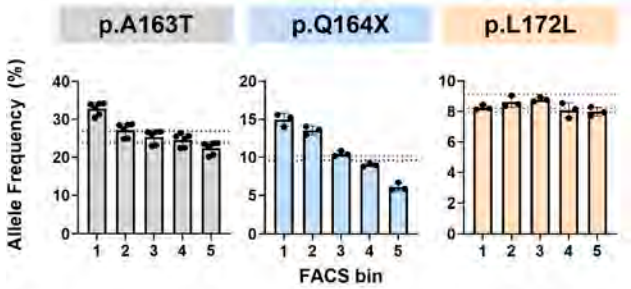


Figure 1: Frequency of base-edited variant in *DNAJC22* relative to wild type. Bin 1 reflects the lowest and Bin 5 reflects the highest lipid droplet accumulation. Dotted lines reflect the frequency of the variant in the unsorted population per replicate

Disclosures: Aaron Hakim:Olix Pharmaceuticals: Advisor, Deep Track Capital, LP: Consultant, James Park:Nothing to Disclose, Brian Hobbs:Regeneron Pharmaceuticals: Employee, Niek Verweij:Nothing to Disclose, Michael Cho:Nothing to Disclose, Naga Chalasani:Madrigal, Eccogene, Insitro, Boston Pharma, Chugai: Consultant, Zydus, GSK, Akero, Plaint, Altimmune: Consultant, Exact Sciences: Grant/Research Support, NIH: Grant/Research Support, Heligenics: Board member, investor, Avant Sante: Board member, investor, Ipsen, Biomea Fusion, Pfizer, Merck: Consultant, Tae-Hwi Schwantes-An:Nothing to Disclose, Jerome Rotter:Nothing to Disclose, John Doench:Nothing to Disclose, Rajat Gupta:Nothing to Disclose.

1088 | SERUM DITHIOTHREITOL-OXIDIZING CAPACITY (DOC) AS A PAN-ETIOLOGY BIOMARKER FOR CHRONIC LIVER DISEASE, INDEPENDENT OF ALT LEVELS

Zhenhua Zhang[1] Zhenhua Zhang[1] Chunhui Tao[1] Pengyue Zhang[1] Zhengqi Gao[1] Lumin Yang[2] Jinsong Zhang[2], [1]Department of Infectious Diseases, the Second Affiliated Hospital of Anhui Medical University, [2]Anhui Agricultural University

Background: Dithiothreitol-oxidizing capacity (DOC) as a novel serum biomarker developed by our group has already shown excellent monitoring capability across all stages of chronic hepatitis B. This study aimed to systematically evaluate the monitoring performance and clinical applicability of DOC in chronic liver disease (CLD) patients with different etiologies. **Methods:** Serum DOC was measured in healthy controls and patients with autoimmune liver disease (AILD), chronic hepatitis C (CHC), alcohol-associated liver disease (ALD), and metabolic dysfunction–associated steatotic liver disease (MASLD). Diagnostic performance, ability to identify disease progression risk and clinical utility of DOC were assessed using receiver operating characteristics (ROC) curve, sensitivity at 95% specificity, stratified and correlation analyses, etc. **Results:** DOC showed robust monitoring performance across the four CLD cohorts and retained effective in CLD patients with normal alanine aminotransferase (ALT), with area under the ROC curve of 0.991 (AILD), 0.958 (CHC), 0.920 (ALD), and 0.837 (MASLD), and sensitivities at 95% specificity of 93.44%, 83.61%, 78.31%, and 60.68%, respectively. DOC levels increased from non-cirrhosis to cirrhosis and were significantly correlated with aspartate aminotransferase-to-platelet ratio index (APRI) (r = 0.47, P < 0.0001) and fibrosis-4 index (FIB-4) (r = 0.48, P < 0.0001). Furthermore, DOC demonstrated superior rule-in and rule-out performance (positive likelihood ratios, LR+ ≥ 15.51; negative likelihood

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ratios, LR− ≤ 0.33), greater net clinical benefit, and improved identification of disease progression risk. Combined use of DOC and ALT enhanced clinical monitoring and facilitated identification more severe disease stages. **Conclusion:** DOC demonstrated strong monitoring performance and clinical applicability across diverse CLD etiologies, particularly in CLD patients with normal ALT levels, supporting its role as a complementary biomarker for CLD screening, monitoring and risk assessment.

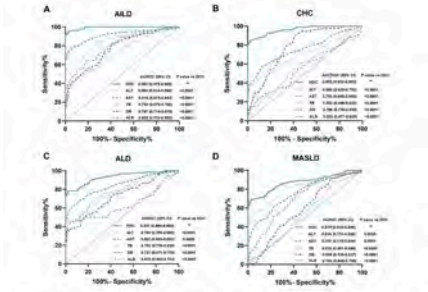


Figure 1. ROC analyses of the AILD (A), CHC (B), ALD (C) and MASLD (D) patients respectively.

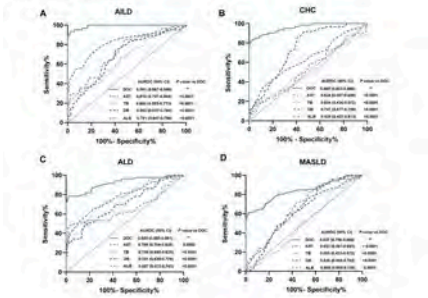


Figure 2. ROC analyses of the AILD (A), CHC (B), ALD (C), and MASLD (D) patients with normal ALT levels.

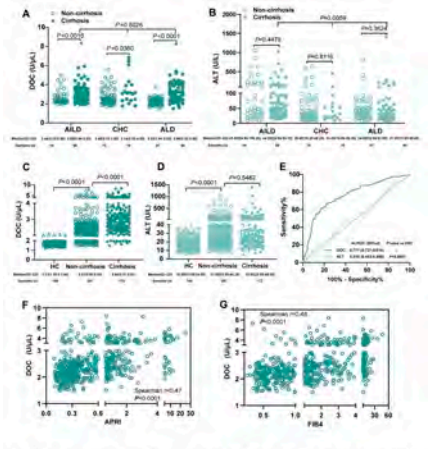


Figure 3. Correlation and stratified analysis of DOC with CLD severity. (A-B) Comparison of DOC (A) and ALT (B) levels between non-cirrhosis and cirrhosis in AILD, CHC, and ALD patients. (C-D) Comparison of DOC (C) and ALT (D) levels between HC, non-cirrhosis and cirrhosis in all CLD patients. (E) ROC analyses of DOC and ALT in non-cirrhosis and cirrhosis patients. (F-G) Spearman correlation analysis between DOC and APRI (F) or FIB-4 (G) in CLD patients.

Disclosures: Zhenhua Zhang:Nothing to Disclose, Zhenhua Zhang:Nothing to Disclose, Chunhui Tao: Nothing to Disclose, Pengyue Zhang:Nothing to Disclose, Zhengqi Gao:Nothing to Disclose, Lumin Yang:Nothing to Disclose, Jinsong Zhang:Nothing to Disclose.

1089 | ALLAGILE SYNDROME-RELATED VARIANTS ASSOCIATED WITH ADULT CHOLESTATIC PHENOTYPES IN THE SETTING OF INTRAHEPATIC CHOLESTASIS OF PREGNANCY (ICP) OR DRUG INDUCED LIVER INJURY (DILI). A CASE SERIES.

Fabian Rodas[1] Sarvanand Patel[2] Carmen Landaverde[3] Prasun Jalal[4] Youseph Karouni[4], [1]University of Texas San Antonio/The Texas Liver Institute, [2]The Texas Liver Institute, [3]University of Texas San Antonio/The Texas Liver Instutute, [4]Baylor College of Medicine

Background: Intrahepatic cholestasis of pregnancy (ICP) was first described in 1999 in patients heterozygous for MDR3 deficiency.(1). Since then, growing evidence shows that individuals with certain cholestatic monogenic variants are potentially linked to chronic liver disease (CLD). (2). The rapidly evolving filed of precision medicine now allow us to understand the human protein funtionality and expand our ability to recognize the disease spectrum in adults. Emergent data reveals that nearly 30% CLD remains unknow, and up to 28% of these cases may be explained to newly discovered cholestatic variants. (3-4). Within this context, we investigated the contributions of variants in genes associated with AGLS, such as JAG1 and NOTCH2, using next-generation sequencing combined with deep clinical phenotyping to better characterized adults with ICP-like phenotypes. **Methods:** Case series of 5 adult female patients from 3 tertiary hepatology centers (UTHSCSA, Texas Liver Institute Austin, Baylor St Luke's Houston). Patients were retrospectively reviewed through institutional electronic medical records (EPIC) from 4/2023 to 5/2026. Inclusion criteria included positive genetic testing for ALGS variants using next-generation sequencing panels. Data collected included GGT, alkaline phosphatase, total bilirubin, serum bile acids, platelet count, liver stiffness measurement, liver histology, MRCP, pruritus (WI-NRS), and comprehensive cholestasis genetic panel during pregnancy or postpartum and during DILI and recovery phase. **Results:** Five females with median age of 35 years (range 31-43), heterozygous JAG1 (n = 2) or NOTCH (n = 3) variants. Three patients presented with ICP-Like phenotype; two of whom subsequently developed postpartum cholestasis/AMA (-) PBC overlap. Two patients presented with drug induced liver injury (DILI) phenotype or

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inflammatory cholangiopathy. The most marked pregnancy-related cholestasis occurred in one NOTCH2 case with serum bile acid peaks of 262 and 442 µmol/L, falling postpartum to 14 and 6 µmol/L. In contrast, both JAG1 cases showed high-GGT cholangiopathy (565 and 1407 U/L), inflammatory bile-duct pathology, and stage 2 fibrosis. Additionally, two patients (2-3) were characterized as ICP but developed cholestasis 3 months postpartum. Available MRCPs were negative in all four evaluated patients. One patient received IBAT therapy for 4 months; WI-NRS improved from 8/10 to 6/10, serum bile acids remained 25 µmol/L, and diarrhea required dose interruption and reduction. **Conclusion:** Heterozygous JAG1 and NOTCH2 variants may predispose adults patients without classic syndromic features of ALGS to pregnancy-triggered cholestasis and postpartum inflammatory cholangiopathy or DILI- phenotypes. Further segregation studies, RNA/functional assays, and systematic extrahepatic ALGS with deep clinical phenotyping are needed.



Disclosures: Fabian Rodas:Mirum Pharmaceutical: Speaking and Teaching, IPSEN: Speaking and teaching, GILEAD: Speaking, INTERCEPT Pharmaceuticals: Speaking and Teaching, COUR Pharmaceuticals: Independent Contractor, Zydus Pharmaceuticals: Independent Contractor, KOWA Pharmaceuticals: Independent Contractor, Sarvanand Patel:Nothing to Disclose, Carmen Landaverde:Madrigal: Speaking and Teaching, GIlead: Speaking and Teaching, Mirum: Advisor, Ipsen: Advisor, Prasun Jalal:Madrigal, GSK, Mirum, Ipsen, Gilead, Genentech, Zydus: Grant/Research Support, Intercept, Genfit: Grant/Research Support, Youseph Karouni:Nothing to Disclose.

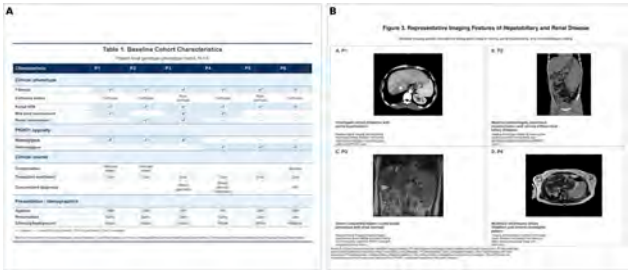
1090 | MONOALLELIC PKHD1 VARIANTS MAY NOT BE PHENOTYPICALLY SILENT: A COMPARATIVE CASE SERIES OF MONOALLELIC AND BIALLELIC VARIANTS

Anish Saikumar[1] Abdullah Zafar[1] Hussein Harb[1] Sarvanand Patel[2] Eugenia Tsai[2] Lisa Pedicone[2] Jan Petrasek[2] Carmen Landaverde[2] Eric Lawitz[2] Fred Poordad[2] Fabian Rodas[2], [1]University of the Incarnate Word, [2]Texas Liver Institute

Background: PKHD1 mutations are implicated in hepatorenal ciliopathies, though genotypic-phenotypic variability remains incompletely understood. While biallelic mutations are classically associated with congenital hepatic fibrosis (CHF) and Caroli syndrome, emerging data suggest select monoallelic variants may contribute to hepatic phenotypes. We present a case series of biallelic and monoallelic PKHD1 variants with heterogeneous hepatic manifestations. **Methods:** Clinical, radiographic, histopathologic, and genetic data were retrospectively reviewed for patients with monoallelic and biallelic PKHD1 variants presenting with hepatic manifestations. **Results:** This series includes six patients (P1-P6): three siblings (P1-3) with biallelic PKHD1 mutations and three unrelated patients (P4-6) with monoallelic variants. The siblings were offspring of a consanguineous union. P1 (26M) developed biopsy-confirmed CHF complicated by portal hypertension (pHTN), recurrent variceal bleeding (VB), and intrahepatic biliary ductal dilatation. P2 (25M) developed CHF with pHTN and recurrent VB without significant biliary involvement. P3 (19F) developed CHF in infancy with subsequent Caroli syndrome. Genetic testing demonstrated homozygous PKHD1 mutations, including c.8518C > T (p.Arg2840Cys) in P1/P2. P4 (40F) was born with congenital biliary atresia and polysplenia with Kasai portoenterostomy performed at birth. She later developed chronic cholangitis, pHTN, multifocal biliary strictures, and hepatic adenoma; testing identified a heterozygous c.5273C > T (p.Ala1758Val) variant. P5 (28M) presented with non-cirrhotic pHTN and mild pericellular fibrosis with a heterozygous c.217C > T (p.Arg73Trp) variant. P6 (59M) with HIV and cryptogenic cirrhosis demonstrated elevated portal pressures without HIV-associated cholangiopathy; testing identified heterozygous c.11260G > A (p.Val3754Met) variant. **Conclusion:** PKHD1 mutations provide a broad spectrum of phenotypic expression. Biallelic mutations do portend clinically relevant disease; however this series highlights that genotype and inheritance pattern does not fully predict disease expression. Among the sibling cohort, one patient developed Caroli syndrome while another demonstrated minimal biliary involvement despite similar genetic findings. Most monoallelic variants manifested predominantly with pHTN rather than overt biliary disease, though one patient demonstrated significant cholangiopathic features, suggesting possible phenotypic overlap between PKHD1-associated disease and congenital biliary disorders. These findings support that select heterozygous PKHD1 variants may contribute to hepatic fibrocystic phenotypes or susceptibility to portal hypertensive disease.

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1091 | CLINICAL UTILITY OF GENETIC EVALUATION IN ADULTS WITH UNEXPLAINED CHOLESTASIS: A MULTICENTER STUDY

Anne Mentzinger[1] Cecelia Tamburro[1] Bonnie Chen[1] Gledys Martinez[2] Daniel Dykas[1] Allen Bale[1] Marina Silveira[1] David Assis[1] Cynthia Levy[2] Silvia Vilarinho[1], [1]Yale School of Medicine, [2]University of Miami

Background: Chronic liver disease affects over 1 billion people worldwide, yet many patients remain undiagnosed. Advances in next-generation sequencing technologies have significantly improved our understanding of the genetic underpinnings of liver disease. Although these disorders have traditionally been recognized in childhood, emerging evidence suggests that these disorders can present as adult-onset idiopathic liver disease. Prior studies from our group and others have demonstrated that whole-exome sequencing (WES) can establish a molecular diagnosis in approximately 25% of patients with otherwise unexplained liver disease, with cholestasis representing a particularly high-yield phenotype category. We sought to determine the diagnostic yield of genetic evaluation in adults with unexplained cholestatic liver disease and to characterize the clinical phenotypes associated with genetic diagnoses made in adulthood. **Methods:** Whole-exome sequencing and respective analysis were performed in 33 adults with unexplained cholestasis recruited from two academic centers following an unrevealing comprehensive diagnostic workup. **Results:** In the 33-patient cohort, 70% were female, 89% were white, and 55% were Hispanic, with a mean age of 42 years. A definitive or presumed genetic diagnosis was identified in 11 patients, indicating a diagnostic yield of 33%. Variants in *ABCB4* were the most frequently identified, accounting for 9 out of 11 diagnoses. The remaining diagnoses included variants in *ABCB11* and *JAG1*. Diagnostic yield was not associated with sex or family history of liver disease. However, younger age at presentation (<40 years-old) was significantly associated with a genetic diagnosis (OR = 13.35 and $p = 0.0089$). Importantly, positive antinuclear antibody (ANA) status did not decrease the likelihood of attaining a genetic diagnosis. **Conclusion:** Our findings support and validate the clinical utility of genetic testing in adults with idiopathic cholestatic liver disease, with a diagnostic yield above 30%. Younger age (<40 years-old) at presentation was significantly associated with an increased likelihood of identifying a monogenic disorder. Importantly, an isolated positive ANA titer should not preclude genetic testing. A genetic diagnosis uncovers the underlying molecular pathogenesis and provides a roadmap for improved management, prognosis and appropriate family counseling.

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1092 | THE IFNL4 GENE POLYMORPHISM IS ASSOCIATED WITH A TRANSCRIPTOMIC SIGNATURE OF INCREASED INTERFERON RESPONSE, LIPID METABOLISM, AND FIBROGENESIS IN THE LIVER

Keisuke Fukutomi[1] Alexis Moore[1] Sabitree Shahi[1] Vicky Chen[2] Marc Ghany[3] Barbara Rehermann[1], [1]Immunology Section, Liver Diseases Branch, NIDDK, National Institutes of Health, [2]Integrated Data Sciences Section, Research Technologies Branch, NIAID, National Institutes of Health, [3]Clinical Hepatology Research Section, Liver Diseases Branch, NIDDK, National Institutes of Health

Background: Interferon lambda 4 (IFNL4) is produced by the ancestral rs368234815-ΔG allele. An additional rs117648444-A/G SNP results in a P70S mutation that attenuates the function of IFNL4, and the rs368234815-TT allele leads to a frameshift that abrogates IFNL4 production. While the IFNL4-producing genotype has been associated with reduced liver inflammation in chronic hepatitis C virus (HCV) infection, it is unknown how IFNL4 affects individual cell populations in the liver and whether these effects persist after treatment-induced HCV clearance. **Methods:** To investigate the effects of *IFNL4* in the liver following HCV clearance, we performed single-cell RNA-seq on liver biopsies from 20 subjects (15 male, 5 female) who cleared HCV five years prior to this study in response to direct-acting antivirals. **Results:** All 20 subjects had minimal liver inflammation (median HAI score 3; 0-18 scale) and fibrosis (median Ishak fibrosis score 0.5; 0-6 scale), normal ALT levels, and undetectable HCV RNA. Fifteen produced IFNL4, of whom two produced a functionally weak IFNL4 due to the P70S mutation. The remaining five subjects did not produce IFNL4.Single-cell RNA-seq identified comparable proportions of immune cell subsets, liver sinusoidal endothelial cells (LSECs), stellate cells, and hepatocytes across all subjects, irrespective of *IFNL4* polymorphism. ISG expression was observed in all cell types. It was strongest in subjects who produced IFNL4 (rs368234815-ΔG/ΔG or -ΔG/TT), moderate in those with the P70S mutation (rs117648444-A/G), and weakest in those without IFNL4 (rs368234815-TT/TT). Of note, ISG expression was significantly higher in males than in females with the IFNL4-producing genotype (without P70S mutation).In hepatocytes, Hallmark gene enrichment analysis revealed an enrichment of the fatty acid degradation pathway and depletion of the steroid biosynthesis pathway in those who produced IFNL4, compared to those who did not, suggesting a beneficial metabolic effect.In LSECs, capillarization-related genes (basement membrane and extracellular matrix-related) transcripts were upregulated, and *KLF2* gene transcripts were downregulated in those who produced IFNL4, suggesting a pro-fibrotic character of LSECs. **Conclusion:** After HCV clearance, the IFNL4-producing genotype is associated with persistent intrahepatic ISG activation across cell types, lipid metabolic reprogramming in hepatocytes, and pro-fibrotic transcriptomic alterations in LSECs.

Disclosures: Keisuke Fukutomi:Nothing to Disclose, Alexis Moore:Nothing to Disclose, Sabitree Shahi: Nothing to Disclose, Vicky Chen:Nothing to Disclose, Marc Ghany:Vir Bio: Grant is to NIDDK, NIH not to Investigator, Barbara Rehermann:Nothing to Disclose.

1093 | A COHORT STUDY OF *ABCB4*-RELATED LIVER DISEASE IN ADULT PATIENTS

Sateesh Maddirevula[1] Abdullah AlFhaid[1] Waleed Al Hamoudi[1] Bandar Aljudaibi[1] Mohammad Shagrani[1] Dieter Broering[1] Saleh Alqahtani[1] Saad Alghamdi[1], [1]King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia

Background: Progressive familial intrahepatic cholestasis (PFIC) has historically been recognized as a pediatric disorder causing early-onset cholestatic liver disease. However, with the increasing incorporation of genetic testing into the evaluation of patients with unexplained cholestasis and cryptogenic cirrhosis, pathogenic variants in cholestasis-related genes are increasingly being identified in adolescents and adults. *ABCB4*-related liver disease demonstrates a heterogeneous clinical phenotype and may progress to advanced liver disease, portal hypertension, and hepatocellular

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carcinoma (HCC). In this study, we describe the genotype-phenotype characteristics and clinical outcomes of a cohort of adult patients with *ABCB4*-related liver disease. **Methods:** We retrospectively collected clinical, biochemical, and genetic data of adult patients ($n = 20$) with molecularly confirmed *ABCB4*-related liver disease from electronic medical records at our center. **Results:** Twenty adult patients with genetically confirmed *ABCB4*-related liver disease were included, of whom 55% were female. All the patients are homozygous for 8 unique variants in *ABCB4*. The mean age at presentation was 22.4 ± 8.5 years, while the mean age at diagnosis was 25.1 ± 8.9 years. A family history of PFIC was identified in 50% of patients. Vast Majority of patients (90%) had evidence of cirrhosis at presentation. Portal hypertension-related complications were common, including varices in 57.9% and ascites in 40.0% of patients. Hepatocellular carcinoma developed in 15.0% of the cohort, and 50.0% required liver transplantation during follow-up.Biochemically, patients demonstrated a predominantly cholestatic liver profile with elevated gamma-glutamyl transferase (mean 256.8 U/L) and bile acid levels (mean 141 µmol/L). Median bilirubin was 49 µmol/L, while median ALT and AST were 70 U/L and 83 U/L, respectively. Autoimmune serologies were infrequently positive. Several patients had been previously misdiagnosed with autoimmune hepatitis (15.8%) or Wilson disease (5.9%). **Conclusion:** Adult *ABCB4*-related liver disease is associated with substantial morbidity, including early-onset cirrhosis, portal hypertension, hepatocellular carcinoma, and frequent need for liver transplantation. The disease may mimic other chronic liver disorders, resulting in delayed or inaccurate diagnosis. Increased awareness and broader utilization of genetic testing may facilitate earlier diagnosis and improve management of affected patients.

Clinical characteristics of adult *ABCB4*-related liver disease

Variable	n (%)
Female	11 (55.0%)
Male	9 (45.0%)
History of ICP	1/20 (5.0%)
Family History	10/20 (50.0%)
ASMA Positive	1/20 (5.0%)
AMA Positive	0/20 (0.0%)
ANA Positive	3/20 (15.0%)
Cirrhosis	18/20 (90.0%)
Varices	11/19 (57.9%)
Ascites	8/20 (40.0%)
HCC	3/20 (15.0%)
Liver Transplant	10/20 (50.0%)
Liver Biopsy Performed	0/16 (0.0%)
Prior Dx: AIH	3/19 (15.8%)
Prior Dx: Wilson Disease	1/17 (5.9%)

Disclosures: Sateesh Maddirevula:Nothing to Disclose, Abdullah AlFhaid:Nothing to Disclose, Waleed Al Hamoudi:Nothing to Disclose, Bandar Aljudaibi: Nothing to Disclose, MOHAMMAD SHAGRANI:Nothing to Disclose, Dieter Broering:Nothing to Disclose, Saleh Alqahtani:Nothing to Disclose, Saad Alghamdi:Nothing to Disclose.

1094 | REFERENCE LANDSCAPE OF HERV-K (HML-2) IN PEDIATRIC NORMAL LIVER

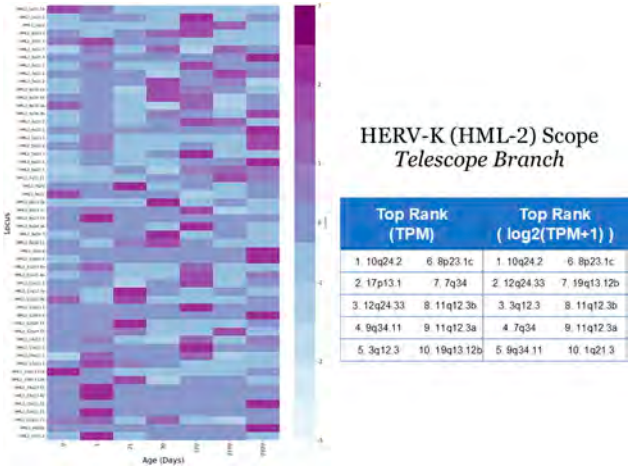
Silvia Carrau[1] Manali Singha[2] Amanda Macke[2] Gary Schweickart[1] KJ Schmidt[1] Eleni Kyriakou[3] Xinlei Li[1] Benjamin Kelly[4] David Brigstock[1] Sara Rasmussen[1], [1]AWRI, Nationwide Children's Hospital, [2]AWRI, Nationwide Children's Hospital, [3]University of Athens, [4]AWRI Nationwide Children's Hospital

Background: Human endogenous retrovirus K (HERV-K, HML-2) expression has been implicated in normal physiology and multiple malignancies. However, baseline HERV-K expression in the pediatric population remains poorly characterized. The limited availability of pediatric normal liver specimens represents a major challenge for studies investigating transposable element expression in hepatoblastoma and other pediatric liver diseases. In addition, repetitive genomic architecture complicates accurate assignment of HERV-derived transcripts using conventional RNA sequencing approaches. To address this gap, we performed locus-specific HERV-K (HML-2) profiling in a rare cohort of pediatric normal liver samples using a curated Telescope-based RNA sequencing analysis pipeline. **Methods:** RNA sequencing data from seven pediatric normal liver samples (from 0 to 8.1 years-old, 25.15 ± 41.62 days, mean ± SD; source Autopsy samples from the Pediatric Division of the Cooperative Human Tissue Network, pCHTN) were analyzed using a locus-specific transposable element pipeline incorporating quality control, trimming, alignment to the hg38 reference genome, and HERV-K (HML-2) assignment using Telescope. Expression profiles were generated at the individual genomic locus level. Heatmap visualization and expression ranking analyses were used to identify recurrently expressed HERV-K loci across samples. Transcript abundance was evaluated using transcripts per million (TPM) and complementary expression ranking metrics. **Results:** Locus-specific analysis identified detectable HERV-K(HML-2) expression across all pediatric normal liver samples. Multiple loci demonstrated recurrent expression patterns across samples, with loci at 10q24.2, 17p13.1, 12q24.33, 3q12.3, and 9q34.11 consistently ranking among the most abundant HERV-K(HML-2) elements. Heatmap visualization demonstrated reproducible expression profiles with inter-sample variability typical of biologic tissue heterogeneity. These findings establish the first reference landscape of HERV-K expression in pediatric normal

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liver tissue and demonstrate the feasibility of applying Telescope-based transposable element analysis to rare pediatric biospecimens. **Conclusion:** This study provides the first locus-specific characterization of HERV-K(HML-2) expression in pediatric normal liver tissue using Telescope-based RNA sequencing analysis. Pediatric normal liver specimens are exceptionally difficult to obtain, and the absence of appropriate pediatric reference controls has limited interpretation of HERV expression studies in pediatric liver tumors. These data establish an important reference resource for future investigations of HERV-K(HML-2) dysregulation in hepatoblastoma and other pediatric liver diseases.



Disclosures: Silvia Carrau:Nothing to Disclose, Manali Singha:Nothing to Disclose, Amanda Macke:Nothing to Disclose, Gary Schweickart:Nothing to Disclose, KJ Schmidt:Nothing to Disclose, Eleni Kyriakou:Nothing to Disclose, Xinlei Li:Nothing to Disclose, Benjamin Kelly: Nothing to Disclose, David Brigstock:Nothing to Disclose, Sara Rasmussen:Nothing to Disclose.

1095 | DEVELOPMENT AND VALIDATION OF A SENSITIVE HBV GENOTYPING ASSAY IN DNA-SUPPRESSED PATIENTS

Kirsteen Maclean[1] Sanne van Gils[1] Joel Meybloom[1], [1]Cerba Research

Background: HBV genotyping is a key parameter in clinical trials, enabling patient stratification and interpretation of genotype-related differences in antiviral response. Today, HBV genotyping conventionally requires detectable plasma HBV DNA. However, for trial participants receiving nucleos(t)ide analogue (NUC) therapy, HBV DNA is often undetectable. Because HBV RNA persists in a subset of these individuals, it provides an alternative target for genotyping. We aimed to validate a novel sequencing assay utilizing both HBV RNA and DNA, alongside a serological backup for non-amplified samples. **Methods:** Reverse transcription followed by nested PCR amplified a fragment spanning the S-gene and RT-domain. Libraries were then sequenced using Illumina short-read technology, with genotypes assigned phylogenetically. When no PCR product is generated, we used the IMMUNIS HBV Genotype EIA kit, which detects genotype-specific PreS2 epitopes (genotypes A–D). **Results:** The sequencing assay achieved sensitivities of 79 copies/mL (HBV RNA) and 6 copies/mL (HBV DNA) and successfully genotyped a 15-sample panel (genotypes A–G). The IMMUNIS assay confirmed the sensitivity indicated by the manufacturer (3 IU/mL) and accurately identified genotypes A–D; however, as expected, genotypes E and G were classified as D, and F remained unclassified. **Conclusion:** This combined sequencing and serological approach provides a highly sensitive workflow for HBV genotyping in NUC–suppressed populations, supporting accurate genotype assignment in clinical trials.

Disclosures: Kirsteen Maclean:Nothing to Disclose, Sanne van Gils:Nothing to Disclose, Joel Meybloom: Nothing to Disclose.

1096 | PHENOTYPIC DELINEATION OF *TULP3*-RELATED HEPATORENOCARDIAC CILIOPATHY

Sateesh Maddirevula[1] Abdullah AlFhaid[1] Hadeel Almanea[1] Mohammad Shagrani[1] Saleh Alqahtani[2] Saad Alghamdi[3], [1]KFSHRC, [2]King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia, [3]King Faisal Specialist Hospital and Research Center

Background: *TULP3,* a ciliary trafficking gene, has been established with progressive degenerative liver fibrosis, fibrocystic kidney disease, and hypertrophic cardiomyopathy, and knockdown models also recapitulated hepatorenocardiac degenerative fibrosis. To this day, 21 patients are reported in the literature with the spectrum of phenotype with variable age onset. **Methods:** *Describtive study of 2 families with several family members affected of this extremely rare disease.* **Results:** We describe four patients from two unrelated families. Family 1 harbored a novel loss of function variant (c.1292dup:p.(Leu432SerfsTer3)) with three affected siblings, and family 2 harbored a biallelic founder variant (c.492+1G > A:p.?) with variable disease onset. We described the spectrum of phenotype by including the available literature to understand the natural history of the disease. Hepatic involvement (cholestasis or jaundice and elevated liver function

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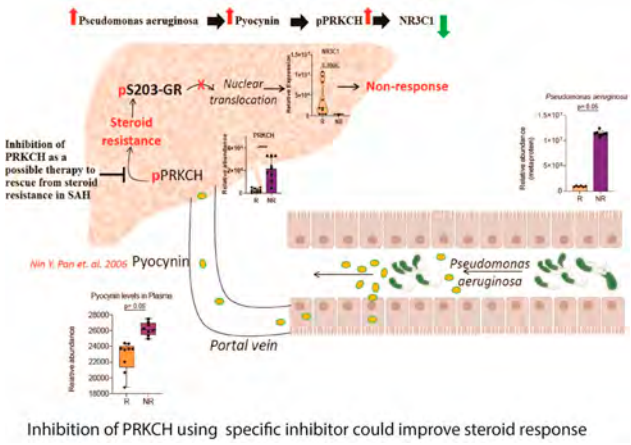
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tests) is highly common; 100% of the patient cohort (n = 25) presented with some form of liver disease. Elevated liver enzymes were the most prevalent specific phenotype at 85%, followed closely by portal hypertension/varices and cirrhosis/bridging fibrosis at 80% each, whereas kidney disease (65%), liver transplantation (20%), and cardiac involvement (15%) were less frequently observed. **Conclusion:** Our study adds more patients with novel and founder variants. Clinical manifestations mimic different types of ciliopathies; molecular testing is highly recommended to diagnose *TULP3* related hepatorenocardiac ciliopathy. **Disclosures:** Sateesh Maddirevula:Nothing to Disclose, Abdullah AlFhaid:Nothing to Disclose, Hadeel Almanea:Nothing to Disclose, MOHAMMAD SHAGRANI:Nothing to Disclose, Saleh Alqahtani:Nothing to Disclose, Saad Alghamdi:Nothing to Disclose.

1097 | ◆ A PSEUDOMONAS-DERIVED METABOLITE; PYOCYANIN LINKS ALCOHOL-ASSOCIATED HEPATIC DYSBIOSIS TO PKC&ETA;-DRIVEN STEROID RESISTANCE IN SEVERE ALCOHOL RELATED HEPATITIS

Jaswinder Maras[1] Manisha Yadav[2] Sanju Rao[2] Gaurav Trapathi[2] Neha Sharma[2] Shimona Ahlawat[2] Kavita Yadav[2] Vipul Sharma[2] Yash Magar[2] Deepanshu Deepanshu[3] Jayesh Kumar Sevak[1] Vasundhra Bindal[2] Babu Mathew[2] Sushmita Pandey[2] Nupur Sharma[2] Anupama Kumari[2] Shvetank Sharma[1] Shiv Kumar Sarin[2], [1]Institute of Liver and Biliary Sciences, [2]ILBS, [3]national institute of immunology

Background: Severe alcohol-related hepatitis (SAH) is a life-threatening disease with ~60% of patients respond to corticosteroids, that too for a short-term. The molecular basis of steroid resistance in SAH remains unclear, particularly how microbial factors alter glucocorticoid signaling and drive steroid non-response. **Methods:** Liver multi-omics of 19 SAH patients (10 responders, 9 non-responders to corticosteroid), identified bacterial-peptides, metabolites, and host kinases linked to glucocorticoid non-response. Findings were validated using immunohistochemistry (n = 20) and RNA-seq (n = 32), followed by functional studies in PBMCs of SAH patients and experimental models of binge alcohol (NIAAA mice model) and 24 weeks chronic alcohol rat model. Pharmacological inhibition of candidate kinases was assessed for restoration of glucocorticoid sensitivity first in SAH PBMC followed by NIAAA mice model. **Results:** Liver metaproteomics showed 9,080 bacterial peptides from 257 species(FDR < 0.01). Non-responders showed distinct alpha/beta diversity ($p < 0.01$) with enrichment of pathogenic Staphylococcus aureus, and Pseudomonas aeruginosa (> 5FC, $p < 0.05$) linked to signal transduction and energy utilization. Liver phospho-proteomics showed 568proteins increased linked to TH17 signaling, CREB phosphorylation, JAK-STAT and glucocorticoid receptor inhibitors (> 2FC, $p < 0.05$), whereas steroid-response proteins HSP90 and DUSP3 were significantly reduced (> 2FC, $p < 0.05$). Non-responders showed increased PRKCH, PRKAA1, and MINK1 activity (> 2FC, $p < 0.05$), with enhanced phosphorylation of NR3C1 at ser201/203 leading to reduced NR3C1 also validated by IHC (> 2FC, $p < 0.05$). Integrated liver metaproteome, functional metabolome, and kinome showed positive associations of PRKCH (↑ in NR) with P. aeruginosa (↑ in NR) and pyocyanin levels (↑ in NR), and negatively with NR3C1 (↓ in NR, $r^2 > 0.7$, $p < 0.01$). Alcohol drive pyocyanin production by increasing liver pyocyanin-biosynthesis metabolites and enzymes (PHZm, PHZs, Shikimic acid > 2-fold, $p < 0.05$), significantly inducing ROS/PRKCH activation (> 3FC, $p < 0.01$) validated in Non-responders, NIAAA mice and 24 weeks alcohol Rat(FC > 2, $p < 0.05$). Pharmacological inhibition of PRKCH using staurosporine (validated using IHC) restored HSP90, DUSP3 (negative-regulator of PRKCH), and NR3C1 expression, boosting prednisolone sensitivity, and reducing inflammatory signaling (NFKB, MAPK signaling, $p < 0.05$) in SAH PBMC and NIAAA model respectively. **Conclusion:** Alcohol-induced hepatic enrichment of Pseudomonas aeruginosa and its metabolite pyocyanin activated PRKCH, impairing NR3C1 nuclear translocation and expression to drive steroid resistance. These findings identify the PRKCH–NR3C1 axis as a therapeutic target, with PRKCH inhibition representing a promising strategy to restore glucocorticoid responsiveness in SAH.



Disclosures: Jaswinder Maras:Nothing to Disclose, Manisha Yadav:Nothing to Disclose, Sanju Rao:Nothing to Disclose, gaurav Trapathi:Nothing to Disclose, Neha Sharma:Nothing to Disclose, Shimona Ahlawat:Nothing to Disclose, Kavita Yadav:Nothing to Disclose, Vipul Sharma:Nothing to Disclose, Yash Magar:Nothing to Disclose, Deepanshu Deepanshu:Nothing to Disclose, Jayesh Kumar Sevak:Nothing to Disclose,

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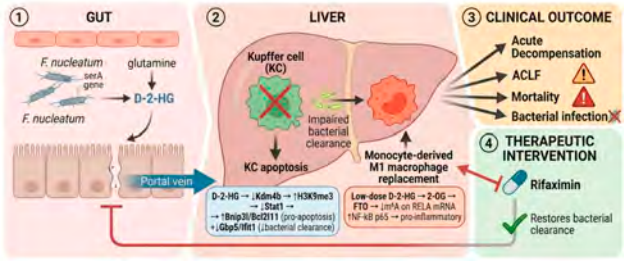
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Vasundhra Bindal:Nothing to Disclose, Babu Mathew: Nothing to Disclose, Sushmita Pandey:Nothing to Disclose, Nupur Sharma:Nothing to Disclose, Anupama Kumari:Nothing to Disclose, Shvetank Sharma:Nothing to Disclose, Shiv Kumar Sarin:Nothing to Disclose.

1098 | ◆ MICROBIOTA-DERIVED D-2-HYDROXYGLUTARATE DRIVES KUPFFER CELLS LOSS AND PRO-INFLAMMATORY MACROPHAGE REPLACEMENT IN CIRRHOSIS

Xixuan Wang[1] Jun Guo[2] Jing Fan[2] Ruiqi Li[2] Shuling Chen[2] Xiaoying Dong[2] Jiale Shen[2] Yuhang Weng[2] Hao Ren[2] Hongli Liu[2] Shangzhen Li[2] Dawei Yang[2] Dandan Yin[2] Caiyun Zhang[2] Wei Chen[2] Changhua Yi[2] Qingfang Xiong[2] Zihao Liang[2] Yongfeng Yang[2], [1]The Second Hospital of Nanjing, Medical School, Southeast Un, [2]The Second Hospital of Nanjing

Background: Gut-liver axis dysfunction drives cirrhosis progression, yet the specific microbial metabolites responsible remain poorly defined. We investigated the role of D-2-hydroxyglutarate (D-2-HG), a gut microbiota-derived metabolite, in hepatic immune microenvironment remodeling during cirrhosis. **Methods:** Fecal and serum D-2-HG were measured in a prospective cohort of healthy controls, compensated cirrhosis (CC), and decompensated cirrhosis (DC) patients (training cohort, n = 295; validation cohort, n = 96) with 24-month follow-up. Fecal microbiota transplantation (FMT) and CCl_4-induced cirrhosis mouse models were used to establish causality. D-2-HG-producing bacteria were identified through integrated metagenomic analysis and isotope tracing. KC-specific AAV8-Clec4f-Stat1 overexpression mice and myeloid-specific FTO knockout mice were generated to dissect mechanisms. Proteomics, ChIP-qPCR, and flow cytometry characterized downstream pathways. **Results:** Fecal and serum D-2-HG increased progressively from HC to CC to DC, predicting acute decompensation (AD), acute-on-chronic liver failure (ACLF), and mortality. Portal vein D-2-HG exceeded peripheral levels, indicating intestinal origin. *Fusobacterium nucleatum* was identified as the primary producer via its *serA* gene using glutamine. In cirrhotic mice, D-2-HG suppressed Kdm4b-mediated H3K9me3 demethylation at the *Stat1* promoter, simultaneously upregulating pro-apoptotic Bnip3l/Bcl2l11 and downregulating antimicrobial Gbp5/Ifit1, driving KC apoptosis and impaired bacterial clearance. At low concentrations, D-2-HG-derived α-ketoglutarate activated FTO-mediated m^6A demethylation of *RELA* mRNA, stabilizing NF-κB p65 and promoting monocyte-derived M1 macrophage recruitment. KC-specific Stat1 overexpression rescued bacterial clearance and attenuated ACLF. Rifaximin reduced *F. nucleatum*, D-2-HG levels, and partially restored hepatic immunity. **Conclusion:** Gut microbiota-derived D-2-HG, predominantly produced by F. nucleatum, drives KC depletion and pro-inflammatory macrophage replacement through Stat1-dependent dual mechanisms, representing a targetable metabolic axis in cirrhosis progression.



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1099 | ◆ GUT MICROBIAL SIGNATURES: POTENTIAL BIOMARKERS LINKING ANTIDIABETIC TREATMENT TO FIBROSIS REGRESSION IN CHRONIC HEPATITIS B

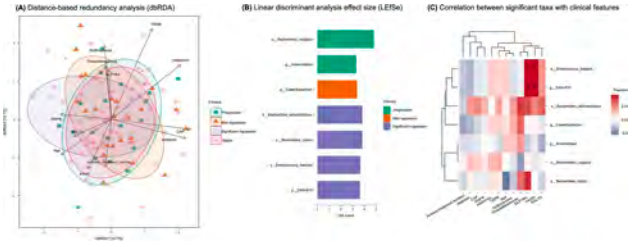
Lu Li[1] Saisai Zhang[1] Wenyi Tan[1] Wenjie Li[1] Man-Fung Yuen[1] Lung-Yi Mak[1] Wai-Kay Seto[1], [1]The University of Hong Kong

Background: Despite the recognized role of the gut-liver axis in chronic hepatitis B (CHB), microbial signatures of fibrosis progression and regression remain poorly defined. We aimed to identify distinct gut microbial biomarkers associated with liver fibrosis in CHB patients with virological suppression under nucleos(t)ide analogue (NA) therapy. **Methods:** We enrolled CHB patients on NA therapy (HBV DNA < 10 U/mL ≥ 12 months) with baseline liver stiffness measurement (LSM) ≥ 7 kPa and follow-up LSM. Fibrosis progression was ≥ 30% LSM increase; regression stages: stable (-30% to +30%), mild (≥ 30% to < 50% decrease), and significant (≥ 50% decrease). Fecal full-length 16S rRNA sequencing (PacBio) was

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performed. Distance-based redundancy analysis (dbRDA) (Bray-Curtis) first assessed the overall microbial differences across stages. Linear discriminant analysis effect size (LEfSe) was then conducted to identify differentially abundant taxa. Correlation analysis evaluated relationships between signature taxa and clinical factors. **Results:** A total of 125 patients (64% with type 2 diabetes [T2D], 62% with liver steatosis, 56.8% on antidiabetics) were included, of whom 70 had stable fibrosis, 19 had progression, 23 had mild regression, and 13 had significant regression. dbRDA revealed moderate separation of significant regression samples from stable and progression groups. Gut microbial β-diversity was significantly associated with T2D ($R2 = 0.39$, $P = 0.001$) and metformin use ($R2 = 0.32$, $P = 0.001$). Notably, use of antidiabetic agents including SGLT2i, DPP4i, and GLP-1RA was positively correlated with regression samples. LEfSe identified enrichment of Bacteroids vulgatus in the progression group, whereas Bacteroides cellulosilyticus, Bacteroides clarus, and Enterococcus faecalis were enriched in the significant regression group (LDA score > 3, $p < 0.05$). Bacteroides vulgatus was enriched in CHB patients using antidiabetic drugs in MaAsLin3 analysis (nominal $p < 0.01$), but this association did not remain significant after multiple-testing correction ($q = 0.96$). Furthermore, correlation analysis revealed Enterococcus faecalis was positively correlated with use of glucagon-like peptide-1 receptor agonist (GLP-1RA) ($r = 0.37$, $p < 0.001$) and insulin ($r = 0.37$, $p < 0.001$); Bacteroides cellulosilyticus was positively correlated with thiazolidinediones ($r = 0.31$, $p < 0.05$); Bacteroides clarus was positively correlated with GLP-1RA ($r = 0.33$, $p < 0.01$). **Conclusion:** This study reveals gut microbial signatures of fibrosis regression in CHB that are linked to antidiabetic drug use, suggesting antidiabetic-driven microbial benefits. These findings suggest that the gut microbiome may act as a mediator of antidiabetic effects and support microbiome-based biomarkers for CHB fibrosis. Supported by Shenzhen Natural Science Foundation Basic Research Fund-General Program (JCYJ20250604180826035).



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1100 | ◆ NOVEL GUT MICROBIOME METAGENOMIC SIGNATURE OF STEATOTIC LIVER DISEASE AMONG PEOPLE WITH HIV

Federica Tavaglione[1] Mark Holton[1] Megan O'Hara[1] Wathnita Sarik[1] Alyssa Ing[1] Ricki Bettencourt[1] Laura Wilson[2] Kara Wegermann[3] Mark Sulkowski[4] Naga Chalasani[5] Rob Knight[1] Guillaume Urtecho[1] Rohit Loomba[1], [1]University of California, San Diego, [2]Johns Hopkins Bloomberg School of Public Health, [3]Duke University, [4]John Hopkins University, [5]Indiana University School of Medicine

Background: Steatotic liver disease (SLD) has emerged as the leading cause of chronic liver disease among people with HIV (PWH). Advanced fibrosis (AF) is the strongest predictor of liver-related morbidity and mortality in individuals with SLD, including PWH, making its identification essential to detect those at highest risk of disease progression. Growing evidence supports gut microbiome profiling as a non-invasive biomarker of SLD severity and progression, but data in PWH with SLD remain limited and may differ from those observed in individuals without HIV. We aimed to identify a gut microbiome metagenomic signature associated with AF in SLD among PWH from the multicenter HIV NASH CRN study. **Methods:** This

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cross-sectional study included 90 prospectively enrolled adult PWH from eight U.S. centers, on stable antiretroviral therapy (ART), with suppressed HIV RNA and without viral hepatitis co-infection, who underwent vibration-controlled transient elastography. Participants were categorized into three groups: SLD–AF (n = 12; CAP ≥ 263 dB/m and LSM ≥ 10 kPa), SLD–No AF (n = 43; CAP ≥ 263 dB/m and LSM < 10 kPa), and control (n = 35; CAP < 263 dB/m and LSM < 8 kPa). Gut microbiome composition was characterized using shotgun metagenomic sequencing of stool samples. An independent U.S. cohort of 86 individuals without HIV with biopsy-proven SLD served as a comparator. **Results:** The median (IQR) age and BMI of PWH were 55.5 (46.3–62.0) years and 29.7 (25.7–34.8) kg/m², respectively. Among PWH, DESeq2 differential abundance analysis identified microbial taxa within the Enterobacterales and Lachnospirales orders that were enriched with SLD and increasing fibrosis stage (**Fig.1A**). Both orders were also significantly associated with CAP as a measure of steatosis, while Lachnospirales were additionally associated with LSM as a measure of fibrosis. When comparing PWH with the non-HIV SLD cohort, taxa within Enterobacterales were associated with AF in both groups, whereas taxa within Lachnospirales were uniquely associated with AF in PWH (**Fig.1B**). Finally, in exploring associations between ART and the microbiome, bictegravir use was associated with a relative depletion of Lachnospirales and Enterobacterales (**Fig.1C**). **Conclusion:** This study identifies a novel gut microbiome metagenomic signature associated with AF in SLD among PWH. The observed association between bictegravir use and SLD-related favorable microbial taxa may reflect relationships between ART exposure, SLD severity, and gut microbiome composition.

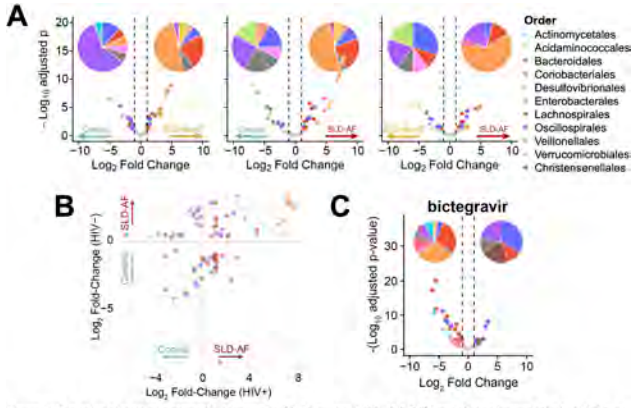


Figure 1: Gut microbiome metagenomic signature of SLD among PWH. (A) Differential enrichment of microbial taxa across the HIV NASH CRN cohort stratified by SLD presence and severity. Points represent individual taxa, with significantly altered taxa (FDR < 0.05) highlighted. **(B) Microbes associated with advanced fibrosis in the HIV NASH CRN cohort (HIV+) versus UCSD biopsy cohort (HIV-).** Scatterplot shows the $\log_2$(fold-change) in microbial abundance between participants with advanced fibrosis vs control group in the two cohorts. **(C) Differential microbial abundance associated with bictegravir use in the HIV NASH CRN cohort.** Volcano plots show DESeq2 differential abundance analyses comparing users versus non-users. AF, advanced fibrosis; SLD, steatotic liver disease.

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1101 | A HUMAN MICROBIOTA-DERIVED *BACTEROIDES UNIFORMIS* STRAIN RESTORES THE GUT–LIVER AXIS AND AMELIORATES PORTAL HYPERTENSION IN CIRRHOSIS

Peishan Wu[1] Cheng-Yen Kao[2] Yu-Cheng Lin[3] Yun-Cheng Hsieh[4] Yi-Tsung Lin[5] Shih-Yun wu[6] Teh-Ia Huo[4] Ming-Chih Hou[1] Han-Chieh Lin[1] Kuei-Chuan Lee[7], [1]Taipei Veterans General Hospital, [2]Institute of Microbiology and Immunology, National Yang Ming Chiao Tung University, Taipei, Taiwan, [3]Department of Dentistry, National Yang Ming Chiao Tung University, Taipei, Taiwan, [4]Division of Gastroenterology and Hepatology, Department of Medicine, Taipei Veterans General Hospita, [5]Division of Infectious Diseases, Department of Medicine, Taipei Veterans General Hospital, Taipei, T, [6]Department of Stomatology, Taipei Veterans General Hospital, Taipei, Taiwan, [7]Division of Gastroenterology and Hepatology, Department of Medicine, Taipei Veterans General Hospit

Background: The gut–liver axis plays a central role in the pathogenesis and progression of cirrhosis. Experimental studies have shown that rodent-derived fecal microbiota transplantation (FMT) ameliorates portal hypertension, but the effects of human-derived FMT (hFMT) in cirrhotic models remain unexplored. This study aimed to evaluate the effects of hFMT on the gut–liver axis in experimental cirrhosis and to identify specific microbial taxa and microbiota-derived metabolites associated with therapeutic benefit. **Methods:** Cirrhosis was induced in Sprague–Dawley rats by bile duct ligation (BDL) or intraperitoneal injection of thioacetamide (TAA, 200 mg/kg twice weekly) for 16 weeks. BDL rats received daily oral gavage of autologous or human FMT for 2 weeks, beginning 2 weeks after surgery; TAA rats received FMT twice weekly during the final 8 weeks of TAA administration. Candidate bacterial strains identified following hFMT were isolated from fecal samples of healthy human donors and administered to both cirrhotic models. Intestinal inflammation, barrier function, endotoxemia, portal pressure, and gut microbiota composition were assessed. Short-chain fatty acid (SCFA) profiles were analyzed *in vitro* and *in vivo*. Human microbiota data were analyzed for translational validation. **Results:** hFMT attenuated intestinal inflammation and restored barrier integrity predominantly in the proximal small intestine of both cirrhotic models, accompanied by reduced endotoxemia and pro-inflammatory cytokine expression. *Bacteroides uniformis* was consistently enriched following hFMT in both TAA and BDL models. Administration of *B. uniformis* CC-143, a strain isolated from human donors, improved proximal intestinal inflammation, tight junction expression, hepatic macrophage infiltration, collagen deposition, and portal pressure. *In vitro* analysis demonstrated that *B. uniformis* CC-143 produced both straight-chain (acetate and propionate) and branched-chain SCFAs (iso-butyric acid and 3-methylbutyric acid). *In vivo*, circulating branched-chain SCFAs were preferentially increased following *B. uniformis* treatment in the BDL model. In the human cohort, *B. uniformis* abundance was significantly higher in healthy adults than in patients with cirrhosis and its abundance was further decreased in patients with more severe portal hypertension. **Conclusion:** hFMT improves gut barrier dysfunction in experimental cirrhosis and identifies *B. uniformis* as a potential mediator of portal hypertension improvement. Through modulation of proximal intestinal inflammation, barrier integrity, and microbiota-derived metabolites, *B. uniformis* may represent a promising candidate for targeted microbiota-based therapy in cirrhosis.

Disclosures: Peishan Wu:Nothing to Disclose, Cheng-Yen Kao:Nothing to Disclose, Yu-Cheng Lin:Nothing to Disclose, Yun-Cheng Hsieh:Nothing to Disclose, Yi-Tsung Lin:Nothing to Disclose, Shih-Yun wu:Nothing to Disclose, Teh-Ia Huo:Nothing to Disclose, Ming-Chih Hou:Nothing to Disclose, Han-Chieh Lin:Nothing to Disclose, Kuei-Chuan Lee:Nothing to Disclose.

1102 | PPARALPHA AGONISM MAY IMPROVE BOTH HEPATIC AND INTESTINAL INFLAMMATION IN PSC-IBD

Mahesh Krishna[1] Yanhong Deng[1] Badr Al Bawardy[1] Marina Silveira[1] James Boyer[1] Clara Abraham[1] David Assis[1], [1]Yale University

Background: Primary sclerosing cholangitis (PSC) is a cholestatic liver disease with no cure and 60-80% concurrence with inflammatory bowel disease (IBD). Compared to PSC or IBD alone, PSC-IBD has distinct

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liver and intestinal characteristics, so it is important to understand the impact of new candidate therapies on the whole gut-liver axis.Peroxisome proliferator-activated receptors (PPAR) agonists are an emerging drug class under active investigation in PSC. We aimed to characterize the impact of PPAR agonists on hepatic and intestinal disease in PSC-IBD. **Methods:** We performed a single-center retrospective cohort study of adult PSC-IBD patients who initiated fenofibrate (a PPARalpha agonist) for PSC as part of real-world care between 2013-2024 with available colonoscopy data pre- and post-fenofibrate. Patients on fenofibrate for < 6 months or with colectomy/liver transplant between endoscopies were excluded.The *primary outcome* for intestinal disease activity was a composite binary outcome of post-index endoscopic disease improvement. This was defined as improvement in disease-specific endoscopic scores (Mayo for ulcerative colitis [UC] and Simple Endoscopic Score for Crohn's disease [CD]) or stable and inactive disease. If there was no disease-specific score, response was adjudicated by 2 gastroenterologists where feasible.The *primary outcome* for PSC activity was > 30% improvement in alkaline phosphatase (ALP) at 6 months.Data was analyzed in R and paired t-test was utilized for analysis. **Results:** Of 22 patients, 15 had UC while 7 had CD. The mean disease duration of IBD at time of fenofibrate was 16 years. 32% of patients were treated with a biologic at time of fenofibrate and 27% had prior exposure to > 1 biologic.The mean disease duration of PSC at time of fenofibrate was 9.75 years; 82% of patients were diagnosed with large-duct PSC.The mean Mayo Endoscopic Score for UC patients (n = 14) mildly improved (0.93 to 0.71, p = 0.49), while the mean Mayo Clinical Score for UC patients (n = 12) significantly improved (1.71 to 0.83, p = 0.027) following fenofibrate treatment. Overall, 73% of all IBD patients (n = 22) met the primary IBD outcome.Mean ALP improved from 429 to 265 U/L (p < 0.001) and 81% of patients met the primary PSC outcome. Total bilirubin (1.30 to 1.05, p = 0.12) and Gamma-Glutamyl Transferase (207 to 159, p = 0.09) showed a trend favoring improvement.Importantly, 81% of patients had a concurrent result for both IBD and PSC primary outcomes. **Conclusion:** Fenofibrate is associated with both intestinal and hepatic clinical improvement, suggesting PPARalpha agonism may benefit each site of disease in PSC-IBD. Prospective, randomized-controlled trials on fenofibrate in PSC, and further research on the impact of PPARalpha agonism on IBD activity and the gut-liver axis in PSC-IBD, are warranted.

Demographics (n=22)	
Age, mean (SD), years	49.3 (15.0)
Female	36%
White/Black/Asian	19/2/1
Hispanic	9%
Never/Former/Current Smoker	16/6/0
IBD Characteristics	
Ulcerative colitis/Crohn's disease	15/7
Mean disease duration at time of fenofibrate (SD), years	16.1 (10.9)
Concurrent biologic at time of fenofibrate	32%
Adalimumab	2/7
Infliximab	1/7
Ustekinumab	3/7
Risankizumab	1/7
Prior exposure to >1 biologic	27%
5-ASA use	32%
Immunomodulator use	9%
PO vancomycin use	14%
Intestinal resection	27%
Pouchitis/Patients with IPAA	4/4
PSC Characteristics	
Small duct/Small to large/Large duct	2/2/18
Autoimmune hepatitis overlap	14%
Mean disease duration at time of fenofibrate (SD), years	9.75 (9.10)
Recurrent PSC at time of fenofibrate	14%
Episodes of cholangitis	50%
Cirrhosis	36%
Compensated Cirrhosis/Total Patients with Cirrhosis	2/6
Presence of extrahepatic biliary disease	59%
IBD Results	
Ulcerative colitis	
Mean Mayo Endoscopic Score (n=14)	
Pre-fenofibrate (SD)	0.93 (1.07)
Post-fenofibrate (SD)	0.71 (1.07)
Mean Clinical Mayo Score (n=12)	
Pre-fenofibrate (SD)	1.71 (1.73)
Post-fenofibrate (SD)	0.83 (1.40)*
Crohn's Disease	
Mean SES-CD (n=2)	
Pre-fenofibrate (SD)	4.00 (1.41)
Post-fenofibrate (SD)	3.50 (0.71)
Change in colonoscopy with fenofibrate (Improved/Stable/Worse)	9/10/3
Inactive disease in patients with stable colonoscopy	70%
Patients that met primary endoscopic outcome	73%
PSC Results	
Mean Alkaline phosphatase (U/L)	
Pre-fenofibrate (SD)	429 (411)
Post-fenofibrate (SD)	265 (318)***
Mean ALT (U/L)	
Pre-fenofibrate (SD)	71 (70)
Post-fenofibrate (SD)	56 (30)
Mean AST (U/L)	
Pre-fenofibrate (SD)	63 (75)
Post-fenofibrate (SD)	58 (46)
Mean Bilirubin (U/L)	
Pre-fenofibrate (SD)	1.30 (1.94)
Post-fenofibrate (SD)	1.05 (1.76)
Mean GGT (U/L)	
Pre-fenofibrate (SD)	207 (115)
Post-fenofibrate (SD)	159 (123)
Patients that met primary liver outcome	81%
Patients with concurrent primary outcomes for IBD and PSC	81%

Table 1. PSC-IBD Patients on Fenofibrate. Demographic data, baseline characteristics, IBD and PSC results pre- and post-fenofibrate. *** p<0.001, *p<0.05.

Disclosures: Mahesh Krishna:Ipsen: Patient Experience Consultant, Esperion: Consultant, Esperion: Patient Experience Consultant, Yanhong Deng:Nothing to Disclose, Badr Al Bawardy:AbbVie: Speaker, Takeda: Advisor, AbbVie: Advisor, Janssen: Advisor, MSD: Advisor, Marina Silveira:Nothing to Disclose, James Boyer:Mirum Pharmaceuticals: grant recipient, IPSEN: Clinical Evenets Committee for clinical trial,

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AstroZenica: Member of Clinical Events Committe, Clara Abraham:Nothing to Disclose, David Assis: Nothing to Disclose.

1103 | *VEILLONELLA DISPAR* TRIGGERS SHARED IMMUNOPATHOGENESIS BETWEEN PRIMARY BILIARY CHOLANGITIS AND SJ&OUML;GREN'S SYNDROME

JinShui Pan[1] Weiwei Zeng[1], [1]the First Affiliated Hospital of Fujian Medical University

Background: The prevalence of primary biliary cholangitis (PBC) and Sjögren's syndrome (SS) shows a marked sex disparity, and the two diseases frequently co-occur, being regarded as manifestations of the same pathological process affecting different target organs (bile ducts and exocrine glands). *Veillonella* are enriched in the gut and oral cavity of patients with PBC and SS. The aim of this study is to elucidate the shared immunopathogenesis by which *Veillonella dispar* drives PBC and SS through testosterone modulation. **Methods:** A male castration model and a *Veillonella dispar* oral gavage model were established. After 12 weeks of treatment in the castration group and the group receiving *Veillonella dispar* gavage combined with intraperitoneal injection of a peptide (The PDC-E2 peptide), serum biochemical parameters, as well as pathological changes in the liver, submandibular glands, and testes, were observed. Changes in salivary flow rate were measured, and the proportions of B lymphocytes in the submandibular gland lymph nodes and liver were detected by immunofluorescence and flow cytometry. **Results:** The castration model exhibited phenotypes such as liver and submandibular gland inflammation, as well as reduced saliva flow rate (Fig 1). Mice treated with 12 weeks of *Veillonella dispar* gavage combined with intraperitoneal injection of the peptide exhibited elevated serum ALP, decreased testosterone levels, elevated serum B-cell activating factor (BAFF) levels, B-cell infiltration in the submandibular glands and pericholangial spaces of the liver, an increased proportion of B lymphocytes in submandibular lymph nodes and the liver, and reduced salivary flow rates, compared to the group receiving PBS gavage combined with intraperitoneal injection of the peptide (Fig 2). Supplementation with testosterone or anti-BAFF treatment alleviated the PBC and SS-like manifestations induced by *Veillonella dispar* (Fig 3). **Conclusion:** *Veillonella dispar* reduces testosterone levels via the gut-testis axis and promotes elevated BAFF levels. This leads to B-cell infiltration in the liver and submandibular glands. This study sheds light on the underlying mechanisms behind the high prevalence of primary biliary cholangitis and Sjögren's syndrome in women. It highlights the significant role of *Veillonella dispar* in both disorders and emphasises its potential as a novel therapeutic target.

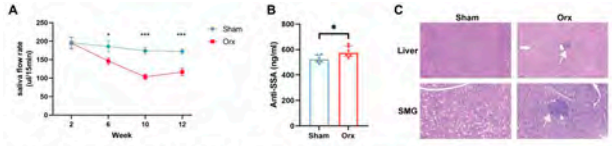


Fig 1. The castration model exhibited inflammation in the liver and submandibular gland.

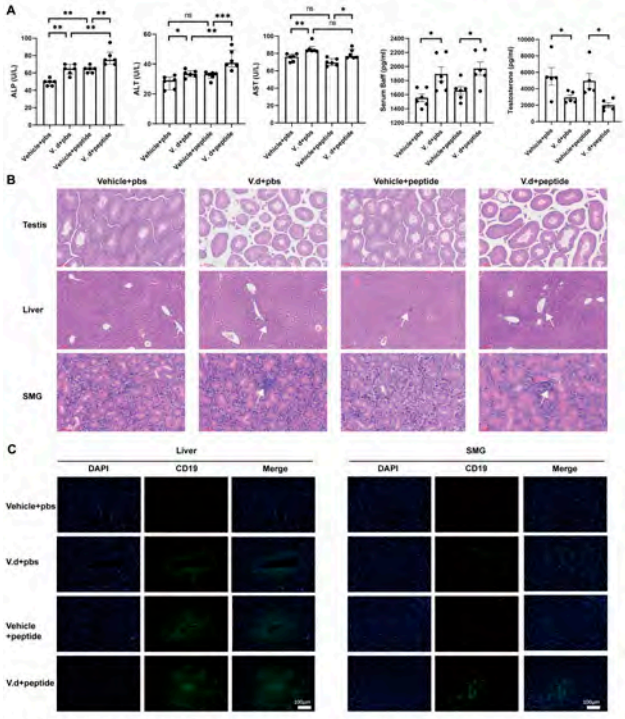


Fig 2. Mice treated with Veillonella dispar gavage combined with intraperitoneal injection of the peptide exhibited symptoms of cholangitis and Sjogren's syndrome. (A) The liver function, serum Baff, and testosterone levels of the model; (B) H&E staining of the model; (C) CD19 expression of the model.

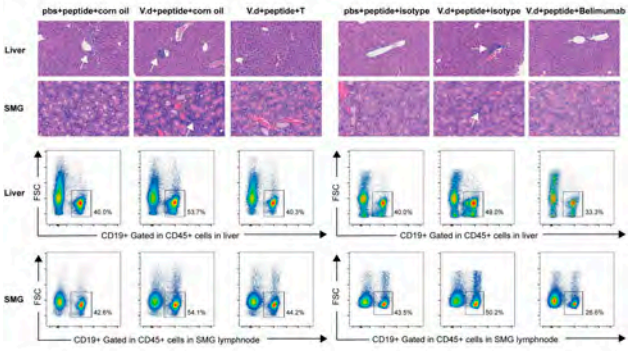


Fig 3. Supplementation with testosterone or anti-BAFF treatment alleviated the PBC and SS-like manifestations induced by Veillonella dispar.

Disclosures: JinShui Pan:Nothing to Disclose, Weiwei Zeng:Nothing to Disclose.

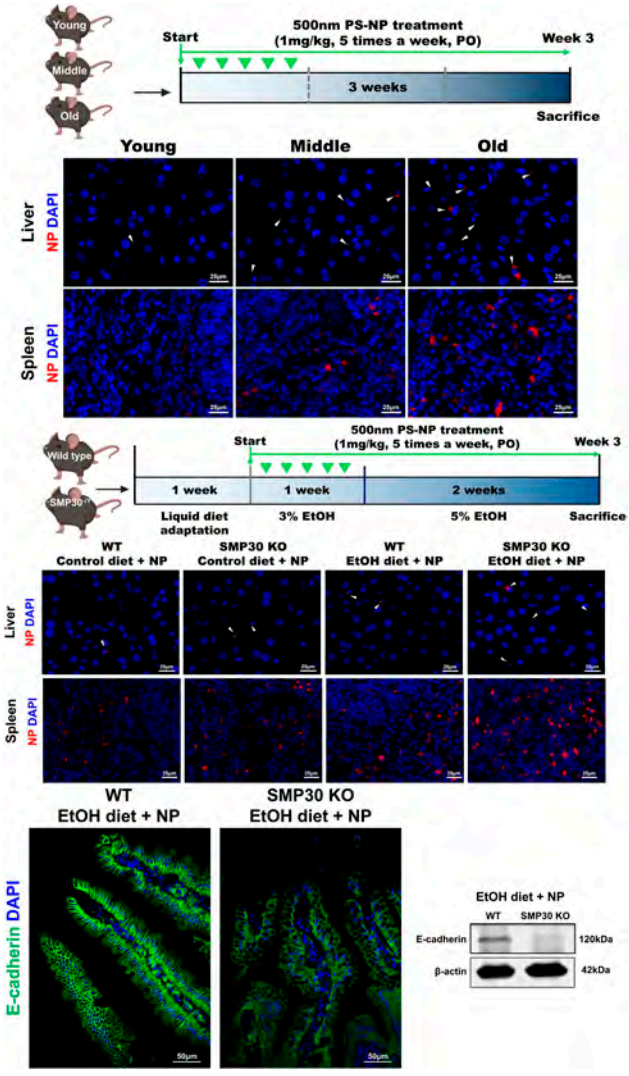
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1104 | AGE-RELATED LEAKY GUT IS MEDIATED BY AGE-DEPENDENT DECREASE OF SMP30-E-CADHERIN PATHWAY

Woo Jun Kim[1] Jae-Hyuk Yim[1] Jin-Kyu Park[1],
[1]Kyungpook National University

Background: Aging is a potential contributor to increased gut permeability. SMP30 (senescence marker protein 30) is a key molecule whose expression downregulates with age. Therefore, we investigated the role of intestinal SMP30 using aged and SMP30 knockout (KO) mouse models. Meanwhile, nanoplastics (NPs) are ubiquitous pollutants that can affect both humans and the environment. Considering the exposure route of NPs, increased gut permeability during aging may aggravate the accumulation of NPs. Overall, we aimed to investigate the role of SMP30 in regulating gut permeability, focusing on the age- and SMP30-dependent distribution of NPs. **Methods:** Aged and SMP30 KO mice were used to investigate the role of intestinal SMP30 and were orally administered fluorescently labeled polystyrene nanoplastics (PS-NPs) five times a week for three weeks. Additionally, an alcohol-induced intestinal permeability mouse model was established using a Lieber-deCarli diet to disrupt barrier function. Histopathological analysis, immunofluorescence, immunohistochemistry, serum biochemistry, ELISA, qPCR, and Western blot were performed to analyze phenotypes and underlying pathogenesis. Transcriptome analysis was performed in alcohol-induced permeability mouse models. To elucidate the underlying mechanisms, SMP30 knockdown was induced in the human colon carcinoma cell line Caco-2 under ethanol treatment. **Results:** In the older age group, more NPs were observed in the liver, spleen, and brain. Serum iFABP (intestinal permeability marker) level was dramatically increased in the older age group. Likewise, the SMP30 KO EtOH (KE) group exhibited more severe vacuolization in the intestinal villi and increased iFABP level compared with the WT EtOH (WE) group. The KE group showed increased NP accumulation in the lamina propria of villi as well as other parenchymal organs. Interestingly, the NP accumulation was significantly higher in SMP30 KO mice than in WT mice regardless of alcohol administration. In transcriptome analysis, actin filament organization or actin binding pathways were significantly downregulated in KE group compared to WE group. Also, the KE group showed decreased F-actin expression in the intestinal villi. Additionally, junctional proteins, such as occludin, claudin-1, and E-cadherin, were evaluated and only E-cadherin protein level was significantly decreased in KE group. SMP30 knockdown (KD) in Caco-2 induced E-cadherin downregulation at the mRNA and protein levels. Moreover, E-cadherin redistribution was promoted by SMP30 KD. **Conclusion:** This study demonstrates that SMP30 deficiency aggravates intestinal permeability via SMP30-Actin-E-cadherin pathway. We elucidate the novel function of SMP30 in intestinal epithelium, emphasizing E-cadherin mediated gut permeability in aged and SMP30 KO mouse models. Given that reduced SMP30 expression during aging, it may represent a promising therapeutic target for regulating gut permeability.



Disclosures: Woo Jun Kim:Nothing to Disclose, Jae-Hyuk Yim:Nothing to Disclose, Jin-Kyu Park:Nothing to Disclose.

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1105 | DREAM PREVENTS INTESTINAL FAILURE-ASSOCIATED LIVER DISEASE BY RESTORING GUT-LIVER BILE ACID SIGNALING IN SHORT BOWEL SYNDROME

Takahiro Ohkura[1] Shun Onishi[2] Chandrashekhara Manithody[2] Miguel Guzman[2] Sherri Besmer[2] Shin Miyata[2] Matthew McHale[2] Chelsea Hutchinson[2] Ajay Jain[2], [1]Saint Louis University / Pediatrics, [2]Saint Louis University

Background: Intestinal failure-associated liver disease (IFALD) is a major complication of short bowel syndrome (SBS), driven by disrupted enteral nutrition, barrier failure, inflammation, and altered bile acid signaling. Our patented DREAM (Distal Recirculation of Enteral contents Augmented Mechanically) system restores sustained enteral nutrient exposure after bowel resection. We tested whether DREAM prevents SBS-associated cholestatic liver injury and preserves gut-liver bile acid signaling. **Methods:** Twenty neonatal pigs were randomized to enteral nutrition control, SBS after 75% small-bowel resection, or DREAM. Serum bilirubin, GGT, bile acids, lipids, inflammatory cytokines, and portal LPS were measured. Liver injury was assessed by histology, cholestasis score, CK7, CD3, and CYP7A1 immunostaining. Hepatic and intestinal bile acid regulatory pathways were evaluated by qPCR and RNA-seq with KEGG and GO enrichment. **Results:** SBS produced severe cholestatic liver injury, while DREAM markedly protected against IFALD. Compared with SBS, DREAM lowered serum bilirubin, 0.11 vs 5.14 mg/dL, $p = 0.0008$; GGT, 23.2 vs 114.6 IU/L, $p < 0.0001$; and bile acids, 9.7 vs 39 µmol/L, $p = 0.0026$, with lipid profiles comparable to enteral controls. DREAM also reduced systemic and portal inflammatory drivers of liver injury, including IFN-γ, $p = 0.0296$; IL-1β, $p = 0.0349$; IL-6, $p = 0.0189$; TNF-α, $p = 0.0166$; and portal LPS, $p = 0.0130$, versus SBS. Histologically, SBS increased hepatic cholestasis score, CK7-positive ductular reaction, CD3-positive T-cell infiltration, and hepatocyte CYP7A1 expression; DREAM prevented these changes and preserved hepatic architecture. Hepatic bile acid signaling was restored with DREAM with preserved FGFR4 expression, BSEP induction was normalized, and CYP7A1 mRNA was reduced compared with SBS, $p = 0.0034$, consistent with restored suppression of bile acid synthesis. Intestinal FXR and TGR5 signaling were reactivated, supporting enterohepatic feedback. Hepatic RNA-seq further showed that DREAM reduced inflammatory mediators, TNF, ICAM1, and CCL2; restored peroxisomal and antioxidant genes, ACOX1, CAT, and SCP2; and improved lipid and redox pathways disrupted by SBS. **Conclusion:** DREAM prevents SBS-associated IFALD by reducing cholestasis, bile acid accumulation, hepatic inflammation, and CYP7A1-driven bile acid synthetic stress while restoring enterohepatic FXR-FGFR4/BSEP signaling. These findings position DREAM as a liver-protective strategy for intestinal failure and a translational platform for studying gut-liver mechanisms of IFALD.

Disclosures: Takahiro Ohkura:Nothing to Disclose, Shun Onishi:Nothing to Disclose, Chandrashekhara Manithody:Nothing to Disclose, Miguel Guzman:Nothing to Disclose, Sherri Besmer:Nothing to Disclose, Shin Miyata:Nothing to Disclose, Matthew McHale:Nothing to Disclose, Chelsea Hutchinson:Nothing to Disclose, Ajay Jain:Nothing to Disclose.

1106 | BILE ACID SIGNATURES OF FIBROSIS SEVERITY AND RELATED MICROBIOME SUBPOPULATIONS IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE MASLD

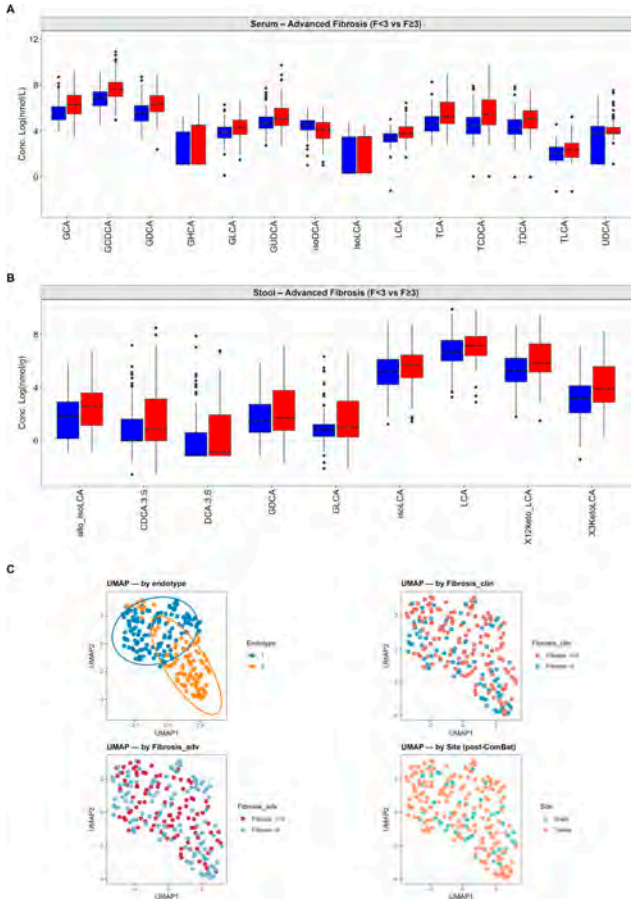
Isabel Veloso Alves Pereira[1] Yusuf Yilmaz[2] Claudia Oliveira[3] Fatih Eren[4] Jose Tadeu Stefano[5] Sebastião Mauro Duarte[5] jason Kang[6] Faridoddin Mirshahi[7] Huiping Zhou[7] Phillip Hylemon[7] Ekaterina Smirnova[7] Arun Sanyal[7], [1]Universidade de São Paulo, [2]Marmara Universitesi Tip Fakultesi, [3]University of Sao Paulo School of Medicine, [4]Marmara University School of Medicine, [5]Faculdade de Medicina da Universidade de São Paulo, [6]Stravitz-Sanyal Institute for Liver Disease and Metabolic Health, [7]Virginia Commonwealth University

Background: Several circulating bile acids are increased with increasing fibrosis in a single-center US cohort with MASH (Smirnova et al. 2022). It was not known if these findings were generalizable and if there were microbial subpopulations associated with distinct bile acid profiles. **Aims:** (1) To define and validate circulating bile acid signatures associated with increasing fibrosis stage. (2) To define microbial endotypes associated with distinct circulating bile acid profiles. **Methods:** A cross-sectional study in 2 cohorts with histologically confirmed MASLD from South America (Brazil, $n = 68$) and Eurasia (Turkey, $n = 170$) was performed ($\geq$ F3 $n = 107$). Bile acids from serum and fecal samples were measured using liquid chromatography-mass spectrometry (LC-MS) .16S rRNA sequencing was performed for microbiome analysis. Unsupervised multi-omics factor analysis (MOFA2) was used to identify endotypes in a joint microbiome-bile acids analysis. Microbiota–fibrosis associations were modeled with MaAsLin3, adjusting for site, age, sex, and BMI. **Results:** Total and glycine conjugated serum bile acids (GCDCA and GDCA) increased with increasing fibrosis stage. Of note, glycine-conjugated

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hyocholic and ursodeoxycholic acid also increased concordantly with GDCA. Fecal bile acid profiles were not significantly different across fibrosis stages. Consistent with the literature *Ruminococcus callidus* was associated with advanced fibrosis (FDR = 0.045). Two endotypes (n = 123/91) were linked to microbiome-circulating bile acid profiles. Endotype 1 (dysfunctional) had more males (60 vs. 44%, p = 0.03) and higher ALT (median 63 vs. 48 U/L, p = 0.02). Endotype 1 was depleted of BSH-encoding *Parabacteroides* and butyrate-producing commensals (*R. bromii*, *F. prausnitzii*), consistent with the accumulation of primary bile acids (CA, UDCA, CDCA) and keto intermediaries (7-ketoDCA, 7-ketoLCA) indicating incomplete 7α-dehydroxylation. In contrast, Endotype 2 (functional) was associated with greater circulating secondary bile acids, including DCA and lithocholic acid and their derivatives. **Conclusion: Conclusion:s:** Circulating glycine-conjugated bile acids increase with fibrosis severity across ethnicities, confirming prior US findings. Integrated multi-omics analysis identified two bile acid–associated gut–liver axis endotypes, independent of fibrosis stage and predominantly driven by bile acid variation, with limited discriminative performance for fibrosis severity.



Disclosures: Isabel Veloso Alves Pereira:Nothing to Disclose, Yusuf Yilmaz:Nothing to Disclose, Claudia Oliveira:Nothing to Disclose, Nothing to Disclose, Fatih Eren:Nothing to Disclose, Jose Tadeu Stefano: Nothing to Disclose, Sebastião Mauro Duarte:Nothing to Disclose, jason Kang:Nothing to Disclose, Faridoddin Mirshahi:Nothing to Disclose, Huiping Zhou: Nothing to Disclose, Phillip Hylemon: Ekaterina Smirnova: Arun Sanyal: Nothing to Disclose.

1107 | *VEILLONELLA DISPAR* TRIGGERS "DUAL-HITS" IN THE PATHOGENESIS OF AUTOIMMUNE HEPATITIS AND PRIMARY BILIARY CHOLANGITIS VIA TESTOSTERONE DEPLETION-BAFF-B CELL AXIS AND TH17 CELL ACTIVATION

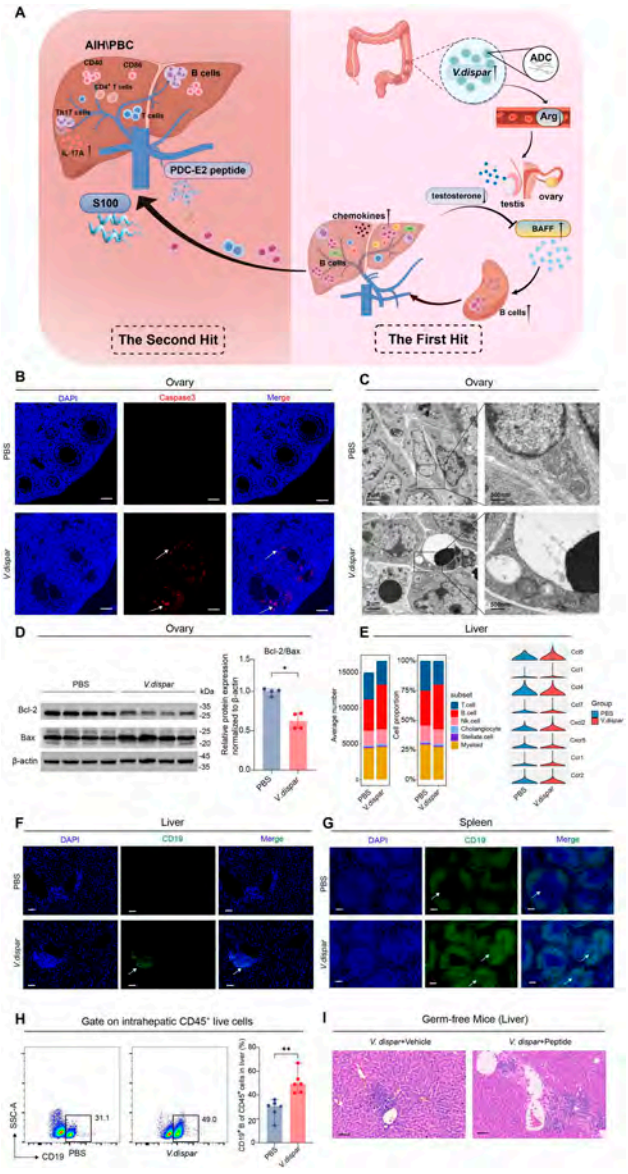
JinShui Pan[1] YaLing Liu[1], [1]the First Affiliated Hospital of Fujian Medical University

Background: Autoimmune hepatitis (AIH) and primary biliary cholangitis (PBC) frequently present as overlap syndromes, characterized by shared sexual dimorphism and elevated intestinal *Veillonella dispar* (*V. dispar*) abundance, yet exhibiting distinct hallmark pathological manifestations. This study aimed to elucidate the shared pathogenesis, phenotypic differentiation mechanisms and sex-specific predisposition of AIH and PBC induced by *V. dispar*. **Methods:** Clean-grade and germ-free (GF) mice were employed to establish AIH and PBC models. Model induction involved oral gavage of *V. dispar* and intraperitoneal injection of either liver-specific antigen S100 (for AIH) or a pyruvate dehydrogenase complex E2 subunit (PDC-E2) mimetic peptide (for PBC). Single-cell RNA sequencing, metabolomics, transmission electron microscopy, western blotting, and flow cytometry were utilized to elucidate the underlying mechanisms. **Results:** *V. dispar* successfully induced autoimmune liver disease-like features in mice, characterized by significant intrahepatic B cell infiltration. Mechanistically, *V. dispar* caused systemic arginine reduction, leading to intrinsic apoptosis of gonadal stromal cells and a subsequent reduction in testosterone. This decreased testosterone weakened its inhibitory effect on B cell activating factor (BAFF) secretion, thereby amplifying B cell-mediated immune responses. Furthermore, in the presence of S100 or PDC-E2 mimetic peptide, *V. dispar* also facilitated Th17 cell activation, which guided the phenotypic differentiation into AIH or PBC, respectively. **Conclusion:** *V. dispar* induces reduced testosterone levels and upregulation of BAFF, leading to intrahepatic B cell expansion, which serves as the common pathogenic basis for AIH and PBC. The presence of S100 and PDC-E2 subsequently drives further maturation of these expanded B cells and promotes Th17 cell activation, thereby

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determining the phenotypic divergence between AIH and PBC.



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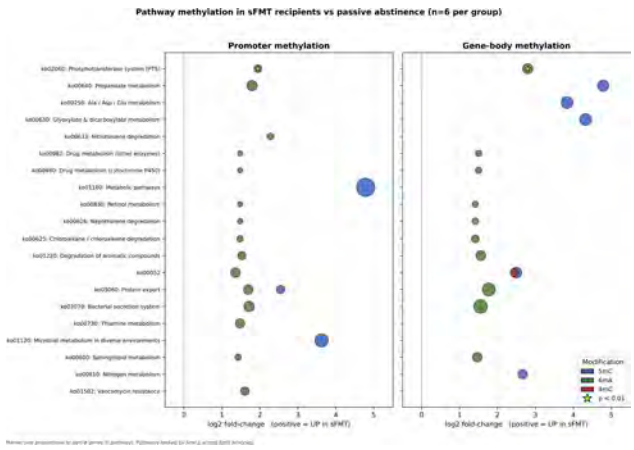
1108 | DONOR METHYLATOR ENGRAFTMENT AND BACTERIAL SAM-CYCLE AXIS EXCLUSIVELY TRACKS MICROBIOME ENGAGED IN FMT MEDIATED RECOVERY IN ALCOHOL-ASSOCIATED LIVER DISEASE MODEL

Shvetank Sharma[1] Kavita Yadav[1] Rosmy Babu[1] Neha Sharma[1] Nishu Choudhary[1] Chhagan Bihari[1] Jaswinder Maras[1] Shiv Kumar Sarin[1], [1]Institute of Liver and Biliary Sciences

Background: Alcohol-associated liver disease (ALD) carries 5-year mortality exceeding 50%, and fecal microbiota transplantation (FMT) shows survival benefit in severe alcoholic hepatitis (SAH), yet its molecular basis is poorly defined. Most studies infer function from microbial abundance shifts rather than active microbial activity. We sought to characterize how the gut bacterial community functionally alters during recovery from ALD, comparing passive abstinence with standard FMT. **Methods:** ALD was induced in C57BL/6N mice (n = 6 per group) using Lieber–DeCarli ethanol + thioacetamide (150 mg/kg, twice weekly) over 12 weeks. Cecal sampling was performed at Wk4/8/12, after 2-week abstinence (Abst), and after 2-week FMT (oral gavage of healthy-donor fecal slurry on the abstinence baseline). Native-DNA Oxford Nanopore long-read sequencing called 5mC/6mA/4mC simultaneously from the same reads. Per-position methylation calls were aggregated to gene, KEGG pathway, and species level . Untargeted LC-MS/MS metabolomics, liver biochemistry and histology were integrated by Spearman correlation with Benjamini-Hochberg FDR. **Results:** The reversal in fibrosis and AST levels achieved by FMT was greater than passive abstinence (fibrosis 19.3 ± 1.1% vs. 14.0 ± 1.1%, $p = 0.0022$; AST 66.4 ± 13.5 vs 91.3 ± 16.4 U/L, $p = 0.041$). The methylating sub-community was significantly group-structured (PERMANOVA $F = 5.54$, $p = 0.002$ FMT vs Abst). Donor Dam (GATC) and Dcm (CCTGG) motif fingerprints transferred intact to FMT recipients (Jaccard = 1.00) but were absent in Abstinence, indicating donor-engrafted rather than expanded resident methylator activity. Pathway-level analysis identified FMT-elevated methylation of cysteine/methionine metabolism (ko00270, the SAM cycle host) and purine metabolism (ko00230) in both promoter and gene-body regions (**Figure**). Bacterial SAM-cycle backbone enzymes (MetK, AhcY, MetH) showed methylation positively correlated with stool 5′-deoxyadenosine ($q < 0.05$) and adenosine ($q < 0.10$) across endpoint samples. Species-level analysis identified *Enterobacter hormaechei* methylation as fibrosis-protective ($\rho = -0.75$, $q = 0.01$) and *Limosilactobacillus reuteri* methylation as disease-tracking (fibrosis $\rho = +0.71$, $q = 0.02$). *Phocaeicola massiliensis* MetK methylation arose exclusively in FMT recipients, a clean signature of donor engraftment. **Conclusion:** Native-DNA long-read methylation profiling identifies a structured gut bacterial methylator sub-community that tracks ALD recovery distinctly from abundance alone. Donor methylator engraftment and a methionine-salvage/SAM-cycle axis is distinct from abstinence recovery, and serves as a functional readout of post-FMT community activity and efficacy.

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Disclosures: Shvetank Sharma:Nothing to Disclose, Kavita Yadav:Nothing to Disclose, Rosmy Babu:Nothing to Disclose, Neha Sharma:Nothing to Disclose, Nishu Choudhary:Nothing to Disclose, Chhagan Bihari: Nothing to Disclose, Jaswinder Maras:Nothing to Disclose, Shiv Kumar Sarin:Nothing to Disclose.

1109 | ORAL CANNABIDIOL AMELIORATED ALCOHOL-ASSOCIATED LIVER INJURY THROUGH INTESTINAL EPITHELIAL CELL AHR ACTIVATION-MEDIATED GUT-LIVER AXIS

Panpan Huang[1] Md Manirujjaman[2] Wenke Feng[1], [1]Tulane University, [2]LSU

Background: Alcohol-associated liver disease (ALD) is a major cause of liver-related morbidity and mortality, and effective therapies remain limited. Disruption of the gut–liver axis, characterized by intestinal barrier dysfunction and bacterial translocation, is central to ALD progression. Cannabidiol (CBD), a non-psychoactive compound from *Cannabis sativa*, has anti-inflammatory and antioxidant properties; however, the effects of oral CBD and its underlying mechanisms in ALD remain unclear. **Methods:** The effects of oral CBD in experimental ALD were evaluated in NIAAA chronic-plus-binge ALD mouse model. Mice were fed alcohol-containing Lieber DeCarli liquid diet for 10 days and one binge alcohol was gavaged to mice 9 hours before tissue harvesting. CBD was orally gavaged to mice at a dose of 2 mg/kg every other day. Liver injury, inflammation, bacterial translocation, and intestinal barrier integrity were assessed by biochemical assays, tissue histology, immunostaining, and hepatic 16S rRNA analysis. The role of aryl hydrocarbon receptor (AhR) was examined using pharmacological inhibitor (CH223191) and in intestinal epithelial cell-specific AhR knockout ($Ahr^{\Delta IEC}$) mice. *In vitro* studies were conducted in intestinal epithelial Caco-2 cells. **Results:** Oral CBD administration significantly reduced serum levels of ALT and AST and attenuated hepatic inflammation. Alcohol feeding increased circulating LPS levels, and hepatic bacterial 16S rRNA and *E. coli* accumulation, which were attenuated by oral CBD administration, indicating a reduction in alcohol-associated bacterial translocation. In the intestine, CBD improved epithelial integrity by restoring crypt architecture, reducing oxidative stress, preserving tight junction organization, enhancing goblet cells numbers and increasing IgA expression. Importantly, these protective effects of oral CBD were abolished by CH223191, an AhR inhibitor, and in $Ahr^{\Delta IEC}$ mice, suggesting a critical role of epithelial AhR activation. Fecal 16S rRNA analysis showed a reshaped gut microbiota homeostasis, such as an enrichment of *Akkermansia muciniphila*, a mucin-degradation commensal bacterium which plays a regulatory role in barrier integrity. In Caco-2 cells, CBD prevented acetaldehyde-induced epithelial cell barrier dysfunction measured by transepithelial electric resistance (TEER) assay, which was inhibited by CH22319. **Conclusion:** In conclusion, these findings demonstrate that the therapeutic effects of oral CBD are mediated by intestinal AhR, which regulates the gut-liver axis to preserve gut barrier integrity, attenuate bacterial translocation to the liver, and ultimately protect against alcohol-induced liver injury.

Disclosures: Panpan Huang:Nothing to Disclose, Md Manirujjaman:Nothing to Disclose, Wenke Feng:Nothing to Disclose.

1110 | *BLAUTIA WEXLERAE* AMELIORATE EXPERIMENTAL MASLD THROUGH GUT-LIVER AXIS RESTORATION AND HEPATIC AUTOPHAGY ACTIVATION

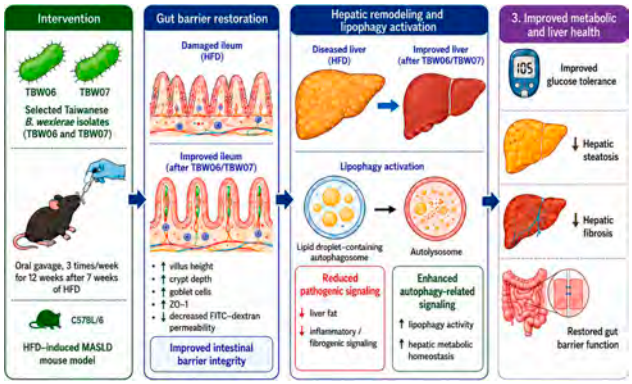
Yu-Cheng Lin[1] Chun-Liang Chen[1] Yun-Er Li[1] Hsueh-Fang Lin[1] Yen-Hsuan Ni[2], [1]Taipei Veterans General Hospital, [2]National Taiwan University Hospital

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is closely linked to gut microbial dysbiosis, yet species-level microbial candidates with therapeutic relevance remain insufficiently defined. In our previous full-length 16S rRNA sequencing analysis of children with obesity, *Blautia wexlerae* was depleted in those with MASLD compared with age-, sex-, and BMI-matched non-MASLD controls, suggesting a potential protective role. We therefore investigated whether selected Taiwanese *B. wexlerae* isolates could ameliorate MASLD and explored the underlying gut-liver axis mechanisms. **Methods:** Seven *B. wexlerae* isolates obtained from healthy Taiwanese individuals were cultured anaerobically. Cell-free culture supernatants were first screened in oleic acid-treated HepG2 cells using Oil Red O staining. Based on anti-steatotic activity, two

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Taiwanese *B. wexlerae* isolates, designated TBW06 and TBW07, were selected for in vivo validation. Male C57BL/6JNarl mice were fed either chow diet or high-fat diet (HFD). After 7 weeks of HFD feeding, mice received oral gavage with TBW06, TBW07, or vehicle three times weekly for 12 weeks. Glucose metabolism, serum biochemistry, hepatic steatosis and fibrosis, hepatic metabolic and autophagy-related signaling, intestinal barrier integrity, and cecal bile acid composition were assessed. **Results:** Supernatants from the two selected Taiwanese *B. wexlerae* isolates reduced lipid droplet accumulation in oleic acid-treated HepG2 cells. In HFD-induced MASLD mice, treatment with these isolates improved glucose tolerance and reduced visceral adiposity. Histological analysis showed that HFD markedly increased hepatic steatosis and fibrosis, with lipid droplet area and collagen proportionate area reaching 42.9% and 10.2%, respectively. TBW06 reduced these values to 18.2% and 4.9%, while TBW07 reduced them to 14.1% and 4.2%. Mechanistically, treatment with the selected isolates suppressed hepatic CD36, p62, p-mTOR, and p-AKT expression, while enhancing LC3-II/I, BECN1, SIRT1, p-AMPK, and p-ULK1, consistent with reduced fatty acid uptake and activation of autophagy-related pathways. These isolates also restored ileal ZO-1 expression, reduced FITC-dextran permeability, and improved villus length, crypt depth, and goblet cell numbers. Cecal bile acid profiling suggested compositional modulation after treatment, although changes did not reach statistical significance. **Conclusion:** Selected Taiwanese *B. wexlerae* isolates ameliorated experimental MASLD by reducing hepatic steatosis and fibrosis, improving glucose metabolism, restoring intestinal barrier integrity, and enhancing hepatic autophagy-related signaling. These findings provide experimental evidence supporting *B. wexlerae*-based strategies as potential microbiota-directed therapeutics targeting the gut-liver axis in MASLD.



Disclosures: Yu-Cheng Lin:Nothing to Disclose, Chun-Liang Chen:Nothing to Disclose, Yun-Er Li:Nothing to Disclose, Hsueh-Fang Lin:Nothing to Disclose, Yen-Hsuan Ni:Nothing to Disclose.

★ 1111 | INTESTINAL EPITHELIAL S1PR2 REGULATES GUT–LIVER LIPID HOMEOSTASIS AND HEPATIC STEATOSIS

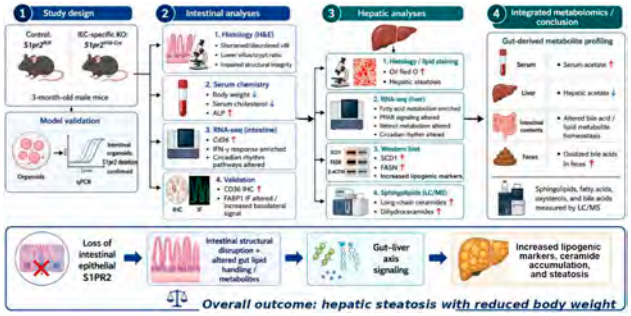
Chen Chen[1] Lianyong Su[1] Meiyi Song[1] Grayson Way[1] Wu Nan[1] Derrick Zhao[1] Yunling Tai[1] Hongkun Lu[2] Hui Li[1] Sareh Bayatpour[1] Xuan Wang[1] Emily Gurley[1] Phillip Hylemon[1] Arun Sanyal[1] Huiping Zhou[1], [1]Virginia Commonwealth University, [2]Virginia Commonwealth Univerisity

Background: S1PR2 is a GPCR involved in bile acid signaling and lipid metabolism. Although hepatic S1PR2 contributes to metabolic regulation, the role of intestinal epithelial S1PR2 in gut–liver crosstalk remains unclear. After observing hepatic lipid accumulation in mice with intestinal epithelial S1pr2 deletion, we examined changes linking intestinal S1PR2 loss to steatotic injury. **Methods:** Male 12-week-old S1pr2fl/fl and intestinal epithelial S1pr2 knockout mice (S1pr2Villi-Cre) were used. S1pr2 deletion was verified in intestinal epithelial organoids. Intestine and liver RNAseq were performed. Targeted LC-MS/MS quantified sphingolipids, fatty acids, and bile acids in liver, serum, intestinal contents, and feces. Phenotypes were assessed by histology, serum biochemistry, western blotting, IHC, and IF. **Results:** S1pr2Villi-Cre mice had reduced epithelial S1pr2 expression and lower body weight than age-matched S1pr2fl/fl mice, with no change in liver/body weight ratio. Intestinal histology showed inflammatory cell accumulation, shortened/disorganized villi, mucosal thinning, and reduced villus/crypt ratio, supporting disrupted mucosal architecture and possible barrier dysfunction. Serum cholesterol decreased, whereas hepatic Oil Red O staining showed increased lipid accumulation. Liver RNAseq showed enrichment of fatty acid metabolism, PPAR signaling, retinol metabolism, and circadian rhythm pathways; SCD1 and FASN proteins increased, consistent with a hepatic lipogenic program. Intestinal RNAseq showed altered circadian genes and immune/inflammatory programs, including IFNγ response, with increased Cd36 expression. CD36 IHC and FABP1 IF supported altered intestinal lipid transporter expression/localization. Metabolomics showed increased circulating but decreased hepatic acetate, increased hepatic ceramide/dihydroceramide pools, and altered oxysterol and bile acid profiles, including elevated fecal oxidized bile acids. These data associate intestinal epithelial S1PR2 deficiency with mucosal injury, altered transporter/metabolite profiles, and hepatic steatosis despite reduced body weight. **Conclusion:** Intestinal epithelial S1PR2 loss is associated with disrupted intestinal architecture, altered gut–liver lipid/metabolite signaling, and hepatic lipid buildup.

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These findings support a role for intestinal S1PR2 in gut–liver metabolic homeostasis and identify barrier function, incretin signaling, and hepatic mitochondrial/ketone metabolism as follow-up targets.

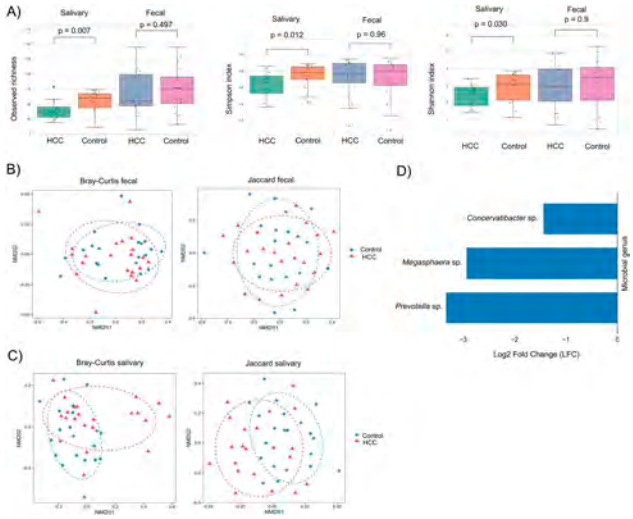


Disclosures: Chen Chen:Nothing to Disclose, Lianyong Su:Nothing to Disclose, Meiyi Song:Nothing to Disclose, Grayson Way:Nothing to Disclose, Wu Nan:Nothing to Disclose, Derrick Zhao:Nothing to Disclose, Yunling Tai:Nothing to Disclose, Hongkun Lu:Nothing to Disclose, Hui Li:Nothing to Disclose, Sareh Bayatpour:Nothing to Disclose, Xuan Wang:Nothing to Disclose, Emily Gurley:Nothing to Disclose, Phillip Hylemon:Nothing to Disclose, Arun Sanyal:Nothing to Disclose..

1112 | ORAL MICROBIOME AND PERIODONTAL DISEASE DISTINGUISH PATIENTS WITH CIRRHOSIS WITH AND WITHOUT HEPATOCELLULAR CARCINOMA

Ângelo Zambam de Mattos[1] Giovana Dumoncel[1] Gabriel Stefani Leão[1] Cristiane Azevedo Alves[1] Luiza Cerutti[2] Raíssa Nunes dos Santos[1] Richard Salvato[1] Rafaela Ramalho Guerra[1] Maximiliano Schunke Gomes[2] Adriana Seixas[1], [1]Federal University of Health Sciences of Porto Alegre, [2]Pontifical Catholic University of Rio Grande do Sul

Background: Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related deaths worldwide. Identifying factors associated with HCC might allow for the development of biomarkers capable of improving surveillance and early detection of this tumor. This study aims at comparing oral and gut microbiome of patients with cirrhosis with and without HCC. **Methods:** This cross-sectional study included individuals with cirrhosis and untreated HCC and a control-group of patients with cirrhosis without HCC, matched by age, etiology of cirrhosis and Child-Pugh classification. Saliva was collected by oral rinsing of sterile saline solution, and feces were collected by rectal swab. All patients underwent oral and dental examination. Saliva and stool samples underwent 16S rRNA gene sequencing (V3–V4 region), and microbial diversity and differential abundance were analyzed using standardized bioinformatic and statistical pipelines with false discovery rate (FDR) control. **Results:** Forty-two patients with cirrhosis were included in the study, 21 with HCC and 21 controls. Demographic and clinical parameters were comparable between groups, except for a non-significant trend towards a higher proportion of men in the HCC-group (52.4% vs 23.8%, $p = 0.112$). Among patients in the HCC-group, 52.4% had tumors within Milan criteria, and the median diameter of the largest tumor was 4.1cm (interquartile range – 2.2-6.8). Patients with HCC exhibited significantly reduced salivary alpha diversity, including lower observed richness ($p = 0.007$) and reduced Simpson-based evenness indices ($p = 0.012$), along with distinct beta diversity clustering compared with controls (Bray-Curtis – $R^2 = 0.034$, $p = 0.009$; Jaccard – $R^2 = 0.026$, $p = 0.002$). Differential abundance analyses consistently identified oral-associated genera contributing to this separation, particularly a significant depletion of Prevotella spp ($Log2FC = -3.33$, FDR < 10%). In parallel to oral dysbiosis, periodontal disease was also associated with HCC (probing depth – $p = 0.005$; attachment loss – $p = 0.049$). In contrast, fecal microbiome showed no significant differences in alpha or beta diversity and lacked a robust differential abundance signature between groups (Figure 1). **Conclusion:** HCC was associated with measurable alterations in the salivary microbiome, but not in fecal microbial diversity or structure within a clinically matched population of individuals with cirrhosis. Moreover, the differential profile of periodontal disease may reflect an inflammatory environment associated with oral dysbiosis. These findings support the oral microbiome as a potential component of host–microbiome interactions in hepatocarcinogenesis and warrant validation in longitudinal, multicenter studies integrating comprehensive oral health parameters and functional microbial analyses.



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1113 | RIFAXIMIN REDUCES LIVER FIBROSIS AND EARLY HEPATOCARCINOGENESIS IN EXPERIMENTAL MASH BY MODULATING THE GUT–LIVER AXIS AND ANGIOGENIC SIGNALING

Kosuke Kaji[1] Norihisa Nishimura[1] Shinya Sato[1] Masafumi Oyama[1] Tatsuya Nakatani[1] Tadashi Namisaki[2] Hitoshi Yoshiji[1], [1]Department of Gastroenterology, Nara Medical University, [2]Nara medical university

Background: The gut–liver axis is critically involved in the progression of metabolic dysfunction–associated steatohepatitis (MASH). Translocation of gut-derived lipopolysaccharide (LPS) activates hepatic inflammation and fibrogenesis through toll-like receptor 4 (TLR4) signaling and contributes to angiogenesis during hepatocarcinogenesis. Rifaximin, a non-systemic antibiotic that acts within the intestine, has been reported to improve intestinal barrier function and decrease endotoxin exposure. The present study examined whether rifaximin could suppress liver fibrosis and early hepatocarcinogenic changes in MASH, focusing on the LPS–epiregulin–IL-8–mediated angiogenic pathway. **Methods:** Male Fischer 344 rats were fed a choline-deficient, L-amino acid-defined high-fat diet (CDAHFD) for 12 weeks to induce MASH. Animals received rifaximin (30 mg/kg/day) or vehicle orally during the feeding period. Liver pathology including fibrosis and preneoplastic alterations was evaluated histologically and biochemically. Portal LPS concentrations, Kupffer cell activation, and hepatic LPS/TLR4 signaling were assessed. Angiogenesis-related factors such as epiregulin, IL-8, CD34-positive microvessels, and proangiogenic gene expression were analyzed. Intestinal barrier integrity was examined through histological evaluation, tight junction protein expression, intestinal LPS levels, and FITC-dextran permeability assays. **Results:** Rifaximin treatment markedly reduced hepatic inflammation and fibrosis in CDAHFD-fed rats, as evidenced by decreased hydroxyproline levels and downregulation of profibrogenic genes. The number of glutathione S-transferase placental form (GST-P)-positive preneoplastic lesions was significantly lower, along with suppression of proliferation-associated genes. Rifaximin also decreased portal endotoxin levels and inhibited Kupffer cell activation, accompanied by reduced expression of Lbp, Cd14, Tlr4, and inflammatory cytokines. Importantly, hepatic expression of epiregulin and IL-8 was significantly diminished, which was associated with reduced CD34-positive neovascularization and downregulation of angiogenesis-related genes. These changes coincided with improved intestinal barrier function, characterized by restoration of villus morphology, increased tight junction protein expression, and reduced intestinal permeability. **Conclusion:** Rifaximin alleviates liver fibrosis and early hepatocarcinogenesis in experimental MASH by strengthening intestinal barrier integrity, reducing gut-derived endotoxin exposure, and inhibiting LPS–TLR4–epiregulin–IL-8–dependent angiogenic signaling. These findings suggest that modulation of the gut–liver axis with rifaximin may represent a potential chemopreventive strategy for MASH-related liver cancer.

Disclosures: KOSUKE KAJI:Nothing to Disclose, NORIHISA NISHIMURA:Nothing to Disclose, Shinya Sato: Nothing to Disclose, Masafumi Oyama:Nothing to Disclose, Tatsuya Nakatani:Nothing to Disclose, Tadashi Namisaki: Nothing to Disclose, Hitoshi Yoshiji:Nothing to Disclose.

1114 | RIFAMYCIN THERAPY DOES NOT SIGNIFICANTLY CHANGE GUT MICROBIAL ANTIBIOTIC RESISTANCE GENE EXPRESSION IN CIRRHOSIS: RESULTS FROM A DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED CLINICAL TRIAL

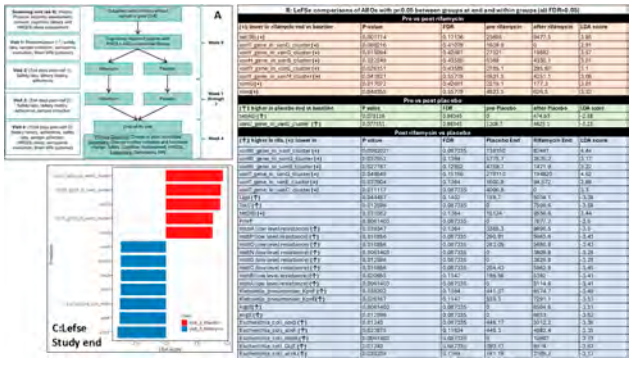
Jasmohan Bajaj[1] Masoumeh Sikaroodi[2] Haley Obolewicz[3] Mary Leslie Gallagher[4] Travis Mousel[3] Puneet Puri[1] Brian Davis[5] Patrick Gillevet[2], [1]Virginia Commonwealth University, [2]George Mason University, [3]Richmond VAMC, [4]McGuire Veterans Affairs Medical Center, [5]Central Virginia VA Health Care System

Background: Antibiotic resistance is a growing issue in cirrhosis. Of late the non-absorbable antibiotic rifaximin has been implicated with emergence of gut microbial antibiotic resistance genes (ARGs), especially with vancomycin resistance, but with unclear clinical implications. The impact of *rifamycin*, a related rifampin antibiotic approved for traveler's diarrhea, on ARGs development in cirrhosis is unclear. **Methods:** The RIVET randomized controlled trial was conducted in compensated outpatients with cirrhosis and minimal HE. Patients were randomized 1:1 into placebo or rifamycin 600mg BID for 30 days in a double-blind manner (Fig A). Stool was collected at baseline and

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drug-end. We performed metagenomics and ARGs and antibiotic resistance ontology (ARO) analysis using the CARD database. ARO abundances were compared between & within groups using LeFSe and using false discovery rates (FDR). **Results:** **Patient characteristics** : 30 patients (15 per group) with MHE without prior overt HE were included. Both groups had similar ages (67 vs 65 yrs mean), 93% men each, & MELDNa (8 vs 9 median). All patients completed the trial, which showed safety, improvement in sarcopenia in rifamycin group, but no change in cognition between groups. MELD score, complications of cirrhosis remained stable between/within groups. There were no infections noted during the follow-up. **AROs changes** pre/post and within groups showed no change that was FDR < 0.05 between or within groups (Fig B). Exploratory analyses were then performed with significant p-value changes. Pre vs post rifamycin : Multiple glycopeptide resistance operon components, including vanB-, vanC-, vanG-, vanL-, and vanM-associated genes, decreased following rifamycin compared to baseline and end-of-study. Remaining ARO changes were lowered tetracycline and nitroimidazole resistance.Pre vs post placebo : Increase in van-U (vancomycin resistance) & tetracycline were seen after placebo (Fig B).Rifamycin-end vs placebo-end : There was a lower vancomycin resistance post-rifamycin vs placebo while the increase in the Enterobacteriaceae were low-level chromosomal changes but high-level transmissible plasmid-driven resistance (Fig B /C). **Conclusion:** A prospective clinical trial of rifamycin versus placebo showed no major infections or safety risk. We found no significant changes in ARO gene expression between or within groups using strict FDR. Exploratory analyses showed a consistent reduction of enterococcal populations harboring van-associated resistance determinants compared to baseline values and at study end versus placebo. Increase in ARO genes post-rifamycin vs placebo were focused on inherent expression of chromosomal low-risk changes adapting to antibiotic exposure rather than high-risk transmissible resistance mechanisms. These findings suggest that rifamycin did not promote expansion of ARO and especially vancomycin-resistance pathways in cirrhosis.



Disclosures: Jasmohan Bajaj:Bausch: Grant/Research Support, Sequana: Grant/Research Support, Grifols: Grant/Research Support, Bausch: Grant/Research Support, Sequana: Grant/Research Support, Grifols: Grant/Research Support, Genfit: Grant/Research Support, Enterobiotix: Advisor, Boehringer Ingelheim: Advisor, Merz: Consultant, Masoumeh Sikaroodi:Nothing to Disclose, Haley Obolewicz:Nothing to Disclose, Mary Leslie Gallagher:Nothing to Disclose, Travis Mousel:Nothing to Disclose, Puneet Puri:Nothing to Disclose, Brian Davis:Nothing to Disclose, Patrick Gillevet:Nothing to Disclose.

1115 | CUMULATIVE BREATH HYDROGEN REFLECTS A COLONIC FERMENTATION PHENOTYPE ASSOCIATED WITH MINIMAL HEPATIC ENCEPHALOPATHY IN MASLD PREDOMINANT CIRRHOSIS

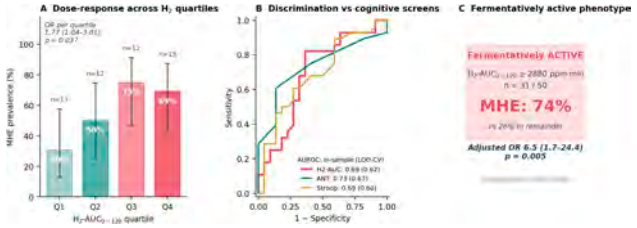
Akash Roy[1] Shummy Das[1] Uday Chand Ghoshal[1] Mahesh Goenka[1], [1]Apollo Multispeciality Hospitals

Background: Hepatic encephalopathy is driven by gut microbial metabolism, yet the lactulose hydrogen breath test is interpreted only categorically in cirrhosis, discarding the quantitative information it generates. We hypothesised that cumulative breath hydrogen quantifies a colonic fermentation phenotype that tracks minimal hepatic encephalopathy (MHE) on an axis independent of liver-disease severity **Methods:** Prospective single-centre cross-sectional study of 50 adults with cirrhosis without overt HE. PHES (reference standard for MHE), Animal Naming Test (ANT) and EncephalApp Stroop were performed. Cumulative breath hydrogen (H2-AUC0–120; ppm·min) was computed from a standardised 10-g lactulose breath test. OCTT was defined by the classical double-peak rule: time to the second (colonic) H2 peak $\geq$ 20 ppm above baseline. Associations used Mann–Whitney U and Fisher tests; Firth-penalised logistic regression adjusted for MELD-Na. Discrimination was reported as in-sample and leave-one-out cross-validated (LOO-CV) AUROC. **Results:** MHE was present in 28/50 (56%); MASLD accounted for 76% of the cohort. H2-AUC showed a graded relationship with MHE with prevalence rising monotonically across quartiles (30%, 50%, 75%,69%; trend p = 0.024), adjusted OR per quartile 1.77 (95% CI 1.04–3.01, p = 0.037). At the Youden-optimal threshold of $\geq$ 2880 ppm·min, the fermentatively active phenotype (n = 31) had 74% MHE versus 26% in the quiescent phenotype; MELD-Na-adjusted OR 6.5 (1.7–24.4), p = 0.005. As a non-cognitive biomarker, H2-AUC discriminated MHE comparably to validated cognitive screens (in-sample / LOO-CV AUROC: H2-AUC 0.69/0.62; ANT 0.73/0.67; Stroop 0.69/0.60). The association was strongest in the MASLD subgroup (H2-AUC 5415 vs 1935 ppm·min in MHE vs no-MHE, p = 0.031). H2-AUC did not

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co-relate with MELD-Na ($\rho = 0.01$), albumin, bilirubin, INR and BMI (all $|\rho| < 0.16$), indicating that fermentative burden indexes a risk axis independent to liver-disease severity. Findings persisted after adjustment for concurrent lactulose and rifaximin use (medication term non-significant, $p = 0.27$). **Conclusion:** In contemporary MASLD predominant cirrhosis, cumulative breath hydrogen reflects a graded colonic fermentation phenotype that identifies MHE independently of liver-disease severity and matches validated cognitive screens despite being a non-cognitive, gut-derived signal. Reframing the lactulose breath test as a quantitative microbiome metabolite assay offers a point-of-care window onto the gut–brain axis, and a potentially modifiable target for microbiome-directed therapy.

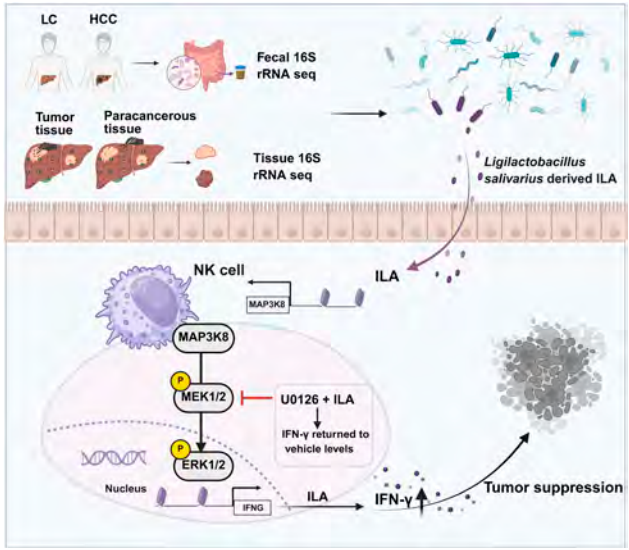


Disclosures: Akash Roy:Nothing to Disclose, Shummy Das:Nothing to Disclose, Uday Chand Ghoshal:Nothing to Disclose, Mahesh Goenka:Nothing to Disclose.

1116 | LIGILACTOBACILLUS SALIVARIUS–DERIVED INDOLE-3-LACTIC ACID ENHANCES NK CELL FUNCTION VIA MAPK SIGNALING TO SUPPRESS HEPATOCELLULAR CARCINOMA PROGRESSION

Zhewen Zhou[1] Xuefeng Huang[2] Yipeng Wang[2] Xiu Sun[3] Minghui Li[2] Ronghai Huang[2] Pu Liang[2] Xi Wang[2] Huichun Xing[2], [1]Beijing Ditan Hospital, Capital Medical University, [2]Beijing Ditan Hospital, [3]Shanxi Bethune Hospital

Background: Gut microbiota, particularly lactobacilli, produce tryptophan-derived metabolites with immunomodulatory potential. However, the metabolites involved in hepatocellular carcinoma (HCC) surveillance and the immune mechanisms remain largely undefined. We investigated the antitumor efficacy of *Ligilactobacillus salivarius* (*L. salivarius*) and its metabolite indole-3-lactic acid (ILA) in HCC and examined how ILA regulates NK cell-mediated immunity. **Methods:** Fecal samples from cirrhosis and HCC patients and paired HCC tumor/nontumor tissues were analyzed for microbiota changes. *L. salivarius* and ILA were evaluated in murine HCC models. Bulk RNA sequencing, assay for transposase-accessible chromatin using sequencing, and single-cell RNA sequencing were used to define ILA-mediated mechanisms in NK cells. In patients with HCC, cytotoxicity of peripheral blood NK cells was correlated with plasma tryptophan metabolites. ILA was evaluated in NSIG mice bearing HepG2 tumors receiving adoptive NK92MI-cell transfer. **Results:** Fecal *Ligilactobacillus*/*Lactobacillus* and tissue *Lactobacillales* were reduced in HCC. *L. salivarius* restored gut microbiota and reduced tumor burden, with increased intratumoral NK-cell infiltration and function. ILA was identified as an effector metabolite that reduced tumor burden, increased intratumoral NK-cell infiltration, and enhanced NK-cell cytotoxicity in vivo and in vitro. Multiomics showed that ILA remodeled NK-cell chromatin, upregulated MAP3K8, and activated MAPK signaling. Clinically, plasma ILA correlated with NK-cell cytotoxicity in HCC, and ILA pretreatment improved adoptively transferred NK92MI-cell efficacy in NSIG mice. **Conclusion:** *L. salivarius* and ILA attenuate HCC progression by enhancing NK-cell infiltration, promoting chromatin remodeling, and activating MAPK signaling, thereby strengthening NK cell-mediated antitumor immunity. Therefore, microbiota-derived ILA may represent a candidate for HCC immunotherapy.



Disclosures: Zhewen Zhou:Nothing to Disclose, Xuefeng Huang:Nothing to Disclose, Yipeng Wang:Nothing to Disclose, Xiu Sun:Nothing to Disclose, Minghui Li:Nothing to Disclose, Ronghai Huang:Nothing to Disclose, Pu Liang:Nothing to Disclose, Xi Wang:Nothing to Disclose, HUICHUN XING:Nothing to Disclose.

1117 | DISTINCT GUT MICROBIOME SIGNATURES AND THEIR ASSOCIATION WITH ALCOHOLIC LIVER DISEASE AND METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

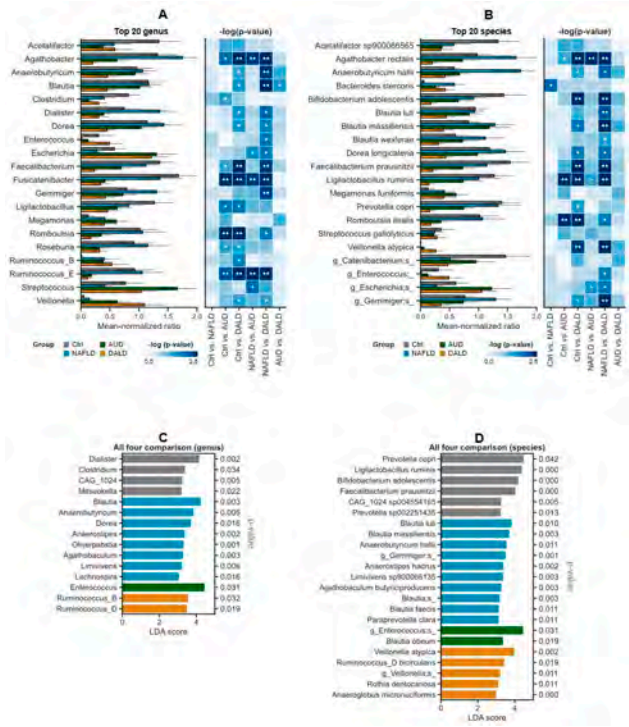
Ajay Jain[1] Mustafa Malvi[2] Manoj Kumar[3] Suchita Jain[4] Shohini Sircar[5], [1]Shalby Hospital, [2]Graphic Era Hospital, [3]ICMR National Institute for Research in

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Environmental Health, [4]Sri Aurobindo Institute of Medical Sciences, [5]Shalby Institute of Gastroenterology

Background: The gut–liver axis, representing the bidirectional communication between the gut microbiome and the liver, has emerged as a key modulator in liver-related disorders. Dysregulation of the gut microbiome has been implicated in several liver pathologies. However, our understanding of specific microbial enterotypes underlying the intricate gut-liver axis in these disorders and their correlations with hepatic injury markers remains largely limited. Therefore, this study aimed to characterize and compare gut microbiota composition in individuals with a decompensated alcoholic liver disease (DALD), alcohol use disorder (AUD), metabolic dysfunction associated steatotic liver disease (MAFLD), and healthy controls, and to identify disease-specific microbial patterns. **Methods:** It's a cross-sectional study enrolling 92 male participants and carried out high-throughput full-length 16S rRNA gene sequencing in their stool samples to compare gut microbiome profiles among patients with DALD, AUD, and MAFLD versus age- and demography-matched healthy controls. Alpha diversity, assessed using the Shannon and Chao1 indices, while Beta diversity analysis using principal coordinate analysis (PCoA) and PERMANOVA **Results:** This study reveals patients with alcohol-related liver diseases present depleted microbial diversity and reduced abundance of Faecalibacterium prausnitzii, Bifidobacterium adolescentis, Ligilactobacillus ruminis, and Prevotella copri, while harbouring a higher population of translocation-prone taxa, including Enterococcus, Veillonella, and Rothia spp. In contrast Phocaeicola. Bifidobacterium, Streptococcus, and Escherichia were reduced in MAFLD patients as compared with controls, while butyrate-producing taxa linked to metabolic disruption were retained. Analysis of shared and unique amplicon sequence variants (ASVs) identified 220 ASVs (1.9%) common to all groups, with group-specific ASVs numbering 3058 (26.4%) in controls, 2178 (18.8%) in AUD, 1779 (15.4%) in DALD, and 2608 (22.5%) in MAFLD. Overall, L. ruminis, B. massiliensis, A. rectalis, and B. adolescentis emerged as recurrent taxa positively associated with favorable liver function and metabolic health, while V. atypica, Enterococcus spp., and Escherichia spp. were consistently observed with the markers of hepatic dysfunction, particularly in alcohol-associated liver disease. **Conclusion:** 1.These findings reveal unique gut microbiome arrays underlying distinct liver disease subtypes, highlighting potential implications of these dysbiotic signatures in the pathophysiology of hepatic inflammation and metabolic regulation.2. Alcohol consumption is associated with distinct gut microbial signatures, with DALD exhibiting the most pronounced differences3.The enrichment of translocation-prone and opportunistic genera, coupled with depletion of beneficial commensals, is linked to advanced liver pathology.



Disclosures: Ajay Jain:Nothing to Disclose, Mustafa Malvi:Nothing to Disclose, Manoj Kumar:Nothing to Disclose, Suchita Jain:Nothing to Disclose, Shohini Sircar:Nothing to Disclose.

1118 | GUT MICROBIOME ALTERATIONS ARE ASSOCIATED WITH HEPATIC FIBROSIS IN PEOPLE WITH HIV

Maria Duarte[1] Bradley Aouizerat[2] Robert Burk[3] Phyllis Tien[1] Steven Wolinsky[4] Mallory Witt[5] Yue Chen[6] Chloe Thio[7] Svenja Albrecht[8] Seble Kassaye[9] Margaret Fischl[10] Deborah Gustafson[11] Cecile Lahiri[12] Michelle Floris-Moore[13] Eric Seaberg[14] Audrey French[15] Jennifer Price[1], [1]University of California, San Francisco, [2]New York University, [3]Albert Einstein College of Medicine, [4]Northwestern University Feinberg School of Medicine, [5]David Geffen School of Medicine at UCLA / Harbor-UCLA Medical Center, [6]University of

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Pittsburgh School of Medicine, [7]Johns Hopkins University, [8]University of Mississippi Medical Center, [9]Georgetown University, [10]University of Miami Miller School of Medicine, [11]SUNY Downstate Health Sciences University, [12]Emory University School of Medicine, [13]University of North Carolina at Chapel Hill, [14]Johns Hopkins Bloomberg School of Public Health, [15]Cook County Health

Background: Liver disease is a leading cause of non-AIDS mortality in people with HIV (PWH). PWH experience a high burden of hepatic fibrosis, and increasing evidence implicates the gut-liver axis as a contributor. Alterations in the gut microbiome, including changes in within-sample (alpha) and between-group (beta) diversity and depletion of short-chain fatty acid (SCFA)-producing taxa, have been linked to fibrosis in populations without HIV, but remain understudied in PWH. **Methods:** We conducted a cross-sectional analysis of PWH without moderate to heavy alcohol use, recent antibiotic use, or viral hepatitis within the MACS/WIHS Combined Cohort Study (MWCCS). Data included and stool-derived 16S rRNA sequencing and vibration-controlled transient elastography (VCTE) performed within 6 months of each other. Microbial diversity was evaluated using alpha (Shannon index) and beta (Bray-Curtis dissimilarity) diversity metrics with PERMANOVA to quantify variation in composition. Analyses were adjusted for age, sex, BMI, race, ethnicity, CD4 count, HIV-1 RNA, ART use and alcohol use. Differential abundance analysis (DAA) (ANCOM-BC2) was used to identify taxa enriched or depleted in those with prevalent F2 or greater fibrosis (VCTE liver stiffness 7.1 kPa) compared to those without fibrosis. **Results:** Among 293 participants, 69% were female, 54% were Black, 74% had HIV-1 RNA < 20 copies/mL, and 22% had fibrosis. In adjusted analyses (Figure 1), alpha diversity did not differ by fibrosis status. However, beta diversity analyses demonstrated a difference in overall microbial community composition between groups ($p = 0.03$, $R^2 = 0.01$). Unadjusted DAA identified multiple taxa associated with fibrosis, including depletion of members of the *Lachno* **Conclusion:** Among PWH, hepatic fibrosis is associated with alterations in gut microbial composition, characterized in part by depletion of SCFA-producing *Lachnospiraceae* taxa, which parallels microbial patterns in people without HIV. However, fibrosis in PWH was also characterized by distinct microbial signatures including an enrichment in *Salmonella*, thereby supporting a role for the gut-liver axis in HIV-specific hepatic fibrosis. Future studies are needed to identify likely causal relationships and evaluate microbiome-targeted interventions.

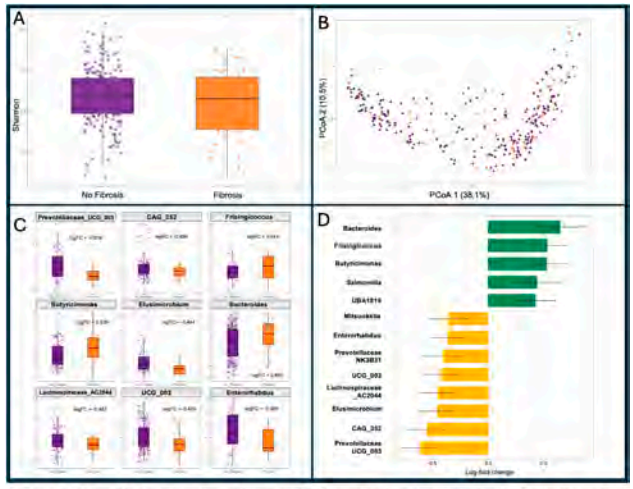


Figure 1: Microbial community analyses and differential abundance testing in PWH with and without hepatic fibrosis. Panel A: Covariate-adjusted alpha diversity (Shannon index) between PWH with and without fibrosis showed no significant differences between groups. **Panel B:** Covariate-adjusted beta diversity differed between groups based on Bray–Curtis dissimilarity (PERMANOVA p=0.01, R^2=0.01). **Panel C:** Differential abundance analysis of taxa associated with fibrosis. Boxplots depict the 9 taxa with the greatest differences in abundance between groups (fibrosis in orange, no fibrosis in purple). Log fold change (logFC) reflects the magnitude and direction of differences in taxon abundance between fibrosis and non-fibrosis groups. **Panel D:** Log-fold plot depicts the top microbial taxa enriched (green) or depleted (yellow) in PWH with hepatic fibrosis.

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1119 | HOST-MICROBE INTERACTIONS IN PORTAL BLOOD MODULATE METABOLIC AND TRANSCRIPTIONAL PROFILING IN HCV CIRRHOSIS

Rownock Afruza[1] Nicole Minerva[2] Yue Zhang[3] Neelam Redekar[3] Jenna Oringher[2] Moumita Chakraborty[2] Rabab Ali[2] Kareen Akiva[2] Grace Zhang[2] Gabriella Quinn[2] Elizabeth Townsend[2] Lisa Scheuing[2] Elliot Levy[4] Ohad Etzion[2] David Kleiner[5] Justin Lack[3] Christopher Koh[2] Theo Heller[2], [1]National Institutes of Health, [2]NIH/NIDDK, [3]NIH/NIAID, [4]NIH/Department of

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Radiology and Imaging Sciences, [5]National Cancer Institute, Bethesda

Background: Portal blood serves as the primary interface of the gut-liver axis, delivering microbial cells, nucleic acids, metabolites, and immune mediators directly from the intestine to the liver. Despite its critical position, the portal blood microbiome remains largely unexplored. Hepatitis C virus (HCV) infection provides an ideal model to study host-microbe dynamics, as antiviral therapy eliminates viral replication while liver injury and fibrosis persist. **Methods:** Cell-free DNA and RNA were extracted from portal plasma of patients with active HCV infection (HCVi, n = 29) and after sustained virologic response (SVR, n = 23). Non-human reads were mapped to the NCBI microbial database to characterize bacteria, fungi, viruses, and archaea. Microbial diversity was assessed using Shannon and Bray-Curtis indices. Cross-kingdom networks were identified via SparCC analysis, while multi-omics integration linked microbial taxa with circulating metabolites and host portal cell-free RNAs. **Results:** Portal microbiomes were dominated by bacteria, followed by fungi, viruses, and archaea. In cirrhotic patients, fungal abundance increased post-SVR while bacterial abundance and fungal diversity declined, with significant compositional shifts (Bray-Curtis, $p = 0.008$). Cross-kingdom analysis revealed that bacteria-fungi interactions accounted for over 80% of microbial correlations, with a fungal hub-driven competitive subnetwork emerging post-SVR in cirrhotics. Specific fungal taxa, including *Malassezia japonica* and *Aspergillus puulaauensis*, were associated with bile acids, lipids, and gamma-glutamyl peptides during advanced fibrosis. Host cfRNA pathways reflected translation and cellular stress during active HCV infection, shifting toward immune remodeling post-SVR. A selective enrichment of mitochondrial protein import and translation pathways (TOMM/TIMM complexes and mitochondrial ribosomal genes) in non-cirrhotics post-SVR only, reflecting preserved bioenergetic capacity after viral clearance. **Conclusion:** Portal microbiome restructuring persists after viral clearance in cirrhotic patients, with sustained dysbiosis and incomplete ecological recovery. Multi-omics integration of the portal blood reveals ongoing metabolic and transcriptional reprogramming driven by host-microbe interactions, highlighting fungi and bile acid signaling as potential therapeutic targets in HCV-associated cirrhosis.

Disclosures: Rownock Afruza:Nothing to Disclose, Nicole Minerva:Nothing to Disclose, Yue Zhang:Nothing to Disclose, Neelam Redekar:Nothing to Disclose, Jenna Oringher:Nothing to Disclose, Moumita Chakraborty:Nothing to Disclose, Rabab Ali:Nothing to Disclose, Kareen Akiva:Nothing to Disclose, Grace Zhang:Nothing to Disclose, Gabriella Quinn:Nothing to Disclose, Elizabeth Townsend:Nothing to Disclose, Lisa Scheuing:Nothing to Disclose, Elliot Levy:Nothing to Disclose, Ohad Etzion:Nothing to Disclose, David Kleiner:Nothing to Disclose, Justin Lack:Nothing to Disclose, Christopher Koh:Nothing to Disclose, Theo Heller:Nothing to Disclose.

1120 | RATIONAL FMT DONOR SELECTION FOR HEPATIC ENCEPHALOPATHY TRIALS USING LACTULOSE FERMENTATION CAPACITY

Soumok Sadhu[1] Katherine Barry[1] Ram Dahal[1] Michael Sadowsky[1] Levi Teigen[1] Jasmohan Bajaj[2], [1]University of Minnesota, [2]Virginia Commonwealth University

Background: Hepatic encephalopathy (HE), a major complication of advanced liver disease, remains a substantial clinical challenge. Current standard therapies, lactulose and rifaximin, target the gut microbiome with prebiotic and antibiotic effects, respectively. In a recent phase 2 randomized trial (THEMATIC), FMT reduced HE over placebo. However, some participants still suffered HE recurrence, highlighting the need for improved donor selection and dosing strategies before larger clinical trials are undertaken. Because the therapeutic effect of lactulose depends on microbial fermentation, we hypothesize that patients with advanced liver disease typically have reduced lactulose fermentation capacity. We further hypothesize that this defect can be restored through engraftment of healthy donor microbiota with high fermentation capacity. **Methods:** We developed an anaerobic mini-bioreactor platform to screen microbiota of FMT donors in our GMP program for lactulose consumption, pH lowering, and SCFA production. Microbiota were purified from stool using a rapid syringe-based method and cultured anaerobically with or without lactulose (~200 µg/mL) at standardized cell counts (~5×10^9 cells/mL) for up to two hours. **Results:** We tested fecal microbiota of 14 healthy individuals (Age 33.6 ± 9.4 years, 8 males, 6 females). We found considerable variability in lactulose utilization and acid production over 2 hours (ANOVA, ~10–90%, $p < 0.0001$), with parallel variability in acidification ($p < 0.0001$) and SCFA production ($p = 0.05$) (Figure 1). Lactulose consumption correlated with acid production (Spearman $r = 0.64$, $p = 0.014$) and SCFA production, establishing $\Delta[H^+]$ as a simple functional biomarker for donor selection. Of note, we could not identify any simple demographic factor predictive of lactulose fermentation capacity. We applied this metric to the 2 donors used in the THEMATIC trial where the recipients of stool from donor#1 showed no HE recurrence, while from

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donor#2 had a 13% recurrence (Figure 1). The lactulose metabolizing capacity was significantly higher in donor#1 vs #2 (82.70% vs 24.63%, p = 0.011). **Conclusion:** Optimal donor-recipient matching is critical to enhance the success of HE-focused FMT. Measurement of lactulose consumption and acid production capacity of fecal microbiota provides a rational method for selection of FMT donors for prevention of HE.

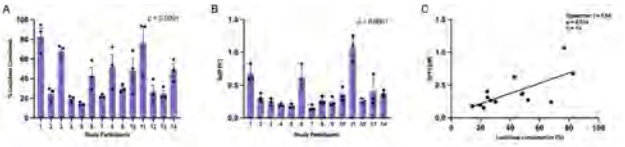


Figure 1. Donor's microbiota differ widely in their ability to ferment lactulose and acidify their environment. **(A)** Lactulose consumption by purified donor microbiota in the anaerobic mini-bioreactor assay varied significantly across donors ($p < 0.0001$). **(B)** Acid production from lactulose fermentation, measured as the change in hydrogen ion concentration ($\Delta[H^+]$), followed the same pattern ($p < 0.0001$), pointing to real differences in how strongly each donor's community acidifies its surroundings. **(C)** Lactulose consumption tracked with acid production (Spearman $r = 0.64$, $p = 0.014$, $n = 14$). Donors that fermented more lactulose also dropped pH further. Values are mean ± SEM of biological triplicates. Healthy donors are not metabolically interchangeable, and a functional readout of this kind may be more useful than composition alone for selecting FMT donors in hepatic encephalopathy.

Disclosures: Soumok Sadhu:Nothing to Disclose, Katherine Barry:Nothing to Disclose, Ram Dahal: Nothing to Disclose, Michael Sadowsky:Nothing to Disclose, Levi Teigen:Nothing to Disclose, Jasmohan Bajaj:Bausch: Grant/Research Support, Sequana: Grant/Research Support, Grifols: Grant/Research Support, Bausch: Grant/Research Support, Sequana: Grant/Research Support, Grifols: Grant/Research Support, Genfit: Grant/Research Support, Enterobiotix: Advisor, Boehringer Ingelheim: Advisor, Merz: Consultant.

1121 | PREVALENCE AND CLINICAL CORRELATES OF SMALL INTESTINAL BACTERIAL AND FUNGAL OVERGROWTH IN DECOMPENSATED CIRRHOSIS AND ACUTE-ON-CHRONIC LIVER FAILURE: A SNAPSHOT FROM NORTH INDIA

Rahul Rahul[1] Sumit Rungta[2], [1]King George Medical University, Lucknow, U.P. India, [2]KGMU

Background: Small intestinal bacterial overgrowth (SIBO) is a recognized feature of gut–liver axis disruption in cirrhosis, yet small intestinal fungal overgrowth (SIFO) is poorly characterized and culture-based Indian data are virtually absent. In this context, the study was aimed to estimate the prevalence of SIBO and SIFO in decompensated chronic liver disease (DCLD) and acute-on-chronic liver failure (ACLF) and examine their association with disease severity and complications. **Methods:** A single centre, hospital-based, analytical cross-sectional study enrolled 130 adults (116 DCLD; 14 ACLF, APASL criteria) who underwent endoscopy-guided duodenal aspiration using a sheathed microbiota sampler with quantitative bacterial and fungal culture. SIBO and SIFO were defined at $\geq 10^3$ CFU/mL; fungi were speciated by VITEK 2 and MALDI-TOF. A pre-specified, directed acyclic graph–guided multivariable analysis with E-value and alcohol-stratified sensitivity analyses was reported per STROBE guidelines. **Results:** Either of the overgrowths occurred in 38.5%: isolated SIBO 30.0%, combined SIBO–SIFO 6.9%, isolated SIFO 1.5%. SIBO prevalence was 36.9% (95% CI 29.1–45.5) and SIFO 8.5% (4.8–14.5). Isolates were 95.9% Gram-negative, with *Pseudomonas* spp. and *E. coli* co-dominant (each 32.7%); all fungi were *Candida* (*C. albicans* 72.7%, *C. tropicalis* 27.3%). Both states rose monotonically across Child–Pugh class and MELD-Na; combined overgrowth occurred only in Child–Pugh C. SIBO and SIFO co-occurred far above chance (OR 7.74; 95% CI 1.83–32.83; p = 0.002), asymmetrically, suggesting bacterial overgrowth precedes fungal proliferation. On adjusted analysis, age (aOR 1.05/year) and MELD-Na (aOR 1.06/unit) independently predicted SIBO, while MELD-Na (aOR 1.13/unit) and SIBO co-positivity (aOR 7.11) predicted SIFO (AU-ROC 0.86). SIFO was strongly linked to spontaneous bacterial peritonitis and prior rifaximin use. No SIFO or combined overgrowth occurred in ACLF despite greater severity. **Conclusion:** In advanced liver disease, small intestinal overgrowth, including an under-recognized fungal component, is common and is associated closely with hepatic severity. SIFO marks an advanced, SIBO-linked dysbiotic phenotype confined to the most decompensated patients.

Disclosures: Rahul Rahul:Nothing to Disclose, SUMIT RUNGTA:Nothing to Disclose.

1122 | BASELINE ORAL MICROBIOME COMPOSITION AND VITAMIN K BIOSYNTHESIS CAPACITY DISTINGUISH PATIENTS WITH LIVER STIFFNESS PROGRESSION IN A DIVERSE URBAN MASLD POPULATION

Adeeba Tak[1] Yulu He[1] Maryfe Coronel Novoa[1] Mark Miller[1] Victor Llanes[1] Asher Leviton[1] Jeremiah Faith[1] Frances Lee[1] Ryan Walker[1] Dania Valvi[1] Scott Friedman[1] Meena Bansal[2] Xiaotao Zhang[1], [1]Icahn School of Medicine at Mount Sinai, [2]Icahn School of Medicine at Mount Sinai (ISMMS)

Background: Fibrosis stage is the strongest predictor of outcomes in MASLD, yet progression is

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heterogeneous and difficult to predict noninvasively. The oral microbiome, linked to metabolic disease and systemic inflammation, may provide a novel risk-stratification biomarker. We assessed whether baseline oral microbiome profiles distinguish MASLD patients with subsequent VCTE-defined liver stiffness progression from those without progression in a diverse urban cohort. **Methods:** Forty-three adults with MASLD from DAMILE prospective cohort underwent baseline oral metagenomic sequencing with taxonomic and pathway profiling. Liver stiffness (LSM) was measured by VCTE at baseline and follow-up; progression was defined as a $\geq$30% liver stiffness increases between scans separated by at least 6 months. Twenty passed longitudinal eligibility. Five progressed and 15 did not (median follow-up 1.4 years). Baseline community structure was tested by PERMANOVA (Aitchison distance), adjusted for age, sex, BMI, and ethnicity. Differential pathway abundance was tested using models adjusted for age, sex, BMI, diabetes, GLP-1 RA use, resmetirom use, ethnicity, baseline LSM, and follow-up duration. Three pre-specified pathway sets and a post-hoc composite of 13 menaquinol biosynthesis pathways were each tested under this adjustment. Given a small subset, all analyses are exploratory and hypothesis-generating. **Results:** Among 20 patients with oral microbiome data, median age was 59 years; 60% were female, 35% Hispanic, and 50% had diabetes. Progressors had higher baseline BMI than non-progressors (34.4 vs. 29.2 kg/m², $p = 0.033$) and more frequent baseline use of GLP-1 RA (60% vs. 27%) and resmetirom (20% vs. 7%). Groups were otherwise similar by age, sex, ethnicity, diabetes status, and baseline liver stiffness. Oral microbiome beta diversity, assessed by Aitchison distance, differed significantly by progression status ($p = 0.012$). In adjusted analyses, a composite of 13 menaquinol biosynthesis pathways was significantly lower among progressors ($\beta = -5.75$, $p = 0.023$) (**Figure 1).** The other pre-specified pathways showed no meaningful difference between groups: sugar metabolism was slightly higher in progressors but not significantly so, and LPS biosynthesis was unchanged. This suggests that the reduced vitamin K2 capacity is a targeted finding rather than a sign of a broadly altered oral microbiome. **Conclusion:** In this exploratory analysis, baseline oral microbiome profiles differed between MASLD patients with and without subsequent liver stiffness progression. Reduced predicted vitamin K/menaquinol biosynthesis capacity was associated with progression, suggesting a potential oral microbial-functional signal. Larger studies are needed to validate these findings and evaluate whether oral microbiome profiling can improve noninvasive risk stratification for fibrosis progression in MASLD.

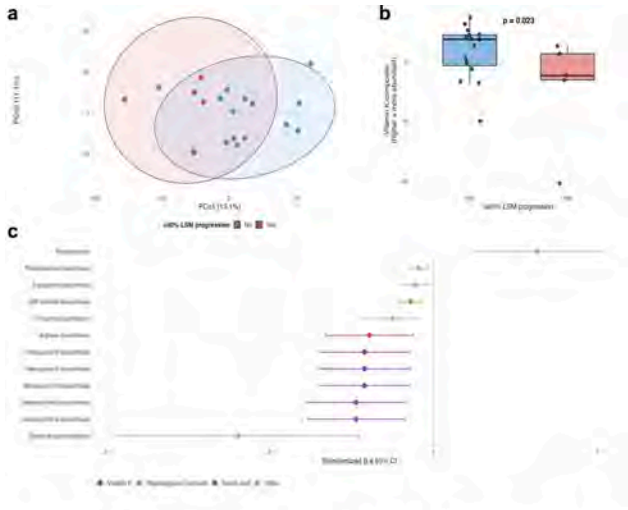


Figure 1. Baseline oral microbiome composition and vitamin K biosynthesis capacity distinguish MASLD patients with liver stiffness progression. DAMILE prospective cohort, longitudinal subset (N=20; 5 progressors, 15 non-progressors); progression defined as ≥30% LSM increase on paired VCTE ≥6 months apart. **(a)** Aitchison-distance PCoA of baseline oral microbiome by progression status with 95% confidence ellipses; PERMANOVA adjusted for age, sex, BMI, and ethnicity, p=0.012. **(b)** PC1 of a 13-pathway menaquinol (vitamin K) biosynthesis composite, significantly lower in progressors under full clinical adjustment (β=−5.75, p=0.023). **(c)** Standardized β (±95% CI) for the top 12 progression-associated pathways, by functional category. Analyses are exploratory and hypothesis-generating.

Disclosures: Adeeba Tak:Nothing to Disclose, Yulu He: Nothing to Disclose, Maryfe Coronel Novoa:Nothing to Disclose, Mark Miller:Nothing to Disclose, Victor Llanes: Nothing to Disclose, Asher Leviton:Nothing to Disclose, Jeremiah Faith:Nothing to Disclose, Frances Lee:Nothing to Disclose, Ryan Walker:Nothing to Disclose, Dania Valvi:Nothing to Disclose, Scott Friedman:89 Bio: Consultant, Boehringer Ingelheim: Consultant, Boston Pharmaceutical: Consultant, Bristol Myers Squibb: Consultant, Merck: Consultant, Glycotest: Consultant, Morphic Therapeutics: Consultant, HepGene: Consultant, North Sea Therapeutics: Consultant, Pfizer Pharmaceuticals: Consultant, Sagimet: Consultant, Scholar Rock: Consultant, Prosciento: Consultant, Seal Rock: Consultant, Surrozen: Consultant, Takeda Pharmaceuticals: Consultant, Junevity: Consultant, Therasid Bio: Consultant, Ochre Bio: Consultant, Gordian Biotechnology: Consultant, Abalone Bio: Grant/Research Support, Prosciento: Consultant, Abbvie: Consultant, Curie Bio: Consultant, Forth Therapeutics: Advisor, Mediar Therapeutics: Consultant, Hepta BIo: Consultant, In sitro: Consultant, Kerna Ventures: Consultant, Resolution Therapeutics: Consultant, Takeda: Consultant, Variant Bio: Consultant, Meena Bansal:Madrigal: Advisor, Fibronostics: Advisor, NOVO Nordisk: Advisor, GSK: Advisor, Merck: Advisor, Boeheringer-Ingelheim: Advisor, Boston Pharma: Advisor, The Kinetix Group: Advisor, Corcept: Advisor, Xiaotao Zhang: Nothing to Disclose.

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1123 | TRANSCRIPTIONAL UPREGULATION OF MICROBIAL MUCIN GLYCAN DEGRADATION IN THE GUT MICROBIOME OF NON-CIRRHOTIC PORTAL HYPERTENSION

Wesam Aleyadeh[1] Jenna Oringher[2] Meital Gewirtz[3] Yue Zhang[4] Neelam Redekar[5] James Haddad[6] Rownock Afruza[7] Moumita Chakraborty[7] Julian Hercun[8] Maria Mironova[9] Justin Lack[4] David Kleiner[10] Michail Lionakis[11] Christopher Koh[7] Theo Heller[12], [1]National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, [2]University of Pittsburgh & Carnegie Mellon University, [3]Northwestern University Feinberg School of Medicine, [4]NIH, [5]NIAID/NIH, [6]University of Wisconsin, [7]NIDDK, NIH, [8]Centre hospitalier de l'Universite de Montreal, [9]UCSD, [10]National Cancer Institute, Bethesda, [11]NIAID, NIH, [12]NIH/NIDDK

Background: Non-cirrhotic portal hypertension (NCPH) produces portal hypertension without the synthetic dysfunction of cirrhosis, offering a model to study portal hypertensive pathobiology without that confounder. Gut dysbiosis is well described in cirrhosis, but the NCPH microbiome remains poorly characterized. **Methods:** Cross-sectional analysis of 26 NCPH patients and 32 healthy controls (HC). DNA and RNA were extracted from stool and shotgun sequenced. Functional profiles were assigned to MetaCyc pathways (HUMAnN3). Metatranscriptomic differential expression was tested with a general linear model adjusted for paired metagenomic abundance, age, BMI, and sex. Community-level pathways differentially expressed in NCPH ($q < 0.1$, Benjamini-Hochberg) were stratified to the species level. **Results:** 111 community-level pathways were differentially expressed, all upregulated in NCPH. Two core mucin O-glycan degradation pathways were among the most strongly enriched: the superpathway of N-acetylglucosamine, N-acetylmannosamine, and N-acetylneuraminate degradation (GLCMANNANAUT-PWY; log2FC 3.34, $q = 0.006$) and the superpathway of N-acetylneuraminate (sialic acid) degradation (P441-PWY; log2FC 2.40, $q = 0.040$). These pathways catabolize the structural and terminal sugars of intestinal mucin. Of 65 differentially expressed species-level pathways, mucin glycan degradation was attributed to *Roseburia inulinivorans* (log2FC 1.30, $q = 0.084$), a host-glycan-foraging member of the Lachnospiraceae. Recognized mucolytic taxa, including *Ruminococcus gnavus* and *R. torques*, were among species associated with NCPH. **Conclusion:** The NCPH gut metatranscriptome shows coordinated upregulation of mucin glycan degradation, indicating increased microbial foraging on the colonic mucus barrier. Because mucus thinning promotes epithelial contact and translocation of microbial products through the portal circulation, this functional shift is a plausible, cirrhosis-independent contributor to portal hypertensive disease. Findings are limited by sample size and cross-sectional design and warrant validation with direct assessment of mucus integrity and gut barrier function.

Disclosures: Wesam Aleyadeh:Nothing to Disclose, Jenna Oringher:Nothing to Disclose, Meital Gewirtz: Nothing to Disclose, Yue Zhang:Nothing to Disclose, Neelam Redekar:Nothing to Disclose, James Haddad:Nothing to Disclose, Rownock Afruza:Nothing to Disclose, Moumita Chakraborty:Nothing to Disclose, Julian Hercun:Gilead: Consultant, Ipsen: Consultant, GSK: Consultant, Advanz: Consultant, Maria Mironova:Nothing to Disclose, Justin Lack: Nothing to Disclose, David Kleiner:Nothing to Disclose, Michail Lionakis:Nothing to Disclose, Christopher Koh:Nothing to Disclose, Theo Heller:Nothing to Disclose.

1124 | AKKERMANSIA MUCINIPHILA ATTENUATES TUMORIGENESIS IN A MOUSE MODEL OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE-ASSOCIATED HEPATOCELLULAR CARCINOMA

Hsin Jou Lee[1] Ting Ting Chang[1], [1]National Yang Ming Chiao Tung University

Background: Metabolic dysfunction-associated steatotic liver disease-associated hepatocellular carcinoma (MASLD-associated HCC) is a common cause of liver disease, with a complex pathology including chronic inflammation, oxidative stress, and gut microbiota dysbiosis. *Akkermansia Muciniphila*, a human intestinal symbiont, has been found to protect the liver by reducing fatty liver and inflammation. The aim of the study was to investigate the beneficial effect and mechanism of heat-inactivated *Akkermansia Muciniphila* on MASLD-associated HCC. **Methods:** To generate a mouse model of MASLD-associated HCC, eighteen-day-old male C57BL/6J mice were administrated diethylnitrosamine via intraperitoneal injection and fed a high-fat diet for 24 weeks. The heat-inactivated *Akkermansia Muciniphila* was administered orally for 4 weeks. Serum fasting glucose, lipid profile, and liver function were followed. Tumor nodules in liver tissues were calculated. Meanwhile, hepatic protein expressions were analyzed using Western blotting. **Results:** The administration of heat-inactivated *Akkermansia Muciniphila* decreased serum triglyceride, total

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cholesterol, alanine transaminase, and aspartate aminotransferase levels in MASLD-associated HCC mice. In parallel, the average hepatic tumor number and liver-to-body weight ratio in MASLD-associated HCC mice were reduced by the treatment of heat-inactivated *Akkermansia Muciniphila*. Moreover, the heat-inactivated *Akkermansia Muciniphila*-treated group showed downregulated proliferative, angiogenic, and inflammatory protein expressions as well as upregulated cell apoptotic protein expressions in the liver tissues of MASLD-associated HCC mice. **Conclusion:** Our current observations suggested that heat-inactivated *Akkermansia Muciniphila* might inhibit tumorigenesis through modulating the proliferative, angiogenic, inflammatory, and cell apoptotic signaling pathways in MASLD-associated HCC. Further experiments are warranted to elucidate the underlying mechanisms and evaluate the clinical potential of these findings.
Disclosures: Hsin Jou Lee:Nothing to Disclose, Ting Ting Chang:Nothing to Disclose.

1125 | A CASE OF FECAL MICROBIOTA TRANSPLANTATION FOR RECURRENT HEPATIC ENCEPHALOPATHY

JIayin Wang[1] Chao Yang[1] Yanchao Fu[1] Huiling Xiang[1], [1]Central Hospital, Tianjin University Tianjin Institute of Hepatobiliary Disease

Background: Hepatic encephalopathy (HE) is a common complication of liver cirrhosis. Standard regimens including lactulose, rifaximin and L-ornithine-L-aspartate are routinely applied, but some patients still experience recurrent episodes, which may lead to irreversible brain injury. Fecal Microbiota Transplantation (FMT) can reconstruct intestinal microecology and provides a novel therapeutic strategy for refractory hepatic encephalopathy. **Methods:** A 59-year-old male had a 6-year history of liver cirrhosis, with comorbidities of upper gastrointestinal bleeding, hypertension, post-splenectomy status, and hypothyroidism after iodine-131 therapy for hyperthyroidism. Over the past year, the patient has repeatedly experienced confusion of consciousness, tremors in the hands, and a decline in calculation ability. Despite conventional treatments such as liver protection and lowering blood ammonia, the effects have been unsatisfactory. Cranial MRI excluded cerebrovascular accidents and intracranial space-occupying lesions. The admission blood ammonia level was 89 μmol/L, and the patient was diagnosed with overt type C hepatic encephalopathy (West-Haven grade 2). Gut microbiota analysis revealed severe dysbiosis: *Veillonella* accounted for 58.95% of the intestinal flora, the B/E ratio was only 0.0164(the normal value was greater than 1.), and microbial diversity was markedly reduced, consistent with grade III intestinal dysbiosis. FMT was recommended. Pretreatment with lactulose and rifaximin was given for 5 days to reduce the abundance of *Veillonella*. Oral FMT capsules were administered (each capsule contained 0.211 g bacterial powder, equivalent to 0.2918×10^{14} CFU). Two days after the initial dose of 6 capsules once daily, the patient developed high fever, general myalgia and upper limb rash, accompanied by significantly elevated inflammatory markers. The presentation was considered a transient Herxheimer reaction related to FMT, which resolved after symptomatic management. A total of 45 capsules were subsequently completed via a dose-escalation regimen with good tolerance. **Results:** The patient was followed up for 11 months after FMT. No recurrence of hepatic encephalopathy symptoms was observed. Repeat examination showed significant recovery of intestinal microbiota diversity, a marked reduction in *Veillonella* abundance, and obvious improvements in the proportion of Lachnospiraceae, B/E ratio and short-chain fatty acid synthesis function. Intestinal mucosal barrier injury was alleviated. No adverse events such as infection, liver failure, liver transplantation or death occurred. **Conclusion:** For patients with recurrent hepatic encephalopathy refractory to conventional treatment, oral capsule-based FMT can effectively correct intestinal dysbiosis and prevent disease recurrence with satisfactory safety, demonstrating high clinical application value.

Table 1 Comparison of data before and after FMT

Index	Before FMT	1 month after FMT	6 months after FMT
Detection date	2025/06/20	2025/09/18	2026/03/12
Intestinal health total score	32	58	57
Microecology health index	42	56	60
Flora balance	Grade III dysbiosis	Grade II dysbiosis	Grade II dysbiosis
Core microbes	Severe deficiency	Low abundance	Low abundance
Beneficial bacteria	Low abundance	Normal	Normal
Diversity index	4.6493	6.4921	7.8137
Intestinal mucosal barrier	Moderate injury	Mild injury	Mild injury
Veillonella (%)	58.95	20.68	6.99
Lachnospiraceae (%)	0.87	5.59	6.67
B/E ratio(Normal value > 1)	0.0164	0.8556	2.6720
Short-chain fatty acid synthesis capacity			
Formic acid(Normal value > 60)	20	71	65
Acetic acid(Normal value > 60)	6	37	22
Propionic acid(Normal value > 60)	98	79	58
Butyric acid (Normal value > 60)	20	66	74
Valeric acid(Normal value > 60)	78	95	99

Disclosures: JIayin Wang:Nothing to Disclose, Chao Yang:Nothing to Disclose, Yanchao Fu:Nothing to Disclose, Huiling Xiang:Nothing to Disclose.

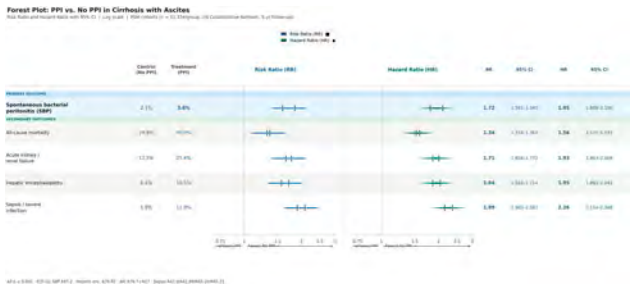
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1126 | PROTON PUMP INHIBITORS AND ADVERSE OUTCOMES IN CIRRHOSIS: A LARGE PROPENSITY-MATCHED U.S. COHORT STUDY

Bolaji Ayinde[1] Bright Nwatamole[2] Abidemi Akinrinmade[3] Ihunanya Kanu[4] Kia Saeian[5], [1]Northeast Georgia Medical Center, [2]Zucker School of Medicine at Hofstra, [3]SUNY Upstate University, [4]Baptist Memorial Hospital- Golden Triangle, [5]Medical college of Wiscosin

Background: Proton pump inhibitors (PPIs) are common in patients with cirrhosis, and studies show inappropriate use in 47–60% of cases, frequently without guideline-concordant indications. Acid suppression can promote small intestinal bacterial overgrowth, and bacteria translocation through changes in the gut microbiome and inhibition of neutrophil oxidative burst may increase the risk for spontaneous bacterial peritonitis (SBP) or other infectious complications. Although PPI exposure has been associated with adverse outcomes in cirrhosis due to ascites, that association remains controversial secondary to a concern about confounding by indication. We investigated the association of PPI exposure with risks of SBP, hepatic encephalopathy, kidney injury, sepsis and mortality in a large real-world cohort. **Methods:** We performed a retrospective cohort study leveraging the US Collaborative Network in TriNetX over 114 million records, between January 1, 2019 and March 29, 2026. Adults with cirrhosis and ascites were identified and stratified by PPI use. Propensity score matching on demographics, malnutrition, and hepatic function panel variables yielded 51,334 patients per cohort. Outcomes were assessed over 5 years post-index. **Results:** PPI use was associated with increased risks of SBP (HR 1.95, 95% CI 1.81–2.11), hepatic encephalopathy (HR 1.95, 95% CI 1.86–2.04), acute kidney injury (HR 1.93, 95% CI 1.86–2.01), sepsis (HR 2.26, 95% CI 2.15–2.37) and all-cause mortality (HR 1.56, 95% CI 1.53–1.59). Kaplan–Meier analyses revealed significantly diminished event-free survival among PPI users (log-rank $p < 0.001$). **Conclusion:** In this large propensity-matched cohort, PPI exposure was associated with significantly increased risks of infectious complications, organ failure, and death in patients with cirrhosis and ascites. However, the retrospective design and reliance on administrative data preclude causal inference; residual confounding by disease severity, PPI indication, dose, and duration cannot be excluded despite matching. These findings support more judicious, guideline-based PPI prescribing in this population and warrant prospective validation.



Disclosures: Bolaji Ayinde:Nothing to Disclose, Bright Nwatamole:Nothing to Disclose, Abidemi Akinrinmade: Nothing to Disclose, Ihunanya Kanu:Nothing to Disclose, Kia Saeian:Abbvie: Grant/Research Support.

1127 | GUT MICROBIOME ALTERATIONS IN PATIENTS WITH CHRONIC HEPATITIS AND CIRRHOSIS: A CROSS-SECTIONAL STUDY

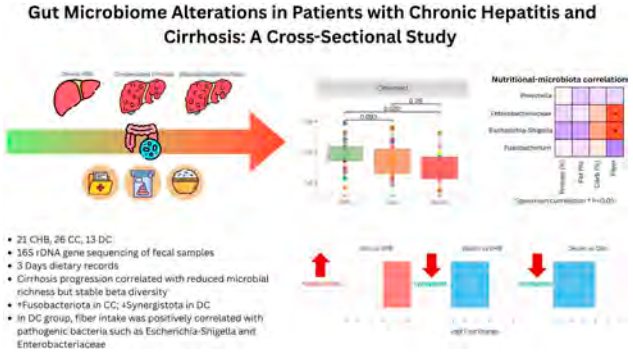
Poonyisa Tangsermvong[1] Pongphob Intaraprasong[1] Tanawat Jongraksak[1] Nantaporn Srivanitchapoom[1] Sarita Ratana-Amornpin[1] Sawannee Sutheeworapong[2] Pinidphon Prombutara[3] Abhasnee Sobhonslidsuk[1], [1]Ramathibodi Hospital, [2]King Mongkut's University of Technology Thonburi, [3]Mod Gut Co., Ltd.

Background: Gut dysbiosis in decompensated cirrhosis contributes to liver-related complications, and its pattern is influenced by ethnicity, dietary intake, and environment. Most current data are derived from Western populations who consume high-fat diets. This study characterizes the gut microbiota of Thai patients with chronic hepatitis B (CHB), compensated cirrhosis (CC), and decompensated cirrhosis (DC) in a population where rice is the primary dietary staple, and also explores the association between microbiota patterns and important factors. **Methods:** 60 participants (21 with chronic hepatitis B, 26 with compensated cirrhosis, and 13 with decompensated cirrhosis) were enrolled. Clinical and nutritional data (3-day dietary records) were collected alongside fecal samples. Gut microbiota was characterized via 16S rRNA gene sequencing on the Illumina MiSeq platform. Bioinformatic analysis was performed to assess microbial composition, alpha and beta diversity, and differential abundance. Spearman's rank correlation was used to evaluate relationships between microbial taxa and clinical/nutritional parameters. **Results:** Microbial richness (Observed index) significantly decreased as disease severity progressed from CHB to DC ($p = 0.022$), although beta diversity remained consistent across groups. At the phylum level, Fusobacteriota was more abundant in the CC

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group, while Synergistota showed a significant reduction in the DC groups (q = 0.002). At the genus level, a distinct finding was that *Faecalibacterium* abundance remained stable across stages, in contrast to the findings from Western studies. This stability may result from high intake of resistant starch type 3 present in rice and low consumption of animal fat. Additionally, fiber intake in the CC group (average 11.1 g/day) showed a strong positive correlation with beneficial *Prevotella* (r = 0.43, p < 0.05). Conversely, in the DC group (average 9.9 g/day), there was an increase in pathogenic bacteria, including *Escherichia-Shigella* (r = 0.67, p < 0.01) and *Enterobacteriaceae* (r = 0.65, p < 0.05). **Conclusion:** Alpha diversity decreased in patients with decompensated cirrhosis. Beneficial bacteria decreased, while pathogenic bacteria increased as the severity of liver cirrhosis worsened. However, in Thai patients with decompensated cirrhosis, the number of Synergistota decreased, but that of *Faecalibacterium* did not change. Differences in dietary patterns and environment may explain the findings. Further study may be warranted.



Disclosures: Poonyisa Tangsermvong:Nothing to Disclose, Pongphob Intaraprasong:Nothing to Disclose, Tanawat Jongraksak:Nothing to Disclose, Nantaporn Srivanitchapoom:Nothing to Disclose, Sarita Ratana-Amornpin:Nothing to Disclose, Sawannee Sutheeworapong:Nothing to Disclose, Pinidphon Prombutara:Nothing to Disclose, Abhasnee Sobhonslidsuk: Nothing to Disclose.

★ 1128 | GUT MUTI-OMICS PROFILES ASSOCIATED WITH SPONTANEOUS HBSAG SEROCLEARANCE IN CHRONIC HEPATITIS B

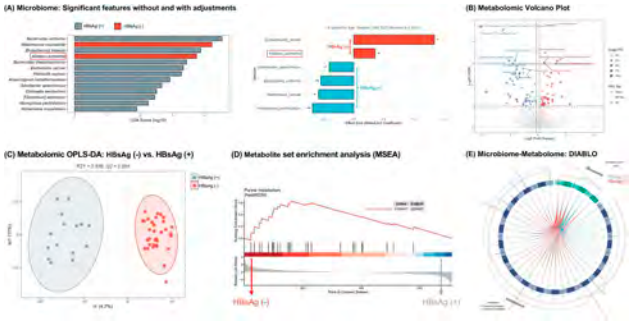
Saisai Zhang[1] Zhe Zhang[2] Lu Li[2] Ning Ma[2] Wenyi Tan[2] Lung-Yi Mak[2] Man-Fung Yuen[2] Wai-Kay Seto[2], [1] 1 The University of Hong Kong; 2 The University of Hong Kong-Shenzhen Hospital, [2] 1 The University of Hong Kong

Background: Seroclearance of hepatitis B surface antigen (HBsAg) is a prerequisite for functional cure in chronic hepatitis B (CHB), yet its underlying mechanisms remain poorly understood. We aimed to characterize gut microbiome and metabolomic signatures associated with spontaneous HBsAg seroclearance using a multi-omics approach. **Methods:** We enrolled 48 treatment-naïve CHB patients with prior documented HBsAg-positivity ≥ 6 months. Of these, 33 individuals achieved sustained HBsAg seroclearance (HBsAg-negative for ≥ 6 months with undetectable HBV DNA < 10 IU/mL), and 15 remained HBsAg positive serving as controls. Fecal samples were subjected to full-length 16S rRNA sequencing (PacBio) and widely targeted metabolomics. Multi-omics integration was performed using Data Integration Analysis for Biomarker discovery using Latent cOmponents (DIABLO). **Results:** Among the participants (38% male, median age 66 years), patients with spontaneous HBsAg seroclearance had a median seroclearance duration of 7.2 years. No significant differences in α-diversity were observed between groups; however, β-diversity analysis demonstrated distinct microbial community structures (PERMANOVA, p = 0.001). Linear Discriminant Analysis Effect Size (LEfSe) identified enrichment of *Alistipes putredinis* in the HBsAg-negative group, whereas *Bacteroides uniformis*, *Bacteroides caccae*, and *Monoglobus pectinilyticus* were enriched in the control group (LDA score > 2, p < 0.05), which remained significant after multivariable adjustment using MaAsLin3 for age, sex, liver stiffness, and T2DM. Metabolomic profiling identified 311 differential metabolites between groups, with 134 metabolites significantly enriched in the HBsAg-negative group. Orthogonal partial least squares discriminant analysis (OPLS-DA) demonstrated a clear separation of metabolomic profiles between the two groups (R^2Y = 0.946, Q^2 = 0.564, p < 0.005). Metabolite set enrichment analysis (MSEA) revealed the significant enrichment of purine metabolism in the HBsAg-negative group (p = 0.005), which has previously been reported associated with immune reprogramming. Integrative analysis using DIABLO and correlation analysis consistently identified 3,4-dimethylbenzoic acid as a key metabolite enriched in the HBsAg-negative group, which was positively correlated with *Alistipes putredinis* and inversely associated with *Bacteroides uniformis* and *Monoglobus pectinilyticus* (|rho| > 0.3, p < 0.05). **Conclusion:** Spontaneous HBsAg seroclearance is associated with distinct gut microbial and metabolomic profiles. The enrichment of *Alistipes putredinis* and its associated metabolite 3,4-dimethylbenzoic acid highlights a potential microbiota-metabolite axis involved in functional cure of CHB. *Supported by Shenzhen Natural Science Foundation Basic Research Fund-*

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General Program (JCYJ20250604180826035).



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★ 1129 | INTESTINAL PATHOBIONT AGGRAVATES LIVER INJURY IN WESTERN DIET INDUCED MASLD

Einav Hubel Manor[1] Mohamed Abdelnabi[1] Henry Nguyen[2], [1]University of Calgary, [2]University of Calgary Cumming School of Medicine

Background: The gut–liver axis integrates dietary, microbial, and immune cues that influence hepatic homeostasis and disease progression. A Western diet rich in fat and sugar (HFHS) promotes metabolic stress, lipid accumulation, and chronic inflammation. These features characterize metabolic-associated steatotic liver disease (MASLD), a growing global health burden linked to obesity and insulin resistance. Progression to steatohepatitis and fibrosis is driven by both metabolic and immune dysregulation. *Helicobacter hepaticus* (Hh) is an intestinal pathobiont capable of aggravating liver steatosis. However, the long-term effects of Hh in shaping immune responses along the gut–liver axis under Western-diet-induced metabolic stress remain poorly defined. We aimed to determine how Hh drives immune activation and fibrogenesis in the liver and colon **Methods:** Male C57BL/6 mice were maintained on an HFHS diet for 40 weeks with or without Hh infection (n = 5 per group). Flow cytometry (FACS) profiled hepatic and colonic leukocytes for $CD45^+$ subsets, including macrophages, T cells ($CD4^+$, $CD8^+$), Th1, Th17, $Foxp3^+$ Tregs, $ROR\gamma t^+$ induced Tregs, dendritic cells (DCs), and neutrophils. Hepatic mRNA expression of inflammatory (*Tnf, Ccl2*) and fibrogenic (*Col1a1, Acta2*) genes were quantified by qPCR. Liver fibrosis was evaluated by Masson's Trichrome staining and scored blinded by a pathologist. **Results:** In the liver, FACS analysis showed that HFHS + Hh mice had elevated $CD45^+$ cell infiltration, T cells, and Th17 populations ($p < 0.01$), along with increased $Foxp3^+$ and $ROR\gamma t^+$ Tregs ($p < 0.05$–0.001) and macrophages. qPCR revealed higher *Tnf*, *Ccl2*, *Col1a1*, and *Acta2* expression, correlating with fibrogenic activation. Histological analysis confirmed greater collagen deposition in HFHS + Hh livers than HFHS alone. In the colon, FACS revealed a parallel trend with increased $CD45^+$ cells, Tc cells, immature thymocytes, DC subsets (moDCs, MoDr DCs), and neutrophils ($p < 0.05$), indicating coordinated immune activation along the gut–liver axis **Conclusion:** Chronic Hh colonization under Western-style dietary stress amplifies immune activation and fibrogenic remodeling within the liver and extends inflammation in the colon. Our parallel observation in the colon supports the idea of coordinated immune signaling along the gut–liver axis in MASLD, though it remains to be determined whether hepatic T cells are locally expanded or recruited from the intestinal compartment.

Disclosures: Einav Hubel Manor:Nothing to Disclose, mohamed Abdelnabi:Nothing to Disclose, Henry Nguyen:Nothing to Disclose.

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1130 | EFFECTS OF *ILEIBACTERIUM VALENS* SUPERNATANT IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE IN MICE

Titilayo Olotu[1] Julie Centofanti[1] Shifat-E Ferdous[1] Matthew Dilts[1] Shannon Boehme[1] Jessica Ferrell[1], [1]Northeast Ohio Medical University

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) has a current prevalence of more than 30% among American adults, and its global prevalence is projected to be 55% by 2040, making this condition a global public health issue. The involvement of glucose, lipid, and inflammatory pathways in MASLD suggests that exploring a range of interventions is necessary. Takeda G protein-coupled receptor 5 (TGR5) is a bile acid receptor that regulates glucose homeostasis, inflammation, and energy expenditure. Previously, our lab discovered that $Tgr5^{-/-}$ mice fed a high-fat, high-fructose diet had increased steatosis but were protected from hepatic inflammation and fibrosis, and simultaneously had significantly increased relative abundance of *Ileibacterium valens* (*I. valens*) in the gut. *I. valens* is a newly identified species of the family Erysipelotrichaceae; prior research regarding the function of *I. valens* with respect to lipid metabolism is limited and controversial. We previously determined that administration of *I. valens* may induce hepatic reverse cholesterol transport in mice. Because evidence suggests that omitting bacteria and administering post-biotics in the form of supernatant may be safer than live probiotics, we next investigated the effects of *I. valens* supernatant in mice. **Methods:** To determine the physiological function of *I. valens* supernatant, we gavaged *I. valens* supernatant (SN) or sterile OTEB (vehicle) twice weekly to male C57BL/6J mice and simultaneously fed a high-fat, high-fructose diet (40% kcal fat, 20% kcal fructose, and 2% cholesterol) for 8 weeks. Lipid metabolism and glucose metabolism were assessed, and histology was performed to determine how *I. valens* supernatant may modulate lipid metabolism *in vivo*. **Results:** *I. valens* supernatant induces a decrease in hepatic free fatty acid (FFA) and a reduced trend in serum triglyceride & FFA. An increase in hepatic glucose uptake (*Glut2, Pygl, Pgcla*, *Cpt2*), and a decrease in steatosis via reduced macrovascular fat droplet counts and sizes. It inhibits hepatic inflammation (*Tnfa, Tnfr1b, NFkb*) & fibrosis (*Col1a2*) signaling. *I. valens* supernatant also induces ileal and colon lipid transporters (*Ldlr, Lxr, Abcg1*). Therefore, *I. valens* supernatant may affect lipid metabolism to alleviate MASLD. **Conclusion:** Our results indicate that *I. valens* supernatant may exert protective effects against diet-induced obesity and MASLD by increasing hepatic glucose uptake to enhance lipid metabolism and inhibiting hepatic inflammatory gene expression.

Disclosures: Titilayo Olotu:Nothing to Disclose, Julie Centofanti:Nothing to Disclose, SHIFAT-E FERDOUS: Nothing to Disclose, Matthew Dilts:Nothing to Disclose, Shannon Boehme:Nothing to Disclose, Jessica Ferrell: Nothing to Disclose.

1131 | CORRELATION-BASED MOLECULAR NETWORKS REVEAL FUNCTIONAL METABOLITE RELATIONSHIPS IN MASLD AND HCC

Huang Lin[1] Lijun Zhang[2] Ali Lotfi[3] Alan Jarmusch[4] Iris Lee[5] Adam Kim[6] James Morton[7] Alexander Aksenov[3], [1]University of Maryland, [2]Tiposi, [3]University of Connecticut, [4]NIH, [5]Washington University in St. Louis, [6]UConn Health, [7]Gutz Analytics L.L.C.

Background: Molecular networking (MN) has transformed mass spectrometry (MS)-based metabolomics. MN organizes complex datasets into graphs that connect structurally related molecules using MS/MS spectral similarity. While powerful for identifying analogs and propagating annotations within spectral families, spectral similarity captures only one axis of molecular relatedness. Metabolites can be functionally related through shared sources, biosynthetic origins, or coordinated regulation despite limited structural similarity. Such relationships may be reflected in correlations across samples. **Methods:** Here we present MetVAE, a variational autoencoder-based framework for constructing correlation based molecular networks from large-scale metabolomics data. MetVAE addresses key statistical challenges of MS metabolomics data, including compositionality, missingness, confounding effects, and high dimensionality. For this study, we apply MetVAE to analyze metabolomics data from the high-fat diet-fed *MUP-uPA* mouse model of MASLD (Metabolic Dysfunction-Associated Steatotic Liver Disease) driven HCC (hepatocellular carcinoma). Then untargeted fecal metabolomics was performed. **Results:** MetVAE links monoacylglycerols, free fatty acids, bile acids, and fatty acid ethyl esters (FAEEs) in animals fed a high-fat diet. These associations raise the possibility of an endogenous "auto-brewery" route in which microbially produced ethanol esterifies with fatty acids to generate FAEEs, lipotoxic metabolites implicated in alcohol-associated liver disease, without alcohol consumption. These results may help contextualize the long-noted overlap between MASLD and alcohol-associated liver disease. Additionally, alcohol is a known carcinogen, so it may contribute to HCC progression in this model.

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Conclusion: Across more than 20,000 samples, MetVAE scales to repository-sized datasets and reduces technical variation while preserving biological signal. Beyond biological discovery, correlation networks enable data-structure diagnostics, including detection of split chromatographic features, tracing metabolites to shared sources, and revealing coordinated metabolic regulation.
Disclosures: Huang Lin:Nothing to Disclose, Lijun Zhang:Nothing to Disclose, Ali Lotfi:Nothing to Disclose, Alan Jarmusch:Nothing to Disclose, Iris Lee:Nothing to Disclose, Adam Kim:Nothing to Disclose, James Morton:Nothing to Disclose, Alexander Aksenov:Nothing to Disclose.

1132 | BIOFILMS ON LONG-TERM ASCITIC DRAINS: EARLY INSIGHTS INTO DEVICE-ASSOCIATED INFECTION A CASE SERIES

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Background: Biofilm formation on indwelling medical devices is recognised as a key driver of chronic infection, antimicrobial tolerance, and device dysfunction. As long-term ascitic drains (LTADs) are increasingly used for refractory ascites and palliative symptom control, device-associated infection remains poorly understood. There is currently no literature specifically examining biofilm formation on LTADs or related microbial and genomic factors. This novel case series investigates biofilms on explanted LTADs using fluorescence microscopy and metagenomic sequencing. **Methods:** LTADs (Rocket® IPC™) from three patients with refractory ascites were collected. Biofilm architecture was assessed using EDIC microscopy and fluorescence imaging, including SYTO9/PI and DAPI/ConA staining. Drain-associated biofilm material and paired ascitic fluid underwent DNA extraction and shotgun metagenomic sequencing (Illumina NovaSeq X Plus, paired-end 150bp). Host depletion and taxonomic classification were perfomed using standard bioinformatics pipelines. Virulence factors (VFs) and antimicrobial resistance (AMR) determinants profiling used VFDB and CARD/RGI databases. **Results:** Median LTAD duration was 12 months (range 5–18). Two patients had persistent drain-associated infections despite multiple antibiotic courses, requiring drain removal. Conventional cultures identified *Staphylococcus epidermidis* and *Pseudomonas aeruginosa*. Underlying aetiologies were MASLD cirrhosis, cystic fibrosis-related liver disease, and hepatic amyloidosis. Median white cell count was 8 $\times 10^9$/L and median CRP 60 mg/L. EDIC and fluorescence microscopy demonstrated structured biofilm formation on all explanted drains, with dense extracellular matrix and bacterial aggregates. Metagenomic sequencing identified polymicrobial communities including *S. epidermidis*, *P. aeruginosa*, *Enterococcus faecalis*, and *Escherichia coli*. VFs associated with adhesion, biofilm maturation, and immune evasion were identified, including MSCRAMM adhesins, autolysins, proteases, lipases, nucleases, and beta-haemolysin. AMR determinants conferring resistance to multiple antibiotic classes were also detected, notably mecA confirming methicillin-resistant S. epidermidis (MRSE), alongside fluoroquinolone, β-lactam and macrolide resistance. **Conclusion:** This case series provides novel evidence of structured biofilm formation on LTADs. Combined microscopy and metagenomic analysis identified polymicrobial communities containing biofilm-associated VFs and AMR determinants. These findings suggest biofilm formation may contribute to persistent colonisation, antimicrobial tolerance, and LTAD-associated infection. Larger studies are needed to determine whether specific microbial or virulence signatures are associated with adverse clinical outcomes and could inform future infection prevention strategies.

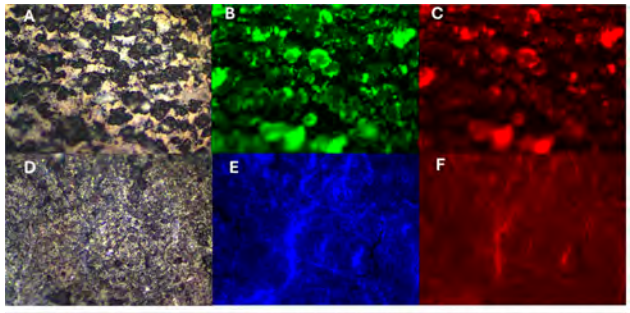


Figure 1. EDIC and fluorescence microscopy of explanted LTAD sections demonstrating structured biofilm formation. A–C: EDIC, SYTO9, and PI staining showing bacterial aggregates. D–F: EDIC, DAPI, and ConA staining highlighting biofilm matrix architecture.

Disclosures: Melissa Zhao:Nothing to Disclose, Sandra Wilks:Nothing to Disclose, Ian Reddin:Nothing to Disclose, Mark Wright:Nothing to Disclose.

1133 | INTEGRATED PLASMA AND FECAL METABOLIC PROFILING IN ALCOHOLIC CIRRHOSIS: ASSOCIATION WITH GUT MICROBIOTA DYSBIOSIS AND ABERRANT BILE ACID–AMINO ACID METABOLISM

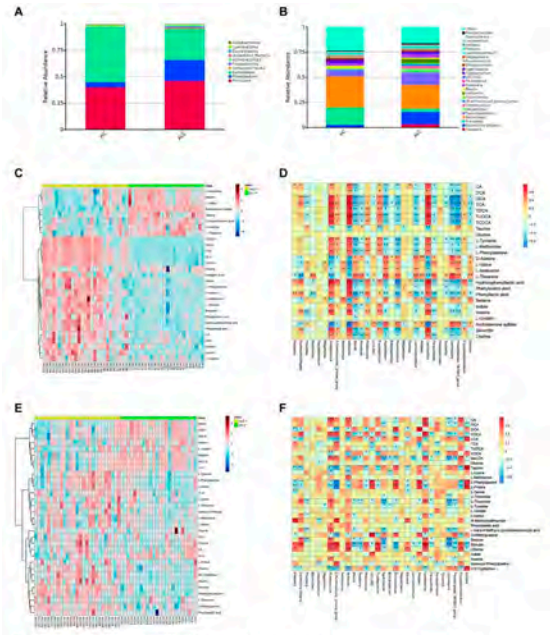
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Background: Gut microbiota critically influences alcohol-associated liver disease progression.

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Although microbial and metabolite alterations are recognized in alcohol-related cirrhosis (ALC), integrated analyses of intestinal microecology together with plasma and fecal metabolomes remain limited. **Methods:** This case-control study compared ALC patients and healthy controls (HC). Fecal microbiota was profiled by 16S rRNA sequencing. Untargeted LC-MS metabolomics was applied to plasma and feces. Group differences and clinical correlations were evaluated. **Results:** 1.Based on the analysis of fecal 16S rDNA amplicon sequencing, the gut microbiota of patients with alcoholic cirrhosis at the genus level exhibits a notable increase in the relative abundances of *Veillonella*, *Lactobacillus*, *Streptococcus*, *Klebsiella*, and *Escherichia*, along with a significant decrease in the relative abundances of *Ruminococcus*, *Bacteroides*, *Alistipes*, *Prevotella*, and other genera.2.The pathway enrichment analysis indicated that bile acid and amino acid metabolism were highly active in plasma. Using VIP values and fold change (FC) screening, we identified significant differences in bile acid- and amino acid-related metabolites. Plasma levels of cholic acid (CA) and deoxycholic acid (DCA) were significantly elevated in patients with alcoholic cirrhosis compared to healthy controls. Additionally, phenylalanine, tyrosine, methionine, indole, phenyllactic acid, phenylacetic acid, inosine, and urobilinogen were increasedns with *Streptococcus*, *Lactobacillus*, and *Veillonella*, while taurine exhibited a negative correlation with these genera.3.The plasma levels of deoxycholic acid (DCA), lithocholic acid (LCA), chenodeoxycholic acid (CDCA), and ursodeoxycholic acid (UDCA) were significantly lower in patients with alcoholic cirrhosis compared to healthy controls, whereas the concentrations of phenylalanine, tyrosine, methionine, threonine, tryptophan, and glycine were elevated. The levels of indole and betaine were relatively reduced. Furthermore, correlation analysis between gut microbiota and fecal differential metabolites revealed that glycoursodeoxycholic acid (GCA), CDCA, and bilirubin exhibited a positive correlation with genera such as *Streptococcus*, *Lactobacillus*, and *Veillonella*. LCA showed a negative correlation with these same genera. Additionally, indole demonstrated a positive correlation with *Streptococcus,* and methionine was positively correlated with *Veillonella*. **Conclusion:** Proliferating opportunistic pathogens (*Streptococcus, Lactobacillus*, *Veillonella*) are positively associated with harmful metabolites (bile acids, aromatic amino acids, indole derivatives) and negatively correlated with beneficial commensals like *Prevotella*. This suggests that specific gut bacteria may drive alcoholic cirrhosis progression via bile acid and amino acid metabolism dysregulation.



A. Alterations in the relative abundance in Phylum level of gut microbiota in patients with alcoholic liver cirrhosis

B. Alterations in the relative abundance in Genus level of gut microbiota in patients with alcoholic liver cirrhosis

C. Heatmap of differential bile acids and amino acid-related metabolites in plasma from patients with alcoholic liver cirrhosis. "Class" indicates the study group: yellow represents the alcoholic liver cirrhosis (ALC) group, and green represents the healthy control (HC) group. Metabolite levels are presented as relative abundances, with red indicating higher levels and blue indicating lower levels.

D. Correlation analysis between differential plasma metabolites and gut microbiota.

E. Heatmap of differential bile acids and amino acid-related metabolites in fecal samples from patients with alcoholic liver cirrhosis. "Class" indicates the study group: yellow represents the alcoholic liver cirrhosis (ALC) group, and green represents the healthy control (HC) group. Metabolite abundance is depicted as relative levels, with red indicating higher abundance and blue indicating lower abundance.

F. Correlation analysis between differential plasma metabolites and gut microbiota. The horizontal axis represents bacterial genera, and the vertical axis represents metabolites. Red denotes positive correlations, blue denotes negative correlations, with color intensity reflecting the strength of the association. * $P < 0.05$, ** $P < 0.01$. ALC: Alcoholic liver cirrhosis group; HC: Healthy control group.

Table1.Alterations in bile acid profiles in plasma and feces among patients with alcoholic liver cirrhosis

			Plasma (ALC/HC)	Feces (ALC/HC)
Unconjugated bile acid	Primary bile acid	cholic acid（CA）	↑	NA
		chenodeoxycholic acid（CDCA）	Undetected	↓
		deoxycholic acid（DCA）	↑	↓
	Secondary bile acid	lithocholic acid（LCA）		↓
		Isolithocholic acid（IsoLCA）	Undetected	NA
		ursodeoxycholic acid（UDCA）		↓
Conjugated bile acid	Primary bile acid	glycocholic acid（GCA）	↑	NA
		taurocholic acid（TCA）	↑	NA
	Secondary bile acid	Tauroursodeoxycholic acid（TCDCA）	↑	Undected
		tauroursodeoxycholic acid（TUDCA）	↑	NA
		taurodeoxycholic acid（TDCA）	↑	Undected

Table2. Alterations in Plasma and Fecal Amino Acid Profiles in Patients with Alcoholic Liver Cirrhosis

Metabolite	Metabolic pathways	Plasma (ALC/HC)	Feces (ALC/HC)
Glycine	Alanine metabolism	NA	↑
	Arginine and proline metabolism		
	Glutathione metabolism		
	Bile acid synthesis		
Taurine	Taurine metabolism	↑	NA
	Bile acid synthesis		
Betaine	Glycine and serine metabolism	↓	↓
	Methionine metabolism		
Methionine	Glycine and serine metabolism	↑	NA
	Methionine metabolism		
Threonine	Glycine and serine metabolism	NA	↑
Choline	Methionine metabolism	↑	↑
Sarcosine	Methionine metabolism	↓	NA
Phenylalanine	Phenylalanine and tyrosine metabolism	↑	↑
Tyrosine	Phenylalanine and tyrosine metabolism	↑	↑
Tryptophan	Tryptophan metabolism	NA	↑
Indole	Tryptophan metabolism	↑	↓
Formylanthranilic acid	Tryptophan metabolism	↑	NA
Leucine	Valine, leucine and isoleucine degradation	↓	↑

NA indicates no statistically significant difference. The red arrow denotes an increase in the alcoholic liver cirrhosis group, while the blue arrow denotes a decrease in the alcoholic liver cirrhosis group.

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Disclosures: Yifan Xu:Nothing to Disclose, HUICHUN XING:Nothing to Disclose, Minghui Li:Nothing to Disclose.

1134 | THE INTRAHEPTIC MICROBIOME OF CIRRHOTIC PATIENTS

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Background: The microbiome has been implicated in numerous pathological processes, including the progression and exacerbation of chronic liver diseases. Significant gut microbial dysbiosis has been demonstrated across multiple etiologies of liver disease and significant associations have been found between microbial species and their contribution to inflammation, fibrosis and disease progression. While internal organs have traditionally been considered sterile, emerging evidence suggests that microbial DNA may be detectable within solid organs, including the liver. The composition and potential relevance of these intrahepatic microbial signatures remain poorly understood. We therefore sought to characterize microbial signatures within human cirrhotic liver tissue in a pilot study. **Methods:** Explanted liver tissue was obtained from patients undergoing orthotopic liver transplantation at our institution or from patients undergoing hepatectomy. DNA was then extracted from tissue and submitted for 16S rRNA gene next-generation sequencing to assess microbial composition and relative abundance within liver tissue. **Results:** Alcohol-associated liver disease (ALD) accounted for 46% of cases, while the remaining patients underwent transplantation for a range of etiologies including primary biliary cholangitis (PBC), acute hepatitis B, biliary atresia, veno-occlusive disease (VOD) and metabolic dysfunction-associated alcohol-related liver disease (Met-ALD). Microbial DNA was detected in liver tissue samples across the cohort. Comparison of patients with alcohol-associated cirrhosis to those with other liver disease etiologies revealed notable differences in microbial composition. The genus *Sphingomonas* accounted for approximately 25% of the relative bacterial abundance in patients with ALD but was virtually absent in patients with non-alcohol related liver diseases. Similarly *Mesorhizobium, Centipeda, Caulobacter and Anaerococcus* were found in ALD patients and not identified in samples from other etiologies. These findings suggest the presence of etiology-specific intrahepatic microbial signatures. **Conclusion:** Our findings provide preliminary evidence supporting the presence of microbial DNA within human cirrhotic liver tissue and suggest that microbial composition may vary according to the underlying etiology of liver disease. Although limited by sample size these observations raise the possibility that distinct intrahepatic microbial communities may contribute to disease-specific pathophysiology. Larger, adequately powered studies are needed to validate these findings and to determine their biological and clinical significance.

Disclosures: Vijay Pandyarajan:Nothing to Disclose, Georgios Voidonikolas:Nothing to Disclose, Ekihiro Seki:Nothing to Disclose.

1135 | ◆ STATIN-USE ASSOCIATED WITH DECREASED DECOMPENSATIONS AND LIVER EVENTS IN PATIENTS WITH PBC

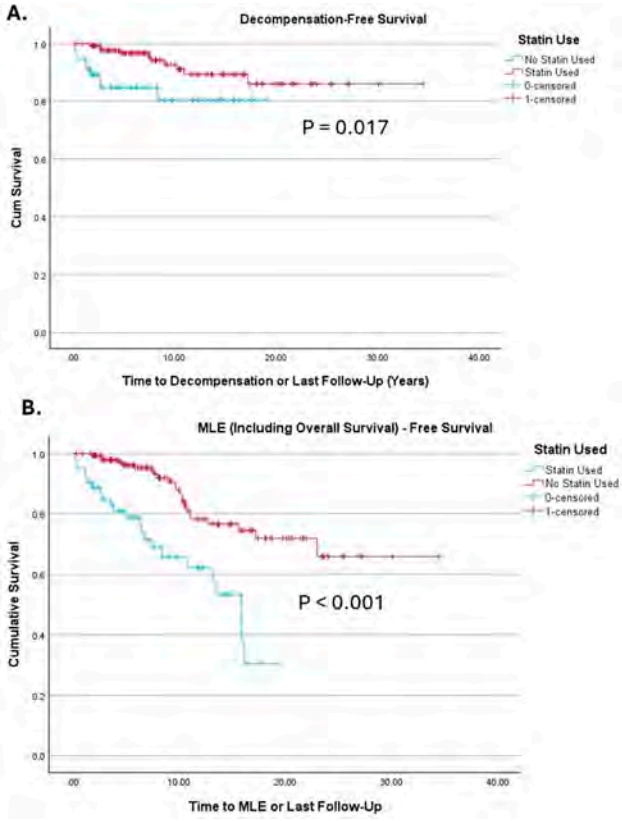
Mark Pedersen[1] Gemma Weijsters[2] Adriaan Van der Meer[3] Gideon Hirschfield[4] Shani Nagler[5] Chloe Nguyen[6] Pietro Invernizzi[7] Marco Carbone[8] Laura Cristoferi[8] Conrado Fernandez Rodriguez[9] Konstantinos Papantoniou[10] Christos Triantos[10] Ellina Lytvyak[11] Aldo Montano-Loza[11] Andrew Mason[11] Guilherme Cancado[12] Claudia Couto[13] Sergio Rodriguez Tajes[14] Helena Hernandez Evole[12] Cynthia Levy[15] Adrielly Martins[16] Xavier Verhelst[17] Agnes Paradissis[18] Alvaro Diaz Gonzalez[19] Henriette Ytting[20] Bettina Hansen[21] Marlyn Mayo[22], [1]UT Southwestern Medical Center, [2]Erasmus MC, Rotterdam, Netherlands, [3]Erasmus University Medical Center, [4]Toronto General Hospital, [5]The Autoimmune and Rare Liver Disease Programme, Division of Gastroenterology and Hepatology, Toron, [6]The Autoimmune and Rare Liver Disease Programme, Division of Gastroenterology and Hepatology, Toront, [7]Fondazione IRCCS San Gerardo dei Tintori, [8]Università degli Studi di Milano-Bicocca, Milano, Italy, [9]Universidad Rey Juan Carlos, Madrid, Spain, [10]University of Patras, Patras, Greece, [11]University of Alberta, Edmonton, Canada, [12]Universidade Federal De Minas Gerais, Belo Horizonte, Brazil, [13]Federal University of Minas Gerais, [14]SRODRIGUEZ@clinic.cat, [15]University of Miami, [16]University of Miami Miller School of Medicine, Miami, United States, [17]Ghent University Hospital, [18]UZ Gent, Gent, Belgium, [19]Hospital Universitario Marqués De Valdecilla, Santander, Spain, [20]Department of Digestive Diseases, Transplantation and General Surgery, Rigshospitalet, [21]Erasmus MC

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Background: The effect of HMG-CoA reductase inhibitors (statins) are underutilized for patients with primary biliary cholangitis (PBC), perhaps due to concerns about liver safety. The effect of statins on liver outcomes in patients with primary biliary cholangitis is not well established. Aim: To investigate the association between statin-use and liver events in patients with PBC. **Methods:** A retrospective chart review at 13 sites across North America, South America, and Europe in the Global PBC Study Group. Decompensation was defined as variceal bleed, ascites, or encephalopathy. A major liver event (MLE) was defined as a decompensation, hepatocellular carcinoma (HCC), liver transplant, or death (any cause). Labs and variables were collected at one year after starting ursodeoxycholic acid (UDCA), which was defined as the T_{12M}. Cox multivariable regression was used to analyze predictors of decompensation and MLE, with statins analyzed as a time-variable covariant. **Results:** 1467 patients with PBC were followed over a mean of 9.7 years. Patients who decompensated were older (56.1 vs. 52.1 years $p < 0.001$), more likely to be cirrhotic at T_{12M} (31.3% vs. 5.7% $p < 0.001$), with a higher alkaline phosphatase (ALP) (225.1 vs 175.4 [CL1] [MP2] IU/L, $p < 0.001$), bilirubin (1.87 vs 0.69 mg/dL, $p < 0.001$) and lower platelets (191 vs. 225 $x10^9$ $p < 0.001$[HL3] [MP4]). There were 234 (16.0%) decompensations, 44 (3.0%) diagnoses of hepatocellular carcinoma, 46 (3.1%) liver transplant, and 162 (17.5%) deaths [CL5] [MP6] (124 [8.5%] liver-related deaths). 224 (17.3%) patients received a statin with a mean statin-use duration of 6.7 years after initiation of UDCA. Statins [CL7] [MP8] was associated with a lower risk of decompensation (aHR 0.22, 0.05-0.93, $p = 0.04$) when controlling for age (aHR 1.07, 1.04-1.09, $p < 0.001$), ALP > 1.67 x upper-limit-of-normal (ULN) (aHR 2.69, 1.65-4.39, <0.001), and bilirubin > ULN (aHR 6.99, 4.25-11.48, $p < 0.001$). Statins was also associated with a lower risk of MLE (aHR 0.49, 0.27-0.88, 0.016), when controlling for age (aHR 1.07, 1.06-1.09, $p < 0.001$), ALP > 1.67x ULN (aHR 1.87, 1.23-2.85, 0.003), and bilirubin > ULN (aHR 6.48, 4.15-10.13, $p < 0.001$[CL9] [CL10] [MP11]). Propensity matched (for bilirubin, ALP, cirrhosis, and age) survival analysis showed improvement in decompensation-free survival and MLE-free survival (both $p = 0.017$ and < 0.001, respectively) [Figure 1]. Only 5 (of 536) patients prescribed a statin stopped treatment due to liver-related issues (elevated liver chemistries). **Conclusion:** In this international cohort, use of statins during the course of PBC-related liver disease was associated with substantially lower risk of cirrhosis-related clinical events.



Disclosures: Mark Pedersen:Gilead: Grant/Research Support, Mirum Pharmaceuticals: Advisor, Ipsen: Advisor, Gemma Weijsters:Nothing to Disclose, Adriaan Van der Meer:Nothing to Disclose, Gideon Hirschfield:Intercept: Consultant, GSK: Consultant, CymaBay: Consultant, Ipsen: Consultant, Falk: Consultant, Pliant: Consultant, Mirum: Consultant, Advanz: Consultant, Chemomab: Consultant, Gilead: Consultant, Kowa: Consultant, Shani Nagler: Nothing to Disclose, Chloe Nguyen:Nothing to Disclose, Pietro Invernizzi:Nothing to Disclose, Marco Carbone:Nothing to Disclose, Laura Cristoferi:Nothing to Disclose, CONRADO FERNANDEZ RODRIGUEZ:Nothing to Disclose, Konstantinos Papantoniou:Nothing to Disclose, Christos Triantos:Nothing to Disclose, Ellina Lytvyak:Nothing to Disclose, Aldo Montano-Loza:Nothing to Disclose, Andrew Mason: Nothing to Disclose, Guilherme Cancado:Nothing to Disclose, Claudia Couto:Nothing to Disclose, Sergio Rodriguez Tajes:Gilead: Grant/Research Support, Ipsen: Grant/Research Support, Mirum: Grant/Research Support, Helena Hernandez Evole:Nothing to Disclose, Cynthia Levy:Gilead: Grant/Research Support, Ipsen: Grant/Research Support, GSK: Grant/Research Support, Intercept: Grant/Research Support, Calliditas: Grant/Research Support, Zydus: Grant/Research Support, LisCure: Grant/Research Support, TARGET RWE: Grant/Research Support,

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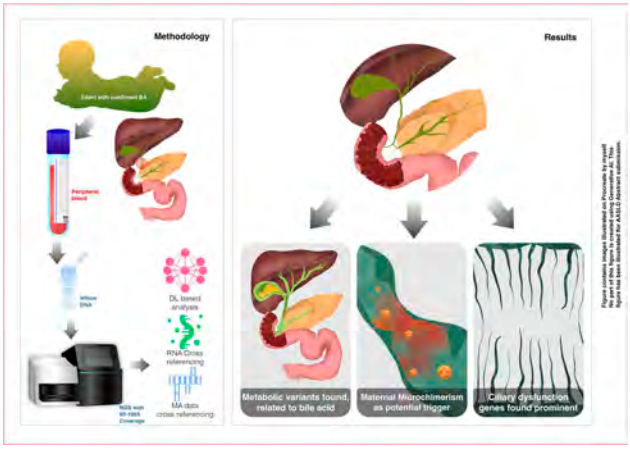
Pliant: Grant/Research Support, NGM: Grant/Research Support, Mitsubishi Tanabe: Grant/Research Support, DISC: Grant/Research Support, Takeda: Grant/Research Support, Kowa: Grant/Research Support, Mirum: Grant/Research Support, Adrielly Martins:Nothing to Disclose, Xavier Verhelst: Ipsen: Speaking and Teaching, Ipsen: Consultant, Gilead: Advisor, Gilead: Grant/Research Support, Gilead: Grant/Research Support, Falk Pharma: Speaking and Teaching, Falk Pharma: Advisor, Mirum: Advisor, Mirum: Speaking and Teaching, Mirum: Consultant, Ipsen: Speaking and Teaching, Ipsen: Consultant, Gilead: Grant/Research Support, Falk Pharma: Advisor, Agnes Paradissis:Nothing to Disclose, ALVARO DIAZ GONZALEZ:IPSEN: Advisor, IPSEN: Speaking and Teaching, IPSEN: Travel and meeting expenses, GILEAD: Advisor, GILEAD: Speaking and Teaching, GlaxoSmithKline: Advisor, Mirum: Advisor, EISAI: Speaking and Teaching, Henriette Ytting:Nothing to Disclose, Nothing to Disclose, Bettina Hansen:Nothing to Disclose, Marlyn Mayo:CymaBay: Grant/Research Support, CymaBay: Consultant, GSK: Grant/Research Support, GSK: Consultant, Intercept: Grant/Research Support, IntraSana: Consultant, Ipsen: Grant/Research Support, Ipsen: Consultant, Mirum: Grant/Research Support, Gilead: Consultant, Gilead: Grant/Research Support, Intercept: Consultant, Mirum: Consultant, Ironwood: Consultant, Kezar: Consultant, Zydus: Consultant.

1136 | ◆ INVESTIGATION OF THE ETIOPATHOGENESIS OF BILIARY ATRESIA USING NEXT-GENERATION SEQUENCING

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Background: Biliary atresia is a disease characterised by partial or complete obstruction of the bile duct in newborns. The result is cholestasis and cirrohsis. It may be fatal. The only management method is a Kasai Portro-enterostomy, which helps the patient survive while waiting for a liver transplant. The exact pathogenesis of BA is partially investigated. Previous studies suggest that the pathogenesis of the disease has a genetic component and may be poly-factorial. In this study, the coding portion (exome) of the patients compared to a healthy exome has been investigated. Variants will be identified and validated through genomic analysis. The impact of the variant on normal physiology and role in biliary atresia will be explored. **Methods:** Peripheral blood was obtained from 5 patients aged 6-8 weeks with confirmed biliary atresia. Whole DNA from peripheral blood was extracted and sequenced with 80-100X coverage on the Illumina platform. The raw data was processed beginning with a quality check, followed by preparation and variant calling compared to control exome. Patient wise pathogenicity and impact scores (such as CADD, PHRED, VEP) were derived. The discovered variants were assigned importance as per their potential impact in the patient and analysed step by step across an inclusive and detailed criteria. To derive a more comprehensive analysis, machine learning and deep learning analysis was also conducted. Publically available data sets were used to obtain expression data for search and validation of findings. **Results:** Detailed analysis from a discovery cohort of 5 patients yielded 29,756 mean variants per patient. The number of missense variants was the largest at 12,474. The variant VCF files were manually filtered for quality and variants potentially playing a role in BA pathology were filtered out for further analysis. From the results, a three-hit explanation of pathogenesis was hypothesized. It was observed that the patient may be experiencing a highly reduced immune tolerance, owing to a variation observed in NOTCH2 (multiple variations in a single patient) and GPC1 (possible frameshift). IL32 was found highly upregulated. It was also observed that loss in the integrity of the epithelial barrier, perhaps because of maternal response to PAMPS, would aggravate Immune response and cause inflammation. Variants in KIF7, TMEM67, CC2D2A, suggest specific failure in duct formation at the embryonic stage. **Conclusion:** The findings provide a potential new understanding of the pathogenesis of biliary atresia. As suggested by previous studies, the disease would begin at birth, from the developmental genetic variants. This may in turn lead to a complex auto-immune response, because of abnormal escalated immune cell activity present in the newborn. The organ specific response, which may be beginning at the closing of the ductus venosus, may be localised in the ciliary epithelium. This creates a progression causing rapid symptoms.

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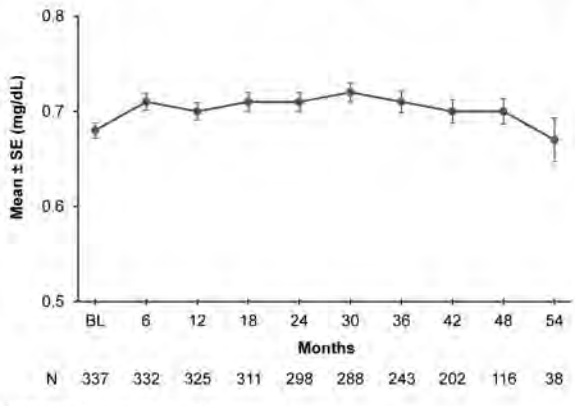
Disclosures: Tarun Sharma:Nothing to Disclose, Yashwant Kumar:Nothing to Disclose, Shailesh Solanki:Nothing to Disclose, Ravi Kanojia:Nothing to Disclose, Sadhna Lal:Nothing to Disclose, Suvradeep Mitra:Nothing to Disclose, Anit Kaur:Nothing to Disclose, Alka Bhatia:Nothing to Disclose.

1137 | ◆ SELADELPAR IS ASSOCIATED WITH STABLE RENAL FUNCTION OVER 5 YEARS OF TREATMENT: INTERIM RESULTS FROM THE ASSURE STUDY

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Background: Seladelpar is a first-in-class delpar (selective PPAR-delta agonist) indicated for the treatment of primary biliary cholangitis in combination with ursodeoxycholic acid (UDCA) in patients (pts) with an inadequate response to UDCA or as monotherapy in pts unable to tolerate UDCA. In the Phase 3, placebo-controlled RESPONSE trial (NCT04620733), mean serum creatinine values were similar overall in the seladelpar and placebo groups, and there were no renal adverse events (AEs). Here, we present an analysis of long-term changes in creatinine, estimated glomerular filtration rate (eGFR), and other assessments of renal safety in pts treated with seladelpar for up to 54 months (M) in the ongoing open-label Phase 3 ASSURE study (NCT03301506). **Methods:** Pts from RESPONSE and legacy seladelpar studies enrolled in ASSURE and received open-label seladelpar 10 mg once daily. Pts were pooled at initiation of seladelpar in either RESPONSE or ASSURE. Mean values and percent change from baseline of creatinine and eGFR were examined up to M54, as were shifts in values from normal to abnormal. Renal-related AEs were assessed using a predefined search strategy. The data cutoff for this interim analysis was Jan 31, 2026. **Results:** This analysis included 337 pts. At seladelpar initiation, mean creatinine and eGFR values were normal (0.68 mg/dL and 97.8 mL/min/1.73 m2) and remained normal through M54 (0.67 mg/dL and 95.6 mL/min/1.73 m2; Figure). Mean (SE) percent changes from baseline at M54 for creatinine and eGFR were 0.1% (2.71) and −1.9% (2.09). Cumulatively through M54, 17 pts (5%) experienced a shift in creatinine from normal to elevated, of which 65% (11/17) resolved while on continued seladelpar treatment (6/17 were either unresolved or unknown as of the data cutoff). Renal-related AEs were infrequent and occurred in 2 pts (0.6%) cumulatively through M54. One pt experienced an event of acute kidney injury secondary to a urinary tract infection and sepsis, and the other pt experienced creatinine increase and proteinuria; both episodes resolved and were assessed by the investigator as not related to seladelpar. **Conclusion:** Renal function remained stable with seladelpar exposure up to M54 in the ASSURE study. Renal-related AEs were infrequent, and there were no events attributed to seladelpar. These data suggest treatment with seladelpar 10 mg has a favorable renal safety profile.

Figure. Mean Creatinine Level Over Time With Seladelpar in Patients With PBC in the ASSURE Study



Data cutoff: January 31, 2026.
BL, baseline; PBC, primary biliary cholangitis.

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1138 | ◆ ALTERED BRAIN REGIONAL FUNCTIONAL NEURAL CONNECTIVITY ASSOCIATES WITH OBJECTIVE MEASURES OF COGNITIVE DYSFUNCTION IN PRIMARY BILIARY CHOLANGITIS

Bradley Goodyear[1] Meredith Borman[1] Laura Stinton[1] Kelly Burak[1] Stephen Congly[1] Mark Swain[2], [1]University of Calgary, [2]University of Calgary Liver Unit

Background: Cognitive impairment is a highly prevalent symptom in primary biliary cholangitis (PBC), involving impairments in memory, attention, and executive function. It occurs in up to 50% of PBC patients and is closely associated with fatigue, however, its neural basis and relationship to clinical features remain unclear. Therefore, we used resting-state functional MRI (fMRI) to investigate associations between clinical variables, changes in inter-brain regional neural functional connectivity (FC), and cognitive performance in PBC. **Methods:** 29 female PBC patients (age 54 ± 10 (SD) years) underwent resting-state fMRI and cognitive testing, including the Trail Making Test (TMT), Digit Span test (DST), and Corsi Block Tapping Task (CBTT). Impairment was defined as ≥ 1 SD below age-matched female controls (n = 12). Nine of the 29 PBC patients had TMT deficits (31%), 15 DST deficits (52%), and 9 CBTT (31%) deficits. Among PBC patients, clinical variables included ALP, ALT, liver stiffness (FibroScan®), symptoms (yes/no; yes for sicca n = 14/29, fatigue n = 16/29, and pruritus n = 10/29), and ursodeoxycholic acid (URSO) status (treatment naïve n = 12/29). FC was computed between predefined brain regions of interest using fMRI. General linear models assessed associations between clinical variables, FC, and cognitive performance controlling for age. **Results:** TMT impairment was directly associated with sicca ($p < 0.001$) and inversely associated with fatigue ($p = 0.023$). DST and CBTT deficits were not directly associated with any clinical variables. TMT impairment was also associated with decreased FC between anterior and posterior cingulate cortices ($p = 0.001$), and between the anterior cingulate and medial visual network ($p = 0.002$), while fatigue was associated with increased FC of these brain region neural connections. Reduced FC between the posterior cingulate and dorsal attention network ($p = 0.002$), and between the right insula and posterior cingulate ($p = 0.004$), were associated with both TMT impairment and sicca. ALT was negatively associated with multiple corticostriatal functional connections involving the basal ganglia (caudate, putamen, pallidum) and insula. **Conclusion:** Cognitive dysfunction in PBC is connected to significant alterations in cingulate-centered and corticostriatal brain networks known to critically regulate cognition, motor control, and memory, and are linked to specific clinical features, particularly sicca and fatigue. Opposing neural connectivity patterns associated with fatigue and TMT impairment suggest compensatory neural network engagement in fatigued individuals, in contrast to reduced neural network integration underlying objective measures of cognitive dysfunction. These findings support neural network-level brain alterations in regulating objective cognitive changes in PBC and highlight their association with fatigue and sicca.

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Novo Nordisk, Mirum: Speaking and Teaching, Ipsen: Speaking and Teaching.

1139 | ◆ REGN22044: A FULLY HUMAN IL-12P35 ANTIBODY POTENTLY AND SPECIFICALLY INHIBITS IL-12

Arielle Glatman Zaretsky[1] Kaitlyn Gayvert[1] Rachna Shah[1] Elsa Au-Yeung[1] Amanda Dorvilliers[1] Brian Hobbs[1] Katherine Siminovitch[1] Erica Ullman[1] Stephen DiMartino[1] Veronica Mas Casullo[1] Wei Keat Lim[1] Andre Limnander[1] Jennifer Maloney[1] Jamie Orengo[1], [1]Regeneron

Background: Primary Biliary Cholangitis (PBC) and Autoimmune Hepatitis (AIH) are rare autoimmune liver diseases with disparate manifestations of pathology. However, PBC and AIH have shared genetic associations, high co-prevalence and are associated with type 1 inflammation. IL-12, composed of IL-12p35 and IL-12p40, drives type 1 immune responses. IL-12 signals through a receptor formed by IL-12RB1 and IL-12RB2. IL-23 shares the IL-12p40 subunit and IL-12RB2 receptor component with IL-12. A monoclonal IL-12p35-specific antibody, REGN22044, has been developed that binds to IL-12p35 and potently and specifically inhibits IL-12 signaling. **Methods:** An IL-12 gene signature was established using RNASeq analysis to identify differentially expressed genes (DEGs) in response to IL-12 signaling. This IL-12 signature was evaluated in liver or PBMC gene expression datasets from patients with PBC or AIH to assess IL-12 signaling compared with healthy controls. Surface plasmon resonance, luciferase reporter and primary cell assays were used to quantify binding affinity, specificity, and functional activity of REGN22044. A xenotransplant mouse model was used to evaluate REGN22044 in vivo and a surrogate mouse IL-12p35 antibody was used to evaluate the relevance of IL-12 signaling in mouse models. **Results:** The IL-12 gene signature included upregulation of known Th1 inflammation genes *IFNG* and *TBX21* in all four immune cell populations evaluated and was upregulated in patients with PBC (*IFNG:* logFC = 6.2, q = 0.0001; *TBX21:* logFC = 3.3, $q = 6.8x10^{-6}$) and AIH (*IFNG:* logFC = 3.8, q = 0.007; TBX21: logFC = 1.7, q = 0.004) compared to controls. Genetics, transcriptomics and disease biology support the relevance of IL-12 signaling in PBC and AIH, motivating development of an IL-12p35 specific antibody. REGN22044 bound human IL-12 with picomolar affinity (KD ≤ 1.3E-11). Complete inhibition of IL-12 signaling by REGN22044 was observed in both luciferase reporter assays and primary human cell based assays, with no impact on IL-23 signaling, unlike an IL-12p40 antibody, which inhibited both IL-12 and IL-23 signaling. In vivo, REGN22044 completely inhibited production of human IFNg, weight loss, and mortality in response to human IL-12 treatment compared to control or anti-IL-12p40 treated animals. Blockade of IL-12 signaling using a mouse surrogate IL-12p35 antibody inhibited a mouse model of autoimmune liver disease. **Conclusion:** These data highlight specific suppression of the IL-12 pathway as a compelling therapeutic target in AIH and PBC. REGN22044 binds to IL-12p35 with high affinity and potently and specifically inhibits IL-12 signaling in vitro and in vivo, supporting its potential as a novel approach to the treatment of PBC and AIH.

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1140 | ◆ THE EMERGING ROLE OF GENETIC TESTING AND THE UNDERSTANDING OF THE DISEASE SPECTRUM IN ADULT MONOGENIC CHOLESTATIC DISEASE THE CLINICIAN ENHANCER

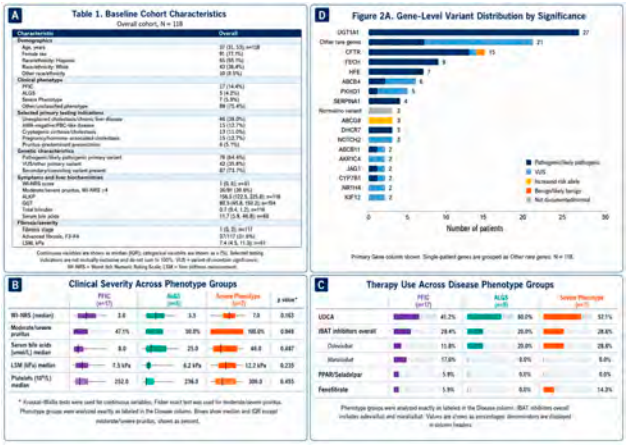
Fabian Rodas[1] Hussein Harb[2] Carmen Landaverde[3], [1]University of Texas San Antonio - The Texas Liver Institute, [2]University Health San Antonio, TIGMER, [3]University Hospital San Antonio / The Texas Liver Institute

Background: Adult cholestatic liver disease presents with a wide variety of clinical manifestations ranging from asymptomatic liver disease to severe cholestatic syndrome. Up to 30 % of chronic liver disease remains unknown. Genetic testing combined with deep clinical phenotyping may clarify undercharacterized cholestasis, define disease spectrum, and guide therapy. **Methods:** We performed a retrospective study of adults undergoing clinical genetic testing for suspected genetic cholestasis from 2/27/2025 to 5/20/2026 across University of Texas San Antonio/ Texas Liver Institute sites in San Antonio and Austin. Among a total of 118 patients, 46 underwent Prevention Genetics testing and 72 underwent Invitae panel testing. Our objective was to identify PFIC, ALGS variants, and a severe phenotype subgroup, (SPS) characterized by ALP ≥ 2x ULN, fibrosis stage ≥ F2, moderate/severe pruritus). **Results:** Among the

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118 adults undergoing genetic testing for unexplained cholestasis, the most common indications were unexplained cholestasis, PBC/AMA-related cholestasis, ICP, and cryptogenic cirrhosis/cholestasis (Table 1). Clinician-assigned phenotype groups included PFIC- associated variants (n = 17, ALGS-associated variants (n = 5), and a SPS (n = 7). Pathogenic/likely pathogenic primary variants were present in 76 patients, and secondary/coexisting variants were common. UGT1A1 variants were most common followed by CFTR and then FECH (Figure 2A). The overall genetic positivity rate was 74.6% using stricter definition excluding low-penetrance and increased risk alleles. Compared with PFIC and ALGS groups, the SPS had greater clinical burden, with higher median WI-NRS (7.0 vs 3.0 and 3.5), serum bile acids (46.0 vs 8.0 and 25.0 umol), and LSM (12.2 vs 7.5 and 6.2 kPa. IBAT inhibitors were used in 29.4% of PFIC, 20 % of ALGS, and 28.6% of SPS patients. Secondary CFTR variants appear clinically enriched for higher WI-NRS, serum bile acids and fibrosis stage and lower platelet counts, likely reflecting co-occurrence with other variants or phenotypes. **Conclusion:** Genetic testing in adults with cholestatic and unexplained adult chronic liver disease identified high proportion of cholestatic variants. Deep clinical phenotyping refined high disease-burden severe phenotype subgroup characterized by severe pruritus, elevated serum bile acids, increased liver stiffness. PFIC-, ALGS-, and SPS-associated variants represented 24.6% of the cohort. However, disease penetrance was heterogenous partcularly among PFIC-associated monogenic variants emphasizing that treatment should be determined by cliniical phenotype rather than genotype. Secondary CFTR variants may act as disease modifiers in selected patients. These findings support integrating genetic testing with structured phenotyping to advance precision hepatology in adult cholestasis.



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1141 | ◆ INFLAMMATORY BOWEL DISEASE IS ASSOCIATED WITH INCREASED HEPATOBILIARY AND PORTAL HYPERTENSIVE COMPLICATIONS IN HOSPITALIZED PATIENTS WITH COMMON VARIABLE IMMUNODEFICIENCY: A NATIONWIDE ANALYSIS

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Background: Common variable immunodeficiency (CVID) is associated with significant immune dysregulation and a broad spectrum of hepatobiliary manifestations, including autoimmune liver disease, portal hypertension, and cholestatic disorders. Inflammatory bowel disease (IBD) has independently been linked to immune-mediated hepatobiliary complications, particularly primary sclerosing cholangitis (PSC). However, the impact of concomitant IBD on hepatobiliary outcomes among hospitalized CVID patients remains poorly characterized. **Methods:** We performed a retrospective cohort study using the Nationwide Readmissions Database (NRD). Adult hospitalizations with CVID were identified using ICD-10-CM codes and stratified by the presence or absence of IBD. Hepatobiliary and pancreatic complications were compared using multivariable logistic regression models adjusted for demographics, payer status, income quartile, hospital characteristics, and urban/rural status. **Results:** Among 181,288 hospitalized CVID patients, 4,383 (2.4%) had concomitant IBD. Patients with concomitant IBD were younger and more commonly represented individuals aged 18–39 years (25.1% vs 13.9%, $p < 0.001$), with higher rates of private insurance coverage (41.7% vs 29.6%, $p < 0.001$). Compared with CVID patients without IBD, the CVID-IBD cohort demonstrated significantly higher

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rates of portal hypertension (2.28% vs 1.59%, p < 0.001), variceal bleeding (1.00% vs 0.69%, p = 0.015), acute pancreatitis (1.48% vs 1.00%, p = 0.002), and chronic pancreatitis (2.14% vs 1.52%, p = 0.001). Age-stratified analyses demonstrated persistently increased PSC rates across all age groups, including patients aged < 40 years (2.69% vs 1.12%, p < 0.001), 40–64 years (1.93% vs 1.07%, p = 0.001), and ≥ 65 years (1.62% vs 0.86%, p = 0.004). On multivariable analysis, IBD remained independently associated with autoimmune hepatitis (aOR 2.06, 95%CI 1.47–2.89), Metabolic dysfunction-associated steatotic liver disease (MASLD) (aOR 1.45, 95%CI 1.21–1.74), acute pancreatitis (aOR 1.41, 95%CI 1.09–1.81), and chronic pancreatitis (aOR 1.40, 95%CI 1.13–1.72). **Conclusion:** Concurrent IBD in hospitalized CVID patients is associated with increased hepatobiliary and portal hypertensive disease burden, including autoimmune liver disease and pancreatic complications. These findings highlight the complex overlap between intestinal immune dysregulation and hepatobiliary disease in CVID, suggest a distinct hepatobiliary disease profile among patients with concomitant IBD, and support closer multidisciplinary hepatology surveillance in this high-risk population.

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1142 | ◆ IMPACT OF FATIGUE ON QUALITY OF LIFE IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS (PBC)

Magnus Doverskog[1] Robert Mitchell-Thain[2] Mo Christie[2] Nekshan Dalal[3] William Lobb[3] Rishi Choudhury[3] David Jones[4], [1]Umecrine Cognition AB, [2]PBC Foundation, [3]Indegene, [4]Newcastle University

Background: Fatigue is a common and debilitating symptom of primary biliary cholangitis (PBC) that markedly reduces health-related quality of life (HRQoL), yet it is often overlooked in routine care. Central fatigue, which manifests as cognitive issues such as what patients routinely characterize as "brain fog," and memory and concentration problems, is a burdensome symptom in PBC. This global study examined the prevalence of central fatigue in patients with PBC and analysed the impact of severity on HRQoL, daily functioning, and employment. **Methods:** An international cohort of 250 patients with PBC completed an online survey through the PBC Foundation app over 3 months. Participants reported PBC symptom burden, completed the EQ-5D-5L and PBC-40 questionnaires, and provided qualitative feedback on their disease experience and treatment expectations.Participants reporting central fatigue were classified as having mild (< 29), moderate (29–39), or severe (≥ 40) fatigue based on PBC-40 fatigue domain scores. Outcomes were compared across the three groups. **Results:** Majority of PBC patients reported central fatigue (92%), followed by bone or joint pain (75%), dry eyes or mouth (69%), peripheral fatigue (68%), and itching/pruritus (49%). Among the 92% who reported central fatigue, 14% (n = 34) were categorized as mild, 42% (n = 106) moderate, and 44% (n = 110) severe.Overall, in the 250 surveyed patients, mean EQ-5D score was 0.697, and mean EQ-VAS score was 65.3, in line with other reports on PBC. However, PBC patients with severe central fatigue reported significantly worse outcomes (p < 0.05) than those with moderate or mild central fatigue; EQ-5D scores (0.549 vs. 0.797 vs. 0.863) and EQ-VAS scores (51 vs. 66 vs. 79).Across EQ-5D dimensions, a substantially higher proportion of PBC patients with severe central fatigue reported limitations in usual activities (79% vs 23% vs 12%) than those with moderate or mild central fatigue.On the PBC-40, patients with severe central fatigue had significantly higher (p < 0.05) mean cognitive and emotional scores than those with moderate or mild central fatigue, indicating worse quality of life (cognitive: 21 vs 16 vs 13; emotional: 12 vs. 9 vs. 7).The impact on employment was staggering with 44% of patients with severe central fatigue stating that they were either unable to work, working part time or retired from work due to illness; rates were significantly lower in patients with moderate (16%) and mild central fatigue (6%).Sixty percent of patients prioritized central fatigue as the one PBC symptom most in need of a treatment. **Conclusion:** Central fatigue is highly prevalent in PBC and is linked to substantial declines in HRQoL, daily functioning, and ability to work, especially among patients with severe symptoms. These findings highlight fatigue as a major unmet need in PBC and underscore the urgent need for treatments that address it.

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1143 | ◆ LOCATION AND ACTIVITY OF INFLAMMATORY BOWEL DISEASE ARE ASSOCIATED WITH COLECTOMY, BUT NOT WITH LIVER TRANSPLANT-FREE SURVIVAL IN PATIENTS WITH PRIMARY SCLEROSING CHOLANGITIS

Dennis Sneek[1] Bregje Mol[2] Marin de Jong[1] Adriaan Van der Meer[1] Pedro Miranda-Afonso[1] Akin Inderson[3] Rinse Weersma[4] Cyriel Ponsioen[2] Bettina Hansen[1] Annemarie de Vries[1], [1]Erasmus University Medical Center, [2]Amsterdam University Medical Center, [3]Leiden University Medical Center, [4]University Medical Center Groningen

Background: Primary sclerosing cholangitis (PSC) is a rare cholestatic liver disease characterized by chronic inflammation of the biliary tree. Up to 80% of patients with PSC are diagnosed with concomitant inflammatory bowel disease (IBD). PSC-associated IBD has been reported to present predominantly in the proximal colon and to follow a mild yet persistent course. We investigated whether IBD type, location, and activity in patients with PSC are associated with colectomy and liver transplant (LT)-free survival. **Methods:** Patients diagnosed with PSC and IBD who had at least one recorded colonoscopy were selected from the EpiPSC2 cohort, a dynamic population-based PSC registry in the Netherlands. Cox regression models were used to study the association of IBD type at diagnosis and time-varying IBD activity and location with colectomy and the composite of LT or PSC-related death. IBD activity was defined as the cumulative inflammatory burden (CIB) over follow-up, using the Mayo endoscopic subscore from 0 (none) to 3 (severe). IBD location was classified as right-sided colitis, left-sided colitis, or pancolitis. The index date was set to the second diagnosis, and the first colonoscopy was treated as the entry time to account for left truncation. **Results:** The analyses included 580 patients who had 3394 colonoscopies (median 5, interquartile range [IQR] 2–9). During follow-up, 221 patients had right-sided colitis at any time, 226 had left-sided colitis, and 277 had pancolitis. Among colonoscopies with active inflammation, the median severity of colitis was mild (Mayo 1, IQR 1–2). In 5509 patient-years of follow-up, 81 colectomies and 125 LTs were performed; 44 patients died of PSC-related causes.Left-sided colitis and pancolitis were associated with a 4-fold higher hazard of colectomy (hazard ratio [HR] 4.1, 95% confidence interval [CI] 2.3–7.5, p < 0.001; and HR 4.4, 95% CI 2.6–7.6, p < 0.001, respectively) than no inflammation, whereas right-sided colitis was not significantly associated (HR 0.7, 95% CI 0.3–2.1, p = 0.54). No differences were observed for the liver-related outcome (Figure 1). The CIB was associated with a 4.4-fold higher hazard of colectomy (95% CI 3.1–6.1, p < 0.001) and showed the strongest association in the left-sided colon (HR 4.3, 95% CI 2.9–6.3, p < 0.001). The CIB was not associated with the LT-free survival (HR 1.1, 95% CI 0.8–1.4, p = 0.68). The IBD type at diagnosis was not associated with either outcome. **Conclusion:** In this study, right-sided colitis, left-sided colitis, and pancolitis occurred with similar frequency in patients with PSC-IBD. Left-sided colitis and pancolitis were associated with a 4-fold higher hazard of colectomy, with a higher risk as the CIB increased. Right-sided colitis was not associated with a higher risk of colectomy as compared to no inflammation, suggesting this may be considered a separate IBD type. In our cohort, location and severity of IBD were not associated with LT-free survival.

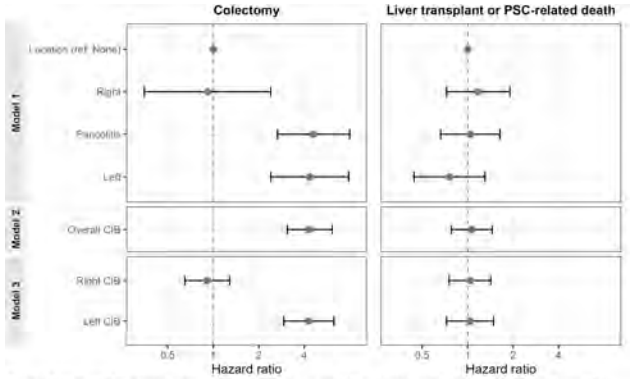


Figure 1 Multivariable Cox regression results. Adjusted hazard ratios and 95% confidence intervals for inflammatory bowel disease (IBD) location and severity. For the colectomy outcome we corrected for sex, age, IBD type, and years with IBD before primary sclerosing cholangitis (PSC) diagnosis. For liver transplant or PSC-related death we corrected for sex, age, IBD type, PSC subtype, colectomy, and years with PSC before IBD diagnosis. CI, confidence interval; CIB, cumulative inflammatory burden; PSC, primary sclerosing cholangitis; Ref, reference category.

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1144 | ◆ CHARACTERIZING AUTOIMMUNE HEPATITIS (AIH) USING COMPLEMENTARY SINGLE-NUCLEI AND SPATIAL TRANSCRIPTOMICS TECHNIQUES

Nikita Sajai[1] Bruce Wang[1] Abhishek Murti[1] Cindy Ament[1] Michele Tana[2], [1]University of California San Francisco, [2]UCSF/ZSFG

Background: Autoimmune hepatitis (AIH) is a chronic liver disease characterized by immune cells attacking hepatocytes, leading to chronic inflammation, cirrhosis, and death if untreated. AIH incidence appears to be on the rise, disproportionately affecting women and people of color. Diagnosis often requires an invasive liver

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biopsy, as serum biomarkers, including autoantibodies, lack sufficient sensitivity and specificity. Treatment can require lifelong immunosuppression with corticosteroids, and up to 25% of patients do not respond to treatment. Much remains unknown about the biological basis of AIH, including the autoantigen that leads to hepatocyte damage, the immune cell profile, and which molecular signaling pathways are active in the disease. **Methods:** Here, we use the Prospective Observational Study to Understand Liver Disease (POSULD), a well-characterized, diverse patient cohort with integrated clinical and molecular data to investigate disease mechanisms in AIH using a combination of single-nuclei RNA sequencing and spatial transcriptomics. To define the cellular and molecular mechanisms driving AIH, we performed single-nuclei RNA sequencing on liver tissues from 7 patients with AIH. We also included publicly available snRNA-seq data from 3 healthy controls. Next, we applied high-resolution spatial transcriptomics using the 10x Xenium platform to characterize disease-related changes in situ. To do so, we created a custom 480-gene human liver panel informed by our single-cell and bulk sequencing data for AIH. We then generated liver tissue microarrays using liver biopsy samples from 54 patients with AIH, control patients with metabolic-associated steatotic liver disease (MASLD), and healthy human controls. This approach enabled high-resolution in situ mapping of liver cell types and spatially informed identification of lobular regions (periportal, pericentral, and portal) using connectivity-based analysis. **Results:** Single-nuclei analysis revealed a massive increase in T lymphocytes in AIH and upregulation of the potential autoantigen AFF3 in periportal hepatocytes, implicating the periportal region in disease pathogenesis. We validated these findings in the spatial transcriptomics data. Unsupervised clustering based on spatial cell-type composition and regional gene expression profiles identified a subset of AIH patients characterized by shrunken periportal regions and expanded portal regions enriched for myeloid and lymphocyte populations. This subgroup also demonstrated elevated AIH panel scores, increased TGF-β signaling, and reduced STAT5B and heme biosynthesis pathway activity, highlighting spatially organized immune-hepatocyte interactions associated with severe disease. The spatial analysis showed that T cell expansion in AIH is localized to the portal region, where they form clusters with B cells. Cell-to-cell signaling analysis of our single-nuclei dataset identified CD40-CD40LG signaling between B and T cells as specifically upregulated in AIH livers, which we validated in the spatial transcriptomics data. **Conclusion:** These findings provide insight into the spatially organized immune-hepatocyte interactions that characterize AIH and highlight candidate pathways for targeted therapeutic intervention, advancing efforts toward precision medicine in this disproportionately affected population. It also demonstrates how a complementary approach combining single-cell and spatial transcriptomics can reveal novel molecular and cellular insights into liver disease pathophysiology.

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1145 | ◆ SERUM IGFBP7 IS A PROGNOSTIC BIOMARKER FOR LIVER-RELATED EVENTS IN PRIMARY BILIARY CHOLANGITIS

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Background: Insulin-like growth factor binding protein 7 (IGFBP7) has been implicated in liver fibrosis, cellular senescence, and tissue remodeling in chronic liver diseases. However, its clinical significance and cellular origin in primary biliary cholangitis (PBC) remain unclear. We investigated whether serum IGFBP7 predicts liver-related events (LREs) and reflects histological disease severity in patients with PBC. **Methods:** This multicenter retrospective study included a biopsy-proven discovery cohort of 204 patients with PBC, excluding prior LREs or follow-up <3 months. Serum IGFBP7 levels were measured using stored baseline samples. LREs were defined as newly developed hepatocellular carcinoma, grade $\geq$II hepatic encephalopathy, refractory ascites requiring hospitalization, or gastroesophageal varices requiring intervention. A validation cohort included 70 patients with serologically diagnosed PBC without liver biopsy. Associations of IGFBP7 with LREs, histological severity, liver stiffness, and established fibrosis-related markers were evaluated. Multivariable Cox regression analysis was adjusted for age, sex, and Nakanuma classification. Single-cell RNA-sequencing data and RNA in-situ hybridization were analyzed to assess hepatic cellular expression of IGFBP7. **Results:** Patients who developed LREs had significantly higher baseline serum IGFBP7 levels than those without LREs. In the discovery cohort, IGFBP7 showed the highest AUROC for LRE development among evaluated markers: IGFBP7, 0.826; ALP, 0.602; FIB-4, 0.681; ALBI, 0.594; hyaluronic acid, 0.613; type IV collagen 7S, 0.657; Mac-2 binding protein glycosylation isomer, 0.649; and autotaxin, 0.768. The optimal IGFBP7 cutoff was 616.5 ng/mL, with 90.0%

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sensitivity and 75.3% specificity. Kaplan–Meier analysis demonstrated a significantly higher cumulative incidence of LREs in patients with high IGFBP7 levels ($\geq$ 616.5 ng/mL; $p < 0.001$). Serum IGFBP7 levels were significantly associated with fibrosis stage, bile duct loss, Nakanuma classification, and Scheuer classification. In the validation cohort, IGFBP7 levels positively correlated with liver stiffness ($r = 0.477$, $p < 0.001$) and were higher in patients with LREs. In multivariable Cox regression analysis, high IGFBP7 levels remained independently associated with LRE development (HR 12.19; $p = 0.021$). Single-cell RNA-sequencing analysis showed increased IGFBP7 expression in fibroblasts, hepatic stellate cells, and sinusoidal endothelial cells in PBC. RNA in-situ hybridization demonstrated enhanced IGFBP7 expression in advanced fibrosis, particularly in portal areas with higher Nakanuma stages. **Conclusion:** Serum IGFBP7 was independently associated with LRE development in PBC and outperformed established fibrosis-related markers. These analyses suggest IGFBP7 reflects portal fibrotic remodeling and may serve as a noninvasive prognostic biomarker in PBC.

Disclosures: Yoshiaki KOBAYASHI:Nothing to Disclose, Takanobu Iwadare:Nothing to Disclose, Takefumi Kimura:Nothing to Disclose.

1146 | ◆ FACTORS INFLUENCING SECOND-LINE TREATMENT PRESCRIPTION IN PBC: A WORLDWIDE SURVEY AMONG PRACTITIONERS

Tiki D Blom[1] Alessandra Bonfichi[2] Merle Vos[1] Maria Papp[3] Jef Verbeek[4] Maria Londoño[5] Andreas Kremer[6] Christoph Schramm[7] Cynthia Levy[8] David Jones[9] Christophe Corpechot[10] Palak Trivedi[11] Emma Culver[12] Ana Lleo[13] João Madaleno[14] Michael Trauner[15] Henning Grønbæk[16] Annika Bergquist[17] George Dalekos[18] Aleksejs Derovs[19] Atsushi Tanaka[20] Gideon Hirschfield[21] Martin Weltman[22] Anna Mrzljak[23] Sona Frankova[24] Tamara Milovanovic[25] Piotr Milkiewicz[26] Ulrich Beuers[27] Marco Carbone[28] Bettina Hansen[1] Alessio Gerussi[29] Adriaan Van der Meer[1], [1]Erasmus University Medical Center, [2]University of Milano-Bicocca, IRCCS San Gerardo dei Tintori, [3]Division of Gastroenterology, Faculty of Medicine, University of Debrecen, [4]Department of Gastroenterology & Hepatology, University Hospitals Leuven, [5]Hospital Clinic Barcelona, [6]Department of Gastroenterology and Hepatology, University Hospital Zürich, University of Zürich, [7]University Medical Centre Hamburg-Eppendorf, [8]University of Miami, [9]Newcastle University, [10]Saint-Antoine Hospital, [11]University of Birmingham, [12]John Radcliffe Hospital and Nuffield Department of Medicine, University of Oxford, [13]Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, [14]Liver Disease Unit - Department of Internal Medicine; Unidade Local de Saúde de Coimbra - Hospitais, [15]Medical University of Vienna, [16]Department of Hepatology & Gastroenterology, Aarhus University Hospital, [17]Karolinska Institutet, [18]University of Thessaly, [19]Riga East university hospital, [20]Teikyo University School of Medicine, [21]The Autoimmune and Rare Liver Disease Programme, Toronto General Hospital, [22]Nepean Hospital, [23]University Hospital Center Zagreb, [24]Department of Hepatogastroenterology, Institute for Clinical and Experimental Medicine, [25]University Clinical Center of Sebia, [26]Liver and Internal Medicine Unit Medical University of Warsaw, [27]Amsterdam University Medical Center, [28]ASST Grande Ospedale Metropolitano Niguarda; University of Milano-Bicocca, [29]University of Milano-Bicocca

Background: The second-line therapy (SLT) landscape for Primary Biliary Cholangitis (PBC) is evolving with the emergence of PPAR agonists and the regional withdrawal of obeticholic acid. This survey aimed to identify dominant factors influencing physicians' choice of bile acid-directed SLT in PBC. **Methods:** This cross-sectional survey among practitioners with experience in PBC was disseminated through international PBC networks via an open-access link. The 37-item survey comprised three sections: participant experience in PBC, ranking of the top 5 factors influencing SLT choice (weighted 5 to 1 points) and preferred SLT option across hypothetical clinical cases. Although participants were aware of regional availability, they were asked to assume all drugs were available for survey responses. **Results:** In total, 250 respondents from 45 countries were included. Of these, 56 (22.4%) were from Italy and 22 (8.8%) from the Netherlands; 204 (81.6%) worked in tertiary centers, and 172 (68.8%) had over 10 years of experience with PBC. When choosing between PPAR and FXR agonism, the three influencing factors with the highest cumulative points were patient symptoms (pruritus, fatigue; 659 pts), biochemical response data (590 pts), and safety profile (507 pts). Biochemical response data most often received the highest weight, 5 points, (45, 18%), followed by long-term outcome data (38, 15.2%) and patient symptoms (37, 14.8%). When selecting among PPAR agonists specifically, safety profile (555 pts), biochemical response data (522 pts), and patient symptoms (513 pts) received the most points, while costs (42, 16.8%), personal experience (41, 16.4%), and in-label versus off-label use (40, 16%) most frequently scored 5 points. In the base case of a 55-year-old patient with ALP 2.2xULN after 1 year of UDCA and F1 fibrosis without additional symptoms or co-morbidities, bezafibrate was most often selected as SLT (29.3%), followed by any in-label PPAR agonist (16.7%) and any PPAR agonist (13.5%). The top three preferred SLT options varied depending on

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additional clinical features: refractory pruritus (Seladelpar [39.5%], Bezafibrate [31.2%], Elafibranor [9.8%]); incapacitating fatigue (Elafibranor [31.2%], Seladelpar [16.3%], Bezafibrate [16.3%]); eGFR 28 mL/min (Seladelpar [29.3%], any in-label PPAR [20.5%], no SLT [15.3%]); and concomitant statin therapy (Seladelpar [28.8%], any in-label PPAR [19.5%], Bezafibrate [15.3%]). **Conclusion:** This international survey shows that patient symptoms, biochemical response data and safety profile were dominant influencing factors when deciding between an FXR agonist and a PPAR agonist or on a specific PPAR agonist as SLT in patients with PBC. Treatment costs was the most frequently selected top ranked factor for selecting the type of PPAR agonist.



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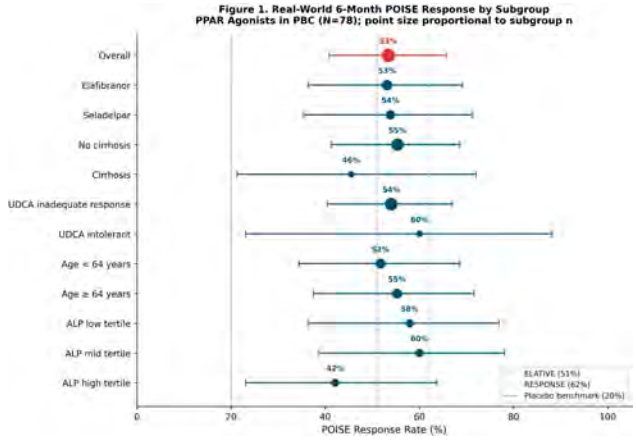
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1147 | ◆ REAL-WORLD BIOCHEMICAL RESPONSE TO PPAR AGONISTS IN PRIMARY BILIARY CHOLANGITIS: A SINGLE-CENTER COHORT STUDY REPLICATING THE RESPONSE AND ELATIVE TRIAL ENDPOINTS

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Background: The PPAR agonists elafibranor and seladelpar achieved POISE composite biochemical response in 51% (ELATIVE) and 62% (RESPONSE) of patients with primary biliary cholangitis (PBC) in their respective pivotal trials. Real-world effectiveness in broader clinical populations is unknown. We applied the same endpoints used by the registrational trials to a consecutive real-world cohort to assess generalizability. **Methods:** Single-center retrospective cohort of 78 PBC patients initiated on a PPAR agonist (elafibranor n = 46, seladelpar n = 32) between June 2024 and April 2026. The primary endpoint was the POISE composite biochemical response at 6 months (ALP < 1.67× ULN AND ≥ 15% reduction AND total bilirubin ≤ ULN), tested against an assumed 20% placebo benchmark. Secondary endpoints included POISE response at 12 months, ALP normalization, percent change in ALP, pruritus improvement, treatment persistence, and adverse events. Pre-specified subgroup analyses examined response by agent, cirrhosis status, UDCA intolerance versus inadequate response, age, and baseline ALP tertile. **Results:** The cohort was 96% female with median age 64 years and median baseline ALP 215 U/L; 20% had baseline cirrhosis and 85% met criteria for UDCA inadequate response. At 6 months, POISE composite response was achieved in 31/58 evaluable patients (53%, 95% CI 40–66; p < 0.001 vs 20% placebo benchmark), closely paralleling the 51–62% rates reported in ELATIVE and RESPONSE. At 12 months, response was 11/31 (35%, 95% CI 21–53). Median ALP fell 38% from baseline at 6 months; ALP normalization occurred in 19%. Pruritus improved in 32/39 patients with baseline symptoms (82%, 95% CI 67–91). Treatment persistence was 92% (6 of 78 discontinued); adverse events occurred in 17%. Response rates were consistent across cirrhosis status, UDCA intolerance versus inadequate response, age, and agent. **Conclusion:** In a real-world PBC cohort treated with PPAR agonists, biochemical response rates and tolerability closely paralleled the ELATIVE and RESPONSE registrational trials, supporting generalizability of trial efficacy data to routine clinical practice. These findings reinforce PPAR agonists as effective second-line therapy across diverse PBC subgroups including patients with cirrhosis and UDCA intolerance.



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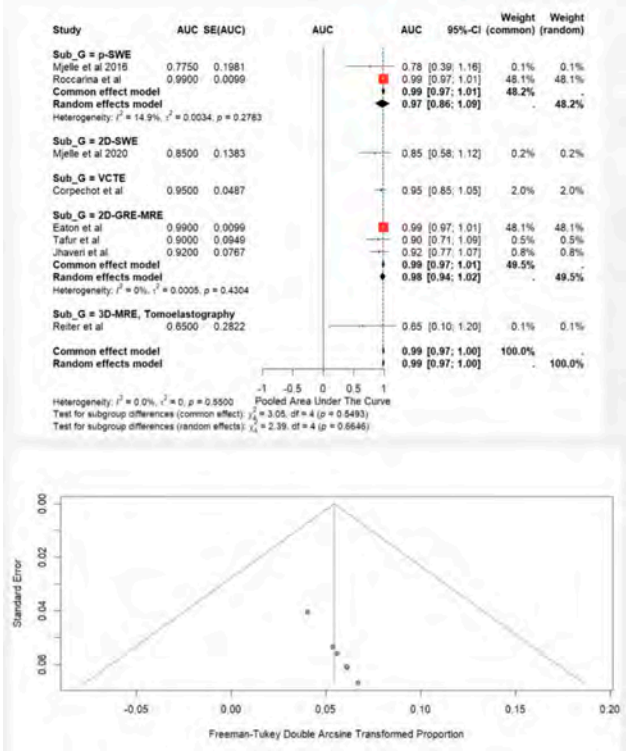
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1148 | ◆ DIAGNOSTIC PERFORMANCE OF ELASTOGRAPHY-BASED IMAGING MODALITIES FOR FIBROSIS ASSESSMENT IN PRIMARY SCLEROSING CHOLANGITIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

Era Gupta[1] Omar Oudit[2] Aryan Gupta[3] Abdullah Sultany[4] Rewanth Katamreddy[4] Gautam Maddineni[5] Dushyant Singh Dahiya[6] Aakash Desai[7], [1]Guthrie/Robert Packer Hospital, PA, USA, [2]Brook Dale University Hospital Medical Centre, NY, USA, [3]Bangalore Medical College And Research Institute, India, [4]Guthrie/Robert Packer Hospital, PA, USA, [5]Creighton University, NE, USA, [6]The university of Kansas School Of Medicine, KS, USA, [7]Allegheny Health Network, PA, USA

Background: Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease associated with progressive biliary fibrosis and cirrhosis. Accurate fibrosis assessment is critical for prognostication and disease monitoring; however, liver biopsy is invasive and limited by sampling variability. Elastography-based modalities have emerged as promising noninvasive alternatives, though their diagnostic performance in PSC remains incompletely defined. We performed a systematic review and meta-analysis evaluating their diagnostic accuracy in PSC. **Methods:** This review followed PRISMA guidelines. PubMed, Google Scholar, and ScienceDirect were searched using a comprehensive strategy. Studies reporting AUC and/or technical failure rates for elastography modalities in PSC were included. Modalities assessed included point shear wave elastography (p-SWE), two-dimensional shear wave elastography (2D-SWE), vibration-controlled transient elastography (VCTE), and magnetic resonance elastography (MRE), including 2D gradient-recalled echo (2D-GRE-MRE) and 3D magnetic resonance elastography (3D-MRE). Data were analyzed using Meta, Metadata, and Metafor packages in R Studio. **Results:** Eight studies comprising 612 patients were included. The pooled AUC for fibrosis was 0.9873 (95% CI 0.97–1.00) , indicating excellent diagnostic performance with low heterogeneity. Among individual modalities, 2D-GRE-MRE demonstrated the highest diagnostic accuracy (AUC 0.9800, 95% CI 0.9400–1.0200), followed by p-SWE (AUC 0.9735, 95% CI 0.8614–1.0856) and VCTE (AUC 0.9500, 95% CI 0.8545–1.0455). 2D-SWE showed moderate performance (AUC 0.8500, 95% CI 0.5790–1.1210), while 3D-MRE/Tomoelastography demonstrated the lowest accuracy (AUC 0.6500, 95% CI 0.0969–1.2031).Technical failure rates were 0% for p-SWE, 6.1% for 2D-SWE, 9.6% for VCTE, and 1–8.4% across 2D-GRE-MRE studies; failure rate data being the highest for VCTE (9.6%). **Conclusion:** Elastography modalities demonstrate excellent diagnostic performance for fibrosis assessment in PSC, with high accuracy across ultrasound- and MRI-based techniques and low between-study heterogeneity. p-SWE and 2D-GRE-MRE showed the highest AUCs while VCTE had the highest failure rate. Stage-specific accuracy and standardized thresholds require further validation in prospective studies with histologic correlation.



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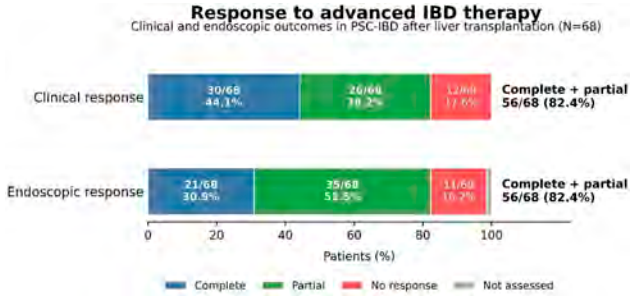
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1149 | ◆ SAFETY AND EFFICACY OF ADVANCED IBD THERAPIES AFTER LIVER TRANSPLANTATION FOR PRIMARY SCLEROSING CHOLANGITIS: A MULTICENTER EXPERIENCE

Hala Nabulsi[1] Fernando Gil-Lopez[1] Jana Hashash[1] Andrew Keaveny[1] Kymberly Watt[2] Darrell Pardi[2] Elizabeth Carey[3] Denise Harnois[1] Omar Mousa[1], [1]Mayo Clinic Florida, [2]Mayo Clinic Rochester, [3]Mayo Clinic Arizona

Background: Management of inflammatory bowel disease (IBD) following liver transplantation (LT) for primary sclerosing cholangitis (PSC) is challenging, and data on advanced therapy in this population remains limited. We aimed to investigate the safety and efficacy of advanced therapy for IBD following LT for PSC. **Methods:** We retrospectively reviewed adult patients who underwent LT for PSC between 1985 and 2022 and received advanced therapy for IBD post-LT at three large transplant centers. Patients with cholangiocarcinoma at LT were excluded. Clinical activity was categorized as no, partial, or complete remission based on IBD symptoms. Endoscopic activity was defined by mucosal healing (disappearance of ulcerations in Crohn's disease and Mayo endoscopic subscore ≤ 1 in Ulcerative Colitis). Post-LT infection rates and malignancy were captured from initiation of advanced therapy to the last follow-up. **Results:** Sixty-eight patients with PSC-IBD were included (44 ulcerative colitis, 23 Crohn's disease, 1 indeterminate colitis); 66.1% male, 91.2% Caucasian, mean recipient age 39.5 $\pm$12.8 years, mean MELD at LT 20.9, 25% living-donor recipients. Median follow-up from advanced therapy initiation was 5.26 years (range 0.12–24.9). The most frequently used agents were vedolizumab (n = 57), infliximab (n = 31), adalimumab (n = 24), ustekinumab (n = 22), risankizumab (n = 12), and upadacitinib (n = 10); 35.3% of patients received $\geq$ 3 sequential advanced agents post-LT. Complete clinical remission was achieved in 44.1% (30/68) and partial clinical remission in 38.2% (26/68); complete endoscopic remission was achieved in 30.9% (21/68) and partial endoscopic improvement in 51.4% (35/68). During cumulative follow-up after advanced therapy initiation, viral infections occurred in 82.3%, bacterial infections in 75.0%, and fungal/parasitic infections in 17.6% of patients; some of these events occurred during periods when advanced therapy was held or discontinued, with patients maintained on standard immunosuppression. The most frequent infections were Clostridioides difficile (39.7%), CMV (38.2%), SARS-CoV-2 (33.8%), Influenza (22%), and bacteremia (22%). Malignancy occurred in 30.8% of patients, most commonly non-melanoma skin cancer (14.7%). There were no reported deaths related to advanced therapy. **Conclusion:** In the largest multicenter PSC-IBD cohort post-LT, use of advanced therapy was associated with clinical and endoscopic improvement in 82.3% of patients. However, cumulative infections and malignancies were common over long-term follow-up. These findings support advanced therapy as a viable option for IBD after LT for PSC while underscoring the need for vigilant infection surveillance and skin-cancer screening in this immunosuppressed population.



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1150 | ◆ THE UK-PBC RISK SCORE PREDICTS LIVER-RELATED OUTCOME IN A NATIONAL COHORT OF INDIVIDUALS WITH PRIMARY BILIARY CHOLANGITIS

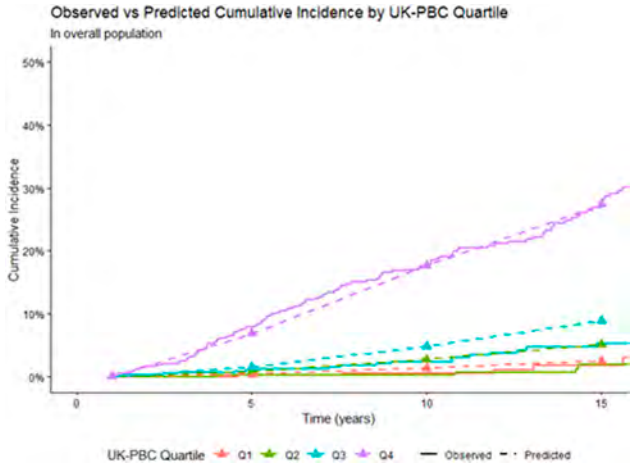
Gemma H.X. Weijsters[1] Ellen Werner[1] Tiki Blom[1] Merle M.F. Vos[1] Maria van Hooff[1] Rozanne de Veer[1] Ulrich Beuers[2] Joost P.H. Drenth[2] Frans J.C. Cuperus[3] Remco van Dijk[4] Bart J. Veldt[5] Michael Klemt-Kropp[6] Suzanne van Meer[7] Robert Verdonk[8] Hajo J. Flink[9] Jan M. Vrolijk[10] Cyriel Y. Ponsioen[2] Matthijs Kramer[11] Paul

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Background: The UK-PBC risk score is used to assess the risk of developing end-stage liver disease (ESLD) in people with primary biliary cholangitis (PBC). The risk score has been validated in a tertiary cohort only. The aim of this study was to externally validate the UK-PBC risk score in a representative, national population of individuals with PBC. **Methods:** The retrospective Dutch PBC Cohort Study includes every identifiable patient with PBC from 1990 up to last data collection (2019-2023) from all 71 hospitals in the Netherlands. Where feasible, laboratory values were imputed using joint model multiple imputation. Patients with auto immune hepatitis, additional therapy (second-line/immunosuppressants) within the 1st year, or with <1 year of follow-up were excluded. The UK-PBC risk score uses baseline albumin and platelet levels, along with total bilirubin, alanine aminotransferase (ALT)/aspartate aminotransferase (AST), and alkaline phosphatase at 1 year. The score was calculated with the corresponding formula at 5, 10 and 15 years. In line with the derivation study, ALT was used by default and otherwise AST. ESLD was defined as liver-related death, liver transplant (LT), or - for people who were still alive and had never undergone LT - serum bilirubin ≥100 µmol/L for the first time. Calibration plots were constructed with the observed and predicted 5-, 10- and 15-year probabilities. Discrimination was assessed using the area under the receiver operating characteristic curve (AUC) at 5, 10, and 15 years. The Integrate Brier Score (IBS) summarized prediction error over time. **Results:** In total, 2770 individuals were included. At diagnosis, median age was 57.7 years (IQR 49.6-67.0), 2422 (87.4%) were female and 185 (6.7%) had cirrhosis. During a median follow-up of 8.3 years (IQR 4.0-13.7), 232 patients experienced the outcome of ESLD: 130 (56.0%) liver-related death, 63 (27.2%) LT and 39 (16.8%) bilirubin ≥100 µmol/L. The 10 year cumulative incidence of liver failure was 5.6% (95%CI 4.5-6.7). Overall, the c-statistic was 0.84 (95%CI 0.85-0.90) with an IBS of 0.02 over 10 years follow-up. In the 25% highest risk patients (UK-PBC score >6.5%), cumulative incidence at 10 years was 17.6% (95%CI 14.1-21.0) vs a predicted of 17.6%; in the 25% lowest risk patients (UK-PBC score <2.0%) the observed 10 year cumulative incidence was 0.5% (95%CI 0.0-1.3) vs predicted of 1.3% (p<.001). The AUC of the UK-PBC risk score was 0.85 (95% CI 0.81-0.90) at 5 years, 0.86 (95% CI 0.82-0.90) at 10 years and 0.82 (95% CI 0.77-0.86) at 15 years. In a subgroup of patients without cirrhosis, the AUC was ≥ 0.77 at 5, 10 and 15 years. **Conclusion:** In this nationwide unbiased cohort of people with PBC, the UK-PBC risk score was validated with high discrimination and accurate calibration for the assessment of liver-related prognosis. Especially in the high risk group, for whom risk prediction is most urgent, the UK-PBC risk score showed excellent prognostic performance.



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Robert Verdonk:Nothing to Disclose, Hajo J. Flink: Nothing to Disclose, Jan M. Vrolijk:Nothing to Disclose, Cyriel Y. Ponsioen:Nothing to Disclose, Matthijs Kramer:Dr Falk: Sponsoring of educational meetings, Paul G. van Putten:Nothing to Disclose, Jeroen D. van Bergeijk:Nothing to Disclose, Gijs J. de Bruin:Nothing to Disclose, Rob P.R. Adang:Nothing to Disclose, Maria N. Aparicio-Pages:Nothing to Disclose, Wink de Boer: Nothing to Disclose, Hanneke van Soest:Nothing to Disclose, Frank ter Borg:Nothing to Disclose, Ulrike de Wit:Nothing to Disclose, Johan P.H. Kuyvenhoven: Nothing to Disclose, Nicole S. Erler:Nothing to Disclose, Bettina E. Hansen:Nothing to Disclose, Harry L.A. Janssen:Nothing to Disclose, Adriaan J. van der Meer:Gilead: Consultant, Mirum: Consultant, Ipsen: Consultant, Gilead: Grant/Research Support, Ipsen: Grant/Research Support, Mirum: Grant/Research Support, dr Falk: Consultant.

1151 | ◆ OBETICHOLIC ACID ADJUNCT TO URSODEOXYCHOLIC ACID VS. UDCA MONOTHERAPY IN PRIMARY BILIARY CHOLANGITIS: A PROPENSITY SCORE–MATCHED COHORT ANALYSIS

Mahmoud Al-Bataineh[1] Jashanveer Johal[1] Archana Salek[1] Bianca Patel[1] Brandon Cunha[1] Abdallah Hussein[1] Jason Hyman[2] Yecheskel Schneider[1], [1]Virtua Health, [2]Einstein Medical Center, Philadelphia

Background: Ursodeoxycholic acid (UDCA) is the first-line treatment for primary biliary cholangitis (PBC), but up to 40% of patients have an inadequate biochemical response. Obeticholic acid (OCA), an FXR agonist, is approved as adjunctive therapy in UDCA-inadequate responders, yet real-world comparative data on hard clinical outcomes including mortality remain limited. **Methods:** We conducted a propensity score–matched retrospective cohort study using the TriNetX Global Collaborative Network (191.9 million patients). Cohort 1 comprised patients with PBC (ICD-10 K74.3) receiving both UDCA and OCA. Cohort 2 comprised PBC patients on UDCA monotherapy without OCA. Both cohorts excluded prior cirrhosis (K74.60), liver transplant status, and concurrent autoimmune hepatitis. Cohorts were balanced via 1:1 PSM yielding 655 patients per arm over a 6–120 month follow-up window. Pre-specified outcomes included liver transplantation, ALP normalization as a biochemical response surrogate, need for pruritus adjunctive therapy as a proxy for OCA-related adverse effect, inpatient encounters, and all-cause mortality. **Results:** Post-PSM cohorts were well-balanced across matched covariates. ALP normalization was significantly more frequent in the OCA adjunct arm (22.9% vs. 40.2%; RR 0.57; HR 0.44, 95% CI 0.36–0.54; log-rank $p < 0.001$), with median time to normalization of 3,149 days vs. 1,772 days in the UDCA-only arm. Need for pruritus adjunctive therapy was significantly higher in the OCA arm (11.9% vs. 6.0%; RR 2.0, OR 2.14; HR 1.89, 95% CI 1.29–2.78; log-rank $p = 0.001$), consistent with OCA's known on-target adverse effect profile. Inpatient encounter rates did not differ significantly between arms (17.7% vs. 24.1%; mean 6.2 vs. 6.6 encounters; $p = 0.75$). All-cause mortality was markedly lower in the OCA adjunct arm (5.2% vs. 11.0%; RR 0.47; HR 0.48, 95% CI 0.31–0.72; log-rank $p = 0.0003$). **Conclusion:** In this propensity-matched real-world cohort, OCA adjunct to UDCA was associated with significantly lower rates of ALP normalization failure, a 53% lower hazard of all-cause mortality, and a predictable increase in pruritus management requirements compared to UDCA monotherapy. These findings support the real-world effectiveness of OCA combination therapy in PBC while reinforcing the need for proactive pruritus monitoring and management. Liver transplant-free survival data should be incorporated in future analyses.

Disclosures: Mahmoud Al-Bataineh:Nothing to Disclose, Jashanveer Johal:Nothing to Disclose, Archana Salek:Nothing to Disclose, Bianca Patel:Nothing to Disclose, Brandon Cunha:Nothing to Disclose, Abdallah Hussein:Nothing to Disclose, Jason Hyman:Nothing to Disclose, Yecheskel Schneider:Nothing to Disclose.

1152 | ◆ FEWER THAN ONE IN FOUR PBC PATIENTS WITH INADEQUATE UDCA RESPONSE RECEIVE SECOND-LINE THERAPY: A DECADE-LONG NATIONWIDE ANALYSIS OF 3,799 PATIENT

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Background: Multiple second-line agents are now approved for primary biliary cholangitis (PBC) patients who fail ursodeoxycholic acid (UDCA), yet the real-world utilization of second-line (2L) treatment remains unknown. We examined real-world prescribing patterns, temporal trends, and clinical determinants of

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second-line therapy initiation across a large US-based cohort spanning the complete regulatory history of 2L PBC therapies. **Methods:** We performed a retrospective cohort study using the TriNetX global research network with deidentified electronic health records from 170 predominantly US healthcare organizations, 2015–2025. Eligible patients were adults with PBC and persistent alkaline phosphatase elevation after ≥12 months of UDCA, without concomitant chronic liver disease, decompensated cirrhosis, previous liver transplantation, malignancy, end stage kidney disease or dementia. Predictors of second-line initiation were identified by multivariable logistic regression. Prescribing trends were analyzed across sequential regulatory periods. **Results:** Of 3,799 patients with documented incomplete biochemical response to UDCA (defined as ALP>3x ULN), only 847 (22.3%) received any second-line therapy, which translates to close to 3,000 eligible patients being untreated over a decade. The cohort was 85.8% female, with a mean age of 66 years; 31% already had cirrhosis. Obeticholic acid was most commonly prescribed (10.9%), followed by fibrates (9.5%), seladelpar (4.4%), and elafibranor (3.2%). Younger age, female sex, and care at academic centers independently predicted 2L treatment uptake. Notably, 2L initiation rates were lower amongst higher risk group including male patients (vs female), and those under 35 years of age (vs >= 35 years) (both $p < 0.01$). Following regulatory approvals in 2025, 2L initiation rates increased modestly (23.1% vs. 19.3%; $p < 0.001$), accompanied by a marked shift from obeticholic acid toward PPAR agonists, though overall utilization remained far below what guideline-eligible disease burden would demand. **Conclusion:** Across 102 US healthcare systems over ten years, close to 3,000 PBC patients with documented UDCA failures, including those with established cirrhosis, never received a second-line agent. Temporal trends reflect increased awareness with new drug approvals, but only marginally increase the treatment coverage. Further work is needed to address this gap for UDCA-refractory PBC patients.

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1153 | ◆ SGLT2 INHIBITORS AND LONG-TERM OUTCOMES IN UDCA-TREATED PRIMARY BILIARY CHOLANGITIS WITH TYPE 2 DIABETES: A PROPENSITY-MATCHED ANALYSIS

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Background: Primary biliary cholangitis (PBC) is frequently accompanied by type 2 diabetes mellitus (DM2), but long-term hepatic and cardiovascular outcomes associated with sodium-glucose cotransporter-2 inhibitor (SGLT2i) use in ursodeoxycholic acid (UDCA)-treated PBC remain uncertain. We evaluated outcomes associated with SGLT2i exposure versus no SGLT2i exposure in UDCA-treated PBC without prior hepatic decompensation. **Methods:** Using the TriNetX Research Network of 111 healthcare organizations, we identified adults with PBC receiving UDCA. SGLT2i users, representing a DM2-enriched subgroup, were compared with UDCA-treated nonusers after 1:1 propensity-score matching on demographics, comorbidities, medications, and laboratory values. Patients with major competing liver diseases or prior hepatic decompensation were excluded. Outcomes were assessed from day 1 after index through 3 and 5 years. The primary outcome was major adverse liver outcomes (MALO), a composite of liver-related events and death. Secondary outcomes included hospitalization, MACE, mortality, pruritus, fatigue, albumin ≤3.5 g/dL, ALP, and incident hepatic decompensation. **Results:** In the 3-year matched cohort, 362 SGLT2i users were compared with 362 nonusers. SGLT2i use was associated with lower hospitalization (23.5% vs 31.8%; RR 0.74, 95% CI 0.58–0.94) and incident hepatic decompensation (4.1% vs 9.4%; RR 0.44, 95% CI 0.25–0.80). MALO was numerically lower by risk analysis (29.3% vs 35.9%; RR 0.82, 95% CI 0.66–1.01) and lower by survival analysis (HR 0.77, 95% CI 0.59–0.99). Mortality was numerically lower but borderline, while MACE, pruritus, fatigue, albumin ≤3.5 g/dL, and ALP did not differ. In the 5-year matched cohort, 433 SGLT2i users were compared with 433 nonusers. SGLT2i use was associated with lower mortality (7.9% vs 14.1%; RR 0.56, 95% CI 0.37–0.83) and incident hepatic decompensation (5.3% vs 11.8%; RR 0.45, 95% CI 0.28–0.72). MALO, hospitalization, and albumin ≤3.5 g/dL were lower by survival analysis, whereas MACE, pruritus, fatigue, and ALP did not differ by risk analysis. **Conclusion:** In this propensity-matched cohort of UDCA-treated PBC enriched for DM2 and without prior hepatic decompensation, SGLT2i exposure was associated with lower incident hepatic decompensation at 3 and 5 years and lower mortality at 5 years, without excess MACE or worsening ALP. Prospective studies are warranted to define the role of SGLT2i in DM2-enriched patients with PBC.

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Table 1. Outcomes after SGLT2i exposure in UDCA-treated PBC with T2DM

1:1 propensity-matched cohorts: n=362 per group at 3 years and n=433 per group at 5 years

Outcome	SGLT2i	No SGLT2i	RR (95% CI)	P (RR/t)	HR (95% CI)	P (HR)
3-year outcomes						
MALO (primary)	29.3%	35.9%	0.82 (0.66–1.01)	0.057	0.77 (0.59–0.99)	0.041
All-cause hospitalization	23.5%	31.8%	0.74 (0.58–0.94)	0.013	0.69 (0.52–0.91)	0.008
MACE	39.2%	34.8%	1.13 (0.93–1.36)	0.218	1.18 (0.93–1.50)	0.173
Follow-up ALP, mean U/L	162.7	179.3	—	0.243	—	—
All-cause mortality	6.9%	11.0%	0.63 (0.39–1.01)	0.051	0.63 (0.38–1.04)	0.068
Pruritus	4.2%	4.2%	1.00 (0.47–2.12)	0.993	1.00 (0.47–2.17)	0.992
Albumin ≤3.5 g/dL	14.9%	18.2%	0.82 (0.52–1.28)	0.378	0.72 (0.44–1.18)	0.192
Fatigue	6.4%	10.2%	0.63 (0.35–1.13)	0.114	0.60 (0.33–1.11)	0.099
Incident hepatic decompensation	4.1%	9.4%	0.44 (0.25–0.80)	0.005	0.43 (0.24–0.80)	0.005
5-year outcomes						
MALO (primary)	30.9%	36.7%	0.84 (0.70–1.02)	0.073	0.79 (0.63–0.99)	0.040
All-cause hospitalization	26.1%	30.7%	0.85 (0.69–1.05)	0.132	0.77 (0.60–0.99)	0.037
MACE	41.1%	38.8%	1.06 (0.90–1.25)	0.488	1.05 (0.85–1.30)	0.645
Follow-up ALP, mean U/L	163.8	182.0	—	0.107	—	—
All-cause mortality	7.9%	14.1%	0.56 (0.37–0.83)	0.003	0.53 (0.35–0.80)	0.002
Pruritus	5.4%	8.8%	0.61 (0.36–1.05)	0.072	0.58 (0.33–1.01)	0.049
Albumin ≤3.5 g/dL	17.6%	25.0%	0.70 (0.49–1.01)	0.052	0.58 (0.39–0.87)	0.008
Fatigue	7.6%	8.6%	0.88 (0.52–1.50)	0.644	0.80 (0.46–1.39)	0.425
Incident hepatic decompensation	5.3%	11.8%	0.45 (0.28–0.72)	0.001	0.42 (0.25–0.68)	<0.001

Abbreviations: PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid; T2DM, type 2 diabetes mellitus; MALO, major adverse liver outcomes; MACE, major adverse cardiovascular events; ALP, alkaline phosphatase.
RR values are from risk analysis; HR values are from time-to-event survival analysis.
P (RR/t) values are from risk analysis, except ALP where they are from t testing;
P (HR) values are from log-rank testing.
For pruritus, albumin ≤3.5 g/dL, and fatigue, analyses excluded patients with the outcome prior to the time window, so row-specific at-risk denominators differed from the matched cohort size.

Disclosures: Mohammad Alabbas:Nothing to Disclose, Akram Alnounou:Nothing to Disclose, Ahmad Alhusen:Nothing to Disclose, Omar Sims:Nothing to Disclose, Dian Chiang:Nothing to Disclose.

1154 | ◆ EARLY DIAGNOSIS AND FAVORABLE RISK PROFILES IN SWISS PATIENTS WITH PRIMARY BILIARY CHOLANGITIS: A COMPARATIVE ANALYSIS USING THE GLOBE AND UK-PBC SCORES

Beatrice Barda[1] Claudai Di Bartolomeo[1] Rossella Forlenza[2] Andrea Cerny[1] Giulia Magini[3] Guido Stirniman[4] David Semela[5] Christine Bernsmeier[6] Andreas E Kremer[7] Christinet Montserrat Fraga,[8] Andrea De Gottardi[9] Magdalena Filipowicz Sinnreich[6] Benedetta Terziroli Piccoli[10] Antonio Galante[11],
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Background: Primary Biliary Cholangitis (PBC) is a chronic cholestatic liver disease with a highly variable natural history. Prognostic tools like the GLOBE and UK-PBC scores have been validated internationally to predict liver-related outcomes. However, regional differences in screening and diagnostic practices may influence the clinical stage at presentation.The aim of our study is to compare the clinical characteristics and predicted outcomes of Swiss PBC patients with the original international GLOBE and UK-PBC derivation cohorts, testing the hypothesis that Swiss patients present at an earlier, less severe disease stage. **Methods:** We performed a retrospective analysis of 159 Swiss PBC patients treated with UDCA. Baseline demographics and biochemical markers (ALP, bilirubin, albumin, platelets) were analyzed. The GLOBE and UK-PBC risk scores were calculated after 12 months of UDCA therapy. Results were compared against published data from the original UK-PBC (n = 1,916) and GLOBE (n = 2,488) study groups. **Results:** In our Swiss cohort, we calculated both the GLOBE and UK-PBC score. In the Globe score cohort, we included 159 patients, the median age at diagnosis was 55.2 (47-64) years, and 135 (85%) were female. Compared to the original international cohorts, Swiss patients exhibited significantly lower baseline ALP levels 1.3 (0.74-2.75) VS 1.9 (1.2-3.5) x ULN and higher platelet ratio 1.65 vs 1. After 12 months of UDCA, ALP levels 1.2 (0.71-1.90) vs 1.34 (0.93-2.26) x ULN and higher platelet counts. In the UK score cohort, we included 115 patients, the median age at diagnosis was 50.3 (43-59) years, and 108 (94%) were female.The median GLOBE score of our cohort was 0.44, which was significantly lower than the derivation mean (0.78-0.86) ($p < 0.05$). Similarly, the UK-PBC 10-year risk of end-stage liver disease was 4.8% compared to 9-15% in the original cohorts. **Conclusion:** Swiss PBC patients appear to present at an earlier disease stage with more favorable prognostic markers than the original UK and Global cohorts. These findings suggest that robust diagnostic pathways in Switzerland may lead to earlier intervention, potentially correlating with improved long-term transplant-free survival.

Disclosures: Beatrice Barda:Nothing to Disclose, Claudai Di Bartolomeo:Nothing to Disclose, Rossella Forlenza:Nothing to Disclose, Andrea Cerny:Nothing to Disclose, Giulia Magini:Nothing to Disclose, Guido Stirniman:Nothing to Disclose, David Semela:Nothing to Disclose, Christine , Bernsmeier:Nothing to Disclose, Andreas E Kremer:Nothing to Disclose, Christinet Montserrat Fraga,:Nothing to Disclose, Andrea De Gottardi:Nothing to Disclose, Magdalena Filipowicz Sinnreich:Nothing to Disclose, Benedetta Terziroli Piccoli:Nothing to Disclose, Antonio Galante:Nothing to Disclose.

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1155 | EVALUATING PREVALENCE OF CHOLESTATIC GENE MUTATIONS IN A MULTIETHNIC US POPULATION: RESULTS FROM THE BIOME BIOBANK

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Background: Intrahepatic cholestasis of pregnancy (ICP) is a liver disease unique to pregnancy associated with significant maternal and fetal morbidity. The long-term implications of ICP on future liver disease remain unclear; however, emerging evidence suggests that gene variants associated with ICP may be associated with future hepatobiliary disease and cholangiocarcinoma. Prior estimates suggest ~20% of patients with severe ICP have pathogenic variants in hepatobiliary transporter genes but were limited by small sample sizes and predominantly European cohorts. We aimed to identify the prevalence of cholestatic gene variants among ICP patients in a diverse US cohort. **Methods:** We performed a retrospective review of exome sequence data from a previously established cohort of patients with ICP identified between 2009-2024 within the Mount Sinai BioMe Biobank, an EHR-linked biobank of 50,000+ consented participants in the New York City metropolitan area. Confirmed ICP was defined as total serum bile acids (TSBA) $\geq$ 10 µmol/L. We evaluated five genes previously implicated in ICP: *ABCB4, ABCB11, ATP8B1, ABCC2* and *TJP2.* Variants were annotated with variant effect predictors (VEP) and evaluated using ClinVar, CADD, REVEL, Polyphen2 and SIFT. Cumulative pathogenicity scores reflected the number of tools whose scores exceeded predefined pathogenic thresholds. **Results:** Of 888 patients with confirmed ICP, 111 had genetic data available in BioMe: 80 (72%) with TSBA 10-39, 17 (15%) with TSBA 40-99, and 14 (13%) with TSBA $\geq$ 100 µmol/L. Mean age was 32.3 years (SD 6.2); the cohort was 37% Hispanic, 34% White, 10% Asian, and 9% Black. Elevated liver enzymes were present in 77 (69%) individuals, and 23 (21%) had preexisting liver disease, led by viral (n = 6) and autoimmune hepatitis (n = 6). Ten individuals (9%) carried 15 variants: TJP2 (n = 5), ABCB11 (n = 3), ABCC2 (n = 3), ABCB4 (n = 2), and ATP8B1 (n = 2). Variants were identified in 6/42 Hispanic patients (14%) and 2/31 patients with TSBA $\geq$ 40 (7%). Seven variants (47%) had a pathogenicity score of 2 and 8 variants (53%) had a score of 1. ClinVar identified one pathogenic stop-gained variant in ATP8B1. **Conclusion:** In this diverse US cohort, 9% of patients with ICP carried potentially pathogenic variants in hepatobiliary transporter genes. TJP2 was the most implicated gene in our cohort – unlike prior studies in which ABCB4 was most common – and four patients carried multiple variants. The prevalence of genetic variants is lower than reported in European studies, which may reflect our inclusion of milder disease and greater ancestral diversity. These candidate variants should be further explored to inform risk stratification for ICP and future hepatobiliary disease.

Demographics, peak bile acids, and peak liver enzymes in patients with cholestatic gene variants

Patient	Gene	Variant	Pathogenicity Score	Race	Ethnicity	Peak Bile Acid	Peak AST	Peak ALT
1	TJP2	9:69151677:C:A_A	1	Other	Hispanic	14.2	28	39
2	TJP2	9:69251072:C:T_T	1	Other	Hispanic	25.0	34	21
	ABCC2	10:99836218:G:T_T	2					
3	ATP8B1	18:57655270:C:T_T	2	Other	Not Hispanic	35.5	44	25
4	ABCB11	2:168927218:C:T_T	2	Black	Hispanic	13.0	80	28
	TJP2	9:69251072:C:T_T	1					
	ABCC2	10:99844350:C:T_T	2					
5	ABCB4	7:87450089:G:C_C	1	Other	Hispanic	36.4	487	599
6	TJP2	9:69251072:C:T_T	1	Black	Not Hispanic	28.0	25	36
7	ABCB11	2:168944606:C:A_A	2	White	Hispanic	12.3	30	32
	ABCC2	10:99797306:G:A_A	2					
8	ABCB4	7:87431528:C:T_T	2	Other	Hispanic	240.0	50	68
	ATP8B1	18:57669422:C:A_A *	1					
9	ABCB11	2:168964291:C:T_T	1	White	Not Hispanic	11.0	22	12
10	TJP2	9:69221022:C:T_T	1	White	Not Hispanic	315.0	288	623

* Indicates pathogenic stop-gain variant identified by ClinVar

Disclosures: Jacqueline Slobin:Nothing to Disclose, Lauren Alpert:Nothing to Disclose, Simon Lee:Nothing to Disclose, Nina Rodriguez:Nothing to Disclose, Rhoda Sperling:Nothing to Disclose, Keith Sigel:Nothing to Disclose, Lea Davis:Nothing to Disclose, Tatyana Kushner:Gilead: Grant/Research Support, Gilead: Advisor, GSK: Advisor, Eiger: Advisor, GSK: Consultant, Madrigal: Advisor, Ipsen: Advisor, Mirum: Advisor, Mirum: Grant/Research Support, Ipsen: Grant/Research Support.

1156 | SAFETY, PHARMACOKINETICS AND TARGET ENGAGEMENT OF AX-0810 A FIRST-IN-CLASS RNA EDITING THERAPY DESIGNED TO MODULATE BILE ACID TRANSPORT FOR CHOLESTATIC DISEASE

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Background: Cholestatic liver disease, such as primary sclerosing cholangitis (PSC) and biliary atresia, involve toxic intrahepatic bile acid (BA) accumulation leading to

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hepatocellular injury, inflammation, and fibrosis. There are no approved disease-modifying therapies for PSC and biliary atresia, and many patients require liver transplantation. Sodium taurocholate co-transporting polypeptide (NTCP; SLC10A1) is the dominant basolateral conjugated BAs transporter and a therapeutic target to reduce hepatocellular BA uptake. AX-0810 is a novel modality and first-in-class GalNAc-conjugated RNA editing oligonucleotide designed to induce a site-specific adenosine-to-inosine edit in NTCP mRNA, leading to reduced NTCP-mediated hepatocellular BA uptake. This first-in-human study evaluates the safety, tolerability, pharmacokinetics (PK), and target engagement of AX-0810 in healthy participants [EU CT number: 2025-521876-77-00]. **Methods:** This ongoing randomized, double-blinded, placebo-controlled, multiple-ascending-dose study evaluates subcutaneous AX-0810 in healthy adults (18–55 years) in 3 sequential dose cohorts (3, 6, and 9 mg/kg; total N = 33), with safety and PK review before dose escalation. Participants received an initial dose followed by a 2-week observation period, then 3 weekly doses with 12-week follow-up. Primary endpoints are safety and tolerability; the secondary endpoint is PK of AX-0810. Exploratory objectives evaluate pharmacodynamics with NTCP biomarker-based target engagement, including total serum BAs, serum BA composition, and the clearance of orally administered tauro-ursodeoxycholic acid (TUDCA) as a functional NTCP biomarker. BAs are measured after a standardized diet with calculated caloric and fat content at baseline and at multiple timepoints during dosing and follow-up. **Results:** Based on interim blinded data from the 3 mg/kg and 6 mg/kg cohorts (22 participants), AX-0810 was well tolerated with no serious adverse events (AEs), or AEs leading to discontinuation of the study treatment. All reported AEs were of mild or moderate severity. No clinically meaningful trends were observed in safety laboratory parameters, vital signs, or other safety assessments. PK parameters were consistent with preclinical predictions and supported the translational assumptions used for dose selection. Target engagement was evaluated through changes in total serum BAs, serum BA composition (conjugated vs unconjugated), and TUDCA clearance. **Conclusion:** AX-0810 is a potential novel hepatoprotective RNA-editing therapy to induce NTCP loss of function in cholestatic liver disease. This first-in-human study combines single and multiple ascending dose features to evaluate safety, PK, and NTCP target engagement using linked biomarkers of NTCP activity. The overall safety, tolerability, and PK profile observed support future studies in patients with cholestatic disease. **Disclosures:** Robert Bart Takkenberg:Nothing to Disclose, Gideon Hirschfield:Intercept: Consultant, GSK: Consultant, CymaBay: Consultant, Ipsen: Consultant, Falk: Consultant, Pliant: Consultant, Mirum: Consultant, Advanz: Consultant, Chemomab: Consultant, Gilead: Consultant, Kowa: Consultant, Henkjan Verkade:Nothing to Disclose, Golnar Karimian:proqr: Employee, Galapagos: Employee, Nicole Cnubben:Nothing to Disclose, Galja Pletikapic: Nothing to Disclose, Sjef de Kimpe:Nothing to Disclose, Lianne Stevens:Nothing to Disclose, Walter Boiten:Nothing to Disclose, Eva Coll de la Rubia:Nothing to Disclose, Francesco De Chiara:Nothing to Disclose, Agathe Plichta: Nothing to Disclose, Robin Besuyen:Nothing to Disclose, Cristina Lopez Lopez:Nothing to Disclose.

1157 | SELADELPAR LEADS TO RAPID AND SUSTAINED ALKALINE PHOSPHATASE REDUCTION, REGARDLESS OF BASELINE LEVELS, OVER 5 YEARS OF TREATMENT IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS

Christopher Bowlus[1] Cynthia Levy[2] Christophe Corpechot[3] Aparna Goel[4] Kyung min Kwon[5] Johnny Chew[5] Valentina Shakhnovich[5] Xin Qi[5] Alejandra Villamil[6], [1]University of California, Davis, [2]University of Miami, [3]Assistance Publique-Hôpitaux de Paris, Sorbonne University, [4]Stanford University Medical Center, [5]Gilead Sciences, Inc., Foster City, CA, United States, [6]The Liver Autoimmunity Unit, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina

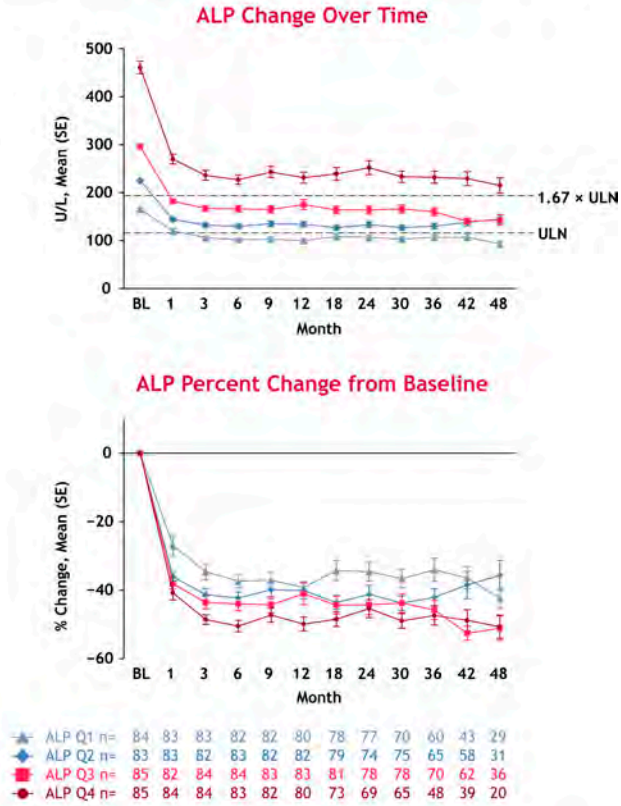
Background: Alkaline phosphatase (ALP) is a key marker of disease activity in primary biliary cholangitis (PBC), with higher ALP levels associated with negative long-term outcomes. In the pivotal placebo-controlled, Phase 3 RESPONSE trial (NCT04620733), seladelpar, a first-in-class delpar indicated for the second-line treatment of PBC, significantly reduced ALP levels compared with placebo. Here, we report changes in ALP across baseline (BL) ALP quartiles, as well as consistency and depth of ALP response, in patients with PBC receiving seladelpar for up to 4 years in the ongoing, open-label, Phase 3 ASSURE study (NCT03301506). **Methods:** Patients from RESPONSE and legacy seladelpar trials enrolled in ASSURE and received seladelpar 10 mg daily. BL was defined as seladelpar initiation either in RESPONSE or ASSURE. Patients were pooled and categorized by BL ALP quartile (data cutoff: Jan 2026). ALP changes from BL, along with depth of response (ALP reductions of $\geq$ 20%, 30%, or 40%), were assessed up to Month (M) 48. ALP changes from BL up to M48 were also assessed in patients who did not achieve ALP normalization and/or composite biochemical response (CBR; defined as ALP $<$ 1.67 × upper limit of normal [ULN], $\geq$ 15% reduction in ALP, and total bilirubin $\leq$ ULN) at M12. Safety was evaluated up to M60. **Results:** Overall, 337 patients were included in the analysis; 94.4% were female and 15.4% had cirrhosis at BL. BL demographics were similar across BL ALP quartiles, defined as: ALP (U/L) $<$ 198.5, Q1; $\geq$ 198.5 to $<$ 259, Q2; $\geq$ 259 to $<$ 352, Q3; and $\geq$ 352, Q4. ALP was reduced at M1 in all quartiles, with reductions

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sustained through M48 (mean change from BL [standard error; SE]: −42.4% [2.98], Q1; −35.7% [4.33], Q2; −51.1% [3.56], Q3; −50.7% [3.42], Q4; **Figure**). In the overall population, 88.8%, 82.8%, and 63.8% of patients achieved ALP reductions of ≥ 20%, 30%, and 40%, respectively, at M48. Of 330 patients evaluable at M12, 228 (69.1%) achieved CBR and 115 (34.8%) achieved ALP normalization. For the 102 (30.9%) who did not achieve CBR, mean (SE) ALP change from BL at M48 was −34.7% (6.18). For the 215 (65.2%) who did not achieve ALP normalization, mean (SE) ALP change from BL at M48 was −43.5% (2.72). Adverse event incidence was similar across quartiles. **Conclusion:** Seladelpar treatment led to rapid reductions in ALP, sustained up to 4 years, across ALP quartiles. Treatment with seladelpar was associated with significant and sustained ALP reductions, including in patients who did not achieve biochemical response at M12. Seladelpar appeared well tolerated regardless of BL ALP.

Figure. ALP Changes in Patients Treated with Seladelpar by Baseline ALP Quartile in ASSURE



ALP Q1: < 198.5 U/L; ALP Q2: ≥ 198.5 to < 259 U/L; ALP Q3: ≥ 259 to < 352 U/L; ALP Q4: ≥ 352 U/L.
The ULN for ALP is 116 U/L for male and female patients.
n = number of evaluable patients at each time point.
ALP, alkaline phosphatase; BL, baseline; Q, quartile; SE, standard error; ULN, upper limit of normal.

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1158 | AI-BASED DIGITAL PATHOLOGY IDENTIFIES CHICKEN-WIRE FIBROSIS ASSOCIATED WITH THE DEVELOPMENT OF PORTAL HYPERTENSION AND PREDICTS CLINICAL OUTCOMES IN EARLY-STAGE PRIMARY BILIARY CHOLANGITIS

Lin Ma[1] Shuxiang Lee[1] Tingting Lv[1] Weijia Duan[1] Sha Chen[1] Hong You[1] Jidong Jia[1] Xinyan Zhao[1], [1]Liver Research Center, Beijing Friendship Hospital, Capital Medical University, Beijing, China

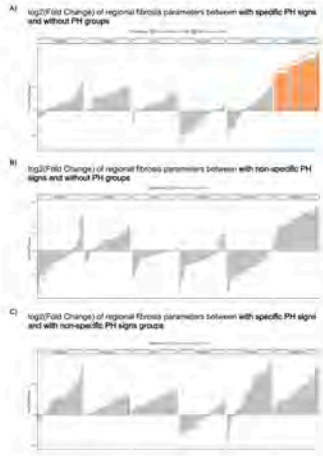
Background: The pathogenesis of portal hypertension (PH) in early-stage primary biliary cholangitis (PBC) remains unclear. This study aimed to explore

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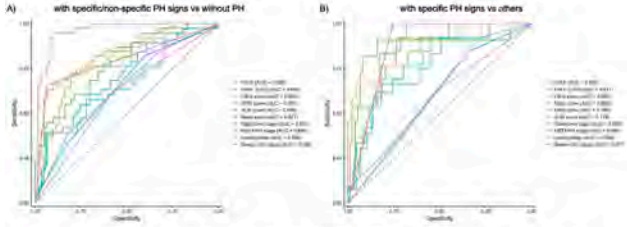
the pathological mechanisms underlying PH in early-stage PBC using an artificial intelligence (AI)-based digital pathology platform. **Methods:** This retrospective study included patients with early-stage PBC (Ludwig stage 0–2) at our institute between June 2008 and September 2025. According to the current diagnostic criteria for porto-sinusoidal vascular disorder, patients were categorized into three groups based on PH manifestations: specific PH signs, non-specific PH signs, and no PH. Second harmonic generation/two-photon excitation fluorescence (SHG/TPEF) microscopy was used to quantify collagen features. Collagen parameters were compared among groups using one-way ANOVA or the Kruskal–Wallis test, as appropriate. A Fibrosis-based Portal Hypertension Index (PHI-F) was developed using a support vector machine (SVM) algorithm with leave-one-out cross-validation based on collagen parameters. Model performance was compared with conventional serological models and histological staging systems using the area under the receiver operating characteristic curve (AUC). Prognostic implications were assessed using Kaplan–Meier analysis and Cox regression with Firth's penalized likelihood. **Results:** A total of 101 patients were enrolled, including 62 without PH, 26 with non-specific PH signs, and 13 with specific PH signs. Among 184 collagen features quantified by SHG/TPEF imaging, 20 showed significant differences among the three groups ($P < 0.05$). Post-hoc analysis revealed that chicken-wire fibrosis parameters were selectively elevated in patients with specific PH signs compared with those without PH. PHI-F accurately discriminated PH status. For distinguishing patients with PH signs from those without PH, the AUC was 0.959 (95% CI, 0.922–0.995) in the full cohort and 0.802 (95% CI, 0.715–0.890) in cross-validation. For distinguishing patients with specific PH signs from the other two groups, the AUC was 0.890 (95% CI, 0.811–0.969) in the full cohort and 0.811 (95% CI, 0.692–0.930) in cross-validation. PHI-F outperformed conventional models, including four scoring systems (FIB-4, ALBI, APRI, and Mayo), three histological staging systems (Ludwig, METAVIR, and Nakanuma), and the Baveno VII criteria. Based on PHI-F predictions, patients were stratified into two prognostic groups with significantly different risks of liver-related death/transplantation and composite endpoints (hepatic decompensation, liver transplantation, or all-cause death) (both log-rank $P < 0.001$). **Conclusion:** AI-based SHG/TPEF quantitative fibrosis analysis identifies chicken-wire fibrosis as a key collagen feature associated with specific PH signs in early-stage PBC. PHI-F accurately identifies PH signs and helps stratify patients at high risk of adverse clinical outcomes.

Figure 1.Quantified fibrosis parameters in different liver regions demonstrated changes in fibrosis among with specific PH signs, with non-specfic PH signs and without PH groups.

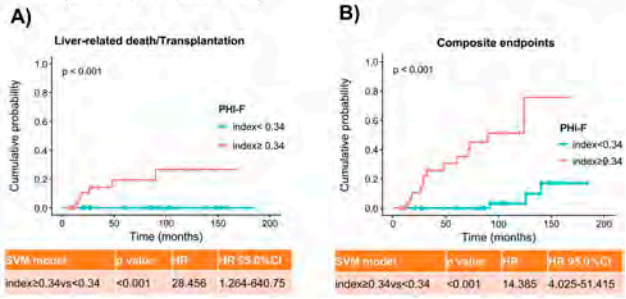


Histogram showing the log2(Fold Change) of liver fibrosis characteristics assessed by regional fibrosis parameters between (A) with specific PH signs and without PH groups, (B) with non-specific PH signs and without PH groups, (C) with specific PH signs and with non-specific PH signs groups (one way-ANOVA or Kruskal-Wallis test). The variables that had been found significant by post hoc testing were colored (Tukey's HSD or Dunn's test).

Figure 2. ROC plots of PHI-F compared with ALBI score, APRI score, Baveno VII criteria, FIB-4 score, Mayo score, Ludwig stage, METAVIR stage and Nakanuma stage for the discrimination between A) with specific/non-specific PH signs vs without PH; B) with specific PH signs vs others. Abbreviation: LOO, leave-one-out



C. Kaplan–Meier time-to-event analysis in Early-stage PBC patients With Different Risks Stratified Using PHI-F for A) liver-related death/liver transplantation, B) composite endpoints (the development of hepatic decompensation, liver transplantation, or all-cause death).



Disclosures: Lin Ma:Nothing to Disclose, Shuxiang Lee:Nothing to Disclose, Tingting Lv:Nothing to Disclose, Weijia Duan:Nothing to Disclose, Sha Chen:Nothing to Disclose, Hong You:Nothing to Disclose, Jidong Jia:Nothing to Disclose, Xinyan Zhao:Nothing to Disclose.

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1159 | FRACTURE EPIDEMIOLOGY FOR ADULTS WITH PRIMARY SCLEROSING CHOLANGITIS, PRIMARY BILIARY CHOLANGITIS, AND CIRRHOSIS: A NATIONWIDE UNITED STATES CLAIMS-BASED COHORT STUDY

Nataliya Razumilava[1] Kurt Hankenson[1] Daniel Whitney[1], [1]University of Michigan

Background: Primary sclerosing cholangitis (PSC), primary biliary cholangitis (PBC), and cirrhosis are chronic liver diseases with extrahepatic consequences in which fractures are increasingly recognized as major contributors to morbidity, mortality, and socioeconomic burden. Non-U.S. population-based data demonstrate increased fracture risk and excess post fracture mortality in cirrhosis and PBC. In contrast, evidence in PSC has largely emphasized low bone mineral density and osteoporosis rather than incident fractures, and contemporary population level estimates of fracture risk remain limited. Aim of this study was to compare data across PSC, PBC, and cirrhosis to quantify fracture risk and to inform targeted surveillance and prevention strategies in different chronic liver disorders and their stages. **Methods:** This retrospective cohort study used private and public nationwide U.S. claims data from calendar years 2017–2023. Adults $\geq$ 18 years of age with PSC, PBC, cirrhosis, or without these conditions (comparator cohort) were included if they had at least 1 year of continuous health plan enrollment. We estimated sex-stratified 1-year period prevalence of fracture at any site (primary outcome), by skeletal region (secondary outcome), and by specific site (tertiary outcome), and compared PSC, PBC, and cirrhosis cohorts with the comparator cohort. Sex-stratified logistic regression estimated odds ratios (ORs) for fracture outcomes using the comparator cohort as the reference and adjusting for age, insurance type, and study entry year. **Results:** There were 3,328 adults with PSC (mean age, 51.4 years; 52.8% women), 10,519 adults with PBC (62.6 years; 89.5% women), 232,452 adults with cirrhosis (62.3 years; 44.8% women), and 10,000,000 adults in the comparator cohort. The 1-year period prevalence of fracture at any site was highest for cirrhosis (men, 16.8%; women, 23.7%), followed by PBC (men, 14.2%; women, 19.4%), PSC (men, 8.4%; women, 12.2%), and the comparator cohort (men, 4.2%; women, 6.1%). The adjusted OR for any fracture increased stepwise from PSC to PBC to cirrhosis, and there was strong evidence of effect modification by age, with PSC and PBC demonstrating a growing fracture risk disparity with aging and cirrhosis showing the greatest relative excess risk in younger adults. **Conclusion:** Adults with PSC, PBC, and cirrhosis have substantially elevated fracture risk compared with the general insured population, with distinct age- and site-specific patterns across liver disease types. These findings position hepatic osteodystrophy as a clinically relevant complication across the spectrum of cholestatic liver disease and cirrhosis and support earlier, liver disease–, site-, and age-specific strategies for fracture risk assessment, bone health surveillance, and fall prevention in clinical practice.

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1160 | SELADELPAR LEADS TO LONG-TERM EFFICACY AND SAFETY IN PATIENTS WITH PRIOR OCA AND/OR FIBRATE EXPOSURE

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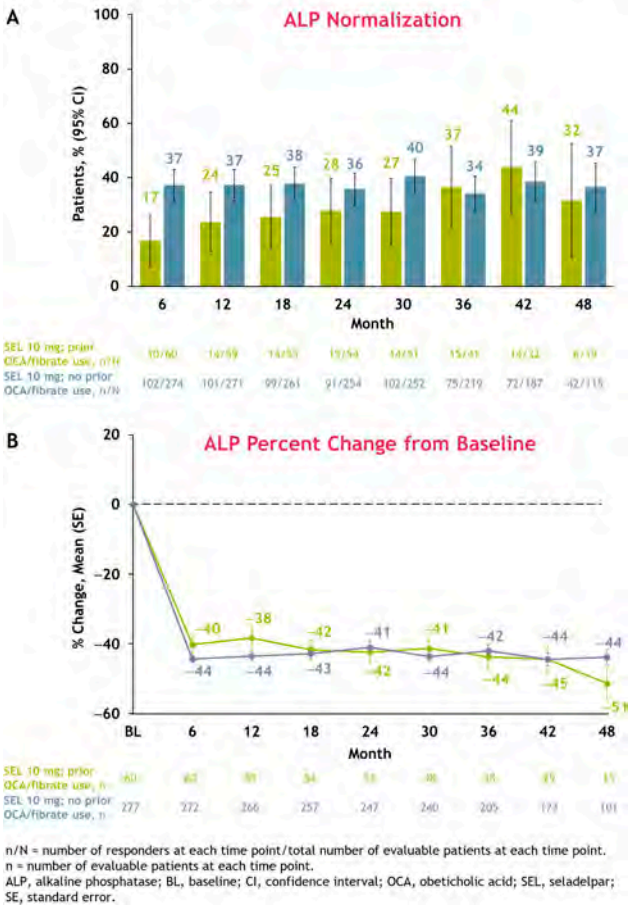
Background: Seladelpar, a first-in-class delpar (selective peroxisome proliferator-activator receptor delta [PPARδ] agonist), is an approved second-line treatment for primary biliary cholangitis (PBC). Second-line obeticholic acid (OCA) was withdrawn from markets due to safety concerns, while off-label fibrates have variable efficacy and safety data. In the pivotal Phase 3 RESPONSE trial (NCT04620733), seladelpar improved alkaline phosphatase (ALP) and pruritus in patients with and without prior OCA/fibrate use, with a similar safety profile to placebo, up to 1 year. Here, we report updated long-term efficacy and safety up to 5 years in patients with or without prior OCA/fibrate use in ASSURE (NCT03301506). **Methods:** ASSURE is an ongoing, open-label study of patients receiving once-daily oral seladelpar 10 mg, who enrolled from RESPONSE or earlier legacy seladelpar studies. OCA and fibrates were prohibited, and a 6-week washout was required prior to study entry. Patients were pooled, with baseline (BL) defined as seladelpar initiation in RESPONSE or ASSURE. Analyses were conducted in patients with prior OCA and/or fibrate vs no prior use. Biochemical efficacy endpoints include ALP normalization and ALP percent change from BL to Month (M) 48. In patients with BL moderate to severe pruritus (numerical rating scale [NRS] $\geq$ 4), clinically meaningful improvement ($\geq$ 3-point reduction) is reported to M36. A subset analysis evaluated biochemical endpoints through

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M36 in patients with prior fibrate-only use. Safety was assessed using all available data through M60 in this interim analysis (data cutoff: Jan 2026). **Results:** Among 337 seladelpar-treated patients, 60 had prior OCA/fibrate use and 277 had no prior use. BL mean ALP was numerically higher in patients with prior vs no prior use (331 U/L and 278 U/L, respectively). At M48, both groups achieved similar ALP normalization rates (32% and 37%) and showed rapid and sustained reductions in ALP from BL (51% and 44%; **Figure 1**). In patients with BL moderate to severe pruritus (prior use: n = 20; no prior use: n = 88), similarly high rates of clinically meaningful improvement were observed at M36 (58% and 65%). In patients with prior fibrate-only use (n = 19), 44% (4/9) of patients achieved ALP normalization at M36, with ALP reductions of 45% from BL. No treatment-related serious adverse events were reported, and no new safety signals were observed in patients with prior OCA/fibrate use. **Conclusion:** Seladelpar led to marked and sustained biochemical response, with pruritus improvement, through up to 4 years in ASSURE, regardless of prior OCA and/or fibrate exposure. Seladelpar was well tolerated in both groups through up to 5 years of treatment.

Figure 1. Biochemical Response through Month 48 by Prior OCA/Fibrate Use



n/N = number of responders at each time point/total number of evaluable patients at each time point.
n = number of evaluable patients at each time point.
ALP, alkaline phosphatase; BL, baseline; CI, confidence interval; OCA, obeticholic acid; SEL, seladelpar; SE, standard error.

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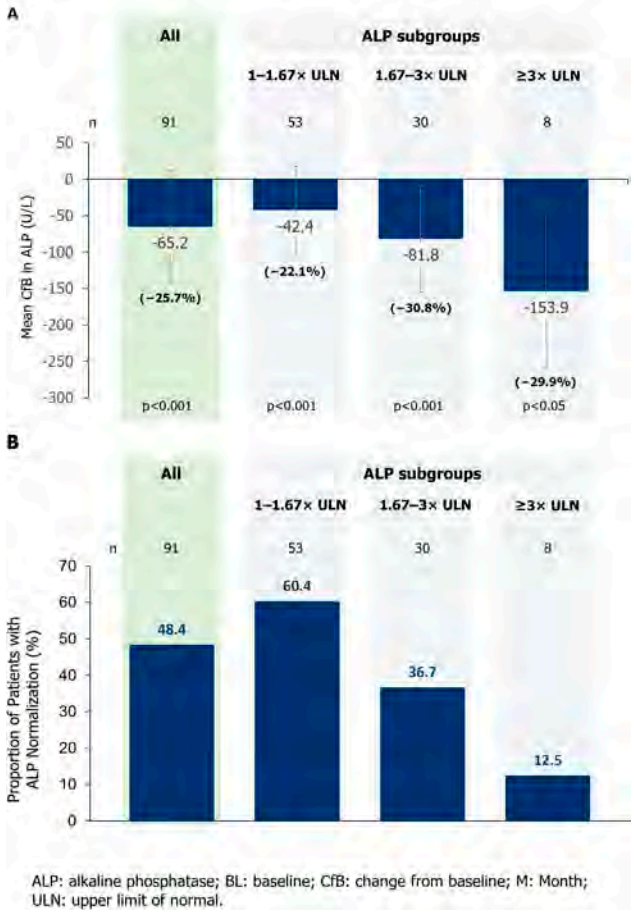
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1161 | IMPACT OF BASELINE ALKALINE PHOSPHATASE LEVELS ON ELAFIBRANOR TREATMENT OUTCOMES IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS IN REAL-WORLD SETTINGS

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Background: Reductions in alkaline phosphatase (ALP) and bilirubin are surrogate markers of disease activity and predictors of long-term clinical outcomes in primary biliary cholangitis (PBC). In the phase III ELATIVE® trial, elafibranor demonstrated rapid and sustained improvements in multiple biochemical markers; in a post hoc analysis, baseline (BL) ALP values were demonstrated to impact biochemical response and ALP normalization rates. Here, we evaluated real-world data to determine if similar patterns with elafibranor are seen in routine clinical practice. **Methods:** This non-interventional, retrospective observational study used medical, pharmacy, and laboratory data from the HealthVerity network. Adult patients with PBC who initiated elafibranor and had BL ALP above the upper limit of normal (ULN) and ≥1 pre-index and ≥1 post-index ALP measurement were included. The date of first observed elafibranor exposure was defined as the index date (BL). Biochemical responses (including change from baseline [CfB]) were assessed using laboratory data through Month (M)6 post-index. Patients were stratified by BL ALP relative to the ULN: >1 to <1.67×, ≥1.67 to <3×, and ≥3×. Outcomes were analyzed using the Wilcoxon test. **Results:** Among 91 patients with PBC who initiated elafibranor with BL ALP >ULN and available pre-and post-index measurements, proportions by BL ALP were: >1–<1.67× ULN (58.2%), ≥1.67–<3× ULN (33.0%), and ≥3× ULN (8.8%). Most patients (93.4%) were female and mean age was 58.9 (SD: 11.4) years at BL. Substantial reductions were observed in mean ALP levels from BL to M6, including in those with mildly elevated BL ALP (>1–<1.67× ULN: −22.1%) and highly elevated BL ALP (≥3x ULN: −29.9%; **Figure A**). At M6, 48.4% of patients achieved normal ALP. ALP normalization was achieved in greater proportions of patients with BL ALP >1–<1.67× ULN (60.4%) and ≥1.67–<3× ULN (36.7%) than those with BL ALP ≥3× ULN (12.5%; **Figure B**); however, overall improvements from BL were observed across all subgroups after up to 6 months of elafibranor treatment. **Conclusion:** This analysis corroborated findings from the ELATIVE® trial, where patients who initiated elafibranor treatment with lower BL ALP values had higher ALP normalization rates compared to those with higher BL ALP. Importantly, reductions in ALP were consistent across all BL ALP subgroups, supporting the effectiveness of elafibranor across BL ALP strata.

Figure. Mean CfB in ALP (A) and proportions of patients with ALP normalization (B) at M6, stratified by ALP level at BL



ALP: alkaline phosphatase; BL: baseline; CfB: change from baseline; M: Month; ULN: upper limit of normal.

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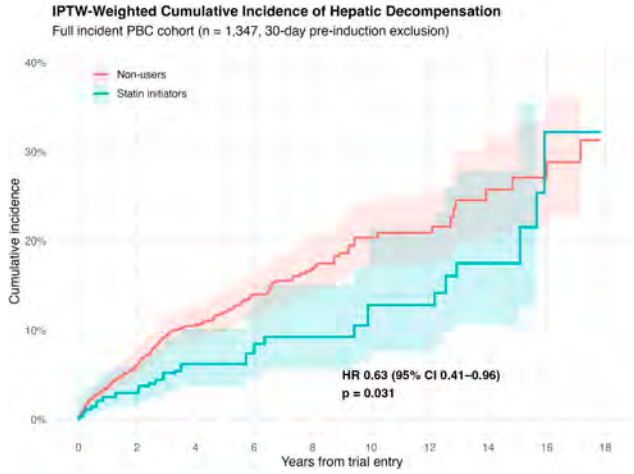
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1162 | STATIN INITIATION AND LOWER HEPATIC DECOMPENSATION RISK IN PRIMARY BILIARY CHOLANGITIS: A POPULATION-BASED TARGET TRIAL EMULATION

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Background: A recent target trial emulation (TTE) reported lower hepatic decompensation risk with statin use in primary biliary cholangitis (PBC). Whether this association persists in a universal health system and among patients with PBC and dyslipidemia is unknown. We emulated a sequential target trial of statin initiation and liver outcomes in incident PBC. **Methods:** EMR-validated incident PBC patients in Alberta, Canada (2005–2024) were identified using linked health data. After excluding prior decompensation, early death, and prevalent statin use, monthly eligibility windows were used in a single-entry target trial emulation. New statin initiators entered at first dispensation and compared with statin-naive non-users assigned one randomly sampled eligible month to preserve temporal alignment. A 30-day pre-induction exclusion was applied before propensity-score weighting. Stabilized inverse probability weights were estimated from demographics, comorbidity, time since PBC diagnosis, ursodeoxycholic acid and cardiovascular medication use, LDL cholesterol, and calendar time. Weighted Cox models with robust standard errors (SEs) estimated hazard ratios (HRs) for hepatic decompensation (ascites, variceal bleeding, encephalopathy/failure, hepatorenal syndrome, or spontaneous bacterial peritonitis). Secondary analyses evaluated major adverse liver outcome (MALO; decompensation, HCC or liver transplantation), a dyslipidemia-restricted active-indication cohort, induction windows, and cumulative statin duration. **Results:** The primary cohort included 1,347 patients (286 statin initiators, 1,061 non-users). After weighting, all standardized mean differences (SMDs) were <0.08. Median follow-up was 5.3 and 4.8 years. During 7,747 person-years, 176 decompensation events occurred: 27 among statin initiators (15.5/1,000 PY) and 149 among non-users (24.8/1,000 PY). Statin initiation was associated with lower decompensation risk (HR 0.63, 95% CI 0.41–0.96; $P=.031$). MALO showed a concordant trend (190 events; HR 0.69, 95% CI 0.47–1.01; $P=.058$). Estimates were stable across 0-, 30-, 60-, and 90-day induction windows (HR range, 0.59–0.63). In the dyslipidemia-restricted cohort ($n=942$), the effect estimate remained similar but not statistically significant (HR 0.66, 95% CI 0.43–1.03; $P=.067$). Brief exposure (<90 days) was not associated with decompensation (HR 0.94; $P=.89$), whereas sustained exposure (≥ 90 days) was associated with lower decompensation risk (HR 0.59, 95% CI 0.37–0.94; $P=.025$), and with lower risk per additional year of use (HR 0.89, 95% CI 0.85–0.93; $P<.001$). **Conclusion:** In this Canadian sequential target trial emulation of incident PBC, statin initiation was associated with lower hepatic decompensation risk in all patients with a similar but not statistically significant estimate in the dyslipidemia-restricted cohort.



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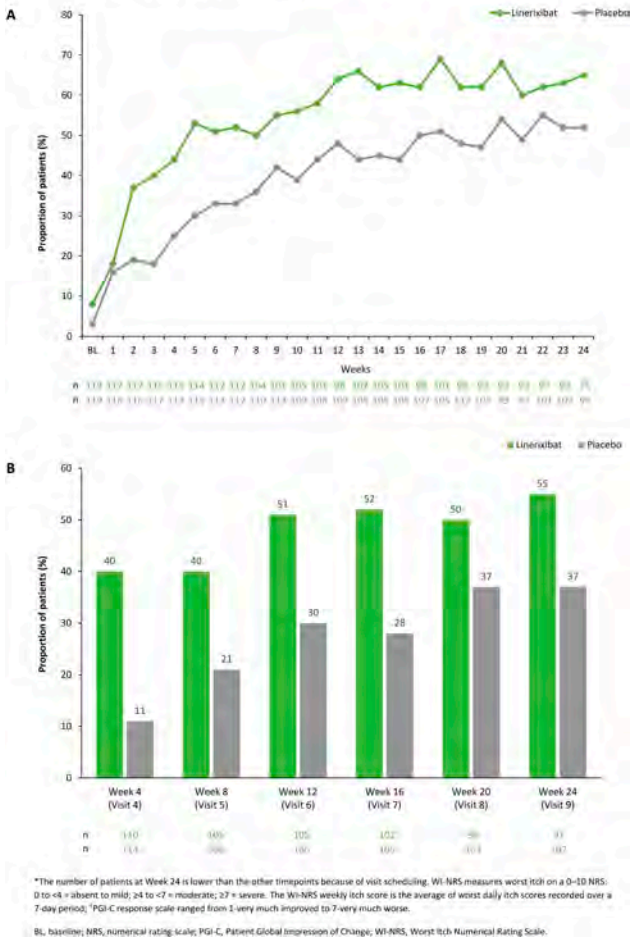
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1163 | CLINICAL MEANINGFULNESS OF LINERIXIBAT EFFICACY IN PRURITUS IN PRIMARY BILIARY CHOLANGITIS (PBC): POST HOC ANALYSES FROM THE PHASE 3 GLISTEN STUDY

Brooke Currie[1] Cynthia Levy[2] David Jones[3] Gideon Hirschfield[4] Ivana Lazic[5] Alexander Cobitz[1] Danielle Podmore[5] Jennifer Shannon[6] Megan McLaughlin[7] Marlyn Mayo[8], [1]GSK, Collegeville, USA, [2]University of Miami, [3]Newcastle University, UK, [4]Toronto General Hospital, [5]GSK, London, UK, [6]GSK, Durham, NC, USA, [7]GSK, Collegeville, USA (at time of study conduct), [8]University of Texas Southwestern Medical Center

Background: Cholestatic pruritus affects up to 89% of patients (pts) with PBC, negatively impacting sleep and quality of life (QoL). Linerixibat, an ileal bile acid transporter inhibitor, is the first medicine approved in the US for the treatment of cholestatic pruritus in pts with PBC, based on the Phase 3 GLISTEN study (NCT04950127), which demonstrated a rapid, significant, and sustained improvement in pruritus and itch-related sleep interference vs placebo. This post hoc analysis further assessed the clinical meaningfulness of GLISTEN efficacy results, including the proportion of pts who achieved a rapid (Week 2) and clinically meaningful (3-point) reduction in Worst Itch Numerical Rating Scale (WI-NRS), the proportion who decreased from moderate–severe itch to mild/no itch, those who reported perceived improvements in itch, and those who experienced improvements in itch-related QoL and sleep interference. **Methods:** Post hoc analyses were performed on patient-reported outcome (PRO) data collected at Week 2 and up to Week 24 of GLISTEN in pts with PBC and moderate-to-severe pruritus (WI-NRS ≥ 4). PROs included: WI-NRS; Sleep Interference NRS (SI-NRS); Patient Global Impression of Severity (PGI-S) and Change (PGI-C); PBC-40. Sleep responders were pts with a ≥ 2.5-point improvement in SI-NRS. **Results:** Cochran-Mantel-Haenszel (CMH) analysis confirmed a significantly higher proportion of itch responders with linerixibat vs placebo for the 3-point reduction in WI-NRS ($p = 0.035$) at Week 2. A higher proportion of pts on linerixibat vs placebo achieved mild/no itch (WI-NRS < 4) across all 24 weeks (Figure A). A higher proportion of pts reported their itch as "very much improved" (PGI-C) with linerixibat vs placebo (Figure B). CMH analysis confirmed a greater proportion of pts on linerixibat had change in itch that was meaningful (PGI-C item 2) compared with placebo across all visits (all $p < 0.02$). Despite not reaching a significant difference at Week 24 as a single timepoint, when itch-related QoL (PBC-40 Itch domain) was evaluated over the whole 24-week period using a mixed-effect model for repeated measures, linerixibat resulted in greater QoL improvement than placebo (least square mean difference [LSMD] −0.88, $p = 0.005$). Pts with moderate–severe sleep impairment (SI-NRS ≥ 4) at baseline experienced a significant improvement in SI-NRS and PBC-40 Sleep item score over 24 weeks with linerixibat vs placebo (SI-NRS: LSMD −0.76, $p = 0.006$; PBC-40 Sleep: LSMD −0.41, $p = 0.003$); there were consistently more sleep responders on linerixibat vs placebo across all weeks, including at Week 24 (72% [58/81] vs 57% [51/90]). **Conclusion:** Linerixibat treatment in pts with PBC and moderate–severe pruritus resulted in clinically meaningful reductions in itch severity, often to mild/no itch, as well as subjective global improvements in itch, improvements in itch-related QoL, and reduced itch-related sleep impairment.

Figure: Proportion of patients (A) achieving mild/no itch (WI-NRS weekly score <4) by week* and (B) reporting itch as "very much improved" based on PGI-C (PGI-C score=1)† by visit in GLISTEN



*The number of patients at Week 24 is lower than the other timepoints because of visit scheduling. WI-NRS measures worst itch on a 0–10 NRS: 0 to <4 = absent to mild; ≥4 to <7 = moderate; ≥7 = severe. The WI-NRS weekly itch score is the average of worst daily itch scores recorded over a 7-day period; †PGI-C response scale ranged from 1-very much improved to 7-very much worse.

BL, baseline; NRS, numerical rating scale; PGI-C, Patient Global Impression of Change; WI-NRS, Worst Itch Numerical Rating Scale.

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1164 | SELADELPAR DOWNREGULATES INFLAMMATORY AND FIBROTIC PATHWAYS: INSIGHTS FROM SERUM PROTEOMIC ANALYSIS

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Background: Seladelpar, a first-in-class selective PPAR-δ agonist (delpar), is approved for second-line treatment of primary biliary cholangitis (PBC) and significantly improved cholestasis and pruritus in the pivotal Phase 3, placebo-controlled RESPONSE study (NCT04620733). In a recent serum proteomic analysis of RESPONSE samples, seladelpar led to reductions in known markers of cholestasis, inflammation, fibrosis, and pruritus, along with increases in serum levels of PPAR-δ targets involved in improving lipid metabolism. The aim of this analysis was to further characterize the top biological processes and pathways affected by seladelpar using an unbiased pathway analysis approach. **Methods:** In the RESPONSE study, 193 patients with PBC were randomized 2:1 to receive seladelpar 10 mg or placebo daily for 12 months. Serum proteomic profiles from 180 patients (862 samples) were measured using the SomaScan 11k Assay version 5.0, which quantifies 9,852 human proteins. Data normalization, calibration, and quality control processes were performed according to the manufacturer's instructions. Longitudinal changes in protein levels at Months 1, 3, 6, and 12 were analyzed using mixed-effects models that estimated placebo-adjusted changes from baseline at each post-baseline time point. Pathway analyses were then conducted for all seladelpar-treated patients and for seladelpar responders based on the magnitude of alkaline phosphatase (ALP) decline, using QIAGEN® Ingenuity Pathway Analysis (IPA®). Adjusted P-values and z-scores were used to infer pathway significance and directionality, respectively. **Results:** Pathway analysis of seladelpar-induced changes in serum proteomic profiles at Month 12 showed significant downregulation of pathways associated with fibrosis and inflammation (adjusted $P < .05$) and upregulation of pathways associated with PPAR agonism (adjusted $P < .05$). Seladelpar treatment downregulated >15 fibrosis-related proteins ($P < .05$) including ACVR1, ITGB1, ACTA2, WNT5A, WNT10A, and LTBP1. Seladelpar treatment also downregulated >20 inflammation-related proteins ($P < .05$) including CHIT1, LGALS3, MIF, HSPA5, RALB, BIRC2, and TRADD. The magnitude of observed reductions in inflammatory and pro-fibrotic pathways increased over time and were stronger in patients with greater ALP reduction. **Conclusion:** Unbiased serum proteomic analysis of 180 patient samples reflects the antifibrotic and anti-inflammatory actions of seladelpar in PBC. In addition to the well-established anticholestatic effects of seladelpar in RESPONSE, these data provide insights into the mechanistic underpinnings for the reduction in liver injury markers, and stabilization or improvement in liver stiffness, with seladelpar treatment.

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1165 | THE UTILITY OF LIVER BIOPSY IN DIAGNOSING AUTOIMMUNE HEPATITIS

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Background: Liver biopsy is recommended to establish the diagnosis of autoimmune hepatitis (AIH). Prior studies have questioned the necessity of histology in diagnosing AIH, especially when typical serologic biomarkers are present. We aimed to evaluate how frequently liver histology altered the probability of an AIH diagnosis as assessed by the simplified AIH (sAIH) score. **Methods:** We identified patients with autoimmune hepatitis (AIH) established with our hepatology group since 2020 using a research repository (STARR, Stanford University). Diagnosis date was defined by earliest use of AIH ICD-9/10 codes or mention of AIH in clinical notes. Serologies and pathology closest to diagnosis date were used. Histology descriptions were analyzed to identify AIH features (interface hepatitis, lymphoplasmacytic inflammation, and hepatic rosettes). A compatible histologic diagnosis of AIH was defined as presence of ≥ 1 and < 3 of these features or inclusion of AIH in the differential diagnosis. A typical histologic diagnosis required presence of 3 of these features. The sAIH score was calculated in two stages: first excluding histology, where a maximum score of 6 denoted probable AIH, and then including histology, where scores of ≥ 7, ≥ 6, and < 6 indicated definite, probable, and possible AIH, respectively. We compared patients whose diagnostic category changed with histology and those whose category remained unchanged. Patients without histology available within 90 days of diagnosis were excluded. Data extraction was done using R (*v.4.5.1, RStudio*) with AI-assisted coding tools (*Claude, Anthropic*) **Results:** There were 130 eligible patients included in the cohort (*Table 1*). Median age at AIH diagnosis was 56 (IQR 39-67) and 107 (82.3%) patients were female. Histology was typical of AIH in 4 (3.1%) patients and otherwise compatible. Excluding histology from the sAIH score, the diagnosis of AIH was probable for 1 patient and possible for 129 patients. Including histology, the diagnosis of AIH was probable or definite for 19 (14.6%) and possible for 111 (85.4%) patients. Of the patients whose probability of AIH increased with histology, 18 (100%) demonstrated ANA and/or ASMA positivity and IgG levels ≥ 1.1 times the upper limit of normal (ULN). In these 18 patients, IgG/ULN ratio was 1.59 (IQR 1.36-2.17) compared to 0.82 (IQR 0.21-1.23,) for those whose diagnostic category of AIH remained unchanged despite histology ($p < 0.001$, Mann-Whitney U). **Conclusion:** In this cohort of AIH patients, histology altered the diagnostic category of AIH in a minority of patients (14.6%), highlighting the limited additional value of liver biopsy in this setting. In certain clinical contexts, serologic parameters - specifically IgG/ULN > 1.1 with concurrent ANA/ASMA positivity - may be sufficient to diagnose AIH without histology. Biopsy may be best reserved for cases where diagnostic uncertainty remains after serologic evaluation.

Table 1. Clinical characteristics of AIH Patients (N = 130)

Characteristic	n (%) or Median [IQR]
Age, years	56 [38.5–66.5]
BMI	26.6 [23.1–30.1]
MELD	15.5 [8–34]
MELD 3.0	13 [5–26]
Sex	
Female	107 (82.3%)
Male	23 (17.7%)
Race / Ethnicity	
Asian/Pacific Islander	19 (14.6%)
Hispanic/Latino/Spanish	40 (30.8%)
Native American	1 (0.8%)
Non-Hispanic Black	4 (3.1%)
Non-Hispanic White	51 (39.2%)
Other	15 (11.5%)
ANA / ASMA Positive	missing: 10
No	31 (23.8%)
Yes	89 (68.5%)
SLA Positive	missing: 103
No	24 (18.5%)
Yes	3 (2.3%)
LKM Positive	missing: 63
No	57 (43.8%)
Yes	10 (7.7%)
IgG ratio > 1.1 (denominator: N = 115 with IgG)	missing: 15
No	72 (62.6%)
Yes	43 (37.4%)
IgG ratio > 1.0 (denominator: N = 115 with IgG)	missing: 15
No	68 (59.1%)
Yes	47 (40.9%)
Biopsy Classification	
Compatible	126 (96.9%)
Typical	4 (3.1%)
AIH Score (without biopsy)	
Possible	129 (99.2%)
Probable	1 (0.8%)
AIH Score (with biopsy)	
Possible	111 (85.4%)
Probable	18 (13.8%)
Definite	1 (0.8%)

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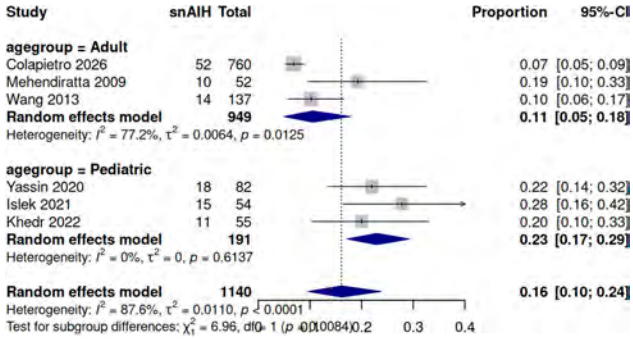
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1166 | TRUE SERONEGATIVE AUTOIMMUNE HEPATITIS IS RARE: A SYSTEMATIC REVIEW AND META-ANALYSIS REVEALS A DIAGNOSTIC GAP DRIVEN BY INCOMPLETE AUTOANTIBODY TESTING

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Background: Seronegative autoimmune hepatitis (snAIH) is reported in 7-35% of clinical cohorts, but prevalence estimates vary widely depending on the autoantibody panel used. No prior meta-analysis has, to our knowledge, quantified the pooled prevalence of apparent snAIH or examined how standardized second-line testing affects classification. We aimed to pool the prevalence of apparent snAIH across published cohorts and to assess the impact of comprehensive autoantibody re-evaluation on seronegative classification. **Methods:** A systematic review of PubMed (2000-2026) identified 22 studies on snAIH. Six cohorts (1,123 patients, 119 seronegative) provided verified raw data for quantitative synthesis. Proportions were pooled using a random intercept logistic regression model with maximum-likelihood estimation and logit transformation. Apparent snAIH was defined as negativity for standard autoantibodies (ANA and/or SMA, with or without LKM1). Statistical analyses were performed in R (meta package). An AI-based tool was used for literature screening assistance and manuscript drafting; all outputs were validated by the authors. **Results:** Apparent snAIH prevalence was 17% (95% CI: 10-28%), but confirmed snAIH after adequate testing was approximately 1%, suggesting that roughly 1 in 6 AIH patients may carry an incorrect seronegative label. Heterogeneity was substantial (I-squared = 91.3%). Pediatric cohorts showed higher apparent prevalence (28%, 95% CI: 20-37%) compared to adult cohorts (10%, 95% CI: 6-16%; p = 0.0003), though limited by small study numbers (k = 3 per group). Among the six pooled cohorts, anti-SLA/LP testing was documented in only 2 (33%). Across all 16 original cohort studies, anti-SLA/LP was documented in 25%, atypical pANCA in 13%, and anti-LC1 in none. In the largest multicenter study (Colapietro et al., 2026; 760 patients), 52 initially seronegative patients (6.8%) were re-evaluated; only 9 (1.18%) remained seronegative after accounting for incomplete serological workup. Given that delayed immunosuppression in AIH is associated with progression to cirrhosis and reduced survival, this diagnostic gap has direct clinical implications. **Conclusion:** Apparent seronegativity is common (approximately 17%), but confirmed seronegativity after comprehensive testing is rare (approximately 1%). The diagnostic gap is primarily driven by omission of anti-SLA/LP testing. Misclassification as seronegative may delay initiation of immunosuppression, risking progression to fibrosis and cirrhosis in patients with otherwise treatable disease. Untreated AIH carries 10-year survival as low as 27%, compared to over 90% with timely immunosuppression. These findings support the implementation of standardized reflexive second-line autoantibody panels before assigning a seronegative diagnosis, to avoid diagnostic delay and preventable disease progression.



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1167 | ORAL VANCOMYCIN IS NOT ASSOCIATED WITH MEANINGFUL CHANGES IN LIVER-RELATED ENDPOINTS AMONG ADULTS WITH PRIMARY SCLEROSING CHOLANGITIS: A RANDOMIZED, PLACEBO-CONTROLLED TRIAL

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Background: Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease without approved medical therapies. We examined the efficacy and safety of oral vancomycin (OV) in those with PSC. **Methods:** In this multicenter, phase 3, 18-month,

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double-blind, placebo-controlled trial, we randomly assigned adults with large duct PSC and a serum alkaline phosphatase (SAP) greater than 1.5 times the upper limit of normal to placebo or oral vancomycin (OV) with dosages ranging from 125-375 mg four times daily pending biochemical response. The primary endpoint was normalization of SAP. **Results:** Of the 82 patients who underwent randomization, 73 individuals had at least one outcome assessment. Individuals who withdrew early were less likely to rate their baseline health as excellent or very good (23.4% vs 54.5%, $p < 0.01$) despite having similar PSC prognostic features to those who completed the study. Except for one subject, all participants receiving OV had their dosages increased at the month 6 and 12 time points. Increasing the OV dose did not impact SAP levels. SAP normalization rates were similar (5% placebo, 6.7% OV, $p = 1.00$) after 18 months. Rates of lowering SAP less than 1.5 times the ULN were identical in both groups by month 18 (20.0% placebo, 20.0% OV, $p = 1.00$). Those who received OV had greater reduction in SAP (+1.2% placebo, -21.9% OV, $p = 0.03$). Six months after stopping OV, there was not a significant change in SAP: 11.2% (95% confidence interval: -1.0% -34.3%). There were no differences in the changes in either the Mayo PSC risk score (-0.1 placebo, -0.1 OV, $p = 0.88$), liver stiffness values (+0.1 kPa placebo, -4.0 kPa OV, $p = 0.15$), and 5-D itch scale (-1.2 placebo, -2.0 OV, $p = 0.46$). Four participants developed at least one episode of ascending cholangitis (4.8% placebo, 5.0% OV, $p = 0.96$) and 2 subjects developed hepatic decompensation (ascites $n = 1$, variceal hemorrhage $n = 1$) (0% placebo, 5.0% OV, $p = 0.14$). One patient who received OV developed cholangiocarcinoma. The proportion of individuals with serious adverse events was similar between groups (placebo 16.7%, OV 12.5%, $p = 0.59$). Discoloration of the teeth and tongue was the most common side effect of OV (17.5%). **Conclusion:** OV was not associated with clinically significant reductions in markers of PSC disease severity. Impairments in quality of life that are independent of liver disease severity may influence patient retention in clinical trials.

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1168 | INVOLVEMENT OF DECREASED PERIBILIARY PLEXUS AND PRIMARY CILIA OF BILIARY EPITHELIAL CELLS ASSOCIATED WITH CELLULAR SENESCENCE IN THE PATHOGENESIS OF PRIMARY BILIARY CHOLANGITIS

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Background: We previously demonstrated that cellular senescence in bile duct lesions—namely chronic non-suppurative destructive cholangitis (CNSDC) and ductular reaction (DR)—may be involved in disease progression in primary biliary cholangitis (PBC). Damages of primary cilia of biliary epithelial cells (BECs) due to ischemia and DNA damage responses (DDR) are reportedly related to biliary epithelial senescence in transplantation-related cholangiopathy. We investigated an association of cellular senescence with the status of primary cilia and peribiliary vascular plexus (PBP) feeding bile ducts, and their clinicopathological significance in PBC. **Methods:** Subjects included liver biopsy and resected liver specimens from 125 patients with PBC (90 and 35 cases with early and advanced stages, respectively) and 115 control liver diseases, including primary sclerosing cholangitis (PSC). Immunohistochemical analyses were performed to evaluate the expression of senescence markers ($p16^{INK4a}$ and $p21^{WAF1/Cip1}$), senescence-associated secretory phenotypes (SASPs; CCL2 and Ifit3), a primary cilia marker alpha-tubulin, a DDR marker gamma-H2AX, PD-L1, and stimulator of interferon genes (STING) in BECs and CD34-positive PBP. An association of senescent BECs with the status of cilia, number of PBP and clinicopathological parameters were analyzed. **Results:** Expression levels of $p16^{INK4a}$ and $p21^{WAF1/Cip1}$, SASPs, gamma-H2AX, PD-L1, and STING were significantly increased in small bile ducts in PBC compared with control livers ($p < 0.01$). In ductular cells, expression of $p16^{INK4a}$ and $p21^{WAF1/Cip1}$ was significantly elevated in advanced-stage PBC, and increased $p16^{INK4a}$ expression correlated with inadequate response for UDCA ($p < 0.01$). PD-L1 expression was localized specifically to bile ducts involved in CNSDC lesions, suggesting heterogeneity among senescent BECs. Primary cilia were decreased in senescent BECs in small bile ducts involved in CNSDC in 75% of PBC and were significantly decreased in bile ductules in advanced stage of PBC, compared with normal liver ($p < 0.05$). Number of PBP was significantly decreased in small bile ducts in PBC, and the decrease was correlated with cholangitis activity and cellular senescence

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($p < 0.01$). **Conclusion:** Decreased primary cilia and PBP in association with biliary epithelial senescence may play roles in the pathogenesis of PBC.
Disclosures: Motoko Sasaki:Nothing to Disclose, Yasunori Sato:Nothing to Disclose, Yasuni Nakanuma:Nothing to Disclose.

1169 | RENALASE IS A NOVEL CANDIDATE BIOMARKER OF HEPATIC INFLAMMATION AND DISEASE ACTIVITY IN AUTOIMMUNE HEPATITIS

Kanika Malani[1] Bonnie Chen[2] Scott Roberts[2] Swathi Krishnan[2] Marina Silveira[2] James Boyer[3] Xiaojia (Sasha) Guo[4] Gary Desir[4] David Assis[3], [1]Department of Medicine; Yale School of Medicine New Haven, CT, [2]Section of Digestive Diseases; Yale School of Medicine New Haven, CT, [3]Yale University, [4]Section of Nephrology; Yale School of Medicine New Haven, CT

Background: Autoimmune hepatitis (AIH) is a chronic immune-mediated liver disease, yet reliable immune-based biomarkers to guide treatment and prognosis are lacking. Renalase (RNLS), a kidney-secreted flavoprotein with immunomodulatory properties, has been implicated in autoimmune disease but has not been evaluated in AIH. We aimed to determine whether peripheral RNLS levels serve as a biomarker of hepatic inflammation and disease activity in AIH. **Methods:** Stored AIH samples were obtained from the Yale Liver Center Patient Biorepository. Free RNLS (F-RNLS) and acid-release RNLS (AR-RNLS) were measured using a validated ELISA. Clinical data (Table 1) were obtained through chart review. Spearman correlations and Mann-Whitney U tests, with Benjamini-Hochberg false discovery rate correction, assessed associations between each RNLS fraction and clinical variables. Among patients with serial RNLS measurements, within-person stability was assessed using Intraclass Correlation Coefficient (ICC). **Results:** The cohort comprised 40 unique patients with AIH (83 RNLS samples; 1–4 samples/patient). Mean age was 57 ± 16 years. 88% were women, 18% Hispanic/Latino, and 32% had cirrhosis (mean fibrosis stage 1.9 ± 1.4). At the time of RNLS collection, 64% were in biochemical remission. F-RNLS and AR-RNLS demonstrated distinct correlation profiles. F-RNLS was higher in biochemical remission than active disease ($r = -0.37$, FDR $p = 0.018$) and correlated positively with histologic grade of inflammation on biopsy ($\rho = +0.28$, FDR $p = 0.041$). AR-RNLS, which can bind to circulating IgG, correlated strongly with IgG ($\rho = +0.49$, FDR $p < 0.001$). Relapses within 6-12 months of RNLS collection were infrequent with no correlation between RNLS levels and AST, ALT, or IgG trends over this period. Among patients with serial RNLS measurements ($n = 24$, 67 samples), F-RNLS was temporally stable (ICC = 0.70) while AR-RNLS varied more (ICC = 0.19); within-patient changes in AR-RNLS over time correlated with changes in IgG ($\rho = +0.36$, $p = 0.023$, $n = 40$ pairs), while changes in F-RNLS did not correlate with any inflammatory marker. **Conclusion:** This is the first study to examine RNLS in AIH. F-RNLS and AR-RNLS reflect distinct biological processes. F-RNLS varies between patients according to degree of hepatic inflammation and disease control. However, within the same patient over time it remains stable and uncorrelated with inflammatory marker changes, consistent with a fixed patient-level process. AR-RNLS correlates with IgG-driven humoral immune activation, a relationship that holds dynamically within the same patients over time. Higher F-RNLS in biochemical remission despite tissue-level inflammation may suggest RNLS is sensitive to subclinical disease activity not reflected by standard labs. Immunohistochemical studies of RNLS in liver tissue are ongoing to address this question. Our findings support RNLS as a promising immune-based candidate biomarker in AIH.

Table 1. Associations Between Circulating Renalase Fractions and Clinical Variables in Autoimmune Hepatitis

Clinical Variable	Free RNLS FDR-adjusted p	Acid-Release RNLS FDR-adjusted p	Median (IQR) or n (%)
Labs (n=83 samples)			
Sodium	0.479	0.039*	139.0 (137.5–140.5)
Blood urea nitrogen	0.042*	0.494	14.0 (12.0–18.0)
Aspartate aminotransferase	0.041*	0.936	23.0 (19.5–41.0)
Hemoglobin	0.010*	0.161	13.5 (12.5–14.7)
Hematocrit	0.041*	0.175	40.4 (37.3–44.1)
Immunoglobulin G (IgG)	0.631	<0.001*	1247.0 (1119.5–1594.5)
Disease Activity & Severity (n=83 samples)			
Biochemical remission	0.018*	0.665	In remission: 53 (64%) Not in remission: 30 (36%)
Grade of inflammation on biopsy (n=70)	0.041*	0.270	2.5 (2.0–3.0)
Elastography CAP (n=18)	0.004*	0.980	242.0 (230.0–279.8)
Demographics (n=83 samples)			
Sex	0.005*	0.821	Women: 35 (88%) Men: 5 (12%)
Hispanic/Latino ethnicity	0.001*	0.667	Hispanic/Latino: 7 (18%)
Serial RNLS Measurements (n=24 patients, 67 samples)			
Intraclass correlation coefficient	0.70	0.19	—
Within-Patient Changes (n=40 consecutive sample pairs)			
Δ Acid-Release RNLS *vs* Δ IgG/ULN	—	0.023* (ρ=+0.36)	—

RNLS: Renalase. FDR: False Discovery Rate. IQR: Interquartile Range. CAP: Controlled Attenuation Parameter. Δ: Change in. ULN: Upper limit of normal.
**FDR-adjusted $p < 0.05$.*

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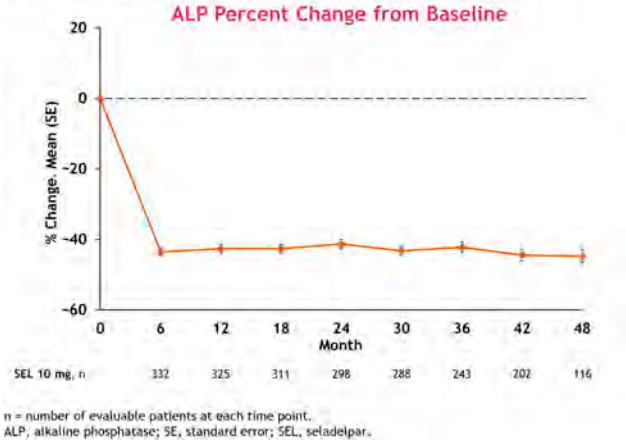
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1170 | SUSTAINED BIOCHEMICAL EFFICACY AND SAFETY OF SELADELPAR IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS, INCLUDING THOSE AT HIGH RISK FOR PROGRESSION, UP TO 5 YEARS OF TREATMENT FROM ASSURE

Kris Kowdley[1] Javier Ampuero Herrojo[2] Cynthia Levy[3] David Jones[4] Pietro Invernizzi[5] Xin Qi[6] Justin Smith[6] Kyung min Kwon[6] Alan Bonder[7], [1]Liver Institute Northwest, [2]Hospital Universitario Virgen del Rocío, Sevilla, Spain, [3]University of Miami, [4]Newcastle University, Newcastle, United Kingdom, [5]European Reference Network on Hepatological Diseases (ERN RARE-LIVER), Hamburg, Germany, [6]Gilead Sciences, Inc., Foster City, CA, United States, [7]Beth Israel Deaconess Medical Center, Boston, MA, United States

Background: Seladelpar (SEL), a first-in-class delpar (selective peroxisome proliferator-activator receptor delta [PPARδ] agonist), is approved as second-line treatment for primary biliary cholangitis (PBC) based on 1-year data in the pivotal RESPONSE study (NCT04620733). PBC is a chronic, slowly progressive disease requiring long-term therapy, making sustained efficacy and safety critical. Here, we report updated long-term efficacy and safety from the ASSURE (NCT03301506) study, including high-risk subgroups. **Methods:** ASSURE is an ongoing, open-label study of SEL 10 mg. Patients enrolled after the placebo-controlled RESPONSE trial or participation in prior SEL legacy trials. Data were pooled from SEL initiation (baseline [BL] defined as RESPONSE entry for patients randomized to SEL, and ASSURE entry for all others). Efficacy endpoints included alkaline phosphatase (ALP) percent change in ALP from BL through Month (M) 48, the latest timepoint with N > 100 patients. Clinically meaningful improvement (≥ 3-point reduction) in pruritus by numerical rating scale (NRS) was assessed in patients with moderate to severe pruritus (BL NRS ≥ 4). ALP percent change was also explored in subgroups considered to be at higher risk of progression, including those age ≤ 62 years and those with liver stiffness measurement (LSM) ≥ 10 kPa at BL. Patients with PBC clinical outcomes or who met liver safety criteria leading to SEL discontinuation were considered non-responders for all subsequent timepoints. Safety was assessed using all available data through M60 in this interim analysis (data cutoff: Jan 2026). **Results:** Among 337 patients, 242 received SEL for ≥ 3 years and 109 for ≥ 4 years, as of the data cutoff. SEL led to sustained ALP reductions, with > 30% achieving ALP NL across annual timepoints. At M48, mean ALP decreased by 45% (**Figure**). In patients with moderate to severe pruritus (N = 108), a sustained proportion achieved NRS change of −3.0 through M48 (55% [18/33]). Patients with age ≤ 62 years (N = 218) and LSM ≥ 10 kPa (N = 104) had higher ALP at baseline (298–308 vs 287 U/L overall) with higher rates of cirrhosis in the LSM ≥ 10 kPa subgroup (42%). SEL led to sustained ALP reductions at M48 (−46% in age ≤ 62; −32% in LSM ≥ 10 kPa). Safety analysis showed no treatment-related serious AEs reported through M60 of SEL exposure. **Conclusion:** Seladelpar led to sustained improvements in biochemical markers of cholestasis, including in high-risk patients, and pruritus reductions observed with long-term treatment. Seladelpar was well tolerated with a consistent safety profile and no new safety signals identified up to 5 years.

Figure. ALP Percent Change from Baseline in the Pooled Population Through 48 Months of Seladelpar Treatment



n = number of evaluable patients at each time point.
ALP, alkaline phosphatase; SE, standard error; SEL, seladelpar.

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1171 | HEALTH-RELATED QUALITY OF LIFE AMONG PATIENTS WITH PBC BY RESPONSE STATUS: ANALYSIS OF A REAL-WORLD DATASET

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Background: Primary biliary cholangitis (PBC) is a chronic, progressive autoimmune disease that damages the liver and can negatively impact quality of life. A key marker of disease activity in PBC is elevated levels of alkaline phosphatase (ALP) which is associated with negative long-term outcomes. Second line (2L) therapies such as seladelpar and elafibranor work by reducing cholestasis measured by ALP and other markers. This abstract aims to compare health-related quality of life (HRQoL) outcomes between patients that have exhibited normalized ALP levels between diagnosis and most recent lab results compared with those that have not. **Methods:** Data were drawn from the Adelphi Real World PBC Disease Specific Programme, a cross-sectional survey, with retrospective data collection in France, Germany, Italy, Spain, United Kingdom and the United States between November 2024 and May 2026. Patients with PBC were invited to complete a questionnaire including the Work Productivity and Activity Index (WPAI), PBC-40, Itch-Numerical Rating Scale (NRS), 5D-Itch, and EuroQol Visual Analogue Scale (EQ-VAS). Patients were grouped into 'abnormal ALP' (ALP >1 × upper limit of normal (ULN = 116 U/L) at diagnosis and most recent) and 'normalized ALP' (ALP >1 × ULN at diagnosis and ≤1 × ULN most recently). Cohorts were compared using bivariate analyses. **Results:** Analysis included 268 patients; 195 with abnormal ALP and 73 with normalized ALP. Those with abnormal ALP reported higher scores across all WPAI domains including impairment while working (33% vs 15%; $P < .0001$) and activity impairment (40% vs 21%; $P < .0001$). Those with abnormal ALP reported lower EQ-VAS scores (64.4 vs 78.1; $P < .0001$). Those with abnormal ALP reported more severe itch via the itch NRS (3.5 vs 2.1; $P = .0003$) and worse HRQoL at PBC-40 itch (6.7 vs 4.3; $P < .0001$) and fatigue (28.2 vs 21.5; $P < .0001$). 5D-Itch indicated that those with abnormal ALP were impacted by itch more than normalized ALP patients; a higher proportion reported experiencing itch 6+ hours a day (44% vs 17%; $P = .0001$), affecting 6+ body parts (33% vs 21%; $P = .0277$). **Conclusion:** Patients with PBC who achieved ALP normalization reported significantly better HRQoL outcomes compared with those who didn't. These findings highlight the clinical importance of achieving ALP normalization and support the need to offer alternative or 2L therapies to those with elevated levels of ALP to improve disease control and reduce the overall burden of PBC.

Table. Patient-reported Outcomes Measures

	Abnormal ALP (ALP >1 × ULN at diagnosis and most recent)	Normalized ALP (ALP >1 × ULN at diagnosis and ≤1 × ULN most recent)	*P* Value
WPAI			
WPAI: Percent work time missed			
Sample size, (n)	**82**	**31**	.5617
Mean [SD]	7.9 [19.3]	5.6 [18.6]	
WPAI: Percent impairment while working			
Sample size, (n)	***107***	**38**	<.0001
Mean [SD]	32.8 [25.5]	14.5 [14.1]	
WPAI: Percent overall work impairment			
Sample size, (n)	**80**	**30**	.0025
Mean [SD]	35.0 [30.2]	16.8 [17.1]	
WPAI: Percent activity impairment			
Sample size, (n)	***183***	**61**	<.0001
Mean [SD]	40.4 [29.2]	20.8 [19.2]	
PBC-40			
PBC-40: Itch			
Sample size, (n)	***183***	**64**	<.0001
Mean [SD]	6.7 [3.4]	4.3 [2.4]	
PBC-40: Fatigue			
Sample size, (n)	***182***	**65**	<.0001
Mean [SD]	28.2 [10.0]	21.5 [9.3]	
PBC-40: Cognitive			
Sample size, (n)	***182***	**64**	<.0001
Mean [SD]	12.5 [5.7]	9.0 [4.4]	
5-D Itch Scale			
5-D Itch Scale: Duration, n (%)			
Sample size, (n)	***179***	**59**	.0001
Less than 6hrs/day	101 (56%)	49 (83%)	
6-12 hrs/day	41 (23%)	10 (17%)	
12-18 hrs/day	18 (10%)	0 (0%)	
18-23 hrs/days	10 (6%)	0 (0%)	
All day	9 (5%)	0 (0%)	
5-D Itch Scale: Degree, n (%)			
Sample size, (n)	***184***	**62**	<.0001
Not present	49 (27%)	29 (47%)	
Mild	58 (32%)	24 (39%)	
Moderate	56 (30%)	9 (15%)	
Severe	21 (11%)	0 (0%)	
Unbearable	0 (0%)	0 (0%)	
5-D Itch Scale: Duration, n (%)			
Sample size, (n)	***181***	**60**	.2341
Completely resolved	38 (21%)	20 (33%)	
Much better, but still present	37 (20%)	12 (20%)	
Little bit better, but still present	43 (24%)	6 (10%)	
Unchanged	60 (33%)	22 (37%)	
Getting worse	3 (2%)	0 (0%)	
5-D Itch Scale: Disability, n (%)			
Sample size, (n)	***138***	***31***	.0076
Never affects this activity	36 (26%)	14 (45%)	
Rarely affects this activity	34 (25%)	10 (32%)	
Occasionally affects this activity	34 (25%)	4 (13%)	
Frequently affects this activity	29 (21%)	2 (7%)	
Always affects this activity	5 (4%)	1 (3%)	
5-D Itch Scale: Distribution, n (%)			
Sample size, (n)	***153***	***38***	.0277
0-2 body parts affected	30 (20%)	14 (37%)	
3-5 body parts affected	72 (47%)	16 (42%)	
6-10 body parts affected	38 (25%)	6 (16%)	
11-13 body parts affected	6 (4%)	2 (5%)	
14-16 body parts affected	7 (5%)	0 (0%)	

*WPAI, higher % = worse outcomes/lower productivity. †PBC-40, higher scores=worse HRQoL.
ALP, alkaline phosphatase; HRQoL, health-related quality of life; PBC, primary biliary cholangitis; ULN, upper limit of normal; WPAI, work productivity and activity index.

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1172 | PRIMARY BILIARY CHOLANGITIS AND PREGNANCY IN ONTARIO: A POPULATION-BASED EVALUATION OF MATERNAL, FETAL, AND LIVER-RELATED OUTCOMES

Kristel Leung[1] Manisha Jogendran[1] Wenbin Li[2] Maria Velez[3] Gail Wright[4] Jennifer Flemming[5] Gideon Hirschfield[6], [1]Queen's University, [2]ICES Queen's, [3]McGill University, [4]PBC Society, [5]Queen's University Cancer Research Institute, [6]Toronto General Hospital

Background: Primary biliary cholangitis (PBC) is a rare autoimmune liver disease predominantly affecting women, with most diagnosed after childbearing years. Despite being the most common autoimmune liver disease, no comparative population-level studies have evaluated how PBC relates to preceding (if age >50 at diagnosis) or subsequent (if age <50 at diagnosis) pregnancy, infertility, or obstetrical complications. **Methods:** Using population-level health administrative databases in Ontario, Canada with linked mother-baby data for deliveries >20 weeks' gestation, we characterized reproductive health patterns and complications in a validated incident cohort of PBC women. For obstetrical complications, comparisons were made to inverse probability weighted general population controls, including composites of severe maternal morbidity (SMM), severe neonatal morbidity (SNM), and multiple secondary outcomes. Liver-related outcomes (liver decompensation, transplant, death) within 1y were assessed if PBC was diagnosed before childbirth. **Results:** Amongst 3,264 women with PBC incident diagnosis from 2002 to 2021, 1,013 (31%) were diagnosed before age 50 (median 44y), while 2,251 (69%) were diagnosed after age 50 (median 61y). Overall, 1,090 women (33%) had at least one pregnancy recorded during the same timeframe, with overall pregnancy incidence of 45.7 per 1000 person-years (95%CI 43.7-47.7). There were 1,069 pregnancies that occurred before PBC diagnosis, with a median time of 17y postpartum to diagnosis (IQR 11-23); 45 pregnancies occurred amongst women already diagnosed with PBC before conception (median time 1y, IQR 1-2). Only 35 women had an estimated conception date within 9 months of PBC diagnosis (21 before, 14 after). Out of all women with a PBC diagnosis, 13% had 1+ infertility healthcare encounter.Women with PBC who had a pregnancy before age 50 (n = 638) experienced more than double the risk of SMM compared to general population controls (adjusted incidence rate ratio [IRR] 2.18, 95%CI 1.32-3.60; p = 0.002). Puerperal sepsis and maternal ICU admission were the most common SMM events among PBC women. There were no significant differences in SNM (IRR 0.86, 95%CI 0.55-1.35; p = 0.51). There were higher proportions of cholestasis of pregnancy, antepartum hemorrhage, hypertensive disorders of pregnancy, neonatal jaundice, and preterm birth compared to the general population (all p < 0.05, Table 1). There were no differences in labour induction, C-section, or forceps-/vacuum-assisted delivery. None of the patients with PBC diagnosed before pregnancy experienced postpartum liver-related complications within 1y of delivery. **Conclusion:** In this epidemiological study, adverse obstetrical outcomes were linked to PBC diagnosis, despite most pregnancies pre-dating PBC diagnosis by several years. These findings suggest that women suspected of having PBC should be evaluated for prior adverse obstetrical history.

Table 1. Population-Level Outcomes for Pregnancies Among Women Who Develop PBC in Their Lifetime, Compared to Inverse Probability Weighted General Population Controls in Ontario, Canada

Variable	PBC Childbirths	Control Childbirths	p-value
C section	216 (34%)	799 (31%)	0.12
Forceps-/vacuum-assisted birth	56 (8.6%)	240 (9.2%)	0.73
Induction of labour	150 (23.5%)	654 (25.1%)	0.40
Postpartum hemorrhage	39 (6.1%)	176 (6.8%)	0.56
Antepartum hemorrhage	66 (10.3%)	199 (7.6%)	0.026*
Cholestasis of pregnancy	25 (3.9%)	17 (0.7%)	<0.001*
Placental abruption	10 (1.6%)	27 (1.0%)	0.26
Placental previa	7 (1.1%)	21 (0.8%)	0.48
Gestational diabetes	43 (6.7%)	212 (8.1%)	0.24
Venous thromboembolism	6 (0.9%)	16 (0.6%)	0.37
Neonatal jaundice	80 (12.5%)	252 (9.7%)	0.033*
Neonatal respiratory distress	72 (11.3%)	241 (9.3%)	0.12
Small for gestational age	67 (10.5%)	246 (9.4%)	0.42
Large for gestational age	77 (12.1%)	297 (11.4%)	0.64
Preterm birth	91 (14.3%)	215 (8.3%)	<0.001*
Fetal congenital anomalies	19 (3.0%)	96 (3.7%)	0.39

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1173 | PATIENT REPORTED PRURITUS WITH HORMONAL CONTRACEPTION USE IN PATIENTS WITH A HISTORY OF INTRAHEPATIC CHOLESTASIS OF PREGNANCY

Laura Bonebrake[1] Cecilia Duenas[2] Gerry Nesbitt[3], [1]SSM Health/St. Louis University, [2]PBC Research Foundation, [3]PBC Ireland

Background: Intrahepatic Cholestasis of Pregnancy (ICP) is a rare, pregnancy liver disorder where bile acid transport is disrupted. The cause is thought to be multifactoral with both hormones and a genetic predisposition contributing. Some ICP patients report continued pruritus postpartum, including with the use of hormonal birth control but incidence has not been published. We aim to assess the incidence of patient-reported pruritus with the use of hormonal contraception after a pregnancy with ICP. **Methods:** Data was obtained from an IRB approved, ICP Patient Registry, in collaboration with a patient advocacy group, ICP Care.Participants with a history of ICP self-reported pregnancy and postpartum data. The key outcome measure was recurrence of pruritus with use of a variety of hormonal contraception types.Patients were also stratified by timing of their ICP diagnosis, including early-onset ICP (less than 28 weeks gestation) and late-onset ICP ($\geq$28 weeks).Due to ICP being a rare disorder in only 0.2-0.5% of pregnancies, we are aware that statistical significance may not be met. **Results:** A total of 102 patients had taken a combination oral contraceptive pill (OCP) containing both estrogen and progesterone. Of these, 23.5% of these patients had pruritus.Further analysis showed that if a patient had intolerance to a combination OCP, they had a 45-53% chance of also reacting to use of a progesterone only birth control method.Pruritus with progesterone only contraceptive methods was then reported. Patients had recurrent pruritus in 18.6% of cases with the progesterone pill and 22.2% of cases with a progestin IUD.In looking at diagnosis timing of ICP, patients with early-onset ICP had recurrent pruritus in 38.2% of patients using combination OCPs while late-onset ICP patients only had a 17% chance of pruritus. Odds Ratio was noted to be 1.34 but not significant (p = 0.37) most likely due to small sample size. **Conclusion:** This data is the first to show the proportion of patients with a history of ICP who experience recurrent pruritus with hormonal contraception. One in four ICP patients exhibit pruritus with an oral contraceptive with both estrogen and progesterone. Fewer patients had pruritus with progesterone only methods, but 1 in 5 patients still had a reaction.Patients with early onset ICP appeared more sensitive to hormone use and more likely to report recurrent pruritus, suggesting a genetic predisposition and possible sub-groups.Further studies are needed to determine predictors of pruritus with hormonal contraception, risks of long-term use of hormones in ICP patients and liver surveillance plans after pregnancy, especially with hormonal use.

Birth Control Method	Pruritus	No Pruritus
Combination Estrogen/Progesterone pill (N=102)	24 (23.5%)	78
Progesterone only pill (N=43)	8 (18.6%)	35
"Mirena" IUD (N=36)	8 (22.2%)	28

Disclosures: Laura Bonebrake:Nothing to Disclose, Cecilia Duenas:Nothing to Disclose, Gerry Nesbitt: Nothing to Disclose.

1174 | CYP2E1 DEFICIENCY DRIVES SPONTANEOUS FEMALE-BIASED CHOLANGIOPATHY WITH FEATURES OF PRIMARY BILIARY CHOLANGITIS

Kristina Stayer[1] Zaria KIllingsworth[1] Kylie Driggers[1] Hyland Gonzalez[1] Alexandra Tomasevich[1] Melinda Engevik[1] Jessica Hartman[1], [1]Medical University of SC

Background: Cytochrome P450 2E1, or CYP2E1, is a mammalian monooxygenase that is expressed at high levels in the liver. While CYP2E1 is well-studied for its role in toxicity of xenobiotic compounds such as benzene or acetaminophen, its role in endogenous metabolism remains incompletely understood. Notably, genetic variation in CYP2E1 regulatory regions has been associated with disease severity in patients with Primary Biliary Cholangitis (PBC), and hepatic CYP2E1 expression is reduced in PBC compared to healthy controls. PBC is a chronic cholestatic autoimmune liver disease that predominantly affects middle-aged women, with female-to-male ratios approaching 9:1. Consistent with these clinical observations, we previously identified spontaneous biliary abnormalities in female Cyp2e1 knockout (KO) mice that resemble features of PBC and are detectable as early as 14 weeks of age. In this study, we evaluated liver pathology in 6-month-old female KO mice using established histopathologic criteria modeled after the Paris classification system used for human PBC.

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Methods: Female WT and Cyp2e1 KO (KO) mice aged 6-7 months were evaluated. Consistent with our previous observations in young mice, approximately 50% of KO females exhibited hepatic pathology in hematoxylin and eosin stained liver slides. Therefore, mice were stratified post-hoc into pathology-positive and pathology-negative groups based on histology. Serum biochemistry was assessed, serum autoreactivity against isolated mitochondrial and nuclear protein fractions was evaluated by Simple Western analysis. Liver pathology was scored by an expert veterinary pathologist using criteria adapted from the Paris classification system for PBC. **Results:** Despite severe liver pathology present in 50% of KO animals, serum biochemistry parameters were not significantly different between WT and KO mice regardless of pathology. In contrast, pathology-positive KO mice exhibited significantly increased serum immunoreactivity toward both mitochondrial and nuclear protein fractions compared with WT and pathology-negative KO animals, consistent with increased autoreactive antibody responses. **Conclusion:** Female Cyp2e1 KO mice develop spontaneous and age-associated liver pathology that is more severe than that observed in male KO animals and is associated with increased serum autoreactivity toward mitochondrial and nuclear antigens. These findings support a previously unrecognized role for CYP2E1 in maintaining liver homeostasis and suggest that loss of CYP2E1 may promote sex-dependent autoimmune or cholangiopathic liver injury. Given the large number of dietary constituents and pharmaceuticals reported to inhibit CYP2E1 activity, reduced CYP2E1 function may represent a previously unappreciated susceptibility factor in females. Ongoing studies are investigating the underlying mechanisms and the translational relevance of this phenotype across species.

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1175 | A 90-DAY POSTPARTUM ALP CUTOFF IDENTIFIES WOMEN WITH PSC AT RISK FOR DISEASE PROGRESSION AFTER PREGNANCY

Katherine Cooper[1] Daniel Pratt[1], [1]Massachusetts General Hospital, Harvard Medical School

Background: Immune-mediated diseases may flare after pregnancy, though data in primary sclerosing cholangitis (PSC) are limited. We previously reported that increased alkaline phosphatase (ALP) following pregnancy may predict changes in magnetic resonance cholangiopancreatography (MRCP). We now aimed to identify clinically meaningful postpartum ALP thresholds associated with MRCP progression after pregnancy. **Methods:** Women with pregnancy after PSC diagnosis were identified from a longitudinal registry at Massachusetts General Hospital. The primary outcome was progression, defined as interval change on MRCP after delivery compared with pre-pregnancy. Pre-pregnancy ALP (Pre-ALP) and post-pregnancy ALP (post-ALP) were defined for each patient using the mean ALP level during the 12 months before conception and 12 months after delivery, respectively. Overall ΔALP was calculated as the relative change between pre- and post-pregnancy ALP. Additional ΔALP measures were calculated using the closest ALP level at 90 and 180 days postpartum. Group differences were compared using Wilcoxon rank-sum tests. Firth logistic regression was used to evaluate the association between ΔALP and progression. Receiver operating characteristic (ROC) curves were used to evaluate discrimination of ALP markers and identify optimal ΔALP thresholds at 90 and 180 days. Longitudinal ALP burden over the first 6 months postpartum was calculated using trapezoidal area-under-the-curve methods based on baseline-normalized ALP. **Results:** Among 28 pregnancies, 28.7% (n = 8) experienced MRCP progression. Pre- ALP was similar between groups (143 vs 125 U/L, p = 0.647), whereas post-ALP (339 vs 136 U/L, p = 0.022) and Overall ΔALP were higher among progressors (118.8% vs 39.5%, p = 0.0015). Each 10% increase in ΔALP was associated with 1.22-fold higher odds of progression (95% CI 1.04–1.52; p = 0.006), persisting after adjustment for pre-ALP and age at delivery (aOR 1.20, 95% CI 1.03–1.54; p = 0.009). Discrimination was strong for 90-day ΔALP and 180-day ΔALP, with AUCs of 0.88 and 0.77, respectively. The optimal 90-day ΔALP threshold was 83.8% (100% sensitivity, 80% specificity) and the optimal 180-day threshold was 58.1%. (87.5% sensitivity, 75% specificity). During the first 6 months postpartum, mean relative ALP burden was higher among progressors, corresponding to 2.4-fold versus 1.4-fold elevation above pre-pregnancy baseline (p = 0.006, Figure 1b). **Conclusion:** Women with PSC who experience MRCP progression after pregnancy demonstrate greater and more persistent postpartum ALP elevation. Incomplete biochemical recovery after delivery may serve as an early marker of postpartum PSC activity, with 90- and 180-day ΔALP thresholds demonstrating strong discrimination for imaging progression, though larger studies are needed to validate these findings.

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ROC Analyses for MRCP Progression	
Pre-ALP	0.56 (0.31-0.81)
Post-ALP	0.78 (0.58-0.99)
Peak ALP	0.70 (0.47-0.93)
ΔALP, Overall	0.89 (0.77-1)
ΔALP, 3 months	0.88 (0.72-1.00)
ΔALP, 6 months	0.87 (0.72-1.00)

Normalized ALP Trajectories Following Delivery



Disclosures: Katherine Cooper:Nothing to Disclose, Daniel Pratt:Ipsen: Advisor, Gilead: Advisor, RegCell: Advisor, Zydus: Advisor, Mirum: Advisor.

1176 | SUBSEQUENT PPAR AGONIST THERAPY AFTER FENOFIBRATE FAILURE OR INTOLERANCE IN PRIMARY BILIARY CHOLANGITIS (PBC): A REAL-WORLD CASE SERIES

Vivian Rotman[1] Mariko Maxwell[2] Yanhong Deng[2] Bonnie Chen[2] Marina Silveira[2] James Boyer[2] David Assis[2], [1]1.Yale University and 2. Federal University of Rio de Janeiro, [2]Yale University

Background: Approximately 40% of patients with PBC treated with ursodeoxycholic acid (UDCA) require add-on therapy to achieve adequate biochemical response. Peroxisome proliferator-activated receptor (PPAR) agonists have become a central therapeutic option in this setting. While seladelpar and elafibranor demonstrated efficacy in phase III trials, fibrates, including fenofibrate and bezafibrate, remain a widely used off-label alternative. However, data regarding subsequent PPAR agonist use, after fibrate failure or intolerance, are scarce. We describe a real-world experience with second-line PPAR agonists in PBC patients with inadequate response or intolerance to UDCA plus fenofibrate. **Methods:** Retrospective case series of PBC patients, at a tertiary referral center, who discontinued second-line fenofibrate due to intolerance or inadequate biochemical response, followed by elafibranor or seladelpar treatment. PBC diagnosis was established according to AASLD criteria. **Results:** A total of 59 PBC patients were treated with fenofibrate associated with UDCA (40 non-responders based on Paris II criteria; 33 based on POISE criteria). The cohort was predominantly female (86.4%) and white, with median age below 50 years at both diagnosis and fenofibrate initiation. Mean liver stiffness (LS) before fenofibrate initiation was 9.2 ± 3.5 kPa.Fenofibrate was discontinued in 6 patients (10% of the cohort) after a median of 3 months (M), due to intolerance (n = 5) or inadequate response (n = 1). Median age at the time of receiving a second PPAR agonist was 65.5 y. Two patients had compensated cirrhosis. Median LS in non-cirrhotics was 7.15 kPa. Obeticholic acid was previously used in 3 and discontinued due to inadequate response or severe pruritus.Seladelpar was initiated in 5 patients and elafibranor in 1, with a median treatment duration of 5.5 M. Baseline median ALP was1.8 x ULN. Five of the 6 achieved normalization of ALP at a median of 6 M. One developed nephrotoxicity during seladelpar therapy. Three reported stable pruritus and fatigue, two experienced symptomatic improvement (one in pruritus and one in fatigue) and one reported worsening of fatigue. **Conclusion:** Sequential second-line PPAR agonist therapy is a feasible and successful therapeutic strategy for select PBC patients with intolerance or inadequate biochemical response to fenofibrate. Further prospective studies to determine optimal sequential treatment strategies with PPAR agonists in PBC are indicated.

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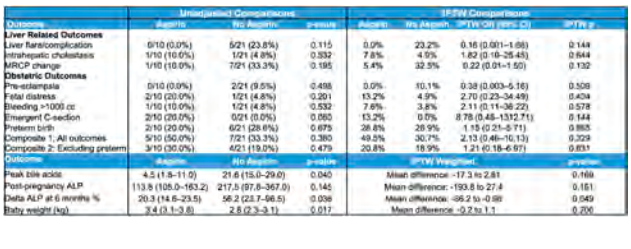
1177 | ASPIRIN USE DURING PREGNANCY IS ASSOCIATED WITH FEWER LIVER-RELATED COMPLICATIONS IN PREGNANT WOMEN WITH PRIMARY SCLEROSING CHOLANGITIS

Katherine Cooper[1] Victoria Abadi-Ron[2] Natalia Rojas Amaris[2] Libby Bell[3] Fernando Munguia[2] Ana Marenco-Flores[2] Vilas Patwardhan[2] Alan Bonder[2] Daniel Pratt[1], [1]Massachusetts General Hospital, Harvard Medical School, [2]Beth Israel Deaconess Medical Center, [3]Indiana University

Background: Aspirin use is indicated for obstetric risk reduction in high risk patients, including those with liver disease and inflammatory bowel disease (IBD). Whether aspirin use influences pregnancy outcomes and postpartum liver-related outcomes in women with primary sclerosing cholangitis (PSC) is not known. **Methods:** We performed a multicentral cohort analysis of pregnancies following PSC diagnosis from two longitudinal PSC registries at Massachusetts General Hospital and Beth Israel Deaconess Medical Center. Patients were categorized by aspirin exposure during pregnancy. Primary liver outcomes included liver complication after delivery (e.g., jaundice, obstruction,

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need for a procedure) and intrahepatic cholestasis of pregnancy (ICP), peak bile acid level, change in alkaline phosphatase (ALP) at six months postpartum relative to pre-pregnancy. Among those with longitudinal imaging data, change in magnetic resonance cholangiopancreatography (MRCP) from pre to post pregnancy also assessed. Pregnancy outcomes included pre-eclampsia, fetal distress, postpartum hemorrhage (PPH), emergent cesarean section, and preterm birth. Unadjusted rates were compared using Fisher's exact test and continuous variables using Wilcoxon rank-sum test. To account for confounding, stabilized inverse probability of treatment weighting (IPTW) was performed using age at PSC diagnosis, IBD status, pre-pregnancy ALP, and ursodiol use. Firth's penalized logistic regression with stabilized weights was applied to all adjusted outcome models and reported as adjusted odds ratios (aOR). **Results:** Among 31 pregnancies, 10 were aspirin-exposed. There were no statistically significant differences in preterm birth (20% vs. 29%), pre-eclampsia (0% vs. 10%), PPH (10% vs. 5%), or emergent cesarean section (20% vs. 0%) in aspirin-exposed compared to unexposed, though birth weight was higher in aspirin-exposed (median 3.4 kg vs. 2.8 kg, p = 0.02). Peak bile acid levels during pregnancy (median 4.5 vs. 21.6 µmol/L, p = 0.04) and relative rise in ALP levels (median 20% vs. 56%, p = 0.040) were significantly lower in aspirin-exposed. There were also fewer cases of postpartum liver complications (0% vs. 23%) and MRCP progression (10% vs. 33%) in the aspirin group as well. In IPTW models, there were trends toward decreased liver complications (aOR 0.16, 95% CI 0.00-1.68, p = 0.14) and MRCP progression (aOR 0.22, 95% CI 0.01-1.50, p = 0.13) while the relative change in ALP at 6 months remained significant lower in the aspirin-exposed group (21% vs. 55%, p = 0.049). **Conclusion:** In this exploratory mutlicenter cohort, aspirin use during pregnancy was associated with more favorable liver outcomes but did not significantly impact pregnancy related outcomes. With small sample size, these may be considered as hypothesis-generating findings to support prospective evaluation of aspirin in pregnant women with PSC.



Outcome	Unadjusted Comparisons			IPTW Comparisons			
	Aspirin	No Aspirin	p-value	Aspirin	No Aspirin	IPTW OR (95% CI)	IPTW p
Liver Related Outcomes							
Liver flare/complication	0/10 (0.0%)	5/21 (23.8%)	0.115	0.0%	23.2%	0.16 (0.001–1.68)	0.144
Intrahepatic cholestasis	1/10 (10.0%)	1/21 (4.8%)	0.532	7.8%	4.9%	1.82 (0.16–25.45)	0.644
MRCP change	1/10 (10.0%)	7/21 (33.3%)	0.195	5.4%	32.5%	0.22 (0.01–1.50)	0.132
Obstetric Outcomes							
Pre-eclampsia	0/10 (0.0%)	2/21 (9.5%)	0.498	0.0%	10.1%	0.38 (0.003–5.16)	0.508
Fetal distress	2/10 (20.0%)	1/21 (4.8%)	0.201	13.2%	4.9%	2.70 (0.23–34.49)	0.404
Bleeding >1000 cc	1/10 (10.0%)	1/21 (4.8%)	0.532	7.6%	3.8%	2.11 (0.11–36.22)	0.578
Emergent C-section	2/10 (20.0%)	0/21 (0.0%)	0.060	13.2%	0.0%	8.78 (0.48–1312.71)	0.144
Preterm birth	2/10 (20.0%)	6/21 (28.6%)	0.679	28.8%	29.9%	1.15 (0.21–5.71)	0.865
Composite 1: All outcomes	5/10 (50.0%)	7/21 (33.3%)	0.380	49.5%	30.7%	2.13 (0.46–10.13)	0.329
Composite 2: Excluding preterm	3/10 (30.0%)	4/21 (19.0%)	0.479	20.8%	18.9%	1.21 (0.18–6.97)	0.831
Outcome	Aspirin	No Aspirin	p-value	IPTW Weighted			p-value
Peak bile acids	4.5 (1.8–11.0)	21.6 (15.0–29.0)	0.040	Mean difference: -17.3 to 2.81			0.169
Post-pregnancy ALP	113.8 (105.0–163.2)	217.5 (97.8–367.0)	0.145	Mean difference: -193.8 to 27.4			0.161
Delta ALP at 6 months %	20.3 (14.6–23.5)	56.2 (23.7–66.5)	0.036	Mean difference: -66.2 to -0.88			0.049
Baby weight (kg)	3.4 (3.1–3.8)	2.8 (2.3–3.1)	0.017	Mean difference -0.2 to 1.1			0.206

Disclosures: Katherine Cooper:Nothing to Disclose, Victoria Abadi-Ron:Nothing to Disclose, Natalia Rojas Amaris:Nothing to Disclose, Libby Bell:Nothing to Disclose, Fernando Munguia:Nothing to Disclose, Ana Marenco-Flores:Nothing to Disclose, Vilas Patwardhan: Nothing to Disclose, Alan Bonder:Nothing to Disclose, Daniel Pratt:Ipsen: Advisor, Gilead: Advisor, RegCell: Advisor, Zydus: Advisor, Mirum: Advisor.

1178 | GLP-1 RECEPTOR AGONISTS ARE ASSOCIATED WITH REDUCED POST-ERCP SEPSIS COMPARED WITH SGLT-2 INHIBITORS: A PROPENSITY-MATCHED RETROSPECTIVE REAL-WORLD ANALYSIS

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Background: Sepsis is among the most feared complications of endoscopic retrograde cholangiopancreatography (ERCP), mostly indicated for malignant biliary strictures and choledocholithiasis. Sepsis arises from instrumentation of an often obstructed, infected biliary tree. GLP-1 receptor agonists (GLP-1RA) and SGLT-2 inhibitors (SGLT-2i) are groundbreaking glucose-lowering agents with benefits beyond glycemic control, and both carry anti-inflammatory properties—GLP-1RA attenuate pro-inflammatory cytokines, while SGLT-2i suppress the NLRP3 inflammasome and lower IL-6 and CRP. Despite this shared mechanistic plausibility, no study to date has compared their independent post-ERCP safety profiles. **Methods:** Using the TriNetX US Collaborative Network, we identified adults (≥ 18 years) undergoing ERCP with antecedent exposure to either a GLP-1RA (n = 3,293) or an SGLT-2i (n = 4,056), with mutually exclusive drug classes. The index event was the patient's first ERCP procedure; outcomes were assessed over the window beginning 1 to 365 days after the index event. Cohorts underwent 1:1 propensity-score matching on 18 covariates spanning demographics (age at index, sex, race, ethnicity) and cardiometabolic comorbidities. Matching yielded 2,195 well-balanced pairs (all standardized differences < 0.1). The primary outcome was incident sepsis, with 9 secondary outcomes, evaluated by risk ratios (RR) and Kaplan–Meier survival **Results:** GLP-1RA exposure was associated with a **significantly lower risk of post-ERCP sepsis**, occurring in **11.4% versus 14.1% of SGLT-2i patients** (absolute risk reduction 2.8%; SGLT-2i RR 1.24, 95% CI 1.04–1.49; p = 0.016). Survival analysis reinforced this protective

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signal: **365-day sepsis-free survival was higher with GLP-1RA (86.5% vs 83.4%; log-rank p = 0.013; HR 1.27, 95% CI 1.05–1.53)**, with an approximate number-needed-to-treat of 37. Among secondary outcomes, SGLT-2i was also associated with significantly higher euglycemic diabetic ketoacidosis (RR 2.59, 95% CI 1.33–5.03; p = 0.003). No significant differences emerged for GI bleeding (RR 1.31; p = 0.075), acute pancreatitis, cholangitis, all-cause mortality, hospital readmission, aspiration pneumonia, or choledocholithiasis. **Conclusion:** Among diabetic patients undergoing ERCP, antecedent GLP-1RA therapy was associated with a **clinically meaningful reduction in post-procedural sepsis** relative to SGLT-2i, despite both classes' recognized anti-inflammatory effects. GLP-1RA suppress sepsis-driven TNF-α via central neuronal GLP-1R signaling, expand regulatory T cells, and fortify the gut barrier through microbiome-mediated butyrate production—while avoiding the glycosuria-related infection risk and osmotic volume depletion seen with SGLT-2i. GLP-1RA may represent a preferable glucose-lowering strategy in patients anticipating biliary intervention. Further prospective studies needed to validate these findings.

Disclosures: Emeka Stanley Obi:Nothing to Disclose, Danielle Luskind:Nothing to Disclose, Adedeji Adenusi: Nothing to Disclose, chimezirim ezeano:Nothing to Disclose, Gedion Amdetsion:Nothing to Disclose, Abdulrahman Atasi:Nothing to Disclose, Javed Jagroo:Nothing to Disclose, Olachi Egbo:Nothing to Disclose, Joshua Kalu:Nothing to Disclose, Nothing to Disclose, Chidiebele Omaliko:Nothing to Disclose, Olanrewaju Adeniran:Nothing to Disclose.

1179 | FIBRATE THERAPY FOR PRIMARY SCLEROSING CHOLANGITIS: SYSTEMATIC REVIEW AND META-ANALYSIS

Gabriel Silva[1] Priscille Jones[2] Bhavya Yarlagadda[3] Carlos Marin[4] Omar Kasimieh[5] Valentina Saracino[6] Glaucia De Souza[7] Ana-Alicia Velarde-Pineda[8] Suellen Da Silva[9] Gabriele De Geroni[10], [1]University of Pernambuco, [2]Universidade de Pernambuco, [3]MUSC Kershaw Medical Center, [4]University of Kansas Medical Center (KUMC), [5]University of the East Ramon Magsaysay Memorial Medical Cent, [6]Cape Fear Valley Medical Center/UNC Health Southeastern, [7]Escola Superior de Ciências da Saúde do Distrito Federal, [8]University Center for Health Sciences (CUCS), [9]National University of Ecology, Santa Cruz de La Sierra, [10]Federal University of Rio Grande do Sul

Background: Primary sclerosing cholangitis (PSC) is a progressive hepatobiliary disease whose pathophysiology relies on fibrotic damage to the bile ducts, leading to cholestasis, which subsequently perpetuates and potentiates sclerosis. Fibrates can alter bile composition, decreasing bile toxicity and potentially reducing cholestasis-driven injury. As they do not act on the core fibrosing process of the disease, it remains uncertain whether they can function as disease-modifying drugs. This study aims to assess the safety and efficacy of fibrates for PSC. **Methods:** A systematic review was conducted to identify randomized controlled trials (RCTs) and observational studies assessing fibrate therapy in patients with PSC. PubMed, Embase, and Cochrane were used as databases. We performed a meta-analysis evaluating changes in laboratory parameters from baseline to the last available follow-up assessment. The primary outcome was the reduction in alkaline phosphatase (ALP) levels. Secondary outcomes included changes in aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), and total bilirubin (TB) levels. All statistical analyses were conducted using R software (version 4.6.0). **Results:** A total of five studies met the inclusion criteria, comprising 85 patients included in the meta-analysis. ALP, GGT, and ALT levels demonstrated statistically significant reductions (ALP: −177.91 [95% confidence interval (CI) −237.69 to −118.12]; GGT: −127.04 [95% CI −163.35 to −90.72]; ALT: −29.82 [95% CI −41.42 to −18.21]). In contrast, reductions in AST and TB did not demonstrate statistically significant improvement (AST: −8.95 [95% CI −19.46 to 1.55]; TB: −0.09 [95% CI −0.27 to 0.09]). **Conclusion:** This is the first meta-analysis to date evaluating the impact of fibrates on liver and cholestatic enzymes in patients with PSC. Reductions in ALP, GGT, and ALT reinforce the potential benefit of fibrates in attenuating cholestatic injury. In contrast, the lack of statistically significant improvement in AST and TB limits conclusions regarding the ability of these agents to mitigate disease progression or substantially improve liver function. Larger RCTs are warranted to determine whether these biochemical improvements translate into clinically meaningful outcomes, including transplant-free survival and quality of life.

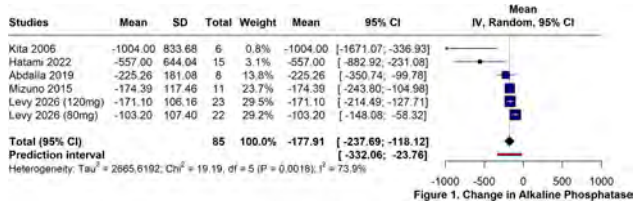


Figure 1. Change in Alkaline Phosphatase

Disclosures: Gabriel Silva:Nothing to Disclose, Priscille Jones:Nothing to Disclose, Bhavya Yarlagadda: Nothing to Disclose, Carlos Marin:Nothing to Disclose,

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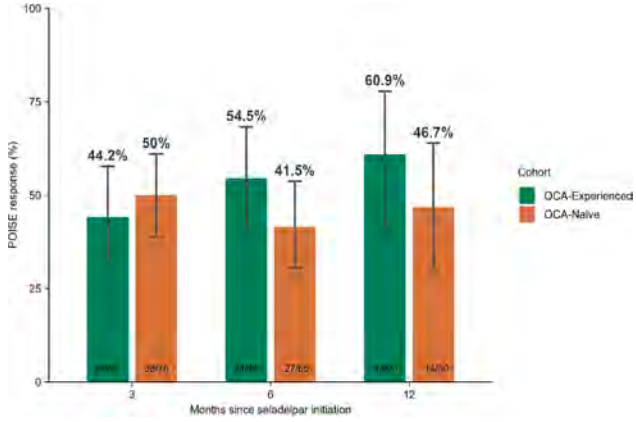
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Omar Kasimieh:Nothing to Disclose, Valentina Saracino:Nothing to Disclose, Glaucia De Souza:Nothing to Disclose, Ana-Alicia Velarde-Pineda:Nothing to Disclose, Suellen Da Silva:Nothing to Disclose, Gabriele De Geroni:Nothing to Disclose.

1180 | SELADELPAR EFFECTIVENESS A SECOND-LINE THERAPY ACROSS PRIOR TREATMENT COHORTS IN PRIMARY BILIARY CHOLANGITIS: A REAL-WORLD STUDY

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Background: Seladelpar, a PPAR-δ agonist, was recently approved as second-line therapy for primary biliary cholangitis (PBC) in patients with inadequate response or intolerance to ursodeoxycholic acid. Many patients reaching seladelpar have prior exposure to obeticholic acid (OCA), the earlier second-line agent, yet real-world effectiveness of seladelpar in OCA-experienced patients is not well characterized. We evaluated the real-world effectiveness of seladelpar across OCA-experienced and OCA-naïve patients in Epic Cosmos. **Methods:** In this retrospective cohort study using Epic Cosmos, we identified adults with PBC who initiated seladelpar following its August 2024 approval, with the index date defined as the first seladelpar dispense. Patients were classified by prior therapy as OCA-experience, OCA-naïve or triple therapy. The primary outcome was POISE biochemical response (alkaline phosphatase [ALP] $<1.67\times$ULN, total bilirubin [TB] $\leq 1.0\times$ULN, and $\geq 15\%$ reduction in ALP from baseline) at 3, 6, and 12 months, assessed among patients with baseline ALP $\geq 1.67\times$ULN; secondary endpoints included ALP normalization and bilirubin response. Response proportions were estimated with Wilson 95% confidence intervals, and OCA-experienced and OCA-naïve cohorts were compared using Fisher's exact test in exploratory analyses. **Results:** Among 851 seladelpar-treated patients (432 OCA-naïve, 374 OCA-experienced, 45 triple therapy), median age was 64 years, 90% were female, and approximately 40% had cirrhosis. Baseline median ALP was 193-199 U/L (1.6-1.7xULN) and TB 0.5-0.6 md/dL (0.5xULN) across cohorts. POISE response in OCA-experienced patients rose from 44.2% at 3 months to 54.5% (95% CI 40.1–68.3) at 6 months and 60.9% (40.8–77.8) at 12 months (Figure). OCA-experienced response exceeded OCA-naïve at 6 and 12 months (+13.0 and +14.2 percentage points), a directionally consistent but non-significant difference (Fisher's $p=0.24$ and 0.41). Approximately 70% of patients across cohorts achieved $\geq 15\%$ ALP reduction at all timepoints. Among cirrhotic patients, POISE response was numerically higher in OCA-experienced patients (45.8% vs 37.1%), and biochemical responses remained stable ($\geq 15\%$ ALP reduction 73.5% vs 63.9%; bilirubin $\leq 0.6\times$ULN 70.2% vs 61.1%). **Conclusion:** In this real-world cohort, seladelpar produced clinically meaningful biochemical responses in OCA-experienced patients with PBC, with POISE response rates comparable to OCA-naïve patients and durable through 12 months. Biochemical activity was preserved across cohorts and in patients with cirrhosis. These findings support seladelpar as an effective second-line option in patients previously treated with OCA, including populations underrepresented in clinical trials.



Disclosures: Adrielly Martins:Nothing to Disclose, Cynthia Levy:Nothing to Disclose.

1181 | VEDOLIZUMAB OR USTEKINUMAB AND BILIARY DISEASE OUTCOMES IN PSC-IBD OVERLAP: A PROPENSITY SCORE–MATCHED COHORT ANALYSIS

Mahmoud Al-Bataineh[1] Jashnaveer Singh Johal[1] Om Patel[1] Abdallah Hussein[1] Yecheskel Schneider[1] Jason Hyman[2], [1]Virtua Health, [2]Virtua

Background: Primary sclerosing cholangitis has no proven pharmacotherapy, yet vedolizumab and ustekinumab are increasingly prescribed off-label in patients with PSC-IBD overlap, vedolizumab via gut-selective α4β7 integrin blockade disrupting hepatic homing of gut-activated lymphocytes, and ustekinumab via IL-12/23 inhibition reducing Th1/Th17-mediated biliary inflammation. Real-world data on biliary disease progression, cholangitis episodes,

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and transplant outcomes with these agents are essentially absent. **Methods:** We conducted a propensity score–matched retrospective cohort study using the TriNetX Global Collaborative Network (191.9 million patients). Cohort 1 comprised adults with both PSC (K83.01) and IBD (K50 or K51) who received vedolizumab or ustekinumab within one year of diagnosis. Cohort 2 comprised PSC-IBD patients receiving conventional IBD therapy (infliximab, mesalamine, or azathioprine) without vedolizumab or ustekinumab. Both cohorts excluded prior HCC, liver transplant, and other cholangitis. Cohorts were balanced via 1:1 PSM yielding 494 patients per arm over a 6–120 month follow-up window. Pre-specified outcomes included ALP normalization as a biochemical biliary response surrogate, acute cholangitis episodes, incident cirrhosis, cholangiocarcinoma, need for ERCP, liver transplant listing, and all-cause mortality. **Results:** Post-PSM cohorts were balanced across matched covariates. ALP normalization rates were equivalent between arms (24.3% vs. 23.3%; HR 0.99, 95% CI 0.70–1.40; p = 0.97). Acute cholangitis episodes did not differ significantly on time-to-event analysis (HR 1.18, 95% CI 0.80–1.75; p = 0.40). Incident cirrhosis was numerically lower in the vedolizumab/ustekinumab arm but did not reach significance (6.0% vs. 7.2%; HR 0.85, 95% CI 0.50–1.44; p = 0.55). Cholangiocarcinoma rates were equivalent (2.4% vs. 2.7%; HR 0.90, 95% CI 0.41–1.98; p = 0.80). Need for ERCP was significantly lower in the vedolizumab/ustekinumab arm on both MOA (6.5% vs. 10.3%; RR 0.63; p = 0.029) and KM analysis (HR 0.60, 95% CI 0.39–0.93; p = 0.022). All-cause mortality was significantly lower in the vedolizumab/ustekinumab arm on both analyses (3.6% vs. 7.9%; RR 0.46; HR 0.45, 95% CI 0.25–0.78; p = 0.004), with proportionality holding (p = 0.33). **Conclusion:** In this propensity-matched real-world cohort of PSC-IBD patients, vedolizumab/ustekinumab were associated with significantly lower need for ERCP and markedly lower all-cause mortality compared to conventional IBD therapy, without significant differences in ALP normalization, cholangitis, cirrhosis, or cholangiocarcinoma rates. Findings suggested that gut-selective immunomodulation may reduce biliary interventions and improve survival in PSC-IBD, though the small cohort size limits causal interpretation. Prospective studies with dedicated biliary endpoints and ALP trajectory monitoring are urgently needed in this population.

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1182 | HEALTHCARE RESOURCE UTILIZATION AND COSTS IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS IN THE UNITED STATES

Robert Wong[1] Robert Gish[2] Ira Jacobson[3] Marvin Rock[4] Garrett Gremel[4] Samina Dhuliawala[4] Gary Leung[4] Maria Agapova[4] Chong Kim[4], [1]Division of Gastroenterology and Hepatology, Stanford University, Stanford, CA, USA, [2]Hepatitis B Foundation, Doylestown, PA, USA, [3]New York University Grossman School of Medicine, New York, NY, USA, [4]Gilead Sciences, Inc., Foster City, CA, USA

Background: Primary biliary cholangitis (PBC) is a chronic cholestatic liver disease associated with significant clinical and healthcare economic burden. Ursodeoxycholic acid (UDCA) is the first-line treatment for PBC; however, up to 40% of patients with PBC have an inadequate response (defined as persistently elevated alkaline phosphatase levels >1.67 times the normal upper limit or abnormal bilirubin levels after 1 year of therapy) and require second-line treatment. We evaluated healthcare resource utilization (HCRU) and costs in untreated and newly treated patients with PBC in the US. **Methods:** In this retrospective observational study, adults ≥18 years of age with a diagnosis of PBC (based on *ICD-10-CM*) and ≥12 months of continuous insurance enrollment pre- and post-index were identified within the study period using the IQVIA US Pharmetrics Plus database from January 1, 2016, to June 30, 2024. The index date was defined as the earliest PBC diagnosis (among untreated) or earliest UDCA or obeticholic acid (OCA) prescription claim (among treated). HCRU and costs were evaluated for untreated, UDCA, and OCA (with or without UDCA) were adjusted and reported in 2025 US dollars (maximum amount payable to provider or sum of paid, copay, coinsurance, and deductible costs). Follow-up ended at treatment discontinuation (treated population), death, end of enrollment, or study end date. All-cause HCRU and costs per patient per month were compared across groups; adjusted analyses used a generalized linear model (GLM) of cost ratios adjusting for baseline demographics and clinical characteristics. **Results:** Among 6,968 adults with PBC, 2,416 (35%) were untreated, and 4,552 (65%) were treated (UDCA, n = 3,893 [86%]; OCA, n = 659 [14%]). Untreated patients had significantly more inpatient and emergency room visits vs UDCA and OCA patients; OCA patients also had significantly lower inpatient ($757) and outpatient ($433) costs vs untreated ($2,719 and $574) and UDCA ($1,596 and $597) patients (**Table**). However, prescription costs were generally lower for untreated and UDCA patients vs OCA patients. Based on the adjusted GLM, costs were lower (cost ratio, 0.81; 95% CI, 0.77–0.86) for UDCA vs untreated patients, but higher (2.26; 95% CI, 2.04–2.50) for OCA vs untreated patients (P < .001 each).

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Conclusion: Patients treated with UDCA and OCA had significantly fewer inpatient and emergency room visits than untreated patients, suggesting reduced HCRU. Further, patients receiving OCA had significantly lower inpatient and outpatient costs vs both untreated and UDCA, indicating reduced healthcare-related costs. Overall, these data suggest that the appropriate implementation of OCA may reduce HCRU and costs for patients with PBC; further data are needed to understand how recent approvals of seladelpar and elafibranor as second-line PBC treatments may impact overall HCRU and costs.

Table. All-Cause Healthcare Utilization and Costs PPPM for Patients With PBC, Untreated vs Treated

HCRU	Untreated (n = 2,416)	UDCA (n = 3,893)	OCA* (n = 659)
Inpatient visits	0.08 (0.07-0.08)	0.03 (0.03-0.04)	0.03 (0.02-0.04)
UDCA, P-value	**<.001**	-	-
OCA, P-value	**<.001**	.188	-
Outpatient visits	0.62 (0.58-0.66)	0.66 (0.62-0.69)	0.59 (0.53-0.65)
UDCA, P-value	.217	-	-
OCA, P-value	.417	.064	-
ER visits	0.11 (0.10-0.12)	0.08 (0.07-0.09)	0.08 (0.06-0.09)
UDCA, P-value	**<.001**	-	-
OCA, P-value	**.001**	.582	-
Prescription claims	2.97 (2.82-3.12)	4.51 (4.38-4.64)	5.50 (5.18-5.82)
UDCA, P-value	**<.001**	-	-
OCA, P-value	**<.001**	**<.001**	-
Cost	**Untreated (n = 2,416)**	**UDCA (n = 3,893)**	**OCA* (n = 659)**
Total, $	5,890 (4,748-7,032)	4,441 (3,860-5,022)	7,807 (7,230-8,384)
UDCA, P-value	**.027**	-	-
OCA, P-value	**.003**	**<.001**	-
Inpatient visits, $	2,719 (1,952-3,487)	1,596 (1,068-2,124)	757 (431-1,083)
UDCA, P-value	**.018**	-	-
OCA, P-value	**<.001**	**.008**	-
Outpatient visits, $	574 (512-635)	597 (530-663)	433 (347-520)
UDCA, P-value	.618	-	-
OCA, P-value	**.010**	**.003**	-
ER visits, $	134 (105-163)	94 (83-104)	104 (59-150)
UDCA, P-value	**.012**	-	-
OCA, P-value	.287	.654	-
Prescription claims, $	478 (420-535)	743 (650-836)	5,317 (4,936-5,697)
UDCA, P-value	**<.001**	-	-
OCA, P-value	**<.001**	**<.001**	-

Data are reported as mean (95% CI) unless otherwise noted. Bold *P*-values indicate statistical significance.
*Patients included in the OCA group received OCA as monotherapy or in combination with UDCA.
ER, emergency room; HCRU, healthcare resource utilization; OCA, obeticholic acid; PBC, primary biliary cholangitis; PPPM, per patient per month; UDCA, ursodeoxycholic acid.

Disclosures: Robert Wong:Theratechnologies: Grant/Research Support, Theratechnologies: Grant/Research Support, Durect: Grant/Research Support, Durect: Grant/Research Support, Gilead Sciences: Grant/Research Support, Gilead Sciences: Grant/Research Support, Exact Sciences: Grant/Research Support, Exact Sciences: Grant/Research Support, Madrigal Pharmaceuticals: Grant/Research Support, Theratechnologies: Grant/Research Support, Theratechnologies: Grant/Research Support, Durect: Grant/Research Support, Durect: Grant/Research Support, Gilead Sciences: Grant/Research Support, Gilead Sciences: Grant/Research Support, Exact Sciences: Grant/Research Support, Exact Sciences: Grant/Research Support, Madrigal Pharmaceuticals: Grant/Research Support, Robert Gish:Genlantis, HepQuant, HepaTx, Virion: Stock – privately held company, Gilead Sciences, GlaxoSmithKline, HHHbio, Helio, HepQuant, Intercept, Ipsen, Madrigal,: Consultant, Mirum, Precision BioSciences, Prodigy, Topography Health, Tune Therapeutics, Virion, Quest: Consultant, AbbVie, AstraZeneca, BlueJay Therapeutics, Brii Bio, EIT Pharma, Genlantis, Gerson Lehrman Group: Consultant, Gilead Sciences Inc., Intercept, Ipsen Biopharmaceuticals, Madrigal, Mallinckrodt, Mirum: Speaking and Teaching, Syneos Health: Data Safety Monitoring Board, Genlantis, Gilead, HepaTX, HepQuant, Intercept, Prodigy: Leadership in Related Society, Board, Journal, Ira Jacobson:Nothing to Disclose, Marvin Rock:Nothing to Disclose, Garrett Gremel:Nothing to Disclose, Samina Dhuliawala:Nothing to Disclose, Gary Leung:Gilead sciences: Employee, Maria Agapova:Nothing to Disclose, Chong Kim:Gilead Sciences, Inc.: Employee.

1183 | HORMONE THERAPY USE ACROSS THE REPRODUCTIVE AGE IN WOMEN WITH PRIMARY BILIARY CHOLANGITIS: AN OPPORTUNITY FOR INTEGRATED CARE

Julia Foote[1] Cynthia Fenton[1] Marcelle Cedars[1] Monika Sarkar[1], [1]University of California, San Francisco

Background: Primary biliary cholangitis (PBC) disproportionately affects women, although the patterns of exogenous hormone use in this population have not been characterized. In the absence of decompensated cirrhosis, hormonal agents are safe for contraception and treatment of menopausal symptoms. Use of exogenous hormone therapy is also relevant regarding second-line PBC treatment, given the potential for drug-drug interactions with elafibrinor. **Methods:** We performed a retrospective cohort study of women with PBC at a tertiary care center between January 1, 2013 and December 31, 2025. Index date was defined as 6 months prior to first hepatology clinic visit. Patients were censored at liver transplantation, death, or loss to follow-up. Systemic hormone exposures, including formulations, dosing, and duration, were captured. Menopausal status was defined first by age (<51 for pre-menopausal women vs $\geq$ 51 years for post-menopausal women) and refined by diagnosis code for menopausal status, documented surgical menopause, and use of menopausal hormone therapy (MHT). Hormone formulations and dosing were reviewed to adjudicate hormonal contraceptive versus MHT exposures. Data were collected on PBC-related comorbidities, MASLD, and PBC-directed treatments. Rates of hormone use were characterized over time with test of trend p-values. **Results:** Among 593 women with PBC, 157 (26.5%) were pre-menopausal and 436 (73.5%) were post-menopausal at index date. Among pre-menopausal women, the median age was 42 years (IQR 35-46 years), 19.1% had concurrent MASLD, and 92.4% had received ursodiol, 10.8% seladelpar, and 3.2% elafibranor. Among post-menopausal women, the median age was 64 years (IQR 57-70 years), 19.7% had concurrent MASLD, and 87.4% had received ursodiol, 5.5% seladelpar, and 1.1% elafibranor. Across the study period, prevalence of hormonal contraceptive and MHT

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use was 17.2% and 3.7%, respectively. Prevalence remained stable over time but lower than contemporary national estimates (Figure 1). Prevalence of MASLD and use of second-line PBC therapies were similar by hormone exposure. **Conclusion:** Compared to national estimates, the use of hormone therapy was lower in both pre- and post-menopausal patients with PBC, suggesting potential underutilization of these therapies. As access to hormone therapies expand, these findings highlight an opportunity to integrate women's health and PBC care.

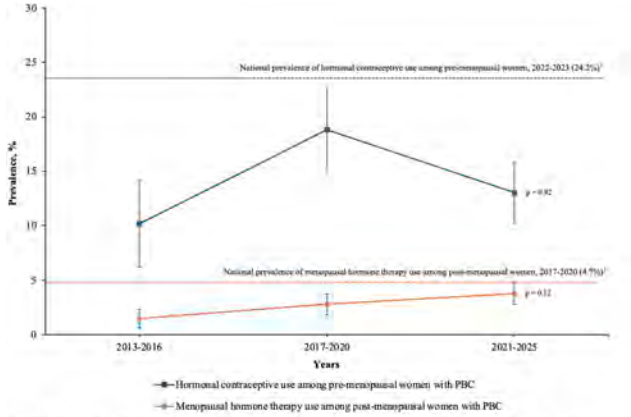


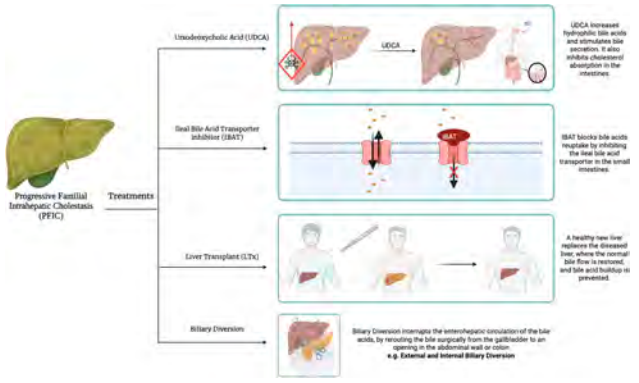
Figure 1. Trends in hormonal contraceptive and menopausal hormone therapy (MHT) use among pre- and post-menopausal women with PBC compared to national estimates. Error bars indicate standard error.
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[2] Yang L, Toriola AT. Menopausal hormone therapy use among postmenopausal women. JAMA Health Forum 2024;5:e243128.

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1184 | PROGRESSIVE FAMILIAL INTRAHEPATIC CHOLESTASIS: FROM DIAGNOSIS TO THE MOST RECENTLY APPROVED TREATMENTS - A SYSTEMATIC REVIEW WITH DESCRIPTIVE ANALYSIS

Parsia Vazirnia[1] Kirellos Mikhail[2] Marie Balfour[3] Kerollos Roufael[4] Yuri Kwon[1] Moura Girgis[2] Matthew Ghebrial[1] Beshoy Yanny[1], [1]University of California, Irvine., [2]University of California, Los Angeles., [3]Univeristy of California, Irvine., [4]California State University, Long Beach.

Background: Progressive Familiar Intrahepatic Cholestasis (PFIC) is a rare group of inherited liver disorders affecting hepatocyte bile secretion occurring in infants, young children, and adults. 13 types of PFIC have been identified based on their specific gene mutations. The most common types include PFIC 1-3. Key lab findings often overlap with other common liver diseases, making diagnosis challenging. Definitive diagnosis requires specialized genetic testing which can occur years after initial presentation typically manifesting as jaundice and severe pruritus. Historically, treatment options were limited to ursodeoxycholic acid (UDCA) or surgical options such as bile diversion or liver transplantation. However, newer therapies such as Ileal Bile Acid Transporter (IBAT) inhibitors are now more commonly used. This study aimed to investigate the efficacy of different PFIC treatment options. **Methods:** A literature review was conducted across PubMed through April 2026. Studies included case reports, case series, and clinical trials. Primary outcomes investigated were improvement in pruritus intensity and labs including serum bile acids, transaminases, GGT, total bilirubin, and alkaline phosphatase. Treatment success was defined as resolution of symptoms and improvement in labs. Secondary outcomes included age of diagnosis, length of time until diagnosis was made, and gender. An illustration of treatment options was created with BioRender.com. **Results:** Twenty-six studies were included, all consisting of case reports and case series; no clinical trials were identified. PFIC 3 was the most common subtype (n = 11), followed by PFIC 2 (n = 4) and PFIC 1 (n = 3). Treatment success was highest with odevixibat (100%) and biliary diversion (87.5%), followed by liver transplant (75%), and lowest with UDCA (37.5%). Liver transplant was associated with the greatest improvement across nearly all laboratory parameters (Table 1). Patient ages ranged from 1 month to 35 years (mean 8 years), with a male predominance (18 male, 12 female). The average time from symptom onset to diagnosis was 5 years. **Conclusion:** The high treatment success rate of odevixibat (100%) is promising, as it offers a nonsurgical alternative with outcomes comparable to biliary diversion (87.5%) and liver transplant (75%). PFIC remains a challenging diagnosis, presenting in early childhood and persisting into adulthood, with an average of 5 years from symptom onset to confirmatory genetic testing. Keeping PFIC on the radar of hepatologists for patients with unexplained cholestasis is important to reduce diagnostic delay and facilitate initiation of effective therapy.



Symbols: ♦, Poster of Distinction; ★, Foundation Award Recipient

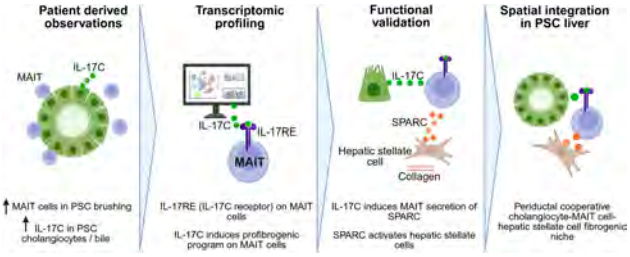
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1185 | A CHOLANGIOCYTE-MAIT CELL-HEPATIC STELLATE CELL AXIS IN PRIMARY SCLEROSING CHOLANGITIS

Adiba Azad[1] Florencia Guttierez[1] Gregory Gores[1] Alexander Wixom[1] Konstantinos Lazaridis[1], [1]Mayo Clinic

Background: PSC is an immune-mediated cholangiopathy in which periductal fibrosis drives strictures, parenchymal injury, and liver failure. MAIT cells are unconventional T cells enriched at barrier surfaces and implicated in tissue repair and mucosal inflammation, but their role within the human bile duct niche in PSC and the cholangiocyte-derived cues that shape them remain unclear. **Methods:** Bile and bile duct brushings/bile obtained at endoscopic retrograde cholangioscopy (ERC) were examined by flow cytometry, ELISA and used to derive cholangiocyte organoids. **Results:** MAIT cells were enriched in PSC bile duct compared to non-PSC controls (40% vs 20% of T cells). PSC cholangiocyte organoid secretome profiling identified IL-17C, and ELISA confirmed 10X enrichment of IL-17C in PSC bile. In situ hybridization localized IL-17C transcripts to PSC cholangiocytes. Secondary analysis of published intrahepatic T cell single cell RNA-seq datasets showed that IL17RE, the cognate receptor for IL-17C, was preferentially enriched on MAIT cells in PSC, but this MAIT cell preference was not observed in primary biliary cholangitis, a disease comparator.IL-17C-treated primary MAIT cells showed activation of hepatic fibrogenesis and T cell activation pathways by RNA-seq. Conditioned media from IL-17C-treated MAIT cells activated hepatic stellate cells (2X), supporting a MAIT cell derived soluble mediator. Targeted profiling of MAIT cell secretome identified secreted protein acidic and rich in cysteine (SPARC), whose release was significantly enhanced by IL-17C (2X). Recombinant SPARC augmented hepatic stellate cell activation, and SPARC was increased in PSC bile and periductal PSC liver tissue.10X Xenium single cell spatial transcriptomics confirm that MAIT cells comprise a substantial fraction of spatially resolved T cells in PSC tissue. In situ annotation using profibrogenic, pro-inflammatory, and regulatory signatures showed that profibrogenic MAIT cells preferentially associated with stellate cell neighborhoods, and stellate cell activation scores were highest in regions containing both MAIT cells and cholangiocytes. **Conclusion:** We identify a cooperative cholangiocyte-MAIT cell-stellate cell niche that promotes periductal fibrogenesis in PSC. We show that PSC cholangiocytes upregulate IL-17C and that its receptor, IL17RE, is preferentially enriched on MAIT cells. IL-17C instructs MAIT cells to express the matricellular protein SPARC, which directly activates hepatic stellate cells and increases collagen production. By integrating bile duct immune profiling, patient-derived cholangiocyte organoids, RNA sequencing, functional assays, and 10X Xenium spatial transcriptomics, this work provides mechanistic evidence that MAIT cells are actively shaped by cholangiocyte-derived cues to drive fibrosis. Thus, the IL-17C-MAIT-SPARC axis, represents a therapeutically actionable driver of fibrosis in PSC.



Disclosures: Adiba Azad:Nothing to Disclose, Florencia Guttierez:Nothing to Disclose, Gregory Gores: Nothing to Disclose, Alexander Wixom:Nothing to Disclose, Konstantinos Lazaridis:Nothing to Disclose.

1186 | IMPACT OF LINERIXIBAT ON METABOLIC PROFILES IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS (PBC) IN THE PHASE 3 GLISTEN STUDY

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Background: PBC is a rare, chronic, autoimmune-mediated liver disease commonly associated with metabolic comorbidities such as dyslipidemia.

Symbols: ♦, Poster of Distinction; ★, Foundation Award Recipient

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Linerixibat is a minimally absorbed ileal bile acid transporter (IBAT) inhibitor recently approved for treatment of cholestatic pruritus in patients (pts) with PBC. Inhibition of IBAT blocks intestinal bile acid reabsorption, forcing greater liver conversion of cholesterol to bile acids (similar to cholestyramine) and modulates farnesoid X receptor, improving lipid and glucose metabolism. This analysis evaluated linerixibat's effect on these metabolic profiles in the Phase 3 GLISTEN study (NCT04950127). **Methods:** GLISTEN was a randomized, multicenter, double-blind, placebo-controlled trial of adults with PBC and moderate-to-severe pruritus.In the primary intervention period, pts received oral linerixibat 40 mg or placebo (pbo) twice daily for 24 weeks. This post hoc analysis of the safety population analyzed change from baseline at Week 24 in lipids (total cholesterol [TC], low-density lipoprotein cholesterol [LDL-c], high-density lipoprotein cholesterol [HDL-c], and triglycerides [TG]) in all pts, pts receiving statins (baseline), pts with high baseline LDL-c ($\geq$160 mg/dL), and IFG (impaired fasting glucose; $\geq$100 mg/dL). **Results:** Of 237 pts included, mean (SD) baseline lipids (mg/dL) in pts receiving linerixibat vs pbo were: TC: 224.8 (61.9) vs 229.4 (65.9); HDL-c: 70.0 (23.9) vs 70.3 (27.1); LDL-c: 127.6 (47.0) vs 130.2 (44.5); TG: 116.9 (50.1) vs 115.9 (56.1). Mean (SD) baseline fasting glucose was: linerixibat, 98.8 (40.7) vs pbo, 95.9 (25.8) mg/dL. Greater improvements from baseline to Week 24 were observed with linerixibat vs pbo in TC (least squares mean difference [LSMD] −11.65 [95% confidence interval, CI: −19.73, −3.57] mg/dL), LDL-c (−14.48 [−21.02, −7.95] mg/dL) and HDL-c (2.77 [−0.99, 6.53] mg/dL); for TG, LSMD was 2.47 (−6.69, 11.63) mg/dL. Of 36 (15%) pts receiving statins, greater improvements in cholesterol from baseline to Week 24 were observed with linerixibat vs pbo (**Table**). Forty-nine (21%) pts had baseline LDL-c $\geq$160 mg/dL (linerixibat n = 20; pbo n = 29); of these, greater improvements in lipids from baseline to Week 24 were observed with linerixibat vs pbo (**Table**). Overall change from baseline in fasting glucose at Week 24 in pts receiving linerixibat vs pbo (LSMD) was −4.51 (95% CI: −8.16, −0.86) mg/dL. Sixty (25%) pts had IFG (linerixibat n = 28; pbo n = 32); in these pts, greater improvements from baseline to Week 24 were also observed with linerixibat vs pbo (**Table**). **Conclusion:** Linerixibat was associated with an improvement in lipid and glucose profiles compared with pbo in pts with PBC, even among those receiving statins, with higher LDL, or IFG at baseline. Aside from effectively treating pruritus, linerixibat may also have metabolic benefits by influencing pathways involved in lipid and glucose metabolism in pts with PBC. Funding: GSK (212620)

Table: Analysis of covariance of change from baseline in lipid and glucose profile at Week 24 in GLISTEN Part A (post hoc analyses)

Treatment group	N (Baseline)	n (Week 24)	Baseline measurements (mean [SD])	Change from baseline at Week 24 (LS mean [95% CI])	Difference vs placebo at Week 24* (LS mean difference [95% CI])
Patients receiving statins at baseline					
Total cholesterol (mg/dL)					
Placebo	21	19	203.5 (83.9)	−1.25 (−17.65, 15.14)	−9.69 (−36.78, 17.39)
Linerixibat	15	11	211.2 (89.6)	−10.95 (−32.50, 10.61)	
LDL-c (mg/dL)					
Placebo	21	19	100.0 (43.5)	−1.08 (−11.75, 9.58)	**−20.31 (−38.08, −2.55)**
Linerixibat	15	11	116.4 (78.2)	**−21.40 (−35.47, −7.33)**	
HDL-c (mg/dL)					
Placebo	21	19	73.8 (46.5)	−1.86 (−7.11, 3.40)	5.91 (−2.84, 14.66)
Linerixibat	15	11	69.6 (19.0)	4.05 (−2.88, 10.98)	
Triglycerides (mg/dL)					
Placebo	21	19	107.2 (34.9)	3.14 (−14.17, 20.45)	10.04 (−18.86, 38.94)
Linerixibat	15	11	109.2 (39.6)	13.18 (−9.67, 36.03)	
Patients with high LDL-c (≥160 mg/dL) at baseline					
Total cholesterol (mg/dL)					
Placebo	29	26	300.5 (46.8)	**−26.47 (−39.97, −12.97)**	**−27.77 (−49.43, −6.10)**
Linerixibat	20	17	317.2 (76.5)	**−54.24 (−70.98, −37.49)**	
LDL-c (mg/dL)					
Placebo	29	26	187.9 (31.9)	**−21.69 (−32.76, −10.61)**	**−30.08 (−47.89, −12.27)**
Linerixibat	20	17	203.0 (53.8)	**−51.77 (−65.52, −38.02)**	
HDL-c (mg/dL)					
Placebo	29	26	81.7 (37.4)	**−7.31 (−12.49, −2.13)**	**10.98 (2.72, 19.25)**
Linerixibat	20	17	74.1 (33.0)	3.67 (−2.74, 10.09)	
Triglycerides (mg/dL)					
Placebo	29	26	122.9 (57.5)	6.36 (−5.41, 18.13)	**−23.17 (−42.24, −4.11)**
Linerixibat	20	17	146.4 (60.8)	**−16.81 (−31.46, −2.16)**	
Patients with impaired fasting glucose (≥100 mg/dL) at baseline					
Fasting glucose (serum) (mg/dL)					
Placebo	32	29	120.6 (39.1)	**−11.20 (−18.18, −4.22)**	**−11.78 (−21.97, −1.59)**
Linerixibat	28	26	128.7 (76.8)	**−22.98 (−30.36, −15.61)**	

*Mean difference >0 favors active treatment, mean difference <0 favors placebo, bold indicates statistical significance (95% CI excludes 0).

CI, confidence interval; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; LS, least squares; SD, standard deviation.

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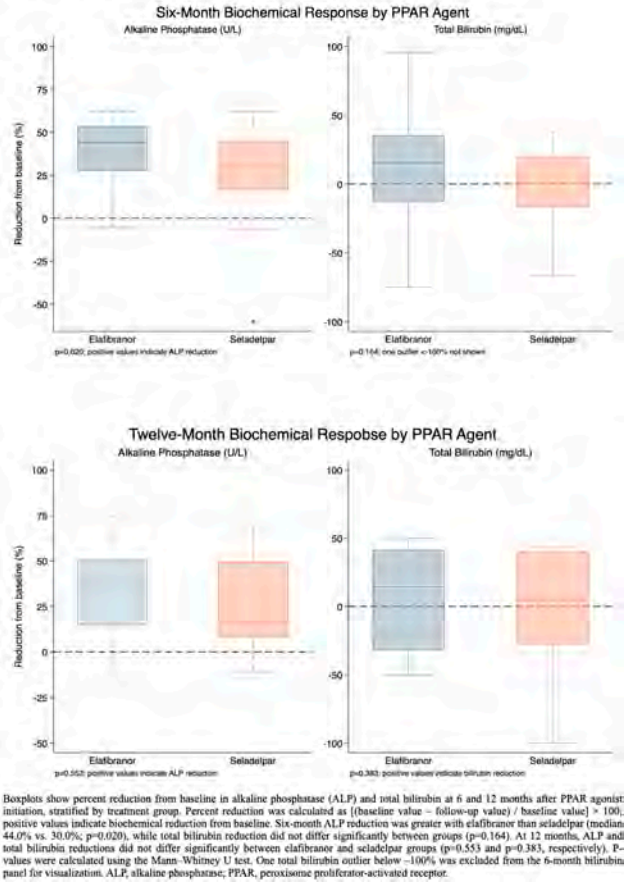
Grant/Research Support, Linda Casillas:Nothing to Disclose, Alexander Cobitz:Nothing to Disclose, Jennifer Shannon:Nothing to Disclose, Megan McLaughlin: Nothing to Disclose, Gideon Hirschfield:Intercept: Consultant, GSK: Consultant, CymaBay: Consultant, Ipsen: Consultant, Falk: Consultant, Pliant: Consultant, Mirum: Consultant, Advanz: Consultant, Chemomab: Consultant, Gilead: Consultant, Kowa: Consultant.

1187 | REAL-WORLD USE OF PPAR AGONISTS IN PBC: INDICATIONS, BIOCHEMICAL RESPONSE, AND TOLERABILITY

Victoria Abadi-Ron[1] Natalia Rojas Amaris[1] Ana Marenco-Flores[1] Fernando Munguia[1] Giuliana Arevalo[2] Romelia Barba[3] Daniela Goyes[4] Esli Medina Morales[5] Leandro Sierra[6] Behnam Saberi[7] Vilas Patwardhan[1] Alan Bonder[1], [1]Beth Israel Deaconess Medical Center, [2]Department of Internal Medicine, University of Miami / Jackson Memorial Hospital, [3]Texas Tech University, [4]Yale School of Medicine, New Haven, [5]Washington University in St Louis, [6]Cleveland Clinic Foundation, [7]BIDMC Harvard Medical School

Background: Peroxisome Proliferator-Activated Receptors (PPAR) agonists are emerging therapies for primary biliary cholangitis (PBC) with inadequate response to ursodeoxycholic acid (UDCA), but real-world data remain limited. We aimed to describe indications, biochemical response, and tolerability of Elafibranor and Seladelpar in patients with PBC and overlap syndromes. **Methods:** We conducted a descriptive real-world analysis of a prospective cohort of patients with PBC as the primary diagnosis, with or without overlap autoimmune liver disease, initiated on PPAR agonists at Beth Israel Deaconess Medical Center from 2024 to present. Data were manually extracted from electronic medical records, including physician notes and routine clinical labs. Inadequate UDCA response was based on treating physician assessment. POISE-like response was defined as ALP $\leq$1.65×ULN, normal total bilirubin, and $\geq$15% ALP reduction; deep biochemical response was defined as ALP normalization with normal total bilirubin. Continuous variables are reported as median (IQR), categorical variables as n (%). Mann–Whitney U and Fisher's exact tests were used. **Results:** Seventy-eight patients were included; 46 (59.0%) initiated elafibranor and 32 (41.0%) seladelpar. Median age was 61.5 vs 67.5 years, and most were female. AIH-PBC overlap was present in 7 (15.2%) vs 4 (12.5%) patients; PBC-PSC overlap was present in 1 (2.2%) elafibranor-treated patient. The main indication was inadequate UDCA response, occurring in 40 (87.0%) vs 26 (81.3%); UDCA intolerance occurred in 3 (6.5%) vs 1 (3.1%). Baseline symptoms were documented in 19 (41.3%) vs 15 (46.9%), most commonly pruritus. Baseline ALP was similar: 218 vs 200.5 U/L; baseline total bilirubin was 0.5 mg/dL in both groups. Baseline FibroScan was 6.9 kPa (5.4–11.0; n = 39) vs 6.8 kPa (6.0–8.8; n = 25). At 6 months, median ALP reduction was greater with elafibranor than seladelpar: 44.0% vs 30.0% (p = 0.020). Total bilirubin remained stable, with median 6-month reduction of 15.5% vs 0.0% (p = 0.164).Six-month treatment completion occurred in 34 (73.9%) vs 27 (84.4%), where POISE-like response was achieved by 21 (65.6%) vs 14 (53.9%) patients (p = 0.425), and deep biochemical response by 11 (34.4%) vs 12 (46.2%) (p = 0.425). Side effects occurred in 8 (17.4%) vs 5 (15.6%), including gastrointestinal symptoms, myalgia, fatigue, pruritus, and headache. Discontinuation occurred in 2 (4.3%) vs 4 (12.5%). **Conclusion:** In this real-world PBC cohort, PPAR agonists were primarily initiated for physician-assessed inadequate UDCA response and were associated with meaningful 6-month ALP improvement. Elafibranor showed greater median ALP reduction, while bilirubin remained stable in both groups. Both agents showed favorable tolerability, with low discontinuation rates often related to insurance/access barriers rather than intolerance.

Figure 1. Six- and Twelve-Month Biochemical Reduction by PPAR Agent



Boxplots show percent reduction from baseline in alkaline phosphatase (ALP) and total bilirubin at 6 and 12 months after PPAR agonist initiation, stratified by treatment group. Percent reduction was calculated as [(baseline value − follow-up value) / baseline value] × 100; positive values indicate biochemical reduction from baseline. Six-month ALP reduction was greater with elafibranor than seladelpar (median 44.0% vs. 30.0%; p=0.020), while total bilirubin reduction did not differ significantly between groups (p=0.164). At 12 months, ALP and total bilirubin reductions did not differ significantly between elafibranor and seladelpar groups (p=0.553 and p=0.383, respectively). P-values were calculated using the Mann–Whitney U test. One total bilirubin outlier below −100% was excluded from the 6-month bilirubin panel for visualization. ALP, alkaline phosphatase; PPAR, peroxisome proliferator-activated receptor.

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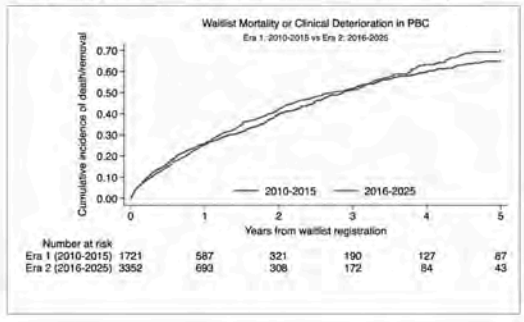
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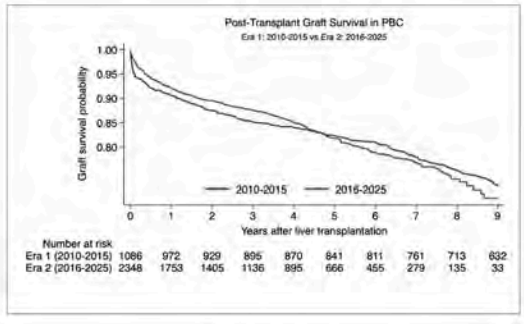
1188 | TEMPORAL TRENDS IN WAITLIST OUTCOMES AND POST-TRANSPLANT SURVIVAL IN PRIMARY BILIARY CHOLANGITIS FOLLOWING INTRODUCTION OF SECOND-LINE THERAPIES: A UNOS ANALYSIS

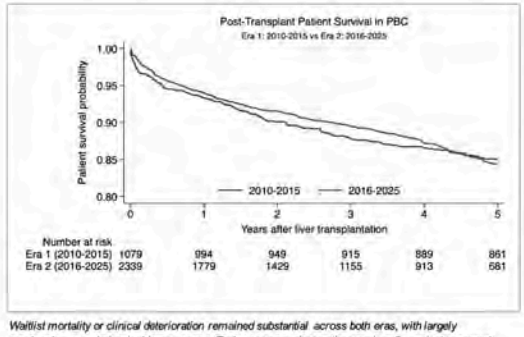
Romelia Barba[1] Ana Marenco-Flores[2] Giuliana Arevalo[3] Victoria Abadi-Ron[2] Natalia Rojas Amaris[2] Fernando Munguia[2] Khawaja Hassam[4] Miriam Paz Sierra[5] Daniela Goyes[6] Behnam Saberi[2] Vilas Patwardhan[2] Alan Bonder[2], [1]Texas Tech University, [2]Beth Israel Deaconess Medical Center, [3]University Of Miami Miller School of Medicine, [4]Lahey Hospital and Medical Center, [5]Texas Tech Medical Center, [6]Yale Medical School

Background: Primary biliary cholangitis (PBC) remains a major indication for liver transplantation despite advances in medical therapy. Prior studies demonstrated disproportionately high waitlist mortality among patients with PBC under the MELD-Na allocation system, suggesting that disease severity may be underestimated in this population. In 2016, obeticholic acid became the first FDA-approved second-line therapy for PBC.We evaluated temporal trends in waitlist mortality or clinical deterioration and post-transplant outcomes among patients with PBC before and after the introduction of second-line therapy in 2016. **Methods:** We performed a retrospective cohort study using the United Network for Organ Sharing (UNOS) database including adult patients with PBC listed for liver transplantation between 2010 and 2025. Patients were stratified into two eras: Era 1 (2010–2015) and Era 2 (2016–2025). The primary waitlist outcome was a composite of death or removal for clinical deterioration. Kaplan–Meier analyses evaluated waitlist outcomes, post-transplant patient survival, and graft survival. Baseline demographic and clinical characteristics were compared using chi-square and Kruskal–Wallis tests. **Results:** A total of 5,076 patients with PBC were identified, including 1,721 in Era 1 and 3,355 in Era 2. Compared with Era 1, patients in Era 2 had higher MELD scores at listing (mean MELD 19.7 vs 17.8, $p < 0.001$). Hispanic recipients represented a larger proportion of the contemporary cohort (23.8% vs 18.4%, $p < 0.001$), while other baseline characteristics were similar between eras. Waitlist mortality or clinical deterioration remained substantial after 2016, with largely overlapping cumulative incidence curves over 5 years of follow-up (Figure1). In the isolated 2016–2025 cohort, estimated freedom from waitlist death or clinical deterioration declined to 74.7% at 1 year, 57.9% at 2 years, 48.8% at 3 years, and 30.1% at 5 years after listing. Post-transplant outcomes showed modest early improvement during Era 2. Patient survival remained approximately 92% at 2 years, 88% at 4 years, and 74% at 9 years in the contemporary cohort. Similarly, graft survival remained approximately 90% at 2 years, 85% at 4 years, and 70% at 9 years after transplantation, although long-term survival curves converged over time. **Conclusion:** Despite the introduction of second-line therapy for PBC after 2016, waitlist mortality and clinical deterioration remain high among patients with advanced disease. Although modest improvements in early post-transplant patient and graft survival were observed in the contemporary era, long-term outcomes remained similar between eras. These findings suggest that advances in pharmacologic therapy have not yet translated into substantial reductions in transplant-related disease burden in PBC and support continued reassessment of transplant allocation strategies for this population.

Figure 1. Waitlist Outcomes and Post-Transplant Survival in Patients with Primary Biliary Cholangitis Before and After Introduction of Second-Line Therapy







Waitlist mortality or clinical deterioration remained substantial across both eras, with largely overlapping cumulative incidence curves. Early post-transplant patient and graft survival appeared modestly improved in the contemporary era, although long-term outcomes converged over extended follow-up.

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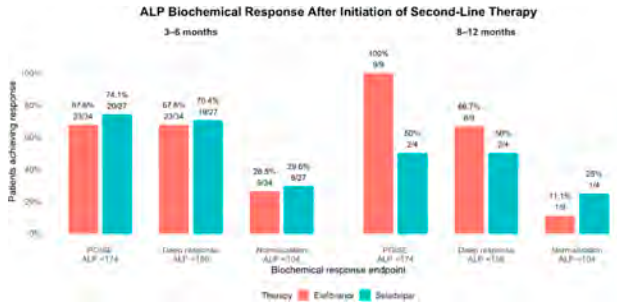
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1189 | REAL-WORLD BIOCHEMICAL RESPONSE TO ELAFIBRANOR AND SELADELPAR IN PRIMARY BILIARY CHOLANGITIS CONTRASTING ALKALINE PHOSPHATASE RESPONSE, DEEP RESPOSE AND NORMALIZATION.

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Background: Persistent elevation of alkaline phosphatase (ALP) and bilirubin in primary biliary cholangitis (PBC) predicts disease progression, liver transplantation, and death. Despite trial efficacy of elafibranor and seladelpar, real-world response across clinically relevant ALP thresholds remains limited. **Methods:** We performed a retrospective real-world cohort study of adults with PBC treated with elafibranor or seladelpar with baseline ALP/bilirubin and follow-up labs. Follow-up windows were 3-6 and 8-12 months post-initiation. ALP response thresholds used ULN = 104 U/L: ALP < 1.67×ULN (< 174 U/L; POISE-like threshold), ALP < 1.5×ULN (< 156 U/L; Paris II ALP threshold), and ALP normalization (< 104 U/L). Paired ALP/bilirubin changes were assessed using Wilcoxon signed-rank testing. Therapies were compared using Fisher exact and Wilcoxon rank-sum tests **Results:** 71 patients were included: 39 received elafibranor and 32 seladelpar. Paired ALP/bilirubin data were available for 61 patients at 3-6 months and 13 at 8-12 months. Median ALP decreased from 218 U/L [IQR, 172-314] to 118 [100-201] at 3-6 months, with median change -79 U/L [-151 to -22] and percent change -41.8% [-56.2 to -11.2] ($p < 0.0001$). At 8-12 months, ALP decreased from 357 [191-400] to 137 [120-162], with median change -196 U/L [-239 to -59] and percent change -55.7% [-59.8 to -37.3] ($p = 0.0017$). At 3-6 months, 43/61 (70.5%) achieved ALP < 1.67×ULN, 42/61 (68.9%) achieved ALP < 1.5×ULN, and 17/61 (27.9%) achieved ALP normalization. At 8-12 months, corresponding rates were 11/13 (84.6%), 8/13 (61.5%), and 2/13 (15.4%). Median bilirubin changed from 0.6 [0.4-0.8] to 0.5 [0.4-0.7] at 3-6 months ($p = 0.0577$) and from 0.5 [0.5-0.7] to 0.5 [0.3-0.7] at 8-12 months ($p = 0.2316$). At 3-6 months, ALP < 1.67×ULN was achieved in 23/34 elafibranor-treated patients (67.6%) and 20/27 seladelpar-treated patients (74.1%; $p = 0.7782$). ALP < 1.5×ULN and normalization rates were also similar between therapies. **Conclusion:** In this real-world PBC cohort, elafibranor and seladelpar were associated with substantial ALP reduction and frequent achievement of trial-informed ALP thresholds by 3-6 months, while bilirubin remained low and stable. Response rates were similar between therapies in exploratory comparisons. Longer-term findings suggest continued ALP response but are limited by small 8-12-month denominators.



Disclosures: Hussein Harb:Nothing to Disclose, Fabian Rodas:Mirum Pharmaceutical: Speaking and Teaching, IPSEN: Speaking and teaching, GILEAD: Speaking, INTERCEPT Pharmaceuticals: Speaking and Teaching, COUR Pharmaceuticals: Independent Contractor, Zydus Pharmaceuticals: Independent Contractor, KOWA Pharmaceuticals: Independent Contractor.

1190 | FAECAL MICROBIOTA TRANSPLANTATION FOR REFRACTORY AUTOIMMUNE LIVER DISEASE: GUT MICROBIOME RESTORATION AND METABOLIC REMODELLING IN A PILOT RANDOMISED CONTROLLED TRIAL

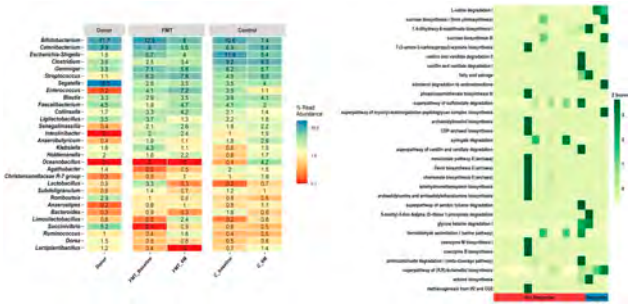
Shalimar[1] Arnav Aggarwal[1] Manjeet Kaur[2] Bharti Kandiyal[2] Samagra Agarwal[1] Sagnik Biswas[1] Bhabatosh Das[2], [1]All India Institute of Medical Sciences, [2]Translational Health Science and Technology Institute

Background: Patients with autoimmune liver disease (AILD) who have an inadequate response to standard immunosuppression remain at risk of progressive liver injury and fibrosis. We evaluated the efficacy, microbiome dynamics, and functional remodelling associated with faecal microbiota transplantation (FMT) in refractory AILD. **Methods:** In this pilot open-label randomized controlled trial, patients with insufficient or non-response to first- or second-line immunosuppression

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were randomized to receive either FMT plus standard immunosuppressive therapy (FMT arm) or standard immunosuppressive therapy (control arm). Clinical outcomes, liver stiffness measurement (LSM), gut microbiome composition, predicted microbial metabolic pathways, donor microbiome engraftment, and presence of antimicrobial resistance (AMR) gene prevalence were assessed at baseline and 6 months. A total of 68 faecal samples from FMT recipients (n = 15), controls (n = 17), and donors (n = 4) underwent microbiome analysis by targeted metagenomics. **Results:** FMT recipients demonstrated significant restoration of gut microbial diversity at 6 months, with post-FMT microbial profiles becoming comparable to donor profiles based on Observed and Shannon diversity indices. Principal coordinate analysis revealed distinct compositional shifts in the FMT group; controls exhibited only modest temporal variation. FMT was associated with trends toward reduced abundance of potentially pathogenic genera, including Klebsiella, Enterobacter, and Escherichia/Shigella, and enrichment of beneficial taxa such as Lachnospira, Agathobacter, and Intestinimonas (Figure). Donor engraftment > 50% occurred in 60% of FMT recipients. Functional profiling identified 61 significantly enriched microbial pathways following FMT, predominantly involving amino acid metabolism, aromatic compound degradation, cofactor biosynthesis, and anti-inflammatory polyphenol metabolism. Responders demonstrated enrichment of pathways linked to metabolic versatility and reduced methanogenesis-associated functions. In contrast, controls exhibited limited functional remodelling. Non-responders in both arms retained higher AMR gene prevalence, whereas FMT responders showed lower detection of several resistance determinants, including CTX-M, TEM, ermB, and qnrS. No major safety concerns were identified. **Conclusion:** FMT induces donor-like microbiome restoration and substantial functional metabolic remodelling in refractory AILD, with distinct microbial and AMR signatures associated with clinical response. These findings support the therapeutic potential of microbiome-directed interventions in difficult-to-treat AILD, warranting evaluation in larger trials (CTRI/2022/10/046773).



Disclosures: Shalimar:Nothing to Disclose, Arnav Aggarwal:Nothing to Disclose, Manjeet Kaur:Nothing to Disclose, Bharti Kandiyal:Nothing to Disclose, Samagra Agarwal:Nothing to Disclose, Sagnik Biswas:Nothing to Disclose, Bhabatosh Das:Nothing to Disclose.

1191 | THE PBC IRELAND PATIENT REGISTRY: REAL-WORLD INSIGHTS INTO THE MEDICAL HISTORY OF PEOPLE LIVING WITH PBC IN IRELAND

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Background: Primary biliary cholangitis (PBC) is a rare, chronic autoimmune liver disease with significant symptom burden and variable treatment response. In Ireland, there is a lack of national real-world data describing patient medical history, limiting understanding of disease characteristics, care gaps and outcomes. The PBC Ireland Patient Registry was established as a patient-led initiative to generate real-world evidence and ensure the patient voice is represented in research and policy. **Methods:** This is an observational, web-based registry of adults (≥ 18 years) with a self-reported diagnosis of PBC. Participants are recruited through patient communities and complete electronic informed consent. Data are collected via a secure, GDPR-compliant platform called CLIRINX and include demographics, detailed medical history, treatment exposure, and clinical investigations. Medical history captures diagnostic timelines, comorbidities, FibroScan and bone density results, and treatment response. **Results:** A total of 65 participants contributed medical history data. Family history of autoimmune or liver disease was reported by 46.2%. Most participants (84.6%) had undergone FibroScan, with 21.6% reporting moderate-to-advanced fibrosis (F2–F4), while 23.1% reported that results were not shared with them. Bone density abnormalities were common, with 29.3% reporting osteopenia or osteoporosis. UDCA use was reported by 95.4%, with 23.1% an inadequate response. Symptom burden remained high, particularly fatigue (87.7%) and pruritus (55.4%), alongside cognitive and musculoskeletal symptoms. Over half of participants reported comorbid autoimmune conditions. **Conclusion:** These findings demonstrate the feasibility of a patient-led registry to capture detailed real-world data in PBC. The data highlight ongoing symptom burden, variable treatment response, and potential gaps in communication and care. This registry provides a foundation for future research, supports patient-centred advocacy, and can inform clinical practice and policy decisions in Ireland.

Disclosures: Gerry Nesbitt:Nothing to Disclose, Alexandra Curley:Nothing to Disclose.

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1192 | BIOCHEMICAL NON-INVASIVE TESTS FOR FIBROSIS AND LIVER STIFFNESS MEASUREMENTS CAN BE USED TO EVALUATE PROGNOSIS IN THE POPULATION WITH PRIMARY BILIARY CHOLANGITIS

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Background: Biochemistry is used to evaluate therapeutic management in people with primary biliary cholangitis (PBC). Liver stiffness measurement (LSM) is considered a non-invasive staging parameter with added prognostic value, but its availability varies. We aimed to assess biochemical non-invasive tests (NITs) for fibrosis as compared to LSM, including their association with clinical outcomes. **Methods:** The Dutch PBC Cohort Study includes every identifiable individual with PBC in the Netherlands from 1990 up to last data collection (2019-2023) across all 71 Dutch hospitals. These analyses included UDCA-treated individuals with ≥1 LSM during follow-up (FU) and available FIB-4 (based on age, AST, ALT and platelets) and APRI (based on AST and platelets) obtained within three months of LSM. In survival analyses of liver transplantation (LT)-free survival and liver disease progression (LDP) (decompensated cirrhosis, LT or liver-related death) first LSM was defined as index date. LSM, FIB4 and APRI were log transformed. A LSM ≥10kPa was considered to indicate advanced disease. **Results:** In total, 728 people were included; 648 (89.0%) were female and median age was 59y (IQR 51–67). First LSM was available after a median FU of 5.2 years (IQR 1.1-10.5). Median LSM was 6.9 kPa (IQR 5.3–10.0), with 184 (25.3%) having a LSM ≥ 10 kPa. Median FIB-4 was 1.3 (IQR 0.97–1.8) and median APRI 0.4 (IQR 0.3–0.7). The LSM correlated weakly with both APRI ($r = 0.4$, $p < 0.01$) and FIB-4 ($r = 0.4$, $p < 0.01$). Using a FIB-4 cutoff of 3.25, specificity for LSM ≥ 10 kPa was 97.9% and sensitivity 23.4%. With an APRI cutoff of 0.54, specificity was 77.8% with a sensitivity of 38.6%. Table 1 shows the decrease in specificity and increase in sensitivity with lower cut-offs of the biochemical NITs, as well as positive and negative predictive values. Median FU after index LSM was 2.7 years (IQR 1.1–4.5), during which 44 patients died, 11 were transplanted and 36 developed decompensated cirrhosis. Univariately, LSM (HR 3.0, 95%CI 2.1–4.3), FIB-4(HR 3.7, 95%CI 2.6–5.2) and APRI (HR 2.2, 95%CI 1.6-2.9) were all associated with LT/death (all $p < 0.01$). The corresponding C-stats were 0.72 for LSM vs 0.77 for FIB-4 ($p = 0.352$), and 0.69 for APRI ($p = 0.474$). Both FIB-4 (aHR 2.9, 95%CI 1.9–4.3) and LSM (aHR 1.9, 95%CI 1.2–2.9) remained associated with LT/death when combined in a model, as was the case for APRI (aHR 1.6, 95%CI 1.2–2.3) combined with LSM (aHR 2.5, 95%CI 1.7–3.7), all $p < 0.01$. Addition of LSM to each NIT improved the C-stat (0.78 for LSM and FIB-4 and 0.73 for LSM and APRI, $p < 0.01$ as compared to the NITs alone. Results were consistent in people 35-65y and when looking to LDP, although effect sizes were more pronounced (all C-stat > 0.80). **Conclusion:** Both FIB4 and APRI showed good prognostic discrimination in patients with PBC and may be considered as a readily available alternative for LSM. However, combining LSM with the biochemical staging parameters improved their prognostic performance.

FIB-4	LSM <10	LSM≥10		APRI	LSM <10	LSM≥10	
FIB-4 > 3.25	12	43	PPV 78.2%	APRI >0.66	90	87	PPV 49.2%
FIB-4 ≤ 3.25	532	141	NPV 79.0%	APRI ≤0.66	454	97	NPV 82.4%
	Specificity 97.8%	Sensitivity 23.4%			Specificity 83.5%	Sensitivity 47.3%	
FIB-4 ≥ 1.45	175	124	PPV 41.5%	APRI >0.54	121	113	PPV 48.3%
FIB-4 < 1.45	389	60	NPV 86.0%	APRI ≤0.54	423	71	NPV 85.6%
	Specificity 67.8%	Sensitivity 67.4%			Specificity 77.8%	Sensitivity 38.6%	

Disclosures: Ellen Werner:Nothing to Disclose, Tiki Blom:Nothing to Disclose, Gemma Weijsters:Nothing to Disclose, Merle M.F. Vos:Nothing to Disclose, Maria van Hooff:Nothing to Disclose, Rozanne de Veer: Nothing to Disclose, Ulrich Beuers:Nothing to Disclose, Joost Drenth:Nothing to Disclose, Frans J.C. Cuperus: Nothing to Disclose, Remco van Dijk:Nothing to Disclose, Bart J. Veldt:Nothing to Disclose, Michael Klemt-Kropp:Nothing to Disclose, Suzanne van Meer: Nothing to Disclose, Robert Verdonk:Nothing to Disclose, Hajo J. Flink:Nothing to Disclose, Jan Maarten Vrolijk:Nothing to Disclose, Cyriel Ponsioen:Nothing to Disclose, Matthijs Kramer:Dr Falk: Sponsoring of educational meetings, J. Kemenade:Nothing to

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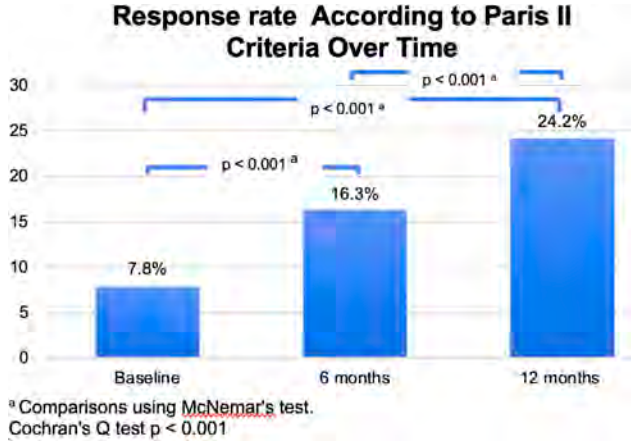
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1193 | WHAT IS IT LIKE TO TREAT PRIMARY BILIARY CHOLANGITIS IN A LOW-RESOURCE SETTING? REAL-WORLD EXPERIENCE FROM A MEXICAN REFERRAL CENTER

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Background: Primary Biliary Cholangitis (PBC) is a relevant cause of cirrhosis worldwide although in Latin America epidemiologic data remain scarce; delayed diagnosis is still a concern. We aimed to describe the clinical characteristics of patients with PBC at a referral center in Mexico City. **Methods:** This retrospective single-center cohort included adults with PBC between May 2012 and May 2026. Data were obtained from medical records. Diagnosis required two of the following: cholestatic biochemical abnormalities, positive antimitochondrial antibodies (AMA), or compatible liver histology. Descriptive statistics summarized demographic, clinical, and treatment variables. Continuous variables were reported as mean ± SD or median (IQR). Categorical comparisons were performed using Cochran's Q and McNemar tests, while agreement between diagnostic approaches was assessed using Cohen's κ coefficient. Analyses were performed using IBM SPSS Statistics version 27.0; $p < 0.05$ considered statistically significant. **Results:** 500 patients were included; 467 (93.4%) were women. Median age at diagnosis was 49 years (IQR 41–58). UDCA and bezafibrate were used in 94.4% and 52.2%, respectively. Pruritus-directed therapy was required in 41.8% of patients; antihistamines were the most common (34%). During the first year after diagnosis, 91.8% reported symptoms; fatigue (77%), pruritus (70.8%), and weight loss (43.6%). Autoimmune disease was present in 69.8%, with 22 disorders identified. Hypothyroidism (28%), systemic sclerosis (21.6%), and Sjogren syndrome (20.6%) were most common. Low bone density was present in 88.6% of patients. AMA were positive in 84%. Cirrhosis at diagnosis was present in 50.8%. Median MELD score was 12 (IQR 8–17); median liver stiffness was 11.1 kPa (IQR 6.8–17.0). Esophageal varices were present in 24% of non-cirrhotic patients undergoing upper endoscopy. After a median follow-up of 4.1 years (IQR 2.0–8.2), 20% of patients had died; pneumonia (26.2%) and acute upper gastrointestinal bleeding (14.6%) were the main causes. Overlap syndrome decreased from 32.4% in medical records to 13.2% after applying Paris criteria ($p < 0.001$; $\kappa = 0.439$). Paris II response rates increased from 7.8% at baseline to 16.3 and 24.2% at 6 and 12 months respectively (all $p < 0.001$). A total of 75 (15%) patients underwent liver transplantation; recurrence and graft rejection were both 24%. **Conclusion:** In this real-world cohort, patients with PBC showed a substantial burden of symptoms, autoimmune comorbidities, advanced liver disease, and low bone mineral density, suggesting delayed diagnosis. Overdiagnosis of overlap syndrome was identified, potentially leading to overtreatment. Biochemical response at 12 months was low, while differences between 6 and 12-month response suggest delayed biochemical improvement in this setting. These findings may also apply to vulnerable subpopulations within high-income countries.



Disclosures: Ricardo Gutierrez Monterrubio:Nothing to Disclose, Nayelli Flores-García:Nothing to Disclose,

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Astrid Ruiz-Margain:Nothing to Disclose, Jose Gonzalez Regueiro:Nothing to Disclose.

1194 | NONINVASIVE PREDICTORS OF HISTOLOGICALLY DEFINED PRECLINICAL PRIMARY BILIARY CHOLANGITIS IN AMA-POSITIVE PATIENTS WITH NORMAL ALKALINE PHOSPHATASE

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Background: Currently, PBC can be diagnosed in most patients without liver biopsy, based on AMA positivity and elevated ALP. This noninvasive criterion overlooks the subgroup of patients with AMA positivity and normal ALP (N-ALP) but with typical PBC lesions on liver biopsy. ALP and baseline histologic stage are two of the main prognostic factors. Therefore, early identification and treatment of these AMA+/N-ALP patients could lead to better outcomes. To date, reliable noninvasive predictors of preclinical PBC have not been established. **Methods:** Prospective study (Sep/25-Apr/26). Liver biopsy (LB) was offered to consecutive patients followed in the Hepatology clinic at our center for AMA >1:40 and persistently N-ALP. Patients with other liver diseases or who declined LB were excluded. LB was evaluated by two expert hepatopathologists. The results were classified as: 1) typical PBC (chronic nonsuppurative destructive cholangitis ± granulomatous inflammation); they were graded and staged according to Nakanuma; 2) possible PBC (foci of bile duct injury, cholangitis, bile duct loss, and/or portal inflammation); and 3) no PBC (other nonimmune diseases or nonspecific changes). Before LB, blood count, biochemistries, bile acids, autoantibodies, immunoglobulins, CRP, Pro-C3 (Roche Diagnostics), and FGF-19, TNFα, IL-6, IL-12, IL-23 and TGFβ (all by Merck) were assessed. Patients with typical PBC were treated with ursodeoxycholic acid. The study was approved by the center's Research Ethics Committee. All patients provided written informed consent. **Results:** We included 76 patients: 55.9 years, female 65 (85.5%), ALP 78.3 U/L ± 30.8 (ULN 116 U/L). Seven patients (9.2%) were receiving steroids, 9 (11.8) immunosuppressants, 3 (3.9%) anti-TNF therapy, 1 (1.3%) IL-6 inhibitors, and 7 (9.2%) hydroxychloroquine for other conditions. The median LB length was 25 ± 3 mm. Typical PBC was identified in 25/76 patients (32.9%; 95%CI 23.4–44.1; Nakanuma stage I 19 [76%], stage II 6 [24%]), possible PBC in 14 (18.4%), and no PBC in 37 (48.7%). Univariate comparisons of clinically relevant variables between no PBC and possible/typical PBC are shown in Table 1. After adjusting for anti-TNF therapy, AMA ≥1:1280 (OR 22.72 [95%CI 4.49–115.1]; p<0.001), ALP (OR 1.06 [95%CI 1.02–1.1]; p=0.002), and TNFα, (OR 1.36 [95%CI 1.1–1.7]; p=0.010) were independently associated with an AUROC of 0.89 (95%CI 0.81–0.96; Se 85.3%, Sp 78.1%, PPV 80.6%, NPV 83.3%). A simplified model using AMA ≥1:1280 and ALP >75 U/L (≍0.6xULN) retained good discrimination (AUROC 0.81, 95%CI 0.7–0.91), identifying patients with both markers as having an 87% probability of possible/typical histological PBC versus 15% in those with neither marker. **Conclusion:** More than half of patients with AMA positivity and normal ALP have definite or possible PBC on liver biopsy. AMA titer, ALP and TNFα levels may help refine the need for liver biopsy in order to start earlier therapeutic intervention.

Table 1. Univariate comparisons between no PBC and possible/typical PBC

Variable	No PBC (n = 37)	Possible/typical PBC (n = 39)	p value
Age, years (mean ± SD)	53.0 ± 10.5	58.7 ± 11.2	**0.025**
Female sex	32	33	1.000
AST, U/L	21 ± 8	26 ± 11	**0.017**
ALT, U/L	26 ± 12	34 ± 23.5	**0.041**
GGT, U/L	23 ± 12	44 ± 56.5	**<0.001**
Alkaline phosphatase, U/L	71 ± 29	86 ± 33	**0.005**
Bile acids, µmol/L	1.7 ± 3.2	2.05 ± 2	0.695
Vitamin D, ng/mL	26 ± 15.2	25 ± 11	0.670
FIB-4	0.82 ± 0.4	1.15 ± 0.6	**0.001**
Pro-C3, ng/mL	37.8 ± 6.3	39.4 ± 10.2	0.118
CRP, mg/L	1.2 ± 1.6	1.85 ± 3.8	**0.030**
IgM, mg/dL	123 ± 92	156 ± 132	0.137
AMA ≥1:1280	8	27	**<0.001**
Anti-sp100 positive	5	2	0.209
Anti-gp210 positive	0	3	0.216
TNFα, pg/mL	8.0 ± 4.92	9.69 ± 3.42	**0.028**
IL-6, pg/mL	2.9 ± 4.62	2.68 ± 2.52	0.942
IL-12, pg/mL	4.81 ± 4.22	4.71 ± 3.36	0.704
IL-23, pg/mL	306 ± 263	357 ± 385	0.280
FGF-19, pg/mL	0.13 ± 0.11	0.13 ± 0.07	0.663
TGF-β1, pg/mL	71,902 ± 24,250	71,288 ± 35,770	0.786
TGF-β2, pg/mL	805 ± 215	918 ± 309	1.000
TGF-β3, pg/mL	546 ± 86	552 ± 27.2	0.515

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1195 | HEIGHTENED KRÜPPEL-LIKE-FACTOR-6 ALTERS TREG LIPID METABOLISM IN AUTOIMMUNE HEPATITIS

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Background: Autoimmune hepatitis (AIH) is a severe liver disease of unknown etiology that typically follows a relapsing/remitting course and often becomes refractory to immunosuppression. In AIH, regulatory T cell (Treg) impairment contributes to T effector-mediated liver damage. We have previously linked the dysfunction of AIH Tregs to altered response to aryl hydrocarbon receptor (AhR) activation. AhR is a transcription factor that modulates Treg immune responses upon binding its canonical partner, aryl hydrocarbon receptor nuclear translocator (ARNT). AhR also binds to Krüppel-like-factor-6 (KLF6), which modulates the expression of genes involved in lipid metabolism, on which Tregs rely for survival and function. We investigated if KLF6 alterations could contribute to Treg dysfunction in AIH. **Methods:** Tregs were isolated from the peripheral blood of AIH patients and age and sex-matched healthy subjects (HS). Treg KLF6 levels were measured by qPCR, flow cytometry, and western blot. KLF6 and AhR interaction in Tregs was verified by co-immunoprecipitation. Intrahepatic $KLF6^+$ Tregs were identified by immunofluorescence. Treg lipid peroxidation was measured by flow cytometry using BODIPY 581/591 C11 undecanoid acid, in the absence or presence of KLF6 silencing via Silencer Select siRNAs. Treg suppressive function was tested in co-culture experiments and measured as inhibition of $CD4^+$ $CD25^-$ responder cell proliferation. **Results:** KLF6 is upregulated in peripheral Tregs of AIH patients at both mRNA and protein levels. Greater levels of KLF6 are bound to AhR in AIH Tregs compared to HS. Higher frequencies of $KLF6^+$ Tregs are noted in liver biopsies of AIH patients compared to HS. It is known that low peroxidation is usually associated with cell survival, and medium/high peroxidation levels result in increased oxidative damage and cell apoptosis. We therefore tested Treg peroxidation levels and found that compared with HS, AIH Tregs display heightened intracellular lipid peroxidation and higher oxidized-to-nonoxidized lipid ratio. Intracellular lipid peroxidation in AIH Tregs is directly correlated with ALT levels. Silencing of KLF6 using specific siRNAs effectively downregulates lipid peroxidation and ameliorates suppressive function in AIH but not HS Tregs. Analysis of publicly available datasets derived from RNAseq studies conducted on Tregs from healthy subjects showed that high KLF6 levels are associated with gene sets linked to T cell activation and inflammation, including PI3K, ERK and Notch signaling pathways. **Conclusion:** KLF6 is aberrantly upregulated in AIH Tregs that also display heightened lipid peroxidation levels. Blockade of KLF6 limits lipid peroxidation and enhances Treg suppression in AIH Tregs. These data suggest that increased KLF6 expression impacts Treg function by altering lipid peroxidation. Blockade of KLF6 may have therapeutic potential by rebalancing Treg lipid metabolism in AIH.

Disclosures: William Li:Nothing to Disclose, Cortney Cagle:Nothing to Disclose, Lina Zhang:Nothing to Disclose, Barbora Gromova:Nothing to Disclose, Silvia Nastasio:Nothing to Disclose, Alan Bonder:Nothing to Disclose, Vilas Patwardhan:Nothing to Disclose, Simon Robson:Purinomia: Scientific founder, ePURINES: Stock – privately held company, Metaphy: Consultant, DynaMed: Independent Contractor, Biolegend: Royalties or patent beneficiary, eBioscience: Royalties or patent beneficiary, Porosome: Advisor, eGenesis: Consultant, Maria Serena Longhi:Nothing to Disclose.

1196 | POST-LIVER TRANSPLANT OUTCOMES IN PSC-AIH OVERLAP SYNDROME COMPARED WITH ISOLATED PSC: A SYSTEMATIC REVIEW

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Background: Primary sclerosing cholangitis–autoimmune hepatitis (PSC-AIH) overlap syndrome is a rare autoimmune condition that may progress to end-stage liver disease requiring liver transplantation (LT). Post-transplant outcomes in PSC-AIH remain

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poorly characterized. We performed a systematic review evaluating post-LT outcomes in PSC-AIH compared with isolated PSC. **Methods:** A PRISMA-guided systematic review protocol was registered on PROSPERO. PubMed, Embase, and Web of Science were searched through January 2026. Of 974 identified records, 32 duplicates were removed. After screening 942 records, 6 full-text studies underwent eligibility assessment and 3 comparative studies were included in the qualitative synthesis. Adult studies reporting LT outcomes in PSC-AIH with a direct PSC comparator group were included. Outcomes extracted included recurrent PSC (rPSC), graft rejection, patient survival, graft survival, and mortality. **Results:** Three retrospective comparative studies comprising over 390 total patients, including approximately 58 PSC-AIH patients, were included. PSC-AIH patients appeared younger at diagnosis and more frequently female compared with isolated PSC cohorts. Across included studies, reported post-LT rPSC rates ranged from 16.6–50.0% in PSC-AIH compared with 19.2–41.3% in isolated PSC cohorts. Rejection rates were also broadly comparable between groups, including chronic rejection rates of 8.0% versus 26.0% and 26.0% versus 17.0% in two cohorts . Mortality outcomes remained similar across studies, with no significant differences in post-transplant patient or graft survival between PSC-AIH and isolated PSC cohorts. (See Table).Disease recurrence remained an important post-transplant complication across studies. **Conclusion:** PSC-AIH overlap syndrome is a progressive autoimmune cholangiopathy that may require LT despite immunosuppressive therapy. Available comparative evidence suggests broadly comparable post-transplant outcomes between PSC-AIH overlap syndrome and isolated PSC, supporting similar therapeutic and surveillance strategy in this population including LT. Larger multicenter prospective studies are needed to better define recurrence risk and long-term outcomes.

Table 2. Summary of Post-Transplant Outcomes Across Included Studies

Study	PSC-AIH (n)	PSC Comparator (n)	rPSC (PSC-AIH vs PSC)	Rejection (PSC-AIH vs PSC)	Mortality (PSC-AIH vs PSC)
Dhanji et al. (2013)	5	84	50.0% vs 29.0%	Chronic rejection: 8.0% vs 26.0%	0.0% vs 19.0%
Péverelle et al. (2025)	47	216	41.8% vs 41.3% p: 0.46	Chronic rejection: 26.0% vs 17.0% p: 0.15	10.6% vs 26.2% p: 0.023
Choudhary et al. (2020)	6	26	16.6% vs 19.2% p: 1.0	Acute rejection: 33.3% vs 12.5% p: 0.245 Chronic rejection: 0.0%	16.6% vs 15.3% p: 1.0

PSC = recurrent primary sclerosing cholangitis

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1197 | ELAFIBRANOR IMPROVES MARKERS OF DISEASE ACTIVITY IN PRIMARY BILIARY CHOLANGITIS ACROSS DISEASE STAGES IN PATIENTS WITH UP TO 4 YEARS OF TREATMENT

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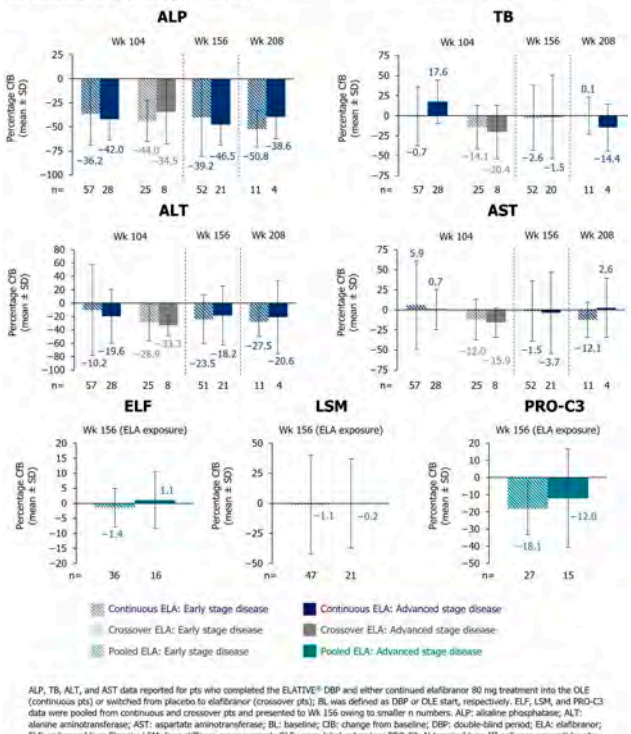
Background: Elafibranor is a second-line treatment for primary biliary cholangitis (PBC). In the phase III ELATIVE® trial (NCT04526665), elafibranor improved markers of disease activity through 52 weeks (wks) in patients (pts) with early or advanced stage PBC at baseline (BL). We evaluated the efficacy and safety of elafibranor, stratified by disease stage at BL, up to Wk 208 (Year 4) of the ELATIVE® open-label extension (OLE). **Methods:** Pts who completed the ELATIVE® double-blind period (DBP) and continued elafibranor 80 mg treatment into the OLE (continuous pts) or switched from placebo to elafibranor (crossover pts) were included; BL was defined as DBP or OLE start, respectively. PBC disease stage was categorized as early or advanced based on liver stiffness measurement (LSM; $\leq$10 or >10 kPa) or histology (Nakanuma fibrosis score <2 [absent/mild fibrosis] or $\geq$2 [bridging fibrosis/cirrhosis]) among pts with a liver biopsy. Mean (standard deviation [SD]) percentage change from BL (CfB) in biochemical markers were reported up to Wk 208. Due to low pt numbers at Wk 208, achievement of biochemical response (alkaline phosphatase [ALP] <1.67× upper limit of normal [ULN] with $\geq$15% reduction from BL, and total bilirubin [TB] $\leq$ULN) and ALP normalization were reported to Wk 156. Data for continuous and crossover pts were pooled for percentage CfB in non-invasive tests (NITs) of fibrosis, also reported to Wk 156. Safety findings were reported to Wk 208. **Results:** For continuous and crossover elafibranor pts, 73 and 31 had early stage and 35 and 14 had advanced stage disease at BL. Pts with advanced vs early stage disease had higher mean (SD) ALP levels at BL (continuous pts: 351.9 [109.1] U/L vs 306.6 [125.7] U/L; crossover pts: 345.9 [162.8] U/L vs 331.3 [200.6] U/L). For continuous pts with early vs

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advanced stage disease, 73.1% vs 52.4% had biochemical response and 28.9% vs 23.8% had ALP normalization at Wk 156. Through Wk 208, continuous pts across disease stages had reductions in ALP and alanine aminotransferase, while TB and aspartate aminotransferase remained stable. In crossover pts with early vs advanced stage, 60.0% vs 37.5% had biochemical response at Wk 104; 24.0% vs 25.0% had ALP normalization. Reductions in biochemical markers were seen in the OLE across disease stages in crossover pts (**Figure**); trends in ALP reductions to Wk 52 were similar to those who received elafibranor in the DBP. In pooled analysis of continuous and crossover pts, mean enhanced liver fibrosis scores, LSM, and PRO-C3 values were stable in both the early and advanced stage disease groups during 156 wks of elafibranor exposure (**Figure**). Elafibranor was well tolerated across early and advanced disease stages. **Conclusion:** Elafibranor was well tolerated and provided a consistent treatment effect regardless of disease stage for up to 4 years, with stabilization or improvements in markers of disease activity and NITs of fibrosis.

Figure. Percentage change from baseline in biochemical markers of disease activity up to Week 208 and non-invasive tests of fibrosis up to Week 156



ALP, TB, ALT, and AST data reported for pts who completed the ELATIVE® DBP and either continued elafibranor 80 mg treatment into the OLE (continuous pts) or switched from placebo to elafibranor (crossover pts); BL was defined as DBP or OLE start, respectively. ELF, LSM, and PRO-C3 data were pooled from continuous and crossover pts and presented to Wk 156 owing to smaller n numbers. ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BL: baseline; CfB: change from baseline; DBP: double-blind period; ELA: elafibranor; ELF: enhanced liver fibrosis; LSM: liver stiffness measurement; OLE: open-label extension; PRO-C3: N-terminal type III collagen propeptide; pts: patients; SD: standard deviation; TB: total bilirubin; Wk: Week.

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1198 | INTERFERON-DRIVEN EXPANSION OF CD169⁺ MONOCYTES AND HEPATIC MACROPHAGES IS ASSOCIATED WITH DISEASE ACTIVITY IN AUTOIMMUNE HEPATITIS

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Background: Autoimmune hepatitis (AIH) is driven by intrahepatic interferon signaling, antigen presentation, and T cell–mediated hepatocellular injury, yet the

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inflammatory macrophage phenotypes shaped within this milieu remain undefined. CD169 (Siglec-1), a type I interferon-inducible sialic acid–binding lectin, marks an inflammatory antigen-presenting monocyte/macrophage phenotype linked to disease activity in other autoimmune disorders but is uncharacterized in AIH. This study aimed to investigate the functional characteristics, and clinical relevance of CD169$^+$ monocytes in patients with AIH. **Methods:** PBMCs and liver biopsy samples were obtained from AIH patients and healthy controls. CD169$^+$ total monocyte frequency was quantified by flow cytometry (Normal; $n = 5$, AIH; $n = 29$) and correlated with clinical parameters; paired PBMC–liver tissue analyses were performed in matched cases. Liver tissue mRNA of CD169, IFN-γ, CD14, and lymphocyte/NK markers (CD3/CD4/CD8/CD56) was assessed by qRT-PCR. CD169 was evaluated by immunohistochemistry (IHC) in 25 AIH biopsies stratified by portal–periportal activity (Low; $n = 10$, High; $n = 15$), with CD68 co-staining for macrophage localization. Sorted CD14$^+$ monocytes from healthy donors were stimulated with recombinant IFN-α, IFN-β, or IFN-γ (10–30 ng/mL, 24–72 h) to assess CD169 induction in vitro. **Results:** The frequency of CD169$^+$ total monocytes was significantly higher in AIH PBMCs than in healthy controls ($p < 0.05$). CD169$^+$ total monocyte frequency correlated positively with serum AST ($R = 0.43$, $p = 0.024$), ALT ($R = 0.45$, $p = 0.020$), and total bilirubin ($R = 0.47$, $p = 0.013$). In paired samples, the CD169$^+$ proportion of monocytes was significantly higher in liver tissue than in matched PBMCs ($p < 0.05$). qRT-PCR of AIH livers showed elevated CD169, IFN-γ, CD14, and lymphocyte/NK marker mRNA compared with normal livers. IHC demonstrated that the CD169$^+$ area was significantly greater in livers with high portal–periportal inflammatory activity than in those with low activity ($p = 0.0219$) and co-localized with CD68$^+$ macrophage-rich regions. In vitro, IFN-γ induced CD169 on sorted CD14$^+$ monocytes time- and dose-dependently; type I interferons (IFN-α, IFN-β) elicited even more potent induction ($> 85\%$ CD169$^+$ at 48–72 h), consistent with Siglec-1 as a canonical type I IFN response gene, while IFN-γ also produced robust induction. **Conclusion:** CD169$^+$ inflammatory monocytes/macrophages are expanded in the circulation of AIH patients, further enriched within the inflamed liver, and tightly linked to biochemical and histological measures of hepatic injury. Both type I and type II interferons drive their induction, defining CD169$^+$ cells as an IFN-driven inflammatory macrophage phenotype that integrates the interferon, antigen-presenting, and T cell–dominated immunopathology of AIH. This phenotype may therefore serve as a clinically relevant biomarker and a therapeutic target in AIH.

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1199 | MODERATE TO SEVERE FATIGUE IS COMMON AND IMPACTFUL, BUT UNDER-RECORDED IN MEDICAL RECORDS OF PATIENTS WITH PRIMARY BILIARY CHOLANGITIS (PBC)

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Background: Fatigue affects up to 80% of patients with primary biliary cholangitis (PBC), with 20% experiencing severe fatigue unrelieved by rest. It substantially impacts daily functioning, work productivity, and emotional well-being. Fatigue correlates poorly with biochemical and histologic markers of PBC, may occur early, and is historically under-recorded in medical records due to a lack of systematic assessment and few effective targeted therapies. We quantify the gap between patient-reported and physician-documented fatigue utilizing data from the PicnicHealth PBC Registry. **Methods:** Cross-sectional, non-interventional analysis of secondary data from the PicnicHealth PBC Registry. Adult US participants with confirmed PBC enrolled January 2021-May 2022 who completed the PBC-40 Fatigue Domain were included, with longitudinal medical record data through August 2025. Index date was date of the first completed PBC-40 Fatigue Domain. PBC-40 fatigue severity was categorized as none (0–11), mild (12–28), moderate (29–39), or severe (≥ 40); moderate-to-severe was ≥ 29. Medical record–documentation (MRD) of fatigue refers to fatigue captured in the medical record on or before index. Clinico-demographic characteristics, fatigue-related treatment use (antidepressants, stimulants, sleep aids), and other PBC-40 domains were summarized descriptively. **Results:** 210 participants were included (at index, mean age was 57 [SD 11] years; 98% female; 93% White; 44% with cirrhosis; mean ALP 157 [SD 131] IU/L; 99% prior UDCA). Mild to severe fatigue was reported in the PBC-40 in 204

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(97%); of these, 166 (81%) reported moderate-to-severe fatigue (**Table**). None of the 6 patients reporting no PBC-40 fatigue had MRD fatigue. Of participants with any PBC-40 reported fatigue, only 93 (46%) had MRD fatigue: 14/38 (37%) with mild fatigue and 79/166 (48%) with moderate-to-severe fatigue, leaving 111 (54%) overall under-recorded. Greater fatigue severity was associated with broader moderate-to-severe impairment across other PBC-40 domains in patients with severe vs mild fatigue: cognitive (89% vs 37%), emotional (93% vs 37%), social (86% vs 11%), itch (70% vs 21%), general symptoms (44% vs 11%). Fatigue-related treatments were more frequently utilized in participants with MRD vs those without: antidepressants 70% vs 44%, sleep aids 48% vs 18%, stimulants 11% vs 5%. **Conclusion:** Almost all patients in the included study cohort reported fatigue. Despite 81% reporting moderate-to-severe fatigue, over half had no medical record documentation, indicating substantial under-recording. Greater fatigue severity was associated with broader health-related quality of life impairment across cognitive, emotional, social, and itch domains. These findings highlight an unmet need for improved fatigue assessment, documentation, and intervention as part of PBC care.

Table. Demographics and Clinical Characteristics by Overlap in Fatigue Documentation Source

Variable	Fatigue Overlap Group[1]		Overall
	Only PRO Fatigue N = 111	Both PRO and MR Fatigue N = 93	N = 204
Age at Index Date (years)			
n	111	93	204
Mean (SD)	57.90 (10.12)	57.25 (11.29)	57.60 (10.65)
Mean 95% CI	(56.06, 59.84)	(55.19, 59.51)	(56.21, 59.02)
Median (IQR)	58.84 (50.61, 65.60)	57.60 (49.83, 65.62)	58.60 (50.60, 65.60)
Median 95% CI	(56.60, 60.61)	(54.60, 60.11)	(56.35, 59.81)
Range	30.7, 79.8	30.6, 81.1	30.6, 81.1
Sex, n (%)			
Female	109 (98.2%)	90 (96.8%)	199 (97.5%)
Male	2 (1.8%)	3 (3.2%)	5 (2.5%)
Race, n (%)			
More than one race	6 (5.5%)	1 (1.1%)	7 (3.5%)
White	103 (93.6%)	83 (93.3%)	186 (93.5%)
Other	1 (0.9%)	5 (5.6%)	6 (3.0%)
Missing	1	4	5
Ethnicity, n (%)			
Hispanic or Latino	7 (6.4%)	5 (5.4%)	12 (5.9%)
Not Hispanic or Latino	102 (92.7%)	84 (91.3%)	186 (92.1%)
Missing	2	4	6
Time from Diagnosis (years)			
n	111	93	204
Mean (SD)	7.45 (5.37)	9.65 (7.01)	8.45 (6.25)
Mean 95% CI	(6.46, 8.48)	(8.32, 11.04)	(7.60, 9.30)
Median (IQR)	6.25 (3.21, 9.82)	7.73 (4.41, 13.66)	6.58 (3.64, 11.72)
Median 95% CI	(5.11, 7.27)	(5.66, 10.35)	(5.61, 7.81)
Range	1.2, 25.6	1.1, 37.1	1.1, 37.1
Cirrhosis at Index, n (%)			
Present	47 (42.3%)	45 (48.4%)	92 (45.1%)
Not Present	64 (57.7%)	48 (51.6%)	112 (54.9%)
ALP at Index, n (%)			
≤ 1x ULN	37 (35.6%)	40 (46.0%)	77 (40.3%)
> 1x and < 1.67x ULN	46 (44.2%)	29 (33.3%)	75 (39.3%)
≥ 1.67x ULN	21 (20.2%)	18 (20.7%)	39 (20.4%)
Missing	7	6	13
PBC Treatment History[2], n (%)			
n	111	93	204
UDCA, n (%)	110 (99.1%)	93 (100.0%)	203 (99.5%)
Obeticholic Acid, n (%)	29 (26.1%)	16 (17.2%)	45 (22.1%)
Fibrates, n (%)	13 (11.7%)	9 (9.7%)	22 (10.8%)
Fatigue Treatments per medical record[2,3], n (%)			
n	111	93	204
Antidepressants, n (%)	49 (44.1%)	65 (69.9%)	114 (55.9%)
Stimulants, n (%)	6 (5.4%)	10 (10.8%)	16 (7.8%)
Sleep Aids, n (%)	20 (18.0%)	45 (48.4%)	65 (31.9%)
No Fatigue Intervention, n (%)	55 (49.5%)	16 (17.2%)	71 (34.8%)
Fatigue Severity[4], n (%)			
None	0	0	0
Mild	24 (22%)	14 (15%)	38 (19%)
Moderate	46 (41%)	39 (42%)	85 (42%)
Severe	41 (37%)	40 (43%)	81 (40%)

[1]'Only PRO Fatigue' = PBC-40 Fatigue Domain score ≥12 and no medical record fatigue documentation. 'Both PRO and MR Fatigue' = PBC-40 Fatigue Domain score ≥12 and medical record fatigue documentation.
[2]Participants can have multiple PBC and Fatigue treatment histories.
[3]Fatigue-related treatments include medical record documented antidepressant, stimulant, or sleep aid use.
[4]PBC-40 Reported Fatigue Severity is defined as none: 0-11, mild: 12-28; moderate: 29-39; severe: ≥40

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1200 | IMPROVEMENTS IN CHOLESTATIC PRURITUS WERE OBSERVED ACROSS MULTIPLE MEASURES AND BASELINE PRURITUS SEVERITY WITH VOLIXIBAT IN PATIENTS WITH PSC: RESULTS FROM THE VISTAS TRIAL

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Background: Primary sclerosing cholangitis (PSC) is a progressive cholestatic liver disease featuring bile duct strictures that lead to hepatic injury, cirrhosis, and liver failure. Cholestatic pruritus is a common and burdensome symptom in PSC that negatively impacts patients' quality of life (QoL), work productivity, activities of daily living, and interpersonal relationships. Volixibat (VLX), a minimally absorbed ileal bile acid transporter inhibitor, interrupts enterohepatic bile acid recirculation. Initial results from the VISTAS study showed statistically significant and clinically relevant improvements in pruritus after treatment with VLX using the Adult Itch Reported Outcome (Adult ItchRO) assessment in participants with moderate-to-severe pruritus. Here, we report pruritus results across multiple patient-reported outcome measures in both the primary and secondary cohorts. **Methods:** VISTAS is a 28-week randomized, multicenter, double-blind, placebo (PBO)-controlled Phase 2b study in participants with PSC and cholestatic pruritus. Following dose selection period and blinded interim analysis, the confirmatory portion evaluated oral VLX 20 mg BID versus PBO. Participants were enrolled into primary (moderate-to-severe pruritus) and secondary (mild pruritus) cohorts based on baseline symptom severity. This analysis evaluated pruritus outcomes across the Adult ItchRO, 5 Dimension-Itch (5D-Itch), and Patient Impression of Severity-Itch (PIS-Itch) measures in both cohorts using mixed models repeated measures and descriptive statistics. **Results:** 111 participants with moderate-to-severe pruritus and 47 with mild pruritus were randomized into the primary (VLX = 54; PBO = 57) and secondary (VLX = 23; PBO = 24) cohorts, respectively. In the primary cohort, significant improvements in pruritus (LS mean [SE]) were observed across all three assessment tools (Adult ItchRO: VLX: -2.72 [0.240], PBO: -1.08 [0.241], $P < 0.0001$; 5D-Itch: VLX: -4.47 [0.755], PBO: -0.83 [0.717], $P = 0.0005$; PIS-Itch: VLX:-0.70 [0.138], PBO: -0.24 [0.131], $P = 0.0142$). Similar improvements were observed in the secondary cohort (Adult ItchRO: VLX:-1.38 [0.1803], PBO:-0.75 [0.1686], $P = 0.0138$; 5D-Itch: VLX:-2.853[0.7351], PBO:-0.2600[0.6432], $P = 0.0108$; PIS-Itch: VLX:-0.3423[0.1661], PBO:-0.02821[0.1384] , $P = 0.1648$). **Conclusion:** These results demonstrate improvements in pruritus with VLX in patients with PSC across all severities of pruritus using multiple assessment tools.

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1201 | REAL-WORLD SURVEY IN PATIENTS WITH PSC ASSESSING THE IMPACT OF PRURITUS ON WORK PRODUCTIVITY IN FRANCE, GERMANY, ITALY AND THE UNITED STATES

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Background: Primary sclerosing cholangitis (PSC) is a chronic, progressive liver disease characterized by damage to intra- and extrahepatic bile ducts. One of the most burdensome PSC symptoms is pruritus, with studies indicating almost 90% of patients with PSC have experienced pruritus at some point in their lives. A recent physicians survey reported that 42% of their patients with PSC had pruritus and almost all physicians (90%) believe that pruritus has a profound impact on a patient's quality of life (QoL). However, there are limited specific data on the impact of pruritus on work productivity. The purpose of the current study is to describe the burden of pruritus on the ability to work and impairment of daily activities among patients with PSC. **Methods:** Data were extracted from the Adelphi Real World PSC Disease Specific Programme™, a cross-sectional survey with retrospective data collection of adult patients ($\geq$18 years old) with PSC in France, Germany, Italy, and the United States from November 2024 to April 2025. The current presentation is focused on patients' perceptions around the impact pruritus had on their ability to work and impairment of activities utilizing the standardized Work Productivity and Activity Impairment (WPAI) assessment tool. Analyses used bivariate and descriptive statistics. **Results:** Results from 187 patients with PSC (Germany: n = 87; France: n = 40; US: n = 36; Italy: n = 24) who had the opportunity to complete the WPAI were included in this analysis. 74% of patients reported pruritus in the last 24 hours (via a numeric rating scale) prior to the survey. Almost 30% (mean: 29.8 [SD: 24.63]) of patients with PSC reported impairment while working, with the highest levels observed in Germany (32.0 [20.12]) and the US (35.8 [30.78]). Similar results were reported in overall work impairment (Global: 30.4 [28.11]; Germany: 34.5 [26.80]; US: 37.8 [33.14]) and activity impairment (Global: 28.7 [23.31]; Germany: 30.8 [20.82]; US: 31.7 [26.67]). Globally, an average of 7.5% (SD: 18.17) of patients with PSC missed work time with the highest impact observed in Germany (mean [SD]; 9.0 [21.53] and the US (8.2 [18.88]). When looking specifically at the impact of pruritus on WPAI,

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there was a significantly greater burden in those currently experiencing pruritus in percent missed work time (pruritus: 10.3 [21.21]; no pruritus: 1.4 [4.37]; P = 0.033), impairment while working (pruritus: 34.3 [24.91]; no pruritus: 16.7 [18.63]; P = 0.0005), overall work impairment (pruritus: 36.5 [29.69]; no pruritus: 17.7 [19.36]; P = 0.0035), and activity impairment (pruritus: 35.0 [22.48]; no pruritus: 13.4 [17.45]; P < 0.0001). **Conclusion:** These initial data highlight the considerable impact that PSC symptoms, and more specifically pruritus, have on patients' ability to work and their daily activities.

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1202 | THE TL1A-DR3 AXIS IS ENGAGED IN PRIMARY SCLEROSING CHOLANGITIS, PROVIDING A RATIONALE FOR ANTI-TL1A THERAPY

Michail Kokkorakis[1] Suyavaran Arumugam[1] Wajahat Mehal[1] Bubu Banini[1] Saumya Srivastava[1] Aida Rodriguez Murillo[1], [1]Yale University

Background: Primary sclerosing cholangitis (PSC) has no approved targeted therapy and frequently progresses to liver disease requiring transplant. Anti-TL1A monoclonal antibodies, including tulisokibart (MK-7240), have shown phase 2 efficacy in IBD, with phase 3 programs underway. 60–80% of patients with PSC have concurrent IBD, which has risk alleles for the TL1A gene (TNFSF15). PSC and IBD share Th1/Th17 epithelial inflammation and fibrogenesis at gut and biliary surfaces. We tested whether there is evidence for engagement of the TL1A-DR3 axis in PSC by examining plasma from patients with PSC, other autoimmune diseases, and healthy controls. **Methods:** Plasma from 110 subjects (43 PSC, 24 PBC, 23 AIH, 20 healthy; 199 samples across two timepoints) was analyzed: TL1A ELISA, a 21-analyte Luminex panel including soluble DR3 (TNFRSF25). In plasma from subjects with 30 PSC (at two time points), and 20 controls, further analysis was performed by Olink Explore HT (5,416 proteins). Within-PSC activity was classified by alkaline phosphatase (ALP) $\geq$ 1.5× ULN. Group comparisons used Kruskal-Wallis / Mann-Whitney; differential protein abundance and ALP correlations applied Benjamini-Hochberg correction across 5,416 proteins. **Results:** Plasma TL1A was detectable above LOD in 33% of PSC samples, 25% of PBC, 13% of AIH, and 0% of controls (PSC vs control q = 0.008; PBC vs control q = 0.037; Fig. A). Soluble DR3 was reduced in PSC vs controls (median 129 vs 326 pg/mL, q = 0.014). Across 132 matched same-patient samples, plasma TL1A and soluble DR3 were inversely correlated (Spearman ρ = −0.18, p = 0.035). On a curated TL1A-DR3 pathway protein set (Olink Explore HT; Fig. B), PSC plasma showed BH q < 0.05 elevation of the decoy receptor DcR3 (TNFRSF6B), Th1 effectors CXCL9, CXCL10 and granzyme B, Th17 cytokine IL-17A, TNF-superfamily co-stimulators OX40 (TNFRSF4) and 4-1BB (TNFRSF9), innate cytokines IL-12p40 (IL12B) and IL-18, and fibrosis marker TIMP-1, with TNFSF15 itself directionally elevated. Within PSC, 82 of 5,416 proteins distinguished ALP-Active from Quiescent samples (q < 0.05), led by biliary epithelial markers (GGT1, ANPEP, CXADR, CEACAM1, and KRT18); 418 proteins correlated with continuous ALP (q < 0.05). Plasma TL1A separated PSC from controls at the cohort level but did not track within-PSC biochemical activity (ρ with ALP $\asymp$ 0). **Conclusion:** Across three orthogonal platforms (ELISA, Luminex, Olink), PSC plasma shows concordant evidence of TL1A-DR3 axis engagement: ligand elevation, decoy-receptor (DcR3) elevation, soluble DR3 depletion, and a coherent downstream Th1/Th17/TNF-superfamily/fibrosis pathway signature. Together with TNFSF15 genetic risk in IBD and overlapping cholangiocyte–intestinal epithelial biology, these data support repurposing anti-TL1A therapy for PSC, with plasma TL1A as a candidate enrollment biomarker and the pathway-protein signature as a pharmacodynamic readout for clinical trials.

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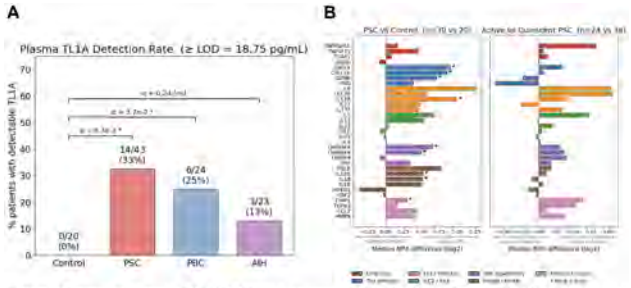


Figure. Plasma evidence of TL1A-DR3 axis engagement in PSC. (A) Plasma TL1A detection rate (≥ LOD 18.75 pg/mL) by group; Fisher's exact vs control, BH-adjusted. (B) Curated TL1A-DR3 pathway proteins (Olink Explore HT) grouped by functional class. NPX (Normalized Protein eXpression) is Olink's arbitrary log2-scale unit of relative protein abundance. Bars = median NPX (log2) difference for PSC vs Control (first TP, n = 30 vs 20; left) and ALP-Active vs Quiescent PSC (n = 24 vs 36; right). Bars extending right indicate higher protein abundance in PSC (left panel) or Active PSC (right panel). Asterisks = BH q < 0.05 within the pathway panel.

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1203 | PREVALENCE OF INDEPENDENTLY ASSESSED PATIENT-REPORTED OUTCOMES IN SUBJECTS WITH CHOLESTATIC LIVER DISEASE AND THEIR IMPACT ON HEALTH-RELATED QUALITY OF LIFE

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Background: Patient-reported outcomes (PROs), such as pruritus, fatigue, and sleep disturbances, are often underreported and overlooked in clinical practice despite their detrimental impact on health-related quality of life (HRQoL). **Aims**: To investigate the prevalence of these PROs in patients with primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC), independently assessed by healthcare personnel not involved in patient care, and to evaluate their impact on HRQoL. **Methods:** Clinical, demographic, and laboratory data were obtained from medical records of patients with PBC and PSC from five referral centers in Brazil. All participants underwent structured interviews conducted by independently trained healthcare personnel using the 5-D Itch Scale, ItchRO, PROMIS Fatigue Short Form (7a), PROMIS Sleep Disturbance Short Form (7b), and the Chronic Liver Disease Questionnaire–Brazilian version (CLDQ-BR). **Results:** A total of 325 patients (265 females; mean age 57 ± 15 years) were included, of whom 238 had PBC (214 females; mean age 61 ± 14 years) and 79 had PSC (55 females; mean age 47 ± 16 years). Lifetime self-reported itching and fatigue were observed in 78% and 71% of patients with PBC and in 75% and 72% of patients with PSC, respectively. Overall, itching in the last month was reported by 106 (33%) patients, with mean ItchRO and 5-D Itch scores of 3 [0–7] and 13 ± 5, respectively. Mean T-scores for PROMIS Fatigue (7a), Sleep Disturbance (7b), and mean CLDQ-BR scores were 44 ± 8, 52 ± 12, and 147 ± 39, respectively. Patients reporting itching in the last month had higher PROMIS Fatigue T-scores (46.5 ± 8.3 vs. 42.6 ± 8.3; $p < 0.001$) and higher PROMIS Sleep Disturbance T-scores (54.2 ± 12.7 vs. 51.0 ± 12.3; $p = 0.035$) compared to those without pruritus. Additionally, CLDQ-BR scores were significantly lower among patients with pruritus (131.2 ± 39.2 vs. 154.3 ± 36.1; $p < 0.001$), indicating worse HRQoL. Moreover, patients with pruritus had significantly higher levels of AST, ALT, ALP and total bilirubin. **Conclusion:** Pruritus is a common and clinically significant symptom in patients with PBC and PSC, strongly associated with impaired HRQoL, fatigue, and sleep disturbance. Routine and independent assessment of PROs should be incorporated into clinical care to better identify and manage this burden.

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1204 | PSC SYMPTOM BURDEN AND SEVERITY ARE PREDICTORS OF ACUTE CHOLANGITIS POST-TREATMENT OUTCOMES INDEPENDENT OF ANTIBIOTIC USE AND HOSPITALIZATION

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Background: Acute cholangitis (AC) is a significant but poorly understood complication of PSC, partly due to the lack of standardized diagnostic and treatment criteria. Proposed diagnostic criteria include worsening liver pain, fever/chills, and other abdominal pain along with LFTs, WBC, and antibiotic use. Despite its frequency, little is known about the patient symptom experience of AC or its relationship to post-treatment outcomes. In prior survey analyses, we found a broader range of symptoms occurring during AC. Here, we further analyze how symptoms during AC relate to post-treatment outcomes, as an initial step toward a simplified risk score. **Methods:** A survey of adults with PSC and ≥ 1 AC episode, distributed by PSC Partners Seeking a Cure and PSC Support UK, captured patient characteristics, AC symptom frequency/severity, antibiotic use, medical interventions, hospitalization, and return to baseline health. A simple screening tool captured the incidence and severity of key symptoms at their worst during the most recent AC episode. Patient-reported outcomes were a return to baseline health, assessed by a binary Patient Global Impression of Change (PGIC) in patients with ≥ 30 days of follow-up. Antibiotic use included oral and/or IV treatment received in a medical facility or self-administered at home. Logistic regression models were used to predict PGIC using the presence and severity of Core Symptoms (CSx: fever/chills, RUQ pain, other abdominal pain) and the aggregate of 6 Expanded Symptoms (ESx: fatigue, other pain/aches, nausea, pruritus, brain fog, jaundice). Model performance was evaluated by area under the ROC curve (AUC), with symptom-based models adjusted for antibiotic use and hospitalization. **Results:** Among 366 respondents, baseline characteristics were consistent with an adult PSC population by sex, age, race/ethnicity, PSC duration, and IBD status. Worsened post-AC health status by PGIC was reported by 28%. Only 45% had all three CSx; 31% had two, 20% had one, and 3% had none. The most frequent CSx was RUQ pain (65%), followed by fever/chills (60%) and other abdominal pain (48%). Antibiotics were used in 63% of patients (oral 37%, IV 5%, IV+oral 53%) and 20% were hospitalized (inpatient or ICU). ESx predicted worsening PGIC better than CSx, even adjusting for antibiotic use or hospitalization (Table 1). Combining CSx and ESx further improved predictive power. Individual ESx showed similar predictive value, but their aggregate performed best. Antibiotic use or hospitalization alone was less predictive than any symptom-based model. **Conclusion:** Patient-reported symptoms predict post-AC health status even without clinical or laboratory data and provide a foundation for a practical risk model. The proposed model uses a simple symptom screening tool that could be readily incorporated into practice. Next steps include model refinement and prospective collection of clinical, laboratory, and additional outcome data.

Table 1: Symptom Burden Logistic Regression Model Performance

Variables in LR Model	Area Under Curve (AUC)	AUC Adjusted for Antibiotics	AUC Adjusted for Hospitalization
Core Symptoms	0.63	0.67	0.68
Expanded Symptoms	0.71	0.72	0.73
Core + Expanded Symptoms	**0.72**	**0.73**	**0.74**

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1205 | FEMALE SEX AND HISPANIC ETHNICITY INDEPENDENTLY PREDICT ADVERSE WAITLIST OUTCOMES DESPITE INCREASED TRANSPLANT ACCESS IN PRIMARY BILIARY CHOLANGITIS: A UNOS COMPETING-RISK ANALYSIS

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Background: Primary biliary cholangitis (PBC) is a female-predominant cholestatic liver disease in which MELD-based allocation may incompletely capture physiologic vulnerability. We evaluated waitlist and post-transplant outcomes among PBC versus non-PBC candidates using competing-risk methods in a national transplant cohort. **Methods:** Adult liver transplant candidates listed in the MELD-era UNOS/OPTN STAR database were identified. Candidates with prior liver transplantation, multiorgan listing, malignancy-related etiologies, or graft failure were excluded. Primary analyses excluded hepatocellular carcinoma. Fine-Gray models evaluated waitlist death/dropout and transplant access while accounting for transplantation as a competing event. Interaction analyses assessed whether sex or MELD strata modified associations between PBC and waitlist outcomes. Cause-specific Cox models served as sensitivity analyses. Kaplan-Meier analyses evaluated post-transplant patient and graft survival. **Results:** A total of 33,588 waitlist candidates without hepatocellular carcinoma were included, including 1,045 with PBC. Compared with non-PBC candidates, PBC patients were older, predominantly female, and had lower MELD scores, creatinine levels, and portal hypertensive burden at listing. Although PBC candidates had worse unadjusted waitlist outcomes despite lower MELD severity, PBC was not independently associated with cumulative waitlist death/dropout after multivariable competing-risk adjustment (SHR 0.96, 95% CI 0.79–1.16, p = 0.66). In contrast, PBC independently predicted greater transplant access (SHR 1.27, 95% CI 1.17–1.37, p < 0.0001). Female sex independently predicted higher waitlist mortality (SHR 1.16, 95% CI 1.08–1.25, p < 0.0001) and lower transplant access (SHR 0.91, 95% CI 0.88–0.94, p < 0.0001). Hispanic ethnicity similarly predicted higher waitlist mortality (SHR 1.31, 95% CI 1.20–1.43, p < 0.0001) and lower transplant probability (SHR 0.84, 95% CI 0.80–0.87, p < 0.0001). No significant interactions were observed between PBC and sex or MELD category. Cause-specific Cox models showed modestly increased mortality hazard among PBC candidates, suggesting that greater transplant access may mitigate cumulative mortality risk. Post-transplant analyses showed superior patient and graft survival among PBC recipients (both log-rank p < 0.0001). **Conclusion:** PBC was not independently associated with cumulative waitlist mortality after competing-risk adjustment, but was associated with greater transplant access and excellent post-transplant outcomes. Female sex and Hispanic ethnicity independently predicted adverse waitlist outcomes and reduced transplant access across models, suggesting that demographic and physiologic vulnerability may drive persistent MELD-era disparities more than liver disease etiology itself.

Table 1. Multivariable Fine-Gray Competing-Risk Model for Waitlist Death or Dropout Among Adult Liver Transplant Candidates

Variable	Subdistribution Hazard Ratio (sHR)	95% Confidence Interval	P value
Primary biliary cholangitis (PBC)	0.96	0.79–1.16	0.66
Age at listing (per year)	1.04	1.04–1.05	<0.001
Female sex	1.16	1.08–1.25	<0.001
Race/Ethnicity			
— Hispanic vs White	1.31	1.20–1.43	<0.001
— Black vs White	1.02	0.86–1.20	0.85
— Asian vs White	1.03	0.82–1.29	0.80
— Other/Unknown vs White	0.96	0.77–1.20	0.71
MELD score at listing (per point)	1.03	1.02–1.03	<0.001
Serum sodium (per mmol/L)	1.02	1.01–1.03	<0.001
Serum albumin (per g/dL)	0.82	0.76–0.87	<0.001
Body mass index (per kg/m²)	1.01	1.00–1.01	0.08

Statistical analysis:

Fine-Gray competing-risk regression analysis evaluating factors associated with waitlist death or dropout. Liver transplantation was treated as a competing event.

Interpretation:

Primary biliary cholangitis was not independently associated with increased waitlist mortality after multivariable adjustment. Female sex and Hispanic ethnicity were independently associated with increased risk of waitlist death or dropout.

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1206 | LIVER ATROPHY PROVIDES INCREMENTAL PROGNOSTIC VALUE BEYOND MELD IN SEVERE ACUTE AUTOIMMUNE HEPATITIS AND AIH-RELATED ACUTE LIVER FAILURE

Keisuke Ojiro[1] Ko Goto[1] Rei Shimizu[1] Makoto Ueno[1] Yukie Nakadai[1] Takaya Tabuchi[1] Ryosuke Kasuga[1] Nobuhito Taniki[1] Shingo Usui[1] Nobuhiro Nakamoto[1] Takanori Kanai[1], [1]Keio University

Background: Liver atrophy is frequently observed in patients with severe acute autoimmune hepatitis (SA-AIH) and AIH-related acute liver failure (AIH-ALF). However, its clinical significance and prognostic impact remain poorly characterized. We aimed to evaluate the prognostic significance of liver atrophy and its incremental value beyond MELD score in patients with SA-AIH/AIH-ALF. **Methods:** We retrospectively analyzed data from a nationwide survey of acute liver failure in Japan. Acute liver failure was defined as PT-INR ≥ 1.5 regardless of the presence of hepatic encephalopathy. Among 2,070 patients, 298 patients with SA-AIH/AIH-ALF were included. Liver atrophy was diagnosed based on CT findings at each participating institution, generally corresponding to a liver volume $\leq 80\%$ of the standard liver volume. The primary endpoint was death or liver transplantation. Logistic regression, Cox proportional hazards, ROC, and Kaplan–Meier analyses were performed using MELD score and liver atrophy. **Results:** Liver atrophy was more frequently observed in AIH patients than in non-AIH patients (44.6% vs. 25.1%, $p < 0.001$). In univariable logistic regression analysis, both MELD score (OR 1.19, 95%CI 1.11–1.28) and liver atrophy (OR 18.70, 95%CI 9.44–40.19) were significantly associated with death or liver transplantation (both $p < 0.001$). Similar findings were observed in Cox proportional hazards analysis, in which MELD score (HR 1.13, 95%CI 1.09–1.17) and liver atrophy (HR 10.56, 95%CI 5.79–19.26) were independently associated with poor outcomes (both $p < 0.001$). The AUC of MELD alone for predicting poor outcomes was 0.673, whereas the addition of liver atrophy significantly improved the AUC to 0.860 (DeLong test $p < 0.001$). Kaplan–Meier analysis demonstrated significant prognostic stratification among four groups classified according to MELD score (cutoff 25.9) and liver atrophy status (log-rank $p < 0.001$). Notably, the MELD value corresponding to a predicted 50% probability of death/transplantation was substantially lower in patients with liver atrophy than in those without atrophy (20.9 vs. 37.9). No significant interaction was observed between MELD score and liver atrophy. **Conclusion:** Liver atrophy is a strong prognostic factor in SA-AIH/AIH-ALF and provides incremental prognostic information beyond MELD score. These findings suggest that liver atrophy may represent an imaging marker associated with severe structural liver injury and impaired hepatic regenerative potential that may not be fully captured by conventional physiological severity scores. Integrating structural imaging findings with physiological severity assessment may improve risk stratification in patients with SA-AIH/AIH-ALF.

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1207 | BURDEN OF RE-TRANSPLANTATION ACROSS TIME AND REGION IN A GLOBALLY REPRESENTATIVE COHORT OF PATIENTS OF >1500 PSC PATIENTS UNDERGOING LIVER TRANSPLANT

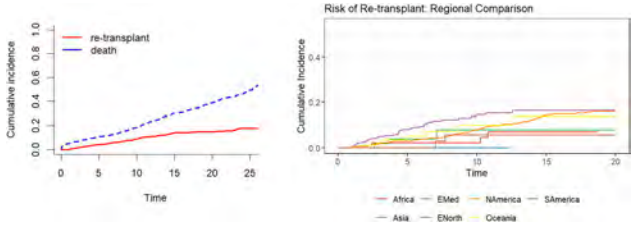
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Background: Primary sclerosing cholangitis (PSC) is an enigmatic chronic cholestatic disease that results in a disproportionate burden of transplant activity across the globe. Herein, we characterize a globally representative cohort of patients (pts) with PSC who underwent liver transplantation (LT) and report burden of re-transplantation across time and region. **Methods:** Descriptive statistics were used to describe baseline characteristics. Summary statistics were reported as proportions and medians with interquartile ranges. Kaplan-Meier analyses were used to evaluate time dependent differences in re-transplantation risk over time and across regions, after excluding early re-transplant within the first year post initial LT. Death was considered as a competing risk in evaluation of survival free of re-LT. **Results:** In total, 1546 pts were included in the analysis from Africa (n = 114), Northern Europe (NE) (n = 405), Mediterranean Europe (n = 61), Oceania (n = 117), North America (NA) (n = 791) and South America (SA) (n = 58). The mean age of PSC diagnosis was 36 (25-48) years

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(yrs), 65% were male, 55% Caucasian, 76% had IBD, and 10% labelled with an autoimmune hepatitis variant. Mean age at LT was 44 yrs (32-57) and median MELD 14 (8-21). Surgically, 61% had a donation after brain death graft, 9% had a donation after cardiac death graft, 16% had a living donor graft, and 55% had a Roux-en-Y anastomosis. UDCA was used in 39% of pts pre-LT and 22% in the first year post LT. Tacrolimus (83%) and mycophenolate mofetil (52%) were the most common immunosuppressive agents used post LT. Re-LT occurred in 14.1% (n = 219). Seventy-nine patients were re-transplanted within the first year post initial transplant and were excluded from the analysis. Survival free of re-LT was 90%, 84%, 77%, and 75% at 5-, 10-, 15-, and 20-years post initial LT. When considering death as competing risk, the cumulative incidence of re-LT was 4% at 5 years, 9% at 10 years, 14% at 15 years and 15% at 20 years post initial LT. There was no significant difference in risk of re-LT across decades of time from 1980-89, 1990-99, 2000-2009, 2010-2019, 2020-present. Furthermore, no significant differences were demonstrated in re-LT across regions, over time ($p = 0.12$, Figure 1) **Conclusion:** PSC pts undergoing LT are at high risk of re-transplantation and this risk has remained consistent over time and is similar across regions. Understanding predictors of such impactful outcomes remains an important priority.



Disclosures: Aisha Alawi:Nothing to Disclose.

1208 | FENOFIBRATE AND LONG-TERM OUTCOMES IN UDCA-TREATED PRIMARY BILIARY CHOLANGITIS WITH COMPENSATED CIRRHOSIS: A PROPENSITY-MATCHED ANALYSIS

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Background: Fenofibrate is used as adjunctive therapy in primary biliary cholangitis (PBC) with incomplete response to ursodeoxycholic acid (UDCA), but outcomes in patients with compensated cirrhosis are uncertain. We evaluated long-term hepatic, cardiovascular, hospitalization, mortality, biochemical, and synthetic-function outcomes associated with fenofibrate exposure versus UDCA alone in PBC with compensated cirrhosis. **Methods:** Using the TriNetX Research Network of 111 healthcare organizations, we identified adults with PBC and compensated cirrhosis receiving UDCA. Compensated cirrhosis was defined by cirrhosis codes without prior hepatic decompensation, including ascites, variceal bleeding, hepatic encephalopathy, portal hypertension, or hepatorenal syndrome. Fenofibrate users were compared with UDCA-treated nonusers after 1:1 propensity-score matching on demographics, comorbidities, medications, and laboratory values. Patients with major competing liver diseases were excluded. Outcomes were assessed from day 1 after index through 3 and 5 years. The primary outcome was major adverse liver outcomes (MALO), a composite of decompensation-related events, hepatocellular carcinoma, and death. Secondary outcomes included hospitalization, MACE, mortality, ALP, albumin ≤ 3.5 g/dL, and incident hepatic decompensation. **Results:** The matched cohort included 194 fenofibrate users and 194 nonusers at both timepoints. At 3 years, fenofibrate was associated with lower MALO (21.6% vs 31.4%; RR 0.69, 95% CI 0.49–0.97), hospitalization (17.5% vs 31.4%; RR 0.56, 95% CI 0.39–0.81), and albumin ≤ 3.5 g/dL (8.9% vs 21.9%; RR 0.41, 95% CI 0.22–0.76). Mortality, MACE, ALP, and incident hepatic decompensation did not significantly differ. At 5 years, fenofibrate remained associated with lower MALO (25.3% vs 42.3%; RR 0.60, 95% CI 0.45–0.80), hospitalization (22.7% vs 37.6%; RR 0.60, 95% CI 0.44–0.83), mortality (7.7% vs 14.9%; RR 0.52, 95% CI 0.29–0.93), albumin ≤ 3.5 g/dL (11.1% vs 28.1%; RR 0.40, 95% CI 0.23–0.69), and incident hepatic decompensation (21.6% vs 32.0%; RR 0.68, 95% CI 0.48–0.95). MACE and ALP did not differ. **Conclusion:** In this propensity-matched cohort of UDCA-treated PBC with compensated cirrhosis, fenofibrate exposure was associated with lower 3- and 5-year MALO, hospitalization, and hypoalbuminemia, with additional reductions in mortality and incident hepatic decompensation at 5 years. These observational findings support prospective evaluation of fenofibrate in carefully selected patients with PBC and compensated cirrhosis.

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1209 | UNMET NEEDS IN PRIMARY BILIARY CHOLANGITIS (PBC): A REAL-WORLD, CROSS-SECTIONAL SURVEY OF THE BURDEN OF PRURITUS AND TREATMENT GAPS FROM THE MULTINATIONAL PBC DISEASE SPECIFIC PROGRAMME™

Zsofia Kiss[1] Hayley Wallinger[2] Will Johnson[2] Nathalie Heirman[3] Ashley Core[4] Megumi Koyano[5] Megan McLaughlin[6] Atsushi Tanaka[7] Mark Swain[8] Sonal Kumar[9] Stephen Ryder[10] Jörn Schattenberg[11] Maria Carlota Londono[12] Afisi Ismaila[13], [1]GSK, Munich, Germany, [2]Adelphi Real World, Bollington, UK, [3]GSK, Wavre, Belgium, [4]GSK, Collegeville, USA, [5]GSK, Tokyo, Japan, [6]GSK, Collegeville, USA (at time of study conduct), [7]Teikyo University School of Medicine, [8]University of Calgary, [9]Weill Cornell Medical College, New York, USA, [10]NIHR Biomedical Research Centre at Nottingham University Hospitals NHS Trust, [11]Saarland University Medical Center, [12]University of Barcelona, [13]GSK, London, UK

Background: PBC is a rare, chronic autoimmune liver disease characterized by progressive destruction of intrahepatic bile ducts. Cholestatic pruritus in PBC is common (25–53% of patients report clinically significant or moderate/severe itch); it impairs daily functioning, contributing to sleep disturbance, fatigue, and depression. Guideline-recommended pruritus therapies have limited efficacy, and safety and/or tolerability concerns. This study describes physician attitudes and behaviors toward PBC management and itch, and patient treatment patterns/satisfaction. **Methods:** Data were taken from the Adelphi PBC Disease Specific Programme™, a real-world, cross-sectional survey of physicians and their patients with PBC in Canada, Europe (France, Italy, Germany, Spain, UK), Japan, and the US (October 2024–June 2025). Physicians completed a survey on their characteristics and attitudes/perceptions regarding itch management and completed patient record forms (PRFs) for their next four consecutive patients (demographics, clinical characteristics, and treatment history). Voluntary patient self-completed forms (SCFs) collected demographics, health-related quality of life (HRQoL), itch severity, and work productivity and impairment (WPAI) data. Pruritus severity was physician-rated (0–10 numerical rating scale [no/mild: 0–3; moderate/severe: ≥4]). All analyses were descriptive. **Results:** Results from 274 physician surveys, 1322 physician-completed PRFs and 420 SCFs were included. Patients (mean 53.8 years) were mostly female (82% [1081/1321]) and White (89% [892/997]). Most physicians agreed that itch has a profound impact on patient QoL, sleep, physical well-being, and emotional state (91%) and that current treatments for PBC do not adequately address itch, so new targeted itch therapies are needed (86%). The most commonly reported current symptoms (n = 1311 PRFs) were pruritus (62%), fatigue (50%), and sleep disturbance due to itch (17%). Cholestyramine was the most common itch therapy for patients with moderate/severe (47%, 191/410) and no/mild (38% [71/188]) itch (between groups p = 0.0507). Physicians reported satisfaction with current pruritus treatment for a lower proportion of patients with moderate/severe itch than no/mild itch (53% [219/410] vs 87% [163/188]; p < 0.0001). A higher proportion of patients with moderate/severe itch reported sleep disturbance as a most bothersome symptom compared to patients with no/mild itch (35% [51/144] vs 4% [9/242]; p < 0.0001). Patients with moderate/severe itch also reported poorer HRQoL outcomes such as work impairment (WPAI) compared to patients with no/mild itch (**Table;** all dimensions/questionnaires p < 0.0001). **Conclusion:** These real-world findings highlight the impact of pruritus on HRQoL (particularly as itch severity increases) and the need for pruritus therapies and improved symptom management for patients with PBC. **Funding:** GSK (223363/223653)

Table: Patient-reported health-related quality of life (PBC-40 and EQ-5D) and work productivity and impairment (WPAI), stratified by physician-reported itch severity*

	No/mild itch (NRS 0–3)	Moderate/severe itch (NRS ≥4)	p-value
PBC-40 questionnaire†			
Symptoms domain (range: 6–35)			
n	248	143	<0.0001
Score, mean (SD)	12.8 (5.1)	16.7 (5.5)	
Itch domain (range: 0–15)			
n	259	147	<0.0001‡
Score, mean (SD)	4.2 (2.6)	8.6 (2.7)	
Fatigue domain (range: 11–55)			
n	261	146	<0.0001
Score, mean (SD)	22.4 (8.5)	30.4 (9.5)	
Cognitive domain (range: 6–30)			
n	259	146	<0.0001
Score, mean (SD)	9.7 (4.7)	13.1 (5.2)	
Emotional domain (range: 3–15)			
n	260	146	<0.0001
Score, mean (SD)	6.6 (2.6)	9.1 (2.7)	
Social domain (range: 8–45)			
n	258	146	<0.0001
Score, mean (SD)	22.5 (7.3)	30.6 (6.2)	
EQ-5D-5L questionnaire†§			
EQ-5D VAS			
n	264	149	<0.0001
Score, mean (SD)	73.6 (15.8)	62.0 (18.3)	
WPAI questionnaire¶			
Percent overall work impairment due to PBC			
n	104	57	<0.0001
Percent, mean (SD)	20.8 (25.5)	45.3 (27.4)	

n represents the number of respondents who completed the question on the form (patient self-completed forms, overall N=420)

*5-D itch questionnaire also collected: patients with physician-reported moderate/severe itch reported significantly higher mean scores (indicating QoL more severely impacted by itch) across all measures (all p<0.0001; data not shown); †higher PBC-40 scores, and lower EQ-5D-5L scores, indicate a larger impact/worse QoL; ‡statistical comparison warrants careful consideration as itch intensity (symptom severity) was used for group stratification; §VAS data shown only; scores were significantly lower (indicating worse QoL) in patients with physician-reported moderate/severe itch versus no/mild across all EQ-5D-5L tariffs measured (Germany, US, Japan, Canada; all p<0.0001); ¶overall work impairment shown only; percent work time missed, percent impairment while working and percent activity impairment due to PBC were also all significantly (all p<0.0001) higher in patients with physician-reported moderate/severe itch versus no/mild itch

EQ-5D-5L, EuroQol 5-Dimension 5-level; NRS, numerical rating scale; PBC, primary biliary cholangitis; QoL, quality of life; SD, standard deviation; WPAI, work productivity and impairment; VAS, visual analog scale.

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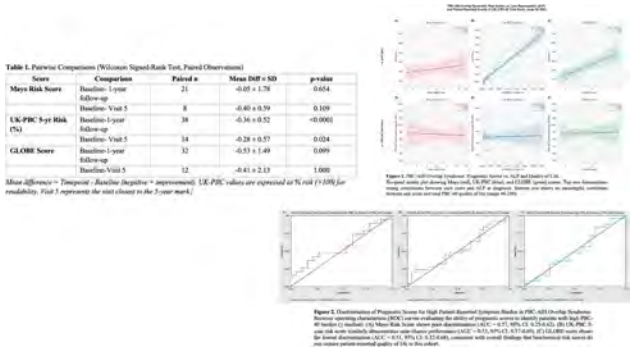
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1210 | PROGNOSTIC RISK SCORES AND QUALITY OF LIFE IN PBC-AIH OVERLAP SYNDROME: A SINGLE-CENTER PROSPECTIVE COHORT ANALYSIS

Ana Marenco-Flores[1] Victoria Abadi-Ron[2] Natalia Rojas-Amaris[3] Fernando Munguia[2] Romelia Barba Bernal[4] Daniela Goyes[5] Esli Medina-Morales[2] Leandro Sierra[6] Behnam Saberi[2] Vilas Patwardhan[2] Alan Bonder[2], [1]Harvard Medical School, [2]Beth Israel Deaconess Medical Center, [3]Beth Israel Deaconess Center, [4]Texas Tech University Health Sciences, [5]Yale Medical School, [6]Cleveland Clinic Foundation

Background: In autoimmune liver disease (AILD), overlap syndrome (OS) refers to conditions with features of more than one disease, including autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC). Reported prevalence ranges from 2-20%, and these conditions remain challenging due to variable disease courses and limited prognostic data. Validated prognostic tools (Mayo, UK-PBC, and GLOBE) predict transplant-free survival in PBC but have not been systematically evaluated in OS, and their relationship with patient-reported outcomes (PROs) is unclear. This study aims to characterize the clinical and quality of life (QoL) profile of PBC-AIH overlap patients using the PBC-40 questionnaire and assess the ability of the Mayo, UK-PBC, and GLOBE risk scores to predict QoL burden. **Methods:** We analyzed 550 prospectively enrolled patients at a U.S. tertiary care center (2018-2025). After excluding AIH-PSC overlap, incomplete PRO data, and non-overlap diagnoses, patients with PBC-AIH overlap meeting Paris II criteria were included. Baseline demographics, liver biochemistry, treatment data, and PBC-40 scores were collected. Mayo Risk, UK-PBC 5-year risk, and GLOBE scores were calculated from baseline laboratory values. Associations between prognostic scores and PBC-40 burden were assessed using Spearman correlation and AUROC analysis for high QoL burden (PBC-40 $\geq$ cohort median). Longitudinal changes in risk scores from baseline to 1-year and $\geq$5-year follow-up were evaluated using Wilcoxon signed-rank tests. **Results:** Sixty-five patients (13%) met inclusion criteria (95.4% female; median age 55.0 years). Median baseline PBC-40 score was 89.5. Baseline prognostic scores included Mayo 1.28 [IQR 1.06-1.50], UK-PBC 5-year risk 0.22% [IQR 0.20-0.22], and GLOBE 1.34 [IQR 0.64-2.37]. UK-PBC and GLOBE scores strongly correlated with ALP (Spearman $\rho = 0.78$ and 0.66, both $p < 0.001$), while Mayo did not ($\rho = 0.22$, $p = 0.18$). None of the prognostic models correlated with PBC-40 burden (all $p > 0.70$), and all showed poor discrimination for high QoL burden (AUROCs: Mayo 0.57, UK-PBC 0.53, GLOBE 0.51). Longitudinally, only UK-PBC improved over time, with lower 5-year risk at 1-year (mean difference -0.36 ± 0.52, $p < 0.0001$) and near 5 years (-0.28 ± 0.57, $p = 0.024$), while Mayo and GLOBE remained stable. **Conclusion:** In this study, prognostic risk scores showed strong biochemical performance but limited ability to capture QoL burden in PBC-AIH OS. These findings highlight a disconnect between traditional measures of disease severity and patients' lived symptom experience. Incorporating PROs into routine assessment may provide a more complete measure of disease impact. Overall, these results support further evaluation of integrated clinical and QoL-based approaches to better characterize disease burden and improve risk stratification in this population.



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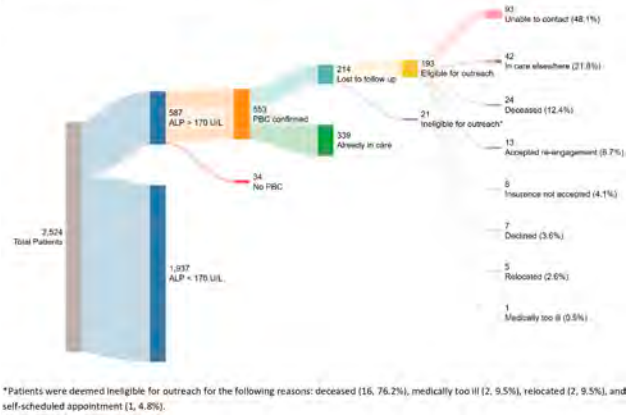
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1211 | INSIGHTS FROM A NOVEL CASE-FINDING AND OUTREACH INITIATIVE FOR LOST TO FOLLOW UP PATIENTS WITH PRIMARY BILIARY CHOLANGITIS

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Background: The availability of effective treatments for primary biliary cholangitis (PBC) heightens the need to identify patients who may benefit, especially those who are lost to follow up (LTFU) with elevated alkaline phosphatase (ALP). Outreach methods used for other therapies (e.g., HCV DAA) have not been evaluated for PBC. We conducted an outreach effort between January and April 2026 at a large urban health center in New York City to re-engage LTFU PBC patients. **Methods:** Adult patients (18+) with a PBC ICD-10 code, ALP > 170 U/L, and ≥ 1 encounter with a provider between January 2000 and November 2025 were identified by EHR review. Records were reviewed in REDCap to confirm diagnosis, demographics, PBC medications, and LTFU status. LTFU patients were contacted using a standardized escalation protocol in this order: calls to patients, MyChart messages, calls to emergency contacts (EC), and mailed letters. Descriptive analyses, including Fisher's exact test and Mann-Whitney test, were completed using R v.4.5.3. **Results:** Of 2,524 patients with PBC dx code, 193 (8%) were eligible for outreach. Patients were deemed ineligible for the following reasons: ALP < 170 (83%), already in care (15%), no PBC via review (1%), deceased (< 1%), medically too ill (< 1%), relocated (< 0.1%), and self-scheduled appointment (< 0.1%) (Figure 1). Those eligible for outreach were predominantly female (90%), had a mean age of 66.4 years (SD = 11.57), and most (78%) had an active ursodiol prescription. Of those eligible, 93 (48%) patients did not respond to contact attempts. Patients were more likely to respond if they had an active ursodiol prescription (P = .015). Thirteen (7%) patients were successfully re-engaged in care. Re-engaged patients had a significantly shorter time since their last liver clinic visit (P < 0.001), with the median being 2 years versus 6 years for non-re-engaged. None of the following demographic or clinical characteristics distinguished re-engaged from non-re-engaged patients: sex, race, ethnicity, age, preferred language, interpreter need, marital status, insurance, previous visits, distance from clinic, training of last seen provider, provider affiliation with clinic, MyChart status, or PBC prescriptions. Escalated outreach did not increase the likelihood of re-engagement. There was no significant difference in total outreach attempts, calls made, or MyChart messages sent between the groups. However, non-re-engaged patients received significantly more EC calls (P = .007) and more letters (P = .003), while re-engaged patients had a mean of zero for both, indicating that re-engaged patients did not require EC calls or letters to re-engage with their care. **Conclusion:** Re-engagement of LTFU PBC patients is most successful for those who have been previously seen within the last two years. Patients who re-engaged in care responded earlier in the outreach process. More effective strategies are needed to improve engagement in PBC care.

Figure 1. *Patient outcomes from outreach efforts*



*Patients were deemed ineligible for outreach for the following reasons: deceased (16, 76.2%), medically too ill (2, 9.5%), relocated (2, 9.5%), and self-scheduled appointment (1, 4.8%).

Disclosures: Christopher Kim:Nothing to Disclose, Francina Collado:Nothing to Disclose, Lital Aliasi-Sinai:Nothing to Disclose, Liliana Vittini Hernandez: Nothing to Disclose, Xiaotao Zhang:Nothing to Disclose, Andrea Branch:Nothing to Disclose, Anna Mageras:The Kinetix Group: Advisor, Novo Nordisk: Advisor, Gilead Sciences: Grant/Research Support, Gilead Sciences: Advisor, Frances Lee:Nothing to Disclose.

1212 | SPATIAL TRANSCRIPTOMIC PROFILING REVEALS THE IMMUNE MICROENVIRONMENT OF AUTOIMMUNE HEPATITIS LIVER BIOPSIES

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Background: Autoimmune hepatitis (AIH) is characterized by portal tract inflammation and interface hepatitis; however, the spatial distribution of immune cells and the local microenvironment surrounding Treg cells remain poorly understood. This study aimed to use CosMx 6K spatial transcriptomics to define spatial immune niches in AIH liver and characterize niche-associated Treg alterations and candidate intercellular communication programs. **Methods:** We analyzed four AIH liver biopsy samples using the CosMx Spatial Molecular Imaging with Human 6K Discovery panel. After quality control and normalization in AtoMx pipeline, downstream analysis was conducted in Seurat. For spatial niche analysis, cells were classified into immune-enriched niches and immune-sparse niches based on local cellular composition. Using SpatialCellChat v3, spatial ligand–receptor interactions were estimated across all samples. **Results:** The median age of the four patients was 73 years, 3 patients were female (75%), and the median AST and ALT levels were 99 and 124 U/L, respectively. 85,678 cells were clustered and annotated into T cells, B cells, Kupffer cells, monocyte-derived macrophages (MoMFs), hepatic stellate cells (HSCs), and endothelial/LSEC subsets. Treg cells within immune-enriched niches showed elevated IFNγ-related pathway activity compared with those in immune-sparse niches. Conversely, TGF-β signaling and FOXP3 and ENTPD1 expression were reduced, suggesting altered suppressive or homeostatic features in inflammatory regions. SpatialCellChat analysis identified candidate communication programs contributing to immune-enriched niche organization. MHC-II signaling suggested antigen-presentation-related interactions from MoMFs and B cells toward the Treg/T-cell compartment. ICAM signaling was prominent around a portal-region endothelial cell-like EC/LSEC subset via ICAM1–integrin interactions, suggesting endothelial adhesion-mediated retention of inflammatory cells. CCL/CXCL signaling was enriched within T-cell compartments, suggesting localized chemokine-dependent T-cell clustering or retention. COLLAGEN signaling suggested an HSC-centered stromal/ECM network involving B cells, cytotoxic T cells, and MoMFs through the collagen–SDC1/CD44 axis. **Conclusion:** Spatial transcriptomics revealed that Treg cells residing within immune-enriched niches in AIH exhibit enhanced IFNγ-related inflammatory signaling and reduced FOXP3, ENTPD1, and TGF-β signaling. Cell-cell interaction analysis further identified candidate intercellular communication programs involved in antigen presentation, endothelial adhesion, chemokine-dependent T-cell clustering, and HSC-centered stromal remodeling. This study spatially links the immune microenvironment surrounding interface hepatitis with Treg alterations in AIH.

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1213 | HEPATIC RECOMPENSATION IMPROVES TRANSPLANT-FREE SURVIVAL IN PRIMARY BILIARY CHOLANGITIS DECOMPENSATED CIRRHOSIS: INTERNATIONAL MULTICENTRE STUDY BY THE GLOBAL-PBC AND BAVENO COOPERATION

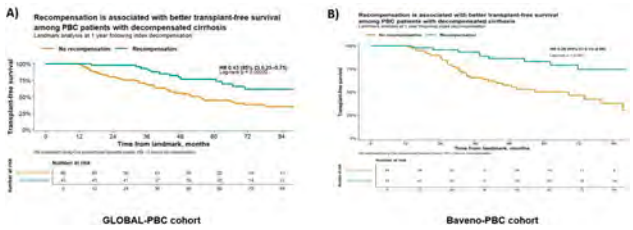
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Background: Studies suggest recompensation may be achieved in patients with PBC decompensated cirrhosis. However, PBC-specific criteria for recompensation and its prognostic impact remain unclear. We aimed to investigate (i) potential defining criteria, (ii) its predictors, and (iii) the prognostic significance of recompensation in two independent international cohort of patients with decompensated PBC cirrhosis. **Methods:** We performed parallel landmark analyses of decompensated PBC patients from the Global PBC cohort (16 centres, 4 continents; n = 348) and the Baveno Cooperation (3 centres, 2 continents, n = 173). Adult PBC patients with index decompensation (ID) were included, with identical definition and analytic methods applied in both cohorts. Patients with hepatocellular carcinoma, prior liver transplantation, or PBC-AIH overlap were excluded. Recompensation was defined at the 12-month after ID as: UDCA treatment, free of new decompensating events, and without diuretics or HE prophylaxis, and synthetic function recovery (MELD 3.0 < 10).Expanded recompensation criteria without requiring cessation of ascites/HE treatment requirement were investigated. Primary outcome was transplant-free survival (TFS) 12 months after ID according to recompensation status. **Results:** A total of 521 patients with decompensated PBC were included. The Global PBC Study Group cohorts included 348 patients (86% female, mean age 54 (SD: ± 13) years, mean MELD 3.0 of 15 (SD ± 6). Recompensation occurred in 12 (3.4%) with strict definition and in 45 (12.9%) by expanded criteria. Over median follow-up of 46 [IQR: 23-92] months, recompensation by expanded criteria was independently associated with longer transplant-free survival (TFS) (HR 0.43, 95% CI: 0.25-0.75) compared to patients without recompensation (*Fig 1A*).The Baveno cohort included 173 patients (85% female, mean age 64 (SD ± 12) years, mean MELD 3.0 of 14 (SD ± 5) months. Of 106 patients eligible at 12 months, recompensation occurred in 16 (9.2%) and in 47 (27.2%) by extended criteria. Over median follow-up of 58.2 (36.2-89.5) months, recompensation defined by expanded criteria was associated with improved TFS (HR 0.28, 95%CI: 0.13-0.58) (*Fig 1B*).Across both cohorts, strict or expanded recompensation criteria yielded comparable long-term TFS. Common predictors for recompensation were better baseline liver function (lower MELD 3.0) and achieving Paris-II biochemical response to UDCA ($p < 0.05$ for all). **Conclusion:** Expanded recompensation criteria (MELD 3.0 < 10 and event-free at 1 year) identifies 1-in-3 decompensated PBC patients, which translate into substantially better transplant-free survival. These findings establish recompensation as clinically meaningful endpoints in decompensated PBC.



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1214 | BEYOND LIPIDS: STATIN THERAPY IS ASSOCIATED WITH IMPROVED LIVER OUTCOMES IN PRIMARY BILIARY CHOLANGITIS

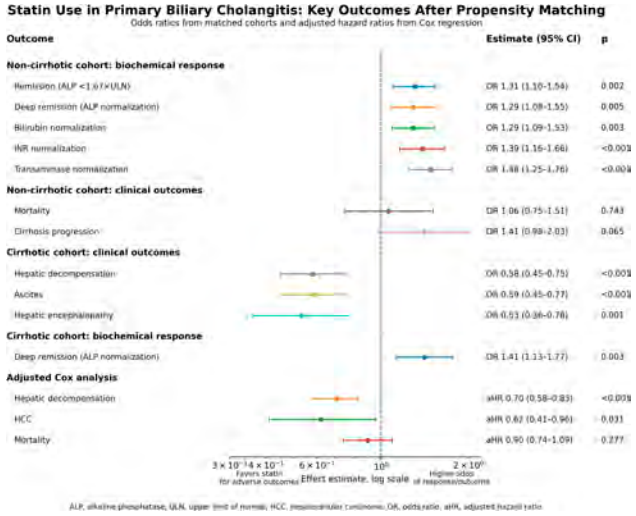
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Background: Statin use in primary biliary cholangitis (PBC) remains controversial due to concerns regarding hepatotoxicity in chronic liver disease, although emerging data suggest hepatoprotective effects in cholestatic diseases and cirrhosis. We evaluated the association of statin therapy with biochemical and clinical outcomes in patients with PBC receiving ursodeoxycholic acid (UDCA) stratified by cirrhosis stage. **Methods:** A retrospective cohort study was done via TrinetX database of adults aged 18–85 years with PBC receiving UDCA (> 3 prescriptions) & statins were included as exposures. Patients with viral & autoimmune hepatitis, alcohol-related liver disease, hemochromatosis, and alpha-1 antitrypsin deficiency were excluded. Propensity score matching was performed for demographics, comorbidities, laboratory variables, and medication exposure. Outcomes were assessed from 180 days to 7 years post-index and included mortality, hepatic decompensation, ascites, hepatic encephalopathy (HE), hepatocellular carcinoma (HCC), remission (alkaline phosphatase [ALP] < 1.67× ULN), and deep remission (normalization of ALP). Multivariable Cox regression analysis was performed to evaluate independent predictors of mortality, decompensation, and HCC. **Results:** In the non-cirrhotic cohort, 1,085 statin-treated patients were matched to 1,085 controls (not on statins). Statin use was associated with higher remission (55.5 % vs 48.4%;OR 1.32, 95% CI: 1.13-1.56 p = 0.002), bilirubin normalization (62.1% vs 54.7%;OR 1.29 95% CI: 1.15–1.60, p = 0.003), INR normalization (37.7% vs 30.3%; OR 1.39, p < 0.001), and transaminase normalization (60.6% vs 50.9%;OR 1.48,

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p < 0.001). Deep remission was higher in statin users. Rate of cirrhosis development and mortality were comparable to controls (7.4% vs 5.4%;OR 1.41, p = 0.065) and (5.9% vs 5.6%; p = 0.743), respectively. In the cirrhotic cohort, 718 statin-treated patients were matched to 718 controls. Statin use was associated with lower decompensation (17.4% vs 26.6%;OR 0.58, p < 0.001), ascites (14.9% vs 23.0%;OR 0.59, p < 0.001), and HE (5.7% vs 10.3%;OR 0.53, p = 0.001). Deep remission was higher with statin use (35.0% vs 27.6%;OR 1.41, p = 0.003). On multivariable Cox analysis, statin use independently reduced risk of hepatic decompensation (aHR 0.70, p < 0.001) and HCC (aHR 0.62, p = 0.031). Male sex independently predicted increased mortality, decompensation, and HCC. **Conclusion:** Among patients with PBC receiving UDCA, statin use was associated with improved biochemical remission in non-cirrhotic patients and reduced hepatic decompensation and HCC risk in cirrhotics. The observed mortality benefit did not persist after multivariable adjustment, potentially reflecting the relatively short follow-up period and favorable baseline transplant-free survival in UDCA-treated PBC cohorts. These findings support the safety and potential hepatoprotective effects of statins in PBC.



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1215 | BURDEN OF DISEASE IN ADULTS WITH ALAGILLE SYNDROME: FINDINGS FROM THE ALGS ADULT PATIENT REGISTRY

Morgan Faist[1] Quinn Rabenau-McDonnell[1] Roberta Smith[2] Cher Bork[2] Desiree Vaz[3] Stephanie Mullett[2] Binita Kamath[4], [1]Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, [2]Alagille Syndrome Alliance, [3]The Hospital for Sick Children, Toronto, Canada, [4]Children's Hospital of Philadelphia and the University of Pennsylvania Perelman School of Medicine

Background: Alagille syndrome (ALGS) is a rare, autosomal dominant disorder associated with cholestatic liver disease and extrahepatic manifestations. While studies to date have focused on childhood, long-term outcomes in adults with ALGS remain poorly understood. We aimed to characterize the disease burden, health-related quality of life and functional outcomes in adults with ALGS. **Methods:** The ALGS Adult Patient Registry is a cross-sectional survey of adults with ALGS, developed by the investigators in collaboration with the Alagille Syndrome Alliance, a family-advocacy group. Participants completed an online disease-specific questionnaire and the Patient-Reported Outcomes Measurement Information System-29 (PROMIS-29) to evaluate burden of disease. PROMIS domain scores were converted to T-scores normalized to the U.S. general population (mean = 50, SD = 10). **Results:** 95 adults (age ≥ 18) with ALGS completed the survey; 76.6% identified as female and 75.6% were born in North America. 43.4% age 25 and older had a bachelor's degree or higher and 69.1% were employed and/or students. 69.6% required no assistance with their own care, and 26.6% were actively providing care to others.24.5% received liver transplantation (LT) at a median age of 13 (IQR 4-22) years. Of these, 21.7% required kidney transplantation a median of 22 (IQR 11-23) years post-LT, compared to only 4.3% of those with native liver (NL).LT and NL PROMIS scores were compared (Table 1). Both groups scored worse than the general population on 6 of 7 domains. Ability to Participate in Social Roles and Activities scores were better than the general population in both groups. Fatigue was the only domain with a significant between-group difference, with the NL group reporting greater mean fatigue (57.8 vs. 51.2; p = 0.01). The NL group also had higher rates of severe fatigue (8.7% vs. 0%) and severe anxiety (17.6% vs. 0%). Among 38 respondents (40.9%) who reported pregnancies, 14 (36.8%) experienced ≥1 miscarriage(s). Of 114 total pregnancies, 35 (30.7%) were miscarriages. **Conclusion:** Preliminary analysis of the ALGS Adult Patient Registry reveals that, despite significant symptom burden, adults with ALGS are engaged in

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employment, education, and caregiving. Severity distributions of the PROMIS anxiety and fatigue scores suggest a subset of the NL group experience higher symptom burden than those with LT, but further study is needed to identify risk factors in this population. LT recipients were more likely to require kidney transplantation post-LT compared to the NL group, highlighting the need for continued investigation into long-term renal outcomes in this population. Fertility challenges were prevalent, with nearly a third of pregnancies ending in miscarriage, estimated to be double the rate in the general population. Future enrollment will expand this registry's power to characterize the adult ALGS experience and guide future research priorities and clinical care.

Table 1. PROMIS-29 domain scores and severity distribution in adults with Alagille Syndrome by liver transplant status

PROMIS-29 Domains Mean (SD) or N (%)	Liver Transplant	Native Liver	p-value
	n=22*	n=69*	
Physical Function T-score	48.8 (7.7)	46.1 (9.6)	0.18
	n=22	n=69	
Ability to Participate in Social Roles and Activities T-score	53.7 (8.5)	50.4 (11.2)	0.15
	n=22	n=70	
Cognitive Function T-score	50.5 (9.0)	46.7 (8.5)	0.08
	n=22	n=68	
Anxiety, T-score	58.3 (7.6)	57.8 (10.6)	0.79
Severe (T-score >70)	0 (0.0%)	12 (17.6%)	
	n=21	n=68	
Depression T-score	54.5 (9.2)	55.1 (10.0)	0.98
	n=22	n=69	
Fatigue T-score	51.2 (9.1)	57.8 (10.6)	**0.01**
Severe (T-score >70)	0 (0.0%)	6 (8.7%)	
	n=22	n=69	
Sleep Disturbance T-score	56.4 (2.5)	56.7 (4.2)	0.60
	n=22	n=69	
Pain Interference T-score	51.4 (9.1)	53.0 (10.7)	0.51

*Subjects were removed from the analysis of a domain if they did not complete all questions.

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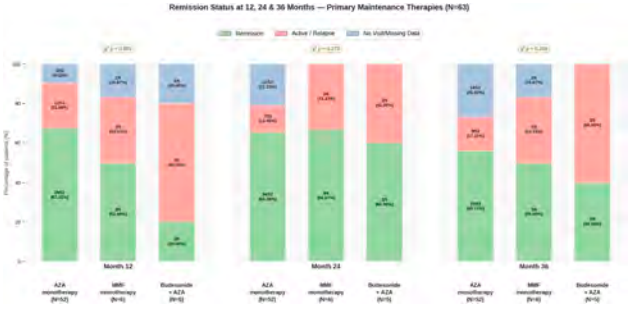
1216 | COMPARATIVE EFFECTIVENESS OF AZATHIOPRINE, MYCOPHENOLATE MOFETIL, AND BUDESONIDE-AZATHIOPRINE THERAPY IN AUTOIMMUNE HEPATITIS

Jayati Anand[1] Ana Marenco-Flores[1] Victoria Abadi-Ron[1] Natalia Rojas-Amaris[1] Fernando Munguia[1] Behnam Saberi[1] Vilas Patwardan[1] Alan Bonder[1], [1]Beth Israel Deaconess Medical Center

Background: Induction therapy for autoimmune hepatitis (AIH) involves prednisone plus azathioprine (AZA), with a transition to maintenance therapy with steroid taper; budesonide may replace prednisone in non-cirrhotic patients, and mycophenolate mofetil (MMF) is used when first-line therapy is not tolerated or effective. Steroid-sparing strategies can minimize toxicity and preserve disease control. Optimal maintenance therapy for AIH with steroid-sparing regimens remains uncertain, particularly regarding remission durability and relapse risk. This study aims to compare long-term remission and active disease/relapse among AIH patients treated with AZA monotherapy, MMF monotherapy, or budesonide-AZA combination therapy. **Methods:** We conducted a retrospective cohort study at a tertiary center in Boston, including >550 adults with AIH. Exclusion criteria included age <18 at diagnosis, <2 follow-up visits, overlap with other autoimmune liver diseases, or incomplete clinical or medication data, leaving 155 patients. Primary analysis focused on 63 patients receiving AZA (n = 52), MMF (n = 6), or budesonide-AZA combination therapy (n = 5). Biochemical remission was defined as normalization of liver chemistries; relapse was defined as the first episode of non-remission after initial remission. Outcomes were assessed at 12, 24, and 36 months and compared using chi-square/Fisher's exact tests for categorical variables. Analyses and data visualization were performed using Stata and Python. **Results:** The baseline characteristics of the patient population by treatment category were similar with no statistically significant differences in demographics or biochemistry. Throughout the study period, there were no statistically significant differences between rates of remission and active disease/relapse between any of the treatment groups. At 12 months, remission rates were: AZA 67%, MMF 50%, budesonide–AZA 20%. At 24 months, remission rates improved in the MMF (67%) and budesonide-AZA groups (60%) and remained stable for AZA alone (65%). At 36 months, remission declined across all groups: AZA 56%, MMF 50%, budesonide–AZA 40%. Active disease/relapse rates were highest in the budesonide-AZA group throughout all three time points. At 12 months: AZA 23%, MMF 33%, budesonide–AZA 60%. At 24 months: AZA 13%, MMF 33%, and budesonide-AZA 40%. At 36 months: AZA 17%, MMF 33%, and budesonide-AZA 60%. **Conclusion:** AZA, MMF, and budesonide–AZA achieved comparable short-term remission with no significant differences in remission or active disease/relapse through 36 months. AZA showed a trend toward more durable remission, while budesonide–AZA had higher late relapse. Limitations of this study include the relatively modest sample sizes, particularly within the MMF and budesonide-AZA groups. Larger studies are needed to define optimal steroid sparing maintenance therapy in AIH.

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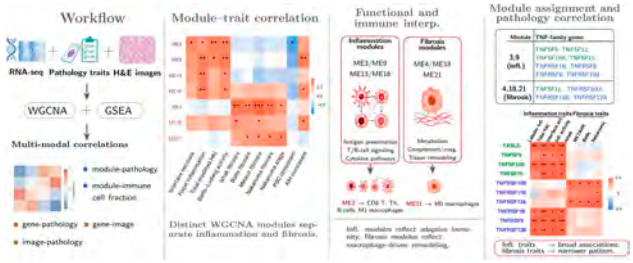


Disclosures: Jayati Anand:Nothing to Disclose, Ana Marenco-Flores:Nothing to Disclose, Victoria Abadi-Ron:Nothing to Disclose, Natalia Rojas-Amaris:Nothing to Disclose, Fernando Munguia:Nothing to Disclose, Behnam Saberi:Nothing to Disclose, Vilas Patwardan: Nothing to Disclose, Alan Bonder:Nothing to Disclose.

1217 | INTEGRATED GENE MODULE ANALYSIS LINKS TNF-SUPERFAMILY SIGNALING TO INFLAMMATORY AND FIBROTIC INJURY IN AUTOIMMUNE LIVER DISEASE

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Background: Autoimmune liver diseases, including primary sclerosing cholangitis (PSC) and autoimmune hepatitis (AIH), show heterogeneous histologic injury. TNF-superfamily signaling participates in liver inflammation and immune activation, but how specific TNFSF/TNFRSF members relate to inflammatory/fibrotic gene programs and pathology features remains unclear. **Methods:** We analyzed 67 liver transcriptomes with matched diagnostic H&E images using an integrated systems biology pipeline combining WGCNA, GSEA, CIBERSORT immune deconvolution, and cross-modal correlation analysis of TNF-superfamily genes, pathology traits, and image features. **Results:** Using WGCNA, we identified seven disease-relevant gene modules associated with pathologist-annotated fibrosis/inflammation/AILD features. Modules ME3, ME9, ME13, and ME16 were associated with inflammatory activity; ME9 and ME16 were also linked to AIH, whereas ME3 was inflammation-positive but PSC-negative. These modules were enriched in immune activation pathways, including antigen presentation and T/B-cell signaling, and were associated with increased CD8 T cells, Tfh cells, B-cell fractions, and M1 macrophages. Several TNFSF/TNFRSF genes mapped to these modules, including TNFSF12, TNFSF13B, TNFRSF1B, and TNFRSF13B. Fibrosis-linked modules ME4, ME18, and ME21 were associated with fibrosis traits, with ME18 also linked to AIH. These modules were enriched in metabolic, complement/coagulation, bile acid, and tissue-remodeling pathways, and ME21 showed a macrophage-associated pattern, especially M0 macrophages. Fibrosis-associated TNFSF/TNFRSF genes included TNFSF11, TNFRSF10B, and TNFRSF12A. Cross-modal analysis showed that TNFSF genes were broadly correlated with portal/lobular inflammation, total modified HAI, periportal interface activity, and H&E intensity features. Fibrosis traits showed a more restricted receptor-dominant pattern involving TNFRSF11B, TNFRSF10B, and TNFRSF12A, with fewer TNFSF associations. **Conclusion:** These results show that fibrosis, inflammation, PSC-related injury, and AIH are associated with distinct co-expression modules and TNFSF/TNFRSF programs, linking immune signaling to coordinated inflammatory and fibrotic gene programs reflected in tissue morphology.



Disclosures: Xiangya Wang:Nothing to Disclose.

1218 | PRIMARY SCLEROSING CHOLANGITIS (PSC) IS ASSOCIATED WITH GREATER FAMILIAL HISTORY OF INFLAMMATORY BOWEL DISEASE (IBD) THAN IBD ALONE

S. Fernanda Quevedo[1] Brian Thorsen[1] Rachel Gomel[1] Sharon Nanz[1] Stephen Rossi[1], [1]PSC Partners Seeking a Cure

Background: Primary sclerosing cholangitis (PSC) is a rare cholestatic disease of largely unknown etiology with both genetic and environmental factors. Previous studies estimate that 1-2% of people with PSC have a family history of PSC. Approximately 70% of people with PSC also have inflammatory bowel disease (IBD). In people with IBD alone, previous data shows 8-12% have familial IBD, more frequently in Crohn's disease (CD) than ulcerative colitis (UC). The rates of IBD familial history in people with PSC-IBD or PSC alone is not currently known. We present familial PSC and IBD rates in a large PSC registry cohort and compare these to established familial rates in IBD alone to further characterize the gut-liver axis in PSC. **Methods:** The PSC Partners Patient Registry collects patient-reported data from people living with PSC worldwide, including

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longitudinal clinical data, family history, and other disease-pertinent information. Most recent survey data was analyzed for rates of familial PSC and IBD. Z-tests were used to compare differences in proportions across groups. **Results:** The registry had complete data for 2472 respondents. The cohort included 72% with IBD (69% UC, 23% CD, 8% indeterminate IBD); 51% were female and 89% were Caucasian. The median age of respondents was 42 years, with a median 5 years duration of PSC and 13 years duration of IBD when present.In the overall registry cohort, familial IBD was reported in 29%, 15% with first-degree relatives with IBD. Both rates were higher than the 12% upper limit previously reported in IBD alone ($p < 0.001$). In respondents with PSC-IBD, 34% reported familial IBD with 20% reporting familial IBD in first-degree relatives. In respondents with PSC alone, 16% had familial IBD, 12% with first-degree relatives, both lower than in PSC-IBD ($p < 0.001$). CD was reported in 26% of PSC-IBD respondents with familial IBD, marginally higher than the 22% CD in PSC-IBD without familial IBD ($p = 0.06$). Consistent with other studies, familial PSC history was reported in 91 (3.5%) respondents, with 52 reporting first-degree relatives, 32 extended, and 7 with both. No significant differences were seen in IBD rates or types in respondents with familial versus sporadic PSC. In respondents with familial PSC, 59% had familial IBD, mainly due to PSC-IBD in the same relative. **Conclusion:** This large cohort reveals familial IBD rates in PSC, both with and without IBD, are higher than in IBD alone. Familial PSC rates are largely consistent with previous studies in PSC. CD was only slightly more common in those with familial IBD, contrary to the several-fold higher inheritability of CD versus UC in the IBD-alone general population. Validation in a cohort containing PSC, PSC-IBD, and IBD without PSC is needed to further investigate the relationship between disease type, genetic inheritability, and environmental exposures.

Disclosures: S. Fernanda Quevedo:Nothing to Disclose, Brian Thorsen:Mirum Pharmaceuticals: Speaking and Teaching, Rachel Gomel:Nothing to Disclose, Sharon Nanz:Nothing to Disclose, Stephen Rossi:Nothing to Disclose.

1219 | ALLOGENEIC MESENCHYMAL STROMAL CELL INFUSION MODULATES REGULATORY T-CELL AND MONOCYTE RESPONSES IN PRIMARY SCLEROSING CHOLANGITIS AND AUTOIMMUNE HEPATITIS: THE MERLIN PHASE II BASKET TRIAL

Julian Yeh[1] Victora Homer[2] Nguyet Luu[3] Sarah Mahgoub[4] Sheeba Khan[4] Annabelle Smith[5] John Cole[6] Rhian Glover[2] Helen Coulthard[2] Anna Rowe[2] Steve Elliman[7] Ye Oo[8] Palak Trivedi[9] Gideon Hirschfield[10] Philip Newsome[11], [1]The Shrewsbury and Telford Hospital Nhs Trust, [2]Cancer Research UK Clinical Trials Unit, University of Birmingham, Birmingham, UK, [3]Centre for Liver & Gastrointestinal Research, Institute of Immunology and Immunotherapy, Universi, [4]University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK., [5]University of Glasgow, [6]Medical, veterinary and life sciences shared research facilities, University of Glasgow, Glasgow, UK, [7]Orbsen Therapeutics, [8]NIHR Biomedical Research Centre, University Hospitals Birmingham & University of Birmingham, UK, [9]University of Birmingham, [10]Toronto General Hospital, [11]King's College London

Background: Primary sclerosing cholangitis (PSC) lacks any licensed disease-modifying therapy and autoimmune hepatitis (AIH) treatment is constrained by corticosteroid toxicity. Mesenchymal stromal cells (MSC) possess immunomodulatory properties relevant to both. MERLIN is an open-label, dose-finding phase II adaptive basket trial of single-dose allogeneic MSC infusion in PSC and AIH. **Methods:** Allogeneic umbilical cord-derived, $CD362^+$ MSC (ORBCEL-C^{TM}) were administered at two doses: 1×10^6 (dose A) and 2.5×10^6 cells/kg (dose B). The Highest Safe Dose (HSD) was determined by dose-limiting toxicity (DLT) within 14 days. Primary clinical outcomes were safety, HSD ascertainment and biochemical change (ALP in PSC; ALT in AIH), with Fibroscan and ELF as exploratory measures. The principal mechanistic outcome was change in circulating regulatory T cells (Treg) across both cohorts; mechanism was further explored by flow cytometry and bulk RNA-seq. **Results:** Eighteen patients were enrolled: AIH ($n = 6$, mean age 48 [28–77]) and PSC ($n = 12$, mean age 41 [27–73], 75% with colitis). The HSD in PSC and AIH was 2.5×10^6 cells/kg; DLTs comprised an ALT/AST rise >10×ULN at dose A and COVID-19–associated viral myocarditis at dose B. In pooled repeated-measures analysis ($n = 18$), the principal mechanistic endpoint was met: circulating $CD25^{HI}$ Tregs increased from 3.12% to 3.84% of $CD4^+$ cells at day 14 ($p = 0.0085$). A subsequent reduction in $CD25{-}CD127^{HI}$ T effectors was observed, from a day-3 peak of 5.06% (SD 3.38) to 4.04% (SD 2.66) by day 28. At the HSD ($n = 3$), AIH patients showed a 42% reduction in ALT by day 28 (95% CI: −70.7 to −12.4). Across the full PSC cohort ($n = 12$), ALP was unchanged while monocyte M1:M2 ratio fell from 5.85 to 4.17 by day 14 ($p = 0.043$); no change was seen in AIH. This paralleled a monocyte- and granulocyte-driven innate response on bulk RNA-seq at 4 hours post-infusion (132 significant gene signatures in PSC; 75 in AIH), with ligand–receptor analysis implicating IL-10, TLR and integrin

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pathways. **Conclusion:** MERLIN established the Highest Safe Dose of allogeneic MSC infusion (2.5×10^6 cells/kg) in both disease cohorts, with relevant immunological changes including expansion of circulating $CD25^{HI}$ Tregs, a subsequent reduction in $CD25{-}CD127^{HI}$ T effectors, and a fall in monocyte M1:M2 ratio in PSC. Biochemical (ALT reduction in AIH) and transcriptomic signals (innate-immune; IL-10, TLR, integrin) support further evaluation of MSC therapy in autoimmune liver disease.

MERLIN: Key Clinical and Mechanistic Findings

Domain	Population	Timepoint	Finding	Statistic / Detail
Safety / HSD	PSC and AIH	Within 14 days	Highest safe dose established	2.5×10^6 cells/kg; DLTs: ALT/AST rise >10×ULN at dose A; suspected viral myocarditis at dose B
Tregs	Pooled cohorts	Day 14	Circulating CD25HI Tregs increased	3.12% to 3.84% of CD4+ cells; p=0.0085
T effectors	Pooled cohorts	Day 3 to Day 28	CD25⁻CD127hi T effectors decreased after peak	Peak 5.06% (SD 3.38) to 4.04% (SD 2.66)
ALT	AIH at HSD	Day 28	ALT reduced	42% reduction; 95% CI −70.7 to −12.4
ALP	PSC	Day 28	No biochemical change detected	ALP unchanged
Bulk RNA-seq	PSC / AIH	4 hours post-infusion	Peak transcriptomic response	132 significant gene signatures in PSC; 75 in AIH

Abbreviations: HSD, highest safe dose; DLT, dose-limiting toxicity; PSC, primary sclerosing cholangitis; AIH, autoimmune hepatitis.

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1220 | FXR AGONISTS VS. PPAR AGONISTS: A REAL-WORLD COMPARISON OF SECOND LINE TREATMENT EFFECTIVENESS IN PRIMARY BILIARY CHOLANGITIS

Ngan Nguyen[1] Kelly Mei[1] Jimyeong Son[1] Sanjaya Satapathy[1] James Park[1], [1]Northwell Health - North Shore University Hospital

Background: Second-line treatment options for primary biliary cholangitis (PBC) historically included the farnesoid X receptor (FXR) agonist obeticholic acid (OCA) and peroxisome proliferator-activated receptor (PPAR) agonists such as fenofibrate prior to the recent approval of elafibranor and seladelpar. Comparative real-world effectiveness data between FXR- and PPAR-based therapies remain limited. **Methods:** We conducted a retrospective cohort study of adults with PBC treated at a tertiary care center between May 2016 and June 2025. Patients received either FXR agonist therapy or PPAR agonist therapy (fenofibrate, elafibranor, or seladelpar), with or without ursodeoxycholic acid. Baseline demographics, liver biochemistries, and liver stiffness measurements were collected. The primary endpoint was biochemical response at 12 months, defined as alkaline phosphatase (ALP) $<1.67\times$ the upper limit of normal (ULN), $>15\%$ ALP reduction from baseline, and normal total bilirubin. Secondary outcomes included ALP normalization, complete biochemical response, liver stiffness changes, and adverse events. **Results:** A total of 114 patients were included. The cohort was predominantly female (91.2%) with a mean age of 59.6 years. Fibrosis stages ranged from F0–F4, including 10.5% with advanced fibrosis (F4). Treatment distribution included 48 patients (42.1%) receiving FXR agonists and 66 patients (57.9%) receiving PPAR agonists, including fenofibrate (60.6%), elafibranor (18.1%), and seladelpar (21.2%). At 12 months, treatment persistence was 56.3% in the FXR group and 63.6% in the PPAR group.PPAR agonists demonstrated significantly higher biochemical response rates at 3 months (56.6% vs. 19.4%; $p<0.0001$), 6 months (50.0% vs. 25.0%; $p=0.0002$), and 12 months (43.6% vs. 24.4%; $p=0.0042$) compared with FXR agonists. PPAR agonists were also associated with greater reductions in alanine aminotransferase levels and higher rates of ALP normalization ($p=0.0006$) and complete biochemical response ($p=0.0003$). FXR agonists reduced liver stiffness ($p=0.028$), but this did not significantly impact fibrosis staging. FXR agonists yielded a higher proportion of patients with bilirubin $<0.6\times$ ULN; however, this effect was attenuated after baseline adjustment. Pruritus was the most frequently reported adverse event and occurred more commonly with FXR agonists. **Conclusion:** In this real-world cohort of patients with PBC, PPAR agonists demonstrated superior biochemical response rates, greater reductions in cholestatic liver enzymes, and improved tolerability. FXR agonists may retain potential benefit in select patients through effects on bilirubin and liver stiffness. These findings support the evolving role of PPAR-based therapies in PBC management and highlight the need for prospective studies evaluating individualized

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treatment sequencing and combination strategies, including potential triple-therapy approaches.

Table 1. Comparative Biochemical and Liver Outcomes Between FXR and PPAR Agonist Therapy in Primary Biliary Cholangitis

Outcome	FXR Agonist (n=48)	PPAR Agonists (n=66)	P-value
Primary Endpoint			
Biochemical response at 3 months, %	19.4	56.6	<0.0001
Biochemical response at 6 months, %	25.0	50.0	0.0002
Biochemical response at 12 months, %	24.4	43.6	0.0042
Secondary Endpoints			
ALP <1.67× ULN, n (%)	17/41 (41.5)	24/39 (61.5)	0.005
>15% ALP reduction from baseline, n (%)	24/41 (58.5)	27/39 (69.2)	0.115
Normalization of total bilirubin, n (%)	34/41 (82.9)	32/39 (82.1)	0.882
Bilirubin normalization in patients with baseline bilirubin ≥1 mg/dL, n (%)	2/7 (28.6)	3/9 (33.3)	0.472
Total bilirubin <0.6× ULN, n (%)	31/41 (75.6)	23/39 (59.0)	0.012
Total bilirubin <0.6× ULN in patients with baseline bilirubin ≥0.6× ULN, n (%)	3/20 (15.0)	7/33 (21.2)	0.255
Relative ALP reduction, median [IQR]	−20.0% [30.6]	−35.0% [38.7]	<0.0001
Absolute ALP reduction (U/L), median [IQR]	−46 [127]	−64 [91]	<0.0001
ALP normalization achieved, n (%)	2/41 (4.9)	14/39 (35.9)	0.0006
Complete biochemical response achieved, n (%)	1/41 (2.4)	13/39 (33.3)	0.0003
Relative ALT reduction, median [IQR]	−26.4% [42.8]	−12.0% [41.1]	0.005
Absolute ALT reduction (U/L), median [IQR]	−14 [25]	−3 [17]	0.0005
Change in fibrosis stage, median [IQR]	0 [2.3]	0 [1.7]	0.515
Relative reduction in liver stiffness, median [IQR]	−48.4% [34.2]	−10.6% [36.7]	0.028
Absolute reduction in liver stiffness (kPa), median [IQR]	−5.6 [4.8]	−0.8 [2.6]	0.028

Disclosures: Ngan Nguyen:Gilead Pharmaceuticals: Advisor, Kelly Mei:Nothing to Disclose, Jimyeong Son: Nothing to Disclose, Sanjaya Satapathy:Gilead Sciences: Grant/Research Support, Durect Pharma: Grant/Research Support, Fibronostics: Grant/Research Support, Novartis: Grant/Research Support, Zydus Pharma: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Intercept Pharma: Grant/Research Support, AKERO: Grant/Research Support, Altimmune: Grant/Research Support, IPSEN: Grant/Research Support, Madrigal: Grant/Research Support, James Park:Nothing to Disclose.

1221 | RISK FACTORS FOR PROGRESSION IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS WHO ARE ELIGIBLE FOR SECOND-LINE TREATMENT: EVIDENCE FROM A REAL-WORLD STUDY

Ira Jacobson[1] Robert Gish[2] Gideon Hirschfield[3] Marvin Rock[4] Chong Hoon Kim[4] Caroline Burk[4] Hayley Wallinger[5] William Johnson[5] Emily Green[5] David Jones[6] Robert Wong[7], [1]NYU Langone Health, New York, NY, USA, [2]Hepatitis B Foundation, Doylestown, PA, USA, [3]UHN's Francis Family Liver Clinic and Toronto Centre for Liver Disease, Toronto, ON, Canada, [4]Gilead Sciences, Inc., Foster City, CA, USA, [5]Adelphi Real World, Bollington, United Kingdom, [6]Newcastle University, Newcastle Upon Tyne, United Kingdom, [7]Stanford University School of Medicine, Palo Alto, CA, USA

Background: Primary biliary cholangitis (PBC) is a chronic autoimmune disease that progressively damages the liver. A major indicator of PBC progression is elevated levels of alkaline phosphatase (ALP). Second-line (2L) treatments such as seladelpar, elafibranor, and fibrates work by reducing cholestasis measured by ALP and other markers. This abstract aims to characterize patients that are eligible for 2L treatment but not on 2L to emphasize the need for more timely escalation to 2L treatment to prevent PBC progression. **Methods:** Data were drawn from the Adelphi Real World PBC Disease Specific Programme, a cross-sectional survey, with retrospective data collection in France, Germany, Italy, Spain, United Kingdom, and United States between November 2024 to May 2026. Physicians completed surveys for their patients with PBC including demographics, clinical characteristics and treatment status. Patients were considered eligible for 2L treatment if they were currently receiving ursodeoxycholic acid (UDCA) monotherapy for ≥12 months, had a most recent ALP result of >1 × upper limit of normal (ULN), and had not received 2L treatment previously. Patients with decompensated cirrhosis were excluded from analysis. Analyses performed were descriptive. **Results:** Data for 146 patients were available (91% female, mean [SD] age of 54.5 [12.2], mean [SD] years diagnosed with PBC 4.7 [4.7] and years on UDCA 4.1 [4.5]). Fatigue (49%) and pruritus/itch (48%) were the most common current symptoms. Of those with pruritus/itch, 46% experienced moderate/severe itch. The majority of most recent biochemical liver test results showed poor levels of control with mean ALP (223.6 U/L [292.4]), gamma-glutamyl transferase (139.6 U/L [370.5]), alanine transaminase (64.2 U/L [177.4]), and aspartate aminotransferase (72.6 U/L [303.8]). A third of patients (32%) had an ALP >1.67 × ULN. 89% of patients had risk factors indicative of poorer prognosis including 75% aged <62 years old, 19% with PBC stage 3 or 4, 10% with a vibration-controlled transient elastography score of >10 kPa and 30% with associated comorbidities. **Conclusion:** Many patients eligible for 2L treatment but not on 2L continue to remain on UDCA monotherapy despite presenting with poor biochemical blood markers, risk factors indicative of poorer prognosis, and persistent symptoms. This data highlights the need for more timely escalation to 2L treatment for these patients to alleviate symptoms and prevent disease progression.

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Time since diagnosis, mean [SD]	
Sample size (n)	***143***
Mean [SD]	4.7 [4.7]
Itch severity, n (%)	
Sample size (n)	**70**
Mild	38 (54%)
Moderate	28 (40%)
Severe	4 (6%)
Fatigue severity, n (%)	
Sample size (n)	**72**
Mild	33 (46%)
Moderate	34 (47%)
Severe	5 (7%)
Most recent biochemical test results, mean [SD]	
ALP (n=146)	223.6 [292.4]
GGT (n=110)	139.6 [370.5]
ALT (n=132)	64.2 [177.4]
AST (n=121)	72.6 [303.8]
Current comorbidities, n (%)	
Sample size (n)	**145**
Any comorbidity associated with poorer liver prognosis	43 (30%)
Dyslipidaemia	27 (19%)
Obesity	11 (8%)
Type 2 diabetes	8 (6%)
Metabolic dysfunction-associated steatohepatitis	5 (3%)
Pre-diabetes	4 (3%)
Type 1 diabetes	1 (1%)
Patient Age, n (%)	
Sample size (n)	***146***
<62 years	109 (75%)
62+ years	37 (25%)
PBC stage currently, n (%)	
Sample size (n)	***113***
Stage 1 – Portal stage associated with bile duct changes, and/or portal inflammation	56 (50%)
Stage 2 – Periportal fibrosis and/or inflammation with dilated but intact portal tracts	36 (32%)
Stage 3 – Septal stage: Septal fibrosis with active inflammation and/or paucicellular septa	13 (12%)
Stage 4 – Cirrhotic: Variously sized nodules and varying degrees of inflammation	8 (7%)
Most recent vibration-controlled transient elastography/ Fibroscan result, n (%)	
Sample size (n)	**59**
≤10 kPa	53 (90%)
>10 kPa	6 (10%)

Abbreviations: ALP: alkaline phosphatase; GGT: gamma-glutamyl transferase; ALT: alanine transaminase; AST: aspartate aminotransferase.

Disclosures: Ira Jacobson:Nothing to Disclose, Robert Gish:Genlantis, HepQuant, HepaTx, Virion: Stock – privately held company, Gilead Sciences, GlaxoSmithKline, HHHbio, Helio, HepQuant, Intercept, Ipsen, Madrigal,: Consultant, Mirum, Precision BioSciences, Prodigy, Topography Health, Tune Therapeutics, Virion, Quest: Consultant, AbbVie, AstraZeneca, BlueJay Therapeutics, Brii Bio, EIT Pharma, Genlantis, Gerson Lehrman Group: Consultant, Gilead Sciences Inc., Intercept, Ipsen Biopharmaceuticals, Madrigal, Mallinckrodt, Mirum: Speaking and Teaching, Syneos Health: Data Safety Monitoring Board, Genlantis, Gilead, HepaTX, HepQuant, Intercept, Prodigy: Leadership in Related Society, Board, Journal, Gideon Hirschfield:Intercept: Consultant, GSK: Consultant, CymaBay: Consultant, Ipsen: Consultant, Falk: Consultant, Pliant: Consultant, Mirum: Consultant, Advanz: Consultant, Chemomab: Consultant, Gilead: Consultant, Kowa: Consultant, Marvin Rock:Nothing to Disclose, Chong Hoon Kim:Gilead Sciences, Inc.: Employee, Caroline Burk:Gilead: Consultant, Hayley Wallinger:Nothing to Disclose, William Johnson:Nothing to Disclose, Emily Green:Nothing to Disclose, David Jones:Nothing to Disclose, Robert Wong:Theratechnologies: Grant/Research Support, Theratechnologies: Grant/Research Support, Durect: Grant/Research Support, Durect: Grant/Research Support, Gilead Sciences: Grant/Research Support, Gilead Sciences: Grant/Research Support, Exact Sciences: Grant/Research Support, Exact Sciences: Grant/Research Support, Madrigal Pharmaceuticals: Grant/Research Support, Theratechnologies: Grant/Research Support, Theratechnologies: Grant/Research Support, Durect: Grant/Research Support, Durect: Grant/Research Support, Gilead Sciences: Grant/Research Support, Gilead Sciences: Grant/Research Support, Exact Sciences: Grant/Research Support, Exact Sciences: Grant/Research Support, Madrigal Pharmaceuticals: Grant/Research Support.

1222 | POSITRON EMISSION TOMOGRAPHY IMAGING OF ACTIVE LIVER FIBROGENESIS IN PRIMARY SCLEROSING CHOLANGITIS

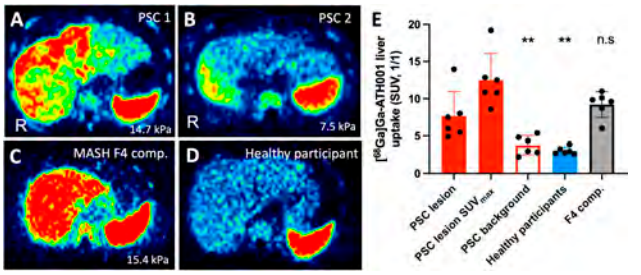
Olof Eriksson[1] Fredrik Rorsman[2] Talakad Lohith[3] Cyrille Sur[4] Zoltan Derdak[5] Paresh Thakker[4] Thuy Tran[6] Lennart Nedar[6] Håkan Ahlström[7] Ayman Abouzayed[8] Edvin Johansson[7] Lars Johansson[7] Håkan Wennbo[4] Johan Vessby[2], [1]Antaros Tracer, [2]Uppsala University Hospital, [3]Takeda, [4]Takeda Development Center Americas, [5]Takeda Pharmaceuticals, [6]Karolinska Institutet, [7]Antaros Medical AB, [8]Antaros Tracer AB

Background: Primary Sclerosing Cholangitis (PSC) is a severe, chronic, progressive fibroinflammatory disease leading to strictures of the bile ducts, ultimately leading to liver cirrhosis. The condition is associated with an increased risk of cholangiocellular carcinoma. There is a lack of non-invasive tests (NITs) to assess disease activity and liver fibrogenesis. Here, we present [^{68} Ga]Ga-ATH001, a novel Platelet Derived Growth Factor Receptor β (PDGFRβ)-targeting Positron Emission Tomography (PET) tracer, for imaging of active liver fibrogenesis, in participants with PSC and healthy controls. **Methods:** Study cohorts recruited were healthy participants without history of liver disease (n = 6), and participants diagnosed with PSC (n = 6), with large-duct intrahepatic involvement according to Magnetic Resonance Cholangiopancreatography (MRCP)). Participants were administered 2.5 MBq/kg [^{68} Ga]Ga-ATH001 (corresponding to < 1µg/kg peptide mass) and examined by PET/ Magnetic Resonance Imaging (MRI) for up to 2 hours. Assessments also included Transient Elastography (TE, FibroScan). PET uptake in liver lesions and liver regions with background uptake was reported as mean and maximum Standardized Uptake Values (SUVs). A cohort of participants with advanced chronic liver disease with non-PSC etiology (n = 6) were also examined with the same PET/MR protocol as part of the study (NCT06562361). **Results:** The uptake of [^{68} Ga]Ga-ATH001 in liver in participants with PSC was highly

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heterogenous (Figure 1A-B and E, SUV scale 0-12), where the high uptake regions exhibited intense tracer uptake (SUV_{mean} 7.6 ± 3.3, SUV_{max}12.5 ± 3.4) compared to liver of healthy participants (3.0 ± 0.5, $p < 0.001$, but comparable to that seen in advanced liver fibrosis (Figure 1C) (SUV_{mean} 9.2 ± 1.7). Low uptake regions in PSC liver (SUV_{mean} 3.8 ± 1.3) were comparable to the intensity of healthy livers (Figure 1D). No adverse events related to administration of [68 Ga]Ga-ATH001 was observed. **Conclusion:** [68 Ga]Ga-ATH001 is a novel PET based NIT for regional assessment of active liver fibrogenesis in participants with PSC. [68 Ga]Ga-ATH001 demonstrates strong heterogenous uptake in affected liver segments in subjects with PSC, while uptake in unaffected liver is low. Further analyses will focus on correlation of PET uptake to established NITs such as Magnetic Resonance Elastography (MRE), Proton Density Fat Fraction (PDFF) and plasma biomarkers.



Disclosures: Olof Eriksson:Antaros Tracer: Employee, Fredrik Rorsman:Nothing to Disclose, Talakad Lohith: Takeda Pharmaceutical Company Limited: Employee, Cyrille Sur:Nothing to Disclose, Zoltan Derdak:Nothing to Disclose, Paresh Thakker:Nothing to Disclose, Thuy Tran:Nothing to Disclose, Lennart Nedar:Nothing to Disclose, Håkan Ahlström:Nothing to Disclose, Ayman Abouzayed:Nothing to Disclose, Edvin Johansson: Nothing to Disclose, Lars Johansson:Antaros Medical: Stock – privately held company, Antaros Medical: Employee, Håkan Wennbo:Takeda: Employee, Johan Vessby:Nothing to Disclose.

1223 | PRURITUS IS ASSOCIATED WITH INCREASED BIOCHEMICAL DISEASE ACTIVITY AND SYMPTOM BURDEN IN PRIMARY BILIARY CHOLANGITIS: FINDINGS FROM THE GLOBAL LIVER REGISTRY

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Background: Pruritus is among the most common and impactful symptoms in primary biliary cholangitis (PBC), yet its association with biochemical disease activity and accompanying symptom burden in real-world cohorts remains incompletely characterized. We aimed to evaluate the association of self-reported pruritus with biochemical disease severity and clinical symptom burden among patients with PBC enrolled in the Global Liver Registry. **Methods:** We performed a cross-sectional analysis of patients with PBC enrolled in the Global Liver Registry between July 2025 and October 2025. Participants were stratified according to the presence or absence of pruritus. Clinical characteristics, liver biochemistries, treatment patterns, and symptom profiles were compared between patients with and without pruritus. **Results:** A total of 102 patients with PBC were included (mean age 51.0 ± 10.8 years; 92.2% female), of whom 45 (44.1%) reported pruritus. Female sex was comparable between patients with and without pruritus (95.6% vs. 89.5%, P = 0.461). Patients with pruritus demonstrated significantly greater biochemical disease activity compared with those without pruritus, including higher alkaline phosphatase levels (median 230.0 vs. 135.0 U/L, P = 0.005), total bilirubin (13.6 vs 9.5 µmol/L, P = 0.029), alanine aminotransferase (29.5 vs 22.0 U/L, P = 0.004), aspartate aminotransferase (36.0 vs 27.0 U/L, P = 0.001), and gamma-glutamyl transferase levels (113.0 vs 47.5 U/L, P = 0.013). Fatigue was more frequently reported among patients with pruritus compared with those without pruritus (68.9% vs. 47.4%, P = 0.029), as was sleep disturbance (64.4% vs. 31.6%, P < 0.001). Rates of ursodeoxycholic acid use and second-line therapy use were similar between groups. **Conclusion:** Pruritus in PBC was associated with greater biochemical disease activity and higher symptom burden, including fatigue and sleep disturbance, in this real-world cohort from the Global Liver Registry. These findings suggest that pruritus may make a clinically more burdensome disease profile and highlight the importance of comprehensive symptom assessment and management in patients with PBC.

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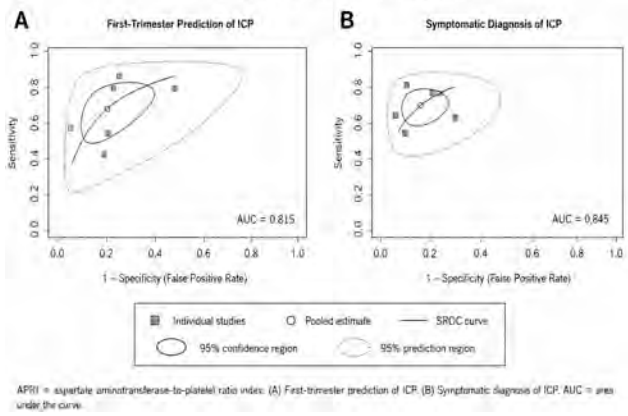
Disclose, Reem Alahmed:Nothing to Disclose, Abdullah Alkhenizan:Nothing to Disclose, Abdullah Alfhaid:Nothing to Disclose, Khalid Alswat:Nothing to Disclose, Fatema Nader:Nothing to Disclose, Faisal Abaalkhail: Nothing to Disclose, Zobair Younossi:Zobair M. Younossi is a consultant or has received research: Consultant, madrigal: Grant/Research Support, Siemens: Research funding, GSK: Consultant, BI: Consultant, Sanofi: Research funding, Waleed Alhazzani: Nothing to Disclose.

1224 | DIAGNOSTIC AND PREDICTIVE VALUE OF THE ASPARTATE AMINOTRANSFERASE-TO-PLATELET RATIO INDEX IN INTRAHEPATIC CHOLESTASIS OF PREGNANCY: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Intrahepatic cholestasis of pregnancy (ICP) is associated with significant fetal morbidity and mortality, while total bile acid testing may be delayed or unavailable in many settings. The aspartate aminotransferase-to-platelet ratio index (APRI) is an inexpensive biomarker derived from routine blood tests. We evaluated the diagnostic, predictive, and severity-discriminating performance of APRI in ICP. **Methods:** We performed a PRISMA-DTA-guided systematic review and diagnostic test accuracy meta-analysis of studies assessing APRI in pregnant women with suspected or confirmed ICP. PubMed, Embase, Web of Science, and Scopus were searched from inception. Estimates were pooled using bivariate random-effects models. **Results:** Twelve studies encompassing 2,198 patients were included. For first-trimester prediction of ICP, the pooled sensitivity was 68.2% (95% CI 52.7%–80.5%), specificity was 81.8% (68.3%–90.4%), and AUC was 0.815, with moderate heterogeneity (I^2 = 54.2%). Preliminary second- and third-trimester prediction analyses, each limited to two studies, yielded supportive specificity estimates of 86.6% and 91.3%, respectively. For symptomatic diagnosis, the pooled sensitivity was 71.4% (63.0%–78.6%), specificity was 84.8% (77.6%–89.9%), positive likelihood ratio was 4.78, negative likelihood ratio was 0.34, AUC was 0.845, and heterogeneity was low (I^2 = 39.5%). In an exploratory analysis of severity discrimination based on two studies, APRI demonstrated a pooled sensitivity of 82.6% (73.1%–89.2%), specificity of 78.0% (64.3%–87.5%), diagnostic odds ratio of 18.50, AUC of 0.823, and minimal heterogeneity (I^2 = 2.7%). **Conclusion:** APRI demonstrates promising predictive and diagnostic utility in ICP, particularly for first-trimester prediction and symptomatic diagnosis. Preliminary data also suggest potential value in severity discrimination, though these findings require validation in larger studies. As a readily available and inexpensive biomarker, APRI may facilitate early triage and risk stratification in settings where bile acid testing is delayed or unavailable, though it should complement rather than replace standard bile acid measurement.

Figure 1. Summary Receiver Operating Characteristic (SROC) Curves for APRI in Intrahepatic Cholestasis of Pregnancy



APRI = aspartate aminotransferase-to-platelet ratio index; (A) First-trimester prediction of ICP; (B) Symptomatic diagnosis of ICP; AUC = area under the curve.

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1225 | MALNUTRITION AS A PREDICTOR OF CLINICAL OUTCOMES IN HOSPITALIZED PATIENTS WITH PRIMARY BILIARY CHOLANGITIS(PBC) IN THE UNITED STATES

Tsegaye Gebreamlak[1] Mahader Wossene[1] Tamrat Petros Elias[2] Albert Gyato[1] Tamiru Dagnachew[3], [1]Loyola Medicine MacNeal Hospital, [2]King Faisal Hospital, University of Rwanda, [3]St. Paul's Hospital Millennium Medical College(SPHMMC)

Background: Malnutrition is a well-recognized complication among patient with primary biliary cholangitis (PBC). Yet the impact of malnutrition on outcomes in patients hospitalized with primary biliary cholangitis (PBC) is poorly characterized. This study aims to evaluate the association of malnutrition on clinical outcomes in patients with primary biliary cholangitis (PBC) by utilizing a national representative cohort. **Methods:** We performed cross-sectional analysis using data collected from the nationwide Inpatient Sample (NIS) database from 2016 to 2022. Hospitalizations of adult patients ($\geq$18 years) with primary biliary cholangitis(PBC) were selected by using ICD10CM codes. Malnutrition was defined as mild/moderate or severe using validated ICD10CM codes. The primary outcome was in-hospital mortality. Secondary outcomes included ascites, hepatic encephalopathy (HE), variceal hemorrhage, spontaneous bacterial peritonitis (SBP), hepatorenal syndrome (HRS), sepsis. We utilized a weighted frequency and contingency table for descriptive statistics. Multivariable logistics and linear regression were utilized for analysis to adjust for confounders including demographics, payer, income quartile, comorbidity, hospital region, bed size, cirrhosis and Hepatocellular carcinoma. Stata was utilized for statistical analysis. **Results:** We identified an estimated 86,130 hospitalizations due to primary biliary cholangitis (PBC) in the nationwide inpatient sample (2016-2022). Roughly 14.3% carried a diagnosis of malnutrition. As expected, females were predominant in both the malnourished and non-malnourished group with more than half of patients aged 65 years or older. After adjusted for cofounders Malnutrition more than doubled the odds of in hospital mortality (aOR 2.40, 95% CI 2.04–2.83; $p < 0.001$). Malnutrition was independently associated with significantly higher odds of ascites (aOR 2.77, 95% CI 2.52–3.04; $p < 0.001$), Hepatic Encephalopathy (aOR 2.04, 95% CI 1.30–3.18; $p < 0.002$), spontaneous bacterial peritonitis (SBP) (aOR 2.88, 95% CI 2.31–3.60; $p < 0.001$), and Hepatorenal syndrome(HRS) (aOR 3.42, 95% CI 2.85–4.10; $p < 0.001$). With regards to Infectious outcome malnutrition was associated with two-fold increase in sepsis (aOR 2.00, 95% CI 1.79–2.24; $p < 0.001$). Similarly, malnutrition more than doubled the odd of AKI (aOR 2.02, 95% CI 1.85–2.21; $p < 0.001$) and intensive care unit (ICU) admission (aOR 2.38, 95% CI 2.02–2.80; $p < 0.001$). A dose-response relationship was observed on clinical outcomes with severity of malnutrition. Severe malnutrition was associated with nearly threefold increased odds of in hospital mortality (aOR 2.80, 95% CI 2.28–3.44; $p < 0.001$) which is higher as compared to mild/moderate malnutrition (aOR 1.77, 95% CI 1.38–2.25). Similarly, significant dose-response relationships were observed across clinical outcomes: ascites (mild/moderate malnutrition aOR 2.20; severe malnutrition aOR 2.78), hepatorenal syndrome (aOR 2.40; 3.40), sepsis (aOR 1.80; 1.98), spontaneous bacterial peritonitis (aOR 2.16; 2.74), acute kidney injury (aOR 1.66; 1.95), and ICU admission (aOR 2.03; 2.29; all $P < 0.001$). **Conclusion:** Malnutrition shows a strong, independent link with adverse clinical outcomes in patients hospitalized with primary biliary cholangitis. Early recognition of malnutrition through targeted nutritional evaluation and intervention may improve patient outcomes.

Disclosures: Tsegaye Gebreamlak:Nothing to Disclose, Mahader Wossene:Nothing to Disclose, Tamrat Petros Elias:Nothing to Disclose, Albert Gyato:Nothing to Disclose, Tamiru Dagnachew:Nothing to Disclose.

1226 | CARDIOMETABOLIC CARE GAPS IN PRIMARY BILIARY CHOLANGITIS: UNDER-SCREENING FOR HYPERLIPIDEMIA AND STATIN UNDERUTILIZATION IN A CONTEMPORARY COHORT

Eleanor Belilos[1] Amanda Rodriguez[1] Ana Maria Davila Morales[1] Nancy Reau[1], [1]Rush University Medical Center

Background: As metabolic dysfunction-associated steatotic liver disease (MASLD) and cardiometabolic comorbidities become increasingly prevalent, patients with primary biliary cholangitis (PBC) may face heightened cardiovascular risk. Despite evidence supporting statin safety in chronic liver disease, concerns regarding hepatotoxicity may contribute to undertreatment of dyslipidemia in PBC. We evaluated lipid screening practices and statin utilization in a contemporary cohort of antimitochondrial antibody-positive (AMA+) PBC patients. **Methods:** We performed a retrospective chart review of adults with confirmed AMA+ PBC evaluated in hepatology clinic at a single academic center between January 2017 and December 2022. Demographics, body mass index (BMI), cardiovascular comorbidities, fasting lipid panel (FLP) screening history, and statin use were collected through chart review. Statin

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eligibility was determined using current United States Preventive Services Task Force recommendations. Descriptive statistics characterized screening and treatment patterns. **Results:** A total of 131 patients with confirmed AMA+ PBC were included. Median age was 63 years and median BMI was 27.7 kg/m²; 120/131 (91.6%) were female. Diabetes mellitus was present in 25/131 (19.0%) and 14/131 (10.6%) had documented atherosclerotic cardiovascular disease (ASCVD). Overall, 56/131 (42.7%) met guideline-based indications for statin therapy. Despite substantial cardiometabolic risk burden, 22/131 patients (16.8%) had no documented prior FLP screening. Among patients with at least one documented FLP (109/131), median age was 64 years and median BMI was 27.9 kg/m². Overall, 48/131 patients (36.6%) were prescribed statin therapy. Among statin-eligible patients, 19/56 (33.9%) were not receiving treatment. In untreated statin-eligible patients, chart documentation frequently cited elevated liver enzymes or underlying liver disease as reasons for withholding therapy. **Conclusion:** In this contemporary AMA+ PBC cohort, substantial gaps in cardiovascular risk assessment and preventive care were identified. Nearly one in six patients had never undergone lipid screening, and one-third of statin-eligible patients were untreated despite established indications. Provider concerns regarding hepatotoxicity appear to contribute to undertreatment despite evidence supporting statin safety in chronic liver disease. These findings highlight the growing overlap between PBC, MASLD, and metabolic dysfunction and support greater integration of hepatology and cardiovascular preventive care in PBC.

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1227 | STATIN USE AND MAJOR ADVERSE CARDIOVASCULAR EVENTS IN PRIMARY BILIARY CHOLANGITIS: A PROPENSITY SCORE–MATCHED COHORT STUDY

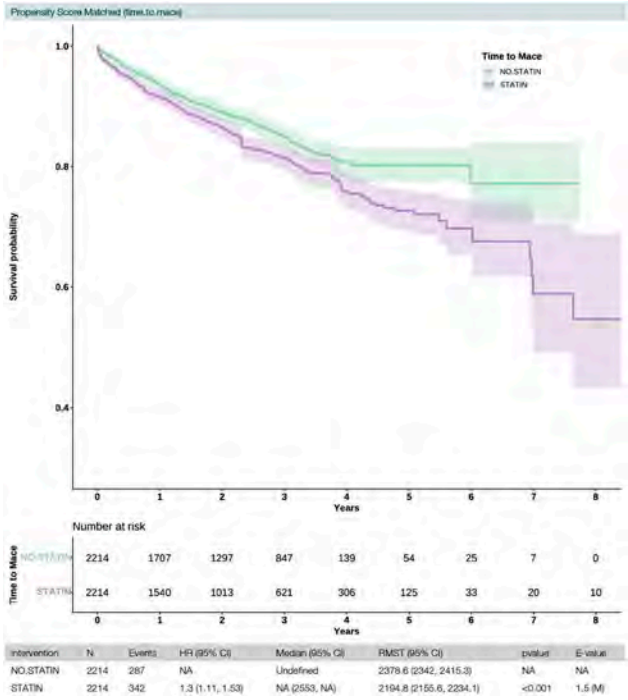
Remco Kersten[1] Honor Magon[2] Cheyne Hoke[2] Carlos Reina[2] Aparna Goel[1], [1]Stanford University Medical Center, [2]Atropos Health

Background: Primary biliary cholangitis (PBC) is characterized by distinctive dyslipidemia and incompletely understood cardiovascular risk. Statins are frequently withheld due to hepatotoxicity concerns and uncertainty surrounding major adverse cardiovascular events (MACE) outcome data in this population. With treatment advances prolonging survival, PBC patients face persistent MACE risk, highlighting the importance of better characterizing current ASCVD risk management practices in this population. **Methods:** This retrospective cohort study used the Apollo dataset (Atropos Health), a de-identified national EHR-claims database of more than 142 million U.S. patients. PBC and MACE were ascertained using ICD-9/10 codes; MACE encompassed MI, unstable angina, heart failure, ischemic and hemorrhagic stroke, TIA, subarachnoid hemorrhage, and cerebrovascular occlusion. Statin initiators were compared to statin-naïve controls with a 3-month washout. Index date was first statin prescription (intervention) or first office visit (controls) after PBC diagnosis. Time to MACE was analyzed via (1) unadjusted Cox regression, (2) basic demographic matching, and (3) propensity score (PS) matching augmented with time from PBC diagnosis to index date, diabetes history, and hypertension history. **Results:** 4,749 statin initiators and 4,661 statin-naïve controls were identified. Statin users were older (64.9 vs. 59.2 years) with higher rates of diabetes (36.0% vs. 16.3%) and hypertension (64.4% vs. 47.9%), confirming confounding by indication. Statin-naïve patients had higher rates of severe liver disease (21.5% vs. 14.4%). PS matching yielded 2,214 well-balanced pairs. MACE risk attenuated across matching steps: unadjusted (976 vs. 515 events; HR 1.54, 95%CI 1.38–1.72), basic matched (736 vs. 473 events; HR 1.30, 1.15–1.46), and PS-matched (342 vs. 287 events; HR 1.30, 1.11–1.53; all $p < 0.001$). An E-value of 1.5 suggests moderate confounding could explain the residual signal. **Conclusion:** Although statin users experienced more MACE in unadjusted analyses, attenuation across adjustment steps is consistent with residual confounding by indication rather than true drug toxicity. Residual associations may reflect dyslipidemia severity, PBC disease stage, and PBC-directed treatment. Higher severe liver disease prevalence among statin-naïve patients introduces competing risks, as advanced PBC may cause

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hepatic decompensation before MACE, artificially improving cardiovascular survival in controls. These data highlight a clinically significant treatment gap: a substantial proportion statin-naïve PBC patients had diabetes and hypertension, conditions (likely) warranting lipid-lowering therapy. Studies incorporating competing-risk methodology and PBC-specific covariates are needed.



Disclosures: Remco Kersten:Nothing to Disclose, Honor Magon:Nothing to Disclose, Cheyne Hoke: Nothing to Disclose, Carlos Reina:Nothing to Disclose, Aparna Goel:Gilead Sciences: Grant/Research Support, Kezar Life Sciences: Consultant, Ipsen Pharmaceuticals: Advisor, Mirum Pharmaceuticals: Advisor, Amgen: Consultant, RegCell: Consultant, DrenBio: Consultant.

1228 | LOSS OF RESPONSE TO FIRST-LINE TREATMENT IMPACTS THE RISK AND TIME TO LONG-TERM OUTCOMES AMONG PATIENTS WITH PRIMARY BILIARY CHOLANGITIS

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Background: Ursodeoxycholic acid (UDCA) is the first-line (1L) treatment for patients (pts) with primary biliary cholangitis (PBC), and response to UDCA is typically defined using biomarkers such as alkaline phosphatase (ALP) levels. Pts with an adequate biochemical response at 12 months (M12) have better long-term outcomes than non-responders. To date, the proportion of patients who maintain adequate response beyond M12 and the impact of loss of response (LoR) to 1L treatment is not well characterized; better understanding of durability of response and impact of LoR may inform timing and urgency of escalation to second-line (2L) therapies. We evaluated the frequency and timing of LoR to UDCA, and its association with long-term liver outcomes. **Methods:** This observational study used electronic medical record data from the Mayo Clinic in the US. Pts with a PBC diagnosis were identified using structured (laboratory results and diagnostic codes) and unstructured (clinical notes) data. Eligible pts included those with PBC initiating UDCA between 1 January 1998−31 July 2024, with $\geq$12 months of UDCA treatment and without advanced liver disease or other predefined cholestatic conditions. Pts were followed from UDCA initiation until liver outcome, death, loss to follow-up, or the end of the study period (31 July 2025). Pts were classified as ALP responders (<1.67×upper limit of normal [ULN]) or non-responders ($\geq$1.67×ULN) at M12. Among responders, LoR was defined as any subsequent ALP $\geq$1.67×ULN after M12; a sensitivity analysis with a stricter definition of two consecutive ALP values $\geq$1.67×ULN was conducted. Long-term liver outcomes (decompensated liver disease, liver transplant, liver cancer, other liver outcomes, and death) were identified using International Classification of Diseases 9th and 10th revisions (ICD-9 and ICD-10) codes and unstructured data. **Results:** Among pts with adequate response to UDCA at M12 (n=265), LoR occurred in 9.1% by M24, 12.8% by M36, and 20.8% by M60. Higher proportions of pts with LoR progressed to adverse liver outcomes vs those without LoR at M24, M36 or M60 (**Figure A**), and survival probability free from any liver outcome was higher in pts without LoR vs with LoR (**Figure B**). Similarly, higher proportions of pts with LoR at M24, M36 and M60 underwent liver transplant (LT) vs those without LoR, with higher transplant-free survival probability observed in pts without LoR; median time to LT in those who had an LT was 5.6 years in pts without LoR vs 2.0 years in pts with LoR by M60 (**Figures C and D**). All findings were corroborated when the more stringent LoR definition of two consecutive ALP values $\geq$1.67×ULN after M12 was used. **Conclusion:** LoR to UDCA was associated with worse liver outcome-free survival than in pts without LoR. These findings highlight the importance

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of ongoing biochemical response monitoring and timely consideration of switching to effective 2L therapy following LoR to improve long-term outcomes.

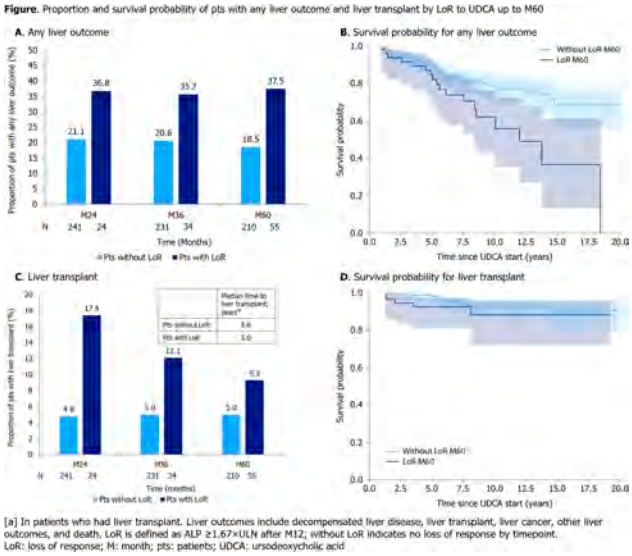


Figure. Proportion and survival probability of pts with any liver outcome and liver transplant by LoR to UDCA up to M60

[a] In patients who had liver transplant. Liver outcomes include decompensated liver disease, liver transplant, liver cancer, other liver outcomes, and death. LoR is defined as ALP ≥1.67×ULN after M12; without LoR indicates no loss of response by timepoint.
LoR: loss of response; M: month; pts: patients; UDCA: ursodeoxycholic acid

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1229 | BONE LOSS TRAJECTORIES IN POSTMENOPAUSAL WOMEN WITH PBC COMPARED WITH MATCHED CONTROLS: A PROPENSITY-MATCHED ANALYSIS USING SERIAL DEXA SCANS

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Background: Primary biliary cholangitis (PBC) is conventionally thought to accelerate postmenopausal bone loss, yet this assertion has not been rigorously tested against matched non-PBC women using serial DEXA scans. We aimed to quantify rapid bone disease progression in postmenopausal PBC women versus propensity-matched non-PBC controls using paired DEXA scans. **Methods:** We performed a retrospective cohort study of postmenopausal women at the Cleveland Clinic Ohio and Florida campuses. Female patients with PBC and non-PBC controls with at least one paired DEXA obtained 12–36 months apart were included. Propensity scores incorporated demographics, laboratory parameters, bone-active medication exposure, supplementation use, and osteoporosis-related comorbidities, followed by 3:1 nearest-neighbor matching. Co-primary outcomes were: (1) rapid progression of bone disease, defined as progression from osteopenia (T-score –1.0 to –2.5) to osteoporosis (T-score ≤–2.5) between paired DEXAs obtained 12–36 months apart, and (2) annualized change in lumbar T-score, lowest-site T-score, and lumbar BMD between serial DEXAs. Within PBC, UDCA biochemical response criteria (Paris-II, UK-PBC, and GLOBE low-risk) were evaluated as predictors of skeletal outcomes. **Results:** Among 551 postmenopausal women (229 PBC; 322 controls), 191 formed the propensity-matched cohort (127 PBC; 64 controls). Baseline osteoporosis prevalence at first DEXA was similar between groups (11.7% vs 11.8%, p = 0.84), as were baseline lumbar T-scores (–1.0 vs –0.9) and lowest-site T-scores (–1.8 vs –1.7). Rapid progression of bone disease between paired DEXAs did not differ between PBC and controls. Rapid lowest-site T-score progression occurred in 21.2% versus 25.0%, respectively (OR 0.18, 95% CI 0.02–1.37, p = 0.097). Similarly, annualized rates of bone loss were comparable between groups. Mean annualized change in lumbar T-score was +0.031/year in PBC versus –0.006/year in controls (β +0.039, p = 0.33), while annualized change in lowest-site T-score was –0.025/year versus –0.045/year, respectively (β +0.009, p = 0.81). Annualized lumbar BMD change was also similar between groups (p = 0.98). Within PBC, Paris-II responders showed improved lumbar T-score compared with non-responders (β +1.07, 95% CI +0.14 to +2.00, p = 0.024). Similarly, UK-PBC responders exhibited improved lowest-site T-score compared with non-responders (β +0.40, 95% CI +0.04 to +0.75, p = 0.028), same for GLOBE low-risk status (β +0.95, p = 0.048). **Conclusion:** Postmenopausal women with PBC did not exhibit accelerated bone loss or increased rapid progression to osteoporosis compared with propensity-matched non-PBC controls. However, biochemical response to UDCA was associated with significantly more favorable bone outcomes compared with non-responders. These findings suggest that PBC non-responders may represent a distinct skeletal risk phenotype.

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Table 1. Rapid bone disease progression and annualized change in bone density, matched cohort: PBC vs Controls

Outcome	PBC	Controls	Effect estimate (95% CI)	p
Binary rapid progression (12–36 mo paired DEXA)				
Rapid lumbar progressor, n (%)	2/22 (9.1)	1/8 (12.5)	OR 0.07 (0.005, 1.00)	0.05
Rapid lowest-site progressor, n (%)	7/33 (21.2)	3/12 (25.0)	OR 0.18 (0.02, 1.37)	0.097
Annualized change between paired DEXAs				
ΔT lumbar / year, mean	+0.031	−0.006	β +0.039 (−0.04, +0.12)	0.33
ΔT lowest-site / year, mean	−0.025	−0.045	β +0.009 (−0.06, +0.08)	0.81
ΔBMD lumbar (g/cm²) / year, mean	−0.002	−0.0015	β +0.0001 (−0.009, +0.009)	0.98

Binary outcomes restricted to patients with baseline osteopenia and paired DEXAs 12–36 months apart. Continuous outcomes use all available paired DEXAs in the matched cohort, with linear regression weighted by propensity matching weights. Negative ΔT and ΔBMD values indicate bone loss; positive values indicate bone gain.

Table 2. UDCA biochemical response status as a predictor of baseline bone density within PBC

Response definition	Outcome	n	β responder vs non (95% CI)	p
Paris-I	Lumbar T-score	146	+1.07 (+0.14, +2.00)	0.024
UK-PBC	Lowest T-score	141	+0.40 (+0.04, +0.75)	0.028
GLOBE low-risk	Lowest T-score	145	+0.95 (−0.003, +1.90)	0.048

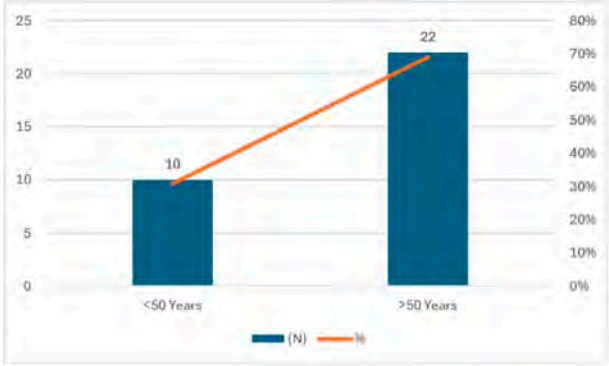
Univariable linear regression of baseline bone outcome on UDCA biochemical response status (responder = 1, non-responder = 0), within PBC cases only. Positive β indicates higher T-score in responders. Three independent response definitions consistently identify responders as having superior baseline bone density.

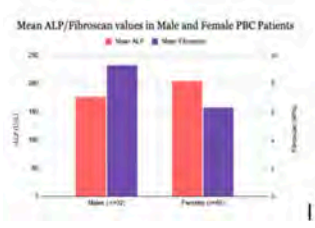
Disclosures: Leandro Sierra:Nothing to Disclose, Hussam Kawas:Nothing to Disclose, Qijun Yang:Nothing to Disclose, Sara Valencia:Nothing to Disclose, Rachel McNulty:Nothing to Disclose, Juan Armijos:Nothing to Disclose, John McMichael:Nothing to Disclose, Mohamad Alabbas:Nothing to Disclose, Li Tang:Nothing to Disclose, Kaylan Bhamidimarri:madrigal: Speaking and Teaching, ipsen: Advisor, mirum: Advisor, orphalan: Advisor, Bobby Zervos:Nothing to Disclose, Omar Sims: Nothing to Disclose, Dian Chiang:Nothing to Disclose.

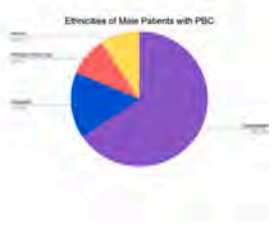
1230 | MALE CHARACTERISTICS IN PRIMARY BILIARY CHOLANGITIS: A SINGLE-CENTER REAL-WORLD ANALYSIS

Abdullah Mubarak[1] Shagun Gupta[2] Shaun Meppidayil[2] Rayaan Malik[2], [1]Liver Center of Texas, PLLC, [2]IIVER CENTER OF TEXAS

Background: Primary Biliary Cholangitis (PBC) is a chronic autoimmune cholestatic liver disease, historically considered a condition of middle-aged women, that affects approximately 110 per million men — a figure likely underrecognized in clinical practice. Male patients may present at a later disease stage with a distinct comorbidity profile, yet sex-based differences remain understudied. This retrospective single-center analysis characterizes the demographic, clinical, and biochemical profile of male patients initiated on ursodeoxycholic acid (UDCA) for PBC or cholestatic liver disease, with a focus on fibrosis burden at presentation. **Methods:** Demographics, race, diagnoses, liver biopsy findings, baseline alkaline phosphatase (ALP), total bilirubin, and transient elastography (Fibroscan, kPa) values were collected and compared between male and female patients. Liver stiffness $\geq$ 9.6 kPa was used as a threshold associated with significantly worse clinical outcomes per AASLD guidance. **Results:** Males comprised one-third of the cohort (mean age 58.9 years vs. 61.0 years in females), with the 60–69 age group most represented and Caucasians comprising the majority of both groups. PBC was the most common diagnosis in males, followed by cirrhosis of various etiologies, with a subset carrying comorbid conditions including MASH, steatosis, and autoimmune cholangiopathy. Male patients had a lower mean baseline ALP compared to females (176.2 U/L vs. 204.1 U/L), though both groups exceeded normal limits. Mean Fibroscan values were notably higher in males, suggesting greater hepatic fibrosis burden at presentation. Most male patients were on UDCA 300 mg/day; notably, no male patient was documented on obeticholic acid (OCA), compared to four female patients, despite a proportion of males likely qualifying based on their fibrosis and ALP profiles. **Conclusion:** This analysis demonstrates that male PBC patients present with higher hepatic fibrosis burden despite similar ages at diagnosis, and reveals a potential gap in second-line therapy utilization. These findings are hypothesis-generating and limited by sample size; prospective studies are needed to better characterize sex-based differences in PBC presentation and management.







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1231 | REAL-WORLD EFFECTIVENESS OF SELADELPAR IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS: EXPERIENCE FROM A COMMUNITY-BASED HEPATOLOGY PRACTICE

Rida Nadeem[1] Anita Kohli[1] Richard Manch[1] Ann Moore[1] Jana Mohamed[1] Cody Chen[1] Justin Reynolds[1] Phuong Nguyen[1] Jessica Omana Castaneda[1] Tessa Janovsky[1], [1]Arizona Liver Health

Background: Primary biliary cholangitis (PBC) is a chronic cholestatic liver disease associated with progressive fibrosis, cirrhosis, and liver-related morbidity. Despite standard therapy with ursodeoxycholic acid (UDCA), a substantial proportion of patients fail to achieve adequate biochemical response. Seladelpar, a peroxisome proliferator-activated receptor (PPAR)-delta agonist, has emerged as a novel therapeutic option for patients with inadequate response or intolerance to UDCA. Real-world data evaluating the effectiveness of seladelpar in routine clinical practice remain limited. **Methods:** We conducted a retrospective real-world analysis of adult patients with PBC treated with seladelpar at a single outpatient hepatology center for at least 12 months. Patients with available baseline and follow-up laboratory data were included. Primary efficacy outcomes included changes in alkaline phosphatase (ALP), total bilirubin normalization, improvement in liver transaminases, and patient reported outcomes following initiation of therapy. **Results:** A total of 37 patients with PBC were included in the final analysis (mean age 65 years; 95.2% females; mean BMI 28.2). Average time on ursodiol before starting a second-line agent was about 3.4 years. Following initiation of seladelpar therapy, patients demonstrated clinically meaningful reductions in ALP levels compared with baseline (mean reduction of 86 IU/L). Mean reduction in total bilirubin of 0.12 mg/dL. Improvements were also observed in cholestatic and hepatic biochemical parameters, including reductions in AST and GGT of 7.5 IU/L and 88.9 IU/L respectively. 13% reported improvement in pruritis. Elafibranor was generally well tolerated in this real-world cohort, with a 11.42% discontinuation rate overall. **Conclusion:** In this real-world community hepatology cohort, seladelpar treatment was associated with improvements in cholestatic liver biochemistries and fibrosis-related markers among patients with PBC. These findings support the effectiveness of seladelpar in routine clinical practice and reinforce its role as a promising therapeutic option for patients with inadequate biochemical response to standard therapy. Larger longitudinal studies are warranted to further evaluate long-term clinical outcomes and treatment durability.
Disclosures: Rida Nadeem:Boehringer Ingelheim: other, Anita Kohli:Nothing to Disclose, Richard Manch:Gilead: Speaking and Teaching, AbbVie: Speaking and Teaching, Intercept: Speaking and Teaching, Madrigal: Speaking and Teaching, Ann Moore:Abbvie: Speaking and Teaching, Gilead: Speaking and Teaching, Ipsen: Speaking and Teaching, madrigal: Speaking and Teaching, Siemans: Consultant, GSK: Advisor, Jana Mohamed:Nothing to Disclose, Cody Chen:Nothing to Disclose, Justin Reynolds:Madrigal: Speaking and Teaching, Novo Nordisk: Speaking and Teaching, Gilead: Speaking and Teaching, Ipsen: Speaking and Teaching, Phuong Nguyen:Nothing to Disclose, Jessica Omana Castaneda:Nothing to Disclose, Tessa Janovsky: Nothing to Disclose.

1232 | MEAN REDUCTION IN ALKALINE PHOSPHATASE AT 6–9 MONTHS FOLLOWING URSODEOXYCHOLIC ACID INITIATION IN PRIMARY BILIARY CHOLANGITIS: A SINGLE-CENTER REAL-WORLD ANALYSIS

Abdullah Mubarak[1] Shagun Gupta[2] Rayaan Malik[2] Shaun Meppidayil[2], [1]Liver Center of Texas, PLLC, [2]Liver Center of Texas

Background: Ursodeoxycholic acid (UDCA) at 13 to 15 mg/kg/day is the established first-line therapy for Primary Biliary Cholangitis (PBC), a chronic cholestatic liver disease marked by progressive bile duct destruction and hepatic fibrosis. UDCA improves liver biochemistries and transplant-free survival, with alkaline phosphatase (ALP) reduction as the primary marker of treatment response. Per AASLD 2021 guidance, ALP assessment at 12 months identifies inadequate responders for second-line escalation; however, early trends at 6 to 9 months may identify non-responders sooner, enabling earlier intervention. **Methods:** This single-center retrospective analysis included 97 patients initiated on UDCA for PBC or cholestatic liver disease, of whom 36 had paired baseline and 6 to 9 month ALP values. Of 88 patients with documented baseline ALP, 27 had ALP above 200 U/L. Among the 36 with paired data, 9 had baseline ALP greater than 200 U/L, enabling assessment of early response in this higher-burden subgroup. **Results:** Mean ALP declined from 182.5 U/L

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at baseline to 158.5 U/L at 6 to 9 months, a reduction of 24.0 U/L. Mean percent change was -1.0% and median was -6.4%, with individual changes ranging from -74.0% to +100.0%. Only 12 of 36 patients (33.3%) achieved the 15% or greater ALP reduction threshold; 24 (66.7%) did not. 31 of 36 (86.1%) achieved ALP below 2 times ULN at 6 to 9 months, and ALP continued declining at 12 months (mean 151.8 U/L), consistent with UDCA's gradual pharmacologic effect. Among 9 patients with baseline ALP greater than 200 U/L, only 2 reached that threshold or below by 6 to 9 months; 4 of 9 did so by 12 months. This suggests limited early response in higher-burden patients, with many remaining above 200 U/L even at 12 months, reinforcing the need for close monitoring and timely escalation in this subgroup. **Conclusion:** In conclusion, mean ALP declined 24.0 U/L at 6 to 9 months on UDCA, yet only 1/3 of patients met the responder threshold and those with baseline ALP greater than 200 U/L showed particularly limited early response. Patient-level monitoring is essential given the variability observed. Inadequate responders at 6 to 9 months, particularly those with ALP above 200 U/L, should be promptly considered for second-line therapy per AASLD 2021 guidance.

Metric	Value
Mean ALP Baseline	182.5 U/L
N baseline	88
Mean ALP at 6–9 Months	158.5 U/L
N 6-9 Months	36
N 12 Months	30
Mean Absolute Reduction	−24.0 U/L
Mean % Change	−1.0%
Median % Change	−6.4%
Responders (≥15% reduction)	12/36 (33.3%)
Non-Responders	24/36 (66.7%)
ALP <2× ULN at 6–9 mo	31/36 (86.1%)
Mean ALP at 12 Months	151.8 U/L



Disclosures: Abdullah Mubarak:Nothing to Disclose, Shagun Gupta:Nothing to Disclose, rayaan malik:Nothing to Disclose, SHAUN MEPPIDAYIL:Nothing to Disclose.

1233 | SELADELPAR LEADS TO DURABLE AND SIGNIFICANT DECREASE IN THE PRURITOGENIC CYTOKINE IL-31, ASSOCIATED WITH PRURITUS IMPROVEMENT: LONG-TERM DATA FROM THE ASSURE STUDY

Marlyn Mayo[1] Kyung min Kwon[2] Gideon Hirschfield[3] Yan Liang[2] Cynthia Levy[4] Christopher Bowlus[5] David Jones[6] Daria Crittenden[2] Peyvand Amini[2] Andreas Kremer[7], [1]University of Texas Southwestern Medical Center, Dallas, TX, USA, [2]Gilead Sciences, Inc., Foster City, CA, USA, [3]UHN's Francis Family Liver Clinic and Toronto Centre for Liver Disease, Toronto, ON, Canada, [4]Miller School of Medicine, University of Miami, Miami, FL, USA, [5]University of California Davis School of Medicine, Sacramento, CA, USA, [6]Newcastle University, Newcastle upon Tyne, United Kingdon, [7]University Hospital Zürich, University of Zürich, Zürich, Switzerland

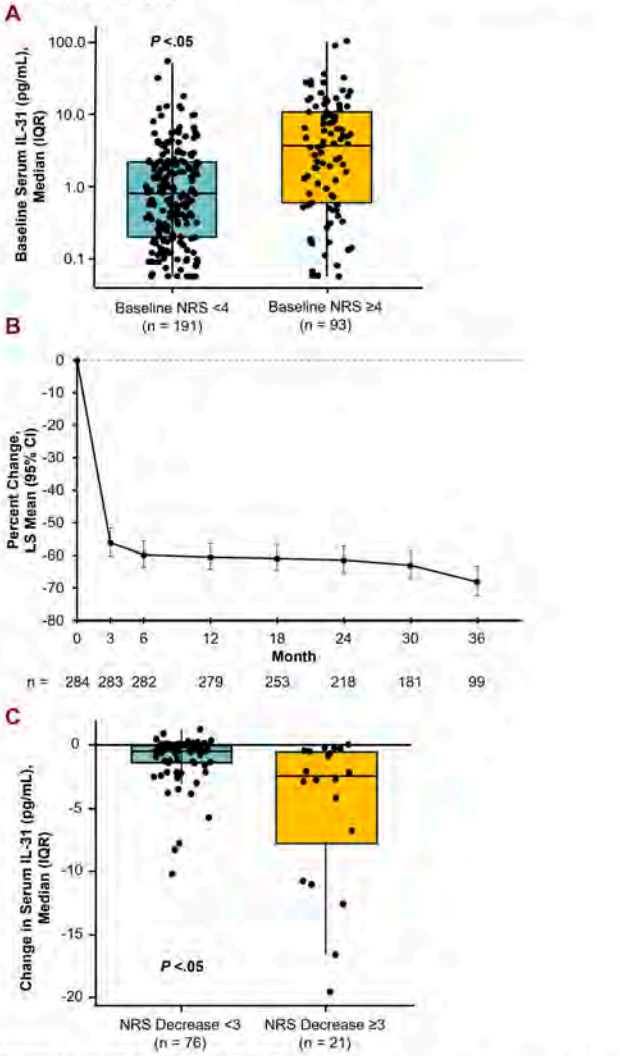
Background: Pruritus affects up to 80% of patients (pts) with primary biliary cholangitis (PBC) and can impair quality of life. Seladelpar (SEL), a first-in-class delpar (selective peroxisome proliferator–activated receptor delta [PPARδ] agonist), is approved as a second-line treatment for PBC and demonstrated durable biochemical efficacy and pruritus improvement in clinical trials. Interleukin 31 (IL-31) is a pruritogenic cytokine elevated in pts with PBC. In the pivotal Phase 3 RESPONSE study (NCT04620733), SEL decreased IL-31 concentrations and reduced pruritus. Here, we present data on long-term changes in IL-31 and their association with pruritus and bile acids in pts with PBC treated with SEL up to 36 months (M) from an interim analysis of the ongoing Phase 3 open-label ASSURE study (NCT03301506). **Methods:** Pts from RESPONSE and legacy SEL studies enrolled in ASSURE and received open-label SEL 10 mg once daily. Pts were pooled at SEL initiation in either RESPONSE or ASSURE. Pts with baseline (BL) and ≥1 post-BL IL-31 concentrations were included in this post hoc analysis. BL pruritus with numerical rating score (NRS) ≥4 was used to define subgroups by pruritus severity. Serum IL-31 concentrations were determined using a single-molecule array ultrasensitive immunoassay (lower limit of quantitation of 0.024 pg/mL). IL-31 levels were assessed over time in the overall population. BL IL-31 levels were compared by BL NRS groups (≥4 vs <4). Changes in IL-31 by NRS improvement status (≥3 points decline vs less improvement) were also assessed. Correlations between IL-31 and NRS or total bile acids (TBAs) were evaluated using Spearman's rank correlation. Data cutoff: Jan 31, 2025. **Results:** Overall, 284 pts were included; 93 pts had BL NRS ≥4. BL median (IQR) IL-31 level was higher in pts with NRS ≥4 vs NRS <4 (3.70 [0.60, 11.00] pg/mL vs 0.81 [0.20, 2.20] pg/mL; Figure A). IL-31 reductions were rapid and sustained up to M36 in the overall population (least squares mean [95% CI], -68% [-63%, -73%]; Figure B) and in pts with BL NRS ≥4 (-74% [-66%, -80%]). At M36, pts with NRS improvement ≥3 points had greater median (IQR) reductions in IL-31 (-2.80 [-10.80, -0.52] pg/mL; n = 21) compared to pts with lower NRS improvement (-0.30 [-1.32, -0.04] pg/mL; n = 76; Figure C). BL IL-

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31 levels were correlated with BL NRS (ρ = 0.39; P < 0.05), as were changes from BL to M36 in IL-31 and NRS (ρ = 0.37; P < 0.05). IL-31 and TBA were correlated at BL (ρ = 0.50; P < 0.05), as were changes from BL to M36 (ρ = 0.52; P < 0.05). **Conclusion:** SEL led to sustained IL-31 reductions through M36. IL-31, a pruritogenic biomarker, was higher in pts with greater pruritus burden, and greater reductions in IL-31 were observed among pts with meaningful improvement of NRS ($\geq$3). IL-31 was correlated with NRS and with TBA levels. Alongside existing evidence, these results—particularly the observed associations between IL-31 and NRS—suggest a mechanistic link between SEL treatment and pruritus improvement.

Figure. (A) Baseline IL-31 by Baseline NRS Subgroup, (B) Percent Change From Baseline in Serum IL-31, and (C) Changes in IL-31 by Decrease in Pruritus NRS at M36



P-values shown are from Wilcoxon rank-sum tests.
In panel B, the y-axis is log-scaled. In panel C, 1 outlier from the 'Decrease in NRS ≥3' group (change in IL-31 = −88.2 pg/mL) was removed for visualization purposes.
IL-31, interleukin 31; LS, least squares; M, Month; NRS, numerical rating score.

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1234 | SEMAGLUTIDE AND LONG-TERM OUTCOMES IN UDCA-TREATED PRIMARY BILIARY CHOLANGITIS WITH OBESITY AND TYPE 2 DIABETES: A PROPENSITY-MATCHED ANALYSIS

Mohammad Alabbas[1] Akram Alnounou[2] Barish Eren[1] Riddhi Machchhar[3] Omar Sims[1] Dian Chiang[4], [1]Cleveland Clinic Foundation, [2]Department of Internal Medicine, Western Michigan University Homer Stryker M.D. School of Medicine, [3]Department of Internal Medicine, Hackensack Meridian Health Ocean University Medical Center, Brick, [4]Cleveland Clinic

Background: Primary biliary cholangitis (PBC) is frequently accompanied by metabolic comorbidity, including obesity and type 2 diabetes. The long-term hepatic and cardiovascular outcomes associated with semaglutide use in ursodeoxycholic acid (UDCA)-treated PBC remain uncertain. We evaluated outcomes associated with semaglutide exposure versus no GLP-1 receptor agonist exposure. **Methods:** Using the TriNetX Research Network of 111 healthcare organizations, we identified adults with PBC receiving UDCA. Semaglutide users, representing an obesity- and type 2 diabetes-enriched subgroup, were compared with UDCA-treated nonusers without GLP-1 receptor agonist exposure after 1:1 propensity-score matching on demographics, comorbidities, medications, and laboratory values. Patients with major competing liver diseases were excluded. Outcomes were assessed from day 1 after index through 3 and 5 years. The primary outcome was major adverse liver outcomes (MALO), a composite of liver-related events and death. Secondary outcomes included hospitalization, MACE, mortality, pruritus, fatigue, albumin $\leq$3.5 g/dL, ALP, and incident hepatic decompensation. **Results:** In the 3-year matched cohort, 482 semaglutide users were compared with 482 nonusers. Semaglutide was associated with lower MALO (22.6% vs 31.1%; RR 0.73, 95% CI 0.59–0.90), hospitalization (13.9% vs 24.9%; RR 0.56, 95% CI 0.43–0.73), MACE (21.0% vs 26.6%; RR 0.79, 95% CI 0.63–0.99), mortality (2.3% vs 8.7%; RR 0.26, 95% CI 0.14–0.50), and incident hepatic decompensation (5.8% vs 12.0%; RR 0.48, 95% CI 0.31–0.74). Pruritus, fatigue, albumin $\leq$3.5 g/dL, and ALP did not significantly differ. In the 5-year matched cohort, 531 semaglutide users were compared with 531 nonusers. Semaglutide remained associated with lower MALO (23.9% vs 36.3%; RR 0.66, 95% CI 0.55–0.80), hospitalization (15.3% vs 29.2%; RR 0.52, 95% CI 0.41–0.67), mortality (3.0% vs 6.6%; RR 0.46, 95% CI 0.26–0.82), albumin $\leq$3.5 g/dL (7.3% vs 17.1%; RR 0.43, 95% CI 0.27–0.69), and incident hepatic decompensation (6.2% vs 14.7%; RR 0.42, 95% CI 0.29–0.62). MACE was directionally lower by risk analysis and significant by survival analysis, while pruritus, fatigue, and ALP did not differ. **Conclusion:** In this propensity-matched cohort of UDCA-treated PBC enriched for obesity and type 2 diabetes, semaglutide exposure was associated with lower long-term MALO, hospitalization, mortality, incident hepatic decompensation, and hypoalbuminemia, without worsening ALP or symptom outcomes. These observational findings support prospective evaluation of semaglutide in metabolically selected patients with PBC.

Table 1. Outcomes after semaglutide vs no GLP-1 RA exposure in UDCA-treated PBC with obesity and T2DM

1:1 propensity-matched cohort, n=482 per group; 3-year outcomes

Outcome (3-year)	Sema, %	No GLP-1 RA, %	RR (95% CI)	P value
MALO (primary)	22.6	31.1	**0.73 (0.59–0.90)**	**0.003**
Hospitalization	13.9	24.9	**0.56 (0.43–0.73)**	**<0.001**
MACE	21.0	26.6	**0.79 (0.63–0.99)**	**0.041**
Mortality	2.3	8.7	**0.26 (0.14–0.50)**	**<0.001**
Incident hepatic decompensation	5.8	12.0	**0.48 (0.31–0.74)**	**0.001**
Pruritus	5.5	6.8	0.81 (0.47–1.40)	0.455
Albumin ≤3.5 g/dL	8.0	11.9	0.68 (0.41–1.12)	0.125
Fatigue	9.9	8.1	1.23 (0.76–1.99)	0.399
ALP (most recent value): mean 141.5 vs 159.8 U/L; p=0.075, NS				

Abbreviations: MALO, major adverse liver outcomes; MACE, major adverse cardiovascular events; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid; ALP, alkaline phosphatase; NS, not significant.

P values are from risk-analysis testing in the propensity-matched cohort.

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1235 | EFFECT OF UDP-GLUCURONOSYLTRANSFERASE (UGT) ENZYME POLYMORPHISMS ON SERUM ALKALINE PHOSPHATASE LEVELS IN PATIENTS WITH PBC RECEIVING ADJUNCT FENOFIBRATE THERAPY

Colleen Hayes[1] Christopher Hemme[1] Mahesh Krishna[2] Scott Roberts[1] Bonnie Chen[2] James Boyer[2] David Assis[2] Nisanne Ghonem[1], [1]University of Rhode Island, [2]Yale University

Background: PBC is characterized by the accumulation of toxic bile acids in the liver. Glucuronidation is a major pathway of bile acid detoxification in which UGT enzymes conjugate glucuronic acid to bile acids to enhance their elimination. Bile acid glucuronidation in humans is catalyzed by UGT1A1, -1A3, -1A4, -2B4, and -2B7 enzymes, which are predominantly regulated by the peroxisome proliferator-activated receptor alpha (PPARα). Importantly, polymorphisms in *UGT1A* and *-2B* genes may alter bile acid glucuronidation and subsequent treatment response to PPARα therapy. This study investigates the effect of UGT polymorphisms on serum alkaline phosphatase (ALP) levels in people with PBC who received treatment with ursodeoxycholic acid (UDCA) ± second-line therapy with fenofibrate (PPARα agonist). **Methods:** Genomic DNA was extracted from plasma samples obtained from de-identified PBC patients who received UDCA ± fenofibrate at the Yale Liver Center Biorepository. Genotyping was performed for *UGT1A1**28, *-1A3* -66T > C, *-1A3* 31T > C, *-2B4* 1374A > T, and *-2B7* 802T > C polymorphisms. Patients were stratified according to treatment response, defined as complete responders, e.g., serum ALP < upper limit of normal (ULN), or incomplete response (ALP > ULN). For paired data, linear regression was performed with samples pre- and post-fenofibrate. UGT genotypes were correlated with clinical variables. **Results:** Among people with PBC who received combination therapy (UDCA + fenofibrate, n = 23), both reference (wild-type) and alternate (heterozygote + homozygote mutant) genotypes were observed. For those who experienced an incomplete response after the addition of fenofibrate, a greater reduction in mean (± SD) serum ALP (-36%) was found with the reference *UGT2B7* 802T > C vs. alternate genotype (153 ± 47 vs. 209 ± 76 U/L, p = 0.24). Interestingly, greater reductions in mean serum ALP were found in those with the alternate *UGT1A3* -66T > C (-14%) and *UGT1A3* 31T > C (-18%) vs. reference genotypes (165 ± 41 vs. 191 ± 81 U/L, and 157 ± 40 vs.191 ± 81 U/L, p = 0.10, respectively). **Conclusion:** Our study identified several UGT polymorphisms in people with PBC, and all three genotypes (wild-type, heterozygous, homozygous mutant) were detected for *UGT1A1**28, *UGT1A3* -66T > C, *-1A3* 31T > C, and *-2B7* 802T > C. Patients who have the alternate *UGT2B7* 802T > C genotype may have a reduced response to second-line therapy with fenofibrate, while those with the alternate *UGT1A3* -66T > C or *-1A3* 31T > C genotype may have a greater response to fenofibrate. These data suggest that UGT polymorphisms may serve as indicators of treatment response to PPAR agonists and warrant further investigation.

Disclosures: Colleen Hayes:Nothing to Disclose, Christopher Hemme:Nothing to Disclose, Mahesh Krishna:Ipsen: Patient Experience Consultant, Esperion: Consultant, Esperion: Patient Experience Consultant, Scott Roberts:Nothing to Disclose, Bonnie Chen: Nothing to Disclose, James Boyer:Mirum Pharmaceuticals: grant recipient, IPSEN: Clinical Evenets Committee for clinical trial, AstroZenica: Member of Clinical Events Committe, David Assis:Nothing to Disclose, Nisanne Ghonem:Nothing to Disclose.

1236 | KETAMINE-INDUCED SCLEROSING CHOLANGIOPATHY MAY BE REVERSIBLE ON STOPPING TREATMENT

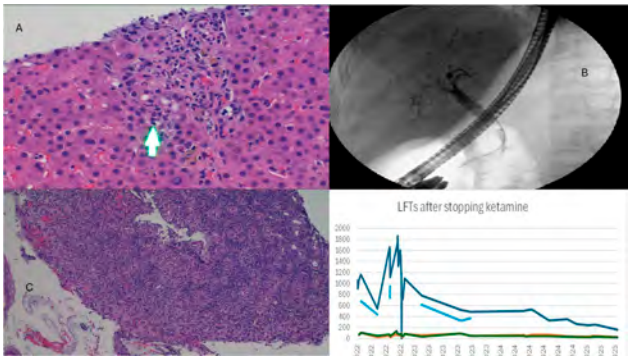
Gerond Lake-Bakaar[1], [1]PSLMC

Background: Chronic recreational ketamine misuse has been linked to severe complications, including ketamine-induced sclerosing cholangitis (KISC). We previously reported a case of KISC in a patient following chronic topical use of ketamine with lidocaine for neuropathic pain. We report a three-year follow-up of this single case study. **Methods:** Case Presentation: A 38-year-old woman with Alport syndrome, hearing impairment and two prior renal transplants (8/2019), first presented in 9/2021 with right upper quadrant pain and elevated levels of serum alkaline phosphatase (AlkP). US showed gallbladder stones. A successful laparoscopic cholecystectomy revealed cholelithiasis and cholecystitis. Between 9/2021 and 11/2022, she had multiple admissions for abdominal pain in the right upper quadrant, nausea, and vomiting, with elevated levels of AlkP (up to 1861 U/l) and normal serum bilirubin.A liver biopsy in 4/2022 showed portal and focal periportal fibrosis and patchy ductular proliferation with associated periductal neutrophils and portal edema consistent with large bile duct obstruction (A). MRCP showed no evidence of stones in the bile duct, but increased peribiliary T2 suggested mild cholangitis. Balloon cholangiography showed bile duct dilation of the left and right intrahepatic branches with peripheral pruning consistent with sclerosing cholangiopathy (B). In 11/2022, a colonoscopy was performed for hematochezia. Multiple ulcers, approximately 2 cm in

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diameter were found in the proximal rectum and in the ascending colon. Smaller ulcers were also noted in the descending colon and scattered throughout the colon. Her RUQ pain was associated with a large ulcer at the hepatic flexure. The appendiceal orifice appeared normal. Histopathology revealed severe ulceration with abundant neutrophils, lymphocytes, and scattered eosinophils consistent with early inflammatory bowel disease (C). Immunohistochemical stain for cytomegalovirus was negative. She admitted to topical use of ketamine mixed with lidocaine for peripheral neuropathy. This was stopped in September 2022. The course of her AlkP levels were followed through the renal transplant clinic at 3-monthly intervals. **Results:** Result: After stopping ketamine, she had no further ER admissions for RUQ pain or hematochezia documented for three years through to 8/2025. Her serum AlkP, monitored at 3-monthly intervals in the renal transplant clinic, fell slowly from a peak of 1861 U/l (Oct 2022) to a trough 131 U/l (Aug 2025) (D). **Conclusion:** Conclusion: Chronic topical ketamine use carries a risk of serious hepatobiliary injury, including KISC, and may be associated with colonic mucosal changes consistent with IBD. Long term follow-up after stopping the drug suggests that the effects of the drug on the liver, as determined by serum AlkP levels, may be directly related to drug exposure and reversible on stopping.

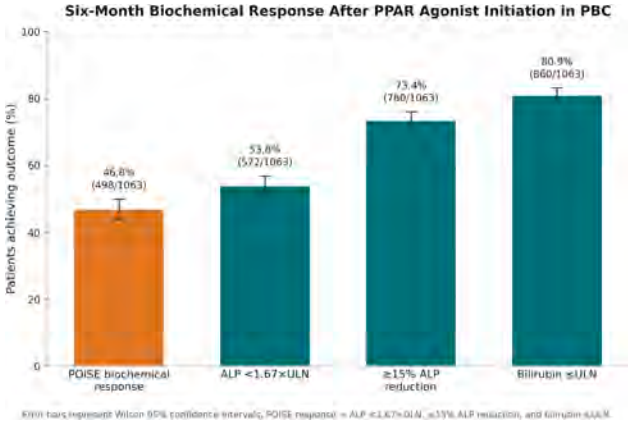


Disclosures: Gerond Lake-Bakaar:Nothing to Disclose.

1237 | REAL-WORLD BIOCHEMICAL RESPONSE TO SELADELPAR AND ELAFIBRANOR IN PRIMARY BILIARY CHOLANGITIS

Shiab Mussad[1] Anna Tylecki[1] Muhammad Ismail[1] Tushar Khanna[1] Mei Lu[1] Stuart Gordon[2], [1]Henry Ford Health, [2]Henry Ford Health System

Background: Seladelpar and elafibranor are newly available peroxisome proliferator-activated receptor (PPAR) agonists for patients with primary biliary cholangitis (PBC) and inadequate biochemical response to ursodeoxycholic acid. They have expanded available treatment options, but real-world outcomes after approval remain limited. We evaluated 6-month biochemical response among PPAR agonist initiators with PBC. **Methods:** We performed a retrospective cohort study using Epic Cosmos, a large multicenter electronic health record database representing more than 300 million patient records. Adults with PBC who initiated seladelpar or elafibranor on or after June 10, 2024, were identified, with the first active PPAR agonist order as the index date. Eligible patients had baseline alkaline phosphatase (ALP) and bilirubin within 6 months before index, repeat labs at 6 months ± 2 months, baseline ALP ≥ 1.67×ULN, and no fibrate fill within 90 days before index. The primary outcome was 6-month POISE biochemical response, defined as ALP < 1.67×ULN, ≥ 15% ALP reduction from baseline, and bilirubin ≤ ULN. **Results:** A total of 1,063 PPAR agonist initiators met inclusion criteria, including 728 treated with seladelpar (68.5%) and 335 treated with elafibranor (31.5%). Median age was 60 years, and most patients were female (89.9%) and White (71.8%); 16.7% were Hispanic or Latino. Median time from first PBC diagnosis to treatment initiation was 44.9 months. Prior obeticholic acid use was present in 21.0%, autoimmune hepatitis overlap in 20.9%, and pre-index evidence of cirrhosis, portal hypertension, or hepatic decompensation in 44.7%. Median baseline ALP was 284 U/L, and median baseline total bilirubin was 0.66 mg/dL. At 6 months, 498 patients achieved POISE biochemical response (46.8%; 95% CI, 43.8-49.8%). Individual response components were common: 572 patients achieved ALP < 1.67×ULN (53.8%), 780 had a ≥ 15% ALP reduction from baseline (73.4%), and 860 had total bilirubin ≤ ULN (80.9%). **Conclusion:** In this real-world cohort of patients with PBC and baseline ALP ≥ 1.67xULN, nearly half of PPAR agonist initiators achieved POISE biochemical response at 6 months, with most achieving meaningful ALP reduction and bilirubin normalization. These findings support real-world biochemical effectiveness of PPAR agonists. Ongoing analyses will evaluate comparative effectiveness versus long-term UDCA users and exploratory differences between seladelpar and elafibranor.



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1238 | PRIMARY SCLEROSING CHOLANGITIS IN OLDER ADULTS: A DISTINCT CLINICAL PHENOTYPE? A COMPARATIVE ANALYSIS OF PRESENTATION BY AGE AT DIAGNOSIS

Deepika Suresh[1] Mary McGrath[1] Daniel Strand[1] Brian Wentworth[1], [1]University of Virginia

Background: Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease commonly diagnosed in early to middle adulthood. The clinical course of PSC is heterogenous, but there is a distinct lack of data regarding patients diagnosed beyond the sixth decade of life. Therefore, we aimed to characterize differences in presentation between patients diagnosed with PSC at age ≥ 65 years compared with those diagnosed prior to age 65. **Methods:** We performed a retrospective cohort study of patients diagnosed with PSC within a single tertiary care / transplant referral center between January 2023 and October 2025. Patients were stratified by age at diagnosis (< 65 vs ≥ 65 years). Demographic characteristics, laboratory values and magnetic resonance cholangiopancreatography (MRCP) findings at presentation, and markers of advanced chronic liver disease were compared between groups. Continuous variables were non-parametric and reported as median [interquartile range]; between group comparisons utilized the Mann-Whitney U test. Categorical variables were presented as counts (%) and analyzed using Chi-square or Fisher's exact tests, as appropriate. **Results:** Forty-five patients met inclusion criteria, including 16 (33%) diagnosed at age ≥ 65. Median age at diagnosis was 32 years [IQR 24–47] in the younger cohort and 76 years [IQR 70–84] in the older cohort (p < 0.001). Sex distribution and race were similar between groups. Older patients demonstrated higher median cholestatic and hepatocellular liver enzyme values, including ALP (414 vs 179 U/L, p = 0.099) and AST (71 vs 41 U/L, p = 0.155), though differences did not reach statistical significance. Median CA 19-9 was significantly higher among patients diagnosed at ≥ 65 years (29.0 vs 4.0 U/mL, p = 0.036). Total bilirubin levels were comparable between groups. The pattern of biliary involvement did not differ significantly by group (p = 0.368). However, a plurality of younger patients had multifocal intrahepatic disease whereas older patients had more combined intra- and extrahepatic involvement. Older patients more frequently had cirrhosis at diagnosis (31% vs 7%, p = 0.079), while rates of portal hypertension were similar between groups (19% vs 17%, p = 1.000). Only one case of cholangiocarcinoma was observed, occurring in a patient aged ≥ 65 years (6% vs 0%, p = 0.356). **Conclusion:** Patients diagnosed with PSC at age ≥ 65 may present with features suggestive of greater disease burden, including higher CA 19-9 levels, cholestatic and hepatocellular liver enzyme values, and increased prevalence of cirrhosis at diagnosis. These findings raise the possibility that later-onset PSC represents a distinct clinical phenotype and/or reflects delayed recognition, warranting further investigation in larger cohorts.

Clinical and Biochemical Characteristics at PSC Diagnosis Stratified by Age

	All (n = 45)	Age <65 (n = 29)	Age ≥65 (n = 16)	p
Age, median [IQR]	47 [29-71]	32 [24-47]	76 [70-84]	<0.001
Male sex (%)	21 (47)	14 (48)	7 (44)	1.000
Caucasian (%)	43 (96)	28 (97)	15 (94)	0.590
AST (U/L), median [IQR]	51 [29-118]	41 [26-118]	71 [45-134]	0.155
ALT (U/L), median [IQR]	61 [24-145]	43 [23-159]	74 [53-114]	0.767
ALP (U/L), median [IQR]	245 [104-597]	179 [86-508]	414 [190-741]	0.099
Total bilirubin, median [IQR]	0.7 [0.5-1.3]	0.7 [0.5-1.0]	0.8 [0.5-2.1]	0.576
CA 19-9 (U/mL)	9.5 [4.0-46.0]	4.0 [4.0-8.0]	29.0 [6.0-77.0]	0.036
Disease burden by MRCP (%)				0.368
Multifocal intrahepatic	15 (33)	11 (38)	4 (24)	
Left-predominant intrahepatic	5 (11)	2 (7)	3 (19)	
Right-predominant intrahepatic	6 (13)	5 (17)	1 (6)	
Peri-hilar intrahepatic	2 (4)	2 (7)	0 (0)	
Extrahepatic only	1 (2)	0 (0)	1 (6)	
Combined intra/extra-hepatic	15 (33)	8 (28)	7 (44)	
None (small-duct PSC)	1 (2)	1 (3)	0 (0)	
Cirrhosis (%)	7 (16)	2 (7)	5 (31)	0.079
Portal hypertension (%)	8 (18)	5 (17)	3 (19)	1.000
Cholangiocarcinoma (%)	1 (2)	0 (0)	1 (6)	0.356

Disclosures: Deepika Suresh:Nothing to Disclose, Mary McGrath:Nothing to Disclose, Daniel Strand:Cook Medical: Consultant, Brian Wentworth:Ipsen: Consultant, Ipsen: Speaking and Teaching, GSK: Consultant, Luna Labs USA: Consultant.

1239 | TARGETING FARNESOID X RECEPTOR WITH INT-787, A HYDROPHILIC BILE ACID-DERIVED AGONIST, INHIBITS EXPERIMENTAL PRIMARY SCLEROSING CHOLANGITIS

Raffaella Gadaleta[1] Maria Arconzo[1] Marica Cariello[1] Silvia Cultrera[1] Angela Tricase[1] Sanjay Kansra[2] Mary Erickson[2] Luciano Adorini[2] Antonio Moschetta[1], [1]University of Bari "Aldo Moro", Bari, Italy, [2]Intercept Pharmaceuticals, Inc. Morristown, New Jersey, USA

Background: Primary sclerosing cholangitis (PSC) is a progressive, immune-mediated cholestatic liver disease associated with increased HCC risk and limited therapeutic options. First-line PSC therapy relies on ursodeoxycholic acid, a hydrophilic secondary bile acid (BA) lacking farnesoid x receptor (FXR) agonistic activity that improves cholestatic liver enzymes and

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bile composition, but has no proven survival benefit and may be harmful at high doses. Obeticholic acid (OCA), a potent BA-derived FXR agonist, showed promising effects in PSC in a Phase 2 study; however, it was not further evaluated in Phase 3 clinical trials. The second-generation BA-derived FXR agonist INT-787 combines high FXR affinity with hydrophilic, non-cytotoxic properties and has demonstrated anti-inflammatory, anti-fibrotic, and metabolic benefits superior to OCA in several preclinical liver disease models, together with a favorable safety profile in healthy volunteers, making it a promising candidate for PSC treatment. **Methods:** We investigated the effects of an INT-787-enriched diet (30 mg/kg/day) in Mdr2-KO mice, a reproducible model of spontaneously progressive chronic biliary liver disease associated with fibrosis and characterized by histological lesions closely resembling human PSC. The study included 3 experimental settings: 2 preventive protocols, with INT-787 administration for 12 or 24 weeks (wk), and 1 therapeutic/curative protocol, in which PSC was established after 16 wk of chow diet before switching to an INT-787-enriched diet for an additional 12 wk. All animal procedures complied with institutional and national guidelines and were approved by relevant ethics committees. **Results:** To confirm pharmacological FXR activation, qRT-PCR analyses of intestinal and hepatic FXR target genes were performed across all 3 settings. INT-787 treatment induced the intestinal FXR target genes *Fgf15* and Ibabp, while hepatic FXR activation was confirmed by Bsep upregulation. In addition, the downstream effect of ileal *Fgf15* induction was reflected by suppression of *Cyp7a1*, the rate-limiting enzyme in BA synthesis. In both preventive settings, the INT-787-enriched diet prevented collagen deposition and fibrosis compared with chow diet (Sirius Red staining) and reduced hepatic cell proliferation (cyclin D1 staining). INT-787 prevented ALT elevation and reduced AST levels compared with chow-fed mice. In the therapeutic setting, INT-787 halted disease progression and reversed collagen deposition, fibrosis, hepatic cell proliferation, and liver transaminase elevations. **Conclusion:** INT-787 demonstrates robust preventive and therapeutic efficacy in experimental PSC, markedly attenuating liver fibrosis, hepatocellular injury, and disease progression. These findings identify INT-787 as a promising and well-tolerated FXR-based therapeutic candidate with the potential to address the substantial unmet clinical need in PSC.

Disclosures: Raffaella Gadaleta:Nothing to Disclose, Maria Arconzo:Nothing to Disclose, Marica Cariello: Nothing to Disclose, Silvia Cultrera:Nothing to Disclose, Angela Tricase:Nothing to Disclose, Sanjay Kansra: Nothing to Disclose, Mary Erickson:Nothing to Disclose, Luciano Adorini:Nothing to Disclose, Antonio Moschetta:Nothing to Disclose.

1240 | REAL-WORLD PATIENT-REPORTED SYMPTOM RESPONSE AFTER ELAFIBRANOR OR SELADELPAR THERAPY IN PRIMARY BILIARY CHOLANGITIS

Hussein Harb[1] Fabian Rodas[2] Toluwalase Okubote[3] Ronnie Scarboro[3] Krishna Venkata[3], [1]Texas Institute of Graduate Medical Education (TIGMER), [2]University of Texas San Antonio / The Texas Liver Institute, [3]The Texas Liver Institute

Background: Pruritus and fatigue are major determinants of impaired quality of life in primary biliary cholangitis (PBC) and may persist despite biochemical improvement. Real-world patient-reported outcome (PRO) data after elafibranor or seladelpar remain limited. **Methods:** We performed a retrospective single-center study of adults with PBC treated with elafibranor or seladelpar after inadequate response to ursodeoxycholic acid. Chart data and a single recall-based phone PRO survey captured baseline, 3-6-month, and available 8-12-month WI-NRS and PROMIS Fatigue 7 responses. The primary PRO analysis compared baseline with 3-6 months; 8-12-month outcomes were analyzed when available using within-patient baseline-to-follow-up pairs. Clinically meaningful improvement was defined as $\geq$3-point WI-NRS decrease and >3-point PROMIS Fatigue T-score decrease. Wilcoxon, Fisher exact, and Spearman tests were used as appropriate. **Results:** Among 41 patients, 23 initiated elafibranor and 18 initiated seladelpar; median age was 59 years [IQR, 52-67.2], and 39/41 (95.1%) were female. Baseline ALP, AST, ALT, total bilirubin, and PRN antipruritic use were similar between groups. Baseline WI-NRS burden was higher with elafibranor, including a higher proportion with baseline WI-NRS >3, supporting sensitivity analysis for itch response. WI-NRS and PROMIS Fatigue T-score improved significantly at 3-6 and 8-12 months. Clinically meaningful improvement was common, with no significant between-therapy differences, including among patients with baseline WI-NRS >3. ALP change was not significantly correlated with WI-NRS or PROMIS Fatigue T-score change. Total bilirubin change was associated with PROMIS Fatigue T-score change at 3-6 months, and this association persisted after excluding patients with bilirubin >2.0 mg/dL. No significant biochemical-PRO correlations were observed at 8-12 months. **Conclusion:** In this small real-world PBC cohort, elafibranor and seladelpar were associated with significant improvements in patient-reported pruritus and fatigue, with symptom improvement evident by 3-6 months and maintained among patients with available 8-12-month data. No clear therapy-specific symptom advantage was observed, including in sensitivity analysis among

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patients with baseline WI-NRS >3. Baseline itch imbalance and small subgroup sizes limit between-therapy comparisons. These findings support incorporating symptom-specific PROs alongside biochemical endpoints when evaluating second-line PPAR agonist therapy in PBC.

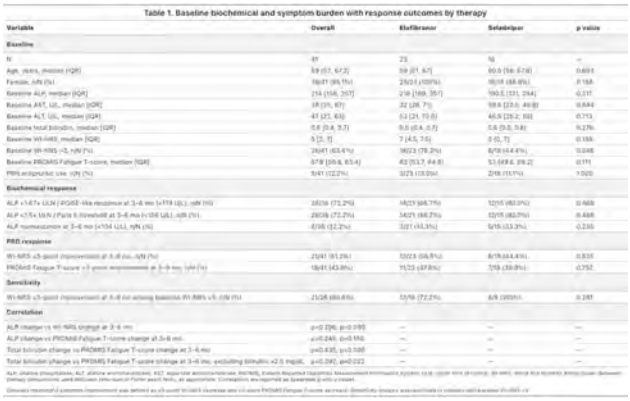


Table 1. Baseline biochemical and symptom burden with response outcomes by therapy

Variable	Overall	Elafibranor	Seladelpar	p value
Baseline				
N	41	21	20	—
Age, years, median (IQR)	59 (52, 67.2)	59 (51, 67)	60.5 (56, 67.8)	0.693
Female, n/N (%)	38/41 (95.1%)	20/21 (100%)	18/20 (88.9%)	0.168
Baseline ALP, median (IQR)	214 (156, 297)	218 (169, 357)	190.5 (151, 264)	0.317
Baseline AST, ULN, median (IQR)	1.8 (1.5, 2.1)	2.2 (1.8, 2.7)	1.6 (1.3, 1.8)	0.004
Baseline ALT, ULN, median (IQR)	1.7 (1.2, 2.5)	2.1 (1.2, 2.7)	1.5 (1.2, 2.2)	0.173
Baseline total bilirubin, median (IQR)	0.6 (0.4, 0.7)	0.6 (0.4, 0.7)	0.6 (0.5, 0.8)	0.276
Baseline WI-NRS, median (IQR)	5 (3, 7)	7 (4.5, 7.5)	5 (3, 7)	0.188
Baseline WI-NRS >3, n/N (%)	29/41 (70.7%)	18/21 (85.7%)	11/20 (55%)	0.048
Baseline PROMIS-Fatigue T-score, median (IQR)	57.8 (55.6, 63.4)	62 (55.7, 64.8)	53.3 (49.4, 59.2)	0.011
PBC antipruritic use, n/N (%)	9/41 (22.0%)	3/21 (14.3%)	6/20 (30%)	0.429
Biochemical response				
ALP <1.67× ULN (POISE-like response) at 3–6 mo (<1.67× ULN), n/N (%)	28/39 (71.8%)	14/21 (66.7%)	12/18 (66.7%)	0.468
ALP <1.5× ULN (Paris II-like) at 3–6 mo (<1.5× ULN), n/N (%)	28/39 (71.8%)	14/21 (66.7%)	12/18 (66.7%)	0.468
ALP normalization at 3–6 mo (<1× ULN), n/N (%)	4/36 (11.1%)	2/21 (9.5%)	2/15 (13.3%)	0.636
PRO response				
WI-NRS ≥3-point improvement at 3–6 mo, n/N (%)	21/41 (51.2%)	12/21 (57.1%)	9/20 (45%)	0.405
PROMIS-Fatigue T-score ≥5-point improvement at 3–6 mo, n/N (%)	18/41 (43.9%)	11/21 (52.4%)	7/19 (36.8%)	0.352
Sensitivity				
WI-NRS ≥3-point improvement at 3–6 mo among baseline WI-NRS >3, n/N (%)	21/29 (72.4%)	12/18 (66.7%)	9/11 (81.8%)	0.641
Correlation				
ALP change vs WI-NRS change at 3–6 mo	ρ=0.296, p=0.070	—	—	—
ALP change vs PROMIS-Fatigue T-score change at 3–6 mo	ρ=0.240, p=0.150	—	—	—
Total bilirubin change vs PROMIS-Fatigue T-score change at 3–6 mo	ρ=0.420, p=0.008	—	—	—
Total bilirubin change vs PROMIS-Fatigue T-score change at 3–6 mo, excluding bilirubin >2.5 mg/dL	ρ=0.392, p=0.022	—	—	—

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PROMIS, Patient-Reported Outcomes Measurement Information System; IQR, interquartile range; ULN, upper limit of normal; WI-NRS, worst-itch numerical rating scale; ρ, Spearman rank correlation coefficient. Between-therapy comparisons used Wilcoxon rank-sum or Fisher exact tests, as appropriate. Correlations are reported as Spearman ρ with p values.

Clinically meaningful symptom improvement was defined as ≥3-point WI-NRS decrease and ≥5-point PROMIS-Fatigue T-score decrease (bimodality analysis identified no natural cutoff between 0 and 10).

Disclosures: Hussein Harb:Nothing to Disclose, Fabian Rodas:Mirum Pharmaceutical: Speaking and Teaching, IPSEN: Speaking and teaching, GILEAD: Speaking, INTERCEPT Pharmaceuticals: Speaking and Teaching, COUR Pharmaceuticals: Independent Contractor, Zydus Pharmaceuticals: Independent Contractor, KOWA Pharmaceuticals: Independent Contractor, Toluwalase Okubote:Nothing to Disclose, Ronnie Scarboro:Nothing to Disclose, Krishna Venkata:Nothing to Disclose.

1241 | IMPACT OF MARALIXIBAT ON CAREGIVER BURDEN FOR PATIENTS WITH ALAGILLE SYNDROME OR PROGRESSIVE FAMILIAL INTRAHEPATIC CHOLESTASIS: 12-MONTH FOLLOW-UP

Natasha Dilwali[1] Fiona Coll[2] Robin Howard[3] Jolan Terner-Rosenthal[3] Douglas Mogul[3] Brandon Vu[4] Rachel Hallum-Montes[2] Wikrom Karnsakul[4], [1]Columbia University, [2]Motivo Insights, [3]Mirum Pharmaceuticals, Inc., [4]Johns Hopkins University

Background: Alagille syndrome (ALGS) and progressive familial intrahepatic cholestasis (PFIC) are rare cholestatic liver diseases (CLD) leading to end-stage liver failure. Patients experience significant pruritus, which impacts quality of life (QoL), sleep, and pruritus is a leading cause of transplant. Maralixibat (MRX) is approved to treat cholestatic pruritus in ALGS/PFIC with trials showing improvements in pruritus are linked to better patient sleep and QoL. We recently reported 6-month interim data demonstrating that MRX treatment may reduce caregiver sleep disruption, likely due to improvements in pruritus severity among patients. This study sought to extend these findings to 12-months of MRX treatment. **Methods:** Beginning in March 2024, caregivers of newly prescribed MRX for patients with ALGS/PFIC were invited to complete a survey assessing caregiver burden. Questions addressed the impact (0 to 10 scale where 0 = no impact, 10 = extreme impact) on sleep, pruritus, financial strain, and mood. Follow-up surveys were completed after 6- and 12-months. The focus of this analysis was on 12-month follow-up data. Data analysis included descriptive statistics. **Results:** A total of ten 12-month follow-up surveys were completed. The majority of respondents were parents of children with ALGS, mostly identified as White, and with a median age range of 30–39 years. 70% of caregivers reported a reduction in the number of hours (mean reduction = 7.3 hours from baseline [BL]) helping patients with activities of daily living. Impact of caregiving on mean productivity (4.3 vs 5.4 at BL), mood (3.9 vs 5.2 at BL), and sleep (6.1 vs 7.7 at BL) scores improved over the 12-month study period. Most (60%) caregivers showed improvements in hours of work missed since patients started MRX (mean reduction = 16 hours from BL). **Conclusion:** These findings demonstrate sustained improvement in caregiver QoL including improvements in sleep, daily activities and work productivity after 12-months of MRX treatment for patients with ALGS or PFIC. Generic instruments were used in this study to measure impact. Results indicate a need for more specific measurements in pediatric CLD to understand true caregiver impact.

Disclosures: Natasha Dilwali:Nothing to Disclose, Fiona Coll:Mirum Pharmaceuticals: Consultant, Robin Howard:Mirum Pharmaceuticals: Stock - publicly traded company, Mirum Pharmaceuticals: Employee, Mirum Pharmaceuticals: Consultant, Jolan Terner-Rosenthal: Mirum Pharmaceuticals, Inc.: Employee, Mirum Pharmaceuticals, Inc.: Stock - publicly traded company, Mirum Pharmaceuticals, Inc.: Employee, Mirum Pharmaceuticals, Inc.: Stock - publicly traded company, Douglas Mogul:Mirum Pharmaceuticals: Employee, Brandon Vu:Nothing to Disclose, Rachel Hallum-Montes:Nothing to Disclose, Wikrom Karnsakul:Nothing to Disclose.

1242 | FENOFIBRATE AS SECOND-LINE THERAPY FOR PRIMARY BILIARY CHOLANGITIS: EFFICACY AND SAFETY IN REAL-WORLD PRACTICE

Mikolas Holinka[1] Jan Šperl[1] Dusan Merta[1] Tomas Nesnidal[1] Tomas Hucl[1] Sona Frankova[1], [1]Institute for Clinical and Experimental Medicine

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Background: The first-line treatment for primary biliary cholangitis (PBC) is ursodeoxycholic acid (UDCA); however, approximately one-third of patients do not achieve an adequate biochemical response. Treatment with fibrates improves ALP activity, the strongest predictor of long-term prognosis; however, data supporting the use of fenofibrate, the only available second-line treatment (SLT) in the Czech Republic after the withdrawal of obeticholic acid, are limited to small, uncontrolled series. The aim of the study was to evaluate the efficacy and safety of fenofibrate as an SLT of PBC. **Methods:** We retrospectively analysed a cohort of 87 patients with PBC treated with fenofibrate (145 mg daily, NanoTab formulation). Eighty patients reached at least 12 months follow-up and could be evaluated for treatment response according to the Toronto criteria (decrease in ALP after 12 months of therapy to less than 1.67xULN; Toronto + group; no response: Toronto - group). The cohort included 72 (91.2%) women; the median age was 56 years (34–82), and the median liver stiffness was 8.8 kPa (4–57). UDCA was concomitantly administered to 78 patients (97.5%). ALP activity and bilirubin concentrations were assessed before treatment and at three-month intervals, as well as the occurrence of adverse events. **Results:** Forty-three patients (53.8%) met the Toronto criteria. Of the remaining 37 patients, 24 (30%) did not meet the Toronto criteria due to an insufficient decrease in ALP, and the remaining 13 (16.2%) due to premature discontinuation of treatment because of adverse events (myopathy 7, hepatotoxicity 2, pruritus 2, GIT complaints 2, self-discontinuation 1). The Toronto + group had significantly lower ALP activity at baseline (2.2x ULN; 0.63–4.4) than the Toronto - group (3.7x ULN; 0.67–11.9; $p < 0.0001$). Initial bilirubin concentrations did not differ significantly between the groups at baseline (0.64 vs. 0.75 mg/dL; N.S.), but during treatment, bilirubin was lower in the Toronto + group at both six and twelve months of treatment (0.57 vs. 0.84 mg/dL; $p = 0.03$, and 0.60 vs. 0.80 mg/dL; $p = 0.006$, respectively). Independent predictors of achieving Toronto + were older age (OR 1.1, 95% CI 1.00–1.20, $p = 0.05$) and baseline ALP activity (OR 0.27, 95% CI 0.11–0.49, $p = 0.0004$). The number of patients who underwent liver transplantation (LTx) did not differ between groups, 4/43 (9.3%) and 3/37 (8.1%) in the Toronto + and Toronto -, respectively (N.S.); none of the patients died. **Conclusion:** 53.8% of patients responded to fenofibrate therapy and met the Toronto criteria at month twelve. Baseline ALP levels and older age were independent predictors of treatment response. The data suggest that the biochemical response to fenofibrate is comparable to that of bezafibrate as SLT PBC therapy; however, there is so far insufficient evidence regarding its effect on survival and the need for LTx.

Disclosures: Mikolas Holinka:Nothing to Disclose, Jan Šperl:Gilead Sciences: Speaking and Teaching, Abbvie: Speaking and Teaching, Ipsen: Speaking and Teaching, Dusan Merta:Nothing to Disclose, Tomas Nesnidal:Nothing to Disclose, Tomas Hucl:Nothing to Disclose, Sona Frankova:Gilead Sciences: Speaking and Teaching, Abbvie: Speaking and Teaching, Ipsen: Speaking and Teaching.

1243 | SINGLE CENTER RETROSPECTIVE STUDY OF CLINICOPATHOLOGICAL FEATURES OF HEPATIC SARCOIDOSIS

Rehan Razzaq[1] Shreya Shah[2] Alexis Kim[2] Matthew Ambrosio[2] Le Kang[2] Thomas Iden[3] Dana Alderson[3] Jessica McLaughlin[3] Huzaefah Syed[3] Neha Gupta[3] Ryan Canissario[3] Jordana Kron[3] Vikram Brar[3] Duaa AbdelHameid[3] Aamer Syed[3] Vaishali Patel[2], [1]VCU Health System, [2]Virginia Commonwealth University, [3]Virginia Commonwealth University Health System

Background: Hepatic sarcoidosis (HS), a rare manifestation of sarcoidosis, can lead to portal hypertension and hepatic decompensation. Most studies presume HS in all patients with sarcoidosis and elevated liver enzymes, leading to variable findings across studies. **Methods:** We performed a retrospective analysis of patients with known systemic sarcoidosis who underwent liver biopsy for unexplained elevated liver enzymes at our multidisciplinary clinic and had a follow up in the last 5 years. We defined Hepatic Sarcoidosis (HS) as noncaseating granulomas on liver biopsy whereas the remainder were classified as Presumed Hepatic Sarcoidosis (pHS). Clinical characteristics were compared using t-tests, chi-square tests, or Fisher's exact tests as appropriate. **Results:** 114 patients with systemic sarcoidosis underwent liver biopsy for unexplained elevated liver enzymes. 68% were female and 78% were Black. 78(68%) had biopsy proven HS and the mean Alkaline Phosphatase (ALP) was significantly elevated in HS compared to pHS (271. 06 vs 177.83, $p = 0.028$). 17% of patients with pHS had hepatic sarcoid nodules on imaging. Of the 16 patients with HS who underwent transjugular liver biopsy, 44% had non-cirrhotic portal hypertension (NCPH). Liver fibrosis was more common in HS vs pHS group (71% vs 56%), and patients with HS were more likely to have advanced fibrosis (F3-4) (29% vs 20%); due to small sample size this was not statistically significant. 2 patients with HS underwent liver transplantation (LT). Black patients with HS had significantly higher incidence of concomitant lung sarcoidosis ($p = 0.026$), however having HS did not

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correspond to severity of lung fibrosis as calculated by Composite Physiological Index (CPI) (p = 0.2). **Conclusion:** Liver biopsy is diagnostic in 68% of patients with HS. ALP and imaging can improve diagnostic probability. Black patients with HS should be assessed for lung sarcoidosis. Given its rarity, developing consensus disease definition followed by multicenter trials are needed for improving patient outcomes.

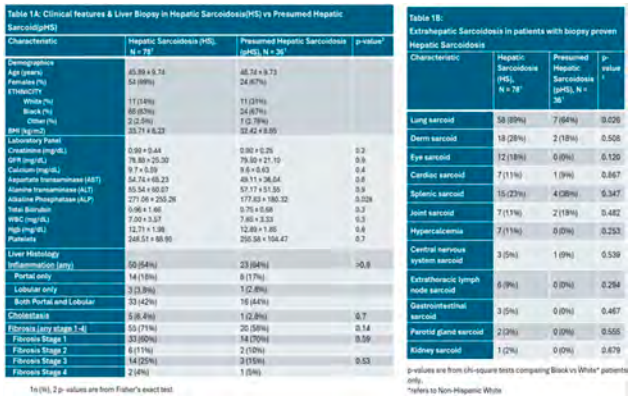


Table 1A: Clinical features & Liver Biopsy in Hepatic Sarcoidosis(HS) vs Presumed Hepatic Sarcoid(pHS)

Characteristic	Hepatic Sarcoidosis (HS), N = 78[†]	Presumed Hepatic Sarcoidosis (pHS), N = 36[†]	p-value[‡]
Demographics			
Age (years)	45.39 ± 9.74	46.74 ± 9.73	
Females (%)	53 (68%)	24 (67%)	
Ethnicity			
White (%)	11 (14%)	11 (31%)	
Black (%)	60 (83%)	24 (67%)	
Other (%)	2 (2.5%)	1 (2.78%)	
BMI (kg/m2)	35.71 ± 8.23	32.42 ± 8.85	
Laboratory Panel			
Creatinine (mg/dL)	0.90 ± 0.44	0.90 ± 0.26	0.3
GFR (mg/dL)	78.80 ± 25.30	79.90 ± 21.10	0.9
Calcium (mg/dL)	9.7 ± 0.59	9.6 ± 0.43	0.4
Aspartate transaminase (AST)	54.74 ± 65.23	49.11 ± 36.64	0.6
Alanine transaminase (ALT)	56.54 ± 60.07	57.17 ± 51.55	0.9
Alkaline Phosphatase (ALP)	271.06 ± 250.26	177.63 ± 180.32	0.028
Total Bilirubin	0.96 ± 1.66	0.75 ± 0.68	0.3
WBC (mg/dL)	7.50 ± 3.37	7.65 ± 3.33	0.3
Hgb (mg/dL)	12.71 ± 1.98	12.89 ± 1.85	0.6
Platelets	248.51 ± 88.90	256.58 ± 104.47	0.7
Liver Histology			
Inflammation (any)	50 (64%)	23 (64%)	>0.9
Portal only	14 (18%)	8 (17%)	
Lobular only	3 (3.8%)	1 (2.8%)	
Both Portal and Lobular	33 (42%)	16 (44%)	
Cholestasis	5 (6.4%)	1 (2.8%)	0.7
Fibrosis (any stage 1-4)	55 (71%)	20 (56%)	0.14
Fibrosis Stage 1	33 (60%)	14 (70%)	0.59
Fibrosis Stage 2	6 (11%)	2 (10%)	
Fibrosis Stage 3	14 (25%)	3 (15%)	0.53
Fibrosis Stage 4	2 (4%)	1 (5%)	

†n (%), ‡ p- values are from Fisher's exact test

Table 1B: Extrahepatic Sarcoidosis in patients with biopsy proven Hepatic Sarcoidosis

Characteristic	Hepatic Sarcoidosis (HS), N = 78[*]	Presumed Hepatic Sarcoidosis (pHS), N = 36[*]	p-value[†]
Lung sarcoid	58 (89%)	7 (64%)	0.026
Derm sarcoid	18 (28%)	2 (18%)	0.506
Eye sarcoid	12 (18%)	0 (0%)	0.120
Cardiac sarcoid	7 (11%)	1 (9%)	0.867
Splenic sarcoid	15 (23%)	4 (36%)	0.347
Joint sarcoid	7 (11%)	2 (18%)	0.482
Hypercalcemia	7 (11%)	0 (0%)	0.253
Central nervous system sarcoid	3 (5%)	1 (9%)	0.539
Extrathoracic lymph node sarcoid	6 (9%)	0 (0%)	0.284
Gastrointestinal sarcoid	3 (5%)	0 (0%)	0.467
Parotid gland sarcoid	2 (3%)	0 (0%)	0.555
Kidney sarcoid	1 (2%)	0 (0%)	0.679

p-values are from chi-square tests comparing Black vs White* patients only.
*refers to Non-Hispanic White

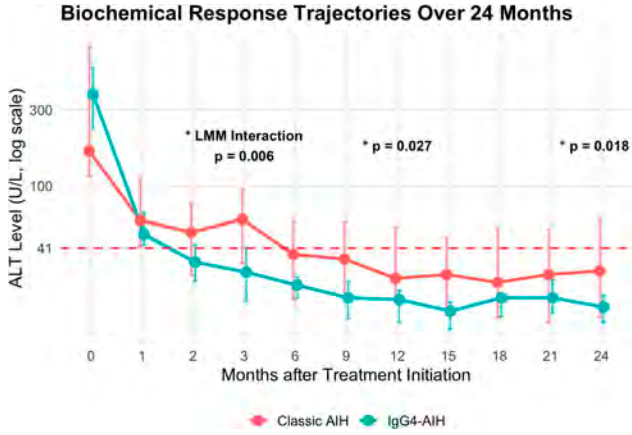
Disclosures: Rehan Razzaq:Nothing to Disclose, Shreya Shah:Nothing to Disclose, Alexis Kim:Nothing to Disclose, Matthew Ambrosio:Nothing to Disclose, Le KANG:Nothing to Disclose, Thomas Iden:Nothing to Disclose, Dana Alderson:Nothing to Disclose, Jessica McLaughlin:Nothing to Disclose, Huzaefah Syed:Nothing to Disclose, Neha Gupta:Nothing to Disclose, Ryan Canissario:Nothing to Disclose, Jordana Kron:Nothing to Disclose, Vikram Brar:Nothing to Disclose, Duaa AbdelHameid:Nothing to Disclose, Aamer Syed:Nothing to Disclose, Vaishali Patel: Nothing to Disclose.

1244 | THE BIPHASIC CLINICAL TRAJECTORY OF IGG4-ASSOCIATED AUTOIMMUNE HEPATITIS: RAPID REMISSION AND LATE CONVERGENCE

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[1]National Taiwan University Hospital

Background: IgG4-associated autoimmune hepatitis (IgG4-AIH) is an emerging entity bridging classical AIH and IgG4-related disease, yet its true clinical trajectory and classification remain debated. We aimed to characterize the dynamic biochemical response and long-term remission durability of IgG4-AIH to establish its unique clinico-pathological identity, ultimately guiding precision-driven therapeutic strategies and personalized long-term management.

Methods: This retrospective cohort study at a tertiary medical center evaluated patients with biopsy-proven AIH. All liver specimens were re-stained for IgG/IgG4 expression and reviewed by two pathologists. Patients were stratified into classic AIH (< 10 IgG4+ cells/high power field [HPF]) and IgG4-AIH (≥ 10 IgG4+ cells/HPF). Baseline clinico-serological profiles and 24-month longitudinal biochemical responses were analyzed. ALT normalization trajectories were mapped using a linear mixed-effects model (LMM), and long-term treatment durability was evaluated using Kaplan-Meier survival analysis. **Results:** Among 54 evaluated AIH patients, baseline sex distribution was comparable between the two cohorts. However, the IgG4-AIH group (N = 13, 24%) was older (median age 70 vs. 60 years), exhibited higher baseline serum IgG4 levels (median 208 vs. 58 mg/dL), and presented with a higher rate of baseline cirrhosis (31% vs. 12%). Despite this potentially more advanced baseline profile, longitudinal LMM analysis revealed a rapid and profound sensitivity to immunosuppression. The IgG4-AIH cohort maintained significantly lower ALT levels throughout the entire treatment trajectory, achieving faster and deeper biochemical remission at both Month 3 (p = 0.006) and Month 24 (p = 0.018). Survival analysis highlighted a prolonged initial remission in IgG4-AIH patients, whereas classic AIH exhibited early and continuous relapses. However, late-onset relapses still occurred in the IgG4-AIH group, leading to a gradual convergence of the survival curves over extended follow-up. **Conclusion:** IgG4-AIH constitutes a unique clinico-pathological entity marked by severe baseline fibrosis and a contrasting rapid response to early immunosuppression. Although IgG4-AIH patients achieve an exceptionally prolonged initial remission compared to classic AIH, they remain susceptible to late-onset relapses that ultimately bridge the long-term prognostic gap. These findings highlight the critical need for early biopsy-driven diagnosis and emphasize that despite a highly favorable initial treatment response, continuous clinical monitoring is essential for long-term management.



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1245 | MECHANISTIC INSIGHTS INTO THE PROTECTIVE EFFECTS OF FAECALIBACTERIUM PRAUSNITZII AND ITS METABOLITE SHORT CHAIN FATTY ACIDS ON BILIARY INJURY IN PRIMARY BILIARY CHOLANGITIS

Qi Wang[1] Xi Wang[1] Chunyang Huang[2] Minghui Li[1] Ronghua Jin[1], [1]Beijing Ditan hospital, [2]Beijing You an hospital

Background: Primary biliary cholangitis (PBC) is a chronic cholestatic liver disease that primarily affects middle-aged women. Studies suggest that alterations in the gut microbiome are closely associated with the pathogenesis and treatment of PBC, but the underlying mechanisms remain unclear. **Methods:** This study first conducted gut microbiota analysis of fecal samples from PBC patients and healthy controls using metagenomic sequencing, with LEfSe and other methods employed to identify differential microbial taxa. Subsequently, a bile duct ligation (BDL) mouse model was established and treated with *F. prausnitzii* (1×10^9 CFU/day), while ductular reaction and liver fibrosis were evaluated through histopathological staining. For in vitro experiments, a GCDC-induced injury model using human primary biliary epithelial cells (HiBECs) was developed, followed by treatment with varying concentrations of short-chain fatty acids (SCFAs). Furthermore, ChIP assays were performed to detect H3K27ac modification levels, elucidating the specific mechanism by which SCFAs exert their effects through epigenetic regulation of the ELF3/PI3K-Akt pathway. All data were statistically analyzed using two-tailed t-tests/ANOVA with FDR correction ($P < 0.05$ considered statistically significant). **Results:** We found that *F. prausnitzii* was significantly reduced in the gut microbiota of PBC patients. Supplementation with *F.prausnitzii* markedly improved BDL-induced biliary injury, including cholangitis, bile duct hyperplasia, and liver fibrosis, while also restoring gut microbial balance and intestinal barrier function. These beneficial effects were linked to short-chain fatty acids (SCFAs) produced by *F. prausnitzii*. Mechanistic studies revealed that *F. prausnitzii*-derived SCFAs enhanced histone H3K27 acetylation, upregulating the transcription factor ELF3 and subsequently activating the PI3K-Akt signaling pathway to promote bile duct cell repair. **Conclusion:** This study demonstrates that *F. prausnitzii* exerts protective effects in PBC. Its depletion in PBC patients and its therapeutic potential in alleviating cholangitis and liver fibrosis, along with restoring gut function, highlight its promising clinical application for PBC treatment.

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1246 | REAL-WORLD EXPERIENCE OF ODEVIXIBAT IN ADULTS WITH PERSISTENT HEPATOCELLULAR SECRETORY FAILURE

Mauro Viganò[1] Francesca Colapietro[1] Maria Iascone[2] Filippo Leonardi[1] Luisa Pasulo[1] Alessandro Loglio[1] Lisa Licini[3] Lorenzo D'Antiga[4] Stefano Fagiuoli[1], [1]ASST Papa Giovanni XXIII, Department of Gastroenterology, [2]ASST Papa Giovanni XXIII, Department of Genetics, [3]ASST Papa Giovanni XXIII, Department of Pathology, [4]ASST Papa Giovanni XXIII, Department of Pediactrics

Background: Persistent hepatocellular secretory failure (PHSF) [van Dijk R, et al. Liver Int. 2015] is a rare but potentially life-threatening condition characterized by sustained impairment of hepatocellular bile secretion, resulting in prolonged cholestasis, jaundice, and hyperbilirubinemia that may persist for months after withdrawal of the offending trigger including drugs, toxins, or transient biliary obstruction. Differential diagnosis with genetic cholestatic disorders remains particularly challenging in adults. We herein describe a case series of five consecutive adult patients presenting with persistent non-mechanical cholestasis at the Hepatology and Liver Transplant Unit, ASST Papa Giovanni XXIII, Bergamo, Italy, between 2024 and 2025. **Methods:** Clinical data, including the severity of pruritus, laboratory parameters [alanine aminotransferase (ALT), bilirubin and serum bile acids (sBAs)], genetic testing and imaging findings were assessed. All patients underwent liver biopsy and were consequently treated with Odevixibat (40 mcg/Kg/day), an Ileal Bile Acid Transporter (IBAT) inhibitor. **Results:** All patients were male, with a median age of 35 years (range 32-60) and exhibited cholestatic abnormalities persisting for at least 30 days (range 25-67 days) after resolution of biliary tract obstruction obtained

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with endoscopic retrograde cholangiopancreatography (ERCP) and antibiotic treatment. Severe pruritus was present in all cases, significantly impairing sleep and quality of life. Mean bilirubin levels at first evaluation were 27.4 mg/dL (SD 7.3 mg/dL), while mean sBAs and median ALT levels were 355.6 ± 125.2 mmol/L and 61 U/L (29-224), respectively. Gamma glutamyl transferase (gGT) levels were completely normal in two patients whereas only mildly elevated in the remaining cases (lower than 2xULN). Magnetic resonance- colangiography excluded biliary obstruction in all patients. Liver histology demonstrated canalicular cholestasis, biliary metaplasia, and variable degrees of ductopenia, initially suggestive of drug-induced-livery injury (DILI), but evolving in some cases toward features consistent with genetic cholangiopathy and ultimately BRIC-like phenotype. Genetic analysis identified ATP8B1 variants in only one patient. During a mean treatment time of 65 days (range 40-120), odevixibat induced rapid normalization of both sBAs and bilirubin levels, accompanied by marked improvement in pruritus, which completely resolved in all patients at the last follow-up. No major safety concerns emerged; only one patient experiencing mild diarrhea, which resolved after dosage adjustment. **Conclusion:** PHSF may represent an overlap condition between DILI and genetic cholestatic disorders. IBAT inhibitors may play a relevant therapeutic role in this setting by effectively reducing both sBAs and bilirubin levels thus improving cholestatic pruritus.

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1247 | HISTOLOGICAL SEVERITY PREDICTS CLINICAL PHENOTYPE AND OUTCOMES IN PEDIATRIC AUTOIMMUNE HEPATITIS

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Background: Pediatric autoimmune hepatitis (AIH) shows a heterogeneous spectrum ranging from acute liver failure to chronic liver disease. The association between histological severity, clinical phenotype, and outcomes remains incompletely understood. We evaluated histological correlates of presentation and outcome in pediatric AIH. **Methods:** We retrospectively analyzed prospectively collected data of children diagnosed with AIH between January 2010 and November 2025. Diagnosis was based on clinical and biochemical profile, compatible histology, elevated IgG, simplified AIH score ≥ 6, and exclusion of other liver diseases. Histological features were compared across presentations: acute liver failure/acute-on-chronic liver failure (ALF/ACLF), decompensated chronic liver disease (DCLD), and acute/chronic hepatitis or compensated chronic liver disease (AH/CH/CCLD). Outcomes assessed included death/liver transplantation (LT) and difficult-to-treat disease (DTT). **Results:** Among 232 children, median age was 10 years (IQR 7–13.3) with female predominance; 17% had AIH-overlap and 28% were seronegative. Presentations included ALF/ACLF in 42 (18%), DCLD in 76 (33%), and AH/CH/CCLD in 114 (49%). Concurrent extrahepatic autoimmune disorders were present in 35%. Median IgG was 24 g/L (IQR 19–29.9), and 5% had normal immunoglobulin levels. ALF/ACLF had higher histological activity index [10 (IQR 7–14)] with more multiacinar necrosis (45.2%) and central perivenulitis (26.2%), whereas DCLD showed advanced fibrosis [Ishak stage 4 (IQR 2–6)] ($p < 0.001$). Seronegative and seropositive AIH had comparable histology and presentation, although fibrosis was lower in seronegative AIH. Type-1 and type-2 AIH showed no significant differences. Among 179 patients with ≥ 12 months follow-up, 33 had poor outcomes (14 deaths, 19 LT) and 43 developed DTT disease. Independent predictors of poor outcomes were ALF/ACLF presentation (OR 4.65, 95%CI 1.57–13.72; $p = 0.005$), elevated INR (OR 1.64, 95% CI 1.00–2.69; $p = 0.049$), and histological cholestasis (OR 2.45, 95%CI 1.00–5.98; $p = 0.050$), while pseudorosettes were protective (OR 0.29, 95%CI 0.11–0.77; $p = 0.012$).Younger age, thrombocytopenia, and elevated GGT independently predicted DTT disease. **Conclusion:** Pediatric AIH demonstrates a heterogeneous clinical and histological spectrum. Histological severity correlates with clinical presentation and independently predicts outcomes. Histological cholestasis and elevated INR identify children at risk of poor outcomes, while younger age, thrombocytopenia, and elevated GGT predict difficult-to-treat disease. Histological assessment provides important prognostic information beyond conventional clinical and biochemical parameters.

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Graph 1: Histological features of different phenotypes of autoimmune hepatitis.

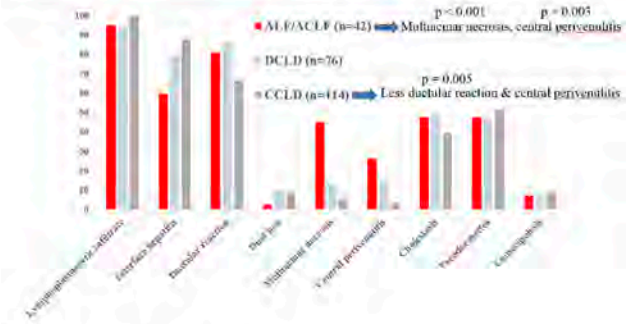


Table 1: Histological predictors of poor outcome (death or Liver transplantation) in children with autoimmune hepatitis

PARAMETERS	Survival with native liver (n=146)	Death or Liver transplantation (n=33)	Odd's ratio (95% CI)	Mean difference (95% CI)	P value
Histological Features					
Cirrhosis	32	11	1.521(0.859-2.693)		0.166
Fibrosis score (Ishak)	2.6 ± 2.0	3.2 ± 2.0		0.59 (-0.19 to +1.37)	0.135
HAI	8.7 ± 3.6	9.4 ± 3.8		0.68 (-0.69 to +2.06)	0.327
Lymphoplasmacytic infiltrate	145	32	0.976 (0.918-1.039)		0.247
Interface hepatitis	120	22	0.811 (0.630-1.044)		0.047
Ductular reaction	108	29	1.188 (1.013-1.393)		0.089
Duct damage	22	8	1.609 (0.787-3.291)		0.203
Duct loss	8	5	2.765 (0.966-7.914)		0.053
Spotty necrosis	61	8	0.580 (0.308-1.092)		0.062
Bridging necrosis	39	6	0.681 (0.315-1.473)		0.308
Confluent necrosis	49	12	1.083 (0.653-1.797)		0.759
Multiacinar necrosis	16	11	3.042 (1.559-5.934)		0.001
Panacinar necrosis	13	7	2.382 (1.031-5.505)		0.062
Central perivenulitis	45	6	0.590 (0.275-1.266)		0.146
Perivenular necrosis	22	6	1.207 (0.532-2.739)		0.657
Cholestasis	53	21	1.753 (1.253-2.452)		0.004
Pseudorosettes	76	9	0.524 (0.294-0.934)		0.010
Parenchymal collapse	33	13	1.743 (1.037-2.928)		0.046
Emperipolesis	13	1	0.340 (0.046-2.511)		0.472
Lobular inflammation	119	23	0.855 (0.674-1.085)		0.130
Periductal fibrosis	5	5	3.539 (1.005-12.470)		0.061
Neutrophilic cholangiolitis	11	4	1.609 (0.503-5.692)		0.390

Table 2: Multivariable binary logistic regression analysis showing independent predictors of poor outcome and difficult-to-treat disease in pediatric autoimmune hepatitis

Outcome	Independent predictors	OR/ Exp(B)	95% CI	p-value
Poor outcome (Death/LT)	ALF/ACLF	4.647	1.574–13.724	0.005
	INR	1.644	1.002–2.695	0.049
	Cholestasis on biopsy	2.445	1.000–5.981	0.050
	Pseudorosettes	0.295	0.113–0.769	0.012
Difficult-to-treat AIH (DTT)	Younger age at diagnosis	0.854	0.769–0.950	0.004
	Platelet count	1.000	1.000–1.000	<0.001
	GGT	1.006	1.001–1.011	0.013

Disclosures: Aditya Soni:Nothing to Disclose, Rajeev Khanna:Nothing to Disclose, Seema Alam:Nothing to Disclose, Bikrant Biharilal Raghuvanshi:Nothing to Disclose, Vikrant Sood:Nothing to Disclose.

1248 | CHARACTERISTICS OF DRUG-INDUCED AUTOIMMUNE-LIKE HEPATITIS: REPORT FROM A REGISTRY OF 535 PATIENTS WITH AIH

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Background: Drug-induced autoimmune-like hepatitis (DIALH) shares clinical, serological, and histological features with *de novo* autoimmune hepatitis (AIH). Prior case series suggest most DIALH patients discontinue all immunosuppression within 6–12 months of diagnosis. We interrogated a large single-center prospective AIH registry, and characterized clinical differences between DIALH and AIH, as well as treatment trajectory and biochemical response. **Methods:** We analyzed AIH cases from the Genetic Repository of Autoimmune Liver Disease and Contributing Exposures (GRACE) registry (N = 535 patients 2014-2024). DIALH (n = 27, 5.0%) was defined by temporally associated drug exposure with confirmed autoimmune-like liver injury. AIH treatment was captured at intervals: 0–3, 3–6, 6–12, 12–24 months following the diagnosis, and most recent visit. **Results:** There were 27 DIALH cases (5%). Antimicrobials (44%) and statins (26%) were the most common implicated drug classes; nitrofurantoin (26%) was the most frequently identified agent, followed by atorvastatin (15%) and minocycline (7%). They had higher transaminases (ALT 354 vs 113 U/L, p = 0.002) and bilirubin (3.2 vs 1.2 mg/dL, p = 0.01) compared to AIH at onset (Table 1). ANA (68% vs 72%), ASMA (68% vs 64%), biopsy AIH-compatibility (96% vs 98%), and HLA-DR3/DR4 carrier rates were not different between groups. Despite higher at diagnosis, bilirubin normalized more rapidly in DIALH (94% vs 76% in 6 months, p = 0.04), yet rates of transaminase decline were similar through the first year compared to AIH. ALT level by year 2 (ALT 15 vs 25 U/L, p = 0.04) and most recent visit (p = 0.01) was lower in DIALH. DIAIH cases received more budesonide early (33% vs 12% at 0–3 months, p = 0.005; 26% vs 11% at 3–6 months, p = 0.03). Only 33% of DIALH patients were off all treatment at most recent visit at a median 3.9 years, not significantly different from AIH (19%, p = 0.08). Zero post-withdrawal relapses occurred in DIALH versus 18% in AIH. Five-year survival was 90% and 93%, respectively (log-rank p = 0.8). **Conclusion:** DIALH constitutes 5% of a large prospective AIH registry and is indistinguishable from de novo AIH clinically, serologically, and genetically. Our experience indicates

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complete withdrawal of immunosuppression was feasible only in 3rd of DIAIH cases during follow-up.

Table 1. Baseline Characteristics, Biochemical Recovery, and Treatment Trajectory between DIALH vs De Novo AIH in the GRACE Registry

Variable	DIALH (n=27)	De Novo AIH (n=508)	P-value
Age, years	56 (46–63)	49 (35–59)	0.1
Female sex	85%	77%	0.34
White (non-Hispanic)	93%	84%	0.41
At Presentation†			
ALT, U/L	354 (166–1089)	113 (46–414)	0.002
AST, U/L	494 (122–963)	100 (43–383)	0.002
Total bilirubin, mg/dL	3.2 (1.1–9.9)	1.2 (0.6–3.5)	0.01
ANA positive, %	68%	72%	0.71
ASMA positive, %	68%	64%	0.68
AIH-compatible biopsy	96%	98%	0.34
HLA-DR3 carrier, % ‡	46% (6/13)	36% (76/214)	0.55
HLA-DR4 carrier, % ‡	8% (1/13)	19% (40/214)	0.47
Biochemical Recovery			
Bilirubin <1.1 mg/dL at 6 months	94%	76%	0.04
ALT at year 1, U/L	24 (18–41)	27 (17–49)	0.92
ALT at year 2, U/L	15 (13–24)	25 (16–53)	0.04
ALT at most recent visit, U/L	16 (10–21)	22 (15–37)	0.01
Treatment — Corticosteroids by Timepoint			
Budesonide at 0–3 months	33%	12%	0.005
Budesonide at 3–6 months	26%	11%	0.03
Prednisone at most recent visit	0%	16%	0.02
Budesonide at most recent visit	7%	6%	0.69
Treatment — Outcomes			
Off all immunosuppression at MRV	33%	19%	0.08
Post-withdrawal relapse	0% (0/10)	18% (27/147)	0.21
Outcomes			
Loss of remission	17%	20%	1.000
5-year transplant-free survival §	90%	93%	0.8

Continuous: median (IQR); †DIALH labs = presenting values at drug-induced event; De Novo AIH = baseline at AIH diagnosis. ‡HLA subset: DIALH n=13 (48%), De Novo n=214 (42%); dominant model. §5-year K-M estimates, log-rank p=0.80. DIALH CI wide (n=11 at-risk at 5yr). MRV = most recent visit. NS = not significant.

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1249 | AUTOIMMUNE HEPATITIS IN MEN: WORSE TRANSPLANT-FREE SURVIVAL AND A SUGGESTIVE *HLA-DR3* *SEX INTERACTION

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Background: Autoimmune hepatitis (AIH) predominantly affects women, leaving male-specific disease behavior poorly characterized. HLA-DR3, the principal AIH susceptibility allele, may interact with sex to modify disease risk, but this has not been evaluated in a robust cohort. We used a large single-center registry to define how men differ from women in clinical course, outcomes, and genetic susceptibility. **Methods:** We analyzed 514 adults with AIH from the GRACE registry. Transplant-free survival (TFS) was time from diagnosis to composite endpoint (liver transplant, death) or last clinical follow-up. 474 patients with available diagnosis dates were included in survival analysis. Multivariate Cox regression estimated the sex-based hazard ratio adjusted for age, cirrhosis, log-bilirubin, and race; loss-of-remission and post-withdrawal relapse were compared by Fisher's exact test. In a genetic sub-cohort (n = 222; 43 men, 179 women), a Cox model with HLA-DR3 strata (ref: female DR3−) assessed gene-sex interaction on TFS. **Results:** Of 109 men and 405 women, fibrosis and synthetic function were equivalent at diagnosis: F3/F4 fibrosis (33.3% vs 34%, p = 1.0), albumin (3.7 vs 3.8 g/dL, p = 0.99), INR (1.2 vs 1.1, p = 0.48) (Table). Men had higher bilirubin (1.4 vs 1.0 mg/dL, p = 0.04) and ALT (152 vs 109 U/L, p = 0.02). Biochemical remission at 6 months (42.9% vs 55.4%, p = 0.25) and 12 months (60.5% vs 63.0%, p = 0.85) did not differ. Men had twice the composite event rate (27.5% vs 14.8%, p = 0.003) and worse 10-year TFS (79.6% vs 87.1%, p = 0.009). Male sex independently predicted worse TFS (HR 2.04, 95% CI 1.17–3.54, p = 0.01). Loss-of-remission was identical (15.9% vs 19.8%, p = 0.45), yet relapse was twice as frequent in men (64.3% vs 31.2%, p = 0.03). *HLA-DR3* was enriched in men (55.8% vs 31.3%, p = 0.004). When the combined effect of sex and DR3 positivity on outcomes was interrogated, there was a significant increasing trend in composite outcome rates across ordered sex/DR3 groups, with male DR3 + subgroups carrying the highest risk (Cochran–Armitage trend test, Z = 3.04, two-sided P = 0.002)

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(Table 1). **Conclusion:** Men with AIH have worse TFS despite presenting similarly to women. DR3 may identify a higher-risk subgroup among men, but this requires prospective validation in larger HLA-typed cohorts.

Table 1. Men vs Women with Autoimmune Hepatitis in the GRACE Registry

Variable	Men (n = 109)	Women (n = 405)	P
Demographics			
Age at diagnosis, mean ± SD (yrs)	45.1 ± 17.0	47.6 ± 17.4	0.2
Follow-up duration, mean ± SD (yrs)	11.0 ± 7.1	10.2 ± 7.7	0.39
Baseline Disease Severity and Synthetic Function			
F3/F4 fibrosis on biopsy, n (%)	31/93 (33.3)	108/318 (34.0)	1
Albumin at diagnosis, median (IQR) g/dL	3.7 (3.3–4.1)	3.8 (3.3–4.1)	0.99
INR at diagnosis, median (IQR)	1.2 (1.1–1.3)	1.1 (1.0–1.3)	0.48
Bilirubin at diagnosis, median (IQR) mg/dL	1.4 (0.8–4.5)	1.0 (0.6–3.2)	0.04
ALT at diagnosis, median (IQR) U/L	152 (65–601)	109 (40–395)	0.02
Treatment Response and Durability			
Biochemical remission at 6 months, n (%)	15/35 (42.9)	72/130 (55.4)	0.25
Loss of remission on treatment, n (%)	14/88 (15.9)	69/348 (19.8)	0.45
Relapse after treatment withdrawal, n (%)	9/14 (64.3)	20/64 (31.2)	0.03
Long-Term Outcomes			
Transplant or death (composite), n (%)	30/109 (27.5)	60/405 (14.8)	0.003
10-year transplant-free survival (KM)	79.6%	87.1%	0.009
Male sex — adjusted Cox HR	HR 2.04 (1.17–3.54)	ref: women	0.01
HLA Genotype and Gene-Sex Analysis (HLA-typed sub-cohort: 43 men, 179 women)			
HLA-DR3 carrier, n (%)	24/43 (55.8)	56/179 (31.3)	0.004
HLA-DR4 carrier, n (%)	4/43 (9.3)	38/179 (21.2)	0.08
4-group analysis (ref=Female DR3−), n=169, 27 events; adj. age, cirrhosis, log-bili			
Female, DR3− (reference)		83.1%	0.002*
Female, DR3+ carriers	—	92.1%	
Male, DR3− non-carriers	90.0%	—	
Male, DR3+ carriers	67.7%	—	

* Two-sided p-value by Cochran–Armitage trend test

Disclosures: Craig Lammert:Eli Lilly: Consultant, Kezar Life Sciences: Consultant, Amgen: Consultant, Autoimmune Hepatitis Association: Consultant, RegCell: Consultant, Regeneron: Consultant, Tae-Hwi Schwantes-An:Nothing to Disclose, Eduardo Vilar-Gomez:Nothing to Disclose, Kelsey Green:Nothing to Disclose, Divya Minnaganti:Nothing to Disclose, Nadia Blessing:Gilead: Speaker Bureau, Naga Chalasani:Madrigal, Eccogene, Insitro, Boston Pharma, Chugai: Consultant, Zydus, GSK, Akero, Plaint, Altimmune: Consultant, Exact Sciences: Grant/Research Support, NIH: Grant/Research Support, Heligenics: Board member, investor, Avant Sante: Board member, investor, Ipsen, Biomea Fusion, Pfizer, Merck: Consultant.

1250 | PERSISTENT PATIENT-REPORTED SYMPTOM BURDEN IN AUTOIMMUNE HEPATITIS REGARDLESS OF BIOCHEMICAL REMISSION OR MASLD OVERLAP

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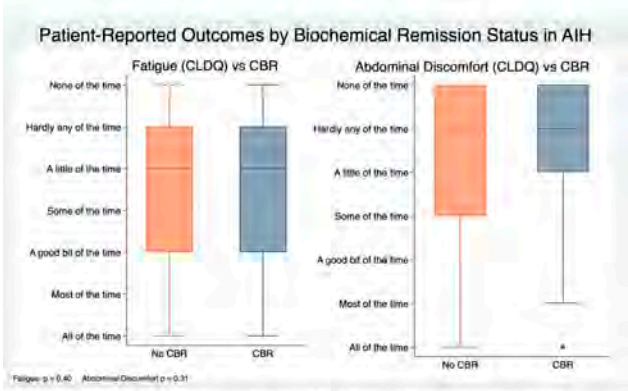
Background: In autoimmune hepatitis (AIH), treatment success is traditionally defined by biochemical remission. However, patient-reported outcomes (PROs) increasingly highlight aspects of disease burden not captured by laboratory markers. Metabolic dysfunction–associated steatotic liver disease (MASLD) frequently coexists with AIH and may contribute to symptom burden, but its role remains unclear. We aimed to evaluate PROs in AIH and assess whether biochemical remission or MASLD overlap reflects patient-reported symptom burden. **Methods:** A cross-sectional analysis was conducted within the Autoimmune Liver Diseases Registry at Beth Israel Deaconess Medical Center (Boston, MA, USA) from 2018 to 2025. Adult patients with a primary diagnosis of AIH who completed the Chronic Liver Disease Questionnaire (CLDQ) were included, regardless of overlap with primary biliary cholangitis, primary sclerosing cholangitis, or prior liver transplantation. MASLD was defined clinically as body mass index ≥ 25 kg/m² in combination with at least one cardiometabolic risk factor, including diabetes mellitus (with or without insulin therapy), hypertension, hyperlipidemia, or coronary artery disease. Complete biochemical remission (CBR) was defined as normalization of aminotransferases and immunoglobulin G. Group comparisons were performed using Fisher's exact test, and PROs were compared using the Mann–Whitney U test. Univariable logistic regression assessed the association between MASLD and CBR. **Results:** Among 178 patients with AIH, 55 (30.9%) met criteria for MASLD. CBR was achieved in 60.1% of the cohort and occurred at similar rates in AIH-only and AIH–MASLD patients (61.0% vs 58.2%, $p = 0.74$). MASLD was not associated with odds of achieving CBR (OR 0.89; 95% CI 0.47–1.70; $p = 0.73$). PROs demonstrated a substantial symptom burden across the cohort. Fatigue and abdominal symptoms were common and persisted even among patients who achieved CBR, with no significant differences by remission status or MASLD overlap (all $p > 0.20$). **Conclusion:** In AIH, patient-reported symptom burden persists despite complete biochemical remission and is not explained by metabolic overlap. These findings highlight a disconnect between enzymatic disease control and patient experience and underscore the importance of incorporating PROs into the assessment of treatment response in AIH.

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Figure 1. **Baseline Characteristics, Complete Biochemical Remission, and Patient-Reported Outcomes in Autoimmune Hepatitis (n = 178)**

Characteristic	No CBR (n = 71)	CBR (n = 107)	P - Value
Age (years), median (IQR)	57 (40-64)	53 (42-60)	0.473
Female sex, n (%)	56 (76.71%)	79 (75.24%)	0.860
BMI (kg/ m²), IQR	27 (23-30.4)	27.4 (23-31.6)	0.583
MASLD overlap, n (%)	24 (32.88%)	31 (29.52%)	0.742
Cirrhosis, n (%)	26 (35.62%)	24 (22.86%)	0.089
ALT (IU/L), IQR	48 (30-94)	18 (13-23)	0.000
AST (IU/L), IQR	51 (34-98)	22 (17.5-27.5)	0.000
IgG (IU/L), IQR	1555 (1243-1911)	1034 (835-1266)	0.000
CLDQ Fatigue score, median (IQR)	5 (3-6)	5 (3-6)	0.788
CLDQ Abdominal discomfort score, median (IQR)	6 (4-7)	6 (5-7)	0.648



Values are presented as median (interquartile range) or number (%). Continuous variables were compared using the Wilcoxonrank-sum test and categorical variables using Fisher's exact test. CLDQ scores range from 1 (worst symptoms) to 7 (no symptoms). CBR = complete biochemical remission; BMI = Body Mass Index; MASLD = metabolic dysfunction–associated steatotic liver disease. Box plots show median, IQR, and range excluding outliers.

Disclosures: Victoria Abadi-Ron:Nothing to Disclose, Natalia Rojas Amaris:Nothing to Disclose, Ana Marenco-Flores:Nothing to Disclose, Fernando Munguia: Nothing to Disclose, Giuliana Arevalo:Nothing to Disclose, Romelia Barba:Nothing to Disclose, Daniela Goyes:Nothing to Disclose, Esli Medina Morales: Nothing to Disclose, Leandro Sierra:Nothing to Disclose, Behnam Saberi:Nothing to Disclose, Alan Bonder:Nothing to Disclose, Vilas Patwardhan:Nothing to Disclose.

1251 | IMPACT OF LINERIXIBAT, AN ILEAL BILE ACID TRANSPORTER (IBAT) INHIBITOR, ON FAT-SOLUBLE VITAMIN (FSV) ABSORPTION IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS (PBC)

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Background: Bile acids act as digestive surfactants, assisting absorption of FSVs. IBAT inhibitors (IBATi) interrupt absorption of primary conjugated bile acids (while maintaining bile acid synthesis), which can potentially lead to FSV deficiencies, as observed with some IBATi in cholestatic diseases. Linerixibat is a minimally absorbed, twice-daily, oral IBATi recently approved in the US for the treatment of cholestatic pruritus in PBC. Here, we report FSV levels with linerixibat treatment in patients (pts) with PBC, and adverse events (AEs) associated with FSV deficiency. **Methods:** The Phase 3 GLISTEN (NCT04950127) and the Phase 2b GLIMMER (NCT02966834) trials were multicenter, randomized, placebo-controlled trials investigating the efficacy and safety of linerixibat in adults with PBC and pruritus. This abstract presents primary and post hoc analyses of FSV levels, and FSV-related AEs in the safety population of GLISTEN and GLIMMER (primary intervention periods). **Results:** The GLISTEN safety population included 237 pts (linerixibat n = 119; placebo n = 118). Most pts had FSV levels within normal range at baseline and throughout the study. No significant differences in absolute values were observed between linerixibat and placebo over 24 weeks. Analysis of covariance for the change from baseline in FSV levels at Week 24 showed no significant reductions with linerixibat vs placebo (**Table**). AEs of FSV decrease/deficiency were experienced in 4 (3%) pts receiving linerixibat and 2 (2%) pts receiving placebo, with no meaningful difference in incidence between groups. All were mild in intensity and not considered treatment-related. Eleven (9%) pts on linerixibat and 3 (3%) on placebo experienced hemorrhage. In these pts, no clinically significant differences were observed between groups in change from baseline in International Normalized Ratio and vitamin K. Fracture occurred in 2 (2%) pts receiving linerixibat (1 had a history of osteoporosis; both had vitamin A levels below lower limit of normal [LLN] at baseline and during the study) and 3 (3%) receiving placebo (1 pt had 2 fractures; 1 had vitamin D levels **Conclusion:** There was no clinical evidence suggestive of a causal association between linerixibat and FSV deficiency-related AEs, possibly due to its unique physicochemical properties that may not impact micellar formation and subsequent FSV absorption and its reversible inhibition compared to other IBATi. Most pts maintained vitamin A, D, E and K parameters within normal range, with no notable differences observed in change from baseline between linerixibat and placebo groups. **Funding:** GSK (212620/201000)

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Table: Analysis of covariance of change from baseline in fat-soluble vitamins at Week 24 in GLISTEN (post hoc analyses; safety population)

Treatment group*	n	Change from baseline (LS mean [95% CI])	Difference vs placebo† (LS mean difference [95% CI])
25-Dihydroxyvitamin D (nmol/L)			
Placebo	106	−0.51 (−5.31, 4.28)	3.54 (−3.29, 10.37)
Linerixibat	103	3.02 (−1.84, 7.89)	
Vitamin A (µmol/L)			
Placebo	105	−0.22 (−0.47, 0.02)	0.06 (−0.28, 0.41)
Linerixibat	104	−0.16 (−0.41, 0.08)	
Alpha tocopherol (µmol/L)			
Placebo	105	−1.18 (−2.38, 0.02)	1.82 (0.12, 3.52)
Linerixibat	104	0.64 (−0.57, 1.85)	
Beta gamma tocopherol (µmol/L)			
Placebo	105	−0.05 (−0.26, 0.15)	0.10 (−0.19, 0.39)
Linerixibat	104	0.05 (−0.16, 0.25)	
Vitamin E (µmol/L)			
Placebo	16	−2.98 (−6.98, 1.01)	1.04 (−4.91, 6.99)
Linerixibat	14	−1.94 (−6.23, 2.34)	
Vitamin K1 (nmol/L)			
Placebo	107	0.02 (−0.10, 0.14)	−0.08 (−0.25, 0.09)
Linerixibat	104	−0.06 (−0.18, 0.06)	

*Total population: placebo N=118, linerixibat N=119; †mean difference >0 favors active treatment; mean difference <0 favors placebo.
CI, confidence interval; LS, least squares.

Disclosures: Gideon Hirschfield:Intercept: Consultant, GSK: Consultant, CymaBay: Consultant, Ipsen: Consultant, Falk: Consultant, Pliant: Consultant, Mirum: Consultant, Advanz: Consultant, Chemomab: Consultant, Gilead: Consultant, Kowa: Consultant, Sadia Halim:GSK: Employee, Alexander Cobitz:GlaxoSmithKline Pharmaceuticals: Employee, Revathi Udayashankar:Nothing to Disclose, Linda Casillas:Nothing to Disclose, Ivana Lazic:GSK: Employee, Jennifer Shannon:Nothing to Disclose, Megan McLaughlin:Nothing to Disclose, Chester Bowen:Nothing to Disclose, Sanjay Kumar:Nothing to Disclose, Brandon Swift:Nothing to Disclose, Cynthia Levy:Gilead: Grant/Research Support, Ipsen: Grant/Research Support, GSK: Grant/Research Support, Intercept: Grant/Research Support, Calliditas: Grant/Research Support, Zydus: Grant/Research Support, LisCure: Grant/Research Support, TARGET RWE: Grant/Research Support, Pliant: Grant/Research Support, NGM: Grant/Research Support, Mitsubishi Tanabe: Grant/Research Support, DISC: Grant/Research Support, Takeda: Grant/Research Support, Kowa: Grant/Research Support, Mirum: Grant/Research Support, Christopher Bowlus:AssemblyBio: Advisor, Astra Zeneca: Advisor, ChemoMab: Grant/Research Support, ChemoMab: Advisor, COUR Pharmaceuticals: Grant/Research Support, Esperion: Advisor, Gilead Sciences: Grant/Research Support, Gilead Sciences: Advisor, GSK Pharmaceuticals: Grant/Research Support, GSK Pharmaceuticals: Advisor, Hanmi Pharmaceuticals: Grant/Research Support, Ipsen Bioscience: Grant/Research Support, Ipsen Bioscience: Advisor, Kezar: Advisor, Mirum Pharmaceuticals: Grant/Research Support, Mirum Pharmaceuticals: Advisor, Novartis: Grant/Research Support, Novo Nordisk: Grant/Research Support, Pliant Pharmaceuticals: Grant/Research Support, Pliant Pharmaceuticals: Advisor, RegCell: Advisor, Zydus: Grant/Research Support, Perspectum: Grant/Research Support, Lilly: Advisor, ICON: Independent Contractor.

1252 | TEMPORAL TRENDS IN AUTOIMMUNE LIVER DISEASES OVER THE LAST THREE DECADES: IMPACT OF THE COVID-19/POST-COVID-19 PANDEMIC, RISING PRIMARY BILIARY CHOLANGITIS FREQUENCY, AND AGING AT DIAGNOSIS IN A MEXICAN REFERRAL CENTER

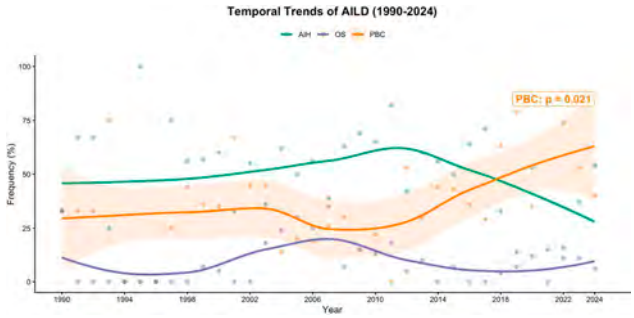
Linda Muñoz-Espinosa[1] Samuel Rivas-Lopez[2] Paula Cordero-Perez[2] Giselle Banda-Alvarez[2] Alexandra Costilla-Martinez[2] Ricardo Rodriguez-Macias[2] Liliana Torres-González[2] Fernando Iglesias-Hernandez[2] Emilia Sepulveda-Gutierrez[3], [1]University Hospital, UANL, [2]Hospital Universitario UANL, [3]Hospital Universitario, UANL

Background: The global impact of autoimmune liver diseases (AILD) poses a major diagnostic challenge. Mexico ranks first in cirrhosis-related mortality in Latin America. Cirrhosis is currently the fourth leading cause of death nationwide. The incidence of AILD, according to international diagnostic criteria, has increased in our center, particularly during the COVID-19 pandemic and post-pandemic periods. Therefore, we aimed to evaluate the distribution of autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), and overlap syndromes (OS; mainly AIH/PBC) across two periods: pre-pandemic (historical cohort) and pandemic/post-pandemic (2020–2024). **Methods:** This analytical, observational, retrospective study included patients with AILD evaluated between 1990 and 2024 at a national referral center, with a minimum follow-up (FU) of 6 months. **Results:** This study represents the largest historical cohort of AILD reported in Mexico to date, including 519 patients: AIH (n = 259, 50%), PBC (n = 203, 39%), and OS (n = 57, 11%). Most patients were female (87%), with a median age at diagnosis of 52 years [IQR 39–59]. Median follow-up was 26 months [IQR 6–72]. At baseline, cirrhosis was present in 153 patients (30%), while an additional 91 patients (25%) who were initially non-cirrhotic developed cirrhosis during FU. Twenty-nine orthotopic liver transplants (OLT; 6%) were performed. Transplant-free survival for the entire cohort at 3, 5, 10, and 20 years was 88.5%, 84.8%, 82.5%, and 80.3%, respectively. AILD diagnoses increased by 48.6% during the last four years compared with the historical period (20.6 vs. 13.9 cases/year; $p < 0.001$), with the highest incidence observed during the COVID-19 pandemic and post-pandemic periods. Linear regression analysis demonstrated a significant upward trend in PBC frequency ($p = 0.021$) (Figure), unlike AIH and OS. Additionally, age at diagnosis progressively increased across the cohort ($p = 0.022$). Specifically, the probability of diagnosis at ≥ 60 years increased by 4% annually ($p = 0.003$; OR 1.04). **Conclusion:** A significant increase in AILD

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diagnoses was observed, particularly during and after the COVID-19 pandemic. PBC showed the greatest increase in frequency in the last decade. These findings highlight the urgent need to improve epidemiological surveillance and reporting of AILD. Furthermore, our data demonstrate a shifting demographic pattern characterized by an increasing age at diagnosis across the cohort.



Disclosures: Linda Muñoz-Espinosa:Nothing to Disclose, Samuel Rivas-Lopez:Nothing to Disclose, Paula Cordero-Perez:Nothing to Disclose, Giselle Banda-Alvarez:Nothing to Disclose, Alexandra Costilla-Martinez:Nothing to Disclose, Ricardo Rodriguez-Macias: Nothing to Disclose, Liliana Torres-González:Nothing to Disclose, Fernando Iglesias-Hernandez:Nothing to Disclose, Emilia Sepulveda-Gutierrez:Nothing to Disclose.

1253 | SWITCHING FROM OBETICHOLIC ACID TO NOVEL PPAR AGONISTS IN PRIMARY BILIARY CHOLANGITIS: EARLY MULTICENTER REAL-WORLD DATA FROM GERMANY

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Background: Primary biliary cholangitis (PBC) requires second-line therapy when response to ursodeoxycholic acid is insufficient. While bezafibrate has been used off-label for years, the recent withdrawal of obeticholic acid (OCA) from the European market resulted in a rapidly shifting treatment landscape. New PPAR agonists elafibranor and seladelpar are increasingly being introduced into clinical practice. Given limited real-world comparative data during this transition period, we evaluated treatment sequencing patterns and biochemical responses in a multicenter German cohort. **Methods:** PBC patients treated at Aachen, Bonn, and Düsseldorf were retrospectively included. Each initiation of OCA, bezafibrate, elafibranor, or seladelpar constituted a treatment episode. Baseline was defined as the closest laboratory value within −90/+14 days of start. Follow-up ended at switch, discontinuation, or last on-treatment test. Response was assessed at 3, 6, and 12 months using POISE-like criteria (AP $<1.67\times$ULN with $\geq 15\%$ reduction and normal bilirubin) and Paris-II criteria (AP $\leq 1.5\times$ULN, AST $\leq 1.5\times$ULN, bilirubin ≤ 1.0 mg/dL). **Results:** Forty-two patients (90% female, median age 56, 14% cirrhosis) contributed 76 episodes (bezafibrate 30, OCA 19, elafibranor 16, seladelpar 11).Response patterns varied by agent. Bezafibrate showed POISE/Paris-II responses of ~50% in early assessments and up to 75% Paris-II in later windows, with median AP reductions of −27.8% (early) and −44.0% (later). OCA responses were lower (POISE ~50% early, 20% later; Paris-II ~50% early, 22% later) with modest AP change (−8.6% to −15.7%). Elafibranor showed intermediate to favourable early responses (POISE 43%, Paris-II 50%) and higher later-window response (67% and 62%), with AP reductions of −17.3% to −19.9%. Seladelpar had limited follow-up but showed consistent biochemical improvement (POISE 17–25%, Paris-II 14–17%) with AP reductions of −22.5% to −20.4%.Overall, treatment sequencing was dominated by OCA → PPAR switching, and most elafibranor (75%) and seladelpar (82%) episodes occurred after prior therapy. Switch analyses suggested biochemical improvement after most OCA → PPAR transitions, although one patient showed progressive biochemical worsening across three therapies. Direct comparison between elafibranor and seladelpar is limited by differences in prior exposure and treatment time frames. **Conclusion:** In this real-world cohort, elafibranor and seladelpar were predominantly used after OCA exposure and were generally associated with biochemical improvement or response maintenance after switching. However, response magnitude and responder rates differed markedly by endpoint definition and treatment sequence. Comparative interpretation between agents is limited due to heterogeneous pretreatment and follow-up duration, and longer follow-up is needed for further analysis.

Therapy	n episodes	Median on-tx (days)	3 months			6 months			12 months				Cumulative on-treatment	
			POISE	Paris-II	Median ΔAP	POISE	Paris-II	Median ΔAP	POISE (on-tx)	POISE (ITT)	Paris-II	Median ΔAP	Best ΔAP	Ever AP ≤1.5×ULN
Bezafibrat	30	913	1/2 (50%)	2/4 (50%)	-27.8%	3/4 (75%)	4/9 (44%)	-44.0%	7/10 (70%)	7/18 (39%)	9/15 (60%)	-39.1%	-39.1%	10/15 (67%)
OCA	19	1096	1/2 (50%)	1/2 (50%)	-8.6%	1/5 (20%)	2/9 (22%)	-15.7%	1/4 (25%)	1/8 (12%)	2/7 (29%)	-30.4%	-33.4%	1/7 (14%)
Elafibranor	16	178	3/7 (43%)	5/10 (50%)	-17.3%	4/6 (67%)	5/8 (62%)	-19.9%	0/5 (0%)	0/16 (0%)	3/6 (50%)	-9.7%	-27.5%	8/13 (62%)
Seladelpar	11	163	1/6 (17%)	1/7 (14%)	-22.5%	1/4 (25%)	1/6 (17%)	-20.4%	-	0/11 (0%)	0/1 (0%)	-	-22.5%	2/8 (25%)

POISE-like response: AP <1.67×ULN AND ≥15% reduction from episode baseline AND total bilirubin ≤ULN.

Paris-II response: AP ≤1.5×ULN AND AST ≤1.5×ULN AND total bilirubin ≤1.0 mg/dL.

Intention-to-treat (ITT): episodes censored for switch or discontinuation before window upper bound were classified as non-responders.

Ever AP ≤1.5×ULN: proportion of episodes that achieved AP ≤1.5×ULN at any on-treatment laboratory.

– : not evaluable (no on-treatment laboratory within the corresponding window).

Across 76 second-line treatment episodes, biochemical response was assessed at three predefined on-treatment time-points using two complementary criteria: a POISE-like composite (AP <1.67×ULN with ≥15% reduction from episode baseline AND total bilirubin ≤ULN) and the Paris-II criteria (AP ≤1.5×ULN AND AST ≤1.5×ULN AND total bilirubin ≤1.0 mg/dL).

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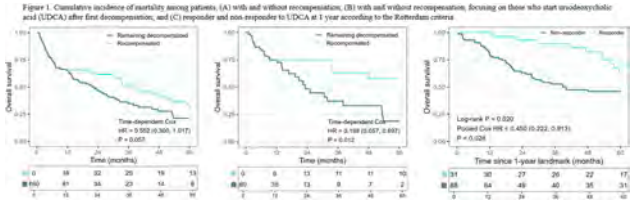
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Disclosures: Universitätsklinik Düsseldorf:Gilead Sciences: Speaking and Teaching, Abbvie: Speaking and Teaching, Smaranda Gliga:Nothing to Disclose, Carolin Angendohr:Nothing to Disclose, Paul Park:Nothing to Disclose, Tony Bruns:Ipsen: Advisor, Gileas: Advisor, Ipsen: Speaking and Teaching, Advanz / Intercept: Advisor, Karsten Grosse:Nothing to Disclose, Philipp Lutz:Nothing to Disclose, Johannes Chang:Nothing to Disclose, Hans Bock:Gilead: Speaking and Teaching, Abbvie: Speaking and Teaching, Ipsen: Speaking and Teaching, Abbvie: Travel grant, Tom Luedde:Nothing to Disclose.

1254 | RECOMPENSATION FOLLOWING PBC-DIRECTED THERAPY IS ASSOCIATED WITH IMPROVED TRANSPLANT-FREE SURVIVAL IN DECOMPENSATED PRIMARY BILIARY CHOLANGITIS: A MULTINATIONAL SOUTHEAST ASIAN STUDY

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Background: Clinical outcomes following hepatic recompensation in primary biliary cholangitis (PBC) have been predominantly characterized in Western population, with limited real-world data from Southeast Asia (SEA). The impact of PBC-directed treatment on recompensation in PBC remains unclear. We evaluated the incidence, predictors, and prognostic implications of clinical recompensation in a multinational Southeast Asian (SEA)-PBC cohort. **Methods:** This retrospective cohort study included adult with decompensated PBC cirrhosis from 9 tertiary centers within the SEA-PBC study group. The baseline was defined as the date of index decompensation. Patients were followed longitudinally until death, liver transplantation or last follow-up. Clinical recompensation was defined according to the Baveno VII criteria as the resolution of decompensation events for at least 12 months with discontinuation of medications for ascites and hepatic encephalopathy. The primary endpoint was transplant-free survival (TFS) beyond a 12-month landmark after index decompensation, stratified by recompensation status. Clinical recompensation was analyzed as a time-dependent covariate using cause-specific Cox regression models. **Results:** 160 decompensated PBC patients included (mean age 72.9 years, 81.9% female), 37 patients (23.1%) achieved clinical recompensation during a median follow-up of 16.6 (IQR: 5.6-41.0) months. Compared to those who remained decompensation, those with recompensation had a lower baseline Child-Pugh score and MELD ($p < 0.001$ for both). Clinical recompensation demonstrated a trend toward improved TFS compared with persistent decompensation (hazard ratio [HR] 0.55, 95% CI 0.30-1.02, $p = 0.057$) **(Figure 1A)** .Notably, patients who initiated ursodeoxycholic acid (UDCA) treatment after index decompensation and subsequently achieved recompensation had significantly superior TFS (HR 0.20, 95% CI 0.06-0.70, $p = 0.012$) **(Figure 1B)**, whereas no survival benefit was observed among patients already receiving UDCA prior to decompensation.Lower baseline MELD score (adjusted cause-specific HR 0.75, 95% CI 0.63-0.90, $p = 0.002$) and variceal hemorrhage as the index decompensation event (adjusted cause-specific HR 0.27 for ascites, 95% CI 0.11-0.67, $p = 0.005$) were independently associated with clinical recompensation. Among the established UDCA treatment response criteria, Rotterdam criteria best stratified TFS (HR 0.45, 95% CI 0.22-0.91, $p = 0.028$) **(Figure 1C)** . **Conclusion:** The association between post-decompensation UDCA initiation, recompensation, and improved outcomes highlights the importance of ongoing PBC-directed therapy even after hepatic decompensation. Rotterdam criteria may be used to define etiological control in PBC recompensation.



Disclosures: Jimmy Che-To Lai:Nothing to Disclose, Junlong DAI:Nothing to Disclose, Jarell Jie-Rae Tan:Nothing to Disclose, Karen Hei-Tung Lai:Nothing to Disclose, Alyssa Shin Yee Sim:Nothing to Disclose, Ian Yang Liew:Nothing to Disclose, Kanokwan Pinyopornpanish:Nothing to Disclose, Chitchai Rattananukrom:Nothing to Disclose, Apichat Kaewdech:Nothing to Disclose, Wah Kheong Chan:Nothing to Disclose, Guan Wee Wong:Nothing to Disclose, Joyce Shin Han Seah:Nothing to Disclose, Senam Kaur:Nothing to Disclose, Terry Cheuk-Fung Yip:Gilead Sciences:

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Consultant, Gilead Sciences: Speaking and Teaching, Gilead Sciences: Grant/Research Support, Altimmune: Advisor, GSK: Advisor, YU JUN WONG:Nothing to Disclose.

1255 | REAL-WORLD DISEASE BURDEN, OUTCOMES AND UNMET NEEDS IN PRIMARY BILIARY CHOLANGITIS: FINDINGS FROM THE MULTINATIONAL SEA-PBC COHORT

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Background: Contemporary understanding of primary biliary cholangitis (PBC) has been largely derived from Western populations, while real-world outcomes and treatment patterns in the Asia Pacific region remain poorly characterized. We aimed to evaluate treatment response, long-term clinical outcomes, and unmet therapeutic needs in a large multinational Southeast Asian PBC cohort. **Methods:** The SEA-PBC cohort is a retrospective international multicenter cohort comprising patients with PBC from 19 tertiary centers across Asia-Pacific region. Patients with autoimmune hepatitis (AIH)-PBC overlap syndrome were excluded. Biochemical response to ursodeoxycholic acid (UDCA) at 12 months was assessed using established response criteria including ALP normalization, Paris-II, POISE, and deep response (normal alkaline phosphatase [ALP] with bilirubin $< 0.6 \times$ upper limit of normal [ULN]). Clinical outcomes included hepatic decompensation, hepatocellular carcinoma (HCC), liver transplantation (LT), and transplant-free survival (TFS). Multivariable logistic and Cox-regression analyses were performed to identify predictors of treatment response and long-term outcomes, respectively. **Results:** A total of 1,776 PBC patients were included. Patients were predominantly female (83.4%) and anti-mitochondrial antibody positive (87.1%), with median age at diagnosis of 65 (54-74) years; 16.1% had cirrhosis at diagnosis. At presentation, 28.5% were symptomatic, including pruritus (17.3%), fatigue (13.5%), or sicca symptoms (6.4%).UDCA was prescribed in 79.9% of patients. In these patients, ALP normalization was achieved in 21.2%, Paris-II in 39.1%, POISE in 49.4%, and deep response in 18.7% after 12 months. Despite inadequate biochemical response in a substantial proportion of patients, uptake rate of second-line therapy remained low (16.1% fibrates, 0.3% obeticholic acid). Over a mean follow-up of 6.5 ± 5.5 years, 13.1% experienced hepatic decompensation, 4.0% developed HCC, and 0.8% underwent LT. Five-year transplant-free survival rates were 80.3%. Higher baseline ALP (per unit of ULN increase; adjusted hazard ratio [aHR] 1.07, 95% CI 1.03 - 1.12; $p = 0.001$) and increasing fibrosis category by Fibrosis-4 index (aHR 1.96, CI 1.62 - 2.37, $p < 0.001$) were independently associated with death or LT. **Conclusion:** This study of a large multinational Southeast Asian PBC cohort demonstrates substantial residual disease burden. Despite UDCA therapy, biochemical remission and deep response rate remained modest, yet the uptake of second-line therapy remained strikingly low. Persistent adverse liver-related outcomes highlight important unmet needs in risk stratification, timely treatment escalation and equitable therapies for Asian patients with PBC.

Disclosures: Eileen Chua:Nothing to Disclose, Karen Lai:Nothing to Disclose, Ian Liew:Nothing to Disclose, Jarell Tan:Nothing to Disclose, Abhimati Ravikulan: Nothing to Disclose, Kanokwan Pinyopornpanish:Nothing to Disclose, Kessarin Thanapirom:Nothing to Disclose, Wah Kheong Chan:Nothing to Disclose, Apichat Kaewdech:Nothing to Disclose, Chitchai Rattananukrom:Nothing to Disclose, Soe Thiha Maung: Nothing to Disclose, Guan Wee Wong:Nothing to Disclose, Shao-Li Huang:Nothing to Disclose, Tung-Hung Su:Nothing to Disclose, Garrett Kang:Nothing to Disclose, Haniza Omar:Nothing to Disclose, Soek-Siam Tan:Nothing to Disclose, Lin Lee Wong:Nothing to Disclose, Tâm Nguyễn Thanh:Nothing to Disclose, Đào Việt Hằng:Nothing to Disclose, Anand Kulkarni:Nothing to Disclose, Senam Kaur:Nothing to Disclose, Jing Hieng Ngu:Nothing to Disclose, Alyssa Sim:Nothing to Disclose, Jimmy Che-To Lai Lai:Nothing to Disclose, Yu Jun Wong:Nothing to Disclose.

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1256 | BINATIONAL COMPARISON OF AUTOIMMUNE HEPATITIS ACROSS MEXICO CITY AND US REVEALS DISTINCT ENDOTYPES, EQUIVALENT TREATMENT RESPONSE, AND EARLY SURVIVAL DISADVANTAGE FOR HISPANIC PATIENTS WITH CIRRHOSIS

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Background: Hispanic patients with autoimmune hepatitis (AIH) are reported to have increased prevalence of cirrhosis at presentation, yet whether this reflects biological differences, diagnostic delay, or limited care access remains unresolved. We tested this question by comparing phenotype, treatment response, and transplant-free survival (TFS) between Mexican (entirely Hispanic) and US (mostly non-Hispanic White) patients. **Methods:** We analyzed 699 AIH patients from Mexico City (MC, n = 185, 93% Hispanic) and Indiana University (IU, n = 514, 4% Hispanic) using multivariable Cox regression, landmark analyses at 6 months, and logistic regression for predictors of incomplete remission. To control for an average 7-year age difference between cohorts at diagnosis, we performed a 1:1 age- and sex-matched analysis (±5 years; n = 322) with time-split Cox models to assess an early survival gap among cirrhotic patients. **Results:** MC patients had a classic autoimmune phenotype: higher IgG (2,311 vs. 1,521 mg/dL), ANA positivity (99% vs. 67%), and anti-LKM positivity (14% vs. 2%) (Table 1). IU patients had a metabolic phenotype: higher BMI (28.4 vs. 26 kg/m²), ALT at diagnosis (170 vs. 69 U/L), and MASH features on biopsy (54% vs. 5%; all p < 0.001). MC patients remained on steroid treatment throughout follow-up (48% on prednisone at most recent visit vs. 17% at IU), while IU shifted maintenance to MMF (29% vs. 9%; all p < 0.001).Despite these differences, biochemical remission at 6 months was identical (50% MC vs. 53% IU, p = 0.64). Incomplete remission was predicted by cirrhosis at diagnosis (OR 5.1, 95% CI 1.87–13.92, p = 0.001), not site or ethnicity. In the full cohort, site did not independently predict TFS after adjustment for cirrhosis, albumin, and sex (HR 0.7, 95% CI 0.44–1.13, p = 0.15), with landmark analyses confirming no residual site effect at 6 months.In the matched cohort, overall TFS was similar (5-year: 85% MC vs. 93% IU; log-rank p = 0.18), but MC patients had a 2.6-fold higher hazard of transplant or death in the first 5 years (HR 2.58, 95% CI 1.14–5.86, p = 0.023), confined to those with cirrhosis at diagnosis (5-year TFS: 58% MC vs. 85% IU, log-rank p = 0.04). Non-cirrhotic patients had equivalent TFS at both sites (97% at 5 years each) and similar incident cirrhosis development (11% vs. 13%, p = 0.88). **Conclusion:** AIH patients present as two distinct endotypes in our cohorts; MC with classic autoimmune phenotype and IU with metabolic phenotype, yet both had equivalent outcomes. Cirrhosis, sex, and albumin are drivers of TFS, not treatment site or ethnicity. An early survival disadvantage of MC patients is confined to patients with cirrhosis.

Table 1. Comparison of AIH Across Mexico City (MC) and Indiana University (IU): Phenotype, Treatment, Response, and Outcomes

Variable	IU	MC	p-value
Demographics - FULL COHORT (IU n=514, MC n=185)			
N	514	185	—
Age at diagnosis, years, median (IQR)	50 (36–59)	41 (28–52)	**<0.001**
Female sex, n (%)	395 (78%)	143 (79%)	0.75
Cirrhosis at diagnosis, n (%)	111/452 (25%)	57/179 (32%)	0.08
Disease Phenotype - MATCHED COHORT (161 per site)†			
IgG, mg/dL, median (IQR)	1,521 (1,212–2,232)	2,311 (1,742–3,014)	**<0.001**
ANA positive, n (%)	88/131 (67%)	158/159 (99%)	**<0.001**
Anti-LKM positive, n (%)	1/55 (2%)	20/144 (14%)	**0.01**
BMI, kg/m², median (IQR)	28.4 (24.0–37.3)	26 (23.4–28.4)	**<0.001**
ALT at diagnosis, U/L, median (IQR)	170 (64–536)	69 (30–206)	**<0.001**
MASH features on biopsy, n (%)	71/132 (54%)	7/152 (5%)	**<0.001**
Cirrhosis at diagnosis, n (%)	36/145 (25%)	50/160 (31%)	0.26
Transplant-Free Survival — FULL COHORT (n=699)			
Adjusted HR, site — MC vs IU (95% CI)	Reference	0.7 (0.44–1.13)	0.15
Adjusted HR, cirrhosis at diagnosis (95% CI)	—	3.76 (2.34–6.03)	**<0.001**
Landmark HR at 6 months (95% CI)	Reference	1.33 (0.77–2.30)	0.31
Transplant-Free Survival — MATCHED COHORT† (161 per site)			
5-year TFS, overall	93%	85%	0.18†
5-year TFS — no cirrhosis at diagnosis	97%	97%	0.61†
5-year TFS — cirrhosis at diagnosis	85%	58%	**0.04†**
Adjusted HR, years 0–5 after diagnosis (95% CI)§	Reference	2.58 (1.14–5.86)	**0.02**
Adjusted HR, years >5 after diagnosis (95% CI)§	Reference	0.71 (0.26–1.91)	0.5
Incident cirrhosis (non-cirrhotic subgroup), n (%)	14/107 (13%)	12/110 (11%)	0.88†

Continuous variables: median (IQR), Mann–Whitney U test. Categorical: n (%), chi-square or Fisher's exact test.
† Matched cohort: 1:1 match on sex and age at diagnosis (±5 years). Total n=322.
§ Cox proportional hazards model restricted to years 0–5 or >5, adjusted for cirrhosis at diagnosis. Time-split analysis pre-specified.
‡ KM-based estimates; p-values are log-rank tests.

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Grant/Research Support, NIH: Grant/Research Support, Heligenics: Board member, investor, Avant Sante: Board member, investor, Ipsen, Biomea Fusion, Pfizer, Merck: Consultant, Craig Lammert:Eli Lilly: Consultant, Kezar Life Sciences: Consultant, Amgen: Consultant, Autoimmune Hepatitis Association: Consultant, RegCell: Consultant, Regeneron: Consultant.

1257 | ADULT TYPE 2 AUTOIMMUNE HEPATITIS: AN IMPORTANT CLASSIFIER OF DISEASE COURSE TO RECOGNISE

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Background: Data on adults living with type two autoimmune hepatitis (AIH-2) is infrequent, given how rare it is. Recent international guidelines advise against classifying adult patients (pts) with AIH based on autoantibody profiles. We sought to describe the clinical characteristics and outcomes of adult pts with AIH-2. **Methods:** We performed a multi-centre (4 centres, 2 countries) retrospective cohort study including pts from 1st January 2017 to 1st May 2026, with a clinical diagnosis of AIH and strongly positive liver-kidney microsomal-1 (LKM-1) and/or liver-cytosol 1 (LC-1) antibodies. **Results:** One hundred and one pts with AIH-2 were identified. Ninety-three (92%) were female, with a median age of 20 (IQR 12-31) years at diagnosis and 34 (IQR 25-52) years at last follow-up. Seventy-six (76%) pts were LKM-1 positive, 33 (33%) were LC-1 positive, and 9 pts had both autoantibodies. The most common clinical presentation was chronic hepatitis (n = 54, 53%), followed by acute hepatitis (n = 22, 23%). Thirty-five (35%) patients had other autoimmune conditions. Twenty-one (21%) pts had relapses at a median of 3.7 (3-5.4) years from diagnosis, and 56 (55%) were on prednisone at last follow-up. Forty-one (41%) pts were on azathioprine and 24 (24%) on mycophenolate maintenance therapy. Twenty-one (21%) pts required third-line therapies (tacrolimus n = 17, cyclosporin n = 2, sirolimus = 1, rituximab n = 1) and three (3%) were on ursodeoxycholic acid. Fifty-nine (58%) pts were diagnosed in adulthood; there were no significant differences in baseline demographics and clinical characteristics between pts with pediatric and adult-onset disease. Adult-onset disease was characterized by a trend toward higher alanine transaminase (145 vs 40 IU/L, p = 0.06) at presentation, a shorter time to first episode of relapse (3.1 vs 4.2 years, p = 0.02), and a higher proportion of cirrhosis at diagnosis and last follow-up (p = 0.01). Eighteen (18%) pts received a liver transplant. **Conclusion:** As AIH-2 is so rare, limited adult data is available. In our large cohort study, we observe a more severe disease phenotype in adult-onset disease and high corticosteroid dependence in the entire cohort. These distinctions, identified by serologic classification, are important for guiding patient care.

Table: Demographics and clinical characteristics of AIH-2 stratified by pediatric or adult-onset disease

Variables	Pediatric onset (n=39)	Adult onset (n=59)	p-value
Age at diagnosis, years, median (IQR)	11 (6.5-15)	28 (21-42)	<0.001
Follow up, years, median (IQR)	17 (9-23)	10 (5-17)	0.04
Female, n (%)	37 (95)	53 (90)	0.60
White, n (%)	28 (74)	44 (75)	0.86
Overlap syndrome, n (%)			0.22
None	35 (90)	56 (95)	
PSC	4 (10)	2 (3.4)	
PBC	0 (0)	1 (1.7)	
Other autoimmune conditions, n (%)	13 (33)	19 (32)	1.0
Clinical presentation, n (%)			0.71
Chronic hepatitis	24 (61)	30 (51)	
Acute hepatitis	9 (23)	13 (22)	
Acute severe hepatitis	3 (8)	11 (19)	
Acute liver failure	1 (2.6)	2 (3.4)	
Acute on chronic liver failure	1 (2.6)	1 (3.4)	
LKM-1 positive, n (%)	32 (82)	42 (71)	0.32
LC-1 positive, n (%)	11 (28)	22 (37)	0.44
Labs at diagnosis, median (IQR)			
IgG (IU/L)	15 (12-27)	18 (13-25)	0.42
Bilirubin (μmol/L)	18 (10-86)	40 (14-195)	0.12
Alkaline phosphatase (IU/L)	147 (75-308)	132 (91-219)	0.79
Alanine transaminase (IU/L)	40 (23-345)	145 (53-457)	0.06
Aspartate aminotransferase (IU/L)	82 (28-638)	210 (48-508)	0.24
INR	1.2 (1.1-1.4)	1.2 (1-1.5)	0.87
Platelets (x10^9/L)	213 (136-265)	130 (74-206)	0.12
Cirrhotic at diagnosis, n (%)	9 (23)	23 (39)	0.16
Liver stiffness at diagnosis, kPa, median (IQR)	9 (7-12)	13 (8-17)	0.38
Liver transplant, n (%)	6 (15)	12 (20)	0.73
Liver transplant indication, n (%)			0.18
End-stage liver disease	4 (80)	6 (50)	
Acute liver failure	0 (0)	3 (25)	
Other	0 (0)	2 (18)	
Unknown	2 (20)	1 (8.3)	
Time to relapse, years (median, IQR)	4 (4-13)	3 (2-4)	0.02
Prednisone at last follow up, n (%)	22 (56)	33 (59)	0.74

*Three patients had unknown date of diagnosis

Abbreviations: IgG; immunoglobulin G; INR; international normalised ratio, kPa; kilopascals, LC-1; anti-liver cytosol 1 antibody; LKM-1; liver-kidney microsomal type 1 antibody, PBC; primary biliary cholangitis, PSC; primary sclerosing cholangitis

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1258 | LARGE-SCALE UNTARGETED PLASMA METABOLOMICS REVEALS SYSTEMIC DISEASE-ASSOCIATED METABOLIC SIGNATURES IN PRIMARY SCLEROSING CHOLANGITIS AND PRIMARY BILIARY CHOLANGITIS

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Background: Primary sclerosing cholangitis (PSC) and primary biliary cholangitis (PBC) are rare immune-mediated cholestatic liver diseases with incompletely understood pathogenesis and limited therapeutic options. Environmental, microbial, and metabolic factors are increasingly recognized as potential contributors to cholestatic liver disease biology. We aimed to define plasma metabolic alterations associated with PSC and PBC by performing a large, comprehensive, untargeted-metabolomic analysis of PSC and PBC patients and matched controls. **Methods:** Plasma samples from patients with PSC (n = 800), PBC (n = 600), and matched controls (PSC controls n = 800, PBC controls n = 600) underwent untargeted metabolomics analysis using ultra-high-resolution liquid chromatography coupled with high-resolution accurate mass spectrometry to profile thousands of small-molecule metabolic features. The dataset was split into exploration and validation cohorts. Metabolic features were extracted with ASARI and annotated using khipu, HMDB, LipidMaps, and microbial metabolite database MIMEDB. Feature-level comparisons between disease and control groups were performed with age- and sex-adjusted linear models. Differentially abundant features were prioritized based on reproducibility across cohorts, annotation confidence, and evidence for microbial or host metabolic origin. **Results:** Both PSC and PBC showed extensive plasma metabolic differences compared with matched controls across HILIC and C18 chromatography columns. Age- and sex-adjusted models identified thousands of differentially abundant features in the exploration cohort, including hundreds of putatively annotated signals in each disease group. Similar disease-associated signals were observed in the validation cohort, supporting reproducibility across independent analytical subsets. Across study, disease, and chromatographic mode comparisons, more than 100 common differentially abundant annotations were recurrently detected, with both increased and decreased abundance in patients. These signals mapped to metabolic processes relevant to cholestatic liver disease, including bile acid and lipid-related metabolism, and putative microbial-derived metabolites supporting a link between these diseases and systemic host-microbial metabolic perturbation. **Conclusion:** PSC and PBC are associated with substantial alterations in the plasma metabolome compared with matched controls, including signals consistent with host metabolic dysregulation and host-microbial co-metabolism. A subset of differentially abundant features mapped to microbial metabolites through MIMEDB, supporting a potential contribution of gut microbial metabolism to systemic metabolic changes in cholestatic liver disease. This large-scale untargeted metabolomics study identifies reproducible disease-associated metabolic signatures and provides a foundation for discovering novel biomarkers and biological pathways relevant to PSC and PBC pathogenesis.

Disclosures: Marios Nikolaidis:Nothing to Disclose, Brian Juran:Nothing to Disclose, Bryan Mccauley: Nothing to Disclose, Erik Schlicht:Nothing to Disclose, Jackie Bianchi:Nothing to Disclose, Ahmad Ali:Nothing to Disclose, Elizabeth Atkinson:Nothing to Disclose, Garry Miller:Nothing to Disclose, Dean Jones:Nothing to Disclose, Grigorios Amoutzias:Nothing to Disclose, Konstantinos Lazaridis:Nothing to Disclose.

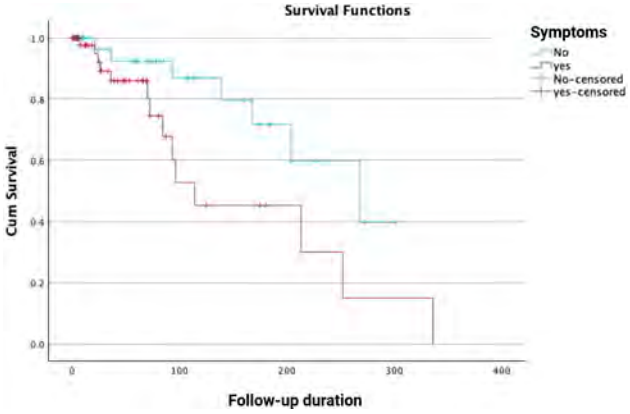
1259 | BASELINE SYMPTOMS PREDICT WORSE SURVIVAL IN NON-CIRRHOTIC AUTOIMMUNE HEPATITIS DESPITE SIMILAR DISEASE SEVERITY: A REAL-WORLD COHORT STUDY

Christos Triantos[1] Konstantinos Papantoniou[1] Vasileios Lekakis[2] Ioanna Aggeletopoulou[1] Maria Bali[1] Odyssefs Ampazis[1] Georgia Diamantopoulou[1] Konstantinos Thomopoulos[1], [1]Division of Gastroenterology, Department of Internal Medicine, University of Patras, 26504, Patras, [2]First Academic Department of Gastroenterology, Medical School of National, Laiko General Hospital,

Background: The prognostic significance of symptomatic presentation in autoimmune hepatitis (AIH) remains unclear. While asymptomatic patients are often considered to have milder disease, available evidence is inconsistent (DOI: 10.1016/j.cgh.2025.04.034). We evaluated whether symptom status at diagnosis is

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associated with disease severity, disease progression, and survival in AIH. **Methods:** We retrospectively analyzed 116 patients with AIH followed at a tertiary referral center. Patients were classified as symptomatic or asymptomatic at diagnosis. Baseline cirrhosis, hepatic decompensation, hepatocellular carcinoma (HCC), and disease progression during follow-up were compared between groups. Overall survival was evaluated using Kaplan–Meier analysis and Cox regression models. **Results:** The cohort included 116 patients (81.9% female) with a median age of 54 years (IQR 42–65); 58.8% were symptomatic at diagnosis. Median follow-up was 48 months (IQR 10–108), and overall mortality was 21.2%. Baseline cirrhosis (22.4% vs 17.0%, p = 0.482), hepatic decompensation (18.8% vs 12.5%, p = 0.699), and HCC (1.5% vs 0%, p = 0.400) were similar between symptomatic and asymptomatic patients. During follow-up, no differences were observed in cirrhosis progression (25.4% vs 21.7%, p = 0.656), hepatic decompensation (41.2% vs 40.0%, p = 0.952), or HCC development (3.0% vs 0%, p = 0.439). Survival was analyzed according to baseline cirrhosis status. Among patients with cirrhosis at diagnosis, symptom status was not associated with survival (log-rank p = 0.142). In 93 patients without cirrhosis at first visit, 53 (60.2%) had symptoms at baseline. Jaundice was the most commonly reported symptom (35.5%), followed by fatigue (9.7%), non-specific symptoms (9.7%) and arthralgias (2.2%). Among non-cirrhotic patients, symptomatic presentation was associated with significantly worse survival (log-rank p = 0.037). In Cox regression analysis, baseline symptoms were independently associated with poorer survival (HR 2.62, 95%CI 1.03–6.69, p = 0.044). **Conclusion:** Symptom status at diagnosis was not associated with baseline disease severity or disease progression in AIH. However, among non-cirrhotic patients, symptomatic presentation was associated with worse overall survival. These findings suggest that symptoms at presentation may identify non-cirrhotic patients at increased risk for adverse long-term outcomes.



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1260 | RECURRENT PRIMARY SCLEROSING CHOLANGITIS AFTER LIVER TRANSPLANTATION IS ASSOCIATED WITH PERSISTENT ENDOSCOPIC INFLAMMATORY BOWEL DISEASE ACTIVITY INDEPENDENT OF COLECTOMY: THE ERA OF ADVANCED THERAPY

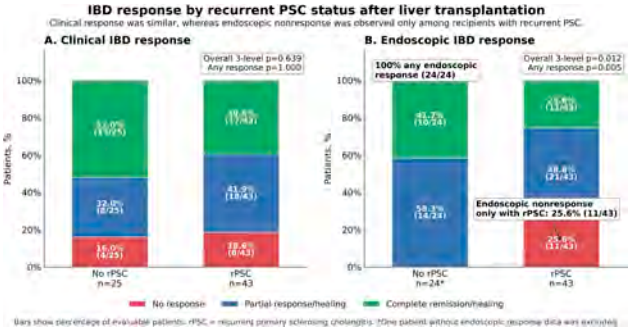
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Background: Recurrent primary sclerosing cholangitis (rPSC) after liver transplantation (LT) compromises allograft and patient survival. The gut-liver axis implicates intestinal inflammation in rPSC pathogenesis, and pretransplant colectomy has been reported to be protective. The relationship between post-LT inflammatory bowel disease (IBD) clinical and endoscopic (mucosal) activity and risk of rPSC in the era of advanced IBD therapy remains poorly defined. We examined associations among post-LT response to IBD therapy, colectomy status, and risk of rPSC. **Methods:** We performed a retrospective 3-center cohort study of LT recipients between 1992-2022 who received a LT for PSC and who had associated IBD for which they received advanced IBD therapy after LT. rPSC was defined by established cholangiographic and/or histologic criteria after exclusion of secondary causes. Post-LT IBD activity was categorized by clinical disease activity based on symptoms (none/partial/complete remission) and endoscopic remission based on disappearance of ulcerations in Crohn's disease (CD) and Mayo endoscopic subscore ≤ 1 in ulcerative colitis (UC) (none/partial mucosal healing/complete remission). Colectomy status, type and timing relative to LT were recorded. Patients with and without rPSC were compared using Fisher exact and Wilcoxon rank-sum tests. **Results:** Among 68 patients (UC 64.7%, CD 33.8%, IC 1.5%; 66.1% male; mean age 39.5 ± 12.8 years; mean MELD at transplant 20.9), rPSC developed in 63.2% (43/68) over similar follow-up time compared to patients without rPSC (median 5.7 vs 4.5 years; p = 0.28). Endoscopic response to therapy strongly separated the groups: every patient without rPSC achieved an

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endoscopic response (24/24, 100%) versus 74% (32/43) with rPSC (p = 0.005), and absence of any endoscopic response occurred only in the rPSC group (11/43, 26% vs 0/24, 0%; p = 0.012). In contrast, clinical IBD response did not predict PSC recurrence: any clinical response occurred in 35/43 (81.4%) with rPSC and 21/25 (84.0%) without rPSC (p = 1.0); complete clinical remission occurred in 17/43 (39.5%) and 13/25 (52.0%), respectively (p = 0.639). Colectomy was not associated with rPSC (any colectomy 56% vs 52%; p = 0.81), irrespective of timing relevant to LT (pre-LT 28% vs 24%; post-LT 28% vs 28%) or surgical type (proctocolectomy with IPAA vs. proctocolectomy with end ileostomy vs. partial colectomy or no colectomy) (p = 0.969). **Conclusion:** In LT recipients with PSC-IBD who received advanced IBD therapy, persistent endoscopic mucosal inflammation, but not clinical symptoms or colectomy status, was associated with the risk of rPSC. This finding suggests that ongoing mucosal inflammation drives the gut-liver axis and that colectomy alone may not be sufficient to mitigate risk, supporting continued aggressive control of mucosal inflammation after LT to protect the liver allograft and warranting prospective study.



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1261 | GLP-1 RECEPTOR AGONISTS IN A VULNERABLE BILIARY TREE: REAL-WORLD BILIARY AND LIVER OUTCOMES IN PRIMARY SCLEROSING CHOLANGITIS WITH TYPE 2 DIABETES

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Background: The biliary safety of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) in primary sclerosing cholangitis (PSC) is uncertain. We evaluated ERCP utilization, bile duct obstruction, and incident cirrhosis among adults with PSC and type 2 diabetes treated with GLP-1 RA/GLP-1-GIP therapy versus no documented GLP-1 exposure. **Methods:** We performed a retrospective TriNetX cohort study of adults with PSC and type 2 diabetes. GLP-1 exposure included GLP-1 analogues, semaglutide, liraglutide, dulaglutide, lixisenatide, or tirzepatide. The comparator cohort had no documented GLP-1 RA/GLP-1-GIP exposure. Outcomes began 1 day after the medication were started. Propensity-score matching yielded 103 patients per group from 115 exposed and 695 unexposed patients. Patients with the outcome before follow-up were excluded from that outcome analysis. Outcomes were analyzed using risk estimates, Kaplan-Meier analysis, hazard ratios (HRs), log-rank testing, and number of outcome instances. **Results:** After matching, mean follow-up was 1192.4 ± 1098.9 days in the GLP-1 group and 1243.7 ± 1231.4 days in the non-GLP-1 group. ERCP utilization occurred in 13/86 GLP-1-exposed patients versus 18/77 unexposed patients (15.1% vs 23.4%; risk difference [RD] -8.3%, 95% CI -20.4% to 3.9%, p = 0.18; risk ratio [RR] 0.647, 95% CI 0.34-1.23; HR 0.63, 95% CI 0.31-1.28; log-rank p = 0.2). Bile duct obstruction occurred in 12/78 versus 16/61 patients (15.4% vs 26.2%; RD -10.8%, 95% CI -24.5% to 2.8%, p = 0.11; RR 0.6, 95% CI 0.3-1.15; HR 0.6, 95% CI 0.23-1.25; log-rank p = 0.16). Incident cirrhosis rates were similar: 13/64 versus 12/55 patients (20.3% vs 21.8%;

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RD -1.5%, 95% CI -16.2% to 13.2%, p = 0.84; RR 0.93, 95% CI 0.46-1.87; HR 1.14, 95% CI 0.51-2.55; log-rank p = 0.76). Mean ERCP instances were similar (3.15 vs 3.17, p = 0.98). **Conclusion:** In this propensity-matched real-world cohort, GLP-1 RA/GLP-1-GIP exposure was associated with numerically lower ERCP utilization and bile duct obstruction, but differences were not statistically significant, and incident cirrhosis was similar. Findings require cautious interpretation given observational design, coding-based ascertainment, residual confounding, and limited granular data on PSC severity, dose, and treatment duration.

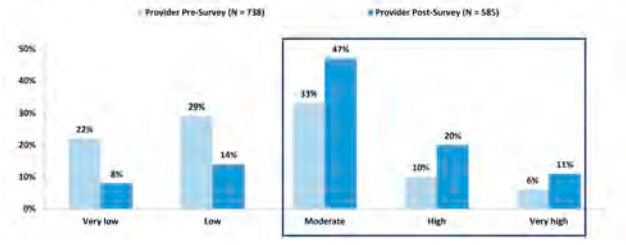
Disclosures: chimezirim ezeano:Nothing to Disclose, Sarpong Boateng:Nothing to Disclose, Ihunanya Kanu: Nothing to Disclose, GUY LOIC NGUEFANG TCHOUKEU:Nothing to Disclose, Emeka Stanley Obi:Nothing to Disclose, IFELUNWA OSANAKPO:Nothing to Disclose, Cherechi Nwabueze:Nothing to Disclose, Onyinyechukwu Ozumba:Nothing to Disclose, Goodness Joseph:Nothing to Disclose, David Narvaez-De los Rios:Nothing to Disclose, Samuel Ayedun:Nothing to Disclose, Chimezie Madu:Nothing to Disclose, Angel Umahi:Nothing to Disclose.

1262 | PBC.CARE WEB APPS: TETHERED PATIENT-PROVIDER TOOLS TO SUPPORT SHARED DECISION-MAKING AND TREATMENT OPTIMIZATION IN PRIMARY BILIARY CHOLANGITIS

Robert Gish[1] Ibiagbani Max-Harry[2] Chelsie Anderson Chadha[2] Jeffrey Carter[2] Megan McLafferty[2] Jennifer Balmer[2] Leah Molloy[2] Laura Simone[2] Cherilyn Heggen[2], [1]Robert G Gish Consultants LLC, [2]PRIME Education

Background: The treatment landscape for primary biliary cholangitis (PBC) has advanced significantly with recent approvals of second-line therapies targeting disease progression and symptoms; however, optimal outcomes remain contingent on effective patient-provider communication and timely treatment escalation. To address the ongoing need for education and shared decision-making, we developed and evaluated companion patient-provider web apps hosted at https://pbc.care/. **Methods:** Patients and providers accessed PBC-focused learning modules and opt-in survey assessments evaluating perceptions, behaviors and clinical practices. Web apps were disseminated nationwide and implemented at 5 hepatology/gastroenterology clinics through workshops, with a follow-up survey conducted post-implementation to evaluate impact. **Results:** Between December 2025 and April 2026, 1430 providers and 749 patients/caregivers accessed the web apps, and surveys were completed by 738 providers (37% physician, 20% NP/PA, 43% other) and 365 patients/caregivers (51% patient, 49% caregiver). Among patients/caregivers, 77% reported moderate-to-extreme impact of PBC on quality of life (QoL). Although 64% reported confidence in discussing symptoms with their provider, only 27% reported doing so regularly. Key barriers included perceptions that symptoms were not taken seriously (22%), insufficient appointment time (18%), and uncertainty describing symptoms (15%). Only 34% of patients felt knowledgeable on when to consider second-line therapy. At baseline, only 46% of providers regularly assessed the impact of PBC symptoms on QoL, and 36% did not consider patient goals/preferences essential to improving outcomes. Web app engagement increased the proportion of providers with confidence in PBC diagnosis and symptom assessment (49% to 78%, p < .0001; figure) and evaluating response to first-line therapy (51% to 65%, p < .0001). Additionally, 60% of providers reported intent to regularly assess the QoL impact of PBC symptoms. The top action providers intended to take after using the web app was providing patients with PBC resources to support shared-decision making. Specialty clinics implementing web apps reported improvement in patient education, symptom control, and QoL. **Conclusion:** Persistent gaps in patient-provider communication, symptom assessment, and treatment escalation remain, however, digital educational tools have potential to improve communication, confidence, and patient-centered PBC care.

Figure. Changes in Provider Confidence in PBC Diagnosis and Symptom Assessment Following Web App Engagement



Disclosures: Robert Gish:Genlantis, HepQuant, HepaTx, Virion: Stock – privately held company, Gilead Sciences, GlaxoSmithKline, HHHbio, Helio, HepQuant, Intercept, Ipsen, Madrigal,: Consultant, Mirum, Precision BioSciences, Prodigy, Topography Health, Tune Therapeutics, Virion, Quest: Consultant, AbbVie, AstraZeneca, BlueJay Therapeutics, Brii Bio, EIT Pharma, Genlantis, Gerson Lehrman Group: Consultant, Gilead Sciences Inc., Intercept, Ipsen Biopharmaceuticals, Madrigal, Mallinckrodt, Mirum: Speaking and Teaching, Syneos Health: Data Safety Monitoring Board, Genlantis, Gilead, HepaTX, HepQuant, Intercept, Prodigy: Leadership in Related Society, Board, Journal, Ibiagbani Max-Harry:Nothing to Disclose, Chelsie Anderson Chadha:Nothing to Disclose, Jeffrey Carter:Nothing to Disclose, Megan McLafferty:Nothing to Disclose,

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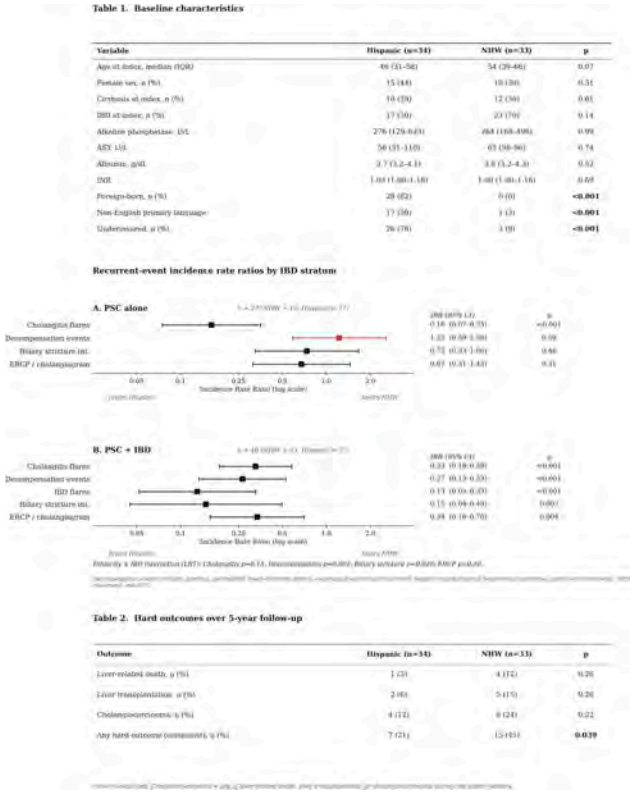
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Jennifer Balmer:Nothing to Disclose, Leah Molloy: Nothing to Disclose, Laura Simone:Nothing to Disclose, Cherilyn Heggen:Nothing to Disclose.

1263 | IBD STATUS MODIFIES ETHNIC DIFFERENCES IN RECURRENT CLINICAL EVENTS IN PRIMARY SCLEROSING CHOLANGITIS

Andrew John Cruz[1] Paul Yoon[1] Gevork Salmastyan[1] Mohamed Mahmoud[1] Jeffrey Kahn[2] Saro Khemichian[2] Damie Odufalu[2] Lily Dara[2], [1]USC/LAG, [2]University of Southern California

Background: Longitudinal PSC data come mostly from transplant registries, capturing endpoints but missing preceding disease activity. PSC-IBD is a phenotype distinct from PSC-alone, yet whether ethnic differences in event rates depend on IBD status is unknown. We compared recurrent hepatobiliary and IBD events in Hispanic vs non-Hispanic White (NHW) PSC patients, stratified by IBD at diagnosis. **Methods:** Retrospective cohort of patients diagnosed May 2001–Feb 2021, followed through May 2026 with 5-year follow-up at dual institutions (Table 1). PSC required cholestatic biochemistry, characteristic cholangiography, and exclusion of secondary causes. Event outcomes: cholangitis, decompensation, IBD flares, ERCP, stricture interventions. Hard outcomes: liver-related death, transplantation, cholangiocarcinoma. Rates per 100 person-years (PY) were compared by Poisson regression with offset, stratified by IBD; ethnicity×IBD interaction tested by likelihood ratio. **Results:** 67 patients (NHW = 33, Hispanic = 34) contributed 291 PY: 27 PSC-alone (105 PY), 40 PSC-IBD (186 PY). In PSC-alone, Hispanic patients had lower cholangitis rates (IRR 0.16, 95% CI 0.07–0.35; $p < 0.001$); decompensation, ERCP, and stricture intervention rates were similar (Figure A). In PSC-IBD, Hispanic ethnicity was associated with lower rates across all outcomes: cholangitis 0.33 ($p < 0.001$), decompensation 0.27 ($p < 0.001$), IBD flares 0.13 ($p < 0.001$), stricture interventions 0.15 ($p = 0.002$), ERCP 0.34 ($p = 0.004$) (Figure B). Ethnicity×IBD interaction was significant for decompensation ($p = 0.002$) and stricture interventions ($p = 0.020$). Any composite hard outcome (death, transplantation, or cholangiocarcinoma; Table 2) was less frequent in Hispanic patients (7/34 vs 15/33, $p = 0.039$). **Conclusion:** Ethnic differences in PSC burden appear phenotype-specific: lower recurrent-event burden in Hispanic PSC-IBD, and limited differences in PSC-alone. The significant ethnicity×IBD interaction—particularly for decompensation and stricture interventions—suggests against access or ascertainment bias alone, which would affect both similarly. The disparity extended to composite hard outcomes, beyond recurrent activity to clinically meaningful endpoints. These findings raise the possibility that gut-liver immune interactions, microbiome composition, dietary factors, or environmental exposures contribute to ethnic heterogeneity in PSC. Multicenter studies with immune and microbiome phenotyping are needed; IBD stratification should be routine in PSC outcome studies.



Disclosures: Andrew John Cruz:Nothing to Disclose, Paul Yoon:Nothing to Disclose, Gevork Salmastyan: Nothing to Disclose, Mohamed Mahmoud:Nothing to Disclose, Jeffrey Kahn:Nothing to Disclose, Saro Khemichian:Nothing to Disclose, Damie Odufalu:Nothing to Disclose, Lily Dara:Intercept Pharmaceuticals: Consultant, Intercept Pharmaceuticals: Grant/ Research Support, Kezar Pharmaceuticals: Consultant, Agios: Consultant, Amgen: Consultant, OPKO: Consultant, Mirum: Consultant, Ipsen: Consultant.

1264 | DETANGLING INCOMPLETE URSODEOXYCHOLIC ACID RESPONSE ACCORDING TO PARIS-II CRITERIA: HIGH AST RATHER THAN ALP HAS CRITICAL PROGNOSTIC IMPLICATIONS

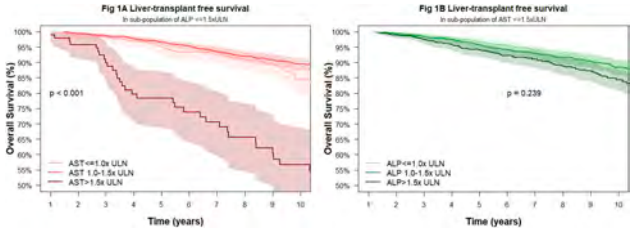
Gemma H.X. Weijsters[1] Ellen Werner[1] Tiki Blom[1] Merle M.F. Vos[1] Maria van Hooff[2] Rozanne de Veer[1] Ulrich Beuers[3] Joost Drenth[3] Frans J.C. Cuperus[4] Remco van Dijk[5] Bart Veldt[6] Michael Klemt-Kropp[7] Suzanne van

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Background: Studies on primary biliary cholangitis (PBC) have focused on alkaline phosphatase (ALP) as surrogate marker for long-term clinical outcome, while aspartate aminotransferase (AST) is associated with disease progression as well. The aim of this study was to compare long-term outcome between subgroups of AST and ALP after 1 year of ursodeoxycholic acid (UDCA) initiation based on PARIS-II cut-offs (1.5x upper limit of normal [ULN]) among people with PBC. **Methods:** The retrospective Dutch PBC Cohort Study includes every identifiable patient with PBC from 1990 up to last data collection (2019-2023) from all 71 hospitals in the Netherlands. Patients were included in case of >1 year follow-up after start of UDCA and without auto-immune hepatitis, second-line therapy or immunosuppressants. Where feasible, laboratory values were imputed using joint model multiple imputation. Kaplan-Meier curves were constructed to analyze liver-transplant (LT)-free survival and liver disease progression (decompensation, LT, or liver-related death). **Results:** In total, 3139 patients were included. At the start of UDCA, median age was 58.0 years (IQR 49.7–67.2), 2745 (87.4%) were female and 203 (6.5%) had cirrhosis. At 1 year UDCA, median ALP was 1.2xULN (IQR 0.9-1.7), median AST was 0.9xULN (IQR 0.6-1.2) and median total bilirubin was 0.5xULN (IQR 0.3-0.7). During a median follow-up of 8.0 years (IQR 3.8–13.3), 295 patients developed decompensated cirrhosis, 78 patients underwent LT, and 584 patients died (152 [26%] liver-related). Overall, at 10 years the LT-free survival was 83.5% (95%CI 81.9-85.2) and the cumulative incidence of liver disease progression was 10.1% (95%CI 8.9-11.3). Among the 2029 patients with an ALP ≤1.5xULN, the 10y LT-free survival was 89.5% (95%CI 87.6-91.5), 84.5% (95%CI 80.1-89.0), and 56.6% (95%CI 45.8-70.0) in those with AST ≤1xULN (n=1501, 74.0%), AST 1-1.5xULN (n=431, 21.2%) and AST >1.5xULN (n=97, 4.8%), respectively (p<.001) (Fig. 1A). For liver disease progression the 10y cumulative incidence was 1.8% (95%CI 1.0-2.6), 7.4% (95% 4.0-10.6), and 32.7% (95% CI 20.6-44.8) in those with an AST ≤1xULN/1-1.5 xULN/ >1.5xULN (p<.001). In contrast, among the 2552 patients with AST ≤1.5xULN, the 10y LT-free survival was 88.3% (95%CI 85.8-90.9), 88.5% (95%CI 86.0-91.0), and 84.3% (95%CI 80.9-87.9) (p=0.239) in those with ALP ≤1 xULN (n=955, 37.4%), ALP 1-1.5 xULN (n=977, 38.3%) and ALP>1.5xULN (n=620, 24.3%) (Fig. 1B). The cumulative incidence of liver disease progression were 2.7% (95%CI 1.4-3.9), 3.2% (95%CI 1.9-4.5), and 6.0% (95%CI 3.8-8.2) in those with ALP ≤1/ 1-1.5/>1.5xULN (p<.001). Similar results were found in the subgroups without cirrhosis at baseline. **Conclusion:** During UDCA monotherapy, an AST level >1.5xULN is infrequent among those with low ALP levels (≤1.5xULN), but represents an unfavorable prognosis. In contrast, high ALP in people with low AST is more common, but has a more limited risk implication.



Disclosures: Gemma H.X. Weijsters:Nothing to Disclose, Ellen Werner:Nothing to Disclose, Tiki Blom: Nothing to Disclose, Merle M.F. Vos:Nothing to Disclose, Maria van Hooff:Nothing to Disclose, Rozanne de Veer:Nothing to Disclose, Ulrich Beuers: Nothing to Disclose, Joost Drenth:Nothing to Disclose, Frans J.C. Cuperus:Nothing to Disclose, Remco van Dijk:Nothing to Disclose, Bart Veldt:Nothing to Disclose, Michael Klemt-Kropp:Nothing to Disclose, Suzanne van Meer:Nothing to Disclose, Robert Verdonk:Nothing to Disclose, Hajo J. Flink:Nothing to Disclose, Jan M. Vrolijk:Nothing to Disclose, Cyriel Y. Ponsioen:Nothing to Disclose, Matthijs Kramer:Dr Falk: Sponsoring of educational meetings, Jerome Sint Nicolaas:Nothing to Disclose, Philip Friederich:Nothing to Disclose, Merel M. Tielemans:Nothing to Disclose, J. Marleen de Vree:Nothing to Disclose, Huseyin Aktas: Nothing to Disclose, Sunje Abraham:Nothing to Disclose, Mariëlle J.F. Meijnen:Nothing to Disclose, Janne E. van Rooij:Nothing to Disclose, Pieter C.J. ter Borg: Nothing to Disclose, Leendert Oterdoom:Nothing to Disclose, Nicole S. Erler:Nothing to Disclose, Harry L.A. Janssen:Nothing to Disclose, Bettina Hansen:Nothing

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to Disclose, Adriaan J. van der Meer:Gilead: Consultant, Mirum: Consultant, Ipsen: Consultant, Gilead: Grant/Research Support, Ipsen: Grant/Research Support, Mirum: Grant/Research Support, dr Falk: Consultant.

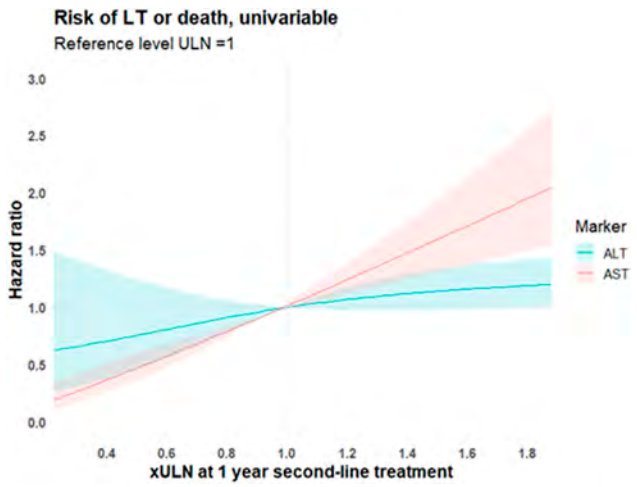
1265 | THE PROGNOSTIC IMPLICATIONS OF THE HEPATIC AMINOTRANSAMINASES DURING SECOND-LINE THERAPY FOR PRIMARY BILIARY CHOLANGITIS DIFFER: AST IS A STRONGER PREDICTOR

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Background: Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are associated with clinical outcomes during ursodeoxycholic acid therapy. The second-line treatment (SLT) options for primary biliary cholangitis (PBC) have shown different biochemical response patterns with respect to the hepatic transaminases. We aimed to assess the association between AST and ALT after one year of SLT with clinical outcomes in people with PBC. **Methods:** We performed an international, retrospective cohort study within the Global PBC database, including 20 centres from 12 countries in Europe, Asia, North America and South America, among patients with PBC treated with either obeticholic acid (OCA) or fibrates. Patients were excluded in case of <1 year of follow-up after the start of SLT or in case of overlap with auto-immune hepatitis. Cumulative liver-transplant (LT)-free survival was assessed with Kaplan-Meier analyses. Cox regression models were used to study the association between AST and ALT with LT-free survival. Continuous variables were fitted as restricted cubic splines in case of non-linearity. **Results:** In total, 1422 patients were included. OCA was started in 816 (57%) patients, and fibrates in 614 (43%) patients. Median age at start of SLT was 57 years (IQR 50-65), 1268 (89%) were female and 225 (25%) had cirrhosis. During a median follow-up of 36 months (IQR 24.0, 60.0), 64 (4.5%) individuals died and 22 (1.5%) underwent LT. At baseline, median AST was 1.13xULN (IQR 0.83-1.67) and median ALT was 1.08 xULN (IQR 0.73-1.73). After 1 year of SLT, these were 0.93 (IQR 0.73-1.29) and 0.79 (IQR 0.54-1.15), respectively. Median percentual change for ALT and AST after 1 year were -21.7% (IQR -45.4; 0.0%) and -11.1% (IQR -33.9; 8.2%), respectively; -28.6 (IQR -49.1; -6.3) and -18.4% (IQR -38.8; 0.0) for OCA and -14.9% (IQR -38.8; 10.0) and -3.8% (IQR -23.3; 14.4) for fibrates. Normalization of AST occurred in 285 (69.9%) of patients receiving OCA and 178 (48.1%) of patients receiving fibrates, which was 396 (69.7%) and 313 (65.5%) for ALT, respectively. OCA was associated with higher odds of normalization of AST (aOR 6.6, 95%CI 3.6-12.8) and ALT (aOR 3.7, 95%CI 2.1-6.5) ($p<0.001$). Patients with an AST $>1.5\times$ULN after 1 year of SLT had a 10 year LT-free survival of 74%, compared to 90% in those with AST $\leq 1.5\times$ULN ($p<0.001$). In contrast, the 10 year LT-free survival was 84.3% for ALT >1.5xULN and 85.1% for ALT ≤ 1.5x ULN ($p=0.03$). While AST showed a log-linear relationship with the risk for LT or death, this relation was non-linear for ALT. In univariable analysis, AST showed a stronger association with the risk of LT or death than ALT (Figure). **Conclusion:** In this large international cohort of patients with PBC treated with SLT, the decline in AST and ALT differed for OCA and fibrates. Both AST and ALT at one year of SLT were associated with risk of LT or death, but AST appeared to be a stronger predictor of outcome.

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1266 | RISK-FACTORS AND INCIDENCE OF BONE DISEASE IN EARLY- VS. LATE-ONSET PRIMARY BILIARY CHOLANGITIS: A PROPENSITY SCORE–WEIGHTED RETROSPECTIVE COHORT STUDY

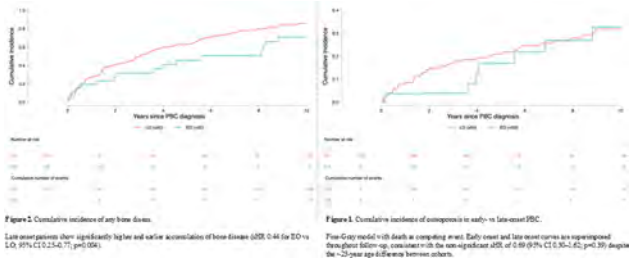
Leandro Sierra[1] Hussam Kawas[2] Qijun Yang[2] Sara Valencia[3] Rachel McNulty[2] Juan Armijos[2] John McMichael[2] Mohamad Alabbas[2] Li Tang[2] Kaylan Bhamidimarri[2] Bobby Zervos[2] Omar Sims[1] Dian Chiang[2], [1]Cleveland Clinic Foundation, [2]Cleveland Clinic, [3]Department of Internal Medicine, University of Arizona, Tucson, AZ, USA

Background: Primary biliary cholangitis (PBC) carries substantial bone disease risk, but available evidence derives almost exclusively from postmenopausal women. The phenotype and risk-factor profile of bone disease in patients diagnosed before age 50 (early-onset PBC) remains poorly characterized. We aimed to compare cumulative incidence of osteoporosis and DEXA screening between early-onset and late-onset PBC, and to determine whether risk-factor profiles for osteoporosis differ between strata. **Methods:** Retrospective cohort study of PBC patients (2000–2024) from the Cleveland Clinic Ohio and Florida campuses. Cohort were classified based on age at PBC diagnosis: early-onset (< 50 years)

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vs late-onset (≥50 years). Primary outcome was time to first confirmed osteoporosis (T-score ≤ −2.5). Secondary outcomes were osteopenia/osteoporosis (T-score ≤ −1.0) and time to first DEXA. Fine-Gray subdistribution hazard models treated death as a competing risk. Inverse probability of treatment weighting (IPTW) balanced demographics (sex, calendar year of diagnosis, race, ethnicity, BMI). Within-stratum Fine–Gray models evaluated predictors; pooled cohort risk factor interaction models assessed risk profiles. **Results:** Of 678 PBC patients, 630 met inclusion criteria (110 early-onset [17.5%], 520 late-onset [82.5%]); 202 had ≥1 eligible DEXA. Early-onset patients had higher baseline alkaline phosphatase (median 192.5 vs 158 U/L, p = 0.07). Early-onset patients were less likely to undergo DEXA (24.5% vs 33.7%, p = 0.05) and significantly less likely to be screened within 2 years of diagnosis (10.0% vs 18.7%, p = 0.029), when compared to late-onset. In IPTW-weighted analyses, early-onset and late-onset had similar osteoporosis incidence (sHR 0.69, 95% CI 0.30–1.62; p = 0.39) despite the 23-year age difference. Early-onset had significantly lower incidence of any bone disease (sHR 0.44, 95% CI 0.25–0.77; p = 0.004) (**Figure**) and a 38% lower hazard of undergoing first DEXA (sHR 0.62, 95% CI 0.38–1.00; p = 0.049), when compared to late-onset. In stratum-specific univariable analyses, the effect of female sex on osteoporosis risk differed significantly between cohorts (p-interaction = 0.029). Baseline ALP, albumin, bilirubin, BMI, autoimmune comorbidities, UDCA exposure, vitamin D and calcium supplementation, smoking, and hormone therapy showed no significant differential effect (all p-interaction > 0.05). **Conclusion:** Patients with early-onset PBC are at risk of osteoporosis at rates comparable to those diagnosed later, while remaining significantly under-screened with DEXA. These findings support bone health screening in young PBC patients.



Disclosures: Leandro Sierra:Nothing to Disclose, Hussam Kawas:Nothing to Disclose, Qijun Yang:Nothing to Disclose, Sara Valencia:Nothing to Disclose, Rachel McNulty:Nothing to Disclose, Juan Armijos:Nothing to Disclose, John McMichael:Nothing to Disclose, Mohamad Alabbas:Nothing to Disclose, Li Tang:Nothing to Disclose, Kaylan Bhamidimarri:madrigal: Speaking and Teaching, ipsen: Advisor, mirum: Advisor, orphalan: Advisor, Bobby Zervos:Nothing to Disclose, Omar Sims: Nothing to Disclose, Dian Chiang:Nothing to Disclose.

1267 | UTILITY OF ANTI-SP100 AND ANTI-GP210 ANTIBODY TEST IN PATIENTS WITH UNEXPLAINED CHOLESTATIC LIVER DISEASES

Jay Patel[1] Saurabh Agrawal[1] Arvind Murali[1],
[1]Orlando Health

Background: Anti-mitochondrial antibody (AMA) detection remains the cornerstone of diagnosis of PBC. Around 5 to 10% of patients with PBC are found to be AMA-negative, leading to diagnostic uncertainty, need for liver biopsy, and delay in treatment. Anti-SP100 and anti-GP210 antibodies have high specificity for PBC and provide a diagnostic alternative in AMA-negative patients. However, testing for anti-SP100 and anti-GP210 antibodies does not appear to be routinely performed. **Methods:** We identified all patients with cholestatic liver diseases referred to the Liver Center at Orlando Health, a large tertiary care center, from April 2023 to April 2026. Patients with cholestatic hepatitis from congestive hepatopathy, drug-induced liver injury, biliary obstruction, and infiltrative conditions were excluded. All patients received evaluation for PBC (AMA, if AMA negative then anti-SP100, anti-GP210 antibodies) and PSC (MRI-MRCP). Liver biopsy was performed whenever deemed necessary. We have reported data on demographics, biochemistry, and response to therapy in AMA negative PBC patients with positive anti-SP100 and anti-GP210 antibodies. **Results:** A total of 123 patients with cholestatic liver diseases were identified. Of these, 68 patients were diagnosed with PBC based on AMA-positivity, 27 patients had PSC, and 28 patients had neither AMA positivity nor evidence of PSC. Among the 28 patients with unexplained cholestatic disease, 5 (18%) had either anti-SP100 (n = 3) or anti-GP210 antibodies (n = 2) suggestive of PBC. Another two of the 28 patients had PBC diagnosed with liver biopsy, and these two patients did not have AMA, anti-SP100, or anti-GP210 antibodies. Thus, among all patients diagnosed with PBC (n = 75), AMA negative PBC was noted in 7 (9.3%) patients, and 5 (71%) of these 7 patients had anti-SP 100 or anti-GP 210 antibodies. Mean age of the five patients was 52, and four were females. The average peak ALP was 261U/L (Table 1). Only one of the five patients had liver biopsy, and findings were typical of PBC. All five patients were started on ursodiol with significant improvement in alkaline phosphatase noted in 4 out of the 5 patients thus far. **Conclusion:** AMA-negative cholestatic liver disease presents a diagnostic dilemma, with liver biopsy traditionally being utilized to clarify underlying disease pathology. Anti-SP100 and anti-GP210 present a diagnostic opportunity to identify PBC in AMA-negative patients and preclude the use of liver

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biopsy which is invasive and has its inherent risks. In our study, anti-GP210 and anti-SP100 antibody helped provide a diagnosis without the need for a liver biopsy in 71% of patients with AMA negative PBC and 18% of all patients with unexplained cholestatic liver disease. We recommend that clinicians incorporate anti-SP100 and anti-GP210 antibodies routinely into their diagnostic algorithm for evaluating AMA-negative cholestatic liver disease prior to proceeding with liver biopsy.

Table 1: Characteristics of patients with AMA negative, anti-SP100 or anti-GP210 positive patients with PBC.

Patient	Age	Gender	Peak Alkaline Phosphatase (U/L)	Anti-SP100 or Anti-GP210 positivity	Liver Biopsy	Fibrosis stage	Response to Ursodiol
1	44	Female	491	Anti-GP210	Yes	F2	Yes
2	32	Female	347	Anti-SP100	No	F4	Yes
3	59	Female	225	Anti-GP210	No	F0-F1	No
4	66	Male	201	Anti-SP100	No	F4	Yes
5	59	Female	118	Anti-SP100	No	F0-F1	Yes

Disclosures: Jay Patel:Nothing to Disclose, Saurabh Agrawal:Nothing to Disclose, Arvind Murali:Madrigal Pharmaceuticals: Speaking and Teaching.

1268 | PRIMARY SCLEROSING CHOLANGITIS AND DELIVERY HOSPITALIZATION OUTCOMES IN THE UNITED STATES: A CONTEMPORARY NATIONAL INPATIENT SAMPLE ANALYSIS

Anas Al Mardini[1] Harika Dadigiri[1] Sabah Kulsum[1] Sowmya Mainog[2] Edward Barbarito[3], [1]NYMC, [2]NYMC-St Clare/St Mary hospital, [3]St Clare hospital

Background: Primary sclerosing cholangitis (PSC) affects reproductive aged individuals and is frequently associated with inflammatory bowel disease (IBD), yet contemporary U.S. data on delivery hospitalization outcomes are limited. We evaluated the prevalence, delivery outcomes, and resource utilization associated with PSC among U.S. delivery hospitalizations **Methods:** We performed a retrospective cross sectional analysis of delivery hospitalizations among patients aged 12-55 years in the 2020-2022 National Inpatient Sample. PSC and IBD were identified using ICD-10-CM codes. Outcomes included severe maternal morbidity (SMM), cesarean delivery, length of stay (LOS), and total hospital charges. Analyses incorporated NIS discharge weights, strata, and hospital clusters. **Results:** Among 10,433,032 weighted delivery hospitalizations, 155 involved PSC, corresponding to 1.49 PSC delivery hospitalizations per 100,000 deliveries. Coexisting IBD was present in 58.1% of PSC delivery hospitalizations. No SMM events were observed among PSC delivery hospitalizations. Cesarean delivery occurred in 35.5% of PSC versus 32.3% of non-PSC delivery hospitalizations; after adjustment for age and IBD, PSC was not significantly associated with cesarean delivery (aOR 0.86, 95% CI 0.42-1.80; P = 0.698). Mean LOS was 3.03 days for PSC versus 2.55 days for non-PSC hospitalizations. Mean total hospital charges were $27,348 versus $24,925, respectively. **Conclusion:** PSC was exceedingly rare among U.S. delivery hospitalizations from 2020-2022, with most PSC delivery hospitalizations involving coexisting IBD. In this national sample, PSC was not associated with increased cesarean delivery, and no SMM events were observed among PSC delivery hospitalizations. Larger longitudinal datasets are needed to clarify rare maternal complications and postpartum outcomes in pregnant patients with PSC.

Disclosures: Anas Al Mardini:Nothing to Disclose, Harika Dadigiri:Nothing to Disclose, Sabah Kulsum: Nothing to Disclose, Sowmya Mainog:Nothing to Disclose, Edward Barbarito:Nothing to Disclose.

1269 | UTILITY OF CHOLESTATIC GENE PANEL TEST IN ADULTS WITH UNEXPLAINED CHOLESTATIC LIVER DISEASES: PROPOSED DIAGNOSTIC ALGORITHM

Arvind Murali[1] Saurabh Agrawal[1], [1]Orlando Health

Background: The gastroenterologist and hepatologist regularly provide care for a substantial cohort of adult patients with cholestatic liver diseases. A subset of these patients remains undiagnosed despite exhaustive serological, histopathological and imaging evaluations. Genetic cholestatic gene testing panel has been recommended for the evaluation of adult patients with cholestatic liver disease of unexplained etiology although there are currently no formal AASLD guidelines in this subject. We report our experience on the utility of cholestatic gene panel analysis in the diagnosis and management of adults with unexplained cholestatic liver diseases. **Methods:** We identified all patients with cholestatic liver disease referred to the liver center at Orlando Health, from April 2023 to April 2026. All patients received an exhaustive work up including for PBC (AMA, if AMA negative then anti-SP 100, anti-GP 210) and PSC (MRI-MRCP). Genetic cholestatic gene panel analysis was performed in patients with unexplained cholestatic liver disease. We collected and reported data on patient demography, biochemistry, genetic mutation identified on cholestatic gene panel test, treatment regimen, and response to treatment. Prevention genetics was used for cholestatic gene analysis. **Results:** A total of 123 patients with cholestatic hepatitis were identified. Of the 123 patients, 75 had PBC; 27 had PSC; and 21 had unexplained cholestatic liver disease on whom

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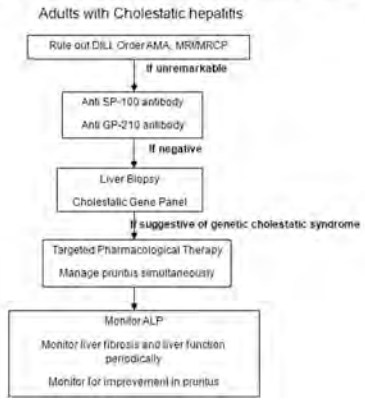
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cholestatic gene testing was performed. Of the 21 patients, 9 (43%) had a mutation implicated in the development of genetic cholestatic syndrome. Age ranged from 19 to 72 years, and 7 (78%) were females. Seven of 9 patients had liver biopsy without evidence of PBC, PSC, or infiltrative liver disease. One patient had homozygous ABCB4 variants, two had heterozygous ABCB4 variants, two had heterozygous Myo5B variants, and one patient each had heterozygous ATP8B1 variant, heterozygous ABCB11 variant, heterozygous Notch 2 variant, and heterozygous CFTR variant. All patients had pruritus, elevated alkaline phosphatase (ALP), and raised bile acids. All patients were initiated on ursodiol. In 5 (56%) patients, ALP improved to < 1.5*ULN, 3 (33%) had partial response, and one had no improvement. Improvement in pruritus and bile acids was seen in 4 (44%) of the 9 patients on ursodiol, while 5 (56%) had no improvement and started on alternate therapies. **Conclusion:** Personalized medicine has arrived as a defining paradigm in modern hepatology. Genetic cholestatic gene testing helps provide diagnosis in adult patients with unexplained cholestatic liver diseases. We thus recommend that adult patients with cholestatic liver diseases, in whom extensive evaluation has not revealed a diagnosis be tested for gene cholestatic syndromes such as PFIC (Progressive Familial Intrahepatic Cholestasis). We have provided simplified algorithm for evaluation of adult patients with cholestatic liver diseases.

Table 1 Characteristics of patients with genetic cholestatic disease

	Age	Sex	Peak ALP	Peak bile acids	Fibrosis stage	Liver biopsy performed	Genetic mutation identified	ALP after initiation of Ursodiol
1	26	M	500	263	F4	No	ABCB4 Homozygous	211
2	36	F	400	125	F1	Yes	ABCB4 Heterozygous	118
3	24	F	327	28	F0-F1	No	ABCB4 Heterozygous	183
4	41	F	503	261	F0	Yes	ATP8B1 Homozygous	129
5	19	F	329	N/A	F0	Yes	NOTCH2 Heterozygous	76
6	72	F	250	19	F3	Yes	CFTR Heterozygous	144
7	70	F	357	28	F1	Yes	Myo5B Heterozygous	190
8	30	M	190	22	F0	Yes	Myo5B heterozygous	138
9	42	F	897	193	F2	Yes	ABCB11 heterozygous	801

Figure 1 Simplified Algorithm to evaluate cholestatic liver disease in adults



Disclosures: Arvind Murali:Madrigal Pharmaceuticals: Speaking and Teaching, Saurabh Agrawal:Nothing to Disclose.

1270 | HIGH METABOLIC COMORBIDITY BURDEN IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS UNDERGOING LIVER TRANSPLANTATION

Dareen Chuy[1] Leandro Sierra[1] Sarah Alharfi[1] John McMichael[1] Dian Jung Chiang[1], [1]Cleveland Clinic Foundation

Background: Primary biliary cholangitis (PBC) is a chronic autoimmune cholestatic liver disease increasingly recognized to coexist with metabolic comorbidities. However, the characterization of this overlap and its effect on PBC outcomes, particularly in the context of liver transplantation, remain as areas of emerging research. We aimed to assess the prevalence of metabolic comorbidities in this population and their impact on post-transplant outcomes. **Methods:** Single-center retrospective cohort of 103 adult patients undergoing liver transplantation for PBC at the Cleveland Clinic, with a median follow up of 5.0 years. Metabolic comorbidities including overweight, hypertension, dyslipidemia, and diabetes were analyzed. The primary composite endpoint was re-transplantation or all-cause mortality. Secondary endpoints were re-transplantation, all-cause mortality, and PBC recurrence on biopsy (binary) analyzed as a competing-risks model with death as the competing event. Time-to-event analyses used Cox proportional hazards regression (composite endpoint, mortality) and Fine-Gray sub-distribution hazards (re-transplantation). PBC recurrence was modeled as a binary outcome with univariable logistic regression. Continuous pre-transplant HbA1c was analyzed in the subset with available values (n = 35) using Firth penalized logistic regression for PBC recurrence given sparse events. All analyses are univariable given the limited number of outcome events; no multivariable adjustment was performed. **Results:** The cohort was characterized by a high burden of metabolic comorbidities, with 63.1% having at least two of four components of metabolic syndrome. 24 patients (23.3%) reached the composite endpoint, 8 (7.8%) underwent re-transplantation, 20 (19.4%) died, and 18 (17.5%) developed PBC recurrence on biopsy. In univariable analyses, no metabolic comorbidity was significantly associated with the composite endpoint, re-transplantation, all-cause mortality, or biopsy-proven PBC recurrence. **Conclusion:** There is a high burden of metabolic comorbidities in PBC patients undergoing liver transplantation. No significant association was found between the presence of these comorbidities and post-transplant outcomes in this cohort. Our results nevertheless highlight the importance of a multidisciplinary approach in the management of these patients.

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Table: Prevalence of metabolic comorbidities in PBC patients undergoing liver transplantation (N = 103)

Component	n (%)
BMI ≥ 25 kg/m²	61 (59.2)
Hypertension (coded diagnosis)	65 (63.1)
Dyslipidemia (coded diagnosis)	56 (54.4)
Diabetes Ever (coded diagnosis or HbA1c ≥ 6.5%)	35 (34.0)
Pre-Transplant Diabetes	15 (14.6)
New-Onset Diabetes After Transplant (NODAT)	20 (19.4)
Metabolic Burden Score, distribution	
0 components	6 (5.8)
1 component	32 (31.1)
2 components	27 (26.2)
3 components	21 (20.4)
4 components	17 (16.5)
High Burden (≥ 2 components)	65 (63.1)
Pre-Transplant HbA1c Available	35 (34.0)
Median (IQR), %	5.10 (4.50–5.95)
Post-Transplant HbA1c Available	30 (29.1)
Median (IQR), %	5.75 (4.93–6.00)

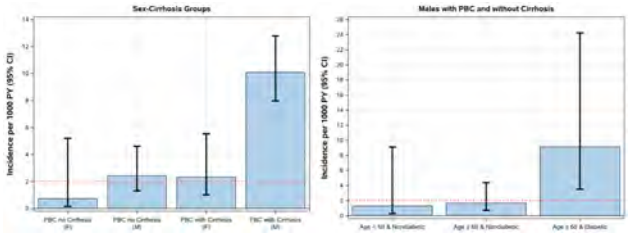
HbA1c values were available for a minority of patients in the chart, limiting power for HbA1c-based analyses.

Disclosures: Dareen Chuy:Nothing to Disclose, Leandro Sierra:Nothing to Disclose, Sarah Alharfi:Nothing to Disclose, John McMichael:Nothing to Disclose, Dian Jung Chiang:Ipsen: Advisor, Gilead: Advisor.

1271 | DO MALE PATIENTS WITH PRIMARY BILIARY CHOLANGITIS WITHOUT CIRRHOSIS REQUIRE SURVEILLANCE FOR HEPATOCELLULAR CARCINOMA? RESULTS FROM A NATIONAL COHORT

Binu John[1] Samuel Soon[2] Bassam Dahman[3] Rithwick Terala[4] Kaley Levitt[5] Dustin Bastaich[2] Cynthia Levy[6] Amit Singal[7], [1]University of Miami and Miami VA, [2]Virginia Commonwealth University, [3]Virginia Conmonwealth University, [4]Jackson Memorial Hospital, [5]Florida International University, [6]University of Miami, [7]University of Texas Southwestern

Background: The AASLD recommends hepatocellular carcinoma (HCC) surveillance in male patients with primary biliary cholangitis (PBC) without cirrhosis, although there is limited data to support this practice. We examined HCC incidence rates in a large cohort of patients with PBC to identify subgroups without cirrhosis in whom annual HCC incidence rates exceed the cost-effective threshold of 0.2% per year (2 per 1000 person-years). **Methods:** This was a retrospective cohort of patients with PBC from the Veterans Health Administration recruited between January 2011 and December 2022 with follow up until December 2025. Patients with an overlap syndrome, hepatitis B or C, liver transplantation prior to HCC, or inadequate follow-up were excluded. The primary exposure was a four-level classification based on sex and cirrhosis status, and the outcome of interest was HCC. Patients were followed from the date of cirrhosis diagnosis or from the date of PBC diagnosis (in those without cirrhosis) up to the onset of HCC, and censored at liver transplantation, death, or the most recent date of follow up. Incidence rates (IR) in age and diabetic subgroups were modeled using Poisson regression. **Results:** We identified 1,788 patients with PBC, of whom 683 (28.2%) did not have cirrhosis during from time of enrolment until last follow up and evaluated in non-cirrhosis cohort, while 1105 individuals who had cirrhosis either at presentation or during the course of follow up, and were included and analyzed in the cirrhosis cohort. During a follow-up of 13,766.4 person-years (PY), 81 patients developed HCC. On multivariable analysis, predictors of HCC included male sex, presence of cirrhosis, older age, and harmful alcohol use, but not UDCA response. Annual HCC rates per 1000 PY were 0.74 (95%CI 0.10-4.66) in females without cirrhosis, 2.44 (95%CI 1.26-4.66) in males without cirrhosis, 2.32 (95%CI 0.97-5.58) in females with cirrhosis, and 10.08 (95%CI 7.92-12.83) among males with cirrhosis. Annual HCC incidences rates with non-cirrhotic PBC were 7.21(95%CI 2.71-19.21) in males with diabetes and 9.13 (95%CI 3.43-24.32) in older (>60 years) males with diabetes. **Conclusion:** HCC rates are elevated above the cost-effectiveness threshold for HCC surveillance in males with PBC without cirrhosis, but not among females without cirrhosis. HCC rates in non-cirrhotic males were as high as that in females with PBC cirrhosis, and older males and patients with diabetes had an even higher risk. Our data supports the AASLD guidance recommending HCC surveillance in males with non-cirrhotic PBC.



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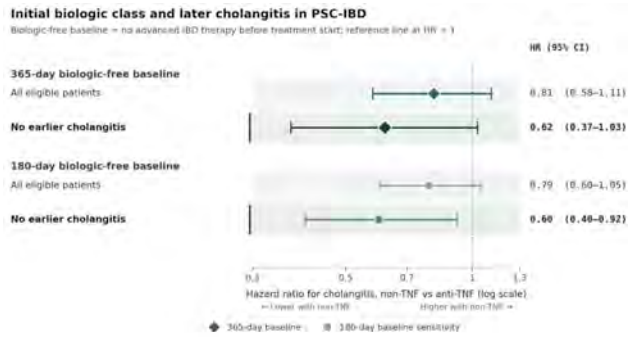
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1272 | NON-TNF VERSUS ANTI-TNF BIOLOGIC INITIATION AND CODED CHOLANGITIS IN PSC-IBD

Nourhan Saleh[1] EzzElDien A. Ibrahim[1] Bjorn Rodriguez[1] Mahmoud Majed Mansour[1] Darian Fard[1] Khulood Ahmed[1], [1]University of Missouri

Background: Adults with primary sclerosing cholangitis and inflammatory bowel disease (PSC-IBD) often require biologic therapy while remaining at risk for recurrent cholangitis. Whether initial biologic class is associated with subsequent cholangitis in real-world practice is uncertain. **Methods:** We used TriNetX Global Collaborative to emulate an active-comparator new-user cohort. Adults with PSC-IBD initiating vedolizumab or ustekinumab after 365 days without advanced IBD therapy were compared with anti-TNF initiators. Follow-up began at first biologic initiation. We matched 1:1 on 24 demographic, liver, IBD, medication, utilization, and laboratory covariates. The primary outcome was exact diagnosis-coded cholangitis over days 1-1095. Sensitivities included analyses excluding earlier cholangitis, a shorter 180-day biologic-free baseline, serious infection, transplant/status, and attempted negative controls. **Results:** The 365-day biologic-free baseline identified 476 non-TNF and 454 anti-TNF initiators; 280 pairs were matched. Inclusive events were 67/280 versus 83/280 (RR 0.81, 95% CI 0.61-1.06; HR 0.81, 95% CI 0.58-1.11). After excluding patients with earlier cholangitis, events were 24/194 versus 39/192 (RR 0.61, 95% CI 0.38-0.97; HR 0.62, 95% CI 0.37-1.03). The 180-day biologic-free baseline sensitivity matched 381 pairs; among patients without earlier cholangitis, events were 35/269 versus 57/262 (RR 0.60, 95% CI 0.41-0.88; HR 0.60, 95% CI 0.40-0.92). Additional outcome checks showed near-null serious infection, higher liver transplant/status coding in non-TNF initiators, and small or suppressed negative-control cells. **Conclusion:** Non-TNF initiation was associated with lower subsequent coded cholangitis in analyses focused on patients without earlier cholangitis, with similar direction across 365- and 180-day biologic-free baseline designs. The transplant/status imbalance keeps residual PSC severity and specialty-care channeling in view, so the findings should not be read as proof that biologic class modifies PSC progression.



Disclosures: Nourhan Saleh:Nothing to Disclose, EzzElDien A. Ibrahim:Nothing to Disclose, Bjorn Rodriguez:Nothing to Disclose, Mahmoud Majed Mansour: Nothing to Disclose, Darian Fard:Nothing to Disclose, Khulood Ahmed:Nothing to Disclose.

1273 | STATIN USE AND LIVER STIFFNESS PROGRESSION IN PRIMARY BILIARY CHOLANGITIS: A RETROSPECTIVE COHORT STUDY

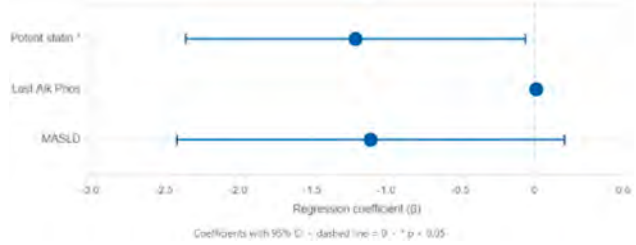
Alexander Zhao[1] Hanna Abuhay[1] Russell Rosenblatt[2], [1]NewYork-Presbyterian Hospital/Weill Cornell, [2]Weill Cornell Medicine

Background: Primary biliary cholangitis (PBC) is a chronic, cholestatic liver disease characterized by immune-mediated destruction of small intrahepatic bile ducts that can lead to fibrosis and cirrhosis. Emerging data suggest statins may have antifibrotic properties in other chronic liver diseases, but evidence in PBC is limited. This is a critical question as most patients with PBC have hyperlipidemia (HL) because of the disease. We evaluated the association between statin use and changes in liver stiffness (LS) measured by transient elastography in patients with PBC. **Methods:** This was a single center

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retrospective cohort study. Adult patients with PBC, confirmed by AASLD diagnostic criteria, were included if they had at least two separate transient elastography tests that were one year apart. Our primary outcome was LS change, which was the difference between the last LS measurement from the first. Subgroup analysis was performed to analyze potent statins vs either non-potent or no statin use. We also assessed the prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD), as assessed by an elevated CAP score. We performed multivariable linear regression models controlling for the last alkaline phosphatase level (as a means to assess disease control) as well as MASLD. **Results:** There were 100 patients with PBC who were included (86% female, 67% with HL). All patients were on ursodeoxycholic acid, and 10% were on fenofibrate, 10% on seladelpar, and 9% on elafibranor. More than half of patients (54%) were taking a statin - 29 atorvastatin, 18 rosuvastatin, 4 simvastatin, 3 pravastatin. Median baseline LS was 5.4 kPa, with no significant difference between statin users and non-users (5.1 kPa vs. 5.7 kPa; $p = 0.33$). Median change in liver stiffness was 0.0 kPa overall, with no significant difference between groups ($p = 0.12$): statin users decreased by -0.15 kPa (IQR -1.1 to 0.3) while non-statin users increased by +0.55 kPa (IQR -0.7 to 1.5). Additionally, 60% met CAP criteria for hepatic steatosis, supporting inclusion of MASLD as a covariate. In multivariable linear regression, while controlling for the last alkaline phosphatase level and comorbid MASLD, statin use trended toward reduced liver stiffness (coefficient -1.11; 95% CI -2.25 to 0.03, $p = 0.056$), while potent statin use was associated with a significant reduction (-1.21; 95% CI -2.35 to -0.06, $p = 0.04$) (Fig. 1). **Conclusion:** In this PBC cohort, potent statin use was independently associated with reduced LS, with a similar trend for any statin use. These findings suggest a potential antifibrotic benefit of statins in PBC, warranting prospective studies to assess effects on long-term outcomes.



Disclosures: Alexander Zhao:Nothing to Disclose, Hanna Abuhay:Nothing to Disclose, Russell Rosenblatt:Gilead: Grant/Research Support.

1274 | REAL-WORLD EFFECTIVENESS AND SAFETY OF SELADELPAR IN PRIMARY BILIARY CHOLANGITIS WITH AIH VARIANT SYNDROME AND MASLD: A NATIONWIDE ELECTRONIC HEALTH RECORD STUDY

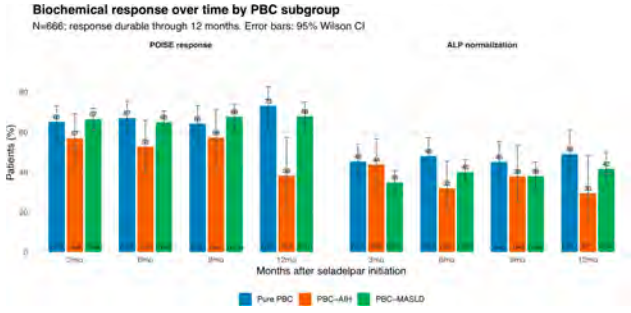
Adrielly Martins[1] Cynthia Levy[2], [1]University of Miami, [2]Division of Digestive and Liver Diseases, University of Miami

Background: Seladelpar, a selective peroxisome proliferator-activated receptor delta (PPAR-δ) agonist, received United States Food and Drug Administration approval in August 2024 as second-line therapy for primary biliary cholangitis (PBC). However, patients with autoimmune hepatitis (AIH) variant syndrome and those with metabolic dysfunction-associated steatotic liver disease (MASLD) were either excluded or underrepresented in pivotal triais, leaving seladelpar's effectiveness in these subpopulations undefined. Real-world durability of response beyond 6 months is also unknown. We evaluated biochemical response through 12 months and safety across PBC subgroups. **Methods:** This retrospective cohort study used Epic Cosmos, a federated electronic health record platform. Adults with PBC prescribed seladelpar after approval were classified into mutually exclusive subgroups: PBC, PBC-AIH variant syndrome, and PBC-MASLD. AIH variant was identified by a validated administrative algorithm, MASLD by hepatic steatosis or metabolic syndrome with cardiometabolic risk factors, and cirrhosis by diagnostic codes and noninvasive criteria. The primary outcome was POISE biochemical response (alkaline phosphatase [ALP] $< 1.67\times$ULN, $\geq 15\%$ ALP reduction or normalization, and total bilirubin ≤ 1.2 mg/dL) at 6 months; secondary outcomes included POISE response at 3, 9, and 12 months, ALP normalization, and hepatotoxicity (ALT > 3 or $> 5\times$ULN), using laboratory-specific ULNs. Subgroups were compared by chi-square, and response was assessed by cirrhosis status. **Results:** Among 666 patients (209 PBC, 76 PBC-AIH, 381 PBC-MASLD; mean age 63.9 years, 89.8% female, 35.6% cirrhotic), POISE response at the primary 6-month endpoint was 64.2% ($n = 425$) and was durable across follow-up (65.1%, 65.6%, and 66.1% at 3, 9, and 12 months; Figure). Response did not differ between PBC-MASLD and PBC at any timepoint (6-month 65.2% vs 67.3%; $p = 0.70$), indicating MASLD did not attenuate response. Response in PBC-AIH was numerically lower throughout (6-month 52.9%; $p = 0.08$). Cirrhotic patients had significantly lower response than non-cirrhotic at every timepoint (6-month 54.8% vs 69.6%; $p = 0.002$), despite comparable baseline ALP (1.6 vs 1.6×ULN; $p = 0.72$). ALT elevations were infrequent and stable ($> 3\times$ULN $\leq 4.0\%$ at

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all timepoints), with no progressive hepatotoxicity. **Conclusion:** In this nationwide real-world study, biochemical response to seladelpar was durable through 12 months and consistent with phase 3 trials. Coexisting MASLD did not attenuate response, whereas PBC-AIH variant syndrome and cirrhosis were associated with numerically and significantly lower response, respectively; the cirrhosis-associated difference was not explained by baseline biochemistry. Seladelpar demonstrated a stable hepatic safety profile across diverse PBC populations, supporting its real-world effectiveness in subgroups underrepresented in clinical trials.



Disclosures: Adrielly Martins:Nothing to Disclose, Cynthia Levy:Nothing to Disclose.

1275 | RISK OF COMBINED HORMONAL CONTRACEPTIVES IN AUTOIMMUNE HEPATITIS: A RETROSPECTIVE COHORT STUDY

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Background: Autoimmune Hepatitis (AIH) is a chronic inflammatory liver disease driven by T-cell-mediated destruction of hepatic autoantigens. Defective regulatory T-cell function permits self-perpetuating hepatic inflammation, which can progress to cirrhosis and end-stage liver disease if untreated. Risk factors include female sex, genetic predisposition, concurrent autoimmune diseases, and environmental triggers. While exact mechanisms remain elusive, estrogen may influence AIH pathogenesis by promoting B-cell hyperactivity and autoantibody production (e.g., anti-SMA, anti-LKM1), inducing T-cell hypoactivity that disrupts T-cell/B-cell homeostasis, and interacting with X-linked genetic factors. Our study aims to examine the association between estrogen-containing combined hormonal contraceptives (CHC) and the risk of developing AIH. This could be informative in the management of these medications in patients with AIH. **Methods:** Data Source and Study Design Using a de-identified US health research network (TriNetX; 112 organizations; IRB-exempt; accessed April 27, 2026), we defined two adult female cohorts: (1) cases with ≥ 6 prescriptions for estrogen-containing contraceptives (estetrol, estradiol, or ethinyl estradiol), and (2) controls with no estrogen-containing medications, antineoplastic hormones, or gonadotropins. The primary outcome was occurrence of autoimmune hepatitis (ICD-10-CM K75.4) at least two months after the index event (contraceptive exposure or in-network gynecologic visit in the CHC and control groups, respectively). Statistical Analysis 1:1 propensity score matching was performed on demographics and comorbidities. Continuous variables were compared using independent t-tests, while categorical variables were analyzed using chi-square tests. Outcomes were evaluated using risk difference with 95% confidence intervals (CIs). All statistical tests were two-sided with a significance level of $\alpha = 0.05$. TriNetX rounds patient counts between 1 and 9 up to 10, which may impact estimates for rare outcomes. **Results:** After propensity score matching, 401,120 individuals were included. Risk of developing AIH was significantly higher in the CHC cohort compared to controls (0.058% vs. 0.045%; risk difference = 0.013%, 95% CI 0.0033%–0.0232%, p = 0.0079). **Conclusion:** Estrogen-containing combined hormonal contraceptive use is associated with a small but statistically significant increase in risk of developing autoimmune hepatitis. Further prospective studies are warranted to elucidate the underlying pathophysiologic mechanisms.

Disclosures: Isabella Hendrickson:Nothing to Disclose, Sahil Sethi:Nothing to Disclose, Jaime Perez: Nothing to Disclose, Sharon Danielson:Nothing to Disclose, Naemat Sandhu:Ultragenyx Pharmaceutical Inc.: Grant/Research Support, Seth Sclair:Nothing to Disclose, Resham Ramkissoon:Nothing to Disclose.

1276 | RELATIONSHIP BETWEEN UDCA TREATMENT RESPONSE AND CHANGE IN ALP AFTER 12 MONTHS OF THERAPY IMPACTS CLINICAL OUTCOMES AMONG PATIENTS WITH PRIMARY BILIARY CHOLANGITIS

Stuart Gordon[1] Amandeep Sahota[2] Trueman Wu[3] Sheri Trudeau[3] Christina Melkonian[3] Meng-Hua Tao[3] Mark Schmidt[4] Lora Rupp[1] Yihe Daida[5] Christopher Bowlus[6] Mei Lu[1], [1]Henry Ford Health System, [2]KPSC,

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[3]Henry Ford Health, [4]KPNW, [5]KPHI, [6]University of California, Davis

Background: Ursodeoxycholic acid (UDCA) is the standard therapy for patients with primary biliary cholangitis (PBC); treatment response is typically defined by reduced alkaline phosphatase (ALP) after 12 months of treatment. Clinicians have noted that ALP levels may continue to increase over time, but the clinical impact of such increases is unknown. We used data from the US Fibrotic Liver Disease (FOLD) Consortium to evaluate ALP levels after 12 months of UDCA treatment and analyzed whether these levels were associated with liver transplantation (LT), all-cause mortality, and healthcare utilization. **Methods:** Patients from 6 FOLD sites were included if they: 1) received UDCA therapy for ≥ 6 months with gaps of < 3 months or treatment coverage $> 90\%$ for the first 12 months; and 2) had appropriate ALP testing at > 12 months. Inadequate UDCA treatment response (ITR) was defined by ALP measured at 9–14 months (levels $\geq 1.67\times$ULN or $< 15\%$ reduction from baseline). Rising ALP (ALP+) was defined as positive longitudinal slope (> 0) derived from subject-specific linear regression using available data for 1-6 years post-UDCA initiation. Generalized mixed spline regression was used to evaluate ALP trajectories across four groups defined by treatment response/ALP+ status. Wilcoxon tests for person-year outcomes and Cox time-to-event regression were used to evaluate their association with time to LT or death. **Results:** A total of 852 patients (6% Black; 10% AAPI; 11% male; 24% Hispanic) were included. At 12 months post-UDCA initiation, response categories were as follows: ITR/ALP+, 38 (5%); ITR, 436 (51%); ALP+, 140 (16%); adequate response, no ALP+ (full responders), 238 (29%). ALP+ was less common among ITR patients than responders (9% vs 25%, $p < 0.001$). ITR/ ALP+ patients were more likely to be men (21% vs 16% [ALP+] vs 9–12% in other groups) and demonstrated higher rates of hepatic decompensation within the first 12 months of UDCA therapy (21% vs 5–7% in other groups). We observed a significant interaction between ITR and ALP+ on longitudinal ALP trajectory ($p < 0.05$, Fig1a). ITR/ALP+ patients demonstrated persistently higher ALP, more frequent UDCA discontinuation, and higher rates of liver-related testing and hospitalization (all $p < 0.05$). No significant differences were observed among groups in rates of DILI, hypersensitivity reactions, or statin use. ALP+ was not associated with risk of LT/ death (aHR 1.16, 95%CI 0.63–2.02) among patients responding to UDCA, but significantly increased risk among patients with ITR (aHR 4.3, 95%CI 1.6–6.6; Fig 1b). **Conclusion:** ITR/ALP+ is associated with persistently elevated ALP, more healthcare utilization, and increased risk of liver transplantation or death. Consideration of longitudinal ALP trajectory may provide additional prognostic value beyond the standard 12-month assessment of UDCA response.

Figure 1A: ALP levels >12 months post UDCA initiation by treatment response and ALP slope group

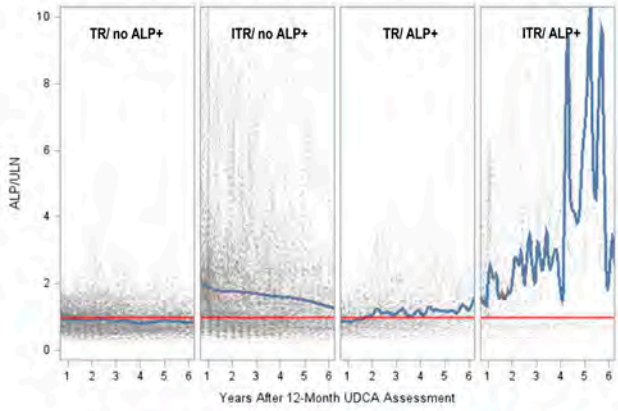
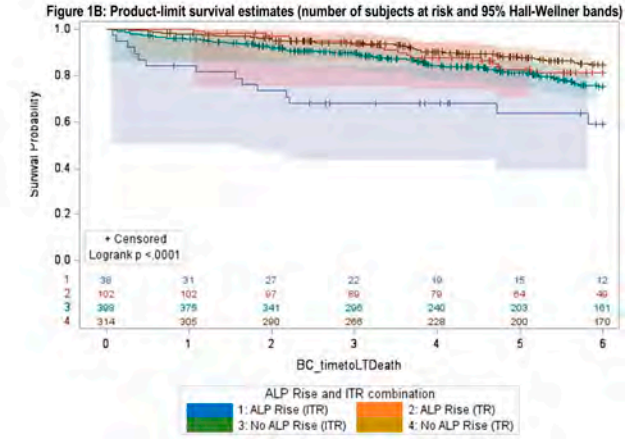


Figure 1B: Product-limit survival estimates (number of subjects at risk and 95% Hall-Wellner bands)



Disclosures: Stuart Gordon:Nothing to Disclose, Amandeep Sahota:Nothing to Disclose, Trueman Wu:Nothing to Disclose, Sheri Trudeau:Nothing to Disclose, Christina Melkonian:Nothing to Disclose, Meng-Hua Tao:Nothing to Disclose, Mark Schmidt: Nothing to Disclose, Lora Rupp:Nothing to Disclose, Yihe Daida:Vir Biotechnology: Grant/Research Support, Sanofi: Grant/Research Support, GSK: Grant/Research Support, Gilead Sciences: Grant/Research Support, Christopher Bowlus:Gilead Biosciences: Grant/Research Support, Intercept Pharmaceuticals: Grant/Research Support, CymaBay Pharmaceuticals: Grant/Research Support, Takeda Pharmaceuticals: Grant/Research Support, GSK: Grant/Research Support, Bristol Myers Squibb: Grant/Research Support, TARGET PharmaSolutions: Grant/Research Support, Novartis: Grant/Research Support, Novo Nordisk: Grant/Research Support, Mirum: Grant/Research Support, Ipsen: Grant/Research Support,

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1277 | PROGNOSTIC FACTORS ASSOCIATED WITH LIVER TRANSPLANTATION IN LATIN AMERICAN PATIENTS WITH AUTOIMMUNE HEPATITIS

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Background: Autoimmune hepatitis (AIH) accounts for 2–5% of liver transplant indications in Latin America. We aimed to identify prognostic factors associated with liver transplantation in a large Latin American AIH cohort. **Methods:** We analyzed data from 1,806 patients enrolled in the ALLATIN cohort, including demographic, clinical, laboratory, and histological variables. Univariable and multivariable Cox proportional hazards regression analyses were performed to identify predictors of liver transplantation. **Results:** Out of 1711 patients, 65 were submitted to liver transplant in a 6,6 years median follow-up. Patients with clinically significant portal hypertension had an approximately 2.2-fold higher risk of liver transplantation during follow-up (HR = 2.17; 95% CI: 1.04–4.55; p = 0.040). Higher albumin levels were associated with an approximately 52% reduction in transplantation risk (HR = 0.48; 95% CI: 0.35–0.66; p < 0.001), while higher platelet counts reduced the risk by approximately 24% for every increase of 50,000 platelets/mm³ (HR = 0.76; 95% CI: 0.61–0.93; p = 0.009). Insufficient biochemical response at 6 and 12 months was also associated with poorer transplantation-free survival; however, these variables were excluded from the final multivariable model due to the high proportion of missing data. **Conclusion:** Clinically significant portal hypertension, low albumin levels, and thrombocytopenia were independently associated with a higher risk of liver transplantation in Latin American patients with AIH.

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Uni and multivariate Cox regression for liver transplant in autoimmune hepatitis patients

Variables	Univariate analysis		Multivariate analysis	
	H.R. (I.C. 95%)	p	H.R. (I.C. 95%)	p
Gender				
Female				
Male	2,14 (1,13; 4,04)	**0,019**		
Age at diagnosis (/5)	0,98 (0,91; 1,06)	0,571		
AIH subtype				
Type I				
Type II	2,41 (0,74; 7,82)	0,144		
No marker	1,50 (0,59; 3,81)	0,394		
Cirrhosis at diagnosis				
Yes	4,99 (2,56; 9,71)	**< 0,001**		
No				
Clinically significant portal hypertension				
Yes	4,82 (2,64; 8,79)	**< 0,001**	2,17 (1,04; 4,55)	**0,040**
No				
IgG at diagnosis	1,00 (1,00; 1,00)	0,061		
AST at diagnosis (/200)	0,91 (0,79; 1,05)	0,180		
ALT at diagnosis (/100)	0,93 (0,85; 1,01)	0,067		
Bilirubin at diagnosis	1,02 (0,99; 1,07)	0,226		
Albumin at diagnosis	0,45 (0,34; 0,59)	**< 0,001**	0,48 (0,35; 0,66)	**< 0,001**
Platelets at diagnosis (/50 mil)	0,70 (0,59; 0,84)	**< 0,001**	0,76 (0,61; 0,93)	**0,009**
Fibrosis F3 at first biopsy				
Yes	0,53 (0,21; 1,35)	0,184		
No				
Fibrosis F4 at first biopsy				
Yes	2,48 (1,38; 4,46)	**0,002**		
No				
Biochemical response in 6 months				
Yes	3,26 (1,34; 7,96)	**0,009**		
No				
Biochemical response in 12months				
Yes	4,34 (1,87; 10,06)	**0,001**		
No				

Database 1.711 patients (Liver transplant - Yes → 65 patients No→ 1.646 patients No transplant → 64 patients)
p → significancy at χ² Wald test
HR → Hazard Ratio - I.C. 95%

Disclosures: Ludmila Guedes:Nothing to Disclose, Guilherme Cancado:Nothing to Disclose, Debora Terrabuio: Nothing to Disclose, Luciana Faria:Inventiva: Subinvestigator study NATIV3, Mirum Pharmaceuticals: Subinvestigator studies VLX-301 e VLX-601, Novo Nordisk: Speaking and Teaching, Gustavo Andre Pedral Diniz Leite:Nothing to Disclose, Ezequiel Ridruejo:Nothing to Disclose, Jhon Edison Prieto Ortiz:Nothing to Disclose, Elze Maria Oliveira:Nothing to Disclose, Alexandra Ginesta Frings:Nothing to Disclose, Rodrigo Zapata: Nothing to Disclose, Juan Diego Córdoba Pérez:Nothing to Disclose, Daniela Moreno :Nothing to Disclose, Sebastián Gil-Tamayo:Nothing to Disclose, Sara L Pinzon:Nothing to Disclose, Carlos B Sanchez:Nothing to Disclose, mirta peralta:Nothing to Disclose, Esteban González:Nothing to Disclose, Lorena Castro Solari: Nothing to Disclose, Edmundo Lopes Neto:Nothing to Disclose, Margarita Anders:Nothing to Disclose, Orlando Orozco:Nothing to Disclose, Eira Cerda Reyes:Nothing to Disclose, Carlos Benitez:Nothing to Disclose, Álvaro Urzúa:Nothing to Disclose, Raúl Lazarte Cuba:Nothing to Disclose, Mario Pessoa:Nothing to Disclose, Nothing to Disclose, Rosamar Rezende:Nothing to Disclose, Rebecca Dias Zaia:Nothing to Disclose, Liliana Mendes: Nothing to Disclose, Marcos de Vasconcelos Carneiro: Nothing to Disclose, Esteban Gonzalez Ballerga:Nothing to Disclose, Gustavo Pereira:Nothing to Disclose, Viridiana Lopez:Nothing to Disclose, Alejandra Villamil: Nothing to Disclose, Andreina Fragenas:Nothing to Disclose, Paulo Bittencourt:Nothing to Disclose, Liana Codes:Nothing to Disclose, Fernando Bessone:Nothing to Disclose, Lydia Falcão:Nothing to Disclose, Pablo Coste: Nothing to Disclose, Ana Clara Porto Carreiro:Nothing to Disclose, Emilia Vera:Nothing to Disclose, Maria Lucia Ferraz:Nothing to Disclose, Antônio Eduardo Benedito Silva:Nothing to Disclose, Raimundo de Araujo Gama: Nothing to Disclose, Miguel Escobedo Belloc:Nothing to Disclose, VIVIAN Rotman:Nothing to Disclose, Andreia Evangelista:Nothing to Disclose, Leonardo Schiavon: Nothing to Disclose, Janaína Narciso-Schiavon:Nothing to Disclose, Danay Guerrero:Nothing to Disclose, Harlim Rodríguez Rodríguez:Nothing to Disclose, Marlen Ivon Castellanos Fernandez:Nothing to Disclose, Angelo Alves de Mattos:Nothing to Disclose, Cristiane Valle Tovo: Nothing to Disclose, Maria Chiara Chindamo:Nothing to Disclose, Melina Almeida Dias Torres:Nothing to Disclose, Claudia Couto:Nothing to Disclose.

1278 | ADHERENCE TO QUALITY INDICATORS IN PRIMARY SCLEROSING CHOLANGITIS AND INFLAMMATORY BOWEL DISEASE CARE

Megan van Niekerk[1] Caterina Prada[2] Mikesh Kansagra[3] Lily Wu[1] Laurence Vaitiekunas[2] Emma Davis[1] Michael Christmas[1] Lauren White[1] Sanchit Sharma[1] Richard Fernandes[3] Rohit Gupta[1], [1]Sunshine Coast University Hospital, [2]Gold Coast University Hospital, [3]Mater Research

Background: Primary sclerosing cholangitis (PSC) is a progressive cholestatic liver disease strongly associated with inflammatory bowel disease (IBD) and an elevated risk of malignancy. In the absence of effective disease-modifying therapies, optimal care depends on structured surveillance, disease monitoring and proactive symptom management. However, real-world adherence to guideline-recommended care in Australian practice remains poorly characterised. This study aimed to evaluate adherence to guideline-recommended quality indicators for patients with PSC and associated inflammatory bowel disease (PSC-IBD) across three tertiary centres in South East Queensland, Australia. **Methods:** We performed a retrospective cohort study of patients with PSC-IBD. Quality indicators were established through multidisciplinary stakeholder consensus involving hepatologists and IBD specialists. Adherence was assessed across five domains: colorectal dysplasia surveillance, hepatobiliary surveillance, disease monitoring, symptom assessment, and preventive care. **Results:** Eighty-nine patients were included across three tertiary centres. Adherence to colorectal dysplasia surveillance was as follows: annual colonoscopy in 84%,

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annual ileal pouchoscopy when indicated in 90%, and segmental biopsies during colonoscopy in 91%. Hepatobiliary surveillance adherence included annual MRCP in 95% of patients and annual gallbladder ultrasound in 70%. Disease monitoring included fibrosis assessment in 63% of patients and faecal calprotectin testing in 73%. Preventive care measures included vitamin D testing in 67% and bone mineral density assessment in 36%. Documentation of patient-reported symptoms included bowel frequency assessment in 99% and pruritus in 75% of cases (Table 1). **Conclusion:** While adherence to select quality indicators was high, there is substantial variability across other key domains of PSC-IBD care. These findings highlight gaps between guideline recommendations and routine clinical practice. Implementation of standardised care pathways, PSC-IBD care bundles, and shared multidisciplinary clinics may enhance adherence to quality indicators and improve patient outcomes.

Table 1: Adherence to PSC-IBD Quality Indicators

Domain	Quality Indicator	Adherence (%)
Symptoms	Pruritus assessment within 12 months	75
	Bowel frequency assessment within 12 months	99
Dysplasia surveillance	Surveillance colonoscopy within recommended interval	84
	Ileal pouchoscopy where applicable	90
	Segmental biopsies during surveillance colonoscopy	91
Hepatobiliary surveillance	Annual MRCP	95
	Annual gallbladder ultrasound	70
Disease monitoring	Fibrosis assessment within 2 years	63
	Faecal calprotectin within 9 months	73
	Treatment escalation in endoscopically active disease	98
Preventive care	Vitamin D assessment within 12 months	67
	Bone mineral density scan within 3 years	36

Disclosures: Megan van Niekerk:Nothing to Disclose, Caterina Prada:Nothing to Disclose, Mikesh Kansagra: Nothing to Disclose, Lily Wu:Nothing to Disclose, Laurence Vaitiekunas:Nothing to Disclose, Emma Davis:Nothing to Disclose, Michael Christmas:Nothing to Disclose, Lauren White:Nothing to Disclose, Sanchit Sharma:Nothing to Disclose, Richard Fernandes:Nothing to Disclose, Rohit Gupta:Nothing to Disclose.

1279 | FROM LIVER TO BRAIN: INTRODUCING THE NEUROLOGICAL FOOTPRINT OF PBC

Natalia Rojas Amaris[1] Ana Marenco-Flores[2] Victoria Abadi-Ron[1] Hamza Khalil[3] Javier Polo-Ibarra[4] Fernando Munguia[1] Romelia Barba[5] Daniela Goyes[6] Esli Medina Morales[7] Behnam Saberi[8] Vilas Patwardhan[1] Alan Bonder[1], [1]Beth Israel Deaconess Medical Center, [2]Harvard Medical School, [3]Tufts Medical Center, [4]Boston Medical Center, [5]Texas Tech University, [6]Yale School of Medicine, [7]Washington University in St Louis, [8]BIDMC Harvard Medical School

Background: Patients with primary biliary cholangitis (PBC) frequently have concomitant extrahepatic autoimmune diseases. However, the prevalence and clinical relevance of neurological disorders in patients with PBC remain poorly characterized. This study aimed to evaluate the prevalence of neurological disorders among patients with PBC and assess their association with clinical outcomes. **Methods:** We conducted an analysis within a prospective cohort of patients with PBC enrolled in the Autoimmune Liver Diseases Registry at Beth Israel Deaconess Medical Center in Boston, MA, between January 2018 and May 2026. Medical records were reviewed to identify the presence and type of neurological disorders. Baseline demographic, clinical, and laboratory characteristics were compared between patients with and without neurological disorders. Univariable and multivariable logistic regression models were used, with multivariable models adjusted for age, sex, and cirrhosis. **Results:** Neurological disorders were present in 18% of patients with PBC. Movement disorders and migraine were the most prevalent conditions (28% each), followed by radiculopathy and epilepsy (22% and 17%, respectively). Biochemical response was similar regardless of neurological comorbidity. However, affected patients were more likely to require second-line therapy, including seladelpar or elafibranor ($p = 0.007$). Additionally, among affected patients, 44% developed their neurological condition several years after PBC diagnosis, with a median interval of 9.5 years. Psychiatric comorbidity was a strong predictor of neurological disorders (OR, 5.35; 95% CI, 1.58–18.07; $p = 0.007$). **Conclusion:** PBC's impact on brain function may extend beyond brain fog. PBC may precede the development of neurological disorders in some individuals, particularly those with concomitant psychiatric comorbidity. These findings highlight the importance of early recognition of neuropsychiatric manifestations during long-term follow-up of individuals with PBC.

Figure 1. Prevalence and types of neurological disorders in patients with primary biliary cholangitis

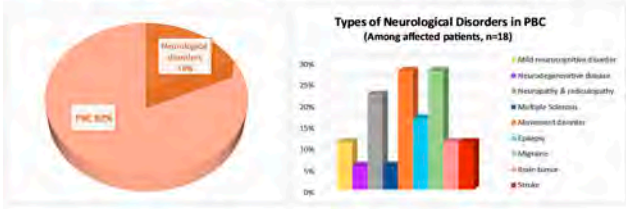
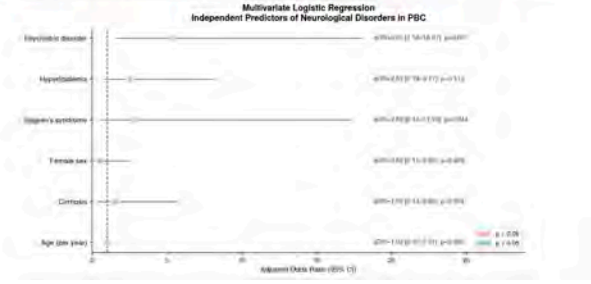


Figure 2. Multivariable logistic regression analysis of independent predictors of neurological disorders in patients with primary biliary cholangitis.



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1280 | STEROID-FREE BIOCHEMICAL REMISSION IN AUTOIMMUNE HEPATITIS WITHOUT OVERLAP: A REAL-WORLD PROSPECTIVE COHORT STUDY

Victoria Abadi-Ron[1] Ana Marenco-Flores[2] Natalia Rojas-Amaris[3] Fernando Munguia[3] Giuliana Arevalo[4] Aman Mohapatra[5] Romelia Barba[6] Daniela Goyes[7] Esli Medina Morales[8] Leandro Sierra[9] Behnam Saberi[10] Alan Bonder[3] Vilas Patwardhan[1], [1]Beth Israel Deaconess Medical Center, [2]Harvard Medical School, [3]Division of Gastroenterology, Hepatology, and Nutrition, Beth Israel Deaconess Medical Center, [4]University Of Miami Miller School of Medicine, [5]Department of Internal Medicine, Beth Israel Deaconess Medical Center, [6]Texas Tech University, [7]Division of Digestive Diseases, Yale School of Medicine, New Haven, [8]Washington University in St Louis, [9]Cleveland Clinic Foundation, [10]BIDMC Harvard Medical School

Background: Treatment for autoimmune hepatitis (AIH) often requires corticosteroids for long-term immunosuppression, yet some patients achieve long term biochemical remission (CBR) with steroid-sparing therapy. We aimed to identify AIH phenotypes where CBR can be maintained on minimal immune suppression including steroid free remission. **Methods:** We conducted a cross-sectional analysis of prospectively collected data from our institutional autoimmune liver disease registry and electronic medical record for patients with pure AIH (without overlap syndromes) followed at Beth Israel Deaconess Medical Center. Patients with available data on liver chemistries, current medications, and relevant clinical covariates were included. CBR was defined as normalization of aminotransferase, with IgG normalization required when available. The primary outcome was CBR without current steroid or off all immunosuppression. Categorical variables were compared using Fisher's exact test and continuous variables using the Mann–Whitney U test. Multivariable logistic regression evaluated factors associated with treatment-minimization CBR, including age, sex, race, alcohol use, smoking, autoimmune disease, and cirrhosis. **Results:** Among 167 classifiable patients, 114 maintained CBR overall. Of these, 48 were maintained on steroid-based therapy, 47 maintained steroid-free CB, and 19 maintained CBR off all immunosuppression. Overall, 56 (33.5%) maintained treatment-minimization CBR. Of the variables investigated there were no factors predictive of which patients maintained CBR without steroids. Cirrhosis was associated with a higher frequency of receiving steroids to maintain CBR on univariable analysis (20.5% vs. 37.5%; Fisher's exact $p = 0.028$) and remained independently associated with lower odds after multivariable adjustment (aOR 0.36, 95% CI 0.15–0.89; $p = 0.027$). Age, sex, race, alcohol use, smoking, and concomitant autoimmune disease were not significantly associated with the outcome. **Conclusion:** Treatment-minimization CBR was maintained in one-third of patients with pure AIH, supporting a rationale for steroid withdrawal strategies in AIH. Cirrhosis patients in our cohort had lower odds of receiving steroid-free immune suppression regimens. These data support a rationale for more aggressive steroid withdrawal strategies in AIH. Further investigation into which patients benefit most from steroid withdrawal strategies is a topic for further investigation.

FIGURE.



Figure1. Frequency of treatment-minimization complete biochemical response in the pure autoimmune hepatitis cohort. The pie chart shows the proportion of patients who maintained treatment-minimization complete biochemical response (CBR) versus those who did not. Treatment-minimization CBR was maintained in 33.5% of patients, while 66.5% did not maintain treatment-minimization CBR. CBR = complete biochemical response.

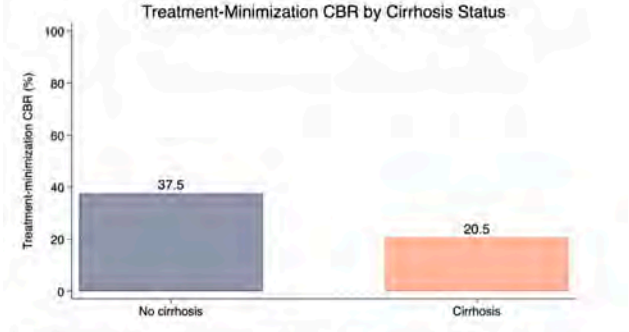


Figure 2. Treatment-minimization complete biochemical response by cirrhosis status. Bars show the proportion of patients achieving treatment-minimization complete biochemical response (CBR) among those without cirrhosis and those with cirrhosis. Treatment-minimization CBR was more frequent in patients without cirrhosis compared with those with cirrhosis (37.5% vs. 20.5%). CBR = complete biochemical response.

Disclosures: Victoria Abadi-Ron:Nothing to Disclose, Ana Marenco-Flores:Nothing to Disclose,

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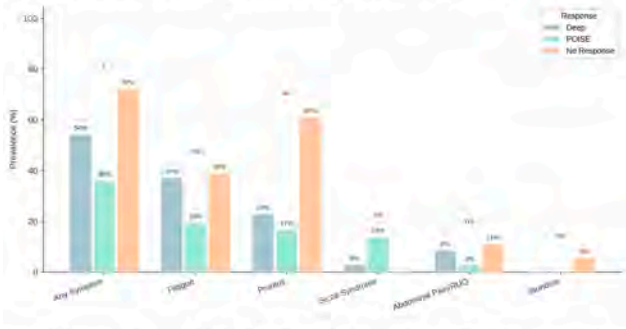
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1281 | CLINICAL SYMPTOMS AT DIAGNOSIS AND RISK OF POOR BIOCHEMICAL RESPONSE IN PRIMARY BILIARY CHOLANGITIS: A U.S. COHORT STUDY

Ana Marenco-Flores[1] Natalia Rojas Amaris[2] Victoria Abadi-Ron[3] Fernando Munguia[2] Javier Polo-Ibarra[4] Romelia Barba[5] Daniela Goyes[6] Esli Medina Morales[7] Behnam Saberi[2] Vilas Patwardhan[2] Alan Bonder[2], [1]Harvard Medical School, [2]Beth Israel Deaconess Medical Center, [3]Beth Israel Deaconess Medical, [4]Boston Medical Center, [5]Texas Tech University, [6]Yale School of Medicine, [7]Washington University in St Louis

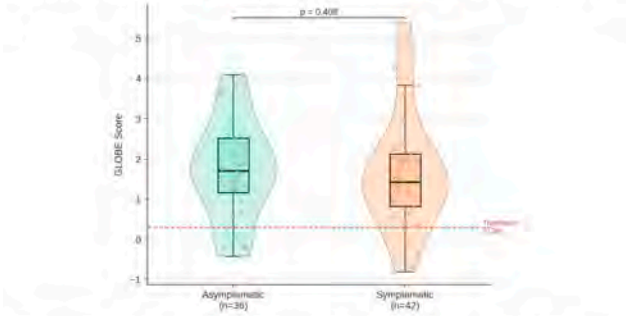
Background: The clinical presentation of primary biliary cholangitis (PBC) varies widely, with some patients presenting with cholestatic liver test abnormalities alone and others experiencing symptoms for months or years before being diagnosed. This study evaluated symptoms reported at diagnosis and its association with biochemical response to treatment in a real-world clinical setting. **Methods:** We analyzed data from patients with PBC or PBC-AIH overlap enrolled in a prospective cohort at Beth Israel Deaconess Medical Center in Boston, MA. Patients who reported fatigue, pruritus, sicca symptoms, abdominal pain, or jaundice at diagnosis were classified as symptomatic. Deep response was defined as normalization of alkaline phosphatase (ALP) and bilirubin, whereas standard (POISE) response was defined as ALP < 1.67× ULN. GLOBE scores were calculated to assess long-term prognosis and evaluate their association with symptoms at diagnosis and biochemical response. Univariable and multivariable logistic regression analyses were used to identify predictors of symptomatic presentation and biochemical response. Data analysis and visualization were performed using Stata and Python. **Results:** A total of 102 patients were included (median age 63 years, 88% female). Nearly half of participants reported symptoms at diagnosis (45%), with fatigue and pruritus being the most frequently reported symptoms (27% and 25%, respectively). Overall, 77% of patients achieved a biochemical response, including 36% deep responders and 41% standard responders, with either UDCA alone or second-line therapy. Among nonresponders, 72% were symptomatic at diagnosis ($p = 0.037$), and pruritus was the most prevalent symptom (61%; $p = 0.002$). Median GLOBE scores were elevated in both groups, suggesting a similarly increased predicted risk of liver transplantation or death. **Conclusion:** Symptomatic presentation at diagnosis was associated with poor biochemical response. Beyond serum biomarkers, symptom assessment at diagnosis may help identify patients who require more careful risk stratification, closer clinical monitoring, and individualized management, particularly among those reporting pruritus at diagnosis.

Figure 1. PBC Symptoms Reported at Diagnosis According to Biochemical Response



Percentages are shown above each bar. *p < 0.05; ** p < 0.01; ns = not significant; RUQ = right upper quadrant.

Figure 2. Distribution of GLOBE Scores by Symptom Presentation at Diagnosis in Patients with PBC



GLOBE score calculated using original formula: 0.044378 × Age + 0.93982 × ln(Bilirubin/ULN) + 0.335648 × ln(ALP/ULN) + 1.16009 × ln(ALT/ULN) − 1.04348 × ln(Platelets/ULN). ULN: bilirubin 1.0 mg/dL, ALP 120 U/L, ALT 35 U/L, platelets 250 K/μL. High-risk threshold: GLOBE > 0.30 (associated with 5-year liver-related mortality > 5%). GLOBE score available for patients with complete laboratory data.

Disclosures: Ana Marenco-Flores:Nothing to Disclose, Natalia Rojas Amaris:Nothing to Disclose, Victoria Abadi-Ron:Nothing to Disclose, Fernando Munguia: Nothing to Disclose, Javier Polo-Ibarra:Nothing to Disclose, Romelia Barba:Nothing to Disclose, Daniela Goyes:Nothing to Disclose, Esli Medina Morales: Nothing to Disclose, Behnam Saberi:Nothing to Disclose, Vilas Patwardhan:Nothing to Disclose, Alan Bonder:Nothing to Disclose.

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1282 | SEVEN-YEAR LONGITUDINAL ASSESSMENT OF COGNITIVE SYMPTOMS IN PRIMARY BILIARY CHOLANGITIS: A U.S. COHORT STUDY

Natalia Rojas Amaris[1] Ana Marenco-Flores[2] Victoria Abadi-Ron[1] Javier Polo-Ibarra[3] Fernando Munguia[1] Romelia Barba[4] Daniela Goyes[5] Esli Medina Morales[6] Behnam Saberi[1] Vilas Patwardhan[1] Alan Bonder[1], [1]Beth Israel Deaconess Medical Center, [2]Harvard Medical School, [3]Boston Medical Center, [4]Texas Tech University, [5]Yale School of Medicine, [6]Washington University in St Louis

Background: Primary biliary cholangitis (PBC) is a chronic cholestatic disorder characterized by ongoing immune-mediated damage to the intrahepatic bile ducts. People living with PBC frequently report cognitive symptoms, typically involving memory impairment, reduced attention or concentration, and psychomotor slowing. Despite the high prevalence of these concerns, little is known about how cognitive symptoms evolve during routine follow-up. This study aimed to characterize longitudinal changes in patient-reported cognitive symptoms using the cognition domain of the PBC-40 questionnaire. **Methods:** We conducted a seven-year longitudinal analysis of a prospective PBC cohort enrolled in the Autoimmune Liver Diseases Registry at a U.S. tertiary medical center (2018–2025). Cognitive symptoms were assessed using the PBC-40 questionnaire, which evaluates self-reported cognitive impairment, with each item scored from 1 to 5 (higher scores indicating greater symptom burden). Patients were eligible if they completed more than one PBC-40 questionnaire and responded to all cognition-domain items. Scores from the first and last visits were compared using paired t-tests. Mean changes, correlation coefficients, and Cohen's d values were calculated. Statistical significance was defined as $p < 0.05$. **Results:** A total of 129 patients were included. The mean age was 54 years, most were female and caucasian, with a median of three visits. The mean cognition score decreased from 2.23 ± 1.18 at baseline to 1.95 ± 1.07 at the final visit, representing an average change of −0.28 ± 1.09 ($p = 0.0046$). This reflects a small but statistically significant improvement in reported cognitive symptoms over time. Among those with more than one assessment, 61 (47.3%) improved, 35 (27.1%) remained stable, and 33 (25.6%) showed worsening symptoms. The correlation between first and last scores was moderate ($r = 0.532$), indicating substantial individual variability in symptom trajectories. **Conclusion:** Self-reported cognitive symptoms and perceived cognitive impairment are common in PBC and demonstrate notable variability over time. Incorporating cognitive screening tools into routine clinical practice may help objectively characterize cognitive dysfunction in PBC. Given the fluctuating nature of symptoms, co-existing factors such as sleep and/or mood symptoms or disorders should also be considered when assessing cognitive function and interpreting longitudinal changes.

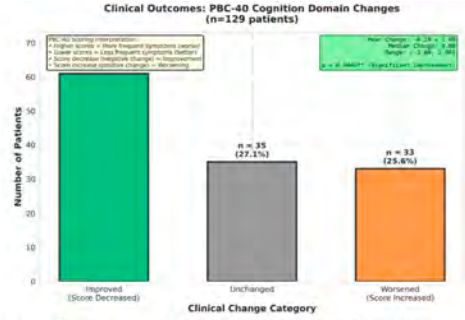


Figure 1. Distribution of cognitive symptom change categories based on PBC-40 cognition scores. Improved (n=61), unchanged (n=35), and worsened (n=33) categories are presented for 129 PBC patients. The average change in PBC-40 cognition scores was −0.28 ± 1.09 (median 0.00; range −3.00 to 3.00), indicating a significant overall improvement over time (p=0.0046). In the PBC-40 cognition domain, lower scores signify fewer cognitive symptoms.

Disclosures: Natalia Rojas Amaris:Nothing to Disclose, Ana Marenco-Flores:Nothing to Disclose, Victoria Abadi-Ron:Nothing to Disclose, Javier Polo-Ibarra: Nothing to Disclose, Fernando Munguia:Nothing to Disclose, Romelia Barba:Nothing to Disclose, Daniela Goyes:Nothing to Disclose, Esli Medina Morales: Nothing to Disclose, Behnam Saberi:Nothing to Disclose, Vilas Patwardhan:Nothing to Disclose, Alan Bonder:Nothing to Disclose.

1283 | EOSINOPHILIC CHOLANGITIS AS AN INDETERMINATE BILIARY MIMIC: A SYSTEMATIC REVIEW OF OUTCOMES

Thomas Stirrat[1] Shankar Thiru[2] Soham Apte[3] Maximilien Wilkey[2] Lovedeep Singh[2] Varat Ransibrahmanakul[2] Michael Flatley[4] Priyanka Kanth[5] Rachel Redfield[5] Amol Rangnekar[6], [1]University of California Los Angeles (UCLA), [2]Georgetown University School of Medicine, [3]Kentucky College of Osteopathic Medicine, [4]University of Colorado Internal Medicine Residency, [5]MedStar Georgetown University Hospital, [6]Georgetown University Hospital

Background: Eosinophilic cholangitis (EC) is a rare benign inflammatory biliary disorder that can mimic primary sclerosing cholangitis and cholangiocarcinoma. We systematically reviewed reported EC cases to define diagnostic features, treatment patterns, and outcomes relevant to indeterminate biliary strictures. **Methods:** Web of Science, PubMed, MEDLINE, Embase, Scopus, and CINAHL were searched from inception through December 31, 2025. Human case reports/series with extractable patient- level diagnostic, management, and outcome data were included. Data

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were synthesized descriptively using available denominators. **Results:** Fifty-five studies describing 55 patients were included. Median age was 46.5 years (IQR, 29-65.8), and sex distribution was balanced among reported cases. Among cases with a preoperative impression (n = 39), malignancy was suspected in 19 (48.7%). Among cases with reported localization (n = 44), 22 (50.0%) had both intra- and extrahepatic involvement, 15 (34.1%) isolated extrahepatic disease, and 7 (15.9%) isolated intrahepatic disease. Tissue eosinophilic infiltration was reported in 52/53 (98.1%). Peripheral eosinophilia was common but not universal; serum IgE, when reported, was normal in 4/15 cases by author classification. Steroids were the primary therapy in 35/42 (83.3%); symptom resolution occurred in 36/37 (97.3%) and biochemical normalization in 39/39 (100%). Recurrence occurred in 8/18 (44.4%; median 2 months), and persistent stricture was reported in 7/11 (63.6%) when assessed. **Conclusion:** EC is a high-impact benign mimic of malignant and fibroinflammatory biliary disease. Recognition should pair guideline-concordant malignancy exclusion with targeted evaluation for eosinophilic/systemic disease and, when appropriate, closely monitored corticosteroid therapy with structured post-treatment surveillance.

Eosinophilic cholangitis: key abstract outcomes

Variable	Value
Studies / patients included	55 / 55
Malignancy suspected preoperatively	19/39 (48.7%)
Tissue eosinophilic infiltration	52/53 (98.1%)
Steroids as primary treatment	35/42 (83.3%)
Symptom resolution	36/37 (97.3%)
Biochemical normalization	39/39 (100%)
Recurrence	8/18 (44.4%)

Disclosures: Thomas Stirrat:Nothing to Disclose, Shankar Thiru:Nothing to Disclose, Soham Apte:Nothing to Disclose, Maximilien Wilkey:Nothing to Disclose, Lovedeep Singh:Nothing to Disclose, Varat Ransibrahmanakul:Nothing to Disclose, Michael Flatley:Nothing to Disclose, Priyanka Kanth:Nothing to Disclose, Rachel Redfield:Nothing to Disclose, Amol Rangnekar:Nothing to Disclose.

1284 | SPECIFICITY OF ANTI-MITOCHONDRIAL ANTIBODY FOR PRIMARY BILIARY CHOLANGITIS: A LIVER EXPLANT-BASED STUDY

Rebecca Aquino[1] Christina Leyson[1], [1]University of Kentucky

Background: Primary biliary cholangitis (PBC) is a rare disease resulting from autoimmune destruction of intralobular bile ducts. Diagnosis is made when 2 of the following are present: elevation in alkaline phosphatase, presence of antimitochondrial antibody (AMA) or other PBC-specific autoantibodies, or histologic evidence of nonsuppurative destructive cholangitis and destruction of interlobular bile ducts. Anti-mitochondrial antibodies (AMAs) have a reported specificity of 96 to 98 percent for the diagnosis of PBC. However, it has been reported that positive AMAs can occasionally be present in other conditions such as systemic sclerosis and other autoimmune connective tissue diseases. Furthermore, research has shown that patients with positive AMAs who did not have PBC at the time of testing were unlikely to be diagnosed with PBC in the future. These findings bring the test's specificity into question. **Methods:** The University of Kentucky's electronic medical record, EPIC, was used to identify liver transplant recipients transplanted from July 1st 2021 to April 13th 2025 who had an abnormal AMA value documented. 30 patient charts were identified for review. Liver explant surgical pathology reports were reviewed and used to determine if explant tissue was compatible with a diagnosis of PBC. For those not consistent with PBC, the diagnosis suggested by the pathology was documented. Additional data recorded included patient age at transplant, sex, highest AMA level, highest alkaline phosphatase level, and presence of other autoimmune diseases. **Results:** This study consisted of 19 men and 11 women with an average age of 50.5 years. 20 percent of patients had liver explant tissue compatible with a diagnosis of PBC and 80 percent had explant tissue suggesting another disease. The average AMA level for the group with pathology consistent with PBC (PBC group) was 121 units (reference range 0 to 24.9 units) and in those with pathology inconsistent with PBC (non-PBC group) was 42 units. 83 percent of patients in the PBC group had other documented autoimmune diseases compared to 16.7 percent in the non-PBC group. The most common diagnoses suggested by explant pathology results were metabolic dysfunction-associated steatotic liver disease (23 percent) and alcohol-associated liver disease (23 percent). **Conclusion:** Despite the reported high specificity of AMA for the diagnosis of PBC, this study suggests that positive AMA levels may be associated with other chronic liver diseases. Our data suggests that there is a correlation between AMA level and the diagnosis, with higher levels being more likely to coincide with a confirmed diagnosis of PBC. The data highlights the prevalence of other autoimmune diseases in patients with PBC. The specificity of the AMA is important for guiding diagnosis which helps identify appropriate treatment. The diagnosis of PBC does not require liver biopsy, but tissue evaluation may be the only way to confirm diagnosis.

Disclosures: Rebecca Aquino:Nothing to Disclose, Christina Leyson:Nothing to Disclose.

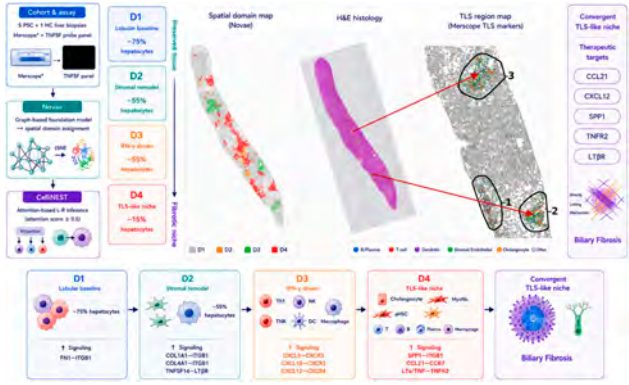
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★ 1285 | SPATIAL TRANSCRIPTOMICS REVEALS A TLS-LIKE IMMUNE-FIBROTIC NICHE DRIVING BILIARY FIBROSIS IN PEDIATRIC PRIMARY SCLEROSING CHOLANGITIS

Yunguan Wang[1] David Adeleke[2] Alexander Miethke[2], [1]Cincinnati Children Hospital, [2]Cincinnati Children's Hospital Medical Center

Background: Pediatric-onset primary sclerosing cholangitis (PSC) is a cholestatic condition in which peribiliary inflammation and fibrosis progressively reorganize hepatic tissue into spatially distinct domains. The intercellular signals activating hepatic stellate cell (HSC) and driving fibrogenesis across spatial domains remain poorly characterized. **Methods:** We performed spatial transcriptomics on liver biopsies from 5 patients with PSC (median age 19 years, 3 males) and one healthy control. Spatial domains were identified using Novae, and cell-cell communications (CCC) were inferred using CellNest. Empirical CCC probability was estimated as the ratio of observed interactions to plausible. Differential communication was assessed using paired Wilcoxon signed-rank tests. **Results:** Novae identified four domains (D1-4) representing a continuum of disease progression. D1 occupied hepatocyte (Hep)-rich lobular regions (75% of cells) with relatively preserved architecture, D2 and D3 represented intermediate states characterized by reduced Hep (55%) and increased plasma cells, NK cells, T cells, and macrophages (MP), consistent with inflammatory infiltration at the portal-parenchymal interface. In contrast, D4 localized to portal and fibrotic periductal regions, was predominately (~85%) consisted of activated HSC, myofibroblasts, cholangiocytes, MP, and lymphoid cells.D4 emerged as the dominant fibrotic niche, with selective enrichment of TNFR2-associated signaling and tertiary lymphoid structure (TLS)-like chemokine programs, including CCL21-CCR7, CCL21-CXCR3, CXCL12-CXCR3, and CXCL12-CXCR4. Key interactions included cholangiocyte-derived SPP1–ITGB1, endothelial-derived CCL21 signaling to dendritic and T cells, and stromal CXCL12-CXCR4 signaling to plasma and T cells, consistent with a TLS-like immune-fibrotic microenvironment. D2 showed enhanced collagen-integrin and TNFSF14 signaling involving activated HSC, LSEC, MPs, and Kupffer cells, consistent with early stromal remodeling and leukocyte adhesion. D3 represented an interferon-γ-driven inflammatory niche dominated by CXCL9, CXCL10, and CXCL12 signaling through CXCR3 and CXCR4, consistent with recruitment of Th1 cells, NK cells, dendritic cells, and MPs. **Conclusion:** PSC progression is characterized by a structured spatial trajectory from disrupted matrix homeostasis to stromal remodeling, interferon-driven immune recruitment, and ultimately a cholangiocyte-centered TLS-like immune-fibrotic niche. The convergence of CCL21, CXCL12, SPP1, TNF, and LIGHT signaling implicates TLS as a central mechanism linking chronic immune activation to biliary fibrosis in pediatric PSC.



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1286 | IMMUNOGLOBULIN G IS ASSOCIATED WITH HIGHER LIVER STIFFNESS IN AUTOIMMUNE HEPATITIS: TIMING MATTERS MORE THAN BIOCHEMICAL CORRECTION

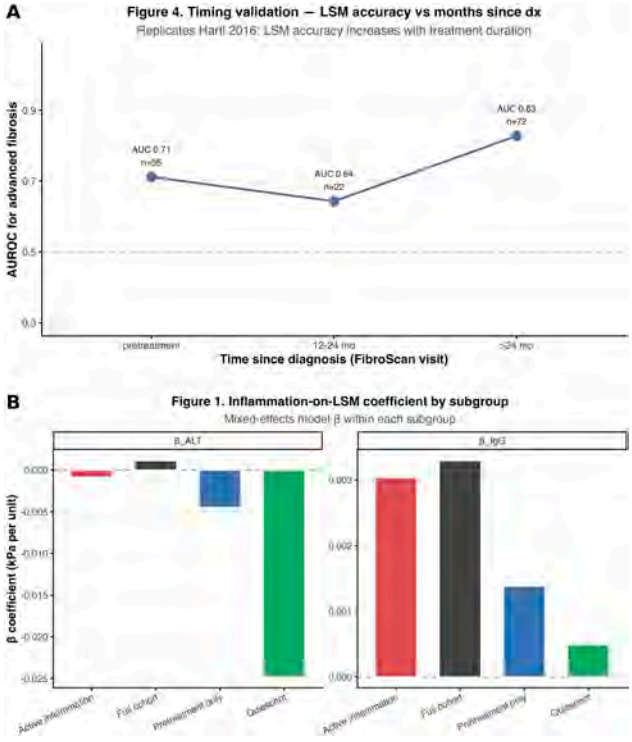
Sebastian Niezen[1] Daniela Goyes[2] Victoria Abadi-Ron[1] Natalia Rojas Amaris[1] Fernando Munguia[1] Ana Marenco-Flores[1] Behnam Saberi[1] Vilas Patwardhan[1] Alan Bonder[1], [1]Beth Israel Deaconess Medical Center, [2]Yale University

Background: Transient elastography (TE) may overestimate fibrosis in autoimmune hepatitis (AIH) because hepatic inflammation can increase liver stiffness measurement (LSM) independently of fibrosis. Whether ALT, IgG, or both confound LSM, and whether a simple algebraic correction improves accuracy, remains undefined. We characterized the inflammation–LSM relationship in AIH and quantified when LSM is reliable for fibrosis staging. **Methods:** Single-center retrospective cohort of adult AIH patients with diagnostic liver biopsy (Metavir staging) and one or more FibroScan measurements with same-visit ALT and IgG. The diagnostic biopsy stage served as the patient-level fibrosis anchor. We fit a mixed-effects linear model with LSM as the outcome and biopsy stage, ALT, IgG, and time since diagnosis as fixed effects, with a patient-level random intercept. An

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inflammation-adjusted LSM was computed by subtracting estimated ALT and IgG contributions centered at upper limits of normal. Spearman correlation with biopsy stage and DeLong-tested AUROC for advanced fibrosis (F3–F4 vs F0–F2) compared measured and adjusted LSM, overall and stratified by inflammation state (active vs quiescent) and by time since diagnosis. The IgG with timing interaction was formally tested. **Results:** We analyzed 208 FibroScan observations from 119 AIH patients with biopsy-defined fibrosis stage, including 49 observations with advanced fibrosis (F3–F4). In the mixed-effects model, IgG was independently associated with LSM (β = +0.003 kPa per mg/dL, p < 0.001), while ALT was not ($\beta \asymp 0$, p = 0.68). The IgG–LSM relationship varied significantly by treatment timing (IgG × 0–6 months interaction p = 0.001; IgG × 12–24 months p = 0.004). A simple ALT/IgG subtraction did not improve discrimination of advanced fibrosis (full-cohort AUROC measured 0.76 vs adjusted 0.72, DeLong p = 0.18). LSM accuracy varied by timing from diagnosis/treatment: AUROC for advanced fibrosis was 0.71 pretreatment (n = 35), 0.64 at 12–24 months (n = 22), and 0.83 beyond 24 months (n = 72). **Conclusion:** In this real-world AIH cohort, IgG was independently associated with higher LSM, with evidence of a time-dependent effect early after diagnosis. However, simple ALT/IgG-based correction did not improve fibrosis discrimination. LSM performed best beyond 24 months, suggesting that timing and biochemical context may be more useful than algebraic correction when interpreting FibroScan in AIH.



Disclosures: Sebastian Niezen:Nothing to Disclose, Daniela Goyes:Nothing to Disclose, Victoria Abadi-Ron:Nothing to Disclose, Natalia Rojas Amaris:Nothing to Disclose, Fernando Munguia:Nothing to Disclose, Ana Marenco-Flores:Nothing to Disclose, Behnam Saberi:Nothing to Disclose, Vilas Patwardhan:Nothing to Disclose, Alan Bonder:Nothing to Disclose.

1287 | VARIANTS IN GENES KNOWN TO BE ASSOCIATED WITH PROGRESSIVE FAMILIAL INTRAHEPATIC CHOLESTASIS (PFIC) AND NON-PFIC CHOLESTATIC GENES ARE THE PRIMARY CAUSE FOR CHOLESTASIS OF UNKNOWN ETIOLOGY IN ADULTS

Mitchell Shiffman[1] Kimberly Taylor[1] Sarah Hubbard[1] Rebecca Rathburn[1] Jennifer Miller[1], [1]Bon Secours Mercy Health

Background: The etiology for cholestatic liver disease in adults encompasses a wide array of disorders. Despite extensive testing the etiology for chronic cholestasis remains undefined in many patients. Genetic causes for cholestasis such as PFIC and Alagille syndrome are well recognized in children and less severe forms of these diseases have recently been recognized in adults. We have hypothesized that variants in genes associated with cholestasis are the primary cause for cholestasis of undefined etiology in adults. **Methods:** A total of 81 patients with cholestasis of unknown etiology were evaluated. The definition of cholestasis in this cohort included at least 2 of the following: persistent or intermittent elevation in ALP for at least 6 months, an elevation in GGT, an elevation in serum bile acids (SBA), unexplained pruritus. All patients underwent extensive biochemical, serologic, radiologic (MRCP in all patients) and histologic evaluation (liver biopsy (54 patients) and/or VCTE (65 patients)) to exclude all known causes of cholestasis. Genetic testing was then performed with the Prevention Genetics Cholestsis panel which screens for variants in 70 genes involved in pathways associated with cholestasis and in the synthesis, uptake, intracellular transplant, and secretion of BA. **Results:** The mean age of the cohort was 55 years, 77% female. Mean liver chemistries were ALP 278 IU/L, TBILI 1.1 mg/dL, GGT 262 IU/L and SBA 40.9 µmol/L. Mild non-specific irregularities in bile ducts without significant inflammation was present in 19% of patients. Stage 0-1 fibrosis was present in 73% of patients but 15% had cirrhosis. A variant in at least one of the genes associated with cholestasis was present in 89% of patients. A variant in 1 or more genes known to be associated with PFIC or

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Alagille syndrome (1 patient) was present in 30% of patients. The mean number of genes with variants was 2.8 per patient. The mean duration of monitoring before genetic testing was 42 (6-198) months. Pruritus was present in 33% of all patients. The severity of pruritus was similar in patients with a known PFIC gene variant, patients with a non-PFIC gene variant and patients with no variants in any of the genes in the cholestatic genetic panel. A significant increase in ALP and ALT but not serum BA was present with increasing severity of pruritus ($p < 0.05$). Itching was severe and refractory to standard medicinal treatments in 20% of all patients but in 44% of patients with a variant in a known PFIC gene ($p < 0.05$). **Conclusion:** Variants in genes associated with cholestasis were present in 89% of patients and this appears to be the most common cause for cholestasis of unknown etiology in adults. 30% of patients with cholestasis of unknown etiology have a variant in a gene known to be associated with PFIC or Alagille syndrome. Patients with severe cholestatic pruritus are more likely to have a PFIC gene variant than a variant not currently recognized as a cause of PFIC.

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1288 | PREVALENCE AND IMPACT OF MALNUTRITION ON CLINICAL OUTCOMES IN AUTOIMMUNE HEPATITIS: A PROPENSITY-MATCHED GLOBAL ANALYSIS

Prerna Ashok Kherajani[1] Savio John[1], [1]Suny Upstate Medical University

Background: Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease characterized by progressive hepatocellular injury that can lead to cirrhosis, hepatic decompensation, and liver transplantation if untreated. Malnutrition is increasingly recognized as an important determinant of morbidity and mortality in chronic liver disease due to its association with sarcopenia, immune dysfunction and impaired hepatic regeneration. While the burden and prognostic impact of malnutrition have been extensively studied in cirrhosis and other chronic liver diseases, limited data exist evaluating its prevalence and clinical significance specifically in patients with AIH. We aimed to determine the prevalence of malnutrition in AIH and evaluate its association with adverse outcomes using a large multicenter database. **Methods:** We conducted a retrospective cohort study using the TriNetX global collaborative network. Adult patients with AIH were identified using ICD-10 codes and stratified into patients with concomitant malnutrition (AIH-Mal) and those without malnutrition (AIH). Propensity score matching (1:1) was performed for demographics, comorbidities, medications (Corticosteroids, Azathioprine and Mycophenolate mofetil), Liver function tests and serum IgG levels, yielding 2,924 patients in each cohort. Primary outcomes included all-cause hospitalization and mortality. Secondary outcomes included liver transplantation, ascites, esophageal varices, hepatic encephalopathy (HE), acute liver failure (ALF) and Hepatocellular carcinoma (HCC). **Results:** Among 38,570 patients with AIH, the prevalence of malnutrition was 7.7%. After propensity matching, patients with AIH-Mal had significantly worse outcomes compared to matched AIH controls. All-cause hospitalization occurred in 68.3% versus 32.5% of patients, respectively (OR 4.47, 95% CI 4.01–4.99, $p < 0.0001$). Mortality was significantly higher in the AIH-Mal cohort (14.3% vs 4.1%; OR 3.92, 95% CI 3.18–4.84, $p < 0.0001$). Malnutrition was additionally associated with increased risk of ascites (35.2% vs 8.1%; OR 6.19, 95% CI 5.31–7.22, $p < 0.0001$), esophageal varices (20.8% vs 5.6%; OR 4.39, 95% CI 3.66–5.26, $p < 0.0001$), hepatic encephalopathy (13.3% vs 2.1%; OR 7.22, 95% CI 5.49–9.51, $p < 0.0001$), and acute

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liver failure (34.0% vs 8.4%; OR 5.60, 95% CI 4.81–6.51, p < 0.0001), liver transplantation (10.9% vs 1.6%; OR 7.76, 95% CI 5.62–10.71, p < 0.0001). No significant difference in hepatocellular carcinoma incidence was observed between groups. **Conclusion:** Malnutrition affects approximately 1 in 13 patients with autoimmune hepatitis and is associated with significantly increased mortality, hospitalization, hepatic decompensation, acute liver failure, and liver transplantation. Early nutritional assessment and intervention may represent an important modifiable target to improve outcomes in AIH.

Variable	Before PSM			After PSM			
	AIH-Mal 2,952	AIH 35,618	p-value	AIH-Mal 2,924	AIH 2,924	p-value	SMD
Age	49.2 ± 17	48.7 ± 16.9	0.1405	49.2 ± 17.1	49.2 ± 17.3	0.9715	0.0009
Sex							
Male	30.40%	25.05%	<0.0001	30.34%	29.93%	0.7323	0.0089
Female	69.60%	74.95%	<0.0001	69.67%	70.10%	0.7323	0.0089
Ethnicity							
Hispanic or Latino	13.74%	8.77%	<0.0001	13.65%	14.54%	0.3285	0.0256
Non-Hispanic or Latino	67.21%	55.18%	<0.0001	67.24%	68.10%	0.4846	0.0183
Race							
White	58.15%	55.27%	0.0025	58.07%	58.90%	0.5242	0.0167
Black or African American	21.85%	13.44%	<0.0001	21.85%	22.50%	0.5498	0.0156
American Indian or Alaska Native	0.98%	0.69%	<0.0610	0.89%	0.72%	0.3359	0.0297
Comorbidities							
Hypertension	34.10%	19.02%	<0.0001	33.86%	33.17%	0.5796	0.0145
Diabetes	18.98%	9.89%	<0.0001	18.81%	16.48%	0.0197	0.0610
Coronary Artery Disease	12.24%	4.98%	<0.0001	12.04%	11.42%	0.4645	0.0191
COPD	16.02%	8.77%	<0.0001	15.83%	15.63%	0.8294	0.0056
Chronic Kidney Disease	12.37%	3.53%	<0.0001	12.37%	11.56%	0.5434	0.0159
Heart Failure	8.93%	2.16%	<0.0001	8.65%	8.00%	0.2964	0.0273
Cerebrovascular Disease	7.16%	2.64%	<0.0001	7.00%	6.56%	0.5323	0.0163
Medications							
Glucocorticoid	44.44%	30.74%	<0.0001	44.25%	43.00%	0.2915	0.0276
Azathioprine	7.57%	7.60%	0.9478	7.56%	6.46%	0.1012	0.0429
Mycophenolate Mofetil	7.46%	2.42%	<0.0001	7.25%	7.05%	0.7607	0.0080

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1289 | DISTINCT PERIPHERAL IMMUNE SIGNATURES IN PRIMARY SCLEROSING CHOLANGITIS REVEALED BY STANDARDIZED IMMUNOPHENOTYPING

Shuhei Tanemura[1] Nobuhito Taniki[2] Haruka Okada[2] Ryosuke Kasuga[2] Yukie Nakadai[2] Makoto Ueno[2] Takaya Tabuchi[2] Shingo Usui[2] Keisuke Ojiro[2] Takanori Kanai[2] Nobuhiro Nakamoto[2], [1]Tanabe Pharma Corporation / Keio University School of Medicine, [2]Keio University

Background: Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease in which reliable serological biomarkers have not been established, and diagnosis as well as disease assessment relies largely on imaging-based evaluation. To date, comprehensive and standardized characterization of systemic immune alterations in PSC remains limited. We aimed to characterize peripheral blood immune cell phenotypes in PSC using a standardized immunophenotyping framework and to identify PSC-specific immune signatures that may serve as a basis for future non-invasive biomarkers. **Methods:** This single-center observational study analyzed peripheral blood mononuclear cells (PBMCs) from patients with PSC (n = 61), with primary biliary cholangitis (PBC) included as a disease control and healthy controls (HC) as reference controls. Multiparameter flow cytometry was performed, and immune cell subsets were defined according to the Human Immunology Project Consortium (HIPC) standardized immunophenotyping guidelines (Maecker HT et al., Nat Rev Immunol 2012). Immune cell frequencies were Z-score normalized to enable cross-population comparison. Group differences were assessed using the Mann–Whitney U test. **Results:** Compared with HC, PSC patients showed a significant reduction in mucosal-associated invariant T (MAIT) cells ($CD3^+CD4^-CD161^+TCRV\alpha7.2^+$, $p < 0.001$), $CD45RA^-$ memory $CD8^+$ T cells ($p < 0.01$), and $HLA\text{-}DR^+CD11c^+$ myeloid dendritic cells ($p < 0.05$). Analysis of Th17-related populations demonstrated no significant difference in total $CCR6^+CD4^+$ T cells; however, activated Th1-like Th17 cells defined as $HLA\text{-}DR^+CXCR3^+CCR6^+CD4^+$ T cells were significantly increased in PSC ($p < 0.05$). Notably, the reduction in memory $CD8^+$ T cells was not observed in patients with primary biliary cholangitis (PBC), indicating a PSC-specific immune alteration distinct from other autoimmune cholestatic liver diseases. **Conclusion:** Using a standardized HIPC-based immunophenotyping approach, we demonstrated distinct systemic immune dysregulation in PSC, characterized by reduction of MAIT cells, memory $CD8^+$ T cells, and myeloid dendritic cells, together with a selective expansion of activated Th1-like Th17 cells. These PSC-associated peripheral immune signatures provide a rationale for the development of immunophenotype-based, non-invasive biomarkers for PSC diagnosis and disease activity assessment.

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1290 | MANAGEMENT AND CARE PATHWAY OF PBC PATIENTS IN NONE UNIVERSITARY HOSPITALS: A NATIONAL MULTICENTER STUDY

Andre Jean Remy[1] Sandrine Barge[2] Edoardo Poli[3] Antonia Le Gruyer[4] Christiane Stern[5] Guillaume Conroy[6], [1]Centre Hospitalier De Perpignan, [2]Centre Hospitalier Intercommunal De Creteil, [3]Centre Hospitalier Nord Essonne, [4]Centre Hospitalier De Saint Brieuc, [5]Centre Hospitalier De Versailles, [6]Centre Hospitalier Regional metz Thionville

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Background: The prevalence rates of primary biliary cholangitis (PBC) are estimated at between 19.1 and 40.2 cases per 100,000 people. Data on the prevalence and care pathway for these patients with PBC come from university hospitals in France, with a majority of second-line patients and/or those with advanced liver disease. No data are available or published on the prevalence and cascade of care for patients with PBC in non-teaching hospitals. **Methods:** It was a national multicentre study to describe the prevalence and care pathway of patients with PBC in hepatogastroenterology departments of general hospitals. **Results:** As of May 12, 2026, 156 patients (91% women) had been included in 19 centers: median age 64 years, 17% overlap syndrome, 4% family history. Liver fibrosis was mainly assessed by FIBROSCAN, both at diagnosis (66%) and at follow-up (89%); mean 7.3 Kpa, 23% of patients F3F4 at diagnosis and during follow-up. After initial treatment with UDCA (for 96%), 30% had a second-line treatment (fibrates 71%, obeticholic acid 29%). The average GLOBE score was -0.56. **Conclusion:** Conclusion : compared to the patients followed in university hospitals, patients followed in non-university hospitals are older, with more moderate liver fibrosis and more often on first-line treatment.

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1291 | BIOCHEMICAL PHENOTYPES IDENTIFY DISTINCT TREATMENT RESPONSE AND PROGNOSTIC TRAJECTORIES IN A LARGE SOUTHEAST ASIAN PRIMARY BILIARY CHOLANGITIS COHORT

Jarell Jie-Rae Tan Tan[1] Eileen Chua[2] Karen Hei-Tung Lai[3] Ian Yang Liew[4] Abhimati Ravikulan[5] Kanokwan Pinyopornpanish[6] Kessarin Thanapirom[7] Wah Kheong Chan[8] Apichat Kaewdech[9] Chitchai Rattananukrom[10] Soe Thiha Maung[11] Guan Wee Wong[12] Shao-Li Huang[13] Tung-Hung Su[13] Garrett Kang[14] Soek-Siam Tan[15] Haniza Omar[16] Lin Lee Wong[17] Tam Nguyen Thi Thanh[18] Đào Việt Hằng[18] Anand Kulkarni[19] Senam Kaur[20] Jing Hieng Ngu[21] Alyssa Shin Yee Sim[4] Jimmy Che-To Lai[22] Yu Jun Wong[23], [1]Department of Gastroenterology & Hepatology, Changi General Hospital, Singapore, [2]Duke-NUS Medical School, Singapore, [3]Medical Data Analytics Centre (MDAC), Department of Medicine and Therapeutics, and Li Ka Shing Insti, [4]Tan Tock Seng Hospital, Singapore, [5]University of Otago, Christchurch Hospital, Christchurch, New Zealand, [6]Chiang Mai University, Thailand, [7]Chulalongkorn University, Thailand, [8]Gastroenterology and Hepatology Unit, Department of Medicine, Faculty of Medicine, Universiti Malay, [9]Gastroenterology and Hepatology Unit, Division of Internal Medicine, Faculty of Medicine, Prince of, [10]Khon Kaen University, Thailand, [11]Faculty of Medicine, Chulalongkorn University, [12]Ng Teng Fong Hospital, Singapore, [13]National Taiwan University, Taiwan, [14]Sengkang General Hospital, Singapore, [15]Selayang Hospital, Malaysia;, [16]Selayang Hospital, Malaysia, [17]Sunway Medical Centre, Malaysia, [18]Hanoi Medical University, Vietnam, [19]Asian Institute of Gastroenterology, [20]Queen Elizabeth Hospital, Kota Kinabalu, Malaysia, [21]Christchurch Hospital, [22]The Chinese University of Hong Kong, [23]Changi General Hospital, Singapore

Background: Histological ductopenia and interface hepatitis predicts adverse outcomes in primary biliary cholangitis (PBC), yet the biochemical correlation and prognostic value of these features remained unknown. Using the multinational SEA-PBC cohort, we evaluated whether baseline biochemical phenotypes identify clinically distinct PBC subgroups associated with differential treatment response, symptom burden and clinical outcomes in an under-characterized cohort in Southeast Asia. **Methods:** From the multinational SEA-PBC consortium **,** we included PBC patients from 18 tertiary institutions. Patients with autoimmune hepatitis (AIH)-PBC overlap or under immunosuppression were excluded. Patients were classified into classical PBC, ductopenic phenotype (ALP > 3x ULN), or inflammatory phenotype (ALT > 3x ULN and ALP < 3x ULN). Biochemical response was assessed using ALP normalization, Paris-II, POISE, and deep response (i.e., normalization of ALP and bilirubin) at 12 months after ursodeoxycholic acid treatment. Clinical outcomes (hepatic decompensation, liver transplantation and death) were analyzed using Cox proportional hazard models, adjusted for age, sex, and baseline MELD. **Results:** Among 1,662 patients from SEA-PBC, 60.2% had classical PBC, 16.9% ductopenic phenotype, and 22.7% inflammatory phenotype. The ductopenic phenotype had significantly lower biochemical response rates than classical PBC across all criteria: ALP normalization 5.7% vs 25.6%, Paris-II response 20.3% vs 62.3%, POISE response 24.9% vs 44.9%, and deep response 3.3% vs 16.3% (all $p < 0.001$). In contrast, inflammatory phenotype showed similar rate of ALP normalization but higher POISE response than classical PBC.Symptom burden differed by phenotypes, with ductopenic PBC associated with more pruritus, fatigue, and sicca symptoms compared with classical PBC.Over median follow-up of 61 (IQR: 25-113) months, ductopenic phenotype was independently

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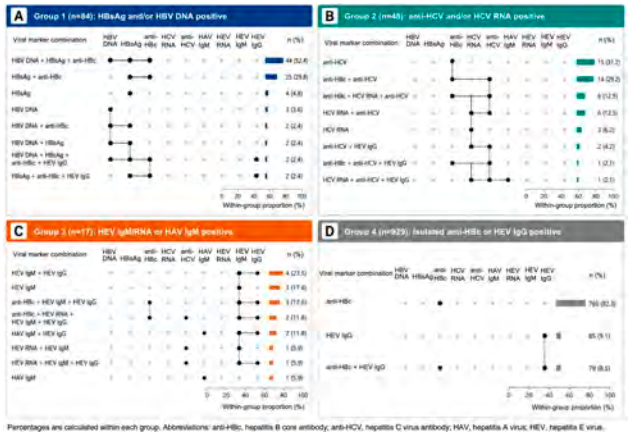
associated with liver transplantation or death compared with classical PBC (adjusted hazard ratio [HR] 1.52, 95% CI 1.19–1.94; $p < 0.001$), whereas the apparent unadjusted survival advantage of inflammatory phenotype was attenuated after adjustment. Ductopenic phenotype was also consistently associated with incident hepatic decompensation across clinically relevant subgroups (AMA-positive, ANA-positive, cirrhosis and non-diabetic patients) ($p < 0.05$). **Conclusion:** In the large Southeast Asian PBC cohort of PBC patients, baseline biochemical patterns identified clinically meaningful subgroups with divergent treatment response and prognosis. The ductopenic phenotype represents a high-risk, treatment-refractory subgroup associated with poor biochemical response, higher symptom burden, and poorer clinical outcomes. These findings support phenotype-based risk stratification and earlier therapeutic escalation in PBC.

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1292 | PROFILES OF VIRAL HEPATITIS MARKERS AND ASSOCIATED CLINICAL PHENOTYPES IN PRIMARY BILIARY CHOLANGITIS: A 10-YEAR REAL-WORLD COHORT FROM CHINA

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[1]Beijing Youan Hospital, Capital Medical University

Background: Viral hepatitis markers are frequently detected in patients with primary biliary cholangitis (PBC). However, their positivity rates, combination patterns, and associated clinical phenotypes remain incompletely characterized in large real-world cohorts. We aimed to define viral hepatitis marker profiles and compare clinical features across viral marker-defined subgroups in patients with PBC. **Methods:** We retrospectively analyzed 3,688 patients with PBC treated at Beijing YouAn Hospital, Capital Medical University, from 2015 to 2024. Viral hepatitis markers for hepatitis A, B, C, and E viruses were extracted from clinical testing records. Patients with positive viral markers were categorized using a hierarchical, mutually exclusive approach: Group 1, HBsAg and/or HBV DNA positive; Group 2, anti-HCV and/or HCV RNA positive; Group 3, HEV IgM/HEV RNA and/or HAV IgM positive; and Group 4, isolated anti-HBc and/or HEV IgG positivity without markers suggestive of current infection. Demographics, liver biochemistry, immunoglobulins, and PBC-related autoantibodies were compared across groups. **Results:** Markers of previous viral exposure were common, whereas markers suggestive of current or potentially active infection were less frequently detected. Among tested patients, anti-HBc and HEV IgG were positive in 41.85% (945/2,258) and 21.50% (184/856), respectively. HBsAg, HBV DNA, anti-HCV, HCV RNA, HEV IgM, HEV RNA, and HAV IgM were detected in 3.34% (79/2,364), 11.62% (53/456), 3.01% (45/1,494), 15.38% (16/104), 1.64% (14/856), 6.90% (4/58), and 0.40% (3/753) of tested patients, respectively. Overall, 1,078 patients had positive viral markers, including 84 in Group 1, 48 in Group 2, 17 in Group 3, and 929 in Group 4. Age, ALT, ALP, GGT, albumin, and hemoglobin differed significantly across groups. Group 3 showed the most prominent hepatocellular injury, with the highest ALT level (257.6 ± 428.0 U/L). In contrast, Group 4 exhibited a more cholestatic phenotype, with the highest ALP (228.5 ± 191.6 U/L) and GGT (221.5 ± 288.6 U/L) levels and the lowest albumin level (36.6 ± 6.7 g/L). PBC-associated autoantibodies remained prevalent across all groups, while IgG, IgA, and IgM concentrations did not differ significantly. **Conclusion:** Previous HBV or HEV exposure was common in patients with PBC, whereas active viral hepatitis markers were uncommon. Distinct clinical phenotypes across viral marker-defined subgroups highlight the value of viral hepatitis marker assessment in PBC.



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1293 | THE IMPACT OF VOLIXIBAT, AN IBAT INHIBITOR, ON FATIGUE AND SLEEP FOR PATIENTS WITH PRIMARY SCLEROSING CHOLANGITIS: DATA FROM VISTAS

Christopher Bowlus[1] Cynthia Levy[2] Mitchell Shiffman[3] Kris Kowdley[4] Marlyn Mayo[5] Palak Trivedi[6] Deepak Joshi[7] Adriaan Van der Meer[8] Verena Keitel[9] Alan Bonder[10] Ira Jacobson[11] Lisa Forman[12] Marco Carbone[13] David Bernstein[14] Walid Ayoub[15] Hallam Gugelmann[16] Erik Ness[16] David Sanchez-Ramos[16] Douglas Mogul[16] Jonathan Ieyoub[16] Jolan Terner-Rosenthal[16] Raul Aguilar[17] Lara Longpre[16] Pamela Vig[16] Joanne Quan[16] Gideon Hirschfield[18], [1]University of California, Davis, [2]University of Miami Miller School of Medicine, [3]Bon Secours Mercy Health, [4]Liver Institute Northwest, [5]University of Texas Southwestern Medical Center, [6]University Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom, [7]King's College Hospital NHS Foundation Trust, [8]Erasmus University Medical Center, [9]University Hospital Magdeburg, [10]Beth Israel Deaconess Medical Center, [11]NYU Grossman School of Medicine, [12]University of Colorado Anschutz Medical Campus, [13]University of Milano-Bicocca, ASST GOM Niguarda, [14]NYU Langone Health, [15]Cedars Sinai Medical Center, [16]Mirum Pharmaceuticals, Inc., [17]Mirum Pharmaceuticals, [18]Toronto General Hospital

Background: Primary sclerosing cholangitis (PSC) is a rare, progressive cholestatic liver disease that substantially impacts health-related quality of life (HRQoL). Pruritus, fatigue, and sleep disturbances are common symptoms in PSC whose burden may be severe and difficult to treat. Volixibat (VLX), a minimally absorbed ileal bile acid transporter inhibitor, blocks enterohepatic bile acid recirculation. Initial results from the VISTAS study demonstrated significant improvements in pruritus with VLX. Here, we present the effects of VLX on fatigue and sleep in participants from VISTAS. **Methods:** VISTAS is a 28-week randomized, multicenter, double-blind, placebo (PBO)-controlled Phase 2b study in adults with PSC and cholestatic pruritus. The primary endpoint, change in pruritus (Adult ItchRO score) from Baseline to Week 28, has been previously reported. Fatigue and sleep through Week 28 were assessed using the validated PROMIS HRQoL measures. Differences in fatigue and sleep between pruritus responders ($\geq$2-point reduction in Adult ItchRO; PR) and non-responders (NR) after treatment were also analyzed. Results were analyzed using a mixed model for repeated measures. **Results:** 111 participants with moderate-to-severe pruritus were randomized (VLX 20mg BID = 54; PBO BID = 57) in the primary cohort. Improvements (LS mean [SE]) favoring VLX treatment were observed in sleep (VLX: -6.47 [1.3], PBO: -0.78 [1.2]; P = 0.0011). Pruritus responders demonstrated greater improvements in fatigue and sleep versus NR, irrespective of treatment assignment (fatigue [mean, SD] PR: [-6.25, 7.8], NR: [-0.34, 6.3], P = 0.0004; sleep: [-7.48, 9,5], NR: [0.18, 6.6], P < 0.0001). However, the magnitude of improvement was greater in the VLX PR vs PBO PR group with significant differences observed with sleep (fatigue: VLX PR: -7.03 [8.7], PBO PR: -4.95 [6.0], P = 0.41; sleep: VLX PR: -10.20 [10.2], PBO PR: -2.93 [6.0], P = 0.0165). **Conclusion:** Initial results from the VISTAS trial in patients with PSC demonstrate that improvements in pruritus were associated with improvements in fatigue and sleep, with greater improvements observed following VLX treatment.

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1294 | REAL-WORLD EFFECTIVENESS OF ODEVIXIBAT IN LATE-ONSET PROGRESSIVE FAMILIAL INTRAHEPATIC CHOLESTASIS (PFIC)

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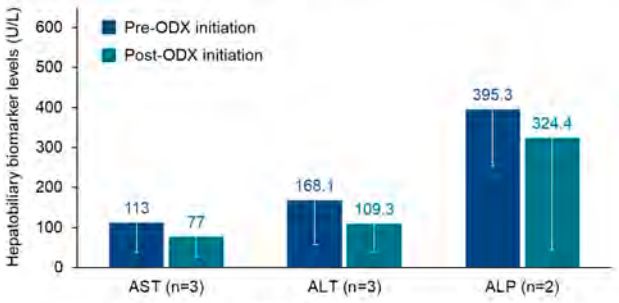
Background: While symptoms for PFIC typically manifest in early childhood, increasing numbers of patients are being diagnosed with late-onset disease in adulthood. Older patients with PFIC often present with heterogeneous and atypical cholestatic phenotypes associated with progressive liver disease. Consequently, clinical management of late-onset PFIC remains poorly defined, and effectiveness of currently available therapies in this population is not well characterized. Odevixibat (ODX) is an ileal bile acid transporter inhibitor approved in the US for treatment of pruritus in patients with PFIC aged at least 3 months and in the EU for patients aged at least 6 months. However, data describing clinical outcomes with ODX in adults with late-onset PFIC remain limited, highlighting the need for additional evidence to support timely diagnosis and informed clinical decision-making. **Methods:** This non-interventional retrospective study focuses on 3 of 14 patients with late-onset PFIC (aged $\geq$18 years; International Classification of Diseases [ICD]-9: 576.8 and/or ICD-10: K76.8; confirmed by manual chart review) who were treated with ODX at Mayo Clinic or Duke Health; data for all 14 patients were characterized in a prior report (Meloni et al. AASLD 2025). The study period was July 20, 2021 to December 31, 2025. Change in pruritus from unstructured notes and change in measured hepatic parameters (aspartate aminotransferase [AST], alanine aminotransferase [ALT], serum bile acid [sBA], and alkaline phosphatase [ALP]) from structured fields were evaluated. To maintain patient confidentiality, only non-identifiable data are presented. **Results:** Mean age (SD) at first record of PFIC was 24.3 (9.7) years and at ODX initiation was 27.0 (11.5) years. Mean (SD) observed time on treatment was 12.3 (7.6) months. All 3 patients had physician interpretation of genetic testing and notable hepatocellular injury pre-ODX. Mean (SD) AST and ALT prior to ODX initiation was 113 (76) and 168.1 (110) U/L, respectively. All 3 patients reported improvements in pruritus within 3 months of ODX initiation and 1 noted resolution of symptoms. Temporary ODX interruption occurred in 2 patients; both reinitiated treatment and subsequently reported pruritus improvement. Of 2 patients with available sBA data, both had reductions while on ODX (by 140 µmol/L and 115 µmol/

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L). Mean levels of AST, ALT, and ALP decreased following ODX initiation (**Figure**). **Conclusion:** Real-world use of ODX in patients with late-onset PFIC was accompanied by meaningful pruritus improvements and sBA reductions, and improvements in hepatobiliary biomarkers. Findings support potential ODX benefit in this understudied population, although further real-world studies are warranted to strengthen the evidence base and optimize management of late-onset PFIC.

Figure: Mean change in AST, ALT, and ALP levels pre- and post-ODX initiation in adults with late-onset PFIC (N=3)



Values shown as mean and SD.

Disclosures: Tatyana Kushner:Gilead: Grant/Research Support, Gilead: Advisor, GSK: Advisor, Eiger: Advisor, GSK: Consultant, Madrigal: Advisor, Ipsen: Advisor, Mirum: Advisor, Mirum: Grant/Research Support, Ipsen: Grant/Research Support, Seema Meloni:Ipsen Biopharmaceuticals: Employee, Omar Almudallal:Ipsen: Employee, Brian He:Nothing to Disclose, Hugo Gomes Da Silva:Nothing to Disclose, Wing-Kin Syn:Zydus: Clinical Trial site - funds to University, Merck: Consultant, Ipsen: Consultant, Zydus: to University, Merck: Consultant.

1295 | MARALIXIBAT, AN IBAT INHIBITOR, IMPROVES CHOLESTATIC PRURITUS IN PFIC PATIENTS WITH COMPOUND HETEROZYGOUS VARIANTS

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Background: Progressive familial intrahepatic cholestasis (PFIC) is a group of rare autosomal recessive liver diseases distinguished by canalicular bile transport defects, which result in disrupted bile formation and progressive cholestasis. It is classically caused by biallelic pathogenic variants in genes such as *ATP8B1*, *ABCB11, ABCB4, TJP2, MYO5B* and *NR1H4*. Patients with PFIC often have elevations in serum bile acid (sBA) levels, abnormalities in liver function tests, and clinical manifestations of chronic cholestasis, including pruritus. Maralixibat (MRX), an ileal bile acid transporter (IBAT) inhibitor, is indicated for the treatment of cholestatic pruritus in patients with PFIC ≥1 year in the US, and for the treatment of PFIC in patients ≥3 months in the EU. Here we describe 5 real-world cases of PFIC with compound heterozygous variants who received MRX. **Methods:** Clinicians treating patients with a diagnosis of PFIC completed an electronic case report form including clinical and biochemical data. Pruritus was assessed with the Clinician Scratch Scale (CSS), a 0-4 scale where 0 = no evidence of pruritus and 4 = cutaneous mutilation, bleeding or scarring; ≥1-point reduction is considered clinically meaningful. Data are presented using medians and min/max, and categorical variables are as counts and percentages. **Results:** Data on 5 patients (3 males) from 5 centers with compound heterozygous variants in the following PFIC genes were included: 1 (20%) *ABCB11* and *MYO5B*, 2 (40%) *ABCB11*, 1 (20%) *FIC1*, and 1 (20%) *MYO5B*. Median age at initiation of treatment was 10 (range 1.25-70) years and duration of treatment was 12 (range 8-84) months with all patients still on MRX. Before treatment, 3 (60%) had CSS of 4, 1 (20%) had a CSS of 3, and 1 (20%) had CSS of 2. Following treatment, all had a clinically meaningful reduction in CSS, with 2 (40%) achieving complete resolution (CSS = 0). 3 of the 5 patients had both pre- and post-MRX sBA levels with all 3 (100%) patients having a substantial reduction in sBA levels (276 to 2, >300 to 4, and 212 to 14 µmol/L). Bilirubin and liver enzymes remained stable or decreased in the majority of patients. AEs were reported in 2 including diarrhea (n = 2; 40%), transaminase increase that normalized by last clinical follow-up (n = 1; 20%), increase in bilirubin (n = 1; 20%), and abdominal pain (n = 1; 20%). There were no discontinuations or severe liver events (e.g., decompensation). **Conclusion:** Patients with PFIC who had heterozygous variants in the same gene or across different genes all displayed similar clinical improvements, highlighting the effect of MRX across multiple PFIC genotypes.

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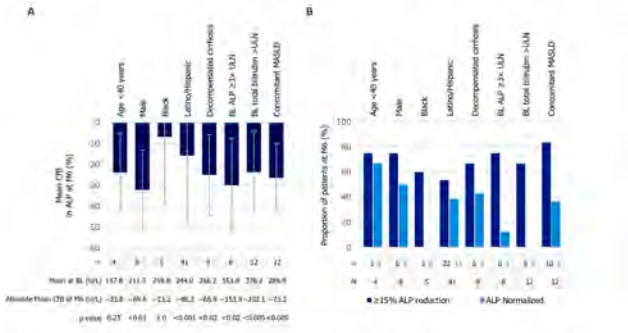
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1296 | REAL-WORLD OUTCOMES OF PATIENTS WITH PRIMARY BILIARY CHOLANGITIS IN CLINICALLY HIGH-RISK SUBGROUPS WHO INITIATED TREATMENT WITH ELAFIBRANOR

Channa Jayasekera[1] Cynthia Levy[2] Seema Meloni[3] Deborah Nikolla[3] Matthew Sobiesk[3] Christelle Pommie[4] Philip Troke[5] Christopher Bowlus[6], [1]Liver Transplant Program, Mayo Clinic Arizona, Pheonix, AZ, USA, [2]Schiff Center for Liver Diseases, University of Miami, Miami, FL, USA, [3]Ipsen, Cambridge, MA, USA, [4]Ipsen, Paris, France, [5]Ipsen, London, UK, [6]Division of Gastroenterology and Hepatology, UC Davis School of Medicine, Sacramento, CA, USA

Background: Primary biliary cholangitis (PBC), a chronic cholestatic liver disease, causes gradual liver dysfunction if untreated. Certain patient (pt) subgroups are at increased risk of disease progression and poor long-term clinical outcomes. Elafibranor, a peroxisome proliferator-activated receptor (PPAR)-α/δ agonist approved as a second-line treatment for PBC, demonstrated rapid and sustained biochemical efficacy in the phase III ELATIVE® trial. However, treatment effects in high-risk pts are less well established. Here, real-world (RW) data were used to assess early biochemical response following elafibranor initiation in pts with PBC within clinically relevant high-risk subgroups. **Methods:** This retrospective, observational study used RW data from the HealthVerity network. Adult pts with PBC who initiated elafibranor and had alkaline phosphatase (ALP) measurements both pre- and post-index were included; the index date was the date of first elafibranor exposure (baseline [BL]). Biochemical responses were assessed using laboratory data through 6 months (M) post-index for pts in high-risk subgroups: age < 40 years, male, those from underrepresented ethnic groups, decompensated cirrhosis 0–3 M before BL, BL ALP ≥ 3× the upper limit of normal (ULN), BL total bilirubin (TB) > ULN, and concomitant metabolic dysfunction-associated steatotic liver disease (MASLD). Results were analyzed using the Wilcoxon test. **Results:** Among 111 pts with PBC who initiated elafibranor with available BL and M6 data: 4 (3.6%) were aged < 40 years, 8 (7.2%) were male, 5 (4.5%) self-identified as Black, 41 (36.9%) self-identified as Latino/Hispanic, 9 (8.1%) had decompensated cirrhosis 0−3 M before BL, 8 (7.2%) had BL ALP ≥ 3× ULN, 12 (10.8%) had BL TB > ULN, and 12 (10.8%) had concomitant MASLD.While sample sizes were small, notable reductions in mean ALP levels were observed from BL to M6 in pts aged < 40 years (−23.9%), male pts (−32.2%), Latino/Hispanic pts (−15.9%), pts with decompensated cirrhosis (−25.0%), pts with BL ALP ≥ 3× ULN (−29.9%), pts with BL TB > ULN (−23.6%), and those with concomitant MASLD (−26.5%; **Figure A**). A smaller mean change from BL in ALP was observed in Black pts overall (−6.9%), however 3/5 (60.0%) of these pts had reductions ≥ 15% by M6. Among pts who had ALP > ULN at BL, ALP normalization was achieved in 2/3 pts aged < 40 years, 3/6 male pts, 13/34 Latino/Hispanic pts, 3/7 pts with decompensated cirrhosis, and 4/11 pts with concomitant MASLD (**Figure B**). **Conclusion:** Reductions in ALP were observed after 6M in high-risk subgroups of pts with PBC receiving elafibranor in RW settings. Given the limited published data, these key early findings suggest that elafibranor may improve liver biochemistry in high-risk pt populations that are not adequately responding to ursodeoxycholic acid.

Figure. ALP outcomes at M6 of elafibranor treatment in clinically high-risk pt subgroups



Error bars present SD. Decompensated cirrhosis recorded 0–3 months before BL. Percent with normalized ALP excludes those with normal ALP at BL. ALP: alkaline phosphatase; BL: baseline; CfB: change from baseline; MASLD: metabolic dysfunction-associated steatotic liver disease; M: Month; SD: standard deviation; ULN: upper limit of normal.

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1297 | ADULT CHOLESTATIC DISEASE BEYOND PFIC: DIVERGENT RESPONSES TO MARALIXIBAT IN TWO COMPLEX ADULT CASES

Dimitrios Papanikolaou[1] Eleni Trifylli[1] Melanie Deutsch[1] Nikolaos Papadopoulos[2], [1]GI-Liver Unit, 2nd Department of Internal Medicine, General Hospital of Athens "Hippocratio", Nation, [2]National Organization for the Prevention and Treatment of Addictions (EOPAE), Athens, Greece

Background: Real-world adult experience with maralixibat (MRX), an ileal bile acid transport (IBAT) inhibitor, remains limited outside pediatric cholestatic disorders. We describe two adult cholestatic cases with divergent responses to IBAT inhibition. **Methods:** Retrospective chart review of clinical, biochemical, elastographic, histologic, and genetic data from two adult female patients treated with MRX for refractory cholestatic pruritus. Pruritus was assessed with the Clinician Scratch Scale (CSS: 0-4; 0 = no evidence of pruritus, 4 = cutaneous mutilation, bleeding, scarring); ≥ 1-point reduction is considered clinically meaningful. **Results:** Case 1 is a 41-year-old woman with Alagille syndrome (ALGS) and compensated cirrhosis (Child-Pugh A5, MELD-Na 8), presenting with severe refractory pruritus (CSS 4) causing major sleep disturbance despite relatively preserved liver biochemistry, albeit with elevated sBA (35 µmol/L). Following 1 year of MRX therapy, pruritus resolved completely (CSS 0) and sBA decreased to 2.2 µmol/L. Follow-up laboratory evaluation demonstrated stable compensated liver disease (Child-Pugh A5, MELD-Na 7). Liver stiffness measurement by transient elastography decreased from 14.5 to 10.2 kPa after approximately 18 months of MRX.Case 2 is a 59-year-old non-cirrhotic woman with severe (CSS 3) cholestatic pruritus, elevated sBA (31.3 µmol/L). Genetic testing identified two rare heterozygous *NPHP3* variants, including a novel likely pathogenic frameshift variant [c.1615_1619del p.(Leu539IlefsTer36)], suggesting a possible underlying ciliopathy-related cholangiopathic predisposition. Initial treatment with UDCA plus MRX resulted in partial biochemical improvement, but sBA increased to 41.3 µmol/L and pruritus persisted without clinical benefit. Liver biopsy subsequently demonstrated chronic cholangiopathy compatible with AMA-negative PBC. Following MRX discontinuation and initiation of fenofibrate in combination with UDCA, liver tests improved, although sBA increased to 82.8 µmol/L and pruritus remained severe. Reintroduction of MRX on background UDCA-fenofibrate therapy resulted in rapid and marked improvement of pruritus (CSS 1), with substantial symptomatic relief reported within weeks, while sBA decreased to 28.3 µmol/L after one month of MRX. **Conclusion:** Maralixibat was associated with marked improvement in pruritus, profound reduction in sBA, and reduction in liver stiffness in ALGS, while therapeutic benefit in AMA-negative PBC emerged after biochemical control with UDCA-fenofibrate. These findings support further evaluation of IBAT inhibition in complex adult cholestatic disease.

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1298 | NEBOKITUG DOWN-REGULATES ECM CORE PROTEINS AND PATHWAYS IN PATIENTS WITH PRIMARY SCLEROSING CHOLANGITIS

Revital Aricha[1] Tom Snir[1] Jack Lawler[1] Dave Weiner[1] Adi Mor[1], [1]Chemomab

Background: Primary sclerosing cholangitis (PSC) is an immune-mediated biliary disease, where the extracellular matrix (ECM) plays a critical role in the structural component of fibrosis. We aim to measure the effects of nebokitug, a CCL24-blocking monoclonal antibody currently in clinical development for PSC, on core ECM proteins and associated molecular pathways, using proteomic profiling of patients with PSC enrolled in the SPRING Phase 2 clinical study (NCT04595825). **Methods:** Serum proteins were quantified using the Olink proximity extension assay (PEA) in healthy

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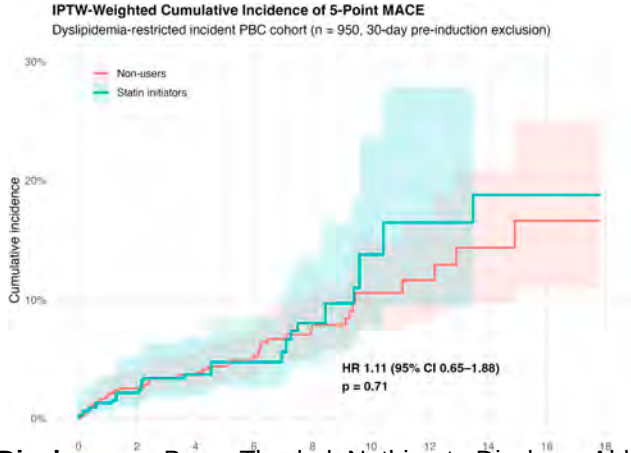
controls (n = 30) and patients with PSC enrolled in the SPRING study and treated with nebokitug 10 mg/kg (n = 21), nebokitug 20 mg/kg (n = 27), or placebo (n = 18) for 15 weeks. Linear regression was fitted to evaluate nebokitug's effect on patients with PSC and corrected for disease severity at baseline. Results were ranked based on a signed significance score and used as a basis for gene set enrichment analysis (GSEA). **Results:** Patients with PSC showed differential expression of ECM proteins, with multiple ECM proteins up regulated compared to healthy controls. Patients treated with nebokitug showed reduction of ECM proteins (collagens, proteoglycans, and glycoproteins) as compared to patients treated with placebo and overtime. This reduction was stronger in nebokitug treated patients with moderate to advanced disease. GSEA showed significant (<0.05 padj) down-regulation of ECM pathways, including ECM regulators, ECM organization, and several matrisome pathways. **Conclusion:** ECM proteins are differentially expressed in sera of PSC patients compared to healthy individuals, with multiple fibrosis driving proteins strongly up-regulated. Treatment with nebokitug resulted in suppression of ECM proteins and pathways, providing evidence of the pharmacological activities of nebokitug on fibrosis and inflammation.

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1299 | STATIN INITIATION AND MAJOR ADVERSE CARDIOVASCULAR EVENTS IN INCIDENT PRIMARY BILIARY CHOLANGITIS: AN ACTIVE-INDICATION TARGET TRIAL EMULATION

Bryce Tkachuk[1] Aldo Montano-Loza[2] Juan Abraldes[2] Jason Jiang[3] Abdel-Aziz Shaheen[1], [1]University of Calgary, [2]University of Alberta, [3]Alberta Health Services

Background: Statins remain inconsistently prescribed in primary biliary cholangitis (PBC) because of potential hepatotoxicity concerns despite hepatoprotective benefits. Whether statin initiation alters major adverse cardiovascular event (MACE) risk in PBC is unknown. We emulated a target trial to estimate the association between statin initiation and MACE among incident PBC patients with dyslipidemia. **Methods:** We assembled 1,470 EMR-validated incident PBC patients in Alberta, Canada (2005-2024), linked to administrative and vital statistics data. After excluding prevalent MACE, early death, and baseline statin use, monthly eligibility windows were used in a single-entry target trial emulation from April 2005 to March 2025. New statin initiators entered at first dispensation and were compared with statin-naive non-users assigned one randomly sample eligible month to preserve temporal alignment. To approximate an active-indication trial, analyses were restricted to documented dyslipidemia (lab defined), and non-users were assigned a randomly sampled eligible trial month to preserve temporal alignment. Follow-up began after a 30-day induction period; early MACE or insufficient follow-up were excluded before propensity-score estimation. Stabilized inverse-probability-of-treatment weights, trimmed at the 1st/99th percentiles, balanced demographics, comorbidity, time since PBC diagnosis, ursodeoxycholic acid (UDCA) and cardiovascular medication use, LDL cholesterol, and calendar time. Weighted Cox models with robust standard errors estimated 5-point MACE (MI, stroke, CV death, heart failure, or revascularization); 3-point MACE was secondary. **Results:** Of 1,101 TTE-eligible patients, 964 had dyslipidemia. After induction exclusion, 950 were analyzed (255 statin initiators; 695 non-users). IPTW achieved excellent balance (all standardized mean differences <0.05): mean age 61 years, 11% male, mean LDL 3.2 mmol/L, and median follow-up 5.6 versus 5.5 years. During 5,906 person-years, 67 5-point MACE events occurred (22 statin, 45 non-user; rates 13.5 vs 10.5/1,000 person-years). Statin initiation was not associated with 5-point MACE (HR 1.11; 95% CI 0.65-1.88; p = 0.71, Figure 1) or 3-point MACE (44 events; HR 1.19; 95% CI 0.62-2.28; p = 0.61). MI was the most frequent event (n = 20), followed by heart failure (n = 18), stroke (n = 13), revascularization (n = 8), and CV death (n = 8). **Conclusion:** In this population-based, EMR-validated incident PBC cohort with dyslipidemia, sequential target trial emulation found no evidence that statin initiation affected MACE risk. These findings support statin prescribing for standard lipid indications, including dyslipidemia and for primary or secondary prevention of atherosclerotic cardiovascular disease.



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1300 | REAL WORLD ANALYSIS OF PRIMARY BILIARY CHOLANGITIS SUBGROUPS AT RISK OF RAPID PROGRESSION

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Background: Primary biliary cholangitis (PBC) is a chronic cholestatic liver disease that can progress to cirrhosis, liver failure, and the need for liver transplant. Despite the availability of ursodeoxycholic acid as first-line treatment, some patients remain at increased risk of disease progression due to inadequate treatment response. This study used United States real-world data to describe demographics and clinical characteristics of high-risk PBC subgroups. **Methods:** This retrospective cohort study identified adults with newly diagnosed PBC and $\geq$6 months of prior continuous enrollment and documented activity in the Veradigm Network Electronic Health Records linked to Komodo Health claims data (Jan 2017–Dec 2025). Pre-defined high-risk subgroups included males, early-onset PBC (diagnosis $\leq$40 years), and markedly elevated baseline alkaline phosphatase (ALP; >2×upper limit of normal [ULN]). Exploratory subgroups of interest included Black and/or Hispanic patients, those with markedly elevated baseline total bilirubin (TB; >1×ULN), and concomitant metabolic dysfunction-associated steatotic liver disease (MASLD). Demographics and clinical characteristics were assessed during the 6-month baseline period. **Results:** The study included 21,406 patients. Among subgroups, 4,796 were males, 2,175 had early-onset PBC, 1,014 had markedly elevated baseline ALP, 2,940 were Black and/or Hispanic, 563 had markedly elevated baseline TB, and 4,414 had concomitant MASLD. Among males, mean (standard deviation [SD]) age was 61.4 (14.7) years and 18.1% had hepatic decompensation (cirrhosis/portal hypertension with diagnosed ascites), with a median (interquartile range [IQR]) ALP of 124.0 U/L (129.0), gamma-glutamyl transferase (GGT) of 151.0 U/L (251.3), and TB of 1.0 mg/dL (0.7). Despite only comprising 22.4% of the study population, males accounted for 41.0% of markedly elevated TB cases. Patients with early-onset PBC were mostly female (78.8%) with a mean (SD) age of 32.3 (6.1) years. This subgroup had the lowest proportion of hepatic decompensation (6.4% versus 9.9% overall). Patients with markedly elevated baseline TB had a median (IQR) platelet count of 165,000/mcL (139,000), the lowest across all subgroups. This subgroup had the highest proportions of portal hypertension (27.7%), hepatic decompensation (32.7%), and fatigue (35.9%) across subgroups (**Table**). **Conclusion:** Baseline disease severity at PBC diagnosis varied across subgroups and compared with the overall study population, with the proportions of hepatic decompensation ranging from 6.4% in early-onset patients to 32.7% in those with markedly elevated baseline TB. Elevated proportions of hepatic decompensation suggest many high-risk patients are beyond the benefit window of and/or may have contraindication for second-line therapy at diagnosis, underscoring the importance of earlier risk-based identification and intervention.

Table. Baseline demographic, clinical, and laboratory characteristics at PBC diagnosis

	All patients (N=21,406)		Males (N=4,796)		Early-onset PBC (N=2,175)		Elevated ALP levels at baseline* (N=1,014)		Elevated TB levels at baseline** (N=563)	
	N/Mean/Median	%/SD/IQR	N/Mean/Median	%/SD/IQR	N/Mean/Median	%/SD/IQR	N/Mean/Median	%/SD/IQR	N/Mean/Median	%/SD/IQR
Age, Index Date (Mean, SD)	60.3	14.3	61.4	14.7	32.3	6.1	61.0	13.0	60.7	13.7
Sex (N,%)										
Male	4,796	22.4	4,796	100.0	462	21.2	142	14.0	231	41.0
Female	16,610	77.6	N/A	N/A	1,713	78.8	872	86.0	332	59.0
ALP, U/L (Median, IQR)	145.0	184.0	124.0	129.0	98.5	120.5	311.0	210.8	198.0	231.5
TB, mg/dL (Median, IQR)	0.8	0.5	1.0	0.7	0.6	0.6	1.0	0.5	1.9	1.3
Albumin, g/dL (Median, IQR)	4.0	0.4	4.0	0.6	4.2	0.6	4.0	0.4	3.7	1.0
GGT, U/L (Median, IQR)	134.0	226.0	151.0	251.3	70.0	88.8	282.0	242.0	129.0	316.0
Platelet count (platelets/mcL) (Median, IQR)	230,000	129,000	188,000	117,000	267,500	112,250	243,000	128,000	168,000	139,000
CCI (Mean, SD)	2.4	2.5	3.2	3.9	1.1	1.7	2.7	2.5	3.9	2.8
Clinical conditions (N, %)										
Autoimmune thyroid disease	4,958	23.2	648	13.5	280	12.9	266	26.2	137	23.6
Fatigue	5,076	23.7	1,207	25.2	473	21.7	281	27.7	202	35.9
Hepatic decompensation†	2,125	9.9	866	18.1	139	6.4	93	9.2	184	32.7
Portal hypertension	1,685	7.9	673	14.0	114	5.2	70	6.9	156	27.7
Raynaud's syndrome	804	3.8	83	1.7	125	5.7	39	3.8	4	0.7
Sjogren's syndrome	577	2.7	24	0.5	48	2.2	29	2.9	3	0.5
SLE	645	3.0	31	0.6	102	4.7	46	4.5	15	2.7

Notes: List values reflect patients with available data at the baseline period, not all patients constituted rich results. *Elevated baseline ALP, defined as >2×ULN, ALP ULN was defined as 129 U/L for males and 104 U/L for females; **Elevated TB levels at baseline were defined as >1×ULN; TB ULN was reported as 1.0 mg/dL; †Including patients with complications of cirrhosis/portal hypertension if the patient also has a diagnosis for ascites.

Abbreviations: ALP, alkaline phosphatase; CCI, Charlson Comorbidity Index; GGT, gamma-glutamyl transferase; IQR, interquartile range; N/A, not applicable; PBC primary biliary cholangitis; SLE, systemic lupus erythematosus; SD, standard deviation; TB, total bilirubin; ULN, upper limit of normal.

Disclosures: Brian Wentworth:Ipsen: Consultant, Ipsen: Speaking and Teaching, GSK: Consultant, Luna Labs USA: Consultant, Sonia Lee:Nothing to Disclose, Anusorn Thanataveerat:Ipsen Biopharmaceuticals: Independent Contractor, Christopher Adams:Ipsen: Independent Contractor, Stephanie Wall:Ipsen Pharmaceuticals: Consultant, Neil Shah:Ipsen: Consultant, GSK: Consultant.

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1301 | PLATELET REACTIVITY AND PLATELET-IMMUNE CELL INTERACTIONS IN PBC ARE LINKED TO ALKALINE PHOSPHATASE LEVELS AND INCOMPLETE RESPONSE TO URSODIOL

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Background: Primary Biliary Cholangitis (PBC) is the most common autoimmune liver disease, and existing therapies still do not serve a substantial number of patients. New insights into disease pathogenesis are needed to identify novel therapeutic targets. Platelets can interact with immune cells in the setting of autoimmune disease, and this study aims to identify the pathological role of platelets in PBC. **Methods:** Platelet flow cytometry was performed from fresh whole blood (n = 10 patients). Banked PBMCs from PBC patients treated with UDCA and either normal (responder) or abnormal (non-responder) alkaline phosphatase (ALP) were included. Amnis Imagestream or CytoFlex LX flow cytometers were used. RNA was isolated from total PBMCs and analyzed with bulk RNAseq. **Results:** In PBC patients (n = 10), platelet reactivity measured by fold-change upregulation of platelet activation markers CD40L ($r2 = 0.48$, $p < 0.05$), CD62P ($r2 = 0.62$, $p < 0.01$), and PAC1 ($r2 = 0.73$, $p < 0.01$) upon collagen stimulation was significantly and positively correlated with ALP levels. Flow cytometry of PBMCs from responders (n = 10, mean ALP 94.2 U/L) vs. non-responders (n = 15, mean ALP 197.1 U/L) and co-staining for platelet marker CD41 identified significantly more platelet-interacting (CD41+) B cells in non-responders vs. responders (18.86%, 12.93%, $p = 0.03$). Platelet interactions in other populations (CD4 T cells, CD8 T cells, monocytes) were observed with no significant differences in non-responders vs. responders. Bulk RNAseq was done from non-responder (n = 10) and responder (n = 9) PBMCs, and deconvolution revealed a "platelet" cluster. This cluster expressed high proportions of T cell, B cell, and monocyte markers, suggesting it consists of platelet-immune cell aggregates. To visualize these aggregates, Amnis Imagestream was used to show discrete platelet (CD41+) events on the surface of lymphocytes in our PBMC samples, indicating cell-cell interactions. Within those aggregates, platelet activation pathways were found to be significantly upregulated in non-responders, suggesting immune cell interaction with more activated platelets in non-responders. Via deconvolution, we performed pathway analysis within total B cells showing upregulation(NES 1.4, FDR < 0.05) of the systemic lupus erythematosus pathway in non-responders. IL10 is a leading-edge gene within this pathway and can have a pathological role in autoimmunity. **Conclusion:** Increased platelet reactivity in PBC patients correlates with serum ALP levels. Platelet-B cell interactions are significantly increased in PBC patients who did not respond to UDCA. Bulk RNAseq and cell-type deconvolution also identify enhanced immune cell interactions with activated platelets, and upregulation of autoimmune signals in B cells, in non-responders. Platelet-B cell interactions may be a mechanism of disease pathogenesis in PBC and a novel candidate target for therapeutic interventions.

Disclosures: Fallyn Kirlin:Nothing to Disclose, Subhasis Mohanty:Nothing to Disclose, Scott Roberts: Nothing to Disclose, Yasuko Iwakiri:Nothing to Disclose, David Assis:Nothing to Disclose, Matthew McConnell:Nothing to Disclose.

1302 | ASSESSING REAL-WORLD OUTCOMES IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS ON ELAFIBRANOR

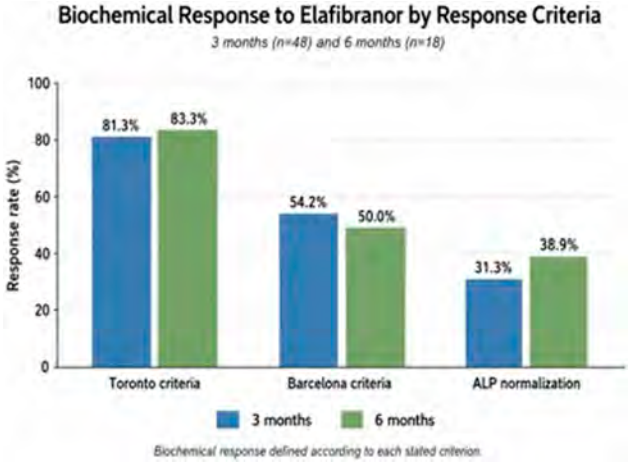
Ibrahim Alomar[1], [1]Division of Gastroenterology and Hepatology, Western University & London Health Sciences Centre

Background: Primary biliary cholangitis is a chronic cholestatic liver disease that may progress to cirrhosis and liver failure. Elafibranor has shown biochemical efficacy in clinical trials, but real-world data remain limited. We aimed to evaluate the effectiveness and safety of elafibranor in patients with PBC treated in routine clinical practice. **Methods:** We conducted a single-center observational cohort study of adults with PBC treated with elafibranor. Clinical, biochemical, treatment, and safety data were collected from medical records. The primary outcome was biochemical response, defined as ALP $< 1.67 \times$ ULN and total bilirubin $\leq$ ULN. Descriptive statistics were used, and logistic regression estimated odds ratios for factors associated with response. **Results:** A total of 51 patients with PBC treated with elafibranor were included. Most patients were female (47/51, 92.2%), with a mean age at PBC diagnosis of 52.3 ± 12.5 years and a mean age at elafibranor initiation of 61.7 ± 10.9 years. Positive autoimmune markers were present in 45/51 patients (88.2%), and AMA positivity was observed in 38/51 (74.5%). At treatment initiation, 13/51 patients (25.5%) had cirrhosis, and baseline ALP was 240.8 ± 109.0. Coexisting liver disease was present in 31/51 patients (60.8%), most commonly MASLD (23/51, 45.1%),

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followed by AIH overlap (8/51, 15.7%), MetALD (2/51, 3.9%), and ALD (1/51, 2.0%); no patients had coexisting PSC (0/51, 0%). All patients had previously received UDCA (51/51, 100%), and elafibranor was combined with UDCA in 47/51 (92.2%); the main indication for elafibranor was inadequate biochemical response (47/51, 92.2%). At 3 months, biochemical response according to Toronto criteria was achieved in 39/48 patients (81.3%), while 26/48 (54.2%) met Barcelona criteria and 15/48 (31.3%) achieved ALP normalization. At 6 months, mean ALP was 152.4 ± 54.7, and 15/18 patients (83.3%) met Toronto criteria, 9/18 (50.0%) met Barcelona criteria, and 7/18 (38.9%) achieved ALP normalization. Adverse events were reported in 11/50 patients (22.0%), most commonly nausea, and treatment discontinuation due to adverse events occurred in 3/51 patients (5.9%).In logistic regression, higher baseline ALP and ALT was associated with lower odds of biochemical response at 3 months (OR 0.99, 95% CI 0.98–1.00; p = 0.016 and OR 0.96, 95% CI 0.93–1.00; p = 0.030), while no significant associations were observed for age, sex, AMA positivity, coexisting MASLD or AIH, cirrhosis, or prior exposure to OCA or fibrates. **Conclusion:** Elafibranor was associated with a high biochemical response rate as early as 3 months in this real-world PBC cohort. Treatment discontinuation was infrequent, and higher baseline ALP and ALT were associated with lower odds of early response.

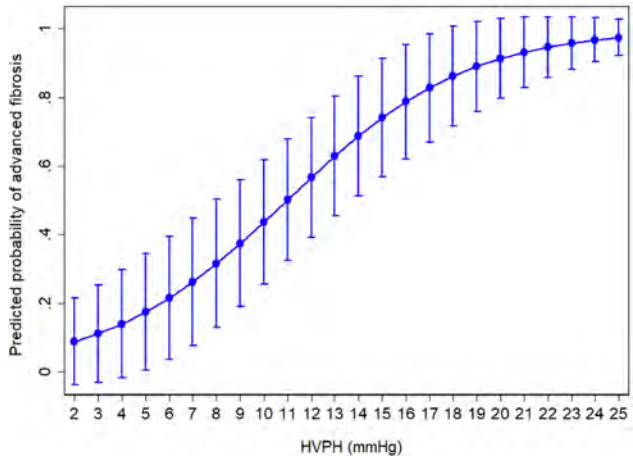


Disclosures: Ibrahim Alomar:Nothing to Disclose.

1303 | THE HEPATIC VENOUS PRESSURE GRADIENT IDENTIFIES HISTOLOGICAL ADVANCED FIBROSIS (F3–F4) IN AUTOIMMUNE HEPATITIS

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Background: The hepatic venous pressure gradient (HVPG) correlates with fibrosis across several liver diseases, but evidence in autoimmune hepatitis (AIH) remains limited. The aim was to assess the association between HVPG and fibrosis, its performance for advanced fibrosis (AF), the optimal cutoff, and its relationship with 6-months biochemical response. **Methods:** Between January 2018 and July 2025, 208 hemodynamic procedures were performed. Of these, 77 had histology consistent with AIH. Overlap syndromes (n = 22), treatment at biopsy (n = 3), post–liver transplant AIH (n = 1), and uninterpretable HVPG due to communicating veins (n = 6) were excluded, yielding 47 treatment-naïve patients with AIH. Patients were classified as without AF (F0–F2) orwith AF (F3–F4). ROC analysis, the Liu method, and univariate logistic regression were performed. The association between HVPG and biochemical response was evaluated. **Results:** Median age was 59 years (17–79), and 74% were women. HVPG was higher in AF than in F0–F2 (15.5 vs 7.0 mmHg; p < 0.001). The AUROC for AF was 0.84 (95%CI 0.72–0.96). Each 1-mmHg increase in HVPG increased the odds of AF by 29% (OR 1.29;95%CI 1.11–1.50; p = 0.001). The optimal cutoff was 10.5 mmHg (sensitivity 0.85; specificity 0.76), above which the odds of AF were 17.6-fold higher. HVPG was not associated with biochemical response (p = 0.701). **Conclusion:** In treatment-naïve AIH, HVPG was associated with AF and showed good diagnostic accuracy. A 10.5-mmHg threshold may help identify AF. HVPG did not predict early 6-months biochemical response.



Disclosures: Álvaro Urzúa:Nothing to Disclose, Víctor Henríquez-Auba:Nothing to Disclose, Daniela Simian: Nothing to Disclose, Diego Lizama:Nothing to Disclose, Jorge Chiong:Nothing to Disclose, Jaime Poniachik: Nothing to Disclose.

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1304 | REAL-WORLD BIOCHEMICAL RESPONSES TO FIRST-LINE AZATHIOPRINE VERSUS MYCOPHENOLATE AND UPON SWITCHING FROM AZATHIOPRINE TO MYCOPHENOLATE IN AUTOIMMUNE HEPATITIS PATIENTS

Astrid Amador[1] Stephen Wong[1], [1]University of Santo Tomas Hospital

Background: Mycophenolate mofetil (MMF) has been found to be comparable to azathioprine (AZA) in achieving biochemical remission in autoimmune hepatitis (AIH). We aimed to compare real-world biochemical responses of first-line AZA and MMF, and responses after switching from AZA to MMF in AIH patients **Methods:** We analyzed a retrospective cohort of AIH patients treated with AZA or MMF. Patients received concomitant steroids 0-14 days prior to AZA or MMF. Biochemical responses were defined as: complete response(CR) = alanine aminotransferase (ALT) normalization; partial response(PR) = ≥50% ALT reduction but above normal upper limits (ULN); non-response(NR) = <50% ALT reduction or ALT increase. We analyzed a subset who switched from AZA to MMF. **Results:** Overall, 67(AZA) and 12(MMF) patients were included. CR progressively increased after 3 (AZA = 52% vs. MMF = 55.6%;p = 0.236), 6 (AZA = 61.7% vs. MMF = 100%;p = 0.760) and 12 months (AZA = 76.9% vs. MMF = 100%;p = 1.0) of treatment, with no difference in NR rates (AZA = 5.1% vs. MMF = 0%;p = 1.0) after 12 months. Despite similar response rates, AZA demonstrated greater median ALT reduction at 3 months vs. MMF (ΔALT −111.8 vs −1.0 U/L;p = 0.008). The reasons for AZA to MMF switch were AZA unavailability (n = 16;76.2%) and side effects to AZA (n = 5;23.8%). Following switching, most patients maintained biochemical stability after 6months (87.5%). However, biochemical flare (ALT ≥ 2×ULN) occurred in 3(14.3%) patients, prompting reversion to AZA. **Conclusion:** Our data support the effectiveness of MMF as first-line therapy. However, switching from AZA to MMF may be associated with biochemical flare in a subset of patients, highlighting the need for cautious use in clinical practice with close biochemical monitoring.

Disclosures: Astrid Amador:Nothing to Disclose, Stephen Wong:Nothing to Disclose.

1305 | PREVALENCE AND CLINICAL OUTCOMES OF MASLD OVERLAP IN PATIENTS WITH AUTOIMMUNE LIVER DISEASE: A DESCRIPTIVE COHORT ANALYSIS

Victoria Abadi-Ron[1] Ana Marenco-Flores[2] Natalia Rojas Amaris[1] Fernando Munguia[1] Giuliana Arevalo[3] Romelia Barba[4] Daniela Goyes[5] Esli Medina Morales[6] Leandro Sierra[7] Behnam Saberi[8] Vilas Patwardhan[1] Alan Bonder[1], [1]Beth Israel Deaconess Medical Center, [2]Harvard Medical School, [3]Department of Internal Medicine, University of Miami / Jackson Memorial Hospital, [4]Texas Tech University, [5]Yale School of Medicine, New Haven, [6]Washington University in St Louis, [7]Cleveland Clinic Foundation, [8]BIDMC Harvard Medical School

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is increasingly recognized as a comorbidity in chronic liver disease, but its prevalence and clinical associations in autoimmune liver diseases (AILD) remain unclear. We evaluated MASLD overlap prevalence in autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC), and its association with clinical features and complete biochemical response (CBR). **Methods:** We performed a cross-sectional analysis using electronic medical records and prospectively collected data from our Autoimmune Liver Diseases Registry at Beth Israel Deaconess Medical Center. Patients with AIH, PBC, or PSC were included. MASLD was defined as body mass index ≥25 kg/m² plus ≥1 cardiometabolic risk factor, including diabetes mellitus, hypertension, hyperlipidemia, or coronary artery disease. CBR was disease-specific: POISE criteria for PBC, alkaline phosphatase below the upper limit of normal for PSC, and normalization of aminotransferases and immunoglobulin G for AIH. Laboratory values recorded as 0 were treated as missing. Continuous variables were compared using Mann–Whitney U tests and categorical variables using Fisher's exact tests. Multivariable logistic regression assessed the association between MASLD overlap and CBR, adjusting for age, sex, AILD subtype, and cirrhosis. **Results:** Among 343 patients with AILD, 103 (30.0%) had MASLD overlap. Prevalence was similar across subtypes: AIH 45/146 (30.8%), PBC 24/94 (25.5%), and PSC 34/103 (33.0%) (p = 0.501). Patients with MASLD overlap had higher BMI (31.0 [27.9–35.5] vs. 25.0 [22.6–28.9] kg/m²; p < 0.001), hyperlipidemia (42.0% vs. 18.7%; p < 0.001), and hypertension (59.4% vs. 24.6%; p < 0.001). Type 2 diabetes was numerically higher but not significant (10.3% vs. 4.7%; p = 0.109). Cirrhosis was less frequent with MASLD overlap (19.4% vs. 29.7%; p = 0.048). CBR was similar between groups (65.0% vs. 63.2%; p = 0.742). Baseline liver biochemistries did not significantly differ. In multivariable analysis, MASLD overlap was not independently associated with CBR (adjusted OR 0.96, 95% CI 0.57–1.63; p = 0.891). **Conclusion:** MASLD overlap was common in AILD, affecting nearly one-third of patients, with similar prevalence across AIH, PBC, and PSC. It was associated with higher BMI and greater metabolic comorbidity burden, but not with lower odds of CBR. These findings support routine metabolic risk assessment in AILD.

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Interpretation is limited by the single-center design and modest cohort size, particularly within disease-specific subgroups; larger multicenter studies are needed to assess long-term outcomes.

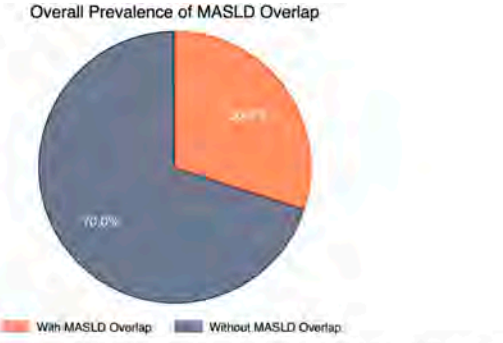


Figure 1. Overall prevalence of MASLD overlap in the autoimmune liver disease cohort. MASLD overlap was present in 103 of 343 patients (30.0%), while 240 of 343 patients (70.0%) had no MASLD overlap. MASLD = metabolic dysfunction-associated steatotic liver disease.

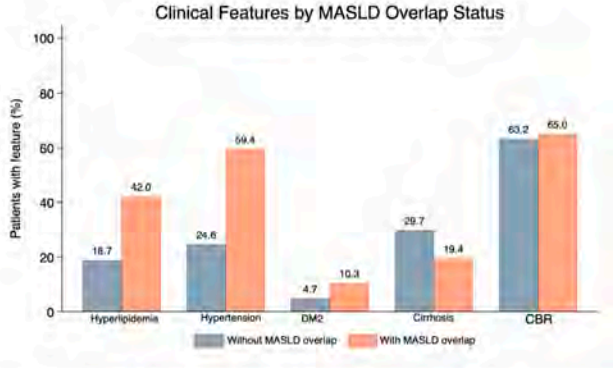


Figure 2. Clinical features by MASLD overlap status. Bars represent the percentage of patients with each feature among patients without MASLD overlap and those with MASLD overlap. Patients with MASLD overlap had higher prevalence of hyperlipidemia (42.0% vs. 18.7%, p<0.001) and hypertension (59.4% vs. 24.6%; p<0.001), while type 2 diabetes mellitus was numerically higher but not statistically significant (10.3% vs. 4.7%; p=0.109). Cirrhosis was less frequent in patients with MASLD overlap (19.4% vs. 29.7%; p=0.048), and complete biochemical response was similar between groups (65.0% vs. 63.2%; p=0.742). P values were calculated using Fisher's exact test. MASLD = metabolic dysfunction-associated steatotic liver disease; DM2 = type 2 diabetes mellitus; CBR = complete biochemical response.

Disclosures: Victoria Abadi-Ron:Nothing to Disclose, Ana Marenco-Flores:Nothing to Disclose, Natalia Rojas Amaris:Nothing to Disclose, Fernando Munguia:Nothing to Disclose, Giuliana Arevalo:Nothing to Disclose, Romelia Barba:Nothing to Disclose, Daniela Goyes: Nothing to Disclose, Esli Medina Morales:Nothing to Disclose, Leandro Sierra:Nothing to Disclose, Behnam Saberi:Nothing to Disclose, Vilas Patwardhan:Nothing to Disclose, Alan Bonder:Nothing to Disclose.

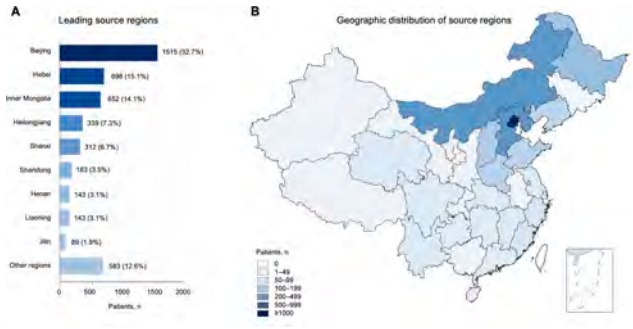
1306 | TEMPORAL TRENDS, SOURCE-REGION DISTRIBUTION, AND CLINICAL PHENOTYPIC HETEROGENEITY OF PRIMARY BILIARY CHOLANGITIS: A 17-YEAR REAL-WORLD COHORT OF 4,646 PATIENTS FROM CHINA

Xiao Lin[1] Chunyang Huang[1] Bin Xu[1] Xue Yang[1],
[1]Beijing Youan Hospital, Capital Medical University

Background: Long-term real-world data on primary biliary cholangitis (PBC) in China remain limited, particularly regarding temporal trends, source-region distribution, and clinical phenotypic heterogeneity. We evaluated annual case volume, source-region composition, and clinical phenotypes in a tertiary liver-center cohort. **Methods:** We retrospectively included 4,646 PBC patients at Beijing YouAn Hospital, Capital Medical University, from January 1, 2008, to December 31, 2024. For repeated visits, the first qualifying record was used. Demographics, source region, liver biochemistry, immunoglobulins, autoantibodies, cirrhosis, histology, concomitant liver diseases, extrahepatic autoimmune diseases, and viral markers were collected. Beijing patients were compared with patients from the top eight non-Beijing source regions. **Results:** Annual PBC case volume showed an overall upward trend. Women accounted for 86.7% of the cohort; mean age was 56.5 ± 11.7 years. AMA, AMA-M2, anti-gp210, and anti-sp100 positivity rates were 87.3%, 89.8%, 30.4%, and 19.1%, respectively. Total bilirubin categories of ≤34, >34–102, >102–170, and >170 μmol/L accounted for 72.5%, 17.6%, 4.0%, and 5.9% of patients; cirrhosis was present in 888 patients (19.1%). Among 4,637 patients with source-region data, Beijing was the leading source region [1,515 (32.67%)], followed by Hebei [698 (15.05%)] and Inner Mongolia [652 (14.06%)]; these regions accounted for 61.79%. Other leading non-Beijing source regions included Heilongjiang, Shanxi, Shandong, Henan, Liaoning, and Jilin. North China and Northeast China accounted for 69.14% and 12.31%, respectively, comprising 81.45% of patients. Beijing patients were older than patients from the leading non-Beijing source regions (60.9 ± 11.7 vs. 54.5 ± 11.2 years, P < 0.001), but had lower ALT, AST, total bilirubin, GGT, ALP, and IgM levels. AMA positivity was lower in Beijing patients [84.3% (1,236/1,466) vs. 87.9% (2,143/2,438), P = 0.002], whereas AMA-M2 positivity was higher [89.8% (1,135/1,264) vs. 86.2% (1,977/2,294), P = 0.002]. Anti-sp100 positivity was slightly higher in Beijing patients [20.8% (266/1,276) vs. 18.0% (388/2,151), P = 0.048], while anti-gp210 positivity was similar (29.1% vs. 30.4%, P = 0.442). Cirrhosis prevalence was comparable [14.3% (217/1,515) vs. 15.5% (393/2,539), P = 0.342]. Overall, 21.1% had concomitant liver diseases, mainly autoimmune hepatitis, drug-induced liver injury, and steatotic liver disease; 311 patients (6.69%) had extrahepatic autoimmune diseases, mainly Sjögren's syndrome. **Conclusion:** In this 17-year real-world PBC cohort, annual recorded case volume showed an overall upward trend, and patient sources were concentrated in North and Northeast China. Differences in age, biochemical activity, and autoantibody profiles between Beijing and major non-Beijing source regions highlight clinical phenotypic heterogeneity in PBC.

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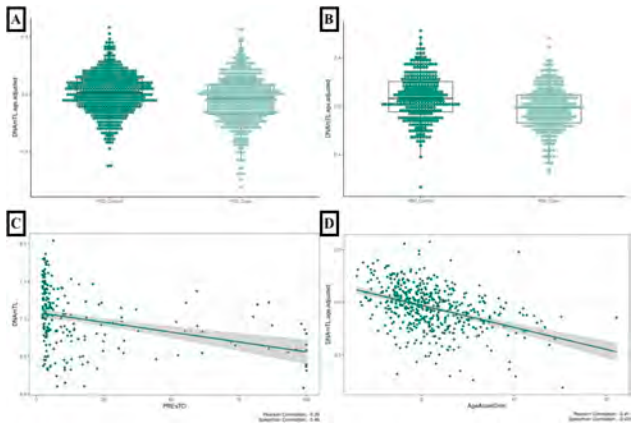


Disclosures: Xiao Lin:Nothing to Disclose, Chunyang Huang:Nothing to Disclose, Bin Xu:Nothing to Disclose, Xue Yang:Nothing to Disclose.

1307 | ACCELERATED BIOLOGICAL AGING IN CHOLESTATIC LIVER DISEASE: TELOMERE ATTRITION AND ASSOCIATION WITH DISEASE SEVERITY

Saqr Alsakarneh[1] Biran Juran[1] Jenna Fernandez[1] Mrinal Patnaik[1] Gregory Gores[1] Nicholas LaRusso[1] Konstantinos Lazaridis[1], [1]Mayo Clinic

Background: Primary sclerosing cholangitis (PSC) and primary biliary cholangitis (PBC) are chronic cholestatic liver diseases associated with progressive fibrosis and hepatic complications. Emerging evidence suggests that accelerated biological aging may contribute to chronic inflammatory diseases. DNA methylation–derived telomere length (DNAmTL), a marker of replicative aging and cellular turnover, has not been characterized in PSC or PBC. We aimed to evaluate DNAmTL in PSC and PBC and assess its relationship with disease severity and epigenetic aging. **Methods:** We analyzed 1,540 individuals from a multicenter cohort with DNA methylation profiling, including PSC (n = 474), PSC controls (n = 484), PBC (n = 291), and PBC controls (n = 291). DNAmTL and age-adjusted DNAmTL were compared across groups. Associations with clinical outcomes were evaluated using nonparametric testing and multivariable logistic regression adjusting for age and sex. Correlations with the Primary Sclerosing Cholangitis Risk Estimate Tool (PRESTO) score and epigenetic age acceleration (AgeAccelGrim) were assessed using linear regression models. **Results:** PSC patients demonstrated significantly shorter age-adjusted DNAmTL compared with controls (median −0.036 vs 0.016; $p < 0.001$; Figure 1-A). Similarly, PBC patients exhibited reduced DNAmTL relative to controls (median 6.814 vs 6.885; $p < 0.001$; Figure 1-B). Within PSC, shorter DNAmTL was associated with cirrhosis and advanced disease, with associations persisting after age adjustment (both $p = 0.001$). In multivariable analyses, shorter DNAmTL independently associated with cirrhosis (OR 0.17, 95% CI 0.05–0.56, $p = 0.0039$) and advanced liver disease (OR 0.17, 95% CI 0.05–0.55, $p = 0.003$). Shorter DNAmTL was also observed in hepatic decompensation and hepatobiliary malignancy, including cholangiocarcinoma. DNAmTL inversely correlated with PRESTO score (Figure 1-C) and strongly correlated with AgeAccelGrim (Figure 1-D) in both PSC and PBC (all $p < 0.001$). **Conclusion:** PSC and PBC are associated with telomere shortening relative to controls, supporting accelerated biological aging in cholestatic liver disease. In PSC, telomere attrition independently associates with disease severity, suggesting DNAmTL may represent a clinically relevant biomarker of progressive disease biology. These findings identify telomere attrition as a clinically relevant and complementary dimension of biological aging in cholestatic liver disease.



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1308 | CLINICAL EXPERIENCE IMPROVES ADHERENCE TO KEY RECOMMENDATIONS IN PRIMARY BILIARY CHOLANGITIS

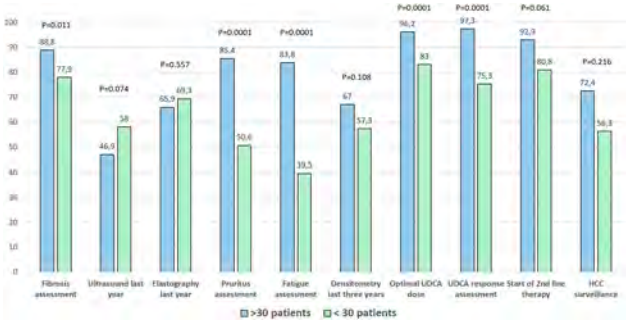
Ignacio López-Bueno[1] Pilar Del Pino[2] María Nieto[1] Miguel Jiménez[3] Carmen Sendra[4] Jose Miguel Rosales-Zabal[5] Marta Casado Martin[6] Germán

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Background: Despite the existence of national and international guidelines for primary biliary cholangitis (PBC), the management of this condition remains highly heterogeneous. Furthermore, data focusing on the PBC care cascade are limited. We characterized the different steps in the PBC care cascade, and evaluated adherence to the key recommendations of the international guidelines for PBC. **Methods:** This multicenter retrospective study included 387 PBC patients from seven hospitals. We collected data on: a) the care cascade (e.g., indications for testing PBC-specific autoantibodies, time to referral to a specialist, and time to PBC diagnosis); b) healthcare-related characteristics (e.g., the clinical unit responsible for patient management, the clinician's experience with PBC, and hospital characteristics); and c) adherence to guideline-recommended standards of care (e.g., comprehensive symptom assessment, evaluation of liver fibrosis, assessment of response to ursodeoxycholic acid and consideration of second-line therapy, and surveillance for complications of cirrhosis). **Results:** Up to 90% of patients were female, with a mean age of 55 years at the time of diagnosis. Advanced fibrosis (F3–F4) was observed in 11.8% of patients, while 9.4% had overlap with autoimmune hepatitis. In addition, 34.5% of patients were symptomatic at baseline. The number of visits required to establish the final diagnosis was 3.2 +/- 3.8.The main reason for assessing PBC-specific autoantibodies was cholestasis (58%), while a history of prior cholestasis was present in up to 87% of patients. Most patients (62.6%) were from urban areas, and 51.3% were treated at a referral center. A total of 51% of patients were diagnosed in Hepatology departments, while 45.9% were diagnosed in Gastroenterology departments. However, 85.9% were ultimately followed up by hepatologists. In addition, 74.6% of patients were managed by specialists with experience in treating more than 30 PBC patients.On the other hand, some adherence to the main recommendations differed significantly between clinicians managing more than 30 patients and those managing fewer than 30 patients (Figure). **Conclusion:** Nearly 90% of patients exhibited cholestasis prior to the diagnosis of PBC; however, cholestasis was the indication for testing PBC-specific autoantibodies in only 60% of cases. In addition, greater clinician experience was associated with better adherence to the key recommendations outlined in the guidelines.



Disclosures: Ignacio López-Bueno:Gilead Science: Grant/Research Support, Pilar Del Pino:Nothing to Disclose, María Nieto:Nothing to Disclose, Miguel Jiménez:Nothing to Disclose, Carmen Sendra:Nothing to Disclose, Jose Miguel Rosales-Zabal:Gilead: Speaking and Teaching, Abbvie: Speaking and Teaching, Astra Zeneca: Speaking and Teaching, Roche: Speaking and Teaching, marta casado martin:Nothing to Disclose, Germán Santamaría:Nothing to Disclose, JOSE MANUEL SOUSA MARTIN:Gilead: Consultant, Ipsen: Speaking and Teaching, Javier Ampuero Herrojo:Nothing to Disclose.

1309 | 肠道微生物群和代谢的变化与PBC的严重程度相关。

Qi Wang[1] Chunyang Huang[1] Minghui Li[1] Ronghua Jin[1], [1]Beijing Ditan hospital

Background: 本研究旨在探讨原发性胆管炎(PBC)患者在代谢特征和肠道微生物群上的差异,这些患者在GP210抗体阳性(GP210_pos)和GP210抗体阴性(GP210_neg)患者之间存在差异。 **Methods:** 本研究采用非靶向代谢组学分析31名GP210抗体阴性患者与13名GP210抗体阳性患者间的血清代谢物差异。此外,还使用16S rRNA测序比较两组患者间肠道微生物群的组成。我们进一步利用桑基图和相关网络图探讨了不同代谢产物与不同细菌属之间的相关性。最后,对每种代谢物进行了ROC曲线分析,以评估其识别和预测GP210抗体阳性PBC的有效性。 **Results:** GP210_pos患者共鉴定出11个差异细菌属,其中4个属的相对丰度显著增加,7个属显著减少,同时发现9个差异代谢物。其中,增加的属如*Gemmiger*、*Faecalibacterium*、嗜血杆菌和巨型酵母属与1-过氧费罗酮类、类固醇O-硫酸盐呈显著负相关,与10,16-二羟基己腺酸呈显著正相关。相反,减少的链球菌属和沙门氏菌属与Synaptolepis K1因子、子甲酰胺F和Cassaidine呈显著负相关。此外,ROC曲线分析显示Chaksine的AUC值最高,达0.74,显示出强烈的预测能力。 **Conclusion:** 本研究发现GP210_pos PBC患者在代谢物谱和肠道微生物组成方面存在显著差异。单变量ROC分析结果特别强调Chaksine在其预测模型中具有强预测能力(AUC = 0.74)。

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Disclosures: Qi Wang:Nothing to Disclose, Chunyang Huang:Nothing to Disclose, Minghui Li:Nothing to Disclose, Ronghua Jin:Nothing to Disclose.

1310 | CLINICAL AND SEROLOGIC CHARACTERISTICS OF PRIMARY BILIARY CHOLANGITIS IN VIETNAM: A REAL-WORLD CASE SERIES

Khiem Pham[1] Khanh Vu Truong[1], [1]Tam Anh General Hospital

Background: Primary biliary cholangitis (PBC) is a chronic autoimmune cholestatic liver disease with heterogeneous clinical and serologic manifestations. Diagnosis may be challenging in patients with atypical biochemical patterns or negative anti-mitochondrial antibody (AMA). Data regarding PBC in Vietnam remain limited. This study aimed to describe the clinical, biochemical, and immunologic characteristics of patients with PBC in a real-world setting in Vietnam. **Methods:** We conducted a retrospective case series of patients diagnosed with PBC at Tam Anh General Hospital between 2022 and 2025. Diagnosis was established based on at least two of the following criteria: cholestatic liver biochemistry, AMA positivity or PBC-specific antinuclear antibodies (anti-Sp100 and/or anti-gp210), and compatible histology. Clinical, biochemical, and immunologic characteristics were analyzed descriptively. Liver injury patterns were classified using the R ratio. **Results:** Sixteen patients were included. Patients were predominantly female (93.8%), with a median age of 59.5 years (IQR 54–65.5). At diagnosis, 43.8% (7/16) were asymptomatic and identified incidentally through abnormal liver biochemistry. Among symptomatic patients, cirrhosis was present in 55.6%, while pruritus and jaundice were each observed in 44.4%.A cholestatic liver injury pattern was observed in 68.8% of patients, whereas hepatocellular and mixed patterns were identified in 18.8% and 12.5%, respectively. AMA positivity was detected in 68.8% (11/16) of patients, while 31.2% (5/16) were AMA-negative and required diagnosis based on PBC-specific antinuclear antibodies. Anti-gp210 and anti-Sp100 antibodies were positive in 43.8% and 26.7% of tested patients, respectively. Time from initial abnormalities to confirmed diagnosis varied substantially, with delays of up to 8 years. **Conclusion:** PBC in this Vietnamese cohort frequently presented with asymptomatic disease, atypical biochemical patterns, and AMA-negative serology, which may contribute to delayed diagnosis in clinical practice. PBC-specific antinuclear antibodies, particularly anti-gp210 and anti-Sp100, provided important diagnostic support in AMA-negative cases. Broader access to specialized autoantibody testing may facilitate earlier diagnosis of PBC in resource-limited settings.

Disclosures: Khiem Pham:Nothing to Disclose, Khanh Vu Truong:Nothing to Disclose.

1311 | SYMPTOM BURDEN IN PEOPLE WITH PSC-ASSOCIATED PRURITUS: A US-BASED SURVEY TO UNDERSTAND PATIENTS' LIVED EXPERIENCES WITH PSC

Jonathan Ieyoub[1] Brian Thorsen[2] Joanne Hatchett[2] Rachel Gomel[2] Mara Peters[1] Jolan Terner-Rosenthal[1] Lindsey Spelying[1] Brandon Gordon[3] Erika Sloan[3] Stephen Rossi[2] Robin Howard[1], [1]Mirum Pharmaceuticals, Inc., [2]PSC Partners Seeking a Cure, [3]Charles River Associates

Background: Primary sclerosing cholangitis (PSC) is a rare, chronic liver disease associated with progressive damage to hepatic bile ducts and cholestasis-related symptoms such as pruritus and fatigue, which have a significant impact on health-related quality of life (HRQoL). People with PSC often report symptom manifestation well before diagnosis, and pruritus and fatigue are largely independent of disease stage. This study aims to better understand and quantify people's experiences with pruritus and with other key symptoms of PSC. **Methods:** A 15-minute de-identified online survey and 45-minute follow-up qualitative interviews to understand the experiences and perspectives of people with PSC-associated pruritus living in the US were conducted in Fall 2025 through PSC Partners Seeking a Cure. Descriptive statistics were performed. Here we report results from the online questionnaire. **Results:** 89 individuals living with PSC all self-reported in screening some level of pruritus currently (52% male; mean [SD] age 42 [12.7] years old; 56% between 41-60 years old) were included. Pruritus was the most common first symptom before diagnosis (30%), more often in those with IBD than without ($P < 0.05$). Symptoms presented, on average, 22 months before diagnosis. 46% of patients have self-reported moderate-severe pruritus, 65% report damage/visible marks to skin, 57% have difficulty sleeping at night due to pruritus, 51% have difficulty sitting still or being comfortable, and 51% report others commenting or asking questions about itching. One-third reported itching is constantly present, but also flares/gets worse at times lasting days to weeks, with 26% of flares lasting ≥ 1 week. Common triggers for flares include heat, stress, clothing, and other PSC symptoms. The most common treatments for pruritus were antihistamines (70%), UDCA (65%), cholestyramine (40%), and rifampicin (25%).13% of patients discontinued ≥ 1 of these treatments at < 1 year of use due to lack of

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symptom improvement. Besides pruritus, fatigue (56%) and difficulty sleeping (43%) were among the most common symptoms noted. Respondents reported pruritus or fatigue having the greatest impact (70% very/extremely impactful) on their HRQoL with it worsening over time and usually flaring together. **Conclusion:** For people with PSC-associated pruritus, initial findings demonstrate that pruritus, fatigue, and difficulty sleeping are some of the most high-impact HRQoL symptoms that people with PSC experience and continue to be a significant burden on their lives without adequate treatments available to provide relief.

Disclosures: Jonathan Ieyoub:Mirum Pharmaceuticals: Employee, Brian Thorsen:Mirum Pharmaceuticals: Speaking and Teaching, Joanne Hatchett:Nothing to Disclose, Rachel Gomel:Nothing to Disclose, Mara Peters:Nothing to Disclose, Jolan Terner-Rosenthal: Mirum Pharmaceuticals, Inc.: Employee, Mirum Pharmaceuticals, Inc.: Stock - publicly traded company, Mirum Pharmaceuticals, Inc.: Employee, Mirum Pharmaceuticals, Inc.: Stock - publicly traded company, Lindsey Spelying:Nothing to Disclose, Brandon Gordon:Nothing to Disclose, Erika Sloan:Nothing to Disclose, Stephen Rossi:Nothing to Disclose, Robin Howard:Mirum Pharmaceuticals: Stock - publicly traded company, Mirum Pharmaceuticals: Employee, Mirum Pharmaceuticals: Consultant.

1312 | ASSESSING THE "FIT-FOR-USE" OF INTERNATIONAL PRIMARY BILIARY CHOLANGITIS (PBC) PATIENT REGISTRIES FOR REAL-WORLD EVIDENCE (RWE) STUDIES INTENDED TO SUPPORT REGULATORY DECISION MAKING

Sandrine Cure[1] Bettina Hansen[2] Adriaan Van der Meer[3] Gideon Hirschfield[4] George Mells[5] Pietro Invernizzi[6] Marco Carbone[7] Alessio Gerussi[8] Umberto Vespasiani-Gentilucci[9] Sandrine Cure[1] Nathalie Dunkel[1] Femi Adekunle[1] Nick Warwick[1] Madeline Cameron[10] Ellen Werner[11] Gemma Weijsters[12] Tiki Blom[11] Laura Cristoferi[13] Elisa Merelli[14] Samuel Igweokpala[15] Irene Pan[15], [1]ADVANZ PHARMA, [2]Erasmus MC Rotterdam, [3]Erasmus University Medical Center, [4]Toronto General Hospital, [5]Newcastle University, Newcastle, UK, [6]Fondazione IRCCS San Gerardo dei Tintori, [7]Liver Unit, ASST Grande Ospedale Metropolitano (GOM) Niguarda, Milan, Italy ;, [8]IRCCS San Gerardo dei Tintori, Monza, Italy;, [9]Department of Hepatology, University Campus Bio-Medico, Rome, Italy, [10]Toronto Centre for Liver Disease and TGHRI, University Health Network, Toronto, Ontario, Canada, [11]Departement of gastroenterology and hepatology, Erasmus University Medical Center, Rotterdam, [12]Departement of gastroenterology and hepatology, Erasmus University Medical Center, Rotterdam,, [13]ERN RARE-LIVER, Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy, [14]IRCCS San Gerardo dei Tintori, Monza, Italy, [15]United BioSource LLC

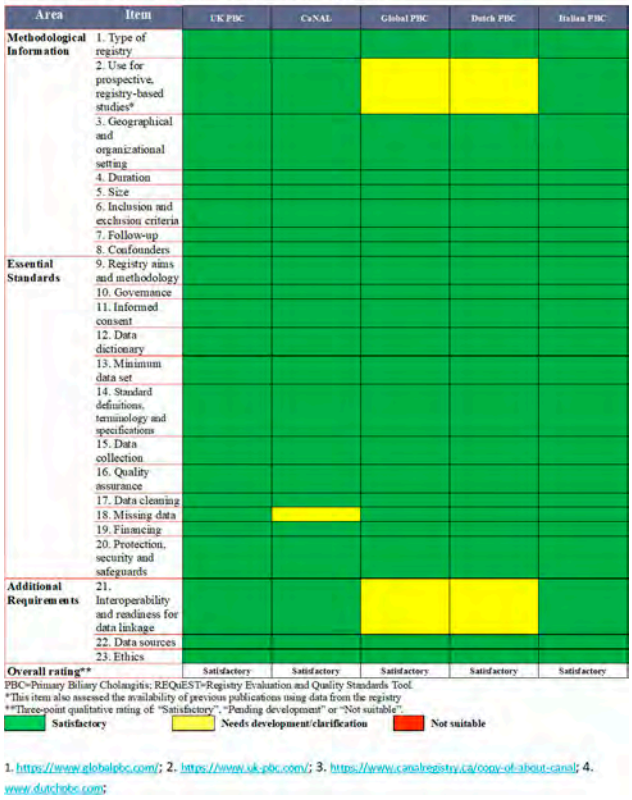
Background: Randomized clinical trials (RCTs) remain the gold standard for regulatory decision-making in primary biliary cholangitis (PBC); however, real-world data may complement RCT evidence, particularly when RCTs are challenging to operationally execute. Regulatory-grade real-world evidence (RWE) requires "fit-for-use" data sources with reliable, reproducible, and well-documented data. No systematic feasibility assessment has previously evaluated PBC registries for this purpose. This study assessed their suitability for regulatory-grade RWE generation. **Methods:** Five registries — Global PBC[1], UK PBC[2], CaNAL[3], Dutch PBC[4], and Italian PBC — were evaluated. Selection of the cohorts was based on long-term follow-up, prior use in RWE studies, representativeness of the PBC population in the relevant country or region, and clinician-collected data supported by verifiable source records. A structured feasibility assessment, including a questionnaire incorporating REQueST (Registry Evaluation and Quality Standards Tool), was conducted to evaluate whether existing registries or cohorts could provide sufficient longitudinal, fit-for-use data from a regulatory perspective, including data accuracy, validity, variability, reliability, and provenance. Two independent reviewers assessed questionnaire responses and supporting documents and resolved discrepancies by consensus. They assigned item-level ratings based on REQueST's minimum standard and assessment criteria for each item (i.e., Methodological Information (8 items), Essential Standards (12 items), and Additional Requirements (3 items). Follow-up meetings with registry representatives were held as needed. Each registry was then assigned an overall rating of "Satisfactory," "Needs development/clarification," or "Not suitable" as a potential data source. **Results:** Across the 23 REQueST areas, all five registries were rated overall as satisfactory (**Table 1**). Identified limitations included restricted prospective use for Global PBC and Dutch PBC, incomplete documentation of missing data management in CaNAL, and restrictions on patient-level data sharing in some registries. The assessment reflected compliance with REQueST criteria rather than full alignment with the specific study research question. **Conclusion:** The qualitative assessment using REQueST found all five PBC registries to be of good quality and suitable for regulatory-grade research. The identified

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limitations were considered manageable operational challenges rather than critical barriers. These findings support the feasibility of using international PBC registries for future regulatory-grade observational studies in PBC.

Table 1. Results of quality assessment based on 23 REQuEST items



1. https://www.globalpbc.com/; 2. https://www.uk-pbc.com/; 3. https://www.canalregistry.ca/copy-of-about-canal; 4. www.dutchpbc.com;

Disclosures: Sandrine Cure:ADVANZ PHARMA: Employee, ADVANZ PHARMA: Employee, Bettina Hansen:Nothing to Disclose, Adriaan Van der Meer: Nothing to Disclose, Gideon Hirschfield:Intercept: Consultant, GSK: Consultant, CymaBay: Consultant, Ipsen: Consultant, Falk: Consultant, Pliant: Consultant, Mirum: Consultant, Advanz: Consultant, Chemomab: Consultant, Gilead: Consultant, Kowa: Consultant, George Mells:Nothing to Disclose, Pietro Invernizzi:Nothing to Disclose, Marco Carbone:Nothing to Disclose, Alessio Gerussi:Nothing to Disclose, Umberto Vespasiani-Gentilucci:Nothing to Disclose, Sandrine Cure:ADVANZ PHARMA: Employee, ADVANZ PHARMA: Employee, Nathalie Dunkel:Nothing to Disclose, Femi Adekunle:Nothing to Disclose, Nick Warwick:Nothing to Disclose, Madeline Cameron:Nothing to Disclose, Ellen Werner:Nothing to Disclose, Gemma Weijsters:Nothing to Disclose, Tiki Blom:Nothing to Disclose, Laura Cristoferi:Nothing to Disclose, Elisa Merelli:Nothing to Disclose, Samuel Igweokpala:Nothing to Disclose, Irene Pan: Nothing to Disclose.

1313 | ASSOCIATION BETWEEN TREATMENT ADHERENCE AND HEALTHCARE UTILIZATION AMONG INDIVIDUALS WITH PRIMARY BILIARY CHOLANGITIS IN THE UNITED STATES

Robert Gish[1] Michel Mendler[2] Edward Mena[2] Chong Hoon Kim[3] Yi Pan[4] Lauren Do[4] Mihail Samnaliev[4] Diane Ito[4] Maria Agapova[3], [1]Robert G Gish Consultants LLC, [2]California Liver Research Institute, Pasadena, CA, [3]Gilead Sciences, Foster City, CA, USA, [4]Stratevi

Background: Primary biliary cholangitis (PBC) is a progressive, chronic autoimmune liver disease that can lead to significant burden for individuals, healthcare systems, and payers. Inadequate disease control, from poor adherence to PBC treatment, can contribute to worsening liver function and increased need for medical care. In previous analyses adherence predicted a lower risk of PBC disease progression and death. This study further evaluated the association between adherence and healthcare resource utilization (HCRU) among individuals with PBC in the United States. **Methods:** We conducted a retrospective cohort study using Komodo's Healthcare Map insurance claims data (January 1, 2016 - December 19, 2024). Adults aged ≥18 years diagnosed with PBC, with continuous health insurance coverage, initiating ursodeoxycholic acid (UDCA), obeticholic acid (OCA), or off-label fibrates following a treatment-free baseline of ≥12 months were included. The treatment initiation date was defined as the index, and individuals were followed until the end of the study window, discontinuation of insurance, or death. Adherence was measured by proportion of days covered (PDC) with continuous treatment with UDCA, OCA, and/or off-label fibrates. Longitudinal negative binomial models with annual intervals estimated associations between PDC ≥80% in the first 12 months post-index and the number of subsequent annualized all-cause HCRU events, including inpatient, outpatient, emergency, and any prescriptions (including PBC treatments) through the end of follow-up. The models controlled for demographics, PBC-related and other select baseline comorbidities, and PBC treatment type. **Results:** 54,034 individuals with PBC met the inclusion criteria. The mean age was 62 (±13) years; most were female (84.9%) and enrolled in Medicare (51.0%). During the 12-month baseline, the average Charlson Comorbidity Index score was 4.7 (±3.1); 18.9% were diagnosed with depression, 21.1% with anxiety, and 25.3% with fatigue. The percentage of individuals with PDC ≥80% was 50.2% in year 1 and decreased thereafter, ranging from 43.1% to 44.5% in years 2 to 7 post-index. Adjusted rate ratios associated with PDC ≥80% were 0.70 (95% CI,

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0.66–0.74) for inpatient, 0.95 (95% CI, 0.93–0.97) for outpatient, 0.75 (95% CI, 0.72–0.79) for emergency room, and 1.08 (95% CI, 1.06–1.10) for prescription counts (all $p < 0.001$). **Conclusion:** In this large real-world cohort of individuals with PBC, only half achieved adherence $\geq 80\%$ in the first year, with further declines over time. Adherence $\geq 80\%$ predicted lower inpatient, emergency department, and outpatient utilization, alongside increased prescription use. These findings highlight the importance of prioritizing access to therapies that support sustained adherence in the management of PBC.

Disclosures: Robert Gish:Genlantis, HepQuant, HepaTx, Virion: Stock – privately held company, Gilead Sciences, GlaxoSmithKline, HHHbio, Helio, HepQuant, Intercept, Ipsen, Madrigal,: Consultant, Mirum, Precision BioSciences, Prodigy, Topography Health, Tune Therapeutics, Virion, Quest: Consultant, AbbVie, AstraZeneca, BlueJay Therapeutics, Brii Bio, EIT Pharma, Genlantis, Gerson Lehrman Group: Consultant, Gilead Sciences Inc., Intercept, Ipsen Biopharmaceuticals, Madrigal, Mallinckrodt, Mirum: Speaking and Teaching, Syneos Health: Data Safety Monitoring Board, Genlantis, Gilead, HepaTX, HepQuant, Intercept, Prodigy: Leadership in Related Society, Board, Journal, Michel Mendler: Nothing to Disclose, Edward Mena:Nothing to Disclose, Chong Hoon Kim:Gilead Sciences, Inc.: Employee, Yi Pan:Nothing to Disclose, Lauren Do:Nothing to Disclose, Mihail Samnaliev:Gilead, Veloxis, Cytokinetics, Dyne, Vertex, Novartis: Consultant, Diane Ito:Gilead Sciences: Consultant, Maria Agapova:Nothing to Disclose.

1314 | CLINICAL IMPACT OF ALCOHOL USE DISORDER ON ONE-YEAR OUTCOMES IN PATIENTS WITH AUTOIMMUNE HEPATITIS: A PROPENSITY SCORE-MATCHED STUDY

Yasameen Muzahim[1] Abdullah Sohail[1] Antonio Sanchez[2] Marta Tejedor[1], [1]University of Iowa Health Care, [2]University of Iowa School of Medicine

Background: Alcohol use disorder (AUD) is associated with progressive liver injury and may worsen outcomes in chronic liver diseases. However, population-level data on the impact of AUD among patients with autoimmune hepatitis (AIH) remain limited. We evaluated one-year hepatic outcomes in patients with AIH with and without AUD using a large federated electronic health record network. **Methods:** We conducted a retrospective cohort study using the TriNetX Research Network, which includes data from 109 healthcare organizations. Adults aged 18–80 years with AIH were identified using ICD-10-CM code K75.4 and stratified by the presence or absence of AUD, identified using ICD-10-CM codes for alcohol abuse or dependence. Patients with viral hepatitis, hemochromatosis, Wilson disease, Budd-Chiari syndrome, non-HCC liver malignancy, unspecified liver disease, or baseline cirrhosis were excluded. Outcomes were assessed from 1 day through 365 days after the index event. Propensity score matching was performed for demographics, cardiometabolic comorbidities, nutritional status, nicotine dependence, and AIH-related immunosuppressive therapies. After matching, 717 patients were included in each cohort. **Results:** Before propensity score matching, 22,442 patients had AIH without AUD, and 723 had AIH with AUD. After matching, baseline characteristics were well balanced (Table 1). At 1 year, mortality was higher in the AIH+AUD cohort than in the AIH-alone cohort (8.8% vs 5.4%; risk difference −3.3%, 95% CI −6.0% to −0.7%; $p = 0.014$) (Table2). Kaplan-Meier analysis showed lower one-year survival in the AIH+AUD cohort (90.25% vs 93.83%; log-rank $p = 0.013$). Liver transplantation rates were not significantly different between AIH+AUD and AIH alone (4.3% vs 3.6%; $p = 0.499$). Acute/subacute liver failure was more frequent in the AIH+AUD cohort (5.7% vs 1.7%; risk difference −4.0%, 95% CI −6.0% to −2.1%; $p < 0.001$), with significant separation on Kaplan-Meier analysis (94.06% vs 98.18%; log-rank $p < 0.001$). There was no significant one-year difference in cirrhosis or hepatocellular carcinoma. **Conclusion:** This propensity score-matched real-world cohort showed that AUD is independently associated with significantly higher one-year mortality and acute/subacute liver failure in patients with AIH. These findings highlight that AUD acts as a major catalyst for adverse short-term outcomes and underscore the critical need for routine early alcohol screening, integrated addiction care, and enhanced surveillance in this high-risk population.

Table 1. Baseline Characteristics Before and After Propensity Score Matching

Characteristic	Before matching			After matching		
	AIH (N = 22,442)	AIH + AUD (N = 723)	SMD	AIH (N = 717)	AIH + AUD (N = 717)	SMD
Demographics						
Age, mean ± SD, y	55.7 ± 17.0	56.6 ± 13.9	0.056	56.5 ± 16.4	56.6 ± 13.9	0.004
Age at index, mean ± SD, y	49.3 ± 17.4	51.0 ± 14.0	0.108	50.9 ± 16.9	51.0 ± 14.0	0.003
Female, n (%)	17,189 (77.0)	411 (56.8)	0.439	397 (55.4)	411 (57.3)	0.039
Male, n (%)	5,120 (22.9)	312 (43.2)	0.440	320 (44.6)	306 (42.7)	0.039
White, n (%)	13,935 (62.4)	490 (67.8)	0.112	503 (70.2)	487 (67.9)	0.048
Black or African American, n (%)	2,909 (13.0)	126 (17.4)	0.122	122 (17.0)	123 (17.2)	0.004
Asian, n (%)	1,390 (6.2)	22 (3.0)	0.152	19 (2.6)	22 (3.1)	0.025
Unknown race, n (%)	2,758 (12.4)	47 (6.5)	0.202	45 (6.3)	47 (6.6)	0.011
Comorbidities						
Hypertensive diseases, n (%)	4,649 (20.8)	326 (45.1)	0.534	318 (44.4)	320 (44.6)	0.006
Ischemic heart diseases, n (%)	1,269 (5.7)	99 (13.7)	0.273	102 (14.2)	97 (13.5)	0.020
Cerebrovascular diseases, n (%)	798 (3.6)	74 (10.2)	0.265	69 (9.6)	70 (9.8)	0.005
Overweight / obesity, n (%)	2,549 (11.4)	175 (24.2)	0.339	165 (23.0)	175 (24.4)	0.033
Thyroid gland disorders, n (%)	2,862 (12.8)	128 (17.7)	0.136	112 (15.6)	126 (17.5)	0.052
Diabetes mellitus, n (%)	2,196 (9.8)	115 (15.9)	0.182	108 (15.1)	113 (15.8)	0.019
Malnutrition, n (%)	388 (1.7)	60 (8.3)	0.304	58 (8.1)	54 (7.5)	0.021
Other nutritional deficiencies, n (%)	2,224 (10.0)	151 (20.9)	0.306	141 (19.7)	147 (20.5)	0.021
Nicotine dependence, n (%)	964 (4.3)	226 (31.3)	0.753	209 (29.1)	220 (30.7)	0.034
Medications						
Methylprednisolone, n (%)	2,699 (12.1)	183 (25.3)	0.344	186 (25.9)	180 (25.1)	0.019
Prednisone, n (%)	4,289 (19.2)	227 (31.4)	0.283	237 (33.1)	222 (31.0)	0.045
Budesonide, n (%)	963 (4.3)	57 (7.9)	0.150	53 (7.4)	56 (7.8)	0.016
Azathioprine, n (%)	1,601 (7.2)	59 (8.2)	0.037	62 (8.6)	59 (8.2)	0.015
Glucocorticoids (class), n (%)	7,936 (35.6)	407 (56.3)	0.425	421 (58.7)	401 (55.9)	0.056
Tacrolimus, n (%)	420 (1.9)	24 (3.3)	0.090	27 (3.8)	22 (3.1)	0.038
Mycophenolate mofetil, n (%)	590 (2.6)	32 (4.4)	0.097	31 (4.3)	30 (4.2)	0.007

Table 2. Clinical Outcomes After Propensity Score Matching (AIH vs. AIH + AUD, N = 717 per cohort)

Outcome	AIH n (%)	AIH + AUD n (%)	Risk Ratio (95% CI)	Odds Ratio (95% CI)	Hazard Ratio (95% CI)	p-value
Mortality	39 (5.4)	63 (8.8)	0.62 (0.42–0.91)	0.60 (0.40–0.90)	0.61 (0.41–0.90)	0.013
Liver transplant	26 (3.6)	31 (4.3)	0.84 (0.50–1.40)	0.83 (0.49–1.42)	0.83 (0.50–1.40)	0.493
ACLF †	12 (1.7)	41 (5.7)	0.29 (0.16–0.55)	0.28 (0.15–0.54)	0.29 (0.15–0.54)	<0.001

† n (%) = patients with the outcome within the 365-day time window / 717 patients per cohort.
Risk, odds, and hazard ratios are expressed for AIH (Cohort 1) relative to AIH + AUD (Cohort 2). A value < 1 indicates higher risk in the AIH + AUD cohort.
p-values in the log-rank and risk-difference and log-rank tests were consistent for all outcomes.

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1315 | 6-MERCAPTOPURINE VS. AZATHIOPRINE AS ADJUNCTIVE THERAPY DURING HIGH-DOSE CORTICOSTEROID INDUCTION IN AUTOIMMUNE HEPATITIS: A PROPENSITY SCORE–MATCHED COHORT ANALYSIS

Bianca Patel[1] Jashanveer Johal[1] Archana Salek[1] Mahmoud Al-Bataineh[1] Brandon Cunha[1] Abdallah Hussein[1] Jason Hyman[1] Yecheskel Schneider[1], [1]Virtua Health

Background: Azathioprine (AZA) is the guideline-standard steroid-sparing adjunct in autoimmune hepatitis (AIH), but 6-mercaptopurine (6-MP), its active metabolite, is used as an alternative in patients with AZA intolerance. Whether 6-MP provides equivalent disease control and safety during the high-dose induction phase of corticosteroid therapy has not been characterized in a real-world matched cohort. **Methods:** Using the TriNetX Global Collaborative Network, we identified AIH patients receiving prednisone (10–50 mg) with either 6-MP or AZA initiated within 1 month. Patients with cirrhosis, primary sclerosing cholangitis, liver transplant, or adrenal insufficiency were excluded. After 1:1 propensity score matching, 166 patients remained in each cohort. Outcomes included IV steroid use, biochemical remission, transition to low-dose prednisone ($\leq$7.5 mg), cytopenia, inpatient encounters, mortality, and incident cirrhosis. **Results:** No outcome differed significantly between groups. IV steroid use was similar (33.1% vs 30.7%; HR 1.00, p = 0.99). AZA showed numerically higher biochemical remission (86.1% vs 78.9%; HR 0.82, p = 0.098) and faster AST/ALT normalization (66 vs 105 days). Transition to low-dose prednisone was more frequent with AZA (53.0% vs 47.6%; HR 0.83, p = 0.24), with shorter time to taper (668 vs 1,311 days). Cytopenia occurred more often with 6-MP (59.0% vs 48.8%; HR 1.33, p = 0.055) and developed earlier (583 vs 1,988 days). Inpatient encounters, mortality, and cirrhosis rates were comparable. **Conclusion:** 6-MP and AZA demonstrated similar clinical outcomes during AIH induction therapy. AZA showed trends toward faster biochemical remission and steroid taper, whereas 6-MP was associated with earlier and more frequent cytopenia. These findings support 6-MP as an alternative for selected patients while underscoring the need for hematologic monitoring.

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1316 | IDIOPATHIC ADULTHOOD DUCTOPENIA: DIAGNOSTIC HETEROGENEITY AND TRANSPLANT OUTCOMES ACROSS REPORTED CASES

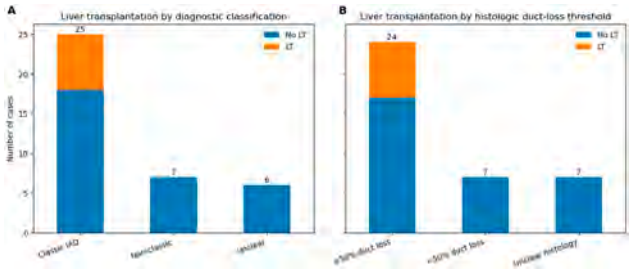
Thomas Stirrat[1] Shankar Thiru[2] Priyanka Solanky[2] Michael Flatley[3] Soham Apte[4] Ashley Trinh[2] Rachel Redfield[5] Amol Rangnekar[6], [1]University of California Los Angeles (UCLA), [2]Georgetown University School of Medicine, [3]University of Colorado Internal Medicine Residency Program, [4]Kentucky College of Osteopathic Medicine, [5]MedStar Georgetown University Department of Transplant Hepatology, [6]Georgetown University Hospital

Background: Background: Idiopathic adulthood ductopenia (IAD) is a rare chronic cholestatic liver disease defined by adult-onset bile duct loss after exclusion of secondary causes. Published cases vary in diagnostic completeness, limiting interpretation of phenotype and outcomes. We reassessed reported cases using conservative case-level adjudication. **Methods:** Methods: Scopus, Web of Science, Embase, PubMed, and MEDLINE were searched from inception through December 31, 2025. Human reports with extractable patient-level data for IAD or closely related adult ductopenic cholestatic syndromes were included. Two reviewers screened studies, extracted data, assessed quality, and classified cases as classic IAD, non- classic, or unclear using Ludwig-based criteria. **Results:** Results: Thirty-eight extracted cases from 33 reports were included. Median age at diagnosis was 30 years (IQR, 20-43.3), and median age at symptom onset was 22 years (IQR, 16-34); 11/37 cases (29.7%) had symptom onset before age 18. Jaundice occurred in 23/32 cases (71.9%) and pruritus in 21/31 (67.7%). Twenty-four cases met the $\geq$50% bile duct-loss threshold. After adjudication, 25/38 cases (65.8%) were classic IAD, 7 (18.4%) non-classic, and 6 (15.8%) unclear. All 7 liver transplantations occurred among classic IAD cases and among cases meeting the $\geq$50% duct-loss threshold; no transplantations were reported among non- classic or unclear cases. Death was reported in 6/38 cases. **Conclusion:** Conclusion: Published IAD reports are diagnostically heterogeneous, and severe reported

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outcomes cluster in conservatively defined classic IAD with substantial duct loss. Future IAD reports should standardize exclusion of mimics, cholangiographic characterization, portal-tract adequacy, duct-loss quantification, treatment response, and longitudinal follow-up.



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1317 | CLINICAL PRESENTATION, CO-PREVALENCE, AND EXPRESSION OF AN IL-12 GENE SIGNATURE LINK PRIMARY BILIARY CHOLANGITIS AND AUTOIMMUNE HEPATITIS WITH ADDITIONAL AUTOIMMUNE DISEASES

Arielle Glatman Zaretsky[1] Stephen DiMartino[1] Kaitlyn Gayvert[1] Wenzhen Ge[1] Keran Moll[1] Dana Murdock[1] Elsa Au-Yeung[1] Rachna Shah[1] Veronica Mas Casullo[1] Wei Keat Lim[1] Andre Limnander[1] Jennifer Maloney[1] Jamie Orengo[1], [1]Regeneron

Background: It has long been recognized that patients with an autoimmune disease may exhibit clinical overlap with other distinct autoimmune diseases. For example, while dry mouth and dry eyes are defining clinical characteristics of Sjogren's disease, these symptoms are also observed in a notable proportion of patients with primary biliary cholangitis (PBC). In addition, PBC and autoimmune hepatitis (AIH) are known to exhibit co-prevalence at a much higher frequency than what would be expected by random chance. These observations highlight the likelihood of common etiologies that are not fully understood. We have recently linked 5 autoimmune conditions to the IL-12 signaling pathway. In this report, we explore common symptomatology, autoantibody profiles, co-prevalence, and gene expression among these diseases. **Methods:** A literature review was performed to determine the frequency of common clinical symptoms and autoantibody specificities in a subset of autoimmune diseases: PBC, AIH, Systemic Sclerosis/scleroderma (SSc), Sjogren's Disease (SjD), and Lupus (SLE). Co-prevalence of these diseases was evaluated in a cross-sectional study using the Komodo claims database. Luminex was performed to evaluate the concentration of inflammatory proteins in plasma from patients with PBC or SSc or healthy controls. An IL-12 gene signature was established using RNASeq analysis to identify differentially expressed genes (DEGs) in response to IL-12 signaling. The IL-12 signature was evaluated in gene expression datasets from relevant tissue sites from patients with PBC, AIH, SSc, SjD, and SLE to assess IL-12 signaling compared with healthy controls. **Results:** A literature review of clinical presentation highlights common symptoms and autoantibody reactivities across PBC, AIH, SSc, SLE and SjD. Komodo claims analysis revealed that the five conditions exhibited a high level of co-prevalence relative to the general population, but not observed with other inflammatory conditions such as psoriasis, type 1 diabetes, or rheumatoid arthritis.As previously reported, in plasma from patients with SSc or PBC, interferon-inducible chemokines, CXCL10, CXCL11, and CXCL13 were increased. Since IL-12 is the dominant upstream inducer of IFNg, an IL-12 signature was defined. This signature was discovered to be elevated in tissue from patients with PBC, AIH, SSc, SjD, and SLE. **Conclusion:** These data suggest common dysregulated pathways are shared across PBC, AIH, SSc, SjD, and SLE, despite disparate canonical presentation and organ involvement. These may indicate shared drivers of disease that could be targeted with therapeutic approaches.

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1318 | THE USE OF THE PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR AGONIST ALPHA AND DELTA ELAFIBRANOR FOR PRIMARY BILIARY CHOLANGITIS IN A REAL-WORLD CASE SERIES WITH FOCUS ON EXTRAHEPATIC MANIFESTATIONS AND FIBROSIS

Momin Masroor[1] Kirellos Mikhail[2] Harry Nguyen[1] Yao (Michelle) Lan[3] Christopher Soriano[1] Beshoy Yanny[1],

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[1]University of California, Irvine, [2]University of California, Los Angeles, [3]UCI Health

Background: Primary Biliary Cholangitis (PBC) is an autoimmune cholestatic liver disease with a strong female predominance, characterized by the serologic hallmark of antimitochondrial antibodies (AMA) and destruction of interlobular bile ducts leading to progression of liver disease, need for liver transplant, or shortening life without disease control. Extrahepatic manifestations include pruritus, and fatigue as most reported. While ursodeoxycholic acid (UDCA) is the first-line treatment, up to 50% of patients have an inadequate response. Peroxisome Proliferator-Activated Receptor (PPAR) agonists are newly FDA approved medications that are utilized in patients with inadequate response or intolerance to UCDA. Real world data for symptom and biochemical improvement is limited. We aim to report real world data of the newly approved PPAR agonists, including safety, efficacy, tolerability and effect on extrahepatic symptoms. **Methods:** We evaluated three patients with an established PBC diagnosis who demonstrated an inadequate response or intolerance to UDCA (13-15 mg/kg). Alternative liver diseases were ruled out via negative viral serologies and normal metabolic panels. Patients were initiated on Eafibranor 80 mg daily and followed with clinical and laboratory assessments conducted at baseline, 3 months, and 12 months. Serial data included symptom severity (Worst Itch Numeric Rating Scale [WI-NRS] and fatigue), liver enzymes, and non-invasive fibrosis markers. Primary outcomes were Alkaline Phosphatase (ALP) reduction, symptomatic improvement, and safety. **Results:** Three consecutive patients (1 male, 2 females; mean age 56.3 years) with inadequate response to UDCA for PBC were evaluated. Over 12 months of Elafibranor therapy, patients demonstrated a clinically significant biochemical and symptomatic response. Mean ALP decreased 58% from a baseline of 348 U/L to 144 U/L. Non-invasive fibrosis markers improved, with liver stiffness decreasing on transient elastography (mean -1.5 kPa). Mean WI-NRS score decreased from 5.3 to 2.0, and all reported improvement of debilitating daytime fatigue. Elafibranor was well-tolerated with no reported adverse events. **Conclusion:** Elafibranor shows positive safety, efficacy, side effect profile, improvement in extrahepatic manifestations including pruritus and fatigue in real world data. Improvement in fibrosis noted on transient elastography in all three patients. More studies are needed to evaluate long term fibrosis improvement, transplant free survival, mortality benefit and effect on extrahepatic manifestations.

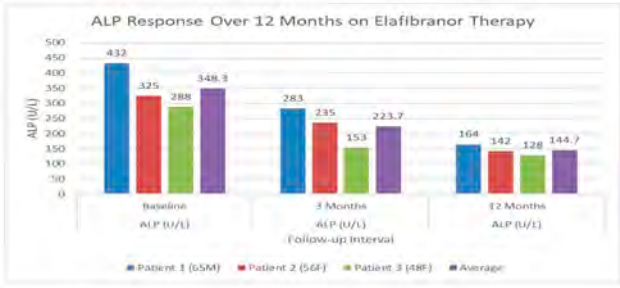


Figure 1: 12-month trajectory of ALP (U/L) in three patients with refractory PBC started on Elafibranor.

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1319 | BASELINE LIVER STIFFNESS DOES NOT PREDICT COMPLETE BIOCHEMICAL RESPONSE IN TREATMENT-NAIVE AUTOIMMUNE HEPATITIS

Leonardo Calabrano[1] Alexis Guzmán[1] Sebastián Carrasco[2] Felipe Matus[2] Benjamín Chahuan[2] Miguel Guerra[3] Daniela Simian[1] Álvaro Urzúa[1], [1]Hospital Clínico Universidad de Chile, [2]Universidad de Chile, [3]Hospital San Borja Arriarán

Background: Liver elastography provides a non-invasive assessment of fibrosis in autoimmune hepatitis (AIH); however, its value for predicting biochemical response to treatment remains uncertain, especially in the presence of active inflammation. The aim was to evaluate whether baseline liver stiffness is associated with complete biochemical response and to assess its diagnostic accuracy for histological fibrosis in treatment-naive AIH patients. **Methods:** Retrospective cohort of 42 patients managed between 2017 and 2025 at a tertiary center, with baseline elastography and biochemical follow-up. Complete response was defined as normalization of AST, ALT, and immunoglobulin G at six months. Liver stiffness was compared according to measurement method and predefined fibrosis cutoffs. **Results:** Eighteen patients (43%) achieved complete biochemical response, whereas twenty-four (57%) did not. Baseline liver stiffness did not differ between groups: ARFI 10.65 versus 11.57 kPa ($p = 0.625$) and FibroScan 13.5 versus 19.3 kPa ($p = 0.565$). Baseline advanced

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fibrosis was also similar: 14/18 (78%) versus 19/24 (79%) (p = 0.914). Elastography was associated with histologic F3–F4 fibrosis (OR 9.3), with sensitivity 92.3%, specificity 43.8%, PPV 73%, and NPV 78%. False-positive cases showed higher inflammatory activity than true positives: AST 581 versus 79 U/L (p = 0.006), ALT 703 versus 66 U/L (p = 0.002), and IgG 2440 versus 1975 mg/dL (p = 0.055). **Conclusion:** Baseline elastography did not predict complete biochemical response, but it identified advanced fibrosis with high sensitivity, although it tended to overestimate fibrosis in patients with greater baseline inflammatory activity.

Association between baseline liver stiffness levels and treatment response in patients with AIH

	Total N = 42	Complete response N = 18 (43%)	Partial response or no response N = 24 (57%)	p value
Method of fibrosis assessment				
ARFI	17 (40)	7 (39)	10 (42)	0.856
Fibroscan	25 (60)	11 (61)	14 (58)	
Liver stiffness (kPa)				
ARFI	11.54 (4.8 – 23)	10.65 (6.3 -23)	11.57 (4.8 – 17.6)	0.625
Fibroscan	16.7 (5.9 – 45)	13.5 (5.9 – 36.6)	19.3 (6.7 – 45)	0.565
Stage of liver fibrosis				
F0	1 (2)	0 (0)	1 (4)	0.851
F1	4 (10)	2 (11)	2 (8)	
F2	4 (10)	2 (11)	2 (8)	
F3	12 (29)	6 (33)	6 (25)	
F4	21 (50)	8 (44)	13 (54)	
Advanced fibrosis	33 (79)	14 (79)	19 (79)	0.914
Fibrosis according to cutoff values	20 (48)	9 (50)	11 (46)	0.789

ARFI: Acoustic Radiation Force Impulse
Fibrosis cutoff values > 10 kPa with Fibroscan and > 13 kPa with ARFI.

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1320 | ◆ HUMAN HEPATOCYTE-BASED FUNCTIONAL ANNOTATION OF MASH-ASSOCIATED GENETIC RISK VARIANTS DEFINES DISTINCT STRESS STATES AND THERAPEUTIC RESPONSE

Takeshi Saito[1] Yein Woo[2] Jinyoung Ahn[2] Masashi Okawa[2] Meng Li[1] Garnik Arustamyan[2], [1]University of Southern California, [2]Keck School of Medicine, University of Southern California

Background: Genetic variants in TM6SF2, PNPLA3, MBOAT7, TRIB1, GPAM, ADH1B, FTO, APOB, MTTP, and other MASH-associated loci are thought to confer variable risks of steatosis, hepatocellular stress, fibrosis, and cirrhosis. However, this concept derives largely from clinical association studies; these variants have not been systematically compared at the cellular and molecular levels for direct effects on metabolic stress pathways or responses to hepatocyte-targeted therapeutics. This study establishes a physiologically relevant platform using our state-of-the-art primary human hepatocyte (HH) culture system to define how MASH-associated genetic risk signatures shape hepatocyte pathophysiology and drug responsiveness. **Methods:** HHs were perturbed using solid-phase siRNA transfection to model MASH-associated risk genes and exposed to a carbohydrate–fatty acid cocktail as the primary MASH-relevant metabolic challenge. Ethanol alone and combined carbohydrate–fatty acid/ethanol exposure were included as comparator and extension arms to test MASH-specific versus shared effects across ALD- and MetALD-like stress contexts. Effects on lipid accumulation, lipotoxicity, oxidative and ER stress, hepatocyte-intrinsic inflammatory signaling, and cell injury were assessed by high-content imaging, biochemical assays, and transcriptomic profiling. Therapeutic responsiveness was evaluated with resmetirom (THR-β agonist) and lanifibranor (pan-PPAR agonist). **Results:** Despite comparable lipid droplet accumulation, individual gene silencing produced distinct metabolic stress and injury signatures under MASH-like challenge and in MetALD/ALD extension arms. Silencing of PNPLA3, MBOAT7, TM6SF2, APOB, and MTTP was strongly associated with metabolic-oxidative stress and cytotoxicity, whereas silencing of GPAM, TRIB1, ADH1B, and FTO caused minimal stress or injury. Therapeutic responses were risk gene–dependent: resmetirom reduced steatosis and stress signaling in PNPLA3-, APOB-, and MTTP-silenced HHs, but the magnitude of lipid reduction, injury mitigation, and stress-gene suppression varied by genetic background. Lanifibranor modestly reduced lipid droplet burden across models but did not significantly reduce cell stress or injury. **Conclusion:** This study establishes a HH-based framework to functionally annotate MASH-associated genetic variants and link genetic risk to molecular pathophysiology and therapeutic response. These findings indicate that MASH risk genes define separable hepatocyte stress states with distinct drug-response profiles across metabolic and alcohol-associated stress contexts. This platform provides a functional approach to stratify MASH risk variants by mechanism and test therapeutic responsiveness in a bona fide human hepatocyte model system.

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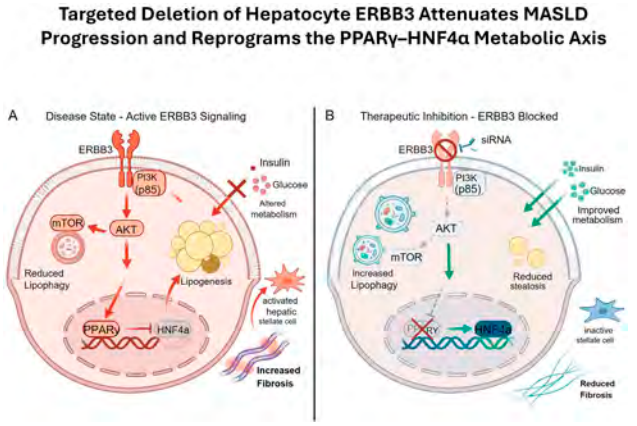
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1321 | ◆ TARGETED DELETION OF HEPATOCYTE ERBB3 ATTENUATES MASLD PROGRESSION AND REPROGRAMS THE PPARΓ–HNF4A METABOLIC AXIS

Shehnaz Bano[1] Joseph Locker[1] Shirish Paranjpe[1] Rodrigo Florentino[1] Alejandro Soto-Gutierrez[1] George Michalopoulos[1] Bharat Bhushan[1], [1]University of Pittsburgh

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) can progress from steatosis to fibrosis and cirrhosis. A key feature of disease progression is hepatocyte reprogramming characterized by induction of PPARγ-dependent lipid storage programs and suppression of HNF4α-governed hepatocyte identity. In the murine fast-food diet (FFD) model, pan-ERBB inhibition reduces steatosis and fibrosis, whereas hepatocyte-specific EGFR deletion does not attenuate steatosis, increases fibrosis, and is associated with compensatory ERBB3 expression and persistent downstream signaling. In parallel, hepatocyte-specific PPARγ deletion has identified an antagonistic PPARγ-HNF4α axis as a key transcriptional regulator of MASLD progression. Here, we investigated whether hepatocyte ERBB3 (HER3) functions upstream of the PPARγ-HNF4α axis in MASLD. **Methods:** Hepatocyte-specific ErbB3 deletion (ERBB3-KO^{Hep}) was achieved in *Erbb3*$^{fl/fl}$ mice using AAV8-TBG-Cre. Mice were fed a fast-food diet (FFD) for 5 months to induce MASLD. Liver injury, lipid accumulation, and fibrosis were assessed by histology, biochemical assays, and western blotting. ERBB3–PI3K (p85) interactions were examined via immunoprecipitation. Therapeutic efficacy was evaluated using LNP-delivered siERBB3 *in vivo* and siRNA-driven knockdown in patient-derived primary human steatotichepatocytes. **Results:** NRG1 levels and ERBB3 expression/activation significantly increased in human and murine MASLD. ERBB3-KO^{Hep} mice were protected against FFD-induced steatosis, showing lower triglyceride content and improved glucose homeostasis compared to WT controls. Mechanistically, ERBB3 deletion attenuates PI3K–AKT–mTOR signaling, suppresses PPARγ, and restores HNF4α expression, thereby reprogramming the metabolic PPARγ–HNF4α axis. Transcriptomic and protein analyses revealed coordinated downregulation of de novo lipogenesis (ACC, SCD1, ACLY), lipid uptake (CD36), and droplet stabilization (PLIN2), alongside activation of autophagy/lipophagy pathways. ERBB3 loss also suppressed fibrogenic gene programs (Col1a1, Col3a1, Acta2) and reduced α-SMA and collagen deposition. Importantly, therapeutic ERBB3 silencing via LNP delivery in vivo, reversed already established MASLD and knockdown in human steatotic hepatocytes, consistently reduced lipid accumulation and reversed PPARγ–HNF4α transcriptional switch. **Conclusion:** Hepatocyte ERBB3 is a critical upstream driver of MASLD that regulates the PPARγ–HNF4α transcriptional switch. Targeted inhibition of ERBB3 restores metabolic homeostasis, induces lipophagy, and attenuates fibrosis, revealing an unexpected role for ERBB3 as a promising therapeutic target for MASLD.



Disclosures: Shehnaz Bano:Nothing to Disclose, Joseph Locker:Nothing to Disclose, Shirish Paranjpe:Nothing to Disclose, Rodrigo Florentino:Nothing to Disclose, Alejandro Soto-Gutierrez:Nothing to Disclose, George Michalopoulos:Nothing to Disclose, Bharat Bhushan:Nothing to Disclose.

1322 | ◆ GALECTIN-1 DRIVES LIVER FIBROSIS IN CHB-MAFLD BY REMODELING THE IMMUNE-METABOLIC LANDSCAPE VIA PKM2-MEDIATED MACROPHAGE GLYCOLYSIS

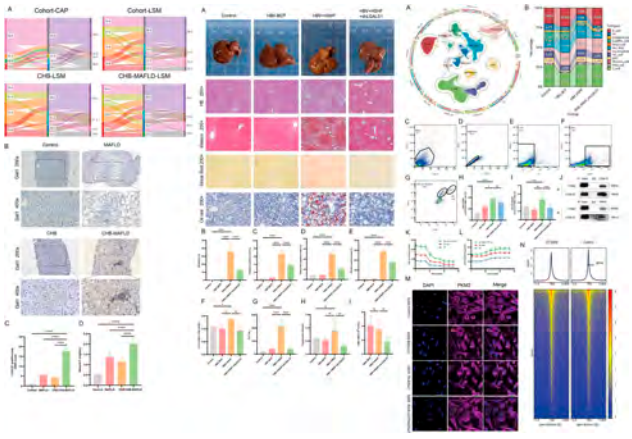
Linlin Zheng[1] Qunyan Yao[2] Fangyuan Chen[2] Shengdi Wu[2] Jiangao Fan[3] Wei Jiang[2], [1]Zhongshan Hospital, [2]Zhongshan Hospital, Fudan University, [3]Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine

Background: Chronic hepatitis B (CHB) remains a global health threat, and its increasing comorbidity with metabolic dysfunction-associated fatty liver disease (MAFLD) significantly accelerates progression to cirrhosis and hepatocellular carcinoma. Current antiviral therapies show limited efficacy in reversing advanced fibrosis in CHB-MAFLD patients compared to those with CHB alone, suggesting a complex pathogenic "cross-talk". Galectin 1 (Gal1, encoded by LGALS1) is a highly conserved glycan-binding protein involved in immune homeostasis and tissue fibrosis. However, its specific role and molecular mechanisms in CHB-MAFLD progression remain unclear. This study aimed to investigate the potential of Gal1 as a therapeutic target for the treatment of CHB-MAFLD. **Methods:** We analyzed 276 patients (MAFLD, CHB, and CHB-MAFLD) with a 5-year follow-up to identify unique clinicopathological features. Transcriptomic analysis of GEO datasets (GSE274114)

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and clinical validation were performed. In vivo, a CHB-MAFLD mouse model was established using HBV-BCP transgenic mice fed a high-sugar high-fat (HSHF) diet. Hepatic Lgals1 was specifically knocked down using AAV-shLGALS1. In vitro, mouse bone marrow-derived macrophages (BMDMs) were used to explore macrophage metabolism. Single-cell RNA sequencing (scRNA-seq) was employed to characterize the hepatic immune microenvironment. **Results:** CHB-MAFLD patients exhibited significantly higher serum Gal1 levels than CHB or MAFLD patients, which positively correlated with the severity of steatosis and fibrosis ($P < 0.05$). Standard antiviral therapy failed to significantly alleviate stage F3/F4 fibrosis in CHB-MAFLD patients over 5 years. HSHF diet significantly induced Gal1 expression in mouse liver tissues. Specific knockdown of hepatic Gal1 in CHB-MAFLD mice significantly reduced body weight, improved glucose tolerance, and ameliorated liver steatosis, inflammatory infiltration, and collagen deposition (Masson/Sirius Red staining, $P < 0.0001$). scRNA-seq and flow cytometry revealed that Gal1 knockdown remodeled the immune microenvironment by decreasing monocyte-derived macrophages (MoMFs) and promoting their polarization from a pro-inflammatory ($CD80^+$ $CD86^+$) to an anti-inflammatory ($CD163^+$ $CD206^+$) phenotype. Gal1 facilitated MoMFs recruitment by upregulating CCR2 expression. Gal1 directly interacted with PKM2, disrupting its tetrameric stability and promoting its transition to low-activity oligomers. This triggered the Warburg effect, mitochondrial dysfunction, and apoptosis. Nuclear translocation of PKM2 subsequently activated PRKAG2 and IP6K3 to drive metabolism remodeling. OTX008 (Gal1 inhibitor) or TEPP-46 (PKM2 activator) reversed these pro-fibrotic effects. **Conclusion:** Gal1 is a key driver of CHB-MAFLD progression. Targeting the Gal1-PKM2 axis offers a promising therapeutic strategy for liver fibrosis in CHB-MAFLD.



Disclosures: Linlin Zheng:Nothing to Disclose, Qunyan Yao:Nothing to Disclose, Fangyuan Chen:Nothing to Disclose, Shengdi Wu:Nothing to Disclose, Jiangao Fan:Nothing to Disclose, Wei Jiang:Nothing to Disclose.

1323 | ◆ LOSS OF TET1 IN T CELLS EXACERBATES MASLD PROGRESSION

Muhammad Nisar[1] Xinjian Li[1] Cian-Ru Yang[1] Tomilola Olaolu[2] Ryan Huang[2] Ruiyu Zhang[1] Chiung-Kuei Huang[1], [1]Stony Brook University, [2]Tulane University School of Medicine

Background: Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) progression is regulated by the inter-hepatic immune system. While T cells are known to play a key role in chronic hepatic inflammation, it is unknown how their regulation of population dynamics under metabolic conditions is regulated. Single-nucleus RNA sequencing (snRNA Seq) showed that DNA demethylation enzyme-TET1 changes across CD4, CD8 and regulatory T cells (Treg) in human MASLD patients closely related to the T cell subsets. Therefore, we aimed to determine the role of TET1 in T cells during MASLD progression. **Methods:** Human MASLD snRNA-seq datasets were used to assess the changes of DNA methylation enzymes in T cells. TET1 chromatin immunoprecipitation (ChIP-Seq) was adopted to investigate molecular regulations. T cell specific TET1 knockout (TKO) mice were used to evaluate how TET1 in T cells modulates MASLD. Transcriptomic analysis was performed in the liver and spleen samples to reveal the molecular regulations. In vitro assays were performed in human T cells using TET1 knockdown or pharmacological TET1 inhibitor to delineate molecular mechanisms. **Results:** TET1 loss in T cells significantly impacted liver injury in mice fed with an high fat diet (HFD). Surprisingly, TKO mice were lower in body weight after HFD, but body weights over liver, fat, and spleen weights were comparable to the control group. Hepatic triglyceride and cholesterol levels did not change between these mice. Histological and immune profiling indicated high F4/80 macrophage infiltration and high total immune cell infiltration in TKO mice. Despite elevated hepatic inflammation and injury, intrahepatic accumulation of CD4 and CD8 T cells was significantly reduced in TKO mice. Spleen RNA-seq suggests that systemic T cell activation, exhaustion markers, and standard surface trafficking receptors were virtually unchanged, suggesting the phenotype is a cell-intrinsic defect, and that cell proliferation or migration is likely involved. Transcriptomic analysis identified Rhou, a Rho GTPase crucial for cell movement, as one of the top robustly downregulated targets of TKO T cells. Simultaneously, TET1 knockdown or

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chemical inhibition in Jurkat cells inhibited Rhou, suppressed cell growth, and reduced migration. Interestingly, the DNA methylation inhibitor, 5-Azacytidine treatment reversed Rhou expression in TET1 deficient T cells. Further, TET1 ChIP-seq confirmed that TET1 bound to the Rhou gene locus, thereby supporting direct epigenetic regulation through DNA methylation. Human MASLD sc/snRNA-seq also validated a significant positive relationship between TET1 and Rhou. **Conclusion:** In conclusion, TET1 deficiency in T cells promoted MALSD progression through targeting T cell mobility and growth. Although targeting hepatic TET1 improved MASLD, the long-term impact of targeting TET1 in MASLD patients with elevated CD4 and CD8 T cells should be monitored carefully.

Disclosures: Muhammad Nisar:Nothing to Disclose, Xinjian Li:Nothing to Disclose, Cian-Ru Yang:Nothing to Disclose, Tomilola Olaolu:Nothing to Disclose, Ryan Huang:Nothing to Disclose, Ruiyu Zhang:Nothing to Disclose, Chiung-Kuei Huang:Nothing to Disclose.

1324 | ◆ RSPO3 PROMOTES LIVER METASTATIC GROWTH THROUGH MODULATION OF HEPATIC ZONATION AND IMMUNE REMODELING IN MASLD

Mustafa Karabicici[1] Jieun Kim[1] Ekihiro Seki[2], [1]CEDARS-SINAI Medical Center(CSMC), [2]Cedars-Sinai Medical Center

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is one of the most prevalent chronic liver diseases worldwide and is increasingly recognized as a major modifier of the hepatic tumor microenvironment. The liver is the most common site of metastasis for gastrointestinal malignancies, yet the mechanisms linking steatotic liver remodeling to metastatic progression remain poorly understood. Hepatic zonation creates distinct metabolic and immunologic niches along the porto-central axis, and these spatial programs become markedly altered in MASLD. R-spondin 3 (RSPO3), primarily expressed by endothelial cells and cytokine-producing hepatic stellate cells (HSCs), is a key regulator of hepatic zonation; however, its role in metastatic tumor progression remains controversial. **Methods:** Spatial transcriptomic, in vitro, and MC38 splenic injection liver metastasis models were used to evaluate RSPO3 regulation and function in steatotic livers under normal chow and high-fat diet conditions. **Results:** Here, we investigated the role of RSPO3 in colorectal cancer (CRC) liver metastasis under steatotic conditions. Our spatial transcriptomic analysis revealed that RSPO3 expression is increased in Zone 3 livers, mainly in endothelial cells and HSCs. As the RSPO3 promoter contains HIF-binding sites and Zone 3 is often hypoxic, RSPO3 may be regulated by hypoxia. Indeed, hypoxic challenge increased RSPO3 expression in HSCs. Furthermore, RSPO3 treatment significantly increased CRC cell proliferation. In vivo, we used the MC38 splenic injection liver metastasis model with high-fat diet (HFD) feeding, in which metastatic tumor growth is increased compared with normal chow (NC) feeding. Anti-RSPO3 treatment markedly reduced tumor burden, along with reduced hepatic lipid accumulation as demonstrated by decreased BODIPY staining. In addition, disruption of normal hepatic zonation patterns was observed following anti-RSPO3 treatment in both NC and HFD livers. The HFD condition also demonstrated increased CYP2E1 expression, consistent with MASLD-associated pericentral remodeling, which was reversed by anti-RSPO3 treatment. Immune profiling further revealed that although total CD3+ T-cell numbers were not significantly altered, the proportion of CD3+TIM3+ exhausted T cells was significantly reduced following anti-RSPO3 treatment in HFD mice. **Conclusion:** Collectively, these findings identify increased RSPO3 expression as an important regulator of the metastatic liver microenvironment in MASLD. RSPO3 may contribute to metastatic progression through alterations in hepatic zonation, lipid accumulation, and T-cell exhaustion. Targeting RSPO3 could therefore represent a potential therapeutic strategy for limiting liver metastasis in steatotic liver disease.

Disclosures: Mustafa Karabicici:Nothing to Disclose, Jieun Kim:Nothing to Disclose, Ekihiro Seki:Nothing to Disclose.

1325 | ◆ ZEB2 PROMOTES THE PROGRESSION OF MASLD BY INDUCING NEUTROPHIL EXTRACELLULAR TRAPS FORMATION

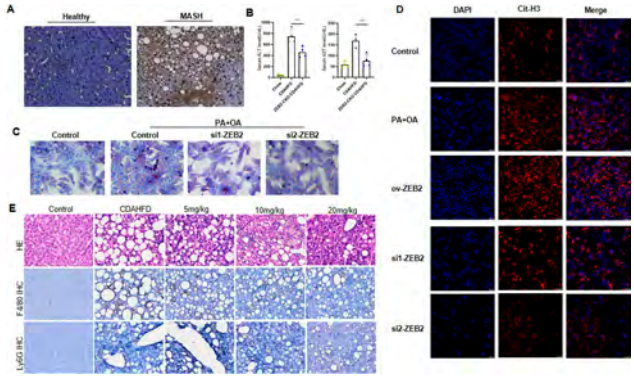
Guangqi Zhu[1] Qianwen Zhao[1] Jie Li[1], [1]Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University

Background: The transcription factor ZEB2 in hepatocytes has been implicated in metabolic dysfunction-associated steatotic liver disease (MASLD), yet its in vivo role and therapeutic potential remain undefined. This study aimed to determine whether hepatocyte ZEB2 drives MASLD via neutrophil extracellular traps (NETs) and whether pharmacological targeting of ZEB2 is feasible. **Methods:** ZEB2 expression was evaluated

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by IHC and IF in MASH patients. Primary mouse hepatocytes were treated with palmitic/oleic acid (PA/OA) with ZEB2 siRNA or overexpression. Hepatocyte-specific ZEB2 knockout (ZEB2-CKO) mice were generated via Cre/LoxP, and hepatocyte-specific overexpression (ZEB2-HTG) via AAV8-TBG. MASLD was induced by high-fat high-fructose (HFFC) or choline-deficient, amino acid-defined high-fat diet (CDA-HFD). NETs formation was measured by serum MPO-DNA ELISA and IF co-staining of NE and Cit-H3. Anti-Ly6G monoclonal antibody or DNase I was administered intraperitoneally to deplete neutrophils or degrade NETs. Virtual screening identified Sitravatinib as a candidate, which was tested in vivo (HFFC and CDA-HFD models with three doses) and in vitro (PA/OA-stimulated hepatocytes). **Results:** ZEB2 was markedly upregulated in MASH livers. ZEB2 knockdown suppressed lipid accumulation and inflammation in vitro, whereas overexpression exacerbated them. In vivo, ZEB2-CKO significantly reduced hepatic steatosis, inflammatory cytokines (IL-1β, IL-6, TNF-α), lipogenic genes (Acc1, Fasn, CD36), serum ALT/AST, total cholesterol and triglycerides (both serum and liver), and improved pyruvate/glucose/insulin tolerance tests in both HFFC and CDA-HFD models. Opposite phenotypes were observed in ZEB2-HTG mice. Mechanistically, RNA-seq and co-culture experiments revealed that ZEB2 enhances hepatocyte-neutrophil adhesion and promotes NETs formation, as evidenced by increased MPO-DNA and NE/Cit-H3 colocalization. Both neutrophil depletion (anti-Ly6G) and NETs disruption (DNase) ameliorated steatosis, inflammation, and liver injury in both dietary models. Finally, Sitravatinib treatment dose-dependently reduced lipid accumulation, inflammatory markers, NETs formation, and hepatic damage in vitro and in vivo, mirroring the protective effects of ZEB2 inhibition. **Conclusion:** Hepatocyte ZEB2 drives MASLD progression by inducing NETs formation, and Sitravatinib represents a promising therapeutic agent targeting this pathogenic axis.



Disclosures: Guangqi Zhu:Nothing to Disclose, Qianwen Zhao:Nothing to Disclose, Jie Li:Nothing to Disclose.

1326 | ◆ GENETIC AND PHARMACOLOGIC INHIBITION OF IL-21R ATTENUATES HEPATIC INFLAMMATION AND FIBROSIS IN MURINE MASH

Lucía Valenzuela-Pérez[1] Hyun Se Kim Lee[1] Rachel Bayer[1] Dina Manna[1] Ester Dohnalkova[1] Ivone Cristina Igreja Sa[1] Adebowale Bamidele[2] Petra Hirsova[2], [1]Mayo Clinic, Rochester, MN, [2]Mayo Clinic Rochester

Background: Metabolic dysfunction-associated steatohepatitis (MASH) is a chronic liver disease in which persistent hepatic inflammation drives fibrosis, yet the immunological mechanisms linking these processes remain incompletely understood. Increasing evidence highlights a central role for $CD4^+$ T cells and cytokine signaling in disease progression. Activated $CD4^+$ T cells are a major source of interleukin 21 (IL-21) and also express IL-21 receptor (IL-21R), suggesting that IL-21 signaling may amplify $CD4^+$ T cell-mediated inflammation through autocrine and paracrine mechanisms and promote fibrotic remodeling in MASH. **Methods:** IL-21R transcript levels were quantified in liver tissue from patients with MASH and murine MASH models by RNA sequencing and qPCR, respectively, and plasma IL-21 levels were measured by ELISA. To define the role of IL-21 signaling, IL-21R-deficient mice were fed a choline-deficient high-fat diet (CD-HFD) for 6 weeks or a high-fat, fructose, and cholesterol (FFC) diet for 24 weeks. Pharmacologic IL-21R inhibition was evaluated using an anti-IL-21R antagonist antibody in FFC-fed mice with established MASH. At study endpoints, hepatic steatosis, injury, inflammation, and fibrosis were assessed, and intrahepatic leukocytes were immunophenotyped by mass cytometry (CyTOF) or flow cytometry. **Results:** Hepatic IL-21R expression was increased in both patients with MASH and mice fed CD-HFD or FFC diets. Plasma IL-21 levels were elevated in patients with MASH compared with obese controls with normal liver histology. In CD-HFD-fed mice, CyTOF analysis revealed reduced hepatic accumulation of monocyte-derived macrophages and overall macrophage abundance in IL-21R-deficient mice compared with wild-type controls. This was accompanied by reduced tissue fibrosis as assessed by Sirius Red staining and immunohistochemistry. IL-21R deficiency also attenuated fibrosis in the FFC model, where flow cytometric analysis showed reduced hepatic and splenic $CD4^+$ T cells, including $Eomes^+$ $CD4^+$ T cells, whereas $CD8^+$ T cells were unchanged. Finally, therapeutic IL-21R blockade in mice with established MASH reduced liver injury and inflammation and reversed fibrosis, indicating that IL-21R inhibition has therapeutic potential in MASH. **Conclusion:** The IL-21–IL-21R axis is upregulated in MASH and contributes to disease progression by amplifying

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inflammatory and fibrotic responses. These findings highlight IL-21R as a promising therapeutic target for MASH.

Disclosures: Lucía Valenzuela-Pérez:Nothing to Disclose, Hyun Se Kim Lee:Nothing to Disclose, Rachel Bayer:Nothing to Disclose, Dina Manna:Nothing to Disclose, Ester Dohnalkova:Nothing to Disclose, Ivone Cristina Igreja Sa:Nothing to Disclose, Adebowale Bamidele:Nothing to Disclose, Petra Hirsova:Nothing to Disclose.

1327 | ◆ RAPID HUMANIZED MOUSE MODELS FOR LIVER FIBROSIS AND MASH

Clothilde Philouze[1] Omayra Martin-Rodriguez[1] Anaïs Meynet-Cordonnier[1] Sebastien Tabruyn[1] Dan Georgess[1], [1]TransCure bioServices

Background: The development of preclinical models integrating human immune components represents a key advance for the predictive evaluation of therapies targeting inflammation, fibrosis and metabolic dysfunction in liver diseases. In this study, we characterized two rapid induction approaches in humanized immune system NCG mice to establish distinct models of liver fibrosis and MASH. **Methods:** NCG mice engrafted with human $CD34^+$ hematopoietic stem cells (HIS-NCG) were exposed either to repeated carbon tetrachloride (CCl4) administration for 23 days or to a 14-day high-fat methionine- and choline-deficient (HFMCD) diet. Liver injury was assessed through clinical monitoring, circulating ALT and LGALS3 quantification, as well as histopathological fibrosis, steatosis and human macrophage infiltration assessment in the liver. **Results:** Both protocols induced rapid health deterioration associated with elevated serum ALT levels compared with control animals. However, the resulting pathological phenotypes differed substantially between models. CCl4-treated HIS-NCG mice developed severe liver fibrosis, with 88% of animals presenting bridging fibrosis (F3) or cirrhotic architecture, without associated steatosis or marked human macrophage infiltration. In contrast, the HFMCD diet induced a broader phenotype consistent with MASH, including advanced steatosis, a NAFLD activity score (NAS) of 6 and early-stage fibrosis (F0-F1), associated with infiltration by human $CD68^+$ macrophages. In both models, increased α-smooth muscle actin expression, indicative of hepatic stellate cell activation, together with elevated circulating galectin-3-binding protein levels, further supported the presence of active fibrotic processes. **Conclusion:** Together, these two HIS models provide well-defined liver phenotype platforms for the evaluation of therapeutic candidates targeting human immune-mediated pathways involved in liver disease.

Disclosures: Clothilde Philouze:Nothing to Disclose, Omayra Martin-Rodriguez:Nothing to Disclose, Anaïs Meynet-Cordonnier:Nothing to Disclose, Sebastien Tabruyn:Nothing to Disclose, Dan Georgess:Nothing to Disclose.

1328 | ◆ MULTIOMICS ON PAIRED FASTED AND FED HUMAN LIVER SAMPLES IDENTIFY IMPAIRED POSTPRANDIAL MITOCHONDRIAL FLEXIBILITY IN MASH

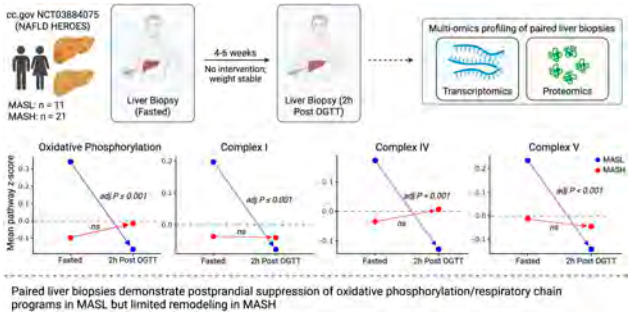
Haressh Sajiir[1] Harish Gopalakrishna[2] Elenita Rivera[3] Yaron Rotman[4], [1]National Institutes of Health/ NIDDK, [2]UTMB, [3]NIH/NIDDK, [4]National Institute of Diabetes and Digestive and Kidney Diseases; National Institutes of Health

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) ranges from simple steatosis (MASL) to steatohepatitis (MASH). MASH drives fibrosis, key to development of adverse clinical outcomes, yet drivers of MASH are not clear. Most human studies profile the fasting state, leaving hepatic adaptation to nutrient challenge poorly defined. We hypothesized that MASH reflects a defect in fasted-to-fed metabolic switching compared with MASL. **Methods:** Subjects with histology-defined MASL (n = 11) or MASH (n = 21) underwent two liver biopsies: one after an overnight fast and a second, 2 hrs after a 75g oral glucose load. Liver tissue was profiled by RNA-seq and proteomics and analyzed using paired, sex-adjusted differential expression/abundance models for fasting differences between groups, within-group post-glucose responses (2-hr post-glucose vs. fasting within MASL and MASH), and group-by-feeding interaction. Results were used for ranked pathway enrichment, with Hallmark pathways for global discovery and MitoCarta3.0 for mitochondrial module resolution. **Results:** Fasting MASH livers were transcriptionally distinct from MASL, with lower oxidative phosphorylation (OXPHOS) pathways compared to MASL but enrichment of protein secretion and cell-cycle pathways, suggesting a shift away from oxidative programs toward secretory/proliferative remodeling. Following oral glucose, MASL livers showed a significant decrease in OXPHOS pathways, whereas MASH had little change (FDR $q < 0.05$ for group-by-feeding interaction). MitoCarta analysis localized this effect to respiratory-chain pathways. MASL showed postprandial suppression of respiratory-chain subunit gene sets across Complexes I, IV, and V, whereas MASH showed limited remodeling from an already low-enrichment fasting state. This pattern was selective, as TCA cycle, fatty acid oxidation, amino acid

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metabolism, carbohydrate metabolism, and small-molecule transport gene sets did not show comparable disease-specific effects. Liver tissue proteomics showed similar findings, with fasting MASH depleted for respiratory-chain proteins and a group-by-feeding signal concentrated in OXPHOS and OXPHOS-subunit proteins. **Conclusion:** In a paired fasted–fed human liver multiomic study of MASLD, we identified physiological postprandial suppression of hepatic respiratory-chain/OXPHOS programs in MASL, consistent with a mitochondrial component of catabolic-to-anabolic metabolic switching. This adaptive response was selectively lost in MASH, reflecting impaired hepatic mitochondrial flexibility. By moving beyond static fasting comparisons, these findings reveal failed adaptive hepatic remodeling after nutrient challenge.



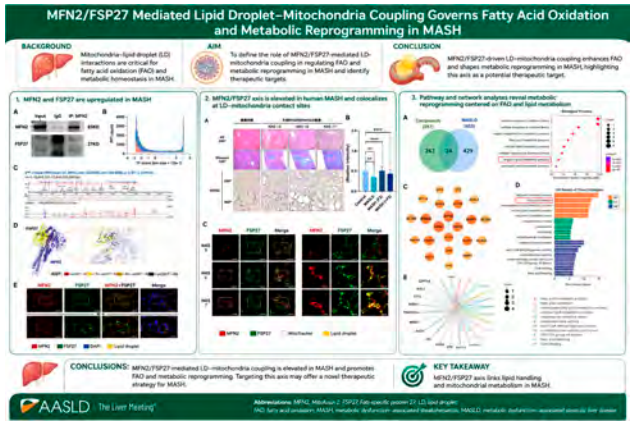
Paired liver biopsies demonstrate postprandial suppression of oxidative phosphorylation/respiratory chain programs in MASL but limited remodeling in MASH

Disclosures: Haressh Sajiir:Nothing to Disclose, Harish Gopalakrishna:Nothing to Disclose, Elenita Rivera: Nothing to Disclose, Yaron Rotman:Nothing to Disclose.

1329 | ◆ MFN2/FSP27 MEDIATED LIPID DROPLET-MITOCHONDRIA COUPLING GOVERNS FATTY ACID OXIDATION AND METABOLIC REPROGRAMMING IN MASH

Qianqian Zheng[1] Yuemin Nan[2] Chao Sun[3] Naoki Tanaka[4], [1]Third hospital of Hebei medical University, [2]Hebei Medical University Third Hospital, [3]The First Affiliated Hospital of Xi'an Medical University, [4]Shinshu University Graduate School of Medicine

Background: Disrupted lipid metabolism and mitochondrial dysfunction are central to metabolic dysfunction-associated steatohepatitis (MASH). However, the molecular mechanisms coordinating lipid droplet (LD)–mitochondria (MT) interactions remain poorly defined. We aimed to determine whether the MFN2–FSP27 complex regulates LD–MT coupling and thereby controls fatty acid oxidation and metabolic homeostasis in MASH. **Methods:** Human liver tissues from MASH patients and healthy controls were analyzed using immunofluorescence, confocal microscopy, and transmission electron microscopy to characterize LD–MT contact sites. MFN2 and FSP27 expression and interaction were assessed by Western blotting and co-immunoprecipitation. Gain- and loss-of-function approaches targeting MFN2 or FSP27 were performed in hepatocyte and adipocyte models to evaluate fatty acid oxidation, metabolic flux, and global metabolic reprogramming using metabolic assays and metabolomics. **Results:** MFN2 expression was markedly reduced in MASH livers, accompanied by decreased LD–MT contact formation and impaired MFN2–FSP27 complex assembly. Restoration of the MFN2–FSP27 axis enhanced LD–MT coupling, facilitated fatty acid trafficking to mitochondria, and significantly increased β-oxidation. In contrast, disruption of this complex led to defective fatty acid utilization, metabolic reprogramming toward lipogenic and pro-inflammatory pathways, and aggravated lipid accumulation and inflammatory responses. **Conclusion:** The MFN2–FSP27 complex is a critical regulator of LD–MT coupling that sustains fatty acid oxidation and metabolic homeostasis. Its dysfunction drives metabolic reprogramming and disease progression in MASH, highlighting a potential therapeutic target.



Disclosures: Qianqian Zheng:Nothing to Disclose, Yuemin Nan:Nothing to Disclose, Chao Sun:Nothing to Disclose, Naoki Tanaka:Nothing to Disclose.

1330 | ◆ GUT MICROBIOTA-DERIVED PHENYLACETIC ACID PROMOTES MASH BY IMPAIRING MITOCHONDRIAL FUNCTION VIA SIRT3-REGULATED HSP60 PHENYLACETYLATION

Yidan Huang[1] Yufeng Li[1], [1]Shanghai Institute of Materia Medica, CAS

Background: Disturbances in the gut microbiota (GM) and their metabolites are pivotal in the

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pathogenesis of metabolic dysfunction-associated steatohepatitis (MASH). These microbial metabolites often function as critical signaling molecules by serving as substrates for host protein post-translational modifications (PTMs), thereby orchestrating host-microbiota crosstalk. While short-chain fatty acid (SCFA)-driven PTMs are established, the capacity for other microbial products to reprogram the host proteome remains unrecognized. Specifically, although phenylacetic acid (PAA) promotes hepatic steatosis, its role as a bioactive acyl donor for protein PTMs is unknown. **Methods:** Kpaa identity was confirmed by HPLC-MS/MS and D_5-phenylacetate tracing. ACSF2/SIRT3 activities were screened using in vitro assays and gain/loss-of-function models. Mitochondrial function/mtUPR were assessed via Seahorse XFe96, TMRE/JC-1, TPE-MI imaging, ATF5 translocation, and HSP60-HSP10 assembly. K481 necessity was validated by K481A mutagenesis and mitochondria-targeted inhibitory peptides. Hepatic Kpaa/SIRT3 in MASH biopsies ($n = 30$) were quantified via multiplex immunohistochemistry (mIHC) and correlated with NAS scores. **Results:** Metaproteomics identified significant accumulation of fecal PAA in HFD-fed mice, associated with an increased abundance of *Clostridium asparagiforme*. Proteome-wide mapping identified 519 Kpaa sites on 236 hepatic proteins, with >75% localized to the mitochondria. Biochemical characterization established ACSF2 as the phenylacetyl-CoA synthetase driving Kpaa, while SIRT3 functioned as the primary mitochondrial dephenylacetylase. Mechanistically, PAA-induced Kpaa at Lys481 (K481) of HSP60 sterically disrupted its interaction with the co-chaperone HSP10. This disruption of the HSP60-HSP10 complex led to impaired mitochondrial proteostasis, as evidenced by ATF5 nuclear translocation and increased TPE-MI fluorescence, ultimately resulting in reduced oxygen consumption rate (OCR) and impaired mitochondrial membrane potential (MMP). These effects were abrogated by the K481A mutation or mitochondria-targeted competitive inhibitory peptides. In vivo, chronic PAA exposure or liver-specific SIRT3 knockdown significantly exacerbated hepatic steatosis and inflammatory infiltration. Clinically, hepatic Kpaa levels were markedly elevated in patients with MASH and showed a strong positive correlation with NAS ($r = 0.67$, $P < 0.001$) and a negative correlation with SIRT3 expression. **Conclusion:** We characterize Kpaa as a novel microbiota-derived PTM driving MASH. SIRT3/ACSF2-dependent HSP60-K481 phenylacetylation links gut-derived PAA to hepatic mitochondrial proteostasis failure, establishing the Kpaa-HSP60 signaling node as a viable therapeutic target for restoring mitochondrial function in MASH.

Disclosures: Yidan Huang:Nothing to Disclose, Yufeng Li:Nothing to Disclose.

1331 | ◆ NOVEL ROLES OF HAF IN REGULATING LIPID METABOLISM IN METABOLIC DYSFUNCTION–ASSOCIATED STEATOTIC LIVER DISEASE AND HEPATOCELLULAR CARCINOMA

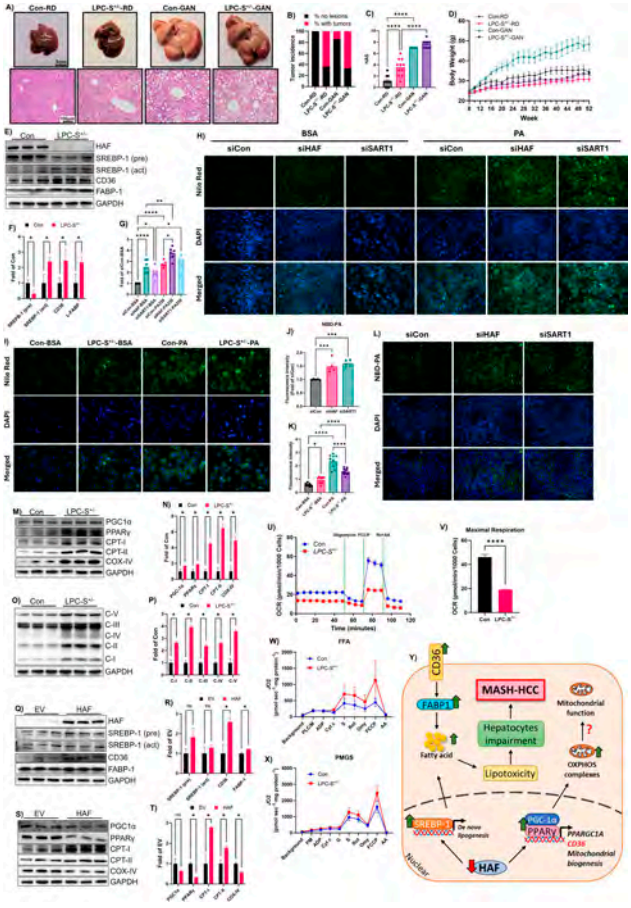
Po-An Hu[1], [1]University of Utah

Background: Hypoxia-associated factor (HAF, *SART1*) has been shown to be an essential regulator of the NF-κB pathway, and loss of HAF in mouse hepatocytes results in increased apoptosis and spontaneous development of steatosis, leading to MASH and HCC. HAF is also decreased in steatotic human livers. However, the mechanisms by which HAF affects lipid metabolism in MASLD remain unknown. **Methods:** To determine the role of HAF in the pathogenesis of MASLD-HCC, we generated mouse models with hepatocyte-specific gain or loss of HAF. We used C57BL/6 mice with hepatocyte-specific *SART1* overexpression mediated by hydrodynamic tail-vein injection (HDTV, gain of HAF) and C57BL/6 mice bearing the floxed SART1 gene crossed with those expressing Alfp-Cre to generate liver-specific HAF knockdown (KD) mice (*LPC-S*$^{+/-}$, loss of HAF). Mouse models were fed the GAN diet for 1 year, then harvested and scored for NAFLD activity score (NAS) to investigate the impact of HAF modulation on MASLD progression. For in vitro experiments, primary hepatocytes from mouse models and the human hepatoma cell line Huh7 were used to support in vivo findings. **Results:** We observed increased tumor incidence and NAS in *LPC-S*$^{+/-}$ mice on a chow diet but no change in HDTVi mice, confirming our previous findings that HAF loss promotes MASH-HCC progression. However, feeding a GAN diet did not further exacerbate the liver pathology in *LPC-S*$^{+/-}$ mice. To characterize the impact of HAF loss, primary hepatocytes from *LPC-S*$^{+/-}$ mice were submitted for mRNA sequencing, which revealed significantly increased levels of genes involved in fatty acid (FA) metabolism. Following this finding, we observed elevated levels of FA uptake-related proteins CD36 and FABP-1, as well as the de novo lipogenesis-related protein SREBP-1 in primary hepatocytes from *LPC-S*$^{+/-}$ mice. Increased FA uptake and *de novo* lipogenesis were confirmed by fluorescence lipid staining and by treatment with a fluorescence probe-conjugated PA, demonstrating that HAF loss promotes FA uptake and lipogenesis. We also observed changes in PPARγ and PGC-1α, transcription factors associated with FA β-oxidation and mitochondrial biogenesis, as well as the mitochondrial marker COX-IV: PPARγ, PGC-1α, and COX-IV were elevated in *LPC-S*$^{+/-}$ hepatocytes and reduced in those from HDTV-HAF

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mice, suggesting that HAF may suppress the function of these proteins. Intriguingly, despite the elevation of these markers, we did not observe an increase in metabolic function using either the Seahorse analyzer or the Oroboros respirometry system. **Conclusion:** Our data suggest that decreased HAF levels may promote MASH-HCC progression, in part by increasing FA uptake and lipogenesis, leading to lipotoxicity. This may promote hepatocyte stress and generate a tumor-permissive environment that could potentiate progression to HCC. The potential mechanisms by which HAF regulates PPARγ and PGC-1α could provide new insights into the pathogenesis of MASH-HCC.

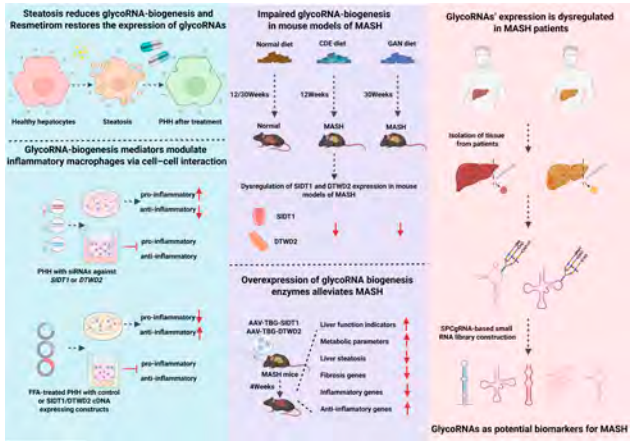


Disclosures: PO-AN HU:Nothing to Disclose.

★ 1332 | ◆ IMPAIRED GLYCORNA BIOGENESIS IN METABOLIC-DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE

Chengji Dong[1], [1]*Hannover Medical School*

Background: Glycosylated proteins and lipids regulate multiple cellular processes and play key roles in organ damage and regeneration. Recently, glycosylated non-coding small RNAs (glycoRNA) have been identified, however, their expression in the liver and their involvement in hepatic pathology has not yet been reported. **Methods:** We detected the presence of glycoRNAs by northern blot and a second method using an imaging approach called sialic acid aptamer and RNA in situ hybridization-mediated proximity ligation assay that enables the direct visualization of glycoRNAs. The in vivo restoration of key mediators of glycoRNA biosynthesis was achieved via adeno-asscoiated viral vectors. **Results:** Here, we show that glycoRNAs are synthesized in human liver tissue, primary hepatocytes and hepatic tumor cells. In tissues from patients with key features of metabolic dysfunction-associated steatotic liver diseases (MASLD), the most prevalent liver disease worldwide, expression of most glycoRNAs was reduced. Mechanistically, we found that the reduced expression of SID1 transmembrane family member 1 (SIDT1) and DTW domain containing 2 (DTWD2), two key mediators of glycoRNA biosynthesis, contribute to loss of glycoRNAs in MASLD. Inhibition of SIDT1 and DTWD2 increased fatty acid load in primary human hepatocytes and enhanced inflammation signals upon co-culture with macrophages. Importantly, adeno-associated viral vector mediated in vivo restoration of SIDT1 and DTWD2 attenuated MASH in a pre-clinical mouse model of MASH. Furthermore, sequencing of enriched glycoRNA samples identified six glycosylated piRNAs and two tRNAs, which were downregulated in steatotic human liver and hepatocytes. **Conclusion:** Collectively, our study demonstrates the presence of glycoRNAs in human hepatocytes and human liver tissues as well as dysregulated expression in experimental steatosis and in MASLD patients.



Disclosures: Chengji Dong:Nothing to Disclose.

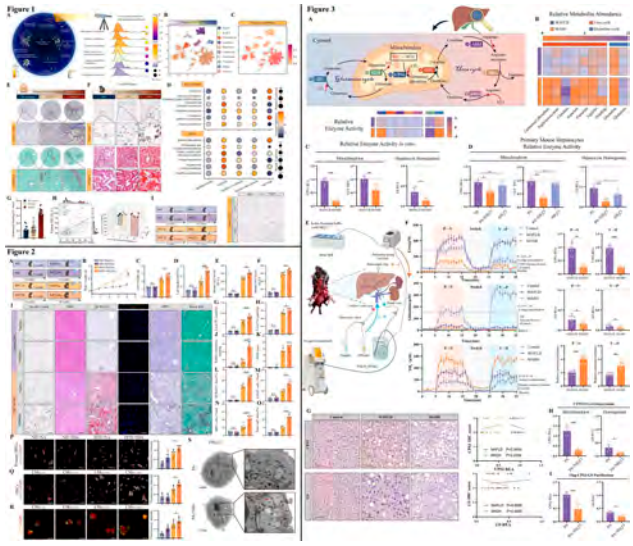
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1333 | ◆ SPATIAL BREAKDOWN OF HEPATIC NITROGEN METABOLISM DRIVES MAFLD PROGRESSION

Feifan Yao[1] Xiaofeng Tie[1] Xuehao Wang[1] Qing Li[1], [1]Nanjing medical university

Background: MAFLD affects approximately 1.7 billion people globally, ranking among the fastest-growing chronic liver diseases. WHO recently recognized it as a rapidly escalating NCD, emphasizing its profound population health hazards. Emerging omics reveal aberrant ammonia metabolism as an independent driver of MAFLD. Physiologically, ammonia detoxification relies on precise spatial zonation: periportal hepatocytes utilize the high-capacity urea cycle, while perivenous hepatocytes employ high-affinity glutamine synthetase. We hypothesize the MAFLD microenvironment disrupts this zonation, causing an occult decline in ammonia clearance that fuels a pathogenic cycle. **Methods:** We integrated human MAFLD/MASH biopsies with a temporal HFCD-HF/G murine model. Systemic ammonia metabolic capacity was quantified via Acute and Chronic Ammonia Tolerance Tests (AATT/CATT). Spatial metabolic architecture was mapped using bidirectional in situ hepatic perfusion. Nessler's staining visualized intrahepatic ammonia. Mass spectrometry evaluated post-translational modifications. In vitro primary and passaged hepatocytes alongside hepatic stellate cells were utilized to assess the pro-pathogenic effects of ammonia. **Results:** In early steatosis, baseline intrahepatic ammonia appeared morphologically normal. However, AATT unmasked a profound, occult deficit in acute clearance capacity. Bidirectional perfusion revealed the precise spatial sequence of this breakdown: lipid accumulation initially targets the PV zone, severely suppressing GS activity. Subsequently, the dysregulated spatial architecture and oxidative stress downregulate PP CPS1 activity. Mass spectrometry revealed that while early-stage protein expression remains stable, aberrant PTMs—specifically palmitoylation and oxidation—significantly impair enzyme functions, precipitating a pan-lobular collapse of nitrogen processing zones. MASH progression triggers massive localized ammonia sequestration. CATT and in vitro assays confirmed this accumulated ammonia acts as a potent secondary hit, exacerbating lipotoxic mitochondrial damage and driving HSC activation and fibrogenesis. This establishes a pathogenic positive feedback loop where early PV-centric clearance impairment promotes ammonia accumulation, reciprocally accelerating MAFLD progression. **Conclusion:** MAFLD is inherently characterized by a progressive, occult downregulation of spatially distributed ammonia detoxification. The pathogenic cascade initiates with lipid-driven palmitoylation suppressing PV GS, precipitating a pan-lobular collapse of nitrogen metabolism. The resulting intrahepatic hyperammonemic microenvironment is a critical concomitant disorder, driving a pleiotropic pathogenic positive feedback loop. Targeting this spatial breakdown to restore zonal ammonia clearance represents a novel therapeutic strategy for halting MAFLD.



Disclosures: Feifan Yao:Nothing to Disclose, xiaofeng Tie:Nothing to Disclose, xuehao Wang:Nothing to Disclose, qing Li:Nothing to Disclose.

1334 | ◆ A+T RICH INTERACTION DOMAIN PROTEIN 3A (ARID3A) IN MACROPHAGES IMPAIRS PROTECTIVE TH17-MEDIATED GUT HOMEOSTASIS IN MASLD

Ruiling Chen[1] Xiong Ma[1], [1]Renji Hospital, Shanghai Jiao Tong University, School of Medicine

Background: Macrophages play a critical role in metabolic dysfunction-associated steatotic liver disease (MASLD). We have previously demonstrated that macrophage Arid3a promotes cholestatic liver injury by impairing Mertk-mediated efferocytosis. However, the role of macrophage Arid3a in MASLD remains unclear. **Methods:** Myeloid-specific Arid3a knockout mice were generated as previously described. Arid3a-deficient mice and control littermates were fed a high-fat diet and housed either separately or in co-housing conditions. Mice were subjected to either oral gavage of Desulfovibrio or its metabolites, or administration of monoclonal antibodies against IL-23p19, IL-17A or IL-22. Metabolic status was assessed using intraperitoneal glucose

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tolerance tests. Serum liver enzyme levels were measured, and the degree of hepatic steatosis was evaluated by H&E staining and oil red O staining. Fecal samples were collected for 16S ribosomal RNA gene sequencing-based microbiome analysis. Flow cytometry was employed to analyze in vitro co-cultured immune cells or primary intestinal immune cells. The accessibility of promoter regions was assessed by ChIP-seq targeting Arid3a. **Results:** Myeloid-specific deletion of Arid3a significantly improved metabolic parameters and alleviated high-fat diet-induced hepatic steatosis. Co-housing Arid3a-deficient mice with control littermates led to the convergence of gut microbiota composition and abolished the phenotypic differences in liver steatosis. Desulfovibrio abundance was positively correlated with metabolic indices, including body weight gain and serum alanine aminotransferase levels. Administration of Desulfovibrio or its metabolites exacerbated liver steatosis in Arid3a-deficient mice. Mechanistically, under high-fat diet conditions, Arid3a-deficient mice exhibited an increased frequency of intestinal Th17 cells expressing IL-17A and IL-22, along with improved gut permeability. In addition, intestinal macrophages from Arid3a-deficient mice showed upregulated expression of IL-23p19 and directly promoted Th17 cell differentiation in vitro. ChIP-seq analysis further demonstrated a direct interaction between Arid3a and the Il23a (IL-23p19) gene promoter in macrophages. Critically, targeting the IL-23-Th17 axis in vivo reversed the protective effect of macrophage-specific Arid3a deficiency against liver steatosis. **Conclusion:** Macrophage Arid3a drives hepatic steatosis by disrupting gut homeostasis through the IL-23-Th17 axis. This study identifies macrophage Arid3a as a critical link between the gut-liver axis and the pathogenesis of MASLD, positioning it as a potential novel therapeutic target for the disease.

Disclosures: RUILING CHEN:Nothing to Disclose, Xiong Ma:Nothing to Disclose.

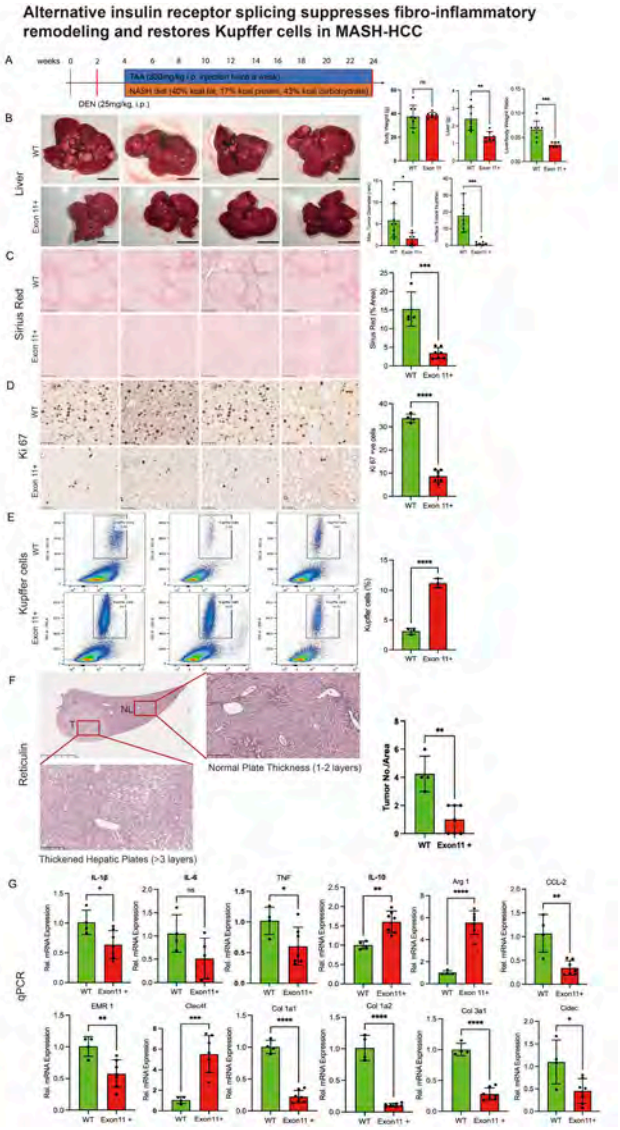
1335 | ◆ ALTERNATIVE INSULIN RECEPTOR SPLICING GOVERNS IMMUNE NICHE REMODELING DURING MASH-DRIVEN HEPATOCARCINOGENESIS

Yanting Wang[1] Manasi Das[1] Yunpeng Yang[1] Isabella Maranan[1] Liping Zeng[1] Nicholas Webster[1], [1]University of California, San Diego

Background: Metabolic dysfunction-associated steatohepatitis (MASH) promotes hepatocellular carcinoma (HCC) through poorly defined mechanisms linking hepatocyte dysfunction to fibro-inflammatory immune remodeling. Loss of the splicing factor SRSF3 induces insulin receptor (INSR) exon 11 skipping, shifting expression from the metabolic IR-B isoform to the mitogenic IR-A isoform and establishing a pathogenic signaling state. We investigated whether restoration of INSR splicing fidelity could reprogram the hepatic immune niche and interrupt progression from chronic metabolic liver injury to hepatocarcinogenesis. **Methods:** We utilized hepatocyte-specific Exon11+ mice, in which Insr exon 11 inclusion is genetically enforced to prevent formation of the mitogenic IR-A isoform. Exon11+ and wild-type littermates underwent DEN plus Western diet/TAA-induced MASH-HCC for 24 weeks. Hepatocarcinogenesis, fibrosis, inflammatory signaling, and hepatic immune niche composition were assessed using histopathology, RT-qPCR, and high-dimensional flow cytometry. **Results:** Restoring INSR splicing fidelity markedly suppressed MASH-driven hepatocarcinogenesis. Compared with wild-type mice, Exon11+ mice exhibited an > 80% reduction in tumor burden ($p < 0.001$) and significantly attenuated hepatic fibrosis by Sirius Red staining and reduced Col1a1 expression (both $p < 0.001$). Exon11+ livers further demonstrated reduced Ki67+ hepatocyte proliferation together with coordinated suppression of inflammatory gene programs, including Il1b, Tnf, Ccl2, and Emr1.High-dimensional flow cytometry revealed remodeling of the hepatic immune niche in Exon11+ livers. Resident F4/80high Kupffer cell populations were markedly restored (~3-fold increase vs WT, $p < 0.0001$), while neutrophil accumulation was reduced, consistent with attenuation of the pro-inflammatory myeloid compartment. Increased expression of the reparative marker Arg1 and the anti-inflammatory cytokine Il10, together with restoration of the Kupffer cell identity marker Clec4f, further supported re-establishment of a Kupffer cell-enriched hepatic microenvironment. **Conclusion:** The SRSF3-INSR splicing axis mechanistically links hepatocyte dysfunction to fibro-inflammatory remodeling and immune dysregulation during MASH-HCC progression. These findings identify hepatocyte-specific alternative splicing as an upstream regulator of hepatic immune niche composition during hepatocarcinogenesis. Blocking the pathogenic IR-A isoform switch restores a tumor-suppressive hepatic immune microenvironment and positions the INSR splicing axis as a mechanistically targetable pathway linking metabolic injury, immune remodeling, and hepatocarcinogenesis.

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Disclosures: Yanting Wang:Nothing to Disclose, Manasi Das:Nothing to Disclose, Yunpeng Yang:Nothing to Disclose, Isabella Maranan:Nothing to Disclose, Liping Zeng:Nothing to Disclose, Nicholas Webster:Nothing to Disclose.

1336 | ◆ GALECTIN-3 DEFICIENCY REVEALS SEX-SPECIFIC DIVERGENCE IN AGING-ASSOCIATED MASLD

Astrid Ardon-Lopez[1] Fernando Flores Guzman[1] Ella Nagaraj[2] Mia Panlilio[1] Clara Eugenia Moreno-Ramirez[3] Osvely Méndez-Guerrero[4] Yuhuan Luo[1] Christene Huang[1] Nalu Navarro-Alvarez[5], [1]University of Colorado Anschutz Medical Campus, [2]University of Colorado Anschutz Medical Campus, [3]Centro Universitario de la Costa, University of Guadalajara, [4]Instituto Nacional de Ciencias Medicas y Nutrición Salvador Zubiran, [5]University of Colorado Anschutz Medical Campus/ Instituto Nacional de Ciencias Médicas y Nutrición

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common chronic liver disease worldwide and shows clear differences by age and sex. Although males have a higher burden earlier in life, disease risk rises in females after menopause, indicating that aging can reshape susceptibility to hepatic steatosis and injury. Galectin-3 (Gal-3), a β-galactoside-binding lectin linked to hepatic steatosis and inflammation, may contribute to this process, but its role in aging-associated MASLD in males and females remains unclear. We examined whether Gal-3 deficiency modifies the development of MASLD in aged male and female mice. **Methods:** Young (1-month-old) and aged (18-month-old) wild-type (WT) and Gal-3 knockout (KO) male and female mice were maintained on standard chow throughout life as a spontaneous aging model. Metabolic parameters, liver weight, clinical chemistry markers (ALT, AST, triglycerides, cholesterol), blood counts, and liver histology were assessed. Liver pathology was scored by H&E staining using NAFLD Activity Score (NAS) analysis by a pathologist blinded to experimental groups. Immunohistochemistry was performed to evaluate hepatic Gal-3 expression and F4/80+ macrophage accumulation. **Results:** Aging increased hepatic Gal-3 expression in WT mice, most prominently in females, and increased body weight and liver weight in both sexes. However, the liver phenotype was strongly male-biased. Aged males had the highest liver weight, higher plasma cholesterol than aged females ($p < 0.01$), and the most severe histologic injury, with increased NAS, steatosis, lobular inflammation, and hepatocellular ballooning compared with young controls. In aged males, Gal-3 deficiency reduced liver weight and was associated with lower steatosis and ballooning degeneration. Steatosis decreased from 51% in aged WT males to 21% in aged Gal-3 KO males, and liver weight positively correlated with steatosis severity.In females, the effect of Gal-3 deficiency was different. Aged females remained largely protected from hepatic fat accumulation, with steatosis below 12% regardless of genotype. Despite this low-steatosis phenotype, aged Gal-3 KO females had higher lobular inflammatory activity than aged WT females. F4/80+ macrophage accumulation was also greater in females than males ($p < 0.01$), independent of age or Gal-3 status. **Conclusion:** Gal-3 deficiency separated two distinct aging-associated liver responses. In aged males, loss of Gal-3 was associated with less steatosis, lower liver weight, and reduced hepatocyte injury. In aged females, low steatosis persisted, but inflammatory activity and macrophage accumulation remained prominent. This sex-dependent divergence places Gal-3 at the intersection of lipid accumulation and hepatic

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inflammation during aging-associated MASLD. Thus, sex and age should be considered when evaluating Galectin-3-targeted therapies for MASLD.

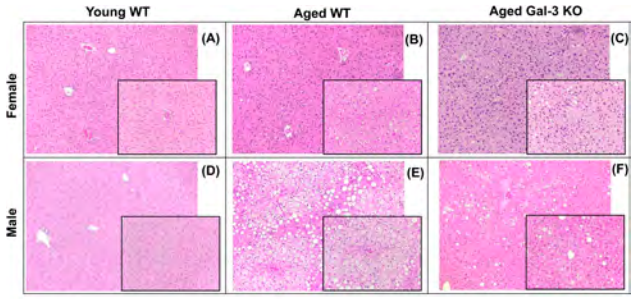


Figure 1. Reduced steatosis in aged Gal-3 KO males compared to aged WT males. Representative liver H&E images of: (A) female WT young, (B) female WT aged, (C) female Gal-3 KO aged, (D) male WT young, (E) male WT aged, and (F) male Gal-3 KO aged.

Disclosures: Astrid Ardon-Lopez:Nothing to Disclose, Fernando Flores Guzman:Nothing to Disclose, Ella Nagaraj:Nothing to Disclose, MIA PANLILIO:Nothing to Disclose, Clara Eugenia Moreno-Ramirez:Nothing to Disclose, Osvely Méndez-Guerrero:Nothing to Disclose, Yuhuan Luo:Nothing to Disclose, Christene Huang:Nothing to Disclose, Nalu Navarro-Alvarez: Nothing to Disclose.

★ 1337 | ◆ TIME-RESTRICTED FEEDING (TRF) ATTENUATES FATTY-LIVER DISEASE AND POTENTIATES THE EFFICACY OF RESMETIROM FOR METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH) RESOLUTION

Shaunak Deota[1] Terry Lin[1] Kelsey Fierro[1] Krushali Powale[1] Ramesh Ramasamy[1] Hiep Le[1] Satchidananda Panda[1], [1]Salk Institute for Biological Studies

Background: Metabolic dysfunction-associated steatohepatitis (MASH) is characterized by liver steatosis, inflammation, and fibrosis, which, if left untreated, can progress to cirrhosis, hepatic decompensation, and cancer (HCC). While exercise, weight loss, and dietary interventions are recommended for managing MASH, two drugs recently received accelerated FDA approval: Resmetirom (a liver-directed Thyroid receptor beta agonist) and Semaglutide (a glucagon-like peptide-1 receptor agonist). However, only 30-50% of patients on these drugs show a reduction in MASH progression and fibrosis, indicating that alternative molecular targets or combination therapies are needed to improve treatment outcomes and reduce disease burden. Time-restricted feeding/eating (TRF/TRE) involves restricting caloric intake to a consistent daily schedule during the active phase. While TRF reduces adiposity, dyslipidemia, and type 2 diabetes and improves liver steatosis in obese mouse models, its role in modulating MASH pathogenesis remains unexplored. **Methods:** We used a mouse model of high-fat, high-cholesterol diet (GAN diet) induced MASH that closely resembles human disease progression and pathophysiology. To test the preventive effect of TRF on MASH pathogenesis, we subjected male and female mice to ad libitum feeding (ALF) of GAN diet for 36 weeks, and the other group was subjected to iso-caloric feeding of the same diet for 9 hours during the dark phase (ZT13-ZT22). To test the therapeutic effect of TRF and resmetirom, we subjected male and female mice to ad libitum feeding (ALF) of GAN diet for 52 weeks to induce MASH, and then divided them into 4 groups: vehicle-treated ALF, resmetirom-treated ALF, vehicle-treated TRF, and resmetirom-treated TRF. Resmetirom treatment was performed by oral gavage for 5 days/week for 8 weeks at 3 mg/kg dose. We performed liver histology, serum and liver biochemical tests, and bulk and single-nuclei RNA sequencing of the liver to identify molecular mechanisms mediating beneficial effects. **Results:** TRF prevented the development of MASH symptoms, including liver steatosis, inflammation, and fibrosis, as assessed by histology, metabolic, and molecular analyses. Furthermore, in mice with established MASH and fibrosis, TRF enhanced the efficacy of resmetirom in resolving MASH and improved the associated metabolic syndrome in both male and female mice. Mechanistically, we observed that TRF and resmetirom increased the expression of genes involved in cholesterol and bile acid synthesis in the liver and reduced FXR-FGF15/19 signaling in the ileum, thus remodeling the gut-liver bile acid axis. **Conclusion:** Together, these results indicate that lifestyle interventions, such as TRF, can prevent the development of MASH and potentiate the effects of approved pharmacotherapies, such as resmetirom, thereby reducing disease progression and improving health.

Disclosures: Shaunak Deota:Nothing to Disclose, Terry Lin:Nothing to Disclose, Kelsey Fierro:Nothing to Disclose, Krushali Powale:Nothing to Disclose, Ramesh Ramasamy:Nothing to Disclose, Hiep Le: Nothing to Disclose, Satchidananda Panda:Nothing to Disclose.

1338 | ◆ INTEGRATING AI-BASED FIBROSIS STAGING AND PATTERN ANALYSIS IN A TRANSLATIONAL MOUSE MODEL OF MASH

Henrik Hansen[1] Denise Oró Bozzini[1] Monika Lewinska[1] Asbjørn Petersen[1] Kristoffer Voldum-Clausen[1], [1]Gubra A/S

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Background: Histopathological fibrosis staging is a key endpoint in metabolic dysfunction-associated steatohepatitis (MASH) research and preclinical drug development. Conventional assessment using the MASH CRN (Kleiner) scoring system assigns a single global fibrosis stage per biopsy and may not adequately capture fibrosis remodeling or spatial heterogeneity within the tissue. This limitation is particularly relevant in treatment studies, where antifibrotic effects may occur without substantial changes in overall fibrosis stage. To address this challenge, we developed GHOST, an AI-based digital pathology platform that integrates clinically relevant fibrosis staging with quantitative analysis of fibrosis patterns from liver histology images. **Methods:** Picrosirius red (PSR)-stained liver sections from 2,321 GAN DIO-MASH mouse liver samples were scanned at 20×. Following AI-based tissue detection, individual biopsies were subdivided into small image regions ("tiles") for analysis. Three convolutional neural networks were trained for fibrosis pattern detection, bridging classification, and PSR-positive fiber segmentation. Tile-level outputs from the trained networks were aggregated into quantitative biopsy-level fibrosis pattern distributions and PSR fraction measurements. These features were integrated into a Random Forest classifier trained to predict fibrosis stage according to the Kleiner scoring system. **Results:** The GHOST platform predicted Kleiner fibrosis stage with a Kappa of 0.85, demonstrating high concordance to manual scoring. Misclassifications were limited to adjacent fibrosis stages, with no major discordant predictions observed. In addition, the platform generated quantitative fibrosis pattern distributions across biopsies, enabling assessment of fibrosis architecture and treatment-associated remodeling. The approach was further evaluated across multiple treatment studies in GAN DIO-MASH mice. In several studies, fibrosis pattern analysis identified treatment-associated remodeling patterns and changes in PSR-positive area despite limited or absent changes in global fibrosis score, including changes consistent with fibrosis improvement following semaglutide treatment. **Conclusion:** GHOST provides clinically interpretable fibrosis staging together with fibrosis pattern analysis from liver histology images. Beyond predicting the Kleiner fibrosis score, the AI-assisted approach enables characterization of dynamic changes in fibrosis architecture across biopsies, supporting sensitive treatment-response assessment in preclinical MASH studies.

Disclosures: Henrik Hansen:Gubra A/S: Employee, Denise Oró Bozzini:Nothing to Disclose, Monika Lewinska:Nothing to Disclose, Asbjørn Petersen:Nothing to Disclose, Kristoffer Voldum-Clausen:Nothing to Disclose.

1339 | ◆ ROLE OF SKELETAL MUSCLE THEM2 IN THE EXTRACELLULAR VESICLE-MEDIATED REGULATION OF HEPATIC LIPID METABOLISM

Sepideh Mikaeeli[1] Ayisha Bushra[1] David Cohen[1],
[1]Cedars-Sinai Medical Center

Background: We previously demonstrated that skeletal muscle-specific deletion of thioesterase superfamily member 2 (Them2) protects against metabolic dysfunction-associated steatotic liver disease (MASLD). The fatty acyl-CoA thioesterase activity of Them2 in skeletal muscle promotes insulin resistance, at least in part, through p38 MAPK signaling. Them2 also controls hepatic lipid metabolism, an effect that may be mediated through extracellular vesicle (EV) signaling from skeletal muscle to the liver. This study explored regulation by Them2 of skeletal muscle-derived EV production, cargo composition, and effects on hepatic lipid metabolism. **Methods:** Global Them2 knockout (*Them2*$^{-/-}$) mice and skeletal muscle-specific Them2 knockout (*S-Them2*$^{-/-}$) mice, generated by intramuscular injection of MCK-AAV8-Cre into *Them2*$^{fl/fl}$ mice, were fed a chow diet. EV were isolated from plasma and media from cultured myotubes. Purified EV were characterized and quantified by transmission electron microscopy (TEM) and nanoparticle tracking analysis (NTA). Functional effects were assessed by treating fatty acid-treated primary hepatocytes with equal concentrations of EV, followed by BODIPY staining to measure lipid droplet (LD) accumulation. To identify bioactive components, EV were sonicated to release their cargo, size-fractionated by microfiltration, and selectively depleted of RNA or lipids. EV cargo composition and skeletal muscle EV biogenesis pathways were analyzed by small RNA sequencing and qPCR. **Results:** Them2 deletion increased plasma EV concentrations, with a similar trend for myotube-derived EV. *Them2*$^{-/-}$ myotube-derived EV significantly reduced LD accumulation in primary hepatocytes relative to EV from wild type myotubes. The absence of Them2 in both *Them2*$^{-/-}$ and *S-Them2*$^{-/-}$ mice was associated with increased skeletal muscle expression of genes involved in EV biogenesis and release, including Rab27a. Small RNA sequencing of skeletal muscle EV revealed significant alterations in the expression of several microRNAs implicated in hepatic lipid accumulation, including downregulation of miR-21, a target of MKP-1-dependent inhibition of p38 MAPK signaling. The lipid-lowering activity of EV from Them2-deficient myotubes on primary hepatocytes was abolished by RNA depletion and by removal of cargo larger than 3 kDa, but not 10 kDa, indicating that active EV components reside within the 3-10 kDa molecular weight range. **Conclusion:** Them2 regulates skeletal muscle EV production, cargo composition, and EV-mediated control of LD accumulation in hepatocytes. Them2 deletion alters pathways of EV biogenesis, conferring protective effects against hepatocyte lipid

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accumulation through specific bioactive cargo, likely microRNAs. We speculate that skeletal muscle EV might be leveraged as a potential therapeutic strategy for the management of MASLD.

Disclosures: Sepideh Mikaeeli:Nothing to Disclose, Ayisha Bushra:Nothing to Disclose, David Cohen: Nothing to Disclose.

1340 | ◆ SENESCENCE MEDIATED HEPATOCYTE INJURY DRIVES MASLD PROGRESSION

Sadam Bhat[1] Mustafa Karabicici[1] Takashi Tsuchiya[1] Vijay Pandyarajan[2] Rie Seki[1] Tiantian Chang[1] Jieun Kim[1] Keiya Watakabe[1] So Yeon Kim[3] Yoon-Seok Roh[4], [1]Cedars Sinai Medical Center, [2]Cedars Sinai Medical Center Hepatology, [3]Cedars-Sinai Medical Center, [4]Chungbuk National University College of Pharmacy

Background: Senescence of hepatocytes is a central driver of MASLD progression, but the mechanisms that initiate and sustain this senescent state remain unclear. Senescence-associated DNA damage, mitochondrial dysfunction, and metabolic reprogramming may contribute to persistent liver injury. In this study, we investigated whether loss of Ubc13, a K63-linked ubiquitin-conjugating enzyme involved in DNA repair and mitochondrial homeostasis, contributes to senescent hepatocyte accumulation and accelerates MASLD progression. **Methods:** Senescence was studied in mice with the conditional deletion of Ubc13 in hepatocytes ($Ubc13^{\Delta hep}$) and littermate WT controls ($Ubc13^{fl/fl}$) fed normal and high-fat diets (HFD). Senescent cells were targeted using dasatinib plus quercetin (D+Q). Liver injury, steatosis, senescence, and regeneration were assessed by ALT/AST, histology, γH2AX, p21, p16, PCNA, transcriptomics, and proteomics. Senescence-associated glutaminolysis was evaluated using CB-839, a glutaminase-1 inhibitor, in human hepatocyte organoids and mice. **Results:** In aged/MASLD human and mouse liver samples, we found an increased expression of senescence markers p21 and p16, while Ubc13 expression was reduced ($p < 0.05$). Senescent hepatocytes were significantly increased in HFD-fed $Ubc13^{\Delta hep}$ mice, with elevated γH2AX and p21, steatosis, and higher ALT/AST compared with HFD-fed WT controls ($p < 0.01$–0.05). Senolytic treatment with D+Q reduced steatosis, ALT/AST, and p21-positive hepatocytes ($p < 0.05$–0.01), supporting senescence as a functional mediator of disease severity. Liver transcriptomic analyses revealed a pro-senescent shift with increased anti-apoptotic genes (Bcl2, Mcl1) and reduced proliferation and ubiquitination pathways ($p < 0.05$), along with increased SASP expression. Pathway analysis showed activation of p53 signaling and cell cycle arrest, with suppression of DNA replication and metabolic pathways. Senescence-associated mitochondrial dysfunction was confirmed by proteomics, with reduced MFN2, OPA1, TOMM20, and TOMM70 under HFD (FD > 1.5, FDR < 0.05); these changes were improved by D+Q and further worsened in $Ubc13^{\Delta hep}$ mice ($p < 0.05$–0.01). Senescence-associated glutaminolysis inhibition by CB-839 reduced lipid accumulation ($p < 0.05$) and p21-positive senescent cell populations ($p < 0.05$) in human hepatocyte organoids and mice. **Conclusion:** Senescence is a major driver of MASLD progression and is further amplified by reduced hepatocyte Ubc13. This promotes a self-sustaining senescent state characterized by DNA damage, mitochondrial dysfunction, and glutaminolytic reprogramming, leading to steatotic liver injury. Senolytic therapy and GLS1 inhibition attenuate these disease features, identifying a senescence-centered Ubc13–mitochondria–glutaminolysis axis as a therapeutically actionable pathway in MASLD.

Disclosures: Sadam Bhat:Nothing to Disclose, Mustafa Karabicici:Nothing to Disclose, TAKASHI TSUCHIYA: Nothing to Disclose, Vijay Pandyarajan:Nothing to Disclose, Rie Seki:Nothing to Disclose, Tiantian Chang: Nothing to Disclose, Jieun Kim:Nothing to Disclose, Keiya Watakabe:Nothing to Disclose, So Yeon Kim:Nothing to Disclose, Yoon-Seok Roh:Nothing to Disclose.

★ 1341 | ◆ DIETARY SUBSTRATE COMPOSITION UNCOUPLES STEATOSIS FROM INFLAMMATION IN PRIMARY HUMAN HEPATOCYTES

Alireza Ramandi[1] Mohammad Kabbani[1] Aditya Upadhyay[1] Leon Seifert[2] Chenhui Zou[1] Corrine Quirk[2] Yichen Zhou[1] Mano Maurya[3] Shankar Subramaniam[3] Luis Chiriboga[4] Clifton Fulmer[4] Eleftherios Michailidis[5] Vijay Soni[1] Ype De Jong[1], [1]Weill Cornell Medicine, [2]Rockefeller University, [3]university of california san diego, [4]new york university, [5]Emory University

Background: Hepatic steatosis is conventionally viewed as the substrate upon which MASLD-associated hepatocellular injury develops. Using human hepatocyte-chimeric huFNRG mice, we tested whether specific dietary macronutrients direct primary human hepatocytes toward distinct steatotic versus inflammatory states in vivo. **Methods:** huFNRG mice were fed for 4 weeks on one of nine dietary conditions: chow, Western diet (WD), WD with 10% sucrose water (WD+10%S), high-fat/low-sugar diet (HFD), high-sugar/low-fat diet (HSD), or chow supplemented with 10% sucrose (10%S), glucose (10%G), fructose (10%F), or high-fructose corn syrup (10%H). Human hepatocyte responses were characterized by histopathology, human-specific RNA-seq, ER stress/qPCR profiling, inflammation secretome analysis, and LC-MS lipidomics. Transcriptional signatures were benchmarked against liver RNA-seq from patients with

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MASL and MASH. **Results:** WD and 10%S each induced steatosis in approximately 50% of human hepatocytes, with no additive effect in the WD+10%S combination, yet each engaged distinct transcriptional programs. HFD produced robust steatosis with limited inflammatory activation, while HSD caused hepatocyte ballooning with minimal lipid accumulation, demonstrating that steatosis and hepatocellular injury are dissociable phenotypes. Among liquid sugar conditions, 10%G, 10%S, and 10%H were consumed in excess and produced moderate steatosis, whereas 10%F was consumed sparingly yet generated comparable ballooning. Multi-omic integration identified fructose-containing diets, particularly 10%S and 10% H, as the principal drivers of inflammatory, ER stress, and immune secretory programs, transcriptionally most closely resembling human MASH. HFD and 10%G, by contrast, recapitulated low-inflammation MASL-like states. Lipidomics revealed that inflammatory states were defined not by total lipid burden but by selective enrichment of saturated and monounsaturated short- to medium-chain triglyceride species, while HFD preferentially expanded long-chain triglycerides consistent with neutral lipid storage. **Conclusion:** Steatosis and inflammatory injury in primary human hepatocytes are nutritionally uncoupled. Dietary fat expands lipid stores with limited inflammatory consequence, whereas fructose-containing sugars selectively engage pathways that phenocopy human MASH. These findings challenge hepatic fat burden as a sufficient proxy for pathogenic MASLD biology and position dietary substrate composition as an important determinant of human hepatocyte injury.

Disclosures: Alireza Ramandi:Nothing to Disclose, Mohammad Kabbani:Nothing to Disclose, Aditya Upadhyay:Nothing to Disclose, Leon Seifert:Nothing to Disclose, Chenhui Zou:Nothing to Disclose, Corrine Quirk:Nothing to Disclose, Yichen Zhou:Nothing to Disclose, Mano Maurya:Nothing to Disclose, Shankar Subramaniam:Nothing to Disclose, Luis Chiriboga: Nothing to Disclose, Clifton Fulmer:Nothing to Disclose, Eleftherios Michailidis:Nothing to Disclose, Vijay Soni: Nothing to Disclose, Ype De Jong:Nothing to Disclose.

★ 1342 | MITOCHONDRIAL OXYSTEROLS AND THEIR SULFATES ESTABLISH A NUCLEAR 25HC/25HC3S AXIS CONTROLLING DNMT1 IN MASLD

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Background: Epigenetic dysregulation, including altered DNA methylation, contributes to metabolic dysfunction–associated steatotic liver disease (MASLD). Prior work shows that mitochondrial oxysterols regulate DNA methyltransferase 1 (DNMT1) in vitro: 25-hydroxycholesterol (25HC) and 27-hydroxycholesterol (27HC) activate DNMT1, whereas cholestenoic acid (CA) is biphasic Their 3-sulfates—25HC-3-sulfate (25HC3S; larsucosterol), 27HC-3-sulfate (27HC3S), and 3-sulfate-cholestenoic acid (3SCA)—inhibit DNMT1. However, cellular metabolism and nuclear access integrate these opposing activities is unknown. We hypothesized that nuclear partitioning of oxysterols and their sulfates form a counter-regulatory axis that control DNMT1 activities. **Methods:** Huh-7 hepatocytes were exposed to exogenous 25HC, 27HC, or CA and harvested at 0, 1.5, 3, 6, 12, and 24 h. Oxysterols in culture media, whole-cell lysates, and nuclear fractions were isolated with a commercial nuclear extraction kit, using isotope-labeled internal standards. Oxysterols and their 3-sulfates in each fraction were quantified by liquid chromatography–tandem mass spectrometry (LC–MS/MS). DNMT1 modulation was evaluated by enzyme-kinetic assays with 25HC3S ± physiological 25HC (3.7 μM). Experiments were performed in 3 independent replicates. **Results:** 25HC rapidly accumulated intracellularly (detectable by 1.5 h) and ~4% localized to nuclei. Under identical conditions, 27HC and CA were not detected in nuclear fractions despite cellular uptake. All three oxysterols underwent extensive sulfation; predominant metabolites were 25HC3S, 27HC3S, and 3SCA. Notably, 27HC was preferentially converted to 3SCA rather than 27HC3S. Among sulfates, only 25HC3S was measurable in nuclei, whereas 3SCA was largely released to the medium, indicating differential nuclear retention/export. Biochemical assays revealed functional coupling: The presence of 25HC increased 25HC3S (larsucosterol) potency against DNMT1 (IC_{50}, from ~4 μM to 0.35 μM). At a 10:1 25HC:25HC3S ratio, 0.35 μM of 25HC3S suppressed DNMT1 activity by ~50%. **Conclusion:** Although 25HC, 27HC, and CA can modulate DNMT1 in vitro, only 25HC is able to enter nuclei, and only its sulfate, 25HC3S, accumulates in nuclei. Together these establish a nuclear 25HC/25HC3S rheostat—25HC (activator) versus 25HC3S (inhibitor)—that likely governs DNMT1-dependent promoter methylation in hepatocytes. In contrast, 27HC and CA appear to act predominantly via exported 3SCA rather than direct nuclear mechanisms. These findings provide a mechanistic framework for epigenetic remodeling in MASLD and nominate the nuclear 25HC:25HC3S ratio as a modifiable target for therapeutic intervention.

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Combined with data from previous publication, we propose that increases in the ratio induce the lipid accumulation, and decreases may serve as an ideal target for therapy of MASLD.
Disclosures: Yaping Wang:Nothing to Disclose, Kevin Ren:Nothing to Disclose, Shunlin Ren:Bausch Health Company: Royalties, Bausch-Durect has licensed our patents..

1343 | SIMULTANEOUS LOSS OF LAP2α ATTENUATES HEPATOCYTE-AUTONOMOUS STEATOHEPATITIS CAUSED BY LAMIN A/C DEFICIENCY THROUGH METABOLIC AND EPIGENETIC REPROGRAMMING

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Background: Hepatocyte-specific *Lmna* deficiency disrupts nuclear lamina function and promotes liver injury characterized by lipid accumulation and steatohepatitis. We previously showed that hepatocyte-specific *Lap2*α deletion protected against diet-induced steatosis and liver injury, identifying LAP2α as a regulator of hepatic lipid metabolism. Because LAP2α binds to and regulates mobility of lamin A/C in the nuclear interior but also regulates other intranuclear proteins including transcription factors and chromatin state modifiers, we investigated whether hepatocyte-specific *Lap2*α deletion could modulate *Lmna* deficiency-induced liver injury and steatohepatitis. **Methods:** Hepatocyte-specific *Lmna/Lap2*α-double knockout (DKO), *Lmna*-knockout ($Lmna^{\Delta Hep}$), and wild-type (WT) littermate C57BL/6j male mice were fed standard chow or a high-fat diet with fructose (40% fat calories, 20 kcal% fructose, 2% cholesterol) for 8 or 16 weeks. Liver injury and steatosis were assessed via histopathology and measurement of serum chemistries and hepatic lipid content. Mechanisms of injury were examined using RNA-seq, RT-qPCR, and western blot. **Results:** DKO mice showed significantly reduced liver injury and hepatic steatosis compared with $Lmna^{\Delta Hep}$ mice, as evidenced by lower serum ALT and hepatic triglyceride levels, and reduced steatosis on H&E-stained liver sections (**Figure 1A**). RNA-seq analysis of liver RNA from young (7-8 weeks of age) chow-fed mice revealed that, while global transcriptomic profiles of $Lmna^{\Delta Hep}$ and DKO livers were similar, DKO livers showed reversion to WT-like expression of a defined gene subset (**Figure 1B**), which included genes related to lipid uptake and *de novo* lipogenesis (*Cd36*, *Srebf1*, *Thrsp*), inflammation (*Mpeg1*, *Ctse*), and mitochondrial and endoplasmic reticulum lipid metabolism (*Acss3*, *Insig2*). Mechanistically, $Lmna^{\Delta Hep}$ livers exhibited increased histone H3K9 acetylation compared to WT, which was prevented in DKO livers. **Conclusion:** DKO mice were protected from *Lmna* deficiency-induced liver injury and steatosis, with transcriptomic data showing locus-specific suppression of pro-steatotic and pro-inflammatory programs rather than global transcriptomic normalization in DKO livers. Reduced H3K9 acetylation in DKO livers points to altered histone acetylation as a potential mechanism underlying the selective protective transcriptional reprogramming in DKO hepatocytes. Together, these data identify transcriptional and metabolic reprogramming and epigenetic regulation as mechanisms by which simultaneous loss of LAP2α attenuates *Lmna* deficiency-induced steatohepatitis and liver injury in DKO mice.

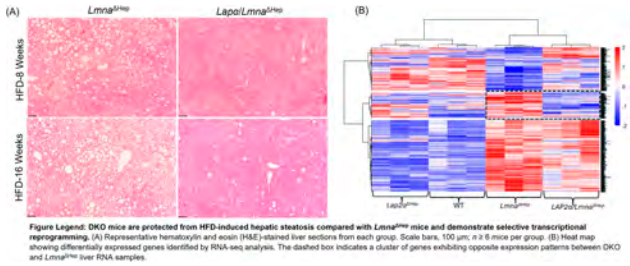


Figure Legend: DKO mice are protected from HFD-induced hepatic steatosis compared with $Lmna^{\Delta Hep}$ mice and demonstrate selective transcriptional reprogramming. (A) Representative hematoxylin and eosin (H&E)-stained liver sections from each group. Scale bars, 100 μm; *n* ≥ 6 mice per group. (B) Heat map showing differentially expressed genes identified by RNA-seq analysis. The dashed box indicates a cluster of genes exhibiting opposite expression patterns between DKO and $Lmna^{\Delta Hep}$ liver RNA samples.

Disclosures: Kapil Upadhyay:Nothing to Disclose, Yunshu Yang:Nothing to Disclose, Chenguang Wang:Nothing to Disclose, Ryan Wilcox:Nothing to Disclose, Roland Foisner:Nothing to Disclose, M. Bishr Omary:Nothing to Disclose, Graham Brady:Orphalan: (note I am a co-I, not a PI), Ultragenyx: (note I am a co-I, not a PI), Vivet Therapeutics: (note I am a co-I, not a PI), Bausch Health US, LLC: (note that I am a co-I, not a PI), Orphalan: (note I am a co-I, not a PI), Ultragenyx: (note I am a co-I, not a PI), Vivet Therapeutics: (note I am a co-I, not a PI), Bausch Health US, LLC: (note I am a co-I, not a PI).

1344 | TISSUE- AND MODEL-SPECIFIC ALTERATIONS OF SELECTED UNSATURATED C18 LYSOPHOSPHATIDYLCHOLINE SPECIES IN MASLD-RELATED MODELS

Taecheol Kwak[1] Siyun Park[1] Suna Sung[1] Taehyun Kim[2] Youngmi Kim[1] Wondong Kim[1], [1]College of Pharmacy, Inst. of Pharmaceutical Science & Technology, Hanyang University, Ansan, Korea,

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is characterized by hepatic lipid accumulation and extrahepatic complications. Lysophosphatidylcholine (LPC) is implicated in metabolic and inflammatory responses. Diet-induced gut microbiota dysbiosis may alter LPC-related glycerophospholipid metabolism, linking diet, microbiome, and lysophospholipid metabolism. However, tissue-specific LPC profiles across MASLD-related mouse models have not been systematically compared. We focused on LPC(18:1), a major C18 LPC species, and compared its distribution across liver, plasma, and kidney in distinct dietary and age-associated MASLD-related models. **Methods:** Male C57BL/6J mice were fed normal diet (ND), high-fat diet (HFD), western diet (WD), or choline-deficient, L-amino acid-defined, high-fat diet (CDAHFD). A separate group of 70-week-old male C57BL/6J mice was divided into four groups by body weight. LPC species in liver, plasma, and kidney were quantified by LC-MS using LPA(17:0) as an internal standard. Hepatic triacylglycerol (TAG) and blood chemistry parameters were measured. **Results:** Hepatic TAG levels were elevated in HFD- and WD-fed mice with the highest levels in WD-fed mice. LPC(18:1) was markedly elevated in liver, plasma and kidney of WD-fed mice. Other unsaturated C18 LPC species varied by tissue and dietary model; hepatic LPC(18:2) and LPC(18:3) were decreased in HFD- and WD-fed mice. CDAHFD-fed mice showed a distinct hepatic LPC pattern, with increased in LPC(18:1) and several other LPC species despite no apparent hepatic TAG increase. In body weight-stratified aged mice, hepatic TAG levels were elevated, whereas ALT, AST, and hepatic LPC species showed no marked group-dependent differences. Overall, LPC(18:1) alterations were most prominent in WD-fed mice. **Conclusion:** LPC(18:1) levels showed tissue- and model-dependent differences across MASLD-related mouse models. These differences were not fully explained by hepatic TAG accumulation, as aged mice exhibited elevated hepatic TAG without comparable LPC changes. Our data provide a targeted multi-tissue analysis of selected LPC species across diet-induced and age-associated MASLD-related contexts. Further analyses of FADS1/2 and SCD1 may determine whether alterations in selected unsaturated C18 LPC species are linked to double bond-dependent changes in hepatic lipid metabolism. In parallel, microbiome-related lipid changes, including odd-chain lysophospholipid species, warrant consideration in future studies.

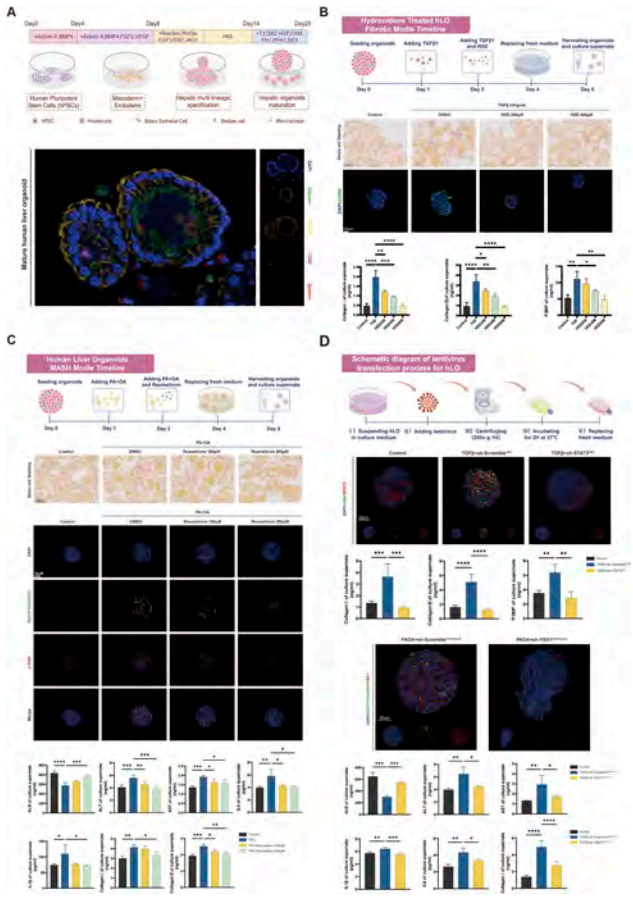
Disclosures: Taecheol Kwak:Nothing to Disclose, Siyun Park:Nothing to Disclose, Suna Sung:Nothing to Disclose, Taehyun Kim:Nothing to Disclose, Youngmi Kim:Nothing to Disclose, Wondong Kim: Nothing to Disclose.

1345 | APPLICATION OF MULTILINEAGE HUMAN LIVER ORGANOIDS IN DISEASE MODELING, DRUG TESTING AND GENETIC INTERVENTION

Qichao Ge[1] Qingqing Zhang[1] Yufei Yang[2] Ling Zhang[3] Ying Luo[3] Lungen Lu[1], [1]Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, [2]Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China bShangh, [3]Continent Pharmaceuticals Co. ,Ltd., Beijing, China

Background: Animal models have limitations in predicting human clinical outcomes, highlighting the need for advanced human-relevant models. We aimed to establish multilineage human liver organoids (hLOs) for modeling fibrosis and metabolic dysfunction–associated steatotic liver disease (MASLD), and for evaluating pharmacological and genetic interventions. **Methods:** hLOs were generated from human induced pluripotent stem cells by stepwise co-differentiation. Fibrosis was induced by transforming growth factor-β (TGF-β), and steatotic injury by free fatty acids. Hydronidone and resmetirom were used for pharmacological studies. Lentiviral knockdown of YB1 in hepatocytes and STAT3 in hepatic stellate cells was used for lineage-restricted genetic perturbation. **Results:** TGF-β induced a fibrotic phenotype in hLOs, with stellate cell activation, increased extracellular matrix secretion, and Sirius Red–positive matrix deposition. Free fatty acid treatment induced an acute lipotoxic MASLD-like phenotype characterized by steatosis, hepatocyte apoptosis, inflammatory activation, and fibrotic remodeling. Hydronidone attenuated fibrotic responses, whereas resmetirom reduced steatosis, inflammation, hepatocyte injury, and fibrosis-associated changes. In parallel, YB1 knockdown in hepatocytes and STAT3 knockdown in stellate cells ameliorated steatotic and fibrogenic phenotypes, respectively. **Conclusion:** Multilineage hLOs provide a human-relevant platform for modeling fibrosis and MASLD and for evaluating therapeutic and genetic interventions in a multicellular liver context.

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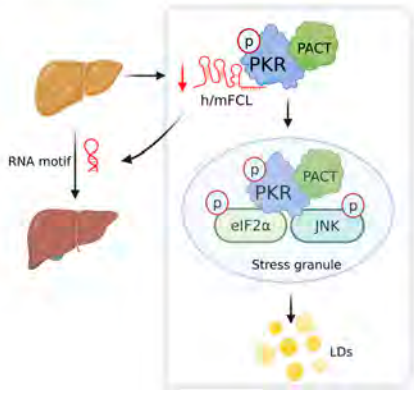
Disclosures: Qichao Ge:Nothing to Disclose, Qingqing Zhang:Nothing to Disclose, Yufei Yang:Nothing to Disclose, Ling Zhang:Nothing to Disclose, Ying Luo:Nothing to Disclose, Lungen Lu:Nothing to Disclose.

1346 | FUNCTIONALLY CONSERVED LONG NONCODING RNA MOTIFS RESTRAIN PROTEIN KINASE R SIGNALING IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

Shuangdi Duan[1] Haiming Cao[1], [1]NIH

Background: Long noncoding RNAs (lncRNAs) have emerged as regulators of metabolic dysfunction-associated steatotic liver disease (MASLD), but limited cross-species conservation hampers mechanistic validation and translation. We aimed to identify functionally conserved lncRNAs (FCLs) that control hepatic metabolism and define their mechanism. **Methods:** Human nonalcoholic fatty liver disease (NAFLD) liver transcriptomes were integrated with long-read nanopore transcriptomes from fasted/refed humanized mouse livers to prioritize metabolically responsive FCLs. Candidate function was tested in lipid-loaded hepatocytes, adenoviral and AAV-mediated hepatic knockdown/rescue models, high-fat diet models, metabolic phenotyping, RNA sequencing, phosphoproteomics, RNA pulldown-mass spectrometry, RNA immunoprecipitation, competitive binding assays, and viral or tri-N-acetylgalactosamine (tri-GalNAc) delivery of minimal RNA motifs. **Results:** This strategy identified a syntenic FCL pair, human FCL (hFCL) and mouse FCL (mFCL), whose expression was suppressed in patient livers, high-fat diet-fed mice, refed liver, and lipid-loaded hepatocytes. mFCL depletion worsened hepatic steatosis, dyslipidemia, glucose intolerance, insulin resistance, and transcriptional programs favoring lipogenesis, gluconeogenesis, and cholesterol synthesis, whereas hFCL restoration reversed these defects and improved oxygen consumption and energy expenditure. Mechanistically, hFCL/mFCL directly bound protein kinase R (PKR; EIF2AK2), reduced PKR interaction with PACT, limited PKR-stress granule colocalization, and suppressed PKR/eIF2α phosphorylation. Minimal human and mouse FCL motifs retained PKR binding, inhibited PKR activity and triglyceride accumulation, and ameliorated steatosis and systemic metabolic dysfunction after AAV or hepatocyte-targeted tri-GalNAc delivery in high-fat diet-fed mice. **Conclusion:** hFCL/mFCL define a conserved lncRNA-PKR signaling axis that protects against metabolic fatty liver disease. Compact FCL-derived motifs may provide a practical RNA-therapeutic strategy for MASLD.

Functionally Conserved Long Noncoding RNA Motifs Restrain Protein Kinase R Signaling in Metabolic Dysfunction-Associated Steatotic Liver Disease



Disclosures: Shuangdi Duan:Nothing to Disclose, haiming Cao:Nothing to Disclose.

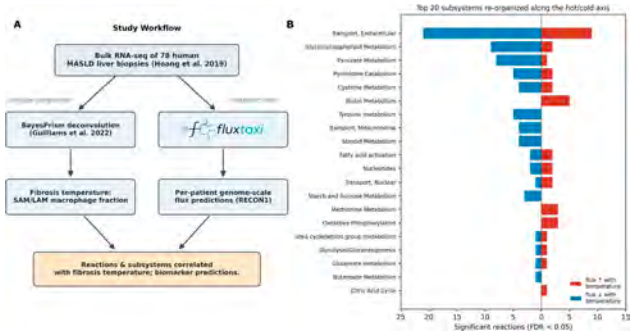
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1347 | PATIENT-LEVEL METABOLIC FLUX MODELING IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) REVEALS DIFFERENTIAL REPROGRAMMING OF HEPATIC METABOLISM IN MACROPHAGE-ENRICHED VERSUS DEPLETED FIBROTIC STATES

Stephen Hoang[1] Justin Taylor[2] Arun Sanyal[1], [1]Virginia Commonwealth University, [2]Genentech

Background: Progressive MASLD is characterized by hepatic metabo-inflammation and fibrosis. The inflammatory link to fibrosis is captured by the macrophage-fibroblast cell circuit theory that defines two stable states: “hot” (macrophage-rich) and “cold” (macrophage-depleted) (Zhou et al. 2018, Alder et al. 2020). The metabolic link to these inflammatory-fibrogenic states is unknown. The aim of this study is to define the metabolic reprogramming associated with hot vs cold fibrosis. **Methods:** We obtained bulk RNA-seq from 78 human MASLD liver biopsies spanning the disease activity and fibrosis spectrum (Hoang et al. 2019). Each sample was analyzed by two parallel pipelines on the same expression data (Figure A). First, cell-type deconvolution against the Guilliams et al. (2022) human liver atlas was used to estimate the proportion of lipid-associated macrophages (LAM) for each sample. This value was used as an operational proxy for fibrogenic temperature (hot to cold). Next, a transcriptomics-constrained flux balance analysis algorithm was applied to a genome-scale human metabolic network. The algorithm fits absolute reaction fluxes to continuous per-reaction targets derived from gene expression data, weighted by differential expression scores. This yielded per-patient flux predictions across all reactions. Predicted fluxes were correlated with fibrosis temperature while controlling for fibrosis stage. **Results:** Fibrosis temperature correlated positively with both NAFLD activity score (rho = 0.4, p = 0.0003) and fibrosis stage (rho = 0.33, p = 0.003), confirming that the temperature proxy generally tracks histologic severity. After controlling for fibrosis stage, the predicted flux of 138 reactions was significantly associated with fibrosis temperature (5% FDR, Figure B). The strongest associations were in reactions mediated by hepatic organic anion transporters (OATPs), consistent with their known regulation under cholestasis, inflammation, and regeneration. Phospholipid metabolism was also significantly altered, converging with independent evidence linking PE / PC ratio to membrane integrity in steatotic liver disease. In addition, over twenty boundary reactions correlated with temperature, defining a candidate serum biomarker list. **Conclusion:** Hepatic metabolism reorganizes systematically along the hot/cold fibrosis axis in human MASLD. Top predictions converge on pathways that have been previously implicated in hepatic injury and disease, providing biological validation. This patient-level metabolic phenotyping approach extends the hot/cold framework with a metabolic dimension and nominates candidate biomarkers for distinguishing fibrosis endotypes.



Disclosures: Stephen Hoang:PS Fertility: Consultant, Remedy Plan Inc.: Consultant, Justin Taylor:Genentech: Employee, Arun Sanyal:Nothing to Disclose.

1348 | *DOREA LONGICATENA* ATTENUATES METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE VIA ACTIVATING THE OVARIAN STEROIDOGENESIS PATHWAY AND MODULATING THE INTESTINAL MICROBIOTA

Xin Ai[1] Xin Wang[1] Zilong Wang[1] Haiying Zhang[1] Xiaoxiao Wang[1] Feng Liu[1] Huiying Rao[1], [1]Peking University People's Hospital

Background: The most prevalent chronic liver disease worldwide is metabolic dysfunction-associated steatotic liver disease(MASLD). The gut microbiota plays a crucial role in its pathogenesis, yet the therapeutic potential of specific microbial species and metabolites remains largely unexplored. **Methods:** We investigated the role of *Dorea longicatena* in MASLD using human stool samples, western diet with fructose/CCl_4 mouse model, and multi-omics approaches. Liver injury was evaluated by biochemical, histological, and molecular analyses. Gut microbiota composition was assessed by 16S rRNA sequencing, while transcriptomics identified functional pathways. **Results:** *Dorea longicatena* abundance was increased in MASLD patients and MASLD mice. Supplementation with *Dorea longicatena* in MASLD mice significantly attenuated hepatic steatosis, inflammation, and fibrosis. Mechanistically, *Dorea longicatena* activating the ovarian steroidogenesis pathway and restoring metabolic homeostasis. Inhibition the ovarian steroidogenesis pathway abolished *Dorea*

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longicatena mediated protection. Furthermore, *Dorea longicatena* promoted the proliferation of well-characterized probiotics and improved gut barrier integrity. **Conclusion:** This study identifies *Dorea longicatena* as a commensal with hepatoprotective effects in MASLD, acting through the ovarian steroidogenesis pathway and gut microbiota modulation. These findings highlight *Dorea longicatena* holds potential as a probiotic for the prevention of MASLD.

Disclosures: Xin Ai:Nothing to Disclose, Xin Wang: Nothing to Disclose, Zilong Wang:Nothing to Disclose, Haiying Zhang:Nothing to Disclose, Xiaoxiao Wang: Nothing to Disclose, Feng Liu:Nothing to Disclose, Huiying Rao:Nothing to Disclose.

1349 | ACTIVATION OF BILE ACID RECEPTOR FXR CHANGES TRANSCRIPTIONAL PROGRAM IN VISCERAL ADIPOCYTES OF OBESE INDIVIDUALS WITH MASLD

Lena Voško[1] Lukas Gulden[1] Judith Sommer[1] Dagmar Silbert-Wagner[1] Emilian Jungwirth[2] Antonio Molinaro[3] Katrin Panzitt[1] Martin Wagner[1], [1]Medical University of Graz, Austria, [2]Center for Biomarker Research in Medicine, Graz, Austria, [3]University of Gothenburg, Sweden

Background: Signaling via the bile acid-sensing farnesoid X receptor (FXR) undergoes adaptive changes in response to the metabolic disturbance in obesity, which is associated with metabolic dysfunction-associated steatotic liver disease. Our previous work showed that metabolic pressure in obesity alters FXR binding and transcriptional activity in the liver, which results in enhanced substrate utilization following ligand activation. Adipose tissue (AT) functions both as energy store and endocrine organ. In obesity, lipid storage capacity and release of fatty acids via lipolysis becomes impaired in adipocytes, which contributes to systemic inflammation. Although hepatic FXR signaling has been extensively investigated, its role in human AT remains poorly understood. Therefore, this study aimed, for the first time in humans, to define the cellular and transcriptional consequences of FXR activation in visceral adipose tissue (VAT) in metabolic disease. **Methods:** We performed single-nuclei RNA sequencing on VAT biopsies derived from non-obese and morbidly obese (BMI > 35 kg/ m2) individuals treated with the FXR agonist obeticholic acid (OCA; 25 mg/ d for 3 weeks) or placebo in a randomized double-blind trial. **Results:** 14 VAT samples (non-obese: 2 OCA, 2 placebo; obese: 5 OCA, 5 placebo) yielded a total of 24,526 quality-filtered nuclei. Adipocytes accounted for 12% and adipose-derived stromal and progenitor cells (ASPCs) for 16% of nuclei. Obesity resulted in increased mitochondrial respiration and lipolytic gene signatures. OCA treatment reversed these effects. Gene set enrichment analysis showed downregulated mitochondrial respiration, oxidative phosphorylation, and ATP synthesis in adipocytes and ASPCs from obese OCA-treated individuals. Additionally, lysosomal pathways and pathways involved in lipid turnover were downregulated in adipocytes in this group, accompanied by lower expression of lipolytic genes. Interestingly, NR1H4/FXR and GPBAR1/TGR5 expression levels were low or absent in most samples, suggesting that adipose tissue may be affected indirectly. The metabolic findings in VAT are much more pronounced than findings in comparable subcutaneous AT where anti-inflammatory events were predominant. **Conclusion:** In obese individuals, transcriptional profiling suggest that FXR activation reduces lipid turnover and mitochondrial oxidation across multiple VAT subpopulations. This contrasts the FXR activating effects in the livers of the same individuals. Minimal local FXR expression suggests that OCA mediated effects are indirect, supporting the existence of a liver-adipose (or intestine-adipose) signaling axis modulating energy production in adipocytes and progenitors.

Disclosures: Lena Voško:Nothing to Disclose, Lukas Gulden:Nothing to Disclose, Judith Sommer:Nothing to Disclose, Dagmar Silbert-Wagner:Nothing to Disclose, Emilian Jungwirth:Nothing to Disclose, Antonio Molinaro:Nothing to Disclose, Katrin Panzitt:Nothing to Disclose, Martin Wagner:Nothing to Disclose.

1350 | THYMIDINE PHOSPHORYLASE RESTRAINS PPARA-DEPENDENT FATTY ACID OXIDATION IN MASLD

Wei Li[1] Hong Yue[1] Adam Belcher[2] Kelli Vaughan[3] Julie Mattison[3] Krista Denning[1] Angela Li[4] Yongke Lu[1] Zander Pinson[1], [1]Joan C. Edwards School of Medicine at Marshall University, [2]Vandalia Health, [3]NIA, [4]Ohio State University

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is characterized by impaired hepatic fuel selection and suppression of fatty acid oxidation (FAO). However, the mechanisms linking metabolic stress to persistent repression of FAO programs remain incompletely understood. We investigated whether thymidine phosphorylase (TYMP) contributes to MASLD through regulation of PPARα-dependent metabolic programs. **Methods:** Wild-type (WT), *Tymp*$^{-/-}$, and *Ppar*$\alpha^{-/-}$ mice were subjected to Western diet (WD) or high-fat diet feeding. Metabolic phenotyping, histology, and molecular analyses were performed. Pharmacologic TYMP inhibition was achieved using tipiracil (TPI). Translational relevance

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was evaluated using obese rhesus monkeys and human liver datasets. **Results:** TYMP expression was markedly increased in the livers of obese mice, rhesus monkeys, and humans with steatotic liver disease. Genetic deletion or pharmacologic inhibition of TYMP attenuated diet-induced obesity, hepatic steatosis, dyslipidemia, and insulin resistance without altering food intake or energy expenditure. TYMP deficiency reduced respiratory exchange ratio, indicating enhanced FAO. Mechanistically, TYMP deficiency increased hepatic PPARα expression and activity under dietary stress, whereas TYMP expression was elevated in *Pparα*$^{-/-}$ livers, demonstrating reciprocal regulation. Importantly, TPI-mediated metabolic protection was abolished in *Pparα*$^{-/-}$ mice. In obese rhesus monkeys, TPI treatment improved metabolic parameters and enhanced hepatic PPARα activity signatures. **Conclusion:** TYMP is a previously unrecognized regulator of hepatic fuel selection that restrains PPARα-dependent FAO programs during MASLD progression. Pharmacologic TYMP inhibition using the clinically approved agent tipiracil may represent a novel therapeutic strategy for MASLD.

Disclosures: Wei Li:Nothing to Disclose, Hong Yue: Nothing to Disclose, Adam Belcher:Nothing to Disclose, Kelli Vaughan:Nothing to Disclose, Julie Mattison: Nothing to Disclose, Krista Denning:Nothing to Disclose, Angela Li:Nothing to Disclose, Yongke Lu: Nothing to Disclose, Zander Pinson:Nothing to Disclose.

1351 | 4-HYDROXYNONENAL PROMOTES HEPATIC FIBROSIS IN MASLD VIA FORMATION OF HEPATIC MACROPHAGE AGGREGATES

Masahiro Yanagi[1] Hidenori Kido[1] Eishiro Mizukoshi[2] Taro Yamashita[1], [1]Kanazawa University Hospital, [2]Kanazawa Medical University Hospital

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the leading cause of chronic liver disease, and fibrosis severity determines long-term prognosis. Oxidative stress and lipid peroxidation are key drivers of disease progression, generating reactive aldehydes such as 4-hydroxynonenal (HNE) that covalently modify cellular proteins. Hepatic macrophages critically orchestrate inflammation and fibrogenesis, but the pathogenic role of HNE-modified macrophages remains undefined. We previously reported that MASLD patients with marked hepatic HNE deposition exhibit advanced inflammation and fibrosis. Here, we investigated how HNE deposition on hepatic macrophages drives fibrosis in MASLD. **Methods:** (1) Liver tissues from MASLD patients and from mice fed a choline-deficient L-amino acid-defined (CDAA) or atherogenic high-fat (AHF) diet were stained for HNE, CD68 (F4/80), α-SMA, and Sirius Red to evaluate HNE deposition on hepatic macrophages and fibrosis. (2) In 60 MASLD patients, hepatic HNE deposition was graded (HNE score: 0–2), and its association with hepatic macrophage aggregates (HMA) number and fibrosis was analyzed. (3) Mice received daily intraperitoneal HNE (10 mg/kg) or vehicle (NC) for 8 weeks; an additional group received HNE plus clodronate liposome (CL) to deplete macrophages. (4) An HNE + Alda-1 group received Alda-1 (ALDH2 agonist, 20 mg/kg, three times weekly) to test the effect of HNE detoxification. (5) CD45+ cells from NC and HNE-treated livers (n = 1 each) underwent single-cell RNA sequencing (scRNA-seq) with macrophage sub-clustering. **Results:** (1) Numerous HMAs were observed in livers from MASLD patients and CDAA- and AHF-fed mice, with strong HNE deposition within HMAs. α-SMA was positive around HMAs, and fibrosis progressed along these aggregates. (2) Higher HNE scores were associated with significantly more HMAs and greater fibrosis. (3) Versus NC, HNE-treated mice showed significantly increased HMA formation with strong HNE deposition, peri-HMA α-SMA expression, and significantly larger α-SMA-positive and fibrotic areas. HMA formation was abolished in the HNE + CL group, with α-SMA-positive and fibrotic areas significantly reduced versus HNE. (4) In the HNE + Alda-1 group, HMA number, α-SMA-positive area, and fibrotic area were all significantly reduced versus HNE. (5) scRNA-seq revealed an *Spp1*+ macrophage subset emerging in HNE-treated mice, with elevated expression of *Trem2*, *Cd9*, *Fabp5*, *Arg1*, *Fn1*, *Olr1*, and *Cd63* — a signature consistent with the scar-associated/lipid-associated macrophage populations previously reported to drive hepatic fibrosis. **Conclusion:** HNE drives the formation of profibrogenic HMAs and hepatic fibrosis progression in MASLD. HNE detoxification may represent a novel therapeutic strategy.

Disclosures: Masahiro Yanagi:Nothing to Disclose, Hidenori Kido:Nothing to Disclose, Eishiro Mizukoshi: Nothing to Disclose, Taro Yamashita:Nothing to Disclose.

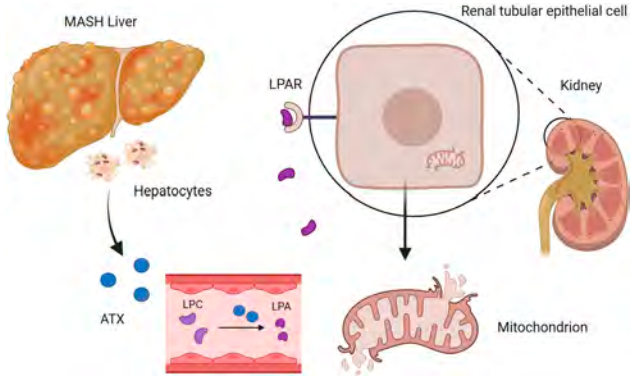
1352 | DYSREGULATION OF THE LPC-ATX-LPA AXIS CONTRIBUTES TO MASLD-ASSOCIATED KIDNEY INJURY

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most prevalent chronic liver disease and has emerged as a global health problem. Accumulating clinical evidence has demonstrated that MASLD is independently associated with an increased risk of chronic kidney disease (CKD). This study aimed to explore the role of the lysophosphatidylcholine (LPC)-autotaxin (ATX)-lysophosphatidic acid (LPA) axis in MASLD-associated kidney injury. **Methods:** A murine model and a human cohort were used to investigate MASLD-associated kidney injury and accompanying circulating metabolic alterations. Male C57BL/6J mice were fed a high-fat, high-cholesterol, and high-fructose diet (HFCFD) for 12, 18, or 24 weeks to recapitulate the temporal progression of MASLD. At each disease stage, mice underwent comprehensive phenotyping, including serum biochemistry, serum cystatin C quantification, hepatic lipid measurement, urinary albumin measurement, and urinary hydrogen peroxide quantification. Histological analyses were performed using liver and kidney tissue sections, and renal ultrastructural changes were further examined by transmission electron microscopy. In parallel, patients were enrolled and stratified according to biopsy-defined MASLD stage, and serum samples were collected for lipidomic profiling. Serum ATX and LPA levels were quantified. Two pharmacological inhibitors were used: the ATX inhibitor PF-8380 and the LPA receptor antagonist Ki16425. After 18 weeks of HFCFD feeding, mice received daily intraperitoneal injections of PF-8380, Ki16425, or vehicle for 6 weeks. **Results:** With the progression of diet-induced MASLD, mice developed progressively worsening kidney injury. Serum cystatin C, urinary albumin, urinary albumin-to-creatinine ratio (UACR), and urinary hydrogen peroxide-to-creatinine ratio were significantly increased across disease stages. Histological analysis showed enlargement of glomerular cross-sectional area. Transmission electron microscopy further revealed segmental podocyte foot process effacement, glomerular basement membrane thickening, and mitochondrial abnormalities in renal tubular epithelial cells. These structural and functional alterations worsened with advancing disease severity. LC-MS-based untargeted serum lipidomic profiling of patients with biopsy-confirmed MASLD revealed that LPCs were the most prominently altered lipid class, with LPC 18:1 and LPC 18:2 progressively decreasing as MASLD advanced. Serum ATX and LPA levels also increased with MASLD progression. Compared with vehicle-treated HFCFD mice, UACR was significantly reduced in PF-8380- and Ki16425-treated mice. **Conclusion:** Our findings indicate that the LPC-ATX-LPA axis is markedly dysregulated during MASLD progression. Pharmacological inhibition of ATX-LPA signaling attenuated MASLD-associated kidney injury.



Disclosures: Mengyuan Wu:Nothing to Disclose, Qin Pan:Nothing to Disclose, Jiangao Fan:Nothing to Disclose.

1353 | CERS6-DEPENDENT HEPATOCYTE-DERIVED EXTRACELLULAR VESICLES INDUCE MACROPHAGE INFLAMMATORY RESPONSES

Joseph Dempsey[1] Carole Smith[1] Benjamin Pryce[1] Christopher Savard[2] Aimee Wu[1] Aletta Li[1] Autumn York[1] Sum Lee[1] George Ioannou[1] Rotonya Carr[3], [1]University of Washington, [2]University of Washington; Veterans Affairs Puget Sound Health Care System, [3]University of Washington Medical Center

Background: The drivers for the transition from metabolic dysfunction-associated steatotic liver disease (MASLD) to metabolic dysfunction-associated steatohepatitis (MASH) remain incompletely understood. Ceramide synthase 6 (CERS6) produces long-chain ceramides (primarily C16:0), which we and others have linked to lipotoxicity and inflammation. C16:0 ceramide is increased in MASLD patients and is present in extracellular vesicles (EVs) in murine and human MASLD. We hypothesize that the accumulation of CERS6-derived C16:0 ceramides and EVs promotes proinflammatory macrophages in the transition from MASLD to MASH. **Methods:** Wild-type (WT) and CERS6 knockout (KO) mice were fed a normal chow or high fat, fructose, and cholesterol (FFC) diet for 4 weeks. EVs were isolated from the serum, liver histology was scored for steatosis and inflammation, and hepatic RNA was sequenced. Hepatocyte-specific EVs were isolated from the media of HepG2 WT and KO cells exposed to control (ctrl) or C16:0 ceramide (C16) for 48 hours. EV particle concentration and size was evaluated by a NanoSight NS300. Bone marrow-derived macrophages (BMDMs) were exposed to EVs for 6 hours. RT-qPCR was performed on RNA from

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HepG2 cells and BMDMs. **Results:** Histologically, compared to normal chow mice, all FFC-fed mice were steatotic, but only FFC-fed WT mice had increased inflammation and a trend toward increased *Cers6* gene expression. In these mice, hepatic RNA expression of the EV biogenesis gene *Rab8* and the EV biogenesis and ceramide synthesis gene *Smpd3* was increased, suggesting a role for EVs and ceramides. *RAB8* and *SMPD3* were also expressed *in vitro* in HepG2 WT and KO cells. In general, EVs isolated from KO cells were larger than their respective controls, and particle size distribution was right-skewed in a CERS6-dependent manner. Compared to WT-ctrl EVs, the mean particle size of KO-ctrl EVs was larger (135 nm vs 148 nm, $p = 0.029$). There was no response by BMDMs to mouse serum-derived EVs, but compared to BMDMs exposed to HepG2 WT-ctrl EVs, BMDMs exposed to WT-C16 EVs had increased RNA expression of the inflammatory markers *Cxcl2* and *Cxcl10*. Compared to WT-C16, BMDMs exposed to KO-C16 EVs had decreased RNA expression of *Cxcl2* and *Il6*, suggesting a CERS6-dependent macrophage inflammatory response. **Conclusion:** In the absence of CERS6, C16 does not overcome the reduced macrophage inflammatory response to EVs. This study suggests that CERS6 may be required for macrophage inflammation in MASLD.

Disclosures: Joseph Dempsey:Nothing to Disclose, Carole Smith:Nothing to Disclose, Benjamin Pryce: Nothing to Disclose, Christopher Savard:Nothing to Disclose, Aimee Wu:Nothing to Disclose, Aletta Li: Nothing to Disclose, Autumn York:Nothing to Disclose, Sum Lee:Nothing to Disclose, George Ioannou: GlaxoSmithKline(GSK): Grant/Research Support, Rotonya Carr:Merck: Grant/Research Support, Intercept: Consultant, Astra Zeneca: Consultant, Novo Nordisc: Consultant, Madrigal: Consultant, Boehringer: Advisor.

1354 | PATIENT-DERIVED IPSC LIVER ORGANOIDS EXHIBIT DONOR-SPECIFIC SUSCEPTIBILITY TO MASH AND DRUG-INDUCED TOXICITY

Ekta Minocha[1] Ashwani Kumar Gupta[1] Nate Schmidt[2] Ivan Sarabia[3] John Purdy[2] Jason Wertheim[2], [1]The University of Arizona, College of Medicine, Tucson, AZ, USA., [2]The University of Arizona, College of Medicine, Tucson, AZ, USA, [3]The University of Arizona, Tucson, AZ, USA

Background: Patient-derived induced pluripotent stem cells (iPSCs) have emerged as a powerful platform for modeling human liver disease by capturing donor-specific genetic backgrounds. As translational applications expand, there is a need for stable, reproducible human-relevant organoid systems that support reproducible analysis of metabolic dysfunction associated steatohepatitis (MASH) and drug-induced toxicity across diverse donors. Reliance on xenogeneic matrices, such as Matrigel introduces variability, underscoring the need for developing Matrigel-free methods for generating liver organoids suitable for disease modeling and toxicity assessment. **Methods:** De-identified control and MASH donor-derived iPSCs were obtained from CDI-CIRM stem cell repository and induced to differentiate into hepatic progenitors. These progenitors were spotted at an air-liquid interface (ALI) to generate highly vascularized, multicellular liver organoids. This 3D organotypic culture condition eliminated the need for Matrigel embedding. Phenotypic and functional analysis were conducted using specific markers and various functional assays. To model MASH, organoids were exposed to free-fatty acids and evaluated using transcriptomics, ELISA, lipidomics and stiffness measurements via nano-indentation as a read-out of fibrosis severity. Drug-induced hepatotoxicity was assessed following acetaminophen (APAP) treatment through apoptotic, transcriptional, and mitochondrial dysfunction analysis. **Results:** Control and MASH donor-derived liver organoids exhibited major hepatic cell types, including hepatocytes, cholangiocytes, stellate cells, sinusoidal endothelial cells, and Kupffer-like cells, confirmed by phenotypic analysis and functional assays. Following free-fatty acid exposure, MASH-donor derived liver organoids exhibited increased susceptibility to steatosis (BODIPY staining), inflammation (elevated expression and secretion of inflammatory cytokines like TNFα, IL-23 and IL-8), and fibrosis (increased COL1A1, TGFβ, and ACTA2 at transcript and protein levels). Lipidomic profiling showed global lipidomic shifts that closely resembled those observed in MASH liver biopsies, and organoid stiffness increased significantly reflecting enhanced fibrotic remodeling. APAP treatment induced a dose-dependent increase in apoptosis, inflammation and mitochondrial oxidative stress, accompanied by reduced ATP levels and downregulation of antioxidant pathways, with MASH-derived organoids exhibiting increased sensitivity to APAP toxicity. **Conclusion:** This study presents a robust, Matrigel-free approach for generating vascularized, multicellular liver organoids and demonstrates their utility for personalized disease modeling, and drug-toxicity assessment.

Disclosures: Ekta Minocha:Nothing to Disclose, Ashwani Kumar Gupta:Nothing to Disclose, Nate Schmidt: Nothing to Disclose, Ivan Sarabia:Nothing to Disclose, John Purdy:Nothing to Disclose, Jason Wertheim: Nothing to Disclose.

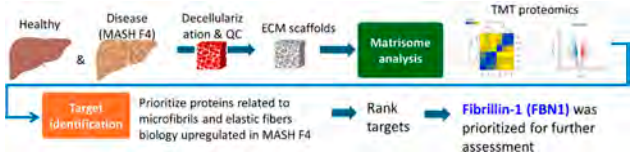
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1355 | IDENTIFICATION OF FIBRILLIN-1 AS A DRIVER OF FIBROGENESIS AND PATHOLOGICAL ELASTIC FIBERS ACCUMULATION IN MASH FIBROSIS

Hiroaki Yashiro[1] Lisa Longato[2] Saman Farahmand[1] Maria Paraskevopoulou[3] Satoru Matsumoto[1] Athiva Shankar[2] Nafia Guljar[2] Ifigeneia Bardi[2] Gareth Muirhead[4] Tu Vinh Luong[5] Andrew Hall[5] Chris Stevenson[2] Giuseppe Mazza[5] Bernard Allan[1], [1]Takeda Pharmaceuticals International Co, [2]Engitix Therapeutics, London, United Kingdom, [3]Takeda Pharmaceuticals, [4]Engitix Therapeutics, London, United Kingdom,, [5]Department of Cellular Pathology, Royal Free London NHS Foundation Trust

Background: The fibrotic extracellular matrix (ECM) is a complex microenvironment of structural proteins, proteoglycans, glycoproteins, ECM regulators and growth factors. Among the ECM components demonstrated to promote resistance to degradation and limiting reversibility of liver fibrosis are elastic fibres, consisting of a scaffold of microfibrillar proteins, interacting with microfibrils-binding proteins and an inner core of elastin. This study aimed to identify and functionally validate regulators of liver fibrosis with emphasis on microfibril biology. **Methods:** Decellularized ECM from healthy and MASH F4 livers was generated and analyzed by tandem-mass-tag proteomics (n = 3/group). Proteins related to microfibrils and elastin fibers biology that were upregulated in the MASH F4 matrisome compared with healthy livers were prioritized for further assessment. Expression and spatial localization were validated using bulk and spatial transcriptomics in independent MASH patients. Target knockdown (KD) was performed in *in vitro* assay with primary human hepatic stellate cells (HSCs) as well as in CDHFD rats of liver fibrosis with robust features of elastin accumulation. **Results:** Proteomics identified enrichment of ECM and elastic fiber proteins in MASH. Fibrillin-1 (*FBN1*), the most upregulated ECM (~15-fold, $P < 0.0001$), was prioritized for assessment as potential regulator of fibrosis based on its structural and regulatory roles. Independent datasets confirmed *FBN1* mRNA upregulation (1.75-fold in F3, n = 16; 2.36-fold in F4, n = 32 vs controls n = 30; $P < 0.05$). *FBN1* mRNA expression was localized to the non-parenchymal component of healthy livers, and its overexpression and localization in the septa in MASH F4 livers was confirmed by singleplex in-situ hybridization and spatial transcriptomics analysis. Gene network analysis of F0 to F4 liver revealed that the disease module with *FBN1* as centre regulates ECM organization and type I/III collagens. In HSCs, *FBN1* KD reduced collagen production and disrupted ECM organization. In CDHFD rats, an advanced liver fibrosis model, progressive elastin deposition correlated with increased *FBN1* expression and LNP-mediated *Fbn1* siRNA KD achieved 74% target reduction ($P < 0.0001$) resulting in 60% reduction in collagen (Picrosirius red staining) and 58% reduction in elastin (Victoria blue) deposition. **Conclusion:** FBN1 is upregulated in MASH fibrosis in humans and its KD in HSCs prevents deposition of key ECM components *in vitro*. Further, using an appropriate *in vivo* model for mechanistic studies aimed at assessing the contribution of elastic fibers to liver fibrosis, we found that FBN1 plays a key role in elastic deposition in liver fibrosis.v



Disclosures: Hiroaki Yashiro:Takeda Pharmaceuticals: Employee, Lisa Longato:Engitix Therapeutics: Employee, Saman Farahmand:Nothing to Disclose, Maria Paraskevopoulou:Nothing to Disclose, Satoru Matsumoto:Nothing to Disclose, Athiva Shankar:Nothing to Disclose, Nafia Guljar:Nothing to Disclose, Ifigeneia Bardi:Nothing to Disclose, Gareth Muirhead:Nothing to Disclose, Tu Vinh Luong:Nothing to Disclose, Andrew Hall:Nothing to Disclose, Chris Stevenson:Nothing to Disclose, Giuseppe Mazza:Nothing to Disclose, Bernard Allan:Nothing to Disclose.

★ 1356 | FXR SIGNALING REWIRES CERAMIDE HOMEOSTASIS AND FERROPTOTIC VULNERABILITY IN MASH

Yasmeen Attia[1] Basma Abdelrahman[2] Rasha Tawfiq[2] Olfat Hammam[3], [1]Faculty of Pharmacy, The British University in Egypt, [2]The British University in Egypt, [3]Theodor Bilharz Research Institute

Background: Metabolic dysfunction-associated steatohepatitis (MASH) emerges when hepatocytes are forced to navigate a hostile landscape of distorted bile acid signaling and lipid overload. Among the most injurious lipid species, ceramides carve a pro-death metabolic signature that destabilizes membranes and primes the liver for ferroptosis, an iron-driven collapse of lipid integrity. Farnesoid X receptor (FXR) activation has been proposed to counter this trajectory, yet whether it intersects with ceramide biogenesis and ferroptotic susceptibility in a MASH setting remains obscure. Here, we explore whether the FXR agonist obeticholic acid (OCA) can recalibrate ceramide synthesis and blunt ferroptotic drive in experimental MASH. **Methods:** A dietary high-fat diet (HFD) model was used to establish experimental MASH. Male C57BL/6 mice were assigned to three groups: a normal chow group, an HFD control group receiving vehicle, and an OCA-treated group maintained on HFD and administered obeticholic acid (5 mg/kg/day, p.o.) starting week 8 for a duration of 4 weeks. Livers were collected for histopathology and molecular analyses. FXR downstream

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signaling was assessed by quantifying hepatic SHP-1 expression *via* qRT-PCR and CYP7A1 protein levels by ELISA. Ceramide metabolism was examined by measuring sphingosine-1-phosphate (S1P) and acid sphingomyelinase (ASMase) to capture catabolic and salvage pathways. Ferroptotic stress was evaluated through GPX4 protein quantification and 4-hydroxynonenal (4-HNE) levels using ELISA, reflecting antioxidant defense status and lipid peroxidation, respectively. **Results:** Histopathological assessment revealed that OCA mitigated key features of MASH in HFD-fed mice, markedly reducing macrovesicular steatosis and lymphocytic infiltration, reflecting an overall reduction in hepatocellular injury and inflammatory burden. Consistent with FXR engagement, OCA treatment induced a clear upregulation of SHP-1 and produced a notable suppression of CYP7A1, which fell by 79% relative to the HFD group, indicating effective restoration of bile acid regulatory signaling. Perturbations in ceramide metabolism were also corrected, as shown by pronounced reductions in hepatic S1P and ASMase levels (63.5% and 49.1%, respectively), suggesting alleviation of ceramide-driven metabolic stress. Ferroptotic drive was similarly attenuated, with GPX4 increasing almost 2-fold and 4-HNE concentrations declining by approximately 37% compared to untreated HFD mice, consistent with strengthened antioxidant capacity and reduced lipid-peroxidation burden. **Conclusion:** Through limiting ceramide buildup and reinforcing anti-ferroptotic defenses, OCA steers the steatotic liver toward a more resilient metabolic trajectory, defining how FXR activation coordinates ceramide remodeling and ferroptotic stress within the integrated landscape of MASH.

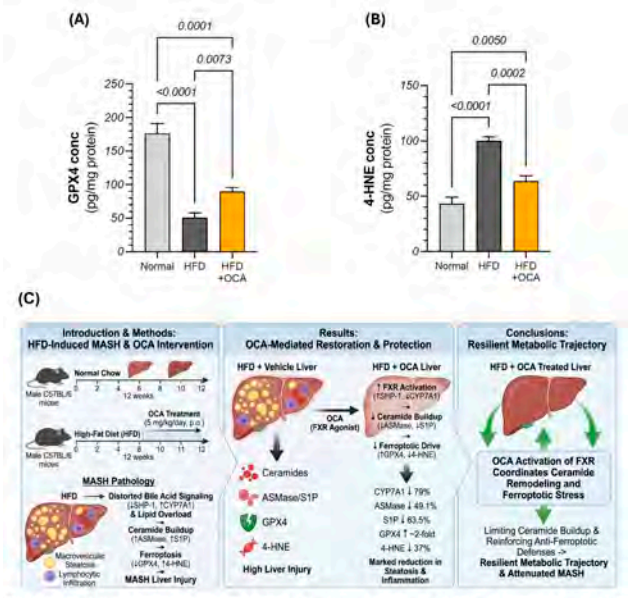


Fig. 1. Protein levels of **(A)** GPX4 and **(B)** 4-HNE in liver tissues from normal, HFD, and HFD+OCA groups. **(C)** Graphical summary demonstrating the proposed mechanism by which FXR recalibrates ceramide synthesis and blunts ferroptotic drive in experimental MASH. Data are presented as mean ± SD. Statistical analysis was performed using one-way ANOVA followed by Tukey's post hoc test for multiple comparisons. P values < 0.05 were considered statistically significant.

Disclosures: Yasmeen Attia:Nothing to Disclose, Basma Abdelrahman:Nothing to Disclose, Rasha Tawfiq:Nothing to Disclose, Olfat Hammam:Nothing to Disclose.

1357 | A HUMAN HIPSC-DERIVED LIVER ORGANOID PLATFORM FOR DILI PREDICTION AND DRUG SCREENING IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH)

Yedam Yoo[1] Jihye Choi[1] Jiseon Kim[1] Sewon Park[1] Joon Chul Kim[1] Seungwoo Cho[1] Yoonhee Jin[1], [1]Cellartgen Inc.

Background: Metabolic dysfunction-associated steatohepatitis (MASH) is driven by lipotoxic stress, inflammatory activation, and hepatic stellate cell-mediated fibrogenesis. Drug-induced liver injury (DILI) also remains a major cause of drug attrition and post-marketing withdrawal. Conventional 2D hepatocyte models, including HepG2 cells, have limited predictive capacity because they lack key non-parenchymal cell components such as hepatic stellate cells (HSCs) and Kupffer cells (KCs). To address these limitations, we established a human induced pluripotent stem cell (hiPSC)-derived multicellular liver organoid platform for DILI prediction and MASH-associated drug screening. **Methods:** Human hiPSC-derived liver organoids containing hepatocyte-like cells, HSCs, and KCs were generated and characterized. Platform reproducibility was assessed by comparing intra- and inter-batch transcriptomic profiles using bulk RNA sequencing. For DILI prediction, organoids were exposed to reference DILI-positive compounds and structurally related DILI-negative analogs, followed by assessment of cell viability and AST leakage. To model MASH-associated liver injury and fibrosis, organoids were treated with free fatty acids and TGF-β. Therapeutic responses were evaluated after treatment with Resmetirom, Semaglutide, or Efruxifermin. Changes in lipid accumulation, fibrosis, lipogenesis, and inflammatory markers were assessed by triglyceride measurement, immunostaining, qRT-PCR, and collagen secretion analysis. **Results:** The differentiated liver organoids reproducibly incorporated hepatocyte-like cells, HSCs, and KCs, with higher expression of liver lineage and non-parenchymal cell markers than HepG2 cells. Transcriptomic analysis demonstrated low intra-batch variability and consistent inter-batch profiles, supporting platform reproducibility. In DILI prediction assays, the organoids selectively detected toxicity of DILI-positive compounds, as shown by reduced cell viability, increased AST leakage, whereas structurally related DILI-negative analogs showed minimal toxicity.FFA and TGF-β treatment induced MASH-associated phenotypes, including lipid droplet accumulation, increased triglyceride content, and upregulation of

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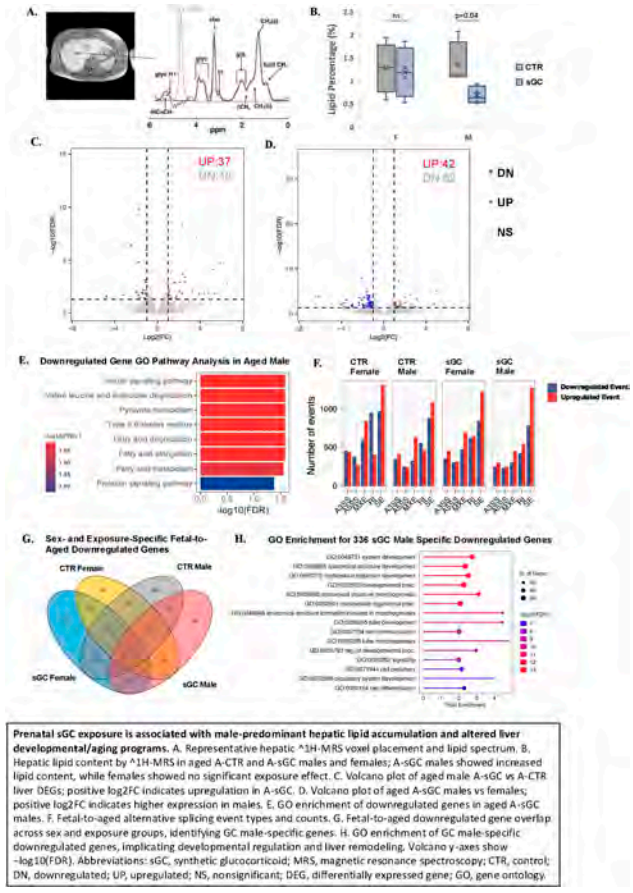
fibrotic and inflammatory markers. In the MASH-induced organoids, Resmetirom, Semaglutide, and Efruxifermin reduced lipid accumulation and attenuated fibrotic and inflammatory responses, as indicated by decreased fibrotic gene expression and collagen secretion. **Conclusion:** This human hiPSC-derived multicellular liver organoid platform recapitulates key cellular and pathological features relevant to DILI and MASH-associated fibrosis. The platform may provide a reproducible and physiologically relevant in vitro system for hepatotoxicity prediction and therapeutic screening in MASH.

Disclosures: Yedam Yoo:Nothing to Disclose, Jihye Choi:Nothing to Disclose, Jiseon Kim:Nothing to Disclose, Sewon Park:Nothing to Disclose, Joon Chul Kim:Nothing to Disclose, Seungwoo Cho:Nothing to Disclose, Yoonhee Jin:Nothing to Disclose.

1358 | PRENATAL SYNTHETIC GLUCOCORTICOID EXPOSURE PROGRAMS SEX-SPECIFIC HEPATIC LIPID ACCUMULATION AND AGE-DEPENDENT LIVER TRANSCRIPTOMIC REMODELING IN BABOONS

Bowen Yang[1] Chen Zhang[2] Feiyang Zhao[2] Hillary Huber[3] Cun Li[4] Peter Nathanielsz[4] Laura Cox[5] Geoffrey Clarke[2] Lu Wang[2], [1]University of Texas Health Science Center at Houston, [2]University of Texas Health Science Center at San Antonio, [3]Texas Biomedical Research Institute, [4]University of Wyoming, [5]Wake Forest University School of Medicine

Background: Developmental programming posits that fetal exposures, including preterm antenatal synthetic glucocorticoid (sGC) therapy for reducing neonatal morbidity, can shape lifelong health risks. This project studied gene regulation in fetal (F) and aged (A) liver tissues obtained from a sGC baboon model and control (CTR) group. In-vivo hepatic lipid content (HLC) was also measured using 3T magnetic resonance spectroscopy (MRS) in the aged subjects. **Methods:** sGC pregnancies received clinically equivalent betamethasone (175 µg/kg/day x2 days at 0.60, 0.64, 0.68 gestation); CTR received saline. Groups were studied by treatment, age, and sex: F-sGC (165 d, 4M/4F), F-CTR (165 d, 4M/4F), A-sGC (4M:16.9 ± 0.8Y; 4F:15.9 ± 0.2Y), and A-CTR (4M:17.4 ± 0.8Y; 4F:15.4 ± 0.9Y). RNA-seq assessed differentially expressed genes (DEGs), pathways, alternative splicing, and RNA-binding protein (RBP) motifs in right-lobe F and A liver samples. Data are reported as mean ± SD. **Results:** Aged GC males had higher HLC by MRS than A-CTR males ($p = 0.04$) but no HLC differences were found in females. Aged liver RNA-seq mirrored this phenotype: A-sGC vs A-CTR males had more DEGs than females (55:37 up/18 down vs 15:9 up/6 down; up/down in A-sGC). Sex differences were minimal in A-CTR (7 DEGs:3 up/4 down in males) but prominent in A-sGC (104 DEGs:42 up/62 down in males). In A-sGC males, downregulated genes involved AMPK/insulin signaling (FBP2, IRS2), whereas upregulated genes involved fatty acid/steroid metabolism (ACSL4, HSD17 family). Cross-sectional fetal-to-aged RNA-seq showed greater age-associated downregulation in sGC than CTR animals, especially in males, with suppression of developmental regulators (ZEB2, SRF, TCF4). Shared sGC-associated changes involved extracellular matrix pathways. Female-specific changes involved inflammatory genes (NLRC4, ZBTB16, IRF8). Fetal-to-aged splicing analyses identified sGC-associated skipped-exon events in males with RBP motif enrichment and retained-intron events in genes enriched for catabolic/metabolic processes (SLC27A5, STAT6) in males and JNK/MAPK/stress-kinase pathways in females. **Conclusion:** Prenatal sGC exposure programs sex-specific hepatic metabolic deviations in baboons, with lipid accumulation in males and disruption of insulin signaling, lipid/steroid metabolism, developmental regulation, and alternative splicing. Cross-sectional fetal-to-aged analyses suggest antenatal sGC reshapes liver development programs creating latent metabolic vulnerability that emerges with aging.



Prenatal sGC exposure is associated with male-predominant hepatic lipid accumulation and altered liver developmental/aging programs. A. Representative hepatic ^1H-MRS voxel placement and lipid spectrum. B. Hepatic lipid content by ^1H-MRS in aged A-CTR and A-sGC males and females; A-sGC males showed increased lipid content, while females showed no significant exposure effect. C. Volcano plot of aged male A-sGC vs A-CTR liver DEGs; positive log2FC indicates upregulation in A-sGC. D. Volcano plot of aged A-sGC males vs females; positive log2FC indicates higher expression in males. E. GO enrichment of downregulated genes in aged A-sGC males. F. Fetal-to-aged alternative splicing event types and counts. G. Fetal-to-aged downregulated gene overlap across sex and exposure groups, identifying GC male-specific genes. H. GO enrichment of GC male-specific downregulated genes, implicating developmental regulation and liver remodeling. Volcano y-axes show −log10(FDR). Abbreviations: sGC, synthetic glucocorticoid; MRS, magnetic resonance spectroscopy; CTR, control; DN, downregulated; UP, upregulated; NS, nonsignificant; DEG, differentially expressed gene; GO, gene ontology.

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Disclosures: Bowen Yang:Nothing to Disclose, Chen Zhang:Nothing to Disclose, Feiyang Zhao:Nothing to Disclose, Hillary Huber:Nothing to Disclose, Cun Li: Nothing to Disclose, Peter Nathanielsz:Nothing to Disclose, Laura Cox:Nothing to Disclose, Geoffrey Clarke:Nothing to Disclose, Lu Wang:Nothing to Disclose.

1359 | LOSS OF LIVER HSD17B13 IMPROVES WHOLE BODY AND MUSCLE INSULIN SENSITIVITY IN OBESE MICE

Allison Wing[1] Yanling Ma[2] Yaron Rotman[3], [1]National Institutes of Health, [2]NIH Clinical Center, [3]National Institute of Diabetes and Digestive and Kidney Diseases; National Institutes of Health

Background: Loss-of-function variants in *HSD17B13* protect against metabolic dysfunction-associated steatotic liver disease (MASLD) progression, and clinical trials targeting HSD17B13 appear promising. HSD17B13 is mostly expressed in the liver, with low expression in the duodenum and pancreas. As MASLD and diabetes are closely associated, we aim to assess the role of HSD17B13 in insulin and glucose homeostasis. **Methods:** Obesity and diabetes were induced in *Hsd17b13*-knockout (KO) mice and littermate controls (WT) by feeding high-fat diet (HFD) for 12 weeks. Glucose and insulin homeostasis were assessed using glucose tolerance test (GTT), glucose-stimulated insulin secretion (GSIS) test, insulin tolerance test (ITT) and hyperinsulinemic euglycemic clamp. Knockdown of hepatocyte *Hsd17b13* was conducted by administering AAV8 containing control (scRNA) or *Hsd17b13*-shRNA (shHsd) via tail vein injection. Conditioned media (CM) was harvested from primary hepatocytes and administered to differentiated L6 skeletal muscle myotubes expressing GLUT4-Myc. Cells were treated with or without insulin and immunostained to quantify GLUT4 translocation. **Results:** After 12 weeks of HFD, obese KO mice demonstrated improved insulin sensitivity by ITT (27%, $p = 0.02$) and hyperinsulinemic euglycemic clamp compared to obese WT controls, with increased glucose uptake into muscle and brain, which lack *Hsd17b13* expression. KO mice also demonstrated decreased GSIS (46%, $p = 0.0002$) and decreased fasting insulin (51%, $p = 0.001$). Interestingly, these opposing phenotypes resulted in no difference in GTT.To determine if improved insulin sensitivity in whole body KO is driven by hepatocyte HSD17B13, we performed hepatocyte-specific knockdown. After 12 weeks of HFD, shHsd mice had improved ITT (20%, $p = 0.01$) and GTT (18%, $p = 0.04$). sh-Hsd mice also had decreased fasting insulin relative to control (38%, $p = 0.04$) but did not have a significant difference in GSIS.Muscle is a major glucose uptake tissue. After treating differentiated L6 muscle cells with CM from primary WT and KO hepatocytes, insulin-induced GLUT4 translocation was increased in L6 cells receiving KO CM, relative to WT (55%, $p = 0.04$). **Conclusion:** Our findings suggests that hepatocyte HSD17B13 modulates whole body and muscle insulin sensitivity in other tissues, likely through circulating mediators. While targeting HSD17B13 appears promising in clinical trials, our data suggest it may also benefit diabetes.

Disclosures: Allison Wing:Nothing to Disclose, Yanling Ma:Nothing to Disclose, Yaron Rotman:Nothing to Disclose.

1360 | REDUCTION IN HEPATIC PC BIOSYNTHESIS PROMOTES MASH THROUGH COPPER DEFICIENCY

Jaclyn Welles[1] Michael Gonzalez[2] James Garifallou[3] David Li[4] Rebecca Wells[4] Dominic Santoleri[4] Gina DeNicola[5] Feroza Choudhury[5] Chang Jiang[5] Ryan Martin[5] Gen Li[6] Christopher Chang[6] Donita Brady[4] Paul Titchenell[4], [1]Northeast Ohio Medical University, [2]University of Pennsylvania - Perlman School of Medicine, [3]Children's Hospital of Pennsylvania, [4]University of Pennsylvania - Perelman School of Medicine, [5]Moffitt Cancer Center, [6]Princeton University

Background: PCYT1A encodes CTP: phosphocholine cytidyltransferase, alpha (CCT-α), a rate-limiting enzyme for ~70% of Phosphatidylcholine (PC) production via the Kennedy pathway. Notably, hepatic PC production is significantly decreased in patients with Metabolic-dysfunction associated steatohepatitis (MASH), a severe disorder affecting a subset of MASLD and T2D patients. MASLD is clinically characterized by hepatic lipid accumulation, while MASH includes hepatic fibrosis, scarring, and inflammation. Interestingly, several variants associated with impairments in PC biosynthesis or homeostasis have emerged in MASLD/MASH patients (e.g., PNPLA3; TM6SF2; HSD17β13). It remains unknown however, how the reduction of hepatic PC biosynthesis, promotes the fibrosis and inflammation observed in MASH patients. **Methods:** We used 10X Single Nuclei RNA-Seq to investigate the functional role of PC in MASH using two models, a genetic model using AAV8-TBG-CRE to KO *PCYT1A* in hepatocytes, and a dietary model where C57BL/6J mice were fed a low methionine choline-deficient HFD (LMCD-HFD) for 4-wks. ICP-MS was also used to perform metallomics

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analysis and quantitatively measure tissue and serum metal abundance. For in vitro studies, human-derived cell lines, HUH-7 and LX-2, along with fluorescent-based reporters, were used for mechanistic studies. **Results:** SEURAT cluster analysis and KEGG pathway analysis revealed DEGs enriched in hepatocytes in mouse MASH models, associated with metal ion binding and signaling. Interestingly, ICP-MS showed a significant decrease in copper content in MASH livers, while serum showed an accumulation, suggesting liver-specific perturbations in copper transport. *In vitro* studies using HUH-7 cells showed that knockdown of *PCYT1A*/CCT inhibited *SLC31A1*/CTR1 localization to the plasma membrane, reducing copper import as confirmed by a fluorescent Cu+2 probe. In LX-2 cells, while copper ($CuSO_4$) alone drove fibrogenesis, $CuSO_4$ with h-TGFß showed a synergistic effect, increasing matrice formations. KO of PM-mediated copper import (siRNA-*SLC31A1*/CTR1) or mitochondria-mediated copper import (siRNA-*SLC25A3*) also inhibited fibronectin deposition in LX-2 cells. *In vivo* studies using the cell-impermeable copper chelator BCS protected against MASH-associated fibrogenesis in both genetic and dietary models. Reductions in fibrosis were observed through decreased Sirius red-positive liver areas (collagen deposition) and pro-fibrogenic gene expression. **Conclusion:** This data supports that MASH-associated lipid remodeling impairs copper transporter localization, causing copper deficiency. Given that the FDA has approved copper chelators for cancer, our work suggests that chelators could be repurposed to treat MASH in the future. This work highlights a gap in our understanding of fibrogenesis and the need for targeted, liver-specific, and cell-type-specific copper therapeutics against MASH.
Disclosures: Jaclyn Welles:Nothing to Disclose, Michael Gonzalez:Nothing to Disclose, James Garifallou:Nothing to Disclose, David Li:Nothing to Disclose, Rebecca Wells:Nothing to Disclose, Dominic Santoleri:Nothing to Disclose, Gina DeNicola:AstraZeneca: Consultant, Feroza Choudhury:Nothing to Disclose, Chang Jiang:Nothing to Disclose, Ryan Martin:Nothing to Disclose, Gen Li:Nothing to Disclose, Christopher Chang:Nothing to Disclose, Donita Brady:Nothing to Disclose, Paul Titchenell:Nothing to Disclose.

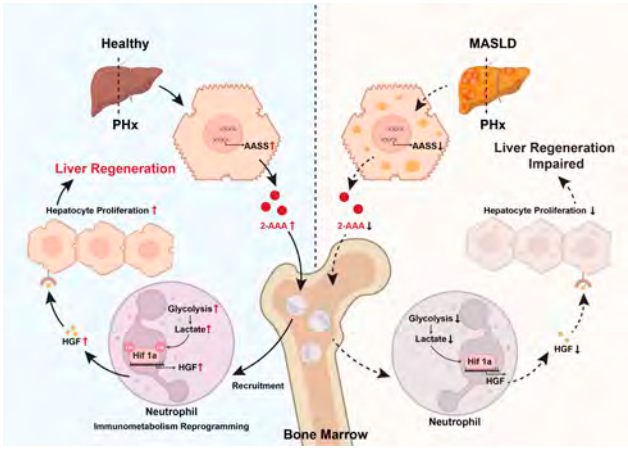
1361 | 2-AAA DRIVES LIVER REGENERATION IN MASLD BY ENHANCING NEUTROPHIL GLYCOLYSIS AND HIF-1A-DEPENDENT HGF EXPRESSION

Bo Wang[1], [1]Zhongshan Hospital, Fudan University

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is characterized by impaired liver regeneration, which contributes to disease progression and poor outcomes following hepatic resection. The molecular mechanisms underlying this regenerative deficit remain poorly understood, and no targeted therapies are currently available. 2-Aminoadipic acid (2-AAA), an intermediate of lysine metabolism, has recently emerged as a potential metabolic regulator of tissue repair. Our previous studies revealed that 2-AAA is significantly upregulated during physiological liver regeneration but fails to increase in MASLD. Exogenous 2-AAA supplementation restored regenerative capacity in MASLD mice, an effect dependent on neutrophils. However, the mechanistic basis for 2-AAA-mediated liver regeneration remains to be fully elucidated. **Methods:** To investigate 2-AAA's role in liver regeneration, we used a MASLD mouse model subjected to 70% partial hepatectomy. Hepatic and serum 2-AAA levels were measured via LC-MS/MS. We modulated endogenous 2-AAA by knocking down its synthetic enzyme AASS with AAV-shRNA and administered exogenous 2-AAA to assess therapeutic effects. Neutrophil glycolysis and lactate production were analyzed, and HIF-1α lactylation and stability were examined. Neutrophil involvement was validated via anti-Ly6G depletion, and hepatocyte proliferation was evaluated by Ki67 and Cyclin A2 staining. **Results:** We found that 2-AAA levels increased significantly in the liver and serum of control mice after PHx, whereas this response was blunted in MASLD mice. Hepatic AASS expression was downregulated in MASLD, and AASS knockdown in normal mice recapitulated the regenerative defect observed in MASLD. Exogenous 2-AAA supplementation improved survival, liver weight recovery, and hepatocyte proliferation in MASLD mice. Mechanistically, 2-AAA enhanced neutrophil glycolysis and lactate production, leading to increased HIF-1α lactylation and protein stabilization. HIF-1α transcriptional activity upregulated HGF expression in neutrophils. Neutrophil depletion abolished the pro-regenerative effect of 2-AAA. In MASLD mice, impaired 2-AAA synthesis resulted in reduced neutrophil recruitment, diminished glycolysis, and disrupted HGF expression, ultimately compromising liver regeneration. **Conclusion:** This study identifies 2-AAA as a critical metabolic signal that promotes liver regeneration by enhancing neutrophil glycolysis and HIF-1α-dependent HGF expression. Impaired 2-AAA synthesis in MASLD contributes to regenerative failure, highlighting the therapeutic potential of targeting the 2-AAA-neutrophil-HGF axis to improve outcomes in patients with MASLD undergoing liver resection.

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1362 | LOSS OF BATF3 REPROGRAMS ADIPOSE–LIVER METABOLIC COMMUNICATION TO ACCELERATE STEATOSIS-TO-FIBROSIS TRANSITION IN HIGH-FAT DIET INDUCED MASLD

Haibo Dong[1] Wei Guo[1] Xinguo Sun[1] Zhanxiang Zhou[1], [1]University of North Carolina at Greensboro

Background: Metabolic dysfunction–associated steatotic liver disease (MASLD) is driven by complex inter-organ communication, particularly between adipose tissue and liver. BATF3, a transcription factor essential for dendritic cell differentiation and immune regulation, has recently been implicated in metabolic processes; however, its role in coordinating adipose–liver homeostasis during MASLD progression remains unclear. **Methods:** To investigate the metabolic function of BATF3, we utilized Batf3$^{-/-}$ mice subjected to a high-fat diet (HFD). Hepatic steatosis, inflammation, and fibrosis were assessed by histological and biochemical analyses. Adipose tissue lipolysis, hepatic lipid uptake, and systemic insulin signaling were evaluated using metabolic assays and immunoblotting. Transcriptomic profiling highlited angiopoietin-like protein 8 (ANGPTL8), a hepatokine involved in inter-organ communication, which was subsequently subjected to functional analysis. **Results:** BATF3 deficiency markedly exacerbated HFD-induced liver pathology, including increased steatosis, inflammatory responses, and fibrotic remodeling. These changes were accompanied by enhanced adipose tissue lipolysis, elevated hepatic fatty acid influx, and impaired insulin–AKT signaling, indicating systemic metabolic imbalance. Mechanistically, we identified ANGPTL8 emerged as a key mediator linked to metabolic alterations in Batf3$^{-/-}$ mice . ANGPTL8 expression was significantly reduced in Batf3$^{-/-}$ mice, suggesting disrupted endocrine regulation between adipose tissue and liver. Functional analyses demonstrated that ANGPTL8 exerts protective effects by suppressing inflammation-induced hepatic stellate cell activation and by differentially regulating lipid metabolism across tissues, reducing hepatic lipid accumulation while limiting adipose tissue lipolysis. **Conclusion:** Our findings reveal a previously unappreciated role of BATF3 in maintaining adipose–liver metabolic homeostasis and identify the BATF3–ANGPTL8 axis as a critical regulator of steatosis-to-fibrosis progression in MASLD. Targeting this pathway may offer a novel therapeutic strategy to prevent disease progression.

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1363 | RAB1A PROMOTES HEPATIC STEATOSIS BY SUPPRESSING MITOPHAGY VIA THE RAF-1/ERK1/2/PINK1 SIGNALING AXIS

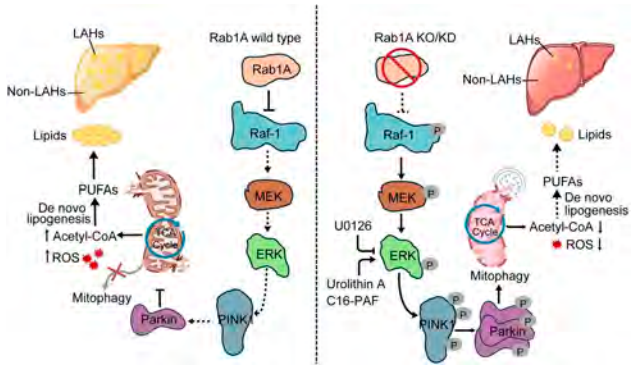
Xin Zhang[1] Li Zhang[2] Jianhua Li[3] Huilu Zhang[4] Qi Qin[5] Xiaofan Tian[6] Yichen Huang[5] Zhengxin Wang[7], [1]Institute of Translational Medicine, [2]Institute for Biomedical Sciences and School of Life Sciences, East China Normal University, [3]Institute of Organ Transplantation, Huashan Hospital, Fudan University, [4]Huashan Hospital, Fudan University, [5]Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, [6]Ernst Mario School of Pharmacy, Rutgers, The State University of New Jersey, [7]Huashan Hospital & Institute of Organ Transplantation, Fudan University

Background: Driven by the Western diet, metabolic dysfunction-associated steatotic liver disease (MASLD) has become a global health crisis, progressing from hepatic triglyceride accumulation to MASH, cirrhosis, and hepatocellular carcinoma. Although the liver displays marked zonation between periportal and pericentral hepatocytes, how the hepatic microenvironment shapes disease progression remains unclear, and the organellar mechanisms driving initial hepatocyte lipid overload during overnutrition are incompletely defined. **Methods:** We integrated single-cell RNA sequencing (scRNA-seq) data from murine and human MASLD cohorts to resolve hepatocyte heterogeneity and nominate candidate regulators. Findings were validated in global Rab1A knockout mice and in adult mice with AAV-mediated, hepatocyte-specific Rab1A knockdown, fed a Western diet or high-fat diet (HFD). Mechanistic dissection combined co-

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immunoprecipitation, in vitro kinase assays, site-directed mutagenesis of PINK1, and pharmacological perturbation with U0126, Urolithin A, and C16-PAF. Clinical relevance was assessed in human MASLD liver specimens. **Results:** scRNA-seq identified a lipid-associated hepatocytes (LAHs) population enriched in MASLD livers, with Rab1A as a prominent driver. Both global Rab1A knockout and liver-specific Rab1A knockdown mitigated diet-induced hepatic steatosis. Mechanistically, Rab1A depletion attenuated lipid accumulation by inducing excessive mitophagy: Rab1A restrains Raf-1 activation and thereby suppresses MEK/ERK1/2 signaling, and U0126 reversed both the lipid-lowering and mitophagy phenotypes of Rab1A-deficient cells. ERK1/2 directly bound and phosphorylated PINK1 at Ser228, triggering PINK1–Parkin-dependent mitophagy. Pharmacological activation of this axis with Urolithin A or C16-PAF alleviated HFD-induced steatosis and attenuated MASLD progression in mice. In human MASLD samples, Rab1A expression inversely correlated with activation of the Raf-1/ERK1/2/PINK1 pathway. **Conclusion:** We identify the Rab1A/Raf-1/ERK1/2/PINK1 axis as a key regulator of hepatocyte mitophagy and MASLD pathogenesis, linking a small GTPase to mitochondrial quality control via MAPK signaling and nominating this pathway as a promising therapeutic target.



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1364 | SIGLEC-H DEFICIENCY LICENSES PATHOGENIC PDC–MACROPHAGE CROSSTALK TO DRIVE FIBROSIS AND HCC IN MASH

James Ahodantin[1] Jiapeng Wu[2] Masaya Funaki[3] Xu Wang[2] Pan Zheng[4] Yang Liu[4] Lishan Su[5], [1]University of Nebraska Medical Center, [2]University of Maryland Baltimore, [3]Kanazawa University, [4]OncoC4, Inc, [5]Institute of Human Virology, University of Maryland School of Medicine

Background: Metabolic dysfunction–associated steatohepatitis (MASH) is driven by chronic immune activation, fibrogenesis, and progressive metabolic injury that culminate in hepatocellular carcinoma (HCC). Although macrophage-mediated inflammation is central to disease progression, the immunoregulatory role of plasmacytoid dendritic cells (pDCs) in MASH remains poorly defined. Siglec-H is a pDC-restricted inhibitory receptor that constrains innate immune activation; however, its contribution to metabolic liver disease is unknown. We investigated whether Siglec-H signaling regulates pDC-driven inflammatory and fibrogenic responses during MASH progression and hepatocarcinogenesis. **Methods:** The functional role of pDCs was evaluated using antibody-mediated pDC depletion and Siglec-H knockout (Siglec-H$^{-/-}$) mice subjected to Western diet (WD) feeding or the STAM model of MASH-associated HCC. Liver injury, steatosis, fibrosis, tumor burden, metabolic parameters, immune composition, and lipidomic remodeling were assessed by histopathology, flow cytometry, metabolic phenotyping, and transcriptomic/lipidomic analyses. Mechanistic studies examined free fatty acid–induced activation of pDCs and macrophages and their downstream effects on hepatic stellate cell activation. **Results:** pDC depletion markedly attenuated hepatic steatosis, inflammatory injury, and fibrosis in WD-fed mice, identifying pDCs as pathogenic mediators of MASH progression. In contrast, Siglec-H deficiency profoundly exacerbated obesity, insulin resistance, hepatic lipid accumulation, fibrosis, and MASH-associated HCC development. Mechanistically, loss of Siglec-H induced broad metabolic reprogramming characterized by enhanced lipogenesis, impaired fatty acid oxidation, and substantial alterations in hepatic and circulating lipid species. Siglec-H$^{-/-}$ pDCs displayed heightened responsiveness to palmitic acid stimulation, producing increased levels of CCL3 and TGF-β that promoted macrophage recruitment and activation. This pDC-macrophage crosstalk amplified profibrotic signaling and induced hepatic stellate cell activation, whereas direct exposure of macrophages and stellate cells to CCL3 and TGF-β recapitulated key inflammatory and fibrogenic phenotypes in vitro. **Conclusion:** Siglec-H functions as a critical immunometabolic checkpoint that restrains pDC-driven inflammatory and fibrogenic remodeling in MASH. Loss of Siglec-H licenses pathogenic pDC-macrophage communication through a CCL3/TGF-β signaling axis, accelerating fibrosis and hepatocarcinogenesis. These findings identify pDCs as central orchestrators of MASH progression and nominate Siglec-H signaling and pDC-macrophage

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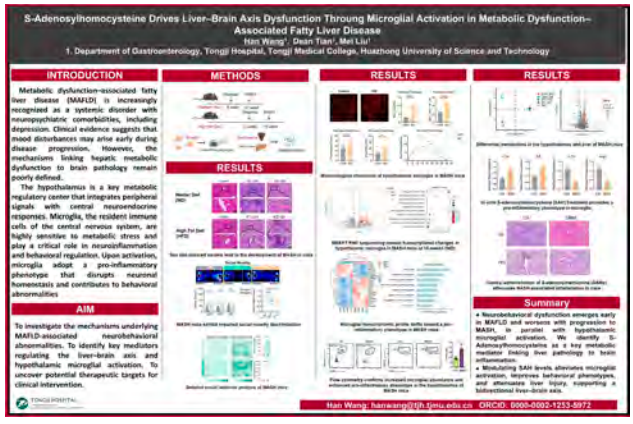
interactions as therapeutic targets for advanced metabolic liver disease.

Disclosures: James Ahodantin:Nothing to Disclose, Jiapeng Wu:Nothing to Disclose, Masaya Funaki: Nothing to Disclose, Xu Wang:Nothing to Disclose, Pan Zheng:Nothing to Disclose, Yang Liu:Nothing to Disclose, Lishan Su:Nothing to Disclose.

1365 | S-ADENOSYLHOMOCYSTEINE DRIVES LIVER–BRAIN AXIS DYSFUNCTION THROUNG MICROGLIAL ACTIVATION IN METABOLIC DYSFUNCTION–ASSOCIATED FATTY LIVER DISEASE

Han Wang[1], [1]Tongji Hospital, Tongji Medical College, Huazhong University

Background: Metabolic dysfunction–associated fatty liver disease (MAFLD) is increasingly linked to neuropsychiatric comorbidities, including depression, yet underlying mechanisms remain unclear. The hypothalamus integrates peripheral metabolic signals with central regulation, and microglia are highly responsive to metabolic stress, contributing to neuroinflammation and behavioral dysfunction. We hypothesized that MAFLD progression induces hypothalamic microglial activation via circulating metabolites, driving liver–brain axis dysfunction. **Methods:** Two diet-induced MAFLD models (high-fat diet, HFD; Western diet, WD) were established, each spanning steatosis to MASH. Behavioral assays were performed longitudinally. Hypothalamic microglia ($CD45^{+}CD11b^{+}$) were isolated and analyzed by SMART RNA sequencing. Untargeted metabolomics was conducted in hypothalamus and liver to identify shared metabolites. Functional validation included in vitro metabolite treatment and in vivo S-adenosylmethionine (SAMe) intervention via central and intraperitoneal administration to modulate S-adenosylhomocysteine (SAH). **Results:** Behavioral abnormalities, including anxiety-like behavior and impaired social interaction and memory, emerged at the steatosis stage and worsened in MASH. Microglial transcriptomics revealed a pro-inflammatory, interferon-responsive activation state, with upregulation of innate immune genes (cd300lb, ifitm3, ifi47, cxcr2, ifitm1, ifi211, clec4a1, ccr1) and downregulation of immunoregulatory genes (parg, cirbp, mef2a, hpgds). Metabolomics identified 60 metabolites elevated in both liver and hypothalamus, among which SAH was prominent. In vitro, SAH induced microglial activation, increasing Il1b, Il6, and Tnf while suppressing Arg1, Mrc1, Il10, and Tgfb1. In vivo, central modulation of SAH using SAMe reduced hypothalamic microglial activation and attenuated liver injury, indicating a brain-to-liver regulatory effect. Systemic SAMe administration similarly decreased hypothalamic SAH levels, suppressed microglial inflammation, and improved behavioral abnormalities. These interventions collectively support a bidirectional liver–brain axis mediated by SAH. **Conclusion:** Neurobehavioral dysfunction emerges early in MAFLD and worsens with progression to MASH, in parallel with hypothalamic microglial activation. We identify S-Adenosylhomocysteine as a key metabolic mediator linking liver pathology to brain inflammation. Modulating SAH levels alleviates microglial activation, improves behavioral phenotypes, and attenuates liver injury, supporting a bidirectional liver–brain axis. These findings provide mechanistic insight into the neuropsychiatric burden of MAFLD and highlight SAH metabolism as a potential therapeutic target for both hepatic and neurobehavioral complications.



Disclosures: Han Wang:Nothing to Disclose.

1366 | NON-CANONICAL MLKL SIGNALING DRIVES HCC PROGRESSION IN OBESITY-ASSOCIATED MASLD

Deepa Sathyaseelan[1], [1]University of Oklahoma Health Campus

Background: MASLD affects over 1 billion people and is the fastest-growing cause of HCC, driven by obesity. No approved targeted therapies exist for MASLD-associated HCC. MLKL, the necroptosis effector, is consistently upregulated in human and experimental MASLD. We hypothesized that under lipotoxic stress, hepatocyte MLKL drives MASLD-to-HCC progression via non-necroptotic mechanisms. **Methods:** Hepatocyte-specific Mlkl knockout ($Mlkl^{HepKO}$) mice were generated using AAV8-TBG-Cre in $Mlkl^{fl/fl}$ mice and fed a Western diet (WD,

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43.7% fat, 0.203% cholesterol) or control diet for 15 months. Endpoints included tumor incidence/burden, histology (H&E, Oil Red O, Sirius Red), necroptosis markers (p-MLKL, MLKL oligomers, RIPK3), liver injury (ALT, AST), RNA-seq, Seahorse MitoStress assay, and stemness/mitochondrial protein expression (Western blot, IHC, qPCR). MLKL knockdown (siRNA) and inhibition (necrosulfonamide, NSA) were tested in AML12, HepG2, and primary hepatocytes. NSA efficacy was assessed in HepG2 xenografts in nude mice. TCGA datasets and tissue microarrays were analyzed for MLKL expression and survival. **Results:** WD induced hepatic MLKL, yet necroptosis markers were undetectable, confirming a non-necroptotic context. *Mlkl*^{HepKO} mice developed significantly fewer and smaller tumors without differences in obesity, fibrosis, or liver injury, demonstrating hepatocyte MLKL promotes HCC independently of existing liver pathology. *Mlkl*^{HepKO} livers showed increased lipid droplets but reduced stemness markers DCLK1 and OCT4. RNA-seq revealed upregulation of mitochondrial OXPHOS and translation pathways. WD suppressed the tumor suppressor Mitofusin 2 (MFN2), and MLKL deficiency restored MFN2, linking MLKL to mitochondrial dysfunction. MLKL knockdown or inhibition reduced HepG2 proliferation, clonogenicity, and enhanced OXPHOS. NSA significantly reduced xenograft tumor volume and weight in vivo. In human HCC, MLKL was upregulated in tumor vs. adjacent tissue and correlated with poor survival. **Conclusion:** Hepatocyte MLKL drives MASLD-HCC via a novel non-necroptotic mechanism: suppression of MFN2 impairs mitochondrial OXPHOS and sustains tumor stemness, defining a new metabolic-oncogenic axis. NSA reduced xenograft tumor growth in vivo, providing proof-of-concept for MLKL as a druggable target. MLKL overexpression predicts poor survival in human HCC. Critically, MLKL loss reduces tumor burden without worsening liver injury or inflammation, establishing a favorable therapeutic window for MLKL inhibition in MASLD-driven HCC.

Disclosures: Deepa Sathyaseelan:Nothing to Disclose.

1367 | HEPATOCYTE S1PR2 PROTECTS AGAINST DIET-INDUCED MASLD BY MAINTAINING LIPID HOMEOSTASIS AND KUPFFER CELL NICHE INTEGRITY

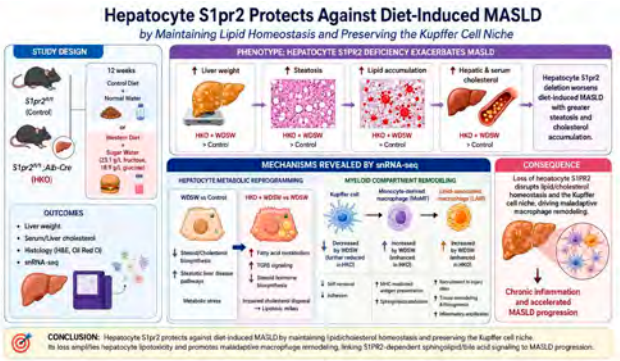
Meiyi Song[1] Grayson Way[1] Chen Chen[1] Nan Wu[1] Lianyong Su[1] Derrick Zhao[1] Yunling Tai[1] Hongkun Lu[1] Hui LI[1] Sareh Bayatpour[1] Xuan Wang[1] Emily Gurley[1] Phillip Hylemon[1] Arun Sanyal[2] Huiping Zhou[1], [1]Virginia Commonwealth University and Richmond Veterans Affairs Medical Center, [2]Virginia Commonwealth University

Background: Sphingosine-1-phosphate receptor 2 (S1PR2), a bile acid-responsive GPCR, regulates hepatic lipid metabolism. Our previous study showed that global S1pr2 knockout significantly accelerated high-fat diet-induced steatohepatitis in mice. Here, we investigated whether hepatocyte S1pr2 protects against diet-induced MASLD by maintaining hepatic lipid homeostasis and preserving the macrophage niche. **Methods:** S1pr2fl/fl and hepatocyte-specific S1pr2 knockout mice (S1pr2fl/fl;Alb-Cre, HKO) were fed control diet/normal water or Western diet plus sugar water (WDSW; 23.1 g/L fructose, 18.9 g/L glucose) for 12 weeks. Steatosis and lipid accumulation were assessed by liver weight, serum/liver cholesterol, H&E, and Oil Red O staining. Whole-liver snRNA-seq was performed to define cell type-specific transcriptional responses and explore potential intercellular communication. **Results:** WDSW increased liver weight and circulating cholesterol in S1pr2fl/fl mice. Hepatocyte S1pr2 deletion exacerbated MASLD, with higher liver weight, more severe histologic steatosis and lipid droplet accumulation, and greater hepatic and serum cholesterol levels. In hepatocytes, WDSW induced broad metabolic reprogramming, including suppression of steroid/cholesterol biosynthesis and enrichment of steatotic liver disease pathways. Under WDSW, HKO hepatocytes showed additional pathway remodeling, with reactivation of fatty acid metabolism, increased TGFβ signaling, and reduced steroid hormone biosynthesis, consistent with impaired cholesterol disposal and a lipotoxic hepatic milieu. snRNA-seq also identified diet- and genotype-dependent remodeling of the myeloid compartment. WDSW was associated with reduced resident Kupffer cells and increased monocyte-derived macrophage and lipid-associated macrophage populations. In HKO mice, Kupffer cells showed reduced self-renewal/adhesion programs, whereas lipid-associated macrophages were enriched for recruitment, tissue remodeling, and fibrogenic programs; monocyte-derived macrophages displayed enhanced MHC-dependent antigen presentation and sphingolipid catabolism. **Conclusion:** Hepatocyte S1pr2 protects against WDSW-induced MASLD by maintaining lipid/cholesterol homeostasis and preserving the Kupffer cell niche. Its loss amplifies hepatocyte lipotoxicity and promotes maladaptive macrophage remodeling, linking S1PR2-dependent sphingolipid/bile acid signaling to inflam-

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matory progression of MASLD.



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1368 | AMELIORATIVE EFFECTS OF COMBINATION THERAPY WITH RESMETIROM, TIRZEPATIDE, AND ROFLUMILAST ON A GAN DIET-MASH MOUSE MODEL

Takumi Sugawara[1] Mitsuharu Matsumoto[1] Sayuri Nakamura[1] Ryotaro Hori[1] Yasunori Nio[1], [1]Axcelead Drug Discovery Partners, Inc.

Background: Metabolic dysfunction–associated steatohepatitis (MASH) is driven by complex interactions between metabolic dysregulation and inflammation. Recently, thyroid hormone receptor-β (THR-β) agonist and glucagon-like peptide-1 receptor (GLP-1R) agonist have been approved for the treatment of MASH. In addition, phosphodiesterase-4 (PDE-4) inhibitors, which have a mechanism distinct from these therapeutic approaches, have been reported to exert ameliorative effects on inflammation and fibrosis in liver of MASH models. The aim of present study is to confirm the combination effects on them using Gubra Amylin (GAN) diet-induced MASH model mouse. **Methods:** To induce disease conditions, male C57BL/6J mice were fed the GAN diet for 43 weeks before treatment. Animals were treated for 16 weeks with a THR-β agonist (Resmetirom, 3 mg/kg, q.d., p.o.), a dual GLP-1/glucose-dependent insulinotropic polypeptide (GIP) receptor agonist (Tirzepatide, 0.1 mg/kg, b.i.w., s.c.), and a PDE-4 inhibitor (Roflumilast, 1 mg/kg, q.d., p.o.), either as monotherapy, dual combinations, or triple therapy. The body composition was measured using Magnetic Resonance Imaging. Energy expenditure was analyzed using Oxymax system. Then, mice were anesthetized and then blood was collected, and the liver was harvested. Plasma and liver were used for biochemical and pathological analyses. **Results:** All monotherapies reduced liver weight and improved metabolic and hepatic injury parameters. Liver weight was further reduced by all combination therapies compared with respective monotherapies and reached levels comparable to the control group. Plasma liver injury markers, such as AST, ALT, were additively reduced by dual combination therapies compared with the respective monotherapies. As reported previously, the GLP-1 analog significantly reduced energy expenditure, and co-treatment with resmetirom tended to recover energy expenditure. Triple therapy did not provide additional benefits beyond dual combinations therapies, suggesting a plateau in therapeutic efficacy. Further analyses of liver pathology, including fibrosis and nonalcoholic fatty liver disease activity score (NAS), will be presented at the conference. **Conclusion:** These findings indicate that simultaneous targeting of two distinct pathways might be sufficient to achieve maximal therapeutic effects in experimental MASH. Triple therapy provided limited additional benefit, supporting the concept that optimized dual combination strategies may represent a rational and clinically relevant therapeutic approach.

Disclosures: Takumi Sugawara:Nothing to Disclose, Mitsuharu Matsumoto:Nothing to Disclose, Sayuri Nakamura:Nothing to Disclose, Ryotaro Hori:Nothing to Disclose, Yasunori Nio:Nothing to Disclose.

★ 1369 | METABOLIC FERROPTOSIS AS TARGETABLE SIGNATURE FOR THE GENETIC SUBTYPE OF MASLD

Erika Paolini[1] Marica Meroni[2] Miriam Longo[3] Sara Badiali[4] Marco Maggioni[5] Anna Ludovica Fracanzani[6] Paola Dongiovanni[2], [1]Medicine and Metabolic Diseases, Fondazione IRCCS Cà Granda, [2]Medicine and Metabolic Diseases, Fondazione IRCCS Cà Granda, Ospedale Maggiore Policlinico, Milan, [3]Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico Milano, [4]Department of Surgery, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy, [5]Department of Pathology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy, [6]University of Milan

Background: The co-presence of the I148M-PNPLA3, rs641738-MBOAT7 and E167K-TM6SF2 polymorphisms enhances the risk of severe MASLD. Emerging evidence highlighted that ferroptosis is essential for developing MASLD/MASH since it promotes oxidative stress, lipid peroxidation and inflammation although the underlying mechanisms are still unknown. Thus, this study investigated the possible crosslink between ferroptosis and the three mutations in hepatic biopsies of MASLD patients, through a spatial transcriptomic (ST) approach. **Methods:**

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ST was performed by Visium CytAssist and data were analyzed using Spaceranger (10x Genomics). Patients, featured by a similar histological severity (NAS≥4) and comparable comorbidities (gender, age, BMI, absence of T2D), were wild type (WT), homozygous for PNPLA3, MBOAT7, TM6SF2 polymorphisms and carriers of the 3 at-risk variants (3NRV) (n = 2/group). **Results:** All samples were integrated and clustered at 0.5 resolution allowing the identification of 7 clusters (cl), annotated as follows: cl0 enriched in periportal HEPs; cl1 in immune cells; cl2 in pericentral HEPs; cl3 in cholangiocytes; cl4 in endothelial cells (ENDOs); cl5 in immune cells; cl6 in NPCs (HSCs, immune cells and ENDOs); cl7 in HEPs. Firstly, we observed that cl4 was more abundant in PNPLA3, MBOAT7, TM6SF2 and 3NRV samples compared to WT, whereas cl6 was mainly enriched in patients carrying the 3 at-risk variants *vs* all. Then, we conducted a Pathway-enrichment analysis by considering differentially expressed genes (DEGs; Log2FC > 0.5 and padj FDR < 0.05) of 3NRV in all clusters *vs* the other samples. The former exhibited increased lipid metabolism, oxidative damage, inflammation, fibrosis, and ferroptosis reflecting a worse clinical *scenario*. By focusing on the ferroptosis pathway, we found that in patients carrying TM6SF2 and MBOAT7 variants, it was mainly espressed in immune cells whereas in *PNPLA3* and 3NRV, also in HEPs. Moreover, cl6 showed the strongest upregulation of a "metabolic" ferroptosis, driven by lipid buildup and mitocondrial dysfunction. It was designed by a signature of 53 unique genes, which was uregulated only in 3NRV patients, thus rappresenting a pathognonomic feature of the "genetic" subtype of MASLD. **Conclusion:** The co-presence of *PNPLA3*, *MBOAT7*, and *TM6SF2* variants may accelerate liver injury by triggering a lipid-metabolism and mitochondrial ferroptosis. Thus, ferroptosis could be a potential druggable signature to tackle 3NRV MASLD patients.

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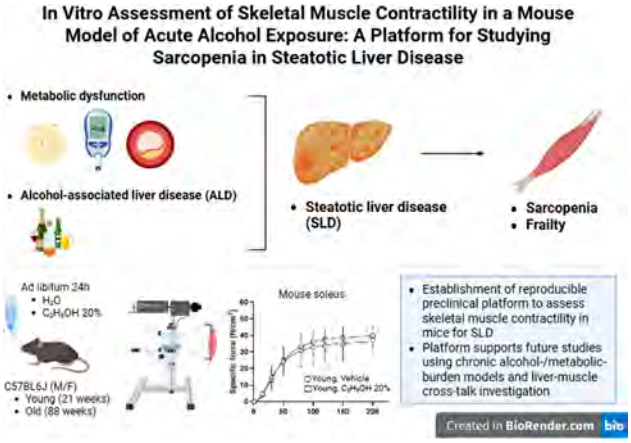
1370 | IN VITRO ASSESSMENT OF SKELETAL MUSCLE CONTRACTILITY IN A MOUSE MODEL OF ACUTE ALCOHOL EXPOSURE: A PLATFORM FOR STUDYING SARCOPENIA IN STEATOTIC LIVER DISEASE

Alexander Kusnik[1] Hwi Young Kim[1] Fedja Rochling[1] Gwenael Layec[2] Dongwoo Hahn[2], [1]University of Nebraska Medical Center, [2]University of Nebraska at Omaha

Background: Steatotic liver disease (SLD) reflects a dual burden of metabolic dysfunction and alcohol-associated liver disease (ALD), with sarcopenia and frailty emerging as prognostically significant complications. Our group's prior preclinical work demonstrated impairment in mitochondrial respiratory function by high-resolution respirometry and vascular function by pressure myography in skeletal muscle, suggesting a plausible mechanistic pathway to muscle weakness in SLD. Despite these findings, preclinical platforms capable of directly assessing skeletal muscle contractile dysfunction in an SLD-relevant context remain underdeveloped. We aimed to establish an in vitro methodology for reproducible assessment of skeletal muscle contractile function in mice following acute alcohol exposure as a foundational step toward etiologic burden-specific mechanistic studies of sarcopenia in SLD. **Methods:** C57BL/6J mice at young (21 ± 4 weeks) and old (88 ± 1 weeks) ages were assigned to vehicle or 20% ethanol solution ad libitum for 24 hours (n = 10/group; 5M/5F). Soleus muscles were dissected and mounted in an in vitro apparatus (Krebs solution, 32° C, oxygenated) to assess force-frequency relationships (absolute force, mN; specific force, N/cm²) across 10 to 200 Hz. Body weight, weight change, liquid consumption, and muscle mass were recorded. Two-way ANOVA evaluated the effects of age, treatment, and their interaction. **Results:** Liquid consumption trended higher in alcohol-exposed groups without reaching significance (treatment $P = 0.076$). Acute alcohol exposure did not significantly alter absolute force, specific force, or soleus muscle mass in young or old mice (treatment $P > 0.05$ for all contractile parameters; soleus weight: age $P = 0.405$, treatment $P = 0.733$). Age significantly affected body weight ($P < 0.05$) and was associated with a treatment-related weight change (treatment $P \leq 0.05$). Force-frequency curves were visually comparable between vehicle and alcohol groups in both age cohorts. **Conclusion:** This study establishes a reproducible preclinical methodology for in vitro assessment of skeletal muscle contractile function in mice that can be incorporated into translational studies of sarcopenia in the SLD spectrum. Despite mitochondrial and vascular dysfunction in the same model, absence of measurable contractile impairment suggests potential dissociation between subcellular and functional endpoints at acute exposure setting. This platform provides a foundation for future investigation of more clinically relevant models incorporating combined alcohol and metabolic burden, sustained exposure, and liver-muscle cross-talk.

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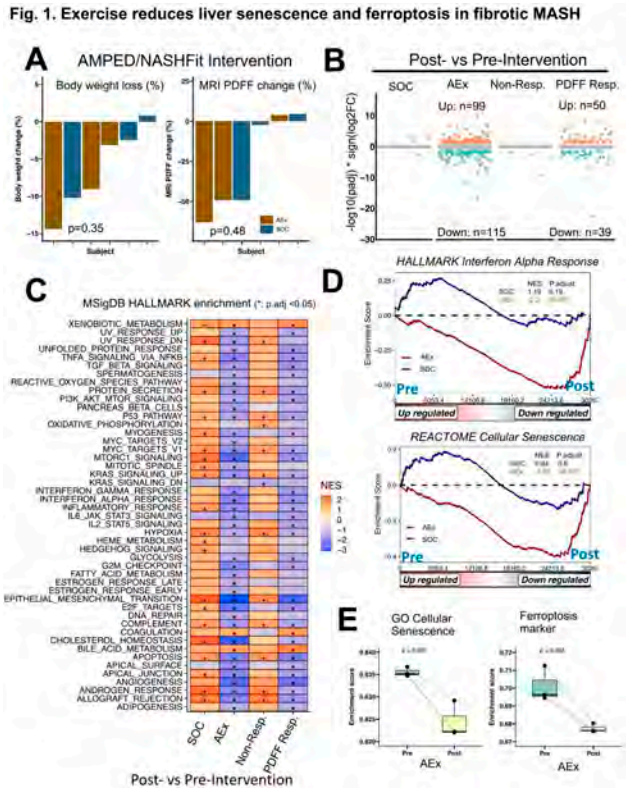
Disclosures: Alexander Kusnik:Nothing to Disclose, Hwi Young Kim:Nothing to Disclose, Fedja Rochling: Nothing to Disclose, Gwenael Layec:Nothing to Disclose, Dongwoo Hahn:Nothing to Disclose.

1371 | EXERCISE-ASSOCIATED HEPATIC TRANSCRIPTOMIC REMODELING OCCURS INDEPENDENT OF LIVER FAT REDUCTION

Hannah Mohr[1] Liuyang Wang[2] Rajesh Dutta[3] Kuo Du[4] Anna Mae Diehl[5] Rajesh Dutta[3] Jonathan Stine[1], [1]Penn State College of Medicine, [2]Department of Molecular Genetics and Microbiology, Duke University; Durham, NC, USA, [3]Division of Gastroenterology & Hepatology, Duke University, Durham NC, USA, [4]University of Kansas Medical Center, [5]Duke University

Background: Aerobic exercise (AEx) is a foundational component of management for MASH, yet the hepatic molecular pathways mediating benefit remain poorly defined. To better characterize exercise-associated hepatic biology, we conducted an exploratory sub-study to assess whether AEx is associated with transcriptomic changes important to MASH and fibrogenesis. **Methods:** A total of 30 patients with fibrotic MASH were randomized to 16 weeks of supervised AEx or standard of care (SOC) (Fig 1A). RNA sequencing was performed on pre- and post-treatment liver biopsies in a subset [AEx n = 3, SOC n = 3]. Differential gene expression was evaluated pre- and post-intervention using a paired intent-to-treat framework comparing AEx versus SOC. Pathway enrichment analyses focused *a priori* on signatures previously associated with MASH severity, including aging-related pathways, cellular senescence, and ferroptosis. **Results:** AEx was associated with a greater number of differentially expressed genes (DEGs) than SOC (214 vs 4 DEGs) (Fig. 1B). In exercisers, post-intervention liver transcriptomes demonstrated consistent down-regulation of pathways previously correlated with fibrosis severity, including GO cellular senescence (NES = -1.85, p < 0.0001), MSigDB interferon alpha response (NES = -2.2, p = 0.025), and ferroptosis marker signature (p = 0.032) (Figs. 1C-E). Exercise was also associated with up-regulation of multiple metallothionein (MT) genes involved in intracellular metal handling and redox homeostasis, and down-regulation of targets MTs are known to suppress, including collagen (data not shown). These transcriptomic changes were not consistently associated with reductions in MRI-PDFF, as the latter occurred in one SOC subject and two AEx subjects (Fig. 1A). Transcriptomic profiles of MRI-PDFF responders demonstrated partial convergence across intervention groups (Fig. 1C), consistent with biologic heterogeneity of treatment response with AEx. In addition, transcriptomic changes were not associated with significant weight loss (Fig. 1A); two AEx subjects and one SOC subject reached the clinically significant threshold of ≥7% total body weight loss. **Conclusion:** In this exploratory sub-study, AEx was associated with favorable hepatic transcriptomic remodeling involving pathways related to biological aging, senescence, ferroptosis, and fibrogenesis, effects not captured by liver fat reduction alone. Notably, these molecular changes were observed despite no significant differences in body weight loss or MRI-PDFF change between SOC and AEx, suggesting that the effects of AEx on hepatic fibrogenic biology may be at least partly independent of weight loss. These findings support a role for exercise in modifying molecular pathways relevant to MASH progression and emphasize the importance of integrative, mechanism-informed endpoints when evaluating lifestyle-based interventions.

Fig. 1. Exercise reduces liver senescence and ferroptosis in fibrotic MASH



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1372 | HARNESSING ENDOGENOUS LIVER REGENERATION FOR MULTIDIMENSIONAL MASH REGRESSION

Tianliang Sun[1] Yizhou Dong[2] Huiping Zhou[3] Federico Di Tullio[4] Sue Yang[2] Lida Yang[5] Bruno Cogliati[2] Shamsa Roshan[2] Kaiyuan Guo[2] Abigail Glezer[2] Lilian Li[2] Marina Barcena-Varela[2] Emily Bramel[2] Anthony Lozano[2] Siddarth Vinod Kumar[2] Lianyong Su[3] Derrick Zhao[3] fanglin ma[2] Jonathan Conrad[2] Amaia Lujambio[2] Sai Ma[2], [1]Icahn School of Medicine at Mount Sanai, [2]Icahn School of Medicine at Mount Sinai, [3]Virginia Commonwealth University, [4]Sanford Burnham Prebys, [5]Icahn School of Medicine at Mount S

Background: Metabolic dysfunction-associated steatohepatitis (MASH) remains a leading cause of cirrhosis, hepatocellular carcinoma (HCC), and liver-related mortality, with limited therapies capable of reversing established disease. In physiologic acute liver injury, tightly regulated activation of WNT/β-catenin signaling orchestrates regenerative repair, metabolic adaptation, and restoration of tissue architecture. We hypothesized that controlled transient reactivation of this endogenous regenerative program in chronic MASH could drive coordinated multidimensional disease regression, offering a regenerative therapeutic strategy grounded in native liver biology. **Methods:** MASH was induced in murine models of fibrosis and tumorigenesis, followed by hepatocyte-specific modulation of ZNRF3/RNF43 using genetic deletion and therapeutic lipid nanoparticle (LNP)-siRNA approaches. Phenotypic regression was assessed by histologic, biochemical, transcriptomic, and immunologic analyses, including evaluation of steatosis, inflammation, fibrosis, bile acid metabolism, regenerative activation, immune remodeling, and tumor safety. **Results:** Hepatocyte-specific activation of the ZNRF3/RNF43-WNT/β-catenin regenerative axis induced rapid and multidimensional regression of established MASH. Regression was characterized by early and active immune remodeling, including marked reshaping of hepatic immune populations preceding structural fibrosis improvement, supporting an active tissue reprogramming process rather than passive disease resolution. Steatosis regression occurred independently and substantially earlier than fibrosis reversal, indicating mechanistically separable therapeutic trajectories. Mechanistically, lipid detoxification was associated with activation of alternative bile acid synthesis pathways, including CYP27A1/CYP7B1-dependent metabolic rewiring, facilitating hepatocellular lipid clearance. Importantly, transient therapeutic pathway engagement using LNP-siRNA provided proof-of-concept feasibility for translational intervention while maintaining a favorable safety profile without evidence of accelerated tumorigenesis under tested conditions. **Conclusion:** Controlled activation of endogenous liver regenerative programs induces coordinated metabolic, immune, and structural remodeling to reverse established MASH. These findings identify transient ZNRF3/RNF43 pathway modulation as a potentially safe and efficient regenerative therapeutic strategy, establishing a framework for multidimensional disease reversal rather than single-axis disease suppression.

Disclosures: Tianliang Sun:Nothing to Disclose, Yizhou Dong:Nothing to Disclose, Huiping Zhou:Nothing to Disclose, Federico Di Tullio:Nothing to Disclose, Sue Yang:Nothing to Disclose, Lida Yang:Nothing to Disclose, Bruno Cogliati:Nothing to Disclose, Shamsa Roshan:Nothing to Disclose, Kaiyuan Guo:Nothing to Disclose, Abigail Glezer:Nothing to Disclose, Lilian Li: Nothing to Disclose, Marina Barcena-Varela:Nothing to Disclose, Emily Bramel:Nothing to Disclose, Anthony Lozano:Nothing to Disclose, Siddarth Vinod Kumar: Nothing to Disclose, Lianyong Su:Nothing to Disclose, Derrick Zhao:Nothing to Disclose, fanglin ma:Nothing to Disclose, Jonathan Conrad:Nothing to Disclose, Amaia Lujambio:Nothing to Disclose, Sai Ma:Nothing to Disclose.

1373 | AGING ACCELERATES METABOLIC AND ALCOHOL-ASSOCIATED LIVER DISEASE (METALD), LIVER FIBROSIS AND TUMOR DEVELOPMENT WITH INCREASED FRAILTY AND MORTALITY

Marti Ortega-Ribera[1] Alejandro Hionides-Gutierrez[1] Marcelle Ribeiro[2] Prashanth Thevkar Nagesh[3] Soham Sudhakaran[1] Bruna Santos[1] Scott Minchenberg[2] Allyson Flavin[1] Siddharth Ghosh Roy[1] Gyongyi Szabo[2], [1]BIDMC - Harvard Medical School, [2]Beth Israel Deaconess Medical Center, [3]Beth Israel Medical Center

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Background: MetALD defines patients with metabolic dysfunction-associated steatotic liver disease with simultaneous alcohol misuse. Both alcohol and metabolic syndrome are recognized as risk factors for hepatocellular cancer. With the increase in life expectancy and the rising prevalence in obesity, alcohol misuse and liver cancer, there is an unmet need for understanding MetALD pathophysiology in the context of aging using relevant preclinical models. **Methods:** Young (2 month) and aged (19 month) C57BL/6N mice (♀ & ♂) were fed with chow diet or high fat diet containing 10gm% cholesterol, 208g/Kg sucrose and 30.8g/Kg fructose (hereinafter MASH diet) for 12 weeks. A subgroup of the mice receiving MASH diet also received weekly alcohol binges (2.5g/Kg) plus 5% alcohol in the drinking water to mimic MetALD pathophysiology. At week 11, mice were scored for frailty and at week 12, tissues were harvested for analysis. **Results:** Young mice had a higher body weight gain compared to their diet-matched aged groups. However, aged mice on MASH diet exceeded chow-fed aged mice in final body weight. Importantly, alcohol consumption was not different between both MetALD groups.Aged MetALD mice showed the greatest liver dysfunction, as evidenced by: 1) elevated ALT levels, compared to young MetALD, aged chow and aged MASH groups, 2) decreased circulating albumin levels, 3) increased expression of fibrotic markers including *Col1a1*, *Tgfb1* mRNA levels and alpha smooth muscle actin protein levels compared to young MetALD group and 4) increased spleen-to-body weight ratio compared with young MetALD & aged MASH groups.Liver tumors were more frequent in aged MetALD mice (31%) followed by aged MASH (6%) and aged chow (11%) while none of the young animals showed tumor burden. The increase in the frequency of liver tumors in the aged MetALD group correlated with the upregulation of malignancy/proliferation markers including *cMyc, Ki67* and protein levels of PCNA. Aged MetALD mice also showed increased expression of epithelial-to-mesenchymal transition markers such as *Snai1* & *Vimentin* and higher levels of cancer stem cell markers including *Cd133* & *Epcam*. MetALD regime in aged mice resulted in decreased % of lean mass and increased % of fat mass compared to aged chow or young MetALD mice in EchoMRI analysis. Finally, age and MetALD diet increased frailty scores in both young and aged groups, with aged MetALD mice exhibiting significantly higher score than young MetALD mice. Consequently, aged MetALD mice exhibited the highest mortality (45%) followed by young MetALD and aged MASH groups (10% and 5% respectively) while all other groups had a 100% survival. **Conclusion:** Our preclinical model reveals that MetALD, is accelerated in aging with exacerbated liver damage, fibrosis and increased activation of tumorigenic pathways in the liver. The combination of age and MetALD also interact to reduce lean mass and increase fat mass, overall leading to higher frailty and mortality.

Disclosures: Marti Ortega-Ribera:Nothing to Disclose, Alejandro Hionides-Gutierrez:Nothing to Disclose, Marcelle Ribeiro:Nothing to Disclose, Prashanth Thevkar Nagesh:Nothing to Disclose, Soham Sudhakaran:Nothing to Disclose, Bruna Santos:Nothing to Disclose, Scott Minchenberg:Nothing to Disclose, Allyson Flavin: Nothing to Disclose, Siddharth Ghosh Roy:Nothing to Disclose, Gyongyi Szabo:CYTA Therapeutics: Consultant, Durect Corporation: Consultant, Pandion Therapeutics: Consultant, Pfizer: Consultant, Surrozen: Advisor, Evive: Advisor, Glympse Bio, Inc (acquired by Sunbird Bio): Advisor, Satellite Biosciences: Advisor, Zomagen Bioscience/Ventyx Biosciences: Consultant, Springer Nature Group: Royalties or patent beneficiary, UpToDate Inc: Royalties or patent beneficiary, Boehiringer Ingelheim: Honoraria, Intercept: Contract, NIAAA-NIA: Grant/Research Support, Novo Nordisk: Honoraria, Yale University School of Medicine: Consultant, Resolution Therapeutics: Consultant, US Patent No. 20110293: Intellectual Property.

1374 | MACROPHAGE-DERIVED ITACONATE AMELIORATES MASH VIA NRF2-MEDIATED FERROPTOSIS INHIBITION

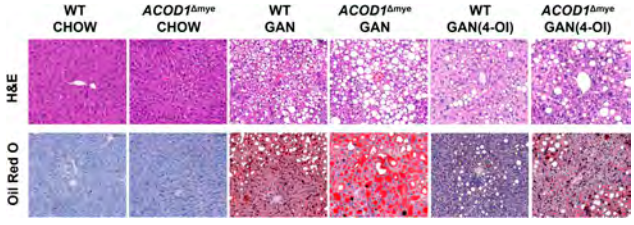
Shaoya Li[1] Qianqian Zheng[1] Jiawei Cui[1] Zhandong Lin[1] Yikang Song[1] Yue Shi[2] Yukai Chen[1] Congyue Zhang[1] Yaoyao Mao[1] Xiangxin Qin[1] Chao Sun[3] Yuemin Nan[1], [1]Hebei Medical University Third Hospital, [2]Hebei Medical University, [3]the First Affiliated Hospital of Xi'an Medical University

Background: Metabolic dysfunction–associated steatohepatitis (MASH), the progressive inflammatory and fibrotic subtype of metabolic dysfunction-associated steatotic liver disease (MASLD), lacks approved pharmacotherapy. Ferroptosis, an iron-dependent lipid peroxidation-driven cell death, critically drives MASH progression. Itaconate, an endogenous immunometabolite with anti-inflammatory and antioxidant properties, has emerged as a key regulator of oxidative stress; however, its role in ferroptosis-mediated MASH remains unclear. **Methods:** Wild-type (WT) and myeloid-specific ACOD1-knockout (KO) mice were fed a high-fat, high-sugar, high-cholesterol (GAN) diet for 21 weeks to establish a robust MASH model, with or without 4-octyl itaconate (4-OI) intervention. AML-12 hepatocytes were exposed to free fatty acids (FFA) to induce steatohepatitis in vitro. Hepatic steatosis, inflammation, fibrosis, oxidative stress, mitochondrial function, and ferroptosis were systematically evaluated. **Results:** Myeloid ACOD1-KO mice exhibited exacerbated hepatic steatosis, inflammation, and fibrosis,

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accompanied by elevated malondialdehyde (MDA), reduced glutathione (GSH), and impaired mitochondrial respiration. Ferroptosis markers (downregulated GPX4, upregulated ACSL) were significantly increased, while Nrf2/HO-1 signaling was markedly suppressed in KO mice. 4-OI administration dose-dependently reduced hepatic triglycerides, inflammatory cytokines, and lipid peroxidation, restored mitochondrial membrane potential, and inhibited ferroptosis in WT mice. In FFA-treated AML-12 cells, 4-OI attenuated lipid accumulation, pro-inflammatory gene expression, and ferroptosis; Nrf2 silencing abrogated these protective effects. **Conclusion:** Itaconate confers hepatoprotection in MASH by activating Nrf2-dependent antioxidant signaling and suppressing ferroptosis, highlighting itaconate as a promising therapeutic target for MASH/MASLD.



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1375 | BOVINE MILK-DERIVED EXTRACELLULAR VESICLES AMELIORATE STEATOHEPATITIS AND HEPATIC FIBROSIS THROUGH RESTORATION OF INTESTINAL BARRIER FUNCTION IN A MURINE MASH MODEL

Shinya Sato[1] Kosuke Kaji[1] Tadashi Namisaki[1] Hitoshi Yoshiji[1], [1]Nara Medical University

Background: Disruption of the gut-liver axis plays a critical role in the progression of metabolic dysfunction-associated steatohepatitis (MASH). Increased intestinal permeability promotes portal endotoxemia and hepatic inflammatory signaling, accelerating liver fibrosis. Bovine milk-derived extracellular vesicles (B-mEVs) contain bioactive microRNAs and have emerged as modulators of intestinal homeostasis. However, their effects on gut barrier dysfunction and liver fibrosis in MASH remain unclear. We investigated whether orally administered B-mEVs attenuate MASH progression through modulation of the gut-liver axis. **Methods:** MASH was induced in mice using a choline-deficient, L-amino acid-defined high-fat diet (CDA-HFD) for 8 weeks. Mice received oral administration of vehicle or B-mEVs. Hepatic injury, steatosis, and fibrosis were assessed by serum biochemistry, histology, hydroxyproline quantification, and fibrogenic gene expression. Intestinal barrier function was evaluated by FITC-dextran permeability assay and tight junction protein expression analyses. Portal lipopolysaccharide (LPS) levels and hepatic inflammatory signaling were examined. In vitro studies were performed using palmitic acid-treated Caco-2 cells. Fecal microbiota was analyzed by 16S rRNA sequencing, and small RNA sequencing of B-mEVs was performed. **Results:** B-mEV administration attenuated CDA-HFD-induced steatohepatitis, as demonstrated by reduced serum AST/ALT levels, hepatic lipid accumulation, and NAFLD activity scores. B-mEVs also suppressed hepatic fibrosis, accompanied by reductions in Sirius Red-positive areas, hepatic hydroxyproline content, and expression of fibrogenic markers, including Acta2, Col1a1, and Tgfb1.B-mEV treatment restored intestinal barrier integrity, evidenced by increased expression of tight junction proteins (ZO-1, Occludin, and Claudin-1) and reduced intestinal permeability. Portal LPS levels were decreased in B-mEV-treated mice, together with suppression of hepatic TLR4/NF-κB signaling and inflammatory cytokine expression. In Caco-2 cells, B-mEVs prevented palmitic acid-induced barrier dysfunction and MLCK upregulation.Microbiome analysis revealed partial restoration of gut dysbiosis without major shifts in microbial composition. Small RNA sequencing demonstrated that B-mEVs contained abundant miRNAs associated with epithelial barrier regulation and inflammatory signaling pathways. **Conclusion:** Orally administered B-mEVs attenuated steatohepatitis and hepatic fibrosis in CDA-HFD-fed mice by restoring intestinal barrier function and suppressing gut-derived endotoxin signaling. These findings identify milk-derived extracellular vesicles as a gut-liver axis-targeted therapeutic strategy for MASH.

Disclosures: Shinya Sato:Nothing to Disclose, KOSUKE KAJI:Nothing to Disclose, Tadashi Namisaki:Nothing to Disclose, Hitoshi Yoshiji:Nothing to Disclose.

1376 | EFFECTS OF A MASH-INDUCING DIET ON INTESTINAL IMMUNITY AND COLORECTAL CANCER DEVELOPMENT

Hiroki Nomura[1] Akihiro Seki[1] Kouki Nio[1] Tetsuro Shimakami[1] Masao Honda[2] Taro Yamashita[1], [1]Kanazawa University, [2]Kanazawa University Graduate School of Medical Science

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Background: Colorectal cancer (CRC) and metabolic dysfunction-associated steatohepatitis (MASH) have been increasing worldwide in association with changes in dietary habits and lifestyle. Epidemiological studies have suggested that MASH is a risk factor for CRC. Although gut-derived metabolites are known to affect the liver, the influence of liver-derived metabolic alterations on intestinal immunity remains unclear. In this study, we investigated the effects of a MASH-inducing diet on colorectal tumor progression and intestinal immune responses. **Methods:** MASH model mice were generated by feeding a high-fat atherogenic diet. Murine colorectal cancer cells were orthotopically transplanted into the intestine, and tumor size and weight were evaluated. Mice fed a normal diet served as controls. Immune dynamics in intestinal and tumor tissues were analyzed by immunohistochemistry (IHC) and flow cytometry (FCM). Gene expression profiling of intestinal tissues was performed using DNA microarray analysis. In addition, fecal samples were collected longitudinally and analyzed by LC/MS-based metabolomics. **Results:** CRC tumors in MASH mice showed significantly greater maximum tumor diameter compared with controls (22.3 mm vs. 13.3 mm, $p = 0.037$). IHC demonstrated increased infiltration of CD8-positive cells in both intestinal and liver tissues during the course of high-fat atherogenic diet feeding. At 8 weeks, the number of CD8-positive cells in the intestine was significantly higher in MASH mice than in controls (16.0 vs. 1.33 cells/field, $p < 0.005$).FCM analysis revealed an increased proportion of effector memory T cells (emT) among intestinal CD8-positive T cells in MASH mice compared with controls (22.3% vs. 13.7%). PD-1 expression in intestinal CD8-positive emT cells also tended to increase (7.91% vs. 3.87%). In tumor tissues, both the proportion of CD8-positive T cells and CD8-positive emT cells were significantly increased in MASH mice (19.2% vs. 4.6% and 39.9% vs. 9.6%, respectively; both $p < 0.005$). PD-1 expression in tumor-infiltrating CD8-positive emT cells also showed an increasing trend in MASH mice (98.8% vs. 94.6%). Metabolomic analysis demonstrated reductions in taurine-conjugated bile acids, primary bile acids, secondary bile acids, and prostaglandins in feces from MASH mice. Gene expression analysis of intestinal tissues revealed downregulation of genes involved in bile acid and peptide transport, including Slc10a2 and Slc15a1. **Conclusion:** A MASH-inducing diet altered intestinal immune dynamics and promoted colorectal tumor progression. Changes in liver-related metabolic pathways, particularly bile acid metabolism, may contribute to a novel liver-gut axis involved in the colorectal tumor microenvironment.

Disclosures: HIROKI NOMURA:Nothing to Disclose, Akihiro Seki:Nothing to Disclose, Kouki Nio:Nothing to Disclose, Tetsuro Shimakami:Nothing to Disclose, Masao Honda:Nothing to Disclose, Taro Yamashita: Nothing to Disclose.

1377 | EXTRACELLULAR ATP (EATP) AND INFLAMMASOME-RELATED PATHWAYS IN THE PROGRESSION OF METABOLIC DYSFUNCTION–ASSOCIATED STEATOTIC LIVER DISEASE (MASLD)

Vanessa Garcia-Fernandez[1] Antonio Gil-Gómez[2] Rocío Muñoz Hernández[3] Sheila Gato-Zambrano[1] Rocio Aller[4] Angela Rojas[1] David Martí[5] Juan Manuel Pericas[6] Paloma Carrillo-Fernández[2] Carola Zurita[2] Isabel Fernandez[2] Rocio Gallego-Duran[7] Douglas Maya-Miles[2] Javier Ampuero[1] Manuel Romero Gómez[1], [1]SeLiver Group. Instituto de Biomedicina de Sevilla (IBiS), Hospital Universitario Virgen del Rocí, [2]SeLiver Group. Instituto de Biomedicina de Sevilla (IBiS), Hospital Universitario Virgen del Rocío, [3]Centro de Investigación Biomédica en Red, [4]Hospital Clinico Universitario de Valladolid, Valladolid, Spain,, [5]Digestive Disease Department, Clinic University Hospital, INCLIVA Health Research Institute, Vale, [6]Vall d'Hebron Institut de Recerca, Vall d'Hebron Barcelona Campus Hospitalari, Barcelona, Spain, [7]Ibis-Biomedicine Institute of Sevilla

Background: Extracellular ATP (eATP) is a damage-associated molecular pattern that promotes inflammation, leading to immune cell recruitment and cytokine release. Ectonucleoside Triphosphate Diphosphohydrolase 1 (ENTPD1) metabolizes eATP, reducing ATP levels and limiting inflammatory signaling. The purinergic receptor P2X7 (P2RX7) is activated by eATP and stimulates the NLR family pyrin domain containing 3 (NLRP3)/interleukin-1b pathway, amplifying liver inflammation. The aim of this study was to determine the role of eATP and the NLRP3 pathway in the progression of MASLD. **Methods:** The study was performed in 20 male C57BL/6J mice fed a High Fat High Carbohydrate and Cholesterol (HFHCC) ($n = 10$) or chow diet ($n = 10$). *Entpd1, P2rx7, Panx1 and Nlrp3* genes and Entpd1 and P2rx7 protein levels were assessed by PCR, IHC and Jess automated Western Blot. In addition, 654 patients were classified according to SAF and NAS Score and P2RX7-rs1718119 was analyzed. Serum ENTPD1 was measured in 170 patients. **Results:** Entpd1 was increased in HFHCC fed mice (fold change 1 ± 0.83 vs 1.97 ± 0.75; $p = 0.0005$). *P2rx7* (1 ± 0.62 vs 2.24 ± 0.58; $p < 0.0001$) and *Nlrp3* (1 ± 0.41 vs 2.28 ± 0.71; $p < 0.0001$) were also upregulated. *Panx1* expression was decreased (fold change 1 ± 0.53 vs 0.32 ± 0.14; $p = 0.0012$).In control mice, Entpd1 protein localized mainly around the central vein whereas in HFHCC fed

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mice, it shifted towards the portal vein area. P2rx7 positive cells/area were higher in HFHCC fed mice (272.4 ± 79.8 *vs.* 391.8 ± 121.8; p = 0.0035).Jess automated Western Blot showed two Entpd1 bands: a 125kDa glycosylated, active form and a 36kDa non-glycosylated, inactive form. In HFHCC mice, the glycosylated Entpd1 form represented 16.8% ± 2.6 of total protein compared with 13.4% ± 1.8 in controls(p = 0.0077). Patients with MASH (1588 ± 1750pg/ml) had higher ENTPD1 levels than those with SS (1136 ± 808pg/ml, p = 0.03). ENTPD1 levels increased with inflammatory activity [none (n = 23), 1477 ± 1131pg/ml; mild (n = 99), 1113 ± 890pg/ml; moderate (n = 48), 1925 ± 2163pg/ml; p = 0.005], with significant difference between mild and moderate inflammation group (p = 0.015). ENTPD1 levels were not significantly associated with ballooning or fibrosis. In a multivariate analysis, adjusted for sex, age, diabetes mellitus, and Body Mass Index, P2RX7 rs1718119 polymorphism was significantly associated with presence of inflammation (n = 654; OR:0.50; IC 95%: 0.27-0.93; p = 0,028) and significant fibrosis (n = 654; OR = 0.58; IC 95%: 0.37-0.89; p = 0,013). **Conclusion:** To conclude, eATP-related pathways are implicated in MASLD progression. Upregulation of Entpd1, P2rx7, and Nlrp3, together with increased Entpd1 and P2rx7 protein levels, supports their role in inflammation-driven disease. Serum ENTPD1 reflects inflammatory activity and P2RX7 rs1718119 is independently associated with inflammation and significant fibrosis, highlighting the purinergic pathway as a potential therapeutic target in MASLD.

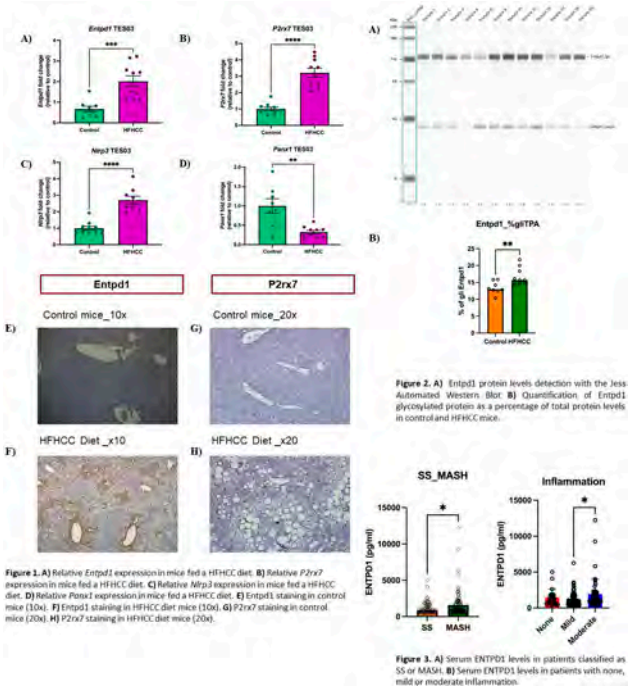


Figure 1. A) Relative *Entpd1* expression in mice fed a HFHCC diet. B) Relative *P2rx7* expression in mice fed a HFHCC diet. C) Relative *Nlrp3* expression in mice fed a HFHCC diet. D) Relative *Pxna1* expression in mice fed a HFHCC diet. E) Entpd1 staining in control mice (10x). F) Entpd1 staining in HFHCC diet mice (10x). G) P2rx7 staining in control mice (20x). H) P2rx7 staining in HFHCC diet mice (20x).

Figure 2. A) Entpd1 protein levels detection with the Jess Automated Western Blot B) Quantification of Entpd1 glycosylated protein as a percentage of total protein levels in control and HFHCC mice.

Figure 3. A) Serum ENTPD1 levels in patients classified as SS or MASH. B) Serum ENTPD1 levels in patients with none, mild or moderate inflammation.

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★ 1378 | PROBING METABOLIC-DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) INDUCED STRUCTURE-FUNCTION CHANGES IN HEPATIC ER-MITOCHONDRIA CONTACTS WITH A FOCUS ON INOSITOL-1,4,5-TRISPHOSPHATE (IP3) RECEPTORS

Arijita Ghosh[1] Prottoy Hasan[1] Marite Castromonte[1] Raghavendra Singh[1] Piyush Mishra[1] Rebecca Thomas[1] Gyorgy Hajnoczky[1], [1]Thomas Jefferson university

Background: MASLD is a widespread chronic liver disease affecting a third of the global population, with limited therapeutic cure demanding better comprehension and detection of early onset of identifiable biomarkers. Closely apposed membrane regions of ER and mitochondria, termed as ER-mitochondria contacts (ERMCs) participate in locally conveying Ca^{2+} signals, lipid exchange, ROS regulation among other essential functions governing cell metabolism. The key player mediating release of Ca^{2+} from ER is the inositol 1,4,5 trisphosphate receptor (IP3R). Dysregulated ER Ca^{2+} handling, IP3R linked Ca^{2+} transfer and mitochondrial dysfunction have been implicated in MASLD, but the mechanistic details are obscure. It is known from previous work that IP3R2 is the predominant IP3R isoform along with the other relevant isoform being IP3R1 in hepatocytes with no detectable IP3R3. IP3R2 has been reported to be the most effective in ER-mitochondria Ca^{2+} transfer in specific cell lines, by our group. IP3R isoform-specific impact on ERMCs and its relevance in MASLD is currently missing in literature. Our hypothesis is that IP3R contributes to ERMC structure-function in MASLD progression. **Methods:** In this work we studied the structure of ERMCs in MASLD in genetic models of control and IP3R knockdown (KD) mice. MASLD was induced with 60% High-fat choline-deficient diet (HFD) for 3- and 7-weeks mimicking inflammation and more severe steatohepatitis (MASH) in the form of fibrosis respectively. **Results:** Efficacy of the diet was validated with histological and biochemical marker measurements showing increased lipid droplet accumulation and higher triglyceride (TG) levels. The

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IP3R triple knockdown (TKD), IP3R1 knockdown (R1KD) and IP3R2 knockdown (IP3R2KD) were validated at the level of expression and Ca^{2+} specific function with fluorometric measurements and imaging studies in hepatocytes derived from control and KD mice which together showed time-dependent abolition of IP3R expression and function. Electron microscopic (EM) analysis showed less tight contacts between ER and mitochondria in absence of IP3R in hepatocytes 0, 3 and 7 weeks of HFD. The HFD treatment induced an increase in tight contacts at 3- vs 7-weeks in mice liver tissue in majority of genotypic groups. The absence of IP3R2 prevented the increase in tight contacts, whereas IP3R1 deletion had no effect at 3-weeks of HFD. **Conclusion:** MASLD specific HFD induced structural reorganization of hepatic ERMCs. IP3R contribute to ERMC structure stabilization in control and MASLD liver. IP3R2 has an isoform specific leverage on MASLD induced liver. The functional relevance of IP3R isoforms and specific impact on ERMCs are being probed currently using multi omics and live cell imaging approaches.

Disclosures: Arijita Ghosh:Nothing to Disclose, Prottoy Hasan:Nothing to Disclose, Marite Castromonte: Nothing to Disclose, Raghavendra Singh:Nothing to Disclose, piyush mishra:Nothing to Disclose, Rebecca Thomas:Nothing to Disclose, Gyorgy Hajnoczky:Nothing to Disclose.

1380 | CYTOSOLIC MITOCHONDRIAL RNA SIGNALING AS A DRIVER INFLAMMATION IN SENESCENCE AND MASH

Stella Victorelli[1], [1]Mayo Clinic

Background: Senescent cells contribute to age-related tissue dysfunction in part through induction of a chronic senescence-associated secretory phenotype (SASP). We have previously shown that mitochondria are key regulators of the SASP, suggesting that mitochondrial pathways may represent therapeutic targets to reduce senescence-driven inflammation in aging and age-related diseases. Mitochondrial double-stranded RNA (mtdsRNA), when released into the cytosol, is highly immunogenic and can trigger inflammatory signaling. Here, we investigated whether cytosolic mtdsRNA contributes to SASP induction in senescent cells and whether this pathway is activated in metabolic dysfunction-associated steatohepatitis (MASH), a disease associated with increased senescent cell burden. **Methods:** Senescent human fibroblasts and AML12 hepatocytes were used to assess cytosolic mitochondrial dsRNA accumulation, activation of RNA-sensing pathways, and SASP induction. To define the contribution of cytosolic RNA sensing to the SASP, RIG-I, MDA5, and MAVS were genetically manipulated. To determine whether mitochondrial outer membrane permeabilization contributes to mtdsRNA leakage, CRISPR-Cas9-mediated deletion of BAX and BAK was performed in senescent cells. In vivo, cytosolic RNA signaling was examined in a diet-induced model of MASH, and the impact of hepatocyte-specific BAX/BAK deletion was assessed by measuring hepatic RNA sensor expression, senescence markers, inflammation, immune infiltration, and fibrosis-associated endpoints. **Results:** Senescent cells exhibited increased levels of cytosolic mtdsRNA, which activated the RNA sensors RIG-I and MDA5 and promoted MAVS aggregation, leading to SASP induction. Inhibition of RIG-I and MDA5 significantly reduced the expression of SASP factors. Deletion of BAX and BAK, which regulate mitochondrial outer membrane permeability, suppressed mtdsRNA leakage and attenuated the SASP. In diet-induced MASH, a condition characterized by increased senescent cell burden, cytosolic RNA signaling was upregulated in the liver. Hepatocyte-specific deletion of BAX and BAK significantly reduced hepatic expression of RNA sensors, decreased expression of the senescence marker p21, diminished MASH-associated inflammation and immune infiltration, and improved markers of liver fibrosis. **Conclusion:** These findings identify cytosolic mtdsRNA as a major contributor to SASP induction in senescent cells and suggest that BAX/BAK-dependent mitochondrial RNA leakage promotes inflammatory signaling in MASH. Together, our results provide proof-of-concept evidence that targeting mechanisms involved in cytosolic mtdsRNA release may represent a novel therapeutic strategy to reduce senescence-associated inflammation and liver injury in MASH.

Disclosures: Stella Victorelli:Nothing to Disclose.

1381 | SEMAGLUTIDE REVERSES CLINICALLY RELEVANT BIOMARKER ALTERATIONS IN THE BIOPSY-CONFIRMED GAN DIO-MASH MOUSE MODEL

Henrik Hansen[1] Jacob Nøhr-Meldgaard[1] Jenny Norlin[2] Sanne Veidal[2] Kristian Bendtsen[2] Kristoffer Niss[2] Markus Latta[2] Susanne Pors[1] Mathilde Dalhoff[1] Kristoffer Voldum-Clausen[1], [1]Gubra A/S, [2]Novo Nordisk A/S

Background: The long-acting glucagon-like peptide-1 (GLP-1) receptor agonist semaglutide was recently approved as the first GLP-1–based therapy for people with metabolic dysfunction-associated steatohepatitis (MASH) and moderate-to-severe fibrosis. Clinical

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studies show that semaglutide not only improves liver health but also reverses several biomarker alterations characteristic of the disease. In this study, we characterized metabolic, histological, and biomarker responses to semaglutide in the Gubra Amylin NASH (GAN) diet-induced obese, biopsy-confirmed mouse model of MASH, and compared these findings with clinical observations. **Methods:** Male C57BL/6 mice were fed GAN diet, high in fat, fructose and cholesterol for 38 weeks prior to study start. A liver pre-biopsy was collected 4 weeks before treatment start. Only GAN DIO-MASH mice with NAFLD Activity Score (NAS $\geq$ 5) and fibrosis stage F2-F3 were included and stratified into treatment groups. Semaglutide (30 nmol/kg) or vehicle was administered subcutaneously once daily for 12 weeks. Vehicle-dosed, chow-fed mice served as healthy controls. Endpoints included aptamer-based SomaScan plasma proteomics, blood/liver biochemistry, pre-to-post individual assessment of NAS and fibrosis stage, and quantitative histology. **Results:** Semaglutide promoted a weight loss of approx. 21% and improved hepatomegaly, plasma transaminases, plasma and hepatic lipid markers, NAS, and quantitative histological measures of steatosis and inflammation. Semaglutide also reduced fibrogenesis by histomorphometric analysis. Notably, the GAN DIO-MASH mouse model recapitulated key human MASH-associated circulating protein changes, including semaglutide-responsive biomarkers related to metabolism, inflammation, and fibrosis. **Conclusion:** The GAN DIO-MASH mouse model exhibits strong translational relevance across metabolic, histological, and molecular domains, offering a robust platform for advancing mechanistic understanding of semaglutide and supporting the development of next-generation MASH therapies.

Disclosures: Henrik Hansen:Gubra A/S: Employee, Jacob Nøhr-Meldgaard:Nothing to Disclose, Jenny Norlin:Novo Nordisk: Employee, Novo Nordisk: Stock - publicly traded company, Sanne Veidal:Nothing to Disclose, Kristian Bendtsen:Nothing to Disclose, Kristoffer Niss:Nothing to Disclose, Markus Latta:Nothing to Disclose, Susanne Pors:Nothing to Disclose, Mathilde Dalhoff:Nothing to Disclose, Kristoffer Voldum-Clausen:Nothing to Disclose.

1382 | SPT6 REGULATES HEPATIC STELLATE CELL FUNCTION TO PROMOTE LIVER FIBROSIS

Nahid Arghiani[1] Amel Ben Saad[1] Benjamin J Toles[1] Raza Ur Rahman[1] Arden Weilheimer[1] Alan Mullen[2], [1]Division of Gastroenterology, University of Massachusetts Chan Medical School, Worcester, MA, USA, [2]University of Massachusetts Medical School

Background: Chronic liver injury leads to fibrosis, which is characterized by excessive extracellular matrix (ECM) protein deposition. Hepatic stellate cells (HSCs) are the primary cell type responsible for ECM production, and inhibiting their fibrogenic activity has the potential to slow or reverse progression of liver fibrosis and development of end stage liver disease. We previously conducted a small interfering (si) RNA screen in primary human HSCs, which identified SPT6 (Suppressor of Ty Homologue-6, encoded by SUPT6H) as a putative regulator of the fibrogenic phenotype. Although SPT6 is known to function as a histone chaperone, regulating nucleosome remodeling and RNA splicing, its function in HSCs has not been explored. **Methods:** Chronic liver injury leads to fibrosis, which is characterized by excessive extracellular matrix (ECM) protein deposition. Hepatic stellate cells (HSCs) are the primary cell type responsible for ECM production, and inhibiting their fibrogenic activity has the potential to slow or reverse progression of liver fibrosis and development of end stage liver disease. We previously conducted a small interfering (si) RNA screen in primary human HSCs, which identified SPT6 (Suppressor of Ty Homologue-6, encoded by SUPT6H) as a putative regulator of the fibrogenic phenotype. Although SPT6 is known to function as a histone chaperone, regulating nucleosome remodeling and RNA splicing, its function in HSCs has not been explored. **Results:** We find that that SPT6 directly promotes gene expression programs to regulate ECM production, cell adhesion, and cell migration. Furthermore, depletion of SUTP6H reduces collagen and alpha-smooth muscle actin (α-SMA) production and cell migration, while promoting lipid droplet accumulation within HSCs, all phenotypic hallmarks of HSC inactivation. These effects are observed with SUPT6H depletion without reducing HSC viability. Furthermore, SPT6 promotes alternative splicing, providing a path to generate protein isoforms that increase the fibrogenic activity of HSCs. **Conclusion:** We find that that SPT6 directly promotes gene expression programs to regulate ECM production, cell adhesion, and cell migration. Furthermore, depletion of SUTP6H reduces collagen and alpha-smooth muscle actin (α-SMA) production and cell migration, while promoting lipid droplet accumulation within HSCs, all phenotypic hallmarks of HSC inactivation. These effects are observed with SUPT6H depletion without reducing HSC viability. Furthermore, SPT6 promotes alternative splicing, providing a path to generate protein isoforms that increase the fibrogenic activity of HSCs.

Disclosures: Nahid Arghiani:Nothing to Disclose, Amel Ben Saad:Nothing to Disclose, Benjamin J Toles: Nothing to Disclose, Raza Ur Rahman:Nothing to Disclose, Arden Weilheimer:Nothing to Disclose, Alan Mullen:Nothing to Disclose.

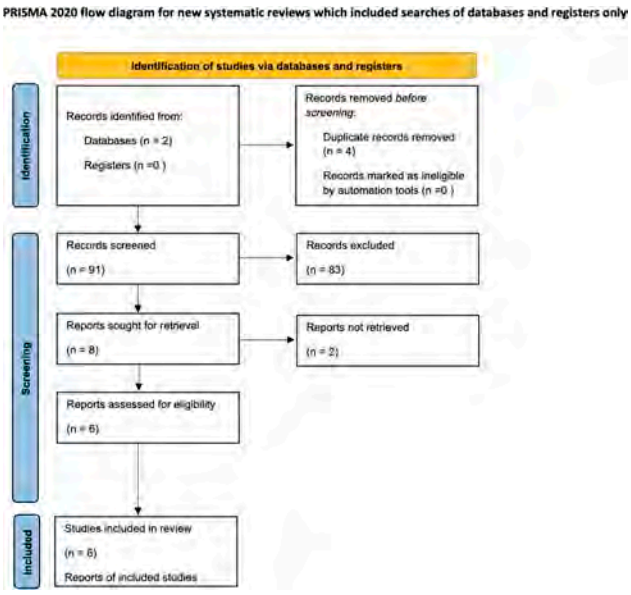
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1383 | LEAN MAFLD IS NOT BENIGN: A SYSTEMATIC REVIEW OF LONG-TERM OUTCOMES

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Background: Metabolic dysfunction-associated fatty liver disease (MAFLD) is increasingly identified in non-obese individuals but is still often presumed benign. Data on long-term cardiovascular and mortality outcomes in lean MAFLD are sparse, leaving its prognostic significance unclear. **Methods:** Following PRISMA 2020, we searched PubMed and the Cochrane Library from January 2016 to May 2026. We included studies of adults 18 years or older with lean MAFLD /MASLD (Metabolic dysfunction-Associated Steatotic Liver Disease) /NAFLD (Non-Alcoholic Fatty Liver Diseas) with a BMI < 25 kg/m2, or < 23 kg/m2 in Asians reporting at least one long-term outcome (fibrosis progression, cardiovascular events, hepatic decompensation, or all cause mortality) over a minimum 12 month follow-up. Cohorts, case-control studies, RCTs, and meta-analyses were eligible; pediatric populations, competing liver disease, and biochemical-only outcomes were excluded. Bias was assessed with the Newcastle-Ottawa Scale and Cochrane RoB (Risk of bias) 2.0. Of 91 records screened, 6 studies (398,599 participants) qualified; heterogeneity precluded meta-analysis, and findings were synthesized narratively following SWiM (Synthesis Without Meta-analysis) guidance. **Results:** In a propensity-matched cohort of 135,038 patients followed to 7 years (Al Ta'ani 2026), lean MASLD carried higher risks of new-onset heart failure (HR 1.23, 95%CI 1.16-1.31), composite cardiovascular events (HR 1.21, 1.13-1.30), cerebrovascular events (HR 1.33, 1.24-1.43), and all-cause mortality (HR 1.48, 1.38-1.59; all $p < 0.0001$) versus non-lean MASLD. In NHANES (Zou 2020, n = 14,365), 15-year all-cause mortality was 51.7% in lean versus 27.2% in non-lean NAFLD ($p < 0.001$), reaching 76.3% in lean patients. A Japanese cohort (Yoshitaka 2017, n = 1,647) found a 10.4-fold adjusted hazard for incident cardiovascular disease in lean NAFLD (95%CI 2.61-44.0, $p = 0.001$). In a 6-year RCT (Wong 2018, n = 154), lifestyle intervention achieved NAFLD remission in 67% of lean patients versus 18% of controls ($p < 0.001$), with ALT normalisation sustained at year 6 (46% vs 17%, $p = 0.013$). Across adjusted analyses, fibrosis and diabetes-not BMI-drove prognosis. **Conclusion:** Lean MAFLD is not benign. These patients face cardiovascular and mortality risks matching or exceeding non-lean counterparts yet respond well to lifestyle change. Clinicians should pursue active cardiometabolic risk stratification and early intervention rather than assuming low BMI is protective.



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1384 | NAD+ DEPLETION MEDIATES CHOLESTEROL-INDUCED HEPATOTOXICITY THROUGH SP1 INACTIVATION AND PARP1-AMPK SUPPRESSION

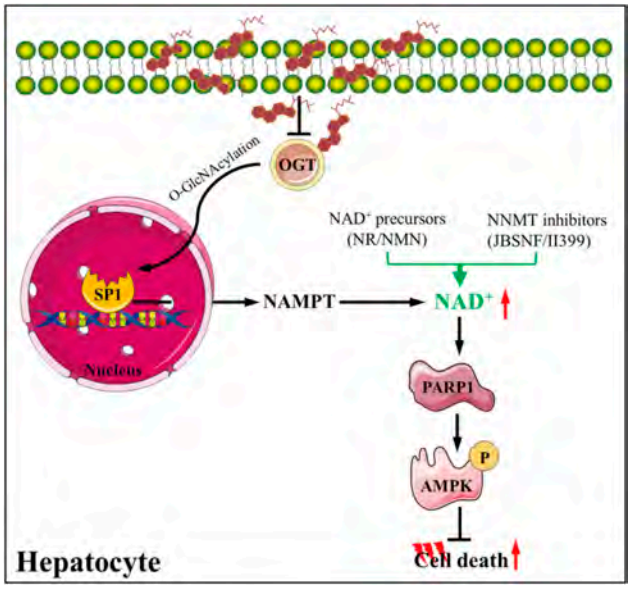
Yanhui Li[1] Zhenyuan Song[1] Rui Guo[1] Izabela Hawro[2] Jose Cordoba Chacon[1], [1]University of Illinois Chicago, [2]University of Illinois at Chicago

Background: Cholesterol accumulation is a key pathogenic feature of metabolic dysfunction-associated steatotic liver disease (MASLD) and alcohol-related liver disease (ALD), yet the mechanisms linking cholesterol overload to hepatocellular injury remain unclear. This study aimed to elucidate how cholesterol perturbs hepatic NAD+ metabolism and contributes to hepatocellular injury. **Methods:** Cholesterol-loading models in hepatocytes and mice were used to assess changes in NAD+ metabolism, PARP1-AMPK signaling, and transcriptional regulation. Pharmacological and genetic approaches were applied to dissect the roles of SP1, OGT, PARP1, and SIRT1 in cholesterol-induced hepatotoxicity. **Results:** Cholesterol overload caused profound hepatic NAD+ depletion by down-regulating NAMPT, a key enzyme for NAD+ biosynthesis, accompanied by reduced PARP1 expression and global protein PARylation. NAD^+ restoration via either precursor supplementation or NNMT inhibition

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and PARG blockade reinstated PARP1 activity, AMPK phosphorylation, and hepatocyte viability. Mechanistically, cholesterol suppressed OGT expression and protein O-GlcNAcylation, leading to SP1 inactivation and transcriptional repression of Nampt. Co-immunoprecipitation assay reveals that PARP1 is directly associated with and PARylates AMPK, and its inhibition diminished AMPK activation and metabolic stress resilience. Unlike palmitate-induced injury, cholesterol toxicity was independent of SIRT1 or mTORC1 signaling, underscoring a distinct form of lipotoxic stress driven by NAD+ depletion, impaired PARP1-AMPK signaling, and defective cellular adaptation to cholesterol overload. **Conclusion:** Our findings identify an unrecognized cholesterol-SP1-NAD+-PARP1-AMPK axis as a central mediator of cholesterol-induced hepatotoxicity. Restoration of NAD+ metabolism or activation of the OGT-SP1 pathway represents a promising therapeutic approach to counter cholesterol-driven liver injury, such as MASLD, ALD, and related metabolic disorders.



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1385 | ADIPOSE FSP27 DEFICIENCY CAUSES A LOSS OF HEPATIC CEACAM1 TO DRIVE MASH AND HEPATIC FIBROSIS

Agnes Portuphy[1] Raziyeh Abdolahipour[1] Getachew Belew[1] Bijinu Balakrishnan[1] Vishwajeet Puri[1] Sonia Najjar[1], [1]Ohio University, Department of Biomedical Science, Heritage College of Osteopathic Medicine

Background: Dysregulated adipose lipolysis is a major contributor to MASH, which is reaching an epidemic rise and is a major cause of hepatic fibrosis and liver transplantation. In the liver, carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1) promotes insulin clearance and mediates the inhibition of fatty acid synthesis in response to acute pulses of insulin release. Hepatic CEACAM1 levels progressively decline as fibrosis severity increases in patients with MASH. Free fatty acids (FFAs) suppress hepatic Ceacam1 transcription via a PPARα-dependent mechanism. In adipocytes, Fat-specific protein 27 (FSP27) interacts with adipose triglyceride lipase (ATGL) to prevent lipolytic flux. Thus, we hypothesized that adipocyte-specific loss of Fsp27 drives hepatic fibrosis via fatty acid-mediated repression of CEACAM1. **Methods:** We generated adipocyte-specific *Fsp27* knockout mice (*Adipo+Fsp27$^{fl/fl}$*) using adiponectin-Cre on a C57BL/6J background. To assess the protective role of CEACAM1, we crossed these *Adipo +Fsp27$^{fl/fl}$* mutants with L-CC1 mice with liver-specific overexpression of wild-type CEACAM1-L driven by the human Apolipoprotein A1 promoter to protect hepatic CEACAM1 expression. The metabolic function was assessed by glucose and insulin tolerance tests, and insulin clearance was evaluated using steady-state C-peptide/insulin molar ratio. Liver steatosis and fibrosis were evaluated by H&E and Sirius Red staining, respectively. Key markers of lipid metabolism, oxidative stress, inflammation, and fibrosis were also examined in plasma and liver tissues using RT-qPCR, Western blot, ELISA, and IHC analysis. **Results:** *Adipo +Fsp27$^{fl/fl}$* , but not *Adipo+Fsp27$^{fl/fl}$ LCC1* exhibited elevated plasma glycerol with lower epididymal WAT. Hepatocytic *Ceacam1* mRNA levels decreased as early as 2-3 months, preceding systemic insulin resistance. This was followed by a progressive decline of hepatic CEACAM1 protein levels starting at 6 months of age and reaching >60% loss by 8-9 months of age. Additionally, *Adipo+Fsp27$^{fl/fl}$* mice developed impairment of insulin clearance, hyperinsulinemia, glucose intolerance, and reduced plasma nitric oxide with increased plasma endothelin-1 levels at 8-9 months. Histology also revealed lipid deposition by 6 months and inflammatory infiltration by 8 months. This was followed by spontaneous chicken-wire pattern of interstitial and perivenular collagen deposition by 12 months. In contrast, these abnormalities were markedly attenuated in *Adipo+Fsp27$^{fl/fl}$ LCC1* mice. **Conclusion:** Elevated lipolysis led to an early decrease in hepatic *Ceacam1*, which preceded lipotoxicity, hyperinsulinemia, oxidative stress, and MASH progression to fibrosis. Restoring hepatic CEACAM1 uncoupled adipose lipolysis from liver injury, identifying CEACAM1 as a central mechanistic node and potential therapeutic target in MASH-associated fibrosis.

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Disclosures: Agnes Portuphy:Nothing to Disclose, Raziyeh Abdolahipour:Nothing to Disclose, Getachew Belew:Nothing to Disclose, Bijinu Balakrishnan:Nothing to Disclose, Vishwajeet Puri:Nothing to Disclose, Sonia Najjar:Nothing to Disclose.

1386 | HEPATOCYTE-SPECIFIC VHL DELETION EXACERBATES HFHC-INDUCED STEATOHEPATITIS IN A SEX-DEPENDENT MANNER

Laura Fàbrega[1] Mariel Gorgon Manrique[2] Laura Conde de la Rosa[1] Susana Nuñez[3] Carmen Garcia-Ruiz[4] Jose Fernandez-Checa[1], [1]Institute of Biomedical Research of Barcelona, [2]Universitat de Barcelona - Universitat Rovira i Virgili, [3]CIBERehd, [4]Spanish National Research Council

Background: The Von Hippel–Lindau (VHL) tumor suppressor is a key regulator of hypoxia signaling and metabolic homeostasis. Although its role in cancer is well established, its contribution to metabolic dysfunction–associated steatotic liver disease (MASLD) and progression to steatohepatitis remains insufficiently defined, particularly in a sex-dependent context. We hypothesized that VHL deletion stabilizes HIF signaling, increasing STARD1-dependent mitochondrial cholesterol trafficking and promoting a self-amplifying loop of mitochondrial dysfunction and liver injury. **Methods:** Nine-week-old male and female Vhl-floxed mice were fed a high-fat high-cholesterol (HFHC) diet (Research Diets, D12011002) for 4 months. Hepatocyte-specific Vhl deletion was induced by tail-vein injection of AAV8-TBG-Cre, with AAV8-TBG-GFP as control. Mice remained on HFHC and were sacrificed one week post-injection. Liver injury, steatosis, fibrosis, cholesterol and bile acids levels, as well as metabolic gene and protein expression were assessed by histology, biochemical assays, immunostaining, qPCR and Western Blot analyses. **Results:** Vhl deletion exacerbated HFHC-induced liver injury in a sex-dependent manner. Vhl-deficient mice fed HFHC diet developed hepatomegaly, angiogenesis, steatosis, and fibrosis, with males showing higher serum transaminases and triglyceride accumulation compared to female mice. Vhl deletion increased hepatic cholesterol and STARD1 protein expression, supporting enhanced mitochondrial cholesterol trafficking. In parallel, mRNA expression of Cyp7a1, Cyp8b1, Cyp27a1, and Cyp7b1 was repressed, suggesting impaired bile acid synthesis. Despite reduced Cyp27a1 expression, residual Cyp27a1 activity and enhanced availability of mitochondrial cholesterol led to chenodeoxycholic acid (CDCA) generation and metabolism into muricholic and taurodeoxycholic acids. Mechanistically, CDCA was associated with reduced Fbp1 and increased Nrf2 expression in male vs female mice, linking bile acid remodeling to metabolic reprogramming and oxidative stress adaptation. Increased STARD1 expression relative to CYP27A1 favored mitochondrial free cholesterol accumulation, resulting in decreased GSH levels, increased ROS production, and inhibition of prolyl hydroxylases, thereby sustaining HIF-1α/HIF-2α stabilization and amplifying liver damage. **Conclusion:** Hepatocyte-specific Vhl deletion exacerbates HFHC-induced MASH in a sex-dependent manner involving hypoxia signaling, STARD1-associated mitochondrial cholesterol accumulation, bile acid remodeling, oxidative stress, and FBP1 repression. These findings identify VHL as a critical regulator of hepatic metabolic adaptation, supporting its role as a potential determinant of MASLD progression to HCC.

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1387 | NOVEL ROLE OF NEURO-IMMUNOMETABOLISM IN THE PATHOGENESIS OF MASH

Miyako Tanaka[1] Takayoshi Suganami[1], [1]Nagoya University

Background: Metabolic dysfunction-associated steatohepatitis (MASH) is the liver phenotype of metabolic syndrome. The "multiple parallel hits hypothesis" proposes the pathological mechanism underlying MASH, emphasizing the significance of various metabolic disorders and inflammatory stimuli. However, the involvement of the central nervous system in the pathogenesis of MASH remains poorly understood. Within the liver, the β2-adrenergic receptor (Adrb2) is a primary receptor for the sympathetic nervous system, the dominant component of the autonomic nervous system. In this study, we focused on Adrb2 to investigate how the sympathetic nervous system regulates hepatic metabolism and inflammation during the development of MASH. **Methods:** We developed two types of MASH models in systemic Adrb2 knockout mice (KO). The first one was a genetic model generated by crossing Melanocortin 4 receptor-KO mice and Adrb2 KO mice, and the second one was a diet-induced model using a Gubra Amylin NASH (GAN) diet. To identify the cell type-specific roles , we created hepatocyte-specific Adrb2 KO mice, generated by crossing albumin-Cre mice with Adrb2 floxed mice, and immune cell-specific Adrb2 KO mice, generated by bone marrow transplantation, and both groups were fed a GAN diet. **Results:** In systemic Adrb2 KO mice, Adrb2 deficiency aggravated hepatic steatosis,

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inflammation, and fibrosis in both genetic and diet-induced models, suggesting a protective role of the sympathetic nervous system during the development of MASH. Hepatocyte-specific Adrb2 KO mice showed similar hepatic phenotypes to those of systemic Adrb2 KO mice to a slightly lesser degree. Immune cell-specific Adrb2 KO mice exhibited enhanced inflammation and fibrosis in the liver without affecting hepatic lipid accumulation. As a potential underlying mechanism, Adrb2 deficiency in macrophages inhibited efferocytosis, and Adrb2 deficiency in hepatocytes increased the expression of genes involved in cholesterol metabolism. **Conclusion:** These findings suggest that Adrb2 plays an important role in cholesterol metabolism and efferocytosis in hepatocytes and macrophages, respectively, during the development of MASH. Our data suggest the involvement of the sympathetic nervous system in the pathogenesis of MASH, in addition to the previously recognized complicated interactions between metabolic disorders and inflammatory stimuli in the liver.

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1388 | INTER-ORGAN GENE REGULATORY NETWORKS REVEAL ADIPOSE–AND MUSCLE–LIVER CROSSTALK UNDERLYING SEMAGLUTIDE-MEDIATED IMPROVEMENT OF MASH

Eveline Gart[1], [1]TNO

Background: Glucagon-like peptide-1 receptor agonists such as semaglutide improve obesity-related metabolic dysfunction including metabolic dysfunction-associated steatohepatitis (MASH). However, their effects extend beyond individual organs and involve coordinated inter-organ communication. Semaglutide-induced weight loss is accompanied by alterations in body composition, raising questions about the metabolic consequences of associated changes in skeletal muscle. Although tissue-level phenotypic effects have been well characterized, the molecular mechanisms underlying inter-organ crosstalk remain poorly understood. This study aimed to delineate cross-tissue regulatory networks linking adipose tissue and skeletal muscle to hepatic processes. **Methods:** Diet-induced obese Ldlr−/−.Leiden mice were treated with semaglutide alone or in combination with exercise. Transcriptomic datasets from liver, adipose tissue, and muscle were integrated using gene regulatory network analysis to identify inter-organ regulators and pathways. This approach enabled us to define how gene expression changes in adipose tissue and muscle drive hepatic molecular remodeling in the context of MASH. **Results:** Semaglutide reduced body weight, fat mass and lean body mass. Despite a reduction in absolute muscle mass, relative muscle mass increased as compared to high-fat diet controls as a result of changes in body composition. Gene regulatory network analysis identified distinct yet partially overlapping regulatory axes linking adipose tissue and muscle to the liver. Comparison of adipose- and muscle-derived networks revealed complementary modes of regulation: adipose tissue predominantly linked to inflammatory and immune signaling pathways, whereas muscle-derived signals were more strongly associated with mitochondrial and metabolic pathways. Importantly, the integration of these networks reveals that semaglutide-induced improvements in hepatic steatosis and inflammation are not solely driven by direct hepatic effects, but are mediated through multi-organ signaling axes. **Conclusion:** Integrated transcriptomic network analysis reveals that semaglutide induces coordinated transcriptional remodeling across adipose tissue, skeletal muscle, and liver. Adipose and muscle derived regulatory networks converge on hepatic pathways central to MASH pathogenesis, providing mechanistic insight into how these tissues specifically contribute to semaglutide-mediated improvements in liver disease.

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1389 | IMMUNE–HEPATIC CROSSTALK DRIVES YAP-ASSOCIATED FIBROGENIC SIGNALING IN HUMAN IPSC-DERIVED MACROPHAGE-INCORPORATED LIVER ORGANOIDS MODELING HIV-ASSOCIATED MASLD

Zeinab Heidariyan[1] Swastika Tripathi[2] Volney Spalding[2] Nadia Alatrakchi[3] Wenyu Lin[4] Yongtao Wang[2] Min Xu[2] Raymond Chung[4] Shadi Salloum[2], [1]MGH-Harvard, [2]Harvard Medical School and Massachusetts General Hospital, [3]Massachusetts General Hospital and Harvard Medical School, [4]Massachusetts General Hospital

Background: People living with HIV (PLWH) exhibit increased susceptibility to metabolic dysfunction–associated steatotic liver disease (MASLD) and liver fibrosis despite effective antiretroviral therapy. Mechanistic understanding remains limited by the lack of

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multicellular human in vitro systems that capture immune–hepatic interactions. We developed a human induced pluripotent stem cell (iPSC)-derived macrophage-incorporated liver organoid (MILO) model to investigate HIV- and metabolic stress–induced inflammatory and fibrogenic signaling. **Methods:** Human liver organoids (HLOs) and functional CD14^{+} macrophages were generated from iPSCs and combined to generate MILO. HLOs, macrophages, and MILO were exposed to HIV, free fatty acids (FFA), or HIV+FFA. Hepatic function, inflammatory signaling, fibrogenic responses, and YAP-associated pathway activation were evaluated using immunofluorescence, flow cytometry, and qPCR. Pathway inhibition studies were performed to assess mechanistic signaling responses. **Results:** HLOs demonstrated hepatocyte-like functionality, including albumin secretion, indocyanine green uptake/release, and FFA-induced lipid accumulation. HIV and/or FFA exposure induced YAP-associated target genes (CTGF, CYR61, ANKRD1) together with fibrosis-associated genes (TIMP1, αSMA, COL1A1). Macrophages demonstrated activation of inflammatory and profibrotic polarization programs following HIV and/or FFA exposure, including induction of CD80, CD86, TLR4, IL1B, IL12, CD206, CD163, and ARG1. Compared with HLOs alone, MILO demonstrated coordinated induction of YAP-associated, inflammatory, metabolic, and fibrosis-related transcriptional programs following HIV +FFA exposure, including increased expression of CTGF (~3.2-fold), TIMP1 (~3.1-fold), and ARG1 (~5.5-fold), supporting a central role for immune–hepatic crosstalk in HIV-associated MASLD progression. Pathway inhibition suppressed treatment-induced YAP-associated signaling, macrophage activation, and fibrosis-related gene expression across macrophages, HLOs, and MILO. **Conclusion:** We established a multicellular human iPSC-derived macrophage-incorporated liver organoid platform that recapitulates HIV- and metabolic stress–associated inflammatory and fibrogenic signaling. These findings identify immune–hepatic crosstalk as a key driver of YAP-associated fibrogenic responses and establish MILO as a scalable platform for transcriptomic profiling and therapeutic testing in HIV-associated MASLD.

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1390 | HEPATIC ARID5A IS INDUCED BY LIPOTOXIC ER STRESS THROUGH THE PERK PATHWAY AND ATTENUATES MURINE MASH

Takahito Nishihara[1] P. Vineeth Daniel[2] Amy Mauer[1] Jasmin Weninger[1] Hanna Erickson[1] Yeriel Yoon[1] Aditya Bhagwate[1] Cristina Correia[3] Harmeet Malhi[1], [1]Mayo Clinic Rochester, [2]SRM Medical College Hospital and Research Center, SRMIST, Kattankulathur, TN, India, [3]Department of Molecular Pharmacology and Experimental Therapeutics, Mayo Clinic, Rochester

Background: The endoplasmic reticulum (ER) is an essential hub of protein folding, lipid biosynthesis, and calcium homeostasis in hepatocytes. The metabolic significance of unfolded protein response (UPR) mediators and ER stress have become increasingly apparent in the context of lipid-overload in obesity and metabolic dysfunction-associated steatohepatitis (MASH). Yet significant gaps remain in our understanding of the full regulatory landscape that governs the ER stress response in MASH. **Methods:** Parallel bulk RNA sequencing (RNA-seq) and assay for transposase-accessible chromatin sequencing (ATAC-seq) were performed in tunicamycin-treated mouse liver tissue along with bulk RNA-seq in palmitate-treated primary mouse hepatocytes. ARID5A expression was measured by qPCR and western blotting. Steatohepatitis was induced by feeding mice a choline-deficient, amino acid-defined high-fat diet (CDAHFD) and MASH was induced by a high Fat, Fructose, and Cholesterol (FFC) diet. Hepatotropic adeno-associated virus (AAV) was injected via tail vein to overexpress ARID5A. **Results:** The integration of bulk RNA-seq and ATAC-seq identified *Arid5a* as one of the significantly upregulated transcripts in proteotoxic and lipotoxic ER stress. Analysis of publicly available human liver bulk RNA sequencing (GSE135251) and qPCR analysis of human steatosis (n = 4) and MASH (n = 4) samples demonstrated upregulation of *Arid5a* transcript in MASH. Murine MASH livers also demonstrated increased transcript and protein expression of ARID5A. Human and mouse hepatocyte-derived cell lines and primary mouse hepatocytes demonstrated palmitate-induced ARID5A upregulation at both transcript and protein level. Using a combination of immunofluorescence and subcellular fractionation, we found that ARID5A, though distributed in the cytosol and nucleus basally, was enriched in the nuclear compartment following palmitate treatment in hepatocytes. Cell lines deficient in each of the three UPR sensor pathways (IRE1α, PERK, and ATF6α) demonstrated palmitate-induced ARID5A upregulation was attenuated only in eIF2α phosphorylation-resistant cells, which is necessary for downstream responses in the

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PERK pathway. Using pharmacological inhibitors and PERK genetic knockdown, we observed that palmitate-induced ARID5A upregulation was attenuated when PERK was inhibited. Overexpression of ARID5A attenuated liver injury, inflammation, and fibrosis in murine models of steatohepatitis and MASH. **Conclusion:** We identified ARID5A as an ER stress-responsive transcript upregulated through the PERK pathway. Overexpression of ARID5A attenuated MASH supporting a protective role for ARID5A and suggesting that ARID5A could be a new therapeutic target in MASH.
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1391 | CEACAM1 PROTECTS AGAINST DIET- INDUCED METABOLIC DYSFUNCTION AND HEPATIC FIBROSIS

Raziyeh Abdolahipour[1] Agnes Portuphy[1] Getachew Belew[1] Sonia Najjar[1], [1]Ohio University

Background: Carcinoembryonic Antigen-related Cell Adhesion Molecule 1 (CEACAM1) is a transmembrane glycoprotein highly expressed in hepatocytes, with lower expression in liver sinusoidal endothelial cells (LSECs) followed by hepatic stellate cells (HSCs). Lipolysis-derived non-esterified fatty acids (NEFA) stimulate PPARα activation to induce its interaction with the well-conserved PPRE-RXRα element in Ceacam1 promoter. This suppresses Ceacam1 transcription. Given that loss of hepatic CEACAM1 causes insulin resistance and hepatic steatosis, the current study investigated whether mutating PPRE-RXRα binding site within the Ceacam1 promoter could protect C57BL/6J mice against the metabolic and histological abnormalities caused by Gubra Amylin-NASH (GAN) diet. **Methods:** A knock-in (KI) mouse model carrying a mutation in the PPRE-RXRα binding site of the Ceacam1 promoter was generated. Male and female WT and KI mice were fed regular diet (RD), high-fat diet (HFD), or GAN diet for 4 and 6 months, respectively, to evaluate the metabolic and histological effects. **Results:** Relative to RD, feeding with HFD and GAN diet for up to 4 months suppressed hepatic CEACAM1 expression in wild-type (WT), but not KI males. Feeding males with HFD diet impaired insulin clearance to cause hyperinsulinemia-driven insulin resistance and hepatic steatosis in WT, but not KI mice. It also reduced energy expenditure and promoted hepatic fibrosis in WT, but not KI males. A parallel analysis was performed in female WT and KI mice fed with regular chow or GAN diet for 6 months. In female mice, GAN feeding similarly repressed CEACAM1 expression in WT but not KI mice, with the most pronounced loss observed in hepatocytes as compared to LSECs and HSCs. Despite the absence of insulin resistance, GAN-fed WT females developed greater steatosis, inflammation, apoptosis, and chicken-wire fibrosis, whereas KI females remained protected. Mechanistically, conditioned media from hepatocytes of GAN-fed WT mice activated HSCs and suppressed Ceacam1 expression, likely through inducing the release of fatty acids. Consistently, CEACAM1 expression was markedly reduced in hepatic stellate cells in patients with MASH, with progressive loss correlating with advanced fibrosis independent of sex or ethnicity. **Conclusion:** These findings identify CEACAM1 repression as a critical driver of MASH progression and hepatic fibrosis in response to GAN diet. Thus, preventing CEACAM1 repression constitutes a therapeutic target in protecting against diet-induced metabolic dysfunction, steatosis, inflammation and hepatic fibrosis.
Disclosures: Raziyeh Abdolahipour:Nothing to Disclose, Agnes Portuphy:Nothing to Disclose, Getachew Belew:Nothing to Disclose, Sonia Najjar:Nothing to Disclose.

1392 | PRECLINICAL CHARACTERIZATION OF ALG-037287 AS A LIVER-TARGETED SMALL MOLECULE INHIBITOR OF FATTY ACID SYNTHASE FOR THE POTENTIAL TREATMENT OF MASH

Jieun Song[1] Alexander Leung[1] Peter Althoff[1] Sarah Stevens[1] Sandra Chang[1] Kusum Gupta[1] Cheng Liu[1] Lillian Adame[1] Antitsa Stoycheva[1] Lawrence Blatt[2] David Smith[1] Julian Symons[1] Xuan Luong[1] Tongfei Wu[1], [1]Aligos Therapeutics, [2]Aligos Therapeutics, Inc.

Background: Fatty acid synthase (FASN) catalyzes the terminal, rate-limiting step in de novo lipogenesis (DNL). In metabolic dysfunction–associated steatohepatitis (MASH), hepatic FASN is upregulated, driving triglyceride accumulation and lipotoxicity. Although the FASN inhibitor denifanstat resulted in significant histological improvement in Phase 2b trials, it is associated with alopecia due to on-target skin effects. Here, we describe ALG-037287, a structurally novel, liver-targeted FASN inhibitor designed to retain efficacy in MASH while reducing skin exposure and other dermatologic side effects. **Methods:** Inhibition of beta-ketoacyl reductase (KR) activity was tested using the full-length human FASN protein in a biochemical assay and in vitro DNL inhibition was assessed in primary human hepatocytes. Antifibrotic effects were assessed by

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quantification of *COL1A1* expression in TGF-β1-activated LX-2 human hepatic stellate cell line. In vitro ADME tox profile was profiled using standard assays. In rats, plasma exposure and liver/skin distribution were assessed after a single oral dose, PK study, and tissue-specific DNL inhibition was quantified in a single oral dose, PK/PD study. **Results:** ALG-037287 demonstrated potent inhibition of the FASN beta-ketoacyl reductase (KR) domain, with an IC50 value approximately 6-fold lower than that of denifanstat. *In vitro*, ALG-037287 showed comparable potency to denifanstat in suppressing *COL1A1* and inhibiting DNL. In a rat PK study, oral administration of ALG-037287 (15 mg/kg) yielded significantly superior liver-to-plasma concentration ratios compared to denifanstat (15 mg/kg) and it was undetectable in skin at 12 hours post-dose. In the rat PK/PD study, single oral doses of ALG-037287 (20 and 60 mg/kg) significantly inhibited hepatic DNL, whereas no significant inhibition was observed in Zymbal's glands and dorsal skin. Furthermore, ALG-037287 exhibited favorable liver microsomal stability across species, with no CYP-mediated drug-drug interactions and no in vitro cardiovascular (hERG, $Na_v1.5$ and Ca_v 1.2) or mutagenic (Ames) liabilities. **Conclusion:** ALG-037287 is a potent, orally bioavailable FASN inhibitor with a differentiated, liver-targeted profile. Its optimized tissue distribution is designed to potentially preserve therapeutic efficacy in MASH while reducing skin exposure and the risk of alopecia and other dermatologic side effects.

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1393 | THE GCKR-CHREBP AXIS REGULATES LIPID AND GLYCOGEN LEVELS IN HUMAN HEPATOMA CELLS

Yue Chen[1] Rawdat Hussain[2] Prabhu Ponnandy[2] Elizabeth Speliotes[3], [1]University of Michigan, [2]University of Michigan Medical School, [3]University of Michigan Medical Center

Background: Human genetic studies have identified a missense variant GCKR P446L (rs1260326) which has been associated with metabolic dysfunction-associated steatotic liver disease (MASLD), hypertriglyceridemia, and diabetes. The exact mechanisms responsible for these phenotypes remain to be fully elucidated. **Methods:** We generated Huh7 cells stably by overexpressing WT or P446L GCKR gene as well as GCK, confirmed by immunoblotting. MLXIPL (ChREBP) was knocked out by CRISPR/Cas9. Cells were cultured under 2 mM glucose condition. Glucose-6-phosphate (G6P), glycogen and triglycerides (TG) levels were measured using biochemical assays. Expression of key genes involved in de novo lipogenesis (ACACA, ACLY, FASN, SCD1), MLXIPL and glycogen synthesis and breakdown (GYS1, GYS2, PYGL, STBD1) were determined with RT-qPCR. The levels of these key enzymes (ACC, FASN, ACLY and GYS1/2) as well as proteins involved in glycogen regulation (GSK-3β, PYGL and STBD1) were determined using immunoblotting. **Results:** GCKR P446L variant significantly increased intracellular glucose-6-phosphate (G6P) levels compared to wild-type GCKR, as well as elevated expression of MLXIPL and its target genes including ACC, ACLY, FASN, and SCD1. P446L cells exhibited increased triglyceride accumulation as well as enhanced glycogen content. Knocking out MLXIPL significantly decreased TG level in GCKR P446L cells as well as increased glycogen content in Huh7 and WT GCKR cells; there was a trending increase in glycogen in GCKR P446L cells. GCKR WT cells showed high levels of phospho-GYS1, the inactive form of the main enzyme that synthesizes glycogen, and low levels of phospho-GSK-3β, its upstream kinase regulator. MLXIPL KO increased phospho-GSK-3β regardless of GCKR background and decreased phospho-GYS1 in Huh7 and GCKR WT cells. **Conclusion:** P446L promotes higher G6P, triglyceride and glycogen levels whereas GCKR WT protects against these. MLXIPL deletion increased glycogen content. Differences in phospho-GYS1 and phospho-GSK-3β correlate with differences in glycogen content. Our results provide new information about how WT and P446L GCKR affect lipid and glycogen metabolism in human liver cells.

Disclosures: Yue Chen:Nothing to Disclose, Rawdat Hussain:Nothing to Disclose, Prabhu Ponnandy:Nothing to Disclose, Elizabeth Speliotes:University of Michigan: Pending patent on use systems for MASLD/insulin resistance.

1394 | THE CELL SPECIFIC ROLE OF SYNDECAN-1 IN THE PATHOPHYSIOLOGY OF MASLD

Greg Callahan[1] Aaron Baker[1], [1]University of Texas at Austin

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Background: Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) is a progressive type of fatty liver disease characterized by fat accumulation in hepatic tissue that is not linked to excessive alcohol consumption. The disease encompasses early stages of metabolic dysfunction-associated fatty liver (MAFL) to more severe stages of metabolic dysfunction-associated steatohepatitis (MASH). It is currently the most common form of chronic liver disease worldwide, with a prevalence of approximately 25% in the general population (~1.8 billion people worldwide). While a few treatments have recently been approved by the FDA, the fundamental mechanisms of MASLD remain an area of active research. Syndecan-1 (SDC-1), a transmembrane protein that binds to heparan sulfate is one of the most important proteoglycans in the liver and its expression levels alter under various pathologies, including MASLD. The extracellular domain of SDC-1 has been detected in serum of patients with liver disease, shed during MASLD by either increased metalloproteinase activity or impaired SDC-1 sulfation. The literature on SDC-1's role in MASLD describe the complex interactions of both cell membrane bound and shed SDC-1 with cytokines and its impact on signaling pathways, lipid transport, and fibrosis. However, they are limited to *in vitro* studies involving one cell type, or *in vivo* studies that focus on hepatocyte syndecan-1. **Methods:** Using a tamoxifen inducible loxP-cre system, we generated cell-specific knockouts of SDC-1 in hepatic stellate cells or endothelial cells. We then fed mice possessing these knockouts a high fat methionine and choline deficient diet to induce inflammatory and fibrotic MASLD in the mice. Following the diet, we conudcted histological staining to study gross tissue morphology, inflammatory cell recrutiment / phenotype, stellate cell activation, and fibrogenesis. **Results:** From these *in vivo* experiments, we have determined that loss of hepatic stellate cell syndecan-1 increases stellate cell activation, indicated by a significant increase in aSMA area, while loss of SDC-1 in endothelial cells significantly decreases stellate cell activation. We also found that while both stellate cell and endothelial SDC-1 KO promoted macrophage recruitment to the liver (increased F4/80 area), only stellate cell SDC-1 promoted the activation of macrophages to pro-inflammatory morphologies such as a hepatic crown structure (forming around a steatotic hepatocyte). **Conclusion:** Taken together, our data suggests that stellate cell SDC-1 plays a key role in stellate cell activation while directing macrophage recruitment and phenotype, though the mechanisms behind some of these effects are still under investigation.
Disclosures: Greg Callahan:Nothing to Disclose, Aaron Baker:Nothing to Disclose.

1395 | CANCER-ASSOCIATED FIBROBLAST-DERIVED ADAMTS7 FACILITATES HEPATOCELLULAR CARCINOMA VIA STAT3/CD36 SIGNALING AXIS

Tian Tian[1] Liya Pi[1], [1]Tulane University School of Medicine

Background: Clinical and genomic evidence links the aberrant activation of ADAMTS7 to the progression of hepatocellular carcinoma (HCC). **Methods:** In mouse models, metalloproteinase ADAMTS7 is markedly upregulated under hepatic stress induced by a high-fat diet (HFD) combined with chronic ethanol exposure or HFD alone, exhibiting strong pro-tumorigenic effects. **Results:** Based on these findings, we successfully generated *ADAMTS7* knockout (KO) mice. *In vivo* functional assays demonstrated that KO of *ADAMTS7* not only dramatically suppressed HFD-induced stromal remodeling, substantially reducing orthotopic liver tumor volume and nodule counts, but also exerted a robust inhibitory effect on distant lung metastasis. In vivo, genetic ablation of ADAMTS7 significantly decreased the infiltration and activation of this of $CD36^{+}$ cancer-associated fibroblast (CAF) population via the suppression of the STAT3 signaling pathway, effectively alleviating the immunosuppressive tumor microenvironment (TME). This stromal reprogramming subsequently enhanced $CD8^{+}$ T cell infiltration and restored their effector function, which remarkably potentiated the efficacy of anti-PD1 (aPD1) immunotherapy. **Conclusion:** Together, our study elucidates a novel microenvironmental mechanism whereby ADAMTS7 drives HCC malignancy and pulmonary metastasis via the STAT3/CD36 axis, highlighting stromal ADAMTS7 as a promising therapeutic vulnerability to overcome immunotherapy resistance in advanced liver cancer.
Disclosures: Tian Tian:Nothing to Disclose, Liya Pi: Nothing to Disclose.

1396 | SEX-SPECIFIC EFFECTS OF MYELOID SMPDL3B DEFICIENCY ON DIET-INDUCED MASH AND HEPATOCELLULAR CARCINOMA PROGRESSION

Shuxia Wang[1] Taesik Gwag[1] Alla Mitrofanova[2] Alissia Fornoni[2] Steven Weinman[3], [1]University of Kentucky, [2]University of Miami, [3]University of Kansas

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) has become the most common chronic liver disease worldwide. Macrophage activation plays a critical role in the progression from

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simple steatosis to metabolic dysfunction-associated steatohepatitis (MASH) and hepatocellular carcinoma (HCC). SMPDL3B (sphingomyelin phosphodiesterase acid-like 3B) is a GPI-anchored membrane protein that negatively regulates Toll-like receptor signaling in macrophages. However, whether SMPDL3B contributes to MASH progression and HCC development has not been determined. In this study, we investigated the in vivo role of myeloid-specific SMPDL3B deficiency in diet-induced MASH and HCC development, with particular attention to sex-specific effects. **Methods:** Both human liver samples and mouse models of diet-induced MASH and HCC were utilized in this study. SMPDL3B expression was examined in normal, MASLD, and MASH human liver samples by qPCR and immunohistochemical staining. For animal studies, myeloid-specific SMPDL3B knockout mice were generated by crossing Smpdl3b floxed mice with LysM-Cre mice. Both male and female knockout and littermate control mice were fed an AMLN diet for 16 or 32 weeks to induce MASLD and MASH, respectively. To accelerate HCC development, mice additionally received CCl4 injections during AMLN feeding. Liver steatosis, inflammation, fibrosis, and tumor development were assessed by histological and molecular analyses. **Results:** SMPDL3B expression was significantly reduced in human MASH liver samples compared with normal controls. In mouse models, myeloid-specific SMPDL3B deletion had minimal effects on diet-induced MASLD or MASH progression in male mice, with similar levels of hepatic lipid accumulation, inflammation, and fibrosis observed between knockout and control groups. In contrast, female myeloid-specific SMPDL3B knockout mice exhibited significantly increased liver inflammation and fibrosis despite showing similar levels of hepatic lipid accumulation compared with female control mice. Furthermore, female knockout mice developed substantially more HCC nodules in the AMLN/CCl4-induced HCC model compared with female control mice. **Conclusion:** These findings identify SMPDL3B as a previously unrecognized sex-dependent regulator of MASH and HCC progression. Myeloid SMPDL3B deficiency selectively exacerbates hepatic inflammation, fibrosis, and HCC development in female mice, while having minimal effects in males. Our study highlights the importance of macrophage lipid signaling pathways in regulating liver disease progression and suggests that sex-specific immune mechanisms may contribute to differential susceptibility to MASH-associated HCC. Targeting SMPDL3B-related pathways may therefore represent a novel therapeutic strategy for inflammation-driven liver disease, particularly in females.

Disclosures: Shuxia Wang:Nothing to Disclose, Taesik Gwag:Nothing to Disclose, Alla Mitrofanova:Nothing to Disclose, Alissia Fornoni:Nothing to Disclose, Steven Weinman:Nothing to Disclose.

1397 | MODELING GENOTYPE-PHENOTYPE RELATIONSHIPS IN HUMAN MASLD USING A MICROPHYSIOLOGICAL SYSTEM

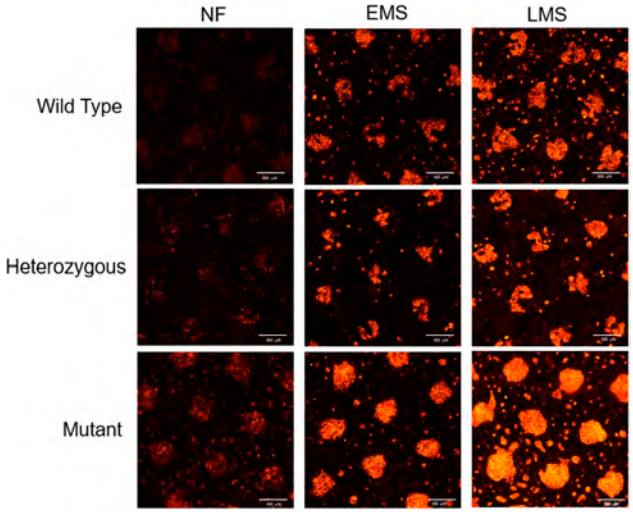
Nathan Shelton[1] Salman Khetani[2], [1]University of Illinois Chicago, [2]University of Illinois at Chicago

Background: Metabolic dysfunction–associated steatotic liver disease (MASLD) affects >30% of people worldwide. While MASLD development involves lifestyle factors, genetic susceptibility is increasingly recognized as a major contributor to disease onset and progression. However, the development of precision therapeutics for MASLD is hampered by a lack of physiologically relevant in vitro human models. To address this need, we utilized primary human hepatocytes (PHHs) genotyped for MASLD-associated variants in PNPLA3 rs738409 and GCKR rs1260326 to establish a model system for investigating genetic predisposition to disease and supporting preclinical therapeutic development. **Methods:** Commercially sourced PHH donors were genotyped for PNPLA3 rs738409 and GCKR rs1260326 using TaqMan SNP genotyping assays to select wild-type, heterozygous, and homozygous mutants. PHHs were then cultured in a well-established micropatterned co-culture (MPCC) model. Briefly, polydimethylsiloxane-based soft lithography was used to pattern collagen I into circular domains (500 μm diameter, 1200 μm spacing center-to-center) within multiwell plates. PHHs adhered to the collagen domains and were subsequently surrounded by stromal fibroblasts to stabilize functions for 3+ weeks. Cultures were then maintained in one of three different media: normal fasting (NF; 5 mM glucose, 500 pM insulin), early metabolic syndrome (EMS; 11 mM glucose, 500 μM fatty acid mixture, 10 nM insulin), or late metabolic syndrome (LMS; as EMS but with 22 mM glucose and 5 ng/mL TGF-β). Hepatic lipids were fluorescently stained with BODIPY, and metabolic-pathway genes were profiled by RT-qPCR. **Results:** The model reproduced human genetic risk in vitro. PHHs carrying risk variants showed greater lipid accumulation than wild-type controls across both EMS and LMS media perturbations, with the highest levels observed in homozygous mutant cells and increasing accumulation from NF to EMS to LMS media (Figure 1). Notably, heterozygous variants also displayed increased lipid accumulation compared to wild type, although to a lesser extent than homozygous risk variants, suggesting a genotype-dependent effect on steatotic burden. In addition to altered lipid accumulation, significant changes were observed in the expression of genes associated with lipid export, fatty acid oxidation, and broader metabolic dysregulation pathways; the direction and magnitude of these changes resolved how homozygous versus heterozygous

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backgrounds reroute key pathways. **Conclusion:** Together, these findings establish a genetically stratified MASLD platform that captures gene-dose susceptibility and links genotype directly to mechanism in human cells. Ongoing work will map genotype-specific metabolic signatures and leverage the platform to test therapeutic responses across defined genetic backgrounds, positioning it as a tool for precision preclinical drug development.



Disclosures: Nathan Shelton:Nothing to Disclose, Salman Khetani:Nothing to Disclose.

1398 | IMEGLIMIN PROVIDES DUAL HEPATIC AND SKELETAL MUSCLE PROTECTION IN EXPERIMENTAL MASH-ASSOCIATED SARCOPENIA

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Background: Metabolic dysfunction-associated steatohepatitis (MASH), frequently complicated by sarcopenia, is partly driven by mitochondrial dysfunction and inflammatory catabolic signaling. The effects of imeglimin, an antidiabetic drug and mitochondrial modulator, against MASH-associated sarcopenia remain unclear. This study evaluated its effect on MASH-associated skeletal muscle atrophy in mice. **Methods:** MASH-associated sarcopenia was induced in mice using a choline-deficient, L-amino acid–defined high-fat diet. Imeglimin (200 mg/kg, b.i.d.) was administered for 6 weeks. Subsequently, muscle phenotype, mitochondrial function, and molecular signaling were assessed. Meanwhile, differentiated C2C12 myotubes were stimulated with interleukin-6 (IL-6). **Results:** Imeglimin alleviated steatohepatitis and restored mitochondrial regulators Ppargc1a and Tfam as well as hepatic and circulating insulin-like growth factor-1 levels. In skeletal muscle, imeglimin improved the psoas muscle index and grip strength; preserved the muscle fiber diameter; and reduced the expression of the atrogenes Fbxo32, Trim63, and Mstn. Mechanistically, imeglimin inhibited the nuclear localization of forkhead box O3 (FOXO3a), restored the phosphorylation of FOXO3a(Ser253), and reactivated AKT–mTOR signaling. Treatment reversed mitochondrial dysfunction, with increased complex I/IV activities alongside mitochondrial biogenesis. Moreover, imeglimin normalized autophagy–lysosome signaling by reducing p62 accumulation and normalizing Lamp2 expression. In C2C12 myotubes, imeglimin concentration-dependently reduced the IL-6–induced upregulation of Fbxo32 and Trim63, restored mitochondrial membrane potential, improved the oxygen consumption rate, and enhanced autophagic flux. **Conclusion:** Imeglimin exerts the protective effect on MASH-associated skeletal muscle atrophy by restoring mitochondrial homeostasis, suppressing FOXO3a-mediated proteolysis, and normalizing autophagy. These findings highlight the possibility of targeting mitochondria to treat MASH-associated sarcopenia.

Disclosures: Yui Osaki:Nothing to Disclose, KOSUKE KAJI:Nothing to Disclose, Satoshi Iwai:Nothing to Disclose, NORIHISA NISHIMURA:Nothing to Disclose, Hitoshi Yoshiji:Nothing to Disclose.

1399 | DIFFERENTIAL STARD1-DEPENDENT MITOCHONDRIAL CHOLESTEROL-STRESS ADAPTATION PROGRAMS DRIVEN BY NRF2 AND FBP1 IN HCC SPHEROIDS

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Background: Hepatocellular carcinoma (HCC) progression is strongly influenced by metabolic reprogramming and tumor-stroma interactions. The outer mitochondrial membrane resident protein STARD1 promotes mitochondrial cholesterol (mitChol) trafficking to the inner membrane and may influence metabolic adaptation and generation of oxysterols and primary bile acids (BA), including 27-hydroxycholesterol (27-HC) and chenodeoxycholic acid, respectively. Similarly, SAB is a mitochondrial outer membrane scaffold protein that amplifies stress

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signaling, ROS production, and JNK activation. In addition, NRF2 is a master regulator of antioxidant/stress responses, whereas FBP1 is a gluconeogenic enzyme with tumor suppressor functions linked to metabolic restraint. We investigated how NRF2 and FBP1 modulate mitochondrial cholesterol handling, oxidative stress, and endoplasmic reticulum (ER) stress in 3D HCC spheroids. **Methods:** The HCC cell line HuH7 and the hepatic stellate LX2 cells were cultured under standard conditions. Stable HuH7-NRF2 and HuH7-FBP1 lines were generated by lentiviral transduction and puromycin selection. STARD1 and SAB knockdown models were generated by CRISPR lentiviral sgRNAs and GFP-based sorting. HCC spheroids (sph) were formed in 96-well ultra-low-attachment plates with or without LX2 cells, cultured for 5 days, and exposed to tunicamycin (Tn,10 µg/ml) during the last 24h. HCC-sph (10 sph/condition) were analyzed by 27-HC ELISA, RNA extraction, histology, and Seahorse XF analyses. **Results:** NRF2-sph showed increased STARD1 and SAB expression, higher mitChol, a stronger stress-responsive phenotype, and an imbalance of Tn-associated 27-HC levels. In contrast, FBP1-sph dysplayed a more heterogeneous profile, with partial suppression of basal ER stress markers, and stromal-sensitive changes in redox state, proliferation and stress-response genes. NRF2-sph showed enhanced GRP94 induction and TP53 responsiveness under ER stress, whereas FBP1-sph exhibited attenuated UPR activation. LX2 co-culture reduced oxidative stress in NRF2-sph and altered proliferation and stress markers in both models. Seahorse XF analysis suggests distinct metabolic adaptations, with NRF2-sph favoring glycolytic flexibility, while FBP1-sph retained a comparatively balanced energetic profile. STARD1 knockdown reduced mitChol loading, decreased 27-HC generation, and attenuated DHE/Ki67-associated phenotypes, particularly in NRF2 cells. SAB knockdown reduced ROS amplification and attenuated Tn-induced ER stress responses. **Conclusion:** These findings support that NRF2 and FBP1 differentially regulate mitochondrial stress adaptation and metabolic plasticity in HCC-sph, including microenvironment-dependent adaptation. Targeting STARD1/SAB-dependent pathways may represent a potential strategy to modulate ER stress tolerance and tumor-stromal adaptation in HCC.

Disclosures: Fabian Arenas Rios:Nothing to Disclose, Yuanqing An:Nothing to Disclose, Susana Nuñez:Nothing to Disclose, Carmen Garcia-Ruiz:Nothing to Disclose, Jose Fernandez-Checa:Nothing to Disclose, Monica Barrios López:Nothing to Disclose.

1400 | LAMTOR1 LACTYLATION MEDIATES MECHANICAL FORCE-INDUCED MACROPHAGE EXTRACELLULAR TRAPS FORMATION AND LIVER FIBROSIS IN MASLD VIA MTORC1 SIGNALING

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Background: Mechanical force acts as an emerging immunomodulator reshaping macrophage function in metabolic dysfunction-associated steatotic liver disease (MASLD), exacerbating liver fibrosis by perturbing hepatic regional immunity (HRI). Since mammalian target of rapamycin complex 1 (mTORC1) activation drives glycolytic reprogramming and lactic acid accumulation, this study investigates whether mechanical signals promote MASLD progression by driving macrophage extracellular traps (METs) formation via protein lactylation modification. **Methods:** Molecular targets were screened using single-cell transcriptomic analysis of liver tissues from MASLD mice. THP-1 cell models were established under conditions of (1) varying substrate stiffness, (2) mechanical force contact, and (3) high lactate exposure. Subsequently, immunofluorescence, co-immunoprecipitation, Western blotting, and qRT-PCR were employed to analyze mTORC1 signaling activation, lysosomal damage, and METs formation. **Results:** (1) Single-cell transcriptomic analysis of liver tissues from MASLD mice revealed increased mTORC1 signaling activation and glycolysis in macrophages, with significant enrichment of lysosomal damage and integrin signaling pathways. (2) Stiff substrates and increased mechanical force promoted mTORC1 signaling activation and lactic acid accumulation in THP-1 cells, inducing lysosomal damage and METs release; these effects were attenuated by integrin α4 knockout, but not PIEZO1 knockout. (3) Single-cell screening identified LAMTOR1 as a potential macrophage target. LAMTOR1 was downregulated in L-Leucyl-L-Leucine methyl ester hydrobromide (LLOMe)-induced lysosomal damage models, and inhibition of mTORC1 signaling with Torin 1 exacerbated this downregulation and promoted METs release. (4) In THP-1 cells cultured on stiff substrates or high lactate exposure, LAMTOR1 was downregulated and underwent lactylation modification. Inhibition of glycolysis with 2-DG reversed these effects and reduced METs release. **Conclusion:** This study elucidates that mechanical force triggers METs via integrin-mediated LAMTOR1 lactylation. We demonstrated that targeting this axis effectively blocks METs release and restores HRI homeostasis, providing a novel mechano-immunomodulatory strategy for the treatment of MASLD-associated liver fibrosis.

Disclosures: Jia-Shen Wu:Nothing to Disclose.

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1401 | SEX DIFFERENCES IN EARLY MASH

Noah Wallace[1], [1]University of Memphis

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is currently the most common chronic liver disease affecting 38% of the global adult population. If left untreated, it has the potential to progress to the more severe form of MASLD called Metabolic dysfunction-associated steatohepatitis (MASH). MASH is characterized by not only steatosis, but also inflammation. MASH can eventually lead to fibrosis, cirrhosis, and/or hepatocellular carcinoma. It is well known that sexual dimorphism exists in the prevalence of various metabolic disorders including MASLD and MASH; however, few mouse studies utilize both male and female mice. Furthermore, investigate the effects of either a high fat (HF) or high sugar (HS) diet as separate components. This study aimed to investigate both. **Methods:** 30 male and female C57bl/6 mice were used for the study. Mice were placed on either control (CON), HF, or HS diets after one week of acclimation for 12 weeks. Bodyweight was measured during the duration of the study along with body composition using ECHO MRI. At sacrifice, portions of liver were frozen in liquid nitrogen or fixed in formalin. Masson's Trichrome stain was used to visualize liver fibrosis. F4/80 immunohistochemistry was used to investigate macrophage infiltration in the liver. qPCR was used to analyze gene expression of inflammatory and fibrotic genes associated with MASH. All data is represented as means ± SEM. Two-way ANOVA was used to investigate diet and sex while a three-way ANOVA was used for diet, sex, and time. GraphPad Prism 8 software was used for all statistical analysis with Tukey post hoc analysis used to examine interactions. Significance was set a $p \leq 0.05$. **Results:** Males on the HF diet showed significantly higher bodyweight than all groups. Males on a HF diet had a 45.36% increase in body weight compared to females on a HF diet gaining only n32.55%. Males on a CON and HS diet showed greater bodyweights when compared to female CON and HS. Males on a HF diet at the end of the study showed the greatest fat percentage when compared to all other groups with an average of 34.54%. While males on the HF diet exhibited some fibrosis, male on the HS diet showed the greatest amount. Males on the HS diet also had the greatest macrophage infiltration with the F4/80 stain. Females on both HF and HS diets did not show fibrosis; however, HF females did show some macrophage infiltration, but not the extend of the Male HS. Main effects of sex and diet and sex was shown for *Cd68* and *Tnf*α, respectively. **Conclusion:** The current study showed after 12 weeks of being on a HF or HS diet, male mice showed the presence of hepatic fibrosis and inflammatory infiltration. While female mice lacked fibrosis, a HS diet did induce macrophage infiltration. Future studies will need to consider duration of diet as well as the effects of young, healthy female mice on study outcomes when investigating diet induced MASH/ **Disclosures:** Noah Wallace:Nothing to Disclose.

1402 | CELL TYPE- AND ZONAL-SPECIFIC HEPATIC EXPRESSION OF THE ISC ASSEMBLY FACTOR *CCDC117*

Isaac Park[1] Kyu-Ho Lee[1] Matthew Savoca[1] John Lemasters[1] Don Rockey[1], [1]Medical University of South Carolina

Background: Coiled-coil domain containing 117 (*Ccdc117*) is part of a cytoplasmic iron-sulfur cluster (FeS) transfer complex that transfers FeS to enzymes critical for cell function. While its function in liver has yet to be defined, its potential modulation by microRNA populations has been previously in a rodent model of alcoholic steatohepatitis (ASH). In order to gain insight into the potential role of Ccdc117 in the liver, we examined the cell-type and spatial distribution of Ccdc117 expression in the liver. **Methods:** *Ccdc117* mRNA expression was determined by qRT-PCR in primary isolates of hepatocytes, Kupffer cells, endothelial cells, and quiescent and activated stellate cells isolated from wild-type C57BL/6 mice. Histological distribution of Ccdc117 protein expression in mouse liver was determined by immunohistochemistry (IHC) and its localization relative to expression of the pericentral marker, glutamine synthase, and to periportal MitoTracker Red staining. Subcellular localization of Ccdc117 under normal and nutrient-deprivation conditions was determined by super-resolution confocal microscopy of HepG2 hepatoma, mouse and human primary cells following vital staining with PK Mito Orange mitochondrial membrane dye and immunostaining for TOMM20A and further quantified by immunoblotting of different cellular compartments **Results:** qPCR analysis revealed that hepatocytes exhibited by far the greatest basal expression of Ccdc117 relative to that of other liver cell types. IHC microscopy and zonal studies revealed that Ccdc117 expression was distinctly enriched in pericentral hepatocytes. In HepG2 cells and primary hepatocytes, Ccdc117 was localized to nuclear, cytosolic and mitochondrial compartments. In hepatocyte mitochondria, Ccdc117 was found to be localized both on the inner and outer mitochondrial membrane compartments. Following nutrient deprivation via incubation with Krebs-Ringers Hepes (KRH) medium, which leads to mitophagy, enhanced Ccdc117 immunofluorescence signal was observed in mitochondria. Further, in HepG2 cells, following incubation with KRH medium, immunoblotting of subcellular fractions revealed increased mitochondrial localization of

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Ccdc117. **Conclusion:** The data suggest that the expression pattern of Ccdc117 in the liver is consistent with a role in the hepatocyte response to metabolic signaling and/or regulation. The shift in Ccdc117 localization to mitochondria induced by nutrient deprivation, while also being consistent with a role in modulation of mitochondrial metabolic function, may indicate a role in autophagic, mitophagic and/or mitochondrial quality control pathways.

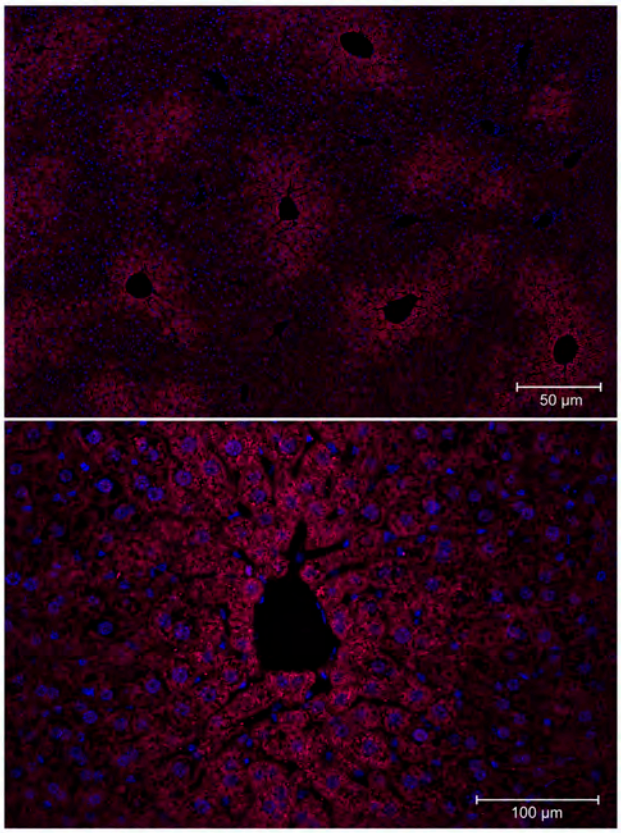


Figure 1. IF of functional liver lobule showing pronounced Ccdc117 expression (**pink**) in zone 3, vs. zones 1 & 2 Hoechst staining (**blue**) marks cell nuclei. Top panel, low magnification; bottom panel, high magnification.

Disclosures: Isaac Park:Nothing to Disclose, Kyu-Ho Lee:Nothing to Disclose, Matthew Savoca:Nothing to Disclose, John Lemasters:Nothing to Disclose, Don Rockey:Nothing to Disclose.

★ 1403 | ASSOCIATION OF LOW VITAMIN D LEVELS WITH NON-ALCOHOLIC FATTY LIVER DISEASE IN LEAN INDIVIDUALS: A SYSTEMATIC REVIEW AND META-ANALYSIS

Raja Khan[1] Nasir Hasan Luck[2] Abbas Ali Tasneem[2] Zain Majid[2] Syed Mudassir Laeeq[3], [1]Bahrain Specialist hospital, [2]Sindh Institute of Urology and Transplantation, [3]Khamis Mushait armed forces Hospital

Background: Non-alcoholic fatty liver disease (NAFLD) is a growing global health concern, affecting approximately 25% of the global population. While traditionally linked to obesity and metabolic syndrome, NAFLD is increasingly recognized in individuals with normal body mass index (BMI), termed 'lean NAFLD.' Identifying risk factors for lean NAFLD is vital, as these individuals often escape routine screening yet may still progress to advanced liver disease. Vitamin D, known for its immunomodulatory and anti-inflammatory effects, has been implicated in liver metabolism and fibrogenesis. Several observational studies have suggested a link between low serum vitamin D levels and NAFLD, but its association in the lean population remains underexplored. This meta-analysis aims to systematically assess the relationship between serum vitamin D levels and NAFLD in lean individuals. **Methods:** A comprehensive literature search was conducted using PubMed, Semantic Scholar, and Google Scholar from January 2002 to May 2025. A total of 276 studies were initially identified. After screening and eligibility assessment, 7 studies were included in the final analysis. Study designs included observational, cross-sectional, and cohort studies. The total number of patients across all studies was 258,354. The effect size was measured using both odds ratios (OR) with 95% confidence intervals (CI) and mean differences in serum vitamin D levels between NAFLD and non-NAFLD lean individuals. A random-effects model was applied to account for between-study heterogeneity. Statistical heterogeneity was assessed using the I^2 statistic, and publication bias was evaluated using funnel plots. **Results:** The pooled analysis demonstrated a significant association between low vitamin D levels and the presence of NAFLD in lean individuals. The mean difference in serum vitamin D levels between lean NAFLD and non-NAFLD groups was −4.28 ng/mL (95% CI: −6.52 to −2.04, $p < 0.001$), indicating significantly lower levels in NAFLD patients. The odds ratio for vitamin D deficiency (< 20 ng/mL) being associated with NAFLD was 1.47 (95% CI: 1.22–1.77). Substantial heterogeneity was observed among studies (I^2 = 91%), which could be attributed to differences in geographic regions, population demographics, and diagnostic thresholds. Funnel plot inspection suggested minimal publication bias. **Conclusion:** This meta-analysis indicates a significant association between low serum vitamin D levels and the risk of non-alcoholic fatty liver disease in lean individuals. Given the emerging prevalence of lean NAFLD and its potential progression to more severe liver diseases, screening for vitamin D deficiency may serve as a valuable adjunct in identifying at-risk individuals. Further prospective studies are warranted

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to explore the causative relationship and potential benefits of vitamin D supplementation in this population.

Disclosures: Raja Khan:Nothing to Disclose, Nasir Hasan Luck:Nothing to Disclose, Abbas Ali Tasneem: Nothing to Disclose, Zain Majid:Nothing to Disclose, Syed Mudassir Laeeq:Nothing to Disclose.

1404 | A NEW FULLY AUTOMATED 3D LIVER ELASTOGRAPHY WORKFLOW IN MICE WITH SINGLE-CLICK ACQUISITION AND ANALYSIS

Thomas Kierski[1] Joseph Betthauser[1] Adam Aji[1] Juan Rojas[1] Ryan Gessner[1] Tomek Czernuszewicz[1], [1]Revvity, Inc.

Background: High-throughput ultrasound platforms such as Vega enable rapid longitudinal assessment of liver disease in preclinical models using shear wave elastography (SWE). However, SWE acquisition and analysis remain multi-step, requiring manual liver localization, region-of-interest (ROI) placement, and post hoc annotation. This study develops and evaluates a fully automated workflow combining AI-based liver localization with a robotic enabled agent-driven acquisition and analysis framework for single-click 3D elastography. **Methods:** A conventional workflow (scout B-mode, manual ROI placement, SWE acquisition, offline analysis) was replaced with a Python-based pipeline. An AI segmentation model identifies the liver from 3D scout scans and generates an organ mask to guide downstream actions. A modified U-Net was trained to delineate liver boundaries from 3D ultrasound datasets (training/validation/test: 536/72/108). Because high-resolution models did not generalize to lower-resolution SWE-paired B-mode images, a second model was developed. Training data were generated by down-sampling high-resolution scans and cropping to match SWE ROIs. An AI agent orchestrates the workflow by selecting optimal ROIs from scout segmentation, triggering acquisition, and refining segmentation on SWE data to compute stiffness metrics in 3D. The process can be executed with a single click or via natural language command. **Results:** The system reduced SWE acquisition and analysis to a single user interaction, enabling operators to prepare subsequent animals during scanning. Segmentation performance remained robust across imaging contexts. On held-out datasets, the high-resolution model achieved a Dice coefficient of 0.87 (R^2 = 0.93), while the SWE-paired model achieved 0.85 (R^2 = 0.96). The full workflow completes in < 4 minutes, including ~30 seconds for scout acquisition, 1-2 seconds each for localization and ROI selection, and ~3 minutes for 3D SWE across entire liver. A higher throughput 2D workflow can be completed in ~35 seconds if users wish to trade off comprehensive organ coverage for speed. **Conclusion:** This work demonstrates the feasibility of a fully automated, AI-driven workflow for 3D liver SWE acquisition and analysis in mice. By combining segmentation models tailored to specific imaging contexts with an agent-based orchestration framework, this approach reduces operator burden, improves reproducibility, and increases throughput. This capability has the potential to accelerate preclinical liver research and enable scalable longitudinal imaging studies.

Disclosures: Thomas Kierski:Nothing to Disclose, Joseph Betthauser:Revvity: Employee, Adam Aji:Nothing to Disclose, Juan Rojas:Nothing to Disclose, Ryan Gessner:Revvity, Inc.: Employee, Tomek Czernuszewicz:Revvity, Inc.: Employee.

1405 | HEPATIC THR-β EXPRESSION ACROSS FIBROSIS STAGES AND NAS SCORES IN MASLD/MASH: IMPLICATIONS FOR THR-β–TARGETED THERAPY

Esteban Arroyave[1] Omar Saldarriaga[1] Kellen Henning[1] Monique Ferguson[1] Deena Kapadia[2] Israa Ali[1] Michael Kueht[1] Heather Stevenson-Lerner[1], [1]University of Texas Medical Branch, [2]Asst Professor Clin Practice

Background: Thyroid hormone receptor beta (THR-β) is a key regulator of hepatic lipid metabolism and the therapeutic target of resmetirom, the first FDA-approved therapy for noncirrhotic metabolic dysfunction-associated steatohepatitis (MASH). Emerging transcriptomic studies suggest that hepatic THRB expression and transcriptional activity decline with fibrosis progression and are associated with adverse clinical outcomes. However, most evidence is derived from RNA-based studies, and protein-level characterization of THR-β across clinically relevant stages of MASLD/MASH remains limited. **Methods:** Archived liver biopsies from patients with MASLD/MASH representing distinct fibrosis stages and NAFLD Activity Scores (NAS) were analyzed using automated immunohistochemistry and multiplex immunofluorescence. THR-β protein expression was assessed using a validated anti-THR-β antibody (NR1A2; Novus Biologicals) on the Ventana platform (Roche Diagnostics) with OPAL 570 detection. Whole-slide multispectral imaging and fluorescence microscopy (Vectra 3, Akoya Biosystems) were used to evaluate THR-β staining patterns. Representative cases included patients with minimal fibrosis (F1/4, NAS 5/8) and advanced fibrosis (F4/4, NAS 5/8). **Results:** THR-β protein was detected predominantly in hepatocytes and demonstrated heterogeneous expression across fibrosis stages. Liver tissue with minimal fibrosis exhibited focal and less

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extensive THR-β staining, whereas advanced fibrotic tissue displayed broader and more heterogeneous immunoreactivity. Differences in staining intensity and distribution were observed despite similar NAS scores, suggesting that fibrosis-associated changes may influence THR-β expression independently of histologic disease activity. The proposed workflow generated robust and reproducible signal with appropriate cellular localization, supporting its utility for systematic THR-β assessment in archived liver tissue. **Conclusion:** Hepatic THR-β expression exhibits substantial heterogeneity across fibrosis stages in MASLD/MASH. These preliminary findings support the concept that THR-β signaling varies across clinically relevant disease phenotypes and may contribute to disease heterogeneity. Reliable quantification of THR-β protein in routine liver biopsies provides a clinically scalable approach for evaluating this pathway and may support future biomarker-driven patient stratification for THR-β–targeted therapies.

Disclosures: Esteban Arroyave:Nothing to Disclose, Omar Saldarriaga:Nothing to Disclose, Kellen Henning: Nothing to Disclose, Monique Ferguson:Nothing to Disclose, Deena Kapadia:Nothing to Disclose, Israa Ali: Nothing to Disclose, Michael Kueht:Nothing to Disclose, Heather Stevenson-Lerner:Nothing to Disclose.

1406 | LA-RELATED PROTEIN 1 (LARP1) AS A DRIVER OF METABOLIC DYSFUNCTION–ASSOCIATED STEATOTIC LIVER DISEASE

Komal Ramani[1] Chandana Thimme Gowda[1] sonal sinha[1] Mario Alba[1] Jose Mato[2] Shelly Lu[1], [1]Cedars-Sinai Medical Center, [2]CICBiogune

Background: Metabolic dysfunction–associated steatotic liver disease (MASLD) can progress from steatosis to MASH and hepatocellular carcinoma (HCC). Methionine adenosyltransferase 1A (*MAT1A*, encodes for MATα1) is responsible for the biosynthesis of S-adenosylmethionine (SAMe) in normal liver and its expression is reduced in human MASLD and HCC. Consistently, *Mat1a* knockout (KO) mice spontaneously develop MASH and HCC and their liver proteomics showed disruptions in mitochondrial, peroxisomal, and translational pathways. The translational regulator, La-related protein 1, LARP1, which binds 5′-terminal oligopyrimidine (TOP) mRNAs, was induced and hyperphosphorylated at T503/S471 (human T449/S471) in *Mat1a* KO, and reversed by SAMe treatment. We assessed the global effects of LARP1 on mRNA translation and expression in SAMe deficient systems and observed that apart from TOP mRNAs, LARP1 influenced non-TOP mRNAs involved in metabolic regulation. We hypothesize that LARP1 drives MASLD by reprogramming non TOP mRNAs and seek to define this axis in disease progression. **Methods:** Actively translated non-TOP mRNAs from LARP1-overexpressing Huh7 cells were detected by RNA seq. Bulk RNA seq detected non-TOP mRNA expression in advanced MASH *Mat1a* KOs with or without *Larp1* silencing (si*Larp1*). Liver steatosis, inflammation, and fibrosis were evaluated by BODIPY, F4/80, and Sirius Red staining. mRNA stability was assessed by actinomycin D chase assays. Metabolite alterations were identified by untargeted metabolomics of the liver. **Results:** LARP1 elevation in de-differentiated primary hepatocytes, diet induced MASH models and in human MASLD was associated with a fall in MATα1. S/T to A mutants of LARP1's SAMe sensitive phospho-sites destabilized the protein in SAMe-deficient cell lines. Beyond canonical TOP mRNAs, LARP1 altered numerous non TOP transcripts involved in hepatic metabolism, including *SIRT5* (peroxisomal β oxidation, PBO), *c-MYC* (aerobic glycolysis), and mitochondrial ribosomal proteins involved in oxidative phosphorylation or OXPHOS (*MRPL13*, *MRPL50*, *MRPL59*). CRISPR deletion of *Larp1* in Mat1a KOs normalized these transcripts and the metabolite profiles associated with these pathways, markedly reducing lipid accumulation, inflammation, and fibrosis. Conversely, LARP1 activation (via increased expression or phosphorylation) in normal liver and primary human hepatocytes increased lipid deposition and impaired mitochondrial respiration. Under SAMe deficiency, LARP1 destabilized *SIRT5* and *MRPLs* while stabilizing *c-MYC*; SAMe treatment reversed these effects. **Conclusion:** Our study reveals a previously unrecognized role for LARP1 activation as a driver of MASLD progression through perturbations in mRNA stability of its targets, disrupting hepatic metabolic homeostasis. Targeting LARP1 activation may offer a novel therapeutic strategy for MASLD.

Disclosures: Komal Ramani:Nothing to Disclose, Chandana Thimme Gowda:Nothing to Disclose, sonal sinha:Nothing to Disclose, Mario Alba:Nothing to Disclose, Jose Mato:Nothing to Disclose, Shelly Lu: Nothing to Disclose.

★ 1407 | AROCLOR1260, PCB126, AND PALMITIC ACID EXPOSURE REGULATE SITE-SPECIFIC M6A MODIFICATIONS IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD)-RELATED GENES IN FETAL FL83B AND ADULT AML12 MOUSE HEPATOCYTES

Carolyn Klinge[1] Belinda Petri[2] Kellianne Piell[1] Abigail Shaw[1] Gjhvona Bryant[1] Julia Chariker[3] Eric Rouchka[1] Matthew Cave[1], [1]University of Louisville School of Medicine, [2]University of Louisville School of Medicine, [3]University of Louisville

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Background: Prenatal and early environmental exposures enhance susceptibility to metabolic disease in later life. Polychlorinated biphenyls (PCBs) act as metabolism disrupting chemicals (MDCs) to promote metabolic dysfunction-associated steatotic liver disease (MASLD) in humans. Post-transcriptional chemical modification of mRNA regulates transcript stability, splicing, and translation. PCB-exposure in combination with a high fat diet (HFD) induced MASLD and progression to metabolic-associated steatohepatitis (MASH) in male mice and resulted in N-6-methyladenosine (m6A) mRNA modifications in differentially expressed genes (DEG) in pathways of MASLD pathogenesis. With the goal of using a tractable system to edit m6A sites in MASLD-related genes regulated by PCB exposure, we examined the impact of PCB exposure on m6A-modified DEG expression in two mouse hepatocyte cell lines. **Methods:** We evaluated the protein abundance of m6A writers, readers, and erasers in FL38B fetal and AML12 adult mouse hepatocyte cell lines by western blot. We compared the response of palmitic acid (as a HFD mimetic)-treated FL38B and AML12 mouse hepatocytes to vehicle control or after exposure to combined Aroclor1260 + PCB126. Integration of short-read Illumina RNA-seq and Nanopore direct long read RNA seq (DRS) identified DEG with site-specific m6A modifications. **Results:** The abundance of m6A writer proteins METTL3 and METTL14 was higher in FL83B whereas METLL16 and the m6A eraser proteins FTO and ALKBH5 were higher in AML12 cells. Cell-specific differences in the levels of specific m6A readers including IGF2BP2, YDHDC1, and YDHDC2 were observed. More DEG correlated with m6A-alterations were found in PCB-exposed FL83B (1,863, including Apob, Gstm2, Cpt1a, Hnf4a, Krt18, and Pparg) than AML12 (54, including Gsr and Gclc) cells. PCB exposure decreased Srebf1 in both cell lines. **Conclusion:** These data suggest that fetal liver may be more susceptible to PCB exposure-induced m6A alteration and downstream pathway changes associated with MASLD and its progression to MASH.

Disclosures: Carolyn Klinge:Nothing to Disclose, Belinda Petri:Nothing to Disclose, Kellianne Piell: Nothing to Disclose, Abigail Shaw:Nothing to Disclose, Gjhvona Bryant:Nothing to Disclose, Julia Chariker: Nothing to Disclose, Eric Rouchka:Nothing to Disclose, Matthew Cave:Nothing to Disclose.

1408 | AWARENESS OF LIVER DISEASE TERMS BY SOURCES OF INFORMATION

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Background: Public awareness of liver disease remains limited, particularly as terminology evolves from widely recognised terms such as fatty liver disease to newer clinical nomenclature including MASLD and MASH. Understanding how familiarity with these terms relates to where individuals perceive they obtain valuable health information is important for informing effective communication strategies. This study therefore examines the association between self-reported health-information sources and awareness of key liver disease terms. **Methods:** We conducted a survey of n = 3,010 US adults using a stratified sampling frame on gender, age, race, and education according to the 2023 American Community Survey distributions. Weighting yielded n = 1,000 respondents who are living with obesity (BMI > 30) or diagnosed with diabetes. We examined the distribution of term awareness by information sources and applied chi-square tests to determine the strength of association between distributions. **Results:** Across the tested terms, there is a positive correlation between being familiar with the term and learning health information of value from any sources. Similarly, among those being unfamiliar with the terms, they tend not to have learned health information of value from any source. **Conclusion:** Familiarity with liver disease terminology varied substantially, with broader recognition of terms such as fatty liver disease and liver cirrhosis and much lower familiarity with newer terms such as MASLD and MASH. Respondents who reported learning valuable health information from sources such as healthcare providers, the internet, social media, and friends or family differed significantly in their familiarity with these terms. Public health practitioners should use clear, consistent terminology across trusted health-information channels and develop messaging that bridges familiar language with newer clinical terms.

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Table 1. Awareness of liver disease terms by sources of information

Conditions		Sources of information: My healthcare provider		Friends and/or family		Internet research (excl. social media)		Social media unintentional scrolling		Social media intentional searches	
		True	False	True	False	True	False	True	False	True	False
Fatty liver disease	Yes (60%)	528 (62%)	72 (49%)	424 (62%)	175 (55%)	481 (65%)	119 (46%)	264 (66%)	334 (56%)	253 (68%)	343 (55%)
	No	325 (38%)	75 (51%)	258 (38%)	143 (45%)	261 (35%)	139 (54%)	138 (34%)	264 (44%)	119 (32%)	285 (45%)
NAFLD	Yes (36%)	321 (38%)	37 (25%)	251 (37%)	105 (33%)	300 (40%)	58 (22%)	162 (40%)	194 (32%)	156 (42%)	198 (31%)
	No	532 (62%)	110 (75%)	431 (63%)	213 (67%)	442 (60%)	200 (78%)	240 (60%)	404 (68%)	216 (58%)	430 (69%)
MASLD	Yes (13%)	112 (13%)	19 (13%)	90 (13%)	42 (13%)	110 (15%)	22 (8%)	60 (15%)	71 (12%)	65 (17%)	65 (10%)
	No	741 (87%)	128 (87%)	592 (87%)	276 (87%)	632 (85%)	236 (92%)	342 (85%)	527 (88%)	307 (83%)	563 (90%)
Liver fibrosis	Yes (24%)	213 (25%)	29 (20%)	175 (26%)	66 (21%)	188 (25%)	53 (21%)	100 (25%)	140 (23%)	102 (28%)	138 (22%)
	No	640 (75%)	118 (80%)	507 (74%)	252 (79%)	554 (75%)	205 (79%)	302 (75%)	458 (77%)	270 (72%)	490 (78%)
Liver cirrhosis	Yes (61%)	548 (64%)	63 (43%)	437 (64%)	172 (54%)	487 (66%)	122 (47%)	264 (66%)	344 (57%)	240 (64%)	368 (59%)
	No	305 (36%)	84 (57%)	245 (36%)	146 (46%)	255 (34%)	136 (53%)	138 (34%)	254 (43%)	132 (36%)	260 (41%)
MASH	Yes (12%)	103 (12%)	17 (11%)	82 (12%)	38 (12%)	99 (13%)	21 (8%)	59 (15%)	61 (10%)	55 (15%)	64 (10%)
	No	750 (88%)	130 (89%)	600 (88%)	280 (88%)	643 (87%)	237 (92%)	343 (85%)	537 (90%)	317 (85%)	564 (90%)

P-value table:

	My healthcare provider	Family and/or friends	Internet research (excl. social media)	Social media unintentional scrolling	Social media intentional searches
Fatty liver disease	1.6E-114	1.2E-112	3.6E-123	5.9E-115	2.4E-118
NAFLD	1.7E-114	2.5E-111	1.4E-122	1.5E-113	1.1E-115
MASLD	9.5E-111	9.5E-111	1.0E-113	1.2E-111	3.3E-115
Liver fibrosis	1.4E-111	4.2E-112	8.7E-112	7.1E-111	1.7E-112
Liver cirrhosis	4.1E-121	9.6E-115	2.2E-122	1.1E-113	3.3E-112
MASH	9.0E-111	9.5E-111	7.1E-113	1.0E-112	8.4E-113

Note: Sources of information item read "*I have learned health information of value to me from …*" and condition item read "*Are you familiar with any of the following terms?*" Full terms and their abbreviations were presented to respondents. Chi-square tests for each association (2x2 squares defined by bolded lines) yielded p-values <0.001.

Disclosures: Trenton White:Nothing to Disclose, Leire Agirre-Garrido:Nothing to Disclose, Lila Neal:Nothing to Disclose, Sonal Kumar:Nothing to Disclose, Melina Manolas:Doximity: Social Media Content Provision, Health Monitor Network: Advisor, Roon: Stock options, Madrigal Pharmaceuticals: Consulting, Scott Isaacs: Nothing to Disclose, Jeffrey Lazarus:Nothing to Disclose.

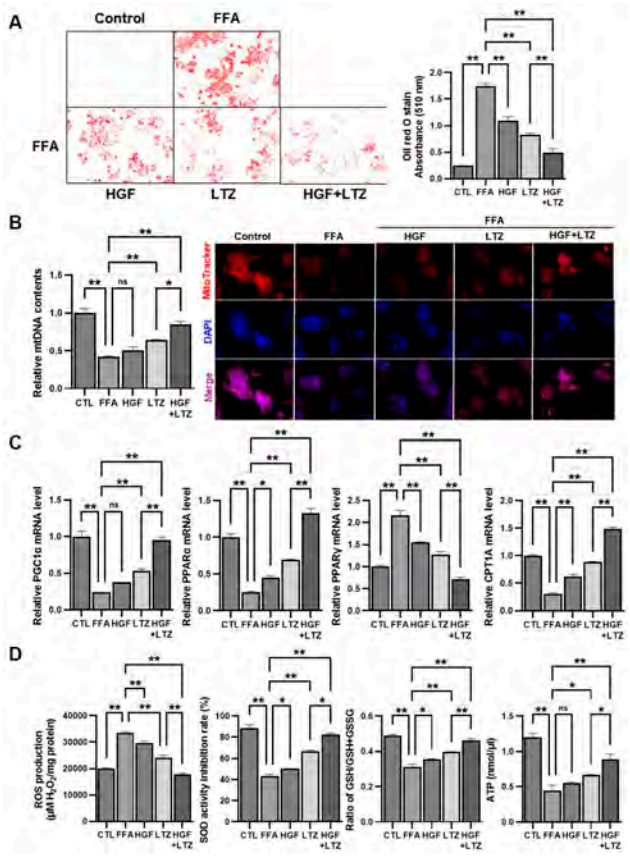
1409 | LOBEGLITAZONE COMBINED WITH HGF ATTENUATES FFA-INDUCED HEPATIC STEATOSIS VIA COORDINATED AMPK–PPARα–PGC1α AXIS ACTIVATION IN HEPG2 CELLS

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Background: Lobeglitazone, a dual peroxisome proliferator-activated receptor α/γ (PPARα/γ) agonist, improves metabolic parameters; however, its therapeutic role in hepatic steatosis remains incompletely characterized. Hepatocyte growth factor (HGF) regulates liver protection and lipid homeostasis through c-MET–AMPK signaling. We investigated the effects of lobeglitazone alone and in combination with HGF on free fatty acid (FFA)–induced hepatic steatosis in HepG2 cells and explored the underlying mechanisms. **Methods:** HepG2 cells were exposed to FFAs to induce intracellular lipid accumulation and subsequently treated with lobeglitazone, HGF, or their combination. Lipid accumulation was evaluated by Oil Red O staining. Mitochondrial function was assessed using mitochondrial DNA quantification and MitoTracker staining. Expression of genes and proteins involved in lipid metabolism and mitochondrial regulation was analyzed using quantitative real-time polymerase chain reaction and Western blotting. Oxidative stress and antioxidant capacity were evaluated by measuring intracellular reactive oxygen species (ROS), superoxide dismutase (SOD) activity, glutathione redox balance, and intracellular ATP levels. **Results:** Lobeglitazone treatment significantly reduced intracellular lipid accumulation in FFA-treated HepG2 cells, and this effect was further enhanced by co-treatment with HGF (Figure 1A). HGF co-treatment more effectively restored mitochondrial DNA content and mitochondrial integrity than either treatment alone (Figure 1B). At the molecular level, lobeglitazone treatment restored expression of PPARα, PGC1α, and CPT1A while attenuating FFA-induced upregulation of PPARγ, and these effects were further enhanced by co-treatment with HGF (Figure 1C). HGF significantly increased AMPK phosphorylation, and this effect was further amplified by lobeglitazone co-treatment. Combined treatment also more substantially improved redox homeostasis, reflected by lower ROS levels, enhanced SOD activity, higher GSH/GSSG ratio, and increased intracellular ATP compared with either monotherapy (Figure 1D). **Conclusion:** Lobeglitazone attenuated FFA-induced intracellular lipid accumulation and mitochondrial dysfunction in steatotic hepatocytes, and these effects were further enhanced by co-treatment with HGF. Combined treatment was associated with coordinated activation of the AMPK–PPARα–PGC1α axis and restoration of redox balance, suggesting a potential synergistic effect on hepatocellular lipid metabolism under lipotoxic conditions.

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Disclosures: Yun Bin Lee:Eisai: Consultant, Gilead Sciences: Consultant, Roche: Consultant, Chong Kun Dang Pharmaceutical Corporation: Grant/ Research Support, Samil Pharmaceutical: Grant/ Research Support, AstraZeneca: Advisor, Se-Mi Jung:Nothing to Disclose, Jeayeon Park:Nothing to Disclose.

1410 | SEX DIFFERENCES IN MASH PROGRESSION ARE UNDERPINNED BY DIVERGENT HEPATIC PROTEOMIC SIGNATURES IN THE GAN DIO MOUSE MODEL

Isabella Simon[1] Samantha Emery-Corbin[2] Timothy Fitchett[2] Alannah Hunt[3] Avik Majumdar[4] Robert Widdop[2] Mark Del Borgo[2], [1]Monash Unviersity, [2]Monash University, [3]Monash Univeristy, [4]Austin Hospital

Background: MASH is the progressive and inflammatory form of steatotic liver disease. Premenopausal women exhibit lower MASH risk than men, but this protection is lost following menopause and underlying mechanisms remain poorly understood with preclinical research remaining predominantly male-biased. This study characterised sex-divergent proteomic and histological MASH trajectories in the GAN DIO mouse model. **Methods:** Male and female C57BL/6J mice were fed Gubra Amylin NASH (GAN) diet or chow for 26 or 40 weeks. Histopathology was assessed by MASH CRN scoring; fibrosis was quantified by picrosirius red staining and SHG imaging. Hepatic proteomes were characterised by DIA-MS on an Orbitrap Astral, processed in Spectronaut (v20.4) against the UniProt mouse proteome; differentially expressed proteins (DEPs) were defined at p.adj < 0.05 and $\log_2$FC ≥ 1. GO enrichment used clusterProfiler (v4.14.6) against 8,769 detected proteins (p.adj < 0.05, q < 0.2). **Results:** Histologically, 100% of males met MASH criteria (NAS ≥ 5) by 26 weeks with clinically significant fibrosis in all animals, versus 40% of females; consistent female MASH was not established until 40 weeks. Females showed lower NAS from 12 weeks, with reduced inflammation, ballooning, and collagen deposition (p < 0.05). By 40 weeks, all males reached F3-4 fibrosis versus 28% of females (p < 0.05). GAN diet induced 663 DEPs in males versus 145 in females at 26 weeks, expanding to 753 versus 205 at 40 weeks. Male GO enrichment at 26 weeks was dominated by ECM upregulation (collagen-containing ECM: 79 proteins; p.adj = 1.3×10^{-27}), innate immune activation (inflammatory response: 97 proteins; p.adj = 1.4×10^{-19}), and pro-inflammatory arachidonate metabolism via Cyp4a12b. Females demonstrated enrichment of anti-inflammatory EET biosynthesis, fatty acid oxidation, and estrogen receptor signalling, consistent with hepatoprotection. By 40 weeks, male ECM remodelling intensified (94 proteins; p.adj = 3.7×10^{-36}) with CYP450 suppression (arachidonate monooxygenase: FE = 28.4; p.adj = 9.8×10^{-13}). Females acquired a male-like immune-inflammatory signature (immune effector process: 40 proteins; p.adj = 5.1×10^{-14}) alongside downregulation of estrogen 16α-hydroxylase (FE = 62.1; p.adj = 2.8×10^{-7}) and arachidonate monooxygenase (FE = 32.8; p.adj = 5.0×10^{-7}). **Conclusion:** Males exhibit early ECM remodelling, innate immune activation, and pro-inflammatory arachidonate metabolism consistent with accelerated liver fibrosis. Females are protected by EET biosynthetic pathways, lipid oxidation, and estrogen signalling, but acquire a male-like inflammatory proteome by 40 weeks, providing a molecular basis for histological convergence. These findings identify CYP450-mediated eicosanoid and estrogen metabolism as critical checkpoints in sex-specific MASH pathogenesis, supporting inclusion of female cohorts across the full disease time-course in preclinical studies.
Disclosures: Isabella Simon:Nothing to Disclose, Samantha Emery-Corbin:Nothing to Disclose, Timothy Fitchett:Nothing to Disclose, Alannah Hunt:Nothing to Disclose, Avik Majumdar:Nothing to Disclose, Robert Widdop:Nothing to Disclose, Mark Del Borgo:Nothing to Disclose.

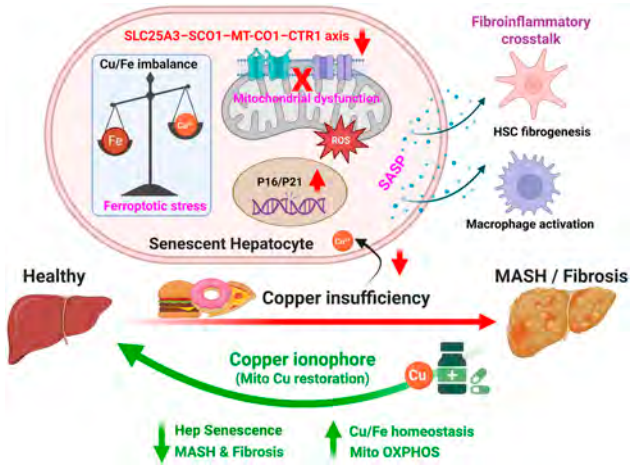
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1411 | DISRUPTED MITOCHONDRIAL COPPER HOMEOSTASIS PROMOTES FERROPTOTIC STRESS, HEPATOCYTE SENESCENCE AND MASLD PROGRESSION

Kuo Du[1] Niansheng Ren[2] Liuyang Wang[2] Rajesh Dutta[2] David Umbaugh[2] Qiaojuan Zhang[1] Seh-Hoon Oh[3] Dennis Ko[2] Ming Song[4] Anna Mae Diehl[3], [1]University of Kansas Medical Center, [2]Duke University, [3]Duke University, [4]University of Louisville

Background: Systemic metabolic dysfunction promotes degenerative diseases in many organs, including liver and kidney. The liver is a master regulator of systemic metal ion homeostasis. Hepatic copper deficiency is increasingly observed in metabolic dysfunction associated steatotic liver disease (MASLD) and is associated with greater disease severity and poor outcomes. However, mechanisms linking copper dysregulation to MASLD and its comorbidities remain poorly defined. We investigated whether impaired mitochondrial copper homeostasis contributes to MASLD-related pathobiology and represents a modifiable therapeutic axis. **Methods:** We employed dietary mouse models of MASLD, in vitro hepatocyte systems, and integrated analyses of human transcriptomic cohorts to investigate the role of mitochondrial copper in disease progression and systemic outcomes **Results:** Using dietary mouse models of MASLD and *in vitro* systems, we found that dietary copper deficiency induces lipotoxicity and suppresses mitochondrial metabolic programs. MASLD livers exhibited marked depletion of copper, impaired cytochrome c oxidase integrity, and bioenergetic failure. Targeted restoration of mitochondrial copper with the copper ionophore normalized copper-handling programs, improved mitochondrial function, and suppressed ferroptotic stress, hepatocyte senescence, and fibroinflammatory remodeling. Mechanistically, reduced expression of the mitochondrial copper transporter *SLC25A3* and *MT-CO1* disrupted the SLC25A3–SCO1–MT-CO1–CTR1 axis, limited copper uptake and destabilized copper-iron balance, promoting maladaptive cell fate changes. Across multiple human cohorts and mouse models, copper-iron imbalance tracks with MASLD progression, clinical outcomes, and multiple extrahepatic comorbidities; restoring copper homeostasis in mice with MASLD attenuates both liver and kidney inflammation and fibrosis. **Conclusion:** Mitochondrial copper deficiency is a mechanistically actionable driver of MASLD that promotes bioenergetic failure, ferroptosis, senescence and fibroinflammatory damage in the liver and other organs. Targeting copper-centered mitochondrial regulation represents a novel biomarker and therapeutic strategy for MASLD and its systemic complications.



Disclosures: Kuo Du:Nothing to Disclose, Niansheng Ren:Nothing to Disclose, Liuyang Wang:Nothing to Disclose, Rajesh Dutta:Nothing to Disclose, David Umbaugh:Nothing to Disclose, Qiaojuan Zhang:Nothing to Disclose, Seh-Hoon Oh:Nothing to Disclose, Dennis Ko:Nothing to Disclose, Ming Song:Nothing to Disclose, Anna Mae Diehl:Nothing to Disclose, Nothing to Disclose, Nothing to Disclose.

1412 | POSTOPERATIVE CALORIC RESTRICTION AMELIORATES MASLD AND REMODELS HEPATIC LIPID PROFILES IN MORBIDLY OBESE RATS UNDERGOING SLEEVE GASTRECTOMY

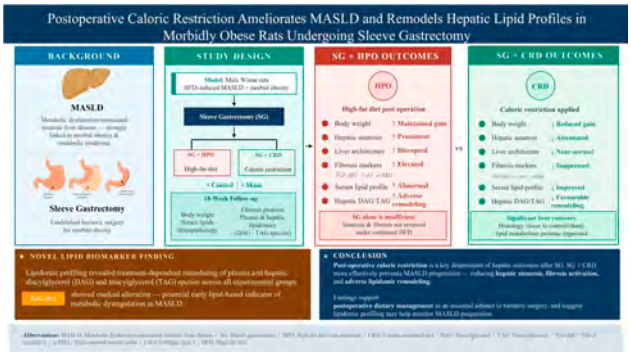
Wei-Yu Kao[1] Ching-Wen Chang[2] Chin-Ying Wu[3] Chun-Chao Chang[4] Shih-Yi Huang[2], [1]Taipei Medical University Hospital, [2]Graduate Institute of Metabolism and Obesity Sciences, Taipei Medical University, Taipei, Taiwan, [3]School of Nutrition and Health Sciences, Taipei Medical University, Taipei, Taiwan, [4]Division of Gastroenterology and Hepatology, Taipei Medical University Hospital

Background: Metabolic dysfunction–associated steatotic liver disease (MASLD) is strongly associated with morbid obesity and metabolic syndrome. Although sleeve gastrectomy (SG) is an established treatment for morbid obesity, whether its hepatic benefits are sustained without postoperative dietary control remains unclear. This study evaluated the effects of caloric restriction after SG on MASLD progression and lipidomic remodeling in morbidly obese rats. **Methods:** Male Wistar rats were used to establish morbid obesity with MASLD. After MASLD induction, rats underwent SG and received either a high-fat diet post-operation (HPO) or calorie-restricted diet (CRD) for 18 weeks. Control and sham-operated groups were included for

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comparison. Body weight, caloric intake, serum biochemical variables, organ weights, hepatic cytokines, gross liver morphology, histopathology, fibrosis-related protein expression, lipid metabolism–related protein expression, and plasma/hepatic lipidomic profiles were assessed. **Results:** Continued HPO after SG maintained weight gain and MASLD-related liver injury, including pale enlarged liver morphology, prominent steatosis, disrupted lobular architecture, hepatic lipid accumulation, and increased fibrosis-related protein expression. SG alone partially improved metabolic parameters but did not sustainably reverse hepatic steatosis or fibrosis under continued HFD exposure. In contrast, CRD after SG reduced caloric intake and body weight gain, improved circulating lipid-related biochemical parameters, and attenuated hepatic lipid accumulation. Histology showed liver morphology and hepatic architecture closer to control/sham groups in CRD-treated rats. CRD also suppressed fibrosis-related markers, including transforming growth factor-β receptor 1, collagen I, and α-smooth muscle actin, and improved hepatic lipid metabolism–related protein expression. Lipidomic profiling demonstrated treatment-dependent remodeling of plasma and hepatic diacylglycerol and triacylglycerol species. Diacylglycerol 38:2 showed marked alteration across MASLD-related metabolic conditions, supporting its potential relevance as an early lipid-based indicator of metabolic dysregulation. **Conclusion:** Postoperative caloric restriction is a key determinant of hepatic outcomes after SG in morbidly obese rats with MASLD. SG combined with an 18-week CRD more effectively prevented MASLD progression than SG with continued HFD by reducing hepatic steatosis, inflammatory activity, fibrosis-related protein activation, and adverse lipidomic remodeling. These findings support postoperative dietary management as an essential adjunct to bariatric surgery and suggest that lipidomic profiling may help monitor MASLD progression.



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1413 | HEPATOCYTE ADENOSINE KINASE SENSITIZES AGED MASLD TO KETOGENIC DIET–INDUCED HEPATOCELLULAR CARCINOMA IN MICE

Chaodong Wu[1] Honggui Li[1] Xiaojing Li[1] Miaoyun Chen[1], [1]Texas A&M University

Background: Aging is a major risk factor that is shown to significantly increases the incidence of hepatocellular carcinoma (HCC) in individuals with metabolic dysfunction–associated steatotic liver disease (MASLD) and steatohepatitis (MASH), the advanced form of MASLD. In the liver, adenosine kinase (ADK) is highly expressed and plays an important role in promoting steatosis and inflammation. While various studies have addressed the effect of ketogenic diet (KD) on metabolic dysfunction and MASLD, the effect of KD on aged MASLD remain unclear. Here, we examined the impact of KD on HCC development in aged MASLD, particularly in an ADK-high context. **Methods:** Human liver specimens from MASLD patients and healthy controls stratified by age (young vs aged) were analyzed by hematoxylin and eosin (H&E) staining and ADK immunohistochemistry. Aged and young mice were fed a MASLD-inducing diet, followed by liver histopathology and RNA sequencing with pathway enrichment analysis to identify aging-associated tumor-related transcriptional programs. To evaluate diet-triggered tumor susceptibility in an ADK-high context, 12-month-old hepatocyte-specific ADK overexpression (Hep-ADK^{Tg}) mice were fed KD for 6 months, with age-matched chow diet (CD)-fed Hep-ADK^{Tg} and KD-fed WT mice as controls, and liver phenotypes and HCC incidence were assessed. **Results:** In human liver specimens, ADK immunohistochemistry showed higher hepatic ADK expression in MASLD patients compared with healthy controls. ADK staining intensity increased with MASLD severity and was more pronounced in aged MASLD patients than in young MASLD patients. In mice, aged MASH exhibited more severe inflammation, hepatocellular ballooning, and steatosis than young MASH. RNA-seq analysis further revealed significant enrichment of tumor-related transcriptional programs in aged MASH livers, including pathways associated with hepatocellular carcinoma development. After 6 months of KD feeding in 12-month-aged mice, HCC incidence was significantly higher in Hep-ADK^{TG} mice, whereas no increase was observed in CD-fed Hep-ADK ^{Tg} mice or KD-fed aged MASLD WT mice. **Conclusion:** Hepatic ADK is elevated in MASLD and is further increased with aging. Aged MASH livers exhibit activation of tumor-related transcriptional programs, indicating a tumor-permissive molecular state. Under conditions of elevated

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hepatocyte ADK, KD exposure may promote HCC development, suggesting that ADK is a potential determinant of diet-dependent tumor susceptibility in aging-associated MASLD.
Disclosures: Chaodong Wu:Nothing to Disclose, Honggui Li:Nothing to Disclose, Xiaojing Li:Nothing to Disclose, Miaoyun Chen:Nothing to Disclose.

1414 | GMFB DRIVES MITOCHONDRIAL DYSFUNCTION AND PROMOTES MASH PROGRESSION VIA INHIBITION OF MITOPHAGY

Zhongquan Sun[1] Weilin Wang[2] Haotian Fu[2] Hongfan Ding[2], [1]Zhejiang University, [2]The Second Affiliated Hospital Zhejiang University School of Medicine

Background: MASH is a chronic inflammatory disease that can progress to cirrhosis and hepatocellular carcinoma (HCC). The key molecular mechanisms underlying this progression remain unclear. **Methods:** Protein expression was evaluated using immunohistochemistry and immunofluorescence. Co-immunoprecipitation (Co-IP), pull-down assays, and mass spectrometry were performed to identify GMFB-interacting proteins and phosphorylation sites. GMFB translocation and mitophagy were assessed by immunoblotting and immunofluorescence. A liver-specific GMFB knockout mouse model was generated to investigate its role in MASH progression in vivo. **Results:** GMFB expression was significantly elevated in MASH tissues. Free fatty acids (FFAs) induced phosphorylation of GMFB at T27 via the ERK signaling pathway, promoting its translocation from the cytoplasm to mitochondria. Mitochondrial GMFB competitively bound to PINK1, thereby impairing PARKIN recruitment and subsequent mitophagy, leading to mitochondrial dysfunction and hepatocyte injury. In vivo, liver-specific GMFB knockout alleviated mitochondrial damage and reduced steatosis, inflammation, and fibrosis in MASH models. Furthermore, in human MASH samples, GMFB expression positively correlated with disease severity and mitochondrial dysfunction. **Conclusion:** This study identifies a novel mechanism whereby FFA-induced phosphorylation and mitochondrial translocation of GMFB inhibit PINK1/PARKIN-mediated mitophagy, thereby contributing to MASH pathogenesis. Targeting GMFB may represent a promising therapeutic strategy for MASH.
Disclosures: zhongquan Sun:Nothing to Disclose, Weilin Wang:Nothing to Disclose, Haotian Fu:Nothing to Disclose, Hongfan Ding:Nothing to Disclose.

1415 | GENETIC AND PHARMACOLOGIC MIR-92A INHIBITION PROVIDES HEPATIC PROTECTION IN EXPERIMENTAL MASH

Philipp Stephan Althaus[1] Eike Fürst[1] Sara Zarei[1] Robert Schierwagen[1] Maximilian Joseph Brol[2] Frank Erhard Uschner[1] Stefanie Dimmeler[3] Jonel Trebicka[1] Sabine Klein[1], [1]University Hospital Münster, Internal Medicine B, Germany, [2]University Hospital Münster, [3]Goethe-University Frankfurt a.M. Institute of Cardiovascular Regeneration, Germany

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is an emerging cause of liver cirrhosis worldwide. Its progressive form, metabolic dysfunction-associated steatohepatitis (MASH), is a major driver of liver-related complications. Given the limited therapeutic options for MASH and the need for innovative biomarkers, this study aimed to define the role of miR-92a in disease progression and to evaluate its translational therapeutic potential through pharmacologic inhibition. **Methods:** miR-92a expression was analyzed in human MASH liver biopsies and in experimental MASH models, including Sprague Dawley (SD) rats and wild-type (wt) mice. Hepatic effects of miR-92a inhibition with LNA92a in wt mice and hepatocyte-specific deletion of miR-92a in Alb-Cre +miR-92a$^{fl/fl}$ (miR-92a$^{\Delta Hep}$) mice were evaluated and compared with wt controls. Hepatic profibrotic and inflammatory gene expression was assessed. Fibrosis was quantified by Sirius-Red (SR) and αSMA staining, hepatocyte injury by serum AST/ALT levels, and portal hypertension by *in-vivo* portal pressure (PP) measurement. **Results:** Hepatic miR-92a expression was upregulated in human MASH biopsies and in experimental MASH models compared to controls. The induction of MASH in miR-92a$^{\Delta Hep}$ and in LNA92a–treated wt mice showed reduced expression of hepatic profibrotic genes (TGFβ and Col1a1). Hepatic stellate cell (HSC) activation was attenuated, reflected by reduced αSMA and PDGF gene expression in LNA92a–treated wt mice with MASH. Subsequently, SR stainings demonstrated reduced collagen deposition while αSMA immunostaining confirmed decreased HSC activation. Markers of mitochondrial dysfunction (EMR1 and CCL2) were associated with decreased chemokine and cytokine release resulting in dampened inflammatory signaling. AST and ALT serum levels were reduced, indicating diminished necroinflammation and hepatocellular injury in miR-92a$^{\Delta Hep}$ mice compared to wt controls. In addition to decreased fibrosis, also PP was lower in both LNA92a–treated and miR-92a$^{\Delta Hep}$ mice. **Conclusion:** miR-92a is a key regulator and biomarker in MASH. Therefore, the inhibition of miR-92a using LNA92a represents a pioneering

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translational therapeutic strategy to improve hepatic function.

Disclosures: Philipp Stephan Althaus:Nothing to Disclose, Eike Fürst:Nothing to Disclose, Sara Zarei: Nothing to Disclose, Robert Schierwagen:Nothing to Disclose, Maximilian Joseph Brol:AbbVie: Consultant, Gilead: Speaking and Teaching, Falk Foundation: Speaking and Teaching, Chiesi: Speaking and Teaching, Chiesi: Grant/Research Support, Frank Erhard Uschner:Nothing to Disclose, Stefanie Dimmeler:Nothing to Disclose, Jonel Trebicka:Nothing to Disclose, Sabine Klein:Nothing to Disclose.

1416 | CARDIOMETABOLIC AND ADIPOSE TISSUE ABNORMALITIES IN THE STAM MOUSE MODEL OF MASH: IMPLICATIONS FOR EXTRAHEPATIC CLINICAL OUTCOMES

Taishi Hashiguchi[1], [1]SMC Laboratories,Inc

Background: MASH is increasingly recognized as a systemic disease associated not only with liver-related events but also with cardiovascular events and multi-organ complications, which represent major determinants of clinical outcomes. However, preclinical MASH models are often evaluated mainly by hepatic histology and fibrosis endpoints. This study aimed to characterize cardiometabolic and adipose tissue-related features in the STAM mouse model, with a focus on endpoints relevant to extrahepatic clinical outcomes. **Methods:** STAM mice were evaluated for cardiometabolic parameters related to cardiovascular risk, including blood pressure and plasma lipid profiles such as triglycerides and HDL cholesterol. In addition, adipose tissue morphology and adipocytokine-related changes were assessed to determine whether systemic metabolic dysfunction accompanies MASH progression in this model. **Results:** STAM mice showed an increase in blood pressure, suggesting the development of a cardiovascular risk-related phenotype. Plasma lipid analysis demonstrated changes in lipid parameters, including triglycerides and HDL cholesterol, consistent with cardiometabolic dysregulation. Histological evaluation of adipose tissue revealed adipose tissue expansion and adipocyte hypertrophy. Furthermore, adiponectin expression was decreased, indicating impaired adipose tissue function and altered adipocytokine regulation. **Conclusion:** These findings indicate that the STAM mouse model recapitulates not only hepatic features of MASH but also extrahepatic abnormalities related to cardiovascular risk, dyslipidemia, adipose tissue dysfunction, and adipocytokine imbalance. Therefore, STAM may be useful as a translational platform to evaluate therapeutic strategies targeting clinical outcomes beyond liver histology, including cardiometabolic risk and multi-organ complications associated with MASH.

Disclosures: Taishi Hashiguchi:Nothing to Disclose.

1417 | ◆ EFFICACY AND SAFETY OF FAZIRSIRAN TREATMENT IN ALPHA-1 ANTITRYPSIN DEFICIENCY-ASSOCIATED LIVER DISEASE: POOLED ANALYSES FROM TWO PHASE 2 CLINICAL TRIALS

Virginia Clark[1] Ying-Wooi Wan[2] Xinhua Hu[2] Seth Pixton[2] Jen-Chieh Chuang[2] Susana Gonzalez[2] Hong Li[2] Lisi Wang[2] Thomas Schluep[3] Rohit Loomba[4] Charlie Strange[5] Pavel Strnad[6], [1]University of Florida, Gainesville, FL, USA, [2]Takeda Development Center Americas, Inc., Cambridge, MA, USA, [3]Arrowhead Pharmaceuticals, Inc., Pasadena, CA, USA, [4]University of California San Diego, San Diego, CA, USA, [5]Medical University of South Carolina, Charleston, SC, USA, [6]University Hospital RWTH, Aachen, Germany

Background: Alpha-1 antitrypsin deficiency (AATD) is characterized by the presence of liver and/or lung disease. Patients (pts) with the protease inhibitor (Pi) *ZZ genotype are at high risk of AATD-associated liver disease (AATD-LD) due to hepatic accumulation of misfolded alpha-1 antitrypsin (Z-AAT). We report pooled safety and efficacy data from two phase 2 trials of fazirsiran, a small interfering RNA therapy, in pts with AATD and a Pi*ZZ genotype. **Methods:** Adults with the Pi*ZZ genotype received placebo (PBO) or fazirsiran 25/100/200 mg in AROAAT-2001 (NCT03945292), or fazirsiran 100/200 mg in AROAAT-2002 (NCT03946449). Dosing occurred on Day 1, Week (W) 4 and then every 12 weeks (Q12W) $\leq$ W48 (primary phase). In the open-label extension (OLE) phase, pts received fazirsiran 200 mg Q12W $\leq$ W196 in AROAAT-2001, and fazirsiran 100/200mg (depending on primary phase dose) Q12W $\leq$ W192 in AROAAT-2002. Liver biopsies were performed at W24 (AROAAT-2002 only), 48, 72 and/or 96. Endpoints included total intrahepatic Z-AAT burden (evaluated by periodic acid–Schiff staining with diastase [PAS-D] and LC-MS), serum Z-AAT, liver enzymes (ALT, AST, GGT), portal inflammation and fibrosis severity (METAVIR, FibroScan®), pulmonary function (FEV1, FVC, DLCO) and treatment-emergent adverse events (TEAEs). **Results:** The analyses included 56 pts (median age: 56 years; 57% male), of which 38 entered the OLE phase. During the primary study phase, a consistent improvement was observed with fazirsiran 200 mg vs PBO for total intrahepatic Z-AAT burden, serum Z-AAT, liver enzymes, portal inflammation and fibrosis severity (**Table**). Higher fazirsiran doses

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(200 mg vs 25/100 mg) led to numerically greater median reductions from baseline (BL) in PAS-D (score change: −5.0 vs −3.5/−5.0, not significant [ns]) and total intrahepatic Z-AAT (% change: −90% vs −84/−88%, ns). In the OLE phase, switching to fazirsiran 200 mg led to geometric mean serum Z-AAT reductions from OLE BL to W24 (switching from PBO: −86%; from fazirsiran 25 mg: −54%; from fazirsiran 100 mg: −40%; all nominal $p < 0.05$ in mixed models for repeated measures); while maintenance of fazirsiran 200 mg led to continuous and sustained reductions in serum Z-AAT to ~W60, followed by a plateau ≤ W140. Liver enzymes broadly declined towards normal ranges and pulmonary function remained stable across all fazirsiran doses, with no evidence of pulmonary decline in the primary or OLE phases. During the OLE phase, 34 pts (90%) reported TEAEs; most were mild/moderate in severity and unrelated to the study drug. **Conclusion:** Fazirsiran 200 mg showed consistent efficacy for Z-AAT burden and other liver-/fibrosis-related endpoints in the primary and OLE phases of two phase 2 studies. Overall, fazirsiran was well tolerated with no safety signals or pulmonary decline. A phase 3 trial is ongoing to evaluate the benefits of fazirsiran 200 mg for AATD-LD further.Writing support provided by E Butcher, Oxford PharmaGenesis.

Table

Endpoint	Change from baseline to end of primary study phase[a]		
	Fazirsiran 200 mg (n = 19)	PBO (n = 9)	*p* value
Z-AAT burden			
Intrahepatic Z-AAT in nmol/g, % change	−89.6 (−94.5, −79.7)	25.5 (−35.4, 93.2)	< 0.001
PAS-D, composite score change	−5.0 (−5.5, −3.5)	0.0 (−1.0, 1.0)	< 0.001
Serum Z-AAT in mg/L, % change	−92.3 (−95.2, −87.0)	−6.9 (−13.1, 4.9)	< 0.001
Liver enzymes			
ALT in U/L, % change	−35.6 (−44.0, 10.0)	12.0 (0.3, 27.2)	0.023
AST in U/L, % change	−19.2 (−32.1, −1.1)	10.5 (1.5, 21.2)	0.008
GGT in U/L, % change	−33.3 (−41.6, −7.4)	8.0 (−1.1, 10.9)	0.003
Inflammation and fibrosis severity			
Portal inflammation score, score change	0.0 (−1.0, 0.0)	0.0 (0.0, 1.0)	0.003
METAVIR, score change	−1.0 (−1.0, 0.5)	0.0 (−1.0, 0.0)	0.74
FibroScan, change in kPa	−1.5 (−2.5, 0.9)	0.3 (−0.9, 1.0)	0.11

[a]All values are median (IQR) change from baseline to end of primary study phase.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase; IQR, interquartile range; METAVIR, Meta-analysis of Histological Data in Viral Hepatitis; PAS-D, periodic acid–Schiff staining with diastase; PBO, placebo; Pi, protease inhibitor; Z-AAT, misfolded alpha-1 antitrypsin produced by the Pi*ZZ *SERPINA1* allele.

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1418 | ◆ RELATION OF AGE, GENDER, AND YEAR OF DIAGNOSIS TO PHENOTYPE AT PRESENTATION IN 3,338 PATIENTS WITH WILSON DISEASE

Karina Rewitz[1] Peter Ott[2] Anna Czlonkowska[3] Aurelia Poujois[4] Eduardo Couchonnal Bedoya[5] Zoe Mariño MENDEZ[6] Luis García-Villarreal[7] Karl Heinz Weiss[8]

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Background: Wilson disease (WD) is a rare inherited disorder (1:30.000) with heterogeneous manifestations. We examined how age at diagnosis, sex, and year of diagnosis were associated with phenotypic presentation. **Methods:** In this cross-sectional study, nine registries contributed data on 3,338 patients with WD diagnosed over a 75-year period (1.1.1950-12.31.2024). Phenotypes could be categorized into three groups: Asymptomatic or hepatic (ASYMP/HEP) (without neurologic symptoms); neuropsychiatric (NEUROPSYC) (with or without hepatic disease); and acute liver failure (ALF). Logistic regression and sensitivity analyses were used to account for confounding, referral, and survivor bias. **Results:** The ASYMP/HEP phenotype decreased steadily from 87.0% at 0-19yr at diagnosis to 41.1% at ages 40-44yr and then rose to 52.9% for age >44yr. The median (IQR) age at diagnosis was 21yr (13-31yr) for all phenotypes, 17.5yr (11-27yr) for ASYMP/HEP and 28yr (20-39yr) for NEUROPSYC. Females more often presented with the ASYMP/HEP phenotypes (females 69.8%, males 63.6%; p = 0.001) or ALF (females 5.7%, males 1.9%, p = 0.001), in both cases mostly driven by individuals being 15–39yr at diagnosis. In contrast to expectations, the median age at diagnosis was relatively constant over the decades, with a modest rise at the end of the period, caused by an increased proportion of diagnoses in patients above 40yr of age from 1% of all diagnoses in 1980-84 to 24% in 2020-2024. In these "late-presenters", the ASYMP/HEP phenotype increased from 30% in 2000-2004 to 71% in 2020-2024, while the ratio between ASYMP/HEP and NEUROPSYC was surprisingly constant during the observation period in patients diagnosed before 39 years of age. **Conclusion:** In this largest-of-its-kind multicenter study, we confirmed that the ASYMP/HEP phenotype dominates in childhood while NEUROPSYC becomes steadily more important until age 44. Female preponderances of the ASYMP/HEP and ALF phenotypes were driven by the 15-39yr age groups, possibly related to hormonal changes. Over the last two decades, WD was more often diagnosed in patients above the age of 40, a subgroup that may have been grossly overlooked in the past and needs better characterization. Despite attempts to prevent development of the NEUROPSYC phenotype through earlier diagnosis, this did not show up in the data. Combining data from multiple registries for patients with WD enables better epidemiologic studies.

Disclosures: Karina Rewitz:Nothing to Disclose, Peter Ott:Nothing to Disclose, Anna Czlonkowska:Nothing to Disclose, Aurelia Poujois:Nothing to Disclose, Eduardo Couchonnal Bedoya:ORPHALAN: Consultant, ZOE MARIÑO MENDEZ:Nothing to Disclose, Luis García-Villarreal:Nothing to Disclose, Karl Heinz Weiss:Nothing to Disclose, Isabelle Mohr:Nothing to Disclose, Piotr Socha:Alexion: Speaking and Teaching, Orphalan: Speaking and Teaching, Univar: Grant/Research Support, Albert Stättermayer:Nothing to Disclose, Anil Dhawan:Nothing to Disclose, Peter Jepsen:Nothing to Disclose, Michael Schilsky:Vivet Therapeutics: Grant/Research Support, Orphalan: Grant and Advisory, DepYmed: Advisor, Arbomed: Advisor and Consultant, Wilson Disease Association: Grant/Research Support, Prime Medicine: Consultant, Eton Pharma: Consultant, Prime Medicine: Advisor, Prime Medicine: Grant/Research Support, Thomas Sandahl:Nothing to Disclose.

1419 | ◆ CAN A NOVEL INSTANT RELEASE TRIENTINE TETRAHYDROCHLORIDE FORMULATION BE EFFECTIVE WHEN ADMINISTERED ONCE-DAILY? RESULTS OF THE TRIUMPH-3 PHARMACOKINETIC STUDY

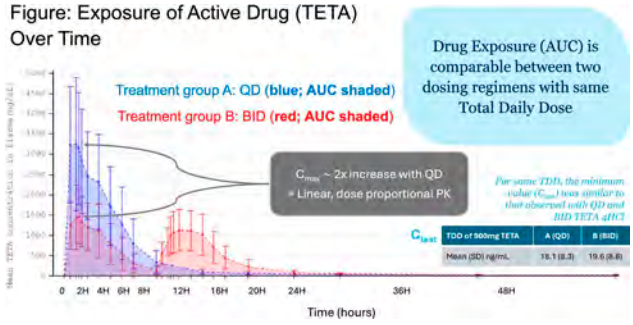
Michael Schilsky[1] Karl Heinz Weiss[2] Thomas Ashdown[3] Ulrike Lorch[3] Nichloas Manamley[4] Farah Lawrence-Wilde[4] C.Omar Kamlin[5], [1]Yale University Medical Center, [2]Krankenhaus Salem der Evang. Stadtmission Heidelberg GmbH, Heidelberg, Germany, [3]Richmond Pharmacology, [4]Orphalan SA, [5]Orphalan

Background: The therapeutic goal of Wilson Disease (WD) is to control copper levels and modify disease progression. Adherence to all approved anti-copper drugs is challenging; need for life-long medication

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with at least twice-daily dosing, food-drug interactions make timing of intake critical. Efficacy of chelation, measured by urinary copper excretion, is determined by total exposure of active drug determined by pharmacokinetic (PK) measure of area under the curve (AUC) independent of dosing frequency[1] . This study describes and compares the PK profile of a novel trientine tetrahydrochloride (TETA 4HCl) administered once a day (QD) with approved TETA 4HCl formulation administered twice daily. **Methods:** A Phase 1 (NCT06128954), single center, randomized, open-label, cross-over study to compare the PK, safety and tolerability of a new 300mg trientine base TETA 4HCl formulation with EU approved 150mg trientine base. A total daily dose of 900mg trientine base was evaluated by comparing QD dosing (x3 tablets = 900mg) with 2 [BID] equally divided doses 8 hours apart (6x150mg trientine base) in a fasted state. Blood samples were taken prior to dosing and at prespecified intervals for 48 hours measuring peak concentration (C_{max}), last sampled concentration (C_{last}), time to C_{max} (T_{max}) followed by a 5–7-day washout period between cross-over. **Results:** 26 participants completed both sequences of the study. PK profiles of the two formulations were as expected, single peak and gradual decline in plasma levels with the QD formulation, and a bimodal pattern, with BID TETA 4HCl. Plasma concentrations of trientine increased to a geometric mean peak of 3436 and 1567 ng/mL, respectively [GMR 2.192, 90% CI 1.882-2.554]) reflecting dose-proportionally higher C_{max} between QD and BID dosing with median T_{max} values of 1h and 1.25h for QD and BID dosing respectively. Figure shows comparable systemic exposure of TETA AUC_{0-24}. The geometric mean ratios (GMR) of the new QD formulation relative to BID TETA 4HCl were the following: C_{max} (2.192), AUC_{0-24} (1.155) AUC_{0-48} (1.14) and AUC_{inf} (1.12). Mean (SD) final concentrations (C_{last}) sampled at 48h were 18.1 (8.3) and 19.6 (8.8) ng/mL for QD and BID dosing respectively. Five participants experienced a total of 8 adverse events (AE); 7 mild, 1 moderate (viral infection). **Conclusion:** The new QD TETA 4HCl with a TDD of 900mg was well tolerated and demonstrated dose proportional and linear pharmacokinetics with a doubling of C_{max} with comparable time to C_{max} with equally divided dose of 450mg of TETA 4HCl. Comparable AUC and values of the last sampled plasma concentration of TETA show that systemic exposure and excretion of TETA for the same TDD is independent of frequency of dosing and supports once daily dosing.Reference: 1. Cho *J Clin Pharmacol 2009* **Figure:** Mean linear TETA concentrations following QD and BID dosing of TDD of 900mg trientine tetrahydrochloride



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1420 | NEUTRAL MOLYBDENUM BALANCE AND LACK OF MOLYBDENUM TOXICITY IN SUBJECTS TREATED WITH TIOMOLIBDATE CHOLINE SUPPORTS SAFETY PROFILE OF TMC

Aftab Ala[1] Valentina Medici[2] Karl Heinz Weiss[3] Chandler Robinson[4] Andrew Cittadine[4] Declan Tuffy[4] Thomas Sandahl[5] Frederick Askari[6], [1]Kings College Hospital, [2]University of California Davis Medical Center, [3]Krankenhaus Salem, [4]Monopar Therapeutics, [5]Aarhus University Hospital, [6]University of Michigan Medical Center

Background: Tiomolibdate choline (TMC; ALXN1840) is an oral, once-daily, novel mechanism albumin-tripartite-complex (ATC) activator in development for Wilson disease (WD). TMC contains tetrathiomolybdate, a molybdenum (Mo)-containing high affinity Cu-binding moiety intended for chronic administration. Because excess Mo exposure presents with hyperuricemia and gout-like symptoms, evaluation of progressive Mo accumulation and serum uric acid levels are important for assessing the safety of chronic TMC treatment. To address both, we present results from a Mo balance study (HV-108) conducted in healthy volunteers administered TMC along with long-term serum uric acid and adverse event (AE) data in WD patients from Phase 2&3 TMC trials. **Methods:** In HV-108, 17 healthy volunteers were admitted to a clinical

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research unit and started on a Mo-controlled diet. Following a 4-day pretreatment period (baseline), volunteers received TMC 30 mg once daily for 15 days followed by a 15-day drug withdrawal period. All intake (food, drink, TMC) and output (urine, stool) during the study were collected and analyzed for Mo content. Daily Mo balances were calculated as Mo intake minus Mo output.In the Phase 3 trial, patients with WD were randomized to standard of care (SoC, n = 70) or TMC (n = 137; 15-30 mg daily) for 48 weeks. Serum uric acid concentrations were evaluated over the study duration and during long-term follow-up. Serum uric acid was also measured in the Phase 2 WTX101-201 trial and included in the analyses (n = 235). For AEs, data from the Phase 2 ALXN1840-WD-204 and ALXN1840-WD-205 trials were additionally included (n = 266). **Results:** At baseline in HV-108, mean daily Mo balance was approximately neutral. Following initiation of TMC, Mo balance increased transiently, then progressively declined as urinary and fecal Mo elimination increased. Neutral Mo balance was achieved by Day 13 even with continued TMC dosing (Figure 1A). After treatment withdrawal on Day 15, Mo elimination continued, primarily through fecal excretion.In the Phase 3 trial, mean serum uric acid remained stable and was similar between TMC and SoC through Week 48. Over 6 years of TMC treatment, mean serum uric acid levels across the 235 WD patients in the Phase 3 and WTX101-201 trials remained within normal limits (Figure 1B), and no AEs of hyperuricemia or gout-like symptoms were reported in 266 WD patients from the Phase 2&3 studies over the same period. **Conclusion:** In HV-108, Mo balance returned to neutral despite continued TMC administration and the overall pattern is consistent with the mechanism of ATC formation. Mean serum uric acid remained stable and within normal range over 6 years of treatment, with no hyperuricemia or gout-related AEs observed. Together, these findings show no evidence of progressive Mo accumulation and the absence of Mo-related toxicity during chronic TMC treatment. These findings contribute to the understanding of the safety of the novel mechanism of TMC.

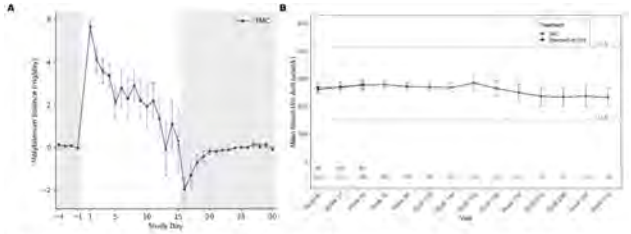


Figure 1A: daily mean Mo balance in healthy volunteers. Mean (± 95% CI) daily Mo balance in healthy volunteers (n=17) measured while on TMC (Days 1 to 15) and off TMC (Days -1 to -4, 16 to 30). Daily Mo balance reached neutral by Day 13 while subjects remained on drug. **Figure 1B: Mean serum uric acid by treatment arm in patients with WD.** Mean (± 95%) serum uric acid in patients with WD treated with TMC (n=235; purple line) and standard of care (n=70, red line). Patients were followed from Baseline through 48 weeks in the standard of care arm and 312 weeks in the TMC arm. Mean levels were within normal limits for both treatment arms at all visits.

Disclosures: Aftab Ala:Nothing to Disclose, Valentina Medici:Orphalan: Advisor, Arbormed: Research Grant, Ultragenix: Grant/Research Support, Vivet: Grant/Research Support, Eton Pharmaceuticals: Consultant, Mars Inc.: Advisor, Prime Medicine: Grant/Research Support, Karl Heinz Weiss:Nothing to Disclose, Chandler Robinson:Nothing to Disclose, Andrew Cittadine: Monopar Therapeutics: Executive role, Monopar Therapeutics: Stock - publicly traded company, Declan Tuffy: Monopar Therapeutics: Employee, Thomas Sandahl: Nothing to Disclose, Frederick Askari:Alexion: Advisor, Ultragenyx Pharmaceutical, Inc.: Advisor, Vivet: Advisor, Deep Genomics: Advisor, Intercept: Advisor.

1421 | IMPAIRED BASELINE KIDNEY FUNCTION IN PATIENTS WITH ACUTE HEPATIC PORPHYRIA ENROLLED IN THE PHASE 3 ENVISION STUDY

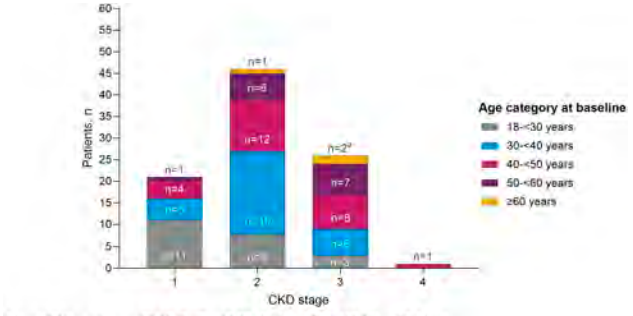
Desmond Murphy[1] Akshata Moghe[2] Paolo Ventura[3] Rebecca Leaf[4] John Quigley[5] Penelope Stein[6] Weiming Du[1] Eliane Sardh[7] Bruce Wang[8] Roy Smith[9], [1]Alnylam Pharmaceuticals, Cambridge, MA, USA, [2]University of Texas Health Science Center at Houston, Houston, TX, USA, [3]Internal Medicine Unit, University of Modena and Reggio Emilia, Modena, Italy, [4]Center for Hematology, Mass General Brigham Cancer Institute, Boston, MA, [5]University of Illinois College of Medicine, Chicago, IL, USA, [6]Haematological Medicine, King's College Hospital, London, UK, [7]Centre for Inherited Metabolic Diseases, Karolinska University Hospital, Stockholm, Sweden, [8]University of California San Francisco, San Francisco, CA, USA, [9]University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

Background: Acute hepatic porphyrias (AHPs) are rare disorders of hepatic heme synthesis that lead to elevated levels of neurotoxic δ-aminolevulinic acid (ALA) and porphobilinogen (PBG). Patients may present to hepatologists with recurrent AHP attacks of severe abdominal pain, nausea, and neuropsychiatric symptoms, and may experience chronic AHP symptoms and low quality of life. Over time, untreated or inadequately managed AHP may result in progressive renal dysfunction because of recurrent attacks and the nephrotoxic effects of ALA and PBG on the glomeruli. Monitoring renal function is recommended in patients with AHP, but the real-world burden of chronic kidney disease (CKD) as a long-term AHP complication has not been well characterized. The phase 3 ENVISION study of givosiran, an RNA interference therapeutic approved for treatment of AHP, included follow up on long-term complications of AHP, including CKD. The objective of this *post hoc* analysis was to characterize baseline CKD prevalence among patients with AHP who were enrolled in ENVISION. **Methods:** ENVISION (NCT03338816) was a multicenter, randomized,

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double-blind, placebo-controlled study enrolling patients ≥12 years old with AHP who had ≥2 attacks requiring hospitalization, urgent care, or intravenous hemin at home in the 6 months before study entry. This *post hoc* descriptive analysis included all patients randomized to givosiran or placebo stratified by CKD stage at baseline (before treatment), as defined by estimated glomerular filtration rate (eGFR [mL/min/1.73m^2]): stage G1, eGFR ≥90; stage G2, eGFR 89-60; stage G3, eGFR 59-30; or stage G4, eGFR <30. **Results:** In total, 94 patients (89% female; mean age 37 years) were included in the analysis. Most patients had CKD stage G2 (n = 21, n = 46, n = 26, and n = 1 for CKD stages G1-4, respectively); 50% of patients (36/72) with CKD stage G2 or G3 were aged 18 to <40 years (**Figure**). Mean (standard deviation) time since diagnosis was 7.22 (9.22) years, 9.82 (10.73) years, 11.85 (9.10) years, and 17.45 (–) years for stages G1-4, respectively. Median (range) annualized attack rates at baseline were 6 (0-34), 10 (2-46), 6 (4-26), and 24 (–) attacks/year among patients with CKD stages G1-4, respectively. **Conclusion:** At baseline, patients with AHP exhibited considerable renal impairment, with the majority at CKD stage 2 or 3. Patients had kidney function below age-matched reference values (Wetzels JF *et al. Kidney Int* 2007;72:632-7), and those with longer disease duration presented with worsened kidney function at baseline. These results demonstrate the additional disease burden outside of AHP attacks and highlight CKD as a potential long-term complication of AHP with high clinical relevance. The findings support ongoing renal monitoring in patients with AHP to help prevent CKD progression, and suggest that AHP should be suspected in patients with unexplained recurrent abdominal pain and impaired kidney function.



Disclosures: Desmond Murphy:Alnylam Pharmaceuticals: Employee, Alnylam Pharmaceuticals: Stock - publicly traded company, Akshata Moghe:Alnylam Pharmaceuticals: Consultant, Recordati Rare Diseases, Inc: Consultant, Paolo Ventura:Alnylam pharmaceuticals: Advisor, Rebecca Leaf:Nothing to Disclose, John Quigley:Nothing to Disclose, Penelope Stein:Nothing to Disclose, Weiming Du:Alnylam Pharmaceuticals: Employee, Eliane Sardh:Nothing to Disclose, Bruce Wang:Nothing to Disclose, Roy Smith: Nothing to Disclose.

1422 | GENETIC MODIFICATION OF WILSON DISEASE ATP7B GENE IN HUMAN CELLS USING RNA-BASED CRISPR/CAS9 TECHNOLOGY

Moritz Marciniak[1] Andree Zibert[1] Oksana Nadzemova[1] Phil-Robin Tepasse[1] Jonel Trebicka[1] Vanessa Sandfort[1], [1]University Hospital Münster, Medical Clinic B

Background: Wilson disease (WD) is a monogenic disorder of copper (Cu) metabolism caused by mutations in the Cu-transporting ATP7B protein and associated with hepatic Cu accumulation. H1069Q is the most frequently reported ATP7B variant in European and North American populations. A previous study by our group demonstrated the feasibility of H1069Q correction using plasmid-based CRISPR/Cas9 (Clustered Regularly Interspaced Short Palindromic Repeats / CRISPR-associated protein 9) molecules in WD-specific induced pluripotent stem cells (iPSCs). After differentiation into hepatocyte-like cells (HLCs), corrected cells showed improved resistance to high Cu concentrations (Iwan et al. 2026). Replacing plasmid-based delivery with transient RNA-based CRISPR/Cas9 molecules may further improve the translational relevance of this approach. **Methods:** A single-guide RNA (sgRNA) targeting the ATP7B H1069Q locus was designed and delivered together with Cas9 mRNA into HEK293 and HepG2 cells by lipofection. Individual clones from both cell lines were screened by Sanger sequencing to identify CRISPR/Cas9-induced deletions or insertions at the target locus. ATP7B expression was analysed by Western blotting (WB) and quantitative PCR (qPCR). Cellular tolerance to high Cu concentrations was assessed using MTT assays. **Results:** RNA-based CRISPR/Cas9 editing generated several ATP7B knockout (KO) clones in HEK293 and HepG2 cells. Sanger sequencing conformed distinct homozygous and heterozygous insertions and deletions at the H1069Q locus. WB analysis showed reduced ATP7B protein expression in KO clones from both cell lines. At the mRNA level, reduced ATP7B expression was observed most consistently in HEK293 clones. MTT assays indicated a functional impact of ATP7B disruption on the cellular response to high Cu concentrations. **Conclusion:** This study demonstrates that RNA-based delivery of Cas9 mRNA and sgRNA can successfully target the ATP7B H1069Q locus and generate

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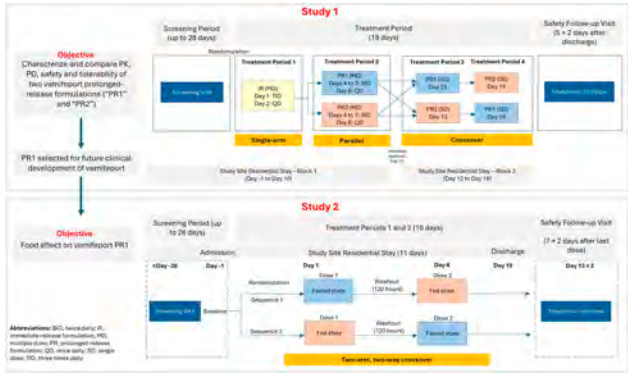
genetically defined ATP7B KO clones in both HEK293 and HepG2 cells. The combination of Sanger sequencing, ATP7B expression analyses and Cu-dependent viability assays provide molecular and functional evidence that ATP7B disruption effects cellular Cu tolerance. These findings establish an RNA-based CRISPR/Cas9 platform for ATP7B editing in vitro and provide a relevant intermediate step towards mutation-specific repair approaches in WD. Future work will focus on RNA-based correction of H1069Q in human cell lines and patient-derived iPSCs using previously validated repair template molecules (Iwan et al. 2026).

Disclosures: Moritz Marciniak:Nothing to Disclose, Andree Zibert:Nothing to Disclose, Oksana Nadzemova:Nothing to Disclose, Phil-Robin Tepasse:Nothing to Disclose, Jonel Trebicka:Nothing to Disclose, Vanessa Sandfort:Nothing to Disclose.

1423 | TWO PHASE 1 STUDIES TO CHARACTERIZE THE PHARMACOKINETICS, PHARMACODYNAMICS, AND SAFETY OF TWO PROLONGED-RELEASE VAMIFEPORT FORMULATIONS IN HEALTHY ADULTS AND TO ASSESS THE EFFECT OF FOOD ON THE FORMULATION SELECTED FOR FUTURE CLINICAL DEVELOPMENT

Sonya Abraham[1] Jens-Alexander Fuchs[2] Yulia Shalaeva[3] Deya Cherpokova[4] Gregory Kato[1], [1]CSL Behring, King of Prussia, Pennsylvania, USA, [2]CSL Behring, Glattbrugg, Switzerland, [3]CSL Vifor, Glattbrugg, Switzerland, [4]CSL Innovation GmbH, Marburg, Germany

Background: Vamifeport is an oral small-molecule hepcidin-mimetic that targets the ferroportin transporter. In two clinical studies in healthy volunteers and one study each in patients with non-transfusion-dependent thalassemia and sickle cell disease, vamifeport immediate-release (IR) formulation reduced circulating iron levels and was generally well tolerated. Here, we report the clinical development path that identified and characterized a new prolonged release (PR) formulation now being used in a phase 2 study in hereditary hemochromatosis (HH; Study CSL624_2001; "Ferroclear"). **Methods:** Two phase 1, open-label studies were conducted **(Figure 1)** . Study 1 included four treatment periods to characterize and compare the pharmacokinetic (PK), pharmacodynamic (PD) and safety of two vamifeport PR formulations ("PR1" and "PR2") across single- and multiple- dose regimens: Period 1 (single-arm; IR three times daily to steady-state); Period 2 (parallel-group; PR1 or PR2 twice daily to steady-state); Periods 3 and 4 (crossover; single dose of PR1 or PR2 in Period 3 and following washout, the alternate formulation in Period 4). Study 2 was a single-dose two-way, two-period crossover study to assess the effect of food on the oral bioavailability of the selected vamifeport PR formulation ("PR1"). In both studies, safety was evaluated, and the PD (serum iron and transferrin saturation [TSAT]) was determined. **Results:** Study 1 (N = 22): When compared with vamifeport IR, both PR formulations showed slower absorption, resulting in increased T_{max}, lower C_{max}, and lower systemic exposure (AUC) (dose-normalized exposures). The reduction of C_{max} was greater than the reduction in AUC, flattening the PK profile and making vamifeport PR favorable over IR. Further, absorption of PR1 was slower and lower compared with PR2, resulting in better safety margins while preserving comparable PD effects between these formulations. Study 2 (N = 28): A high-fat breakfast reduced C_{max} of vamifeport PR1 by 40.6% (fed:fasted ratio = 0.594; 90% CI: 0.522, 0.675) and delayed T_{max} by 2 h, but the ratio and 90% confidence interval for overall exposure ($AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$) remained within the bioequivalence limits of 0.8 and 1.25. The observed changes in the absorption phase were within the range of inter-subject variability and did not impact the TSAT profiles, which were comparable between both states. In both studies, vamifeport was well tolerated. **Conclusion:** The selected vamifeport PR formulation provided a flatter PK and PD profile and increased C_{max}-based safety margins when compared with equal doses of vamifeport IR. Also, vamifeport PR can be administered with or without food, providing superior flexibility in studies involving patients compared with vamifeport IR. In both studies, vamifeport PR was well tolerated. Based on these results, vamifeport PR progressed to a phase 2 study in HH (NCT07332091).



Disclosures: Sonya Abraham:CSL Behring: Employee, Jens-Alexander Fuchs:Nothing to Disclose, Yulia Shalaeva:Nothing to Disclose, Deya Cherpokova:CSL: holds equity in CSL, Gregory Kato:CSL: Employee, CSL: Stock - publicly traded company.

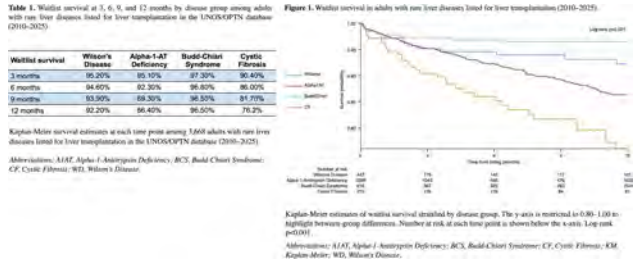
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1424 | CYSTIC FIBROSIS PATIENTS HAVE THE LOWEST TRANSPLANT ACCESS AND HIGHEST WAITLIST MORTALITY AMONG ADULTS LISTED FOR RARE LIVER DISEASES: A CONTEMPORARY UNOS ANALYSIS

Rebeca Sierra[1] Maria Saavedra-Martinez[1] Marcela Cuellar-Lobo[2] Butros Fakhoury[3] Pojsakorn Danpanichkul[4] Leandro Sierra[5], [1]Universidad De La Sabana, [2]Cardiovascular Division, Beth Israel Deaconess Medical Center, [3]Virginia Commonwealth University, [4]Texas Tech University Health Sciences Center, [5]Cleveland Clinic Foundation

Background: Efforts in liver transplant research have left rare liver diseases behind. There are currently no contemporary analyses of waitlist attrition, transplant access, and outcomes across rare liver diseases in the U.S. Understanding the risk profile of every liver condition, including those that are less common, is necessary to inform organ allocation decisions. **Methods:** Using the Scientific Registry of Transplant Recipients, we retrospectively analyzed adults listed for liver transplantation from 2010 to 2025. Rare liver diseases were selected based on U.S. prevalence below 200,000 (Rare Diseases Act of 2002) and the absence of a national-registry analysis published after 2015. Of seven plausible diseases, three were excluded: primary hyperoxaluria (insufficient sample size of 40 subjects), hepatic sarcoidosis (no dedicated OPTN diagnosis code), and congenital hepatic fibrosis/Caroli disease (national analysis published in 2021). The final cohort comprised Wilson disease (WD), alpha-1 antitrypsin deficiency (A1AT), Budd-Chiari syndrome (BCS), and cystic fibrosis (CF). Annual listing trends were assessed with the Cochran-Armitage test. Waitlist mortality or dropout and access to transplantation were evaluated using Kaplan-Meier estimation and adjusted Cox regression. **Results:** A total of 3,668 adults were included: A1AT (n = 2,399, 65.4%), BCS (n = 617, 16.8%), WD (n = 442, 12.1%), and CF (n = 210, 5.7%). Annual listing trends were stable across the study period for all four diseases. Transplant rates differed substantially across groups (A1AT 78.2%, WD 71.7%, BCS 51.7%, CF 29.0%; p < 0.001). Among CF patients not reaching transplantation (n = 149, 71.0%), 39 (26.2%) died on the waitlist and 38 (25.5%) were removed for clinical deterioration. Waitlist survival differed across groups (log-rank p < 0.001). CF had the lowest survival at every time point, falling to 90.4% at 3 months and 76.2% at 12 months, while BCS had the highest survival throughout (97.3% at 3 months, 96.5% at 12 months). Median waitlist time was shortest in WD (43 days; IQR 7-308) and longest in BCS (215 days; IQR 35-790). **Conclusion:** Among adults listed for transplantation with rare liver diseases, CF carries the lowest transplant access and the highest waitlist attrition, with one in four CF patients dying on the waitlist and another quarter removed for clinical deterioration. In contrast, Budd-Chiari syndrome carries the most favorable waitlist survival. The progressive extrahepatic disease in CF not captured by MELD 3.0 might be limiting its overall survival. Policies that apply exception pathways for CF patients must be considered.



Disclosures: Rebeca Sierra:Nothing to Disclose, Maria Saavedra-Martinez:Nothing to Disclose, Marcela Cuellar-Lobo:Nothing to Disclose, Butros Fakhoury: Nothing to Disclose, Pojsakorn Danpanichkul:Nothing to Disclose, Leandro Sierra:Nothing to Disclose.

1425 | REAL WORLD EVIDENCE OF THERAPY IMPACT OF NON-CERULOPLASMIN BOUND COPPER BY SPECIATION AS A NOVEL MONITORING TOOL IN NEWLY DIAGNOSED WILSON DISEASE

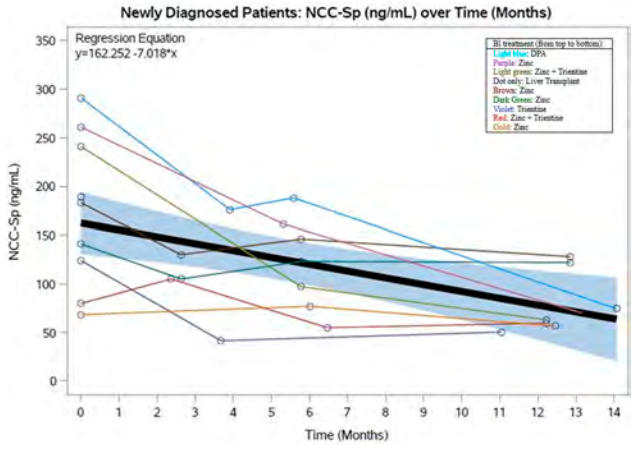
Michael Schilsky[1] Regino Gonzalez-Peralta[2] Amanda Cheung[3] Valentina Medici[4] James Hamilton[5] Cynthia Levy[6] Kalyan Bhamidimarri[7] Steven Lobritto[8] Amy Brown[9] C.Omar Kamlin[10] Jamie Heise[11] Brenda Gorsett[10] Nick Manamley[10] Frederick Askari[12], [1]Yale University Medical Center, [2]AdventHealth for Children, [3]Northwestern Memorial Hospital/Northwestern University, [4]University of California Davis Medical Center, [5]Johns Hopkins University, [6]University of Miami, [7]Cleveland Clinic, [8]Columbia University, [9]Vanderbilt University, [10]Orphalan, [11]Orphalan Inc, [12]University of Michigan Medical Center

Background: Monitoring of treatment for Wilson disease (WD) remains challenging, underscoring a substantial unmet need for accurate and clinically practical biomarkers to assess treatment response. **Aim:** To describe the response of non-ceruloplasmin bound copper by speciation (NCC-Sp), a measurement of circulating bioavailable copper, at key time points in newly diagnosed WD in relation to therapy initiation and change . **Methods:** The REASON study (NCT05783687) was a non-interventional, prospective study conducted across 9 U.S. sites between June 2023 and October 2025. Blood samples for NCC-Sp measurement were collected at baseline (BL), during

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standard of care (SOC) visits, and at end of study (EOS). NCC-Sp was analyzed following EOS visit, thus treating physicians were blinded to these values and clinical decision-making was independent of contemporaneous NCC-Sp values. NCC-Sp was evaluated at baseline, SOC visits and EOS or in association with therapy change. Findings were compared with liver enzyme (AST, ALT) changes and 24-hour urinary copper excretion (UCE) where available. **Results:** Of 9 newly diagnosed patients (2 asymptomatic), 1 underwent liver transplantation following enrollment and contributed baseline data only. Among the 8 treated patients, baseline therapies included zinc monotherapy (n = 4), combination zinc/trientine (n = 2), trientine monotherapy (n = 1), and D-penicillamine (n = 1). Two patients changed therapy during the 12-month follow-up: 1 initiated on zinc and added trientine at 5 months, and 1 on combination therapy discontinued zinc at 2 months. Therapy assignments are illustrated in the accompanying figure. NCC-Sp mean (SD) at BL was elevated to 175.32 (78.83) ng/ml and declined by 95.69 (85.59) ng/ml by EOS, aligned with previously reported values for chronically treated patients in the CHELATE trial (NCT03539952). Among patients with both BL and EOS liver enzymes, mean AST and ALT demonstrated slight reductions compared to the NCC-Sp trends. UCE data was limited; 4 patients with paired data, mean (SD) BL UCE of 523.72 (679.16) mcg/d increased by 83.0 (118.79) mcg/d at EOS. Clinical Global Impression of Change (CGIC) scale indicated improvement in all (5 much improved, 3 minimal). **Conclusion:** In treatment naïve WD patients, NCC-Sp declined consistently across all therapy groups with concurrent trends toward clinical stability and liver enzyme improvement, supporting NCC-Sp as a potential biomarker for monitoring copper-directed therapy. Larger studies are needed for validation.



Disclosures: Michael Schilsky:Vivet Therapeutics: Grant/Research Support, Orphalan: Grant and Advisory, DepYmed: Advisor, Arbomed: Advisor and Consultant, Wilson Disease Association: Grant/Research Support, Prime Medicine: Consultant, Eton Pharma: Consultant, Prime Medicine: Advisor, Prime Medicine: Grant/Research Support, Regino Gonzalez-Peralta:Nothing to Disclose, Amanda Cheung:Novo Nordisk: Speaking and Teaching, Petauri Kinect: Grant/Research Support, Rubio Metabolomics: Grant/Research Support, Orphalan: Consultant, Valentina Medici:Orphalan: Advisor, Arbormed: Research Grant, Ultragenix: Grant/Research Support, Vivet: Grant/Research Support, Eton Pharmaceuticals: Consultant, Mars Inc.: Advisor, Prime Medicine: Grant/Research Support, James Hamilton:orphalan pharmaceuticals: Advisor, mirum pharmacueticals: Advisor, Cynthia Levy:Gilead: Grant/Research Support, Ipsen: Grant/Research Support, GSK: Grant/Research Support, Intercept: Grant/Research Support, Calliditas: Grant/Research Support, Zydus: Grant/Research Support, LisCure: Grant/Research Support, TARGET RWE: Grant/Research Support, Pliant: Grant/Research Support, NGM: Grant/Research Support, Mitsubishi Tanabe: Grant/Research Support, DISC: Grant/Research Support, Takeda: Grant/Research Support, Kowa: Grant/Research Support, Mirum: Grant/Research Support, Kalyan Bhamidimarri:orphalan: Advisor, ipsen: Advisor, egenesis: Advisor, mallinckrodt: Advisor, albireo: Advisor, Steven Lobritto:Orphalan: Grant/Research Support, Mirum: Advisor, Ibsen: Speaking and Teaching, IPRO: Consultant, NIH: Grant/Research Support, Amy Brown:Nothing to Disclose, C. Omar Kamlin:Orphalan: Employee, jamie Heise:Orphalan Inc: Employee, Brenda Gorsett:Orphalan: Employee, Nick Manamley:Mundipharma: Employee, Orphalan: Employee, Mundipharma: Employee, Orphalan: Employee, Frederick Askari:Alexion: Advisor, Ultragenyx Pharmaceutical, Inc.: Advisor, Vivet: Advisor, Deep Genomics: Advisor, Intercept: Advisor.

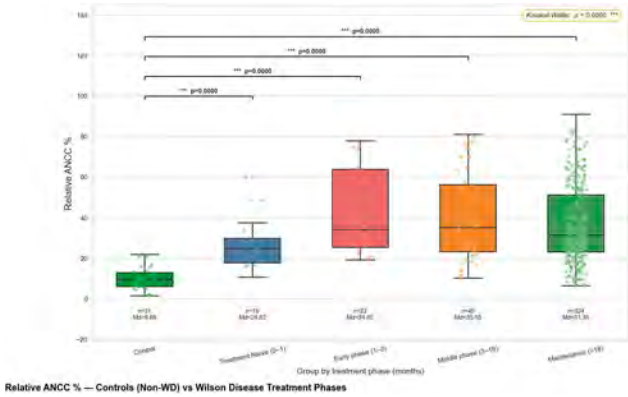
1426 | EVALUATING RELATIVE ACCURATE NON- CERULOPLASMIN COPPER (RELANCC) FOR DIAGNOSING WILSON DISEASE

Michael Schilsky[1] Asim Ulcay[1] Hatice Maras[1] Sefa Keserci[1] Rima Fawaz[1] Chris Harrington[2] Geoff Carpenter[3] Leisa Douglas[3] Uyen To[4] Regino Gonzalez-Peralta[5] Sanjiv Harpavat[6] Thomas Sandahl[7] Sihoun Hahn[8], [1]Yale University School of Medicine, [2]SAS Trace Element Laboratory, Royal Surrey Hospital, Guildford, UK, [3]SAS Trace Element Laboratory,Royal Surrey Hospital, Guildford, UK, [4]Hartford Healthcare, [5]AdventHealth for Children, [6]Texas Children's Liver Center - Baylor College of Medicine, [7]Aarhus University Hospital, [8]Seattle Children's Hospital/Univ of Washington

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Background: The ratio of bioavailable Cu to the total Cu in the circulation can help discriminate Wilson disease (WD) from non-affected individuals. A highly accurate method for determining non-ceruloplasmin copper (ANCC) utilizing anion exchange chromatography linked to ICP mass spectrometry can provide information on the total and bioavailable Cu needed to calculate the ratio of bioavailable Cu to total serum copper, the RelANCC (Harrington et al *Clinical Chemistry and Laboratory Medicine* 2025) . RelANCC was able to distinguish acute liver failure (ALF) due to WD from ALF due to other causes of liver disease (Sandahl et al *Am J Gastroenterol*. 2025). Only limited data is available on RelANCC in WD outside of those with ALF due to WD. The Wilson disease registry (WDR) based at Yale is a multicenter, multinational registry of patients with WD coupled with a biorepository, allowing the correlation of specimen analysis with information related to patient treatment needed for exploring the RelANCC in the larger population of patients with WD. **STUDY AIM** : To determine the range of values for RelANCC in a large population of patients with a chronic presentation of WD, and if RelANCC is affected by copper directed treatment specific for WD. **Methods:** Total Cu and ANCC determined from serum obtained from patients in the WDR at time of study entry and at least annually thereafter was used to calculate RelANCC. The phases of treatment of WD for patients in the WDR include naïve patients (0-1 month (m) of treatment), patients treated from 1-3 m, from >3-18 m, and > 18 m. Control patients included those without liver disease from the laboratory. A total of 407 observations from 150 unique subjects with WD were included in the analysis. The cohort had a mean age of 35.5 ± 19.2 years (median 33.1; range 1.1–78.6), and 82 subjects (54.7%) were male. Cu-directed treatment with either Zn or chelation therapy was recorded at time of measurement. **Results:** Among controls without WD (n = 31), median RelANCC was 9.66% (IQR 6.09–12.5%). In treatment-naïve WD patients, median RelANCC was 24.9% (IQR 17.8–29.9%). The Youden-optimized cutoff distinguishing the two groups was 16.8%. Median RelANCC during Cu directed therapy for 1–3 m (n = 23) was 34.1% (IQR 25.4–63.6%); for 3–18 m (n = 45) 35.2% (IQR 23.4–56.1%) and for >18 m (n = 324) 31.4% (IQR 23.1–51.0%). The greatest number of RelANCC below 16.8% was found in patients treated >18m, and these individuals were older and treated predominantly with Zn. **Conclusion:** The predictive value of RelANCC is highest in untreated patients with WD. Cu directed treatment for WD reduces the discriminatory ability of RelANCC in some patients, and for those treated with Zn more so than on treatment with chelation. Further studies are needed to further validate RelANCC as a diagnostic test for WD and establish cut-off ranges that yield the highest predictive value for this test. Funding: NIDDK DK137861, Wilson Disease Association.



Relative ANCC % — Controls (Non-WD) vs Wilson Disease Treatment Phases

Disclosures: Michael Schilsky:Vivet Therapeutics: Grant/Research Support, Orphalan: Grant and Advisory, DepYmed: Advisor, Arbomed: Advisor and Consultant, Wilson Disease Association: Grant/Research Support, Prime Medicine: Consultant, Eton Pharma: Consultant, Prime Medicine: Advisor, Prime Medicine: Grant/Research Support, ASIM ULCAY:Nothing to Disclose, Hatice Maras:Nothing to Disclose, Sefa Keserci:Nothing to Disclose, Rima Fawaz:Mirum: Consultant, Albireo: Data Safety Monitoring Board, Chris Harrington:Nothing to Disclose, Geoff Carpenter:Nothing to Disclose, Leisa Douglas:Nothing to Disclose, Uyen To:Nothing to Disclose, Regino Gonzalez-Peralta:Nothing to Disclose, Sanjiv Harpavat:Syneos Health: I sit on a Data Safety Monitoring Board, Thomas Sandahl:Nothing to Disclose, Sihoun Hahn:Nothing to Disclose.

1427 | PSYCHOMETRIC DEVELOPMENT AND HEPATIC CORRELATION OF A BRIEF CROSS-DIAGNOSTIC MENTAL HEALTH ASSESSMENT FOR WILSON DISEASE USING ITEM RESPONSE THEORY

Hatice Maras[1] Asim Ulcay[1] Sefa Keserci[1] Paula Zimbrean[1] Susan Rubman[1] Regino Gonzalez-Peralta[2] Isabelle Mohr[3] Aftab Ala[4] Sanjiv Harpavat[5] Thomas Sandahl[6] Michael Schilsky[1], [1]Yale University School of Medicine, [2]AdventHealth for Children, [3]Universitats Klinikum Heidelberg, [4]Kings College Hospital, [5]Texas Children's Liver Center - Baylor College of Medicine, [6]Aarhus University Hospital

Background: Psychiatric symptoms have a lifetime occurrence of up to 71% in Wilson disease (WD) with 30–40% manifesting symptoms at diagnosis. Despite this, screening protocols to detect the need for formal mental health evaluation remain unstandardized, and

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the relationship between psychiatric symptoms and hepatic disease severity undefined. **STUDY AIM:** to develop a screening instrument 'WD Mental Health Impact Battery (WD-MHIB)' using selected items from PHQ-9, GAD-7, and PSS-10 to evaluate longitudinal associations between mental health and liver disease in WD. **Methods:** Data from 164 participants from the WD Registry (85 female; mean age 39.3 y, range 18–75) included 591 survey responses for PHQ-9, GAD-7, and PSS-10 that were analyzed. Psychometric properties were evaluated using polychoric correlation matrices and Item Response Theory (IRT) graded response models (Reise SP, Rodriguez A. Psychol Med. 2016;46(10):2025-39). Items were selected based on discrimination (α) and threshold parameters. The resulting 9-item WD-MHIB comprised of top-performing items from PHQ-3 (1, 2, 9), GAD-3 (1, 2, 3), and PSS-3 (reverse-coded 5, 7, 8), was validated against the SF-12 Mental Component Summary (MCS) using Pearson correlation. Associations between mental health scores (WD-MHIB, PHQ-9, GAD-7, PSS-10) and hepatic variables including AST, ALT, FIB-4, and cirrhosis status were evaluated using linear mixed-effects models with patient-specific random intercepts and Mann–Whitney U tests (See Table). **Results:** Selected items demonstrated peak discrimination: GAD-3 (α = 3.21–5.39), PHQ-3 (α = 2.97–3.79), and PSS-3 (α = 2.16–3.41). WD-MHIB demonstrated robust convergent validity with SF-12 MCS (r = -0.78, p < 0.001). After adjustment for time, AST (p = 0.126) and ALT (p = 0.235) were not significantly associated with mental health scores. Elevated FIB-4 scores ($\geq$ 2.67) were associated with lower PHQ-9 (p = 0.002), GAD-7 (p = 0.004), and composite survey z-scores (p = 0.006), while WD-MHIB did not differ significantly (p = 0.072). Cross-sectional analyses demonstrated lower mental health scores in cirrhotics versus non-cirrhotics (median composite score 12.0 vs 19.0; p < 0.001), including WD-MHIB, PHQ-9, GAD-7 (all p < 0.001), and PSS-10 (p = 0.045). Longitudinal analyses demonstrated decline in WD-MHIB scores over time (β = −0.226 points/year; p = 0.003). **Conclusion:** WD-MHIB, can facilitate efficient mental health screening and the need for formal psychiatric consultation in WD as recommended by the recent AASLD guidance (Hepatology 2025). WD-MHIB scores appeared independent from the presence of advanced hepatic fibrosis. Validation of optimal cutoffs for clinical decision-making is needed for the use of WD-MHIIB as a screening instrument and for monitoring. Further work is needed to evaluate the association between liver disease severity and mental health concerns in WD. Funding: NIH DK137861, Wilson Disease Association.

Table 1. Associations Between Mental Health Survey Scores and Hepatic Disease Severity Measures in Wilson Disease

Measure	Analysis Type	WD-MHIB (p value)	N	PHQ-9 (p value)	N	GAD-7 (p value)	N	PSS-10 (p value)	N
SF-12 MCS	Pearson correlation	<0.001	591	—	—	—	—	—	—
AST	Linear mixed-effects model	0.126	574	0.126	574	0.126	574	0.126	574
ALT	Linear mixed-effects model	0.235	574	0.235	574	0.235	574	0.235	574
FIB-4 <2.67	Mann-Whitney U	0.072	522	0.002	522	0.004	522	0.990	522
FIB-4 ≥2.67	Mann-Whitney U	0.072	54	0.002	54	0.004	54	0.990	54
No cirrhosis	Mann-Whitney U	<0.001	134	<0.001	134	<0.001	134	0.045	134
Cirrhosis	Mann-Whitney U	<0.001	30	<0.001	30	<0.001	30	0.045	30
Longitudinal change over time	Linear mixed-effects model	0.003	574	—	—	—	—	—	—

Disclosures: Hatice Maras:Nothing to Disclose, ASIM ULCAY:Nothing to Disclose, Sefa Keserci:Nothing to Disclose, Paula Zimbrean:ultragenyx: Consultant, Susan Rubman:Nothing to Disclose, Regino Gonzalez-Peralta:Nothing to Disclose, Isabelle Mohr:Nothing to Disclose, Aftab Ala:Nothing to Disclose, Sanjiv Harpavat:Syneos Health: I sit on a Data Safety Monitoring Board, Thomas Sandahl:Nothing to Disclose, Michael Schilsky:Vivet Therapeutics: Grant/Research Support, Orphalan: Grant and Advisory, DepYmed: Advisor, Arbomed: Advisor and Consultant, Wilson Disease Association: Grant/Research Support, Prime Medicine: Consultant, Eton Pharma: Consultant, Prime Medicine: Advisor, Prime Medicine: Grant/Research Support.

1428 | VIRTUAL CME SIMULATION IMPROVES MULTI-SPECIALTY PERFORMANCE IN THE DIAGNOSIS AND MANAGEMENT OF WILSON DISEASE

Margaret Harris[1] Jovana Lubarda[1] Karen Badal[1], [1]Medscape Education

Background: Wilson disease (WD) is a rare but treatable genetic disorder of copper metabolism that requires a high index of clinical suspicion for timely diagnosis. Clinical gaps exist regarding the recognition of varied presentations and the selection of evidence-based maintenance therapies. The objective of this educational initiative was to improve clinician awareness of clinical red flags and optimize the management and monitoring of patients with WD. **Methods:** This virtual medical simulation educational activity engaged learners in two objective-based interactive patient cases involving a treatment-naïve patient and a patient requiring maintenance therapy. Clinical competence was assessed using a pre-guidance vs. post-guidance methodology. Statistical significance was determined via McNemar's test. The activity launched on September 19, 2025, with data collected through February 2026. The analysis included n = 162 for Case 1 and n = 99 for Case 2. **Results:** A total of 9,061 learners participated.

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Performance data for Gastroenterologists/Hepatologists (Gastros) and Neurologists demonstrated significant gains across core learning objectives (LO): **Diagnostic Workup (LO1):** In Case 1, Neurologists saw a 24% relative increase in diagnostic accuracy (P < .01) , while Gastros showed a 16% improvement (P < .001). Both groups saw significant lifts in recognizing extrahepatic cues, specifically requesting slit-lamp exams (Gastros: +18%; Neurologists: +24%). **Treatment Selection (LO2):** Sharpest gains were seen in this domain. In the setting of chelator intolerance (Case 1), Neurologists' selection of zinc salts rose by 56% (P < .001) compared to a 40% increase among Gastros (P < .001). In maintenance management (Case 2), adoption of trientine tetrahydrochloride increased by 21% for Neurologists and 19% for Gastros (P < .05 and P < .001, respectively). **Monitoring Success (LO3):** Gastros improved significantly in longitudinal care elements, including follow-up intensity (+16%) and patient education (+12%). Neurologists improved most in patient education (+11%). **Top Practice Changes & Barriers: Planned Changes:** 76% of learners plan to make one or more practice changes. **Primary Barriers:** Persistent obstacles to therapy adoption include unfamiliarity (reported up to 65%), cost (up to 42%), and insurance/access constraints. **Conclusion:** This online simulation effectively bridged gaps in WD clinical performance, yielding significant improvements in diagnostic workup and evidence-based treatment selection for both Gastroenterologists and Neurologists. With 97% of learners agreeing the education will impact their practice , this program potentially impacts 2,243 patient visits monthly.

Disclosures: Margaret Harris:Nothing to Disclose, Jovana Lubarda:Nothing to Disclose, Karen Badal: Nothing to Disclose.

1429 | WHOLE-BLOOD TRANSCRIPTOMIC PROFILING REVEALS DISTINCT FEATURES IN CIRRHOTIC PATIENTS CARRYING PI*MZ *SERPINA1* GENOTYPE

Mariia Lunova[1] Sona Frankova[2] Jan Kubovciak[3] Mikolas Holinka[2] Katerina Plchova[2] Tomas Nesnidal[2] Tomas Hucl[2] Milan Jirsa[2] Jan Sperl[2], [1]mariia.lunova@ikem.cz, [2]Institute for Clinical and Experimental Medicine, [3]Institute of Molecular Genetics of the Czech Academy of Sciences

Background: The *SERPINA1* Pi*MZ genotype is notably prevalent in the general population and is associated with an increased risk of liver disease and cirrhosis. While the role of the Pi*ZZ genotype in liver disease has been increasingly studied, little is known about blood-associated molecular changes linked to end-stage liver disease in Pi*MZ carriers. We aimed to determine whether whole-blood transcriptomic profiling identifies molecular signatures in Pi*MZ carriers with cirrhosis compared with Pi*MM cirrhotic patients and healthy Pi*MM controls. **Methods:** Whole-blood PAXgene RNA sequencing was performed in cirrhotic patients with alcoholic or metabolic dysfunction-associated liver disease carrying the Pi*MZ (n = 6) or cirrhotic patients with the same underlying liver disease carrying Pi*MM (n = 4) SERPINA1* genotype, and healthy Pi*MM controls (n = 2). Differential gene expression analysis was used to identify genotype-associated transcriptional changes, followed by gene set enrichment tests. We focused on the expression profiles of genes associated with inflammatory signaling (*LY96, IL1B, SOCS3, TNFAIP6, CKLF, GPR84*), cell stress and survival response (*BCL2A1, GADD45A, GADD45B, NAIP, SERPINB1, RAB20*), granulocyte inflammatory markers (*S100A8, S100A9, S100A12, MS4A3CLE 4D, AZU1, MPO, ELANE, PRTN3, CTSG*), and genes associated with acute-phase features (*B2M, ORM, LILRA5, MCEMP1*). Blood count parameters were evaluated to determine whether the observed signals reflected differences in circulating immune cell abundance. **Results:** Compared with Pi*MM cirrhotic patients, Pi*MZ carriers demonstrated a distinct blood transcriptomic profile characterized by increased expression of genes associated with neutrophil granules biology. The strongest signals included *AZU1* (log2 fold change (FC) 3.38, false discovery rate (FDR) < 0.05), *MPO* (log2 FC 1.18, FDR < 0.05), and *CTSG* (log2FC 1.32, FDR < 0.05). Evaluation of blood count parameters did not support a simple increase in total neutrophil counts, suggesting that the observed transcriptional changes may reflect altered immune-cell activation states or differences in cellular composition not captured by routine blood measurements. **Conclusion:** Cirrhotic Pi*MZ *SERPINA1* carriers present with a distinct whole-blood transcriptomic profile characterized by increased expression of genes associated with neutrophil granule biology in the absence of differences in total neutrophil count. These findings support the need for further investigation of immune-related alterations and blood-associated molecular signatures in alpha-1 antitrypsin–related liver disease.

Disclosures: Mariia Lunova:Nothing to Disclose, Sona Frankova:Gilead Sciences: Speaking and Teaching, Abbvie: Speaking and Teaching, Ipsen: Speaking and Teaching, Jan Kubovciak:Nothing to Disclose, Mikolas Holinka:Nothing to Disclose, Katerina Plchova:Nothing to Disclose, Tomas Nesnidal:Nothing to Disclose, Tomas Hucl:Nothing to Disclose, Milan Jirsa:Nothing to Disclose, Jan Sperl:Nothing to Disclose.

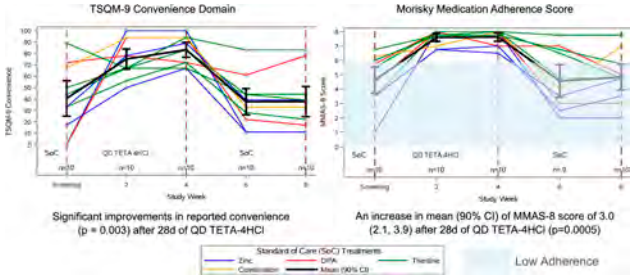
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1430 | UNDERSTANDING THE DRIVERS OF TREATMENT EXPERIENCE AND ADHERENCE IN WILSON DISEASE – WHAT DO PATIENT INTERVIEWS AND REPORTED OUTCOMES FROM A PHASE 2 STUDY EVALUATING A NEW TRIENTINE TETRAHYDROCHLORIDE FORMULATION TELL US?

C.Omar Kamlin[1] Courtney Hurt[2] Chelsea Perschon[2] John Peipert[3] Aftab Ala[4] Andrew Holt[5] Richard Parker[6] Joanna Moore[7] Elaine Kamara[8] Carla Bennett[8] Nick Manamley[8] Emmanuel Tsochatzis[9], [1]Orphalan, [2]Northwestern University, [3]University of Birmingham, [4]Kings College Hospital, [5]University Hospital Birmingham, [6]Leeds Teaching Hospitals NHS Trust, [7]Leeds University Hospital, [8]Orphalan SA, [9]Royal Free Hospital, London

Background: Wilson disease (WD) is a rare disorder of impaired copper transport requiring lifelong therapy with challenging circumstances (pharmacological and human factors) impacting medication adherence. Patient reported outcomes (PROs) are direct reports from patients without interpretation by a healthcare professional or anyone else, but no WD-specific treatment satisfaction PRO exists. The Food and Drug Administration (FDA) encourages the inclusion of the patient voice in medical product development. Following literature review and prior qualitative interviews, the objective of this study was to describe the patient experience following a switch from standard of care (SoC) to a novel trientine tetrahydrochloride formulation administered once-a-day (QD TETA4) using patient interviews and PRO responses. **Methods:** Phase 2 decentralized study (NCT07010575) of adults with WD (Leipzig score ≥ 4) on maintenance therapy prescribed at least twice daily either a chelator, zinc salts, or combination were switched to QD TETA4 (mg-for-mg rounded to nearest full tablet for chelators or 600mg [2 tablets] for zinc conversion) for 28-days followed by return to SoC for 28-days. Online interviews were conducted by PRO development experts. PROs included Treatment Satisfaction Questionnaire for Medication (TSQM-9 covering convenience, effectiveness, satisfaction domains) and Morisky Medication Adherence Scale (MMAS-8; less than 6 considered poorly adherent). **Results:** Ten (7 male) patients, mean (range) age 35.3 (21-55) years were enrolled with hepatic (2), neurologic (3), mixed (3), asymptomatic (2) phenotypes. SoC therapies were trientine (4), zinc (3), DPA (2) and combination trientine and zinc (1). All subjects were switched to either 2 or 3 QD TETA-4HCl tablets. Nine AEs (8 mild, 1 moderate) were reported in 7 subjects. In interviews, treatment satisfaction was high (5 patients selecting "Very much" and 3 "Quite a bit" to indicate level of satisfaction) with 80% of patients preferring QD TETA4, citing dosing schedule (n = 5), mental load (n = 3), adaptations/planning (n = 2), side effects (n = 2) as benefits over their SoC with a diversity of preference drivers (n = 11) documented. Of those participants asked, QD was rated as "much less challenging" for adherence and "much less disruptive" to daily life (7/9;[78%]). None reported treatment experience worsening. Responses from generic TSQM-9 convenience domain and MMAS-8 are shown in figure. **Conclusion:** Interview insights from people living with WD suggest that QD TETA-4HCl meaningfully reduces treatment burden through dosing simplification, reduced mental load, and fewer planning demands and were corroborated by self-reported improved convenience and adherence after 28 days of QD TETA-4HCl treatment compared to their SoC dosing regimen.



Disclosures: C.Omar Kamlin:Orphalan: Employee, Courtney Hurt:Orphalan SA: Independent Contractor, Chelsea Perschon:Nothing to Disclose, John Peipert: Orphalan: Consultant, Aftab Ala:Nothing to Disclose, Andrew Holt:Nothing to Disclose, Richard Parker: Nothing to Disclose, Joanna Moore:Nothing to Disclose, Elaine Kamara:Nothing to Disclose, Carla Bennett:Nothing to Disclose, Nick Manamley:Mundipharma: Employee, Orphalan: Employee, Mundipharma: Employee, Orphalan: Employee, Emmanuel Tsochatzis:Nothing to Disclose.

1431 | AGREEMENT BETWEEN MRI-PROTON DENSITY FAT FRACTION AND CONTROLLED ATTENUATION PARAMETER FOR DIAGNOSING HEPATIC STEATOSIS IN A COMMUNITY POPULATION

Linmei Yao[1] Minghui Li[2] Ruyu Liu[2], [1]Department of Hepatology Division 2, Beijing Ditan Hospital, [2]Department of Hepatology Division 2, Beijing Ditan Hospital, Capital Medical University

Background: Magnetic resonance imaging–proton density fat fraction (MRI-PDFF) is the noninvasive reference standard for quantifying hepatic steatosis. Controlled attenuation parameter (CAP) is increasingly used for population screening. We aimed to evaluate the diagnostic accuracy of CAP, determine its optimal cutoff, investigate the impact of age, BMI, and triglyceride (TG) on diagnostic consistency, and

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quantify the agreement between CAP and MRI-PDFF in a large community-based population. **Methods:** A total of 1571 community participants were enrolled. Anthropometric, metabolic, and laboratory data were collected. Using MRI-PDFF ≥5% as the reference standard, receiver operating characteristic (ROC) analysis was performed to obtain the optimal CAP threshold. Stratified ROC analyses by age, BMI, and TG were conducted. Spearman correlation and κ statistics were used to assess correlation and agreement. **Results:** CAP was strongly correlated with MRI-PDFF (Spearman ρ = 0.727, 95% CI: 0.698–0.752, P < 0.001). The optimal CAP cutoff was 246 dB/m, with an AUC of 0.849 (95% CI: 0.831–0.868), sensitivity 74.9%, specificity 79.0%, positive predictive value 82.7%, and negative predictive value 70.3%. Stratified analyses showed higher diagnostic performance in participants aged < 60 years (AUC = 0.933), BMI 24–28 kg/m² (AUC = 0.912), and TG < 1.7 mmol/L (AUC = 0.921). Linear weighted κ for four-grade steatosis was 0.469, and binary κ was 0.532 (both P < 0.001), indicating moderate agreement. **Conclusion:** In a general community population, CAP shows good diagnostic accuracy for hepatic steatosis with an optimal cutoff of 246 dB/m. Age, BMI, and TG significantly influence CAP performance. CAP has moderate agreement with MRI-PDFF and is a valid noninvasive tool for population-level screening of hepatic steatosis.

Disclosures: Linmei Yao:Nothing to Disclose, Minghui Li:Nothing to Disclose, Ruyu Liu:Nothing to Disclose.

1432 | EPIDEMIOLOGICAL TRENDS, TREATMENT MODALITIES, AND GENOTYPE-PHENOTYPE CORRELATIONS IN WILSON'S DISEASE: A COMBINED ANALYSIS OF A NATIONWIDE COHORT AND A MULTICENTER STUDY

Seong Hee Kang[1] Hyung Joon Yim[1] Young Kul Jung[1] Eun Ju Cho[2] Hye Won Lee[3] Young-Sun Lee[1] Hyo Jung Cho[4] Ji Hoon Kim[1] Jong Eun Yeon[1], [1]Korea University College of Medicine, [2]Seoul National University Hospital, [3]Yonsei University College of Medicine, [4]Ajou University College of Medicine

Background: This study aimed to investigate the nationwide epidemiological shifts, treatment patterns, and mortality risk factors of Wilson's disease (WD) in South Korea, while integrating a multicenter cohort to elucidate specific ATP7B genotype-phenotype correlations and long-term clinical outcomes. **Methods:** We analyzed data from a comprehensive nationwide registry cohort (2008–2022) alongside detailed clinical and genetic datasets from a multicenter cohort (5 centers) of 121 patients who underwent ATP7B mutation testing. Survival analyses and genotype-phenotype evaluations were performed. **Results:** Between 2008 and 2022, the nationwide registry cohort demonstrated that the age-standardized prevalence of WD steadily increased from 4.30 to 12.71 per 100,000 population, consistently showing a male predominance (14.81 vs. 10.61 per 100,000 in 2022). Genetic diagnoses dramatically escalated after 2014, peaking in 2021 (n = 472), and were primarily clustered in the 0–19 age group. Clinical complications significantly increased mortality, with liver cirrhosis (HR 7.99, p < 0.001) and hepatocellular carcinoma (HCC) (HR 1.53, p = 0.007) acting as major independent risk factors. Regarding pharmacotherapy, D-penicillamine and trientine combination therapy significantly reduced the mortality risk (HR 0.43).In the multicenter cohort, ATP7B mutational mapping identified compound heterozygotes (54.5%), heterozygotes (15.7%), homozygotes (13.2%), and wild-type cases (9.1%). Heterozygotes and compound heterozygotes presented at an earlier age (mean 12.9–15.7 years) with lower baseline ceruloplasmin levels. Crucially, homozygous Type 1 (1/1) patients exhibited an exceptionally high rate of liver cirrhosis (56.3%) and a correspondingly high liver transplantation rate (18.8%, p = 0.024). Wild-type patients experienced a significantly delayed diagnosis (mean age 24.8 years) and presented predominantly with neuropsychiatric symptoms (45.5%). **Conclusion:** The prevalence and genetic detection rates of WD are rising continuously in South Korea. Patient clinical trajectories and long-term prognoses are profoundly dictated by ATP7B mutation types. Genotype-stratified risk assessment, and optimal selection of combination pharmacotherapies are crucial to mitigate fatal outcomes driven by hepatic complications.

Disclosures: Seong Hee Kang:Nothing to Disclose, Hyung Joon Yim:Nothing to Disclose, Young Kul Jung:Nothing to Disclose, Eun Ju Cho:Nothing to Disclose, Hye Won Lee:Nothing to Disclose, Young-Sun Lee:Nothing to Disclose, Hyo Jung Cho:Nothing to Disclose, Ji Hoon Kim:Nothing to Disclose, Jong Eun Yeon:Nothing to Disclose.

1433 | NON-INVASIVE ULTRASOUND AND PHOTOACOUSTIC IMAGING OF HEPATIC COMPOSITION AND BIOMECHANICS IN PRECLINICAL MODELS OF METABOLIC LIVER DISEASE USING THE VEVO F2XC AND LAZR-X20

Barry Campbell[1] Anna St. Lorenz[1] Laura Griffin[2] Steven Yeung[3] Sridhar Radhakrishnan[4] Kristiina Aasa[5] Stephen Buttars[1] Stephanie Ly[1] Sarah Burris[1], [1]Fujifilm

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VisualSonics Inc., [2]Taconic, [3]Research Diets Inc., [4]Research Diets, [5]Fujifilm VisualSonics Inc

Background: Metabolic liver disease encompasses a spectrum of conditions from steatosis to inflammation, fibrosis, and liver failure. These stages involve changes in hepatic biochemical composition and mechanical properties. Traditional preclinical methods relying on terminal tissue collection, limit longitudinal monitoring of disease progression and therapeutic response in the same animal. To overcome this, our study applied a multimodal imaging approach to acquire anatomical and functional data using ultra-high frequency ultrasound, combined with photoacoustic imaging (PAI) to monitor disease progression. Employing a diet-induced obesity (DIO) mouse model (Taconic Biosciences) of metabolic dysfunction-associated steatohepatitis (MASH), we quantitatively assessed liver stiffness over time, enabling characterization with real-time, non-invasive imaging. **Methods:** Longitudinal imaging was performed on mice fed a high-fat diet (60% kcal fat, Research Diets) using the FUJIFILM VisualSonics Vevo F2xc LAZR-X20, capturing the model's progression from steatosis to fibrosis. Real-time shear wave elastography, a push button mode on the system, measured liver tissue stiffness, while PAI mapped lipid and theoretical collagen content based on distinct spectral signatures. **Results:** Distinct hepatic phenotypes emerged in the DIO model. Although no significant changes were seen with collagen, PAI revealed a strong correlation between liver lipid content and duration of high-fat diet feeding (R^2 = 0.8), indicating progressive fat accumulation. SWE detected early decrease in liver stiffness at 14 weeks, reflecting tissue softening due to increased lipid content, followed by a significant increase at 22 weeks ($p < 0.005$), consistent with presumed maturation of lipid droplets or remodeled extracellular matrix (ECM). These results demonstrate the ability of combined SWE and PAI to differentiate steatosis-associated softening from pre-fibrotic stiffening within the same tissue over time. **Conclusion:** The Vevo F2xc LAZR-X20 integrates shear wave elastography and PAI into a powerful, non-invasive platform for comprehensive, longitudinal liver phenotyping in preclinical models. These studies reveal a biphasic pattern driven by lipids as opposed to fibrosis. Early steatosis softens the liver tissue, consistent with lipid droplets acting to disrupt cytoskeletal tension. The subsequent liver stiffening at 22 weeks, absent of changes in collagen deposition, suggests a fibrosis-independent mechanism such as lipid droplet maturation or ECM remodeling. We plan to expand SWE and PAI applications to other metabolic and vascular models, including atherosclerosis and diet-induced MASH. This will leverage quantitative assessment of stiffness alongside molecular markers such as collagen, and lipids providing comprehensive multimodal insights into disease progression and treatment efficacy.

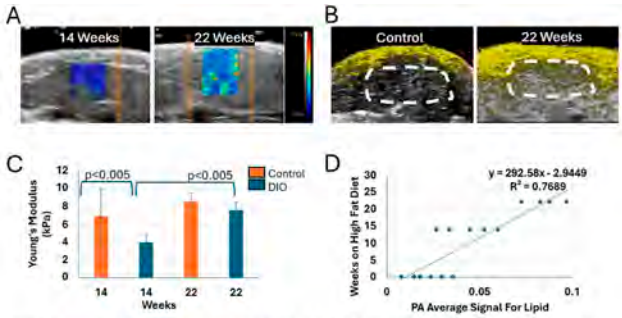


Figure 1. Combined SWE and photoacoustic imaging (PAI) capture lipid-driven, biphasic mechanical responses in pre-fibrotic DIO mice. (A) High-frequency ultrasound and real-time SWE imaging of livers from 14-week (left) and 22-week (right) DIO model mice. **(B)** Unmixed PAI images of lipid (yellow) in a 22-week DIO model mouse (right) and an age-matched control (left). Quantified data were obtained from the region of interest (ROI) within the liver tissue, beneath the fat pad. **(C)** DIO animals exhibited a significant decrease in liver stiffness at 14 weeks compared to age-matched controls, with no significant difference observed at 22 weeks. **(D)** A strong positive linear correlation exists between weeks on the high-fat diet and lipid deposition, as determined by PAI (R^2 = 0.769).

Disclosures: Barry Campbell:Nothing to Disclose, Anna St. Lorenz:Nothing to Disclose, Laura Griffin: Nothing to Disclose, Steven Yeung:Nothing to Disclose, Sridhar Radhakrishnan:Nothing to Disclose, Kristiina Aasa:Nothing to Disclose, Stephen Buttars: Nothing to Disclose, Stephanie Ly:Nothing to Disclose, Sarah Burris:Nothing to Disclose.

1434 | DE-CENTRALIZED CLINICAL TRIALS IN RARE DISEASE; INCORPORATING THE PATIENT VOICE IN THE EVALUATION OF TOLERABILITY, TREATMENT SATISFACTION AND ADHERENCE OF A NOVEL TRIENTINE TETRAHYDROCHLORIDE FORMULATION FOR THE TREATMENT OF WILSON DISEASE

Emmanuel Tsochatzis[1] Aftab Ala[2] Andrew Holt[3] Richard Parker[4] Joanna Moore[5] Elaine Kamara[6] Carla Bennett[6] Nick Manamley[6] C.Omar Kamlin[7], [1]Royal Free Hospital, [2]Kings College Hospital, [3]University Hospital, Birmingham, [4]Leeds Teaching Hospitals NHS Trust, [5]Leeds University Hospital, [6]Orphalan SA, [7]Orphalan

Background: Wilson disease (WD) is a rare disorder of impaired copper transport requiring lifelong therapy where suboptimal adherence is increasingly recognised. As per US Federal Drugs Agency (FDA)

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guidance, decentralized trials (DT) may reduce participant burden and improve trial efficiency and access to participants, important considerations for rare disease studies. To support the clinical development of a new trientine tetrahydrochloride formulation administered once daily (QD TETA4), a DT was designed to assess tolerability and patient perspective before and after a switch in therapy. **Methods:** Phase 2 DT (NCT07010575) approved by a single centralized ethics committee enrolled adults with WD (Leipzig score ≥ 4) in a single arm switch study identified and referred by 6 UK centres of excellence to a virtual clinical trial centre (VCTC, UK). Medications were dispensed and returned to a remote pharmacy. Assessments (blood draws, online study visits with investigators, completion of patient reported outcome (PRO) questionnaires and online semi-structure patient interviews) were conducted at participants' homes. Participants switched from their standard of care (SoC) maintenance therapy to QD TETA4 (mg-for-mg rounded to nearest full tablet for chelators or 600mg [2 tablets] for zinc conversion) for 28-days followed by return to SoC for 28-days. Adverse events (AEs) were collected. Paper PROs (treatment satisfaction questionnaire for medication [TSQM-9] and Morisky medication adherence score [MMAS-8]) were mailed and collected by courier on 5 fixed dates. **Results:** Ten (7 male) multi-ethnic (>4 groups) individuals, mean (range) age 35.3 (21-55) years were enrolled from 3 major cities in the UK (London, Birmingham, Leeds) with hepatic (2), neurologic (3), mixed (3), asymptomatic (2) phenotypes. SoC therapies were trientine (4), zinc (3), DPA (2) and combination trientine and zinc (1). Nine AEs (8 mild, 1 moderate) were reported in 7 subjects and all resolved. TSQM-9 convenience domain showed significant improvements; mean (90% CI) at baseline, 28d after QD TETA-4HCl and 28d after SoC was 43.1 (26.3, 59.9), 85.0 (78.4, 91.6) [p = 0.008], and 40.7 (26.9, 54.4), respectively. At the same timepoints, TSQM-9 Effectiveness did not change, TSQM-9 Satisfaction improved but not significantly. At same timepoints, adherence significantly improved; MMAS-8 score was 4.8 (3.7, 5.8), 7.7 (7.4, 8.0) [p = 0.002] and 5.0 (4.0, 5.9). A selection of study metrics is shown in the table. **Conclusion:** In the absence of benchmarking for DT trials in WD, our findings confirm the feasibility of successfully completing a DT in rare liver disease with nationwide enrollment, diverse ethnicities and phenotypes reflective of the national population, successful home blood collection with central laboratory analyses. All PROs were fully completed indicating positive impact on convenience and adherence after 28d of well tolerated QD TETA-4HCl treatment.

Study Activity	Start	Complete	Comments	
Internal Kick-off		14Oct24		
Final Protocol (v1.0)		20Jan25		
Final Protocol (v2.0)		27Mar25	Updates made as requested following MHRA review	
Contracting with VCTC	Start-up agreement – FE 08Nov24	Full contracting FE 13Mar25	Full contract using adapted Model CTA template	
Regulatory/Ethics Submission in UK (via IRAS)	17Feb25	23Apr25		
Contracting with 6 COEs		Site A 06Jun25 Site B 13Jun25 Site C 16Jun25 Site D 28Jul25 Site E 04Sep25	only 5 completed agreements by LPLV	
Study set up activities (SIV, remote pharmacy visit, IMP shipment through to start of study screening)	SIV (on-hold) 19May25 IMP Shipment 03Jun25 Remote Pharmacy visit 27Jun25 Greenlight (screening) 15Jul25 Full site release – 04Aug25			
FP first screening visit	30JUL2025 (first consent)	22OCT2025 (last consent)	Informed consent signed	
FP dosing	21AUG2025	24OCT2025	Complete is when last patient had first dose	
LPLV	16OCT2025 (FV)	18DEC2025		
Final DBL		09FEB2026	First lock	
Trial Specific Activities	**On time / complete**		**% completion**	**Comments**
PRO questionnaires	All complete		100%	
IMP Dosing & compliance	All complete		90%	1 subject took 1 tablet/day instead of 2 tablets/day; discovered on pill count reconciliation
Blood sampling and analyses	All complete		100%	Central laboratory
Online Cognitive debriefing interviews	All complete		100%	Completed by all participants (1 required two sessions)

Footnote:
VCTC: virtual clinical trial centre; COE: WD centres of excellence; SIV: site-initiation visit; IMP: investigational medicinal product; FP: first patient; LPLV: last patient last visit; DBL: database lock; CSR: clinical study report; PRO: patient reported outcomes;

Disclosures: Emmanuel Tsochatzis:Nothing to Disclose, Aftab Ala:Nothing to Disclose, Andrew Holt: Nothing to Disclose, Richard Parker:Nothing to Disclose, joanna Moore:Nothing to Disclose, Elaine Kamara:Nothing to Disclose, Carla Bennett:Nothing to Disclose, Nick Manamley:Mundipharma: Employee, Orphalan: Employee, Mundipharma: Employee, Orphalan: Employee, C.Omar Kamlin:Orphalan: Employee.

1435 | EFFICACY OF SEMAGLUTIDE AND RELATED DRUGS IN ANIMAL MODELS OF VARIOUS DISEASES

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Background: The glucagon-like peptide-1 (GLP-1) receptor, GLP-1R, and its agonists have become the focal point in recent years, due to its novel mechanism, significant efficacy and broad potential in

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treating various diseases. We sought to determine the efficacy of GLP-1 peptides and a GLP-1R agonist in animal (rodents and nonhuman primate, NHP) models of various diseases. **Methods:** We selected natural occurring obese cynomolgus monkeys to test semaglutide and orforglipron (small molecule GLP-1R agonist). Rodent models of diet-induced obesity (DIO) were used to test semaglutide, tirzepatide (dual GLP-1 and GIP agonist), bimagrumab (promoting muscle growth) and combination of semaglutide and bimagrumab. Humanized hGLP-1R transgenic mouse was tested for the efficacy of danulipron. Tirzepatide and semaglutide were tested in mouse models for type 2 diabetes (T2D) and MASH, respectively. In addition, rodent models for heart failure with preserved ejection fraction (HFpEF) and alcohol addiction were used to test tirzepatide and semaglutide, respectively. **Results:** 1) In the NHP study, the efficacy of both semaglutide and orforglipron was observed as determined by weight loss. However, the loss of fat mass was accompanied by the loss of lean mass, as seen in the clinics. 2) In a mouse model of DIO, weight loss was observed with tirzepatide, semaglutide + bimagrumab and semaglutide treatments. The level of weight loss correlated with loss of fat mass. The loss of lean mass was observed with tirzepatide and semaglutide, the latter of which was reserved by bimagrumab. Similar results were observed in rats. 3) When danuglipron was tested DIO hGLP-1R mouse, significant weight loss was observed, together with loss of both fat and lean mass. 4) The efficacy of tirzepatide was observed in db/db T2D models. 4) In a CDAHFD rat model for MASH, semaglutide significantly improved steatosis and fibrosis. In a HFD+CCL4 mouse MASH model, similar results were observed. We also performed RNA seq profiling of semaglutide and resmetirom and will share the results. 5) In an HFD+L-NAME induced DIO and HFpEF model, tirzepatide was shown to improve several heart failure-related cardio functions. 6) We are testing semaglutide in a mouse model of alcohol addiction and will share the results. **Conclusion:** The weight loss efficacy of semaglutide and other GLP-1R agonists was observed in DIO models in rodents and NHP. In all cases, weight loss was associated with loss of both fat and lean mass. Bimagrumab prevents loss of lean mass without impacting weight loss. These results are consistent with what has been observed in the clinics. Semaglutide and other agonists were efficacious in rodent models for diabetes, heart failure and MASH. Semaglutide is mechanistically different from resmetirom in treating MASH. We are currently exploring semaglutide in a rodent model for alcohol addiction.

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1436 | CONSENSUS PATHOLOGY PANEL READING FOR METAVIR FIBROSIS STAGING AND PAS+D SCORING IN ALPHA-1 ANTITRYPSIN DEFICIENCY CLINICAL TRIALS

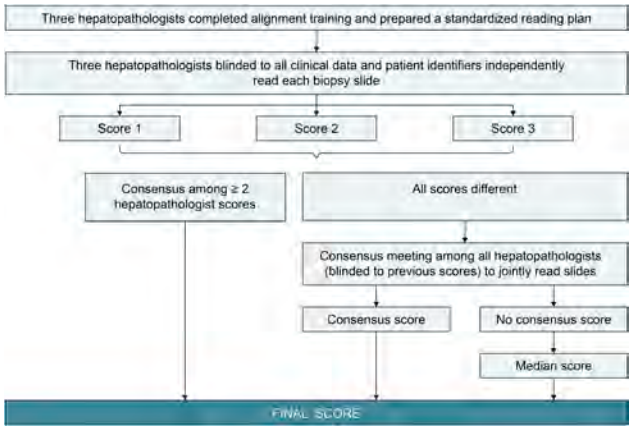
Vandana Gupta[1] Seth Pixton[1] Chantal Beauchemin[1] Jen-Chieh Chuang[1] Natasha Darras[1] Jennifer Green[1] Susana Gonzalez[1] Hong Li[1] Divya Shakti[1] Tom Davis[2] Reema Kainth[2] Caitlin Langford[2] Thomas Schluep[3] Virginia Clark[4] Pavel Strnad[5] Cynthia Behling[6] Kay Washington[7] Romil Saxena[8], [1]Takeda Development Centre Americas, Inc., Cambridge, MA, USA, [2]Perspectum Limited, Oxford, UK, [3]Arrowhead Pharmaceuticals, Inc., Pasadena, CA, USA, [4]University of Florida, Gainesville, FL, USA, [5]University Hospital RWTH Aachen, Aachen, Germany, [6]University of California San Diego, San Diego, CA, USA, [7]Vanderbilt University Medical Center, Nashville, TN, USA, [8]Emory University School of Medicine, Atlanta, GA, USA

Background: In alpha-1 antitrypsin deficiency-associated liver disease (AATD-LD), disease burden is determined using biopsy-based METAVIR fibrosis staging and assessment of hepatic accumulation of misfolded Z-alpha-1 antitrypsin by periodic acid–Schiff staining with diastase (PAS+D). However, these measures are subject to inter- and intra-reader variability. Regulatory guidance supports the use of histological endpoints in clinical trials if variability is minimized through standardization (reader training, calibration and consensus-based assessments). In AATD-LD clinical trials, harmonization of METAVIR and PAS+D-based scores ensure consistent and reliable biopsy interpretation. This study aimed to establish a consensus scoring method for METAVIR fibrosis staging and PAS+D. **Methods:** Archived liver biopsy samples from adults with AATD-LD, viral hepatitis or metabolic dysfunction-associated steatohepatitis were analyzed for METAVIR fibrosis stage and PAS+D burden (AATD-LD samples only). Slides stained with both Masson's trichrome and hematoxylin and eosin from 55 biopsy samples were used for METAVIR fibrosis staging, and 86 biopsy samples (across two batches) were analyzed for PAS+D burden. Digitized slides were assessed independently by three hepatopathologists who had previously completed alignment training and prepared a standardized reading plan. METAVIR fibrosis stage was scored from F0 to

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F4, and PAS+D components (zonal location, percent portal tract involvement, percent of zone 1 periportal involvement and number of hepatocytes involved per high power field) were scored from 0 to 3 (least severe to most severe) for each component. The consensus method is shown in the **Figure** . **Results:** For METAVIR fibrosis staging (n = 55), consensus agreement (≥ 2 hepatopathologists) was 94.5% and inter-reader concordance (overall Krippendorff's alpha [K-a]: 0.71) was consistent with the literature for well harmonized readers. After a 4-week washout period, there was good intra-reader reproducibility following slide re-scoring (overall percent intra-reader agreement for each hepatopathologist ranged between 72.2% to 90.9% and K-a ranged from 0.81 to 0.94). Across two batches assessed for PAS+D burden, consensus across PAS+D components was 86.4% to 97.6%. When all readers assigned different scores, a consensus meeting resulted in an agreed score for METAVIR fibrosis stage and individual PAS+D components. **Conclusion:** This study demonstrated a robust and reproducible consensus multi-reader approach for METAVIR fibrosis staging and PAS+D burden. These data support the utility of longitudinal histological assessment in the ongoing phase 3 fazirsiran trial in AATD-LD.Writing support provided by R Tooze, Oxford PharmaGenesis.



Disclosures: Vandana Gupta:Nothing to Disclose, Seth Pixton:Nothing to Disclose, Chantal Beauchemin:Nothing to Disclose, Jen-Chieh Chuang:Nothing to Disclose, Natasha Darras:Nothing to Disclose, Jennifer Green:Nothing to Disclose, Susana Gonzalez:Nothing to Disclose, Hong Li:Nothing to Disclose, Divya Shakti:Nothing to Disclose, Tom Davis:Nothing to Disclose, Reema Kainth:Nothing to Disclose, Caitlin Langford:Nothing to Disclose, Thomas Schluep:Nothing to Disclose, Virginia Clark:Nothing to Disclose, Pavel Strnad:Nothing to Disclose, Cynthia Behling: Nothing to Disclose, Kay Washington:Takeda Pharmaceuticals: Consultant, Romil Saxena:Nothing to Disclose.

1437 | LONG-TERM OUTCOMES OF ZINC THERAPY IN WILSON DISEASE: A 25-YEAR RETROSPECTIVE STUDY

Frederick Askari[1] Ashley Page[2] Graham Brady[2] Matthew Lorincz[2], [1]University of Michigan Medical Center, [2]University of Michigan

Background: Wilson Disease is a disorder of copper metabolism characterized by toxic copper accumulation in the liver and central nervous system, requiring lifelong treatment. Zinc monotherapy is widely utilized for maintenance therapy due to its ability to inhibit intestinal copper absorption. However, there is limited data at two decades of use on long-term clinical outcomes, real-world adherence, and tolerability. **Methods:** Retrospective chart review identified Wilson Disease patients managed primarily with zinc for 20 years or more at the University of Michigan. Medical charts assessed the availability and frequency of clinical data, including disease presentation, liver biochemistry, and non-invasive markers (APRI, MELD, FIB-4), and 24 hour urinary copper and zinc levels. Adherence and adverse effects were evaluated by urinary zinc levels and systematic review of clinical documentation. **Results:** The cohort included 21 patients (mean age 58, 60% female) with hepatic, and/or neuropsychiatric, as well as asymptomatic individuals. Hepatic function remained stable with long-term zinc therapy. Mean laboratory cumulative mean values included AST 39.5 IU/L, ALT 54.6 IU/L, albumin 4.3 g/dL, and INR 1.2. Noninvasive fibrosis markers were relatively stable, with mean APRI 0.81 (Δ -0.35), FIB-4 2.09 (Δ 0.17), and cumulative MELD score 9.17 (Δ 0.90); Δ values represent cumulative changes from baseline to most recent measurement. Adequate zinc therapy was associated with urinary copper excretion < 100 µg/24 hours. Approximately 71% of patients experienced periods of nonadherence, demonstrated by intermittent urinary copper elevations (> 100−200 µg/24 hours), fluctuating urinary zinc levels, and difficulty maintaining TID dosing regimens. Wide ranges of urine copper levels (6.1−942 µg/24 hours) were observed, with higher values partly explained by transient use of combination chelation therapy. Gastrointestinal adverse effects (nausea, vomiting, abdominal discomfort) were observed and necessitated antiemetics, zinc dose adjustments, or change in treatment. Five patients temporarily transitioned to chelation therapy, and two permanently discontinued zinc due to intolerance and adherence burden.Two deaths were observed: a 65-year-old male while carrying a diagnosis of cholangiocarcinoma and 84-year-old female in the setting of senescence, dementia, anxiety, and cholangiocarcinoma. **Conclusion:**

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Long-term zinc therapy is effective and safe when adherence is maintained, supporting hepatic stability. However, real-world effectiveness is limited by challenges with adherence and gastrointestinal intolerance. These findings underscore the need for improved zinc formulations and drug delivery strategies to reduce treatment burden and optimize long-term outcomes.

Table 1: Cumulative Cohort Characteristics and Changes Over Time

Variable	Cumulative Mean ± SD	Cumulative Median (Range)	Δ Cumulative Mean (Baseline → Recent)	Δ Cumulative Median (Baseline → Recent)
Age (years)	58.0 ± 12.3	61.1 (35.7–82.7)	—	—
Urine Copper (µg/24h)	77.85 ± 60.43	67.50 (5.1–842)	-44.86 ± 182.33	-15.3 (-803.4 to 123.9)
Urine Zinc (µg/24h)	4639.49 ± 2620.06	4262.00 (117–21696)	-172.67 ± 3064.37	-1018 (-4360 to 6915)
AST (U/L)	39.50 ± 39.06	30.00 (10–440)	-17.14 ± 35.54	-3 (-84 to 34)
ALT (U/L)	54.67 ± 81.42	36.00 (4–644)	-31.62 ± 49.01	-17 (-126 to 51)
Albumin (g/dL)	4.31 ± 0.87	4.30 (1.60–9.95)	-0.22 ± 1.56	0.2 (-4.95 to 1.3)
INR	1.23 ± 0.46	1.10 (0.90–4.49)	0.01 ± 0.36	0 (-1 to 1.22)
APRI	0.81 ± 1.32	0.45 (0.14–13.61)	-0.35 ± 0.57	-0.06 (-1.65 to 0.40)
FIB-4 Score	2.09 ± 2.14	1.38 (0.22–25.56)	0.17 ± 1.72	0.20 (-3.07 to 4.69)
MELD Score	9.17 ± 3.79	8 (6–36)	0.90 ± 3.17	0 (-7 to 9)

* Δ cumulative mean and median values reflect the change within the cumulative cohort from baseline to the most recent measurement.

Disclosures: Frederick Askari:Alexion: Advisor, Ultragenyx Pharmaceutical, Inc.: Advisor, Vivet: Advisor, Deep Genomics: Advisor, Intercept: Advisor, Ashley Page:Nothing to Disclose, Graham Brady:Orphalan: (note I am a co-I, not a PI), Ultragenyx: (note I am a co-I, not a PI), Vivet Therapeutics: (note I am a co-I, not a PI), Bausch Health US, LLC: (note that I am a co-I, not a PI), Orphalan: (note I am a co-I, not a PI), Ultragenyx: (note I am a co-I, not a PI), Vivet Therapeutics: (note I am a co-I, not a PI), Bausch Health US, LLC: (note I am a co-I, not a PI), Matthew Lorincz:Nothing to Disclose.

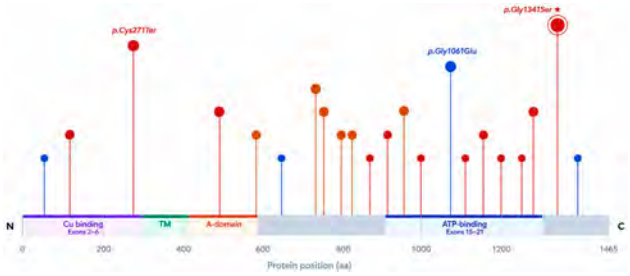
1438 | P.GLY1341SER AS A FREQUENT REGIONAL ATP7B VARIANT IN WILSON DISEASE: GENOTYPIC SPECTRUM AND AGE-STRATIFIED CLINICAL HETEROGENEITY FROM A SOUTH INDIAN REFERRAL CENTER

Rajat Prabhakar Pande[1] Vivek Ashokan[1] Blessline Sampath Kumar[2] MadhuSuriya M[1] Joeimon JL[1] PremKumar K[1] PremKumar K[1], [1]Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai., [2]Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai

Background: Wilson Disease is a rare autosomal recessive disorder of impaired copper metabolism. Despite a well characterized pathophysiology, genotype- phenotype heterogeneity persists across age groups. Mutational data from South India remain sparse; regional founder variants may distinctly alter the local phenotypic landscape. **Methods:** This is an ambispective single-center study involving Wilson disease patients aged >13 years with hepatic involvement (**pure neurological Wilson disease excluded**). Standard clinical, biochemical, and imaging parameters were recorded. Next-generation sequencing of *ATP7B* was performed. The patients were further **divided into three groups based on their age, Group A (13-17 years), Group B (18-25 years), Group C (> 25 years) to ascertain genotype- phenotype correlates and clinical outcomes. Results:** The study involved 86 cases with a mean age of 23.11 ± 8.07 including 52.3% males. Decompensated cirrhosis was the predominant presentation across all groups (42.9% vs 44.1% vs 32.6%), followed by neurohepatic disease (30.7% vs 23.5% vs35.2%) **ALF/ACLF was significantly high in adolescent age group (14.3% vs 2.9% vs 5.0%) Neuro-Hepatic phenotypes demonstrated delayed diagnosis and higher disability burden despite lower hepatic biochemical severity.** On a median follow up of 1358 days, the adolescent group recorded highest event burden (23.3% vs 11.7% vs 17.6%) although event-free survival did not differ significantly across age groups (log-rank p = 0.291) Genetic sequencing of 33 patients identified 18 distinct ATP7B variants, **Notably, p.Gly1341Ser (exon 19), identified in 15.2% of patients and infrequently reported from India, emerged as one of the most common mutations in our cohort surpassing established pan Indian variants** followed by c.813C > A (p.Cys271Ter) in 12.1% and c.3182G > A (p. Gly1061Glu) in 9.1% and other rare variants. **Missense mutations predominated (60%)** followed by frameshift (15%) and stop-gained variants (12.5%). **On genotype–phenotype correlation analysis, hepatic manifestations were more frequent among homozygous patients compared to neurohepatic disease (59.1% vs 40.9%) however, zygosity pattern was not significantly associated with clinical phenotype (p = 0.493).** Substantial **phenotypic heterogeneity persisted despite a high prevalence of homozygous mutations (60.6%) and consanguinity (42.2%) Conclusion:** Wilson disease demonstrates marked age-dependent phenotypic heterogeneity with **genotype-phenotype discordance transcending zygosity. The regional predominance of p.Gly1341Ser over the established pan-Indian variant p.Cys271Ter reinforces the necessity of comprehensive genetic analysis** in patients with Wilson disease. These findings underscore the need for **region-specific mutational registries to refine phenotypic correlation, risk stratification, and advance precision medicine-based management strategies** in South Asian populations.

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Disclosures: RAJAT PRABHAKAR PANDE:Nothing to Disclose, Vivek Ashokan:Nothing to Disclose, Blessline Sampath Kumar:Nothing to Disclose, MadhuSuriya M: Nothing to Disclose, Joeimon JL:Nothing to Disclose, PremKumar K:Nothing to Disclose, Nothing to Disclose, PremKumar K:Nothing to Disclose, Nothing to Disclose.

1439 | EVALUATION OF DIGITIZED WHOLE SLIDE IMAGING FOR METAVIR LIVER FIBROSIS STAGING: CONCORDANCE WITH CONVENTIONAL GLASS SLIDE READING

Jennifer Green[1] Adam Tellier[1] Vandana Gupta[1] Jen-Chieh Chuang[1] Susana Gonzalez[1] Paresh Thakker[1] Tom Davis[2] Reema Kainth[2] Caitlin Langford[2] Thomas Schluep[3] Kay Washington[4], [1]Takeda Development Center Americas, Inc., Cambridge, MA, USA, [2]Perspectum Limited, Oxford, UK, [3]Arrowhead Pharmaceuticals, Inc., Pasadena, CA, USA, [4]Vanderbilt University Medical Center, Nashville, TN, USA

Background: Liver biopsy is the reference standard for fibrosis assessment in patients with alpha-1 antitrypsin deficiency-associated liver disease (AATD-LD). Histopathologist-assigned METAVIR fibrosis staging defines liver fibrosis severity and is a key regulatory endpoint for evaluating treatment efficacy in clinical trials. However, conventional glass slide review by histopathologists imposes substantial operational burden. Modernized digital pathology approaches that permit efficient and robust METAVIR fibrosis staging by multiple readers in parallel can streamline histopathologist scoring of clinical trial endpoints in fibrotic liver diseases, including AATD- LD. We evaluated agreement between review of digitized whole slide images (WSI) and conventional glass slides to support METAVIR fibrosis staging in clinical trials. **Methods:** Liver biopsy samples from patients with fibrosis (F0–F4) and/or metabolic dysfunction-associated steatohepatitis (MASH) were evaluated on stained slides (Masson's trichrome [MT; n = 60] or hematoxylin and eosin [H&E; n = 20]). Sample processing, sectioning and slide staining was performed in a central lab using standardized methods and slides were scanned at 40x magnification. Paired digitized WSI and glass slides were evaluated in a blinded, randomized manner by an expert hepatopathologist according to the College of American Pathologists' guidelines (sequential 1-week glass and WSI reads separated by a 2-week wash-out period with no reads performed). Agreement between digitized WSI and glass slides was evaluated for specimen quality, number of complete portal tracts (< 6 vs ≥ 6), METAVIR fibrosis stage and presence/absence of MASH. Overall percent agreement (OPA) and weighted Cohen's kappa (κ) statistics were calculated. **Results:** There was strong agreement between the 80 digitized WSI and glass slides for the number of portal tracts (< 6 or ≥ 6); OPA was 97.5%. Specimen quality showed 100% agreement, with 2/80 slides (one MT- and one H&E-stained) deemed unacceptable by both digitized WSI and glass slides. For the 59 MT-stained samples with acceptable quality, there was high agreement for METAVIR fibrosis staging with an OPA of 88.1% and weighted Cohen's κ of 0.97. For the samples with disagreement, all were within one stage difference. For the 19 H&E-stained samples with acceptable quality, there was complete agreement (100%) for the assessment of presence/absence of MASH. **Conclusion:** Digitized WSI demonstrated strong agreement with conventional glass slide reading for portal tract assessment, METAVIR fibrosis staging and MASH classification. These findings support the use of digital WSI as a robust method for histological assessment and highlight its potential as a scalable option for pathology evaluation in clinical trials requiring METAVIR fibrosis evaluation.Writing support provided by C Bartley, Oxford PharmaGenesis.

Disclosures: Jennifer Green:Nothing to Disclose, Adam Tellier:Nothing to Disclose, Vandana Gupta: Nothing to Disclose, Jen-Chieh Chuang:Nothing to Disclose, Susana Gonzalez:Nothing to Disclose, Paresh Thakker:Nothing to Disclose, Tom Davis:Nothing to Disclose, Reema Kainth:Nothing to Disclose, Caitlin Langford:Nothing to Disclose, Thomas Schluep:Nothing to Disclose, Kay Washington:Takeda Pharmaceuticals: Consultant.

1440 | FROM INFANTILE HYPERTRIGLYCERIDEMIA TO HEPATOCELLULAR CARCINOMA AT AGE 46: THE FIRST REPORTED CASE OF GPD1 DEFICIENCY CAUSING CIRRHOSIS AND LIVER CANCER IN AN ADULT

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Background: Transient infantile hypertriglyceridemia (HTGTI) is a rare autosomal recessive disorder caused by mutations in the *GPD1* gene. Although HTGTI typically presents in early childhood with hepatomegaly, hepatic steatosis, and hypertriglyceridemia, adult presentation is exceedingly rare. Progression to cirrhosis and hepatocellular carcinoma (HCC) has rarely been described. **Methods:** A 46-year-old woman with short stature (height 144 cm, weight 45 kg, BMI 21.7 kg/m^2) and a history of hypertriglyceridemia presented with recurrent liver dysfunction for more than one year. Routine evaluation excluded common etiologies, including viral, alcoholic, drug-induced, liver parasitosis and cholestatic liver diseases. Transient elastography demonstrated significant steatosis (CAP 278 dB/m) and cirrhosis (LSM 21.7 kPa). Contrast-enhanced MRI/CT demonstrated a hypervascular nodule in segment II, concerning for HCC, and the patient subsequently underwent partial hepatectomy. Histopathology confirmed moderately differentiated HCC with underlying cirrhosis and macrovesicular steatosis. Given the cryptogenic nature of the liver disease, whole-exome sequencing was performed and identified a homozygous pathogenic variant in the *GPD1* gene. **Results:** Despite mildly elevated AMA-M2, histopathology revealed no evidence of autoimmune hepatitis, primary biliary cholangitis, or primary sclerosing cholangitis. Imaging revealed cirrhosis, steatosis, splenomegaly, portal hypertension, and a segment II hypervascular lesion. Pathology confirmed moderately differentiated HCC on a cirrhotic background. To further clarify the cause of the disease, genetic testing identified a homozygous splice-site variant in *GPD1*(chr12:50499329; c.220-2A > G), with parental and offspring testing confirming heterozygous carrier status. To our knowledge, this is the first reported case of genetically confirmed HTGTI caused by *GPD1* deficiency presenting with both cirrhosis and HCC in a 46-year-old adult. Following treatment with fenofibrate and ursodeoxycholic acid, triglyceride levels normalized, liver function improved, and liver stiffness decreased . **Conclusion:** We recommend that genetic testing for *GPD1* deficiency be performed routinely in all adults presenting with cryptogenic cirrhosis or HCC, as long as hypertriglyceridemia and short stature are present. Screening for HTGTI prevents misdiagnosis, minimizes therapeutic delays, and enables early intervention—including family counseling—prior to the onset of irreversible liver failure or malignancy.

Disclosures: HuiDan Sun:Nothing to Disclose, Dazhi Zhang:Nothing to Disclose, Yu Lei:Nothing to Disclose, Ying Huang:Nothing to Disclose.

1441 | PLASMA ZINC AS A MARKER OF ADHERENCE TO ZINC THERAPY IN WILSON DISEASE

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Background: Zinc is widely used for maintenance therapy in Wilson disease (WD), but poor adherence to the multiple daily dosing required for copper control remains a major challenge. Monitoring adherence to zinc therapy typically relies on 24-hour urinary zinc excretion (U-zinc), which reflects both zinc intake and absorption. Plasma zinc (P-zinc) offers an alternative that does not require 24-hour urine collection, but its clinical utility as an adherence marker remains unclear. We evaluated the relationship between P-zinc and U-zinc, and the performance of P-zinc for identifying adherence to zinc therapy in WD. **Methods:** In this retrospective multicentre study, patients with WD receiving zinc therapy at three tertiary referral centres were included if paired P-zinc and U-zinc measurements obtained within 30 days were available. Adherence thresholds were defined as > 19 µmol/L for P-zinc and > 18 µmol/24h for U-zinc, corresponding to the upper limit of normal (ULN) for both markers. U-zinc served as the reference standard for adherence classification as adherent or non-adherent. Patients were stratified by treatment regimen into zinc monotherapy or combination therapy with zinc and chelation therapy. Associations between P-zinc and U-zinc adherence classifications were evaluated using Fisher's exact test. **Results:** 74 patients were included: 53 on zinc monotherapy and 21 on combination therapy. In patients receiving monotherapy, P-zinc adherence classifications were significantly associated with U-zinc classifications ($p = 0.0001$). P-zinc identified adherence with 96 % sensitivity and a positive predictive value (PPV) of 93 % (Figure 1A). As expected with concomitant chelation therapy, no significant association between P-zinc and U-zinc classifications was observed in patients receiving combination therapy ($p = 0.2620$). Misclassifications were substantially more frequent in this group, particularly false negatives (Figure 1B). Median P-zinc concentrations were 27.6 µmol/L (IQR 22.0-31.4) during monotherapy and 15.0

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µmol/L (IQR 13.2-20.0) during combination therapy. Median U-zinc concentrations were 45.7 µmol/24h (IQR 24.7-63.2) and 36.6 µmol/24h (IQR 18.6-63.7), respectively. **Conclusion:** P-zinc may serve as a practical rule-in marker of adherence in patients with WD receiving zinc monotherapy, with potential utility as a simplified monitoring tool in routine care. However, this measure may not be as useful for combination therapy. P-zinc should therefore be interpreted as a complementary marker of zinc intake and absorption rather than a standalone measure of treatment efficacy or copper control.

A

Zinc Monotherapy		U-zinc > 18 µmol/24h		
		Adherent	Non-Adherent	Total
P-zinc > 19 µmol/L	Adherent	42	3	45
	Non-Adherent	2	6	8
	Total	44	9	53

B

Zinc Combination Therapy		U-zinc > 18 µmol/24h		
		Adherent	Non-Adherent	Total
P-zinc > 19 µmol/L	Adherent	6	0	6
	Non-Adherent	10	5	15
	Total	16	5	21

Figure 1: *2x2 contingency tables of adherence classifications based on P-zinc versus U-zinc in patients receiving (A) zinc monotherapy and (B) zinc combination therapy. Thresholds for adherence were defined as > 19 µmol/L for P-zinc and > 18 µmol/24h for U-zinc. U-zinc was used as the reference standard for adherence classification.*

Disclosures: Klara Marie Evensen:Nothing to Disclose, Camilla Lorenzen:Nothing to Disclose, Karen Boysen:Nothing to Disclose, Tea Laursen:Nothing to Disclose, Chris Harrington:Nothing to Disclose, Karl Heinz Weiss:Nothing to Disclose, Isabelle Mohr:Nothing to Disclose, Peter Ott:Nothing to Disclose, ASIM ULCAY:Nothing to Disclose, Michael Schilsky:Vivet Therapeutics: Grant/Research Support, Orphalan: Grant and Advisory, DepYmed: Advisor, Arbomed: Advisor and Consultant, Wilson Disease Association: Grant/Research Support, Prime Medicine: Consultant, Eton Pharma: Consultant, Prime Medicine: Advisor, Prime Medicine: Grant/Research Support, Thomas Sandahl:Nothing to Disclose.

1442 | NEW SUBMISSION PHARMACOKINETIC DIFFERENCES BETWEEN TRIENTINE DIHYDROCHLORIDE CAPSULE FORMULATIONS: A RANDOMIZED CROSSOVER STUDY

Steffen Wahler[1] Karl Heinz Weiss[2], [1]St. Bernward GmbH, [2]Heidelberg University

Background: Trientine dihydrochloride is an established copper chelator for Wilson disease. Because treatment is lifelong, pharmacokinetic (PK) differences between formulations may be clinically relevant when products are initiated or switched. We compared a 250 mg test capsule with a 300 mg reference capsule. The products differed in marketed strength and capsule/formulation characteristics, providing a setting to assess formulation-specific PK behavior. **Methods:** This randomized, open-label, balanced, two-treatment, two-period crossover study enrolled 36 healthy adults under fasting conditions. Test and reference products were administered as single doses separated by a 7-day washout. Plasma trientine and N1-acetyl-triethylenetetramine were measured by validated LC-MS/MS up to 48 h. PK parameters were derived by non-compartmental analysis. Bioequivalence was assessed using log-transformed Cmax and AUC0-t. Exploratory pooled analyses across 70 PK observations evaluated associations between baseline characteristics and Cmax or AUC0-t. **Results:** Thirty-five subjects completed both periods and were included in PK analyses. Absorption was faster with the test product, with median Tmax 1.25 h versus 2.25 h for reference ($p < 0.0001$). Mean Cmax was 934.0+/-345.0 versus 832.3+/-370.9 ng/mL, AUC0-t 4,525.4+/-2,354.6 versus 3,503.7+/-1,898.0 h*ng/mL, and AUC0-inf 4,771.2+/-2,450.1 versus 3,684.7 +/-1,968.7 h*ng/mL. Half-life was comparable (11.3 +/-7.5 vs 9.5+/-5.8 h). Unadjusted test/reference ratios were 114.96% for Cmax and 109.36% for AUC0-t, with 90% CIs 104.40-126.60% and 98.40-121.55%; dose-normalized ratios increased to 137.95% and 131.24%. Metabolite exposure was similar (Cmax 610.5+/-248.5 vs 661.3+/-311.1 ng/mL; AUC0-t 6,367.0+/-2,308.0 vs 6,820.7+/-2,955.6 h*ng/mL).In exploratory analyses, higher AUC0-t was observed in males versus females (3,850.6 vs 2,606.9 h*ng/mL, $p = 0.040$), serum creatinine > 0.92 versus $<= 0.92$ mg/dL (4,295.6 vs 3,083.1, $p = 0.008$), urinary pH $<= 6$ versus > 6 (4,205.1 vs 3,036.3, $p = 0.010$), and epithelial cells 0-1 versus higher categories (4,829.5 vs 3,089.0/3,137.4, $p = 0.001$). Lower leukocytes were associated with higher Cmax and AUC0-t.Five mild, non-drug-related

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adverse events occurred; no serious adverse events occurred. **Conclusion:** The 250 mg test capsule showed faster absorption and higher exposure per mg than the 300 mg reference product, while both formulations were well tolerated. Exploratory pooled analyses suggest that sex, creatinine, leukocyte count, urinary pH, and urinary epithelial cells may contribute to interindividual trientine exposure variability. These hypothesis-generating findings require confirmation in multivariable analyses and patient cohorts.

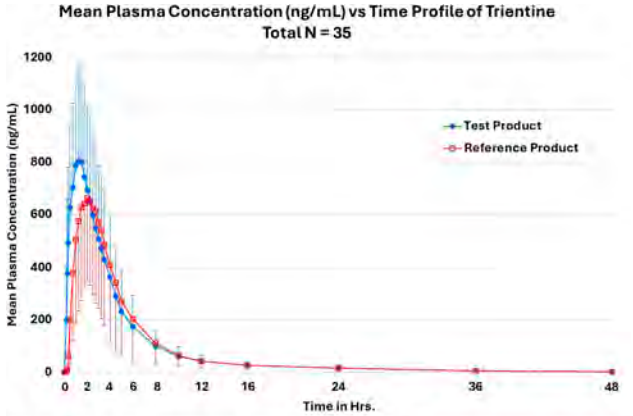


Figure. Mean plasma concentration-time profile of trientine after single oral administration of the 250 mg test and 300 mg reference formulations under fasting conditions (n=35). Error bars represent standard deviations.

Disclosures: Steffen Wahler:Nothing to Disclose, Karl Heinz Weiss:UNivar BV: Consultant, Ultragenyx: Consultant, Indeogen: Advisor, Orphalan: Advisor, MonoparTx: Advisor, Desitin: Advisor, Roche: Speaking and Teaching.

1443 | MODERN PATIENT PERSPECTIVES IN ALPHA-1 ANTITRYPSIN DEFICIENCY

Sheryl Denker[1] Wes Anderson[1] Gina DeAngelo[1] Jon Hagstrom[2] Kitty Bogy[1] Collin Hovinga[1], [1]Critical Path Institute, [2]Alpha-1 Foundation

Background: Alpha-1 antitrypsin deficiency affects 3+ million people globally; there is no cure. For 30 years, augmentation therapy has been the only option for pulmonary disease, with no option other than liver transplant for hepatic disease. As innovations in molecular, oral, and chaperone therapies work their way through clinical trials, the imperative exists to update the patient perspective for modern times. This is particularly true for alpha-1 antitrypsin deficiency (AATD), where a Patient Focused Drug Development meeting was last held by the FDA in 2015. A 2025 workshop and survey held by the Critical Path Institute's alpha-1 consortium addressed current knowledge gaps. **Methods:** In September 2025 over 100 patients, clinicians, industry members and advocates convened in Washington, DC and virtually for the workshop, *Shaping the Future of AATD: Patient Perspectives to Drive the Next Decade of Innovation in Alpha-1 Antitrypsin Deficiency*. In parallel, an online patient/caregiver survey, C PA -1 P atient E xperience S urvey U pdate for iN novation (CAPESUN), was developed in partnership with CPA-1 member patient advocacy groups. Survey data were analyzed using R [4.5.2]. Categorical variables were compared using Chi-Squared analysis or Fischer's Exact test based on data frequency, with $p < 0.05$ as statistically significant. Key themes discussed during the workshop were determined by analysis of the de-identified transcript. **Results:** Workshop attendance included 46% alpha-1 patients/caregivers; thematic analysis identified seven categories of concerns emphasizing the multisystem nature of the disease with substantial burden beyond lung and liver. 713 self-identifying patients/caregivers responded to CAPESUN with 22 genotypes represented: ZZ (60%), MZ (22%), SZ (10%), and MS (1.7%). Half (55%) of ZZ respondents reported having liver elastography; 58% of MS indicated steatosis/fatty liver disease, and 13% of MZ indicated intrahepatic cholestasis of pregnancy. Across all genotypes, 22% participated in clinical trials. Oxygen use and liver transplant status were used to determine disease severity cohorts; cohort analysis revealed willingness to participate in placebo controlled clinical trials is influenced by lung but not liver disease severity. Both transcript and CAPESUN indicated patients with advanced liver disease have higher tolerance for uncertainty and risk when participating in clinical trials. **Conclusion:** This work captures a comprehensive view of the alpha-1 patient perspective in modern day drug development. Those with serious liver disease will accept more risk in clinical trials although biopsy is burdensome and limiting; patients want non-invasive testing. Patients indicate endpoints and biomarkers do not reflect their lived experience, and they describe a range of clinically meaningful benefit: maintain current liver function, prevent additional decline, or ultimately repair damage.

Disclosures: Sheryl Denker:L-Nutra: Investor, Wes Anderson:Nothing to Disclose, Gina DeAngelo:Nothing to Disclose, Jon Hagstrom:Nothing to Disclose, Kitty Bogy: Nothing to Disclose, Collin Hovinga:Nothing to Disclose.

1444 | THE CONNECTION BETWEEN HEREDITARY HEMOCHROMATOSIS & PORPHYRIA CUTANEA TARDA: A SYSTEMATIC REVIEW AND META-ANALYSIS OF POPULATION-BASED STUDIES

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Background: Hereditary hemochromatosis (HH) is a prevalent autosomal recessive disorder caused primarily by HFE gene mutations, especially C282Y and H63D, resulting in systemic iron overload. Porphyria Cutanea Tarda (PCT), the most common porphyria and manifests photosensitivity and hepatic siderosis and is believed to be triggered by iron overload. This systematic review and meta-analysis assess the relationship between HFE gene mutations and the risk of PCT. **Methods:** A comprehensive literature search was conducted using PubMed, Scopus, and Web of Science databases through May 2025. Inclusion criteria were population-based or clinical cohort studies reporting the prevalence of HFE mutations in individuals with PCT. Ten studies met inclusion criteria, with over 800 PCT cases. Data extraction included study design, population demographics, genotype prevalence, and odds ratios (ORs). A random-effects model was used to calculate pooled odds ratios with 95% confidence intervals (CIs). **Results:** The pooled analysis demonstrated a significant association between HFE mutations and PCT with an odd's ratio of 2.85 with a confidence interval of 95%. The majority of the studies determined that the C282Y homozygosity conferred the highest predisposition to PCT. Additionally, most studies reported iron overload and hepatic siderosis among mutation carriers. Geographic differences were acknowledged, but the findings remained consistent across all diverse populations. **Conclusion:** There is a strong association between HFE mutations particularly C282Y and PCT. Genetic screening for hereditary hemochromatosis in patients with PCT should be considered to enable early detection and iron-reduction therapy, potentially preventing progression of disease. Future prospective studies should explore whether early intervention alters the clinical course of PCT.

Disclosures: Somtochukwu Abazu:Nothing to Disclose, Arif Qazi:Nothing to Disclose.

1445 | ALPHA-1 FOUNDATION RESEARCH REGISTRY: LIVER AFFECTED ALPHA-1 ANTITRYPSIN DEFICIENCY PATIENTS AND WORKPLACE TOXIN EXPOSURE IN THE UNITED STATES

Nadine Nuchovich[1] Alison Keaveny[1] Jennifer Illarramendi[1] Randel Plant[1] Monica Goldklang[2] Jeanine D'Armiento[3], [1]Alpha-1 Foundation, [2]Columbia University Irving Medical Center, [3]Columbia University Irving Medical Center and Alpha-1 Foundation

Background: Alpha-1 Antitrypsin Deficiency (AATD) is a rare genetic condition that leads to increased risk of liver disease, particularly when compounded with workplace exposures to environmental hepatotoxins. Patients' career choices may cause long-term exposure to toxicants, and with millions of adults in industrial and agricultural professions, it is critical to examine a snapshot of liver-affected AATD patients and their workplace exposures. **Methods:** We looked at 1054 who reported yes to liver disease (fatty liver, cirrhosis, cholestasis and severe liver disease manifestations) and further examined 412 A1F Registry adult participants who reported yes to liver hepatotoxin workplace exposure including agricultural and organic dusts, combustion, smoke and exhaust, as well as metal fumes and industrial process particles. **Results:** Participants with liver disease and workplace exposures to liver toxicants reported a mean age of 54.95 (+/- 14.85), with a quarter of patients (32.5%) below the age of 50 (N = 412). Half were female (52.4%),predominantly PiZZ (38.8%) or PiMZ genotype (27.6%), and reported average age of AATD diagnosis 46.08 yrs (+/-16.01). Participants largely report being exposed to fire, smoke, or other combustion particles (63.1%), indoor fuel powered motors, compressors, or engines (45.4%), silica, sand, concrete and cement dust (36.7%), cadmium, batteries, or other metal dust or fumes (37.8%), and/or welding or flame cutting (27.2%). Lifestyle behaviors showed high rates of current drinking (45.1%) but low current smoking (10.6%). Patients largely reported fatty liver (64.8%), with 18.4% reporting cirrhosis, 5.6% with cholestasis and 27.7% report having symptoms of severe liver disease such as ascites (8.3%), variceal bleeding (2.9%) and bacterial peritonitis (1.7%). Patients also report high rates of lung disease including emphysema (33.2%), COPD (45.7%), bronchiectasis (24.3%) and adult asthma (39.5%) and are largely tested due to lung symptoms (43.4%). 8.2% of patients report having been to the hospital due to Alpha-1 in the previous 12 months an average of 2.28 times. Current AAT replacement therapy was noted in a third of the cohort (32.2%), and 22% required current supplemental oxygen. **Conclusion:** A significant number of liver affected A1F participants report exposure to workplace hepatotoxin particulates which may exacerbate AATD liver disease. In AATD, proactive counseling and patient education on minimizing environmental exposures, and lifestyle behavior risks, is crucial to guide occupation decisions that may affect disease progression. While there is currently no cure for AATD related liver disease, career choices can impact exposure to these toxins that can further impair liver health.

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1446 | METABOLIC AND CIRCADIAN PATHWAY DYSREGULATION IN WILSON DISEASE: INSIGHTS FROM TRANSCRIPTOMIC ANALYSIS

Doyoon Kim[1] Jayden Trac[1] Nora Spuler[1] Marie Heffern[1] Noreene Shibata[1] Valentina Medici[1], [1]University of California Davis

Background: Wilson disease (WD) is an inherited disorder caused by pathogenic variants affecting the ATP7B gene, leading to impaired biliary copper excretion and progressive accumulation of copper in the liver, brain, and other tissues. WD demonstrates marked clinical heterogeneity, with hepatic, neurologic, and psychiatric manifestations that vary substantially in age of onset, severity, and progression. This phenotypic variability remains incompletely understood and cannot be fully explained by genotype alone. Sleep disturbances have been extensively described in WD and may have an impact on clinical outcomes as it has been proven in common metabolic liver diseases. Growing evidence indicates that an interplay between genetic and metabolic factors, including those regulated by the circadian cycle, may combine to affect the disease phenotype. We hypothesize that gene expression in WD is regulated through the circadian cycle with differential gene expression in the liver and in the intestine. **Methods:** Experiments were performed in female *Atp7b*$^{-/-}$ knockout mice, a model of genetic copper accumulation, and *Atp7b*$^{+/-}$ heterozygous mice with normal copper metabolism (n = 3/genotype and time point). Sixteen-week-old mice were euthanized at 12:00 pm (day) and 12:00 am (night). At the end of the experiment, livers and intestines were obtained for bulk RNA-sequencing. **Results:** RNA sequencing analysis identified 6,384 liver genes differentially expressed in *Atp7b*$^{-/-}$ vs *Atp7b*$^{+/-}$ during the day and 9,902 liver genes at night. In addition, a larger number of liver transcripts differentiated *Atp7b*$^{-/-}$ mice day vs night compared to *Atp7b*$^{+/-}$ mice day vs night. The analysis also identified 628 intestine genes differentially expressed in *Atp7b*$^{-/-}$ mice vs *Atp7b*$^{+/-}$ during the day and 665 intestine genes at night. A larger number of intestine transcripts also differentiated Atp7b$^{-/-}$ mice day vs night compared to intestine *Atp7b*$^{+/-}$ mice day vs night. Enrichment analyses identified pathways related to circadian rhythm regulation, lipid and fatty acid metabolism, mitochondrial energetics, oxidative phosphorylation, inflammatory signaling, and cellular stress responses. **Conclusion:** These findings support a model in which phenotypic presentation in WD may arise not only from ATP7B genetic variants but also from circadian cycle-regulated disturbances in metabolic and mitochondrial pathways.

Disclosures: Doyoon Kim:Nothing to Disclose, Jayden Trac:Nothing to Disclose, Nora Spuler:Nothing to Disclose, Marie Heffern:Nothing to Disclose, Noreene Shibata:Nothing to Disclose, Valentina Medici:Orphalan: Advisor, Arbormed: Research Grant, Ultragenix: Grant/Research Support, Vivet: Grant/Research Support, Eton Pharmaceuticals: Consultant, Mars Inc.: Advisor, Prime Medicine: Grant/Research Support.

1447 | NATURAL HISTORY OF PATIENTS WITH WILSON'S DISEASE: A SINGLE CENTER EXPERIENCE

Youseph Karouni[1] Clavia Ruth Wooton-Kee[1] Karim Adhem[1] Ximena Ramirez Morlaes[1] Mohamad Ali Ibrahim[1] Nagham Ramadan[1] Mazen Elsheikh[1] Prasun Jalal[1], [1]Baylor College of Medicine

Background: Wilson's Disease (WD) is a rare (about 1 in 30,000) autosomal recessive liver disease caused by mutations in the ATP7B gene, resulting in excess copper deposition in the eyes, liver, and brain. This can manifest in patients as acute liver failure, chronic liver disease and neuro-psychiatric disorder. Several Wilson's Centers of Excellence have been established to provide specialized medical care and community for these patients. The aim of this study was to outline the outcome of patients with WD at Baylor College of Medicine. **Methods:** We performed a retrospective chart review of patients identified in an electronic database search (search terms: penicillamine, trientine, zinc (any formulation); Wilson's Disease diagnosis code in the period between 2015-2026). A diagnosis of Wilson's disease was confirmed based on AASLD/EASL guidance: clinically via Leipzig score and/or copper quantification, a biopsy that returns > 55 mcg Cu, and/or any confirmatory genetic testing for a mutation in ATP7B). The outcome was transplant, death or clinical stability on follow-up. Adherence to clinic visit and copper-related tests were reviewed **Results:** The search returned 53 patients, and after review, 13 patients were found to have diagnoses other than Wilson's, such as PBC, MASLD Cirrhosis, or Hereditary Hemochromatosis. Out of 40 patients, 31 White non-Hispanic, 4 White Hispanic, 4 Asian and 1 African American. Patients were receiving maintenance therapy (n = 28) or had a liver transplant (n = 12). In the maintenance group, 24 received a biopsy as part of their workup, 13 had genetic testing done, and 8 were diagnosed through clinical work-up (symptoms, Labs with Leipzig score). In the maintenance therapy group, 10 were diagnosed with cirrhosis, and 13 were non-cirrhotic. All patients in the transplant group had cirrhosis prior to transplant, 9 were mixed etiology, and 3 had no competing etiology. 17 patients are on

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trientine, 4 are on Zinc alone, 4 are on a combination of trientine and zinc, 1 on penicillamine. Six patients were lost to follow up. Monitored patients remain clinically stable without worsening. **Conclusion:** Wilson's disease therapy requires long term commitment to therapy and close monitoring. The care pathway in centers of excellence needs further optimization to improve outcome.

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1448 | METABOLOMICS AND COPPER-FOCUSED PROTEOMICS IN DOGS WITH COPPER-ASSOCIATED AND IMMUNE-MEDIATED CHRONIC HEPATITIS

Tarini Ullal[1] Jacob Padilla[1] Marie Heffern[1] Sarah Shropshire[2] Cecilia Giulivi[1] Valentina Medici[3], [1]University of California, Davis, [2]Colorado State University, [3]University of California Davis Medical Center

Background: Copper-associated chronic hepatitis (CAH) in dogs causes excessive hepatic copper accumulation, analogous to Wilson Disease (WD) in humans, resulting in oxidative stress, mitochondrial injury, and necroinflammation. These derangements are apparent in metabolomic and proteomic analyses of WD patients, but have not been evaluated in dogs with CAH or immune-mediated chronic hepatitis (ICH). **Methods:** Serum samples were collected from dogs diagnosed and untreated for CAH (n = 14), immune-mediated chronic hepatitis (ICH) (n = 18), and healthy controls (n = 20). Metabolomic evaluation of primary metabolites, biogenic amines, and complex lipids was performed using gas chromatography/time-of-flight mass spectrometry and compared between groups using sparse partial least squares discriminant analysis, hierarchical clustering, and a limma framework adjusting for covariates (age, sex, clinical signs, liver values, hepatic copper) with random forest classification. Copper-focused proteomics was performed on a serum subset of 12 dogs per group. A copper(II) iminodiacetic acid immobilized metal affinity chromatography (Cu-IMAC) was paired with liquid chromatography tandem mass spectrometry to identify differentially abundant proteins. **Results:** Metabolomics showed no significant differences between CAH and ICH. Dogs with CAH relative to healthy controls showed significantly higher copper (2.15 fold increase), upregulation in amino acids (ornithine, phenylalanine, quinolonic acid), uracil, beta-alanine, and fatty acids (oleic and palmitoleic acids) (range: 0.7 to 1.4 fold increase), and downregulation in markers of phospholipid metabolism (O-phosphoethanolamine, glycerophosphoric acid), purine metabolism (inosine, guanosine), and hydroxyproline (range: -0.6 to -1.4 fold decrease). Cu-IMAC enriched a population of proteins with copper (II)-binding capacity in dogs with CAH, showing upregulation of immune response proteins (inter-alpha-trypsin inhibitor heavy chains (H3,H4), polymeric immunoglobulin receptor, galectin-3-binding protein, alpha-2-macroglobulin, and CD14) and a downregulation of hepatic function proteins (apolipoproteins, coagulation factor XIII A chain, transthyretin) relative to healthy controls. No significant proteomic differences were found between CAH and ICH. **Conclusion:** CAH in dogs was characterized by high hepatic copper, lipid and phospholipid dysregulation, oxidative stress and mitochondrial dysfunction, amino acid/purine turnover, necroinflammation, and impaired hepatic function relative to healthy controls, mirroring human WD. Similar pathways were altered in dogs with ICH. Upregulated metabolites and proteins identified in this study could represent potential biomarkers for canine chronic hepatitis, though might not reliably differentiate copper from auto-immune etiologies.

Disclosures: Tarini Ullal:Nothing to Disclose, Jacob Padilla:Nothing to Disclose, Marie Heffern:Nothing to Disclose, Sarah Shropshire:Nothing to Disclose, Cecilia Giulivi:Nothing to Disclose, Valentina Medici:Orphalan: Advisor, Arbormed: Research Grant, Ultragenix: Grant/Research Support, Vivet: Grant/Research Support, Eton Pharmaceuticals: Consultant, Mars Inc.: Advisor, Prime Medicine: Grant/Research Support.

1449 | PERSISTENT BIOCHEMICAL ACTIVITY PREDICTS ADVERSE OUTCOMES IN WILSON DISEASE: DEVELOPMENT OF PROGNOSTIC INDICES

Esra Durmazer[1] Elvan Işık[2] Ilker Turan[2] Fulya Gunsar[2] Zeki Karasu[2] Ulus Akarca[2], [1]Ankara University Faculty of Medicine, [2]Ege University Faculty of Medicine

Background: Wilson disease (WD) is a rare but potentially fatal disorder of copper metabolism characterized by progressive hepatic and neurological injury. Although medical therapy is available, a subset of patients develops progressive liver disease requiring transplantation or resulting in death. Predictors of adverse outcomes in WD remain insufficiently

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characterized. We aimed to identify factors associated with death or liver transplantation and to develop prognostic indices for poor outcomes in WD. **Methods:** In this retrospective longitudinal cohort study, consecutive patients with WD followed at Ege University Faculty of Medicine between January 2000 and August 2024 were evaluated. The primary endpoint was a composite of death or liver transplantation. Continuous laboratory variables were categorized using predefined clinically relevant thresholds. Multivariable logistic regression analyses were performed to identify independent predictors of adverse outcomes and to construct prognostic indices. Discriminative performance of the derived indices was internally evaluated using ROC curve analysis. **Results:** A total of 105 patients with WD were included, of whom 54 (51.4%) were male. Median age at diagnosis was 19 years (95% CI, 15–20). During follow-up, liver transplantation was performed in 9 patients (8.6%), while 8 patients (7.6%) died, including 2 following transplantation. Overall, 15 patients (14.3%) reached the composite endpoint of death or liver transplantation. In multivariable logistic regression analysis, lower baseline creatinine levels ($p = 0.02$) and lower white blood cell counts ($p = 0.004$) were independently associated with adverse outcomes. Continuous laboratory variables were categorized using predefined clinically relevant thresholds. Creatinine levels < 0.7 mg/dL ($p = 0.019$) and white blood cell counts $\leq 4000/\mu L$ ($p = 0.001$) were associated with poor outcomes. Prognostic indices derived from regression coefficients of significant variables demonstrated strong discriminative performance for adverse outcomes (AUC 0.816, 95% CI 0.713–0.894). Persistent biochemical activity, defined by AST elevation above the upper limit of normal and INR > 1.3 during follow-up, remained strongly associated with adverse outcomes (OR 17.7, 95% CI 1.86–168.7, $p = 0.0123$; OR 11.4, 95% CI 2.03–63.9, $p = 0.005$, respectively). A treatment-period prognostic index incorporating AST and INR demonstrated excellent discriminative performance (AUC 0.909, 95% CI 0.822–0.962). **Conclusion:** Persistent biochemical activity despite treatment is strongly associated with death or liver transplantation in Wilson disease. Our laboratory-based prognostic indices demonstrated strong discriminative ability for adverse outcomes and may improve early risk stratification in clinical practice. The association between lower creatinine levels and adverse outcomes warrants further investigation in patients with WD.

Disclosures: Esra Durmazer:Nothing to Disclose, Elvan Işık:Nothing to Disclose, ILKER TURAN:Nothing to Disclose, Fulya Gunsar:Nothing to Disclose, Zeki Karasu:Nothing to Disclose, Ulus Akarca:Nothing to Disclose.

1450 | ◆ CHOLANGIOCYTE YAP1-MEDIATED DUCTULAR REACTION EXACERBATES CIRRHOTIC PORTAL HYPERTENSION BY PROMOTING CCN1-REGULATED DISRUPTION OF HEPATIC MICROCIRCULATION

Jinbo Zhao[1] Zhenhao Wu[1] Guqing Luo[1] Mengting Li[1] Hongjie Li[1] Jiayun Lin[1] Chihao Zhang[1] Guangbo Wu[1] Meng Luo[1] Lei Zheng[1], [1]Ninth People's Hospital, School of Medicine, Shanghai Jiaotong University

Background: Portal hypertension (PHT) is a severe life-threatening complication of advanced chronic liver disease, primarily resulting from increased intrahepatic vascular resistance. Hepatic Microcirculation, including Liver sinusoidal dysfunction and pathological angiogenesis, was well recognized to play pivotal roles in the initiation and progression of cirrhotic PHT; however, their upstream regulatory molecular networks remain poorly defined. Emerging evidence indicates that ductular reaction (DR), which has been proven to impair the intrahepatic homeostasis microenvironment in various chronic liver diseases yet remained poorly investigated in cirrhotic PHT, may serve as a critical driver of disease progression. Herein, we combined clinical specimen analysis, in vivo animal models and in vitro cell experiments to explore the core pathological mechanism by which DR contributes to cirrhotic PHT, and to screen potential therapeutic targets. **Methods:** Clinical specimen and immunofluorescence analysis: Clinical samples from patients with cirrhosis and cirrhotic portal hypertension (PHT) were collected to analyze the correlation between ductular reaction (DR) and disease progression. Immunofluorescence staining was further performed to clarify the relationships of DR with pathological angiogenesis and liver sinusoidal dysfunction. Animal model construction and in vivo intervention: Three classic mouse PHT models were established via BDL surgery, DDC diet and CCl_4 injection. A Hnf1β-promoter-driven adeno-associated virus (AAV) was constructed to achieve specific knockout of YAP1 or Cyr61(CCN1) in cholangiocytes, so as to explore their functional roles in PHT. In addition, pharmacological inhibition of YAP1 was conducted in BDL and DDC models using Verteporfin. In vitro mechanistic experiments: YAP1 expression in cholangiocytes was genetically manipulated. Cell co-culture combined with supernatant mass spectrometry was applied to evaluate the effects of cholangiocyte-derived secretory factors on HUVEC tube formation and proliferation, as well as LSEC capillarization. In vitro rescue assays were used to validate the direct regulatory effect of cholangiocyte-secreted CCN1 on HUVEC and LSEC biological functions. Furthermore, blockade of the CCN1 receptor integrin αvβ3 on endothelial cells was performed to explore its mediating

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role in CCN1-induced pro-pathological phenotypes. **Results:** Clinical specimen analysis revealed a significant correlation between DR and the progression of liver cirrhosis. Immunofluorescence staining further confirmed that DR was closely associated with the progression of pathological phenotypes, including pathological angiogenesis and liver sinusoidal dysfunction. YAP1 was identified as a core molecular regulator of DR. To further elucidate the biological function of YAP1 in cholangiocytes, we established an AAV-Virus driven by the Hnf1β-promoter to achieve cholangiocyte-specific YAP1 knockout in vivo. In BDL, DDC and CCl_4-induced PHT mouse models, Cholangiocyte-specific YAP1 ablation markedly attenuated liver injury, as evidenced by reduced portal pressure, alleviated DR, improved liver sinusoidal dysfunction and suppressed pathological angiogenesis. In addition, pharmacological inhibition of YAP1 with Verteporfin in BDL and DDC mice further validated that YAP1 suppression significantly alleviated the pathological phenotypes of cirrhotic PHT. Combined with the findings from clinical cirrhotic PHT samples, our results suggest that DR promotes pathological angiogenesis and liver sinusoidal dysfunction. In vitro experiments demonstrated that intervention of YAP1 expression in cholangiocytes, followed by cell co-culture and supernatant mass spectrometry analysis, revealed that cholangiocyte-derived secretory factors prominently promoted HUVEC tube formation and proliferation, as well as LSEC capillarization. CCN1 was subsequently identified as a key secreted protein. Consistently, Hnf1β-promoter-mediated cholangiocyte-specific CCN1 knockout recapitulated the protective effects observed upon cholangiocyte YAP1 ablation. Rescue experiments in vitro further verified that cholangiocyte-secreted CCN1 directly facilitated HUVEC tube formation and proliferation, as well as LSEC capillarization. Moreover, blockade of the predicted receptor integrin αvβ3 on HUVEC or LSEC substantially abrogated the pro-pathological effects of CCN1. **Conclusion:** In conclusion, our findings demonstrate that cholangiocyte YAP1 accelerates the progression of cirrhotic PHT by facilitating DR, and further induces pathological angiogenesis and LSEC capillarization via paracrine CCN1. This study provides novel mechanistic insights and a promising targeted therapeutic strategy for the treatment of cirrhotic PHT.

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1451 | ◆ REGRESSION OF PORTAL HYPERTENSION IN RECOMPENSATED CIRRHOSIS, ITS PROGNOSTIC IMPLICATIONS, AND THE UTILITY OF NON-INVASIVE TESTS TO EVALUATE CSPH RESOLUTION

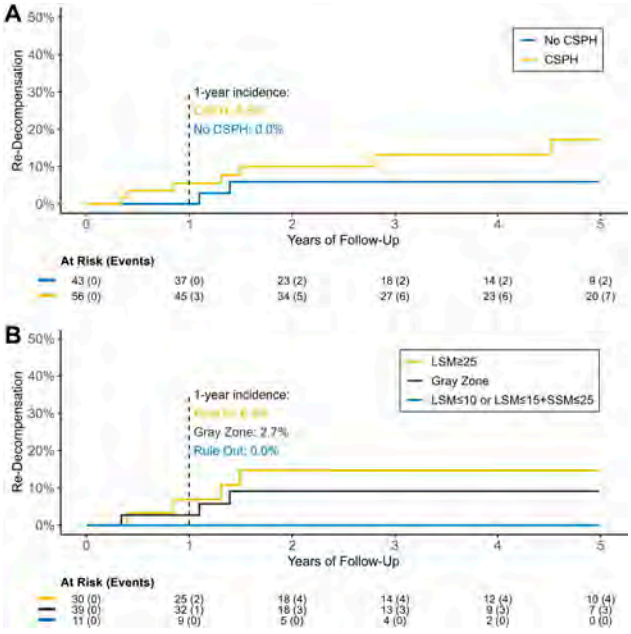
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Background: Aetiological therapy enables hepatic recompensation in decompensated cirrhosis. However, portal hypertension dynamics in recompensated cirrhosis, the utility of non-invasive tests (NITs) for clinically significant portal hypertension (CSPH) in this setting, and the prognostic implications of CSPH and of NITs after recompensation remain unclear. **Methods:** This Baveno-endorsed multicentre study included 102 patients undergoing hepatic venous pressure gradient (HVPG) measurement after achieving recompensation (Baveno VII criteria; all Child-Pugh A). Platelet count, liver (LSM; n = 83), and spleen (SSM; n = 46) stiffness measurements were collected at HVPG (±90 days). **Results:** Aetiologies included alcohol-related liver disease (ALD; 70.6%), hepatitis B (4.9%), hepatitis C (9.8%), or combined viral/ALD (14.7%). Median HVPG after recompensation was 11 (8-13) mmHg, and CSPH resolved in 43%.Fifty-two patients had paired pre-recompensation HVPG/NIT assessments available: HVPG decreased by -50% ([-57]-[-23]%; $p < 0.001$) from the decompensated stage. LSM also decreased significantly after recompensation (-57% [(-70)-(-36)%]; $p < 0.001$), yet changes in platelets were heterogeneous (+5% [(-21)-(+40)%]; $p = 0.777$), and thrombocytopenia persisted in 57% despite CSPH resolution.LSM

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and SSM showed high diagnostic accuracy for persistent CSPH in recompensated patients (AUROC: 0.890 / 0.911), whereas platelet count was uninformative (AUROC: 0.613). LSM ≥25 kPa reliably ruled in CSPH with 100% positive predictive value/specificity (CSPH n = 31/31). LSM ≤10 kPa and SSM ≤30 kPa both ruled out CSPH with 100% negative predictive value (NPV)/sensitivity (CSPH n = 0/6 and n = 0/13). SSM ≤25 kPa combined with LSM ≤15 kPa maintained 100% NPV/sensitivity (CSPH n = 0/5) and may provide an additional safety margin.After HVPG, 99 patients were followed for 36.5 (18.3-72.8) months. 13 patients returned to a decompensated state, with a 3-year cumulative incidence of 10%. Higher HVPG (SHR /mmHg: 1.178; 95%CI: 1.069-1.298; p < 0.001) and persistent CSPH (SHR: 3.996; 95%CI: 0.880-18.154; p = 0.073; Fig. 1A) at recompensation were linked to a higher re-decompensation risk. No patient with resolved CSPH re-decompensated within the first year. However, late re-decompensation occurred in 2 patients, related to recurrent liver disease (i.e., alcohol relapse) in one patient and presumably to portal vein thrombosis in the other. Importantly, no patient with LSM ≤10 kPa or SSM ≤25 kPa + LSM ≤15 kPa re-decompensated (Fig. 1B). **Conclusion:** CSPH may resolve in a considerable proportion of patients after recompensation, yet persistent CSPH is associated with a higher re-decompensation risk. LSM ≥25 kPa reliably rules in persistent CSPH after recompensation, while LSM ≤10 kPa or LSM ≤15 kPa plus SSM ≤25 kPa rule out CSPH and identify patients with negligible re-decompensation risk if the aetiology remains controlled.



Disclosures: Benedikt Hofer:Ipsen: Travel support, Falk Pharma: Travel support, Gilead: Travel support, Gilead: Speaking and Teaching, Ipsen: Speaking and Teaching, Georg Semmler:Amgen: Travel Support, DaiSorin: Speaking and Teaching, Dario Saltini:Nothing to Disclose, Luis Tellez:Nothing to Disclose, Anna Brujats:Nothing to Disclose, Angela Puente:Nothing to Disclose, Josune Cabello:Nothing to Disclose, Susana Rodrigues:Nothing to Disclose, Petra Fischer:Nothing to Disclose, Fernando Cao:Nothing to Disclose, Zouhir Gadi:Nothing to Disclose, Dominik Bettinger:Nothing to Disclose, Xiaofeng Zhang:Nothing to Disclose, Yu Wang:Nothing to Disclose, Vincenza Calvaruso:Nothing to Disclose, Jan Embacher:Nothing to Disclose, Mattias Mandorfer:Nothing to Disclose, Antonio Piscopo:Nothing to Disclose, Amparo Moscardó Ribes: Nothing to Disclose, Horia Stefanescu:Nothing to Disclose, Sven Francque:Nothing to Disclose, Salvatore Petta:Madrigal: Consultant, Novonordisk: Consultant, Boehringer: Consultant, Jidong Jia:Nothing to Disclose, Jinjun Chen:Nothing to Disclose, Wilhelmus Kwanten:Nothing to Disclose, Elba Llop:Nothing to Disclose, Bogdan Procopet:Nothing to Disclose, Annalisa Berzigotti:Nothing to Disclose, Jonel Trebicka: Nothing to Disclose, Jose Ignacio Fortea:Grifols: Speaking and Teaching, Edilmar Alvarado:Nothing to Disclose, Agustin Albillos:Nothing to Disclose, Filippo Schepis:Nothing to Disclose, Thomas Reiberger:Nothing to Disclose.

1452 | ◆ MIDODRINE AND ALBUMIN IN PATIENTS WITH REFRACTORY ASCITES. A DOUBLE BLIND RANDOMISED CONTROLLED TRIAL

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Background: Long-term human albumin (HA) administration has shown inconsistent results in control of ascites and survival in patients with cirrhosis. Midodrine, an oral α1- adrenergic agonist has also been used in refractory ascites (RA) with variable results. The aim of this study was to evaluate the effects of long-term administration of HA and midodrine on control of ascites and survival at one year in patients with cirrhosis and refractory ascites. **Methods:** We studied 114 patients with RA in a randomised, double blind, placebo-controlled trial between January 2021 and March 2025. Group A (n = 38) received long-term midodrine and HA with Standard Medical therapy (SMT); group B (n = 38) received long-term HA along with placebo and group C (n = 38) received SMT with placebo. The group A and B received HA in 1.5 gm/kg/

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weekly for 2 weeks along with Midodrine 7.5 mg three times a day and SMT. This was followed by HA 40 grams every 7days. The primary end point was the control of ascites at 1 year and secondary end points were survival at 1-year, mean arterial pressure, change in serum and 24-hour urinary sodium, incidence of AKI and hyponatremia. **Results:** At 12 months, control of ascites was achieved in 8 (21.1%) patients of group A, 2(5.3%) patients of group B and none in group C (p = 0.003). One year mortality was significantly lower in the group A as compared to group B and group C (57.9% vs 86.8% vs 97.4%) (p < 0.001). On multivariable logistic regression analysis, midodrine therapy independently predicted improved control of ascites (OR 16.84, 95% CI 2.41–117.62; p = 0.004). Higher mean arterial pressure (OR1.15, 95% CI 1.03–1.29; p = 0.014), increased 24-hour urinary sodium excretion (OR 1.09, 95% CI 1.02–1.17; p = 0.009), and urine volume (OR 1.003, 95% CI 1.001–1.005; p = 0.006) were also independently associated with sustained ascites control. In comparative analysis between albumin and SMT group, the control of ascites (p = 0.152) as well as survival (p = 0.168) was not significantly different. AKI developed in 31.5%, 55% and 68.4% of patients in group A, B and C, respectively (p = 0.014) and new onset hyponatremia in 23.6% vs 44.3% vs 63.2% of patients in group A, B and C, respectively (p = 0.04) during the follow up. **Conclusion:** Midodrine in combination with HA significantly improved control of ascites and one year mortality compared to long term albumin and SMT alone in patients with refractory ascites. However, long term HA did not improve control of ascites or survival in comparison to SMT. New onset hyponatremia and AKI were more common in SMT and albumin groups. (NCT:04621617)

Disclosures: Virendra Singh:Nothing to Disclose, Amandeep Singh:Nothing to Disclose, Arka De:Nothing to Disclose, Sayan Malakar:Nothing to Disclose, Nitesh Bassi:Nothing to Disclose, Upasna Chauhan:Nothing to Disclose, Simrat Kaur:Nothing to Disclose, Jahnvi Dhar:Nothing to Disclose.

1453 | ◆ HEPATIC RECOMPENSATION OCCURS AT SIMILAR RATES IN ALCOHOL- AND VIRAL HEPATITIS-RELATED CIRRHOSIS AND IS CONSISTENTLY ASSOCIATED WITH REDUCED MORTALITY AND HCC RISK

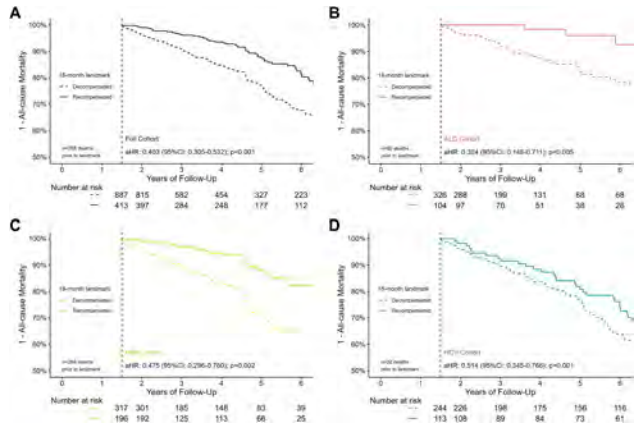
Benedikt Hofer[1] Georg Semmler[1] Terry Cheuk-Fung Yip[2] Hong You[3] Wen Xie[3] Javier Ampuero Herrojo[4] Marta Tonon[5] Alberto Zanetto[5] Salvatore Piano[5] Sabela Lens[6] Inmaculada Fernandez[7] Sonia Alonso Lopez[8] Monica Pons[9] Benjamin Maasoumy[10] Dalila Costa[11] Elisa Pose[6] Paolo Caraceni[12] Celia Pérez-Estrada[4] Isabel Carmona[13] José Miguel Rosales[14] Horia Stefanescu[15] Hélène Larrue[16] Annalisa Berzigotti[17] Emmanuel Tsochatzis[18] Luis Tellez[19] Rafael Bañares[8] Joan Genesca[9] Marika Rudler[20] Alexander Zipprich[21] Jonel Trebicka[22] Zhiying He[3] You Deng[3] Bingqiong Wang[3] Xiaoning Wu[3] Jimmy Che-To Lai[2] Jidong Jia[3] Mattias Mandorfer[1] Thomas Reiberger[1], [1]Medical University of Vienna, [2]The Chinese University of Hong Kong, [3]Beijing Friendship Hospital, Capital Medical University, [4]Hospital Universitario Virgen del Rocío, [5]University of Padua, [6]Hospital Clínic de Barcelona, [7]Hospital Universitario 12 De Octubre, [8]Hospital General Universitario Gregorio Marañón, [9]Vall d'Hebron University Hospital, [10]Hannover Medical School, [11]Braga Hospital, [12]University of Bologna, [13]Hospital Universitario Virgen Macarena, [14]Hospital Universitario Costa del Sol, [15]Regional Institute of Gastroenterology and Hepatology Cluj-Napoca, [16]University Hospital and Toulouse III - Paul Sabatier University, [17]Bern University Hospital, [18]Royal Free Hospital and UCL, [19]Hospital Universitario Ramón y Cajal, [20]Sorbonne University, [21]Jena University Hospital, [22]University of Münster

Background: Aetiological cure enables hepatic recompensation in decompensated cirrhosis, yet reported rates and prognostic implications of recompensation were heterogeneous across aetiologies. This study assessed differences in recompensation incidence and subsequent risk of hepatocellular carcinoma (HCC) and liver-related mortality. **Methods:** This Baveno-endorsed multicentre study enrolled patients with decompensated cirrhosis at time of aetiological treatment until December 2022, i.e., start of abstinence in alcohol-related liver disease (ALD) or initiation of antiviral treatment in hepatitis B (HBV) or C (HCV). Recompensation was defined by Baveno VII criteria: (i) resolution of ascites and hepatic encephalopathy (off treatment), (ii) no variceal bleeding for 1 year, and (iii) improved hepatic function. Alcohol/viral recurrence and liver transplantation led to censoring. Multivariable models included age, sex, MELD, platelet count, alanine transaminase, and centre/cohort as random effect. **Results:** 1838 patients were included, with ALD in 34% (n = 633), HBV in 43% (n = 792), and HCV in 22% (n = 413). Baseline hepatic dysfunction was most pronounced in ALD (median MELD: 17), followed by HBV (14) and HCV (11; p < 0.001).During a median follow-up of 4.4 years, 674 patients achieved recompensation. After 3 years, the overall cumulative incidence of recompensation was 33%, being highest in HCV (37%), followed by HBV (35%), and ALD (29%). However, on adjusted analysis, recompensation probability did not differ between aetiologies (adjusted subdistribution hazard ratios (aSHRs): 0.987 (p = 0.963) for HBV vs. ALD, 1.149

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(p = 0.759) for HCV vs. ALD, and 1.165 (p = 0.759) for HCV vs. HBV).During follow-up, 648 patients died; 59% from liver-related causes. Recompensation (time-dependent covariate) was independently associated with reduced all-cause mortality, with adjusted hazard ratios (aHR) of 0.403 (p < 0.001) in the full cohort, 0.324 (p = 0.005) in ALD, 0.475 (p = 0.002) in HBV, and 0.514 (p = 0.001) in HCV (Fig. 1). Similarly, recompensation reduced the risk of liver-related mortality in HBV (aHR: 0.222; p < 0.001) and HCV (aHR: 0.285; p < 0.001); no liver-related deaths occurred in recompensated ALD.De novo HCC was diagnosed in 257 patients, with a significantly higher risk in viral liver disease (HBV vs. ALD aSHR: 7.506; p < 0.001 / HCV vs. ALD aSHR: 6.457; p < 0.001). Recompensation was linked to a significantly reduced HCC risk in HBV (aHR: 0.528; p = 0.040) and HCV (aHR: 0.549; p = 0.040), and no recompensated ALD patient developed HCC. **Conclusion:** When accounting for baseline disease severity, the incidence of hepatic recompensation is comparable across ALD, HBV and HCV. Recompensation significantly improves survival and reduces the risk of HCC across all aetiologies. HCC risk in recompensated patients remains higher with viral hepatitis than in ALD.



Disclosures: Benedikt Hofer:Ipsen: Travel support, Falk Pharma: Travel support, Gilead: Travel support, Gilead: Speaking and Teaching, Ipsen: Speaking and Teaching, Georg Semmler:Amgen: Travel Support, DaiSorin: Speaking and Teaching, Terry Cheuk-Fung Yip:Gilead Sciences: Consultant, Gilead Sciences: Speaking and Teaching, Gilead Sciences: Grant/Research Support, Altimmune: Advisor, GSK: Advisor, Hong You:Nothing to Disclose, wen Xie:Nothing to Disclose, Javier Ampuero Herrojo: Nothing to Disclose, Marta Tonon:Nothing to Disclose, Alberto Zanetto:Nothing to Disclose, Salvatore Piano: Nothing to Disclose, Sabela Lens:Nothing to Disclose, Inmaculada Fernandez:Nothing to Disclose, Sonia Alonso Lopez:Nothing to Disclose, Monica Pons:Nothing to Disclose, Benjamin Maasoumy:Nothing to Disclose, Dalila Costa:Nothing to Disclose, Elisa Pose:Nothing to Disclose, Paolo Caraceni:Grifols SA: Speaking and Teaching, Grant Research support, CSL Behring: Speaking and teaching, Octapharma SA: Grant Research support, Gilead SA: Speaking and Teaching, Abbvie SA: Speaking and Teaching, Takeda: Speaking and Teaching, Grifols: Speaking and Teaching, Col Behring: Speaking and Teaching, Octapharma: Speaking and Teaching, Baush Health: Advisor, Alphasigma: Speaking and Teaching, Celia Pérez-Estrada:Nothing to Disclose, Isabel Carmona: Nothing to Disclose, José Miguel Rosales:Nothing to Disclose, Horia Stefanescu:Nothing to Disclose, Hélène Larrue:Nothing to Disclose, Annalisa Berzigotti:Nothing to Disclose, Emmanuel Tsochatzis:Nothing to Disclose, Luis Tellez:Nothing to Disclose, Rafael Bañares:Nothing to Disclose, Joan Genesca:Nothing to Disclose, Marika Rudler:Gore: Speaking and Teaching, Gilead: Speaking and Teaching, Mirum: Speaking and Teaching, Alexander Zipprich:Nothing to Disclose, Jonel Trebicka:Nothing to Disclose, Zhiying He:Nothing to Disclose, You Deng: Nothing to Disclose, Bingqiong Wang:Nothing to Disclose, Xiaoning Wu:Nothing to Disclose, Jimmy Che-To Lai: Nothing to Disclose, Jidong Jia:Nothing to Disclose, Mattias Mandorfer:Nothing to Disclose, Thomas Reiberger:Nothing to Disclose.

1454 | ◆ CIRRHOSIS HIDDEN IN PLAIN SIGHT: AN AGENTIC LLM PIPELINE OPERATIONALISES BAVENO VII CACLD/CSPH FROM FREE-TEXT CT REPORTS AND QUANTIFIES THE CARE ACTION GAP IN MIMIC-IV

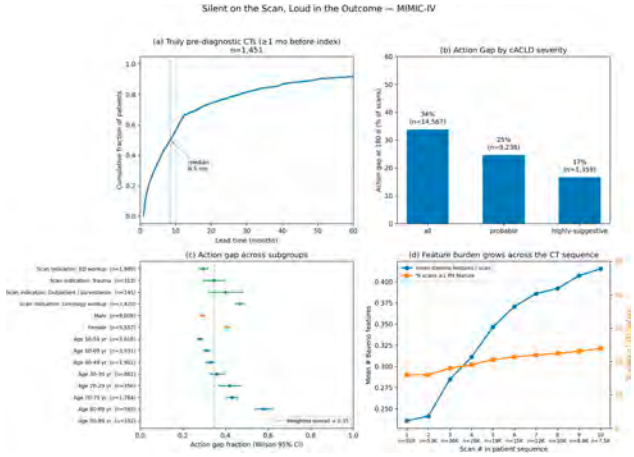
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Background: The compensated phase of cirrhosis is often undiagnosed; routine cross-sectional imaging often visualises portal-hypertensive features long before cirrhosis is diagnosed in structured EHR data. It remains to be established whether free-text CT abdomen reports prior to the first cirrhosis ICD code contain operationalisable Baveno VII evidence of compensated advanced chronic liver disease (cACLD) and clinically significant portal hypertension (CSPH) at a population scale and whether that imaging signal results in clinician action. **Methods:** MIMIC-IV cirrhosis cohort (n = 7,874; index = earliest cirrhosis-coded discharge) and non-cirrhotic CT-control cohort (n = 87,439, matched on age/sex/race/scan year/indication). All 343,128 abdominal CT reports were processed via an agentic LLM pipeline (Gemini-2.5-Flash-Lite; 128-way concurrent; 98.9% extraction success) emitting a Baveno-VII-grounded schema with required supporting spans; a NegEx shadow extractor ran in parallel with a conservative downgrade on disagreement. Headline metrics are computed on the

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case cohort; controls provide background PH-feature prevalence for specificity. Four outcomes: (1) Silent-CT fraction: PH-positive scans with no cirrhosis impression mention and no cirrhosis ICD within 90 days; (2) Care Action Gap: no hepatology referral, surveillance imaging, or NSBB within 180 days, stratified by cACLD severity; (3) lead time from earliest pre-index PH-positive CT to first cirrhosis ICD (scans ≥ 30 days pre-index); (4) action-gap disparities by sex, age band, and scan indication (Wilson 95% CIs). Sensitivity: IPTW target-trial emulation for 24-month decompensation. **Results:** 14,567 pre-index PH-positive CT reports identified. Silent-CT: 38% (5,497/14,567) had no cirrhosis impression mention and no cirrhosis ICD within 90 days. Care Action Gap at 180 days: overall 34% (n = 14,567) probable cACLD 25% (n = 9,238); highly suggestive 17% (n = 1,359). Lead time (n = 1,451 scans ≥ 30 days pre-index): median 8.5 months (IQR 3.2–21.0) 16% predated the first cirrhosis ICD by ≥ 1 year. Disparities: women 41% vs men 29% age 80–89 58% vs 50–59 28% Black 40% vs Hispanic/Latino 26% oncology 47% vs ED workup 30%. Largest absolute gaps in older adults, women, Black patients, and incidental oncology CTs. IPTW sensitivity confirmed indication-driven confounding (E-value 2.37) action-gap metrics were reported as care-delivery indicators, not causal estimates. **Conclusion:** An agentic LLM pipeline operationalises Baveno VII cACLD/CSPH from 343,128 free-text CT reports at full MIMIC-IV scale. More than one in three PH-positive CT scans had no documented hepatology evaluation within six months, with disproportionate gaps in women, older adults, Black patients, and oncology CTs. Deployable on a HIPAA-eligible endpoint for prospective referral flagging, the action-gap metric serves as an equity-sensitive system level quality indicator



Disclosures: Harika Dadigiri:Nothing to Disclose, Srinivas Venkatanarayanan:Nothing to Disclose, Anas Al Mardini:Nothing to Disclose, Jeril Lasington:Nothing to Disclose, Edward Barbarito:Nothing to Disclose.

1455 | ◆ WHOLE-GENOME METAGENOMICS ENABLES RAPID PATHOGEN DETECTION, QUANTITATIVE BACTERIAL BURDEN, AND ANTIMICROBIAL RESISTANCE (AMR) ACROSS SPONTANEOUS BACTERIAL PERITONITIS PHENOTYPES

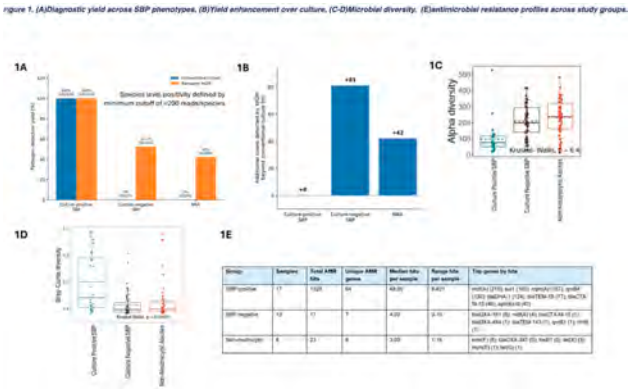
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Background: Spontaneous bacterial peritonitis (SBP) carries > 20% 30-day mortality in decompensated cirrhosis. Conventional culture detects pathogens in < 50% cases, requires 3-5 days, and cannot assess bacterial burden or antimicrobial resistance (AMR). We applied nanopore whole-genome metagenomics to quantify bacterial burden, identify mortality-associated taxa, and map AMR gene landscapes across culture-positive SBP, culture-negative SBP, and non-neutrocytic ascites (NNA). **Methods:** Treatment-naive adults with decompensated cirrhosis (culture-positive SBP n = 100, culture-negative SBP n = 155, NNA n = 100) underwent low-biomass DNA extraction and sequencing on Oxford Nanopore P2 Solo. Diversity metrics, bacterial burden, mortality associations, and AMR gene profiling were analysed (Kruskal-Wallis; Bray-Curtis PERMANOVA). **Results:** Among 355 patients (median age 51, male-predominant, alcohol/NASH etiology, MELD-Na 20/20/23), metagenomics detected bacterial DNA in 100/100 (100%) of culture-positive SBP, 81/155, (52.2%) of culture-negative SBP, and 42/100 (42%) of NNA, with a 10-hour turnaround vs. 5 days by culture. Alpha diversity was lowest in culture-positive SBP (p = 6.4x10-8); beta-diversity differed across groups (PERMANOVA p = 0.00037). Culture-positive SBP was dominated by *Escherichia coli*, *Stenotrophomonas maltophilia*, *Acinetobacter baumannii*, *Salmonella enterica*, and *Chryseobacterium indologenes*; culture-negative SBP harboured these pathogens at 4.8-fold lower read counts; NNA showed 6.8-fold lower burden. One-month septic shock mortality was 11%, 6.2%, and 4.8%; all fatal cases were enriched for *Stenotrophomonas maltophilia* (53,477 reads/sample, OR 9.90, 95% CI 8.71–11.25) establishing bacterial burden as a mortality biomarker. AMR profiling detected 1,363 resistance hits (69 unique genes), highest in culture-positive SBP (1,323 hits; 64 genes) vs. culture-negative SBP (17 hits) and NNA (23 hits). Key resistance genes-blaCTX-M-15, blaTEM-1B, qnrB4, mph (A), sul1, tet (B)-conferred resistance to beta-lactams, fluoroquinolones, aminoglycosides, and macrolides. **Conclusion:** In this metagenomics cohort of SBP phenotypes (n = 355), nanopore sequencing delivered rapid (10-hour) pathogen identification, bacterial burden stratification, and AMR profiling unattainable by culture. Stenotrophomonas maltophilia burden correlated with mortality. AMR gene profiles

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can be helpful for targeted antibiotic selection.



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1456 | ◆ SGLT2 INHIBITOR USE AND FUTURE PARACENTESIS BURDEN IN RECURRENT ASCITES: A RETROSPECTIVE MULTICENTER ANALYSIS

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Background: Recurrent paracentesis-requiring ascites reflects advanced portal-hypertensive fluid dysregulation and remains a major unmet need in cirrhosis. SGLT2i promote osmotic diuresis and natriuresis, but whether they reduce future drainage burden in patients with established recurrent ascites is unknown. **Methods:** We performed a multicenter retrospective study using the TriNetX U.S. Collaborative Network. Adults with cirrhosis receiving furosemide and spironolactone were included if they had recurrent paracentesis-requiring ascites, defined as ≥2 abdominal paracenteses performed ≥14 days apart within 3 months between 2015 and 2024. CKD stage 5/ESRD, dialysis dependence, or hepatocellular carcinoma were excluded. SGLT2i plus standard diuretics was compared with standard diuretics alone using 1:1 PSM. Matching covariates included demographics, cirrhosis etiology/decompensation burden, MELD parameters, HF, CKD, DM, insulin use, and sarcopenia. The index date was when patients met recurrent paracentesis and medication-strategy assignment criteria. Outcomes were assessed from day 31 through day 365. The primary outcome was repeat paracentesis. Fluid-management failure was repeat paracentesis, TIPS, liver transplantation (LT), or death. Advanced liver decompensation was HRS, SBP, HE, variceal bleeding, TIPS, LT, or death. The safety composite included ketoacidosis, hypoglycemia, genitourinary infection, sepsis/bacteremia, or hypotension. **Results:** 1,749 pairs were analyzed after PSM. SGLT2i use was associated with lower risk of repeat paracentesis (777 vs 951 events; HR 0.71, 95% CI 0.65–0.78; p < 0.001), higher 1-year paracentesis-free survival (49.8% vs 36.9%, NNT 7.75), and fewer mean post-index paracentesis encounters (4.39 vs 5.22; p = 0.014). SGLT2i use was also associated with lower fluid-management failure (HR 0.68, 95% CI 0.62–0.74), advanced liver decompensation (HR 0.80, 95% CI 0.73–0.88), and LT or death (HR 0.82, 95% CI 0.73–0.94). HE was numerically higher but not significant (HR 1.09, 95% CI 0.95–1.25). TIPS was numerically decreased but not significantly (HR 0.74, 95% CI 0.54–1.02). The safety composite was not statistically significant (HR 0.93, 95% CI 0.83–1.05). Findings were directionally consistent across subgroups, in a ≥30-day separation sensitivity analysis, and in an exploratory 3-year follow-up for repeat paracentesis (HR 0.53, 95% CI 0.47–0.61). **Conclusion:** In patients with recurrent paracentesis-requiring cirrhotic ascites despite standard diuretics, SGLT2i use was associated with lower future paracentesis burden and fewer fluid-management failures without an increase in composite safety events. Although causal inference cannot be established from this analysis, findings support prospective evaluation of SGLT2i as a potential adjunctive fluid-management strategy for recurrent ascites.

Outcomes of SGLT2 Inhibitor Use in Recurrent Paracentesis-Requiring Cirrhotic Ascites

Panel A. Main outcomes, procedure burden, and safety

Outcome	Events/values (SGLT2i vs control)	HR/estimate (95% CI)	p-value
Primary outcome and procedure burden			
Repeat paracentesis	777/1,749 vs 951/1,749	0.710 (0.646–0.781)	<0.001
Paracentesis encounters, mean ± SD	4.392 ± 9.547 vs 5.220 ± 10.277	Mean difference -0.83	0.014
Key composite outcomes			
Fluid-management failure	929/1,749 vs 1,145/1,749	0.680 (0.623–0.743)	<0.001
Advanced liver decompensation	813/1,749 vs 930/1,748	0.800 (0.728–0.879)	<0.001
Renal decompensation	604/1,749 vs 891/1,749	0.842 (0.765–0.926)	<0.001
Liver transplantation or death	411/1,488 vs 529/1,533	0.824 (0.726–0.936)	0.003
Secondary individual outcomes			
All-cause hospitalization	822/1,749 vs 859/1,749	0.901 (0.819–0.991)	0.032
All-cause mortality	399/1,634 vs 504/1,570	0.738 (0.647–0.842)	<0.001
TIPS placement	66/1,749 vs 86/1,749	0.738 (0.535–1.017)	0.062
Spontaneous bacterial peritonitis	163/1,749 vs 187/1,749	0.837 (0.678–1.033)	0.096
Hepatorenal syndrome	151/1,749 vs 171/1,749	0.849 (0.682–1.057)	0.142
Hepatic encephalopathy	434/1,749 vs 386/1,749	1.093 (0.953–1.254)	0.203
Acute kidney injury	635/1,749 vs 664/1,749	0.915 (0.821–1.021)	0.111
Variceal bleeding	101/1,749 vs 132/1,748	0.735 (0.567–0.952)	0.019
Safety outcomes			
Safety composite	588/1,749 vs 607/1,749	0.934 (0.834–1.046)	0.235
Diabetic ketoacidosis	19/1,579 vs 16/1,579	1.149 (0.591–2.234)	0.682
Hypoglycemia	47/1,579 vs 47/1,579	0.961 (0.643–1.440)	0.846
UTI/pyelonephritis/genital candidiasis	162/1,579 vs 190/1,579	0.814 (0.660–1.003)	0.053
Sepsis/bacteremia	226/1,579 vs 255/1,579	0.848 (0.709–1.014)	0.071
Hypotension	363/1,579 vs 324/1,579	1.094 (0.942–1.271)	0.237

Panel B. Subgroup, sensitivity, and exploratory analyses

Subgroup/analysis	Pairs	Repeat paracentesis	Fluid-management failure	Advanced liver decompensation
Demographic subgroups				
Male	1,008	0.720 (0.635–0.816)	0.730 (0.652–0.819)	0.888 (0.782–1.008)
Female	573	0.727 (0.617–0.856)	0.686 (0.589–0.798)	0.789 (0.672–0.927)
Cardiometabolic subgroups				
Type 2 diabetes	1,116	0.795 (0.706–0.894)	0.759 (0.682–0.845)	0.844 (0.752–0.948)
No type 2 diabetes	387	0.698 (0.555–0.878)	0.651 (0.528–0.802)	0.716 (0.563–0.910)
Chronic kidney disease	632	0.772 (0.655–0.910)	0.736 (0.636–0.852)	0.880 (0.753–1.029)
No chronic kidney disease	908	0.738 (0.646–0.842)	0.707 (0.627–0.798)	0.828 (0.725–0.945)
Heart failure	718	0.761 (0.656–0.884)	0.755 (0.660–0.862)	0.817 (0.704–0.949)
No heart failure	815	0.682 (0.594–0.784)	0.696 (0.613–0.794)	0.882 (0.769–1.011)
Obesity	646	0.746 (0.637–0.873)	0.726 (0.631–0.837)	0.827 (0.712–0.960)
No obesity	916	0.694 (0.609–0.791)	0.691 (0.612–0.779)	0.793 (0.694–0.906)
Combined cardiometabolic phenotype				
Type 2 diabetes / Heart failure	576	0.648 (0.55–0.764)	0.659 (0.568,0.764)	0.736 (0.626,0.866)
Type 2 diabetes / No heart failure	581	0.794 (0.674–0.935)	0.757 (0.652–0.878)	0.865 (0.739–1.012)
No type 2 diabetes / Heart failure	173	0.849 (0.626–1.152)	0.861 (0.654–1.133)	0.829 (0.598–1.150)
No type 2 diabetes / No heart failure	134	0.562 (0.391–0.808)	0.505 (0.357–0.714)	0.870 (0.584–1.296)
Etiology subgroups				
MASLD-related cirrhosis	289	0.793 (0.633–0.992)	0.757 (0.618–0.926)	0.695 (0.560–0.862)
Alcohol-related cirrhosis	403	0.571 (0.466–0.699)	0.548 (0.455–0.660)	0.684 (0.556–0.841)
Sensitivity and exploratory analyses				
Paracenteses separated ≥30 days	1,281	0.652 (0.587–0.724)	0.647 (0.587–0.713)	0.775 (0.696–0.863)
3-year follow-up	821	0.534 (0.465–0.614)	0.543 (0.480–0.615)	0.687 (0.604–0.780)

Symbols: ◆, Poster of Distinction; ★, Foundation Award Recipient

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Disclosures: Ali Emre Bardak:Nothing to Disclose, Nazli Begum Ozturk:Nothing to Disclose, Gizem Teker: Nothing to Disclose, Kamran Qureshi:Nothing to Disclose.

1457 | ◆ SAFETY OF SODIUM-GLUCOSE COTRANSPORTER 2 INHIBITORS IN PATIENTS WITH AND WITHOUT CIRRHOSIS: EMULATION OF A STRATIFIED TARGET TRIAL

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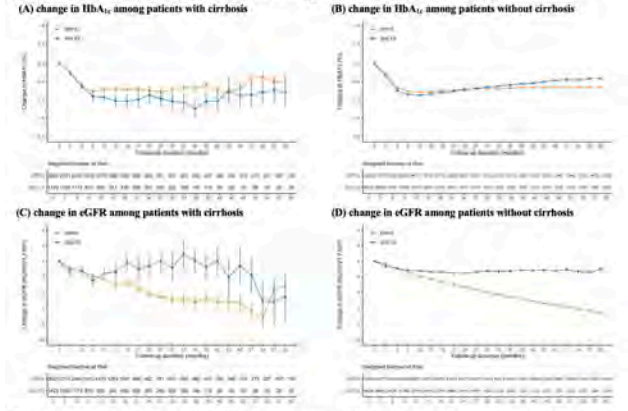
Background: Emerging evidence suggests that sodium-glucose cotransporter 2 inhibitors (SGLT2i) can improve steatohepatitis and liver-related outcomes. However, data on the safety of SGLT2i in patients with cirrhosis remains scarce. We examined the safety of SGLT2i vs dipeptidyl peptidase 4 inhibitors (DPP4i) in patients with type 2 diabetes mellitus (T2DM), with and without cirrhosis. **Methods:** Adults newly initiated on SGLT2i or DPP4i for T2DM between March 2015 and December 2023 were identified from clinics and hospitals in Hong Kong. Safety of SGLT2i vs DPP4i was estimated using a target trial emulation framework with randomisation stratified by cirrhosis status at treatment assignment. The primary outcome was acute kidney injury (AKI). Secondary outcomes were genito-urinary infections, diabetic ketoacidosis (DKA), fractures, and lower limb amputations. Long-term hemoglobin A_{1c} (HbA_{1c}) and estimated glomerular filtration rate (eGFR) changes were assessed. Inverse probability of treatment weighting was used to balance baseline characteristics between the SGLT2i and DPP4i groups within each cirrhosis stratum, and inverse probability of censoring weighting was applied to account for treatment discontinuation. Intention-to-treat and per-protocol effects were estimated using inverse probability-weighted marginal structural Cox models. **Results:** Overall, 193,794 patients with T2DM were included, 4,584 with cirrhosis (mean age, 73.5 ± 12.2 years; baseline eGFR 68.0 ± 23.8 mL/min/1.73 m²; 1,430 SGLT2i vs 3,154 DPP4i initiators) and 189,210 without cirrhosis (mean age, 65.6 ± 12.4 years; baseline eGFR 78.9 ± 23.3 mL/min/1.73 m²; 65,173 SGLT2i vs 124,037 DPP4i initiators). SGLT2i was associated with lower AKI risk than DPP4i use in patients with cirrhosis (adjusted hazard ratio [HR], 0.63; 95% CI, 0.50 to 0.80; adjusted rate difference, −49.72 per 1,000 person-years; 95% CI, −74.46 to −21.37), and without cirrhosis (adjusted HR, 0.71; 95% CI, 0.68 to 0.75; adjusted rate difference, −9.47 per 1,000 person-years; 95% CI, −10.93 to −8.09). No statistically significant interaction was observed between treatment and cirrhosis status for AKI risk (p for interaction = 0.456, Table 1). SGLT2i use was associated with no increased risks of genitourinary infections, diabetic ketoacidosis, fracture, or lower limb amputation in cirrhosis; treatment effect on adverse events did not differ by cirrhosis status (Table 1). Per-protocol analyses showed consistent results. SGLT2i was associated with more favourable long-term HbA_{1c} (Figure 1A and 1B) and eGFR trajectories (Figure 1C and 1D) than DPP4i in patients with and without cirrhosis. **Conclusion:** SGLT2i in adults with T2DM and cirrhosis was associated with a lower risk of AKI than DPP4i and no increase in genitourinary infections, DKA, fractures, and lower limb amputations. The safety of SGLT2i did not differ by cirrhosis status.

Table 1. Intention-to-treat analysis of the association between sodium-glucose co-transporter 2 inhibitor (SGLT2i) use and safety outcomes in patients with and without cirrhosis.

	SGLT2i No. of events (incidence rate per 1000 person-years)		DPP4i No. of events (incidence rate per 1000 person-years)		Adjusted rate difference per 1000 person-years (95% CI)*	Adjusted HR (95% CI)	*p* value	Adjusted *p* value**	*p* for interaction
	Unweighted	IPTW weighted	Unweighted	IPTW weighted					
Primary outcome									
AKI									
With cirrhosis	283 (134.89)	285 (106.67)	1,126 (160.34)	1072 (156.05)	-49.72 (-74.46 to -21.37)	**0.63 (0.50 to 0.80)**	**< 0.001**	**< 0.001**	0.456
Without cirrhosis	3,809 (27.47)	4,385 (30.35)	17,029 (42.55)	15,899 (39.87)	-9.47 (-10.93 to -8.09)	**0.71 (0.68 to 0.75)**	**< 0.001**	**< 0.001**	
Secondary outcomes									
Genitourinary infections									
With cirrhosis	68 (30.55)	76 (26.98)	475 (64.15)	417 (57.37)	-30.61 (-42.50 to -17.72)	**0.43 (0.28 to 0.68)**	**< 0.001**	**0.001**	0.312
Without cirrhosis	1,398 (9.94)	1793 (12.25)	9,080 (22.38)	8104 (20.01)	-7.76 (-8.79 to -6.78)	**0.56 (0.52 to 0.60)**	**< 0.001**	**< 0.001**	
DKA									
With cirrhosis	5 (2.20)	9 (2.99)	20 (2.49)	16 (2.07)	0.86 (-2.20 to 5.88)	1.55 (0.23 to 10.31)	0.637	0.999	0.999
Without cirrhosis	227 (1.60)	361 (2.43)	794 (1.89)	700 (1.67)	0.76 (0.36 to 1.21)	**1.39 (1.14 to 1.69)**	**0.001**	**0.004**	
Fracture									
With cirrhosis	34 (15.11)	53 (18.78)	187 (24.19)	175 (23.21)	-4.41 (-14.36 to 8.42)	0.76 (0.43 to 1.35)	0.346	0.999	0.764
Without cirrhosis	1,173 (8.34)	1483 (10.13)	5,106 (12.42)	4635 (11.31)	-1.18 (-2.00 to -0.35)	**0.85 (0.79 to 0.92)**	**< 0.001**	**< 0.001**	
Lower limb amputation									
With cirrhosis	1 (0.44)	1 (0.23)	10 (1.24)	9 (1.21)	-0.99 (-1.95 to -0.08)	0.22 (0.02 to 2.36)	0.180	0.719	0.110
Without cirrhosis	122 (0.86)	165 (1.11)	453 (1.08)	444 (1.07)	0.05 (-0.28 to 0.37)	1.04 (0.76 to 1.43)	0.817	0.999	

* Derived from IPTW weighted incidence rate, 95% CIs were estimated using 1,000 bootstrap resamples.
** Adjusted for multiple comparisons using the gatekeeping strategy and Bonferroni correction.
AKI, acute kidney injury; CI, confidence interval; DKA, diabetic ketoacidosis; DPP4i, dipeptidyl peptidase-4 inhibitor; HR, hazard ratio; IPTW, inverse probability of treatment weighting; SGLT2i, sodium-glucose co-transporter 2 inhibitor.

Figure 1. Long-term change in HbA1c and eGFR among patients with and without cirrhosis



* Points represent the pooled means of change in HbA1c or eGFR, and error bars represent the pooled standard errors across five imputed datasets using Rubin's rules. The weighted number at risk represents the per-protocol population, adjusting using inverse probability of treatment weighting (IPTW) for baseline characteristics balance and inverse probability of censoring weighting (IPCW) to account for informative censoring (discontinuation of the initial drug or initiation of combination therapy). DPP4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; HbA1c, haemoglobin A1c; SGLT2i, sodium-glucose co-transporter 2 inhibitor.

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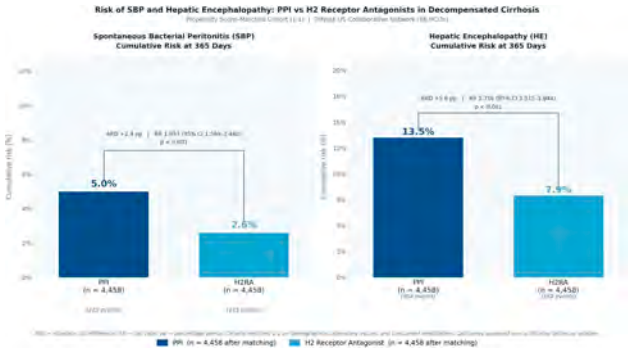
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1458 | ◆ NOT ALL ACID SUPPRESSION IS EQUAL: PPIS ARE ASSOCIATED WITH HIGHER RISKS OF SPONTANEOUS BACTERIAL PERITONITIS AND HEPATIC ENCEPHALOPATHY THAN H2 RECEPTOR ANTAGONISTS IN DECOMPENSATED CIRRHOSIS

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Background: Proton pump inhibitors (PPIs) are prescribed in up to 60% of patients with cirrhosis, often without a clear indication. Emerging evidence suggests PPIs promote gut dysbiosis and bacterial translocation, potentially increasing the risk of spontaneous bacterial peritonitis (SBP) and hepatic encephalopathy (HE). Whether PPIs confer greater risk of these complications compared to H2 receptor antagonists (H2RAs), an alternative acid suppression strategy, remains unclear. We compared the cumulative risk of SBP and HE among patients with decompensated cirrhosis newly initiated on PPIs versus H2RAs. **Methods:** We performed a retrospective propensity score-matched cohort study using the TriNetX US Collaborative Network (66 healthcare organizations). Adults with decompensated cirrhosis newly initiated on a PPI or H2RA within one year of hepatic decompensation were included using an active-comparator, new-user design. Patients with concurrent use of both drug classes,or prior liver transplantation were excluded. Patients with prior SBP or HE were retained, with baseline history incorporated into propensity matching to evaluate both incident and recurrent events. Cohorts were matched 1:1 for demographics, liver disease severity, comorbidities, and concurrent medications. Primary outcomes were SBP and HE within 365 days. Risk ratios (RRs) with 95% confidence intervals (CIs) were calculated. **Results:** Before matching, 133,995 PPI users and 4,777 H2RA users were identified. After 1:1 propensity matching, 4,458 patients remained in each cohort with well-balanced baseline characteristics (standardized mean differences < 0.1). PPI use was associated with significantly higher cumulative risk of SBP compared with H2RA use (5.0% vs 2.6%; RR 1.96, 95% CI 1.57–2.44; p < 0.001), corresponding to an absolute risk increase of 2.4%. Similarly, PPI users had higher cumulative risk of HE (13.5% vs 7.9%; RR 1.72, 95% CI 1.52–1.94; p < 0.001), with an absolute risk increase of 5.6%. Kaplan-Meier analysis demonstrated lower SBP-free survival among PPI users compared with H2RA users at 365 days (93.6% vs 97.0%; log-rank p < 0.001). **Conclusion:** In this large propensity score-matched real-world cohort study, PPI use in patients with decompensated cirrhosis was associated with significantly increased risks of both SBP and HE compared with H2RA use. Given the frequent use of PPIs without clear indication in this population, these findings support careful reassessment of acid suppression strategies in patients with decompensated cirrhosis. Prospective studies are needed to confirm causality and define optimal approaches to gastric acid suppression in this vulnerable population.



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1459 | ◆ NEW SUBMISSION CIRRHOTIC CARDIOMYOPATHY INCREASES THE RISK OF DEATH ON THE LIVER TRANSPLANT WAITLIST

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Background: Cirrhotic cardiomyopathy (CCM) is chronic cardiac dysfunction arising from cirrhotic

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physiology in patients with end-stage liver disease. Patients with CCM may have increased rates of adverse outcomes after transplantation, largely due to cardiac comorbidities. However, the impact of CCM on mortality while on the liver transplant waitlist has yet to be studied. We aim to define the association between the diagnosis of CCM and liver transplant waitlist mortality. **Methods:** We performed a retrospective cohort study of adult patients with cirrhosis listed for liver transplant at a large academic center in North America between 11/1/2020 and 4/1/2025. Out of 878 patients on the liver transplant waitlist, 617 met inclusion criteria, from which 453 had sufficient data to determine CCM diagnosis. Patients with primary cardiac pathology were excluded. We adjusted for age and MELD-3.0 using a Fine-Gray model, with transplant and delisting as competing events. **Results:** A total of 81 patients met criteria for CCM and 372 did not meet CCM criteria. In our age and MELD 3.0 adjusted model, CCM was independently associated with an increased risk of death while on the waitlist (HR 2.59; 95% CI 1.23-5.46; p = 0.013). However, when treating waitlist death and delisting for being too sick as a composite outcome, CCM was no longer associated with an increased risk of waitlist mortality (HR 1.73, 95% CI 0.94-3.20, p = 0.078). The one-year cumulative incidence of waitlist death was 4.7% for no CCM versus 9.7% for CCM (p = 0.007), whereas the one-year cumulative incidence of death or delisting for being too sick was 7.9% for no CCM and 14% for CCM (p = 0.062). Of the four diastolic dysfunction echo parameters composing CCM criteria, only peak early septal diastolic velocity (septal e') of < 7 cm/s was associated with increased waitlist mortality and delisting for being too sick (HR 2.80, 95% CI 1.47-5.36, p = 0.002). **Conclusion:** Cirrhotic cardiomyopathy is associated with increased rates of death while on the liver transplant waitlist. However, when also accounting for patients who are delisted for being too sick for transplant, a diagnosis of CCM is not significantly associated with increased waitlist mortality. Importantly, abnormally low septal e' was the most predictive echocardiographic parameter of waitlist mortality.

Table 1
Association of CCM Across Competing Transplant Waitlist Outcomes

Outcome	Events (n = 452)	Hazard Ratio (95% CI)	P-value
Transplant	347	0.92 (0.64-1.33)	0.657
Composite: Waitlist Death + Delisted Too Sick	53	1.73 (0.94-3.20)	0.078
Waitlist Death	30	2.59 (1.23–5.46)	**0.013**
Delisted Too Sick	23	0.78 (0.23-2.61)	0.687
Delisted Too Well	16	0.00 (0.00-0.00)	**<0.001**
Delisted Other	16	0.80 (0.19-3.40)	0.759
Censored	20	-	-

Disclosures: Andre Hall:Nothing to Disclose, Murray Coetzee:Nothing to Disclose, Rawia Aburumman:Nothing to Disclose, Christopher Slaughter:Nothing to Disclose, Ashley Spann:Bristol Myers Squibb Foundation: Grant/Research Support, Novo Nordisk: Consultant, Madrigal Pharmaceuticals: Consultant, Deepak Gupta:Nothing to Disclose, Anthony Dreher:Nothing to Disclose, Manhal Izzy:Mallinckrodt: Speaking and Teaching, Madrigal: Advisor, Natera: Advisor, Mirum: Advisor.

1460 | ◆ EUS-GUIDED COIL AND GLUE INJECTION IN ADDITION TO ß-BLOCKERS LEADS TO LOWER RATES OF GASTRIC VARICEAL BLEEDING COMPARED TO ß-BLOCKERS ALONE FOR PRIMARY PROPHYLAXIS OF GASTRIC VARICES IN CIRRHOSIS – A MULTICENTRE PROPENSITY MATCHED ANALYSIS FROM INDIA

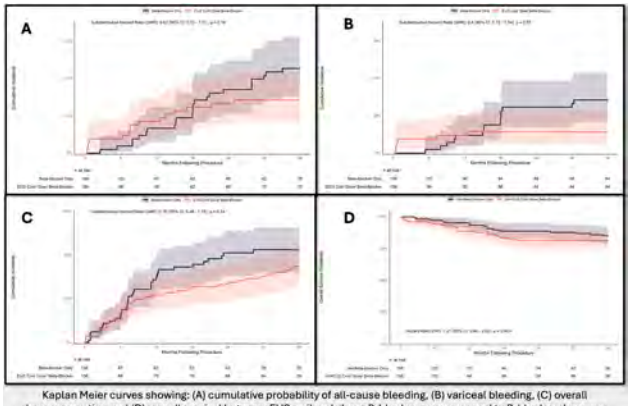
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Background: Gastric variceal bleeding (GVB) is associated with high morbidity and mortality. EUS-guided coil and cyanoacrylate injection (EUS-CG) has been shown to be an effective therapy for bleeding gastric varices and secondary prophylaxis, however, there is a paucity of data on primary prophylaxis of gastric varices. We compared the efficacy of addition of EUS-CG to ß-blockers against ß-blockers alone for primary prophylaxis of gastric variceal bleeding. **Methods:** This multi-centre observational study included patients across 11 tertiary care centres in India. Adult patients with cirrhosis and large gastric varices (F2 or F3) without prior bleeding were included. Baseline demographics, prior non-bleeding decompensating events and clinical outcomes including bleeding, hepatic decompensation and mortality were reviewed. Patients ß-blockers undergoing EUS-CG (EUS-CG + ß-

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blocker arm) were compared with propensity-matched (PSM) patients on ß-blockers alone (ß-blocker arm). Competing risk analysis was performed to assess the risk of bleeding and hepatic decompensation, with mortality and liver transplantation as competing events. The primary outcome was to compare the incidence of first gastric variceal (GV) bleeding. **Results:** Of 366 patients, 106 who underwent EUS-CG and received ß-blockers were compared with 106 propensity-matched cases who received ß-blockers alone. Patients who underwent EUS-CG and received ß-blockers had significantly lower incidence of GV bleeding at 3 years compared to patients who received ß-blockers alone (5.7% vs 14.2%; p = 0.04). There was no significant difference in the probability of being free from overall bleeding (sHR: 0.63, 95% CI:0.33-1.21;p = 0.17), freedom from hepatic decompensation (sHR:0.76, 95% CI:0.49-1.20 ;p = 0.24) and overall survival (sHR: 1.31, 95% CI: 0.68-2.52; p = 0.43) between the 2 groups. On sub-group analysis, lower rates of GV bleeding were observed in the EUS-CG and ß-blocker arm in patients with IGV1 varices (sHR: 014, 95% CI: 0.03-0.67; p = 0.01), F3 varices (sHR: 0.27, 95% CI: 0.10-0.74; p = 0.01) and patients with red colour sign (RCS) on endoscopy (sHR: 019, 95% CI: 0.06-0.63; p = 0.01). On multivariate regression analysis, higher MELD-Na score alone was a significant predictor of bleeding (aOR:1.12,95%CI:1.06-1.19;p = 0.03) and mortality (aOR: 1.23,95%CI:1.11-1.34;p = 0.02). **Conclusion:** In patients with cirrhosis and large gastric varices, addition of EUS-coil and glue injection to ß-blockers was superior to ß-blockers alone for the prevention of first GV bleeding. Lower rates of GV bleeding were specifically noted in patients with IGV1 varices, F3 varices and patients with RCS on endoscopy.



Kaplan Meier curves showing: (A) cumulative probability of all-cause bleeding, (B) variceal bleeding, (C) overall decompensation and (D) overall survival between EUS-coil and glue + B-blocker arm compared to B-blocker alone arm

Disclosures: Shubham Mehta:Nothing to Disclose, Arka De:Nothing to Disclose, Jimil Shah:Nothing to Disclose, Pawan Khatri:Nothing to Disclose, D. Vignesh:Nothing to Disclose, Shrihari Anikhindi:Nothing to Disclose, Hitesh Panchal:Nothing to Disclose, Nikhil Sonthalia:Nothing to Disclose, Pankaj Gupta: Nothing to Disclose, Ankit Agarwal:Nothing to Disclose, Ashish Agarwal:Nothing to Disclose, Aditya Vikram Pachisia:Nothing to Disclose, Chalapathi Rao Achanta: Nothing to Disclose, pawan rawal:Nothing to Disclose, SUNIL TANEJA:Nothing to Disclose, Rajesh Puri: Nothing to Disclose.

1461 | ◆ REMIMAZOLAM VERSUS PROPOFOL FOR PROCEDURAL SEDATION DURING UPPER ENDOSCOPY IN PATIENTS WITH CIRRHOSIS: A SYSTEMATIC NARRATIVE REVIEW OF SAFETY EVIDENCE ACROSS CHILD-PUGH SUBGROUPS

Neev Mehta Ishan Antony[1], [1]Lahey Clinic

Background: Patients with cirrhosis require repeated EGD for variceal surveillance amid portal hypertension, low vascular resistance, and hepatic encephalopathy (HE). Propofol has replaced midazolam as preferred sedative because it does not worsen subclinical HE. Remimazolam, metabolized by tissue esterases rather than CYP450, offers hemodynamic stability and flumazenil reversibility, but raises concerns in advanced cirrhosis where esterase activity is substantially reduced. **Methods:** We conducted a PRISMA-compliant systematic narrative review. PubMed, Embase, and Cochrane Library were searched through March 2024 using MeSH terms: “remimazolam,” “propofol,” “liver cirrhosis,” “endoscopy,” and “hepatic encephalopathy.” Two authors independently screened records; disagreements resolved by consensus. Eligible studies were RCTs or systematic reviews reporting sedation safety, or pharmacokinetic studies in hepatic impairment; studies lacking a comparator were excluded. Risk of bias was assessed using Cochrane RoB2 (RCTs) and AMSTAR-2 (meta-analyses). Outcomes including respiratory depression, hypoxemia, hypotension, HE worsening, and recovery time, were stratified by Child-Pugh class. No primary data accessed. **Results:** Across 26 RCTs (n = 3,641), remimazolam reduced respiratory depression (RR 0.40), hypoxemia (RR 0.34), hypotension (RR 0.36), and bradycardia (RR 0.34) vs. propofol (all $p < 0.01$, GRADE High for most; Table 1). The advantages amplified in cirrhosis, where low vascular resistance heightens susceptibility to propofol-induced compromise. Child-Pugh stratification revealed a key gradient (Table 2). In Child-Pugh A, clearance is preserved. In Child-Pugh B, esterase activity falls ~38%, extending recovery to ~12–14 minutes. In Child-Pugh C, clearance drops ~75% and recovery doubles to ~16.7 minutes, making flumazenil a clinical necessity. On HE, evidence favors propofol (Table 3): multiple RCTs confirm no worsening of subclinical HE across cirrhosis

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subgroups. Remimazolam's HE data are limited to one underpowered RCT; a GABA-ergic class effect in Child-Pugh C cannot be excluded. **Conclusion:** Remimazolam offers a meaningful hemodynamic and respiratory advantage in Child-Pugh A and B cirrhosis. In Child-Pugh C, impaired clearance and unresolved HE risk favor propofol for HE prevention. A prospective RCT in decompensated cirrhosis with neuropsychometric and hemodynamic endpoints is needed. Until then, remimazolam in Child-Pugh C warrants dose reduction, flumazenil availability, and extended monitoring.

Table 1. *Remimazolam vs. propofol: pooled safety outcomes (Zhao et al., Int J Surg 2023; 26 RCTs, n = 3,641)*

Safety outcome	Remimazolam	Propofol	Risk ratio (95% CI)	p-value	GRADE
Respiratory depression	~8%	~20%	0.40 (0.28–0.57)	< 0.01	High
Hypoxemia	~6%	~17%	0.34 (0.23–0.49)	< 0.01	High
Hypotension	~7%	~19%	0.36 (0.26–0.48)	< 0.01	Low
Bradycardia	~5%	~14%	0.34 (0.23–0.51)	< 0.01	High
Injection site pain	< 1%	~16%	0.06 (0.03–0.13)	< 0.01	High

RR < 1.0 favors remimazolam. GRADE ratings from source meta-analysis. Source: Zhao et al., Int J Surg 2023;109(11):3566–77.

Table 2. *Remimazolam pharmacokinetics and clinical implications by Child-Pugh class*

Child-Pugh class	Esterase clearance vs. healthy	Recovery time	Remimazolam considerations	Propofol considerations
A — compensated	Normal	~8 min	Standard dosing; predictable offset; flumazenil available	Preferred; does not worsen HE; rapid recovery
B — moderate	↓ ~38%	~12–14 min	Dose reduction advised; extended monitoring; flumazenil an advantage	Hemodynamic vigilance; hypotension risk in moderate decompensation
C — decompensated	↓ ~75%	~16.7 min	Prolonged sedation; accumulation risk; flumazenil reversal critical; use with caution	Severe hypotension risk; low SVR amplifies vasodepressor effect

Recovery time: ~16.7 min (severe hepatic impairment) vs. 8.0 min (healthy). Sources: Murrell & Hartleroad; Eur J Drug Metab Pharmacokinet 2025; Frontiers in Medicine 2026.

Table 3. *Post-procedural HE worsening: key evidence by sedative agent*

Study	Agent	n	HE assessment	Key finding
Riphaus et al., J Hepatol 2010	Propofol vs. midazolam	61	NCT pre/post EGD	Propofol: no HE worsening; midazolam: NCT delayed
Suh et al., Korean J Hepatol 2013	Propofol (deep sedation)	20	PHES + CFF	No overt HE; CFF unchanged in non-MHE patients
Nishizawa et al., J Hepatol 2014	Propofol vs. + midazolam	132	NCT at 2 h post-EGD	Propofol alone safe; midazolam regimens: NCT worsened
Cao et al., Med Sci Monit 2022	Remimazolam tosylate	Cirrh*	AE monitoring	No HE events reported; favorable hemodynamics
Moraru et al., Am J Ther 2025	Review: remimazolam in HE	N/A	Narrative synthesis	Flumazenil key advantage; CP-C HE risk unresolved

**Cirrhosis patients; not stratified by Child-Pugh. NCT, number connection test; CFF, critical flicker frequency; MHE, minimal HE; AE, adverse event.*

Disclosures: Neev Mehta:Nothing to Disclose, Ishan Antony:Nothing to Disclose.

1462 | ◆ ADVANCED LIVER FIBROSIS IS ASSOCIATED WITH SKELETAL MUSCLE DISRUPTED HOMEOSTASIS AND INCREASED INFLAMMATION

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Background: The loss of skeletal muscle mass, or sarcopenia, is a common finding in patients with cirrhosis and observed in 50% of patients assessed for liver transplantation. Sarcopenia is associated with mortality pre- and post-liver transplantation, a higher rate of infection, hepatic encephalopathy, poor quality of life, and increased healthcare cost. However, the characterization of the skeletal muscles remains elusive and is the scope of this study. **Methods:** Livers and dorsal skeletal muscles of 62 healthy individuals or patients with metabolic-associated steatotic liver disease (MASLD) liver fibrosis were imaged using magnetic resonance (MRI). Individuals were sex, age and BMI-matched. Skeletal muscle area was normalized to the thoracic cage surface (Mu-Tho ratio). Human skeletal muscles were characterized by H&E and bulk RNA-seq. Large extracellular vesicles (lEVs) from human sera were analyzed by mass spectrometry. Liver fibrosis in C57Bl/6 or Alb-Cre mice was induced by carbon tetrachloride (CCl_4) and mouse skeletal muscles were characterized by H&E, BODIPY staining and immunostaining. **Results:** Mu-Tho ratio decreased in patients with stage F2-F3 liver fibrosis (3.5 kPa < liver stiffness < 5 kPa) and F4 liver fibrosis (liver stiffness > 5 kPa) compared to patients with F0-F1 liver fibrosis (liver stiffness < 3.5 kPa) (4.2, 4.2, 5.1, respectively, $p < 0.05$). Utilizing the Spearman correlation, Mu-Tho ratio positively correlated with muscle stiffness and negatively correlated with muscle fat fraction and liver stiffness, suggesting that muscle loss is associated with liver fibrosis and muscle fat. RNA-seq of human skeletal muscles revealed that patients with liver cirrhosis (liver stiffness > 5 kPa) had increased expression of inflammatory genes such as CCL2 (112-fold) and IL6 (47-fold) compared to healthy individuals ($p < 0.05$). Infiltrating cells were present in these muscles, suggesting that skeletal muscles from individuals with cirrhosis are inflamed. Circulating lEVs from patients with Child-Pugh C cirrhosis were enriched with liver-specific proteins such as SerpinA7 and ApoA5, suggesting that liver might affect skeletal muscles through lEVs. In mice, Alb-Cre mice with liver fibrosis and injected with AAV8-GFP (green hepatocytes) contained green vesicles in the tibialis anterior muscle as compared to olive oil controls, suggesting that fibrotic liver-derived EVs are taken up by skeletal muscles. In addition, mice with liver fibrosis had sarcopenia as attested by a 10% reduction of gastrocnemius muscle weight ($p < 0.05$) and 2-fold decrease of myofiber diameter ($p < 0.001$), suggesting that this model recapitulates sarcopenia. **Conclusion:** These results suggest that liver fibrosis is associated with skeletal muscle inflammation and dysregulated homeostasis and EVs might be involved in liver-skeletal muscle axis.

Disclosures: Enis Kostallari:Nothing to Disclose, Nothing to Disclose, Kate Kurotani:Nothing to Disclose, Charles Cox:Nothing to Disclose, Peng Xu:Nothing to Disclose, Marion Tanguy:Nothing to Disclose, Zeba Firdaus:Nothing to Disclose, Alexander Washington: Nothing to Disclose, Timucin Taner:Nothing to

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Disclose, Julie Heimbach:Nothing to Disclose, Patrick Starlinger:Nothing to Disclose, Pierre-Emmanuel Rautou:Genfit: Consultant, Jazz: Speaking and Teaching, Cook: Consultant, AstraZeneca: Consultant, Meng Yin: Resoundant, Inc.: Stock – privately held company, Enis Kostallari:Nothing to Disclose, Nothing to Disclose.

1463 | ◆ CANNABIS USE AND DECOMPENSATION OUTCOMES IN CIRRHOSIS: A PROPENSITY SCORE–MATCHED COHORT ANALYSIS

Brandon Cunha[1] Jashanveer Johal[1] Archana Salek[1] Bianca Patel[1] Mahmoud Al-Bataineh[1] Abdallah Hussein[1] Jason Hyman[2] Yecheskel Schneider[1], [1]Virtua Health, [2]Einstein Medical Center, Philadelphia

Background: Background:: Cannabinoid receptor signaling exerts divergent effects in cirrhosis: CB1 activation promotes portal vasodilatation, splanchnic pooling, and stellate cell activation, whereas CB2 signaling may exert anti-inflammatory and antineoplastic effects. However, the impact of cannabis use on decompensation, HCC incidence, and mortality in cirrhosis remains poorly characterized despite increasing cannabis use prevalence. **Methods: Methods::** We performed a propensity score–matched retrospective cohort study using the TriNetX Global Collaborative Network (191.9 million patients). Cohort 1 included adults with non-alcoholic, non-viral cirrhosis (K74.6) and cannabis use disorder (F12.10, F12.20, F12.90). Cohort 2 included matched cirrhotic patients without cannabis use. Patients with alcoholic liver disease/cirrhosis, alcohol or opioid dependence, and chronic hepatitis B/C were excluded. Cohorts were balanced via 1:1 PSM yielding 9,464 patients per arm over a 6–120 month follow-up window. Prespecified outcomes included new or progressive ascites, hepatic encephalopathy (HE), esophageal varices (EV), spontaneous bacterial peritonitis (SBP), incident HCC, all-cause mortality, and inpatient encounters. **Results: Results::** Post-PSM cohorts were well-balanced across matched covariates. Cannabis use was associated with significantly higher rates of portal hypertensive decompensation. HE occurred more frequently in cannabis users on both MOA (18.8% vs. 15.3%; RR 1.23; $p < 0.001$) and KM analysis (HR 1.28, 95% CI 1.20–1.37; $p < 0.001$). EV incidence was higher in the cannabis cohort (11.1% vs. 10.0%; HR 1.14, 95% CI 1.04–1.24; $p = 0.004$), as was SBP (4.0% vs. 3.1%; HR 1.34, 95% CI 1.15–1.56; $p = 0.0002$). Ascites rates were similar on time-to-event analysis (HR 1.05, 95% CI 1.00–1.11; $p = 0.053$). Incident HCC was significantly lower among cannabis users (2.0% vs. 2.8%; HR 0.76, 95% CI 0.63–0.92; $p = 0.005$), as well as all-cause mortality (23.8% vs. 29.6%; HR 0.82, 95% CI 0.78–0.87; $p < 0.001$). Median survival was not reached in the cannabis cohort versus 2,758 days in controls. Inpatient encounter burden was higher in the cannabis arm (58.3% vs. 50.8%; HR 1.29, 95% CI 1.24–1.34; $p < 0.001$), with a shorter median time to first encounter (241 vs. 564 days). **Conclusion: Conclusion::** In this propensity-matched real-world cohort, cannabis use in cirrhosis was associated with higher rates of portal hypertensive complications, including HE, EV, and SBP, but lower HCC incidence and all-cause mortality. These findings suggest divergent hepatic associations of cannabis use in cirrhosis. The observed reduction in mortality despite increased decompensation events may reflect residual confounding by age, physiologic reserve, and unmeasured liver disease severity, including lack of MELD stratification. Prospective fibrosis stage–stratified studies are needed to clarify the net hepatic impact of cannabis use.

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1464 | ◆ THE OBESITY PARADOX IN SPONTANEOUS BACTERIAL PERITONITIS: ASSESSING OUTCOMES IN PATIENTS WITH CIRRHOSIS

Arti Patel[1] Sujay Singh[1] Homan Abdollahzadeh[1], [1]Eisenhower Medical Center

Background: Spontaneous bacterial peritonitis (SBP) is a serious complication of cirrhosis associated with substantial morbidity and mortality. Obesity has traditionally been linked to adverse health outcomes; however, emerging evidence suggests the presence of an obesity paradox, where higher body mass index may be associated with improved outcomes. We evaluated the impact of obesity on clinical characteristics and outcomes among hospitalized patients with cirrhosis and SBP. **Methods:** This retrospective cohort study used the National Inpatient Sample (NIS) to identify adults between 2019 and 2022 with cirrhosis and SBP, comparing patients with obesity to those without obesity. Demographics, comorbidities, inpatient complications, and hospitalization outcomes were analyzed. Univariate analyses were performed using STATA software. **Results:** Of the 105,405 patients who met the inclusion criteria, 62.2% were male and the mean age was similar between groups (60.0 vs 57.3 years, $P \geq 0.05$); however, females were more likely to be obese ($P < 0.05$). White patients were more

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likely (OR 1.236, 95% CI 1.128-1.353), while Black (OR 0.659, 95% CI 0.554-0.783), Asian (OR 0.517, 95% CI 0.365-0.732), and patients of other races (OR 0.724, 95% CI 0.563-0.931) were less likely to be obese; no significant differences were seen among Hispanic and Native American patients ($P \geq 0.05$). Chronic obstructive pulmonary disease, congestive heart failure, diabetes, and hypertension were more common among obese patients, whereas alcohol use, cancer, malnutrition, and smoking were less common ($P < 0.05$). No significant differences were observed in dementia and end-stage renal disease ($P \geq 0.05$). Obese patients had lower odds of variceal bleeding (OR 0.824, 95% CI 0.706-0.962), hepatocellular carcinoma (OR 0.814, 95% CI 0.683-0.970), and inpatient mortality (OR 0.846, 95% CI 0.752-0.952), but higher odds of acute kidney injury (OR 1.116, 95% CI 1.031-1.208). No differences were seen in rates of paracentesis, hepatic encephalopathy, acute liver failure, liver transplantation, ICU admission, length of stay, and total hospitalization charges ($P \geq 0.05$). **Conclusion:** Among patients with cirrhosis and SBP, obesity was associated with higher risk of acute kidney injury. However, it was found to be protective for variceal bleeding and associated with lower overall mortality. Our finding of an obesity paradox in cirrhosis may reflect differences in patients' nutritional status; further studies are necessary to better understand this association.

Table 1: Demographics

	With Obesity (n = 14,395)	Without Obesity (n = 91,010)	P value	Odds Ratio (95% CI)
Mean Age, years	60.0	57.3	0.202	-
Gender, n				
Male	8490 (59.0%)	57105 (62.7%)	<0.001	0.854(0.788-0.925)
Female	5905 (41.0%)	33905 (37.3%)	<0.001	1.171(1.081-1.270)
Race, n				
White	9735 (67.6%)	57190 (62.8%)	<0.001	1.236(1.128-1.353)
Black	780 (5.4%)	7280 (8.0%)	<0.001	0.659(0.554-0.783)
Hispanic	2700 (18.8%)	16775 (18.4%)	0.704	1.022(0.914-1.142)
Asian	190 (1.3%)	2295 (2.5%)	<0.001	0.517(0.365-0.732)
Native	295 (2.0%)	2190 (2.4%)	0.276	0.849(0.631-1.140)
Other	345 (2.4%)	2985 (3.3%)	0.012	0.724(0.563-0.931)
Alcohol Use, n	8185 (56.9%)	61960 (68.1%)	<0.001	0.618(0.592-0.671)
Cancer, n	1120 (7.8%)	8315 (9.1%)	0.021	0.839(0.723-0.974)
Chronic Obstructive Pulmonary Disease (COPD), n	1685 (11.7%)	9105 (10.0%)	0.005	1.193(1.054-1.350)
Congestive Health Failure (CHF), n	2845 (19.8%)	12960 (14.2%)	<0.001	1.484(1.340-1.642)
Dementia, n	180 (1.3%)	1480 (1.6%)	0.136	0.766(0.540-1.087)
Diabetes, n	5830 (40.5%)	24645 (27.1%)	<0.001	1.833(1.689-1.989)
End-Stage Renal Disease (ESRD), n	1095 (7.6%)	7790 (8.6%)	0.089	0.880(0.759-1.020)
Hypertension, n	4420 (30.7%)	22175 (24.4%)	<0.001	1.376(1.257-1.505)
Malnutrition, n	1275 (8.9%)	10855 (11.9%)	<0.001	0.718(0.618-0.834)
Smoking, n	5485 (38.1%)	38345 (42.1%)	<0.001	0.846(0.778-0.919)

Table 2: Hospitalization Co-illnesses, Length of Stay, and Cost of Admission

	With Obesity (n = 14,395)	Without Obesity (n = 91,010)	p value	Odds Ratio (95% CI)
Variceal Bleed, n	965 (6.7%)	7300 (8.0%)	0.014	0.824(0.706-0.962)
Paracentesis, n	2975 (20.7%)	19655 (21.6%)	0.259	0.946(0.869-1.042)
Hepatic Encephalopathy (HE), n	440 (3.1%)	2880 (3.2%)	0.995	1.001(0.794-1.261)
Acute Kidney Injury (AKI), n	8150 (56.6%)	49065 (53.9%)	0.007	1.116(1.031-1.208)
Hepatocellular Carcinoma (HCC), n	800 (5.6%)	6135 (6.7%)	0.022	0.814(0.683-0.970)
Acute Liver Failure (ALF), n	1470 (10.2%)	9920 (10.9%)	0.275	0.930(0.816-1.060)
Liver Transplant, n	315 (2.2%)	1675 (1.8%)	0.208	1.193(0.907-1.571)
Intensive Care Unit (ICU) Admission, n	2080 (14.4%)	13765 (15.1%)	0.362	0.948(0.845-1.064)
Mortality, n	1960 (13.6%)	14290 (15.7%)	0.005	0.846(0.752-0.952)
Length of Stay (LOS), days	8.7	8.8	0.659	-
Total Charge, dollars	$113,220.30	$114,853.90	0.613	-

Disclosures: Arti Patel:Nothing to Disclose, Sujay Singh:Nothing to Disclose, Homan Abdollahzadeh: Nothing to Disclose.

1465 | ◆ LONGITUDINAL TRAJECTORIES OF IL-6 AND VWF PREDICT CLINICAL OUTCOMES IN ADVANCED CHRONIC LIVER DISEASE INDEPENDENT OF LIVER FUNCTION

Georg Kramer[1] Dalila Costa[2] Benedikt Hofer[3] Benedikt Simbrunner[1] Ana Frias[2] Ricardo Silvestre[2] Joana Camoes Neves[2] João Belmiro Martins[2] Kerstin Zinober[3] Vlad Taru[3] Christian Sebesta[3] Paul Thöne[3] Marlene Hintersteininger[3] Lorenz Balcar[3] Lukas Hartl[3] Mathias Jachs[3] Georg Semmler[1] Michael Trauner[3] Carla Rolanda[3] Thomas Reiberger[1], [1]Medical University of Vienna, [2]Life and Health Sciences Research Institute (ICVS), University of Minho, [3]Medical University of Vienna, Vienna, Austria

Background: Systemic inflammation (SI) and portal hypertension (PH) are drivers of disease progression in cirrhosis. We investigated longitudinal, stage-dependent patterns of Interleukin-6 (IL-6), a surrogate for SI, and von Willebrand factor antigen (vWF), a surrogate of PH, across compensated (cACLD), decompensated (dACLD), and recompensated advanced chronic liver disease (ACLD), and assessed their association with subsequent clinical transitions. **Methods:** In this prospective two-center cohort study (Vienna/Braga, 2017-2024), ACLD patients were enrolled at their first combined IL-6 and vWF assessment. Inclusion required at least two longitudinal measurements of IL-6, vWF, and MELD, with a minimum interval of 6 months between the first and last assessment. Clinical disease evolution was modeled using a 5-state multi-state model (cACLD, first and further decompensation, clinical recompensation, liver-related death [LRD]). Bayesian joint models linked biomarker trajectories to transition-specific hazards, adjusted for time-updated MELD. **Results:** This study included 472 patients (273 cACLD, 199 dACLD, mean age 53.5 ± 12.8 years, 67.1% steatotic liver disease, median MELD 11 [IQR: 8-15]) contributing 3,954 vWF and 2,918 IL-6 measurements. Over a median follow-up of 35.5 months, 138 transitions to first decompensation, 124 to further decompensation, 56 to clinical recompensation, and 35 to LRD occurred. Rising IL-6 independently predicted the transition to first decompensation, further decompensation, and LRD, with adjusted hazard ratios (aHR) per 20% increase of 1.21, 1.17, and 1.15, respectively (all $p < 0.001$). Conversely, decreasing IL-6 was associated with transition to clinical recompensation from first and further decompensation, with aHR per 20% decrease of 1.17 ($p = 0.007$) and 1.18 ($p < 0.001$), respectively. Increasing vWF predicted first and further decompensation, with aHR per 20% increase of 1.39

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and 1.19 (both p < 0.001), respectively, while declining vWF levels were not significantly associated with recompensation or lower risk of LRD. **Conclusion:** Longitudinal modeling shows that dynamics in biomarkers of systemic inflammation (IL-6) and portal hypertension (vWF) are associated with ACLD progression independently of MELD. Rising vWF was most strongly linked to progression toward first decompensation, whereas IL-6 trajectories also reflected course in dACLD, predicting further decompensation and liver-related death when increasing, and clinical recompensation when decreasing.

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★ 1466 | ◆ IMPLICATION OF MULTIPLE FIRST DECOMPENSATION EVENTS ON THE DEFINITION OF FURTHER DECOMPENSATION

Jimmy Che-To Lai[1] Junlong DAI[1] Vincent Wong[1] Grace Wong[1] Terry Cheuk-Fung Yip[1], [1]The Chinese University of Hong Kong

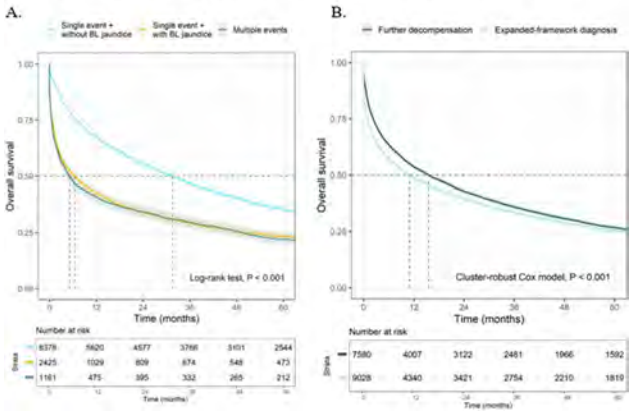
Background: The upcoming Baveno VIII proposes an expansion of the definition of further decompensation by including multiple first decompensation events and/or jaundice. However, there is a lack of evidence to support this proposal. We aimed to assess the clinical implication of the proposed expanded definition. **Methods:** This was a retrospective cohort study on patients with decompensated cirrhosis between 2000 and 2020 in Hong Kong. Patients were classified into three groups, namely “single event without jaundice” (Group A), “single event with jaundice” (Group B) and “multiple events” (Group C), where jaundice was defined as bilirubin ≥ 85μmol/L at the time of first decompensation. Groups B and C were further classified as further decompensation according to the expanded definition and compared to those fulfilling the original Baveno VII definition using a cluster-robust Cox model. The primary endpoint was all-cause mortality. **Results:** 11,964 patients (Group A: 8,378; Group B: 2,425; Group C: 1,161) with decompensated cirrhosis were identified. Most had chronic hepatitis B and were male. The mean age ranged from 61.0-67.0 years. Patients in group B and C had poorer liver function (Child-Pugh scores 9, 11 and 12, respectively for Groups A-C, p < 0.001; median Model for End-stage Liver Disease [MELD] scores 12.0, 19.1 and 16.9, respectively, p < 0.001). The 1-year cumulative incidences of all-cause mortality were 32.7% (95% CI 31.6-33.6%), 57.5% (55.4-59.4%) and 58.9% (56.0-61.7%) for Groups A-C, respectively (p < 0.001) **(Figure 1A)** . Compared to single event without jaundice, single event with jaundice (adjusted hazard ratio [aHR] 1.27, 95% CI 1.20-1.35) and multiple events (aHR 1.37, 95% CI 1.28-1.48) were independent risk factors for mortality. An additional 1,448 patients with multiple decompensation events were classified as further decompensation based on the expanded definition (mean Child-Pugh score 11, median MELD score 25.1). The 1-year cumulative incidences of all-cause mortality were not different between the expanded definition and the Baveno VII definition (51.3% [95% CI 50.2-52.3%] vs 46.4% [45.3-47.5%] respectively, p = 0.208) **(Figure 1B)** . Adopting the expanded definition allowed an earlier identification of further decompensation by a median 1.8 (IQR 0.3-19.3)

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months. The sensitivity analysis yielded similar results when jaundice was defined as bilirubin ≥50μmol/L. **Conclusion:** Patients with multiple decompensation events and/or jaundice had worse clinical outcomes than those with single decompensation event. Expanding the definition of further decompensation to these patients led to an earlier identification of the at-risk population, validating the use of the Baveno VIII-proposed definition of further decompensation. **Financial support:** This study is supported by the Health and Medical Research Fund of Health Bureau of HKSAR Government (Reference number: 11222426) to Jimmy Lai.

Figure 1. Cumulative incidence of mortality, (A) among Groups A-C and (B) among patients fulfilling the Baveno VII and expanded definition for further decompensation.



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1467 | ◆ CALIBRATION AND THRESHOLD PERFORMANCE OF LIVER DISEASE SEVERITY SCORES IN OPEN-HEART SURGERY: A PROPENSITY-MATCHED MULTICENTRIC ANALYSIS

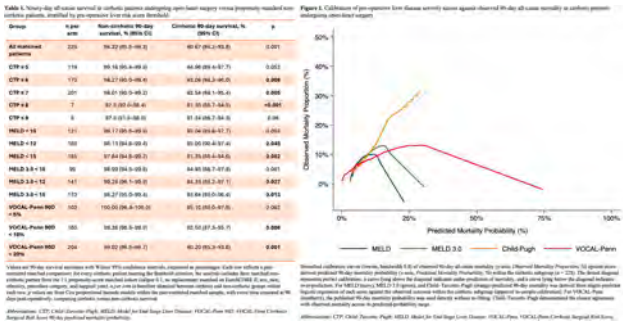
Leandro Sierra[1] Zainab Ifthikar[1] Walaa Mahmoud[2] Nicholas Ruthman[2] John McMichael[2] Tang Li[2] Omar Sims[1] William Carey[2], [1]Cleveland Clinic Foundation, [2]Cleveland Clinic

Background: Many tools have been developed to risk-stratify (RS) those with cirrhosis (C) in need of surgery. We have recently shown limitations of Mayo Clinic, and Vocal-Penn Scores in the context of open-heart surgery (OHS) (1). Aim: In patients with C undergoing OHS to 1) compare the fidelity of various RS tools in predicting mortality; 2) ascertain optimal time horizon to capture risk. **Methods:** MELD, MELD 3.0, CTP, and VOCAL-Penn (VPS) predictors of mortality were compared. We conducted a multicenter retrospective cohort study comparing adults with and without cirrhosis (C versus NoC) undergoing OHS at Cleveland Clinic Main Campus and Cleveland Clinic Florida (2014–2024). Patients on therapeutic anticoagulation without standardized washout and those with incomplete preoperative laboratories were excluded. 1:1 propensity-score matching (caliper 0.1, no replacement) on EuroSCORE II, sex, race, ethnicity, procedure category, and surgical year yielded 225 cirrhotic and 225 non-cirrhotic patients. For each score, we identified the threshold at which 30 and 90-day mortality in C diverged from matched NoC patients using Kaplan–Meier and Cox proportional hazards analyses. Score calibration was assessed graphically within the cirrhotic subgroup by lowess smoothing of observed against predicted 90-day mortality. **Results:** Thirty-day mortality did not differ significantly between C and matched NoC patients (2.22% vs 1.33%; HR 2.59, 95% CI 0.50–13.35, P = 0.26) but diverged sharply by 90 days (9.33% vs 1.78%; HR 7.48, 95% CI 2.23–25.07, P = 0.001). C patients with CTP score =5, MELD or MELD 3.0 < 10, or VPS 90 day prediction < 5% did not experience higher 90 day mortality.(Table 1) Ninety-day mortality increased with CTP score, with a threshold transition at CTP 6: CTP 5, 5.04% (HR 3.95, P = 0.052); CTP 6, 11.11% (HR 9.29, P = 0.002); CTP 7, 10.71% (HR 8.82, P = 0.008); CTP 8, 42.86% (HR 34.64, P < 0.001). On calibration (Figure 1), CTP closely tracked observed mortality across the full predicted range; MELD and MELD 3.0 over-estimated risk above predicted values of approximately 10%; VOCAL-Penn 90D showed the most pronounced miscalibration, with observed mortality plateauing near 13% despite predicted values

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reaching 75%. **Conclusion:** Cirrhosis-attributable mortality after OHS is not apparent at 30 days but emerges clearly by 90-days. OHS in C confers no added mortality risk when CTP = 5, MELD, MELD 3.0 < 10, or VPS 90 day risk < 5%. Among current RS scores, CTP had the best agreement between predicted and observed 90-day mortality; VPS, MELD, and MELD 3.0 substantially over-estimated mortality risk. These findings validate continued use of CTP as a primary means of RS in cirrhotics undergoing OHS. Development of a dedicated cardiac-surgery–specific hepatic risk score is needed.[1] **Jenkins H** et al H. JTCVS Open. 2026 Mar 6;30:101718. doi: 10.1016/j.xjon.2026.101718. eCollection 2026 Apr.PMID: 42079952



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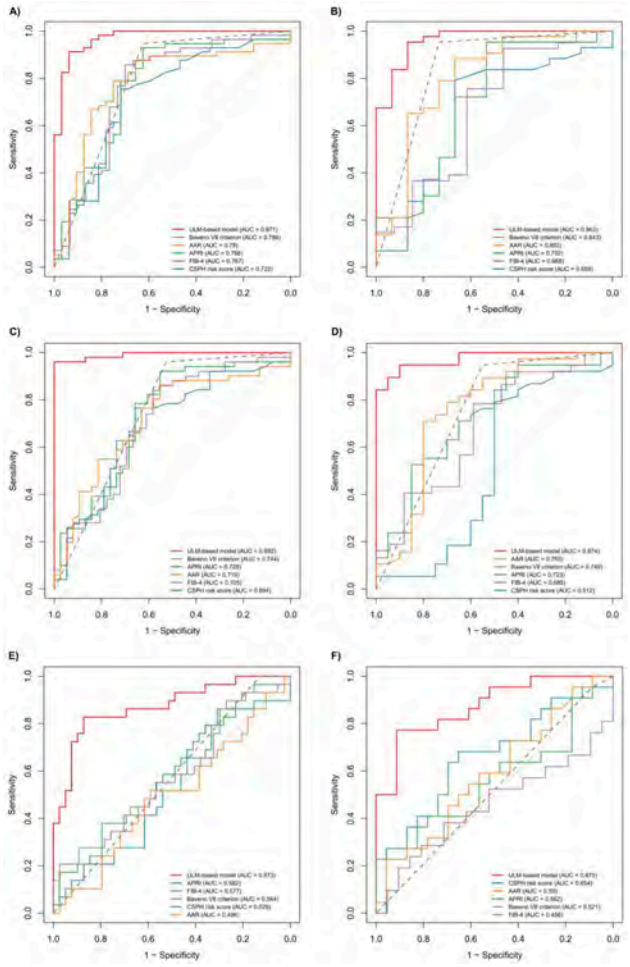
1468 | ◆ ULTRASOUND LOCALIZATION MICROSCOPY FOR DIAGNOSIS OF CLINICALLY SIGNIFICANT PORTAL HYPERTENSION: A PROSPECTIVE MULTICENTER STUDY

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Background: Hepatic venous pressure gradient (HVPG) is the gold standard for diagnosing clinically significant portal hypertension (CSPH), but its invasive nature limits routine use. Existing noninvasive methods mostly rely on indirect indicators such as liver stiffness and have diagnostic “grey zones”. Ultrasound localization microscopy (ULM) can noninvasively visualize microvascular perfusion and morphology in the liver with super-resolution. This study aimed to assess the feasibility and accuracy of ULM for noninvasive diagnosis of CSPH. **Methods:** This prospective, multicenter diagnostic study enrolled patients with chronic liver disease from eight hospitals between October 2024 and May 2026. CSPH was defined as HVPG ≥ 10 mmHg. ULM images were acquired to extract perfusion and morphological parameters, including vessel density (VD) and flow-weighted vessel density (FWVD). LASSO regression was used for feature selection, and a logistic regression prediction model was developed and internally validated in an independent validation cohort. The performance of the ULM-based model was compared with the Baveno VII criteria, APRI, and FIB-4. **Results:** A total of 147 patients (median age 52 years) were enrolled, with a CSPH prevalence of 68.0%. ULM parameters showed that, compared with the non-CSPH group, the CSPH group had significantly lower VD, FWVD, perfusion index, directional variance, and velocity entropy (all $P < 0.01$), but significantly higher velocity variance and coefficient of variation of velocity ($P < 0.01$), indicating reduced microvascular perfusion, disturbed flow, and increased vascular tortuosity in CSPH patients. The final prediction model included six variables: hemoglobin, platelet count, albumin (ALB), international normalized ratio (INR), VD, and FWVD. In the derivation cohort, the model achieved an AUC of 0.971 (95% CI: 0.931–0.996) for predicting CSPH, significantly outperforming other noninvasive scores. In the validation cohort, the AUC was 0.963 (95% CI: 0.901–0.999), with good calibration and significant net clinical benefit. The model also showed the best performance for diagnosing HVPG ≥ 12 mmHg and HVPG ≥ 20 mmHg. **Conclusion:** The ULM-based prediction models accurately diagnose HVPG ≥ 10 mmHg (CSPH), HVPG ≥ 12 mmHg, and HVPG ≥ 20 mmHg, reflecting portal pressure changes from the perspectives of microvascular perfusion and morphology. It offers excellent discrimination, calibration, and clinical utility, providing a novel imaging tool for noninvasive assessment and dynamic monitoring of portal hypertension in cirrhosis.

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1469 | ◆ ASSOCIATION OF MIDODRINE USE WITH RENAL AND TRANSPLANT OUTCOMES IN PATIENTS WITH HEPATORENAL SYNDROME–CHRONIC KIDNEY DISEASE: A PROPENSITY SCORE-MATCHED ANALYSIS

Abdullah Sohail[1] Sara Naimimohasses[1] Jackson Snyder[2], [1]The University of Iowa Hospitals and Clinics, [2]Roy J. and Lucille A. Carver College of Medicine

Background: Midodrine is frequently used as an oral vasoconstrictor in patients with cirrhosis and hepatorenal syndrome–chronic kidney disease (HRS-CKD), particularly when intravenous vasopressors or terlipressin are not feasible. However, real-world data evaluating its association with renal outcomes in this population remain limited. We assessed whether midodrine use was associated with differences in clinical outcomes at 6 months and 1 year. **Methods:** We conducted a retrospective cohort study using data from the TriNetX Research Network, which encompasses data from 109 healthcare organizations. Adults aged ≥18 years with HRS-CKD were identified using ICD-10-CM codes. The treatment cohort included patients who received midodrine; the control cohort included patients without midodrine exposure. Patients with pre-existing acute kidney failure, end-stage kidney disease, dialysis dependence, dialysis-related encounters, or prior kidney transplant were excluded. Outcomes were assessed from 1 day after the index event through 180 and 365 days. Propensity score matching was performed on demographics, liver disease diagnoses, cardiovascular comorbidities, and relevant medications, including diuretics, beta-blockers, albumin, octreotide, and terlipressin. After matching, 1,625 patients were included in each cohort. **Results:** At 180 days, mortality was similar between the control and midodrine cohorts (34.2% vs. 33.0%; OR 1.06, 95% CI 0.91–1.22; p = 0.458). Dialysis initiation occurred less frequently in the midodrine cohort (2.4% vs. 3.9%; OR 1.64, 95% CI 1.09–2.46; p = 0.016), with time-to-event analysis confirming a lower dialysis risk (HR 1.58, 95% CI 1.06–2.36; log-rank p = 0.023). Kidney transplantation (1.0% vs. 1.6%; p = 0.167) and liver transplantation (11.2% vs. 12.0%; p = 0.476) did not differ significantly between groups.At 365 days, mortality remained similar (37.1% vs. 36.0%; OR 1.05, 95% CI 0.91–1.21; p = 0.512). Dialysis initiation remained less frequent in the midodrine cohort (2.8% vs. 4.5%; OR 1.62, 95% CI 1.11–2.35; p = 0.012), with consistent findings on time-to-event analysis (HR 1.55, 95% CI 1.08–2.25; log-rank p = 0.018). Kidney transplantation and liver transplantation rates did not differ significantly between groups at 1 year. **Conclusion:** In this large propensity score-matched cohort of patients with HRS-CKD, midodrine use was associated with a significantly lower risk of dialysis initiation at both 6 months and 1 year, while mortality, kidney transplantation, and liver transplantation rates did not differ significantly. These findings suggest that midodrine may confer a renal-protective benefit in HRS-CKD, although prospective trials are required to validate these findings.

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Table 1. Baseline Characteristics Before and After Propensity Score Matching

Midodrine in hepatorenal syndrome with CKD — Control vs. Midodrine — Source: TriNetX Research network (109 HCOs)

Characteristic	Before matching				After matching			
	Control (N=1,636)	Midodrine (N=2,598)	P	SMD	Control (N=1,625)	Midodrine (N=1,625)	P	SMD
Demographics								
Age, current — yr (mean ± SD)	70.7 ± 12.6	66.9 ± 13.3	<0.001	0.315	70.6 ± 12.6	70.6 ± 12.7	0.935	0.001
Age at index — yr (mean ± SD)	64.4 ± 12.8	60.1 ± 13.2	<0.001	0.328	64.3 ± 12.8	64.2 ± 12.9	0.858	0.006
Male	1,006 (61.6%)	1,623 (61.1%)	0.733	0.011	999 (61.5%)	1,010 (62.2%)	0.691	0.014
Female	627 (38.4%)	1,158 (38.8%)	0.784	0.008	626 (38.5%)	625 (37.8%)	0.691	0.014
White	940 (57.6%)	1,680 (63.3%)	<0.001	0.118	936 (57.8%)	925 (56.9%)	0.620	0.017
Black or African American	146 (8.9%)	239 (8.0%)	0.274	0.033	145 (8.9%)	144 (8.9%)	0.961	0.002
Asian	186 (11.6%)	256 (8.5%)	0.001	0.101	186 (11.6%)	198 (12.2%)	0.568	0.019
Unknown race	298 (17.5%)	452 (15.1%)	0.036	0.064	281 (17.3%)	292 (18.0%)	0.613	0.018
Comorbidities (diagnoses)								
Fibrosis & cirrhosis of liver (K74)	1,017 (62.3%)	1,768 (59.2%)	0.040	0.063	1,012 (62.3%)	1,004 (61.8%)	0.772	0.010
Other diseases of liver (K76)	965 (58.1%)	1,695 (63.5%)	0.033	0.091	962 (59.2%)	945 (58.2%)	0.545	0.021
Hepatic failure, NEC (K72)	619 (37.9%)	1,201 (40.2%)	0.116	0.048	617 (38.0%)	589 (36.2%)	0.292	0.037
Chronic hepatitis, NEC (K73)	107 (6.6%)	151 (5.1%)	0.035	0.064	106 (6.5%)	115 (7.1%)	0.531	0.022
Other inflammatory liver disease (K75)	319 (19.5%)	458 (15.3%)	<0.001	0.110	318 (19.6%)	301 (18.5%)	0.448	0.027
Alcoholic liver disease (K70)	508 (31.2%)	1,146 (38.4%)	<0.001	0.152	507 (31.2%)	495 (30.5%)	0.649	0.016
Ascites (R18)	788 (48.3%)	1,448 (48.5%)	0.890	0.005	785 (48.3%)	766 (47.1%)	0.505	0.023
Abdominal & pelvic pain (R10)	532 (32.6%)	874 (29.3%)	0.020	0.071	529 (32.6%)	513 (31.6%)	0.548	0.021
Hypertensive diseases (I10–I1A)	1,038 (63.6%)	1,396 (46.8%)	<0.001	0.342	1,030 (63.4%)	990 (61.4%)	0.247	0.041
Other heart disease (I30–I5A)	711 (43.5%)	1,013 (33.9%)	<0.001	0.198	705 (43.4%)	680 (41.8%)	0.375	0.031
Ischemic heart disease (I20–I25)	450 (27.6%)	538 (18.0%)	<0.001	0.229	446 (27.4%)	424 (26.1%)	0.383	0.031
Cerebrovascular disease (I60–I69)	219 (13.4%)	283 (9.5%)	<0.001	0.124	219 (13.4%)	210 (12.9%)	0.678	0.015
Medications								
Diuretics	1,158 (70.8%)	2,091 (70.1%)	0.551	0.018	1,152 (70.9%)	1,126 (69.4%)	0.358	0.032
Beta-blockers / related	860 (53.9%)	1,431 (48.0%)	<0.001	0.119	876 (53.9%)	848 (52.2%)	0.325	0.035
Octreotide	151 (9.2%)	498 (16.7%)	<0.001	0.223	151 (9.3%)	120 (7.4%)	0.049	0.069
Terlipressin	173 (10.6%)	271 (9.1%)	0.096	0.051	172 (10.6%)	194 (11.9%)	0.222	0.043
Albumin (aggregated)	10 (0.6%)	10 (0.3%)	0.170	0.040	10 (0.6%)	10 (0.6%)	1.000	<0.001

Table 2. Clinical Outcomes by Follow-up Window (Propensity Score–Matched Cohorts)

Control vs. Midodrine — N = 1,625 per group — Ratios are Control relative to Midodrine (>1 = higher event rate in control)

Outcome	Follow-up	Control n (risk)	Midodrine n (risk)	Risk Ratio (95% CI)	Hazard Ratio (95% CI)	Log-rank P	Event-free survival (Control vs Midodrine)
Mortality	6 mo	556 (34.2%)	536 (33.0%)	1.04 (0.94–1.14)	1.01 (0.90–1.14)	0.826	60.5% vs 61.3%
	12 mo	603 (37.1%)	585 (36.0%)	1.03 (0.94–1.13)	1.01 (0.90–1.13)	0.910	56.3% vs 58.5%
Dialysis	6 mo	53 (3.3%)	39 (2.4%)	**1.42 (1.09–2.36)**	**1.58 (1.06–2.36)**	0.023	94.9% vs 96.5%
	12 mo	73 (4.5%)	46 (2.8%)	**1.59 (1.10–2.28)**	**1.55 (1.08–2.25)**	0.018	93.4% vs 95.3%
Renal transplant	6 mo	26 (1.6%)	17 (1.0%)	1.53 (0.83–2.81)	1.48 (0.81–2.75)	0.195	97.7% vs 98.3%
	12 mo	34 (2.1%)	25 (1.5%)	1.36 (0.82–2.27)	1.32 (0.79–2.22)	0.288	96.5% vs 97.1%
Liver transplant	6 mo	195 (12.0%)	182 (11.2%)	1.07 (0.89–1.30)	1.06 (0.86–1.28)	0.643	84.3% vs 84.9%
	12 mo	222 (13.7%)	207 (12.7%)	1.07 (0.90–1.28)	1.06 (0.87–1.27)	0.626	80.1% vs 80.7%

Disclosures: Abdullah Sohail:Nothing to Disclose, Sara Naimimohasses:Nothing to Disclose, Jackson Snyder:Nothing to Disclose.

1470 | ◆ PULMONARY HEMODYNAMIC RESPONSE TO PORTOSYSTEMIC SHUNT OCCLUSION IN PORTAL HYPERTENSION: IMPACT OF SHUNT CHARACTERISTICS ON BRTO RESPONSE

Tsuyoshi Ishikawa[1] Aika Kirihara[1] Maho Egusa[1] Natsuko Nishiyama[1] Daiki Kawamoto[1] Ryo Sasaki[1] Tatsuro Nishimura[1] Taro Takami[1], [1]Yamaguchi University Graduate School of Medicine

Background: Spontaneous portosystemic shunts (PSSs) may contribute to pulmonary hemodynamic abnormalities in portal hypertension by promoting hyperdynamic circulation and systemic exposure to vasoactive mediators. However, the effects of PSS occlusion on pulmonary hemodynamics and predictors of treatment response remain unclear. This study evaluated cardiopulmonary hemodynamic changes after balloon-occluded retrograde transvenous obliteration (BRTO) and factors associated with treatment response. **Methods:** This single-center retrospective study included 28 patients with portal hypertension and spontaneous PSSs who underwent transthoracic echocardiography both before and 1 month after initial BRTO between January 2020 and December 2025. Tricuspid regurgitation pressure gradient (TRPG), cardiac output (CO), endothelin-1 (ET-1), and 5-hydroxytryptamine (5-HT) levels were evaluated. PSS characteristics and portal-splenic hemodynamics were assessed using contrast-enhanced CT and indirect portography. **Results:** Compared with patients with lower baseline TRPG, those with high baseline TRPG ($\geq$22.0 mmHg; cohort median) more frequently had splenic vein (SpV)-derived shunts (100.0% vs 69.2%, p = 0.0203) and hepatofugal SpV flow (66.7% vs 23.1%, p = 0.0211), whereas PSS size was not associated with baseline TRPG. BRTO significantly reduced TRPG (23.8 ± 7.3 to 21.6 ± 6.5 mmHg, p = 0.0050), accompanied by significant reductions in CO (p = 0.0030), ET-1 (p = 0.0458), and 5-HT (p = 0.0248). TRPG reduction was observed in 75.0% of patients. In contrast to factors associated with baseline TRPG, PSS size, namely maximum shunt diameter, was the only factor significantly associated with TRPG reduction after BRTO (17.3 ± 4.9 vs 12.1 ± 4.4 mm, p = 0.0204). The optimal cutoff value was 12.5 mm (AUROC 0.7959, sensitivity 71.4%, specificity 81.0%). Patients with large PSSs ($\geq$12.5 mm) showed significant improvements in cardiopulmonary hemodynamics and hepatic functional reserve after BRTO, whereas those with smaller shunts showed no significant changes. **Conclusion:** PSS occlusion by BRTO improved cardiopulmonary hemodynamics in patients with portal hypertension. Larger PSS diameter was associated with greater hemodynamic response to BRTO. Imaging assessment of spontaneous PSS characteristics may help identify patients most likely to benefit from BRTO-induced cardiopulmonary hemodynamic modulation.

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1471 | ◆ ATORVASTATIN FOR PREVENTION OF FIRST HEPATIC DECOMPENSATION IN HIGH-RISK COMPENSATED CIRRHOSIS: 24-WEEK INTERIM RESULTS OF A RANDOMIZED PLACEBO-CONTROLLED TRIAL

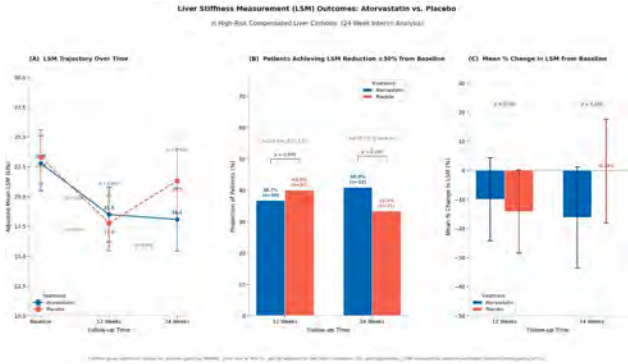
Chitchai Rattananukrom[1] Tanapon Jeerawattanasuk[1] Tanita Suttichaimongkol[1] Witsarut Manasirisuk[1]

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Background: Portal hypertension drives hepatic decompensation and mortality in liver cirrhosis, yet effective pharmacological prevention remains an unmet need. Statins' pleiotropic effects on intrahepatic vascular resistance and portal pressure offer compelling biological rationale, but prospective evidence supporting atorvastatin for preventing first decompensation in compensated cirrhosis is strikingly scarce. We conducted the first randomized controlled trial in an Asian cohort to rigorously evaluate atorvastatin 20 mg daily on dynamic liver stiffness and hepatic decompensation incidence. **Methods:** This prospective, single-center, double-blind, placebo-controlled trial enrolled adults (18–65 years) with compensated cirrhosis (CTP score ≤ 6) and ≥ 1 high-risk feature: LSM ≥ 20 kPa, platelets $\leq 150\times10^9$/L, esophageal varices, or portosystemic collaterals. Participants were randomized 1:1 to atorvastatin 20 mg or matching placebo for 96 weeks. The primary endpoint was LSM response ($\geq 30\%$ reduction or LSM < 20 kPa) at 12, 24, and 48 weeks by VCTE. Secondary endpoints included time to first hepatic decompensation and safety outcomes. Analyses used intention-to-treat MMRM and multivariable logistic regression. **Results:** Sixty-four patients were randomized (atorvastatin n = 32; placebo n = 32) with well-matched baseline LSM (23.6 vs. 23.8 kPa; P = 0.88). At 24 weeks, LSM response was achieved in 40.9% vs. 33.3% (adj.OR 2.07; 95%CI 0.46–9.39; P = 0.345). Critically, LSM trajectories diverged after week 12—the atorvastatin group demonstrated sustained decline (−16.2%) while the placebo group stabilized (−0.3%), suggesting an emerging biological effect. Within-group analysis confirmed a significant and durable LSM reduction only in the atorvastatin arm at 24 weeks (−4.71 kPa; P = 0.048). At 24 weeks, one patient (4.8%) in the placebo group developed ascites, while one patient (4.3%) in the atorvastatin group developed HCC. No additional liver-related complications or deaths were observed during follow-up. Atorvastatin was associated with modestly higher ALT at 24 weeks (+11.10 U/L; P = 0.038) and greater aminotransferase elevation $> 3\times$ULN (30.4% vs. 4.8%; P = 0.048); however, no CTCAE Grade ≥ 3 hepatotoxicity, rhabdomyolysis, or clinically significant myopathy occurred. Creatine kinase remained comparable throughout. **Conclusion:** At this 24-week interim analysis, atorvastatin 20 mg demonstrated an acceptable safety profile in high-risk compensated cirrhosis without severe hepatotoxicity or muscle injury. Although the primary endpoint did not reach statistical significance, diverging LSM trajectories and sustained within-group LSM reduction represent encouraging early biological signals. Completion of the full 96-week follow-up is essential to establish whether atorvastatin prevents hepatic decompensation in this underrepresented Asian population.



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1472 | ◆ U-SHAPED ASSOCIATION BETWEEN PORTAL PRESSURE REDUCTION AND POST-TIPS OUTCOMES SUGGESTS A RELATIVE LOW-RISK INTERVAL FOR POST-TIPS COMPLICATIONS

Zhiling Zhou[1] Dazhi Zhang[2] Qiongfang Zhang[1] Chang Shu[1] YuanKang Luo[1] HuiMin Fan[1] ZhiHan Zhang[1] Yang Lv[1], [1]Chongqing Medical University, [2]Chongqing Medical University

Background: Transjugular intrahepatic portosystemic shunt (TIPS) is an effective treatment for complications of portal hypertension, but hepatic encephalopathy (HE) remains a major limitation. Portal pressure gradient (PPG)-based targets, derived largely from the bare-stent era, remain the standard framework for procedural guidance. However, clinically relevant complications continue to occur even when target PPG reduction is achieved, suggesting that static pressure thresholds may not fully capture individual hemodynamic responses in contemporary covered-stent TIPS. Portal venous pressure (PVP) provides a direct measure of intra-procedural pressure change and may offer complementary information to PPG-based assessment. We therefore evaluated the association between portal pressure reduction and post-TIPS outcomes, with particular emphasis on hepatic encephalopathy (HE), to investigate a relative low-risk decompression range. **Methods:** We retrospectively analyzed 175 patients who underwent

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covered-stent TIPS between 2018 and 2025. Portal venous pressure (PVP) was measured before and after the procedure. Absolute (ΔPVP) and relative (ΔPVP%) pressure reductions were calculated. Post-TIPS complications included HE, variceal rebleeding, new-onset ascites or pleural effusion, and shunt dysfunction. Restricted cubic spline, Kaplan–Meier, and multivariable Cox regression analyses were performed. **Results:** During follow-up, 71 patients (40.6%) developed post-TIPS complications, including HE in 38 (21.7%). ΔPVP demonstrated significant U-shaped associations with both overall complications and HE. A relative low-risk interval for overall complications was observed at approximately 11–19 mmHg, within which HE risk was lowest at approximately 13–17 mmHg. Kaplan–Meier analyses showed significant differences across ΔPVP groups ($P = 0.043$ for overall complications; $P = 0.032$ for HE). Both lower and higher ΔPVP were independently associated with increased HE risk (both $P < 0.05$). In contrast, post-TIPS PVP was not significantly associated with outcomes, while ΔPVP% showed similar but non-significant nonlinear trends. **Conclusion:** Portal pressure reduction after covered-stent TIPS demonstrated a U-shaped association with post-procedural outcomes, suggesting a non-linear and structured relationship between decompression magnitude and clinical risk. A relative low-risk interval was identified for overall complications, within which HE risk followed a narrower distribution. These findings suggest that ΔPVP may serve as a complementary hemodynamic parameter to conventional PPG-based assessment, potentially aiding individualized risk stratification and helping to reduce post-TIPS complications in clinical practice.

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1473 | INTEGRATED CLINICAL AND EXPERIMENTAL CHARACTERIZATION OF CARDIAC REMODELING IN CHRONIC LIVER DISEASE

Hyo-Jin Park[1] Shoma Bommena[2] Ege Kacira[3] Nickolaus Lorson[1] Amaya Bruner[1] Marjan Aghajani[3] Steven Kawut[4] Tobias Jakobi[3] Shirin Doroudgar[3] Michael Fallon[5], [1]University of Arizona, College of Medicine-Phoenix, [2]Banner University Medical Center-Tucson, University of Arizona, College of Medicine-Tucson, [3]Translational Cardiovascular Research Center, University of Arizona, College of Medicine-Phoenix, [4]Perelman School of Medicine, University of Pennsylvania, [5]Banner University Medical Center-Phoenix, University of Arizona, College of Medicine-Phoenix

Background: Cardiac dysfunction in chronic liver disease is a major contributor to morbidity and mortality despite the absence of overt cardiovascular disease. Although 30-70% of patients with advanced liver disease develop cardiac abnormalities, the mechanisms linking liver fibrosis to myocardial remodeling remain poorly defined. We hypothesized that liver fibrosis generates a distinct circulating milieu that drives cardiac structural and functional adaption. This study aimed to define myocardial phenogroups in cirrhosis and identify liver-derived mediators associated with cardiac remodeling and dysfunction. **Methods:** We performed unbiased clinical and echocardiographic phenotyping analysis in 454 adults with cirrhosis from the Pulmonary Vascular Complications of Liver Disease 2 cohort. Unsupervised machine learning integrated cardiac and clinical variables to identify myocardial phenogroups associated with liver disease severity and outcomes. Circulating mediators were assessed using targeted plasma biomarker analysis. Complementary animal studies utilized common bile duct ligation (CBDL)-induced liver fibrosis and partial portal vein ligation (PPVL)-induced portal hypertension mouse models. Advanced echocardiography assessed cardiac structure and function, and plasma endostatin levels were quantified by ELISA. **Results:** Three myocardial phenogroups were identified in cirrhosis. Group 1 “Reductive” demonstrated the lowest left ventricular mass index (LVMI), preserved ejection fraction (EF), low stroke volume, and compensatory increased heart rates, despite the lowest MELD scores, indicating uncoupling of mortality from liver disease severity. Group 2 “Concentric Remodeling” exhibited increased LVMI and metabolic dysregulation, while Group 3 “Hyperdynamic/Eccentric” demonstrated the highest MELD scores, frailty, and eccentric remodeling. Distict circulating factor signatures differentiated each phenogroup. Notably, Group 1 patients exhibited significantly elevated circulating endostatin, a collagen XVIII-derived factor, compared with other groups. In experimental studies, CBDL mice developed reduced LVMI and preserved EF, recapitulating key features of human Group 1 phenotype. Both CBDL and PPVL models exhibited diastolic dysfunction, although dysfunction was more severe in CBDL mice. Consistent with human findings, circulating endostatin levels were significantly elevated in CBDL but not PPVL mice, supporting a fibrosis-dependent mechanism linking liver injury to myocardial remodeling. **Conclusion:** Cardiac dysfunction in chronic liver disease comprises distinct

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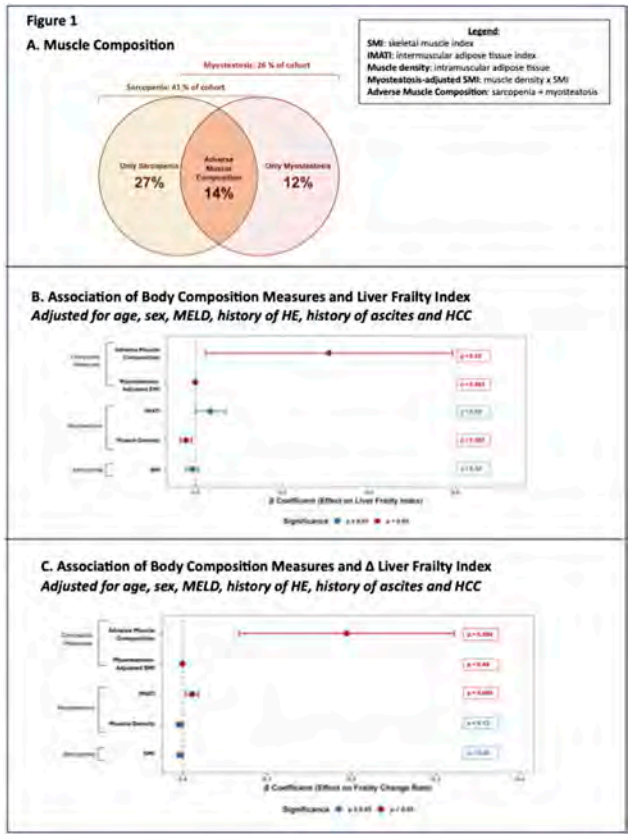
myocardial phenogroups associated with unique circulating factor profiles and clinical outcomes. Identification of fibrosis-associated liver factors provides a mechanistic framework for liver-heart crosstalk and highlights endostatin signaling as a potential therapeutic target.

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1474 | MUSCLE QUALITY, RATHER THAN MUSCLE MASS ALONE, IS INDEPENDENTLY ASSOCIATED WITH FRAILTY SEVERITY AND FRAILTY PROGRESSION IN CIRRHOSIS

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Background: Frailty is associated with increased mortality in cirrhosis. Although frailty is linked to sarcopenia, there is poor correlation between the Liver Frailty Index (LFI) and the Skeletal Muscle Index (SMI), the imaging gold standard measure of sarcopenia. Myosteatosis, characterized by intra/intermuscular fat deposition, has emerged as a predictor of mortality in cirrhosis and may better reflect impaired muscle function than muscle quantity alone. We hypothesized that poor muscle quality is a driver of frailty in cirrhosis. **Methods:** We performed a retrospective single center study of adults with cirrhosis who underwent abdominal CT within 6 months of LFI assessment, with ≥ 1 follow-up LFI. Muscle composition was assessed at the L3 vertebral level. Sarcopenia was measured using SMI. Intramuscular fat was measured by muscle density (Hounsfield units) and intermuscular fat by height-adjusted intermuscular adipose tissue (IMATI). Composite measures of muscle quality and quantity included the "myosteatosis-adjusted SMI," defined as SMI x muscle density, and "adverse muscle composition," defined as concomitant sarcopenia and myosteatosis using established sex-specific cutoffs. Frailty progression was assessed by longitudinal change in LFI (ΔLFI - change in LFI between frailty assessments adjusted for time). Multivariable linear and logistic regression analyses evaluated associations between body composition parameters and frailty outcomes. **Results:** Among 177 patients (68% male, mean age 60 ± 8 years, mean MELD 13 ± 5), 49% had ascites, 43% hepatic encephalopathy (HE) and 72% hepatocellular carcinoma (HCC). Mean baseline LFI was 3.7 ± 0.8: 24% were frail, 64% pre-frail and 12% robust. On baseline CT, 41% were sarcopenic, 26% had myosteatosis and 14% met criteria for adverse muscle composition (Figure 1A). On multivariable analysis adjusting for age, sex, MELD, ascites, HE and HCC, lower muscle density (greater intramuscular fat) (estimate [est] -0.02, $p = 0.002$) and adverse muscle composition (est 0.31, $p = 0.03$) were associated with greater frailty (higher LFI). Higher myosteatosis-adjusted SMI (est -0.0003, $p = 0.003$) was associated with less frailty (lower LFI), whereas standard SMI was not associated with frailty (est -0.007, $p = 0.34$) (Figure 1B). Among robust patients, IMATI (est 0.01, $p = 0.005$), myosteatosis-adjusted SMI (est -6.84 x 10^{-5}, $p = 0.04$) and adverse muscle composition (est 0.19, $p = 0.004$)—but not sarcopenia alone—were associated with ΔLFI (Figure 1C). **Conclusion:** Muscle impairment, reflected by myosteatosis and adverse muscle composition, is independently associated with frailty and progression of frailty in cirrhosis. These findings support the incorporation of muscle composition assessment into frailty evaluation and identify robust patients with adverse muscle composition as high-yield targets for early preventative frailty interventions.



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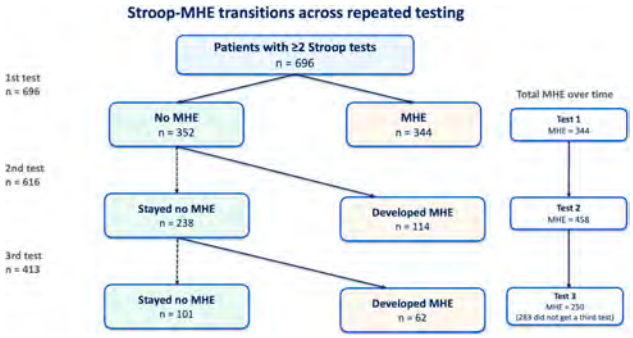
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1475 | STROOP-DEFINED MINIMAL HEPATIC ENCEPHALOPATHY IS STABLE AND RESPONSIVE TO CLINICAL EVENTS IN A MULTI-CENTER CIRRHOSIS COHORT

Vinay Jahagirdar[1] Scott Silvey[2] Dan Park[1] Ali Khan[1] K Rajender Reddy[3] Puneeta Tandon[4] Jennifer Lai[5] Jacqueline O'Leary[6] Florence Wong[7] Guadalupe Garcia-Tsao[8] Hugo Vargas[9] Philip Vutien[10] Scott Biggins[11] Brian Bush[1] Jasmohan Bajaj[12], [1]Virginia Commonwealth University, Richmond, VA, [2]Virginia Commonwealth Universtiy, Richmond, VA, [3]University of Pennsylvania, Philadelphia, PA, [4]University of Alberta, [5]University of California, San Francisco, CA, [6]UT Southwestern Medical Center, North Texas VA Health Care System, Dallas, TX, [7]University of Toronto, [8]Yale School of Medicine, New Haven, CT, [9]Mayo Clinic Arizona, Scottsdale, AZ, [10]University of Washington, Seattle, WA, [11]University of Pittsburgh, Pittsburgh, PA, [12]Virginia Commonwealth University

Background: Background: Minimal hepatic encephalopathy (MHE) is a neurocognitive complication of cirrhosis that precedes overt HE (OHE), hospitalizations & death. With longer timeframes needed for hard endpoints to occur in clinical trials, considering Stroop-defined MHE as a potential surrogate endpoint may be possible. However, the stability of MHE and responsiveness of this diagnosis to important clinical events. Aim: To define MHE stability using Stroop & determine if it changes over time in those with and without subsequent clinical events. **Methods:** Outpatients with cirrhosis from two tertiary centers and the separate NACSELD3 cohort, all of who underwent Stroop testing at ≥ 2 time points. US-based norms defined MHE and intermediate clinical events (hospitalizations, OHE with new lactulose/rifaximin) were collected. Intraclass correlation coefficients (ICCs) assessed within-patient stability. Generalized linear mixed-effects models with logit link and patient-specific random intercepts evaluated associations between MHE and subsequent events, and between interval events and Stroop-MHE at the next test. The latter outcome was persistent MHE or progression from no-MHE to MHE **Results:** The cohort included 696 patients who underwent ≥ 2 Stroop tests (Fig A). Median age was 61 years, 50% men, 37% alcohol-related cirrhosis & median MELD 11. At baseline 49% had MHE, who persisted with MHE throughout (ICC: 0.76); none went from MHE to no-MHE. Median intervals between tests were 6 months. Of the 352 no-MHE patients,32% developed MHE on the second test, and 26% developed MHE after the second test. Clinical events occurred in 25.5% between tests 1 & 2 and 23.3% after test 2. MHE patients were more likely to develop a clinical event vs those without MHE (30.5% vs 16.1%, $p < 0.001$). Across repeated intervals, clinical events were associated with higher odds of Stroop-MHE (OR 2.10, 95% CI 1.58–2.79; $p < 0.001$). Clinical events were also associated with persistence of previously detected MHE or progression to MHE from no-MHE at the next assessment (OR 1.82, 1.03–3.22; $p = 0.039$). **Conclusion:** In a multi-center cohort, Stroop-defined MHE was present in almost half of patients and did not regress. With clinical events, a quarter of patients without MHE developed MHE over time. Stroop-defined MHE is stable when patients are stable and responsive to clinical events, and with prior studies indicating prediction of OHE could be a potential surrogate.



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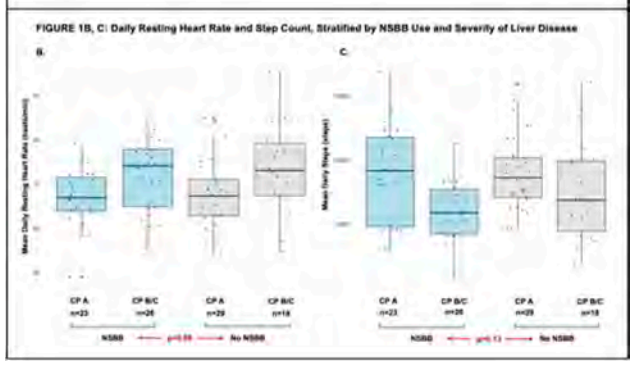
1476 | MUCH ADO ABOUT HEART RATE: REASSESSING BETA-BLOCKER TOLERABILITY IN PATIENTS WITH CIRRHOSIS

Avesh Thuluvath[1] Kamaryn Tanner[2] Jessica Siguencia[3] Olivia Blocker[3] Joel Castro[1] Nayda Pichardo-Fernandez[1] Robert Brown[3] Alan Cohen[2] Adam Buckholz[4] Elizabeth Verna[1], [1]Columbia University Medical Center, [2]Mailman School of Public Health, Columbia University, [3]Weill Cornell Medicine, [4]New York Presbyterian Hospital Program

Background: Non-selective beta blockers (NSBB) are a cornerstone of cirrhosis management and increasingly used to prevent hepatic decompensation. The benefits of NSBBs are well-established but their true effect on resting heart rate (RHR) remains unclear, as RHR data are limited to intermittent clinic visits. Moreover, clinicians may underutilize NSBBs given concerns over fatigue or bradycardia. We used digital wearables (Oura Rings) to assess the association between NSBBs, RHR and physical activity in cirrhosis. **Methods:** Adults (≥18 years) with cirrhosis were prospectively enrolled at two centers from 8/2023-11/2025. Those on selective beta-blockers were excluded. Patients completed the Chronic Liver Disease Questionnaire (CLDQ) and were provided Oura rings to measure RHR and daily steps for 6 months. Linear mixed effects models estimated the association between NSBBs and primary outcomes (RHR, daily steps and baseline CLDQ activity/fatigue scores). **Results:** Of the 96 patients (Figure 1A) included, 49% were on a NSBB (carvedilol/nadolol/propranolol). Those on a NSBB had a higher mean MELD (11.2 vs. 9.3, p = 0.04) and were more likely to have a history of variceal hemorrhage (25 vs 6%, p = 0.03) than those not on a NSBB. Overall, the mean RHR was 69.2 (± 8.6) beats/min and median daily steps was 7401 (IQR 4651-9652) steps/day. Compared to those not on a NSBB, those on a NSBB had a similar mean RHR (69.7 vs 69.7 beats/min, p = 0.98), median daily step count (6997 vs 7904 steps/day, p = 0.13), CLDQ fatigue score (4.2 vs 4.1, p = 0.61) and CLDQ activity score (4.4 vs 4.2, p = 0.57) (Figure 1B,C). The mean RHR was higher (72.2 vs. 66.7 beats/min, p = 0.001) in those with CP B/C cirrhosis compared to those with CP A cirrhosis. The median daily step count (6403 vs. 8219 steps/day, p = 0.001), mean CLDQ activity score (3.9 vs 4.7, p = 0.02) and CLDQ activity score (3.8 vs 4.4, p = 0.02) were lower in those with CP B/C cirrhosis compared to those with CP A cirrhosis. After adjusting for age, sex, CP status and weekday/weekend status (given changes in physical activity on weekends), NSBB use was not associated with the log of daily steps (estimate [est] -0.12, p = 0.22), RHR (estimate -0.14, p = 0.93), CLDQ fatigue score (est 0.18, p = 0.55) or CLDQ activity score (est 0.25, p = 0.46). CT B/C status was associated with a higher RHR (est 5.92, p < 0.001) and lower log daily step count (est -0.37, p < 0.001), CLDQ fatigue (est -0.90, p = 0.003) and CLDQ activity (est -1.13, p = 0.001) scores on multivariable analysis. **Conclusion:** NSBB use is not associated with lower RHR or activity levels in cirrhosis. Non-adherence cannot be excluded, but our findings suggest that clinicians are not optimizing NSBB dose and should not be overly concerned that NSBBs will cause symptomatic bradycardia or decreased physical activity. Use of digital wearables offers the ability to monitor and maximize NSBB use while minimizing potential toxicity.

FIGURE 1A: Clinical Characteristics, Stratified by NSBB Use

Clinical Characteristics	Total n=96	No NSBB n=47	NSBB n=49	P-value
Age, mean (SD)	54.9 (11.1)	54.0 (11.9)	55.7 (10.3)	0.47
Female, N (%)	46 (47.9)	26 (53.3)	20 (40.8)	0.22
MELD 3.0, mean (SD)	10.3 (4.6)	9.3 (4.3)	11.2 (4.8)	**0.04**
CP Category, n (%)				0.21
CP A	52 (54.2)	29 (61.7)	23 (46.9)	
CP B/C	44 (45.8)	18 (38.3)	26 (53.1)	
Decompensated, n (%)	64 (66.1)	25 (54.3)	39 (81.2)	**0.01**
History of HE, n (%)	37 (39.4)	17 (37.0)	20 (41.7)	0.80
History of Ascites, n (%)	34 (35.4)	12 (25.5)	22 (44.9)	0.08
History of Variceal Hemorrhage, n (%)	15 (15.8)	3 (6.4)	12 (25.0)	**0.03**



Disclosures: Avesh Thuluvath:Nothing to Disclose, Kamaryn Tanner:Nothing to Disclose, Jessica Siguencia:Nothing to Disclose, Olivia Blocker:Nothing to Disclose, Joel Castro:Nothing to Disclose, Nayda Pichardo-Fernandez:Nothing to Disclose, Robert Brown:Gilead: Consultant, Intercept: Consultant, Abbvie: Consultant, Madrigal: Consultant, GSK: Consultant, eGenesis: Consultant, mirum: Consultant, mallinckrodt: Consultant, Alan Cohen:Nothing to Disclose, Adam Buckholz:Tortugas Neurosciences: Consultant, Elizabeth Verna:Nothing to Disclose.

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1477 | COMMERCIAL WEARABLES RAPIDLY ESTABLISH RELIABLE DEEP SLEEP HRV BASELINES THAT REFLECT LIVER DISEASE SEVERITY

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Background: Heart rate variability (HRV) is a non-invasive marker of autonomic dysfunction associated with cirrhosis, but its use as a longitudinal biomarker is limited by circadian variability and physiologic fluctuation during wakefulness. Sleep may provide an ideal window for assessment because HRV can be measured repeatedly and passively under largely stable conditions. We evaluated whether sleep-stage specific nocturnal HRV identifies disease-related abnormalities and establishes stable individualized baselines for longitudinal monitoring. **Methods:** We analyzed longitudinal wearable data from 104 participants with cirrhosis using the Oura Ring and ≥14 valid wear days with ≥80% wear time and analyzable sleep-stage HRV. HRV was calculated as RMSSD from 30-second sleep-stage epochs and summarized across deep, light, REM, and awake periods. Mixed-effects models evaluated associations between MELD 3.0 or Child-Turcotte-Pugh (CTP) score and sleep-stage specific HRV after adjustment for age, sex, and beta blocker use. Night-to-night HRV variability was compared between compensated and decompensated cirrhosis. Within-individual reliability of nightly HRV was assessed using the single-night intraclass correlation (ICC) and the Spearman-Brown projection of the number of nights required for a reliable per-person average; the stabilization of each participant's running median was summarized as the proportion within 10% of their final value by a given number of tracking days. **Results:** Across 12,221 analyzed nights, higher MELD 3.0 was associated with lower nocturnal HRV overall (-0.84 ms RMSSD per MELD point, 95% CI -1.27, -0.41). The strongest association was observed during deep sleep, where a 1-SD increase in MELD corresponded to a 4.29 ms reduction in RMSSD (95% CI -6.49, -2.09), with similar directional effects across sleep stages (A). CTP score demonstrated a similar stage-specific pattern. Decompensated disease was associated with significantly greater night-to-night instability in deep sleep HRV, including increased within-subject variability on rolling 7-day analyses (adjusted fold-change in SD 1.16, adjusted p = 0.023). Reliable individualized HRV estimates were achieved rapidly (deep-sleep single-night ICC 0.55; reliability ≥0.80 within 4 nights, while within-individual medians stabilized quickly, 75% within 10% of stable values by day 14 (B-D). **Conclusion:** Advanced cirrhosis was associated with progressive impairment and greater instability of deep sleep HRV, suggesting that restorative sleep may represent a vulnerable physiologic state in progressive liver disease with associated autonomic dysfunction. Commercial wearables captured longitudinal HRV abnormalities and suggest deep-sleep HRV may represent a scalable digital biomarker capable of establishing both stable individualized baselines and detecting physiologic deterioration before clinically apparent decompensation.

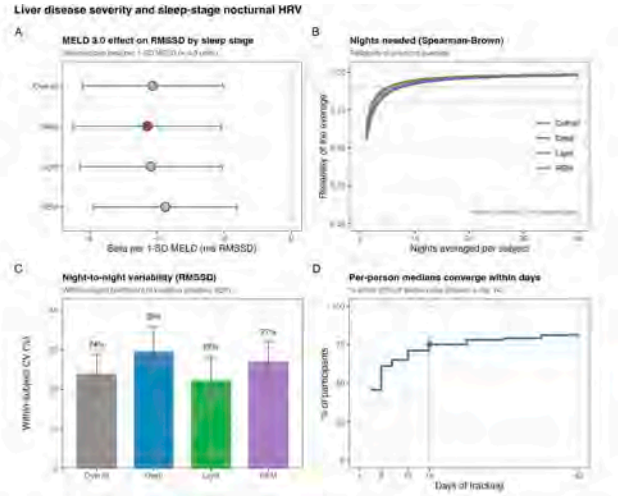


Figure 1. Sleep-stage nocturnal HRV and liver disease severity. (A) Standardized MELD 3.0 effect on mean nightly RMSSD by sleep stage and overall: beta (95% Wald confidence interval) per 1-SD increase in MELD 3.0 (1 SD = 4.9 units); negative coefficients across strata indicate lower HRV at higher disease severity. Linear mixed-effects models with subject random intercept, adjusted for age and beta-blocker use. (B) Spearman-Brown reliability of a k-night per-subject average by stage, derived from single-night intraclass correlations. Reference lines mark reliability 0.8 (dotted) and 0.9 (dashed); annotation gives the median nights collected per subject. (C) Within-subject coefficient of variation of nightly RMSSD by stage, shown as median (bar) and IQR (error bars) across subjects with at least 5 valid nights per stratum. (D) Within-individual establishment of a personal deep-sleep HRV baseline: percentage of participants whose cumulative running median of nightly RMSSD falls within 10% of their final value by elapsed day of tracking (final value anchored on subjects with at least 14 valid nights). Rapid convergence supports the use of wearable nocturnal HRV for remote monitoring, where a stable individual baseline is the reference against which clinically meaningful change is detected. Vertical line at day 14.

Disclosures: Adam Buckholz:Tortugas Neurosciences: Consultant, Himel Mallick:Nothing to Disclose, Avesh Thuluvath:Nothing to Disclose, Alec Chang: Nothing to Disclose, Jayden Maramis:Nothing to Disclose, Lara Phipps:Nothing to Disclose, Ana Krieger:Nothing to Disclose, Robert Brown:Gilead: Consultant, Intercept: Consultant, Abbvie: Consultant, Madrigal: Consultant, GSK: Consultant, eGenesis: Consultant, mirum: Consultant, mallinckrodt: Consultant.

1478 | RECOMPENSATION AND RENAL RECOVERY AFTER TIPS PLACEMENT: A MULTICENTER RETROSPECTIVE COHORT STUDY

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Background: Transjugular intrahepatic portosystemic shunt (TIPS), commonly performed in appropriate patients with refractory ascites and/or variceal bleeding, has been associated with improvement in liver disease severity. Recompensation, an emerging entity in the natural history of liver disease, is defined as per Baveno VII consensus as resolution of ascites without diuretics, hepatic encephalopathy without lactulose or rifaximin, and absence of recurrent variceal hemorrhage for at least 12 months, along with stable improvement in liver function tests. Although recompensation is defined in the setting of removal, suppression, or cure of the primary etiology of cirrhosis, recompensation has been observed after TIPS. However, the data on this are limited. **Methods:** We conducted a multicenter retrospective study of adults with cirrhosis who underwent TIPS at three tertiary academic institutions. The following outcomes were examined at 1 year: patient survival, improvement in MELD score and in renal function, hepatic recompensation as per Baveno VII consensus definition, and clinical (modified) recompensation, defined as resolution of decompensation events (absence of ascites, hepatic encephalopathy, or variceal bleeding), bilirubin ≤ 1.1, INR ≤ 1.1, and albumin ≥ 3.5. Collected variables included procedure date, indication, cirrhosis etiology, bilirubin, creatinine, sodium, albumin, INR, MELD score, age, sex, ethnicity, survival status, recompensation date, and last follow-up. **Results:** Among 644 patients (mean age 57.9 yrs., 56.4% male), 78.8% survived by 1 year after TIPS (59.6% for refractory ascites and 38.4% for variceal bleeding). A total of 32 liver transplants (LT) were performed within 12 months, with LT-free survival of 73.9%. MELD score worsened or decreased by < 3 in 36%, decreased by 3 to 5 points in 3.5%, and decreased by ≥ 5 in 4.2%, while this was indeterminate in 56.2% of cases. Using a cutoff of 10, 23% had MELD ≥ 10, 22% had MELD < 10, and 55% were indeterminate. Among 77 patients with pre-TIPS creatinine > 1.5 mg/dL, 17% improved to < 1.5 mg/dL, 24.7% improved but remained ≥ 1.5 mg/dL, and 58.3% were indeterminate. In a subgroup of 251 patients, 87 (34.7%) achieved recompensation, while 10 patients (4% of the subgroup) achieved clinical (modified) recompensation. The data were indeterminate in 50.2% patients. **Conclusion:** In this multicenter cohort, about 79% of patients survived at 1 year, with about 74% surviving without LT. Liver disease improved in a significant proportion of patients, with over a third of patients achieving recompensation. Clinical modified recompensation was observed in 4% of patients. Future prospective studies are needed to longitudinally assess liver function, renal function, and control of cirrhosis etiology to better identify independent predictors and effects of recompensation in patients with decompensated cirrhosis who undergo placement of TIPS.

Disclosures: Jamil Abdo:Nothing to Disclose, Wanyu Zhang:Nothing to Disclose, Gavisha Waidyaratne: Nothing to Disclose, Kanit Bunnag:Nothing to Disclose, Harsh Tiwari:Nothing to Disclose, Eisha Saadat:Nothing to Disclose, Suvisesh Pothuraju:Nothing to Disclose, Shahzad Ashraf:Nothing to Disclose, Sajid Jalil: Nothing to Disclose, Khalid Mumtaz:Nothing to Disclose, Paul Kwo:Arbutus: Advisor, Aligos: Advisor, Ausper Bio: Grant/Research Support, Altimmune: Grant/Research Support, Amgen: Advisor, Eiger: Consultant, Eiger: Grant/Research Support, Inventiva: Consultant, Novo Nordisk: Consultant, Novo Nordisk: Grant/Research Support, Takeda: Grant/Research Support, Madrigal: Grant/Research Support, Gilead: Consultant, Gilead: Grant/Research Support, Salix: Advisor, Ultragenyx: Grant/Research Support, Hepquant: Consultant, Target Registries: Grant/Research Support, Abbvie: Consultant, Mallinckrodt: Advisor, Takeda: Grant/Research Support, Genentech: Consultant, Glaxo Smith Kline: Consultant, Akero: Grant/Research Support, 89Bio: Grant/Research Support, Vir Bio: Grant/Research Support, Precision BioSciences: Consultant, Tune Therapeutics: Consultant, Mirum: Consultant, Target Registries: Advisor, Takeda: Advisor, Lygenesis: Advisor, Ausper Bio: Advisor, Maiying Kong:Nothing to Disclose, Ashwani Singal: Madrigal: Speaking and Teaching, Pleiogenix: Stock – privately held company, Pleiogenix: Consultant, CLD Foundation: Advisor, Medical Speaker's Network: Speaking and Teaching, Up-to-Date: Royalties or patent beneficiary, Medscape: Speaking and Teaching, University of Louisville School of Medicine: Employee, NIAAA: Grant/Research Support, Gastro Endo News: Executive role, Durect: Advisor, University of Louisville Health: Other.

1479 | ASSOCIATION OF LEFT VENTRICULAR EJECTION FRACTION WITH TERLIPRESSIN RESPONSE AND SAFETY IN HEPATORENAL SYNDROME-ACUTE KIDNEY INJURY: RESULTS FROM THE HRS-HARMONY CONSORTIUM

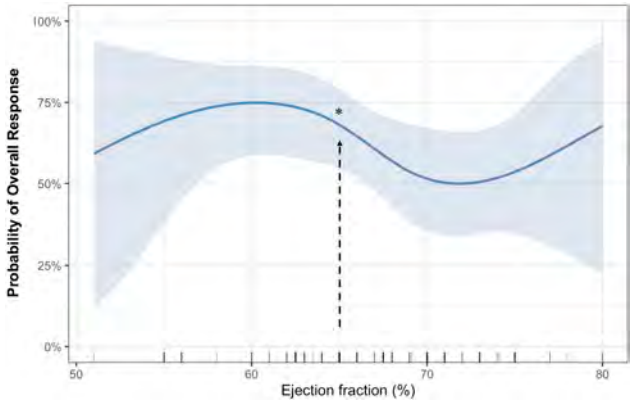
Sanad Dawod[1] Neev Patel[2] Andrew Allegretti[3] Manhal Izzy[4] Tianqi Ouyang[3] Sydney Whittaker[5] Jevon Robinson[3] J. Pedro Teixeira[6] Adam Dossaji[7] Xingxing

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Background: Response to terlipressin in hepatorenal syndrome-acute kidney injury (HRS-AKI) is variable, and practical predictors of non-response or intolerance are limited. Hyperdynamic circulatory physiology may influence response and cardiopulmonary safety in HRS-AKI. We tested whether left ventricular ejection fraction (EF), a routinely reported marker of hyperdynamic circulation, was associated with overall response, terlipressin-associated cardiopulmonary decompensation, and 90-day mortality. **Methods:** We analyzed consecutive HRS-AKI patients treated with terlipressin in the HRS-HARMONY registry (n = 243) who had transthoracic echocardiography (TTE) prior to or on the day of terlipressin initiation (n = 107). The primary outcome was overall response, defined as complete or partial response. Secondary outcomes were terlipressin-associated cardiopulmonary decompensation (respiratory failure and/or volume overload) and 90-day mortality. The relationship between EF and Overall Response was evaluated using cubic spline logistic regression. Youden's index identified an optimal EF threshold, and outcomes were compared above and below this threshold. **Results:** Median age was 58 years, 61% were male, 63% had alcohol-associated cirrhosis, 53% had refractory ascites, median MELD 3.0 was 31 (IQR 26–36), and 43% had ACLF grade 3. Median EF was 66% (IQR 63–71), and no patient had EF < 50%. Overall response occurred in 67 patients (63%), cardiopulmonary decompensation in 10 (9.3%), and 90-day mortality in 41 (38%). Cubic spline modeling suggested lower predicted response probabilities at higher EF values, with a potential inflection near 65% (**Figure**). Youden's index identified 64.5% as the optimal EF threshold; using 65% as a clinically interpretable cutoff, 71 patients had EF ≥ 65% and 36 had EF < 65%. EF < 65% was more common among responders than non-responders (43.3% vs 17.5%; p = 0.012), whereas EF ≥ 65% was more common among non-responders (82.5% vs 56.7%). Cardiopulmonary decompensation also clustered at higher EF: affected patients had higher median EF (69.5% vs 66.0%; p = 0.025), and all events occurred in patients with EF ≥ 65% (10/10; p = 0.044). EF was not significantly associated with 90-day mortality; EF ≥ 65% was present in 70.7% of patients who died and 63.6% of survivors (p = 0.586). **Conclusion:** In this multicenter real-world cohort of terlipressin-treated HRS-AKI, EF ≥ 65% was associated with lower overall response and terlipressin-associated cardiopulmonary decompensation, but not 90-day mortality. These findings raise the possibility that a hyperdynamic circulatory phenotype contributes to terlipressin non-response and cardiopulmonary intolerance. Prospective echocardiographic studies are needed to validate EF as a pragmatic risk marker and define which cardiac parameters best predict terlipressin response and safety.



Disclosures: Sanad Dawod:Nothing to Disclose, Neev Patel:Nothing to Disclose, Andrew Allegretti:Nothing to Disclose, Manhal Izzy:Mallinckrodt: Speaking and Teaching, Madrigal: Advisor, Natera: Advisor, Mirum: Advisor, Tianqi Ouyang:Nothing to Disclose, Sydney Whittaker: Nothing to Disclose, Jevon Robinson:Nothing to Disclose, J. Pedro Teixeira:Eli Lilly: Stock - publicly traded company, Novo Nordisk: Stock - publicly traded company, Pfizer: Stock - publicly traded company, Outset Medical: Consultant, Jolla Pharmaceutical Company/Innoviva: Grant/Research Support, Eli Lilly and Company: Stock - publicly traded company, Novo Nordisk A/S: Stock - publicly traded company, Pfizer Inc.: Stock - publicly traded company, Mallinckrodt: Consultant, Vantive: Consultant, Talphera: Consultant, Adam Dossaji:Nothing to Disclose, Xingxing Cheng:Nothing to Disclose, Kavish Patidar:Madrigal Pharmaceuticals: Medical Advisory Board, Mallincrodt Pharmaceuticals: Consultant, HepQaunt: Consultant, Mallinckrodt Pharmaceuticals: Medical Advisory Board, OrganOx: Advisor, Madrigal Pharmaceuticals: Advisor, Keenova Therapeutics: Advisor and Consultant., Keenova Therapeuatics: Advisor and Consultant, Novo Nordisk: Advisor, HepQaunt: Consultant, Keenova Therapeutics: Advisor and Consultant, HepQuant: Consultant.

1480 | HEPATIC OUTCOMES AND MORTALITY ASSOCIATED WITH GLP-1 RECEPTOR AGONISTS AND SGLT2 INHIBITORS IN PATIENTS WITH CIRRHOSIS AND TYPE 2 DIABETES

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Background: Patients with cirrhosis and type 2 diabetes mellitus (T2DM) are at increased risk for hepatocellular carcinoma (HCC), hepatic decompensation, and mortality. While glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium-glucose cotransporter-2 (SGLT2) inhibitors improve cardiometabolic outcomes, their comparative hepatic benefits in patients with cirrhosis remain poorly defined. **Methods:** We conducted a retrospective cohort study using the TriNetX U.S. Collaborative Network. Adults ≥18 years with T2DM and cirrhosis were included, excluding those with prior HCC or liver transplantation. Patients were categorized into GLP-1 RA, SGLT2 inhibitor, or control (other antidiabetic therapies without GLP-1 or SGLT2 exposure) groups, with mutual exposure excluded. Outcomes assessed ≥30 days after the index event and included HCC, hepatic decompensation, all-cause mortality, liver transplantation, and ICU admission. One-to-one propensity score matching adjusted for demographics, comorbidities, medications, and laboratory values. Adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs) were reported. **Results:** After matching, 22,362 patients per group were included in the GLP-1 RA versus SGLT2 comparison. GLP-1 RA use was associated with lower risks of HCC (6.5% vs 7.3%; aHR 0.80, 95% CI 0.74–0.85), hepatic decompensation (21.1% vs 23.6%; aHR 0.78, 95% CI 0.75–0.81), all-cause mortality (aHR 0.87, 95% CI 0.83–0.92), and ICU admission (13.8% vs 15.1%; aHR 0.78, 95% CI 0.74–0.81) (all $p < 0.001$). Liver transplantation rates were low and did not differ significantly.Compared with matched controls, GLP-1 users had a significantly lower risk of HCC (aHR 0.74, 95% CI 0.69–0.78; $p < 0.001$), all-cause mortality (aHR 0.59, 95% CI 0.56–0.61; $p < 0.001$), and hepatic decompensation (aHR 0.61, 95% CI 0.59–0.63; $p < 0.001$). LT rates were lower in the GLP-1 cohort (aHR 0.71, 95% CI 0.60–0.83; $p < 0.001$) and ICU admissions (aHR 0.65, 95% CI 0.63–0.68; $p < 0.001$). Compared to matched controls, HCC was lower in the SGLT2 cohort (aHR 0.94, 95% CI 0.89–1.00; $p = 0.04$), in addition to all-cause mortality (aHR 0.70, 95% CI 0.68–0.72; $p < 0.001$), hepatic decompensation (aHR 0.82, 95% CI 0.80–0.85; $p < 0.001$), and ICU admission (aHR 0.92, 95% CI 0.89–0.95; $p < 0.001$). LT was infrequent and did not differ significantly between groups (aHR 0.89, 95% CI 0.75–1.06; $p = 0.19$). **Conclusion:** In patients with cirrhosis and T2DM, GLP-1 receptor agonists and SGLT2 inhibitors are associated with significantly improved hepatic outcomes and survival compared with other antidiabetic therapies. GLP-1 RAs demonstrated the greatest overall benefit, including reduced risks of HCC, hepatic decompensation, and mortality. These findings support preferential use of incretin-based and SGLT2 therapies in this high-risk population.

Characteristic	After Matching GLP-1 (n = 22,362)	After Matching SGLT2 (n = 22,362)
Age, mean ± SD (years)	63.3 ± 10.5	63.3 ± 10.9
Female sex, n (%)	10,366 (46.4)	10,224 (45.7)
White race, n (%)	16,368 (73.2)	16,427 (73.5)
Black race, n (%)	2,547 (11.4)	2,467 (11.0)
Hispanic ethnicity, n (%)	2,453 (11.0)	2,775 (12.4)
Hypertension, n (%)	17,728 (79.3)	17,842 (79.8)
Ischemic heart disease, n (%)	8,639 (38.6)	8,652 (38.7)
Heart failure, n (%)	5,937 (26.5)	5,950 (26.6)
Chronic kidney disease, n (%)	6,920 (30.9)	6,951 (31.1)
BMI, mean ± SD (kg/m²)	35.2 ± 7.9	31.6 ± 7.4
Albumin, mean ± SD (g/dL)	3.8 ± 0.6	3.7 ± 0.7
Platelets, mean ± SD (×10³/μL)	188.9 ± 86.9	184.8 ± 94.0

Table 1. Baseline Characteristics Before and After Propensity Score Matching

Disclosures: Razan Aburumman:Nothing to Disclose, Sarine Tahmazian:Nothing to Disclose, Saqr Alsakarneh:Nothing to Disclose, Reena Salgia:Eisai: Speaking and Teaching, Eisai: Speaking and Teaching, AstraZeneca: Advisor, Eisai: Speaking and Teaching, Cook: Speaking and Teaching, AstraZeneca: Advisor, AstraZeneca: Advisor, Cook: Speaking and Teaching, Cook: Speaking and Teaching, Gilead Sciences: Speaking and Teaching, Eisai: Speaking and Teaching, Eisai: Speaking and Teaching, AstraZeneca: Advisor, Eisai: Speaking and Teaching, Cook: Speaking and Teaching, AstraZeneca: Advisor, AstraZeneca: Advisor, Cook: Speaking and Teaching, Cook: Speaking and Teaching, Gilead Sciences: Speaking and Teaching, Eisai: Speaking and Teaching, Eisai: Speaking and Teaching, AstraZeneca: Advisor, Eisai: Speaking and Teaching, Cook: Speaking and Teaching, AstraZeneca: Advisor, AstraZeneca: Advisor, Cook: Speaking and Teaching, Cook: Speaking and Teaching, Gilead Sciences: Speaking and Teaching.

1481 | SARCOPENIA AND MORTALITY IN PATIENTS WITH ADVANCED LIVER FIBROSIS OR CIRRHOSIS: A LONGITUDINAL COHORT STUDY

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Symbols: ♦, Poster of Distinction; ★, Foundation Award Recipient

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Background: Sarcopenia is increasingly recognized as a prognostic factor in cirrhosis, but whether its impact differs by severity stage remains incompletely understood. We evaluated the association of sarcopenia severity with all-cause and liver cirrhosis-related mortality in patients with advanced liver fibrosis or cirrhosis. **Methods:** Using UK Biobank data, we identified participants with advanced liver fibrosis or cirrhosis at baseline, defined by FIB-4 index ≥ 2.67 or validated ICD codes, and excluded those with a history of malignancy. Sarcopenia was classified according to EWGSOP2 criteria as probable sarcopenia (low muscle strength alone), or confirmed/severe sarcopenia (low muscle strength plus low muscle mass and/or poor physical performance), based on grip strength, appendicular skeletal muscle mass estimated from bioimpedance analysis, and self-reported physical performance. Mortality data were identified through linked national death registries. Cox proportional hazards models were used to estimate hazard ratios (aHRs) and 95% confidence intervals (CIs), with adjustment for demographics, education level, BMI, smoking, and alcohol consumption. **Results:** Among 10,328 participants (mean age 64 years; 64.5% male), 1,400 (13.6%) had probable sarcopenia and 511 (4.9%) had confirmed/severe sarcopenia. During a median 10-year follow-up, 1,295 deaths occurred, including 126 liver cirrhosis-related deaths. Sarcopenia showed a graded association with mortality. For all-cause mortality, probable sarcopenia was associated with higher risk (aHR 1.44, 95% CI 1.24–1.67; $P < 0.001$), and confirmed/severe sarcopenia was associated with a greater risk (aHR 3.76, 3.18–4.44; $P < 0.001$). For liver cirrhosis-related mortality, the corresponding aHRs were 1.92 (1.22–3.02; $P = 0.005$) and 3.52 (2.10–5.92; $P < 0.001$), respectively. In sex-stratified analyses, the association with liver cirrhosis-related mortality was more pronounced in males, with significant associations for both probable sarcopenia (aHR 2.00, 1.15–3.48; $P = 0.015$) and confirmed/severe sarcopenia (aHR 4.46, 2.46–8.09; $P < 0.001$). In females, confirmed/severe sarcopenia remained associated with all-cause mortality (aHR 3.60, 2.63–4.93; $P < 0.001$), whereas neither probable nor confirmed/severe sarcopenia was significantly associated with liver cirrhosis-related mortality. Kaplan-Meier survival curves detailed in Figure 1. **Conclusion:** In patients with advanced liver fibrosis or cirrhosis, sarcopenia was associated with increasing mortality risk in a severity-dependent manner. The prognostic association was evident at the probable stage and strongest at the confirmed/severe stage. Sex-stratified analyses suggested that the association with liver cirrhosis-related mortality was more evident in males. These findings support routine sarcopenia assessment and severity-based risk stratification in advanced liver disease.

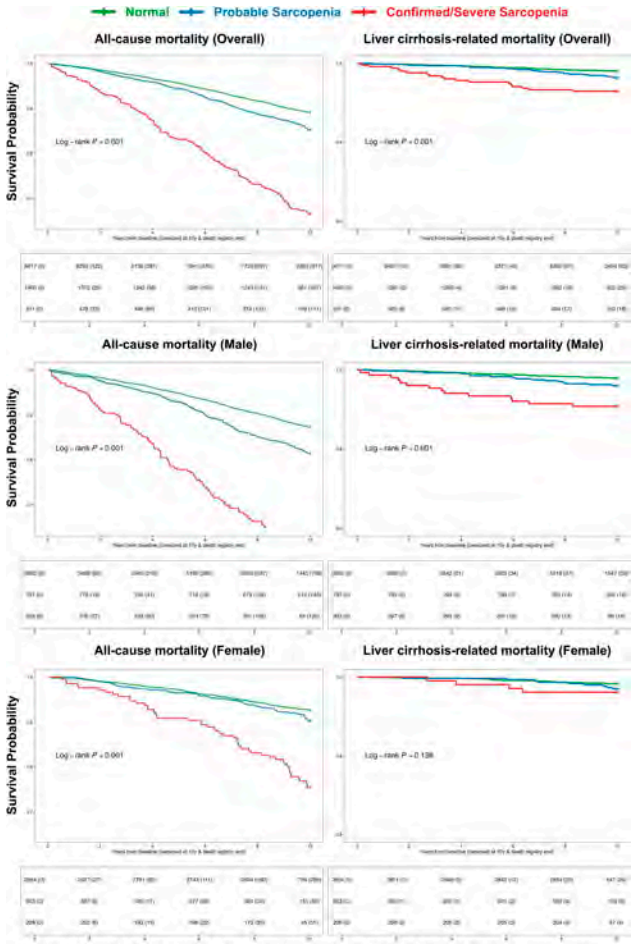


Figure 1. Kaplan–Meier curves for all-cause and liver cirrhosis-related mortality by sarcopenia severity in the overall cohort and by sex. Sarcopenia was classified as normal, probable sarcopenia, or confirmed/severe sarcopenia using EWGSOP2 criteria. Log-rank P values are shown in each panel. Numbers at risk are displayed below the curves.

Disclosures: Yi Liu:Nothing to Disclose, Bowen Qin: Nothing to Disclose, Xiao Yuan:Nothing to Disclose, Qiaoman Fei:Nothing to Disclose, Xin Liu:Nothing to Disclose, Sikai Qiu:Nothing to Disclose, Jia Yuan: Nothing to Disclose, Xinyuan He:Nothing to Disclose, Haidan Shi:Nothing to Disclose, Xiaofan Song:Nothing to Disclose, Xinrong Zhang:Nothing to Disclose, Lei Zhang:Nothing to Disclose.

1482 | PORTAL HYPERTENSION SEVERITY PARALLELS SUBCLINICAL MYOCARDIAL DYSFUNCTION ACROSS PORTO-SINUSOIDAL VASCULAR DISORDER AND CIRRHOSIS: EVIDENCE FOR A HEMODYNAMICALLY DRIVEN HEPATIC–CARDIAC AXIS

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Background: Porto-sinusoidal vascular disorder (PSVD) is a heterogeneous group of vascular liver diseases that generate portal hypertension (PH) in the absence of cirrhosis. In contrast to cirrhotic cardiomyopathy(CCM), cardiac involvement in PSVD remains poorly delineated. We aimed to compare structural and functional cardiac alterations in patients with PSVD versus cirrhosis, and to examine the association between PH severity and cardiac involvement. Because PSVD provides a clinical setting in which PH arises largely independently of advanced parenchymal injury, comparing PSVD with cirrhosis offers a unique opportunity to dissect the cardiac consequences attributable to portal hemodynamic perturbation per se. **Methods:** In this single-center retrospective cohort study (December 2019 to December 2020), consecutive patients with cirrhosis or PSVD scheduled for transjugular intrahepatic portosystemic shunt (TIPS) underwent a comprehensive echocardiographic evaluation within 48 hours preceding the procedure. Three-dimensional speckle-tracking echocardiography (3D-STE) parameters, including left ventricular ejection fraction, left ventricular global longitudinal strain (LVGLS), global circumferential strain, and systolic dyssynchrony index, were calculated using commercially available software. Patients were subsequently stratified by the severity of the invasive portal pressure gradient (PPG) obtained during the TIPS procedure, with a pre-specified cut-off of 20 mmHg. **Results:** A total of 92 patients were enrolled, including 22 in the PSVD group (mean age 48 ± 15 years; female 8/22, 36%) and 70 in the cirrhosis group (mean age 49 ± 9 years; female 23/70, 33%). Applying the 2019 Cirrhotic Cardiomyopathy Consortium criteria, the prevalence of CCM was comparable between groups (PSVD 31.8% vs. cirrhosis 32.9%; P = 0.928). Relative to the cirrhosis group, PSVD patients exhibited a lower left atrial volume index (LAVI, 34.08 ± 14.84 vs. 37.11 ± 10.47 mL/m²; P = 0.001) but demonstrated impaired right ventricular function, as reflected by RV global longitudinal strain. In PPG-stratified subgroup analyses, higher PPG was associated with more impaired 3D-LVGLS in both cohorts (PSVD: −16.78 ± 4.33% vs. −20.76 ± 3.36%, P = 0.028; cirrhosis: −18.48 ± 3.69% vs. −21.34 ± 5.53%, P = 0.004). 3D-LVGLS correlated with PPG in both cohorts (PSVD: r = −0.343, P = 0.049; cirrhosis: r = −0.235, P = 0.049). **Conclusion:** Patients with PSVD show a prevalence of CCM comparable to that in cirrhosis, despite differing patterns of chamber-specific involvement. Across both etiologies, the degree of subclinical myocardial dysfunction tracks the severity of portal hypertension, supporting a hemodynamically driven hepatic–cardiac axis.

Disclosures: Yaozu Liu:Nothing to Disclose, Fangmin Meng:Nothing to Disclose, Jingqin Ma:Nothing to Disclose, Wen Zhang:Nothing to Disclose, Zhiping Yan:Nothing to Disclose, Jianjun Luo:Nothing to Disclose, Cuizhen Pan:Nothing to Disclose.

1483 | METABOLIC AND RENAL COMORBIDITY PREDICT HEPATIC ENCEPHALOPATHY AND MORTALITY AFTER TIPS: A REAL-WORLD COHORT STUDY

Gloria Sanchez Antolín[1] Elena Velasco Martinez[2] Natalia Marcos Carrasco[2] Carolina Almohalla Alvarez[2] María Jordán de la Fuente[2] Pilar Hernandez Manchado[2] Laura Jimenez Gonzalez[2] Celia Portela Guerra[2] Maria Pina Pallin[2] Elena Villacastin-Ruiz[2] Rebeca Pintado Garrido[2], [1]Hepatology Unit. Hospital Universitario Rio Hortega, [2]Hospital Universitario Rio Hortega

Background: Transjugular intrahepatic portosystemic shunt (TIPS) is an effective treatment for complications of portal hypertension, but post-TIPS hepatic encephalopathy (HE) remains a major limitation. The impact of metabolic and renal comorbidity on HE and survival after TIPS is incompletely defined **Methods:** We performed a retrospective observational study of 119 patients who underwent TIPS at a hepatology unit. Demographic characteristics, liver disease etiology, comorbidities, liver disease severity, indication for TIPS, clinical response, complications, HE, early HE ($\leq$30 days), and survival were analyzed. Overall survival was assessed using Kaplan-Meier methods. Factors associated with HE and mortality were evaluated by univariable and multivariable analyses. **Results:** Most patients were male (83.3%), with a median age of 64 years. Alcohol-related liver disease was the most frequent etiology (63.9%). The most common comorbidities were diabetes mellitus (42.9%) and chronic kidney disease (16.8%). Main indications for TIPS were variceal bleeding (50.4%) and refractory ascites (42.9%). Clinical efficacy was high, with recurrent ascites or bleeding observed in 13.7% of patients. Overall, 66.4% developed complications; HE was the most frequent event (48.7%), and TIPS reduction was required in 7.6%. HE was significantly associated with age $\geq$65 years (p = 0.003), diabetes mellitus (p = 0.023), chronic kidney disease (p = 0.010), and advanced liver functional stage (Child-Pugh B/C; p = 0.035), but not with etiology or MELD score. Median overall survival was 1,116 days. Survival was significantly worse in patients with MELD $\geq$15 (p = 0.007), advanced liver functional stage (p = 0.007), and chronic obstructive pulmonary disease (p = 0.003). In multivariable analysis, diabetes mellitus (HR 2.29, 95% IC;

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p = 0.008) and chronic kidney disease (HR 2.15, 95% CI p = 0.042) were independently associated with increased mortality. Overall HE was not significantly associated with survival, although early HE showed a trend toward higher early mortality **Conclusion:** TIPS was highly effective in this real-world cohort, but post-procedure HE was frequent. Older age, diabetes, chronic kidney disease, and impaired liver functional reserve identified patients at increased risk of HE. Diabetes and chronic kidney disease were also independently associated with mortality, supporting the integration of metabolic and renal comorbidity into pre-TIPS risk stratification and post-TIPS monitoring.
Disclosures: Gloria Sanchez Antolín:Nothing to Disclose, Elena Velasco Martinez:Nothing to Disclose, Natalia Marcos Carrasco:Nothing to Disclose, Carolina Almohalla Alvarez:Nothing to Disclose, María Jordán de la Fuente:Nothing to Disclose, Pilar Hernandez Manchado:Nothing to Disclose, Laura Jimenez Gonzalez:Nothing to Disclose, Celia Portela Guerra:Nothing to Disclose, Maria Pina Pallin:Nothing to Disclose, Elena Villacastin-Ruiz:Nothing to Disclose, Rebeca Pintado Garrido:Nothing to Disclose.

1484 | TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT VS. REPEAT LARGE-VOLUME PARACENTESIS FOR CIRRHOTIC ASCITES: RENAL AND CLINICAL OUTCOMES IN A PROPENSITY SCORE–MATCHED COHORT ANALYSIS

Archana Salek[1] Jashanveer Johal[1] Bianca Patel[1] Mahmoud Al-Bataineh[1] Brandon Cunha[1] Abdallah Hussein[1] Jason Hyman[2] Yecheskel Schneider[1], [1]Virtua Health, [2]Einstein Medical Center, Philadelphia

Background: Refractory ascites in cirrhosis portends significant morbidity, and the choice between transjugular intrahepatic portosystemic shunt (TIPS) and repeat large-volume paracentesis (LVP) as definitive management carries important implications for renal function, hepatic decompensation, and survival. Real-world comparative data on renal-specific outcomes between these strategies remain limited. **Methods:** We conducted a propensity score–matched retrospective cohort study using the TriNetX Global Collaborative Network (191.9 million patients). Cohort 1 comprised adult cirrhotic patients (K74.6) with ascites (R18) and portal hypertension (K76.6) who underwent TIPS placement. Cohort 2 comprised cirrhotic patients with ascites and portal hypertension who underwent repeat paracentesis without TIPS. Both cohorts excluded prior liver transplant, ESRD, heart failure, and hepatocellular carcinoma. Cohorts were balanced via 1:1 PSM yielding 3,934 patients per arm over a 6–120 month follow-up window. Pre-specified outcomes included acute kidney injury (AKI), progression to ESRD or dialysis initiation, development of hepatorenal syndrome (HRS), need for repeat paracentesis, development of hepatic encephalopathy (HE), liver transplant listing, ICU admission, and all-cause mortality. **Results:** Post-PSM cohorts were well-balanced across all matched covariates. TIPS was associated with significantly lower rates of AKI (27.4% vs. 36.3%; HR 0.63, 95% CI 0.57–0.70; p < 0.001), HRS (7.2% vs. 12.3%; HR 0.50, 95% CI 0.43–0.58; p < 0.001), and progression to ESRD or dialysis (6.3% vs. 6.5%; HR 0.84, 95% CI 0.70–1.00; p = 0.047). Need for repeat paracentesis was dramatically lower in the TIPS arm (39.0% vs. 64.7%; HR 0.44, 95% CI 0.41–0.47; p < 0.001), with a median time to repeat paracentesis of 32 days in the LVP-only arm. TIPS patients had significantly higher rates of new or worsened hepatic encephalopathy (52.6% vs. 41.2%; HR 1.28, 95% CI 1.15–1.42; p < 0.001), with a shorter median time to HE onset (366 vs. 680 days). Liver transplant listing rates were higher in the TIPS arm on MOA analysis (8.4% vs. 6.5%; RR 1.30; p = 0.002) but did not reach significance on time-to-event analysis (HR 1.11, 95% CI 0.93–1.32; p = 0.25). All-cause mortality was significantly lower in the TIPS arm (30.4% vs. 43.2%; HR 0.57, 95% CI 0.53–0.61; p < 0.001). **Conclusion:** In this large propensity-matched real-world cohort, TIPS was associated with substantially lower rates of AKI, HRS, ESRD progression, repeat paracentesis, and all-cause mortality compared to LVP-only management in cirrhotic ascites. These benefits came at the cost of significantly higher rates of hepatic encephalopathy, consistent with the known hemodynamic tradeoff of portal decompression. These findings support TIPS as the preferred strategy in eligible patients with refractory ascites and reinforce the need for proactive HE surveillance post-procedure.
Disclosures: Archana Salek:Nothing to Disclose, Jashanveer Johal:Nothing to Disclose, Bianca Patel:Nothing to Disclose, Mahmoud Al-Bataineh:Nothing to Disclose, Brandon Cunha:Nothing to Disclose, Abdallah Hussein:Nothing to Disclose, Jason Hyman:Nothing to Disclose, Yecheskel Schneider:Nothing to Disclose.

1485 | SGLT2 INHIBITOR USE IS ASSOCIATED WITH REDUCED PARACENTESIS, SPONTANEOUS BACTERIAL PERITONITIS, HEPATORENAL SYNDROME, AND MORTALITY IN PATIENTS WITH CIRRHOSIS AND ASCITES: A PROPENSITY-MATCHED MULTICENTER ANALYSIS

Muhammad Ali Ibrahim Kazi[1] Sanmeet Singh[2] Maham Siddiqui[2], [1]Anne Arundel Medical Centre, [2]Anne Arundel Medical Center

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Background: Management of ascites in cirrhosis remains challenging, and therapies that may reduce portal hypertensive and renal complications are needed. Sodium-glucose cotransporter-2 inhibitors have mild natriuretic and diuretic effects, but their association with clinical outcomes in patients with cirrhosis and ascites remains unclear. We evaluated whether SGLT2 inhibitor use was associated with improved outcomes among adults with cirrhosis and ascites. **Methods:** We conducted a retrospective cohort study using the TriNetX Research Network, which included 111 healthcare organizations. Adults aged ≥18 years with cirrhosis and ascites were identified. Patients receiving SGLT2 inhibitors were compared with patients with cirrhosis and ascites without SGLT2 inhibitor exposure. Outcomes were assessed beginning 90 days after the index event. The primary outcome was need for abdominal paracentesis. Secondary outcomes included spontaneous bacterial peritonitis, hepatorenal syndrome, hyponatremia, and all-cause mortality. Propensity score matching was performed for 43 demographic, comorbidity, procedure, and medication covariates, yielding 21,977 patients in each cohort. **Results:** After propensity matching, SGLT2 inhibitor use was associated with significantly lower risk of abdominal paracentesis compared with non-use: 12.2% vs 15.8%; risk ratio [RR] 0.772, 95% CI 0.737–0.809; hazard ratio [HR] 0.816, 95% CI 0.775–0.858. SGLT2 inhibitor use was also associated with lower risk of spontaneous bacterial peritonitis: 3.5% vs 5.2%; RR 0.677, 95% CI 0.620–0.740; HR 0.771, 95% CI 0.703–0.845. Hepatorenal syndrome occurred less frequently among SGLT2 inhibitor users: 3.8% vs 5.0%; RR 0.759, 95% CI 0.695–0.829; HR 0.890, 95% CI 0.813–0.975. Hyponatremia was modestly reduced: 17.8% vs 19.5%; RR 0.908, 95% CI 0.873–0.944, although time-to-event analysis did not demonstrate a significant difference. All-cause mortality was substantially lower among SGLT2 inhibitor users: 18.4% vs 31.5%; RR 0.584, 95% CI 0.564–0.604; HR 0.681, 95% CI 0.655–0.708. **Conclusion:** In this large propensity-matched multicenter cohort of patients with cirrhosis and ascites, SGLT2 inhibitor use was associated with lower risks of paracentesis, spontaneous bacterial peritonitis, hepatorenal syndrome, and mortality. These findings suggest a potential role for SGLT2 inhibitors in improving decompensation-related outcomes in cirrhosis with ascites. Prospective studies are warranted to validate these findings and clarify patient selection, safety, and mechanisms of benefit.

Study cohort: TriNetX Research Network; adults with cirrhosis and ascites. After propensity score matching, each cohort included 21,977 patients. Outcomes were assessed beginning 90 days after the index event.

Outcome	SGLT2i Cohort n/N (%)	Non-SGLT2i Cohort n/N (%)	Risk Ratio (95% CI)	Risk Difference	Hazard Ratio (95% CI)	P value
Abdominal paracentesis	2,680/21,977 (12.2%)	3,474/21,977 (15.8%)	0.772 (0.737–0.809)	-3.6%	0.816 (0.775–0.858)	<0.001
Spontaneous bacterial peritonitis	776/21,977 (3.5%)	1,150/21,977 (5.2%)	0.677 (0.620–0.740)	-1.7%	0.771 (0.703–0.845)	<0.001
Hepatorenal syndrome	833/21,977 (3.8%)	1,099/21,977 (5.0%)	0.759 (0.695–0.829)	-1.2%	0.890 (0.813–0.975)	0.012*
Hyponatremia	3,901/21,977 (17.8%)	4,296/21,977 (19.5%)	0.908 (0.873–0.944)	-1.8%	1.023 (0.979–1.069)	0.309*
All-cause mortality	4,041/21,977 (18.4%)	6,923/21,977 (31.5%)	0.584 (0.564–0.604)	-13.1%	0.681 (0.655–0.708)	<0.001

*P value reflects log-rank test for survival analysis where noted. Risk analysis p values were reported as 0.000 in TriNetX for all listed outcomes.

Disclosures: Muhammad Ali Ibrahim Kazi:Nothing to Disclose, Sanmeet Singh:Nothing to Disclose, Maham Siddiqui:Nothing to Disclose.

1486 | CARVEDILOL IS ASSOCIATED WITH LOWER HEPATIC DECOMPENSATION COMPARED WITH PROPRANOLOL/ NADOLOL AND SELECTIVE BETA-BLOCKERS IN COMPENSATED CIRRHOSIS: A POPULATION-BASED TARGET TRIAL EMULATION

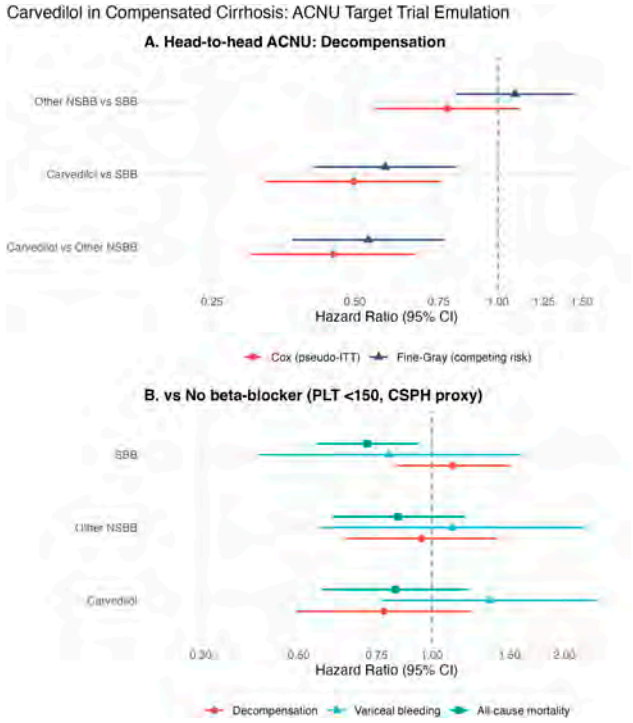
Abdel-Aziz Shaheen[1] Mark Swain[1] Juan Abraldes[2], [1]University of Calgary, [2]University of Alberta

Background: Carvedilol may prevent decompensation in compensated cirrhosis, but comparative effectiveness versus propranolol/nadolol and selective beta-blockers (SBBs) remains uncertain. We compared beta-blocker strategies using a target trial emulation. **Methods:** Alberta administrative data (2012-2025) identified 8,093 adults with compensated cirrhosis. After a 12-month beta-blocker washout, new users of carvedilol (n = 618), propranolol/nadolol (n = 477), and SBBs (n = 808) entered single-entry active-comparator new-user trials at first dispensation. A 30-day pre-induction exclusion was applied. Stabilized inverse probability of treatment weighting (IPTW) balanced age, sex, alcohol etiology, Charlson index, platelets, MELD-Na, varices, rurality, and diagnosis year. Outcomes were hepatic decompensation, variceal bleeding, and mortality. IPTW-weighted Cox models were primary; Fine-Gray models addressed death/transplant. Follow-up was capped at 3 y. A secondary analysis compared each beta-blocker with no beta-blocker in patients with platelets < $150^{10\text{^}9}$ /L (n = 2,397), using random temporal assignment for non-users. **Results:** In the head-to-head beta-blocker cohort (n = 1,903), median age was 58 y (IQR 50-66), 57% were male, 68% had alcohol etiology, median platelets were 153 x 10^9/L, median MELD-Na was 10, and varices were detected in 32%. Carvedilol was associated with lower decompensation risk than propranolol/nadolol (HR 0.45, 95% CI 0.30-0.67; Fine-Gray SHR 0.53, 0.37-0.77; as-treated HR 0.50, 0.32-0.77) and SBBs (HR 0.50, 0.33-0.76; Fine-Gray SHR 0.58, 0.41-0.82; as-treated HR 0.49, 0.30-0.78). Propranolol/nadolol did not differ from SBBs for decompensation (HR 0.78, 0.55-1.11; Fine-Gray SHR 1.09, 0.82-1.44), Figure 1A. Carvedilol was not significantly associated with variceal bleeding (HR 0.78, 0.50-1.21) or mortality (HR 1.12, 0.82-1.52) versus propranolol/nadolol. Results were similar by alcohol etiology (HR 0.47, 0.29-0.74) and non-alcohol etiology (HR 0.44, 0.20-0.94), by platelets < 150 (HR 0.42, 0.26-0.68), and across induction

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periods (30-180 days; HR range 0.40-0.48) and washout windows (6-24 months; HR range 0.44-0.45). Duration estimates versus propranolol/nadolol were HR 0.46 (0.29-0.73) for > = 365 days. The negative-control fracture outcome was not significant (HR 0.88, 0.46-1.68; p = 0.691). In the platelet-restricted analysis versus no beta-blocker, carvedilol was not significantly associated with decompensation, variceal bleeding, or mortality, Figure 1B. **Conclusion:** Carvedilol was associated with lower hepatic decompensation risk than propranolol/nadolol and SBBs, with consistent estimates across different sensitivity analyses. No significant differences in bleeding or mortality were observed.



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1487 | COMBINED FLUID OVERLOAD AND MALNUTRITION IDENTIFIES A HIGH-RISK PHENOTYPE WITH POORER 365-DAY OUTCOMES IN CIRRHOSIS

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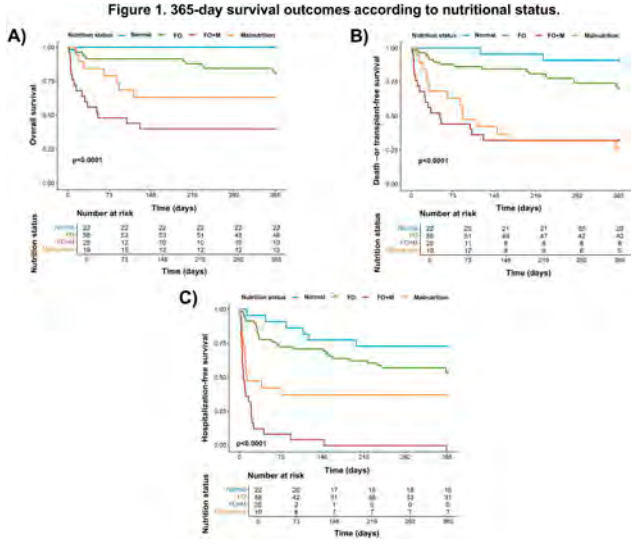
Background: Malnutrition and fluid overload frequently coexist in cirrhosis and are each associated with systemic inflammation and adverse outcomes, yet they are typically evaluated as separate complications. Whether their combination identifies a clinically distinct phenotype with added prognostic value remains unclear. We aimed to determine whether bioelectrical impedance vector analysis (BIVA)-defined nutritional and hydration phenotypes capture differences in systemic inflammation and clinical outcomes in cirrhosis. **Methods:** In this prospective cohort study, patients with cirrhosis were followed for 12 months. Nutritional and hydration status were assessed using BIVA and classified as normal, fluid overload (FO), malnutrition, or combined fluid overload and malnutrition (FO+M). Baseline liver disease severity was assessed using Child-Pugh and MELD-Na scores. Galectin-3 and neutrophil-to-lymphocyte ratio (NLR) were measured as markers of systemic inflammation. The discriminative ability of galectin-3 and NLR for identifying BIVA-defined phenotypes was evaluated using ROC curves. Overall survival, death- or transplant-free survival, and hospitalization-free survival were estimated using Kaplan-Meier curves and compared across phenotypes using log-rank tests. **Results:** A total of 124 patients were included. BIVA classified patients into four

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nutritional/hydration phenotypes: normal status (n = 22, 17.74%), FO (n = 58, 46.77%), FO+M (n = 25, 20.16%), and malnutrition (n = 19, 15.32%). FO+M represented the highest-risk subgroup, characterized by more advanced liver disease, with most patients classified as Child-Pugh C (72%) and the highest MELD-Na scores (26 [18–30]). Alcohol-related and autoimmune liver disease were the most frequent etiologies within this group. This phenotype also showed the highest inflammatory burden, with higher galectin-3 (25.35 [20.08–39.87] ng/mL) and NLR (11.15 [5.85–18.27]) than other phenotypes ($p < 0.001$). Galectin-3 and NLR showed strong discriminative ability for identifying the combined phenotype (AUC: 0.893; 95% CI: 0.831–0.954). Over 365 days, FO+M consistently showed the poorest outcomes across all survival endpoints, including the lowest overall survival, death- or transplant-free survival, and hospitalization-free survival (log-rank $p < 0.001$ for all). The separation between groups was most pronounced for hospitalization-free survival, where FO+M declined early and remained the worst-performing phenotype throughout follow-up (**Figure 1**). **Conclusion:** The coexistence of fluid overload and malnutrition defines a clinically distinct, high-risk phenotype in cirrhosis that is not captured when these features are considered separately. This phenotype aligns with increased inflammatory burden and identifies patients with worse clinical outcomes.

Figure 1. 365-day survival outcomes according to nutritional status.



Disclosures: Anaisa Carranza-Carrasco:Nothing to Disclose, Osvely Méndez-Guerrero:Nothing to Disclose, Claudia López-López:Nothing to Disclose, Rodrigo Guerrero-Guerrero:Nothing to Disclose, Farid Tejeda-Dominguez:Nothing to Disclose, Graciela Castro-Narro:Novonordisk: Speaker honoraria and advisory board, Gilead: Speaker honoraria, Grünanthalñ: Speaker honoraria, Boehringer Ingelheim: Speaker honoraria, Lilia Castillo-Martínez:Nothing to Disclose, Nalu Navarro-Alvarez:Nothing to Disclose.

1488 | COMPARISON OF PHARMACOLOGICAL, ENDOSCOPIC, AND INTERVENTIONAL STRATEGIES FOR PRIMARY AND SECONDARY PROPHYLAXIS OF VARICEAL BLEEDING: A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

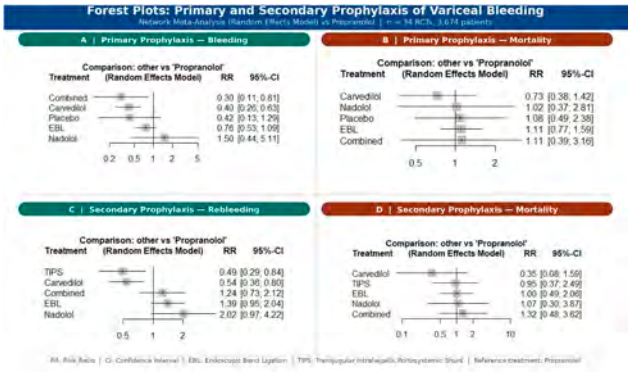
Mujtaba Moazzam[1] Hasnain Saqib[2] Rehman Bashir[2] Talha Khan[2] Mahad Ahmad[2] Marjan Haider[3] Michael Fine[3], [1]Corewell Health William Beaumont University Hospital, [2]Islamic International Medical College, Rawalpindi, Pakistan, [3]Trinity Health, Ann Arbor, Michigan, USA

Background: Gastroesophageal variceal bleeding carries significant morbidity and mortality in patients with portal hypertension. Multiple pharmacological, endoscopic, and interventional strategies have emerged for prophylaxis, yet no network meta-analysis has comprehensively compared the full treatment spectrum across both primary and secondary prophylaxis settings. We aimed to evaluate their relative efficacy within a single unified framework. **Methods:** We conducted a systematic review and frequentist random-effects NMA of RCTs comparing propranolol, nadolol, carvedilol, EBL, combination therapy (EBL plus beta-blocker), and TIPS. Databases searched included PubMed/MEDLINE, Embase, Cochrane CENTRAL, Scopus, and ClinicalTrials.gov through January 2026 (PROSPERO: CRD420261304355). Outcomes included bleeding/rebleeding risk and all-cause mortality. Risk of bias was assessed using Cochrane RoB 2. Treatment ranking used SUCRA values. Consistency was evaluated using design-by-treatment interaction models and TSA assessed conclusiveness of mortality evidence. **Results:** Thirty-four RCTs enrolling 3,674 patients were included. In primary prophylaxis, combination therapy (RR 0.30, 95% CI 0.11-0.81; SUCRA 0.86) and carvedilol (RR 0.40, 95% CI 0.26-0.63; SUCRA 0.76) significantly reduced first bleeding versus propranolol. In secondary prophylaxis, TIPS (RR 0.49, 95% CI 0.29-0.84; SUCRA 0.92) and carvedilol (RR 0.54, 95% CI 0.36-0.80; SUCRA 0.88) most effectively reduced rebleeding. No intervention demonstrated a statistically significant mortality benefit in either setting; carvedilol showed consistent directional trends toward lower mortality in both primary (RR 0.73, 95% CI 0.38-1.42) and secondary (RR 0.35, 95% CI 0.08-1.59) prophylaxis, though TSA confirmed evidence remains below the required information size. Sensitivity analyses were robust to exclusion of high-risk-of-bias studies. **Conclusion:** This first comprehensive NMA across the full prophylaxis spectrum demonstrates that combination therapy is the most effective strategy for

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primary prophylaxis, while TIPS leads in secondary prophylaxis. Carvedilol's consistent directional mortality advantage warrants investigation in adequately powered trials. These findings provide a comparative framework to inform clinical practice and guideline development.

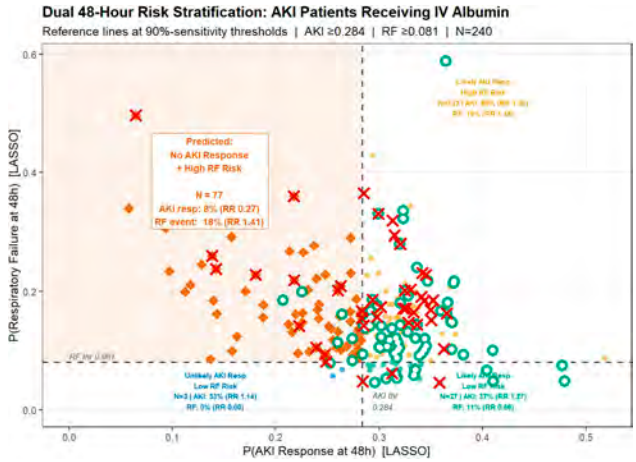


Disclosures: MUJTABA MOAZZAM:Nothing to Disclose, Hasnain Saqib:Nothing to Disclose, Rehman Bashir:Nothing to Disclose, Talha Khan:Nothing to Disclose, Mahad Ahmad:Nothing to Disclose, Marjan Haider:Nothing to Disclose, Michael Fine:Nothing to Disclose.

1489 | THE ALARM SCORE: DUAL RISK STRATIFICATION AFTER ALBUMIN INFUSION IN CIRRHOSIS

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Background: Albumin infusion is first line therapy for patients with cirrhosis, ascites, and acute kidney injury (AKI). However, albumin therapy also may cause respiratory failure. Models to jointly predict AKI response and respiratory failure after albumin infusion are lacking. Herein, we develop and internally validate the ALARM score (ALbumin response And Respiratory Model). **Methods:** We retrospectively identified 1,096 hospitalized patients with cirrhosis who received IV 25% albumin from 2015–2025. Patients in shock, receiving positive pressure ventilation, hospitalized for < 48 hours, on dialysis, or with prior TIPS or liver transplantation were excluded. Respiratory failure and AKI response were assessed 48 hours after first albumin infusion. Separate LASSO-regularized logistic regression models for respiratory failure and AKI response were developed using clinical, vital sign, and laboratory data available at infusion and internally validated using 5-fold cross-validation. Model performance was compared with reduced models including MELD 3.0 variables alone. Because the primary clinical objective was high-sensitivity risk stratification, models were evaluated at thresholds corresponding to 90% sensitivity. **Results:** Patients had a median MELD 3.0 of 26, bilirubin 2.7 mg/dL, MAP 75 mmHg, and SpO2 97%; 888 (81.7%) were on room air at infusion. Among 381 patients with AKI at infusion, 70 (29.2%) experienced AKI response at 48 hours, while 101 patients (12.9%) developed respiratory failure. The ALARM respiratory failure model achieved an AUC of 0.71 versus 0.62 for MELD 3.0 and at 90% sensitivity threshold it significantly reclassified patients (NRI 0.3, $p < 0.01$) with a NPV of 0.94. For AKI response, the ALARM model achieved an AUC of 0.70 versus 0.60 for MELD 3.0 alone, with NPV 0.91but did not significantly reclassify patients. A combined risk model identified a subgroup with a 40% higher risk of respiratory failure and four times lower likelihood of AKI response (Figure). **Conclusion:** The ALARM model jointly predicts respiratory failure and AKI response following albumin infusion and may support high-sensitivity clinical risk stratification in patients with cirrhosis and AKI.



Disclosures: Nikhilesh Mazumder:Nothing to Disclose, John Rice:Nothing to Disclose, Laura Mariani:Boehringer ingelheim: Advisor, vera therapeutics: Consultant, Travere Therapeutics: Consultant, Dimerix: Consultant, Takeda Pharmaceuticals: Grant/Research Support, HiBio: Grant/Research Support, Calliditas Therapeutics: Grant/Research Support, Novartis: Consultant, Otsuka: Grant/Research Support, Reliant Glycosciences: Grant/Research Support, Kayvan Najarian: Nothing to Disclose, Anna Lok:Abbott Diagnostics: Consultant, Chroma: Consultant, Grifols: Consultant, GlaxoSmithKline: Consultant, Novo Nordisk: Advisor, Pfizer: Consultant, Precision Biosciences: Consultant, Roche Diagnostics: Consultant, Virion: Consultant, Zenasbio: Consultant, Brii Biosciences: Advisor, Moderna: Advisor, Pioneering: Advisor, Arbutus: Consultant, Elliot Tapper:Madrigal: Grant/Research Support, Gilead: Consultant, Ipsen: Consultant, Merz: Consultant.

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1490 | NIGHT MOVES: DELAYED NOCTURNAL ACTIVITY IS ASSOCIATED WITH HEPATIC ENCEPHALOPATHY WHEN MEASURED LONGITUDINALLY WITH COMMERCIAL FITNESS TRACKERS

Adam Buckholz[1] Sophie Silbert[2] Kamaryn Tanner[3] Avesh Thuluvath[4] Lara Phipps[2] Jayden Maramis[2] Elizabeth Verna[5] Edwin Kan[6] Ana Krieger[2] Robert Brown[7], [1]New York Presbyterian Hospital Program, [2]NewYork-Presbyterian/Weill Cornell Medical Center, [3]NewYork-Presbyterian/Columbia University Medical Center, [4]Columbia University Irving Medical Center, [5]Columbia University Medical Center, [6]Cornell University, [7]Weill Cornell Medicine

Background: Hepatic Encephalopathy (HE) is a complex complication of portal hypertension, with sleep disturbances and day-night reversal a commonly reported symptom. Despite this, longitudinal monitoring to detect and manage HE is understudied, leading to frequent hospitalizations and impaired outcomes. Commercial wearables permit passive, continuous assessment of nocturnal behavior in real-world settings. We evaluated whether commercially available fitness trackers detect altered nocturnal activity patterns associated with HE. **Methods:** We analyzed activity after sleep onset in 102 participants who were followed with an Oura fitness tracker a median of 177 days (range 40-180). Activity was assessed using its internal accelerometer and reported as metabolic equivalent of task (MET)-minutes, a continuous measure where <1 is considered rest; MET minutes, activity level, and sleep status were analyzed in 5-minute epochs. HE was defined as a previous episode of overt HE and active treatment with lactulose/rifaximin. Impaired cognition was defined as PHES $\leq$ -4 regardless of prior overt episode. Sleep onset was defined as initiation of the longest sleep period in each 24-hour epoch. Mixed-effects models accounting for repeated measurements evaluated associations between HE/cognition and weeknight nocturnal activity trajectories after adjustment for age, sex, and MELD score. **Results:** In 102 participants, 46.1% were female, 45.1% had CTP B/C cirrhosis, 39 had prior overt HE and 34 had PHES $\leq$-4. In mixed-effects models, HE was associated with greater odds of being active overnight (MET >1.0) compared to participants without HE (OR 1.19, $p=0.01$). Nocturnal activity trajectories were significantly different from normal/unimpaired in patients with both HE ($p = 0.01$) and/or cognitive impairment ($p = 0.04$). Participants with OHE demonstrated higher late-night activity intensity during the 4–8 hour post-sleep onset period (mean difference 0.024 in 75th percentile MET; 95% CI −0.002 to 0.051; $p=0.073$). **Conclusion:** Commercial wearable devices identified delayed nocturnal activity patterns consistent with digitally quantifiable day-night reversal in with HE and cognitive impairment in cirrhosis. These findings suggest wearable-derived longitudinal activity metrics may enable scalable, passive longitudinal monitoring of HE-related neurocognitive dysfunction between clinic visits. Such activity may also be one of the complex mechanisms by which sleep and HE are related to worsened daytime cognitive function. Future studies should consider whether shape and timing of nocturnal activity can adequately identify patients at risk for HE.

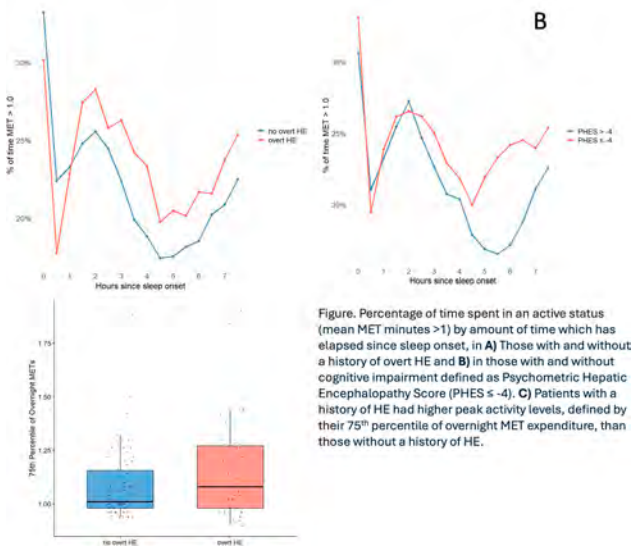


Figure. Percentage of time spent in an active status (mean MET minutes >1) by amount of time which has elapsed since sleep onset, in **A)** Those with and without a history of overt HE and **B)** in those with and without cognitive impairment defined as Psychometric Hepatic Encephalopathy Score (PHES ≤ -4). **C)** Patients with a history of HE had higher peak activity levels, defined by their 75th percentile of overnight MET expenditure, than those without a history of HE.

Disclosures: Adam Buckholz:Tortugas Neurosciences: Consultant, Sophie Silbert:Nothing to Disclose, Kamaryn Tanner:Nothing to Disclose, Avesh Thuluvath:Nothing to Disclose, Lara Phipps:Nothing to Disclose, Jayden Maramis:Nothing to Disclose, Elizabeth Verna:Nothing to Disclose, Edwin Kan:Nothing to Disclose, Ana Krieger:Nothing to Disclose, Robert Brown:Gilead: Consultant, Intercept: Consultant, Abbvie: Consultant, Madrigal: Consultant, GSK: Consultant, eGenesis: Consultant, mirum: Consultant, mallinckrodt: Consultant.

1491 | SURVIVAL OF PATIENTS WITH NODULAR REGENERATIVE HYPERPLASIA: A MAYO CLINIC PLATFORM USE CASE

Bridgette McNally[1] W. Ray Kim[1], [1]Mayo Clinic Arizona

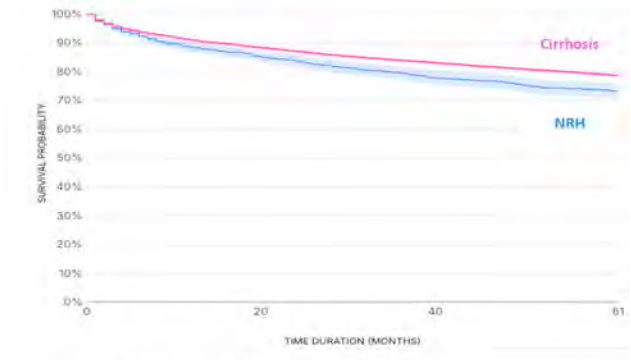
Background: The Mayo Clinic Platform (MCP) is Mayo Clinic's enterprise-level data and analytics infrastructure designed to enable healthcare innovation using large-scale clinical data. It provides aggregated de-identified patient data and enables tools for analytics, artificial intelligence, and research, allowing collaborations between Mayo and external partners. In this work, we demonstrate its use for investigation of rare conditions such as nodular regenerative hyperplasia (NRH) of the liver. **Methods:** Using the MCP, a

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search for patients with biopsy confirmed NRH with or without cirrhosis was conducted. For comparison, an equivalent search for biopsy confirmed, non-NRH cirrhosis was performed. Comparison between these two cohorts was conducted using MCP analytic tools. **Results:** Out of 8,171,580 unique patients included in MCP, 1,294 patients were identified in the NRH cohort and 14,907 patients in the non-NRH cirrhosis cohort. The average age and sex demographics were similar between the two groups. Total bilirubin, INR, ALT and AST were higher and platelet count was lower in the non-NRH cirrhosis group. Albumin was similar between the two groups. Most notably, survival probability at 61 months in the NRH cohort was near 82% compared to near 89% in the non-NRH cirrhosis group. **Conclusion:** MCP is an innovative and user-friendly tool, which harnesses the power of artificial intelligence and data networks; it can be utilized to study rare diseases such as NRH. As demonstrated in our current study, liver synthetic function was better preserved in the NRH cohort; however, survival probability was markedly lower in the NRH cohort. This emphasizes the importance of timely evaluation to determine the underlying etiology of NRH, which would allow for disease directed monitoring and therapy that may lead to improved survivability in this group.

Figure 1. Survival Probability Comparison



Legend: NRH (nodular regenerative hyperplasia)

Disclosures: Bridgette McNally:Nothing to Disclose, W. Ray Kim:Nothing to Disclose.

1492 | PROGNOSTIC PERFORMANCE OF MELD-BASED SCORES AND CLIF-C ACLF FOR 90-DAY MORTALITY IN HRS-AKI AT TERLIPRESSIN INITIATION: RESULTS FROM THE HRS-HARMONY CONSORTIUM

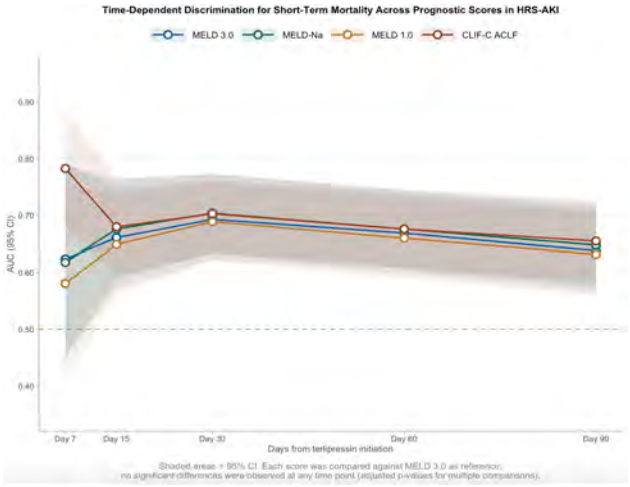
Xing Li[1] Tianqi Ouyang[1] R. Todd Frederick[2] Nneka Ufere[1] Douglas Simonetto[3] Constantine Karvellas[4] Hugo Vargas[5] Raymond Chung[1] Pratima Sharma[6] Clara Tow[7] J. Pedro Teixeira[8] Zachary Fricker[9] Stevan Gonzalez[10] Javier Neyra[11] Jevon Robinson[1] Sydney Whittaker[1] Kavish Patidar[12] Andrew Allegretti[1], [1]Massachusetts General Hospital, [2]California Pacific Medical Center, [3]Mayo Clinic Rochester, [4]University of Alberta, [5]Mayo Clinic Arizona, [6]University of Michigan Medical Center, [7]Albert Einstein College of Medicine, [8]University of New Mexico, [9]Beth Israel Deaconess Medical Center, [10]Baylor Scott and White All Saints Medical Center Fort Worth, [11]University of Alabama at Birmingham, [12]Houston Methodist Hospital

Background: HRS-AKI carries high short-term mortality, yet the prognostic performance of existing risk scores remains uncertain. MELD-based scores were developed to estimate transplant waitlist mortality and may not capture the distinct risk profile in HRS-AKI, especially in those treated with terlipressin. We sought to evaluate the discrimination of MELD-based scores and CLIF-C ACLF for short-term outcomes in HRS-AKI patients treated with terlipressin. **Methods:** We analyzed a multicenter retrospective cohort of 243 adults with HRS-AKI treated with terlipressin across 16 U.S. academic centers. MELD 1.0, MELD-Na, MELD 3.0, and CLIF-C ACLF scores were calculated at terlipressin initiation. The primary outcome was 90-day mortality, with liver transplantation (LT) not modeled as a competing risk in the primary analysis. Time-dependent ROC analysis using inverse probability of censoring weighting was used to assess discrimination at 7, 15, 30, 60, and 90 days. Secondary outcomes included terlipressin response, in-hospital renal replacement therapy (RRT). Reclassification analyses for 90-day mortality compared MELD 3.0 and MELD-Na using categorical and continuous Net Reclassification Improvement (NRI). **Results:** Among 243 patients, median MELD 3.0 was 35, and 90-day mortality was 42%. 28% underwent LT by 90 days. Non-survivors had significantly higher scores at terlipressin initiation (all $p < 0.001$). Discrimination for 90-day mortality was modest across all scores (AUCs: MELD 1.0 0.632, MELD-Na 0.648, MELD 3.0 0.638, CLIF-C ACLF 0.655), with no significant differences between scores (Figure). CLIF-C ACLF showed numerically higher discrimination at 7 days (AUC 0.783), though this was not statistically significant or sustained over time. Discrimination for terlipressin response and in-hospital RRT was similarly modest (AUCs 0.566–0.655). Categorical reclassification using pre-specified strata of clinical severity showed no meaningful improvement of MELD 3.0 over MELD-Na (NRI 0.03, $p = 0.63$), as MELD 3.0 shifted both survivors and non-survivors into higher risk strata, gaining sensitivity at the expense of specificity. Continuous NRI suggested modest improvement in risk ranking (NRI 0.19, $p = 0.007$) that did not translate into clinically meaningful reclassification. **Conclusion:** In HRS-AKI patients treated with terlipressin, MELD-based scores and CLIF-C ACLF

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demonstrated only modest discrimination for short-term mortality, with no score outperforming others and MELD 3.0 offering no meaningful advantage over prior iterations. These findings highlight the limitations of current scores in a high-risk population and underscore the unmet need for dynamic, disease-specific prognostic models in HRS-AKI.



Disclosures: Xing Li:Nothing to Disclose, Tianqi Ouyang:Nothing to Disclose, R. Todd Frederick:Nothing to Disclose, Nneka Ufere:Nothing to Disclose, Douglas Simonetto:Mallinckrodt: Consultant, BioVie: Consultant, Resolution Therapeutics: Consultant, Evive: Consultant, Iota: Consultant, Novo Nordisk: Consultant, Astra Zeneca: Consultant, Constantine Karvellas:Grifols: Consultant, Miromatrix: Consultant, Baxter: Advisor, Mallinckrodt: Consultant, Genfit: Consultant, Vantive: Ad hoc consultant, Cytotherix: Ad hoc consultant, Hugo Vargas:Sequana Medical: Consultant, Mallinckrodt: Consultant, Ocelot: Grant/Research Support, Arrowhead Phama: Grant/Research Support, Takeda: Grant/Research Support, Durect: Grant/Research Support, Durect: Grant/Research Support, River2Renal: Grant/Research Support, Genfit: Grant/Research Support, Kezar Pharmaceuticals: Grant/Research Support, Kezar Pharmaceuticals: Grant/Research Support, Bausch: Grant/Research Support, Raymond Chung:GSK: Grant/Research Support, Salix: Grant/Research Support, GSK: Consultant, Precision Biosciences: Consultant, Boehringer: Grant/Research Support, BMS: Grant/Research Support, Aligos: Grant/Research Support, Curve: Grant/Research Support, Pratima Sharma:Nothing to Disclose, Clara Tow:Nothing to Disclose, J. Pedro Teixeira:Eli Lilly: Stock - publicly traded company, Novo Nordisk: Stock - publicly traded company, Pfizer: Stock - publicly traded company, Outset Medical: Consultant, Jolla Pharmaceutical Company/Innoviva: Grant/Research Support, Eli Lilly and Company: Stock - publicly traded company, Novo Nordisk A/S: Stock - publicly traded company, Pfizer Inc.: Stock - publicly traded company, Mallinckrodt: Consultant, Vantive: Consultant, Talphera: Consultant, Zachary Fricker:Lipocine, Inc: Grant/Research Support, Pick Research: Consultant, River2Renal Corp: Grant/Research Support, Bausch, Inc.: Grant/Research Support, Guidepoint Global, LLC: Consultant, WL Gore: Speaking and Teaching, Stevan Gonzalez:Mallinckrodt Pharmaceuticals: Speaking and Teaching, Mallinckrodt Pharmaceuticals: Consultant, Madrigal Pharmaceuticals: Advisor, HEPQuant: Advisor, Javier Neyra:Nothing to Disclose, Jevon Robinson:Nothing to Disclose, Sydney Whittaker:Nothing to Disclose, Kavish Patidar:Madrigal Pharmaceuticals: Medical Advisory Board, Mallincrodt Pharmaceuticals: Consultant, HepQaunt: Consultant, Mallinckrodt Pharmaceuticals: Medical Advisory Board, OrganOx: Advisor, Madrigal Pharmaceuticals: Advisor, Keenova Therapeutics: Advisor and Consultant., Keenova Therapeuatics: Advisor and Consultant, Novo Nordisk: Advisor, HepQaunt: Consultant, Keenova Therapeutics: Advisor and Consultant, HepQuant: Consultant, Andrew Allegretti:Nothing to Disclose.

1493 | EFFECT OF COMBINED VILDAGLIPTIN AND SACUBITRIL/VALSARTAN THERAPY ON PORTAL HYPERTENSION IN CIRRHOTIC RATS

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Background: Portal hypertension (PH) is a major complication of cirrhosis, and conventional therapy with β-blockers is often limited by adverse effects such as hypotension, highlighting the need for novel pharmacological approaches. Recent studies have implicated increased activity of soluble epoxide hydrolase (sEH) and reduced levels of epoxyeicosatrienoic acids (EETs) in the pathogenesis of PH. Dipeptidyl peptidase-4 inhibitors (DPP-i) and angiotensin receptor–neprilysin inhibitors (ARNI) have been suggested to preserve EET bioactivity via suppression of sEH; however, their combined effects remain unclear. Therefore, we investigated the effects of these agents on portal pressure and liver fibrosis. **Methods:** Two rat cirrhosis models were used: a dietary model induced by a choline-deficient, L-amino acid-defined high-fat diet (CDAHFD) and a surgical model induced by bile duct ligation (BDL). Rats received vildagliptin (DPP-i; 10 mg/kg), sacubitril/valsartan (ARNI; 30 mg/kg), DPP-i + ARNI, or carvedilol (NSBB; 10 mg/kg). Portal pressure, hemodynamics, sEH activity, EET levels, endothelial function, vascular remodeling, and fibrosis were assessed by ELISA, qPCR, Western blotting, and

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immunohistochemistry. **Results:** In CDAHFD rats, portal pressure elevation was significantly attenuated by DPP-i or ARNI, and combination therapy showed a reduction comparable to NSBB. Unlike NSBB, DPP-i and ARNI did not alter mean arterial pressure, heart rate, or cardiac output. Both drugs increased vasodilatory markers (Gch, Ddah1), enhanced eNOS phosphorylation, and reduced moesin phosphorylation. Sinusoidal capillarization (CD34), pathological angiogenesis (Vegfa, Ptgs2, Pigf, Vwf), Hedgehog pathway activation, and profibrotic gene expression (Acta2, Col1a1, Tgfb1, Ctgf) were suppressed. sEH expression and activity were elevated in CDAHFD rats and were reduced by both agents, with concomitant increases in hepatic EETs. Similar therapeutic effects were observed in BDL rats, confirming efficacy across two distinct PH models. **Conclusion:** DPP-i and ARNI improved portal hypertension and liver fibrosis and demonstrated additive benefits when combined. This therapeutic strategy may represent a novel treatment option for cirrhosis-associated portal hypertension.
Disclosures: Masafumi Oyama:Nothing to Disclose, KOSUKE KAJI:Nothing to Disclose, Hitoshi Yoshiji: Nothing to Disclose.

1494 | PRESS-DERIVED ESTIMATED HVPG PREDICTS THE FULL CLINICAL COURSE OF CIRRHOSIS: FROM ACUTE DECOMPENSATION TO ACLF AND MORTALITY (PRESS : PORTAL PRESSURE REGRESSION AND ESTIMATION USING SIMPLE SERUM MARKERS)

Seul Ki Han[1] Hyung Tark Lee[1] Euiyoung Oh[1] Sang Gyune Kim[2] Soon Koo Baik[3] Hyun Jung Chung[1] Moon Young Kim[1], [1]Yonsei University Wonju College of Medicine, [2]Soonchunhyang University Bucheon Hospital, [3]Yonsei University Wonju College of Medicine, Wonju

Background: Hepatic venous pressure gradient (HVPG) is the gold standard for quantifying portal hypertension, but its invasiveness limits routine use. Non invasive test was widely used to cover up these limitations. **Methods:** We identified 670 patients with cirrhosis who underwent HVPG measurement and followed them longitudinally. External validation was performed in an independent cohort of 151 patients from a separate institution. We developed PRESS framework (Portal pressure Regression and Estimation using Simple Serum markers) model, a clinically interpretable regression-based model to (i) estimate continuous HVPG and (ii) classify clinically significant portal hypertension (CSPH; HVPG $\geq$10 mmHg) using routinely available variables. **Results:** After feature selection using repeated cross-validation, final models were comprised of five laboratory variables (INR, albumin, platelet count, total bilirubin, sodium). Regression analysis was applied to establish PRESS framework. Estimated HVPG (eHVPG) correlated with measured HVPG (Pearson r = 0.53). For CSPH classification, the model demonstrated an AUROC of 0.83 in the internal cohort and 0.73 in the external validation cohort. For acute decompensation, PRESS model stratified 1-year AD risk more sharply than measured HVPG (log-rank $p = 3.61\times10^{-10}$ vs 6.28×10^{-6}). This superiority was sustained over long-term follow-up for further AD ($p = 1.38\times10^{-17}$ vs 6.52×10^{-16}), ACLF ($p = 3.77\times10^{-16}$ vs 1.1×10^{-6}) and ACLF-related mortality ($p = 3.64\times10^{-14}$ vs 1.2×10^{-6}), with steeper Cox hazard gradients for both outcomes (further AD: HR = __vs ,ACLF: HR = 1.181 vs 1.084; ARM: HR = 1.178 vs 1.088; all $p < 0.001$). In a transient elastography included subset (n = 306), addition of liver stiffness measurement to PRESS model further improved CSPH prediction (AUROC 0.827 > 0.883). **Conclusion:** Using only routinely available variables, the PRESS model provides an interpretable, non-invasive estimate of portal pressure and predicts CSPH with external validation. It further enables clinically meaningful risk stratification for 1-year acute decompensation, subsequent decompensation, ACLF, and ACLF-related mortality.

Table 1. Multivariable Cox regression analyses for clinical outcomes according to measured HVPG and PRESS model.

Model	Outcome	Variable	HR (95% CI)	P
Age, Sex, MELD adjusted	1-year AD	HVPG	1.05 (1.02-1.09)	<0.001
		PRESS	1.13 (1.05-1.22)	<0.001
	Further AD	HVPG	1.07 (1.05-1.10)	<0.001
		PRESS	1.11 (1.07-1.16)	<0.001
	ACLF	HVPG	1.05 (1.02-1.09)	<0.001
		PRESS	1.15 (1.07-1.23)	<0.001
	LRM	HVPG	1.07 (1.03-1.10)	<0.001
		PRESS	1.14 (1.07-1.21)	<0.001
Age, Sex, CTP score adjusted	1-year AD	HVPG	1.05 (1.02-1.08)	0.002
		PRESS	1.10 (1.04-1.17)	0.002
	Further AD	HVPG	1.08 (1.05-1.10)	<0.001
		PRESS	1.14 (1.09-1.20)	<0.001
	ACLF	HVPG	1.06 (1.02-1.09)	<0.001
		PRESS	1.14 (1.08-1.21)	<0.001
	LRM	HVPG	1.06 (1.03-1.10)	<0.001
		PRESS	1.12 (1.04-1.21)	<0.001

HRs are presented per 1-mmHg increase in measured HVPG or PRESS.
AD : Acute decompensation, ACLF : Acute on chronic liver failure, LRM : Liver related mortality

Disclosures: Seul Ki Han:Nothing to Disclose, Hyung Tark Lee:Nothing to Disclose, Euiyoung Oh:Nothing to Disclose, Sang Gyune Kim:Nothing to Disclose, Soon Koo Baik:Nothing to Disclose, Hyun Jung Chung: Nothing to Disclose, Moon Young Kim:Nothing to Disclose.

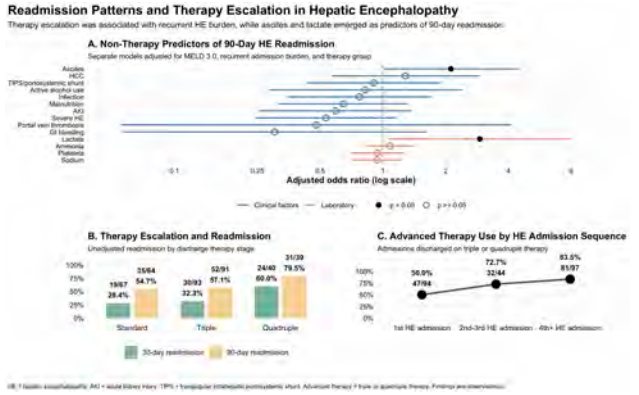
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1495 | THERAPY ESCALATION AND READMISSION PATTERNS IN HOSPITALIZED PATIENTS WITH HEPATIC ENCEPHALOPATHY

Joshua Pagán-Busigó[1] Elizabeth Peck[1] Yash Shah[1] Zachary Israeli[1] Lucie Pham[1] Rohan Karkra[1] Paul Gaglio[2], [1]Rutgers New Jersey Medical School, [2]Rutgers NJ Medical School

Background: Hepatic encephalopathy (HE) is associated with frequent recurrent hospitalizations, yet real-world therapy escalation patterns and their relationship to readmission risk remain incompletely characterized. We evaluated whether adjunctive therapy use identifies patients with more severe or recurrent HE at higher risk for readmission, while also assessing clinical and laboratory predictors of 90-day readmission. **Methods:** We performed a retrospective cohort study of patients admitted with HE at a tertiary academic center from January 2024 to January 2026. Admission-level data were collected across index and recurrent HE hospitalizations. Discharge therapy was classified as standard therapy (lactulose ± rifaximin), triple therapy (lactulose/rifaximin/zinc), or quadruple therapy (lactulose/rifaximin/zinc/levocarnitine). Primary outcomes were 30-day and 90-day HE readmission. Readmission rates were compared across therapy groups, and multivariable logistic regression was used to evaluate therapy strategy and non-therapy predictors of 90-day readmission, with standard errors clustered by patient. **Results:** A total of 102 patients contributed 347 HE admissions. Patient-level demographics and overall comorbidity burden were not independently associated with readmission. Readmission rates were highest among patients discharged on quadruple therapy. Thirty-day HE readmission was 28.4%, 32.3%, and 60.0% for standard, triple, and quadruple therapy, respectively. Ninety-day HE readmission was 54.7%, 57.1%, and 79.5%, respectively. Therapy strategy was not independently associated with readmission after adjustment. In adjusted non-therapy models, ascites was associated with 90-day readmission (OR 2.12, 95% CI 1.01–4.42, p = 0.046), as was admission lactate level (OR 2.92 per 1-unit increase, 95% CI 1.07–7.94, p = 0.036). In a separate model evaluating advanced therapy use, each additional HE admission increased the odds of discharge on triple or quadruple therapy (OR 1.42, 95% CI 1.17–1.73, p < 0.001). **Conclusion:** In this real-world HE cohort, triple and quadruple therapy were associated with higher unadjusted readmission rates but were not independently associated with readmission after adjustment. Ascites and admission lactate level emerged as potential markers of 90-day readmission risk. Advanced therapy use was more common during later HE admissions, suggesting that therapy escalation likely reflects recurrent HE burden and illness severity rather than a causal effect of therapy itself. These findings support further evaluation of whether earlier risk stratification and timely consideration of adjunctive therapy could reduce recurrent HE admissions.



Disclosures: Joshua Pagán-Busigó:Nothing to Disclose, Elizabeth Peck:Nothing to Disclose, Yash Shah:Nothing to Disclose, Zachary Israeli:Nothing to Disclose, Lucie Pham:Nothing to Disclose, Rohan Karkra:Nothing to Disclose, Paul Gaglio:Nothing to Disclose.

1496 | TNF-α-ASTROCYTE-VEGF-C AXIS-DRIVEN MENINGEAL AND NASOPHARYNGEAL COMPENSATORY LYMPHANGIOGENESIS PROTECTS AGAINST HEPATIC ENCEPHALOPATHY IN LIVER CIRRHOSIS

Shao-Jung Hsu[1] Yu-Tang Chang[2] Ming-Chih Hou[1] Yasuko Iwakiri[3] Fa-Yauh Lee[4], [1]Taipei Veterans General Hospital, [2]University of California, Berkeley, [3]Yale University, [4]National Yang-Ming University

Background: Neuroinflammation and hyperammonemia drive hepatic encephalopathy (HE), a critical complication of liver cirrhosis. The clearance of cerebrospinal fluid (CSF) relies heavily on both the meningeal lymphatic network and the nasopharyngeal lymphatic plexus. While previous research established that increased meningeal lymphangiogenesis mitigates HE and neuroinflammation during early cirrhosis, this current investigation evaluates these broader CSF clearance mechanisms in advanced cirrhosis models and explicitly validates these pathways in human clinical cohorts. **Methods:** Advanced cirrhosis was induced in male Sprague-Dawley rats via common bile duct ligation. Clinically, MRI assessed nasopharyngeal drainage and meningeal lymphatic

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flow in cirrhotic patients, comparing cohorts with and without HE. Additionally, *in vitro* studies utilized human primary astrocytes and an astrocyte cell line to assess underlying mechanisms. **Results:** Compared to early-stage counterparts, rats exhibiting advanced cirrhosis demonstrated upregulated nasopharyngeal and meningeal lymphangiogenesis. Notably, the severity of HE and neuroinflammation remained comparable between the two groups, despite exacerbated hyperammonemia and portal hypertension in advanced cirrhosis. Disruption of this compensatory lymphatic drainage—achieved surgically via deep cervical lymph node ligation or pharmacologically using lenvatinib—aggravated HE and neuroinflammation in the cirrhotic rat models. Strikingly, in the human clinical cohort (n = 42), cirrhotic patients suffering from HE demonstrated significantly diminished nasopharyngeal drainage alongside restricted flow in meningeal lymphatic channels compared to patients without HE. Mechanistically, *in vitro* analyses revealed that TNF-α upregulates VEGF-C (lymphangiogenic factor) protein expression within astrocytes. *In vivo*, acute lipopolysaccharide (LPS) administration significantly boosted blood TNF-α and cerebral VEGF-C levels in cirrhotic rats, whereas prolonged TNF-α blockade successfully inhibited both brain VEGF-C expression and subsequent meningeal lymphangiogenesis. **Conclusion:** Advanced liver cirrhosis induces compensatory nasopharyngeal and meningeal lymphangiogenesis through a TNF-α–astrocyte–VEGF-C signaling pathway, enhancing CSF drainage and limiting neuroinflammation and hepatic encephalopathy despite worsening hyperammonemia and portal hypertension. Disruption of these lymphatic networks aggravates neuroinflammation and HE in cirrhotic rats. Crucially, direct imaging of human patients confirms this functional relationship, demonstrating impaired meningeal and nasopharyngeal lymphatic drainage in cirrhotic patients with HE. Together, these translational findings identify compensatory lymphatic remodeling as an important protective mechanism against HE in advanced cirrhosis.

Disclosures: Shao-Jung Hsu:Nothing to Disclose, Yu-Tang Chang:Nothing to Disclose, Ming-Chih Hou: Nothing to Disclose, Yasuko Iwakiri:Nothing to Disclose, Fa-Yauh Lee:Nothing to Disclose.

1497 | LIVERRISK SCORE CORRELATED WITH HEPATIC VEIN PRESSURE GRADIENT IN LIVER CIRRHOSIS

Hsin-Hua Lai[1] Pei-Shan Wu[2] Yun-Cheng Hsieh[3] Han-Chieh Lin[1] Ming-Chih Hou[1] Kuei-Chuan Lee[3], [1]Taipei Veterans General Hospital, [2]Taipei Veterans General Hospital, Taipei, Taiwan, [3]Taipei Veterans General Hospital, Taipei, Taiwan.

Background: Portal hypertension is a major complication of liver cirrhosis and is associated with adverse clinical outcomes. Although hepatic venous pressure gradient (HVPG) remains the gold standard for assessing portal hypertension, it requires invasive procedure. The LiverRisk Score (LRS) is a recently proposed scoring system that correlated with liver stiffness and predicted liver-related complications. Evaluating the association between LRS and HVPG may provide insight into its potential utility for identifying patients at high risk of portal hypertension. **Methods:** Patients with cirrhosis were retrospectively enrolled between March 2011 and November 2024. HVPG measurements and clinical parameters for calculating LRS, MELD, Child–Pugh, ALBI, APRI, and FIB-4 were collected. Spearman's correlation and linear regression analyses were performed to evaluate associations between HVPG and clinical parameters. ROC analysis was used to assess the predictive performance of each parameter for different HVPG level. Cox proportional hazards regression analysis was performed to identify predictors of clinical outcomes. **Results:** A total of 74 patients were analyzed (mean age 61.84 ± 11.72 years; 79.7% male), with hepatitis B being the most common etiology (41.9%). The mean LRS was 8.75 ± 2.34, and the mean HVPG was 17.19 ± 4.82 mmHg.LRS was significantly correlated with HVPG in Spearman's analysis ($r_s = 0.258$, $p = 0.027$). In univariate linear regression, LRS was positively associated with HVPG ($\beta = 0.308$, $R^2 = 0.095$, $p = 0.008$) and remained the only significant parameter in multivariable analysis ($\beta = 0.327$, $p = 0.008$). In patients with HVPG ≥ 16 mmHg, LRS demonstrated the only significant predictive performance (area under the ROC curve 0.711, $p = 0.001$), with an optimal cutoff value of 7.33.Regarding clinical outcomes, LRS was independently associated with new-onset hepatic encephalopathy (Hazard ratio = 1.244, $p = 0.027$) and acute kidney injury (Hazard ratio = 1.220, $p = 0.029$) during one-year follow-up in Cox multivariable regression. **Conclusion:** LRS is independently correlated with HVPG and demonstrates significantly predictive ability for patients with HVPG ≥ 16 mmHg. Additionally, LRS independently predicts new-onset hepatic encephalopathy and acute kidney injury, supporting its potential role as a non-invasive risk stratification tool in liver cirrhosis.

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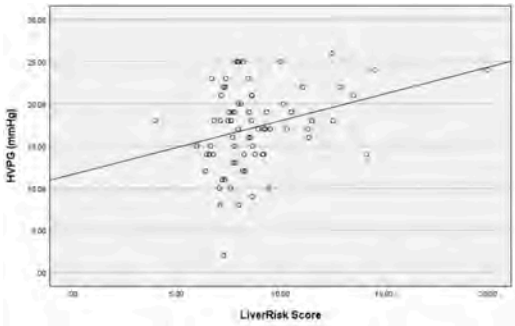
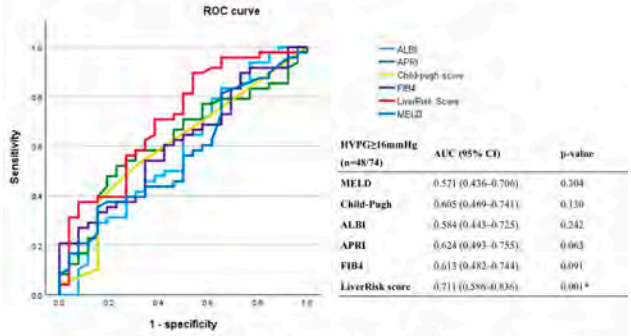


Figure 1. The association of LiverRisk score and HVPG.
The figure demonstrated the correlation between LiverRisk score and HVPG. Spearman's coeffeicient (r_s) was 0.258 with p-value=0.027.



HVPG≥16mmHg (n=48/74)	AUC (95% CI)	p-value
MELD	0.571 (0.436–0.706)	0.304
Child-Pugh	0.605 (0.469–0.741)	0.130
ALBI	0.584 (0.443–0.725)	0.242
APRI	0.624 (0.493–0.755)	0.063
FIB4	0.613 (0.482–0.744)	0.091
LiverRisk score	0.711 (0.586–0.836)	0.001*

Figure 2. ROC curve and analysis for predictors of HVPG≥16mmHg

Table 1. Multivariable linear regression analysis for predictors of HVPG

Variable (n=74)	B (95% CI)	β	p-value	Tolerance	VIF
MELD	0.174 (-0.372 – 0.720)	0.120	0.528	0.351	2.852
Child-Pugh score	-0.081 (-1.252 – 1.089)	-0.032	0.890	0.243	4.114
ALBI	1.480 (-1.468 – 4.429)	0.175	0.320	0.413	2.420
APRI	-0.014 (-2.003 – 1.975)	-0.003	0.989	0.235	4.263
FIB-4	0.036 (-0.347 – 0.418)	0.043	0.852	0.243	4.123
Liver risk Score	0.676 (0.181 – 1.170)	0.327	0.008	0.871	1.148

Disclosures: Hsin-Hua Lai:Nothing to Disclose, Pei-Shan Wu:Nothing to Disclose, Yun-Cheng Hsieh: Nothing to Disclose, Han-Chieh Lin:Nothing to Disclose, Ming-Chih Hou:Nothing to Disclose, Kuei-Chuan Lee:Nothing to Disclose.

1498 | FRAILTY AS A PREDICTOR OF POST-TIPS HEPATIC ENCEPHALOPATHY, ACUTE KIDNEY INJURY, AND REHOSPITALIZATION

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Background: Transjugular Intrahepatic Portosystemic Shunt (TIPS) placement is complicated by hepatic encephalopathy (HE) in up to 40% of patients, yet pre-procedural risk stratification remains imprecise. Frailty, a state of reduced physiologic reserve is highly prevalent in cirrhosis and predicts adverse outcomes including waitlist mortality, independent of ascites and HE. Whether frailty independently predicts post-TIPS HE, acute kidney injury (AKI), and rehospitalization has not been studied in a large real-world cohort. **Methods:** We conducted a retrospective cohort study using the TriNetX federated network (111 health systems). Adults undergoing TIPS (CPT 37182) were stratified by frailty using a modified frailty index (mFI): frail (≥ 2 of: diabetes, hypertension, heart failure, COPD, CKD, dementia) vs. non-frail (< 2). Cohorts were matched 1:1 on age, sex, race, and ethnicity. Primary outcome was 1-year incident HE (K76.82). Secondary outcomes included 1-year AKI (N17), rehospitalization, and mortality. Kaplan-Meier and Cox regression adjusting for age, sex, alcoholic cirrhosis, ascites, and esophageal varices were performed. **Results:** Of 12,284 TIPS patients, 8,667 (70.6%) met frailty criteria. After 1:1 matching (n = 1,239 per group), frail patients had higher 1-year HE (25.8% vs. 15.2%; HR 1.708, 95% CI 1.364–2.140, $p < 0.0001$), AKI (45.1% vs. 25.5%; HR 1.724, 95% CI 1.494–1.989, $p < 0.0001$), and rehospitalization (HR 1.115, 95% CI 1.016–1.224, $p < 0.0001$). Frailty remained an independent predictor of HE on multivariable Cox regression (aHR 1.889, 95% CI 1.638–2.178, $p < 0.0001$), alongside ascites (aHR 1.490) and esophageal varices (aHR 1.486). Frail patients paradoxically demonstrated lower 1-year mortality (21.9% vs. 28.2%; aHR 0.632, $p < 0.0001$), potentially reflecting indication bias from emergent TIPS in non-frail patients. **Conclusion:** Frailty was present in over 70% of TIPS recipients and independently predicted 1-year HE and AKI after adjustment for liver disease severity. These findings suggest that pre-procedural frailty assessment may identify patients warranting intensified post-TIPS surveillance, prophylactic lactulose, or enhanced shared decision-making. Additionally, prehabilitation with physical therapy and nutrition counseling may help ameliorate frailty and thus improve post-TIPS outcomes in this vulnerable population. The paradoxical mortality finding likely reflects differential TIPS indications by frailty status. Frailty screening should be incorporated into pre-TIPS risk stratification.

Table 1. Kaplan-Meier Outcomes: Frail vs. Non-Frail TIPS Patients (Matched Cohorts, n=1,239 each)

Outcome	Frail: n/N (%)	Non-frail: n/N (%)	HR (95% CI)	p-value
90-Day Outcomes				
Hepatic encephalopathy	155/938 (17.6%)	91/1,010 (9.9%)	1.681 (1.298–2.178)	< 0.0001
Acute kidney injury	405/1,239 (33.4%)	273/1,239 (23.0%)	1.439 (1.234–1.678)	< 0.0001
Rehospitalization†	883/1,239 (71.3%)	819/1,239 (66.1%)	1.078 (0.981–1.186)	0.065
1-Year Outcomes				
Hepatic encephalopathy	214/938 (25.8%)	118/1,010 (15.2%)	1.708 (1.364–2.140)	< 0.0001
Acute kidney injury	525/1,239 (45.1%)	291/1,239 (25.5%)	1.724 (1.494–1.989)	< 0.0001
Rehospitalization	944/1,239 (76.2%)	842/1,239 (68.0%)	1.115 (1.016–1.224)	< 0.0001
Overall mortality	271/1,239 (21.9%)	350/1,239 (28.2%)	0.609 (0.520–0.714)	0.0002

HR = hazard ratio from Kaplan-Meier log-rank analysis. All outcomes measured after index TIPS date. HE analysis excludes patients with prior HE. † Log-rank p=0.065; HR p<0.0001.

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Disclosures: Abhinav Birda:Nothing to Disclose, Sahak Hovsepian:Nothing to Disclose, Nakul Ganju:Nothing to Disclose, Gevork Davtian:Nothing to Disclose.

1499 | EMERGING SAFETY, PHARMACOKINETIC, AND PHARMACODYNAMIC RESULTS OF THE FIRST MULTIPLE-ASCENDING DOSE COHORT FROM THE PHASE 1 PHIN-001 STUDY OF PHIN-214 IN ADULTS WITH DECOMPENSATED CIRRHOSIS

Eric Lawitz[1] Tarek Hassanein[2] Jacqueline O'Leary[3] Anita Kohli[4] Mangesh Pagadala[5] Ethan Weinberg[6] Christina Lindenmeyer[7] Gary Reiss[8] Douglas Simonetto[9], [1]Texas Liver Institute, University of Texas Health San Antonio, [2]Southern California Research Center, [3]Dallas VAMC, [4]Arizona Liver Health, [5]The Liver Institute at Methodist Dallas, [6]University of Pennsylvania, [7]Cleveland Clinic, [8]Tandem Clinical Research, [9]Mayo Clinic Rochester

Background: Portal hypertension drives decompensation in cirrhosis, but outpatient treatment options are limited. PHIN-214 is a novel vasopressin analogue with partial V1a receptor agonism and reduced V2 activity, designed to induce splanchnic vasoconstriction and increase effective arterial volume. PHIN-214 is being developed for once-daily, subcutaneous, self-administration for outpatient management of portal hypertension and its associated complications. **Methods:** PHIN-001 (NCT05490888) is an ongoing Phase 1 dose-optimization study evaluating single ascending dose (SAD, completed) and multiple ascending doses (MAD, enrolling) of PHIN-214 in adults with cirrhosis. The primary objectives included safety, tolerability, pharmacokinetic, and pharmacodynamic assessments. **Results:** The first MAD cohort comprised of 6 diuretic-dependent participants with Child-Pugh Class B cirrhosis, who were treated over a 28-day dosing period. The first subject developed grade 4 hyponatremia after 4 consecutive daily doses. For the 5 subsequent subjects, an every-other-day lead-in dosing was administered to allow serum sodium to stabilize, followed by daily dosing through day 28. All 5 subjects discontinued diuretics prior to PHIN-214 dosing and remained off diuretics, completing the 28-days of dosing without worsening ascites or statistically significant increases in weight. Apart from the first subject, all adverse events considered at least possibly related to PHIN-214 were grade 1-2, generally transient (resolving within the first week), and included hyponatremia, abdominal discomfort, diarrhea, transient left leg swelling in one participant and injection-site blanching in one participant. To date, baseline demographics across SAD and MAD include 22 subjects ranging from 24–72 years of age [mean: 54], including 10 females and 12 males, with 11 Child-Pugh A and 11 Child-Pugh B patients. PHIN-214 produced on-target physiologic effects with mean eGFR [CKD-EPI cystatin C] improving by 31% (SD 22%, $p = 0.0019$) within 12 hours of dosing, with the magnitude of improvement correlated with PHIN-156 (active metabolite) exposure. Intra subject PK was stable across 28 days with no PHIN-214 or PHIN-156 accumulation. **Conclusion:** In decompensated cirrhotic subjects, 28 days of subcutaneous PHIN-214 with an every-other-day lead-in was well tolerated and produced rapid, exposure dependent improvements in eGFR consistent with selective V1a engagement. These data support continued MAD dose escalation and evaluation of PHIN-214 as an outpatient therapy for portal hypertension. Data from additional MAD cohorts will be presented.

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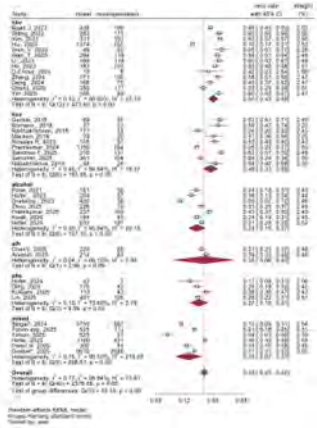
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1500 | CIRRHOSIS RECOMPENSATION: A SYSTEMATIC REVIEW WITH AGGREGATE META-ANALYSIS BY ETIOLOGY OF CIRRHOSIS

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Background: Recompensation is a recent stage of cirrhosis in which a patient with decompensated cirrhosis (ascites, variceal hemorrhage and/or encephalopathy) regresses to a compensated stage following elimination/suppression of etiological agent. Since its first definition at Baveno VII, an increasing number of studies have emerged describing a large variability in the rate of recompensation (10-65%). **Methods:** We performed a systematic review with aggregate data meta-analysis of studies on recompensation stratified by etiology of cirrhosis. The study protocol is registered in PROSPERO CRD420251091140 and complies with PRISMA recommendations. We included RCTs or observational studies reporting recompensation published between January 2014 and March 2026 using PubMed, Embase and Cochrane databases; studies including patients with metabolic-associated liver disease were excluded. Pooled estimates were computed by random effects and heterogeneity by I^2 statistics. **Results:** We identified 39 studies (28 full reports, 11 abstracts) totaling 27,047 patients with decompensated cirrhosis. Etiology was HBV in 13 studies, HCV in 9, alcohol in 7, autoimmune in 2, biliary in 4, mixed in 5. Recompensation was defined according to Baveno VII criteria in 27 studies. The pooled recompensation rate was 35% (CI 29-42; I^2 = 98%): HBV 50% (42-59; I^2 = 95%), HCV 46% (33-59; I^2 = 95%), alcohol 24% (15-37; I^2 = 95%), autoimmune 35% (6-83; I^2 = 66%), biliary 27% (16-41; I^2 = 74%) mixed etiologies 15% (7-31; I^2 = 99%). There was significant heterogeneity both between and within etiologies, in part explained by the severity of liver dysfunction, with patients with greater severity being less likely to recompensate. The pooled recompensation rate was not significantly different according to the definition of recompensation, type of publication, or risk of bias. Recompensation was associated with a 70% lower risk of death (95% CI: 57%–79%) overall and by etiology. **Conclusion:** In the largest published cohort of patients with decompensated cirrhosis to date, recompensation occurred in 35% of patients following elimination or sustained suppression of the underlying etiology, with rates highest in HBV-related cirrhosis, followed by HCV-, alcohol-, and other etiologies. Recompensation was associated with significantly reduced mortality.

Meta-analysis of recompensation according to etiology



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1501 | RICE RECOMBINANT VERSUS PLASMA-DERIVED HUMAN ALBUMIN IN LIVER CIRRHOSIS

Yanhang Gao[1] Guiqiang Wang[2] Zhijie Qin[3] Liang Hong[4] Yue Chen[5] Xing Li[6] Cuisong Wu[7] Zong Zhang[8] Lvfeng Yao[9] Lei Yu[10] Caibin Huang[11] Zujiang Yu[12] Yawen Luo[13] Mingjuan Yuan[14] Qinming Hu[15] Hui Chen[16] Minghua Su[17] Guoqiang Zhang[18] Xuan An[19] Heng Zhang[20] Zhongjie Hu[0] Jinhui Yang[22] Mingqin Lu[23] Xiaoping Wu[24] Zhanzhou Lin[25] Xiaolin Zhou[26] Xiaoxiong Hu[27] Huizhen Fan[27] Zhilan Liu[28] Jidong Jia[29] Jia You[30] Lichun Wang[31] Ling Du[32] Gang Chen[32] Ye Gu[33] Xiaofeng Wu[33] Jinlin Hou[34] Xudong Hu[35] Guangming Li[36] Bingliang Lin[37] Bin Li[38] Dazhi Zhang[39] Yida Yang[40] Zhongyin Zhou[41] Lei Fu[42] Xinrui Wang[43] Hongyan Ma[3] Rajiv Jalan[44] Cliff Y. Yang[3] Daichang Yang[3] Junqi Niu[1], [1]The First Hospital of Jilin University, Changchun, China-Singapore Belt and Road Joint Laboratory, [2]Peking University First Hospital, [3]Healthgen Biotech, [4]The Third Affiliated Hospital of Wenzhou Medical University, [5]Taihe Hospital, Shiyan, [6]Pingxiang People's Hospital, [7]The Third People's Hospital of Zhenjiang, [8]Shandong Public Health Clinical Center, [9]Mengchao Hepatobiliary Hospital of Fujian Medical University, [10]The Fourth Hospital of Harbin Medical University, [11]The First Affiliated Hospital of Gannan Medical College, [12]The First Affiliated Hospital of Zhengzhou University, [13]Affiliated Hospital of Zunyi Medical University, [14]Yueyang Central Hospital, [15]Jingzhou Central Hospital, [16]Hepatobiliary Hospital of Jilin, [17]The First Affiliated Hospital of Guangxi Medical University, [18]Luoyang City Center Hospital, [19]Chongqing University Three Gorges Hospital, [20]Wuhan Central Hospital, [0]Liver Disease Center, Beijing You'an Hospital, Capital Medical University, Beijing, China , [22]The Second Affiliated Hospital of Kunming Medical University, [23]The First Hospital of Wenzhou Medical University, [24]The First Affiliated Hospital of Nanchang University, [25]Huizhou Central People's Hospital, [26]Yichang Central People's Hospital, [27]Yichun people's hospital, [28]Qinghai Provincial People's Hospital, [29]Beijing Friendship Hospital, Capital Medical University, [30]The First Hospital of Fujian Medical University, [31]West China Hospital of Sichuan University, [32]Liuzhou Workers' Hospital, [33]The Sixth People's Hospital of Shenyang, [34]Nanfang Hospital, Southern Medical University, [35]Wuhan Jinyintan Hospital, [36]Department of Hepatology, Affiliated Infectious Disease Hospital of Zhengzhou University, [37]The Third Affiliated Hospital, Sun Yat-sen University, [38]Affiliated Hospital of Guilin Medical University, [39]The Second Affiliated Hospital of Chongqing Medical University, [40]The First Affiliated Hospital, Zhejiang University School of Medicine, [41]Wuhan University People's Hospital, [42]Xiangya Hospital Central South University, [43]The First Hospital of Jilin University, Changchun, China-Singapore Belt and Road Joint Laboratory, [44]University College London Medical School

Background: Despite potential contamination risk and inadequate supply, human plasma has remained the only source for human serum albumin (pHSA) intravenous administration (IV) since the 1940s. Here we report a pivotal trial of OsrHSA, a recombinant HSA purified from bioengineered Oryza sativa (rice) endosperm (seeds). **Methods:** We conducted a randomized, positive-controlled, double-blind, and non-inferiority phase 3 trial with patients with liver cirrhosis and serum albumin $\leq$30 g/L. 328 patients with liver cirrhosis were randomly assigned (1:1) to once-daily 20g IV of OsrHSA or pHSA for up to 2 weeks. The primary outcome was the proportion of patients to reach a serum albumin level of 35g/L (non-inferiority margin $<$-0.16). Key secondary outcomes included colloid osmotic pressure, time-to-event (reaching a serum albumin level of 35 g/L), ascites severity and serum albumin. **Results:** 328 patients were randomly assigned: 165 patients were assigned to OsrHSA, and 163 to pHSA. OsrHSA was non-inferior to pHSA in primary outcome in the intent-to-treat (difference = -5.39%; lower limit of 97.5% CI = -0.1147), as-treated (difference = -6.98%; lower limit of 97.5% CI = -0.1252) and per-protocol (difference = -6.08%; lower limit of 97.5% CI = -0.1201) sets. There was no significant difference between OsrHSA and pHSA in all secondary outcomes. There were no clinically significant anti-drug or anti-host-cell-protein antibodies. Adverse events (OsrHSA, 87.8%; pHSA, 86.4%) or serious adverse events (OsrHSA, 12.2%; pHSA, 10.5%) were comparable. There were no treatment-related serious adverse events or deaths. **Conclusion:** Rice-derived HSA is non-inferior to plasma-derived HSA in efficacy and safety.

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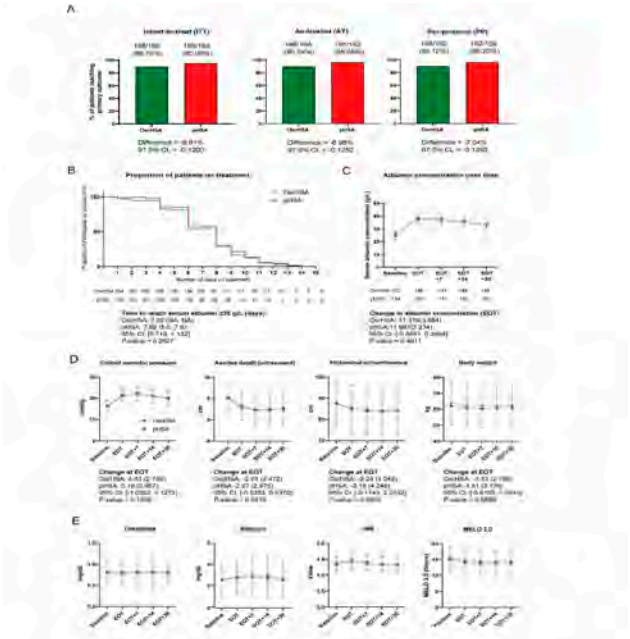


Figure : Outcomes. (**A**) Non-inferiority analysis of primary outcome in ITT, AT and per-protocol (PP) sets. PP included patients included all participants in the AT who did not have a major protocol deviation. The difference and lower 97.5% confidence level (CL) were calculated using Newcombe confidence interval. The non-inferiority margin was -16%. Hypothetical strategy MI imputation and stratified analysis was used for AT, ITT and PP. (**B**) Kaplan-Meier analysis of time to reach primary outcome (AT). P-value was analyzed using Logrank test and Cox regression models. (**C**) Serum albumin from predose to end of follow-up (albumin population, defined by patients in the AT who did not use other albumin products by EOT+30. OsrHSA, n=152; pHSA, n=154). Changes at EOT was calculated as adjusted least square means (SE). P-value was analyzed using an analysis of Covariance (ANCOVA). (**D**) Colloid osmatic pressure (albumin population, defined by patients in the AT who did not use other albumin products by EOT+30, OsrHSA, n=152; pHSA, n=154), ascites depth, abdominal circumference and body weight (ascites population, defined as patients who was diagnosed with ascites at baseline, OsrHSA, n=111, pHSA, n=119) were measured at baseline, EOT, EOT+7, EOT+14 and EOT+30. Changes at EOT was calculated as adjusted least square means (SE). P-value was analyzed using an analysis of Covariance (ANCOVA). (**E**) Serum creatinine, bilirubin, INR and MELD 3.0 scores were measured from baseline to end of follow-up (laboratory population, defined by patients in the AT who had at least one serum laboratory value after treatment). Datapoints are mean and error bars are standard deviation.

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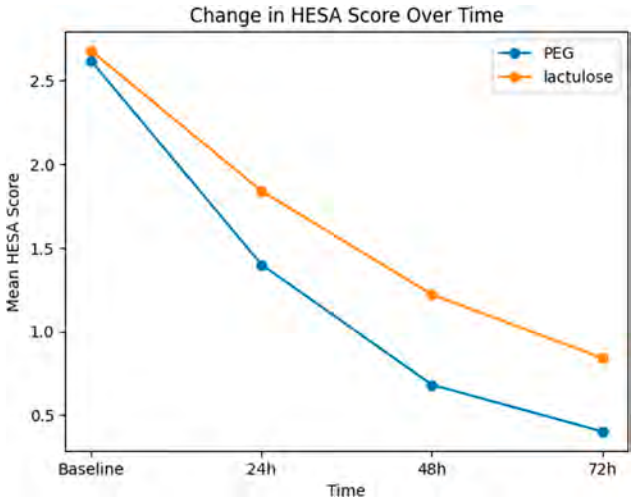
1502 | COMPARATIVE EFFECTIVENESS OF POLYETHYLENE GLYCOL ELECTROLYTE SOLUTION VERSUS LACTULOSE FOR TREATMENT OF HEPATIC ENCEPHALOPATHY: A SINGLE BLIND, RANDOMISED CONTROL TRIAL

Sunil Dadhich[1] Arihant Seth[1] Saurabh Jain[1], [1]Dr. Sampurnanand Medical College, Jodhpur

Background: Hepatic encephalopathy (HE) is a common and serious complication of cirrhosis. Lactulose is the standard therapy, but its use is limited by gastrointestinal side effects and poor compliance. Polyethylene glycol (PEG) has emerged as a potential alternative with a faster onset of action. This study compared the efficacy and safety of PEG versus lactulose in overt HE. **Methods:** In this prospective, randomized, single-blind study, 100 patients with overt HE presenting with acute decompensation were included, of whom 37 had acute-on-chronic liver failure and 63 had acute decompensation without ACLF. Patients were randomized to receive lactulose (n = 50) or PEG (n = 50). The primary outcome was change in mean HESA score at 24, 48, and 72 hours. Secondary outcomes included time to resolution of HE, duration of hospital stay, changes in serum ammonia, and adverse events. **Results:** Baseline characteristics were comparable. The PEG group showed greater reduction in mean HESA scores at 24 hours (−0.44; 95% CI −0.80 to −0.08; p = 0.017), 48 hours (−0.54; 95% CI −0.92 to −0.16; p = 0.007), and 72 hours (−0.44; 95% CI −0.76 to −0.12; p = 0.008). Time to resolution and hospital stay were shorter with PEG but not statistically significant. Ammonia reduction was comparable. Adverse events were more frequent with lactulose (26% vs 10%, p = 0.038). Subgroup analysis suggested a trend toward greater benefit of PEG in patients with more severe disease (ACLF). **Conclusion:** PEG results in

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faster clinical improvement and better tolerability than lactulose in overt HE and may be an effective alternative, particularly in hospitalized patients.



Disclosures: Sunil Dadhich:Nothing to Disclose, Arihant Seth:Nothing to Disclose, Saurabh Jain:Nothing to Disclose.

★ 1503 | RISK FACTORS ASSOCIATED WITH FALLS IN PATIENTS WITH LIVER CIRRHOSIS

Ester Palacio[1] Carlos Cespedes[1] Monica Pons[1] Sergi Quiroga[1] Nuria Roson[1] Elena Vargas-Accarino[1] Cristina Dopazo[1] Guillermo Cardenas[1] Victor Vargas[1] Macarena Simon-Talero[1] Lluis Castells[1] Isabel Campos-Varela[1], [1]Liver Unit. Hospital Vall d'Hebron

Background: Falls in patients with cirrhosis have been associated with worse quality of life, functional impairment, and death. There is evidence of a correlation between frailty, sarcopenia, and falls in the elderly population. We aimed at evaluating the role of muscle and frailty on falls in patients with cirrhosis. **Methods:** Single-center cross-sectional study. Patients with cirrhosis who underwent an abdominal computed tomography (CT) for any reason (June/2020- April/2024) were included. Sarcopenia was defined by the CT-based skeletal muscle index (SMI) at L3: <39 cm²/m² in women and <50 cm²/m² in men. Myosteatosis was assessed by measuring muscle attenuation on abdominal CT: <41 HU for BMI <25 kg/m² and <33 HU for BMI ≥ 25 kg/m². Frailty was defined by the Liver Frailty Index: frail >4.5. Sarcopenia was also evaluated by means of anthropometry, bioimpedance and ultrasonography of thigh and psoas muscle. Thigh muscle thickness index (TMTI) and psoas muscle thickness index (PMTI) were measured. Thigh elastography was also measured. Clinical, anthropometric, and quality-of-life data were also collected. **Results:** 248 patients with cirrhosis were included (26% women), median age of 62 years (IQR 56–68). The most common causes of cirrhosis were alcohol-related liver disease (42%), metabolic liver disease (22%), and hepatitis C virus infection (20%). Sarcopenia was present in 94 participants (38%), frailty in 92 (37%), and both were present in 37 patients (14.9%). Myosteatosis was present in 113 (46%) patients. Seventy-four subjects experienced falls, of whom 36% were women.In the univariate analysis, factors associated with a higher risk of falls were female sex (OR = 2.12; 95% CI 1.17–3.86; p = 0.01), diabetes (OR = 1.99; 95% CI 1.14–3.48; p = 0.01), hepatic encephalopathy (HE) (OR = 2.88; 95% CI 1.28–6.50; p = 0.01), myosteatosis (OR = 2.23; 95% CI 1.28–3.88; p = 0.005), and frailty (OR = 1.84; 95% CI 1.05–3.21; p = 0.03). Hospitalization was also associated with a higher risk of falls (OR = 1.77; 95% CI 1.02–3.08; p = 0.04). Neither sarcopenia, liver dysfunction, nor disease stage was associated with an increased risk of falls.In the multivariable model, the associations remained similar in magnitude and direction. Female sex (OR = 2.05; 95% CI 1.10–3.84; p = 0.02), diabetes (OR = 1.85; 95% CI 1.03–3.31; p = 0.04), myosteatosis (OR = 1.82; 95% CI 1.02–3.27; p = 0.04), and encephalopathy (OR = 2.42; 95% CI 1.00–5.85; p = 0.049) were significantly associated with an increased risk of falls, independently of disease severity, MELD-Na (OR = 0.99; 95% CI 0.95–1.04; p = 0.95). **Conclusion:** In patients with cirrhosis, female sex, diabetes, hepatic encephalopathy, and poor muscle quality (myosteatosis) were associated with an increased risk of falls, independently of disease stage. In our cohort, neither sarcopenia nor frailty were independently associated with an increased risk of falls.
Disclosures: Ester Palacio:Nothing to Disclose, Carlos Cespedes:Nothing to Disclose, Monica Pons:Nothing to Disclose, Sergi Quiroga:Nothing to Disclose, Nuria Roson:Nothing to Disclose, Elena Vargas-Accarino:Nothing to Disclose, Cristina Dopazo:Nothing to Disclose, Guillermo Cardenas:Nothing to Disclose, Victor Vargas:Nothing to Disclose, Macarena Simon-Talero:Nothing to Disclose, Lluis Castells:Nothing to Disclose, Isabel Campos-Varela:Chiesi: Speaking and Teaching, Astellas: Speaking and Teaching.

1504 | ASSESSMENT OF NON-INVASIVE TESTS FOR PREDICTION OF FIRST DECOMPENSATION IN COMPENSATED ADVANCED CHRONIC LIVER DISEASE: A MULTI-CENTRE COHORT STUDY

Kai Yi Benjamin Nah[1] Margaret Teng[2] Selvakumar Vigneshwaran[3] N Apoorva Sasikumar[4] Vincent Chen[5] Jimmy Che-To Lai[6] Karn Wijarnpreecha[7] Rahul Kumar[8]

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Background: Accurate prediction of first hepatic decompensation in compensated advanced chronic liver disease (cACLD) remains an important unmet clinical need. We aimed to evaluate and compare the prognostic performance of commonly used non-invasive tests (NITs) for predicting first hepatic decompensation in cACLD. **Methods:** We performed a retrospective multicentre longitudinal cohort study using data from the Cirrhosis Outcomes and Research Endeavour (CORE) consortium, comprising 19 tertiary centres across nine countries. Adults with cACLD, defined as liver stiffness measurement (LSM) $\geq$10 kPa by vibration-controlled transient elastography and no prior hepatic decompensation, were included. Evaluated NITs were Fibrosis-4 index (FIB-4), NAFLD Fibrosis Score (NFS), AST-to-platelet ratio index (APRI), Model for End-Stage Liver Disease (MELD) 3.0, LSM, AGILE 3+, and AGILE 4. Prognostic performance for first hepatic decompensation was assessed using discrimination and calibration metrics. **Results:** A total of 2,895 patients were included; median age was 58.0 years, median BMI was 28.0 kg/m², and 46% were male. 435 patients (15.0%) developed first hepatic decompensation after a median of 32.1 months. AGILE 4 demonstrated the best discrimination (Harrell's C-statistic 0.759), followed by AGILE 3+ (0.744), NFS (0.720), FIB-4 (0.706), MELD 3.0 (0.685), LSM (0.680), and APRI (0.664). AGILE 4 also showed the best calibration, with a Brier score of 0.069. However, all models exhibited only moderate prognostic performance overall and showed calibration drift over time. **Conclusion:** AGILE 4 showed the best performance among the evaluated NITs, although its predictive accuracy was moderate. More robust prognostic models, incorporating disease-specific and dynamic longitudinal factors, are needed.

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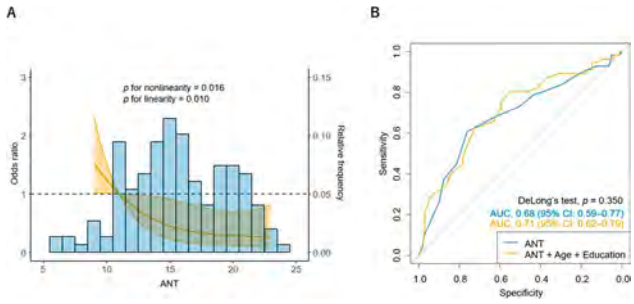
1505 | ANIMAL NAMING TEST CAN IDENTIFY COVERT HEPATIC ENCEPHALOPATHY IN PATIENTS WITH CIRRHOSIS WITH LIMITED INFLUENCE FROM AGE OR EDUCATIONAL LEVE

Takao Miwa[1] Shinji Unome[1] Masashi Aiba[1] Sachiyo Hirata[2] Satomi Nakashima[2] Kayoko Nishimura[2] Yoshiyuki Miwa[3] Teruo Maeda[4] Masahito Shimizu[1], [1]Gifu University, [2]Gifu University Hospital, [3]Miwa Clinic, [4]Nishimino Kosei Hospital

Background: The usefulness of the animal naming test (ANT) in identifying covert hepatic encephalopathy (CHE) is limited because adjustments for age and educational level are necessary. This study aimed to validate the ANT in Japanese patients with cirrhosis and to clarify whether such adjustments affect diagnostic performance. **Methods:** This multicenter cross-sectional study included Japanese patients with cirrhosis and healthy controls. Independent CHE factors were assessed using a logistic regression model, and the discriminative ability of the ANT alone versus an adjusted model was compared using the area under the receiver-operating characteristic curve (AUC). To demonstrate the association between the performance of ANT and the odds ratio (OR) of CHE, an adjusted restricted cubic spline (RCS) model with three knots was applied. **Results:** Among the 152 patients with cirrhosis and 56 controls, propensity score matching identified 43 individuals in each group. Patients with CHE had the lowest ANT scores, followed by those without CHE and healthy controls (14 vs. 17 vs. 19). A multivariable analysis showed that the ANT was an independent factor for identifying CHE (OR, 0.88; 95% confidence interval, 0.80-0.97; p = 0.009), whereas age and educational level were not. The RCS model revealed a rapid increase in the ORs of CHE with a decline in ANT performance **(Figure 1A)** . The AUC for the ANT alone in CHE diagnosis was comparable to that for the adjusted model using age and educational level (0.68 vs. 0.71; p = 0.350; **Figure 1B**). ANT performance was not influenced by age or educational level among those with CHE. The ANT's optimal, rule-out (90% sensitivity), and rule-in (90% specificity) cut-off values for identifying CHE were 15, 20, and 11, respectively. **Conclusion:** The ANT can identify CHE in Japanese patients with cirrhosis, and adjustment for age and educational level has a limited influence on its diagnostic performance.

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1506 | EFFECT OF PROBIOTIC THERAPY ON FRAILTY IN PATIENTS WITH DECOMPENSATED CIRRHOSIS: A RANDOMIZED CONTROLLED TRIAL

Sunil Taneja[1] Savneet Singh[2] Harish Bhujade[3] Yaswant Kumar[2] Amol Patil[2] Kannupriya .[2] Arka De[2] Nipun Verma[2] Madhumita Premkumar[1] Ajay Duseja[1], [1]Postgraduate Institute of Medical Education & Research, [2]Postgraduate Institute of Medical education & Research, Chandigarh, India, [3]Postgraduate Institute of Medical Education & Research, Chandigarh, India

Background: Frailty is increasingly recognised as a major determinant of adverse outcomes in patients with decompensated cirrhosis. Microbiome-directed therapies, such as probiotics, may improve frailty by modulating systemic inflammation and ammonia metabolism. This study aimed to evaluate the impact of six months of probiotic therapy on frailty in patients with decompensated cirrhosis. **Methods:** This single-centre, prospective, open-label, randomized controlled trial included adults aged 18–75 years with decompensated cirrhosis and frailty. Frailty was assessed using the Liver Frailty Index(LFI). A total of 104 patients were randomized in a 1:1 ratio to receive either probiotics (VSL3 dose) plus standard medical treatment (pSMT; n = 52) or standard medical treatment alone (SMT; n = 52). The primary endpoint was the change in LFI at 6 months. Secondary endpoints included changes in MELD and MELD-Na scores, inflammatory markers (IL-6, CRP, ESR), serum ammonia, sarcopenia assessed by CT-derived skeletal muscle index (SMI), hospitalisation rates, survival, and adverse events. **Results:** The mean age was 51.9 ± 9.6 years, and 75% (n = 78) were males. Alcohol-associated liver disease was the most common aetiology (41.3%, n = 45), followed by MASLD (24.0%, n = 25). Mean MELD score was 13.46 ± 2.82, and median baseline LFI was 4.74(4.5-5.1) in pSMT group and 4.72(4.6-4.8) in SMT group)(p:0.81). Baseline inflammatory markers, ammonia levels and SMI were comparable between groups (p = > 0.05). At 6 months, patients receiving probiotics demonstrated significant improvement in frailty, with median LFI improving from 4.74 (4.5–5.1) at baseline to 4.28 (4.09–4.5) (p < 0.001) versus 4.72(4.6–4.8) to 4.73 (4.44–5.27) (p = 0.56) in SMT group. On multivariable analysis, inclusion in the probiotic arm (OR 0.12, 95% CI 0.04–0.36; p < 0.001), higher baseline SMI (OR 0.99, 95% CI 0.98–0.99; p = 0.001), and lower IL-6 levels (OR 0.12, 95% CI 0.04–0.36; p = 0.045) independently predicted improvement in frailty. There was significant improvement MELD Na score 16(13-18) to 14(11-16) (p = 0.001) in probiotic group as compared to 17.5(15.8-19.2) to 16.5(14-19)(p = 0.09) in SMT group. Median IL-6 levels declined from 17 pg/mL to 4 pg/mL (p < 0.001) and CRP decreased from 12.6 mg/L to 4 mg/L (p < 0.001) in the probiotic group. Serum ammonia levels also improved significantly from 128 mg/dL to 78 mg/dL (p < 0.001). Ten patients (19.2%) in the probiotic arm required hospitalisation versus twenty patients (38.5%) in the SMT group (p = 0.029), corresponding to an absolute risk reduction of approximately 19% and a number needed to treat of five. No significant difference in overall survival was observed between the two groups. (p = 0.10). **Conclusion:** Probiotic therapy in patients with decompensated cirrhosis significantly improves frailty, inflammatory markers, and serum ammonia levels while reducing hospitalization rates with no significant difference in survival rates.

Parameter	pSMT (n = 52) Baseline	pSMT 6 Months	Δ	p Within	SMT (n = 52) Baseline	SMT 6 Months	Δ	p Within	p Between Groups (Δ)
LFI	4.74 (4.5–5.1)	4.28 (4.09–4.5)	−0.49 (0.37–0.66)	<0.001	4.72 (4.6–4.8)	4.73 (4.44–5.27)	−0.05 (−0.26–0.22)	0.56	<0.001
Hand Grip (kg) – Male	20.0 (15.3–25.6)	25.0 (21.1–29.3)	3.67 (2.0–6.0)	<0.001	20.0 (17.83–23.50)	20.67 (17.33–24.00)	0.17 (−2.00–1.34)	0.97	0.01
Hand Grip (kg) – Female	18.7 (17.3–22.2)	23.7 (22.7–26.5)	5.3 (4.7–6.0)	0.002	16.0 (14.83–21.34)	17.33 (13.00–19.67)	0.00 (−2.50–1.33)	0.10	0.003
Balance (sec)	24.0 (20–30)	30.0 (27–30)	3.0 (0–7)	<0.001	27.0 (20–30)	28.0 (20–30)	0.0 (−2–2)	0.18	0.02
5 Chair Stand (sec)	19.0 (16.5–23.00)	17.0 (15–20.8)	1.9 (−0.42–5)	0.62	21.76 (19–25.75)	22.0 (17–31)	2.0 (−4–6)	0.63	0.96
IL-6 (pg/ml)	17.0 (11–42.2)	4.0 (3–10.5)	−10.0 (4–16.5)	<0.001	22.0 (10–48.5)	13.5 (5–38)	4.50 (−0.5–10)	0.02	0.003
CRP (mg/L)	12.60 (6–23.5)	4.0 (2.0–13.2)	−4.20 (1.47–17.2)	<0.001	8.50 (3.75–17.2)	6.50 (3–14.8)	1.0 (−2–3)	0.76	<0.001
ESR (mm/hr)	69.0 (49.5–80.0)	22.0 (13.0–32.0)	−30.5 (13–47.5)	<0.001	51.0 (39.0–77.2)	44.0 (21.8–69.5)	5.50 (2–16.8)	<0.001	<0.001
Serum Ammonia (mg/dl)	128.0 (97–195)	78.5 (62–102)	−50.5 (20–94.2)	<0.001	128.0 (82.8–220)	124.0 (73.8–191)	5.50 (2–16.8)	0.03	<0.001
CTP Score	7.0 (7–9)	7.0 (7–8)	0.0 (−1 to 1)	0.420	7.0 (7–8)	7.0 (6.0–9.0)	0.0 (−1.0 to 1.0)	0.73	0.320
MELD-Na Score	16.0 (13.0–18.0)	14.0 (11.0–16.0)	−2.0 (−4.0 to −1.0)	0.001	17.5 (15.8–19.2)	16.5 (14.0–19.0)	−1.0 (−2.0 to 0.0)	0.091	<0.001
SMI (cm^2/m^2) – Males	43.4 (38.0–49.0)	42.0 (36.3–49.5)	−0.4 (−2.0–2.8)	0.86	41.7 (36.9–47.0)	42.0 (36.0–45.0)	−1.0 (−2.0–1.0)	0.16	0.61

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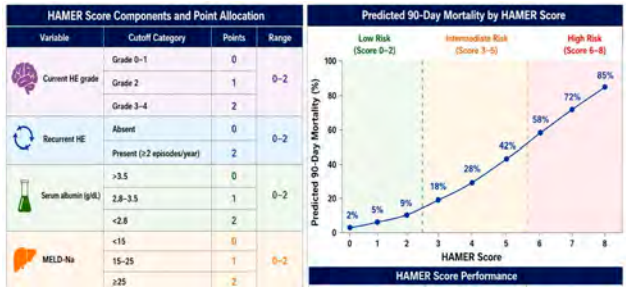
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1507 | HEPATIC ENCEPHALOPATHY SEVERITY AND RECURRENT EPISODES IMPROVE MORTALITY PREDICTION BEYOND MELD-NA: DEVELOPMENT OF THE HAMER SCORE

Ashok Kumar Choudhury[1] Divya Jaiswal[2] Radhika Sharma[2] Jitendra Singh[2] Roshan Koul[1] Manoj Sharma[1] Anoop Saraya[1] Shiv Kumar Sarin[2], [1]Institute of Liver and Biliary Sciences, [2]Institute of Liver and Billiary Sciences

Background: Hepatic encephalopathy (HE) is associated with poor survival in cirrhosis; however, not incorporated into the current MELD-Na–based liver allocation for transplant or prognostication. We evaluated the impact of severity and recurrence of HE on short-term mortality in hospitalized patients with cirrhosis. **Methods:** In this retrospective electronic medical record–based study, hospitalized patients with cirrhosis and HE were evaluated for 90-day mortality. Independent predictors identified on multivariate analysis were used to develop a simplified prognostic scoring system. **Results:** A total of 2,458 patients with HE were included, with a mean age of 44.3 ± 10.8 years, with predominant etiology being alcohol (72.8%) and MASLD (16.7%) with a 90-day mortality of 16.8%(414/2458). Grade 2, 3 or 4 HE at presentation was seen in 46.3%, 17.2% and 13.4% patients respectively. Recurrent HE was present in 10.1% patients and was associated with higher mortality compared to index HE episode (16.4% vs. 8.8%; $p < 0.001$). Prior TIPS placement was noted in 113 (4.6%) patients and was not associated with mortality. Spontaneous portosystemic shunt related HE in 44 (1.8%) and was associated with higher serum albumin, lower bilirubin, lower MELD-Na scores (22.6 ± 6.8 vs. 27.6 ± 8.9; $p = 0.008$), and lower mortality (4.5% vs. 17.1%; $p = 0.04$).On multivariate logistic regression, admission HE grade (OR 1.56, 95% CI 1.39–1.76; $p < 0.001$), recurrent HE (OR 1.88, 95% CI 1.34–2.65; $p < 0.001$), serum albumin (OR 0.61, 95% CI 0.49–0.77; $p < 0.001$), and MELD-Na (OR 1.13, 95% CI 1.11–1.15; $p < 0.001$) independently predicted mortality. Based on these variables, a simplified cutoff-based prognostic model, the HAMER score (HE grade–Albumin–MELD-Na–Recurrent HE), was developed. Scores were assigned as: HE grade 0–1 (0 points), grade 2 (1 point), and grade 3–4 (2 points); recurrent HE (≥2 episodes/year) was 2 points; serum albumin >3.5 g/dL (0 points), 2.8–3.5 g/dL (1 point), and <2.8 g/dL (2 points); and MELD-Na <15 (0 points), 15–25 (1 point), and ≥25 (2 points). The HAMER score ranged from 0–8 and stratified patients into low-risk (0–2), intermediate-risk (3–5), and high-risk (6–8) categories with corresponding 90-day mortality rates of <10%, 11%–35%, and > 50% respectively.The HAMER score reliably predicted mortality, higher score correlated with greater mortality (figure) The model showed a 25% relative improvement in predictive discrimination over HE grade alone and a 7.6% improvement over MELD-Na alone. **Conclusion:** HE severity and recurrent HE are independently associated with increased short-term mortality in cirrhosis. Incorporation of these along with serum albumin significantly improved prognostic discrimination beyond MELD-Na. The HAMER score is a simple bedside tool that may aid prognostication, escalation of care, ICU triage, and early liver transplant evaluation in patients hospitalized with HE, pending more future studies.



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1508 | POST-TIPS HEPATIC ENCEPHALOPATHY IS MORE FREQUENT AND EARLIER IN MASH THAN IN ALCOHOL-ASSOCIATED CIRRHOSIS DESPITE COMPARABLE MORTALITY

Mohamed Nadeem[1] Qijun Yang[2] Amrit Khooblall[2] Jamile Wakim-Fleming[2] Sameer Gadani[2] Shilpa Junna[2], [1]Cleveland Clinic Foundation, [2]Cleveland Clinic

Background: Transjugular intrahepatic portosystemic shunt (TIPS) is an established therapy for complications of portal hypertension. The role of cirrhosis etiology in the development of post-TIPS HE, waitlist mortality, and overall mortality has not been well studied in a large study cohort. To compare post-TIPS clinical outcomes between patients with metabolic dysfunction-associated steatohepatitis (MASH) and alcohol-associated liver disease (ALD). **Methods:** Single-center retrospective cohort study of adults undergoing TIPS, identified from an institutional

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registry of 1,507 procedures. MASH-associated liver disease also included cases of cryptogenic cirrhosis; ALD included alcohol alone or in combination with chronic viral hepatitis. Outcomes were ascertained at 30 days, 90 days, and 1 year. Continuous variables were compared by Wilcoxon rank-sum test and categorical variables by chi-square or Fisher's exact test. Survival was estimated by Kaplan–Meier methods and compared by log-rank test. **Results:** Of 1,507 procedures, 958 patients met the inclusion criteria (MASH n = 458; ALD n = 500). MASH patients were older (median 63 vs 53 years, p < 0.001) and more often female (57% vs 29%, p < 0.001); ALD patients had higher rates of pre-TIPS hepatic encephalopathy (HE) (49% vs 31%, p = 0.004) and emergent TIPS (26% vs 20%, p = 0.025). Post-TIPS HE occurred more often in MASH (33.4% vs 21.8%, p < 0.001) and at every landmark: 30 days 18.6% vs 9.4%, 90 days 25.1% vs 13.2%, and 1 year 31.0% vs 17.2% (all p < 0.001). Time to HE was shorter in MASH (median 25 vs 45 days, p = 0.025). Post-TIPS liver failure (2.8% vs 3.8%, p = 0.52), transplant waitlist mortality (37.1% vs 39.7%, p = 0.46), and overall mortality (38.2% vs 40.3%, p = 0.56) did not differ; Kaplan–Meier curves showed no separation at any landmark. **Conclusion:** Despite comparable post-TIPS mortality, MASH-related cirrhosis is associated with more frequent and earlier post-TIPS hepatic encephalopathy than ALD-related cirrhosis. These findings support etiology-tailored counseling and intensified HE surveillance in the MASH population after TIPS.

Table 1. Patient characteristics by liver disease etiology group

Characteristic	N	Overall N = 958	MASH N = 458	ALD N = 500	p-value
Age, years	956	58.0 [50.0, 65.0]	63.0 [55.0, 68.0]	53.0 [48.0, 60.0]	**<0.001**
Gender	957				**<0.001**
Male		554 (57.9%)	197 (43.1%)	357 (71.4%)	
Female		403 (42.1%)	260 (56.9%)	143 (28.6%)	
Ethnicity	854				**0.011**
White		735 (86.1%)	364 (89.0%)	371 (83.4%)	
Asian		8 (0.9%)	4 (1.0%)	4 (0.9%)	
Black		66 (7.7%)	18 (4.4%)	48 (10.8%)	
Hispanic/Latino		18 (2.1%)	8 (2.0%)	10 (2.2%)	
American Indian/Alaskan Native		3 (0.4%)	1 (0.2%)	2 (0.4%)	
Unknown		24 (2.8%)	14 (3.4%)	10 (2.2%)	
Hepatic encephalopathy before TIPS	290				**0.004**
No		167 (57.6%)	97 (66.9%)	70 (48.3%)	
Yes		116 (40.0%)	45 (31.0%)	71 (49.0%)	
Missing/Unknown		7 (2.4%)	3 (2.1%)	4 (2.8%)	
Indication for TIPS	957				—
Ascites		283 (29.6%)	129 (28.2%)	154 (30.9%)	
Variceal bleed		356 (37.2%)	163 (35.6%)	193 (38.7%)	
Hydrothorax		43 (4.5%)	27 (5.9%)	16 (3.2%)	
Ascites & variceal bleed		104 (10.9%)	45 (9.8%)	59 (11.8%)	
Ascites & hydrothorax		56 (5.9%)	31 (6.8%)	25 (5.0%)	
Variceal bleed & hydrothorax		9 (0.9%)	2 (0.4%)	7 (1.4%)	
Ascites, variceal bleed, & hydrothorax		11 (1.1%)	4 (0.9%)	7 (1.4%)	
Other		95 (9.9%)	57 (12.4%)	38 (7.6%)	
Emergent TIPS	905				**0.025**
No		694 (76.7%)	344 (80.2%)	350 (73.5%)	
Yes		210 (23.2%)	85 (19.8%)	125 (26.3%)	
Unknown		1 (0.1%)	0 (0.0%)	1 (0.2%)	
Liver transplant prior to TIPS	855				>0.99
No		839 (98.1%)	404 (98.3%)	435 (98.0%)	
Yes		15 (1.8%)	7 (1.7%)	8 (1.8%)	
Missing/Unknown		1 (0.1%)	0 (0.0%)	1 (0.2%)	
Liver resection prior to TIPS	852				>0.99
No		849 (99.6%)	408 (99.8%)	441 (99.5%)	
Yes		2 (0.2%)	1 (0.2%)	1 (0.2%)	
Missing/Unknown		1 (0.1%)	0 (0.0%)	1 (0.2%)	

Continuous variables: median [Q1, Q3]; categorical variables: n (%). N = patients with non-missing data, percentages are among non-missing. p-values: Wilcoxon rank-sum (continuous); Pearson's chi-squared with Yates' continuity correction or Fisher's exact test (categorical). Bold indicates $p < 0.05$.

Disclosures: Mohamed Nadeem:Nothing to Disclose, Qijun Yang:Nothing to Disclose, Amrit Khooblall:Nothing to Disclose, Jamile Wakim-Fleming:Nothing to Disclose, Sameer Gadani:Nothing to Disclose, Shilpa Junna:Nothing to Disclose.

1509 | LACTULOSE PLUS POLYETHYLENE GLYCOL VS. LACTULOSE MONOTHERAPY AFTER A FIRST HEPATIC ENCEPHALOPATHY EPISODE IN CIRRHOSIS: A PROPENSITY SCORE–MATCHED COHORT ANALYSIS

Mahmoud Al-Bataineh[1] Jashnaveer Johal[1] Archana Salek[1] Bianca Patel[1] Brandon Cunha[1] Abdallah Hussein[1] Jason Hyman[2] Simona Rossi[1] Yecheskel Schneider[1], [1]Virtua Health, [2]Einstein Medical Center, Philadelphia

Background: Lactulose is the cornerstone of both treatment and secondary prophylaxis of hepatic encephalopathy (HE) in cirrhosis, but recurrence rates remain high. Polyethylene glycol 3350 (PEG) has emerged as an effective acute HE treatment, yet its role as an adjunct to lactulose for secondary prevention after a first HE episode is unknown. **Methods:** We conducted a propensity score–matched retrospective cohort study using the TriNetX Global Collaborative Network (191.9 million patients). Cohort 1 comprised cirrhotic patients (K74.6) with a first documented HE episode (K76.82) who were prescribed both lactulose and PEG 3350 within 6 months of their index event. Cohort 2 comprised cirrhotic patients with a first HE episode prescribed lactulose alone, with explicit exclusion of any PEG use. Both cohorts excluded prior hepatocellular carcinoma, liver transplant status, and prior TIPS procedure. Cohorts were balanced via 1:1 PSM yielding 1,565 patients per arm over a 6–12 month follow-up window. Pre-specified outcomes included repeat HE episodes, hepatic failure, need for intubation, ICU admission, hypotension, and all-cause mortality. **Results:** Post-PSM cohorts were well-balanced across matched covariates. Repeat HE episodes were paradoxically more frequent in the combination arm on MOA analysis (50.9% vs. 44.7%; RR 1.14, OR 1.28; p = 0.0006), though time-to-event analysis did not reach significance (HR 1.10, 95% CI 0.99–1.21; p = 0.072), with median time to recurrence of 135 vs. 233 days respectively. Hepatic failure rates did not differ significantly between arms (26.3% vs. 23.1%; HR 1.15, 95% CI 0.85–1.55; p = 0.37). Need for intubation was similar across both arms (9.3% vs. 8.0%; HR 1.11, 95% CI 0.88–1.41; p = 0.38). ICU admissions yielded zero events in either arm. Hypotension occurred significantly less frequently in the combination arm (76.5% vs. 80.8%; RR 0.95, OR 0.77; HR 0.82, 95% CI 0.76–0.89; p < 0.001), with a notably shorter median time to hypotension in the

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lactulose-only arm (4 vs. 11 days). All-cause mortality was significantly lower in the combination arm (34.2% vs. 39.7%; RR 0.86, OR 0.79; HR 0.81, 95% CI 0.72–0.91; p = 0.0003). **Conclusion:** In this propensity-matched real-world cohort of cirrhotic patients following a first HE episode, lactulose plus PEG combination therapy was associated with significantly lower all-cause mortality and reduced hypotension compared to lactulose monotherapy, despite a higher observed rate of repeat HE documentation. These findings likely reflect a detection and engagement bias rather than therapeutic failure, and support prospective evaluation of PEG as a lactulose adjunct for secondary HE prophylaxis in cirrhosis.

Disclosures: Mahmoud Al-Bataineh:Nothing to Disclose, jashnaveer Johal:Nothing to Disclose, Archana Salek:Nothing to Disclose, Bianca Patel:Nothing to Disclose, Brandon Cunha:Nothing to Disclose, Abdallah Hussein:Nothing to Disclose, Jason Hyman:Nothing to Disclose, simona rossi:Nothing to Disclose, Yecheskel Schneider:Nothing to Disclose.

1510 | POLYPHARMACY AND POTENTIALLY INAPPROPRIATE MEDICATION USE AS INDEPENDENT PREDICTORS OF HEPATIC DECOMPENSATION AND MORTALITY IN COMPENSATED CIRRHOSIS: A NATIONWIDE MULTI-INSTITUTIONAL COHORT STUDY

Noor Albusta[1] Mohamed Abdulla[2], [1]Lahey Hospital and Medical Center, [2]Royal College of Surgeons in Ireland

Background: Patients with cirrhosis frequently experience polypharmacy and are often exposed to potentially inappropriate medications (PIMs), including PPIs, opioids, benzodiazepines, and NSAIDs, each linked to adverse hepatic outcomes. However, whether cumulative medication burden, concurrent exposure to multiple PIMs, and underuse of indicated therapies independently predict decompensation and mortality remains unclear. We aimed to evaluate the dose-response relationship between polypharmacy, PIM burden, and outcomes in compensated cirrhosis. **Methods:** Using TriNetX, we studied adults (≥ 18 y) with compensated cirrhosis (no decompensation within 6 months of diagnosis) from Jan 2017–Dec 2024 with ≥ 12-month follow-up. Medication exposure was assessed during a 6-month landmark period. Polypharmacy: none (0–4 medications), moderate (5–9), severe (≥ 10). PIMs included opioids, benzodiazepines, systemic NSAIDs, and PPIs without indication; a PIM burden score (0–4) was calculated. Adherence to indicated medications (NSBB, lactulose/rifaximin, SBP prophylaxis) was assessed concurrently; a "dual medication gap" was defined as ≥ 1 PIM plus underfilling of ≥ 1 indicated medication. Primary outcome: time to first decompensation (ascites, HE, variceal hemorrhage, SBP, hepatorenal syndrome). Secondary outcomes: ACLF, 1-year mortality, 30-day readmission, AKI. Propensity score matching (1:1) on 32 covariates; Cox models estimated adjusted HRs. Subgroup analyses by etiology, age, and PIM class. **Results:** Among 64,218 adults (mean age 58.4 ± 11.2 y, 46.2% female; MASLD 36.8%, ALD 32.4%, viral 19.6%), median concurrent medications were 7 (IQR 4–12). At least one PIM was prescribed in 65.2%, and 28.6% had a dual medication gap. Over median 2.8-year follow-up, 28.7% decompensated. After matching, polypharmacy and PIM burden showed graded dose-response associations with decompensation (Table 1). Each PIM class drove decompensation through distinct mechanisms: PPIs via infection/HE, opioids/benzodiazepines via HE, NSAIDs via AKI/ascites. The dual medication gap conferred the highest risk (HR 1.72, 95% CI 1.58–1.87). Severe polypharmacy was associated with increased 1-year mortality (HR 1.36), ACLF (HR 1.54), and readmission (HR 1.42; all p < 0.001). Associations were strongest in ALD and age ≥ 65 (Table 2). **Conclusion:** Polypharmacy and PIM use independently accelerate decompensation in compensated cirrhosis in a dose-response manner, with exposure to all four PIM classes conferring a 2.4-fold increased hazard. Nearly one-third exhibited simultaneous overprescribing of harmful medications and underprescribing of indicated therapies — the highest-risk combination. These findings support cirrhosis-specific medication reconciliation and pharmacist-led deprescribing while optimizing guideline-indicated therapy.

Table 1. Dose-Response Association of Polypharmacy and PIM Burden with Hepatic Decompensation

Exposure	Decompensation HR (95% CI)	HE HR (95% CI)	AKI HR (95% CI)	1-Year Mortality HR (95% CI)
Polypharmacy				
None (0–4 meds, ref)	1.00	1.00	1.00	1.00
Moderate (5–9)	1.22 (1.16–1.28)	1.18 (1.10–1.26)	1.24 (1.14–1.35) *	1.14 (1.04–1.25) †
Severe (≥10)	1.48 (1.40–1.57)	1.42 (1.32–1.53)	1.58 (1.46–1.71)	1.36 (1.26–1.47)
PIM burden score				
0 (ref)	1.00	1.00	1.00	1.00
1	1.26 (1.20–1.33)	1.22 (1.14–1.31)	1.18 (1.08–1.29) †	1.12 (1.02–1.23) †
2	1.58 (1.47–1.70)	1.48 (1.34–1.63)	1.52 (1.36–1.70)	1.34 (1.20–1.50)
3	1.94 (1.72–2.19)	1.82 (1.56–2.12)	1.86 (1.58–2.19)	1.58 (1.34–1.86)
4	2.42 (1.88–3.12)	2.18 (1.62–2.94)	2.34 (1.72–3.18)	1.94 (1.42–2.65)
Individual PIMs				
PPIs (no indication)	1.38 (1.31–1.45)	1.44 (1.34–1.55)	1.16 (1.06–1.27) †	1.22 (1.12–1.33) *
Opioids	1.32 (1.25–1.39)	1.54 (1.43–1.66)	1.12 (1.02–1.23) †	1.28 (1.18–1.39) *
Benzodiazepines	1.28 (1.18–1.39)	1.68 (1.52–1.86)	1.08 (0.94–1.24)	1.24 (1.10–1.40) *
Systemic NSAIDs	1.56 (1.42–1.72)	1.14 (0.98–1.32)	2.14 (1.86–2.46)	1.64 (1.42–1.89) *
Dual medication gap	1.72 (1.58–1.87)	1.64 (1.48–1.82)	1.68 (1.50–1.88)	1.48 (1.32–1.66)

p<0.001; †p<0.05. All HRs after propensity score matching. AKI, acute kidney injury; CI, confidence interval; HE, hepatic encephalopathy; HR, hazard ratio; meds, medications; NSAIDs, nonsteroidal anti-inflammatory drugs; PIM, potentially inappropriate medication; PPIs, proton pump inhibitors.

Table 2. Subgroup Analyses: Polypharmacy–Decompensation Association by Etiology and Age

Subgroup	Severe Polypharmacy HR (95% CI)	Opioid–HE HR (95% CI)	NSAID–AKI HR (95% CI)	PIM Prevalence, %
By etiology				
ALD	1.62 (1.48–1.78)	1.72 (1.54–1.92)	2.28 (1.82–2.86) *	72.4
MASLD	1.46 (1.34–1.59)	1.48 (1.32–1.66)	2.08 (1.72–2.52) *	61.8
Viral hepatitis	1.34 (1.22–1.48)	1.36 (1.18–1.57)	1.92 (1.52–2.42) *	58.6
p-interaction	0.006	0.01	0.24	—
By age				
≥65 years	1.58 (1.44–1.73)	1.62 (1.42–1.85)	2.32 (1.88–2.86) *	71.4
65 years	1.38 (1.28–1.49)	1.44 (1.30–1.59)	1.96 (1.64–2.34) *	60.8
p-interaction	0.01	0.04	0.12	—

p<0.001. AKI, acute kidney injury; ALD, alcohol-associated liver disease; CI, confidence interval; HE, hepatic encephalopathy; HR, hazard ratio; MASLD, metabolic dysfunction-associated steatotic liver disease; NSAIDs, nonsteroidal anti-inflammatory drugs; PIM, potentially inappropriate medication.

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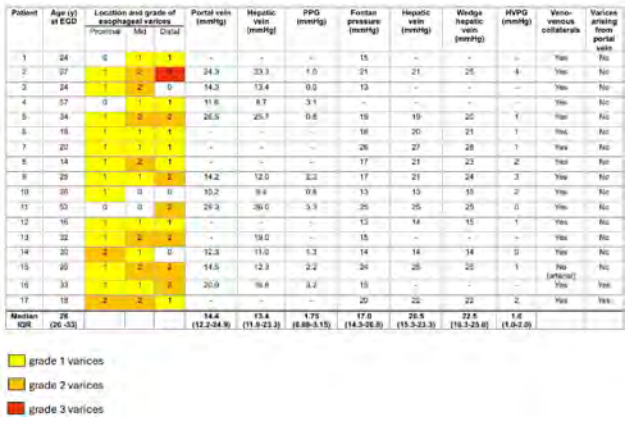
Disclosures: Noor Albusta:Nothing to Disclose, Mohamed Abdulla:Nothing to Disclose.

1511 | ENDOSCOPIC ESOPHAGEAL VARICES COMMONLY REPRESENT VENOVENOUS COLLATERALS IN PATIENTS WITH FONTAN CIRCULATION

Jordan Sack[1] Ayaz Aghayev[1] Marvin Ryou[1] Fred Wu[2] Stephen Zucker[1], [1]Brigham and Women's Hospital, [2]Boston Chilcren's Hospital

Background: The presence of esophageal varices has been considered a determining factor as to whether individuals with Fontan circulation should undergo combined heart-liver transplantation. However, these patients commonly develop venovenous collaterals, some of which course through the esophagus. We aimed to determine the prevalence and location of esophageal collaterals in patients with Fontan circulation who have endoscopic evidence of esophageal varices. **Methods:** This is a retrospective case series of 17 patients with Fontan circulation and endoscopic findings of esophageal varices. Cross-sectional abdominal imaging (cardiac MR, CT) was reviewed to determine the origin, course, and termination of submucosal esophageal veins. Findings were correlated with lab tests, imaging features, and hepatic and portal vein pressures measured using an endoscopic ultrasound-guided transgastric approach and/or during cardiac catheterization. **Results:** In 14 of 17 patients (82%), esophageal varices solely reflected venovenous collaterals arising from the central venous system and terminating in the pulmonary veins. Two patients (12%) with “classic” distal esophageal varices arising from the left gastric vein also manifested venovenous collaterals in the upper esophagus. In one patient, esophageal vessels arose directly from the aorta. The presence and grade of varices in the distal esophagus was associated with higher central venous pressures. There were no demographic, laboratory, imaging, or pressure correlates of “classic” esophageal varices, and no patient had a hepatic vein to portal pressure gradient above 4 mmHg. **Conclusion:** In patients with Fontan circulation, esophageal varices most commonly represent venovenous collaterals and are not indicative of portal hypertension. The endoscopic presence of esophageal varices generally reflects the patient’s cardiac status and is not a reliable indicator of the severity of underlying liver disease. That esophageal vessels may have an arterial origin in some patients suggests caution when contemplating endoscopic intervention.

Correlation between venovenous collaterals, endoscopy findings and vascular pressure measurements



grade 1 varices
grade 2 varices
grade 3 varices

Disclosures: Jordan Sack:Nothing to Disclose, Ayaz Aghayev:Nothing to Disclose, Marvin Ryou:Nothing to Disclose, Fred Wu:Nothing to Disclose, Stephen Zucker:Nothing to Disclose.

1512 | NATURAL LANGUAGE PROCESSING (NLP) AND LARGE LANGUAGE MODEL (LLM) ALGORITHMS OUTPERFORM ICD CODES FOR IDENTIFYING COMPENSATED CIRRHOSIS (CC) AND REVEAL HIGH RATES OF DECOMPENSATION AND MORTALITY IN A LARGE URBAN ACADEMIC COHORT

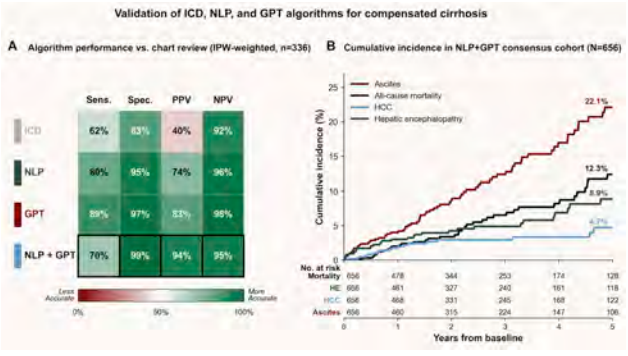
Giuseppe Cullaro Chip Bowman[1] Elina Stoffel[1] Eytan Palte[1] Elizabeth Verna[2], [1]Columbia University, [2]Columbia University Medical Center

Background: ICD-based algorithms are increasingly used to identify compensated cirrhosis (CC) in electronic health record and claims databases, but their accuracy for this phenotype is unknown. We compared ICD, rule-based natural language processing (NLP), and GPT-5.2 head-to-head, then quantified decompensation outcomes in the cohort from the most precise model. **Methods:** Adults ≥ 18 with any chronic liver disease ICD-10 code at Columbia University Irving Medical Center (2015–2025) and abdominal imaging within ± 365 days of baseline ($n = 6,843$) were classified by (1) ICD cirrhosis codes excluding decompensation codes, (2) NLP applied to imaging and notes, and (3) GPT-5.2 integrating notes, imaging, and labs. A stratified chart-review sample ($n = 336$, 8 algorithm-agreement strata) with CC defined per national definitions served as the gold standard; inverse probability weighting recovered population-level performance with bootstrap 95%

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CIs.In the cohort of 656 patients meeting CC criteria by NLP + GPT-5.2 algorithms, we computed 1-, 3-, and 5-year Kaplan–Meier cumulative incidence of ascites (defined by imaging and/or medications), hepatic encephalopathy (HE) (medications), hepatocellular carcinoma (HCC) (imaging), and all-cause mortality. **Results:** Among the 6,843 screened patients, ICD codes identified the most as CC (24%), then GPT-5.2 (16%), then rule-based NLP (14%). On chart-review validation, ICD was the weakest classifier (Sens 62%, Spec 83%, PPV 40%, NPV 92%). NLP beat ICD on every metric (Sens 80%, Spec 95%, PPV 74%, NPV 96%; PPV vs ICD $p = 0.006$). GPT-5.2 was the best single algorithm (Sens 89%, Spec 97%, PPV 83%, NPV 98%; PPV vs NLP $p < 0.001$). Requiring NLP+GPT agreement maximized precision (Sens 70%, Spec 99%, PPV 94%, NPV 95%; PPV vs GPT $p < 0.001$).The NLP+GPT consensus cohort comprised 656 patients with a median age of 60 years; 54% were male, 38% were Hispanic, and 11% were non-Hispanic Black. MASLD was the leading etiology (27%), followed by viral hepatitis (18%), alcohol-related liver disease (15%), and autoimmune-related liver disease (12%). Baseline laboratory values: median platelet count 187 $\times 10^9$/L (IQR 123–242), total bilirubin 0.6 mg/dL (IQR 0.4–1.0), albumin 4.3 g/dL (IQR 3.9–4.6), and INR 1.1 (IQR 1.0–1.2). Median follow-up was 2.0 years (IQR 0.9–4.1).Cumulative incidence of incident outcomes at 1, 3, and 5 years was: ascites 4/13/22%, HE 3/5/9%, HCC 2/3/5%, and any decompensation 11/21/33%. All-cause mortality at the same timepoints was 2/7/13%. **Conclusion:** Accurately modeling CC in EHR- or claims-based datasets requires NLP and/or LLM-based analysis of unstructured fields — structured diagnosis codes alone are insufficient, misclassifying the majority of patients, and thereby limiting the interpretability and generalizability of these findings.



Disclosures: Giuseppe Cullaro:Ocelot Bio: Consultant, Retro Sciences: Consultant, Ipsen: Consultant, Chip Bowman:Nothing to Disclose, Elina Stoffel:Nothing to Disclose, Eytan Palte:Nothing to Disclose, Elizabeth Verna:Nothing to Disclose.

1513 | CRP AND IL-6 IDENTIFY PATIENTS WITH DACLD AT HIGH RISK OF FURTHER DECOMPENSATING EVENTS

Christian Sebesta[1] Benedikt Simbrunner[1] Georg Kramer[1] Paul Thöne[1] Marlene Hintersteininger[1] Jan Embacher[1] Lucie Simonis[1] Lorenz Balcar[1] Benedikt Hofer[1] Lukas Hartl[1] Mathias Jachs[1] Georg Semmler[1] Philipp Schwabl[1] Bernhard Scheiner[1] Dalila Costa[2] Albert Stättermayer[3] Michael Trauner[1] Mattias Mandorfer[1] Thomas Reiberger[1], [1]Medical University of Vienna, [2]University of Minho, Braga, Portugal, [3]AKH Vienna

Background: In decompensated advanced chronic liver disease (dACLD), hepatic dysfunction, portal hypertension (PH), and systemic inflammation (SI) may contribute differentially to the risk of further decompensation (FD) and liver-related death (LRD). We aimed to investigate previously proposed SI biomarker thresholds, C-reactive protein (CRP) ≥ 0.5 mg/dL and Interleukin-6 (IL-6) ≥ 14 pg/mL, in a temporal validation cohort, specifically in regards to their incremental predictive value for FD and LRD beyond MELD and hepatic venous pressure gradient (HVPG). **Methods:** Patients with dACLD underwent assessment of SI biomarkers (CRP, IL-6), MELD, and HVPG, and were prospectively followed. Multivariable regression models incorporated MELD, HVPG, and SI biomarkers for FD and LRD at short term (90 days, D90) and one year (Y1) were computed. Additional subgroup analyses were performed using thresholds for MELD ≥ 15 (i.e., transplant-relevant liver disease severity), and HVPG ≥ 16 mmHg (i.e., severe PH). **Results:** A total of 278 patients with dACLD (64% male; median age: 56 years; 66% alcohol-related liver disease) were included. At baseline, decompensation was evident by ascites in 92%, hepatic encephalopathy in 29%, and previous variceal bleeding in 8%. Median MELD was 13 and median HVPG was 19 mmHg. At Y1, the cumulative incidence of FD and LRD was 27.7% and 13.7%, respectively, while 6.5% of patients underwent liver transplantation.In multivariable Cox regression models adjusted for MELD and HVPG, both SI biomarkers were independently associated with FD: Specifically, higher CRP was linked to increased risk of D90 (adjusted hazard ratio [aHR] for logCRP: 2.48; $p < 0.001$) and Y1 (aHR: 2.30; $p < 0.001$) risk of FD. Similarly, higher IL-6 predicted D90 (aHR: 1.48 for logIL-6; $p = 0.004$) and Y1 (aHR: 1.37; $p = 0.007$) risk of FD.In models assessing LRD, additionally adjusted for age, CRP remained significantly associated with D90 LRD (aHR: 2.50; $p = 0.035$), whereas IL-6 showed only borderline association for D90 LRD (aHR: 1.63; $p = 0.054$). Neither SI biomarker was independently associated

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with LRD at Y1.Competing-risk analyses accounting for liver transplantation and non–liver-related death as competing events showed that patients with CRP $\geq$0.5 mg/dL or IL-6 $\geq$14 pg/mL had a significantly higher cumulative incidence of FD (both $p < 0.05$). Importantly, stratification by these SI biomarker cut-offs consistently identified patients at particularly high risk of FD across MELD ($\geq$15 vs. <15) and HVPG strata ($\geq$16 vs. <16 mmHg). **Conclusion:** In patients with dACLD, CRP and IL-6 independently predict FD beyond MELD and HVPG. These findings support the use of SI biomarkers for refined clinical risk stratification and enrichment of trials with patients at particularly high short-term risk of FD events.

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1514 | CIRRHOSIS ETIOLOGY AFFECTS PORTAL HYPERTENSION PROGRESSION

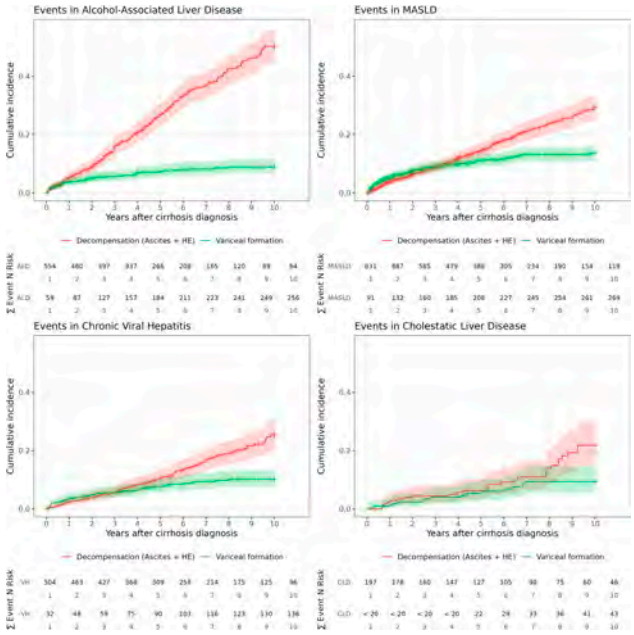
Nikhilesh Mazumder[1] Emma Ulrich[2] Chinmay Raut[2] Antonino Oliveri[2] Lishi Yin[2] Yanhua Chen[2] Elizabeth Speliotes[3], [1]University of Michigan Hospitals and Health Centers, [2]University of Michigan, [3]University of Michigan Medical Center

Background: Models of portal hypertensive (PH) progression developed in historical viral hepatitis (VH) cohorts propose that patients develop non-bleeding varices before decompensating. However the rising rate of steatotic (alcohol-associated [ALD], metabolic-associated [MASLD]) liver diseases relative to viral etiologies raise questions as to if this schema still holds given known differences in disease trajectory. We examine how patients with compensated cirrhosis experience PH events differently based on cause of liver disease. **Methods:** Adult patients included in the NIH *All of Us* Research Program were included at their first diagnosis of compensated cirrhosis. We used ICD codes to determine liver disease etiology (ALD, MASLD, VH, cholestatic [CLD]) as well as first decompensation (Ascites or HE) and included only individuals with liver disease from a single etiology. Patients were excluded if they had a decompensating event at time zero or within 30 days of inclusion, or if labs in the one year leading up to inclusion suggested undiagnosed liver disease. We determined each patient's first PH event via ICD codes, CPT procedural codes, and medications. We generated cumulative incidence estimates stratified by liver disease etiology. To quantify differences in disease trajectory, we ascertained the time in the first ten years during which the incidence of decompensation (ascites or HE) was greater than the incidence of non-bleeding variceal formation using bootstrapping. **Results:** Our cohort included 2,476 patients with compensated cirrhosis followed for a median of 4.4 years. Cause of liver disease was 27% ALD, 42% MASLD, 22% VH, and 9% CLD. The first diagnosed PH event in the cohort is 12% ascites, 7% HE, and 9% variceal formation, with 72% experiencing no event during follow-up. The 10-year cumulative incidence of any event was highest in ALD (59%), followed by MASLD (43%), VH (36%), and CLD (31%). Furthermore, we find that the trajectory of disease as measured by the divergence of the decompensation and variceal formation curves is highest in ALD at 18 months of follow-up, 6 years in MASLD and VH, and 9 years in CLD. **Conclusion:** We find that patients with ALD have the most rapidly progression of portal hypertensive complications, followed by MASLD and viral causes and trailed by CLD. This suggests that progression through disease stages is not monotonic and is dependent on etiology of liver disease. This

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result emphasizes the importance of considering etiology when advising patients on their risk of future decompensation and informs changing patterns of complications as steatotic causes of liver disease increase in prevalence.



Disclosures: Nikhilesh Mazumder:Nothing to Disclose, Emma Ulrich:Nothing to Disclose, Chinmay Raut: Nothing to Disclose, Antonino Oliveri:Nothing to Disclose, Lishi Yin:Nothing to Disclose, Yanhua Chen: Nothing to Disclose, Elizabeth Speliotes:University of Michigan: Pending patent on use systems for MASLD/ insulin resistance.

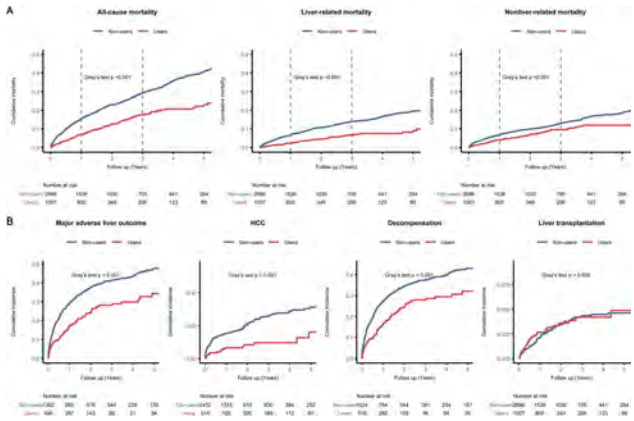
1515 | IMPACT OF SGLT2 INHIBITORS AND/OR GLP-1 RECEPTOR AGONISTS ON LIVER OUTCOMES AND MORTALITY IN PATIENTS WITH CIRRHOSIS OF DIVERSE ETIOLOGIES

Bowu Chen[1] Rui Huang[2] Taotao Yan[3] Xianhua Mao[4] Danfeng Ren[3] Sicheng Gao[5] Jie Wang[6] Yu Shi[6] Mingjuan Jin[7] Changqing Zhao[1] Ramsey Cheung[4] Mindie Nguyen[4], [1]Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, [2]Nanjing Drum Tower Hospital, [3]The First Affiliated Hospital of Xi'an Jiaotong University, [4]Stanford University Medical Center, [5]Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of TCM, [6]The First Affiliated Hospital, School of Medicine, Zhejiang University, [7]Department of Public Health, Second Affiliated Hospital, Zhejiang University School of Medicine

Background: The prevalence of both cirrhosis and metabolic dysfunction is increasing. Sodium-glucose cotransporter-2 inhibitors (SGLT2-I) and glucagon-like peptide-1 receptor agonists (GLP-1RA) have broad benefits in diabetes and MASLD, but their effects on cirrhosis of diverse etiologies remain limited. This study evaluated the impact of SGLT2-I and/or GLP-1RA on mortality and clinical outcomes in this high-risk population. **Methods:** We conducted a retrospective cohort study of SGLT2-I and/or GLP-1RA users and nonusers with cirrhosis at a large U.S. university medical center from January 2010 to June 2025. We evaluated all-cause, liver-related and nonliver-related mortality, obtained by individual medical record review and supplemented by National Death Index search. We also evaluated major adverse liver outcomes (MALO): HCC, liver decompensation and transplantation (LT). Baseline characteristics were balanced via 1:4 propensity score matching (PSM, caliper 0.1). Associations with outcomes were evaluated using Fine-Gray competing risk models (competing events: LT, death or alternate cause of death where applicable). Robustness was assessed with demographic and clinical subgroup analyses including user groups (SGLT2-I alone, GLP-1RA alone and combination), 12- and 24-month landmark analyses and sensitivity analyses including time-varying Cox regression, stricter-caliper PSM (0.01) and inverse probability of treatment weighting (IPTW) as alternative matching method. **Results:** Our study included 14,687 adult patients with cirrhosis (1,150 users and 13,537 nonusers) after excluding HIV infection, LT before index, or study medication use before cirrhosis. PSM yielded a cohort of 1,007 users and 2,696 nonusers with balanced characteristics (standardized mean difference [SMD] $\leq$ 0.1). All-cause, liver-related and nonliver-related mortality were lower in users than nonusers (64.45 vs. 122.97, 26.51 vs. 55.88, and 33.27 vs. 55.70 per 1,000 person-years, respectively), as well as incidence rates of MALO, HCC and liver decompensation (122.93 vs. 188.60, 10.26 vs. 25.74, and 121.15 vs. 170.47 per 1,000 person-years, respectively) (all $P < 0.001$) (Figure 1). On multivariable regression analyses, compared with nonusers, users had lower risks of all-cause (sHR 0.52, 95% CI 0.43–0.63), liver-related (sHR 0.48, 95%CI 0.36–0.64), and nonliver-related mortality (sHR 0.63, 95%CI 0.48–0.83), as well as lower risks of MALO (sHR 0.55, 95%CI 0.46–0.66), HCC (sHR 0.39, 95%CI 0.24–0.64), and liver decompensation (sHR 0.61, 95% CI 0.49–0.74). Findings were consistent across subgroup, landmark, and sensitivity analyses. **Conclusion:** SGLT2-I and/or GLP-1RA use was associated with lower risks of adverse liver events and improved survival both from liver and nonliver causes in patients with cirrhosis and should be further studied in this population.

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1516 | IMPACT OF PRE-EXISTING CKD SEVERITY ON CLINICAL OUTCOMES IN CIRRHOSIS: A PROPENSITY SCORE-MATCHED COHORT ANALYSIS

Bianca Patel[1] Jashanveer Johal[1] Archana Salek[1] Mahmoud Al-Bataineh[1] Brandon Cunha[1] Abdallah Hussein[1] Jason Hyman[2] Yecheskel Schneider[1], [1]Virtua Health, [2]Einstein Medical Center

Background: Chronic kidney disease (CKD) is a well-recognized comorbidity in cirrhosis, but the degree to which baseline CKD severity independently predicts hepatic decompensation, infection, bleeding, and mortality in this population has not been well characterized in large real-world cohorts. **Methods:** Using the TriNetX Global Collaborative Network, we performed a propensity score–matched retrospective cohort study of adults with cirrhosis and pre-existing CKD stage 1–3 versus CKD stage 4–5. Patients with ESRD, HCC, liver transplant, HIV, chronic viral hepatitis, or SLE were excluded. One-to-one matching yielded 3,165 patients per cohort. Outcomes included ascites, hepatic encephalopathy (HE), hospitalization/ED visits, bleeding, infection, mortality, and renal failure/hemodialysis. **Results:** Post-PSM cohorts were well-balanced across matched covariates. All-cause mortality was markedly higher in the CKD 4-5 cohort (31.3% vs. 20.0%; HR 0.53, 95% CI 0.48–0.59; log-rank $p < 0.001$), representing the dominant finding across the study. New ascites did not differ significantly between CKD stages on time-to-event analysis (HR 0.91, 95% CI 0.73–1.13; $p = 0.39$). HE was modestly more frequent in the CKD 1-3 arm on cumulative risk analysis (3.6% vs. 2.6%; RR 1.40; $p = 0.024$) but did not reach significance on KM analysis (HR 1.18, 95% CI 0.87–1.59; $p = 0.29$). ED visits and inpatient admissions were slightly higher in the CKD 1-3 arm by fixed-time risk (53.1% vs. 48.9%; $p = 0.0009$) with nearly identical time-to-event rates (HR 0.97; $p = 0.39$) and median time to first encounter of 160 vs. 156 days. Clinical bleeding trended higher in the CKD 1-3 arm on cumulative risk (9.5% vs. 7.1%; $p = 0.0006$) but did not reach significance on KM analysis (HR 1.17, 95% CI 0.99–1.39; $p = 0.072$). Infection rates did not differ significantly on time-to-event analysis (HR 0.96, 95% CI 0.87–1.06; $p = 0.46$). Renal failure or need for hemodialysis was significantly more frequent in the CKD 4-5 arm on KM analysis (HR 0.76, 95% CI 0.63–0.93; $p = 0.007$) despite a non-significant MOA result, reflecting higher event clustering over time in the advanced CKD group. **Conclusion:** In this propensity-matched cohort, CKD stage 4–5 in cirrhosis was associated with higher all-cause mortality and renal failure than CKD stage 1–3, with no significant differences in ascites, hepatic encephalopathy, or infection on time-to-event analysis. These findings identify advanced CKD as a key prognostic marker and support early nephrology co-management. Higher rates of HE, hospitalization, bleeding, and infection observed in the CKD 1–3 group likely reflect competing mortality in the CKD 4–5 cohort, resulting in less time at risk for nonfatal outcomes.

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1517 | SPIRONOLACTONE IS ASSOCIATED WITH IMPROVED SURVIVAL AND RENAL OUTCOMES COMPARED WITH FUROSEMIDE IN CIRRHOSIS-RELATED ASCITES: A PROPENSITY-MATCHED COHORT STUDY

Delano Carty[1] Dilcia Maldonado[1] FNU Deepali[1] Cameron Gill[1] Damion Persad[1] Ghideon Ezaz[1], [1]Jefferson Einstein Philadelphia

Background: Diuretics are central to the management of ascites in cirrhosis, with current guidelines favoring mineralocorticoid receptor antagonists (MRAs) as first-line therapy. However, real-world comparative

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outcomes between MRAs and loop diuretics remain incompletely defined **Methods:** We conducted a retrospective cohort study using the TriNetX US Collaborative Network (2010–2026). Adult patients with cirrhosis and ascites were stratified by exposure to spironolactone (MRA group) or furosemide (loop diuretic group). Patients with end-stage renal disease, malignancy, liver transplantation, or overlapping diuretic exposure were excluded. Propensity score matching (1:1) was performed to balance demographics, liver disease severity, renal function, and comorbidities, yielding 38,271 patients per cohort. Outcomes included all-cause mortality, acute kidney injury (AKI), hepatorenal syndrome (HRS), spontaneous bacterial peritonitis (SBP), hospitalization, paracentesis, esophageal varices, and hepatic encephalopathy over a 5-year follow-up period. **Results:** After matching, furosemide use was associated with higher mortality compared with spironolactone (32.7% vs 29.5%; HR 1.14, 95% CI 1.11–1.17; $p < 0.001$). The furosemide group also demonstrated increased risk of AKI (23.2% vs 19.1%; RR 1.21), HRS (4.4% vs 3.8%; RR 1.14), hospitalization (39.2% vs 34.9%; RR 1.12), and paracentesis (13.3% vs 12.7%; RR 1.06) (all $p < 0.01$). There was no significant difference in SBP incidence between groups. Spironolactone use was associated with slightly higher rates of esophageal varices (20.3% vs 18.8%) and hepatic encephalopathy (12.8% vs 12.0%), though effect sizes were modest. **Conclusion:** In this large propensity-matched cohort of patients with cirrhosis and ascites, spironolactone use was associated with improved survival and lower risk of renal complications compared with furosemide. These findings support guideline-recommended use of MRAs as first-line therapy and highlight potential risks associated with loop diuretic–dominant strategies in cirrhosis.

Disclosures: Delano Carty:Nothing to Disclose, Dilcia Maldonado:Nothing to Disclose, FNU Deepali:Nothing to Disclose, Cameron Gill:Nothing to Disclose, Damion Persad:Nothing to Disclose, Ghideon Ezaz:Nothing to Disclose.

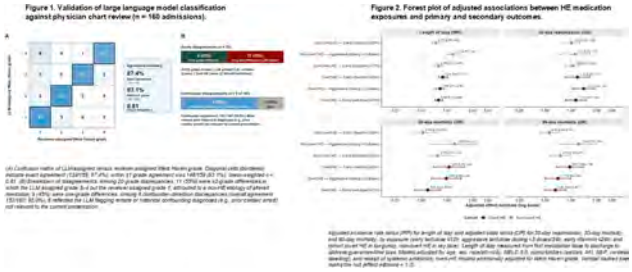
1518 | IMPACT OF TIMING AND INTENSITY OF LACTULOSE AND RIFAXIMIN ADMINISTRATION ON OUTCOMES IN HOSPITALIZED PATIENTS WITH HEPATIC ENCEPHALOPATHY

Sandeep Sikerwar[1] Elizabeth Verna[1] Arun Jesudian[2] Giuseppe Cullaro[1], [1]Columbia University Medical Center, [2]Weill Cornell Medicine

Background: Hepatic encephalopathy (HE) is a leading cause of preventable readmission in cirrhosis, yet no prior study has systematically evaluated whether timing and intensity of inpatient lactulose and rifaximin administration affect outcomes. We assessed whether early lactulose (≤ 12 hours), aggressive initial lactulose dosing (> 3 doses/24 hours), and early rifaximin (≤ 24 hours) were associated with improved outcomes in hospitalized patients with HE. **Methods:** We conducted a retrospective cohort study of hospitalized patients with cirrhosis who received either lactulose or rifaximin at Columbia University Irving Medical Center from November 2019–December 2025. Admissions were classified as overt HE or non-overt HE using a large language model (LLM; GPT 5.5) with hepatologist validation. Length of stay (LOS; negative binomial regression, measured from first dose to discharge to address guarantee-time bias), 30-day readmission, and 30-day mortality were analyzed using multivariable models. **Results:** A total of 4,520 HE hospitalizations were identified (1,361 overt, 3,159 non-overt). Mean LOS was 7.4 days in overt and 8.3 days in non-overt HE, 30-day readmission was 31% in both groups, and 30-day mortality was 17% in overt and 9% in non-overt HE. In a sample of 160 notes stratified by West Haven (WH) grade and LLM confidence level, exact agreement between the LLM and physician reviewer was 87.4% (140/160; $\kappa = 0.81$). After adjusting for age, sex, race/ethnicity, admission MELD 3.0, ICD-coded ascites, AKI, spontaneous bacterial peritonitis, variceal bleeding, and systemic antibiotic use, early lactulose was associated with a 19% shorter LOS in both overt HE (IRR 0.81, 95% CI 0.74–0.90) and non-overt HE (IRR 0.81; 95% CI 0.73–0.89). Aggressive lactulose was associated with a 16% shorter LOS in overt HE (IRR 0.84; 95% CI 0.75–0.94), and early rifaximin was associated with a 25% shorter LOS in non-overt HE (IRR 0.75; 95% CI 0.68–0.83). After the same adjustment, aggressive lactulose was associated with increased 30-day readmission in overt HE (OR 1.42, 95% CI 1.05–1.92), attenuated in patients without AKI (OR 0.85, 95% CI 0.46–1.53). Early lactulose was associated with 40% lower odds of 30-day mortality in overt HE (OR 0.60, 95% CI 0.42–0.85), and early rifaximin with 47% lower odds of 30-day mortality in non-overt HE (OR 0.53, 95% CI 0.37–0.75), preserved among rifaximin-naïve patients (OR 0.41, 95% CI 0.24–0.66). **Conclusion:** Earlier inpatient lactulose administration is associated with shorter LOS and decreased mortality in patients with both overt and non-overt HE. Early rifaximin is associated with shorter LOS and decreased mortality in non-overt HE. Aggressive lactulose is associated with decreased LOS in overt HE but increased readmission risk that may be driven by concurrent AKI. These findings support treating HE as a time-sensitive condition and motivate prospective evaluation of timing-based treatment protocols.

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1519 | DO PROBIOTICS IMPROVE OUTCOMES IN SPONTANEOUS BACTERIAL PERITONITIS? A REAL-WORLD MULTICENTER COHORT STUDY

Adham Obeidat[1] Ahmad Alqam[2] Scott Kuwada[3], [1]Presbyterian Medical Group, [2]University of New Mexico, [3]University of Hawaii

Background: Spontaneous bacterial peritonitis (SBP) remains a severe complication of decompensated cirrhosis, with high recurrence and mortality. Antibiotic treatment for SBP can disrupt the gut microbiota and increase the risk of Clostridioides difficile infection (CDI) and antibiotic-associated diarrhea. Probiotic supplementation has been proposed as a strategy to restore colonization resistance and reduce these complications; however, its role in patients undergoing treatment for SBP remains uncertain. **Methods:** We performed a retrospective cohort study using the TriNetX network including adults with SBP treated with systemic antibiotics. Patients were stratified by probiotic exposure versus no probiotic use. Propensity score matching was used to balance baseline characteristics and comorbidities between cohorts. The primary outcome was CDI. Secondary outcomes included antibiotic-associated diarrhea, mortality, hyponatremia, sepsis, hepatic encephalopathy, and hepatorenal syndrome (HRS). Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for all outcomes. **Results:** After propensity score matching, baseline characteristics were well balanced between cohorts. Probiotic use was associated with a higher chance of CDI but lower mortality compared with controls. Rates of antibiotic-associated diarrhea, hyponatremia, sepsis, and hepatic encephalopathy were comparable between groups, whereas HRS was less frequent among patients receiving probiotics (Table 1). **Conclusion:** In this multicenter cohort of patients with SBP receiving systemic antibiotics, probiotic use was not associated with reduced CDI, antibiotic-associated diarrhea, sepsis, hyponatremia, or hepatic encephalopathy. However, probiotics were associated with lower in-hospital mortality and reduced hepatorenal syndrome. To our knowledge, this is among the first large multicenter studies evaluating probiotics in antibiotic-treated SBP patients. These findings are hypothesis-generating and warrant prospective randomized studies to better define the role of probiotics in this high-risk population.

Table 1. Clinical Outcomes Among Patients With Spontaneous Bacterial Peritonitis Receiving Antibiotics With Versus Without Probiotic Therapy

Outcome	Probiotics n/N (%)	No Probiotics n/N (%)	Risk Difference (95% CI)	Odds Ratio (95% CI)	P Value
C. difficile colitis	115/523 (22.0%)	96/655 (14.7%)	0.073 (0.029 to 0.118)	1.641 (1.216–2.214)	0.001
Mortality	174/782 (22.3%)	238/778 (30.6%)	−0.083 (−0.127 to −0.040)	0.649 (0.517–0.815)	<0.001
Antibiotic-associated diarrhea	44/793 (5.5%)	29/793 (3.7%)	0.019 (−0.002 to 0.040)	1.548 (0.958–2.500)	0.072
Hyponatremia	296/793 (37.3%)	328/793 (41.4%)	−0.040 (−0.088 to 0.008)	0.844 (0.690–1.033)	0.100
Sepsis	346/793 (43.6%)	332/793 (41.9%)	0.018 (−0.031 to 0.066)	1.075 (0.881–1.311)	0.477
Hepatic encephalopathy	187/793 (23.6%)	191/793 (24.1%)	−0.005 (−0.047 to 0.037)	0.973 (0.772–1.225)	0.814
Hepatorenal syndrome	102/793 (12.9%)	141/793 (17.8%)	−0.049 (−0.085 to −0.014)	0.683 (0.518–0.900)	0.007

Disclosures: Adham Obeidat:Nothing to Disclose, Ahmad Alqam:Nothing to Disclose, Scott Kuwada: Nothing to Disclose.

★ 1520 | BEYOND MELD-NA: A LASSO-INTEGRATED URINARY BIOMARKER MODEL REWRITES 3-MONTH MORTALITY PREDICTION IN PATIENTS WITH CIRRHOSIS AND ACUTE KIDNEY INJURY

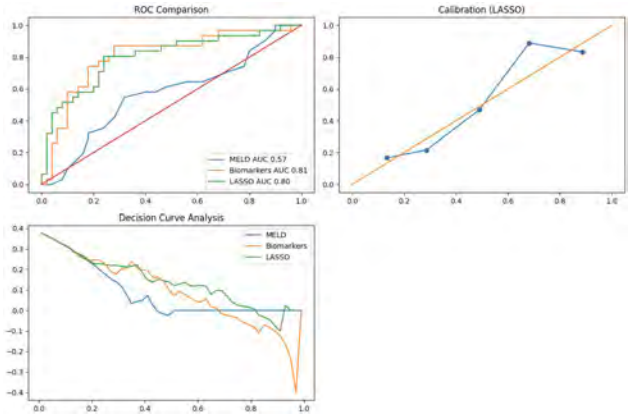
Deep Patel[1] Ajay Kumar[1] Ujjwal Sonika[1] Aman Agrawal[1] Ashok Dalal[1] Siddharth Srivastava[1] Sanjeev Sachdeva[1], [1]G.B.Pant Hospital (GIPMER, New Delhi)

Background: Acute kidney injury (AKI) in cirrhosis is a major determinant of short-term mortality, yet current prognostic tools remain suboptimal. MELD-Na relies on serum creatinine, which poorly reflects renal structural injury in cirrhosis due to altered physiology. Urinary biomarkers such as NGAL and IL-18 capture tubular

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injury and may enhance risk prediction beyond conventional models. This study compares the predictive performance of MELD Na, urinary Neutrophil gelatin-associated lipocalcin (uNGAL), urinary Interleukin-18 (uIL-18) and a LASSO-derived multivariate model for 3-month mortality in cirrhotic patients with AKI. **Methods:** Patients with decompensated cirrhosis with AKI admitted in tertiary care centre from January 2023 to December 2025 screened and enrolled after excluding patients with Chronic kidney disease, Hepatocellular Carcinoma, respiratory or circulatory failure and recent coronary intervention. Baseline demographic, clinical and laboratory parameters including day 3 uNGAL and uIL-18 recorded. Patients were followed up for 3 months. Primary outcome was 3-month all-cause mortality and predictor discrimination assessed using AUROC and Delong's test. LASSO regression model analysed with Discrimination curve and Net Reclassification Improvement (NRI) analysis. **Results:** Total of 81 patients were enrolled. The 3-month all-cause mortality was 38.27% (31 patients) with 29 liver-related events. MELD-Na AUROC 0.57 (95% CI 0.44-0.70), Biomarker-based model AUROC 0.81 (95% CI 0.70-0.89) and the LASSO model (combining MELD Na with biomarkers) AUROC 0.80 (95% CI 0.69-0.87, bootstrap-corrected 0.77). Both biomarker and LASSO models significantly outperformed MELD-Na ($p < 0.001$). The LASSO model showed substantial risk reclassification improvement (NRI 96% vs MELD, 63% vs Biomarker model) and superior clinical utility on decision curve analysis. **Conclusion:** Urine NGAL and IL-18 improve prediction of 3-month mortality beyond MELD Na in Cirrhotic AKI. A LASSO-integrated model provides superior discrimination, calibration and reclassification, supporting its role in advancing precision prognostication in cirrhosis.



Disclosures: Deep Patel:Nothing to Disclose, Ajay Kumar:Nothing to Disclose, Ujjwal Sonika:Nothing to Disclose, Aman Agrawal:Nothing to Disclose, Ashok Dalal:Nothing to Disclose, Siddharth Srivastava:Nothing to Disclose, Sanjeev Sachdeva:Nothing to Disclose.

1521 | COMPLEMENTARY PROGNOSTIC VALUE OF MAGNETIC RESONANCE ELASTOGRAPHY–BASED SPLEEN AND LIVER STIFFNESS IN ADVANCED CHRONIC LIVER DISEASE

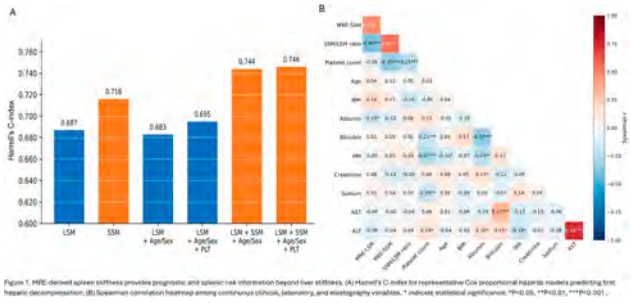
Caixin Qiu[1] Maysa Eslami[1] Jiahui Li[1] Hao Wu[1] Kevin Glaser[1] Sudhakar Venkatesh[2] Fang-Shu Ou[1] Alina Allen[2] Vijay Shah[2] Richard Ehman[2] Meng Yin[1], [1]Mayo Clinic, [2]Mayo Clinic Rochester

Background: Portal hypertension drives hepatic decompensation in compensated advanced chronic liver disease (cACLD), and spleen stiffness measurement (SSM) is an emerging noninvasive marker of portal hypertension–related risk. Current SSM largely relies on ultrasound-based elastography, which may be limited by technical challenges and separate liver-spleen acquisitions. Magnetic resonance elastography (MRE) enables standardized, concurrent assessment of liver and spleen stiffness. We evaluated whether MRE-derived SSM provides independent prognostic information for decompensation beyond liver stiffness measurement (LSM) alone. **Methods:** Patients with cACLD who underwent index MRE between March 2022 and September 2024 were included if they had elevated MRE-LSM (>3.6 kPa) or liver biopsy stage $\geq$F3, without ascites, hepatic encephalopathy, or variceal bleeding before or at the time of index MRE. The primary outcome is time to first hepatic decompensation, defined as the time from index MRE date to first hepatic decompensation, with patients who did not experience decompensation censored at their last documented follow-up. Cox proportional hazards regression was used to assess associations of LSM and SSM with the development of decompensation. Multivariable models sequentially adjusted for age, sex, LSM, platelet count, and splenomegaly. Harrell's C-index was used to assess model discrimination. Spearman correlation was used to evaluate associations among continuous clinical, laboratory, and elastography variables. $P<0.05$ was considered significant. **Results:** This study includes 283 patients (mean age, 56.3 ± 13.4 years; 48.1% women) with cACLD; 69 (24.4%) patients developed hepatic decompensation during a median follow-up of 961 days. LSM was associated with decompensation in univariable Cox analysis, HR 1.39 per 1 kPa, 95% CI 1.25–1.55, $P<0.001$, C-index 0.687 (Figure 1A). After adjustment for age, sex and platelet, LSM remained significant (HR 1.36, 95% CI 1.22–1.52, $P<0.001$). SSM showed higher discrimination in univariable analysis (HR 1.42 per 1 kPa, 95% CI 1.29–1.57, $P<0.001$, C-index 0.716). After adjustment for age, sex, and LSM, SSM remained independently associated with decompensation (HR 1.40, 95% CI 1.24–1.57, $P<0.001$, C-index 0.746). This association persisted after additional adjustment for platelet and splenomegaly (HR 1.28, 95% CI 1.10–1.50, $P=0.001$). SSM was inversely correlated with platelet

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count, Spearman r = -0.354, P < 0.001, whereas LSM was not, r = -0.093, P = 0.118 (Figure 1B). **Conclusion:** MRE-derived spleen stiffness is independently associated with first hepatic decompensation beyond liver stiffness. Spleen stiffness may capture complementary splenic and portal hypertension–related risk not fully reflected by liver stiffness alone.



Disclosures: Caixin Qiu:Nothing to Disclose, Maysa Eslami:Nothing to Disclose, Jiahui Li:Nothing to Disclose, Hao Wu:Nothing to Disclose, Kevin Glaser: Nothing to Disclose, Sudhakar Venkatesh:Nothing to Disclose, Fang-Shu Ou:Nothing to Disclose, Alina Allen:Novo Nordisk: Grant/Research Support, Novo Nordisk: Advisor, Target Pharma: Grant/Research Support, Boehringer Ingelheim: Advisor, Madrigal: Advisor, GSK: Advisor, Oncoustics: Grant/Research Support, Escopics: Grant/Research Support, Astra Zeneca: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Madrigal: Grant/Research Support, Siemens: Grant/Research Support, Galectin: Advisor, Astra Zeneca: Advisor, Vijay Shah:Boehringer Ingelheim: Consultant, GSK: Consultant, GENFIT SA: Consultant, Intercept Pharmaceuticals, Inc.: Advisor, Korro Bio, Inc.: Consultant, Novo Nordisk A/S: Consultant, Resolution Therapeutics, Ltd.: Advisor, Seal Rock Therapeutics, Ltd.: Consultant, Surrozen: Advisor, Dexcel Pharma Technologies, Ltd.: Consultant, Dimension Inx.: Advisor, Enveda: Consultant, Ochre Bio: Consultant, Satellite Biosciences, Inc.: Consultant, Richard Ehman:Resoundant Inc.: Royalties or patent beneficiary, Resoundant Inc.: Stock – privately held company, Resoundant: Uncompensated role assigned by my employer, Mayo Clinic, Meng Yin:Resoundant, Inc.: Stock – privately held company.

1522 | ACUTE MORTALITY ASSOCIATED WITH CHEST TUBE PLACEMENT IN HEPATIC HYDROTHORAX

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[1]Virginia Commonwealth University

Background: Hepatic hydrothorax is a serious complication of advanced cirrhosis occurring in 4-12% of patients with portal hypertension. Chest tube placement is generally discouraged due to concerns about continuous pleural fluid drainage worsening circulatory dysfunction and precipitating renal failure, infection, and electrolyte disturbances. Nevertheless, chest tube use continues in clinical practice with increasing trends reported over time. We compared risks of acute kidney injury, shock, and mortality following chest tube placement versus therapeutic thoracentesis in patients with cirrhosis and hepatic hydrothorax. **Methods:** This retrospective cohort study used the TriNetX U.S. Collaborative Network, which aggregates de-identified electronic health records from over 60 U.S. health care organizations. We identified adults with cirrhosis, ascites, pleural effusion, and diuretic use (spironolactone or furosemide) between January 2012 and January 2025. The index date was the first instance of chest tube placement or therapeutic thoracentesis. Patients were excluded if they had an alternative cause of pleural effusion before or up to 2 days from index date, prior liver transplantation, missing laboratory values within 90 days, or acute kidney injury or shock within 7 days before the index procedure. Propensity score matching (1:1) was performed using demographics, MELD-Na components, markers of hepatic decompensation, and critical illness indicators. Primary outcomes were 30-day acute kidney injury, shock, and all-cause mortality. Time-to-event analyses used Kaplan-Meier estimates and Cox proportional hazards models. **Results:** After propensity score matching, 463 patients in each group had balanced baseline characteristics (mean age 58 years, 62% male, mean bilirubin 3.9 mg/dL, albumin 2.7 g/dL, INR 1.6). Within 30 days, chest tube placement was associated with significantly higher risks of acute kidney injury (14.7% vs 10.6%; HR, 1.45; 95% CI, 1.00-2.09; P = 0.02), shock (8.0% vs 4.5%; HR, 1.81; 95% CI, 1.06-3.09; P = 0.03), and death (9.9% vs 5.6%; HR, 1.79; 95% CI, 1.11-2.90; P = 0.02) compared with thoracentesis. Liver transplantation rates did not differ significantly (3.5% vs 2.2%; HR, 1.62; 95% CI, 0.73-3.56; P = 0.23). **Conclusion:** In this propensity-matched cohort, chest tube placement in hepatic hydrothorax was associated with higher 30-day risks of acute kidney injury, shock, and mortality compared with therapeutic thoracentesis. These findings support current guideline recommendations to avoid chest tube placement when safer alternatives exist, favoring thoracentesis with early evaluation for definitive therapies like TIPS or liver transplantation.

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Figure 1. Thirty-Day Outcomes Following Chest Tube Placement Versus Therapeutic Thoracentesis in Patients With Hepatic Hydrothorax.

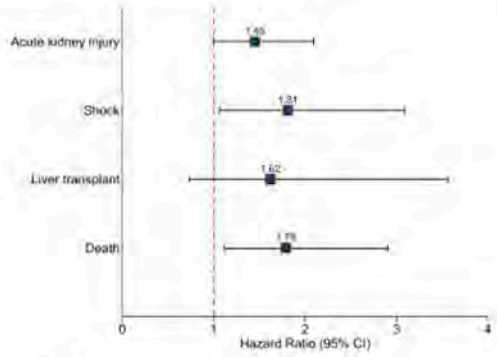


Table 1. Key Baseline Characteristics (After PSM)

Variable	Chest Tube (n=463)	Thoracentesis (n=463)	SMD
Age, mean (SD), y	58.3 (10.9)	58.4 (11.4)	0.010
Sex, Male, No. (%)	285 (61.6%)	291 (62.9%)	0.027
Critical care services, No. (%)	97 (21.0%)	98 (21.2%)	0.005
Hepatic failure (w/o coma), No. (%)	182 (39.3%)	186 (40.2%)	0.018
Total bilirubin, mean (SD), mg/dL	3.93 (4.33)	3.94 (4.59)	0.004
Creatinine, mean (SD), mg/dL	0.92 (0.49)	0.90 (0.49)	0.047
Sodium, mean (SD), mEq/L	134.0 (5.54)	135.0 (4.97)	0.073
INR, mean (SD)	1.61 (0.50)	1.64 (0.54)	0.065
Albumin, mean (SD), g/dL	2.73 (0.63)	2.70 (0.65)	0.048

Disclosures: Butros Fakhoury:Nothing to Disclose, Ali Khan:Nothing to Disclose, OMAR ALBHAISI:Nothing to Disclose, Shaurya Prakash:Nothing to Disclose, Amon Asgharpour:Nothing to Disclose, Juan Pablo Arab: Nothing to Disclose.

1523 | TWO INDEPENDENT CARDIAC RISK FACTORS FOR HEPATIC DECOMPENSATION IN CIRRHOSIS: QTC PROLONGATION AND CIRRHOTIC CARDIOMYOPATHY

Takashi Kitagataya[1] Goki Suda[1] Kiko Toda[1] Daisuke Yokoyama[1] Takatsugu Tanaka[1] Akimitsu Meno[1] Masatsugu Ohara[1] Masato Nakai[1] Takuya Sho[1] Naoya Sakamoto[1], [1]Hokkaido University

Background: Cardiac complications, including cirrhotic cardiomyopathy (CCM) and QTc prolongation, are common in liver cirrhosis and are associated with disease progression. CCM, diagnosed by the 2019 Cirrhotic Cardiomyopathy Consortium criteria, encompasses structural and functional myocardial abnormalities, while QTc prolongation reflects electrophysiological derangements. Notably, QTc prolongation was removed from the 2019 CCM diagnostic criteria due to concerns about specificity and unclear mechanistic links to cardiac dysfunction. Whether these two cardiac abnormalities independently predict hepatic decompensation and whether they identify distinct patient populations remains to be established. **Methods:** This retrospective cohort study enrolled 78 patients with liver cirrhosis confirmed by transient elastography (liver stiffness $\geq$12.5 kPa) who underwent both echocardiographic assessment for CCM and electrocardiographic evaluation for QTc measurement at Hokkaido University Hospital (January 2014–April 2024). QTc prolongation was defined using sex-specific thresholds (>450 ms in males, >470 ms in females) with the Fridericia correction. CCM was diagnosed according to the 2019 Cirrhotic Cardiomyopathy Consortium criteria. The primary endpoint was hepatic decompensation (ascites, variceal bleeding, or overt hepatic encephalopathy). Time-to-event analyses used the Kaplan–Meier method and Cox proportional hazards regression. **Results:** CCM was present in 50.0% (39/78) and QTc prolongation in 15.4% (12/78), with co-occurrence in only 9.0% (7/78). Hepatic decompensation incidence was significantly higher in both the CCM-positive group (HR 3.23, 95% CI 1.34–7.77; p = 0.009) and the QTc-prolonged group (HR 2.68, 95% CI 1.12–6.42; p = 0.023). No differences were observed in overall survival or cardiovascular events. Multivariate Cox regression identified QTc prolongation (HR 2.52, 95% CI 1.04–6.12, p = 0.042) and CCM (HR 2.64, 95% CI 1.07–6.49, p = 0.035) as independent predictors, alongside Child-Pugh grade B/C (HR 3.57, p = 0.002) and HCC beyond Milan criteria (HR 3.94, p = 0.004). QTc prolongation was more strongly associated with decompensation in Child-Pugh grade A patients (HR 3.81, 95% CI 1.17–12.45, p = 0.017) than in grade B/C patients (p = 0.578). **Conclusion:** QTc prolongation and CCM are independent predictors of hepatic decompensation with limited phenotypic overlap (9.0%), suggesting they represent distinct cardiac manifestations in cirrhosis. Comprehensive cardiac assessment incorporating both electrocardiographic and echocardiographic evaluation may improve risk stratification, particularly in compensated cirrhosis.

Disclosures: Takashi Kitagataya:Nothing to Disclose, Goki Suda:Nothing to Disclose, Kiko Toda:Nothing to Disclose, Daisuke Yokoyama:Nothing to Disclose, Takatsugu Tanaka:Nothing to Disclose, Akimitsu Meno:Nothing to Disclose, Masatsugu Ohara:Nothing to Disclose, Masato Nakai:Nothing to Disclose, Takuya Sho:Nothing to Disclose, Naoya Sakamoto:Nothing to Disclose.

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1524 | INDETERMINATE PERITONITIS IN CIRRHOSIS: A DISTINCT HIGH-RISK PHENOTYPE BETWEEN SECONDARY AND SPONTANEOUS BACTERIAL PERITONITIS

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Background: Distinguishing secondary peritonitis (SecP) from spontaneous bacterial peritonitis (SBP) in cirrhotic patients is critical, as SecP often requires procedural intervention. However, a subset of patients present with features overlapping both, including elevated polymorphonuclear cells (PMNs), polymicrobial or fungal cultures, or biochemical abnormalities consistent with Runyon's criteria. These "indeterminate peritonitis" (IP) cases are frequently managed variably in clinical practice. We aimed to compare clinical characteristics, peritoneal fluid profiles, management patterns, and outcomes across SecP, IP, and SBP. **Methods:** We performed a retrospective cohort study of cirrhotic patients admitted with peritonitis (n = 401), classified as SecP (n = 72), IP (n = 61), or SBP (n = 268) based on clinical, microbiologic, and biochemical criteria. Baseline characteristics, peritoneal fluid analyses, microbiology, antibiotic utilization, procedural interventions, and clinical outcomes were compared across groups using appropriate statistical tests. **Results:** There were no significant differences in age, sex, race, comorbidities, cirrhosis etiology, hepatic encephalopathy, or varices. SecP had a lower median admission MELD 3.0 (21.5 [16–28.2]) compared to IP (25 [21–32]) and SBP (24 [19–30]; $p = 0.018$). Early and late peritoneal fluid analyses demonstrated lower glucose and higher LDH in SecP and IP versus SBP, with no differences in PMNs, albumin, or protein. Peritoneal fluid cultures were more frequently positive in SecP (86.1%) and IP (50.8%) versus SBP (25%; $p < 0.001$), with higher rates of fungal (31.9% vs 9.8%) and polymicrobial infections (44.4% vs 16.4%) in SecP versus IP (both $p < 0.001$). Multidrug-resistant organisms were more common in SecP (27.8%) than IP (6.6%) or SBP (6.3%; $p < 0.001$). SecP patients received more inpatient antibiotics (5 [3-8]) than IP (3 [2-5]) and SBP (0 [0-1]) and underwent more abdominal procedures (43.1% vs 4.9% vs 7.5%) (both $p < 0.001$). ICU admission, vasopressor use, and mechanical ventilation were highest in SecP and IP (all $p \leq 0.005$). Median length of stay was longest in SecP (14.5 days) versus IP (9) and SBP (7.5; $p < 0.001$). SBP patients were more often discharged home (48.5% vs 22.2% vs 29.5%; $p < 0.001$) and more frequently received prophylactic antibiotics. Median time to readmission was shortest in SecP (23 days), 28 in IP and longest in SBP (47.5; $p = 0.011$). Mortality at 30, 60, and 90 days was highest in IP, followed by SecP, and lowest in SBP (all $p < 0.001$). **Conclusion:** Indeterminate peritonitis represents a clinically distinct and high-risk group with outcomes comparable to SecP, despite overlapping features with SBP. Biochemical and microbiologic profiles suggest closer alignment with SecP, while management patterns remain heterogeneous. Improved classification frameworks may improve risk stratification and guide more consistent treatment strategies in this population.

Disclosures: Kahler Doyle:Nothing to Disclose, Brayden Doyle:Nothing to Disclose, Viraj Gandhi:Nothing to Disclose, Mohammad Ashfaq:Nothing to Disclose.

1525 | AMBIENT SLEEP MONITORING IDENTIFIES SLEEP ALTERATIONS ASSOCIATED WITH DISEASE SEVERITY IN DECOMPENSATED CIRRHOSIS

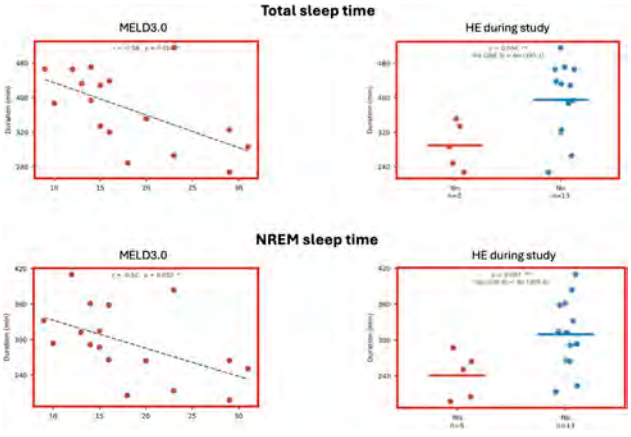
Alberto Calleri[1] Ali Mirzazadeh[2] Camille Kezer[1] Diego Drumond Westgeest e Sousa[1] Yigit Yazarkan[1] Kamalpreet Hara[1] Katherine Williams[1] Daniel Penrice[3] Patrick Kamath[1] Vijay Shah[1] Dina Katabi[4] Douglas Simonetto[1], [1]Mayo Clinic Rochester, [2]Massachusetts Institute of Technology, Cambridge, MA, USA, [3]Mayo Clinic Health System - Eau Claire, [4]Massachusetts Institute of Technology; Emerald Innovations Inc., Cambridge, MA, USA

Background: Sleep disturbances are common in patients with cirrhosis and hepatic encephalopathy (HE). However, longitudinal characterization of sleep patterns in real-world home settings remains limited. EMERALD is an ambient wireless sensor capable of passively monitoring sleep characteristics. We evaluated the feasibility and clinical correlates of wireless sensor-derived sleep metrics in patients with decompensated cirrhosis. **Methods:** Patients with decompensated cirrhosis were prospectively enrolled in a 3-month cirrhosis-specific remote patient monitoring (CiRPM) program integrating EMERALD sensors. Devices were installed in patient bedrooms and continuously captured sleep metrics including total sleep duration, non-rapid eye movement (NREM) sleep, deep sleep (N3), longest uninterrupted sleep period, and number of sleep periods per night. Sleep parameters were analyzed according to baseline demographics, liver disease severity (MELD 3.0), Liver Frailty Index (LFI), Animal Naming Test (ANT), history of HE and HE-related index hospitalization. **Results:** Among 18 patients included in the analyses, median age was 55 years (IQR 53-67), 50% were female, median BMI was 28.0 kg/m² (IQR 24-32), and median MELD 3.0

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was 16 (IQR 14-23). Fourteen patients (77.8%) had a prior history of HE, while 5 (27.8%) were hospitalized for HE during the study period. During follow-up, EMERALD successfully captured 982 nights of home sleep data. More advanced liver disease was consistently associated with worse sleep domains: MELD 3.0 inversely correlated with total sleep duration ($r = -0.58$, $p = 0.014$), NREM sleep ($r = -0.52$, $p = 0.032$), N3 sleep ($r = -0.49$, $p = 0.046$), and longest sleep period ($r = -0.56$, $p = 0.019$), while showing increased sleep fragmentation ($r = 0.61$, $p = 0.009$). Patients with MELD 3.0 ≥ 15 had significantly shorter total sleep time compared with those with MELD < 15 (5.7 vs 7.3 hours/night, $p = 0.004$). Presence of HE was similarly associated with impaired sleep characteristics: patients admitted for HE had shorter total sleep (4.8 vs. 6.6 hours/night, $p = 0.004$) and NREM sleep (4.0 vs. 5.2 hours/night, $p = 0.007$) compared with those admitted for non-HE etiologies; patients with prior HE history had lower total sleep (5.8 vs. 7.1 hours/night, $p = 0.017$) and N3 sleep (28.7 vs. 44.6 min, $p = 0.048$) compared with those without. No consistent significant associations between sleep metrics and LFI or ANT assessed at baseline were identified. **Conclusion:** Passive, continuous ambient sleep monitoring is feasible in patients with decompensated cirrhosis and identifies sleep alterations associated with disease severity and history of HE, supporting its potential as a digital biomarker for longitudinal home monitoring in advanced liver disease.



Disclosures: Alberto Calleri:Nothing to Disclose, Ali Mirzazadeh:Nothing to Disclose, Camille Kezer:Nothing to Disclose, Diego Drumond Westgeest e Sousa: Nothing to Disclose, Yigit Yazarkan:Nothing to Disclose, Kamalpreet Hara:Nothing to Disclose, Katherine Williams:Nothing to Disclose, Daniel Penrice:Nothing to Disclose, Patrick Kamath:Sequana: Advisor, NovoNordisk: Advisor, GSK: Advisor, Vijay Shah:Boehringer Ingelheim: Consultant, GSK: Consultant, GENFIT SA: Consultant, Intercept Pharmaceuticals, Inc.: Advisor, Korro Bio, Inc.: Consultant, Novo Nordisk A/S: Consultant, Resolution Therapeutics, Ltd.: Advisor, Seal Rock Therapeutics, Ltd.: Consultant, Surrozen: Advisor, Dexcel Pharma Technologies, Ltd.: Consultant, Dimension Inx.: Advisor, Enveda: Consultant, Ochre Bio: Consultant, Satellite Biosciences, Inc.: Consultant, Dina Katabi:Nothing to Disclose, Douglas Simonetto: Mallinckrodt: Consultant, BioVie: Consultant, Resolution Therapeutics: Consultant, Evive: Consultant, Iota: Consultant, Novo Nordisk: Consultant, Astra Zeneca: Consultant.

1526 | BENZODIAZEPINE/Z-DRUG INITIATION IN CIRRHOSIS: HIGHER MORTALITY WITHOUT EXCESS HEPATIC ENCEPHALOPATHY IN A PROPENSITY-MATCHED REAL-WORLD COHORT

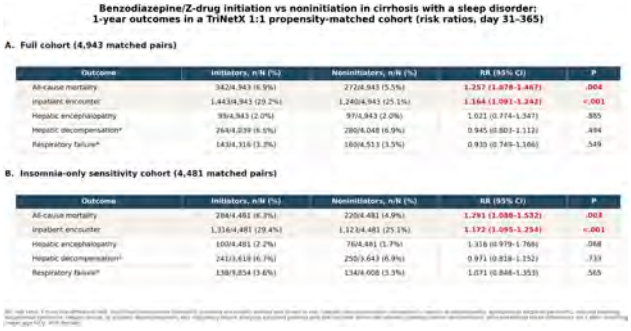
Akram Alnounou[1] Mohammad Alabbas[2] Ezzeldien Ibrahim[3] Ahmad Alhusen[4] Riddhi Machchhar[5] Eric Sieloff[6] Syed-Mohammed Jafri[7], [1]Western Michigan University Homer Stryker M.D. School of Medicine, Kalamazoo, MI, [2]Cleveland Clinic Foundation, Cleveland, OH, [3]University of Missouri-Columbia, Columbia, MO, [4]Advocate Illinois Masonic Medical Center, Chicago, IL, [5]Hackensack Meridian Ocean University Medical Center, [6]Western Michigan University Homer Stryker M.D. School of Medicine, [7]Henry Ford Health System

Background: Benzodiazepines and non-benzodiazepine ("Z-drug") hypnotics are commonly prescribed for sleep disturbance in cirrhosis despite concern that sedation may precipitate hepatic encephalopathy (HE). Whether initiating these agents after a sleep-disorder diagnosis is safe in cirrhosis is uncertain. We compared initiation with noninitiation for incident HE, mortality, and inpatient encounters. **Methods:** Adults aged ≥ 18 years with cirrhosis and a sleep-disorder diagnosis at least 1 month after cirrhosis were identified in the TriNetX Research Network (111 health care organizations). After a 1-year washout, initiators had a benzodiazepine/Z-drug medication record within 1 month after sleep diagnosis; noninitiators had none in that window. Patients with prior HE, liver transplant, palliative-care encounter, or decompensation or death during the first month after sleep diagnosis were excluded. Cohorts were 1:1 propensity-score matched on demographics, liver-related diagnoses, comorbidities, respiratory failure/sleep apnea, opioids, CNS-active medications, and cirrhosis medications. Outcomes were assessed from day 31 through day 365 and reported as risk ratios (RRs) with 95% CIs. **Results:** After matching, 4,943 initiators and 4,943 noninitiators were analyzed. Initiation was not associated with incident HE (99/4,943 [2.0%] vs 97/4,943 [2.0%]; RR 1.021, 95% CI

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0.774–1.347; P = .885). Initiation was associated with higher mortality (342/4,943 [6.9%] vs 272/4,943 [5.5%]; RR 1.257, 95% CI 1.078–1.467; P = .004) and inpatient encounters (1,443/4,943 [29.2%] vs 1,240/4,943 [25.1%]; RR 1.164, 95% CI 1.091–1.242; P < .001), whereas a hepatic decompensation composite (RR 0.945, 95% CI 0.803–1.112) and respiratory failure (RR 0.935, 95% CI 0.749–1.166) did not differ. In an insomnia-only cohort, mortality (6.3% vs 4.9%; RR 1.291, 95% CI 1.088–1.532; P = .003) and inpatient encounters (29.4% vs 25.1%; RR 1.172, 95% CI 1.095–1.254; P < .001) remained higher, while HE remained non-significant (2.2% vs 1.7%; RR 1.316, 95% CI 0.979–1.768; P = .068). **Conclusion:** In this matched EHR cohort, benzodiazepine/Z-drug initiation after a sleep-disorder diagnosis in cirrhosis was not associated with incident HE but was associated with higher 1-year mortality and inpatient encounters. Prospective studies should test cirrhosis-specific sleep-treatment strategies with direct measures of medication use, liver disease severity, and cause of death.


Benzodiazepine/Z-drug initiation vs noninitiation in cirrhosis with a sleep disorder: 1-year outcomes in a TriNetX 1:1 propensity-matched cohort (risk ratios, day 31-365)

A. Full cohort (4,943 matched pairs)

Outcome	Initiators, n/N (%)	Noninitiators, n/N (%)	RR (95% CI)	P
All-cause mortality	342/4,943 (6.9%)	272/4,943 (5.5%)	1.257 (1.078-1.467)	.004
Inpatient encounter	1,443/4,943 (29.2%)	1,240/4,943 (25.1%)	1.164 (1.091-1.242)	<.001
Hepatic encephalopathy	99/4,943 (2.0%)	97/4,943 (2.0%)	1.021 (0.774-1.347)	.885
Hepatic decompensation*	264/4,039 (6.5%)	280/4,048 (6.9%)	0.945 (0.803-1.112)	.494
Respiratory failure*	143/4,316 (3.3%)	160/4,513 (3.5%)	0.935 (0.749-1.166)	.549

B. Insomnia-only sensitivity cohort (4,481 matched pairs)

Outcome	Initiators, n/N (%)	Noninitiators, n/N (%)	RR (95% CI)	P
All-cause mortality	284/4,481 (6.3%)	220/4,481 (4.9%)	1.291 (1.086-1.532)	.003
Inpatient encounter	1,316/4,481 (29.4%)	1,123/4,481 (25.1%)	1.172 (1.095-1.254)	<.001
Hepatic encephalopathy	100/4,481 (2.2%)	76/4,481 (1.7%)	1.316 (0.979-1.768)	.068
Hepatic decompensation*	241/3,618 (6.7%)	250/3,643 (6.9%)	0.971 (0.818-1.152)	.733
Respiratory failure*	138/3,854 (3.6%)	134/4,008 (3.3%)	1.071 (0.846-1.353)	.565

Disclosures: Akram Alnounou:Nothing to Disclose, Mohammad Alabbas:Nothing to Disclose, Ezzeldien Ibrahim:Nothing to Disclose, Ahmad Alhusen:Nothing to Disclose, Riddhi Machchhar:Nothing to Disclose, Eric Sieloff:Nothing to Disclose, Syed-Mohammed Jafri:Takeda: Speaking and Teaching, Gilead: Speaking and Teaching, Abbvie: Speaking and Teaching, Ironwood: Advisor, Intercept: Speaking and Teaching.

1527 | ASCITES CHARACTERISTICS IN ADULTS WITH FONTAN CIRCULATION

Wesley Dixon[1] Sean Sanker[2] Michael Rosamilia[1] Stephen Zucker[1] Fred Wu[3] Jordan Sack[1], [1]Mass General Brigham, [2]Boston Children's Hospital, [3]Boston Children's Hospital

Background: Ascites is a late complication of the Fontan operation arising from a multifactorial pathophysiology that includes elevated central venous pressure, lymphatic congestion, and hepatic fibrosis. Characteristics of Fontan-related ascites and their clinical implications have not been systematically described. **Methods:** We retrospectively analyzed adults across two centers who underwent ≥1 paracentesis ≥5 years after Fontan. Demographic and clinical characteristics were from the time of initial paracentesis. Hemodynamics and hepatic pressures were obtained within 6 and 18 months of initial paracentesis, respectively. When available, liver histology and stiffness were recorded. Outcomes included varices, hepatic encephalopathy, hepatocellular carcinoma, transplant, and death. Serum-ascites albumin gradient (SAAG), total protein (TP), and neutrophil count were collected from each paracentesis. High SAAG and high TP were defined as ≥1.1 g/dL and ≥2.5 g/dL, respectively. First and last paracenteses were compared using linear mixed-effect modeling. **Results:** Among 41 adults with Fontan circulation (49% male; 39% atriopulmonary, 32% extracardiac, 24% lateral tunnel, 5% Kawashima), index paracentesis occurred at median 32.9 (IQR 30.0-41.9) years, or 27.7 (21.4-30.6) years after Fontan (**Figure 1A**). No patient had malignant or nephrotic ascites. Patients with high SAAG (44%) more commonly had hepatitis C infection or protein-losing enteropathy, and had a higher risk of death or transplant (**Figure 1B**). Presence of bridging fibrosis on liver biopsy was similar between groups. However, high SAAG was not associated with time to death or transplant by Cox proportional hazards analysis (HR 1.82, 95% CI 0.79-4.22). Compared to low TP, patients with high TP (88%) had less protein-losing enteropathy (8.3% vs. 60%; p = 0.017), less hepatocellular carcinoma (2.8% vs. 40%; p = 0.035), and similar rates of death or transplant (53% vs. 80%; p = 0.40). Among 30 patients with serial paracenteses, only 20% changed SAAG/TP category, with transition from low to high SAAG being most common [4 (13%)]. SAAG remained stable over time ($\beta = 0.0071$ g/dL/year, p = 0.57), whereas ascitic total protein tended to decrease ($\beta = -0.082$ g/dL/year, p = 0.0060). Median index ascitic neutrophil count was 63.5 (26.0-578.4) cells/mL; 19 (46%) ever had neutrophil count ≥250 cells/mL and 4 (9.8%) had ≥250 cells/mL on paracenteses >1 month apart, but these had no association with death or transplant (p = 0.90 for both). **Conclusion:** Approximately half of Fontan patients with ascites have low SAAG, an unexpected finding that may challenge the assumption that Fontan ascites behaves like typical portal hypertensive ascites. Ascites characteristics were generally stable within patients, though TP did demonstrate a modest decrease over time. Higher SAAG trended towards worse survival.

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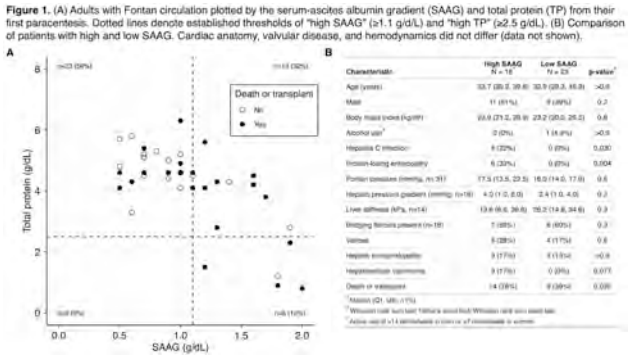


Figure 1. (A) Adults with Fontan circulation plotted by the serum-ascites albumin gradient (SAAG) and total protein (TP) from their first paracentesis. Dotted lines denote established thresholds of "high SAAG" (≥1.1 g/d/L) and "high TP" (≥2.5 g/dL). (B) Comparison of patients with high and low SAAG. Cardiac anatomy, valvular disease, and hemodynamics did not differ (data not shown).

Disclosures: Wesley Dixon:Nothing to Disclose, Sean Sanker:Nothing to Disclose, Michael Rosamilia:Nothing to Disclose, Stephen Zucker:Nothing to Disclose, Fred Wu: Nothing to Disclose, Jordan Sack:Nothing to Disclose.

1528 | EARLY OUTCOMES AFTER EMERGENT VS NON-EMERGENT TIPS: 90-DAY MORTALITY, HEPATIC ENCEPHALOPATHY, AND MELD 3.0 TRAJECTORY

Ashley Lamba[1] Eusha Hasan[2] Ian Rumball[3] Ethan Davoudzadeh[4] Nayan Tiwary[5] Anwesha Satapathy[2] Craig Greben[2] Jonathan Weinstein[2] Sanjaya Satapathy[2], [1]UCLA, [2]Northwell Health, [3]Medical College of Wisconsin, [4]Memorial Sloan Kettering, [5]Morristown Medical Center

Background: Transjugular intrahepatic portosystemic shunt (TIPS) is an established therapy for complications of portal hypertension, including refractory ascites and uncontrolled variceal hemorrhage. Hepatic encephalopathy (HE) remains one of the most frequent and clinically impactful complications after TIPS, contributing to readmissions and early morbidity. Outcomes following TIPS may vary by procedural urgency, particularly regarding short-term mortality and HE. This study evaluated 90-day outcomes and MELD 3.0 trajectories after emergent versus non-emergent TIPS in a sensitivity cohort excluding patients with baseline HE. **Methods:** In this HE-excluded cohort, 90-day survival was compared using Kaplan–Meier analysis with log-rank testing. Incident HE within 90 days was assessed using Fine–Gray competing-risks regression (event = HE; competing event = death), adjusted for age and baseline MELD 3.0. MELD 3.0 trajectories at baseline, 1 week, and 1 month were analyzed using a linear mixed-effects model with repeated measures and unstructured covariance. **Results:** A total of 128 patients underwent TIPS placement, including 42 emergent and 86 non-emergent procedures. Emergent TIPS patients had significantly lower albumin (2.62 vs 3.26 g/dL, p < 0.0001) and higher INR (1.58 vs 1.36, p = 0.0053) at baseline, consistent with greater clinical acuity. Variceal hemorrhage accounted for 90.5% of emergent TIPS indications, whereas refractory ascites accounted for 53.5% of non-emergent cases (p < 0.001). Baseline MELD 3.0 was the strongest independent predictor of mortality (HR 1.14 per point; p = 0.0035).In the sensitivity cohort excluding patients with baseline HE (n = 116; 37 emergent, 79 non-emergent), 90-day mortality was higher after emergent TIPS (21.6% vs 7.6%), with significantly worse survival (log-rank p = 0.0251). Emergent TIPS was associated with an increased risk of 90-day HE (adjusted subdistribution hazard ratio [sHR] 2.14; 95% CI, 1.12–4.08; p = 0.0206). MELD 3.0 scores increased significantly over time (p < 0.0001), but neither TIPS urgency (p = 0.3475) nor the urgency-by-time interaction (p = 0.6724) was significant. **Conclusion:** In patients without baseline HE, emergent TIPS was associated with higher 90-day mortality and a greater risk of incident HE compared with non-emergent TIPS. Despite these differences in clinical outcomes, MELD 3.0 trajectories over early follow-up were similar between groups, suggesting that excess early mortality after emergent TIPS may reflect pre-procedural clinical acuity rather than accelerated hepatic deterioration after shunt placement. These findings highlight the need for intensified monitoring in the early post-procedural period for emergent TIPS recipients.

Disclosures: Ashley Lamba:Nothing to Disclose, Eusha Hasan:Nothing to Disclose, Ian Rumball:Nothing to Disclose, Ethan Davoudzadeh:Nothing to Disclose, Nayan Tiwary:Nothing to Disclose, Anwesha Satapathy:Nothing to Disclose, Craig Greben:Nothing to Disclose, Jonathan Weinstein:Boston Scientific: Consultant, Sanjaya Satapathy:Gilead Sciences: Grant/Research Support, Durect Pharma: Grant/Research Support, Fibronostics: Grant/Research Support, Novartis: Grant/Research Support, Zydus Pharma: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Intercept Pharma: Grant/Research Support, AKERO: Grant/Research Support, Altimmune: Grant/Research Support, IPSEN: Grant/Research Support, Madrigal: Grant/Research Support.

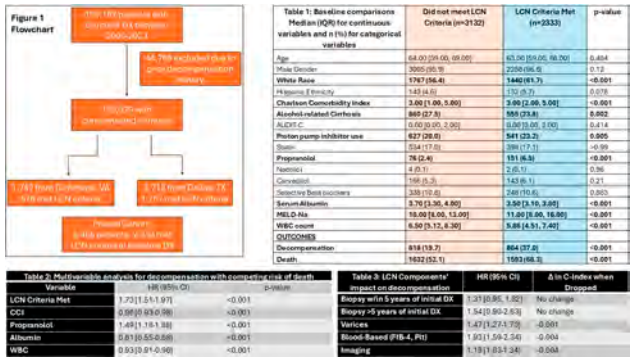
1529 | VALIDATION OF LIVER CIRRHOSIS NETWORK CRITERIA FOR CIRRHOSIS DIAGNOSIS USING NATURAL LANGUAGE PROCESSING FOR PREDICTING DECOMPENSATION USING A MULTI-CENTER STUDY

Scott Silvey[1] Nilang Patel[2] Jacqueline O'Leary[3] Jasmohan Bajaj[1], [1]Virginia Commonwealth University, [2]Richmond VA Medical Center, [3]Dallas VAMC

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Background: The NIH-sponsored liver cirrhosis network (LCN) provided a consensus clinical definition for cirrhosis diagnosis, which includes a liver biopsy, blood-based, elastography, or imaging-based biomarkers. However, these need validation. **Aim:** Validate LCN criteria for cirrhosis for predicting decompensation. **Methods:** LCN criteria : (liver bx w cirrhosis < 5 yrs or 2 of the following: cirrhosis liver bx > 5 yrs, varices (< 3 yrs), imaging (nodularity +splenomegaly/collaterals < 1 yr), blood-based (FIB-4 > 2.67 or Platelets < 150/mL < 6 mths) or elastography (VCTE > 12.5 Kpa/MRE > 5Kpa < 1 yr).Cohort : We used the Veterans Affairs Corporate Data Warehouse (VA-CDW) charts from Richmond and Dallas VAs to create a cohort with initial cirrhosis diagnosis between 2009-2023 through ICD-9/10 codes. Using a combination of natural language processing (NLP) through record review, we determined LCN criteria & excluded pts with decompensation/events occurring within 30 days. Cohort details between LCN criteria yes/no were compared. We performed time-to-event analysis using competing risks regression for new decompensation (ascites, SBP, HCC, HE, or variceal bleed) between groups till Jan 1 2024, at which point those without new decompensation were censored. Multivariable models for decompensation were created. Then each LCN component's relative importance was measured using model coefficient comparison & decline in C-Index after removal. **Results:** We included 5465 compensated cirrhosis pts (Fig 1, 64 yrs, 96.3% men, 25.9% alcohol). 2333 (42.7%) met the LCN criteria [7.5%) liver Bx w/in 5 yrs, 93.7% blood-based, 37.0% varices, 89.5% imaging & 1.3% liver bx > 5 yrs]. MRE/VCTE was not widely done. Those who met LCN criteria were more likely to be White, less likely to have an alcohol etiology, were more likely to be on propranolol/PPI, higher CCI/MELD-Na, with lower albumin and WBC counts (Table 1).27.1% had a decompensating event & 59.0% died. Median time-to-first decompensation was 3.96 yrs, & median follow-up time/pt was 7.38 years. On time-to-event analysis with competing risk of death, LCN criteria pts had a higher risk of new decompensation (sub-distribution HR (sHR) 2.04 [1.83-2.28], $p < 0.001$), which persisted on multivariable analysis (Table 2, adj. sHR: 1.73 [1.51-1.97], $p < 0.001$). Others were lower CCI, propranolol, lower albumin, & lower WBC.Components : Blood-based (FIB-4/Platelet) features had the greatest relative importance & led to the greatest drop in C-index when removed (Table 3). Having more LCN components also raised decompensation risk (adj. sHR: 1.45 [1.35-1.55] X risk for each extra component, $p < 0.001$). **Conclusion:** Fulfilling the LCN criteria detected through NLP for cirrhosis diagnosis was associated with a significantly higher rate of decompensation versus conventional clinical criteria across two large VA sites. Blood-based biomarkers had the highest impact on LCN criteria's impact on decompensation.



Disclosures: Scott Silvey:Nothing to Disclose, Nilang Patel:Nothing to Disclose, Jacqueline O'Leary:Genfit: Consultant, CVS: Stock - publicly traded company, Mallinckrodt: Advisor, PharmaIn: Advisor, PharmaIn: Consultant, Genfit: Consultant, PharmaIn: Consultant, Genfit: Consultant, Jasmohan Bajaj:Bausch: Grant/Research Support, Sequana: Grant/Research Support, Grifols: Grant/Research Support, Bausch: Grant/Research Support, Sequana: Grant/Research Support, Grifols: Grant/Research Support, Genfit: Grant/Research Support, Enterobiotix: Advisor, Boehringer Ingelheim: Advisor, Merz: Consultant.

1530 | SHORT- AND LONG-TERM OUTCOMES OF TERLIPRESSIN + ALBUMIN VS TRIPLE THERAPY IN HEPATORENAL SYNDROME: A U.S. REAL-WORLD COHORT STUDY

Islam Rajab[1] Ahmed Emara[2] Ameer Awashra[3] Mohamed Saad Rakab[4] Mohammad Kathem Salah[3] Zaid Sawaftah[3] Ahmed Sawafta[5] Ali Bani Odeh[3] Osama Nizar Jaber[3] Dhruv Patel[6] Mina Alkomos[7] Mohamed Elnaggar[8] Walid Baddoura[7] Nikolaos Pyrsopoulos[9], [1]Department of Internal Medicine, St. Joseph University Medical Center, Paterson, NJ, USA, [2]Faculty of Medicine, Al-Azhar University, Cairo, Egypt, [3]Department of Medicine, An-Najah National University, Nablus, West Bank, Palestine, [4]Faculty of Medicine, Mansoura University, Mansoura, Egypt, [5]. Department of Medicine, An-Najah National University, Nablus, West Bank, Palestine., [6]Department of Gastroenterology and Hepatology, St. Joseph

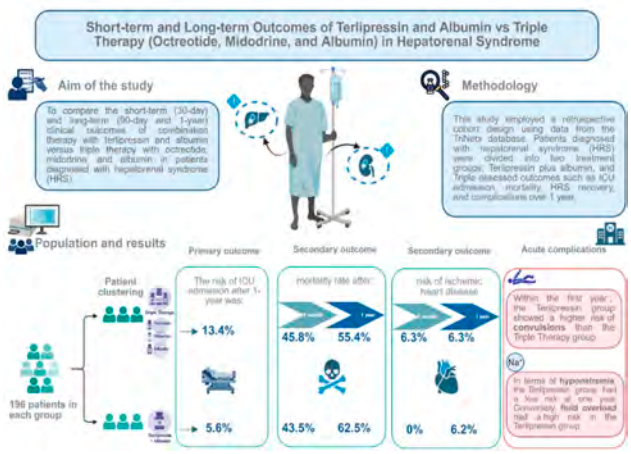
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University Medical Center, Paterson, NJ, U, [7]Department of Gastroenterology and Hepatology, St. Joseph University Medical Center, Paterson, NJ,US, [8]Hospital Medicine department, Hartford healthcare, Hartford, CT. USA, [9]Liver Disease in New Jersey, NYU Grossman School of Medicine,NYU Langone Transplant Institute, NJ.US

Background: Terlipressin plus albumin is now the preferred therapy for hepatorenal syndrome–acute kidney injury (HRS-AKI), yet real-world comparative data against midodrine–octreotide–albumin (MOA) in the United States remain limited. We evaluated short- and long-term outcomes of both regimens using a large, multi-center electronic health-record network. **Methods:** Adults with HRS were identified in the TriNetX U.S. Collaborative Network (data cutoff July 2025). Cohorts included patients receiving terlipressin + albumin versus MOA. After applying prespecified exclusions, 8,692 patients were eligible. Propensity-score matching (1:1; caliper 0.1) balanced demographics, comorbidities, and laboratory values, yielding 196 patients per group. Outcomes included ICU admission (primary) and mortality, hyponatremia, arrhythmia, pulmonary edema, ischemic heart disease (IHD), fluid overload, and HRS recovery (secondary). Kaplan–Meier estimates and hazard ratios (HRs) were computed at 1 month, 3 months, and 1 year. **Results:** Among 392 matched patients (mean age 60.8 years; 68.6% male), terlipressin was associated with significantly fewer ICU admissions at 1 month (HR 0.30; 95% CI 0.095–0.97), 3 months (HR 0.21; 95% CI 0.07–0.63), and 1 year (HR 0.23; 95% CI 0.085–0.62). One-year ICU admission occurred in 5.6% with terlipressin vs 13.4% with MOA (risk difference –7.8%, p = 0.017). Mortality did not differ at any interval: 1-month HR 0.97 (p = 0.85); 3-month HR 1.08 (p = 0.58); 1-year HR 1.09 (p = 0.52). Terlipressin was associated with higher risk of fluid overload at 3 months and 1 year (HR 2.73; 95% CI 1.10–6.76). No significant between-group differences were observed in arrhythmia, pulmonary edema, hyponatremia, or renal replacement therapy. HRS recovery at 1 year was similar (26.5% vs 24.1%). IHD showed a temporal pattern: lower early events with terlipressin but convergence by 1 year. **Conclusion:** In this large U.S. real-world analysis, terlipressin + albumin significantly reduced ICU admissions compared with MOA across all time-points, with no mortality advantage and a higher rate of fluid overload over long-term follow-up. These findings support current guidance favoring terlipressin for HRS-AKI while underscoring the need for careful volume and respiratory monitoring. Further prospective studies are warranted to optimize patient selection and mitigate adverse-event risk.

Grahical Abstract



Disclosures: Islam Rajab:Nothing to Disclose, Ahmed Emara:Nothing to Disclose, Ameer Awashra:Nothing to Disclose, Mohamed Saad Rakab:Nothing to Disclose, Mohammad Kathem Salah:Nothing to Disclose, Zaid Sawaftah:Nothing to Disclose, Ahmed Sawafta:Nothing to Disclose, Ali Bani Odeh:Nothing to Disclose, Osama Nizar Jaber:Nothing to Disclose, Dhruv Patel:Nothing to Disclose, Mina Alkomos:Nothing to Disclose, Mohamed Elnaggar:Nothing to Disclose, Walid Baddoura:Nothing to Disclose, Nikolaos Pyrsopoulos:Nothing to Disclose.

1531 | THE ORAL CHOLATE CHALLENGE TEST (HEPQUANT DUO®) DISCRIMINATES DECOMPENSATION IN ADVANCED CHRONIC LIVER DISEASE

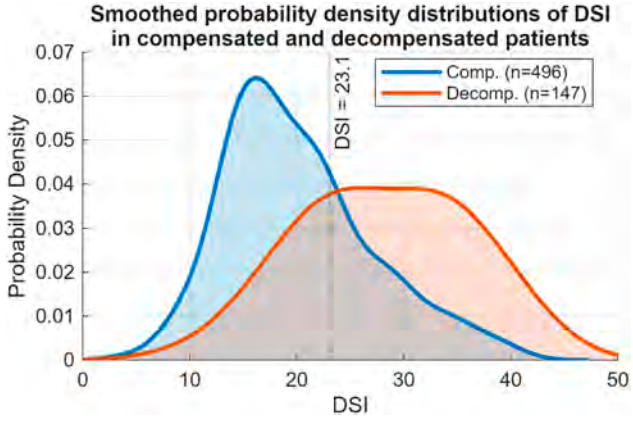
Michael McRae[1] Joanne Imperial[2] Gregory Everson[3], [1]Custom DX Solutions LLC, [2]HepQuant LLC, [3]HepQuant

Background: Identifying patients with compensated advanced chronic liver disease (CLD) who are at risk for decompensation (DC) remains a central clinical goal. The Disease Severity Index (DSI), derived from the oral cholate challenge test (OCCT), is a quantitative measure of global liver disease severity ranging from 0 (healthy) to 50 (severe dysfunction). This analysis evaluated whether DSI identifies patients with advanced CLD who had DC or subsequently experience liver-related clinical progression. **Methods:** Data from 6 clinical studies were analyzed, representing a total of 643 subjects. Baseline DSI was evaluated for discrimination of Child-Pugh (CP) B at baseline or subsequent liver-related clinical progression during follow-up (liver-related death, CP progression, variceal hemorrhage, ascites, and/or encephalopathy). The OCCT involved oral administration of deuterium-labelled (d4-) cholate, blood

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sampling at 20 and 60 minutes, and quantification of the d4-cholate by LC-MS/MS. Test parameters, including DSI, were calculated for each subject. Optimal thresholds for discriminating compensated versus decompensated were selected using Youden's index, 90% sensitivity (rule-out), and 90% specificity (rule-in). Distributional separation was visualized using kernel density estimates. Discrimination was assessed by AUROC, sensitivity, and specificity. Multivariable logistic regression (LR) evaluated the association of DC status with DSI adjusted for disease etiology. **Results:** The cohort had mean age 56 ± 11 years, BMI 31 ± 6 kg/m^2, and 57% were male. Liver disease etiologies included chronic hepatitis C (51%), MASH (18%), PSC (8%), alcohol-associated liver disease (7%), and other (16%). A total of 147 subjects (23%) had CP B cirrhosis or experienced a clinical progression event during follow-up. Higher DSI values were associated with greater odds of DC, and DSI discriminated decompensated/progressed from compensated subjects with an AUROC of 0.78 (95% CI 0.73–0.82). The Youden index threshold was DSI >23.1 with sensitivity 0.71 (0.61–0.85) and specificity 0.72 (0.58–0.82). Rule-out and rule-in thresholds were DSI ≤17.8 and >30.1, respectively. In multivariable LR adjusted for disease etiology, DSI remained independently associated with decompensated liver disease, with an adjusted odds ratio of 1.17 per unit increase (95% CI 1.13–1.20, p < 0.0001). Compared with hepatitis C, MASH was associated with lower adjusted odds of DC, whereas PSC was associated with higher adjusted odds. **Conclusion:** The OCCT-derived DSI identified patients with prior or subsequent liver-related DC and remained independently associated with DC after adjustment for etiology. DSI thresholds selected herein may support future external validation of clinically useful risk strata for patients with advanced CLD. Further prospective validation is warranted to define its role in DC risk assessment and clinical decision-making.



Disclosures: Michael McRae:HepQuant, LLC: Independent Contractor, Joanne Imperial:Nothing to Disclose, Gregory Everson:Nothing to Disclose.

1532 | METHYLGLYOXAL DETOXIFICATION MITIGATES ENDOTOXIN-INDUCED PORTAL HYPERTENSION AGGRAVATION VIA RESTORATION OF LIVER SINUSOIDAL ENDOTHELIAL CELL MITOCHONDRIAL FUNCTION AND VASCULAR INTEGRITY

Dinesh Mani Tripathi[1] Vaibhav Tiwari[1] Rajni Yadav[1] Manisha .[1] Bitan Guchhait[1] Himanshi .[1] Aishwarya Bhatnagar[1] Savneet kaur[1] anupam kumar[1] Shiv Kumar Sarin[1], [1]Institute of Liver and Biliary Sciences

Background: Endotoxemia contributes to portal hypertension (PHT) in both cirrhotic and non-cirrhotic patients, mainly due to impaired liver sinusoidal endothelial cell (LSEC) function. We hypothesised that endotoxemia-driven glycolytic rewiring in LSECs promotes the pathological accumulation of methylglyoxal (MGO), thereby impairing mitochondrial bioenergetics and contributing to the development of PHT. We investigated the roles of MGO accumulation and its detoxification in restoring LSEC mitochondrial function and vascular homeostasis **Methods:** Endotoxemia was induced via 50% caecal ligation and puncture (CLP) in non-cirrhotics and via lipopolysaccharide (1mg/kg b.wt intraperitonially) in CCl_4-cirrhotic rats. MGO detoxification was achieved by activating Glo-1 with hesperetin (40 mg/kg b.wt, orally, 7 days). Systemic and hepatic Hemodynamic parameters, LSEC functionality and sinusoidal remodelling were assessed. Intracellular MGO levels, Glo-1 enzymatic activity, and D-lactate production were quantified. Metabolomic profiling and mitochondrial bioenergetics of LSECs were analysed. Endothelial integrity using trans-endothelial electrical resistance (TEER), vascular permeability assays (Lucifer yellow, Dextran 40 kDa), tube formation, and leukocyte adhesion assays was assessed. Molecular profiling of Glo-1, MCP1, HMGB1, junctional markers (VE-cadherin and Claudin-5) and survival analysis was performed. **Results:** Hesperetin-mediated Glo-1 activation significantly attenuated portal pressure and hyperdynamic circulation in both cirrhotic (CCl_4+LPS) (-20%) and non-cirrhotic (CLP) (-33%) models. MGO detoxification was validated by a significant reduction in intracellular MGO levels and an increase in D-lactate production (p < 0.001). LCMS-based LSECs Metabolomic profiling revealed that Go-1 activation (Hesperetin) reversed mitochondrial impairment, evidenced by restored mitochondrial respiration (OCR) (p < 0.01) and reduced glycolytic stress (ECAR) (p < 0.001). Structurally, LSECs fenestrae restoration, mitochondrial biomass, and mitochondrial potential, and a reduction in mitochondrial ROS was observed upon Glo-1 activation. TEER and vascular permeability, increased levels of the endothelial junctional proteins VE-cadherin and Claudin-5 confirmed the restored endothelial barrier integrity (p < 0.01).

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Improved Tube-formation capacity, and leukocyte adhesion was significantly reduced upon treatment. Pro-inflammatory mediators were downregulated in both LSECs and hepatic tissue following hesperetin treatment ($p < 0.02$). Consequently, survival increased by 28% in cirrhotics (N = 8 each group) **Conclusion:** Pharmacological detoxification of methylglyoxal mitigates LSEC mitochondrial impairment, thereby improving mitochondrial function and integrity, attenuating portal hypertension, and improving survival during sepsis in cirrhosis

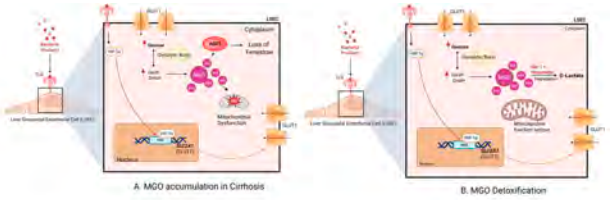


Figure. Schematic of the molecular mechanism by which methylglyoxal detoxification restores liver sinusoidal endothelial cell (LSEC) function and mitigates the aggravation of endotoxin-induced portal hypertension.

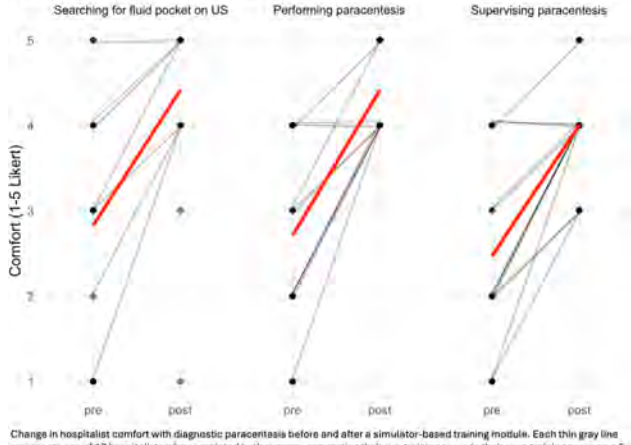
Disclosures: Dinesh Mani Tripathi:Nothing to Disclose, Vaibhav Tiwari:Nothing to Disclose, Rajni Yadav:Nothing to Disclose, Manisha .:Nothing to Disclose, Bitan Guchhait:Nothing to Disclose, Himanshi .:Nothing to Disclose, Aishwarya Bhatnagar:Nothing to Disclose, Savneet kaur:Nothing to Disclose, anupam kumar:Nothing to Disclose, Shiv Kumar Sarin:Nothing to Disclose.

1533 | JUST-IN-TIME, SIMULATION-BASED PARACENTESIS TRAINING FOR HOSPITAL MEDICINE TEAMS: A PILOT STUDY

Bryan Kim[1] Jeemin Kwon[2] Jonathan Helali[3] Sean McCarthy[3] Marco Castelo[3] Christopher Moriates[3] Alexander Monto[1] Satya Patel[3] Arpan Patel[1], [1]Division of Gastroenterology, Hepatology, and Nutrition, VA Greater Los Angeles Healthcare System, [2]David Geffen School of Medicine at UCLA, [3]VA Greater Los Angeles Healthcare System

Background: Despite guideline recommendations for timely bedside paracentesis in hospitalized patients with ascites, hospital medicine teams are performing fewer procedures, underscoring the need for scalable approaches to procedural training. To address this gap, we developed and pilot tested a just-in-time, simulation-based paracentesis training curriculum at a Veterans Affairs (VA) medical center. **Methods:** The curriculum was designed using principles of adult learning theory and human-centered design to align procedural education with hospitalist workflow, learner needs, and bedside practice. Training included hands-on ultrasound-guided procedural simulation and real-time feedback from experienced procedural instructors. Hospitalists completed anonymous pre- and post-training surveys assessing comfort with ultrasound-guided paracentesis tasks and supervision, as well as acceptability, feasibility, and simulation fidelity. All items used 5-point Likert scales (1 = strongly disagree; 5 = strongly agree). Pre-post differences were analyzed using Wilcoxon signed-rank tests. **Results:** Nineteen hospitalists completed matched surveys. Comfort improved significantly across all procedural domains, including identifying a safe pocket (median 3 [interquartile range (IQR) 2–4] vs. 5 [4–5], $p < 0.01$), performing paracentesis (3 [2–4] vs. 4 [4–5], $p < 0.01$), and supervising a trainee (2 [2–4] vs. 4 [4–5], $p < 0.01$) (**Figure 1**). Acceptability (n = 19) was uniformly high, with a median rating of 5 [5–5] on six of eight items. All respondents (100%) agreed or strongly agreed that the module met their approval as a learner, that the time required was appropriate, that they would welcome future use, and that it was preferable to other methods of procedural skills education. Simulation fidelity received slightly lower ratings, specifically tactile feel (median 4, IQR 4–5) and overall accuracy of the experience (median 4, IQR 4–5), although at least 95% still rated each above or equal to 4. The majority of respondents who provided optional qualitative comments expressed interest in using this 'just-in-time' model to teach residents. **Conclusion:** A brief, just-in-time, simulation-based paracentesis curriculum was highly acceptable and feasible to hospitalists. Despite lower ratings of simulator fidelity, confidence in all domains improved, suggesting that high tactile realism may not be required. These findings support scalable, workflow-aligned approaches to strengthening bedside procedural competency among hospital medicine teams. Future work includes spreading training to internal medicine residents and examining whether training improves timely bedside paracenteses rates and reduces referral rates to interventional radiology.

Figure 1: Changes in Comfort Levels with Just-in-Time, Simulation-Based Paracentesis Simulation Training



Change in hospitalist comfort with diagnostic paracentesis before and after a simulator-based training module. Each thin gray line represents one of 17 hospitalists who completed both surveys, connecting their pre-training score to their post-training score on a 5-point Likert scale (1 = not at all comfortable; 2 = somewhat comfortable, 3 = neutral, 4 = somewhat comfortable, 5 = very comfortable). The red line indicates the group mean at each timepoint. Comfort improved significantly on all three domains: identifying a safe fluid pocket on ultrasound (median 3 → 5, Wilcoxon signed-rank $p < .001$), performing a diagnostic paracentesis (median 3 → 4, $p < .001$), and supervising a trainee performing the procedure (median 2 → 4, $p < .001$).

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Disclosures: Bryan Kim:Nothing to Disclose, Jeemin Kwon:Nothing to Disclose, Jonathan Helali:Nothing to Disclose, Sean McCarthy:Nothing to Disclose, Marco Castelo:Nothing to Disclose, Christopher Moriates: Nothing to Disclose, Alexander Monto:Nothing to Disclose, Satya Patel:Nothing to Disclose, Arpan Patel:Nothing to Disclose, Nothing to Disclose.

1534 | REAL-WORLD TERLIPRESSIN TREATMENT PATTERNS AND OUTCOMES IN HEPATORENAL SYNDROME-ACUTE KIDNEY INJURY (HRS-AKI): PRELIMINARY DATA FROM NINE US HOSPITALS

Stevan Gonzalez[1] Aanchal Kapoor[2] A. Sidney Barritt[3] Todd Frederick[4] Brian Wentworth[5] Justin Belcher[6] Mary Thomson[7] Sajid Jalil[8] Elsa Solà[8] Xingyue Huang[9] Sneha Kelkar[10] Rishi Verma[10] Kyle Roney[10] Mary Panaccio[9] Christopher White[9], [1]Baylor Scott and White All Saints Medical Center Fort Worth, [2]Cleveland Clinic, Cleveland, OH, [3]University of North Carolina, Chapel Hill, NC, [4]California Pacific Medical Center, San Francisco, CA, [5]University of Virginia Medical Center, Charlottesville, VA, [6]Yale School of Medicine, New Haven, CT, [7]University of Minnesota, Minneapolis, MN, [8]Stanford University, Palo Alto, CA, [9]Keenova Pharmaceuticals, Bridgewater, NJ, [10]OPEN Health, New York, NY

Background: Despite being the only FDA approved pharmacological therapy indicated to improve kidney function in adults with hepatorenal syndrome-acute kidney injury (HRS-AKI) and recommended by multiple clinical guidelines, terlipressin use in real-world US settings remains limited. This study evaluates characteristics, treatment patterns, and clinical outcomes of HRS-AKI treated with terlipressin in real-world US clinical settings. **Methods:** A multi-center, retrospective chart review study was conducted among adults hospitalized between 2023-2026 with cirrhosis and HRS-AKI. Terlipressin was administered as part of clinical care in a real-world setting according to current FDA labelling guidance (ACLF < 3, SCr < 5). Response to terlipressin was evaluated based on SCr at end of treatment or day-14 relative to baseline defined as complete response (CR; SCr < 0.3 mg/dL above baseline value), partial response (PR; SCr ≥ 0.3 mg/dL above baseline value and regression of AKI stage) or no response (no regression of AKI stage). Verified HRS reversal was evaluated among patients with ≥ 3 days terlipressin use and was defined as two consecutive SCr values ≤ 1.5 mg/dL measured on separate days and alive without renal replacement therapy (RRT) at day 10. **Results:** Nine hospitals provided data for 98 patients (average age 57.5 years (standard deviation ± 11.6); 78% White; 61% male). Terlipressin was first-line vasoconstrictor (mono- or combination therapy) in 34% of patients. Other first-line therapies included midodrine and/or octreotide (60%) and norepinephrine (5%). Average duration of terlipressin use was 6.5 days, with administration in the general ward (55%), intensive care unit (24%), step-down unit (17%), or a combination (3%). Average SCr at initiation was 2.9 (0.9). CR to terlipressin was observed in 38% of patients, PR in 28%, and no response in 34%. Verified HRS reversal was achieved in 31% of patients. Complete response and HRS reversal rates were higher among patients with lower SCr at terlipressin initiation (Table 1). Terlipressin-related adverse events were reported in 30% (29/98) of patients, most commonly respiratory failure (6/98, 6%). After terlipressin initiation, 22% of patients required RRT and 18% underwent liver transplant. In-hospital mortality was 17%, with 81% alive 30 days after discharge. Among 81 patients alive at discharge, most were discharged home to self-care (50%) or home health care (5%), 10% to hospice, 8% to rehabilitation facility, and 9% to other facilities. **Conclusion:** Two-thirds of HRS-AKI patients experienced CR or PR to terlipressin and almost one-third achieved verified HRS reversal, providing real-world validation to the findings from the pivotal Phase III CONFIRM trial. Patients initiating terlipressin treatment with lower SCr had higher rates of CR and verified HRS reversal, suggesting benefit to earlier initiation in clinical practice.

Table 1. Response and verified HRS reversal by SCr at terlipressin initiation

Variable	Statistic or Category	Overall patients	SCr <2 mg/dL at terlipressin initiation	SCr 2 to <3 mg/dL at terlipressin initiation	SCr: 3 to <5 mg/dL at terlipressin initiation
		(N = 98)	(N = 17)	(N = 41)	(N = 40)
HRS-AKI response*, N (%)	Complete Response	34 (37.8)	7 (46.7)	16 (41.0)	11 (30.6)
	Partial Response	25 (27.8)	4 (26.7)	12 (30.8)	9 (25.0)
	No Response	31 (34.4)	4 (26.7)	11 (28.2)	16 (44.4)
		(N = 80)	(N = 15)	(N = 34)	(N = 31)
Verified HRS Reversal, N (%)	Yes	25 (31.3)	8 (53.3)	13 (38.2)	4 (12.9)
	No	55 (68.8)	7 (46.7)	21 (61.8)	27 (87.1)

*Percents may not add up to 100% due to rounding

SCr: serum creatinine; HRS-AKI: hepatorenal syndrome-acute kidney injury

Disclosures: Stevan Gonzalez:Mallinckrodt Pharmaceuticals: Speaking and Teaching, Mallinckrodt Pharmaceuticals: Consultant, Madrigal Pharmaceuticals: Advisor, HEPQuant: Advisor, Aanchal Kapoor:Nothing to Disclose, A. Sidney Barritt:Nothing to Disclose, Todd Frederick:Madrigal: Consultant, Mallinckrodt: Consultant, Salix: Grant/Research Support, Astra Zeneca: Grant/Research Support, River2Renal: Grant/Research Support, Ipsen: Consultant, HepQuant: Consultant, Miromatrix: Consultant, HepQuant: Consultant, Brian Wentworth:Ipsen: Consultant, Ipsen: Speaking and Teaching, GSK: Consultant, Luna Labs USA: Consultant, Justin Belcher:Mallinckrodt Pharmaceuticals:

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Advisor, Mary Thomson:Nothing to Disclose, Sajid Jalil: Nothing to Disclose, Elsa Solà:Nothing to Disclose, Xingyue Huang:Nothing to Disclose, Sneha Kelkar: Nothing to Disclose, Rishi Verma:Keenova: Consultant, Kyle Roney:Nothing to Disclose, Mary Panaccio:Nothing to Disclose, Christopher White:Keenova Therapeutics: Employee, Intercept Pharmaceuticals: Employee.

1535 | VITRO SCORE PREDICTS ACUTE KIDNEY INJURY, HEPATIC ENCEPHALOPATHY, AND SPONTANEOUS BACTERIAL PERITONITIS IN PATIENTS WITH CIRRHOSIS

Yun-Cheng Hsieh[1] Pei-Chang Lee[1] Kuei-Chuan Lee[1] Pei-Shan Wu[1] Yu-Jen Chen[1] Han-Chieh Lin[1] Ming-Chih Hou[1], [1]Taipei Veterans General Hospital

Background: Von Willebrand factor (vWF), a marker of endothelial dysfunction, reflects portal hypertension in cirrhosis. The vWF-to-thrombocyte ratio (VITRO) score has been reported as a noninvasive biomarker for predicting hepatic decompensation and mortality. However, its direct correlation with hepatic venous pressure gradient (HVPG) and its specific predictive value for distinct decompensating events remain to be fully elucidated. We investigated the clinical significance and prognostic utility of the VITRO score in patients with cirrhosis. **Methods:** Between 2000 and 2020, 183 patients with cirrhosis were prospectively enrolled at Taipei Veterans General Hospital. Among them, 77 patients underwent HVPG measurement. Plasma vWF levels were measured by ELISA, and the VITRO score was calculated by dividing vWF levels (mIU/mL) by platelet counts (10^9 /L). **Results:** Among the 183 patients, 141 were male (77%); 67 (37%) and 28 (15%) had Child-Pugh class B and C cirrhosis, respectively. The VITRO score increased with Child-Pugh class (A: 19.00 ± 13.99; B: 35.12 ± 33.48; C: 39.36 ± 28.82; $p < 0.001$) and correlated with MELD score ($r = 0.449$, $p < 0.001$). Notably, the VITRO score significantly correlated with HVPG ($r = 0.252$, $p = 0.027$), and patients with high-risk esophageal varices had higher VITRO scores (31.53 ± 23.20 vs. 27.02 ± 27.03, $p = 0.042$). During a median follow-up of 25.6 months (IQR, 10.2–35.9), 40 patients died. In multivariable analysis, a higher VITRO score (≥ 20) independently predicted acute kidney injury (HR, 2.14; 95% CI, 1.20–3.82), hepatic encephalopathy (HR, 2.29; 95% CI, 1.09–4.80), and spontaneous bacterial peritonitis (HR, 2.51; 95% CI, 1.03–6.12). However, VITRO score was not associated with variceal bleeding, new ascites formation, or survival. **Conclusion:** The VITRO score reflects portal hypertension and hepatic dysfunction. Furthermore, it independently predicts the occurrence of acute kidney injury, hepatic encephalopathy, and spontaneous bacterial peritonitis, supporting its potential role as a noninvasive risk stratification marker in patients with cirrhosis.

Disclosures: Yun-Cheng Hsieh:Nothing to Disclose, Pei-Chang Lee:Nothing to Disclose, Kuei-Chuan Lee: Nothing to Disclose, Pei-Shan Wu:Nothing to Disclose, Yu-Jen Chen:Nothing to Disclose, Han-Chieh Lin: Nothing to Disclose, Ming-Chih Hou:Nothing to Disclose.

1536 | NATIONAL MORTALITY TRENDS IN CIRRHOSIS WITH CONCURRENT HEART FAILURE AND PORTAL HYPERTENSION IN THE UNITED STATES: A CDC WONDER ANALYSIS, 1999–2024

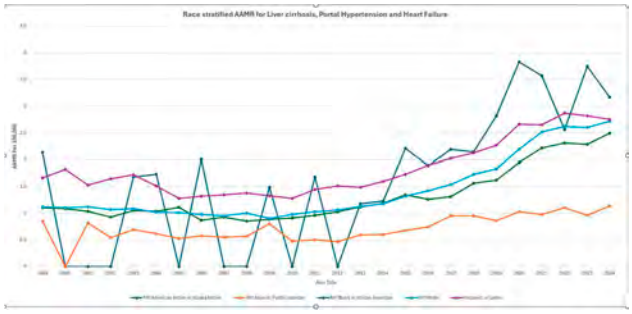
Neha Singh[1] Manish Kc[1], [1]North Alabama Medical Center

Background: Cirrhosis, portal hypertension, and heart failure frequently coexist constituting a complex clinical entity recognised as cirrhotic cardiomyopathy and cardiorenal syndrome. These disorders share the same pathophysiology such as neurohormonal activation leading to major challenges in clinical management. Despite the growing burden of these comorbid conditions, national long term mortality trends remain poorly studied. This study aims to analyse the mortality trends and demographic disparities related to concurrent cirrhosis, portal hypertension, and heart failure in the United States from 1999 to 2024. **Methods:** We performed a national level mortality analysis with the help of CDC WONDER Database from 1999-2024 among patients for Heart Failure (ICD-10 codes: I50), Portal hypertension (ICD code: K76.6 and Fibrosis and cirrhosis of Liver (ICD-10 codes:K74). Data were stratified by Race (American Indian or Alaska Native, Asian or Pacific Islander, Black or African American, White, Hispanic or Latino), sex and age groups (25-85+). We calculated age-adjusted mortality rates per 100,000 population based on the 2000 US standard population. Temporal trends were analyzed using Joinpoint regression to calculate annual percent change (APC), with statistical significance defined by $p < 0.05$. **Results:** Mortality rates for cirrhosis associated with heart failure and concurrent portal hypertension were consistently rising throughout the study period in all demographic populations, with a more significant trend noticed after 2010. Females demonstrated a statistically significant upward trend (2010-2018, APC = 7.43%, $p < 0.05$) from 2010 to 2021, with more rapid increase seen after 2018 (2018-2021, APC = 15.54%, $p < 0.05$). The trend stabilized after 2021 (APC = 2.10%, p =

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0.28) and maintained it until the end of the study period. Males exhibited similar upward trend (2010-2018, APC = 7.58%, p < 0.05) along with rise observed after 2018 (2018-2021, APC = 12.96%, p < 0.05), but they maintained increasing pattern even after 2021 (APC = 3.14%, p < 0.05). While White subgroup displayed a significant rise between 2018 and 2021 (APC = 14.09%, p < 0.05), a statistically significant rise in AAMRs was observed during 2010-2024 (APC = 7.90%, p < 0.05) among Black/African American populations. The longest duration of upward trend in AAMRs from 2009 to 2024 (APC = 6.07%, p < 0.05) was identified among Hispanic/Latino populations. Among American Indian/Alaska Native populations, the highest mortality rates with sustained growth were observed. **Conclusion:** This analysis shows a marked and continuous increase in death rates among patients with cirrhosis, portal hypertension, and heart failure over the past 20 years. Mortality began rising more rapidly between 2010 and 2018 and worsened further during 2018–2021, suggesting that current treatment approaches may not be adequately addressing the combined impact of these serious conditions.



Disclosures: Neha Singh:Nothing to Disclose, MANISH KC:Nothing to Disclose.

1537 | CYSTATIN C VERSUS CREATININE FOR MORTALITY PREDICTION IN PATIENTS WITH CIRRHOSIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

Eliabe Abreu[1] Bernardo Moraes[2] Gabriel Prusch Fernandes[3] Diego Sousa[1] Luisa Visentini[4] Yigit Yazarkan[1] Yohanna Idsabella Rossi[5] Ana Francesca Leite[6] Sriharsha Koduru[7] Manal Abdelmalek[1] Patrick Kamath[1] Guilherme Cancado[8], [1]Mayo Clinic Rochester, [2]Universidade Federal de Minas Gerais, Belo Horizonte, Brazil, [3]Montefiore Medical Center, New York, USA, [4]Universidade do Oeste Paulista, Presidente Prudente, Brazil., [5]Universidade Federal de Ciências da Saúde de Porto Alegre, Porto Alegre, Brazil, [6]Universidade do Estado de Minas Gerais, Passos, Brazil, [7]Jawaharlal Institute of Postgraduate Medical Education and Research, Pondicherry, India, [8]Universidade Federal de Minas Gerais; Hospital da Polícia Militar de Minas Gerais, Brazil.

Background: Accurate short-term mortality prediction is central to risk stratification and transplant prioritization in patients with cirrhosis. MELD models are creatinine-based and remain the cornerstone of prognostication. Cystatin C (CysC) has emerged as an alternative marker to creatinine for renal function assessment. We conducted a systematic review and meta-analysis to compare the prognostic performance of CysC and creatinine for mortality prediction in patients with cirrhosis. **Methods:** PubMed, EMBASE, and Web of Science were systematically searched for studies comparing CysC with creatinine for mortality prediction in adults with cirrhosis. Studies enrolling patients with ACLF or evaluating post-LT or post-TIPS outcomes were excluded. Random-effects meta-analyses were performed using the ratio of hazard ratios (RHRs), ratio of adjusted hazard ratios (RaHRs), and pooled areas under the receiver operating characteristic curve (AUCs), when available. Prespecified subgroup analyses were performed to evaluate the prognostic performance according to the baseline acute kidney injury status and clinical setting. **Results:** Ten studies, including 2,149 patients, met the inclusion criteria. Overall, 66.0% (n = 1,419) were male, but no data were available on sarcopenia. The leading etiologies of cirrhosis were viral hepatitis (n = 656, 30.5%) and alcohol-related disease (n = 641, 29.8%). In the overall analysis, CysC was not significantly superior to creatinine for mortality prediction (RHR 1.19, 95% CI 0.99–1.42; $I^2 = 59.5\%$; 1,530 patients). However, subgroup analyses suggested improved prognostic performance of CysC among patients without acute kidney injury at baseline (RHR 1.17, 95% CI 1.05–1.30; $I^2 = 0\%$; 1,092 patients) and in non-hospitalized cohorts (RHR 1.18, 95% CI 1.04–1.33; 877 patients). No statistically significant difference was found when stratifying according to compensation status (p = 0.716). For 90-day mortality prediction, the pooled AUCs were 0.805 for CysC and 0.713 for creatinine (p = 0.5). **Conclusion:** In this meta-analysis, CysC outperformed creatinine in predicting mortality in patients with cirrhosis without AKI at baseline and in an outpatient setting. Although CysC may be superior to creatinine in predicting outcomes in some patients with cirrhosis, the implementation of CysC-based models is constrained by limited availability and higher costs. Prospective studies with better patient stratification according to age, gender, muscle mass, hospital setting, compensation status, and measured GFR are needed to understand whether the prognostic power of CysC outweighs its restricted availability and increased expense compared to creatinine.

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Table 1. Summary of results comparing cystatin C with creatinine for mortality prediction in patients with cirrhosis

	Mortality - Ratio of Hazard Ratio				
Cystatin C vs. Creatinine	Number of Studies	Number of Patients	RHR (95% CI)	p-value	Heterogeneity (I2)
Main Analysis (r=0.5)	6	1530	1.19 [0.99; 1.42]	0.061	59.50%
Subgroup: Setting					
Outpatient	3	877	1.18 [1.04; 1.33]	0.7049	0%
Inpatient	2	438	0.78 [0.21; 2.88]		89.30%
Inpatient + Outpatient	1	215	0.97 [0.50; 1.87]		-
Subgroup: Status					
Compensated	1	112	1.08 [0.15; 7.95]	0.7157	-
Decompensated	3	959	0.95 [0.48; 1.87]		82.40%
Compensated + Decompensated	2	459	1.27 [1.02; 1.58]		0%
Subgroup: AKI					
Without AKI	4	1092	1.17 [1.05; 1.30]	0.9044	0%
Not described	1	110	0.38 [0.16; 0.87]		-
With and without AKI	1	328	1.43 [1.18; 1.73]		-
Sensitivity analysis (r=0.25)	6	1530	1.20 [1.01; 1.42]	0.035	51.80%
Sensitivity analysis (r=0.75)	6	1530	1.15 [0.93; 1.43]	0.203	69.90%

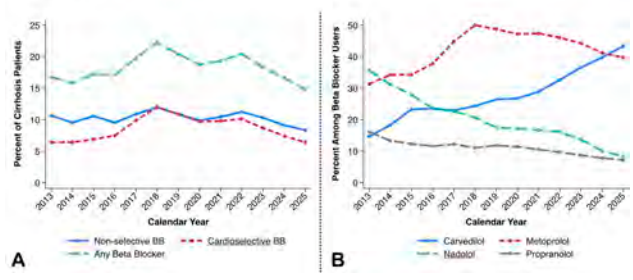
Disclosures: Eliabe Abreu:Nothing to Disclose, Bernardo Moraes:Nothing to Disclose, Gabriel Prusch Fernandes:Nothing to Disclose, Diego Sousa:Nothing to Disclose, Luisa Visentini:Nothing to Disclose, Yigit Yazarkan:Nothing to Disclose, Yohanna Idsabella Rossi:Nothing to Disclose, Ana Francesca Leite:Nothing to Disclose, Sriharsha Koduru:Nothing to Disclose, Manal Abdelmalek:89Bio, Akero, Madrigal, Inventiva, Novo Nordisk, , Intercept, Merck,: Advisor, Hanmi, Novo Nordisk: Consultant, Madrigal, Gilead, Inventiva, 89Bio, Akero, Hanmi: Grant/Research Support, Medscape; Clinical Care Options; Fishawack Inc, LLC; CLDF: Speaking and Teaching, Up-to-Date: Royalties or patent beneficiary, Prometheus: Advisor, Novo Nordisk: Consultant, Boehringer-Ingelheim: Grant/Research Support, Patrick Kamath:Sequana: Advisor, NovoNordisk: Advisor, GSK: Advisor, Guilherme Cancado:Nothing to Disclose.

1538 | BETA-BLOCKER PRESCRIBING TRENDS IN CIRRHOSIS FROM 2013–2025: INCREASING CARVEDILOL USE AND RESIDUAL METOPROLOL EXPOSURE IN PATIENTS WITH POTENTIAL CSPH

Ashley Zhang[1] Farinaz Ghodrati[1] Marina Serper[1] David Kaplan[1] Nadim Mahmud[1], [1]Hospital of the University of Pennsylvania

Background: In patients with compensated cirrhosis, clinically significant portal hypertension (CSPH) is a key driver of decompensation. Recent years have seen a paradigm shift towards earlier use of non-selective beta-blockers (NSBBs), namely carvedilol, to reduce portal pressure and prevent first decompensation. However, real-world beta-blocker prescribing patterns in cirrhosis remain poorly characterized, including the extent to which patients with potential CSPH continue to receive cardioselective rather than portal hypertension-directed beta-blockers. We aimed to evaluate temporal trends in beta-blocker prescribing among patients with cirrhosis and characterize noninvasive evidence of CSPH among metoprolol-treated patients without NSBB exposure. **Methods:** This was a retrospective cohort study using a single-institution patient registry (CDOTS). Adult patients with cirrhosis from 2013 to 2025 were identified. Demographic data included age, sex, and race. Beta-blockers were classified into NSBBs and cardioselective. Linear regression was used to evaluate temporal trends in overall beta-blocker prescribing amongst cirrhosis patients, which was further stratified by specific beta-blocker. Among patients receiving metoprolol without evidence of portal hypertension-directed NSBB therapy, we also evaluated transient elastography and platelet data (within 180 days) to assess noninvasive evidence of CSPH, classified according to Baveno VII-aligned criteria. **Results:** A total of 18,226 patients with cirrhosis from 2013 to 2025 were included; with a median age of 59 years, 62.1% were male, and 64.1% self-identified as White. Over time, the use of beta-blockers, regardless of selectivity, has remained stable (beta 0.01, 95% CI -0.35 to 0.37, $p = 0.94$; **Figure panel A**). When focusing on specific agents, the use of carvedilol has increased significantly over time (beta 2.05, 95% CI 1.68 to 2.42, $P < 0.001$), while nadolol and propranolol have declined (e.g., -2.00 for nadolol, 95% CI -2.31 to -1.70, $p < 0.001$; **Figure panel B**). The use of metoprolol remained stable ($p > 0.05$) though was overtaken by carvedilol as the most commonly prescribed beta blocker in 2025. Among 3,330 cirrhosis patients treated with metoprolol without prior NSBB therapy, only 277 (8.3%) had paired elastography and platelet measurements. Among these, 39 (14.1%) met at least one noninvasive criterion for CSPH, including 32 with liver stiffness ≥ 25 kPa consistent with ruled-in CSPH. **Conclusion:** Carvedilol use increased significantly over time and became the most commonly prescribed beta blocker by 2025 in cirrhosis patients. Among metoprolol-treated patients without portal hypertension-directed NSBB therapy, noninvasive portal hypertension assessment was infrequently performed, yet 14.1% of phenotyped patients met CSPH criteria, suggesting a potentially underrecognized population who may benefit from evaluation for NSBB therapy.

Figure - Temporal Trends in Beta Blocker Prescribing Among Patients with Cirrhosis: (A) Population-Level Beta Blocker Exposure and (B) Composition of Beta Blocker Use Among Treated Patients



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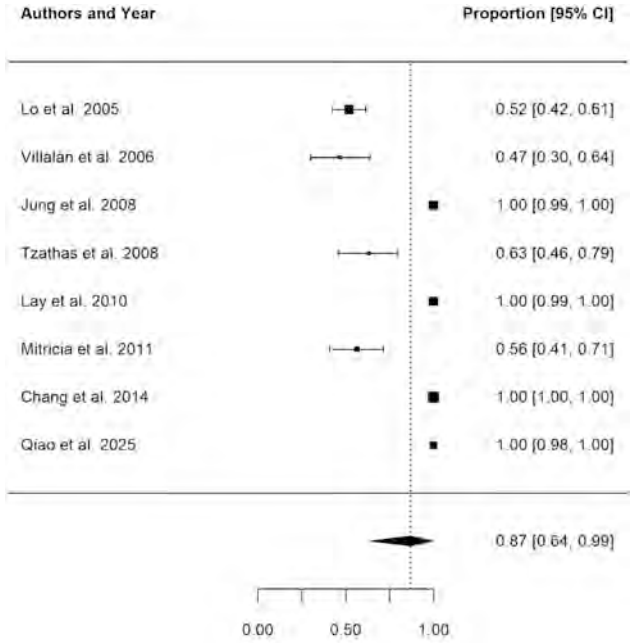
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1539 | HELICOBACTER PYLORI INFECTION AND PEPTIC ULCER RECURRENCE IN CIRRHOTIC PATIENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

Yusuf Kagzi[1] Harjot Bath[2] Sonu Dhillon[3], [1]University of Illinois College of Medicine Peoria, [2]Fellow, [3]Program Director

Background: Peptic ulcer disease (PUD) is associated with higher mortality in cirrhotic patients in comparison to the general population. Helicobacter pylori (H. pylori) is one of the leading causes of PUD globally. The goal of eradication therapy is to promote healing and reduce recurrence in the general population however its efficiency in cirrhotic patients remains unclear. This meta-analysis evaluates recurrence, eradication outcomes, and ulcer healing in PUD secondary to H. pylori infection in cirrhotic patients. **Methods:** A systematic search of electronic databases was performed from inception through May 2026 to identify studies evaluating recurrent PUD and H. pylori in patients with cirrhosis. The primary outcome was ulcer recurrence following H. pylori therapy. The secondary outcomes were H. pylori prevalence, eradication rate, ulcer healing, and other clinical characteristics. Studies lacking extractable data or including non-cirrhotic populations were excluded. Pooled proportions were calculated using a random-effects model. Arcsine square root transformation was applied to stabilize variances prior to pooling. Statistical heterogeneity was assessed using Cochran's Q test and the I^2 statistic. All analyses were performed using the metafor package (version 4.8-0) in R version 4.5.1. **Results:** Eight studies including 719 patients with cirrhosis-associated PUD were included, 74% were male. Alcoholic cirrhosis accounted for 30.46% (95% CI 26.34-33.53), while 69.54% (95% CI 67.47-74.53) had non-alcoholic cirrhosis. The pooled study population included 51.66% (95% CI 51.61-51.71) Child-Pugh A patients and 48.34% (95% CI 48.29-48.39) Child-Pugh B/C. The pooled prevalence of esophageal varices was 60.36% (95% CI 60.30-60.41). The mean treatment duration across studies was 3.25 ± 1.03 weeks.The pooled prevalence of cirrhotic patients with H. Pylori induced PUD was 87.10% (95% CI 64.30-99.10) (Figure 1). Following treatment, the pooled H. pylori eradication rate was 80.11% (95% CI 63.44-93.78). Endoscopic ulcer healing following H. pylori eradication was observed in 86.28% (95% CI 73.95-95.02).Following H. pylori eradication, the pooled ulcer recurrence rate was 87.21% (95% CI 58.30-100.00), with H. pylori positivity observed in 84.40% (95% CI 80.60-88.20) of recurrent ulcers. In the recurrent ulcer subgroup, 40.43% (95% CI 40.37-40.49) were Child–Pugh A and 59.57% (95% CI 59.51-59.63) were Child–Pugh B/C. The prevalence of portal hypertensive gastropathy was 60.22% (95% CI 60.13-60.32). **Conclusion:** Cirrhotic patients demonstrated significant H. pylori prevalence with favorable eradication and healing outcomes; however, ulcer recurrence remained common. Further studies are necessary to identify the risk factors involved in recurrence in cirrhotic patients.



H. pylori prevalence among cirrhotic patients with PUD

Disclosures: Yusuf Kagzi:Nothing to Disclose, Harjot Bath:Nothing to Disclose, Sonu Dhillon:Nothing to Disclose.

1540 | SSI-2D-SHEAR-WAVE-ELASTOGRAPHY–DERIVED MODELS FOR PREDICTING HEPATIC DECOMPENSATION

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Hintersteininger[2] Emilia Korn[2] Mathias Jachs[2] Lukas Hartl[2] Benedikt Simbrunner[1] Georg Semmler[2] Michael Trauner[2] Albert Stättermayer[2] Mattias Mandorfer[1] Thomas Reiberger[1] David Bauer[2], [1]Medical University of Vienna, [2]Division of Gastroenterology and Hepatology, Department of Medicine III,Medical University of Vienna

Background: Prediction of hepatic decompensation in compensated advanced chronic liver disease (cACLD) remains challenging. We assessed whether liver and spleen stiffness measurements obtained using Supersonic Imagine 2D-shear wave elastography (SSI-LSM and SSI-SSM), alone or incorporated into composite scores, improve risk stratification for hepatic decompensation. **Methods:** We performed a prospective study including patients with cACLD, who underwent hepatic venous pressure gradient (HVPG) assessment with same-day SSI-LSM and SSI-SSM. Patients with unreliable SSI-LSM, defined as an IQR/median >30% (n = 55), were excluded. The associations between SSI-LSM, SSI-SSM, and combined elastography-based prediction models with hepatic decompensation were evaluated using Fine–Gray competing-risk regression, considering liver transplantation and death as competing events. Predictive discrimination was quantified using time-dependent C-statistics adapted for competing risks at 1 year (Y1), and clinical utility was explored by decision-curve analysis (DCA). SSI-LSPS (LSM-Spleen size-to-platelet ratio), SSI-ANTICIPATE (LSM, PLT) and SSI-LPS (LSM-platelet-SSM) were calculated according to their original publications. **Results:** The cohort comprised 142 patients. Median age was 56 years, 76% were male, median HVPG was 11 mmHg, 57.7% had CSPH, and the Y1 cumulative incidence of hepatic decompensation was 9.2%. Median SSI-LSM was 24.6 kPa (IQR 13.3–50.0), while median SSI-SSM was 50.4 kPa (IQR 30.9–66.0). 52% of patients had SSI-LSM values >21 kPa and 65% had SSI-SSM values >40 kPa.In Fine–Gray competing-risk models, higher SSI-LSM was associated with an increased risk of Y1 hepatic decompensation, with an sHR of 1.02 per 1-kPa increase (95% CI 1.01–1.03). Similarly, per IQR increase, SSI-LSPS, SSI-LPS, and SSI-ANTICIPATE were all associated with subsequent decompensation, with sHRs of 2.53 (95% CI 1.69–3.79), 3.14 (95% CI 1.79–5.52), and 3.15 (95% CI 1.78–5.58), respectively; all p values were <0.001. At Y1, time-dependent AUROCs were 0.73 for SSI-LSM, 0.67 for SSI-SSM, and 0.83 for HVPG. Compared with SSI-LSM alone, discrimination improved significantly with SSI-LPS and SSI-ANTICIPATE, both achieving an AUROC of 0.77, with p values of 0.031 and 0.016, respectively. SSI-LSPS showed the highest numerical AUROC among the elastography-based composite models at 0.81, although this did not reach statistical significance compared with SSI-LSM alone (p = 0.053). In DCA, SSI-LSPS provided the most consistent net benefit across clinically relevant thresholds, whereas SSI-ANTICIPATE showed the greatest utility at intermediate risk thresholds. **Conclusion:** SSI-2D-SWE–derived models may improve prediction of hepatic decompensation in patients with cACLD compared with SSI-LSM alone. These findings support the use of SSI-models for risk stratification, while the added value of SSI-SSM needs further investigation.

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1541 | WEEKEND AND HOLIDAY ADMISSIONS ARE ASSOCIATED WITH DELAYED DIAGNOSTIC PARACENTESIS AND HIGHER IN-HOSPITAL MORTALITY AMONG PATIENTS WITH CIRRHOSIS AND ASCITES

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Background: Timely diagnostic paracentesis is critical for hospitalized patients with cirrhosis and ascites to rule out spontaneous bacterial peritonitis. While early paracentesis is associated with reduced mortality, prior literature specifically examining the weekend effect on diagnostic paracentesis is limited primarily to administrative database analyses lacking granular clinical detail. We examined whether weekend or holiday admission was associated with delays in diagnostic paracentesis and adverse in-hospital outcomes among patients with cirrhosis and ascites. **Methods:** We conducted a retrospective cohort study of adults with cirrhosis and ascites hospitalized at a tertiary care safety-net hospital between 2023 and 2024 who underwent diagnostic paracentesis performed by interventional radiology. Weekend or holiday admission was defined as admission occurring on Friday after 2:00 PM, Saturday, Sunday, or a United States national holiday. Primary outcomes were time from first physician contact to diagnostic paracentesis and in-hospital mortality. Secondary outcomes included length of stay, acute kidney injury, and 30-day readmission. Associations with in-hospital mortality were evaluated using multivariable regression adjusting for age and MELD-Na. **Results:** Among 141 patients, 44 (31%) were admitted on a weekend or holiday and 97 (69%) on a weekday. Median time to diagnostic paracentesis was significantly longer among weekend or holiday admissions than among weekday admissions (61.5 vs 27.0 hours; p = 0.018). In-hospital mortality was higher among weekend or holiday admissions (29.5% vs 12.4%; p = 0.013). After adjustment for age and MELD-Na, weekend or holiday admission remained independently associated with higher in-hospital mortality (adjusted OR 3.91, 95% CI 1.46–10.49, p = 0.007). Length of stay, acute kidney injury, and 30-day readmission did not differ significantly between groups. **Conclusion:** Weekend or holiday admission is associated with delayed diagnostic paracentesis and higher in-hospital mortality among patients with cirrhosis and ascites, independent of liver disease severity. These findings highlight a systems-level gap in access to time-sensitive diagnostic procedures on weekends and holidays and identify an important target for quality improvement interventions.

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1542 | COMPARISON OF CIRRHOSIS DECOMPENSATION OUTCOMES BETWEEN TYPE 1 AND TYPE 2 DIABETES IN A PROPENSITY-MATCHED COHORT

Darya Herscovici[1] Ami Patel[1] Emilee Herringshaw[1] Chimsom Agbim[1] Deepika Devuni[1], [1]University of Massachusetts Chan Medical School

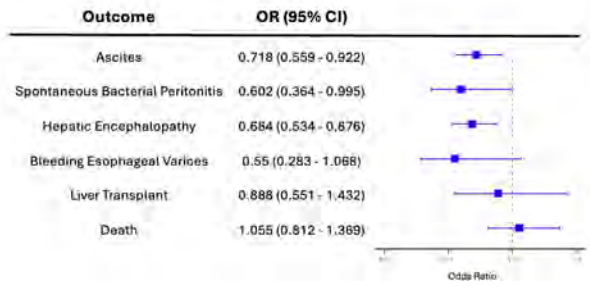
Background: Diabetes is a known risk factor for cirrhosis and has been associated with increased risk for hepatic encephalopathy (HE) in prior studies. Although Type 2 diabetes mellitus (T2DM) has been shown to be an independent risk factor for poor prognosis in patients with cirrhosis, it remains unclear whether outcomes differ between Type 1 diabetes mellitus (T1DM) and T2DM given their distinct disease pathophysiology. This study aimed to assess whether decompensation outcomes of cirrhosis differ between patients with T1DM and T2DM. **Methods:** Data was collected using a TriNetX query of the United States Collaborative Network – an electronic network of 66 healthcare organizations. Adults with a history of either T1DM or T2DM prior to cirrhosis diagnosis between 1/1/2015-1/1/2025 were identified by ICD-10 codes, excluding those with hepatocellular carcinoma and cholangiocarcinoma. Propensity score matching (PSM) was used to balance cohorts 1:1 by age, sex, race, ethnicity, cardiometabolic risk factors, complications of diabetes, A1c, BMI, insulin use, and GLP-1 use. Outcomes included ascites, spontaneous bacterial peritonitis (SBP), HE, bleeding esophageal varices (BEV), liver transplantation (LT), and death up to 10 years post diagnosis. Data were analyzed using univariate and multi-variate analyses and reported using odds ratio (OR) with 95% confidence intervals.

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Results: Before PSM, patients with T2DM and cirrhosis (n = 124,412) were more likely to be older (57.9 vs 49.5, p < 0.01), be of Hispanic or Latino ethnicity (12.9% vs 7.9%, p < 0.01), male (56.3% vs 48.9%, p < 0.01) and more likely to have comorbid hypertension (54.0% vs 34.4%, p < 0.01), hyperlipidemia (29.3% vs 14.9%, p < 0.01), coronary artery disease (16.3% vs 7.9%, < 0.01), and heart failure (16.7% vs 10.0%, p < 0.01) compared to patients with T1DM and cirrhosis (n = 610). After PSM, cirrhosis and T1DM (n = 605) was associated with a lower risk of ascites (OR 0.72, 95% CI 0.56-0.92), SBP (OR 0.60, 95% CI 0.36-0.99), HE (OR 0.68, 95% CI 0.53-0.88) and a trend toward lower incidence of BEV (OR 0.55, 95% CI 0.28-1.07) as compared to T2DM. There were no significant differences in LT (5.6% vs 6.3%, p = 0.63) and death (25.3% vs 24.3%, p = 0.69) between cohorts. **Conclusion:** Among patients with cirrhosis and diabetes, T1DM was significantly associated with decreased risk of ascites, SBP, and HE compared to T2DM. In contrast, need for LT and mortality were similar between cohorts. These findings suggest that insulin resistance, suggestive of a pro-inflammatory state, may exacerbate metabolic and inflammatory pathways involved in cirrhosis decompensation for patients with T2DM. Further studies are needed to better characterize the mechanistic differences between T1DM and T2DM in cirrhosis.

Figure 1: Forest plot of odds ratios for cirrhosis decompensation outcomes in patients with T1DM vs T2DM after propensity score matching



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1543 | BEYOND DIURESIS: SGLT2 INHIBITORS AS A NOVEL STRATEGY FOR HYPONATREMIA AND HEPATIC COMPLICATIONS IN CIRRHOSIS

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Background: Hyponatremia affects nearly half of cirrhotic patients with ascites and independently predicts major complications including hepatic encephalopathy, hepatorenal syndrome, and spontaneous bacterial peritonitis. Current treatments are inadequate: fluid restriction fails most patients, tolvaptan is limited by hepatotoxicity and restricted to short-term use. SGLT2 inhibitors promote electrolyte-free water clearance through osmotic diuresis We hypothesized that SGLT2i, added to standard diuretic therapy, would enhance sodium correction in cirrhotic patients with hyponatremia and ascites. **Methods:** Using the TriNetX US Collaborative Network (66 healthcare organizations), we conducted a 1:1 propensity score–matched retrospective cohort study of adults with cirrhosis, ascites, and hyponatremia (serum sodium $\leq$130 mEq/L). Patients receiving SGLT2 inhibitors plus standard diuretics were compared to those on standard diuretics alone. Those with malignant ascites, liver or kidney transplant history, type 1 diabetes, or end-stage renal disease were excluded. The primary outcome was sodium correction to $\geq$135 mEq/L within 180 days. Secondary outcomes included hepatic encephalopathy, hepatorenal syndrome, and spontaneous bacterial peritonitis. Safety outcomes included AKI, UTI, and diabetic ketoacidosis. **Results:** After propensity score matching, 800 patients were retained per cohort with well-balanced baseline characteristics. The primary outcome of sodium correction to $\geq$135 mEq/L was achieved in 67.3% of SGLT2i patients versus 63.8% of diuretic-only patients, a difference that did not reach statistical significance (RR 1.055, 95% CI 0.982–1.133; p = 0.141). However, SGLT2i use was associated with a significantly lower likelihood of persistent hyponatremia at 180 days (68.4% vs. 73.1%; HR 0.792; p < 0.001) and a reduced incidence of hepatic encephalopathy (13.0% vs. 16.8%; HR 0.691; p = 0.004). Safety outcomes also favored the SGLT2i group, with lower rates of AKI (36.0% vs. 38.4%; HR 0.843; p = 0.037) and urinary tract infection (8.8% vs. 11.0%; HR 0.706; p = 0.029), while rates of spontaneous bacterial peritonitis, hepatorenal syndrome, and diabetic ketoacidosis did not differ significantly between groups. **Conclusion:** In this propensity score–matched real-world study of cirrhotic patients with ascites and hyponatremia, SGLT2i added to standard diuretic therapy did not significantly improve sodium correction to $\geq$135 mEq/L compared to diuretics alone. However, SGLT2i use was associated with a significantly lower risk of HE and reduced likelihood of persistent hyponatremia, without a significant increase in AKI, UTI, or DKA. These exploratory findings suggest a potential hepatoprotective benefit of SGLT2i in this population and support the need for prospective trials to evaluate their role in managing hyponatremia and cirrhosis-related complications.

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Disclosures: Shreya Sanghvi:Nothing to Disclose, FNU Deepali:Nothing to Disclose, Ghideon Ezaz: Nothing to Disclose.

1544 | PROFILE OF ACUTE KIDNEY INJURY IN DECOMPENSATED CHRONIC LIVER DISEASE AND CORRELATION OF VARIOUS GRADES OF AKI WITH OUTCOME: A PROSPECTIVE OBSERVATIONAL STUDY

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Background: Acute kidney injury (AKI) is a serious and frequent complication occuring in up to 20–50% of hospitalized cirrhotics and contributing to in-hospital morbidity and mortality. Traditional diagnostic thresholds based on absolute serum creatinine values underestimate renal impairment in cirrhotic patients due to reduced muscle mass, altered creatinine metabolism, and volume distribution. The revised International Club of Ascites (ICA) AKI criteria — based on dynamic changes in creatinine ($\geq$0.3 mg/dL within 48 hours or $\geq$50% increase within 7 days) — offer a more sensitive and clinically actionable classification. Hence, we aimed **to study the clinical, biochemical, and microbiological profile of AKI in hospitalized cirrhotic patients using ICA-AKI criteria, and to evaluate the correlation of AKI severity grade with in-hospital outcomes, including metabolic complications, requirement for renal replacement therapy, and mortality. Methods:** This was a prospective observational study conducted over 13 months. All cirrhotic patients admitted during the study period, those who developed AKI as defined by ICA-AKI criteria, were enrolled. Patients with pre-existing chronic kidney disease, renal calculi, or prior renal/liver transplantation were excluded. AKI was staged into Grades 1, 2, and 3 as per ICA criteria. Clinical features, etiology, comorbidities, liver severity scores (Child-Turcotte-Pugh [CTP], MELD, MELD-Na), biochemical parameters, microbiological culture results, and in-hospital outcomes (acidosis, hyperkalaemia, haemodialysis, discharge, death) were systematically recorded. **Results:** Of 314 admitted cirrhotic patients, 93 (29.6%) developed AKI. The median age was 48 years (IQR: 42.0–64.5); 87.1% were male. Of these 93; 36 patients (38.7%) had grade I; 30 (32.3%) had grade II; 27 (29.0%) had grade III AKI. The dominant etiology was alcohol (62.4%), followed by MASLD (15.1%), Hepatitis B (11.8%), Hepatitis C (5.4%), and autoimmune hepatitis (5.4%). The majority (73.1%) were CTP class C. Serum creatinine, SGOT, GGT, and albumin differed significantly across AKI grades ($p < 0.05$), with higher grades showing greater enzyme elevation and lower albumin. Ascites was significantly more prevalent in higher AKI grades ($p = 0.028$). Urine culture was positive in 50.5%; blood culture in 18.3%, ascitic fluid culture in 6.5%, sputum in 2.2%, and bile in 1.1% of patients. Overall in-hospital mortality was 8.3% in Grade 1 to 59.3% in Grade 3 ($p < 0.001$). **Conclusion:** AKI affects nearly one-third of patients hospitalized with cirrhosis and is multifactorial in origin. Infections, particularly urinary are the most common precipitating factor.The ICA-AKI staging system correlates robustly with liver disease severity. Higher AKI grades are independently associated with greater rates of metabolic acidosis, hyperkalaemia, requirement for renal replacement therapy, and markedly increased in-hospital mortality.

Key parameters by AKI grade:

Parameter	Grade 1 (n=38)	Grade 2 (n=30)	Grade 3 (n=27)
MELD Score (mean)	21.69	25.26	31.29
MELD-Na Score (mean)	24.1	27.8	32.4
Metabolic Acidosis	5.6%	26.7%	59.3%
Hyperkalaemia	8.3%	26.7%	40.7%
Haemodialysis Required	2.8%	20.0%	40.7%
In-Hospital Mortality	8.3%	33.3%	59.3%
Discharged (Survivors)	91.7%	66.7%	40.7%

All inter-grade differences for MELD/MELD-Na, acidosis, hyperkalaemia, haemodialysis, and mortality were statistically significant ($p<0.05$ to $p<0.001$).

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1545 | GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS AND OUTCOMES IN PATIENTS WITH CIRRHOSIS AND PORTAL HYPERTENSION: A SYSTEMATIC REVIEW AND META-ANALYSIS

Rayan Alataa[1] Mohamed Farag[1] Abeer Qasim[1] Harish Patel[1], [1]Bronxcare Hospital

Background: Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have demonstrated profound metabolic and histologic benefits in metabolic dysfunction-associated steatohepatitis (MASH). However, their efficacy and safety in patients with established cirrhosis and portal hypertension remain incompletely characterized. Recent updates to practice guidelines highlight the urgent need to synthesize data on liver-specific outcomes in this high-risk population. This systematic review and meta-analysis evaluates the impact of GLP-1 RAs on hepatic decompensation, portal hypertension

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events, hepatocellular carcinoma (HCC), and liver-related mortality in patients with cirrhosis. **Methods:** A comprehensive literature search of PubMed/MEDLINE, EMBASE, Cochrane Library, and Web of Science was conducted from inception to May 2026. We included cohort studies, target trial emulations, and randomized controlled trials comparing GLP-1 RA users to non-users or users of other glucose-lowering medications in patients with compensated or decompensated cirrhosis. The primary outcome was the incidence of hepatic decompensation. Secondary outcomes included portal hypertension events (ascites, variceal bleeding, hepatic encephalopathy), incident HCC, and liver-related mortality. Pooled hazard ratios (HR) with 95% confidence intervals (CI) were calculated using a DerSimonian-Laird random-effects model. Heterogeneity was assessed via the I^2 statistic. **Results:** Eighteen studies comprising approximately 2.4 million patients were included. GLP-1 RA use was associated with a significant 42% reduction in the risk of hepatic decompensation compared to control therapies (pooled HR 0.58, 95% CI 0.47–0.72, $P < 0.001$; $I^2 = 52\%$). Furthermore, GLP-1 RAs significantly reduced the incidence of specific portal hypertension events, including ascites and variceal bleeding (HR 0.55, 95% CI 0.41–0.74, $P < 0.001$). The risk of incident HCC was also significantly lower in the GLP-1 RA cohort (HR 0.61, 95% CI 0.48–0.77, $P < 0.001$). Crucially, GLP-1 RA therapy was associated with a 36% reduction in liver-related mortality (HR 0.64, 95% CI 0.51–0.80, $P < 0.001$). **Conclusion:** In patients with cirrhosis, GLP-1 RA therapy is associated with substantial reductions in hepatic decompensation, portal hypertension events, HCC, and liver-related mortality. These findings support the expanding role of GLP-1 RAs beyond metabolic control, positioning them as a potentially disease-modifying therapy for advanced chronic liver disease. Prospective trials specifically powered for portal hypertension outcomes are warranted to confirm these observational findings.

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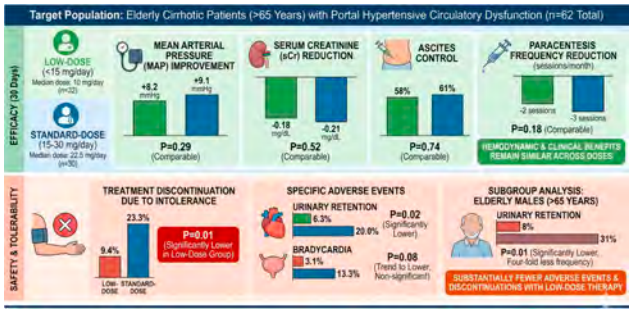
1546 | LOW-DOSE MIDODRINE ACHIEVES COMPARABLE HEMODYNAMIC BENEFIT WITH FEWER ADVERSE EVENTS COMPARED WITH STANDARD-DOSE THERAPY IN ELDERLY CIRRHOTIC PATIENTS

Vinod Arora[1] Shiv Kumar Sarin[2] Rajan Vijayaraghavan[1] Imran Khan[2], [1]Institute of Liver and Biliary Sciences, [2]ILBS

Background: Midodrine is commonly used in cirrhosis patients with hypotension and concurrent use of non-selective beta-blockers (NSBB) and in management of refractory ascites;. Administration of higher doses in advanced cirrhosis is frequently limited by supine hypertension, reflex bradycardia, and urinary retention, particularly in elderly patients. Whether lower-dose midodrine can maintain clinical efficacy with improved tolerability has is not known. We evaluated the efficacy and safety of low-dose (< 15 mg/day) versus standard-dose (15–30 mg/day) midodrine in elderly cirrhotic males. **Methods:** In this retrospective cohort analysis conducted at ILBS, New Delhi between December 2024-March 2026 we evaluated 62 cirrhotic patients age > 65 years receiving midodrine for refractory ascites were analysed; low-dose group (median dose 10 mg/day, n = 32) and standard-dose group (median dose 22.5 mg/day, n = 30). Primary endpoint was improvement in mean arterial pressure (MAP) at 30 days. Secondary endpoints included change in serum creatinine, ascites control, reduction in paracentesis requirement, incidence of adverse events (urinary retention, bradycardia, supine hypertension), treatment discontinuation, and subgroup safety analysis in elderly males aged > 65 years. **Results:** Baseline characteristics were comparable between the low-dose and standard-dose groups, including mean age was comparable (69.2 ± 3.4 vs 68.8 ± 3.7 years; p = 0.65); MELD score (18 ± 4.2 vs 19 ± 4.5; p = 0.48); MAP (62 ± 5.5 vs 63 ± 6.1 mmHg; p = 0.61), and serum creatinine (1.3 ± 0.4 vs 1.4 ± 0.5 mg/dL; p = 0.44). Most frequent etiologies of cirrhosis were MASLD (13 [41%] vs 12 [40%]) and alcohol (10 [31%] vs 9 [30%]), which were comparable (p = 0.85). Primary indications for midodrine included refractory ascites (n = 43, 69%) and HRS-AKI (n = 19, 31%). Concomitant use of non-selective beta-blockers was present in 31% (n = 10) of the low-dose cohort and 30% (n = 9) of the standard-dose cohort (p = 0.92).At end of the 30 days, improvement in MAP was similar between low-dose and standard-dose groups (+8.2 vs +9.1 mmHg; p = 0.29), as was improvement in serum creatinine (-0.18 vs -0.21 mg/dL; p = 0.52). Ascites control rates were comparable between low-dose and standard-dose groups (58% vs 61%; p = 0.74), with similar reduction in median paracentesis requirement (-2 [IQR -4 to 0] vs -3 [IQR -5 to -1] sessions/month; p = 0.18).Adverse events were significantly lower with low-dose therapy, including urinary retention (4/62 [6.5%] vs 13/62 [21.0%]; p = 0.02), supine hypertension (2/62 [3.2%] vs 8/62 [12.9%]; p = 0.04), and treatment discontinuation due to intolerance (5/62 [8.1%] vs 15/62 [24.2%]; p = 0.01). **Conclusion:** Low-dose midodrine achieved comparable hemodynamic and renal benefit with substantially fewer adverse events compared with standard-dose therapy, particularly in elderly cirrhotic males.

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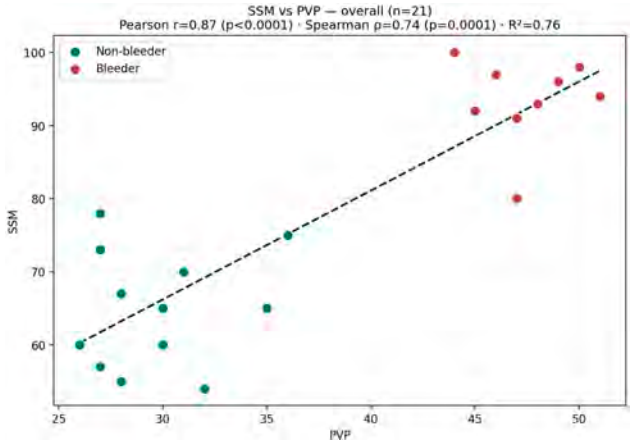


Disclosures: Vinod Arora:Nothing to Disclose, Shiv Kumar Sarin:Nothing to Disclose, Rajan Vijayaraghavan:Nothing to Disclose, Imran Khan:Nothing to Disclose.

1547 | ENDOSCOPIC ULTRASOUND-GUIDED PORTAL PRESSURE GRADIENT MEASUREMENT (EUS-PPG) IN PATIENTS WITH NON-CIRRHOTIC PORTAL FIBROSIS (NCPF): SAFETY, FEASIBILITY, AND CORRELATION WITH HISTOLOGICAL SUBTYPE — THE EU-PORTAL STUDY

Harsh Tevethia[1] Sanda Kavitha[2] Vinod Arora[2] Chhagan Bihari[2] Guresh Kumar[2] Shiv Kumar Sarin[2], [1]Institute of Liver and Biliary Sciences(ILBS),New Delhi, [2]ILBS

Background: Portal Venous Pressure (PVP) truly reflects the pre-and peri-sinusoidal resistance to flow of blood in patients with Non-cirrhotic portal fibrosis (NCPF). Hepatic venous pressure gradient (HVPG) is classically lower in NCPF patients and does not reflect the true PVP. Splenic stiffness measurement (SSM) remains the only indirect method to assess PVP. EUS -guided PVP is reliable and using the hepatic vein pressure measurement gives PVP gradient (EUS-PPG). Although data in cirrhotic patients has been encouraging, whether EUS-PPG is safe in NCPF patients who have disproportionately large spleen and collaterals, and whether it correlates with histological subtypes that define this condition has not been studied. We designed this study to evaluate the safety, technical feasibility, and clinical utility of EUS-PPG in patients with NCPF. **Methods:** Twenty-one consecutive patients with NCPF underwent EUS-PPG measurement between January 2025 and March 2026. Each patient had baseline clinical, biochemical data recorded alongside HVPG measurement, liver biopsy with histopathological subtyping, and a detailed assessment of technical success and procedural safety. PPG was measured with a 25G EUS FNA needle, transducer and patient monitor with pressure module. The intrahepatic left portal vein as well as left/middle hepatic vein was punctured and a total of 3 readings were taken. The objectives included correlation with HVPG, variceal bleed,Portal vein pressure(PVP) with SSM, safety, and histological subtypes in NCPF. **Results:** The study population had predominant males (71.4%), mean age 32.01 ± 4.2 years, mean HVPG 7.02 ± 2.2 mmHg, liver stiffness measurement (LSM) 10.06 ± 1.78kPa and Splenic stiffness measurement (SSM) 77.71 ± 14.2kPa. Mean portal vein diameter was 13.70 ± 2.06, EUS guided direct PVP was 37.33 ± 9.28 mmHg and PPG was 16.02 ± 2.70 mmHg. Clinically significant portal hypertension (HVPG > 10 mmHg) did not corelate with PPG (r = 0.083). Patients with a history of variceal bleeding (n = 9, 42.9%) had significantly higher PVP (42.89 vs 34.92 mmHg, p < 0.001) and PPG (18.49 vs 14.18 mmHg, p < 0.001) compared to non-bleeders. PVP corelated with SSM (r = 0.87). SSM values were significantly higher in bleeders as compared to the non bleeders(93.4 ± 5.8 vs 64.9 ± 8.0 kpa p = 0.00) clearly reflecting higher PVP as a predictor. On liver biopsy, incomplete septal cirrhosis was associated with the higher PPG values than obliterative porto-venopathy and nodular regenerative hyperplasia subtypes (18.51 vs 13.87 mmHg, p < 0.001), suggesting that EUS-PPG can detect haemodynamic differences across histological subtypes.Technical success was 100% with no major post-procedure complication. **Conclusion:** EUS-PPG is safe and helpful in segregating NCPF patients with high risk of bleeding. While HVPG has little clinical relevance , PVP corelates strongly with SSM, portal hypertensive complications and histopathological subtype



Disclosures: Harsh Tevethia:Nothing to Disclose, Sanda Kavitha:Nothing to Disclose, Vinod Arora:Nothing to Disclose, Chhagan Bihari:Nothing to Disclose, GURESH KUMAR:Nothing to Disclose, Shiv Kumar Sarin:Nothing to Disclose.

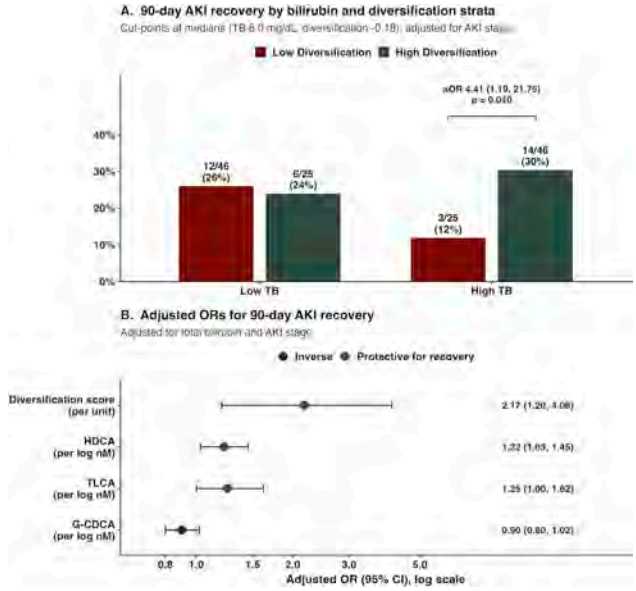
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1548 | A DIVERSE BILE ACID POOL PREDICTS 90-DAY KIDNEY RECOVERY IN HOSPITALIZED PATIENTS WITH DECOMPENSATED CIRRHOSIS AND ACUTE KIDNEY INJURY

Giuseppe Cullaro Brendan Blackburn[1] Elizabeth Verna[2], [1]Columbia University, [2]Columbia University Medical Center

Background: Acute kidney injury (AKI) is common in hospitalized patients with cirrhosis and recovery is heterogeneous. AKI and its recovery in cirrhosis are the cumulative result of multiple insults, of which the circulating bile acid (BA) pool is one. We profiled the BA pool by both its size and its composition and tested the association of each with 90-day AKI recovery. **Methods:** We performed targeted LC-MS quantification of 23 BAs (e.g., conjugated, unconjugated, sulfated) in paired protein-bound and protein-depleted serum fractions from the first specimen per hospitalization in a two center prospective cohort of patients with decompensated cirrhosis. AKI stage was assigned by KDIGO using outpatient baseline creatinine (bCr) and serum creatinine (sCr) at time of specimen collection. The primary outcome was 90-day AKI recovery (AKI-R), defined as a reduction sCr to within 150% of bCr. A *diversification score* was the mean of z-scored proportions of secondary BAs, UDCA-pathway species, and sulfated metabolites in the combined bound + unbound pool. Logistic regression for recovery was adjusted for total bilirubin (TB) and AKI stage at specimen collection. A 2×2 model partitioned the AKI cohort at the medians of TB and diversification, with the worst-prognosis cell (high-TB / low-div) as the reference. **Results:** Among 142 patients with 152 unique hospitalizations, 7 had no AKI, 66 had Stage 1, and 79 had ≥ Stage 2 AKI. Median age was 55; 43% female, 22% MASH, 41% ALD. albumin was 3.3 g/dL, INR 2.1, bCr 0.9 mg/dL, sCr at draw 1.7.Median total Bilirubin (TB) was 6.0 mg/dL. The total serum BA pool (bound + unbound) correlated with TB ($\rho = 0.37$, $p < 0.001$). Median pool size was 140,100 / 167,000 / 136,100 nM and median diversification was −0.32 / −0.24 / −0.14 in no AKI / Stage 1 / ≥ Stage 2.After adjusting for TB and AKI stage, diversification was associated with AKI recovery (adjusted OR 2.17 per unit, 95% CI 1.20–4.08). Driving species included the microbial-derived secondary BAs HDCA (aOR 1.22, $p = 0.04$) and TLCA (aOR 1.25, $p = 0.05$); non-diverse G-CDCA (primary) trended inversely (aOR 0.90, $p = 0.09$). In the 2×2 model (TB cut-point 6.0 mg/dL, diversification cut-point −0.18, adjusted for AKI stage), high-TB / low-diversification carried the lowest recovery (12%); relative to this reference, recovery rose to 26% in low-TB / low-div (aOR 3.23, 0.87–15.76), 24% in low-TB / high-div (aOR 2.64, 0.60–14.15), and 30% in high-TB / high-div (aOR 4.41, 1.19–21.75; $p = 0.040$) — high diversification rescued recovery even among bilirubin-high patients. **Conclusion:** A diverse circulating BA pool predicts 90-day kidney recovery in hospitalized patients with decompensated cirrhosis and AKI, independent of TB level and AKI severity — even among the most cholestatic patients. These data support the serum BA pool not only as a targetable entity to promote AKI recovery, but also as a measurable index of disease severity in hospitalized decompensated cirrhosis.



Disclosures: Giuseppe Cullaro:Ocelot Bio: Consultant, Retro Sciences: Consultant, Ipsen: Consultant, Brendan Blackburn:Nothing to Disclose, Elizabeth Verna: Nothing to Disclose.

1549 | ASSESSMENT OF DISCORDANCE OF GLYCEMIC INDICATORS IN CIRRHOSIS

Norah Liang[1] Celeste Thomas[1] Mary Rinella[1] Raghavendra Mirmira[1] Alan Hutchison[1], [1]The University of Chicago

Background: Background: and Aims: Cirrhosis contributes to disruptions in glucose metabolism. As a result, traditional approaches to diagnosing and managing diabetes are often discordant and not reflective of dysglycemia. This complicates screening and surveillance of diabetes, leading to under diagnosis and missed treatment opportunities. We aimed to identify factors predictive of diabetes biomarker concordance in individuals with cirrhosis. **Methods: Methods::** We identified subjects in the National Health And Nutrition Examination Survey (NHANES) database cohort from

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2017-2020 with liver elastography measurements. Additionally, we enrolled individuals with cirrhosis without diabetes under evaluation for liver transplantation. We continuously collected subject laboratory evaluations across both inpatient hospitalizations and outpatient encounters. We developed multivariable equations using fasting plasma glucose (FPG), hemoglobin A1c (HbA1c), serum albumin, creatinine, total bilirubin, hemoglobin, sodium, and in the prospective data only, mean cellular volume, INR, fructosamine, and 1,5-anhydroglucitol. **Results: Results::** In the NHANES database, multivariable linear regression confirmed fasting plasma glucose significantly predicted hemoglobin A1c (HbA1c) globally (β = 0.025, $p < 0.001$) and in advanced liver tissue stiffness subsets (kPa $\geq$ 15: β = 0.021, $p < 0.001$). However, covariance profiles shifted when stratified by distinct elastography bands (5-10 kPa: R^2 = 0.75 vs. 15-20 kPa: R^2 = 0.45; Figures A, B). In the institutional validation cohort (N = 66 observations), multi-imputation covariance maps were generated across 10 iterations (Figure C). Clinical setting time interval matching demonstrates an environmental decoupling in biomarker tracking (Figure D). Inpatient encounters (n = 10) preserved a positive trending profile between FPG and HbA1c (R^2 = 0.38, p = 0.056), whereas outpatient encounters (n = 56) had a negative correlation (R^2 = 0.13, p = 0.0064). In multivariable Multiple Imputation by Chained Equations regression to account for missing data, fasting plasma glucose lost all independent predictive value for HbA1c (β = 0.002, p = 0.297), while fructosamine emerged as a significant but weak metabolic predictor (β = 0.004, p = 0.005). **Conclusion: Conclusion::** The NHANES data stratifying by liver stiffness kPa showed greater concordance of HbA1c and FPG than the prospective cohort of individuals with cirrhosis without diabetes undergoing liver transplant evaluation. This suggests that Hba1c-FPG discordance may be worse in decompensated cirrhosis that is not captured by liver stiffness measurements. Future work will need to better risk-stratify individuals with cirrhosis who may have discordance between their HbA1c and FPG measurements.

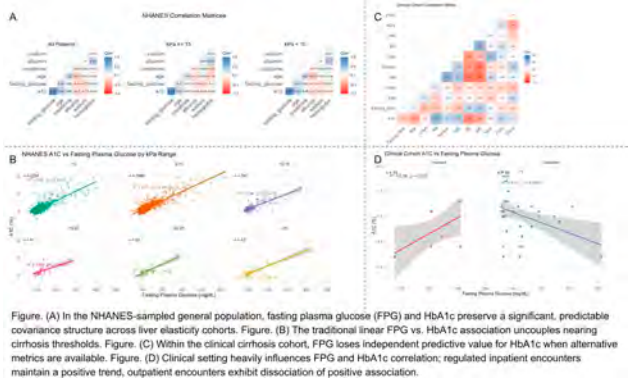


Figure. (A) In the NHANES-sampled general population, fasting plasma glucose (FPG) and HbA1c preserve a significant, predictable covariance structure across liver elasticity cohorts. Figure. (B) The traditional linear FPG vs. HbA1c association uncouples nearing cirrhosis thresholds. Figure. (C) Within the clinical cirrhosis cohort, FPG loses independent predictive value for HbA1c when alternative metrics are available. Figure. (D) Clinical setting heavily influences FPG and HbA1c correlation; regulated inpatient encounters maintain a positive trend, outpatient encounters exhibit dissociation of positive association.

Disclosures: Norah Liang:Nothing to Disclose, Celeste Thomas:Nothing to Disclose, Mary Rinella:akero: Consultant, akero: Consultant, 89Bio: Consultant, 89Bio: Consultant, Boehringer Ingelheim: Consultant, Boehringer Ingelheim: Consultant, Cytodyn: Consultant, Cytodyn: Consultant, Echosens: Consultant, Echosens: Consultant, Histoindex: Consultant, Histoindex: Consultant, Intercept: Consultant, Intercept: Consultant, Madrigal: Consultant, Madrigal: Consultant, GSK: Consultant, GSK: Consultant, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Eli Lilly: Consultant, Eli Lilly: Consultant, Takeda: Consultant, Takeda: Consultant, Sagimet: Consultant, Sagimet: Consultant, Sonic Incytes: Consultant, Sonic Incytes: Consultant, NGM Bio: Consultant, NGM Bio: Consultant, Regeneron: Consultant, Boston Pharma: Consultant, Eccogene: Consultant, Inventiva: Consultant, Sagimet: Consultant, Madrigal: Consultant, akero: Consultant, akero: Consultant, 89Bio: Consultant, 89Bio: Consultant, Boehringer Ingelheim: Consultant, Boehringer Ingelheim: Consultant, Cytodyn: Consultant, Cytodyn: Consultant, Echosens: Consultant, Echosens: Consultant, Histoindex: Consultant, Histoindex: Consultant, Intercept: Consultant, Intercept: Consultant, Madrigal: Consultant, Madrigal: Consultant, GSK: Consultant, GSK: Consultant, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Eli Lilly: Consultant, Eli Lilly: Consultant, Takeda: Consultant, Takeda: Consultant, Sagimet: Consultant, Sagimet: Consultant, Sonic Incytes: Consultant, Sonic Incytes: Consultant, NGM Bio: Consultant, NGM Bio: Consultant, Regeneron: Consultant, Boston Pharma: Consultant, Eccogene: Consultant, Inventiva: Consultant, Sagimet: Consultant, Madrigal: Consultant, Raghavendra Mirmira:Nothing to Disclose, Alan Hutchison:Madrigal Pharmaceuticals: Research support to my institution for a clinical trial.

1550 | EARLY TIPS VS EXTENDED-INTERVAL PREEMPTIVE TIPS FOR ESOPHAGEAL VARICEAL BLEEDING: A MULTI-INSTITUTIONAL PROPENSITY-MATCHED ANALYSIS FROM THE TRINETX RESEARCH NETWORK

Avleen Kaur[1] Savio John[2], [1]Upstate Medical University, [2]Suny Upstate Medical University

Background: Preemptive TIPS (pTIPS) within 72 hours of variceal bleeding improves survival in high-risk cirrhosis, yet fewer than 10% of eligible patients receive pTIPS within this window due to logistical barriers. This multi-institutional study analyzes outcomes and mortality after extending the pTIPS window beyond 72 hours. **Methods:** Retrospective cohort study using TriNetX (44 HCOs). Adults with cirrhosis undergoing TIPS within

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28 days of variceal bleeding were stratified into early (≤72h) and extended-interval (days 4–28) cohorts. 1:1 propensity score matching adjusted for age, MELD variables, dialysis, hepatic encephalopathy, ascites, diabetes, CKD, vasopressors, critical care needs, and pleural effusion. Primary outcome: 1-year all-cause mortality. Secondary outcomes included decompensation events. **Results:** A total of 547 patients were included: 295 in the early TIPS group and 252 in the extended-interval TIPS group, with follow-up of 175.8 and 172.6 person-years, respectively. The mean age was 53.5 years across both cohorts; 77% were White and 69% were male. Beta-blocker utilization was lower among early TIPS recipients (49% vs. 78%). Median MELD-Na scores were similar between groups (16 [11–21] vs. 16 [12–20]). Vasopressor use and critical care utilization were comparable. Prior to matching, the extended-interval TIPS cohort demonstrated higher prevalence of ascites (76.19% vs. 47.46%, p = 0.01), hepatic failure (61.11% vs. 45.76%, p = 0.01), CKD (20.24% vs. 8.81%, p = 0.01), and carvedilol use (28.18% vs. 14.24%, p = 0.01).Following 1:1 propensity score matching, 187 pairs were evaluated with balanced baseline characteristics (SMD < 0.2). One-year mortality trended higher in the early TIPS cohort (30.48% vs. 23.52%; OR 1.43, 95% CI 0.83–2.07; p = 0.13), similarly for 2-year mortality (33.71% vs. 25.71%; OR 1.47, 95% CI 0.93–2.33; p = 0.10); however, neither achieved statistical significance. Hepatic encephalopathy was similar between groups (21.25% vs. 28.09%; OR 0.69, 95% CI 0.34–1.40; p = 0.30). No episodes of recurrent variceal bleeding were recorded in either cohort following matching Table 1. **Conclusion:** In this extended-interval preemptive TIPS analysis, delayed TIPS placement demonstrated comparable one-year mortality relative to early TIPS, aligning with findings reported by Dunne et al. (2023)[1] and Dong et al. (2024)[2]. Study limitations include reliance on administrative coding and the lack of detailed clinical variables such as Child-Pugh score. Prospective studies are needed for confirmation. Dunne et al. Effect of time to pre-emptive transjugular intrahepatic portosystemic shunt on patient outcome, a UK multicentre cohort study. *Aliment Pharmacol Ther.* 2023. Dong et al.The time window for pre-emptive transjugular intrahepatic portosystemic shunt could be extended to 5 days. *Heliyon.* 2024 Feb 15.

Clinical Outcomes After Propensity Matching

Outcome	TIPS in 3 Days	TIPS in 28 Days	Odds Ratio (95% CI)	p-value
One-Year Mortality (n=187 vs 187)	30.48%	23.52%	1.43 (0.83, 2.07)	0.13
2-Year Mortality (n=175 vs 175)	33.71%	25.71%	1.47 (0.93, 2.33)	0.10
Variceal Bleeding (n=186 vs 186)	0%	0%	—	—
Hepatic Encephalopathy (n=83 vs 88)	21.25%	28.09%	0.69 (0.34, 1.40)	0.30

Disclosures: Avleen Kaur:Nothing to Disclose, Savio John:Nothing to Disclose.

1551 | ASSOCIATIONS BETWEEN CT-DERIVED ORGAN AND MUSCLE MORPHOLOGY AND CONTINUOUS GLYCEMIC PATTERNS IN CIRRHOSIS WITHOUT DIABETES

Yousef Husein[1] Alan Hutchison[1] Mary Rinella[1] Raghavendra Mirmira[1] Celeste Thomas[1], [1]The University of Chicago

Background: Cirrhosis is associated with changes in insulin resistance, altered body composition, and an increased risk of hypoglycemia and hyperglycemia. Although glucose dysregulation and body composition changes in cirrhosis have been studied, the relationship between quantitative CT-derived organ and muscle morphology and continuous glycemic patterns in cirrhosis remains poorly understood. **Methods:** Continuous glucose monitoring (CGM; Abbott Libre Pro) and CT scans from forty-six individuals with cirrhosis without diabetes were collected. TotalSegmentator, a deep learning-based tool, was used to segment organs and muscles from CT scans and to compute volume (mm3) and intensity (Hounsfield units) values for each scan. Percentages were calculated to quantify the proportion of time each patient spent in hypoglycemia (< 70 mg/dL), normoglycemia (70–139 mg/dL), mild hyperglycemia (140–179 mg/dL), and hyperglycemia (≥ 180 mg/dL). CT-derived volumes and attenuation measurements, along with CGM-derived glycemic metrics relationships, were analyzed. **Results:** Greater liver volume (normalized by height) was associated with less time in normoglycemia (< 70 mg/dL or > 179 mg/dL; Pearson's r = -0.51, p = 0.02), and more time in time in hypoglycemia (< 70 mg/dL; r = 0.52, p = 0.02) . Greater gluteus maximus volume (normalized by height) was associated with greater time in normoglycemia (> 70 mg/dL and < 180 mg/dL; r = 0.92, p = 0.001). A decrease in pancreatic attenuation (corresponding to higher pancreatic fat content) was associated with more time in mild hyperglycemia (≥ 140 mg/dL, < 180 mg/dL; r = -0.58, p = 0.02) and hyperglycemia (≥ 180; r = -0.49, p = 0.05). **Conclusion:** In individuals with cirrhosis without diabetes, CT-derived liver and gluteus maximus muscle volumes showed an association with glucose levels. In metabolic dysfunction-associated liver disease hepatomegaly is associated with insulin resistance - we show this here in cirrhosis as well. Additionally, pancreatic fat content shows a significant relationship with hyperglycemia, confirming known pathophysiology previously less described in cirrhosis. These results suggest that conducting a CT scan body morphology analysis can help identify those at risk of glycemic dysregulation.

Disclosures: Yousef Husein:Nothing to Disclose, Alan Hutchison:Madrigal Pharmaceuticals: Research support to my institution for a clinical trial, Mary Rinella:akero: Consultant, akero: Consultant, 89Bio: Consultant, 89Bio:

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1552 | COMPARATIVE EFFECTIVENESS OF SPLENIC-PROBE VERSUS STANDARD LIVER-PROBE TRANSIENT ELASTOGRAPHY FOR THE PREDICTION OF CLINICAL DECOMPENSATION IN PATIENTS WITH CIRRHOSIS

Sanda Kavitha[1] Sudhir Verma[2] Ishank Johri[3] Srajit Singh[3] Vinod Arora[3] Rajan Vijayaraghavan[3] Satender Pal Singh[3] Sarthak Chanana[3] Ananthu Naryanan[3] Shiv Kumar Sarin[3], [1]Institute Liver and Biliary Sciences, [2]King George Medical University, [3]Institute of Liver and Biliary Sciences

Background: Non-Invasive assessment of portal hypertension is evolving. Utility of Standard liver-probe (75MHz) liver stiffness measurement (LSM) plateaus in advanced cirrhosis due to an artificial ceiling effect failing to reflect portal hypertension dynamics. As clinical decompensation is primarily driven by rapid rise in portal pressure, there is need for a higher stiffness measurement tool. We evaluated the performance of splenic-probe LSM against standard liver-probe LSM and traditional biomarkers for predicting clinical decompensation **Methods:** We conducted a retrospective cohort analysis of 181 patients with cirrhosis. Primary composite decompensation was defined as the presence of ascites , Hepatic encephalopathy (HE), clinical jaundice (Bilirubin > 2mg/dl), or Upper gastrointestinal bleeding (UGIB). Diagnostic performance was evaluated using Receiver Operating Characteristic (ROC) curve analysis, and Area Under the Curve (AUC) values were compared using DeLong's test. Optimal cutoffs were derived via the Youden Index **Results:** The analysed cohort consisted of 181 patients with a mean age of 53.4 + 8.2 years, with a male predominance (72%), with most common etiology associated with Alcohol-Associated Liver Disease (AALD -54%) and Metabolic Dysfunction-Associated Steatohepatitis (MASH- 36%). When evaluated for its global ability to predict the primary composite endpoint Splenic-Probe LSM demonstrated superior with AUC of 0.89 (95% CI: 0.84-0.93), outperforming total bilirubin (AUC 0.79), standard liver-probe LSM (AUC 0.74), and platelet Count (AUC 0.71).The optimal LSM cutoff was in with splenic probe 81.5 kPa (sensitivity -88.2% , specificity-82.4%), whereas the liver probe exhibited low specificity (58.1%) due to capped values. For isolated secondary endpoints, the splenic probe performed better particularly for development of moderate-severe ascites (0.91vs. 0.72) and UGIB (0.87 vs. 0.70). **Conclusion:** In cirrhosis, a higher frequency splenic-probe elastography was found superior compared to conventional liver probe in assessment of risk of acute decompensation . As the splenic probe elastography provides more accurate data for prediction of portal hypertension driven complications , it is recommended in patients with LSM 70 or above in cirrhosis.

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1553 | RESTRICTED VERSUS STANDARD ALBUMIN DOSING FOR SPONTANEOUS BACTERIAL PERITONITIS: A SYSTEMATIC REVIEW, META-ANALYSIS, TRIAL SEQUENTIAL ANALYSIS, AND BAYESIAN SYNTHESIS

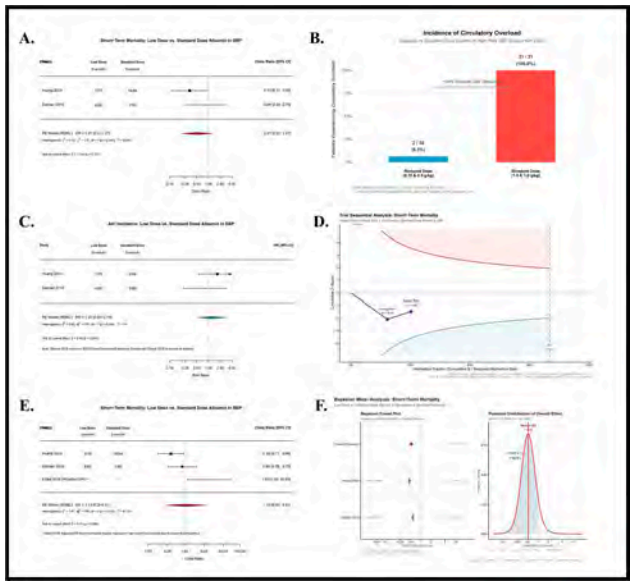
Sri Ram Charan Gundapaneni[1] Sampurna Sengupta[2] Sunanda Chagam Reddy[3] Muhammad Zuhaz Azeem[4] Reshma Agarwal[5] Ashwin Rumalla[1] Sameer Kumar

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Background: Albumin is the standard of care in spontaneous bacterial peritonitis (SBP) to prevent renal dysfunction and reduce mortality, but standard weight-based dosing may increase volume-related complications. Evidence supporting lower or restricted dosing remains limited. **Methods:** PubMed, Ovid, and Embase were searched for studies evaluating restricted or reduced albumin dosing compared with standard albumin dosing in adults with SBP. Pooling was performed when at least two studies reported comparable outcomes. Random-effects meta-analyses were used for acute kidney injury (AKI), short-term mortality, and circulatory overload. Trial sequential analysis (TSA) and Bayesian meta-analysis were performed for mortality. **Results:** Seven studies were included. Four studies contributed to quantitative or sensitivity analyses, while three were retained for narrative synthesis because they were not suitable for pooling. Among the narrative studies, one non-comparative cohort lacked a dose comparator, one mechanistic study primarily reported inflammatory, hemodynamic, and renal Doppler outcomes rather than clinical endpoints, and one large real-world utilization study highlighted gaps in albumin adherence, access, and institutional delivery. Together, they highlight heterogeneity in albumin protocols, outcome definitions, adherence, and access. In pooled prospective cohorts, restricted dosing was not associated with a significant difference in AKI compared with standard dosing (RR 1.22, 95% CI 0.53-2.78; $p = 0.644$; $I^2 = 0\%$), although AKI definitions differed. Short-term mortality favored restricted dosing but did not reach statistical significance (OR 0.51, 95% CI 0.20-1.27; $p = 0.147$; $I^2 = 26.8\%$). TSA estimated a required information size of 840 patients; available prospective-cohort data represented less than 30% of this threshold, with the final cumulative Z score remaining within monitoring boundaries, indicating insufficient evidence for a definitive frequentist conclusion. Bayesian synthesis supported the same direction of effect, with a posterior median OR of 0.53 and a 90.5% posterior probability that restricted dosing reduced short-term mortality. For safety, one standalone study reported markedly lower circulatory overload with reduced dosing compared with standard weight-based albumin (2/32 [6.2%] vs 31/31 [100%]; RR 0.077, 95% CI 0.023-0.254; $p < 0.0001$), suggesting a strong but preliminary safety signal. **Conclusion:** Across seven studies, restricted albumin dosing in SBP showed no clear increase in AKI, a consistent but inconclusive signal toward lower short-term mortality, and lower circulatory overload in standalone safety data. The evidence remains small, heterogeneous, and underpowered. Adequately powered randomized trials are needed to define an albumin strategy that balances renal protection, survival, and volume-related safety.



Disclosures: Sri Ram Charan Gundapaneni:Nothing to Disclose, Sampurna Sengupta:Nothing to Disclose, Sunanda Chagam Reddy:Nothing to Disclose, Muhammad Zuhaz Azeem:Nothing to Disclose, Reshma Agarwal:Nothing to Disclose, Ashwin Rumalla:Nothing to Disclose, Sameer Kumar Majety:Nothing to Disclose.

1554 | DISCORDANCE BETWEEN ICD CODES, LACTULOSE/RIFAXIMIN EXPOSURE, AND NOTE-DERIVED DOCUMENTATION FOR HEPATIC ENCEPHALOPATHY: A MIMIC-IV STUDY

Thanathip Suenghataiphorn[1] Narathorn Kulthamrongsri[2] Pojsakorn Danpanichkul[3], [1]Yale/Griffin Hospital, [2]University of Hawaii, [3]Texas Tech University Health Sciences Center

Background: Hepatic encephalopathy is commonly identified in observational studies using administrative diagnosis codes, but coding may incompletely capture clinically documented disease. Medication-based definitions using lactulose or rifaximin may improve sensitivity but can capture non-HE indications or treatment exposure without explicit diagnostic attribution. We evaluated overlap and discordance among ICD codes, medication exposure, and discharge-summary-derived documentation for hepatic encephalopathy in MIMIC-IV. **Methods:** We performed a retrospective cohort study of adult MIMIC-IV hospitalizations with cirrhosis or

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suspected chronic liver disease and available clinical data. Hepatic encephalopathy was identified using three approaches: ICD diagnosis codes for hepatic encephalopathy or hepatic coma; medication exposure defined by lactulose and/or rifaximin use during hospitalization or at discharge; and note-derived NLP identifying discharge-summary documentation of hepatic encephalopathy, liver-attributed altered mental status, hyperammonemia-related encephalopathy, asterixis, or lactulose/rifaximin use specifically attributed to hepatic encephalopathy. We quantified overlap across definitions and compared ICU admission, mechanical ventilation, hospital length of stay, in-hospital mortality, discharge disposition, and 30-day readmission across discordant groups. **Results:** Among 49,460 eligible hospitalizations, 34,122 (69.0%) met at least one hepatic encephalopathy definition. ICD codes identified 25,929 admissions (52.4%), medication exposure identified 15,415 (31.2%), and note-derived extraction identified 12,083 (24.4%). Only 5,404 admissions, representing 15.8% of HE-positive admissions, were positive by all three methods. Among note-derived HE admissions, 4,869 (40.3%) lacked an HE ICD code. ICD-negative/note-positive admissions included 2,658 medication-positive and 2,211 medication-negative admissions. Patients who were ICD-negative, medication-positive, and note-positive had median MELD-Na proxy 22.8, ICU admission rate 23.8%, mechanical ventilation rate 8.9%, median length of stay 5 days, in-hospital mortality 6.3%, and 30-day readmission 33.5%. **Conclusion:** ICD codes, lactulose/rifaximin exposure, and discharge-summary-derived documentation identified substantially overlapping but discordant hepatic encephalopathy populations. ICD-only definitions may miss clinically documented HE, while medication-only definitions may capture treatment exposure without explicit HE attribution. Multimodal phenotyping may improve cohort construction for hepatic encephalopathy research using electronic health record data.

Disclosures: Thanathip Suenghataiphorn:Nothing to Disclose, Narathorn Kulthamrongsri:Nothing to Disclose, Pojsakorn Danpanichkul:Nothing to Disclose.

1555 | PREVALENCE, RISK FACTORS, AND CLINICAL IMPACT OF LOWER EXTREMITY EDEMA AFTER TIPS: AN ALTA GROUP STUDY

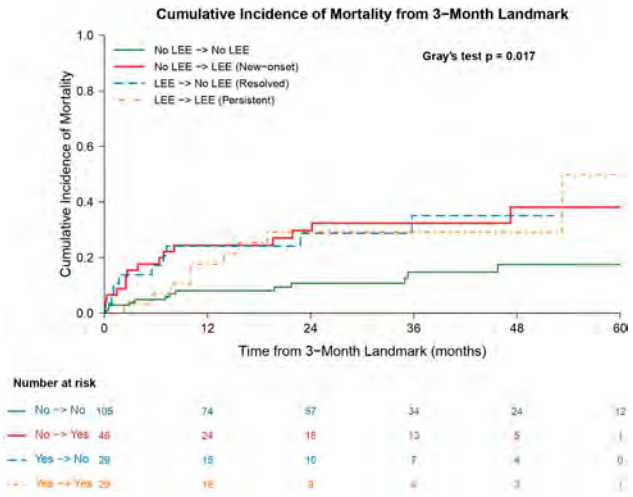
Tsung-Chieh Yang[1] K. Pallav Kolli[1] Justin Boike[2] Mike Fallon[3] Bartley Thornburg[2] Lisa VanWagner[4] Elizabeth Verna[5] Jennifer Lai[1], [1]University of California-San Francisco, San Francisco, California, USA, [2]Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA, [3]University of Arizona College of Medicine-Phoenix, Phoenix, Arizona, USA, [4]University of Texas Southwestern Medical Center, Dallas, Texas, USA, [5]Columbia University Irving Medical Center, New York, New York, USA

Background: Lower extremity edema (LEE) is a common yet underrecognized complication following transjugular intrahepatic portosystemic shunt (TIPS) placement. We aimed to characterize the prevalence, risk factors, and prognostic significance of post-TIPS LEE trajectories, including new-onset, persistent, and resolved LEE. **Methods:** Adults with portal hypertension undergoing TIPS placement between July 2019 and January 2025 were prospectively enrolled at 13 U.S. centers in the Advancing Liver Therapeutic Approaches (ALTA) Study Group. Among 852 patients, 489 with documented baseline LEE status were included after excluding TIPS failure, undeployed TIPS, poor data quality, and 302 patients without baseline physical examination documentation of LEE status. LEE status was recorded as present or absent at baseline and protocolized 1-, 3-, 6-, and 12-month follow-up visits. Patients surviving with evaluable 3-month LEE data constituted the M3 landmark cohort for mortality analyses. Primary outcomes were LEE development and resolution; the secondary outcome was all-cause mortality from M3 by LEE trajectory. Outcomes were analyzed using competing risk regression, with death, liver transplantation (LT), and TIPS occlusion as competing events for LEE outcomes, and LT and TIPS occlusion for mortality. **Results:** Among 489 patients, median age was 58 years, 59.3% were male, median MELD-Na was 15, and 45.2% underwent TIPS for ascites. At baseline, 119 (24.3%) had LEE. By 12 months, new-onset LEE developed in 29.2% without baseline LEE, while LEE resolved in 50.7% with baseline LEE. In multivariable analyses, higher pre-TIPS right atrial pressure (RAP) (OR 1.12, 95% CI 1.02–1.22; p = 0.016), higher MELD-Na score (OR 1.09, 95% CI 1.01–1.19; p = 0.030), and TIPS for ascites (OR 2.39, 95% CI 1.13–5.12; p = 0.024) were independently associated with new-onset LEE, whereas lower MELD-Na score predicted LEE resolution (OR 0.91, 95% CI 0.83–0.99; p = 0.043). Mortality differed across the four LEE trajectory groups (Gray's test, p = 0.017; Figure 1). Compared with patients who never developed LEE, those with new-onset LEE had higher mortality from 12 months (24.3% vs. 8.1%; p = 0.021) through 60 months (38.1% vs. 17.5%; p = 0.042). In multivariable competing risk models, new-onset LEE (sHR 2.23, 95% CI 1.05–4.74; p = 0.036), age, and MELD-Na score were independently associated with mortality. **Conclusion:** New-onset LEE is common and independently associated with increased post-TIPS mortality. Higher pre-TIPS RAP, MELD-Na score, and ascites indication identify patients at greatest risk for LEE development, while lower MELD-Na score predicts LEE resolution. These findings support more rigorous pre-procedural cardiovascular assessment, including echocardiography with strain imaging, and cardiology

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involvement to optimize risk stratification, counseling, and post-TIPS management.



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1556 | SHORT-COURSE TERLIPRESSIN IS AS EFFECTIVE AND SAFE AS STANDARD THERAPY FOR ACUTE VARICEAL BLEEDING: A META-ANALYSIS OF RANDOMIZED TRIAL

Erick Brandon[1] Jasper Polloso[2], [1]St. Luke's Medical Center Quezon City, [2]St. Luke's Medical Center

Background: Terlipressin is a key component of acute variceal bleeding (AVB) management, traditionally continued for 2–5 days after achieving endoscopic hemostasis. However, the optimal duration of therapy remains uncertain. Earlier randomized trials suggested that shorter courses may be sufficient, but previous meta-analyses did not include newer high-quality trials and lacked detailed safety assessment. This updated meta-analysis evaluates the efficacy and safety of short-course (<48 hours) versus standard-course (>72 hours) terlipressin therapy following endoscopic variceal ligation. **Methods:** A systematic search identified randomized controlled trials comparing short- and standard-course terlipressin in adults with cirrhosis and AVB. Five RCTs (n = 569) met inclusion criteria. Pooled risk ratios (RRs) were calculated using a random-effects model. Primary outcomes were 5-day rebleeding and mortality; secondary outcomes included overall and category-specific adverse events. **Results:** Short-course terlipressin demonstrated no significant difference in 5-day rebleeding compared with standard therapy (RR 1.03; 95% CI 0.59–1.80; p = 0.90). Long-term mortality and rebleeding at 30–42 days were also similar between groups. Overall adverse events were significantly lower in the short-course arm (RR 0.71; 95% CI 0.60–0.83; p = 0.01), though subgroup analyses of cardiovascular, gastrointestinal, and infection-related events did not reach significance due to low event counts. **Conclusion:** Short-course terlipressin (?48 hours) is as effective as standard-course therapy (48–120 hours) for preventing rebleeding and mortality in acute variceal bleeding and is associated with a lower overall risk of adverse events. These findings support shorter terlipressin regimens as a safe and potentially more cost-effective approach. Larger, multicenter, double-blind trials are warranted to confirm non-inferiority and clarify safety outcomes.



Disclosures: Erick Brandon:Nothing to Disclose, Jasper Polloso:Nothing to Disclose.

1557 | LONG-TERM RIFAXIMIN USE IS ASSOCIATED WITH INCREASED ANTIMICROBIAL RESISTANCE AND ESBL-PRODUCING ORGANISMS IN DECOMPENSATED CIRRHOSIS PATIENTS WITH FIRST-EPISODE SPONTANEOUS BACTERIAL PERITONITIS

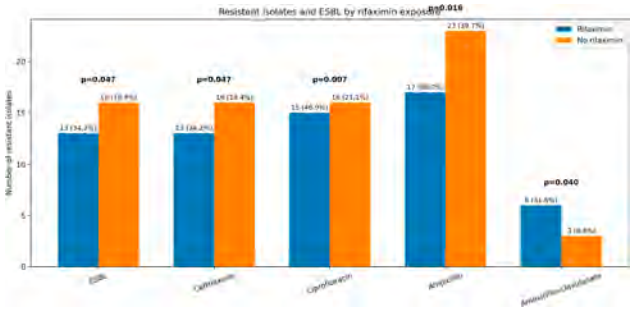
Issac Vargas Olmos[1] Graciela Castro-Narro[2], [1]Instituto Nacional de Ciencias Medicas y Nutricion Salvador,

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Background: Bacterial infections are a leading cause of mortality in patients with cirrhosis, with spontaneous bacterial peritonitis (SBP) representing one of the most severe complications. Rifaximin is widely used for hepatic encephalopathy; however, its potential impact on antimicrobial resistance remains uncertain. We aimed to evaluate the association between long-term rifaximin use and antimicrobial resistance, including extended-spectrum beta-lactamase (ESBL)-producing organisms, in patients with decompensated cirrhosis and a first episode of SBP. **Methods:** We conducted a retrospective study including cirrhotic patients with a first episode of SBP between 2016 and 2022. Inclusion criteria were diagnostic paracentesis within 24 hours of admission and no antibiotic exposure within the previous 90 days. Patients were stratified in two groups according to long-term rifaximin use ($\geq$30 days). Descriptive statistics were summarized using measures of central tendency and proportions. Group comparisons were performed using cross-tabulations with chi-square or Fisher's exact tests, as appropriate. Subgroup analyses were conducted according to cirrhosis etiology. **Results:** A total of 140 patients were included, of whom 39 (27.9%) had long-term rifaximin exposure and 101 (72.1%) did not. Baseline clinical characteristics were comparable between groups. The distribution of causative organisms was similar. Escherichia coli was the most frequent isolate in both groups (51.3% vs 52.5%), followed by Streptococcus spp. (23.1% vs 21.8%), Klebsiella spp. (10.3% vs 7.9%), Enterococcus spp. (2.6% vs 2.0%), other Gram- positive organisms (5.1% vs 4.0%), and other Gram-negative organisms (7.7% vs 11.9%). In contrast, antimicrobial resistance was higher among patients receiving rifaximin. ESBL-producing organisms were more frequent (34.2% vs 18.4%, p = 0.047), as was resistance to ceftriaxone (34.2% vs 18.4%, p = 0.047). Increased resistance was also observed for ciprofloxacin (46.9% vs 21.1%, p = 0.007), ampicillin (68.0% vs 39.7%, p = 0.016), and amoxicillin-clavulanate (31.6% vs 8.6%, p = 0.040). Subgroup analysis by cirrhosis etiology showed that this association was most pronounced in patients with cryptogenic cirrhosis (p = 0.048). **Conclusion:** Long-term rifaximin use is associated with increased antimicrobial resistance and ESBL-producing organisms in patients with decompensated cirrhosis and first-episode SBP, without changes in pathogen distribution. These findings support a more selective use of rifaximin and highlight the importance of balancing its clinical benefits against the potential risk of promoting antimicrobial resistance



Disclosures: Issac Vargas Olmos:Nothing to Disclose, Graciela Castro-Narro:Novonordisk: Speaker honoraria and advisory board, Gilead: Speaker honoraria, Grünanthalñ: Speaker honoraria, Boehringer Ingelheim: Speaker honoraria.

1558 | COMPARATIVE EFFECTIVENESS OF CIPROFLOXACIN VS TRIMETHOPRIM-SULFAMETHOXAZOLE FOR SECONDARY SBP PROPHYLAXIS IN CIRRHOSIS WITH ASCITES: A PROPENSITY-MATCHED NATIONAL COHORT STUDY

Delano Carty[1] Dilcia Maldonado[1] FNU Deepali[1] Cameron Gill[1] Ghideon Ezaz[1], [1]Jefferson Einstein Philadelphia

Background: Secondary prophylaxis for spontaneous bacterial peritonitis (SBP) is standard of care in cirrhosis; however, the optimal antibiotic regimen remains uncertain. Fluoroquinolones are widely used but concerns regarding antimicrobial resistance and adverse outcomes persist and comparative effectiveness data with alternative regimens are limited. **Methods:** We conducted a retrospective cohort study using the TriNetX US Collaborative Network (2010–2026). Adult patients ($\geq$18 years) with cirrhosis, ascites and prior SBP were identified.Patients were stratified by exposure to ciprofloxacin or trimethoprim-sulfamethoxazole, with the index date defined as first prescription. Patients were required to have no prior exposure to the comparator antibiotic before index or any recent antibiotic exposure, secondary peritonitis, ESRD/CKD.Propensity score matching (1:1) using a nearest-neighbor algorithm with a caliper of 0.1 was performed to adjust for demographics, markers of liver disease severity(MELD score), hepatic encephalopathy, varices, comorbidities (diabetes melitus, chronic kidney disease and or ESRD), prior infections, prior antibiotic exposure, medication use (rifaximin, proton pump inhibitors), and healthcare utilization. Covariate balance was confirmed using standardized mean differences $<$0.1. Matched cohorts included 21,532 patients per group.Outcomes over 3 years included all-

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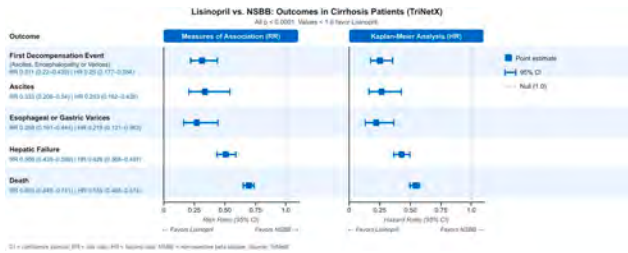
cause mortality, hepatorenal syndrome, acute kidney injury, sepsis, recurrent SBP, multidrug-resistant organism infection (ESBL E. Coli, Klebsiella), and *Clostridioides difficile* infection. Time-to-event analyses were performed using Kaplan-Meier methods and Cox proportional hazards models. **Results:** Over 3 years, ciprofloxacin use was associated with significantly higher **all-cause mortality** compared with TMP-SMX (38.8% vs 29.1%; **HR 1.58, 95% CI 1.53–1.63; p < 0.001**).Ciprofloxacin was also associated with increased risk of: **Hepatorenal syndrome** (6.0% vs 1.9%; RR 3.12) **Acute kidney injury** (33.0% vs 28.1%; RR 1.18) **Sepsis** (15.3% vs 14.5%; RR 1.05) (all $p < 0.05$) Recurrent SBP was infrequent but more common in the ciprofloxacin group (0.1% vs 0.05%; **HR 2.86; p = 0.002**).There were **no significant differences** in multidrug-resistant organism infection or *Clostridioides difficile* infection between groups. **Conclusion:** In this large propensity-matched cohort of patients with cirrhosis, ascites and prior SBP, ciprofloxacin prophylaxis was associated with **higher mortality, increased risk of renal complications, Sepsis, recurrent SBP** compared with TMP-SMX, without evidence of reduced multidrug-resistant infections. These findings suggest that fluoroquinolone-based prophylaxis **may be associated with worse clinical outcomes** and support the need for prospective studies to re-evaluate optimal strategies for secondary SBP prophylaxis.

Disclosures: Delano Carty:Nothing to Disclose, Dilcia Maldonado:Nothing to Disclose, FNU Deepali:Nothing to Disclose, Cameron Gill:Nothing to Disclose, Ghideon Ezaz:Nothing to Disclose.

1560 | LISINOPRIL VERSUS NON-SELECTIVE BETA BLOCKER FOR PREVENTION OF DECOMPENSATION IN COMPENSATED LIVER CIRRHOSIS: A RETROSPECTIVE COHORT STUDY

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Background: Liver cirrhosis is a major healthcare burden, and median survival varies from compensated phase (>12 years) to decompensated phase (~2 years). Conversion to decompensation occurs at 5-7% annually, with roughly 58% within 10 years. Progressive portal hypertension (driven by nitric oxide release, renin-aldosterone angiotensin system-RAAS) is the main factor for decompensation, leading to mainly ascites, varices, and encephalopathy. Only non-selective beta blockers (NSBBs- especially carvedilol) are recommended by AASLD, but no other agent is recommended for prevention. Liver injury stimulates expressions of RAAS components (ACE and angiotensin receptor 1), driving inflammation and fibrogenesis. ACE inhibitors therefore have theoretical benefits in cirrhosis. From the same class, Lisinopril does not require hepatic activation, making it suitable for study in liver cirrhosis. **Methods:** A retrospective cohort study was conducted using the TriNetX database (2001 to 2025). Cohorts were defined as adults (18-90 years) with 'Fibrosis and Cirrhosis of Liver' (ICD-10 K74) who were prescribed lisinopril or NSBBs (Carvedilol, Propranolol, or Nadolol), while excluding any decompensation, hepatocellular carcinoma, and pregnancy before starting any medication. Propensity score matching was applied to balance characteristics. The first decompensation event, individual event, hepatic failure, and all-cause mortality in 10 years were studied as outcomes using relative risk (RR-cumulative) and hazard ratio (HR-time dependent) calculation by an in-built statistical tool. Forest plot images were created with assistance from Claude AI. **Results:** After matching, each cohort included 10,437 patients (mean age ~58 years, SD < 0.1). Patients receiving lisinopril had a lower risk of developing any first decompensation event (RR 0.311, 95% CI 0.220-0.439; HR 0.25, 0.177-0.354) as compared to NSBB in 10 years. It also had a lower risk of ascites and varices. Analysis also showed reduced hepatic failure (RR 0.506, 0.435-0.589; HR 0.426, 0.365-0.497) and all-cause mortality (RR 0.693, 0.649-0.741; HR 0.535, 0.498-0.574) in the lisinopril cohort. P-values were < 0.0001 for all outcomes. **Conclusion:** In this study, lisinopril demonstrated superior efficacy compared to NSBB (standard of care) in preventing hepatic decompensation. It is likely due to its effects on hemodynamics (reduction of portal pressure) as well as liver inflammation and fibrogenesis by blocking RAAS. Hepatic failure was selected as a surrogate for liver-related mortality (no liver-related death in TriNetX). Reduced 10-year all-cause mortality can be confounded due to cardiovascular benefits. Lisinopril or ACE inhibitor as a group is commonly prescribed and are affordable (one third of all antihypertensives). This study demonstrated the potential benefits of lisinopril in cirrhosis, but prospective studies are warranted to confirm these findings.



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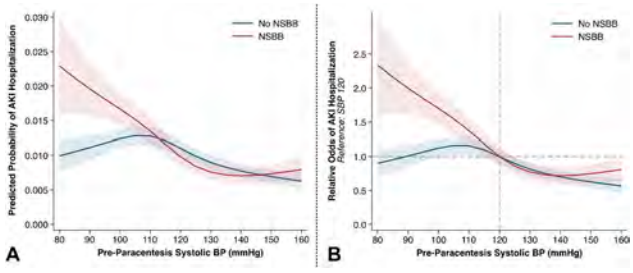
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Disclosures: Balkrishna Sapariya:Nothing to Disclose, Prince Gosai:Nothing to Disclose, Ciandra D'Souza: Nothing to Disclose.

1561 | LOW SYSTOLIC BLOOD PRESSURE IDENTIFIES INCREASED RISK OF AKI HOSPITALIZATION AMONG PATIENTS ON NONSELECTIVE BETA-BLOCKERS UNDERGOING OUTPATIENT PARACENTESIS

Kai Fu[1] Marina Serper[1] Siqi Zhang[1] Nadim Mahmud[1], [1]Hospital of University of Pennsylvania

Background: Nonselective beta-blockers (NSBBs) can reduce portal hypertension and prevent variceal bleeding in patients with cirrhosis. However, their safety in advanced cirrhosis remains debated, as NSBBs may also exacerbate renal hypoperfusion and cause acute kidney injury (AKI), particularly in patients with hypotension, infection, and refractory ascites. We evaluated whether pre-paracentesis systolic blood pressure modifies the association between NSBB use and risk of AKI hospitalization after outpatient paracentesis. We also aimed to identify ranges of systolic blood pressure below which NSBBs may be associated with increased AKI hospitalization. **Methods:** We conducted a national retrospective cohort study of 9,245 Veterans with cirrhosis undergoing 55,525 outpatient paracenteses. The primary exposure was an active NSBB prescription at the time of paracentesis. The primary outcome was hospitalization with AKI within 7 days. Relevant demographic, clinical, laboratory, medication, and procedural variables were obtained. Pre-paracentesis systolic blood pressure was transformed using restricted cubic splines to account for non-linearity. Adjusted mixed-effects logistic regression was used to evaluate the association between NSBB use, systolic blood pressure, and AKI hospitalization, including an interaction between NSBB use and systolic blood pressure, with random effects for patient and center. **Results:** Among 55,525 outpatient paracenteses, 14,231 (25.6%) occurred in patients receiving NSBBs, and 1,003 (1.8%) led to hospitalizations with AKI within 7 days. Compared with non-users, patients on NSBBs had similar MELD-Na scores and systolic blood pressure, but higher rates of diabetes mellitus, coronary artery disease, diuretic use, and hepatic encephalopathy medication use (each $p < 0.001$). Systolic blood pressure significantly modified the association between NSBB use and AKI hospitalization ($p = 0.029$). Albumin administration was associated with lower odds of hospitalization with AKI (OR 0.62, 95% CI 0.50-0.76), whereas lower sodium, higher bilirubin, lower eGFR, diabetes mellitus, and prior antibiotic use were associated with higher odds. Adjusted predicted risk curves demonstrated a higher predicted risk of AKI hospitalization among patients on NSBBs at lower systolic blood pressure levels, particularly below 100 mmHg, with attenuation of this difference at higher levels (Figure 1). **Conclusion:** In this national cohort of Veterans undergoing outpatient paracentesis, lower pre-paracentesis systolic blood pressure modified the association between NSBB use and AKI hospitalization risk. At systolic blood pressure levels below approximately 100 mmHg, patients receiving NSBBs had significantly higher predicted risk of AKI hospitalization, suggesting that pre-paracentesis blood pressure may help identify patients who warrant closer monitoring or individualized NSBB management.



Disclosures: Kai Fu:Nothing to Disclose, Marina Serper:Nothing to Disclose, Siqi Zhang:Nothing to Disclose, Nadim Mahmud:Nothing to Disclose.

1562 | BRTO FACILITATES RECOMPENSATION IN DECOMPENSATED CIRRHOSIS WITH PORTOSYSTEMIC SHUNT SYNDROME

Aika Kirihara[1] Tsuyoshi Ishikawa[1] Natsuko Nishiyama[1] Maho Egusa[1] Ryo Sasaki[1] Tatsuro Nishimura[1] Taro Takami[1], [1]Yamaguchi University Graduate School of Medicine

Background: Portosystemic shunt (PSS) syndrome is increasingly recognized as a contributor to hepatic encephalopathy and liver dysfunction in decompensated cirrhosis. Meanwhile, recompensation and expanded recompensation have emerged as important therapeutic goals in cirrhosis management. However, the impact of PSS occlusion on these outcomes remains unclear. We evaluated recompensation outcomes after balloon-occluded retrograde transvenous obliteration (BRTO) for PSS syndrome. **Methods:** We retrospectively analyzed 32 patients with decompensated cirrhosis who underwent BRTO for PSS syndrome and were followed for ≥ 12 months. Eligible patients had Child-Pugh class B/C cirrhosis and/or prior

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decompensating events, including variceal bleeding, hepatic encephalopathy, or ascites. Recompensation was defined as sustained resolution of decompensating events without ongoing therapy together with improved liver function at 12 months. Expanded recompensation was assessed using modified criteria allowing stable low-dose maintenance therapy reflective of real-world clinical practice. Predictors associated with recompensation outcomes were analyzed. **Results:** The rates of recompensation and expanded recompensation after BRTO were 28.1% and 62.5%, respectively. Lower baseline serum creatinine was significantly associated with recompensation, whereas lower liver stiffness by transient elastography was significantly associated with expanded recompensation. Receiver operating characteristic analysis identified optimal cutoff values of creatinine $\leq$0.63 mg/dL (AUROC 0.81) for recompensation and liver stiffness $\leq$26.3 kPa (AUROC 0.77) for expanded recompensation. Kaplan–Meier analysis demonstrated significant differences in cumulative overall survival among patients who achieved recompensation (n = 9), those who achieved only expanded recompensation (n = 11), and those who achieved neither criterion (n = 12) (log-rank p = 0.0028). **Conclusion:** PSS occlusion with BRTO may facilitate recompensation in patients with decompensated cirrhosis and PSS syndrome. Baseline renal function and liver stiffness may help identify patients most likely to benefit from shunt occlusion. These findings suggest that PSS syndrome may represent a potentially reversible driver of decompensation in cirrhosis.

Disclosures: Aika Kirihara:Nothing to Disclose, Tsuyoshi Ishikawa:Nothing to Disclose, Natsuko Nishiyama:Nothing to Disclose, Maho Egusa:Nothing to Disclose, Ryo Sasaki:Nothing to Disclose, Tatsuro Nishimura:Nothing to Disclose, Taro Takami:Nothing to Disclose.

1563 | MICROBIAL SPECTRUM AND ANTIMICROBIAL RESISTANCE IN SPONTANEOUS BACTERIAL PERITONITIS: A MULTICENTER STUDY FROM FOUR TERTIARY CENTERS IN INDIA

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Background: Spontaneous bacterial peritonitis (SBP) is a life-threatening complication of cirrhosis. The antimicrobial landscape is rapidly evolving, driven by rising rates of multidrug-resistant (MDR), extensively drug-resistant (XDR), and pandrug-resistant (PDR) organisms, alongside a shift in the microbiological profile of causative pathogens, threatening the adequacy of empirical therapy. We aimed to study culture positivity rates, causative organisms, and antimicrobial resistance patterns in patients with cirrhosis and SBP. **Methods:** We conducted a multicenter study across four university hospitals in southern India. Patients with cirrhosis and ascitic culture-positive SBP (ascitic fluid PMN $\geq$ 250/mm³) were enrolled, and antibiotic susceptibility patterns were analyzed. Resistance profiles were classified per standard definitions; MDR: non-susceptible to $\geq$1 agent in $\geq$3 antibiotic categories; XDR: non-susceptible to all but $\leq$2 antibiotic categories; PDR: non-susceptible to all categories tested (Clin Microbiol Infect 2012;18:268–281) **Results:** A total of 118 culture-positive SBP episodes were analyzed (mean age 51 years; bilirubin 7.4 mg/dL; albumin 2.3 g/dL; INR 2.11; creatinine 1.61 mg/dL; sodium 130 mEq/L). Gram-negative organisms predominated (79.7%; n = 94), with *E. coli* (30.5%), *Klebsiella pneumoniae* (24.6%), and *Acinetobacter baumannii* (5.9%) being the most common. Gram-positive organisms accounted for 20.3% (n = 24), including *Staphylococcus haemolyticus*, *Enterococcus faecium*, and *Enterococcus faecalis*. Notably, several rare and previously unreported isolates were identified in SBP such as *Stenotrophomonas maltophilia*, *Serratia marcescens*, *Sphingomonas paucimobilis*, *Providencia rettgeri*, *Roseomonas gilardii*, *Chryseobacterium indologenes*, and *Bordetella bronchiseptica*.Resistance profiles were alarmingly high: MDR organisms accounted for 49.2% (n = 58), XDR for 34.7% (n = 41), and PDR for 3.4% (n = 4) with a combined difficult-to-treat burden of over 50%, seriously undermining the adequacy of empirical antibiotic regimens in SBP. **Conclusion:** SBP microbiology has undergone a paradigm shift. Rising MDR/XDR/PDR rates render cephalosporins and fluoroquinolones increasingly inadequate as empirical therapy, while carbapenem utility is also declining (~39% resistance). The isolation of rare and unprecedented environmental pathogens (*Roseomonas*, *Chryseobacterium*, *Sphingomonas*, *Bordetella bronchiseptica*) likely reflects profound immunosuppression in these patients and antibiotic selection pressure. Center-specific antibiograms, culture-directed therapy, and antimicrobial stewardship are now essential. International society guidelines must acknowledge the heterogeneity of antimicrobial resistance patterns across regions and move toward greater individualization of empiric therapy, incorporating local microbiologic data and stewardship principles.

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Table 1 showing antimicrobial resistance rates.

Antibiotic	Tested (n)	Resistant (n)	% Resistant
Cefuroxime	70	54	77.10%
Cefotaxime	74	52	70.30%
Ceftriaxone	60	41	68.30%
Ciprofloxacin	108	73	67.60%
Ceftazidime	69	44	63.80%
Tetracycline	46	27	58.70%
Doxycycline	43	24	55.80%
Cefoperazone+Sulbactam	62	34	54.80%
Piperacillin-Tazobactam	79	41	51.90%
Cotrimoxazole	89	45	50.60%
Ertapenem	43	17	39.50%
Imipenem	61	24	39.30%
Meropenem	78	29	37.20%
Minocycline	11	4	36.40%
Gentamicin	96	31	32.30%
Netilmicin	61	19	31.10%
Tigecycline	43	10	23.30%
Amikacin	83	18	21.70%
Vancomycin	13	2	15.40%
Colistin	43	1	2.30%
Linezolid	11	0	0.00%

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1564 | EARLY VS DELAYED INITIATION OF NONSELECTIVE BETA-BLOCKERS AFTER SPONTANEOUS BACTERIAL PERITONITIS: IMPLICATIONS FOR OUTCOMES IN CIRRHOSIS

Lan Nguyen[1] Sandra Chehayeb[1] Mahinaz Mohsen[2] Anthony Martinez[1], [1]University at Buffalo, [2]Rutgers New Jersey Medical School

Background: Nonselective beta-blockers (NSBB) are frequently withheld during acute spontaneous bacterial peritonitis (SBP) due to concerns for hemodynamic dysfunction. Although reinitiation of NSBB after clinical stabilization is recommended, the optimal timing remains unclear. We therefore conducted a retrospective study to compare outcomes associated with early versus delayed NSBB reinitiation following SBP, aiming to identify a clinically relevant therapeutic window. **Methods:** A retrospective cohort study was performed using the TriNetX network, including adults with cirrhosis and SBP between 1/1/2010 and 1/1/2026. Patients were stratified by timing of NSBB exposure (carvedilol, nadolol, or propranolol): within 1 month or between 1 and 2 months after SBP. Propensity score matching balanced baseline demographics, comorbidities, and medications. Outcomes included hepatorenal syndrome (HRS), ascites, variceal bleeding, hypotension, undifferentiated shock, liver transplantation, and all-cause mortality at 3 months, 6 months, 1 year, and 2 years. Hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated using Kaplan-Meier analysis. **Results:** Compared with NSBB use between 1 to 2 months, exposure within 1 month after SBP was associated with a higher risk of HRS at 3 months (HR 1.41; CI 1.11-1.79), 6 months (HR 1.33; CI 1.11-1.59), 1 year (HR 1.34; CI 1.15-1.56), and 2 years (HR 1.30; CI 1.13-1.49). Early reinitiation also carried an increased risk of undifferentiated shock from 3 months (HR 1.32; CI 1.08-1.61) to 2 years (HR 1.15; CI 1.02-1.30). All-cause mortality was similarly greater in the early reinitiation cohort from 3 months (HR 1.41; CI 1.25-1.58) to 2 years (HR 1.29; CI 1.20-1.40). No significant differences were observed in ascites, hypotension, variceal bleeding, or liver transplantation across all time points. **Conclusion:** NSBB reinitiation within 1 month after SBP was linked to higher risks of HRS, undifferentiated shock, and all-cause mortality compared with that between 1 to 2 months. These findings suggest that the first month after SBP may represent a more vulnerable period for NSBB therapy. However, delaying reinitiation beyond the first month may allow recovery of effective arterial blood volume and renal perfusion, improving clinical outcomes. Incorporating a more standardized timeline for NSBB therapy into post-discharge care may help reduce adverse outcomes in patients with cirrhosis. Future studies should prioritize confirming these findings and further refining the optimal timing for NSBB reinitiation following SBP.

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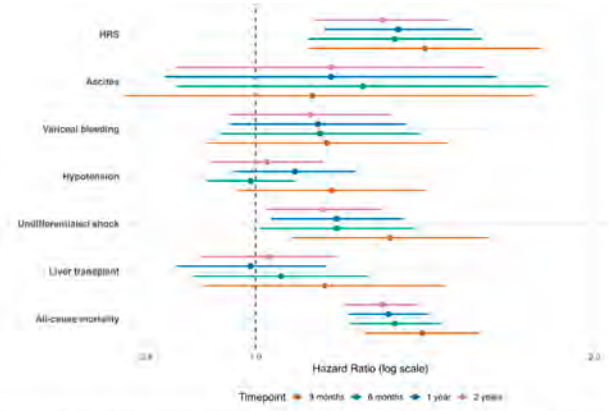


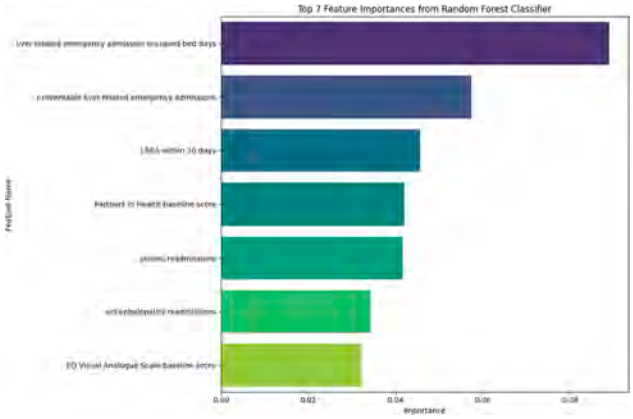
Figure 1. Forest plot demonstrating hazard ratios with 95% confidence intervals for clinical outcomes following NSBB initiation within 1 month versus 1-2 months after SBP in patients with cirrhosis. Outcomes were evaluated at 3 months, 6 months, 1 year, and 2 years. The vertical dashed line represents a HR of 1.0 (no difference between cohorts). HRs greater than 1 indicate increased risk associated with NSBB initiation within 1 month after SBP.

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1565 | CONSTRUCTION OF A MACHINE LEARNING MODEL FOR PREDICTING READMISSIONS IN CIRRHOSIS: A MULTI-CENTER STUDY

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Background: Patients hospitalized with cirrhosis have high rates of early, unplanned readmissions. These are expensive and associated with worse outcomes. Identifying patients at high risk of readmission will allow appropriate distribution of resources to these patients to prevent readmissions and improve outcomes. Current prediction models demonstrate suboptimal performance, limiting their clinical utility. Our aim was to construct a machine learning model (MLM) predicting liver related emergency admissions (LREA) from a multicenter patient cohort. **Methods:** LREA data was analyzed from the multicenter Australian Liver Failure (ALFIE) trial database of 146 patients. Patients were enrolled following an inpatient admission with a complication of cirrhosis. Over 80 variables were analyzed and pre-processed. The cohort was split into a training and test cohort for internal validation. A random forest classifier model was constructed. Coding for the construction of the MLM was performed in Google Colab. Model performance was evaluated for accuracy and area under receiver operating curve (AUROC). Feature importance was analysed. **Results:** A total of 384 LREA occurred over a median follow-up of 2.0 years, with 116 patients (79%) having at least one LREA. The accuracy of the MLM was 0.628 and the AUROC was 0.904. Variables with highest feature importance included those with previous readmissions for ascites or encephalopathy, baseline Partners in Health score and baseline EQ Visual Analogue Scale score (Figure 1). **Conclusion:** We internally validated a MLM predicting LREA in a real-world multicenter cohort with fair accuracy and excellent AUROC. Variables with highest feature importance included self-reported patient knowledge and health-related quality of life measures which are rarely incorporated in current prediction models.



Disclosures: Peter Rose:Nothing to Disclose, Richard Woodman:Nothing to Disclose, Sumudu Narayana: Nothing to Disclose, Alan Wigg:Nothing to Disclose, ALFIE Investigator Group:Nothing to Disclose.

1566 | COMPARATIVE EFFICACY OF ALBUMIN-BASED AND OTHER INTERVENTIONS FOR HYPONATREMIA, PLASMA RENIN ACTIVITY, AND CREATININE IN DECOMPENSATED CIRRHOSIS: A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS

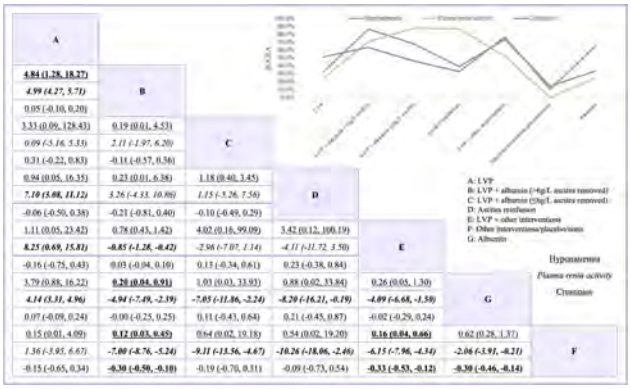
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Background: Human albumin infusion is widely used in the treatment of decompensated cirrhosis, yet evidence from randomized controlled trials (RCTs) remains inconsistent regarding its effects on neurohumoral

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activation and renal function. We conducted a systematic review and network meta-analysis (NMA) to evaluate the comparative efficacy of human albumin-based and other interventions on hyponatremia incidence, plasma renin activity (PRA), and serum creatinine. **Methods:** We searched Web of Science, PubMed, and Embase from inception to February 2025 for RCTs evaluating human albumin in patients with decompensated cirrhosis. Seven intervention strategies (A-G, see figure legend for details) were compared. Outcomes were post-treatment hyponatremia, changes in PRA and creatinine. A frequentist random-effects NMA was performed, and treatment rankings were estimated using surface under the cumulative ranking curve (SUCRA). Systematic Review Registration: PROSPERO CRD420261374214. **Results:** A total of 44r RCTs involving 4,771 participants were included. For hyponatremia (17 trials, n = 1,582), large volume paracentesis (LVP) combined with high-dosage albumin (> 6 g/L ascites removed) was associated with the greatest reduction compared with control strategies (odds ratio [OR] 0.12, 95% CI 0.03–0.45) and had the highest ranking probability (SUCRA 87.2%). For PRA (18 trials, n = 1,207), most active interventions, except LVP alone, inhibited PRA elevation, with LVP combined with low-dosage albumin showing the highest ranking (SUCRA 88.3%). For serum creatinine (28 trials, n = 2,134), LVP combined with other colloids/vasoactive agents, albumin alone, and LVP combined with high-dosage albumin all demonstrated modest reductions versus control, with no significant differences among them. Sensitivity analyses supported the robustness of findings. **Conclusion:** In patients with decompensated cirrhosis, LVP combined with high-dosage albumin is the most effective treatment for reducing hyponatremia risk. Multiple albumin-based regimens similarly suppress renin-angiotensin-aldosterone system activation and stabilize PRA and creatinine.



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1567 | TRANSITIONS OF CARE AMONG PATIENTS HOSPITALIZED WITH RADIOGRAPHIC FINDINGS SUGGESTIVE OF CIRRHOSIS

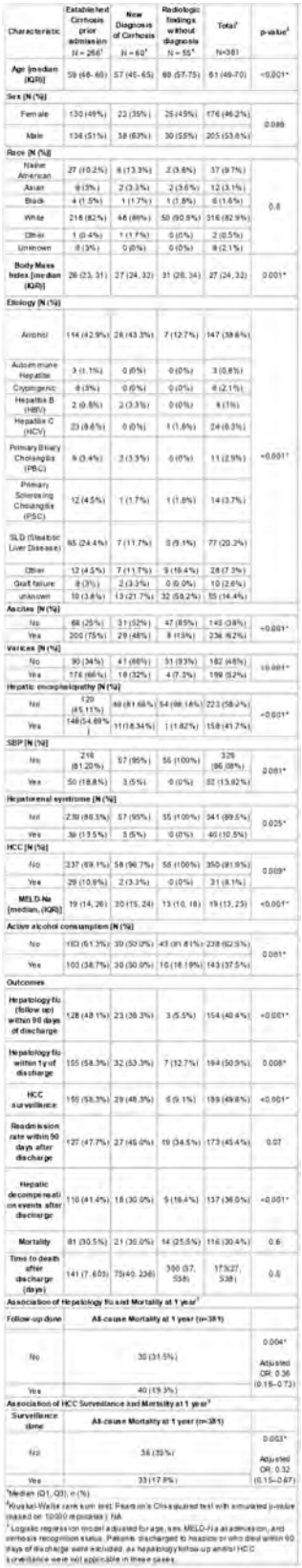
Hugo Vargas[1] Sharon Lechtig-Wasserman[1] Fatmaelzahraa Abdelfattah[1] Stacey Rolak[1] Fares Jamal[1] Abdullah Hamad[1], [1]Mayo Clinic Arizona

Background: Cirrhosis is associated with high readmission rates and adverse outcomes but is often unrecognized during acute care encounters. We evaluated rates of recognition and follow-up among patients with radiographic findings suggestive of cirrhosis. **Methods:** Retrospective single-center cohort study of patients presenting to the ED or hospitalized between 1/2022–1/2023. Abdominal US, CT, and MR reports were screened for findings suggestive of cirrhosis, including “nodular liver,” “portal hypertension,” and “cirrhosis.” Patients were stratified by the presence of a prior cirrhosis diagnosis using ICD-10 codes. Cases without a prior diagnosis were further evaluated using Liver Cirrhosis Network (LCN) criteria. Transitions of care after discharge were assessed including hepatology follow-up, hepatocellular carcinoma (HCC) surveillance (defined as imaging semiannually and/or Alpha-fetoprotein), liver transplant evaluation, and outpatient diagnostic work-up. The primary outcome was all-cause mortality according to recognition status and completion of liver-related follow-up. Secondary outcomes included decompensation events and hospital readmission. **Results:** 381 patients with radiologic findings suggesting cirrhosis were identified. Of these, 266 (69.8%) had an established diagnosis of cirrhosis (group A); 60 (15.7%) were diagnosed during admission (group B), and 55 (14.4%) remained undiagnosed despite suggestive imaging findings (group C). During hospitalization, 91.4% of patients in group A met LCN criteria for cirrhosis, compared with 66.7% and 47.3% in groups B and C, respectively ($p < 0.001$). Appropriate hepatology follow-up within 90 days occurred in 48.1%, 38.3%, and 5.5% of patients in groups A, B, and C, respectively ($p < 0.001$). HCC surveillance occurred in 58.3%, 48.3%, and 9.1% of patients, respectively ($p < 0.001$). Hospital readmission within 90 days, 1-year mortality, and time to death from discharge did not differ between groups (Table 1). Proper HCC surveillance and hepatology follow-up were independently associated with lower 1-year mortality in the overall cohort [OR 0.32 (95% CI 0.15–0.67), p = 0.003 and OR 0.36 (95% CI 0.18–0.73), p = 0.004, respectively]. **Conclusion:** Patients with unrecognized cirrhosis demonstrated substantial gaps in transitions of care, with markedly lower rates of hepatology follow-up and HCC surveillance. Despite these differences, mortality and readmission rates were similar across groups, suggesting that even patients with subtle radiologic findings remain at significant risk for adverse outcomes. Notably, both hepatology follow-up and appropriate HCC surveillance were independently associated with significantly

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lower 1-year mortality in the overall cohort. Improving recognition of liver disease and timely linkage to hepatology care may improve long-term outcomes.



Characteristic	Established Cirrhosis prior admission N = 256[1]	New Diagnosis of Cirrhosis N = 60[1]	Radiologic findings without diagnosis N = 55[1]	Total[1] N=381	p-value[2]
Age (median (IQR))	59 (48-68)	57 (45-65)	69 (57-75)	61 (49-70)	<0.001*
Sex (N (%))					
Female	130 (48%)	22 (35%)	25 (45%)	176 (46.2%)	0.088
Male	134 (51%)	38 (63%)	30 (55%)	205 (53.8%)	
Race (N (%))					
Native American	27 (10.2%)	8 (13.3%)	2 (3.6%)	37 (9.7%)	0.6
Asian	8 (3%)	2 (3.3%)	2 (3.6%)	12 (3.1%)	
Black	4 (1.5%)	1 (1.7%)	1 (1.8%)	6 (1.6%)	
White	218 (82%)	48 (80%)	50 (90.9%)	316 (82.9%)	
Other	1 (0.4%)	1 (1.7%)	0 (0%)	2 (0.5%)	
Unknown	8 (3%)	0 (0%)	0 (0%)	8 (2.1%)	
Body Mass Index (median (IQR))	28 (23, 31)	27 (24, 32)	31 (28, 34)	27 (24, 32)	0.001*
Etiology (N (%))					
Alcohol	114 (42.9%)	26 (43.3%)	7 (12.7%)	147 (38.6%)	<0.001*
Autoimmune Hepatitis	3 (1.1%)	0 (0%)	0 (0%)	3 (0.8%)	
Cryptogenic	8 (3%)	0 (0%)	0 (0%)	8 (2.1%)	
Hepatitis B (HBV)	2 (0.8%)	2 (3.3%)	0 (0%)	4 (1%)	
Hepatitis C (HCV)	23 (8.6%)	0 (0%)	1 (1.8%)	24 (6.3%)	
Primary Biliary Cholangitis (PBC)	8 (3.4%)	2 (3.3%)	0 (0%)	11 (2.9%)	
Primary Sclerosing Cholangitis (PSC)	12 (4.5%)	1 (1.7%)	1 (1.8%)	14 (3.7%)	
SLD (Steatotic Liver Disease)	65 (24.4%)	7 (11.7%)	5 (9.1%)	77 (20.2%)	
Other	12 (4.5%)	7 (11.7%)	5 (18.4%)	24 (7.3%)	
Graft failure	8 (3%)	2 (3.3%)	0 (0.0%)	10 (2.6%)	
unknown	10 (3.8%)	13 (21.7%)	32 (58.2%)	55 (14.4%)	
Ascites (N (%))					
No	68 (25%)	31 (52%)	47 (85%)	146 (38%)	<0.001*
Yes	200 (75%)	29 (48%)	8 (15%)	236 (62%)	
Varices (N (%))					
No	90 (34%)	41 (68%)	31 (93%)	182 (48%)	<0.001*
Yes	174 (66%)	19 (32%)	4 (7.3%)	199 (52%)	
Hepatic encephalopathy (N (%))					
No	129 (45.11%)	49 (81.66%)	54 (98.18%)	223 (58.2%)	<0.001*
Yes	148 (54.89%)	11 (18.34%)	1 (1.82%)	158 (41.7%)	
SBP (N (%))					
No	218 (81.20%)	57 (95%)	55 (100%)	329 (86.08%)	0.001*
Yes	50 (18.8%)	3 (5%)	0 (0%)	53 (13.92%)	
Hepatorenal syndrome (N (%))					
No	239 (89.5%)	57 (95%)	55 (100%)	341 (89.5%)	0.025*
Yes	36 (13.5%)	3 (5%)	0 (0%)	40 (10.5%)	
HCC (N (%))					
No	237 (89.1%)	58 (96.7%)	55 (100%)	350 (91.9%)	0.009*
Yes	29 (10.9%)	2 (3.3%)	0 (0%)	31 (8.1%)	
MELD-Na (median, (IQR))	19 (14, 26)	20 (15, 24)	13 (10, 18)	19 (13, 25)	<0.001*
Active alcohol consumption (N (%))					
No	110 (61.3%)	30 (50.0%)	43 (81.81%)	238 (62.5%)	0.001*
Yes	100 (38.7%)	30 (50.0%)	10 (18.19%)	143 (37.5%)	
Outcomes					
Hepatology fu (follow up) within 90 days of discharge	128 (48.1%)	23 (38.3%)	3 (5.5%)	154 (40.4%)	<0.001*
Hepatology fu within 1y of discharge	155 (58.3%)	32 (53.3%)	7 (12.7%)	194 (50.9%)	0.008*
HCC surveillance	155 (58.3%)	29 (48.3%)	5 (9.1%)	189 (49.6%)	<0.001*
Readmission rate within 90 days after discharge	127 (47.7%)	27 (45.0%)	19 (34.5%)	173 (45.4%)	0.07
Hepatic decompensation events after discharge	110 (41.4%)	18 (30.0%)	9 (16.4%)	137 (36.0%)	<0.001*
Mortality	81 (30.5%)	21 (35.0%)	14 (25.5%)	116 (30.4%)	0.6
Time to death after discharge (days)	141 (7, 603)	75(40, 236)	300 (37, 538)	173(27, 538)	0.8
Association of Hepatology fu and Mortality at 1 year[3]					
Follow-up done	All-cause Mortality at 1 year (n=381)				
No	30 (31.5%)				0.004* Adjusted OR: 0.36 (0.18–0.73)
Yes	40 (15.3%)				
Association of HCC Surveillance and Mortality at 1 year[3]					
Surveillance done	All-cause Mortality at 1 year (n=381)				
No	36 (39%)				0.003* Adjusted OR: 0.32 (0.15–0.67)
Yes	33 (17.8%)				

[1]Median (Q1, Q3); n (%)
[2]Kruskal-Wallis rank sum test; Pearson's Chi-squared test with simulated p-value (based on 10000 replicates); NA
[3]Logistic regression model adjusted for age, sex, MELD-Na at admission, and cirrhosis recognition status. Patients discharged to hospice or who died within 90 days of discharge were excluded, as hepatology follow-up and/or HCC surveillance were not applicable in these cases.

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1568 | RICE RECOMBINANT HUMAN ALBUMIN IS NOT FULLY EQUIVALENT TO PLASMA-DERIVED HUMAN ALBUMIN IN TERMS OF POST-TRANSLATIONAL MODIFICATIONS AND IMMUNOGENICITY PROFILE

Anna Mestre[1] Raquel Horrillo[1] Jordi Vidal[1] Isabel Bravo[1] Montse Costa[1], [1]Grifols

Background: Recombinant human albumin (rHA) is emerging as a therapeutic alternative to plasma-derived human albumin (pdHA), with several programs in clinical development. Recently, for the first time a rHA (from Healthgen Biotechnology) has received regulatory approval in China for the treatment of hypoalbuminemia in patients with liver cirrhosis. Despite these advances, safety and immunogenicity of rHA remain as key concerns considering the final aim of treating human patients with a recombinant protein in gram's doses. In this context, understanding how rice rHA compares with pdHA is of critical importance. Therefore, this study presents the comparative assessment of albumin post-translational modifications (PTMs) profile and ex vivo immunogenicity in human cells for rice-derived rHA vs pdHA. **Methods:** PTMs of pdHA and rice rHA were assessed on the intact protein mass (top-down) using ultra high-performance liquid chromatography coupled to electrospray ionization quadrupole time-of-flight mass spectrometry (LC-ESI-qTOF-MS). PTMs were tentatively assigned by exact mass comparison with reported modifications and expressed as percentage of relative intensity. Immunogenicity risk within the adaptive immunity was assessed using a dendritic cell-T cell (DC-T) proliferation assay, employing human leukocyte antigen-typed peripheral blood mononuclear cells from 40 healthy donors. Monocyte-derived DCs were loaded with either albumin (15 µM) and co-cultured with autologous T cells labeled with carboxyfluorescein succinimidyl ester. CD4+ T cell proliferation was measured by flow cytometry at day 7. The response index (RI) was calculated considering the strength of the response as well as the frequency of that

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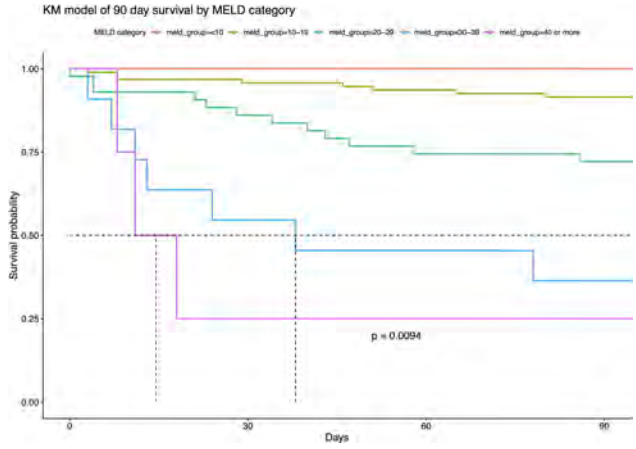
response. Both assessments were performed by two independent CROs under blind conditions. **Results:** Remarkable differences in albumin PTMs were observed between rice-derived rHA and pdHA. rHA showed an increased N-terminal truncation (HSA-DA 18.5% vs 4.08% for pdHA), which is associated with reduced metal-binding and antioxidant capacity, and increased glycated isoforms (sum of glycated forms: 22.5% vs 12.8%), consistent with protein expression in rice. In the DC-T assay, rHA induced CD4+ T cell responses in 57.5% of donors (23/40; 20 of them with ANOVA $p \leq 0.05$) with a strength of response of 2.39, resulting in a RI of 1.376. The RI for rHA exceeded the threshold of 1, indicative of elevated antigenicity risk for biotherapeutics and consistent with its higher PTM burden, whereas pdHA remained well below this threshold (RI: 0.273), supporting a lower antigenicity risk profile. **Conclusion:** Compared with pdHA, rHA displays a distinct PTM profile characterized by increased truncation and glycation, together with substantially higher antigenicity in adaptive immunity. While not a predictor of clinical outcomes, these results provide early immunogenicity risk evidence supporting non-equivalence between rHA and pdHA.

Disclosures: Anna Mestre:Grifols: Employee, Raquel Horrillo:Grifols: Employee, Jordi Vidal:Grifols: Employee, Isabel Bravo:Grifols: Employee, Montse Costa:Nothing to Disclose.

1569 | NATURAL HISTORY FOLLOWING FIRST EPISODE OF DECOMPENSATION IN LIVER CIRRHOSIS: A RETROSPECTIVE COHORT STUDY WITH MORTALITY LINKAGE IN A METROPOLITAN AUSTRALIAN HEALTH NETWORK

Edward Meehan[1] Nicholas Mulkearns[1] Chuanxin (Tony) Jia[1] Cindy Truong[1] Marjorie Zhang[2] Liam Brennan-Xie[1] Ella Yang[1] Manal Ajmal[1] Niranjan Arachchi[1] Zina Valaydon[1], [1]Western Health, [2]Wesetern Health

Background: Life expectancy following presentation with first episode decompensation of cirrhosis has been minimally described in a contemporary Australian context. We aimed to describe patient characteristics, estimate life expectancy, and assess associations between 90-day survival and MELD score, in a metropolitan health network (Western Health) in Victoria, Australia. **Methods:** We retrospectively enrolled all adults with liver cirrhosis hospitalised at Western Health from 01/01/2019 to 30/04/2023 primarily for a first decompensation episode, defined by presence of ascites, variceal bleeding, hepatic encephalopathy, or jaundice (HREC/23/WH/101106). We excluded patients whose first decompensation occurred prior to 2019 or outside our network, or who had hepatocellular carcinoma (HCC) at index presentation. Patients who subsequently developed HCC were censored from survival analysis at the time of HCC diagnosis. The primary outcome was death, and we performed data linkage with the Births, Deaths, and Marriages Registry up to 02/02/2026. We performed survival analysis with Kaplan-Meier curves and log-rank testing for MELD-score category. **Results:** 162 patients were hospitalised for a first episode decompensation of cirrhosis during the study period. 61.1% were male, and median age was 56.5 years (IQR 46 - 67). The median follow-up period was 1037.5 days (IQR 262 - 1855.3). The aetiology involved alcohol in 82.1% of patients, 72.9% of whom were still drinking, viral hepatitis in 16.7%, metabolic dysfunction in 14.8%, and autoimmune disease in 1.9%. The median Elixhauser comorbidity index score was 3 (IQR 1 - 4), and the median MELD score was 18 (IQR 13 – 22). The median INR was 1.5 (IQR 1.3 - 1.9), bilirubin was 66 (IQR 29 – 143), and albumin 26 (IQR 22 – 29). 117 patients (72.2%) had ascites, 37 (22.8%) had hepatic encephalopathy, and 35 (21.6%) had variceal bleeding. 14 (8.6%) were admitted to intensive care, and 8 (4.9%) discharged against medical advice. 5 (3.1%) developed HCC during follow up. 89 patients (54.9%) died, and median survival time was 1687 days (95% CI 896 – NA). 11 (6.8%) died during their initial presentation, and 30 (18.5%) died within 90 days of it, including 75% with a MELD score of 40 or more ($p = 0.0094$) (Figure 1). **Conclusion:** We found high rates of 90-day and overall mortality and significant associations with MELD score in this contemporary Australian cohort. Overall mortality across follow-up was similar to that seen among patients with cirrhosis and decompensation in a cohort in Queensland, Australia, while 90-day mortality was slightly higher than rates seen in the original prospective validation study of the MELD score. Limitations included the retrospective design, and the absence of a cancer registry to confirm HCC incidence. First episode decompensation continues to portend a poor prognosis, and the MELD score remains a useful tool in contemporary Australian patients.



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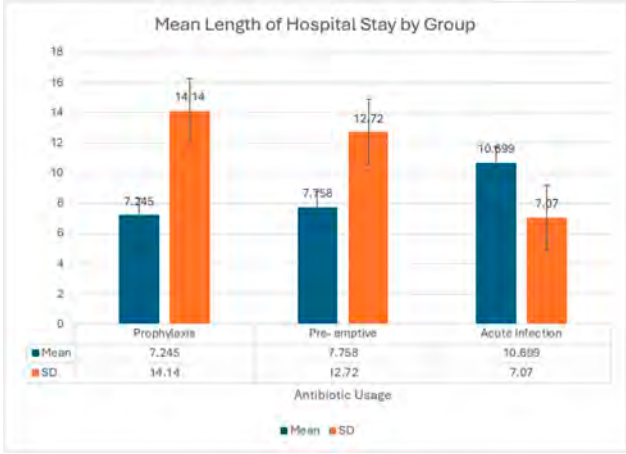
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1570 | ASSOCIATION BETWEEN ANTIBIOTIC INDICATION ON LENGTH OF HOSPITAL STAY IN HOSPITALIZED PATIENTS WITH CIRRHOSIS

Ruwani Alwis[1] Shahid Habib[1] Meghana Vukkhadkar[1], [1]Liver Institute PLLC

Background: Bacterial infections are a major cause of morbidity and mortality in patients with cirrhosis, contributing to prolonged hospitalizations and increased healthcare costs.This study aimed to evaluate the association between antibiotic indication (prophylaxis, preemptive therapy, or treatment of acute infection) and hospital length of stay (LOS) in hospitalized patients with cirrhosis. **Methods:** This IRB-approved retrospective single-center study included 353 hospitalized patients with cirrhosis of any etiology who received systemic antibiotics during inpatient admission. Patients were categorized into three groups based on antibiotic indication: prophylaxis, preemptive therapy, or treatment of acute infection. Outcomes included age, sex, mean highest Model for End-Stage Liver Disease (MELD) score, and LOS. Between-group comparisons of LOS were performed using one-way analysis of variance (ANOVA) with post hoc pairwise t-tests. **Results:** Among the 353 patients included, 121 received prophylactic antibiotics, 64 received preemptive therapy, and 168 were treated for acute infection.The prophylaxis group included 85 male and 36 female patients, with a mean age of 54 years, mean MELD score of 16.86, and mean LOS of 7.24 days.The preemptive therapy group included 39 male and 25 female patients, with a mean age of 56.5 years, mean MELD score of 22.48, and mean LOS of 7.75 days.The acute infection group included 93 male and 75 female patients, with a mean age of 56.36 years, mean MELD score of 19.49, and mean LOS of 10.69 days.Overall differences in LOS among the three groups were statistically significant (one-way ANOVA, p = 0.003). Post hoc pairwise t-tests demonstrated longer LOS in the acute infection group compared with both the prophylaxis group (p = 0.001) and the preemptive therapy group (p = 0.02). No significant difference in LOS was observed between the prophylaxis and preemptive therapy groups (p = 0.66). **Conclusion:** Among hospitalized patients with cirrhosis receiving antibiotics, treatment for acute infection was associated with significantly longer hospital LOS compared with prophylactic or preemptive antibiotic use. These findings suggest that acute infection may contribute substantially to hospitalization burden in patients with cirrhosis.



Disclosures: Ruwani Alwis:Nothing to Disclose, Shahid Habib:Nothing to Disclose, Meghana Vukkhadkar: Nothing to Disclose.

1571 | TRIMETHOPRIM-SULFAMETHOXAZOLE VERSUS CIPROFLOXACIN FOR SECONDARY PROPHYLAXIS OF SPONTANEOUS BACTERIAL PERITONITIS: A TARGET TRIAL EMULATION ANALYSIS IN A U.S. MULTICENTER COHORT

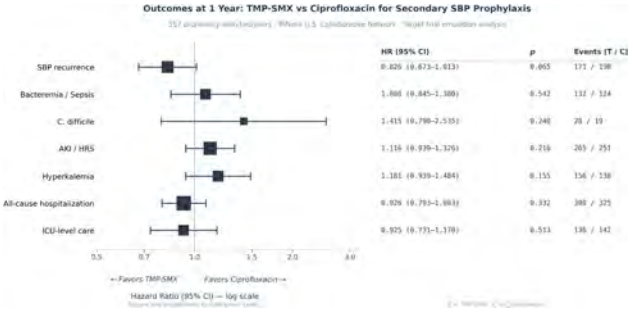
Ali Emre Bardak[1] Nazli Begum Ozturk[2] Hind El Naamani[1] Ahmet Gurakar[3], [1]Boston Medical Center - Brighton, Boston, MA, USA, [2]Saint Louis University School of Medicine, St. Louis, MO, USA, [3]Johns Hopkins University School of Medicine, Baltimore, MD, USA

Background: After first-episode spontaneous bacterial peritonitis (SBP), secondary antibiotic prophylaxis is standard of care. With norfloxacin unavailable in the U.S., trimethoprim-sulfamethoxazole (TMP-SMX) and ciprofloxacin are the practical alternatives despite no head-to-head randomized trials, and major guidelines treat them as equivalent. **Methods:** Using a target trial emulation analysis framework, we compared TMP-SMX versus ciprofloxacin for secondary SBP prophylaxis in the TriNetX U.S. Collaborative Network. Eligible

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patients were adults with cirrhosis (K70.3, K74.6) and a first SBP episode (K65.2) between 2015 and 2025 who received TMP-SMX or ciprofloxacin 7-14 days post-SBP. To isolate prophylactic from therapeutic intent, patients with any study antibiotic within 6 days of SBP or any concurrent extra-peritoneal infection (urinary, respiratory, skin, intra-abdominal, ENT) within 14 days of SBP were excluded. 1:1 propensity score matching was used to balance covariates, including demographics, cirrhosis etiology, decompensation burden, cardiometabolic comorbidities, CKD stage, beta-blockers, diuretics, MELD-component labs, hemoglobin, and platelet count. Outcomes were assessed from day 7 through day 365 by Kaplan-Meier analysis. Primary outcome was SBP recurrence; secondary outcomes were bacteremia/sepsis, C. difficile, AKI/HRS, hyperkalemia, all-cause hospitalization, and ICU-level care. **Results:** Before matching, 565 TMP-SMX and 1,797 ciprofloxacin recipients met criteria; 557 patients were matched in each group. After matching, 1-year SBP cumulative incidence was 35.4% with TMP-SMX vs 42.6% with ciprofloxacin (171 vs 198 events; HR 0.826, 95% CI 0.673–1.013; p = 0.065). No significant differences were observed for bacteremia/sepsis (HR 1.080, 95% CI 0.845–1.380; p = 0.542), C difficile infection (HR 1.415, 95% CI 0.790–2.535; p = 0.240), AKI/HRS (HR 1.116, 95% CI 0.939–1.326; p = 0.216), hyperkalemia (HR 1.181, 95% CI 0.939–1.484; p = 0.155), all-cause hospitalization (HR 0.926, 95% CI 0.793–1.083; p = 0.332), or ICU-level care (HR 0.925, 95% CI 0.731–1.170; p = 0.513). **Conclusion:** In a U.S. real-world cohort emulating a head-to-head trial of TMP-SMX versus ciprofloxacin for secondary SBP prophylaxis, no statistically significant differences were observed in infectious, renal, healthcare utilization, or hyperkalemia outcomes at 1 year, supporting current guideline equipoise. A directional 7-percentage-point absolute reduction in 1-year SBP recurrence with TMP-SMX did not reach statistical significance but warrants prospective evaluation.



Disclosures: Ali Emre Bardak:Nothing to Disclose, Nazli Begum Ozturk:Nothing to Disclose, Hind El Naamani:Nothing to Disclose, Ahmet Gurakar: DURECT: Grant/Research Support, Orphalan: Advisor, ETON: Advisor.

1572 | IMMUNOMETABOLISM OF T CELLS FROM ASCITES IN PATIENTS WITH ADVANCED CHRONIC LIVER DISEASE

Hannah Schwarz[1] Ingrid Wei Zhang[1] Pavitra Kumar[1] Hasan Tarik Cosgun[1] Charalampos Pavlidis[1] Juan Wang[1] Frank Tacke[1] Linda Hammerich[1] Cornelius Engelmann[1], [1]Department of Hepatology & Gastroenterology, Charité – Universitätsmedizin Berlin

Background: Patients with advanced liver cirrhosis develop ascites as one of the first signs of decompensation. This is associated with an increased risk of infections such as spontaneous bacterial peritonitis (SBP), in which cirrhosis-associated immune dysfunction plays a pathogenic role. While immune dysfunction and metabolic perturbations in circulating immune cells are well described, their role in the peritoneal compartment has remained unclear. We therefore aim to characterize the metabolic and functional properties of ascites T lymphocytes, as the predominant population in ascites. **Methods:** Peripheral blood and ascites samples were obtained from patients with acutely decompensated cirrhosis without SBP. $CD3^+$ T cells were isolated by magnetic cell separation and subjected to phenotypic and metabolic analyses using the Seahorse XF Analyzer and Spectral Flow Cytometry. **Results:** A total of 30 patients were included (63.3% male, 36.7% female), with alcohol-related liver disease as the predominant etiology (66.7%) and a median MELD score of 16.6. Ascites T cells show a more antigen-experienced phenotype with increased memory $CD4^+$ T cells ($CD45RO^+$) (61.05% vs. 36.31%, adjusted $p < 0.0001$), elevated TIGIT expression and significantly higher frequency of $PD\text{-}1^+$ $CD4^+$ T cells (33.09% vs. 14.17% adjusted $p < 0.001$). Regulatory T cells were more abundant in peripheral blood (6.74% vs. 9.36%, adjusted $p < 0.005$). Along with these phenotypic changes, ascites T cells show comparable basal respiration (ascites: 4.028, n = 24 vs. blood: 3.594, n = 21 pmol O_2/min/µg protein), but significantly higher maximal respiration (21.52, n = 24 vs. 13.29, n = 21 pmol O_2/min/µg protein, $p < 0.001$) and spare respiratory capacity (504.2%, n = 24 vs. 327.1%, n = 21, p = 0.0003). Elevated proton leak (0.40, n = 24 vs. 0.28, n = 15 pmol O_2/min/µg protein, p = 0.0204) and reduced coupling efficiency (88.71% n = 24 vs. 92.55% n = 21, p = 0.1071) indicated impaired mitochondrial energy production despite unchanged ATP-linked respiration (3.67 n = 24 vs 3.52 n = 21 pmol O_2/min/µg protein , p = 0.5024). Additionally, T cells from ascites showed higher glycolytic capacity compared to blood T cells (p = 0.0232). Given the mitochondrial dysfunction in ascites T cells, we investigated whether Elamipretide, a cardiolipin-stabilizing tetrapeptide targeting the electron transport chain, could restore mitochondrial health. Indeed,

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Elamipretide treatment led to a partial recovery of mitochondrial function in ascites T cells. **Conclusion:** T cells from ascites display enhanced mitochondrial respiratory capacity but reduced energetic efficiency. Spectral Flow Cytometry analysis further reveals an enrichment of PD-1^{+} T cells. These findings suggest a functionally impaired T cell state, potentially driven by extrinsic factors within the ascites environment, which may increase the risk of infectious complications.

Disclosures: Hannah Schwarz:Nothing to Disclose, Ingrid Wei Zhang:GlaxoSmithKline: Employee, Pavitra Kumar:Nothing to Disclose, Hasan Tarik Cosgun: Nothing to Disclose, Charalampos Pavlidis:Nothing to Disclose, Juan Wang:Nothing to Disclose, Frank Tacke:Gilead: Grant/Research Support, MSD: Grant/Research Support, AstraZeneca: Grant/Research Support, Agomab: Grant/Research Support, NovoNordisk, Boehringer, Gilead, MSD, GSK: Consultant, Pfizer, Sanofi: Advisor, Madrigal, Mirum, Ipsen: Consultant, Sanofi: Advisor, Falk: Speaking and Teaching, Linda Hammerich:Nothing to Disclose, Cornelius Engelmann: Nothing to Disclose.

1573 | SAFETY AND EFFICACY OF LOW-DOSE ALBUMIN IN PATIENTS WITH SPONTANEOUS BACTERIAL PERITONITIS: A PROPENSITY SCORE-MATCHED ANALYSIS

Sayan Malakar[1] Virendra Singh[1] Sumit Rungta[2] Rahul Jangra[2] Amandeep Singh[1] Jahnvi Dhar[1] Upasna Rajput[1] Anmol Anmol[1], [1]Punjab Institute of Liver and Biliary Sciences, [2]KGMU

Background: Intravenous antibiotics and standard dose of albumin (1.5g/kg/day on day 1 and 1 g/kg/day on day 3) remain the mainstay of therapy in patients with spontaneous bacterial peritonitis (SBP). We aimed to evaluate the safety and efficacy of low-dose albumin (20 grams/ day on days 1 and 3) in patients with SBP. **Methods:** In this exploratory retrospective cohort study, 161 patients with SBP were included. Of 161 patients, 58 received low-dose albumin, and 103 received standard-dose albumin. After propensity-score matching (PSM), 52 patients were included in each group. Primary outcomes inclde resolution of SBP, reversal of acute kidney injury (AKI) and 90-day mortality . Secondary outcome measures were length of hospital stays and adverse events. Primary and secondary outcomes were estimated and compared between two groups. **Results:** In the unmatched cohort, the age at presentation was 45.4 ± 10.58 years (males: 84.5%). Following PS matching (1:1), there were no significant differences between their demographics, laboratory and severity (Table 1). In the PSM cohort, concomitant AKI was present in 54 patients [26 (50%) in the standard albumin group vs 28 (53.8%) in the low-dose albumin group; p = 0.85]. After 48 hours, SBP resolution was noted in 40 patients (76.9%) in the standard albumin group and 42 (80.8%) in the low-dose albumin group (p = 0.81). There was no significant differences in day-3, day-7 AKI resolution [10 (19.2%) vs 14 (27%); p = 0.12 and 16 (38.7%) vs 13 (34%); p = 0.14, respectively], hospital stay [12.52 ± 3.79 days vs 12.71 ± 3.90 days; p = 0.79] and 90-day mortality [8 (15.3%) vs 11 (21.1%); p = 0.30] between the two groups. Adverse events were higher in the standard dose albumin group [9 (17.3%) vs 2 (3.8%); p = 0.01] **.** In the Kaplan-Meier analysis in the PSM cohort, there was no difference in mortality between the standard- and low-dose albumin groups when adjusted for Child-Turcot-Pugh and Model for End Stage Liver Disease-Sodium (MELD-Na) score [ajusted hazard ratio: 1.01 (95% confidence interval : 0.48-2.12), p = 0.94]. **Conclusion:** Low-dose albumin is safe and effective in managing SBP.

Table: 1

Demographic, clinical, biochemical parameters and outcome after propensity-score matched cohorts of standard dose and low dose albumin group

Variable	Overall (n=104)	Standard dose albumin (n=52)	Low Dose albumin (n=52)	p-value
Age of onset (years)	47.87 ± 10.63	49.13 ± 10.03	45.60 ± 10.82	0.59
Gender (Male)	Male 88 (84.6%)	Male 88 (84.6%)	Male 40 (76.9%)	0.05
Hemoglobin (g/dL)	7.45 ± 2.0	7.32 ± 2.0	7.65 ± 1.86	0.56
Total leukocyte count (per mm^3)	8130.26 ± 4252.49	7412.25 ± 4384.18	8848.27 ± 4031.09	0.05
Platelets (per mm^3)	1.09 ± 0.59	1.11 ± 0.56	1.06 ± 0.62	0.64
Total Bilirubin (mg/dL)	8.34 ± 6.66	7.88 ± 8.76	8.79 ± 4.21	0.50
Conjugated Bilirubin (mg/dL)	4.18 ± 5.22	5.07 ± 6.97	3.28 ± 2.18	0.06
Aspartate aminotransferase (U/L)	71.16 ± 46.07	74.60 ± 55.50	67.73 ± 34.40	0.45
Alanine aminotransferase (U/L)	42.57 ± 28.49	43.54 ± 18.87	40.90 ± 34.78	0.32
Alkaline phosphatase U/L)	188.36 ± 92.27	189.73 ± 72.91	186.98 ± 102.65	0.59
Albumin (g/dL)	2.74 ± 0.49	2.65 ± 0.55	2.83 ± 0.39	0.06
Protein U/L)	6.28 ± 1.00	6.56 ± 0.93	6.01 ± 1.01	0.51
International normalized ratio	2.02 ± 0.69	2.15 ± 0.87	1.90 ± 0.41	0.06
Creatinine (mg/dL)	1.74 ± 0.88	1.73 ± 1.08	1.75 ± 0.63	0.89
Sodium (mmol/L)	140.55 ± 6.66	140.79 ± 4.83	130.31 ± 8.13	0.71
Child Turcot Pugh Score	9.54 ± 1.43	9.48 ± 1.66	9.63 ± 1.18	0.73
Model for end-stage liver disease-Sodium	24.37 ± 4.82	24.81 ± 3.91	24.13 ± 5.26	0.39
Varices	97(93.2%)	48 (92.3%)	49 (94.2%)	0.82
Hepatic encephalopathy	45 (43.2%)	21 (40.3%)	24 (46.1%)	0.57
Outcome				
Day 3 AKI Resolution	24/ 102 (23%)	10 (19.2%)	14 (27%)	0.12
Day 7 AKI Resolution	29/ 78 (37.1%)	16/42 (38.7%)	13/38 (34%)	0.14
SBP Resolution	82 (78.8%)	40 (76.9%)	42 (80.8%)	0.81
Hospital stays (days)	12.62 ± 3.82	12.52 ± 3.79	12.71 ± 3.90	0.79
Adverse events	11 (10.5%)	9 (17.3%)	2 (3.8%)	0.01
90-day mortality	18(17.3%)	8(15.3%)	11(21.1%)	0.50

Disclosures: Sayan Malakar:Nothing to Disclose, Virendra Singh:Nothing to Disclose, SUMIT RUNGTA: Nothing to Disclose, Rahul Jangra:Nothing to Disclose, Amandeep Singh:Nothing to Disclose, Jahnvi Dhar: Nothing to Disclose, Upasna Rajput:Nothing to Disclose, Anmol Anmol:Nothing to Disclose.

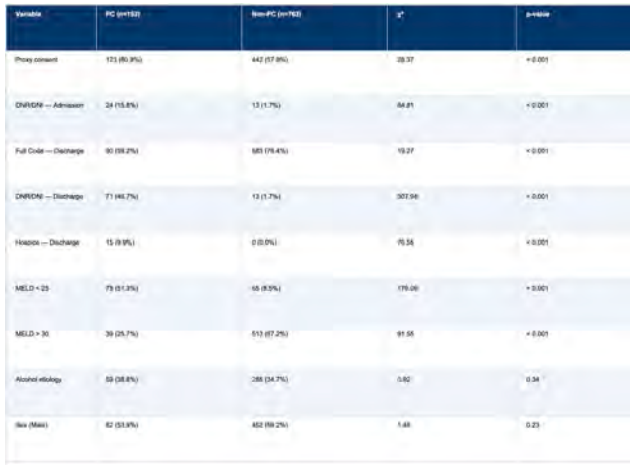
1574 | PREDICTORS OF MORTALITY IN PATIENTS WITH HEPATORENAL SYNDROME AT A SOUTH TEXAS NON-TRANSPLANT CENTER

Keila Carrera Mejias[1] Rishika Trivedi[1] Fernado Membreno[1] Asif Zamir[1] Genesis Camacho[1], [1]DHR Health

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Background: Hepatorenal syndrome (HRS) is a form of kidney dysfunction that occurs in patients with liver cirrhosis. It recognizes HRS-AKI, characterized by an abrupt impairment of kidney function and HRS-CKD with eGFR of < 60ml/min/1.73m > 90 days. In hospital mortality associated with HRS has decreased from 44% to 24% between 2005 and 2014 data from the National Inpatient Sample (NIS) database, showing a decline attributed to increased rates of liver transplantation and expanded use of renal replacement therapy. **Methods:** This is a retrospective study. Data were obtained from a non-liver transplant medical center in South Texas covering the period 2020–2023. We assessed factors associated with overall mortality in patients with HRS. Statistical analyses included descriptive statistics, independent samples t-tests, chi-square analysis, and binary logistic regression to identify independent predictors of overall mortality. **Results:** In this retrospective cohort of patients with hepatorenal syndrome (HRS) from a non-transplant center serving a predominantly Hispanic population in South Texas, overall mortality was 23%, reflecting the persistently poor prognosis of HRS in community-based settings. HRS-AKI was the predominant phenotype (75%), with alcohol-related liver disease (43%) and MASH (39%) representing the leading etiologies of underlying cirrhosis. MELD score emerged as the sole independent predictor of overall mortality, with each one-point increase conferring 11% higher odds of death (OR 1.11, 95% CI 1.003–1.228, p = 0.044). Among patients requiring ICU-level care, both age and MELD score were significant predictors of ICU mortality each additional year of age increased the odds by 4.6% **(** OR 1.046, p = 0.002), while each one-point rise in MELD increased the odds by 35% **(** OR 1.35, p = 0.04). Among clinical precipitants, acute hepatic encephalopathy was the most frequent, occurring in 28% of patients. Treatment utilization reflected the real world, resource limited context of this cohort: Midodrine/octreotide: 45.8% , albumin challenge: 27.9, and vasopressors 14.7% **Conclusion:** This study provides important real-world data from a predominantly Hispanic population in South Texas and highlights the urgent need for earlier recognition, risk stratification, and improved access to advanced liver care for patients with HRS managed outside transplant referral centers which remain challenge. It is important to note that terlipressin was approved at our institution in late 2023. Therefore, most patients in this cohort (2020–2023) were managed according to prior guidelines.



Disclosures: Keila Carrera Mejias:Nothing to Disclose, Rishika Trivedi:Nothing to Disclose, Fernado Membreno:Nothing to Disclose, Asif Zamir:Nothing to Disclose, Genesis Camacho:Nothing to Disclose.

1575 | EFFICACY AND SAFETY OF PERCUTANEOUS ASPIRATION SCLEROTHERAPY WITH MINOCYCLINE FOR SYMPTOMATIC HEPATIC CYSTS

Tomohiro Oikawa[1] Takayuki Kogure[1] Mari Satoh[1] Kennichi Satoh[1], [1]Tohoku Medical and Pharmaceutical University

Background: Laparoscopic deroofing surgery is the standard treatment for patients with symptomatic hepatic cysts. Alternatively, aspiration sclerotherapy is a minimally invasive treatment considered for patients unable to tolerate surgery. While most reports describe the use of ethanol as a sclerosing agent, fewer studies have cited polidocanol, tetracycline, or minocycline. The efficacy of aspiration sclerotherapy remains limited compared with surgical intervention due to inadequate destruction of the inner cystic epithelium. Minocycline, a broad-spectrum antibiotic, is highly acidic and induces inflammation and tissue damage in the cyst epithelium. However, detailed reports on its therapeutic efficacy and safety are limited. Here, we evaluate a modified method of minocycline aspiration sclerotherapy (MINO sclerotherapy) for symptomatic hepatic cysts, which achieved a low recurrence rate. **Methods:** This study was approved by the ethics committee of our institution. Between 2020 and 2026, 10 patients

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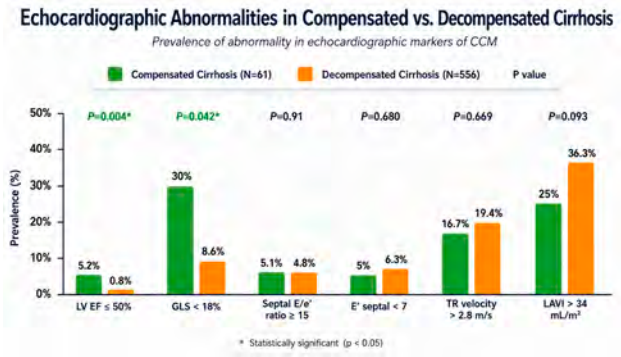
underwent MINO sclerotherapy at our institution. Ultrasound-guided cyst aspiration was performed using a pigtail catheter system. Following complete fluid drainage, the cyst was washed with saline through the catheter. The catheter was left open until the following morning. Thereafter, a minocycline solution (200 mg in 10 mL of saline) was injected into the cyst, and the catheter was clamped for at least 8 hours. This minocycline administration was repeated daily for 3 to 4 days. **Results:** The indications for cyst aspiration included liver function abnormalities and cholangitis due to bile duct stenosis (n = 3), bacterial infection of the cyst fluid (n = 6), and intracystic hemorrhage (n = 1). Pre-treatment cyst diameters ranged from 5 to 15 cm (median: 11.6 cm, mean: 10.2 cm). The treatment achieved a reduction in cyst size ranging from 71.2% to 86.7% (median: 76.7%, mean: 77.2%). Following drainage, all symptoms and clinical findings resolved. During a follow-up period of 6 months or longer, no patients exhibited cyst regrowth or recurrence of symptoms. Regarding treatment-related complications, mild pain at the catheter insertion site occurred in all cases, with 6 patients requiring acetaminophen. One patient developed a transient fever during minocycline infusion; however, no other adverse events were observed. **Conclusion:** Percutaneous aspiration sclerotherapy with minocycline is an effective and safe procedure for symptomatic hepatic cysts. This treatment represents a viable option for patients who are not candidates for deroofing surgery or those requiring urgent drainage due to severe cyst fluid infection.

Disclosures: Tomohiro Oikawa:Nothing to Disclose, Takayuki Kogure:Nothing to Disclose, MARI SATOH: Nothing to Disclose, Kennichi Satoh:Nothing to Disclose.

1576 | THE PRESENCE OF CIRRHOTIC CARDIOMYOPATHY IS NOT EXCLUSIVE TO DECOMPENSATED CIRRHOSIS: A RETROSPECTIVE COHORT STUDY

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Background: Cirrhotic cardiomyopathy (CCM) is an underrecognized complication of advanced liver disease characterized by impaired cardiac function in the absence of underlying primary heart disease. While prior studies showed that CCM affects a large proportion of patients with decompensated cirrhosis, the existence of CCM in the setting of compensated disease is yet to be explored. In this study, we aim to compare the prevalence of CCM between compensated and decompensated cirrhosis and evaluate associated echocardiographic characteristics. **Methods:** We performed a retrospective analysis of adult patients with cirrhosis who were wait-listed for liver transplantation at a large academic center in North America between 11/2020 and 4/2025. Patients with primary cardiac pathology prior transplant were excluded. Patients were stratified into compensated versus decompensated cirrhosis based on having > 1 decompensating event (i.e., ascites, hepatic encephalopathy, bleeding varices). CCM prevalence and echocardiographic parameters were compared between groups. **Results:** The study included 617 patients of whom 61 (9.9%) had compensated cirrhosis and 556 (90.1%) had decompensated cirrhosis. When comparing compensated vs. decompensated groups, median age (61 vs. 60, $p = 0.86$) and body mass index (29.5 vs. 29.6, $p = 0.39$) were comparable between groups and the majority were non-Hispanic white (82% vs. 92%, $p = 0.004$). MASLD was present in 37.4% of the decompensated group and 29.5% of the compensated group. The prevalence of CCM didn't differ significantly between compensated and decompensated patients (16.7% vs. 15.8%, $p = 0.87$). However, compensated patients had higher prevalence of abnormal left ventricular ejection fraction (EF) $\leq 50\%$ (5.2% vs. 0.8%, $p = 0.004$), and global longitudinal strain (GLS) $< 18\%$ (30.0% vs. 8.6%, $p = 0.042$). Both groups have had comparable rates of abnormalities in the diastology variables of CCM. **Conclusion:** This exploratory analysis is the first to demonstrate that CCM exists in patients with compensated cirrhosis and is not exclusive to decompensated disease. These findings highlight the complexity of cardiac dysfunction in cirrhosis and pave the path for investigation of CCM impact on compensated disease.



Disclosures: Rawia Aburumman:Nothing to Disclose, Andre Hall:Nothing to Disclose, Murray Coetzee:Nothing to Disclose, James Slaughter:Nothing to Disclose, Ashley Spann:Bristol Myers Squibb Foundation: Grant/Research Support, Novo Nordisk: Consultant, Madrigal

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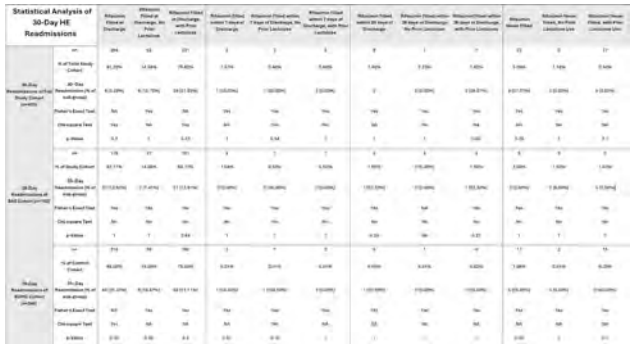
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Pharmaceuticals: Consultant, Deepak Gupta:Nothing to Disclose, Anthony Dreher:Nothing to Disclose, Manhal Izzy:Mallinckrodt: Speaking and Teaching, Madrigal: Advisor, Natera: Advisor, Mirum: Advisor.

1577 | RIFAXIMIN MEDS TO BEDS: A RETROSPECTIVE ANALYSIS OF RIFAXIMIN FILLING TIME AND THE IMPACT ON 30-DAY READMISSION FOR HEPATIC ENCEPHALOPATHY

Daniel Cain[1] Kailey Nguyen[2] Mufaddal Jafferjee[1] Sidart Pradeep[3] Nina Kanase[1] Simran Demla[1] Bilal Khoncarly[1] Samar Taqvi[1] Sabine Itani[1] Indudeep Bedi[1] Jordan Santos[1] Caroline Gregory[1] Sanjay Shori[4] Apurva Modi[5] Shovendra Gautam[1], [1]Baylor Scott & White- All Saints Medical Center, [2]Baylor Scott & White- All Saints Medical Center I, [3]Transplant Hepatology at UT Health San Antonio, [4]Texas Christian University Burnett School of Medicine, [5]Baylor Health, Liver Consultants of Texas

Background: Hepatic encephalopathy (HE) is a well-known complication of chronic liver disease (CLD), and the non-systemic antibiotic rifaximin has been well documented in reducing this complication. The purpose of this study is to determine if the timing of rifaximin access after hospital discharge for HE impacted the 30-day readmission rates for HE. **Methods:** This is a two-center retrospective analysis within the same metroplex, using two liver transplant centers. The primary objective was to evaluate the impact of the timing for medication access to rifaximin on 30-day readmissions for hepatic encephalopathy (HE). The time intervals evaluated were: day of discharge, within 7-days of discharge, within 30-days of discharge, and never filled. Patients were selected from January 2021 to March 2024 who had HE as a primary diagnosis with their charts then manually reviewed. Exclusion criteria were applied to create study populations from each hospital (Baylor Scott & White- All Saints Medical Center in Fort Worth, TX (BAS) and Baylor Scott & White- Baylor University Medical Center in Dallas, TX (BUMC)). 192 patients from BAS and 240 patients from BUMC met inclusion criteria. Statistical analysis of the entire study cohort, BAS and BUMC Cohorts individually, and BAS vs BUMC was then done. **Results:** Rifaximin refill timing did not show statistical significance in 30-day HE related readmissions at any time point or when evaluating the study cohort as a whole or by individual site (See Table). Filling rifaximin at discharge was not associated with reduced readmission at BAS (OR 0.89, 95% CI 0.19–4.24, p = 0.70) or BUMC (OR 0.62, CI 0.24-1.59, p = 0.32). Filling rifaximin within 7 days of discharge was not associated with lower readmission (BAS: OR 1.30, CI 0.03-54.76, p = 0.81; BUMC: OR 2.23, CI 0.21-23.54, p = 0.51), although subgroup sizes were small. Likewise, filling within 30 days of discharge did not show significant impact at BAS (OR 3.44, CI 0.30-39.37, p = 0.44) or BUMC (OR 0.93, CI 0.10-8.46, p = 0.95). **Conclusion:** This study was unable to find a significant impact in the timing of rifaximin prescription access after hospital discharge on 30-day readmissions for HE across all time intervals (0-days, 7-days, 30-days, and never filled). The impact of using only transplant centers, which have additional resources, and the low power of some subgroups likely led to these results. The authors believe further evaluation incorporating non-liver transplant institutions would provide additional insight into the timing of rifaximin access and 30-day hospital readmissions. The benefits of rifaximin for HE have been well documented and a study with increased power in the above-mentioned sub-groups may provide additional insight on how timing of access plays a key role in ensuring this population has the best management and outcomes.



Disclosures: Daniel Cain:Nothing to Disclose, Kailey Nguyen:Nothing to Disclose, Mufaddal Jafferjee:Nothing to Disclose, Sidart Pradeep:Nothing to Disclose, Nina Kanase:Nothing to Disclose, Simran Demla: Nothing to Disclose, Bilal Khoncarly:Nothing to Disclose, Samar Taqvi:Nothing to Disclose, Sabine Itani: Nothing to Disclose, Indudeep Bedi:Nothing to Disclose, Jordan Santos:Nothing to Disclose, Caroline Gregory:Nothing to Disclose, Sanjay Shori:Nothing to Disclose, Apurva Modi:Nothing to Disclose, Shovendra Gautam:Nothing to Disclose.

1578 | RESPONSE TO LOW FIXED DOSE ALBUMIN FOR THE TREATMENT OF SPONTANEOUS BACTERIAL PERITONITIS: A RETROSPECTIVE ANALYSIS

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Symbols: ♦, Poster of Distinction; ★, Foundation Award Recipient

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Background: Spontaneous bacterial peritonitis (SBP) is a life-threatening condition associated with an increased risk of acute kidney injury (AKI). Current AASLD guidelines recommend high-dose albumin administration on day 1 and day 3 following SBP detection to reduce the risk of AKI; however, fluid overload may limit tolerability. At a quaternary hospital in South India, patients are treated with low-dose daily albumin due to a perceived higher occurrence of fluid overload with standard dosing, but the optimal duration of this lower dose remains unclear. This study aimed to analyze the incidence of new-onset AKI among patients with SBP treated with low-dose daily albumin for $\leq$ 3 days vs > 3 days. **Methods:** Using a retrospective cohort from 2024-2025, we identified adults admitted with SBP treated with fixed low-dose albumin (0.3 g/kg/day). Patients were grouped based on albumin duration ($\leq$3 days vs >3 days). Patients with chronic kidney disease, obstructive causes of AKI, and urinary tract infections were excluded. New onset AKI on day 5 was assessed using the KDIGO criteria. **Results:** A total of 123 patients with SBP treated with low-dose daily albumin were included in the analysis. Of these patients, 45 received low-dose albumin for $\leq$3 days and 78 received it for >3 days. Patients who received albumin for >3 days had more severe liver disease at baseline, indicated by higher rates of tense ascites (96.2% vs 80.0%, p=0.008), higher total bilirubin (6.70 vs. 3.50, p=0.006), higher INR (2.30 vs 1.87, p=0.049), and higher MELD (22.69 vs 19.51, p=0.018) and MELD-Na scores (26.49 vs. 22.38, p=0.003).New-onset AKI occurred in 4 patients in the $\leq$3 days group and 2 patients in the >3 days group (8.9% vs. 2.6%, p=0.19). SBP resolution rates (84.4% vs 74.4%, p=0.259), reported symptoms of fluid overload (4.4% vs 3.8%, p=1.000), and survival at discharge (91.9% vs. 92.3%, p= 1.000) were similar. Patients treated for >3 days had significantly longer hospital stays (6 vs 4 days, p<0.001).Lower sodium and higher baseline total bilirubin were associated with AKI at day 5 on univariate analysis. Lower sodium independently predicted mortality on multivariate analysis (OR 0.812, 95% CI 0.812-0.997, p=0.044). **Conclusion:** Patients treated with low-dose daily albumin for > 3 days and for $\leq$ 3 days had a similar rate of AKI at day 5. There was no difference in the rate of reported fluid overload symptoms. These findings suggest that prolonged courses of low-dose daily albumin in SBP patients may not provide short term clinical benefit. Prospective comparative studies are needed to evaluate the efficacy and safety of low-dose albumin administration compared to standard dosing.

Variable	Total (n=123)	Albumin ≤3 days (n=45)	Albumin >3 days (n=78)	P value
Total Bilirubin (mg/dL)	5.11 (2.33-9.66)	3.50 (1.90-5.60)	6.70 (2.91-10.61)	0.006
INR	2.25 (1.62-2.77)	1.87 (1.43-2.53)	2.30 (1.85-2.79)	0.049
Creatinine at admission (mg/dL)	0.90 ± 0.22	0.88 ± 0.20	0.90 ± 0.23	0.637
Creatinine at Day 3 (mg/dL)	0.78 (0.62-0.96)	0.78 (0.62-1.03)	0.79 (0.62-0.95)	0.885
Creatinine at Day 5 (mg/dL)	0.73 (0.61-0.91)	0.76 (0.62-0.93)	0.72 (0.60-0.91)	0.803
AKI at day 5	6 (4.9%)	4 (8.9%)	2 (2.6%)	0.190
SBP Response	96 (78.0%)	38 (84.4%)	58 (74.4%)	0.259
Ascitic fluid TC at 48 hours (/cumm)	320.00 (180.00-1100.00)	300.00 (165.00-600.00)	350.00 (200-1222.50)	0.186
Ascitic fluid neutrophils at 48 hours (%)	78.00 (50.00-89.00)	72.00 (39.50-89.50)	80.00 (55.75-87.75)	0.377
Complications of albumin	5 (4.1%)	2 (4.4%)	3 (3.8%)	1.000
Hospital stay among survivors (days)	5.00 (4.00-7.00)	4.00 (3.00-5.00)	6.00 (5.00-8.25)	<0.001
Alive at discharge	113 (91.9%)	41 (91.1%)	72 (92.3%)	1.000

Table. Baseline characteristics of hospitalized patients with cirrhosis and spontaneous bacterial peritonitis comparing patients receiving ≤3 vs > 3 days of fixed low-dose intravenous albumin

Disclosures: Dylan Nunn:Nothing to Disclose, Arun Chacko:Nothing to Disclose, Shaik Riyaz:Nothing to Disclose, Jamil Abdo:Nothing to Disclose, Uday Zachariah:Nothing to Disclose, CE Eapen:Nothing to Disclose, Ashish Goel:Nothing to Disclose, Santosh Kumar:Nothing to Disclose, Ashwani Singal:Madrigal Pharmaceuticals: Speaking and Teaching, Pleiogenix Pharmaceuticals: Stock – privately held company, Bausch Pharmaceuticals: Advisor, NIAAA: Grant/ Research Support, Up-to-Date: Royalties or patent beneficiary, Practice Point: Speaking and Teaching, Gastro Endo News: Executive role.

1579 | CT-DERIVED BODY COMPOSITION AND OUTCOMES AFTER TIPS IN CIRRHOSIS AND NON-CIRRHOTIC PORTAL HYPERTENSION: AN ALTA GROUP STUDY

Tsung-Chieh Yang[1] K. Pallav Kolli[1] Bo Fan[1] Justin Boike[2] Mike Fallon[3] Bartley Thornburg[2] Lisa VanWagner[4] Elizabeth Verna[5] Giuseppe Morelli[6] Consuelo Soldevila-Pico[6] Margarita German[7] Jennifer

Symbols: ♦, Poster of Distinction; ★, Foundation Award Recipient

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Background: The impact of computed tomography (CT)-derived body composition on outcomes after transjugular intrahepatic portosystemic shunt (TIPS) placement remains unclear, particularly in non-cirrhotic portal hypertension (PH). This study evaluated associations between CT-derived body composition and post-TIPS outcomes. **Methods:** Adults with PH undergoing TIPS placement between July 2019 and January 2025 were prospectively enrolled at 13 U.S. centers in the Advancing Liver Therapeutic Approaches (ALTA) Study Group. This sub-study included patients from five ALTA centers with baseline CT images. CT measures at L3 included skeletal muscle index (SMI), muscle attenuation, visceral adipose tissue index (VATI), subcutaneous adipose tissue index (SATI), total adipose tissue index, VATI/SATI ratio, sarcopenia, and myosteatosis. Sarcopenia was defined as SMI <50 cm²/m² in men and <39 cm²/m² in women; myosteatosis as muscle attenuation <41 HU for body mass index <25 kg/m² and <33 HU for ≥ 25 kg/m². CT images were analyzed by trained personnel blinded to outcomes. The primary endpoint was all-cause mortality, with subgroup analyses by PH etiology, TIPS indication, and sex. Secondary endpoints included any/overt hepatic encephalopathy (HE) hospitalization, post-TIPS hospitalization rates, and MELD-Na increase ≥ 5. Competing risk regression considered liver transplantation (LT)/TIPS occlusion for mortality and death/LT/TIPS occlusion for secondary time-to-event endpoints. Models adjusted for age, sex, PH etiology, history of ascites, history of HE, and baseline MELD-Na. **Results:** Among 255 patients (201 cirrhosis; 54 non-cirrhotic PH), median age was 57 years, 62.7% were male, median MELD-Na was 13, and sarcopenia prevalence was 45.9%. During a median follow-up of 25.8 months, 65 (25.5%) deaths occurred. In multivariable analysis, sarcopenia (sHR 2.04, 95% CI 1.22–3.42; $p = 0.007$) and age (sHR 1.07 per year; $p < 0.001$) independently predicted mortality, whereas myosteatosis and adipose tissue indices did not. The association between sarcopenia and mortality was consistent across PH etiologies (cirrhosis, $p = 0.007$; non-cirrhotic PH, $p = 0.010$; Figure 1), sex subgroups (male, $p = 0.004$; female, $p = 0.029$), and TIPS indications for gastrointestinal bleeding ($p = 0.031$) or portal vein thrombosis ($p = 0.002$), but not ascites ($p = 0.570$). No CT-derived body composition measure was associated with any/overt HE hospitalization, post-TIPS hospitalization rates, or MELD-Na worsening. **Conclusion:** Among CT-derived body composition measures, sarcopenia independently predicted post-TIPS mortality in both cirrhosis and non-cirrhotic PH, whereas myosteatosis and adipose tissue indices were not associated with mortality or other outcomes. Routinely acquired pre-TIPS CT may support risk stratification and identify sarcopenia as a potentially modifiable target to improve survival.



Disclosures: Tsung-Chieh Yang:Nothing to Disclose, K. Pallav Kolli:Nothing to Disclose, Bo Fan:Nothing to Disclose, Justin Boike:W. L. Gore and Associates: Grant/Research Support, Echosens: Consultant, W. L. Gore and Associates, Inc.: Consultant, Novo Nordisk: Speaking and Teaching, Mike Fallon:Nothing to Disclose, Bartley Thornburg:Nothing to Disclose, Lisa VanWagner:W.L. Gore & Associates: Grant/Research Support, Akero: Grant/Research Support, Madrigal: Grant/Research Support, Gerson Lehrman Group: Consultant, Madrigal: Advisor, Slingshot Insights: Consultant, Antheneum Partners: Consultant, Gerson Lehrman Group: Consultant, Alpha Insights: Consultant, Slingshot Insights: Consultant, Madrigal Pharmaceuticals: Grant/Research Support, W.L. Gore & Associates: Grant/Research Support, BD: Grant/Research Support, Medicolegal consulting: Consultant, Elizabeth Verna:Nothing to Disclose, Giuseppe Morelli:Nothing to Disclose, Consuelo Soldevila-Pico:Nothing to Disclose, Margarita German:Nothing to Disclose, Jennifer Lai: Nestle Nutrition Institute: Grant/Research Support, Novo Nordisk: Consultant, Genfit: Consultant, Boehringer Ingelheim: Advisor, Lipocine: Site PI, Gilead: Site PI, Insmed: Consultant, Cosmo: Advisor.

1580 | DISEASE PROGRESSION AND OUTCOMES OF ACUTE KIDNEY INJURY IN ALCOHOL-RELATED VERSUS MASH CIRRHOSIS

Karim Besir[1] Don Rockey[1], [1]Medical University of South Carolina (MUSC)

Symbols: ♦, Poster of Distinction; ★, Foundation Award Recipient

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Background: Acute kidney injury (AKI) is a common complication in patients with cirrhosis and is associated with significant morbidity and mortality. Although both alcohol-related (ETOH) and metabolic dysfunction-associated steatohepatitis (MASH) cirrhosis represent leading causes of end-stage liver disease, data comparing AKI severity, progression, and hospitalization outcomes between these etiologies remain limited. Here, we hypothesized that renal disease progression and clinical outcomes differ among patients with ETOH and MASH cirrhosis hospitalized with AKI. **Methods:** We retrospectively examined electronic health records of hospitalized patients with cirrhosis admitted to the Medical University of South Carolina (MUSC) between 2012 and 2023 with AKI defined by the Acute Kidney Injury Network (AKIN) criteria. Patients with ETOH and MASH cirrhosis were compared for baseline characteristics, renal disease progression, and hospitalization outcomes. A power calculation was performed assuming that patients with ETOH cirrhosis would have greater AKI severity reflected by at least a 0.5 mg/dL greater delta creatinine (peak creatinine minus baseline creatinine) compared to patients with MASH cirrhosis. This yielded a total requirement for 163 patients, including 112 and 51 patients with ETOH and MASH cirrhosis, respectively. Multivariable logistic regression analyses were performed using SPSS. **Results:** A total of 180 patients with cirrhosis admitted with AKI were included - 116 patients with ETOH cirrhosis, 52 patients with MASH cirrhosis, and 12 patients with other cirrhosis etiologies. Patients with MASH cirrhosis were older and more frequently had diabetes mellitus and CKD (**Table 1**). Patients with ETOH cirrhosis were more commonly male. Baseline creatinine was higher among patients with MASH cirrhosis (1.2 vs 1.0 mg/dL, $p = 0.026$), while patients with ETOH cirrhosis had higher admission creatinine (2.6 vs 2.1 mg/dL, $p = 0.200$) and peak creatinine (3.2 vs 2.5 mg/dL, $p = 0.046$). In addition, patients with ETOH cirrhosis had a significantly greater change in creatinine from baseline to peak levels compared with patients with MASH cirrhosis (2.2 vs 1.3 mg/dL, $p = 0.043$). Rates of intensive care unit admission (43% vs 26%, $p = 0.183$) and in-hospital mortality (28% vs 21%, $p = 0.657$) were higher among patients with ETOH cirrhosis following regression analysis, though these differences were not statistically significantly different. **Conclusion:** Among hospitalized patients with cirrhosis and AKI, patients with ETOH cirrhosis had significantly greater progression of renal dysfunction, reflected by a larger increase in creatinine from baseline to peak levels, than patients with MASLD. These findings may reflect the systemic and nephrotoxic effects of alcohol, including oxidative stress and hemodynamic dysregulation, which may contribute to a more severe AKI phenotype and worse clinical course in this population.

Table 1. Characteristics and Outcomes Among Patients with ETOH vs MASH Cirrhosis

Variable	ETOH (n=116)	MASH (n=52)	p-value
Age (years ± SD)	58 ± 11.0	67 ± 11	<0.001
BMI (kg/m² ± SD)	26 ± 5	28 ± 5	0.100
Females (%)	21 (19)	24 (46)	0.023
Diabetes mellitus (%)	23 (20)	33 (64)	<0.001
Chronic kidney disease (%)	12 (10)	13 (25)	0.032
Ascites (%)	74 (64)	30 (57)	0.680
Hepatic encephalopathy (%)	38 (33)	15 (29)	0.868
ICU admission (%)	50 (43)	13 (26)	0.183
Baseline creatinine (mg/dL ± SD)	1.0 ± 0.3	1.2 ± 0.3	0.026
Admission creatinine (mg/dL ± SD)	2.6 ± 2.1	2.1 ± 1.7	0.200
Peak creatinine (mg/dL ± SD)	3.2 ± 2.2	2.5 ± 1.7	0.046
Delta creatinine (mg/dL ± SD)	2.2 ± 2.2	1.3 ± 1.7	0.043
In-hospital mortality (%)	33 (28)	11 (21)	0.657

Disclosures: Karim Besir:Nothing to Disclose, Don Rockey:Nothing to Disclose..

1581 | BETA-BLOCKER UTILIZATION IN U.S. VETERANS WITH CIRRHOSIS AND CLINICALLY SIGNIFICANT PORTAL HYPERTENSION

Claire Durkin[1] Vera Yakovchenko[2] Patrick Spoutz[3] Sumedha Chhatre[4] Shari Rogal[1], [1]University of Pittsburgh, [2]VA Pittsburgh Healthcare System, [3]U.S. Department of Veterans Affairs, [4]Philadelphia Corporal Michael J. Crescenz VA Medical Center

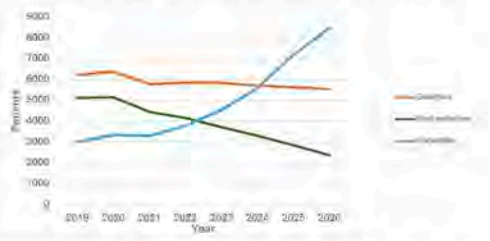
Background: Recent AASLD guidelines and Baveno VII criteria recommend carvedilol for clinically significant portal hypertension (CSPH) in cirrhosis due to greater portal pressure reduction, hepatic decompensation prevention, and potential survival benefit compared to traditional non-selective beta blockers (BBs). However, its adoption into routine clinical practice remains poorly characterized. **Methods:** This retrospective cohort study used Veterans Health Administration (VA) data to evaluate adults (≥ 18 years) with cirrhosis and CSPH from 2019–2025. Cirrhosis was identified using ≥ 1 inpatient or ≥ 2 outpatient ICD-10 codes. CSPH was defined by platelet count $< 150 \times 10^9$/L. Patients with prior liver transplant or transjugular intrahepatic portosystemic shunt were excluded. Clinical and demographic characteristics were compared by BB exposure group based on any prescription fill: carvedilol, non-selective BB (propranolol, nadolol, or labetalol), selective BB, or no BB. Multivariable logistic regression identified factors associated with carvedilol receipt, adjusting for age, sex, race/ethnicity, Charlson comorbidity index, cirrhosis etiology, Model for End-Stage Liver Disease (MELD) 3.0, ascites, encephalopathy, variceal hemorrhage, VA facility complexity level, gastroenterology (GI) visit within 1 year, and esophagogastroduodenoscopy (EGD) within 3 years. **Results:** From 2019-2025, Veterans with

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cirrhosis and CSPH receiving carvedilol increased nearly 3-fold (2,998 to 8,487), while non-selective BB use declined by over half (5,128 to 2,359; **Figure**). In contrast, selective BB and no BB use remained stable, as did annual EGD rates (23.9-29.9%). Although MELD scores were similar (range 9-11), history of hepatic decompensation was more frequent among patients receiving non-selective BB (66%) versus carvedilol (44%), selective BB (36%), or no BB (40%), including ascites, encephalopathy, and variceal bleeding (all $p < 0.001$). Metabolic dysfunction-associated liver disease (MASLD) was more common among patients receiving carvedilol (20%) and selective BB (18%) compared to non-selective BB (13%; $p < 0.001$). Carvedilol and non-selective BB recipients were more likely to receive GI care and EGD screening (both $p < 0.001$). Factors associated with carvedilol receipt included older age, male sex, Black race, greater comorbidities, MASLD, higher MELD, variceal bleeding, higher VA facility complexity, and GI consultation, whereas encephalopathy and recent EGD were associated with lower odds of carvedilol receipt (all $p < 0.05$, **Figure**). **Conclusion:** Carvedilol use rapidly increased and surpassed non-selective BB use among Veterans with cirrhosis and CSPH over the past 5 years, suggesting early adoption of evidence-based practice. Variation in carvedilol use by clinical characteristics and healthcare utilization highlights opportunities to improve implementation of CSPH management across VA settings.

Figure:
(A) Temporal trends in beta blocker utilization among U.S. Veterans with cirrhosis and portal hypertension



(B) Multivariable logistic regression model for carvedilol utilization among U.S. Veterans with cirrhosis and portal hypertension

	Adjusted Odds Ratio	95% Confidence Interval	p-value
Age	1.00	0.99 – 1.00	0.023
Sex (male)	1.29	1.19 – 1.39	<0.001
Race/ethnicity			
Non-Hispanic White	Reference	Reference	Reference
Non-Hispanic Black	1.28	1.23 – 1.34	<0.001
Hispanic	1.04	0.99 – 1.09	0.113
Other	1.09	1.02 – 1.17	0.008
Charlson comorbidity index	1.09	1.09 – 1.10	<0.001
Cirrhosis etiology			
MASH/MASLD	Reference	Reference	Reference
Alcohol	0.79	0.76 – 0.82	<0.001
Hepatitis C	0.74	0.71 – 0.77	<0.001
Hepatitis B	0.71	0.57 – 0.86	0.001
Other	0.87	0.82 – 0.92	<0.001
MELD 3.0 (per point)	1.03	1.03 – 1.04	<0.001
Ascites	1	0.97 – 1.04	0.790
Encephalopathy	0.88	0.85 – 0.91	<0.001
Variceal bleeding	1.4	1.34 – 1.47	<0.001
VA Facility Complexity			
1a	Reference	Reference	Reference
1b	1	0.96 – 1.04	0.945
1c	0.84	0.81 – 0.87	<0.001
2	0.86	0.81 – 0.92	<0.001
3	0.91	0.85 – 0.97	0.006
GI visit within the past year	1.96	1.90 – 2.02	<0.001
EGD within the past 3 years	0.96	0.93 – 0.99	0.006

Abbreviations: EGD=esophagogastroduodenoscopy, GI=gastroenterology, MASH=metabolic dysfunction-associated steatohepatitis, MASLD=metabolic dysfunction-associated steatotic liver disease, MELD=Model for End-Stage Liver Disease, VA=Veterans Health Administration

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1582 | CAP-ASSISTED ENDOSCOPIC POLIDOCANOL SCLEROTHERAPY FOR BLEEDING INTERNAL HEMORRHOIDS IN CIRRHOSIS: LONG-TERM RESULTS OF A RANDOMIZED TRIAL OF LIQUID VERSUS FOAM

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Background: Lower gastrointestinal bleeding in cirrhosis is frequently multifactorial, with internal hemorrhoids, rectal varices, and portal hypertensive colopathy often coexisting. Evidence for hemorrhoid-directed therapy in portal hypertension remains limited. We evaluated the safety, hemostatic efficacy, and long-term outcomes of cap-assisted endoscopic sclerotherapy using liquid versus foam polidocanol in cirrhotic patients with bleeding internal hemorrhoids. **Methods:** In this single-center prospective randomized trial, adults with cirrhosis/portal hypertension and anorectal bleeding were screened between November 2023 and July 2025. Patients with confirmed bleeding internal hemorrhoids were randomized 1:1 to cap-assisted endoscopic sclerotherapy with either 1.5% liquid polidocanol or Tessari-method foam polidocanol. Injections were delivered submucosally using a standardized left-posterior-right-anterior sequence under cap visualization. The primary endpoint was complete bleeding cessation by day 7. Secondary endpoints included 8-week bleeding control, post-procedure pain, rescue transfusion/therapy, adverse events, and long-term rebleeding during follow-up until May 2026. **Results:** Of 180 screened patients, internal hemorrhoids were identified in 103 patients, 57%. Twenty-five patients were randomized: foam $n = 12$ and liquid $n = 13$. Coexisting rectal varices were present in 8/25 patients, 32%, and portal hypertensive colopathy in 13/25, 52%, highlighting the diagnostic complexity of anorectal bleeding in cirrhosis. Day-7 bleeding cessation occurred in 22/25 patients, 88% overall: 10/12, 83.3%, with foam and 12/13, 92.3%, with liquid; $p = 0.42$. At 8 weeks, bleeding control remained high at 90% among evaluable patients, with no early rebleeding in the liquid arm. Immediate post-procedure pain was higher with foam; $p = 0.028$. Rescue transfusion was numerically more frequent with foam, OR 5.14; 95% CI 0.46–56.9. During extended follow-up censored in May 2026, median follow-up was

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20 months. Long-term outcomes favored liquid polidocanol, with more durable bleeding control and fewer late rebleeding events compared with foam. No major procedure-related adverse event, ulcer-related bleeding, sepsis, or hepatic decompensation occurred. **Conclusion:** Cap-assisted endoscopic polidocanol sclerotherapy achieved rapid hemostasis and durable bleeding control in cirrhotic patients with diagnostically complex anorectal bleeding. Liquid polidocanol was associated with lower post-procedure pain and more favorable long-term bleeding outcomes than foam. These findings support liquid CAES as a standardized, minimally invasive treatment option for bleeding internal hemorrhoids in portal hypertension and justify validation in larger multicenter trials.

Table

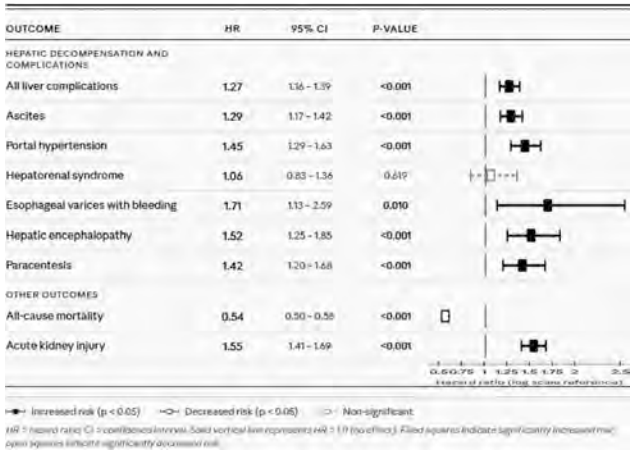
Per protocol analysis	Total (N = 25)	Foam sclerotherapy group (N = 12)	Liquid sclerotherapy group (N = 13)	Odd's ratio (CI)
Complete bleeding cessation at 7 days	22 (88%)	10 (83.4%)	12 (92.3%)	0.42 (0.03-5.30)
Complete bleeding cessation till 4 weeks	19/24 (79.2%)	9/11 (82%)	10/13 (77%)	0.74 (0.10-5.5)
Complete bleeding cessation till 8 weeks	19/21 (90%)	9/11 (82%)	10/10 (100%)	0.18 (0.008-4.27)

Disclosures: Srajit Singh:Nothing to Disclose, Vikram Bhatia:Nothing to Disclose, Ishank Johri:Nothing to Disclose.

1583 | GUIDELINE-DIRECTED MEDICAL THERAPY IN PATIENTS WITH CONCURRENT HFREF AND COMPENSATED CIRRHOSIS: REAL-WORLD OUTCOMES

Basil Jalamneh[1] Abdallah Hatem[2] Mohammed Alabbas[3] Mohamed Noor AbuHammor[1] Aravinthan Vignarajah[1] Omar Sims[1] Dian Chiang[1], [1]Cleveland Clinic Foundation, [2]Virtua Health, [3]Cleveland Clinid Foundation

Background: Patients with cirrhosis have been systematically excluded from landmark heart failure trials, leaving a critical evidence gap regarding the safety and hepatic consequences of guideline-directed medical therapy (GDMT) in this population. Despite concerns about renal dysfunction, hypotension, and portal hemodynamic perturbation, GDMT is increasingly prescribed in patients with compensated cirrhosis and heart failure with reduced ejection fraction (HFrEF). Real-world data on liver-related outcomes in this context are lacking. **Methods:** We conducted a retrospective comparative effectiveness study using the TriNetX US Collaborative Network (66 healthcare organizations) to evaluate adults with HFrEF and compensated cirrhosis without prior hepatic decompensation. Patients receiving full or near-complete GDMT ($\geq$3 of 4 pillars) were compared to those receiving incomplete or no GDMT ($\leq$2 pillars). Propensity score matching (1:1) balanced demographics, cardiovascular comorbidities, and hepatic and renal laboratory parameters. The observation period was 12 months. Primary outcomes included a composite of liver-related complications (ascites, hepatic encephalopathy [HE], hepatorenal syndrome [HRS], and variceal bleeding) and paracentesis. Secondary outcomes included acute kidney injury (AKI), hepatocellular carcinoma (HCC), and all-cause mortality. **Results:** The analysis yielded 5,052 matched patients in each cohort. Compared with incomplete or no GDMT, full or near-complete GDMT was associated with significantly higher rates of composite liver complications (HR 1.26; 95% CI 1.15–1.38; $p < 0.001$), ascites (HR 1.28; 95% CI 1.17–1.42), HE (HR 1.52; 95% CI 1.24–1.85), portal hypertension (HR 1.44; 95% CI 1.28–1.62), esophageal variceal bleeding (HR 1.71; 95% CI 1.13–2.58), AKI (HR 1.54; 95% CI 1.41–1.69), and need for paracentesis (HR 1.41; 95% CI 1.19–1.68). Risk of HRS did not differ significantly between groups (HR 1.06; 95% CI 0.83–1.35). Conversely, full or near-complete GDMT was associated with substantially lower all-cause mortality (HR 0.53; 95% CI 0.49–0.58; $p < 0.001$) and a lower incidence of HCC. Figure-1. **Conclusion:** In this large real-world cohort of patients with compensated cirrhosis and HFrEF, full or near-complete GDMT was associated with increased rates of hepatic decompensation events, portal hypertensive complications, and AKI, yet conferred a significant survival benefit. These findings reveal a clinically important trade-off between cardiac optimization and hepatic risk in this vulnerable population. They underscore the need for individualized, multidisciplinary management and prospective studies to define the optimal therapeutic approach for patients with concomitant HFrEF and cirrhosis. The survival benefit despite the hepatic risk observed could be related to improved cardiovascular outcomes, but more investigation is warranted.



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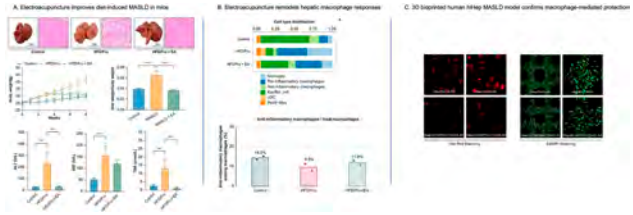
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Disclosures: Basil Jalamneh:Nothing to Disclose, Abdallah Hatem:Nothing to Disclose, Mohammed Alabbas:Nothing to Disclose, Mohamed Noor AbuHammor:Nothing to Disclose, Aravinthan Vignarajah:Nothing to Disclose, Omar Sims:Nothing to Disclose, Dian Chiang:Nothing to Disclose.

1584 | EUS-GUIDED DIRECT PORTAL PRESSURE GRADIENT (EUS-PPG) CORRELATES WITH MEANINGFUL LONG-TERM CLINICAL OUTCOMES

Tyler Doty[1] Don Rockey[2] Lindi Newton[1] Kevin Pak[1] Jerome Edelson[1], [1]Brooke Army Medical Center, [2]Medical University of South Carolina

Background: The hepatic venous pressure gradient (HVPG) has long been used a prognostic indicator for predicting variceal hemorrhage (VH), decompensation, and other clinical outcomes. EUS-guided direct portal pressure gradient (EUS-PPG) allows for direct measurements of portal pressure. Data correlating the PPG to long-term clinical outcomes is lacking. We aimed to characterize the relationship between PPG and clinical outcomes. **Methods:** We retrospectively evaluated consecutive patients at our facility who underwent EUS-PPG measurement to evaluate the severity of liver disease from 2021-2025. Extensive clinical data were abstracted, including demographics, liver function tests, pressure measurements, additional interventions, and adverse events. Outcomes over a 4-year follow-up period, including liver decompensation events such as hepatic encephalopathy (HE), VH, and ascites, hospitalizations, and initiation or changes to non-selective beta blocker (NSBB) therapy were recorded. We also evaluated whether PPG measurements lead to initiation or changes in medical management as well as any directly visualized disease progression noted on endoscopy such as new or worsening esophageal or gastric varices. **Results:** A total of 57 patients underwent EUS-PPG during the study period. The mean age was 62, and women made up 49% of the cohort. 29 patients had cirrhosis, with 5 diagnosed post-procedure. The most common cause of liver disease was MASLD. At the time of PPG measurement, 24 of 29 with cirrhosis were compensated. 21 patients had endoscopic evidence of portal hypertension (pHTN), including 14 with portal hypertensive gastropathy, 7 with esophageal varices, and 1 with gastric varices. The mean PPG in patients with endoscopic evidence of pHTN was 8.4 compared to 4 in those without pHTN. 10 patients had varices at time of EUS-PPG, and the mean PPG was 9mmHg. 12 patients were initiated on NSBBs or changed dosage after EUS-PPG. There were 7 decompensations during the 4-year follow up period after PPG measurement, including 4 patients with worsening ascites, 2 with HE, and 3 patients with VH. Patients with higher PPG values were more likely to decompensate while those with lower values less likely to decompensate (**Figure**). Higher MELD-NA, APRI, and FIB-4 scores directly correlated with higher mean EUS-PPG ($p = 0.037$). A total of 5 cirrhotics (17%) died during the 4-year follow up period. The mortality did not correlate with PPG. **Conclusion:** In patients with underlying liver disease, EUS-PPG correlates with meaningful clinical features, including markers of fibrosis and MELD-Na. PPG values also correlated with clinical outcomes, including decompensation events.



Disclosures: Tyler Doty:Nothing to Disclose, Don Rockey:Nothing to Disclose, Lindi Newton: Nothing to Disclose, Kevin Pak:Ipsen: Advisor, Jerome Edelson:Nothing to Disclose.

1585 | EFFECTIVENESS OF TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT IN IMPROVING CLINICAL OUTCOMES OF PATIENTS WITH HEPATORENAL SYNDROME: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Hepatorenal syndrome (HRS) is a life-threatening complication in patients with cirrhosis with limited treatment options. Although transjugular intrahepatic portosystemic shunt (TIPS) may serve as a salvage or alternative therapy for portal hypertension-

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related complications, its role in HRS has not been clearly established. This study aimed to evaluate the effects of TIPS on renal function and survival in patients with HRS through a systematic review and meta-analysis. **Methods:** A comprehensive literature search was conducted in PubMed, Embase, the Cochrane Library, and KoreaMed from inception to July 14, 2025, to identify studies reporting outcomes of TIPS in patients with HRS. The primary outcome was changes in renal function, assessed by serum creatinine (sCr) and urine output. Secondary outcomes included in-hospital mortality and survival rates at 3, 6, and 12 months. Pooled estimates were calculated using random-effects models. **Results:** Sixteen studies were included, comprising 10 single-arm and 6 comparative studies. Following TIPS placement, renal function improved significantly, with a mean reduction inserum creatinine of 1.07 mg/dL (95% CI, −1.45 to −0.70) and a mean increase in urine output of 1,007.14 mL (95% CI, 620–1,395). TIPS was associated with a lower risk of in-hospitalmortality than non-TIPS management (OR 0.50; 95% CI, 0.33–0.77). The pooled survival rates at 3, 6, and 12 months were 85%, 77%, and 59%, respectively. Complications werevariably reported across studies, and hepatic encephalopathy was the most commonly reported adverse event. **Conclusion:** TIPS was associated with improved renal function and reduced in-hospital mortality in selected patients with HRS.
Disclosures: Yeonjung Ha:Nothing to Disclose, Young Chang:Nothing to Disclose, Do Seon Song:Nothing to Disclose.

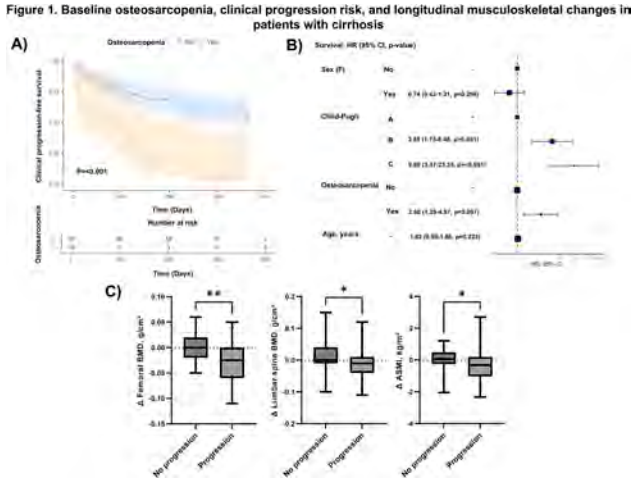
1586 | BASELINE OSTEOSARCOPENIA AND LONGITUDINAL MUSCULOSKELETAL DECLINE ARE ASSOCIATED WITH CLINICAL PROGRESSION IN CIRRHOSIS

Anaisa Carranza-Carrasco[1] Osvely Méndez-Guerrero[2] Yesica Meraz Arredondo[1] Rodrigo Guerrero-Guerrero[1] Claudia López-López[1] Fabiola M Del Razo-Olvera[1] Alma Estanes-Hernández[1] Graciela Castro-Narro[3] Nalu Navarro-Alvarez[4], [1]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, [2]Instituto Nacional de Ciencias Medicas y Nutrición Salvador Zubiran, [3]Hospital Médica Sur, Ciudad de México. Instituto Nacional de Ciencias Médicas y Nutrición, [4]University of Colorado Anschutz Medical Campus/ Instituto Nacional de Ciencias Médicas y Nutrición

Background: Clinical progression in cirrhosis is often assessed by liver disease severity, but patients with similar hepatic function can follow very different clinical trajectories. Loss of bone and skeletal muscle may capture a broader state of systemic vulnerability that is not fully reflected by conventional liver scores. Osteosarcopenia, defined by the coexistence of osteoporosis and sarcopenia, may therefore identify patients at higher risk for decompensation and death. We evaluated whether baseline osteosarcopenia was associated with clinical progression in cirrhosis and whether patients who progressed had greater longitudinal loss of bone density (BMD) and skeletal muscle mass. **Methods:** We conducted a prospective cohort study of patients with cirrhosis followed for one year. Clinical progression was defined as first decompensation, further decompensation, or death; liver transplantation was treated as a censoring event. Baseline liver disease severity was assessed using Child-Pugh classification. Baseline osteosarcopenia and longitudinal musculoskeletal changes were evaluated by DXA. Clinical progression-free survival was evaluated using Kaplan-Meier curves and the log-rank test. Cox proportional hazards regression was used to assess the association between baseline osteosarcopenia and clinical progression, adjusted for age, sex, and Child-Pugh class. In the subgroup with follow-up DXA assessment, changes in femoral BMD, lumbar spine BMD, and appendicular skeletal muscle index (ASMI) were compared by progression status. **Results:** A total of 100 patients were included, of whom 53 developed clinical progression during follow-up. Baseline osteosarcopenia was associated with lower clinical progression-free survival (log-rank $p < 0.001$) and remained independently associated with clinical progression after adjustment for age, sex, and Child-Pugh class (HR 2.50, 95% CI 1.29-4.87; $p = 0.007$). Patients who progressed were older than those who did not (56 [50-62] vs. 53 [45.5-59.5] years; $p = 0.045$), while sex distribution was similar. Alcohol-related cirrhosis was more frequent among patients with progression (26.42% vs. 6.38%; $p = 0.013$). Patients who progressed also had more advanced liver disease at baseline, with fewer Child-Pugh A patients and more Child-Pugh B/C patients ($p < 0.001$). Among patients with follow-up DXA ($n = 75$), clinical progression was accompanied by greater declines in femoral BMD, lumbar spine BMD, and ASMI (Figure 1). **Conclusion:** Osteosarcopenia was independently associated with clinical progression and lower progression-free survival in patients with cirrhosis. Patients who progressed also had greater longitudinal loss of bone density and skeletal muscle mass. Bone and muscle assessment may add clinically useful information to progression risk assessment in cirrhosis.

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1587 | REAL-WORLD EVALUATION OF A MULTIMODAL SYMPTOM-DIRECTED CARE STRATEGY FOR MUSCLE CRAMPS IN AMBULATORY PATIENTS WITH CIRRHOSIS

Manasa Alla[1] Anand Kulkarni[2] Mithun Sharma[1] Padaki Nagaraja Rao[1] Sowmya T R[1] Shantan Venishetty[1], [1]AIG hospitals, [2]Asian Institute of Gastroenterology

Background: Muscle cramps are common in cirrhosis and are frequently associated with impaired sleep, frailty, and reduced quality of life. Existing therapeutic data are limited and largely focused on isolated pharmacological interventions. We evaluated the effect of a structured multimodal symptom-directed intervention on muscle cramps and patient-centered outcomes in ambulatory cirrhosis patients. **Methods:** This retrospective study included adult ambulatory patients with clinically or radiologically diagnosed cirrhosis and clinically significant muscle cramps attending a tertiary care hepatology outpatient department between July 2025 and February 2026. Patients with overt hepatic encephalopathy grade ≥ 2, active infection, severe renal dysfunction, hepatocellular carcinoma, or severe neurological illness were excluded. Patients received a 12-week multimodal intervention comprising taurine 3 g/day, L-carnitine 1.2–1.8 g/day, dietary protein optimization, bedtime snack advice, and counselling for mild resistance exercises. Baseline demographic and clinical parameters, frailty assessment (SARC-F and chair-stand testing), and sleep quality using Pittsburgh Sleep Quality Index (PSQI) were recorded. Primary outcome was change in muscle cramp frequency and severity at 12 weeks. Secondary outcomes included changes in sleep quality, frailty parameters, falls, and patient-reported functional status **Results:** A total of 50 patients were included with a mean age of 52.6 ± 10.9 years; 70% were male. Alcohol-related liver disease (41%) and MASLD (29%) were the predominant etiologies. Ascites was present in 48% and refractory ascites in 31% of patients. Baseline poor sleep quality (PSQI >5) and frailty were present in 68% and 36% of patients, respectively. At 12 weeks, median weekly cramp frequency reduced from 5 (IQR 4–7) to 2 (IQR 1–4) episodes/week ($p<0.001$), while median cramp severity score improved from 7 (IQR 6–8) to 3 (IQR 2–5) ($p<0.001$). Overall, 72% of patients achieved $\geq 50\%$ reduction in cramp frequency. Mean PSQI scores improved significantly from 10.2 ± 3.1 to 6.1 ± 2.8 ($p<0.001$), with reduction in nocturnal cramp-related awakenings from 64% to 29% ($p<0.001$). Significant improvement was also observed in frailty measures, with mean SARC-F scores improving from 4.1 ± 1.2 to 2.9 ± 1.1 ($p=0.01$). Patients adherent to both supplementation and resistance exercise demonstrated greater symptomatic improvement compared to partially adherent patients (78% vs 46%, $p=0.02$).No major treatment-related adverse events were observed. Mild gastrointestinal intolerance occurred in 8% of patients and did not require discontinuation **Conclusion:** A multimodal symptom-directed intervention integrating taurine, L-carnitine, nutritional optimization, and resistance exercise was associated with significant improvement in muscle cramp burden, sleep quality, and functional status in ambulatory patients with cirrhosis.

Disclosures: Manasa Alla:Nothing to Disclose, Anand Kulkarni:Nothing to Disclose, Mithun Sharma:Nothing to Disclose, Padaki Nagaraja Rao:Nothing to Disclose, Sowmya T R:Nothing to Disclose, Shantan Venishetty: Nothing to Disclose.

1588 | ADVERSE EFFECTS OF ALBUMIN THERAPY IN CIRRHOSIS-ASSOCIATED ACUTE KIDNEY INJURY

Karim Besir[1] Don Rockey[1], [1]Medical University of South Carolina (MUSC)

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Background: Acute kidney injury (AKI) is a frequent and serious complication in cirrhosis, associated with high morbidity and mortality. Albumin is well established in the management of hepatorenal syndrome (HRS-AKI); however, its role in non-HRS AKI remains unclear, with prior studies showing conflicting results regarding renal recovery and survival. Given these inconsistencies and the lack of reliable data, we evaluated the association between albumin therapy and clinical outcomes among hospitalized cirrhotic patients with AKI. **Methods:** This retrospective cohort study used the TriNetX Global Collaborative Network, including adults ≥18 years with a diagnosis of cirrhosis who were hospitalized with AKI. Patients were identified and stratified into two cohorts: Cohort 1 (N = 42,568) did not receive albumin, and Cohort 2 (N = 23,506) received albumin. Propensity score matching was performed to balance demographics, comorbidities, concurrent medications, and relevant laboratory values between groups. The index event was defined as the onset of AKI, and patients with HRS-AKI and/or clinical outcomes prior to the index event were excluded. The primary outcome was mortality within 30 days of hospital admission, and secondary outcomes included the development of pulmonary edema, heart failure, a composite of liver-related complications (spontaneous bacterial peritonitis (SBP), hepatic encephalopathy (HE), ascites, esophageal variceal bleeding (EVB)) and incident infection within 30 days of hospital admission. **Results:** A total of 87,514 patients with cirrhosis hospitalized with acute kidney injury (AKI) were identified (mean age 66 ± 13 years). Among these, 25,836 patients received albumin, 46,031 did not receive albumin, and exposure data were not available on the remaining patients. After propensity score matching, two well-balanced cohorts were generated (N = 22,808 in each). Albumin use in patients hospitalized with AKI was associated with a significantly higher 30-day mortality compared to no albumin (31% vs 17%; OR 2.29; $p < 0.0001$), as well as higher rates of in-hospital pulmonary edema, heart failure, and infection (**Table 1**). Additionally, liver-related complications, including SBP, HE, ascites, and EVB were significantly higher in the albumin group (14% vs 5%; OR 3.1; $p < 0.0001$). In addition, 1-year mortality was 46% in the albumin group vs. 28% in the no-albumin group (OR 2.21; $p < 0.0001$). **Conclusion:** Our results show that patients who received albumin during hospitalization for AKI experienced higher 30-day mortality rates, pulmonary edema, heart failure, liver-related complications, and infections despite rigorous matching. These findings suggest that albumin should be used cautiously in patients with cirrhosis and AKI.

Table 1. Outcomes

	No Albumin* N (%)	Albumin N (%)	Odd's ratio (CI)	p-value
Pulmonary edema	400 / 21,661 (2)	996 / 20,722 (5)	2.68 (2.32–3.11)	<0.0001
Heart failure	316 / 18,316 (2)	474 / 18,024 (3)	1.54 (1.33–1.78)	<0.0001
Any liver complication	726 / 14,042 (5)	1398 / 9,674 (14)	3.10 (2.82–3.41)	<0.0001
Infection*	584 / 8,267 (7)	778 / 7,239 (11)	1.59 (1.43–1.77)	<0.0001
30-day mortality	3,589 / 21,566 (17)	6,971 / 22,195 (31)	2.29 (2.19–2.40)	<0.0001
1-year mortality	5,430 / 19,492 (28)	9,264 / 20,104 (46)	2.21 (2.12–2.31)	<0.0001

*Denominator totals vary because some patients had incomplete data or were lost to follow-up.
*Infections included SBP, pneumonia, UTI, skin/soft tissue, and bacteremia

Disclosures: Karim Besir:Nothing to Disclose, Don Rockey:Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose.

1589 | COMPARATIVE RISKS OF GABAPENTIN VERSUS OPIOIDS AND NSAIDS IN VETERANS WITH CIRRHOSIS: HARM TRADE-OFFS FROM A TARGET TRIAL EMULATION

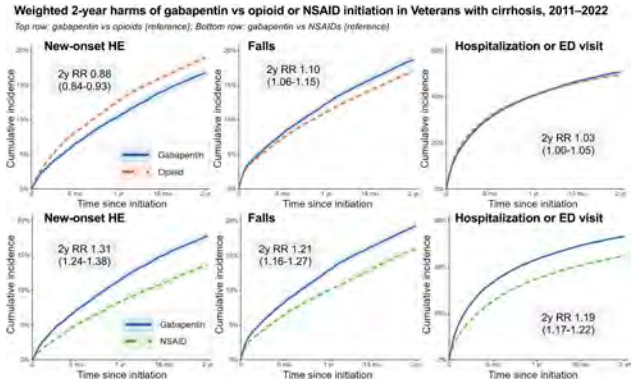
Jessica Rubin[1] Rebecca Loeb[2] Catherine Lee[2] Hui Shen[3] Katherine Hoggatt[1] Salomeh Keyhani[1] Jennifer Lai[2], [1]Center for Data to Discovery and Delivery Innovation (3DI); University of California, San Francisco, [2]University of California, San Francisco, [3]San Francisco VA Health Care System; University of California, San Francisco

Background: Up to 80% of patients with cirrhosis suffer from chronic pain, but every analgesic class carries meaningful risk. Amid efforts to reduce opioid use, gabapentin prescribing has risen sharply, now reaching up to a quarter of patients with cirrhosis. Gabapentin's central nervous system (CNS) harms (e.g., falls, sedation) are increasingly recognized in high-risk groups such as older adults but remain understudied in cirrhosis, where renal impairment, polypharmacy, and impaired neurocognitive reserve may heighten susceptibility. Without cirrhosis-specific comparative data, it remains unclear whether rising gabapentin use reflects safer prescribing or a new source of harm. **Methods:** Using SOOTHE (Safety and Outcomes related to Opioids and other Therapeutics in End-stage liver disease), a national cohort of Veterans with cirrhosis, we emulated two target trials with a new-user, active-comparator design, comparing gabapentin initiation to opioids (primary) and NSAIDs (secondary). Eligible Veterans

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were ≥18 years with cirrhosis and chronic pain. For each analysis, index date was the first qualifying fill after a 12-month washout of both drugs in that comparison; those initiating both within 14 days were excluded. Separate propensity models per comparison were used to estimate stabilized IPTW. By intention-to-treat, we estimated weighted 2-year cumulative incidence and relative risks (RR) for new hepatic encephalopathy (HE; among those without baseline HE), falls, and hospitalization or ED visit, treating death and transplant as competing events. **Results:** We identified 14,448 gabapentin and 31,312 opioid initiators, and 18,438 gabapentin and 20,563 NSAID initiators. In the primary comparison, median age was 64y, 96% were male, 43% had ascites, and 17% prior HE; median MELD 3.0 was 11. After weighting, all measured covariates were balanced (SMDs <0.1), despite large pre-weighting differences in disease severity and comorbidity. Versus opioid initiators, gabapentin initiators had a lower 2-year risk of new HE (16.8% vs 19.0%; RR 0.88, 0.84-0.93) but a higher fall risk (18.7% vs 16.9%; RR 1.10, 1.06-1.15); hospitalization was similar (RR 1.03, 1.00-1.05). Versus NSAID initiators, gabapentin initiators had a higher risk of falls, HE, and hospitalization (RRs 1.19-1.31) **(Fig)** . **Conclusion:** Despite its rising use, gabapentin was not a uniformly safer analgesic among Veterans with cirrhosis and chronic pain. Gabapentin initiation carried higher fall risk than both opioid and NSAID initiation, consistent with its known CNS harms; it conferred lower HE risk than opioids, which are recognized HE precipitants. Weighting balanced measured confounders but cannot fully account for unmeasured confounding (e.g., frailty, functional status, pain severity). Yet the consistent excess in falls across comparators supports genuine gabapentin-related harm and cautions against reflexive substitution of gabapentin for opioids.



Disclosures: Jessica Rubin:Nothing to Disclose, Rebecca Loeb:Nothing to Disclose, Catherine Lee: Nothing to Disclose, Hui Shen:Nothing to Disclose, Katherine Hoggatt:Nothing to Disclose, Salomeh Keyhani:Nothing to Disclose, Jennifer Lai:Nestle Nutrition Institute: Grant/Research Support, Novo Nordisk: Consultant, Genfit: Consultant, Boehringer Ingelheim: Advisor, Lipocine: Site PI, Gilead: Site PI, Insmed: Consultant, Cosmo: Advisor.

1590 | PREDICTORS OF SEVERE FALLS IN A MULTICENTER NORTH AMERICAN COHORT OF OUTPATIENTS WITH CIRRHOSIS

Puneeta Tandon[1] Jacqueline O'Leary[2] Jennifer Lai[3] K Rajender Reddy[4] Florence Wong[5] Guadalupe Garcia-Tsao[6] Scott Biggins[7] Philip Vutien[8] Hugo Vargas[9] Patrick Kamath[10] Ana Teresa Limon-Miro[1] Brian Bush[11] Scott Silvey[11] Jasmohan Bajaj[11], [1]University of Alberta, [2]Dallas VA Medical Center, [3]University of California San Francisco, [4]University of Pennsylvania, [5]University of Toronto, [6]Yale University, [7]University of Pittsburgh, [8]University of Washington, [9]Mayo Clinic Arizona, [10]Mayo Clinic, Rochester, [11]Virginia Commonwealth University

Background: Falls are increasingly recognized as a major contributor to morbidity and mortality in patients with cirrhosis. Prior studies demonstrate strong associations between minimal hepatic encephalopathy, sarcopenia, frailty, cognitive impairment, and fall risk. The North American Consortium for the Study of End-Stage Liver Disease (NACSELD) is a prospective cohort of outpatients with compensated and decompensated cirrhosis recruited from 11 centers across North America. This cohort provides a unique opportunity to examine falls in a large, multicenter sample with prospectively collected, multidimensional data. **Methods:** Patients were assessed at baseline for a history of severe falls (those requiring hospitalization or resulting in a fracture) in the three months prior to enrollment. Baseline variables were summarized and compared between patients with and without a history of severe falls using the Wilcoxon rank-sum test or Pearson's chi-squared test as appropriate. Multivariable logistic regression models were fit to identify independent predictors of severe falls, including all variables that were statistically significant ($p < 0.05$) on univariable comparison. **Results:** 1007 outpatients with cirrhosis (median age 62 [IQR 55–68], 69% male, median Model for End-Stage Liver Disease [MELD] 3.0 score 11 [IQR 8–16], 39% compensated), all with controlled liver disease etiology, were prospectively enrolled. One hundred fourteen participants (11.3%) reported a severe fall in the three months prior to enrollment. On univariable analysis, patients who fell had higher MELD-3.0 scores, higher Charlson Comorbidity Index scores, greater opioid use, higher Clinical Frailty Scale (CFS) and Liver Frailty Index scores, longer EncephalApp Stroop times, and lower Duke Activity Status Index (DASI) scores (all p0.05). On multivariable logistic regression, current opioid use (adjusted odds ratio [aOR] 2.29, 95% CI: 1.30–3.92, $p = 0.003$), higher CFS score (aOR 1.39, 95% CI:

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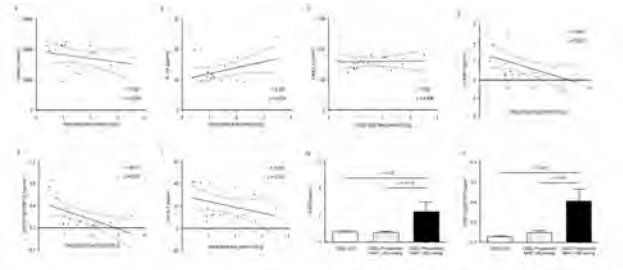
1.11–1.73, p = 0.004), and lower DASI score (aOR 0.97, 95% CI: 0.95–0.99, p < 0.001) were the only independent predictors of severe falls. **Conclusion:** In this contemporary, multicenter outpatient cohort of patients with etiology-controlled cirrhosis, opioid use, frailty, and reduced functional capacity were identified as independent predictors of severe falls and represent actionable targets for fall prevention.

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1591 | URINARY L-FABP AND [TIMP-2]×[IGFBP7] DETECT EARLY RENAL HYPOPERFUSION IN PROPRANOLOL-TREATED CIRRHOTIC RATS

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Background: Non-selective beta-blockers (NSBBs) are the mainstay of treatment for variceal hemorrhage in cirrhotic patients. However, the safety of NSBBs in decompensated cirrhosis has been questioned due to concerns about triggering hemodynamic derangement, which could adversely affect renal function. The development of hypotension and renal hypoperfusion are clinical signs of circulatory dysfunction. Thus, we investigate the thorough hemodynamics of rats with common bile duct ligation (CBDL)-induced liver cirrhosis receiving propranolol treatment. Also, we studied the diagnostic utility of several urinary biomarkers respectively for early detection of renal hypoperfusion in propranolol-treated CBDL rats. **Methods:** Four weeks after CBDL, rats were randomized to receive oral distill water (DW) or propranolol (30 mg/kg/day) for 2 weeks then placed individually in the polycarbonate metabolic cages to collect 24-hour urine on the 15th day. The urinary NGAL, IL-18, KIM-1, L-FABP, TIMP-2, IGFBP7, and CHI3L1 levels were measured. On the 16th day post treatment, systemic and renal hemodynamics were evaluated, and blood was collected for the assessment of concentrations of albumin, alanine transaminase (ALT), aspartate aminotransferase (AST), total bilirubin, blood urea nitrogen (BUN), creatinine, tissue necrosis factor-α (TNF-α), interleukine-1β (IL-1β), and interleukine-6 (IL-6). **Results:** Propranolol treatment led to significant decreases in mean arterial pressure (MAP), heart rate, portal pressure (PP), and renal blood flow (RBF) in CBDL rats (p < 0.05). Both MAP and PP significantly correlated with RBF, while RBF inversely correlated with urinary liver-type fatty acid-binding protein (L-FABP) and the combination of tissue inhibitor of metalloproteinase-2 and insulin-like growth factor binding protein-7 ([TIMP-2]x[IGFBP7]) levels in propranolol-treated CBDL rats (p < 0.05). Propranolol-treated CBDL rats with severe hypotension (MAP < 65 mmHg) showed significantly higher IL-1β, but lower IL-6 levels than those with MAP ≥ 65 mmHg (p < 0.05). **Conclusion:** NSBBs treatment in cirrhosis may need to be individualized accompanied by careful monitoring of blood pressure and inflammatory condition. Urinary biomarkers, such as L-FABP and [TIMP-2]x[IGFBP7] serve as good candidates for detecting renal hypoperfusion following NSBBs treatment. The changes in MAP, serum IL-1β and IL-6 over time might allow the physicians to predict the possibility of NSBBs-induced AKI in cirrhotic patients.



Correlation between renal blood flow and urinary levels of NGAL (A), IL-18 (B), KIM-1 (C), L-FABP (D), [TIMP-2]x[IGFBP7] (E), and CHI3L1 (F) in propranolol-treated common bile duct ligated (CBDL) rats. CHI3L1, Chitinase-3-like protein 1; IGFBP7, insulin-like growth factor-binding protein 7; IL-18, interleukin-18; KIM-1, kidney injury molecule 1; L-FABP, liver-type fatty acid-binding protein; NGAL, neutrophil gelatinase-associated lipocalin; TIMP-2, tissue inhibitor of metalloproteinases-2. Urinary values of L-FABP (G) and [TIMP-2]x[IGFBP7] (H) increased in propranolol-treated CBDL rats with MAP < 65 mmHg. DW, distilled water.

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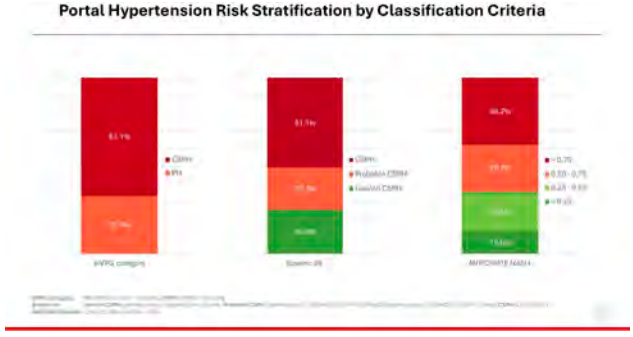
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1592 | CORRELATION OF BAVENO VII AND ANTICIPATE-NASH NONINVASIVE MODELS WITH HVPG IN PATIENTS WITH MASH CIRRHOSIS: FINDINGS FROM A PHASE 2B BELAPECTIN TRIAL

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Background: Belapectin is a novel galectin-3 inhibitor was evaluated in the Phase 2b GT-026 trial in patients with MASH cirrhosis and portal hypertension. Belapectin 2 mg/kg previously demonstrated lower hepatic venous pressure gradient (HVPG) and reduced incidence of varices in subjects without baseline varices. In recent years, noninvasive tests (NITs) have increasingly been utilized to assess portal hypertension and clinically significant portal hypertension (CSPH). We evaluated the correlation of two NIT-based models, Baveno VII criteria and ANTICIPATE-NASH, with HVPG, the gold standard assessment for portal hypertension. **Methods:** Subjects with compensated MASH cirrhosis underwent HVPG assessment at baseline. Portal hypertension was defined as HVPG ≥ 6 to < 10 mmHg and CSPH as HVPG ≥ 10 mmHg. Baveno VII categories (CSPH, probable CSPH, low/no risk CSPH) were defined using liver stiffness measurement (LSM) and platelet count. The ANTICIPATE-NASH model incorporates LSM, platelet count, and body mass index to estimate CSPH probability. Probability categories included 0–25%, 25–50%, 50–75%, and $\geq 75\%$, with $\geq 75\%$ considered rule-in for CSPH and $\geq 50\%$ representing an enrichment population for clinical trials. Agreement between HVPG-defined CSPH and NIT-based models was assessed using kappa statistics. **Results:** Of 161 patients with HVPG data, 131 had lab data to calculate Baveno/ANTICIPATE-NASH criteria. At baseline, HVPG assessment identified CSPH in 67.1% (n = 108) of subjects, with the remaining 32.9% (n = 53) having portal hypertension without CSPH. By Baveno VII criteria, 51.1% (n = 67) met CSPH criteria, 23.7% (n = 31) were probable CSPH, and 25.2% (n = 33) were low/no risk. Agreement between HVPG-defined and Baveno VII CSPH classification yielded a kappa of 0.44 (95% CI 0.24–0.58; $p < 0.001$). By ANTICIPATE-NASH model, CSPH probability distribution was: 0–25% in 13.0% (n = 17), 25–50% in 22.1% (n = 29), 50–75% in 26.7% (n = 35), and $\geq 75\%$ in 38.2% (n = 50). Agreement between HVPG-defined CSPH and ANTICIPATE-NASH $\geq 75\%$ probability yielded a kappa of 0.41 (95% CI 0.28–0.61; $p < 0.001$).Among subjects with HVPG-defined CSPH, 62.6% met CSPH criteria by Baveno VII, 48.4% met the $\geq 75\%$ CSPH probability threshold using the ANTICIPATE-NASH model. **Conclusion:** In this Phase 2b cohort of compensated MASH cirrhosis, both Baveno VII and ANTICIPATE-NASH demonstrated moderate concordance vs HVPG-defined CSPH. The prevalence of CSPH by HVPG was higher than estimated by either noninvasive model, suggesting that both algorithms may underestimate the true burden of CSPH in this population. Baveno VII demonstrated slightly greater concordance and broader clinical stratification vs HVPG-defined CSPH than ANTICIPAT E NASH model, which may need revisiting to further refine CSPH in MASH cirrhosis. These findings support the role of noninvasive risk stratification tools in identifying patients with CSPH to enrich clinical trial populations in MASH cirrhosis.



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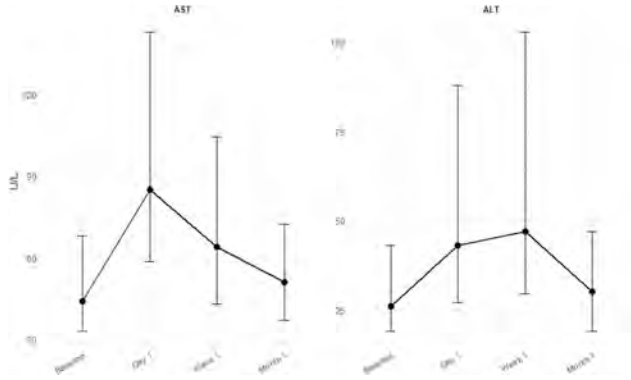
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1593 | CLINICAL SIGNIFICANCE OF EARLY RISES IN ASPARTATE- AND ALANINE AMINOTRANSFERASE ON HEPATIC ENCEPHALOPATHY POST-TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT

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Background: Transjugular intrahepatic portosystemic shunt (TIPS) is an established treatment for portal hypertensive complications. Aspartate- and alanine aminotransferase (AST, ALT) rises occur in up to 95% of patients post-TIPS, but their clinical significance remains unclear. We hypothesized that early AST/ALT elevations reflect shunt-related hepatic changes and are associated with increased ammonia exposure, increasing the risk of hepatic encephalopathy (HE). **Methods:** This retrospective study included consecutive cirrhotic patients undergoing TIPS between January 2007 and December 2023 at tertiary centers in the Netherlands and Germany. TIPS indications were set by treating hepatologists. AST/ALT was recorded at baseline, day one and seven post-TIPS, when available by using predefined windows. The primary endpoint was early HE (eHE), defined as any HE-grade within 30 days post-TIPS. **Results:** We included 547 patients; 368 male (67%), with a median age of 58 (IQR 52 – 65). The most common etiology of cirrhosis was alcohol-related in 296 (54%) patients, and refractory ascites was the main TIPS-indication (n = 285, 52%).Median baseline AST and ALT were 44 (IQR 33 – 78) and 26 U/L (IQR 19 – 45). On day one, AST and ALT increased in 257 (85%) and 234 (75%) patients. Median Δ AST and Δ ALT were 32 (IQR 8 – 75) and 12 U/L (IQR 1 – 33) on day one. Among patients with all available labs that had an AST increase on day one, 65% (106/164) had a subsequent decline on day seven, compared with 42% (72/170) for ALT.Within 30 days post-TIPS, 125 patients experienced eHE (23%). Each 50 U/L increase in Δ AST on day one was associated with a borderline increase in eHE risk (OR 1.01 , 95% CI 1.00 – 1.02, p = 0.06), but this was weakened when adjusting for MELD, age and prior HE (OR 1.01, 95% CI 0.99 – 1.02). Δ ALT on day one was not related to eHE (OR 1.03, 95% CI 0.99 – 1.07). Given the rise-fall pattern of AST post-TIPS, we evaluated patients who retained high AST (≥ 100 U/L) on day seven, despite a decline from peak level. Using Firth's penalization to account for small sample size (n = 164), this was associated with eHE (OR 3.69, 95% CI 1.45 - 10.09, p = 0.01). **Conclusion:** Early post-TIPS rises in AST and ALT are common, typically mild, and not independently associated with eHE. Persistent AST elevation on day seven, in contrast, could be linked to increased risk of eHE. Given that this observation is limited by small sample size, this finding must be confirmed. While early transaminase rises likely overlap with other risk factors for eHE, they may still signal an adverse clinical phenotype and support consideration of preventive HE strategies.



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1594 | GUIDELINE ADOPTION AFTER BAVENO VII: TRENDS IN ENDOSCOPIC SURVEILLANCE AMONG COMPENSATED ADVANCED CHRONIC LIVER DISEASE PATIENTS ON NON-SELECTIVE BETA BLOCKER

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Background: Baveno VII guidelines (2022) recommend that patients with compensated advanced chronic liver disease (cACLD) on a non-selective beta blocker (NSBB) can forgo screening esophagogastroduodenoscopy (EGD). Whether this recommendation has been adopted in clinical practice remains unknown. We evaluated trends in EGD screening among cACLD patients on NSBBs before and after Baveno VII publication. **Methods:** Using the TriNetX US Collaborative Network (67 institutions), we identified two cohorts of cACLD patients initiated on an NSBB (carvedilol, propranolol, or nadolol): pre-Baveno VII (January 2019-April 2022) and post-Baveno VII (May 2022-May 2024). cACLD was defined by cirrhosis ICD-10 codes and absence of prior decompensation events (ascites, variceal bleeding, or hepatic encephalopathy) and hepatocellular carcinoma. Index date was the first NSBB prescription within the observation window. Patients were followed for 24 months. Propensity score matching (1:1) was performed on age, sex, race, ethnicity, cirrhosis etiology, MELD component laboratories, and comorbidities. The primary outcome was EGD within 24 months of NSBB initiation, excluding patients who underwent EGD within the 12 months preceding NSBB initiation. A pre-specified subgroup analysis was performed in patients with documented non-bleeding esophageal varices. A sensitivity analysis excluding carvedilol was performed to address potential indication bias. **Results:** After propensity matching, each cohort included 35,601 patients (pre- vs post-Baveno VII). All standardized mean differences were <0.1. EGD rates were 13.3% pre- vs 14.1% post-Baveno VII (OR 0.934, 95% CI 0.889 - 0.981, $p=0.006$), indicating no reduction in endoscopic surveillance following guideline publication. This finding was consistent after excluding carvedilol users (14.4% vs 15.9%; OR 0.891, 95% CI 0.822 - 0.965, $p=0.005$; $n=12,136$ matched pairs). In subgroup analysis among 13,675 matched pairs with known non-bleeding varices, EGD rates were 24.6% pre- vs 27.0% post-Baveno VII (OR 0.883, 95% CI 0.824–0.947, $p<0.001$), demonstrating persistently high and increasing surveillance rates. Carvedilol use increased significantly post-Baveno VII across all analyses (43.4% to 46.2% in the primary cohort; 31.9% to 36.7% in the variceal subgroup), while propranolol and nadolol use declined. **Conclusion:** Despite Baveno VII recommendations, EGD surveillance rates among cACLD patients on NSBBs have not declined in a large real-world US cohort, with rates remaining highest in patients with known non-bleeding varices. These findings suggest significant guideline-to-practice gaps and highlight the need for targeted educational interventions to promote appropriate de-escalation of endoscopic surveillance in this population.

Table 1. EGD rates within 24 months of NSBB initiation across primary, sensitivity, and subgroup analyses

Outcomes assessed after propensity score matching (1:1). Patients with EGD within 12 months prior to index NSBB prescription are excluded from primary outcome analysis.

Analysis	Matched pairs (n)	Pre-Baveno VII EGD rate	Post-Baveno VII EGD rate	Risk difference (95% CI)	Odds ratio (95% CI)	p-value
Primary analysis All NSBBs	35,601	13.3% (3,581 / 27,025)	14.1% (3,786 / 26,927)	−0.008 (−0.014, −0.002)	0.934 (0.889–0.981)	0.006
Sensitivity analysis Propranolol + nadolol only	12,136	14.4% (1,329 / 9,218)	15.9% (1,475 / 9,272)	−0.015 (−0.025, −0.005)	0.891 (0.822–0.965)	0.005
Subgroup analysis Known non-bleeding varices, all NSBBs	13,675	24.6% (2,039 / 8,292)	27.0% (2,206 / 8,181)	−0.024 (−0.037, −0.010)	0.883 (0.824–0.947)	<0.001

A negative risk difference indicates higher EGD rates in the post-Baveno VII cohort. EGD = esophagogastroduodenoscopy; NSBB = non-selective beta blocker; CI = confidence interval. cACLD defined by cirrhosis ICD-10 codes and absence of decompensation events. Index date = first NSBB prescription within the observation window.

Disclosures: Muhammad Ali Butt:Nothing to Disclose, Timothy Davie:Nothing to Disclose, Abdul Wasaay Khurram:Nothing to Disclose, Prowpanga Udompap: Nothing to Disclose.

1595 | ANTIBIOTIC EXPOSURE AND OUTCOMES IN SPONTANEOUS BACTERIAL PERITONITIS: MORTALITY, RESISTANCE, AND RECURRENCE

Samuel Levine[1] Nishanth Eluri[1] Halicki Barbara[1] Frank Lin[1] Daniel Guirguis[1] Ibrahim Ragab[1] Het Patel[1] Ashley Tran[2], [1]St. Luke's University Hospital, [2]St. Luke's University Health Network

Background: Prophylaxis against spontaneous bacterial peritonitis (SBP) is recommended for patients with decompensated cirrhosis at high risk for, or have a history of, SBP. Ciprofloxacin, and trimethoprim-sulfamethoxazole (TMP-SMX) have been traditionally used for these indications. However, emerging data

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suggest SBP prophylaxis may be associated with adverse outcomes, including multidrug-resistant organisms, breakthrough infection, recurrence, and mortality, likely driven by rising antimicrobial resistance. This study evaluated the effects of recent antibiotic exposure on mortality and antimicrobial resistance in patients presenting with an index episode of SBP, as well as the association between secondary SBP prophylaxis and recurrence. **Methods:** This retrospective chart review included patients with cirrhosis admitted with an index episode of SBP between 2021 and 2024 across the St. Luke's University Health Network. Multivariable regression models were used to assess 30- and 90-day mortality, while unadjusted relative risks evaluated antimicrobial resistance and SBP recurrence within 180 days. **Results:** 120 patients with cirrhosis and index SBP were identified. 30- and 90-day mortality were 23.3% and 27.5% respectively. 64 patients (53.3%) had antibiotic exposure within 3 months prior to SBP presentation. Antibiotic exposure was not associated with 30-day (RR 0.87, 95% CI 0.45-1.68) or 90-day mortality (RR 0.80, 95% CI 0.45-1.44) after adjusting for age, sex, BMI, comorbidities, MELD 3.0, and recent hospitalizations. Of 25 ascitic fluid cultures with speciation, 7 (28.0%) demonstrated antibiotic resistance to fluoroquinolones, TMP-SMX, or both. Resistance was observed in 6 of 14 (42.9%) cultures from patients with prior antibiotic exposure compared to 1 of 11 (9.1%) without exposure, although this difference was not statistically significant ($p = 0.061$). 19 patients developed recurrence of SBP within 180 days, including 15 who received secondary prophylaxis. Patients receiving secondary prophylaxis had an increased risk of SBP recurrence (RR 4.83, 95% CI 1.71-13.69, $p < 0.001$). **Conclusion:** Recent studies have challenged the practice of SBP prophylaxis in patients with cirrhosis. In this analysis, prior antibiotic exposure was not associated with increased mortality, which may reflect the high burden of comorbidities in the study population. A substantially higher proportion of resistant ascitic fluid cultures was observed among patients with prior antibiotic exposure compared to those without; however, this relationship approached, but did not reach, statistical significance, likely due to limited sample size. Notably, secondary SBP prophylaxis was associated with an increased risk of recurrent SBP. These findings highlight the need to re-evaluate SBP prophylaxis strategies.

Disclosures: Samuel Levine:Nothing to Disclose, Nishanth Eluri:Nothing to Disclose, Halicki Barbara: Nothing to Disclose, Frank Lin:Nothing to Disclose, Daniel Guirguis:Nothing to Disclose, Ibrahim Ragab: Nothing to Disclose, Het Patel:Nothing to Disclose, Ashley Tran:Nothing to Disclose.

1596 | HYPER-ACUTE LIVER INJURY FOLLOWING TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT PLACEMENT: EARLY PREDICTORS OF 30-DAY MORTALITY

Anna Thiemann[1] Todd Frederick[1] Yohanna Khachiyan[1] Shruti Vaidya[1] Sylvia Sudat[1], [1]California Pacific Medical Center

Background: Transjugular intrahepatic portosystemic shunt (TIPS) is a well-established intervention for portal hypertension and its complications. Hyperacute liver injury immediately following the procedure is rare and poorly characterized. In a retrospective cohort at a single tertiary care center in Northern California, we previously observed that marked abnormalities in AST, ALT, INR, and total bilirubin within 48 hours after TIPS placement were strongly associated with mortality after 30 days. In this study, we sought to determine whether the magnitude of post-procedural laboratory changes predicts 30-day mortality. **Methods:** We performed a retrospective review of all patients who underwent TIPS at our center between March 2015 and January 2024. The primary outcome was all-cause mortality at 30 days. Differences in laboratory deltas between survivors and non-survivors were assessed using the Mann-Whitney U test given non-normal data distributions. ROC analysis was performed to assess the discriminatory ability of individual markers. Youden index-optimal cutoffs were identified for each marker, and PPV, NPV, and OR were calculated via binary logistic regression. **Results:** 561 patients underwent TIPS during the study period. 9 were excluded due to signs of severe liver injury prior to TIPS (AST and/or ALT >10 ULN). 29 (5.3%) died within 30 days. Most common causes of death included hemorrhagic complications (32%), hepatic decompensation (24%), sepsis (9%), and respiratory failure (9%). Non-survivors demonstrated significantly higher post-procedural Δ AST compared to survivors (median 53 vs. 21 U/L, $p = 0.0002$), higher Δ ALT (median 18 vs. 9 U/L, $p = 0.007$), and higher Δ bilirubin (median 1.00 vs. 0.30 mg/dL, $p = 0.025$). Δ INR did not differ significantly between groups (median 0.20 vs. 0.10, $p = 0.234$). On ROC analysis, Δ AST demonstrated the highest discriminatory ability (AUC 0.707), followed by Δ ALT (AUC 0.649) and Δ bilirubin (AUC 0.623). Δ AST ≥ 50 U/L, yielded an OR of 3.50 (95% CI 1.64–7.47, $p = 0.001$).

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Δ bilirubin ≥1.0 mg/dL demonstrated an OR 4.14 (95% CI 1.94–8.85, p < 0.001). And Δ ALT ≥30 U/L produced an OR of 3.03 (95% CI 1.42–6.50, p = 0.004). Across all significant markers, NPV consistently exceeded 95%, while PPV remained < 20%. **Conclusion:** Post-procedural elevations in AST, ALT, and bilirubin were each significantly associated with 30-day mortality following TIPS. Specific laboratory thresholds (Δ AST ≥50, Δ ALT ≥30, and Δ bilirubin ≥1) identify patients at substantially elevated mortality odds, and may be useful in identifying low-risk patients after TIPS due to their high NPV. These findings support the hypothesis that hyper-acute liver injury following TIPS, potentially ischemic in etiology, portends poor short-term outcomes. Prospective validation is needed to determine whether early identification of these laboratory patterns can guide post-procedural monitoring or intervention strategies to improve survival.

Table 1

Post-procedural laboratory delta values by 30-day mortality status (n=552). Patients with AST or ALT >10x ULN excluded. Median (IQR); Mann-Whitney U test.

	Overall (n=552)	Survived (n=523)	Died at 30d (n=29)	p-value
COHORT				
30-day mortality	29 (5.3%)	–	–	–
LABORATORY DELTAS (POST − PRE), median (IQR)				
Δ AST (U/L)	24 (9–54)	21 (9–51)	53 (28–200)	0.0002
Δ ALT (U/L)	9 (3–25)	9 (2–24)	18 (6–80)	0.007
Δ Total bilirubin (mg/dL)	0.30 (0.00–0.80)	0.30 (0.00–0.80)	1.00 (0.10–1.50)	0.025
Δ INR	0.10 (0.00–0.20)	0.10 (0.00–0.20)	0.20 (0.00–0.30)	0.234
DISCRIMINATORY PERFORMANCE (AUC)				
Δ AST	0.707	Best individual predictor		
Δ ALT	0.649			
Δ Total bilirubin	0.623			
Δ INR	0.564			

Bold red = p<0.05. AUC = area under ROC curve. IQR = interquartile range. ULN = upper limit of normal.

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1597 | OPTIMAL BIOCHEMICAL CRITERIA FOR HEPATIC RECOMPENSATION IN HEPATITIS B VIRUS-RELATED CIRRHOSIS

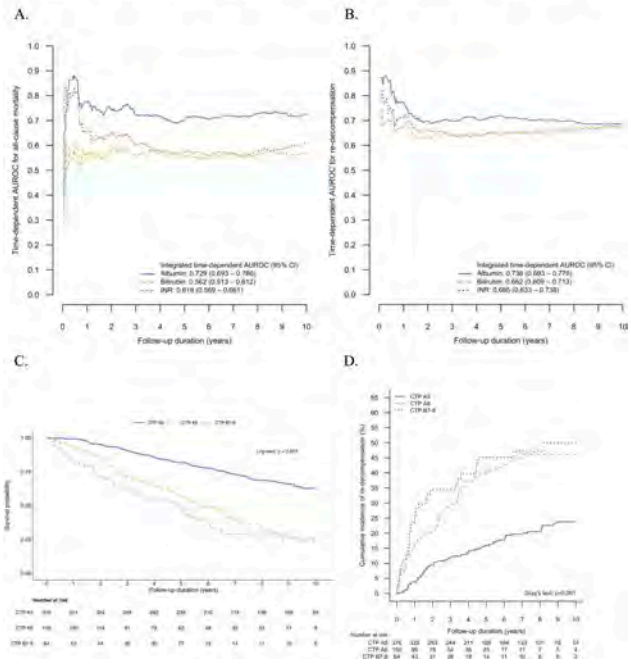
Yangyue Zhang[1] Vincent Wong[1] Terry Cheuk-Fung Yip[1] Jimmy Che-To Lai[1] Xinrui Jin[1] Vicki Hui[1] Junlong DAI[1] Grace Wong[1], [1]The Chinese University of Hong Kong

Background: Under Baveno VII, hepatic recompensation requires stable biochemical improvement in liver function tests including albumin, international normalised ratio (INR), and bilirubin, but the prognostic implication of each parameter remain unclear. We aimed to evaluate the discriminatory and prognostic performance of these parameters and to validate the clinical utility of the Child-Pugh score in patients with hepatitis B virus (HBV)-related cirrhosis. **Methods:** This retrospective cohort study identified patients with HBV-related cirrhosis and prior hepatic decompensation from a territory-wide electronic healthcare database in Hong Kong. All had complete HBV DNA suppression and absence of decompensation events for at least 12 months. The primary outcome was all-cause mortality, and the secondary outcome was re-decompensation. Analyses were performed on both multiply imputed and complete-case datasets. **Results:** 871 patients were included (67.4 % male; median age 62.4 years). Over a median follow-up of 65.7 (IQR 30.7-109.6) months, 320 (36.7%) patients died and 274 (31.5%) developed re-decompensation. Albumin showed the highest discriminatory performance for mortality (integrated time-dependent area under the receiver operating characteristic curve 0.729 [95% CI 0.693-0.766]), followed by INR (0.618 [95% CI 0.569-0.661]) and bilirubin (0.562 [95% CI 0.513-0.612]). A similar pattern was observed for re-decompensation. All three parameters were significantly associated with mortality and re-decompensation after adjustment for age and sex in the restricted cubic spline analyses. In the multivariable model, however, albumin was the only independent predictor of mortality (adjusted hazard ratio 0.910 [95% CI 0.891-0.929]). In contrast, all three parameters independently predicted re-decompensation, with adjusted subdistribution hazard ratios (95% CI) of 0.917 (0.892-0.943) for albumin, 1.014 (1.001-1.026) for bilirubin, and 1.314 (1.148-1.504 per 0.1-unit increase) for INR. Similar results were observed in both the imputed and complete-case analyses. The 5-year survival probability decreased from 81.6%, 57.7%, to 48.6% in patients with Child-Pugh scores of A5, A6, and B7-8, respectively (log-rank test, p < 0.001). The stepwise increase was observed in the cumulative incidence of re-decompensation across the Child-Pugh score categories. **Conclusion:** Albumin is the strongest predictor of mortality and re-decompensation in patients with clinical recompensation. Patients with Child-Pugh A5 at clinical recompensation had the lowest risk of adverse outcomes.

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Figure. Integrated time-dependent area under the receiver operating characteristic curve (AUROC) for albumin, bilirubin, and international normalised ratio (INR) in predicting A) all-cause mortality and B) re-decompensation in the imputed cohort. C) Kaplan-Meier survival probability and D) cumulative incidence of re-decompensation stratified by Child-Pugh (CTP) score among patients who met the Baveno VII criteria for recompensation (N=590).



Disclosures: Yangyue Zhang:Nothing to Disclose, Vincent Wong:Abbott: Speaking and Teaching, AbbVie: Advisor, AbbVie: Speaking and Teaching, Boehringer Ingelheim: Advisor, Echosens: Advisor, Echosens: Speaking and Teaching, Gilead Sciences: Advisor, Gilead Sciences: Speaking and Teaching, Gilead Sciences: Grant/Research Support, Novo Nordisk: Advisor, Pfizer: Advisor, TARGET PharmaSolutions: Advisor, Illuminatio Medical Technology: Stock – privately held company, Eli Lilly: Consultant, Merck: Consultant, Altimmune: Consultant, AstraZeneca: Consultant, Roche Diagnostics: Consultant, Furui: Consultant, Terry Cheuk-Fung Yip:Gilead Sciences: Consultant, Gilead Sciences: Speaking and Teaching, Gilead Sciences: Grant/Research Support, Altimmune: Advisor, GSK: Advisor, Jimmy Che-To Lai:Nothing to Disclose, Xinrui Jin:Nothing to Disclose, Vicki Hui:Nothing to Disclose, Junlong DAI: Nothing to Disclose, Grace Wong:Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens, Fe: Speaking and Teaching, AstraZeneca, Barinthus, Gilead Sciences, GlaxoSmithKline, IntegerBio, Janssen and Virion: Advisor, Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens: Speaking and Teaching, Ferring, Gilead Sciences, GlaxoSmithKline, Janssen, Otsuka, Roche and Virion: Speaking and Teaching, Gilead Sciences: Grant/Research Support.

1598 | BRIDGING THE OXYGEN GAP: LEVERAGING ARTIFICIAL INTELLIGENCE TO UNMASK HEPATOPULMONARY SYNDROME

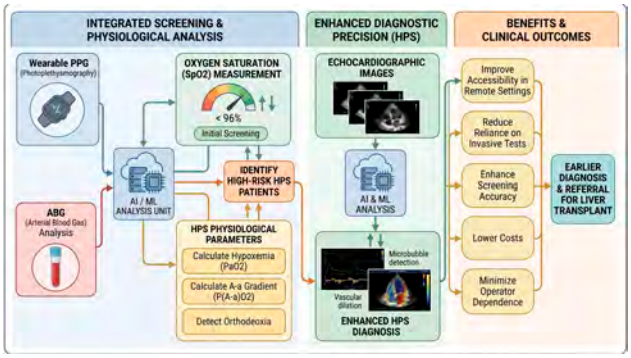
Joshika Agarwal[1] Jahnavi Mikkilineni[2] Avneet Kaur[3] Ridhi Malhotra[4] Shivaram Poigai Arunachalam[5], [1]Mercy Catholic Medical Center, Darby, PA, [2]John Hopkins University, [3]Medstar Georgetown University(Baltimore) program, [4]Manipal College of Medical Sciences, Pokhara, Nepal, [5]Mayo Clinic, Rochester, MN

Background: Most patients with hepatopulmonary syndrome (HPS) are asymptomatic, leading to delayed diagnosis and increased mortality, given that the only definitive treatment is liver transplant. The current gold standard diagnostic test includes contrast-enhanced echocardiography (CE) or a technetium-99m macroaggregated albumin (Tc-MAA) scan, accompanied by arterial-blood gas (ABG) analysis or pulmonary angiography. However, it is expensive, time-consuming, invasive, and not widely accessible. Noninvasive screening with pulse oximetry (SPO2) also lacks both sensitivity and specificity, resulting in underdiagnosis. These limitations highlight the need for advanced diagnostic methods through artificial intelligence (AI). **Methods:** A literature search including original studies was conducted using PubMed, NEJM, Lancet, and Google Scholar using broad terms related to HPS and AI. Outcomes assessed included AI performance in diagnosis, risk stratification, and prediction compared with standard diagnostic modalities. **Results:** HPS is quantitatively described by liver disease, hypoxemia (PaO_2 <80 mmHg), elevated alveolar–arterial gradient (≥ 15–20 mmHg), and intrapulmonary vascular dilatations (IPVD) causing right-to-left shunting. Orthodeoxia (≥ 3–5% rise in SpO2 in supine position) is specific. These non-invasive variables can be combined with AI-algorithms and machine learning (ML) methods for prompt screening. A study by Li YJ et al. showed a two-step ML model using ABG to predict IPVD in cirrhotic patients followed by targeted CE, attaining 87.2% accuracy. Wearable photoplethysmography (PPG) and ABG analysis integrated with AI may enable measurement of oxygen saturation of less than 96% as an initial screening tool to further calculate hypoxemia (PaO2), alveolar-arterial gradient and orthodeoxia, helping in detecting high-risk patients and enabling real-time exposure of subtle physiological changes. AI and ML can be applied to analyze echocardiographic images from CE to enhance diagnostic precision in HPS. Machine learning can improve accessibility of these screening tests in remote settings, reduce reliance on invasive tests, enhance screening accuracy, lower costs, and minimize operator dependence, facilitating earlier diagnosis of HPS and referral for liver transplant. **Conclusion:** AI-integrated methods for early, efficient

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HPS diagnosis has significant potential and scope in upcoming future. However, these are theories, yet to be studied and applied in real-life scenarios. There is a growing need for the research with large sample size, data standardization, validation and generalizability. Overcoming challenges such as 'black box' nature of ML is important for widespread clinical adoption.

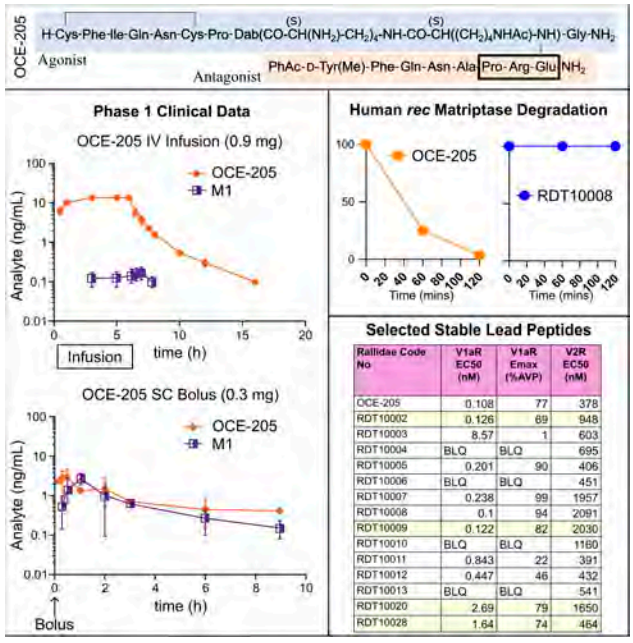


Disclosures: Joshika Agarwal:Nothing to Disclose, Jahnavi Mikkilineni:Nothing to Disclose, Avneet Kaur: Nothing to Disclose, Ridhi Malhotra:Nothing to Disclose, Shivaram Poigai Arunachalam:Nothing to Disclose.

1599 | RATIONAL DESIGN OF A BIFUNCTIONAL VASOPRESSIN 1A RECEPTOR (V1AR) PARTIAL AGONIST FOR SUBCUTANEOUS OUTPATIENT DELIVERY: LESSONS FROM THE CLINICAL DEVELOPMENT OF OCE-205

Ed Cable[1] Kazimierz Wiśniewski[1] John Lucas[1] Glenn Croston[1], [1]Rallidae Therapeutics

Background: Decompensated cirrhosis remains associated with a broad range of severe consequences and high mortality. V1aR agonism is clinically validated by decades of experience with terlipressin, which partially corrects the vasodilatory circulatory dysfunction of advanced cirrhosis, reducing portal hypertension, increasing arterial pressure, enhancing renal perfusion and reducing hypoxia-driven renal injury. Additionally, continuous terlipressin infusion decreases ascites and sarcopenia. These clinical benefits occur in spite of terlipressin, a prodrug of lysine vasopressin, being a full agonist at both V1aR and V2R.OCE-205, the selective V1aR partial agonist, demonstrated clinical translation in healthy volunteers producing an increase of 10-15 mm Hg in mean arterial pressure with no evidence of excess vasoconstriction. Proteolytic degradation of OCE-205 following SC delivery produces an active, V1aR full agonist metabolite, changing the agonist-antagonist balance and increasing the E_{max} about 15%. Therefore, OCE-205 is now limited to IV delivery where little proteolysis is observed (Fig). Building upon the clinical findings of OCE-205, the putative protease substrate site (box) and candidate protease, matriptase, were identified. *In vitro* studies demonstrated matriptase-mediated metabolism of OCE-205 and analogs incorporating modifications within the substrate recognition site eliminated matriptase degradation *in vitro*, with several analogs retaining V1aR partial agonist activity and increased V1aR selectivity relative to OCE-205 (Table). **Methods:** The Expasy Peptide-Cutter was used to analyze OCE-205. Human V1aR and V2 receptor *in vitro* assays were performed with commercially available methods, using AVP and OCE-205 as controls. Proteolytic stability was tested *in vitro* with recombinant enzymes, and reaction products were analyzed by HPLC and UV/Vis or HPLC/MS. **Results:** Novel V1aR partial agonists have been identified, including analogs that are resistant to matriptase cleavage. These matriptase resistant analogs are also V1aR-selective partial agonists, with selectivity for human V1aR vs V2R even greater than that of OCE-205. **Conclusion:** The first-generation bifunctional, selective V1aR partial agonist, OCE-205, provided V1aR partial agonist clinical validation of safety and efficacy with IV delivery butcould not be developed for outpatient SC administration due to the formation of a full agonist metabolite catalyzed by a trypsin-like protease. The current work identifies novel V1aR partial agonists that are no longer matriptase substrates. Development of a bifunctional V1aR partial agonist that is no longer proteolytically degraded will provide important progress for decompensated cirrhosis patients, providing SC outpatient delivery to favorably reduce the hemodynamic imbalances responsible for the broad range of decompensation events and mortality.



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Disclosures: Ed Cable:CymaBay Therapeutics: Employee, Rallidae Therapeutics: Executive role, Kazimierz Wiśniewski:Nothing to Disclose, John Lucas: Nothing to Disclose, Glenn Croston:Nothing to Disclose.

1600 | RISING PREVALENCE OF HYPONATREMIA IN HEPATORENAL SYNDROME HOSPITALIZATIONS AND ITS ASSOCIATION WITH IN-HOSPITAL MORTALITY AND RESOURCE UTILIZATION

Nishanth Eluri[1] Brett Cohen[1] Daniel Guirguis[1] Renata Lerer[2], [1]St. Luke's University Hospital, [2]St. Luke's University Hospital Network

Background: Hepatorenal syndrome (HRS) is a life-threatening complication of advanced cirrhosis marked by severe circulatory dysfunction and high short-term mortality. Hyponatremia, reflecting impaired free water clearance, is common in decompensated cirrhosis and linked to poor outcomes. Contemporary data on its epidemiology and clinical significance in HRS remain limited. We evaluated temporal trends and the association of concurrent hyponatremia with mortality and healthcare utilization in US HRS hospitalizations. **Methods:** Using the National Inpatient Sample (2018–2022), HRS hospitalizations were identified and stratified by hyponatremia status. Survey-weighted logistic regression estimated crude and adjusted odds ratios for in-hospital mortality, adjusting for demographics, comorbidities, and hospital characteristics; survey-weighted linear regression assessed length of stay and total charges. **Results:** The weighted HRS subpopulation comprised approximately 262,895 hospitalizations (n = 52,579 unweighted). HRS incidence rose from 0.121% in 2018 to 0.180% in 2022, and the prevalence of concurrent hyponatremia rose from 45.7% to 54.0%.Crude in-hospital mortality was 25.5% (95% CI 24.9%–26.1%) with hyponatremia and 26.6% (95% CI 26.0%–27.1%) without. Unadjusted, hyponatremia was associated with modestly lower odds of death (OR 0.947, 95% CI 0.910–0.985, p = 0.006); this persisted after adjustment for demographic and hospital-level factors (aOR 0.944, 95% CI 0.905–0.984, p = 0.007).Hyponatremia was associated with longer LOS (mean 12.2 vs. 10.3 days; β = +1.83 days, 95% CI 1.58–2.09, p < 0.001) and higher total charges (mean $192,968 vs. $168,435; β = +$24,466, 95% CI $17,805–$31,127, p < 0.001).Patients with hyponatremia had higher rates of malnutrition (23.2% vs. 18.5%), while those without more frequently had DM2 (34.8% vs. 26.2%), hyperlipidemia (22.6% vs. 17.5%), CAD (14.5% vs. 9.9%), CKD3 (36.5% vs. 27.7%), and ESRD (13.2% vs. 11.0%). Shock (29.2% vs. 27.7%) and vasopressor use (10.3% vs. 9.7%) were more common with hyponatremia. **Conclusion:** Among US HRS hospitalizations, concurrent hyponatremia has become increasingly prevalent and associated with greater healthcare utilization despite lower adjusted in-hospital mortality. This likely reflects residual confounding from differences in comorbidity profiles, coding patterns, and treatment selection rather than a true protective effect. Hyponatremia in HRS identifies a complex, high-resource complication warranting further study to define its prognostic significance.

Disclosures: Nishanth Eluri:Nothing to Disclose, Brett Cohen:Nothing to Disclose, Daniel Guirguis:Nothing to Disclose, Renata Lerer:Nothing to Disclose.

1601 | NON-INVASIVE FIBROSIS INDICES PREDICT LIVER-RELATED EVENTS ACROSS ETIOLOGIES IN A LONG-TERM COHORT OF COMPENSATED ADVANCED CHRONIC LIVER DISEASE

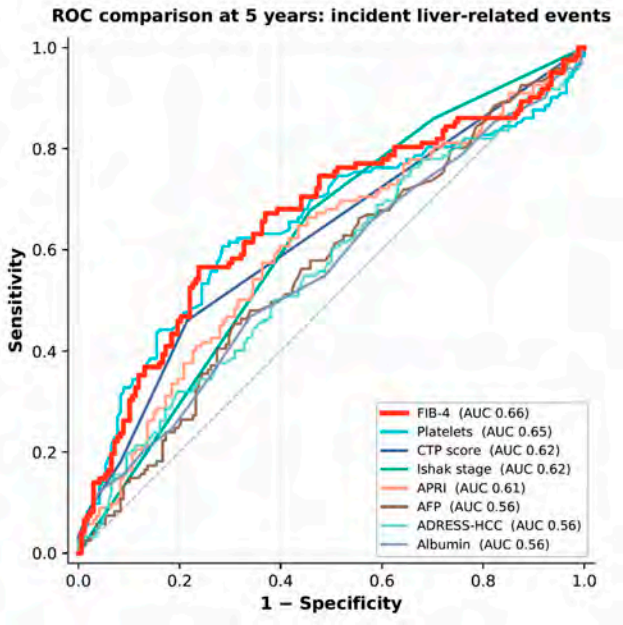
Wesam Aleyadeh[1] Jonathan Lim[1] Christopher Sollenberger[2] Christine Hsu[3], [1]National Institutes of Health, [2]Perelman School of Medicine, [3]National Institute of Diabetes, Digestive

Background: Non-invasive tests (NITs) have been validated for fibrosis staging but their performance in predicting LREs in patients with compensated advanced liver disease (cACLD) irrespective of etiology is less defined. We evaluated baseline NITs as predictors of incident LREs and hepatocellular carcinoma (HCC) in an etiologically diverse cACLD cohort. **Methods:** This is a retrospective study at a single tertiary center of patients with a diagnosis of cACLD (Ishak 4-6 or clinical diagnosis). Follow-up date started at the time of cACLD diagnosis. The primary outcome was a composite LRE (incident varices on imaging or endoscopy, ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, HCC, or liver-related death). Baseline FIB-4, APRI, Child-Turcotte-Pugh (CTP) score, ADRESS-HCC, Ishak stage, and laboratory values were tested in Cox models adjusted for age and sex. In a sensitivity analysis, etiology on impact of LRE was evaluated. Discrimination was assessed by time-dependent AUC. **Results:** 429 had cACLD daignosis and 39 patients with history of LRE on or before index date were excluded, yielding 390 patients. 59% were male and the mean age 48 ± 13 years. 81% viral (HCV 57%, HBV 14%, HDV 11%) and 8.3% MASLD. 55% were Caucasian, 20% were black, and 17% Asian. At baseline, 56% of HCV and 91% of HBV patients were treated. Over a median 6.4 years (IQR 2.1-11.2), 199 patients (51%) had an LRE, 46 (12%) HCC, and 99 (25%) died. Adjusted for age and sex, FIB-4 > 2.67 was

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associated with the composite LRE (aHR 2.27, 95% CI 1.66-3.11), as were APRI >1.0 (HR 1.76), CTP score (HR 1.45/point), Ishak score (HR 1.59/point), splenomegaly (HR 1.95), and lower albumin (HR 0.63 per g/dL). Five-year cumulative LRE incidence was 52% with FIB-4 >2.67 versus 25% <2.67 (log-rank P<0.001). At 5 years, FIB-4 and platelet count showed the highest discrimination for the composite LRE (AUC 0.66 and 0.65, respectively). For HCC, AFP and APRI >1 (HR 2.36) had the strongest associations, while discrimination was highest for ADRESS-HCC and FIB-4 (AUC 0.82 and 0.80 at 1-year; 0.69 and 0.70 at 5-years). **Conclusion:** In a long-term cACLD cohort, baseline FIB-4 independently predicted 2-fold higher risk of incident LREs with moderate discrimination. FIB-4 and ADRESS-HCC showed good discrimination for HCC. This validates FIB-4's ability to risk stratify but suggests it is better for group-level stratification alongside other prognostic scores.



Disclosures: Wesam Aleyadeh:Nothing to Disclose, Jonathan Lim:Nothing to Disclose, Christopher Sollenberger:Nothing to Disclose, Christine Hsu:Nothing to Disclose.

1602 | DOES CIRRHOSIS ETIOLOGY MATTER? OUTCOMES IN PERITONITIS BY UNDERLYING LIVER DISEASE

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Background: Cirrhosis etiology influences disease progression, comorbidity burden, care needs, and outcomes. However, differences in readmission and survival among patients with alcohol-associated liver disease (EtOH), hepatitis C virus (HCV), and metabolic dysfunction–associated steatohepatitis (MASH)-related cirrhosis presenting with peritonitis remain incompletely characterized. **Methods:** We performed a retrospective cohort study of cirrhotic patients admitted with peritonitis, stratified by etiology: EtOH, HCV, or MASH-related cirrhosis. Demographics, comorbidities, microbiologic findings, management patterns, follow-up, readmission, and mortality were compared using univariate analyses. Competing-risk regression evaluated readmission, and Kaplan–Meier analysis assessed overall survival. Artificial intelligence (AI)–assisted tools were used to improve readability and language clarity. **Results:** A total of 286 patients were included: EtOH n = 163, HCV n = 53, and MASH n = 70. Patients with MASH-related cirrhosis were older than those with EtOH-related cirrhosis (66.0 vs 56.0 years, p < 0.001) and had a higher burden of metabolic comorbidities, including diabetes (62.9%, OR 7.82 vs EtOH), obesity (41.4%, OR 4.10), hyperlipidemia (38.6%, OR 3.47), and hypothyroidism (27.1%, OR 6.37) (all p < 0.001).MASH-related cirrhosis demonstrated higher cumulative readmission than EtOH (Gray's p = 0.006), with increased 90-day (50.0% vs 32.5%, OR 2.08), 180-day (54.3% vs 37.4%, OR 1.99), and 1-year readmission (61.4% vs 40.5%, OR 2.34). They were more likely to receive outpatient gastroenterology (45.7% vs 16.0%, OR 4.44) and hepatology follow-up (44.3% vs 19.6%, OR 3.25), suggesting greater specialty-care utilization after hospitalization. Despite these differences, overall survival did not differ significantly by Kaplan–Meier analysis (log-rank p = 0.420), although patients with MASH-related cirrhosis exhibited higher long term mortality compared with EtOH patients on univariate analysis (5-year mortality 84.3% vs 68.7%, OR 2.44, p = 0.016). HCV patients had higher rates of malignancy-related findings, including positive cytology (OR 11.06) and hepatocellular carcinoma (OR 2.48). **Conclusion:** Among cirrhotic patients admitted with peritonitis, etiology was associated with distinct comorbidity profiles, care patterns, readmission risk, and malignancy findings. MASH-related cirrhosis was characterized by older age, substantial metabolic comorbidity burden, increased specialty follow-up, and higher readmission rates, while HCV-related cirrhosis was associated with greater malignancy-related findings. Although overall survival did not differ significantly across etiologies, these findings suggest that etiology-specific risk profiles may inform post-discharge planning, outpatient surveillance, and interventions to reduce recurrent hospitalization in this complex population.

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1603 | CULTURE-POSITIVE VS CULTURE-NEGATIVE CIRRHOTIC PERITONITIS: CLINICAL DIFFERENCES AND OUTCOMES

Kahler Doyle[1] Brayden Doyle[2] Viraj Gandhi[1] Mohammad Ashfaq[3], [1]TCU Anne Burnett School of Medicine, [2]TCU College of Science and Engineering, [3]Baylor Scott & White Liver Consultants of Texas

Background: Peritoneal fluid culture (PFC) positivity may identify a distinct subset of cirrhotic patients with peritonitis, though its impact on management and outcomes remains incompletely defined. We compared clinical characteristics, treatment patterns, and longitudinal outcomes between culture-positive and culture-negative peritonitis. **Methods:** We conducted a retrospective cohort study of cirrhotic patients admitted with peritonitis, stratified by PFC status. Clinical variables, microbiology, treatment patterns, procedures, and outcomes were compared using univariate analyses with odds ratios (OR) and 95% confidence intervals (CI). Time-to-event outcomes were assessed using Kaplan–Meier survival analysis and competing-risk regression for readmission, with log-rank and Gray's tests. Artificial intelligence (AI)–assisted tools were used to enhance clarity and readability. **Results:** A total of 386 patients were included (culture-negative n = 225; culture-positive n = 161). Culture-positive peritonitis was associated with longer length of stay (7.0 [5.0–14.0] vs 10.0 [5.0–18.0], p = 0.010) and greater inflammatory burden, including higher early PFA PMNs and lower glucose. Blood culture positivity was more frequent (OR 1.73, 95% CI 1.06–2.80).Culture-positive patients demonstrated greater illness severity and resource utilization, including higher rates of ICU consultation (OR 2.67, 1.75–4.08), ICU admission (OR 2.44, 1.39–4.26), mechanical ventilation (OR 3.88, 1.99–7.56), vasopressor use (OR 2.46, 1.32–4.58), and central venous access (OR 1.76, 1.17–2.66). Procedural burden was also increased, including exploratory laparotomy (OR 6.10, 2.00–18.60), abscess drainage (OR 3.48, 1.31–9.25), and non-paracentesis abdominal procedures (OR 2.54, 1.39–4.64).Microbiologic complexity and treatment intensity were greater among culture-positive patients, with increased infectious disease consultation (OR 1.89, 1.26–2.85), broader antimicrobial use including MRSA (OR 3.23), antifungal (OR 3.28), anaerobic (OR 2.92), and broad-spectrum therapy (OR 1.98), and higher rates of multidrug-resistant and polymicrobial infections.Outcomes were worse among culture-positive patients, including higher 30-day (OR 1.59), 90-day (OR 1.76), 180-day (OR 1.79), 3-year (OR 1.59), 4-year (OR 1.33), and 5-year mortality (OR 1.64). They were less likely to be discharged home (OR 0.41, 0.27–0.62) and more likely to require skilled nursing facility placement (OR 2.30, 1.05–5.05). Cumulative incidence of readmission did not differ significantly (Gray's p = 0.268). **Conclusion:** Culture-positive peritonitis in cirrhosis is associated with greater infection severity, increased procedural and critical care utilization, and worse short- and long-term survival. PFC positivity appears to be a meaningful prognostic marker and may identify patients requiring more aggressive management and closer follow-up.

Disclosures: Kahler Doyle:Nothing to Disclose, Brayden Doyle:Nothing to Disclose, Viraj Gandhi:Nothing to Disclose, Mohammad Ashfaq:Nothing to Disclose.

1604 | TIME-TO-TAP MATTERS: MORTALITY AND KIDNEY OUTCOMES WITH EARLY VS DELAYED PARACENTESIS IN SBP-ASSOCIATED HE

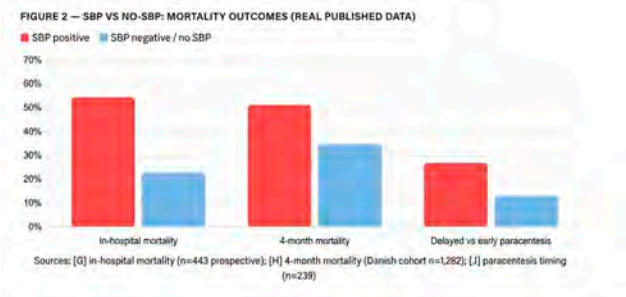
Azfar Hameed[1] Zakia Hameed[2] Diana Chavez Velasquez[3] Jorge Chavez Velasquez[3], [1]Hendrick Medical Center, [2]CMH Institute of Medical Sciences, Bahawalpur, Pakistan, [3]Universidad Privada Antenor Orrego

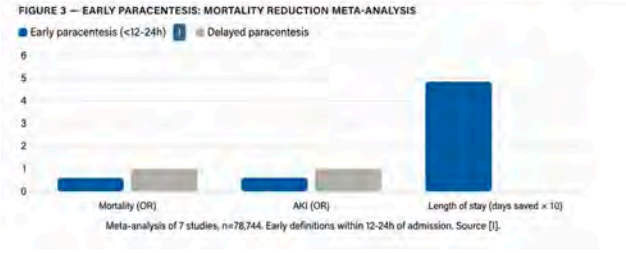
Background: Spontaneous bacterial peritonitis (SBP) is a high-impact, often clinically silent precipitant of hepatic encephalopathy (HE) in cirrhosis, with up to 50% lacking fever, leukocytosis, or abdominal tenderness. Although guidelines recommend diagnostic paracentesis for all hospitalized cirrhotics with ascites, real-world adherence remains inconsistent. We synthesized contemporary evidence to estimate SBP prevalence in this setting, quantify associated mortality, and evaluate whether early diagnostic paracentesis improves outcomes. **Methods:** Multi-source evidence synthesis included: a worldwide epidemiologic meta-analysis (99 studies; n = 5,861,142); a prospective ascites cohort (n = 443); a Danish national cohort (n = 1,282); two meta-analyses comparing early vs delayed paracentesis (n = 78,744 and n = 116,174); an SBP cohort study (n = 239); a national inpatient sample (n = 17,711); and ICU cohorts from MIMIC-III (n = 620) and MIMIC-IV (n = 601). SBP was defined as ascitic PMN $\geq$ 250 cells/mm³. Outcomes were in-hospital and 4-month mortality, acute kidney injury (AKI), and length of stay. **Results:** Across datasets, SBP occurred in 10%–30% of hospitalized cirrhotics with ascites and was associated with markedly higher mortality than sterile ascites (in-hospital 54.5% vs 22.8%; p < 0.001).

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Four-month mortality was 51.2% vs 34.7% without SBP (adjusted HR 1.54; 95% CI 1.18–2.00). In ICU HE cohorts, 28-day mortality was 18.64%. Despite risk, only 55.5% of hospitalized patients with HE and/or ascites underwent paracentesis. Early paracentesis ($\leq$12–24 hours) was associated with lower in-hospital mortality (OR 0.61; 95% CI 0.46–0.82; p = 0.001), reduced AKI (OR 0.62), and shorter hospitalization (−4.85 days; p < 0.001). In an SBP cohort, delayed paracentesis was associated with higher mortality (27% vs 13%; p = 0.007). **Conclusion:** SBP is a frequent and lethal, yet modifiable, contributor to adverse outcomes in cirrhotic HE. Evidence across large independent sources supports early diagnostic paracentesis as a scalable, quality-improvement target. Coagulopathy alone should not delay the procedure, given published safety data at INR up to 8 and platelets as low as 19,000/µL without prophylactic transfusion. Establishing universal early paracentesis for HE admissions with ascites may reduce preventable inpatient deaths.





Disclosures: Azfar Hameed:Nothing to Disclose, Zakia Hameed:Nothing to Disclose, Diana Chavez Velasquez:Nothing to Disclose, Jorge Chavez Velasquez: Nothing to Disclose.

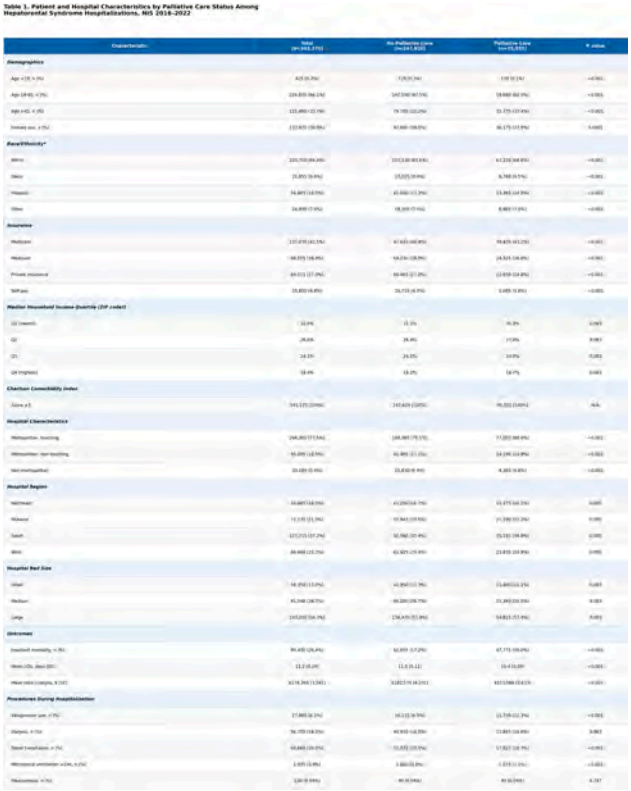
1605 | IMPACT OF PALLIATIVE CARE ON RESOURCE UTILIZATION AMONG HOSPITALIZATIONS WITH HEPATORENAL SYNDROME: A US NATIONAL STUDY (2016 TO 2022)

Abhin Sapkota[1] Anas Almoghrabi[2] Kriti Katuwal[3], [1]John H. Stroger Jr. Hospital of Cook County, [2]John H. Stroger, Jr. Hospital of Cook County, [3]Lumbini Medical College, Palpa, Nepal

Background: Hepatorenal syndrome (HRS) is associated with high morbidity, mortality, and healthcare utilization. Palliative care consultation (PCC) may promote goal-concordant care and optimize resource use, yet trends and disparities in PCC among HRS hospitalizations as well the impact on resource utilization remain unclear. We evaluated temporal trends, sociodemographic disparities, and the association of PCC with resource utilization in HRS hospitalizations across the United States. **Methods:** We performed a retrospective cohort study using the National Inpatient Sample from 2016 to 2022. Adult hospitalizations with a primary or secondary diagnosis of HRS were identified using ICD-10-CM code K76.7. PCC was identified using the validated ICD-10-CM code. Survey weights were applied to generate national estimates. Multivariable survey logistic regression identified predictors of PCC, adjusting for demographic factors, comorbidities and hospital characteristics. Resource utilization outcomes included total hospital charges, length of stay, vasopressor use, mechanical ventilation, blood transfusion, dialysis, and paracentesis. Temporal trends in PCC utilization were assessed across study years. **Results:** An estimated 343,175 hospitalizations with HRS were identified during the study period, of which 95,555 (27.8%) received PCC. In adjusted analysis, Hispanic patients had lower odds of receiving PCC compared with White patients, adjusted (aOR 0.77, p < 0.001) . Females also had lower odds compared with males (aOR 0.93, p < 0.001). PCC was more likely in metropolitan teaching hospitals, (aOR 1.59, p < 0.001) compared to rural hospitals, and among Medicaid (aOR 1.19, p < 0.001) and self-pay patients (aOR 1.59, p < 0.001) compared with Medicare beneficiaries. Mean total hospital charges were significantly lower in the PCC group (153,068 dollars vs 182,579 dollars, p < 0.001). Length of stay was shorter among patients receiving PCC, (10.44 vs 11.51 days, p < 0.001). Mortality was higher in the PCC group, approximately 50% versus 17%. Vasopressor use (aOR 1.65, p < 0.001) and ventilator use (aOR 1.47, p < 0.001) were more likely among PCC group, likely reflecting greater illness severity at the time of consultation. Blood transfusion (aOR 0.90, p < 0.001) was less likely among PCC group whereas dialysis and paracentesis rates were similar between groups. PCC utilization increased modestly from 25.3% in 2016 to 28.6% in 2022. **Conclusion:** From 2016 to 2022, PCC utilization among HRS hospitalizations increased slightly but has remained limited. Significant sociodemographic and hospital-level disparities persist. PCC was associated with reduced hospital charges and shorter length of stay, supporting its potential role in improving value-based care in this high-risk population. Strategies to promote equitable and timely access to palliative care in HRS are warranted.

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Disclosures: Abhin Sapkota:Nothing to Disclose, Anas Almoghrabi:Nothing to Disclose, Kriti Katuwal:Nothing to Disclose.

1606 | POST-TIPS URSODEOXYCHOLIC ACID USE AND RISK OF OVERT HEPATIC ENCEPHALOPATHY: A PROPENSITY SCORE–MATCHED REAL-WORLD STUDY

Miao Yi[1] Xiaoze Wang[1] Li Yang[2] Yi Fang[1] Yi Shen[1], [1]West China Hospital, Sichuan University, [2]Sichuan University, West China Hospital

Background: Transjugular intrahepatic portosystemic shunt (TIPS) is an established treatment for complications of portal hypertension in patients with cirrhosis; however, post-TIPS overt hepatic encephalopathy (OHE) remains a major limitation. Ursodeoxycholic acid (UDCA) modulates bile acid metabolism and may exert anti-inflammatory effects, potentially influencing OHE development through metabolic and neuroinflammatory pathways along the gut–brain axis. However, the association between postoepratie UDCA use and post-TIPS OHE remains unclear. This study aimed to evaluate the association between UDCA use and the risk of OHE after TIPS. **Methods:** We retrospectively included patients with cirrhosis undergoing TIPS at a single center from May 2015 to January 2025. Patients were classified by postoperative UDCA use (13–15 mg/kg/day). The primary outcome was OHE within 3 months. Secondary outcomes included OHE at 6 months and 1 year, 1-year rebleeding, HE-related readmission, transplant-free survival, and recurrent OHE. Propensity score matching and multivariable models were used. OHE was analyzed using Fine–Gray competing-risk models with death and liver transplantation as competing events. **Results:** Among 1,025 patients, 111 received UDCA and 914 did not. After matching, 91 UDCA users and 209 non-users were retained with balanced baseline characteristics. UDCA use was associated with a lower 3-month cumulative incidence of OHE (adjusted sHR 0.46, 95% CI 0.23–0.93; P = 0.032). Sensitivity analysis showed consistent results (sHR 0.48, 95% CI 0.25–0.90; P = 0.023). UDCA use showed non-significant trends toward lower OHE at 6 months and 1 year, without significant associations with other secondary outcomes. **Conclusion:** Postoperative UDCA use was associated with reduced short-term OHE risk after TIPS, warranting prospective validation. **Disclosures:** Miao Yi:Nothing to Disclose, Xiaoze Wang:Nothing to Disclose, Li Yang:Nothing to Disclose, Yi Fang:Nothing to Disclose, Yi Shen:Nothing to Disclose.

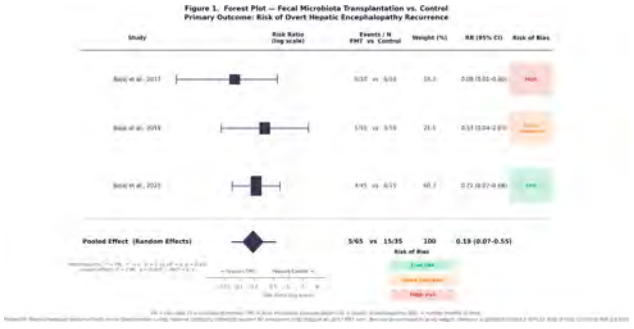
1608 | FECAL MICROBIOTA TRANSPLANTATION FOR HEPATIC ENCEPHALOPATHY IN CIRRHOSIS: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

Rohan Karkra[1] Mahinaz Mohsen[1] Sameer Rao[1] Ethan Shamsian[1] Sai Vendidandi[1] Ahmed Al-Khazraji[1] Zaid Tafesh[1] Paul Gaglio[1], [1]Rutgers New Jersey Medical School

Background: Hepatic Encephalopathy (HE) is a debilitating neuropsychiatric complication of cirrhosis associated with frequent hospitalizations and poor quality of life. Despite standard-of-care therapy with lactulose and rifaximin, a substantial proportion of patients experience recurrent episodes. Fecal Microbiota Transplantation (FMT) has emerged as a microbiome-targeted intervention with mechanistic plausibility, as it modulates the gut-liver-brain axis and may shift the colonic microbiome toward a less encephalopathogenic milieu. We conducted a systematic review and meta-analysis of all published randomized controlled trials (RCTs) evaluating FMT in patients with cirrhosis and HE. **Methods:** We conducted a systematic search of PubMed, Embase, and ClinicalTrials.gov databases through January 2026 to identify all trials evaluating

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FMT in HE. The primary outcomes analyzed with meta-analysis were HE recurrence within a 6-month follow-up period and FMT-related serious adverse events. Secondary outcomes included hospitalization, cognitive function (Psychometric Hepatic Encephalopathy Score [PHES]), quality of life (Sickness Impact Profile), mortality, and microbiome engraftment. Risk of bias was assessed using the Cochrane RoB 2.0 tool. Pooled Risk Ratios (RRs) were derived using the Mantel-Haenszel random-effects method. This study conformed to PRISMA guidelines. **Results:** We identified 3 RCTs involving 100 patients (86% male; 63.3 ± 8.2 years). Pooled RR for HE recurrence with FMT was approximately 0.19 (95% CI: 0.07–0.55; $p < 0.05$), representing an 81% relative risk reduction. No FMT-related adverse events were reported in the RCT participants. We also identified a non-randomized study ($n = 10$, no control arm) that showed a cognitive benefit (PHES +3.1 points at 4-weeks post-FMT, $p < 0.05$) and documented the sole FMT-related adverse event: a case of ESBL-producing E. coli bacteremia transmitted through FMT capsules. Hospitalization rates, cognitive function, and microbial engraftment consistently favored FMT across all studies ($p < 0.05$). 0 deaths were reported in any patient, except 1 who was transitioned to hospice. FMT increased beneficial, SCFA-producing bacteria and reduced pathobionts, while patients in the placebo group had worsening dysbiosis. Successful donor engraftment was highest with combined oral and enema interventions. To note, all RCTs originated from a single investigator group. **Conclusion:** FMT was consistently efficacious in reducing HE recurrence and hospitalization in patients with cirrhosis on standard therapy, with an 81% relative risk reduction across 3 RCTs. The aggregate safety profile is highly favorable in the RCT setting, though the documented ESBL E. coli bacteremia in one study underscores the need for rigorous donor pathogen screening and careful patient selection. Independent multicenter phase 3 trials are required before guideline adoption.



Disclosures: Rohan Karkra:Nothing to Disclose, Mahinaz Mohsen:Nothing to Disclose, Sameer Rao:Nothing to Disclose, Ethan Shamsian:Nothing to Disclose, Sai Vendidandi:Nothing to Disclose, Ahmed Al-Khazraji: Nothing to Disclose, Zaid Tafesh:Nothing to Disclose, Paul Gaglio:Nothing to Disclose, Nothing to Disclose, Nothing to Disclose.

1609 | COMPARATIVE EFFECTIVENESS OF TERLIPRESSIN VERSUS MIDODRINE/OCTREOTIDE FOR

Razan Aburumman[1] Saqr Alsakarneh[2] Kevin Harris[1] Suraj Suresh[1], [1]Henry Ford Hospital, [2]The Mayo Clinic, Rochester

Background: Hepatorenal syndrome (HRS) is a severe, life-threatening complication of advanced cirrhosis and liver failure. While terlipressin has been approved for treatment of HRS, real-world comparative effectiveness data against standard medical therapy remain limited. **Methods:** We conducted a retrospective cohort study using the TriNetX US Collaborative Network, including 66 healthcare organizations. Adult patients with cirrhosis who were diagnosed with HRS were identified and stratified into two cohorts. The first group included patients who received terlipressin, and the control group included patients who received standard therapy (midodrine, octreotide, and albumin). Patients with a history of HCC or liver transplantation (LT) before the index event were excluded. Outcomes were assessed at 30 and 90 days following the index event. Propensity score matching (1:1) was performed using 29 variables, including demographics, comorbidities, medications, and laboratory values. Primary outcomes included mortality, dialysis requirement, ICU admission, intubation, respiratory failure, pulmonary edema, kidney transplant (KT), and LT. Kaplan-Meier survival analyses were used to compare outcomes between cohorts, with hazard ratios (HRs) and 95% confidence intervals (CIs) reported. **Results:** Before matching, 393 patients received terlipressin and 12,322 received standard therapy. After propensity matching, 380 patients remained in each group for the 30-day analysis and 242 patients per group for the 90-day analysis. At 30-days, terlipressin use was associated with a significantly lower risk of ICU admission (HR 0.734, 95% CI 0.580–0.927; $p = 0.010$) and mortality (HR 0.732, 95% CI 0.573–0.936; $p = 0.012$). There were no significant differences between groups in dialysis (HR 0.919, 95% CI 0.660–1.280; $p = 0.616$), respiratory failure (HR 0.933, 95% CI 0.714–1.219; $p = 0.627$), intubation (HR 0.705, 95% CI 0.465–1.067; $p = 0.097$), or pulmonary edema (HR 1.150, 95% CI 0.799–1.654; $p = 0.445$). However, terlipressin was associated with a significantly higher likelihood of LT within 30 days (HR 2.078, 95% CI 1.201–3.595; $p = 0.007$).At 90 days, there was no significant

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difference in requiring dialysis (HR 1.062, 95% CI 0.685–1.646; p = 0.788), ICU admission (HR 0.970, 95% CI 0.734–1.282; p = 0.869), mortality (HR 0.853, 95% CI 0.650–1.119; p = 0.247), intubation (HR 0.813, 95% CI 0.519–1.273; p = 0.366), respiratory failure (HR 1.243, 95% CI 0.911–1.697; p = 0.161), pulmonary edema (HR 1.297, 95% CI 0.832–2.022; p = 0.247) or KT. However, terlipressin remained associated with a higher likelihood of LT (HR 2.031, 95% CI 1.151–3.586; p = 0.012). There was also no difference in KT rates between groups (HR 0.945, 95% CI 0.417–2.142; p = 0.893). **Conclusion:** Terlipressin was associated with improved 30-day outcomes. The absence of sustained benefit at 90 days suggests that its primary role may be as a bridge to transplantation.

Variable	Before Matching Terlipressin (n=393)	Before Matching Control (n=12,322)	Std Diff	After Matching Terlipressin (n=380)	After Matching Control (n=380)	Std Diff
Age, mean ± SD	57.2 ± 12.4	62.2 ± 12.6	0.403	57.2 ± 12.5	56.7 ± 12.9	0.040
Female, %	42.2	40.4	0.037	42.6	42.9	0.005
White, %	77.4	76.2	0.027	76.8	75.3	0.037
Hepatic encephalopathy, %	72.3	33.6	0.839	71.6	71.8	0.006
Ascites, %	78.6	71.9	0.157	78.7	77.1	0.038
Chronic kidney disease, %	54.2	42.8	0.229	54.2	59.2	0.101
Diabetes mellitus, %	36.1	32.8	0.070	36.8	41.1	0.086
Heart failure, %	18.8	18.9	0.002	18.9	20.5	0.040
Beta-blockers, %	47.6	47.4	0.004	48.7	47.9	0.016
ACEi/ARB, %	12.7	8.4	0.142	13.2	13.2	<0.001
NSAIDs, %	15.5	17.1	0.042	16.1	17.6	0.042
Aldosterone antagonists, %	52.9	53.6	0.013	53.9	52.4	0.032
Proton pump inhibitors, %	75.6	70.2	0.120	75.5	78.7	0.075
Lactulose, %	74.3	65.9	0.185	73.9	74.7	0.018
Rifaximin, %	50.4	45.1	0.105	49.5	51.6	0.042
Albumin (g/dL), mean ± SD	3.2 ± 0.7	2.8 ± 0.7	0.481	3.2 ± 0.7	2.9 ± 0.7	0.442
Creatinine (mg/dL), mean ± SD	2.9 ± 1.3	2.8 ± 2.7	0.021	2.9 ± 1.3	2.9 ± 1.8	0.007
BUN (mg/dL), mean ± SD	54.5 ± 25.7	48.4 ± 28.5	0.225	54.4 ± 25.9	48.6 ± 30.6	0.205
Sodium (mmol/L), mean ± SD	132.0 ± 5.8	131.9 ± 6.6	0.022	132.1 ± 5.7	132.4 ± 6.3	0.060
INR, mean ± SD	2.0 ± 0.8	2.0 ± 0.9	0.057	2.0 ± 0.8	2.1 ± 1.0	0.043
Platelets (×10³/μL)	115.2 ± 81.6	123.0 ± 85.5	0.093	115.0 ± 80.7	115.8 ± 78.2	0.010
Total bilirubin (mg/dL)	10.5 ± 12.7	10.4 ± 11.6	0.010	10.4 ± 12.7	10.8 ± 11.5	0.035

Table 1. Baseline Characteristics Before and After Propensity Score Matching

Disclosures: Razan Aburumman:Nothing to Disclose, Saqr Alsakarneh:Nothing to Disclose, Kevin Harris: Nothing to Disclose, Suraj Suresh:Nothing to Disclose.

1610 | THE USE OF MIDODRINE IN LIVER CIRRHOSIS PATIENTS WITH HYPERVOLEMIC HYPONATREMIA: LARGEST SYSTEMATIC REVIEW

Beshoy Yanny[1] Momin Masroor[2] Peter Nguyen[2] Michelle Nguyen[1] Marie Balfour[1] Yao (Michelle) Lan[2] Lora Ibrahim[1] Trinity Michael[1] Kirellos Mikhail[3],
[1]University of California, Irvine, [2]UCI Health, [3]University of California, Los Angeles

Background: Hypervolemic hyponatremia is a challenging complication that occur in patients with hepatic cirrhosis. Hyponatremia is an independent predictor of mortality and is incorporated into the MELD score to better risk stratify cirrhosis severity. Midodrine is an alpha-1 adrenergic agonist and can counteract with splanchnic vasodilation. This will improve hemodynamics associated with RAAS and free water excretion. Our systematic review aims to study the efficacy of midodrine to improve hyponatremia in such patients. **Methods:** Literature review was done using multiple databases, including PubMed and ClinicalTrials.gov through April 2026. Included studies evaluated the administration of midodrine compared to standard of care in adult and pediatric patients with liver cirrhosis and concurrent hypervolemic hyponatremia. The primary efficacy outcomes were the incidence of hyponatremia and mean change in sodium levels. Secondary outcomes included the incidence of acute kidney injury and mean change in serum creatinine from baseline. **Results:** Six randomized controlled trials comprising 340 patients (305 adult patients and 35 pediatric patients) were included. Midodrine significantly reduced the overall incidence of hypervolemic hyponatremia (RR 0.47, 95% CI 0.28-0.78, p = 0.004). While short-term sodium changes were comparable to standard care, subgroup analysis revealed midodrine provided a significant serum sodium increase during medium-to-long-term follow-up (≥ 28 days) with a mean difference of +1.39 mEq/L (95% CI 0.24-2.55, p = 0.018). Furthermore, acute kidney injury (AKI) incidence was significantly lower in the midodrine arm (12.2% vs 23.8%; RR 0.56, 95% CI 0.35-0.90, p = 0.017), although overall mean creatinine reduction was non-significant (-0.06 mg/dL, p = 0.188). **Conclusion:** Treatment with Midodrine as an alpha-1 adrenergic agonist is effective for hypervolemic hyponatremia and AKI in advanced cases of hepatic cirrhosis. Sodium correction is believed to support overall survival and quality of life. Further large-scale, multicenter studies are needed to validate these findings and establish standardized dosing protocols.



Figure 2: Forest plot comparing the mean difference in serum sodium levels between midodrine and control therapies. While the overall pooled effect crosses the line of no effect, subgroup analysis reveals a distinct temporal trend: short-term administration (≤7 days) yields comparable sodium stabilization to standard care, whereas midodrine provides a statistically significant improvement in maintaining higher serum sodium during medium-to-long-term follow-up (≥28 days).

Disclosures: Beshoy Yanny:IPSEN Pharmaceuticals: Speaker, IPSEN Pharmaceuticals: Speaker, Madrigal Pharmaceutical: Speaker, Momin Masroor:Nothing to Disclose, Peter Nguyen:Nothing to Disclose, Michelle Nguyen:Nothing to Disclose, Marie Balfour:Nothing to Disclose, Yao (Michelle) Lan:Nothing to Disclose, Lora Ibrahim:Nothing to Disclose, Trinity Michael:Nothing to Disclose, Kirellos Mikhail:Nothing to Disclose.

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1611 | ENDOTOXIN ACTIVITY PREDICTS FIRST AND FURTHER DECOMPENSATION IN CIRRHOSIS

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Background: Endotoxemia contributes to systemic inflammation and disease progression in cirrhosis; however, its association with hepatic decompensation based on the Baveno VII consensus remains unclear. We investigated whether endotoxin activity predicts first and further decompensation in cirrhosis. **Methods:** We retrospectively analyzed 431 patients with compensated cirrhosis evaluated between January 2014 and December 2024. Among 78 patients who developed first decompensation during follow-up, predictors of further decompensation were additionally analyzed. First and further decompensation were defined according to the Baveno VII consensus. Serum endotoxin activity was assessed using the Endotoxin Activity Assay (EAA). Clinical variables including hepatic reserve, renal function, inflammatory markers, and fibrosis-related parameters were evaluated. Cox proportional hazards models were used to identify independent predictors of decompensation. Receiver operating characteristic (ROC) analyses were performed to assess predictive performance, and Kaplan–Meier analyses were used to compare cumulative incidence rates according to EAA stratification. **Results:** The mean age was 69.5 years, and 263 patients (61.0%) were male. Etiologies included HCV (n = 114), HBV (n = 40), ALD (n = 93), MetALD (n = 29), MASH (n = 89), and others (n = 66). During follow-up, 78 patients developed first decompensation, and 49 subsequently developed further decompensation. Multivariate Cox proportional hazards analysis identified low albumin levels and high EAA values as independent predictors of first decompensation. In ROC analysis, EAA showed good predictive performance (AUC 0.752), comparable to albumin (AUC 0.735; p = 0.699). Patients with elevated EAA values demonstrated significantly higher cumulative incidences of both first and further decompensation than those with low EAA values. High EAA values were also independently associated with further decompensation and showed favorable predictive ability (AUC 0.783). These findings suggest that endotoxemia may contribute not only to initial hepatic deterioration but also to progression toward recurrent decompensating events. **Conclusion:** Elevated endotoxin activity was independently associated with both first and further decompensation in cirrhosis. EAA may serve as a useful biomarker for risk stratification based on the Baveno VII framework and may help identify patients at high risk for progressive hepatic decompensation requiring closer monitoring and early therapeutic intervention.

Disclosures: Akihiko Shibamoto:Nothing to Disclose, Tadashi Namimsaki:Nothing to Disclose, Yui Osaki: Nothing to Disclose, Hitoshi Mori:Nothing to Disclose, Shinya Sato:Nothing to Disclose, NORIHISA NISHIMURA:Nothing to Disclose, KOSUKE KAJI:Nothing to Disclose, Hitoshi Yoshiji:Nothing to Disclose.

1612 | EVALUATING THE IMPACT OF PRIMARY PROPHYLAXIS FOR SPONTANEOUS BACTERIAL PERITONITIS ON INFECTIOUS AND SAFETY OUTCOMES IN PATIENTS WITH CIRRHOSIS

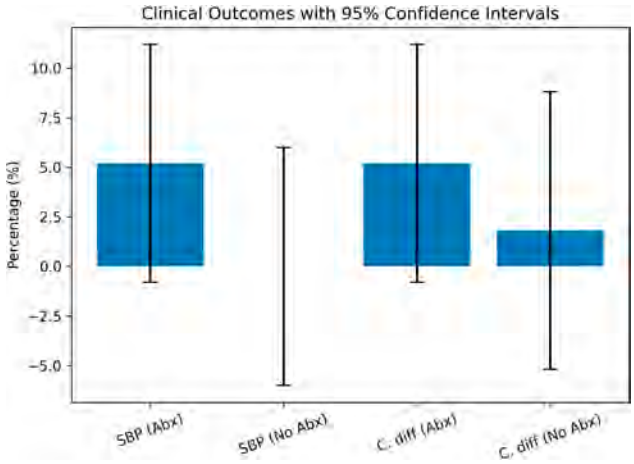
Alekhya Mannava[1] Gokturk Tepe[2] Katie Zhang[3] Jaime Perez[2] Resham Ramkissoon[2], [1]University Hospitals Cleveland Medical Center, Case Western, [2]University Hospitals Cleveland Medical Center, Case Western Reserve University, [3]Case Western Reserve University School of Medicine

Background: Spontaneous bacterial peritonitis (SBP) is a serious complication of cirrhosis. Although AASLD guidelines recommend primary antibiotic prophylaxis for high-risk patients, supporting evidence remains limited, with concerns regarding C. difficile infection, drug toxicity, and antimicrobial resistance. This study examined prophylaxis eligibility, prescribing patterns, and safety outcomes in hospitalized cirrhotic patients. **Methods:** We conducted a retrospective chart review of 114 adults with cirrhosis evaluated at our tertiary care center over a 10-year period. Demographic, clinical, and laboratory data were collected at the index paracentesis, including renal and liver function markers, MELD-3.0 score, and ascitic fluid studies. Patients were categorized by whether they met AASLD criteria for primary SBP prophylaxis and whether prophylactic antibiotics were prescribed. Outcomes included SBP, C. difficile infection, antimicrobial resistance, and culture results. **Results:** Of 114 patients, 70% met criteria for primary prophylaxis and 51% received antibiotics. Those meeting criteria had more advanced disease, with higher creatinine (1.9 vs. 0.7 mg/dL, p0.001), BUN (29.9 vs. 14.4 mg/dL, p0.001), bilirubin (5.9 vs. 1.4 mg/dL, p0.001), INR (1.7 vs. 1.4, p0.001), MELD-3.0 (24.3 vs. 13.7, p0.001), WBC (9.3 vs. 7.0 $\times 10^3/\mu L$, p = 0.006), and AST (92.1 vs. 43.2 U/L, p0.001).Prophylaxis recipients were younger (59.9 vs. 64.8 years, p = 0.043), had more alcohol-associated liver disease (81.0% vs. 58.9%, p = 0.010), lower sodium (134.3 vs. 136.4 mmol/L, p = 0.031), higher MELD-3.0 (22.5 vs. 19.5, p = 0.046), and lower hemoglobin (9.0 vs. 9.7 g/dL, p = 0.016). C. difficile infection was uncommon (3.5%) with no difference by antibiotic

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exposure (5.2% vs. 1.8%; p = 0.619). SBP incidence was low (2.6%), occurring only in antibiotic recipients (5.2% vs. 0%; p = 0.244). Secondary prophylaxis was rare (6.2%) and strongly associated with prior SBP (71.4% vs. 1.9%; p0.001). No antibiotic-resistant or multidrug-resistant organisms were identified. **Conclusion:** Nearly half of patients meeting AASLD criteria for primary SBP prophylaxis did not receive recommended therapy, revealing a substantial guideline adherence gap. Clinical decision-making appeared driven by subjective severity impressions rather than established criteria, contributing to both underuse in high-risk patients and use in lower-risk individuals. These findings identify an actionable opportunity to standardize prophylaxis practices and potentially reduce preventable SBP. Adverse events among antibiotic recipients, including C. difficile and antimicrobial resistance, were rare, suggesting prophylaxis was generally well tolerated, though low event rates limit efficacy conclusions. These findings highlight variability in patient severity and underscore the need for larger studies to define the benefit–risk profile of primary SBP prophylaxis.



Disclosures: Alekhya Mannava:Nothing to Disclose, Gokturk Tepe:Nothing to Disclose, Katie Zhang:Nothing to Disclose, Jaime Perez:Nothing to Disclose, Resham Ramkissoon:Nothing to Disclose.

1613 | VARIABILITY AND CLINICAL CORRELATES OF AMMONIA IN COMPENSATED CIRRHOSIS: A MULTICENTER STUDY FROM THE LIVER CIRRHOSIS NETWORK

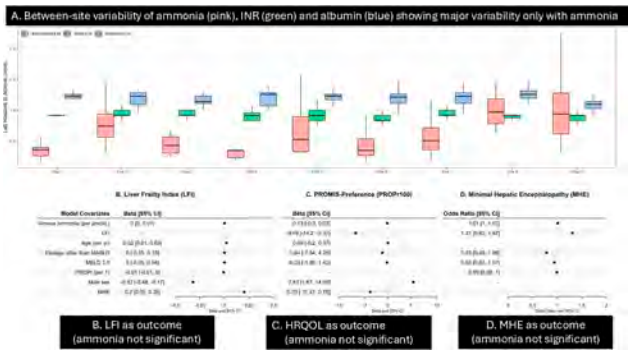
Jasmohan Bajaj[1] Elliot Tapper[2] David Goldberg[3] Douglas Simonetto[4] Mandana Khalili[5] Srinivasan Dasarathy[6] Elizabeth Verna[7] Arun Sanyal[1] Neehar Parikh[2] Bilal Hameed[8] Vijay Shah[4] Andrew Scheinberg[3] Giuseppe Cullaro[9] Nicole Welch[6] Miranda Gurra[10] Lauren Bonner[10], [1]Virginia Commonwealth University, [2]University of Michigan Medical Center, [3]University of Miami, [4]Mayo Clinic Rochester, [5]University of California, San Francisco, [6]Cleveland Clinic, [7]Columbia University Medical Center, [8]UCSF, [9]Columbia University, [10]Northwestern University

Background: Elevated blood ammonia is implicated in hepatic encephalopathy, frailty, and cognitive impairment in cirrhosis, but ammonia measurement is difficult to standardize across institutions. We characterized between-site variability in ammonia levels and evaluated the association of elevated ammonia levels with frailty, cognitive function [minimal hepatic encephalopathy (MHE) on EncephalApp Stroop], and health-related quality of life (HRQOL) in compensated cirrhosis. Aim: Determine whether ammonia levels predicted cognitive impairment, frailty, or HRQOL. **Methods:** Cross-sectional analysis of a prospective cohort of adults with compensated cirrhosis enrolled at 7 centers (9 clinical sites) of the NIH-supported Liver Cirrhosis Network (LCN). Each sample was tested at the local laboratory for each site. Variations between sites were assessed as levels above the upper limit of normal (ULN) for ammonia and INR, and below the lower limit of normal (LLN) for serum albumin. Outcome measures were: Frailty using Liver Frailty Index (LFI), cognitive function using MHE on Stroop, and health-related quality of life using the PROPr (0–100). Multivariable linear regression evaluated the association of venous ammonia with PROPr and LFI while logistic regression was done for MHE, adjusting for the other two outcome measures and clinical covariates. MHE and ULN ammonia percent were compared. **Results:** Among 334 participants (mean age 61 years, 59% male, 44% with MASLD, mean MELD 3.0 of 9), 56% had MHE. 60 (19%) had an ammonia level ≥ ULN. Ammonia levels (and ULN) varied substantially across the 9 sites, while albumin and INR were relatively consistent (Fig A). 14% with ammonia. Ammonia > ULN proportion was statistically similar in MHE/not (14 vs 22%, p = 0.07). In multivariable models, higher ammonia levels were not independently associated with MHE on Stroop (OR 1.01, 95% CI 1.00-1.03; p = 0.2, Fig B), PROPr (β = −0.13; 95% CI −0.30 to 0.03; p = 0.12, Fig C) or with LFI (β = 0.00; 95% CI 0.00 to 0.01; p = 0.4, Fig D). However, LFI was independently associated with both Stroop time (β = 19; 95% CI 8.3 to 30; p < 0.001) and PROPr (β = −10; 95% CI −15 to −5.8; p < 0.001). **Conclusion:** In a multicenter cohort of patients with compensated cirrhosis, venous ammonia levels varied markedly across institutions while standard liver synthetic markers did not. After multivariable adjustment, higher laboratory values for venous ammonia were not independently associated with MHE, frailty, or health-related quality of life. Ammonia levels do not significantly affect clinical,

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HRQOL, cognitive, and frailty measures in a multicenter compensated cirrhosis cohort and have limited clinical utility.



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1614 | REAL-WORLD PATTERNS OF RIFAXIMIN PROPHYLAXIS AROUND TIPS: A MULTICENTRE COHORT STUDY OF HEPATIC ENCEPHALOPATHY PREVENTION

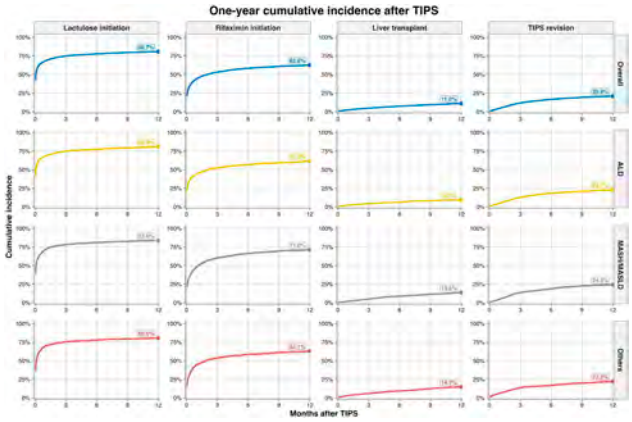
Yee Hui Yeo[1] Sheng-Yin Chen[2] Hanyou Loh[3] Peng-Sheng Ting[4] Dian-Jung Chiang[5] Chuanlong Zhu[6] Feng Zhang[7], [1]Cedars Sinai Medical Center, [2]Massachusetts General Hospital and Harvard Medical School, [3]Canton Medical Education Foundation, [4]Tulane University School of Medicine, [5]Cleveland Clinic Foundation, [6]The First Affiliated Hospital with Nanjing Medical University, [7]Affiliated Hospital of Medical School, Nanjing University

Background: Recent professional guideline recommended starting rifaximin prophylaxis from 14 days before elective transhepatic intrahepatic portosystemic shunt (TIPS) through at least 6 months after to prevent post-TIPS hepatic encephalopathy (HE). Due to rifaximin cost and access disparities, real-world uptake of guideline-adherent prophylaxis remains uncertain. We evaluated peri-TIPS HE-directed therapy use and the cumulative incidence of TIPS revision. **Methods:** We performed a retrospective cohort study using the TriNetX US Collaborative Network (66 healthcare organizations) on adults with cirrhosis undergoing TIPS between 1/1/2006 and 3/30/2026. Patients with prior TIPS or liver transplant were excluded. Outcomes included the prescription of lactulose, rifaximin, liver transplant, and TIPS revision. Follow-up extended to 12 months post-TIPS or outcome occurrence. Kaplan-Meier analyses were stratified by etiology. Pre-TIPS medication exposure, including prophylaxis window (-14 to 0 days) and baseline treatment window (-180 to -15 days), was assessed. **Results:** The cohort included 8,839 patients who underwent TIPS (mean age 57.5 ± 11.2 years; 62.5% male). ALD was the most common etiology (N = 2,829, 32%), followed by MASH/MASLD (N = 1,738, 19.7%). Patients with MASH demonstrated the highest proportions of hypertension (70.9%), diabetes (72.5%), and obesity (BMI ≥ 30: 47.5%). Within 14 days before TIPS, lactulose use was observed in 24.8% of patients, while rifaximin use was documented in only 14.3%. The prevalence of lactulose prescription increased to 42% on the first day post-TIPS, while it was 20.8% for rifaximin. Kaplan-Meier analyses demonstrated substantial

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cumulative incidence of HE-directed treatment after TIPS across all etiologies, and about a fifth of patients across all etiologies went on to require TIPS revision within a year after the procedure. Notably, there were 29.4% and 17.7% using lactulose and rifaximin, respectively, during the -180 to -15 day baseline window, indicating a significant proportion of patients with underlying/treated HE received TIPS. **Conclusion:** In this large real-world cohort, peri-TIPS rifaximin prophylaxis was infrequently used despite evolving guideline recommendations. These findings highlight an implementation gap between evidence-based recommendations and clinical practice, potentially driven by medication cost, access, and subspecialty care disparities.



Disclosures: Yee Hui Yeo:Nothing to Disclose, Sheng-Yin Chen:Nothing to Disclose, Hanyou Loh:Nothing to Disclose, Peng-Sheng Ting:Nothing to Disclose, Dian-Jung Chiang:IPSEN: Medical Advisory Board, Gilead: Advisor, Chuanlong Zhu:Nothing to Disclose, Feng Zhang:Nothing to Disclose.

1616 | INTESTINAL COLONIZATION WITH MULTIDRUG-RESISTANT ORGANISMS IN PATIENTS WITH CIRRHOSIS: PREVALENCE, RISK FACTORS AND CLINICAL SIGNIFICANCE

Krystalia Dimitriou[1] Vasileios Sevastianos[2] Florentia Athanasaki[1] Nektarios Karamanolis[1] Larisa Vasilieva[3] Dimitra Krystallaki[1] Eleni Geladari[2] Helen Sambatakou[1] Georgia Vrioni[4] Alexandra Alexopoulou[1], [1]Hippokration General Hospital, Athens, Greece, [2]Evangelismos General Hospital, Athens, Greece, [3]Department of Gastroenterology, "Alexandra" Hospital, Athens, Greece, [4]Department of Microbiology, Medical School, NKUA, Greece

Background: Bacterial infections (BIs) caused by multidrug-resistant organisms (MDROs) have emerged as a major global healthcare concern. In patients with liver cirrhosis (LC), pathological bacterial translocation of gut-derived bacteria commonly occurs, leading to endogenous BIs such as spontaneous bacterial peritonitis and spontaneous bacteremia. Therefore, intestinal colonization (IC) by MDROs is of clinical importance. The aim of this study was to evaluate the characteristics of patients with LC colonized by MDROs and to investigate the potential role of these colonizing organisms in the development of subsequent endogenous BIs. **Methods:** Rectal swab samples were collected within one hour of presentation. Cultures were performed on chromogenic media, followed by identification of isolated microorganisms using mass spectrometry. Detection of carbapenem-resistant *Enterobacterales* (CRE) was carried out using immunochromatographic methods, while antimicrobial susceptibility testing and minimum inhibitory concentrations were determined. Patients were followed for 6 months after rectal sampling, and all culture-positive BIs were recorded. **Results:** A total of 71 consecutive patients [80.3% male, median age (IQR) 63 (54–77) years, Child-Pugh score 9 (7–10)] were enrolled. The etiology of LC was viral at 52.1%, alcohol-related at 14.1%, and other in 33.8%. IC by MDROs was identified in 40.8% of patients. Among colonized individuals, 72.4% demonstrated polymicrobial IC (≥ 2 bacterial species). Extensively drug-resistant (XDR) were the most frequently isolated (62.1%), followed by multidrug-resistant (MDR) (31%) and pandrug-resistant (PDR) organisms (6.9%). The most isolated bacteria were vancomycin-resistant Enterococcus faecium (VRE) (47%), carbapenem-resistant Enterobacterales (CRE) producing *Klebsiella pneumoniae* carbapenemase (KPC-CRE) (9.8%), and CRE co-producing KPC and New Delhi metallo-β-lactamase (KPC/NDM-CRE) (9.8%).In univariate analysis, recent antibiotic use, rifaximin exposure, history of hepatic encephalopathy, high Child-Pugh score, and recent hospitalization were associated with IC by MDROs. In multivariate analysis, only recent antibiotic exposure remained independently associated with IC by MDROs (OR 6.19, 95% CI 1.44–26.55, $p = 0.014$). During follow-up, a subsequent culture-positive BI was documented in 22 and endogenous BIs accounted for 15 patients. In 10 (45.5%), the isolated pathogen was identical to the colonizing strain. **Conclusion:** Patients with LC demonstrate high rates of IC by MDROs, with XDR representing the predominant resistance phenotype. Recent antibiotic exposure was identified as the only independent risk factor for MDRO colonization. In nearly half of culture-positive BIs, the isolated pathogen matched the IC strain, suggesting a possible association between IC and subsequent endogenous infection.

Disclosures: Krystalia Dimitriou:Nothing to Disclose, Vasileios Sevastianos:Nothing to Disclose, Florentia Athanasaki:Nothing to Disclose, Nektarios

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Karamanolis:Nothing to Disclose, Larisa Vasilieva: Nothing to Disclose, Dimitra Krystallaki:Nothing to Disclose, Eleni Geladari:Nothing to Disclose, Helen Sambatakou:Nothing to Disclose, Georgia Vrioni:Nothing to Disclose, Alexandra Alexopoulou:Nothing to Disclose.

1617 | NEW SUBMISSIONHIGH VS NORMAL AMMONIA-TO-UREA RATIO AND CLINICAL OUTCOMES IN CIRRHOSIS: A MULTICENTER RETROSPECTIVE COHORT STUDY

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Background: Hyperammonemia contributes to cirrhosis-related complications, yet serum ammonia alone incompletely reflects hepatic nitrogen handling. An elevated ammonia-to-urea (A:U) ratio has been linked to portal hypertension and varices, but its association with clinical outcomes in cirrhosis is not well characterized.We evaluated the association between a high A:U ratio phenotype and major cirrhosis-related decompensation outcomes in a large, multicenter cohort. **Methods:** We conducted a retrospective cohort study using the TriNetX Global Collaborative Network, including adults ($\geq$18 years) with cirrhosis defined by ICD-10 codes K74.x or K70.3. The benchmark for a high A:U ratio was derived from Ouahbi et al., who identified an A:U ratio >1.53 mg/g as predictive of clinically significant portal hypertension, unit harmonization yielded a clinically equivalent cutoff of ammonia/BUN > 1.92. The high A:U cohort was defined by ammonia $\geq$50 µmol/L and BUN $\leq$15 mg/dL, while the normal A:U cohort was defined by ammonia $\leq$49 µmol/L and BUN $\geq$16 mg/dL.Propensity score matching (1:1) balanced baseline characteristics, yielding 12,488 patients per cohort. Outcomes were identified using ICD-10 and CPT codes and included hepatic encephalopathy (HE), portal hypertension, variceal bleeding, spontaneous bacterial peritonitis (SBP), hepatorenal syndrome (HRS), gastrointestinal bleeding, ascites, and transjugular intrahepatic portosystemic shunt (TIPS). Risk differences (RD), risk ratios(RR), odds ratios (OR), Kaplan–Meier analyses with log-rank testing, hazard ratios (HR), and number-of-instances t-tests were performed **Results:** Compared with the normal A:U cohort, the high A:U cohort had higher risk of HE (30.7% vs 16.4%; RD −0.143 [95% CI −0.154 to −0.132], RR 0.535 [0.508–0.563], OR 0.443 [0.415–0.474]; log-rank p<0.001; HR 0.503 [0.475–0.533]), variceal bleeding (13.2% vs 8.4%; RD −0.048 [−0.057 to −0.040], RR 0.635 [0.588–0.687], OR 0.602 [0.552–0.657]; log-rank p<0.001; HR 0.633 [0.583–0.687]), portal hypertension (34.7% vs 26.5%; log-rank p<0.001; HR 0.741 [0.701–0.783]), and TIPS placement (3.0% vs 1.4%; log-rank p<0.001; HR 0.494 [0.413–0.592]). Conversely, the high A:U cohort had lower risk of HRS (4.5% vs 10.9%; RD 0.064 [0.057–0.071], RR 2.410 [2.188–2.656], OR 2.584 [2.329–2.866]; log-rank p<0.001; HR 2.548 [2.305–2.816]) and SBP (5.6% vs 7.6%; RD 0.020 [0.014–0.026]; log-rank p<0.001; HR 1.411 [1.277–1.559]). Overall gastrointestinal bleeding rates were similar between groups (18.6% vs 18.9%; p=0.612). **Conclusion:** High ammonia-to-urea ratio was associated with increased risks of HE, portal hypertension, variceal bleeding, and TIPS placement, but lower rates of HRS and SBP. Impaired hepatic urea synthesis and nitrogen detoxification, rather than hyperammonemia alone, may drive specific decompensation pathways.. This readily available laboratory phenotype may refine prognostication in cirrhosis

Disclosures: chimezirim ezeano:Nothing to Disclose, Moises Garcia:Nothing to Disclose, Jaimy Villavicencio Kim:Nothing to Disclose, Siddesh Besur:Nothing to Disclose.

1618 | PLATELET COUNT <135/MM^3 PREDICTS SBP RECURRENCE ON SECONDARY SBP PROPHYLAXIS IN A NATIONAL CIRRHOSIS COHORT

Scott Silvey[1] Nilang Patel[1] Jacqueline O'Leary[2] Heather Patton[3] Sofia Jakab[4] Timothy Morgan[5] Shari Rogal[6] Jasmohan Bajaj[7], [1]VCU, [2]UTSW, [3]VA San Diego Healthcare, [4]Yale University, [5]VA Long Beach Healthcare System, [6]University of Pittsburgh, [7]Virginia Commonwealth University

Background: The effectiveness of secondary SBP prophylaxis (SecSBPPr) for preventing SBP recurrence is being questioned. However, the predictors of success with SecSBBPr (i.e. prevention of recurrence) in the current situation are unclear. **Aim** : Determine clinical predictors associated with lower recurrence after SecSBPPr that can maximize effectiveness. **Methods:** We created a cohort of pts with first (index) SBP who had SecSBPPr initiated (continuous ciprofloxacin/Bactrim post-SBP with $\geq$1 additional outpatient refill up to 120 days post-initiation) using the VA Corporate data warehouse (CDW) between 2009-2019. Follow-up was 30 days post-discharge through 2 yrs post-initiation. Those who died, received a liver transplant (LT), or were lost to follow-up were excluded. SBP recurrence: defined as a new episode $\geq$30 days post-index case. Demographics, cirrhosis severity & Charlson comorbidity index (CCI) were collected &

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compared between with/without recurrence. Death and LT were considered competing events. Time-to-event analyses of cause-specific hazards were performed for SBP recurrence. We separately analyzed death post-SBP recurrence as well. **Results:** Of the 2,539 patients with a first SBP episode started on SecSBPPr, 609 (24.0%) patients developed recurrent SBP, 1,564 (61.6%) died, and 88 (3.5%) received LT. 25% (390) of the deaths occurred after a recurrent SBP episode. Younger age, white race/Hispanic ethnicity, lower CCI, lower WBC and platelets counts, and lactulose usage were significantly associated with SBP recurrence while statin usage was associated with a reduced risk of recurrence (Table 1).Multivariable analysis revealed that only lower platelet counts (HR: 0.78 (0.71-0.87) per-100 units, $p < 0.001$) were independently associated with a higher risk of SBP recurrence. The median platelet count was 101 [66-170] and we found that above a platelet cutoff of 135, the risk of recurrence was 5.9% compared to 18.0% with ≥ 135 ($p = 0.001$) (Fig. 1). Of the entire cohort, 34% had platelet count < 135.In the subgroup of those who died post-recurrence, higher age (HR: 1.03 (1.01-1.04, $p < 0.0001$) and MELD-Na (HR: 1.06 (1.04-1.08, $p < 0.0001$) were associated with a higher risk of mortality. **Conclusion:** Secondary SBP prophylaxis after index SBP in a National VA cohort results in a recurrence rate of 24% over 2 years, which impacts mortality. The prevention of SBP recurrence is most effective with SecSBPPr in patients with platelet counts >135/mm3. Consideration of restriction for SecSBPPr to these individuals could potentially reduce antibiotic resistance and overuse and streamline potential effectiveness.

Table 1	NO RECURRENCE (n=1930)	SBP RECURRENCE (n=609)	p-value
LABS/DEMOGRAPHICS			
Age	62.00 [57.00, 66.00]	61.00 [57.00, 65.00]	0.047
Male Sex	1864 (96.7)	586 (96.7)	0.968
White Race	1457 (80.9)	475 (84.7)	0.016
Hispanic Ethnicity	178 (9.6)	74 (12.6)	0.046
Alcohol Etiology	758 (39.3)	241 (39.6)	0.933
Charlson Comorbidity Index	5.00 [4.00, 7.00]	5.00 [3.00, 7.00]	0.034
MELD-Na	16.00 [14.00, 22.00]	16.00 [14.00, 21.00]	0.507
Platelet Count (10^3/L)	105.00 [67.00, 180.00]	92.00 [62.00, 165.00]	<0.001
Albumin (g/dL)	2.80 [2.30, 3.20]	2.80 [2.40, 3.20]	0.213
White Blood Cell Count (10^3/L)	5.90 [4.20, 8.30]	5.60 [3.90, 7.60]	0.006
VA Complexity, Level 1	1844 (95.5)	584 (95.9)	0.798
North Atlantic Region	147 (18.0)	49 (14.6)	0.053
MEDICATIONS			
Proton Pump Inhibitors	778 (40.3)	250 (41.1)	0.782
Statins	201 (10.4)	44 (7.2)	0.025
Lactulose	695 (36.0)	253 (41.5)	0.016
Rifaximin	276 (14.3)	88 (14.4)	0.98
Propranolol	367 (19.0)	114 (22.0)	0.12
Nadolol	64 (3.3)	19 (3.1)	0.915
Carvedilol	88 (4.6)	19 (3.1)	0.154
Selective Beta-Blocker	187 (9.7)	58 (9.5)	0.967

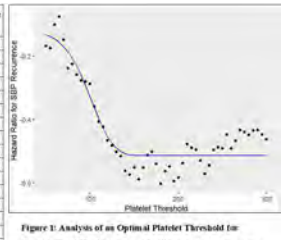


Figure 1: Analysis of an Optimal Platelet Threshold for Prediction of SBP Recurrence. Cutoffs for platelet counts were assessed at a range of values. Cubic splines were fit to the raw data, and the elbow point of the curve was calculated, where increasing the platelet count no longer provided added benefit

Disclosures: Scott Silvey:Nothing to Disclose, Nilang Patel:Nothing to Disclose, Jacqueline O'Leary:Genfit: Consultant, CVS: Stock - publicly traded company, Mallinckrodt: Advisor, PharmaIn: Advisor, PharmaIn: Consultant, Genfit: Consultant, PharmaIn: Consultant, Genfit: Consultant, Heather Patton:Bristol-Myers Squibb: Spouse is employee of BMS, Sofia Jakab: Nothing to Disclose, Timothy Morgan:Nothing to Disclose, Shari Rogal:Nothing to Disclose, Nothing to Disclose, Jasmohan Bajaj:Bausch: Grant/Research Support, Sequana: Grant/Research Support, Grifols: Grant/Research Support, Bausch: Grant/Research Support, Sequana: Grant/Research Support, Grifols: Grant/Research Support, Genfit: Grant/Research Support, Enterobiotix: Advisor, Boehringer Ingelheim: Advisor, Merz: Consultant.

1619 | ADIPOSE AND MUSCLE COMPARTMENT BASED ENDOTYPES REVEAL SEXUAL DIMORPHISM AND DIFFERENTIAL EFFECTS ON FRAILTY INDICES IN CIRRHOSIS DUE TO METABOLIC DYSFUNCTION ASSOCIATED STEATOHEPATITIS (MASH)

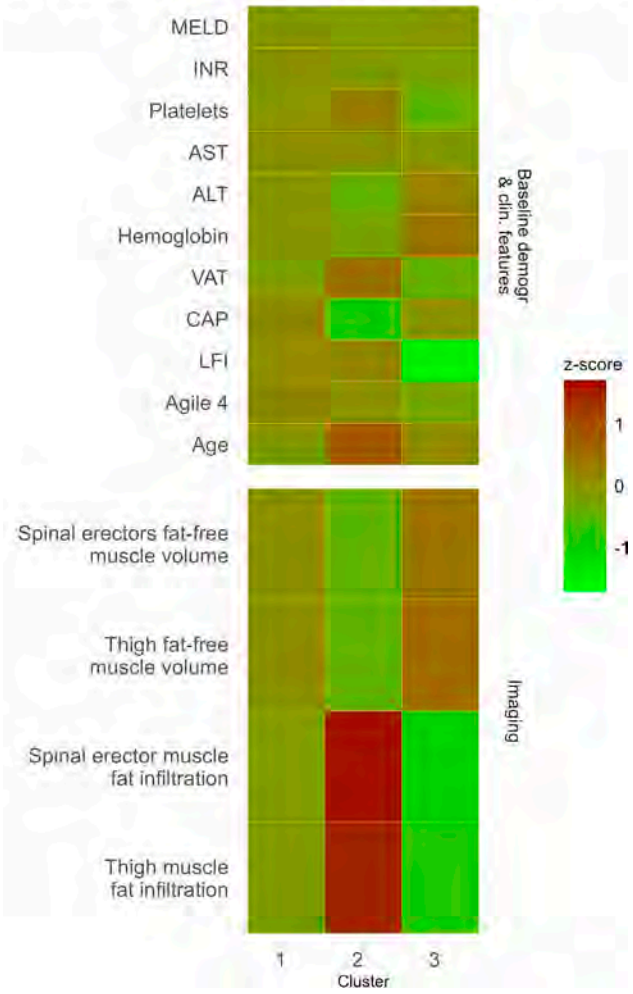
Mohammad Siddiqui[1] Manal Abdelmalek[2] Mikael Forsgren[3] Danielle Kirkman[4] Samar Okaily[4] Ekaterina Smirnova[4] Arun Sanyal[4], [1]University of Virginia, [2]Mayo Clinic, [3]AMRA Medical AB, [4]Virginia Commonwealth University

Background: Frailty is linked to poor outcomes in cirrhosis and is associated with adiposity, sarcopenia and myosteatosis which however vary across individuals. It is not known if there are distinct metabo-phenotypes based on these features with differential impact on frailty independent of liver injury, function, fibrosis burden and portal hypertension. **Aims:** To define if there are distinct metabo-phenotypes associated with frailty in those with compensated cirrhosis due to MASH **Methods:** A prospective cohort study of compensated MASH cirrhosis was performed. Metabo-phenotypic parameters included visceral and subcutaneous adipose tissue (VAT, SAT respectively), fat-free muscle volume and muscle fat index and quantified by MRI. Frailty was assessed by the liver frailty index (LFI). Liver and spleen stiffness were measured by elastography (LSM, SSM respectively) as surrogates of fibrosis burden and portal hypertension respectively. K-medoid clustering based on metabo-phenotyping parameters and the distribution of frailty, clinical and laboratory indices evaluated across groups. Regression was used to model independently predictive of frailty. Significance was set at $p < 0.05$. **Results:** 81 persons with compensated cirrhosis, based on biopsy (n = 55) or Agile4 scores (n = 26) were studied. They were predominantly white (90%), female (71%) and over 50 years of age (median 63 yrs). The mean (SD) for the LFI was 3.91 (0.83). Metabo-phenotype clustering identified three clusters with 59, 13 and 9 individuals. Cluster 3 had lower thigh (5.75 ± 1) and spinal erector (8.2 ± 2) muscle fat infiltration compared to clusters 1 (8.2 ± 2 and 14.2 ± 4) and 2 (12.0 ± 3 and 22.9 ± 4) $p < 0.001$. Cluster 3 (vs clusters 1 and 2) also had higher fat-free thigh (mean 12.11 vs 9.78 vs 9.69, $p < 0.02$) and spinal erectors muscle volumes (mean 0.83

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vs 0.62 vs 0.63, p < 0.02) and lower VAT (5.56 vs 5.72 vs 9.13 l, p < 0.001). Cluster 3 had lower LFI (2.6 ± 0.9) compared to clusters 1 (3.9 ± 0.7) and cluster 2 (4.0 ± 0.6) p < 0.001. Cluster 3 was comprised entirely of males whereas cluster 1 and 2 had 81% and 69% females. Cluster 3 also had higher hemoglobin (14.9 ± 1.6) vs clusters 1 (13.5 ± 1.6) and 2 (12.9 ± 2) p = 0.02). The clusters were otherwise not distinguishable by LSM, SSM or liver function. Regression models identified percent fat ratio and left anterior thigh fat free muscle volume as independent predictors of frailty (adj. R-squared = 0.31). **Conclusion:** Frailty measures vary in compensated MASH cirrhosis and are linked to gender and metabo-phenotypes rather than liver-related parameters.

Figure 1: Heatmap of baseline demographic, clinical, and imaging features (y-axis) for 3 clusters (x-axis). Measures are represented as z-scores with color intensity ranging from green for lower (z=-1.7) to red for high (z=1.7).



Disclosures: Mohammad Siddiqui:NovoNordisk: Grant/Research Support, 89Bio: Consultant, Sagimet: DSMB, Manal Abdelmalek:Nothing to Disclose, Mikael Forsgren:AMRA Medical AB: Employee, AMRA Medical AB: Stock – privately held company, Danielle Kirkman:Nothing to Disclose, Samar Okaily:Nothing to Disclose, Ekaterina Smirnova:Nothing to Disclose, Arun Sanyal:Nothing to Disclose..

1620 | RIFAXIMIN VS. FLUOROQUINOLONE-BASED SECONDARY PROPHYLAXIS FOLLOWING SPONTANEOUS BACTERIAL PERITONITIS IN CIRRHOSIS WITHOUT PRIOR HEPATIC ENCEPHALOPATHY: A PROPENSITY SCORE–MATCHED COHORT ANALYSIS

Jashanveer Johal[1] Brandon Cunha[1] Mahmoud Al-Bataineh[1] Archana Salek[1] Bianca Patel[1] Abdallah Hussein[1] Yecheskel Schneider[1] Jason Hyman[2] simona rossi[1], [1]Virtua Health, [2]Einstein Medical Center, Philadelphia

Background: Norfloxacin and ciprofloxacin represent guideline-standard options for secondary SBP prophylaxis in cirrhosis, but rifaximin is increasingly prescribed off-label given its favorable resistance profile and non-systemic absorption. Prior analyses have been confounded by rifaximin's co-indication for hepatic encephalopathy (HE). We examined outcomes in HE-naive patients to reduce channeling bias and better isolate the prophylactic effect. **Methods:** We conducted a propensity score–matched retrospective cohort study using the TriNetX Global Collaborative Network (191.9 million patients). Cohort 1 comprised cirrhotic patients with ascites and a documented SBP episode who received rifaximin within one year of index SBP, without prior HE or concurrent fluoroquinolone use. Cohort 2 comprised matched patients receiving norfloxacin or ciprofloxacin without rifaximin, also HE-naive. Both cohorts excluded prior HCC, liver transplant, and ESRD. 1:1 PSM yielded 2,587 patients per arm over a 6–120 month follow-up. Outcomes included SBP recurrence, gram-negative sepsis, HRS, C. difficile infection, ESRD progression, transplant listing, and all-cause mortality. **Results:** SBP recurrence was lower in the rifaximin arm on cumulative risk analysis (32.6% vs. 37.5%; RR 0.87; p = 0.0002), though KM analysis was equivalent (HR 1.02; p = 0.81), reflecting competing mortality differences. Gram-negative sepsis was higher in the rifaximin arm on KM analysis (HR 1.44, 95% CI 1.24–1.68; p < 0.001). C. difficile infection was lower with rifaximin (4.3% vs. 5.6%; RR 0.77; p = 0.029). ESRD progression was higher with rifaximin (11.4% vs. 7.3%; HR 2.01; p < 0.001). All-cause mortality was significantly higher in the rifaximin arm (57.6% vs. 41.9%; HR 1.98; p < 0.001), with median survival of 128 vs. 1,391 days. **Conclusion:** In this HE-naive propensity-matched cohort, rifaximin was associated with lower cumulative SBP recurrence and reduced C. difficile incidence, but with higher rates of ESRD progression and all-cause mortality compared to

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norfloxacin or ciprofloxacin. The mortality and ESRD differentials more plausibly reflect residual confounding by disease severity than direct drug toxicity. These findings reinforce the need for prospective, severity-stratified trials before rifaximin can be recommended as first-line secondary SBP prophylaxis over standard fluoroquinolone-based regimens.

Disclosures: Jashanveer Johal:Nothing to Disclose, Brandon Cunha:Nothing to Disclose, Mahmoud Al-Bataineh:Nothing to Disclose, Archana Salek:Nothing to Disclose, Bianca Patel:Nothing to Disclose, Abdallah Hussein:Nothing to Disclose, Yecheskel Schneider: Nothing to Disclose, Jason Hyman:Nothing to Disclose, simona rossi:Nothing to Disclose.

1621 | UTILITY OF SPLEEN ELASTOGRAPHY IN ADULT PATIENTS WITH FONTAN PHYSIOLOGY: A PILOT STUDY

Edward Cytryn[1] Renata Mazurek[1] Thomas Schiano[2] Ali Zaidi[1] Lauren Grinspan[2], [1]Icahn School of Medicine at Mount Sinai, [2]Recanati/Miller Transplantation Institute at Mount Sinai

Background: Fontan-associated liver disease (FALD) has emerged as a significant long-term complication in the growing population of Fontan patients. It remains a challenge to non-invasively assess disease progression as well as monitor for the development of portal hypertension. Vibration controlled transient elastography (VCTE) is an established method for non-invasive evaluation of liver fibrosis and steatosis. In addition to liver stiffness measurement (LSM), VCTE has also been used to measure spleen stiffness (SSM), however, to our knowledge, no studies have evaluated the utility of measuring SSM with VCTE in Fontan patients. **Methods:** A prospective pilot study of adult patients with Fontan physiology was initiated to evaluate both LSM and SSM using VCTE. Baseline LSM and SSM were measured in 10 patients between March 2024 and November 2025. 6-month and 12-month follow-up measurements were obtained in 9 and 4 patients to date, respectively, with additional follow-up data collection ongoing. Baseline invasive (congenital cardiac catheterization) and non-invasive (MELD-XI) clinical markers were also collected. When applicable, a Pearson's correlation was used to compare SS with MELD-XI. **Results:** Of the 10 patients currently enrolled, 7 are male, median age at start was 35.5 years and median MELD-XI score is 10 (range: 4-17). The underlying congenital heart disease diagnoses represented are tricuspid atresia (n = 4), double outlet right ventricle (n = 3), hypoplastic left heart syndrome (n = 1), hypoplastic right heart syndrome with pulmonary atresia (n = 1), and double inlet left ventricle (n = 1). At baseline (n = 10), the mean hepatic vein pressure was 9 mmHg and mean hepatic wedge pressure was 11 mmHg (Table 1). Mean SSM was 40.7 kPA (SE 3.4) while average LSM was 19.9 kPA (SE 2.6). Mean SSM at 6 months remained higher than mean LSM (n = 9) at 47.3 kPA (SE 6.2) vs. 20.6 kPA (SE 2.9), respectively. Among the 4 patients who have completed 12-month follow-up, mean SSM was 61.3 kPA (SE 10.5) and mean LSM was 21.6 kPA (SE 3.3). No statistically significant correlation was found between baseline SSM and MELD-XI ($r = 0.3732$, $p = 0.29$). **Conclusion:** VCTE is an established modality for non-invasive measurement of liver fibrosis. The clinical utility of SSM measurement using VCTE in Fontan patients is not well established and may become elucidated through a larger cohort. In this pilot study, no clear correlation was noted between SSM and MELD-XI score or hepatic venous pressures. This is limited by small sample size and additional data collection is needed. Given the progressive nature of FALD into more advanced liver disease and cirrhosis, continued investigation into the utility of SSM compared to LSM in these patients is essential.

Table 1. Baseline patient characteristics

Fontan patient characteristics (n = 10)	
Sex	
Female	3
Male	7
Age (years)	35.5
Time from Fontan procedure (years)	32
CHD Diagnosis	
Tricuspid atresia	4
Double outlet right ventricle	3
Hypoplastic left heart syndrome	1
Hypoplastic right heart syndrome with pulmonary atresia	1
Double inlet left ventricle	1
Mean free hepatic vein pressure (mmHg)	9
Mean hepatic venous pressure gradient (mmHg)	2
Mean MELD-XI	10
SSM mean ± SE (kPa)	40.7 ± 3.4
LSM mean ± SE (kPa)	19.9 ± 2.9
SSM/LSM ratio mean ± SE (kPa)	2.5 ± 0.4

CHD = congenital heart disease; SSM = spleen stiffness measurement; LSM = liver stiffness measurement

Disclosures: Edward Cytryn:Nothing to Disclose, Renata Mazurek:Nothing to Disclose, Thomas Schiano:Nothing to Disclose, Ali Zaidi:Nothing to Disclose, Lauren Grinspan: Nothing to Disclose.

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1622 | ALBUMIN-BILIRUBIN SCORE VERSUS MELD 3.0 FOR PREDICTING 90-DAY MORTALITY AFTER TIPS

John Guieb[1] Giorgio Roccaro[1] Jay Jung[1] Michael Yu[1] Brandon Lei[1] Peter Park[1] Bryan Swilley[1], [1]Emory University School of Medicine

Background: Risk stratification before transjugular intrahepatic portosystemic shunt (TIPS) remains challenging as metabolic dysfunction-associated steatotic liver disease (MASLD) accounts for an increasing proportion of cirrhosis. Patients with MASLD often have chronic kidney disease (CKD) and metabolic comorbidities that may influence creatinine independent of hepatic function. Because MELD incorporates creatinine, it may overestimate procedural risk when elevations are driven primarily by renal factors, especially in elective TIPS candidates. The albumin-bilirubin (ALBI) score, a liver-specific metric derived from albumin and bilirubin, excludes creatinine. We evaluated whether ALBI predicts 90-day post-TIPS mortality and compared its performance with MELD 3.0. **Methods:** We conducted a retrospective cohort study of adults undergoing TIPS at a large academic medical center from 2022 to 2025. The primary outcome was 90-day post-TIPS mortality. The primary predictor was pre-TIPS ALBI score; pre-TIPS MELD 3.0 was the comparator. Groups were compared using Mann-Whitney U testing. Logistic regression estimated odds ratios (ORs), and discrimination was evaluated by area under receiver operating curve (AUC). Paired DeLong testing compared correlated AUCs. Prespecified subgroups included MASLD, ascites indication, MELD >18, elective TIPS, no malignancy, no pre-TIPS hepatic encephalopathy, and ALBI grade. **Results:** Among 260 patients, 28 (10.8%) died within 90 days of TIPS. Pre-TIPS ALBI differed between survivors and non-survivors ($p = 0.018$). Higher ALBI was associated with increased odds of 90-day mortality (OR 1.82 per 1-point increase; 95% CI 1.05-3.16; $p = 0.034$), with modest discrimination (AUC 0.637). MELD 3.0 was more strongly associated with mortality (OR 1.16 per 1-point increase; 95% CI 1.10-1.22; $p < 0.001$) and superior discrimination (AUC 0.814). By DeLong testing, MELD outperformed ALBI (AUC difference 0.177 favoring MELD; 95% CI for ALBI-MELD, -0.295 to -0.058; $p = 0.004$). In a combined model, ALBI was not independently associated with mortality (OR 0.84; 95% CI 0.43-1.64; $p = 0.608$), whereas MELD remained significant (OR 1.17; 95% CI 1.10-1.24; $p < 0.001$). Subgroup analyses did not identify a population in which ALBI outperformed MELD. **Conclusion:** Pre-TIPS ALBI was associated with 90-day mortality on univariable analysis but demonstrated modest discrimination and did not add prognostic value beyond MELD. MELD remained the dominant predictor across analyses and had higher discrimination. Although ALBI did not outperform MELD 3.0, the hypothesis remains relevant given rising CKD prevalence in MASLD, where creatinine-driven MELD elevations may misrepresent hepatic reserve. Larger studies incorporating granular renal function measures and well-defined elective versus emergent TIPS cohorts are needed to clarify whether ALBI offers incremental risk stratification in this setting.

Table 1: Paired DeLong Comparison of ALBI and MELD 3.0 for Prediction of 90-Day Mortality After TIPS

Cohort / Subgroup Analysis	N	90-Day Deaths	ALBI AUC	MELD AUC	AUC Difference, ALBI–MELD	95% CI for ALBI–MELD	DeLong p-value
Overall cohort	260	28	0.637	0.814	-0.177	-0.295 to -0.058	0.004
MASLD cirrhosis etiology	81	5	0.511	0.884	-0.374	-0.726 to -0.021	0.038
Ascites indication for TIPS	108	10	0.493	0.777	-0.283	-0.546 to -0.020	0.035
MELD >18	62	18	0.388	0.701	-0.313	-0.518 to -0.109	0.003
Outpatient/elective TIPS	39	3	0.769	0.852	-0.083	-0.364 to 0.197	0.561
No malignancy	221	22	0.632	0.819	-0.187	-0.317 to -0.057	0.005
No pre-TIPS hepatic encephalopathy	200	19	0.637	0.804	-0.167	-0.317 to -0.017	0.029
ALBI grade 3	72	10	0.640	0.677	-0.037	-0.200 to 0.126	0.655
ALBI grade 1-2	188	18	0.667	0.858	-0.191	-0.343 to -0.040	0.013

Abbreviations: ALBI, albumin-bilirubin; AUC, area under the receiver operating curve; MASLD, metabolic dysfunction-associated steatotic liver disease; MELD, Model for End-Stage Liver Disease; TIPS, transjugular intrahepatic portosystemic shunt.

Table note: AUC difference and 95% CI are reported as ALBI AUC − MELD AUC. Negative values indicate higher discrimination for MELD.

Disclosures: John Guieb:Nothing to Disclose, Giorgio Roccaro:Nothing to Disclose, Jay Jung:Nothing to Disclose, Michael Yu:Nothing to Disclose, Brandon Lei:Nothing to Disclose, Peter Park:Nothing to Disclose, Bryan Swilley:Nothing to Disclose.

1623 | DO OUTCOMES AFTER TIPS DEPEND ON THE UNDERLYING CIRRHOSIS ETIOLOGY?

Ian Tobal[1] Ricardo David-Espinosa[1] Sameera Shuaibi[1] Patt Panuncillon[1] Daniyaal Kamran[1] Elizabeth Howard[1] Tyler Sandow[2] Juan Gimenez[2] George Therapondos[3], [1]Ochsner Clinic Foundation, [2]Ochsner Department of Interventional Radiology, [3]Ochsner Department of Hepatology and Transplant Hepatology

Background: Transjugular intrahepatic portosystemic shunt (TIPS) is performed in patients who suffer from complications related to portal hypertension, most commonly in cirrhotic patients with refractory ascites or refractory variceal bleeding due to alcohol, viral hepatitis, and metabolic dysfunction-associated steatotic liver disease (MASLD). Data related to TIPS

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outcomes based on the etiology of cirrhosis are lacking. The underlying cause of cirrhosis is often treated in alcohol-related disease and viral hepatitis but not in MASLD. We hypothesized that post-TIPS survival and the number of further decompensating events may depend on cirrhosis etiology. **Methods:** In this retrospective analysis, we reviewed patients with cirrhosis due to MASLD, alcohol use, viral hepatitis, or other etiologies who underwent TIPS placement at any Ochsner Health facility between 2015-2020, with a follow-up period of 5 years. All patients over 18 years old were included unless they had a history of liver transplant or HCC prior to TIPS. Overall survival and episodes of further decompensating events post procedure were recorded. **Results:** 161 cirrhotic patients (mean age 57.3, 88% male) were included in this analysis. 66 patients had MASLD, 43 had alcohol-related disease, 39 had viral hepatitis, and 13 had cirrhosis from other causes. 83 patients had refractory ascites, 62 had refractory variceal bleeding, 10 had portal vein thrombosis, and 6 had refractory hepatic hydrothorax as their initial TIPS indication. For overall 5-year survival, viral hepatitis served as the reference group (HR = 1). The HR for MASLD was 1.51, 95% CI 0.62–3.68 (p = 0.364). The HR for alcohol-related disease was 1.16, 95% CI 0.48–2.84 (p = 0.743) and 1.96, 95% CI 0.59–6.52 (p = 0.270) for cirrhosis from other causes. The 5-year rate of further decompensating events, defined as episodes of GI bleeding, ascites requiring paracentesis, hepatorenal syndrome, hepatopulmonary syndrome, portal vein thrombosis, and hepatic hydrothorax was 95.5% (95% CI 84.9-100) in patients with MASLD, 63.4% (95% CI 44-83) in those with alcohol-related disease, and 90.6% (95% CI 75.9-100) in those with viral hepatitis. A rate could not be calculated for those who had cirrhosis from other causes. **Conclusion:** Patients with MASLD had a 51% higher adjusted hazard of death after 5-years, but this difference was not statistically significant. Patients with alcohol-related disease had a similar mortality risk to viral hepatitis. No statistically significant differences in survival were observed across etiologies, though the point estimates suggest a higher hazard in the MASLD group. MASLD and viral hepatitis had the highest cumulative rate of further decompensating events at 5 years, with alcohol-related disease having the lowest.

Disclosures: Ian Tobal:Nothing to Disclose, Ricardo David-Espinosa:Nothing to Disclose, Sameera Shuaibi: Nothing to Disclose, Patt Panuncillon:Nothing to Disclose, Daniyaal Kamran:Nothing to Disclose, Elizabeth Howard:Nothing to Disclose, Tyler Sandow:Boston Scientific: Consultant, Sirtex: Consultant, TriSalus: Consultant, ABK: Consultant, AstraZeneca: Consultant, Juan Gimenez:Boston Scientific: Consultant, SIRTEX: Consultant, Aztra Zeneca: Consultant, George Therapondos:Novo Nordisk: Consultant, Intercept: Speaking and Teaching, Madrigal: Speaking and Teaching, Ipsen: Speaking and Teaching, Gilead: Speaking and Teaching.

1624 | WHEN ASCITES RECURS: SGLT2 INHIBITORS VERSUS DPP-4 INHIBITORS AND LIVER-RELATED OUTCOMES IN DIABETIC CIRRHOSIS

Chimezirim Ezeano[1] Ifelunwa Osanakpo[2] Sarpong Boateng[3] Ihunanya Kanu[4] Emeka Stanley Obi[5] Guy Loic Nguefang Tchoukeu[6] Cherechi Nwabueze[7] Goodness Joseph[8] David Narvaez-De los Rios[9] Onyinyechukwu Ozumba[10] Samuel Ayedun[11] Madu Chimezie[0] Angel Umahi[0], [1]Advocate Aurora Healthcare, [2]Carle Foundation Hospital, [3]Yale New Haven Health, Bridgeport Hospital, [4]Baptist Memorial Hospital- Golden Triangle, [5]Brookdale University Hospital and Medical Center, [6]Texas Tech University Health Science Center, Permian Basin, [7]John H. Stroger Jr. Hospital of Cook County, [8]Nnamdi Azikiwe University Teaching Hospital, [9]Universidad Icesi, [10]Dept of Internal medicine Cape fear valley North Carolina, [11]Montefiore Medical Center, Bronx NY, [0] University of Lancashire School of medicine and dentistry

Background: Although SGLT2 inhibitors (SGLT2i) have been linked to improved outcomes in type 2 diabetes mellitus (T2DM) and cirrhosis, evidence in established decompensation remains limited. In recurrent ascites, their natriuretic effect is appealing, but renal vulnerability raises concern for acute kidney injury and hepatorenal syndrome. We compared SGLT2i versus DPP-4 inhibitors (DPP4i) in adults with T2DM and procedurally defined recurrent ascites. **Methods:** We performed a retrospective 1:1 propensity score-matched cohort study using the TriNetX Global Collaborative Network (16 healthcare organizations). Adults aged at least 18 years with type 2 diabetes, cirrhosis, ascites, and recurrent abdominal paracentesis were included. Patients with hepatocellular carcinoma, malignant ascites, portal vein thrombosis, peritoneal malignancy, or type 1 diabetes were excluded. After matching, 286 patients remained in each group. The primary outcome was a liver-related composite of hepatic encephalopathy, variceal bleeding, and liver transplant status. Secondary outcomes were acute kidney injury, hepatorenal syndrome, and all-cause mortality. **Results:** Before matching, 593 SGLT2i-treated and 578 DPP4i-treated patients met eligibility criteria; after matching, 286 patients remained per cohort. SGLT2i were associated with lower liver-related event-free

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hazard than DPP4i (18.20% vs 24.90%; RD −0.07, p = 0.11; RR 0.73; OR 0.67; HR 0.63, 95% CI 0.41–0.97; log-rank p = 0.04). Renal and survival outcomes were similar between groups: acute kidney injury occurred in 35.10% vs 37.00% (RD −0.02, p = 0.76; HR 0.88, log-rank p = 0.54), all-cause mortality in 40.00% vs 42.70% (RD −0.03, p = 0.52; HR 0.85, log-rank p = 0.20), and hepatorenal syndrome in 7.30% vs 9.00% (RD −0.02, p = 0.47; HR 0.75, log-rank p = 0.34). **Conclusion:** In this paracentesis-defined recurrent-ascites cohort, SGLT2i were associated with better liver-related event-free survival than DPP4i without higher observed acute kidney injury, hepatorenal syndrome, or mortality. These findings extend prior SGLT2i data into a higher-risk decompensated population and support prospective studies to define patient selection, renal safety, and hepatic benefit.

Disclosures: chimezirim ezeano:Nothing to Disclose, IFELUNWA OSANAKPO:Nothing to Disclose, Sarpong Boateng:Nothing to Disclose, Ihunanya Kanu:Nothing to Disclose, Emeka Stanley Obi:Nothing to Disclose, GUY LOIC NGUEFANG TCHOUKEU:Nothing to Disclose, Cherechi Nwabueze:Nothing to Disclose, Goodness Joseph:Nothing to Disclose, David Narvaez-De los Rios:Nothing to Disclose, Onyinyechukwu Ozumba:Nothing to Disclose, Samuel Ayedun:Nothing to Disclose, Madu Chimezie:Nothing to Disclose, Angel Umahi:Nothing to Disclose.

1625 | BEYOND AKI: ACUTE KIDNEY DISEASE PREDICTS POOR OUTCOMES IN DECOMPENSATED CIRRHOSIS. A PROSPECTIVE REAL-WORLD STUDY

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Background: Acute kidney disease (AKD), recently redefined by the ADQI–ICA consensus, captures persistent or subacute kidney dysfunction in cirrhosis, either following acute kidney injury (AKI-AKD) or occurring without overt AKI (NAKI-AKD). Its prognostic impact in stable outpatients with decompensated cirrhosis remains unclear.The aim of the study was to evaluate the impact of AKD and its phenotypes (AKI-AKD and NAKI-AKD) on cirrhosis-related complications and mortality in outpatients with stable decompensated cirrhosis. **Methods:** We conducted a prospective single-center cohort study including 131 adults with clinically stable decompensated cirrhosis and preserved kidney function at baseline. Patients were followed for up to 60 months. AKD and its phenotypes were defined according to ADQI–ICA criteria. Cirrhosis-related complications, hospitalizations, liver transplantation and mortality were prospectively recorded. Associations with outcomes were assessed using cause-specific Cox models adjusted for liver disease severity and competing-risk analyses with liver transplantation as a competing event. **Results:** During a mean follow-up of 26.4 ± 14.2 months, AKD developed in 51/131 patients (38.9%): 33 (64.7%) had NAKI-AKD and 18 (35.3%) had AKI-AKD. AKD patients had more cirrhosis-related complications than those with preserved kidney function, including diuretic-intolerant ascites (35.3% vs 1.4%), hepatic encephalopathy (49.0% vs 10.8%), spontaneous bacterial peritonitis (31.4% vs 4.1%), non-SBP bacterial infections (49.0% vs 10.8%), bacteremia (13.7% vs 1.4%) and acute-on-chronic liver failure (33.3% vs 2.7%). Mortality was higher among AKD patients (70.5% vs 14.9%), and AKD was independently associated with death in competing-risk analysis (sHR 5.32, 95%CI 2.73–10.40; p < 0.001), remaining significant across multivariable models. AKI-AKD identified the highest-risk phenotype, with more infections, longer hospitalization and higher mortality than NAKI-AKD (sHR 2.18, 95%CI 1.80–5.19; p = 0.006). However, NAKI-AKD also conferred increased mortality compared with preserved kidney function (sHR 3.86, 95%CI 1.86–8.02; p < 0.001). AKD resolution occurred mainly in NAKI-AKD patients and was associated with improved survival (sHR 0.10, 95%CI 0.01–0.75; p = 0.025). **Conclusion:** AKD is common in stable outpatients with decompensated cirrhosis and independently predicts complications and death. Phenotypic stratification identifies AKI-AKD as the highest-risk subgroup, while NAKI-AKD represents a clinically relevant and potentially reversible stage of kidney dysfunction.

Disclosures: Vasileios Lekakis:Nothing to Disclose, Jiannis Vlachogiannakos:Nothing to Disclose, George Papatheodoridis:Nothing to Disclose, Evangelos Cholongitas:Nothing to Disclose.

1626 | DIAGNOSTIC PERFORMANCE OF ARTIFICIAL INTELLIGENCE MODELS FOR PREDICTING ESOPHAGEAL VARICES AND VARICEAL BLEEDING RISK IN CIRRHOSIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

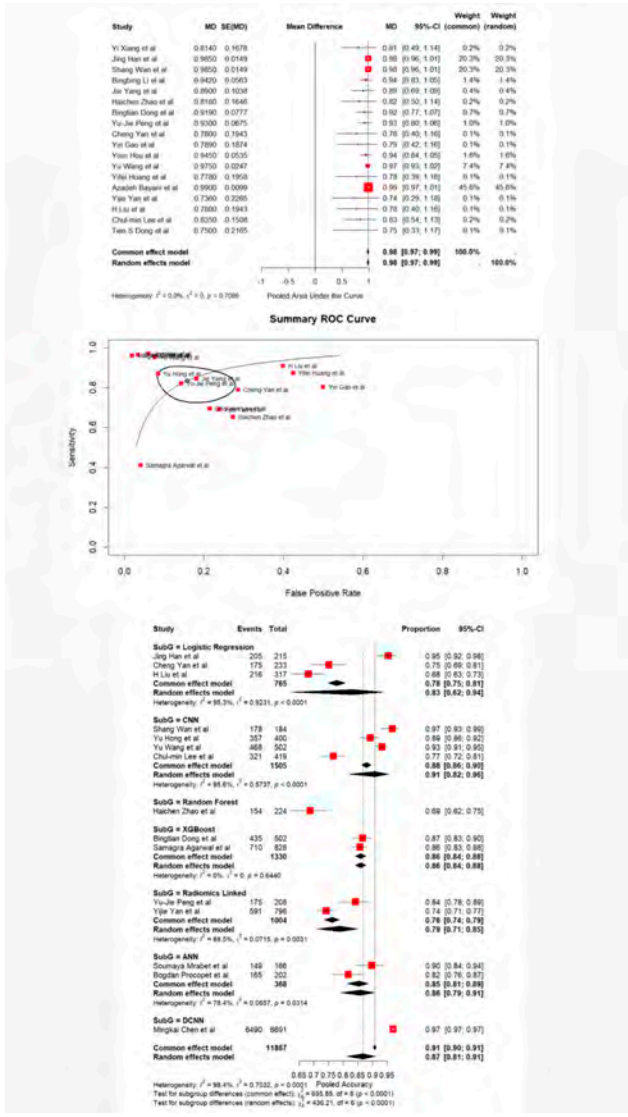
Era Gupta[1] Aryan Gupta[2] Solomon Anighoro[3] Raja Chandra Chakinala[3] Rewanth Katamreddy[4] Dushyant Singh Dahiya[5] Michelle Bernshteyn[4], [1]Guthrie/ Robert Packer Hospital, PA, USA, [2]Bangalore Medical College

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and Research Institute, India, [3]Guthrie/robert Packer Hospital, PA, USA, [4]Guthrie/Robert Packer Hospital, [5]The University of Kansas School of Medicine, KS, USA

Background: Esophageal varices are a major complication of liver cirrhosis and carry substantial morbidity and mortality because of the risk of variceal hemorrhage. Early identification of high-risk varices remains essential for timely surveillance and prophylactic intervention. In recent years, artificial intelligence (AI)- and machine learning (ML)-based models have emerged as promising tools for predicting the presence, severity, and bleeding risk of esophageal varices using clinical, laboratory, imaging, and endoscopic parameters. Several studies have reported favorable predictive performance of these models; however, variability in model architecture, validation strategies, and study methodology has limited the generalizability of existing findings. We performed a systematic review and meta-analysis evaluating the diagnostic performance of AI- and ML-based models for predicting esophageal varices and variceal bleeding risk in patients with cirrhosis. **Methods:** This review was conducted following PRISMA guidelines. PubMed, Google Scholar, and ScienceDirect were systematically searched using a comprehensive strategy. Studies assessing AI models for predicting the presence or bleeding risk of esophageal varices in patients with liver cirrhosis were included. Diagnostic performance measures, including sensitivity, specificity, accuracy, and area under the curve (AUC), were extracted and analyzed. The meta, metadata, and metafor packages, along with mada functions, were used in RStudio. Data were analyzed using random-effects models, and heterogeneity was assessed using the I^2 statistic. **Results:** A total of 23 studies were included in the final analysis. The pooled AUC of AI models was 0.98 (95% CI, 0.97–0.99). The pooled accuracy was 0.87 (95% CI, 0.81–0.91), with convolutional neural network (CNN) models demonstrating the highest accuracy (0.91). The pooled sensitivity and specificity were both 0.85, with 95% confidence intervals of 0.76–0.90 and 0.76–0.91, respectively. **Conclusion:** AI- and ML-based predictive models demonstrate promising diagnostic performance for identifying esophageal varices and assessing variceal bleeding risk in patients with cirrhosis. These tools may improve noninvasive risk stratification and optimize endoscopic surveillance strategies. However, heterogeneity in model development, validation methods, and study quality limits current clinical applicability. Further large-scale prospective studies with standardized validation frameworks are needed to support integration into routine hepatology practice.



Disclosures: Era Gupta:Nothing to Disclose, Aryan Gupta:Nothing to Disclose, Solomon Anighoro:Nothing to Disclose, Raja Chandra Chakinala:Nothing to Disclose, Rewanth Katamreddy:Nothing to Disclose, Dushyant Singh Dahiya:Nothing to Disclose, Michelle Bernshteyn:Nothing to Disclose.

1627 | PORTAL HYPERTENSION BURDEN CORRELATES WITH SUBCLINICAL LEFT VENTRICULAR SYSTOLIC DEFORMATION ASSESSED BY GLOBAL LONGITUDINAL STRAIN IN CIRRHOSIS: A RETROSPECTIVE HVPG-BASED STUDY

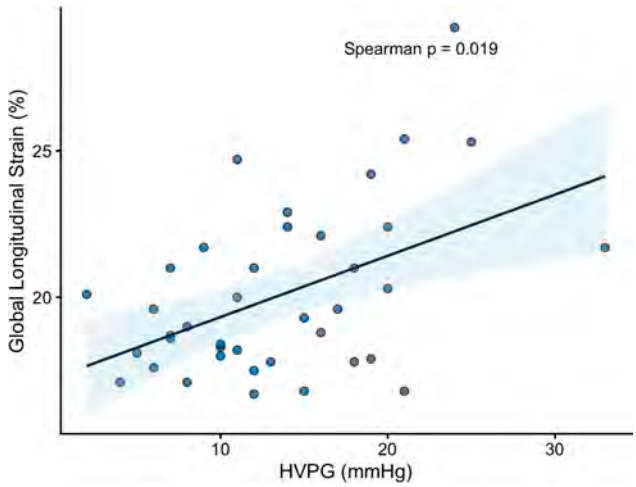
Tommaso Giovanni Rinaldi[1] Olivia Portolese[1] Tania D'Amico[1] Rumbola' Lucas[1] Desantis Francesco[1] Adriano Pellicelli[1] Claudia Telesca[1] Fabrizio Recchia[1]

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Sperduti Nicolo'[2] Domenico Cartoni[3] Shirin Demma[1] Valerio Giannelli[1], [1]Liver Unit, Ospedale San Camillo Forlanini, Rome, Italy, [2]Internal Medicine, Ospedale San Camillo Forlanini, Rome, Italy, [3]Servizi cardiologici integrati, Ospedale San Camillo Forlanini, Rome, Italy

Background: Cirrhotic cardiomyopathy is increasingly recognized as a subclinical cardiac disorder in cirrhosis, often undetected by conventional echocardiography. Left ventricular ejection fraction (LVEF) frequently remains preserved despite early myocardial involvement, limiting its sensitivity for detecting subtle systolic abnormalities. Global longitudinal strain (GLS) is a more sensitive marker of left ventricular systolic performance, but its relationship with portal hypertension severity remains unclear. **Methods:** We retrospectively analyzed 34 patients with cirrhosis of different etiologies who underwent invasive HVPG measurement and transthoracic echocardiography including GLS assessment. Echocardiographic evaluation included LVEF, GLS, E/e', left atrial volume index (LAVI), TAPSE, and pulmonary artery systolic pressure (PAPs). Patients with significant arrhythmic, structural, ischemic, or known heart disease were excluded. Correlations between HVPG and echocardiographic parameters were assessed using Spearman analysis. Exploratory analyses also evaluated portal hypertension-related complications (esophageal varices, ascites, hepatic encephalopathy, hypersplenism), liver disease etiology, and beta-blocker exposure. **Results:** HVPG modestly correlated with worsening GLS values (rho = 0.369, p = 0.019), suggesting a relationship between increasing portal pressure burden and less favorable left ventricular systolic deformation. By contrast, HVPG did not correlate with LVEF (rho = 0.189, p = 0.243), E/e' (rho = −0.022, p = 0.891), or LAVI (rho = −0.069, p = 0.706). A non-significant trend was observed for PAPs (rho = 0.286, p = 0.073).GLS progressively worsened across increasing HVPG quartiles, with median GLS values rising from 17.85% in the lowest quartile to 22.40% in the highest quartile (Kruskal-Wallis p = 0.022). Worsening GLS also correlated with the cumulative burden of portal hypertension-related complications (rho = 0.370, p = 0.031). Exploratory sensitivity analyses did not demonstrate significant correlations between GLS and cirrhosis etiology, particularly MASLD and alcohol-related liver disease, nor with beta-blocker exposure. **Conclusion:** In our cohort, portal hypertension severity correlated with subclinical alterations in left ventricular systolic deformation assessed by GLS despite preserved LVEF and absence of significant correlations with conventional diastolic parameters. These findings support a potential cardio-hepatic hemodynamic interplay in early cirrhotic cardiac involvement and reinforce the concept that conventional echocardiographic parameters may underestimate early myocardial impairment in cirrhosis. Larger prospective studies are warranted to validate these findings and define the clinical role of GLS in the early phenotyping of cirrhotic cardiomyopathy.



Disclosures: Tommaso Giovanni Rinaldi:Nothing to Disclose, Olivia Portolese:Nothing to Disclose, Tania D'Amico:Nothing to Disclose, Rumbola' Lucas:Nothing to Disclose, Desantis Francesco:Nothing to Disclose, Adriano Pellicelli:Nothing to Disclose, Claudia Telesca: Nothing to Disclose, Fabrizio Recchia:Nothing to Disclose, Sperduti Nicolo':Nothing to Disclose, Domenico Cartoni:Nothing to Disclose, Shirin Demma:Nothing to Disclose, Valerio Giannelli:Nothing to Disclose.

1628 | EVALUATING PREDICTIVE MODELS OF CLINICAL OUTCOMES FOLLOWING TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT PLACEMENT FOR ACUTE VARICEAL HEMORRHAGE

Makeda Dawkins[1] Wei Tang[1] Daniel Basta[1] Sarah Rahni[1] Shekher Maddineni[2] Tsipora Huisman[1], [1]Westchester Medical Center, [2]Westchester Medicine Center

Background: Acute variceal hemorrhage (AVH) remains the strongest indication for transjugular intrahepatic portosystemic shunt (TIPS) placement, providing survival benefit and improving transplant-free survival. Many multivariate analyses note increased mortality risk in patients, specifically with a total bilirubin (TB) of or greater than 4 mg/dL. Treatment dilemmas arise particularly in cases of acute severe alcohol-associated hepatitis in which hyperbilirubinemia is driven by inflammation-driven bilirubinostasis, hepatocyte dedifferentiation, and transporters downregulation rather than reduced hepatocyte mass and distortion seen in advanced fibrosis. This study aimed to identify predictors of outcomes after salvage, rescue, preemptive and elective TIPS placement for AVH. **Methods:** In this retrospective cohort study, electronic medical records from a five-year period were reviewed for patients

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≥ 18 years old carrying the ICD-10 code 37182. TIPS placed for ascites, gastric varices, or ectopic varices were excluded from the analysis. Simple logistic regression was used to evaluate the association between continuous variables and binary outcomes. Continuous variables were also evaluated using point-biserial correlation. Dichotomous features were analyzed with Fisher's exact test and Cramer's V to assess significance and size. Outcomes were examined according to liver disease etiology, age, comorbid conditions, TB, sodium, Child-Pugh score, and classical MELD. Adverse outcomes included post-TIPS liver failure, rebleeding, mortality, and hepatic encephalopathy. **Results:** This single center study included 65 patients. 44% carried a diagnosis of severe acute alcoholic hepatitis. Additional variables analyzed included: BMI, TB (baseline,1 week, 1 month), Δ TB (1 week, 1 month), freiburg index score, TIPS classification, HVPG (pre-, post- and Δ), AST (1 week, 1 month and Δ), ALT (1 week, 1 month and Δ). There was no statistically significant difference in post-TIPS mortality by TB pre-TIPS ($p = 0.6826$), at 1 Week ($p = 0.4293$), 1 week Δ ($p = 0.1523$), at 1 month ($p = 0.3648$), Δ at 1 month ($p = 0.3648$), total bilirubin >4mg/dL ($p = 0.4213$). The highest TB included was 11.2 mg/dL. There was no statistically significant difference in post-TIPS mortality by classical MELD >18 ($p = 0.5408$). **Conclusion:** No statistically significant association was identified between MELD score or total bilirubin and adverse outcomes following TIPS placement. Although the study was limited by sample size, the findings support level II-2 evidence suggesting hyperbilirubinemia alone is not an absolute contraindication to TIPS placement for AVH and should be considered after multidisciplinary evaluation in the absence of alternative therapies. Furthermore, hyperbilirubinemia in the setting of acute severe alcoholic hepatitis may carry a different post-TIPS prognosis compared with hyperbilirubinemia observed in end-stage liver disease.

Disclosures: Makeda Dawkins:Nothing to Disclose, Wei Tang:Nothing to Disclose, Daniel Basta:Nothing to Disclose, Sarah Rahni:Nothing to Disclose, Shekher Maddineni:Nothing to Disclose, Tsipora Huisman:Nothing to Disclose.

1629 | HIGHER MELD SCORES ARE ASSOCIATED WITH WORSE TRANSVERSE COLON BOWEL PREPARATION IN PATIENTS WITH CIRRHOSIS

Tayna Latortue[1] Andrew Kleehammer[1] Ashrita Budharaju[1] Natalie Rosseau[1] Ang Li[1] Josiah McCain[1] Tiffany Chua[1], [1]University of Florida

Background: Patients with cirrhosis frequently undergo colonoscopy for colorectal cancer screening and liver transplant evaluation. Advanced liver disease may predispose patients to suboptimal bowel cleansing. We aimed to evaluate the association between liver disease severity and bowel preparation quality, with emphasis on segment-specific Boston Bowel Preparation Scale (BBPS) scores. **Methods:** We performed a retrospective cohort study at a tertiary academic center. A total of 400 patients with cirrhosis who underwent colonoscopy between 1/1/2015 and 12/30/2020 were initially identified using ICD and CPT codes. Patients were excluded if cirrhosis was not confirmed on manual chart review of if a MELD score was unavailable within 3 months of colonoscopy. Liver disease severity was assessed using MELD, MELD-Na, and MELD 3.0 scores. Patients were stratified into higher and lower liver disease severity groups using cohort-specific median MELD (12.83), MELD-Na (13.53), and MELD 3.0 (14.34) values. Bowel preparation quaality was evaluated using total and segment-specific BBPS scores. Secondary outcomes included cecal intubation rate, cecal intubation time, polyp detection, and repeat colonoscopy recommendations. **Results:** A total of 233 patients met inclusion criteria. Mean total BBPS scores were numerically lower among patients wirh higher MELD scores, although differences in overall BBPS were not consistently significant. In contrast, transverse colon bowel preparation quality was significantly worse in patients with more advanced liver disease. Patients with higher MELD-Na scores had significantly lower transverse BBPS scores compared with lower MELD-Na patients (2.01 ± 0.86 vs 2.27 ± 0.69, $p = 0.04$). Similar findings were observed using traditional MELD stratification (2.01 ± 0.83 vs 2.27 ± 0.72, $p = 0.04$). Right and left colon BBPS scores trended in higher MELD groups but were not statistically significant. Cecal intubation rate, cecal intubation time, polyp detection, and repeat colonoscopy recommendations did not significantly differ between groups. **Conclusion:** Increasing liver disease severity was associated with significantly worse transvere colon bowel preparation quality in patients with cirrhosis undergoing colonoscopy. These findings suggest that advanced liver disease may disproportionately impair clearing of the transverse colon and highlight the importance of optimizing bowel preparation strategies in this high-risk population.

Table 1. Transverse Colon BBPS Scores by MELD-Based Severity Score

Segment-specific bowel preparation quality according to MELD-based severity groups. Values are presented as mean ± SD. Severity groups were defined using cohort-specific median MELD, MELD-Na, and MELD 3.0 values.

MELD-Based Score	Lower Severity Group	Higher Severity Group	p-value
MELD (<12.85 vs ≥12.85)	2.27 ± 0.72	2.01 ± 0.83	0.040
MELD-Na (<13.53 vs ≥13.53)	2.27 ± 0.69	2.01 ± 0.86	0.040
MELD 3.0 (<14.34 vs ≥14.34)	2.25 ± 0.71	2.04 ± 0.85	0.106

Disclosures: Tayna Latortue:Nothing to Disclose, Andrew Kleehammer:Nothing to Disclose, Ashrita Budharaju:Nothing to Disclose, Natalie Rosseau:

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Nothing to Disclose, Ang Li:Nothing to Disclose, Josiah McCain:Nothing to Disclose, Tiffany Chua:Nothing to Disclose.

1630 | COMPARATIVE PERFORMANCE OF MELD-BASED SCORING SYSTEMS FOR PREDICTING COLONOSCOPY QUALITY IN PATIENTS WITH CIRRHOSIS

Tayna Latortue[1] Andrew Kleehammer[1] Ashrita Budharaju[2] Natalie Rosseau[1] Ang Li[1] Josiah McCain[1] Tiffany Chua[3], [1]University of Florida, [2]Univeristy of Florida, [3]Univerisity of Florida

Background: Patients with cirrhosis are at increased risk for impaired bowel preparation and reduced colonoscopy quality. We compared traditional MELD, MELD-Na, and MELD 3.0 scores in predicting colonoscopy quality outcomes in cirrhosis. **Methods:** We performed a retrospective cohort study at a tertiary academic center. A total of 400 patients with cirrhosis who underwent colonoscopy between 1/1/2015 and 12/30/2020 were identified using ICD and CPT codes. Patients were excluded if cirrhosis was not confirmed on manual chart review or if a MELD score was unavailable within 3 months of colonoscopy. Liver disease severity was assessed using MELD, MELD-Na, and MELD 3.0 scores. Patients were stratified into higher and lower liver disease severity groups using cohort-specific median MELD (12.83), MELD-Na (13.53), and MELD 3.0 (14.34) values. Bowel preparation quality was evaluated using total and segment-specific Boston Bowel Preparation Scale (BBPS) scores. Secondary outcomes included cecal intubation rate, cecal intubation time, polyp detection, and repeat colonoscopy recommendations. **Results:** A total of 233 patients met inclusion criteria. Higher MELD-Na scores were associated with significantly lower transverse colon BBPS compared with lower MELD-Na scores (2.01 ± 0.86 vs 2.27 ± 0.69, $p = 0.04$). Similar findings were observed using traditional MELD stratification ($p = 0.04$). MELD 3.0 demonstrated the strongest association with cecal intubation rate, with lower completion rates in higher MELD 3.0 patients (86.5% vs 94.4%, $p = 0.063$). Traditional MELD was significantly associated with shorter cecal intubation time in higher MELD patients (9.08 vs 11.15 minutes, $p = 0.039$). No scoring was associated with polyp detection or repeat colonoscopy recommendations. **Conclusion:** MELD-based soring systems demonstrated differing relationships with colonoscopy quality outcomes in cirrhosis. MELD-Na was most strongly associated with impaired transverse colon bowel preparation quality, while MELD 3.0 demonstrated the strongest relationship with reduced cecal intubation rates. These findings suggest MELD-based scores may help identify patients at risk for impaired colonoscopy quality in advanced liver disease.

Table 1. Patient Demographics

Patient demographics. Continuous variables presented as mean (SD); categorical variables presented as N (%).

Demographic Variables	Included Patients (N=233)
Sex	
Female	113 (48.5%)
Male	120 (51.5%)
Age, mean (SD)	58 (11.6)
BMI, mean (SD)	30 (6.5)
Race/Ethnicity	
White	189 (81.1%)
Black	18 (7.7%)
Hispanic	17 (7.3%)
Asian	2 (0.9%)
Other	7 (3.0%)
Cirrhosis Etiology	
Alcohol-associated liver disease	71 (30.5%)
Hepatitis C	60 (25.8%)
MASLD	36 (15.5%)
Other etiologies	66 (28.3%)
Diabetes mellitus	94 (40.3%)
Colonoscopy Characteristics	
Outpatient procedure	134 (57.5%)
Chronic lactulose use	69 (29.6%)
Colonoscopy Indication	
Colorectal cancer screening	105 (45.1%)
Gastrointestinal bleeding	57 (24.5%)
Anemia	29 (12.4%)
Diarrhea	20 (8.6%)
Other indications	22 (9.4%)

Disclosures: Tayna Latortue:Nothing to Disclose, Andrew Kleehammer:Nothing to Disclose, Ashrita Budharaju:Nothing to Disclose, Natalie Rosseau:Nothing to Disclose, Ang Li:Nothing to Disclose, Josiah McCain:Nothing to Disclose, Tiffany Chua:Nothing to Disclose.

1631 | PREVALENCE AND CLINICAL OUTCOMES OF RESPIRATORY SYNCYTIAL VIRUS ACROSS LIVER DISEASE SPECTRUM – A MULTI-CENTER RETROSPECTIVE COHORT STUDY

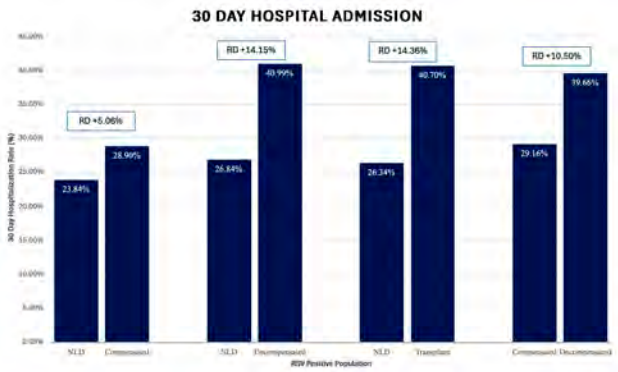
Mridula Bethi[1] Khurram Bari[2] Jordan Voss[3], [1]University of Cincinnati Medical Center, [2]University of Cincinnati, University Hospital Inc Program, [3]University of Cincinnati

Background: Respiratory Syncytial Virus (RSV) causes significant morbidity in immunocompromised adults. In 2023, the FDA approved RSV vaccination for adults >60 years old and those aged 50-59 with

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certain comorbidities including chronic liver disease and immunocompromised. RSV burden across the spectrum of liver disease, including after liver transplantation, remains poorly characterized. By evaluating RSV prevalence and clinical outcomes among patients with cirrhosis and liver transplant, we aim to understand the benefits of more widespread adoption of RSV immunization in this population. **Methods:** We performed a multi-center retrospective cohort study between January 2018 – January 2026 using TriNetX. Patients ($\geq$ 18 years old) were stratified into four distinct groups: no liver disease (NLD), compensated cirrhosis, decompensated cirrhosis, and liver transplant recipients. RSV negative and positive populations within each cohort and RSV positive populations across cohorts were analyzed for 30-day hospitalization, composite severe outcomes (ICU, Mechanical Ventialtion, Mortality), mortality, and rates of RSV immunization. The cohorts were propensity score matched on age, sex, ethnicity, and eleven clinical co-morbidities. Risk differences (RD) and Risk ratio (RR) were calculated. **Results:** 94.3 million patients were included. RSV incidence increased progressively as follows: 1.1 per 1,000 patients in NLD, 5.1 in compensated cirrhosis, 6.9 in decompensated cirrhosis, and 8.8 in liver transplant patients. Within matched cohorts, RSV positive patients demonstrated significant increase in 30 day hospitalization, mortality, and composite across compensated, decompensated, and liver transplant groups in comparison to RSV negative patients ($p < 0.0001$). Vaccination rates were 6.3 per 1,000 patients in NLD, 22.3 in compensated, 14.1 in decompensated, and 18.9 in transplant patients. Among RSV positive patients, compared to NLD, 30 day hospitalization was elevated in compensated cirrhosis (RD +5.1%, RR 1.21 (1.09 - 1.35), $p = 0.0003$), decompensated cirrhosis (RD +14.1%, RR 1.53 (1.40 - 1.67), $p < 0.0001$), and transplant patients (RD +14.4%, RR 1.54 (1.33 - 1.80), $p < 0.0001$). Compared to the RSV positive compensated cohort, decompensated RSV positive cohort had a higher 30 day hospitalization (RD +10.5%, RR 1.36 (1.23 - 1.50), $p < 0.0001$) and mortality (RD +4.4%, RR 2.26 (1.65 - 3.07), $p < 0.0001$). **Conclusion:** RSV prevalence and morbidity increase progressively across liver disease severity. RSV positive decompensated cirrhosis, liver transplant, and compensated cirrhosis cohorts have higher hospitalization than those without liver disease. The decompensated cirrhosis cohort had higher 30-day hospitalization and mortality than compensated cirrhosis. Despite elevated RSV risk, vaccination rates remain suboptimal and paradoxically lowest in decompensated cirrhosis underscoring an urgent preventive care gap.



Disclosures: Mridula Bethi:Nothing to Disclose, KHURRAM BARI:Madrigal: Advisor, Mallinckrodt: Speaking and Teaching, Jordan Voss:Nothing to Disclose.

1632 | EFFICACY AND SAFETY OF FECAL MICROBIOTA TRANSPLANTATION FOR HEPATIC ENCEPHALOPATHY: A SYSTEMATIC REVIEW AND META-ANALYSIS

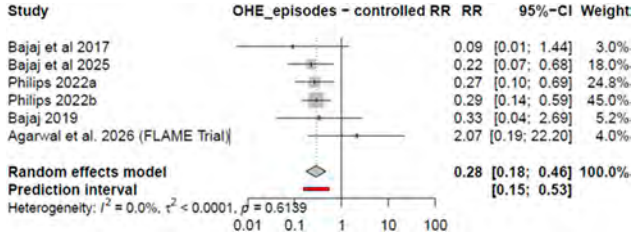
Parul Berry[1] Patricia Bloom[1] Danielle Gerberi[1] Sahil Khanna[2], [1]Mayo Clinic, Rochester, [2]Mayo Clinic Rochester

Background: Gut microbiota dysbiosis is associated with the pathophysiology of hepatic encephalopathy (HE) through hyperammonemia, systemic inflammation, and direct neurotoxin production. Experimental therapies like fecal microbiota transplantation (FMT) for HE may work through modulation of gut microbiota. Despite promising early-phase data, the safety and efficacy of FMT for HE remains uncertain. **Methods:** In this meta-analysis, we included randomized trials, controlled observational studies, single-arm studies, and case series evaluating resolution of covert HE or incidence of overt HE in adults with liver cirrhosis of any etiology. Intervention was FMT by any route of delivery compared with standard of care. Controlled binary outcomes were pooled as risk ratios (RR), continuous outcomes as mean differences in change, and single-arm outcomes separately as proportions. Random-effects models were used. Not all studies reported all outcomes and denominators varied by endpoint. **Results:** After duplicate removal, 1,769 records were screened, and 18 studies (5 randomized controlled trials and 13 nonrandomized studies, including controlled cohorts, single-arm studies, case series, and 1 case report) comprising 618 patients were included. FMT arm had a total of 378 patients with 240 patients in comparator arm. Mean age of population was

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52.6 years with 92% males. Most studies were single centers with 3 multicenter studies. FMT delivery routes were upper gut delivery in 9/18 studies, lower gastrointestinal enema/colonoscopy in 6/18, capsule-only in 2/18, and combined capsule plus enema delivery in 1/18. Among 6 controlled studies reporting OHE recurrence, FMT was associated with reduced risk (RR 0.28, 95% CI 0.18–0.46; $I^2 = 0\%$; $p < 0.001$). FMT was not associated with increased adverse events in controlled studies (5 studies; RR 0.70, 95% CI 0.37–1.33) and decreased serious adverse events (8 studies; RR 0.43, 95% CI 0.25–0.79). Hospitalization was numerically lower but insignificant (4 studies; RR 0.50, 95% CI 0.17–1.48). Mortality was lower in overall controlled analysis (7 studies; RR 0.62, 95% CI 0.42–0.92). Among controlled continuous outcomes, pooled changes were not statistically significant for PHES (5 studies; MD +1.22, 95% CI −0.43 to 2.88), Stroop/EncephalApp time (4 studies; MD −17.3 sec, 95% CI −54.5 to 19.9), serum ammonia (3 studies; MD −12.7, 95% CI −35.3 to 9.8), MELD (4 studies; MD −0.10, 95% CI −1.46 to 1.26), or MELD-Na (3 studies; MD +0.38, 95% CI −0.79 to 1.56). In single-arm studies, pooled proportions were 18.7% for OHE recurrence/events, 22.3% for serious adverse events, and 7.2% for mortality. **Conclusion:** This study suggests that FMT significantly reduces overt HE recurrence without an increase in adverse or serious adverse events. These findings support the advancement of FMT into phase III trials with HE recurrence as a pre-specified primary endpoint to definitively establish its therapeutic role.



Disclosures: Parul Berry:Nothing to Disclose, Patricia Bloom:Vedanta Biosciences: Research grant, Nexilico: Consultant, Boehringer Ingelheim: Consultant, Danielle Gerberi:Nothing to Disclose, Sahil Khanna:Ferring: Consultant, Nestle: Consultant, ProBiotech: Consultant, Rise: Consultant, IQVIA: Consultant.

1633 | SEVERE STEATOSIS AND OBESITY INFLUENCE THE PROGNOSTIC INTERPRETATION OF LIVER STIFFNESS IN COMPENSATED ADVANCED CHRONIC LIVER DISEASE (CACLD)

Anahita Rabiee[1] Christina Lindenmeyer[2] Atoosa Rabiee[3] Cyrus Mowdawalla[4] Sebastian Arambulo-Castillo[5] Matthew Davidsohn[6] Clara Tow[7] Timothy Ring[8] Kelly Bowen[9] Sobia Laique[2] Diego Drumond Westgeest e Sousa[10] Elliot Tapper[11] Michelle Ng[11] Manhal Izzy[12] Anika Shah[13] Todd Frederick[14] Robert Enders[14] Beatriz Sordi Chara[15] Denise Shkurovich[13] Jessica Davis[3] Qusai Al Zureikat[16] Andres Duarte-Rojo[17] Sarang Thaker[18] Louis Guzman[17] Qijun Yang[2] Juan Abraldes[19] Guadalupe Garcia-Tsao[1] Douglas Simonetto[20] Brett Fortune[21], [1]Yale University, [2]Cleveland Clinic, [3]Washington DC VA Medical Center, [4]Montefiore Medical Center, [5]Albert Einstein College of Medicine, Montefiore Einstein Medical Center, Bronx, United States, [6]Albert Einstein College of Medicine, Montefiore Einstein Medical Center, Brox, NY, United States, [7]Albert Einstein College of Medicine, Montefiore Einstein Medical Center, Bronx, NY, United States, [8]Hepatology and Nutrition, Cleveland Clinic; Cleveland, United States, [9]Department of Gastroenterology, Hepatology and Nutrition, Cleveland Clinic; Cleveland, United States, [10]Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, United States, [11]University of Michigan Medical Center, [12]Vanderbilt University Medical Center, [13]Vanderbilt University, [14]California Pacific Medical Center, [15]Yale New Haven Hospital/ Yale School of Medicine, [16]Washington DC Veterans Affairs Medical Center,, [17]Northwestern University, [18]Northwestern University Feinberg School of Medicine, [19]University of Alberta, [20]Mayo Clinic Rochester, [21]Miami Transplant Institute, Jackson Health System

Background: Liver stiffness measurement (LSM) by vibration-controlled transient elastography (VCTE) is widely used for risk stratification in compensated advanced chronic liver disease (cACLD). However, severe obesity and hepatic steatosis may influence LSM independent of fibrosis severity. We evaluated the association of body mass index (BMI) and controlled attenuation parameter (CAP) with hepatic decompensation in a large multicenter U.S. cohort of patients with cACLD. **Methods:** We performed a retrospective multicenter cohort study of patients with cACLD, defined by baseline LSM $\geq$10 kPa by VCTE, across 9 U.S. centers. The primary outcome was hepatic decompensation, defined as ascites, hepatic encephalopathy or variceal bleeding and/or liver-related death. Non-liver related death, liver transplantation, or hepatocellular carcinoma prior to decompensation were treated as competing events. We performed 2 separate analyses to evaluate the role of obesity and CAP in hepatic decompensation. In our primary analysis, patients were stratified based on LSM into three groups: 10 to <15 kPa, 15 to <25 kPa, and $\geq$25 kPa. Within each LSM stratum, primary outcome was compared according to BMI categories (<30, 30 to <35, and $\geq$35 kg/m^2) using univariate Fine–Gray competing risks regression. In a secondary analysis, we used multivariable Fine–Gray competing risks regression model to evaluate the association between CAP (using a threshold of 280 dB/m) and

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hepatic decompensation adjusting for age, baseline albumin, MASLD etiology, and baseline LSM (using a threshold of 25 kPa). **Results:** Among 934 patients with cACLD, median age was 58.5 years, 44.4% were male, median BMI was 32.7kg/m², and the predominant etiology was MASLD (65.5%). Median follow-up was 5 years. Within each LSM stratum, patients with BMI $\geq$35 kg/m² had a significantly lower cumulative incidence of decompensation compared to those with BMI <30. In the secondary multivariable analyses, CAP $\geq$ 280 dB/m was independently associated with lower subdistribution hazard of hepatic decompensation (sHR 0.34, 95% CI 0.19–0.61, p<0.001). LSM $\geq$25 kPa, lower albumin and older age were associated with higher risk of hepatic decompensation (Table 1). **Conclusion:** Severe obesity and higher CAP values were associated with lower rates of hepatic decompensation despite similar liver stiffness measurements. These findings suggest that obesity and hepatic steatosis may affect the prognostic significance of elevated liver stiffness measurements.

Table . Multivariable Fine–Gray model for the 5-year primary outcome

Characteristic	sHR	95% CI	p-value
CAP at index fibroscan			
<280	—	—	
>=280	0.34	0.19, 0.61	**<0.001**
LSM at index fibroscan			
<25	—	—	
>=25	2.96	1.66, 5.28	**<0.001**
Age at index fibroscan	1.03	1.00, 1.05	**0.018**
Albumin at index fibroscan	0.51	0.30, 0.85	**0.01**
MASLD with BMI >=30			
No	—	—	
Yes	0.87	0.48, 1.58	0.64

Abbreviations: CI = Confidence Interval, sHR = Subdistribution Hazard Ratio

Disclosures: Anahita Rabiee:Grifols: Investigator-initiated studies (IIS), Grifols: Investigator-initiated studies (IIS), Grifols: Investigator-initiated studies (IIS), Grifols: Investigator-initiated studies (IIS), Christina Lindenmeyer: Nothing to Disclose, Atoosa Rabiee:Nothing to Disclose, Cyrus Mowdawalla:Nothing to Disclose, Sebastian Arambulo-Castillo:Nothing to Disclose, Matthew Davidsohn: Nothing to Disclose, Clara Tow:Nothing to Disclose, Timothy Ring:Nothing to Disclose, Kelly Bowen:Nothing to Disclose, Sobia Laique:Madrigal Pharmaceuticals Inc: Advisor, Madrigal Pharmaceutical: Consultant, Novo Nordisk: MASH Curriculum Steering Committee, Diego Drumond Westgeest e Sousa:Nothing to Disclose, Elliot Tapper:Madrigal: Grant/Research Support, Gilead: Consultant, Ipsen: Consultant, Merz: Consultant, Michelle Ng: Nothing to Disclose, Manhal Izzy:Mallinckrodt: Speaking and Teaching, Madrigal: Advisor, Natera: Advisor, Mirum: Advisor, Anika Shah:Nothing to Disclose, Todd Frederick: Madrigal: Consultant, Mallinckrodt: Consultant, Salix: Grant/Research Support, Astra Zeneca: Grant/Research Support, River2Renal: Grant/Research Support, Ipsen: Consultant, HepQuant: Consultant, Miromatrix: Consultant, HepQuant: Consultant, Robert Enders:Nothing to Disclose, Beatriz Sordi Chara:Nothing to Disclose, Denise Shkurovich:Nothing to Disclose, Jessica Davis:Eli Lilly: Stock - publicly traded company, Qusai Al Zureikat:Nothing to Disclose, Andres Duarte-Rojo:Echosens: Grant/Research Support, Echosens: Grant/Research Support, CIMA Sciences: Consultant, HepQuant: Advisor, Merz: Advisor, CIMA Sciences: Grant/Research Support, Merz Therapeutics: Advisor, Sarang Thaker:Madrigal Pharmaceuticals: Consultant, Ipsen: Consultant, Louis Guzman: Nothing to Disclose, Qijun Yang:Nothing to Disclose, Juan Abraldes:Gilead: Grant/Research Support, 89bio: Consultant, Boston Pharmaceuticals: Consultant, Novo Nordisk: Consultant, Boehringer Ingelheim: Consultant, Astra Zeneca: Consultant, Agomab: Consultant, Terumo: Speaking and Teaching, Cook: Grant/Research Support, Bausch: Consultant, biossil: Stock – privately held company, biossil: Consultant, Madrigal: Consultant, Guadalupe Garcia-Tsao:Nothing to Disclose, Douglas Simonetto: Mallinckrodt: Consultant, BioVie: Consultant, Resolution Therapeutics: Consultant, Evive: Consultant, Iota: Consultant, Novo Nordisk: Consultant, Astra Zeneca: Consultant, Brett Fortune:Nothing to Disclose.

1634 | DIAGNOSTIC ACCURACY OF ENCEPHALAPP/STROOP FOR MINIMAL AND COVERT HEPATIC ENCEPHALOPATHY: A SYSTEMATIC REVIEW AND META-ANALYSIS

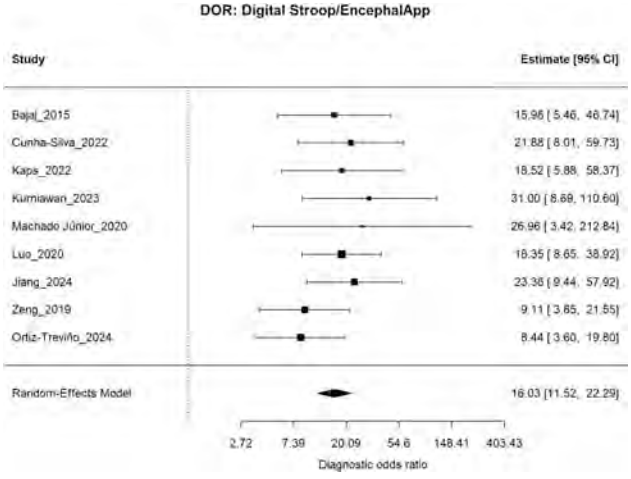
Parul Berry[1] Patricia Bloom[1] Danielle Gerberi[1] Sahil Khanna[2], [1]Mayo Clinic, Rochester, [2]Mayo Clinic Rochester

Background: Minimal and covert hepatic encephalopathy (MHE/Covert HE) are common but under-recognized complications of cirrhosis and are associated with impaired quality of life, falls, hospitalizations, and progression to overt HE. EncephalApp/Stroop is a scalable smartphone-based cognitive test for point-of-care assessment, but reported diagnostic accuracy varies across studies. No prior meta-analysis has quantitatively synthesized EncephalApp/Stroop diagnostic accuracy. **Methods:** We performed a systematic review and diagnostic test accuracy meta-analysis to evaluate the performance of EncephalApp/Stroop for detecting minimal/covert HE. Through systematic literature search, we reviewed studies evaluating digital biomarkers in adults with cirrhosis and identified studies evaluating EncephalApp/Stroop's diagnostic accuracy for MHE or covert HE. Two-by-two tables were extracted directly or reconstructed from disease-positive

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and disease-negative counts with sensitivity and specificity. Pooled sensitivity and specificity were estimated using bivariate diagnostic test accuracy modeling with summary receiver operating characteristic curve estimation. **Results:** After deduplication, 6789 studies were screened and 207 studies underwent full text review. Nine EncephalApp/Stroop cohorts met criteria for primary diagnostic accuracy of meta-analysis. The reference standard was study-defined psychometric or neurocognitive diagnosis of minimal/covert HE, most commonly the Psychometric Hepatic Encephalopathy Score or locally validated psychometric criteria. Pooled sensitivity was 0.85 (95% CI, 0.79–0.89), specificity was 0.74 (95% CI, 0.65–0.81), and area under the summary receiver operating characteristic curve was 0.87. The diagnostic odds ratio was 16.0 (95% CI, 11.5–22.3), with positive likelihood ratio (LR) of 3.13 and a negative LR of 0.22. Sensitivity heterogeneity was moderate (I^2 = 36.4%, p = 0.127), whereas specificity heterogeneity was substantial (I^2 = 76.4%, p < 0.0001). Study-specific positive thresholds varied, most commonly using On-time + Off-time cutoffs ranging from approximately 186 to 270 seconds, which likely contributed to specificity heterogeneity. In subgroup analyses, for MHE studies (n = 5), pooled sensitivity was 0.83 (95% CI, 0.75–0.89) and specificity was 0.77 (95% CI, 0.71–0.82). For covert HE studies (n = 4), pooled sensitivity was 0.86 (95% CI, 0.79–0.91) and specificity was 0.68 (95% CI, 0.51–0.82). **Conclusion:** The EncephalApp Stroop test shows good diagnostic accuracy for covert HE and MHE. Its high sensitivity and low negative likelihood ratio support its use as a scalable screening tool to help rule out minimal/covert hepatic encephalopathy, while moderate specificity suggests that positive results may require confirmation with established psychometric criteria. Standardized cutoffs and reference standards are needed to improve future validation.



Disclosures: Parul Berry:Nothing to Disclose, Patricia Bloom:Vedanta Biosciences: Research grant, Nexilico: Consultant, Boehringer Ingelheim: Consultant, Danielle Gerberi:Nothing to Disclose, Sahil Khanna:Ferring: Consultant, Nestle: Consultant, ProBiotech: Consultant, Rise: Consultant, IQVIA: Consultant.

1635 | SEDATING MEDICATIONS INCREASE THE RISK OF FALLS, HOSPITALIZATION, AND HEPATIC ENCEPHALOPATHY IN PATIENTS WITH CIRRHOSIS

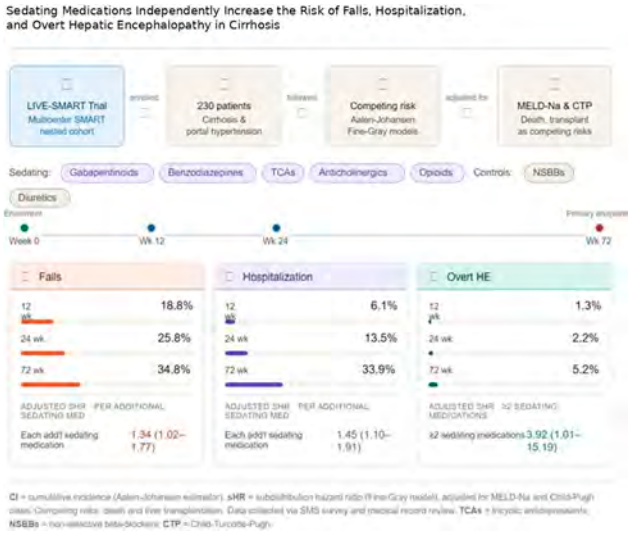
Beanna Martinez[1] Samantha Nikirk[1] Sumeet Asrani[2] Xi Chen[1] Marina Serper[3] Elliot Tapper[4], [1]University of Michigan, [2]Baylor Scott & White, [3]University of Pennsylvania Health System, [4]University of Michigan Medical Center

Background: Falls are common and lethal in cirrhotic patients. Medications used to manage symptoms carry problematic side effects like sedation that may increase fall risk. While these same medications are treated with caution in older adults, prospective data evaluating their contribution to fall risk in cirrhosis are lacking. **Methods:** In a prospective cohort study nested within a multicenter Sequential Multiple Assignment Randomized Trial (LIVE-SMART), competing risk was assessed using the Aalen-Johansen estimator and Fine-Gray subdistribution hazard models to track falls over 72 weeks with 230 patients with cirrhosis and portal hypertension. Death and transplantation were treated as competing risk. Data were collected using SMS-based surveys and medical record review. Sedating medications included gabapentinoids, tricyclic antidepressants (TCAs), benzodiazepines, anticholinergics, and opioids. Diuretics and NSBBs were examined as positive controls. **Results:** The overall cumulative fall incidence was 18.8% (95% CI, 13.7–23.9%) at 12 weeks, 25.8% (95% CI, 20.0–31.6%) at 24 weeks, and 34.8% (95% CI, 28.4–41.2%) at 72 weeks. Cumulative fall incidence was higher among participants on anticholinergics (44.4%), gabapentinoids (41.7%), and benzodiazepines (38.9%). In Fine-Gray models adjusted for liver disease severity, each additional sedating medication was independently associated with falls (sHR 1.34, 95% CI, 1.02–1.77) and hospitalization (sHR 1.45, 95% CI, 1.10–1.91). The total number of medications was similarly associated with falls (sHR 1.22, 95% CI 1.02–1.47) and hospitalization (sHR 1.30, 95% CI, 1.09–1.54). Overt HE risk for participants taking two or more sedating medications was nearly four times higher when adjusting for MELD-Na and Child-Pugh Class (sHR 3.92, 95% CI, 1.01, 15.19). Polypharmacy (5 or more medications), nonselective beta blockers (NSBBs), and diuretics were not associated with falls, hospitalization, or HE. **Conclusion:** Sedating medications were independently associated with increased fall risk,

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hospitalizations, and HE among patients with cirrhosis and portal hypertension. These findings call for routine medication review as part of fall-risk assessment in cirrhosis, with particular attention to gabapentinoids, benzodiazepines, anticholinergics, and TCAs.



Disclosures: Beanna Martinez:Nothing to Disclose, Samantha Nikirk:Nothing to Disclose, Sumeet Asrani: Nothing to Disclose, Xi Chen:Nothing to Disclose, Marina Serper:Transplant Genomics: Grant/Research Support, Grifols: Grant/Research Support, Elliot Tapper:Madrigal: Grant/Research Support, Gilead: Consultant, Ipsen: Consultant, Merz: Consultant.

1636 | IMPACT OF THE NUMBER OF REMAINING NATURAL TEETH ON DECOMPENSATION AND SURVIVAL IN PATIENTS WITH COMPENSATED LIVER CIRRHOSIS

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Background: To evaluate the clinical impact of oral health, assessed by the number of remaining natural teeth, on hepatic decompensation and overall survival in patients with compensated liver cirrhosis, and to explore its association with endotoxemia and sarcopenia. **Methods:** This retrospective cohort study included 106 patients with liver cirrhosis classified as Child–Pugh class A who were followed at a single tertiary center between April 2017 and March 2024 . Patients with hepatocellular carcinoma were excluded. Oral health status was assessed by the number of remaining natural teeth at baseline, and patients were stratified into two groups (<20 vs. ≥ 20 teeth). Baseline clinical and laboratory data, including prothrombin activity (PA) and serum sodium (Na), were collected. Sarcopenia was evaluated based on skeletal muscle mass, and endotoxin activity was measured using an endotoxin activity assay (EAA). The primary outcomes were hepatic decompensation and overall survival. Kaplan–Meier analysis and Cox proportional hazards models were used to identify prognostic factors. **Results:** During the follow-up period, 26 patients (24.5%) developed hepatic decompensation and 26 patients died . Patients with fewer than 20 natural teeth had significantly higher rates of both decompensation and mortality compared with those with ≥ 20 teeth. In multivariate analysis, PA $<75\%$ (hazard ratio [HR]: 2.86) and <20 teeth (HR: 2.46) were independent predictors of hepatic decompensation. For overall survival, serum Na ≤ 138 mEq/L (HR: 2.93) and <20 teeth (HR: 2.85) were identified as independent prognostic factors. Kaplan–Meier analysis demonstrated that combining tooth count with PA or Na improved risk stratification, with the highest risk observed in patients with both unfavorable clinical parameters and fewer teeth. The predictive performance of tooth count was comparable to that of conventional markers. Furthermore, patients with fewer than 20 teeth had a significantly higher prevalence of sarcopenia and elevated endotoxin activity, suggesting a mechanistic link between poor oral health, systemic inflammation, and disease progression. In addition, patients with preserved dentition who attended regular dental visits showed the most favorable outcomes. **Conclusion:** The number of remaining natural teeth is a simple and clinically meaningful predictor of hepatic decompensation and mortality in patients with compensated liver cirrhosis. Poor oral health is associated with increased endotoxemia and sarcopenia, indicating potential pathophysiological mechanisms. Incorporating oral health assessment into routine clinical evaluation may improve risk stratification and highlight the importance of multidisciplinary management, including dental care, in patients with cirrhosis.

Disclosures: Tadashi Namisaki:Nothing to Disclose, KOSUKE KAJI:Nothing to Disclose, Hitoshi Yoshiji: Nothing to Disclose.

1637 | QUANTITATIVE ASSESSMENT OF HEMOSTATIC FUNCTION USING A NOVEL MICROFLUIDIC DEVICE IN PATIENTS WITH CIRRHOSIS

Yuhei Matsumoto[1] Norihiro Imai[1] Yuki Takagi[2] Masashi Otsuki[2] Shinya Yokoyama[1] Kenta Yamamoto[1] Takanori Ito[1] Yoji Ishizu[1] Takashi Honda[1] Hiroki

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Background: Patients with cirrhosis often exhibit bleeding tendencies due to thrombocytopenia and coagulation abnormalities; however, quantitative assessment of global hemostatic function remains challenging. The Total Thrombus-formation Analysis System (T-TAS®) enables evaluation under physiologic flow conditions using a microfluidic device. This study aimed to assess hemostatic function in patients with cirrhosis, including those with thrombocytopenia, using a novel T-TAS HD assay that integrates primary and secondary hemostasis, and to compare it with the conventional T-TAS AR assay in patients with relatively preserved platelet counts. **Methods:** We enrolled 50 hospitalized patients with cirrhosis and platelet counts $\leq$150,000/μL. Bleeding time was measured by the Ivy method under 40 mmHg cuff pressure and a 23G lancet. The HD assay was performed using citrated whole blood, and the AR assay was additionally performed in patients with platelet counts >90,000/μL. Correlations between bleeding time, T-TAS assay parameters, and clinical variables were analyzed. **Results:** Thirteen patients (26%) had prolonged bleeding time ($\geq$5 minutes). Bleeding time significantly correlated with prothrombin activity (PT) (R = -0.693), platelet count (R = -0.620), and HD assay (R = -0.705) (all P < 0.001). Patients with bleeding time $\geq$5 minutes showed significantly lower HD assay values (1317.15 vs 835.42), PT (83.7% vs 46.3%), and platelet count (9.38×10^4/μL vs 5.73×10^4/μL) (all P < 0.001). ROC analysis demonstrated AUC values of 0.942 for the HD assay, 0.897 for PT, and 0.840 for platelet count, indicating superior discriminative ability of the HD assay for prolonged bleeding time. In 16 patients with platelet counts >90,000/μL, AR and HD assays were significantly correlated (R = 0.769, P = 0.0005). The AR assay correlated with bleeding time but not with PT or platelet count. Moreover, the correlation with bleeding time was stronger in the AR assay than the HD assay in patients with platelet counts >90,000/μL. Although bleeding time reflects global hemostatic function under physiologic conditions, its clinical use is limited by complexity. The HD assay strongly correlated with bleeding time and showed superior diagnostic performance compared with conventional parameters. In patients with preserved platelet counts, the AR assay also correlated with bleeding time, suggesting better reflection of global hemostasis than conventional parameters; however, it is not applicable in severe thrombocytopenia, which the HD assay overcomes. **Conclusion:** The novel T-TAS HD assay enables quantitative evaluation of hemostatic function in thrombocytopenic patients with cirrhosis and may facilitate bleeding risk stratification, preprocedural assessment, and patient education. The AR assay remains a useful complementary tool in patients with cirrhosis and preserved platelet counts.

Disclosures: Yuhei Matsumoto:Nothing to Disclose, Norihiro Imai:ZACROS Corporation: Grant/Research Support, Yuki Takagi:Nothing to Disclose, Masashi Otsuki:Nothing to Disclose, Shinya Yokoyama:Nothing to Disclose, Kenta Yamamoto:Nothing to Disclose, Takanori Ito:Nothing to Disclose, yoji ishizu:Nothing to Disclose, Takashi Honda:Nothing to Disclose, Hiroki Kawashima:Nothing to Disclose.

1638 | SEQUENTIAL 100-HZ SPLEEN STIFFNESS AND ANTICIPATE-NASH IMPROVE THE REAL-WORLD DETECTION OF ESOPHAGEAL VARICES: A THAI ADVANCED CHRONIC LIVER DISEASE COHORT

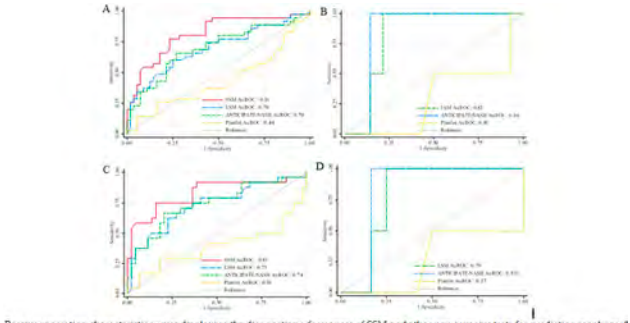
Kwanchat Krairaweengarmwijitr[1] Supatsri Sethasine[2], [1]Vajira Hospital, [2]Faculty of Medine Vajira Hospital

Background: Spleen stiffness measurement (SSM) is an established non-invasive marker of portal hypertension, but its performance in real-world settings with diverse etiologies remains incompletely defined. We evaluated whether a sequential strategy integrating 100-Hz SSM and the metabolic-adjusted ANTICIPATE-NASH model improves the detection of esophageal varices (EV) in patients with advanced chronic liver disease (aCLD). **Methods:** This diagnostic accuracy study was conducted at Vajira Hospital, Bangkok, Thailand, between August 2025 - January 2026. A total of 91 patients with aCLD underwent vibration-controlled transient elastography (100-Hz SSM and liver stiffness measurement [LSM]) followed by endoscopy within 3 months. The ANTICIPATE-NASH score was calculated. The primary outcome was the presence of EV of any grade. High-risk varices were defined as medium-to-large varices or small varices with high-risk stigmata. Diagnostic performance was assessed using area under the receiver operating characteristic curve (AUROC), with subgroup analyses according to SSM strata and non-selective beta-blocker (NSBBs) exposure. **Results:** EV were present in 35/91 patients (38.5%), including 9 (25.7%) with high-risk varices. SSM demonstrated the strongest overall discriminative ability (AUROC 0.81; 95% CI 0.72-0.91), with an optimal cutoff of $\geq$ 40.6 kPa yielding 77.1% sensitivity and 76.8% specificity. LSM and the ANTICIPATE-NASH score showed modest performance (AUROC 0.70), while platelet count performed poorly (AUROC 0.44). Performance varied across SSM strata. In patients with SSM < 21 kPa, LSM and ANTICIPATE-NASH showed higher discrimination (AUROC 0.82 and 0.86, respectively), whereas SSM remained dominant in higher strata. In patients not receiving beta-blockers (n = 68), SSM retained robust performance (AUROC 0.83), and the incremental value of ANTICIPATE-

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NASH in the low-SSM subgroup persisted. **Conclusion:** In real-world clinical practice, 100-Hz SSM provides robust overall discrimination for EV but exhibits stage-dependent performance. A sequential framework incorporating the ANTICIPATE-NASH model, tailored to Asian metabolic profiles, enhances diagnostic precision and patient safety, particularly in individuals with lower spleen stiffness. This multidimensional approach supports a more refined endoscopic triage and warrants further prospective validation across diverse clinical settings.



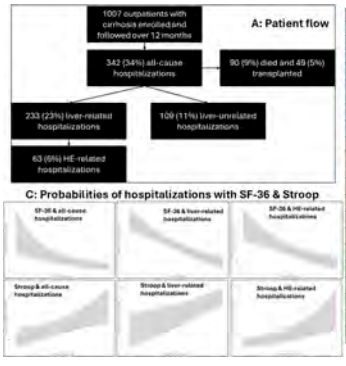
Receiver operating characteristic curves displaying the diagnostic performances of SSM and other non-invasive tests for predicting esophageal varices. A: total patients; B: patients with SSM <21 kPa; C: Non-NSBBs use patients; D: Non-NSBBs use patients with SSM <21 kPa
Abbreviations: ANTICIPATE-NASH: ANTICIPATE-non-alcoholic steatohepatitis; AUROC: area under receiving operating curve; LSM: liver stiffness measurement; SSM: spleen stiffness measurement

Disclosures: Kwanchat Krairaweengarmwijitr:Nothing to Disclose, Supatsri Sethasine:Nothing to Disclose.

1639 | ALTERED COGNITION AND PATIENT-REPORTED OUTCOMES PREDICT 1-YEAR HOSPITALIZATION RISK IN A MULTI-CENTER OUTPATIENT CIRRHOSIS COHORT

Jasmohan Bajaj[1] Jacqueline O'Leary[2] Jennifer Lai[3] Puneeta Tandon[4] Florence Wong[5] Guadalupe Garcia-Tsao[6] Scott Biggins[7] Philip Vutien[8] Patrick Kamath[9] Hugo Vargas[10] Scott Silvey[11] Brian Bush[11] K Rajender Reddy[12], [1]Virginia Commonwealth University, [2]UTSW, [3]UCSF, [4]University of Alberta, [5]University of Toronto, [6]Yale University, [7]UPMC, [8]UW, [9]Mayo Rochester, [10]Mayo Clinic Arizona, [11]VCU, [12]University of Pennsylvania

Background: The clinical characteristics of patients with cirrhosis are changing, and many continue to have complications despite having a controlled etiology. Patient-reported outcomes (PROs) & cognition could impact clinical outcomes. Aim : In a contemporary cohort, to evaluate the impact of PROs and cognition on risk for future hospitalization in addition to cirrhosis-related parameters. **Methods:** 1007 outpatients with cirrhosis, median MELD 11, 39% compensated, 61% decompensated, all with controlled liver disease etiology (no alcohol, HCV SVR, suppressed HBV), were prospectively enrolled at 11 centers across North America in NACSELD-3 (North American Consortium for the Study of End-Stage Liver Disease). Clinical, comorbidity (Charlson comorbidity index, CCI) and demographic data were captured. All patients underwent baseline testing for SF-36 and Stroop and were systematically followed for 1-year through in-person visits and calls. Outcomes: Non-elective hospitalizations at 1 year. These were grouped as all-cause, liver-related or hepatic encephalopathy (HE) related. Crude comparisons between groups were & logistic regression for the 3 outcomes was performed. **Results:** 1007 patients across 11 sites (61yrs, 69% men, 42% alcohol, 39% compensated , MELD3.0 11) were enrolled. 26% had prior HE, 23% ascites, 31% were on PPIs & 30% on statins. SF-36 general health was 45[30-65] &l Stroop time was 177 [155-206] seconds. Outcomes : 34% had all-cause, 23% liver & 6% HE-related hospitalizations (FigA). 9% died & 5% got LT. Crude comparisons : Pts who got hospitalized (all-cause, liver, or HE) had worse cirrhosis severity, CCI, Stroop time (high = worse) & SF-36 general health (high = good). Multivariable model (Fig B): Age, CCI, Stroop time, SF-36 general health & MELD3.0 predicted risk for all-cause hospitalization. Modifiable risk factors of liver-related hospitalization included PPI (9% rise) & statin (43% decrease). HE was predicted by prior HE as well. Only Stroop time &SF-36 general health score predicted all three hospitalization types (all-cause, liver-related, HE-related) regression.Predicted probabilities of hospitalization-based outcomes at increasing levels of total Stroop Time and SF-36 general health score with plotted probability of each outcome over range of PRO are in figure C (negative with SF-36 & positive with Stroop). **Conclusion:** In a multicenter cohort of >1000 etiology-controlled cirrhosis outpatients; one-third required non-elective hospitalization by 1-year. PROs using SF-36 & cognition using Stroop synergized with liver-related & comorbid conditions to predict future risk of all-cause, liver-related & HE-related hospitalizations. A holistic view of liver health is needed to improve prognostication.



B: Logistic regression for the three outcomes

Multi-variable model for All-cause Hospitalizations

Variable	p-value	OR (95% CI)
Age	0.03	0.98 (0.96-0.99)
Charlson Comorbidity Index	0.02	1.12 (1.02-1.24)
Total Stroop Time	<0.001	1.015 (1.006-1.023)
SF-36 General Health Score	<0.001	0.98 (0.97-0.99)
MELD-3.0	<0.001	1.08 (1.05-1.11)

Multi-variable model for Liver-Related Hospitalizations

Variable	p-value	OR (95% CI)
MELD-3.0	<0.001	1.12 (1.09-1.16)
Statin	0.007	0.57 (0.38-0.86)
Total Stroop Time	0.002	1.09 (1.03-1.15)
SF-36 General Health Score	<0.001	0.98 (0.97-0.99)
PPI	0.01	1.09 (1.03-1.15)

Multi-variable model for HE-Related Hospitalizations

Variable	p-value	OR (95% CI)
Total Stroop Time	<0.001	1.015 (1.003-1.02)
SF-36 General Health Score	<0.001	0.98 (0.96-0.99)
Non-Selective Beta-Blockers	0.015	2.07 (1.19-3.65)
Prior HE	<0.001	3.05 (1.73-5.40)

Disclosures: Jasmohan Bajaj:Bausch: Grant/Research Support, Sequana: Grant/Research Support, Grifols: Grant/Research Support, Bausch: Grant/Research Support, Sequana: Grant/Research Support,

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1640 | SECONDARY SBP PROPHYLAXIS AND LONG-TERM OUTCOMES IN CIRRHOSIS: BEYOND RECURRENCE PREVENTION

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Background: Spontaneous bacterial peritonitis (SBP) is a major event in cirrhosis, as bacterial translocation, systemic inflammation, and hemodynamic changes can precipitate further decompensation. Although secondary prophylaxis is recommended to reduce SBP recurrence, its impact on long-term cirrhosis outcomes remains unclear. Thus, we aim to evaluate whether secondary prophylaxis provides benefits beyond preventing SBP recurrence. **Methods:** We performed a retrospective cohort study using TriNetX database global research network. Adults with cirrhosis and at least one SBP episode between 1/1/2010 and 1/1/2026 were included. Patients were stratified by use of secondary prophylaxis, defined as ciprofloxacin, norfloxacin, or trimethoprim-sulfamethoxazole started within one month of SBP. Propensity score matching balanced baseline demographics, comorbidities, and medication use. Outcomes of recurrent SBP, ascites, hepatic encephalopathy (HE), hepatorenal syndrome (HRS), variceal bleeding, multidrug-resistant (MDR) infection, fungal infection, and all-cause mortality were assessed at 3, 6, 12, and 24 months. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using Cox proportional hazards models. **Results:** A total of 1,860 patients received secondary prophylaxis, while 10,538 did not. Prophylaxis was associated with a lower risk of variceal bleeding only at 6 months (HR 0.67, CI 0.47-0.95). However, it was associated with reduced ascites, HE, and all-cause mortality at all time points. A decrease in recurrent SBP was noted at 3 months (HR 0.80, CI 0.68-9.93) and 6 months (HR 0.67, CI 0.47-0.96). Meanwhile, a reduction in HRS emerged later at 12 months (HR 0.72, CI 0.55-0.95) and 24 months (HR 0.73, CI 0.56-0.96). No significant increase in MDR or fungal infections was observed. Detailed results are summarized in Figure 1. **Conclusion:** Secondary SBP prophylaxis was associated with sustained reductions in ascites, HE, and all-cause mortality, with a transient decrease in variceal bleeding. Its effect on recurrent SBP was greatest early after the index episode, while its benefit in HRS appeared delayed. The value of secondary prophylaxis, therefore, may extend beyond preventing SBP recurrence to modifying the disease trajectory. Despite no significant increase in fungal and MDR infections, concerns remained for prolonged use of antibiotics. Future studies should confirm these findings and develop tools to guide individualized prophylaxis duration rather than routine indefinite therapy.

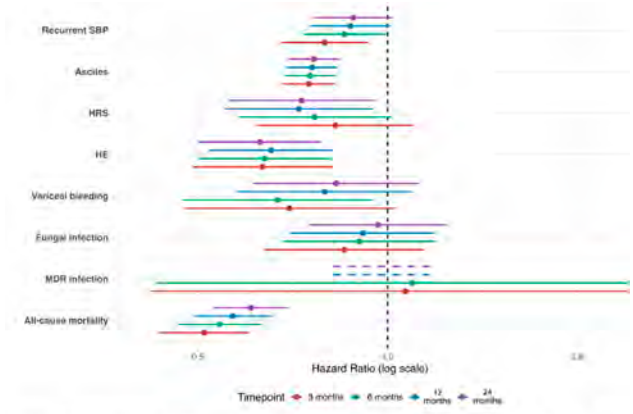


Figure 1. Hazard ratios with 95% confidence intervals for clinical outcomes between patients with and those without secondary SBP prophylaxis at 3, 6, 12, and 24 months after propensity-score matching. The dashed vertical line represents an HR of 1.0, indicating no difference between groups. HRs < 1 favor cohort with secondary SBP prophylaxis. Dashed lines denote outcomes with limited event counts (< 10 events) for stable Cox model estimation.

Disclosures: Lan Nguyen:Nothing to Disclose, Sandra Chehayeb:Nothing to Disclose, Mahinaz Mohsen:Nothing to Disclose, Anthony Martinez:Gilead: Consultant, Gilead: Speaking and Teaching, Abbvie: Consultant, Abbvie: Speaking and Teaching, Arbutus: Consultant, Braeburn: Speaking and Teaching, Sirtex: Consultant, Roche: Consultant, Syneos/VBI: Consultant, Madrigal:

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1641 | ASSESSING PERFORMANCE OF MODELS PREDICTING 30-DAY READMISSIONS IN CIRRHOSIS

Peter Rose[1] Alan Wigg[1] Richard Woodman[2], [1]South Australia Liver Transplant Unit, [2]Flinders University

Background: Patients hospitalized with cirrhosis have high rates of early, unplanned readmission within 30 days. These are expensive and associated with worse outcomes. We performed a scoping review of the literature to assess reporting quality of current models predicting 30-day readmissions in cirrhosis and their performance. **Methods:** Preferred Reporting Items for Systematic Reviews and Meta-analysis extension for scoping reviews (PRISM-ScR) guidelines were followed. PubMed, EMBASE and Web of Science were systemically searched from inception to January 2025. Studies reporting a model predicting 30-day readmissions in cirrhosis were eligible. Adherence to the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) statement was assessed. Patient sample, type of model, presence of a validation cohort and measures of model performance was analysed. **Results:** Out of thirteen studies proposing prediction models, there were six multicentre databases, two two-centre studies and five single-centre studies, of which one was prospective. Logistic regression was used in eleven studies, Cox regression in two studies and machine learning (ML) models in one study. No studies explicitly documented adherence to TRIPOD or other established reporting guideline. Poorly adhered checklist components were establishment of an appropriate sample size (no studies), missing data handling (three studies) and potential predictor variable handling (two studies). Internal validation was performed in four studies and external validation in three studies. Only one internally validated model demonstrated at least fair discrimination (C-statistic > 0.7). No externally validated nor ML model demonstrated at least fair discrimination. Only five studies provided examples of real-world translation of constructed models. **Conclusion:** Studies reporting prediction models for early readmission in cirrhosis do not adhere to established reporting guidelines. Overall model performance was suboptimal. Inclusion of more sophisticated psychosocial covariates in models and better adherence to reporting guidelines may improve model performance and their clinical utility.

Disclosures: Peter Rose:Nothing to Disclose, Alan Wigg:Nothing to Disclose, Richard Woodman:Nothing to Disclose.

1642 | BALLOON-OCCLUDED RETROGRADE TRANSVENEOUS OBLITERATION FOLLOWING PARTIAL SPLENIC ARTERY EMBOLIZATION FOR GASTRIC VARICES

Miyu Fujita[1] Takeharu Asano[1] Shuhei Yoshikawa[1] Shinichi Asabe[1] Hirosato Mashima[1], [1]Saitama Medical Center, Jichi Medical University

Background: Background:: Gastric varices are characterized by large diameters and high blood flow. Therefore, for the treatment of gastric varices, balloon-retrograde variceal embolization (BRTO) is recommended over endoscopic treatment alone for the prevention of rebleeding. Partial splenic artery embolization (PSE) is expected to reduce portal blood flow and portal pressure, thereby also reducing blood flow to esophageal and gastric varices. We evaluated the efficacy of BRTO in cases at our hospital where it was performed following PSE. **Methods: Methods::** Among the cases treated for gastric varices at our hospital between 2014 and 2024, we included 33 cases that underwent BRTO alone and 10 cases in which PSE was performed first, with BRTO added within 4-8 weeks. We compared and analyzed pre-treatment data (before BRTO and PSE) with data taken 3 months after treatment. The initial post-treatment evaluation was performed within 3-6 months using endoscopy and contrast-enhanced CT. **Results: Results:: 1)** The reduction or disappearance rate of gastric varices after BRTO was 94% (31/33) in the BRTO-alone group and 100% (10/10) in the PSE-first BRTO group. The rate of esophageal variceal worsening within one year after BRTO was 15% (5/33) in the BRTO-alone group and 10% (1/10) in the PSE-first BRTO group. **2)** In the BRTO-alone group, a significant decrease in ammonia levels (57 to 39 μg/dl) and a significant improvement in the prognostic nutrition index (PNI) (42.6 to 45.2) were observed 3 months after treatment. In the PSE-first BRTO group, in addition to significant improvements in ammonia levels (57 to 42.5 μg/dl) and PNI (38.8 to 43.5), a significant increase in platelet count (90,000 to 120,000/μL) was observed. No new cases of portal vein thrombosis were observed postoperatively in either group. **Conclusion: Conclusion::** BRTO following PSE for gastric varices showed a significant decrease in serum ammonia and increases in PNI and platelets. The treatment success rate was high and the rate of postoperative worsening of esophageal varices was

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low, suggesting it is an effective treatment for gastric varices.

Disclosures: Miyu Fujita:Nothing to Disclose, Takeharu Asano:Nothing to Disclose, Shuhei Yoshikawa: Nothing to Disclose, Shinichi Asabe:Nothing to Disclose, Hirosato Mashima:Nothing to Disclose.

1643 | INCIDENCE AND ASSOCIATED RISK FACTORS FOR RECURRENCE OF HEPATORENAL SYNDROME-ACUTE KIDNEY INJURY (HRS-AKI) IN PATIENTS WITH CIRRHOSIS

Sanjit Kumar[1] Sumit Rungta[1], [1]King Geroge's Medical University

Background: Hepatorenal syndrome-acute kidney injury (HRS-AKI) is a severe complication of cirrhosis. While vasoconstrictors and albumin can achieve initial response, subsequent recurrence poses major therapeutic challenges. The true incidence and independent predictors of HRS-AKI recurrence remain poorly defined. Recurrent HRS-AKI presents significant therapeutic issues, especially in areas with low resources where liver transplantation, the final treatment, may not be easily accessible and optimizing medical management becomes crucial. **Methods:** This longitudinal observational study included cirrhotic patients with ascites who fulfilled ICA criteria for HRS-AKI and achieved complete response to standard medical therapy. Patients were followed for 3 months. Recurrence was defined as $\geq$50% increase in serum creatinine from the lowest post-treatment value, final creatinine >1.5 mg/dL, and meeting HRS-AKI criteria. Clinical, laboratory and hemodynamic parameters were analyzed. Multivariate linear regression identified independent predictors of recurrence. **Results:** Among 72 enrolled patients (mean age 50.4±8.5 years, 86.1% male, mean MELD-Na 28.4±5.6, mean arterial pressure (MAP) 82.3±11.6 mmHg), HRS-AKI recurrence occurred in 21/71 (one patient expired before the first scheduled visit) (29.6%) over 3 months (7.0% at 2 weeks, 4.2% at 4 weeks, 12.7% at 2 months, 5.6% at 3 months). On univariate analysis, patients with recurrence had significantly lower baseline MAP (78.2±11.0 vs. 84.2±11.5 mmHg, p=0.047), higher CTP score (11.3±1.96 vs. 9.96±1.68, p=0.004), higher MELD-Na (31.3±3.9 vs. 26.9±5.6, p=0.002), higher total bilirubin (4.34±2.9 vs. 2.83±2.2 mg/dL, p=0.020), higher INR (2.37±1.11 vs. 1.87±0.65, p=0.022), and lower serum sodium (127.7±5.2 vs. 131.0±4.9 mEq/L, p=0.012). On multivariate analysis, only MAP at 4 weeks (β=-0.239, p=0.027) and MAP at 3 months (β=-0.438, p<0.001) remained independent predictors of recurrence (model R^2=0.777). **Conclusion:** HRS-AKI recurrence occurs in nearly one-third of cirrhotic patients within 3 months of successful initial treatment. While baseline liver disease severity markers (CTP, MELD-Na, bilirubin, INR, sodium) are associated with recurrence in univariate analysis, sustained hemodynamic stability—specifically MAP at 4 weeks and 3 months—is the only independent predictor. These findings highlight that preventing recurrence depends less on initial liver failure severity and more on maintaining systemic perfusion pressure, advocating for prolonged hemodynamic monitoring and MAP-targeted strategies post-HRS-AKI resolution.

Disclosures: Sanjit kumar:Nothing to Disclose, SUMIT RUNGTA:Nothing to Disclose.

1644 | HOW LARGE IS THE IMPACT OF ANTIBIOTICS ON MORTALITY IN SPONTANEOUS BACTERIAL PERITONITIS? A REGRESSION DISCONTINUITY ANALYSIS IN US VETERANS

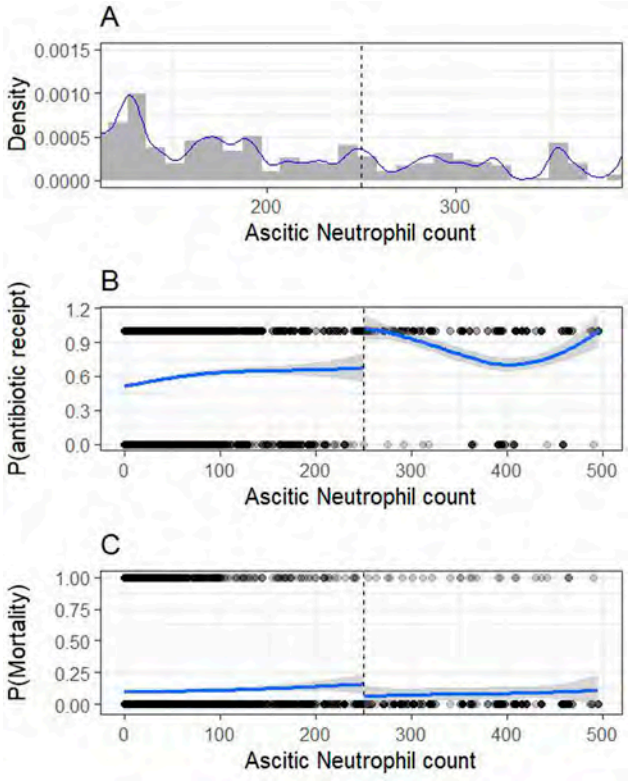
Melis Celdir[1] Christine Bricker[2] Tomohiro Tanaka[3], [1]Washington University School of Medicine, [2]Iowa City VA Health Care System, [3]University of Iowa

Background: Spontaneous bacterial peritonitis (SBP) carries high mortality, yet the benefit of antibiotic therapy has not been well quantified. We used a quasi-experimental fuzzy regression discontinuity design (RDD) leveraging the 250 cells/mm³ neutrophil threshold to estimate the causal effect of antibiotics on 90-day mortality. **Methods:** We conducted a retrospective cohort study of Veterans with advanced chronic liver disease and ascites who underwent paracentesis within the VA system (2015-2023). Patients with ascitic neutrophil counts >500 cells/mm³ were excluded to define an appropriate RDD bandwidth. The neutrophil threshold indicator (below vs. at/above 250 cells/mm³) served as an instrumental variable for antibiotic receipt, defined as intravenous antibiotics within 72 hours of paracentesis. Two-stage nonlinear models estimated local average treatment effects. In the first stage, antibiotic receipt was modeled as a function of the threshold indicator, continuous neutrophil count, demographics, liver disease etiology, MELD 3.0, and Elixhauser comorbidities. In the second stage, daily mortality was modeled using generalized estimating equations with robust standard errors, adjusting for age, sex, MELD 3.0, and a flexible baseline hazard. Two specifications were implemented: two-stage predictor substitution (2SPS) and two-stage residual inclusion (2SRI). Missing MELD 3.0 components (2.4-5.7%)

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were handled via multiple imputation. **Results:** Among 2,451 patients (mean age 64.6, 96.1% male, mean MELD 3.0: 19.7). The distribution of ascitic neutrophil counts showed no evidence of manipulation around the threshold (Figure A). Antibiotic receipt probability increased sharply at the 250 cells/mm³ threshold (Figure B), with a corresponding reduction in mortality also suggested at the discontinuity (Figure C). In the first stage regression model, crossing the threshold of 250 was strongly associated with antibiotic receipt ($p < 0.001$). In second-stage models, antibiotic therapy was associated with an approximately 80% reduction in daily hazard of death (2SPS: HR 0.19, 95% CI 0.04-0.95; 2SRI: HR 0.20, 95% CI 0.04-1.02). Modeled 90-day cumulative mortality was 39.7% with treatment versus 98.3% without. **Conclusion:** In this national VA cohort, antibiotic therapy at the 250 cells/mm³ neutrophil threshold was associated with markedly lower 90-day mortality among compliers. These findings reinforce the importance of prompt antibiotic treatment for suspected SBP, and the large observed effect supports further investigation of antibiotic initiation at lower neutrophil thresholds.



Disclosures: Melis Celdir:Nothing to Disclose, Christine Bricker:Nothing to Disclose, Tomohiro Tanaka: Nothing to Disclose.

1645 | INPATIENT NATIONAL TRENDS AND PREDICTORS OF HEPATOPULMONARY SYNDROME HOSPITALIZATIONS: A U.S. RETROSPECTIVE ANALYSIS

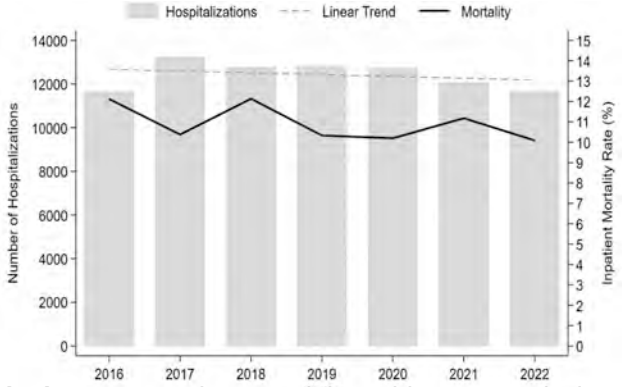
Islam Rajab[1] Mohamed S. Elgendy[2] Muhammad Saad Jamil[3] Mahmoud Shaaban Abdelgalil[4] Belal Mohamed Hamed[5] EzzElDien A. Ibrahim[6] Abdallfatah Abdallfatah[7] Ameer Awashra[8] Alveen Majeed[9] Mohamed Elnaggar[10] Walid Baddoura[11] Nikolaos Pyrsopoulos[12], [1]St joseph University Medical Center, [2]. Faculty of Medicine, Tanta University, Tanta, Egypt, [3]Department of Medicine, Quaid-e-Azam Medical College Bahawalpur, Pakistan, [4]Faculty of Medicine, Ain- Shams University, Cairo, Egypt, [5]Faculty of Medicine, Al-Azhar University, Cairo, Egypt, [6]. Department of Medicine, University of Missouri-Columbia, MO, USA, [7]Faculty of Medicine, October 6 University, Giza, Egypt, [8]Department of Medicine, An-Najah National University, Nablus, West Bank, Palestine, [9]Internal Medicine Department, Henry Ford St John Hospital, Detroit, MI, USA, [10]Hospital Medicine department, Hartford Healthcare, Hartford CT. USA, [11]Department of Gastroenterology and Hepatology, St. Joseph University Medical Center,Paterson, NJ,USA, [12]Division of Gastroenterology and Hepatology, Department of Medicine, Rutgers New Jersey, USA

Background: Hepatopulmonary syndrome (HPS) is a pulmonary vascular complication of chronic liver disease that carries a clinical and economic burden. Contemporary national data describing inpatient outcomes in HPS remain limited. **Methods:** We performed a retrospective analysis of adult HPS hospitalizations in the National Inpatient Sample during 2016–2022. HPS was identified using the ICD-10-CM code K76.81. Survey-weighted methods generated national estimates. Temporal trends and predictors of in-hospital mortality, length of stay (LOS), and total hospital charges were evaluated using multivariable regression adjusted for demographic, socioeconomic, clinical, and hospital-level factors. **Results:** The cohort included 17,400 HPS hospitalizations. Mean age was 56.0 ± 14.8 years; 50.6% were male, 67.6% were White, and Medicare was the most common payer (41.2%). Most hospitalizations involved comorbidity burden, with 86.6% having a Charlson Comorbidity Index ≥ 3. Across the study period, hospitalization volume and mortality remained stable while unadjusted annual mean LOS did not differ significantly, although adjusted LOS showed a small positive association with calendar year. Overall, in-hospital mortality was 10.9%, mean LOS was 9.7 ± 11.6 days, and mean hospital

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charges were $143,167 ± $240,908. In the adjusted analysis, mortality was associated with older age, Medicaid insurance, self-pay status, other-payer status, and a Charlson Comorbidity Index ≥3. Female sex was associated with lower mortality, shorter LOS, and lower charges. Higher comorbidity burden, urban teaching hospitals, and large hospital bed size were associated with greater LOS and charges. **Conclusion:** From 2016 to 2022, HPS hospitalizations in the United States showed stable national inpatient outcomes but persistent resource-intensive care. Mortality and utilization were driven by comorbidity burden, insurance status, and hospital characteristics, highlighting the need for earlier recognition, equitable specialty access, and optimized inpatient management.



Disclosures: Islam Rajab:Nothing to Disclose, Mohamed S. Elgendy:Nothing to Disclose, Muhammad Saad Jamil:Nothing to Disclose, Mahmoud Shaaban Abdelgalil:Nothing to Disclose, Belal Mohamed Hamed:Nothing to Disclose, EzzElDien A. Ibrahim:Nothing to Disclose, Abdallfatah Abdallfatah:Nothing to Disclose, Ameer Awashra:Nothing to Disclose, Alveen Majeed:Nothing to Disclose, Mohamed Elnaggar:Nothing to Disclose, Walid Baddoura:Nothing to Disclose, Nikolaos Pyrsopoulos:Nothing to Disclose.

1646 | HIGHER RISK OF ASCITES AND SPONTANEOUS BACTERIAL PERITONITIS IN ALPHA-1 ANTITRYPSIN DEFICIENCY-ASSOCIATED CIRRHOSIS COMPARED TO OTHER CIRRHOSIS ETIOLOGIES

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Background: Alpha-1 antitrypsin deficiency (AATD) is an inherited disorder where accumulation of misfolded alpha-1 antitrypsin proteins damages the liver, leading to progressive hepatic fibrosis and cirrhosis. Unfortunately, AATD is still underdiagnosed and recognized at later stages, increasing risk of decompensation. However, data comparing patterns of decompensation in AATD cirrhosis compared to other cirrhosis etiologies are limited. We aimed to evaluate the ascites and spontaneous bacterial peritonitis (SBP) outcomes in patients with AATD-associated cirrhosis compared to those with cirrhosis secondary to other etiologies. **Methods:** Using the TriNetX Research Network, we conducted a retrospective cohort study identifying two cohorts via ICD-10 codes: one cohort with diagnoses of cirrhosis and AATD and a comparison cohort with cirrhosis without AATD. To reduce confounding, patients with concurrent alcohol-associated cirrhosis were specifically excluded from the AATD cohort. Propensity-score matching was performed to balance age, sex, race, and alcohol use disorder. Outcomes analyzed included ascites and SBP using risk ratios, odds ratios, and number of outcome instances. **Results:** After propensity matching, 3005 patients per cohort were identified. The AATD cirrhosis group demonstrated significantly higher rates of ascites compared to non-AATD cirrhosis (39.77% vs 30.28%, Risk Ratio (RR) 1.31, $p < 0.0001$) as well as increased burden of ascites events (mean instances: 9.23 vs 7.35, $p = 0.0038$). Similarly, risk of SBP was greater in the AATD cohort (7.12% vs 4.29%, Risk Ratio (RR) 1.66, $p < 0.0001$). **Conclusion:** To our knowledge, this is the largest real-world study to date analyzing ascites and SBP outcomes in AATD-associated cirrhosis. This study showed AATD-associated cirrhosis is associated with increased risk of both ascites and SBP as well as greater total ascites events compared to cirrhosis of other etiologies, even after excluding concomitant alcohol-associated cirrhosis and propensity-matching for alcohol use. Potential mechanisms may include late recognition of AATD resulting in more advanced portal hypertension at diagnosis, gut microbiome alterations, and impaired immune protection due to defective neutrophil mobilization and phagocytosis. Furthermore, prospective studies are critical to further characterize these risks and determine whether enhanced hepatology surveillance and optimized preventive strategies are needed in this high-risk population.

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1647 | SAFETY OF SCREENING COLONOSCOPY IN PATIENTS WITH CIRRHOSIS: A REAL-WORLD ANALYSIS FROM THE TRINETX DATABASE

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Background: Patients with cirrhosis often require colonoscopy for various indications, however, the safety of screening colonoscopy in cirrhosis patients remains poorly defined. We aimed to evaluate post-screening colonoscopy complications in patients with compensated versus decompensated cirrhosis using a large, multicenter database. **Methods:** We queried the TriNetX database to identify adult cirrhotic patients (≥ 45 years) who underwent screening colonoscopy (identified by CPT© codes) between 2010 and 2025. Patients were stratified into compensated, decompensated cirrhosis, and controls. Individuals with high risk for colorectal cancer or prior total abdominal colectomy were excluded. Propensity score matching (1:1) was used to adjust for baseline demographics, comorbidities, and laboratory values. Post-colonoscopy outcomes were assessed within 30 days after colonoscopy using hazard ratios (HR) with 95% confidence intervals (CI). **Results:** We identified 18,862 patients with compensated cirrhosis, 51,945 with decompensated cirrhosis, and 1,257,361 control patients who underwent screening colonoscopy. After matching, when compared to non-cirrhotic controls (N = 48,171 per group), patients with decompensated cirrhosis had significantly higher odds of post-colonoscopy bleeding (1.5% vs. 1.0%; HR 1.52, 95% CI 1.34–1.74, p < 0.001), perforation (0.3% vs. 0.1%; HR 2.70, 95% CI 2.14–3.43, p < 0.001), and infection (3.1% vs. 1.5%; HR 2.02, 95% CI 1.85–2.21, p < 0.001). Decompensated cirrhosis was also associated with increased 30-day overall mortality (2.0% vs. 1.3%; HR 1.46, 95% CI 1.32–1.61, p < 0.001), which could be related to cirrhosis (Table 1).When compared to non-cirrhotic controls, patients with compensated cirrhosis (N = 18,861 per group) had non-significant differences in post-colonoscopy bleeding (HR 0.9, 95% CI 0.69–1.18, P = 0.5), perforation (HR 1.62, 95% CI 0.39-6.76, p < 0.8), and infection (HR 0.97, 95% CI 0.76-1.23, p = 0.07) (Table 2). **Conclusion:** In this large, real-world cohort, screening colonoscopy was safe in patients with compensated cirrhosis. In contrast, there was a significant increased risk of bleeding, perforation, and infection in decompensated cirrhosis patients compared to non-cirrhotic controls. These findings suggest that the severity of liver disease should be a critical consideration when assessing the risks and benefits of surveillance colonoscopy.

Table 1. Clinical outcomes of decompensated cirrhosis vs. non-cirrhotic controls

Outcomes	Decompensated N= 48,171	Control N= 48,171	HR (95% CI)	P value
Bleeding, n (%)	557/36,363 (1.5%)	374/38,374 (1.0%)	1.52 (1.34-1.74)	<0.001
Perforation, n (%)	132/47,230 (0.3%)	32/47,731 (0.1%)	2.70 (2.14-3.43)	<0.001
Infection, n (%)	1,502/48,171 (3.1%)	725/48,171 (1.5%)	2.02 (1.85-2.21)	<0.001
30-day Overall mortality, n (%)	959/48,006 (2.0%)	635/48,060 (1.3%)	1.46 (1.32-1.61)	<0.001

Table 2. Clinical outcomes of compensated cirrhosis vs. non-cirrhotic controls.

Outcomes	Compensated N= 18,861	Control N= 18,861	HR (95% CI)	P value
Bleeding, n (%)	104/15,651 (0.7%)	112/15,621 (0.7%)	0.90 (0.69-1.18)	0.5
Perforation, n (%)	≤10*/18,812 (0.1%)	≤10*/18,779 (0.1%)	1.62 (0.39-6.76)	0.5
Infection, n (%)	129/18,861 (0.7%)	130/18,861 (0.7%)	0.97 (0.76-1.23)	0.8
30-day Overall mortality, n (%)	91/18,809 (0.5%)	114/18,831 (0.6%)	0.77 (0.59-1.02)	0.07

*To protect patient privacy, numbers are rounded up to 10. This may impact results, particularly for small cohorts and infrequent outcomes.

Disclosures: Ahmed Ibrahim:Nothing to Disclose, Mohamed Eldesouki:Nothing to Disclose, Fatima Israr:Nothing to Disclose, Muhamad Oum:Nothing to Disclose, Sajid Jalil:Nothing to Disclose.

1648 | SBP-ASSOCIATED ACUTE KIDNEY INJURY DEFINES A HIGH-MORTALITY PHENOTYPE BEYOND MELD-NA IN PATIENTS WITH ASCITES

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Background: Spontaneous bacterial peritonitis (SPB) is a major complication of decompensated cirrhosis & ACLF; however, mortality may be driven more by associated renal dysfunction. We aimed to determine SBP-associated AKI predicts in-hospital mortality beyond MELD-Na in patients with ascites. **Methods:** We analyzed a database of patients with ascites. The cohort included patients with ascites and outcomes of death or discharge. Definite SBP was defined by ascitic PMN ≥ 250 cells/mm³. AKI followed standard criteria. Patients were categorized as SBP and SBP+AKI. The primary outcome was in-hospital mortality. Logistic regression assessed mortality predictors, including MELD-Na. Subgroup analysis was conducted in exclusive ACLF and DCLD groups. **Results:** Among 135 patients with ascites, 46 died and 89 were discharged, with 34.1% mortality. SBP occurred in 36 patients, AKI in 59. Mortality by SBP–AKI phenotypes: 11.9% in no SBP/no AKI, 17.6% in SBP, 60.0% in AKI, 63.2% in SBP+AKI (p < 0.001). SBP wasn't significantly linked to mortality (OR 1.57, 95% CI 0.71–3.44; p = 0.262). AKI was strongly linked to death (OR

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10.33, 95% CI 4.43–24.08; p < 0.001). MELD-Na was independently linked to death (OR 2.62, 95% CI 1.22–5.62; p = 0.014). Adding SBP–AKI phenotype to MELD-Na improved mortality discrimination from AUROC 0.77 to 0.83. ACLF patients had higher mortality than DCLD: 48.4% vs 18.4% (p = 0.001). In ACLF, mortality rose from 10.5% in no SBP/no AKI to 72.7% with AKI, 76.9% with SBP+AKI (p < 0.001). In DCLD, AKI also increased mortality. **Conclusion:** In ascites patients, mortality was mainly due to AKI rather than SBP alone. SBP-associated AKI indicated a high-risk phenotype and predicted in-hospital mortality beyond MELD-Na, especially in ACLF. Early recognition of renal dysfunction in SBP may enhance risk stratification with decompensated cirrhosis.

Table 1. MELD-Na adjusted mortality model and AUROC comparison

Variable / Model	Adjusted OR / AUROC	95% CI	p value / note
SBP only vs No SBP/No AKI	1.60	0.24–10.73	0.626
AKI only vs No SBP/No AKI	7.02	1.87–26.36	0.004
SBP + AKI vs No SBP/No AKI	15.04	2.60–86.85	0.002
MELD-Na per 10-point increase	2.62	1.22–5.62	0.014
MELD-Na alone	AUROC 0.771		Model discrimination
SBP-AKI phenotype alone	AUROC 0.772		Model discrimination
MELD-Na + SBP-AKI phenotype	AUROC 0.833		Combined model

Disclosures: Anmol Anmol:Nothing to Disclose, Nitesh Bassi:Nothing to Disclose, Sayan Malakar:Nothing to Disclose, Amandeep Singh:Nothing to Disclose, Jahnvi Dhar:Nothing to Disclose, Virendra Singh:Nothing to Disclose, Upasna Chauhan:Nothing to Disclose.

1649 | IMPACT OF RIGHT HEART FAILURE AND TRICUSPID REGURGITATION ON OUTCOMES IN HOSPITALIZED PATIENTS WITH DECOMPENSATED CIRRHOSIS

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Background: Cirrhosis is associated with substantial morbidity and mortality in the United States. Right heart failure (RHF) and tricuspid regurgitation (TR) may exacerbate hepatic congestion, but their impact on outcomes in decompensated cirrhosis remains unclear. We evaluated the association of RHF and TR with mortality, complications, and healthcare utilization among hospitalizations for decompensated cirrhosis. **Methods:** We performed a retrospective cross-sectional study using the National Inpatient Sample (2016–2020). Adult admissions with cirrhosis and ≥1 decompensating event (hepatic encephalopathy [HE], ascites, hepatorenal syndrome [HRS], spontaneous bacterial peritonitis [SBP], or gastrointestinal bleeding [GIB]) were included. Cardiac cirrhosis, portal vein thrombosis, Budd-Chiari syndrome, and liver transplantation were excluded. Exposures were RHF and TR. The primary outcome was in-hospital mortality. Secondary outcomes included length of stay (LOS), hospitalization cost, cirrhosis-related complications, mechanical ventilation, and discharge disposition. Multivariable analyses adjusted for demographics, obesity, sepsis, Elixhauser Comorbidity Index, and cirrhosis etiology. A sensitivity analysis additionally adjusted for decompensation type. Diagnoses were identified using ICD-10-CM codes. **Results:** Among 1,463,715 hospitalizations, 6,725 (0.5%) had RHF and 16,545 (1.1%) had TR. Both RHF and TR were associated with lower in-hospital mortality (aOR 0.82, 95% CI 0.67–0.99 and aOR 0.67, 95% CI 0.58–0.76, respectively). RHF was not associated with differences in LOS or hospitalization cost, whereas TR was associated with increased LOS (aIRR 1.14) and cost (aIRR 1.15). Both RHF and TR were associated with higher odds of ascites (aOR 2.15 and aOR 2.05) and lower odds of HE, GIB, HRS, SBP, and mechanical ventilation. Both were associated with increased routine discharge and decreased discharge to skilled nursing facilities. After adjustment for decompensation type, RHF was no longer associated with lower mortality (aOR 0.88, 95% CI 0.72–1.08), whereas TR remained associated with lower mortality. No difference was observed in mechanical ventilation in this adjustment model, and other outcomes were otherwise consistent. **Conclusion:** RHF and TR were associated with lower in-hospital mortality among patients hospitalized with decompensated cirrhosis. Both were associated with a higher proportion of ascites-related hospitalizations but lower odds of other decompensating events, including SBP and HRS. TR was additionally associated with increased healthcare utilization. After adjustment for decompensation type, the association between RHF and lower mortality was attenuated, suggesting that differences in mortality were at least partly explained by variation in decompensation event type. In contrast, the association between TR and lower mortality persisted after adjustment.

Table 1: Multivariable Analysis of Outcomes by RHF and TR Status

Outcome	Right Heart Failure (aOR/aIRR, 95% CI)	Tricuspid Regurgitation (aOR/aIRR, 95% CI)
Primary Outcome		
In-hospital mortality	0.82 (0.67-0.99)	0.67 (0.58-0.76)
In-hospital mortality, adjusted for decompensation type	0.88 (0.72-1.08)	0.73 (0.63-0.83)
Resource Utilization		
LOS	1.06 (0.99-1.12)	1.14 (1.10-1.18)
Hospitalization Cost	1.07 (0.99-1.14)	1.15 (1.11-1.20)
Cirrhosis Complications		
Ascites	2.15 (1.84-2.51)	2.05 (1.87-2.26)
Hepatic encephalopathy	0.64 (0.57-0.73)	0.60 (0.55-0.64)
Spontaneous bacterial peritonitis	0.78 (0.61-0.99)	0.61 (0.51-0.73)
Hepatorenal syndrome	0.80 (0.66-0.97)	0.75 (0.66-0.85)
Gastrointestinal bleed	0.55 (0.47-0.65)	0.66 (0.60-0.73)
Clinical Outcomes		
Mechanical ventilation	0.74 (0.60-0.90)	0.83 (0.73-0.94)
Mechanical ventilation, adjusted for decompensation type	0.82 (0.67-1.01)	0.92 (0.81-1.05)

aOR = adjusted odds ratio, aIRR = adjusted incidence rate ratio. All aOR/aIRR compared to patients without RHF/TR. All estimates were adjusted for age, sex, race, obesity, sepsis, Elixhauser Comorbidity Index, and cirrhosis etiologies. Outcomes labeled "adjusted for decompensation type" were additionally adjusted for hepatic encephalopathy, ascites, hepatorenal syndrome, spontaneous bacterial peritonitis, and gastrointestinal bleeding.

Disclosures: Anderson Huang:Nothing to Disclose, Raffi Karagozian:Nothing to Disclose, Gregory Fan: Nothing to Disclose.

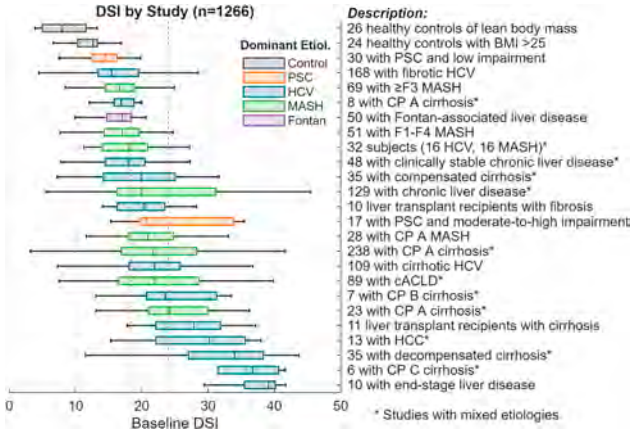
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1650 | THE ORAL CHOLATE CHALLENGE TEST (HEPQUANT DUO®) STRATIFIES LIVER DISEASE SEVERITY IN ADVANCED CHRONIC LIVER DISEASE

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Background: Identifying patients with compensated advanced chronic liver disease who are at increased risk for decompensation remains a central clinical goal. The Disease Severity Index (DSI), derived from the oral cholate challenge test (OCCT), is a quantitative measure of global liver disease severity ranging from 0 (healthy) to 50 (severe dysfunction). This analysis evaluated whether DSI differentiates liver disease severity subgroups according to two clinically relevant thresholds (DSI 18.3 and 24). **Methods:** Data from 17 published studies and real-world cohorts were pooled, representing a total of 1266 participants with baseline OCCT results. The OCCT involved oral administration of deuterium-labelled (d4-) cholate, blood sampling at 20 and 60 minutes, and quantification of the d4-cholate by LC-MS/MS. Test parameters, including DSI, were calculated for each participant. The studies were further subdivided into cohorts based on disease severity (i.e., Child-Pugh class, compensated versus decompensated disease, F1-F3 versus F4, and PSC progressors). Distributions of DSI within each subgroup were visualized by boxplots sorted by median DSI value. **Results:** The cohort had mean age 55 ± 13 years, BMI 31 ± 7 kg/m^2, and 56% were male. Liver disease etiologies included chronic hepatitis C (30%), MASH (26%), alcohol-associated liver disease (6%), primary sclerosing cholangitis (5%), Fontan-associated liver disease (4%), healthy controls (4%), autoimmune hepatitis (3%), cryptogenic cirrhosis (3%), primary biliary cholangitis (1%), and other etiologies (13%). The mean DSI overall was 21 ± 8 and ranged from 3 to 45 (Figure). Median DSI values were relatively low in healthy controls: 8 (range 4–13) in lean controls and 13 (7–17) in overweight controls. Median DSI values were significantly higher for subgroups with greater disease severity: 34 (15–42) for decompensated patients, 37 (15–42) for patients with Child-Pugh C, and 39 (29–42) for patients with end-stage liver disease. In treatment trials, the higher the baseline DSI, the longer it took for effective therapy to demonstrate a decrease in DSI and functional improvement (O'Leary et al. 2014). **Conclusion:** These results support use of DSI cutpoints of 18.3, indicating elevated risk for large esophageal varices and transition to clinically significant portal hypertension, and DSI 24, corresponding to transition from clinical compensation to clinical decompensation. OCCT-derived DSI may provide a quantitative, noninvasive measure of global liver disease severity for use in both clinical practice and clinical trials.



Disclosures: Edward Mena:Nothing to Disclose, Michael McRae:HepQuant, LLC: Independent Contractor, Joanne Imperial:Nothing to Disclose, Gregory Everson:Nothing to Disclose.

1651 | NATIONAL TRENDS AND DEMOGRAPHIC DISPARITIES IN CARVEDILOL USE FOR PRIMARY PREVENTION OF DECOMPENSATION IN COMPENSATED CIRRHOSIS

Meghana Kakarla[1] Harsha Bopanna[2] Krystal Cruz[3] Mark Shokralla[3] Aaron Jabir[3] Pradeep Yarra[3] Christina Awad[4], [1]infirmary health, [2]Nassau University Medical Center, [3]University of Texas San Antonio, [4]UT health San Antonio

Background: Carvedilol is strongly recommended per Baveno VII guidelines forpreventing first decompensation in compensated cirrhosis with clinically significantportal hypertension (CSPH), defined by hepatic venous pressure gradient ≥10 mmHg orliver stiffness ≥25 kPa, significantly lowering the risk of new ascites and prolongingdecompensation-free survival. Despite these clear benefits, real-world prescribingpatterns and potential demographic disparities in uptake following guideline adoptionremain poorly understood. This study examined national carvedilol prescribing trendsbefore and after Baveno VII dissemination, focusing on demographic differences. **Methods:** Using the TriNetX US Collaborative Network, we identified adults with compensated cirrhosis and portal hypertension across 70 healthcare organizations using ICD 10 codes . Carvedilol exposure was identified using RxNorm codes. Prescribing patterns were evaluated during pre-Baveno VII (2020–2022) and post-Baveno VII (2023–2025) periods using incidence proportion, prevalence, and incidence rate (per 10,000 person-days). Analyses were stratified by age, sex, race, and ethnicity. **Results:** Carvedilol use increased markedly from the pre- to post-Baveno VII period. Overall

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prevalence more than doubled (12.5% to 25.9%) and incidence rate rose over3-fold (0.74 to 2.31 per 10,000 person-days). Substantial demographic disparities wereevident in both periods:Sex: Men had consistently higher use (post-period prevalence: 26.9% vs. women24.4%; pre-period: 13.2% vs. 11.4%).Age: Adults aged 20–29 showed the highest post-period incidence proportions (19.7–20.1%), representing the largest relative increase from pre-period baselines(3.7–5.7%).Race: Black adults had the highest prevalence in both periods (19.5% pre, 31.2% post)which could be misleading given the fact that carvedilol is also prescribed for other co-morbidities common in black adults. White adults had the lowest (11.9% pre, 24.8%post). Asian (12.4% to 30.2%) and Pacific Islander (14.4% to 30.9%) adults showed thelargest relative increases.Ethnicity: Hispanic/Latino adults showed the greatest relative increase in incidenceproportion (5.6% to 19.6%) despite the lowest pre-period prevalence (10.6%) which isnotable. **Conclusion:** Carvedilol prescribing for compensated cirrhosis with CSPH more thandoubled following Baveno VII, confirming broad guideline adoption. However, persistentdisparities by sex, age, race, and ethnicity were present both before and after guidelinedissemination, suggesting longstanding differences in care delivery rather thandifferential guideline response. These findings underscore the need for targetedimplementation strategies to ensure equitable access to carvedilol therapy.

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1652 | AMIKACIN USE AND RISK OF NEPHROTOXICITY IN PATIENTS WITH LIVER CIRRHOSIS HOSPITALIZED FOR SEPSIS

Jaime Poniachik[1] Alonso Saez[1] Carlos Padilla[1] Juan Medel[1] Daniela Simian[1] Gabriel Méndez-Valdés[2] María Gómez[2] Álvaro Urzúa[1] Juan Roblero[1], [1]Hospital Clínico Universidad de Chile, [2]Universidad de Chile

Background: Aminoglycosides are broad-spectrum antibiotics mainly active against gram-negative bacteria. Nephrotoxicity has been reported in 10–20% of cases and may be more frequent in patients with liver cirrhosis. Amikacin is commonly used in sepsis; however, data regarding its nephrotoxic risk in cirrhotic patients remain limited. The aim was to evaluate the association between amikacin use and acute kidney injury (AKI) in patients with liver cirrhosis and sepsis. **Methods:** We conducted a retrospective, observational, analytical study including adult patients with cirrhosis hospitalized for sepsis between 2017 and 2023 who received antibiotic therapy. AKI was defined as an increase in serum creatinine $\geq$0.3 mg/dL within the first 7 days of hospitalization. Clinical variables, AKI, and mortality were compared between patients who received amikacin and those who did not. Multivariate analysis was adjusted for age, sex, Child-Pugh class, and MELD-Na score. Statistical analysis was performed using Stata 15.0, with a significance level of 0.05. **Results:** A total of 227 patients were included, with a median age of 65 years (IQR 54–70); 99 (44%) were women, and 69 (30%) received amikacin. Patients receiving amikacin had a higher frequency of AKI compared with those who did not receive amikacin (35% vs 21%; OR 2.02, 95% CI 1.07–3.78; p = 0.028). In subgroup analyses, AKI was more frequent among patients receiving amikacin with baseline serum creatinine $\geq$2.0 mg/dL, Child-Pugh C cirrhosis, and MELD-Na $\geq$20. In multivariate analysis, MELD-Na score remained independently associated with AKI (OR 1.08, 95% CI 1.02–1.14; p = 0.002), while amikacin use showed a non-significant trend toward increased AKI risk (OR 1.8, 95% CI 0.9–3.5; p = 0.081). **Conclusion:** AKI was more frequent among cirrhotic patients receiving amikacin for sepsis, particularly in those with advanced liver disease. However, after adjustment, liver disease severity, especially MELD-Na score, appeared to be the main factor independently associated with AKI.

Table. Evaluation of the development of renal function deterioration in different groups of patients depending on the use or not of Amikacin

		AKI	No AKI	Valor p
According to baseline serum creatinine				
Creatinine < 1.5 (N = 166)	Amikacin	13 (36)	35 (27)	0.282
	Without Amikacin	23 (64)	95 (73)	
Creatinine 1.5 – 1.99 (N = 33)	Amikacin	4 (33)	4 (19)	0.357
	Without Amikacin	8 (67)	17 (81)	
Creatinine ≥ 2.0 (N =28)	Amikacin	7 (78)	6 (32)	**0.029**
	Without Amikacin	2 (22)	13 (68)	
Initial suspicion of infection by Gram (-) bacteria according to infectious focus				
Suspected Gram (-) infection (N = 171)	Amikacin	21 (48)	41 (32)	0.066
	Without Amikacin	23 (52)	86 (68)	
Without suspicion of Gram (-) infection (N = 57)	Amikacin	4 (28)	4 (9)	0.071
	Without Amikacin	10 (71)	39 (91)	
According to septic shock				
With septic shock (N = 74)	Amikacin	16 (57)	22 (48)	0.437
	Without Amikacin	12 (43)	24 (52)	
Without septic shock (N = 154)	Amikacin	9 (30)	23 (19)	0.165
	Without Amikacin	21 (70)	101 (81)	
According to Child-Pugh Score				
Child-Pugh A – B (N = 104)	Amikacin	10 (34)	18 (24)	0.280
	Without Amikacin	19 (66)	57 (76)	
Child-Pugh C (N = 123)	Amikacin	14 (50)	27 (28)	**0.033**
	Without Amikacin	14 (50)	68 (72)	
According to MELD-Na Score				
MELD-Na < 20 (N = 77)	Amikacin	3 (25)	14 (21)	0.524
	Without Amikacin	9 (75)	51 (78)	
MELD-Na ≥ 20 (N = 150)	Amikacin	21 (47)	31 (30)	**0.034**
	Without Amikacin	24 (53)	74 (70)	

Disclosures: Jaime Poniachik:Nothing to Disclose, Alonso Saez:Nothing to Disclose, Carlos Padilla:Nothing to Disclose, Juan Medel:Nothing to Disclose,

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Daniela Simian:Nothing to Disclose, Gabriel Méndez-Valdés:Nothing to Disclose, María Gómez:Nothing to Disclose, Álvaro Urzúa:Nothing to Disclose, Juan Roblero:Nothing to Disclose.

1653 | IMPACT OF SPONTANEOUS BACTERIAL PERITONITIS ON MORTALITY AND HEALTHCARE UTILIZATION IN HOSPITALIZATIONS FOR HEPATORENAL SYNDROME: A NATIONAL INPATIENT SAMPLE ANALYSIS (2018–2022)

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Background: Spontaneous bacterial peritonitis (SBP) is a common and serious infection in decompensated cirrhosis and a key precipitant of circulatory dysfunction and hepatorenal syndrome (HRS). The overlap of SBP and HRS may identify a particularly high-risk population, yet contemporary nationwide data on its burden and clinical impact remain limited. We evaluated the association of concurrent SBP with in-hospital mortality and healthcare utilization among US HRS hospitalizations. **Methods:** Using the National Inpatient Sample (2018–2022), HRS hospitalizations were identified and stratified by concurrent SBP status. Survey-weighted logistic regression estimated crude and adjusted odds ratios for in-hospital mortality, adjusting for demographics, comorbidities, and hospital characteristics; survey-weighted comparisons assessed length of stay (LOS) and total charges. **Results:** The weighted HRS subpopulation comprised approximately 262,950 hospitalizations, of which SBP was present in 12.1% (n ≍ 31,695 unweighted).In-hospital mortality was markedly higher among HRS patients with SBP than without (33.0% vs. 25.1%). SBP was associated with higher odds of in-hospital death in both crude (OR 1.47, 95% CI 1.39–1.56, $p < 0.001$) and adjusted (aOR 1.45, 95% CI 1.37–1.54, $p < 0.001$) models.SBP was associated with longer LOS (mean 12.6 vs. 11.1 days; SD 14.0 vs. 13.1; $p < 0.001$) and higher total charges (mean $207,021 vs. $177,273; SD $405,319 vs. $344,272; $p < 0.001$). In-hospital complications were more frequent with SBP, including shock (41.5% vs. 26.7%), ICU admission (29.4% vs. 23.0%), mechanical ventilation (22.1% vs. 18.7%), and vasopressor use (14.1% vs. 9.5%).With respect to comorbidities, HRS patients with SBP had higher rates of malnutrition (26.1% vs. 20.1%), while those without SBP more frequently had DM2 (31.2% vs. 24.6%), hyperlipidemia (20.8% vs. 14.5%), CAD (12.7% vs. 8.0%), and CKD stage 3 (32.7% vs. 27.1%). **Conclusion:** Among US hospitalizations for HR S, concurrent SBP was associated with substantially higher in-hospital mortality and greater healthcare utilization, including markedly higher rates of shock, ICU admission, and organ support. These associations persisted after adjustment, identifying SBP as a marker of severe illness in HRS. The concentration of metabolic comorbidities in the non-SBP group may reflect differences in patient phenotype and coding patterns and warrants cautious interpretation. These findings underscore the prognostic importance of identifying and aggressively managing SBP in patients hospitalized with HRS.

Disclosures: Nishanth Eluri:Nothing to Disclose, Brett Cohen:Nothing to Disclose, Kyle Tio:Nothing to Disclose, Barbara Halicki:Nothing to Disclose, Renata Lerer:Nothing to Disclose.

1654 | ATHEROSCLEROTIC CARDIOVASCULAR DISEASE AS A CONTRIBUTOR TO MORTALITY IN OLDER ADULTS WITH CIRRHOSIS: A POPULATION-BASED STUDY

Bland Ahmed[1] Palwasha Farooqi[1] Mahrukh Mahrukh[2] Sahar Zafar[2] Hajra Umar Jaspal[3] Shehryar Rasheed Sohail[4] Arishman Yasin Chaudhary[2] Zainab Attiq[2] Ehsanullah Alokozay[5], [1]Desert Regional Medical Center, Palm Springs, Ca, USA, [2]University Medical and Dental College, University of Faisalabad, Faisalabad, Pakistan, [3]University College of Medicine and Dentistry (UCMD), The University of Lahore, Lahore, Pakistan, [4]Jinnah Sindh Medical University, [5]Faculty of Medicine, Kandahar University, Kandahar, Afghanistan

Background: Cirrhosis is an increasing cause of mortality among older adults in the United States. In addition to hepatic complications, atherosclerotic cardiovascular disease (ASCVD) is an important contributor to adverse outcomes in this population. However, national trends and demographic disparities in ASCVD-related mortality among elderly patients with cirrhosis remain poorly defined. Characterizing these trends is essential for optimizing risk assessment and cardiovascular preventive care in this vulnerable population. **Methods:** Death certificates for adults aged ≥ 65 years with cirrhosis (ICD-10: K74.0-K74.6) as the underlying cause of death and ASCVD (ICD-10: I20–I25, I63, I70,171.1-171.9,172.1-I74, I77.8-177.9) as contributing cause were extracted from the CDC WONDER database from 1999–2025. Age-adjusted mortality rates

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(AAMRs) per 100,000 were calculated using the 2000 U.S. standard population. Joinpoint regression identified annual percent change (APC) and average annual percent change (AAPC). Mortality trends were stratified by age group, sex, race, census region, and urbanization status. **Results:** A total of 17,290 deaths were identified over 27 years. The overall AAMR declined from 1.37 to 1.21 per 100,000 from 1999-2014 (APC: −1.29; 95% CI: −2.32 to −0.55), then significantly rose to 1.82 per 100,000 by 2025 (APC: +3.58; 95% CI: 2.67–4.93), with an overall AAPC of +0.74 (95% CI: 0.41–1.09). Men consistently exhibited higher AAMRs than women, reaching 2.49 per 100,000 in 2025 compared with 1.30 per 100,000 among women. However, women showed a sharper recent rise from 2018–2025 (APC: +6.64; 95% CI: 3.54–15.01) compared with men from 2011–2025 (APC: +2.75%; 95% CI: 2.06–3.82). By age group, the ≥85-year cohort demonstrated the steepest rise from 2015 to 2025 (APC: +7.11), followed by the 75–84-year group (APC: +4.63), while the 65–74-year group showed a non-significant overall trend (AAPC: +0.13). The South showed the highest regional burden (AAPC: +1.81), while the Northeast exhibited a steady overall decline (AAPC: −2.10). Rural areas showed a notable rise from 2009 to 2020 (APC: +2.79), while urban areas had no significant overall change (AAPC: −0.17). **Conclusion:** ASCVD mortality in older adults with cirrhosis followed a biphasic pattern, with a post-2014 resurgence that was most pronounced in the ≥85-year cohort, men, Southern states, and rural communities, highlighting that ASCVD represents a crucial contributor to death in this population.

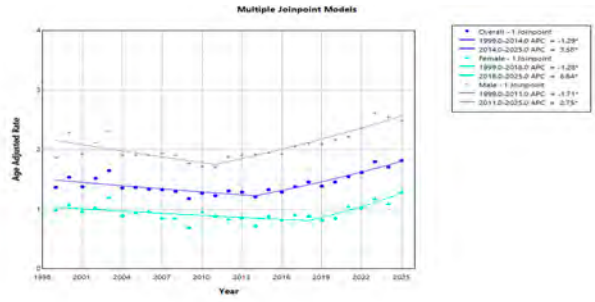


Figure 1: Age Adjusted Mortality Rates due to Atherosclerotic Cardiovascular Disease in older adults with Cirrhosis in the United States, Overall and Gender from 1999-2025

Disclosures: BLAND AHMED:Nothing to Disclose, Palwasha Farooqi:Nothing to Disclose, Mahrukh Mahrukh:Nothing to Disclose, Sahar Zafar:Nothing to Disclose, Nothing to Disclose, Hajra Umar Jaspal: Nothing to Disclose, Shehryar Rasheed Sohail:Nothing to Disclose, Arishman Yasin Chaudhary:Nothing to Disclose, Zainab Attiq:Nothing to Disclose, Ehsanullah Alokozay:Nothing to Disclose.

1655 | USING NON-INVASIVE LIVER FIBROSIS INDICES TO PREDICT VARICEAL BLEEDING IN CIRRHOTIC PATIENTS PRESENTING WITH UPPER GASTROINTESTINAL BLEEDING: A RETROSPECTIVE COHORT STUDY

Yi Nong Song[1] Eddie He[1] Marco Puglia[1], [1]McMaster University

Background: Liver cirrhosis leads to increased portal pressure, predisposing patients to the development of gastroesophageal varices—a complication present in 50–60% of compensated and up to 80% of decompensated cirrhotics. Variceal bleeding carries a 6-week mortality rate of 15–20%, making it one of the most life-threatening complications of cirrhosis. In contrast, non-variceal upper gastrointestinal (GI) bleeding carries a lower mortality rate of 1.1–11%. Differentiating variceal from non-variceal bleeding based solely on clinical presentation remains challenging. Empirically managing all upper GI bleeds as variceal events can lead to unnecessary healthcare expenditures and overtreatment with medications such as vasoactive agents and antibiotics. Non-invasive fibrosis indices have been validated for estimating liver fibrosis and portal hypertension, but their ability to predict variceal bleeding has not been evaluated. Our aim is to assess whether non-invasive liver fibrosis indices can be used to stratify the risk of variceal versus non-variceal upper GI bleeding in patients with cirrhosis. **Methods:** This retrospective cohort study included adult patients admitted to Hamilton Health Sciences between June 6, 2022 and October 23, 2024with a history of cirrhosis and a presenting diagnosis of upper GI or variceal bleeding. Patient data were extracted from electronic medical records and entered into a REDCap database. Non-invasive fibrosis indices (APRI, NFS, BARD, FNI, and FIB-4) were calculated where data were available. Prognostic scores (MELD 3.0 and Child–Pugh) were also calculated for comparison. Statistical analyses included one-tailed t-tests, sensitivity, specificity, area under the receiver operating characteristic curve (AUC) were calculated. **Results:** Table 1 includes diagnostic performance of scores for predicting variceal bleeds. The test with best AUC (FNI) was then compared to other tests with DeLong's test. **Conclusion:** APRI, NFS, and FIB-4 demonstrated modest discriminatory ability (AUC 0.48–0.61). The BARD score showed poor sensitivity but high specificity. APRI and FIB-4 both had high sensitivity, but poor specificity. FNI achieved the highest accuracy (AUC 0.75), though optimal threshold determination was limited by small sample size and resulted in high sensitivity but poor specificity. Differences in AUC between FNI and most non-invasive fibrosis and prognostic scores were not statistically

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significant, except for BARD, where FNI showed superior discrimination (AUC 0.75 vs 0.45 p = 0.04). Traditional prognostic models including MELD 3.0 and Child-Pugh performed poorly as diagnostic tools, likely reflecting their role inassessing liver disease severity rather than bleeding risk. Larger, prospective studies are warranted to validate these findings and explore integration with additional non-invasive modalities (e.g., transient elastography) to enhance diagnostic accuracy.

Index	n	Optimal Cut-off (Youden's index)	Sensitivity	Specificity	AUC (95% CI)
APRI	60	0.25	100%	3.1%	0.57 (0.43-0.72)
NFS	60	1.68	67.9%	40.6%	0.48 (0.33-0.63)
BARD	60	≥3	17.9%	96.9%	0.61 (0.48-0.75)
FNI	25	0.20	93.3%	0%	0.75 (0.06-0.44)
FIB-4	59	1.06	96.4%	9.7%	0.59 (0.44-0.74)
MELD 3.0	60	24.5	28.6%	75%	0.55 (0.40-0.70)
Child-Pugh	60	12.5	10.6%	90.6%	0.54 (0.39-0.69)

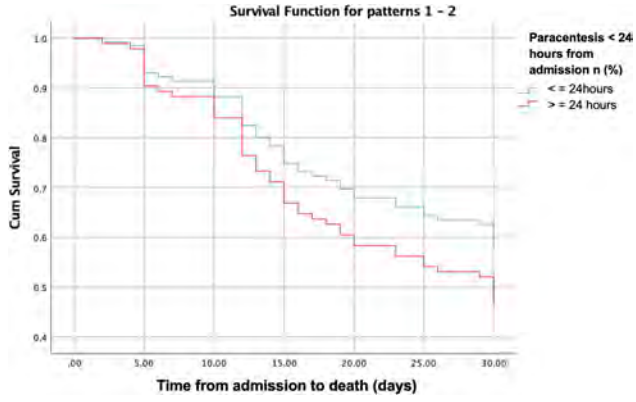
Table 1. Diagnostic performance of non-invasive fibrosis and prognostic scores for predicting variceal bleeds. ROC analysis was performed for all patients.

Disclosures: Yi Nong Song:Nothing to Disclose, Eddie He:Nothing to Disclose, Marco Puglia:Nothing to Disclose.

1656 | EARLY PARACENTESIS AND IN-HOSPITAL MORTALITY IN PATIENTS WITH DECOMPENSATED CIRRHOSIS AND SUSPECTED SPONTANEOUS BACTERIAL PERITONITIS AT A SINGLE CENTER IN MEXICO CITY

Alejandra Díaz Jarquín[1] Froylan Martinez Sanchez[2] Jacqueline Cordova Gallardo[3] Samantha Armendáriz Pineda[1] Scarlet Espinosa Castrejón[1], [1]Hospital General Dr. Manuel Gea Gonzalez, [2]Centro de Investigación y Gastroenterología S.C, [3]Hospital General Dr Manuel Gea González

Background: Introduction: Decompensated cirrhosis is a frequent cause of hospital admission and is associated with high mortality, especially when spontaneous bacterial peritonitis (SBP) is suspected. In this scenario, diagnostic paracentesis is useful for confirming the diagnosis and initiating timely treatment. However, in daily clinical practice, it is not always performed immediately after the patient's admission. Although studies have shown that delaying paracentesis is associated with worse outcomes, most of this information comes from populations outside of Latin America and from healthcare systems with different characteristics. **Objectives:** To evaluate the association between early paracentesis (≤ 24 hours from hospital admission) and in-hospital mortality in patients with decompensated cirrhosis and suspected SBP in Mexican population. **Methods: Methods::** This was a retrospective observational study including hospitalized adults with decompensated cirrhosis and SBP at a referral center in Mexico. Patients were classified according to the timing of paracentesis: early (≤ 24 hours) or delayed (> 24 hours). Clinical, laboratory, and survival outcomes were compared between groups. Cox regression analysis was performed to evaluate the association between early paracentesis and in-hospital mortality. **Results: Results::** A total of 102 patients were included. The mean age was 54.7 ± 13.6 years, and 63.7% were men. Early paracentesis was performed in 33.3% of patients, whereas 66.7% underwent delayed paracentesis. In-hospital mortality was significantly lower in the early paracentesis group compared with the delayed group (38.2% vs 61.8%, p = 0.021). Six-month survival was also higher in patients undergoing early paracentesis (58.8% vs 38.8%, p = 0.045). Patients with delayed paracentesis had significantly higher bilirubin levels (14.02 vs 4.52 mg/dL, p = 0.007), AST (104.5 vs 59.5 U/L, p = 0.001), and ALT levels (52.5 vs 31.5 U/L, p = 0.004). On Cox regression analysis, early paracentesis was independently associated with lower in-hospital mortality (HR 0.383, 95% CI 0.164–0.894, p = 0.026). **Conclusion: Conclusion:s:** Early paracentesis within the first 24 hours of admission was independently associated with lower in-hospital mortality in patients with decompensated cirrhosis and suspected SBP. Timely diagnostic paracentesis may represent an important quality-of-care measure in hospitalized patients with cirrhosis



Disclosures: Alejandra Díaz Jarquín:Nothing to Disclose, Froylan Martinez Sanchez:Nothing to Disclose, Jacqueline Cordova Gallardo:Nothing to Disclose, Samantha Armendáriz Pineda:Nothing to Disclose, Scarlet Espinosa Castrejón:Nothing to Disclose.

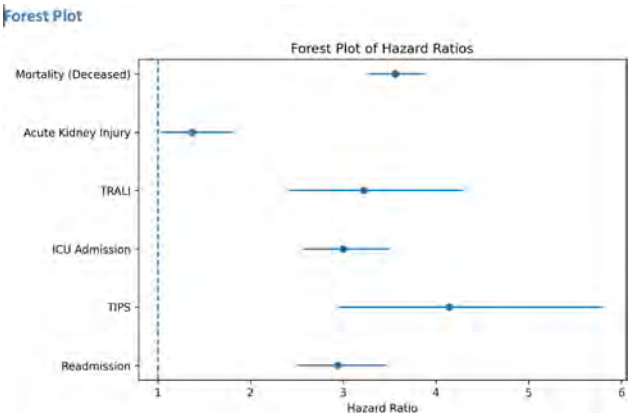
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1657 | HEMOSTATIC BLOOD PRODUCT USE IN CIRRHOTIC PATIENTS WITH ACUTE GASTROINTESTINAL HEMORRHAGE: A PROPENSITY-MATCHED ANALYSIS OF REAL-WORLD OUTCOMES

Bolaji Ayinde[1] Abidemi Akinrinmade[2] Bright Nwatamole[3] Ihunanya Kanu[4] Kia Saeian[5], [1]Northeast Georgia Medical Center, [2]SUNY Upstate University, [3]Zucker school of medicine at Hofstra, [4]Baptist Memorial Hospital- Golden Triangle, [5]Medical college of Wiscosin

Background: Current AASLD guidance recommends against liberal hemostatic blood product (HBP) transfusion in acute variceal hemorrhage, citing potential harm including worsening portal pressure and transfusion-related complications. However, large-scale real-world data examining outcomes associated with HBP use across diverse healthcare settings remain limited. This study examined the association between HBP administration and clinical outcomes in cirrhotic patients with acute gastrointestinal (GI) hemorrhage using a multi-institutional real-world data network. **Methods:** Using the TriNetX US Collaborative Network (66 healthcare organizations, 216,202 cirrhotic patients with GI hemorrhage), adult patients with cirrhosis (ICD-10: K74.x, K70.3x) and acute GI hemorrhage (K92.0, K92.1, K92.2, I85.01, I85.11) were identified. Patients receiving fresh frozen plasma, platelets, and/or cryoprecipitate within 3 days of presentation (HBP cohort) were compared to non-recipients. Propensity score matching (1:1) on demographics, comorbidities, medications (octreotide, terlipressin), and MELD component laboratory values (creatinine, bilirubin, INR, sodium), as well as platelets and fibrinogen, yielded 4,806 patients per arm. Risk ratios (RR) and hazard ratios (HR) were estimated over a 45-day follow-up window. **Results:** HBP recipients had significantly higher 45-day mortality (43.2% vs. 15.1%; RR 2.85, 95% CI 2.64–3.08; HR 3.56, 95% CI 3.27–3.88; p0.001). HBP use was also associated with increased ICU admission (25.8% vs. 10.4%; HR 3.00, p0.001), hospital readmission (30.7% vs. 12.3%; HR 2.94, p = 0.008), TRALI/ARDS (4.1% vs. 1.4%; HR 3.22, p = 0.024), and TIPS placement (3.5% vs. 0.9%; RR 3.77, p0.001). Acute kidney injury showed a non-significant trend on risk analysis (RR 1.22, p = 0.159) with a modest signal on survival analysis (HR 1.37, p = 0.029) and evidence of non-proportional hazards. **Conclusion:** In this large, multi-institutional propensity-matched cohort, HBP use was consistently associated with worse short-term outcomes across multiple domains. While residual confounding by indication likely contributes, and the observed effect sizes may overestimate any true causal effect, the magnitude and consistency of these associations reinforce current guideline recommendations against liberal hemostatic transfusion in cirrhotic GI hemorrhage and support the need for prospective, severity-adjusted trials incorporating viscoelastic testing-guided protocols.



Disclosures: Bolaji Ayinde:Nothing to Disclose, Abidemi Akinrinmade:Nothing to Disclose, Bright Nwatamole:Nothing to Disclose, Ihunanya Kanu:Nothing to Disclose, Kia Saeian:Abbvie: Grant/Research Support.

1658 | PARACENTESIS TIMING AND MORTALITY RATES IN PATIENTS WITH SPONTANEOUS BACTERIAL PERITONITIS

Ramanpreet Bajwa[1] Lovepreet Singh[1] Deepa Kumarjiguda[1] Aleena Moin[1] Lifang Zhang[1] Alberto Unzueta[1], [1]Geisinger Medical Center

Background: Patients with cirrhosis who are admitted to the hospital with decompensating events should undergo diagnostic paracentesis to rule out spontaneous bacterial peritonitis (SBP). Timing of paracentesis is crucial in the management of SBP and previous studies have identified that early paracentesis results in better patient outcomes. This study evaluated patients with decompensated cirrhosis and SBP within our institution in order to examine the relationship between paracentesis timing, mortality and readmission rates. **Methods:** We conducted a retrospective chart review of patients with decompensated cirrhosis admitted to our institution from 2016-2023. Inclusion criteria included confirmed spontaneous bacterial peritonitis. We examined timing of paracentesis, mortality at less than 30 days and > 90 days. Secondary outcomes included assessing hospital readmissions. Variables analyzed included administration of empiric antibiotics, MELD 3.0 and Child Pugh scores. All statistical analyses were conducted using SAS Enterprise Guide version 8.3. Statistical significance was assessed

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at an alpha level of 0.05. **Results:** A total of 101 patients were included in the analysis. Patients had a mean age of 63.8 years, 54.5% were male, and 99% of the cohort identified as White. Mortality rates were 100% amongst the cohort during the evaluated period. 24 patients underwent paracentesis $\leq$24 hours and 77 patients underwent paracentesis >24 hours (p = 0.9713). In the group who underwent paracentesis $\leq$24 hours, the mortality at 0-30 days and >90 days was 25% and 50% (p = 0.9713) respectively. In the group who underwent paracentesis >24 hours, similar trends were seen with mortality at 0-30 days and >90 days, 27.3% and 44.2 % (p = 0.9479) respectively. Mean MELD 3.0 score in the group with paracentesis $\leq$24 hours was 21.5 (SD 7.37) and 22.7 (SD 7.83) in >24 hours group (p = 0.6085). Empiric antibiotics were given in 47.8% of the cohort. Child Pugh Class B comprised the most patients in both groups. Readmission rates in paracentesis $\leq$24 hours vs >24 hours at 30 days were 33.3% and 28.6% respectively (p = 0.9679). There was no statistically significant association identified between the timing of paracentesis ($\leq$24 hours vs. >24 hours after paracentesis) and MELD 3.0 score, empiric antibiotic use, or Child-Pugh score. **Conclusion:** Patients with SBP have a high mortality rate despite undergoing early paracentesis. Liver transplant evaluation and/or palliative care management should be considered after SBP in most patients.

Disclosures: Ramanpreet Bajwa:Nothing to Disclose, Lovepreet Singh:Nothing to Disclose, Deepa Kumarjiguda:Nothing to Disclose, Aleena Moin:Nothing to Disclose, Lifang Zhang:Nothing to Disclose, Alberto Unzueta:Nothing to Disclose.

1659 | ACUTE-ON-CHRONIC LIVER FAILURE (ACLF) AND SHOCK AT PRESENTATION PREDICT 6-WEEK MORTALITY IN ACUTE VARICEAL BLEEDING

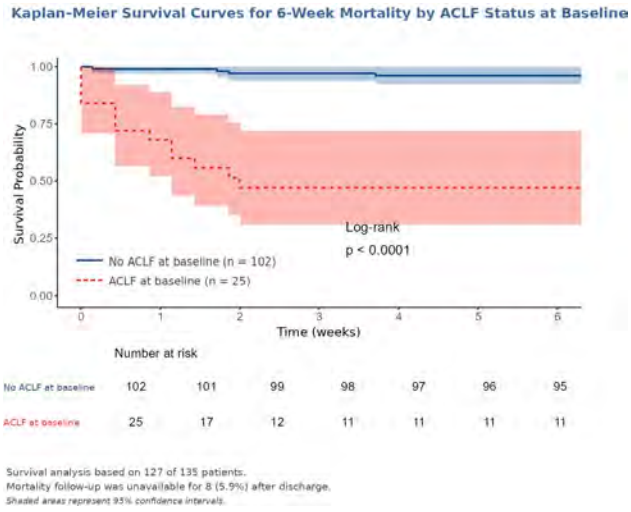
Aashi Aggarwal[1] Ishaan Gupta[1] Kriti Kriti[1] Trivendar Jangir[1] Tejasvi R[1] Mahendra Rajput[1] Suraj Bhagat[1] Rohit Mehtani[2], [1]Amrita Institute of Medical Sciences and Research Centre, Faridabad, [2]BLK-Max Super Speciality Hospital, Delhi

Background: Portal hypertension–related upper gastrointestinal (GI) bleeding remains a major cause of morbidity and mortality in cirrhosis. Predictors of short-term mortality following acute variceal bleeding (AVB), particularly in Indian cohorts, remain limited. **Methods:** Retrospective analysis of a prospectively maintained database of patients with cirrhosis and portal hypertension–related upper GI bleeding between September 2022 and April 2026 was done. AVB was managed according to international guidelines, including intravenous antibiotics, vasoconstrictors and early upper GI endoscopy. Baseline demographic, clinical, laboratory, and endoscopic variables were analysed. Mortality, rebleeding and further decompensations were assessed at 6-weeks. Univariate and multivariable logistic regression analyses were performed to identify predictors of 6-week mortality in AVB. Kaplan–Meier survival analysis with log-rank testing was performed for 6-week mortality. **Results:** A total of 135 patients were included (81.5% male; age 52.8 ± 13.9 years). Most common cause of cirrhosis was alcohol-related liver disease (66; 48.8%) followed by metabolic-dysfunction associated steatohepatitis (43; 31.9%). Acute variceal bleeding was seen in 62 (45.9%) patients (Esophageal varices–40[29.6%], Gastric varices–10[7.4%], both–7[5.2%] and post EVL ulcer bleed-5[3.7%]). Nineteen patients (14.1%) had bleeding from severe portal hypertensive gastropathy (PHG) and 5(3.7%) from gastric vascular ectasia (GVE). TIPSS was done in 7 patients (5.2%) – 1 rescue, 6 pre-emptive. Six-week mortality was 13.4% (n = 17) while 8 (5.9%) underwent liver transplant. Kaplan-Meier analyses demonstrated significantly reduced survival in patients with ACLF (HR 19.41, 95% CI 6.29–59.92; log-rank p < 0.0001; Figure 1). Among patients with AVB (n = 62), 6-week mortality and rebleeding were 11.3%(n = 7) and 14.5% (n = 9) respectively. Further decompensation occurred in 23 patients (37.1%). Patients who rebled at 6-weeks had higher MELD score when compared to those who did not rebleed (24 [17-31] vs 15.5[7.5-23.5]; p = 0.034). Patients who died within 6-weeks had more severe liver disease (CTP – 12.5 vs 8, p = 0.021; MELD – 39 vs 17, p = 0.006), shock (83% vs 19.1%; p = 0.004), grade 3/4 HE (50.0% vs 10.6%; p = 0.006), AKI (66.6% vs 6.3%; p = 0.002) and ACLF (83.3% vs 6.3%; p < 0.001) at presentation. A multivariable log regression model incorporating HE grade, shock at admission, and creatinine demonstrated strong predictive performance (Nagelkerke $R^2 = 0.763$, p < 0.001). A simpler model comprising only ACLF and shock at admission also predicted mortality ($R^2 = 0.663$, p < 0.001), requiring fewer variables. **Conclusion:** Short-term mortality following AVB appears to be driven predominantly by organ failures and ACLF at presentation. ACLF, shock, HE

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grade, and renal impairment were each strong predictors of mortality and may aid early risk stratification.



Disclosures: Aashi Aggarwal:Nothing to Disclose, Ishaan Gupta:Nothing to Disclose, Kriti Kriti:Nothing to Disclose, Trivendar Jangir:Nothing to Disclose, Tejasvi R:Nothing to Disclose, Mahendra Rajput:Nothing to Disclose, Suraj Bhagat:Nothing to Disclose, Rohit Mehtani:Nothing to Disclose.

1660 | SELECTIVE SEROTONIN REUPTAKE INHIBITOR USE AND RISK OF GASTROINTESTINAL BLEEDING IN PATIENTS WITH CIRRHOSIS: A PROPENSITY SCORE–MATCHED COHORT STUDY

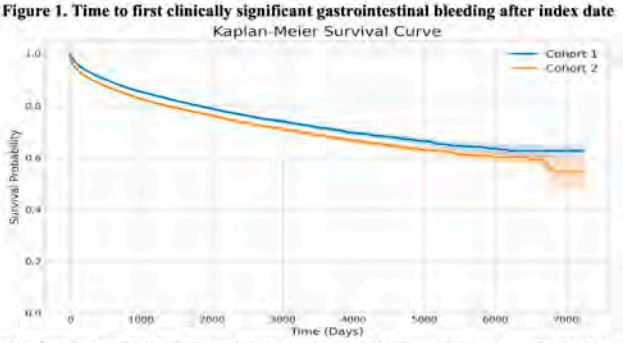
Mohamed Alharami[1] Omar Khattab[2] Frhaan Zahrawi[3] Omar Alwan[4] Mohammad Alali[5] Judy Sheffeh[6] Fatima Elmustafa[7] Mohammed Barawi[6], [1]Henry Ford Warren Hospital, [2]University of California Riverside, [3]Franciscan Olympia Field Health, [4]Hamilton Medical Center, [5]Henry Ford Macomb, [6]Henry Ford St. John Hospital, [7]Henry Ford Warren

Background: Selective serotonin reuptake inhibitors (SSRIs) have been associated with increased gastrointestinal (GI) bleeding risk in the general population, likely due to serotonin-mediated platelet dysfunction. However, the relevance of this association in cirrhosis is unclear. Cirrhosis is characterized by a "rebalanced hemostasis", and most clinically significant bleeding is driven by portal hypertension rather than platelet dysfunction. Prior studies largely excluded cirrhotic patients and often did not adequately adjust for key confounders such as NSAIDs and anticoagulants. We aimed to evaluate the association between SSRI use and GI bleeding risk in patients with cirrhosis. **Methods:** We conducted a retrospective cohort study using the TriNetX network. Among 123,415,579 patients in the database, 2,416,965 adults with cirrhosis were identified using ICD-10 codes. The exposed cohort included patients initiating SSRIs with no prior use in the preceding 12 months, while controls had no SSRI exposure. Patients with prior GI bleeding, unrelated bleeding disorders, or organ transplantation were excluded. Propensity score matching (1:1) was performed using demographics, liver disease severity, laboratory values, comorbidities, and concomitant medications. The primary outcome was time to first gastrointestinal bleeding event. Secondary outcomes included cumulative bleeding incidence at 30, 90, and 365 days. **Results:** After matching, 61,019 patients were included in each cohort. GI bleeding occurred in 14.2% of SSRI users vs 16.6% of controls. SSRI use was associated with a lower hazard of GI bleeding (HR 0.82, 95% CI 0.80–0.85; $p < 0.0001$). At 30 days, bleeding occurred in 2.0% vs 3.8% (RR 0.53); at 90 days, 3.4% vs 5.3% (RR 0.64); and at 1 year, 6.8% vs 8.9% (RR 0.76), all $p < 0.0001$. Absolute risk differences ranged from −1.76% to −2.10%. Risk reduction was greatest early and attenuated over time but remained significant. **Conclusion:** In this large propensity score–matched study, SSRI use in cirrhosis was not associated with an increased risk of gastrointestinal bleeding and was instead associated with a modest reduction in bleeding. These findings contrast with prior general-population studies and highlight the importance of cirrhosis-specific pathophysiology, in which bleeding is largely portal pressure–driven within a state of rebalanced hemostasis rather than true hypocoagulability. Prior associations may also reflect confounding from concomitant medications. Overall, SSRI therapy appears safe from a bleeding standpoint in cirrhosis and should not be withheld solely due to this concern.

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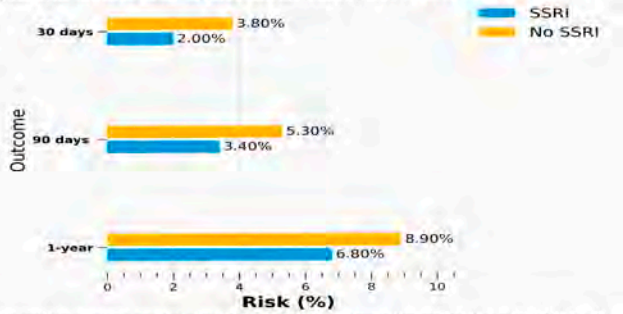
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Figure 1. Time to first clinically significant gastrointestinal bleeding after index date



Kaplan–Meier curves compare cirrhotic patients initiating selective serotonin reuptake inhibitors (SSRIs) at index (Cohort 1) versus matched cirrhotic controls without SSRI exposure (Cohort 2). Time zero represents the index date, and follow-up began 1 day after index. Shaded areas indicate 95% confidence intervals. Hazard ratios were estimated using Cox proportional hazards models and compared using the log-rank test. Patients were censored at the time of outcome occurrence or last recorded clinical encounter.

Figure 2. Cumulative risk of gastrointestinal bleeding at 30 days, 90 days, and 1 year after index in SSRI-exposed and matched non-SSRI cirrhosis cohorts.



Horizontal bar plots depict the cumulative incidence of clinically significant gastrointestinal bleeding at fixed follow-up intervals (30 days, 90 days, and 1 year) after the index date among propensity score–matched patients with cirrhosis treated with selective serotonin reuptake inhibitors

Disclosures: Mohamed Alharami:Nothing to Disclose, Omar Khattab:Nothing to Disclose, Frhaan Zahrawi:Nothing to Disclose, Omar Alwan:Nothing to Disclose, Mohammad Alali:Nothing to Disclose, Judy Sheffeh:Nothing to Disclose, Fatima Elmustafa:Nothing to Disclose, Mohammed Barawi:Nothing to Disclose.

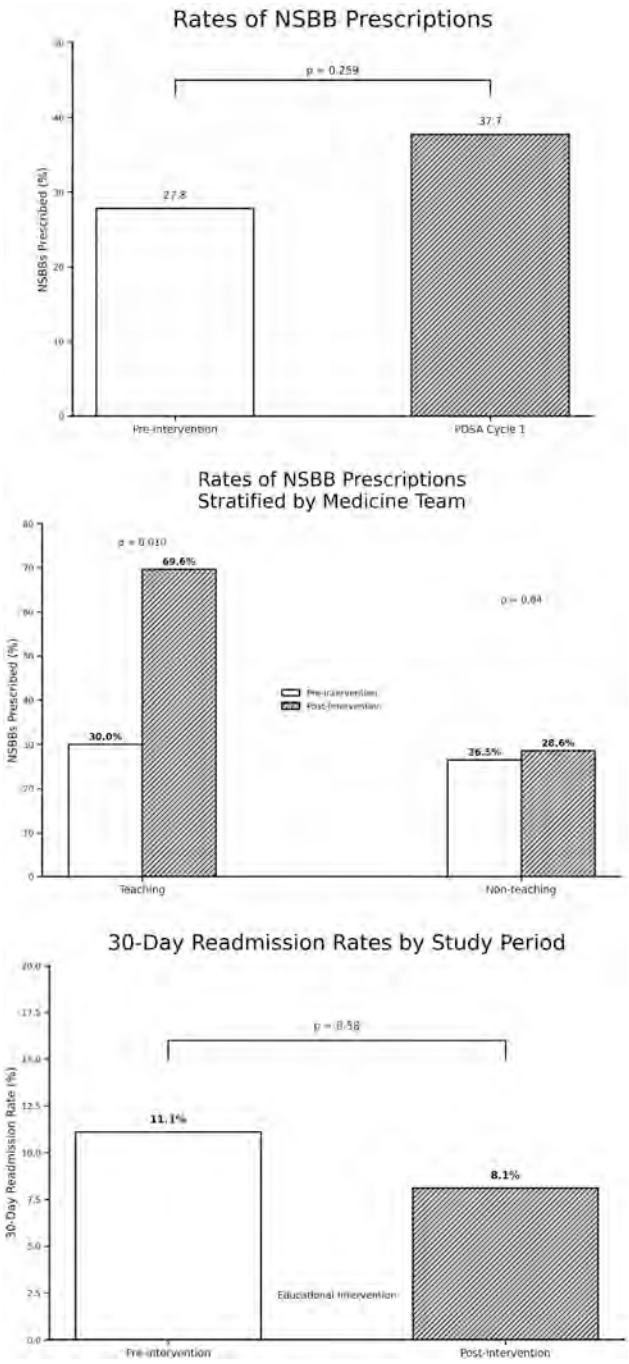
1661 | BETA BEATS BLEEDS:

Haniya Waseem[1] Ramish Rafay[1] Muhammad Umair[1] Muhammad Adnan[1], [1]Advent Health Tampa

Background: Patients with cirrhosis and variceal hemorrhage have a high risk of rebleeding and hospital readmission . Guidelines recommend non-selective beta-blockers (NSBBs) as part of secondary prophylaxis, yet these therapies are frequently under-prescribed at hospital discharge. We aimed to improve appropriate NSBB prescribing through a resident-led quality improvement intervention. **Methods:** We conducted a single-center QI project at an academic tertiary care hospital using the PDSA framework. Adult patients with decompensated cirrhosis eligible for secondary variceal prophylaxis were identified through retrospective review of the Epic electronic medical record. The pre-intervention cohort included patients hospitalized between August-Sept 2025. Adult patients ($\geq$18 years) admitted with upper GI bleeding and established decompensated cirrhosis were included. Patients without confirmed cirrhosis or without acute GI bleeding were excluded. Carvedilol was the preferred nonselective beta-blocker (NSBB); however, any prescribed NSBB was considered for analysis. A multifaceted educational intervention was implemented in November 2025, consisting of resident-focused teaching sessions and a hospital-wide awareness campaign (“Beta Beats Bleeds”) with visual reminders placed in physician work areas to reinforce guideline-concordant prescribing. The post-intervention cohort included patients hospitalized between Dec 2025 - Feb 2026. The primary outcome was prescription of nonselective beta-blockers (NSBBs) at hospital discharge. Secondary outcome was 30-day all-cause readmission. Pre- and post-intervention outcomes were compared using chi-square. **Results:** 57 patients were included in the pre-intervention cohort and 65 in the post-intervention cohort. Appropriate NSBB prescribing at discharge increased from 27.8% pre-intervention to 37.7% post-intervention ($p = 0.259$).In subgroup analysis, teaching teams had a significant improvement in prescribing (30.0% vs 69.6%, $p = 0.010$), whereas non-teaching teams showed no meaningful change (26.5% vs 28.6%, $p = 0.84$). 30-day readmission rates decreased from 11.1% to 8.1% following the intervention, though this was not statistically significant ($p = 0.58$). . **Conclusion:** A low-cost, resident led educational intervention improved guideline-concordant NSBB prescribing at discharge, with the greatest impact on teaching services. These findings suggest that education-based strategies are more effective in academic settings, while non-teaching teams may require system-level approaches such as EMR prompts or standardized workflows.Interpretation is limited by the single-center design, small sample size, and short follow-up, reducing power to detect clinical differences.These results show the need for targeted, setting-specific interventions to optimize evidence-based cirrhosis care.

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Disclosures: Haniya Waseem:Nothing to Disclose, Ramish Rafay:Nothing to Disclose, Muhammad Umair:Nothing to Disclose, Muhammad Adnan:Nothing to Disclose.

1662 | COMPARATIVE PERFORMANCE OF PROGNOSTIC RISK SCORES FOR PREDICTING POST-TIPS OUTCOMES AT A CANADIAN TERTIARY CARE CENTRE

Yashasavi Sachar[1] Derek Little[2] David Peck[3] Amol Mujoomdar[3] Derek Cool[3] David Hocking[3] Anouar Teriaky[3] Karim Qumosani[3] David Hudson[3] Ephraim Tang[3] Anton Skaro[3] Mayur Brahmania[4] Juan Pablo Arab[5] Mohammad Qasim Khan[3], [1]Western University, [2]Trillium Health Partners, [3]University of Western Ontario, [4]University of Calgary, [5]Virginia Commonwealth University

Background: Transjugular intrahepatic portosystemic shunt (TIPS) can be associated with high-risk mortality in cirrhosis. Multiple prognostic models have been developed to risk-stratify patients with advanced liver disease in this context. We compared the discriminatory performance of commonly used models, including MELD-Na, MELD 3.0, Child-Pugh-Turcotte (CTP), Albumin-Bilirubin Index (ALBI), and Freiburg Index of Post-TIPS Survival (FIPS), for predicting post-TIPS mortality. **Methods:** A retrospective cohort study was generated, consisting of adults undergoing TIPS at a tertiary Canadian center from 2013–2023. Patients undergoing repeat or revisional TIPS were excluded. Baseline demographic and laboratory data closest to the time of procedure were used to calculate each risk model. The primary outcomes were 6-week and 1-year all-cause mortality. Discrimination was assessed using receiver operating characteristic (ROC) analyses and area under the curve (AUC). Optimal thresholds were identified using the Youden index, from which sensitivity and specificity were derived. For CTP, ROC analysis compared Child-Pugh class C versus classes A/B combined. Separate age- and sex-adjusted logistic regression models were fitted for each score-outcome pair. ALBI, FIPS, MELD 3.0, and MELD-Na were modeled as continuous variables, while CTP was modeled as a 3-level categorical variable corresponding to Child-Pugh classes A, B, and C. **Results:** The cohort included 136 patients, with a mean age of 58.7 years, and 58.1% (n = 79) were male. The most common liver disease etiologies were ALD (27.9%), MASLD (26.5%), and MET-ALD (18.4%), followed by viral hepatitis (13.2%). Median (IQR) baseline scores were ALBI -1.72 (-2.18 to -1.42), FIPS -0.36 (-1.09 to 0.08), MELD 3.0 15 (12–19), MELD-Na 16 (13–20), and the majority of patients (69%) were CTP-B. Six-week mortality occurred in 17 patients (12.5%), and 1-year mortality in 24 patients (17.6%). For 6-week mortality, MELD 3.0 showed the highest discrimination (AUC 0.737), followed by CTP (AUC 0.733). For 1-year mortality, MELD 3.0 again performed best (AUC 0.739), followed by MELD-Na (AUC 0.716) and FIPS (AUC 0.695). In adjusted analyses, higher FIPS, MELD 3.0, and MELD-Na were significantly associated with both outcomes; CTP class C, but not class B, was also associated with both outcomes relative to class A, whereas ALBI was not. Full AUC and logistic regression results are shown in Table 1. **Conclusion:** Among commonly used prognostic models assessing mortality after TIPS, MELD 3.0 provided the most consistent

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discrimination for 6-week and 1-year mortality, while the FIPS model also demonstrated robust prognostic utility in adjusted analyses. Overall model performance was moderate, suggesting that existing risk scores are useful for post-TIPS risk stratification but remain imperfect as standalone decision tools.

Table 1: Logistic Regression and ROC Analysis of Prognostic Risk Scores for 6-Week and 1-Year Mortality After TIPS

Outcome	Score*	AUC	Sensitivity	Specificity	Youden index
6-Week Mortality	ALBI	0.66	0.71	0.64	0.35
	FIPS	0.69	0.47	0.92	0.40
	MELD 3.0	0.74	0.71	0.73	0.44
	MELD Na	0.70	0.76	0.70	0.47
	CTP	0.73	0.59	0.87	0.46
1-Year Mortality	ALBI	0.55	0.54	0.63	0.17
	FIPS	0.69	0.44	0.93	0.36
	MELD 3.0	0.74	0.71	0.76	0.46
	MELD-Na	0.72	0.71	0.72	0.43
	CTP	0.67	0.48	0.87	0.36
Outcome	**Score***	**OR**	**CI lower**	**CI upper**	**P**
6-Week Mortality	ALBI	1.76	0.82	3.77	0.15
	FIPS	2.66	1.41	5.04	<0.01
	MELD 3.0	1.20	1.07	1.34	<0.01
	MELD-Na	1.16	1.03	1.29	0.01
	CTP B**	1.14	0.13	10.3	0.90
	CTP C**	10.4	1.15	93.8	0.04
1-Year Mortality	ALBI	1.65	0.82	3.28	0.16
	FIPS	2.53	1.42	4.48	<0.01
	MELD 3.0	1.22	1.10	1.36	<0.01
	MELD-Na	1.18	1.07	1.31	<0.01
	CTP B**	0.89	0.17	4.54	0.88
	CTP C**	6.72	1.19	37.7	0.03

* ALBI, Albumin-Bilirubin Index; FIPS, Freiburg Index of Post-TIPS Survival; MELD-Na, Model for End-Stage Liver Disease Sodium; MELD 3.0, Model for End-Stage Liver Disease 3.0; CTP, Child-Pugh-Turcotte score.

** CTP was analyzed categorically with Child-Pugh A as the reference; CTP B and C denote comparisons of class B vs A and class C vs A

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1663 | AVATROMBOPAG IN CIRRHOTIC PATIENTS UNDERGOING INVASIVE PROCEDURES: INSIGHTS FROM REAL-WORLD PRACTICE

Mikolas Holinka[1] Dusan Merta[1] Jan Sperl[1] Tomas Nesnidal[1] Tomas Hucl[1] Sona Frankova[1], [1]Institute for Clinical and Experimental Medicine

Background: Thrombocytopenia-related bleeding is one of the major complications in cirrhosis; therefore, periprocedural bleeding risk management is an essential strategy in planning invasive procedures. Thrombopoietin receptor agonists (TPO-RA) are emerging as the standard for managing thrombocytopenia in cirrhotic patients. Our study aims to assess the efficacy and safety of avatrombopag, TPO-RA, in the prevention of periprocedural bleeding in cirrhotic patients. **Methods:** We retrospectively evaluated a cohort of 42 cirrhotic patients who underwent 59 invasive procedures between 2022 and 2025. The median age was 53 years (range 28–75); 20 patients were female, the median MELD score was 15 (range 9–23) and the median baseline platelet count 37/µL (21–49). The aetiology of liver cirrhosis was alcoholic (16), autoimmune (7), viral (9), MASLD (8) or other (2). The most common procedures were teeth extractions (20/59, 34%), followed by gynaecology procedures (7/59, 11.9%), major abdominal surgeries (6/59, 10.2%), TACE (4/59, 6.8%), colon polypectomy (2/59, 3.4%, and others (20/59, 33.8%). All patients received avatrombopag for 5 days, at 60 or 40 mg daily, depending on platelet counts of less than 40/µL (45 procedures) and 40–50/µL (14 procedures), respectively, in accordance with the manufacturer's recommendations. **Results:** The median increase of platelet count was 43/µl (6–147). In 53 (89.8%) procedures, the platelet count exceeded the required target of 50 platelets /µl before the procedure. None of the procedures was postponed or cancelled owing to thrombocytopenia; platelet transfusion was not administered to any patient before the procedure. In 4 patients (6,8%), a bleeding complication was reported: 1 inguinal hematoma, 1 post-polypectomy bleeding, 1 skin wound bleeding, 1 bleeding after pancreatectomy; the last three events required endoscopy/surgical treatment and blood transfusion administration. Except for one, all bleeding events occurred in patients with an adequate platelet increase before the procedure. None of the pre-procedural clinical characteristics (platelet count, haemoglobin level, MELD score, age) predicted the risk of non-response to avatrombopag or bleeding in the multivariate analysis. No thromboembolic events or deaths were reported. **Conclusion:** Avatrombopag was safe and effective in managing periprocedural thrombocytopenia. Bleeding complications were infrequent and not predictable by baseline clinical or laboratory parameters.

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1665 | FALSE-POSITIVE DOPPLER ULTRASONOGRAPHY FOR PORTAL VEIN THROMBOSIS IN DECOMPENSATED CIRRHOSIS: A CASE SERIES WITH FOCUS ON PATIENT CHARECTARISTICS

Harry Trieu[1] Michelle Nguyen[1] Parsia Vazirni[1] Yuri Kwon[1] Beshoy Yanny[1], [1]University of California, Irvine

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Background: Portal vein thrombosis in liver cirrhosis is often incidentally diagnosed and has a reported incidence of 10.42% and prevalence of 13.92%. Doppler ultrasonography (DUS) is the first-line imaging modality for PVT and has a sensitivity and specificity ranging from 66-100% [PMID 26684272], however it is limited by body habitus, presence of intestinal gas, and experience of the ultrasonographer. We present three patients with liver cirrhosis who were admitted to the University Medical Center with Doppler ultrasonography of the liver showing PVT and confirmatory multiphase CT or MR venography showing lack of PVT suggesting poor diagnostic value in a certain patient population. In this limited case series we explore the limitations of abdominal doppler ultrasound in patients with decompensated liver cirrhosis **Methods:** Retrospective care series conducted. Three consecutive patients were admitted to the university hospital with decompensated liver cirrhosis. Patient demographics, clinical characteristics, laboratory values, imaging findings, and time interval between DUS and confirmatory imaging were collected and analyzed. **Results:** Three patients 33% female, mean age 53 years old. All patients had large ascites on admission. All patient had thrombocytopenia with mean platelet count of 48,000. History of gastrointestinal bleeding was presents in 100% of patients, esophageal varices present in 100% of patient, and mean MELD 3.0 was noted to be 28. Doppler ultrasound was obtained in 100% of patients in the emergency department and showed portal vein thrombosis in all patients. Cross sectional imaging obtained in all 3 patients showing no evidence of portal vein thrombosis in 100% of the patients. All three high risk patients avoided anticoagulation based on cross sectional imaging. Abdominal doppler ultrasound showed false positive values in 100% of patient. **Conclusion:** Doppler ultrasound of the abdomen has limited utility to evaluate for PVT and high false positive rates in patients with MELD 3.0 score equal to or above 20, thrombocytopenia, hepatosplenomegaly and ascites as shared by our patients. These features may cause marked reduced portal venous flow velocity, which can appear like absent flow or thrombosis on DUS. Consider moving directly to cross sectional imaging in this select group of patients to avoid unnecessary anticoagulation in patients with high risk of bleeding. More studies are needed to risk stratify the appropriateness of doppler ultrasound in decompensated liver cirrhosis patients.

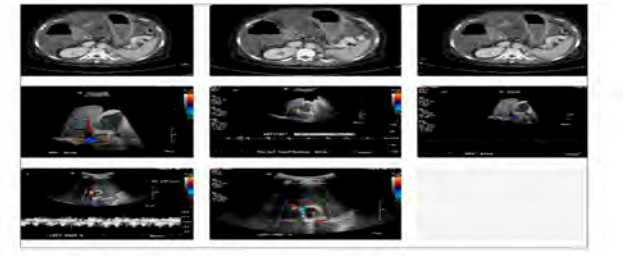


Figure 1 showing discrepancy between results of ultrasound doppler and 4 phase CT of the abdomen highlighting false positive PVT diagnosis

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1666 | A CLUSTER ANALYSIS OF COAGULATION DYSFUNCTION IN DECOMPENSATED LIVER CIRRHOSIS PATIENTS

Jinglan Jin[1] Zian Wang[1] Hongqin Xu[1], [1]Department of Hepatology, First Hospital of Jilin University

Background: The coagulation dysfunction could perform as either elevated thromboembolism events or increased bleeding risk in decompensated liver cirrhosis. To find the risk factors and excavate the underlying mechanism of coagulation dysfunction, a cluster analysis was conducted. **Methods:** We selected 619 patients who initially admitted for decompensated liver cirrhosis in stage 3 or 4 according to the 2025 edition of Clinical Diagnosis and Treatment Guidelines for Liver Cirrhosis released by the Chinese Medical Association, without blood system disorders or diseases may cause abnormal coagulation function (nephrotic syndrome, systemic lupus erythematosus, etc.) in Department of Hepatology, First Hospital of Jilin University during 2021 to 2025. Proportions of portal vein thrombosis (PVT), venous thromboembolism (VTE) or non-portal hypertension related bleeding were collected from their inpatient data. **Results:** 3 subgroups were classified through k-means analysis: group 1 (bleeding group), characterized as prolonged APTT with higher bleeding percentages; group 2 (thrombosis group), featured as both increased PVT and VTE cases; group 3 (simple portal hypertension group), featured as only PVT risk elevated. Univariate analysis showed significantly increased total bilirubin level and decreased albumin level in group 1 compared with another groups, while a significant elevated neutrophil rate and reduced lymphocyte rate in group 2. **Conclusion:** In the context of decompensated liver cirrhosis, progressive liver dysfunction may be related towards higher bleeding risk, while neutrophil-mediated inflammation could be considered related to venous thrombosis. However, due to the small proportion of bleeding events observed, specific risk factors correlated with non-hypertension related bleeding should be discovered by deeper investigating patients' medical histories and signs.

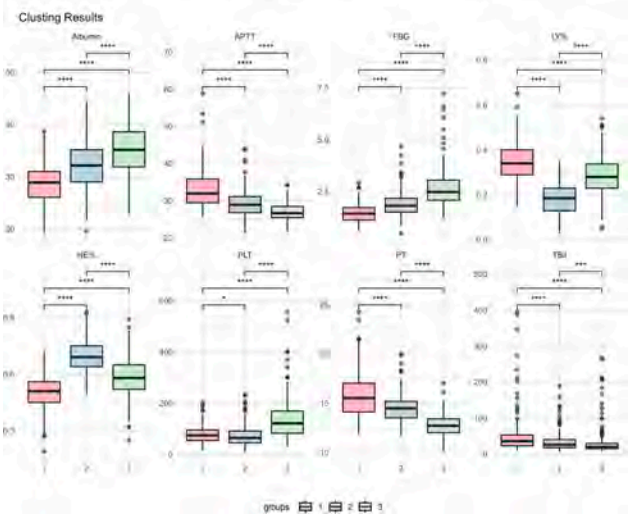
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Table

Variables	Group1 (n=175)	Group2 (n=222)	Group3 (n=222)	p1	p2	p3
Gender	58.90%	62.60%	60.80%	0.511	0.771	0.770
splenectomy	2.30%	0.50%	9%	0.240	0.010	0.000
Varices	24.60%	53.20%	39.60%	0.000	0.002	0.006
Bleeding	3.40%	1.40%	2.30%	0.298	0.688	0.721
GVB	21.70%	42.80%	25.20%	0.000	0.485	0.000
Peritonitis	3.40%	0.90%	1.40%	0.156	0.298	1.000
ascites	33.70%	31.10%	21.60%	0.653	0.010	0.031
HE	5.70%	3.20%	2.30%	0.316	0.126	0.770
PVT	1.10%	7.70%	6.30%	0.005	0.019	0.710
Icterus	9.70%	1.80%	7.70%	0.001	0.585	0.007
Infection	4%	2.70%	5%	0.662	0.833	0.323
VTE	1.70%	9.90%	3.20%	0.002	0.558	0.007
Age	56 (50, 65)	59 (52, 66)	58 (51, 68)	0.094	0.096	0.832
Child score	8 (7, 9)	7 (6, 8)	6 (5, 7)	0.000	0.000	0.000
MELD	20.299 (17.883, 23.024)	18.729 (16.093, 21.311)	15.804 (13.358, 18.598)	0.000	0.000	0.000
FIB-4	7.192 (5.084, 10.506)	6.167 (4.332, 8.669)	3.591 (2.377, 5.605)	0.010	0.000	0.000

Note: p1: Group1 vs Group2; p2: Group1 vs Group3; p3: Group2 vs Group3. GVB: gastrointestinal varices bleeding; HE: hepatic encephalopathy; PVT: portal vein thrombosis; VTE: venous thromboembolism; MELD: model for end-stage liver disease; FIB-4: fibrosis-4 index.

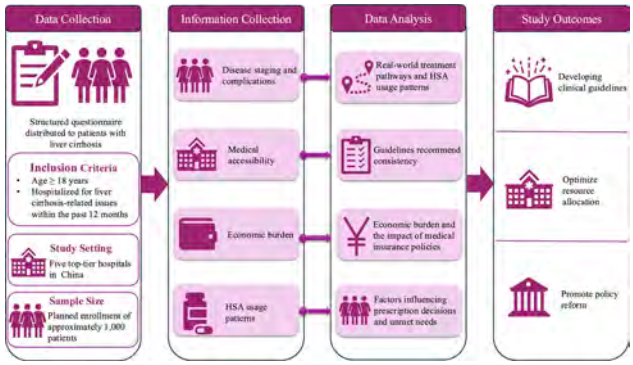


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1667 | PATIENT JOURNEY MAPPING OF LIVER CIRRHOSIS MANAGEMENT AND HUMAN SERUM UTILIZATION PATTERNS: A MULTICENTER CROSS-SECTIONAL MIXED-METHODS STUDY IN CHINA

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Background: China bears a substantial burden of liver disease. Although human serum albumin (HSA) is widely used in the treatment of cirrhosis, real-world prescribing patterns and factors influencing its use in China remain poorly characterized. This mixed-methods study aims to examine patient journeys and patterns of HSA use across the cirrhosis care continuum. **Methods:** This multicenter, cross-sectional, mixed-methods study is being conducted across five top-tier hospitals in China, with a planned enrollment of approximately 1,000 patients with cirrhosis, including 30% with compensated and 70% with decompensated disease. The study integrates patient and physician interviews, medical record abstraction, and questionnaire-based data collection. Qualitative interviews focus on care pathways, experiences with HSA use, economic burden, and long-term disease management to characterize clinical decision-making processes and their determinants. Quantitative data include disease stage, complications, healthcare access, financial burden, and patterns of HSA use. **Results:** A patient journey–based structured questionnaire and interview guide have been developed based on clinical pathways and guideline recommendations. Using these tools, this study aims to characterize the real-world care pathways and patterns of HSA use among patients with cirrhosis in China. It will examine HSA utilization across different clinical scenarios and complications, while also assessing concordance with guideline recommendations. Additionally, it will assess the economic burden associated with HSA use and the impact of reimbursement policies on treatment accessibility. Key factors influencing prescribing decisions will be identified, and continuity of long-term management and unmet needs will be assessed from the patient perspective. **Conclusion:** The findings will provide evidence to inform clinical guidelines, optimize resource allocation, and support policy reforms aimed at improving the quality, equity, and efficiency of cirrhosis care in China.



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1668 | EFFICACY AND SAFETY OF FECAL MICROBIOTA TRANSPLANTATION FOR PREVENTION OF HEPATIC ENCEPHALOPATHY RECURRENCE: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

Yusuf Atef[1] Omar Rageh[2] Basma Salhin[3] Ahmed Hany Kamel Elshafie[4] Muhammad Minisy[5] Basma Amin[3] Basma Abushosha[6] Camelia Ciobanu[7] Hazem Abosheaishaa[8]

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Background: Hepatic encephalopathy (HE) is a major complication of cirrhosis associated with recurrent hospitalizations and poor clinical outcomes. Gut dysbiosis plays a key role in HE pathogenesis, making fecal microbiota transplantation (FMT) a promising therapeutic strategy. We conducted a systematic review and meta-analysis to evaluate the efficacy and safety of FMT in patients with cirrhosis and HE. **Methods:** A systematic literature search was performed in PubMed, Scopus, Web of science, Embase, and Medline from 1997 until 2026. Randomized controlled trials evaluating FMT in adult patients with HE were included. Studies comparing FMT with placebo or standard care were eligible. Six RCTs met inclusion criteria and two of them were excluded from quantitative synthesis due to non-comparable intervention design and insufficient outcome data. Different FMT administration routes, including capsules, enema, nasogastric tube, and colonoscopy, were included. Data extraction and risk of bias assessment were performed independently by 2 reviewers. Meta-analysis was conducted using a random-effects model, and pooled risk ratios (RRs) with 95% confidence intervals (CIs) were calculated. Statistical heterogeneity was assessed using the I^2 statistic. **Results:** Four randomized comparisons involving 90 patients were included in the quantitative synthesis. FMT significantly reduced the risk of HE recurrence compared with placebo or standard care (RR 0.24, 95% CI 0.09–0.62; P = 0.003), I^2 = 0%. No significant statistical heterogeneity was observed among included studies due to limited sample size. Safety analysis demonstrated that FMT was associated with lower rates of serious adverse events compared with control therapy (RR 0.33, 95% CI 0.11–0.96; P = 0.04), with moderate heterogeneity among studies: I^2 = 56%. Across studies, FMT was administered through multiple delivery routes including oral capsules, enema, colonoscopy, and nasogastric tube. Despite methodological variations in FMT protocols, the direction of treatment effect was consistent across studies. **Conclusion:** FMT may reduce recurrence of hepatic encephalopathy in patients with cirrhosis and was not associated with increased serious adverse events. These findings support the therapeutic potential of microbiome modulation in HE management. Larger multicenter randomized trials are warranted to confirm long-term efficacy and establish standardized FMT protocols.

Disclosures: Yusuf Atef:Nothing to Disclose, Omar Rageh:Nothing to Disclose, Basma Salhin:Nothing to Disclose, Ahmed Hany Kamel Elshafie:Nothing to Disclose, Nothing to Disclose, Muhammad Minisy:Nothing to Disclose, Basma Amin:Nothing to Disclose, Basma Abushosha:Nothing to Disclose, Camelia Ciobanu:Nothing to Disclose, Hazem Abosheaishaa:Nothing to Disclose.

1669 | ◆ MOLECULAR PROFILING OF LIVER TUMORS IN VASCULAR LIVER DISORDERS REVEALS DISTINCT GENOMIC FEATURES AND REDUCES DIAGNOSTIC UNCERTAINTY

Sabrina Sidali[1] Jihyun An[2] Valerie PAradis[3] Catherine Guettier[4] Julien Calderaro[5] Marianne Ziol[6] Patricia De La Cruz[1] Long Pan[1] Shuoshuo Jin[1] Mylene Sebagh[7] Sophie Branchereau[8] Emmanuel Gonzales[9] Aurore Pire[10] Marianna Cornet[10] Paulette Bioulac-Sage[11] Théo Hirsch[1] Sandra Rebouissou[1] Dominique Wendum[12] Claudia Campani[13] Aurelie Beaufrere[14] Nathalie Ganne Carrie[13] Alicia Furumaya[1] Maxime Ronot[15] Aurelie Plessier[16] Pierre-Emmanuel Rautou[16] Janick Selves[17] Sandrine Imbeaud[1] Jessica Zucman-Rossi[18] Jean Charles Nault[19], [1]INSERM UMRS 1138, FunGeST Team, Cordeliers Research Center, Paris France, [2]INSERM UMRS 1138, FunGeST team, Paris, France. Hepatology, College of Medecine, Guri, South Korea, [3]Department of Pathology, Beaujon hospital, Clichy France, [4]Service d'anatomie pathologique, hôpitaux Bicêtre-Paul Brousse-Béclère, Le Kremlin-Bicêtre, France, [5]Pathology Department, Henri Mondor Hospital, Créteil, France, [6]Pathology Department, Avicenne hospital, Bobigny, France, [7]Hôpital Paul-Brousse, Laboratoire d'Anatomopathologie, Villejuif, France, [8]Pediatric Surgery Unit, Ern Transplant Child, Bicêtre Hospital, Le Kremlin-Bicêtre, France, [9]Hopital Bicetre, [10]INSERM UMRS 1138, FunGeST Team, Cordeliers Research Center, Paris France. Necker Hospital. Paris, [11]University of Bordeaux, INSERM,

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Background: Primary liver tumors arising in vascular liver disorders (VLD) pose significant diagnostic challenges, and their molecular characteristics remain poorly understood. We aimed to characterize their mutational and transcriptomic landscape and its impact on patient management. **Methods:** Sixty-three liver tumors from 47 VLD patients were analyzed by whole-genome and/or whole-exome and RNA sequencing and compared to 473 hepatocellular adenomas (HCA) and 385 hepatocellular carcinomas (HCC) not developed on VLD with available molecular data. Pathological diagnoses were classified as certain or uncertain based on original reports (n = 63) and expert reviewing (n = 48). A molecular diagnosis was assigned based on driver mutations, copy number variation, and transcriptomic profiles. **Results:** Molecular profiling reduced diagnostic uncertainty from 30% of tumors on initial pathological report and 46% after expert review to 8%, identifying 27 HCC, 1 borderline HCA /HCC, 29 HCA, 5 regenerative macronodules and 1 hepatic angiosarcoma. Among 5 focal nodular hyperplasia-like, 4 were reclassified as regenerative macronodules due to absence of somatic mutations and clustering with non-tumoral liver tissue without forming a distinct transcriptomic entity. The remaining focal nodular hyperplasia-like was reclassified as bex3HCA due to *CTNNB1* exon 3 somatic mutation. Compared to control HCC, VLD-associated HCC occurred more frequently in women ($P < 0.001$) and exhibited enrichment of *CTNNB1* exon 3 mutations ($P = 0.011$), and a lower prevalence of *TP53* mutations ($P = 0.003$). Patients with VLD-associated HCA were less frequently female compared with HCA not developed on VLD (39.1% in VLD versus 86.4% in control, $P < 0.001$). Among women, those with VLD-associated HCA were less likely to have a history of estrogen-based contraception use (50% in VLD versus 89.4% in control, $P < 0.001$). Compared to control HCAs, VLD-associated HCAs exhibited a higher proportion of bex3HCA ($P < 0.001$) and of malignant transformation (14.3% vs. 3%, $P < 0.001$), and a lower prevalence of inflammatory HCAs ($P = 0.008$). *HNF1A*-inactivated HCA in VLD presented an atypical non-steatotic phenotype driven by suppression of lipogenic pathways in both tumor and adjacent non-tumoral liver. **Conclusion:** Comprehensive molecular profiling substantially improves the classification of primary liver tumors arising in VLD and reduces diagnostic uncertainty supporting its integration in clinical practice. Moreover, we uncover a distinct genomic landscape reflecting the strong relationship between these rare chronic liver diseases and the molecular profiles of primary liver tumors.

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1670 | ◆ LONG-TERM ANTICOAGULATION REDUCES BLEEDING AND THROMBOTIC OUTCOMES IN NON-CIRRHOTIC CHRONIC PORTAL VEIN THROMBOSIS

Jackie Bitton[1] Jean-Paul Cervoni[2] Odile Goria[3] Isabelle Ollivier-Hourmand[4] Christophe Bureau[5] Armelle Poujol-Robert[6] Anne Minello[7] Pauline Houssel-Debry[8] Dominique Valla[1] Audrey Payance[9] Pierre Deltenre[10] Onorina Bruno[11] Jules Gregory[11] Olivier Roux[12] Valérie

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Background: In the RIPORT study, rivaroxaban 15 mg reduced recurrent venous thrombosis without increased bleeding incidence over a median follow-up of 12 months in patients with non-cirrhotic chronic portal vein thrombosis (NC-PVT). However, long-term outcomes beyond the trial period remain poorly characterized. **Methods:** Multicenter retrospective cohort study including patients previously enrolled in the RIPORT trial and followed in the RIPORT2 extension. Main objective was occurrence of a composite endpoint including death, major bleeding, clinically relevant non-major bleeding (CRNMB)*, recurrent deep vein thrombosis (RVT), and arterial event. Secondary end points were individual events. Data included clinical, biological, radiological, anticoagulation exposure, and NGS results. Lost to follow-up patients were excluded. Follow-up was divided into anticoagulated and non-anticoagulated periods and crude incidence rates were estimated. IRRs were estimated using Univariate Poisson regression. * Defined according to ISTH criteria **Results:** 100/111 patients (60 men; median age 49.8 years), were included in the extension study, with a median follow-up of 7.9 years from RIPORT (IQR 7; 8.5). Risk factors were low-risk thrombophilia in 93 patients (93.9%) and a local cause in 17 (15%). Median exposure time to anticoagulant was 85.9 months (70.3; 96.5) overall. During follow-up, 93 (93%) patients received anticoagulation (DOACs (85%), LMWH (8%), VKAs (13%)). The primary composite endpoint occurred at a significantly lower rate in anticoagulated versus non-anticoagulated exposition (5.77 vs 25.71 per 100 patient-years; IRR 0.22 (0.14; 0.36), $p < 0.001$). Only one mortality event occurred during the non-exposure period (0.83 vs 0.00 per 100 patient-years), following sepsis after severe gastric variceal bleeding. Venous thrombosis recurred in 13 patients in RIPORT, and 8 patients in RIPORT2 (19 patients overall). RVT occurred less frequently during exposure to anticoagulation (0.96 vs 14.10 per 100 patient-years; IRR 0.07 (0.03; 0.17), $p < 0.001$). Incidence of major bleeding was lower during exposed periods to anticoagulation (1.60 vs 5.81 per 100 patient-years; IRR 0.28 (0.11; 0.73), $p = 0.009$). CRNMB and arterial ischemic events were numerically lower during anticoagulation exposure, without statistical significance. **Conclusion:** In non-major risk factor non-cirrhotic PVT, long-term anticoagulation, mainly with reduced dose DOACS, significantly prevents thrombotic and severe bleeding events. As in deep vein thrombosis it seems to be an excellent and safer alternative in this population.

Disclosures: Jackie Bitton:Nothing to Disclose, Jean-Paul Cervoni:Nothing to Disclose, Odile Goria: Nothing to Disclose, Isabelle Ollivier-Hourmand:Abbvie: Speaking and Teaching, Ipsen: travel for congress, roche: Speaking and Teaching, Astra zeneca: Speaking and Teaching, Christophe Bureau:Gore: Speaking and Teaching, Abbvie: Consultant, Gilead: Speaking and Teaching, Ipsen: Speaking and Teaching, Alfasigma: Consultant, Borhinger: Grant/Research Support, Mirum: Speaking and Teaching, Falk Farma: Consultant, Armelle Poujol-Robert:GILEAD: EASL ongress invitation, Anne Minello:Nothing to Disclose, Pauline Houssel-Debry:Nothing to Disclose, Dominique Valla:Nothing to Disclose, Audrey Payance:Nothing to Disclose, Pierre Deltenre:Nothing to Disclose, Onorina Bruno:Nothing to Disclose, Jules Gregory:Nothing to Disclose, Olivier Roux: Nothing to Disclose, Valérie Vilgrain:Nothing to Disclose, Valérie Paradis:inventiva: Consultant, Catherine TRICHET:Nothing to Disclose, Emmanuelle De Raucourt:Nothing to Disclose, Carine Roy:Nothing to Disclose, Najeh Daabek:Nothing to Disclose, Marion Schneider:Nothing to Disclose, Axelle Dupont:Nothing to Disclose, Pierre-Emmanuel Rautou:Cook: Consultant, Genfit: Consultant, Jazz: Consultant, Astra Zeneca: Consultant, Leo Pharma: Speaking and Teaching, Aurélie Plessier:Nothing to Disclose.

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1671 | ◆ INCIDENT PORTAL VEIN THROMBOSIS IN CIRRHOSIS: A LARGE COMPETING-RISK ANALYSIS IDENTIFYING REDUCED PORTAL VEIN VELOCITY AS THE STRONGEST PREDICTOR

Babu Lal Meena[1] Shiv Kumar Sarin[1] Ashok Kumar Choudhury[1] Vinod Arora[1] sarthak Chanana[1] Srinivas Reddy[1] shalini ThaparLaroia[1] Amar Mukund[1] Ankit Bhardwaj[1] Chitranshu Vashishtha[1] Deepti Sharma[1] Manoj Sharma[1] Omkar Rudra[1], [1]Institute of Liver and Biliary Sciences

Background: Portal vein thrombosis (PVT) is a major complication of cirrhosis associated with adverse outcomes. However, predictors of incident PVT accounting for competing clinical events remain inadequately characterized. We evaluated the incidence, predictors, and natural history of incident PVT in a large cohort of patients with cirrhosis using competing-risk methodology. **Methods:** We conducted a retrospective cohort study of consecutive adults with cirrhosis undergoing at least 2 year or more of regular longitudinal follow-up at a tertiary liver center. Patients with baseline PVT, portal cavernoma, or non-cirrhotic portal hypertension, HCC, hepatocellular carcinoma, prior liver transplantation, or on anti-coagulants were excluded. Incident PVT was diagnosed on follow-up imaging. Cumulative incidence functions accounting for death, TIPS, and liver transplantation as competing events were estimated. Independent predictors were evaluated using multivariable Fine–Gray competing-risk regression analysis. **Results:** A total of 4,986 patients with cirrhosis were included (mean age 49.3 ± 11.9 years; 79.2% male). During a mean follow-up of 2.9 ± 0.6 years, 1,445 patients (29.0%) patients developed incident PVT. Alcohol-related liver disease was the most common etiology (43.5%), followed by MASLD (36.6%), viral hepatitis (11.0%), and other causes (8.8%). Mean time to PVT occurrence progressively decreased with worsening Child–Turcotte–Pugh (CTP) class ($p < 0.001$). The cumulative incidence of PVT increased progressively over follow-up, whereas competing events demonstrated substantially lower cumulative incidences. Patients with advanced liver disease (CTP class C) and portal vein velocity < 12 cm/s demonstrated the highest cumulative risk of incident PVT. On multivariable competing-risk regression analysis, portal vein velocity < 12 cm/s emerged as the strongest independent predictor of incident PVT (sub-distribution hazard ratio [sHR] 6.41, 95% confidence interval [CI] 5.35–7.69; $p < 0.001$). Additional independent predictors included serum albumin < 3 g/dL (sHR 2.14, 95% CI 1.86–2.48; $p < 0.001$), increasing CTP class (sHR 1.76, 95% CI 1.61–1.92; $p < 0.001$), presence of portosystemic collaterals (sHR 1.50, 95% CI 1.34–1.68; $p < 0.001$), and male sex (sHR 1.13, 95% CI 1.01–1.28; $p = 0.04$). Spontaneous recanalization occurred in 28% of patients versus 60–75% with anticoagulation. Recanalization was higher in partial versus complete thrombosis and recurrence rates were lower with enoxaparin and DOACs. **Conclusion:** Incident PVT is common in cirrhosis, particularly in patients with advanced liver disease and reduced portal vein velocity. Reduced portal vein velocity was the strongest predictor of incident PVT. Competing-risk analysis provides clinically meaningful thrombotic risk estimation and may improve risk stratification and surveillance in cirrhosis.

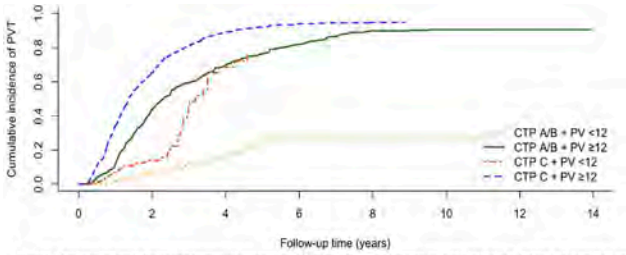


Figure 1. Cumulative incidence of portal vein thrombosis according to combined Child–Turcotte–Pugh class and portal vein velocity. Patients with advanced liver disease (CTP C) and reduced portal vein velocity (<12 cm/s) demonstrated the highest cumulative risk of incident PVT. Death, TIPS and liver transplantation was treated as competing events.

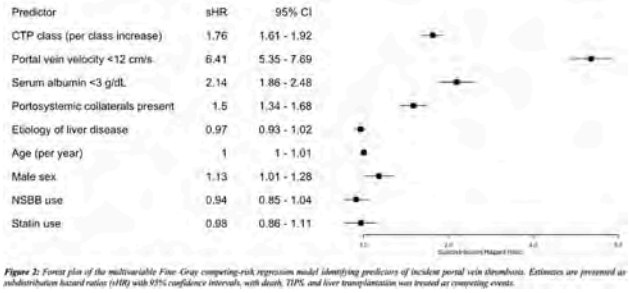


Figure 2: Forest plot of the multivariable Fine–Gray competing-risk regression model identifying predictors of incident portal vein thrombosis. Estimates are presented as subdistribution hazard ratios (sHR) with 95% confidence intervals, with death, TIPS, and liver transplantation was treated as competing events.

Disclosures: Babu Lal Meena:Nothing to Disclose, Shiv Kumar Sarin:Nothing to Disclose, Ashok Kumar Choudhury:Nothing to Disclose, Vinod Arora:Nothing to Disclose, sarthak Chanana:Nothing to Disclose, Srinivas Reddy:Nothing to Disclose, shalini ThaparLaroia:Nothing to Disclose, Amar Mukund:Nothing to Disclose, Ankit Bhardwaj:Nothing to Disclose, Chitranshu Vashishtha:Nothing to Disclose, Deepti Sharma:Nothing to Disclose, Manoj Sharma:Nothing to Disclose, Omkar Rudra:Nothing to Disclose.

1672 | LONG-TERM OUTCOMES IN PATIENTS WITH BUDD–CHIARI SYNDROME (BCS) : A RETROSPECTIVE COHORT STUDY OF 989 PATIENTS

Akash Shukla[1] Gautam Jain[2] Ankita Singh[2] Megha Meshram[2] Tanmay Laxane[2] Shashank Pujalwar[3] Dominique Valla[4] Abu Aasim Ansari[2] Kranti Rathod[2] Pranoy De[2] Yash Harwani[2] Vinay Borkar[2], [1]Seth GS Medical College & KEM Hospital, [2]Seth GS Medical

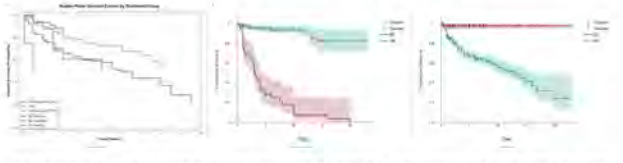
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Background: BCS is a rare but life-threatening hepatic venous outflow disorder. Long-term outcome data from large cohorts is lacking.This study examined clinical profile, treatment response rates, predictors of medical therapy failure, and long-term survival across nearly two decades of follow-up. **Methods:** Retrospective analysis of a prospectively maintained registry at a dedicated BCS clinic (January 2006–January 2025). Clinical presentation, anatomic pattern of venous obstruction, and treatment modality were systematically recorded. Predictors of medical therapy failure were identified by multivariate logistic regression. Survival was estimated using Kaplan–Meier analysis; competing-risk analysis using the Fine–Gray subdistribution hazard model was applied to account for loss to follow-up **Results:** 989 patients were enrolled; median age 29 years (54.5% men). The vast majority (93.6%) presented with chronic disease. Ascites was the dominant presenting feature (72%), followed by jaundice(30.1%), acute variceal haemorrhage(21.4%), and hepatic encephalopathy (6.6%). Isolated hepatic vein obstruction was the most frequent anatomic pattern (56.4%), followed by combined IVC and hepatic vein obstruction (37.1%). Mean MELD score was 14 ± 6.Anticoagulation alone was administered in 60% of patients; 39% underwent endovascular intervention (TIPS 21%, hepatic vein stenting 9%, IVC stenting 6%, balloon angioplasty 3%). Complete response was achieved in only 16% with medical therapy versus 85.6% following endovascular intervention; a 5.4-fold difference. Among medically treated patients, 73% were classified as non-responders. On multivariate logistic regression, low platelet count and low serum albumin at baseline independently predicted failure of medical therapy (both $p < 0.001$). Treatment response was an independent determinant of overall survival ($p < 0.001$ for both modalities). On a per protocol analysis, 73% patients were alive at a median follow-up of 4 years. **Conclusion:** Medical therapy alone achieves complete response in only one in six BCS patients. Endovascular intervention is markedly superior. Low albumin and platelet count should prompt early escalation to intervention. Treatment response was a dominant determinant of survival ($p < 0.001$ for both modalities).

Figure 1. Kaplan–Meier Survival Analysis in Budd–Chiari Syndrome (n=989)



Panel A: Kaplan–Meier survival curves stratified by treatment modality (n=510 with follow-up data). Anticoagulation alone was associated with significantly higher mortality than TIPS (38.2% vs. 25.0%; p=0.009) and hepatic vein stenting alone (38.2% vs. 15.0%; p=0.005). **Panel B:** Survival in patients undergoing endovascular intervention, stratified by treatment response (CR, n=197 vs. PR, n=46). CR was associated with 7.1% mortality versus 87.0% for PR (log-rank p<0.001). Shaded areas represent 95% confidence intervals. **Panel C:** Survival in patients receiving medical therapy, stratified by treatment response (CR, n=149 vs. NR, n=299). CR was associated with 3.4% mortality versus 48.5% for NR (log-rank p<0.001). Shaded areas represent 95% confidence intervals.

AC = anticoagulation, CR = complete response, HVS = hepatic vein stenting, NR = no response, PR = partial response, TIPS = transjugular intrahepatic portocaval shunt.

Disclosures: Akash Shukla:Nothing to Disclose, Gautam Jain:Nothing to Disclose, Ankita Singh:Nothing to Disclose, Megha Meshram:Nothing to Disclose, Tanmay Laxane:Nothing to Disclose, Shashank Pujalwar: Nothing to Disclose, Dominique Valla:Nothing to Disclose, Abu Aasim Ansari:Nothing to Disclose, Kranti Rathod:Nothing to Disclose, Pranoy De:Nothing to Disclose, Yash Harwani:Nothing to Disclose, Vinay Borkar:Nothing to Disclose.

1673 | MICROVESSEL DENSITY DEFINES IMMUNOSUPPRESSIVE SPATIAL NICHES IN HEPATOCELLULAR CARCINOMA

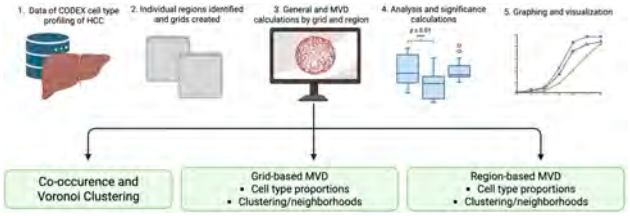
Venika Kakarla[1] Renumathy Dhanasekaran[2], [1]Stanford, [2]Stanford University

Background: Hepatocellular carcinoma (HCC) is one of the most vascularized solid tumors, and pathological angiogenesis is a defining hallmark of its progression. Microvessel density (MVD), a histological measure of intratumoral vascular content, has been associated with poor prognosis in HCC, yet how vascular architecture spatially organizes immune cell neighborhoods has not been systematically characterized at single-cell resolution. **Methods:** We performed spatially resolved, multicellular profiling of endothelial cell neighborhoods across 124 HCC tumors (n = 1,065,284 cells) using CODEX multiplexed spatial proteomics (n = 54 markers). Six complementary analytical approaches were applied: whole-region cell-type proportion analysis, radius-based endothelial interaction mapping, region-averaged and grid-based MVD stratification, cellular co-occurrence in vascular neighborhoods, and Voronoi-based spatial clustering. Findings were validated in an independent cohort of HCC with single-cell spatial proteomics with CODEX (n = 843,647 cells). **Results:** In HCC, high-MVD tumors (n = 32) were enriched for Tregs ($p = 6.0x10-34$), $CD206^+$ macrophages ($p = 0.019$), $PD\text{-}L1^+$ macrophages, and both memory ($p = 3.97\times10^{-4}$) and effector ($p = 0.035$) $CD8^+$ T cells, consistent with an immunosuppressive, exhaustion-prone niche. Low-MVD regions (n = 36) showed greater infiltration of anti-tumor immune cells like $CD4^+$ T cells, neutrophils ($p = 0.026$), and monocytes ($p = 0.016$). Spatial neighborhood analysis revealed that in high-MVD tumors, endothelial cell neighborhoods were significantly enriched with M2-like CD206+ macrophages ($p = 4.68\times10^{-8}$) across spatial radii of 50-200 microns, indicating that high-vascularity HCC establishes a tolerogenic perivascular niche characterized by immunosuppressive macrophage co-localization. High-MVD regions markedly overexpressed tumor-associated stemness marker CK19 and the immune checkpoint PDL1. In an independent validation cohort, MVD-stratified immune distribution patterns were reproduced

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across high (n = 61) and low (n = 61) MVD regions. Higher MVD regions again lacked neutrophils ($p = 2.97\times10^{-4}$), effector $CD4^+$ T cells ($p = 2.2\times10^{-4}$), memory $CD8^+$ T cells ($p = 4.4\times10^{-4}$), and monocytes ($p = 7.47\times10^{-6}$). **Conclusion:** Using two independent large-scale spatial atlases for discovery and validation, we demonstrate that angiogenesis defines reproducible immune neighborhoods within HCC. High-MVD regions are characterized by coordinated enrichment of Tregs, M2-polarized macrophages, and aggressive tumor programs. Together, these data reveal that pathological angiogenesis extends beyond vascular expansion to spatially organize immunosuppressive cellular ecosystems, providing a single-cell view of how the vascular niche may contribute to immune evasion in HCC.



Disclosures: Venika Kakarla:Nothing to Disclose, Renumathy Dhanasekaran:Nothing to Disclose.

1674 | LIVER DISEASE MANIFESTATIONS IN STAT1 GOF DISEASE

Sawsan Fathma[1] Nehna Abdul Majeed[2] Sana Pirzada[1] Wesam Aleyadeh[1] Sharifeh Almasaid[3] Alexandra Freeman[4] Steven Holland[4] Jenna Bergersen[4] Bernadette Redd[5] Christopher Koh[1] David Kleiner[6] Theo Heller[1], [1]NIH/NIDDK, [2]University of Maryland, [3]SUNY Upstate, [4]NIAID/NIH, [5]National Institutes of Health, [6]National Cancer Institute, Bethesda

Background: Signal transducer and activator of transcription 1 (STAT1) gain-of-function (GOF) disease cause impaired dephosphorylation and prolonged nuclear accumulation of phosphorylated STAT1, leading to excessive and sustained interferon signaling. This hyperactivation causes immune dysregulation characterized by chronic mucocutaneous candidiasis and recurrent infection. However, the hepatic manifestations of STAT1 GOF remain poorly defined. We aimed to characterize the presentation and outcomes of liver disease in STAT1 GOF. **Methods:** We performed a retrospective study of patients with genetically confirmed STAT1 GOF evaluated at the National Institutes of Health (NIH) Clinical Center between 1996 and 2026. Clinical, laboratory, imaging, and histopathologic data were analyzed to characterize and describe liver involvement. **Results:** Sixty-eight patients with STAT1 GOF were included; 28 (41%) met criteria for liver disease. At baseline, Alanine and Aspartate aminotransferases were significantly different between two groups (p = 0.006 and 0.015 respectively) while synthetic function, and platelet count, did not differ between the groups. During follow-up, all biochemical markers remained largely normal, but platelet count declined significantly in the liver disease group (median 246.5 to 163.5; $p = 4.1 \times 10^{-6}$), representing the only parameter that differed between groups. Imaging showed hepatomegaly in 24 of 28 patients with liver disease, often with splenomegaly. Liver biopsy in twelve patients revealed porto-sinusoidal vascular disease (PSVD) in five and features suggestive of PSVD in two, closely correlating with declining or persistently low platelet counts. All-cause mortality was higher among patients with liver disease compared with those without liver disease (25% vs 15%). Kaplan–Meier survival analysis demonstrated a trend toward earlier mortality among patients with liver disease. Median age at death was lower in patients with liver disease (29 years) compared with those without liver disease (52.5 years). The Gehan-Breslow-Wilcoxon test approached significance (p = 0.084), suggesting a tendency toward earlier death among patients with liver disease. **Conclusion:** Liver disease is a common manifestation of STAT1 GOF disease and may be associated with increased and earlier all-cause mortality. This cohort showed that histopathology frequently demonstrates PSVD, linking STAT1 GOF to vascular liver pathology. Recognizing and characterizing liver involvement in STAT1 GOF not only improves clinical care for these patients but also offers a unique opportunity to deepen our understanding of PSVD pathophysiology, a condition for which underlying mechanisms remain poorly defined.

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1675 | THE ORAL CHOLATE CHALLENGE TEST (HEPQUANT DUO®) MAY PREDICT TRANSPLANT-FREE SURVIVAL IN FONTAN-ASSOCIATED LIVER DISEASE

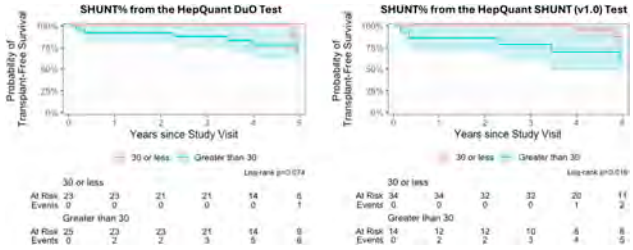
Maarouf Hoteit[1] Daniel Ganger[2] Alexis Tomlinson[3] Jack Rychik[3] Michael McRae[4] Joanne Imperial[5] Gregory Everson[6] Yuli Kim[1], [1]Hospital of the University of Pennsylvania, [2]Northwestern Memorial Hospital,

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[3]Children's Hospital of Philadelphia, [4]Custom DX Solutions LLC, [5]HepQuant LLC, [6]HepQuant

Background: Adults with Fontan circulation are at risk for heart failure and progressive Fontan-associated liver disease, but the optimal timing of transplant referral, including consideration of combined heart-liver transplantation, remains uncertain. The oral cholate challenge test (OCCT) quantifies apparent hepatic cholate clearance and estimates portal-systemic shunting, which may reflect both liver dysfunction and adverse Fontan hemodynamics. We hypothesized that elevated SHUNT% quantified by the OCCT may be associated with reduced transplant-free survival. **Methods:** From 2015 to 2022, 50 adults with Fontan circulation from two academic centers underwent cholate challenge testing and were prospectively followed. Participants were administered d4-cholate orally, followed by peripheral venous blood sampling at 20 and 60 minutes. Cholate concentrations were measured by LC-MS/MS, and the degree of portal-systemic shunting (SHUNT%) was estimated. The primary outcome was transplant-free survival. Kaplan-Meier analysis compared participants with SHUNT% $>30\%$ versus $\leq 30\%$ using the log-rank test. Results with the OCCT were compared to the full SHUNT test, which measured the same test parameters but additionally involved intravenously administered 13C-cholate and blood sampling at 0, 5, 20, 45, 60, and 90 minutes. **Results:** The cohort had a median age of 31 years (IQR, 25–38), 52% were female, and generally well-preserved routine laboratory values. Despite the benign clinical and laboratory profile, significant clinical outcomes were observed over a median of 4.4 years (IQR, 3.5–5.5): 6 deaths, 6 transplants, 4 heart failure, 3 HCC, and 3 protein losing enteropathy. Kaplan-Meier analysis demonstrated lower transplant-free survival among participants with SHUNT% $>30\%$ compared with SHUNT% $\leq 30\%$ (Figure). Separation between groups was apparent early and persisted over follow-up. By 5 years, the SHUNT% $>30\%$ group had more cumulative events than the SHUNT% $\leq 30\%$ group, regardless of test version (OCCT: 6 vs 1 events, log-rank $p=0.074$; SHUNT test: 5 vs 2 events, log-rank $p=0.016$). **Conclusion:** Elevated SHUNT% as measured by OCCT is associated with adverse mid-term clinical outcomes in adults with Fontan circulation. If validated, the OCCT could be a useful tool to guide surveillance strategy and timing of transplant referral. The excellent discrimination of SHUNT% at four years suggests the retest interval for OCCT should be 2–4 years. Larger studies are needed, however, to confirm the prognostic threshold and define how this metric should be integrated into clinical decision-making.



Disclosures: Maarouf Hoteit:Nothing to Disclose, Daniel Ganger:WCG: Consultant, Alexis Tomlinson: Nothing to Disclose, Jack Rychik:Nothing to Disclose, Michael McRae:HepQuant, LLC: Independent Contractor, Joanne Imperial:Nothing to Disclose, Gregory Everson:Nothing to Disclose, Yuli Kim:Nothing to Disclose.

1676 | NATURAL HISTORY, CLINICAL SPECTRUM, AND LONG-TERM OUTCOMES OF PORTAL BILIOPATHY IN EXTRAHEPATIC PORTAL VEIN OBSTRUCTION: A 34-YEAR TERTIARY-CENTER EXPERIENCE

Babu Lal Meena[1] Shiv Kumar Sarin[1] Manoj Sharma[1] Rajeev Khanna[1] Ashish Kumar[2] Adarsh Chaudhary[3], [1]Institute of Liver and Biliary Sciences, [2]Sir Ganga Ram Hospital, [3]Medanta Hospital, Gurugram

Background: Portal biliopathy (PB), a term coined in 1992 by our group, has been reported frequently in patients with extrahepatic portal vein obstruction (EHPVO). Long-term data regarding its natural history, therapeutic burden, and progression to secondary biliary cirrhosis (SBC) remain limited. We evaluated the clinical spectrum, radiological characteristics, management strategies, and long-term outcomes of PB in a large longitudinal EHPVO cohort. **Methods:** We analyzed records of consecutive patients with EHPVO managed at two tertiary centers between 1983 and 2017. PB was diagnosed by MRCP/ERCP demonstrating biliary abnormalities in the setting of portal cavernoma after exclusion of other biliary diseases. Demographic, laboratory, radiological, endoscopic, surgical, and outcome data were analyzed. PB was anatomically classified as type 1 (extrahepatic), type 2 (intrahepatic), type 3a (extrahepatic with unilateral intrahepatic involvement), and type 3b (extrahepatic with bilateral intrahepatic involvement). SBC was diagnosed using persistent cholestasis with imaging and/or histological evidence of biliary cirrhosis despite adequate decompression. **Results:** Altogether, 774 patients with complete records were included (67.2% males; mean age

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20 ± 14 years). Variceal bleeding was the commonest presentation (87.1%). Thrombophilia was identified in 20% of patients, most commonly MTHFR mutation (22.6%) and protein C deficiency (20.6%). At presentation, PB was present in 571/774 (73.8%) patients, although only 7.1% were symptomatic. During follow-up, PB was detected in 767/774 (99.1%) patients, with 26.9% becoming symptomatic. Combined intrahepatic and extrahepatic involvement (type 3b) was the predominant pattern (80.7%). Varicoid morphology was most common (56.2%), followed by fibrotic (29.7%) and mixed morphology (9.7%). Imaging frequently demonstrated ductal irregularity (90.6%), CBD dilatation (83.9%), and CBD angulation < 145° (62.8%). Gallbladder stones and CBD stones were observed in 19.4% and 12.6%, respectively. Among 208 symptomatic patients, 131 (62.9%) required ERCP, with a mean of 6.25 ± 2.6 procedures per patient. Durable symptom relief after a single ERCP session was achieved in only 26%, whereas 74% required repeated interventions. Over the follow-up period, SBC developed in 5.3% at a mean duration of 9.9 ± 2.9 years. Overall mortality was low (1.7%) and was mainly related to cholangitis (46%) and SBC (31%). Cholangiocarcinoma occurred in 0.4% of patients. **Conclusion:** Portal biliopathy is nearly universal in long-standing EHPVO, although symptomatic disease develops in only a minority. Symptomatic PB frequently requires repeated ERCP and shunt surgery; however, progression to secondary biliary cirrhosis and mortality remain uncommon on long-term follow-up.

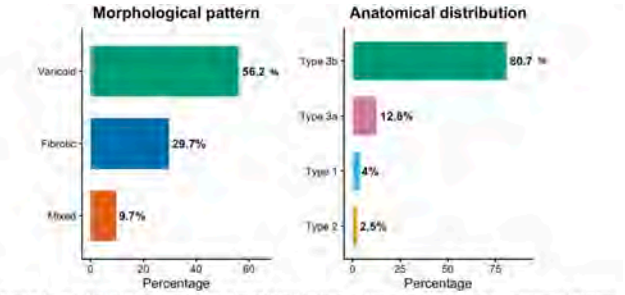


Figure 1. Radiological phenotype distribution of portal biliopathy showing morphological and anatomical patterns.

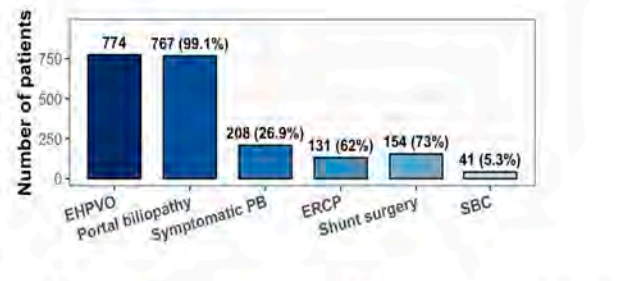


Figure 2. Natural history and therapeutic burden of portal biliopathy in extrahepatic portal vein obstruction

Disclosures: Babu Lal Meena:Nothing to Disclose, Shiv Kumar Sarin:Nothing to Disclose, Manoj Sharma: Nothing to Disclose, Rajeev Khanna:Nothing to Disclose, Ashish Kumar:Roche: Consultant, Viatris: Consultant, Sun Pharma: Advisor, Astra Zeneca: Advisor, Adarsh Chaudhary:Nothing to Disclose.

1677 | A VASCULAR MRI SIGNATURE OUTPERFORMS CONVENTIONAL SCORES FOR PREDICTING LIVER-RELATED OUTCOMES IN NON-CIRRHOTIC PORTAL HYPERTENSION

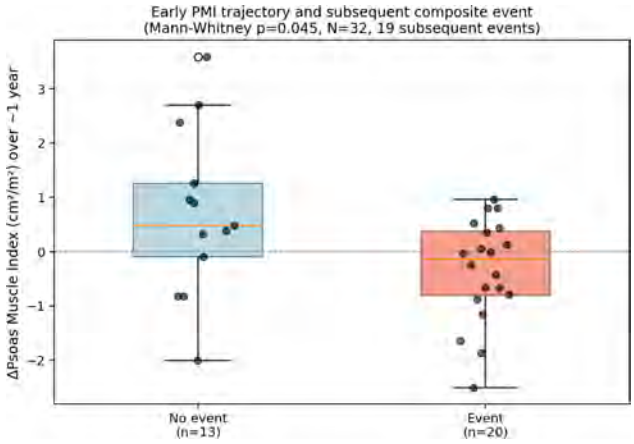
Wesam Aleyadeh[1] Maria Mironova[2] Ahmed Gharib[3] Jaha Norman-Wheeler[4] David Kleiner[5] Bernadette Redd[3] Christopher Koh[4] Theo Heller[6], [1]National Institutes of Health, [2]UCSD, [3]NIH, [4]NIDDK, NIH, [5]National Cancer Institute, Bethesda, [6]NIH/NIDDK

Background: Non-cirrhotic portal hypertension (NCPH), including porto-sinusoidal vascular disorder (PSVD), produces clinically relevant portal hypertension while liver synthetic function remains preserved, usually in the absence of fibrosis. Conventional risk tools were built for cirrhosis and may not capture risk in a predominantly presinusoidal disease. MRI is obtained routinely in these patients, yet its ability to predict outcomes has not been defined. **Methods:** We followed 50 adults with NCPH evaluated with serial protocolized MRI and follow-up for liver-related outcomes. MRIs were reviewed for vascular features of portal hypertension and for psoas muscle index. MR elastography, proton-density fat fraction, and liver iron were available in a subset. The primary endpoint was a composite of new hepatic decompensation, esophageal variceal bleed, liver transplantation, or death. We examined associations using Cox regression, time-dependent AUC at 5 years, and derived a combined imaging score. **Results:** Median age was 50 years, 40% were female, and the leading etiology was common variable immunodeficiency (34%). A porto-sinusoidal vascular lesion was present on biopsy in 74% of the cohort (37 of 50; 79% of those biopsied). Synthetic function was preserved (median MELD-Na 8) despite marked hypersplenism (median platelets 97 $\times 10^9$/L). Over a median 4.0 years, 27 patients (54%) reached the composite endpoint, including 5 deaths, 4 transplants, and 4 variceal bleeds. Porto-systemic collaterals was the strongest predictor for developing LRO (HR 6.07, 95% CI 2.20-16.75, 5-year AUC 0.70), followed by esophageal varices (HR 4.59, AUC 0.68) and periportal venous change (HR 4.47, AUC 0.67). Each outperformed MELD-Na (AUC 0.65), FIB-4 (AUC 0.61), and APRI (AUC 0.57). A simple imaging score combining collaterals, periportal change, and smaller liver length achieved a C-index of 0.66 and 5-year

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AUC of 0.73. In a landmark analysis, 1-year change in psoas muscle index independently separated patients with LRO from those who remained event-free (median ΔPMI −0.24 vs +0.48, p = 0.046). On MR elastography (n = 10), liver stiffness was low (median 3.5 kPa, 9 of 10 below the 4.7 kPa non-cirrhotic threshold) while spleen stiffness was high (median 12.0 kPa), with a uniformly elevated spleen-to-liver stiffness ratio (median 3.45, all ≥1.23) and normal hepatic fat and iron in every patient. **Conclusion:** In NCPH, a vascular MRI signature anchored by porto-systemic collaterals and periportal venous change predicts decompensation, transplantation, and death more accurately than conventional cirrhosis-based scores, and a simple combination of three routinely reported features stratifies long-term risk. MR elastography confirms a low-liver-stiffness, high-spleen-stiffness phenotype with no parenchymal fat or iron, reinforcing that the prognostic signal is vascular. Prospective validation of the imaging score is warranted.



Disclosures: Wesam Aleyadeh:Nothing to Disclose, Maria Mironova:Nothing to Disclose, Ahmed Gharib: Nothing to Disclose, Jaha Norman-Wheeler:Nothing to Disclose, David Kleiner:Nothing to Disclose, Bernadette Redd:Nothing to Disclose, Christopher Koh: Nothing to Disclose, Theo Heller:Nothing to Disclose.

1678 | HISTOLOGIC FEATURES AND MARKERS OF PORTAL HYPERTENSION IN PORTO-SINUSOIDAL VASCULAR DISEASE ACROSS SERIAL BIOPSIES

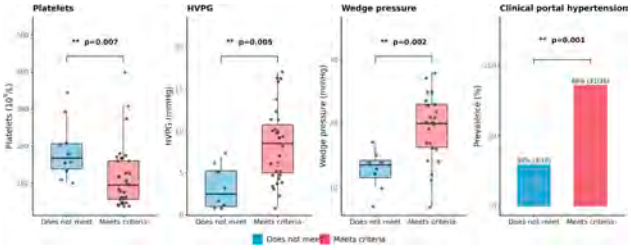
Wesam Aleyadeh[1] Maria Mironova[2] Jaha Norman-Wheeler[3] Christopher Koh[4] David Kleiner[5] Theo Heller[6], [1]National Institutes of Health, [2]UCSD, [3]NIH, [4]NIDDK, NIH, [5]National Cancer Institute, Bethesda, [6]NIH/NIDDK

Background: Histologic features are central to the diagnosis of porto-sinusoidal vascular disease (PSVD) and define the major and minor criteria of the 2026 consensus. The longitudinal correlation between individual lesions and laboratory or clinical markers of portal hypertension is not established. We assessed associations between histologic features and laboratory, fibrosis, and hemodynamic markers at index and follow-up biopsy. **Methods:** Single-center retrospective cohort at the NIH Clinical Center. Biopsies were scored by one hepatopathologist for three major and three minor consensus features and assigned a histologic criteria score (0/2/5). Laboratory values, fibrosis indices (FIB-4, APRI, transient elastography), composite scores (ALBI, PALBI, MELD 3.0), and hemodynamic measurements (HVPG, wedge and free hepatic venous pressures) were analyzed against histologic features at index and follow-up biopsy. Within-patient concordance across paired biopsies was assessed by Cohen kappa. Multivariable logistic models, ROC analysis, and progressors-to-fibrosis comparisons were also performed. **Results:** Forty-six patients comprised the index cohort (median age 45 years, 41% female; common variable immunodeficiency in 44%). Twenty-one underwent at least one repeat biopsy (27 follow-up biopsies, median interval 4.5 years). At index, 36/46 (78%) met histologic criteria. Meeting criteria was associated with lower platelets (95 vs 168 x10^9 /L, p = 0.007), higher HVPG (8.5 vs 2.5 mmHg, p = 0.004) and wedge pressure (20 vs 14 mmHg, p = 0.002), higher liver stiffness, FIB-4, APRI and PALBI. Clinical portal hypertension was more frequent (86% vs 30%; adjusted OR 14.9, p = 0.002), and all clinically significant portal hypertension (HVPG > = 10) occurred in this group. Isolated regenerative changes showed the inverse pattern, with lower portal pressures. Follow-up biopsies had similar findings: 22/27 (81%) met criteria with lower platelets and higher liver stiffness. Within-patient histologic concordance was modest (Cohen kappa 0.50 for NRH, 0.62 for regenerative changes, 0.46 for meeting criteria, and ≤0.25 for the remaining features). Among 21 paired patients, 7 (33%) experienced composite portal hypertension worsening, most commonly de novo varices (4/9 eligible), collaterals (3/7), or PHG (3/8). Histologic worsening occurred in parallel, with 6/15 (40%) eligible patients acquiring de novo PV stenosis ≥50% by follow-up; all worsened patients were NRH-positive at index, and 6/7 had CVID. **Conclusion:** The histologic criteria for PSVD identify a consistent portal hypertensive phenotype across hemodynamic and laboratory markers at both index and follow-up biopsy. Isolated regenerative changes mark a milder subgroup rather than early disease, suggesting the consensus features are not prognostically equivalent. Modest within-patient concordance indicates that single-biopsy assessment

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may be incomplete.



Disclosures: Wesam Aleyadeh:Nothing to Disclose, Maria Mironova:Nothing to Disclose, Jaha Norman-Wheeler:Nothing to Disclose, Christopher Koh:Nothing to Disclose, David Kleiner:Nothing to Disclose, Theo Heller:Nothing to Disclose.

1679 | INVERSE ASSOCIATION BETWEEN METABOLIC DYSFUNCTION-ASSOCIATED FATTY LIVER DISEASE ACTIVITY AND PORTO-SINUSOIDAL VASCULAR DISEASE

Weihua Cao[1] Yao Xie[1] Minghui Li[1], [1]Beijing Ditan Hospital, Capital Medical University

Background: Porto-sinusoidal vascular disease (PSVD) is a major cause of non-cirrhotic portal hypertension, but its pathogenesis remains unclear. Whether metabolic dysfunction-associated fatty liver disease (MAFLD) contributes to the development of PSVD is still controversial. This study aimed to compare the clinical and pathological characteristics between patients with MAFLD alone and those with MAFLD combined with PSVD, and to explore the association between MAFLD and PSVD. **Methods:** A total of 381 patients with biopsy-proven MAFLD were retrospectively enrolled, including 258 with MAFLD alone and 123 with MAFLD combined with PSVD. Propensity score matching (PSM, 1:2) was performed to balance age, sex, BMI, hypertension, and diabetes history between the two groups. Clinical, biochemical, and pathological parameters were compared before and after matching. Univariate and multivariate logistic regression analyses were used to identify independent factors associated with PSVD. Subgroup analyses were further conducted according to fibrosis stage (F0-1 vs F2-3) and NAS score (<4 vs ≥ 4). **Results:** After PSM, there were no significant differences in age, sex, BMI, hypertension, or diabetes history between the two groups ($P>0.05$) in Table 1. Compared with the MAFLD alone group, the MAFLD+PSVD group had significantly lower NAS score (3.00 vs 4.50, $P<0.001$), lower prevalence of MASH (10.57% vs 31.71%, $P<0.001$), lower steatosis grade ($P<0.001$), lower inflammation grade ($P<0.001$), and lower fibrosis stage ($P<0.001$) in Table 1. Moreover, serum ALT, AST, triglycerides, liver stiffness measurement (LSM), and controlled attenuation parameter (CAP) were all significantly reduced in the MAFLD+PSVD group ($P<0.01$) in Table 1. Multivariate logistic regression showed that CAP (OR = 0.988, 95%CI 0.983-0.994, $P<0.001$) and NAS score (OR = 0.476, 95%CI 0.287-0.789, $P=0.004$) were independent negative correlates of PSVD in Table 2. In the F0-1 subgroup, the PSVD group still had lower NAS score, MASH rate, CAP, and ALT ($P<0.05$) in Table 3. In the F2-3 subgroup, the PSVD group had significantly lower NAS score, MASH rate, ALT, AST, and CAP than the MAFLD alone group ($P<0.01$) in Table 4. Further analysis revealed that the prevalence of PSVD in patients with NAS <4 was 60.2%, significantly higher than that in patients with NAS ≥ 4 (17.3%; OR = 7.37, 95%CI 4.63-11.75, $P<0.001$) in Figure 1. **Conclusion:** The severity of MAFLD is inversely associated with the occurrence of PSVD , suggesting that PSVD tends to develop in the early stages of MAFLD (NAS <4, mild fibrosis) rather than as an advanced complication of MAFLD. This finding challenges the intuitive assumption that “more severe MAFLD confers higher PSVD risk”, and implies a potential reverse selection or hemodynamic interaction between MAFLD and PSVD. Clinically, for MAFLD patients with low NAS score (especially <4) who present with unexplained portal hypertension, the possibility of PSVD should be considered.



Disclosures: Weihua Cao:Nothing to Disclose, Yao Xie:Nothing to Disclose, Minghui Li:Nothing to Disclose.

1680 | WHOLE-EXOME SEQUENCE PROFILING OF PATIENTS WITH BUDD CHIARI SYNDROME TO IDENTIFY THE PATHOGENIC GERM LINE VARIANTS, MUTATIONAL SIGNATURES, AND POSSIBLE THERAPEUTIC TARGETS

Sonu Kumar[1] Sagnik Biswas[1] Harsh Goel[1] Samagra Agarwal[1] Ayush Agarwal[1] Sarthak Saxena[1] Pranay

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Tanwar[2] Baibaswata Nayak[1] Shalimar .[1], [1]AIIMS New Delhi, [2]AIIMS New Delhi

Background: Budd-Chiari syndrome (BCS) is a rare vascular disorder of the liver, characterized by hepatic venous outflow tract obstruction (HVOTO) secondary to thrombosis or intrinsic vascular abnormalities. Obstruction may affect the inferior vena cava (IVC), hepatic veins (HV), or both. Clinical presentation, disease progression, and management vary according to site, extent, and duration of obstruction. The majority of BCS cases are attributed to an underlying hypercoagulable disorder. Despite its clinical significance, data on the genetic causes and biomarkers underlying BCS remain limited. Here in this study, we performed whole-exome sequencing in BCS cases and healthy controls to explore the mutational landscape in BCS-affected subjects. **Methods:** We enrolled BCS (n = 77) and Healthy controls (n = 24) patients. Subjects were prospectively enrolled after informed consent. The study was reviewed and approved by the AIIMS, New Delhi, Institute Ethics Committee as per IEC-629/03.11.2017, RP-19/2018. WES was performed using the Twist Comprehensive Exome kit on the Illumina platform, followed by quality checks and analysis using the GATK pipeline. Pathogenic/likely pathogenic variants were filtered out from the exonic part of the annotated variant calling file. rsID and Cosmic IDs databases were used to define the mutations. Kyoto Encyclopedia of Genes and Genomes (KEGG) and Gene Ontology analysis were done for pathogenic gene variants. Validation of the most frequent pathogenic mutations in cases was done by Sanger sequencing in an Independent BCS Cohort. **Results:** We enrolled patients with mean age 27(15-61) years. Majority of them were females **.** In all cases a total of 10394 genes were observed having a variant. In each of these genes 1-173 variants per gene were observed. C > T transition was the most frequent variant observed in all cases. Pathogenic mutations were observed in the 1732 genes. The most frequent genes that have germline pathogenic mutations were HLA-DRB1(c.A455G, p.Y152C), ABCB5(c.G1094T, p.G365V), MTHFR (c.C788T, p.A263V), and A2ML1 (c.G1436A, p.C479Y). KEGG pathway analysis for all pathogenic mutation showed that Hippo, MYC, NOTCH, PI3K, RTK-RAS, WNT, Cell-cycle TP53 and TGF Beta are the key cellular pathways that were found having a regulatory role BCS patients. In gene ontology analysis, we observed that at the molecular level, these genes having a role in actin and tubulin binding, may be a part of the structural binding process. Genes JAK2, HLA-DRB1, APOH, PROS, PROC were found having druggable targets. **Conclusion:** 1732 genes were having pathogenic/likely pathogenic mutations in our BCS cohort. These genes are involved in Hippo, MYC, NOTCH, PI3K, RTK-RAS, WNT, Cell-cycle TP53 and TGF Beta pathways. Genes JAK2, HLA-DRB1, APOH, PROS, PROC were found to have druggable targets.

Disclosures: Sonu Kumar:Nothing to Disclose, Sagnik Biswas:Nothing to Disclose, Harsh Goel:Nothing to Disclose, Samagra Agarwal:Nothing to Disclose, Ayush Agarwal:Nothing to Disclose, Sarthak Saxena:Nothing to Disclose, Pranay Tanwar:Nothing to Disclose, Baibaswata Nayak:Nothing to Disclose, Shalimar .: Nothing to Disclose.

1681 | STAGE-DEPENDENT NATURAL HISTORY, PROGRESSION, AND PREDICTORS OF ADVERSE OUTCOMES IN NON-CIRRHOTIC PORTAL FIBROSIS: VALIDATION OF THE APASL 2024 STAGING SYSTEM

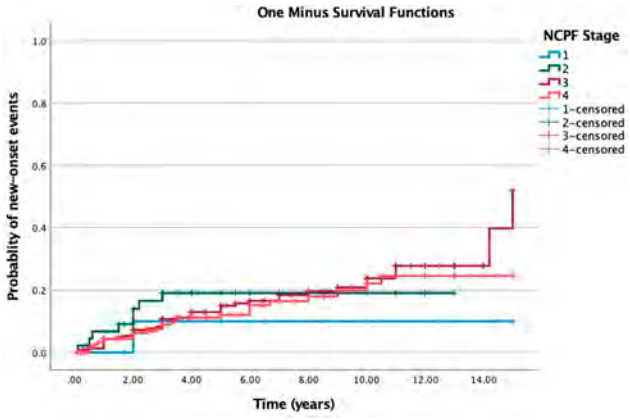
Omkar Rudra[1] Chhagan Bihari[1] Akash Shukla[2] Babu Lal Meena[3] Archana Rastogi[1] Ajay Duseja[4] Shiv Kumar Sarin[1], [1]Institute of Liver and Biliary Sciences, [2]Seth GS Medical College & KEM Hospital, [3]PGIMER, Chandigarh, [4]Postgraduate Institute of Medical Education & Research

Background: Non-cirrhotic portal fibrosis (NCPF) or portosinusoidal vascular disease (PSVD) is a distinct presinusoidal portal hypertensive disorder with generally preserved hepatic synthetic function despite progressive vascular injury. The APASL 2024 guidelines introduced a four-stage framework for NCPF, but stage-specific natural history and prognostic markers remain insufficiently defined. We aimed to characterize the clinical course, stage migration, and predictors of adverse outcomes in a large multicenter cohort of histologically confirmed NCPF patients. **Methods:** We performed an ambispective analysis of histologically confirmed NCPF patients (Multisociety consensus, 2026) from three Indian centers seen between 2009 and 2024. Histopathological subgroups included obliterative portovenopathy (OPV), OPV with fibrosis (OPV-F), incomplete septal cirrhosis (ISC) and nodular regenerative hyperplasia (NRH). Clinical staging was assigned according to APASL 2024 criteria. Primary outcomes included portal vein thrombosis (PVT), ascites, variceal bleeding, liver transplantation (LT), and mortality. **Results:** Altogether 475 patients met inclusion criteria (median age 35 years; 58.3% male). Baseline stages were Stage I (n = 11, 2.3%), Stage II (n = 45, 9.5%), Stage III (n = 229, 48.2%), and Stage IV (n = 190, 40.0%). The predominant histopathological features were OPV:347 (73.1%) and OPV-F:71 (14.9%). Over a median follow-up of 6 years, transplant requirement and mortality were significantly higher in Stage 4. Independent predictors of clinically significant new onset events included baseline spleen size for

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PVT (HR 1.11, 95% CI 1.01–1.21; p = 0.028), serum albumin for ascites (HR 0.64; 95% CI 0.441–0.934; p = 0.020), and baseline LSM for variceal bleeding risk (HR 1.056; 95% CI 1.039–1.073; p < 0.001). Independent predictors of mortality and transplant requirement included age (HR 1.05; 95% CI 1.01–1.10; p = 0.024), histological OPV-F/ISC pattern (HR 4.7; 95% CI 2.4–9.3; p < 0.001), and serum albumin (HR 0.33; 95% CI 0.14–0.78; p = 0.012). **Conclusion:** APASL based staging system clearly identified that early-stage NCPF patients follow a largely uneventful course for years, whereas advanced-stage patients carry a substantial risk of complications. The OPV-F/ISC histology correlates with a higher-risk subgroup, likely to develop complications early.



Disclosures: Omkar Rudra:Nothing to Disclose, Chhagan Bihari:Nothing to Disclose, Akash Shukla:Nothing to Disclose, Babu Lal Meena:Nothing to Disclose, Archana Rastogi:Nothing to Disclose, Ajay Duseja:Nothing to Disclose, Shiv Kumar Sarin:Nothing to Disclose.

1682 | INCIDENCE AND MANAGEMENT OF ISCHEMIC HEPATITIS ("SHOCK LIVER") AND PATTERNS OF N-ACETYLCYSTEINE UTILIZATION IN CRITICALLY ILL ADULTS: A RETROSPECTIVE STUDY

Elan Adhami[1] Paul Alvarez[1] Davis Kuruvilla[1] Amanda Julia-Rios[1] John Nahas[1] Aya Akhras[1] Waseem Wahood[2] Samer Wahood[3] Arthur Martinyan[4] Bernardo Reyes[1], [1]HCA Florida Aventura Hospital, [2]University of Miami, [3]Warren Alpert Medical School, [4]FIU Herbert Wertheim College of Medicine

Background: Ischemic hepatitis is an acute liver injury caused by hepatic hypoperfusion and is associated with substantial morbidity and mortality in critically ill patients. Although N-acetylcysteine (NAC) has demonstrated benefit in select causes of acute liver failure, evidence supporting its use in ischemic hepatitis remains limited. This study evaluated outcomes associated with NAC administration in patients with ischemic hepatitis requiring intensive care. **Methods:** We conducted a retrospective cohort study using the TriNetX database. Adult patients (> 18 years old) with ischemic hepatitis were identified using laboratory criteria of alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) ≥ 1000 U/L with lactate dehydrogenase (LDH) ≥ 3750 U/L in the setting of hypotension or ICU-level critical illness. Patients with other causes of liver injury, including cirrhosis, viral hepatitis, alcoholic liver disease, toxic liver injury, acetaminophen toxicity, liver trauma, or prior liver transplantation, were excluded. Cohorts were stratified by receipt of intravenous NAC. Propensity score matching was performed to balance demographics and comorbidities. Outcomes assessed within 30 days included all-cause mortality, vasopressor utilization, and hospital readmission. Kaplan-Meier survival and risk analyses were performed, with p < 0.05 considered significant. **Results:** A total of 4,114 patients were included in this study, including 3,847 patients with no NAC exposure and 267 patients treated with NAC. After propensity score matching, 264 patients remained in each cohort. Baseline demographics and comorbidities were well balanced following matching. There was no significant difference in 30-day mortality between cohorts that were and were not treated with NAC (48.2% vs 51.2%; OR 1.13, 95% CI 0.77–1.66; p = 0.529). Kaplan-Meier analysis similarly demonstrated no significant survival difference (HR 1.09, 95% CI 0.83–1.44; p = 0.655). Vasopressor utilization was also similar between groups (28.8% vs 23.5%; OR 0.76, 95% CI 0.31–1.83; p = 0.540), with no difference in the number of vasopressor-use instances (p = 0.765). Notably, patients receiving NAC had significantly higher rates of hospital readmission compared with patients who did not receive NAC (61.7% vs 50.4%; OR 0.63, 95% CI 0.45–0.89; p = 0.009). **Conclusion:** In this large real-world analysis of critically ill patients with ischemic hepatitis, NAC administration was not associated with improved short-term mortality, survival probability, or vasopressor requirements. NAC use was associated with increased hospital readmission rates. These findings do not demonstrate a clear clinical benefit for NAC in ischemic hepatitis and underscore the need for prospective studies to better define its therapeutic role in this high-risk population.

Disclosures: Elan Adhami:Nothing to Disclose, Paul Alvarez:Nothing to Disclose, Davis Kuruvilla:Nothing to Disclose, Amanda Julia-Rios:Nothing to Disclose, John Nahas:Nothing to Disclose, Aya Akhras:Nothing to Disclose, Waseem Wahood:Nothing to Disclose, Samer Wahood:Nothing to Disclose, Arthur Martinyan:Nothing to Disclose, Bernardo Reyes:Nothing to Disclose.

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1683 | CIRCULATING FIBRONECTIN REFLECTS DISEASE SEVERITY AND PREDICTS VARICEAL BLEEDING IN ADVANCED CHRONIC LIVER DISEASE

Georg Kramer[1] Irina Lie-Ungurean[2] Mathias Jachs[2] Lorenz Balcar[2] Benedikt Hofer[2] Lukas Hartl[2] Paul Thoene[2] Marlene Hintersteininger[2] Philipp Schwabl[1] Michael Trauner[2] Mattias Mandorfer[1] Thomas Reiberger[1] Benedikt Simbrunner[1], [1]Medical University of Vienna, [2]Medical University of Vienna, Vienna, Austria

Background: Fibronectin is an extracellular matrix protein with roles in hemostasis, immune signaling, and tissue repair. Its clinical relevance in advanced chronic liver disease (ACLD), however, remains incompletely defined. We therefore evaluated whether circulating fibronectin reflects major pathophysiological domains of ACLD and whether it is associated with subsequent decompensation-related outcomes. **Methods:** Patients with ACLD undergoing hepatic venous pressure gradient (HVPG) measurement were prospectively included, and serum fibronectin levels were assessed at the same time point. Associations between fibronectin and pathophysiological biomarkers were evaluated using correlation analyses and systems modeling. Associations with clinical outcomes were assessed using competing-risk regression models. **Results:** The study cohort comprised 298 patients with a median HVPG of 17 mmHg (IQR 12-21) and a median MELD 3.0 of 12 (IQR 9-17). Fibronectin levels were lower in decompensated compared with compensated ACLD (30.3 vs. 38.8 µg/mL; $p < 0.001$). Fibronectin correlated with markers of hepatic synthesis, particularly cholinesterase (Spearman's $r = 0.64$; $p < 0.001$), and was inversely correlated with MELD 3.0 ($r = -0.47$; $p < 0.001$). While fibronectin was inversely associated with the enhanced liver fibrosis (ELF) score, a marker of extracellular matrix remodeling, in univariable analysis ($r = -0.20$; $p < 0.001$), ELF showed an independent positive association after adjustment for liver function and portal hypertension (standardized $\beta = 0.19$; $p < 0.001$). In systems modeling, hepatic synthetic function was the main determinant of fibronectin variance, with cholinesterase accounting for 37%, followed by fibrinolysis, represented by antiplasmin (14%), and ELF (12%). Higher fibronectin levels were independently associated with variceal bleeding (adjusted subdistribution hazard ratio [aSHR] 4.46; $p = 0.038$), whereas lower fibronectin levels predicted portal vein thrombosis (aSHR 0.20; $p = 0.023$), after adjustment for HVPG, MELD 3.0, or IL-6. No association was observed with other hepatic decompensation events or liver-related mortality. **Conclusion:** Circulating fibronectin correlates with hepatic synthetic capacity and extracellular matrix remodeling and is associated with hemorrhagic and thrombotic complications in ACLD, suggesting that fibronectin may serve as a marker of disturbed hemostatic balance in ACLD.

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1684 | ESTABLISHMENT AND VALIDATION OF A RISK PREDICTION MODEL FOR PORTAL VEIN THROMBOSIS IN PATIENTS WITH HEPATIC CIRRHOSIS

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Background: Portal vein thrombosis (PVT) is a serious complication of liver cirrhosis associated with increased morbidity and mortality. Reliable prediction tools to identify high-risk patients in clinical practice remain

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limited. **Methods:** We retrospectively enrolled 1,463 cirrhotic patients admitted to Sichuan Provincial People's Hospital (January 2018–May 2025), including 133 with PVT and 1,330 without PVT. A total of 99 candidate variables—spanning demographics, comorbidities, medications, laboratory parameters, imaging findings, and liver function scores—were evaluated. Following feature selection, 10 predictors were retained. Six feature-selection methods were combined with seven machine-learning (ML) algorithms (logistic regression, Gaussian naïve Bayes, K-nearest neighbors, support vector machine, GBDT, XGBoost, LightGBM) to construct PVT risk models. Model performance was assessed by 10-fold cross-validation and an independent test set using AUC, accuracy, precision, recall, F1-score, Brier score, calibration curves, and decision curve analysis (DCA). Subgroup analyses were performed by sex, disease severity, splenectomy status, non-selective beta-blocker (NSBB) use, and antithrombotic therapy. SHAP (SHapley Additive exPlanations) values were used for model interpretability. **Results:** The XGBoost model with random forest feature selection achieved the best performance: AUC 0.942 (95% CI 0.912–0.966), recall 0.825, F1-score 0.600, and Brier score 0.073. Subgroup analyses demonstrated robust discrimination across most strata; sensitivity was modestly reduced in patients with low MELD scores, post-splenectomy status, and NSBB use. SHAP analysis identified the top predictors as: alpha-fetoprotein, esophageal varices, Child–Pugh class, fibrinogen, portal vein diameter, sex, procoagulant agent use, diuretic use, bacterial infection, and splenomegaly. **Conclusion:** A machine learning-based model integrating clinical, laboratory, and imaging variables demonstrated excellent discriminative performance (AUC 0.942) for PVT prediction in cirrhotic patients. An interpretable web-based tool was developed to facilitate risk stratification and guide individualized prevention strategies. External multicenter validation is warranted.

Disclosures: fengjiao kang:Nothing to Disclose, yuan Bian:Nothing to Disclose, Feng Guo:Nothing to Disclose.

1685 | CT-BASED

Yanna Liu[1] Qian Yu[2] Yanglan He[1] Ying Han[1] Hui Liu[1] Chunlei Fan[1] Yanjing Wu[1] A-Juan Zeng[1] Jing Chang[1] Shuzhen Wang[1] Qi Li[1] Yijie Yan[1] Xueying Liang[1] Keke Jin[1] Lingna Lv[1] Yadi Li[1] Fuquan Liu[3] Yu Wang[4] Calvin Pan[5] Huiguo Ding[1], [1]Beijing Youan Hospital, [2]Southeast University, [3]Beijing Shijitan Hospital, [4]Beijing Friendship Hospital, [5]NYU Langone Health, NYU School of Medicine

Background: Porto-sinusoidal vascular disorder (PSVD) is a major cause of non-cirrhotic portal hypertension impacting patient prognosis. Differentiating PSVD from cirrhosis remains challenging due to overlapping clinical features and routine imaging findings. We aimed to develop and validate a CT-based radiomics model, termed *r*PSVD, for differentiating PSVD from cirrhosis, specifically focusing on patients with inconclusive LSM results. **Methods:** This retrospective, multicenter diagnostic study (2010–2023) included 600 portal hypertension patients (200 PSVD, 400 cirrhosis) with CT scans and liver biopsies. Patients were allocated into training cohort (n = 237), internal (n = 234), and external cohorts (n = 129). The *r*PSVD model utilized liver and spleen features selected via minimum redundancy maximum relevance and least absolute shrinkage and selection operator algorithms (Figure A). The primary outcome was diagnostic accuracy, assessed by area under the receiver operating characteristic curve (AUC) and compared with liver stiffness measurement (LSM) using DeLong's test. **Results:** The primary outcome, *r*PSVD performance, achieved AUCs of 0.85 (95% CI, 0.80–0.90), 0.82 (0.76–0.88), and 0.80 (0.70–0.89) in the training, internal, and external validation cohorts, respectively. Combining *r*PSVD and LSM improved performance over LSM alone (AUC 0.91 vs. 0.85, $P < 0.05$) (Figure B&C). In the LSM "gray zone" (10–20 kPa), *r*PSVD significantly outperformed LSM (AUC 0.83 vs. 0.69, $P < 0.05$) and demonstrated higher clinical net benefit in decision-analytic evaluations. **Conclusion:** The CT-based *r*PSVD model is a novel and non-invasive toll for differentiating PSVD from cirrhosis. It provides significant diagnostic value for portal hypertension patients, especially as a secondary test for the target population where LSM results are indeterminate.

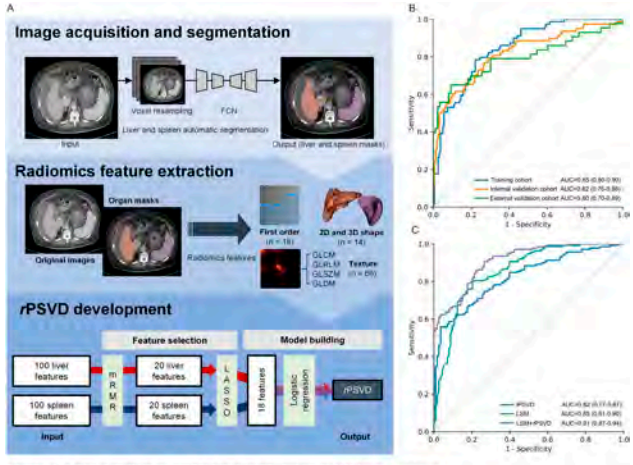


Figure. CT-based radiomics model for distinguishing PSVD from cirrhosis.
(A) Flow chart for development of *r*PSVD. (B) ROC curves of the *r*PSVD in the training, internal validation, and external validation cohorts. (C) ROC curves comparing *r*PSVD, LSM-only, and the combined *r*PSVD+LSM models. FCN, fully convolutional networks; mRMR, minimum redundancy maximum relevance; LASSO, least absolute shrinkage and selection operator; *r*PSVD, CT-based radiomics model for porto-sinusoidal vascular disorder; ROC curve, the receiver operating characteristic curve; AUC, area under the receiver operating characteristic curve; LSM, liver stiffness measurement.

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1686 | DIAGNOSTIC ACCURACY OF NON-INVASIVE TESTINGS (NITS) FOR FONTAN-ASSOCIATED LIVER DISEASE (FALD): A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS

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Background: Fontan-associated liver disease (FALD) causes progressive liver fibrosis and is a key driver of morbidity following the Fontan operation. Although liver biopsy remains the gold standard for liver fibrosis assessment, it is invasive and impractical for routine monitoring. This network meta-analysis (NMA) compared the diagnostic accuracy of non-invasive tests (NITs) such as magnetic resonance elastography (MRE), vibration-controlled transient elastography (VCTE), and serum-based biomarkers for detecting advanced fibrosis in FALD. **Methods:** We conducted a systematic review of studies indexed in MEDLINE, Scopus, and CENTRAL from inception to 31 March 2026. NMA was performed to compare the diagnostic accuracy of NITs for fibrosis assessment in FALD. Studies using liver biopsy or MRE as the reference standard were included. Reported AUCs were pooled using random-effects models with restricted maximum likelihood estimation and stratified by test. Network ranking was performed using AUC as the effect measure, with higher values indicating superior diagnostic performance. Publication bias was assessed using a comparison-adjusted funnel plot. **Results:** Of 1,510 screened articles, seven studies with 633 participants were included. Six and one studies used liver biopsy and MRE as the reference standard. However, only studies using liver biopsy as the reference were included in meta-analysis. Overall, NITs demonstrated modest diagnostic accuracy for advanced FALD, with a pooled AUROC of 0.66 (95% CI: 0.61–0.72). In the network analysis, MRE yielded the highest accuracy with an AUROC of 0.74 (95% CI: 0.59–0.89: SUCRA 0.9), followed by APRI (AUROC 0.68, 95% CI: 0.59–0.77: SUCRA 0.7), FIB-4 (AUROC 0.66, 95% CI: 0.58–0.75: SUCRA 0.6), and VCTE (AUROC 0.65, 95% CI: 0.47–0.83: SUCRA 0.6). SWE demonstrated the lowest diagnostic performance (AUROC 0.48, 95% CI: 0.31–0.66: SUCRA 0.2). **Conclusion:** Non-invasive testings (NITs) showed modest diagnostic accuracy for detecting advanced fibrosis in Fontan-associated liver disease (FALD). MRE demonstrated the best overall diagnostic performance and ranked highest in the network analysis. APRI, an easily available serum-based score, also showed relatively good performance and may be used as a screening tool in patients with Fontan operation. FIB-4 and VCTE demonstrated modest diagnostic accuracy, while SWE showed the lowest performance.

Table 1. League table of non-invasive tests for advanced FALD using liver biopsy as reference.

0.65 (0.47,0.83)	0.48 (0.31,0.66)	0.74 (0.59,0.89)	0.66 (0.58,0.75)	0.68 (0.59,0.77)
VCTE	-0.17 (-0.42,0.09)	0.09 (-0.14,0.33)	0.01 (-0.19,0.22)	0.03 (-0.17,0.23)
	SWE	0.26 (0.03,0.49)	0.18 (-0.01,0.37)	0.20 (0.00,0.39)
		MRE	-0.08 (-0.25,0.09)	-0.06 (-0.24,0.11)
			FIB-4	0.02 (-0.11,0.14)
				APRI

Disclosures: Buddhida Kijdamrongwattanakul:Nothing to Disclose, Tanawat Jongraksak:Nothing to Disclose, Amarit Tansawet:Nothing to Disclose, Pongphob Intaraprasong:Nothing to Disclose, Sarita Ratana-Amornpin:Nothing to Disclose, Tarinee Tangcharoen:Nothing to Disclose, Alisa Limsuwan:Nothing to Disclose, Abhasnee Sobhonslidsuk:Nothing to Disclose.

1687 | TRANEXAMIC ACID-ASSOCIATED HEPATIC VENO-OCCLUSIVE DISEASE/SINUSOIDAL OBSTRUCTION SYNDROME: A FAERS DISPROPORTIONALITY ANALYSIS (1987-2025)

Fidan Gurbanzade[1] Meki Çakmak[2] Alara Apa[1], [1]Acibadem Mehmet Ali Aydinlar University School of Medicine, [2]Bahcesehir University School of Medicine

Background: Tranexamic acid (TXA), a synthetic analog of amino acid lysine, is a potent antifibrinolytic agent. While it is approved by Food and Drug

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Administration (FDA) for heavy menstrual bleeding and prevention of bleeding episodes in hemophilia patients undergoing dental procedures, its prophylactic use to reduce hemorrhage has been widely adopted across surgical specialties. However, emerging case reports have suggested a potential association between TXA exposure and hepatic veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS), raising concerns regarding a potential thrombotic safety signal. This study aims to evaluate the association between tranexamic acid exposure and VOD/SOS using the FDA Adverse Event Reporting System (FAERS) database. **Methods:** This was an observational, retrospective and pharmacovigilance study based on FAERS, between January 1987 and December 2025. Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms were used to determine the reaction term, venoocclusive liver disease. Products included in the analysis were Tranexamic Acid (G), Tranexamic Acid (P), and Tranexamic Acid In Sodium Chloride (P). Demographics, indications and outcomes were descriptively summarized. Reporting odds ratio (ROR) with 95% confidence intervals (CI) was calculated to evaluate the disproportionality. An ROR > 1.0 with lower 95% CI above 1.0 was considered significant, pointing to a signal. **Results:** There were 17 reports of VOD/SOS linked to TXA, all occurred after 2020. A significant disproportionality signal was identified: ROR 28.43 (95% CI 17.64 to 45.82); thresholds were met. Cases predominantly involved pediatric patients, with a median age of 56 months; with sex not specified in 82%. Three separate cohorts were determined after stratification by outcome severity: life-threatening events (n = 11) were observed in an age range of 22 months to 59 years with various indications; all hospitalized cases (n = 2) had co-reactions and none of them received TXA as monotherapy; other serious outcomes (n = 4) occurred exclusively in preschoolers and toddlers, two of whom received TXA during hematopoietic stem cell transplantation (HSCT) conditioning for neuroblastoma. Established VOD/SOS-associated agents, particularly busulfan and melphalan, were concomitantly reported in 11 cases (65%), representing a potential source of confounding. Hemorrhage was the leading indication (78%) for tranexamic acid use in this cohort. **Conclusion:** FAERS analysis identified a significant disproportionality signal for VOD/SOS in association with tranexamic acid. Given the inherent limitations of spontaneous reporting systems, these findings should be interpreted cautiously. Further research is required to establish causality. Nevertheless, the potential association with VOD/SOS should be carefully considered during tranexamic acid administration for hemorrhage prophylaxis.

Disclosures: Fidan Gurbanzade:Nothing to Disclose, Meki Çakmak:Nothing to Disclose, Alara Apa:Nothing to Disclose.

1688 | EFFICACY AND SAFETY OF DIRECT ORAL ANTICOAGULANTS IN BUDD–CHIARI SYNDROME AFTER ENDOVASCULAR INTERVENTION: A PROPENSITY SCORE-MATCHED ANALYSIS

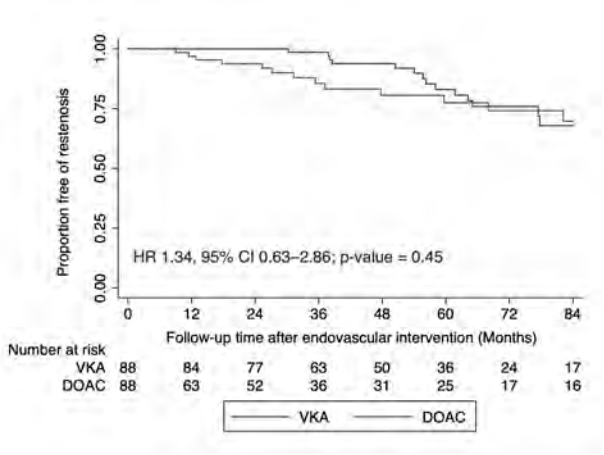
Ayush Agarwal[1] Ankush Garg[1] Shubham Jain[1] Sarthak Saxena[1] Sejal Kotwani[1] Vishal Chauhan[1] Samagra Agarwal[1] Sagnik Biswas[1] Shalimar Shalimar[1], [1]All India Institute of Medical Sciences, New Delhi

Background: Anticoagulation is essential to maintain vessel patency following endovascular intervention in Budd–Chiari syndrome (BCS). Vitamin K antagonists (VKAs) are limited by the need for regular monitoring, while direct acting oral anticoagulants (DOACs) have emerged as potential alternatives, but data in BCS are scarce. We aimed to compare the efficacy and safety of DOACs versus VKAs in patients with BCS following endovascular intervention. **Methods:** We performed a retrospective analysis of a prospectively maintained database of patients with BCS who underwent endovascular intervention at a tertiary care centre in North India. Patients receiving DOACs were compared with those receiving VKAs using propensity score matching (nearest neighbour matching in a 1:1 ratio with a caliper of 0.05), incorporating age, sex, and type of venous obstruction. Outcomes assessed included restenosis and bleeding events. **Results:** A total of 176 patients were included, with 88 patients each receiving DOACs and VKAs. Baseline characteristics were similar between groups (median age 34 [27–40] years; 48% male; level of obstruction: inferior vena cava 2%, hepatic vein 35%, and combined 63%). Among patients receiving DOACs, 55 received dabigatran, 27 apixaban, and 6 rivaroxaban, while all patients in the VKA group received acenocoumarol. Follow-up duration was longer in the VKA group than in the DOAC group (53.8 [IQR 34.7–74.4] months vs 25.3 [IQR 8.1–52.0] months). Restenosis rates were similar in the DOAC and VKA groups (14.8% [95% CI 8.8–23.7] vs 15.9% [95% CI 9.7–25.0]; HR 1.34, 95% CI 0.63–2.86; P = 0.45). Bleeding rates were also similar in the DOAC and VKA groups (20.5% [95% CI 13.3–30.0] vs 30.7% [95% CI 22.0–41.0]; HR 1.18, 95% CI 0.65–2.16; P = 0.58). The proportion of patients experiencing major bleeding (8.0% in the DOAC group vs 12.5% in the VKA group, P = 0.32) was also similar between the two groups. **Conclusion:** DOACs demonstrated comparable efficacy and safety to VKAs in patients with BCS following endovascular intervention, offering a practical

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alternative when maintaining a therapeutic INR is challenging. Future prospective studies are warranted to determine optimal anticoagulation strategies in these patients.



Disclosures: Ayush Agarwal:Nothing to Disclose, Ankush Garg:Nothing to Disclose, Shubham Jain: Nothing to Disclose, Sarthak Saxena:Nothing to Disclose, Sejal Kotwani:Nothing to Disclose, Vishal Chauhan:Nothing to Disclose, Samagra Agarwal:Nothing to Disclose, Sagnik Biswas:Nothing to Disclose, Shalimar Shalimar:Nothing to Disclose.

1689 | BETWEEN CLOT AND BLEED: LOW-MOLECULAR-WEIGHT VERSUS UNFRACTIONATED HEPARIN AND 2-, 7-, AND 28-DAY SAFETY OUTCOMES IN ICU-LEVEL CIRRHOSIS

Chimezirim Ezeano[1] David Kramer[2] Rodolfo Alpizar-Rivas[1], [1]Aurora Healthcare, [2]Aurora Health Care

Background: ICU-level patients with cirrhosis have competing thrombotic and bleeding risks, and the safest pharmacologic prophylaxis strategy remains uncertain. We compared short-term bleeding and mortality among patients receiving low-molecular-weight heparin (LMWH) versus unfractionated heparin (UFH). **Methods:** We performed a retrospective TriNetX cohort study of adults aged 18–75 years with ICD-10-coded cirrhosis. ICU-level care was defined by critical-care CPT charges 99291/99292. LMWH included enoxaparin or dalteparin; UFH included injectable heparin. Follow-up began at the first qualifying prophylaxis exposure among patients with ICU-level care, with exposure occurring within 2, 7, or 28 days after a critical-care charge. Other antithrombotic exposures, heparin flushes, and continuous heparin infusions were excluded around index. The primary outcome was coded bleeding; the secondary outcome was all-cause mortality. Venous thromboembolic events were assessed but were not reportable. Propensity score matching was performed separately for each window; no-antithrombotic comparator cohorts were exploratory. **Results:** Pre-match LMWH/UFH: 3,710/4,658 (2d), 3,692/4,699 (7d), 3,717/4,767 (28d); exploratory no-antithrombotic cohorts: 19,452, 18,115, and 17,129. Matched: 3,076, 3,094, and 3,132 per arm before outcome-specific exclusions. LMWH had lower bleeding at 2d (3.0% vs 4.8%; RD -1.7% [-2.8, -0.6]; RR 0.6; HR 0.6; $p = 0.002$), 7d (3.0% vs 5.5%; RD -2.5% [-3.7, -1.4]; RR 0.5; HR 0.5; $p < 0.001$), and 28d (4.5% vs 6.7%; RD -2.3% [-3.6, -1.0]; RR 0.7; HR 0.7; $p = 0.001$). Mortality was lower for LMWH at 2d (1.2% vs 4.8%; RD -3.6% [-4.5, -2.8]; RR 0.3; HR 0.2), 7d (2.8% vs 8.0%; RD -5.2% [-6.3, -4.1]; RR 0.4; HR 0.3), and 28d (6.1% vs 13.1%; RD -7.0% [-8.4, -5.5]; RR 0.5; HR 0.4; all $p < 0.001$). Exploratory: LMWH had lower 28-day mortality than no-antithrombotic (7.0% vs 10.5%; RR 0.7; $p < 0.001$), whereas UFH did not (21.4% vs 19.9%; RR 1.1; $p = 0.14$). **Conclusion:** Among prophylaxed ICU-level patients with cirrhosis, LMWH was associated with lower coded bleeding and mortality than UFH across all windows. Prophylaxis choice reflects clinician judgment about competing thrombotic and bleeding risks; early 2-day separation suggests residual confounding and selection bias rather than treatment effect alone. This supports the need for prospective studies in this patient group. Limitations include code-defined cirrhosis and ICU-level care, residual confounding, and around-index exclusions; these data address safety and survival, not thromboprophylactic efficacy.

Disclosures: chimezirim ezeano:Nothing to Disclose, David Kramer:Nothing to Disclose, Rodolfo Alpizar-Rivas:Nothing to Disclose.

1690 | ENDOTHELIAL DYSFUNCTION RATHER THAN PROCOAGULANT STATE IS INDEPENDENTLY ASSOCIATED WITH FIBROGENESIS AND DISEASE PROGRESSION IN ADVANCED CHRONIC LIVER DISEASE

Paula Höfinger[1] Benedikt Simbrunner[1] Ida Villesen[2] Georg Kramer[1] Lorenz Balcar[1] Bernhard Scheiner[1] Rodrig Marculescu[1] Michael Trauner[1] Morten Karsdal[3] Thomas Reiberger[1] Diana Leeming[3] Ton Lisman[4] Mattias Mandorfer[1] Georg Semmler[1], [1]Medical University of Vienna, Vienna, Austria, [2]Odense University Hospital, Odense, Denmark; University of Southern Denmark, Odense, Denmark, [3]Nordic Bioscience, Herlev, Denmark, [4]University of Groningen, Groningen, The Netherlands

Background: Advanced chronic liver disease (ACLD) is characterized by a rebalanced hemostatic system. Experimental studies suggest that a procoagulant state may promote hepatic fibrogenesis and disease

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progression, however clinical evidence linking endogenous thrombin potential (ETP) to fibrogenesis on a cross-sectional or disease progression on a longitudinal level remains limited.Therefore, we investigated the association between biomarkers of coagulation and endothelial dysfunction on the one hand and fibrogenesis on the other hand, while accounting for portal hypertension severity by adjusting for hepatic venous pressure gradient (HVPG). Moreover, direct clinical endpoints were evaluated. **Methods:** This retrospective study includes 138 patients with ACLD undergoing paired HVPG measurement at the Vienna Hepatic Hemodynamic Laboratory between 2017 and 2020. Biomarkers of coagulation (ETP by thrombomodulin-modified thrombin generation assay and thrombin–antithrombin complex) and endothelial dysfunction (VWF antigen) as well as extracellular matrix remodeling/fibrogenesis (ProC3, ProC4, ProC6, and ELF test) were assessed from blood samples obtained at the time of HVPG measurement. Spearman and HVPG-adjusted partial Spearman correlation analyses as well as univariable Cox regression (in cACLD, the endpoint was first hepatic decompensation, whereas in dACLD the endpoint was liver-related death) analyses were performed. **Results:** Among 138 patients, 52 (37.7%) had cACLD and 86 (62.3%) had decompensated cirrhosis. ETP correlated significantly with ELF (r_s = 0.22, p = 0.012), whereas no significant associations were observed with ProC3, ProC4, or ProC6. TAT was not associated with markers of fibrogenesis. In contrast, VWF showed significant correlations with ProC3 (r_s = 0.20, p = 0.018), ProC6 (r_s = 0.26, p = 0.002), and ELF (r_s = 0.44, p < 0.001). However, after adjustment for disease stage (HVPG) using partial Spearman correlation analyses, ETP and TAT showed no correlation to markers of fibrogenesis, whereas VWF remained significantly associated with ProC6 and ELF. Finally, ETP (HR 1.18, p = 0.129) and TAT (HR 0.81, p = 0.147) were not associated with risk of hepatic decompensation/liver-related death. **Conclusion:** After adjustment for liver disease severity, thrombin generation capacity (ETP) and coagulation activation (TAT) were no longer associated with biomarkers of fibrogenesis in ACLD, whereas endothelial dysfunction (VWF) remained independently associated with ECM remodeling. Whether the latter is due to causal interference (e.g., hepatic sinusoidal crosstalk) or a common cause (e.g., systemic inflammation) remains to be determined.

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1691 | TPO RECEPTOR AGONISTS VERSUS PLATELET TRANSFUSION FOR PROCEDURAL THROMBOCYTOPENIA IN CIRRHOSIS: A PROPENSITY-MATCHED COHORT STUDY

Archana Salek[1] Jashanveer Johal[1] Bianca Patel[1] Mahmoud Al-Bataineh[1] Brandon Cunha[1] Abdallah Hussein[1] Jason Hyman[2] Yecheskel Schneider[1], [1]Virtua Health, [2]Einstein Medical Center, Philadelphia

Background: Thrombocytopenia is a common complication of cirrhosis and frequently defers or complicates invasive hepatic procedures. Platelet transfusion has historically been the standard peri-procedural strategy, but TPO receptor agonists (TPO-RAs) — including romiplostim, eltrombopag, avatrombopag, and lusutrombopag — offer an oral alternative for procedural platelet optimization. Real-world comparative data on downstream outcomes between these strategies remain limited. **Methods:** We conducted a propensity score–matched retrospective cohort study using the TriNetX Global Collaborative Network (191.9 million patients). Cohort 1 included cirrhotic patients with thrombocytopenia who underwent invasive hepatic procedures (liver biopsy, paracentesis, or portal decompression procedures) and received a TPO-RA within 6 months prior to the procedure, excluding prior HCC, liver transplant, ITP, and ESRD. Cohort 2

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comprised matched patients receiving platelet transfusion within 1 month prior to the same procedures. 1:1 propensity score matching (PSM) yielded 160 patients per arm. Outcomes assessed over a 6–120 monthfollow-up window included GI bleeding, blood transfusion, hepatic encephalopathy (HE), and all-cause mortality, analyzed by measures of association (MOA) and Kaplan-Meier (KM) survival analysis. **Results:** After PSM, cohorts were well-balanced across demographic and comorbidity variables. GI bleeding occurred in 30.6% of the TPO-RA arm versus 34.4% of the platelet transfusion arm (RR 0.89; 95% CI 0.65–1.22; p = 0.47); KM analysis showed a trend toward improved event-free survival with TPO-RA use (HR 0.79; 95% CI 0.54–1.16; p = 0.24). Blood transfusion rates were 40.0% vs. 48.8% (RR 0.82; p = 0.12), with a KM HR of 0.72 (p = 0.055) favoring TPO-RAs. HE occurred in 41.9% vs. 46.3% (RR 0.91; p = 0.43; HR 0.83; p = 0.27). All-cause mortality was 50.0% in the TPO-RA arm versus 58.1% in the platelet transfusion arm (RR 0.86; p = 0.14), with a median survival of 389 vs. 224 days and a KM HR of 0.80 (p = 0.15). **Conclusion:** In this propensity-matched cohort of cirrhotic patients with thrombocytopenia undergoing invasive hepatic procedures, TPO-RA use was associated with consistently lower point estimates across GI bleeding, blood transfusion requirement, HE, and all-cause mortality compared to platelet transfusion, including a near-significant reduction in transfusion burden (p = 0.055) and a 165-day median survival advantage. While no outcome reached statistical significance, likely reflecting the modest cohort size post-matching, the directional consistency of these findings supports the hypothesis that procedural platelet optimization with TPO-RAs may confer clinical benefit beyond simple platelet count elevation. Larger, prospective trials are warranted to validate these observations and define optimal agent selection and timing in this population.

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1692 | *NOT JUST DVT: A RARE CASE OF PORTAL VEIN THROMBOSIS ASSOCIATED WITH HORMONE THERAPY*

Teresa Del Rio Montesinos[1] Teresa Montesinos Roig[2], [1]Virginia Mason Medical Center, [2]Hostos Medical Service

Background: Hormone replacement therapy (HRT) is an established treatment for menopausal symptoms, and evolving regulatory guidance from FDA has expanded therapeutic options for women. As the use of HRT increases, it is important to recognize its potential adverse effects. Well-documented complications include cardiovascular disease, venous thromboembolism (VTE), and endometrial cancer. However, portal vein thrombosis (PVT) is a rare and underreported complication. We present the case of a female patient who was initiated on HRT and subsequently developed PVT, with portosystemic changes. The condition was identified early and managed promptly; however, if left untreated, it could have resulted in significant morbidity or mortality. **Methods:** Patient presented with abdominal fullness and postprandial reflux of acute onset. Baseline laboratory studies were obtained, including CBC and CMP. The CMP revealed abnormalities, including alkaline phosphatase (ALP) 489 U/L, aspartate aminotransferase (AST) 78 U/L, and alanine aminotransferase (ALT) 125 U/L. This prompted a comprehensive hepatic evaluation, which demonstrated an elevated gamma-glutamyl transferase (GGT) of 205 U/L and 5′-nucleotidase of 22 U/L. An abdominal US with splenomegaly. This was followed by a four-phase contrast-enhanced computed tomography (CT) scan of the liver, which revealed chronic portal vein thrombosis (PVT) with porta hepatis, and small gastroesophageal varices. **Results:** A 60 yo F with no pmhx, was initiated on HRT for menopausal symptom of joint pain. Her regimen consisted of oral progesterone 200 mg daily and transdermal estrogen 0.05 mg/day. She had been on this therapy for 6 months prior to the onset of symptoms. Laboratory and imaging confirmed chronic PVT and anticoagulation therapy was initiated with DOAC and HRT was stopped. An EGD performed 3 months after initiation of treatment demonstrated resolution of previously noted varices. **Conclusion:** This case highlights a rare but clinically significant complication of HRT in a patient without prior thrombotic risk factors. While estrogen-containing therapies are known to increase the risk of VTE, thrombosis at atypical sites such as the portal venous system remains poorly characterized and likely underrecognized. Although PVT is rarely reported with menopausal HRT, available evidence suggests hormonal therapy may precipitate thrombosis in unusual vascular territories even in the absence of other risk factors. This case underscores the importance of maintaining a high index of suspicion in patients presenting with nonspecific abdominal symptoms while on HRT. Early recognition and prompt anticoagulation are essential to prevent complications and increased morbidity and mortality. As HRT use grows, clinicians should evaluate thrombotic risk and estrogen route. Further research is needed to clarify this association and guide care.

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Disclosures: Teresa Del Rio Montesinos:Nothing to Disclose, Teresa Montesinos Roig:Nothing to Disclose.

1693 | RARE BUT RISING: TWO DECADES OF U.S. HOSPITALIZATIONS FOR BUDD–CHIARI SYNDROME

Azfar Hameed[1] Diana Chavez Velasquez[2] Zakia Hameed[3] Jorge Chavez Velasquez[2], [1]Hendrick Medical Center, [2]Universidad Privada Antenor Orrego, [3]CMH Institute of Medical Sciences, Bahawalpur, Pakistan

Background: Budd-Chiari syndrome (BCS) is an uncommon but life-threatening hepatic venous outflow obstruction, frequently linked to prothrombotic disorders, myeloproliferative neoplasms, and oral contraceptive exposure. Heterogeneous presentation contributes to delayed diagnosis. Although Doppler ultrasonography is recommended first-line, published performance estimates vary. We synthesized epidemiology, diagnostic accuracy, etiologies, and treatment outcomes to clarify global burden and real-world results. **Methods:** Multi-source evidence synthesis included: meta-analysis of global incidence and prevalence (6 studies, Europe/Asia); US National Inpatient Sample trend analysis (1998–2017); meta-analysis of imaging accuracy versus venography/surgery (11 studies); nationwide South Korea cohort (2009–2013, n = 424); French national multicenter survey (48 centers); US single-center outcomes cohort (n = 23); and prospective Egyptian outcomes registry (n = 194; TIPS sub-cohort). **Results:** Pooled annual incidence was 1 per million (95% CI 0.225–3) and pooled prevalence 11 per million (95% CI 4–21). US hospitalization rates rose from 4.96 to 10.44 per million from 1998 to 2017 (annual percentage change +4.41%). In South Korea, prevalence was 5.29 per million with female:male ratio 1.8, median age 51 years, and annual case-fatality 2.8%. In France, leading etiologies were myeloproliferative neoplasms (48%), oral contraceptives (35%), and factor V Leiden (16%). In the US cohort, 82% developed ascites, 35% underwent TIPS, and 44% required liver transplantation. Doppler ultrasound pooled sensitivity was 89% (95% CI 81–94%) with specificity 68%, comparable to CT sensitivity 89% (95% CI 77–95%). Ascites typically demonstrates SAAG > 1.1 g/dL with high protein. In the Egyptian registry, post-TIPS 1-year survival was 89.7% with 1-year shunt patency 80.2%. **Conclusion:** BCS is a rare vascular liver disease with an annual incidence of approximately 1 per million globally, yet its hospitalization rate in the US has more than doubled over two decades, underscoring increasing clinical recognition. The condition predominates in women of reproductive age, with myeloproliferative neoplasms, oral contraceptive use, and inherited thrombophilias as the principal modifiable and identifiable risk factors that must be systematically excluded at diagnosis. Doppler ultrasonography is the appropriate first-line modality with sensitivity near 89%, and a high SAAG ascitic fluid profile should prompt immediate vascular imaging even in the absence of classic peritoneal signs. TIPS achieves durable one-year survival approaching 90%, with liver transplantation reserved for refractory cases. Untreated BCS progresses to end-stage liver failure within approximately three years, making early diagnosis a critical determinant of survival.

Etiology and outcomes by published cohort

Parameter	Value	Cohort / n	Source
Myeloproliferative neoplasm (France)	48%	French national survey, 48 centers	[1]
Oral contraceptive use (France)	35%	French national survey	[1]
Factor V Leiden (France)	16%	French national survey	[1]
Myeloproliferative neoplasm (US cohort)	57%	US single-center, n=23	[2]
Required TIPS (US cohort)	35%	US single-center, n=23	[2]
Required liver transplantation (US cohort)	44%	US single-center, n=23	[2]
SAAG in BCS ascites	>1.1 g/dL + protein >2.5 g/dL	Published guideline review	[3]
South Korea: female-to-male ratio	1.8 : 1; median age 51 yrs	Nationwide, n=424	[1]
South Korea: annual case-fatality rate	2.8%	Nationwide, n=424	[1]
Untreated BCS: progression to liver failure	~3 years	Published natural history data	[4]

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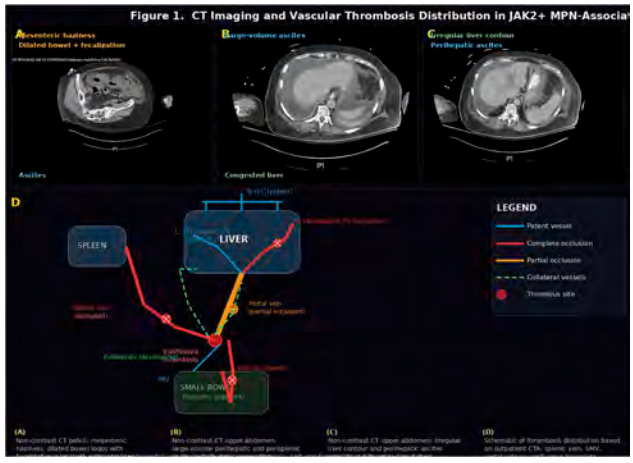
1694 | EXTENSIVE PORTAL-MESENTERIC VENOUS THROMBOSIS FROM OCCULT JAK2-POSITIVE MYELOPROLIFERATIVE NEOPLASM PRESENTING AS SMALL BOWEL OBSTRUCTION WITH BOWEL NECROSIS

Arshiya Shabnam[1] Utsav Patel[1] Prathima Guntipalli[1] DIsha Patel[1] Rayees Konduru[1], [1]New york medical college

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Background: Portal-mesenteric venous thrombosis (PMVT) secondary to JAK2-positive myeloproliferative neoplasms (MPNs) is a recognized but underdiagnosed entity. However, presentation as acute bowel necrosis requiring emergent surgery — with the MPN entirely occult at the time of thrombotic catastrophe — remains rarely reported. Thrombotic complications may precede hematologic diagnosis by months to years, as characteristic blood count elevations can be masked by portal hypertension, hepatic ischemia, or acute illness, making early recognition clinically challenging. **Methods:** We report a single case of extensive PMVT secondary to an occult JAK2-positive MPN presenting as acute SBO with bowel necrosis. Clinical, laboratory, operative, and follow-up data were reviewed from the inpatient and outpatient medical record. **Results:** A 70-year-old female with hypothyroidism and hypertension presented with acute altered mental status, nausea, vomiting, and abdominal distension. Initial labs revealed hyponatremia (Na 122), hyperkalemia (K 6.3), AKI(Cr 2.55), and markedly elevated ammonia (238 mcmol/L). Notably, Hb was 17.1 g/dL, Hct 51.6%, and platelets 675,000/mcL — findings consistent in retrospect with an underlying MPN. CT abdomen/pelvis showed mesenteric haziness, dilated bowel loops with fecalization, and large-volume ascites (Figure 1A–C). She was intubated and initiated on vasopressors. Given hemodynamic deterioration, emergent exploratory laparotomy revealed 1.9L of murky peritoneal fluid and a 20 cm segment of ischemic, nonviable jejunum adherent to the sigmoid colon with extensive adhesions. Small bowel resection with primary anastomosis was performed. The postoperative course was complicated by septic shock, shock liver (AST 458, ALT 433, ammonia 546 mcmol/L), and AKI without need for RRT. Outpatient workup confirmed JAK2 V617F mutation. Bone marrow biopsy established a diagnosis of polycythemia vera, more likely than prefibrotic primary myelofibrosis. Repeat CTA demonstrated chronic occlusion of the splenic and superior mesenteric veins, partial portal vein occlusion, and evolving collateral formation (Figure 1D). Fibroscan showed S3 steatosis with F2 fibrosis. She was initiated on hydroxyurea 500 mg twice daily and apixaban 5 mg twice daily. **Conclusion:** Finally, PMVT should prompt a thorough thrombophilia workup including JAK2 mutation testing, even in the absence of overt hematologic abnormalities as the progression from MVT to bowel necrosis can be rapid and life-threatening, requiring a low threshold for surgical exploration in patients with peritoneal signs. The complex interplay between the prothrombotic, pro-inflammatory, and endothelial-activating effects of the JAK2 mutation underscores the need for continued research into targeted therapies that address the vascular pathology of MPNs beyond conventional anticoagulation and cytoreduction.



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2002 | HEPATOCYTE P53–LIF AXIS DRIVES INFLAMMATORY CELL RECRUITMENT AND EXACERBATES ACUTE LIVER FAILURE.

Jihyun Sung[1] Yuki Makino[1] Seiya Kato[2] Yasuharu Kawamoto[1] Yoichi Sasaki[1] Kenji Fukumoto[1] Yuta Myojin[1] Kazuhiro Murai[1] Yoshinobu Saito[3] Hayato Hikita[3] Takahiro Kodama[4], [1]Department of Gastroenterology and Hepatology, The University of Osaka Graduate School of Medicine., [2]The University of Osaka, [3]Osaka University Graduate School of Medicine, [4]Osaka University

Background: Acute liver failure (ALF) is characterized by massive hepatocyte death, with no effective treatment except liver transplantation. We previously reported that constitutive activation of p53 in hepatocytes induces cell death, resulting in liver fibrosis and carcinogenesis; however, its role in ALF remains unknown. This study aims to define the role of p53 in ALF. **Methods:** RNA-seq analysis of human ALF liver (GDS4387) was performed using the Gene Expression Omnibus (GEO). Acetaminophen (APAP) or anti-Fas antibodies were used to induce ALF in mice. Genetically engineered mouse models included hepatocyte-specific Mdm2-deficient mice (Alb-CreER Mdm2fl/fl + tamoxifen; Mdm2Δhep), Mdm2/p53 double-deficient mice (Alb-CreER Mdm2fl/fl p53fl/fl + tamoxifen; Mdm2/p53Δhep), and Lif-deficient mice (LIF+/-). Human samples included liver biopsy samples (54 ALF and 48 controls for mRNA, 8 ALF for CosMx spatial transcriptomics), and serum samples (54 ALF and 68 controls). Hepatocyte cell lines (HepG2, BNL CL.2), a hepatic stellate cell line (LX-2), and a liver sinusoidal endothelial cell line (TMNK-1) were used for in vitro experiments. **Results:** In the GEO dataset, Hallmark p53 pathway was upregulated in ALF patients. In APAP- and anti-Fas antibody–treated mice, hepatic p53 protein and CDKN1A mRNA levels were increased, indicating activation of the p53 pathway. In Mdm2Δhep mice, p53 activation caused extensive hepatocyte death, elevated ALT and bilirubin levels, increased infiltration of CD11b positive-positive macrophages, and 100% mortality within 7 days. These phenotypes were completely rescued by p53 co-deletion. Single-cell RNA-seq and cytokine assays demonstrated robust induction of inflammatory cytokines, such as Lif, Ccl2, IL6 and IL8, in hepatocytes, non-parenchymal cells, and serum. According to the RNA-seq, Lif was the most prominently upregulated cytokine in the liver of Mdm2Δhep mice. Lif expression was consistently increased in Mdm2Δhep, APAP, and anti-Fas models, as well as in human ALF at both mRNA and serum levels. In vitro, Mdm2 inhibitor (Nutlin-3) increased Lif expression, whereas p53 knockdown suppressed it in HepG2 and BNL CL.2. ChIP-PCR confirmed direct binding of p53 to the Lif promoter. Recombinant Lif induced cytokine expression and amplified Lif production in LX-2 and TMNK-1 cells, indicating activation of non-parenchymal cells. In APAP and anti-Fas models, Lif-deficient mice showed improved outcomes with reduced CD11b-positive macrophage infiltration, while antibody-mediated CD11b depletion attenuated ALF severity. Spatial transcriptomics revealed that Lif-expressing hepatocytes form inflammatory clusters, where CCL2, IL6, and IL8-expressing LSECs and HSCs, along with CD11b-positive cells, were spatially co-localized. **Conclusion:** Hepatocyte p53 activation drives ALF progression through LIF upregulation. p53–LIF axis could be a novel therapeutic target in ALF.

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2003 | HIF-1α INHIBITION IN MACROPHAGES PROTECTS AGAINST ACUTE LIVER FAILURE

Zhifu Xie[1] Jingya Li[2], [1]Shanghai Institute of Materia Medica, [2]SIMM

Background: Acute liver failure (ALF) is a life-threatening condition characterized by excessive inflammatory responses that drive hepatocyte death and disease progression. Hypoxia-inducible factor-1α (HIF-1α), a stress-responsive transcription factor in macrophages, promotes the production of pro-inflammatory cytokines such as interleukin-1β (IL-1β). IL-1β, through activation of its receptor (IL-1R) on hepatocytes, induces apoptosis and necrosis, thereby exacerbating liver injury. The therapeutic potential of pharmacological HIF-1α inhibition in ALF remains unclear. **Methods:** Bone marrow–derived macrophages (BMDMs) were employed evaluate the effects of the HIF-1α inhibitor PX-478 on inflammatory cytokine production. An established lipopolysaccharide/D-galactosamine (LPS/D-GalN)-induced ALF mouse model was used to assess the hepatoprotective efficacy of PX-478, administered alone or in combination with a TNFα-neutralizing antibody under both preventive and therapeutic regimens. In parallel, a phytochemical investigation of Phyllanthus franchetianus was conducted to isolate and structurally characterize bioactive constituents. The anti-inflammatory activities of the isolated compounds were evaluated in vitro, and the hepatoprotective effect of the lead compound was subsequently validated in vivo. **Results:** PX-478 selectively suppressed the expression and secretion of IL-1β in BMDMs without affecting TNFα production, which indicates a targeted disruption of the IL-1β-driven inflammatory axis rather than a non-specific broad immunosuppressive effect. In vivo experiments demonstrated that pretreatment with PX-478 markedly attenuated liver injury in lipopolysaccharide/D-galactosamine (LPS/D-GalN)-induced ALF mice, accompanied by a substantial reduction in hepatic inflammatory responses. This finding supports an important role of macrophage HIF-1α in mitigating cytokine storm-mediated liver injury. Furthermore, both preventive and therapeutic administration of PX-478 in combination with TNFα neutralization exerted a synergistic effect, which significantly improved the survival rate and alleviated liver injury in ALF mice. In parallel, we identified PKC-2a, a novel HIF-1α inhibitor isolated from the Chinese medicinal plant Phyllanthus franchetianus. In vitro studies showed that PKC-2a treatment reduced the transcription and secretion of IL-1β, while in vivo experiments confirmed that PKC-2a conferred robust hepatoprotective activity at a low dose (3 mg/kg, oral administration, once daily). **Conclusion:** Pharmacological HIF-1α inhibition (PX-478, PKC-2a) alleviates ALF by targeting IL-1β, with PKC-2a being a promising natural lead for treating inflammation-driven liver injury. **Disclosures:** ZHIFU XIE: Nothing to Disclose, Jingya Li: Nothing to Disclose.

2004 | RECOMBINANT ADAMTS13 AMELIORATES LIVER INJURY AND IMPROVES HEPATIC MICROCIRCULATION IN A MURINE ACUTE-ON-CHRONIC LIVER FAILURE MODEL

Norihisa Nishimura[1] Kosuke Kaji[1] Shinya Sato[1] Akihiko Shibamoto[1] Yui Osaki[1] Hitoshi Mori[1] Tadashi Namisaki[1] Hitoshi Yoshiji[1], [1]Nara Medical University

Background: Acute-on-chronic liver failure (ACLF) is a distinct clinical condition characterized by sudden liver failure in patients with pre-existing chronic liver disease, leading to high short-term mortality. However, effective medical therapies for ACLF remain limited. We have previously reported that an imbalance in the a disintegrin-like and metalloprotease with thrombospondin type 1 motif 13 (ADAMTS13) / von Willebrand factor (vWF) axis contributes to disease progression in liver cirrhosis and exacerbates acute kidney injury associated with ACLF. We also found that recombinant ADAMTS13 (rAD) improves renal injury in an ACLF-like mouse model. In this study, we investigated whether rAD exerts direct therapeutic effects on ACLF-like liver injury. **Methods:** Male C57BL/6J mice were subjected to chronic carbon tetrachloride (CCl_4) administration followed by acute CCl_4 and lipopolysaccharide challenge to induce ACLF-like liver injury. Mice were assigned to control, ACLF, and ACLF + rADAMTS13 groups. Plasma ADAMTS13 activity, VWF antigen, platelet counts, hepatic and renal microcirculatory blood flow, histological changes, and hepatic gene expression were evaluated. Endothelial tube formation assays were performed using human umbilical vein endothelial cells under oxidative stress conditions. **Results:** Compared with untreated ACLF mice, rAD-treated mice showed significant improvements in liver weight, serum AST and ALT levels, platelet counts, serum albumin levels, and hepatic tissue blood flow. Immunohistochemical analysis revealed marked vWF upregulation and excessive platelet aggregation in ACLF mice, which were significantly suppressed by rAD administration. Inflammatory cytokine expression, including TNF-α, IL-1β, and IL-6, as well as infiltration of F4/80-positive inflammatory cells, were markedly reduced in the rAD group. Hepatocellular necrosis and apoptosis were attenuated by rAD treatment. In contrast, CD34-positive endothelial cells and A6-positive hepatic progenitor cells, indicative of angiogenesis and liver regeneration, were

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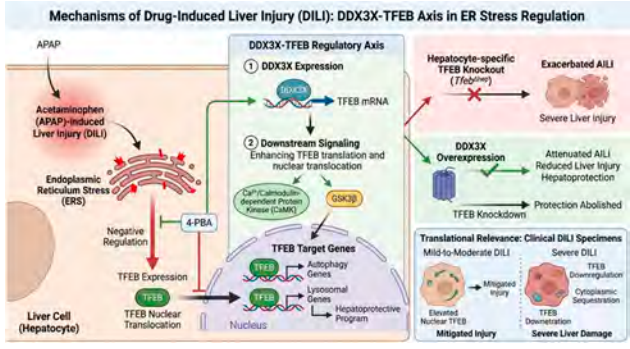
significantly increased in rAD-treated mice. *In vitro*, rADAMTS13 partially restored impaired tube formation and increased *VEGFA* and *VEGFR2* expression in HUVECs exposed to oxidative stress. **Conclusion:** Recombinant ADAMTS13 ameliorates liver injury in ACLF by suppressing excessive platelet aggregation, improving hepatic microcirculation, and attenuating inflammation, while promoting angiogenesis and liver regeneration. Given its current clinical availability, rAD may represent a promising therapeutic option for hepatoprotection in ACLF.

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2006 | ENDOPLASMIC RETICULUM STRESS ORCHESTRATES THE DDX3X-TFEB AXIS IN DRUG-INDUCED LIVER INJURY

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Background: Drug-induced liver injury (DILI) remains a major clinical challenge lacking effective therapeutic options. While endoplasmic reticulum stress (ERS) is implicated in DILI pathogenesis, the underlying regulatory mechanisms remain elusive. This study investigated the role of transcription factor EB (TFEB) in ERS regulation during DILI and characterized its upstream regulatory pathways. **Methods:** Using a murine model of acetaminophen (APAP)-induced liver injury (AILI), we characterized ERS markers, assessed biochemical and histopathological injury severity, and monitored TFEB expression dynamics. To modulate ERS activity, we employed pharmacological intervention (4-PBA) genetic approaches, and using hepatocyte-specific TFEB knockout (TfebΔhep) mice, as well as TFEB knockdown and overexpression strategies to regulate the expression of TFEB. Bioinformatics analysis (GTEx), RNA immunoprecipitation (RIP), and clinical DILI specimens were utilized to elucidate the molecular machinery and translational relevance. **Results:** Pharmacological inhibition of ERS with 4-PBA attenuated liver injury and enhanced TFEB expression and nuclear localization. Genetically, TfebΔhep mice exacerbated APAP-induced injury, whereas TFEB overexpression or genetic rescue of TfebΔhep mice was highly protective. We identified dynamic expression of the expression of DDX3X during AILI; DDX3X knockdown aggravated injury, while its overexpression protected against it. Mechanistically, DDX3X directly bound to TFEB mRNA to enhance its translation and nuclear translocation via Ca^{2+}/calmodulin-dependent protein kinase (CaMK) and GSK3β signaling. Crucially, TFEB knockdown completely abolished the hepatoprotection conferred by DDX3X overexpression. In clinical DILI specimens, hepatic TFEB expression inversely correlated with injury severity; mild-to-moderate cases exhibited elevated nuclear TFEB, whereas severe DILI featured TFEB downregulation and cytoplasmic sequestration. **Conclusion:** ERS drives DILI progression by suppressing TFEB expression and nuclear translocation. The DDX3X-TFEB axis represents a novel regulatory pathway wherein DDX3X exerts robust hepatoprotection by promoting TFEB translation and nuclear localization. These findings position the DDX3X-TFEB axis as a promising therapeutic target and suggest TFEB subcellular dynamics as a potential diagnostic biomarker for DILI.



Disclosures: Ling Xu: Nothing to Disclose, Yao Gao: Nothing to Disclose, Zihao Fan: Nothing to Disclose, Feng Ren: Nothing to Disclose.

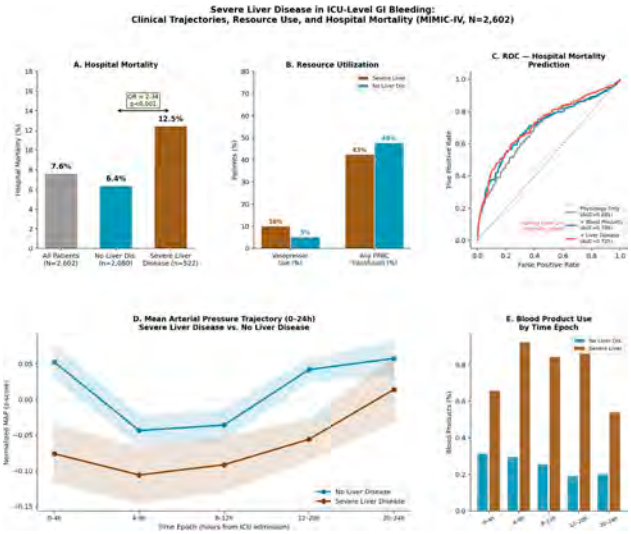
2007 | HEMODYNAMIC INSTABILITY AND SEVERE LIVER DISEASE SYNERGISTICALLY PREDICT ICU MORTALITY IN GI BLEEDING: A TIME-SERIES ANALYSIS

Innocent Lutaya[1] Brian Xu[1] Vicki Oladoyin[1] Theophilus Boakye[1] Shanelle Brodeur[1] Emmanuel marfo[1] Nicolas Bakinde[1] Abisola Ajayi[1] Shaikhoon Mohammed[1] Chima Amadi[1], [1]Morehouse School of Medicine

Background: Gastrointestinal (GI) bleeding in patients with severe liver disease (SLD) carries substantially higher mortality than GI bleeding in patients without liver disease, driven by portal hypertension, coagulopathy, and impaired hemodynamic reserve. Bedside monitors generate continuous hemodynamic data, but this information is rarely used to predict outcomes. We leveraged time-series hemodynamic data from the Trajectory of Floor-to-ICU Monitoring (TFM) dataset to determine whether MAP instability, combined with severe liver disease markers, improves

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mortality prediction in ICU patients with GI bleeding. **Methods:** We analyzed the TFM ICU Trajectories dataset, which is a high-frequency multi-parameter ICU monitoring database containing vital signs sampled at 1 to 5 minute intervals for up to 24 hours post-ICU admission. Adult ICU patients with GI bleeding were stratified by SLD status (ICD-coded cirrhosis, portal hypertension, or hepatic failure). Hemodynamic trajectories including heart rate variability (HRV), mean arterial pressure (MAP) variability, vasopressor use, and transfusion requirements were compared. The primary outcome was in-hospital mortality. Multivariable logistic regression with Area Under the Receiver Operating Characteristic curve (AUROC) analysis was used to evaluate predictive performance. **Results:** Among 2,602 ICU patients with GI bleeding, 522 (20.1%) had severe liver disease. SLD patients had significantly higher in-hospital mortality (12.5% vs. 6.4%, $p < 0.001$), greater vasopressor use (10.2% vs. 5.2%, $p < 0.001$), lower MAP variability (SD 0.55 vs. 0.59, $p < 0.001$), and more blood product transfusions ($p = 0.024$). In multivariable logistic regression adjusting for hemodynamic parameters, SLD independently predicted mortality (aOR 1.89, 95% CI 1.30-2.74; $p = 0.001$). The combined hemodynamic + SLD model achieved an AUROC of 0.725, significantly outperforming SLD status alone (AUROC 0.691). **Conclusion:** Severe liver disease independently doubles mortality risk in ICU-admitted GI bleeding patients, with distinct hemodynamic signatures characterized by reduced MAP variability and higher vasopressor requirements. High-frequency hemodynamic data substantially improves mortality prediction, suggesting that real-time monitoring could help identify the highest-risk patients earlier.



Disclosures: Innocent Lutaya: Nothing to Disclose, Brian Xu: Nothing to Disclose, Vicki Oladoyin: Nothing to Disclose, Theophilus Boakye: Nothing to Disclose, Shanelle Brodeur: Nothing to Disclose, Emmanuel marfo: Nothing to Disclose, Nicolas Bakinde: Nothing to Disclose, Abisola Ajayi: Nothing to Disclose, Shaikhoon Mohammed: Nothing to Disclose, Chima Amadi: Nothing to Disclose.

2008 | LARSUCOSTEROL DECREASES MORTALITY IN LPS ENDOTOXEMIA BY REVERSING PROMOTER HYPERMETHYLATION

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Background: Lipopolysaccharide (LPS) drives systemic inflammation and organ injury in experimental endotoxemia. We newly show that LPS acutely induces global promoter CpG hypermethylation, a response largely mediated by DNA methyltransferase-1 (DNMT1). Larsucosterol (25HC3S, DUR928) is an endogenous DNMT1 inhibitor. The current study aim to confirm that larsucosterol reduces mortality in LPS-induced endotoxemia by reversing promoter hypermethylation and restoring pro-survival transcriptional programs. **Methods:** THP-1 cells were differentiated to macrophages with PMA, pretreated with larsucosterol (20 μM, 0.5 h) or vehicle, then exposed to LPS (2 μg/mL, 6 h). Global methylation (LINE-1), promoter CpG methylation of apoptosis/mitochondrial-stress pathways (MAPK; calcium/AMPK), DNMT1 activity, reactive oxygen species (ROS), and expression of PGC-1α and COX-2 were measured. RNA-seq profiled LPS ± larsucosterol effects. In vivo, C57BL/6J mice received LPS to induce endotoxemia and were treated with vehicle or Larsucosterol; survival was monitored to 72 h and liver injury biomarkers (AST, ALT, alkaline phosphatase) were assessed. An independent fecal-suspension polymicrobial sepsis model (16S-validated composition) provided orthogonal validation. **Results:** LPS significantly increased global DNA methylation in macrophages (LINE-1). RNA-seq showed broad reprogramming with 2,722 genes upregulated and 2,731 downregulated, enriched across more than 50 KEGG pathways. Larsucosterol attenuated LPS-induced transcriptional activation, suppressing cytokine–cytokine receptor interaction, MAPK, NOD-like receptor, TNF, and Toll-like receptor signaling pathways. Mechanistically, larsucosterol shifted promoter methylation toward demethylation at anti-apoptotic and mitochondrial-stability genes, reduced DNMT1 activity, lowered oxidants including malondialdehyde (MDA), increased PGC-1α, and decreased COX-2 under LPS/TNFα challenge. In LPS endotoxemia, larsucosterol improved survival versus vehicle and reduced biochemical and histologic liver injury. In

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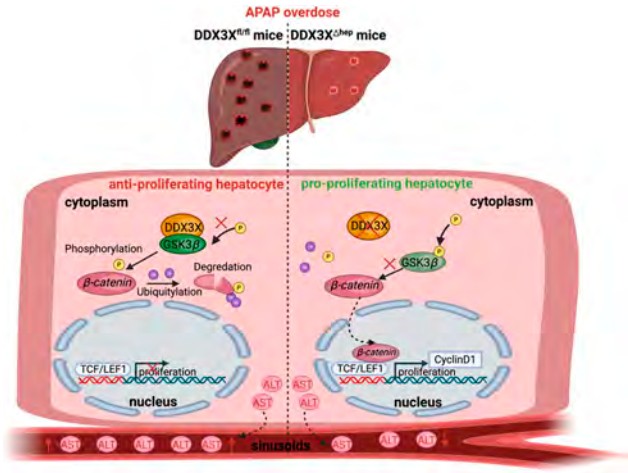
the polymicrobial model, controls reached 100% mortality by 14 h, whereas larsucosterol delayed the first death to 26 h, produced at least one complete survivor, and lowered AST/ALT with minimal change in alkaline phosphatase. **Conclusion:** LPS induces endotoxemia by increasing DNA promoter CpG methylation and suppressing anti-apoptotic gene expression. Larsucosterol decreases the LPS-induced promoter CpG methylation and increases the gene expression involved in pro-survival, mitochondrial integrity, reducing oxidative stress, and improves survival in vitro and in vivo sepsis models. These findings indicate that larsucosterol has the potential to serve as an endogenous epigenetic regulator for treating endotoxemia and sepsis.

Disclosures: Yaping Wang: Nothing to Disclose, Kevin Ren: Nothing to Disclose, Shunlin Ren: Bausch Health Company: Royalties, Bausch-Durect has licensed our patents..

2009 | DDX3X-GSK3β INTERACTION REGULATES LIVER REGENERATION AND RECOVERY FROM ACETAMINOPHEN-INDUCED LIVER INJURY IN MICE

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Background: Drug-induced liver injury is a global health concern, with acetaminophen (APAP)-induced liver injury (AILI) accounting for the majority of cases. Liver regeneration is a critical process in AILI, but the underlying mechanism remains unknown. Here, we investigate the role of DEAD-box helicase 3 X-linked (DDX3X) in liver regeneration after AILI in mice. **Methods:** Liver injury was induced in C57BL/6J mice via APAP (300 mg/kg or 500 mg/kg) overdose. Hepatocyte-specific DDX3X knockout ($DDX3X^{\Delta Hep}$), DDX3X overexpression ($DDX3X^{OE}$) and control ($DDX3X^{fl/fl}$) mice were utilized. Primary hepatocytes and AML-12 cell lines were treated with APAP (20 mM). The expression of DDX3X and its impact on APAP metabolism were measured in mice. Liver injury and regeneration were evaluated after APAP administration. **Results:** Our results revealed hepatic DDX3X expression were upregulated during the early stages of AILI in mice. At 24 hours post-APAP overdose in mice, DDX3X deficiency markedly promoted liver regeneration, as evidenced by increased expression of proliferative markers, including PCNA and Ki67. DDX3X deficiency did not alter the expression of CYP2E1 or hepatic glutathione. Both in vivo and in vitro experiments demonstrated that DDX3X deficiency promoted the phosphorylation of glycogen synthase kinase-3β (GSK-3β) at Ser9 and enhanced β-catenin signaling. In contrast, DDX3X overexpression impaired liver regeneration and suppressed β-catenin signaling in AILI mice. Furthermore, pharmacological inhibition of GSK3β using SB216763 in DDX3XOE mice partially rescued β-catenin signaling and liver regeneration compared with DDX3XOE mice alone. Mechanistically, cytoplasmic colocalization of GSK3β and DDX3X was observed in AML-12 cells and gradually diminished following APAP exposure. This interaction inhibits the phosphorylation of GSK3β at Ser9. **Conclusion:** DDX3X deficiency promotes liver regeneration in AILI by relieving GSK3β inhibition and activating β-catenin signaling. This DDX3X-GSK3β-β-catenin axis thus represents a critical molecular mechanism and a promising therapeutic target for liver regeneration and recovery.



Disclosures: Zihao Fan: Nothing to Disclose, Yinkang Mo: Nothing to Disclose, Jihui Jia: Nothing to Disclose, Ling Xu: Nothing to Disclose, Feng Ren: Nothing to Disclose.

2010 | INFLUENCE OF XENOGENEIC MISMATCH ON HEPATOCYTE CELL THERAPY EFFICACY

Sophie Cazanave[1] Sunil Mallanna[1] Morgan Jamiel[1] Krista Farrington[1] Marcus Lehmann[1] Abhijith Kudva[1] Krina Shah[1] David Broderick[1] Konstantinos Chatziantoniou[1] Julie Morse[1] Tom Lowery[1] Arnav Chhabra[1], [1]Satellite Bio

Background: Hepatocyte transplantation is a promising therapy for liver-based metabolic disorders. Expanded human hepatocytes (EHH), derived from primary human hepatocytes (PHH) retain key hepatic functions and show in vivo activity comparable to PHH in FRG (Fah−/−, Rag2−/−, IL-2RG−/−) mice.

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However, defining the minimum effective engraftment level for human liver cell therapy remains a major barrier to clinical translation, as dose prediction based on preclinical models is confounded by species mismatch effects. Addressing these limitations is essential for accurately translating hepatocyte-based therapies to patients. **Methods:** EHH, PHH and primary mouse hepatocyte (PMH) cells or vehicle media were injected into female FRG mice via intrasplenic injection. We performed a dose-response study with cells in which we varied the duration of NTBC cycling to achieve a range of liver repopulation levels, and therefore different effective engrafted levels (ELs) at the start of NTBC withdrawal from EL1 up to EL3. Engraftment was confirmed by human albumin or immunohistochemistry (IHC). Liver function upon NTBC withdrawal was evaluated by blood biomarkers (ALT, BUN, Bilirubin, Albumin and Prothrombin time (PT)) and animal survival. The minimum EL was extrapolated based on FAH IHC, normalized to cells per kilogram and contextualized against biological activity readouts. **Results:** Increasing levels of engraftment of PHH or EHH were confirmed by plasma human albumin levels at ~0.024 mg/mL at EL1, ~0.286 mg/mL at EL2 and ~5.8 mg/mL at EL3. Upon NTBC withdrawal, we observed a clear relationship between EL and efficacy when compared to non-repopulated vehicle controls (survival $p < 0.0001$, albumin $p < 0.0001$, BUN $p = 0.0083$, PT $p = 0.0004$, bilirubin $p = 0.091$, ALT $p = 0.32$). When estimating the minimum engraftment level required for efficacy, we found that high doses of human cells (> 360 million cells/kg) were required to achieve measurable rescue in FRG mice. Dose-response engraftment of PMH was assessed by FAH-positive staining which represented ~0.37% at EL1, 1.17% at EL2 and 9.31% at EL3 of the total liver area. In contrast to human cells, PMH demonstrated significant improvement in survival and blood biomarkers (survival $p < 0.0001$, albumin $p < 0.0001$, BUN $p = 0.0062$, PT $p < 0.0001$, bilirubin $p < 0.0001$, ALT $p < 0.0001$), upon relatively short NTBC cycling times (20-30 days compared to 75-150 days for EHH and PHH). A minimum engraftment level of 28 million cells/kg of PMH, almost 10-fold lower than PHH or EHH, was required to achieve a comparable benefit in the FRG model, consistent with doses shown to be efficacious in prior clinical case studies. **Conclusion:** This study illustrated the impact of species mismatch on efficacy in nonclinical studies. It also highlighted that cross-species transplantation (human-to-mouse) requires higher repopulation thresholds, underscoring the importance of species-matched data for translation of clinical dose levels.

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2011 | ACUTE LIVER FAILURE IN INDIA, 1986–2025: ETIOLOGICAL TRENDS, CLINICAL PROFILE, AND OUTCOMES — A SYSTEMATIC ANALYSIS OF 6,382 PATIENTS FROM 85 STUDIES

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Background: Acute liver failure (ALF) in India is predominantly driven by infectious etiologies, in sharp contrast to Western registries where acetaminophen and indeterminate etiologies predominate. The etiological and epidemiological spectrum of ALF in India has evolved considerably over time This study characterizes the etiology, biochemical profile, and outcomes of ALF in India over nearly four decades, with particular emphasis on drug-induced liver injury (DILI). **Methods:** A comprehensive literature search was conducted across major electronic databases. We identified 85 published studies and case reports from India (1986–2025) encompassing 6,382 patients with ALF. Demographics, biochemical parameters (bilirubin, INR, creatinine, and MELD score), etiology, DILI causative agents, hospital stay, mortality, and liver transplantation rates were systematically extracted and analyzed. **Results:** A total of 6,382 patients were identified. Mean age was 26 years, MELD score 32, total bilirubin 11.8 mg/dL, INR 3.8, serum creatinine 1.5 mg/dL, and hospital stay 7.6 days. Overall mortality was 37% (2,357/6,382), and liver transplantation was performed in only 323 patients (5.1%).A striking temporal rise in Hepatitis A-related ALF was observed: of 499 cases reported over 39 years, 279 (56%) occurred in 2023–2025 alone, compared to 220 (44%) in the preceding 37 years (1986–2023), suggesting a rapidly shifting epidemiology.Among 484 DILI cases, 173 resulted in death (35.7%). Anti-tubercular therapy (ATT) was the leading cause (n = 352; 72.7%), accounting for 157 deaths (90.8% of DILI-related mortality). Other causative agents included complementary and alternative medicines (CAM; n = 42; 8.7%), acetaminophen (n = 28; 5.8%), antiepileptics (n = 21; 4.3%), dapsone

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(n = 10; 2.1%), antiretroviral agents (n = 7; 1.4%), and others (n = 24; 5.0%). Case fatality rates by agent were: ATT 45%, antiepileptics 29%, dapsone 20%, acetaminophen 7%, and CAM 5%. Notably, ferrous sulfate (2/2) and pirfenidone (1/1) carried a 100% case fatality rate, though based on limited cases. **Conclusion:** ALF in India is predominantly caused by viral hepatitis, with HEV remaining the leading etiology. A striking recent surge in HAV-related ALF was observed, with 56% of cases occurring in 2023–2025 alone. Undetermined and non A-E hepatitis together account for >35% of cases, representing a critical diagnostic gap. ATT-related DILI dominates drug-induced ALF (72.7%; mortality 45%). Dengue (4%) and Wilson disease (2.4%) are under-recognized causes with significant mortality. Liver transplantation was performed in only 5% which highlights the critical unmet need for expanded transplant access.

Etiology	Total Cases (n)	Total Deaths (n)	Mean MELD score	Mean Age (years)	Mean Bilirubin (mg/dl)	Mean creatinine (mg/dl)
Hepatitis E	1889 (29.6%)	665 (35.2%)	32.8	27.2	17	1.2
Undetermined	1544 (24.2%)	782 (50.6%)	34.4	28.2	15.8	0.8
Non A-E Hepatitis	721 (11.3%)	363 (50.3%)		27.9	23	2.0
DILI	484 (7.6%)	173 (35.7%)	33.4	30.5	9.3	1.1
Hepatitis A	469 (7.3%)	59 (12.6%)	24.1	33.5	18	1.3
Dengue	263 (4.1%)	102 (38.8%)	23.3	26.5	5.5	1.6
Hepatitis B	240 (3.8%)	97 (40.4%)	33.6	25.9	17.9	1.2
Wilson Disease	152 (2.4%)	58 (38.2%)	32.6	20.2	15.8	1.0
Yellow Phosphorus	111 (1.7%)	25 (22.5%)	33.4	24.4	7.4	0.8
Others	509 (8.0%)	Variable				

Disclosures: Aashik Y S: Nothing to Disclose, Yashwanth M: Nothing to Disclose, Ekta Pareek: Nothing to Disclose, Harshad Devarbhavi: Nothing to Disclose.

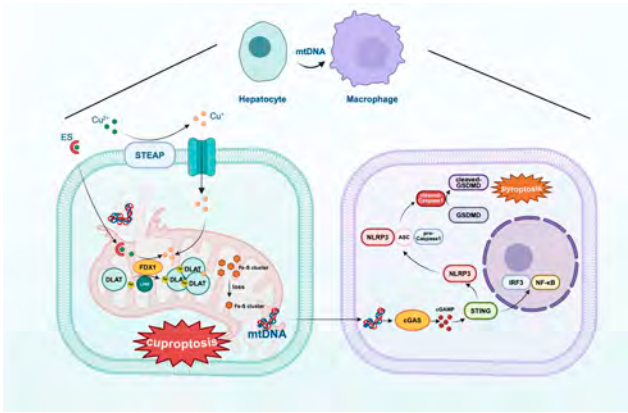
2012 | CUPROPTOSIS PROMOTES ACUTE LIVER FAILURE THROUGH CGAS-STING-ASSOCIATED PYROPTOSIS

Xiaoxuan Liu[1] Qi Yang[1] Li Bai[1] Yu Chen[1] Ming Kong[1] Manman Xu[1] Huixin Tang[2], [1]Beijing YouAn Hospital, Capital Medical University, [2]Department of Gastroenterology, Jining No.1 People's Hospital, Jining

Background: Acute liver failure (ALF) is characterized by massive hepatocyte death and severe inflammatory injury with high short-term mortality. Cuproptosis is a newly identified copper-dependent form of regulated cell death. Previous studies in tumor have shown that cuproptosis may promote mtDNA release and activate the cGAS-STING signaling. In addition, STING activation has been reported to promote pyroptosis. However, whether cuproptosis participates in ALF through cGAS-STING-associated pyroptosis remains unclear. **Methods:** Cuproptosis was induced in hepatocytes using $CuSO_4$ plus elesclomol (Cu-ES) with or without TTM treatment, a specific cuproptosis inhibitor. Cuproptosis levels were assessed by cell viability, WB and qPCR detection for key signaling molecules. In vivo, the extent of hepatic damage and cuproptosis levels were evaluated in D-GalN/LPS-induced ALF mice with or without TTM treatment. mtDNA release was detected in the supernatant of Cu-ES-treated hepatocytes with or without TTM treatment. The levels of cGAS-STING signaling and pyroptosis upon cuproptosis activation were assessed. In addition, pyroptosis levels upon STING activation and inhibition were evaluated. Moreover, the levels of cuproptosis and pyroptosis upon cuproptosis activation plus STING inhibition were detected. Finally, the levels of cuproptosis-STING-pyroptosis axis were analyzed in ALF livers. **Results:** Cell viability in Cu-ES-induced hepatocytes was significantly elevated upon TTM treatment. Cuproptosis-related molecules were downregulated in Cu-ES group, which could be reversed by TTM treatment. TTM pretreatment alleviated liver injury and cuproptosis levels in ALF mice. mtDNA levels were significantly increased in Cu-ES-conditioned medium. In macrophages, Cu-ES-conditioned medium increased the expression of cGAS-STING and pyroptosis-related molecules, which was attenuated by TTM pretreatment. Consistently, cGAS-STING signaling and pyroptosis-related molecules were significantly upregulated in ALF mice and partially reversed by TTM treatment. Moreover, DMXAA promoted, whereas STING-IN-2 suppressed, cGAS-STING signaling and pyroptosis in vitro and in vivo. STING-IN-2 reduced pyroptosis- without affecting cuproptosis-related genes, indicating cGAS-STING acts downstream of cuproptosis. IHC staining showed decreased FDX1 and DLAT, together with increased STING and caspase-1 expression in liver tissues from ALF patients. **Conclusion:** Cuproptosis critically involves in the development of ALF. Cuproptosis triggers cGAS-STING signaling and pyroptosis via mtDNA release. cGAS-STING signaling likely acts downstream of cuproptosis and upstream of pyroptosis. Collectively, cuproptosis promotes ALF by activating STING signaling and pyroptosis. Our work provides novel insights into the molecular mechanisms and potential therapeutic targets of ALF.

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2013 | MORTALITY BENEFIT OF THERAPEUTIC PLASMA EXCHANGE IN ACUTE AND ACUTE-ON-CHRONIC LIVER FAILURE: A SYSTEMATIC REVIEW AND UPDATED META-ANALYSIS

Rohan Karkra[1] Mahinaz Mohsen[1] Joshua Pagan Busigo[1] Michael Bebawy[1] Steven Rella[1] Muhammad Maan[1] Zaid Tafesh[1] Paul Gaglio[1], [1]Rutgers New Jersey Medical School

Background: Acute Liver Failure (ALF) and Acute-on-Chronic Liver Failure (ACLF) are life-threatening syndromes characterized by rapid hepatic deterioration and multiorgan failure. Mortality estimates for ALF without liver transplant are as high as 50% in ALF and 70% in ACLF. Since both syndromes are characterized by a dysregulated systemic cytokine inflammatory response, therapeutic plasma exchange (TPE) has been proposed as a potential therapy. TPE addresses several pathophysiological mechanisms simultaneously by removing circulating endotoxins, pro-inflammatory cytokines, damage-associated molecular patterns, and ammonia, while replenishing coagulation factors and hepatoprotective proteins. We performed a comprehensive systematic review and updated meta-analysis of TPE in ALF and ACLF. **Methods:** We searched PubMed, Embase, and Cochrane from inception through April 15, 2026. Studies comparing TPE (any volume) against standard medical therapy (SMT) in adults with ALF or ACLF were included. Primary outcomes were 30-day and 90-day all-cause mortality. Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using the DerSimonian-Laird random-effects model. Heterogeneity was assessed using Cochran's Q and I^2 statistic. This study conformed to PRISMA guidelines. **Results:** A total of 33 studies were included: 27 in ACLF and 6 in ALF, comprising 5,795 patients (TPE: 2,925; SMT: 2,870). ACLF studies contributed 5,609 patients (TPE: 2,830; SMT: 2,779), while ALF studies contributed 186 patients (TPE: 95; SMT: 91). Among 22 ACLF studies reporting sex data, 83.6% of participants were male (N = 3,755); in ALF studies, 31.2% were male (N = 112).In ACLF, 20 studies (N = 4,256) reported 30-day mortality. Crude mortality was 37.9% (812/2,141) with TPE versus 56.4% (1,192/2,115) with SMT, an absolute risk reduction of 18.5%. Meta-analysis showed significantly lower 30-day mortality with TPE (OR 0.43, 95% CI 0.34–0.54; $p < 0.0001$; $I^2 = 56.2\%$).Nineteen ACLF studies (N = 3,274) reported 90-day mortality. Crude mortality was 49.4% (790/1,598) with TPE versus 62.5% (1,047/1,676) with SMT. TPE was associated with lower 90-day mortality (OR 0.56, 95% CI 0.44–0.72; $p < 0.0001$; $I^2 = 51.5\%$).In ALF, 5 studies (N = 186) reported 30-day mortality. Mortality was 29.5% (28/95) with TPE versus 51.6% (47/91) with SMT. Pooled analysis demonstrated significantly lower mortality with TPE (OR 0.33, 95% CI 0.16–0.66; $p = 0.0017$), with no heterogeneity ($I^2 = 0\%$). **Conclusion:** TPE significantly reduces 30-day mortality in both ALF and ACLF. Evidence of a 90-day survival benefit is present in ACLF. TPE also maintains a transplant-free mortality benefit in ACLF. TPE may be considered as a bridge therapy in patients without immediate transplant access.



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2014 | CLINICAL CHARACTERISTICS OF HEPATITIS E AND RISK FACTORS FOR PROGRESSION TO LIVER FAILURE IN NORTHWEST CHINA

Xiaoqin Hu[1] Yuzhen Zhao[1] Chongyu Zhang[1] Na Huang[1] Yunyu Zhao[1] Yishan Liu[1] Lanting Zhang[1] Fu Wei[2] Fanpu Ji[1] Dou Qu[1], [1]The Second Affiliated Hospital of Xi'an Jiaotong University, [2]Xi'an People's Hospital (Xi'an Fourth Hospital)

Background: Hepatitis E is one of the leading causes of acute viral hepatitis worldwide. However, systematic surveillance, diagnostic tools, and the widespread use of vaccines for this disease remain relatively limited globally.This study aimed to analyze the clinical characteristics of hospitalized patients with hepatitis E in Northwest China and to identify factors associated with progression to liver failure. **Methods:** A retrospective analysis was conducted on 188 patients with hepatitis E admitted to the Second Affiliated Hospital of Xi'an Jiaotong University between January 2009 and September 2025. Liver failure (LF) was defined according to the Chinese liver failure criteria (INR $\geq$ 1.5 or PTA $\leq$ 40%, and TBil $\geq$ 171 μmol/L). Patients were divided into LF and non-LF groups. Baseline demographics, underlying diseases, clinical signs and symptoms, and laboratory parameters at admission were compared between groups. Continuous variables were analyzed using the Mann–Whitney U test, and categorical variables using the chi-square test. Logistic regression was employed to identify independent risk factors for LF progression and for mortality or liver transplantation. **Results:** Among the 188 patients with hepatitis E virus infection, 145 (77.1%) were male, with a mean age of 54.6 ± 14.4 years. The most common clinical manifestations were gastrointestinal symptoms (fatigue, anorexia, nausea) and jaundice (88.3%). Ascites (27.1%) and cholestasis (21.8%) were the most frequent complications. Baseline cirrhosis was present in 17.0% of patients, and 17.0% had HBV co-infection. Liver failure developed in 61 patients (32.5%). Among these, 15 (24.6%) died or underwent liver transplantation (14 deaths, 1 transplant). Compared with non-LF patients, those with LF were older (P = 0.016) and had higher proportions of males (P < 0.001), alcohol consumption (P = 0.021), and cirrhosis (P = 0.002). Multivariable logistic regression identified male sex (OR = 17.29, 95% CI: 2.72–109.97), cirrhosis (OR = 3.62, 95% CI: 1.11–11.76), higher neutrophil count (NEUT, OR = 1.42, 95% CI: 1.17–1.73), and prolonged thrombin time (TT, OR = 1.28, 95% CI: 1.08–1.51) as independent risk factors for LF (table 1). Higher total cholesterol (TC) was protective (OR = 0.35, 95% CI: 0.21–0.58). A predictive model combining these factors achieved an AUC of 0.90 (95% CI: 0.85–0.95). In the LF subgroup, multivariable analysis confirmed INR (OR = 9.09, 95% CI: 1.39–59.37), total bilirubin (TB, OR = 1.01, 95% CI: 1.01–1.02), and cystatin C (CysC, OR = 6.20, 95% CI: 1.29–29.68) as independent predictors of death. **Conclusion:** Male sex, cirrhosis, higher neutrophil count, and prolonged thrombin time predict progression to liver failure in hospitalized patients with hepatitis E. INR, total bilirubin, and cystatin C identify those at high risk of death.

Table1. Univariate and Multivariate Logistic Regression Analysis of Risk Factors for Liver failure in Patients with Hepatitis E

Variables	Univariate		Multivariate	
	OR (95%CI)	P	OR (95%CI)	P
Age	**1.04 (1.01 – 1.06)**	**0.005**		
Male	**8.89 (2.63 – 30.09)**	**<.001**	**17.29 (2.72 – 109.97)**	**0.003**
Cardiovascular disease	1.53 (0.77 – 3.02)	0.223		
Diabetes	1.56 (0.74 – 3.27)	0.243		
Cirrhosis	**3.38 (1.55 – 7.38)**	**0.002**	**3.62 (1.11 – 11.76)**	**0.033**
Hepatitis B	0.94 (0.41 – 2.12)	0.874		
Neutrophil count	**1.25 (1.09 – 1.43)**	**0.001**	**1.42 (1.17 – 1.73)**	**<.001**
Thrombin time	**1.31 (1.16 – 1.49)**	**<.001**	**1.28 (1.08 – 1.51)**	**0.004**
Albumin	**0.86 (0.81 – 0.92)**	**<.001**		
Total cholesterol	**0.30 (0.19 – 0.46)**	**<.001**	**0.35 (0.21 – 0.58)**	**<.001**

Disclosures: Xiaoqin Hu: Nothing to Disclose, Yuzhen Zhao: Nothing to Disclose, Chongyu Zhang: Nothing to Disclose, Na Huang: Nothing to Disclose, Yunyu Zhao: Nothing to Disclose, Yishan Liu: Nothing to Disclose, Lanting Zhang: Nothing to Disclose, Fu Wei: Nothing to Disclose, Fanpu Ji: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Dou Qu: Nothing to Disclose.

2015 | ◆ IMPROVING RISK STRATIFICATION IN ALCOHOL-ASSOCIATED ACLF THROUGH TNF-α-AUGMENTED PROGNOSTIC MODELS

Julian Pohl[1] Cristina Sanchez Garrido[2] Maria Papp[3] Charalampos Pavlidis[4] Paolo Caraceni[5] carlo alessandria[6] Martin Janicko[7] Agustin Albillos[8] Victor

Symbols: ◆, Poster of Distinction; ★, Foundation Award Recipient

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Background: Acute-on-chronic liver failure (ACLF) is associated with high mortality and is frequently precipitated by alcohol-associated hepatitis (AH) or infections. The role of precipitating events in the clinical course of ACLF, as well as the applicability of established prognostic scores, remains incompletely understood but has major implications for therapeutic targets and the design of future clinical trials. The aim of this study was to evaluate biomarkers as predictors of mortality in AH-ACLF with or without concomitant infection. **Methods:** A total of 785 patients with AH from the CANONIC, PREDICT, and ACLARA studies were included. ACLF was defined according to EASL-CLIF and A-TANGO criteria. Baseline characteristics, organ failures, and cumulative incidence were compared. The predictive performance of prognostic scores and cytokine-augmented models was assessed using AUC, Brier score, and cross-validation, with comparisons performed using the DeLong test. AH and infection status were defined by the treating physician; biomarker analyses are therefore exploratory. **Results:** In addition to EASL-CLIF definition, we also applied the A-TANGO definition to assess AH-ACLF, identifying 239 and 316 patients, respectively. AH-ACLF was associated with a high incidence of liver (61.1%) and coagulation (42.7%) failure. Concomitant infections were present in 46% of patients and, compared with AH-ACLF without infection, were associated with higher creatinine (1.2 vs 1.7 mg/dL; $p = 0.01$) and CRP levels (31 vs 47 mg/L; $p < 0.001$). These patients also had higher rates of circulatory (9 vs 25%; $p = 0.001$) and cerebral failure (16 vs 27%; $p = 0.026$). Overall 28-day mortality was 42.2%, it was significantly higher in patients with concomitant infection than in those without infection (53.6% vs. 33.4%; $p = 0.002$) in EASL-CLIF-defined ACLF. Competing-risk multivariate regression analyses identified TNF-α as an independent predictor of mortality. Addition of TNF-α to established prognostic scores (e.g., CLIF-C OF and ACLF) significantly increased the AUC across all models; for example, the AUC of the CLIF-C ACLF + TNF-α + albumin model increased from 0.699 to 0.778 ($p = 0.007$). In patients without infection, TNF-α resulted in a substantially greater improvement across all models, for example from 0.747 to 0.899 for CLIF-C ACLF + TNF-α + albumin ($p = 0.003$). Additionally, these findings were confirmed in patients with ACLF according to the A-TANGO definition. **Conclusion:** Incorporation of TNF-α improves prognostic discrimination in AH-ACLF, particularly in patients without infection. TNF-α should be validated in independent cohorts as a biomarker for risk stratification in AH-ACLF. These findings require external validation before clinical use and support phenotype-specific approaches in future trial design.

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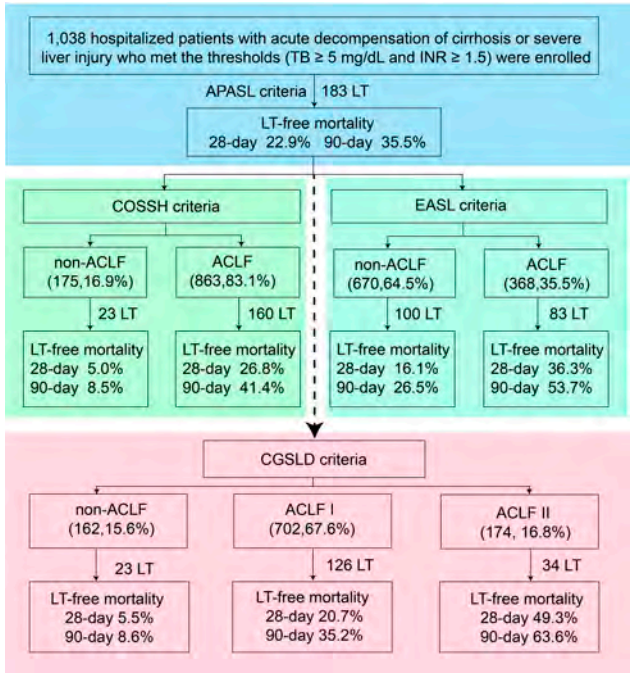
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Cyberliver: Founder, Johanna Catharina Kerbert: Nothing to Disclose, Cornelius Engelmann: Nothing to Disclose.

2016 | ◆ RISK STRATIFICATION AND MORTALITY OF ACUTE-ON-CHRONIC LIVER FAILURE ACROSS DIFFERENT DIAGNOSTIC CRITERIA: A MULTICENTER COHORT STUDY

Wenling Wang[1] Manman Xu[1] Yu Chen[1], [1]Beijing youan hospital, capital medical university

Background: Acute-on-chronic liver failure (ACLF) is a heterogeneous syndrome with high short-term mortality. Despite multiple proposed definitions, universally accepted and standardized diagnostic criteria are lacking. The Chinese Medical Association (CMA) has released the new China Guidelines for the Diagnosis and Treatment of ACLF (2025), and this study aims to evaluate the compatibility and comprehensiveness of these guidelines. **Methods:** In this prospective, multicenter study, clinical data were collected between September 2023 and May 2025 across multiple centers in China within the CGSLD consortium. Eligible patients were those with acute decompensation of cirrhosis or severe liver injury who met predefined thresholds (total bilirubin [TB] $\geq$ 5 mg/dL and international normalized ratio [INR] $\geq$ 1.5). Organ failure is defined according to the consensus criteria from *Defining Organ Failures in Patients with Cirrhosis: Consensus Statements*. Baseline characteristics, clinical course, and outcomes were analyzed to compare existing diagnostic frameworks (APASL-, COSSH-, EASL-ACLF). **Results:** Among 1,038 patients, all met APASL-ACLF criteria (28-/90-day mortality: 22.9%/35.5%), while 83.1% and 35.5% met COSSH- and EASL-ACLF criteria, with higher mortality rates of 26.8%/41.4% and 36.3%/53.7%, respectively, indicating heterogeneity in patient identification.To harmonize definitions, patients were reclassified according to the CMA-aligned CGSLD-ACLF criteria.CGSLD-ACLF I was defined as acute severe liver injury on chronic liver disease with TB $\geq$ 12 mg/dL and INR $\geq$ 1.5, accounting for 67.7of patients, with 28-/90-day mortality of 20.7%/35.2%. Stratification by INR (1.5–<2.0, 2.0–<2.5, $\geq$2.5) demonstrated a clear stepwise increase in mortality (8.1%/19.7%, 22.1%/33.7%, and 40.0%/58.2%).CGSLD-ACLF II was defined as TB $\geq$7.5mg/dL with INR $\geq$1.5, complicated by renal dysfunction or extrahepatic organ failure within 1 week, accounting for 16.8% of patients. This group showed significantly higher mortality (49.3%/63.6%), with further stratification (renal dysfunction, single, and multiple organ failure) yielding mortality rates of 25.7%/37.1%, 58.0%/66.7%, and 70.8%/91.7%, respectively. Patients not meeting CGSLD criteria (15.6%) had low mortality (5.5%/8.6%), indicating improved specificity. **Conclusion:** The CGSLD-ACLF classification demonstrated improved risk stratification compared with existing criteria, with clearer separation of mortality across stages.



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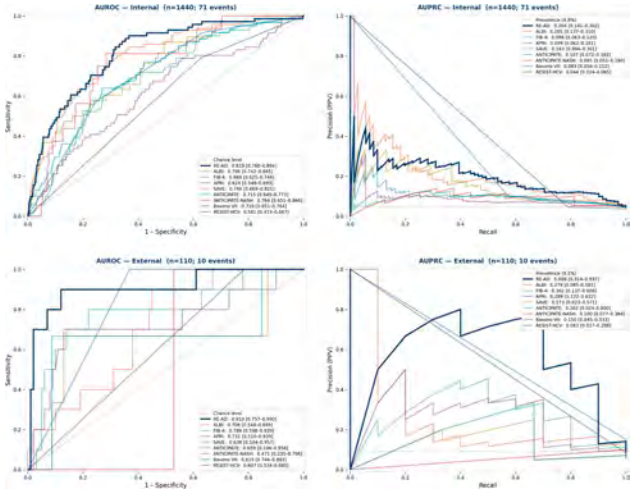
2017 | ◆ DEVELOPMENT AND EXTERNAL VALIDATION OF THE READ SCORE: A MACHINE LEARNING TOOL FOR ACUTE DECOMPENSATION PREDICTION IN COMPENSATED ADVANCED CHRONIC LIVER DISEASE.

Marco Vicardi[1] Lorenz Balcar[2] Filippo Cattazzo[1] Leonardo Natola[1] Manuele Bicego[1] Vincenzo Di Maria[1] Michele Bevilacqua[3] Anna Mantovani[1] Laura Alaimo[1] Georg Semmler[2] David Poulakos[2] Adrina Wunderbaldinger[2] Lucie Simonis[2] Jan Embacher[2] Veronica Paon[1] Donatella Ieluzzi[1] Nicola Zeni[4] Roberta Gagliardi[4] Rosa Lombardi[5] David Sacerdoti[1] Mattias Mandorfer[2] Salvatore Piano[4] Andrea Dalbeni[1], [1]University of Verona, [2]Medical University of Vienna, [3]Universiy of Verona, [4]University of Padova, [5]University of the Study of Milan

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Background: Patients with compensated advanced chronic liver disease (cACLD) face significant risk of acute decompensation (AD), including acute-on-chronic liver failure (ACLF), with increased mortality. Most established prognostic tools include substantial non-acute decompensation (NAD) components, making accurate short-term AD prediction challenging. We aimed to develop and externally validate the Risk Estimation of Acute Decompensation (RE-AD) score using machine learning models for predicting AD within 12 months in cACLD patients. **Methods:** This multicenter retrospective cohort study enrolled consecutive cACLD patients from Verona and Vienna University Hospitals between January 2017 and December 2024. Patients were followed-up for 12 months, or until AD occurred. The combined cohort (n = 1440) was used for model development using regularized ML techniques with LOOCV and LASSO feature selection. External validation was performed in an independent cohort of 110 patients from Padua University Hospital. Model performance was assessed in terms of discrimination, calibration, and clinical utility. The RE-AD score was compared with established prognostic scores, including FIB-4, APRI, MELD, Child–Pugh, ALBI, RESIST-HCV, ANTICIPATE ± NASH, Baveno VII criteria, SAVE. Post-hoc recalibration using Platt scaling was applied in the external cohort to account for differences in baseline risk. **Results:** Overall, 81 of 1,550 patients (5.2%) developed AD within 12 months. The RE-AD score included age, number of elective and non-elective hospital admissions and infection episodes requiring antibiotic treatment in the preceding 12 months, serum albumin, and INR. In internal validation, RE-AD demonstrated good discrimination (AUC 0.818, 95% CI 0.78–0.85), acceptable calibration, and a high negative predictive value (99.1%). RE-AD showed numerically higher discrimination than most established prognostic scores, while it did not outperform ALBI and SAVE. In external validation, RE-AD maintained excellent discrimination (AUC 0.910, 95% CI 0.84–0.98), ranking higher than all comparator scores. Initial calibration improved substantially after Platt scaling (Brier score reduction from 0.070 to 0.054). The score retained high sensitivity (90.0%) and negative predictive value (98.9%), supporting its role as a rule-out tool. **Conclusion:** RE-AD is a clinically interpretable ML-based score designed to predict short-term acute decompensation in cACLD, addressing a clinical gap not fully covered by existing tools. The score demonstrated preserved discrimination across internal and external cohorts and relies exclusively on routinely available clinical variables, unlike some established scores (e.g. SAVE) requiring less frequently assessed information such as varices. These features support the use of RE-AD for individualized risk stratification and rule-out strategies in cACLD.



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2018 | ◆ DEVELOPMENT OF A PBMC TRANSCRIPTOMIC MACHINE-LEARNING MODEL FOR 90-DAY ADVERSE OUTCOME PREDICTION IN HBV-RELATED ACUTELY DECOMPENSATED CIRRHOSIS

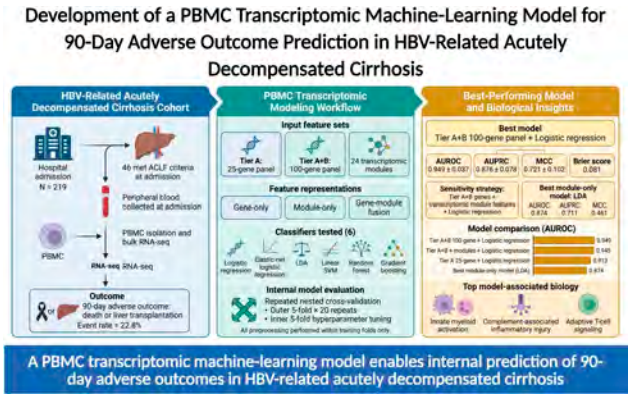
Jiyang Chen[1] Sisi Yang[1] Zelu Meng[1] Xianbin Xu[1] Xia Yu[1] Ying Nie[1] Liya Wang[1] Yani Zhou[1] Yining Zhang[1] Siqi Sun[1] Yan Lv[1] Yingfeng Lu[1] Yu Shi[1] Yida Yang[1], [1]The First Affiliated Hospital, Zhejiang University School of Medicine

Background: Short-term prognostication in hepatitis B virus (HBV)-related acutely decompensated cirrhosis remains difficult because of heterogeneous immune dysfunction and rapid progression to acute-on-chronic liver failure (ACLF) or death. PBMC

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transcriptomics may offer a minimally invasive readout of systemic immune dysregulation. We aimed to develop and internally evaluate a PBMC transcriptomic machine-learning model for predicting 90-day adverse outcomes, defined as death or liver transplantation. **Methods:** We enrolled 219 patients with HBV-related acutely decompensated cirrhosis and collected admission PBMC samples for bulk RNA sequencing. Forty-six patients met ACLF criteria at admission, and the 90-day adverse outcome rate was 22.8%. Three transcriptomic input spaces were evaluated: a Tier A 25-gene panel, a Tier A+B 100-gene panel, and 24 transcriptomic module features. Five feature representations, including gene-only, module-only, and gene–module fusion spaces, were benchmarked across six classifiers: logistic regression, elastic-net logistic regression, linear discriminant analysis, linear support vector machine, random forest, and gradient boosting. Performance was assessed by repeated nested cross-validation, with outer 5-fold cross-validation repeated 20 times and inner 5-fold tuning. All preprocessing steps were confined to training folds. Metrics included AUROC, AUPRC, Matthews correlation coefficient, and Brier score. **Results:** The Tier A+B 100-gene panel combined with logistic regression performed best, achieving AUROC 0.949 ± 0.037, AUPRC 0.876 ± 0.078, MCC 0.721 ± 0.102, and Brier score 0.081 across repeated outer test folds. A sensitivity strategy integrating Tier A+B genes with transcriptomic modules showed similar but slightly lower performance, with AUROC 0.945, AUPRC 0.870, MCC 0.702, and Brier score 0.084. Compared with the Tier A 25-gene panel, the 100-gene panel improved logistic model performance, with mean gains of ΔAUROC +0.037, ΔAUPRC +0.093, and ΔMCC +0.113. Module-only models were less predictive than gene-level feature spaces. The strongest module-only model achieved AUROC 0.874, AUPRC 0.711, and MCC 0.461. Key genes and modules mapped to disease-relevant immune programs, including myeloid activation, complement-associated inflammatory injury, and adaptive T-cell signaling. **Conclusion:** A 100-gene PBMC transcriptomic logistic model showed strong internal discrimination, favorable prediction error, and biological interpretability for 90-day adverse outcome prediction in HBV-related acutely decompensated cirrhosis. Transcriptomic modules aided biological interpretation but did not improve prediction. Independent multicenter validation, calibration assessment, threshold robustness testing, and model simplification are needed before clinical implementation.



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2019 | ◆ VALIDATION OF THE 2025 GLOBAL EXPERT PANEL CONSENSUS ON ACUTE-ON-CHRONIC LIVER FAILURE IN AN ASIAN POPULATION

Jingjing Chen[1] Wenling Wang[1] Yu Wu[1] Yanrong Yang[1] Xiao Che[2] Rui Zhao[2] Manman Xu[2] Yu Chen[2], [1]Beijing You'an Hospital, Capital Medical University, [2]Beijing Youan Hospital, Capital Medical University

Background: The 2025 Global Expert Panel Consensus (GEC) for acute-on-chronic liver failure (ACLF) redefined organ failure (OF) thresholds and integrated gastrointestinal (GI) failure. We evaluated GEC criteria in an Asian cohort and compared its performance with European Association for the Study of the Liver-Chronic Liver Failure (EASL-CLIF) criteria. **Methods:** Cirrhotic patients with acute hepatic insult were retrospectively enrolled. Primary endpoints were 28/90-day transplant-free survival (TFS). Independent predictors were identified via Cox regression. Performance was assessed using area under the receiver operating characteristic curve (AUROC), C-index, and Net Reclassification Index (NRI). **Results:** Among 410 patients, 181 (44.1%) fulfilled GEC-ACLF criteria. GI failure was the most prevalent OF (79.0%). The 28/90-

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day TFS rates were significantly lower in GEC-ACLF versus non-ACLF (28/90-day: 44.2%/59.7% vs. 8.7%/13.1%, $P < 0.001$). GEC identified 91 high-risk patients (50.3% of GEC-ACLF) categorized as non-ACLF by EASL-CLIF, who exhibited a 49.5% 90-day event rate (death or transplantation). Compared to EASL-CLIF, GEC demonstrated superior 90-day AUROC (0.759 vs. 0.678, $P = 0.010$), C-index (0.706 vs. 0.653, $P = 0.019$), and reclassification improvement (NRI: 26.7%, $P < 0.001$). Multivariate Cox analysis confirmed GEC-ACLF as a potent independent predictor (90-day adjusted HR 6.06, $P < 0.001$), with liver (aHR 6.58) and GI failure (aHR 3.01) identified as the strongest organ-specific predictors (both $P < 0.01$). Subgroup analyses confirmed GEC's reliability across etiologies, infection status, and cirrhosis stages (all $P < 0.001$). **Conclusion:** GEC criteria enhance prognostic stratification by capturing previously under-recognized high-risk individuals. The substantial prognostic weight of GI failure supports its clinical relevance, providing evidence for global ACLF standardization.

Disclosures: Jingjing Chen: Nothing to Disclose, Wenling Wang: Nothing to Disclose, Yu Wu: Nothing to Disclose, Yanrong Yang: Nothing to Disclose, Xiao Che: Nothing to Disclose, Rui Zhao: Nothing to Disclose, manman xu: Nothing to Disclose, yu chen: Nothing to Disclose.

2020 | ◆ ANGIOPOETIN-1/WNT AXIS PROTECTS FROM SEPSIS-INDUCED ACUTE-ON-CHRONIC LIVER FAILURE BY PRESERVING HEPATOCYTE DIFFERENTIATION

Michael Schonfeld[1] Samson Mah[1] Kruti Nataraj[1] Steven Weinman[2] Irina Tikhanovich[1], [1]The University of Kansas Medical Center, [2]University of Kansas Medical Center

Background: Sepsis is a common precipitating factor for acute-on-chronic liver failure (ACLF). In our previous work we identified angiopoietin-1/angiopoietin-2 imbalance as a key mechanism of sepsis-induced ACLF. However, the mechanism of angiopoietin-mediated changes in the liver were not fully understood. **Methods:** 8 weeks old male C57Black6/J mice were fed high fat western diet with 20% alcohol in the drinking water (WDA model of liver disease) for 16 weeks followed by 4 weeks recovery. Sepsis was induced with a cecal ligation and puncture (CLP). To test the role of *Angpt1* in the liver, we overexpressed *Angpt1* gene under the control of TBG promoter using an AAV vector. The role of WNT ligand expression was assessed by AAV-mediated *Wnt2* and *Rspo3* overexpression. The mechanism of angiopoietin-mediated changes was assessed by a combination of scATAC-seq analysis and spatial transcriptomics (5k Xenium panel, 10x Genomics). **Results:** Mice treated with WDA followed by sepsis induction (WDA-CLP) showed elevated liver injury (ALT), reduced liver function (increased bilirubin, prothrombin time), and markers of kidney dysfunction (BUN and serum creatinine). *Angpt1* overexpression protected mice from ACLF by reducing liver injury, inflammation, and preserving liver function. Kidney dysfunction was similarly ameliorated. To assess the mechanism of *Angpt1*-mediated protection, we used a combination of scATAC-seq analysis and spatial transcriptomics (5k gene panel, Xenium). We found that *Angpt1* overexpression resulted in an increase of *Wnt2* and *Rspo3* expressing endothelial cells and an increase in *Lrp5* expressing hepatocytes, suggesting that WNT signaling mediates *Angpt1* overexpression effects. WNT activation correlated with increased hepatocyte differentiation, reestablished liver zonation, and a dramatically reduced number of immature SOX9-positive progenitor-like cells. *In vitro* analysis confirmed that ANG-1 treatment promoted endothelial cell *Wnt2* expression under inflammatory conditions and promoted the ability of endothelial cells to preserve hepatocyte differentiation in an LRP5-dependent way. *In vivo* AAV-mediated *Wnt2* or *Rspo3* overexpression mimicked the effects of *Angpt1* overexpression in preserving hepatocyte differentiation in an ACLF model. **Conclusion:** Angiopoietin 1 protects from sepsis-induced ACLF via WNT signaling activation.

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2021 | ◆ PROGNOSTIC ANALYSIS OF ARTIFICIAL LIVER SUPPORT SYSTEM THERAPY GUIDED BY THE SYSTEMIC INFLAMMATION RESPONSE INDEX FOR ACUTE-ON-CHRONIC LIVER FAILURE

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Background: The Artificial Liver Support System (ALSS) effectively removes circulating toxins and

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inflammatory mediators and has been widely utilized in the clinical management of Acute-on-Chronic Liver Failure (ACLF). However, due to the substantial heterogeneity in patients' baseline conditions, the survival benefits of ALSS exhibit significant inter-individual variability in clinical practice, highlighting an urgent need for reliable biomarkers to guide precise patient stratification. This study aims to investigate the impact of ALSS therapy—specifically, the Double Plasma Molecular Adsorption System combined with Plasma Exchange (DPMAS+PE)—on the prognosis of patients with ACLF across different levels of the Systemic Inflammation Response Index (SIRI). **Methods:** A total of 788 patients with ACLF were enrolled in this prospective cohort study and followed up for 28-day and 90-day clinical outcomes. Patients were divided into the ALSS group and the control group (receiving standard medical therapy) based on their treatment modalities, and Cox regression analysis was performed to identify independent prognostic factors. Patients were further stratified by SIRI to investigate the specific therapeutic efficacy of ALSS under varying systemic inflammatory statuses. **Results:** Multivariate analysis demonstrated that ALSS was an independent protective factor for 28-day (HR = 0.71, 95% CI: 0.52–0.97) and 90-day (HR = 0.79, 95% CI: 0.63–0.99) outcomes, whereas an elevated SIRI significantly increased the risk of mortality at 28 days (HR = 1.02, 95% CI: 1.01–1.04) and 90 days (HR = 1.01, 95% CI: 1.00–1.03) (all $P < 0.05$). Restricted Cubic Spline (RCS) analysis revealed a significant non-linear relationship between SIRI and mortality ($P < 0.05$), identifying SIRI = 3 as the optimal stratification threshold. Subgroup analysis confirmed that among patients with high inflammation levels (SIRI $\geq$ 3), the survival rates were significantly higher in the ALSS group compared with the Control group (28-day: 78.0% vs. 63.6%; 90-day: 55.3% vs. 43.2%, $P < 0.05$), Furthermore, within this high-inflammation stratum, ALSS intervention significantly reduced the risk of 28-day (HR = 0.62, 95% CI: 0.41–0.93) and 90-day (HR = 0.74, 95% CI: 0.54–1.00) mortality. **Conclusion:** Both SIRI and ALSS (DPMAS+PE) are independent prognostic factors for patients with ACLF. The SIRI serves as a valuable clinical stratification indicator to identify ideal candidates who will benefit from ALSS therapy. For ACLF patients presenting with a high systemic inflammatory response (SIRI $\geq$ 3), ALSS therapy significantly improves survival rates and effectively mitigates the risk of both short-term (28-day) and mid-term (90-day) mortality.

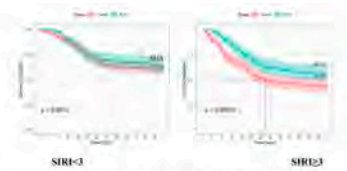


Figure 3 Risk of 90-Day Mortality Stratified by SIRI

Table 5 Univariate and multivariable Cox regression analysis based on 28-day mortality among patients with SIRI ≥ 3

	单因素			多因素		
	HR	*P*	*95%CI*	*HR*	*P*	*95%CI*
Gender (ref. male)	0.93	0.763	0.57 - 1.51			
Age	1.03	0.002	1.01 - 1.04	1.02	0.004	1.01-1.04
ALSS	0.52	0.001	0.35 - 0.77	0.62	0.022	0.41-0.93
BMI	1.00	0.795	0.98 - 1.02			
Compensated cirrhosis (ref. Non-cirrhosis)	0.75	0.299	0.43 - 1.29			
Decompensated cirrhosis (ref. Non-cirrhosis)	1.00	0.998	0.63 - 1.60			
Underlying disease	0.91	0.647	0.62 - 1.34			
MELD-Na	1.06	<0.001	1.04 - 1.08	1.05	<0.001	1.03-1.07
HE	0.86	0.440	0.58 - 1.27			
EASL-CLIF C	1.87	0.002	1.25 - 2.80	1.23	0.354	0.79-1.91
WBC	1.00	0.642	0.98 - 1.01			
SIRI	1.01	0.465	0.99 - 1.03			
log (PLT)	0.43	0.016	0.22 - 0.86	0.75	0.420	0.38-1.49
CRP	1.00	0.615	0.99 - 1.01			
PCT	1.02	0.279	0.99 - 1.05			
ALB	0.97	0.075	0.93 - 1.00			

Table 5 Univariate and multivariable Cox regression analysis based on 90-day mortality among patients with SIRI ≥ 3

	单因素			多因素		
	HR	*P*	*95%CI*	*HR*	*P*	*95%CI*
Gender (ref. male)	1.01	0.951	0.71 - 1.45			
Age	1.03	<0.001	1.01 - 1.04	1.02	<0.001	1.01-1.03
ALSS	0.66	0.006	0.49 - 0.89	0.74	0.047	0.54-1.00
BMI	0.99	0.369	0.96 - 1.02			
Compensated cirrhosis (ref. Non-cirrhosis)	0.88	0.595	0.56 - 1.40	0.78	0.297	0.49-1.24
Decompensated cirrhosis (ref. Non-cirrhosis)	1.62	0.015	1.10 - 2.39	1.43	0.082	0.96-2.13
Underlying disease	1.08	0.584	0.81 - 1.45			
MELD-Na	1.04	<0.001	1.02 - 1.05	1.03	<0.001	1.02-1.03
HE	0.92	0.570	0.68 - 1.23			
EASL-CLIF C	1.47	0.011	1.09 - 1.97	1.21	0.251	0.88-1.66
WBC	0.99	0.450	0.97 - 1.01			
SIRI	1.00	0.541	0.99 - 1.02			
log (PLT)	0.46	0.004	0.27 - 0.78	0.72	0.240	0.42-1.24
CRP	0.99	0.192	0.99 - 1.00			
PCT	1.02	0.103	1.00 - 1.05			
ALB	0.97	0.035	0.94 - 1.00	0.99	0.345	0.96-1.01

Disclosures: Xiao Che: Nothing to Disclose, Rui Zhao: Nothing to Disclose, Manman Xu: Nothing to Disclose, yu chen: Nothing to Disclose.

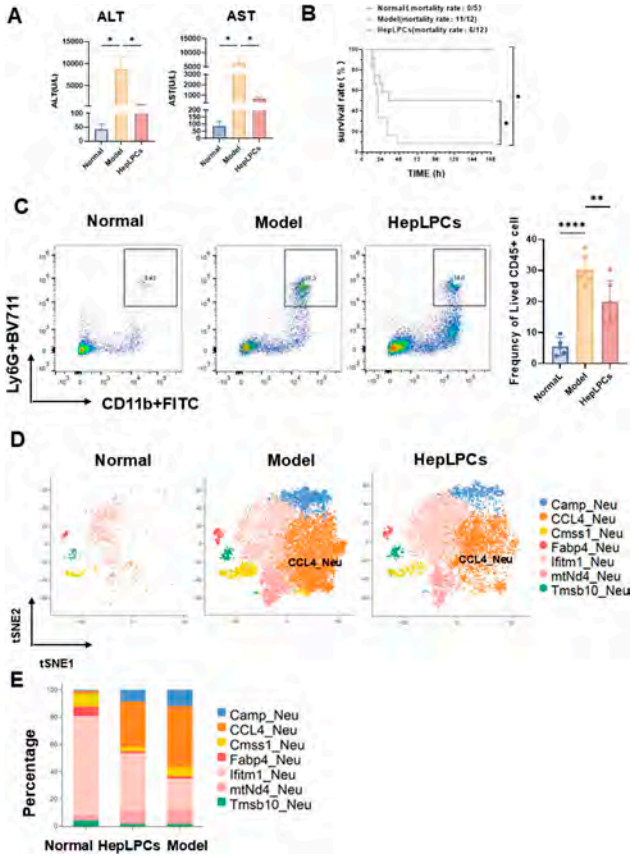
2022 | HEPATOCYTE-DERIVED LIVER PROGENITOR-LIKE CELLS SUPPRESS CCL4⁺ INFLAMMATORY NEUTROPHILS IN ACUTE-ON-CHRONIC LIVER FAILURE

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Background: Acute-on-chronic liver failure (ACLF) is a life-threatening syndrome with high short-term mortality, and effective treatment options remain limited beyond liver transplantation. We previously generated hepatocyte-derived liver progenitor-like cells (HepLPCs) through small molecule-based reprogramming. Although our preliminary studies suggested that HepLPCs exert immunomodulatory effects, the mechanisms by which HepLPCs alleviate systemic inflammation in ACLF remain unclear. **Methods:** A concanavalin A (ConA)-induced mouse model was used to recapitulate the systemic inflammatory features of ACLF. HepLPCs were administered via tail vein injection (8×10^6 cells/kg). Single-cell RNA sequencing (scRNA-seq) and flow cytometry were performed to evaluate changes in hepatic immune cell composition after treatment. scRNA-seq data were analyzed using t-SNE, followed by subclustering, differential gene expression, and GO/KEGG pathway enrichment analyses. Bulk RNA sequencing and secretome proteomic analysis of HepLPCs were performed to identify potential immunomodulatory factors. In vitro, HepLPC-conditioned medium was incubated with PMA-stimulated primary mouse bone marrow-derived neutrophils, and neutrophil extracellular trap formation was assessed. **Results:** Following HepLPC administration, ConA-treated mice showed improved liver function and increased survival. scRNA-seq of liver tissues and flow cytometry demonstrated a marked reduction in hepatic neutrophil infiltration after HepLPC treatment. Further dimensional reduction and subclustering of neutrophils identified a CCl4-expressing inflammatory neutrophil subset, which was decreased following HepLPCs administration. GO enrichment analysis revealed that HepLPC treatment alleviated endoplasmic reticulum stress in $CCl4^+$ inflammatory neutrophils. In addition, the expression of key glycolysis-related genes was reduced after treatment, suggesting that HepLPCs may improve neutrophil status by modulating neutrophil metabolism, thereby limiting the recruitment of inflammatory neutrophils.In vitro, HepLPC-conditioned medium suppressed PMA-induced neutrophil extracellular trap formation in primary mouse bone marrow-derived neutrophils, as measured by SYTOX Green staining. **Conclusion:** Our study highlights the therapeutic potential of HepLPCs in alleviating neutrophil-driven liver inflammation in acute-on-chronic liver failure. HepLPCs reduce $CCl4^+$ inflammatory neutrophil infiltration and suppress NETs formation, suggesting that HepLPC-based therapy may represent a promising strategy for the treatment of ACLF.



Disclosures: XIAOYAN JIN: Nothing to Disclose, WEIJIAN HUANG: Nothing to Disclose, FAN LI: Nothing to Disclose, SHIBO WANG: Nothing to Disclose, MENGTING WANG: Nothing to Disclose, HEXIN YAN: Nothing to Disclose.

2023 | CIRRHOTIC CARDIOMYOPATHY INCREASES THE RISK FOR ACUTE-ON-CHRONIC LIVER FAILURE, PARTICULARLY CIRCULATORY FAILURE, IN WAITLISTED PATIENTS.

Murray Coetzee[1] Andre Hall[2] Rawia Aburumman[1] James Slaughter[1] Ashley Spann[1] Deepak Gupta[1] Manhal Izzy[1], [1]Vanderbilt University Medical Center, [2]Vanderbilt University School of Medicine

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Background: Cirrhotic cardiomyopathy (CCM) is cardiac dysfunction in patients with advanced cirrhosis without primary cardiac disease . While CCM has been shown to influence post-transplant cardiac outcomes, its impact on acute on chronic liver failure and hepatorenal syndrome-acute kidney injury is less defined. **Methods:** We performed a retrospective cohort study of adults with cirrhosis waitlisted for liver transplantation at a large academic center in North America between 1 Nov 2020 and 1 Apr 2025. Outcomes of interest were acute-on-chronic liver failure (ACLF), its components (circulatory, renal, cerebral or pulmonary failure) and hepatorenal syndrome–acute kidney injury (HRS-AKI). ACLF outcomes were analysed using multivariable logistic regression. HRS-AKI was analysed with Fine–Gray competing-risk regression treating transplantation as the competing event. ACLF analyses incorporated inverse probability weighting using prespecified demographic and liver disease covariates, whereas circulatory failure models were adjusted for age and MELD 3.0 and HRS-AKI models for MELD 3.0. **Results:** Among 453 candidates with sufficient echocardiographic data to define CCM, 81 had CCM and 372 did not (prevalence 18%). CCM was independently associated with higher odds of ACLF (30.9 % vs 19.4 %; aOR 1.75, 95 % CI 1.02–3.01). Among ACLF components, the strongest association with CCCM was for circulatory failure (17.3 % vs 7.3 %; aOR 2.47, 95 % CI 1.22–4.99). Renal failure, as part of ACLF, was more frequent in CCM but was not significant after adjustment (11.1 % vs 5.1 %; aOR 2.15, 95 % CI 0.93–4.99). CCM was not associated with HRS-AKI (19 total events; adjusted sHR 0.85, 95 % CI 0.25–2.94). **Conclusion:** Among liver transplant waitlist candidates, CCM was associated with increased risk of ACLF, particularly circulatory failure, but not with increases in HRS-AKI. These findings suggest hemodynamic consequences for CCM in patients with ACLF; the HRS-AKI estimates should be interpreted cautiously because of limited event counts.

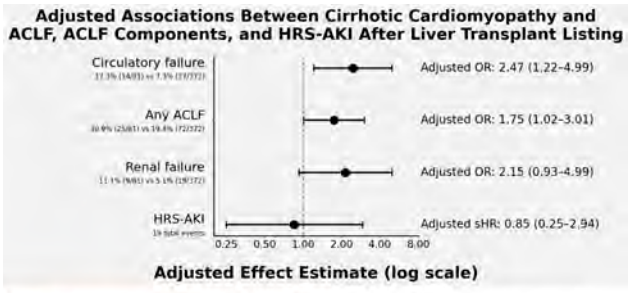


Figure 1: Adjusted associations between cirrhotic cardiomyopathy and ACLF, its components, and HRS in waitlisted patients. Points represent adjusted odds ratios for ACLF outcomes and adjusted subdistribution hazard ratio for HRS-AKI; horizontal lines represent 95

Disclosures: Murray Coetzee: Nothing to Disclose, Andre Hall: Nothing to Disclose, Rawia Aburumman: Nothing to Disclose, James Slaughter: Nothing to Disclose, Ashley Spann: Bristol Myers Squibb Foundation: Grant/Research Support, Novo Nordisk: Consultant, Madrigal Pharmaceuticals: Consultant, Deepak Gupta: Nothing to Disclose, Manhal Izzy: Mallinckrodt: Speaking and Teaching, Madrigal: Advisor, Natera: Advisor, Mirum: Advisor.

2024 | VISCO-ELASTIC TESTING GUIDED RESTRICTIVE TRANSFUSION REDUCES BLOOD PRODUCT UTILIZATION WITHOUT INCREASING PROCEDURE-RELATED COMPLICATIONS IN PATIENTS OF ACLF-INTERIM RESULTS OF A RANDOMIZED CONTROLLED TRIAL. (NCT06831565)

Sanda Kavitha[1] Manoj Sharma[2] Ashok Choudhury[1] Satender Pal[1] Satender Pal[1] Sugunasree Aakula[1] Chitranshu Vashishtha[1] Sarthak Chanana[1] Ananthu Naryanan[1] ShivKumar Sarin[1], [1]Institute Liver and Biliary Sciences, [2]Institute of Liver and Biliary Sciences

Background: Patients with acute-on-chronic liver failure (ACLF) had a state of balanced coagulation despite systemic inflammation, infection, multiorgan dysfunction and severe coagulopathy. Invasive procedure in these patient and the transfusion strategy is not known, leading to frequent transfusion and associated complications. The aim of the current prospective randomised study is to evaluate the safety of the transfusion of the blood products and the procedure-related outcomes of ROTEM-guided versus standard transfusion strategies in ACLF patients undergoing invasive procedures **Methods:** In this prospective randomized controlled trial, 158 patients fulfilling APASL ACLF criteria and requiring invasive procedures were randomized into three transfusion strategy arms: High-demand (minimal transfusion threshold), Low-demand (standard liver transplant-based transfusion strategy), and On-demand (no prophylactic transfusion, only used when clinically indicated). Outcome evaluated in relation to blood product utilization, procedure-related complications, requirement for procedure-related interventions, and procedure-related mortality **Results:** A total of 158 ACLF patients undergoing invasive procedures were randomized to the High-demand (n = 53), Low-demand (n = 51), and On-demand (n = 54) arms, with mean CTP score of 12.36 ± 1.70, MELD score of 31.04 ± 6.95, AARC ACLF score of 10.27 ± 2.11, CLIF-C ACLF score of 54.06 ± 12.87. The majority were male (91.8%). ACLF grades were distributed as Grade 1 (38.3%), Grade 2 (25.2%), and Grade 3 (23.4%). Paracentesis was the most frequently performed procedure (46.8%), followed by central venous/haemodialysis catheter insertion

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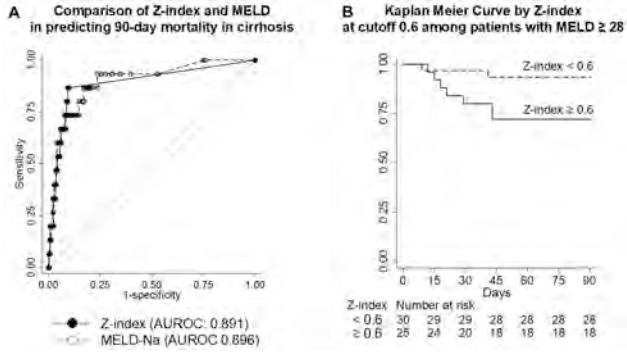
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(32.9%). Fresh frozen plasma transfusion rates were 1.9%, 17.0%, and 19.4% in the High-demand, Low-demand, and On-demand groups, respectively ($p = 0.012$). Cryoprecipitate transfusion rates were 1.9%, 34.0%, and 27.0%, respectively ($p < 0.001$). Despite significant differences in transfusion exposure, procedure-related adverse outcomes were uncommon. Procedure-related complications and mortality occurred in only two patients (1.3%), both in the On-demand arm, with no statistically significant difference between groups ($p = 0.142$). **Conclusion:** Among ACLF patients undergoing invasive procedures, restrictive ROTEM-guided transfusion strategies substantially reduced blood product utilization without increasing procedure-related complications, intervention requirements, or mortality. These interim findings support the safety and clinical feasibility of individualized, restrictive transfusion approaches guided by viscoelastic testing in patients with ACLF undergoing invasive procedures
Disclosures: Sanda Kavitha: Nothing to Disclose, Manoj Sharma: Nothing to Disclose, Ashok Choudhury: Nothing to Disclose, Satender Pal: Nothing to Disclose, Nothing to Disclose, Satender Pal: Nothing to Disclose, Nothing to Disclose, Sugunasree Aakula: Nothing to Disclose, Chitranshu Vashishtha: Nothing to Disclose, sarthak Chanana: Nothing to Disclose, Ananthu Naryanan: Nothing to Disclose, ShivKumar Sarin: Nothing to Disclose.

2025 | LIPOPROTEIN Z IS A BIOMARKER OF LIVER DECOMPENSATION ASSOCIATED WITH HIGH MORTALITY

Shanshan Su[1] Sebastian Niezen[2] Michelle Lai[2] Zachary Fricker[2] Alan Bonder[2] Vilas Patwardhan[2] Margery A. Connelly[3] Z. Gordon Jiang[2], [1]1. Division of Gastroenterology and Hepatology, Beth Israel Deaconess Medical Center, Harvard Medic, [2]Division of Gastroenterology and Hepatology, Beth Israel Deaconess Medical Center, Harvard Medica, [3]Labcorp, Morrisville, NC 27560

Background: Lipoprotein metabolism is a core hepatic function that is frequently disrupted in liver failure and decompensated cirrhosis. We previously identified elevated levels of lipoprotein X (LP-X) and lipoprotein Z (LP-Z), abnormal low-density lipoprotein (LDL)-like particles enriched with free cholesterol (FC) and triglycerides (TG) in patients with severe alcohol-associated hepatitis (AH). In this study, we investigate whether LP-Z is present across other liver diseases, identify clinical factors associated with LP-Z levels, and evaluate its utility in predicting patient outcomes. **Methods:** A total of 896 patients were identified from five registries at Beth Israel Deaconess Medical Center, comprising 364 patients with various liver disease diagnoses and 532 with cirrhosis. Nuclear magnetic resonance (NMR) lipoprotein profiling was performed to quantify lipoprotein subclass concentrations, including LP-X and LP-Z. A Z-index was defined as the ratio of LP-Z to the sum of very low-density lipoprotein (VLDL), LDL, and LP-Z, representing total apolipoprotein B-containing lipoproteins. **Results:** All patients with detectable LP-X also had detectable LP-Z, confirming that these particles co-exist, while LP-X alone was frequently unreliable when quantified from frozen samples. LP-Z was found in 70 patients, almost exclusively in patients with cirrhosis. Although most prevalent in AH and alcohol-associated cirrhosis (AC), these abnormal lipoproteins were also detected in patients with cirrhosis due to metabolic dysfunction-associated steatotic liver disease (MASLD), hepatitis C, autoimmune hepatitis, and primary sclerosing cholangitis. LP-Z levels correlated strongly with MELD score, with total bilirubin showing the strongest individual association. Notably, every patient with a bilirubin level exceeding 15 mg/dL had detectable LP-Z. Patients with circulating LP-Z had significantly lower LDL and HDL levels compared to those with cirrhosis but without LP-Z. While the Z-index demonstrated prognostic value comparable to MELD-Na for overall mortality prediction (Fig. 1A), a Z-index threshold of 0.6 offered significant additional predictive value for 90-day mortality in patients with severe liver decompensation (MELD $\geq$ 28) (Fig. 1B). **Conclusion:** LP-Z is a late-stage biomarker of liver failure or decompensation in cirrhosis, reflecting the breakdownof lipoprotein metabolism. A Z-index cutoff of 0.6 independently risk-stratifies patients at high risk of mortality beyond MELD-Na and may serve as a valuable tool in clinical decision-making.



Disclosures: shanshan su: Nothing to Disclose, Sebastian Niezen: Nothing to Disclose, Michelle Lai: Nothing to Disclose, Zachary Fricker: Lipocine, Inc: Grant/Research Support, Pick Research: Consultant, River2Renal Corp: Grant/Research Support, Bausch, Inc.: Grant/Research Support, Guidepoint Global, LLC: Consultant, WL Gore: Speaking and Teaching, Alan Bonder: Nothing to Disclose, Vilas

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Patwardhan: Nothing to Disclose, Margery A. Connelly: Labcorp: Employee and stock holder, Z. Gordon Jiang: Olix Pharmaceutical: Consultant.

2026 | VITAL SIGNS OUTPERFORM MELD 3.0 AND CLIF-C AD IN DYNAMICALLY PREDICTING DETERIORATION AMONGST INPATIENTS WITH DECOMPENSATED CIRRHOSIS

Jason Hearn[1] Surain Roberts[2] Matthew Wankiewicz[2] Sahar Saeed[1] Wei Tu[1] Lauren Lapointe-Shaw[3] Siddhartha Srivastava[1] Amol Verma[3] Fahad Razak[3] Florence Wong[3] Gideon Hirschfield[4] Jennifer Flemming[5] Kristel Leung[1], [1]Queen's University, [2]Unity Health, [3]University of Toronto, [4]Toronto General Hospital, [5]Queen's University Cancer Research Institute

Background: Predicting rapid deterioration of decompensated cirrhosis inpatients remains one of the most elusive problems in hepatology. Existing prognostic scores (e.g. MELD 3.0, CLIF-C AD) have focused on bloodwork and clinical features, without consideration of vital signs. We sought to develop supervised machine learning models incorporating vital signs to predict deterioration amongst decompensated cirrhosis inpatients, and to compare model performance with existing clinical scores. **Methods:** We included patients with decompensated cirrhosis admitted to medicine wards across 7 hospitals in Ontario, Canada (Apr. 2016 to Oct. 2021). Demographic, vital sign and lab data were extracted and cleaned (e.g. values outside predefined limits were removed). The primary outcome of deterioration was defined as admission to the intensive care unit or death. Admissions less than 84 hours were excluded. The final 12 hours of data prior to the outcome or discharge (if outcome was not met) were removed. Each encounter was divided into one or more 72-hour windows, with each window assigned a binary indicator denoting whether the outcome occurred at 12 hours post-window. In each window, features were calculated for vital sign data, and the most recent lab values were extracted. The MELD 3.0 and CLIF-C AD scores were calculated for windows containing their respective required components. Three random forest models were generated using features derived from: (1) vital signs, (2) labs, and (3) combined vital signs and labs. Generalized linear models were created using the MELD 3.0 and CLIF-C AD scores to serve as comparators. All models were trained and assessed using a 100-iteration Monte Carlo cross-validation. Performance was quantified using area under the precision-recall curve (AUPRC), which measures the trade-off between sensitivity and positive predictive value across all probability thresholds. **Results:** A total of 8,744 windows were derived from 3,722 hospital admissions. Of the generated windows, 631 (7.2%) were followed by deterioration at 12 hours post-window. The random forest models outperformed the traditional scores, with mean AUPRCs of 0.33 for the vital signs model and 0.38 for the combined vital signs and labs model (compared to 0.21 [CLIF-C AD] and 0.22 [MELD 3.0]). The combined vital signs and labs model achieved a mean accuracy of 0.81, sensitivity of 0.73, specificity of 0.81, positive predictive value of 0.24 and negative predictive value of 0.98, based on probability thresholds optimized using Youden's method (Figure 1). **Conclusion:** Models incorporating vital signs outperformed existing clinical scores in predicting deterioration in 12 hours amongst patients admitted with decompensated cirrhosis. Integrating such models with existing clinical workflows may improve our ability to identify patients at risk for deterioration in real-time, allowing for timely intervention and improved patient outcomes.

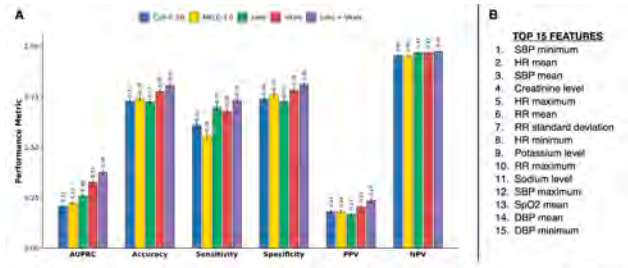


Figure 1. A) Performance metrics (mean ± 95% confidence interval) achieved by the assessed models based on probability thresholds optimized using Youden's method, where AUPRC = area under the precision-recall curve, CLIF-C AD = Chronic Liver Failure Consortium Acute Decompensation, MELD = Model for End-Stage Liver Disease, NPV = negative predictive value, and PPV = positive predictive value. **B)** Most predictive features (as per permutation importance) in the combined vital signs and labs model, where DBP = diastolic blood pressure, HR = heart rate, RR = respiratory rate, SBP = systolic blood pressure, and SpO2 = peripheral oxygen saturation.

Disclosures: Jason Hearn: Nothing to Disclose, Surain Roberts: Nothing to Disclose, Matthew Wankiewicz: Nothing to Disclose, Sahar Saeed: Novo Nordisk: Consultant, Wei Tu: Nothing to Disclose, Lauren Lapointe-Shaw: Nothing to Disclose, Siddhartha Srivastava: Nothing to Disclose, Amol Verma: Nothing to Disclose, Fahad Razak: Nothing to Disclose, Florence Wong: Nothing to Disclose, Gideon Hirschfield: Intercept: Consultant, GSK: Consultant, CymaBay: Consultant, Ipsen: Consultant, Falk: Consultant, Pliant: Consultant, Mirum: Consultant, Advanz: Consultant, Chemomab: Consultant, Gilead: Consultant, Kowa: Consultant, Jennifer Flemming: Nothing to Disclose, Kristel Leung: Nothing to Disclose.

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2027 | ACUTE HEMODYNAMIC RESPONSE TO CARVEDILOL PREDICTS 28-DAY TRANSPLANT-FREE SURVIVAL IN ACUTE-ON-CHRONIC LIVER FAILURE: THE ACT-C ACLF STUDY.

Garvit Mundra[1] Ishank Johri[2] Chitranshu Vashishtha[3] Shiv Kumar Sarin[4], [1]Institute of liver and billiary sciences ILBS, [2]Institute of liver and billiary sciences, [3]ILBS, [4]ILBS Newdelhi

Background: Elevated hepatic venous pressure gradient (HVPG) drives outcomes in acute-on-chronic liver failure (ACLF). In cirrhotic patients, ≥20% reduction in HVPG with non-selective beta blockers improves survival. However, the prognostic significance of acute HVPG reduction and the optimal cutoff to define response in ACLF remain unknown. We evaluated whether acute hemodynamic response (AHR) to a single oral dose of carvedilol predicts short-term transplant-free survival in ACLF **Methods:** In this prospective interventional cohort study, consecutive patients fulfilling APASL ACLF criteria undergoing HVPG assessment were enrolled. HVPG was repeated 1 hour after oral carvedilol 12.5 mg administration. The primary and secondary outcomes were 28-day and 90-day transplant-free survival, respectively. AHR was defined using percentage reduction in HVPG among 28-day survivors by receiver operating characteristic (ROC) analysis and Youden's Index. **Results:** Eighty-eight patients were analysed and 65 (73.9%) achieved 28-day transplant-free survival. Baseline demographic and disease severity variables including age, gender, etiology, Child–Turcotte–Pugh (CTP), MELD, AARC score, lactate, TNF-α, IL-6 and CRP were evaluated. Baseline HVPG was comparable between 28-day survivors and non-survivors (18.52 ± 4.35 vs 19.43 ± 5.81 mmHg; p = 0.497). However, survivors demonstrated significantly greater acute portal pressure reduction with lower post-dose HVPG (13.03 ± 4.22 vs 16.52 ± 5.35 mmHg; p = 0.008) and greater percentage HVPG reduction (31.16% vs 14.73%; p = 0.001). ROC analysis identified an optimal AHR cutoff of ≥20.7% to predict 28-day survival (AUC 0.764; sensitivity 73.9%; specificity 70.5%). Kaplan–Meier analysis demonstrated significantly superior transplant-free survival among responders (≥20% HVPG reduction) compared with non-responders at both 28 days (85.2% vs 55.9%; log-rank p = 0.0027) and 90 days (79.6% vs 47.1%; log-rank p = 0.0014). Multivariable Cox proportional hazards regression confirmed acute HVPG response (adjusted HR 0.198, 95% CI 0.045–0.865; p = 0.031) and serum lactate (adjusted HR 3.095, 95% CI 1.157–8.282; p = 0.024) as independent mortality predictors. **Conclusion:** Acute HVPG reduction following carvedilol predicts 28-day and 90-day transplant-free survival in ACLF. An acute HVPG reduction of approximately 20% identifies hemodynamic responders and may serve as an early functional biomarker for individualized beta-blocker therapy in ACLF.

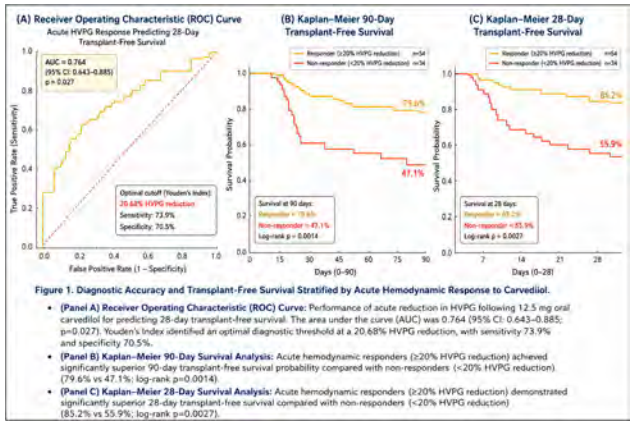


Figure 1. Diagnostic Accuracy and Transplant-Free Survival Stratified by Acute Hemodynamic Response to Carvedilol.

- **(Panel A) Receiver Operating Characteristic (ROC) Curve:** Performance of acute reduction in HVPG following 12.5 mg oral carvedilol for predicting 28-day transplant-free survival. The area under the curve (AUC) was 0.764 (95% CI: 0.643–0.885; p=0.027). Youden's Index identified an optimal diagnostic threshold at a 20.68% HVPG reduction, with sensitivity 73.9% and specificity 70.5%.
- **(Panel B) Kaplan–Meier 90-Day Survival Analysis:** Acute hemodynamic responders (≥20% HVPG reduction) achieved significantly superior 90-day transplant-free survival probability compared with non-responders (<20% HVPG reduction) (79.6% vs 47.1%; log-rank p=0.0014).
- **(Panel C) Kaplan–Meier 28-Day Survival Analysis:** Acute hemodynamic responders (≥20% HVPG reduction) demonstrated significantly superior 28-day transplant-free survival compared with non-responders (<20% HVPG reduction) (85.2% vs 55.9%; log-rank p=0.0027).

Disclosures: Garvit Mundra: Nothing to Disclose, Ishank Johri: Nothing to Disclose, Chitranshu Vashishtha: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose.

2028 | *EARLY PLASMA EXCHANGE REDUCES 7-DAY MORTALITY, IMPROVES RENAL RECOVERY, AND CREATES A BRIDGE-TO-TRANSPLANT WINDOW IN VERY SEVERE ALCOHOL-ASSOCIATED HEPATITIS*

Vinod Arora[1] Ashok Kumar Choudhury[1] Rakhi Maiwall[1] Anand Kulkarni[2] Ashish Kumar[3] Anil Arora[3] Ajay Duseja[4] Akash Shukla[5] Akash Roy[6] Abraham Koshy[7] Ajit Sood[8] Ajay Patwa[9] Ajay Kumar Mishra[10] Amna Butt[11] Ajay Kumar[12] Arun Valsan[13] Ashish Jha[14] Ameet Mandot[15] Chandan Kumar Kedarisetty[16] Diana Payawal[17] Dibya Locan Praharaj[18] Dinesh Kumar Jothimani[19] Dong Joon Kim[20] Zhongping Duan[21] Fazal Karim[22] Gamal Shiha[23] Girish Kumar Pati[24] Guan-Huei Lee[25] H. Janaka De Silva[26] Harshad Devarbhavi[27] Hasmik Ghazinyan[28] Joy Varghese[29] Javed P[30] Jidong Jia[31] Jinhua hu[32] Jose D Sollano[33] Kemal Kalista[34] Kessarin Thanapirom[35] Krishnadas Devadas[36] Mamun Mahtab[37] Manoj Sahu[18] Man-Fung Yuen[38] Mithra Prasad[39] Mithun Sharma[40] Mohamed Rela[19] Neeraj Saraf[41] Narendra Choudhary[41] Nipun Verma[42] Omesh Goyal[43] Padaki Nagaraja Rao[44] Pravin Rathi[45] Qin Ning[46] Radha Dhiman[10] Ravikiran Maghade[15] Rino Gani[34] Saeed Hamid[47] Samir Shah[15] Sanjiv Saigal[48] Shahinul Alam[49] Sombat Treeprasertsuk[50] Sudhir Maharshi[51] Sunil Dadhich[52] Sunil Taneja[42] Suprabhat Giri[18] Surender Singh[53] Tao Chen[46] Tarana Gupta[54] V.G. Mohan Prasad[39] V M Dayal[14] Vandana Midha[8] Wasim Jafri[11] Zaigham Abbas[55] Nurgul Toktogulova[56] Gupse Adali[57] Murat Harputluoglu[58] Senam Kaur[59]

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Background: Very severe alcohol-associated hepatitis (V-SAH) [SS1] with Maddrey's discriminant function (mDF) > 120 is extremely sick cohort of patient and is associated with extremely high short-term mortality. Therapeutic plasma exchange (PLEX) may improve inflammatory burden and organ dysfunction, potentially providing a bridge-to-transplant (LT) window in carefully selected patients. We evaluated temporal mortality patterns, organ failure burden, renal recovery, bilirubin kinetics, sepsis, and the impact of PLEX intensity in severe AH. **Methods:** Retrospective analysis was done; 532 patients were evaluated with AH and very high (mDF > 120) and underwent PLEX (atleast 1 session). Primary endpoint was mortality at 7, 28, and 90 days. Secondary endpoints were longitudinal reduction in severity scores (mDF, MELD) and inflammatory markers (WBC) by Day 7, incidence and impact of new-onset sepsis, and stratification of Day 7 bilirubin response into rapid decliners vs low decliners and non-decliners; 28- and 90-day mortality. **Results:** The cohort (86.8% male, mean age 45.1 ± 12.0 years) was very sick with mean mDF 163.2 ± 49.9; MELD 31.7 ± 8.2; SOFA 9.1 ± 2.5; CLIF-SOFA 12.8 ± 6.0 and baseline OF noted in 68.4% . Baseline number of organ failure was 2.5 ± 1.2. Renal failure was present in 309/532 (58.1%), hepatic encephalopathy in 330/532 (62.0%), circulatory failure in 207/532 (38.9%), respiratory failure in 96/532 (18.0%), and coagulation failure in 378/532 (71.1%). PLEX limited 7-day mortality to 10.2% (54/532) and facilitated successful LT in 4.5% (n = 24) of this highly unstable cohort, Renal recovery post-PLEX by day 7 occurred in 132 patients (24.8%). Greater early bilirubin decline after PLEX, reflected by both higher mean reduction (14.8 ± 8.2 vs 6.1 ± 5.4 mg/dL) and median reduction [12.6 (IQR 8.4–18.2) vs 4.3 mg/dL (IQR 1.9–8.1)], strongly correlated with improved 28-day and 90-day [SS1] survival, renal recovery, and reduced progression of organ failure. Most notably, the mean mDF demonstrated a sharp decline to 106.2 ± 64.8, alongside parallel reductions in MELD (to 28.3 ± 8.3) and total WBC (17.2 to 15.6 × 10^3/mm^3),

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reflecting robust SIRS attenuation. Patients with greater Day-7 bilirubin reduction demonstrated lower 28-day mortality (18%, n = 48/267 vs 46%, n = 123/265) and lower 90-day mortality (32%, n = 85/267 vs 61%, n = 162/265) [SS2] compared with poor biochemical responders. New-onset sepsis within 7 days post-PLEX occurred in 10.0% (n = 53), and in led to high 90-day mortality. Overall 28-day and 90-day mortality were 37.0% and 63.9%, respectively. **Conclusion:** In verysevere alcoholic hepatitis, PLEX helps to improve organ failure and reduces 7-day mortality and increases transplant window Post-PLEX sepsis mandates rigorous infection surveillance.

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2029 | GLP-1 RECEPTOR AGONIST INITIATION AND RISK OF ACUTE-ON-CHRONIC LIVER FAILURE IN PATIENTS WITH CIRRHOSIS

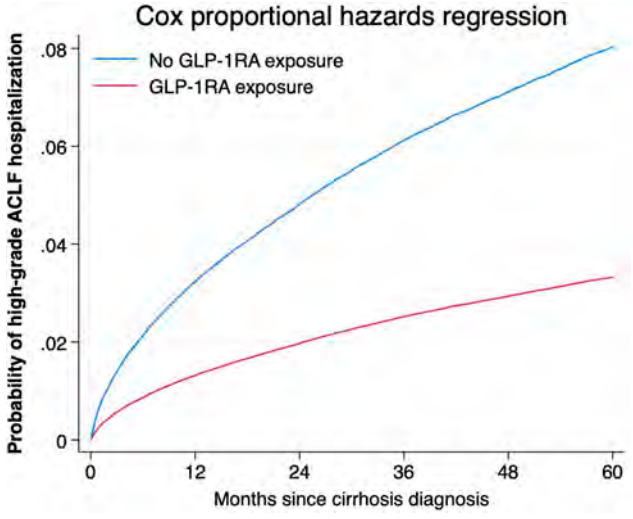
Snehitha Talugula[1] David Kaplan[1] Nadim Mahmud[2], [1]University of Pennsylvania, [2]Hospital of the University of Pennsylvania

Background: Acute-on-chronic liver failure (ACLF) is a major complication of cirrhosis associated with high short-term mortality. Few therapies reduce the risk of ACLF or modify disease progression. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have demonstrated cardiometabolic benefits, including reduced cardiovascular risk, with emerging evidence suggesting additional anti-inflammatory and metabolic effects beneficial in chronic liver disease. However, data evaluating the impact of GLP-1RA therapy on clinically significant outcomes in cirrhosis remain limited. We aimed to evaluate the association between GLP-1RA initiation and risk of incident high-grade ACLF hospitalization in patients with cirrhosis. **Methods:** We performed a retrospective cohort study using data from

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VOCAL, a national Veterans Health Administration cohort of patients with incident diagnoses of cirrhosis. Patients with prior GLP-1RA exposure were excluded. Data regarding demographics, comorbidities, etiology of liver disease, and MELD-Na were obtained. The primary exposure was GLP1-RA initiation identified from VHA pharmacy records and modeled as a time-updated variable. Major cardiometabolic comorbidities were also modeled as time-updated variables. The primary outcome was incident hospitalization with high-grade ACLF (grade 2 to 3), defined per EASL criteria using a previously validated VHA algorithm. Follow-up was censored at death, liver transplantation, or 5 years. Multivariable Cox proportional hazards models with clustered standard errors were used to evaluate the association between GLP-1RA exposure and ACLF hospitalization. **Results:** Among 158,571 patients with cirrhosis, 6,859 (4.3%) initiated GLP-1RA therapy during follow-up. Compared with patients without GLP-1RA exposure, GLP-1RA initiators were younger (mean 61.7 vs. 63.9 years, $p < 0.001$), had higher BMI (34.7 vs. 28.3, $p < 0.001$), and were more likely to have MASLD or MetALD etiologies and metabolic comorbidities (e.g., diabetes 96.0% vs. 47.8%, $p < 0.001$). Over 5 years of follow-up, time-updated GLP-1RA exposure was associated with significantly lower risk of incident high-grade ACLF hospitalization (adjusted hazard ratio [aHR] 0.54, 95%CI 0.44 to 0.65, $p < 0.001$). Adjusted cumulative incidence curves demonstrated substantially lower probability of high-grade ACLF hospitalization among GLP-1RA-exposed patients over time (approximately 3.2% vs. 8.0% at 60 months; **Figure**). **Conclusion:** In this national cohort study of patients with cirrhosis, GLP-1RA initiation was associated with significantly lower risk of incident high-grade ACLF hospitalization. These findings suggest that GLP-1RA therapy may be beneficial in cirrhosis. Further prospective longitudinal studies are needed to determine whether these associations are causal, evaluate effects across cirrhosis etiologies, and assess impacts on mortality and other liver-related outcomes.



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2030 | DEFINING THE GOLDEN WINDOW FOR LIVER TRANSPLANTATION IN ACUTE-ON-CHRONIC LIVER FAILURE: A SYSTEMATIC REVIEW

Roy Khalaf[1] Daljeet Chahal[2], [1]University of Calgary, [2]University of British Columbia

Background: Acute-on-chronic liver failure (ACLF) is characterized by rapid clinical deterioration, multiorgan failure, and high short-term mortality. Liver transplantation (LT) remains the only definitive treatment for many patients with severe ACLF; however, the optimal timing of transplantation remains poorly defined. We performed a systematic review and meta-analysis evaluating timing-related outcomes in ACLF patients undergoing LT. **Methods:** A systematic review was conducted according to PRISMA guidelines. MEDLINE and Embase were searched from inception to February 2026 for studies evaluating LT timing, waitlist mortality, post-transplant survival, or allocation-related outcomes in adult ACLF patients. Thirteen studies met inclusion criteria. Studies with overlapping registry populations were excluded from pooled analyses. Random-effects meta-analysis using logit-transformed proportions was performed for 1-year post-transplant survival outcomes. **Results:** Across included studies, earlier transplantation was consistently associated with improved outcomes, particularly among patients with ACLF-3. In a large UNOS registry analysis of 7,607 ACLF-3 patients, transplantation within 7 days of listing was associated with improved 1-year survival compared with transplantation between days 8–28 (87.1% vs 83.6%). Multiple studies demonstrated rapid clinical deterioration in the absence of transplantation, with mortality frequently occurring within days of hospitalization or urgent listing. Prospective cohorts identified the first week following hospitalization or listing as a critical period associated with substantial waitlist mortality. Increasing ACLF severity was associated with a progressively narrower transplant window, with median time-to-transplant decreasing from 20 days in ACLF-1 to 5 days in ACLF-3 in the ECLIS cohort. Significant heterogeneity

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was observed in timing definitions across studies, including transplantation timing measured from hospital admission, ACLF diagnosis, or waitlist registration. Pooled analysis of non-overlapping cohorts demonstrated a 1-year post-transplant survival of 83.8% (95% CI 80.6–86.5%; $I^2 = 72.4\%$). **Conclusion:** The available literature supports LT as a highly time-sensitive intervention in severe ACLF, with delayed transplantation associated with rapid clinical deterioration and substantial waitlist mortality. The transplant window appears to narrow with increasing ACLF severity, particularly in ACLF-3. However, substantial heterogeneity in timing definitions limits direct comparison across studies. Future prospective studies using standardized and clinically meaningful timing frameworks are needed to better define the optimal timing of LT in ACLF.

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2031 | INTENSITY OF BASELINE MALADAPTIVE EMERGENCY MYELOPOIESIS IS A DETERMINANT OF SHORT-TERM DEATH IN PATIENTS ADMITTED FOR ACUTELY DECOMPENSATED CIRRHOSIS (ADC)

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Background: Whether amplified maladaptive emergency myelopoiesis (MEM) that occurs in patients with ADC contributes to or correlates with 90-day mortality is unclear. This study aimed to address this question. **Methods:** Both "bulk" whole blood RNA-seq data (which capture RNA features from myeloid cells) obtained on nonelective admission (baseline) of 694 ADC patients (including 164 ACLF) and from 25 matched healthy subjects and single-cell whole blood RNA-seq data obtained in 10 additional patients were used to compute metrics assessing low, average and high baseline MEM intensity relative to healthy status. The risk of death by 90 days was assessed with semiparametric Fine–Gray competing-risk models with liver transplantation (LT) treated as a competing risk of death. After handling missing data using multiple imputation by chained equations, univariable and multivariable regression models were fitted in the imputed datasets. The overall contribution of MEM intensity was assessed using pooled type III Wald tests based on the D1 method (two-sided) comparing full models with nested models excluding MEM intensity. **Results:** As compared with healthy subjects, ADC patients exhibited amplified MEM at baseline, i.e., they had neutrophilia and monocytosis developed at the expense of lymphoid lineages, and blood enrichment with RNA features indicating increases in bone marrow outputs of immature and mature myeloid cells exhibiting actuated immunosuppressive gene programs. Of the 694 patients, 47 (7%) received a LT by 90 days; of the 647 nontransplanted patients 193 (30%) died by 90 days. Patients with low or average MEM intensity at baseline had significantly lower risks of 90-day transplant-free death than those with high MEM intensity (low versus high intensity: subdistribution hazard ratio [sHR], 0.30; 95% CI, 0.20-0.46; average versus high: sHR, 0.45; 95% CI, 0.33-0.61; type III $P < 0.0001$). All associations were preserved after adjustments that included age, CLIF-C

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organ failure score, blood cytokine levels, differential neutrophil counts, and recent use of immunosuppressants. Then, analyzing MEM intensity according to patients' phenotypes determined by the presence or absence of ACLF at baseline, we found that average or low MEM intensity was associated with significantly lower risk of death for each phenotype, as compared with high MEM intensity (both type III $P < 0.05$). Notably, among patients without ACLF, those with low MEM intensity had a 64% lower risk of death, compared with those who had high MEM intensity. **Conclusion:** Our findings identify the intensity of baseline MEM as an unrecognized determinant of 90-day transplant-free mortality among ADC patients, with and without ACLF, highlighting potential implications for patient stratification and the development of therapeutic strategies that dampen MEM intensity.

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2032 | CANDIDATE BIOMARKERS IDENTIFIED BY MULTIMODAL ARTIFICIAL INTELLIGENT INFORM LIVER TRANSPLANTATION DECISIONS IN ACUTE-ON-CHRONIC LIVER FAILURE (ACLF)

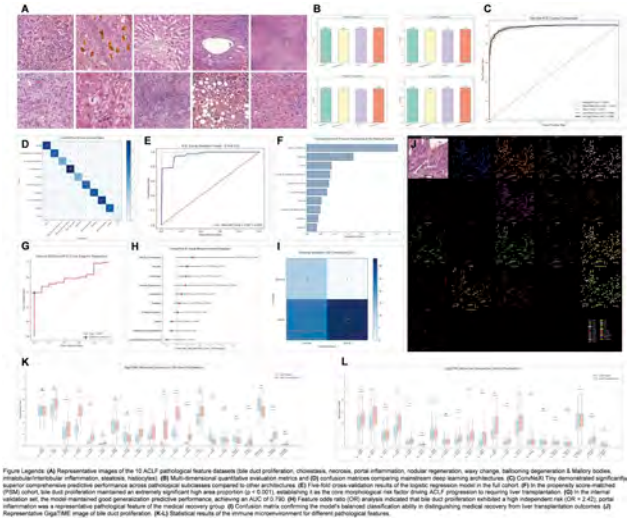
Rui Zhao[1] Jingran Jiao[1] Xiao Che[1] Manman Xu[1] Wenling Wang[1] Pengfei Yu[1] Yu Chen[1], [1]Fourth Department of Liver Disease, Beijing You'An Hospital, Capital Medical University

Background: Liver transplantation (LT) is a key treatment for ACLF, requiring refined patient classification to guide rational clinical decisions. Recent advances in Artificial intelligent (AI) make it possible to re-assess digital pathology for candidate biomarker discovery. **Methods:** 117 ACLF patients was conducted (source of pathological specimens: medical recovery group (LT-free): liver biopsy, $n = 36$; LT group: explant, $n = 81$). A patch-level dataset of 1,469 patches covering 10 ACLF pathological features (bile duct proliferation, cholestasis, necrosis, et al) was built by liver pathology diagnostic physicians through manual annotation. A ConvNeXt-Tiny model was trained with 5-fold cross-validation (AdamW optimizer, learning rate 1e-4, data augmentation) and achieved high accuracy for feature classification. Tissue ratios were computed. Logistic regression identified features associated with LT in full and matched cohorts. Recently reported virtual spatial proteomics technology GigaTIME converted key regions into virtual 21-marker multiplex immunofluorescence (mIF) with patient-level equal sampling. Mean intensities were compared. Mann-Whitney U test was used (two-sided, $p < 0.05$). **Results:** ConvNeXt-Tiny achieved a mean AUC of 0.984 for 10 histological features, outperforming ResNet50, EfficientNet-v2-s, and Swin-T. In the full cohort, LR coefficients highlighted bile duct proliferation (2.26), portal inflammation, ballooning/Mallory, and steatosis as top contributors to LT. After propensity score matching (age, MELD score), bile duct proliferation remained the dominant risk factor (coefficient 1.33, $p < 0.001$), while portal inflammation showed protective effect. In internal validation, multivariate LR model had AUC 0.790; bile duct proliferation OR was 2.42, and SHAP analysis confirmed the protective role of portal inflammation. GigaTIME revealed that in portal inflammation areas, Transgelin was significantly higher in LT-free patients. In bile duct proliferation regions, LT patients exhibited upregulation of T-bet, CD11c, PD-L1, and PHH3-B, and decreased CK and Caspase3-D, indicating inflammatory storm and immune exhaustion with disordered proliferation. Tryptase emerged as a candidate secreted biomarker for LT decision-making, elevated in LT cases. These findings suggest that AI-based pathology combined with spatial proteomics can refine LT candidate selection. **Conclusion:** This study applies AI based multi omics to ACLF pathology, offering a new perspective to refine LT decision making in ACLF. We emphasize that our findings are intended to assist LT decisions rather than replace them—according to recent insights,ignoring this distinction would overlook the subgroup of patients who

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achieve favorable long-term survival (>2 years) after transplantation.

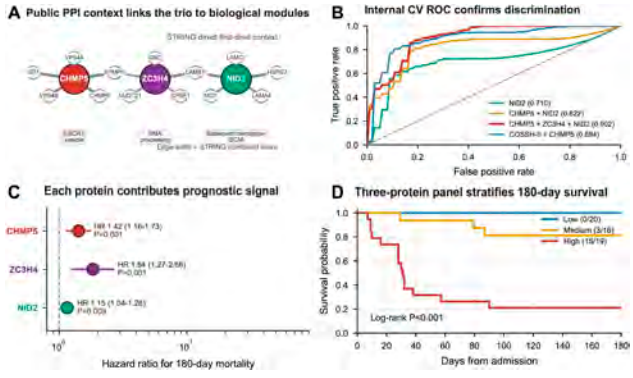


Disclosures: Rui Zhao: Nothing to Disclose, Jingran Jiao: Nothing to Disclose, Xiao Che: Nothing to Disclose, manman xu: Nothing to Disclose, Wenling Wang: Nothing to Disclose, Pengfei Yu: Nothing to Disclose, yu chen: Nothing to Disclose.

2033 | PLASMA PROTEOMICS STRATIFIES HIDDEN MORTALITY RISK IN THE MELD HIGH-RISK GREY ZONE OF HBV-RELATED ACUTE-ON-CHRONIC LIVER FAILURE

Fuxia Ta[1] Jinwen Feng[2] Bingyao Wang[1] Mengmeng Wang[1] Mengqi Zhu[3] Yilei Cao[4] Jian-Ming Zheng[5], [1]Huashan Hospital, Fudan University, [2]Human Phenome Institute, Fudan University, Shanghai, China, [3]Huashan Hospital, Fudan University, Shanghai, China, [4]Shanghai Medical College, Fudan University, Shanghai, China, [5]Huashan Hospital Fudan University

Background: Prognostication remains challenging in patients with HBV-related acute-on-chronic liver failure (HBV-ACLF), particularly once conventional clinical scores already indicate high risk. We aimed to determine whether baseline plasma proteomics could further stratify mortality risk within the MELD high-risk grey zone. **Methods:** We profiled baseline plasma from 55 patients with HBV-ACLF using data-independent acquisition mass spectrometry (DIA-MS). The primary outcome was 180-day mortality. Patients with MELD ≥25 were analyzed as the high-risk grey-zone subgroup. Mortality-associated proteins were prioritized using differential abundance analysis, pathway and protein-interaction context, low-dimensional protein-only model benchmarking, Cox analysis, and Kaplan-Meier risk stratification. **Results:** Overall, 18 of 55 patients died by 180 days. Within the MELD ≥25 subgroup, MELD did not distinguish 180-day survivors from non-survivors (P = 0.395), indicating limited prognostic resolution among clinically severe patients. Death-associated plasma proteins were enriched for extracellular matrix (ECM)/adhesion, membrane-trafficking and stress-related programs. STRING contextualization identified complementary mortality-associated biology represented by CHMP5, linked to ESCRT and vesicle sorting; ZC3H4, linked to RNA and nuclear regulation; and NID2, linked to basement membrane and extracellular matrix remodeling (**Figure 1A**). In repeated cross-validation, the three-protein CHMP5/ZC3H4/NID2 model achieved an internal cross-validated AUC of 0.902 and outperformed the best single- and two-protein models, while adding a fourth protein produced minimal incremental gain (**Figure 1B**). This supported the three-protein panel as the parsimonious model. Each protein was associated with increased 180-day mortality risk in Cox analysis (**Figure 1C**). A three-protein risk score sharply separated outcomes: no deaths occurred in the low-risk group, whereas 15 of 19 high-risk patients died by 180 days (Kaplan-Meier P < 0.001, **Figure 1D**). **Conclusion:** Plasma proteomics revealed a parsimonious CHMP5/ZC3H4/NID2 mortality signature that identifies hidden risk within the MELD high-risk grey zone of HBV-ACLF. These findings suggest that cellular stress, membrane-trafficking, and ECM/basement-membrane remodeling programs may capture mortality biology not resolved by conventional severity scoring, supporting further validation of this candidate risk-stratification strategy for clinically severe HBV-ACLF.



Disclosures: Fuxia Ta: Nothing to Disclose, Jinwen Feng: Nothing to Disclose, Bingyao Wang: Nothing to Disclose, Mengmeng Wang: Nothing to Disclose, Mengqi Zhu: Nothing to Disclose, Yilei Cao: Nothing to Disclose, Jian-Ming Zheng: Nothing to Disclose.

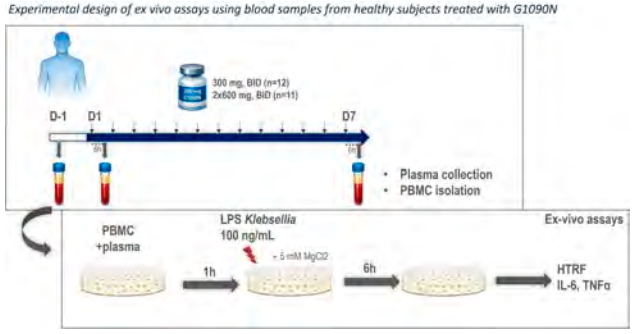
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2034 | *EX VIVO* BLOOD ASSAYS DEMONSTRATE SYSTEMIC ANTI-INFLAMMATORY ACTIVITY OF G1090N, A NOVEL FORMULATION OF NITAZOXANIDE; AND SUPPORT FURTHER CLINICAL EVALUATION IN ACUTE-ON-CHRONIC LIVER FAILURE (ACLF)

Debaecker Simon[1] Marie Bobowski-Gerard[1] Alexandra Pruvost[1] Manon Clarisse[1] Virginie Galoseau[1] Anthony Rabat[1] Jérémy Magnanensi[1] Camille Vanbésien[1] Jean-Marie Brusq[1] Jonel Trebicka[2] Bart Staels[3] Zouher Majd[1] Sakina Sayah Jeanne[4], [1]GENFIT SA, [2]University Hospital Münster, Münster, Germany, [3]Univ. Lille, Institut Pasteur de Lille, CHU Lille, Inserm U1011, Lille, France, [4]Genfit

Background: G1090N, a novel formulation of nitazoxanide (NTZ), is an investigational drug under development for the treatment of ACLF, a severe complication of acutely decompensated cirrhosis characterized by organ failures and high-short term mortality. Systemic inflammation, triggered by bacteria or pathogen-associated molecular patterns such as lipopolysaccharide (LPS), is a key driver of ACLF. Oral NTZ has been shown to protect against systemic inflammation and organ damage in animal models of ACLF. This study aimed to confirm the anti-inflammatory activity of NTZ using human peripheral blood mononuclear Cells (PBMCs) from subjects enrolled in a G1090N Phase 1 study and blood samples from cirrhosis patients. **Methods:** In the NCT07110441 Phase 1 clinical trial, healthy participants received 300 mg (n = 12) or 600 mg (n = 11) G1090N twice daily for 7 days. PBMCs and plasma were isolated from blood samples collected at baseline (D-1, before treatment), after a single dose (D1, T+6h), and after repeated doses (D7, T+6h). PBMCs were cultured in the presence of 50% of their autologous plasma for 1h before stimulation with LPS (100 ng/mL) for 6h (Figure).*Ex vivo* assays were also performed using whole blood obtained from healthy (n = 13 pool) and cirrhotic (n = 5) donors collected at EFS and Cerba laboratories, respectively. Blood samples were incubated with 60-120 µM tizoxanide (TZ), the active metabolite of NTZ for 1h prior to stimulation with LPS (50 ng/mL) for 4h.Homogenous Time-Resolved Fluorescence (HTRF) quantified cytokines levels in supernatants. **Results:** In clinical trial *ex vivo* assays, PBMCs and plasma from healthy subjects treated with 300 mg G1090N exhibited reduced LPS-induced cytokine secretion, compared with LPS-stimulated samples at baseline (D-1, untreated): by 62% ($p = 0.03$) and 74% ($p < 0.001$) for IL-6, and by 53% ($p = 0.03$) and 65% ($p < 0.001$) for TNFα, after a single dose (D1) or repeated doses (D7), respectively. Similar effects were observed with the 600 mg dose of G1090N, with IL-6 reductions of 46% at D1 and 43% at D7 (both $p < 0.001$), and TNFα reductions of 19% at D1 ($p = 0.002$) and 20% at D7 ($p = 0.001$).In *ex vivo* assays from cirrhotic and healthy blood, TZ treatment attenuated LPS-induced cytokine secretion in a dose dependent manner, with maximal inhibition of 68% and 63% for TNFα, and 85% and 84% for IL-6, respectively ($p < 0.001$). Notably, we observed greater anti-inflammatory activity in the cirrhotic group at low and intermediate doses compared to the healthy group. **Conclusion:** Single or repeated G1090N doses used in the first-in-human study were sufficient to achieve robust ex-vivo anti-inflammatory activity. These findings were confirmed in cirrhotic blood, indicating NTZ's potential in conditions associated with heightened systemic inflammation. Together with previously reported organ-protective properties of NTZ in disease models, these data support phase 2 clinical investigation of G1090N in patients with ACLF.



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2036 | TIGIT EXACERBATES ACUTE-ON-CHRONIC LIVER FAILURE INFECTION AND MORTALITY THROUGH CD8⁺ T CELL EXHAUSTION

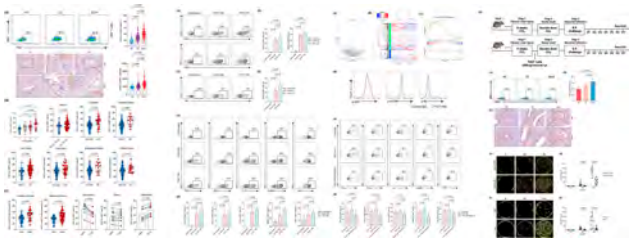
Yidi Jia[1] Yao Zhang[2] Xueyun Zhang[2] Yan Wang[2] Yuxian Huang[2] Jiming Zhang[2], [1]Fudan University, [2]Huashan Hospital

Background: Overwhelming infection caused by immunity deficiency contributes to the high short-term mortality in acute-on-chronic liver failure (ACLF). T-cell Immunoreceptor with Ig and ITIM domains (TIGIT) regulates T cell function in oncology, but its role in anti-

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infection immunity in ACLF remains unclear. We aimed to investigate the pathogenic role and therapeutic potential of TIGIT in ACLF. **Methods:** TIGIT expression and function on $CD8^+$ T cells was examined in blood and liver samples from ACLF patients, cirrhosis (LC), and healthy controls (HCs). RNA-seq was employed to investigate the pathways, which was verified by phosphoflow cytometry. To model ACLF conditions, we established an ACLF mouse model involving chronic liver injury (CCl4 injection for 8 weeks), acute insult (double-dose CCl4 injection), and Klebsiella pneumoniae (K.P.) challenge, according to Xiang et al. Two groups of ACLF mice were developed: TIGIT-knockout ($TIGIT^{-/-}$) versus wild-type (WT) ACLF mice and anti-TIGIT mAb treated versus control-IgG treated ACLF mice. **Results:** TIGIT expression on $CD8^+$ T cells was significantly increased in ACLF patients compared to HCs and LC patients. Immunohistochemical analysis of liver tissue corroborated these findings. Higher TIGIT expression on $CD8^+$ T cells correlated with worse prognostic scores, organ failure, infections and 28-/90-day non-survival status in ACLF patients. During hospitalization, TIGIT expression increased in deterioration, decreased in improvement, and unchanged in stable patients. Blockade with anti-TIGIT monoclonal antibody (mAb) improved activation (CD25, CD69), proliferation (Ki67) and cytokine production (IFN-γ, IL-2, TNF-α, Granzyme B, Perforin) in $CD8^+$ T cells isolated from ACLF PBMCs. RNA-seq-based gene expression profiling of anti-TIGIT mAb-treated $CD8^+$ T cells, followed by GSEA analysis, identified the PI3K-AKT-mTOR pathway as a key mediator. Anti-TIGIT mAb increased p-AKT, p-mTOR, and p-S6 in $CD8^+$ T cells. Rapamycin (mTOR inhibitor) intervention abolished elevated $CD8^+$ T cell function mediated by anti-TIGIT mAb. In a mouse model of ACLF, treatment with anti-TIGIT mAb upregulated CD25, CD69, IFN-γ, TNF-α, and Granzyme B in $CD8^+$ T cells, significantly improved survival rates, and reduced Klebsiella pneumoniae (K.P.) loads at 24 and 48 hours post-bacterial challenge. Similarly, $TIGIT^{-/-}$ ACLF mice exhibited higher expression of these cytokines, better survival, and lower K.P. burdens. **Conclusion:** Blockade of TIGIT leads to improvement of $CD8^+$ T cell function and anti-infection immunity in ACLF. The findings clarify ACLF pathogensis and nominate TIGIT as a promising therapeutic target.



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2037 | TYPE A AND TYPE B ACLF BY KYOTO CLASSIFICATION CLEARLY CHARTERS NATURAL DISEASE COURSE AT BASELINE AND GUIDES THERAPEUTIC INTERVENTIONS -A COHORT STUDY

Rakhi Maiwall[1] Samba Siva Rao Pasupuleti[2] Shiv Kumar Sarin[1], [1]Institute of Liver and Biliary Sciences, [2]Pachhunga University College Mizoram University (A Central University)

Background: Systemic inflammation is a key driver of organ failures in acute on chronic liver failure (ACLF). The Kyoto Consensus classified ACLF into Type A and Type B, emphasizing a liver-centric paradigm with hepatic failure as primary and excluding patients with prior episodes of decompensation to define ACLF. This could be relevant as immune dysregulation in the critically ill are specific to the host maladaptation to cytokine amplification during sepsis. **Methods:** Retrospective cohort of consecutive patients admitted to the liver intensive care unit (n = 600) with ACLF defined according to Kyoto consensus, [Type A, n = 148 (25.7%); Type B, n = 452 (75.3%)] were evaluated. Patients who succumbed in first 72 hours were excluded. **Results:** Type B ACLF were more prevalent (75.3% vs. 25.7%),being older [(49.9 ± 10.9) vs. (43.8 ± 11.2); $p < 0.001$] with higher prevalence diabetes [(15.5% vs.7.4%); $p = 0.013$], hypertension [(9.1% vs. 2%);$p = 0.004$] and higher incidence of acute variceal bleed [(23% vs. 12.8%); $p = 0.008$] and refractory ascites [(20% vs.10.8%);$p = 0.009$] respectively. A similar prevalence of sepsis and alcohol as the dominant etiology [(71.7% vs. 71.6%)] was noted. Type A had deep jaundice [(22.3 (11.3) vs. 8.2(8.7); $p < 0.001$], coagulopathy [4.1(2.9) vs. 3.2(2.5); $p < 0.001$] and severe SIRS (1: 2: > 2 components) (50% vs. 32.4%) vs. (35% vs. 41.2%) vs. (14.2% vs. 25.7%) than type B. The need of mechanical ventilation (39.2% vs. 32.5%), with lower PaO2/FiO2 ratio [284 (161.4) vs. 311.6(169.4)], comparable grades of hepatic encephalopathy 1: 2: 3: 4 [(10.1 vs 5.8%) vs. (18.9% vs 17.5%) vs. (16.2% vs. 21.2%) vs. (23.6% vs.22.3%), arterial lactate [3.49(3.1) vs. 3.4(2.65) umol/L] with similar proportion of patients on vasopressors. More severe kidney involvement with significantly higher serum creatinine [2.3(1.7) vs. 1.94(1.51) mg/dl], lower urine output [39.7(34.7) vs. 53.7(65.7)], higher KDIGO stage 3(43.2% vs. 35.2%) stage 2(31.8% vs.

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21.8%) vs. stage 1(8% vs. 17.9%),need of dialysis (2.7% vs.0.7%), higher uNGAL [1446.1(904.4) vs. 1073 (546.5) ng/ml] and Cystatin C [2.49(0.76) vs. 2.18 (0.67)] was seen in Type A ACLF. On multivariable Cox-regression analysis, Type A patients had higher 30-day mortality [37.2%vs.23%; 1.37, (1.09-1.71); $p < 0.001$] alongside higher arterial lactate, need of mechanical ventilation and sepsis. **Conclusion:** ACLF type A patients are younger with more severe liver failure, intense systemic inflammation, kidney failure, and significantly higher mortality possibly needing bridging therapies ameliorating hepatic inflammation. Type B patients have more frequent portal-hypertension driven complications and more comorbid diseases signifying distinct systemic inflammation and immunometabolic phenotypes. The segregation into Type A and B is relevant for developing therapeutic strategies and selection for an early liver transplant for patients with cirrhosis and organ failures.

Disclosures: Rakhi Maiwall: Nothing to Disclose, Samba siva rao Pasupuleti: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose.

2038 | COMPARISON OF ALCOHOLIC LIVER DISEASE VS METABOLIC DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE RELATED ACLF IN AARC DATABASE: A RETROSPECTIVE ANALYSIS

Tarana Gupta[1] Ashok Kumar Choudhury[2] Rakhi Maiwall[3] Vinod Arora[2] Anand Kulkarni[4] Anand Kulkarni[4] Anand Kulkarni[4] Ashish Kumar[5] Anil Arora[6] Ajay Duseja[7] Akash Shukla[8] Akash Roy[9] Abraham Koshy[10] Ajit Sood[11] Ajay Kumar Mishra[12] Amna Butt[13] Ajay Kumar[14] Arun Valsan[15] Ashish Jha[16] Ameet Mandot[17] Chandan Kumar Kedarisetty[18] Diana Payawal[19] Dibyalochan Praharaj[20] Dinesh Kumar Jothimani[21] Dong Joon Kim[22] Zhongping Duan[23] Md Karim[24] Gamal Shiha[25] Girish Kumar Pati[26] Guan Huei Lee[27] Harshad Devarbhavi[28] Maria Harutyunyan[29] Joy Varghese[30] Javed P[31] Jidong Jia[32] Jinhua Hu[33] Kemal Kalista[34] MSc MD[35] Krishnadas Devadas[36] Mamun Mahtab[37] Manoj Kumar Sahu[20] Man-Fung Yuen[38] Mithra Prasad[39] Mithun Sharma[40] Mohamed Rela[41] Neeraj Saraf[42] Narendra Choudhary[43] Nipun Verma[44] Omesh Goyal[45] Radha Dhiman[46] Shalimar kumar[47] Shalimar kumar[47] Sanjiv Saigal[48] Sudhir Maharshi[49] Sunil Dadhich[50] Sunil Taneja[44] Gupse Adali[51] Senam Kaur[52] Shiv Kumar Sarin[2], [1]Pt Bhagwat Dayal Sharma Institute of Medical Sciences Rohtak, [2]ILBS Delhi, [3]Institute of Liver and Biliary Sciences, [4]Asian Institute of Gastroenterology, [5]Sir Ganga Ram Hospital, [6]Sir Ganga Ram Hospital Delhi, [7]Postgraduate Institute of Medical Education & Research, [8]Seth GS Medical College & KEM Hospital, [9]Apollo Multispeciality Hospital, Kolkata, India, [10]Lakeshore Hospital, [11]Dayanand Medical College, Ludhiana, India, [12]Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India., [13]Department of Medicine, Aga Khan University Hospital, Karachi, Pakistan, [14]Govind Ballabh Pant Hospital, New Delhi, India, [15]Amrita Hospital ,Kochi, Kerala, India, [16]Indira Gandhi Institute of Medical Sciences (IGIMS), Bely Road Patna, [17]Department of Hepatology, Global Hospitals, Mumbai, India, [18]Global Hospitals, Hyderabad, [19]Fatima University Medical Cent, [20]Kalinga Institute of Medical Sciences (KIMS), Bhubaneshwar, India, [21]Dr. Rela Institute, Chennai (India), [22]Hallym University Medical Center, [23]Hepatology Institute Capital Medical University, China, [24]Sir Salimullah Medical College Hospital, Bangladesh, [25]Egyptian Liver Research Institute And Hospital, Egypt, [26]Department of Gastroenterology and Hepatology Sciences, IMS & SUM Hospital, Bhubaneswar, Odisha, [27]Division of Gastroenterology and Hepatology, Department of Medicine, National University Health, [28]Department of Hepatology, St John Medical College, Bangalore, India, [29]Head of Gastroenterology and Hepatology service, Yerevan Medical Scientific Center, Armenia, [30]Gleneagles Global Health City, Chennai, India, [31]Aster MIMS Hospital, [32]Beijing Friendship Hospital, Capital Medical University, [33]The Fifth Medical Center of Chinese PLA General Hospital, Beijing, China, [34]Cipto Mangunkusumo Hospital, Indonesia, [35]Department of Medicine, Chulalongkorn University, Bangkok, Thailand, [36]Government Medical College, Thiruvananthapuram, [37]Department of Hepatology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh, [38]The University of Hong Kong, [39]Department of Gastroenterology, VGM Hospital, Coimbatore, India, [40]AIG Hospitals, [41]Dr. Rela Institute, Chennai, India, [42]Institute of Digestive & Hepatobiliary Sciences, [43]Medanta Hospital Delhi, [44]PGIMER Chandigarh, [45]D.M.C. and Hospital, [46]Sanjay Gandhi Postgraduate Institute of Medical Sciences, [47]AIIMS, Delhi, [48]Max Super Specialty Hospital, Saket New Delhi, India, [49]SMS Jaipur, India, [50]Dr Sampurnanand Medical College, Jodhpur, [51]University of Health Sciences Istanbul Umraniye Training and Research Hospital, [52]Queen Elizabeth Hospital in Kota Kinabalu, Sabah, Malaysia

Background: There is a paradigm shift in etiology of cirrhosis from viral to predominantly alcoholic followed by MASLD. MASLD is accompanied by comorbidities like diabetes, hypertension and dyslipidemia which may impact the outcomes. **Methods:** This was a retrospective observational study. The data was collected from

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APASL ACLF research consortium (AARC) database from 2020 to 2025. Out of 3498 patients of ACLF, alcohol and MASLD were etiology of chronic liver diseases in 2534 (73%) and 128 (3.6%) patients respectively. Propensity score matching (PSM) was performed to minimize baseline differences between the study groups and reduce selection bias. Patients were matched using relevant demographic and clinical variables bilirubin, INR, creatinine, albumin, HE, ascites, hemoglobin, TLC and platelet counts with nearest-neighbor matching and a predefined caliper width. Finally, 125 patients in each ALD ACLF and MASLD ACLF groups were analyzed. **Results:** In ALD-ACLF, patients were younger and majority were male as compared to MASLD-ACLF (45 vs 48 years, P = 0.04 and 83% vs 64%, P = 0.001) respectively. In comparison to ALD-ACLF, MASLD-ACLF had significantly more female patients (17% vs 36%, P = 0.001) respectively. ALD-ACLF had significantly lower platelets than MASLD-ACLF (131 vs 150, P = 0.02). MASLD-ACLF had higher prevalence of jaundice than ALD-ACLF (94% VS 77%, P = < 0.05). Liver failure and acute variceal bleed (AVB) was present in (32% vs 28%, P = 0.49 and 4% vs 7%, P = 0.27) patients in ALD-ACLF and MASLD-ACLF respectively. There was no significant difference in 90-day mortality between ALD-ACLFand MASLD-ACLF.The multivariable Cox proportional hazards regression analysis was performed to evaluate the impact of different parameters in whole cohort on 90-day mortality. Controlling for other covariates like age, sex and different groups, liver failure and acute variceal bleed (AVB) were predictors of 90-day mortality with HR = 1.785 (95% CI 1.196-2.663, P = 0.005) and HR = 1.810 (95%CI 1.020-3.213, P = 0.043) respectively. Further, cox regression analysis of different parameters of ALD-ACLF revealed that serum bilirubin was predictor of increased 90-day mortality with HR = 1.037[95%CI 1.002-1.074, P = 0.040]. In MASLD-ACLF, liver failure, INR and AVB were predictors of increased 90-day mortality with HR 3.015 [95%CI 1.553-5.852, P = 0.001], HR 2.477 [95%CI 1.198-5.122, P = 0.014] and HR 1.491 [955CI 1.057-2.103, P = 0.023] respectively. On the other hand, male sex was associated with decreased risk of 90-day mortality with HR 0.565 [95% CI 0.335-0.953, P = 0.032] **Conclusion:** MASLD is involving more female patients with worst outcomes as compared to ALD. Presence of liver failure, deranged INR and AVB in these patients predict increased 90-day mortality in this group. We need prospective studies to further evaluate this subgroup for presence of comorbidities and their impact on outcomes.

Disclosures: Tarana Gupta: Nothing to Disclose, Ashok Kumar Choudhury: Nothing to Disclose, Rakhi Maiwall: Nothing to Disclose, Vinod Arora: Nothing to Disclose, Anand Kulkarni: Nothing to Disclose, Nothing to Disclose, Anand Kulkarni: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Anand Kulkarni: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Ashish Kumar: Roche: Consultant, Viatris: Consultant, Sun Pharma: Advisor, Astra Zeneca: Advisor, Anil Arora: Nothing to Disclose, Ajay Duseja: Nothing to Disclose, Akash Shukla: Nothing to Disclose, Akash Roy: Nothing to Disclose, Abraham Koshy: Nothing to Disclose, AJIT SOOD: Nothing to Disclose, Ajay Kumar Mishra: Nothing to Disclose, Amna Butt: Nothing to Disclose, Ajay Kumar: Nothing to Disclose, Arun Valsan: Nothing to Disclose, Ashish Jha: Nothing to Disclose, Ameet Mandot: Nothing to Disclose, Chandan kumar Kedarisetty: Nothing to Disclose, Diana Payawal: Nothing to Disclose, Dibyalochan Praharaj: Nothing to Disclose, Dinesh Kumar Jothimani: Nothing to Disclose, Dong Joon Kim: Nothing to Disclose, Zhongping Duan: Nothing to Disclose, Md Karim: Nothing to Disclose, Gamal Shiha: Nothing to Disclose, Girish Kumar Pati: Nothing to Disclose, GUAN HUEI LEE: Nothing to Disclose, Harshad Devarbhavi: Nothing to Disclose, Maria Harutyunyan: Nothing to Disclose, Joy Varghese: Nothing to Disclose, Javed P: Nothing to Disclose, Jidong Jia: Nothing to Disclose, jinhua hu: Nothing to Disclose, Kemal Kalista: Nothing to Disclose, MSc MD: Nothing to Disclose, Krishnadas Devadas: Nothing to Disclose, Mamun Mahtab: Nothing to Disclose, MANOJ KUMAR SAHU: Nothing to Disclose, Man-Fung Yuen: AbbVie, Abbott Diagnotics, Aligos Therapeutics: Consultant, Arbutus Biopharma, Arrowhead Pharmaceuticals, Assembly Biosc: Consultant, Clear B Therapeutics, Dicerna Pharmaceuticals, Immuncore: Consultant, Fujirebio Incorporation, GSK, Gilead Sciences: Consultant, Immunocore, Janssen, Precision BioSciences: Consultant, Roche, Sysmex Corporation, Tune Therapeutics: Consultant, Vir Biotechnology and Visirna Therapeutics: Consultant, AbbVie, Assembly Biosciences, Arrowhead Pharmaceuticals, Aligos Therapeutics, Arbutus Biopharma: Grant/Research Support, Fujirebio Incorporation, Gilead Sciences, Immunocore, Clear B Therapeutics, GSK, Janssen: Grant/Research Support, Sysmex Corporation and Roche: Grant/Research Support, Fujirebio Incorporation, Gilead Sciences, Roche, Sysmex Corp, Aligos Therapeutics, Arbutus Biopharma: Speaking and Teaching, Precision BioSciences: consultancy, Ausperbio: consultancy, IntergerBio: consultancy, Tune Therapeutics: consultancy, Clear B Therapeutics, GSK, Immuncore, Janssen, Vir Biotechnology: Speaking and Teaching, Mithra Prasad: Nothing to Disclose, Mithun Sharma: Nothing to Disclose, Mohamed Rela: Nothing to Disclose, Neeraj Saraf: Nothing to Disclose, Narendra Choudhary: Nothing to Disclose, Nipun Verma: Nothing to Disclose, Omesh Goyal: Nothing to Disclose, Radha Dhiman: Nothing to Disclose, Shalimar kumar: Nothing to Disclose, Nothing to Disclose, Shalimar kumar: Nothing to Disclose, Nothing to Disclose, Sanjiv Saigal: Nothing to Disclose, Sudhir Maharshi: Nothing to Disclose, Sunil Dadhich: Nothing to Disclose, SUNIL

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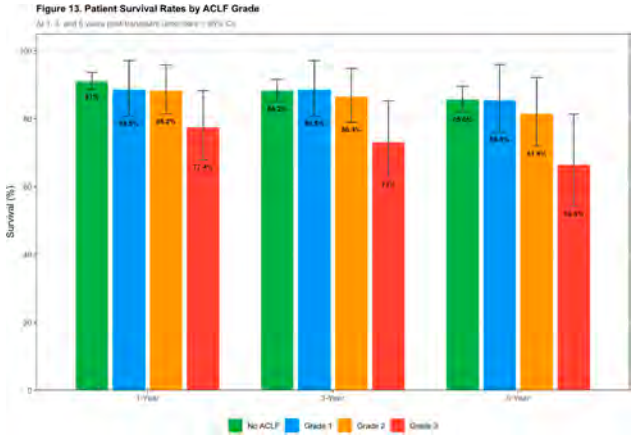
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TANEJA: Nothing to Disclose, Gupse Adali: Nothing to Disclose, Senam Kaur: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose.

2039 | LIVER TRANSPLANT OUTCOMES IN ACLF PATIENTS MANAGED IN A DEDICATED LIVER ICU

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Background: Dedicated liver intensive care units (LICU) may improve outcomes in critically ill liver patients, though their role remains controversial. We analyzed outcomes among Acute-on-Chronic Liver Failure (ACLF) patients managed in a dedicated LICU at a single tertiary care center who underwent liver transplantation (LT) over an 11-year period. **Methods:** We conducted a retrospective study evaluating outcomes among 816 LT recipients managed in Emory University's dedicated LICU between 2014 and 2025, including 244 patients with ACLF. Primary outcomes included 1-, 3-, and 5-year patient and graft survival comparing ACLF versus non-ACLF patients and stratified by ACLF grade (1-3). Secondary outcomes included total hospital length of stay, post-LT ICU length of stay, discharge disposition, and 30-day readmission rates. ChatGPT (OpenAI) was used solely to assist with language refinement and improve readability of the abstract. **Results:** Patients without ACLF demonstrated significantly better patient and graft survival compared to patients with ACLF. The presence of ACLF was associated with a 67% higher risk of mortality (HR 1.67, 95% CI 1.17–2.39, p = 0.005) and a 65% higher risk of graft loss (HR 1.65, 95% CI 1.16–2.35, p = 0.005). These differences were driven by poorer outcomes among patients with ACLF grade 3, whereas patients with ACLF grades 1 and 2 had survival rates comparable to those without ACLF (Figure 1). Both patient survival (log-rank p = 0.001) and graft survival (log-rank p = 0.0004) differed significantly across ACLF grades, with each incremental increase in ACLF grade associated with a 30% higher risk of mortality and graft loss (HR 1.30 for both, p < 0.001). Patients with ACLF grade 3 had a 2.32-fold higher risk of death (HR 2.32, 95% CI 1.48–3.65, p = 0.0003) and a 2.44-fold higher risk of graft loss (HR 2.44, 95% CI 1.56–3.81, p < 0.0001) compared to non-ACLF and ACLF grade 1 and 2 patients. ACLF was also associated with substantially greater healthcare utilization, particularly among ACLF grade 3 patients, who experienced significantly longer total hospital length of stay (median 35 vs 9 days, p < 0.001), longer ICU stay following transplant (median 8 vs 3 days, p < 0.001), and longer post-transplant length of stay (median 18 vs 8 days, p < 0.001) compared to non-ACLF patients. ACLF grade 3 patients were also significantly more likely to require inpatient rehabilitation (49% vs 4.4%, p < 0.001) and less likely to be discharged home (37% vs 93%, p < 0.001). **Conclusion:** Patients with ACLF Grades 1 and 2 managed in a dedicated LICU achieved post-liver transplant outcomes comparable to patients without ACLF. Although ACLF Grade 3 patients had worse outcomes, their 1-year survival still approached 80%, consistent with published literature despite the severity of illness in this population. Prospective multicenter studies are needed to further evaluate the impact of dedicated LICU care on post-transplant outcomes in ACLF patients.



Disclosures: Kathryn Thompson: Nothing to Disclose, Jake MacDonald: Nothing to Disclose, Nishita Sunkara: Nothing to Disclose, Naveena Murugan: Nothing to Disclose, Michael Yu: Nothing to Disclose, Hima Veeramachaneni: Nothing to Disclose, Ram Subramanian: Baxter: Consultant, Organox: Consultant, eGenesis: Consultant, Grifols: Consultant, Vantive: Consultant, Organox: Advisor, eGenesis: Advisor, Vignesh Jayaraman Muralidharan : Nothing to Disclose, Nader Dbouk: Nothing to Disclose.

2040 | THREE DATA-DRIVEN IMMUNOLOGICAL DIMENSIONS IMPROVE ACLF PREDICTION BEYOND MELD IN ACUTELY DECOMPENSATED CIRRHOSIS: AN AMBISPECTIVE COHORT STUDY

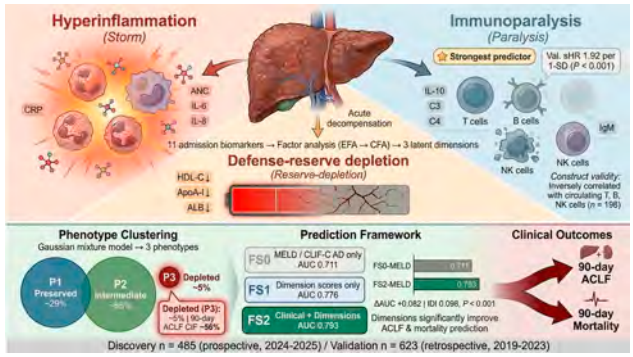
Ruiqi Li[1] Hao Ren[2] Jiale Shen[2] Jun Guo[2] Xiaoying Dong[2] Shū Jí Chén[2] Hongli Liu[2] Caiyun Zhang[2]

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Changhua Yi[2] Wei Chen[2] Qingfang Xiong[2] Xixuan Wang[2] Yongfeng Yang[2], [1]The Second Hospital of Nanjing, Southeast University, [2]The Second Hospital of Nanjing

Background: Immune dysregulation drives progression from acute decompensation of cirrhosis (ADC) to acute-on-chronic liver failure (ACLF), yet conventional clinical scores (MELD, CLIF-C AD) do not capture the underlying immunological heterogeneity. We aimed to discover and externally validate data-driven immunological dimensions from routine biomarkers, identify immunological phenotypes, and assess their incremental predictive value for ACLF and mortality beyond established clinical scores. **Methods:** In a prospective discovery cohort (n = 485) of hospitalized ADC patients, exploratory and confirmatory factor analysis (EFA/CFA) identified three latent dimensions from 11 routine biomarkers: hyperinflammation (CRP, ANC, IL-6, IL-8), immunoparalysis (IL-10, C3, C4, IgM), and defense-reserve depletion (HDL-C, ApoA-I, albumin). Gaussian mixture modeling on dimension scores classified patients into three phenotypes. Fine-Gray competing-risks models assessed 90-day ACLF risk (subdistribution hazard ratio [sHR]; death/transplantation as competing events), and Cox models assessed 90-day mortality. Prediction frameworks were compared: FS0 (clinical score alone), FS1 (dimension scores alone), and FS2 (clinical score + dimension scores). A retrospective validation cohort (n = 623) from the same center underwent one-shot frozen evaluation with no parameter modification. **Results:** The CFA model showed acceptable-to-good fit (discovery CFI = 0.954; validation CFI = 0.974, RMSEA = 0.050). Three phenotypes were identified: Preserved (P1, 28.7%), Intermediate (P2, 66.2%), and Depleted (P3, 5.2%). Compared with P1, P3 had markedly higher 90-day ACLF risk (sHR 5.94, 95% CI 2.90-12.20 in discovery; 11.93, 5.86-24.29 in validation; both P < 0.001) and 90-day mortality (HR 24.41, 8.77-67.95 and 6.59, 2.72-15.98, respectively). 90-day restricted mean survival time was 87.1, 79.2, and 50.9 days for P1, P2, P3, respectively. All three dimensions independently predicted ACLF and mortality after mutual adjustment (all P < 0.01). Adding dimension scores to MELD improved validation AUC for 90-day ACLF (FS2 0.793, 0.748-0.832 vs FS0 0.711, 0.661-0.756; delta-AUC = +0.082) and 90-day mortality (FS2 0.824, 0.777-0.863 vs FS0 0.754, 0.701-0.805; delta-AUC = +0.070). Construct validity was confirmed through immune cell correlations in a cytological subgroup (n = 196). Results were robust across CLIF-C AD-based models and five sensitivity analyses. **Conclusion:** Three data-driven immunological dimensions capturing hyperinflammation, immunoparalysis, and defense-reserve depletion significantly improve ACLF and mortality prediction beyond conventional clinical scores in ADC patients. This routine-biomarker-based framework enables mechanistically informed risk stratification at hospital admission and may guide phenotype-targeted management strategies.



Disclosures: Ruiqi Li: Nothing to Disclose, Hao Ren: Nothing to Disclose, Jiale Shen: Nothing to Disclose, Jun Guo: Nothing to Disclose, Xiaoying Dong: Nothing to Disclose, Shū Líng Chén: Nothing to Disclose, Hongli Liu: Nothing to Disclose, Caiyun Zhang: Nothing to Disclose, Changhua Yi: Nothing to Disclose, Wei Chen: Nothing to Disclose, Qingfang Xiong: Nothing to Disclose, Xixuan Wang: Nothing to Disclose, Yongfeng Yang: Nothing to Disclose.

2041 | SERUM GALECTIN-3 IS ASSOCIATED WITH ORGAN FAILURE BURDEN AND IMPROVES MORTALITY RISK STRATIFICATION IN ACUTE-ON-CHRONIC LIVER FAILURE

Osvely Méndez-Guerrero[1] Claudia Daniela López-López[2] Anaisa Carranza-Carrasco[2] Yesica Meraz Arredondo[2] Rodrigo Guerrero-Guerrero[2] Alfonso Rodriguez-Espada[3] Alma Estanes-Hernández[2] Aldo Torre[4] Ignacio Garcia Juarez[5] Graciela Castro-Narro[6] Ashuin Kammar García[7] Nalu Navarro-Alvarez[8], [1]Instituto Nacional de Ciencias Medicas y Nutrición Salvador Zubiran, [2]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, [3]Panamerican University School of Medicine, [4]Medical Center ABC. Mexico City., [5]The National Institute of Medical Science and Nutrition, [6]Hospital Médica Sur, Ciudad de México. Instituto Nacional de Ciencias Médicas y Nutrición, [7]Instituto Nacional de Geriatría, [8]University of Colorado Anschutz Medical Campus/Instituto Nacional de Ciencias Médicas y Nutrición

Background: Short-term mortality in acute-on-chronic liver failure (ACLF) is driven by the interaction between hepatic decompensation, systemic inflammation, and extrahepatic organ failure. Although MELD, Child-Pugh, and CLIF-C ACLF are widely used for prognostic assessment, biomarkers that reflect inflammatory and tissue-remodeling pathways may improve early risk stratification. Galectin-3 (Gal-3), a macrophage-derived lectin involved in fibrosis, inflammation, and tissue injury, has been associated with

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cirrhosis severity and adverse outcomes. Despite its biological relevance in cirrhosis, Gal-3 has received limited attention in ACLF, a syndrome defined by acute inflammation, organ failure, and early mortality. We evaluated admission Gal-3 in relation to ACLF severity, organ failure burden, short-term mortality, and prognostic performance beyond CLIF-C ACLF. **Methods:** In this prospective cohort study, patients admitted with acute decompensation were screened for ACLF according to EASL-CLIF criteria within the first 7 days of hospitalization. Serum Gal-3 levels were measured at admission by ELISA, and patients were categorized according to Gal-3 tertiles. The primary outcome was all-cause mortality at 7, 28, and 90 days. Prognostic performance was evaluated using Harrell's C-index. **Results:** A total of 131 patients with ACLF were included. Median age of 54 years and mean MELD score of 28 ± 7. Patients were stratified by serum Gal-3 tertiles: T1 < 14.6 ng/mL, T2 14.6–27.1 ng/mL, T3 > 27.1 ng/mL. Higher Gal-3 levels were associated with greater disease severity, with progressively higher MELD scores across T1, T2, and T3 (26 ± 5 vs. 29 ± 7 vs. 30 ± 8; p = 0.019), CLIF-C ACLF scores (49 ± 7 vs. 52 ± 11 vs. 56 ± 11; p = 0.006), and CLIF-OF scores [11 (10–12) vs. 11 (10–13) vs. 12 (11–14); p = 0.004]. The proportion of patients with ACLF grade 3 also increased across Gal-3 tertiles (20.5% vs. 34.1% vs. 48.8%; p = 0.013). Among individual organ failures, liver failure (34.1% vs. 52.3% vs. 69.8%; p = 0.001) and renal failure (27.3% vs. 47.7% vs. 53.5%; p = 0.033) increased significantly with higher Gal-3 levels, whereas other organ failures did not differ across tertiles. Adding Gal3 to the CLIF-C ACLF model improved discrimination for 7, 28, and 90-day mortality, with C-index values of 0.801, 0.766, and 0.718 compared with 0.782, 0.731, and 0.681 for CLIF-C ACLF alone. During 90-day follow-up, mortality increased stepwise across T1, T2, and T3 (48.8% vs. 72.1% vs. 79%; log-rank p < 0.001), with significantly reduced survival among patients with higher Gal-3 levels (Figure 1). **Conclusion:** Elevated serum Gal-3 levels identify patients with ACLF who have greater disease severity, higher liver and renal failure burden, and worse short-term survival. The addition of Gal-3 improved mortality discrimination beyond CLIF-C ACLF alone, supporting its potential role as an admission biomarker for prognostic stratification in ACLF.

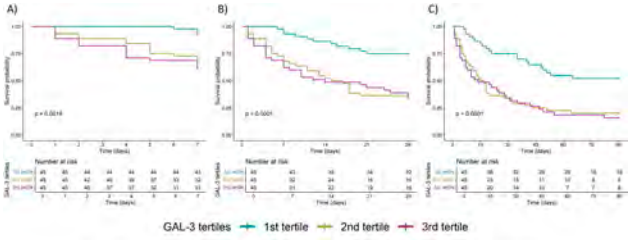


Figure 1. Kaplan–Meier survival analysis at 7, 28, and 90 days according to serum Gal-3 tertiles.

Disclosures: Osvely Méndez-Guerrero: Nothing to Disclose, Claudia Daniela López-López: Nothing to Disclose, Anaisa Carranza-Carrasco: Nothing to Disclose, Yesica Meraz Arredondo: Nothing to Disclose, Rodrigo Guerrero-Guerrero: Nothing to Disclose, Alfonso Rodriguez-Espada: Nothing to Disclose, Alma Estanes-Hernández: Nothing to Disclose, Aldo Torre: Nothing to Disclose, Ignacio Garcia Juarez: Nothing to Disclose, Graciela Castro-Narro: Novonordisk: Speaker honoraria and advisory board, Gilead: Speaker honoraria, Grünanthalñ: Speaker honoraria, Boehringer Ingelheim: Speaker honoraria, Ashuin Kammar García: Nothing to Disclose, Nalu Navarro-Alvarez: Nothing to Disclose.

2043 | OMENTIN-1 DERIVED FROM M2-LIKE MACROPHAGES IN THE FIBROTIC LIVER MEDIATES THE HEPATOPROTECTION AGAINST ACUTE INSULT IN ACUTE-ON-CHRONIC LIVER FAILURE BY INHIBITING FERROPTOSIS SIGNALING

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Background: Acute-on-chronic liver failure (ACLF) is a life-threating clinical syndrome characterized by acute onset of hepatic dysfunction superimposed on underlying chronic liver disease, with high short-term mortality and limited effective therapeutic strategies. Omentin-1 is an adipokine predominantly secreted by visceral adipose tissue, which has been reported to exert protective effects against metabolic disorders and inflammatory responses. However, its specific role and underlying mechanism in the progression of ACLF remain to be elucidated. **Methods:** Control and fibrotic mice were challenged with D-GalN/LPS, omentin-1 levels were detected by WB, IHC and qPCR. Gain-of-function experiment (recombinant omentin-1) was conducted in ALF mice, and hepatic damage was assessed. The correlation between omentin-1 and M2 macrophage markers was analyzed. Macrophage depletion was performed in fibrotic mice, and omentin-1 expression was evaluated. Fibrotic mice upon macrophage depletion were treated with recombinant omentin-1, and hepatic injury was assessed. Ferroptosis levels were evaluated in fibrotic mice or ALF mice upon omentin-1 treatment. **Results:** The gene and protein expression of omentin-1 was significantly up-regulated in fibrotic mice compared to ALF mice, regardless of acute insult. Recombinant omentin-1 conferred mice enhanced resistance upon acute insult, as manifested by elevated survival rate, improved hepatic histopathology, and reduced levels of serum aminotransferases. Omentin-1 was co-localied with CD206, a representative M2 macrophage activation marker. Moreover, the expression of omentin-1 was positively correlated with the levels of M2 markers TGF-β and Arg-1. In addition, the administration of recombinant omentin-1 led to the reduced expression of M1 markers

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and elevated M2/M1 ratios. When we depleted M2-like macrophages in fibrotic livers, the gene and protein expression of omentin-1 was obviously decreased. Macrophage depletion in the fibrotic mice resulted in aggravated hepatic damage, however, the administration of recombinant omentin-1 restored hepatic function, as shown by decreased levels of aminotransferases. Ferroptosis levels assessed by MDA and GSH were remarkably reduced in the fibrotic livers compared with those in ALF mice, regardless of acute insult. On the other hand, recombinant omentin-1 also brought about the evident reduction in ferroptosis levels. Interestingly, the administration of ferroptosis inducer erastin destroyed the hepatoprotection mediated by recombinant omentin-1 against acute insult. **Conclusion:** Omentin-1 derived from M2-like macrophages in the fibrotic liver mediates the hepatoprotection against acute insult in ACLF by inhibiting ferroptosis signaling. Our work provides novel insights into the pathogenesis and treatment of ACLF.

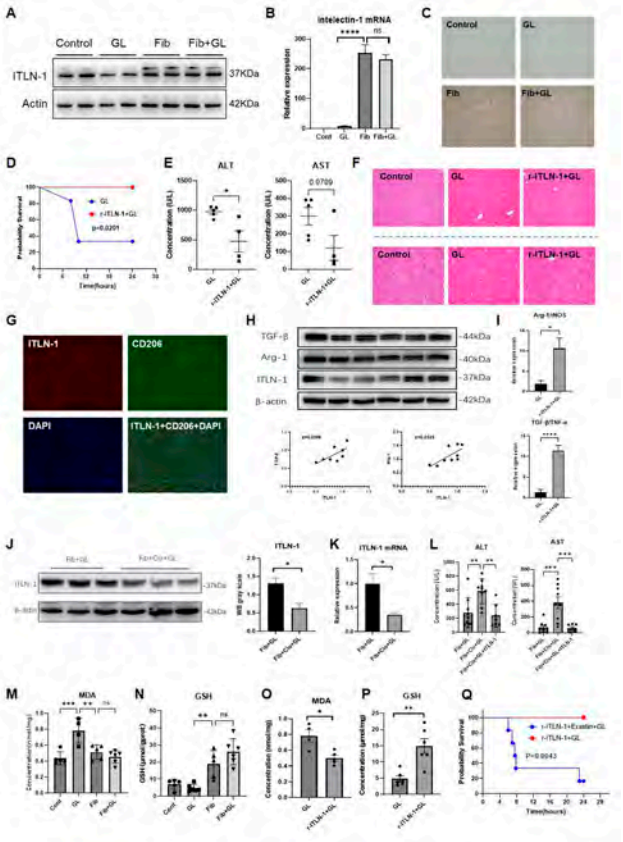


Figure: Omentin-1 (ITLN1) protects against ferroptosis-mediated liver injury by promoting M2 macrophage polarization in acute-on-chronic liver failur (ACLF). (A, B, C) Gene and protein expression of omentin-1 (ITLN1) was upregulated in fibrotic livers compared to acute liver failure (ALF) mice. (D, E, F) Administration of recombinant omentin-1 (r-ITLN1) conferred enhanced resistance to acute insult in ALF mice. (G, H, I) Immunofluorescence showed that ITLN1 co-localized with the M2 macrophage marker CD206. Western blot analysis revealed positive correlations between ITLN1 and M2 markers (TGF-β and Arg-1). Furthermore, r-ITLN1 treatment reduced M1 marker expression while increasing the M2/M1 ratio. (J, K, L) Depletion of M2 macrophages reduced ITLN1 expression and aggravated liver injury, whereas r-ITLN1 administration restored hepatic function. (M, N) Ferroptosis levels, assessed by MDA and GSH, were significantly lower in fibrotic livers compared with those in ALF mice, regardless of acute insult. (O, P) Administration of r-ITLN1 led to a significant reduction in ferroptosis levels. (Q) Erastin destroyed r-ITLN1-mediated hepatoprotection.

Disclosures: Yanrong Yang: Nothing to Disclose, Huixin Tang: Nothing to Disclose, Qi Yang: Nothing to Disclose, Xiaoxuan Liu: Nothing to Disclose, Li Bai: Nothing to Disclose, yu chen: Nothing to Disclose.

2044 | FLUX-CENTRIC COARSE-GRAINING OF HEPATIC METABOLISM CAPTURES ACUTE-ON-CHRONIC DYNAMICS IN ALCOHOL-ASSOCIATED LIVER DISEASE

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Background: Alcohol-associated liver disease (ALD) and its most severe manifestation, alcohol-induced hepatitis (AH), carry short-term mortality rates of 30–50%, yet therapeutic options remain limited. A central barrier is an incomplete understanding of the metabolic mechanisms driving hepatic failure. Existing frameworks largely focus on isolated pathway defects, but metabolic dysfunction in AH likely reflects coordinated dysregulation across interconnected subsystems. We propose that hyperammonemia, a hallmark of severe AH, arises not as a direct product of ethanol metabolism, but as an emergent property of resource competition between the glutathione, methionine, urea, and fatty acid biosynthesis cycles under oxidative stress. **Methods:** We developed a reduced-order, flux-centric model coarse-graining hepatic metabolism into four interacting metabolic modules (glutathione, methionine, urea, and fatty acid biosynthesis cycles) derived from the Human1 genome-scale metabolic network. Module interactions were encoded via a biochemically derived adjacency matrix. Patient-specific initial velocities were estimated from RNA sequencing data of 90 human liver biopsies spanning seven disease states using the Pheflux entropy-maximization algorithm. Ethanol was introduced as an external forcing term driving oxidative and metabolic burden, with resource reallocation governed by a priority-weighted allocation rule. Uncertainty quantification was performed over physiologically constrained parameter ranges using variance-based sensitivity analysis. **Results:** Across a broad parameter space, the model reproduced key features of ethanol-induced metabolic dysfunction: decreased methylation capacity, impaired nitrogen metabolism, mitochondrial glutathione depletion, and increased fatty acid biosynthesis. GSH depletion matched mouse experimental data within 5% at 2 and 6 hours post-ethanol exposure. Further, simulated corticosteroid response rates (70–76%) bracketed a published clinical benchmark of 75% without calibration. The trajectory space partitioned into four mechanistically distinct failure regimes defined by oxidative failure and metabolic

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decompensation. Sensitivity analysis revealed that repeated ethanol exposure shifts system behavior from parameter-driven to interaction-dominated dynamics, consistent with loss of compensatory capacity. **Conclusion:** This coarse-grained, resource-allocation framework reproduces emergent features of ALD progression and identifies bifurcation-like stability thresholds separating recoverable from non-recoverable metabolic states. The results support a network-level view of ALD in which disease severity reflects coordinated subsystem dysregulation rather than isolated pathway failure, offering a mechanistically interpretable and computationally tractable tool for studying metabolic resilience and therapeutic response.
Disclosures: Madison Shoraka: Nothing to Disclose, Rajanikanth Vadigepalli: Nothing to Disclose.

2045 | HEPATIC DECOMPENSATION AS A MORTALITY MULTIPLIER IN INFLAMMATORY BOWEL DISEASE HOSPITALIZATIONS: TRANSFER BURDEN, SEVERE INPATIENT OUTCOMES, AND RESOURCE USE IN A CONTEMPORARY NATIONAL ANALYSIS

Anas Al Mardini[1] Sabah Kulsum[2] Harika Dadigiri[2] Prathuima Guntipalli[2] Edward Barbarito[3], [1]NYMC, [2]NYMC-St Clare/St Mary hospital, [3]St Clare hospital

Background: Inflammatory bowel disease (IBD) is associated with hepatobiliary comorbidity, yet the inpatient impact of hepatic decompensation among IBD hospitalizations is not well defined. We evaluated whether compensated cirrhosis and hepatic decompensation were associated with mortality, transfer burden, severe inpatient outcomes, and resource use among U.S. IBD hospitalizations. **Methods:** We performed a retrospective cross sectional analysis of adult IBD hospitalizations in the 2020-2022 National Inpatient Sample. Crohn's disease and ulcerative colitis were identified using ICD-10-CM codes. Hospitalizations were categorized as IBD without cirrhosis/decompensation, IBD with compensated cirrhosis, or IBD with hepatic decompensation, defined by ascites, hepatic encephalopathy, variceal bleeding, spontaneous bacterial peritonitis, or hepatorenal syndrome. Outcomes included in-hospital mortality, acute-care transfer-in, sepsis, acute kidney injury (AKI), mechanical ventilation, discharge to facility, length of stay (LOS), and total hospital charges. Survey-weighted models adjusted for age, race/ethnicity, payer, and ZIP-code income quartile. **Results:** Among 929,629 weighted adult IBD hospitalizations, 2.08% had compensated cirrhosis and 3.34% had hepatic decompensation. Weighted mortality increased from 1.91% in IBD without cirrhosis/decompensation to 3.59% with compensated cirrhosis and 10.21% with hepatic decompensation. Compared with IBD without cirrhosis/decompensation, compensated cirrhosis was associated with increased adjusted odds of mortality (aOR 1.85, 95% CI 1.54-2.22), while hepatic decompensation was associated with a sixfold increase (aOR 6.24, 95% CI 5.67-6.88; both $P < 0.001$). Hepatic decompensation was also associated with higher odds of acute transfer-in (aOR 1.76, 95% CI 1.61-1.91), sepsis (aOR 2.68, 95% CI 2.52-2.84), AKI (aOR 2.58, 95% CI 2.43-2.75), mechanical ventilation (aOR 4.80, 95% CI 4.38-5.25), and discharge to facility (aOR 1.96, 95% CI 1.84-2.09). Resource use was markedly higher with hepatic decompensation, with mean LOS of 10.58 versus 5.49 days and mean charges of $150,476 versus $68,779. **Conclusion:** In this contemporary national analysis, hepatic decompensation was a powerful mortality multiplier among IBD hospitalizations and was associated with greater transfer burden, organ failure, mechanical ventilation, non-home discharge, and resource use. These findings support early recognition of hepatic decompensation as a high-risk inpatient phenotype in IBD and may inform triage, transfer, and multidisciplinary management strategies.
Disclosures: Anas Al Mardini: Nothing to Disclose, Sabah Kulsum: Nothing to Disclose, Harika Dadigiri: Nothing to Disclose, Prathuima Guntipalli: Nothing to Disclose, Edward Barbarito: Nothing to Disclose.

2046 | ISCHEMIC HEPATITIS CARRIES A 9-FOLD INCREASED ICU MORTALITY RISK: A POPULATION-LEVEL ANALYSIS OF 5,473 CASES

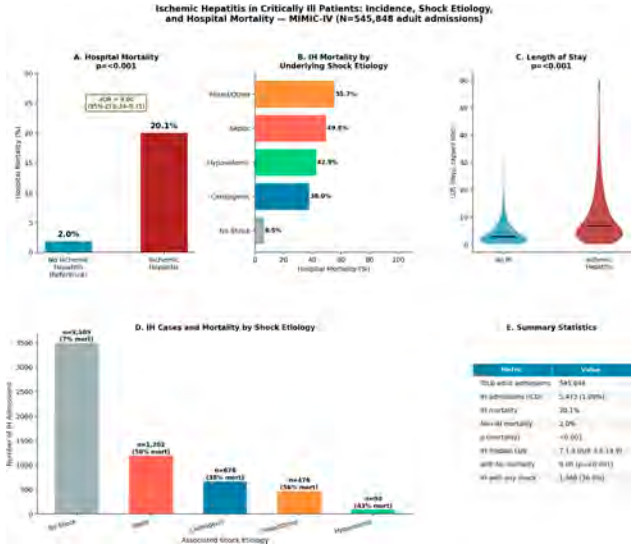
Innocent Lutaya[1] Vicki Oladoyin[1] Brian Xu[1] Emmanuel Marfo[1] Shanelle Brodeur[1] Abisola Ajayi[1] Shaikhoon Mohammed[1] Chima Amadi[1] Nicolas Bakinde[1] Henok Tafasse[1], [1]Morehouse School of Medicine

Background: Ischemic hepatitis (IH), or hypoxic hepatitis, arises from acute hepatocellular hypoperfusion and is encountered across diverse ICU populations. Despite its clinical significance, population-level incidence, shock-type-specific associations, and independent contribution to its mortality in a large unselected hospital cohort remain poorly characterized. **Methods:** We performed a retrospective cohort study using MIMIC-IV v3.1 comprising of 545,848 adult hospital admissions (2008-2022). IH was defined by ICD-10/ICD-9 codes for ischemic hepatitis, toxic liver disease, or acute hepatic failure (K76.89, K76.00, K72.00-11, K72.90-91, K76.2; ICD-9: 570.9, 573.0,

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573.1). Shock was classified by ICD codes into cardiogenic, septic, hypovolemic, and mixed/other subtypes. Primary outcome was in-hospital mortality. Logistic regression provided adjusted odds ratios (aOR) for IH-associated mortality; Mann-Whitney U test compared length of stay. **Results:** IH was identified in 5,473 admissions (1.00%; 58.7% male, median age 59). In-hospital mortality was 20.1% in IH vs. 2.0% in non-IH patients ($p < 0.001$; aOR 9.00, 95% CI 8.34-9.71). Median hospital LOS was 7.1 days (IQR 3.5-14.9) in IH vs. 2.8 days (IQR 1.1-5.6) in non-IH patients ($p < 0.001$). Shock was present in 36.0% of IH patients vs. 11.3% of non-IH patients ($p < 0.001$). Septic shock conferred the highest IH-associated mortality (49.8%), followed by cardiogenic shock (38.0%), hypovolemic shock (32.7%), and mixed/other shock (30.9%). IH without any shock carried 10.6% mortality, which suggested a 5-fold higher than non-IH controls. **Conclusion:** Ischemic hepatitis affects 1% of hospital admissions in a large tertiary-care database and independently carries a 9-fold increase in mortality risk. Shock is present in one-third of IH cases, with septic shock associated with highest mortality. IH without identifiable shock still carries substantial excess mortality, highlighting the importance of IH recognition across the full spectrum of hemodynamic instability.



Disclosures: Innocent Lutaya: Nothing to Disclose, Vicki Oladoyin: Nothing to Disclose, Brian Xu: Nothing to Disclose, Emmanuel marfo: Nothing to Disclose, Shanelle Brodeur: Nothing to Disclose, Abisola Ajayi: Nothing to Disclose, Shaikhoon Mohammed: Nothing to Disclose, Chima Amadi: Nothing to Disclose, Nicolas Bakinde: Nothing to Disclose, Henok Tafasse: Nothing to Disclose.

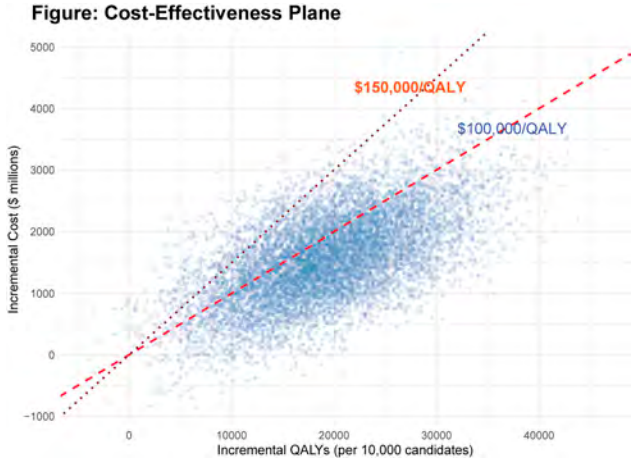
2047 | IS PRIORITIZING ACLF-3 FOR LIVER TRANSPLANTATION COST-EFFECTIVE? A COST-EFFECTIVENESS ANALYSIS

Tomohiro Tanaka[1] Dan Shane[2], [1]University of Iowa, [2]University of Iowa College of Public Health

Background: Acute-on-chronic liver failure grade 3 (ACLF-3) carries 28-day transplant-free mortality approaching 80%, yet MELD-based liver transplant (LT) allocation does not account for this short-term acuity. Although expedited allocation for ACLF-3 has gained clinical interest, the economic implications of such a policy have not been formally evaluated. **Methods:** A state-transition (Markov) model was constructed from the US healthcare payer perspective to compare two allocation strategies for a simulated cohort of 10,000 adult LT candidates listed with ACLF-3: (1) standard MELD-based allocation and (2) a top-priority strategy analogous to Status 1A designation. Pre-transplant probabilities were derived from US registry data. Post-transplant outcomes for the priority arm were based on counterfactual survival estimates from a previously published marginal structural model applied to OPTN data. The model incorporated three post-transplant health states (Stable, Deteriorated, Death) over a 20-year horizon, with monthly Markov cycles. The primary outcome was the incremental cost-effectiveness ratio (ICER) at a contemporary willingness-to-pay threshold of $150,000/QALY. One-way deterministic and probabilistic sensitivity analyses (10,000 Monte Carlo iterations) were performed. **Results:** Under the priority strategy, 93% of candidates received transplantation compared with 75.6% under MELD-based allocation, with the difference attributable to averted waitlist deaths. Over 20 years, the priority strategy generated 74,208 QALYs at a total cost of $6.80 billion versus 62,558 QALYs at $5.43 billion for the MELD strategy. The incremental gain was 1.2 QALYs per patient at an additional cost of $137,015 per patient (ICER: $117,608/QALY), below the $150,000/QALY threshold. In one-way sensitivity analyses, the ICER remained below $150,000/QALY in most scenarios. > Probabilistic sensitivity analysis demonstrated a 95% probability of cost-effectiveness at $150,000/QALY, with the majority of simulations falling within the cost-effective region of the cost-effectiveness plane (**Figure**). **Conclusion:** Granting top-priority LT allocation to ACLF-3 candidates is likely cost-effective over a 20-year horizon in the US. These findings provide economic support for ACLF-specific allocation reform and warrant prospective validation.

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Disclosures: Tomohiro Tanaka: Nothing to Disclose, Dan Shane: Nothing to Disclose.

2048 | PROGNOSTIC VALUE OF IMMUNITY, INFLAMMATION AND NUTRITION-RELATED BIOMARKERS FOR 28-DAY MORTALITY IN SEPSIS PATIENTS WITH CIRRHOSIS: A RETROSPECTIVE STUDY FROM MIMIC IV AND EICU

Yunhan Zhao[1] Jiamiao Shi[1] Kai Lu[1], [1]Xian Jiaotong University

Background: Sepsis in patients with cirrhosis is associated with markedly high short-term mortality, driven by a complex interplay of immune dysfunction, systemic inflammation, and hepatic decompensation. Reliable, readily available biomarkers for early risk stratification remain limited in this vulnerable population. This study aimed to identify and validate a robust immune-inflammatory-nutritional index for predicting 28-day mortality in cirrhotic patients with sepsis. **Methods:** Adult patients with a diagnosis of sepsis and cirrhosis were retrospectively enrolled from the MIMIC-IV database. Key candidate biomarkers were selected using the Boruta algorithm and LASSO regression. The independent prognostic value of selected indices was assessed by Cox proportional hazards regression, Kaplan–Meier survival analysis, and SHAP analysis. The primary index (PALBI) was further validated in an internal training/validation split and an external eICU cohort. Restricted cubic spline and segmented regression analyses were performed to explore dose-response and threshold effects, and subgroup analyses were conducted to assess effect modification. **Results:** Four indices (NPR, NMAR, BAR, and PALBI) were identified as candidate predictors, among which PALBI emerged as the most important. PALBI showed significant and consistent associations with 28-day mortality across internal and external validation cohorts. Restricted cubic spline and threshold analyses revealed a nonlinear relationship, with a critical inflection point at PALBI = -2.66, above which the risk of mortality increased sharply. The prognostic effect of PALBI remained stable across most subgroups, with a significantly stronger association observed in female patients. **Conclusion:** PALBI is a robust, externally validated biomarker for predicting short-term mortality in cirrhotic patients with sepsis. Its threshold-dependent association with mortality supports its use in early risk stratification, and may help guide individualized management strategies in this highrisk population.

Disclosures: Yunhan Zhao: Nothing to Disclose, Jiamiao Shi: Nothing to Disclose, Kai Lu: Nothing to Disclose.

2049 | VISTA DEFICIENCY EXACERBATES THE DEVELOPMENT OF ACUTE-ON-CHRONIC LIVER FAILURE BY PROMOTING TC1 DIFFERENTIATION

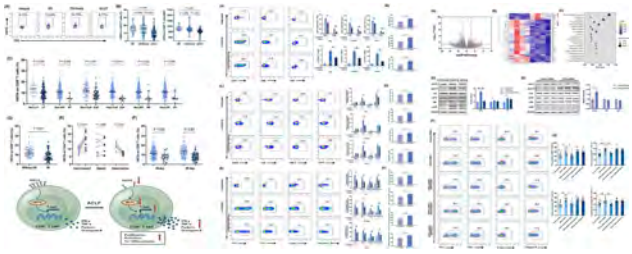
Yao Zhang[1] Yidi Jia[2] Xueyun Zhang[2] Jiming Zhang[2], [1]Huashan Hospital, Fudan University, [2]Huashan Hospital

Background: Acute-on-chronic liver failure (ACLF) has a high early mortality, and there is abundant evidence that persistent inflammatory response and immune activation are the core pathogenesis of ACLF. However, the mechanism of immune disorder has not been fully clarified. Previous studies have shown that deficiency of V-type immunoglobulin domain-containing suppressor of T-cell activation (VISTA) exacerbates the progression of inflammatory diseases. Moreover, the immune response mediated by CD8+T cells can directly cause liver damage and is closely related to the dysregulation of inflammatory response in ACLF patients. Our study was designed to investigate the role of VISTA expression on CD8+T cells in the pathogenesis of ACLF. **Methods:** We assessed the expression and function of VISTA on CD8+ T cells in blood samples from healthy controls, patients with stable cirrhosis, and ACLF patients. Transcriptome sequencing was performed to determine the relevant pathways, which was then verified by Western blot. Inhibitors of relevant signaling pathways were added to the CD8+ T cells to explore the key signal mechanism. **Results:** In ACLF patients, the expression of VISTA was significantly reduced in the CD8+ T cells compared with healthy subjects and stable cirrhosis patients, especially in the effector memory and terminally differentiated effector memory cells with high CD45RA

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expression subsets. The expression of VISTA on CD8+ T cells was associated with disease severity and prognosis. VISTA downregulation contributed to the activation and proliferation of CD8+ T cells, and enhanced the differentiation of type 1 cytotoxic T cells (Tc1), as well as heightened inflammatory cytokine secretion. This effect was mediated through the activation of the extracellular signal-regulated kinase 1 and 2 (Erk1/2) signaling pathway. **Conclusion:** Our study reveals that VISTA downregulation drives ACLF progression by amplifying Tc1-mediated inflammation. This insight not only advances the mechanistic understanding of ACLF pathogenesis but also nominates VISTA as a potential candidate for therapeutic intervention.

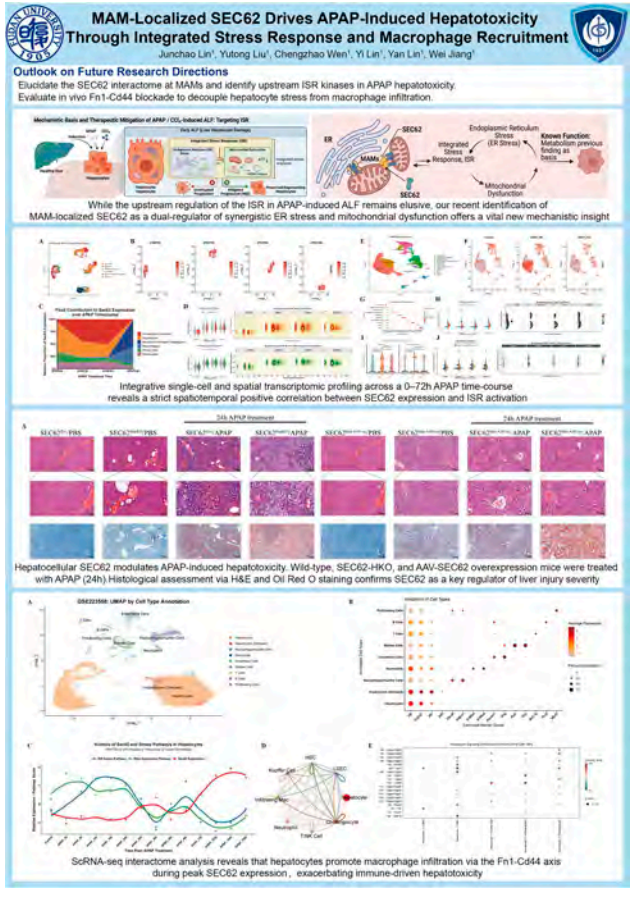


Disclosures: Yao Zhang: Nothing to Disclose, Yidi Jia: Nothing to Disclose, Xueyun Zhang: Nothing to Disclose, Jiming Zhang: Nothing to Disclose.

2050 | MAM-LOCALIZED SEC62 DRIVES APAP-INDUCED HEPATOTOXICITY THROUGH INTEGRATED STRESS RESPONSE AND MACROPHAGE RECRUITMENT

Junchao Lin[1], [1]Zhongshan Hospital Affiliated to Fudan University

Background: Acetaminophen (APAP) overdose causes acute liver failure (ALF) through endoplasmic reticulum (ER) stress and mitochondrial dysfunction, which trigger the Integrated Stress Response (ISR) and hepatocyte death. The upstream regulators of ISR activation remain unclear. We previously established that SEC62, localized at mitochondria-associated endoplasmic reticulum membranes (MAMs), regulates organelle homeostasis. This study investigates the spatiotemporal role of MAM-localized SEC62 in ISR activation and immune microenvironment remodeling during APAP-induced hepatotoxicity. **Methods:** Wild-type (WT), hepatocyte-specific SEC62 knockout (SEC62-HKO), and AAV-SEC62 overexpression mice received APAP. Liver tissues were collected across a 0-72h time course. We assessed histological severity and lipid accumulation at 24h using H&E and Oil Red O staining. We performed single-cell RNA sequencing (scRNA-seq) and spatial transcriptomics on liver tissues to evaluate transcriptional kinetics. Cell-cell communication analysis mapped ligand-receptor interactions and hepatocyte-macrophage crosstalk. **Results:** Combined scRNA-seq and spatial transcriptomics over a 0-72h APAP time-course showed a spatiotemporal positive correlation between hepatic SEC62 expression and ISR activation. *In vivo*, histological assessment at 24h showed SEC62-HKO attenuated, while AAV-SEC62 overexpression aggravated, APAP-induced liver necrosis and lipid accumulation, confirming SEC62 mediates injury severity. ScRNA-seq interactome analysis demonstrated that during peak SEC62 expression, hepatocytes promote macrophage infiltration via the Fn1-Cd44 axis, contributing to immune-mediated liver injury. **Conclusion:** MAM-localized SEC62 regulates APAP-induced ALF progression. Intracellularly, SEC62 upregulation mediates hepatotoxicity by activating the ISR. Extracellularly, SEC62 promotes macrophage recruitment via the Fn1-Cd44 axis. Our multi-omics and *in vivo* data show hepatocellular SEC62 drives APAP hepatotoxicity through intracellular stress and immune infiltration, identifying it as a potential therapeutic target.



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2051 | MYELOID 5-LIPOXYGENASE ACTIVATION DRIVES SYSTEMIC INFLAMMATION AND LIVER INJURY IN ACUTE-ON-CHRONIC LIVER FAILURE

Huilan Tu[1] Jing Guo[2] Ruoqi Zhou[1], [1]The First Affiliated Hospital of Zhejiang University, [2]Stanford University School of Medicine

Background: Acute-on-chronic liver failure (ACLF) is characterized by systemic inflammation, immune dysregulation, and high short-term mortality. However, the lipid inflammatory circuits that sustain myeloid activation and propagate liver injury remain incompletely defined. We investigated whether myeloid 5-lipoxygenase (5-LOX) activation contributes to inflammatory amplification in ACLF. **Methods:** We integrated single-cell RNA sequencing, bulk transcriptomics, targeted plasma oxylipid metabolomics, synchronized peripheral-portal-hepatic venous sampling, liver tissue validation, hepatocyte assays, and pharmacologic intervention in murine acute liver failure and acute-on-chronic liver injury models. 5-LOX pathway activity was assessed across immune compartments, disease stages, circulating lipid mediators, liver tissues, and experimental injury models. Hepatocyte responses to 5-oxo-ETE were evaluated under subthreshold ferroptotic stress. **Results:** 5-LOX pathway activity was predominantly enriched in monocytes/macrophages and neutrophils and increased with disease severity. In ACLF, neutrophils shifted from an interferon-high state toward an IL1R2^{+} inflammatory amplification state, while cell-cell communication analysis supported a leukotriene-centered myeloid-to-neutrophil signaling circuit. Circulating 5-LOX-derived oxylipins, including 5-HETE, 5-oxo-ETE, and LTB4, were elevated in ACLF. Tri-venous profiling demonstrated consistent peripheral enrichment of 5-oxo-ETE compared with portal and hepatic venous compartments, supporting extrahepatic generation. In liver tissues, 5-LOX expression was associated with infiltrating inflammatory myeloid cells. Functionally, 5-oxo-ETE increased hepatocyte susceptibility to subthreshold ferroptotic stress and induced rapid ERK activation. Across multiple murine liver injury models, 5-LOX inhibition with zileuton attenuated systemic inflammation, liver injury, and ferroptosis-related injury signatures. **Conclusion:** ACLF is characterized by a compartmentalized myeloid 5-LOX axis that links inflammatory oxylipid production to neutrophil activation, systemic inflammation, and liver injury. These findings identify 5-LOX as a mechanistically relevant and potentially targetable inflammatory pathway in ACLF.

Disclosures: Huilan Tu: Nothing to Disclose, Jing Guo: Nothing to Disclose, Ruoqi Zhou: Nothing to Disclose.

2052 | PBMC TRANSCRIPTOMICS REVEALS RISK-STRATIFIED MYELOID ACTIVATION AND IL1R2-ASSOCIATED INFLAMMATION IN HBV-ACLF

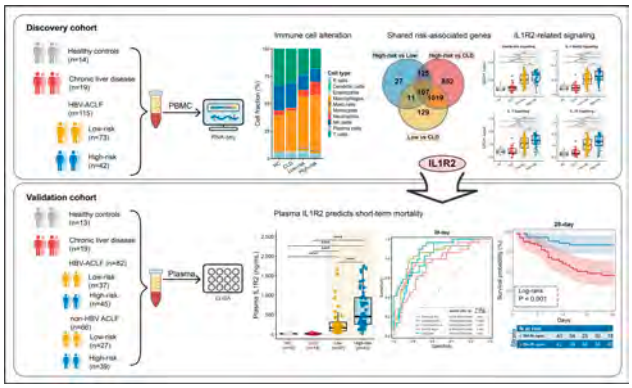
Jun Li[1] Xiao Wu[1] Xi Liang[1] Jiaojiao Xin[1] Dongyan Shi[1] Jing Jiang[1], [1]The First Affiliated Hospital, Zhejiang University School of Medicine

Background: Acute-on-chronic liver failure (ACLF) carries high short-term mortality, and risk stratification is clinically used to identify patients at increased risk of early death. This study aimed to characterize PBMC transcriptomic profiles across COSSH-ACLF II risk strata and evaluate plasma IL1R2 associated with risk and outcome in HBV-related ACLF. **Methods:** PBMC transcriptomes were profiled in healthy controls (n = 14), chronic liver disease (n = 19), low-risk HBV-ACLF (n = 73), and high-risk HBV-ACLF (n = 42), according to COSSH-ACLF II stratification. Representative immune genes were examined in experimental models, and plasma IL1R2 was measured by ELISA in independent HBV-related and non-HBV ACLF validation cohorts. **Results:** COSSH-ACLF II risk groups differed significantly in 28-day survival, with poorer survival in high-risk than low-risk HBV-ACLF (log-rank $P < 0.001$). High-risk ACLF showed increased monocyte, macrophage, and neutrophil signatures, together with reduced NK-cell and T-cell signatures, consistent with myeloid activation. Across risk-stratified comparisons, 107 shared risk-associated genes were identified, and leading immune pathways involved immune recognition, cytokine signaling, and innate effector responses. IL1R2 ranked among the top 10 shared risk-associated genes and was represented in four interleukin-related cytokine pathways, particularly IL-1 family signaling and IL-1 signaling. After immune-cell adjustment, IL1R2 remained associated with inflammatory signatures, whereas its inverse association with NK/T-cell signatures was largely attenuated. Representative genes from these immune categories were concordantly induced in acute liver failure mouse liver and LPS-stimulated RAW264.7 macrophages. Metabolic pathway alterations involved mitochondrial energy and carbohydrate metabolism, lipid and bile acid metabolism, amino-acid stress responses, and glycan remodeling, and were associated with IL1R2 and representative immune pathways. Plasma IL1R2 increased in high-risk patients, ACLF-2/3, and non-survivors with HBV-related ACLF. Plasma IL1R2 showed moderate discrimination for 28-day and 90-day mortality, with AUROCs of 0.738 and 0.723, and patients with plasma IL1R2 $\geq$304.58 ng/mL had poorer short-term survival. **Conclusion:** PBMC profiling revealed risk-associated myeloid activation and

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metabolic pathway alterations in HBV-related ACLF. IL1R2 represents a plasma-detectable candidate marker associated with higher risk, disease severity, and poor short-term outcome.



Disclosures: Jun Li: Nothing to Disclose, Xiao Wu: Nothing to Disclose, Xi Liang: Nothing to Disclose, Jiaojiao Xin: Nothing to Disclose, Dongyan Shi: Nothing to Disclose, Jing Jiang: Nothing to Disclose.

2053 | SINGLE-CELL MAPPING REVEALS CXCR2⁺ NEUTROPHIL–NETS AXIS DRIVING HEPATOCYTE NECROPTOSIS ACROSS ACLF ETIOLOGIES

Jun Li[1] Jinjin Luo[1] Xi Liang[1] Qian Zhou[1] Jiaojiao Xin[1] Jing Jiang[1] Meiqian Hu[1] Wei Qiang[1] Dongyan Shi[1], [1]The First Affiliated Hospital, Zhejiang University School of Medicine

Background: Acute-on-chronic liver failure (ACLF) is a life-threatening syndrome driven by dysfunction of multiple immune cell types and can arise from various etiologies. This study aims to comprehensively characterize the immune landscapes of ACLF across different etiologies and identify potential therapeutic targets. **Methods:** Single-cell sequencing was performed on peripheral blood mononuclear cells (49 samples) and hepatic non-parenchymal cells (12 samples) from ACLF, cirrhosis, chronic liver disease and healthy controls. Findings were validated by bulk transcriptomics, immunostaining, in vitro assays and murine ACLF models. **Results:** Single cell transcriptomic profiling of 594,255 cells revealed etiology dependent differences in the intrahepatic immune landscape. Hepatitis B virus (HBV)-ACLF was characterized by preserved but functionally exhausted lymphocytes, whereas non-HBV-ACLF showed enrichment of activated neutrophils and monocyte macrophage populations, while peripheral immune trajectories converged toward a terminal phenotype marked by aberrant myeloid expansion and amplified inflammatory cascades. CXCR2⁺ mature neutrophil was identified as an expanded subset in both the circulation and the liver of ACLF patients. Bulk liver transcriptomics and immunostaining from human and mouse samples confirmed enhanced neutrophil infiltration and widespread formation of neutrophil extracellular traps (NETs) in ACLF, which positively correlated with necroptosis pathways. In murine ACLF models, blockade of CXCR2 or inhibition of PADI4-dependent NET formation reduced NET generation, alleviated hepatic inflammatory injury, suppressed hepatocyte necroptosis, and improved survival outcomes. Clinically, plasma CXCR2 levels in ACLF patients correlated with liver injury, ACLF severity scores, and short-term mortality. **Conclusion:** CXCR2⁺ neutrophils represent a distinct subset driving hyperinflammation and immune exhaustion in ACLF, a syndrome that exhibits intrahepatic immune heterogeneity but peripheral convergence across different etiologies. Targeting the CXCR2–NETs axis may provide a promising immunomodulatory strategy for ACLF treatment.

Disclosures: Jun Li: Nothing to Disclose, Jinjin Luo: Nothing to Disclose, Xi Liang: Nothing to Disclose, Qian Zhou: Nothing to Disclose, Jiaojiao Xin: Nothing to Disclose, Jing Jiang: Nothing to Disclose, Meiqian Hu: Nothing to Disclose, Wei Qiang: Nothing to Disclose, Dongyan Shi: Nothing to Disclose.

2054 | DEFINING THE LIVER FAILURE CUT-OFF FOR SERUM TOTAL BILIRUBIN AND PT-INR AND IMPACT OF PRIOR DECOMPENSATION IN A COHORT OF 10,058 PATIENTS WITH CIRRHOSIS REQUIRING NON-ELECTIVE HOSPITALISATION.

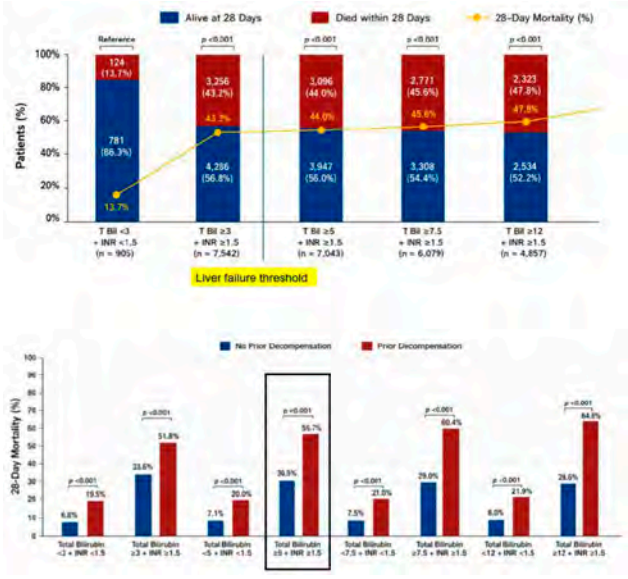
Ashok Kumar Choudhury[1] Garima Singhal[2] Shruti Reddy[3] Satender Pal Singh[1] Sanda Kavitha[2] Amanjot Kaur[2] Vinod Arora[2] Manoj Sharma[1] Shiv Kumar Sarin[2], [1]Institute of Liver and Biliary Sciences, [2]Institute of Liver and Biliary Science, [3]Institute of Liver Biliary Sciences

Background: Liver failure in patients with cirrhosis is associated with poor survival and the impact of prior decompensation is not well characterised among them. We aimed to identify bilirubin and INR thresholds associated with 28-day mortality in patients of cirrhosis with non-elective hospitalisation. **Methods:** This retrospective observational study included consecutive patients with cirrhosis admitted non-electively to the hospital. Clinical and laboratory parameters were retrieved from hospital medical records and analysed for 28-day survival outcomes. Previously established bilirubin and INR cut-offs were evaluated and compared according to index presentation and also correlated with index decompensation versus

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prior decompensation status. **Results:** A total of 10,058 patients with chronic liver disease [SS1] were included. The mean age was 46.0 ± 11.5 years, and 86.0% were male. Alcohol-related liver disease was the commonest etiology (58.4%), followed by viral liver disease (17.6%). The cohort represented a relatively sick population, with mean serum total bilirubin of 14.83 mg/dL, mean INR of 2.24, and anoverall 28-day mortality of 36.4%. Using the cut-off of total bilirubin <3 mg/dL with INR <1.5, 905 patients were categorised into a low-risk group, with a 28-day mortality of 13.7%.Increasing the bilirubin threshold to ≥ 5 mg/dL with INR ≥ 1.5 was associated with a significant rise in mortality to 44.0%. Further escalation of bilirubin thresholds to ≥ 7.5 mg/dL or ≥ 12mg/dL with INR ≥ 1.5 did not significantly improve sensitivity, specificity, PPV, or NPV for predicting 28-day mortality (Figure). Among patients with prior decompensation,mortality was consistently higher across all categories ($p < 0.01$). Mortality increased to 55.7% for the bilirubin ≥ 5 mg/dL with INR ≥ 1.5 category, to 60.4% for bilirubin ≥ 7.5 mg/dL with INR ≥ 1.5, and from 21.9% to 64.6% for bilirubin ≥ 12 mg/dL with INR ≥ 1.5 in presence of prior decompensation. **Conclusion:** Increasing total bilirubin thresholds with elevated INR and history of prior decompensation identifies the group with high mortality. A cut-off of serum total bilirubin ≥ 5 mg/dL with INR ≥ 1.5 identifies high-risk patients early and represents a data driven and clinically relevant definition of 'liver failure' associated with adverse short-term outcomes in cirrhosis.



Disclosures: Ashok Kumar Choudhury: Nothing to Disclose, Garima Singhal: Nothing to Disclose, Shruti Reddy: Nothing to Disclose, Satender Pal Singh: Nothing to Disclose, Sanda Kavitha: Nothing to Disclose, Amanjot Kaur: Nothing to Disclose, Vinod Arora: Nothing to Disclose, Manoj Sharma: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose.

★ 2055 | ROLE OF PLASMA EXCHANGE IN ACUTE-ON-CHRONIC LIVER FAILURE DUE TO HEPATITIS B REACTIVATION

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Background: Hepatitis B virus reactivation is an important cause of acute-on-chronic liver failure, particularly in Asia. Plasma exchange has been used to reduce serum bilirubin, bile acids, inflammatory mediators, and circulating toxins in patients with acute liver failure as a bridge to liver transplantation. However, its benefit in HBV-related ACLF remains variable across studies. **Methods:** Records of 200 patients with ACLF due to hepatitis B reactivation observed over the past 10 years were reviewed; 8 were excluded due to incomplete baseline data. 39 of 192 (20%) underwent therapeutic plasma exchange (PLEX) based on clinical deterioration, worsening LFTs and coagulopathy. All patients received standard medical treatment (SMT) in the ICU, including nutrition, diuretics and protocol based antibiotics and antifungals. Propensity score matching was performed to select 68 patients; 34 each in the PLEX plus SMT and SMT alone group. HBV reactivation was defined by serum HBV DNA $>20{,}000$ IU/mL, reappearance of HBsAg and/or HBV DNA, or a two-log increase in HBV DNA from baseline with ALT flare >5 times ULN. All patients received potent antiviral therapy; tenofovir alafenamide or entecavir. Outcomes included changes in MELD, bilirubin, albumin, ALBI, creatinine, INR, and predictors of mortality. **Results:** The baseline demographics were comparable between PLEX and SMT groups, with 76.5% being male. The mean age of the entire cohort was 50.72 ± 14.07, and baseline MELD score was 28.95 ± 7.2. Both PLEX and SMT groups had low albumin level (2.78 ± 0.5 vs 2.8 ± 0.76; p = 0.82) and high creatinine levels (1.27 ± 1.35 vs 1.7 ± 1.59; p = 0.23), with AKI in 50% and 64.7% respectively. In the PLEX group, compared to baseline, the post-PLEX serum bilirubin decreased from 24.87 ± 11.15 mg/dL

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to 20.89 ± 13.12 mg/dL and serum albumin increased from 2.86 ± 0.55 g/dL to 3.21 ± 0.55 g/dl (p 0.003). ALBI score improved from −0.73 ± 0.45 to −1.11 ± 0.51(p 0.001), serum albumin increased from 2.86 ± 0.55 g/dL to 3.21 ± 0.55 g/dl (p 0.003). However, the MELD score post-PLEX did not improve [29.15 ± 6.59 to 31.03 ± 11.56 (p = 0.23)], and it correlated with mortality(29.4%).Univariate analysis of predictors for mortality at baseline included MELD, creatinine, and haemoglobin. Multivariate analysis showed baseline creatinine [OR 1.57, 95% CI 1.03–2.4; p value 0.037] contributed to mortality at baseline. MELD was not an independent predictor of mortality (OR 0.97, 95% CI 0.88–1.07; p = 0.53). **Conclusion:** Plasma exchange in hepatitis B reactivation-related acute-on-chronic liver failure was associated with improvements in bilirubin and albumin levels, indicating short-term laboratory improvements. However, the MELD score did not improve significantly, and mortality was attributed to baseline disease severity, especially MELD score, and creatinine. Larger prospective studies are needed to determine whether plasma exchange offers a survival benefit in this high-risk population.

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2056 | PRE-TRANSPLANT ICU LENGTH OF STAY IS A STRONG PREDICTOR OF MORTALITY AFTER LIVER TRANSPLANT IN ACLF PATIENTS

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Background: Acute-on-chronic liver failure (ACLF) is characterized by multiorgan dysfunction and high mortality rates. Although post-liver transplant (LT) survival is significantly better than transplant-free survival, outcomes remain worse compared to patients without ACLF. Identifying predictors of post-LT mortality is important to optimize candidate selection given the scarcity of liver allografts. We evaluated the impact of pre-transplant ICU length of stay on survival post-LT in ACLF patients managed in a dedicated Liver ICU (LICU). **Methods:** We conducted a retrospective study to evaluate the impact of pre-transplant ICU length of stay on post-liver transplant survival in 244 patients with ACLF compared to 572 patients without ACLF who underwent liver transplantation between 2014 and 2025 at Emory University. ChatGPT (OpenAI) was used solely to assist with language refinement and improve readability of the abstract. **Results:** Compared to non-ACLF patients, ACLF patients undergoing liver transplantation were younger (median age 54 vs 58 years, p < 0.001) and had significantly greater illness severity at transplant, including higher MELD (33 vs 17) (p < 0.001). Alcohol-associated liver disease was more common among ACLF patients (45% vs 26%) (p < 0.001). ACLF patients also had substantially higher rates of CKD/ESRD (48% vs 22%), vasopressor use (24% vs 1.1%), pre-transplant intubation (14% vs 0.7%), infection prior to transplant (44% vs 4.4%), and hemodialysis/CRRT use (55% vs 1.0%) (all p < 0.001). ACLF patients demonstrated significantly inferior patient survival on Kaplan-Meier analysis (both log-rank p = 0.004) with 1-, 3-, and 5-year patient survival rates of 84.8%, 82.7%, and 77.7% in ACLF patients versus 91.0%, 88.2%, and 85.6% in non-ACLF patients, respectively. ACLF patients also had significantly greater healthcare utilization, including longer total hospital length of stay (LOS) (median 26 vs 9 days, p < 0.001) and longer post-transplant ICU LOS (median 5 vs 2 days, p < 0.001). Pre-transplant ICU LOS was a strong predictor of outcomes, with each additional ICU day associated with a 5% increased risk of mortality (HR 1.05, 95% CI 1.03–1.07, p < 0.001) and graft loss (HR 1.05, 95% CI 1.03–1.07, p < 0.001). Post-transplant ICU LOS was also associated with worse patient survival (HR 1.01, 95% CI 1.00–1.03, p = 0.034) and graft survival (HR 1.01, 95% CI 1.00–1.03, p = 0.030). Patients with prolonged post-transplant ICU stays (≥ 3 days) had significantly worse patient survival on Kaplan-Meier analysis (log-rank p = 0.02). **Conclusion:** In a cohort of 244 ACLF patients who received LT, pre-transplant ICU LOS had a significant impact on post-transplant survival, with each additional ICU day associated with a 5% increase in mortality risk. These findings suggest that prolonged pre-transplant ICU stay may be an important consideration when evaluating transplant candidacy in this high-risk patient population.

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Table 1: Baseline Characteristics by ACLF Status

Characteristic	Overall N = 816	No ACLF N = 572	ACLF N = 244	p-value
Age at transplant (years)	56 (53) / 57 [47,63]	58 (62) / 58 [49,63]	52 (12) / 54 [45,61]	<0.001
Race				0.8
White	597 (73%)	425 (74%)	172 (71%)	
Black or African American	147 (18%)	100 (17%)	47 (19%)	
Asian	33 (4.0%)	20 (3.5%)	13 (5.3%)	
American Indian or Alaska Native	4 (0.5%)	3 (0.5%)	1 (0.4%)	
Native Hawaiian or Other Pacific Islander	0 (0%)	0 (0%)	0 (0%)	
Other	8 (1.0%)	6 (1.0%)	2 (0.8%)	
Hispanic	22 (2.7%)	16 (2.8%)	6 (2.5%)	
Unknown	4 (0.5%)	2 (0.3%)	2 (0.8%)	
Unknown	1	0	1	
Sex/gender				0.2
Male	512 (63%)	368 (64%)	144 (59%)	
Female	304 (37%)	204 (36%)	100 (41%)	
Non-binary/Other	0 (0%)	0 (0%)	0 (0%)	
Unknown	0 (0%)	0 (0%)	0 (0%)	
Primary etiology				<0.001
ALD	257 (32%)	148 (26%)	109 (45%)	
MASH/Metabolic	188 (23%)	148 (26%)	40 (16%)	
HCV	160 (20%)	126 (22%)	34 (14%)	
HBV	12 (1.5%)	8 (1.4%)	4 (1.6%)	
Autoimmune Hepatitis	32 (3.9%)	22 (3.9%)	10 (4.1%)	
PBC	26 (3.2%)	17 (3.0%)	9 (3.7%)	
PSC	38 (4.7%)	32 (5.6%)	6 (2.5%)	
Cryptogenic	34 (4.2%)	24 (4.2%)	10 (4.1%)	

[1] Mean (SD) / Median (Q1,Q3); n (%)

[2] Wilcoxon rank sum test; Fisher's exact test; Fisher's Exact Test for Count Data with simulated p-value (based on 10000 replicates); Pearson's Chi-squared test

Characteristic	Overall N = 816	No ACLF N = 572	ACLF N = 244	p-value
DILI	10 (1.2%)	4 (0.7%)	6 (2.5%)	
Other	56 (6.9%)	41 (7.2%)	15 (6.2%)	
Unknown	3	2	1	
Any secondary etiology	270 (33%)	205 (36%)	65 (27%)	0.011
History of CKD				<0.001
None	571 (70%)	444 (78%)	127 (52%)	
CKD/ESRD	243 (30%)	127 (22%)	116 (48%)	
Unknown	2	1	1	
History of diabetes mellitus	250 (31%)	198 (35%)	52 (21%)	<0.001
Unknown	2	1	1	
History of CAD	185 (23%)	141 (25%)	44 (18%)	0.040
Unknown	2	1	1	
BMI at transplant (kg/m²)	30 (7) / 29 [25,34]	30 (7) / 29 [25,34]	31 (8) / 30 [26,34]	0.075
Unknown	9	9	0	
MELD at transplant	23 (10) / 21 [15,29]	19 (7) / 17 [13,23]	34 (7) / 33 [29,39]	<0.001
MELD-Na at transplant	24 (10) / 24 [16,31]	20 (7) / 20 [14,26]	35 (5) / 35 [31,40]	<0.001
MELD 3.0 at transplant	25 (10) / 24 [17,31]	20 (7) / 21 [15,25]	35 (6) / 35 [30,40]	<0.001
Unknown	1	1	0	
Vasopressors pre-transplant	63 (7.7%)	6 (1.1%)	57 (24%)	<0.001
Unknown	3	1	2	
Intubated pre-transplant	38 (4.7%)	4 (0.7%)	34 (14%)	<0.001
Infection pre-transplant	132 (16%)	25 (4.4%)	107 (44%)	<0.001
Return to OR (takeback)	119 (15%)	76 (13%)	43 (18%)	0.10
Unknown	4	1	3	
Hemodialysis/CRRT pre-transplant	139 (17%)	6 (1.0%)	133 (55%)	<0.001

[1] Mean (SD) / Median (Q1,Q3); n (%)

[2] Wilcoxon rank sum test; Fisher's exact test; Fisher's Exact Test for Count Data with simulated p-value (based on 10000 replicates); Pearson's Chi-squared test

Disclosures: Nishita Sunkara: Nothing to Disclose, Jake MacDonald: Nothing to Disclose, Kathryn Thompson: Nothing to Disclose, Naveena Murugan: Nothing to Disclose, Vignesh Jayaraman Muralidharan: Nothing to Disclose, Michael Yu: Nothing to Disclose, Hima Veeramachaneni: Nothing to Disclose, Ram Subramanian: Baxter: Consultant, Organox: Consultant, eGenesis: Consultant, Grifols: Consultant, Vantive: Consultant, Organox: Advisor, eGenesis: Advisor, Nader Dbouk: Nothing to Disclose.

2057 | CURRENT UTILISATION AND IMPACT OF PLASMA EXCHANGE TO TREAT ACUTE-ON-CHRONIC LIVER FAILURE PATIENTS IN USA: A NATIONAL INPATIENT SAMPLE ANALYSIS

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Background: Plasma exchange (PLEX) is a frequently used bridging therapy for patients with acute-on-chronic liver failure (ACLF) with studies reporting improved survival in patients with APASL and EASL defined ACLF (with no sepsis and shock). However, there is no data regarding utilisation of PLEX and its effect on in-hospital mortality in NACSELD defined ACLF which we aimed to assess. **Methods:** Using the National Inpatient Sample (NIS) database (2017–2023), we identified hospitalizations for ACLF based on NACSELD criteria. ICD-10 diagnosis and procedure codes were used. Patients with pre-existing neurologic or autoimmune conditions were excluded. PLEX-treated ACLF patients were matched to ACLF patients not receiving PLEX using propensity score matching (PSM). Matching variables included age, sex, liver disease etiology, comorbidities, and the need for invasive mechanical ventilation, vasopressors (shock), or renal replacement therapy (dialysis). Logistic regression was performed to identify independent predictors of in-hospital mortality. **Results:** Of 1,546,499 hospitalizations with cirrhosis, 207,362 (13.6%) met NACSELD ACLF criteria: Grade 1 (n = 163,217; 10.7%), Grade 2 (n = 38,965; 2.6%), and Grade 3 (n = 5,180; 0.3%). Only 267 (0.13%) patients underwent PLEX (Grade 1: 177, Grade 2: 80, Grade 3: 10). In a 1: 10 PSM cohort of ACLF grades 2 and 3 (42 PLEX vs. 420 SMT), in-hospital mortality was similar comparing the two groups (38% vs. 49.5%, p = 0.16). In a 1: 5 PSM cohort of Grade 1 ACLF (170 PLEX vs. 850 SMT), the PLEX group was younger and had lower rates of alcoholic cirrhosis, hepatic encephalopathy, and diabetes. However, the PLEX group had a higher prevalence of sepsis and required higher rates of mechanical ventilation and hemodialysis (Table 1). In-hospital mortality, total hospital charges, and length of stay were higher in the PLEX group. Among

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Grade 1, after adjusting for confounders, in-hospital mortality was similar in PLEX vs. SMT groups (OR 0.92; 95% CI, 0.56–1.5). Independent predictors of mortality among Grade 1 were invasive ventilation (OR 4.7; 95% CI, 3.3–6.6), shock (OR 4.3; 95% CI, 2.1–8.6), and hemodialysis (OR 2.5; 95% CI, 1.7–3.7). **Conclusion:** PLEX is rarely utilized for patients with NACSELD defined ACLF in the US and is not associated with reduced in-hospital mortality. Prospective studies are needed to examine the benefit of PLEX in patients with ACLF in US before multiorgan failure sets in.

Table 1: Comparison between PLEX and SMT treated PS matched ACLF grade 1 patients from National In-patient Sample 2017-2023 cohort

Parameters	PLEX (N=170)	SMT(N=850)	P value
Age (Mean±SD)	51.1±18.8	58.1±12.3	<0.001
Sex (female)	78 (45.9%)	327 (38.4%)	0.08
Etiology			
Alcohol associated cirrhosis	51 (30%)	388 (45.6%)	<0.001
HCV cirrhosis	10 (5.8%)	43 (5%)	0.66
HBV cirrhosis	2 (1.18%)	9 (1.06%)	0.89
Alcohol associated hepatitis	25 (14.7%)	129 (15.2%)	0.87
Hepatic encephalopathy	71 (41.8%)	570 (67.1%)	<0.001
Diabetes Mellitus	40 (23.5%)	271 (31.9%)	0.04
Obesity	14 (8.2%)	51 (6%)	0.27
Shock	10 (5.8%)	32 (3.7%)	0.2
Invasive Ventilation	100 (58.8%)	282 (33.2%)	<0.001
Sepsis	56 (32.9%)	169 (19.9%)	<0.001
Hemodialysis	67 (39.4%)	132 (15.5%)	<0.001
Outcomes:			
In-hospital mortality	57 (33.5%)	201 (23.6%)	0.009
Total charges (Mean±SD) in USD	481291±634993	142696±196160	<0.001
Length of stay (Mean±SD)	20.9±18.4	11.7±12.3	<0.001

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2058 | PREDICTION OF ACLF DEVELOPMENT IN A MULTI-CENTER OUTPATIENT CIRRHOSIS COHORT ACROSS NORTH AMERICA

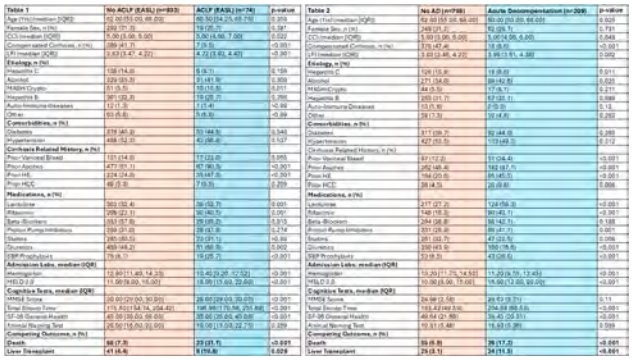
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Background: ACLF is variously defined worldwide using EASL, NACSELD and APASL definitions. Most ACLF diagnoses are made in inpatients, which is often too late to intervene. Predicting ACLF development in stable outpatients could improve prognostication & preventive strategies. **Aim**: Define determinants of ACLF development in a prospective multi-center outpatient etiology-controlled cirrhosis cohort. **Methods:** NACSELD-3 (North American Consortium for the Study of End-Stage Liver Disease) is a consortium that enrolls a compensated/decompensated outpatient cirrhosis cohort from 11 centers. Pts are etiology-controlled (no active alcohol/HCV/HBV) and followed systematically over 12 mths for hospitalizations. We excluded hospitalizations that were < 1 day, elective, or those when pt received LT. At baseline pts underwent frailty and cognitive testing and laboratory/medication evaluations. Determinants of time to ACLF by EASL, APASL, & NACSELD criteria and acute decompensation (AD) during hospitalizations were evaluated. Survival analysis for time-to-first ACLF & AD was performed accounting for the competing risks of death/LT. **Results:** Cohort : 1007 pts were included (Age 62 yrs, 69% men, 36% alcohol). 342 (33.9%) were hospitalized, of which 74 (22%) developed EASL-ACLF (Grade 1: 51, Grade 2: 22, Grade 3: 1), 15 (4.4%) developed NACSELD-ACLF & 11 (3.2%) developed APASL-ACLF. AD was seen in 209 (21%) patients. 9.0% died & 4.9% got LT.Baseline comparisons: EASL-ACLF pts had higher CCI , frailty index, were more likely to have decompensated cirrhosis/prior ascites/HE & related medications at baseline, had lower hemoglobin, higher MELD3.0, and worse cognition (Table 1). AD patients showed similar trends (Table 2).Time to event : Due to small N for others, we only did this for EASL-ACLF: ascites (adj. sHR: 3.28 [1.36-7.90], p = 0.008) & baseline MELD3.0 (adj. sHR: 1.14 [1.08-1.21], p < 0.001) were associated. Within hospitalized patients only, these associations persisted. Using AUC, the optimal MELD3.0 cutoff was 14 (AUC: 0.753, sHR: 3.93 [2.95-5.25], p < 0.001).*For time-to-AD*, ascites (adj. sHR: 2.79 [1.32-5.90], p = 0.007), HCC (adj. sHR: 2.18 [1.15-4.15], p = 0.017), PPI (adj. sHR: 2.54 [1.07-2.19], p = 0.019), & hemoglobin (adj. sHR: 0.81 [0.74-0.90], p < 0.001) were associated, which persisted on analysis of hospitalized patients only.

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Conclusion: Despite enrolling stable and etiology-controlled outpatients with cirrhosis, 34% required hospitalizations for acute decompensation over 12 months. 22% of these hospitalizations resulted in EASL-defined ACLF development. NACSELD and APASL-defined ACLF development were significantly lower. The presence of ascites tripled the risk, and each MELD3.0 point increased the risk by 14% of EASL-CLIF ACLF development. Even in stable outpatients, there is a substantial risk for ACLF development over one year, which can help early prognostication.



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2059 | EXTERNAL VALIDATION OF THE SALT-M SCORE IN LIVING DONOR LIVER TRANSPLANTATION FOR ACUTE-ON-CHRONIC LIVER FAILURE

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Background: The Sundaram Acute-on-Chronic Liver Failure–Liver Transplant Mortality (SALT-M) score predicts 1-year post-transplant mortality in patients with severe ACLF undergoing deceased donor liver transplant (DDLT). Its performance in living donor liver transplantation (LDLT) remains unknown **Methods:** We conducted an external validation of SALT-M in two independent ACLF cohorts undergoing LDLT: one from King Faisal Specialist Hospital and Research Centre (KFSHRC), Riyadh, Saudi Arabia (n = 121) and 57 patients that represent a global cohort from the International LDLT Registry. Model performance was assessed by predicted mortality distribution, association with observed outcomes, and comparison with MELD-based scores **Results:** One-year mortality was 14.9% in the KFSHRC cohort and 21.1% in the global cohort. Thirty-day and 90-day mortality were 4.1% and 8.3% in the KFSHRC cohort and 14.0% and 21.1% in the global cohort. SALT-M–predicted mortality was $\leq$ 30% in 95.9% and 98.2% of patients, respectively. In the KFSHRC cohort, median predicted mortality was 11.4% (IQR 6.5) and did not differ between survivors and non-survivors ($p = 0.435$). SALT-M predictions were not associated with observed 1-year mortality (OR 1.005, 95% CI 0.930–1.087; $p = 0.889$). In contrast, MELD-Na and MELD 3.0 were significantly higher in non-survivors in the global cohort ($p = 0.027$ and $p = 0.015$). White blood cell count was associated with mortality in the KFSHRC cohort ($p < 0.001$). **Conclusion:** In LDLT-dominant ACLF cohorts characterized by stringent candidate selection and restricted risk distributions, SALT-M demonstrates limited standalone discrimination for post-transplant mortality. These findings indicate the importance of case-mix–aware external validation and suggest that SALT-M should be applied cautiously as an adjunctive risk stratification

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tool rather than a universal threshold for transplant candidacy

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2060 | PROTON PUMP INHIBITOR PROMOTES GUT–LIVER AXIS DISRUPTION AND IMPAIR LIVER REGENERATION DURING ACUTE-ON-CHRONIC LIVER FAILURE

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Background: Proton pump inhibitors (PPIs) are widely prescribed in patients with cirrhosis and have been associated with gut dysbiosis, bacterial translocation, and adverse clinical outcomes. However, their impact on the development and progression of acute-on-chronic liver failure (ACLF) remains unclear. This study investigated whether PPI administration aggravates ACLF and explored the underlying mechanisms, with a particular focus on disruption of the gut–liver axis. **Methods:** ACLF was induced in cirrhotic mice established by chronic carbon tetrachloride (CCl4) administration, followed by acute double-dose CCl4 and lipopolysaccharide (LPS) exposure. Esomeprazole was administered before and during ACLF induction. Liver injury, inflammation, hepatic regeneration, renal dysfunction, intestinal barrier integrity, and gut microbiota alterations were evaluated using histological and molecular analyses, microcirculatory blood flow assessment, intestinal permeability assays, and 16S rRNA sequencing. **Results:** Esomeprazole significantly reduced survival and aggravated liver injury in ACLF mice, accompanied by enhanced hepatic macrophage infiltration and upregulation of proinflammatory cytokines. PPI treatment increased portal LPS levels, impaired intestinal barrier function, and induced gut dysbiosis characterized by reduced microbial diversity and depletion of barrier-protective taxa. Hepatic regeneration was markedly suppressed, as evidenced by decreased hepatocyte proliferation and reduced HNF4α expression, along with a shift toward aberrant progenitor cell–driven repair associated with impaired angiogenic maturation. Furthermore, esomeprazole exacerbated acute kidney injury, renal inflammation, microcirculatory dysfunction, and intrarenal microthrombosis. **Conclusion:** PPI administration worsens ACLF by disrupting the gut–liver axis, amplifying endotoxin-driven inflammation, impairing effective hepatic regeneration, and exacerbating renal injury. These findings suggest that cautious use of PPIs may be warranted in patients with ACLF.

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2061 | SENESCENT HEPATOCYTES HINDER UCMSCS PROLIFERATION BY UPREGULATING SSBP1 THROUGH THE IL-17 PATHWAY

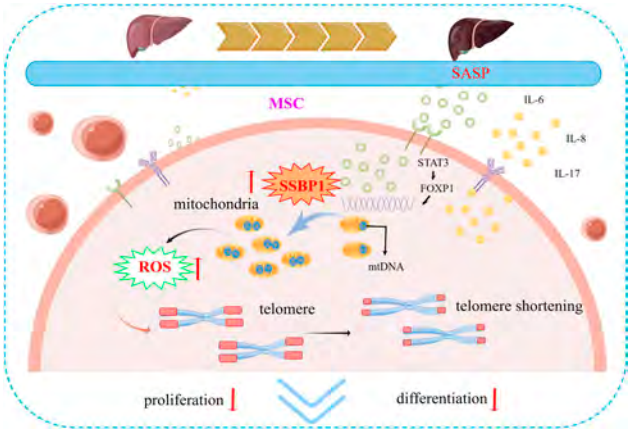
Min Qiu[1] Jiaqi Pan[1] Ka Zhang[1], [1]the Third Affiliated Hospital of Sun Yat-Sen University

Background: End-stage liver disease (ESLD) is prevalent and has a poor outlook. Mesenchymal stem cells (MSCs) are promising for ESLD treatment, but their effectiveness varies among individuals, possibly due to a senescent microenvironment with chronic inflammation and mitochondrial dysfunction. Single-stranded DNA-binding protein 1 (SSBP1) is key in mitochondrial biogenesis and repair, but it's unclear if this environment impacts MSC proliferation via SSBP1 expression. **Methods:** Doxorubicin (DOX) induced senescence in THLE-2 cells, and we used a Transwell co-culture system to study the effects of senescent hepatocytes on UCMSCs, measuring SSBP1 expression, cell viability, and apoptosis. We confirmed IL-17 role in regulating SSBP1 after screening inflammatory factors. Mitochondrial structure and function were evaluated in UCMSCs with SSBP1 overexpression or knockdown using CCK-8, flow cytometry, TEM, and western blotting. **Results:** DOX triggered dose-dependent senescence in THLE-2 cells. Senescent hepatocytes paracrinally upregulated SSBP1 in UCMSCs, accompanied by impaired cell viability and enhanced apoptosis. Persistently high IL-17 induced SSBP1expression time dependently. Either SSBP1 overexpression or knockdown inhibited UCMSC proliferation. SSBP1 overexpression increased morphologically abnormal mitochondria without altering membrane potential and ROS. SSBP1 knockdown reduced mitochondrial number, disrupted structure and raised

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membrane potential and ROS. COX IV was upregulated under both interventions. **Conclusion:** Senescent hepatocytes promote the upregulation of SSBP1 in UCMSCs via IL-17 signaling, thereby impairing the proliferative capacity of UCMSCs. Both the overexpression and knockdown of SSBP1 lead to the suppression of UCMSC proliferation. Thus, maintaining a balanced expression of SSBP1 is essential for preserving mitochondrial homeostasis and facilitating the proliferation of UCMSCs.



Disclosures: Min Qiu: Nothing to Disclose, Jiaqi Pan: Nothing to Disclose, Ka Zhang: Nothing to Disclose.

2062 | RACIAL DISPARITIES IN OUTCOMES OF ACUTE ON CHRONIC LIVER FAILURE IN THE UNITED STATES.

Ifelunwa Osanakpo[1] Cindy Onumajuru[1] Ihunanya Kanu[2] Cherechi Nwabueze[3] Emeka Stanley Obi[4] Chimezirim Ezeano[5], [1]Carle Foundation Hospital, [2]Baptist Memorial Hospital- Golden Triangle, [3]John H. Stroger Jr. Hospital of Cook County, [4]Brookdale University Hospital and Medical Center, [5]Advocate Aurora Healthcare

Background: Acute-on-chronic liver failure (ACLF) is characterized by multi-organ failure and is associated with worse outcomes. Few studies have assessed the impact of race on outcomes in patients with ACLF. We sought to determine whether racial and ethnic disparities affect outcomes in patients with ACLF. **Methods:** The study conducted a retrospective analysis of the National Inpatient Sample (NIS) Database from 2016 to 2022 to identify hospitalized patients with liver cirrhosis. ACLF was defined as two or more extrahepatic organ failures in patients with cirrhosis. The study population was divided into four major racial/ethnic groups: Non-Hispanic White (NHW), non-Hispanic Black (NHB), Hispanic, and Asian. The primary outcomes were in-hospital mortality, palliative referrals, liver transplantation, endoscopic therapy, and bleeding requiring transfusion. We conducted a weighted multivariate logistic regression to evaluate in-hospital outcomes. **Results:** Of 714,358 admissions for cirrhosis (2016 – 2022), 497,914 (69.7%) were NHW, 73,195 (10.2%) were NHB, 128,551 (18.0%) were Hispanic, and 14,698 (2.1%) were Asian. Hispanics were more likely to be younger (56.3 years vs. Asians 60.3, vs. NHB 58.1, vs. NHW 59.2 years). NHB were more likely to be female (NHB 40.0%; NHW 38.4%; Asians 36.1%; Hispanics 31.1%). Hispanics were more likely to be Medicaid-insured (38.1% vs. NHB 32.6% vs. Asians 27.4% vs. NHW 23.2%). NHB were in the lowest-income quartile and had a higher prevalence of comorbidities. ACLF severity was higher among NHB and Asians. Compared with NHW patients, in-hospital mortality was significantly higher in Black patients (aOR 1.11, 95% CI 1.07-1.45) and in Asian patients (aOR 1.23, 95% CI 1.15-1.31), and lower in Hispanics (aOR 0.92, 95% CI 0.89-0.95). Palliative referrals were similar among NHW, NHB, and Asian patients but were significantly lower among Hispanics than among NHW (aOR 0.78, 95% CI 0.67-0.85). The rates of liver transplantation were significantly lower among NHB (aOR 0.76, 95% CI 0.67-0.85) but higher among Asians (aOR 1.26, 95% CI 1.08-1.47). The rates of endoscopy were similar among NHB and Hispanics but significantly higher among Asians (aOR 1.09, 95% CI 1.04-1.15). The rates of bleeding requiring transfusion were significantly higher in all three racial/ethnic groups compared with NHW (NHB: aOR 1.12, 95% CI 1.08-1.16; Hispanic: aOR 1.25, 95% CI 1.21-1.29; Asians: aOR 1.39, 95% CI 1.30-1.48). **Conclusion:** Racial disparities in outcomes are observed among patients hospitalized with cirrhosis, highlighting the need for healthcare strategies stratified by race to mitigate the increased risk of adverse outcomes. Further research into the possible causes and social determinants of health that contribute to worse outcomes in Black and Hispanic patients is imperative.

Disclosures: IFELUNWA OSANAKPO: Nothing to Disclose, Cindy Onumajuru: Nothing to Disclose, Ihunanya Kanu: Nothing to Disclose, Cherechi Nwabueze: Nothing to Disclose, Emeka Stanley Obi:

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Nothing to Disclose, chimezirim ezeano: Nothing to Disclose.

2063 | DETERMINANTS OF PERSISTENT EARLY ACUTE KIDNEY INJURY AFTER LIVER TRANSPLANTATION: DISTINCT ROLES OF FRAILTY, RENAL RESERVE, AND PERIOPERATIVE INJURY

Ahmed Aboseria[1] Tasmia Promi[1] Michael Attanasi[1] Jade Pace[1] Justin Lin[1] Anwesha Satapathy[1] William Han[1] James Park[2] Nazia Qazi[2] Nabil Dagher[2] Sanjaya Satapathy[3], [1]North Shore University Hospital/Long Island Jewish Medical Center, [2]Northwell Health, [3]Northshore University Hospital/Northwell Health

Background: Frailty is increasingly recognized as an important determinant of outcomes in cirrhosis and liver transplantation (LT), but its relationship with postoperative acute kidney injury (AKI) remains unclear. We evaluated the association of frailty with persistent early postoperative AKI, renal recovery, and perioperative outcomes after LT. **Methods:** We performed a retrospective study of 208 adult LT recipients with pretransplant frailty assessment and postoperative renal data. Frailty was defined by Liver Frailty Index (LFI) ≥ 4.5. Persistent postoperative AKI was defined using KDIGO-based renal trajectory phenotypes with sustained AKI through postoperative day 7. Renal recovery was assessed by an estimated glomerular filtration rate (eGFR) at days 14, 30, and 90. Multivariable Firth logistic regression identified predictors of persistent postoperative AKI. **Results:** Among 208 recipients, 87 (41.8%) were frail and 100 (48.1%) developed persistent postoperative AKI. Frail recipients had lower baseline eGFR (63 vs 88 mL/min/1.73m², $p = 0.021$), higher prevalence of baseline eGFR < 60 mL/min/1.73m² (44.8% vs 28.9%, $p = 0.018$), greater perioperative transfusion requirements (22 vs 18 units, $p = 0.032$), and longer hospital stay (26 vs 19 days, $p = 0.0002$). However, frailty was not associated with persistent AKI, severe AKI, or renal recovery at 14, 30, or 90 days. In multivariable analysis, baseline eGFR < 60 mL/min/1.73m² was independently associated with lower odds of persistent AKI (OR 0.30, 95% CI 0.15–0.60, $p = 0.001$), while transfusion burden independently predicted persistent AKI (OR 1.017 per unit, 95% CI 1.002–1.033, $p = 0.033$). Frailty was not independently associated with persistent AKI (OR 0.72, 95% CI 0.38–1.34, $p = 0.31$). **Conclusion:** Frailty was associated with impaired baseline renal reserve, increased perioperative transfusion requirements, and prolonged hospitalization, but was not independently associated with persistent early postoperative AKI or renal recovery following LT. Persistent postoperative AKI appears to be driven predominantly by perioperative injury burden and renal adaptive physiology rather than frailty status alone. These findings suggest that frailty, renal reserve, and perioperative injury represent distinct but interconnected determinants of postoperative recovery after LT.

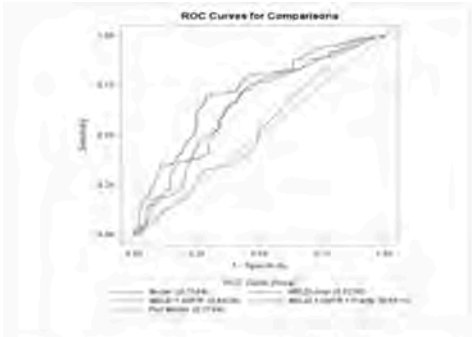


Figure 1. Receiver operating characteristic (ROC) curve analysis for prediction of persistent early postoperative acute kidney injury after liver transplantation. Receiver operating characteristic (ROC) curves demonstrating the discriminative performance of sequential predictive models for persistent early postoperative acute kidney injury (AKI). The MELD-only model demonstrated poor predictive ability (AUC 0.523). Addition of baseline renal reserve using pre-transplant eGFR improved discrimination (AUC 0.643), while inclusion of frailty provided minimal incremental improvement (AUC 0.652). The final multivariable model, incorporating frailty, baseline renal reserve, perioperative transfusion burden, and additional clinical covariates, demonstrated the highest predictive performance (AUC 0.718). These findings suggest that baseline renal physiology and perioperative injury burden contribute more substantially to persistent postoperative AKI risk than frailty status alone.

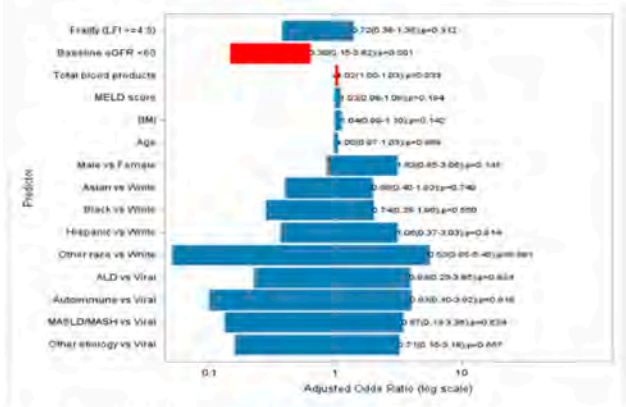


Figure 2. Multivariable predictors of persistent early postoperative AKI. Forest plot showing adjusted odds ratios and 95% confidence intervals from the missing-adjusted Firth penalized logistic regression model. Persistent postoperative AKI was defined using KDIGO-based early postoperative renal trajectory phenotypes. Red markers indicate predictors with $p<0.05$. Baseline eGFR <60 mL/min/1.73m² and total blood product utilization were independently associated with persistent AKI, while frailty was not independently associated.

Disclosures: Ahmed Aboseria: Nothing to Disclose, Tasmia Promi: Nothing to Disclose, Michael Attanasi: Nothing to Disclose, Jade Pace: Nothing to Disclose, Justin Lin: Nothing to Disclose, Anwesha Satapathy: Nothing to Disclose, William Han: Nothing to Disclose, James Park: Nothing to Disclose, Nazia Qazi: Nothing to Disclose, Nabil Dagher: Nothing to Disclose, Sanjaya Satapathy: Gilead Sciences: Grant/Research Support, Durect Pharma: Grant/Research Support, Fibronostics: Grant/Research Support, Novartis: Grant/Research Support, Zydus Pharma: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Intercept Pharma: Grant/Research Support, AKERO: Grant/Research Support, Altimmune: Grant/Research

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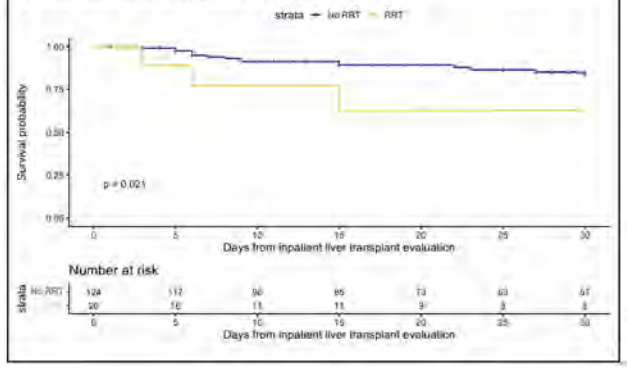
2064 | PALLIATIVE CARE CONSULTATION MODIFIES MORTALITY IN PATIENTS WITH RENAL REPLACEMENT THERAPY UNDERGOING INPATIENT LIVER TRANSPLANT EVALUATION

Katherine Cooper[1] Kathy Nguyen[2] Adil Fazir[3] VanAnh Pham[3] Navine Nasser-Ghodsi[4], [1]Massachusetts General Hospital, Harvard Medical School, [2]University of Massachusetts School of Medicine, [3]University of Massachusetts Chan Medical School, [4]University of Massachusetts Memorial Health Care

Background: Inpatient liver transplant evaluation (iLTE) is usually reserved for the subset of patients with acute on chronic liver failure (ACLF) who are too ill for routine outpatient evaluation. Outcomes for those who do not undergo liver transplant (LT) during iLTE are not well described, particularly for patients initiated on renal replacement therapy (RRT). **Methods:** This is a retrospective analysis of iLTEs at our center from 2019–2023. Patients were categorized based on need for RRT during iLTE (RRT vs. no RRT). Inpatient mortality was assessed in the full cohort and in the subgroup of patients who did not undergo LT during the index admission. Logistic regression was used to examine the association between RRT, palliative care (PC) consultation, and their interaction with inpatient mortality. Estimated probabilities of mortality were calculated and reported as percentages. **Results:** One in three patients (35%, n = 94) required RRT during iLTE. The RRT group was younger (50 vs. 54, p = 0.01) but did not differ in race (p = 0.52), sex (p = 0.27), or liver disease etiology (p = 0.24) compared to no RRT. During iLTE, RRT patients had increased ICU admission (79% vs. 30%, < 0.01), vasopressor initiation (68% vs. 12%, p < 0.01), and PC consultation (16% vs. 9%, p = 0.01); they were also more likely to be approved for LT during index admission (59% vs. 39%, p < 0.01). Among those not transplanted (n = 197), inpatient mortality was significantly higher in the RRT group (71% vs. 11%, p < 0.01). On logistic regression, both RRT (OR 27.3, 95% CI 11.5-64.90) and PC consult (OR 3.5, 95% CI 0.8-15.0) were associated with increased mortality; there was also a significant interaction between RRT and PC consult (OR 0.12, 95% CI 0.02-0.85, p = 0.034), indicating attenuated mortality risk when both were present. The interaction variable remained significant after adjustment for age, sex, and MELD (aOR 0.08, 95% CI 0.01-0.72, p = 0.02). Estimated probability of inpatient mortality was 20% lower in RRT patients with a PC consult compared to no PC consult. In contrast, estimated probability of death was 18% higher in non-RRT patients with a PC consult compared to no PC consult. Among patients discharged without LT, RRT was associated with increased post-discharge 30-day mortality (Figure 1); post-discharge death was numerically lower in RRT patients with compared to without PC consult (16.7% vs. 40.0%). **Conclusion:** These results demonstrate RRT as a dominant risk factor for short-term mortality among patients undergoing expedited, inpatient evaluation for LT. PC consultation was associated with different mortality patterns according to RRT status, with lower predicted mortality among non-transplanted patients requiring RRT who received PC consultation. These findings support timely PC integration for patients requiring RRT during iLTE, particularly when LT candidacy is uncertain or transplantation is not achieved.

Group	All patients: Probability of Death	Patients without LT: Probability of Death
No RRT + No Palliative	7.7 (4.4-13.1)	9.7 (5.6-16.3)
No RRT + Palliative	20.0 (6.6-47.0)	27.3 (9.0-58.6)
RRT + No Palliative	48.1 (37.3-59.0)	74.5 (60.9-84.6)
RRT + Palliative	40.0 (19.2-65.2)	54.5 (26.8-79.7)

Figure 1: Survival following discharge from inpatient liver transplant evaluation without receiving a LT in patients with RRT (Yellow, n=20) vs. No RRT (Blue, n=124). Mortality was significantly greater in patients with RRT .



Disclosures: Katherine Cooper: Nothing to Disclose, Kathy Nguyen: Nothing to Disclose, Adil Fazir: Nothing to Disclose, VanAnh Pham: Nothing to Disclose, Navine Nasser-Ghodsi: Nothing to Disclose.

2065 | DUAL VERSUS SINGLE ANTIVIRAL THERAPY IN HBV-RELATED ACUTE-ON-CHRONIC LIVER FAILURE PATIENTS

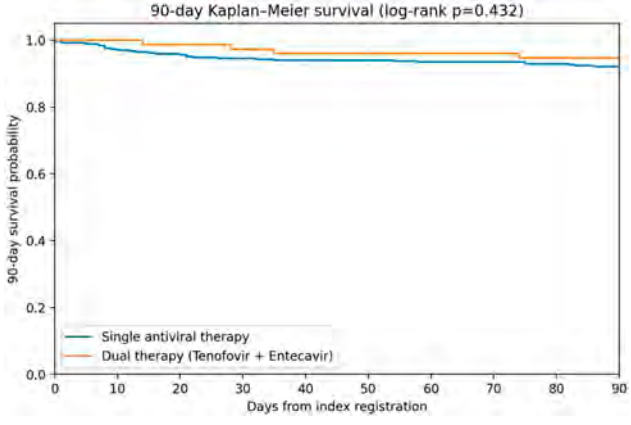
Shreya Singh[1], [1]Institute of Liver and Biliary Sciences

Background: HBV-related acute-on-chronic liver failure (HBV-ACLF) carries high short-term mortality despite antiviral therapy. Data comparing dual antiviral therapy with potent single antiviral therapy remain limited. We compared survival, virological response, and clinical outcomes between the two strategies in HBV-ACLF patients. **Methods:** This retrospective observational cohort study included consecutive HBV-

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ACLF patients admitted to ILBS, New Delhi over 17 years. Patients receiving single antiviral therapy (Tenofovir or Entecavir) between 2009–2017 were compared with those receiving dual antiviral therapy (Tenofovir + Entecavir) between 2018–2026. Baseline demographic, biochemical, virological, and clinical parameters including MELD, MELD-Na, CTP, AARC score, HE, ascites, AKI/HRS, and sepsis were analyzed. Primary outcomes included overall and 28-day mortality. Secondary outcomes included HBV DNA decline, MELD improvement, 90-day mortality, LT-free survival, and organ failure progression. Kaplan–Meier survival analysis and Cox regression were performed. **Results:** A total of 442 patients were included (single therapy: n = 367; dual therapy: n = 75). Baseline MELD (27.48 ± 7.28 vs 27.45 ± 7.62; p = 0.78) and HBV DNA levels (7.28 ± 1.12 vs 7.05 ± 1.01 log10 IU/mL; p = 0.28) were comparable between groups. Overall mortality (10.35% vs 9.33%; p = 0.81), 28-day mortality (5.45% vs 2.67%; p = 0.29), 90-day mortality (7.9% vs 5.3%; p = 0.47), LT-free survival (87.7% vs 88.0%; p = 0.94), ICU requirement, AKI/HRS development, and MELD improvement were similar between groups. A ≥2-log HBV DNA decline was numerically higher with dual therapy (28.4% vs 19.9%) but was not significant. HBV DNA decline modestly correlated with MELD improvement (r = 0.285; p < 0.001). Kaplan–Meier analysis showed no survival difference (log-rank p = 0.432). On multivariate Cox regression, increasing age (HR 1.04; p = 0.0049) and higher baseline MELD (HR 1.06; p = 0.0107) independently predicted mortality. **Conclusion:** HBV DNA decline correlated with MELD improvement. However, dual antiviral therapy did not demonstrate more rapid virological decline or survival benefit over potent single antiviral therapy in HBV-ACLF. Baseline liver disease severity and age remained the major predictors of mortality. Larger prospective studies are required to define the role of combination antiviral therapy in HBV-ACLF.



Disclosures: Shreya Singh: Nothing to Disclose.

2066 | THERAPEUTIC PLASMA EXCHANGE (TPE) AS AN ADJUNCT TO STANDARD MEDICAL THERAPY IN ACUTE-ON-CHRONIC LIVER FAILURE: A PROSPECTIVE COHORT STUDY FROM INDIA

Apalak Garg[1] Virendra Singh[1] Bisman Khurana[2] Shweta Aghi[3] Nitesh Bassi[4] Tanvi Sood[1] Amandeep Singh[1] Narayana Yaddanapudi[1] Jahnvi Dhar[1] Sayan Malakar[1] Mehakdeep Kaur[1] Swapnil /[1] Kandagaddala Raja Sekhar[1], [1]Punjab Institute of Liver and Biliary Sciences Mohali Punjab India, [2]Punjab Institute of Liver and Biliary Sciences, Mohali Punjab India, [3]Punjab Institute Of Liver and Biliary Sciences, Mohali, Punjab, [4]Punjab Institute of Liver and Biliary Sciences, Mohali, Punjab India

Background: Acute-on-chronic liver failure (ACLF) is characterised by severe systemic inflammation, multi-organ dysfunction, and high short-term mortality. Therapeutic plasma exchange (TPE) has emerged as a potential adjunctive therapy because of its ability to remove inflammatory mediators and circulating toxins, particularly in developing countries where immediate liver transplantation is often unavailable. **Methods:** A study was conducted at a tertiary care liver institute. Ninety-two patients diagnosed with ACLF were enrolled and divided into SMT (n = 46) and SMT+TPE (n = 46) groups. Baseline demographic, clinical, laboratory, prognostic, and organ failure parameters were analysed. The primary outcomes were 28-day and 90-day mortality.Standard-volume TPE was performed using a centrifugal apheresis technique with exchange of 1.5 times the estimated plasma volume per session. Univariate and multivariate logistic regression analyses were performed to identify predictors of mortality. Absolute risk reduction (ARR), relative risk (RR), and relative risk reduction (RRR) were calculated to assess survival benefit. The incidence of sepsis and other TPE-related complications was also evaluated **Results:** A total of 92 patients with ACLF were included in the study. Alcohol was the predominant etiology in both groups (91.3% in SMT vs 93.5% in SMT+TPE). The SMT+TPE group had significant baseline disease severity, higher MELD (34.1 ± 6.5 vs 28.9 ± 5.7, p < 0.001), serum bilirubin (26.6 ± 9.2 vs 12.8 ± 6.1 mg/dL, p < 0.001), and INR (2.3 ± 0.6 vs 1.8 ± 0.4, p < 0.001). Serum creatinine (2.4 ± 1.3 vs 1.8 ± 1.0 mg/dL, p = 0.006) and prevalence of acute kidney injury (63.0% vs 43.5%, p = 0.048) were higher in the SMT +TPE group.Despite baseline severity the SMT+TPE group demonstrated lower mortality at 28 days (21.7% vs 30.4%) and 90 days (37.0% vs 47.8%). Survival benefit analysis showed an ARR of 4.3%, RR of 0.87, and RRR of 13.3%.Univariate analysis, elevated serum creatinine (OR 1.83, p = 0.005) and systemic

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inflammatory response syndrome (SIRS) (OR 5.29, p = 0.005) were significant predictors of mortality. Multivariate analysis, SIRS emerged as the strongest independent predictor of mortality (adjusted OR 8.04, 95% CI 2.11–30.62, p = 0.002).TPE-related adverse events were generally mild and manageable, with fever, shivering, and electrolyte abnormalities being the most common complications. Sepsis is a major concern with extracorporeal therapies, including TPE; however, the incidence of sepsis in our cohort was relatively low (15%), which may be attributed to strict adherence to aseptic precautions and meticulous infection-control practices **Conclusion:** Therapeutic plasma exchange demonstrated a favourable trend toward improved short-term survival in patients with ACLF despite significantly greater baseline hepatic and renal dysfunction in the TPE cohort. Systemic inflammation was the strongest independent determinant of mortality.

Table 1: Comparison of study participants from the SMT and SMT plus TPE cohorts

Variables	Overall cohort (N=92)	SMT (n=46)	SMT plus TPE (n=46)
Age (years)	48.8 ± 12.9	56.0 ± 11.8	40.1 ± 12.7
Male	85 (92.4%)	42 (91.3%)	43 (93.5%)
Female	7 (7.6%)	4 (8.7%)	3 (6.5%)
Etiology			
Alcohol	85 (92.4%)	42 (91.3%)	43 (93.5%)
HCV	76 (82.6%)	40 (87.0%)	36 (78.3%)
Hematological and Biochemical Parameters			
Hemoglobin (g/dL)	9.1 ± 1.8	8.9 ± 1.9	9.3 ± 1.6
TLC (×10³/L)	11.2 ± 5.8	8.7 ± 4.2	13.6 ± 6.3
Platelets (×10³/mm³)	148.2 ± 74.5	112.4 ± 61.8	184.1 ± 72.6
Bilirubin (mg/dL)	19.7 ± 10.3	12.8 ± 6.5	26.6 ± 9.2
INR	2.1 ± 0.6	1.8 ± 0.4	2.3 ± 0.6
Creatinine (mg/dL)	2.1 ± 1.2	1.6 ± 1.0	2.4 ± 1.1
CRP (mg/L)	39.8 ± 21.5	34.2 ± 18.4	45.4 ± 23.1
Procalcitonin (ng/mL)	0.93 ± 0.54	0.76 ± 0.41	1.08 ± 0.61
Sodium (mEq/L)	130.8 ± 5.9	131.6 ± 5.3	129.9 ± 6.2
Prognostic Scores			
MELD score	31.5 ± 6.8	28.9 ± 5.7	34.1 ± 6.5
CLIF-C ACLF score	47.9 ± 8.1	46.3 ± 7.2	49.5 ± 8.6
AARC score	10.7 ± 2.1	9.8 ± 1.8	11.6 ± 2.0
Child–Pugh score	11.2 ± 1.5	10.6 ± 1.3	11.8 ± 1.4
Grade of ACLF			
Grade 1	14 (15.2%)	9 (19.6%)	5 (10.9%)
Grade 1A	3 (3.3%)	2 (4.3%)	1 (2.2%)
Grade 1B	18 (19.6%)	11 (23.9%)	7 (15.2%)
Grade 2	39 (42.4%)	18 (39.1%)	21 (45.7%)
Grade 3A	13 (14.1%)	5 (10.9%)	8 (17.4%)
Organ Failure(s)			
Hepatic failure	72 (78.3%)	26 (56.5%)	46 (100.0%)
Coagulation failure	47 (51.1%)	21 (45.7%)	26 (56.5%)
Renal failure	20 (21.7%)	6 (13.0%)	14 (30.4%)
Cerebral failure	12 (13.0%)	9 (19.6%)	3 (6.5%)
Mortality Outcomes			
28-day mortality	34 (26.1%)	14 (30.4%)	20 (21.7%)
90-day mortality	39 (42.4%)	23 (47.8%)	17 (37.0%)

Abbreviations: HCV, Hepatitis C virus; TLC, Total Leukocyte Count; INR, International Normalized Ratio; CRP, C-Reactive Protein; MELD, Model for End-Stage Liver Disease; CLIF-C ACLF, Chronic Liver Failure Consortium Acute-on-Chronic Liver Failure; AARC, APASL ACLF Research Consortium;

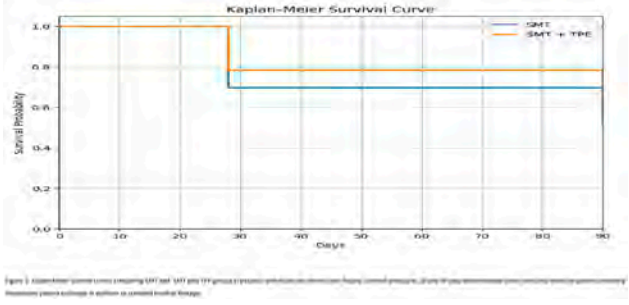


Figure 1: Kaplan–Meier survival curves comparing SMT and SMT plus TPE groups. Survival probability (y-axis) is plotted against days (x-axis). The SMT plus TPE group demonstrated a consistently higher survival probability throughout the observation period, with a separation between the curves emerging early and maintained over the 90-day follow-up.

Disclosures: Apalak Garg: Nothing to Disclose, Virendra Singh: Nothing to Disclose, Bisman Khurana: Nothing to Disclose, Shweta Aghi: Nothing to Disclose, Nitesh Bassi: Nothing to Disclose, Tanvi Sood: Nothing to Disclose, Amandeep Singh: Nothing to Disclose, Narayana Yaddanapudi: Nothing to Disclose, Jahnvi Dhar: Nothing to Disclose, Sayan Malakar: Nothing to Disclose, Mehakdeep Kaur: Nothing to Disclose, Swapnil /: Nothing to Disclose, Kandagaddala Raja Sekhar: Nothing to Disclose.

2067 | HISTOPATHOLOGICAL HETEROGENEITY AND ITS CLINICAL RELEVANCE IN ACUTE-ON-CHRONIC LIVER FAILURE

Jingran Jiao[1] Rui Zhao[1] Man Lai[2] Manman Xu[1] Hui Liu[3] Yu Chen[1], [1]Fourth Department of Liver Disease, Beijing You'an Hospital, Capital Medical University, [2]Department of Critical Care Medicine, Beijing You'an Hospital, Capital Medical University, [3]Department of Pathology, Beijing You'an Hospital, Capital Medical University

Background: Acute-on-chronic liver failure (ACLF) exhibits marked histopathological heterogeneity, while the clinical significance of different pathological injury patterns remains unclear. This study aimed to systematically evaluate the histopathological features of ACLF and analyze their associations with clinical disease severity. **Methods:** This single-center retrospective study included 78 ACLF patients who underwent liver transplantation for various etiologies. Histological assessments were performed by experienced pathologists. Semi-quantitative analyses were conducted for histopathological features including hepatocellular necrosis, cholestasis, portal inflammation, and steatosis. Patients were stratified according to the presence or absence of cirrhosis to evaluate histopathological heterogeneity in ACLF. Clinical parameters were further compared across different grades of pathological injury, and disease severity scores were applied to assess liver dysfunction and organ failure, in order to analyze the relationship between histopathological alterations and clinical severity. **Results:** Among the 78 ACLF patients who underwent liver transplantation, 52 (66.7%) had cirrhosis. Comparisons between cirrhotic and non-cirrhotic patients demonstrated significant differences in histopathological features, including hepatocellular necrosis (p = 0.009), bile duct proliferation (p = 0.041), liver progenitor cell-derived regeneration (p = 0.050), and ductular cholestasis (p = 0.047). With increasing grades of hepatocellular necrosis, ALT, AST, and serum sodium levels progressively increased. ALT levels in grades 1, 2, and 3 hepatocellular necrosis were 144 U/L, 285 U/L, and 713 U/L, respectively, while AST levels were 183 U/L, 271 U/L, and 541 U/L, respectively. Analysis by ductular cholestasis grades showed progressive increases in both TBiL (p = 0.006) and DBiL (p = 0.004). TBiL levels were 322 μmol/L in patients without ductular cholestasis and 488 μmol/L in those with severe ductular cholestasis, while DBiL levels were 209 μmol/L and 311 μmol/L, respectively. ALT and INR levels also increased with higher grades of portal inflammation. These findings indicate that more severe histopathological injury is associated with greater clinical severity, and that hepatocellular necrosis,

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cholestatic injury, and portal inflammation may be associated with disease progression in ACLF. **Conclusion:** Patients with ACLF exhibit significant histopathological heterogeneity, with a certain correlation between different pathological damage patterns and clinical disease severity. Among these, pathological changes such as necrosis, cholestasis, and portal inflammation may be significant in reflecting disease activity and clinical deterioration, providing histological evidence for further understanding the pathological features and progression of ACLF.

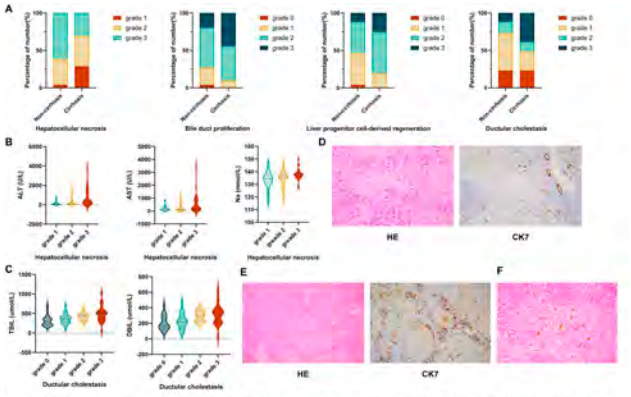


Figure 1. (A) Comparison of histopathological heterogeneity between cirrhotic and non-cirrhotic ACLF patients.**(B)** Comparison of clinical parameters according to hepatocellular necrosis grades (grade 1–3).**(C)** Comparison of clinical parameters according to ductular cholestasis grades (grade 0–3).**(D)** Representative HE staining and CK7 immunohistochemical staining of ACLF liver tissue with semi-quantitative scores of grade 3 hepatocellular necrosis, grade 1 ductular reaction, grade 1 liver progenitor cell-derived regeneration, and grade 1 ductular cholestasis.**(E)** Representative HE staining and CK7 immunohistochemical staining of ACLF liver tissue with semi-quantitative scores of grade 1 hepatocellular necrosis, grade 3 ductular reaction, grade 3 liver progenitor cell-derived regeneration, and grade 1 ductular cholestasis.**(F)** Representative HE staining of ACLF liver tissue with grade 3 ductular cholestasis. ACLF, acute-on-chronic liver failure; HE, hematoxylin and eosin.

Disclosures: Jingran Jiao: Nothing to Disclose, Rui Zhao: Nothing to Disclose, Man Lai: Nothing to Disclose, manman xu: Nothing to Disclose, Hui Liu: Nothing to Disclose, yu chen: Nothing to Disclose.

2068 | DYNAMIC IMMUNE CELL INTERACTIONS IN LIVER FAILURE: MULTI-OMICS ANALYSES UNCOVER A HYPERINFLAMMATORY CD40+ MONOCYTE SUBSET ASSOCIATED WITH DISEASE PROGRESSION

YuanKang Luo[1] Dazhi Zhang[1] Qiongfang Zhang[1] Chang Shu[1] Zhiling Zhou[1] HuiMin Fan[1] ZhiHan Zhang[1] Yang Lv[1], [1]Chongqing Medical University

Background: Liver failure is a clinical syndrome associated with extremely high mortality. Its core pathological mechanism involves massive hepatocyte necrosis or apoptosis, ultimately leading to multi-organ dysfunction and failure. Increasing evidence demonstrates that immune dysregulation plays a pivotal role throughout the onset and progression of liver failure. Therefore, elucidating the dynamic alterations and interaction networks of specific immune cell subsets during liver failure development is of great significance for understanding disease pathogenesis. **Methods:** Randomization analysis, single-cell transcriptomic analysis, and composite machine-learning models were used to explore the associations between immune cell phenotypes and liver failure. Flow cytometry was constructed to confirm the abnormal distribution of immune cell subsets in patients with liver failure. **Results:** Mendelian randomization revealed a causal link between CD40 on CD14+CD16+ monocytes and liver failure. Single-cell transcriptomics and flow cytometry confirmed this monocyte subset upregulation in liver failure patients compared with healthy controls. Pseudotime trajectory analysis clarified the differentiation path from classical to intermediate (CD40 −→CD40+) and then to non-classical monocytes, with the CD40 state representing a specialized intermediate stage characterized by increased expression of genes such as HLA-DRB1, indicating enhanced inflammatory activity. Cell-cell communication analysis showed that overall immune interactions were weakened in ACLF, but CD40 intermediate monocytes exhibited enhanced interactions with immune cells such as B cells and NK cells through signaling axes including TNFSF14. Transcriptome profiling revealed a 'high inflammation–high metabolism' dual activation phenotype, with pathway enrichment in antigen processing, phagosome formation, and related pathways. WeIdentified differentially expressed genes and used machine learning methods to construct a prediction model. **Conclusion:** This study comprehensively delineates the interaction network between intermediate monocytes and liver failure, offering potential directions for early intervention strategies.

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2069 | PRIOR DECOMPENSATION SHAPES THE CLINICAL PHENOTYPE AND THE PROGNOSTIC PERFORMANCE OF BIOCHEMICAL LIVER-FAILURE CRITERIA IN HOSPITALISED CIRRHOSIS: A MULTICENTRE STUDY

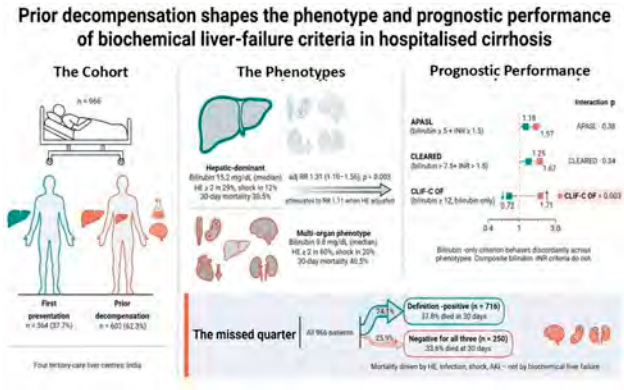
Akash Roy[1] Arun Valsan[2] Karan Kumar[3] Pasham Satwika[4] Gowripriya Nair[5] Soumya Iyengar[4] Manasa Alla[4] Shantan Venishetty[4] Mithun Sharma[4] Vivek Saraswat[6] Mahesh Goenka[7] Nagaraj Rao Padak[4] D Nageshwar Reddy[4] Anand Kulkarni[4], [1]Apollo Multispeciality Hospitals, [2]Amrita Hospital, Kochi,

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Background: Biochemical liver-failure definitions for ACLF do not distinguish first-presentation from prior decompensation, despite their differing clinical trajectories. We evaluated whether prior decompensation defines a distinct acute decompensation (AD) phenotype and whether APASL, CLEARED and EASL-CLIF liver-failure thresholds retain consistent prognostic performance across phenotypes. **Methods:** In this multicentre cohort, 966 adults hospitalized with acute decompensation across four Indian centres were stratified as first-presentation (n = 364) or prior-decompensation (n = 602). Biochemical liver-failure thresholds were assessed using APASL criteria: bilirubin ≥ 5 mg/dL and INR ≥ 1.5; CLEARED criteria: bilirubin ≥ 7.5 mg/dL and INR ≥ 1.5; and the EASL-CLIF liver component: bilirubin ≥ 12 mg/dL. The primary outcome was 30-day mortality **Results:** Patients with prior decompensation were older, more often had MASLD-related cirrhosis (21.3% vs 10.7%), and had greater extra-hepatic organ failure. Thirty-day mortality was higher after prior decompensation than at first presentation (40.5% vs 30.5%; adjusted RR 1.31, 95% CI 1.10–1.56; p = 0.003) after adjustment for MELD and baseline infection, but was attenuated after additional adjustment for hepatic encephalopathy. In the overall cohort, APASL and CLEARED criteria modestly predicted 30-day mortality (OR 1.36 and 1.41), whereas the EASL-CLIF bilirubin threshold did not. Stratified analysis showed phenotype-dependent performance: biochemical thresholds predicted mortality better in prior-decompensation patients (APASL OR 1.57; CLEARED OR 1.67; EASL-CLIF OR 1.71). The bilirubin-only EASL-CLIF liver component captured the fewest deaths and showed significant phenotype-dependent prognostic behaviour. Those without biochemical liver failure thresholds are predominantly MASLD, have high baseline infection (57.1%) and predominantly extrahepatic organ failures driving mortality (33.6%). **Conclusion:** Prior decompensation identifies a clinically distinct, high-risk acute decompensation phenotype, with excess mortality partly mediated by hepatic encephalopathy. Established biochemical liver-failure thresholds show discordant prognostic performance across decompensation phenotypes. ACLF liver-failure definitions may require decompensation phenotype-aware recalibration



Disclosures: Akash Roy: Nothing to Disclose, Arun Valsan: Nothing to Disclose, Karan Kumar: Nothing to Disclose, Pasham Satwika: Nothing to Disclose, Gowripriya Nair: Nothing to Disclose, Soumya Iyengar: Nothing to Disclose, Manasa Alla: Nothing to Disclose, Shantan Venishetty: Nothing to Disclose, Mithun Sharma: Nothing to Disclose, Vivek Saraswat: Nothing to Disclose, Mahesh Goenka: Nothing to Disclose, Nagaraj Rao Padak: Nothing to Disclose, D Nageshwar Reddy: Nothing to Disclose, Anand Kulkarni: Nothing to Disclose.

2070 | INCIDENCE AND PREDICTORS OF RECOMPENSATION IN ACUTE-ON-CHRONIC LIVER FAILURE

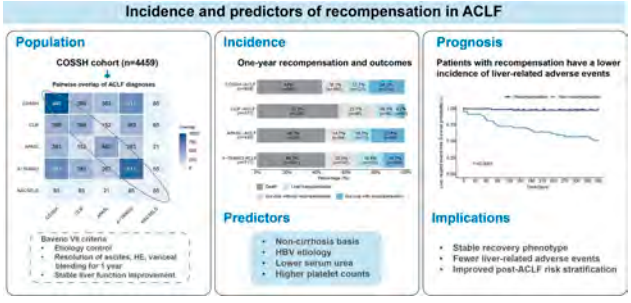
Jun Li[1] Wei Qiang[1] Jinjin Luo[1] Xi Liang[1] Jiaojiao Xin[1] Dongyan Shi[1] Jing Jiang[1], [1]The First Affiliated Hospital, Zhejiang University School of Medicine

Background: Acute-on-chronic liver failure (ACLF) is a complicated syndrome with high short-term mortality. However, the long-term trajectory remains unclear. We aimed to evaluate the incidence and predictors of recompensation in ACLF patients. **Methods:** A total of 4,459 enrolled patients with acute deterioration of chronic liver disease from the Chinese Group on the Study of Severe Hepatitis B (COSSH) prospective open cohort were assessed for recompensation at 1 year using Baveno VII criteria. **Results:** ACLF was identified in 948 patients by COSSH criteria (28/90/360-day liver transplant (LT)-free mortality: 30.2%/44.6%/53.7%), 398 by CLIF (45.3%/59.4%/72.4%), 480 by APASL (31.6%/45.8%/54.2%), 65 by NACSELD (52.8%/61.5%/75.5%), and 811 by A-TANGO (29.9%/45.8%/58.1%). The COSSH-ACLF II score

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showed the highest discriminative ability for 28/90/360-day mortality among six prognostic scores. One-year recompensation rates among LT-free survivors eligible for assessment were 66.9% (97/145) under COSSH, 12.1% (4/33) under CLIF, 65.0% (39/60) under APASL, 14.3% (1/7) under NACSELD criteria, and 36.8% (35/95) under A-TANGO. After inverse probability weighting, one-year estimated recompensation rates in the whole ACLF populations were 24.2%, 4.7%, 22.8% and 14.7% under COSSH, CLIF, APASL and A-TANGO criteria, respectively. Recompensation was lower in patients with cirrhotic basis than those without (16.2% vs. 58.1%), in non-HBV-related ACLF than HBV-related ACLF (6.4% vs. 33.1%), and in ACLF grade 2/3 than grade 1 (8.2% vs. 33.3%). Cirrhotic basis, HBV etiology, serum urea level, and platelet count were major predictors among 37 candidate variables. During the second year after enrollment, recompensated patients had a lower incidence of liver-related adverse events than non-recompensated patients (3.0% vs. 57.9%). **Conclusion:** Recompensation is achievable in ACLF patients. Major predictors include cirrhotic basis, HBV etiology, serum urea, and platelet count.



Disclosures: Jun Li: Nothing to Disclose, Wei Qiang: Nothing to Disclose, Jinjin Luo: Nothing to Disclose, Xi Liang: Nothing to Disclose, Jiaojiao Xin: Nothing to Disclose, Dongyan Shi: Nothing to Disclose, Jing Jiang: Nothing to Disclose.

2071 | THE ACLF RESCUE GAP: HIGH-INTENSITY DEATH WITHOUT PALLIATIVE CARE AND DISPARITIES AMONG HOSPITALIZATIONS WITH ACUTE-ON-CHRONIC LIVER FAILURE

Anas Al Mardini[1] Harika Dadigiri[2] Aatman Shah[2] Edward Barbarito[2], [1]NYMC, [2]NYMC-St Clare/St Mary hospital

Background: Acute-on-chronic liver failure (ACLF) carries high inpatient mortality, yet mortality alone does not capture the intensity or quality of end-of-life care. Whether patients with severe ACLF experience disparities in palliative care and high-intensity death without palliative support is poorly understood. We evaluated high-intensity death without palliative care as a national rescue-gap phenotype among U.S. ACLF hospitalizations. **Methods:** We performed a retrospective cross sectional analysis of adult cirrhosis hospitalizations in the 2020-2022 National Inpatient Sample. ACLF grade was defined by organ failure burden across kidney, respiratory, circulatory, neurologic, infectious, and bleeding/coagulation domains and categorized as cirrhosis without ACLF, ACLF-1, ACLF-2, and ACLF-3+. High-intensity care was defined as mechanical ventilation, dialysis, vasopressor use, or cardiopulmonary resuscitation. The primary outcome was high-intensity in-hospital death without a palliative care encounter. Secondary outcomes included mortality, palliative care, and high-intensity care. Survey-weighted models adjusted for age, sex, race/ethnicity, payer, and ZIP-code income quartile. A prespecified ACLF-3+ subgroup analysis evaluated disparities among the sickest hospitalizations. **Results:** Among 2,480,109 weighted adult cirrhosis hospitalizations, 34.8% had ACLF-1, 17.9% ACLF-2, and 13.3% ACLF-3+. Mortality increased stepwise from 0.57% without ACLF to 2.08% in ACLF-1, 7.31% in ACLF-2, and 34.54% in ACLF-3+. Palliative care use also increased with severity but remained limited, occurring in 2.89%, 5.82%, 11.96%, and 26.81%, respectively. High-intensity death without palliative care occurred in 0.22% of ACLF-1, 1.47% of ACLF-2, and 13.84% of ACLF-3+ hospitalizations. Among ACLF-3+ hospitalizations, Black (aOR 0.91), Hispanic (aOR 0.70), Asian/Pacific Islander (aOR 0.76), and Other race/ethnicity (aOR 0.85) patients had lower adjusted odds of palliative care. Conversely, these groups had higher adjusted odds of high-intensity death without palliative care: Black aOR 1.61, Hispanic aOR 1.31, Asian/Pacific Islander aOR 1.39, and Other race/ethnicity aOR 1.56. Medicaid and self-pay status were also associated with higher odds of high-intensity death without palliative care, while residence in the highest ZIP-income quartile was protective (aOR 0.76). **Conclusion:** In this contemporary national analysis, ACLF severity was associated with escalating mortality and high-intensity death without palliative care. Among ACLF-3+ hospitalizations, racial/ethnic minority and socioeconomically vulnerable patients had lower palliative care use and higher odds of high-intensity death without palliative support. These findings identify a measurable ACLF rescue gap and support earlier, equitable integration of hepatology palliative care for patients with severe ACLF.

Disclosures: Anas Al Mardini: Nothing to Disclose, Harika Dadigiri: Nothing to Disclose, Aatman Shah: Nothing to Disclose, Edward Barbarito: Nothing to Disclose.

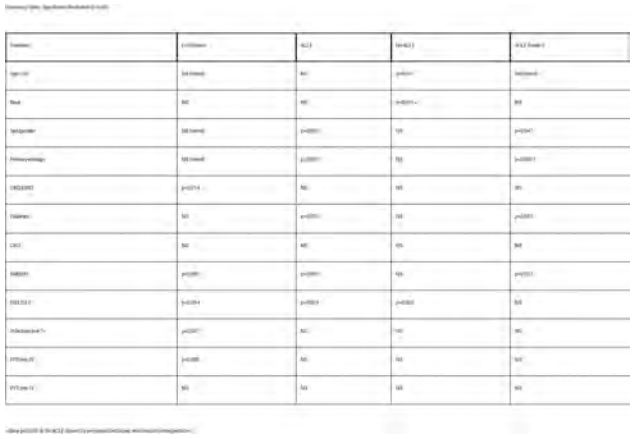
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2072 | FEMALE GENDER AND ALD PREDICT SUPERIOR PATIENT SURVIVAL AFTER LIVER TRANSPLANTATION IN ACLF

Jake MacDonald[1] Nishita Sunkara[1] Kathryn Thompson[1] Naveena Murugan[1] Vignesh Jayaraman Muralidharan[1] Hima Veeramachaneni[1] Andrew Yu[1] Ram Subramanian[2] Nader Dbouk[1], [1]Emory University School of Medicine, [2]Emory University

Background: Acute-on-chronic liver failure (ACLF) is characterized by multiorgan dysfunction and very high mortality rates. Although liver transplantation (LT) significantly improves survival, outcomes remain worse than in patients without ACLF. Identifying predictors of post-LT mortality is important to optimize candidate selection. We therefore evaluated the impact of demographic, clinical, and transplant-related variables—including age, gender, race, BMI, primary etiology, CAD, DM, CKD, PVT, and MELD score—on post-LT outcomes in ACLF versus non-ACLF patients. **Methods:** We conducted a retrospective study evaluating the impact of multiple clinical and demographic variables on post-liver transplant survival among 244 patients with ACLF and 572 patients without ACLF who underwent liver transplantation at Emory University between 2014 and 2025. ChatGPT (OpenAI) was used solely to assist with language refinement and improve readability of the abstract. **Results:** Female ACLF patients demonstrated significantly superior patient and graft survival compared to males (log-rank $p = 0.006$ and $p = 0.002$, respectively), with the survival advantage increasing over time. Five-year patient survival was 88.6% in females versus 71.4% in males, and this disparity was even more pronounced in ACLF Grade 3 patients, where 5-year survival was 83.5% in females compared to 57.8% in males ($p = 0.047$). Primary etiology was also highly predictive of outcomes in ACLF patients ($p < 0.0001$). Patients with alcohol-associated liver disease (ALD) had the best outcomes, with 1-, 3-, and 5-year survival rates of 92.4%, 92.4%, and 86.7%, respectively, compared to lower 5-year survival in MASH/metabolic liver disease (81.2%) and markedly worse outcomes in HCV-related ACLF (54.2%). In ACLF Grade 3 patients, ALD maintained stable survival of 86.8% at 1, 3, and 5 years, compared to 61.9% for MASH/metabolic disease and 50.0% for HCV at 5 years. Older age was not a significant predictor of survival in the overall ACLF cohort; however, among ACLF Grade 3 patients, age >55 years was associated with a clinically meaningful trend towards reduction in 5-year survival (55.9% vs 76.7%) ($p = 0.145$). Obesity (BMI ≥ 30) and diabetes mellitus were also associated with significantly inferior outcomes in ACLF patients at all time points, particularly in Grade 3 disease, where obese patients had a 5-year survival of 54.8% compared to 82.4% in non-obese patients ($p = 0.005$), and diabetic patients had markedly lower 5-year survival compared to non-diabetics (50% vs 70.2%, $p = 0.032$). Race, CAD, and portal vein thrombosis were not significant predictors of survival. **Conclusion:** Female sex and ALD as the primary etiology emerged as strong predictors of improved post-liver transplant survival in ACLF patients, whereas these associations were not observed in non-ACLF patients. These findings may help inform transplant candidate selection in this high-risk population



Disclosures: Jake MacDonald: Nothing to Disclose, Nishita Sunkara: Nothing to Disclose, Kathryn Thompson: Nothing to Disclose, Naveena Murugan: Nothing to Disclose, Vignesh Jayaraman Muralidharan: Nothing to Disclose, Hima Veeramachaneni: Nothing to Disclose, Andrew Yu: Nothing to Disclose, Ram Subramanian: Baxter: Consultant, Organox: Consultant, eGenesis: Consultant, Grifols: Consultant, Vantive: Consultant, Organox: Advisor, eGenesis: Advisor, Nader Dbouk: Nothing to Disclose.

2073 | LUMICAN IS PROGRESSIVELY ACTIVATED DURING ACLF-ASSOCIATED FIBROGENIC REMODELING AND PROMOTES HEPATIC FIBROSIS THROUGH H3K18 LACTYLATION

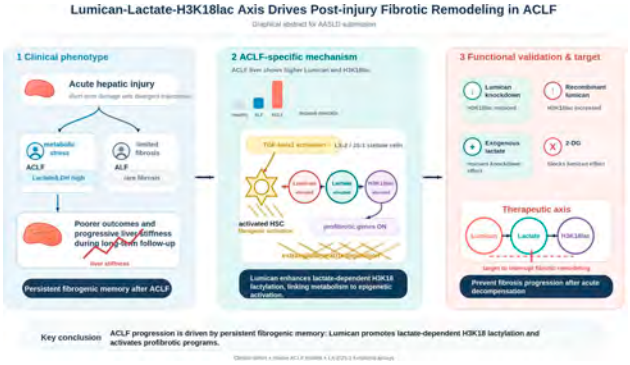
Lingxiao Zhu[1] Qi Jiang[2] Yan Lv[3] Xiaowei Xu[3], [1]The First Affiliated Hospital of Zhejiang University, [2]Institute of Pathogen Biology, Chinese Academy of Medical Sciences & Peking Union Medical College, [3]he First Affiliated Hospital, Zhejiang University School of Medicine

Background: ALF and ACLF can both be precipitated by acute hepatic insults, but they differ in disease context and long-term trajectory. ALF usually occurs without pre-existing chronic liver disease and rarely progresses to sustained fibrosis after a single acute injury. In contrast, ACLF develops on a chronically injured liver, where acute decompensation may amplify inflammation, extracellular matrix deposition, and aberrant repair, promoting fibrosis

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during recovery. However, mechanisms driving post-injury fibrotic progression in ACLF remain poorly understood. Lumican, an extracellular matrix proteoglycan implicated in fibrotic diseases, may regulate matrix remodeling and fibrogenic activation. We investigated whether lumican promotes ACLF-associated fibrosis through H3K18 lactylation. **Methods:** Clinical information from ACLF, ALF, and healthy controls was retrospectively collected from the First Affiliated Hospital, Zhejiang University School of Medicine; no human biospecimens were used. C57BL/6 mice were used to establish ACLF, ALF, chronic fibrosis, and healthy control models. Mouse liver tissues were analyzed by single-nucleus RNA sequencing and bulk RNA sequencing to define cell-type-specific and global transcriptional programs related to lumican expression and fibrotic remodeling. Liver injury and collagen deposition were assessed by hematoxylin and eosin staining and Sirius Red staining. qPCR and western blotting were performed to validate lumican expression, fibrogenic markers, and H3K18 lactylation. **Results:** During acute injury, ACLF patients showed elevated serum lactate and LDH levels, which were associated with poorer outcomes and progressive liver stiffness during long-term follow-up, whereas ALF patients rarely developed post-injury fibrosis. In mouse models, ACLF livers exhibited increased lumican mRNA and protein expression and enhanced H3K18 lactylation compared with healthy and ALF controls. TGF-β1-induced fibrogenic activation increased lumican protein expression in LX-2 and JS-1 cells. Functionally, lumican knockdown reduced H3K18 lactylation, whereas recombinant lumican increased H3K18 lactylation. Exogenous lactate rescued the inhibitory effect of lumican knockdown, while 2-DG blocked lumican-induced H3K18 lactylation, supporting a lactate-dependent lumican–H3K18lac axis in ACLF-associated fibrotic remodeling. **Conclusion:** ACLF progression involves a persistent fibrogenic memory after acute hepatic injury. Lumican promotes post-injury fibrotic remodeling by enhancing lactate-dependent H3K18 lactylation, linking metabolic dysregulation to epigenetic activation of profibrotic programs. The lumican–lactate–H3K18lac axis may represent a novel therapeutic target for preventing fibrosis progression after acute decompensation.



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2074 | ACUTE-ON-CHRONIC LIVER FAILURE IN SEPSIS: NATIONAL TRENDS, PREDICTORS, AND OUTCOMES IN THE UNITED STATES

Eunice Omeludike[1] Cherechi Nwabueze[2] Obinna Orji[1] Eunice Aregbesola[3] Nzubechukwu Okeke[4] Sarpong Boateng[5] Ihunanya Kanu[6] Yetunde Akande[2], [1]Piedmont Athens Regional Medical Centre, [2]John H. Stroger Jr. Hospital of Cook County, [3]University of Missouri, Columbia, [4]Zucker school of medicine at Hofstra/Northwell at Vassar Brothers Medical Center, [5]Yale New Haven Health, Bridgeport Hospital, [6]Baptist Memorial Hospital- Golden Triangle

Background: Acute-on-chronic liver failure (ACLF) in the setting of sepsis is associated with high mortality, but its national burden, predictors, and outcomes remain incompletely defined. We evaluated trends, predictors, and outcomes of ACLF among septic hospitalizations in the United States using a nationally representative database. **Methods:** We conducted a retrospective cohort study of adult hospitalizations in the National Inpatient Sample (2016–2022). Sepsis was identified using ICD-10-CM codes. ACLF was defined as the coexistence of chronic liver disease (alcohol-associated liver disease, chronic hepatitis, fibrosis/cirrhosis, portal hypertension, or hepatorenal syndrome) and acute organ failure (hepatic failure, acute kidney injury, respiratory failure, or shock). Survey-weighted regression models assessed temporal trends, predictors of ACLF among septic patients with chronic liver disease, and outcomes associated with ACLF in the full sepsis cohort, adjusting for demographics, comorbidities, insurance, socioeconomic status, and hospital factors. **Results:** Among 41,015,057 adult hospitalizations, 3,900,437 (9.5%) involved sepsis. Chronic liver disease was present in 4.4% of septic admissions. ACLF occurred in 3.3% of all septic hospitalizations (approximately 1 in 30) and in 74.6% of septic patients with underlying chronic liver disease. The prevalence of ACLF among septic hospitalizations increased from 3.1% in 2016 to 3.6% in 2022 (adjusted OR per year 1.034, 95% CI 1.029–1.040; $P < 0.001$). Among septic patients with chronic liver disease, older age, higher comorbidity burden, chronic kidney disease, COPD, non-private insurance, and admission to large urban teaching hospitals were independently associated with ACLF. In the full sepsis cohort, ACLF was associated with significantly higher in-hospital mortality (aOR 1.90,

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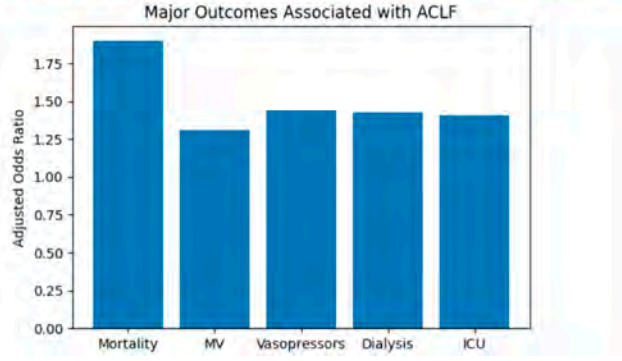
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95% CI 1.86–1.94), increased use of mechanical ventilation (aOR 1.31), vasopressors (aOR 1.44), and dialysis (aOR 1.43), and greater ICU-level intervention (aOR 1.41). ACLF was also strongly associated with gastrointestinal bleeding (aOR 33.1), hepatic encephalopathy (aOR 24.1), coagulopathy/DIC (aOR 1.83), and procedural interventions including paracentesis (aOR 17.7). Overall, ACLF was associated with higher complication burden (aOR 1.37) and increased palliative care consultation (aOR 1.70). **Conclusion:** ACLF complicates approximately 1 in 30 septic hospitalizations in the United States, and its prevalence is increasing. Among septic patients with chronic liver disease, nearly three-quarters develop ACLF. Its presence is associated with substantially higher mortality, organ support requirements, and healthcare utilization. These findings highlight the need for early recognition and risk stratification of ACLF in septic patients with chronic liver disease.

Figure 1. Temporal Trend of ACLF in Sepsis



Figure 2. Major Outcomes Associated with ACLF



Disclosures: Eunice Omeludike: Nothing to Disclose, Cherechi Nwabueze: Nothing to Disclose, Obinna Orji: Nothing to Disclose, Eunice Aregbesola: Nothing to Disclose, Nzubechukwu Okeke: Nothing to Disclose, Sarpong Boateng: Nothing to Disclose, Ihunanya Kanu: Nothing to Disclose, Yetunde Akande: Nothing to Disclose.

2075 | DAILY STEP COUNT AS A PROGNOSTIC INDICATOR OF SURVIVAL IN ADULTS WITH LIVER CIRRHOSIS

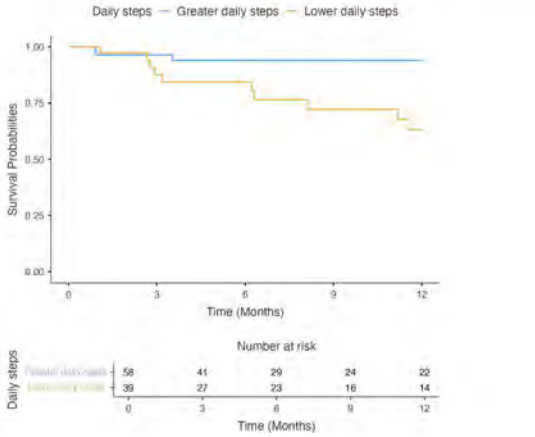
Araceli López Nepomuceno[1] Orfanel Sebastian Pineda-Arzate[2] Alondra Rosales-Padrón[2] Luis Fernando Rubio-Acosta[2] Claudia Daniela López-López[2] Osvely Méndez-Guerrero[2] Ignacio García-Juárez[2], [1]National Institute of Medical Sciences and Nutrition Salvado, [2]National Institute of Medical Sciences and Nutrition Salvador Zubirán

Background: Liver cirrhosis is a major cause of morbidity and mortality worldwide. Although several prognostic tools are available, the role of objective physical performance measures in predicting clinical outcomes remains unclear. For the above, the objective this study was to evaluate the prognostic impact of daily step count on survival, acute-on-chronic liver failure (ACLF), and liver transplantation in adults with cirrhosis. **Methods:** This prospective cohort study included 98 outpatients with liver cirrhosis in Mexico City. Functional status was assessed using the ECOG, Karnofsky Performance Status, and 6-minute walk distance. Daily step count was measured using pedometry (Garmin Vivosmart 5) as a 3-day average. Patients were followed for 12 months to evaluate hospitalization, ACLF, liver transplantation, and mortality. Statistical analyses included ROC curves, Cox regression, and Kaplan-Meier survival analysis. **Results:** Among 98 patients, 48 had decompensated cirrhosis. ROC analysis identified <3750 daily steps as the optimal cutoff for reduced physical performance. Lower daily step count was associated with older age ($p=0.018$) and lower Karnofsky scores ($p<0.001$), but not with Child-Pugh or MELD scores. Reduced daily step count was independently associated with higher risk of ACLF (HR 3.07, $p=0.048$), mortality (HR 3.02, $p=0.021$), and lower likelihood of liver transplantation (HR 0.52, $p=0.022$). Daily step count demonstrated greater prognostic performance than Karnofsky score and 6-meter walking speed. **Conclusion:** Lower daily step count was associated with ACLF and mortality independently of conventional liver severity scores, supporting its use as a simple and objective prognostic tool in cirrhosis.

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Figure 1. Kaplan-Meier survival curve for mortality in patients with liver cirrhosis



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2076 | CLINICAL PROFILE, ORGAN FAILURE PATTERN, AND PROGNOSTIC UTILITY OF SERIAL SCORING SYSTEMS IN ACUTE-ON-CHRONIC LIVER FAILURE

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Background: Acute-on-chronic liver failure (ACLF) is a rapidly progressive syndrome characterized by acute hepatic decompensation, systemic inflammation, multi-organ failure, and high short-term mortality in patients with underlying chronic liver disease. Owing to its highly dynamic clinical course, static prognostic scores assessed only at admission may inadequately predict outcomes. Serial reassessment of prognostic scores may provide superior prognostic accuracy; however, prospective data evaluating this approach in Indian populations remain limited. **Methods:** This prospective observational study included 130 patients diagnosed with ACLF according to APASL criteria at a tertiary care center in North India. Demographic, clinical, laboratory, microbiological, and organ failure profiles were recorded at admission. AARC, CLIF-C ACLF, MELD-Na, and Child–Turcotte–Pugh (CTP) scores were assessed serially on day 1, day 4, and day 7.The primary outcome was 28-day in-hospital mortality. ROC analysis was performed to compare prognostic accuracy of different scoring systems using AUROC, sensitivity, specificity, and optimal cutoff values. **Results:** A total of 130 ACLF patients were enrolled, predominantly middle-aged males with alcohol-related liver disease as the most common etiology and precipitating insult. The 28-day mortality rate was 33.1%, with most deaths occurring between day 7 and day 14. Jaundice, ascites, hepatic encephalopathy, coagulopathy, and renal dysfunction were the predominant clinical manifestations. Non-survivors had significantly higher bilirubin, INR, creatinine, leukocyte count, serum lactate, circulatory dysfunction, and ICU requirement.Liver failure was the most common organ failure followed by coagulation and renal failure. Mortality increased progressively with increasing organ failures, with no survival in patients with six organ failures. Grade III hepatic encephalopathy strongly predicted mortality with 62.8% sensitivity and 94.3% specificity.Among prognostic models, AARC showed the best baseline predictive accuracy on day 1 (AUROC 0.788). Serial monitoring significantly improved prognostic performance, with AARC AUROC increasing to 0.955 on day 4 and 0.965 on day 7. Persistently elevated day 7 AARC scores (>12) were strongly associated with mortality and need for urgent liver transplantation evaluation. **Conclusion:** ACLF is associated with high short-term mortality, particularly in patients with advanced hepatic encephalopathy and multiple organ failures. Serial AARC assessment demonstrated superior prognostic accuracy compared with single baseline evaluation. Daily score monitoring during the first week may help identify high-risk patients requiring aggressive organ support and early liver transplantation evaluation.

Table 30: Summary Table for Comparison efficiency of different prognostic scores at different days of assessment for prediction of in-hospital mortality as per Receiver Operator Characteristic Curve

SN	Type of score	AUC±SE	95% CI	'p' value	Sensitivity	Specificity	Cut-off value	J-Index
Day 1								
1.	MELD-Na	0.639± 0.054	0.539-0.744	0.010	39.5%	88.5%	37.50	0.280
2.	CLIF-ACLF	0.765± 0.047	0.672-0.857	<0.001	62.8%	88.5%	52.50	0.513
3.	CTP	0.738± 0.048	0.644-0.833	<0.001	65.0%	73.6%	12.50	0.387
4.	AARC	0.788± 0.046	0.697-0.879	<0.001	81.4%	70.1%	10.50	0.515
Day 4								
1.	MELD-Na	0.783± 0.045	0.694-0.872	0.045	55.8%	90.8%	36.50	0.466
2.	CLIF-ACLF	0.851± 0.037	0.778-0.824	<0.001	65.1%	93.1%	53.50	0.582
3.	AARC	0.955± 0.019	0.918-0.993	<0.001	95.3%	85.1%	10.50	0.804
Day 7								
1.	MELD-Na	0.917± 0.026	0.865-0.969	<0.001	75.7%	95.4%	36.50	0.711
2.	CLIF-ACLF	0.902± 0.037	0.829-0.974	<0.001	83.8%	92.0%	49.50	0.757
3.	AARC	0.965± 0.019	0.928-1.000	<0.001	89.2%	97.7%	11.5	0.869

Disclosures: anubhavsingh pawar: Nothing to Disclose, SUMIT RUNGTA: Nothing to Disclose.

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2077 | INVESTIGATING THE ASSOCIATION OF STATIN INTENSITY WITH REDUCTION IN RISK FOR HEPATOCELLULAR CARCINOMA IN PATIENTS WITH CHRONIC LIVER DISEASE

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Background: Statins have demonstrated chemopreventive potential against hepatocellular carcinoma (HCC) in chronic liver disease (CLD), with meta-analyses showing a 40–50% risk reduction. However, no study has evaluated whether the ACC/AHA-defined statin intensity classification (high, moderate, low) differentially affects HCC risk. The objective of this study is to evaluate the association between statin intensity and incident HCC across hepatitis C virus (HCV), alcohol-associated liver disease (ALD), and metabolic dysfunction-associated steatotic liver disease (MASLD). **Methods:** This retrospective cohort study utilized the TriNetX federated research network. Adults with CLD attributable to HCV, ALD, or MASLD were stratified into high-, moderate-, and low-intensity statin groups per 2026 ACC/AHA guideline classifications. Sustained statin use was confirmed by requiring prescriptions within 1 year, 1 to 2 years, and 2 to 3 years of diagnosis. Within each etiology, pairwise propensity score-matched cohorts were constructed. Cox proportional hazards regression was used to compare time to HCC. **Results:** No statistically significant differences in HCC risk by statin intensity were observed within any etiology after applying sustained-use criteria. In MASLD, hazard ratios were 0.966 (95% CI 0.714–1.308, p = 0.53) for high vs. moderate, 0.844 (0.45–1.586, p = 0.29) for high vs. low, and 0.798 (0.431–1.479, p = 0.42) for moderate vs. low. In HCV, high vs. moderate showed an HR of 0.91 (0.677–1.223, p = 0.91), high vs. low 0.969 (0.47–1.998, p = 0.66), and moderate vs. low 0.93 (0.453–1.909, p = 0.41). In ALD, only the high vs. moderate comparison was analyzed, as the low-intensity group had insufficient sample size for reliable analysis; this comparison yielded an HR of 0.673 (0.419–1.083, p = 0.62). Despite the absence of individual significance, point estimates in ALD suggested a trend favoring higher-intensity therapy. **Conclusion:** In this large retrospective cohort requiring sustained statin use, statin intensity was not significantly associated with differential HCC risk across HCV, ALD, or MASLD. However, a trend toward greater HCC risk reduction with higher-intensity statins was observed in ALD, suggesting this etiology may warrant further investigation in prospective studies. The lack of significance may reflect reduced statistical power after applying strict sustained-use exposure definitions, and future studies with larger sample sizes may be needed to clarify these associations.

Disclosures: Pranav Jayakumar: Nothing to Disclose, Naveen Raj: Nothing to Disclose, Yash Gupta: Nothing to Disclose, Resham Ramkissoon: Nothing to Disclose.

2078 | LIVER TRANSPLANTATION FOR TYPE A ACUTE-ON-CHRONIC LIVER FAILURE : AN UNMET NEED

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Background: Acute-on-Chronic Liver Failure (ACLF) Type A is a liver centric definition by APASL which is characterized by high short term mortality. A liver transplantation (LT) vis required early in the course of ACLF in non-responding patients. Often LT is not feasible in view of extrahepatic organ failure, donor fitness/unavailability, or non-availability of LT. **Methods:** The study was done to determine the percentage of patients with ACLF, who could undergo LT, and determinants of conversion to LT. This study included 1043 patients from the APASL ACLF Research Consortium (AARC) database, in year 2025. **Results:** The study population aged 44.5 ± 11.4 years, 85% of the patients were male. The jaundice to hospital admission interval was 18.3 ± 7.8 days. Alcohol was the most common acute etiology (n = 475, 45.54%), followed by hepatitis B (n = 143, 13.71%). Alcohol was the chronic etiology in 67.1% patients. A total of 80 (7.6%) patients underwent LT. Overall mortality was 48%, which was significantly more in the non-LT group (50.4%), versus 25% in the LT group, p < 0.001. The MELD and AARC scores were not significantly different at baseline (MELD 29.9 ± 5.4 and 29.2 ± 6.7, AARC 9.04 ± 1.8 vs 9.1 ± 1.4). The MELD score at day 7 was significantly higher in the non-LT group (26.8 ± 8.6 vs 22.1 ± 2.6, p 0.017). The following parameters were significantly different between the non-LT and LT groups: a delayed presentation (duration from jaundice to admission, 18 ± 7 vs 15 ± 5 days, p < 0.001), circulatory failure (63% vs 22%, p < 0.001). The presence of renal failure at presentation was higher (26% vs 16%) but not statistically significant (p 0.062) in the non-LT group. Patients who underwent LT had higher bilirubin (21.8 ± 19.9 m/dl vs 19.1 ± 9.4, p 0.022), lower total leucocyte count (9.4 ± 6.7 vs 15.5 ± 15 x 10^3, p < 0.001), higher hemoglobin (11.5 ± 1.6 vs 10.3 ± 2.6, p 0.003), lower platelet count (100.9 ± 63.6 vs 143.2 ± 86.9 x 10^3, p < 0.001) and higher INR (2.5 ± 0.5 vs 2.3 ± 0.5, p < 0.001). **Conclusion:** The mortality of patients with ACLF was 50.5% in the non-LT group. Only 7.6% patients with ACLF could have an LT. It represents a big unmet need. Extrahepatic organ failure appears to be significant barrier to LT.

Disclosures: Neeraj Saraf: Nothing to Disclose, Narendra Choudhary: Nothing to Disclose, Ashok Choudhury: Nothing to Disclose, Anand Kulkarni: Nothing to Disclose, Ashish Kumar: Roche: Consultant, Viatris: Consultant, Sun Pharma: Advisor, Astra Zeneca: Advisor, Anil Arora: Nothing to Disclose, Ajay Duseja: Nothing to Disclose, Akash Shukla: Nothing to Disclose, Akash Roy: Nothing to Disclose, Abraham Koshy: Nothing to Disclose, AJIT SOOD: Nothing to Disclose, Ajay Patwa: Nothing to Disclose, Ajay Kumar Mishra: Nothing to Disclose, Amna Butt: Nothing to Disclose, Ajay Kumar: Nothing to Disclose, Arun Valsan: Nothing to Disclose, Ashish Jha: Nothing to Disclose, Ameet Mandot: Nothing to Disclose, Dibyalochan Praharaj: Nothing to Disclose, Dinesh Kumar Jothimani: Nothing to Disclose, Dong Joon Kim: Nothing to Disclose, Zhongping Duan: Nothing to Disclose, Md Karim: Nothing to Disclose, Gamal Shiha: Nothing to Disclose, Girish Kumar Pati: Nothing to Disclose, Guan Lee: Nothing to Disclose, H. Janaka De Silva: Nothing to Disclose, Harshad Devarbhavi: Nothing to Disclose, Maria Harutyunyan: Nothing to Disclose, Joy Varghese: Nothing to Disclose, Javed P: Nothing to Disclose, Jidong Jia: Nothing to Disclose, jinhua hu: Nothing to Disclose, Jose Sollano: Nothing to Disclose, Kemal Kalista: Nothing to Disclose, MSc MD: Nothing to Disclose, Krishnadas Devadas: Nothing to Disclose, Mamun Mahtab: Nothing to Disclose, MANOJ KUMAR SAHU: Nothing to Disclose, Man-Fung Yuen: AbbVie, Abbott Diagnotics, Aligos Therapeutics: Consultant, Arbutus Biopharma, Arrowhead

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2079 | ◆ ADVANCED-PRACTICE-NURSE-LED LIFESTYLE INTERVENTION AFTER AUTOMATED MASLD CASE-FINDING IN PRIMARY CARE: 24-WEEK OUTCOMES FROM LIVERSEEK

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Background: Lifestyle modification remains the foundation of MASLD management, including in patients with significant fibrosis or steatohepatitis, but scalable primary-care (PC) delivery models are limited. LiverSeek is a laboratory-driven, passive case-finding program that identifies PC patients with metabolic risk and elevated FIB-4. We assessed 24-week changes in liver and metabolic parameters after a structured advanced-practice-nurse (APN)-led intervention in LiverSeek-identified patients with abnormal non-invasive tests (NITs). **Methods:** Patients identified through LiverSeek at 11 PC centres in Madrid (serving ~350,000 residents) with elevated FIB-4 underwent reflex second-line NITs. Those with ≥ 1 positive NIT (VCTE ≥ 8 kPa, ELF ≥ 9.8 or MASEF ≥ 0.33) were referred to an APN visit including baseline anthropometry/BIA, Mediterranean-diet and physical-activity assessment and structured barrier review. Personalised SMART intervention included brief Mediterranean-diet counselling, progressive physical-activity prescription and weekly self-weighing. Reassessment at 24 weeks included VCTE (LSM, CAP), liver biochemistry, HbA1c and FIB-4. Paired changes were tested with Wilcoxon signed-rank using available paired data; responder analyses used prespecified thresholds. **Results:** 146 patients with ≥ 1 positive baseline NIT completed paired 24-week assessment (age 61.5 ± 6.0y, 32% female, BMI 32.0 ± 4.8, T2D 67%, hypertension 62%). Significant improvements were observed: LSM 9.8→9.0 kPa (Δ−0.86; $p = 0.0001$), CAP 301.5→283.4 dB/m (Δ −18.1; $p < 0.0001$), ALT 67.0→46.9 U/L (Δ−20.1; $p < 0.0001$), AST 51.2→38.4 U/L (Δ−12.9; $p < 0.0001$), GGT 107.6→77.3 U/L (Δ−30.4; $p < 0.0001$), HbA1c 7.01→6.50% (Δ−0.51; $p < 0.0001$) and FIB-4 2.11→1.86 (Δ−0.25; $p < 0.0001$). Responder rates were: LSM reduction $\geq 20\%$, 25%; CAP reduction ≥ 30 dB/m, 37%; among patients with baseline LSM ≥ 10 kPa, 33% migrated to < 10 kPa; elevated baseline ALT normalized in 43%; HbA1c decreased $\geq 0.5\%$ in 35%. **Conclusion:** In LiverSeek-identified PC patients with abnormal NITs, a structured 24-week APN-led lifestyle intervention was associated with clinically meaningful improvements in LSM, CAP, liver enzymes, glycaemic control and FIB-4. These findings support nurse-led lifestyle care as a scalable first-line pathway after automated MASLD case-finding and a practical bridge to selecting patients who may require MASLD-targeted pharmacotherapy.

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2080 | PHARMACIST-LED IMPLEMENTATION OF AASLD RESMETIROM PRACTICE GUIDANCE: A REAL-WORLD EXPERIENCE AT A HEPATOLOGY CLINIC IN ACADEMIC MEDICAL CENTER

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Background: Resmetirom is the first FDA-approved therapy for metabolic dysfunction–associated steatohepatitis (MASH) with moderate to advanced fibrosis. Following approval, the American Association for the Study of Liver Diseases (AASLD) published practice guidance on patient selection and safety monitoring. Implementation of these recommendations requires substantial longitudinal coordination among patients and clinical staff. At this academic medical center, a Clinical Pharmacist Practitioner (CPP) is embedded within the hepatology clinic to support medication management, patient education, and therapy monitoring processes. This study evaluated CPP-supported follow-up among patients receiving resmetirom. . **Methods:** A retrospective, single-center chart review was conducted among adults prescribed resmetirom between March 2024 and August 2025 at an academic hepatology clinic. Patients were stratified into pre-guidance and post-guidance cohorts. Outcomes included time to first liver function test (LFT), completion of LFT monitoring at 3, 6, and 12 months, documentation of laboratory reminder outreach, hepatotoxicity events, and discontinuation rates. The embedded CPP supported implementation of guidance recommendations through laboratory coordination, patient outreach, reminder documentation, and longitudinal monitoring follow-up. **Results:** Ninety-nine patients were included (pre-guidance n = 28; post-guidance n = 70). Median time to first LFT was similar between cohorts (102 days [IQR 67–117] vs 90 days [IQR 78–102]; p = 0.12). Completion of 3-month LFT monitoring occurred in 71.4% versus 81.7% (p = 0.26), while 6-month monitoring occurred in 50% versus 73.7% (p = 0.055) in the pre- and post-guidance cohorts, respectively. CPP-documented laboratory reminder outreach increased substantially following guidance publication (3.6% vs 43.7%; p < 0.001). Hepatotoxicity events were uncommon (0% vs 4.3%; p = 0.57). Resmetirom discontinuation occurred less frequently in the post-guidance cohort (42.9% vs 15.5%; p = 0.055). **Conclusion:** In this academic hepatology clinic, safety monitoring for resmetirom was frequently performed even prior to AASLD guidance publication. However, integration of CPP-supported workflows improved longitudinal laboratory monitoring and increased documentation of patient outreach. Lower treatment discontinuation rates were observed with pharmacist-led implementation of AASLD guidance which may warrant further investigation in future. These findings highlight the important role of embedded hepatology pharmacists in monitoring patients receiving novel MASH therapies while reducing the burdent of hepatology providers.

Table 1. Baseline Characteristics and Results

	Pre-Guidance (n=28)	Post-Guidance (n=70)
Age, years	56.7	53.5
Female – no. (%)	14 (50.0%)	37 (52.1%)
BMI, kg/m^2	34.2	33.6
Fibrosis Stage II – no. (%)	7 (25.0%)	26 (36.6%)	
Fibrosis Stage III – no. (%)	16 (57.1%)	41 (57.7%)
Median time to first LFT, days	102.5	90
3-month LFT completion – no. (%)	20 (71.4%)	58 (81.7%)
6-month LFT completion – no. (%)*	14 (50.0%)	42 (73.7%)
12-month LFT completion – no. (%)†	12 (42.9%)	15 (53.6%)
Documented laboratory reminders – no. (%)	1 (3.6%)	31 (43.7%)
Hepatotoxicity events – no. (%)	0 (0.0%)	3 (4.3%)
Resmetirom discontinuation – no. (%)	12 (42.9%)	13 (18.8%)

*6-month monitoring assessed only among patients eligible for 6-month follow-up at time of chart review.
†12-month monitoring assessed only among patients eligible for 12-month follow-up at time of chart review.

Disclosures: Jane Giang: GSK: Consultant, Madison Owen: Nothing to Disclose, Brianna Wagoner: Nothing to Disclose.

2081 | IMPLEMENTATION OF A NURSE PRACTITIONER–LED FIBROSCAN REFERRAL PATHWAY IMPROVES HEPATOLOGY LINKAGE TO CARE IN A MASLD SCREENING PROGRAM

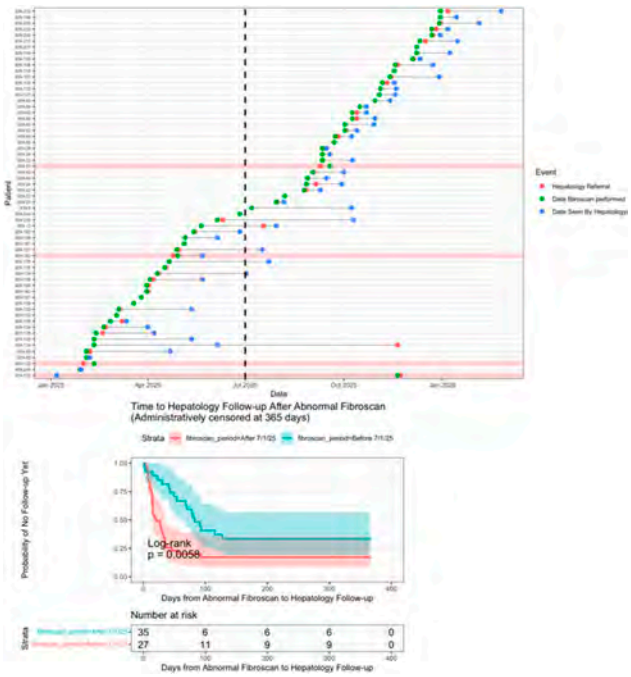
Amanda Cheung[1] Andres Castillo[2] Kenny Chen[1], [1]Northwestern University, [2]Northwestern Memorial Hospital

Background: FibroScan-based liver stiffness measurement (LSM) is increasingly incorporated into metabolic dysfunction–associated steatotic liver disease (MASLD) screening programs. However, abnormal screening results do not consistently result in timely hepatology evaluation. Delays in specialty referral and fragmented care coordination remain major implementation barriers within MASLD screening programs. To address this gap, we implemented a nurse practitioner (NP)–led FibroScan-triggered referral pathway on July 1, 2025, to facilitate expedited hepatology consultation after abnormal fibrosis screening and evaluated the impact of this pathway on time to hepatology follow-up and identified clinical factors associated with abnormal FibroScan findings. **Methods:** We conducted a prospective quality improvement study of 253 adults undergoing FibroScan assessment in 2025 within a MASLD screening pathway. Abnormal FibroScan was defined as LSM > 8 kPa. Demographic, metabolic, and social determinant variables were collected, including age,

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sex, race/ethnicity, language, insurance status, obesity, diabetes, hypertension, and dyslipidemia. Among patients with abnormal FibroScan results, time to hepatology follow-up was defined as days from FibroScan completion and first hepatology encounter. Patients without follow-up were censored at 365 days. Kaplan-Meier and multivariable Cox proportional hazards analyses compared patients undergoing FibroScan for 6 months before versus after July 1, 2025, when the FibroScan-triggered hepatology referral protocol was implemented. **Results:** The cohort had a median age of 63 years, 56% were male, and median BMI was 30.1 kg/m². Diabetes and hypertension were present in 41% and 47% of patients, respectively. Overall, 25% of patients had elevated LSM. Patients with abnormal FibroScan LSM had significantly higher BMI (32.5 vs 29.3 kg/m², $p < 0.001$) and higher prevalence of obesity (66% vs 44%, $p = 0.004$) and diabetes (61% vs 34%, $p < 0.001$). In multivariable logistic regression, morbid obesity (OR 8.92, 95% CI 1.67–71.4, $p = 0.018$) and diabetes (OR 3.11, 95% CI 1.62–6.10, $p < 0.001$) were independently associated with abnormal FibroScan findings. Implementation of the NP-led referral pathway was associated with significantly faster hepatology consultation (HR 3.68, 95% CI 1.66–8.16, $p = 0.001$) with median time to hepatology evaluation decreasing from 61 days before implementation to 15 days after implementation [see Figure]. **Conclusion:** Implementation of a structured NP-led FibroScan-triggered referral pathway significantly improved linkage to hepatology care within a MASLD fibrosis screening program, reducing median follow-up time from 61 to 15 days. This NP-led care coordination pathway represents an effective and scalable implementation strategy to improve specialty access and longitudinal liver care within MASLD screening programs.



Disclosures: Amanda Cheung: Novo Nordisk: Speaking and Teaching, Petauri Kinect: Grant/Research Support, Rubio Metabolomics: Grant/Research Support, Orphalan: Consultant, Andres Castillo: MIrum: Speaker Bureau, Salix Pharmaceuticals: 1 Advisory board meeting, Mallinckrodt: 1 advisory board meeting, Kenny Chen: Nothing to Disclose.

★ 2082 | ASSESSING THE EFFECT OF SEMAGLUTIDE IN PATIENTS WITH MASLD: REAL-WORLD EXPERIENCE FROM A PHARMACIST-LED SUB-CLINIC

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Background: Semaglutide has demonstrated efficacy in improving histologic and metabolic outcomes in metabolic dysfunction-associated steatohepatitis (MASH). To expand access to glucagon-like peptide-1 receptor agonist (GLP-1RA) therapy in patients with metabolic dysfunction-associated steatotic liver disease (MASLD), our institution developed a pharmacist (PharmD)-led sub-clinic focused on GLP-1 initiation, titration, and longitudinal monitoring. We evaluated the real-world effectiveness and implementation outcomes of this multidisciplinary care model. **Methods:** We performed a retrospective cohort study of adults with MASLD referred to a PharmD-led GLP-1 sub-clinic at a tertiary hepatology center between January 2022 and March 2024. Patients underwent structured medication counseling, monthly telehealth follow-up, dose titration, and lifestyle education. Baseline demographics, fibrosis stage, cardiometabolic parameters, insurance outcomes, and treatment-related adverse events were collected. The primary outcome was achievement of $\geq 10\%$ weight loss within 12 months of injectable semaglutide therapy. Secondary outcomes included changes in elastography parameters, glycemic indices, treatment persistence, and medication tolerability. **Results:** A total of 118 patients were included. Mean age was 54.3 years, 55.1% were female, and mean body mass index was 35.6 kg/m². Comorbid diabetes and dyslipidemia were present in 40.7% and 66.9% of patients, respectively. Fibrosis stages ranged from F0–F4, with 14.4% demonstrating advanced fibrosis (F4). PharmD involvement resulted in 100% insurance approval, with treatment initiation occurring within a median of 5 days. Maximum tolerated dose was achieved within a median of 119 days, and 42.4% of patients reached semaglutide doses ≥ 2 mg/week. Weight reduction thresholds of $\geq 5\%$, $\geq 7\%$, and $\geq 10\%$ were achieved in 41%, 31%, and 20% of patients, respectively. Median weight loss at 12 months was -8%. Among 22 patients with paired elastography data, median liver stiffness decreased by 1.0 kPa ($p = 0.009$) and controlled

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attenuation parameter decreased by 31 dB/m (p = 0.027). Hemoglobin A1c decreased by a median of 0.4%. Nausea was the most common adverse event, reported in 44.9% of patients, with 21% discontinuing therapy because of intolerance. **Conclusion:** A PharmD-led GLP-1 sub-clinic facilitated rapid semaglutide initiation, equitable medication access, and clinically meaningful weight loss in patients with MASLD in a real-world setting. Improvements in steatosis, liver stiffness, and cardiometabolic parameters were also observed. Although weight loss outcomes were lower than those reported in randomized trials, likely reflecting real-world barriers including medication supply limitations, copay burden, and less intensive lifestyle supervision, this multidisciplinary model represents a scalable strategy to improve MASLD care delivery.



Disclosures: Ngan Nguyen: Gilead Pharmaceuticals: Advisor, Erica Kohen: Nothing to Disclose, Martin Gozar: Nothing to Disclose, Sanjaya Satapathy: Gilead Sciences: Grant/Research Support, Durect Pharma: Grant/Research Support, Fibronostics: Grant/Research Support, Novartis: Grant/Research Support, Zydus Pharma: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Intercept Pharma: Grant/Research Support, AKERO: Grant/Research Support, Altimmune: Grant/Research Support, IPSEN: Grant/Research Support, Madrigal: Grant/Research Support.

2084 | REBUILDING RESILIENCE: ADDRESSING PROVIDER BURNOUT TO ENHANCE PROFESSIONAL FULFILLMENT

Sarah Johnson[1] Andrea Benton[2], [1]The Ohio State University, [2]The Ohio State University Wexner Medical Center

Background: The purpose of this descriptive study is to identify the levels of burnout in APP's within the outpatient arm of a major medical center, and to identify factors that may be contributing to or mitigating burnout. The study included a survey that will be distributed to APP's employed by the outpatient arm of a major medical center. By completing this research, we hope that institutions and individuals can implement interventions that may mitigate burnout, thus increasing job satisfaction, provider retention, and long-term productivity. **Methods:** A common tool identified within the literature to assess occupational burnout is the Maslach Burnout Inventory Human Services Survey for Medical Personal (MBI). The MBI– the gold standard for evaluating provider burnout—is a brief 22 statement survey that is accessed online. Upon completion of individual surveys, participants were provided with an individual analysis report, and we were provided a group report of the emotional exhaustion, depersonalization and personal accomplishment scores. The group scores were compared to 11,000+ people in the human services profession who also completed this survey. The MBI survey was distributed electronically in 2024 and again in 2025 via email to all APPs within the GHN Division prior to interventions. 13 APPs were included with a 100% response rate for ongoing evaluation. 11 APPs were retained from initial survey and 2 APPs were new hires. Statistical analysis was not performed due to small sample size. **Results:** The research supports that addressing burnout through individualized targeted interventions positively influences job satisfaction and retention amongst healthcare providers. Furthermore, early identification provides the institution with clear goals to individualize and support providers who are experiencing different levels of burnout. Common factors among engaged APPs included: having an average of six years of experience in their role and a patient care schedule limited to four days per week. These APPs also reported taking personal time at least once a month and expressed intentions to maintain their current FTE status moving forward. **Conclusion:** Organizations must prioritize system-level changes over individual responsibility by using tools like the MBI survey to identify and address the structural causes of stress. Building resilience requires a long-term, integrated approach that combines employee support with organizational responsibility, using updated data to continuously adapt policies and create environments that promote psychological safety and sustainable performance.While the challenges of provider burnout are significant, the growing awareness, innovation, and commitment to change leaves hope that the next chapter in healthcare will be one where Advanced Practice Providers can thrive. **Disclosures:** Sarah Johnson: Nothing to Disclose, Andrea Benton: Nothing to Disclose.

2085 | ◆ TRENDS AND PREDICTORS OF NON-PHARMACOLOGIC MANAGEMENT OF PAIN AMONG VETERANS WITH CIRRHOSIS

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Background: Up to 80% of patients with cirrhosis experience chronic pain, yet nearly every analgesic class carries elevated risk of hepatotoxicity, renal impairment, or hepatic encephalopathy in this population. Non-pharmacologic modalities (NPM) are therefore an attractive alternative. The Veterans Health Administration (VHA) expanded NPM access following the 2013 Opioid Safety Initiative and through its Whole Health System transformation, yet NPM utilization among veterans with cirrhosis remains poorly characterized. **Methods:** Using national VHA Corporate Data Warehouse and linked CMS data, we identified veterans with cirrhosis who were in care between 2010 and 2024. We defined annual NPM use as ≥ 1 CPT/HCPCS/CHAR code within following pain-focused modalities: acupuncture, massage, chiropractic care, osteopathic manipulation, biofeedback, clinical hypnosis, and mind-body interventions (yoga/tai chi/mindfulness). Physical therapy, occupational therapy, psychotherapy, exercise therapy, and education-based interventions were categorized separately, given their non-specificity for analgesia. Trends in NPM use were examined annually. Baseline demographics, medical and psychiatric comorbidities, substance use, and cirrhosis complications were compared between ever-users and non-users of NPM using Wilcoxon rank-sum and chi-square tests. **Results:** Of 344,443 Veterans with cirrhosis, 77,561 (22.5%) ever used a pain-focused NPM. Annual NPM use more than doubled from 5.3% in 2010 to 12.1% in 2024, with growth across all modalities (**Figure 1**). Acupuncture (0.3% to 3.0%), chiropractic care (2.0% to 3.9%), and massage (3.3% to 8.7%) experienced the most significant growth. A pandemic-related dip was observed in 2020. Compared to never-users, NPM users were younger (median age 64.8 vs. 66.4 yrs) and more likely to be married (49.0% vs. 42.0%). They had higher rates of depression (31.0% vs. 26.6%), anxiety (23.8% vs. 20.2%), and PTSD (11.0% vs. 7.9%), but lower rates of alcohol use disorder (32.7% vs. 37.8%), illicit drug use (23.8% vs. 25.5%), and current tobacco use (33.1% vs. 41.3%). NPM users also demonstrated lower rates of decompensated cirrhosis (40.6% vs. 56.2%), including ascites (31.6% vs. 47.3%) and hepatic encephalopathy (10.1% vs. 16.2%) ($p < 0.001$ for all comparisons). Among Veterans with a documented chronic pain diagnosis (n = 194,688), only 26% had ever received any NPM over the study period. **Conclusion:** Despite a more than two-fold increase in annual NPM use over 15 years, fewer than 1 in 8 Veterans with cirrhosis receive these therapies in any given year, and 3 in 4 of those with a documented chronic pain diagnosis have never received any NPM. Uptake is lowest among Veterans with decompensated disease and active substance use, the populations with the fewest safe pharmacologic options. These findings reveal substantial equity gaps in NPM access for the highest-risk segment of the cirrhosis population.

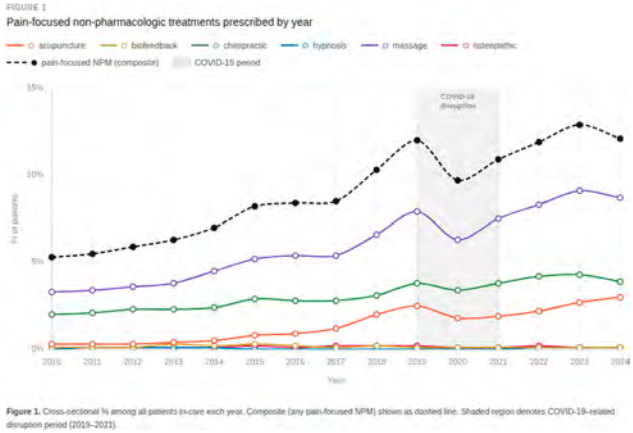


Figure 1. Cross-sectional % among all patients in-care each year. Composite (any pain-focused NPM) shown as dashed line. Shaded region denotes COVID-19–related disruption period (2019–2021).

Disclosures: Prajwal Gowda: Nothing to Disclose, Rebecca Loeb: Nothing to Disclose, Sophie Phillips: Nothing to Disclose, Hui Shen: Nothing to Disclose, Katherine Hoggatt: Nothing to Disclose, Jennifer Lai: Nestle Nutrition Institute: Grant/Research Support, Novo Nordisk: Consultant, Genfit: Consultant, Boehringer Ingelheim: Advisor, Lipocine: Site PI, Gilead: Site PI, Insmed: Consultant, Cosmo: Advisor, Jessica Rubin: Nothing to Disclose.

2086 | ◆ UNLOCKING THE POWER OF LIVED EXPERIENCE: A QUALITATIVE STUDY EXPLORING THE ROLE OF PEER NAVIGATORS IN A MOBILE HEPATITIS C CLINIC

Bharathi Selvan[1] Zainab Fatima[1] Meghan Morris[1] Pauli Gray[1] Cecilia Rivas Alfaro[1] Rosaura Camberos[1] Yesenia Laguardia[1] Sophie Stern[1] Jennifer Price[1], [1]University of California San Francisco

Background: Disparities in linkage to hepatitis C virus (HCV) treatment impact marginalized populations,

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including people who use drugs and those experiencing housing instability. Peer interventions have shown promise in improving care linkage, but how these interventions succeed and what experiences constitute a successful peer navigator are unclear. We conducted a qualitative study of the Lived Experience Alliance (LEA) peer navigation program in an urban mobile HCV clinic. **Methods:** The UCSF DeLIVER van is a mobile liver care unit offering free HCV screening and on-site treatment. We implemented a peer navigator program to assist clients navigating HCV treatment. We conducted semi-structured interviews with 4 peer navigators (referred to as LEAs), 6 clients who were partnered with a LEA, and 2 mobile clinic staff, using purposeful convenience sampling. An interview guide elicited 1) participants' background and introduction to the LEA program 2) perception of peer role 3) support provided 4) barriers and challenges and 5) sustainability and next steps. Transcripts were coded deductively, and data analysis began after 9 interviews were conducted. **Results:** Three major themes emerged (Table). First, clients and LEAs felt they shared common lived experiences. HCV was the primary unifying lived experience- three out of four LEAs had been cured of HCV. LEAs' lived experiences with HCV promoted self-confidence in clients and normalized experiences related to treatment (e.g., side effects, challenges with daily pills). Other shared social identities like current or prior substance use and housing instability contributed to peer relatability and allowed LEAs to support clients during their treatment. Secondly, LEAs facilitated treatment by meeting and walking with people where they were, often literally. For many clients, HCV cure was attributed to their LEAs meeting them where they resided multiple times a week to provide reminders to pick up or take their medications. LEAs would also walk with them to the mobile clinic for medication pickup or appointments. Third, LEAs' professional identities were characterized by a strong commitment to give back to their community, shaped largely by their prior experiences with street homelessness and HCV. **Conclusion:** Peer navigators have a unique role in HCV linkage to care, particularly for patients who face barriers to receiving traditional HCV care. Our study highlights that peer navigators enhance treatment success by building a relationship, based on a shared lived experience with HCV or other salient social identities. They lower barriers for clients with competing factors by meeting them where they are at and guiding them. Our findings underscore that patient and peer experiences are improved through the integration of a peer navigator program within a mobile HCV clinic. Recognizing the role of lived experience and replicating similar programs elsewhere may support HCV elimination goals.

Theme	Illustrative Quotes
Role of lived experience	"We had a lot in common in that aspect, like, we both, used the needle at one time in our lives, you know, like, we both did stuff like that, so it was really helpful to have somebody that had experience the same experiences that I did to do, you know?" "He's completed it (HCV treatment), though you know what I mean? Like, that just shows, like, it could be done." "He's done the hep C treatment before, too, so… you know what I mean? He knows exactly, what it's like, what the side effects are, and, you know what I'm saying? Like, how you could fall off, and all the things necessary that you would want to know."
Supporting clients by meeting them where they are	"The most helpful? Him coming and picking me up every week. Coming to the door to tell me to take my pills. Like, everything he did was helpful, like, walking me down there" "He just walked up and would get me every week, and then we'd walk down together."
Sense of contributing to community	"I'd had Hep C myself, and was cured, and… in a way for me to… to get further involved in my community, and to help wipe out… hopefully wipe out Hep C completely." "Just because, the people we're trying to reach, it's not always easy for them to remember things, and I've been in their, the exact position before, so I know how hard it is, and it's really rewarding being able to give back where it's needed most, in my opinion."

Disclosures: Bharathi Selvan: Nothing to Disclose, Zainab Fatima: Nothing to Disclose, Meghan Morris: Nothing to Disclose, Pauli Gray: Nothing to Disclose, Cecilia Rivas Alfaro: Nothing to Disclose, Rosaura Camberos: Nothing to Disclose, Yesenia Laguardia: Nothing to Disclose, Sophie Stern: Nothing to Disclose, Jennifer Price: AbbVie: Grant/Research Support, Gilead: Grant/Research Support, VIR: Grant/Research Support, Cepheid: Grant/Research Support, Aligos: Grant/Research Support, Meridian: Grant/Research Support.

2087 | ◆ ETHNIC AND SOCIOECONOMIC DISPARITIES IN FIBROSIS DETECTION AND OUTCOMES FROM A DIVERSE UK COMMUNITY LIVER SCREENING PROGRAMME

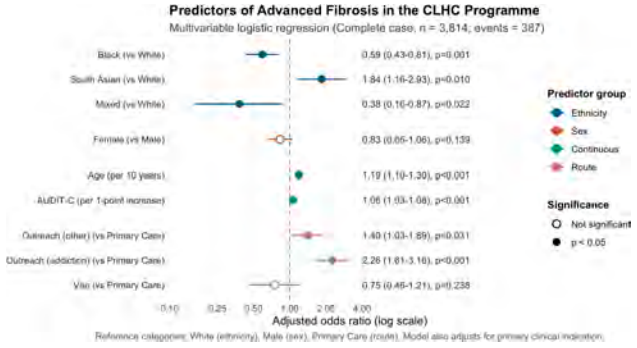
Thomas McKane[1] Kaushik Agarwal[1] Neha Mehta[1] María Guerra veloz[1], [1]Institute of Liver Studies, King's College Hospital

Background: The Community Liver Health Check (CLHC) is a National Health Service England pilot using transient elastography (TE FibroScan) for early detection of chronic liver disease (CLD) in poorly engaged populations at high risk (alcohol excess, metabolic risk or viral hepatitis). Ethnic disparities in ALD/MASLD are reported globally but ethnicity is poorly characterised as risk factor for CLD in UK data. The aim of this project was to assess risk factors associated with advanced fibrosis detection and clinical outcomes in a deprived, multiethnic South East London cohort. **Methods:** Patients meeting CLHC eligibility criteria were enrolled prospectively via community

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outreach, primary care and a mobile unit from March 2022 to March 2026. Advanced fibrosis was defined as TE LSM ≥8.5 kPa (as per national guidance). Demographics, AUDIT-C score, deprivation decile and housing status were collected. Retrospective electronic record review for engagement rate, diagnosis confirmation and adverse outcomes was performed in those with advanced fibrosis. Adjusted logistic regression was performed to assess risk factors associated with advanced fibrosis. **Results:** 5,175 valid scans were performed. The population was 52.3% White, 25.1% Black, 4.0% South Asian, 3.0% Asian (other), 7.2% Mixed/Other and 8.5% Not Stated. 73% with a recorded address lived in the more deprived half of England and 19.4% of patients were homeless. The prevalence of advanced fibrosis was 10.4%, highest in South Asian patients (16.4%). After adjustment, South Asian ethnicity was an independent predictor of advanced fibrosis (aOR 1.84, 95% CI 1.16–2.93), strengthening to aOR 2.29 (1.30–4.04) for LSM ≥11.5 kPa. Black ethnicity had lower adjusted odds (aOR 0.59, 0.43–0.81). The South Asian finding was robust across multiple sensitivity analyses. Other significant predictors were Outreach (addiction services) (aOR 2.26, 1.61-3.16), AUDIT-C (per point, aOR 1.06, 1.03-1.08) and age (per 10 years, aOR 1.19, 1.09-1.31). 98.7% of those with advanced fibrosis had an accessible health record. 71.6% were linked to secondary care, 68.9% of whom attended hepatology appointment. Attendance did not differ by ethnicity, but in those with a confirmed outcome, was lower in homeless patients (70.6% vs 85.3%, p = 0.015). The predominant diagnoses were ALD (53%) and MASLD (34%). Rates of all-cause mortality & decompensation events in patients with advanced fibrosis were 5.8% & 7.7%. These were higher in homeless patients (12.7%, p = 0.015; 13.9%, p = 0.037) despite similar baseline LSM. **Conclusion:** The CLHC programme achieved high-yield fibrosis detection and engaged an ethnically and socioeconomically diverse cohort. South Asian ethnicity emerged as an independent risk factor for advanced fibrosis and may warrant inclusion in screening criteria. Targeted strategies may be needed to improve engagement and reduce adverse outcomes in at-risk groups, particularly homeless patients.



Disclosures: Thomas McKane: Nothing to Disclose, Nothing to Disclose, Kaushik Agarwal: Nothing to Disclose, Neha Mehta: Nothing to Disclose, María Guerra veloz: Nothing to Disclose.

2088 | ◆ TEN YEAR TRENDS IN HEPATOCELLULAR CARCINOMA SURVEILLANCE AND STAGE AT DIAGNOSIS

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Background: Hepatocellular carcinoma (HCC) is a low survival cancer with a rising incidence in Australia. Ultrasound surveillance enables earlier diagnosis and improved outcomes. We aimed to describe trends and risk factors for non-surveillance and cancer stage in patients with a new diagnosis of HCC over a ten year period. **Methods:** Patients with newly diagnosed HCC at three tertiary hospitals in Western Australia between 2015-2024 were retrospectively identified. Patient variables at diagnosis, including demographics, underlying liver disease, participation in surveillance and Barcelona Clinic Cancer (BCLC) stage were ascertained from prospective databases and electronic records. Multivariate logistic regression was used to identify factors associated with non-surveillance and HCC stage at diagnosis. Variables were included in multivariate analysis if there was a strong epidemiological basis or they were statistically significant on univariate analysis. **Results:** Overall, 1,168 individuals with a new diagnosis of HCC were identified with 81.5% being male, 73.3% cirrhotic and an average age 66.8 years. Of these, 437 (37.4%) were not known to have liver disease prior to HCC diagnosis. The proportion of patients not in a surveillance program at diagnosis was 59.2% (691/1168), which did not change over the decade (p = 0.43). Patients not in surveillance were more likely to present with late-stage HCC (BCLC C or D) (OR 4.28, 95%CI 3.13-5.94). Risk factors for a non-surveillance HCC diagnosis among patients with cirrhosis included rural residence (OR 1.74, 1.25-2.45) and alcohol-related liver disease (OR 1.45, 1.05-2.01), while hepatitis C was associated with lower odds (OR 0.58, 0.40-0.84). The proportion of late-stage HCC cases was 27.7% and did not change over 10 years (p = 0.52). No factors were associated with a higher odds for late-stage HCC, but there were lower odds among patients with metabolic dysfunction-associated steatotic liver disease (MASLD) (OR 0.47, 0.33-0.66). Early-stage HCC (BCLC 0 or A) was less likely to be

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diagnosed in rural patients (OR 0.62, 0.46-0.83) and more likely to be diagnosed in patients with MASLD (OR 1.68, 1.24-2.29), hepatitis B (OR 1.65, 1.10-2.49) and hepatitis C (OR 1.39, 1.01-1.91). **Conclusion:** Most HCC cases are not detected through surveillance and a significant proportion have unrecognized chronic liver disease at diagnosis. Surveillance and early diagnosis rates have not improved over the past decade, with rural residence and alcohol-related liver disease associated with non-surveillance diagnosis, while rural residence is associated with a lower likelihood of early-stage HCC.

Table 1. Multivariate logistic regression showing association between demographics, cirrhosis, site and etiology with non-surveillance diagnosis and HCC stage.

	Non-surveillance diagnosis*		Advanced or end-stage (BCLC# C or D)		Early stage (BCLC# 0 or A)	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Demographics						
Age	1.01	(0.99- 1.03)	1.00	(0.99 -1.01)	0.99	(0.98- 1.01)
Male	1.04	(0.71- 1.54)	0.92	(0.65 -1.31)	0.82	(0.60- 1.13)
Rural	1.74	(1.25- 2.45)	1.32	(0.97 -1.78)	0.62	(0.46- 0.83)
Cirrhosis & Child Pugh score						
Cirrhosis	*Not adjusted**		0.97	(0.70 -1.34)	2.23	(1.63- 3.07)
Child Pugh A	Reference					
Child Pugh B	1.62	(1.14- 2.32)				
Child Pugh C	4.59	(2.42- 9.36)				
Hospital^						
Hospital 2	1.14	(0.79- 1.63)	0.74	(0.53 -1.03)	1.30	(0.96- 1.77)
Hospital 3	1.73	(1.24- 2.44)	0.85	(0.62 -1.16)	1.24	(0.92- 1.66)
Aetiology						
Alcohol	1.45	(1.05- 2.01)	1.22	(0.90 -1.65)	0.87	(0.66- 1.16)
Hepatitis C	0.58	(0.40- 0.84)	0.80	(0.57 -1.11)	1.39	(1.01- 1.91)
Hepatitis B	0.60	(0.35- 1.03)	0.77	(0.49 -1.20)	1.65	(1.10- 2.49)
MASLD	1.04	(0.72- 1.52)	0.47	(0.33 -0.66)	1.68	(1.24- 2.29)

* Non-surveillance diagnosis model is restricted to only patients with cirrhosis
Barcelona Clinic Liver Cancer (BCLC) staging system for hepatocellular carcinoma
^ Reference is Hospital 1
All covariates shown are adjusted for in respective models

Disclosures: Richard O'Halloran: Nothing to Disclose, Weiyuan Fan: Nothing to Disclose, Thisuri Jayawardena: Nothing to Disclose, Phoebe Sun: Nothing to Disclose, Andrea Jasareno: Nothing to Disclose, Wei Ling Teh: Nothing to Disclose, Andrew Chin: Nothing to Disclose, Kazuya Miyamoto: Nothing to Disclose, Wesley Billingham: Nothing to Disclose, Tim Mitchell: Nothing to Disclose, Simon Hazeldine: Nothing to Disclose, Chloe Attree: Nothing to Disclose, George Garas: Nothing to Disclose, Angus Jeffrey: Nothing to Disclose, Gary Jeffrey: Nothing to Disclose, Gerry MacQuillan: Nothing to Disclose, Briohny Smith: Nothing to Disclose, Michael Wallace: Nothing to Disclose, Leon Adams: Novo Nordisk: Advisor, SCL Behring: Advisor, Dr Falk: Speaking and Teaching, Novo Nordisk: Grant/Research Support, Boehringer Ingelheim: Speaking and Teaching.

2089 | BEYOND COVERAGE: STRUCTURAL BARRIERS AND COST-RELATED MEDICATION NON-ADHERENCE FOR INDIVIDUALS WITH HBV IN THE US

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Background: Medication adherence is essential for effective treatment of chronic hepatitis B (HBV), yet cost-related medication non-adherence (CRN) remains poorly characterized. Using the All of Us Research Program, we evaluated socioeconomic and structural factors associated with CRN in a nationally representative, diverse cohort. **Methods:** Adults with HBV were identified in the All of Us Database. CRN was defined as affirmative responses to any of the four cost-related medication behaviors in the past 12 months: not obtaining medications, skipping doses, taking less than prescribed, and delaying refills. Sociodemographic characteristics, insurance coverage, and healthcare access were compared by CRN status using Chi-square and Wilcoxon rank-sum tests. Inverse probability weighting (IPW) was applied to address potential selection bias from missing data. Multivariable logistic regression was adjusted for age, sex, race, ethnicity, income, and insurance type to identify factors independently associated with CRN. **Results:** Of 2,323 individuals with HBV, 838 individuals answered cost-related medication behavior questions, and 167 (20%) experienced CRN. Individuals who experienced CRN were more likely to have lower income ($\leq$\$50K: 76% vs 48%, $p < 0.001$), lower education ($p = 0.021$), and be younger (62 vs 66 years, $p < 0.001$). Despite majority having insurance coverage, those with CRN were less frequently covered (92% vs 96%, $p = 0.026$), although with similar insurance types ($p = 0.09$). Individuals with CRN more commonly reported inability to afford emergency (16% vs 1.3%), mental health (22% vs 2.2%), dental (54% vs 10%), and specialist care (34% vs 5.6%), $p < 0.001$. They also more frequently delayed care due to rural residence (12% vs 2.8%), lack of transportation (31% vs 7.6%), and inability to take time off work (15% vs 5.2%), $p < 0.001$. Individuals who experience CRN had lower perceived respect in healthcare interactions (21% vs 45%) and worse self-rated health (46% vs 28%), $p < 0.001$.On multivariable analysis, older age and higher income were associated with lower odds of CRN, while Hispanic and multiracial identity were associated with higher odds. Compared to uninsured individuals, patients covered by Medicaid had lower odds of CRN. **Table 1 Conclusion:** One in five individuals with HBV experienced CRN, and many experienced other structural barriers, including socioeconomic disadvantages, access constraints, and differences in healthcare experiences. These patterns persist despite high overall insurance coverage, suggesting coverage alone does not ensure

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affordable or accessible care. It is critical to address affordability and structural barriers to improve adherence and reduce inequities in HBV management.

Characteristic	OR	95% CI	p-value
Age	0.96	0.94, 0.98	**<0.001**
Sex			
Female	-	-	
Male	0.62	0.37, 1.05	0.08
Race			
White	-	-	
Black	0.94	0.51, 1.72	0.8
Asian	0.53	0.21, 1.30	0.2
Multi-Race	2.66	1.15, 6.16	**0.02**
Ethnicity			
Not Hispanic	-	-	
Hispanic	5.32	1.55, 18.3	**0.008**
Income			
Up to $50K	-	-	
$50K-$100K	0.35	0.16, 0.77	**0.009**
$100K-$150K	0.12	0.03, 0.45	**0.002**
$150K-$200K	0.95	0.32, 2.77	>0.9
More than $200K	0.18	0.03, 0.90	**0.04**
Insurance			
None	-	-	
Medicaid	0.28	0.08, 0.93	**0.038**
Medicare	0.97	0.30, 3.16	>0.9
Private	0.43	0.12, 1.56	0.2
Other	0.62	0.16, 2.43	0.5

Table 1. Multivariable analysis of factors associated with cost-related medication non-adherence among patients with HBV, adjusted for age, sex, race, ethnicity, income, and insurance type.

Abbreviations: OR = Odds Ratio; CI = Confidence Interval

Disclosures: Xiaohan Ying: Nothing to Disclose, Jacky Choi: Nothing to Disclose, Himel Mallick: Nothing to Disclose, Tatyana Kushner: Gilead: Grant/Research Support, Gilead: Advisor, GSK: Advisor, Eiger: Advisor, GSK: Consultant, Madrigal: Advisor, Ipsen: Advisor, Mirum: Advisor, Mirum: Grant/Research Support, Ipsen: Grant/Research Support.

2090 | FASTER NATIONAL DEVELOPMENT AMPLIFIES MASLD BUT NOT VIRAL HEPATITIS OR ALCOHOL-ASSOCIATED LIVER DISEASE

James Paik[1] Eliabe Abreu[2] Annette Paik[3] Khalid AlNaamani[3] Mohamed El-Kassas[4] Cristiane Villela-Nogueira[3] Saleh Alqahtani[3] Zobair Younossi[3], [1]Global NASH/MASH Council, [2]Mayo Clinic Rochester, [3]The Global NASH/MASH Council, [4]Capital University

Background: The global burden of MASLD is rising, yet whether development velocity (the rate of national development improvement) independently amplifies this burden, and whether this effect is disease-specific, remains unknown. This study examined whether development velocity amplifies MASLD burden relative to viral hepatitis and ALD. **Methods:** A multinational country level analysis was conducted using GBD and WHO Global Health Observatory data for 204 countries. A 2-dimensional framework combining baseline Socio-demographic Index (SDI, 2005 to 2007; median 0.60) and development velocity (SDI change, 2006 to 2023; median 8.1%) classified countries into 4 groups: Rapid Risers (low SDI, fast velocity; n = 75), Late Accelerators (high SDI, fast velocity; n = 27), Stalled (low SDI, slow velocity; n = 27), and Plateaued (high SDI, slow velocity; n = 75). Outcomes were age-standardized MASLD prevalence (2019 to 2021) and liver mortality for MASLD, ALD, HBV, and HCV (2023). Dominant liver disease per country was defined as the disease with the highest age-standardized mortality rate. Interaction regression models, adjusted for urbanization, healthcare quality, and political stability, were used to test whether velocity modified each liver outcome. **Results:** While MASLD prevalence differed significantly across 4 groups ($p = 0.002$), highest in Late Accelerators, followed by Rapid Risers, Stalled, and Plateaued countries, MASLD mortality did not differ significantly ($p = 0.199$; Table 1). Despite high MASLD prevalence, MASLD did not emerge as the leading cause of liver death in any group. HBV predominated in Rapid Risers and Stalled countries, whereas ALD led in Plateaued countries, which demonstrated the highest per capita alcohol supply (Table 1). Notably, Late Accelerators showed the narrowest gap between MASLD and viral hepatitis mortality (Table 1), indicating an approaching disease transition. Loess regression identified a crossover point at SDI 0.60, where MASLD mortality converges with HBV. Velocity-SDI interaction analysis revealed that development velocity significantly amplifies the relationship between SDI and MASLD for both prevalence ($\beta = +299.1$, $p < .001$, $\Delta R^2 = 0.074$) and liver mortality ($\beta = +34.3$, $p = 0.049$), whereas velocity showed no effect for HBV ($p = 0.626$), HCV ($p = 0.532$), or ALD ($p = 0.533$), establishing MASLD as the only velocity-sensitive liver disease. **Conclusion:** The rising burden of liver disease linked to development velocity requires dual, concurrent strategies. Currently, we must prioritize viral hepatitis control in Rapid Risers and Stalled nations and ALD reduction in Plateaued countries. Simultaneously, we must establish MASLD prevention infrastructure, especially in Late Accelerator and Rapid Riser countries to prevent disease transition before MASLD becomes the dominant cause of liver mortality.

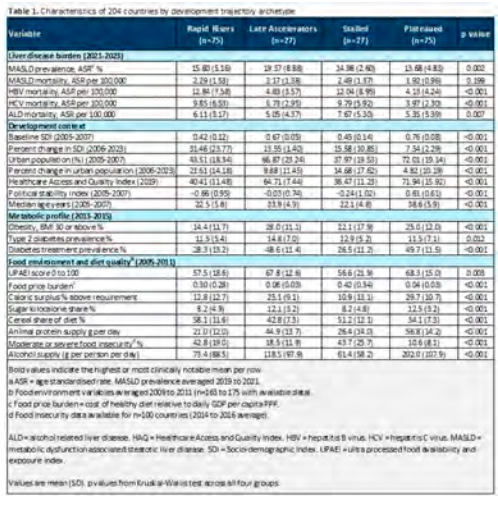


Table 1. Characteristics of 204 countries by development trajectory archetype

Variable	Rapid Risers (n=75)	Late Accelerators (n=27)	Stalled (n=27)	Plateaued (n=75)	p value
Liver disease burden (2021-2023)					
MASLD prevalence, ASR[a] %	15.80 (1.59)	19.57 (8.88)	14.98 (2.40)	13.68 (4.83)	0.002
MASLD mortality, ASR per 100,000	2.29 (1.58)	3.17 (1.33)	2.49 (1.37)	1.92 (0.99)	0.199
HBV mortality, ASR per 100,000	12.84 (7.58)	4.83 (3.57)	12.04 (8.99)	4.13 (4.24)	<0.001
HCV mortality, ASR per 100,000	9.85 (5.53)	5.73 (2.95)	9.79 (5.92)	3.97 (2.30)	<0.001
ALD mortality, ASR per 100,000	6.11 (5.17)	5.05 (4.37)	7.67 (5.30)	5.35 (5.39)	0.007
Development context					
Baseline SDI (2005-2007)	0.42 (0.12)	0.67 (0.05)	0.45 (0.14)	0.76 (0.08)	<0.001
Percent change in SDI (2006-2023)	31.46 (23.77)	13.55 (1.40)	15.58 (10.85)	7.34 (3.29)	<0.001
Urban population (%) (2005-2007)	43.51 (18.54)	66.87 (20.24)	37.97 (19.51)	72.01 (19.14)	<0.001
Percent change in urban population (2006-2023)	23.61 (14.18)	9.88 (11.45)	14.68 (7.62)	4.82 (10.19)	<0.001
Healthcare Access and Quality Index (2019)	40.41 (11.48)	64.71 (7.44)	36.47 (11.28)	71.94 (15.92)	<0.001
Political stability index (2005-2007)	-0.66 (0.95)	-0.03 (0.74)	-0.24 (1.02)	0.61 (0.61)	<0.001
Median age (years) (2005-2007)	32.5 (5.6)	33.9 (4.9)	22.1 (4.6)	38.6 (5.9)	<0.001
Metabolic profile (2015-2015)					
Obesity, BMI 30 or above %	14.4 (11.7)	28.0 (11.1)	12.1 (17.9)	25.0 (12.0)	<0.001
Type 2 diabetes prevalence %	11.3 (5.4)	14.8 (7.0)	12.9 (5.2)	11.5 (7.1)	0.053
Diabetes treatment prevalence %	28.3 (13.2)	48.6 (11.4)	26.5 (11.2)	49.7 (11.5)	<0.001
Food environment and diet quality[b] (2005-2011)					
UPAE[c] score 0 to 100	57.5 (18.6)	67.8 (12.8)	56.6 (21.9)	68.3 (15.0)	0.008
Food price burden[c]	0.30 (0.28)	0.06 (0.03)	0.40 (0.34)	0.04 (0.03)	<0.001
Caloric surplus % above requirement	12.8 (12.7)	25.1 (9.1)	10.9 (11.1)	28.7 (10.7)	<0.001
Sugar calorie share %	8 (2.9)	12.1 (3.2)	8.2 (4.8)	12.5 (3.2)	<0.001
Cereal share of diet %	58.1 (11.9)	42.8 (7.3)	51.2 (12.1)	34.1 (7.3)	<0.001
Animal protein supply g per day	21.0 (12.0)	44.9 (13.7)	26.4 (14.0)	58.8 (14.2)	<0.001
Moderate or severe food insecurity[d] %	42.8 (19.0)	18.5 (11.9)	43.7 (25.7)	10.6 (8.1)	<0.001
Alcohol supply (g per person per day)	78.4 (68.5)	118.5 (97.9)	61.4 (58.2)	202.0 (107.9)	<0.001

Bold values indicate the highest or most clinically notable mean per row.
a ASR = age-standardised rate. MASLD prevalence averaged 2019 to 2021.
b Food environment variables averaged 2005 to 2011 (n=161 to 175 with available data).
c Food price burden = cost of healthy diet relative to daily GDP per capita PPP.
d Food insecurity data available for n=100 countries (2014 to 2016 average).

ALD = alcohol-related liver disease. HAQ = Healthcare Access and Quality Index. HBV = hepatitis B virus. HCV = hepatitis C virus. MASLD = metabolic dysfunction-associated steatotic liver disease. SDI = Socio-demographic Index. UPAE = ultra-processed food availability and exposure index.

Values are mean (SD). p values from Kruskal-Wallis test across all four groups.

Disclosures: James Paik: Nothing to Disclose, Eliabe Abreu: Nothing to Disclose, Annette Paik: Nothing to Disclose, Khalid AlNaamani: Nothing to Disclose, Mohamed El-Kassas: Nothing to Disclose, Cristiane

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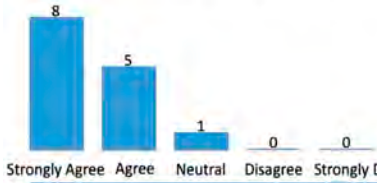
Villela-Nogueira: Nothing to Disclose, Saleh Alqahtani: Nothing to Disclose, Zobair Younossi: Zobair M. Younossi is a consultant or has received research: Consultant, madrigal: Grant/Research Support, Siemens: Research funding, GSK: Consultant, BI: Consultant, Sanofi: Research funding.

2091 | LIVERLINK LOUNGE: FEASIBILITY AND ACCEPTABILITY OF A MULTISITE VIRTUAL PEER SUPPORT INTERVENTION FOR PATIENTS WITH HEPATOCELLULAR CARCINOMA

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Background: Patients with hepatocellular carcinoma (HCC) experience substantial psychosocial burden, including isolation, uncertainty, and difficulty navigating complex care pathways. Despite these challenges, scalable psychosocial interventions are not routinely integrated into HCC care. LiverLink Lounge is a live, virtual peer support intervention developed through iterative Explore, Create, and Test human-centered design (HCD) phases. We evaluated the feasibility and acceptability of cross-site implementation across two academic transplant centers. **Methods:** LiverLink Lounge were virtual peer support groups led by transplant social workers from Indiana University and Johns Hopkins. Participants were patients with HCC froom both centers enrolled from a prospective LiverLink cohort focused on individuals experiencing barriers to care, including adverse social determinants of health. Session content was informed by prior HCD work with this popuation identifying needs related to communication, emotional support, medical mistrust, and coping. Sessions were conducted monthly via video platform with phone participation available. Feasibility was assessed through successful session delivery and multisite participation. Acceptability was evaluated using post-session Likert-scale surveys and qualitative feedback. **Results:** Eight sessions were conducted between July 2025 and March 2026, with simultaneous participation from both institutions in most sessions. Attendance ranged from 1–4 participants per session. Among survey respondents (n = 14), 93% agreed or strongly agreed that participation positively impacted emotional well-being (Figure 1). Qualitative analysis demonstrated three major themes: reduced isolation through emotionally safe peer connection, improved coping and communication skills, and strong desire for continued participation. Participants valued structured facilitation and opportunities to share experiences across institutions and disease stages. Representative comments included: “Being able to talk freely and be vulnerable without being judged was so helpful” and “I got a lot of good ideas on how to communicate with my doctors and advocate for myself". **Conclusion:** A multi-institution, live, and virtual peer support intervention for patients with HCC is feasible and highly acceptable. Integration of patient-informed content derived from iterative HCD phases and multi-site implementation support scalability and inform future trials integrating psychosocial and educational interventions into HCC care.

Figure 1. Impact and Patient Experience of Virtual Peer Support Intervention
A. Impact on Emotional Well-Being (n=14 responses)



Theme	Representative Quote
Emotional Support & Reduced Isolation	Being able to talk freely and be vulnerable without being judged was so helpful.
Improved Coping & Communication	I got a lot of good ideas on how to communicate with my doctors and advocate for myself.
High Acceptability & Desire for Continuity	I want to continue attending sessions if I can... the group helps me feel better.

Disclosures: Lauren Nephew: NovoNordisk: Consultant, NovoNordisk: Consultant, NovoNordisk: Consultant, NovoNordisk: Consultant, Samantha Ky: Nothing to Disclose, Courtney Moore: Nothing to Disclose, Lisa Parks: Nothing to Disclose, Allison McKay: Nothing to Disclose, Sebastian Abad: Nothing to Disclose, Susan Rawl: Nothing to Disclose, Joshua Sumner: Nothing to Disclose, Juliette Dixon: Nothing to Disclose, Kathy Liu: Nothing to Disclose, Alexandra Strauss: Nothing to Disclose.

2092 | RACIAL AND ETHNIC DISPARITIES IN LIVER TRANSPLANT EVALUATION, WAITLISTING, AND OUTCOMES IN THE POST-ACUITY CIRCLE ERA: A NATIONWIDE MULTI-INSTITUTIONAL COHORT STUDY

Noor Albusta[1] Sara Isa[2] Mohamed Abdulla[2], [1]Lahey Hospital and Medical Center, [2]Royal College of Surgeons in Ireland

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Background: Racial disparities in liver transplant (LT) access are well-documented, yet most studies rely on UNOS registry data capturing only waitlisted patients — missing the referral-to-evaluation gap where the largest disparities likely exist. The 2020 acuity circle (AC) policy aimed to improve geographic equity but has not demonstrably reduced racial disparities. No multi-institutional study has examined the full LT care cascade across all racial/ethnic groups using EHR data with pre- vs. post-AC and etiology-specific stratification. **Methods:** Using the TriNetX Global Collaborative Network (>120 healthcare organizations), we conducted a retrospective cohort study of adults (≥18 y) with cirrhosis and either MELD-Na ≥15 or ≥1 hepatic decompensation event from Jan 2016–Dec 2024. Patients were stratified by race/ethnicity (NHW, NHB, Hispanic, Asian, AI/AN) and era (pre-AC: 2016–2020; post-AC: 2020–2024). Primary outcomes were LT evaluation probability, waitlisting, and all-cause mortality at 1 and 3 years. Propensity score matching (1: 1) was performed between each minority group and NHW on 38 covariates including age, sex, cirrhosis etiology, MELD-Na components, insurance type, Elixhauser comorbidity index, and HCC status. Subgroup analyses were performed by etiology, insurance type, and AC era. Cox and Fine-Gray competing risk models estimated adjusted HRs with 95% CIs. **Results:** Among 87,342 adults (NHW 60%, NHB 17%, Hispanic 15%, Asian 5%, AI/AN 3%), mean age was 59.7 ± 10.4 y, 43.8% female, with leading etiologies of ALD (38.2%), MASLD (31.4%), and viral hepatitis (18.6%). NHB patients had higher Medicaid/uninsured rates (52.3% vs. 31.6% NHW, p < 0.001) despite similar MELD-Na scores. After matching, NHB and AI/AN patients had 33% and 44% lower odds of LT evaluation, respectively (Table 1). Median time from decompensation to evaluation was 14.2 months (NHB) and 16.7 months (AI/AN) vs. 9.6 months (NHW; p < 0.001). Three-year mortality was highest among AI/AN (48.2%) and NHB (44.6%) vs. NHW (36.8%). Among LT recipients (n = 4,218), NHB patients had lower 1-year post-LT survival (86.4% vs. 91.2%; HR 1.42, p < 0.001). The AC policy increased overall evaluation rates (16.8% to 20.2%, p < 0.001) but did not attenuate racial gaps (NHB-NHW gap: 5.4% pre vs. 5.8% post, p-interaction = 0.62). Disparities were most pronounced in ALD and among Medicaid/uninsured patients (Table 2; p-interaction < 0.001). **Conclusion:** Significant racial and ethnic disparities persist across the full LT care cascade, greatest at the evaluation stage — upstream of allocation. Black and AI/AN patients face 33–44% lower odds of evaluation and 24–38% higher mortality vs. White patients, unmitigated by the AC policy. Disparities were most severe in ALD and among publicly insured patients, identifying modifiable targets for equity-focused interventions at the referral and evaluation stages.

Table 1. Liver Transplant Care Cascade Outcomes by Race/Ethnicity After Propensity Score Matching

Outcome	NHW (ref)	NHB	Hispanic	Asian	AI/AN
LT evaluation, %	19.8	14.2	15.9	18.4	11.8*
aOR for evaluation (95% CI)	1.00	0.67 (0.63–0.72)	0.78 (0.73–0.84)	0.93 (0.84–1.03)	0.56 (0.48–0.66)
Median time to evaluation, mo (IQR)	9.6 (4.2–19.8)	14.2 (6.8–28.4)	11.8 (5.4–22.6)	10.2 (4.8–20.4)	16.7 (7.4–31.2) *
Waitlisted among evaluated, %	54.2	45.8	50.6†	52.8	38.4
aOR for waitlisting (95% CI)	1.00	0.72 (0.65–0.80)	0.88 (0.79–0.98)	0.94 (0.82–1.08)	0.54 (0.42–0.69)
3-year all-cause mortality, %	36.8	44.6	40.2	37.4	48.2*
Mortality HR (95% CI)	1.00	1.24 (1.18–1.30)	1.12 (1.06–1.19)	1.04 (0.94–1.15)	1.38 (1.24–1.54)
1-year post-LT survival, %	91.2	86.4*	90.8	92.6	88.2

p<0.001; †p<0.05 vs. NHW. aOR, adjusted odds ratio; AI/AN, American Indian/Alaska Native; CI, confidence interval; HR, hazard ratio; IQR, interquartile range; LT, liver transplant; NHB, non-Hispanic Black; NHW, non-Hispanic White.

Table 2. Disparities in LT Evaluation by Cirrhosis Etiology, Insurance Type, and Acuity Circle Era

Subgroup	NHB vs. NHW aOR (95% CI)	AI/AN vs. NHW aOR (95% CI)	Hispanic vs. NHW aOR (95% CI)
By etiology			
ALD	0.58 (0.52–0.65)	0.49 (0.39–0.62)	0.72 (0.64–0.81) *
MASLD	0.74 (0.67–0.82)	0.61 (0.49–0.76)	0.82 (0.74–0.91) *
Viral hepatitis	0.71 (0.63–0.80) *	0.68 (0.52–0.89) †	0.84 (0.74–0.96) †
By insurance			
Private	0.82 (0.74–0.91) *	0.72 (0.58–0.89) †	0.88 (0.79–0.98) †
Medicaid/uninsured	0.58 (0.52–0.65)	0.44 (0.35–0.56)	0.68 (0.60–0.77) *
By AC era			
Pre-AC (2016–2020)	0.68 (0.62–0.75)	0.58 (0.47–0.71)	0.79 (0.72–0.87) *
Post-AC (2020–2024)	0.66 (0.61–0.72)	0.54 (0.45–0.65)	0.77 (0.71–0.84) *
p-interaction (AC era)	0.62	0.54	0.71

p<0.001; †p<0.05. AC, acuity circle; ALD, alcohol-associated liver disease; AI/AN, American Indian/Alaska Native; aOR, adjusted odds ratio; CI, confidence interval; LT, liver transplant; MASLD, metabolic dysfunction-associated steatotic liver disease; NHB, non-Hispanic Black; NHW, non-Hispanic White.

Disclosures: Noor Albusta: Nothing to Disclose, Sara Isa: Nothing to Disclose, Mohamed Abdulla: Nothing to Disclose.

2093 | SOCIOECONOMIC DISPARITIES IN SURGICAL RESECTION AND SURVIVAL AMONG PATIENTS WITH INTRAHEPATIC CHOLANGIOCARCINOMA DESPITE SIMILAR STAGE AT PRESENTATION: A POPULATION-BASED SEER ANALYSIS

Hamza Khan[1] Ritu Yadav[1] Mansha Gupta[1], [1]Northern Arizona Healthcare

Background: Intrahepatic cholangiocarcinoma (ICC) is an aggressive hepatobiliary malignancy for which surgical resection remains the primary potentially curative therapy. The impact of socioeconomic status (SES) on treatment utilization and survival outcomes in ICC remains incompletely characterized. This study aimed to evaluate socioeconomic and racial disparities in stage at diagnosis, receipt of surgical resection, and

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overall survival among patients with ICC. **Methods:** A retrospective cohort study was performed using the Surveillance, Epidemiology, and End Results (SEER) database, including adults diagnosed with ICC between 2004 and 2022. Patients were categorized into low-, middle-, and high-income groups based on county-level median household income. Multivariable logistic regression identified factors associated with advanced stage at diagnosis and receipt of surgical resection. Cox proportional hazards models evaluated overall survival after adjustment for demographic, socioeconomic, and clinical variables. **Results:** Among 16,235 patients with ICC, 17.98% underwent surgical resection. Resection rates differed significantly by income level ($p = 0.006$). In a subgroup analysis restricted to localized or regional disease, middle-income patients had higher odds of resection compared with low-income patients (OR 1.28, 95% CI 1.09–1.50, $p = 0.003$), while high-income patients demonstrated 48% greater odds of undergoing surgery (OR 1.48, 95% CI 1.25–1.75, $p < 0.001$). Income was not associated with advanced stage at diagnosis. In adjusted survival analyses, middle-income (HR 0.89, 95% CI 0.84–0.95, $p < 0.001$) and high-income patients (HR 0.86, 95% CI 0.81–0.92, $p < 0.001$) experienced significantly improved survival compared with low-income patients. American Indian/Alaska Native patients had increased mortality (HR 1.32, 95% CI 1.05–1.67, $p = 0.017$). Surgical resection was independently associated with markedly improved survival (HR 0.32, 95% CI 0.30–0.34, $p < 0.001$). Kaplan-Meier analysis demonstrated significant survival differences across income strata (log-rank $p < 0.001$). **Conclusion:** Significant socioeconomic disparities exist in access to potentially curative surgery and survival among patients with ICC. Despite presenting at similar stages, higher-income patients were substantially more likely to undergo surgical resection and experienced superior survival outcomes. These findings suggest that socioeconomic barriers may influence access to definitive hepatobiliary cancer care and contribute to outcome disparities in ICC.

Table 1. Multivariable Predictors of Surgical Resection Among Patients with Localized/Regional ICC

Variable	Adjusted OR	95% CI	P value
Middle Income vs Low	1.28	1.09–1.50	0.003
High Income vs Low	1.48	1.25–1.75	<0.001
NH Asian/API vs Reference	1.38	1.13–1.67	0.001
Male Sex	0.86	0.78–0.96	0.006
Regional vs Localized Disease	0.43	0.39–0.48	<0.001
Age (per year)	0.96	0.96–0.97	<0.001

Adjusted Predictors of Surgical Resection Among Patients with Potentially Operable Intrahepatic Cholangiocarcinoma

Disclosures: Hamza Khan: Nothing to Disclose, Ritu Yadav: Nothing to Disclose, Mansha Gupta: Nothing to Disclose.

2094 | INDIVIDUAL PATIENT ACCESS TO LIFESAVING INTERVENTIONS IS A BETTER PREDICTOR OF INPATIENT MORTALITY THAN WORLD BANK COUNTRY INCOME IN A GLOBAL INPATIENT CIRRHOSIS COHORT

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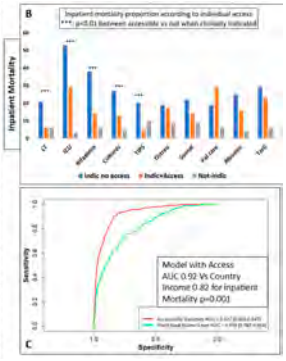
Background: Cirrhosis care varies worldwide due to differing etiologies, and access to care & interventions. Prior analyses have focused on either regional or country income-based evaluations. **Aim** : Determine

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individual patient-level access to important interventions and it's impact on inpatient cirrhosis outcomes. **Methods:** CLEARED Consortium recruits cirrhosis inpatients globally and follows them for inpatient mortality or liver transplant (LT). Data collected included demographics, cirrhosis details, medications, inpatient course data and country-level income according to the World Bank. Centers were divided into those belongng to high (HIC), upper middle (UMIC) & low/low-middle (LIC) income countries. We collected availability, affordability, and clinical need for important drugs (IV albumin, rifaximin, octreotide, somatostatin, terlipressin), interventions (LT, TIPS) & services (ICU, microbiology cultures, palliative care). For each, we asked whether it was clinically indicated or not. If indicated, we collected % receiving, % not receiving due to unavailability or unaffordability deemed lack of access. Logistic regression models using either lack of access or country income for inpatient mortality prediction were created using variables significantly different on crude analysis and compared using AUC. **Results:** 1612 patients (57 yrs, 61% men, 38% alcohol) were recruited from 53 centers. 27% were from HIC, 42% from UMIC) & 31% LICs. 167 (10%) died during the admission and were more likely to be from LICs, with more advanced cirrhosis (Fig A). Lack of access: Was highest in LIC: LT (28.5%), followed by terlipressin (8.5%), Palliative care (8.5%), TIPS (7.2%), somatostatin (6.8%), Octreotide (5.9%), ICU (5.6%), rifaximin (5.1%), Cultures (4.2%), & albumin (3.8%). LT access was also not easily accessible in UMICs (24.1%). Lack of access was linked with higher inpatient mortality (Fig A/B), with the largest differences for ICU, LT, rifaximin, cultures & TIPS. Regression Models: Model with access variables showed lack of LT (adj OR 4.5, 1.8-13, $p = 0.003$ vs access), ICU (adj. OR: 2.8,1.4-5.7, $p = 0.003$) & rifaximin access (adj. OR: 2.7,1.0-7.1, $p = 0.048$) were significant for increased mortality in addition to prior HE (2.1, 1.2-3.6, $p = 0.009$) & MELD-Na (1.06, 1.02-1.09, $p < 0.001$). Comparison of multivariable models containing access versus country income showed superiority of access model for inpatient mortality prediction (Fig C). **Conclusion:** Individual patient access to lifesaving interventions such as LT, ICU care, rifaximin, blood cultures are major determinants of inpatient mortality in a global cirrhosis cohort. Using patient-level access is significantly more predictive than crude country-level income level metrics and should be used to enhance prognostication and identify patients who will benefit from improving access.

A: Median(IQR)/ N (%)	No Inpt Death (n=1445)	Inpt Death (n=167)	p-value
Age	57.00 [48.00, 66.00]	57.00 [47.00, 66.50]	0.826
Male	884 (61.2)	106 (63.5)	0.622
World Bank Income			<0.001
High-income	415 (28.7)	25 (15.0)	
Low/low-middle	426 (29.5)	73 (43.7)	
Upper middle income	604 (41.8)	69 (41.3)	
Alcohol vs not	547 (37.9)	67 (40.1)	0.625
Diabetes	444 (30.7)	42 (25.1)	0.162
Prior Ascites	926 (64.1)	116 (69.5)	0.197
Prior HE	399 (27.6)	80 (47.9)	<0.001
Prior Hyponatremia	212 (14.7)	39 (23.4)	0.005
Prior AKI	194 (13.4)	42 (25.1)	<0.001
Prior Hydrothorax	91 (6.3)	9 (5.4)	0.771
Prior 6mo Hospit	620 (42.9)	73 (43.7)	0.907
Prior 6mo Infection	243 (16.8)	35 (21.0)	0.218
Prior LT Listing	103 (7.1)	7 (4.2)	0.207
Beta Blocker	558 (38.6)	44 (26.3)	0.003
Diuretic	795 (55.0)	68 (40.7)	0.001
Lactulose	545 (37.7)	81 (48.5)	0.009
SBPPr	185 (12.8)	28 (16.8)	0.19
Statin	137 (9.5)	6 (3.6)	0.017
PPI	615 (42.6)	72 (43.1)	0.957
Antiviral	246 (17.0)	24 (14.4)	0.447
Infection on Admission	321 (22.2)	58 (34.7)	<0.001
Hemoglobin	10.00 [8.20, 11.90]	10.00 [8.10, 11.90]	0.701
WBC	5.10 [2.79, 8.70]	8.34 [2.65, 13.54]	<0.001
Albumin	2.95 [2.50, 3.40]	2.60 [2.21, 3.10]	<0.001
MELD-Na	20.89 (7.84)	29.28 (8.00)	<0.001



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Abate Shewaye: Nothing to Disclose, Adam Doyle: Nothing to Disclose, JOSE VELARDE RUIZ VELASCO: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose, Jacqueline Cordova Gallardo: Nothing to Disclose, Maria González Huezo: Nothing to Disclose, Brian Bush: Nothing to Disclose, Qing Xie: Nothing to Disclose, peter hayes: Nothing to Disclose, Aldo Torre: Nothing to Disclose, Wai-Kay Seto: MSD: Speaking and Teaching, Echosens: Speaking and Teaching, Pfizer: Grant/Research Support, 89Bio: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Ribo Life Science: Grant/Research Support, AstraZeneca: Grant/Research Support, Gilead: Grant/Research Support, Gilead: Speaking and Teaching, Gilead: Consultant, Abbott: Consultant, Abbott: Speaking and Teaching, Ashok Kumar Choudhury: Nothing to Disclose.

2095 | MULTILEVEL DETERMINANTS OF LIVER TRANSPLANT EVALUATION CLOSURE AT A LARGE TEXAS TRANSPLANT CENTER

Kishore Botla[1] Olgert Bardhi[1] Amy Hughes[1] Alaina Beauchamp[2] Rutu Rathod[3] Alvaro Noriega Ramirez[1] Dyanna Gregory[1] Lisa VanWagner[1] Amit Singal[1] Sarah Lieber[1], [1]University of Texas Southwestern Medical Center, [2]University of Kansas Medical Center, [3]University of Arkansas for Medical Sciences

Background: Liver transplant evaluation (LTE) is critical to accessing transplantation, yet many patients who begin LTE are never listed. LTE closure (i.e., decline to place a patient on the waitlist), occurs for medical and psychosocial reasons. Identifying individual and neighborhood-level factors associated with LTE closure may reveal modifiable barriers to liver transplant (LT) access. **Methods:** This retrospective cohort study of adults undergoing LTE from 2014-2023 matched patients with LTE closure to those waitlisted/transplanted by date, age, sex, and alcohol-related versus non-alcohol-related LT indication. Sociodemographic, clinical, and psychosocial factors were manually abstracted from the electronic health record. Primary reasons for closure and incomplete LTE components were abstracted from selection committee documentation. Patient addresses were geocoded to census tracts to characterize neighborhood socioeconomic context including social deprivation, ethnic enclave status, alcohol outlet density, retail food environment, walkability, transit access, and rurality. Multivariable logistic regression estimated adjusted odds ratios (aORs) for LTE closure. **Results:** Among 885 patients, 466 (52.7%) had LTE closure and 419 (47.3%) were waitlisted/transplanted. LTE closure was most often due to medical/physical (67.5%), followed by psychosocial/financial (27.5%) reasons and personal choice (4.9%). Medical closures were most commonly due to non-liver comorbidities (46.9%) or clinical improvement (26.1%); psychosocial/financial closures were due to ongoing/relapsed substance use (40.6%) or inadequate social support (26.6%). More than one-third of patients (34.9%) did not complete all LTE components, most commonly cardiac (23.6%) and preventative health clearance (21.9%). In multivariable analysis, any psychiatric history was associated with higher odds of closure (aOR 1.68, 95% CI 1.16-2.44). Non-liver comorbidity burden showed a graded association with closure: mild (aOR 1.90, 95% CI 1.23-2.99), moderate (aOR 2.91, 95% CI 1.78-4.83), and severe (aOR 7.28, 95% CI 2.79-21.6) compared to none. Neighborhood mapping suggests spatial overlap between area deprivation and Hispanic enclave status, with broadly low walkability and healthy retail food access across Texas (**Figure 1**). **Conclusion:** More than half of evaluated patients were closed due to medical and potentially modifiable psychosocial factors. Psychiatric history and non-liver comorbidity burden were independently associated with closure, supporting earlier behavioral health integration and targeted evaluation support to improve transplant access, particularly around the completion of required pre-transplant clearance testing. Neighborhood-level mapping provides a structural context for these barriers and may help identify communities where pre-evaluation outreach and resource navigation are most needed.



MULTIVARIABLE REGRESSION: PREDICTORS OF LTE CLOSURE

Variable		aOR[1]	95% CI[1]	p-value[1]
Race/Ethnicity				0.8
	White	Referent	Referent	
	Non-White	1.56	0.45, 5.38	
	Missing/Unknown	1.02	0.72, 1.44	
Any Psychiatric History (non-Substance Use)				0.006
	No	Referent	Referent	
	Yes	1.68	1.16, 2.44	
History of Tobacco Use				0.058
	No	Referent	Referent	
	Yes	1.54	0.99, 2.44	
MELD 3.0 Score at Evaluation		0.99	0.97, 1.01	0.4
Non-Liver Comorbidity Burden				<0.001
	None (0)	Referent	Referent	
	Mild (1-2)	1.90	1.23, 2.99	
	Moderate (3-4)	2.91	1.78, 4.83	
	Severe (≥5)	7.28	2.79, 21.6	
Evidence of Liver Decompensation				0.3
	No	Referent	Referent	
	Yes	0.80	0.52, 1.22	

[1]Adjusted odds ratios (aOR) and 95% confidence intervals (CI) for the likelihood of LTE closure were calculated using multivariable logistic regression.

Figure 1. Neighborhood context and multivariable predictors of liver transplant evaluation closure. Maps show selected tract-level neighborhood characteristics across Texas. The regression table displays adjusted odds ratios (aORs) for LTE closure across a variety of clinical and sociodemographic parameters.

Disclosures: Kishore Botla: Nothing to Disclose, Olgert Bardhi: Nothing to Disclose, Amy Hughes: Nothing to Disclose, Alaina Beauchamp: Nothing to

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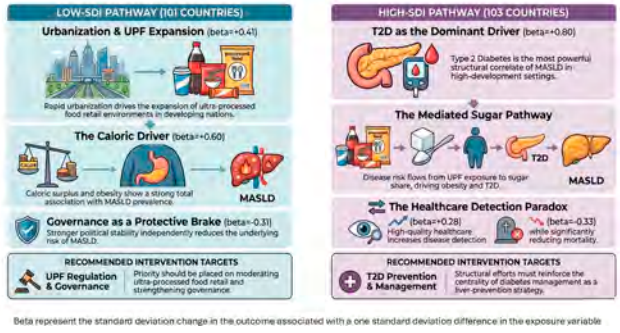
Disclose, Rutu Rathod: Nothing to Disclose, Alvaro Noriega Ramirez: Nothing to Disclose, Dyanna Gregory: Nothing to Disclose, Lisa VanWagner: W.L. Gore & Associates: Grant/Research Support, Akero: Grant/Research Support, Madrigal: Grant/Research Support, Gerson Lehrman Group: Consultant, Madrigal: Advisor, Slingshot Insights: Consultant, Antheneum Partners: Consultant, Gerson Lehrman Group: Consultant, Alpha Insights: Consultant, Slingshot Insights: Consultant, Madrigal Pharmaceuticals: Grant/Research Support, W.L. Gore & Associates: Grant/Research Support, BD: Grant/Research Support, Medicolegal consulting: Consultant, Amit Singal: Genentech: Consultant, AstraZeneca: Consultant, Bayer: Consultant, Eisai: Consultant, Exelixis: Consultant, Merck: Consultant, Elevar: Consultant, FujiFilm Medical Sciences: Consultant, Exact Sciences: Consultant, Glycotest: Consultant, Boston Scientific: Consultant, Sirtex: Consultant, HelioGenomics: Consultant, ImCare: Consultant, DELFI: Consultant, Curve Biosciences: Consultant, Catalym: Consultant, Verve: Consultant, Sarah Lieber: Nothing to Disclose.

2096 | THE DEVELOPMENT DIVIDE: HOW FOOD SYSTEMS DRIVE METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) THROUGH DIFFERENT STRUCTURAL PATHWAYS ACROSS 204 COUNTRIES

James Paik[1] Markos Kalligeros[2] Shira Zelber-Sagi[3] Annette Paik[2] Carina Kugelmas[4] Saleh Alqahtani[2] Zobair Younossi[2], [1]Global NASH/MASH Council, [2]The Global NASH/MASH Council, [3]The University of Haifa, [4]Denver Health

Background: Food systems shape metabolic diseases globally, yet their causal pathways to MASLD remain unmapped across each country's economic contexts. We applied structural equation modeling to elucidate how food-system characteristics, mediated through obesity and type 2 diabetes (T2D), drive MASLD prevalence and mortality across 204 countries stratified by development level. **Methods:** Cross-national ecological study harmonizing Global Burden of Disease, NCD Risk Factor Collaboration, Food and Agriculture Organization of the United Nations Statistics Database (FAOSTAT), and World Bank data. Food-system exposures (2005–2011), metabolic mediators (2013–2015), and liver outcomes (2019–2023) were analyzed separately for low-SDI (n = 101) and high-SDI (n = 103) countries. **Results:** Despite similar age-standardized MASLD prevalence (low-SDI: 15.58% vs. high-SDI: 15.19%, p = 0.055), causal pathways diverged fundamentally. In low-SDI countries, urbanization-driven ultra-processed food (UPF) expansion increased the prevalence of obesity and MASLD while political stability independently reduced MASLD risk **(Figure)** . In high-SDI countries, UPF drove dietary sugar consumption, which drove obesity and T2D, the dominant MASLD correlate (β = +0.80). A healthcare detection paradox emerged: greater healthcare access increased MASLD detection (β = +0.28) but reduced mortality (β = −0.33) **(Figure)** . **Conclusion:** MASLD prevention requires development-stratified structural interventions: UPF regulation and governance strengthening in low-SDI nations while T2D prevention in high-SDI nations.

Figure. The Development Divide: Divergent Global Pathways to MASLD



Disclosures: James Paik: Nothing to Disclose, Markos Kalligeros: Nothing to Disclose, Shira Zelber-Sagi: Nothing to Disclose, Annette Paik: Nothing to Disclose, Carina Kugelmas: Nothing to Disclose, Saleh Alqahtani: Nothing to Disclose, Zobair Younossi: Zobair M. Younossi is a consultant or has received research: Consultant, madrigal: Grant/Research Support, Siemens: Research funding, GSK: Consultant, BI: Consultant, Sanofi: Research funding.

2097 | A CULTURALLY COMPETENT HISPANIC LIVER TRANSPLANT PROGRAM: IMPROVED ACCESS, INCREASED LIVING DONOR LIVER TRANSPLANTATION, AND REDUCED DISPARITIES

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Background: Hispanic patients face persistent disparities in liver transplantation (LT). In 2010, a HispanicLiver Transplant Program (HLTP) was implemented to provide culturally and linguistically competent care through bilingual staff, Spanish-language education, and navigation support. We evaluated whether HLTP implementation was associated with improved Hispanic access to LT care. **Methods:** OPTN (Organ Procurement & Transplantation Network(OPTN)/UNOS (United Network for Organ Sharing) data were used to compare LT access metrics at Northwestern Medicine (NM),Illinois (IL), and the United States across three eras: pre-HLTP (2000-2009), post-HLTP (2011-2020), and recent era (2021-2025). The implementation year, 2010, was excluded. Outcomesincluded waitlist additions, overall LT, and living donor liver transplantation (LDLT). Waitlistadditions were used as a metric for access to transplant care. To account for volume changes, wecalculated a Hispanic-to-non-Hispanic White (NHW) equity ratio: [Hispanic outcome/totaloutcome]/[NHW outcome/total outcome]. Higher ratios indicate movement toward parity andreduced disparity. **Results:** A culturally competent HLTP was associated with improved Hispanic accessacross the LT pathway, including waitlist additions, overall LT, and LDLT. The observedimprovement in Hispanic/NHW equity ratios suggests narrowing disparities in LT. These findings parallel prior kidney transplant experience, supporting that culturally competent transplant care is not organ-specific. At NM, mean annual Hispanic waitlist additions increased from 13.4 to 21.7 (+62%), while the Hispanic/NHW waitlist equity ratio increased from 0.10 to 0.21 (+114%). Mean annual Hispanic LT increased from 8.5 to 15.6 (+84%), with the LT equity ratio increasing from 0.11 to 0.20 (+76%). During the same period, the LT equity ratio increased by 20% in IL and 18% nationally. Hispanic LDLT at NM increased from 0.8 to 1.6/year (+100%), while the LDLT equity ratio increased from 0.07 to 0.17 (+146%), compared with +26% in IL and +0.7% nationally. NM's mean annual NHW LT volume remained stable (74.9 to 77.9). By 2021-2025, Hispanic LT reached 24.2/year and the Hispanic/NHW LT equity ratio rose to 0.27, suggesting sustained improvement in access and continued narrowing of the LT disparity. **Conclusion:** Implementation of a culturally competent HLTP was associated with improved Hispanic accessacross the LT pathway, including waitlist additions, overall LT, and LDLT. The observedimprovement in Hispanic/NHW equity ratios suggests narrowing disparities in livertransplantation. The HLTP was modeled after a renal transplant program within the same instutionon that demonstrated a similar reduction in disparities. These findings parallel prior kidney transplant experience, supporting thatculturally competent transplant care is not organ-specific; it is an access design strategy acrossorgan systems.

HLTP Impact Compared With Illinois and U.S. Benchmarks

Cells show Hispanic mean/year / NHW mean/year / Hispanic-to-NHW equity ratio

Domain	Geography	Pre-HLTP 2000-2009 Hisp/NHW/Ratio	Post-HLTP 2011-2020 Hisp/NHW/Ratio	Equity ratio change vs Pre	Recent era 2021-2025 Hisp/NHW/Ratio	Equity ratio change vs Pre
Access to care	Study center	13.4 / 137.2 / 0.10	21.7 / 103.0 / 0.21	+114%	29.6 / 110.2 / 0.26	+160%
Access to care	Illinois	72.1 / 631.2 / 0.11	64.8 / 288.3 / 0.22	+98%	123.8 / 321.4 / 0.38	+77%
Access to Care	United States	1,508.7 / 7,540.0 / 0.20	2,043.2 / 8,560.5 / 0.24	+15%	2,837.6 / 9,857.8 / 0.29	+44%
Transplant Volume	Study center	8.5 / 74.9 / 0.11	15.6 / 77.9 / 0.20	+76%	24.2 / 91.2 / 0.27	+134%
Transplant Volume	Illinois	43.3 / 176.0 / 0.25	51.1 / 172.8 / 0.30	+20%	96.0 / 256.0 / 0.38	+52%
Transplant Volume	United States	953.9 / 4,244.2 / 0.13	1,155.2 / 5,383.2 / 0.21	+58%	1,950.6 / 5,206.2 / 0.27	+94%
Living donation	Study center	0.9 / 11.3 / 0.07	1.6 / 9.2 / 0.17	+140%	2.0 / 10.0 / 0.20	+183%
Living donation	Illinois	6.8 / 19.6 / 0.34	7.5 / 11.6 / 0.64	+26%	8.4 / 22.3 / 0.38	+10%
Living donation	United States	42.3 / 253.7 / 0.17	46.3 / 221.1 / 0.21	+26%	103.6 / 467.0 / 0.22	+30%

HLTP, Hispanic Liver Transplant Program; LT, Liver transplantation; LDLT, living donor liver transplantation; NHW, non-Hispanic White.
Equity ratio = Hispanic mean annual outcome / NHW mean annual outcome. Higher ratios indicate proportionally greater activity with respect to NHW.
Data source: OPTN/UNOS; Illinois, and United States data supplied for abstract analysis.

Disclosures: AMANDA PIROLA: Nothing to Disclose, veronica boratyn: Nothing to Disclose, rachel orbuch: Nothing to Disclose, Andres Duarte-Rojo: Echosens: Grant/Research Support, Echosens: Grant/Research Support, CIMA Sciences: Consultant, HepQuant: Advisor, Merz: Advisor, CIMA Sciences: Grant/Research Support, Merz Therapeutics: Advisor, Juan Caicedo: Nothing to Disclose, Daniel Ganger: WCG: Consultant, WCG: Consultant, Daniel Ganger: WCG: Consultant, WCG: Consultant, Daniel Borja-Cacho: Nothing to Disclose.

2098 | USING NATURAL LANGUAGE PROCESSING TO EXTRACT SOCIAL DETERMINANTS OF HEALTH DATA FROM TRANSPLANT NOTES: A MULTI-CENTER FEASIBILITY STUDY

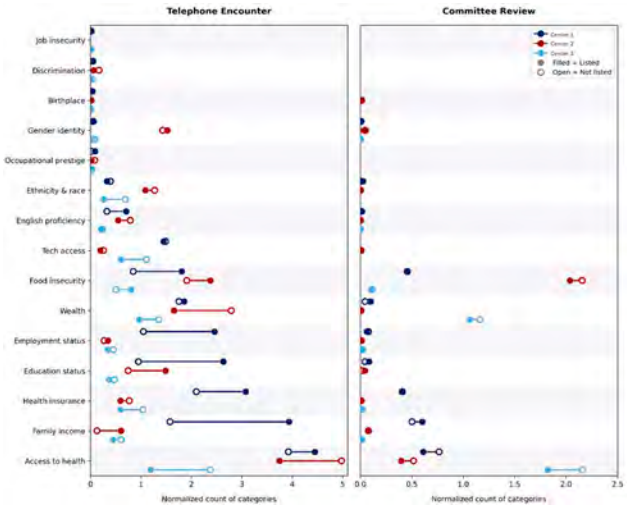
Alexandra Strauss[1] Hamed Zaribafzadeh[2] Mia Grayson[2] Jennifer Gagnon[2] Tyrus Vong[3] Sue Hyon Kim[4] Marina Serper[5] Ricardo Henao[2] Lisa McElroy[6], [1]Johns Hopkins University, [2]Duke, [3]Johns Hopkins, [4]U of pennsylvania, [5]University of Pennsylvania Health System, [6]Duke University

Background: Disparities in liver transplant access are well documented, but rigorous study of modifiable social determinants of health (SDOH) is limited by sparse and inconsistently captured structured data. Because SDOH are often documented in free-text transplant notes, natural language processing (NLP) may augment missing structured data and improve inference. Our prior single-center work showed that rule-based NLP can identify SDOH terms in transplant notes at one institution. Here, we sought to assess the feasibility of this approach across centers with different note formats and documentation practices and to assess similarities and differences in SDOH documentation. **Methods:** We applied a rule-based spaCy NLP pipeline to telephone encounter and committee review notes from transplant patients at 3 centers from 2016-2025. Token-based rules were used to identify and count the SDOH terms per patient. Term and category

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counts were stratified by transplant listing status and normalized by the number of patients in each group. **Results:** We analyzed notes from 9,509 referred patients. Figure 1 showed marked between-site variation in SDOH documentation, but similar broad patterns across centers. Telephone Encounters contained substantially higher and more diverse SDOH content than sparse committee review notes (eg, access to health, financial factors, family support, education). Center 1 had higher normalized counts for employment, education, insurance, and family income. Conversely, Center 2 shows pronounced spikes in areas such as wealth and food insecurity. Center 3 demonstrates lower but more stable counts. In Telephone Encounters, the listed vs unlisted "dumbbell" gaps suggested pre-listing differences in documentation density for several domains, including family income (Center 1) and wealth (Center 2). **Conclusion:** Rule-based NLP successfully extracted SDOH content from transplant notes across 3 centers, with consistent finding of greater SDOH density in telephone encounters than committee review notes. Although the frequency and mix of SDOH categories varied by center, the same broad domains were detectable across institutions and waitlist status, supporting the feasibility of multi-center SDOH extraction from free text. These findings suggest that NLP can help overcome missingness in structured SDOH data and enable future multi-center work focused on causal inference, disparities, and center-level variation in transplant evaluation and listing.



Disclosures: Alexandra Strauss: Nothing to Disclose, Hamed Zaribafzadeh: Nothing to Disclose, Mia Grayson: Nothing to Disclose, Jennifer Gagnon: Nothing to Disclose, Tyrus Vong: Nothing to Disclose, Sue Hyon Kim: Nothing to Disclose, Marina Serper: Transplant Genomics: Grant/Research Support, Grifols: Grant/Research Support, Ricardo Henao: Nothing to Disclose, Lisa McElroy: CareDx: Grant/Research Support, Veloxis: Grant/Research Support, NIMHD: Grant/Research Support, NIDDK: Grant/Research Support.

2099 | EARLY MORTALITY IN POTENTIALLY CURABLE HEPATOCELLULAR CARCINOMA IS ASSOCIATED WITH HIGHER POOR SOCIAL DETERMINANTS OF HEALTH BURDEN

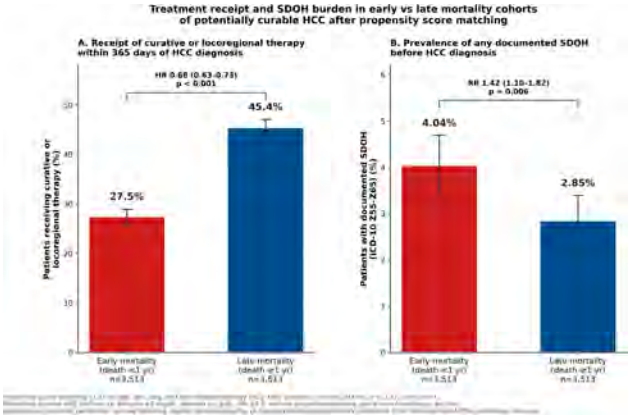
Ali Emre Bardak[1] Nazli Begum Ozturk[2] Okan Cetin[1] Kamran Qureshi[2], [1]Boston Medical Center - Brighton, [2]Saint Louis University School of Medicine

Background: Despite advances in curative therapies for hepatocellular carcinoma (HCC), substantial variation in outcomes persists. Social determinants of health (SDOH) – non-medical factors such as housing stability, food security, financial resources, and social support that influence access to care – may drive disparities in treatment access and survival, but evidence in potentially curable cancer populations is limited. We examined whether early mortality among potentially curable HCC patients is associated with higher SDOH burden after control for demographic and etiologic confounders. **Methods:** We performed a retrospective cohort study using the TriNetX US Collaborative Network (66 healthcare organizations, 113.9 million patients). Adults with HCC (ICD-10 C22.0) diagnosed between 2010 and 2025 were eligible if: total bilirubin ≤ 3 mg/dL, albumin ≥ 3 g/dL, INR ≤ 1.5 at the time of HCC diagnosis, without distant metastases, portal vein thrombosis, ascites, spontaneous bacterial peritonitis, variceal bleeding, hepatic encephalopathy, or hepatorenal/hepatopulmonary syndrome. Among patients with documented mortality, two cohorts were defined: early mortality (death within 1 year of HCC diagnosis) and late mortality (death ≥ 1 year after HCC diagnosis). Cohorts were 1: 1 propensity score matched on age, sex, race, and liver disease etiology (HCV, HBV, alcoholic cirrhosis, MASH). Outcomes included receipt of any SDOH documentation (ICD-10 Z55–Z65) before HCC diagnosis, and curative-intent or locoregional therapy (liver transplant, resection, ablation, TACE, TARE) within 365 days post-diagnosis. Kaplan-Meier analysis was performed. **Results:** Of 13,224 potentially curable HCC patients with documented mortality identified, 3,513 per cohort remained after matching. Despite matching on demographic and etiologic factors, early-mortality patients had significantly higher prevalence of any documented SDOH (4.04% vs 2.85%; RR 1.42, 95% CI 1.10–1.82; $p = 0.006$). Compared with late-mortality patients, those who died within 1 year had significantly lower

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receipt of curative-intent or locoregional therapy (27.5% vs 45.4%; HR 0.68, 95% CI 0.63–0.73; p < 0.001). **Conclusion:** Among potentially curable HCC patients matched on demographic and etiologic factors, early mortality is independently associated with higher documented SDOH burden and reduced receipt of curative therapy, when compared with patients who survived at least 1 year after the HCC diagnosis. These findings suggest SDOH influences access to curative care beyond tumor biology and hepatic reserve. Targeted SDOH screening and intervention may improve treatment access and survival in potentially curable HCC.

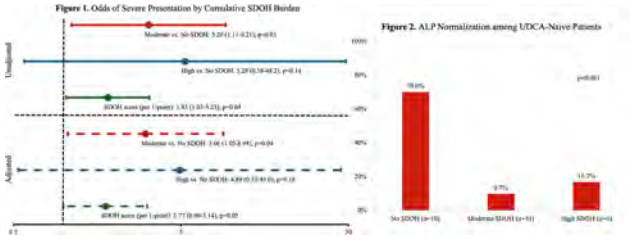


Disclosures: Ali Emre Bardak: Nothing to Disclose, Nazli Begum Ozturk: Nothing to Disclose, Okan Cetin: Nothing to Disclose, Kamran Qureshi: Nothing to Disclose.

2100 | CUMULATIVE SOCIAL DETERMINANTS OF HEALTH BURDEN IDENTIFIES SEVERE PRESENTATION AND IMPAIRED BIOCHEMICAL RESPONSE IN PRIMARY BILIARY CHOLANGITIS: RESULTS FROM THE ELLA-PBC COHORT

Paul Yoon[1] Isabel Obias[1] Sade Brown[1] Jennifer Dodge[1] Ani Kardashian[1] Jeffrey Kahn[1] Saro Khemichian[1] Lily Dara[1], [1]University of Southern California Keck School of Medicine

Background: Social determinants of health (SDOH) may contribute to delayed recognition and incomplete biochemical response in primary biliary cholangitis (PBC), but data in underrepresented populations are limited. We examined whether cumulative SDOH burden was associated with baseline disease severity and 1-year alkaline phosphatase (ALP) normalization after ursodeoxycholic acid (UDCA) initiation. **Methods:** The East Los Angeles Latinx PBC (ELLA-PBC) cohort includes predominantly Hispanic patients (≥18 years) with PBC treated at the University of Southern California Medical Centers (2006-2022). SDOH domains were measured using validated PhenX Toolkit surveys. A 5-component SDOH score included insurance status, discrimination burden, health literacy, educational attainment, and access to health services. The composite score was categorized as none (0), moderate (1-2), or high (≥3). The primary outcome was severe baseline presentation, defined as the presence of ≥1 of the following: cirrhosis, decompensation, hepatocellular carcinoma, ALP >2x the upper limit of normal (ULN), or bilirubin >ULN. Logistic regression models estimated odds ratios (OR), adjusting for age and sex. Secondary analyses examined 1-year ALP normalization among UDCA-naive patients. **Results:** Among 95 patients, median age was 54 years, 94% were female, and 73% were Hispanic. SDOH burden was none in 27 (28%), moderate in 58 (61%), and high in 10 (11%) patients. Median baseline ALP was 271 U/L (IQR 159-436) overall and increased across SDOH burden: 181 vs. 304 vs. 405 for none, moderate, and high burden, respectively (p = 0.01). Severe presentation occurred in 79% patients and increased with SDOH burden (63% for none vs. 85% for moderate vs. 90% for high, p = 0.05). In adjusted models, moderate SDOH burden had 3-fold higher odds of severe presentation compared with no SDOH burden (OR 3.06, 95% CI 1.05-8.94, p = 0.04), while high SDOH burden had nearly 5-fold higher odds (OR 4.89, 95% CI 0.53-45.0, p = 0.16). Each 1-point increase in SDOH burden corresponded to 77% higher odds of severe presentation (OR 1.77, 95% CI 0.99-3.14, p = 0.05). Among 47 UDCA-naive patients with 1-year follow-up data, ALP normalization was achieved by 11 (23%) and was lower with SDOH burden: 7 (70%) with no burden, 3 (10%) with moderate burden, and 1 (17%) with high burden (p < 0.001). **Conclusion:** Cumulative SDOH burden was associated with a higher baseline ALP, higher odds of severe presentation, and lower ALP normalization after UDCA initiation. These findings support integrating structured SDOH screening into PBC care to guide risk stratification and targeted interventions to improve early diagnosis, monitoring, and treatment optimization.



Disclosures: Paul Yoon: Nothing to Disclose, Isabel Obias: Nothing to Disclose, Sade Brown: Nothing to Disclose, Jennifer Dodge: Nothing to Disclose, Ani Kardashian: Nothing

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to Disclose, Saro Khemichian: Nothing to Disclose, Lily Dara: Ipsen: Consultant, Mirum: Consultant, Amgen: Consultant, Agios: Consultant, OPKO: Consultant.

2101 | THE PATH TO THE LIST: PROVIDERS&RSQUO; PERSPECTIVES ON EQUITY GAPS IN LIVER TRANSPLANT EVALUATIONS

Zamzam Ismail Artan Ali[1] Mohamed Addani[1] David Chascsa[2] Denise Harnois[3] Blanca Lizaola-Mayo[2] Kasey Boehmer[4] Lewis Roberts[5], [1]Mayo Clinic, [2]Mayo Clinic Arizona, [3]Mayo Clinic Florida, [4]Mayo Clinic, Rochester, [5]Mayo Clinic Rochester

Background: End Stage Liver Disease (ESLD) is an emerging public health concern with more than 15,000 hospitalizations each year in the United States. Together with cirrhosis, it is considered the 14th leading cause of death in the world. Liver transplantation (LT) is considered the only curative treatment for ESLD. More than 10,000 patients are currently awaiting LT in the USA. Unfortunately, about 20% of people will die while waiting for LT. Disparities in access to LT outcomes are influenced by a complex interplay of social determinants of health. The LT evaluation process is susceptible to structural inequities, but these effects are often masked by its clinical, logistical, and ethical complexities. Moreover, a recent scoping review found that female patients, Black race, and patients with Medicare insurance were less likely to be referred and evaluated for LT. Therefore, there is a need to investigate and identify mechanisms between social determinants of health and inequities in access to LT. **Methods:** This qualitative study is part of a mixed methods project examining disparities in access to LT. It is a multicenter study including Mayo Clinic LT centers in Minnesota, Florida, and Arizona. It utilizes 1: 1 in depth interviews with both healthcare providers and LT patients, aiming to understand upstream barriers to LT access for underrepresented communities. 23 interviews were conducted between Nov 2024-March 2026 with healthcare providers[figure1]. **Results:** Five main themes emerged from this study,[Figure1].Theme 1 explores language barriers and how it impacts care through time constraints, limitations in technology used and available resources to navigate this challenge. Many participants discussed socioeconomic and financial barriers in Theme 2. They highlighted insurance, lifelong medication costs, and distance from healthcare centers as factors limiting equal access to LT evaluation. Theme 3 discussed subjectivity of psychosocial assessment and how personality, social support and history of substance abuse can impact decision-making. Teamwork and power dynamics were emerging areas discussed by participants in Theme 4 stating the importance of shared leadership across disciplines and collective accountability. Final theme discussed patient empowerment and awareness of rights within the system. This included cultural differences in self-advocacy, medical literacy and disconnect between available resources and patients' knowledge. Overall, providers believed it's critical to establish partnerships and transparent relations with patients, to optimize equitable access to LT **Conclusion:** Mitigating LT barriers requires patient empowerment and effective language and system navigation. Providers identified critical gaps in care that require innovative and patient's involve solutions. Next phase of this project will collect patients' input, allowing them to share their voices, needs and lived experiences



Specialty	Number	Location
Hepatologist	5	RST-FL-ARZ
Surgeon	5	RST-FL-ARZ
Social worker	4	RST-ARZ
RN coordinator	4	FL-ARZ
Psychiatry	2	FL-ARZ
Patient Navigator	2	ARZ
Addiction counselor	1	ARZ

Disclosures: Zamzam Ismail Artan Ali: Nothing to Disclose, Mohamed Addani: Nothing to Disclose, David Chascsa: Nothing to Disclose, Denise Harnois: Nothing to Disclose, Blanca Lizaola-Mayo: Nothing to Disclose, Kasey Boehmer: Nothing to Disclose, Lewis Roberts: Nothing to Disclose.

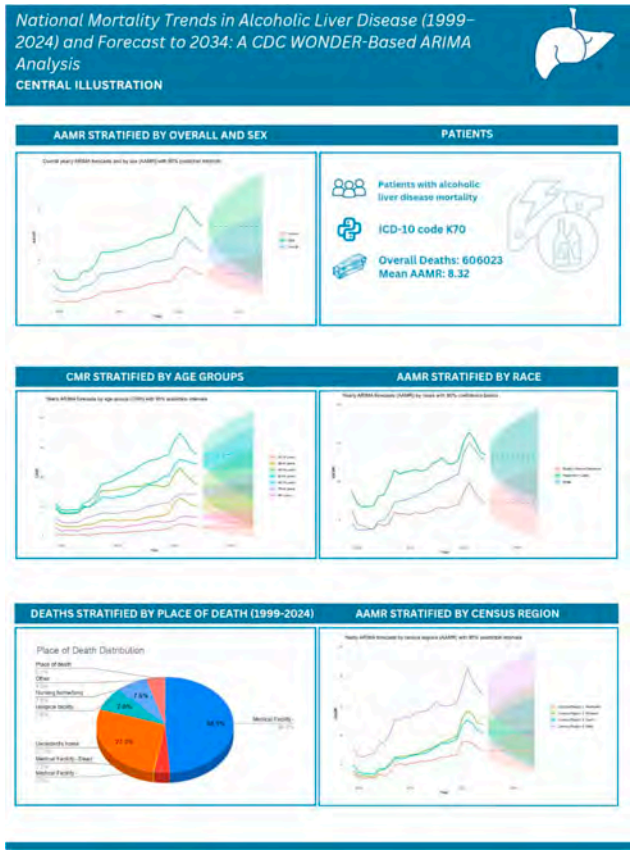
2102 | NATIONAL MORTALITY TRENDS IN ALCOHOLIC LIVER DISEASE (1999–2024) AND FORECAST TO 2034: A CDC WONDER-BASED ARIMA ANALYSIS

Simran Joshi[1] Muhammad Umar[2] Faizan Faisal[2] Hannan Sharif[2] Hadia Arshad[2] Humna sohail[2] Ali Shan Hafeez[3] Hamza Sajid[4] Cheng-Hung Tai[1] Mohammad Aatiq Islam[1], [1]Yale New Haven Health, [2]Akhtar Saeed Medical and Dental College Lahore, Pakistan, [3]CMH Multan Institute of Medical Sciences, [4]Allama Iqbal Medical College, Lahore, Pakistan

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Background: Alcoholic liver disease (ALD) is a leading driver of morbidity and mortality in the United States accounting for roughly one quarter of cirrhosis deaths. ALD is also the principal indication for liver transplantation reflecting a growing clinical and an economic burden. In this study, we aim to evaluate and predict alcoholic liver disease mortality trends among US individuals aged ≥15 from 1999-2034. **Methods:** Mortality data was extracted from the CDC WONDER database for individuals aged ≥15 years with alcoholic liver disease (ICD: K70). We assessed age-adjusted mortality rates (AAMRs) per 100,000 population as stratified by sex, age, race/ethnicity, U.S. Census regions, and 2013 urbanization categories. Annual Percent Change (APC) with 95% confidence intervals (CI) was estimated using Joinpoint regression; $p < 0.05$ was considered statistically significant. Future AAMRs through 2034 were forecasted using Autoregressive Integrated Moving Average (ARIMA) models with model selection based on corrected Akaike Information Criterion (AICc). **Results:** From 1999 to 2024, 606,023 deaths occurred among U.S individuals aged ≥15 years. The overall AAMR rose from 5.11 to 11.77. The trend increased non-linearly through 2021, then showed a modest decline from 2021 to 2024 (APC -6.48%, $p < 0.001$). AAMRs were consistently higher in men (13.29) than in women (5.04). Racial and ethnic disparities were evident with, Hispanic or Latinos bearing the most burden (11.20), followed by non-Hispanic Whites (8.47), non-Hispanic Others (6.58), and non-Hispanic Blacks or African Americans (6.12). The burden was the greatest in the Western region (13.85) and in non-metropolitan areas compared to metropolitan areas (8.43 vs 7.39). ARIMA forecasting indicates that mortality will continue to remain elevated through 2034. The overall AAMR is projected to be 11.75 in 2034, with a sustained sex-specific gap of 16.46 in men and 7.41 in women. By age, the highest projected rates are in adults aged 65-74 years (30.21) and 55-64 years (27.63), whereas adults aged 25-34 years remain lowest (2.94). Among racial/ethnic groups, Hispanic or Latino adults remain highest in 2034 (13.45), followed by White adults (12.73) and Black or African American adults (7.25). The West continues to show the highest projected regional rate (16.91), emphasising ongoing and widening inequities. **Conclusion:** Despite a modest decline in mortality from 2021 onwards, the overall burden remains markedly elevated with persistent disparities in alcoholic liver disease mortality projected for all stratifications through 2034. These projections provide insight into the growing burden of alcoholic liver disease as a contributor of mortality while highlighting inequities across various groups. These findings can guide targeted prevention strategies, early diagnosis and treatment efforts for this preventable cause of liver failure.



Disclosures: Simran Joshi: Nothing to Disclose, Muhammad Umar: Nothing to Disclose, Faizan Faisal: Nothing to Disclose, Hannan Sharif: Nothing to Disclose, Hadia Arshad: Nothing to Disclose, Humna sohail: Nothing to Disclose, Ali Shan Hafeez: Nothing to Disclose, Hamza Sajid: Nothing to Disclose, Cheng-Hung Tai: Nothing to Disclose, Mohammad Aatiq Islam: Nothing to Disclose.

2103 | RAPID INCREASES IN POPULATION-BASED ACCESS TO LIVER TRANSPLANT FOR ALCOHOL-ASSOCIATED HEPATITIS COMPARED TO OTHER STEATOTIC LIVER DISEASES

Sharmitha Yerneni[1] Russell Rosenblatt[2] Eytan Palte[1] Giuseppe Cullaro[1] Elizabeth Verna[3] Gene Im[1], [1]NYP - Columbia University Irving Medical Center, [2]Weill Cornell Medicine, [3]NYP - Columbia University Medical Center

Background: Population-based measures of liver transplant (LT) access that incorporate disease-attributable mortality can help identify disparities in care across disease etiologies and geographic regions. We used this framework to evaluate temporal and regional

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trends in population-based LT access for steatotic liver diseases (SLD), including metabolic dysfunction-associated liver disease (MASLD), alcohol-associated cirrhosis (AC), and alcohol-associated hepatitis (AH). **Methods:** We conducted a retrospective study of the UNOS and CDC WONDER databases from 2011 to 2024. Adults waitlisted for LT with MASLD, AC, or AH, along with deaths attributed to these conditions, were included. The primary outcome was the listing-to-death ratio (LDR), calculated as the ratio of LT waitlist registrations to disease-attributable deaths. LDR provides a population-based measure of LT access. Secondary outcomes included transplant-to-death ratio (TDR). Ratios were calculated nationally and stratified by state to assess temporal and geographic variations in LT access. **Results:** Over the 13-year study period, MASLD consistently had the highest LDR, remaining stable between 2011 and 2019 with LDR 0.36-0.42 before declining after 2020 to 0.20 by 2024 (Figure 1a). In contrast, LDR for AC increased by 73% from 0.11 in 2011 to 0.19 in 2024. AH demonstrated the most dramatic increase in LDR over the study period. AH waitlist registrations were initially very low, below 0.05 through 2016, but increased substantially after 2017. The LDR for AH surpassed AC (0.19 vs. 0.15) by 2021 and MASLD (0.62 vs. 0.30) by 2023. The most notable increase occurred between 2022 to 2024, during which LDR for AH rose from 0.25 to nearly 0.70, a 180% increase that temporally aligned with the new UNOS AH diagnosis codes. Trends in TDR were similar. In 2024, AH waitlist registrations were predominantly concentrated in the Southern and Northeastern United States (Figure 1b). Texas accounted for the largest proportion of listings (153; 16.5%), followed by New York (85; 9.2%), Florida (68; 7.3%), and Pennsylvania (66; 7.1%). **Conclusion:** Among patients with SLD, MASLD had the highest access to LT relative to disease-attributable mortality until 2023, when it was surpassed by AH. While new UNOS diagnosis codes for AH can partially explain this rapid rise in LDR, our findings also support the growing evidence that LT for AH may be underreported as AC, the MELD advantage in AH, and increasing adoption of LT for AH particularly in Texas and the Northeast.

Figure 1a.

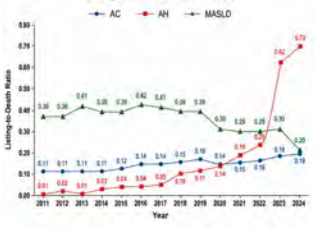


Figure 1b.



Disclosures: Sharmitha Yerneni: Nothing to Disclose, Russell Rosenblatt: Gilead: Grant/Research Support, Eytan Palte: Nothing to Disclose, Giuseppe Cullaro: Ocelot Bio: Consultant, Retro Sciences: Consultant, Ipsen: Consultant, Elizabeth Verna: Nothing to Disclose, Gene Im: KorroBio: Consultant, Echosens: Device support for research, Novo Nordisk: Advisor, Alimentiv: Consultant, GSK: Consultant, Altimmune: Consultant, Bayer: Consultant.

2104 | THE LIVER CANCER EQUITY PROJECT: CHARACTERIZING ADVERSE SOCIAL DETERMINANTS OF HEALTH IN A PROSPECTIVE COHORT OF PATIENTS WITH HEPATOCELLULAR CARCINOMA

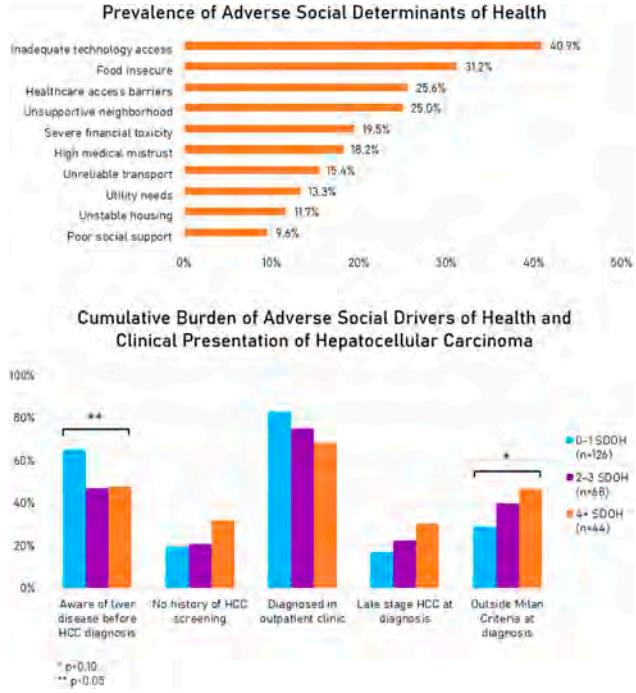
Alison Ly[1] Jennifer Tsui[2] Myles Cockburn[2] Norah Terrault[3] Kali Zhou[3], [1]Keck School of Medicine at USC, Los Angeles General Medical Center, [2]Keck School of Medicine at USC, USC Norris Comprehensive Cancer Center, [3]Keck School of Medicine of USC

Background: Social determinants of health (SDOH) are key contributors to differential screening rates and cancer stage for individuals with hepatocellular carcinoma (HCC), though reported associations usually employ macro-level proxies such as area-level indices, race/ethnicity, and insurance. To address this gap, we developed the Liver Cancer Equity Project, a unique prospective cohort of HCC patients that links clinical history with a robust characterization of patient-level social needs through a multi-lingual survey. **Methods:** Adults with a diagnosis of HCC were surveyed from Hepatology and Oncology clinics at an academic transplant center and safety net hospital between 6/2024-3/2026. The 63-item survey of demographics, social needs, and liver disease knowledge/history was adapted from multiple validated questionnaires and offered in six languages. We examined ten adverse SDOH: unstable housing, utility needs, food insecurity, unreliable transportation, low neighborhood/social support, inadequate technology access, severe financial toxicity, high medical mistrust, and healthcare access barriers. Patients were grouped by total number of adverse SDOH: 0-1, 2-3, and >4. Clinical outcomes of liver disease awareness, HCC screening, and stage at diagnosis were compared by SDOH category. **Results:** The survey response rate was 82.6%, with 238 patients included (49% non-English surveys; 34% safety-net). The cohort's median age was 66 years (IQR 60-72), 71.8% were male, and 72.9% Hispanic/15.7% Asian/8.3% White/1.7% Black, with 69.0% reporting high school or less education. 38.2% had metabolic liver disease, 33.6% alcohol, and 22.7% viral hepatitis; 72.3% were ECOG

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0, 67.5% CPT-A and 79.1% BCLC 0-A. Individual prevalence of adverse SDOH ranged from 9.6-40.9% (see Figure), with inadequate technology access defined by lack of a computer or stable internet and food insecurity the most frequently reported and unstable housing and insufficient social support least reported (see Figure). The median number of adverse SDOH per participant was 1 (IQR 1-3) with 52.9%, 28.6%, and 18.5% having 0-1, 2-3, and >4 SDOH factors, respectively. Compared to 0-1, patients with ≥2 SDOH were significantly less likely to be aware of their liver disease prior to HCC diagnosis ($p = 0.03$; see Figure). Higher SDOH groups were also more likely to report no HCC screening, be diagnosed in an acute care setting, have late-stage HCC, and fall outside of Milan Criteria, though these differences were not statistically significant. **Conclusion:** In the Liver Cancer Equity Project prospective cohort, 77% reported at least one adverse SDOH, with nearly one in five reporting greater than four. Higher adverse SDOH burden was linked to lower liver disease awareness, an essential first step to early detection of HCC, highlighting the need for targeted interventions to increase cirrhosis detection in socially at-risk populations.



Disclosures: Alison Ly: Nothing to Disclose, Jennifer Tsui: Nothing to Disclose, Myles Cockburn: Nothing to Disclose, Norah Terrault: Elseiver: Royalties or patent beneficiary, GSK: Grant/Research Support, Elseiver: Royalties or patent beneficiary, Elseiver: Royalties or patent beneficiary, Eiger Pharmaceuticals: Grant/Research Support, GSK: Grant/Research Support, GSK: Grant/Research Support, Helio Health: Grant/Research Support, Eiger Pharmaceuticals: Grant/Research Support, Eiger Pharmaceuticals: Grant/Research Support, Durect Corp: Grant/Research Support, Helio Health: Grant/Research Support, ImmunoCore: Grant/Research Support, Helio Health: Grant/Research Support, Durect Corp: Grant/Research Support, HBV Foundation: Board member, Durect Corp: Grant/Research Support, AASLD: Executive role, ImmunoCore: Grant/Research Support, ImmunoCore: Grant/Research Support, Genentech-Roche: Grant/Research Support, HBV Foundation: Board member, HBV Foundation: Board member, Hepatitis B Foundation: Executive role, AASLD: Executive role, AASLD: Executive role, Genentech-Roche: Grant/Research Support, Genentech-Roche: Grant/Research Support, Hepatitis B Foundation: Executive role, Hepatitis B Foundation: Executive role, Elseiver: Royalties or patent beneficiary, GSK: Grant/Research Support, Elseiver: Royalties or patent beneficiary, Elseiver: Royalties or patent beneficiary, Eiger Pharmaceuticals: Grant/Research Support, GSK: Grant/Research Support, GSK: Grant/Research Support, Helio Health: Grant/Research Support, Eiger Pharmaceuticals: Grant/Research Support, Eiger Pharmaceuticals: Grant/Research Support, Durect Corp: Grant/Research Support, Helio Health: Grant/Research Support, ImmunoCore: Grant/Research Support, Helio Health: Grant/Research Support, Durect Corp: Grant/Research Support, HBV Foundation: Board member, Durect Corp: Grant/Research Support, AASLD: Executive role, ImmunoCore: Grant/Research Support, ImmunoCore: Grant/Research Support, Genentech-Roche: Grant/Research Support, HBV Foundation: Board member, HBV Foundation: Board member, Hepatitis B Foundation: Executive role, AASLD: Executive role, AASLD: Executive role, Genentech-Roche: Grant/Research Support, Genentech-Roche: Grant/Research Support, Hepatitis B Foundation: Executive role, Hepatitis B Foundation: Executive role, Elseiver: Royalties or patent beneficiary, GSK: Grant/Research Support, Elseiver: Royalties or patent beneficiary, Elseiver: Royalties or patent beneficiary, Eiger Pharmaceuticals: Grant/Research Support, GSK: Grant/Research Support, GSK: Grant/Research Support, Helio Health: Grant/Research Support, Eiger Pharmaceuticals: Grant/Research Support, Eiger Pharmaceuticals: Grant/Research Support, Durect Corp: Grant/Research Support, Helio Health: Grant/Research Support, ImmunoCore: Grant/Research Support, Helio Health: Grant/Research Support, Durect Corp: Grant/Research Support, HBV Foundation: Board member, Durect Corp: Grant/Research Support, AASLD: Executive role, ImmunoCore: Grant/Research Support, ImmunoCore: Grant/Research Support, Genentech-Roche: Grant/Research Support, HBV Foundation: Board member, HBV Foundation: Board member, Hepatitis B Foundation: Executive role, AASLD: Executive role, AASLD: Executive role, Genentech-Roche: Grant/Research Support,

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Genentech-Roche: Grant/Research Support, Hepatitis B Foundation: Executive role, Hepatitis B Foundation: Executive role, Kali Zhou: Gilead Sciences Inc: Grant/Research Support, Merck: Grant/Research Support.

2105 | SOCIODEMOGRAPHIC DISPARITIES IN DIETARY QUALITY AMONG PATIENTS WITH CIRRHOSIS: A MULTICENTER SURVEY STUDY

Nicole Rich[1] Mohammed Al-Hasan[2] Yan Liu[3] Jennifer Kramer[3] Juana Campos[3] Lisa Quirk[1] Diya Kar[1] Janha Anyanwu[3] Amanda Gibbons[3] Valeria Londono[3] Gabriela Morales Pielago[3] Aaron Nguyen[3] Dalal Youssef[3] Fasiha Kanwal[4] Amit Singal[1], [1]UT Southwestern Medical Center, [2]University of Texas Southwestern Medical Center, [3]Baylor College of Medicine, [4]Michael E. DeBakey VA Medical Center

Background: Nutritional health is an important modifiable factor in cirrhosis management, yet real-world dietary behaviors among patients with cirrhosis remain poorly characterized. We evaluated diet quality across sociodemographic and clinical subgroups in a multicenter cohort of patients with cirrhosis. **Methods:** We conducted a prospective survey study of adults with cirrhosis across four U.S. health systems. Diet behaviors were assessed using the 13-item Latino Dietary Behaviors Questionnaire (LDBQ), a validated dietary behavior instrument with scores ranging from 13-47, where higher scores indicate a healthier diet. Total scores and individual dietary behaviors were compared across sex, household income, race/ethnicity, liver disease etiology and cirrhosis severity. **Results:** Among 1,319 patients with cirrhosis (mean age 60.0 ± 10.6 years; 58.9% men), 42.1% were non-Hispanic White, 21.5% Black, 34.0% Hispanic. Most patients reported annual household income < $50,000 (69.0%), and 25.5% reported limited health literacy. The most common liver disease etiologies were HCV (29.5%), ALD (27.2%) and MASLD (27.1%). Mean LDBQ score was 23.4 ± 6.0, consistent with suboptimal diet behaviors. Patients with annual household income < $50,000 reported poorer diet quality, including more frequent consumption of fast food, fried food, and sugar-sweetened beverages (all $p < 0.05$). Women demonstrated healthier diet behaviors than men across several domains, including lower intake of soft drinks and more frequent portion control (both $p < 0.001$). Dietary quality also varied across racial/ethnic groups and liver disease etiologies. Less healthy diet behaviors were more commonly observed among patients with ALD and MASLD compared to those with HCV, while differences by Child Pugh score were less pronounced. **Conclusion:** Substantial sociodemographic disparities in diet quality exist among patients with cirrhosis. Less healthy dietary behaviors were more commonly observed among patients with lower household income, men, and those with MASLD or ALD, highlighting the importance of incorporating social and behavioral determinants into nutrition-focused interventions for chronic liver disease.

Disclosures: Nicole Rich: AstraZeneca: Advisor, AstraZeneca: Advisor, Genentech: Consulting, Genentech: Consulting, Exelixis: Advisor, Exelixis: Advisor, Eisai: Advisor, Eisai: Advisor, Madrigal: Advisor, Madrigal: Advisor, AstraZeneca: Advisor, AstraZeneca: Advisor, Genentech: Consulting, Genentech: Consulting, Exelixis: Advisor, Exelixis: Advisor, Eisai: Advisor, Eisai: Advisor, Madrigal: Advisor, Madrigal: Advisor, Mohammed Al-Hasan: Nothing to Disclose, Yan Liu: Nothing to Disclose, Jennifer Kramer: Nothing to Disclose, Juana Campos: Nothing to Disclose, Lisa Quirk: Nothing to Disclose, Diya Kar: Nothing to Disclose, Janha Anyanwu: Nothing to Disclose, Amanda Gibbons: Nothing to Disclose, Valeria Londono: Nothing to Disclose, Gabriela Morales Pielago: Nothing to Disclose, Aaron Nguyen: Nothing to Disclose, Dalal Youssef: Nothing to Disclose, Fasiha Kanwal: Nothing to Disclose, Amit Singal: Genentech: Consultant, AstraZeneca: Consultant, Bayer: Consultant, Eisai: Consultant, Exelixis: Consultant, Merck: Consultant, Elevar: Consultant, FujiFilm Medical Sciences: Consultant, Exact Sciences: Consultant, Glycotest: Consultant, Boston Scientific: Consultant, Sirtex: Consultant, HelioGenomics: Consultant, ImCare: Consultant, DELFI: Consultant, Curve Biosciences: Consultant, Catalym: Consultant, Verve: Consultant.

2106 | EVALUATING LARGE LANGUAGE MODELS FOR REPRODUCING DIRECTIONALITY OF EPIDEMIOLOGIC ASSOCIATIONS IN HEPATITIS C RISK AMONG PEOPLE WHO INJECT DRUGS

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Background: People who inject drugs (PWID) account for most new Hepatitis C virus (HCV) infections in the United States. Large language models (LLMs) are increasingly being explored for synthetic data generation and epidemiologic modeling, but it remains unclear whether LLM-generated outputs preserve epidemiologic relationships relevant to HCV transmission. We evaluated whether

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contemporary LLMs reproduce literature-supported directional associations between housing status and HCV-related risk behaviors among PWID. **Methods:** We conducted a controlled simulation study using three LLMs (Claude Sonnet 4.5, Amazon Nova 2 Lite, and OpenAI GPT-OSS-120B). PWID profiles informed by longitudinal Chicago cohort and surveillance data were evaluated under two hypothetical housing conditions (homeless versus stable; N = 224 per condition per model). Prompts were standardized across conditions. Selected LLMs generated structured outputs describing injection and alternative drug use practices, syringe sharing, withdrawal frequency, treatment engagement, social network characteristics, and HCV outcomes in a fentanyl-era context. Paired effect sizes, bootstrap confidence intervals, subgroup analyses, and pairwise correlations were used to assess directional consistency and cross-model agreement. **Results:** Across selected LLMs, homelessness was consistently associated with greater public/shelter-based injecting behaviors (Cohen's d: 1.12–3.94) and higher likelihood of positive HCV status (d: 0.13–0.42), consistent with prior epidemiologic evidence. However, several expected associations varied in direction across LLMs, including injection frequency (d: −0.24–0.02), withdrawal frequency (d: −0.15–0.29), and proportion of injection partners with HCV (d: −0.13–0.20). Baseline profile characteristics such as injection frequency and syringe-sharing behaviors also showed minimal variation relative to corresponding LLM-generated outputs. **Conclusion:** Current LLMs partially reproduce established epidemiologic relationships relevant to HCV transmission, but inconsistencies in association direction, effect sizes, subgroup differences, and correlation structures suggest that behavioral outputs may reflect model-specific representations rather than stable epidemiologic patterns. This reinforces the importance of empirical validation and cross-model evaluation before applying LLM-generated behavioral outputs in transmission or policy modeling.

Cohen's d (homeless minus stable housing) with 95% confidence intervals across models (N = 224 per condition per model)

Variable	Expected Direction	GPT-OSS-120B	Claude Sonnet 4.5	Nova 2 Lite
Public or Shelter Use	↑	3.94 (3.52, 4.47)	3.64 (3.13, 4.30)	1.12 (1.00, 1.26)
Positive HCV status	↑	0.23 (0.15, 0.29)	0.42 (0.31, 0.52)	0.13 (-0.07, 0.20)
Partner Count	↑	0.15 (0.02, 0.28)	0.19 (0.08, 0.29)	-0.06 (-0.18, 0.07)
Partners with HCV	↑	-0.13 (-0.19, -0.07)	0.20 (0.08, 0.32)	
Withdrawals	↑	-0.15 (-0.30, -0.02)	0.30 (0.17, 0.42)	-0.08 (-0.17, 0.06)
Injection Frequency	↑	-0.24 (-0.36, -0.13)	-0.07 (-0.21, 0.05)	0.02 (-0.12, 0.12)
Receptive Sharing	↑	0.13 (0.02, 0.22)	0.08 (-0.06, 0.18)	0.02 (-0.03, 0.04)
Distributive Sharing	↔	-0.05 (-0.14, 0.10)	-0.02 (-0.20, 0.12)	-0.07 (-0.62, 0.39)
Treatment	↓	-0.31 (-0.41, -0.20)	-0.74 (-0.85, -0.64)	
Alternative Routes	↓	-0.26 (-0.41, -0.11)	-0.53 (-0.62, -0.45)	

↑, ↓, and ↔ indicate expected positive, negative, or no clear direction of association between homelessness and each variable, based on prior literature. "-" indicates no variation in model outputs across conditions.

Disclosures: Sophia Mao: Nothing to Disclose, Alexander Gutfraind: Amazon Inc.: Employee, Keshav Gandhi: Nothing to Disclose.

2107 | WHEN LOW SOCIAL STATUS MEETS LIVER DISEASE, OUTCOMES ARE WORSE: INTERIM ANALYSIS FROM THE ITALIAN MASLD COHORT

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Background: Social Determinants of Health (SDoH) are non-clinical factors that drive unequal exposure to health risks and inequalities in health outcomes. This interim analysis evaluates their role in liver disease severity in Italian patients in care recently enrolled in the ITA-MASLD (Italian Metabolic Dysfunction-Associated Steatotic Liver Disease) cohort. Currently over 30 clinical centers have put clinical and SDoH data of the consecutively enrolled patients. This interim analysis focused on the evaluation of the association of SDoH (when available) with the fibrosis progression (Metavir classification) as a proxy of liver cancer risk. **Methods:** Data on SDoH (available for 169 patients) were assessed using standardised questionnaires across domains including education, social context, environment, and financial stability. A composite indicator of economic insecurity was derived from individual items. These metrics were integrated with anthropometric data to explore associations with clinical risk factors. **Results:** As shown in Table 1, better socioeconomic conditions were associated with milder liver disease. A significantly higher prevalence of advanced fibrosis was observed among economically insecure patients (55.6% vs. 35.4%, p = 0.020) and those with lower educational attainment (57.8% vs. 34.0%, p = 0.004).Multivariable analysis included adjustments for BMI overweight/obesity, because a significant relationship between overweight/obesity (versus underweight/ normal) and economic insecurity (p = 0.034) was observed whereas other factors correlated with MASLD (diabetes, hypertension or dyslipidemia) were not included as no associations were found with SDoH indicators. According to the multivariable analysis, economic insecurity (OR = 2.48, 95% CI 1.12 to 5.70) and age (OR = 1.07/year, 95% CI 1.02 to 1.12) were associated with F3-F4 fibrosis stage. Conversely, occupational status (OR = 2.11, 95% CI 0.79 to 5.95), low education (OR = 2.13, 95% CI 0.99 to 4.75), overweight/obesity (OR = 1.01, 95% CI 0.22 to 4.04) and sex (OR = 0.50, 95% CI 0.21 to 1.15) were not significantly associated with F3-F4 fibrosis stage (Table 1). **Conclusion:** Social disadvantage is a key determinant of liver disease severity across etiologies. These findings support the integration of SDoH assessment into clinical risk

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stratification, allowing social vulnerability to be translated into actionable information. Collecting SDoH data may help design more targeted care pathways and reduce inequalities in advanced liver disease and liver cancer risk. Tailored public health interventions and integrated clinical care pathways will prove essential to mitigate health disparities and improve long-term prognostic outcomes.

Table. Factors associated with severe fibrosis in the MASLD cohort: baseline characteristics and multivariable analyses

Variable	No severe fibrosis N = 53[1]	Severe fibrosis N = 116[1]	p-value[2]
Epidemiological features			
Age	61 (51, 67)	64 (56, 71)	**0.017**
Sex			0.061
Female	14 (26.4%)	48 (41.4%)	
Male	39 (73.6%)	68 (58.6%)	
BMI			>0.999
Underweight-normal	4 (8.0%)	11 (9.8%)	
Overweight-obese	46 (92.0%)	101 (90.2%)	
Social Determinants of Health			
Economic insecurity			**0.020**
Secure	31 (64.6%)	48 (44.4%)	
Insecure	17 (35.4%)	60 (55.6%)	
Education level			**0.004**
High school diploma	35 (66.0%)	49 (42.2%)	
No high school diploma	18 (34.0%)	67 (57.8%)	
Occupational status			0.301
Not employed	24 (46.2%)	63 (54.8%)	
Employed	28 (53.8%)	52 (45.2%)	
Multivariable Regression Model	**OR**	**95% CI**	**p-value**
Age (yearly increase)	1.07	1.02, 1.12	**0.005**
Sex (ref. female)	0.50	0.21, 1.15	0.11
BMI (ref. underweight-normal)	1.01	0.22, 4.04	>0.9
Economic insecurity (ref. secure)	2.48	1.12, 5.70	**0.028**
Education level (ref. high school diploma)	2.13	0.99, 4.75	0.057
Occupational status (ref. not employed)	2.11	0.79, 5.95	0.14

[1]Median (Q1, Q3); n (%)

[2]Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

Abbreviations: CI = Confidence Interval, OR = Odds Ratio.

Significant p-values (<0.05) are highlighted in bold.

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2108 | ETHNICITY MODIFIES THE ASSOCIATION OF DIET AND INSURANCE WITH LIVER STIFFNESS IN A DIVERSE URBAN MASLD POPULATION

Maryfe Coronel Novoa[1] Adeeba Tak[1] Julia Napoli[1] Yulu He[1] Kamileh Rivera[1] Mark Miller[1] Victor Llanes[1] Asher Leviton[1] Megan Miller[1] Frances Lee[1] Ryan Walker[1] Dania Valvi[1] Emanuela Taioli[1] Scott Friedman[1] Meena Bansal[2] Xiaotao Zhang[1], [1]Icahn School of Medicine at Mount Sinai, [2]Icahn School of Medicine at Mount Sinai (ISMMS)

Background: MASLD disproportionately affects Hispanic individuals, who have higher US prevalence, advanced fibrosis, and liver-related mortality than non-Hispanic counterparts. Genetic susceptibility may contribute, but the role of social determinants of health (SDOH) including neighborhood disadvantage, diet quality, and healthcare access in ethnicity-specific fibrosis outcomes remains understudied. **Methods:** We analyzed 125 patients from the Mount Sinai MASLD/MASH Registry, including 54 Hispanic and 71 non-Hispanic patients. Liver stiffness measurement (LSM) was assessed by FibroScan. Significant fibrosis, advanced fibrosis, and cirrhosis were defined as LSM $\geq$8, $\geq$12, and $\geq$14 kPa, respectively. SDOH measures included 2023 Area Deprivation Index (ADI), diet quality by NCI Dietary Screener Questionnaire composite z-score, insurance type, and language preference. Multivariable linear regression tested ethnicity interactions for SDOH predictors of log-LSM, adjusting for age, sex, BMI, and diabetes. Exploratory Hispanic subgroup analyses compared Caribbean, Mexican/Central American, and South American patients. **Results:** Hispanic and non-Hispanic patients were similar in age, sex, diabetes, and diet quality. Hispanic patients had significantly higher obesity prevalence (61% vs. 41%, p = 0.039), higher ADI (13.5 vs. 9.0, p = 0.054), more Medicaid coverage (30% vs. 13%, p = 0.033), and greater fibrosis burden, including significant fibrosis (30% vs. 20%), advanced fibrosis (20% vs. 9.9%), and cirrhosis (17% vs. 4.2%). ADI was not associated with LSM. A significant diet-by-ethnicity interaction was observed (p = 0.003): each 1-SD higher diet-quality score was associated with 19% lower LSM in Hispanic patients (95% CI, 5.9%–30.3%; p = 0.008), but not in non-Hispanic patients. Medicare coverage, versus commercial insurance, was associated with 99.8% higher LSM in Hispanic patients (95% CI, 26.3%–216.1%; p = 0.004), but not non-Hispanic patients. Language preference was not associated with LSM. Among Hispanic subgroups, diet quality differed by region of origin, with highest scores among Caribbean patients (p = 0.020). **Conclusion:** In this diverse urban MASLD cohort, ethnicity modified the associations of diet quality and insurance type with liver stiffness. Higher diet quality was associated with lower LSM only among Hispanic patients, despite similar diet quality by ethnicity, supporting further study of diet–genetic susceptibility interactions, especially *PNPLA3*. Medicare coverage was associated with higher LSM only among Hispanic patients, suggesting possible cumulative access barriers or residual clinical complexity. These findings support culturally tailored dietary interventions, equitable access strategies, and larger studies with *PNPLA3* genotyping and Hispanic subgroup oversampling.

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2109 | LOST IN TRANSLATION: MACHINE TRANSLATION SIGNIFICANTLY IMPACTS READABILITY OF LLM-GENERATED PATIENT EDUCATION MATERIALS FOR CHRONIC LIVER DISEASE IN ENGLISH AND SPANISH

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Background: Health literacy is a critical social determinant of health, with lower health literacy being associated with poor clinical outcomes and healthcare disparities. Although the Agency for Healthcare Research and Quality (AHRQ) recommends that all patient educational materials (PEMs) be written at a 6th -grade reading level or below, a large percentage of PEMs in English and Spanish do not reach this standard, including those written for patients with chronic liver conditions, contributing to a health literacy gap. Tools like large-language models (LLMs) with certain prompt engineering techniques have shown promise in addressing this in English, but the extent to which this benchmark can be achieved in other languages remains undertested. Furthermore, for providers in resource-limited settings, machine translation is often the most widely available tool in creating PEMs, but the effects of translation on readability is also understudied. This study seeks to address this by testing various prompt engineering techniques in English and Spanish, and assessing the readability of the outputs, pre- and post-translation. **Methods:** Three prompt engineering techniques (Zero-Shot, Constrained, Contextualized) were asked to ChatGPT 5.5 Instant, Gemini 3.5 Flash, and Claude Sonnet 4.6 in English and in Spanish to explain hepatitis, MASLD, MASH, cirrhosis, and hepatocellular carcinoma. Google Translate was then utilized to translate the outputs from one language to the other. The readability of the outputs and translations was assessed with the Python texstat library, which yielded language-appropriate metrics – SMOG for English, and SOL for Spanish, which both report a grade level metric. Readability was compared by prompt, and data underwent a One-Way ANOVA followed by a Post-Hoc analysis. The comparison between Original and Translated readability was conducted with a Student's t-test, with $p < 0.05$ deemed significant. **Results:** No prompt in English or Spanish averaged at or below a 6th grade reading level. The Contextualized prompt came close in Spanish (6.45 ± 0.62). The effects of machine translation, however, varied. The Spanish-to-English translation was significantly less complex than the Native English outputs (-0.5 to -1.36 grades, $p < 0.05$) while the English-to-Spanish translation was significantly more complex than the Native Spanish outputs (+1.53 to +2.22 grades, $p < 0.01$). **Conclusion:** Modern LLM and prompt engineering techniques continue to struggle to meet AHRQ recommendation regarding PEMs. In addition, machine translation can significantly worsen the readability of LLM-generated patient materials for liver conditions, particularly when going from English-to-Spanish. For physicians in resource-limited settings using LLMs, we recommend prompting in the native or target language, in order to continue to strive to reach patients where they are in terms of health literacy.

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2110 | SOCIAL DETERMINANTS OF HEALTH PREDICT FRAILTY AMONG LIVER TRANSPLANT CANDIDATES AT A SAFETY-NET MEDICAL CENTER

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Background: Frailty is a strong predictor of poor outcomes among patients awaiting liver transplantation (LT) and is associated with increased post-LT mortality and greater post-LT healthcare utilization. However, the association between neighborhood-level social determinants of health (SDoH) and pre-LT frailty remains poorly characterized. **Methods:** All adult liver transplant (LT) candidates undergoing LT evaluation (January 2025 – April 2026) at an academic liver transplant center serving as a safety-net provider were included. Pre-LT frailty was assessed in either the ambulatory or inpatient setting using the Liver Frailty Index (LFI) (http://liverfrailtyindex.ucsf.edu), with robust defined as LFI <3.2, prefrail as $3.2–<4.5$, and frail as ≥ 4.5. Neighborhood social determinants of health (SDoH) were measured by the Social Vulnerability Index (SVI), a CDC tool that assesses community resilience based on 16 US Census variables grouped into four themes: socioeconomic status (SES), household composition, minority status, and housing & transport; higher scores indicate greater social vulnerability (https: //www.atsdr.cdc.gov/placeandhealth/svi/index.html). Logistic regression was used to examine the association between neighborhood SDoH and pre-LT frailty (prefrail/frail vs. robust), adjusting for age, sex, and insurance type as a surrogate for individual-level socioeconomic status. In the logistic regressio, each SDoH indicator was dichotomized at the 25th percentile, with the bottom quartile (least vulnerable) serving as the reference group. **Results:** Among 106 LT candidates, 18 (17.0%) were robust, 42 (39.6%) were prefrail, and 46 (43.4%) were frail (Table 1). Fifty-one (48.1%) were female, with a median age of 57 years (IQR 46–66). After adjusting for age, sex, and insurance type, higher SVI minority status (Q2–Q4 vs. Q1) was significantly associated with increased odds of being prefrail or frail (OR 3.39, 95% CI 1.13–10.21, $p = 0.030$), and a borderline association was observed for SVI housing & transport (OR 2.72, 95% CI 0.86–8.54, $p = 0.087$) (Table 2). SVI overall, SVI SES, and SVI household composition also showed positive associations with the odds of being prefrail or frail, though these did not reach statistical significance. **Conclusion:** The prevalence of frailty in this safety-net medical center cohort undergoing evaluation for LT was 43.4%, nearly double the 21% reported in the Multi-Center Functional Assessment in Liver Transplantation (FrAILT) Study. Neighborhood-level SDoH, particularly minority status vulnerability, was associated with pre-LT frailty. These findings lay the groundwork for future studies investigating whether targeted prehabilitation interventions among LT candidates residing in high social vulnerability neighborhoods can improve post-LT outcomes and reduce healthcare resource utilization.

Table 1 - Baseline Characteristics of Liver Transplant Candidates (n = 106)

Group[1]	Robust (n=18)	Prefrail (n=42)	Frail (n=46)	Overall (n=106)
DEMOGRAPHICS				
Female, n (%)	7 (38.9%)	22 (52.4%)	22 (47.8%)	51 (48.1%)
Age, median [IQR]	54 [46, 62]	58 [46, 67]	58 [47, 66]	57 [46, 66]
SOCIAL VULNERABILITY INDEX (SVI)[2]				
SVI Overall, median [IQR]	0.398 [0.135, 0.622]	0.446 [0.268, 0.7]	0.479 [0.294, 0.772]	0.446 [0.235, 0.73]
SVI – SES, median [IQR]	0.279 [0.182, 0.5]	0.399 [0.234, 0.764]	0.491 [0.263, 0.724]	0.419 [0.233, 0.733]
SVI – Household, median [IQR]	0.425 [0.173, 0.771]	0.506 [0.266, 0.72]	0.51 [0.27, 0.757]	0.501 [0.216, 0.726]
SVI – Minority, median [IQR]	0.29 [0.186, 0.693]	0.43 [0.289, 0.61]	0.44 [0.29, 0.651]	0.427 [0.276, 0.648]
SVI – Housing & Transport, median [IQR]	0.407 [0.21, 0.713]	0.509 [0.265, 0.72]	0.557 [0.284, 0.788]	0.514 [0.255, 0.754]

Continuous variables: median [IQR]. Categorical variables: n (%).
[1] Liver Frailty Index (LFI): a validated measure of physical frailty in patients with chronic liver disease, calculated from grip strength, balance, and chair stand performance. Available at: [redacted] LFI was used to categorize patients as robust (LFI <3.2), prefrail (LFI 3.2–<4.5), or frail (LFI >=4.5).
[2] Social Vulnerability Index (SVI): a CDC measure of community resilience based on 16 US Census variables grouped into four themes – socioeconomic status, household composition & disability, minority status & language, and housing type & transportation. Scores range from 0 (least vulnerable) to 1 (most vulnerable). Available at: [redacted]

Table 2 - Association between Higher Social Vulnerability and Odds of Being Prefrail/frail (n = 106)

Variable[1]	Adjusted OR (95% CI)[2]	p-value
SVI Overall	2.52 (0.82, 7.71)	0.105
SVI – SES	2.54 (0.81, 7.92)	0.108
SVI – Household	2.33 (0.78, 6.94)	0.130
SVI – Minority	3.39 (1.13, 10.21)	0.030 *
SVI – Housing & Transport	2.72 (0.86, 8.54)	0.087 †

* p<0.05 † p<0.10
[1] Social Vulnerability Index (SVI): a CDC measure of community resilience based on 16 US Census variables grouped into four themes – socioeconomic status, household composition & disability, minority status & language, and housing type & transportation. Scores range from 0 (least vulnerable) to 1 (most vulnerable). Available at: [redacted]
[2] Logistic regression with adjustment for age, sex, and insurance type was used to examine the association between neighborhood SDoH and liver frailty (binary outcome, prefrail/frail vs robust, with robust group as the reference). Liver Frailty Index (LFI) was used to categorize patients as robust (LFI <3.2), prefrail (LFI 3.2-<4.5), or frail (LFI >=4.5). The main exposure variables (SVI) were dichotomized into two groups, with the lowest quartile indicating the least socially vulnerable group and treated as the reference group. Therefore, the adjusted odds ratio (aOR) shows the association between higher social vulnerability and odds of being Prefrail/Frail.

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2111 | HEALTH RELATED SOCIAL NEEDS SCREENING AND COMMUNITY RESOURCE REFERRALS WITHIN GENERAL AND TRANSPLANT HEPATOLOGY CLINICS

Rebecca Kim[1] April Ballantyne[1] Gregory Stoddard[1] Jiawen Guo[1] Bob Wong[1] John Inadomi[1] Molly Conroy[1] Jennifer Price[2] Andrea Wallace[1], [1]University of Utah, [2]University of California San Francisco

Background: Health related social needs (HRSN) contribute to worse outcomes in chronic liver disease

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(CLD). HRSN screening and resource referral programs have led to improved health outcomes among patients with chronic diseases, yet routine HRSN screening remains uncommon in hepatology practice. To address this gap, we aimed to identify HRSN and refer patients to community resources by implementing HRSN screening and resource referrals in hepatology clinic. **Methods:** From 12/2024-03/2026, a 10-item HRSN screener was integrated into hepatology care through electronic health record-based workflows. Screening was completed via MyChart or during visit check-in. Patients requesting assistance were referred to available resources including transportation services, food pantries, utility assistance, etc. Descriptive analyses included mean and frequency. Comparative analyses were performed using Chi-Square and Fisher's exact tests. **Results:** Among 3,480 unique liver clinic patients screened, 54% were female, 74% White, 11% Hispanic (**Table A**). Most (96%) spoke English; commercial insurance was most common (54%). Most (85%) were seen in general hepatology clinic, and 3,141 (90%) had CLD. Overall, 1,348 (39%) patients reported 1 or more need within the 16-month period. Reported needs included limited finances for household items (16%), food insecurity (14%), and as listed in **Table A** .No significant differences in HRSN were found by gender, language, or clinic visit type. However, statistically significant differences by race and insurance provider were identified ($p < 0.02$). Several HRSN were more often reported among American Indian/Alaska Native (AI/AN), Black, Hispanic and Native Hawaiian/Pacific Islander (NH/PI) populations, and among patients with Medicaid. Additionally, those with CLD compared to without, reported a higher prevalence of food insecurity (15% vs 10%, $p = 0.045$), utility insecurity (12% vs 9%, $p = 0.04$), and housing costs (11% vs 6%, $p = 0.01$).Overall, 171 patients (5%) requested a referral to resources, including 142 patients (11%) who reported HRSN. Among them, 54% female, 61% White, 20% Hispanic, and 98% with CLD (**Table B**). A larger proportion of AI/AN, Black, Hispanic, and NH/PI patients were referred to resources than White patients ($p < 0.001$); as well as 12% of Spanish-speaking patients and 13% with Medicaid. The most common HRSN among those requesting resources were food insecurity, limited funds for home items, and utility insecurity (**Table B**). **Conclusion:** HRSN screening and community resource referrals were successfully integrated into hepatology clinics. HRSN are prevalent within our hepatology patient population, particularly among racial minority groups. People interested in resources can be referred to community programs through healthcare-based referrals, though our referral rate was low. The impact of this intervention on CLD outcomes requires ongoing longitudinal follow up.

Tables A) Characteristics for Total Study Population, N=3,480; B) Characteristics of Patients Referred to Resources from Hepatology Clinic, N=171

A) Patient Characteristics, N=3,480	n (%)
Gender	
Female	1887 (54)
Male	1597 (46)
Non-binary	1 (0)
Race	
American Indian/Alaska Native	97 (3)
Asian	151 (4)
Black or African American	53 (2)
Hispanic	395 (11)
Native Hawaiian/Pacific Islander	25 (<1)
White	2577 (74)
Not disclosed	182 (5)
Language	
English	3339 (96)
Spanish	100 (3)
Other	41 (1)
Insurance	
Self-pay or uninsured	97 (3)
Medicaid	373 (11)
Misc Government or Non-Government	58 (2)
Medicare	1071 (31)
Commercial	1881 (54)
Clinic type	
General hepatology	2974 (85)
Transplant hepatology	506 (15)
Chronic liver disease diagnosis	3141 (90)
Health Related Social Needs*	
Transportation needs, n=3383	130 (4)
Medical expenses, n=3327	238 (7)
Medication expenses, n=3359	181 (5)
Food insecurity, n=3305	469 (14)
Limited funds for home items, n=3292	538 (16)
Utility insecurity, n=3294	396 (12)
Housing costs, n=3270	335 (10)
Unstable housing, n=3371	67 (2)
Unemployment, n=3303	344 (10)
Caregiving interference, n=3352	55 (2)

*Prevalence among yes/no responses for that specific question

B) Characteristics of Patients Referred to Resources, N=171	n (%)	p-value‡
Gender		0.940
Female	92 (54)	
Male	79 (46)	
Non-binary	-	
Race		<0.001
American Indian/Alaska Native	16 (9)	
Asian	2 (1)	
Black or African American	7 (4)	
Hispanic	35 (20)	
Native Hawaiian/Pacific Islander	3 (2)	
White	105 (61)	
Not disclosed	3 (2)	
Language		0.004
English	157 (92)	
Spanish	12 (7)	
Other	2 (1)	
Insurance		<0.001
Self-pay or uninsured	6 (4)	
Medicaid	48 (28)	
Misc Government or Non-Government	5 (3)	
Medicare	57 (33)	
Commercial	55 (32)	
Clinic type		0.967
General hepatology	146 (85)	
Transplant hepatology	25 (15)	
Chronic liver disease diagnosis	167 (98)	<0.001
Health Related Social Needs*		
Transportation needs, n=163	34 (21)	<0.001
Medical expenses, n=159	43 (27)	<0.001
Medication expenses, n=157	31 (20)	<0.001
Food insecurity, n=159	81 (51)	<0.001
Limited funds for home items, n=156	84 (53)	<0.001
Utility insecurity, n=158	80 (51)	<0.001
Housing costs, n=151	69 (46)	<0.001
Unstable housing, n=165	25 (15)	<0.001
Unemployment, n=153	53 (35)	<0.001
Caregiving interference, n=160	12 (8)	<0.001

‡Comparison of patients who requested referrals to those who did not

Disclosures: Rebecca Kim: Nothing to Disclose, April Ballantyne: Nothing to Disclose, Gregory Stoddard: Nothing to Disclose, Jia-wen Guo: Nothing to Disclose, Bob Wong: Nothing to Disclose, John Inadomi: JAMA: Associate Editor, Molly Conroy: Nothing to Disclose, Jennifer Price: AbbVie: Grant/Research Support, Gilead: Grant/Research Support, VIR: Grant/Research Support, Cepheid: Grant/Research Support, Aligos: Grant/Research Support, Meridian: Grant/Research Support, Andrea Wallace: Nothing to Disclose.

2112 | UNEQUAL BURDEN: INCOME-RELATED DISPARITIES IN CIRRHOSIS

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Background: Cirrhosis disproportionately affects socioeconomically disadvantaged populations, with substantial morbidity and mortality. Income-related disparities may influence disease severity, healthcare access, and outcomes. This study evaluates the association between income level and demographics, comorbidities, healthcare utilization, and inpatient outcomes in hospitalized patients with cirrhosis. **Methods:** This retrospective cohort study used the National Inpatient Sample (NIS) database to identify adults with cirrhosis between 2019 and 2022. Patients were stratified by income into the lowest (first) quartile versus higher quartiles to compare their demographics, comorbidities, hospital characteristics, and inpatient outcomes. Statistical analyses were performed using STATA software. **Results:** A total of 3,229,299 patients with cirrhosis were included; 32.8% were in the first income quartile and were younger (59.8 vs 61.0 years, $P < 0.05$). Racial distribution differed by income, with White (OR 0.564, 95% CI 0.545-0.584) and Asian (OR 0.350, 95% CI 0.323-0.380) patients less likely to be in the first income quartile,

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while Black (OR 2.601, 95% CI 2.505-2.701), Hispanic (OR 1.399, 95% CI 1.332-1.469), and Native American (OR 2.166, 95% CI 1.981-2.368) patients more likely to be in the first income quartile. Charlson Comorbidity Index (CCI) differed, with higher intermediate comorbidity burden (CCI 4-6, $P < 0.05$) in the first income quartile. These patients were more likely to be treated in the South and at large hospitals, and less likely in the Northeast and West ($P < 0.05$), with no difference in the Midwest ($P \geq 0.05$). They also had higher Medicaid use (OR 1.325, 95% CI 1.296-1.355) and lower private insurance use (OR 0.639, 95% CI 0.622-0.656). Patients in the first income quartile had lower rates of ascites, spontaneous bacterial peritonitis (SBP), variceal bleeding, hepatocellular carcinoma (HCC), liver transplantation, and hospitalization charges, but higher ICU admission and mortality ($P < 0.05$). There were no significant differences in rates of hepatic encephalopathy, acute liver failure, length of stay, or discharge disposition to home ($P \geq 0.05$). **Conclusion:** Patients with cirrhosis in the first income quartile were predominantly Black, Hispanic, and Native American. Their care was more often provided in large hospitals and had higher rates of ICU admission and mortality. However, there was a lower rate of ascites, SBP, variceal bleeding, and HCC. This may reflect less severe disease in these patients or possibly ascertainment bias from limited healthcare in this population.

Table 1: Demographics

	First Income Quartile (n = 1,060,480)	Higher Income Quartile (n = 2,168,819)	p value	Odds Ratio (95% CI)
Mean Age, years	59.836	60.976	<0.001	-
Gender, n				
Male	629970 (59.4%)	1298799 (59.9%)	0.002	0.980(0.968-0.993)
Female	430510 (40.6%)	870020 (40.1%)	0.002	1.020(1.010-1.033)
Race, n				
White	596825 (56.3%)	1507829 (69.5%)	<0.001	0.564(0.545-0.584)
Black	168920 (15.9%)	147245 (6.8%)	<0.001	2.601(2.505-2.701)
Hispanic	209340 (19.7%)	324340 (15.0%)	<0.001	1.399(1.332-1.469)
Asian	9785 (0.9%)	56200 (2.6%)	<0.001	0.350(0.323-0.380)
Native American	29200 (2.8%)	27990 (1.3%)	<0.001	2.166(1.981-2.368)
Other	24160 (2.3%)	61495 (2.8%)	<0.001	0.799(0.740-0.862)
Charlson Comorbidity Index, n				
≤3	461625 (43.5%)	966899 (44.6%)	<0.001	0.958(0.946-0.971)
4	171310 (16.2%)	344665 (15.9%)	0.008	1.020(1.005-1.035)
5	144410 (13.6%)	289525 (13.3%)	0.004	1.023(1.007-1.040)
6	95735 (9.0%)	186025 (8.6%)	<0.001	1.058(1.037-1.078)
≥7	187480 (17.7%)	381840 (17.6%)	0.564	1.005(0.988-1.022)
Hospital Size, n				
Small	198195 (18.7%)	477074 (22.0%)	<0.001	0.815(0.773-0.859)
Medium	295190 (27.8%)	615339 (28.4%)	0.327	0.974(0.923-1.027)
Large	567175 (53.5%)	1076540 (49.6%)	<0.001	1.167(1.112-1.224)
Hospital Location, n				
Northeast	117020 (11.0%)	409085 (18.9%)	<0.001	0.534(0.496-0.573)
Midwest	213870 (20.2%)	441495 (20.4%)	0.668	0.988(0.937-1.043)
South	559585 (52.8%)	737924 (34.0%)	<0.001	2.165(2.062-2.274)
West	170185 (16.0%)	580450 (26.8%)	<0.001	0.523(0.487-0.562)
Insurance, n				
Medicaid	305620 (28.8%)	507535 (23.4%)	<0.001	1.325(1.296-1.355)
Other	41825 (3.9%)	78080 (3.6%)	0.002	1.099(1.036-1.167)
Private	153970 (14.5%)	455320 (21.0%)	<0.001	0.639(0.622-0.656)
Medicare	491790 (46.4%)	1027710 (47.4%)	<0.001	0.960(0.944-0.976)

Table 2: Hospitalization Co-illnesses, Lenth of Stay, Cost of Admission, and Disposition

	First Income Quartile (n = 1,060,480)	Higher Income Quartile (n = 2,168,819)	p value	Odds Ratio (95% CI)
Ascites, n	422230 (39.8%)	900250 (41.5%)	<0.001	0.932(0.920-0.945)
Spontaneous Bacterial Peritonitis , n	33065 (3.1%)	72345 (3.3%)	<0.001	0.933(0.904-0.962)
Variceal bleed, n	73580 (6.9%)	157435 (7.3%)	<0.001	0.953(0.931-0.974)
Hepatic Encephalopathy (HE), n	17235 (1.6%)	36380 (1.7%)	0.248	0.968(0.917-1.023)
Hepatocellular Carcinoma (HCC), n	42225 (4.0%)	89530 (4.1%)	0.030	0.963(0.931-0.996)
Acute Liver Failure (ALF), n	64505 (6.1%)	129980 (6.0%)	0.240	1.016(0.990-1.043)
Liver Transplant, n	19295 (1.8%)	41130 (1.9%)	0.041	0.959(0.921-0.998)
ICU Admission, n	89675 (8.5%)	178750 (8.2%)	0.018	1.028(1.005-1.053)
Mortality, n	70820 (6.7%)	139730 (6.4%)	0.001	1.039(1.016-1.063)
Length of Stay (LOS), days	6.431	6.426	0.835	-
Total Charge, dollars	$78,115.37	$86,389.29	<0.001	-
Discharge Location to Home, n	740445 (69.8%)	1514264 (69.8%)	0.995	1.000(0.986-1.014)

Disclosures: Arti Patel: Nothing to Disclose, Sujay Singh: Nothing to Disclose, Homan Abdollahzadeh: Nothing to Disclose.

2113 | HEALTH RELATED SOCIAL NEEDS SCREENING IN HEPATOLOGY CLINICS MAY UNDERESTIMATE SOCIAL NEEDS PREVALENCE, PARTICULARLY AMONG VULNERABLE POPULATIONS

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Background: Vulnerable populations are disproportionately impacted by liver disease, and patients with health related social needs (HRSN) suffer from worse health outcomes. To systematically identify and reduce HRSN within our hepatology patient population, HRSN screening and resource referrals were incorporated into hepatology clinic. While we previously confirmed screening acceptability using mixed methods analyses, we aimed to re-evaluate patients' response rate after HRSN screening was integrated into clinical practice. **Methods:** From 12/2024-03/2026, HRSN screening was completed during routine hepatology care through electronic health record-based workflows. The HRSN screener includes 10 yes/no questions, with the option "prefer not to answer". Screening was completed via MyChart or during pre-visit check-in. Patients reporting HRSN and/or interest in assistance were referred to resources. Descriptive analyses included mean and frequency. Comparative analyses were performed using Chi-Square and Fisher's exact tests. **Results:** Among 3,480 unique liver clinic patients screened, 87% of patients answered all 10 questions with a yes or no response. The rate of "prefer not to answer" (PNA) responses for each question were similar, ranging from 3% (n = 97) for question 1, transportation needs, to 6% (n = 210) for question 7, housing costs, and 5% for most other questions. The sub-population who selected PNA for ≥ 1 question, when compared to the majority who answered all with yes or no, had a higher prevalence of Hispanic patients (19% vs 10%), non-English speaking patients (9% vs 3%), patients with Medicaid (21% vs 9%), and had a ≥ 2x prevalence of all HRSN ($p < 0.001$), (**Table**). There were no differences by gender or clinic type.If PNA responses are considered missing data and are excluded from analysis, then 448 patients with disproportionately higher HRSN prevalence are dropped. Alternatively, if PNA is interpreted as a "yes", the increase in each HRSN is notable: transportation needs increase from 4% to 7%, utility insecurity 12% to

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17%, housing costs 10% to 16%, medical expenses 7% to 11%, medication expenses 5% to 9%, food insecurity 14% to 19%, limited funds for home items 16% to 21%, unstable housing 2% to 5%, unemployment 10% to 15%, and caregiving interference 2% to 5%. **Conclusion:** Most patients seen in hepatology clinics answered all HRSN screening questions. However, Hispanic patients, non-English speaking patients, and those with Medicaid were more likely to select PNA. Moreover, among the yes/no responses provided by those who selected PNA for ≥1 question, HRSN were twice as common. These findings may suggest patients from vulnerable populations experience more discomfort answering HRSN screening questions resulting in an underestimation of their needs. A response of PNA, similar to a "yes," should be explored by the healthcare team to better understand if HRSN may be present and if resources may be of interest to that patient.

Table. Patient Characteristics by Health Related Social Needs Screening Response, n=3,480

Patient Characteristics by HRSN Screening Responses, n (%)			
	Yes/No for All 10 Questions, n=3032	≥1 Response "Prefer not to Answer", n=448	p-value
Gender, n (%)			0.825
Female	1641 (54)	246 (55)	
Male	1390 (46)	202 (45)	
Non-binary	1 (0)	--	
Race			<0.001
American Indian/Alaska Native	78 (3)	19 (4)	
Asian	134 (4)	17 (4)	
Black or African American	47 (2)	6 (1)	
Hispanic	312 (10)	83 (19)	
Native Hawaiian/Pacific Islander	21 (1)	4 (1)	
White	2287 (75)	290 (65)	
Not disclosed	153 (5)	29 (6)	
Language			<0.001
English	2928 (97)	411 (92)	
Spanish	75 (2)	25 (6)	
Other	29 (1)	12 (3)	
Insurance			<0.001
Self-pay or uninsured	83 (3)	14 (3)	
Medicaid	281 (9)	92 (21)	
Misc Government or Non-Government	51 (2)	7 (2)	
Medicare	958 (32)	113 (25)	
Commercial	1659 (55)	222 (50)	
Clinic type			0.789
General hepatology	2593 (86)	381 (85)	
Transplant hepatology	439 (14)	67 (15)	
Health Related Social Needs		=n/N* (%)	
Transportation needs, n=3383	91 (3)	39/351 (11)	<0.001
Medical expenses, n=3327	178 (6)	60/295 (20)	<0.001
Medication expenses, n=3359	141 (5)	40/327 (12)	<0.001
Food insecurity, n=3305	394 (13)	75/273 (27)	<0.001
Limited funds for home items, n=3292	446 (15)	92/260 (35)	<0.001
Utility insecurity, n=3294	315 (10)	81/262 (31)	<0.001
Housing costs, n=3270	274 (9)	61/238 (26)	<0.001
Unstable housing, n=3371	46 (2)	21/339 (6)	<0.001
Unemployment, n=3303	278 (9)	66/271 (24)	<0.001
Caregiving interference, n=3352	37 (1)	18/320 (6)	<0.001

*Prevalence of "yes" answers from the total of yes/no responses

Disclosures: Rebecca Kim: Nothing to Disclose, April Ballantyne: Nothing to Disclose, Gregory Stoddard: Nothing to Disclose, Jia-wen Guo: Nothing to Disclose, Bob Wong: Nothing to Disclose, John Inadomi: JAMA: Associate Editor, Molly Conroy: Nothing to Disclose, Jennifer Price: AbbVie: Grant/Research Support, Gilead: Grant/Research Support, VIR: Grant/Research Support, Cepheid: Grant/Research Support, Aligos: Grant/Research Support, Meridian: Grant/Research Support, Andrea Wallace: Nothing to Disclose.

2114 | DIGITAL HEALTH LITERACY AND CARDIOMETABOLIC DISEASE BURDEN IN U.S. ADULTS: A NATIONAL SURVEY ANALYSIS

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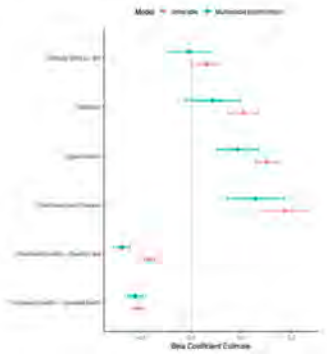
Background: Metabolic-associated steatotic liver disease (MASLD) and its cardiometabolic comorbidities, including obesity, type 2 diabetes, hypertension (HTN), and cardiovascular disease (CVD), represent a growing public health burden. Digital health tools have emerged as promising platforms for chronic disease self-management, yet inequities in digital health literacy (DHL) may limit their benefit to those most at risk. We examined DHL as a modifiable determinant of cardiometabolic disease burden and health perception in a nationally representative U.S. adult population. **Methods:** We analyzed cross-sectional 2024 Health Information National Trends Survey 7 data of U.S. adults aged ≥18 years, excluding respondents with ≥15% missing data. Survey-weighted methods with JK1 jackknife variance estimation over 50 replicate weights generated nationally representative estimates. Factor Analysis of Mixed Data across >240 variables identified two latent dimensions of digital health variation: 1) Healthcare Interaction Quality/Telehealth Engagement, 2) DHL/Technology Adoption. Associations with obesity (BMI ≥30), diabetes, HTN, CVD, and perceived quality of care and general health scores (range 1-5) were tested by survey-weighted regression adjusted for demographic, socioeconomic, and clinical covariates. **Results:** Of 5,203 included respondents (mean age 55 years, 48.7% female, 75.2% non-Hispanic White, 94.0% insured), frequent internet use was reported by 86.8% and electronic physician messaging ranged from 53.1% to 86.2% across income groups. Cardiometabolic outcomes were prevalent (37.9% with obesity, 21.8% diabetes, 41.6% HTN, 10.2% CVD) with mean perceived quality of care and general health scores of 3.83 and 3.32, respectively. The Healthcare Interaction Quality/Telehealth Engagement axis had a median score of -5.61 (range −8.10 to 49.66) and the DHL/Technology Adoption axis had a median score of 0.07 (range −7.54 to 15.77). Healthcare Interaction Quality/Telehealth Engagement axis was not significantly associated with cardiometabolic outcomes. In contrast,

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poorer DHL/Technology Adoption was significantly associated with obesity (OR 1.03, 95% CI 1.00–1.06), diabetes (OR 1.11, 95% CI 1.08–1.15), HTN (OR 1.16, 95% CI 1.14–1.19), CVD (OR 1.21, 95% CI 1.15–1.26), and lower perceived quality of care (β −0.08, 95% CI −0.09 to −0.07) and general health (β −0.11, 95% CI −0.12 to −0.10). After adjustment, the association with obesity and diabetes was attenuated whereas the other outcomes remained statistically significant (Figure 1). **Conclusion:** Lower DHL and technology adoption are associated with greater cardiometabolic disease burden and poorer perceived health. Given the role of these comorbidities in MASLD progression, these findings highlight DHL as a potential intervention target for reducing metabolic and liver disease disparities.

Figure 1. Univariable and Multivariable Associations Between Axis 2 (Digital Health Literacy / Technology Adoption) and Cardiometabolic Outcomes.



Disclosures: Somaya Albhaisi: Nothing to Disclose, Sevan Esaian: Nothing to Disclose, Payal Shah: Nothing to Disclose, Jennifer Dodge: Nothing to Disclose, Norah Terrault: Elseiver: Royalties or patent beneficiary, GSK: Grant/Research Support, Elseiver: Royalties or patent beneficiary, Elseiver: Royalties or patent beneficiary, Eiger Pharmaceuticals: Grant/Research Support, GSK: Grant/Research Support, GSK: Grant/Research Support, Helio Health: Grant/Research Support, Eiger Pharmaceuticals: Grant/Research Support, Eiger Pharmaceuticals: Grant/Research Support, Durect Corp: Grant/Research Support, Helio Health: Grant/Research Support, ImmunoCore: Grant/Research Support, Helio Health: Grant/Research Support, Durect Corp: Grant/Research Support, HBV Foundation: Board member, Durect Corp: Grant/Research Support, AASLD: Executive role, ImmunoCore: Grant/Research Support, ImmunoCore: Grant/Research Support, Genentech-Roche: Grant/Research Support, HBV Foundation: Board member, HBV Foundation: Board member, Hepatitis B Foundation: Executive role, AASLD: Executive role, AASLD: Executive role, Genentech-Roche: Grant/Research Support, Genentech-Roche: Grant/Research Support, Hepatitis B Foundation: Executive role, Hepatitis B Foundation: Executive role, Elseiver: Royalties or patent beneficiary, GSK: Grant/Research Support, Elseiver: Royalties or patent beneficiary, Elseiver: Royalties or patent beneficiary, Eiger Pharmaceuticals: Grant/Research Support, GSK: Grant/Research Support, GSK: Grant/Research Support, Helio Health: Grant/Research Support, Eiger Pharmaceuticals: Grant/Research Support, Eiger Pharmaceuticals: Grant/Research Support, Durect Corp: Grant/Research Support, Helio Health: Grant/Research Support, ImmunoCore: Grant/Research Support, Helio Health: Grant/Research Support, Durect Corp: Grant/Research Support, HBV Foundation: Board member, Durect Corp: Grant/Research Support, AASLD: Executive role, ImmunoCore: Grant/Research Support, ImmunoCore: Grant/Research Support, Genentech-Roche: Grant/Research Support, HBV Foundation: Board member, HBV Foundation: Board member, Hepatitis B Foundation: Executive role, AASLD: Executive role, AASLD: Executive role, Genentech-Roche: Grant/Research Support, Genentech-Roche: Grant/Research Support, Hepatitis B Foundation: Executive role, Hepatitis B Foundation: Executive role.

2115 | SOCIAL DISADVANTAGE IS ASSOCIATED WITH FIBROSIS SEVERITY AND GLP-1 RECEPTOR AGONIST UTILIZATION IN MASLD

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Background: Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are increasingly used for metabolic diseases including MASLD, whereas treatment discontinuation and differential access may limit their long-term impact on the outcomes. Because social

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determinants of health (SDoH) may influence both MASLD burden and medication utilization, the aims were to evaluate the association of overlapping SDoH domains with MASLD presence and severity and GLP-1RA utilization. **Methods:** Using the National Health and Nutrition Examination Surveys (NHANES) and Medical Expenditure Panel Survey (MEPS) data (2017–2023), we conducted two retrospective analyses as independent cohorts. SDoH scores were stratified into three levels (low, medium, high). GLP-1RA utilization was identified through prescription medication records. Survey-weighted multivariable logistic regression models were used separately for each cohort to examine associations between SDoH and the following outcomes: 1) GLP-1RA utilization; 2) MASLD prevalence; and 3) significant fibrosis (liver stiffness > 8kPa) among individuals with MASLD. The models were adjusted for age, sex, and geographic region (in MEPS). Sensitivity analyses were conducted to examine the impact of individual SDoH variables. **Results:** In NHANES, MASLD prevalence was 36.4% in 2017–2020 and 33.9% in 2021–2023. Among participants with MASLD, the prevalence of significant fibrosis was 17.2% in 2017–2020 and 19.4% in 2021–2023. Higher SDoH burden was associated with greater fibrosis severity (OR 1.994, 95% CI 1.302–3.054), while its association with MASLD prevalence was less consistent across survey periods (OR 1.018, 95% CI 0.818–1.265 in 2017–2020; OR 1.263, 95% CI 0.999–1.596 in 2021–2023). In the sensitivity analysis, high food security was associated with lower fibrosis burden in 2021–2023 (OR 0.544, 95% CI 0.386–0.765), while higher educational attainment was associated with lower odds of MASLD prevalence (OR 0.637, 95% CI 0.457–0.886). In MEPS, individuals with medium and high SDoH burden had lower odds of GLP-1 RA use than those with low SDoH burden (OR 0.559, 95% CI 0.470–0.664 [medium] and OR 0.482, 95% CI 0.391–0.594 [high] in 2021–2023; OR 0.586, 95% CI 0.449–0.764 [high] in 2017–2020). In the sensitivity analysis of individual SDoH domains, high food security was associated with lower GLP-1RA use in both 2017–2020 (OR 0.597, 95% CI 0.381–0.934) and 2021–2023 (OR 0.722, 95% CI 0.524–0.995), while improved healthcare access (OR 3.691, 95% CI 2.480–5.493) and higher educational attainment (OR 1.882, 95% CI 1.253–2.825) were associated with higher GLP-1RA utilization in 2021–2023. **Conclusion:** Social disadvantage may be linked to treatment access and utilization as well as disease severity among individuals with MASLD, suggesting the importance of incorporating SDoH into assessment of disease progression and access to newer therapies.

Disclosures: Ridhi Chaudhary: Nothing to Disclose, Hwi Young Kim: Nothing to Disclose, Yeongjin Gwon: Nothing to Disclose, Holland Stevenson: Nothing to Disclose, Avry Logeman: Nothing to Disclose.

2116 | AN EXPLORATION OF STRUCTURAL AND CONTEXTUAL BARRIERS TO LIVER CANCER SCREENING IN THE HEPATOLOGY CLINIC AT MONTEFIORE MEDICAL CENTER

Kristen Gotsis[1] Cyrus Mowdawalla[2] Lydia Bioh[1] Kush Desai[1] Kylie Heering[1] Iman Siddiqui[1] Courtney Balgobin[2] Andrew Takchi[3] Adebola Adedimeji[4] David Lounsbury[4] Bahar Laderian[5] Clara Tow[6] Yvonne Saenger[7], [1]Albert Einstein College of Medicine, Bronx, NY, USA, [2]Department of Medicine, Montefiore Medical Center, Bronx, NY, USA, [3]Department of Medicine, Jacobi Medical Center, Bronx, NY, USA, [4]Dept. of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY, USA, [5]Department of Oncology, Montefiore Medical Center, Bronx, NY, USA, [6]Department of Medicine, Division of Transplant Hepatology, Montefiore Medical Center, Bronx, NY, USA, [7]Montefiore Einstein Comprehensive Cancer Center, Bronx, NY, USA

Background: Hepatocellular carcinoma (HCC) is the fourth leading cause of cancer-related mortality worldwide and the most common primary liver cancer. Prognosis is highly dependent on the stage at diagnosis. Montefiore Medical Center (MMC) serves a diverse population with a high proportion of socioeconomically disadvantaged patients. HCC screening rates, patient understanding of liver cancer, and the role of socioeconomic and structural barriers to liver cancer screening have not been well characterized in this population. **Methods:** Patients receiving care at MMC hepatology clinics were recruited. Eligible participants included adults over the age of 18 who met criteria for HCC screening: those with advanced fibrosis, cirrhosis, and/or chronic hepatitis B infection. Patients with a history of HCC or undergoing surveillance of other liver lesions were excluded. Participants completed a questionnaire-based survey assessing HCC screening history, understanding of liver cancer, and barriers to screening. EMR review was performed to verify true screening frequency with screening defined as abdominal ultrasound, MRI, or CT evaluating the liver. **Results:** A total of 157 patients completed the survey, with demographics summarized in Table 1. 57.3% of patients reported undergoing liver cancer screening within the last 7 months, 1.3% reported screening within 7 months to 1 year, 27.4% reported no screening within the past 12 months, and 14% of patients could not remember. EMR review demonstrated higher than reported screening rates, with 66.2% of patients screened within the last 7 months, 9.6% screened between 7 months to 1 year, and 24.2% receiving no screening within 12 months. Knowledge gaps

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regarding liver cancer were substantial. Over half of patients were unable to identify any symptoms of liver cancer, and 28.6% were unable to identify any risk factors for liver cancer. Regarding barriers to screening, 55.4% of patients reported no barriers, 29.3% reported one, and 15.3% reported two or more. Commonly reported barriers included unreliable transportation, scheduling and work conflicts, high copays, and anxiety surrounding testing. **Conclusion:** Despite receiving specialty hepatology care, many patients demonstrated limited understanding of liver cancer risk and surveillance, with gaps in knowledge regarding symptoms and risk factors for HCC. Patients often underestimated the extent of screening they had undergone, suggesting poor understanding of screening practices and the purpose of screening. Structural barriers also remained prevalent within this population. These findings suggest that access to specialty care alone may be insufficient to optimize HCC surveillance adherence. Targeted patient education initiatives and system-level interventions addressing socioeconomic barriers may be necessary to improve surveillance engagement and reduce disparities in HCC outcomes among vulnerable populations.

	N	%	Mean	Standard Deviation
Age			59.97	12.32
Gender				
Male	73	46.50		
Female	84	53.50		
Non-Binary	0	0.00		
No response	0	0.00		
Race*				
White	22	14.01		
Black	63	40.13		
Asian	10	6.37		
Other/No response	65	41.40		
Ethnicity				
Hispanic	74	47.13		
Non-Hispanic	83	52.87		
Average annual income				
< $35,000	76	48.41		
$36,000-50,000	25	15.92		
$50,000-70,000	20	12.74		
> $70,000	13	8.28		
Prefer not to say	23	14.65		
Health insurance status**				
Medicaid	90	57.32		
Medicare	68	43.31		
Private insurance	41	26.11		
Veterans insurance	0	0.00		
Insured, unsure what type	2	1.27		
No insurance	0	0.00		

Table 1: Demographics of 157 study participants.
* Some participants indicated >1 race.
** Some participants indicated >1 health insurance type.

Disclosures: Kristen Gotsis: Nothing to Disclose, Cyrus Mowdawalla: Nothing to Disclose, Lydia Bioh: Nothing to Disclose, Kush Desai: Nothing to Disclose, Kylie Heering: Nothing to Disclose, Iman Siddiqui: Nothing to Disclose, Courtney Balgobin: Nothing to Disclose, Andrew Takchi: Nothing to Disclose, Adebola Adedimeji: Nothing to Disclose, David Lounsbury: Nothing to Disclose, Bahar Laderian: Nothing to Disclose, Clara Tow: Madrigal: Advisor, Yvonne Saenger: Nothing to Disclose.

2117 | CLOSING THE HCC SCREENING GAP: AN ADVOCACY DRIVEN MULTIDISCIPLINARY WORKGROUP TO DEVELOP EQUITY-CENTERED IMPLEMENTATION RECOMMENDATIONS

Sandra Ponce[1] Amit Singal[2] Jesse Powell[3] Lily Benig[4], [1]Global Liver Institute, [2]UT Southwestern Medical Center, [3]Hennepin Healthcare, [4]Consultant

Background: Hepatocellular carcinoma is a leading cause of cancer-related death in the United States, with most cases diagnosed at advanced stages due to underuse of guideline-recommended surveillance. While early-stage diagnosis is associated with >70% five-year survival, advanced-stage survival remains below 20%. System, provider, and patient-level barriers, including fragmented EHR systems, limited provider awareness, and structural inequities, continue to limit effective surveillance implementation. This workgroup developed practical, equity-centered recommendations to improve HCC screening implementation. **Methods:** Global Liver Institute convened the HCC Screening Guidelines Workgroup, a multidisciplinary panel of 15 stakeholders including hepatologists, oncologists, primary care physicians, advanced practice providers, radiologists, and two patient advocates with lived HCC experience. Participants were selected based on clinical expertise, geographic diversity, and representation of high-burden communities. Using a structured consensus-based process across three meetings, the workgroup reviewed clinical guidelines, peer-reviewed literature, and health systems data. Pre- and post-session surveys assessed barriers, feasibility, and intervention priorities. Recommendations were refined through iterative discussion and consensus prioritization. **Results:** Phase I workgroup discussions identified interconnected system, provider, and patient-level barriers limiting consistent semiannual HCC surveillance. System barriers included fragmented care pathways, limited specialist and imaging capacity, inconsistent radiology quality, and EHR limitations

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affecting identification and tracking of high-risk patients. Provider barriers included variable awareness of surveillance guidelines, limited primary care support, time constraints, and unclear ownership of surveillance. Patient barriers included low awareness of liver cancer risk, stigma, mistrust of health systems, language and cultural discordance, transportation, and insurance-related challenges.In response, the workgroup developed four consensus recommendations: (1) a simplified, one-page primary care roadmap translating HCC surveillance guidelines into actionable steps for non-specialist providers; (2) automated EHR-based identification of at-risk patients; (3) standardized EHR-embedded care pathways defining referral and follow-up responsibilities; and (4) expansion of culturally responsive patient navigation programs to address barriers to surveillance adherence. **Conclusion:** Phase I produced actionable, equity-centered recommendations emphasizing system-level change, provider support, and patient navigation to improve HCC surveillance uptake. Phase II will pilot these strategies in high-burden communities to evaluate scalability and implementation effectiveness.

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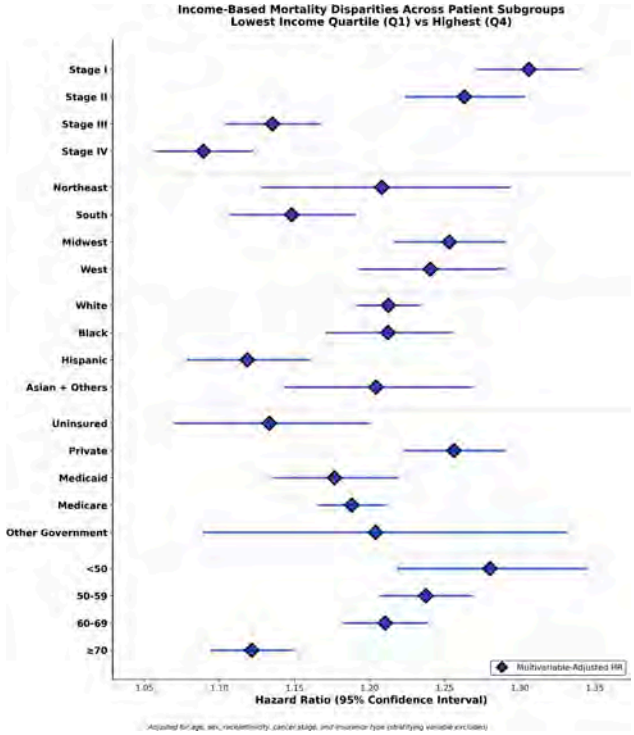
2118 | INCOME DISPARITIES IN HEPATOCELLULAR CARCINOMA OUTCOMES: IMPACT OF COVID 19 PANDEMIC AND INSIGHT FROM TREATMENT MEDIATION ANALYSIS

Neil Sundaram[1] Hyunseok Kim[1] Michael Luu[1] Paul Martin[1] Alexander Kuo[2] Walid Ayoub[2] Yun Wang[1] Aarshi Vipani[2] Nicole Rich[3] Neehar Parikh[4] Kambiz Kosari[1] Nicholas Nissen[1] Cristina Ferrone[1] Amit Singal[3] Ju Dong Yang[2], [1]Cedars Sinai Medical Center, [2]Cedars-Sinai Medical Center, [3]University of Texas Southwestern Medical Center, [4]University of Michigan Medical Center

Background: In the United States, HCC disproportionally affects persons from racial and ethnic minority groups and those from low socioeconomic status (SES) neighborhoods. While recent large studies have documented a clear relationship between SES and HCC mortality, the exact contributions of treatment and the recent COVID-era years (2020 – 2023) to existing disparities have yet to be described. **Methods:** Using data from the National Cancer Center Database (NCDB), we examined the relationship between income and HCC mortality at the national level and conducted a treatment-mediation analysis. Data on 247,192 patients with a diagnosis of HCC and neighborhood-level income were collected from 2004 through 2023. Survival outcomes were assessed using Kaplan-Meier methods and Cox proportional hazards regression models estimated hazard ratios (HR). Multivariate models were controlled for age, sex, race, geographic region, disease stage, and insurance status. Treatment mediation analysis was conducted by calculating the HR attenuation after stratifying by curative or non-curative treatment. Results were further stratified by pre-COVID (2004 – 2019) and COVID (2020-2023) eras. **Results:** The cohort had a mean age of 64.7 years and was predominantly male (76%), White (60%), Medicare-insured (49%), stage I disease (30.6%), and located in the South (39%). Approximately 26% received curative surgical treatment (resection, ablation, liver transplantation) and 44% received non-curative (locoregional, systemic therapy) HCC treatment. Lower income quartile (Q1 vs. Q4) was independently associated with increased HCC mortality HR 1.20 (95% CI 1.19 – 1.22, $P < 0.001$). Subgroup analyses demonstrated the greatest income-related mortality disparities among patients who were age < 50 years, Black, privately insured, had stage I HCC, or resided in the Midwest (all $p < 0.001$) (Figure). Treatment mediation analysis revealed that 25% of the income-related mortality disparities may be attributable to HCC treatment receipt (curative or non-curative) with an absolute HR reduction from 1.20 (95% CI 1.19 – 1.22) to 1.15 (95% CI 1.14 – 1.17). During the COVID-era, Asian and Black Americans experienced the largest worsening income-related HCC mortality disparities by 2.9 fold (from HR 1.16 to 1.46, $p < 0.001$) and 1.5 fold (1.20 to 1.29, $p < 0.001$) increases, respectively. **Conclusion:** Neighborhood-level income independently predicts HCC mortality beyond insurance status, cancer stage, and geographic region. Variations in treatment receipt explain only 25% of the income-related disparity in HCC mortality. These findings highlight the need for interventions that not only promote equitable access to treatment but also address social determinants of health to mitigate income-based disparities among patients with HCC.

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2119 | COMPARING ASSOCIATIONS OF SOCIAL, BEHAVIORAL AND DIETARY RISK FACTORS WITH HEPATIC FIBROSIS AMONG US ADULTS IN POST-PANDEMIC ERA, ARE TRENDS CHANGING?

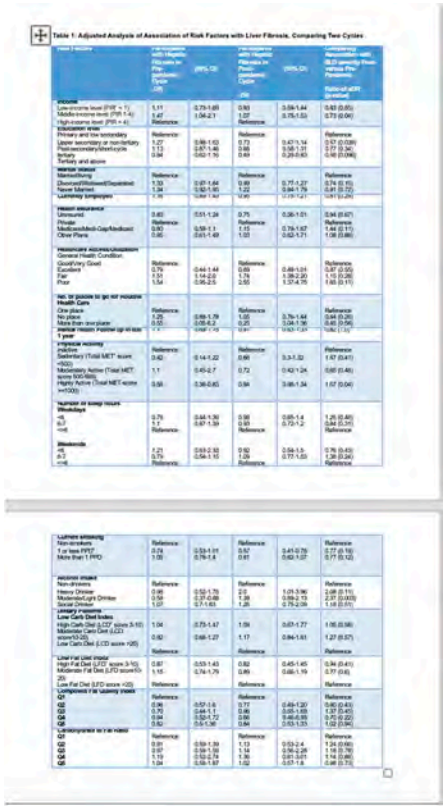
Iqra Arshad[1] Xinyuan Zhang[2], [1]Saint Louis University Hospital, [2]Brigham and Women's Hospital and Harvard Medical School

Background: In addition to known cardiometabolic risk factors, e.g., morbid obesity, type 2 diabetes; social, behavioral and dietary factors serve as key players in shaping risk of developing fatty liver disease and advanced fibrosis. Despite stable reported prevalence of steatotic liver disease (SLD)[1-2] since pandemic, data to assess associations of these risk categories with liver fibrosis seems limited. Current study aims to evaluate whether associations of these risk categories with liver fibrosis are changing since pandemic. **Methods:** Using National Health and Nutrition Examination Survey (NHANES) data, we performed a cross-sectional observational study. Data on sociodemographic, behavioral and dietary factors were extracted from pre-pandemic(2017-2020) and post-pandemic (2021-2023) cycles. Outcome was the presence of liver fibrosis, defined as liver stiffness measure (LSM) score $\geq$8.0 kPa. Missing data on key predictors were handled using Multiple Imputations Chain Equation method. Univariate regression models were used to assess prevalence, and multivariate models to evaluate associations with outcome in each cycle. Associations between cycles were compared as a ratio of adjusted odds ratio and effect modification by time was used for statistical significance. A two-tailed p-value $<$0.05 was set as significant. **Results:** In both cycles, SLD participants with liver fibrosis (11.2% in pre- and 12.9% in post-

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pandemic) showed similar trends, i.e., were less likely to have higher education and mental health follow-ups, more likely to belonging to middle-income group, having obesity, medical comorbidities and being in higher quintiles of poor fat and low fiber diets intake compared to their controls. In the adjusted analysis, among social factors, increasing trends of associations of liver fibrosis with being covered by non-private payers, and in overall fair to poorer health conditions were observed, but findings were non-significant (p-value >0.05). Among lifestyle factors, higher levels of physical activity were significantly associated with lower odds of fibrosis ($_a$OR; 0.56 [0.38-0.83]) in pre-pandemic and non-significantly associated with fibrosis ($_a$OR; 0.94 [0.66-1.34]) in post-pandemic era. The associations remained statistically stronger (ratio; 1.67 [p 0.04]) comparing the cycles. Moderate drinking was not significantly associated with higher odds of fibrosis ($_a$OR;1.38,[0.89-2.13]) in post-pandemic era, although overall association seems significantly stronger (ratio; 2.37 [p 0.003]) over time.Among dietary habits, a low fiber diet was associated with a higher risk of fibrosis, although findings did not reach statistical significance in each cycle and over time. [Table 1]. **Conclusion:** Study supports evidence on protective role of higher physical activities and high fiber in diet in reducing risk of liver fibrosis and reinforces their integration through education and policy since pandemic.



Disclosures: Iqra Arshad: Nothing to Disclose, Xinyuan Zhang: Nothing to Disclose.

2120 | NATIONAL TRENDS AND INSURANCE-BASED DISPARITIES IN LIVER TRANSPLANTATION, TIPS, AND OUTCOMES AMONG HOSPITALIZED PATIENTS WITH ACUTE-ON-CHRONIC LIVER FAILURE

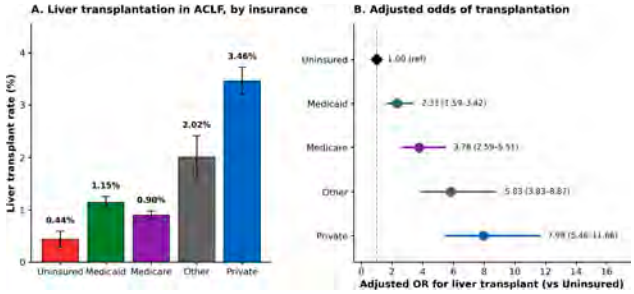
Gedion Yilma Amdetsion[1] Amir Sultan[2] Chun-Wei Pan[3] Fnu Vikash[4] Hiwot Tebeje[5] Emeka Stanley Obi[6] Yonas Fetie[7] Yetunde Akande[8] Edgar Arza Basualdo[8] Ayokunle Abegunde[8], [1]John H Stroger Hospital, [2]Mayo clinic, Rochester, [3]U Mass Chan, [4]Cleveland Clinic, [5]WASHU, [6]Brookdale University Hospital and Medical Center, [7]Marshall University, [8]John H Stroger Hospital of Cook County

Background: Acute-on-chronic liver failure (ACLF) carries the highest short-term mortality in hepatology, and rescue depends on two procedures with sharply different resource footprints: TIPS for portal decompression and liver transplantation. Whether a decade of national expansion in these procedures has narrowed insurance-based access gaps is unknown. **Methods:** We analyzed 1,924,619 weighted ACLF hospitalizations in the National Inpatient Sample (2016–2022), defining ACLF by ≥1 extrahepatic organ failure (renal, circulatory, respiratory, cerebral, coagulation) using EASL-CLIF–adapted ICD-10-CM/PCS codes, graded 1–3. This coding algorithm was adapted from previously validated ICD-10 ACLF definitions in administrative data. Survey-weighted logistic and Poisson models compared in-hospital mortality (primary outcome), liver transplantation, TIPS, palliative care, and discharge against medical advice (AMA) across payers (Uninsured = reference), adjusting for demographics, all five organ failures, decompensation features, ACLF grade, and hospital characteristics. Findings were independently verified using entropy balancing on covariate means and IPWRA. Sensitivity analyses restricted to strict ACLF, and transplant-eligible patients (defined by absence of absolute contraindications per ICD-10 coding). **Results:** Uninsured patients (5.1%) were younger (mean 51.0 vs 68.6 yrs Medicare) yet carried equivalent organ failure burden (mean 1.84 vs 1.82). Liver transplantation showed the steepest disparity: 0.44% of uninsured underwent transplant versus 3.46% of privately-insured patients (aOR 7.98, 95% CI 5.46–11.66). TIPS use among ACLF hospitalizations rose ≍20-fold nationally from 2016 to 2022, yet insurance-based differences in TIPS receipt remained unchanged across the decade (Private vs Uninsured aOR 1.51, 1.29–1.77). Uninsured patients were 2.8-fold more likely to leave AMA (aOR Private 0.40, 0.36–0.44) and were less likely to receive palliative care (aOR 0.62 vs insured, adjusted for mortality risk). Adjusted in-hospital mortality was

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modestly but consistently lower among insured patients (Private aOR 0.78, 0.74–0.82), with a widening payer-related mortality disparity at ACLF-3 (interaction $p < 0.05$; aOR grade 3 vs grade 1: 13.6). **Conclusion:** A decade of dramatic national expansion in ACLF procedural care has not narrowed insurance-based disparities. Uninsured patients, equally sick, often younger, remain systematically diverted away from rescue therapies and toward AMA discharge. The transplant access gap may represent the most consequential and actionable disparity in modern hepatology.



Disclosures: Gedion Yilma Amdetsion: Nothing to Disclose, Amir Sultan: Nothing to Disclose, Chun-Wei Pan: Nothing to Disclose, Fnu Vikash: Nothing to Disclose, Hiwot Tebeje: Nothing to Disclose, Emeka Stanley Obi: Nothing to Disclose, Yonas Fetie: Nothing to Disclose, Yetunde Akande: Nothing to Disclose, Edgar Arza Basualdo: Nothing to Disclose, Ayokunle Abegunde: Nothing to Disclose.

2121 | POPULATION SCREENING FOR LIVER DISEASE USING EXISTING BLOOD TESTS DOES NOT EXCLUDE CORE20 DEPRIVED POPULATIONS: RESULTS FROM THE LIVEWELL STUDY

Timothy Jobson[1] Katie Denver[2] Christina Owen[1] Neil Stevens[2] Axelle Caudrillier[3] Yasmin Hamadache[3] Heath O'Brien[3] Louise Campbell[4] Patrick Short[3] Jamie Webb[3] Katie Barnes[3], [1]Somerset NHS Foundation Trust, [2]Predictive Health Intelligence, [3]Sanogenetics, [4]Tawazun Health

Background: The LiveWell study evaluated whether combining longitudinal blood test results with a polygenic risk score supports population-level liver disease screening. Hospital admissions for advanced liver disease are 3-fold higher in the most deprived populations compared to the least. We present the results of the analysis of the impact of deprivation on invitation and uptake of screening in a research context. hepatoSIGHT, an NHS-adopted tool, was used to risk stratify the Somerset population. Eligible individuals were invited by letter, linked to an e-enrolment platform and underwent saliva based genetic analysis and transient elastography. **Methods:** Index of Multiple Deprivation (IMD) decile distributions were compared across: 1) general Somerset population; 2) hepatoSIGHT-identified cohort (n = 61,116; aged 25-35 or 45-55, with at least one liver function test in five years, with no ALT > 500) 3) high-risk active subgroup, (highest 7% of the population, based on cumulative ALT) 4) the consented cohort (n = 996, cases plus controls). Analyses used Pearson chi-squared, standardised residuals, and odds ratios (OR) with Wilson 95% confidence intervals (CI). CORE20 was defined as IMD deciles 1-2. **Results:** The hepatoSIGHT-identified cohort contained more CORE20 individuals than predicted (IMD 1-2 12.12% vs Somerset 8.91%; OR 1.41, 95% CI 1.36-1.46; $p < 0.0001$), with excess in IMD 1-5 and deficit in 7-10, indicating deprived populations had more blood tests. Risk stratification pronounced this difference (active group IMD 1-2 13.53%, OR 1.60 vs Somerset; active vs control OR 1.15, 95% CI 1.05-1.26, $p = 0.002$). The recruitment step reduced deprivation weighting: study recruited IMD 1-2 9.72%; no different from Somerset population ($p = 0.37$) but lower than the eligible-pool (eligible vs recruited OR 1.28, 95% CI 1.04-1.58, $p = 0.025$; active vs recruited OR 1.45, 95% CI 1.16-1.82, $p = 0.001$).Data-driven liver disease screening does not systematically exclude deprived populations. CORE20 patients are over-represented at the cohort generation and risk-stratification stages, reflecting higher disease prevalence and historic blood test availability. In LiveWell, the enrollment rate was lower in CORE20 patients, but in line with population baseline, showinf data-driven recruitment may recruit individuals from deprived areas more effectively than traditional encounter based recruitment. **Conclusion:** Data-driven liver disease screening does not systematically exclude deprived populations. CORE20 patients are over-represented at the cohort generation and risk-stratification stages, reflecting higher disease prevalence and greater historic blood test availability. In LiveWell, the enrollment rate was lower in CORE20 patients, but still in line with population baseline, demonstrating data-driven recruitment may recruit individuals from deprived areas more effectively than traditional encounter based recruitment.

Disclosures: Timothy Jobson: Predictive Health Intelligence Ltd: Executive role, Predictive Health Intelligence Ltd: Stock – privately held company, Katie Denver: Nothing to Disclose, Christina Owen: Nothing to Disclose, Neil Stevens: Nothing to Disclose, Axelle

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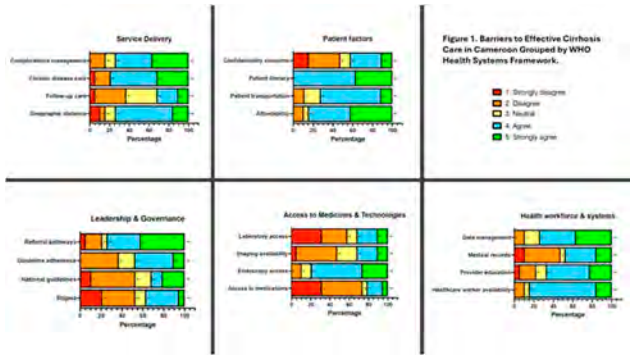
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Caudrillier: Nothing to Disclose, Yasmin Hamadache: Nothing to Disclose, Heath O'Brien: Nothing to Disclose, Louise Campbell: Nothing to Disclose, Patrick Short: Nothing to Disclose, Jamie Webb: Nothing to Disclose, Katie Barnes: Nothing to Disclose.

2122 | BARRIERS TO EFFECTIVE CIRRHOSIS CARE IN CAMEROON: PERSPECTIVES FROM FRONTLINE PHYSICIANS

Maitri Patel[1] Ikechukwu Eze[1] Kasopefoluwa Oguntuyo[1] Abdoulaye Epse Mohamadou Balkissou[2] Tidang Tchinda Carinele[2] Baiye William Abange[2] Mathurin Kowo[2] Sofia Jakab[1], [1]Yale University, [2]University Teaching Hospital of Yaounde

Background: There is limited systematic data on cirrhosis healthcare delivery in sub-Saharan Africa. The Pathways to Cirrhosis Care in Cameroon Project seeks to characterize access patterns and barriers amongst patients presenting with cirrhosis at a large tertiary care center in Yaoundé, Cameroon. **Methods:** As part of our project, we conducted a cross-sectional physician survey amongst internal medicine and gastroenterologist trainees and attendings, evaluating perceived barriers to chronic liver disease management within their tertiary care, academic hospital. Survey domains were based on the World Health Organization (WHO) health systems framework and included leadership and governance, service delivery, workforce and health systems, access to medicines and technologies, and patient-related factors. Due to low sample size, this study focused on descriptive analyses. **Results:** A total of 19 (82.6%) survey responses were collected amongst 23 eligible physicians. 18 (95%) of these responses were from physician trainees. No survey responders reported any experience at a liver transplant center. Within leadership and governance, most respondents felt strongest about deficiencies in referral pathways (74%), while liver disease stigma (37%) and national policy availability (32%) were ranked as lowest concerns. Service delivery barriers included geographic distance from care (74%), chronic disease management infrastructure (79%), and management of cirrhosis complications (74%). Inadequate healthcare worker availability (84%), insufficient provider education (67%), and poor data management capabilities (74%) were ranked highest among workforce and infrastructure limitations. Within medicine and technology domains, endoscopy access was the primary barrier (79%). Key patient-related challenges included affordability concerns (84%), transportation limitations (72%), and confidentiality issues (42%). Patient literacy was universally identified as a barrier by all respondents (100%). Interestingly, "traditional medicine" was commonly noted in the free-text section of the survey inquiring about additional barriers. **Conclusion:** This study identified multilevel barriers to cirrhosis care in Cameroon, including endoscopy access, chronic disease infrastructure, data management, and low patient health literacy. These findings highlight opportunities for targeted interventions including expansion of endoscopy services, implementation of standardized cirrhosis documentation templates, and data management strategies to strengthen longitudinal liver disease care.



Disclosures: Maitri Patel: Nothing to Disclose, Ikechukwu Eze: Nothing to Disclose, Kasopefoluwa Oguntuyo: Nothing to Disclose, ABDOULAYE Epse MOHAMADOU Balkissou: Nothing to Disclose, Tidang Tchinda Carinele: Nothing to Disclose, Baiye William Abange: Nothing to Disclose, Mathurin Kowo: Nothing to Disclose, Sofia Jakab: Nothing to Disclose.

2123 | ECONOMIC VALUE WITHOUT EQUITY? A SYSTEMATIC REVIEW OF TRIAL-LINKED COST-EFFECTIVENESS, HEALTHCARE DELIVERY, AND PATIENT FINANCIAL BURDEN STUDIES IN LIVER DISEASE

Rubab Fatimaa[1] Rida Fatima[2], [1]Fatima Jinnah Medical University, [2]Shaukat Khanum Hospital

Background: Cost-effectiveness evidence guides liver care, but average value may not translate into equitable value when studies omit access barriers, patient-borne costs, and underserved populations. We mapped value conclusions, patient financial burden, and equity reporting across liver economic and delivery studies. **Methods:** PubMed/Embase were searched from January 2015 to May 2025 for adult liver disease studies linked to RCTs, pragmatic trials, or trial-derived models reporting costs, ICERs, QALYs, utilisation, linkage-to-care efficiency, or financial burden. Two reviewers screened studies following PRISMA 2020. Studies

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were classified into five domains; equity domains were race/ethnicity, insurance, income/education, language, safety-net setting, rurality, and patient-borne costs. **Results:** Twenty-three studies were included: HCC systemic therapy (n = 10), MASH therapeutics (n = 2), transplant/infectious prophylaxis (n = 3), surgery/procedural care (n = 3), and surveillance/delivery/patient burden (n = 5). Equity reporting was critically limited: among 20 CEA studies, only 2 (10%) reported equity stratification and 18 (90%) reported none. HCC systemic therapy had the broadest ICER range ($26,477-$782,105/QALY; median $135,789 across 14 estimates); 8/14 (57%) were below the $150,000/QALY US threshold, though value was highly sensitive to comparator, setting, and pricing. Second-line agents were unfavourable: regorafenib ($201,797-$268,506/QALY) and ramucirumab ($782,105/QALY) exceeded thresholds. Resmetirom for MASH was estimated cost-effective at list price but with substantial projected budget impact. Procedural and delivery interventions more consistently generated dominant or favourable value: preemptive CMV therapy reduced disease (9% vs 19%) and saved $8,707/patient; laparoscopic hemihepatectomy yielded €36,677/QALY; ERAS reduced costs and morbidity; and mailed HCC outreach cost $32.45/patient in year 1 while generating 300 additional QALYs per 10,000 patients. Patient financial burden was substantial: 21.8% of screened cirrhosis patients reported moderate-to-severe burden, and Medicare HCC patients incurred median first-year payments of $66,338 and patient liabilities of $10,008, exceeding cirrhosis-only comparators by $50,110 and $7,166, respectively. **Conclusion:** Liver economic evidence estimates average population value without determining who accesses benefit or bears disproportionate financial harm. Procedural and delivery interventions deliver consistent value, whereas HCC systemic therapy cost-effectiveness is price- and setting-dependent. Future liver health technology assessments should disaggregate ICERs by insurance, race/ethnicity, and treatment access, and incorporate patient-borne costs, so cost-effective liver care is also equitable liver care.

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2124 | RACIAL VARIATION IN MORTALITY, SEPSIS, AND ORGAN FAILURE AFTER TIPS: A CONTEMPORARY NATIONAL INPATIENT SAMPLE ANALYSIS (2019–2022)

Amna Naveed Butt[1] Anjum Dhamani[1] Maher Taha[1] Bryce Mays[1] Scott Keeney[1], [1]Texas Health Resources

Background: Racial disparities in outcomes of end-stage liver disease remain a continuing concern, yet contemporary national data on transjugular intrahepatic portosystemic shunt(TIPS) outcomes are limited. We evaluated racial differences in in-hospital mortality and clinical outcomes using the 2019-2022 National Inpatient Sample (NIS). **Methods:** Adult hospitalizations undergoing TIPS were identified using ICD-10 -PCS procedure code 06183J9 from the NIS 2019-2022. Survey weights were applied to generate national estimates. Race was categorized as White, Black, Hispanic, Asian/Pacific Islander, Native American, and Other. The primary outcome was in-hospital mortality. Secondary outcomes included acute kidney injury (AKI), sepsis, shock, hepatic encephalopathy, discharge disposition, and hospital characteristics. Weighted chi-square tests and t-tests compared baseline characteristics. Survey-weighted logistic regression estimated crude and adjusted odds ratios (ORs) for mortality. **Results:** A weighted total of 26,064 TIPS procedures were identified. The cohort was 70.9% White, 4.7% Black, 16.9% Hispanic, 2% Asian/Pacific Islander, 1.9% Natie American, and 3.5% Other. Overall, the in-hospital rate was 9 %. Mortality differed significantly by race ($p < 0.001$): White 8.1%, Black 18%, Hispanic 7.2%, Asian/Pacific Islander 12%, Native American 16.7%, and Other 13.4%. AKI occurred in 32.4% of cases, sepsis in 10 %, and shock in 22.9%, each displaying significant racial variation. Crude mortality associations included race (OR 1.11; 95% CI 1.03-1.19), age (OR 0.99; $p = 0.001$), and Elixhauser score (OR 1.18; $p < 0.001$). Race-stratified mortality odds were highest among Black patients (OR 7.88; 95% CI 5.63-11.02). In the fully adjusted model, significant predictors of mortality included Black race (OR 1.97; 95% CI 1.12-3.47), AKI (OR 4.46; $p < 0.001$), shock (OR 2.31; $p < 0.001$), sepsis (OR 2.58; $p < 0.001$), and mechanical ventilation (OR 7.54; $p < 0.001$). Hospital region, teaching status, and bed size were not independently associated with mortality. **Conclusion:** In this contemporary national cohort, racial disparities in TIPS outcomes persist. Black patients experienced nearly double the in-hospital mortality compared with White patients, even after adjustments for co-morbidities and organ failure. These findings highlight ongoing inequities in liver disease care and underscore the need for targeted interventions to address pre-procedure optimization, access to specialty care, and system-wide barriers.

Disclosures: Amna Naveed Butt: Nothing to Disclose, Anjum Dhamani: Nothing to Disclose, Maher Taha: Nothing to Disclose, Bryce Mays: Nothing to Disclose, Scott Keeney: Nothing to Disclose.

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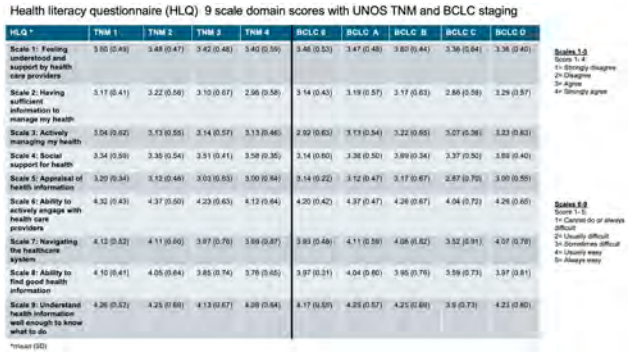
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2125 | HEALTH LITERACY IS AN IMPORTANT DETERMINANT OF HEALTH OUTCOMES IN HEPATOCELLULAR CARCINOMA

Hannah Lee[1] Alana Saddic[1] Beomchang Kim[1] Priyam Das[1] Deborah DiazGranados[2] Grant Chin[1] Mary Kate Lantzy[1] Spencer Rice[1] Antara Sarkar[1] Richard Sterling[1], [1]Virginia Commonwealth University, [2]Virginia Commonwealth Universty

Background: Health literacy (HL), defined as the ability to access, understand, appraise, and apply health information to manage one's health, is important in addressing cancer care and chronic disease. Hepatocellular cancer (HCC) is a major cause of liver related morbidity/ mortality with suboptimal outcomes. The HL status of HCC patients and its relationship to disease status is unknown. We hypothesize that lower HL is associated with decreased HCC surveillance and greater disease burden at presentation. Our aims were: (1) to asses the HL status of HCC patients and (2) to evaluate the relationship of HL measures to HCC disease status. **Methods:** In a single center prospective study, the Health Literacy Questionnaire (HLQ), a globally validated instrument, was administered to HCC patients. Demographic, laboratory, imaging data were obtained from medical records. UNOS TNM and Barcelona Clinic Liver Cancer (BCLC) staging were used to assess disease status. Quality of life (QOL) was assessed by the Edmonton Symptoms Assessment System (ESAS). Logistic ordinal and linear regression were performed to determine the relationship between HL and HCC status, screening and QOL. Significance was set at $p < 0.05$. **Results:** 100 patients (mean age: 66 yrs, males 77%, White 72%, Black 18%, Latino 5%, other 5%, 38% ALD, 27% MASLD, 11% MetALD, 41% HCV, 12% other, 95% cirrhosis (CTP 77% A,15% B, 8% C) were studied. TNM stage 1 was 10%, 2 51%, 3 21%, and 4 18%. BCLC stage 0 was 7%, A 59%, B 13%, C 14%, and D 7%. Mean MELD was 12. Education was 53% =/< high school, 37% college,10% > college. For HLQ part 1 (response scale 1-4/ mean ± SD), scores for "Feeling understood/ supported by healthcare providers (HCP)" (3.46 ± 0.49) were the highest. "Appraisal of health information" (3.09 ± 0.53) were the lowest. For part 2 of the HLQ (response scale 1-5), scores for "Ability to actively engage with HCP" (4.29 ± 0.55) were the highest. "Ability to find good health information" (3.96 ± 0.65) were the lowest. Lower HL scores for "Having sufficient information to manage my health" (OR = 0.103; 95% CI [0.016,0.665]), $p = 0.0169$), and "Navigating the health care system" (OR = 0.091,95% CI [0.009,0.913]),$p = 0.0416$) were more likely to have higher TNM stage. Lower HL scores for "Ability to actively engage with HCP" (b = -22.6098, 95% CI [-42.0702, -3.1494], $p = 0.0237$) had higher ESAS scores. Higher HL scores for "Ability to actively engage with HCP" (OR = 51.516; 95% CI [1.213, 2186.593], $p = 0.0393$) were more likely diagnosed with HCC during screening. Higher HL scores for "Having sufficient information to manage my health" (OR = 15.812; 95% CI [1.150, 217.369], $p = 0.0390$] were more likely in surveillance. **Conclusion:** Lower HL was associated with more advanced HCC and poorer QOL. Higher HL was associated with diagnosis of HCC by screening and were in routine surveillance. This novel data provides opportunities for targeted interventions to address areas of poor HL that could improve HCC screening, outcomes and QOL.

Health literacy questionnaire (HLQ) 9 scale domain scores with UNOS TNM and BCLC staging



Disclosures: Hannah Lee: Nothing to Disclose, Alana Saddic: McKesson: Stock - publicly traded company, Eli Lilly: Stock - publicly traded company, Beomchang Kim: Nothing to Disclose, Priyam Das: Nothing to Disclose, Deborah DiazGranados: Nothing to Disclose, Grant Chin: Nothing to Disclose, Mary Kate Lantzy: Nothing to Disclose, Spencer Rice: Nothing to Disclose, Antara Sarkar: Nothing to Disclose, Richard Sterling: ABIM: GI Specialty Board, Abbott: Grant/Research Support, GSK: Grant/Research Support, HCV Vax: Grant/Research Support, Gilead: Grant/Research Support, Zydus: Grant/Research Support, Vertex: Consultant, Madrigal: Advisor, Gigagen: Grant/Research Support, Atea: Grant/Research Support, Cima Science: Consultant, Celaris: Consultant, GSK: Advisor.

2126 | HETEROGENEOUS PATTERNS OF HEPATIC DECOMPENSATION ACROSS RACIAL AND ETHNIC GROUPS: A PROPENSITY SCORE-MATCHED ANALYSIS OF U.S. ADULTS WITH CIRRHOSIS

Rowan Bandaranaike[1] Samuel Tarwater[2] Travis Rutland[2] Adam Edwards[2] George Nelson[3], [1]Southeast

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Background: Racial and ethnic disparities in chronic liver disease are well described; however, the relative burden of portal hypertensive and decompensation-related outcomes across racial groups after adjustment for comorbidities remains incompletely defined. Prior studies suggest differences in decompensation risk across racial groups, but large propensity score-matched analyses in diverse U.S. populations, including Hispanic and Asian patients, are limited. **Methods:** We performed a retrospective cohort study using a federated electronic health record network (TriNetX). Adults ($\geq$18 years) with cirrhosis were stratified by race/ethnicity (White, Black, Hispanic, Asian). Three pairwise 1: 1 propensity score-matched analyses were conducted (White vs each comparator), adjusting for age and baseline comorbidities including hypertension (I10), type 2 diabetes (E11), chronic hepatitis C (B18.2), obesity (E66), alcohol-associated liver disease (K70.1), and insurance insufficiency (Z59.71). The primary outcome was a composite of portal hypertensive and decompensation-related events within one year. Time-to-event analyses were performed using Kaplan-Meier methods and Cox proportional hazards models. **Results:** A total of 563,625 adults with cirrhosis were identified. After matching, cohorts included White vs Black (n = 62,973/arm), White vs Hispanic (n = 55,720/arm), and White vs Asian (n = 32,828/arm), with good covariate balance. A heterogeneous pattern in outcomes was observed. White patients had higher risk compared with Black (22.4% vs 17.1%; HR 1.38, 95% CI 1.34-1.42; $p < 0.0001$) and Asian patients (37.0% vs 22.5%; HR 2.09, 95% CI 2.02-2.16; $p < 0.0001$), but lower risk compared with Hispanic patients (23.3% vs 25.4%; HR 0.88, 95% CI 0.85-0.90; $p < 0.0001$). Observed differences in outcome rates across comparisons partly reflect cohort-specific matching and exclusion of patients with prevalent decompensation at baseline. Baseline prevalence of decompensation-related diagnoses was higher among White compared with Asian patients (38.6% vs 20.5%), suggesting differences in disease stage at diagnosis. One-year decompensation-free survival was 80.6% (Black), 77.5% (White), 74.5% (Hispanic), and 63.0% (Asian) in matched cohorts. **Conclusion:** In this large propensity score-matched analysis, cirrhosis outcomes varied substantially across racial and ethnic groups without a uniform direction of risk. These findings suggest that factors beyond race alone including differences in disease phenotype, stage at presentation, and underlying etiology, may contribute to these observed disparities. Further studies incorporating detailed etiologic and severity measures are needed to clarify the mechanisms underlying these differences. Race-stratified risk models for cirrhosis decompensation may require etiology-specific calibration.

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2127 | BEYOND SOCIOECONOMIC STATUS: PERSISTENT RACIAL AND ETHNIC DISPARITIES IN CARE ESCALATION AMONG HOSPITALIZED PATIENTS WITH ALCOHOL-ASSOCIATED HEPATITIS

Hassan Sinan[1] Jazmin Mexia Cabrales[1] Philip Juliano[1] Frances Lee[2], [1]Icahn School of Medicine at Mount Sinai / Elmhurst, [2]Icahn School of Medicine at Mount Sinai

Background: Alcohol-associated hepatitis (AH) is a severe manifestation of alcohol-associated liver disease associated with high morbidity, frequent hospitalizations and substantial healthcare utilization. Racial, ethnic, and socioeconomic disparities have been increasingly recognized as key determinants of outcomes in chronic liver disease and alcohol-related conditions, but these disparities remain incompletely characterized. We aim to evaluate the association of race/ethnicity and socioeconomic status (SES) with short and medium-term outcomes among patients hospitalized with AH. **Methods:** We performed a retrospective cohort study of adults hospitalized with AH between January 2022 and January 2026 at a large urban safety-net hospital in a major metropolitan area. Patients with other chronic liver diseases were excluded. Patients were stratified by race/ethnicity and SES, defined by insurance type and ZIP code–based deprivation indices. Demographic, clinical, and laboratory variables reflecting disease severity were extracted at index admission. Primary outcomes included in-hospital and post-discharge clinical events, disease progression, and mortality. **Results:** 740 patients with AH were included. Most were male (91.1%), Hispanic (73.6%), and median age 44 years [IQR 37–52]). 10.1% identified as White, 87% Other and 2.9% Black. Most were insured through Medicaid (75.8%) in the middle-income group (75.3%). 25.8% had cirrhosis with 29.5% severe AH (Maddrey DF

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≥32). Hispanics had higher rates of 30-day readmission (16.7% vs. 10.3%, p = 0.041), ascites (34.7% vs. 25.6%, p = 0.025), esophageal varices (9.9% vs. 4.6%, p = 0.033), and more inpatient (p = 0.003) and ED visits (p < 0.01) in the prior 12 months vs non-Hispanics. No differences in prednisone/prednisolone use were noted. No differences were observed for portal hypertension complications among races. On multivariable logistic regression, Hispanic patients had significantly higher odds of 30-day readmission in the unadjusted model (OR 1.75, 95% CI 1.07–3.01, p = 0.032), but this association was attenuated after adjustment for SES (OR 1.55, 95% CI 0.87–2.87, p = 0.148). No racial differences were noted for 30-day readmission or 90-day mortality. Hispanics had lower odds of ICU admission even after adjustment for SES and clinical factors (OR 0.60, 95% CI 0.40–0.90, p = 0.014). Similarly, Black patients had significantly lower odds of ICU admission compared to non-black even after adjustment for SES (OR 0.17, 95% CI 0.04–0.76, p = 0.02). **Conclusion:** While SES partially explains disparities in healthcare access among Hispanic patients with higher rates of readmissions, disparities in ICU admissions in both Hispanic and black patients persist despite adjusting for SES, suggesting disparities in care escalation. Further studies are needed to better understand the structural and healthcare-system factors contributing to these observed differences.

Table: Baseline characteristics and clinical outcomes in patients with alcohol-associated hepatitis stratified by ethnicity.

	Overall (n=740)	Non-Hispanic or Latin (n=195)	Hispanic or Latin (n=545)	p-value
Baseline demographics, comorbidities and socioeconomic factors				
Age, median [IQR]	44.0 [37.0, 52.0]	47.0 [39.0, 55.5]	43.0 [36.0, 51.0]	**<0.001**
Male, n (%)	674 (91.1)	160 (82.1)	514 (94.3)	**<0.001**
BMI, median [IQR]	26.6 [23.8, 30.1]	25.4 [22.7, 27.9]	27.2 [24.4, 30.9]	**<0.001**
Diabetes, n (%)	135 (18.2)	27 (13.8)	108 (19.8)	0.09
Hypertension, n (%)	114 (15.4)	40 (20.5)	74 (13.6)	**0.03**
Chronic Kidney Disease, n(%)	7 (0.9)	2 (1.0)	5 (0.9)	1
Coronary artery disease, n(%)	12 (1.6)	7 (3.6)	5 (0.9)	**0.03**
Hyperlipidemia, n(%)	66 (8.9)	23 (11.8)	43 (7.9)	0.14
Insurance, n (%)				
Medicaid	561 (75.8)	120 (61.5)	441 (80.9)	
Medicare	10 (1.4)	9 (4.6)	1 (0.2)	
Self-pay	77 (10.4)	17 (8.7)	60 (11.0)	**<0.001**
Commercial	86 (11.6)	48 (24.6)	38 (7.0)	
Income group				
High income	145 (19.9)	68 (35.8)	77 (14.3)	**<0.001**
Middle income	550 (75.3)	116 (61.1)	434 (80.4)	
Low income	35 (4.8)	6 (3.2)	29 (5.4)	
Current Smoker, n(%)	144 (19.5)	58 (29.7)	86 (15.8)	**<0.001**
Ever Smoker, n(%)	242 (46.8)	70 (54.3)	172 (44.3)	0.06
Alcohol use (number of drinks per week), mean (SD)	2.81 (11.21)	3.15 (11.72)	1.85 (9.64)	0.163
Alcohol use disorder, n(%)	372 (50.3)	75 (38.5)	297 (54.5)	**<0.001**
MELD-Na, median [IQR]	12.7 [7.9,22.5]	10.8 [7.7, 22.29]	13.4 [8.07,22.56]	0.31
Maddrey DF, median [IQR]	12.6 [2.2, 36.8]	10.7 [1.2, 38.5]	13.1 [3.9, 38.6]	0.191
Steroid prescribed during admission, n(%)	63 (8.5)	49 (9.0)	14 (7.2)	0.530
Ascites, n (%)	239 (32.3)	50 (25.6)	189 (34.7)	**0.025**
Esophageal varices, n (%)	63 (8.5)	9 (4.6)	54 (9.9)	**0.033**
Portal Hypertension, n(%)	15 (2.0)	1 (0.5)	14 (2.6)	0.14
Hepatic encephalopathy, n (%)	24 (3.2)	2 (1.0)	22 (4.0)	0.07
Short- and medium-term clinical outcomes				
30-day readmission, n (%)	111 (15.0)	20 (10.3)	91 (16.7)	**0.041**
90-day mortality, n (%)	48 (6.5)	15 (7.7)	33 (6.1)	0.530
12-month ED visits, mean (SD)	3.94 (7.85)	3.2 (9.14)	4.2 (7.34)	**<0.001**
12-month inpatient-admissions, mean (SD)	0.63 (1.38)	0.41 (0.92)	0.77 (1.5)]	**0.003**

Disclosures: Hassan Sinan: Nothing to Disclose, Jazmin Mexia Cabrales: Nothing to Disclose, Philip Juliano: Nothing to Disclose, Frances Lee: Nothing to Disclose.

2128 | DEPRESSIVE SYMPTOM SEVERITY IS NOT INDEPENDENTLY ASSOCIATED WITH LIVER FIBROSIS AFTER ADJUSTMENT FOR METABOLIC, BEHAVIORAL, AND SOCIOECONOMIC FACTORS

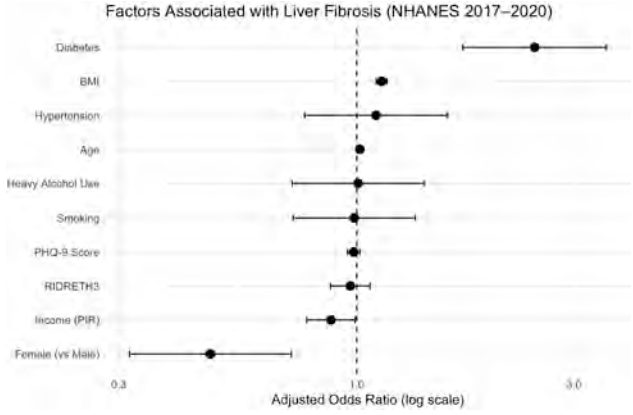
Matthew Solway[1] Nazli Begum Ozturk[2] Ahmet Gurakar[3], [1]Henry Ford Hospital, [2]St. Louis University, [3]Johns Hopkins University

Background: Depression has been proposed to contribute to chronic liver disease through behavioral and metabolic pathways; however, its independent association with liver fibrosis remains uncertain. We evaluated the relationship between depressive symptom severity and liver fibrosis in a nationally representative U.S. cohort, accounting for metabolic, behavioral, and socioeconomic confounders. **Methods:** We performed a cross-sectional analysis of 8318 adults from the NHANES 2017–2020 cycle with available vibration-controlled transient elastography (VCTE) data. Depressive symptoms were assessed using the PHQ-9 as a continuous variable. Liver fibrosis was defined using VCTE-derived liver stiffness (≥8 kPa). Survey-weighted multivariable logistic regression was performed using MEC exam weights, adjusting for age, sex, race/ethnicity, body mass index (BMI), diabetes, hypertension, alcohol use, smoking status, income-to-poverty ratio, and education. A secondary analysis was performed using survey-weighted linear regression to assess the association between depressive symptom severity and continuous fibrosis stage. **Results:** In survey-weighted multivariable logistic regression analysis, depressive symptom severity was not associated with liver fibrosis (OR per 1-point increase in PHQ-9: 0.98, 95% CI 0.95–1.02, p = 0.29). Increasing age was independently associated with higher odds of fibrosis (OR 1.02 per year, 95% CI 1.00–1.03, p = 0.009), while female sex was associated with lower odds compared to males (OR 0.48, 95% CI 0.32–0.72, p = 0.002). Among metabolic factors, higher BMI was strongly associated with fibrosis (OR 1.13 per unit increase, 95% CI 1.10–1.16, p < 0.001), and diabetes was associated with more than two-fold increased odds (OR 2.46, 95% CI 1.71–3.54, p < 0.001). Hypertension was not significantly associated with fibrosis (OR 1.10, 95% CI 0.77–1.58, p = 0.56). Behavioral factors including heavy alcohol use (OR 1.01, 95% CI 0.72–1.41, p = 0.96) and smoking (OR 0.99, 95% CI 0.72–1.34, p = 0.93) were not significantly associated with fibrosis. Higher income-to-poverty ratio was independently associated with lower odds of fibrosis (OR 0.88, 95% CI 0.78–0.99, p = 0.038), while education level was not significantly associated. In complementary linear regression models evaluating fibrosis severity, depressive symptom severity was not associated with fibrosis

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stage (β = −0.0004, SE 0.0011, p = 0.74). Consistent with the primary analysis, higher BMI (β = 0.019, p < 0.001) and diabetes (β = 0.165, p < 0.001) were independently associated with greater fibrosis severity, while female sex was associated with lower fibrosis stage (β = −0.064, p = 0.001). **Conclusion:** In a nationally representative cohort of U.S. adults, depressive symptom severity was not independently associated with liver fibrosis after comprehensive adjustment for metabolic, behavioral, and socioeconomic factors. Fibrosis risk appears to be driven primarily by metabolic disease and social determinants of health rather than depressive symptom burden. These findings suggest that previously observed associations between depression and liver disease may reflect confounding by metabolic and socioeconomic factors rather than a direct effect.



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2129 | BURDEN AND DETERMINANTS OF STIGMATIZATION IN PATIENTS WITH CHRONIC LIVER DISEASE: A CROSS-SECTIONAL STUDY FROM PERU

Daniel Chacón[1] Pedro Montes[2] Hector Pastrana[1] Yadhira Requena[1] Kevin Gutierrez[1] Gunther Coronado[2] Stalin Yance[2] Diego Rosales[2] Alissa Garcia-Reyes[1], [1]Universidad Nacional Mayor de San Marcos, [2]Hospital Nacional Daniel A. Carrión

Background: Stigmatization is increasingly recognized as a major psychosocial burden in patients with chronic liver disease (CLD), negatively impacting quality of life, social functioning, and healthcare engagement. However, data from Latin America remain scarce. We aimed to evaluate the prevalence, domains, and determinants of stigmatization among patients with cirrhosis and chronic liver disease in a tertiary referral center in Peru. **Methods:** We conducted a cross-sectional study including 97 adult patients with chronic liver disease attending a tertiary hospital in Lima, Peru. Demographic and clinical data, including cirrhosis stage, Child-Pugh class, MELD score, and liver disease etiology, were collected. Stigmatization was assessed using a structured questionnaire evaluating multiple domains of perceived and internalized stigma. Positive stigma responses were defined as agreement or strong agreement with questionnaire items. The total stigma burden was calculated as the number of positive responses. Univariate and multivariate analyses were performed to identify factors associated with higher stigma scores **Results:** Mean age was 64.3 ± 9.6 years, and 55.7% had decompensated cirrhosis. The predominant etiology was MASLD (60.8%), followed by alcohol-related liver disease (18.6%). Overall, 95.9% of patients reported at least one stigma-related experience, and the mean stigma score was 6.8 ± 3.8 items.The most frequent stigma-related perceptions were assumptions of prior alcohol misuse (61.9%), perceived personal responsibility for liver disease (53.6%), and negative impact on work capacity (50.5%).The predominant stigma domains included: Patient-blaming perceptions (“people assume I must have been a drinker,” “I am partially responsible for my disease”);Self-stigma and shame (“I feel less competent,” “defective or incomplete”); Social isolation and concealment (“I avoid telling others,” “I avoid public activities”); andOccupational and functional impairment.These findings suggest a substantial burden of both social stigma and internalized stigma, particularly related to alcohol-associated perceptions and functional deterioration.Stigma burden increased according to liver disease severity: Child A: 6.3 ± 4.1Child B: 7.1 ± 4.0Child C: 10.1 ± 4.3 (p = 0.037) Patients with alcohol-related etiologies demonstrated the highest stigma scores (mean 9.0). In multivariate linear regression analysis, alcohol-related liver disease remained independently associated with higher stigma burden (β = 2.39, p = 0.027), whereas MELD score and decompensation status were not independently significant. **Conclusion:** These findings from a Latin American cohort underscore the need for culturally adapted psychosocial interventions and stigma-reduction strategies in hepatology care, particularly for patients with alcohol-associated liver disease and advanced cirrhosis.

Disclosures: Daniel Chacón: Nothing to Disclose, Pedro Montes: Nothing to Disclose, Nothing to Disclose, Hector Pastrana: Nothing to Disclose, Yadhira Requena: Nothing to Disclose, Kevin Gutierrez: Nothing to Disclose, Gunther Coronado: Nothing to Disclose, Stalin Yance: Nothing to Disclose, Diego

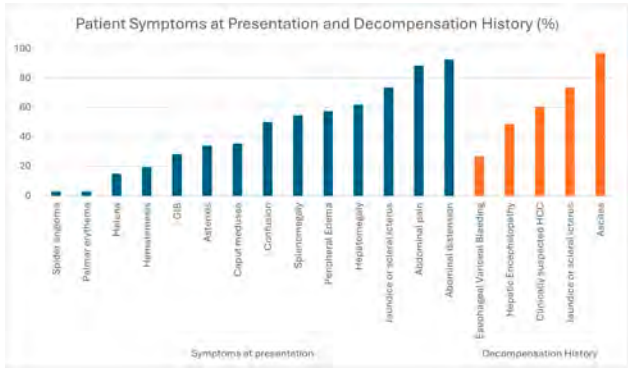
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Rosales: Nothing to Disclose, Alissa Garcia-Reyes: Nothing to Disclose.

2130 | BURDEN OF DECOMPENSATED CIRRHOSIS IN A TERTIARY REFERRAL CENTER IN CAMEROON

Maitri Patel[1] Ikechukwu Eze[1] Mathurin Kowo[2] Claudia Suiru[2] Kasopefoluwa Oguntuyo[1] Sofia Jakab[1], [1]Yale University, [2]University Teaching Hospital of Yaounde

Background: There is limited systematic assessment of cirrhosis healthcare delivery in sub-Saharan Africa. The Pathways to Cirrhosis Care in Cameroon Project seeks to characterize barriers, facilitators, and access patterns for patients presenting with cirrhosis at a large tertiary care center in Yaoundé, Cameroon. **Methods:** We performed a retrospective analysis of all adult hepatology hospitalizations from 2023-2025. We collected data from handwritten charts on demographics, presenting symptoms, liver disease etiology, decompensation, recommended interventions, and medications. Due to extensive missing data, this study was not powered to conduct hypothesis testing and focused on descriptive assessment of current practices. **Results:** Of the 138 patients identified in the hospital registry as admissions for cirrhosis management, only 68 (49%) charts could be physically located for data extraction. Most patients were male (51, 75%), and traveled greater than 30 minutes to reach care (38, 58%). Viral hepatitis and alcohol-associated liver disease were found in most patients: hepatitis B (38, 56%), hepatitis C (23, 34%), alcohol (27, 40%), and mixed (25, 37%). Cirrhosis diagnosis was based on clinical criteria (exam, laboratory, and ultrasound data). Cirrhosis decompensation was present in almost all patients: ascites (66, 97%), jaundice (50, 74%), hepatic encephalopathy (33, 49%), variceal bleeding (18, 28%). There was more than one decompensation in 38 patients (56%). Hepatocellular carcinoma was suspected by ultrasound and elevated alpha-fetoprotein in 41 patients (60%), with confirmatory contrast study performed in 7 patients. Within one year from presentation, 37 patients died (54%).Standardized liver disease severity metrics were inconsistently collected: Child-Turcotte-Pugh (CTP) score could be calculated in 31 (46%), and MELD 3.0 score in 11 (16%) patients. Endoscopy was completed in 14 of 25 (56%) of patients referred; 9 of 18 (50%) patients with known or suspected varices were prescribed a beta-blocker. Anti-viral therapy was prescribed in 20 of 38 HBV patients (53%). No patients underwent liver transplantation (which would entail international travel). **Conclusion:** Patients with cirrhosis admitted for tertiary care in Cameroon frequently presented with multiple cirrhosis decompensations or liver cancer and had high mortality, highlighting the need for earlier linkage to hepatology care especially given low transplant availability. Gaps in documentation and evaluation limited standardized disease assessment and stratification. Low follow-through with recommended care reflected barriers in care coordination, patient retention, and treatment access. These findings identify areas of improvement across the cirrhosis care continuum, including medical record infrastructure, management pathways, and access to treatment.



Disclosures: Maitri Patel: Nothing to Disclose, Ikechukwu Eze: Nothing to Disclose, Mathurin Kowo: Nothing to Disclose, Claudia Suiru: Nothing to Disclose, Kasopefoluwa Oguntuyo: Nothing to Disclose, Sofia Jakab: Nothing to Disclose.

2131 | DIFFERENCES IN TIPS VS TRANSPLANT: THE IMPACT OF SOCIAL FACTORS ON TREATMENT PATHWAYS IN PATIENTS WITH ESLD

Urania Argueta[1] Diana Jimenez-Briseno[2] Jessica Menjivar Cruz[2] Arzoo Manandhar[2] Shenise Gilyard[2], [1]David Geffen School of Medicine, UCLA, [2]Ronald Reagan UCLA Medical Center, Interventional Radiology

Background: Liver transplantation (LT) is one of the mainstays of treatment for advanced chronic liver disease. Bridging therapies, like placement of a transjugular intrahepatic portosystemic shunt (TIPS), are used to control sequelae of portal hypertension such as ascites and varices. However, health disparities affect disease management, particularly among racial minorities. Studies show that Black and Latino patients are less likely to undergo TIPS placement and LT compared to white patients. Our study aims to characterize the clinical outcomes of patients with ESLD in the US and assess the effect of social determinants of health on treatment pathways. **Methods:** This is a retrospective cross-sectional study analyzing data from the National Inpatient Sample (NIS) from 2018-2022. The NIS is an all-payer US inpatient database representing 20% of US

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hospitalizations. For all years, each individual hospitalization is deidentified and carries demographic details, including age, sex, race/ethnicity, insurance provider, and zip code-based income quartile. Our study selected patients across these years admitted with cirrhosis and/or sequelae of portal hypertension, and further stratified clinical outcomes per each cohort according to year. Admissions were included if they contained at least 1 cirrhosis-related International Statistical Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) code and/or at least 1 ICD-10-CM code related to ascites or varices. Variables were analyzed using Odds Ratio. **Results:** Among 155,413 hospitalizations analyzed between 2018-2022, patients were further stratified by ethnicity, zip code-based income quartile, insurance provider. 64% identified as QWhite, 7.7% as Black, 18.5% as Latino, 1.9% as Asian or Pacific Islander, 1.9% as Native American and 3.3% as Other. Most White patients presented with Medi-Care as their primary health insurance, while most Black, Latino, and Asian patients presented with Medicaid as their primary health insurance. By 2022, Black patients were had an increased risk of in-hospital mortality compared to White patients (OR, 1.72; 95% CI, 1.44-2.04) while Latino patients had a decreased risk of in-hospital mortality (OR, 0.79; 95% CI, 0.68-0.92). Black patients are also less likely to undergo TIPS placement compared to White patients (OR, 0.52; 95% CI, 0.37-0.73). Our study suggests there is additional work to be done to ameliorate disparities in healthcare outcomes. **Conclusion:** Black patients were less likely to receive care for decompensated cirrhosis. Many prior studies have suggested healthcare access as a driver for poor health outcomes, however, a majority of patients were on Medicaid or Medi-Care which suggests there may be other social factors driving disparities.

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2132 | STAGNANT HOSPICE AND HOME-BASED END-OF-LIFE CARE UTILIZATION AMONG PATIENTS WITH END-STAGE LIVER DISEASE IN THE UNITED STATES, 2018–2024: A POPULATION-BASED ANALYSIS

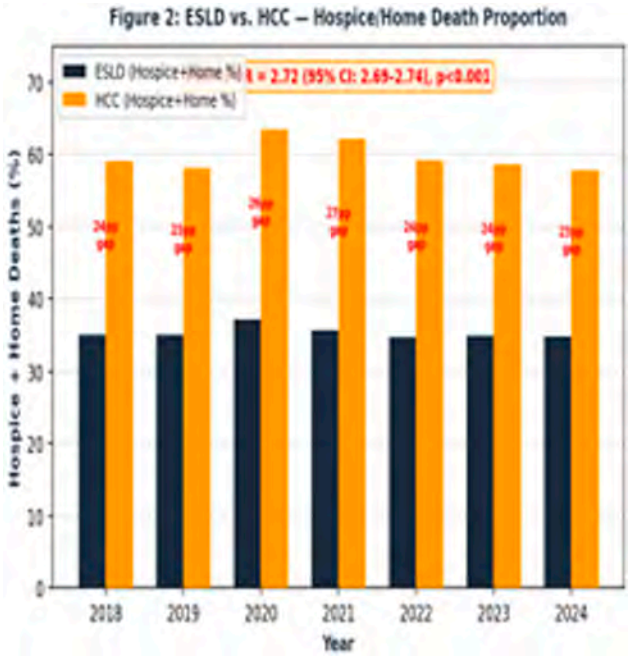
Saba Irfan[1] Javeria Sana[2], [1]University of Texas Rio Grande Valley, [2]Rawalpindi Medical University

Background: End-stage liver disease (ESLD) carries high symptom burden and poor prognosis comparable to many cancers, yet palliative and hospice care utilization remains understudied at the population level. Nationally, ESLD-related deaths increased 28.5% from 85,026 in 2018 to a peak of 109,245 in 2021, accumulating 697,580 deaths over the 7-year study period.Recent ACG guidelines recommend goals-of-care discussions for patients with acute-on-chronic liver failure, yet the extent to which ESLD patients access hospice services nationally is unknown. We aimed to characterize temporal trends in place of death for ESLD, identify racial/ethnic and demographic disparities, and compare hospice utilization with hepatocellular carcinoma (HCC). **Methods:** We conducted a retrospective cross-sectional analysis of 697,580 adults ($\geq$ 25 years) who died from ESLD (ICD-10: K70.3, K72.0-K72.9, K74.0-K74.6, K76.6-K76.7) between 2018 and 2024 using the CDC WONDER Multiple Cause of Death database. HCC deaths (C22.0-C22.9; N = 226,380) served as comparators. Primary outcome was proportion of deaths occurring in hospice facilities or decedent's home. Cochran-Armitage trend tests, chi-square analyses, and odds ratios with 95% CIs were calculated. **Results:** ESLD mortality increased 28.5% from 2018 (85,026) to 2021 (109,245), stabilizing at 103,923 by 2024. Only 35.3% of ESLD deaths occurred in home-based settings (home or hospice facility) compared with 59.7% of HCC deaths (OR = 2.72; 95% CI: 2.69–2.74; $p < 0.001$). The hospice +home proportion remained unchanged over seven years (35.0% in 2018 vs. 34.8% in 2024; $p = 0.514$ for linear trend), while hospital inpatient deaths dominated at 50.1%. Significant disparities were observed: Black patients had the lowest home-based death proportion (26.1% vs. White 36.7%; $\chi^2 = 849.12$; $p < 0.001$); Hispanic patients showed a declining trend (32.9%→30.8%); females were lower than males (33.6% vs. 36.4%; $\chi^2 = 581.92$; $p < 0.001$); younger patients aged 25–34 had half the rate of those $\geq$ 85 years (22.9% vs. 42.1%); and the Northeast (29.2%) significantly lagged behind the South (38.3%; $\chi^2 = 2,948.83$; $p < 0.001$). **Conclusion: :** ESLD mortality increased 28.5% from 2018 (85,026) to 2021 (109,245), stabilizing at 103,923 by 2024. Only 35.3% of ESLD deaths occurred in home-based settings (home or hospice facility) compared with 59.7% of HCC deaths (OR = 2.72; 95% CI: 2.69–2.74; $p < 0.001$). The hospice+home proportion remained unchanged over seven years (35.0% in 2018 vs. 34.8% in 2024; $p = 0.514$ for linear trend), while hospital inpatient deaths dominated at 50.1%. Significant disparities were observed: Black patients had the lowest home-based death proportion (26.1% vs. White 36.7%; $\chi^2 = 849.12$; $p < 0.001$); Hispanic patients showed a declining trend (32.9%→30.8%); females were lower than males (33.6% vs. 36.4%; $\chi^2 = 581.92$; $p < 0.001$); younger patients aged 25–34

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had half the rate of those ≥85 years (22.9% vs. 42.1%);

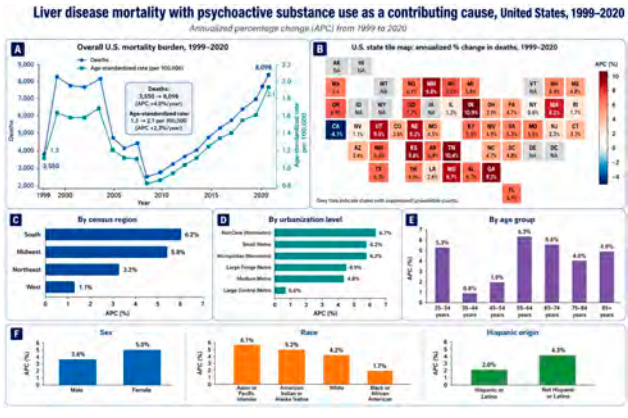


Disclosures: Saba Irfan: Nothing to Disclose, Javeria Sana: Nothing to Disclose.

2133 | ◆ RISING U.S. MORTALITY FROM LIVER DISEASE WITH PSYCHOACTIVE SUBSTANCE USE AS A CONTRIBUTING CAUSE, 1999–2020: GEOGRAPHIC, RURAL–URBAN, AND DEMOGRAPHIC DISPARITIES

Mounika Kotte[1] Jagadish Koyi[2] Serene Sara John[3] Sri Ram Charan Gundapaneni[4] Nayanika Tummala[5] Digantkumar Patel[6] Pragathi Munnangi[7] Hardik Dineshbhai Desai[8], [1]Prime south consortium, [2]Integris Health, Oklahoma City, Oklahoma. USA. 73112, [3]Detroit medical center, Detroit, Michigan, 48201, [4]UCF/HCA Florida Ocala Hospital, Ocala, Florida, United States, 34471, [5]NYMC St Mary's and St Clare's, [6]Springfield Clinic, Springfield, IL, USA, [7]BronxCare Health System , Bronx , New York - 10457, [8]AB Plus Multispecialty Hospital, Ahmedabad, Gujarat, India

Background: Mortality involving liver disease with psychoactive substance use as a contributing cause is an emerging intersection of hepatology, addiction medicine, and population health, but its long-term U.S. patterns across geography, urbanicity, and sociodemographic groups remain insufficiently defined. **Methods:** Using CDC WONDER Multiple Cause of Death data, we analyzed U.S. deaths from 1999–2020 with liver disease as the underlying cause and psychoactive substance use as a contributing cause. Outcomes included deaths, crude rates, and age-standardized rates per 100,000. Annualized percentage change (APC) from 1999–2020 was calculated as compounded yearly change for overall burden, census region, state, 2013 urbanization category, 10-year age group, sex, race, and Hispanic origin. **Results:** National deaths increased from 3,550 in 1999 to 8,098 in 2020, a 128% increase and APC of +4.0%/year. The crude rate rose from 1.3 to 2.5 per 100,000, and the age-standardized rate increased from 1.3 to 2.1 per 100,000 (APC +2.3%/year), indicating that growth was not explained only by population aging. Regional APC in deaths was highest in the South (+6.2%/year; 865 to 3,057 deaths) and Midwest (+5.8%/year; 638 to 2,095), followed by the Northeast (+3.2%/year) and West (+1.1%/year). State-level APC ranged from −4.1%/year in California to +10.9%/year in Indiana, +10.4%/year in Tennessee, +9.8%/year in Minnesota and Kansas, and +9.2%/year in Nebraska and Georgia. By urbanization, increases were greatest in noncore nonmetro (+6.7%/year; 211 to 823 deaths), small metro (+6.2%/year), and micropolitan areas (+6.2%/year), compared with +0.6%/year in large central metros. By age, APC was highest in adults 55–64 years (+6.3%/year; 817 to 2,950 deaths), 65–74 years (+5.6%/year), and 25–34 years (+5.3%/year). Female deaths increased faster than male deaths (+5.0% vs +3.6%/year), although 2020 deaths remained higher in males (5,467 vs 2,631). Among racial groups, APC was highest in Asian or Pacific Islander (+6.1%/year) and American Indian/Alaska Native populations (+5.2%/year); non-Hispanic deaths increased faster than Hispanic deaths (+4.3% vs +2.0%/year). **Conclusion:** U.S. mortality involving liver disease and psychoactive substance use rose markedly from 1999–2020, with disproportionate growth in the South, Midwest, rural/nonmetro communities, mid-to-older adulthood, females, and selected racial groups. These findings support targeted prevention, earlier substance-use treatment integration into liver care, and regionally tailored public health strategies.



Disclosures: Mounika Kotte: Nothing to Disclose, Jagadish Koyi: Nothing to Disclose, Serene Sara John: Nothing to

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Disclose, Sri Ram Charan Gundapaneni: Nothing to Disclose, Nayanika Tummala: Nothing to Disclose, Digantkumar Patel: Nothing to Disclose, Pragathi Munnangi: Nothing to Disclose, Hardik Dineshbhai Desai: Nothing to Disclose.

2134 | ◆ BEYOND MASLD: PREVALENCE AND INDEPENDENT PREDICTORS OF ADVANCED FIBROSIS BY HISPANIC ETHNICITY ACROSS THE FULL STEATOTIC LIVER DISEASE SPECTRUM IN ADULTS WITH OVERWEIGHT AND OBESITY

Monica Tincopa[1] Ricki Bettencourt[2] Seema Singh[2] Egbert Madamba[2] Lisa Richards[1] Rohit Loomba[1], [1]University of California, San Diego, [2]UCSD

Background: Hispanic/Latinx adults are disproportionately affected by metabolic dysfunction-associated steatotic liver disease (MASLD), yet the full spectrum of steatotic liver disease (SLD) — including MetALD and alcohol-associated liver disease (ALD) — remains poorly characterized in this population. Critically, whether Hispanic ethnicity is independently associated with advanced fibrosis (AF) across SLD after accounting for metabolic and socioeconomic risk factors is an important knowledge gap. We determined SLD prevalence, fibrosis burden and predictors of AF by Hispanic ethnicity in a prospective cohort of adults with overweight and obesity undergoing MRI phenotyping. **Methods:** This is a cross-sectional analysis of prospectively enrolled adults with overweight and obesity [body mass index (BMI) ≥ 25 kg/m^2]) from primary care and community settings. Participants underwent laboratory testing, vibration controlled transient elastography (VCTE) and MR elastography (MRE) with proton density fat fraction (PDFF). Alcohol use was assessed with AUDIT-C, Skinner Lifetime Drinking History and phosphatidylethanol (PEth).Participants were placed in SLD subcategories based on validated self-reported alcohol measures and AASLD definitions. At risk-MASH was defined among those with liver biopsy (N = 106). AF was defined as liver stiffness measurement (LSM) on MRE ≥ 3.63 kPa or ≥ 12 kPa on VCTE. Multivariate logistic regression identified independent predictors of AF in those with SLD. **Results:** The cohort included 989 individuals with a median (IQR) age of 53 yrs (19), 52% female, 38.5% Hispanic (N = 381), 23% had diabetes with a mean (± SD) BMI of 32.3 kg/m^2 (± 5.8). Compared to non-Hispanic participants, Hispanic participants: were younger, had higher BMI, MRI-PDFF, and triglycerides; lower alcohol consumption, income and formal education. Prevalence in Hispanic compared to non-Hispanic adults was 75% vs 67.5% for SLD, 68% vs 59.1% for MASLD, 48.9% vs 44.1% for at risk MASH, 4.5% vs 5.3% for MetALD, and 2.1% vs 3.1% for ALD, respectively. AF was significantly more prevalent among Hispanic vs non-Hispanic adults (8.7% vs. 4.4%, p < 0.01) (**Figure**). AF was independently associated with age, Hispanic ethnicity (OR 2.19, p = 0.04), diabetes, and ALT (**Table**). **Conclusion:** In a large, prospective cohort of adults with overweight and obesity who underwent MRI phenotyping, SLD was significantly more prevalent and severe in Hispanic compared to non-Hispanic adults. Despite lower alcohol consumption, Hispanic adults had twice the prevalence of AF compared to non-Hispanic adults. Hispanic ethnicity remained an independent predictor of AF after adjustment for metabolic and socioeconomic factors. These findings highlight the urgent need for targeted, real-world SLD screening and risk stratification strategies in Hispanic adults.

Figure. Prevalence and Staging of SLD by Hispanic Ethnicity

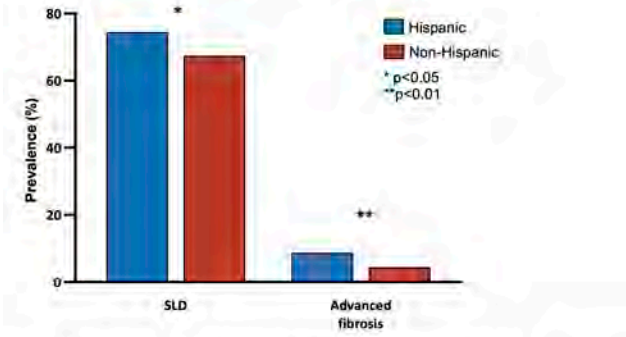


Table. Logistic regression for predictors of advanced fibrosis in those with SLD

Variable	Univariate OR (95% CI)	p-value	Multivariate OR (95% CI)	p-value
Age	1.04 (1.01-1.07)	**0.003**	1.06 (1.03-1.09)	**0.0006**
Female	2.29 (1.21-4.35)	**0.01**	1.96 (0.93-4.14)	0.08
Hispanic ethnicity	2.22 (1.23-4.00)	**0.008**	2.19 (1.03-4.71)	**0.04**
Obesity	1.96 (0.96-4.00)	0.06	--	--
T2DM	4.00 (2.22-7.23)	**<0.0001**	2.61 (1.33-5.17)	**0.005**
TG>150	1.08 (0.59-1.95)	0.60	--	--
Low HDL	1.49 (0.83-2.69)	0.18	--	--
Positive PEth	0.58 (0.24-1.41)	0.23	--	--
ALT (per 10)	1.15 (1.08-1.23)	**<0.0001**	1.25 (1.15-1.35)	**<0.0001**
MRI-PDFF	0.98 (0.94-1.03)	0.23	--	--
< HS education*	4.86 (2.35-10.07)	**<0.0001**	2.09 (0.83-5.24)	0.12

*Less than high school education used as the primary social determinant of health variable due to collinearity with other social determinant of health variables and education having the strongest difference in prevalence between Hispanic and non-Hispanic participants
— Variable not carried forward in multivariate model (univariate p>0.05).
ALT, alanine aminotransferase; CI, confidence interval; HDL, high-density lipoprotein; HS, high school; MRI-PDFF, magnetic resonance imaging proton density fat fraction; OR, odds ratio; PEth, phosphatidylethanol; T2DM, type 2 diabetes mellitus; TG, triglycerides.

Disclosures: Monica Tincopa: Nothing to Disclose, Nothing to Disclose, Ricki Bettencourt: Nothing to Disclose, Seema Singh: Nothing to Disclose, Egbert Madamba: Nothing to Disclose, Lisa Richards: Nothing to Disclose, Rohit Loomba: Eli Lilly and Company: Consultant, 89bio: Consultant, Aardvark Therapeutics: Consultant, Altimmune: Consultant, Alnylam/Regeneron: Consultant, Amgen: Consultant, Arrowhead Pharmaceuticals: Consultant, AstraZeneca: Consultant, Bristol Myers Squibb: Consultant, CohBar:

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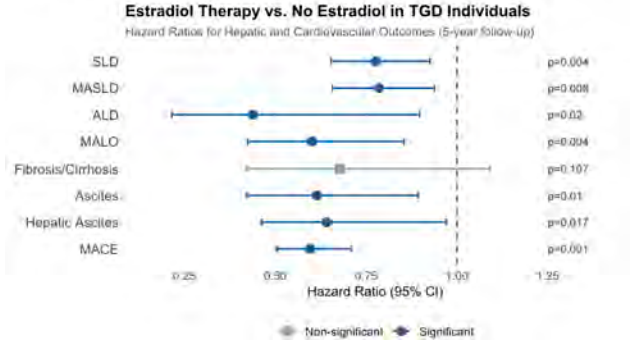
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2135 | ◆ ESTRADIOL THERAPY IS ASSOCIATED WITH REDUCED RISK OF LIVER DISEASE AND CARDIOVASCULAR EVENTS IN TRANSGENDER AND GENDER DIVERSE INDIVIDUALS: A PROPENSITY-MATCHED COHORT STUDY

Ximena Parraga[1] Kaanthi Rama[1] Hyundam (Dami) Gu[1] Omar Albhaisi[1] Juan Pablo Arab[1] Hanna Blaney[1],
[1]Virginia Commonwealth University

Background: Sex hormones are known modulators of hepatic metabolism, inflammation, and fibrosis pathways, but their role in liver disease progression remains largely unexplored. Yet the long-term hepatic effects of estradiol-based gender-affirming hormone therapy in transgender and gender diverse (TGD) individuals remain poorly characterized, representing a critical gap in clinical practice. We aimed to evaluate the impact of estradiol therapy on hepatic and cardiometabolic outcomes in this population. **Methods:** A retrospective cohort study was conducted using the TriNetX Global Collaborative Network between January 2010 and January 2020, with outcomes followed over 5 years. TGD individuals were identified using ICD-10 F64 codes (gender incongruence); patients with viral hepatitis, autoimmune hepatitis, and other competing chronic liver diseases were excluded. Individual gender identity could not be further characterized within the dataset. The exposure cohort included TGD patients on estradiol (n = 10,441) and the comparator cohort TGD patients not receiving estradiol (n = 10,441). The comparator cohort was not restricted to exclude individuals receiving testosterone or other gender-affirming therapies. Outcomes included SLD, MASLD, ALD, fibrosis/cirrhosis, MALOs, ascites, and MACE.Kaplan-Meier survival analyses with HRs and log-rank p-values were reported. **Results:** After 1: 1 propensity score matching, both cohorts comprised 10,441 well-balanced TGD individuals. Estradiol therapy was associated with statistically significant risk reductions across most hepatic and cardiovascular outcomes over 5 years. The strongest effect was observed for MACE (214 vs. 342 events; HR 0.596, 95% CI 0.503–0.708, p < 0.001), followed by ALD (11 vs. 24 events; HR 0.439, p = 0.020), MALO (51 vs. 81 events; HR 0.601, p = 0.004), ascites (45 vs 70 events; HR 0.614, p = 0.010), MASLD (221 vs. 268 events; HR 0.785, p = 0.008), and SLD (231 vs. 238 events; HR 0.777, p = 0.004). Absolute risk differences were small, reflecting the young median age of the cohort. Fibrosis and cirrhosis showed a protective but non-significant trend (29 vs. 41 events; HR 0.678, p = 0.107). **Conclusion:** Estradiol therapy demonstrated a consistent hepatoprotective and cardiometabolic signal in TGD individuals across 5 years. These preliminary real-world findings warrant further investigation in older populations with established metabolic risk factors.

Figure 1. Hazard Ratios for Hepatic and Cardiovascular Outcomes Among TGD Individuals Receiving Estradiol Therapy vs. No Estradiol (5-Year Follow-Up).



Disclosures: Ximena Parraga: Nothing to Disclose, Kaanthi Rama: Nothing to Disclose, Hyundam (Dami) Gu: Nothing to Disclose, OMAR ALBHAISI: Nothing to

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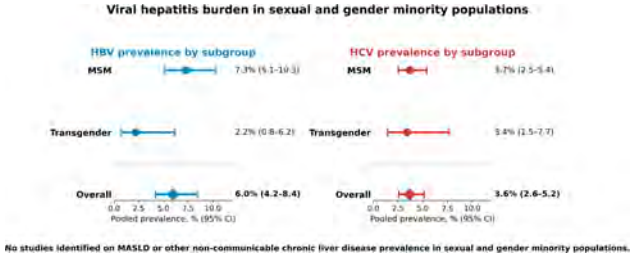
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Disclose, Juan Pablo Arab: Nothing to Disclose, Hanna Blaney: Nothing to Disclose.

2136 | CHRONIC LIVER DISEASE IN SEXUAL AND GENDER-DIVERSE MINORITY POPULATIONS: A GLOBAL SCOPING REVIEW AND META-ANALYSIS HIGHLIGTHING CRITICAL EVIDENCE GAPS BEYOND VIRAL HEPATITIS

Felice Cinque[1] Carlos Myers-Ascencio[2] Sahar Saeed[3] Carla Coffin[4] Radin Pakseresht[5] Duy Dinh[3] Genevieve Gore[2] Jihoon Lim[6] Rosa Lombardi[7] Bertrand Lebouche[8] Giovanni Guaraldi[9] Keyur Patel[10] Tzu-Hao Lee[11] Giada Sebastiani[2], [1]University of Milan, [2]McGill University, [3]Queen's University, [4]University of Calgary, [5]University of Western Ontario, [6]Research Institute of the McGill University Health Centre, [7]University of the Study of Milan, [8]McGill University Health Centre, [9]University of Modena and Reggio Emilia, [10]University of Toronto, [11]Baylor College of Medicine

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) and other non-communicable chronic liver diseases (CLDs) are major global health challenges, yet their burden among sexual and gender minority populations remains poorly characterized. These populations disproportionately experience adverse social and structural determinants of health—including stigma, barriers to inclusive healthcare, mental health disorders, and substance use—which may amplify liver disease risk. Existing data focus on viral hepatitis among men who have sex with men (MSM), with limited representation of transgender, lesbian, and non-binary populations. We conducted a global scoping review and meta-analysis to characterize the epidemiology of non-communicable and viral CLDs across sexual and gender minority populations. **Methods:** This scoping review and meta-analysis was conducted in accordance with PRISMA guidelines. Six electronic databases (MEDLINE, Embase, CENTRAL, Web of Science, Global Health, and Global Index Medicus) were systematically searched from inception through May 31, 2025. Two reviewers independently screened titles, abstracts and full texts, and performed standardized data extraction. Pooled prevalence estimates were calculated using random effects models. **Results:** Among 6,459 records screened for non-communicable CLDs and viral hepatitis in sexual and gender minority populations, 117 studies met inclusion criteria. No study reported prevalence data on MASLD or other non-communicable CLDs. In addition, lesbian and non-binary populations were almost entirely absent from the literature. Across 63 studies, pooled hepatitis B virus (HBV) prevalence was 6.0% (95% CI 4.2–8.4), with the highest observed in Africa (8.4%; 95% CI 4.8–14.1) and the lowest in Asia/Pacific (3.2%; 95% CI 1.4-7.1). HBV prevalence was significantly higher among MSM (7.3%) than transgender individuals (2.2%). Across 88 studies, pooled hepatitis C virus (HCV) prevalence was 3.6% (95% CI 2.6–5.2), with comparable estimates across geographic regions and between MSM and transgender populations (Figure). Meta-regression analyses showed a gradual decline in HBV and HCV prevalence since the 1980s. Funnel plot asymmetry showed possible small-study effects for HBV, whereas no evidence of publication bias was observed for HCV. **Conclusion:** There is a profound global evidence gap regarding MASLD and other non-communicable CLDs in sexual and gender minority populations, especially in lesbian and non-binary individuals. Despite declining viral hepatitis prevalence over time, HBV and HCV continue to disproportionately affect MSM and transgender populations. These findings highlight an urgent need for inclusive liver disease research and equitable prevention, screening, and care strategies for MASLD and non-communicable CLDs in historically underserved sexual and gender minority populations.



Disclosures: Felice Cinque: Nothing to Disclose, Carlos Myers-Ascencio: Nothing to Disclose, Sahar Saeed: Novo Nordisk: Consultant, Carla Coffin: Gilead: Grant/Research Support, GSK: Grant/Research Support, Janssen: Grant/Research Support, Gilead (paid to the University of Calgary): Consultant, Roche (paid to the University of Calgary): Consultant, GSK: Consultant, Gilead (paid to the University of Calgary): Speaking and Teaching, GSK (paid to the University of Calgary): Speaking and Teaching, Ausperbio: Funds Paid to the University of Calgary, Vir Pharmaceuticals: Funds Paid to the University of Calgary, Radin Pakseresht: Nothing to Disclose, Duy Dinh: Nothing to Disclose, Genevieve Gore: Nothing to Disclose, Jihoon Lim: Nothing to Disclose, Rosa Lombardi: Nothing to Disclose, Bertrand Lebouche: Merck Canada: Speaking and Teaching, Gilead: Speaking and Teaching, ViiV

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healthcare: Speaking and Teaching, Gilead: Grant/Research Support, Merck: I score study and core set study managed by RI-MUHC, ViiV: PIVHOT progra mfro patients managed by RI-MUHC, Merck Canada: Grant/Research Support, Giovanni Guaraldi: Nothing to Disclose, Keyur Patel: Novo-Nordisk: Consultant, Gilead Sciences: Consultant, Merck: Consultant, Resalis: Advisor, Boehringer Ingelheim: Advisor, Inipharm: Advisor, Tzu-Hao Lee: Nothing to Disclose, Giada Sebastiani: Novo Nordisk: Consultant, Abbvie: Speaking and Teaching, Merck: Consultant, Gilead: Speaking and Teaching, Eli Lilly: Consultant, GSK: Advisor, Novo Nordisk: Consultant, Novo Nordisk: Grant/Research Support, Lupin: Speaking and Teaching, Gilead: Advisor, Boheringer Ingelheim: Speaking and Teaching, Echosens: Advisor.

2137 | RACE AND ETHNICITY REPORTING AND REPRESENTATION IN CONTEMPORARY LIVER DISEASE CLINICAL TRIALS: A SYSTEMATIC REVIEW AND BENCHMARKING ANALYSIS

Meena Tadros[1] Yiwei Hang[1] Nicol Tugarinov[1] Claudio Salinas[1] Anna Goebel[1] Nadim Mahmud[2], [1]University of Pennsylvania, [2]Hospital of the University of Pennsylvania

Background: Racial and ethnic disparities are well established in chronic liver disease (CLD). Representation within clinical trials remains poorly characterized. Prior studies have focused primarily on whether race or ethnicity was reported, without evaluating if enrolled populations reflect underlying disease epidemiology. We performed a systematic review of contemporary liver disease clinical trials to assess trends in race/ethnicity reporting and quantify representation relative to disease-specific population benchmarks. **Methods:** We utilized Medical Subject Headings (MeSH) to search PubMed for English language randomized controlled trials (RCTs) published from 2013 to 2024 across major categories including metabolic dysfunction-steatotic associated liver disease (MASLD), cirrhosis/transplant, hepatocellular carcinoma (HCC), and non-MASLD CLD. Sample size, racial and ethnic reporting and composition, study location, and funding source were extracted. Race and ethnicity reporting rates were evaluated over time via linear regression and stratified by US versus non-US studies. Among US studies with race/ethnicity data, representation was assessed using participation-to-prevalence ratios (PPRs), defined as the observed trial proportion divided by disease-specific epidemiologic benchmarks. PPR < 0.8 was considered underrepresentation. **Results:** A total of 1,593 RCTs were included, of which 415 (26.1%) reported race and 225 (14.1%) reported ethnicity. Studies reporting race were larger (median 150 vs. 80 participants, $p < 0.001$), more often US-based (48.4% vs. 4.6%, $p < 0.001$), and more commonly industry-funded (72.3% vs. 24.2%, $p < 0.001$). Race reporting was higher in US versus non-US studies over time (**Panel A**); ethnicity reporting increased modestly over time only among US studies (β 0.019/year, 95% CI 0.002-0.036; $p = 0.025$). Among US studies, Black participants were consistently underrepresented across disease categories, with median PPRs often below 0.8. Hispanic underrepresentation was most pronounced in HCC trials (**Panel B**). White participants were generally proportionally represented or overrepresented, while Asian representation varied greatly by disease category. Temporal analyses showed persistent underrepresentation of Black participants over time despite modest improvements in reporting practices (**Panel C**). **Conclusion:** Contemporary CLD trials often do not report participant race/ethnicity. Among studies reporting race and ethnicity, participants do not reflect disease burden. Our benchmarking analysis using CLD-specific epidemiology shows that Black participants are underrepresented in CLD trials relative to their disease burden. Asian participants are underrepresented most in cirrhosis/transplant trials, while Hispanic participants are often underrepresented in HCC trials. This disease burden-specific analysis highlights critical inequities.

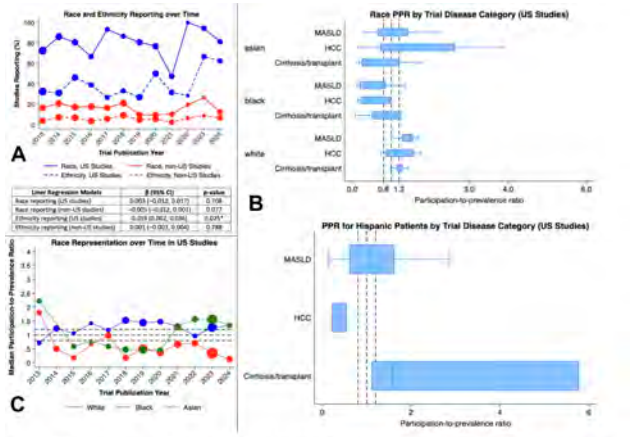


Figure 1. Linear regression modeling for reporting of race/ethnicity (A); Participation-to-Prevalence Ratio (PPR) for participants stratified by race and ethnicity (B); Time based trends for PPR by race (C).

Disclosures: Meena Tadros: Nothing to Disclose, Yiwei Hang: Nothing to Disclose, Nicol Tugarinov: Nothing to Disclose, Claudio Salinas: Nothing to Disclose, Anna Goebel: Nothing to Disclose, Nadim Mahmud: Nothing to Disclose.

2138 | HEPATITIS B SCREENING GAPS AMONG FOREIGN-BORN ADULTS IN THE UNITED STATES: A NATIONALLY REPRESENTATIVE PRE-GUIDELINE BASELINE USING A NATIONAL NUTRITION SURVEY, 2013–2020

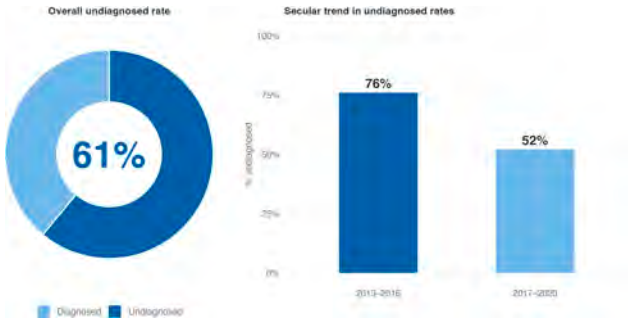
Rakshana Ravichandran[1] Ravi Patel[1] Aditya Kohli[1] Keeranmayee Mishra[2] Sonu Dhillon[3], [1]Trinity Health

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Oakland/wayne State School Of Medicine, [2]Trinity Health,Oakland/Wayne State University Program, [3]University of Illinois College of Medicine Peoria

Background: Hepatitis B virus (HBV) infection disproportionately affects foreign-born individuals from high-endemicity regions, yet the proportion living with undiagnosed infection in the United States remains unknown. In March 2020, the U.S. Preventive Services Task Force (USPSTF) expanded HBV screening to adults at increased risk, including foreign-born persons from countries with hepatitis B surface antigen (HBsAg) prevalence ≥2%. Nationally representative estimates of undiagnosed HBV in this population prior to guideline expansion are lacking. **Methods:** We analyzed National Health and Nutrition Examination Survey (NHANES) 2013–March 2020 pre-pandemic cycles. Adults ≥18 years were stratified by nativity (DMDBORN4). HBV infection was defined as HBsAg positivity (LBDHBG), consistent with chronic infection at the population level though acute infection cannot be excluded. Undiagnosed infection was defined as HBsAg positivity without self-reported prior diagnosis (HEQ010). Secular trends were examined across 2013–2016 and 2017–2020. Univariable logistic regression was used to explore predictors of undiagnosed status. All analyses incorporated complex survey design weights to account for NHANES sampling methodology. **Results:** Among 20,624 adults, 6,108 (30%) were foreign-born; 393 lacked HBsAg data and were excluded. Of 88 HBsAg-positive foreign-born adults, 87 comprised the final analytic sample. HBsAg prevalence was 1.24% (SE 0.0017). Of HBsAg-positive participants, 61% were undiagnosed, representing an estimated 313,000 undiagnosed individuals nationally (95% CI 202,000–425,000). Undiagnosed rates declined from 76% (2013–2016) to 52% (2017–2020), predating the USPSTF update and likely reflecting secular community awareness trends. Absence of insurance (OR 1.75), lack of usual care (OR 1.85), and non-Asian race/ethnicity (OR 2.22) showed trends toward higher odds of undiagnosed infection; no predictor reached statistical significance (n = 52 events). **Conclusion:** Prior to the 2020 USPSTF expansion, 61% of HBsAg-positive foreign-born adults were undiagnosed — 313,000 individuals at risk for cirrhosis and hepatocellular carcinoma (HCC) without access to antiviral therapy or surveillance. The decline from 76% to 52% reflects encouraging progress with potential for further gains through systematic guideline implementation. Limitations include cross-sectional design, HBsAg subsample missingness, and recall bias. These findings establish a pre-guideline baseline for evaluating future guideline impact. Targeted screening addressing insurance and primary care gaps is urgently needed to support WHO 2030 HBV elimination targets.



Disclosures: Rakshana Ravichandran: Nothing to Disclose, Ravi Patel: Nothing to Disclose, Aditya Kohli: Nothing to Disclose, Keeranmayee Mishra: Nothing to Disclose, Sonu Dhillon: Nothing to Disclose.

2139 | RACIAL DIFFERENCES IN SYMPTOMATIC PRURITUS BURDEN AMONG BLACK AND WHITE PATIENTS WITH PRIMARY BILIARY CHOLANGITIS

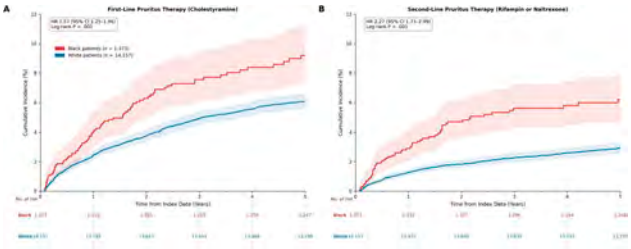
Basil Jalamneh[1] Dian Chiang[1] Omar Sims[1], [1]Cleveland Clinic Foundation

Background: Pruritus is the predominant symptomatic burden in primary biliary cholangitis (PBC), adversely affecting quality of life, sleep, and daily functioning. Despite growing recognition of racial disparities in chronic liver disease, whether the pruritus burden differs by race remains undefined. We evaluated racial differences in antipruritic treatment patterns as real-world proxies of symptom severity among Ursodeoxycholic acid (UDCA)-treated patients with PBC. **Methods:** Using the TriNetX Research Network — a federated electronic health record platform spanning 110 U.S. healthcare organizations — we conducted a retrospective cohort study of adults (≥18 years) with PBC (ICD-10: K74.3) initiated on UDCA. Patients were stratified into two mutually exclusive cohorts by documented race (Black or White). Exclusions included prior liver transplantation, primary sclerosing cholangitis, intrahepatic bile duct carcinoma, and digestive organ malignancy. The index date was defined as the first concurrent documentation of PBC diagnosis and UDCA prescription. Outcomes were assessed from 30 days through 5 years post-index. Pruritus burden was operationalized via time to initiation of first-line therapy (cholestyramine) and second-line therapy (rifampin or naltrexone). Kaplan–Meier analysis and multivariable Cox proportional hazards regression were used for between-group comparisons. **Results:** Of 15,530 eligible patients, 1,373 were Black and 14,157 were White. Black patients were younger (mean age 64.8 vs. 68.5 years) and demonstrated greater baseline disease severity, including higher alkaline phosphatase, total bilirubin, ascites, jaundice,

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abdominal pain, and malnutrition. At 5-year follow-up, Black patients were significantly more likely to initiate first-line antipruritic therapy (cholestyramine: 6.4% vs. 4.3%; HR 1.57, 95% CI 1.25–1.96; P < .001) and second-line therapy (rifampin or naltrexone: 4.5% vs. 2.1%; HR 2.27, 95% CI 1.73–2.99; P < .001). Figure-1. **Conclusion:** In this large real-world cohort of UDCA-treated patients with PBC, Black patients faced a disproportionately higher antipruritic treatment burden, with more than twice the hazard of requiring second-line therapy compared to White patients. These findings highlight the need for earlier symptom recognition, equitable access to emerging antipruritic therapies, and further investigation into biologic and healthcare factors driving racial differences in symptom experience among patients with PBC.



Disclosures: Basil Jalamneh: Nothing to Disclose, Dian Chiang: Nothing to Disclose, Omar Sims: Nothing to Disclose.

2140 | IMPROVING MASLD RISK AWARENESS IN AN UNDERSERVED POPULATION USING AN AI-VIDEO AS AN INNOVATIVE EDUCATIONAL TOOL: ANALYZING THE IMPACT OF ETHNICITY AND EDUCATION LEVEL

David Weinstein[1] Mitchelle Zolotarevsky[1] Keon Karimabady[1] Raza Muhammad[1] Athanasios Kondilis[1] Madhav Patel[1] Ruxandra Dane[1] Elizabeth Ward[1], [1]Endeavor Health

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is widely prevalent yet underdiagnosed, with low screening rates in primary care contributing to poor patient awareness. Patient education remains a critical and underutilized tool in bridging this gap. Educational videos have improved patient comprehension in various clinical settings. Our goal was to determine whether ethnicity or education level influenced patients' accurate perception of their MASLD risk and whether an AI-driven, multilingual educational video improved patient understanding and self-identification of risk status. **Methods:** We conducted a single-blind prospective study of 200 underserved adult patients in a resident clinic at risk for, or diagnosed with, MASLD based on 2022 AASLD–AACE criteria. Participants completed the validated Public Awareness of Non-Alcoholic Fatty Liver Disease (PAN-AFLD) survey assessing baseline MASLD knowledge and perceived risk. Participants then viewed an original AI-generated video, in English and validated in Spanish, discussing MASLD pathophysiology, complications, and lifestyle strategies, followed by a post-intervention PAN-AFLD survey. Ethnicity was categorized as: Caucasian, Hispanic, Asian/Pacific Islander, African-American, or Other, and education level as Elementary School, High School, College, Postgraduate, or None. **Results:** Of the 200 patients enrolled, 5 were excluded due to incomplete questionnaires. The cohort was predominantly Hispanic (45.6%, n = 89). In terms of education, 17.4% had elementary school education (n = 34), and 10.3% had postgraduate education (n = 20). Among ethnic groups, Hispanic patients had the highest post-video risk awareness (87.6%, n = 78), up from 66.3% (n = 59), a 1.32-fold increase. Among education groups, patients with elementary school education showed a 1.48-fold increase, from 61.8% (n = 21) to 91.2% (n = 31). Postgraduate patients demonstrated the greatest relative improvement at 1.86-fold, increasing from 35% (n = 7) to 65% (n = 13). **Conclusion:** Our preliminary data show that perceived MASLD risk increased across all ethnicity and education groups. Notably, Hispanic patients, who bear the highest burden of MASLD compared to non-Hispanics, comprised the largest proportion of our cohort and had the highest absolute post-video risk awareness. Among education groups, postgraduate patients showed the greatest relative improvement despite having the lowest baseline awareness, which may reflect that higher educational attainment enhances receptiveness to new health information. These findings suggest that AI-driven multilingual education may be particularly effective in diverse, underserved populations where language and educational barriers have historically limited health literacy. Correct risk perception is a critical first step toward lifestyle modification and, hopefully, decreased MASLD risk and progression.

Disclosures: David Weinstein: Nothing to Disclose, Mitchelle Zolotarevsky: Nothing to Disclose, Keon Karimabady: Nothing to Disclose, Raza Muhammad: Nothing to Disclose, Athanasios Kondilis: Nothing to Disclose, Madhav Patel: Nothing to Disclose, Ruxandra Dane: Nothing to Disclose, Elizabeth Ward: Nothing to Disclose.

2141 | GENDER AUTHORSHIP IN GASTROENTEROLOGY AND HEPATOLOGY: TRENDS AND PERSISTENT SENIORITY GAPS

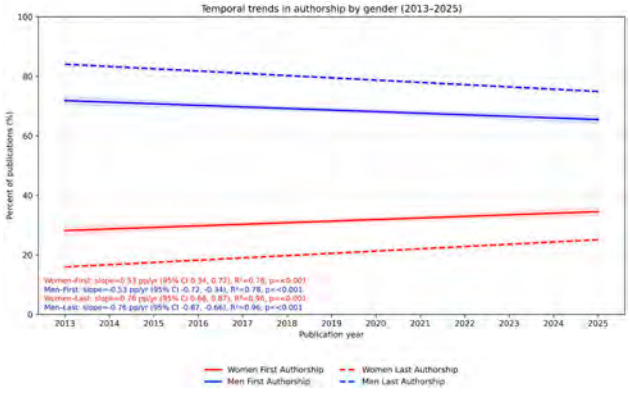
Thomas Stirrat[1] Shankar Thiru[2] Bojia Hu[2] Michael Flatley[3] Soham Apte[4] Lovedeep Singh[2] Annesha Sarkar[2] Zeba Bhanji[2] Waluma Fofung[2] David Kim[2] Jenny Chia-Chen Chang[2] Joseph Jennings[5] Amol Rangnekar[6] Rachel Redfield[7] Zachariah Foda[8] David

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Limsui[9] Priyanka Kanth[7], [1]University of California Los Angeles (UCLA), [2]Georgetown University School of Medicine, [3]Colorado University, [4]Kentucky College of Osteopathic Medicine, [5]MedStar Georgetown University, [6]Georgetown University Hospital, [7]MedStar Georgetown University Hospital, [8]Johns Hopkins University, [9]Stanford University

Background: Publication leadership influences promotion and visibility, yet contemporary authorship equity across gastroenterology and hepatology journals is incompletely characterized. We evaluated women's lead and senior authorship and first–last author concordance across selected specialty journals. **Methods:** We analyzed PubMed-indexed publications from 14 prespecified gastroenterology/hepatology journals from 2013 through 2025. First and last individual authors were proxies for lead and senior authorship. Gender was inferred from first names using Genderize.io with manual adjudication of missing/ambiguous cases; temporal trends, journal heterogeneity, and first–last gender concordance were assessed. **Results:** Among 60,453 publications, women represented 19,045/60,453 first authors (31.5%) and 12,579/60,453 last authors (20.8%), yielding a 10.7 percentage-point seniority gap and last- to-first leadership ratio of 0.66. Women's first authorship ranged from 18.7% to 43.8% across journals and last authorship from 11.5% to 31.3% ($p < 0.001$ for both). From 2013 to 2025, women's first authorship rose from 29.5% to 34.6% (+0.53 percentage points/year; 95% CI 0.34-0.72), and last authorship rose from 17.0% to 24.8% (+0.76 percentage points/year; 95% CI 0.66-0.87). Articles with women first authors were more likely to have women last authors than articles with men first authors (29.0% vs 17.0%; OR 1.99, 95% CI 1.91-2.07). **Conclusion:** Women's authorship increased across selected GI/hepatology journals, but senior authorship remained substantially lower than lead authorship. Journal-level heterogeneity and first–last author concordance suggest that equitable sponsorship, editorial representation, and research leadership pathways remain priority targets.



Disclosures: Thomas Stirrat: Nothing to Disclose, Shankar Thiru: Nothing to Disclose, Bojia Hu: Nothing to Disclose, Michael Flatley: Nothing to Disclose, Soham Apte: Nothing to Disclose, Lovedeep Singh: Nothing to Disclose, Annesha Sarkar: Nothing to Disclose, Zeba Bhanji: Nothing to Disclose, Waluma Fofung: Nothing to Disclose, David Kim: Nothing to Disclose, Jenny Chia-Chen Chang: Nothing to Disclose, Joseph Jennings: Nothing to Disclose, Amol Rangnekar: Nothing to Disclose, Rachel Redfield: Nothing to Disclose, Zachariah Foda: Nothing to Disclose, David Limsui: Nothing to Disclose, Priyanka Kanth: Nothing to Disclose.

2142 | HEALTH OUTCOMES IN SEXUAL AND GENDER MINORITY POPULATIONS WITH CHRONIC LIVER DISEASE: A SYSTEMATIC REVIEW

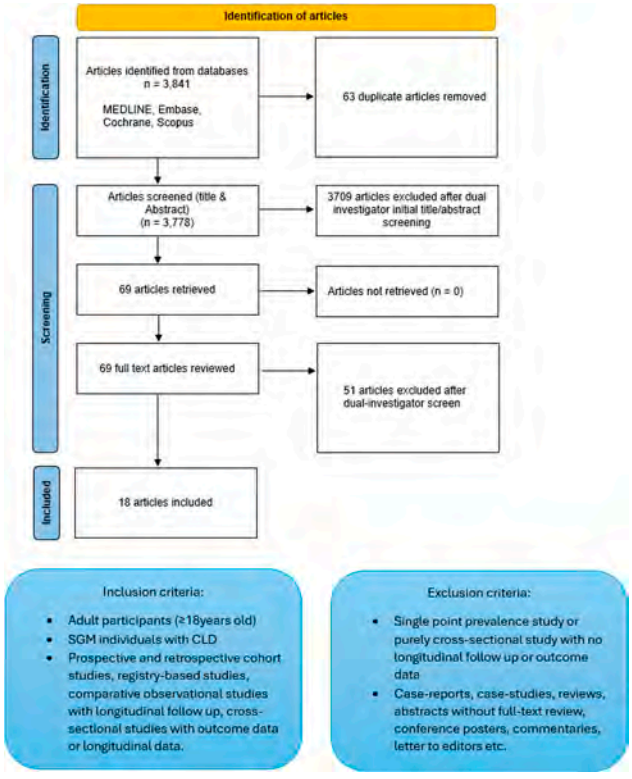
Kamalpreet S. Hara[1] Tulio Correa[2] Alberto Calleri[1] Sonali Paul[3] Alexandra Strauss[4] Nikki Duong[5] Victor Chedid[1] Douglas Simonetto[1], [1]Mayo Clinic Rochester, [2]University of Pittsburgh, [3]University of Chicago Medical Center, [4]Johns Hopkins School of Medicine, [5]Stanford University

Background: Sexual and gender minority (SGM) individuals face persistent disparities in healthcare access, utilization and outcomes driven by stigma, discrimination, and barriers to care. While these inequities are increasingly recognized, no systematic review has examined chronic liver disease (CLD) outcomes among SGM populations. **Methods:** A comprehensive search of MEDLINE, Cochrane, Embase and Scopus databases was performed through April 15, 2025, using controlled vocabulary supplemented with keywords. Studies including adult SGM individuals (≥ 18 years) with CLD reporting longitudinal follow-up or outcome data were included. Study designs were substantially heterogeneous across SGM ascertainment, outcome definitions, among others, which precluded a meta-analysis, hence our findings were synthesized narratively. Review was prospectively registered on PROSPERO (CRD420251033801). **Results:** Our search yielded 3,841 studies, of which 18 were included in the final synthesis (Figure 1). Included studies were primarily observational cohort and database studies across 10 countries, predominantly in Europe. Of note, SGM populations were predominantly represented through behavioral transmission risk categories, particularly men who have sex with men (MSM), with substantial underrepresentation of broader SGM community and identities. One study used self-reported gender identity but was limited to 60 transgender participants, another captured transgender adults at national scale but relied on diagnostic coding rather than self-reporting. Majority

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of evidence focused on viral hepatitis, HBV (n = 9) and HCV (n = 8) deriving primarily from HIV-coinfected cohorts. Among HIV-positive MSM with HCV, significant fibrosis (METAVIR ≥ F2) developed in 39.4% and cirrhosis in 11.6%; however, successful antiviral therapy drove substantial regression, with 78.3% maintaining FIB-4 < 1.45 at 3.5-year follow-up. Among HIV/HBV coinfected MSM, liver-related mortality was highest (14.2 per 1,000 person-years) which declined markedly after tenofovir-containing ART introduction (aHR 0.29; 95%CI 0.11–0.75) reflecting the hepatoprotective impact of modern antiretroviral therapy. Transgender adults carried more than double the age-standardized cirrhosis prevalence of cisgender adults (1,285 vs 561 per 100,000) with disproportionate psychosocial comorbidity. In MASLD-focused data, steatosis burden was numerically higher in transgender women versus cisgender comparators (54% TW vs 44%CM vs 49%CW) despite being younger, while transgender women receiving gender-affirming hormone therapy demonstrated slightly lower steatosis burden. **Conclusion:** CLD outcomes across the broader SGM spectrum remain critically understudied. The systematic review underscores the unmet need of standardized SOGI data collection and prospective SGM-focused hepatology cohorts to better understand outcomes of CLD in this population.



Disclosures: Kamalpreet S. Hara: Nothing to Disclose, Tulio Correa: Nothing to Disclose, Alberto Calleri: Nothing to Disclose, Sonali Paul: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Alexandra Strauss: Nothing to Disclose, Nikki Duong: Nothing to Disclose, Victor Chedid: Takeda: Consultant, Johnson and Johnson: Ad Board for Tremfya, Pfizer: Grant/Research Support, Douglas Simonetto: Mallinckrodt: Consultant, BioVie: Consultant, Resolution Therapeutics: Consultant, Evive: Consultant, Iota: Consultant, Novo Nordisk: Consultant, Astra Zeneca: Consultant.

2143 | HIGH ACCEPTABILITY OF COMMUNITY-BASED LIVER DISEASE SCREENING AMONG PEOPLE EXPERIENCING HOMELESSNESS AND HOUSING INSECURITY

Roshawn Jamasi[1] George Tadros[2] Yeabsera Ephrem[1] Kathan Pathak[1] AJ Tran[1] Henry Huynh Nguyen[2],
[1]Alberta Homeless Foundation, [2]Liver Health Connect

Background: People experiencing homelessness face elevated risks for viral hepatitis, alcohol-associated and metabolic liver disease, cirrhosis, and barriers to preventive and longitudinal care. Low-barrier community screening may improve detection and linkage to care. We aimed to characterize liver disease history, healthcare access, barriers, and acceptability of liver testing among people experiencing homelessness or housing insecurity in Calgary, Alberta to further refine education and outreach efforts. **Methods:** Alberta Homeless Foundation and Liver Health Connect conducted a cross-sectional survey of people experiencing homelessness or housing insecurity in Calgary. Participants were recruited from downtown service-adjacent areas, public spaces, and all public transit stations. Surveys assessed healthcare sources, recent physician/nurse contact, sleeping location, liver disease history, interest in testing, willingness to attend a free liver clinic, and barriers to care. Percentages used non-missing denominators. Totals may exceed 100% because respondents could select multiple options. Associations were assessed using Pearson's chi-square or Fisher's exact tests when expected counts were < 5. AI statement: ChatGPT 5.4 was used to improve grammar and readability. **Results:** Of 112 respondents, 17/109 (15.6%) reported being told they had a liver problem, and 18/107 (16.8%) reported a named liver diagnosis, including hepatitis C (10, 9.3%), cirrhosis (5, 4.7%), hepatitis B (2, 1.9%), and fatty liver (1, 0.9%). 90/110 (81.8%) would want testing if it could prevent serious illness, and 96/109 (88.1%) would attend or try a free liver clinic offering food, hygiene essentials, and snacks. Among those with a named diagnosis, 18/18 (100.0%) were willing to attend a free liver clinic. Testing interest was associated with willingness to attend compared with those not interested or unsure (86/90, 95.6% vs. 10/19, 52.6%; p < 0.001). Healthcare access gaps were common. Of 111 responses, 42 (37.8%) reported regular emergency or urgent care use, while 33 (29.7%) reported no regular care site or not

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seeking care. Barriers to care were reported by 78 respondents (76.5%), including judgment or disrespect (21, 20.6%), lack of transit fare (19, 18.6%), lack of ID/health card (12, 11.8%), and mental health/substance use concerns (10, 9.8%). Respondents reporting any barrier were more likely to endorse willingness to attend a liver clinic than those reporting none (74/78, 94.9% vs. 19/24, 79.2%; p = 0.031). **Conclusion:** In this community-based survey of people experiencing homelessness or housing insecurity, self-reported liver disease and interest in testing were high. Most respondents were willing to attend a free liver clinic, especially those with barriers. Findings suggest barriers reflect unmet need rather than lack of interest and support low-barrier community liver screening to improve detection and linkage to care.

Disclosures: Roshawn Jamasi: Nothing to Disclose, George Tadros: Nothing to Disclose, Yeabsera Ephrem: Nothing to Disclose, Kathan Pathak: Nothing to Disclose, AJ Tran: Nothing to Disclose, Henry Huynh Nguyen: Nothing to Disclose.

2144 | DIFFERENCES IN METABOLIC PROFILE AND FIBROSIS SEVERITY AMONG PATIENTS UNDERGOING VIBRATION-CONTROLLED TRANSIENT ELASTOGRAPHY IN A SAFETY-NET HOSPITAL

Dominique Mosley[1] Kathryn Thompson[2] Lesley Miller[2], [1]Emory University, Internal Medicine Residency Program, [2]Emory University

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) disproportionately affects racial and ethnic minority populations in the United States. Hispanic/Latino populations experience the highest prevalence of MASLD and are at increased risk for progression to advanced fibrosis and cirrhosis, while Black patients, despite lower overall prevalence, remain at risk for severe liver-related complications once diagnosed. We aimed to evaluate differences in metabolic characteristics and vibration-controlled transient elastography (VCTE) findings among patients with MASLD in a large urban safety-net health system. **Methods:** We performed a retrospective cohort study of 305 adults with MASLD who underwent VCTE at Grady Memorial Hospital between January 2018 and March 2024. Demographic data, metabolic comorbidities, laboratory data, and VCTE findings were collected. Individual two-sample t-tests were conducted among three different racial/ethnic groups (Hispanic/Latino, Black/African American (AA), White/Caucasian) to identify differences in metabolic risk factors and VCTE findings among groups. **Results:** Of 305 patients with MASLD undergoing VCTE, 46.9% were Hispanic/Latino, 41% were Black/AA, and 8.9% were White/Caucasian. Hispanic patients underwent VCTE at a younger age compared to AA patients (48.2 vs. 55.5 years, p < 0.001). Hispanic patients demonstrated lower mean liver stiffness measurements compared to AA patients (7.1 vs 9.0 kPa, p = 0.009), while controlled attenuation parameter (CAP) scores were similar between groups (305.7 vs 292.0 dB/m, p = 0.051). Hispanic patients had higher ALT (60.5 vs 37.0 U/L, p < 0.001) and triglyceride levels (213.5 vs 128.7 mg/dL, p < 0.001), along with lower HDL levels (46.1 vs 52.4 mg/dL, p = 0.002) compared to AA patients. Rates of diabetes and hyperlipidemia were similar between groups. AA patients had significantly higher rates of hypertension (80.0% vs 42.7%, p < 0.001). **Conclusion:** Significant racial/ethnic differences were observed in screening patterns, metabolic risk factors, and fibrosis severity among patients with MASLD undergoing VCTE in a safety-net health system. Hispanic/Latino patients underwent screening at younger ages and demonstrated greater steatotic and metabolic lab abnormalities, whereas Black patients had higher liver stiffness measurements and greater cardiometabolic comorbidity burden. These findings may help inform targeted screening strategies and risk stratification in underserved populations.

Disclosures: Dominique Mosley: Nothing to Disclose, Kathryn Thompson: Nothing to Disclose, Lesley Miller: Gilead Sciences: Grant/Research Support, AbbVie: Advisor.

2145 | CO-OCCURRENCE PATTERNS AND SHARED RISK FACTORS OF CHRONIC LIVER DISEASES AND DIABETES: A SYSTEMATIC ANALYSIS BASED ON SPATIAL EPIDEMIOLOGY

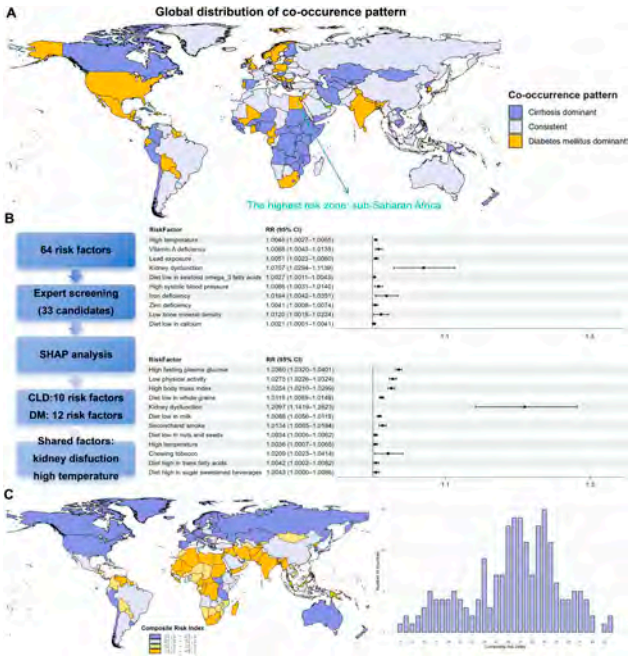
Yujiao Deng[1] Xubing Zhou[1] Xiao Yuan[1] Qiaoman Fei[1] Zhanpeng Yang[1] Yixin Guo[1] Jingyue Tan[1] Meijuan Han[1] Haidan Shi[1] Bowen Qin[1] Si Yang[2] Yuan Wang[1] Fanpu Ji[1], [1]The Second Affiliated Hospital of Xi'an Jiaotong University, [2]Air Force Medical University

Background: Chronic liver diseases (CLD) and diabetes mellitus (DM) are major public health concerns. Previous studies have addressed them separately, leaving their co-occurrence underexplored. We aimed to characterize the global co-occurrence pattern of CLD and DM and identify shared risk factors. **Methods:** Using GBD 2023 data, we extracted age-standardized incidence rates (ASIRs, per 100,000 persons) for both diseases and exposure data for 64 risk factors across 204 countries. According to the quartiles of global incidence rates for both diseases, countries were categorized into three co-occurrence regions: consistent, CLD-dominant, and DM-dominant

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areas. Employing machine learning algorithms alongside negative binomial regression models, we identified and quantified the impact of relevant risk factors. The population-attributable fraction and a composite risk index were subsequently calculated to assess the disease burden associated with CLD and DM. **Results:** Matched concurrence occurred in 67 countries, CLD-predominant in 69, and DM-predominant in 68. Twenty risk factors were classified into common and specific features. Kidney dysfunction and high temperature were identified as the two common risk factors shared by both conditions. Kidney dysfunction exerted the strongest effect on both CLD (RR = 1.07, 95% CI 1.03–1.11) and DM (RR = 1.21, 95% CI 1.14–1.28). The composite risk index exhibited a pronounced right-skewed distribution. Geographically, sub-Saharan Africa emerged as the primary cluster of high-risk zones (35.0–46.0), whereas Europe, North America, and northern Russia were predominantly characterized by low-risk areas (11.0–25.0). This spatial pattern closely mirrors the incidence burden distribution of CLD and DM. Among the eight specific risk factors that affect CLD, iron deficiency has the greatest impact. For diabetes, among the ten specific risk factors, high fasting plasma glucose has the greatest influence. The spatial distribution characteristics of common risk factors reveal significant regional disparities in kidney dysfunction and high temperature exposure (Figure 1). **Conclusion:** The co-occurrence of CLD and DM is a growing global health challenge. Kidney dysfunction and high temperature were identified as the two common risk factors. Targeting these shared determinants through integrated interventions could substantially reduce the global burden of both diseases.



Disclosures: Yujiao Deng: Nothing to Disclose, Xubing Zhou: Nothing to Disclose, Xiao Yuan: Nothing to Disclose, Qiaoman Fei: Nothing to Disclose, Zhanpeng Yang: Nothing to Disclose, Yixin Guo: Nothing to Disclose, Jingyue Tan: Nothing to Disclose, Meijuan Han: Nothing to Disclose, Haidan Shi: Nothing to Disclose, Bowen Qin: Nothing to Disclose, Si Yang: Nothing to Disclose, Yuan Wang: Nothing to Disclose, Fanpu Ji: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose.

2146 | FEASIBILITY AND ACCEPTABILITY OF A BRIEF INTERVENTION TARGETING SUGAR-SWEETENED BEVERAGE CONSUMPTION IN LATINO PATIENTS WITH CIRRHOSIS

Vanessa Torres[1] Arleth Escoto[1] Jailene Cruz[1] Paulina Monteon-Garcia[1] Liana Gutierrez[1] Edward Mena[2], [1]Cedars-Sinai, [2]California Liver Reasearch Institiute

Background: Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality among U.S. patients with cirrhosis, with Latino adults disproportionately affected due to higher rates of chronic liver disease. High sugar-sweetened beverage (SSB) consumption, along with chronic disease and dietary management challenges, contributes to poorer liver cancer outcomes among Latinos. Brief interventions are recognized as effective strategies for targeting modifiable behaviors, yet few have been adapted among this population. In this study, we assessed the feasibility and acceptability of a contextually tailored brief intervention to reduce SSB consumption among Latino patients with cirrhosis. **Methods:** We developed and pilot tested a brief intervention to reduce SSB consumption among Latino patients with cirrhosis. Eligibility criteria included being 18 years or older, fluency in English or Spanish, and diagnosed with cirrhosis (Child Pugh A or B). Participants received a 25-minute intervention delivered by trained bilingual research staff. Participants completed baseline and 4–8-week follow-up semi-structured interviews. Descriptive statistics were used to summarize participant characteristics, SSB intake, and feasibility outcomes (e.g., recruitment and retention). Interviews assessing intervention acceptability were analyzed using direct content analysis guided by the Theoretical Framework of Acceptability. **Results:** Of the 32 eligible patients screened, 20 were enrolled (63% recruitment) and all participants completed follow-up interviews (100% retention). Participants had a mean age of 66 years, and most were women (80%), born in Mexico (60%), Spanish-speaking (60%), and had less than a high school education (55%). SSB intake was low to moderate at baseline. Qualitative findings demonstrated high acceptability of the intervention. Participants described the “Rethink Your Drink” sugar demonstration as the most impactful component, increasing awareness of hidden sugars and motivating healthier beverage choices. The intervention was

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perceived easy to follow and integrate into daily routines, with few reported barriers. Participants reported difficulties identifying hidden sugars in culturally familiar foods and drinks, managing hydration and protein intake, accessing nutrition support, and coping with hepatic encephalopathy, while emphasizing the importance of family support for healthy behavior change. **Conclusion:** A brief intervention targeting SSB consumption among Latino patients with cirrhosis was feasible and acceptable. Future interventions should address nutrition-related challenges, hepatic encephalopathy related to cognitive barriers, and family support to improve behavior change. Future contextually tailored interventions may help address modifiable behavioral risk factors relevant to liver disease progression and HCC risk among Latinos with cirrhosis.

Disclosures: Vanessa Torres: Nothing to Disclose, Arleth Escoto: Nothing to Disclose, Jailene Cruz: Nothing to Disclose, Paulina Monteon-Garcia: Nothing to Disclose, Liana Gutierrez: Nothing to Disclose, Edward Mena: Nothing to Disclose.

2147 | UNDERSTANDING DISPARITIES: IDENTIFYING REASONS FOR LIVER TRANSPLANTATION DEFERRAL OR DENIAL AMONG AMERICAN INDIAN PATIENTS

Brett Chy[1] Stephen Xie[1] Meghan Fuller[1] Chloe Raygoza[1] Yunzhe Hu[1] Elena Dreisbach[1] Sandra Elmasry[2] David Chascsa[2], [1]Mayo Clinic Alix School of Medicine, [2]Mayo Clinic Arizona

Background: American Indians (AI) experience the highest liver disease mortality in the USA yet remain among the least likely to receive liver transplantation (LT). Prior studies show AI patients face greater psychosocial barriers to LT than non-White Hispanic (NHW) patients, but the barriers remain poorly characterized. A better understanding of reasons for deferral and denial may identify modifiable drivers of disparities in LT access. **Methods:** We performed a retrospective, single-center, matched cohort study including all AI patients who were deferred or denied LT between 2017 and 2022. A NHW cohort was matched by age, sex, and transplant indication. For patients who underwent transplant selection committee review, "explicit" committee-documented reasons for deferral or denial were collected and coded using a hierarchical coding scheme. Additional "implicit" concerns documented by hepatology, psychiatry, or social work throughout evaluation were collected and coded using the same scheme. For patients who did not reach committee review, reasons for attrition were collected as implicit barriers. **Results:** A total of 118 patients were included in the analysis, including 56 AI and 62 NHW patients.Among explicit committee-documented reasons, AI patients were more frequently deferred or denied for inadequate caregiver planning (14.3% vs 4.8%), need for psychiatric clearance (12.5% vs 4.8%), and inability to follow a complex care plan (10.7% vs 3.2%) than NHW.When considering both explicit reasons and implicit concerns, AI patients more frequently had documented substance use within their social environment (10.7% vs 1.6%), inadequate financial planning (16.1% vs 8.1%), and inability to follow a complex care plan (17.9% vs 6.5%) than NHW patients.Among patients who reached selection committee review, AI patients had a higher median number of uniquely coded barriers, both implicit and explicit, than NHW patients (5 vs 3). (Figure 1) **Conclusion:** AI patients deferred or denied LT were more likely to have psychosocial barriers documented throughout the evaluation process than matched NHW patients, reflected in both explicit reasons and implicit concerns. Disparities were particularly evident in caregiver planning, financial planning, psychiatric clearance, substance use related concerns, and inability to follow a complex care plan. A higher overall number of barriers were documented for AI patients during evaluation than for NHW patients, suggesting a more complex pathway to LT candidacy. Overall, these findings highlight the need for earlier, targeted interventions aimed at reducing psychosocial and structural barriers to LT among AI patients. Potential strategies include implementation of culturally appropriate caregiver programs, expanded financial assistance, and improved access to addiction services both for patients and members of their social circles.

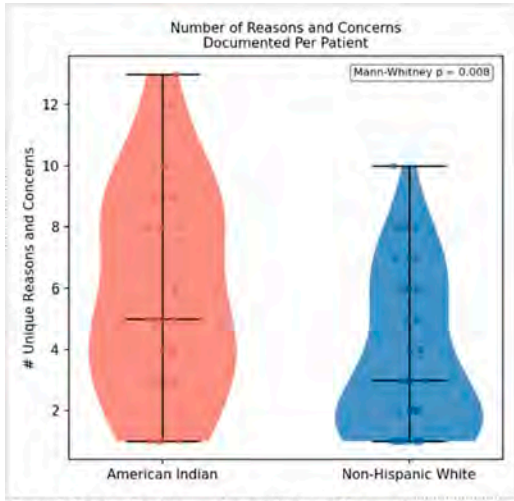


Figure 1. Violin plot showing the distribution of the number of uniquely coded explicit reasons and implicit concerns documented per patient. AI patients demonstrated a higher median number of barriers than NHW patients (5 vs 3, Mann-Whitney p=0.008).

Disclosures: Brett Chy: Nothing to Disclose, Stephen Xie: Nothing to Disclose, Meghan Fuller: Nothing to Disclose, Chloe Raygoza: Nothing to Disclose, Yunzhe Hu: Nothing to Disclose, Elena Dreisbach: Nothing to Disclose, Sandra Elmasry: Nothing to Disclose, David Chascsa: Nothing to Disclose.

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2148 | METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) IN ASIAN AMERICAN CHILDREN

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[2]University of Miami Miller School of Medicine

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common chronic liver disease in children. In the United States, MASLD affects up to 38% of children with obesity. MASLD is a silent disorder that is underdiagnosed, particularly in individuals with a normal body mass index (BMI). Asian adults are known to be at higher metabolic risk at a lower BMI. However, it remains unknown whether Asian American children are similarly at higher risk for MASLD at a lower BMI. Racial and ethnic differences in the prevalence of MASLD among children remain underexplored. The objective of this study was to compare the prevalence of MASLD between Asian American and non-Hispanic White (NHW) children and to determine the association of Asian race with MASLD. **Methods:** This cross-sectional study analyzed nationally representative pooled data from the 2017–2022 National Health and Nutrition Examination Survey (NHANES) on US children aged 12–17 years who underwent liver ultrasound transient elastography (FibroScan) with controlled attenuation parameter (CAP) scoring. Children who self-identified as Asian American or non-Hispanic White were included. MASLD was defined as steatotic liver disease on FibroScan (CAP >237 dB/m) in the absence of other causes, with evidence of at least one cardiometabolic risk factor: BMI z-score ≥1 or WC ≥ over 95%, fasting glucose ≥100 mg/dL or prediabetes/type 2 diabetes mellitus, blood pressure ≥95th percentile or ≥130/80 mmHg for children <13 years and ≥130/85 mmHg or specific antihypertensive drug treatment for ≥ 13 years, triglycerides ≥150 mg/dL, or HDL <40 mg/dL. The prevalence of MASLD was compared between Asian American and NHW children using the chi-square test. Regression models adjusted for age, sex, poverty income ratio (PIR), and BMI z-score examined the association of Asian American race (NHW as reference) with CAP score, liver stiffness, and MASLD. Complex survey design procedures were applied throughout. **Results:** Among 234 Asian American children (mean age 14.45 ± SE 0.12 years) and 2,541 NHW children (mean age 14.41 ± SE 0.14 years), Asian American children had significantly lower BMI z-scores, lower rates of obesity, and higher PIR compared to NHW children (Table 1). The prevalence of MASLD was significantly lower in Asian American children (1.1% ± SE 1.1%) compared to NHW children (8.3% ± 1.1%; p = 0.03). In adjusted regression analysis, Asian American race was independently associated with a greater CAP score (β = 17.67, 95% CI: 2.99–32.35; p = 0.02). Race was not independently associated with liver stiffness (p = 0.1) or MASLD (p = 0.43) in adjusted models (Table 2). **Conclusion:** This study demonstrates a lower prevalence of MASLD in Asian American children compared to NHW children using the current 2023 revised criteria diagnostic criteria. However, in regression analysis which adjusted for BMI, Asian American race was not associated with MASLD. The observed disparity in prevalence may reflect the fact that Asian American children have significantly lower BMI values and therefore may not meet the current BMI-dependent diagnostic thresholds for MASLD, potentially underestimating their true disease burden. Notably, despite significantly lower BMI, Asian American children tended toward higher CAP scores compared to their NHW counterparts, suggesting heightened hepatic fat accumulation at lower body weights: a pattern consistent with "lean" MASLD described in Asian American adults. These findings underscore the potential accuracy of current diagnostic criteria when applied to Asian American pediatric populations and support future investigation into ethnicity-specific BMI thresholds for MASLD diagnosis in children.

Table 1: Demographic and Clinical Characteristics of Study Population

N= 2775 Mean (SE) or %	Asian American n=234	Non-Hispanic White n=2541	P-Value
Age (years)	14.45(0.12)	14.41(0.14)	0.83
Male	43.2% (5.2%)	52.5% (3.2%)	0.12
Poverty Income Ratio	3.69 (0.30)	3.10 (0.14)	0.07
BMI Z-score	-0.01 (0.25)	0.61 (0.10)	0.04
Obesity	5% (2.8%)	13.8% (2%)	0.08
Systolic Blood Pressure Index	0.78 (0.03)	0.81 (0.01)	0.37
Diastolic Blood Pressure Index	0.75(0.03)	0.76(0.01)	0.59
Hypertensive Blood Pressure	2.2% (1.3%)	2.6% (0.7%)	0.812
Triglycerides (mg/dl)	66.2 (4.4)	70.3 (1.96)	0.14
HDL (mg/dl)	54.4 (1.1)	51.8 (0.47)	0.05
Fasting Glucose (mg/d)	93.37 (1.03)	94.86 (0.52)	0.3
Diabetes	0% (0)	0.2% (0.1)	0.06
CAP Score	212.64(6.77)	208.81(3.11)	0.57
Liver Stiffness E	5.30 (0.41)	4.92 (0.10)	0.40

Table 2: Regression analysis of Asian American race (reference non-Hispanic White) predicting liver tests

OR or ß (95% confidence interval)	Crude	Adjusted
CAP	3.82(-10.21-17.85) P=0.57	ß 17.67(2.99-32.35) P=0.02
Liver Stiffness E	0.38(-0.56-1.31) P=0.40	ß 0.85(-0.22-1.9) P=0.1
MASLD	OR 0.24 (0.07, 0.8) P=0.02	OR 0.613(0.17, 2.22) P=0.43

Disclosures: Jaden Ruffy: Nothing to Disclose, Johanna Ferreira: Nothing to Disclose, Christine Sethna: Nothing to Disclose.

2149 | IMPROVING MASLD RISK AWARENESS IN AN UNDERSERVED POPULATION USING AN AI-VIDEO AS AN INNOVATIVE EDUCATIONAL

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TOOL: ANALYZING THE IMPACT OF LOW VERSUS ELEVATED FIB-4 SCORES

David Weinstein[1] Mitchelle Zolotarevsky[1] Keon Karimabady[1] Raza Muhammad[1] Athanasios Kondilis[1] Madhav Patel[1] Ruxandra Dane[1] Elizabeth Ward[1], [1]Endeavor Health

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is widely prevalent yet underdiagnosed, with low screening rates in primary care contributing to poor patient awareness. Patient education remains a critical and underutilized tool in bridging this gap. Educational videos have improved patient comprehension in various clinical settings. Our goal was to determine whether patients with low or elevated FIB-4 scores accurately perceived their MASLD risk and whether an AI-driven, multilingual educational video improved patient understanding and self-identification of risk status. **Methods:** We conducted a single-blind prospective study of 200 underserved adult patients in a resident clinic at risk for, or diagnosed with, MASLD based on 2022 AASLD–AACE criteria and the Fibrosis-4 (FIB-4) index. At a routine visit, participants completed the validated Public Awareness of Non-Alcoholic Fatty Liver Disease (PANAFLD) survey assessing baseline MASLD knowledge, perceived risk, alcohol use (AUDIT-C), dietary habits (MINI-EAT), and physical activity using the International Physical Activity Questionnaire (IPAQ). FIB-4 scores were calculated retrospectively using age-adjusted cutoffs to classify patients as low or elevated risk. Participants then viewed an original AI-generated video, in English and validated in Spanish, using Synthesia software discussing MASLD pathophysiology, complications, and lifestyle strategies, followed by a post-intervention PANAFLD survey. **Results:** Of the 200 patients, 5 were excluded due to incomplete questionnaires. Among these, 75.9% (n = 148) had a low FIB-4 score, while 24.1% (n = 47) had an elevated FIB-4 score. Overall, perceived MASLD risk increased from 52.3% (n = 102) to 76.4% (n = 149) following the video. In the low FIB-4 group, perceived risk increased from 47.3% (n = 70) to 78.4% (n = 116). In the elevated FIB-4 group, perceived risk increased from 68.1% (n = 32) to 70.2% (n = 33). Notably, among the 36.9% (n = 72) of patients whose doctor had previously mentioned fatty liver, perceived risk increased from 38.9% (n = 28) to 80.6% (n = 58). **Conclusion:** Our preliminary data show that patient perception of risk for MASLD in the low FIB-4 group increased by 66% after the video. Most patients with elevated FIB-4 scores already understood their risk for MASLD, which modestly improved post-video. Interestingly, among patients whose doctor had previously mentioned fatty liver, risk perception increased by 107%, suggesting that prior clinical priming enhances receptiveness to targeted education. These findings indicate that AI-driven patient education can meaningfully improve patients' awareness of MASLD in an underserved primary-care resident clinic setting. Correct risk perception is a critical first step toward lifestyle modification and, hopefully, decreased MASLD risk and progression.

Disclosures: David Weinstein: Nothing to Disclose, Mitchelle Zolotarevsky: Nothing to Disclose, Keon Karimabady: Nothing to Disclose, Raza Muhammad: Nothing to Disclose, Athanasios Kondilis: Nothing to Disclose, Madhav Patel: Nothing to Disclose, Ruxandra Dane: Nothing to Disclose, Elizabeth Ward: Nothing to Disclose.

2150 | LIVER HEALTH CONNECT: A COMMUNITY-FIRST APPROACH TO ADVANCING LIVER HEALTH AWARENESS AND ENGAGEMENT

George Tadros[1] Henry Nguyen[2], [1]University of Calgary, [2]University of Calgary Cumming School of Medicine

Background: Liver Health Connect (LHC) is a newly established, community-first non-profit organization in Calgary, Alberta, dedicated to promoting liver health, reducing stigma surrounding chronic liver disease, and improving public awareness through education. LHC engages directly with diverse populations by participating in cultural festivals, community outreach events, and health fairs, and by providing accessible liver health resources via its website and social media. The purpose of this organization is to identify existing gaps in public knowledge and perceptions of liver health, and to assess community interest and willingness to participate in liver health education and outreach activities. **Methods:** All members of the public who directly interacted with LHC volunteers at festivals and community seminars (July-December 2025) were given the option to fill out an anonymous survey via an online secure platform. LHC utilizes these surveys to tailor its content and better serve its community partners based on identified needs. Surveys collected participant demographics, liver health knowledge, current engagement with liver testing, as well as their perception of the importance of liver health and need for further information and education in the community. **Results:** 459 participants were surveyed across the events, with 306 being female (66.7%), with a mean age of 38 years (SD = 16). Participants came from a variety of ethnicities with East Asian (135, 29.4%) and Caucasian (129, 28.1%) being most represented and Indigenous (3, 0.7%) and Southeast Asian (8, 1.7%) being least represented. Participants came from all 4 quadrants of the city (NW: 27%, NE: 19.8%, SW:

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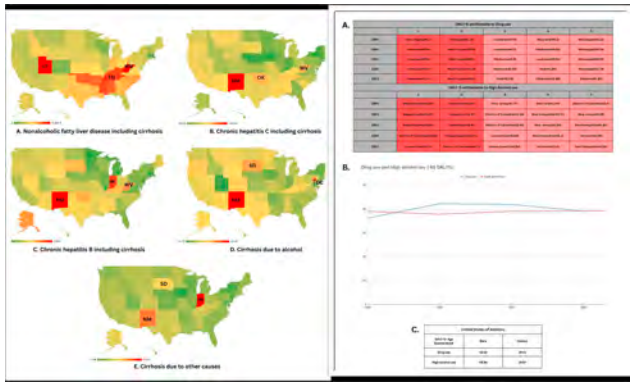
30.5%, SE: 14.2%). Importantly, only 280 (61%) of participants reported having a regular healthcare provider that they can talk to about liver health, and only 123 (26.8%) reported ever having their liver health tested. A total of 294 participants (64.1%) reported having little to no familiarity with liver health topics. However, 301 (65.6%) participants reported that liver health was extremely or very important to them and their family, and 290 (63.2%) expressed a need for more information about liver testing and education in the community, with a further 107 (23.3%) expressing interest in receiving such information **Conclusion:** Preliminary findings indicate a significant gap in both liver health awareness and access to liver testing in the community, despite widespread acknowledgment of the liver's importance to overall health. Survey responses show strong public interest in accessible, free educational opportunities, highlighting an appetite for community-based learning and engagement. These findings demonstrate a clear need for inclusive, culturally responsive liver health education, which remains the core mission of Liver Health Connect (LHC)

Disclosures: George Tadros: Nothing to Disclose, Henry Nguyen: Nothing to Disclose.

2151 | GEOGRAPHIC, SEX AND AGE DISPARITIES IN CIRRHOSIS AND OTHER CHRONIC LIVER DISEASES: INSIGHTS FROM GBD 2023

Sri Ram Charan Gundapaneni[1] Sameer Kumar Majety[2] Praneeth Koushik Sriramaneni[3] Madhu Babu Adusumilli[1] Moksha Prasoona Avvaru[4] Ashwin Rumalla[1], [1]UCF/HCA Florida Ocala, [2]Xiamen University School of Medicine, [3]Kamineni Academy of Medical Sciences and Research Center, [4]Harnett Health

Background: Cirrhosis and chronic liver disease (CLD) remain major causes of morbidity in the United States. Using Global Burden of Disease (GBD) 2023 estimates, we described national and state level patterns, age and gender differences, and temporal trends. **Methods:** Age standardized incidence, prevalence, mortality, and DALY rates were obtained from the Institute for Health Metrics and Evaluation Global Burden of Disease 2023 study using the IHME GBD Results Tool. Burden was assessed for NAFLD including cirrhosis, chronic hepatitis C, chronic hepatitis B, alcohol related cirrhosis, and other causes. Age specific, gender specific, and state patterns were evaluated. Estimated annual percent change (EAPC) with 95 percent confidence intervals was calculated. **Results:** NAFLD had the highest national burden (9543.63 per 100000), followed by chronic hepatitis C (1035.29), chronic hepatitis B (259.25), alcohol related cirrhosis (67.23), and other causes (41.86). NAFLD burden was highest in West Virginia (11527.80), Utah (11514.18), and Tennessee (11041.05) and lowest in Massachusetts (8064.12), the District of Columbia (8419.89), and Colorado (8554.98). Hepatitis C burden peaked in New Mexico (1426.52) and West Virginia (1201.30). Alcohol related cirrhosis was highest in New Mexico (101.51). Other cause cirrhosis peaked in Indiana (77.45).Age patterns showed very low burden in children with sharp increases through adulthood. Prevalence peaked at 36367.89 in males aged 80 to 84 years and 32658.30 in females aged 85 years and older. Mortality was highest at 76.20 in males aged 65 to 69 years and 53.74 in females aged 85 years and older. DALY rates peaked at 2107.60 in males and 1153.48 in females aged 60 to 64 years. Case counts were highest in adults aged 15 to 49 years, with 10551156.24 cases in males and 7041155.24 in females.Gender differences were largest in New Hampshire and Oregon and smallest in Hawaii and West Virginia, with no reversed patterns.Temporal trends showed rising burden. Incidence increased with an ASIR EAPC of 0.58 (95 percent CI 0.54 to 0.62). Prevalence rose with an ASPR EAPC of 0.60 (95 percent CI 0.56 to 0.64). DALYs increased with an ASDALYR EAPC of 0.55 (95 percent CI 0.46 to 0.63). Mortality increased with an ASDR EAPC of 0.69 (95 percent CI 0.61 to 0.78). **Conclusion:** Cirrhosis and CLD show wide geographic variation, with the highest burden in West Virginia, New Mexico, and surrounding regions. NAFLD accounts for most disease. Rising EAPC values across all indicators highlight growing national impact and the need for state targeted strategies focusing on metabolic risk, alcohol use, and timely CLD management.



Disclosures: Sri Ram Charan Gundapaneni: Nothing to Disclose, Sameer Kumar Majety: Nothing to Disclose, Praneeth Koushik Sriramaneni: Nothing to Disclose, Madhu Babu Adusumilli: Nothing to Disclose, Moksha Prasoona Avvaru: Nothing to Disclose, Ashwin Rumalla: Nothing to Disclose.

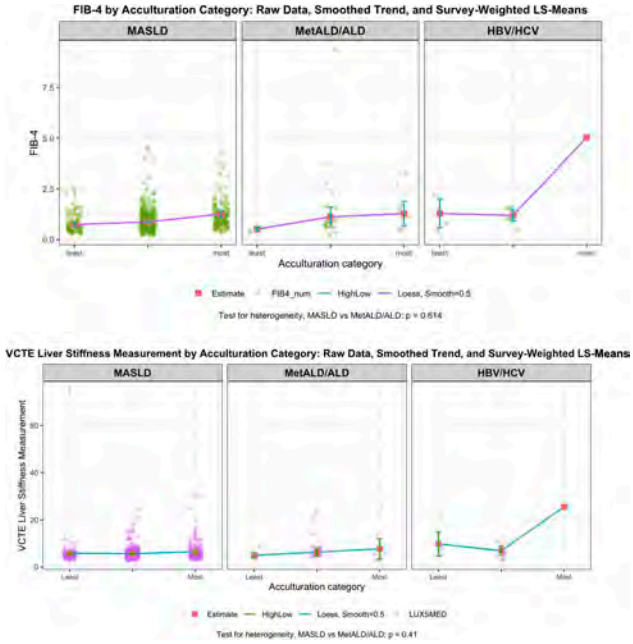
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2152 | ACCULTURATION AND LIVER HEALTH INEQUITIES: NATIONAL PATTERNS IN STEATOSIS AND FIBROSIS SEVERITY AMONG U.S. IMMIGRANTS

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Background: Steatotic liver disease (SLD) disproportionally affects minority and immigrant populations, a disparity largely driven by inequities in social determinants of health and higher metabolic risk factors. Acculturation—the process by which immigrants adapt to the cultural, social, behavioral, and linguistic norms of a new country—may be an important mediator of social determinants of health by impacting health behaviors, healthcare access, and health outcomes. This study aims to address this gap by investigating the association between acculturation and SLD severity among U.S. immigrants using nationally representative data. **Methods:** Patients (n = 676) with MASLD, metALD, ALD, hepatitis B, and hepatitis C were identified from the NHANES 2017-2020 dataset with acculturation data. Acculturation scores were generated based on interview language, language spoken at home, and length of residence in the U.S. We utilized Fibrosis-4 (FIB-4) Index as well as Controlled Attenuation Parameter (CAP) and Liver Stiffness Measurement (LSM) from vibration controlled transient elastography. Weighted analyses, multivariate analysis, and linear regression explored relationships between acculturation scores and measures of liver severity by SLD type. **Results:** Of the 676 patients, there were 624 MASLD patients, 23 metALD patients, 15 ALD patients, and 14 hepatitis B or C patients. Participants were predominantly Hispanic White (36.6%) and non-White Hispanic (26.0%). Acculturation scores were similar across different SLD types. More acculturated individuals had a higher cardiometabolic burden ($p = 0.009$), higher prevalence of diabetes ($p = 0.005$), and higher FIB-4 score ($p < 0.001$). In adjusted linear models, composite acculturation independently predicted higher FIB-4 ($p < 0.001$) and CAP scores ($p = 0.023$) but not LSM. Single proxy variables of acculturation like interview language and length of residence in the United States were also associated with higher FIB-4 and CAP scores. Higher acculturation is associated with three times greater odds of high-risk fibrosis based on FIB-4 independent of metabolic risk factors or etiology of liver disease (adjusted OR = 3.00; 95% CI 1.01-8.96). The single hepatitis patient with high acculturation also had high FIB-4 and LSM, but we were unable to do a full regression analysis due to low sample size. **Conclusion:** This study demonstrates that acculturation may contribute a meaningful role in markers of liver fibrosis and steatosis. Continued investigation is needed to clarify how acculturation shapes SLD severity. Expanding sample size through further iterations of NHANES and exploring how acculturation mediates lifestyle and diet will be critical to fully define this relationship and strengthen its implications for liver disease risk stratification.



Disclosures: Michelle Zhao: Nothing to Disclose, Yunxi Pu: Nothing to Disclose, Xiaotao Zhang: Nothing to Disclose, Frances Lee: Nothing to Disclose.

2153 | TRENDS AND DISPARITIES IN SEPSIS AND LIVER CIRRHOSIS IN UNITED STATES FROM 1999-2020: A CDC-WONDER DATABASE STUDY

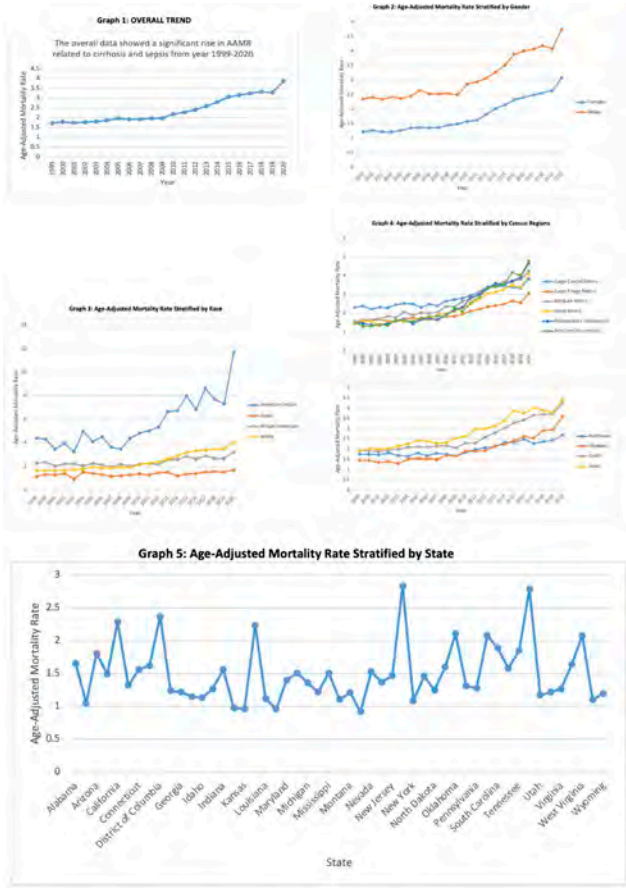
Simran Joshi[1] Syed Irtiza Imam[2] Hania Haque[2] Laiba Tanveer[2] Sufyan Raza Khan[2] Preeti Advani[2] Marium Jawaid[2] Marium Jawaid[2] Muhammad Owais[3] Jeevin Singh Sandhu[4] Corrine Caissie[1] Mohammed Aatiqul Islam[1], [1]Yale New Haven Health, [2]Jinnah Sindh Medical University, Karachi, Pakistan, [3]Liaqut University of Medical and Health Sciences, Jamshoro, [4]Methodist Dallas Medical Center

Background: Sepsis and liver cirrhosis are major causes of morbidity & mortality worldwide. Patients with cirrhosis are vulnerable to infections and sepsis due to cirrhosis-associated immune dysfunction,

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leading to worse clinical outcomes. However, limited data exist on mortality trends among patients with both sepsis and cirrhosis.Therefore, this study aimed to evaluate temporal trends and demographic disparities in mortality among adults with sepsis and cirrhosis in the United States from 1999 to 2020. **Methods:** Individuals aged 25 and older who died from sepsis and cirrhosis were identified in the CDC WONDER database using ICD codes A40.0-A40.3, A40.8-A40.9, A41.0-A41.9 (sepsis) and K70.3, K74.0-K74.6 (cirrhosis) for the years 1999–2020. Mortality patterns were analyzed using the Age-Adjusted Mortality Rate (AAMR) per 100,000 population. Join point Regression 5.0 was applied to calculate the Average Annual Percent Change (AAPC), with p-values assessing statistical significance. Age-adjusted mortality rates were standardized to the 2000 U.S. Standard Population. The urban-rural stratification was based on the 2013 NCHS Urban–Rural Classification Scheme. Trends were examined by stratifying data by gender, race, urbanization, census region and state. **Results:** From 1999 to 2020, a total of 120,124 sepsis and cirrhosis related deaths were reported in the United States, with age-adjusted mortality rates (AAMR) increasing from 1.73 to 3.87 per 100,000. Mortality rose modestly from 1999–2008 (APC 1.45) followed by a significant increase from 2008–2020 (APC 5.61, $p < 0.05$). Males consistently exhibited higher mortality than females, with AAMR reaching 4.75 (4.88-4.63) vs 3.09 (3.19-2.99) in 2020. American Indian/Alaska Native populations had the highest mortality with AAMR 11.69 (12.96-10.42) in 2020, followed by Whites AAMR: 4.03 (4.12-3.95) and Blacks 3.19 (3.39-2.99), while Asians had the lowest rates 1.74 (1.96-1.53). Mortality increased across all racial groups, with the highest rise among American Indian/Alaska Native populations. Non-metropolitan areas demonstrated higher mortality than metropolitan regions, particularly in non-core areas AAMR 4.79 (5.15-4.43). Regionally, the West AAMR 4.42 (4.6-4.25) and South 4.23 (4.36-4.1) exhibited higher mortality compared to the Midwest 3.60 (3.76-3.43) and Northeast 2.68 (2.83-2.53). At the state level, New Mexico (2.84) and Texas (2.79) had the highest AAMRs, while Nebraska (0.92) and Kansas (0.96) had the lowest. **Conclusion:** Mortality related to sepsis and cirrhosis has steadily increased in the United States. Notable differences across sex, race, region, and rural versus urban areas highlight important gaps that warrant focused attention. These findings emphasize the need for targeted prevention strategies, improved resource allocation and further research to understand the causes and risk factors of rising trends in sepsis and cirrhosis related deaths.



Disclosures: Simran Joshi: Nothing to Disclose, Syed Irtiza Imam: Nothing to Disclose, Hania Haque: Nothing to Disclose, Laiba Tanveer: Nothing to Disclose, Sufyan Raza Khan: Nothing to Disclose, Preeti Advani: Nothing to Disclose, Marium Jawaid: Nothing to Disclose, Nothing to Disclose, Marium Jawaid: Nothing to Disclose, Nothing to Disclose, Muhammad Owais: Nothing to Disclose, Jeevin Singh Sandhu: Nothing to Disclose, Corrine Caissie: Nothing to Disclose, Mohammed Aatiqul Islam: Nothing to Disclose.

2154 | REDUCING HEALTH DISPARITIES IN CROATIAN WAR VETERANS: MOBILE LIVER SCREENING, TRUST-BASED OUTREACH, AND LINKAGE-TO-CARE OUTCOMES (2024–2025)

Tatjana Reic[1] Anna Mrzljak[2] Magda Pletikosa Pavic[3] Diana Nonkovic[3] Ivona Reic[4] Ana Visic[1] Viktor Domislovic[2], [1]Croatian Society for the Liver Diseases "Hepatos", [2]University Hospital Center Zagreb, [3]Teaching Institute for Public Health Split -Dalmatia County, [4]Croatian society for Liver Diseases Hepatos

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Background: War veterans represent a vulnerable population with increased cardiometabolic burden and lifestyle-related risk factors contributing to metabolic-associated steatotic liver disease (MASLD) and progressive liver fibrosis. Croatia, with one of the largest veteran populations in the European Union (≍11%), provides an important setting for evaluating long-term health disparities. We aimed to assess the prevalence and severity of hepatic steatosis and fibrosis in Croatian war veterans using transient elastography and to promote a mobile, community-based liver screening model. **Methods:** During 2024–2025, the Society Hepatos implemented a nationwide outreach program using a mobile clinic in collaboration with the Ministry of Veterans' Affairs, public health institutions, hospitals/hepatologists, and veterans' organizations. Participants underwent non-invasive liver assessment using FibroScan® with liver stiffness measurement (LSM) and controlled attenuation parameter (CAP). Clinically significant fibrosis was defined as ≥F2 and advanced fibrosis as F3–F4. Significant steatosis was defined as CAP ≥238 dB/m. Demographic, anthropometric, and clinical variables were collected, and multivariable logistic regression analyses identified factors associated with liver disease severity. **Results:** Among 448 participants, 72.0% were male, with a mean age of 51.3 ± 23.4 years. Mean BMI was 29.7 ± 10.1 kg/m² and waist circumference 100.9 ± 16.0 cm. Clinically significant fibrosis (≥F2) was identified in 18.1% and advanced fibrosis (F3–F4) in 6.5% of participants. Significant steatosis (≥S2) was detected in 63.8%, while severe steatosis (S3) was present in 44.5%. Arterial hypertension was present in 52.2%, dyslipidemia in 42.2%, active smoking in 23.9%, and ongoing alcohol consumption in 2.9%. Significant fibrosis was independently associated with alcohol consumption (OR 5.73, p = 0.006), arterial hypertension (OR 2.40, p = 0.008), and higher CAP values (OR 1.016, p < 0.001). Advanced fibrosis was associated with alcohol consumption (OR 11.29, p = 0.001) and higher CAP values (OR 1.021, p < 0.001). Significant steatosis was independently associated with higher BMI (OR 1.12, p = 0.008). **Conclusion:** Croatian war veterans carry a substantial burden of steatosis and liver fibrosis accompanied by high rates of metabolic comorbidities, highlighting important health disparities. Mobile, community-based liver screening provided linkage-to-care, increased participation, and facilitated earlier identification of individuals at risk for progressive liver disease. This scalable model may help reduce healthcare inequities and improve liver-related outcomes in growing veteran populations across Europe.
Disclosures: Tatjana Reic: Nothing to Disclose, Anna Mrzljak: Nothing to Disclose, Magda Pletikosa Pavic: Nothing to Disclose, Diana Nonkovic: Nothing to Disclose, Ivona Reic: Nothing to Disclose, Ana Visic: Nothing to Disclose, Viktor Domislovic: Nothing to Disclose.

2155 | PERSISTENT RACIAL AND ETHNIC DISPARITIES AND CONTRAINDICATED DISULFIRAM EXPOSURE IN 3,076 PATIENTS WITH ALCOHOL-ASSOCIATED CIRRHOSIS: A TEMPORALLY-ANCHORED ANALYSIS IN THE ALL OF US RESEARCH PROGRAM

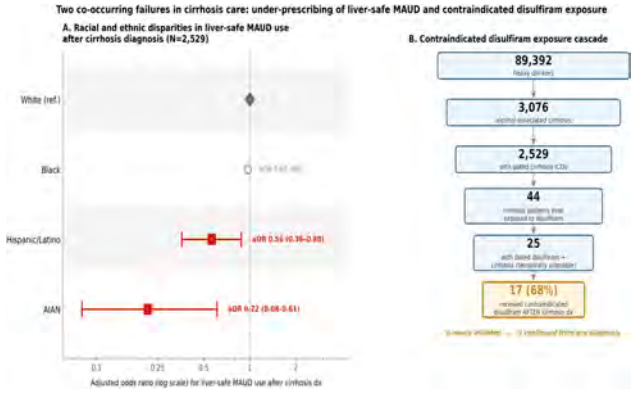
Sophia Yang[1] Walid Ayoub[2] Alexander Kuo[1] Paul Martin[1] Aarshi Vipani[1] Yun Wang[1] Yee Hui Yeo[1] JuDong Yang[1] Hyunseok Kim[2], [1]Cedars Sinai Medical Center, [2]Cedars-Sinai Medical Center

Background: Medications for alcohol use disorder (MAUD) reduce mortality and hepatic complications in alcohol-associated cirrhosis but are persistently underprescribed. Whether population-level prescribing disparities persist in cirrhotic patients, and whether contraindicated disulfiram exposure continues or initiates after cirrhosis is documented, has not been characterized in a diverse, temporally-anchored cohort. **Methods:** From 89,392 heavy drinkers in the All of Us Research Program, we identified 3,076 with alcohol-associated cirrhosis (2,529 with dated cirrhosis ICD codes enabling temporal alignment). Post-cirrhosis prescribing rates were calculated requiring ≥3 prescriptions per ingredient initiated or continued after the documented cirrhosis diagnosis. Multivariable logistic regression adjusted for demographic and metabolic risk factors. Disulfiram, hepatotoxic and contraindicated in cirrhosis, was temporally aligned with cirrhosis diagnosis dates to distinguish historical pre-diagnosis exposure from continued or de novo prescribing afterward. **Results:** Among 2,529 cirrhotic patients with dated cirrhosis, only 11.3% received any AUD-specific MAUD after diagnosis; 8.1% received liver-safe MAUD (baclofen or acamprosate); 4.8% received naltrexone. Racial and ethnic disparities observed at the population level among heavy drinkers persisted in this cirrhotic cohort with similar magnitude, even when treatment indication was strongest. For liver-safe MAUD after cirrhosis diagnosis (vs White non-Hispanic): Hispanic/Latino aOR 0.564 (95% CI 0.36-0.88, p = 0.011); American Indian and Alaska Native (AIAN) aOR 0.216 (0.08-0.61, p = 0.004), a 78% relative reduction; Black-White equivalence (aOR 0.974, p = 0.89). Among 44 cirrhotic patients exposed to disulfiram, 25 had dated diagnoses enabling temporal alignment. 17 (68%) received contraindicated disulfiram after cirrhosis was documented: 8 newly initiated and 9 continuing from pre-diagnosis

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prescriptions. Median continued post-diagnosis exposure was 1,110 days (~3 years). **Conclusion:** Among patients with established alcohol-associated cirrhosis, evidence-based MAUD prescribing remains low overall (8.1% liver-safe), with substantial Hispanic and AIAN disparities that persist even at the highest level of clinical need. Concurrently, contraindicated disulfiram exposure occurred in 68% of disulfiram-exposed cirrhotic patients with multi-year continued prescribing after diagnosis. These two co-occurring failures, under-prescribing of safe MAUD and persistent disulfiram exposure despite documented cirrhosis, are potential targets for hepatology-led quality improvement.



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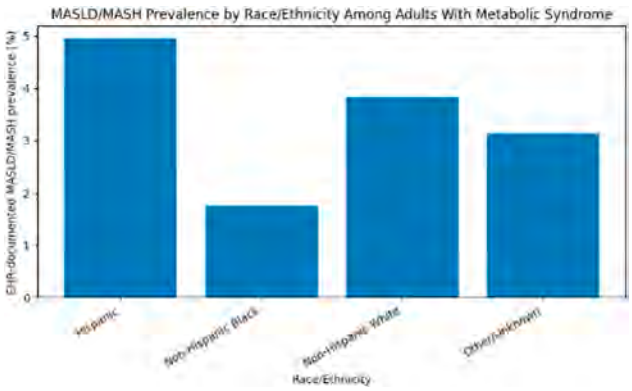
2156 | SOCIAL RISK AND RACIAL DISPARITIES IN EHR-DOCUMENTED MASLD AMONG ADULTS WITH METABOLIC SYNDROME

Ihunanya Kanu[1] Bolaji Ayinde[2] Ankita Verma[3] Yetunde Akande[4] Yousef Ebrahim[3] Richard Heard[3], [1]Baptist Memorial Hospital- Golden Triangle, [2]Northeast Georgia Medical Center, [3]Baptist Memorial Hospital - Golden Triangle, [4]John H Stroger Jr. hospital of cook county

Background: MASLD is the hepatic manifestation of metabolic dysfunction and is strongly associated with obesity, type 2 diabetes, hypertension, and dyslipidemia. Population-based studies show racial/ethnic differences in MASLD burden, with higher prevalence among Hispanic adults and lower documented prevalence among non-Hispanic Black adults. Social risks, including food insecurity and difficulty affording healthcare, may influence MASLD screening and EHR documentation. We examined whether these factors were associated with EHR-documented MASLD/MASH among adults with metabolic syndrome and whether associations differed by race/ethnicity. **Methods:** We conducted a cross-sectional analysis of adults $\geq$18 years with EHR data in the All of Us Controlled Tier Dataset v8. Metabolic syndrome was defined as $\geq$3 of 5 components: BMI $\geq$30 kg/m², type 2 diabetes, hypertension, triglycerides $\geq$150 mg/dL, and low HDL cholesterol using sex-specific cutoffs. EHR-documented MASLD/MASH was identified using diagnosis concepts for nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, and NASH-related cirrhosis, excluding alcoholic fatty liver and acute fatty liver of pregnancy. Food insecurity was defined as worrying that food would run out before money was available to buy more. Healthcare access barrier was defined as inability to afford a healthcare provider. Multivariable logistic regression assessed associations with MASLD/MASH, adjusting for age, BMI, sex at birth, race/ethnicity, diabetes, and SDOH variables. Interaction terms tested effect modification by race/ethnicity. Analyses used Python in Jupyter Notebook. **Results:** Among 388,424 adults with EHR data, 63,659 met criteria for metabolic syndrome. EHR-documented MASLD/MASH was identified in 2,114 participants (3.32%) and increased with metabolic syndrome burden: 2.89% with 3 components, 3.93% with 4, and 5.13% with 5. Among 18,966 participants with complete SDOH data, 4,111 (21.7%) reported food insecurity and 1,316 (6.9%) reported a healthcare access barrier. MASLD/MASH prevalence was 3.38% in food-secure versus 3.92% in food-insecure participants and varied by race/ethnicity: Hispanic 4.94%, non-Hispanic White 3.82%, Unknown 3.14%, and non-Hispanic Black 1.75%. After adjustment, food insecurity (aOR 1.06, 95% CI 0.87–1.28) and healthcare access barriers (aOR 1.03, 95% CI 0.77–1.40) were not independently associated with MASLD/MASH. Non-Hispanic Black participants had lower adjusted odds of MASLD/MASH than Hispanic participants (aOR 0.31, 95% CI 0.22–0.46) **Conclusion:** Food insecurity and healthcare affordability barriers were common but not independently associated with EHR-documented MASLD/MASH after adjustment. Persistent racial/ethnic differences, including lower documentation among non-Hispanic Black participants, suggest possible gaps in recognition and support equitable MASLD screening in high-risk populations.

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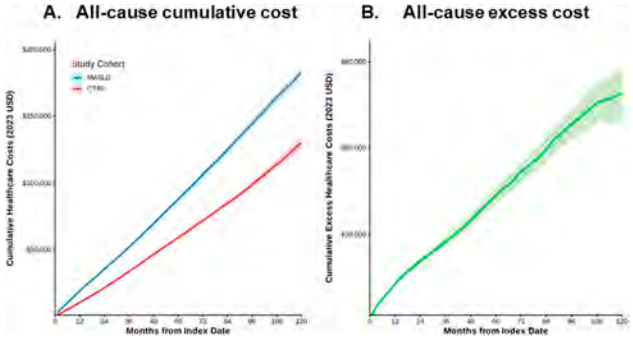


Disclosures: Ihunanya Kanu: Nothing to Disclose, Bolaji Ayinde: Nothing to Disclose, Ankita Verma: Nothing to Disclose, Yetunde Akande: Nothing to Disclose, Yousef Ebrahim: Nothing to Disclose, Richard Heard: Nothing to Disclose.

2157 | EXCESS ECONOMIC AND HEALTHCARE UTILIZATION BURDEN OF MASLD VERSUS NON-MASLD CONTROLS: A NATIONWIDE LONGITUDINAL STUDY

Xiaonan Su[1] Xianhua Mao[2] Hong Fan[2] Rui Huang[3] Bowu Chen[4] Danfeng Ren[5] Ramsey Cheung[2] Mindie Nguyen[2], [1]The First Affiliated Hospital, Zhejiang University School of Medicine, [2]Stanford University Medical Center, [3]Nanjing Drum Tower Hospital, [4]Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, [5]The First Affiliated Hospital of Xi'an Jiaotong University

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the leading cause of chronic liver disease globally, incurring substantial economic and healthcare utilization burden. We aimed to quantify the excess burden attributable to MASLD. **Methods:** Using data from the Merative™ MarketScan® databases (2007–2023), patients with MASLD and non-MASLD controls with at least a 2-year look-back period prior to baseline were matched 1: 1 to non-MASLD controls via a sequential matching strategy of exact matching on index year and sociodemographic characteristics followed by stratified propensity score matching on smoking, obesity, T2D, hyperlipidemia, hypertension, CVD, CKD, non-liver cancer, co-hepatic diseases, cirrhosis, HCC, CCI score and historical health care costs and resource utilization (HCRU). To estimate the excess 10-year cumulative health care costs and HCRU attributable to MASLD, we calculated the difference between these cohorts using a Horvitz–Thompson estimator with monthly updated inverse probability of censoring weighting (IPCW). **Results:** From the initial populations of 272,087 patients with MASLD and 62,444,397 patients without MASLD, 71,018 pairs of MASLD and non-MASLD patients were identified following the two-staged matching strategy. The 10-year cumulative all-cause excess cost in MASLD (vs non-MASLD controls) was $52,886 (95% CI, $46,054-$59,173) per patient with an associated cost ratio (CR) of 1.41 (95% CI, 1.35-1.46) (Figure 1). Outpatient services constituted the largest component of the excess cost ($24,340; CR, 1.37), followed by pharmacy ($15,822; CR, 1.47), inpatient ($10,767; CR, 1.40), and emergency department care cost ($2,035; CR, 1.47), and with excess cost by facility fees ($23,163; CR, 1.39) more than double those of physician fees ($10,065; CR, 1.35). In subgroup analyses, CRs remained consistently and significantly higher than those of controls across all strata defined by sex, age, insurance type, and specific metabolic comorbidities. In the secondary exact-matched cohort without adjustment for differences in patient background comorbidities, excess costs were substantially larger ($162,883; CR, 2.34). **Conclusion:** Newly diagnosed MASLD incurs substantial long-term excess healthcare cost across care settings and domains, especially without statistical adjustment for comorbidities, many of which are associated with MASLD.



Disclosures: Xiaonan Su: Nothing to Disclose, Xianhua Mao: Nothing to Disclose, Hong Fan: Nothing to Disclose, Rui Huang: Nothing to Disclose, Bowu Chen: Nothing to Disclose, Danfeng Ren: Nothing to Disclose, Ramsey Cheung: Nothing to Disclose, Mindie Nguyen: Pfizer, Astra Zeneca, Aligos, GSK, Delfi, Innogen, Exact Sci: Grant/Research Support, GSK: Advisor.

2158 | CIRRHOSIS HEALTHCARE COSTS TRIPLED IN MANITOBA FROM 2010–2022: VOLUME, NOT INTENSITY, DRIVES THE BURDEN

Nabiha Faisal[1] Harminder Singh[1] Randy Walld[1], [1]University of Manitoba

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Background: Cirrhosis is a major contributor to healthcare spending, U.S. direct costs reached $32.5 billion in 2016, with over 65% from inpatient and emergency department (ED) care yet longitudinal Canadian data across cirrhosis etiologies are limited. We evaluated temporal trends in etiology-specific healthcare utilization and direct medical costs among adults with cirrhosis in Manitoba, 2010–2022. **Methods:** We conducted a population-based cohort study using Manitoba Centre for Health Policy (MCHP) linked administrative databases (hospital discharges, physician claims, outpatient prescription dispensings, and ED visits), 2010–2022. Adults (≥18 years) with cirrhosis were identified using a validated case-finding algorithm and classified hierarchically into mutually exclusive etiologies: alcohol-associated liver disease (ALD); metabolic dysfunction-associated steatotic liver disease (MASLD); autoimmune liver disease (AIH, PBC, PSC); and viral hepatitis (HBV/HCV). Direct costs were estimated using standardized MCHP methodologies; hospitalization from resource intensity weights and provincial cost estimates, physician services from claims, prescriptions from dispensing records, and ED from Canadian Institute of Health Information (CIHI) Manitoba average cost per visit × visit frequency. Total, annual aggregate, and per-person annual costs were calculated using a one-year active denominator in Canadian dollars and compared across etiologies and over time. **Results:** The prevalent cirrhosis population in Manitoba nearly tripled between 2010 and 2022 (4,625 to 13,839), and total annual healthcare expenditures rose 2.6-fold ($56.7M to $147.3M). Per-person annual cost declined modestly ($12,270 to $10,645), indicating that rising aggregate cost reflected case-volume growth rather than per-patient cost intensity. Hospitalizations dominated spending across all etiologies ($95.7M, 65% of 2022 expenditures). By 2022, autoimmune liver disease was the most expensive etiology per patient ($16,486), overtaking ALD ($13,444), a reversal from 2010 when ALD was highest ($15,076). This shift was driven by autoimmune inpatient cost, which reached $11,332/person in 2022, the highest of any etiology. Viral hepatitis prescription costs peaked at $11,421 per person in 2015 with HCV direct-acting antiviral rollout before declining to $2,892 by 2022. MASLD had the lowest per-person cost ($7,755) but, with 8,006 patients (58% of cohort), contributed $62.1M (42%) of total spending, the largest population-level burden. **Conclusion:** Rising cirrhosis costs in Manitoba reflect case-volume growth rather than per-patient cost intensity, with hospitalizations dominant across all etiologies. Etiology-specific prevention, particularly for MASLD and ALD and strategies to reduce avoidable hospitalizations are the key policy levers to decrease direct healthcare costs associated with cirrhosis.



Disclosures: Nabiha Faisal: Intercept: Consultant, Mirium: Advisor, Gilead: Advisor, Advanz: Advisor, GSK: Advisor, Harminder Singh: Nothing to Disclose, Randy Walld: Nothing to Disclose.

2159 | COST-EFFECTIVENESS OF SEQUENTIAL NON-INVASIVE TESTING (NIT) FOR DYSFUNCTION–ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) RISK STRATIFICATION IN US PRIMARY CARE: A LIFETIME MARKOV ANALYSIS

Zobair Younossi[1] Khalid AlNaamani[1] Cristiane Villela-Nogueira[2] Fatema Nader[1] Saleh Alqahtani[3] Laurent Castera[4] James Paik[5], [1]The Global NASH/MASH Council, [2]Universidade Federal do Rio de Janeiro, [3]King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia, [4]Hopital Beaujon, [5]Global NASH/MASH Council

Background: To identify at risk MASLD patients, current guidelines recommend sequential NIT algorithms using FIB-4 followed by vibration-controlled transient elastography (VCTE) or FIB-4 followed by enhanced liver fibrosis (ELF) score in patients with type 2 diabetes (T2D) or medically complicated obesity (MCO). We evaluated the cost-effectiveness of this sequential testing strategy in the US primary care setting. **Methods:** We developed a 14-state lifetime Markov model (US healthcare payer perspective; 3% discount rate; 2025 US dollars). Populations comprised 36.4 million adults with T2D and 56.8 million with MCO derived from NHANES 2017-2020. Prevalence of advanced fibrosis among patients with T2D (9.7%) and MCO (6.0%), fibrosis stage distribution, and the diagnostic performance of NITs were further characterized using Global MASLD Project (≥21,000 biopsy-confirmed cases) and adjusted for referral and spectrum bias. Four strategies were compared: 1) current standard of care (comparator), 2) FIB-4 followed by VCTE, 3) FIB-4 followed by ELF and 4) FIB-4 followed by either VCTE (70%) or ELF (30%) based on available modality. Patients were stratified into 3 risk groups: (1) Low risk [1st NIT: FIB-4 (<1.3) or 2nd NIT: VCTE/ELF (<8 kPa/<9.2)], (2) Treatment-eligible (F2-F3),

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(3) Cirrhosis. Fibrosis stage distributions were estimated using Bayesian analysis combining NIT test performance (Global MASLD Project) with NHANES population prevalence priors, yielding posterior probabilities reflecting primary care populations. These distributions served as Markov model starting states for each group. Treatments included resmetirom, semaglutide, and lifestyle intervention with real-world adherence, persistence, and price erosion. **Results:** Across the combined target population of 93.2 million US adults, the base case yielded a combined incremental cost-effectiveness ratio (ICER) of $27,523 per quality-adjusted life-year (QALY) gained versus standard of care. Individual cohort ICERs were $49,852/QALY (T2D) and $16,870/QALY (MCO). Results were consistent across NIT strategies (combined: $27,497 to $27,583/QALY). Over lifetime horizon, this strategy substantially reduced the risk of complications by preventing cirrhosis, DCC and liver-related deaths (Table). **Conclusion:** Sequential NIT-based MASLD risk stratification is cost-effective in US primary care patients with T2D and MCO. This supports systematic implementation in primary care to identify at-risk patients.

Table. Lifetime Clinical Impact of Sequential NIT-Based MASLD Risk Stratification Versus Standard of Care in High-Risk Primary Care Populations

Outcome	Type 2 Diabetes			Medically Complicated Obesity		
	Cases prevented	Reduction	NNS	Cases prevented	Reduction	NNS
Compensated cirrhosis	1,107,806	22%	33	2,050,563	20%	28
Decompensated cirrhosis	846,094	24%	43	1,567,566	25%	36
Liver-related deaths	166,488	16%	219	287,705	18%	197

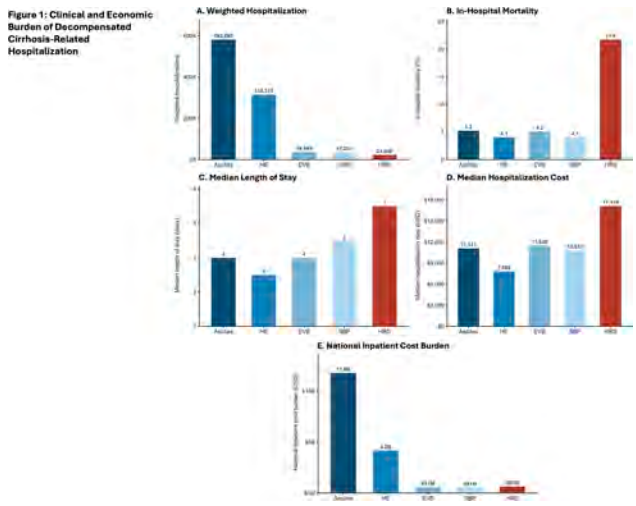
- Lifetime cumulative events prevented by the base case strategy (FIB-4 followed by VCTE in 70% or ELF in 30% of patients) versus current standard of care across 93.4 million adults with type 2 diabetes and 56.8 million with medically complicated obesity.
- Percentage reduction represents relative risk reduction versus standard of care.
- NNS, number needed to screen to prevent one outcome event over a lifetime horizon.

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2160 | INPATIENT HEALTHCARE UTILIZATION AND ECONOMIC BURDEN OF DECOMPENSATED CIRRHOSIS IN THE UNITED STATES

Kartik Dapke[1] Spencer Goble[2] Timothy Davie[3] Jesse Fletcher[3] Anna Strauss[3] Serena Brosten[3] Giovanni Roldan[2] Prowpanga Udompap[4], [1]Department of Medicine, Saint Vincent Hospital, Worcester, MA, [2]Division of Gastroenterology, Hepatology and Nutrition, University of Minnesota, [3]Department of Medicine, University of Minnesota, [4]Division of Gastroenterology, Minneapolis VA Health System

Background: The prevalence of decompensated cirrhosis has tripled in the United States since 1990, and it now ranks among the costliest inpatient conditions. Although its per-patient costs exceed those of heart failure and chronic obstructive pulmonary disease, subtype-specific data on clinical outcomes and national cost burden is lacking. **Methods:** We conducted a retrospective analysis using the National Inpatient Sample (NIS) database from January 1, 2016, to December 31, 2022 and identified adult hospitalizations with cirrhosis-related decompensation using ICD-10-CM codes. Decompensation was stratified by subtype: ascites, hepatic encephalopathy (HE), esophageal variceal bleeding (EVB), spontaneous bacterial peritonitis (SBP), and hepatorenal syndrome (HRS). Outcomes included in-hospital mortality, length of stay, total hospitalization cost, and discharge disposition. Weighted national estimates were derived and clinical outcomes were compared across subtypes. **Results:** Decompensated cirrhosis accounted for approximately 1,000,085 hospitalizations and $17.8 billion in national costs. Ascites was the most common subtype (583,885 admissions; national burden $11.8 billion (B); median cost $11,141), followed by HE (316,375 admissions; $4.2B; median cost $7,869). HRS, though least common (24,000 admissions), had the highest in-hospital mortality (21.8%), longest median LOS (7 days; IQR 4-12), and highest median per-admission cost ($17,139; IQR $9,592-$30,455) (Figure 1). HRS also had the highest rates of renal replacement therapy (17.8%), vasopressor use (6.0%), and sepsis (9.7%). Among survivors, 58.8% of HRS patients were discharged home versus 85.3% for EVB. **Conclusion:** Decompensated cirrhosis contributes about $17.8 billion to the total inpatient costs in the United States. HRS carries the highest per-admission mortality, resource use, and cost despite its low prevalence. Ascites has the largest share of national expenditure due to its high volume.



Disclosures: Kartik Dapke: Nothing to Disclose, Spencer Goble: Nothing to Disclose, Timothy Davie:

Symbols: ♦, Poster of Distinction; ★, Foundation Award Recipient

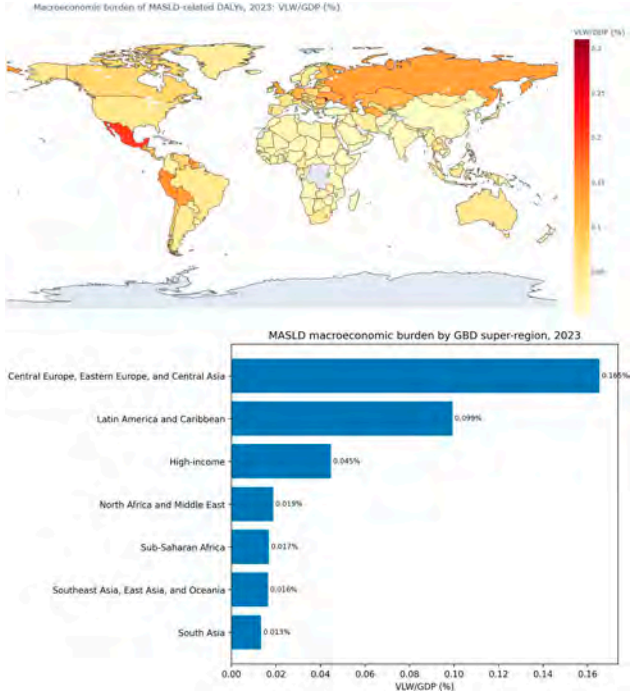
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Nothing to Disclose, Jesse Fletcher: Nothing to Disclose, Anna Strauss: Nothing to Disclose, Serena Brosten: Nothing to Disclose, Giovanni Roldan: Nothing to Disclose, Prowpanga Udompap: Nothing to Disclose.

2161 | THE GLOBAL MACROECONOMIC CONSEQUENCES OF MASLD: GLOBAL VALUE-OF-LOST-WELFARE LOSSES AND REGIONAL INEQUITIES ACROSS 193 COUNTRIES

Jagadish Koyi[1] Hardik Dineshbhai Desai[2] Digantkumar Patel[3] Mounika Kotte[4] Sri Ram Charan Gundapaneni[5] Serene Sara John[6] Pragathi Munnangi[7], [1]Integris Health, Oklahoma City, Oklahoma. USA. 73112, [2]AB Plus Multispecialty Hospital, Ahmedabad, Gujarat, India, [3]Springfield Clinic, Springfield, IL, USA, [4]Prime south consortium, Weslaco, Texas, USA,78596, [5]UCF/HCA Florida Ocala Hospital, Ocala, Florida, United States, 34471, [6]Detroit medical center, Detroit, Michigan, 48201, [7]BronxCare Health System , Bronx , New York - 10457

Background: Metabolic dysfunction–associated steatotic liver disease (MASLD) is now a dominant driver of chronic liver disease, yet its macroeconomic burden remains poorly quantified. We estimated global, regional, and national welfare losses attributable to MASLD-related disability-adjusted life years (DALYs). **Methods:** We used Global Burden of Disease 2023 estimates for MASLD-related burden, and World Bank 2023 gross domestic product (GDP), GDP per capita, and population data. Value of lost welfare (VLW) was estimated as DALYs multiplied by GDP per capita adjusted for purchasing power parity (PPP). VLW/GDP (%) quantified macroeconomic loss relative to national economic output. **Results:** Across 193 countries, MASLD accounted for 2.52 million DALYs in 2023. Global MASLD-attributable value of lost welfare was $81.56 billion, equivalent to 0.044% of global GDP. The largest absolute welfare losses occurred in the United States ($13.91 billion; 0.050% of GDP), Russian Federation ($8.66 billion; 0.134%), Mexico ($6.65 billion; 0.206%), Germany ($6.50 billion; 0.113%), and the United Kingdom ($5.08 billion; 0.128%). The highest VLW/GDP was observed in Republic of Moldova (0.310%), followed by Mexico (0.206%), Puerto Rico (0.204%), Ecuador (0.154%), Peru (0.152%), Guyana (0.151%), United States Virgin Islands (0.146%), Bolivia (0.137%), Ukraine (0.136%), and El Salvador (0.136%). By GBD super-region, High-income countries had the largest absolute VLW ($39.95 billion; 52.5% of global VLW), followed by Latin America and Caribbean ($12.29 billion; 16.2%), Central Europe, Eastern Europe, and Central Asia ($11.37 billion; 14.9%), and Southeast Asia, East Asia, and Oceania ($7.63 billion; 10.0%). However, VLW/GDP was highest in Central Europe, Eastern Europe, and Central Asia (0.165%), followed by Latin America and Caribbean (0.099%) and High-income countries (0.045%). From 1990 to 2023, MASLD DALYs increased in all GBD super-regions. The largest proportional increases occurred in Latin America and Caribbean (+208.1%), Central Europe, Eastern Europe, and Central Asia (+185.7%), Sub-Saharan Africa (+162.9%), and North Africa and Middle East (+157.9%). VLW/GDP increased most prominently in Central Europe, Eastern Europe, and Central Asia (+0.096 percentage points) and Latin America and Caribbean (+0.051 percentage points), indicating worsening relative macroeconomic strain in these regions. **Conclusion:** MASLD imposes a measurable global macroeconomic burden exceeding $81 billion annually, with disproportionate relative losses in Eastern Europe/Central Asia and Latin America. These findings support prioritizing MASLD prevention, early fibrosis detection, and metabolic-risk control as economic as well as hepatologic imperatives.



Disclosures: Jagadish Koyi: Nothing to Disclose, Hardik Dineshbhai Desai: Nothing to Disclose, Digantkumar Patel: Nothing to Disclose, Mounika Kotte: Nothing to Disclose, Sri Ram Charan Gundapaneni:

Symbols: ♦, Poster of Distinction; ★, Foundation Award Recipient

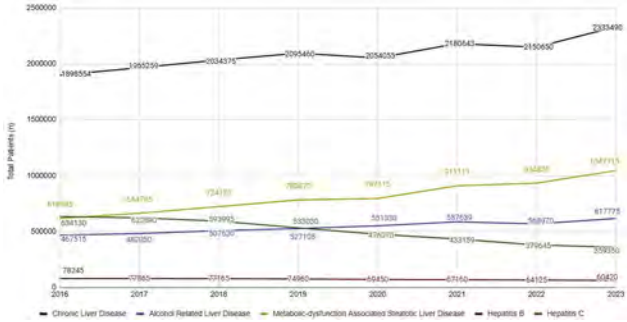
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Nothing to Disclose, Serene Sara John: Nothing to Disclose, Pragathi Munnangi: Nothing to Disclose.

2162 | CONTEMPORARY TRENDS IN CHRONIC LIVER DISEASE AMONG HOSPITALIZED PATIENTS IN THE UNITED STATES: A NATIONWIDE ANALYSIS (2016-2023)

Aalam Sohal[1] Mariam Alamgir[1] Carol Singh[2] Kris Kowdley[1], [1]Liver Institute Northwest, [2]Dayanand Medical College and Hospital

Background: The epidemiologic landscape of chronic liver disease (CLD) in the United States is rapidly evolving, with metabolic-associated steatotic liver disease (MASLD) emerging as the most common cause of CLD. During the COVID-19 pandemic, there has been an increase in the rates of both MASLD and alcohol use. The study examines recent national trends in the burden and cost of CLD-related hospitalizations between 2016 and 2023. **Methods:** Adult hospitalizations with CLD were identified using the National Inpatient Sample from 2016 to 2023. Patient demographics, liver disease etiology, cirrhosis, decompensated cirrhosis and acute-on-chronic liver failure (ACLF) were identified among patients with CLD. The total healthcare cost was estimated using the cost-to-charge ratio and adjusted for inflation to 2023 dollars. Multivariate logistic regression was used to evaluate temporal trends in hospitalizations for chronic liver disease. **Results:** A total of 16.7 million hospitalizations with CLD were identified. Total CLD hospitalizations increased from 1.9 million in 2016 to 2.3 million in 2023 (aOR 1.04, $p < 0.001$) (Fig 1). Total hospitalization costs in patients with CLD increased from $37.8 billion in 2016 to $55.1 billion in 2023. The total hospitalization cost among patients with CLD during the study period was $383 billion dollars. The proportion of hospitalizations with cirrhosis and decompensated cirrhosis increased from 40.8% to 45.9%, and 19.6% to 26.3%, respectively. The costs for patients with cirrhosis and decompensated cirrhosis increased from $16 billion to $27 billion and from $9.9 billion to $17.5 billion. The proportion of ACLF hospitalizations increased from 3.4% to 7.7% during the study period. Costs for ACLF increased from $3.9 billion to $8.7 billion, a 126% increase. MASLD was the most common CLD, increasing from 618,535 in 2016 to 1.04 million in 2023 (aOR 1.09, $p < 0.001$). Costs of MASLD hospitalizations increased from $12 billion in 2016 to $23.7 billion in 2023, a 100% increase during the study period. An increase in alcohol-related liver disease (ALD) hospitalizations from 467,515 in 2016 to 617,775 in 2023 (aOR: 1.05, $p < 0.001$) was also observed. Costs for ALD hospitalizations increased from $8.8 billion in 2016 to $13.6 billion in 2023. Hospitalizations for hepatitis C (aOR 0.93, $p < 0.001$) and hepatitis B (aOR 0.98, $p < 0.001$) decreased during the study period. The in-hospital mortality rate increased from 4.4% in 2016 to 5.6% in 2021, then decreased to 4.7% in 2023. **Conclusion:** Our study reports an alarming increase in CLD hospitalizations, driven by a striking increase in hospitalizations for MASLD and ALD. This represents the changing landscape as well as the rising healthcare and economic burden of CLD hospitalizations at a national level. Public health interventions aimed at reducing alcohol use, lifestyle modifications, and new pharmacologic therapies will be beneficial in curbing the healthcare burden.



Disclosures: Aalam Sohal: Nothing to Disclose, Mariam Alamgir: Nothing to Disclose, Carol Singh: Nothing to Disclose, Kris Kowdley: Nothing to Disclose.

2163 | THE IMPACT OF CARDIOMETABOLIC RISK FACTORS ON HEALTH CARE RESOURCE USE IN ADULT PATIENTS LIVING WITH STEATOTIC LIVER DISEASE

Guanghao Zhang[1] Abdalla Aly[1] Andres Quintero[1] David Shi[1] Aidan McGovern[1] Hashem El-Serag[2], [1]Novo Nordisk, [2]Baylor College of Medicine

Background: Steatotic liver disease (SLD), including alcohol-related liver disease (ALD) and metabolic dysfunction–associated steatotic liver disease (MASLD) poses a growing healthcare burden in the US. Studies have shown that the number of cardiometabolic risk factors (CMRFs) is associated with advanced hepatic fibrosis and mortality, but limited data exist on their impact on health care resource use (HCRU). The objective of this analysis was to estimate the burden of SLD by subtype and compare the impact of CMRFs (number and type) on HCRU and costs in patients living with SLD by subtype. **Methods:** This retrospective study used Komodo data from Jan 2017-Nov 2023. Adults with ≥ 2 outpatient or ≥ 1 inpatient diagnosis for ALD or MASLD (index was the first qualifying diagnosis) and ≥ 12 months of pre- and post-

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index enrollment were included. Patients with other liver diseases or decompensation were excluded. Outcomes were per patient per year (PPPY) total costs and all-cause HCRU (outpatient [OP], inpatient [IP], emergency room [ER], intensive care unit [ICU]). Negative binomial and gamma models estimated adjusted rate ratios (RRs) and cost ratios (CRs) for the association between number and type of CMRFs (hypertension, dyslipidemia, overweight/obesity, type 2 diabetes using ICD-10 codes) on HCRU and costs by SLD subtype, using interaction terms, controlling for demographics, comorbidities, and baseline HCRU. **Results:** The study included 995,114 SLD patients (MASLD: 92.7%, ALD: 7.3%). Almost all patients with ALD had $\geq$1 CMRF (97%). Compared to the MASLD group, the ALD group had greater proportions of patients who were male (68% vs 40%), had Medicaid insurance (37% vs 24%), 3+ Quan Comorbidity Index (45% vs 25%). Compared to the MASLD group, the PPPY adjusted total medical costs were 73% higher in the ALD group (CR: 1.73, 95% CI 1.68-1.77) and the PPPY adjusted HCRU was also higher in the ALD group (RR for OP: 1.10 (1.08-1.11), INP: 2.44 (2.35-2.52), ER: 1.57 (1.53-1.61), ICU: 3.59 (3.39-3.80). In the MASLD group, patients with 4 CMRFs were associated with 46% higher costs (CR: 1.46, 95% CI 1.45-1.47) than patients with only 1 CMRF. A similar, yet smaller in magnitude, association was observed in the ALD group (CR: 1.13, 95% CI 1.10-1.16). The highest effect sizes were for hypertension and type 2 diabetes (Figure). **Conclusion:** ALD was associated with substantially higher economic burden per patient than MASLD. The number of CMRFs significantly adds more burden to patients living with SLD, especially in MASLD.

		MASLD					ALD				
		$	OUP	INP	ER	ICU	$	OUP	INP	ER	ICU
# of CMRFs	2	1.20*	1.15*	1.19*	1.16*	1.35*	1.12*	1.14*	1.07*	1.08*	1.09*
	3	1.31*	1.22*	1.22*	1.25*	1.57*	1.10*	1.21*	0.97	1.08*	0.99
	4	1.46*	1.28*	1.24*	1.29*	1.75*	1.13*	1.28*	0.89*	1.10*	0.91*
Type of CMRF	OW/OBE	0.93*	0.99	0.76*	0.91*	0.63*	0.88*	0.99	0.89*	0.93*	0.83*
	DYSL	1.02*	1.05*	0.94*	1.02*	1.08*	0.92*	1.04*	0.84*	0.97*	0.84*
	T2D	1.15*	1.06*	1.09*	1.06*	1.21*	1.14*	1.12*	1.05*	1.09*	1.11*
	HTN	1.33*	1.18*	1.50*	1.31*	2.00*	1.49*	1.26*	1.37*	1.32*	1.59*

MASLD, metabolic dysfunction-associated steatotic liver disease, **ALD**, alcohol-related liver disease, **CMRF**, cardiometabolic risk factor, **OUP**, Outpatient, **INP**, inpatient, **ER**, emergency room, **ICU**, intensive care unit, **HTN**, hypertension; **T2D**, type 2 diabetes; **DYSL**, dyslipidemia; **OW/OBE**, overweight/obesity.
*= statistically significant at $p < 0.05$ for cost ratios (for $) and rate ratios (for OUP, INP, ER, ICU), # of CMRFs reference group is 1 CMRF; Type of CMRF reference group is the no group e.g., HTN vs no HTN.

Disclosures: Guanghao Zhang: Novo Nordisk Inc.: Employee, Abdalla Aly: Novo Nordisk Incorporated: Employee, Novo Nordisk Incorporated: Stock - publicly traded company, Andres Quintero: Novo Nordisk: Employee, Pfizer, Inc: Stock - publicly traded company, Viking Therapeutics: Stock - publicly traded company, Eli Lilly: Stock - publicly traded company, David Shi: Nothing to Disclose, Aidan McGovern: Nothing to Disclose, Hashem El-Serag: Nothing to Disclose, Nothing to Disclose.

2164 | POPULATION-LEVEL TRENDS IN CIRRHOSIS-RELATED HOSPITAL ENCOUNTERS AND RELATED HEALTHCARE COSTS IN ALBERTA

Puneeta Tandon[1] Ting Wang[2] Kinjal Patel[1] Samina Khan[1] Mayur Brahmania[2], [1]University of Alberta, [2]University of Calgary

Background: Cirrhosis-related hospitalizations are increasing globally, driven largely by alcohol-associated liver disease and metabolic dysfunction-associated steatotic liver disease. This has implications for healthcare utilization, mortality, and expenditures. We evaluated temporal trends in cirrhosis-related hospital burden and associated healthcare costs across Alberta. **Methods:** We performed a retrospective population-based study of adult patients with cirrhosis-related hospital encounters in Alberta between 2024 and 2025 using validated ICD-10 coding algorithms derived from administrative and electronic medical record data. Cirrhosis-related encounters included emergency department visits and inpatient hospitalizations. Outcomes of interest included hospitalization frequency, readmission within 7 and 30 days, mortality rates within 30 and 90 days, and total healthcare costs. Temporal trends across the study period were stratified by provincial zone and hospital. **Results:** Alcohol-related cirrhosis of the liver and mental/behavioural disorders associated with alcohol use and withdrawal were the two most frequent primary diagnoses among cirrhosis-related hospital encounters. Most patients were admitted to General Medicine units, accounting for 81% of total admissions. Patients aged 59-61 accounted for the highest proportion of these encounters. In 2024 and 2025, there were 3,301 and 3,090 cirrhosis-related hospital visits, respectively, involving 1,966 and 1,905 distinct patients. 7-day readmission rates were 28.65% and 28.39%, and 30-day readmission rates were 50.14% and 50.20%. 30-day mortality rates were 13.61% and 8.01%, and 90-day mortality rates were 18.42% and 10.26%. Concurrently, total healthcare costs were $243.5 million in 2024 and $236.6 million in 2025, highlighting the substantial healthcare burden associated with cirrhosis in Alberta. **Conclusion:** Cirrhosis-related healthcare utilization and associated costs remain high across Alberta, reflecting the substantial burden of cirrhosis and the need for targeted preventative and resource-allocation strategies. These findings emphasize the need for upstream interventions to mitigate the determinants of health and disease associated with cirrhosis.

Disclosures: Puneeta Tandon: Nothing to Disclose, Ting Wang: Nothing to Disclose, Kinjal Patel: Nothing to

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Disclose, Samina Khan: Nothing to Disclose, Mayur Brahmania: Nothing to Disclose.

2165 | ◆ HEPATOLOGIST-LED POINT-OF-CARE ELASTOGRAPHY (H-POCE): IMPLEMENTATION AND DELIVERED QUALITY OF A BEDSIDE LIVER ASSESSMENT SERVICE

Akash Roy[1] Suhita Dutta[1] Shardhya Chakroborty[1] Shruti Keyal[1] Surabhi Jajodia[1] Mahesh Goenka[1], [1]Apollo Multispeciality Hospitals

Background: Liver elastography is central to risk stratification in hepatology, yet access is frequently rate-limited by dependence on radiology or technician-led services, creating referral delays and fragmented, multi-visit pathways. A hepatologist-led, point-of-care (POC) model in which the treating clinician acquires and interprets elastography within the same clinical encounter could improve access and consolidate assessment, However, its real-world feasibility and delivered quality remains poorly characterised **Methods:** We established a hepatologist led , point-of-care 2D shear-wave elastography (h-POCE) service and prospectively enrolled consecutive patients with hepatologist acquiring and interpreting all examinations at the POC, generating liver stiffness (LSM), liver attenuation metrics and per-examination quality indices (interquartile-range-to-median ratio [IQR/M]; reliability measurement index [RMI]) Implementation was characterised by throughput (patients per scan day), referral case-mix, and proportion receiving a complete assessment in one encounter. Delivered technical quality was assessed against pre-specified IQR/M thresholds (accepted $\leq$30%; stringent $<$15%), including in patients in whom acquisition is conventionally difficult **Results:** Within the first six weeks the service assessed 140 consecutive patients across 32 scan days (4.4 patients/day; median age 48 years; 59% male; median BMI 25.5 Kg/m^2). The case-mix was weighted toward early case-finding: 62% (87/140) were MASLD screening referrals, 16% were serial LSM monitoring and 16% were chronic viral hepatitis. A complete LSM result was delivered at the point of care in 140/140 patients (100%) and a full multiparametric assessment (stiffness, attenuation and fat) in 108 (77%), all within a single clinician encounter **.** Delivered quality met accepted standards : all 140 examinations satisfied the IQR/M $\leq$30% criterion (100%; 95% CI 97.3–100) and 95.7% (134/140; 95% CI 91.0–98.0) met the stringent $<$15% criterion. Reliability was preserved in groups conventionally considered difficult to image (100% obese patients and 100% of operator-rated difficult scans). RMI tracked an acquisition-quality gradient (median 0.84 easy/moderate vs 0.72 difficult). Clinically, the single-encounter pathway reclassified 21% of FIB-4 low-risk patients toward possible significant fibrosis **Conclusion:** A h-POCE service was rapidly implementable and delivered a complete, reliable liver assessment within a single clinical encounter consolidating a pathway that conventionally requires separate referral. Delivered quality met accepted reliability standards in all patients, including the obese and technically difficult, and actionable risk reclassification was available at the bedside. This care-delivery model offers a scalable route to expand hepatology led POC elastography.

Table. Implementation and delivered-quality metrics of a hepatologist-led point-of-care elastography service.

Metric	n / value	IQR/M ≤30%	IQR/M <15%	Median RMI
Patients assessed	**140**	**100%**	**95.7%**	**0.82**
Throughput (patients/scan day)	4.4	—	—	—
Screening referrals	87 (62%)	—	—	—
Complete result, single encounter	140/140	—	—	—
Full multiparametric, single encounter	108 (77%)	—	—	—
Delivered technical quality, by acquisition difficulty				
Skin-capsule ≤2.0 cm	82	100%	99%	0.83
Skin-capsule 2.0–2.5 cm	30	100%	90%	0.81
Skin-capsule >2.5 cm (deep)	13	100%	92%	0.82
Obese (BMI ≥30)	22	100%	95%	0.82
Operator-rated difficult [1]	38	100%	84%	0.72
Easy / moderate [2]	100	100%	100%	0.84

IQR/M, interquartile-range-to-median ratio; RMI, reliability measurement index (0–1, higher = better). [1] Operator-rated difficulty prospectively recorded with documented reasons (impaired breath-hold n=24, obesity n=13, narrow intercostal window n=11, ascites n=3, other n=5). [2] Easy n=90 and moderate n=10 combined.

Disclosures: Akash Roy: Nothing to Disclose, Suhita Dutta: Nothing to Disclose, Shardhya Chakroborty: Nothing to Disclose, Shruti Keyal: Nothing to Disclose, Surabhi Jajodia: Nothing to Disclose, Mahesh Goenka: Nothing to Disclose.

2166 | ◆ THE EFFECT OF MEDICAID EXPANSION ON LIVING DONOR LIVER TRANSPLANT RATES

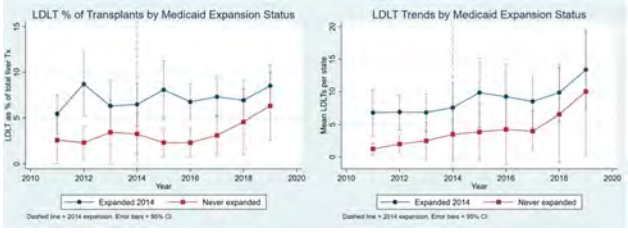
Christopher McLaughlin[1] Yael Nobel[1] Russell Rosenblatt[2], [1]Columbia University Irving Medical Center, [2]Weill Cornell Medicine

Background: Living donor transplantation (LDLT) is one tool to overcome the longstanding issue of organ shortage. LDLT represents only 6% of liver transplants, a figure that remains largely unchanged over the past decade. Financial costs are a significant barrier to LDLT, and insurance status is a potentially modifiable input. Medicaid coverage rose from 13% to 19% of liver transplants from 2013 to 2023, likely reflecting increased Medicaid enrollment following the 2014 Medicaid expansion under the Affordable Care Act. We examined whether Medicaid expansion is associated with differential increases in LDLT utilization among Medicaid-insured patients in expansion versus non-expansion states. **Methods:** We included

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patients in the UNOS STAR file from 2011-2019 residing in states that expanded Medicaid eligibility in 2014 (n = 20) or did not (n = 10). States with fewer than 10 total LDLTs per year were excluded. The primary outcome was change in LDLT volume per state-year from pre-expansion (2011–2013) to post-expansion (2014–2019). DDLT volume, which requires less support and resources, was a secondary outcome. Medicare and private insurance cohorts were also analyzed. A difference in difference (DiD) analysis was performed with fixed effects for state and year. **Results:** Mean LDLT per state-year increased overall (4.8 to 7.6) but did not significantly differ between expanding (6.5 to 9.2) and nonexpanding (1.5 to 4.3) states (DiD -0.47, $p > 0.10$) (**Figure**). LDLT as a proportion of total LTs also increased (4.1% to 5.0%), with no significant group difference (expanding: 5.6% to 6.3%; nonexpanding: 1.3% to 2.7%; DiD -0.52, $p > 0.10$). Similarly, no significant treatment effect on LDLT volume was seen for patients with Medicare (DiD 0.13, $p > 0.10$) or private insurance (DiD -0.82, $p > 0.10$). In contrast, DDLT volume for Medicaid patients significantly increased in expanding states (18.9 to 30.6) but not non-expanding states (16.3 to 16.1; DiD 10.97, $p < 0.01$), representing a 54% relative increase (DiD log+1 0.44, $p < 0.01$), with divergence beginning in 2016. **Conclusion:** Following Medicaid expansion, total volume and percentage of LDLT increased similarly in states, irrespective of Medicaid expansion or patient insurance. DDLT volume for Medicaid patients increased significantly more in states that expanded Medicaid eligibility. While LDLT trends beyond 2019 were not assessed, our findings suggest that while increasing access to health insurance increases access to DDLT, it may not be sufficient to increase utilization of LDLT due to the potential need for additional support and other direct or indirect costs.



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2167 | ◆ GLOBAL VARIABILITY IN HEPATOLOGY TRAINING: RESULTS OF THINK COLLABORATIVE INTERNATIONAL MULTINATIONAL SURVEY

Sanjaya Satapathy[1] Tiffany Sahadeo[2] Kenan Moral[3] Zita Galvin[4] Marta Tejedor[5] Kymberly Watt[6], [1]Northshore University Hospital/Northwell Health, [2]Northwell Health, [3]Lokman Hekim University, [4]St. Vincent's Private Hospital, [5]James A. Clifton Digestive Health Center, University of Iowa Health Care, [6]Mayo Clinic, Rochester, Minnesota

Background: Hepatology training pathways vary considerably worldwide, with limited contemporary data evaluating differences in curriculum structure, procedural competency expectations, transplant exposure, and competency-based educational frameworks across regions. We conducted an international multinational survey to characterize current hepatology training models and identify areas of global convergence and variability. **Methods:** A cross-sectional international survey assessing hepatology training structure, curriculum content, procedural competencies, teaching methodologies, transplant exposure, research requirements, and competency-based curriculum implementation was distributed globally. Survey responses underwent quality assessment, and low-quality responses were excluded prior to analysis. Descriptive analyses were performed, and regional comparisons were evaluated using chi-square and Fisher exact tests where appropriate. **Results:** Ninety respondents from more than 30 countries across North America, Europe, Asia-Pacific, Latin America, and the Middle East/Africa were included. Hepatology was a standalone specialty in 31.1% of programs, a gastroenterology subspecialty in 24.4%, and integrated within gastroenterology training in 5.6%. Core topics—including chronic liver disease, viral hepatitis, cholestatic and autoimmune liver disease, MASLD/MASH, and drug-induced liver injury—were included in over 94% of curricula. Alcohol-associated liver disease, fibrosis assessment, and radiology/imaging training were less common (75.6%, 76.7%, and 58.9%, respectively). Procedural competency expectations varied considerably. Therapeutic upper endoscopy, upper GI bleeding management, and paracentesis were included in over 80% of programs, whereas liver biopsy (46.7%), liver ultrasound (36.7%), ultrasound-guided procedures (35.6%), and transjugular liver biopsy (3.3%) were less frequently required. Regional differences were significant. Standalone hepatology training ranged from 81.8% in North America to 5.1% in Asia-Pacific ($p < 0.0001$).

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Mandatory transplant rotations varied from 75% in Europe to 0% in North America ($p < 0.0001$), and research requirements also differed by region ($p = 0.0007$). Overall, 68.9% supported a unified global hepatology curriculum. **Conclusion:** Global hepatology training demonstrates substantial heterogeneity in specialty structure, transplant exposure, procedural competency expectations, and educational frameworks despite broad consensus regarding core hepatology curriculum content. Important gaps were identified in radiology/imaging training and advanced procedural exposure. These findings support the need for increased international collaboration and consideration of harmonized competency-based hepatology training standards worldwide.

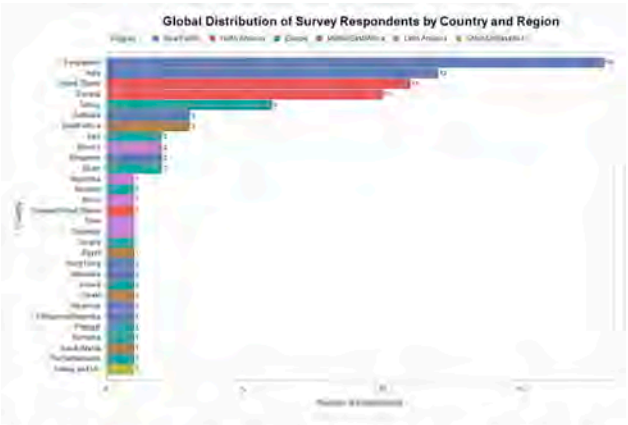


Figure 1. Geographic distribution of respondents participating in the international multinational hepatology training survey. Respondents represented more than 30 countries across North America, Europe, Asia-Pacific, Latin America, and the Middle East/Africa regions. Countries with at least two respondents are shown in the primary figure display.

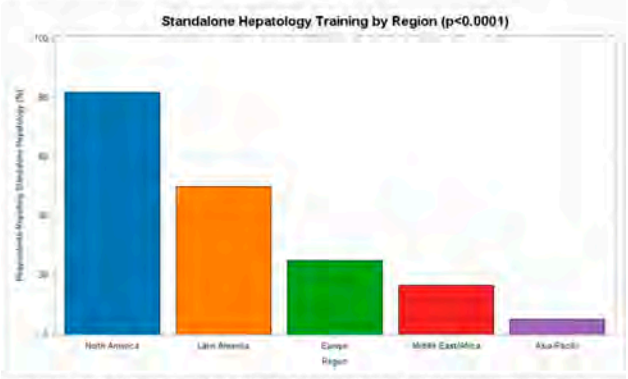


Figure 2. Regional variability in standalone hepatology training models. Bars represent the percentage of respondents within each geographic region reporting hepatology as a standalone specialty. Significant regional differences were observed, with the highest prevalence reported in North America and the lowest in the Asia-Pacific region (p<0.0001).

Disclosures: Sanjaya Satapathy: Gilead Sciences: Grant/Research Support, Durect Pharma: Grant/Research Support, Fibronostics: Grant/Research Support, Novartis: Grant/Research Support, Zydus Pharma: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Intercept Pharma: Grant/Research Support, AKERO: Grant/Research Support, Altimmune: Grant/Research Support, IPSEN: Grant/Research Support, Madrigal: Grant/Research Support, Tiffany Sahadeo: Nothing to Disclose, Kenan Moral: Nothing to Disclose, Zita Galvin: Nothing to Disclose, Marta Tejedor: Nothing to Disclose, Kymberly Watt: Madrigal: Stock - publicly traded company, Viking: Stock - publicly traded company, Novo Nordisk: Speaking and Teaching.

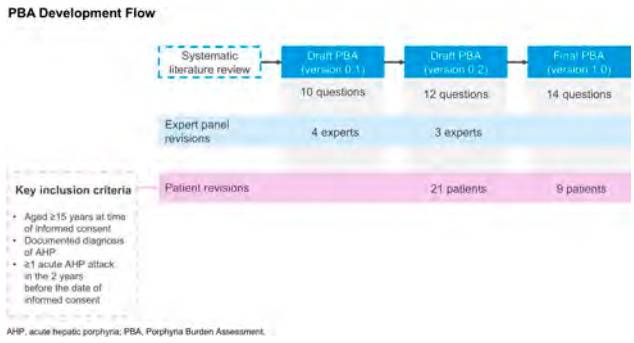
2168 | ◆ DEVELOPMENT OF THE PORPHYRIA BURDEN ASSESSMENT, A PATIENT-REPORTED OUTCOMES MEASURE TO ASSESS THE BURDEN OF CHRONIC SYMPTOMS OF ACUTE HEPATIC PORPHYRIA

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Background: Acute hepatic porphyrias (AHPs) are rare diseases characterized by acute attacks and chronic symptoms between attacks, resulting in diminished health-related quality of life (HRQoL). Owing to the heterogeneous presentation of AHP, generic patient-reported outcome measures (PROMs) may not sufficiently assess disease burden from the patient perspective. To support a clearer understanding of the full burden of AHP, we developed the Porphyria Burden Assessment (PBA): an AHP-specific PROM that assesses the cardinal symptoms and HRQoL impacts of AHP outside of attacks. **Methods:** A systematic literature review was conducted to identify the key signs, symptoms, and HRQoL impacts of AHP. Utilizing

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FDA guidance and best practices for questionnaire development, findings were used to develop a conceptual disease model and an initial draft (version 0.1) of the PBA. Draft versions of the PBA underwent iterative review by AHP clinical experts and patients with AHP (**Figure**).The PBA was reviewed by patients who were ≥15 years old, had experienced ≥1 self-reported AHP attack in the past 2 years, were not receiving hemin prophylaxis, and had not received givosiran within 6 months before the date of informed consent. Patients completed a demographic and health information questionnaire and a two-part, semi-structured, qualitative 90-minute interview by telephone or virtually. During the first part of the interview, patients spontaneously described their experience of AHP-related signs, symptoms, and HRQoL impacts; researchers asked targeted questions to further explore specific symptom concepts. In the second part of the interview, patients completed the draft PBA using a 'think-aloud' approach to assess its readability, comprehensibility, relevance, and comprehensiveness. Six interview waves, each including approximately five participants, informed iterative refinements to the draft PBA. **Results:** The conceptual disease model identified six symptom concepts and four HRQoL impact domains for inclusion in version 0.1 of the PBA. Following expert review, two additional symptom concepts were added. A total of 30 participants completed the interviews; concepts were further refined following patient interviews and review of the draft PBA. The final PBA (version 1.0) comprises 14 items which generate domain-level scores for symptom severity and HRQoL impact, as well as a total score. Testing of the final PBA confirmed questions were relevant to and understandable for patients. The full PBA will be presented. **Conclusion:** The PBA is a content valid tool designed to assess the burden and disease-specific impacts of AHP, including chronic symptoms and how these affect patients' lives. This tool may empower patients to fully communicate their needs, support shared/patient-centered decision-making with their healthcare professionals, and facilitate a comprehensive understanding of the disease burden associated with AHP.



Disclosures: Teresa Kauf: Alnylam, Inc: Employee, Mural Oncology: Stock - publicly traded company, Alkermes, Inc: Stock - publicly traded company, Alnylam, Inc: Stock – privately held company, Hetanshi Naik: Alnylam Pharmaceuticals: Consultant, Francesca Granata: Nothing to Disclose, Liz Gill: Alnylam: Other - travel grant recipient paid to British Porphyria A, Rebecca Leaf: Nothing to Disclose, Susana Monroy-Santoyo: Nothing to Disclose, Eliane Sardh: Nothing to Disclose, Michael Scott: Alnylam: Advisor, Recordati: Advisor, Pfizer: Speaking and Teaching, Pfizer: Advisor, Kye Pharmaceuticals: Advisor, Sobi: Speaking and Teaching, Khure Health: Consultant, Disc Medicine: Grant/Research Support, Paulo Sgobbi de Souza: Nothing to Disclose, Ulrich Stölzel: Alnylam: Speaking and Teaching, Brittany Klooster: Nothing to Disclose, Ben Banderas: Nothing to Disclose, Ilaria Olivetti: Nothing to Disclose, Sabina Wiekhorst: Alnylam Pharmaceuticals: Employee.

2169 | LINKAGE TO CARE AMONG HEPATITIS B AND C PATIENTS FOLLOWING PATIENT NAVIGATION IN A FEDERALLY QUALIFIED HEALTH CENTER IN SAN DIEGO COUNTY

Sydney Sharp[1] Monica Vidaurrazaga[1], [1]Family Health Centers of San Diego

Background: San Diego County has large populations at increased risk for chronic hepatitis B (HBV) and hepatitis C (HCV) including people who inject drugs, people who are unhoused, and foreign-born individuals. Barriers to care include lack of insurance, treatment costs, limited access for vulnerable populations, and low awareness of disease and treatment options. Family Health Centers of San Diego (FHCSD), a federally qualified health center, adapted established HIV linkage-to-care models to implement a patient navigation program aimed at improving reengagement in HBV/HCV care among patients not currently receiving treatment. **Methods:** The program was funded by the Center for Disease Analysis Foundation Relink Initiative and operated from March 2024 to June 2025. Eligible FHCSD patients met one of the following criteria: (1) positive quantitative viral load laboratory results for HBV and/or HCV, or (2) reactive antibody or antigen laboratory results for HBV and/or HCV without a documented viral load test. Outreach was conducted in English, Spanish, and Haitian Creole through phone calls, text messages, and email. Navigators performed standardized chart reviews to assess care status and patients received up to four contact attempts. Transportation assistance through Uber Health was available but rarely used. Data were analyzed using univariate logistic regression with HCV as the reference group. **Results:** Over 15 months, patient navigators attempted outreach to 3,678 patients: 731 with HBV, 2,935 with HCV, and 12 with both infections. Table 1 shows patient demographics. The HBV population demonstrated greater demographic diversity, including a more balanced sex distribution (58.0% male, 42.0% female), more evenly distributed employment status (26.8% employed, 39.7% unemployed, 21.9% unknown), and greater racial diversity

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(30.9% White, 25.7% Black/African American, and 24.6% Asian/Pacific Islander). Additionally, 25.7% of HBV patients reported a preferred language other than English or Spanish.HBV patients had significantly greater odds of successful contact compared with HCV patients (OR = 5.33, 95% CI: 3.93-7.25; p < 0.001). HBV patients also had four times the odds of appointment completion (OR = 4.05, 95% CI: 2.23-7.45; p < 0.001). **Conclusion:** Despite using various contact methods, successful contact was achieved for only 10% of patients. HBV patients had higher odds of successful contact and appointment completion, potentially reflecting greater awareness of HBV diagnosis and treatment due to the longstanding emphasis on HBV vaccination and education. Low appointment completion may also reflect structural barriers. Limitations of this study included no in-person or mail outreach and underutilization of transportation assistance. Overall, low rates of successful contact and appointment completion underscore the persistent barriers to hepatitis care engagement among underserved populations.

Table 1. Patient Demographics

Variable, N (%)	Overall N = 3678	HCV Only N = 2935	HBV Only N = 731	HBV & HCV N = 12
Age Study End				
30-39	779 (21.2%)	613 (20.9%)	165 (22.6%)	1 (8.3%)
Under 30	154 (4.2%)	85 (2.9%)	69 (9.4%)	0 (0.0%)
40-49	777 (21.1%)	601 (20.5%)	175 (23.9%)	1 (8.3%)
50-59	701 (19.1%)	555 (18.9%)	140 (19.2%)	6 (50.0%)
60-69	900 (24.5%)	775 (26.4%)	122 (16.7%)	3 (25.0%)
70+	367 (10.0%)	306 (10.4%)	60 (8.2%)	1 (8.3%)
Sex at Birth				
Male	2,584 (70.3%)	2,151 (73.3%)	424 (58.0%)	9 (75.0%)
Female	1,094 (29.7%)	784 (26.7%)	307 (42.0%)	3 (25.0%)
Ethnicity				
Latino/Hispanic	1,071 (29.1%)	930 (31.7%)	140 (19.2%)	1 (8.3%)
Non-Latino/Hispanic	2,113 (57.4%)	1,608 (54.8%)	495 (67.7%)	10 (83.3%)
Unknown	494 (13.4%)	397 (13.5%)	96 (13.1%)	1 (8.3%)
Race				
White	2,228 (60.6%)	1,991 (67.8%)	226 (30.9%)	11 (91.7%)
Black/African American	531 (14.4%)	342 (11.7%)	188 (25.7%)	1 (8.3%)
Asian/Pacific Islander	237 (6.4%)	57 (1.9%)	180 (24.6%)	0 (0.0%)
Multi-racial	180 (4.9%)	161 (5.5%)	19 (2.6%)	0 (0.0%)
Other	95 (2.6%)	83 (2.8%)	12 (1.6%)	0 (0.0%)
Unknown	407 (11.1%)	301 (10.3%)	106 (14.5%)	0 (0.0%)
Education				
Less than HS	855 (23.2%)	703 (24.0%)	148 (20.2%)	4 (33.3%)
High School	1,932 (52.5%)	1,620 (55.2%)	305 (41.7%)	7 (58.3%)
College or Post Graduate	396 (10.8%)	221 (7.5%)	174 (23.8%)	1 (8.3%)
Unknown	495 (13.5%)	391 (13.3%)	104 (14.2%)	0 (0.0%)
Employment Status				
Employed	506 (13.8%)	308 (10.5%)	196 (26.8%)	2 (16.7%)
Student or Retired	280 (7.6%)	195 (6.6%)	85 (11.6%)	0 (0.0%)
Unemployed	2,149 (58.4%)	1,850 (63.0%)	290 (39.7%)	9 (75.0%)
Unknown	743 (20.2%)	582 (19.8%)	160 (21.9%)	1 (8.3%)
Housing Status				
Own	194 (5.3%)	118 (4.0%)	76 (10.4%)	0 (0.0%)
Rent	1,225 (33.3%)	702 (23.9%)	521 (71.3%)	2 (16.7%)
Doubling Up	332 (9.0%)	281 (9.6%)	47 (6.4%)	4 (33.3%)
Homeless	1,773 (48.2%)	1,707 (58.2%)	60 (8.2%)	6 (50.0%)
Unknown	154 (4.2%)	127 (4.3%)	27 (3.7%)	0 (0.0%)
Language				
English or English Proficient	3,264 (88.7%)	2,779 (94.7%)	473 (64.7%)	12 (100.0%)
Spanish	157 (4.3%)	87 (3.0%)	70 (9.6%)	0 (0.0%)
Other	213 (5.8%)	25 (0.9%)	188 (25.7%)	0 (0.0%)
Unknown	44 (1.2%)	44 (1.5%)	0 (0.0%)	0 (0.0%)
Payer Group				
Medicaid	1,949 (53.0%)	1,507 (51.3%)	435 (59.5%)	7 (58.3%)
Medicare	407 (11.1%)	326 (11.1%)	80 (10.9%)	1 (8.3%)
Other Public or Programmatic	263 (7.2%)	233 (7.9%)	29 (4.0%)	1 (8.3%)
Private Non-Managed Care	63 (1.7%)	27 (0.9%)	36 (4.9%)	0 (0.0%)
Self Pay	583 (15.9%)	493 (16.8%)	88 (12.0%)	2 (16.7%)
Unknown	413 (11.2%)	349 (11.9%)	63 (8.6%)	1 (8.3%)

Disclosures: Sydney Sharp: Nothing to Disclose, Monica Vidaurrazaga: Nothing to Disclose.

2170 | IMPACT OF THE SURREY COMMUNITY LIVER HEALTH CHECK PROGRAMME ON EARLY DETECTION OF CIRRHOSIS AND HEPATOCELLULAR CARCINOMA: A 4-YEAR REGIONAL EVALUATION

Janani Ragavan[1] Romanie Westwood[1] Regelien Ariola[1] Charish Pria[1] Paul Obeney[1] Maisie Gadsby[1] Adam Nigh[1] Tina Zackova[1] Kusum Gurung[1] Philippa Cobb[1] Michelle Gallagher[1], [1]Royal Surrey Hospital

Background: Hepatocellular cancer (HCC) is one of the fastest growing causes of cancer mortality in the UK, with approximately 7000 cases per year anticipated to rise by 40% by 2040. Whilst HCC is associated with deprivation it does not exclusively affect people living with health inequalities. Surrey, a relatively affluent region, was one of the first ten NHSE funded community liver health check (CLHC) operational delivery networks (ODNs). The aim of the CLHC was to use transient elastography (FibroScans) to identify liver disease early in at-risk populations. **Methods:** Targeted screening was offered to individuals with liver disease risk factors – hazardous alcohol consumption, risk of current or previous Hepatits B/C virus and metabolic disease (Type 2 diabetes/obesity/hepatic steatosis). To improve accesibility FibroScans were delivered in clinics and on a mobile screening van across multiple locations within the community such as drug and alcohol services and homeless shelters. The team also partnered with GP practices in deprived areas to identify patients with risk factors and invite them to book appointments in CLHC clinics.Liver stiffness measurements (LSM) were categorised as negative (<8.5 kPa), moderate (8.5–11.4 kPa), or positive (>11.5 kPa). All participants received lifestyle advice. Secondary care hepatology referrals were made for people with positive scans; moderate fibrosis patients were recalled at 2 years. **Results:** A total of 11,275 FibroScans were performed over the four-year period (Table 1). 504 individuals were referred for specialist assessment: 322 remain in active HCC surveillance. 42 patients were discharged following clinical review, 54 moved away, 42 refused to engage and 41 are deceased.To date, 4 surveillance patients have been diagnosed with HCC, all of which were early stage (BCLC Stage A) and one other is on intensive surveillance due to an indeterminent (LI-RADS 3) lesion.Moderate LSM values were identified in 653 (6%) of initial scans. 96 patients, out of 272 recalled at the 2 year mark, had a repeat scan ; 81% demonstrated improvement with lower LSM on follow-up, while 16% showed an increase in LSM. All patients progressing to advanced disease had evidence of severe hepatic steatosis at baseline.Drug and alcohol services achieved the highest yield, despite accounting for only

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12% of patients scanned. **Conclusion:** The Surrey ODN has delivered 5% conversion to specialist referral. Linkage to specialist care was high, resulting in the identification of four early-stage HCCs. The majority of those with moderate fibrosis rescanned had improved LSM at 2 years demonstrating the benefits of early lifestyle intervention and education given at the initial scan. Targeted screening optimised the finding of cases while also improving access to healthcare. Outcomes within the Surrey ODN compare favourably to programmes with similar demographics such as Bristol and Severn and North London.

Table 1: Indications, demographics and diagnostic yield of 11,275 scans in Surrey (June 2022 to May 2026)

Catergory	Subgroup	Result	Percentage (%)	Positive yield (%)	Moderate yield (%)
Scan results	Positive (>11.5 kPa)	504	5%		
	Moderate (8.5–11.4 kPa)	653	6%		
	Negative (<8.5 kPa)	10118	89%		
Indication	Risk of / previous Hep B/C	1543	14%		
	Excess alcohol	2553	23%		
	Metabolic RF (T2DM, High BMI, NAFLD)	5855	52%		
	Two or more risk factors	1324	11%		
Location	GP	3223	28%	4%	6%
	Drug & Alcohol Service	1346	12%	6%	7%
	Events	2142	19%	2%	4%
	Clinics (eg: Bariatric, Diabetes)	4301	38%	6%	6%
	Homeless shelters	263	3%	6%	4%
Gender	Male	6380	57%		
	Female	4895	43%		
Ethnicity	White British	6638	59%		
	White – Other	1047	9%		
	Black	361	3%		
	Asian	1314	12%		
	Other/Mixed	1915	17%		
Country of Birth	UK	8244	73%		
	Non-UK	3031	27%		

81% of Surrey residents are UK born white British. Targeted screening engaged non-UK birth cohorts with risk factors

Disclosures: Janani Ragavan: Nothing to Disclose, Romanie Westwood: Nothing to Disclose, Regelien Ariola: Nothing to Disclose, Charish Pria: Nothing to Disclose, Paul Obeney: Nothing to Disclose, Maisie Gadsby: Nothing to Disclose, Adam Nigh: Nothing to Disclose, Tina Zackova: Nothing to Disclose, Kusum Gurung: Nothing to Disclose, Philippa Cobb: Nothing to Disclose, Michelle Gallagher: Nothing to Disclose.

2171 | GAPS AND INCONSISTENCIES IN HEPATOCELLULAR CARCINOMA SURVEILLANCE ARE ASSOCIATED WITH MORE ADVANCED TUMOR STAGE AT DIAGNOSIS AMONG U.S. SAFETY-NET POPULATIONS

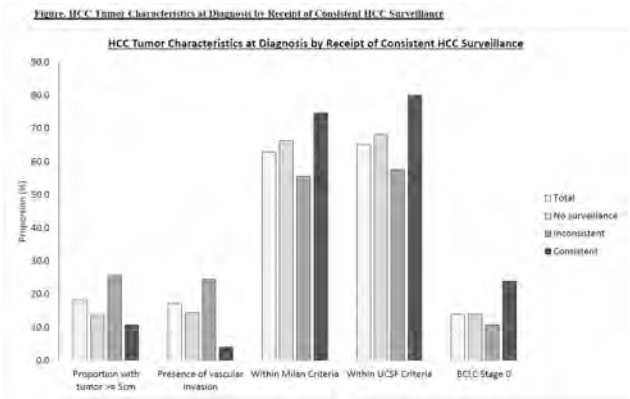
Robert Wong[1] Patricia Denise Jones[2] Bolin Niu[3] Paulo Pinheiro[4] Mae Thamer[5] Onkar Kshirsagar[6] Yi Zhang[6] Ronnie Fass[3] Jasmine Davis[4] Lisa Quirk[7] George Therapondos[8] Amit Singal[7] Mandana Khalili[9],

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Background: Current practice guidelines recommend semiannual hepatocellular carcinoma (HCC) surveillance in patients with cirrhosis. However, consistent HCC surveillance remains suboptimal in real-world practice. We aim to evaluate gaps in guideline-concordant HCC surveillance and its impact on tumor stage at diagnosis among U.S. adults. **Methods:** Adults with cirrhosis who were diagnosed with HCC from 3/1/2018 – 2/29/2024 across four U.S. safety-net health systems were evaluated. Surveillance in the 12 months prior to HCC diagnosis was categorized as consistent (semiannual HCC surveillance), inconsistent (annual HCC surveillance), and no surveillance. HCC surveillance was determined by CPT codes for imaging type and associated ICD-9/10-CM codes for indication. HCC characteristics at diagnosis included number and size of tumors, presence of vascular invasion (VascInv), Barcelona Clinic Liver Cancer (BCLC) stage, and whether HCC was within Milan criteria. **Results:** Among 622 adults with HCC (mean age 61.8y, 74.6% men, 46.0% Hispanic, 28.8% non-Hispanic white, 16.1% African American, 1.0% Asian, 33.3% Medicare, 25.4% Medicaid, 23.3% commercial, 12.2% uninsured/indigent care), etiology of cirrhosis was 45% chronic hepatitis C, 42% alcohol-associated liver disease, 7% chronic hepatitis B, and 7% metabolic dysfunction-associated steatohepatitis. At HCC diagnosis, 18.3% had HCC $\geq$ 5cm, 17.3% had VascInv, 14% had very early stage (BCLC stage 0), and 62.9% was within Milan criteria. In the 12 months prior to HCC diagnosis, 12.5% had consistent surveillance, 41.8% inconsistent, and 45.7% no surveillance. Consistent surveillance was associated with greater proportion of HCC within Milan criteria, and with BCLC stage 0, and lower proportion with HCC $\geq$5cm or with VascInv compared to inconsistent or no surveillance (Figure). For example, compared to no surveillance, patients who received consistent surveillance had lower proportion with VascInv (4.1% vs. 14.4%) and greater proportion within Milan criteria (74.7% vs. 66.3%), and BCLC stage 0 (24.0% vs. 14.1%), all $p < 0.05$. **Conclusion:** Among a multi-center safety-net cohort of patients with cirrhosis who developed HCC, only 1 in 8 received guideline-concordant semiannual surveillance prior to HCC diagnosis. This is particularly alarming given that consistent surveillance was associated with earlier tumor stage and more favorable tumor characteristics at diagnosis, which ultimately leads to improved options for HCC treatment.

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2172 | RATES, TIMING, AND CONTENT OF DOCUMENTED GOALS OF CARE DISCUSSIONS IN DECOMPENSATED CIRRHOSIS

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Background: Patients with decompensated cirrhosis experience high symptom burden, mortality, and exposure to life-sustaining treatments. Goals of care discussions are an important component of high-quality care. To identify opportunities for improvement, we aimed to describe patterns and content of documented GOC discussions in hospitalized adults with decompensated cirrhosis. **Methods:** We identified adults with decompensated cirrhosis who had $\geq$ 1 hospitalization within our health system between 1/1/2025–4/4/2026 using validated ICD-10 codes. During this timeframe, we captured demographics, mortality, transplant status (ever evaluated, listed, transplanted), presence of any palliative care consultation, and any hospice referral. Any GOC discussions ever documented using a long-standing electronic health record (EHR) template were captured. Logistic regression examined factors associated with documented GOC discussions. To contextualize discussions, we performed content analysis of first GOC discussions recorded from 38 decedent charts using maximum variation sampling, stratified by timing before death, palliative care involvement, and transplant status. A hybrid inductive-deductive approach was used. **Results:** Among 516 patients across 730 hospitalizations, mean age was 63 years (SD: 17), 38% were White, 39% Latino, 7% Asian, 5% Black, and 5% Other Race. Half underwent liver transplant evaluation; 25% died during the study period. Palliative care consultations (17%) and hospice referrals (4%) were uncommon. Thirty percent had any documented GOC discussion. In fully adjusted analyses, palliative care consultation (OR 32.1, 95% CI 14.1–73.1), death (OR 9.78, 95% CI 5.47–17.5), and Other versus White race (OR 3.38, 95% CI: 1.24–9.20) were associated with GOC documentation. Of 384 documented discussions, 89% occurred inpatient; hospital medicine (34%) and palliative care (33%) providers documented most conversations. Median time from first GOC discussion to death or hospice was 4 (IQR 1–23) days. Content analysis identified 4 patterns: 1) conversations were often crisis-triggered and focused on prognosis and treatment limits; 2) family decision-making often predominated due to patient incapacity; 3) transplant candidacy strongly shaped timing and content despite

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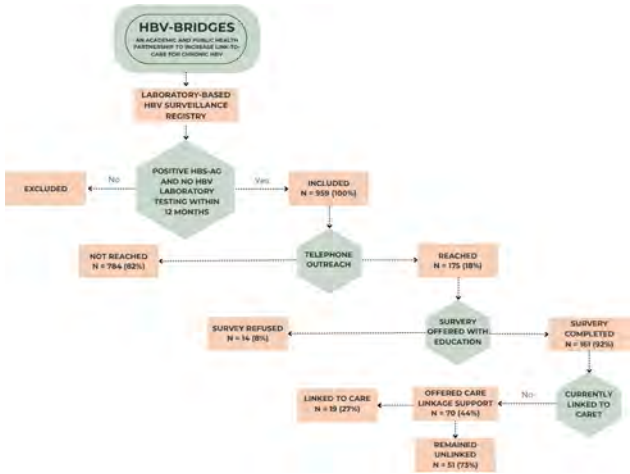
limited gastroenterology/transplant team involvement; and 4) outpatient discussions addressed broader serious illness communication domains. **Conclusion:** Among hospitalized adults with decompensated cirrhosis, fewer than one-third had any documented GOC discussion and among decedents, first documented discussions occurred shortly before death. Content analysis suggested that earlier discussions before acute clinical deterioration may improve patient participation and anticipatory communication around evolving transplant status and serious illness outcomes.

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2173 | HBV-BRIDGES: AN ACADEMIC-PUBLIC HEALTH PARTNERSHIP TO INCREASE LINKAGE TO CARE AMONG RESIDENTS WITH CHRONIC HEPATITIS B IN LOS ANGELES COUNTY

Kevin Sun[1] Cierra LeBlanc[2] Mark Wang[1] Ariel Lee[1] Justin Ong[1] Anusha Koka[1] Nikhilesh Kumar[1] Alison Ly[1] Sophia Paik[1] Sabrina Zhang[1] Prabhu Gounder[2] Kali Zhou[1], [1]University of Southern California, [2]Los Angeles County Department of Health Services

Background: Chronic hepatitis B virus (HBV) infection disproportionately affects Los Angeles County (LAC) residents, where one in three are foreign-born. Prior studies have shown that many chronic HBV-infected are unaware of their diagnosis and/or not linked to care, leading to liver-related complications. University of Southern California (USC) researchers in collaboration with the LAC Department of Public Health (LADPH) developed the HBV-BRIDGES Program, a county-wide population-based multilingual initiative, to directly address this problem. **Methods:** The HBV-BRIDGES Program utilized the LADPH laboratory-based HBV surveillance registry to identify potentially out of care LAC residents 18 years or older with a positive hepatitis B surface antigen test after January 2025. “Out of care” was defined as no HBV-related laboratory testing within 12 months after initial positive HBsAg. Patient navigators from USC made up to three telephone attempts per resident, conducted a brief voluntary survey assessing linkage-to-care/treatment status and barriers to each, and delivered targeted HBV education to promote linkage. Calls were conducted in the resident's preferred language with professional interpreter assistance when needed. Linkage-to-care was defined as any HBV-related laboratory test reported to LADPH after initial contact. **Results:** To date, 959 individuals have been contacted, of which 175 (18%) were reached (82% on first attempt). Those who were reached were more likely to be aged 40-60 (50% vs 39%; $p < 0.05$), with no difference in sex (52% vs 53% female). Of the 175 residents reached, 161 (92%) completed the survey and education (see flowchart in Figure). Survey respondents were predominantly Asian (66%), followed by Hispanic (19%) and White (6%). 21%, 44%, and 27% of respondents were < 40, 40-60, and 60+ years, respectively, with 47% female sex. Of survey respondents, 54 (34%) reported being unaware of their HBV diagnosis. A total of 70 (44%) residents reported no linkage-to-care. Asians were much more likely to have already been linked than Hispanics (71% vs 20%, $p < 0.01$). The most common barrier to linkage was being unaware of HBV diagnosis (64%), followed by not knowing ongoing follow-up was necessary (13%), and no primary care provider (6%). 91 individuals (65%) were not currently receiving HBV treatment; of these, 46 (52%) expressed interest in starting treatment if eligible. Lastly, 19 (27%) residents had subsequent linkage-to-care, with a median of 6.2 months (IQR: 4.9-8.7) from initial contact to HBV laboratory testing. **Conclusion:** The HBV-BRIDGES Program reached approximately 20% of eligible LAC residents, of which nearly half were unlinked, and one-third had objective evidence of linkage to care at 6 months. This academic-public health partnership leveraging telephone outreach through a laboratory-based surveillance registry is a promising, replicable model for other counties.



Disclosures: Kevin Sun: Nothing to Disclose, Cierra LeBlanc: Nothing to Disclose, Mark Wang: Nothing to Disclose, Ariel Lee: Nothing to Disclose, Justin Ong:

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Nothing to Disclose, Anusha Koka: Nothing to Disclose, Nikhilesh Kumar: Nothing to Disclose, Alison Ly: Nothing to Disclose, Sophia Paik: Nothing to Disclose, Sabrina Zhang: Nothing to Disclose, Prabhu Gounder: Nothing to Disclose, Kali Zhou: Gilead Sciences Inc: Grant/Research Support, Merck: Grant/Research Support.

2174 | STAKEHOLDER-DRIVEN DEVELOPMENT OF A HEPATOLOGY QI DASHBOARD: A HUMAN-CENTERED DESIGN STUDY

Julia Gips[1] Tyrus Vong[1] Danielle Piccinini-Black[2] Vedant Jain[3] Valerie Thompson[1] Carolina Lopez-Silva[1] Lynette Sequeira[4] Kathy Liu[3] Alexandra Strauss[1], [1]Johns Hopkins School of Medicine, [2]Johns Hopkins Carey Business School, [3]Johns Hopkins Department of Gastroenterology, [4]Johns Hopkins Hospital

Background: Hepatology providers lack systematic access to individualized feedback on patient outcomes. Clinician educator frameworks emphasize that physicians require structured, outcomes-based feedback to sustain reflective practice and drive continous improvement, yet no mechanism currently exists to deliver this data. Existing QI dashboards typically present aggregate, department-level metrics rather than individualized data, limiting clinical relevance. Additionally, dashboards built without end-user input are frequently underutilized: when tools do not reflect user priorities and workflows, adoption fails. We applied human-centered design (HCD) to develop a provider-facing QI dashboard grounded in end-user needs, ensuring clinical relevance and sustained engagement. **Methods:** Using a multi-phase HCD approach, we engaged multi-disciplinary stakeholders. Phase 1 comprised a needs assessment survey distributed to hepatology faculty (n = 12) to identify the highest-priority quality metrics for dashboard inclusion. Phase 2 comprised an in-person group session (n = 9; attendings, fellows, pharmacist; 1–34 years of experience) employing established HCD methods: "headline from the future," journey mapping, rose–bud–thorn analysis, and prioritization of pre-surveyed care metrics. Phase 3 consisted of semi-structured individual interviews (n = 14) exploring metric prioritization, data visualization preferences, and workflow integration. Qualitative thematic analysis was performed on transcripts and artifacts to identify consensus priorities and usability requirements that informed iterative dashboard prototypes. **Results:** Across all phases, providers consistently prioritized guideline-concordant, actionable metrics over administrative data. Top-ranked metrics included: timely diagnostic paracentesis (within 24 hours of admission), transplant evaluation phase and rationale for listing decisions, 30-day readmission rates, and inpatient mortality. Key design requirements included interactive, color-coded benchmarking against AASLD guidelines and historical data, drill-down functionality to individual patient data, and longitudinal filtering by time window. Providers expressed concerns about data accuracy, the display of metrics without clear reference benchmarks, and the potential for metrics to feel punitive rather than educational. **Conclusion:** HCD methodology produced a provider-informed hepatology QI dashboard aligned with clinical workflows, educational goals, and AASLD quality benchmarks. This iterative, stakeholder-driven approach revealed design requirements, particularly around data quality, benchmarking, and interactivity, that would not have emerged from administrator-driven development alone. This model offers a blueprint for participatory QI tool development in complex clinical environments and is scalable across institutions and specialties.

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2175 | TRENDS IN HEPATOCELLULAR CARCINOMA DIAGNOSIS OVER A 10 YEAR PERIOD: A MULTI-CENTRE COHORT STUDY

Richard O'Halloran[1] Thisuri Jayawardena[1] Weiyuan Fan[2] Andrea Jasareno[3] Phoebe Sun[3] Wei Ling Teh[3] Andrew Chin[2] Wesley Billingham[4] Kazuya Miyamoto[5] Tim Mitchell[2] Simon Hazeldine[3] Chloe Attree[1] George Garas[6] Gary Jeffrey[1] Angus Jeffrey[1] Gerry MacQuillan[1] Briohny Smith[1] Michael Wallace[1] Leon Adams[6], [1]Sir Charles Gairdner Hospital, [2]Royal Perth Hospital, [3]Fiona Stanley Hospital, [4]The Kids Institute, [5]The University of Western Australia, [6]University of Western Australia

Background: Hepatocellular carcinoma (HCC) is a low survival cancer with a rising incidence in Australia. We aimed to describe temporal changes in underlying liver disease aetiology and patient characteristics in in patients with a new diagnosis of HCC over a 10-year period. **Methods:** Patients with newly diagnosed HCC at three tertiary hospitals in Western Australia between 2015-2024 were retrospectively identified. Patient variables at cancer diagnosis, including demographics, underlying liver disease, Barcelona Clinic Liver Cancer (BCLC) staging and functional status, were ascertained from prospective databases and electronic records. Trends in case numbers over time were analysed using Poisson regression. The change in relative proportion over time was analysed for underlying liver disease,

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sex, cirrhosis or late-stage HCC using logistic regression, with linear regression used for age and Eastern Cooperative Oncology Group (ECOG) status at diagnosis. **Results:** Overall, 1,168 new diagnoses of HCC were identified [81.5% male, 73.3% cirrhotic]. HCC cases increased 8.7% per year from 83 in 2015 to 163 in 2024 ($p < 0.001$). Alcohol was the commonest aetiology (33.9%) followed by hepatitis C (24%), metabolic dysfunction-associated steatotic liver disease (MASLD) (22%) and hepatitis B (9.1%). All aetiological sub-groups increased in case numbers over time, including MASLD (12.3%/year, $p < 0.001$), alcohol (8.4%/year, $p < 0.001$), hepatitis B (6.1%/year, $p = 0.042$) and hepatitis C (4.4%/year, $p = 0.015$). However, the proportion related to hepatitis C decreased (OR 0.94, 95% CI 0.90-0.98), whereas the proportion related to MASLD (OR 1.05, 1.00-1.09) increased. There was also an increase in the proportion of HCC diagnoses in both those with unrecognized chronic liver disease at diagnosis (OR 1.05, 1.01-1.10), and those with no known risk factors for liver disease even on further review (OR 1.10, 1.02-1.19). The proportion of HCC due to alcohol and hepatitis B remained constant over the decade. The average age at diagnosis increased from 62.8 years in 2015-16 to 69.6 years in 2023-24 (coefficient = 0.82/ year; $p < 0.001$). Mean ECOG score at diagnosis increased significantly over time (coefficient = 0.02/year; $p = 0.002$). The proportion of cases with male sex, cirrhosis, late-stage disease (BCLC C or D) or diagnosed in a surveillance program did not change over time. **Conclusion:** In Western Australia, HCC case numbers are increasing with the proportion related to MASLD and in those without known liver disease increasing, whilst decreasing for hepatitis C. Patients with newly diagnosed HCC are becoming older and have an increasingly poorer performance status.

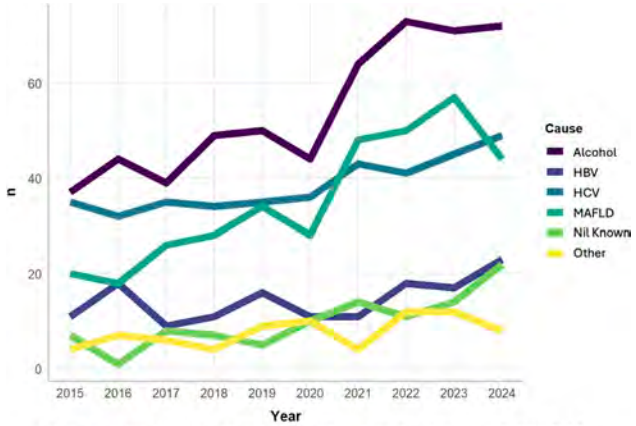


Figure 1. Cases of HCC over time by cause (regardless of co-occurrence), 2015-2024

Disclosures: Richard O'Halloran: Nothing to Disclose, Thisuri Jayawardena: Nothing to Disclose, Weiyuan Fan: Nothing to Disclose, Andrea Jasareno: Nothing to Disclose, Phoebe Sun: Nothing to Disclose, Wei Ling Teh: Nothing to Disclose, Andrew Chin: Nothing to Disclose, Wesley Billingham: Nothing to Disclose, Kazuya Miyamoto: Nothing to Disclose, Tim Mitchell: Ipsen: Speaking and Teaching, Norgine: Speaking and Teaching, Simon Hazeldine: Nothing to Disclose, Chloe Attree: Nothing to Disclose, George Garas: Nothing to Disclose, Gary Jeffrey: Nothing to Disclose, Angus Jeffrey: Nothing to Disclose, Gerry MacQuillan: Nothing to Disclose, Briohny Smith: Nothing to Disclose, Michael Wallace: Nothing to Disclose, Leon Adams: Novo Nordisk: Advisor, SCL Behring: Advisor, Dr Falk: Speaking and Teaching, Novo Nordisk: Grant/ Research Support, Boehringer Ingelheim: Speaking and Teaching.

2176 | UNMET NEED FOR NUTRITION AND PHYSICAL THERAPY CONSULTATION AMONG HOSPITALIZED PATIENTS WITH ALCOHOL-ASSOCIATED HEPATITIS: A NATIONWIDE ANALYSIS, 2011–2022

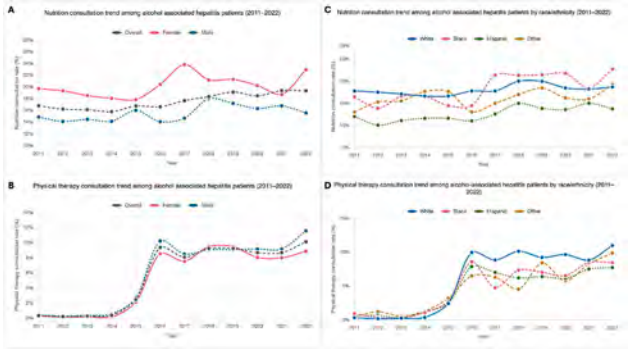
Yee Hui Yeo[1] Lingyu Bao[2] Sheng-Yin Chen[3] Hanyou Loh[4] Peng-Sheng Ting[5] Ju Dong Yang[1] Hyunseok Kim[6] Karn Wijarnpreecha[7] Dian Chiang[8] Wei Zhang[3] Whitney Jackson[9] Fanpu Ji[10] Chun-Ying Wu[11], [1]Cedars-Sinai Medical Center, [2]Children's Hospital at Montefiore, [3]Massachusetts General Hospital, [4]Canton Medical Education Foundation, [5]Tulane University School of Medicine, [6]Cedars Sinai Medical Center, [7]University of Arizona College of Medicine-Phoenix, [8]Cleveland Clinic, [9]University of Colorado Denver, [10]Xi'an Jiaotong University, [11]National Yang MIng Chiao Tung University, Taiwan

Background: Alcohol-associated hepatitis (AH) is associated with high morbidity, functional decline, and complex supportive care needs. Nutrition consultation (NC) and physical therapy consultation (PT) may address modifiable risks, including poor intake, muscle wasting, frailty, and deconditioning. Nationwide patterns and predictors of NC and PT use in patients hospitalized with AH remain poorly characterized. **Methods:** We performed a retrospective study of the National Inpatient Sample (NIS) from 2011 to 2022. Adult hospitalizations with a primary diagnosis of AH (ICD-9: 571.1; ICD-10: K70.10/K70.11) were identified. NC and PT were identified using ICD diagnosis and procedure codes. Multivariable survey-weighted logistic regression was performed, adjusting for age, sex, race/ethnicity, income quartile, insurance type, Charlson Comorbidity Index (CCI), hospital region, teaching status, and bed size. **Results:** A total of 72,240 weighted AH hospitalizations were identified (mean

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age 46.5 years; 40.2% female). In 2022, NC and PT utilization rates were 19.3% and 10%, respectively. NC rates showed no significant temporal improvement overall or across any subgroup. PT utilization increased sharply after 2015, coinciding with the ICD-9 to ICD-10 transition, with rates remaining relatively stable before and after. On multivariable analysis, female sex (vs. male, OR 1.37, 95% CI 1.22–1.54), CCI ≥ 3 (vs. CCI = 1, OR 2.26, 95% CI 1.94–2.63), South/Midwest/West region (vs. Northeast region, OR 1.62–1.89), and older age (vs. younger age, OR 1.01, 95% CI 1.00–1.02) were associated with higher odds of NC. Hispanic ethnicity was associated with lower NC odds (vs. non-Hispanic, OR 0.68, 95% CI 0.55–0.85). For PT, compared to non-Hispanic white, non-Hispanic Black (OR 2.61, 95% CI 1.00–6.78), Hispanic (OR 2.55, 95% CI 1.02–6.35), and other race (OR 3.41, 95% CI 1.37–8.53) patients demonstrated higher odds. In contrast, urban teaching hospitals were associated with lower PT odds (vs. urban non-teaching, OR 0.14, 95% CI 0.03–0.61). **Conclusion:** Utilization of NC and PT in AH remain persistently low nationwide with no improvement over 12 years, representing a critical unmet need. Observed sociodemographic differences suggest potential inequities in multidisciplinary supportive care for AH. Systematic approaches to nutrition assessment and functional evaluation may help address modifiable risks during AH hospitalization.



Disclosures: Yee Hui Yeo: Nothing to Disclose, lingyu bao: Nothing to Disclose, Sheng-Yin Chen: Nothing to Disclose, Hanyou Loh: Nothing to Disclose, Peng-Sheng Ting: Nothing to Disclose, Ju Dong Yang: Exact Sciences: Consultant, Exact Sciences: Consultant, AstraZeneca: Consultant, AstraZeneca: Consultant, Eisai: Consultant, Eisai: Consultant, Fujifilm Medical Sciences: Consultant, Fujifilm Medical Sciences: Consultant, Exact Sciences: Consultant, Exact Sciences: Consultant, AstraZeneca: Consultant, AstraZeneca: Consultant, Eisai: Consultant, Eisai: Consultant, Fujifilm Medical Sciences: Consultant, Fujifilm Medical Sciences: Consultant, Hyunseok Kim: Nothing to Disclose, Karn Wijarnpreecha: Nothing to Disclose, Dian Chiang: Nothing to Disclose, Wei Zhang: Nothing to Disclose, Whitney Jackson: Nothing to Disclose, Fanpu Ji: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Chun-Ying Wu: Nothing to Disclose.

2177 | RECENT TRENDS IN ALCOHOL CONSUMPTION ACROSS LARGE UNITED STATES POPULATION-BASED SURVEY

Olajide Adekunle[1] Katharine Bradley[2] Lidia Rodriguez[3] Thanh Bui[4] Daniel Jonas[5] Sudie Back[6] Ha Tran[1] Phuc Le[1], [1]Cleveland Clinic, [2]Kaiser Permanente Washington Health Research Institute, [3]Case Western Reserve University, [4]The University of Oklahoma Health Sciences, [5]Ohio State University, [6]Medical University of South Carolina

Background: To assess the comparability of alcohol consumption estimates across population-based surveys and how changes in survey design and administration may affect temporal trends, we compared the average daily consumption (ADC) and prevalence of WHO-drinking risk levels in US adults across five major surveys. **Methods:** A repeated cross-sectional analysis was conducted using data from Population Assessment of Tobacco and Health Study (PATH), Behavioral Risk Factor Surveillance System (BRFSS), National Health Interview Survey (NHIS), National Health and Nutrition Examination Survey (NHANES), and National Survey on Drug Use and Health (NSDUH) from 2015 to 2024 or the most recent year available. ADC in grams per day (g/d) and the prevalence of drinking risk levels were estimated overall and stratified by age, sex, and race and ethnicity. Drinking risk levels were defined as abstinence (< 1 g/d), low-risk drinking (1-20 g/d among women and 1-40 g/d among men), and moderate-to-very-high-risk drinking (≥ 21 g/d among women and ≥ 41 g/d among men). All analyses accounted for complex survey design and were age- and sex-standardized. **Results:** Sample sizes ranged from 9,254 to 486,303 participants. ADC increased during COVID-19 pandemic across surveys and, in 2023, was lowest in NHIS (6.7 g/d) and highest in NSDUH (11.9 g/d). Although ADC decreased with increasing age, it remained stable or increased over time in older adults. In 2023, the prevalence of abstinence was lowest in NHIS (47.9%) and highest in BRFSS (58.2%), whereas the prevalence of low-risk drinking was highest in NHIS (47.9%) and lowest in BRFSS (37.5%). Over time, low-risk drinking increased in adults ≥ 50 years and women. In 2023, the prevalence of moderate-to-very-high risk drinking ranged from 3.9% in BRFSS to 7.2% in NHANES, which increased over time in most surveys except NSDUH and PATH. In NHANES, moderate-to-very-high-risk drinking increased among men, non-

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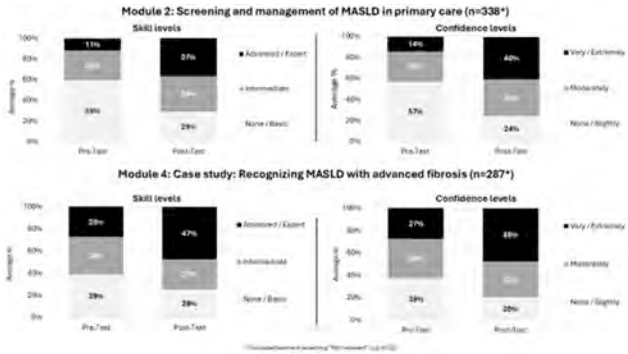
Hispanic White and Hispanic individuals, and adults >25 years. **Conclusion:** Alcohol consumption estimates varied across major US population-based surveys, with greater divergence after the COVID-19 pandemic. Differences in survey design and administration should be considered when interpreting temporal trends in alcohol consumption.

Disclosures: Olajide Adekunle: Nothing to Disclose, Katharine Bradley: Nothing to Disclose, Lidia Rodriguez: Nothing to Disclose, Thanh Bui: Nothing to Disclose, Daniel Jonas: Nothing to Disclose, Sudie Back: Nothing to Disclose, Ha Tran: Nothing to Disclose, Phuc Le: Nothing to Disclose.

2178 | UNMASKING MASH AND MASLD: INSIGHTS FROM AN ONLINE EDUCATIONAL PROGRAM

Laura Shelters[1] Deborah Talamonti[2] Steven Folstein[1] Leah Eberhardt[3] Lyndsey Aspaas[4] Patrice Lazure[2] Stephen Legault[4] Cara Orr[5] Sarah Repking[6] Hillary Lois[7] Niharika Samala[8] Suzanne Murray[2] Robert Fontana[9], [1]AASLD, [2]AXDEV Group Inc., [3]American Academy of PAs, [4]American College of Osteopathic Family Physicians, [5]Temple University Health System, [6]Rush University Medical Center, [7]VCOM-Virginia Campus, [8]Indiana University, [9]University of Michigan Hospitals and Health Centers

Background: Recent changes in the nomenclature and practice guidance of steatotic liver disease (SLD) called for educational efforts to disseminate the new terminologies. This study evaluates an educational program designed to enhance healthcare professionals' (HCPs') competence in screening, assessing, and managing patients with, or at risk of, SLD. **Methods:** An accredited educational program comprised of four 15-minute online modules (two didactic (1, 3), two skill-based (2,4)) was launched October 2025, targeting physicians, physician associates/nurse practitioners (PA/NP), and medical students/residents in primary care, general or internal medicine (primary audience) or gastroenterology, endocrinology, or hepatology (secondary audience). Each module included pre-/post-tests and evaluations. Knowledge-based multiple-choice questions were paired with confidence ratings to derive confidence-based learning (in which mastery corresponds to a good response provided with high confidence) before and after the education. Perceived skills and confidence in performing tasks related to patient management were assessed using Likert-type scales. Statistical analyses included Wilcoxon signed-rank tests (pre/post comparisons), Kruskal-Wallis tests (subgroup analyses), chi-square tests (categorical data), and thematic analysis (open-ended questions). **Results:** At month 3 of 12, 875 total learners accessed the program, with 735 modules completed. Participants were categorized as primary (36%); secondary (18%); and non-targeted audience (46%).Significant gains were observed for all modules (Figure 1) in confidence-based learning (% of completers who achieved mastery increased by 38.5% on average across 14 SLD-related knowledge questions, $p < .001$), skills and confidence (26% average gains respectively, across 9 questions, $p < .05$). Compared to the secondary audience, the primary and non-targeted groups gained greater knowledge across 7 SLD management-related items ($p < .05$), and increased their confidence in using primary assessment tools ($n = 274$, $\chi2 = 8.79$, $p = .012$) and in determining appropriate referral pathways ($n = 274$, $\chi2 = 9.70$, $p = .008$).Moreover, learners from the primary audience reported greater intention to improve screening of at-risk patients ($n = 334$ $\chi2 = 63.74$, $p < .001$) and patient referral ($n = 334$, $\chi2 = 15.06$, $p < .001$), whereas learners from the secondary audience reported wanting to improve patient education on lifestyle changes ($n = 281$ $\chi2 = 23.12$, $p < .001$). **Conclusion:** This 1-hour online educational program had a positive impact on HCPs' competence and intention to change clinical practice for patients with, or at risk of, SLD. Insights from this evaluation informed the adaptation of content for live educational activities, expanding the reach and potential impact of the program.



Disclosures: Laura Shelters: Nothing to Disclose, Deborah Talamonti: Nothing to Disclose, Steven Folstein: Nothing to Disclose, Leah Eberhardt: Nothing to Disclose, Lyndsey Aspaas: Nothing to Disclose, Patrice Lazure: Nothing to Disclose, Stephen Legault: Nothing to Disclose, Cara Orr: Nothing to Disclose, Sarah Repking: Ipsen: Consultant, Hillary Lois: Nothing to Disclose, Niharika Samala: Novo Nordisk: Consultant, Madrigal: Advisor, Petauri Kinect: Grant/Research Support, Eli Lilly: Grant/Research Support, Regeneron: Grant/Research Support, GSK: Grant/Research Support, Suzanne Murray: Nothing to Disclose, Robert Fontana: kezar pharmaceuticals: Grant/Research Support, Takeda Pharmaceuticals: Grant/Research

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2179 | HUMAN AUDITS IMPROVE EHR-BASED HCV PATIENT RE-ENGAGEMENT: RESULTS FROM A US PROGRAM

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Background: Re-engaging patients who are lost to follow-up (LTFU) aids hepatitis C virus (HCV) elimination. The Relink grant funds US programs that re-engage LTFU HCV patients. Electronic health records (EHRs) connect patient data across health institutions, however, the completeness and usability of EHR data for LTFU HCV patient case-finding and re-engagement is underexplored. **Methods:** We examined factors linked to successful contact and re-engagement of LTFU HCV patients from Epic EHR-using and non-using organizations. Data came from 29 sites in diverse clinical and geographic settings. Pre-contact investigation (PCI), defined as human effort to verify LTFU status beyond EHR output, was encouraged. Exclusion criteria were standardized across sites. Re-engagement was defined as post-outreach laboratory or treatment provider visit. Fisher's Exact test, Chi-square tests, and Firth (penalized) logistic regression were performed for effects and significance. Regression variables included demographic and system-level factors. Results were analyzed in R v4.6.0. Copilot was used to troubleshoot R code. **Results:** 24,245 cases contacted from January 2024 to December 2025 were analyzed. Table 1 shows patient characteristics and outcomes. In-person contact (IPC) was used in 8% of cases and accounted for 22% of contact successes. Large registries (n > 5,000) had high odds of Epic use, and low odds of PCI, IPC and successful re-engagement. PCI alone weakly improved contact but with Epic

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use, contact odds rose by 62%. IPC alone led to a 9-fold and 3-fold higher odds of contact and re-engagement respectively. In the multivariable models, Epic use was associated with extremely low contact (OR 0.06 CI: 0.05 – 0.07) and re-engagement (OR 0.02 CI: 0.01 – 0.03) odds. PCI overwhelmingly reversed Epic-use odds for both contact (OR 33.8 CI: 28.4 – 40.2) and re-engagement (OR 39.6 CI: 22.0 – 73.0). Adding IPC to the model dampened but did not negate PCI's effect on contact (OR 10.4 CI: 8.5 – 12.8) or re-engagement (OR 24.4 CI: 13.3 – 45.4). All effects were significant, and estimates were well-defined despite large test statistics. **Conclusion:** PCI remains linked to dramatically improved odds of contact and re-engagement in the multivariable models, even after adjusting for Epic use and IPC. This indicates human-mediated audits mitigate EHR data entry and resultant quality issues upstream of outreach. This supports better contact and re-engagement outcomes.

Table 1: Patient characteristics and re-engagement outcomes

Category	Contact Failure	Contact Success	Enrolled	Linked	% of Successful Contacts	% Linked of Successful Contacts	% Linked of All Contacts
Overall	16,042	5,001	3,450	2,792	34%	34%	12%
Female	5,666	2,289	1,394	1,108	37%	34%	12%
Male	10,403	4,914	2,039	1,684	32%	34%	11%
American Indian or Alaska Native	112	51	24	22	31%	43%	13%
Asian	221	247	29	23	52%	9%	5%
Bi-racial or multi-racial	244	122	59	44	33%	36%	12%
Black or African American	4,788	1,730	443	293	27%	17%	5%
Native Hawaiian or Other Pacific Islander	40	18	4	4	31%	22%	7%
White	10,637	9,016	2,970	2,402	39%	40%	14%
Age <29	28	16	5	4	32%	31%	10%
20-29	494	352	203	174	42%	49%	21%
30-39	3,126	2,066	1,148	960	42%	42%	18%
40-49	3,002	1,792	650	510	37%	45%	17%
50-59	2,929	1,274	496	398	33%	31%	10%
60-69	4,829	1,812	501	343	29%	19%	5%
70-79	1,864	781	116	76	29%	10%	3%
80+	249	128	12	8	34%	6%	2%
Baby Boomer Cohort	7,669	3,178	800	580	29%	18%	5%
Non-Baby Boomer Cohort	8,273	5,025	2,600	2,212	38%	44%	17%
Pre-Contact Investigation	6,657	5,214	2,074	1,586	44%	30%	19%
No Pre-Contact Investigation	8,085	2,989	1,356	1,206	33%	40%	12%
Epic	9,039	3,783	1,227	788	30%	21%	6%
No Epic	7,012	4,410	2,266	1,964	39%	45%	17%
In Person Contact =0	10,628	6,277	1,862	1,704	29%	29%	6%
In Person Contact >=1	13	1,626	1,501	1,488	99%	91%	91%
Registry Size >5,000	8,001	2,176	396	168	22%	8%	2%
Registry Size <5,000	8,041	6,027	3,055	2,624	42%	44%	19%

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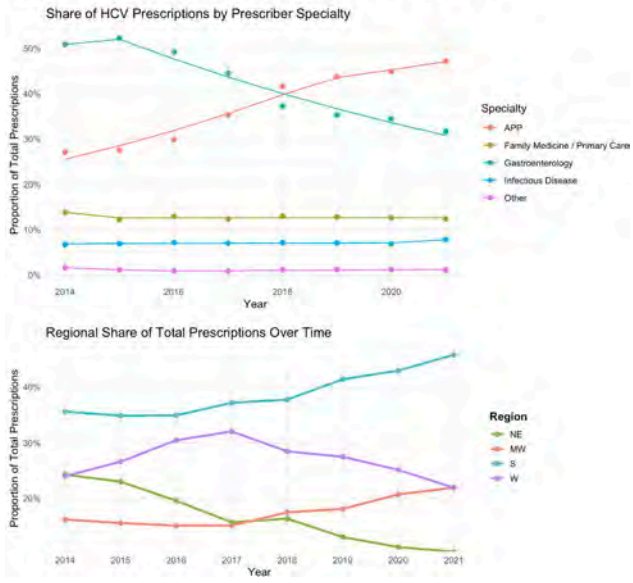
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2180 | TRENDS IN DIRECT-ACTING ANTIVIRAL PRESCRIPTIONS AMONG MEDICARE BENEFICIARIES: EXPANDING ROLE OF ADVANCED PRACTICE PROVIDERS AND REGIONAL DISPARITIES IN HEPATITIS C CARE

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Background: Hepatitis C virus (HCV) infection affects approximately 2.4 million US adults. Yet despite direct-acting antivirals (DAAs) that achieve sustained virologic response (SVR) in >95% of cases, only 30% of Medicare beneficiaries with HCV receive timely, curative treatment within 12 months. Advanced practice providers (APP) have been proposed as key contributors to expanding DAA access, yet national prescribing patterns and regional distribution of DAA use remain incompletely characterized. We examined trends in provider type and regional variability in DAA prescribing among Medicare beneficiaries. **Methods:** We performed a retrospective, cross-sectional analysis of publicly available Medicare part D data from 2014-2021. Seven medications were included in this study: Harvoni®, Sovaldi®, Epclusa®, Mavyret®, Vosevi®, generic ledipasvir-sofosbuvir, generic sofosbuvir-velpatasvir. Outcomes included annual 30-day DAA prescriptions, number of beneficiaries receiving treatment, prescriber specialty (APP, gastroenterology [GI], primary care, infectious disease [ID], and other), and US Census region. Joinpoint regression was performed using R to evaluate temporal trends and annual percent change (APC) with 95% confidence intervals (CI). **Results:** From 2015 to 2021, the annual number of Medicare beneficiaries receiving DAAs declined despite increasing HCV rates among Medicare-eligible populations. APP involvement in DAA prescribing increased substantially, accounting for 27.1% of prescriptions in 2014 and 47.2% in 2021 (APC 9.52; 95% CI 7.5–11.5; $p < 0.001$). In contrast, GI specialists demonstrated the greatest decline in prescribing share among physician specialties (APC −7.53; 95% CI −8.99 to −6.05; $p < 0.0001$), with comparatively smaller contributions from ID and primary care providers. Regional analysis demonstrated declining DAA prescriptions across all US Census regions after 2015. The South accounted for the largest and increasing proportion of prescriptions over time (APC 4.05; 95% CI 2.89–5.23; $p < 0.001$), whereas prescribing shares declined in the Northeast and remained relatively stable in the West and Midwest. **Conclusion:** Although APPs now account for an increasing share of DAA prescribing among Medicare beneficiaries, overall DAA utilization has declined since 2015. Furthermore, the areas of highest HCV prevalence showed relative limited access to APP support, which may make progress towards HCV elimination difficult. Thus, persistent regional variation in treatment patterns highlights the need for targeted strategies to improve treatment access and delivery.

Figure 1. Share of HCV prescriptions by (a) prescriber specialty and (b) region.



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2181 | CLINICAL SPECTRUM AND DISEASE BURDEN OF SYMPTOMATIC POLYCYSTIC LIVER DISEASE: A NATIONWIDE STUDY IN JAPAN

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Background: Polycystic liver disease (PLD) is often asymptomatic, but some patients develop clinically relevant symptoms or complications requiring specialized and multidisciplinary care. However, the nationwide burden, clinical spectrum, and healthcare needs of symptomatic PLD remain unclear. **Methods:** We conducted a two-stage nationwide epidemiological survey in Japan. In the first-stage survey, 3,127 of 10,270 institutions were selected by stratified random sampling and asked to report patients with symptomatic PLD treated or followed between 2021 and 2023. Symptomatic PLD was defined as ≥ 10 hepatic cysts with hepatic cyst-related symptoms or complications. In the second-stage survey, patient-level data were collected from institutions reporting symptomatic patients in 2023. **Results:** In the first-stage survey, 1,608 institutions responded (51.4%), and 2,684 patients were reported during 2021–2023. The estimated number of patients with symptomatic PLD was 6,500 (95% confidence interval [CI], 4,990–8,020) during 2021–2023 and 3,570 (95% CI, 2,780–4,360) in 2023, corresponding to period prevalences of 52.0 and 28.6 per million, respectively. In the second-stage survey, 557 patients were analyzed. The mean age was 63.7 years, and 344 of 555 patients (62.0%) were female. The median maximum hepatic cyst diameter was 8.1 cm; 218 patients (40.9%) had cysts ≥ 10 cm; and Gigot type III disease was observed in 121 of 543 patients (22.3%). Renal cysts were present in 453 of 547 patients (82.8%), and 368 (67.3%) fulfilled the definition of polycystic kidney disease. Older age was significantly associated with larger maximum cyst diameter (Spearman's $\rho = 0.33$, $P < 0.0001$). Patients with Gigot type III disease were younger and had higher frequencies of polycystic kidney disease and a higher proportion of deaths. The most frequent symptoms or complications were abdominal distension (39.7%), abdominal pain (21.0%), and cyst infection (18.3%). Larger maximum cyst diameter was associated with higher frequencies of mass-related symptoms, including abdominal distension, abdominal pain, loss of appetite, exercise limitation, and dyspnea. A history of hepatic cyst treatment was reported in 308 of 555 patients (55.5%). Cyst fenestration was reported as effective in 59 of 77 treatments (76.6%). Multidisciplinary consultation or inter-institutional referral was reported in 335 of 555 patients (60.4%), and 22 patients (3.9%) died. **Conclusion:** This nationwide survey estimated the burden of symptomatic PLD in Japan and identified clinically relevant patterns of disease severity, including age-related cyst enlargement and the association of Gigot type III disease with polycystic kidney disease and mortality. These findings provide baseline data for developing severity classification criteria, treatment strategies, and healthcare support systems for symptomatic PLD.

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2182 | TARGETED HEPATITIS C TESTING AND LINKAGE AMONG UNHOUSED POPULATION IN SOUTHERN NEVADA THROUGH COMMUNITY-BASED OUTREACH AND CROSS-SECTOR COLLABORATION, 2024-2025

Shannon Pickering[1] Lourdes Yapjoco[1], [1]Southern Nevada Health District

Background: Southern Nevada Health District's Sexual Health Clinic and Sexual Health Outreach and Prevention Programs (SHOPP) have systematically increased the number of Hepatitis C (HCV) screenings conducted annually, aligning with the goals of the Viral Hepatitis National Strategic Plan. This national framework emphasizes testing and awareness, specifically among affected populations. Recognizing the elevated vulnerability of unhoused populations due to factors such as injection drug use, shared personal hygiene items, incarceration history, mental illness, and decreased access to healthcare, SHOPP intensified targeted HCV testing efforts among this group in 2025 as well as maximizing team resources to focus on increasing linkage to first provider visits. **Methods:** Data from 2024 and 2025 were compared, including testing volume, positivity rates, housing status, and linkage to care. In 2025, SHOPP expanded outreach partnerships with SNHD's Division of Disease Surveillance and Control, Help of Southern Nevada, and Nevada Homeless Alliance. Multidisciplinary teams (nurses, community health workers, and disease investigators) conducted testing in non-clinical settings. Staff also increased engagement through a whole person approach with unhoused clients, often providing transportation to first provider visits. **Results:** In 2024, 3,478 HCV tests identified 30 RNA-positive clients (0.86%), including 3 unhoused. Outreach accounted for 50 tests and 4 positives. Of all positives, 16 (53.3%) were linked to care; none of the unhoused clients were linked.In 2025, 4,626 tests identified 43 positives (0.93%), including 15 unhoused. Expanded outreach accounted for 130 tests and 16 positives. Of the 43 positives, 22 (51.2%) were linked to first provider visits, including 7 of 15 unhoused clients (46.7%).The proportion of positive clients who were unhoused increased from 10% to 34.9%, reflecting targeted outreach rather than increased prevalence. Linkage to care among unhoused individuals improved from 0% to 46.7%. **Conclusion:** The 2025 expansion of

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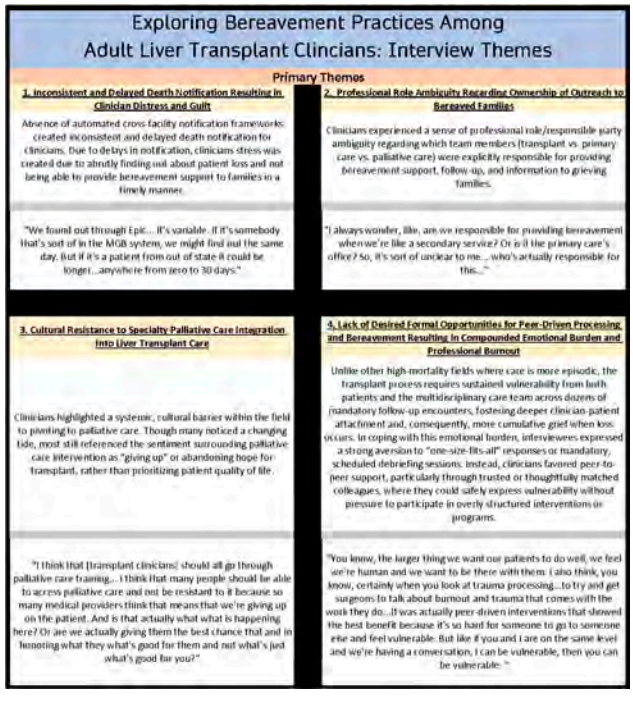
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targeted HCV testing among unhoused individuals by SHOPP demonstrates an effective strategy for improving identification in high-risk groups. By shifting clinic-based staff to street outreach and strengthening partnerships, SNHD increased testing and detection while addressing social determinants of health. Overall, linkage to first provider visits for Hepatitis C positive clients remain a significant challenge and even more so for the unhoused. However, with a whole person approach to linkage to care a significant improvement was made in 2025 linking unhoused clients . Expanding mobile, field-based care is critical to close gaps and advance HCV elimination goals. **Disclosures:** Shannon Pickering: Nothing to Disclose, Lourdes Yapjoco: Nothing to Disclose.

2183 | "IT NEVER GETS EASIER": EXPLORING BEREAVEMENT PRACTICES AMONG ADULT LIVER TRANSPLANT CLINICIANS

William Munroe[1] Anushka Dalvi[2] Grace Bizup[1] Malia Armstrong[3] Bailey Marshall[1] Abigail Scherrer[1] Ana Ivkovic[1] Kerry O'Brien[1] Laura Sterritt[1] Jane Lavallee[1] Nancy Mason[1] Sara Kenimer[1] Kirsten Engel[1] Michelle Diop[1] Karen O'Brien[1] Chengbo Zeng[4] Rennie Bimman[5] Nneka Ufere[1], [1]Massachusetts General Hospital, [2]Wayne State, [3]Duke University, [4]Brigham and Women's Hospital, [5]McGill University

Background: Advanced liver disease (AdvLD) is the 9th leading cause of death in the United States. Processing patient death is an inevitable part of the job of clinicians providing care to patients with AdvLD and their families. However, little is known about grief and bereavement practices among adult liver transplant (LT) clinicians. **Methods:** We conducted a mixed-methods study at a large academic LT center. Between 5/2025-6/2025, we surveyed adult LT clinicians to characterize their current bereavement practices and explore what resources could help clinicians process loss following patient death. Clinicians who completed the survey were invited to participate in individual semi-structured interviews conducted between 9/2025-5/2026 to further explore systemic and cultural barriers and facilitators to: 1) clinician outreach to bereaved caregivers and 2) opportunities for clinicians to emotionally process patient loss. We conducted a team-based qualitative thematic analysis of interview data to identify grief-related perspectives and processes. **Results:** In total, 73/114 (64%) clinicians completed the survey (20 hepatologists, 4 surgeons,16 fellows, 6 social workers, 11 APPs, 5 transplant coordinators, 5 nurses, 4 psychiatrists, 1 dietitian, 1 anesthesiologist). Following patient death, 61/73 (84%) clinicians reported contacting the primary caregiver or family to acknowledge the loss. However, only 17/61 (28%) reported providing material support to grieving families, which most commonly included social work follow-up, one-on-one psychological support, and referral to bereavement support groups. A majority of respondents expressed interest in expanding support for both grieving families and staff-facing bereavement through recurring remembrance ceremonies(n = 62, 85%), a standardized bereavement packet for families (n = 56; 77%), and formal bereavement training (n = 40, 55%). We conducted semi-structured interviews with 18 clinicians (4 hepatologists, 2 surgeons, 3 transplant coordinators, 1 fellow, 2 APPs, 2 nurses, 2 psychiatrists, 2 social workers). Qualitative analysis revealed four core themes: 1) Inconsistent and delayed death notification resulting in clinician distress and guilt; 2) Professional role ambiguity regarding ownership of outreach to bereaved families; 3) Cultural resistance to specialty palliative care integration in LT care; and 4) Lack of desired formal opportunities for peer-driven processing and bereavement resulting in compounded emotional burden and professional burnout. **Conclusion:** Although most LT clinicians identified bereavement outreach as a professional responsibility, inconsistent death notification, cultural resistance to palliative care, and role ambiguity were reported as barriers to engagement. Enhancing bereavement support in LT is crucial to improve clinicians' emotional processing after patient loss and mitigate professional burnout.



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2184 | IMPROVING VIRAL HEPATITIS CARE ENGAGEMENT AND SHARED DECISION-MAKING THROUGH A GLOBAL PATIENT AND PROVIDER EDUCATION INITIATIVE

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Background: Despite advances in antiviral therapies and updated guideline recommendations, including treatment simplification, major gaps in viral hepatitis awareness, diagnosis, linkage to care, and treatment persist among vulnerable populations worldwide. **Methods:** From September 2025 – February 2026, a global initiative across the U.S., Europe, and Asia was conducted to improve HBV, HCV, and HDV screening, engagement, and treatment through (1) Community Care Forums (CCFs) for patients and vulnerable populations and (2) Clinical Practicums (CPs) for healthcare professionals (HCPs). CPs incorporated real-world patient perspectives and case-based learning tailored to regional needs. Pre- and post- surveys were administered for all sessions. **Results:** A total of 253 individuals participated in the CCFs (Table 1). Following the sessions, participants were more likely to perceive themselves at risk for HBV/HDV and HCV exposure in the next 6 months (HBV/HDV: 17% vs. 37%, p = 0.002; HCV: 30% vs. 63%, p < 0.001). The patient-reported likelihood of hepatitis testing within the next 30 days also increased significantly (HBV/HDV: 53% vs. 67%; p = 0.021; HCV: 45% to 71%, p = 0.005). Participants in the HCV CCFs gained confidence in their ability to protect themselves from HCV (67% vs. 92%, p < 0.001). In the HBV CCFs, while only 38% had completed HBV vaccination prior to the session, 77% of those who were unvaccinated reported they were somewhat or very likely to get vaccinated after the session.The initiative identified critical gaps in shared decision-making (SDM). Among patients, key barriers were difficulty understanding medical terminology (36%) and insufficient information from HCPs (35%), whereas 87% of HCPs reported lack of time during appointments as their primary barrier. Although 56% of all participants desired to be very involved in their own care, only 18% of participants with viral hepatitis (n = 38) reported being very involved. The most cited facilitator of follow-up care among those with hepatitis was a supportive HCP who clearly explained the benefits of regular monitoring.There were 102 HCPs who participated in the CPs with significant gains in HCP knowledge and confidence, including recognition of the burden of undiagnosed viral hepatitis (40% vs. 89%, p < 0.001), confidence in culturally competent communication (54% vs. 82%, p < 0.001), and commitment to incorporating SDM into hepatitis care (76% vs. 100%, p < 0.001). **Conclusion:** This viral hepatitis educational initiative improved perceived risk, screening intent, and engagement in care among vulnerable populations globally. Additionally, it improved HCP confidence in and commitment to incorporating shared decision-making in their care of individuals with viral hepatitis. Multi-platform educational strategies for both patients and HCPs remain essential to equip providers to deliver optimal care and achieve WHO hepatitis elimination targets.

Table 1. Demographics of Participants in Community Care Forums (N = 253)

Demographics	Hepatitis B & D Community Care Forums (N = 186) N (%)	Hepatitis C Community Care Forums (N = 67) N (%)
Age, mean (SD)	37 (17)	49 (10)
Country Living In		
Vietnam	70 (38%)	N/A
Taiwan	54 (29%)	18 (27%)
United Kingdom	16 (9%)	16 (24%)
United States	46 (25%)	33 (49%)
Racial/Ethnic Background		
Asian	154 (83%)	39 (58%)
Black or African descent	5 (3%)	3 (4%)
Middle Eastern or North African	1 (1%)	0
Hispanic/Latinx	3 (2%)	5 (7%)
White/European descent	12 (6%)	31 (46%)
Pacific Islander	11 (6%)	16 (24%)
Self-described Gender		
Woman	122 (66%)	36 (53%)
Man	61 (33%)	29 (43%)
Nonbinary/Other/Prefer not to answer	3 (2%)	2 (3%)
Previous hepatitis testing		
Yes	54%	73%
No	32%	23%
Unsure/Prefer not to answer	13%	3%

Disclosures: Mark Sulkowski: AbbVie: Advisor, Arbutus: Advisor, Aligos: Advisor, Gilead: DSMB member, Precision Biosciences: Advisor, Vir: Advisor, Vir: Grant/Research Support, GSK: Advisor, GSK: Grant/Research Support, Virion: Advisor, ImmunoCore: DSMB member, Pfizer: Advisor, Tanyaporn Wansom: Nothing to Disclose, Kosh Agarwal: Nothing to Disclose, Leah Molloy: Nothing to Disclose, Laura Simone: Nothing to Disclose, Jenniffer Meza Jimenez: Nothing to Disclose, Jeffrey Carter: Nothing to Disclose, Cherilyn Heggen: Nothing to Disclose, Kelly Pillinger: Nothing to Disclose.

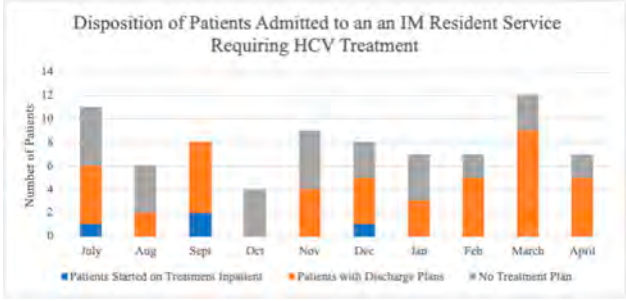
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2185 | INCREASING HEPATITIS C TREATMENT INITIATION AND LINKAGE TO CARE AMONGST PATIENTS HOSPITALIZED IN A SAFETY-NET ACUTE CARE SETTING: A RESIDENT-LED QUALITY IMPROVEMENT PROJECT

Bharathi Selvan[1] Chelsea Pan[2] Emma McCune[1] Joanna Krupp[1] Katie Leiner[1] Austin Peer[1] Madeline Stewart[1] Hannah Tierney[1] Lou Xie[1] Alexandra Moss[3] Lisa Winston[1] Anne Luetkemeyer[1], [1]University of California San Francisco, [2]University of California, San Francisco, [3]San Francisco Department of Health

Background: Despite curative direct-acting antivirals, HCV treatment uptake remains low in high-prevalence populations including people who use drugs and underserved groups. Hospitalization offers an opportunity to identify and treat patients not engaged in outpatient care. At our safety-net teaching hospital, patients hospitalized for >7 days and eligible per AASLD/IDSA guidelines for simplified HCV treatment can initiate treatment inpatient. However, fewer than 10% of eligible patients were started on treatment from Nov 2023- Nov 2024. **Methods:** We conducted a resident-led quality improvement project from July 1, 2025 to April 30, 2026 to improve inpatient HCV treatment initiation. Stakeholder interviews and a root cause analysis identified the lack of a standardized workflow and clinician knowledge of HCV treatment as core issues. A workflow was created, including treatment initiation criteria and instructions for medication approval (glecaprevir/ pibrentasvir or sofosbuvir/velpatasvir) and coordination with the specialty pharmacy. This was coupled with a shared tool in the electronic health record (EHR) that provided guidance regarding baseline labs, fibrosis scoring, and treatment plan options for use in progress notes and discharge summaries. For patients unable to start treatment inpatient, we recommended referrals to low barrier outpatient care and patient navigation. The initiative was presented to IM residents during didactics and reinforced with flyers, and monthly reminder emails. The percentage of admitted patients who were started on HCV treatment or discharged with an outpatient referral was tracked via a report in the EHR. **Results:** During this 10-month period, 168 patients with untreated HCV were admitted to our safety-net hospital of which 79 patients (47%) were cared for by an IM resident service. Of these, 21 patients were eligible for inpatient treatment initiation per project guidelines, and 4 patients (19% of those eligible) were started on inpatient treatment, which is double the historic 10% baseline. A majority, 43 patients (54%) were discharged with a low barrier outpatient HCV treatment referral, including to walk-in clinics, street medicine, treatment navigation, and primary care, ID, or hepatology follow up. Referral rates increased over the project period. **Conclusion:** Implementation of EHR-based tools and targeted education increased inpatient HCV treatment initiation above baseline and improved linkage to care, reinforcing the opportunity that hospital admissions provide for engaging patients in HCV care. Despite availability of robust low barrier resources, discharge referrals were only provided to half of patients, underscoring the need for further recognition of untreated HCV as well as innovation in HCV care delivery.



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2186 | UNDERSTANDING PATIENT PERSPECTIVES ON RISK-STRATIFIED APPROACHES TO HCC SURVEILLANCE

Thomas Hunold[1] Rachel Bergmans[1] Neehar Parikh[1], [1]University of Michigan Medical Center

Background: Surveillance for hepatocellular carcinoma is associated with early tumor detection and improved survival; however, adherence to HCC surveillance is poor with only one quarter of patients receiving recommended testing. Risk-stratification for HCC risk is one novel approach to improve benefits and adherence to HCC surveillance in high-risk patients while minimizing harms to low-risk patients. We aimed to characterize patient Preferences surrounding HCC surveillance and attitudes toward risk-based surveillance paradigms. **Methods:** Patients with cirrhosis eligible for liver cancer screening were identified through the electronic health record. We performed a purposeful sampling with a balance of ages, genders, etiologies of liver disease, and adherence to surveillance recommendations. We conducted semi-structured interviews using a prespecified guide to allow the interviewer to explore patient understanding of liver

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disease, current surveillance recommendations, experiences completing HCC surveillance recommendations, and perspectives on transitioning to a risk-stratified surveillance approach. Interviews were completed via Zoom video calls (or audio, if video unavailable), recorded, and transcribed. Thematic analysis was performed using rapid analysis techniques allowing for reflexive thematic analysis to develop preliminary themes. **Results:** A total of 3,119 patients were identified for potential inclusion. 419 charts were screened and 237 patients were contacted to enroll a total of 30 patients whose characteristics are shown in the Table 1. Four core themes emerged from the interviews: 1) a lack of information related to their liver disease (ie: severity of disease, implications of liver disease, and relationship to liver cancer), 2) scheduling of imaging tests became harder after this was no longer done at check-out from clinic visits, 3) transportation to imaging tests limited the ability of patients to complete their screening, 4) patients would be amenable to a risk-based screening approach as long as their physician had the ability to use clinical judgement outside of a strict surveillance protocol. Additionally, many patients were unable to provide a HCC risk level at which they would be willing to skip their next screening noting that they would rather have a false positive than skip a screening test if they were determined to be low risk for HCC. **Conclusion:** Patients in this study identified several barriers to completing HCC surveillance including a lack of information, trouble scheduling tests, and lack of transportation. While patients said they would be amenable to a risk-based surveillance approach, patients could not identify a threshold for de-escalation of surveillance, potentially limiting the implementation of risk-based surveillance in clinical practice.

Table 1. Characteristics of Included Patients

Characteristic	N = 30
Age, Median (q1-q3)	57.5 (36.5-63)
Female, % (n)	46.7% (14)
Race, % (n)	
White or Caucasian	93.3% (28)
Other	3.3% (1)
Not Specified	3.3% (1)
Not Hispanic or Latino, % (n)	100% (30)
Primary Etiology of Liver Disease, % (n)	
ALD	23.3% (11)
Met-ALD	3.3% (1)
MASLD	20.0% (6)
Viral	13.3% (4)
Autoimmune	10.0% (3)
Metabolic	6.7% (2)
Other	10.0% (3)
MELD, Median (q1-q3)	10 (8-13.75)
Child-Pugh Class, % (n)	
A	80% (24)
B	20% (6)
Up-To-date on Surveillance, % (n)	50% (15)

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2187 | A MULTI-MODAL APPROACH TO IDENTIFYING ALPHA-1 ANTITRYPSIN DEFICIENCY ASSOCIATED LIVER DISEASE IN LARGE ADMINISTRATIVE DATABASES USING NATURAL LANGUAGE PROCESSING, DIAGNOSTIC CODES, AND SERUM BIOMARKERS

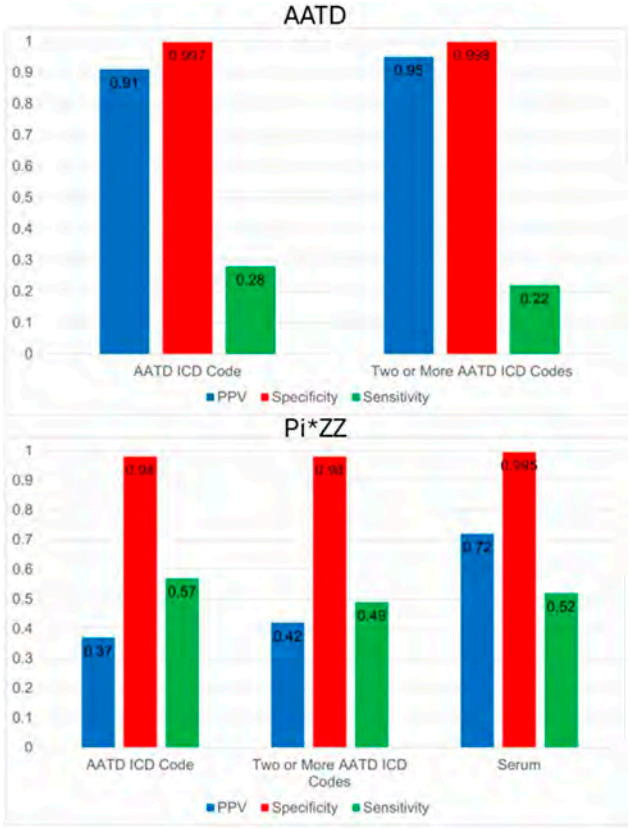
Dustin Bastaich[1] Bassam Dahman[1] Austen Hentschel[2] Chitra Karki[3] Tami Nussbaum[3] Suna Park[3] Seth Spector[4] Gregory Bigford[5] Brian Garnet[4] Michael Campos[4] John Binu[4], [1]Virginia Commonwealth University and Miami VA, [2]Florida International University and Miami VA, [3]Takeda, [4]University of Miami and Miami VA, [5]Miami VA

Background: Alpha-1 antitrypsin deficiency (AATD) increases susceptibility to chronic liver disease but remains underdiagnosed and insufficiently documented. Underdiagnosis occurs due to infrequent testing of both AAT levels and genotypes in patients with liver disease, while insufficient documentation is attributable to systematic under coding practices where providers fail to document and assign appropriate internal classification of diseases (ICD) codes. These issues may introduce bias in outcome studies. This study evaluated the diagnostic performance ICD9/10 codes for identifying AATD among patients with liver disease and assessed whether alpha-1 antitrypsin (AAT) serum levels < 50 mg/dl accurately identify patients with protease inhibitor (Pi)*ZZ genotype. **Methods:** This was a retrospective cohort study using Veterans Health Administration (VHA) database from January 2000 to April 2025. Veterans were included if they had a classifiable genotype at any time during the study period. Genotypes were ascertained using previously validated natural language processing (NLP) applied on medical records and lab comments, with high agreement with manual chart review (Kappa = 0.89). AATD was identified using ICD codes of 273.4 and E88.01, respectively. **Results:** There were 782 participants with an ICD code for AATD, and 2,540 participants with AATD genotypes (Pi* MZ, SZ or ZZ) identified by NLP-however, only 28.1% (n = 714) of participants with AATD had a corresponding ICD code. Coding prevalence varied by genotype: 17.2% among Pi*MZ,

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41.0% among Pi*SZ, and 57.3% among Pi*ZZ. Of 782 participants with an ICD code for AATD, 714 had genotype-confirmed AATD (PPV = 0.91) with a specificity of 0.997 and sensitivity of 0.28. Restricting the definition of AATD to ≥2 ICD codes (n = 584) resulted in only a marginal increase in PPV to 0.95 and specificity to 0.998, but reduced sensitivity to 0.22. For identifying Pi*ZZ genotype specifically, ICD 9/10 codes had lower performance (PPV = 0.37, specificity = 0.98, and sensitivity = 0.57). Restricting to ≥2 ICD codes modestly increased PPV to 0.42, while reducing sensitivity to 0.49 (specificity = 0.98).Of 290 participants with AAT serum level < 50 mg/dL (a surrogate for Pi*ZZ), 209 had Pi*ZZ genotype (PPV = 0.72). However, misclassification remained: 10.0% Pi*MM, 10.3% Pi*SZ, and 7.6% Pi*MZ, corresponding to specificity of 0.995 and sensitivity of 0.52 for identifying Pi*ZZ using AAT < 50 mg/dl **Conclusion:** While ICD codes for AATD demonstrate high specificity, they capture fewer than one-third of genotype-confirmed cases and perform poorly for identifying Pi*ZZ specifically. In contrast, an AAT serum level threshold of < 50 mg/dL offers a pragmatic surrogate for Pi*ZZ identification, outperforming ICD-based approaches. However, an NLP based approach identifying AATD genotype outperforms both ICD and AAT level-based approach to study AATD outcomes in administrative databases.



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2188 | TRENDS IN AND DETERMINANTS OF HCC SURVEILLANCE ADHERENCE: A NATIONWIDE COHORT STUDY

Mohamed Moussa[1] Dave Sprengers[1] Willem Pieter Brouwer[1] Raoel Maan[1] Harry Janssen[1] Adriaan Van der Meer[1] Milan Sonneveld[1], [1]Erasmus University Medical Center

Background: Current guidelines recommend bi-annual liver imaging in patients with cirrhosis as it facilitates early diagnosis and potentially curative treatment. Previous studies in highly selected patient populations suggest suboptimal adherence to surveillance. However, real-world data on longitudinal adherence and contemporary disparities remain limited. We aimed to study time-trends in and determinants of HCC surveillance adherence in a nationwide sample. **Methods:** We identified patients receiving hospital-based care for cirrhosis in the Netherlands from 2015 to 2023 through a search of the Dutch Central Bureau of Statistics (CBS) database. Information on diagnostic procedures was obtained through cross-referencing with insurance claims databases. Adherence was assessed in 14-month intervals, with optimal adherence defined as ≥ 2 abdominal imaging studies within that timeframe. Longitudinal trends in adherence were analyzed using Generalized Estimating Equations (GEE), while a multivariable logistic regression model was fit adjusted for sex, etiology of cirrhosis (viral/non-viral), cirrhosis status (compensated/decompensated), hospital type (academic/general), socioeconomic status, and country of birth (Netherlands/elsewhere) to identify contemporary determinants of non-adherence in the most recent year (2023-2024). **Results:** We identified 23,467 individuals with cirrhosis (63% compensated), the majority of whom were male (60%). Mean age was 62.1 years (SD ± 12.4) and non-viral etiology predominated (85%). Between 2015 and 2023, the number of patients increased by 65% (from 5,521 to 9,133). The rate of optimal adherence increased from 17% to 40% (Annual percentage change [APC]: 11.3% [95% CI: 10.6–12.1]; p < 0.001), while the proportion of patients who underwent no surveillance at all declined from 24% to 14%. Multivariable GEE models identified management in an academic hospital (aOR: 1.44 [95% CI: 1.37–1.52]; p < 0.001) and decompensated cirrhosis (aOR: 1.08 [95% CI: 1.04–1.13]; p < 0.001) as independent predictors of optimal adherence. Among

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patients in care in 2023 (n = 9,133), management in an academic hospital remained associated with a higher likelihood of optimal adherence (aOR: 1.40 [95% CI: 1.23–1.58]; p < 0.001), while lower socioeconomic status was associated with a reduced likelihood of optimal surveillance (aOR: 0.90 [95% CI: 0.82–1.00]; p = 0.04). **Conclusion:** Although HCC surveillance adherence appears to be improving over time, biannual imaging rates remain suboptimal. As we observed disparities across hospitals and socioeconomic statuses, our findings call for initiatives to ensure the equitable delivery of this life-saving preventative care.
Disclosures: Mohamed Moussa: Roche Diagnostics: Grant/Research Support, Dave Sprengers: Nothing to Disclose, Willem Pieter Brouwer: Nothing to Disclose, Raoel Maan: Nothing to Disclose, Harry Janssen: Gilead Sciences: Grant/Research Support, GlaxoSmithKline: Grant/Research Support, Janssen: Grant/Research Support, Roche: Grant/Research Support, Vir Biotechnology Inc.: Grant/Research Support, Aligos: Consultant, Gilead Sciences: Consultant, GlaxoSmithKline: Consultant, Grifols: Consultant, Roche: Consultant, Vir Biotechnology Inc: Consultant, Precision Biosciences: Consultant, Academic Medical Education: Consultant, H.C. Wainwright & Co: Consultant, AbbVie: Consultant, AbbVie: Grant/Research Support, Aligos: Grant/Research Support, Fujirebio: Grant/Research Support, AstraZeneca: Consultant, Brii: Consultant, nChroma: Consultant, Integer-Bio: Consultant, Arbutus: Consultant, Viroclinics: Consultant, Janssen: Consultant, Clear-B: Consultant, Adriaan Van der Meer: Nothing to Disclose, Milan Sonneveld: Nothing to Disclose.

2189 | MACHINE LEARNING IDENTIFIES SURVEILLANCE ENTRY AS THE OPTIMAL WINDOW FOR HEPATOCELLULAR CARCINOMA SURVEILLANCE INTERVENTION IN A SAFETY-NET POPULATION

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Background: Hepatocellular carcinoma (HCC) surveillance adherence is suboptimal in safety-net populations, yet clinicians lack pragmatic tools to identify patients at high risk for surveillance dropout early enough to target intervention. We aimed to develop a model using clinical characteristics to predict surveillance non-adherence and assessed how long these baseline risk factors retain utility relative to dynamic factors on follow-up. **Methods:** We used data from 1,004 adults (mean age 60 years; 56% male) undergoing ultrasound-based HCC surveillance at an urban safety-net health system between June 2020 and December 2024 (median follow-up 50 months; up to 6 visits). HCC surveillance adherence was categorized as full, partial, or non-adherent based on AASLD guidelines. Twenty-three prespecified baseline demographic, clinical, behavioral, and access-related variables were used to fit logistic regression (LR) and two tree-based models (random forest and XGBoost) to predict non-adherence. We then applied the baseline model to visits 2–6 to evaluate the persistence of the predictive utility of risk factors identified at baseline over time. Separately, we developed a visit-level model that included the following dynamic variables on follow-up: US findings (US LI-RADS categories and visualization scores), time since the prior ultrasound, and surveillance adherence at the prior visit to predict full adherence at the next visit. **Results:** At baseline, the LR model matched or outperformed tree-based models in predicting adherence, suggesting a predominantly linear relationship between risk factors associated with non-adherence. The model predicted future non-adherence with an AUC of 0.76 and conversely, full adherence with an AUC of 0.75. The strongest baseline predictors included older age, BMI, prior ultrasound completion, hepatology clinic attendance, and current smoking or alcohol use. Performance was highest at baseline and remained modest through visit 4 (AUC 0.59–0.70), with attenuation at later visits as the non-adherent subgroup declined from 331 patients at visit 1 to 11 at visit 6, leaving an increasingly homogeneous adherent cohort. In the visit-level model, time since prior ultrasound was the strongest predictor of next-visit adherence and outperformed baseline characteristics. **Conclusion:** A pragmatic risk score predicts HCC surveillance non-adherence, with peak performance at baseline, supporting surveillance entry as the optimal time for targeted equity-focused adherence interventions in the safety-net population. The length of time between surveillance visits, on the other hand, provides a simple real-time signal for outreach to enhance adherence once surveillance is underway.
Disclosures: Leila Taj: Nothing to Disclose, Kang Wang: Nothing to Disclose, Violet Wolfe: Nothing to Disclose, Hailey Choi: Nothing to Disclose, Mandana Khalili: gilead sciences: Grant/Research Support, GSK pharmaceuticals: Consultant, Intercept pharmaceuticals: Grant/Research Support, Gilead Sciences Inc: Consultant, Resolution Therapeutics: Consultant.

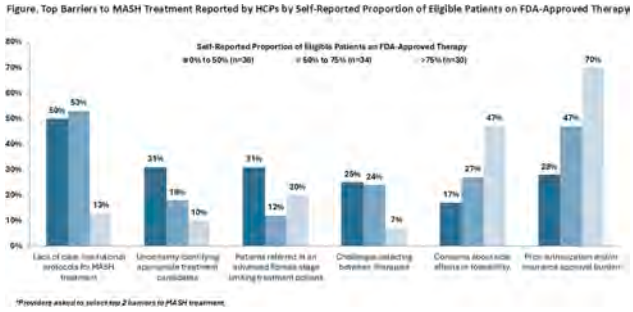
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2190 | CLINICAL PRACTICE PATTERNS IN THE ASSESSMENT AND TREATMENT OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH)

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Background: Management of metabolic dysfunction-associated steatohepatitis (MASH) is rapidly evolving with increasing validation of noninvasive liver disease assessments (NILDAs) and recent FDA-approval of two treatment options for patients with stage F2–F3 fibrosis; however, real-world practice patterns remain unclear. We sought to evaluate current practices for MASH assessment and treatment and identify opportunities to improve care. **Methods:** A nationwide survey was disseminated in March 2025 via email to hepatology and gastroenterology providers as part of an educational initiative. Survey items assessed approaches to fibrosis staging, use of NILDAs, treatment practices, and barriers to care. **Results:** A total of 100 healthcare professionals completed the survey, including gastroenterologists (80%), hepatologists (5%), advanced practice providers (10%) and other providers (5%) practicing across private (57%), academic (18%), hospital outpatient (16%), and specialty (7%) settings. Most providers reported using NILDAs for fibrosis assessment, including the FIB-4 index (76%), vibration-controlled transient elastography (VCTE; 83%), Enhanced Liver Fibrosis (ELF) test (49%), and magnetic resonance elastography (MRE) (20%), while 21% reported use of liver biopsy. Although 82% reported liver biopsy is not routinely required prior to treatment, 55% cited uncertainty regarding NILDA selection and sequencing as a key challenge. Treatment of patients with F2–F3 MASH varied substantially; 36% reported fewer than half of eligible patients were receiving FDA-approved therapy (resmetirom and/or semaglutide). Among lower adopters, top barriers were lack of institutional protocols (50%), uncertainty identifying treatment candidates (31%), and referral of patients at advanced fibrosis stages (31%), whereas higher adopters more frequently cited prior authorization burden (70%) and safety/tolerability concerns (47%) (Figure). **Conclusion:** Although noninvasive tests are widely replacing biopsy for fibrosis assessment and treatment decision-making, uncertainty persists in their application. Use of FDA-approved therapies for eligible patients varies substantially, with lower adopters more frequently citing foundational knowledge gaps and lack of protocols as key barriers. These findings suggest a need for targeted education and practical tools to support consistent, evidence-based integration of noninvasive assessment strategies and new therapies into clinical practice.



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2191 | SCIENTIFIC INEQUALITIES AND EMERGING HEPATOLOGY RESEARCH ECOSYSTEMS IN LATIN AMERICA

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Background: Scientific production reflects research capacity, innovation, and healthcare priorities within hepatology systems. However, contemporary analyses evaluating scientific asymmetries and thematic transition across Latin American hepatology are limited. **Methods:** We performed a scientometric analysis of 191 abstracts submitted to ALEH 2025. Abstracts were categorized according to thematic area, methodological design, country of origin, and multinational collaboration. Scientific productivity was normalized per million inhabitants, and countries were grouped into exploratory research ecosystem clusters according to production volume and thematic diversification. **Results:** MASLD was the leading research topic (21.5%), followed by cirrhosis/portal hypertension (18.3%), HCC (14.1%), and viral hepatitis (13.1%), reflecting the evolving regional liver disease burden. Scientific production was highly concentrated, with Mexico (n = 44), Brazil (n = 41), and Colombia (n = 23) accounting for most submissions. However, normalization by population revealed disproportionately high productivity in Uruguay (1.71 abstracts/million inhabitants), Costa Rica (1.13), and Chile (0.85). Observational studies represented 76.4% of submissions, whereas clinical trials (1.6%) and AI/big-data studies (3.1%) were uncommon, suggesting limited interventional and technological research capacity. Only 19 abstracts involved multinational collaborations. **Conclusion:** Latin American hepatology demonstrates increasing thematic diversification but persistent scientific concentration, low interventional research density, and limited technological innovation. Scientometric ecosystem analysis may help identify strategic opportunities for regional collaboration, research prioritization, and capacity development in emerging hepatology systems.

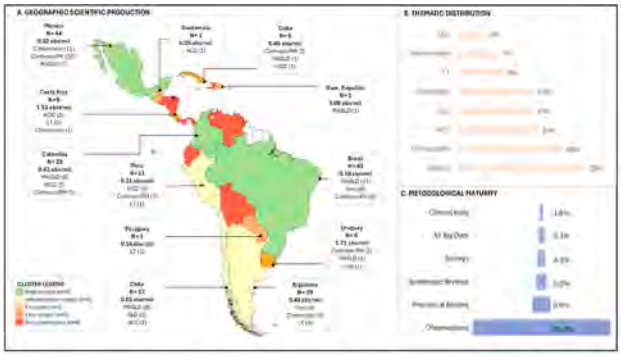


Figure 1. Geographic scientific production, thematic specialization patterns, and methodological composition of hepatology research across Latin America based on ALEH 2025 abstract submissions. Countries were categorized into exploratory research ecosystem clusters according to abstract volume and thematic diversification. Boxes summarize total scientific production, abstracts normalized per million inhabitants (abs/million), and dominant thematic areas. Panel B displays the overall thematic distribution of submitted abstracts, whereas Panel C illustrates methodological composition and research maturity across the region.

Disclosures: Francisco Vargas-Navarro: Nothing to Disclose, Wagner Ramirez: Nothing to Disclose, María Fernanda Lynch Mejía: Nothing to Disclose, Marco Arrese: Nothing to Disclose, Nothing to Disclose, Ezequiel Ridruejo: Nothing to Disclose, Daniel Pérez-Muñoz: Nothing to Disclose, Fiorella Ajún-Ulate: Nothing to Disclose, Andrés Solera-Vega: Nothing to Disclose, Pablo Coste: Nothing to Disclose.

2192 | GENERAL POPULATION CIRRHOSIS SCREENING - LONGITUDINAL FERRITIN DATA COMBINED WITH A CUMULATIVE LIVER DAMAGE INDEX ENHANCES POPULATION-LEVEL DETECTION OF CIRRHOSIS: SECONDARY ANALYSIS OF THE LIVEWELL TRIAL.

Katie Denver[1] Christina Owen[2] Neil Stevens[1] Axelle Caudrillier[3] Yasmin Hamadache[3] Heath O'Brien[3] Louise Campbell[4] Patrick Short[3] Jamie Webb[3] Katie Barnes[3], [1]Predictive Health Intelligence, [2]Somerset NHS Foundation Trust, [3]Sano Genetics, [4]Tawazun Health

Background: We have previously demonstrated that the Cumulative Liver Damage Index (CLDI), integrating longitudinal routine alanine aminotransferase (ALT) data from patient records, identifies clinically significant fibrosis (F2+) with receiver operator characteristic area under the curve (ROC-AUC) 0.884, outperforming published FIB-4 population benchmarks (LiveWell study; presented EASL 2026). CLDI independently predicted cirrhosis (F4; OR 5.02, $p < 0.01$). Ferritin, a marker of hepatic inflammation and metabolic dysfunction, may provide a discriminatory signal for advanced fibrosis. We hypothesised that mean longitudinal ferritin would enhance F4 prediction using routinely available blood test results. **Methods:** Secondary analysis of LiveWell study data (994 participants, aged 25-55, Somerset, United Kingdom). The cohort with complete transient elastography (TE) data (N = 627) included 51 F2+ cases (TE ≥ 8kPa) and 18 F4 cases (TE ≥ 12kPa). Logistic regression models (age, sex, BMI, log-CLDI, mean platelets) were evaluated with and without mean ferritin (60-month window) for both F2+ and F4 outcomes. Blood-test-only models (substituting BMI with platelet minimum and HbA1c mean) were assessed. The impact of mean red blood cell volume (MCV) was analysed as a potential marker of alcohol use. Performance was quantified by 5-fold cross-validated AUC (CV-AUC) and DeLong comparison. F4 analyses are exploratory given low event rate. **Results:** The F2+ base model achieved CV-AUC 0.879. Adding ferritin produced no significant improvement on DeLong comparison ($p = 0.37$), confirming no additional benefit of using ferritin for moderate fibrosis. For F4, the base model achieved apparent ROC-AUC

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0.904. Ferritin was independently associated with cirrhosis (p = 0.008) and improved apparent ROC-AUC from 0.904 to 0.924; DeLong comparison did not reach significance (p = 0.25), consistent with insufficient power at 18 events. Blood-test-only models demonstrated consistent directionality (apparent ROC-AUC 0.870; +ferritin 0.891; DeLong p = 0.052). The ferritin association was specific to F4 across all model variants. MCV had no effect on the performance of any of these models **Conclusion:** Longitudinal ferritin adds a consistent signal for cirrhosis detection, but no significant improvement on DeLong comparison for F2+ fibrosis (p = 0.37), supporting a potentially distinct role in advanced liver disease. The lack of signal for MCV would suggest this is mediated via metabolic hyperferritinaemia rather than alcohol. These preliminary findings require validation in a larger cohort. Routine identification of previously undiagnosed cirrhosis would define patients requiring enrolment in hepatocellular carcinoma (HCC) surveillance programmes and recruitment to emerging cirrhosis-specific therapeutic trials, representing a high-value application of population-level longitudinal data.

Disclosures: Katie Denver: Nothing to Disclose, Christina Owen: Nothing to Disclose, Neil Stevens: Nothing to Disclose, Axelle Caudrillier: Nothing to Disclose, Yasmin Hamadache: Nothing to Disclose, Heath O'Brien: Nothing to Disclose, Louise Campbell: Nothing to Disclose, Patrick Short: Nothing to Disclose, Jamie Webb: Nothing to Disclose, Katie Barnes: Nothing to Disclose.

2193 | CLINICALLY SIGNIFICANT LIVER STIFFNESS AND ROUTINE DETECTION GAPS IN YOUNG ADULTS IN THE U.S.

Ariana Bockstahler[1] Megan Roach[1] Jeffrey Schwimmer[1], [1]University of California, San Diego

Background: Liver disease presenting clinically in young adulthood is increasing, yet fibrosis risk assessment is oriented toward selected high-risk groups which may not adequately capture young adults. Vibration-controlled transient elastography (VCTE) can identify clinically concerning liver stiffness before overt clinical recognition. We estimated the national prevalence of elevated liver stiffness and clinically significant liver stiffness among young adults in the U.S. and assessed how often these findings occurred in the absence of potential clinical triggers for further fibrosis evaluation. **Methods:** We analyzed adults aged 18–34 years in the 2017–March 2020 National Health and Nutrition Examination Survey with valid VCTE. Liver stiffness measurement (LSM) was categorized as <8, ≥ 8, and ≥ 12 kPa. LSM ≥ 8 kPa was defined as elevated liver stiffness in a fibrosis range. LSM ≥ 12 kPa was defined as clinically significant liver stiffness. We assessed whether elevated liver stiffness occurred in young adults without potential clinical triggers for further fibrosis evaluation. The potential clinical triggers were defined as ALT > laboratory reference range, clinical or laboratory evidence of diabetes, class 2 or 3 obesity (BMI $\geq$ 35 kg/m²), and elevated FIB-4 (≥ 1.3). Survey-weighted prevalence estimates, 95% confidence intervals, and U.S. population counts were calculated using NHANES examination weights and design variables. **Results:** The analytic sample included 2,175 young adults, representing 68.4 million young adults in the U.S. aged 18–34 years. LSM ≥ 8 kPa was present in 6.1% (95% CI, 4.7%–8.0%), corresponding to 4.19 million young adults. LSM ≥ 12 kPa was present in 1.8% (95% CI, 1.1%–3.0%), corresponding to 1.25 million young adults. Among young adults with LSM ≥ 8 kPa, 64.6% had ALT within the laboratory reference range, 97.7% had no clinical or laboratory evidence of diabetes, 43.1% had BMI <35 kg/m², and 99.2% had FIB-4 <1.3. Among those with LSM ≥ 12 kPa, 62.5% had ALT within the laboratory reference range, 99.0% had no clinical or laboratory evidence of diabetes, 26.1% had BMI <35 kg/m², and 99.0% had FIB-4 <1.3. **Conclusion:** In a nationally representative sample, approximately 4.2 million young adults in the U.S. had elevated liver stiffness and 1.25 million had clinically significant liver stiffness. Most young adults with clinically significant liver stiffness had ALT within the laboratory reference range, no clinical or laboratory evidence of diabetes, and FIB-4 <1.3. These findings identify a young-adult detection gap in liver fibrosis risk assessment and support development of age-appropriate strategies to recognize clinically important liver stiffness earlier in adulthood.

Disclosures: Ariana Bockstahler: Nothing to Disclose, Megan Roach: Nothing to Disclose, Jeffrey Schwimmer: Nothing to Disclose.

2194 | MASLD SCREENING KNOWLEDGE ASSESSMENT: A QUALITY IMPROVEMENT SURVEY AT A RESIDENT PRIMARY CARE CLINIC

Kimberly Ho[1] Alex Chang[1] Rebekah Gardner[1] Paige McLean Diaz[2], [1]Brown University, [2]Brown Medicine/ Brown University Health

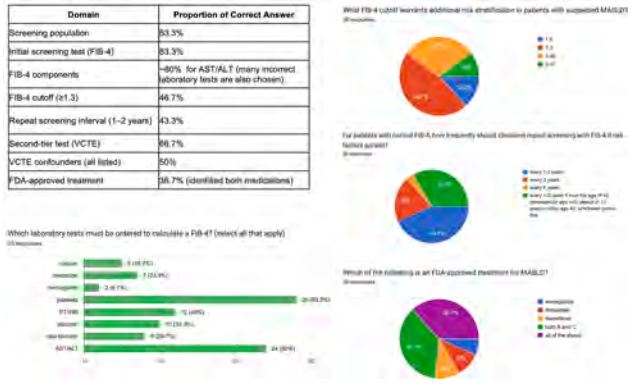
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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) remains largely underdiagnosed in the routine clinical care of patients outside hepatology clinics. The 2025 American Diabetes Association (ADA) consensus recommends systematic fibrosis screening in high-risk patients using the Fibrosis-4 (FIB-4) index in primary care settings. We assessed baseline knowledge of MASLD screening and management among clinicians at our resident primary care clinic as part of a QI initiative to improve FIB-4 screening rates. **Methods:** We administered an 8-question survey to residents and attendings who practice at an internal medicine residency-affiliated primary care clinic. Questions assessed knowledge in three domains: (1) target population and screening interval, (2) FIB-4 interpretation and ordering, and (3) management of abnormal results. We identified questions in which more than half of responses were incorrect as representing a significant knowledge gap. Respondent demographics and self-reported guideline familiarity were also collected. **Results:** Among the 30 respondents, half were attendings (53.3%) and the remainder were PGY-3 residents (6.7%), PGY-2 residents (30.0%), and PGY-1 residents (10.0%). 90% of respondents had not yet read the ADA guidelines on MASLD screening, and 83.3% reported being "not at all" or only "slightly" familiar with them. Correct response rates varied substantially across domains, with an average score of 4.33/8 points. 83.3% correctly identified FIB-4 as the initial screening test, and 66.7% identified transient elastography (VCTE) as the appropriate second-tier test for MASLD. While 80% recognized AST/ALT as required FIB-4 components, 40% also incorrectly included PT/INR. Fewer than half of respondents selected the guideline-recommended FIB-4 cutoff of $\geq$1.3 for further risk stratification (46.7%) and the recommended 1-2 year rescreening interval (43.3%). Only a third (36.7%) correctly identified both FDA-approved treatments for MASH. **Conclusion:** This baseline survey revealed knowledge gaps in MASLD screening and management among primary care clinicians, particularly regarding FIB-4 components, the $\geq$1.3 cutoff threshold, and current FDA-approved pharmacotherapy. These findings, in the context of very low self-reported guideline familiarity, identify high-yield targets for educational intervention as part of our QI initiative to implement systematic FIB-4 screening in clinic. Planned interventions for this QI project include clinician education sessions, increase uptake of FIB-4 calculation into the electronic health record, and development of a clinical decision support algorithm based on the two-tier FIB-4/VCTE screening pathway.

Figure 1. Survey results and frequently missed questions.

Domain	Proportion of Correct Answer
Screening population	53.3%
Initial screening test (FIB-4)	83.3%
FIB-4 components	~80% for AST/ALT (many incorrect laboratory tests are also chosen)
FIB-4 cutoff (≥1.3)	46.7%
Repeat screening interval (1–2 years)	43.3%
Second-tier test (VCTE)	66.7%
VCTE confounders (all listed)	50%
FDA-approved treatment	36.7% (identified both medications)



Disclosures: Kimberly Ho: Nothing to Disclose, Alex Chang: Nothing to Disclose, Rebekah Gardner: Nothing to Disclose, Paige McLean Diaz: Nothing to Disclose.

2195 | DISCHARGE DISPOSITION IS INDEPENDENTLY ASSOCIATED WITH 90-DAY READMISSION FOLLOWING CIRRHOSIS HOSPITALIZATION

Yiwei Hang[1] Jonathan Heintz[2] Nadim Mahmud[1], [1]Hospital of the University of Pennsylvania, [2]University of Pennsylvania

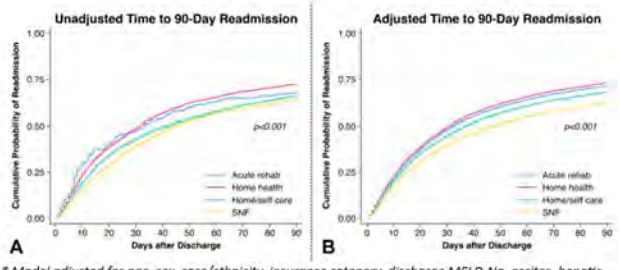
Background: Cirrhosis is associated with high rates of hospitalization, readmission, and mortality, making transitions of care a critical target to improve outcomes and to reduce healthcare utilization. Discharge disposition, defined as the level and location of care after hospitalization, may influence post-discharge outcomes in patients with cirrhosis. We aimed to evaluate the association between discharge disposition after an index hospitalization for cirrhosis and subsequent hospital readmission. **Methods:** We conducted a retrospective cohort study of patients with a first cirrhosis-related hospitalization within the University of Pennsylvania Health System from 1/1/2016 to 1/1/2026, excluding those who did not survive to discharge. Eligible patients were identified through The Center for Data, Outcomes, & Team Science (CDOTS) registry. Demographics, cirrhosis decompensations, comorbidities, insurance status, and hospitalization data were obtained. The primary exposure was discharge disposition, classified as skilled nursing facility (SNF), home health (HH), home/self-care, and acute rehabilitation. The primary outcome was time to hospital readmission within 90 days, using Kaplan-Meier and multivariable Cox proportional hazards models for unadjusted and adjusted analyses, respectively, with censoring at death or end of follow-up. **Results:** A total of 6,331 first hospitalizations for

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cirrhosis were included. The most common discharge disposition was home/self-care (44.7%), followed by HH (35.7%), SNF (16.9%), and acute rehabilitation (2.8%). Patients discharged to SNF were older (median age 67.3) and more likely to have Medicare (65.7%), whereas those discharged to home were more likely to have Medicaid (22.6%) or commercial insurance (39.2%). Comorbid conditions such as ascites, hepatic encephalopathy, diabetes, congestive heart failure, chronic kidney disease, and chronic obstructive pulmonary disease differed significantly across discharge disposition groups. Time to hospital readmission differed by discharge disposition in Kaplan-Meier analysis (log-rank $p < 0.001$; **Figure 1A**). In adjusted Cox regression analyses, discharge with HH was associated with increased hazard of 90-day readmission compared with home/self-care (HR 1.15, $p < 0.001$), whereas discharge to SNF was associated with lower risk (HR 0.85, $p = 0.003$; **Figure 1B**). **Conclusion:** Among patients surviving a first cirrhosis-related hospitalization, discharge disposition was independently associated with 90-day readmission risk. The lower observed readmission risk among patients discharged to SNF, despite greater baseline clinical vulnerability, highlights the complexity of using readmission as a post-discharge quality metric in this population. These findings support further evaluation of how discharge setting, patient severity, and post-discharge care structure interact to shape outcomes in cirrhosis.

Figure 1: Time to Post-Discharge Readmission in (A) Unadjusted Kaplan-Meier and (B) Adjusted Cox Regression Models*



* Model adjusted for age, sex, race/ethnicity, insurance category, discharge MELD-Na, ascites, hepatic encephalopathy, diabetes mellitus, heart failure, CKD, COPD, mechanical ventilation, and length of stay

Disclosures: Yiwei Hang: Nothing to Disclose, Jonathan Heintz: Nothing to Disclose, Nadim Mahmud: Nothing to Disclose.

2196 | HOW LIVER CIRRHOSIS AFFECTS CLINICAL OUTCOMES OF ACUTE PANCREATITIS: A NATIONWIDE ANALYSIS

Ahmed Ali Aziz[1] Sara Rahman[2] Muhammad Ali Aziz[3] Taseen Ahmed Syed[1] Rehan Shah[4] Muhammad Amir[1] Ijlal Akbar Ali[5], [1]INTEGRIS Health Baptist Medical Center, Oklahoma City, Oklahoma, [2]Services Institute of Medical Sciences, Lahore, Pakistan, [3]University of Kentucky School of Medicine, Lexington, Kentucky, [4]Bayonne Medical Center, Bayonne, New Jersey, [5]University of Pennsylvania, Philadelphia, Pennsylvania

Background: Acute pancreatitis (AP) is a leading cause of gastrointestinal-related hospitalizations in the United States and is associated with significant morbidity, mortality, and healthcare expenditures. Patients with liver cirrhosis (LC) exhibit immune dysregulation, portal hypertension, altered hemostasis, and reduced physiologic reserve, which may adversely affect outcomes during acute inflammatory illnesses. We aimed to evaluate the impact of concomitant liver cirrhosis on hospitalization outcomes among patients admitted with acute pancreatitis.
Methods: We conducted a retrospective cohort study using the Nationwide Inpatient Sample (NIS) database from 2020–2022. Adult hospitalizations with a primary discharge diagnosis of acute pancreatitis were identified using ICD-10-CM codes. Patients were stratified by the presence or absence of a secondary diagnosis of liver cirrhosis. The study included 14,179 hospitalizations with cirrhosis and 723,959 without cirrhosis. Multivariable regression analyses adjusted for demographics, hospital characteristics, and relevant comorbidities. Outcomes included in-hospital mortality, shock, acute renal failure (ARF), venous thromboembolism (VTE), intensive care unit (ICU) admission, length of stay (LOS), and total hospitalization costs adjusted to 2022 U.S. dollars.
Results: Patients with cirrhosis experienced significantly worse outcomes compared with those without cirrhosis. Liver cirrhosis was independently associated with increased odds of in-hospital mortality (aOR 1.72, 95% CI 1.22–2.42, $p = 0.002$), shock (aOR 1.87, 95% CI 1.42–2.46, $p < 0.001$), ARF (aOR 1.44, 95% CI 1.30–1.49, $p < 0.001$), ICU admission (aOR 1.62, 95% CI 1.38–1.91, $p < 0.001$), and VTE (aOR 1.65, 95% CI 1.29–2.11, $p < 0.001$). Cirrhosis was also associated with longer LOS (β +0.46 days, 95% CI 0.25–0.66, $p < 0.001$) and higher hospitalization costs (β +$4,163.48, 95% CI $1,530.94–$6,796.02, $p = 0.002$). **Conclusion:** Among patients hospitalized with acute pancreatitis, concomitant liver cirrhosis is associated with significantly higher mortality, greater risk of shock, renal failure, VTE, and ICU utilization, as well as prolonged hospitalization and increased healthcare costs. These findings suggest that cirrhosis is an important prognostic marker in acute pancreatitis and may identify a high-risk population that could benefit from closer monitoring, early recognition of complications, and more intensive multidisciplinary management.

Disclosures: AHMED ALI AZIZ: Nothing to Disclose, Sara Rahman: Nothing to Disclose, Muhammad Ali Aziz: Nothing to Disclose, Taseen Ahmed Syed: Nothing to Disclose, Rehan Shah: Nothing to Disclose,

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Muhammad Amir: Nothing to Disclose, Ijlal Akbar Ali: Nothing to Disclose.

2197 | LEVERAGING A SYSTEM-LEVEL PROVIDER-FACING FIBROSIS SCREENING DASHBOARD: SIGNALING THE NEED FOR A MASH QUALITY MEASURE

Anna Mageras[1] Arshad Rahim[2] Alexandra Ingber[2] Kristie Heiden[2] Christopher Pae[2] David Lam[1] Xiaotao Zhang[3] Francis Lobo[4] Suneil Hosmane[4] Grace Kiernan[5] Meena Bansal[6], [1]Icahn School of Medicine at Mount Sinai, New York, NY, USA, [2]Mount Sinai Health System, New York, NY, USA, [3]Icahn School of Medicine at Mount Sinai, [4]Madrigal Pharmaceuticals, Conshohocken, PA, USA, [5]MASHNET (Liver Health Leaders Network), New York, NY, USA, [6]Icahn School of Medicine at Mount Sinai (ISMMS)

Background: With the underdiagnosis of MASH with significant fibrosis, there is a growing need for tools that will support health system–level screening. To this end, we developed a primary care (PC) and endocrinology (endo)–facing fibrosis dashboard in the electronic health record (EHR) for patients living with diabetes (PWD) as a demonstration project for health systems to automate reporting and streamline adherence to a MASH Care Pathway (CP). **Methods:** Stakeholders including internal Epic IT team, population health leaders, and front-line providers were convened to build a provider-facing dashboard using a screening algorithm. For adult patients in the Mount Sinai Diabetes Registry, the algorithm calculates a FIB-4 score for each patient based on their most recent lab results. Patients are sorted into a) Intermediate Risk (age 18-64: FIB-4 1.3-2.67, 65-84: FIB-4 2.0-2.67), and b) High Risk (FIB-4 > 2.67). Quarterly metrics with a 36-month lookback include the number and percentage of patients who have a FIB-4 score, and who have received referrals and completed secondary testing based on FIB-4 values. Patients age 85+ and those in care with hospice or palliative care were excluded. The dashboard enables specialty, clinic, and provider-level reporting, as well as lists of patients who still need labs or referrals. The dashboard also has built-in bulk orders for FIB-4 labs, bulk referrals for secondary testing, and bulk personalized patient messaging in the patient-facing portal. Baseline metrics and cohort characteristics were extracted for primary care and endocrinology and compared using Chi-square tests in SAS. **Results:** The baseline population included 57,196 PWD across endo and PC who were eligible for fibrosis screening. Demographics, FIB-4 scores, and HbA1c levels were similar across clinic types. Among 10,223 PWD seen by both PC and endo, 92% had a calculatable FIB-4, versus 63% of 13,965 seen in endo only, versus 91% of 33,008 seen in PC only. Platelets in endocrinology were the most frequently missing lab (35%). Of those with intermediate or high FIB-4 scores, 15% of those seen in PC and endo had received a referral, versus 11% in endo, versus 10% in PC ($p < 0.001$). Ten percent seen in both had completed their referral, versus 8% in endo, and 7% in PC ($p < 0.001$). (Table 1). **Conclusion:** A system-level provider-facing dashboard that automates FIB-4 fibrosis screening provides a robust, cross-sectional, and longitudinal reporting tool. At baseline, patients seen by both PC and endo had the highest rates of FIB-4 labs, while endo-only patients had the lowest. FIB-4-score distribution was similar across populations, and most patients did not see both types of providers, reinforcing the need to screen in both endo and PC. Referral and completion rates were low but similar across departments. These findings indicate the ability to build and quantify a quality measure using automated FIB-4 scoring to screen for fibrosis due to MASH in PWD.

Table 1: MASH Care Pathway Outcomes and Patient Characteristics by Clinic Type, Reported in the Fibrosis Dashboard

	Both		Endocrinology Only		Primary Care Only		Total		Chi-square p-value
	N	% of Prior Milestone	N	% of Prior Milestone	N	% of Prior Milestone	N	% of Prior Milestone	
Eligible	10,223		13,965		33,008		57,196		
Screened	9,441	92.4%	8,782	62.9%	30,159	91.4%	48,382	84.6%	<0.001
Low Risk	7,847	77.8%	6,586	75.0%	23,269	77.2%	37,202	76.9%	<0.001
Intermediate Risk	1,572	16.7%	1,668	19.0%	5,225	17.3%	8,465	17.5%	
High Risk	522	5.5%	528	6.0%	1,665	5.5%	2,715	5.6%	
Intermediate Risk Referred	223	14.2%	173	10.4%	514	9.8%	910	10.8%	<0.001
Intermediate Risk Completed	157	70.4%	126	72.8%	353	68.7%	636	69.9%	0.0001
High Risk Referred	86	16.5%	62	11.7%	189	11.4%	337	12.4%	0.007
High Risk Completed	50	58.1%	42	67.7%	115	60.8%	207	61.4%	0.127
	N	% of Eligible	N	% of Eligible	N	% of Eligible	N	% of Eligible	
Screening Labs Missing*									
AST Missing	353	3.5%	2,635	18.9%	2,077	6.3%	5,045	8.8%	<0.001
ALT Missing	268	2.6%	2,525	18.1%	1,851	5.6%	4,644	8.1%	<0.001
Platelets Missing	659	6.4%	4,825	34.6%	2,106	6.4%	7,590	13.3%	<0.001
Most Recent HbA1c									
Median (IQR	6.8	1.7	6.9	1.8	6.6	1.3	6.7	1.4	<0.001
Age									
Median (IQR	63	19	62	21	66	18	64	19	<0.001
18-35	648	6.3%	1,478	10.6%	974	3.0%	3,100	5.4%	<0.001
36-50	1,528	14.9%	2,247	16.1%	3,965	12.0%	7,740	13.5%	
51-64	3,504	32.3%	4,417	31.6%	10,495	31.8%	18,216	31.8%	
65-85	4,847	47.4%	5,930	42.5%	17,832	54.0%	28,609	50.0%	
Sex									
Female	5,869	57.4%	7,022	50.3%	16,638	50.4%	29,529	51.6%	<0.001
Male	4,457	43.6%	7,043	50.5%	16,628	50.4%	28,131	49.2%	
Race									
White	3,582	35.1%	4,949	35.4%	10,543	31.9%	18,874	33.0%	<0.001
Black	2,336	22.9%	2,520	18.0%	6,941	21.0%	11,797	20.6%	
Asian	1,024	10.0%	1,307	9.4%	2,987	9.0%	5,318	9.3%	
Other/Unknown	3,585	35.1%	5,296	37.9%	12,795	38.8%	21,676	37.9%	
Ethnicity									
Hispanic/Latino	2,757	27.0%	3,046	21.8%	7,505	22.7%	13,308	23.3%	<0.001
Non-Hispanic	5,934	58.5%	7,586	54.4%	18,017	54.6%	31,537	55.2%	
Unknown	1,586	15.5%	3,430	24.6%	7,744	23.5%	12,760	22.3%	
Preferred Language									
English	9,210	90.1%	12,593	90.2%	29,372	89.0%	51,175	89.5%	<0.001
Spanish	893	8.7%	1,091	7.8%	3,034	9.2%	5,018	8.8%	
Other	224	2.2%	387	2.8%	849	2.6%	1,460	2.6%	
Online Patient Portal Status									
Activated	9,583	93.7%	11,842	84.8%	27,806	84.2%	49,231	86.1%	<0.001
GLP-1 or SGLT-2 Prescription									
Yes	2,782	27.2%	2,767	19.8%	5,661	17.2%	11,210	19.6%	<0.001

*Missing values excluded from percentage calculations and chi-square tests. Low risk = 1.3 for ages 18-64, <2.0 for ages 85+, Intermediate risk 1.3-2.67 for ages 18-64, 2.0-2.67 for ages 85+, High risk > 2.67. IQR = interquartile range, HbA1c = hemoglobin A1c, SGLT-2 = sodium/glucose cotransporter-2 inhibitor, GLP-1 = glucagon-like peptide-1 receptor agonist.

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Hosmane: Nothing to Disclose, Grace Kiernan: Nothing to Disclose, Meena Bansal: Madrigal: Advisor, Fibronostics: Advisor, NOVO Nordisk: Advisor, GSK: Advisor, Merck: Advisor, Boeheringer-Ingelheim: Advisor, Boston Pharma: Advisor, The Kinetix Group: Advisor, Corcept: Advisor.

2198 | CAREGIVER PERSPECTIVES ON END-OF-LIFE CARE FOR VETERANS WITH CIRRHOSIS: A QUALITATIVE ANALYSIS OF THE VA BEREAVED FAMILY SURVEY

Kanika Malani[1] Tulio Correa[2] Olivia Belliveau[3] Ramsey Cheung[4] Neha Jakhete[5] Sofia Jakab[6] Catherine Mezzacappa[3] Anna Nobbe[7] Jacqueline O'Leary[8] Shari Rogal[2] Anne Walling[9] Karleen Giannitrapani[10] Tamar Taddei[6] Arpan Patel[9], [1]Yale New Haven Hospital, [2]University of Pittsburgh, [3]Yale School of Medicine, [4]Stanford University Medical Center, [5]University of Maryland, [6]VA Connecticut Healthcare System, [7]VA Cincinnati Healthcare System, [8]VA North Texas Healthcare System, [9]VA Greater Los Angeles Healthcare System, [10]VA Palo Alto Healthcare System

Background: The end of life (EOL) experience for adults with cirrhosis includes repeated hospitalizations and a high frequency of life-sustaining treatments. While caregivers face significant burden throughout the illness trajectory, their specific experiences in navigating EOL care have not been reported. Our aim is to identify major themes of their experience through qualitative analysis of the Veterans Affairs Bereaved Family Survey (VA BFS). **Methods:** The VA BFS is a validated, national post-death survey used to assess the quality of EOL care delivered to Veterans who die in VA settings. In addition to standardized quantitative measures, the BFS includes 2 open-ended items ("Is there anything else that you would like to share about the Veteran's care during his/her last month of life?; Is there anything else that you would like to share about how the care could have been improved for the Veteran?") that provide insight into caregiver experiences, unmet needs, perceived strengths, and gaps in EOL care delivery. We randomly selected 100 Veterans with cirrhosis out of 1,330 whose caregivers completed the BFS from 2023-2025. Open coding of free-text responses was conducted by 9 hepatology clinicians (physicians, advance practice practitioners, residents). All responses were compiled, summarized, and analyzed by 3 coders (2 residents, 1 hepatologist), who applied a hybrid inductive/deductive approach to identify domains and themes, which were modified iteratively until content was non-overlapping. **Results:** Of 100 caregiver survey responses, 85 included substantive comments that yielded 22 distinct themes organized within 6 domains: Patient Needs, Family Needs-Communication, Family Needs-Administrative and Logistical, Family Needs-Emotional Support, Facility and Organizational Characteristics, and Clinical Teams and Personnel **(Table)** . The most frequent themes were: clear communication about the patient's condition and treatment options (n = 17), smoother transfer between facilities (n = 8), alerting family of the patient's final hours (n = 7), and improved care team collaboration (n = 7). In a sub-analysis of responses coded within the Family Needs-Communication domain (n = 19), the majority reflected low-quality communication experiences (n = 17), most commonly pertaining to staff not keeping family members informed of the patient's condition or planned procedures (n = 11). **Conclusion:** Clear communication emerged as the dominant theme among bereaved caregivers of decedent Veterans with cirrhosis. The majority described low-quality interactions in regard to prognosis and decision making. Teams invested in caring for this population should consider strategies to meet such informational needs proactively in order to improve the EOL experience for caregivers.

Table. Domains, Themes, and Representative Quotes for Major End of Life Experiences for Caregivers of Veterans with Cirrhosis



Disclosures: Kanika Malani: Nothing to Disclose, Tulio Correa: Nothing to Disclose, Olivia Belliveau: Nothing to Disclose, Ramsey Cheung: Nothing to Disclose, Neha Jakhete: Gilead: Advisor, Ipsen: Advisor, Sofia Jakab: Nothing to Disclose, Catherine Mezzacappa: Nothing to Disclose, Anna Nobbe: Nothing to Disclose, Jacqueline O'Leary: Genfit: Consultant, CVS: Stock - publicly traded company, Mallinckrodt: Advisor, PharmaIn: Advisor, PharmaIn: Consultant, Genfit: Consultant, PharmaIn: Consultant, Genfit: Consultant, Shari Rogal: Nothing to Disclose, Nothing to Disclose, Anne Walling: Nothing to Disclose, Karleen Giannitrapani: Nothing to Disclose, Tamar Taddei: Nothing to Disclose, Arpan Patel: Nothing to Disclose, Nothing to Disclose.

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2199 | EVALUATING ASCITES CARE IN HOSPITALIZED PATIENTS WITH DECOMPENSATED CIRRHOSIS IN ONTARIO, CANADA: INSIGHTS AND LIMITATIONS OF HEALTH RECORD DATA

Shadia Adekunte[1] Matthew Wankiewicz[2] Surain Roberts[2] Lauren Lapointe-Shaw[3] Siddhartha Srivastava[1] Sahar Saeed[1] Michelle Ricci[1] Florence Wong[4] Gideon Hirschfield[4] Fahad Razak[4] Amol Verma[4] Jennifer Flemming[1] Kristel Leung[1], [1]Queen's University, Kingston, Ontario, Canada, [2]Li Ka Shing Knowledge Institute, Unity Health, Toronto, Ontario, Canada, [3]Institute of Health Policy, Management and Evaluation, Toronto, Ontario, Canada, [4]University of Toronto, Toronto, Ontario, Canada

Background: There is growing interest in evaluating care quality across hospitals using structured data. We aimed to evaluate whether adherence to ascites-related evidence-based quality indicators and outcomes could be assessed using health record data in Ontario. **Methods:** Using electronic health record (EHR) and administrative data from >60% of medicine/ICU admissions in Ontario (April 2016-June 2023), decompensated cirrhosis admissions were identified using validated algorithms. Decompensation events and procedures were determined using ICD-10-CA and CCI codes; diuretics (furosemide and spironolactone) and albumin transfusions were retrieved. Quality indicators assessed included paracentesis, combination diuretics use, and albumin use amongst coded ascites encounters. Outcomes explored included in-hospital mortality, ICU use, 7-day, and 30-day readmission to GEMINI hospitals. Associations were assessed with logistic regression adjusted for age and sex. **Results:** A total of 43,428 decompensated cirrhosis admissions were identified (25,426 individuals, median 63y, 59% male; MASLD 60%, ALD 33%). Admissions with coded ascites (n = 19,745, 45%) had less frequent concurrent variceal bleeding (12 vs. 22%) and HE (16 vs. 37%) codes, but more HRS (6.4 vs. 4.7%) and AKI (33 vs. 28%) than admissions without coded ascites (all $p < 0.001$). These admissions also had reduced in-hospital mortality (aOR 0.85, 95%CI 0.81-0.90) and ICU use (aOR 0.70, 95%CI 0.67-0.73), but higher readmission (7 days: aOR 1.14, 95%CI 1.06-1.23; 30 days: aOR 1.28, 95%CI 1.22-1.34). Of note, 9,705 admissions had 1+ recorded paracentesis or both diuretics prescribed, but no ascites code. Among coded ascites admissions, paracentesis (n = 12,490, 63%) was not significantly associated with in-hospital mortality but was associated with reduced ICU use (aOR 0.85, 95%CI 0.79-0.92), increased 7-day (aOR 1.14, 95%CI 1.02-1.28), and 30-day readmission (aOR 1.23, 95%CI 1.15-1.32). Albumin use with coded ascites and 1+ paracentesis (n = 4,727, 38%) was associated with in-hospital mortality (aOR 1.81, 95%CI 1.65-1.99) and ICU use (aOR 2.05, 95%CI 1.87-2.25) but not associated with 7-day or 30-day readmission. Diuretics use with coded ascites admissions had reduced in-hospital mortality (aOR 0.49, 95%CI 0.45-0.53) and ICU entry (aOR 0.82, 95%CI 0.76-0.88); however, 30-day readmission (but not 7-day readmission) was increased (aOR 1.31, 95%CI 1.22-1.40). **Conclusion:** Ascites codes were associated with less concomitant decompensation complications, which may explain lower in-hospital mortality/ICU use, higher readmission rates, and variably associated quality metrics (i.e. paracentesis, diuretics, albumin transfusion) with outcomes. Further validation of codes and objective clinical severity parameters are required prior to using such data to inform targeted quality improvement strategies and reduce practice variability across hospitals.

Disclosures: Shadia Adekunte: Nothing to Disclose, Matthew Wankiewicz: Nothing to Disclose, Surain Roberts: Nothing to Disclose, Lauren Lapointe-Shaw: Nothing to Disclose, Siddhartha Srivastava: Nothing to Disclose, Sahar Saeed: Novo Nordisk: Consultant, Michelle Ricci: Nothing to Disclose, Florence Wong: Nothing to Disclose, Gideon Hirschfield: Intercept: Consultant, GSK: Consultant, CymaBay: Consultant, Ipsen: Consultant, Falk: Consultant, Pliant: Consultant, Mirum: Consultant, Advanz: Consultant, Chemomab: Consultant, Gilead: Consultant, Kowa: Consultant, Fahad Razak: Nothing to Disclose, Amol Verma: Nothing to Disclose, Jennifer Flemming: Nothing to Disclose, Kristel Leung: Nothing to Disclose.

2200 | RISK STRATIFICATION FOR MAJOR ADVERSE LIVER OUTCOMES IN THE VETERANS HEALTH ADMINISTRATION SYSTEM USING FIB-4 VERSUS SAFE SCORES

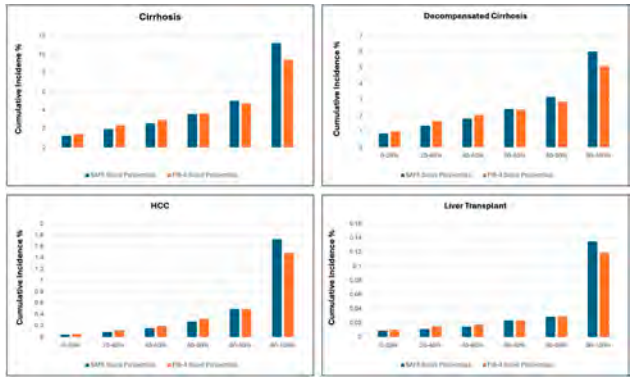
George Ioannou[1] Shari Rogal[2] Prowpanga Udompap[3] Heather Patton[4] Sumedha Chhatre[5] Patrick Spoutz[6] W. Ray Kim[7] Timothy Morgan[8], [1]University of Washington, [2]University of Pittsburgh, [3]Minneapolis VA Medical Center, [4]VA San Diego Healthcare, [5]University of Pennsylvania, [6]Boise VA Medical Center, [7]Mayo Clinic Arizona, [8]VA Long Beach Healthcare System

Background: Major adverse liver outcomes (MALOs), including cirrhosis, decompensation (DC), and hepatocellular carcinoma (HCC), are a major source of morbidity and mortality in the Veterans Health Administration (VHA) system. Scalable tools for population-

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level risk stratification are needed to enable early detection and intervention. In this work, we compared 10-year risk prediction of MALOs in a national VHA cohort using the FIB-4 index versus and the Steatosis-Associated Fibrosis Estimator (SAFE) score. **Methods:** Starting with 6.15 million VHA enrollees with at least one encounter in 2013-14, we excluded subjects with known liver disease (e.g., hepatitis C and cirrhosis at baseline), incomplete data for FIB-4 and SAFE, or deceased as of 12/31/2014. Individuals were followed for 10 years starting on 01/01/2015 for the cumulative incidence of MALOs using diagnostic codes, with death as a competing risk. We estimated associations between baseline FIB-4 or SAFE, categorized into percentiles (0-20%, 20-40%, 40-60%, 60-80%, 80-90% and 90-100%) and 10-year risks of MALOs. **Results:** A total of 3,007,621 VHA enrollees met the eligibility criteria. The mean age was 62.3 years and 92% were male. Obesity (BMI $\geq$ 30) was present in 43%, including 17% with BMI $\geq$ 35. Diabetes was present in 27.6%. In the Figure, risks of all MALOs rose progressively with increasing FIB-4 or SAFE. For FIB-4, compared to subjects in 0-20th percentile, subjects in the 90-100th percentile category had a hazard ratio for 6.85 (95% confidence interval [CI] 6.68 - 7.01) for cirrhosis, 5.19 (95% CI: 5.04 - 5.35) for DC and 30.12 (95% CI: 26.79 - 33.86) for HCC. For SAFE, the corresponding hazard ratios were larger - 9.49 (95%CI: 9.26-9.73) for cirrhosis, 7.03 (95% CI: 6.82-7.25) for DC, and 39.97 (95% CI: 35.31 - 45.24) for HCC. Compared to these relative risks, absolute risks are more informative for potential future screening implementation. For example, if the top 10% with the highest risk were to be prioritized for the VHA system screening resources, SAFE would outperform FIB-4, identifying 19% more cirrhosis (33,822 versus [vs] 28,313), 18% more DC (18,179 vs 15,363), 17% more HCC (5,252 vs 4,497) and 13% more liver transplants (407 vs 360), given the same number of subjects tested (n = 300,762). However, even with the better performing SAFE score, the top decile only identified a relative minority of those with future MALOs (32% of cirrhosis, 27% of DC, 51% HCC and 48% liver transplant correctly detected). **Conclusion:** In this large population-based study with long term follow-up, FIB-4 and SAFE scores risk stratified the 10-year risk of MALOs. The top 10% of veterans with the highest SAFE scores suffered 13-19% more liver outcome events over 10 years than the top 10% of FIB-4 scores. These risk stratification, although imperfect, may advance systematic, evidence-based strategies to reduce the impact of liver disease in the VHA system.



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2201 | LEVERAGING A COUNTYWIDE HEPATITIS B AND HEPATITIS C VIRUS REGISTRY TO LINK PERSONS WITH A HISTORY OF EXPERIENCING HOMELESSNESS TO CARE — LOS ANGELES COUNTY, JANUARY–MAY, 2025.

Prabhu Gounder[1] Jennifer Paul[2] Sophie Varma[3] Mirna Jewell[3] Heidi Behforouz[2], [1]Los Angeles County Department of Health Services, [2]LA County Department of Homeless Services and Housing, [3]LA County Department of Public Health

Background: The Los Angeles County Homeless Services and Housing (HSH) agency provides supportive housing for persons who are at-risk for or currently experiencing homelessness (PEH). The hepatitis C virus (HCV) prevalence among PEH in the Skid Row area of LAC was 27% in one study. It can be challenging to do phlebotomy and retain PEH in HBV or HCV care before addressing other social determinants of health such as housing and access to healthcare. The LAC Department of Public Health (DPH) maintains a Countywide registry of all persons reported with chronic hepatitis B virus (HBV) and HCV infection. We describe a data exchange collaboration between HSH and DPH to identify PEH with HBV or HCV and link them to care by using existing resources during January–May 2026. **Methods:** Clinical laboratories are mandated to report to DPH all positive test

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results indicating current or past HBV or HCV infection and negative HCV polymerase chain reaction (PCR) results. All test results are related to unique persons to create a HBV and HCV registry. Persons with a positive anti-HCV or HCV PCR without a subsequent negative PCR are defined as having diagnosed but untreated (DBU) HCV. Persons without a positive hepatitis B surface antigen, HBV PCR, or hepatitis B e antigen reported in >12 months were classified as DBU per AASLD HBV disease monitoring recommendations. We cross-referenced the HBV and HCV registry with the HSH client list to identify DBU persons and their assigned HSH case managers (CMs) worked to link them to care (attending a first appointment for HBV or HCV care). **Results:** In January 2026, we cross-referenced 31,418 HSH clients against the DPH HBV and HCV registry and identified 255 (1%) HBV and 1,530 (5%) HCV DBU clients represented by CMs at 110 agencies. Among HBV DBU, 44 (17%) were successfully contacted by a CM and 7 (3%) were linked to care; 37 (14%) were not linked (6 declined care, 21 already treated or in care, relocated 2). Among HCV DBU, 236 (16%) were successfully contacted by a CM and 48 (3%) were linked to care, 52 had pending appointments as of May 22; 136 (9%) were not linked (37 declined care, 80 already treated or are in care, 19 for various other reasons). **Conclusion:** Our collaboration demonstrates 1) the potential for improved data exchange to identify persons with known HBV and HCV without the need for repeat phlebotomy, and 2) for State or Local Public Health Departments to partner and leverage available resources to link persons in hard to reach populations to HBV or HCV care. We presented preliminary results from an ongoing effort and anticipate that a greater proportion of HBV and HCV DBU will be linked to care by the end of this effort. This model could be adapted to other high prevalence settings, such as jails.

Disclosures: Prabhu Gounder: Nothing to Disclose, Jennifer Paul: Nothing to Disclose, Sophie Varma: Nothing to Disclose, Mirna Jewell: Nothing to Disclose, Heidi Behforouz: Nothing to Disclose.

2202 | PRACTICE PATTERNS AND BARRIERS AFFECTING GOALS OF CARE COMMUNICATION AMONG HEPATOLOGY CLINICIANS WITHIN THE VETERANS HEALTH ADMINISTRATION

Likith Surendra[1] Jacqueline O'Leary[2] Sofia Jakab[3] Jasmohan Bajaj[4] Jennifer Anwar[5] Nicole Prause[6] Abbey Barnard Giustini[7] Ponni Perumalswami[8] Neha Jakhete[9] Heather Patton[10] Timothy Whitworth[11] Ashley Lane[12] Thuy-Van Hang[13] Timothy Morgan[5] Anne Walling[14] Shari Rogal[15] Arpan Patel[16], [1]Department of Medicine, University of California Los Angeles, Los Angeles, CA, USA, [2]Division of Gastroenterology, VA North Texas Healthcare System, Dallas, TX, [3]Division of Gastroenterology, VA Connecticut Healthcare System, New Haven, CT, [4]Division of Gastroenterology, VA Richmond Healthcare System, Richmond, VA, [5]Division of Gastroenterology, VA Long Beach Healthcare System, Long Beach, CA, [6]Vatche and Tamar Manoukian Division of Digestive Diseases, University of California Los Angeles, Los, [7]Division of Gastroenterology, VA Puget Sound Healthcare System, Puget Sound, WA, [8]Division of Gastroenterology, VA Ann Arbor Healthcare System, Ann Arbor, MI, [9]Division of Gastroenterology, VA Maryland Healthcare System, Baltimore, MD, [10]Division of Gastroenterology, VA San Diego Healthcare System, San Diego, CA, [11]Division of Gastroenterology, VA Illiana Healthcare System, Danville, IL, [12]Division of Gastroenterology, VA Eastern Colorado Healthcare System, Aurora, CO, [13]Division of Gastroenterology, VA Atlanta Healthcare System, Decatur, GA, [14]Division of General Internal Medicine, VA Greater Los Angeles Healthcare System, Los Angeles, CA, [15]Division of Gastroenterology, VA Pittsburgh Healthcare System, Pittsburgh, PA, [16]Division of Gastroenterology, VA Greater Los Angeles Healthcare System, Los Angeles, CA

Background: Cirrhosis is a life-limiting illness affecting nearly 100,000 Veterans each year. Goals of care communication (GOCC) helps ensure value-aligned care at the end of life. Within the Veterans Health Administration (VA), the largest integrated health system within the United States, GOCC occurs infrequently (30% of the time) and late (median of 37 days before death). Our aim was to identify practice patterns, as well as clinician and organizational factors affecting GOCC, among VA hepatology clinicians. **Methods:** We administered a brief, 26-item survey to hepatology clinicians within the VA. Items included demographics and a short-form version of the Goals of Care Communication Survey (n = 14 items), an assessment that captures clinician and organizational factors affecting GOCC: 1) *Knowledge, skills, and beliefs about capabilities*; 2) *Beliefs about consequences*, 3) *Intentions*; 4) *Social Influences*, and 5) *Organizational context*. We used 5 and 7-point Likert scales to capture responses, which were rescaled to all range from 0-100, where lower scores indicate greater barrier to GOCC. **Results:** A total of 52 out of 190 hepatology clinicians (response rate = 27%) across 35 facilities completed the survey. Most were White (58%), female (65%), physicians (60%), practicing non-transplant hepatology (58%), and with a predominantly outpatient

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practice (median 80%). About half (48%) reported discussing prognosis with seriously ill patients 75-100% of the time, but fewer reviewed goals and values (33%) or preferences for life-sustaining treatments (23%). Median scores for *knowledge, skills and beliefs about capabilities* (80, interquartile range [IQR] = 70-90), *beliefs about consequences* (80, IQR = 80-100), *intentions* (80, IQR = 75-100), and *social influences* (80, IQR = 60-80) for GOCC were high. However, the median score for *organizational context* was lower (66, IQR = 52-72). Individual items with the lowest scores were: "My organization provides me feedback on the quality of my goals of care discussions with seriously ill patients" (40, IQR = 20-60) and "I have sufficient time for conducting goals of care discussions with seriously ill patients in the outpatient setting" (60, IQR = 40-80). Only 25% of clinicians reported receiving simulation with supervised observation and structured feedback in GOCC. **Conclusion:** We found multiple positive influences for GOCC, indicating that VA hepatology clinicians were highly invested in providing value-aligned care for seriously ill patients, but they reported that discussions on goals/values/preferences occur infrequently. They cited insufficient feedback on GOCC and limited time in the outpatient setting as the greatest barriers. Structural changes in hepatology practice, including workflow support tools, GOCC training, and collaboration with palliative care may be needed to prioritize specific and frequent GOCC.

Disclosures: Likith Surendra: Nothing to Disclose, Jacqueline O'Leary: Nothing to Disclose, Sofia Jakab: Nothing to Disclose, Jasmohan Bajaj: Nothing to Disclose, Jennifer Anwar: Nothing to Disclose, Nicole Prause: Nothing to Disclose, Abbey Barnard Giustini: Nothing to Disclose, Ponni Perumalswami: Nothing to Disclose, Neha Jakhete: Nothing to Disclose, Heather Patton: Nothing to Disclose, Timothy Whitworth: Nothing to Disclose, Ashley Lane: Nothing to Disclose, Thuy-Van Hang: Nothing to Disclose, Timothy Morgan: Nothing to Disclose, Anne Walling: Nothing to Disclose, Shari Rogal: Nothing to Disclose, Nothing to Disclose, Arpan Patel: Nothing to Disclose, Nothing to Disclose.

2203 | EXPERIENCES WITH VETERANS ADMINISTRATION AND COMMUNITY-BASED TRANSPLANT CARE FOLLOWING THE MISSION ACT

Claire Durkin[1] Nicole Beyer[2] Kristina Hruska[2] Anne-Marie Sheilds[2] Maria Mor[2] Michael Fine[3] Steven Weisbord[4] Shari Rogal[1], [1]University of Pittsburgh, [2]VA Pittsburgh Healthcare System, [3]University of PIttburgh, VA Pittsburgh Healthcare System, [4]University of Pittsbugh, VA Pittsburgh Healthcare System

Background: The MISSION Act of 2018 expanded Veterans' eligibility to receive community care outside the Veterans Health Administration (VA). However, the impact of this expanded access on Veterans' transplant experiences remains unclear. This study qualitatively evaluated facilitators and barriers to kidney and liver transplant care through VA and community programs. **Methods:** We conducted semi-structured interviews with Veterans, VA transplant providers, and VA operations leaders across the U.S. from 8/2022-6/2024 to explore VA, community, and dual transplant care experiences. Purposive sampling captured perspectives across transplant type (kidney or liver), stage (waitlisted or post-transplant), and care setting (VA, community, or dual). Interviews were transcribed and analyzed using deductive and inductive approaches. Double-coding 20% of interviews ensured intercoder reliability. **Results:** We interviewed 66 Veterans (29 kidney, 37 liver; 27 waitlisted, 39 transplanted) and 52 providers/operations leaders. Most Veterans reported being offered VA-only (39%) or dual-care (44%) pathways, while fewer were offered community care alone (17%). Veterans identified patient preference (56%), lower cost (30%), transplant outcomes/reputation (21%), and travel/lodging support (20%) as key facilitators of VA transplant care. The main barrier was travel burden (35%). Liver transplant patients more commonly emphasized continuity of care, communication, and Veteran-centered support as reasons for choosing VA care than kidney patients. Facilitators of community care included trust in community programs (32%) and proximity to care (20%). Veterans offered dual care often described communication gaps and logistical complexity.Providers and operations leaders identified continuity of care and communication (75%), travel/lodging support (48%), patient preference (40%), and provider experience with VA transplant centers (39%) as major strengths of VA care. Key barriers included travel limitations (54%) and difficulty identifying support persons (54%). They viewed community care as improving geographic access (50%), but cited administrative barriers (50%), communication challenges (33%), and variable oversight (17%) as concerns. Across all groups, participants emphasized the need for improved patient education, care coordination, earlier referral, and transplant navigation support. **Conclusion:** Following the expansion of community care access for Veterans, transplant site selection was strongly influenced by patient preference, geographic access, and perceptions of quality and trust. While VA transplant centers were seen as providing strong continuity and coordinated care, maintaining these strengths was challenging within community and dual-care models. Improved education, navigation, and coordination may optimize transplant experiences and care delivery for Veterans across all settings.

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Disclosures: Claire Durkin: Nothing to Disclose, Nicole Beyer: Nothing to Disclose, Kristina Hruska: Nothing to Disclose, Anne-Marie Sheilds: Nothing to Disclose, Maria Mor: Nothing to Disclose, Michael Fine: Nothing to Disclose, Steven Weisbord: Nothing to Disclose, Shari Rogal: Nothing to Disclose, Nothing to Disclose.

2204 | IMPROVING HEPATOCELLULAR CARCINOMA (HCC) SCREENING RATES IN PATIENTS WITH CIRRHOSIS AT THE LOUISVILLE VA MEDICAL CENTER

Cristina Chiodi[1] Ashutosh Barve[1] Alicia Clum[2] Priya Krishnan[3], [1]University Of Louisville - Gastroenterology, Hepatology and Nutrition - LOUISVILLE, KY, [2]University of Louisville Internal Medicine, [3]Louisville VA Medical Center

Background: Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality among patients with cirrhosis. Six-month surveillance with abdominal ultrasound is recommended, yet adherence at our institution remains suboptimal. At the Louisville VA Medical Center, only 38% of eligible patients were up to date with HCC screening, increasing the risk of delayed diagnosis and limited treatment options. Contributing factors included inaccurate identification of cirrhosis, lack of standardized workflows, provider knowledge gaps, and challenges in patient follow-up. The objective of this project is increase the rate of appropriate HCC screening in patients with cirrhosis at the Louisville VAMC. **Methods:** We conducted a QI initiative using iterative interventions informed by a retrospective review. Among 782 patients coded with cirrhosis, 488 lacked appropriate surveillance; chart review showed 43.1% were miscoded and 17.3% had uncertain diagnoses. A multidisciplinary team comprised of the Chief Resident, Primary Care, Nursing, and GI providers implemented interventions targeting system and provider-level barriers, including (1) refinement of the "Advanced Liver Disease" dashboard to improve cohort accuracy, (2) provider education and deployment of electronic clinical reminders, and (3) nursing education and workflow optimization. The primary outcome measure was the amount of patients with cirrhosis receiving appropriate 6-month HCC screening. Secondary measures included qualitative assessment of barriers to screening completion. **Results:** 6-month screening rates improved from 38% in Q1 2025 to 60.4% in Q4 2025. In Q1 2026, 6-month screening rates declined slightly to 57.7%. Repeat analysis revealed disparities by care setting: patients followed in GI clinic had 100% ordering rates while those managed exclusively in primary care had significantly lower rates (11.8%). Persistent barriers to screening completion included patient no-shows and refusal. Continued data review also identified ongoing misclassification, with 22% lacking confirmed cirrhosis. **Conclusion:** Targeted data validation and provider-focused interventions led to a 20% increase in HCC screening rates. Accurate cohort identification was essential to avoid both under- and over-screening. Differences between specialty and primary care highlight the need for improved care coordination for surveillance. Patient engagement remains a critical barrier, particularly in specialty settings where missed appointments reduce screening completion. Limitations include data autocorrelation and reliance on electronic health record data, which may not capture external imaging. Ongoing efforts will focus on sustaining gains through continued cohort refinement, enhanced primary care collaboration, and implementation of a nurse navigator model to address patient-level barriers and improve adherence to surveillance guidelines.

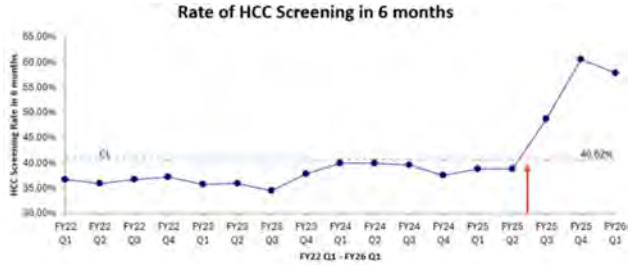


Figure 1: This run chart depicts quarterly data for HCC screening within 6 months at the Louisville VA. The red arrow denotes the initiation of the project with first intervention (database refinement).

Disclosures: Cristina Chiodi: Nothing to Disclose, Ashutosh Barve: Nothing to Disclose, Alicia Clum: Nothing to Disclose, Priya Krishnan: Nothing to Disclose.

2205 | IMPROVING MANAGEMENT OF PATIENTS WITH ACUTE KIDNEY INJURY AND CIRRHOSIS ACROSS A TERTIARY CARE HEALTH SYSTEM – A QUALITY IMPROVEMENT INITIATIVE

Max Schechter[1] Sara Schwenk[1] Marina Serper[2], [1]University of Pennsylvania, [2]University of Pennsylvania Health System

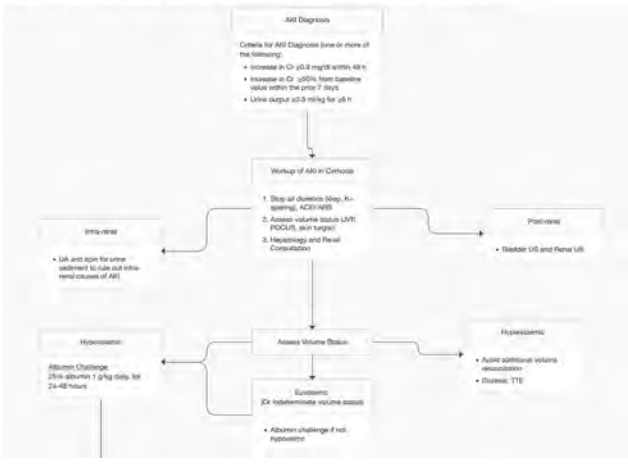
Background: Acute kidney injury (AKI) is common amongst inpatients with decompensated cirrhosis and can lead to significant morbidity and mortality, especially amongst patients with hepatorenal syndrome (HRS). The management of these patients with careful volume assessment and albumin challenge has been well established however variability into the use of albumin and initiation of terlipressin exists within our healthcare system. **Methods:** Using a quality improvement framework, we interviewed relevant stakeholders and developed a process map involving the current management of patients with AKI on the inpatient liver service. We

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developed the following goal: Increase the administration of albumin by 25% to inpatients on the general medicine floors with a goal to reduce length of stay (LOS) by 48 hours amongst patients with cirrhosis and AKI over the next 6 months. The intervention developed was a Clinical Decision Pathway to help guide the diagnosis and management of AKI in patients with cirrhosis. Pre-intervention data was obtained from Vizient and Epic SlicerDicer utilizing ICD-10 coding and included inpatients on the General Medicine service from 09/01/2023 through 10/31/2025. **Results:** A clinical decision pathway was developed, guiding the diagnosis and management of AKI in cirrhosis, stratified by volume status. The pathway included information on albumin challenge followed by prompt initiation of terlipressin in patients meeting diagnostic criteria for hepatorenal syndrome (Figure 1). Pre-intervention data consist of 785 hospital encounters with a mean age of 60.6 (STD = 13.0) and was 58% male. The data demonstrates that inpatients with a diagnosis of cirrhosis and AKI have a 30.7% ICU upgrade rate, 15.3% observed mortality rate, 9.7% 14-day readmission rate, and a mean observed LOS of 9.98 days (STD = 9.44 days). 419 (53.4%) of hospital encounters received albumin, 67 (8.5%) received a combination of albumin, midodrine, and octreotide (MAO), and 39 (5.0%) received terlipressin. **Conclusion:** Hospitalized patients with cirrhosis and AKI are particularly vulnerable to increased morbidity and mortality. Amongst our general medicine floors, only 5% of patients with a diagnosis of AKI and cirrhosis received terlipressin. A quality improvement framework was used to assess areas for improvement in caring for patients with AKI and cirrhosis and to ultimately develop a clinical decision pathway. Post-implementation data will be assessed in a future study.

Figure 1: Part 1 of clinical decision pathway for management of AKI in cirrhosis



Disclosures: Max Schechter: Nothing to Disclose, Sara Schwenk: Nothing to Disclose, Marina Serper: Transplant Genomics: Grant/Research Support, Grifols: Grant/Research Support.

2206 | IMPACT OF SERUM SEPARATOR TUBE SELECTION ON ROUTINE LIVER FUNCTION TESTING: A COMPARISON OF V-PRO® AND GREINER VACUETTE® TUBES

Somaya Alqattan[1] Safiah Almushawwah[2] Manar Sultan[2] Muzan Ismail[2], [1]Advance Medical Co, [2]Advance Medical Co.

Background: Preanalytical variability during blood collection remains a major source of laboratory error and may affect the accuracy of liver function testing and subsequent patient management. Blood collection tube composition can influence analyte stability and assay performance, potentially impacting interpretation of hepatic biomarkers. This study aimed to compare the analytical performance of V-PRO® Serum Separator Tubes (SSTs) with Greiner VACUETTE® CAT SST for routine liver function testing, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT), in accordance with CLSI recommendations. **Methods:** This comparative study included 20 healthy volunteers. For each participant, 10 mL of venous blood was collected and allocated between V-PRO® SST and Greiner VACUETTE® CAT SST tubes (5 mL each). Blood collection and sample processing were performed using standardized venipuncture and preanalytical procedures in accordance with CLSI GP41-Ed7 guidelines. Liver function biomarkers, including ALT, AST, ALP, and GGT, were analyzed using the Beckman Coulter DxC 700 AU chemistry analyzer. Agreement between tube types was evaluated using total allowable error, Bland–Altman analysis, Deming regression, and unpaired t-test with GraphPad Prism version 10.6.0. **Results:** No statistically significant differences were observed between V-PRO® SST and Greiner VACUETTE® CAT SST tubes for ALT, AST, ALP, or GGT measurements. Deming regression and Bland–Altman analyses demonstrated excellent agreement between tube types across all analytes, with strong correlations (r = 0.994–0.998) and minimal analytical bias. All specimens met CLIA allowable total error criteria, indicating analytical equivalence between the two serum separator tube devices. **Conclusion:** V-PRO® SST demonstrate strong analytical agreement with Greiner VACUETTE® SST for routine liver function testing, including ALT, AST, ALP, and GGT measurements. Mean bias values remained minimal and within CLIA allowable total error. Deming regression and Bland–Altman analyses confirmed excellent agreement between tube types, indicating no clinically significant differences affecting routine laboratory interpretation or

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clinical decision-making. These findings support the use of V-PRO® SST as a reliable alternative blood collection system for hepatic biochemistry testing. Further studies involving larger and clinically diverse populations are warranted.

Figures

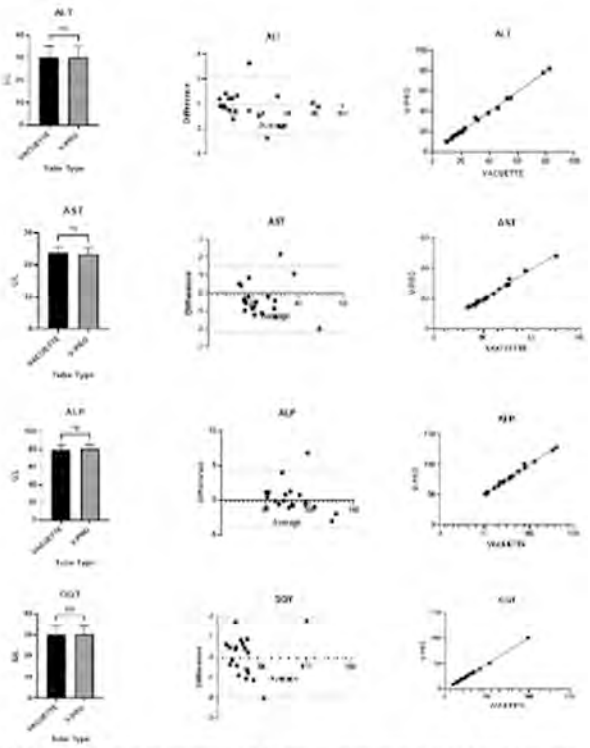


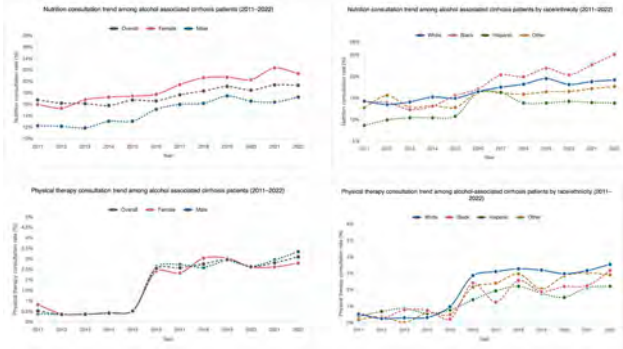
Figure 1. Comparison of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT) measurements between V-PRO® and Greiner VACUETTE® serum separator tubes. Error bars represent standard deviation (SD).

Disclosures: Somaya Alqattan: Advance Medical Co: Grant/Research Support, Safiah Almushawwah: Advance Medical Company: Employee, Manar Sultan: Advance Medical Company: Employee, Muzan Ismail: Advanced Medical Company: Employee.

2207 | LOW NATIONWIDE UTILIZATION OF NUTRITIONAL AND PHYSICAL THERAPY CONSULTATION AMONG HOSPITALIZED PATIENTS WITH ALCOHOL-ASSOCIATED CIRRHOSIS BETWEEN 2010 AND 2022

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Background: Malnutrition and functional decline are highly prevalent in alcohol-associated cirrhosis (AC). Guidelines from professional societies recommend nutrition and physical therapy assessments, yet national patterns of use of nutritional and physical therapy consultations among hospitalized AC patients remain poorly characterized. **Methods:** We performed a retrospective study of the National Inpatient Sample from 2010 to 2022. Adult hospitalizations with a primary diagnosis of AC (ICD-9: 571.2; ICD-10: K70.30/K70.31) were identified using ICD diagnostic codes. Nutritional consultation (NC) and physical therapy consultation (PT) were identified using a combination of ICD diagnosis procedure codes. Multivariable logistic regression was performed, adjusting for age, sex, race/ethnicity, income quartile, insurance type, Charlson Comorbidity Index, hospital region, hospital teaching status, and bed size. **Results:** A total of 241,943 weighted AC hospitalizations were identified (mean age 53.7 years; 27.3% female). NC showed a modest numerical increase over time, with consistently higher rates among female and Black patients and the lowest rates among Hispanic patients. PT increased after 2015, coinciding with the ICD-9 to ICD-10 transition, with rates remaining relatively stable before and after. On multivariable analysis, female sex (OR 1.36, 95% CI 1.27–1.46), CCI $\geq$ 3 (OR 1.17, 95% CI 1.05–1.31), and non-Northeast region (OR 1.54–1.62, all 95% CI lower bounds $\geq$ 1.27) were associated with higher odds of NC. Hispanic ethnicity (OR 0.69, 95% CI 0.61–0.77), Medicaid (OR 0.86, 95% CI 0.78–0.94), and self-pay/other insurance (OR 0.83, 95% CI 0.74–0.93) were associated with lower NC odds. For PT, the highest income quartile (OR 2.21, 95% CI 1.37–3.57) and Hispanic ethnicity (OR 2.09, 95% CI 1.36–3.23) were associated with higher odds, while urban non-teaching hospital status was strongly associated with lower PT odds (OR 0.09, 95% CI 0.02–0.32). **Conclusion:** Utilization of NC and PT in AC in AH remains persistently low nationwide, representing a critical unmet need given the high burden of malnutrition, sarcopenia, and functional decline in cirrhosis. Significant sociodemographic disparities underscore the need for systematic, equitable integration of nutritional and rehabilitative care for all high-risk AC patients.



Disclosures: Yee Hui Yeo: Nothing to Disclose, lingyu bao: Nothing to Disclose, Sheng-Yin Chen: Nothing to Disclose, Hanyou Loh: Nothing to Disclose.

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2208 | TAKING IT TO THE STREETS: A SCALABLE APPROACH TO EMBEDDING HCV SCREENING & CARE FOR HOMELESS HEALTH

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Background: People experiencing homelessness have a high burden of hepatitis C virus (HCV) infection & face substantial barriers to health screening & care. To improve access to HCV care, Decera Clinical Education partnered with the Street Medicine Institute & Circle the City, a Federally Qualified Health Center (FQHC) with mobile clinics & street outreach teams in Maricopa County, Arizona, to embed simplified HCV screening & treatment into street medicine workflows. **Methods:** This pilot program integrated education, protocol development, mentorship, & workflow design within Circle the City's mobile & street medicine program. Components included development of a simplified guideline-aligned opt-out screening & treatment algorithm, healthcare professional (HCP) & staff training, monthly implementation mentorship from an experienced street medicine HCV HCP, & prospective collection of screening & treatment data. Primary implementation outcomes were changes in screening volume, rates of HCV test positivity, & rates of treatment initiation by the outreach team activities. Secondary observations included rate of adoption by nonspecialist HCPs. **Results:** Between 3/1/25-11/30/25, 1574 patients were screened, surpassing the program's 6-month target of 250. Compared with baseline screening of 20 patients/month before the program launch, the pilot averaged 175 patients/month, a 775% increase in screening volume. Rapid HCV antibody screening positivity was 9.7%, & confirmatory RNA testing showed a presence of active HCV disease in 7%, ultimately identifying 103 patients with active HCV infection requiring linkage to care. Of these, 34 patients (33%) initiated HCV treatment (compared to the 3 years prior to this pilot program, where Circle the City had only rare instances of treatment initiation for active HCV disease). Of the remaining patients with active HCV infection but not on treatment, most are in the process of completing linkage to care, including obtaining treatment medication from a specialty pharmacy, pending specialist consultation, or attempting to locate & follow up with the patient. Following this program's education & mentorship, all HCPs who had not previously treated HCV (i.e. MDs,PAs,NPs) began initiating therapy independently, & pharmacy collaboration helped streamline access to initial treatment & refills. **Conclusion:** Embedding simplified HCV care into an existing street medicine program through an interprofessional collaboration among a medical education provider, a street medicine network, & a homeless health FQHC was feasible, & it rapidly expanded access to HCV screening for a highly underserved population. Early treatment starts & HCP uptake suggest this model can improve delivery of HCV care outside specialty settings. This pilot offers a scalable framework for mobile & community-based programs seeking to reduce access barriers & improve quality of care for people experiencing homelessness.
Disclosures: Manav Patel: Nothing to Disclose, Zachary Schwartz: Nothing to Disclose, Jeanne Forrester: Nothing to Disclose, Jack Palmer: Nothing to Disclose, Amanda Rosecrans: Nothing to Disclose.

2209 | TRENDS IN CHRONIC LIVER DISEASE MORTALITY IN ITALY IN THE DIRECT-ACTING ANTIVIRAL ERA: PROGRESS TOWARD WHO HEPATITIS ELIMINATION TARGETS

Stefano Rosato[1] Maria Giovanna Quaranta[1] Paola D'Errigo[1] Valerio Manno[1] Giorgia Stoppa[2] Annibale Biggeri[3] Dolores Catelan[2] Giada Minelli[1] Loreta A Kondili[1], [1]Istituto Superiore di Sanità, Rome, Italy, [2]University of Padua, Padua, Italy, [3]Univerity of Padua, Padua, Italy

Background: Viral hepatitis has represented a major public health challenge in Italy, with one of the highest burden in Europe. Expanded access to direct-acting antivirals (DAAs), with more than 280,000 patients treated to date, the highest number in Europe, has substantially changed liver disease epidemiology. This study assessed temporal trends in chronic liver disease (CLD) mortality in Italy, focusing on HCV-related mortality, and evaluated progress toward WHO elimination targets. **Methods:** ICD codes related to CLDs were extracted from multiple causes of death records (2003–2022), considering all causes reported on death certificates and selecting deaths with CLD as the underlying cause. Analyses focused on HCV-related mortality. Trends in age-standardised mortality rates were assessed by geographical macro-area using Joinpoint regression analyses. Progress toward the WHO 2030 mortality target was preliminarily estimated using age- and sex-specific Poisson models.Updated national active HCV screening program data for the key and general populations born 1969-1989, in place since 2020, were also analysed to contextualise the observed mortality trends. **Results:** A total of 375,622 CLD-related deaths were recorded among individuals aged $\geq$35 years (61.8% men); 25,418 deaths were attributable to alcohol-related liver diseases (81.8% men) and 41,416 to HCV (54.9% men). Age-standardised CLD

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mortality rates steadily declined across all geographical areas, although Southern Italy continued to have the highest rates.HCV-related mortality peaked in 2013, followed by a marked annual decline (annual per cent change [APC] −12.5%) from 2014 onward, with a further acceleration after 2017 concurrent with unrestricted DAA access. By 2022, HCV-related mortality had declined by approximately 55% compared with 2015, and preliminary estimates suggest that Italy may achieve the WHO 2030 mortality target as early as 2025.More than 3 million individuals have been screened through the national active HCV screening program, resulting in the identification of over 20,000 with active HCV infection. However, important gaps remain. Only approximately 20% of the target birth cohort (1969–1989) has been screened to date, while older birth cohorts (1948–1968), estimated to carry the highest prevalence of active HCV infection, are not yet systematically included in national screening strategies. **Conclusion:** Italy rapidly implemented broad and equitable access to DAA treatment and national screening interventions, resulting in a substantial decline in HCV-related mortality, positioning the country most likely to achieve the WHO hepatitis elimination mortality targets. However, achieving overall HCV elimination targets in Italy will require expansion of screening and treatment strategies, particularly targeting older birth cohorts with a high residual burden of undiagnosed infection.

Disclosures: Stefano Rosato: Nothing to Disclose, Maria Giovanna Quaranta: Gilead: Grant/Research Support, Paola D'Errigo: Nothing to Disclose, Valerio Manno: Nothing to Disclose, Giorgia Stoppa: Nothing to Disclose, Annibale Biggeri: Nothing to Disclose, Dolores Catelan: Nothing to Disclose, Giada Minelli: Nothing to Disclose, Loreta A Kondili: Nothing to Disclose.

2210 | THE PROVIDER EXPERIENCE OF CARING FOR PATIENTS WITH MASLD

Alana Saddic[1] Jessica Mittler[1] Arun Sanyal[1] Deborah DiazGranados[1], [1]Virginia Commonwealth University

Background: MASLD is associated with multiple metabolic-dysfunction mediated end-organ diseases necessitating care from various HCPs. There are no established paradigms for integration of care across specialties in these patients. This study was undertaken to understand knowledge, attitude, and practice patterns among hepatologists and PCPs through discussing their lived experiences of caring for MASLD patients. **Methods:** HCPs completed a multisystem metabolic disease knowledge questionnaire, which was scored to evaluate group differences. Hepatology and PCPs participated in focus groups amongst other members of their specialties. Transcripts underwent inductive thematic analysis to identify and analyze core patterns. **Results:** 5 hepatologists (4 MD, 1 APP) and 2 PCPs (1 MD, 1 APP) participated. Years of practice were < 5 years (n = 3), 5-10 (n = 2), 11-20 (n = 1), > 20 years (n = 1). Overall 57.1% of the questions were answered correctly (hepatologists 58.7%, PCP 53.3%, MD 57.33%, APP 56.7%), The highest scoring question (100%) regarded Fib-4 utilization. The lowest scoring questions (14%), regarded renal dysfunction management. Hepatologists felt that they play a key role in MASLD patients care; especially those with significant fibrosis. They estimated 50% of referred patients were unaware of having MASLD. Perceived barriers to optimal MASLD care include: inadequate screening, insurance coverage, patient low health literacy, lack of time/knowledge among PCPs, lack of financial incentives, lack of supply of hepatologists and other specialists. Things that help them provide optimal care/suggested solutions include: incorporating other members of the care team (RDs, APPs, nurse navigators) and utilizing technology (embedding Fib-4 into the EMR, EMR provider communication, and providing patient education). The PCPs viewed themselves as the first-line point-person for MASLD care-including identifying/ referring patients with MASLD, providing education, and managing comorbidities. Perceived barriers to optimal MASLD care include: screening methods that do not catch MASLD early enough, lack of knowledge of liver directed therapies, patients' lack of time/knowledge. Things that help them provide optimal care/suggested solutions include: comprehensive hepatology consults, increased MASLD offerings for their professional education, e-consults with endocrinologists, EMR communication between specialists, coordinated RD/lifestyle coaching and suggested use of best practice advisories in the EMR. **Conclusion:** Both groups prioritized screening protocols for early MASLD identification. Barriers to optimal MASLD care include insufficient screening, lack of knowledge among patients and providers, lack of financial incentives, lack of sufficient specialists. They acknowledge the importance of multidisciplinary team management and both suggest the use of EMR embedded technology to aid in patient care.

Disclosures: Alana Saddic: McKesson: Stock - publicly traded company, Eli Lilly: Stock - publicly traded company, Jessica Mittler: Nothing to Disclose, Arun Sanyal: Nothing to Disclose, Deborah DiazGranados: Nothing to Disclose.

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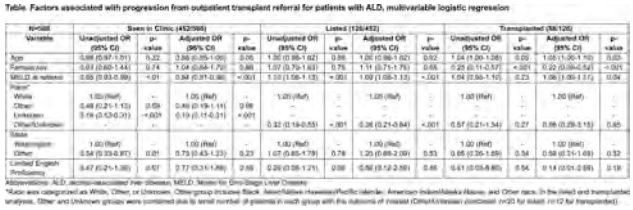
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2211 | ACCESS TO LIVER TRANSPLANTATION AMONG PATIENTS WITH ALCOHOL-ASSOCIATED LIVER DISEASE: A MULTISTAGE ANALYSIS

Sienna Lila[1] Daniel Huynh[1] Philip Vutien[1] Meredith Pearson[1] Meagan Alvarado[1] Lei Yu[1] Iris Liou[1] Renuka Bhattacharya[1] Anne Larson[1] Rotonya Carr[1] Erin Cleveland[1] Muyi Li[1] Nicole Kim[2], [1]University of Washington, [2]University of Washington Medical Center

Background: Despite being the most common indication for liver transplantation (LT), patients with alcohol-associated liver disease (ALD) can face various barriers to LT. We aimed to identify the sociodemographic factors associated with failure to progress through the LT evaluation process to determine which stages present the greatest barriers for patients with ALD. **Methods:** We conducted a single center, retrospective cohort study of adults (≥18 years) with ALD referred for LT in the outpatient setting from 1/1/2022 to 5/9/2024. The outcome of the first outpatient referral for each patient was considered. Medical records were queried for sociodemographic data, including age, sex, race, state of residence, primary language, and Model for End-Stage Liver Disease (MELD) score at the time of referral (MELD 3.0 when available, otherwise MELD-Na). Multivariable logistic regression was used to identify factors associated with the following outcomes: seen in liver transplant clinic, listed for transplant, and transplanted. **Results:** A total of 568 patients with ALD were referred for LT evaluation in the outpatient setting. The cohort was majority male (59%), White (61%), with a median age of 53 years (IQR 44-60) and median MELD of 19 (IQR 13-24). There was no difference in median MELD at referral between males and females. Of the patients referred, 452 (80%) were seen in transplant clinic, 126 (22%) were listed, and 88 (15%) were transplanted. In a multivariable model of patients with ALD referred for LT, a higher MELD score at referral was associated with lower odds of being seen in transplant clinic (OR 0.94, p < .001; Table). However, among those who did engage in transplant evaluation, a higher MELD score increased the likelihood of progressing to listing (OR 1.09, p < .001) and transplant (OR 1.08, p = 0.04). Once listed, female patients (vs. male) with ALD were less likely to be transplanted (OR 0.22, p < .001), while older patients (vs. younger patients) were more likely to be transplanted (OR 1.05, p = 0.03). Geography (state of residence at referral) was not associated with progression to transplant. Non-White/unknown race was independently associated with a lower likelihood of being listed for transplant (OR 0.36, p < .001). **Conclusion:** Patients with ALD experienced substantial attrition along the pathway to LT, with only 22% of all referrals and 28% of those evaluated in clinic ultimately listed for transplant. Higher MELD scores were associated with lower odds of initial transplant clinic engagement, but increased the likelihood of listing and transplant among individuals seen in clinic. Among those listed for LT, women experienced a markedly lower odds of transplantation, highlighting a potential sex-based disparity in LT access among patients with ALD. Further studies and analyses are needed to assess the factors that may contribute to this disparity.

Table. Factors associated with progression from outpatient transplant referral for patients with ALD, multivariable logistic regression



Disclosures: Sienna Lila: Nothing to Disclose, Daniel Huynh: Nothing to Disclose, Philip Vutien: Nothing to Disclose, Meredith Pearson: Nothing to Disclose, Meagan Alvarado: Nothing to Disclose, Lei Yu: Nothing to Disclose, Iris Liou: Nothing to Disclose, Renuka Bhattacharya: Nothing to Disclose, Anne Larson: Nothing to Disclose, Rotonya Carr: Merck: Grant/Research Support, Intercept: Consultant, Astra Zeneca: Consultant, Novo Nordisc: Consultant, Madrigal: Consultant, Boehringer: Advisor, Erin Cleveland: Nothing to Disclose, Muyi Li: Nothing to Disclose, Nicole Kim: Madrigal: Grant/Research Support, Madrigal Pharmaceuticals: Clinical trial (to institution), Madrigal: Grant/Research Support.

2212 | HOSPITALIZATION AS A "REACHABLE MOMENT": NURSE NAVIGATOR-DRIVEN IDENTIFICATION AND MITIGATION OF BARRIERS TO HEPATITIS C LINKAGE-TO-CARE COMBINED WITH TEST-AND-TREAT APPROACH LEADS TO HIGH RATES OF SUSTAINED VIROLOGIC RESPONSE

Patricia Werner[1] Madeline McCrary[1] Laura Marks[1] Jennifer Mullersman[1] Megan Curtis[1] Tracey Habrock-Bach[1], 1. Division of Infectious Diseases, Washington University School of Medicine, St. Louis, MO USA

Background: Hospitalization offers a "reachable moment" for Hepatitis C virus (HCV) screening, diagnosis, and treatment. We evaluated patient barriers to care and effectiveness for a hospital-based HCV treatment program. **Methods:** In 2022, we implemented a program to offer direct acting antivirals

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(DAAs) to hospitalized patients at discharge through inpatient Infectious Diseases (ID) consultation with ID pharmacy support. In March 2024, we implemented a nurse navigation program with electronic medical record-prompted HCV screening. Nurse Navigators identify HCV by running daily laboratory reports. Nurse navigators provide education, assess patient reported barriers to care and facilitate linkage to HCV DAA treatment initiation, including on hospital discharge. Delivery of DAAs is facilitated by collaboration with pharmacy staff. We assessed effectiveness using sustained virologic response (SVR) after end of therapy. **Results:** From January 2022-February 2026, 290 patients were prescribed DAAs through the "Meds to Beds" program. Of the 277 who survived SVR, 62% (171) achieved SVR. The most common patient-reported barriers to care were: not having been offered linkage to HCV treatment previously (44.8%), transportation difficulties, pharmacy or labs (23.1%), housing insecurity (10.5%), and lacking access to a phone for coordinating care (8.5%). **Conclusion:** Integration of HCV screening, diagnosis, and treatment as a bundled approach during inpatient hospitalization leverages the central role of the hospital within public healthcare and bridges the gap in care for populations who may be disconnected from outpatient healthcare systems. Dispensing HCV DAAs directly at the point of HCV testing in the hospital eliminates the need for patients to travel to a separate outpatient clinic appointment after discharge for a visit with an HCV treatment provider, resolving one of the most common patient-reported barriers to HCV treatment. By reducing multiple transitions, hospital-based HCV treatment can strengthen the HCV care continuum. Next steps include ensuring all patients can be seen by prescribers during hospital admission and improving processes to access patient assistance for DAAs for those without health insurance. **Disclosure of Interest Statement:** ***See example below:*** *L.M.M and L.R.M report funding by Gilead's Frontlines of Communities in the United States (FOCUS) program. FOCUS funding supports HIV, HCV, and hepatitis B virus screening and linkage to the first medical appointment after diagnosis; FOCUS funding does not support any activities beyond the first medical appointment and is agnostic to how FOCUS partners handle subsequent patient care and treatment.* **Disclosures:** Patricia Werner: Nothing to Disclose, Madeline McCrary: Gilead FOCUS: Grant/Research Support, Abbvie: Grant/Research Support, Laura Marks: Nothing to Disclose, Jennifer Mullersman: Nothing to Disclose, Megan Curtis: Nothing to Disclose, Tracey Habrock-Bach: Nothing to Disclose.

2213 | THE MISSED OPPORTUNITY FOR HEPATOCELLULAR CARCINOMA SURVEILLANCE BEGINS IN PRIMARY CARE

Antoine Sassine[1] Christopher Murphy[1], [1]Trinity Health Grand Rapids

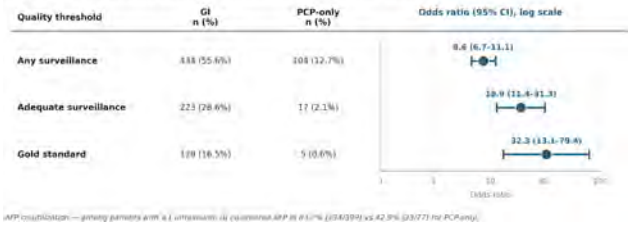
Background: Hepatocellular carcinoma (HCC) surveillance rates remain suboptimal among patients with cirrhosis despite established guideline recommendations. Low surveillance rates are frequently attributed to barriers in follow-up and access to specialty care; however, surveillance patterns among patients who remain actively engaged in primary care are less well characterized. We assessed HCC surveillance ordering among patients with cirrhosis and documented primary care follow-up and examined how gastroenterology/hepatology involvement influenced surveillance rates. **Methods:** We studied 1,602 adults with cirrhosis and ≥ 1 primary care visit in 2025 within a single integrated multi-specialty health system. Using order records, HCC surveillance over 12 months was categorized on an ordinal scale as gold-standard (biannual ultrasound [US] + biannual alpha-fetoprotein [AFP]), acceptable (biannual US ± AFP or contrast-enhanced CT/MRI spanning both half-years), incomplete (imaging in only one half-year), or none. All measures reflect ordering, irrespective of completion. We recorded each patient's contact with primary care (PCP) and gastroenterology/hepatology (GI) and identified the department responsible for each surveillance order. Associations were assessed using Fisher exact tests and odds ratios (OR), with MELD-adjusted analyses where available. **Results:** All patients had at least one primary care encounter, but only 781 (49%) also had GI involvement. Adequate surveillance was ordered for just 15% of the cohort, while 66% had no surveillance ordered. Surveillance rates differed substantially according to specialty involvement: among the 821 patients (51%) without GI care, only 2% received adequate surveillance and 87% had no surveillance orders, compared with 29% adequate surveillance among patients seen by GI (OR 18.9, 95% CI 11.4–31.3; MELD-adjusted OR 17.1). The GI advantage widened with screening quality, from any imaging (OR 8.6) to gold-standard surveillance (OR 32.3; Figure 1). Among patients with at least one ultrasound order, AFP was co-ordered in 84% of GI patients versus 43% of patients without GI involvement. Analysis of ordering providers demonstrated that GI accounted for the majority of surveillance

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orders, whereas primary care accounted for 21%. **Conclusion:** The missed opportunity for HCC surveillance begins at the primary care encounter. Despite universal primary care engagement in this cohort, only a minority of patients received guideline-concordant surveillance, and surveillance was strongly concentrated among those who reached gastroenterology/hepatology care. The large proportion of patients who never accessed specialty care accounted for a substantial share of missed surveillance opportunities, highlighting the need for strategies that improve surveillance delivery within primary care and facilitate access to specialty care.

Figure 1. Odds of HCC Screening Ordering — GI vs. PCP-only



Disclosures: Antoine Sassine: Nothing to Disclose, Christopher Murphy: Nothing to Disclose.

2214 | FINDINGS FROM A CROSS-SECTIONAL STUDY ON THE HEALTH-RELATED QUALITY OF LIFE IN ACUTE HEPATIC PORPHYRIA

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Background: Acute hepatic porphyrias (AHPs) are characterized by acute attacks, possible chronic symptoms, and low health-related quality of life (HRQoL). This noninterventional cross-sectional HRQoL study, conducted as part of research activities to explore the lived experience of patients with AHP, utilized standard patient-reported outcome measures (PROMs) to characterize the chronic symptom burden of AHP in patients who had and had not recently experienced an AHP attack. **Methods:** Eligible patients with AHP were ≥15 years old, had experienced ≥1 self-reported attack in the past 2 years, and had not received treatment up to two weeks before completing the PROMs. Patients completed the 12-Item Short-Form Health Survey version 2 (SF-12; capturing global HRQoL and overall health status over the last 4 weeks); the Work Productivity and Activity Impairment Questionnaire (WPAI): General Health version 2 (capturing impairments over the last 7 days); and two pain severity items (capturing worst and least severity of AHP-related pain over the last 7 days). All outcomes were summarized descriptively and patients were stratified by whether they did or did not have an attack in the past 30 days, per self-reporting at the time of response to the PROMs. **Results:** Overall, 30 patients (mean age 47.4 years; 77% female; 67% with acute intermittent porphyria) were included, of whom 13 (43%) reported an attack within 30 days of the PROM (**Table**). Mean (standard deviation [SD]) SF-12 Physical Component Summary (PCS) and Mental Component Summary (MCS) scores in the overall sample were 39.30 (11.40) and 42.81 (10.33), respectively; both scores were below the population norm of 50 (SD, 10), and PCS scores were one SD below the population norm. Mean (SD) SF-12 PCS and MCS scores were lower in patients who had an attack in the past 30 days than in those who did not (**Table**). Participants in the overall sample reported WPAI impairments in all domains; the most impacted domain was activity impairment (mean [SD] impairment, 49.00% [28.93%]). Impairments in the WPAI were generally worse among patients who had an attack in the past 30 days than in patients who did not (**Table**). Mean (SD) worst pain severity score was 4.60 (2.61) in the overall sample and was greater in patients who had an attack in the past 30 days than in those who did not (**Table**). Mean (SD) least pain severity score was 2.50 (2.54) overall and was similar between patients who did and did not have an attack in the past 30 days (**Table**). **Conclusion:** Patients with AHP experience diminished HRQoL as measured by the SF-12, WPAI, and pain severity regardless of whether they have had a recent AHP attack. Similarities in least pain severity scores between groups may indicate chronic mild pain. These findings show that patients with AHP experience disease burden outside of attacks, and the development of an AHP-specific PROM designed for use in clinical and real-world practice may enable a more comprehensive assessment of the burden of AHP.

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Patient Characteristics, Disease Burden, and HRQoL

Characteristic	Had AHP attack in past 30 days (n=13)[a]	Did not have AHP attack in past 30 days (n=17)	Overall (n=30)
Age, years, mean (SD)	47.2 (12.4)	47.5 (17.6)	47.4 (15.3)
Sex, n (%)			
Male	1 (8)	6 (35)	7 (23)
Female	12 (92)	11 (65)	23 (77)
Region, n (%)			
USA	12 (92)	14 (82)	26 (87)
Canada	1 (8)	3 (18)	4 (13)
AHP subtype, n (%)			
AIP	9 (69)	11 (65)	20 (67)
HCP	3 (23)	2 (12)	5 (17)
VP	1 (8)	3 (18)	4 (13)
Unknown	0	1 (6)	1 (3)
Had ≥1 AHP attack requiring medical treatment in past 6 months, n (%)	5 (38)	7 (41)	12 (40)
Number of AHP attacks requiring medical treatment in past 6 months,[b,c] mean (SD)	n=4 2.5 (0.6)	n=7 1.9 (0.9)	n=11 2.1 (0.8)
Previous or current treatment for AHP, n (%)			
First-line/foundational	12 (92)	14 (82)	26 (87)
Acute attack management	9 (69)	15 (88)	24 (80)
Preventive/maintenance (for recurrent attacks)	7 (54)	10 (59)	17 (57)
Hormonal treatment	0	3 (18)	3 (10)
Advanced/targeted therapies	2 (15)	2 (12)	4 (13)
Other	8 (62)	6 (35)	14 (47)
None	1 (7.7)	2 (11.8)	3 (10.0)
SF-12 scores[d]			
PCS, mean (SD)	36.34 (9.86)	41.57 (12.25)	39.30 (11.40)
MCS, mean (SD)	38.97 (10.68)	45.74 (9.31)	42.81 (10.33)
WPAI: General Health scores[e]			
Activity impairment, %, mean (SD)	n=13 63.08 (24.96)	n=17 38.24 (27.67)	n=30 49.00 (28.93)
Work productivity loss, %, mean (SD)	n=2 57.99 (6.37)	n=9 40.64 (31.22)	n=11 43.80 (28.86)
Absenteeism,[f] %, mean (SD)	n=2 15.99 (12.74)	n=9 10.81 (22.89)	n=11 11.75 (20.97)
Presenteeism,[g] %, mean (SD)	n=2 50.00 (0.00)	n=9 33.33 (27.39)	n=11 36.36 (25.41)
Pain severity scores[h]			
Least pain severity, mean (SD)	2.85 (3.11)	2.24 (2.08)	2.50 (2.54)
Worst pain severity, mean (SD)	5.54 (2.11)	3.88 (2.78)	4.60 (2.61)

Patients can provide multiple responses; the total percentage may be ≥100%.
[a]At the time of PROM completion, 12 patients reported that their AHP attack occurred before their study interview date and was not serious enough to require hospitalization. One patient reported having had an AHP attack 4 days after their interview date.
[b]One patient in the 'had an attack in the past 30 days' group reported their number of attacks requiring medical treatment in the past 6 months as "3 × per week for 6 months" and was excluded from the summary statistics for this parameter.
[c]Calculated among patients who reported ≥1 AHP attack requiring medical treatment in the past 6 months.
[d]Measured over the past 4 weeks; higher scores indicate better HRQoL.
[e]Measured over the past 7 days; higher scores indicate greater impairment and less productivity.
[f]Absenteeism was defined as absence from work due to health.
[g]Presenteeism was defined as impaired productivity while physically present at work due to health.
[h]Measured over the past 7 days; higher scores indicate worse pain.
AHP, acute hepatic porphyria; AIP, acute intermittent porphyria; HCP, hereditary coproporphyria; HRQoL, health-related quality of life; MCS, Mental Component Summary; PCS, Physical Component Summary; PROM, patient-reported outcome measure; SD, standard deviation; SF-12,12-item Short-Form Health Survey; VP, variegate porphyria; WPAI, Work Productivity and Activity Impairment Questionnaire.

Disclosures: Teresa Kauf: Alnylam, Inc: Employee, Mural Oncology: Stock - publicly traded company, Alkermes, Inc: Stock - publicly traded company, Alnylam, Inc: Stock – privately held company, Hetanshi Naik: Alnylam Pharmaceuticals: Consultant, Brittany Klooster: Nothing to Disclose, Roger Lamoureux: Alnylam Pharmaceuticals: Employee of Adelphi Values, which has been compensated, Rianna Leighton: Alnylam Pharmaceuticals: provides biostatistical support, Sabina Wiekhorst: Alnylam Pharmaceuticals: Employee, Samantha Hurley: Alnylam Pharmaceuticals: Employee.

2215 | PBC CASE-FINDING LOGIC REVEALS LIMITATIONS OF STRUCTURED EMR DATA AND NEXT STEPS TOWARD IDENTIFYING TRUE AND MISSED DIAGNOSES

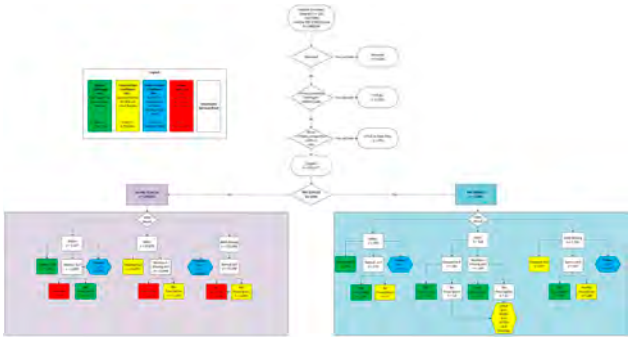
Anna Mageras[1] Andrea Branch[2] Christopher Kim[1] Francina Collado[1] Douglas Dieterich[1] Frances Lee[1], [1]Icahn School of Medicine at Mount Sinai, New York, NY, USA, [2]Icahn School of Medicine at Mount Sinai (ISMMS)

Background: We used retrospective, cross-sectional electronic medical record (EMR) data to create a logic flowchart to help assess patients' likelihood of having primary biliary cholangitis (PBC) and prioritize them for care management in our large New York City health system. We aimed to a) confirm the status of patients with a PBC ICD-9/10 diagnosis (Dx) code and b) identify overlooked cases without a PBC ICD-9/10 code. **Methods:** We selected adult patients who ever had an ALP result ≥ 120, AMA result, and/or PBC dx code in their EMR (n = 268,394). We extracted most recent Dx codes; outpatient lab results (excluding inpatient, emergency, and oncology); and ursodiol, obeticholic acid, elafibranor, and seladelpar prescriptions from our EPIC EMR from 01/2000 – 1/2025. Patients with a recorded death date, a primary sclerosing cholangitis Dx code, or an isolated code for unspecified biliary cirrhosis were excluded. The likelihood of PBC was determined for the remaining patients (n = 252,677) by applying AASLD diagnostic guidance and our clinical judgement. ALP ≥ 120 U/L indicated elevation. Data were processed using pandas and NumPy in Python 3.13. Counts were summarized in Excel. The logic flowchart was created using Microsoft Visio. **Results:** The cohort with a PBC Dx code (n = 2,646) included 787 AMA+ patients (30%), 328 (12%) AMA-, and 1,531 (58%) missing AMA. According to our schema (Figure 1), 1,305 (50%) members of this cohort had highest likelihood of PBC, 750 (28%) had intermediate likelihood PBC, and 591 (22%) had indeterminate likelihood and needing follow-up testing. Among 250,031 without a PBC dx code, 1,427 (1%) were AMA+, 26,019 (10%) AMA-, and 222,585 (89%) missing AMA. We labeled 460 (0.2%) as highest likelihood PBC, 9,026 (4%) intermediate likelihood, 94,643 (38%) lowest likelihood, and 145,902 (58%) as needing follow-up testing. Manual review of 5 random charts with a PBC Dx code and missing AMA revealed testing outside our health system. This highlights the limitations of structured EMR data. Next steps are 1) extracting Anti-Sp100, Anti-GP210, and histology

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results and 2) performing manual chart review to better understand the ground truth of patients in green and yellow categories. We will then review random samples from the red boxes to confirm negative logic. **Conclusion:** Structured data alone are insufficient for PBC case-finding in our system. In the future, we will aim to incorporate unstructured data obtained from the EMR using AI methods, such as natural language processing. Once we have refined and validated our schema and identified our system's true PBC cohort, we will develop a longitudinal care continuum that charts treatment response and escalation. We will aim to link undiagnosed patients to liver care. We will also engage primary care providers, hepatologists, and gastroenterologists to assess provider knowledge of PBC and encourage full diagnostic testing for patients with incomplete results.



Disclosures: Anna Mageras: The Kinetix Group: Advisor, Novo Nordisk: Advisor, Gilead Sciences: Grant/Research Support, Gilead Sciences: Advisor, Andrea Branch: Nothing to Disclose, Christopher Kim: Nothing to Disclose, Francina Collado: Nothing to Disclose, Douglas Dieterich: Nothing to Disclose, Frances Lee: Nothing to Disclose.

2216 | REAL-WORLD EMR DATA SHOWS HIGHER RATES OF PBC TESTING AND FIRST-LINE TREATMENT FOR PATIENTS WITH BOTH PBC AND CIRRHOSIS DIAGNOSES

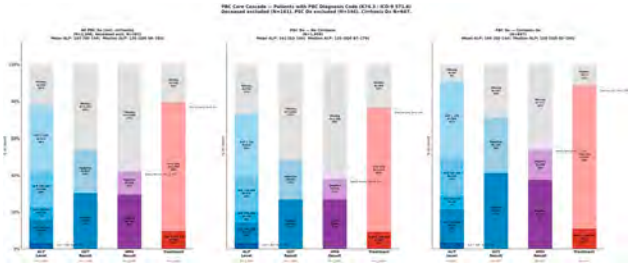
Anna Mageras[1] Xiaotao Zhang[2] Francina Collado[1] Douglas Dieterich[1] Frances Lee[1], [1]Icahn School of Medicine at Mount Sinai, New York, NY, USA, [2]Icahn School of Medicine at Mount Sinai

Background: As a first step toward developing a care cascade for primary biliary cholangitis (PBC), we aimed to create a snapshot of testing and treatment received by patients with a PBC ICD-9/10 diagnosis (Dx) code in our health system.

Methods: Adult, alive patients with a PBC Dx code and no PSC Dx code were included. We extracted the following variables from our EPIC electronic medical record (EMR), selecting most recent values 01/2000–10/2025: PBC and related Dx codes; outpatient labs (excluding inpatient, emergency, and oncology); ursodiol, obeticholic acid (OCA), elafibranor, and seladelpar prescriptions (Rx); and relevant outpatient visits. Diagnostic testing and treatment rates were compared between patients with and without cirrhosis Dx using chi-square tests. Multivariable logistic regression was used to assess clinical predictors of 1) any therapy and 2) combined first line (1L) and second line (2L) therapy. Data were processed using pandas and NumPy and analyzed using statsmodels in Python 3.13. **Results:** Of 2,646 included patients, the subset with a cirrhosis Dx code (n = 647) had higher rates of testing and 1L Rx versus patients without a cirrhosis Dx; 91% vs. 73% had ALP ($p < 0.001$); 72% vs. 48% had GGT ($p < 0.001$); 58% vs. 41% had AMA ($p < 0.001$); 78% vs. 67% had one Rx ($p < 0.001$), and 11% vs. 9% had 1L plus 2L ($p = 0.23$). In multivariable regression, all ALP categories > 120 had higher odds of any Rx than ALP < 120. Positive AMA had higher odds of Rx than negative (aOR: 2.50, (1.64-3.80)). Cirrhosis Dx and osteoporosis Dx were both positively associated with any Rx. Engagement with hepatology plus primary care or hepatology alone had higher odds of any Rx compared to engagement with neither (aOR: 3.72 (2.35-5.88); aOR: 3.89 (2.94-5.16)). Low platelets had lower odds of any Rx than normal (aOR: 0.55 (0.38-0.79)). In the second model, all ALP categories > 120 had higher odds of combined 1L plus 2L, and abnormal bilirubin (total bilirubin > 1.3) had lower odds (OR: 0.56 (0.32-0.97)). **Conclusion:** High 1L rates indicate most patients with PBC Dx codes receive standard care in our health system. Our results highlight clinical markers of PBC, cirrhosis Dx, osteoporosis Dx, and engagement in hepatology as positive predictors of 1L treatment. Correlation with cirrhosis Dx may indicate higher levels of care for sicker patients or be a proxy for higher patient engagement. The inverse associations between low platelets and 1L and abnormal bilirubin and 2L may reflect gaps in care or inaccurate Dx coding. 2L rates were low relative to elevated ALP rates across groups, though cross-sectional analysis limited our ability to assess appropriate escalation. Our data also did not capture care received outside our health system. Future directions include development of a longitudinal care continuum including treatment response, escalation, and transition from OCA to newer 2L therapies.

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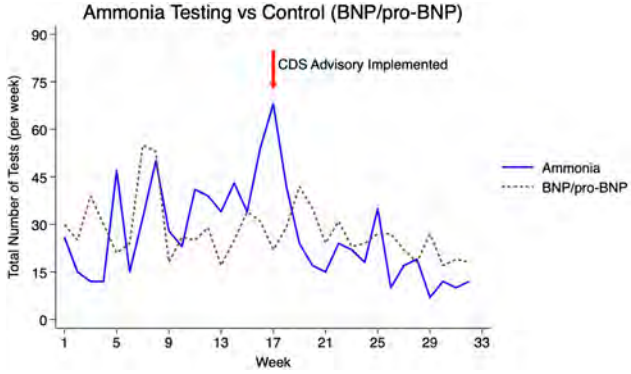


Disclosures: Anna Mageras: The Kinetix Group: Advisor, Novo Nordisk: Advisor, Gilead Sciences: Grant/Research Support, Gilead Sciences: Advisor, Xiaotao Zhang: Nothing to Disclose, Francina Collado: Nothing to Disclose, Douglas Dieterich: Nothing to Disclose, Frances Lee: Nothing to Disclose.

2217 | A NOVEL CLINICAL DECISION SUPPORT INTERVENTION REDUCES AMMONIA TESTING IN CHRONIC LIVER DISEASE PATIENTS

Michael Gianarakis[1] Adam Mikolajczyk[2], [1]University of Illinois at Chicago, [2]University of Illinois Chicago

Background: Liver society guidelines in North America discourage ammonia testing in chronic liver disease (CLD) patients for diagnosing, excluding, or monitoring hepatic encephalopathy (HE). Despite this, guideline-discordant ammonia testing remains prevalent and contributes to wasteful spending. While clinical decision support (CDS) interventions have improved other aspects of liver-related care, no studies have evaluated interventions targeting ammonia overuse in patients with CLD. We evaluated the impact of a novel CDS advisory on ammonia utilization and testing behavior. **Methods:** We performed a prospective pre-post intervention study evaluating an interruptive CDS advisory implemented at a tertiary referral center in January 2026. The advisory was triggered when ammonia testing was ordered for patients with CLD and provided guideline-based recommendations on test utilization. Testing was compared across 16-week pre- and post-intervention periods. Data was extracted for inpatient, emergency department (ED) and outpatient encounters. Weekly ammonia testing trends were compared with brain natriuretic peptide testing as a control. Advisory-level characteristics were also analyzed. Multivariable logistic regression was performed to identify factors associated with alert acceptance. **Results:** Total ammonia tests decreased from 505 to 352 post-intervention, representing a 30.3% reduction and >$40,000 in cost savings ($264/test). Mean weekly testing decreased from 31.6 ± 13.7 to 22.0 ± 15.3 tests/week (p = 0.038). Reductions were observed among internal medicine (IM) (8.13 ± 4.10 vs 4.93 ± 4.80 tests/week, p = 0.020), medical critical care (CC) (12.94 ± 10.49 vs 9.67 ± 14.55, p = 0.235), and ED providers (3.64 ± 1.82 vs 2.46 ± 1.20 tests/week, p = 0.067). The number of patients undergoing repeat testing (>1 test) also declined (67 vs 47), particularly in the ED and CC department. Among 237 CDS advisories triggered, the acceptance rate was 41.4%. Among 55 patients at risk for serial testing, 25 (45.45%) of providers did not attempt to reorder and 10 (18.18%) accepted subsequent alerts. In multivariable analysis, patients with a primary diagnosis of HE (OR 0.25, 95% CI 0.06–0.97, p = 0.044) and liver transplant-related diagnoses (OR 0.17, 95% CI 0.03–0.94, p = 0.042) had lower odds of advisory acceptance. Compared with IM, there was a trend toward higher acceptance among ED providers [aOR 2.5 (95% CI 0.71–8.88), p = 0.156]. **Conclusion:** Implementation of a novel CDS advisory was associated with a significant reduction in ammonia testing and a trend toward decreased serial testing, particularly in high-utilization departments such as IM, CC, and ED. These findings support CDS tools as an effective strategy for de-implementing low-value liver care. Lower acceptance rates in patients with a primary diagnosis of HE suggests persistent reliance on ammonia testing where HE is the primary reason for presentation.



Disclosures: Michael Gianarakis: Nothing to Disclose, Adam Mikolajczyk: Nothing to Disclose.

2218 | "THERE&RSQUO;S A PARADOX HERE": A QUALITATIVE EXPLORATION OF THE RESIDENT EXPERIENCE CARING FOR PATIENTS UNDER EVALUATION FOR LIVER TRANSPLANT

Annie Cravero[1] Justin Bullock[1] Mary White[2] Vandana Khungar[3] Kathleen Raskob[1], [1]University of Washington, [2]Yale-New Haven Hospital, [3]Yale University

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Background: Studies predict a 35% shortage in hepatologists by 2033 and efforts are needed to better understand resident experiences in order to support recruitment into hepatology careers. At many transplant centers, residents are on the front lines of clinical care for patients with end stage liver disease who are under consideration for liver transplant, and these experiences shape their initial impressions of hepatology. Few studies have described how learners experience the transplant evaluation process. This exploratory study aims to understand the experiences of internal medicine residents caring for patients under evaluation for liver transplant. **Methods:** This was a multi-institutional, qualitative study. The investigators purposefully sampled internal medicine residents at the University of Washington (UW) and Yale University who had cared for at least 1 hospitalized patient under evaluation for liver transplant. Participants completed a reflective drawing exercise followed by a semi-structured interview. Methodologically, we employed phenomenology to explore the nature and meaning of these experiences for residents. During analysis, we continuously moved between discussion of the component parts of the experience and the broader whole or global themes that define this experience for residents. **Results:** Fourteen internal medicine residents were interviewed; 8 from UW and 6 from Yale. The resident experience of the liver transplant evaluation process was defined by three paradoxes, or situations that held an inherent contradiction or conflict. Paradox 1: residents worked to keep a patient stable, while knowing that the patient would have more transplant priority if they clinically worsened. Paradox 2: residents attempted to serve as the primary provider for a patient, but lacked a full understanding of or control over the clinical plan (Figure 1). Paradox 3: patients with end stage organ failure and many disease related symptoms would typically receive a palliative approach to care, but in this situation have the most potential benefit from transplant and thus receive more aggressive interventions. The extent of interventions performed in the face of uncertain transplant candidacy was challenging for residents to reconcile (Figure 2). These paradoxes resulted in residents feeling dread, frustration, and insecurity in communicating with patients. Factors that mitigated discomfort with confronted paradoxes were 1) increased experience with pre-transplant patients, 2) transparency in the purpose of transplant related processes and procedures, and 3) effective interprofessional communication with transplant hepatologists. **Conclusion:** In order to bolster trainee interest in careers in hepatology, transplant hepatologists have the opportunity to support residents in navigating key paradoxes that can contribute to disempowerment and disillusionment when caring for pre-transplant patients.



Figure 1: Drawing by Participant 10 depicting their experience caring for a patient under evaluation for liver transplant. They described their drawing with the following quote: *"...when we were taking care of him every day, there would be a lot of discussion about whether or not he would be listed. And there's so many factors that go into that that I feel like we weren't privy to, so it was a lot of questions we couldn't answer. That's why there's a cloud around us talking to the patient."*

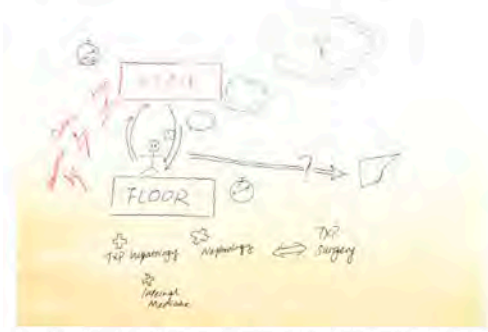


Figure 2: Drawing by Participant 6 depicting their experience caring for a patient under evaluation or liver transplant. The participant described their drawing with the following quote: *"...she was [transferred] to the ICU, and then after some stabilization, went to the [acute care] floor, and back and forth- that's what the arrows are saying. She's not happy. Then the whole team, including me, have this distant goal of, 'oh, things will just get better when she gets a transplant', but I don't really have an idea of when she's going to get the transplant or under what condition. So that's why I drew a long arrow towards this right side, towards this liver, but with a question mark saying that nobody has a crystal ball, and it very much depends on how often she goes to the ICU and for what reason. But time is ticking."*

Disclosures: Annie Cravero: Nothing to Disclose, Justin Bullock: Nothing to Disclose, Mary White: Nothing to Disclose, Vandana Khungar: Madrigal Pharmaceuticals: grant support, Bausch pharmaceuticals: site PI for alcohol associated hepatitis study, Kathleen Raskob: Nothing to Disclose.

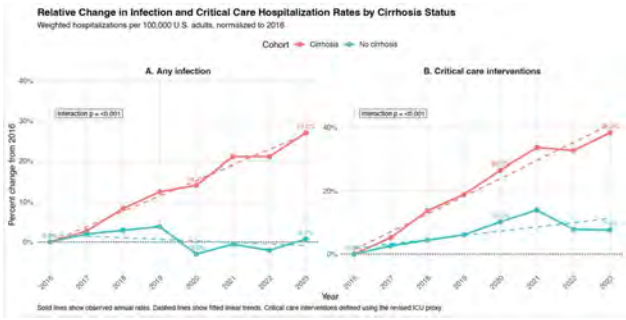
2219 | NATIONAL TRENDS IN INFECTION RELATED HOSPITALIZATIONS AND CRITICAL CARE RECEIPT AMONG ADULTS WITH CIRRHOSIS FROM 2016-2023

Charles Marvil[1] Sarpong Boateng[2] Bahar Saberzadeh-Ardestani[3] Tamar Taddei[4] Catherine Mezzacappa[5], [1]Yale New Haven Hospital, Yale University School of Medicine, [2]Department of Medicine Yale New Haven Health, Bridgeport Hospital, [3]Department of Internal Medicine, Yale School of Medicine, [4]VA Connecticut Health Care ,Department of Internal Medicine, Digestive Diseases, Yale University, [5]Deapartment of Internal Medicine, Division of Digestive Diseases, Yale School of Medicine

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Background: Patients with cirrhosis are at increased risk of infection secondary to immune dysfunction, leading to hepatic decompensation, hospitalization, and antibiotic use. Despite this, recent estimates of infection-related hospitalizations for adults with cirrhosis in the United States are lacking. We hypothesized that infection-related hospitalizations and critical illness have increased among adults with cirrhosis in the United States. **Methods:** The Nationwide Inpatient Sample includes a representative sample of adult hospitalizations from 2016–2023. Cirrhosis was defined using a validated ICD-10 consensus code set, infections using diagnosis codes adapted from prior literature, and critical care receipt using ICD-10 codes for critical care diagnoses and procedures. Weighted annual hospitalization rates with infection or critical care were calculated per 100,000 U.S. adults stratified by cirrhosis status. Rates were normalized to 2016 to assess relative change over time, and linear regression was used to compare temporal trends. **Results:** From 2016–2023, there were an estimated 233,774,384 hospitalizations. Of these, 7,145,693 (3.06%) were for individuals with cirrhosis and 47,941,391 (20.51%) involved infection of any type. Critical care was administered in 19,178,847 (8.2%). There were 2,113,884 (0.90%) hospitalizations with cirrhosis and infection and 1,292,320 (0.55%) with cirrhosis and critical care receipt. The relative change in hospitalization rates with any infection from 2016–2023 was greater for adults with cirrhosis than those without (+27.0% vs +0.7%; $p < 0.001$) (Figure 1A). Rates increased more rapidly for bacteremia/sepsis (+47.3% vs +26.4%; $p < 0.001$), cellulitis (+22.5% vs −2.8%; $p = 0.002$), endocarditis (+67.6% vs +21.8%; $p < 0.001$), fungal infection (+71.0% vs +14.7%; $p = 0.009$), and septic arthritis (+76.1% vs +49.6%; $p = 0.041$). Pyelonephritis/UTI rates remained stable among patients with cirrhosis and declined in those without (+1.1% vs −21.5%; $p < 0.001$). Critical care receipt similarly increased faster among patients with cirrhosis (+38.3% vs +7.7%; $p < 0.001$) (Figure 1B). In patients with cirrhosis, increases in critical care receipt were similar in those with (+37.5%) and without infection (+39.2%) ($p = 0.634$). **Conclusion:** In hospitalized patients with cirrhosis, diagnosis of any infection has increased rapidly since 2016, driven by serious bacterial and fungal infections. While hospitalizations requiring critical care interventions have also increased significantly compared to those without cirrhosis, infection was not associated with this increase in critical care receipt. These findings highlight the need for ongoing research to better understand the intersection of cirrhosis, infection, and critical illness.



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2220 | PREVALENCE AND RISK FACTORS OF LIVER FIBROSIS AND STEATOSIS IN GANSU, CHINA: A PROSPECTIVE COMMUNITY-BASED COHORT STUDY

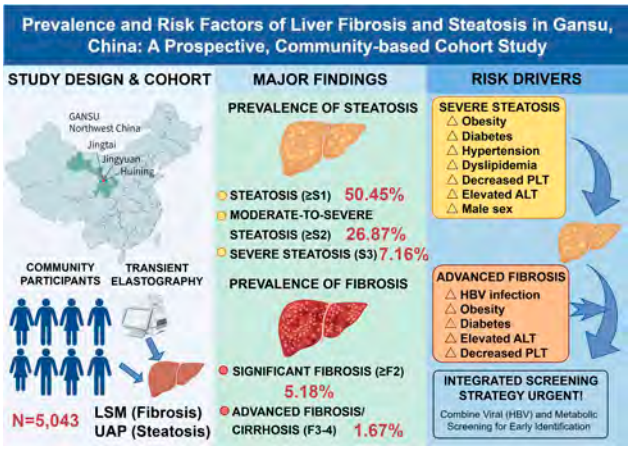
Xueni Ma[1] Junhong Yang[2] Bin Peng[3] Min Zhang[4] Chengbo Yang[5] Yan Yang[6] Jianping Ji[7] Weidong Ren[7] Anxing Zhang[8] Xinjian Yang[9] Deqiang Luo[10] Liang Wang[1], [1]Department of Infectious Diseases, The Second Hospital of Lanzhou University, [2]Baiyin Central Hospital, Baiyin, China, [3]Department of Infectious Diseases, Jingtai County People's Hospital, Baiyin, China, [4]Department of Infectious Diseases, Huining County People's Hospital, Baiyin, China, [5]Department of Geriatrics, Jingyuan County People's Hospital, Baiyin, China, [6]Physical Examination Center, Baiyin Central Hospital, Baiyin, China, [7]Health Management Center, The First People's Hospital of Baiyin, Baiyin, China, [8]Department of Gastroenterology, Baiyin Second People's Hospital, Baiyin, China, [9]Department of Ultrasound, Baiyin Second People's Hospital, Baiyin, China, [10]Medical Affairs Department, Baiyin Central Hospital, Baiyin, China

Background: The epidemiology of chronic liver disease in China is shifting from viral hepatitis to metabolic-associated liver disease. However, population-based data from Northwest China remain scarce. This study aimed to assess the prevalence and independent risk factors of liver fibrosis and steatosis in the general population of Gansu Province, China. **Methods:** This prospective, community-based cohort study enrolled 5,043 eligible participants across three regions in Gansu (Huining, Jingtai, and

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Jingyuan) in 2025. All participants underwent anthropometric measurements, laboratory tests, transient elastography (TE), and a structured questionnaire. Fibrosis and steatosis were assessed via liver stiffness measurement (LSM) and ultrasound attenuation parameter (UAP). Fibrosis was staged as F0 (<7.3 kPa), F1 (7.3–7.84 kPa), F2 (7.85–9.9 kPa), and F3-4 (≥10.0 kPa). Steatosis grades S1, S2, and S3 were defined using UAP cutoffs of 244, 269, and 296 dB/m, respectively. Independent risk factors were identified using multivariate logistic regression. **Results:** Among 5,043 participants (median age 46 years; 59.8% female), significant fibrosis (≥F2) was present in 5.18% (95% CI, 4.56-5.79), while advanced fibrosis/cirrhosis (F3-4) was detected in 1.67% (95% CI, 1.31-2.02). The prevalence of steatosis (≥S1) was 50.45% (95% CI, 49.07-51.85), including 26.87% with moderate-to-severe steatosis (≥S2) and 7.16% with severe steatosis (S3). Independent predictors of advanced fibrosis included HBV infection (OR 3.19, 95% CI 1.72-5.92), obesity (OR 5.14, 95% CI 4.14-8.42), diabetes (OR 3.55, 95% CI 2.02-6.25), elevated ALT (OR 3.86, 95% CI 2.96-7.60), and decreased platelet count (OR 6.45, 95% CI 2.03-20.52). Severe steatosis was independently associated with obesity (OR 17.62, 95% CI 13.50-23.01), diabetes (OR 1.73, 95% CI 1.17-2.55), hypertension (OR 1.50, 95% CI 1.14-1.96), dyslipidemia (OR 1.36, 95% CI 1.04-1.78), decreased platelet count (OR 4.16, 95% CI 1.46-11.84), elevated ALT (OR 2.17, 95% CI 1.46-3.22), and male sex (OR 1.70, 95% CI 1.18-2.46). **Conclusion:** Liver fibrosis and steatosis are highly prevalent in the community population of Gansu Province, driven by concurrent metabolic dysfunction and chronic HBV infection. These findings highlight the urgent need for integrated metabolic and viral screening strategies to facilitate early identification and prevent progression to advanced liver disease in this region.



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2221 | GENERATIVE AI IN SHAPING THE PATIENT-CLINICIAN INTERACTION IN LIVER DISEASE CARE

Mustafa Behan[1] Jutta Kurz[1] Rachma Purnama[2] Tresha Elaine Ramonal[1] Lorrinda Gray-Davis[3] Youssef Amjahdi[4] Richard Jaenisch[3] David Jaenisch[3] Michael Tunkelrott[2] Emmanuel Gorospe[5] Tarek Hassanein[6], [1]Amsety, [2]Amsety LLC, [3]None, [4]WhoFinance/Amsety, [5]Burrell College of Osteopathic Medicine, [6]Southern California Liver Centers

Background: Generative AI (Gen AI) is reshaping how patients (pts) access health information by offering personalized conversational support. With high-reaching tools such as ChatGPT, pts are increasingly turning to AI for health-related information, especially among those with chronic conditions like liver disease. With the boom in reliance on search engines and AI sources over healthcare professionals, it is critical to address questions about trust, the ability to discern information from misinformation, the evolving patient-doctor relationship as well as how Gen AI can be integrated to the benefit of pts with liver disease, including pt engagement and shared decision-making. **Methods:** The Amsety database consists of 650,000 individuals living with liver diseases in the US. We report on the results of 210 respondents surveyed about Generative AI. The survey assessed awareness and use of Gen AI, as well as its perceived usefulness, trust, accuracy, and how pts compared and integrated AI insights with advice from healthcare professionals. **Results:** 70% were recently diagnosed with liver condition (up to 3 years earlier). 32% have MASLD/MASH and 14% Alcoholic Liver Disease. 13% had cirrhosis. 53% of respondents are managed by specialists and 32% by primary care. 50% use AI for medical information, 40% have not used it but are curious, and 10% have no interest. Among users, 38% use AI several times a week, mainly ChatGPT (70%), Google Gemini (57%), and Meta AI (35%). AI is used for understanding diagnosis/disease stage (76%), explaining test results (59%), and dietary/nutrition guidance (54%). Overall experience of liver pts after using AI: 55% feel more informed about their condition, 45% are more confident speaking with their doctors, and 39% understand their treatment plan more clearly. Main concerns of use include accuracy (62%), privacy (37%), and over-reliance on AI (26%). Other sources of information include specialist/care team

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(67%), health websites (50%), and hospital/clinic portals (38%). After using AI, 64% bring the information to their provider while 36% rarely or never do. 74% change diet or eating habits after AI advice, 31% request a test/referral, and 22% start or stop using a supplement. **Conclusion:** Generative AI is becoming a common tool for liver disease patients to understand their condition and well-being. It helps pts feel more informed and is frequently used as a resource to better understand clinical discussions. However, trust in AI remains dependent on alignment with professional medical advice, with ongoing concerns regarding accuracy and data privacy. There's a need to develop curated, evidence-based AI platforms to deliver trusted, high-quality pt information. This will better enable providers to integrate Gen AI into their clinical practice to support informed decision-making, enhance patient education, and ensure its safe and effective use in liver care.

Disclosures: Mustafa Behan: Nothing to Disclose, Jutta Kurz: Nothing to Disclose, Rachma Purnama: Amsety GmbH: Employee, Tresha Elaine Ramonal: Amsety GmbH: Employee, Lorrinda Gray-Davis: Nothing to Disclose, Youssef Amjahdi: Nothing to Disclose, Richard Jaenisch: Nothing to Disclose, David Jaenisch: Nothing to Disclose, Michael Tunkelrott: Nothing to Disclose, Emmanuel Gorospe: Castle Biosciences: Employee, Tarek Hassanein: AbbVie: Speaker and Research Support, Gilead: Speaker and Research Support, HepQuant Shunt: Advisor, Madrigal: Advisor and Research Support, Amgen: Grant/Research Support, Astra Zeneca: Grant/Research Support, Boehringer- Ingelheim: Grant/Research Support, COUR: Grant/Research Support, Escient: Grant/Research Support, Galectin: Grant/Research Support, Grifols: Grant/Research Support, Intercept: Grant/Research Support, Janssen: Grant/Research Support, Merck: Grant/Research Support, Mirum: Grant/Research Support, NeuroBo: Grant/Research Support, Novartis: Grant/Research Support, Novo Nordisk: Grant/Research Support, Pfizer: Grant/Research Support, Regeneron: Grant/Research Support, Salix Pharmaceuticals: Grant/Research Support, Takeda: Grant/Research Support, Akero: Grant/Research Support, Ipsen: Grant/Research Support, Kowa: Grant/Research Support, Bristol-Myers Squibb: Grant/Research Support, DURECT: Grant/Research Support, HepQuant: Grant/Research Support, Terns Pharmaceuticals: Grant/Research Support, Mallinckrodt: Speaker and Research Support, Eli Lilly: Grant/Research Support, PharmaIn: Grant/Research Support, Sonic incytes: Grant/Research Support, Tensor Bio: Grant/Research Support, 89Bio: Grant/Research Support, Terns Pharmaceuticals: Grant/Research Support, Nterica: Consultant, Atea: Grant/Research Support, Harbinger: Grant/Research Support, Sanofi-Aventis: Grant/Research Support, CurveBio: Grant/Research Support, AbbVie: Speaker and Research Support, Gilead: Speaker and Research Support, HepQuant Shunt: Advisor, Madrigal: Advisor and Research Support, Amgen: Grant/Research Support, Astra Zeneca: Grant/Research Support, Boehringer- Ingelheim: Grant/Research Support, COUR: Grant/Research Support, Escient: Grant/Research Support, Galectin: Grant/Research Support, Grifols: Grant/Research Support, Intercept: Grant/Research Support, Janssen: Grant/Research Support, Merck: Grant/Research Support, Mirum: Grant/Research Support, NeuroBo: Grant/Research Support, Novartis: Grant/Research Support, Novo Nordisk: Grant/Research Support, Pfizer: Grant/Research Support, Regeneron: Grant/Research Support, Salix Pharmaceuticals: Grant/Research Support, Takeda: Grant/Research Support, Akero: Grant/Research Support, Ipsen: Grant/Research Support, Kowa: Grant/Research Support, Bristol-Myers Squibb: Grant/Research Support, DURECT: Grant/Research Support, HepQuant: Grant/Research Support, Terns Pharmaceuticals: Grant/Research Support, Mallinckrodt: Speaker and Research Support, Eli Lilly: Grant/Research Support, PharmaIn: Grant/Research Support, Sonic incytes: Grant/Research Support, Tensor Bio: Grant/Research Support, 89Bio: Grant/Research Support, Terns Pharmaceuticals: Grant/Research Support, Nterica: Consultant, Atea: Grant/Research Support, Harbinger: Grant/Research Support, Sanofi-Aventis: Grant/Research Support, CurveBio: Grant/Research Support.

2222 | A CUMULATIVE LIVER DAMAGE INDEX DERIVED FROM ROUTINE BLOOD TESTS HAS THE POTENTIAL TO TRACK POPULATION METABOLIC HEALTH AND THE RESPONSE TO POPULATION-LEVEL INTERVENTIONS

Katie Denver[1] Timothy Jobson[1] Christina Owen[1] Neil Stevens[2] Axelle Caudrillier[3] Yasmin Hamadache[3] Heath O'Brien[3] Louise Campbell[4] Patrick Short[3] Jamie Webb[3] Katie Barnes[3], [1]Somerset NHS Foundation Trust, [2]Predictive Health Intelligence, [3]Sanogenetics, [4]Tawazum Health

Background: The Cumulative Liver Damage Index (CLDI), derived from longitudinal routine alanine aminotransferase (ALT) data, identifies clinically significant hepatic fibrosis (F2+) with ROC-AUC 0.884 and number-needed-to-scan of 8 in the LiveWell study (EASL 2026). We hypothesised that CLDI risk group classification captures underlying metabolic phenotype, and that serial population-level CLDI distributions could therefore serve as a novel marker of population metabolic health to track the impact of population-level

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interventions including NHS weight management programmes and GLP-1 prescribing, as well as longitudinal surveillance of the global trajectory of obesity and metabolic dysfunction. **Methods:** Secondary analysis of the LiveWell study (994 participants, aged 25-55, Somerset, United Kingdom). Participants were classified as control or high CLDI risk group. Four metabolic markers were compared between groups: BMI, hepatic steatosis by controlled attenuation parameter (CAP score, available in FibroScan-confirmed participants, N = 627), mean HbA1c (24-month window), and mean LDL cholesterol (24-month window). Comparisons were made across six pre-specified strata: sex (female/male) by age group (all/25-35/45-55). Wilcoxon rank-sum tests were used with rank-biserial correlation (r) as effect size. Zeros were treated as missing values for HbA1c and LDL, consistent with non-measurement in primary care records. **Results:** The high CLDI risk group had consistently higher BMI across all six sex and age strata ($p < 0.05$ in all; $r = 0.23$-0.57) and higher CAP score in five of six strata ($r = 0.30$-0.38), directly demonstrating that CLDI classification captures hepatic steatosis at a population level. HbA1c was significantly elevated in the high-risk group in female strata (all-age females $p < 0.0001$, $r = 0.21$; 45-55 females $p < 0.0001$, $r = 0.24$), with a consistent but non-significant directional trend in males, consistent with known sex differences in glycaemic risk trajectories. LDL was elevated in females (all-age $p = 0.046$) but attenuated or reversed in male strata, most plausibly reflecting differential statin prescribing in higher-risk male patients. Direction of effect was positive (higher in high-risk) for 22 of 24 comparisons across all variables and strata. **Conclusion:** CLDI risk group classification is consistently associated with higher BMI and hepatic steatosis, and with glycaemic stress particularly in women, demonstrating that CLDI functions as a metabolic health indicator rather than a liver-specific signal. Because CLDI is computable from routine blood test records, serial population-level CLDI distributions represent a novel, low-cost tool for tracking population metabolic health over time. Any health community with access to longitudinal routine ALT data — including those implementing hepatoSIGHT — can apply this approach to evaluate the impact of population health interventions.

Disclosures: Katie Denver: Nothing to Disclose, Timothy Jobson: Predictive Health Intelligence Ltd: Executive role, Predictive Health Intelligence Ltd: Stock – privately held company, Christina Owen: Nothing to Disclose, Neil Stevens: Nothing to Disclose, Axelle Caudrillier: Nothing to Disclose, Yasmin Hamadache: Nothing to Disclose, Heath O'Brien: Nothing to Disclose, Louise Campbell: Nothing to Disclose, Patrick Short: Nothing to Disclose, Jamie Webb: Nothing to Disclose, Katie Barnes: Nothing to Disclose.

2223 | UNDERSTANDING LIVER HEMANGIOMAS IN THE ERA OF ARTIFICIAL INTELLIGENCE: A READABILITY ANALYSIS OF WEB-BASED AND LLM-GENERATED CONTENT

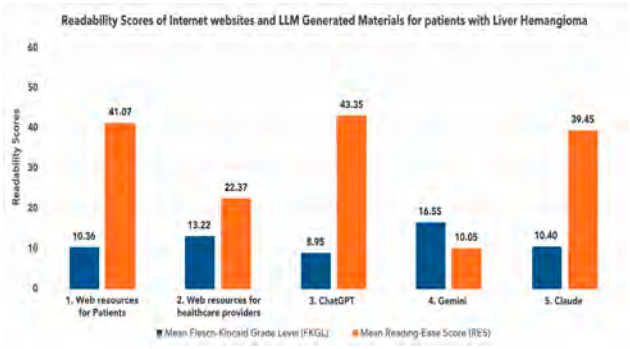
Medha Sharath[1], [1]University of South Dakota

Background: Liver hemangiomas are the most common benign liver tumors. While their exact cause and indications for surgery remain unclear, most lesions are asymptomatic and only require monitoring. Due to the uncertainty surrounding this diagnosis, many patients seek information online in addition to guidance from their physicians. With the increasing use of large language models (LLMs) such as ChatGPT, Gemini, and ClaudeAI, online medical information is becoming more accessible. Because the American Medical Association (AMA) recommends that patient education materials be written at or below a 6th-grade reading level, we evaluated and compared the readability of internet-based and LLM-generated content on liver hemangiomas. **Methods:** A Google search query for the term “liver hemangioma” was used to retrieve the top 100 results. Websites were excluded due to irrelevance, duplication, or video format. The remaining websites were categorized according to their intended audience: either patients or healthcare professionals (HCPs). In parallel, ChatGPT 5.5, Gemini 3.5 Flash, and Claude Sonnet 4.6 were each prompted with two standard questions: “What is liver hemangioma?” and “How is liver hemangioma treated?”. The readability of patient and HCP focused websites, and the 3 LLM outputs was evaluated using Flesch Reading Ease Scores (RES) and Flesch-Kincaid Grade Levels (FKGL), with categories ranging from 5th grade (90-100), 6th grade (80-90), 7th grade (70-80), 8th-9th grade (60-70), 10th-12th grade (50-60), College (30-50), to College Graduate (0-30). Statistical analysis was performed using one-way ANOVA. **Results:** Out of the 100 websites, 64 were included in the final analysis. 43 (67.2%) websites were patient directed and 21 (32.8%) were HCP directed. Mean Flesch-Kincaid Grade Level was $M = 10.36$ ($SD = 2.16$) for patient directed websites, $M = 13.22$ ($SD = 2.37$) for HCP directed websites, $M = 8.96$ ($SD = 1.45$) for ChatGPT, $M = 16.55$ ($SD = 0.05$) for Gemini, and $M = 10.40$ ($SD = 1.00$) for Claude. Mean Reading Ease Score also varied across groups: $M = 41.07$ ($SD = 12.42$) for patient directed websites, $M = 22.37$ ($SD = 11.56$) for HCP directed websites, $M = 43.35$ ($SD = 11.85$) for ChatGPT, $M = 10.05$ ($SD = 0.05$) for Gemini, and $M = 39.45$ ($SD = 10.65$) for Claude. One-way ANOVA test demonstrated a significant difference in the FKGL amongst the five groups ($F(4, 65) = 9.16$, $p < .001$, $\eta^2 = 0.36$), indicating a large effect size. There was also a

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significant magnitude of difference in RES across the groups ($F(4, 65) = 10.37$, $p < .001$, $\eta^2 = 0.39$). **Conclusion:** Both website based and LLM generated content exceeded the 6th-grade reading level recommended by the AMA. Most patient education materials were at a college reading level. While ChatGPT performed better, it still remained at a 10th-12th grade level. These findings highlight the need for the development of more appropriate patient facing materials at suitable reading levels in order to improve understanding of liver hemangiomas.

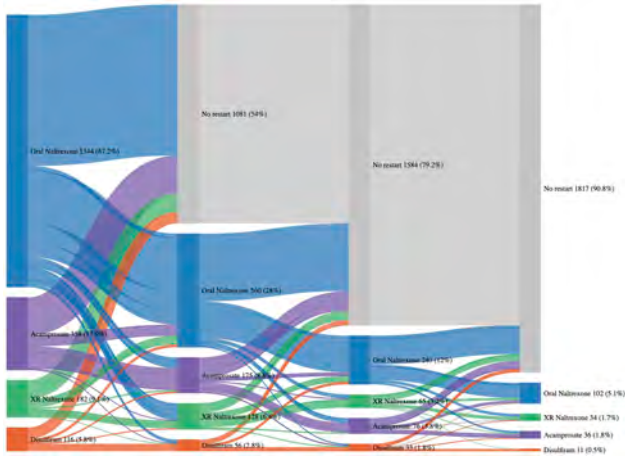


Disclosures: Medha Sharath: Nothing to Disclose.

2224 | ALCOHOL USE DISORDER TREATMENT DISCONTINUATION AND RE-INITIATION PATTERNS AMONG ALL OF US RESEARCH PROGRAM PARTICIPANTS

Lidia Rodriguez[1] Michael Rothberg[2] Ha Tran[2] Hamlet Gasoyan[2] Katharine Bradley[3] Phuc Le[2], [1]Case Western Reserve University, [2]Cleveland Clinic, [3]Kaiser Permanente Washington Health Research Institute

Background: Despite the availability of FDA-approved medications for alcohol use disorder (AUD), real-world treatment persistence of AUD medications remains low. Understanding patterns of AUD medication discontinuation and re-initiation, and associated factors, is essential for developing interventions that support long-term treatment engagement. **Methods:** We conducted a retrospective cohort study using All of Us v8 data. Adults aged ≥ 18 with AUD diagnoses were included if they initiated AUD medications (naltrexone, acamprosate, or disulfiram) between January 1, 2018 and October 1, 2022, with follow-up through October 1, 2023. New use was defined with a 180-day medication-free washout period before the initiation (index) date, discontinuation as the first gap ≥ 60 days without medication after the index date, and re-initiation as the first new medication record after discontinuation. We estimated the probability of discontinuation within 1 year of treatment initiation and re-initiation within 1 year of discontinuation using Kaplan-Meier curves. Time to each outcome and associated patient factors were examined by Cox proportional hazards models. **Results:** Among 2000 patients initiating AUD medications (mean age 55.7 years; 58.9% male; 52.9% Non-Hispanic White), 39.5% (95% CI: 37.3%-41.7%) discontinued within one year; oral naltrexone had the lowest discontinuation rate (37.1%, 95% CI: 34.4%-39.7%). Among those who discontinued any AUD medication ($N = 919$), the median time to discontinuation was 150 days (IQR: 192), and 70.8% (95% CI: 67.8%-73.8%) re-initiated within one year. Re-initiation rates did not differ by medication ($p = 0.10$). Among those who re-initiated, median time to re-initiation was 102 days (IQR: 181). Oral naltrexone was the most common re-initiation medication (Figure). In multivariable models, alcohol-related conditions in the past year and extended-release (vs. oral) naltrexone as index medication were positively associated with discontinuation, while having less than high-school degree was negatively associated. Among patients who discontinued, those not working (vs. working) were more likely to re-initiate. **Conclusion:** Over one-third of patients discontinued AUD medications within one year of initiation, but the majority of them reinitiated within the following year. Discontinuation rate significantly differed by medication while re-initiation rate did not. Interventions to address early treatment discontinuation and support re-initiation after treatment gap in AUD care are needed.



Disclosures: Lidia Rodriguez: Nothing to Disclose, Michael Rothberg: Moderna: Stock - publicly traded company, Ha Tran: Nothing to Disclose, Hamlet Gasoyan: Nothing to Disclose, Katharine Bradley: Nothing to Disclose, Phuc Le: Nothing to Disclose.

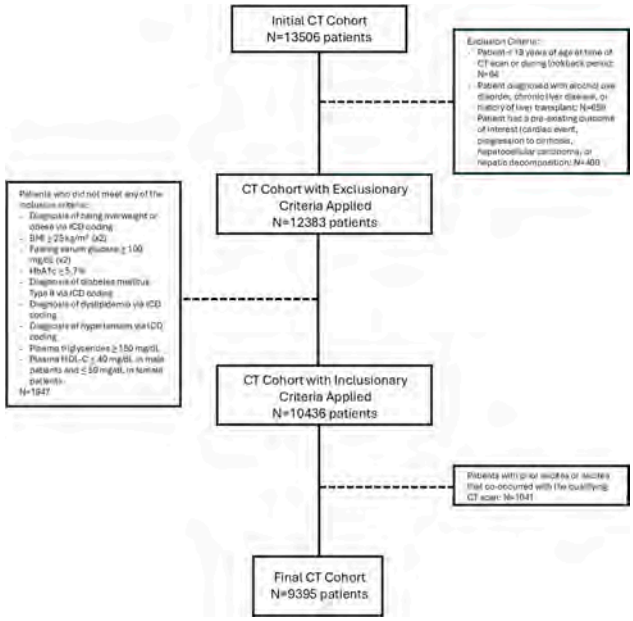
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2225 | ICD-CODED STEATOTIC LIVER DISEASE IS A MARKER OF ADVANCED DISEASE IN PATIENTS WITH CARDIOMETABOLIC RISK IN A REAL-WORLD OPPORTUNISTIC CT COHORT

Vignesh Rajasekaran[1] Asad Aali[2] Alexandria Jensen[3] Allison Kwong[4] Andrew Johnston[5] Ates Fettahoglu[2] Hye Na[5] Luyao Shen[5] Taiyo Shimizu[5] Luke Yoon[5] David Svec[6] Robert Boutin[5] Jason Hom[6] Akshay Chaudhari[2] Laura Derry[6], [1]Stanford University, Department of Internal Medicine, [2]Stanford University, Department of Biomedical Physics, [3]Stanford University, Quantitative Sciences Unit, [4]Stanford University Medical Center, [5]Stanford University, Department of Radiology, [6]Stanford University, Department of Hospital Medicine

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is highly prevalent yet frequently underrecognized until advanced disease. We previously demonstrated that opportunistic CT-based detection using Comp2Comp, a validated deep learning algorithm, identifies substantially more patients with steatotic liver disease (SLD) than standard clinical workflows. Whether formally recognized (ICD-coded) SLD represents distinct clinical risk compared with imaging-detected disease has not been directly examined. We compared all-cause mortality, cirrhosis progression, and hepatic decompensation between clinically recognized and unrecognized SLD in patients with ≥1 cardiometabolic risk factor for MASLD. **Methods:** We conducted a retrospective cohort study of adults ≥18 years old who had ≥ 1 cardiometabolic risk factor for MASLD in the 3 years preceding the qualifying contrast-enhanced or non-contrast abdominal CT at a multisite academic health system (2013–2018, 2021–2024). Patients were classified into two groups: (1) ICD-coded SLD prior to or within 30 days of the qualifying CT scan (clinically recognized [CR]) or (2) incidentally detected SLD by radiology report or Comp2Comp without ICD-coding (clinically unrecognized [CU]). Patients with ICD-9 or ICD-10 diagnosis codes for other chronic liver disease (including cirrhosis), alcohol use disorder, prior hepatic decompensation, prior hepatocellular carcinoma (HCC), liver transplant, or a cardiovascular event within 30 days of qualifying CT were excluded. All-cause mortality, incident progression to cirrhosis, and incident hepatic decompensation were modeled with modified Poisson regression and multivariable Cox analysis adjusted for demographics and comorbidities. **Results:** Among 2,361 patients with evidence of SLD on CT (CR n = 553; CU n = 1,808), median follow up was 2.2 years (IQR, 0.85, 3.41). CU was associated with lower all-cause mortality (RR 0.59; 95% CI 0.45–0.76), incident cirrhosis (n = 62 events; RR 0.20; 95% CI 0.15–0.27), and incident hepatic decompensation (n = 139 events; RR 0.44; 95% CI 0.32–0.59), all p < 0.001, compared to CR. In multivariable Cox models adjusted for demographics and comorbidities, CU patients had substantially lower hazards of death (HR 0.56; 95% CI 0.42–0.76), incident cirrhosis (HR 0.19; 95% CI 0.11–0.33), and incident hepatic decompensation (HR 0.41; 95% CI 0.29–0.58), all p < 0.001. HCC (n = 8) and liver transplant (n = 3) were too infrequent for formal modeling. **Conclusion:** Clinically recognized SLD in patients with cardiometabolic risk was associated with worse mortality and liver-related outcomes than imaging-detected but unrecognized disease, likely reflecting a sicker, more advanced cohort despite adjustments for comorbidities. Imaging-detected but unrecognized SLD may represent an earlier, still-actionable disease stage and high-yield target for FIB-4-first risk stratification pathways.



Disclosures: Vignesh Rajasekaran: Nothing to Disclose, Asad Aali: Nothing to Disclose, Alexandria Jensen: Nothing to Disclose, Allison Kwong: Nothing to Disclose, Andrew Johnston: Nothing to Disclose, Ates Fettahoglu: Nothing to Disclose, Hye Na: Nothing to Disclose, Luyao Shen: Nothing to Disclose, Taiyo Shimizu: Nothing to Disclose, Luke Yoon: Nothing to Disclose, David Svec: Nothing to Disclose, Robert Boutin: GE Healthcare: Grant/Research Support, Jason Hom: Cognita Imaging: Stock – privately held company, Akshay Chaudhari: Nothing to Disclose, Laura Derry: Nothing to Disclose.

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2226 | PREVALENCE OF HEPATITIS B VIRUS INFECTION, TOTAL ANTI-HBC POSITIVITY, AND ISOLATED ANTI-HBC AMONG 118,141 INDIVIDUALS UNDERGOING ROUTINE HEALTH CHECK-UPS AT MEDIC MEDICAL CENTER IN THE SOUTH OF VIETNAM

Thuy Pham[1] Dat Ho Tan[2] Nguyen Bao Toan[3] Hai Phan[3] Vi Nguyen Thi Tuong[3], [1]Medic Medical Center, Phan Chau Trinh University, [2]Medic Medical Center - Ho Chi Minh City- Viet Nam, [3]Medic Medical Center Ho Chi Minh City Vietnam

Background: This study aimed to (1) determine the prevalence of HBV serologic subgroups identified by the triple test, particularly iAHBc, among individuals in Southern Vietnam; (2) assess the associations of HBsAg positivity, anti-HBc positivity, and iAHBc with age and sex; and (3) examine the associations between HBV serologic subgroups and both liver fibrosis severity and HCC risk. **Methods:** In this cross-sectional study, at MEDIC Medical Center, HCM City (January 2023–December 2025), were simultaneously tested for HBsAg, anti-HBs, and anti-HBc; Participants were classified into five serologic groups: at risk (all negative), vaccine-induced immunity (anti-HBs only), resolved infection (anti-HBs and anti-HBc positive, HBsAg negative), iAHBc (anti-HBc only), and current infection (HBsAg positive). Liver fibrosis was staged by FibroScan (F0–F4), and HCC was ascertained from clinical records. Multivariable logistic regression estimated prevalence odds ratios (PORs) and 95% confidence intervals (CIs) for associations of serologic subgroups with age, sex, liver fibrosis, and HCC. **Results: :** Among 118,141 individuals (55.5% women, 44.5% men; mean age 44 ± 14 years), the prevalences of HBsAg, anti-HBs, and anti-HBc positivity were 6.3%, 56.1%, and 44.1%, respectively. Based on triple-test results, participants were classified as at risk (31.6%), vaccine-induced immunity (24.3%), resolved HBV infection (31.7%), iAHBc (6.2%), or current HBV infection (6.3%). At-risk and vaccine-induced immunity groups predominated among women and younger individuals, whereas resolved infection, iAHBc, and HBsAg positivity were more frequent in men. Resolved infection and iAHBc increased monotonically with age, while HBsAg positivity peaked at 40–49 years (7.5%) and declined thereafter ($p < 0.001$). In multivariable analysis, men had higher odds of HBsAg, anti-HBc, and iAHBc positivity than women (POR = 1.47, 1.39, and 1.55, respectively; $p < 0.001$). Relative to age < 20 years, HBsAg positivity peaked at 40–49 years (POR = 3.41; 95%CI 2.77-4.26), whereas anti-HBc and iAHBc increased monotonically, reaching PORs of 45.16 and 33.85, respectively, at ≥ 60 years. Compared with the at-risk group, the iAHBc group showed markedly higher advanced fibrosis prevalence (F3–F4: 21.9% vs. 9.3%) and higher odds of HCC (POR = 2.77; 95%CI 1.59-4.98), second only to current HBV infection (POR = 9.91; 95%CI 6.05-17.0). This pattern was consistent in both sexes. **Conclusion:** This is the largest study in Vietnam to apply a triple HBV serologic testing panel. Importantly, iAHBc was associated with 2.77-fold higher odds of HCC and a substantially higher prevalence of advanced fibrosis (F3–F4) compared with triple-seronegative individuals. These findings support consideration of the triple-marker panel for routine HBV screening in Vietnam.
Disclosures: Thuy Pham: Nothing to Disclose, Dat Ho Tan: Nothing to Disclose, NGUYEN BAO TOAN: Nothing to Disclose, Hai Phan: Nothing to Disclose, Vi Nguyen Thi Tuong: Nothing to Disclose.

2227 | PUBLIC DISCOURSE AND GOOGLE SEARCH PATTERNS AROUND NON-FDA-APPROVED WEIGHT LOSS COMPOUNDS: A MULTI-PLATFORM INFODEMIC ANALYSIS

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Background: Non-FDA-approved compounds, including investigational drugs (retatrutide, cagrilintide), grey-market peptides (BPC-157, ipamorelin), and research chemicals (MK-677), are increasingly discussed online as weight loss alternatives. We hypothesized that GLP-1 coverage restrictions may drive health-seeking behavior toward these alternatives. Their use remains poorly characterized at the population level. Social media platforms offer insights into emerging trends warranting clinical and research attention. **Methods:** We conducted a longitudinal digital analysis of Reddit posts (Arctic Shift archive, 30+ subreddits, January 2025–May 2026) and Google Trends data (pytrends, 72 weeks) for 48 non-FDA-approved weight loss compounds classified into three groups: investigational pharmaceuticals, grey-market peptides, and non-peptide research chemicals. Compound mentions, context themes (liver, cost, insurance, side effects, stacking, sourcing), and US state signals were extracted via keyword flagging. VADER sentiment analysis was applied to all compound-mentioning posts. Pearson correlations assessed synchrony between Reddit volume and Google search interest at compound and temporal levels. **Results:** Of 1,269 cleaned Reddit posts, 1,059 (83%) mentioned at least one compound. Retatrutide (GIP/GLP-1/glucagon agonist) dominated (920 posts, 86.9%), followed by BPC-157 (gut peptide) (111, 10.5%), MOTS-c (mitochondrial peptide)(76,

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7.2%), tesamorelin (a growth hormone-releasing factor) (68, 6.4%), and ipamorelin (ghrelin mimetic)(67, 6.3%). Liver-related terms co-occurred in 474 posts (44.8%) − the single most prevalent context theme, exceeding cost (9.1%), insurance (4.2%), side effects (21.8%), and weight loss (21.3%). Sentiment was strongly positive across all compounds (68% positive, avg VADER score 0.379), including among liver-mentioning posts (74.9% positive). Google Trends showed normalized search index >10 (out of 100) for 43 of 48 compounds; sermorelin, melanotan, and retatrutide led cumulative search volume. Eight compounds showed statistically significant Reddit–Google temporal correlation, with the strongest synchrony for retatrutide ($r = +0.837$), tesamorelin ($r = +0.783$), and ipamorelin ($r = +0.756$; all $p < 0.05$). Reddit liver discussion volume remained consistently elevated (30–60% of posts monthly), while Google liver search interest rose sharply in early 2026 ($r = -0.443$, $p = 0.075$), suggesting divergent hepatic concern triggers across platforms. **Conclusion:** Online discourse around unregulated weight loss compounds rose notably in early 2026 following GLP-1 coverage restrictions. Liver-related discussions dominated, appearing in nearly half of relevant posts, yet sentiment remained persistently positive. These findings highlight an emerging infodemic with implications for hepatology practice, patient counseling, and regulatory surveillance.

Figure 1. Online Discourse Around Non-FDA-Approved Weight Loss Compounds: Platform-Specific Liver Signal Divergence (United States, January 2025–May 2026)

Monthly Reddit liver discussion versus Google liver search interest (Pearson r=−0.443, p=0.075).



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2228 | EFFECTIVE STRATEGIES FOR PEOPLE WHO INJECT DRUGS TOWARD HCV ELIMINATION IN JAPAN

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Background: The World Health Organization aims to eliminate hepatitis C virus (HCV) infection by 2030. In Japan, improving access to HCV testing and treatment among people who inject drugs (PWID) remains a major challenge because this population has a high prevalence of HCV infection. Since the budget for HCV treatment in prisons is limited, only a small number of incarcerated individuals can receive direct-acting antiviral (DAA) therapy. Therefore, establishing an effective care cascade linking released individuals to community-based medical care is essential. We report our institutional efforts to construct an effective HCV care cascade for PWID using Japan's unique community-based rehabilitation model and Hepatitis Medical Care Coordinator (HMCC) system. **Methods:** Following an official notification issued in February 2024 by the Correction Bureau and Rehabilitation Bureau of the Ministry of Justice encouraging collaboration between regional liver disease centers and probation services, our institution initiated cooperation with the Yamaguchi Probation Office and volunteer probation officers. Educational lectures regarding liver disease and HCV elimination among PWID were provided to probation officers, and educational materials promoting HCV testing and medical consultation were distributed. We also visited a Drug Addiction Rehabilitation Center (DARC), where lectures and questionnaire surveys were conducted to identify barriers to HCV care among PWID and explore effective intervention strategies. **Results:** More than 60 volunteer probation officers attended the educational sessions, and three probation officers were newly certified as HMCCs in fiscal year 2025. Educational sessions were also conducted for eight PWID residents at the DARC facility. Questionnaire surveys revealed insufficient knowledge regarding HCV transmission risks associated with drug use and highlighted the presence of strong social stigma toward drug users in Japan. We additionally found that many DARC residents regularly attended psychiatric hospitals for addiction treatment. Based on this finding, a collaborative liver disease care system was established with a psychiatric hospital. Consequently, two previously untreated patients with chronic HCV infection, including PWID, were promptly introduced to inpatient DAA therapy and successfully achieved sustained virological response. **Conclusion:** Collaboration among probation services, volunteer probation officers, DARC facilities, and psychiatric hospitals enabled effective outreach and reliable HCV treatment intervention for PWID. These activities may contribute to establishing a sustainable and effective HCV care cascade for PWID in Japan.

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2229 | FIB-4 PERFORMANCE FOR RULING OUT ADVANCED FIBROSIS IN A PREDOMINANTLY BLACK PRIMARY CARE COHORT

Alexander Zhu[1] Meghan Cloutier[1] Melissa Bravo[1] Amera Alsalahi[1] Eliane Atallah[1] Jenna Dawson[1] Ravneet Kaur[1] Edward Tamale[1] Lan Nguyen[1] Mark Rayev[1] Inioluwa Dada[1] Brady Jensen[1] Ikjot Singh[1] Anthony Martinez[1], [1]University at Buffalo

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) affects roughly 25–30% of US adults, and advanced fibrosis is the strongest predictor of liver-related mortality. The 2023 American Association for the Study of Liver Diseases (AASLD) guidance endorses the Fibrosis-4 (FIB-4) index as first-line non-invasive testing for advanced fibrosis in primary care, with age-adjusted low cutoffs (<1.3 if age <65, <2.0 if ≥ 65) and a high cutoff of ≥ 2.67. Data on FIB-4 performance for ruling out advanced fibrosis in predominantly Black US primary care populations are limited. We evaluated FIB-4's performance in this setting. **Methods:** We conducted a retrospective single-center analysis of adults seen at an academic internal medicine clinic from March 2024 to December 2025. Inclusion required at least one clinic visit and a computable FIB-4. Diagnostic accuracy was evaluated in the subset who also had abdominal imaging or vibration-controlled transient elastography (VCTE). FIB-4 was stratified into low-, indeterminate-, and high-risk categories using AASLD age-adjusted cutoffs. The composite advanced-fibrosis outcome was defined as cirrhosis or portal hypertension on cross-sectional imaging, or F3–F4 fibrosis or liver stiffness ≥ 12 kPa on VCTE. Diagnostic performance at the low cutoff was assessed using Wilson 95% CIs; discrimination was assessed using area under the curve (AUC) with DeLong 95% CIs. **Results:** Of 1,906 adults meeting inclusion criteria (mean age 61 years, 50% male, 53% Black, 34% White, 17% with diabetes, 77% with hypertension), 541 (28%) had imaging or VCTE, and 39 (7.2%) met the composite advanced-fibrosis outcome. At the AASLD age-adjusted low cutoff, FIB-4 achieved sensitivity 71.8% (95% CI 56.2–83.5), NPV 96.7% (94.2–98.2), specificity 64.5% (60.3–68.6), PPV 13.6% (9.6–18.9), and AUC 0.71 (95% CI 0.611–0.802). Rate of advanced fibrosis on imaging or VCTE increased with FIB-4 risk category: 3.3% in low-risk (11/335), 9.7% in indeterminate-risk (13/134), and 20.8% in high-risk (15/72). FIB-4 correlated with age (Spearman $\rho = 0.580$, $p < 0.001$), supporting age-adjusted cutoffs. NPV exceeded 95% in all subgroups

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except diabetes (90.4%, 95% CI 79.4–95.8). NPV was comparable between Black (96.8%, 95% CI 93.1–98.5) and White (97.2%, 95% CI 92.1–99.0) participants. **Conclusion:** In this predominantly Black primary care cohort, FIB-4 with age-adjusted cutoffs ruled out advanced fibrosis with NPV 96.7%, matching published estimates. AUC was 0.71 (95% CI 0.611–0.802), overlapping published ranges. These findings support FIB-4 as first-line testing in this underrepresented population. A lower NPV in the diabetes subgroup (90.4%) is consistent with reported reductions in FIB-4 accuracy in diabetes and suggests that additional fibrosis assessment may be warranted in these patients.

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2230 | ASSESSING UTILIZATION OF HEPATOLOGY E-CONSULTS FOR MASLD IN VETERANS

Anika Mittal[1] Yolanda Rodriguez Villalvazo[1] Kyle Brown[1], [1]University of Iowa Health Care

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is increasingly prevalent among the veteran population, underscoring the need for early identification and risk stratification to prevent disease progression and prioritize in-person hepatology care for veterans with advanced liver disease. The Veterans Affairs (VA) e-consult program aims to expand access to specialty services while reducing unnecessary in-person visits and travel for veterans. Prior literature has demonstrated that gastroenterology e-consults can address many clinical questions that can be managed by primary care providers (PCPs) without in-person specialist evaluation. However, the use of hepatology e-consults as potential decision support tools for PCPs remains understudied. This study evaluated hepatology e-consults utilization at the Iowa City VA Medical Center (IC VAMC), the proportion related to diagnosis and management of MASLD, frequency of recommended in-person evaluation, and the extent to which e-consult recommendations are implemented. **Methods:** This retrospective cohort study evaluated 786 hepatology e-consults submitted between May 2016 and May 2025 at the IC VAMC. Metabolic risk factors were identified through chart review of clinical, laboratory, and imaging data. Implementation of hepatologist recommendations was assessed through review of notes and orders within 6 months of the consultation date. **Results:** In this study, 39% of e-consults addressed MASLD, making it the most common indication for consultation, compared to other liver-related diseases, including alcohol-associated liver disease, abnormal imaging findings, and viral hepatitis. Primary care providers accounted for 91% of hepatology e-consults, including 40% from NPs, 14% from PAs, 34% from MD/DOs, and 10% from resident trainees. Of the 786 consults, only 10% resulted in a recommendation for in-person evaluation by a hepatologist. Among the MASLD-related consults, 52% of patients had documented implementation of at least one hepatologist recommendation, including management of metabolic comorbidities or referral for weight management services. **Conclusion:** MASLD is the leading reason for hepatology e-consultation in this veteran population, yet only a minority require further in-person hepatology evaluation. While e-consults provide actionable guidance, recommendations were only implemented in about half of MASLD-related e-consults. This highlights an opportunity to strengthen education on MASLD identification, risk-stratification, and management practices among primary care providers. Furthermore, this study reinforces the need to use guideline-based recommendations to improve care efficiency and clinical outcomes for veterans with metabolic liver disease. Future interventions should explore how embedding risk-stratification frameworks into e-consults could improve management of MASLD by PCPs.

Disclosures: Anika Mittal: Nothing to Disclose, Yolanda Rodriguez Villalvazo: Nothing to Disclose, Kyle Brown: Nothing to Disclose.

2231 | IMPLEMENTATION OF A INPATIENT TELEHEPATOLOGY AND TELEPSYCHIATRY SERVICE ACROSS THE UNIVERSITY OF MICHIGAN STATE NETWORK TO IMPROVE ACCESS TO LIVER TRANSPLANT–RELATED CARE.

Alexandra Shingina[1] Seth Waits[1] Sarah Uttal[1] Michelle Muza-Moons[2] Abhishek Satishchandran[3] Ammar

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Hassan[1] Kinza Tareen[1], [1]University of Michigan, [2]University of Michigan Health-West, [3]Sparrow Hospital

Background: Telemedicine-based inpatient transplant hepatology care delivers liver-related expertise directly to patients at regional network hospitals, reducing unnecessary transfers to the main academic campus. This model improves access to transplant hepatology, accelerates multidisciplinary decision-making, and is especially valuable for patients with acute alcohol-associated hepatitis requiring timely psychosocial evaluation for sobriety protocol eligibility. **Methods:** A combined inpatient telehepatology and telepsychiatry consultation model was implemented between the University of Michigan (U-M) main campus and regional network hospitals using HIPAA-compliant telehealth equipment. Transplant hepatologist, transplant surgeon and transplant psychiatrist were telecredentialed at each site and documented consults within the network hospital's EMR. Local providers initiated consultations through M-Line, U-M's centralized consultation services line. Two sites launched: Site 1 in October 2025 and Site 2 in March 2026. **Results:** Across both sites, 21 telehepatology and 10 telepsychiatry consultations were completed, most common reason for cosnult was decompensated cirrhosis. Overall, 10 patients were transferred for transplant evaluation at the main campus, yielding 3 completed transplants and 1 active listing.At Site 1, 12 patients received telehepatology and 8 telepsichiatry consultations; 8 were transferred for transplant evaluation, resulting in 2 transplants, 3 deaths during workup, 2 closures after clinical improvement, and 1 deferral. Mean visit and documentation times were 20 and 17 minutes. At Site 2, 9 telehepatology and 2 telepsychiatry consultations were completed; 2 patients were transferred to main campus, with 1 transplanted and 1 actively listed. Mean visit and documentation times were 17 and 15 minutes. **Conclusion:** A statewide telehepatology consultation service is a feasible strategy to expand transplant hepatology access, improve transfer coordination, and preserve main-campus bed capacity. Early experience across two network hospitals demonstrates the model's ability to identify urgent transplant candidates, integrate telepsychiatry into transplant assessment, and facilitate appropriate high-priority transfers. This program has strong potential to enhance patient and provider experience, broaden access to U-M hepatology and liver transplant services, and strengthen the statewide network's capacity to deliver efficient, patient-centered care.

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2232 | MASLD IS INDEPENDENTLY ASSOCIATED WITH HIGH FINANCIAL BURDEN AMONG PATIENTS WITH CIRRHOSIS IN A PROSPECTIVE STUDY: RESULTS FROM LIVE-SMART

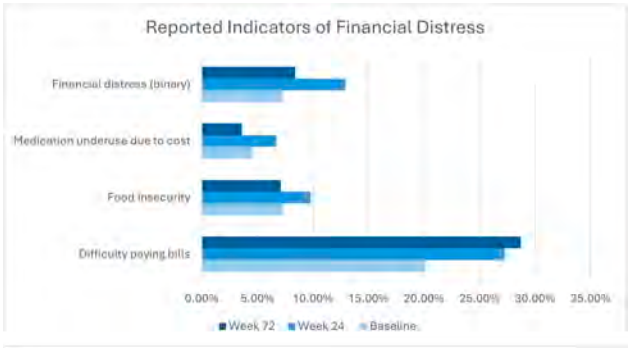
Anvi Sonarikar[1] Jacqueline Theroux[1] Samantha Nikirk[2] Richard Mason[1] Sumeet Asrani[3] Donna Evon[4] Elliot Tapper[5] Marina Serper[6], [1]Division of Gastroenterology and Hepatology, University of Pennsylvania, [2]Division of Gastroenterology and Hepatology, University of Michigan, [3]Liver Consultants of Texas, [4]UNC SOM, [5]University of Michigan Medical Center, [6]University of Pennsylvania Health System

Background: Cirrhosis is associated with significant financial strain, which may negatively impact health outcomes and quality of life. However, prospective longitudinal data evaluating financial burden in cirrhosis are limited. **Methods:** We report a pre-registered ancillary study from LIVE-SMART, a prospective randomized trial designed to reduce falls in patients with cirrhosis (NCT#07140120). We aimed to quantify self-reported healthcare utilization, financial distress, financial toxicity, and work productivity, as well as identify patient factors associated with high financial burden. Financial distress was defined as the presence of two or more of the following due to cost on the Health and Retirement Survey (HRS): difficulty paying bills, food insecurity, and medication underuse. Financial toxicity was assessed using the Comprehensive Score for Financial Toxicity – Functional Assessment of Chronic Illness Therapy (COST-FACIT) survey. Work productivity was assessed using the Work Productivity and Activity Impairment (WPAI) questionnaire. The primary outcome, high financial burden, was defined as either financial distress (2 or more HRS-based financial difficulties) or financial toxicity (corrected COST-FACIT score < 26). **Results:** Among 230 participants, the mean age was 61.8; 92.6% were White; and 60% were female, 37% were college educated, and 26.3% resided in rural areas. Participants were recruited from MI, TX, and PA. Rates of financial distress fluctuated over time (Figure 1). At 72 weeks post-enrollment, financial distress was present in 28.7% of participants, most commonly reported as having difficulty paying bills, which increased over time. Healthcare utilization was high across multiple domains, particularly medication use (66.1%) and laboratory/imaging/diagnostic testing (41.7%). Nearly half of patients engaged in primary care visits (43.5%), and 35.7% reported specialty care visits within the prior 3 months. Only 34% of participants were employed; of these, 21% reported absenteeism (chronic absence from work), and 24% reported presenteeism (working at a reduced capacity while sick). In a multivariable model adjusted

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for age, sex, education, liver disease severity, medications, and comorbidities, metabolic dysfunction-associated steatotic liver disease (MASLD) was the only factor independently associated with high financial burden (OR = 12.22, p = 0.01). **Conclusion:** Patients with liver cirrhosis experience substantial healthcare utilization and considerable financial burden, likely related in part to comorbid conditions. MASLD was independently associated with a higher financial burden. Interventions to reduce financial strain in this population are needed.



Disclosures: Anvi Sonarikar: Nothing to Disclose, Jacqueline Theroux: Nothing to Disclose, Samantha Nikirk: Nothing to Disclose, Richard Mason: Nothing to Disclose, Sumeet Asrani: Nothing to Disclose, Donna Evon: Nothing to Disclose, Elliot Tapper: Madrigal: Grant/Research Support, Gilead: Consultant, Ipsen: Consultant, Merz: Consultant, Marina Serper: Transplant Genomics: Grant/Research Support, Grifols: Grant/Research Support.

2233 | CHANGE IN CARE-SEEKING INTENTION AFTER TRANSIENT ELASTOGRAPHY AND COUNSELING: A COMMUNITY-BASED PRE-POST INTERVENTION STUDY

Tiange Zhang[1] Kali Zhou[1] Jennifer Dodge[1] Andrea Amaro[2] Michael Betel[3] Michael McTighe[4] Sherri Brown[3] Norah Terrault[1], [1]University of Southern California, [2]USC, [3]Fatty Liver Alliance, [4]Aegle Medical

Background: Transient elastography (TE) is increasingly used in community settings and may promote liver health. Prior studies suggest that TE may motivate lifestyle modifications; however, its influence on subsequent care-seeking remains unclear. We evaluated whether a community-based liver health intervention using TE and counseling was associated with changes in care-seeking intention. **Methods:** We conducted a pre-post intervention study among adults aged ≥21 years attending a community TE screening event. Participants completed surveys before and immediately after TE and counseling. TE measured steatosis and liver stiffness. Counseling was delivered by a trained community health worker and medical resident in the participant's preferred language and tailored to the TE result. The primary outcome was change in care-seeking intention score (range 3-12), derived from three 4-point Likert scale items assessing intention to talk to, schedule visit with, or seek help from a provider regarding liver health. Participants were classified into 3 groups: significant fibrosis (stiffness ≥7.3 kPa, equivalent to ≥F2, with or without steatosis), any steatosis (steatosis ≥238 dB/m) without significant fibrosis, no steatosis nor significant fibrosis. Within-group changes were assessed using paired t tests. **Results:** 121 of 125 participants had valid TE measurements (IQR/median ≤30%) and were included in the analysis. The median age was 53 (IQR, 26), with 74% female and 85% Hispanic. Median liver stiffness was 5.0 kPa (IQR, 2.1) and median steatosis was 284 dB/m (IQR, 54). 19 (16%) participants had significant fibrosis, 87 (72%) had steatosis without significant fibrosis, and 15 (12%) had no steatosis/significant fibrosis. Most participants had seen a primary care provider in the last year (78%). 64% had previously heard of fatty liver disease, while 18% reported a prior diagnosis. 53%, 41%, 31%, and 42% of participants self-reported overweight/obesity, prediabetes/diabetes, hypertension, and cholesterol problems, respectively. Mean care-seeking intention score before intervention was 9.37 (SD, 1.82). Mean intention score increased by 1.74 points in the significant fibrosis group (9.47 to 11.21; p < 0.001) and by 0.23 points in the steatosis without significant fibrosis group (9.34 to 9.57; p = 0.003). The no steatosis/no significant fibrosis group showed no significant change (9.40 to 9.67; mean change 0.27; p = 0.10) (**Table 1**). **Conclusion:** Community-based TE screening identified a substantial number (1 in 6) with significant liver fibrosis. Care-seeking intention significantly increased after TE with tailored counseling among participants with significant fibrosis, with no decrease in intention among those with no steatosis nor significant fibrosis, suggesting appropriate care-seeking motivation without false reassurance. Future studies should test whether TE leads to objective care-seeking.

Table 1. Change in care-seeking intention score pre- and post-intervention by TE groups

TE groups	Mean pre-test intention score (SD)	Mean post-test intention score (SD)	Change in intention score (SD)	p-value
No steatosis/no significant fibrosis (n=15)	9.40 (2.13)	9.67 (1.95)	0.27 (0.59)	0.104
Steatosis without significant fibrosis (n=87)	9.34 (1.9)	9.57 (1.71)	0.23 (0.71)	0.003
Significant fibrosis (n=19)	9.47 (1.12)	11.21 (1.23)	1.74 (1.41)	<0.001

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2234 | CHANGING HEPATOCELLULAR CARCINOMA ETIOLOGY IN ALASKA

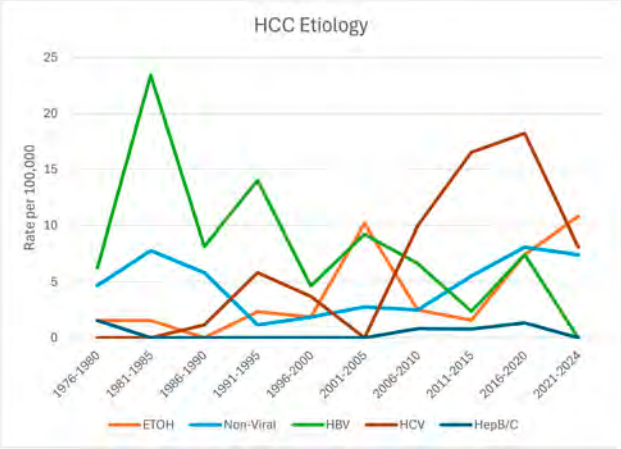
Lesleigh Kowalski[1] Brian McMahon[2] Lisa Townshend-Bulson[3], [1]Alaska Native Tribal Health Consortium, [2]Alaska Native Medical Center, [3]Alaska Native Tribal Consortium

Background: Hepatocellular carcinoma (HCC) etiology varies, and rates are expected to increase worldwide. HCC rates were previously high among Alaska Native and American Indian (ANAI) peoples in Alaska yet are expected to change in parallel with changes in underlying causes of liver disease. The aim of this abstract is to describe the current etiology and survival rates of ANAI peoples with HCC living in Alaska. **Methods:** The cause of HCC was determined by the treating medical provider and maintained in a clinical registry. Incidence is reported as new HCC diagnosis within the ANAI population living in Alaska per 5-year cumulative incidence from 1970 to 2024. HCC by stage used diagnosis years 2018-2023 as the most recent six years of data. HCC observed 5-year survival among ANAI peoples diagnosed with liver cancer between 1992-2023 using an actuarial method. **Results:** HCC due to HBV decreased from its highest rate of 23.40 per 100,000 between 1981-1985 to 6.65 per 100,000 between 2016-2020 to 0 per 100,000 between 2021-2024. Incidence of HCC from HCV peaked at 18.23 per 100,000 between 2016-2020 and then declined to 8.10 per 100,000 between 2021-2024. Incidence of HCC from ALD increased between 2011-2015 from 2.50 per 100,000 and 2021-2024 to numbers 10.80 per 100,000. Incidence of HCC from non-viral causes increased from years prior to 7.80 per 100,000 between 2016-2020 and 7.43 between 2021-2024. Between 2021 and 2024 among ANAI peoples, 0% of HCC cases were attributed to HBV, 41% were attributed to ALD, 31% were attributed to HCV, and 28% were attributed to non-viral causes, including MASLD/MASH, PBC, or AIH. Specific stage at diagnosis breakdown between 2018-2023 includes stage I at 35.8%, stage II at 24.7%, stage III at 13.6%, stage IV at 17.3%, and

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other at 8.6%. Among ANAI peoples in Alaska with HCC, 89.5% diagnosed with stage I or II liver cancer survived to 12 months and 47.4% of people survived to 60 months. For those diagnosed with stage III or IV liver cancer, 21.7% survived 12 months and 0% survived to 60 months. Five-year survival of liver cancer demonstrated a decreasing trend among women: between 1992-2013 the survival at 60 months post-diagnosis was nearly 38% (95% CI [20.90, 54.90]); for women diagnosed between 2014-2018 the survival at 60 months decreased to 25% (95% CI [7.80, 47.20]) while survival increased in men from 31.30% (95% CI [20.70, 42.50]) survival at 60 months between 1992-2013 to 42.90% (95% CI [21.90, 62.30]) survival at 60 months between 2014-2018. **Conclusion:** The US, and specifically Alaska, is experiencing changing trends in HCC etiology. Historically, viral hepatitis such as HBV and HCV have caused the most cases of liver cancer. However, both causes are decreasing as it relates to HCC. An increase was notable in HCC caused by MASLD and ALD, specifically among women, which highlights the need for robust preventive, interprofessional care in the treatment of early-stage MASLD and screening for ALD.



Disclosures: Lesleigh Kowalski: Nothing to Disclose, Brian McMahon: Nothing to Disclose, Lisa Townshend-Bulson: Nothing to Disclose.

2235 | SPECIALTY CARE IN CIRRHOTIC PERITONITIS: DOES HEPATOLOGY CONSULTATION MATTER?

Kahler Doyle[1] Brayden Doyle[2] Viraj Gandhi[1] Mohammad Ashfaq[3], [1]TCU Anne Burnett School of Medicine, [2]TCU College of Science and Engineering, [3]Baylor Scott & White Liver Consultants of Texas

Background: Hepatology consultation is commonly involved in managing cirrhotic patients with peritonitis, yet its relationship to disease severity, care patterns, and outcomes is not well defined. We compared clinical characteristics, management, and longitudinal outcomes between patients who did and did not receive hepatology consultation during hospitalization. **Methods:** We performed a retrospective cohort study of cirrhotic patients admitted with peritonitis, stratified by hepatology consultation status. Demographics, laboratory data, microbiology, treatment patterns, consultations, and outcomes were compared using univariate analyses with ORs and 95% CIs. Time-to-event outcomes were assessed using Kaplan–Meier survival analysis and competing-risk regression for readmission, with log-rank and Gray's tests. AI-assisted tools improved readability and language clarity. **Results:** We included 401 patients (no hepatology consult n = 221; hepatology consult n = 180). Consulted patients had longer length of stay (7.0 [5.0–13.0] vs 10.0 [5.0–17.0], p = 0.002) and greater disease severity, including higher admission MELD 3.0 (23.0 vs 25.0, p = 0.004) and discharge MELD 3.0 (21.0 vs 24.0, p = 0.003).Hepatology consultation was associated with increased diagnostic and treatment intensity, including greater repeat paracentesis (late PFA obtained OR 3.98, 95% CI 2.62–6.04), earlier antibiotic initiation, and higher use of antifungal (OR 3.35, 1.79–6.26), broad-spectrum (OR 2.98, 1.55–5.74), and anaerobic therapy (OR 1.86, 1.03–3.36), with longer treatment durations. Prophylaxis prescribing was more common (OR 2.12, 1.38–3.27), including fluoroquinolone prophylaxis (OR 2.32, 1.44–3.74).Patients with hepatology consultation demonstrated increased healthcare utilization, including higher rates of central venous access (OR 2.01, 1.34–3.00), nephrology consultation (OR 1.75, 1.17–2.60), cardiology consultation (OR 2.03, 1.14–3.63), and imaging utilization. Microbiologic complexity was also greater, including increased multidrug-resistant organisms (OR 2.19, 1.07–4.48) and fungal peritonitis (OR 2.31, 1.02–5.22).Despite higher acuity, hepatology consultation was associated with improved long-term outcomes, including reduced 3-year (OR 0.56, 0.36–0.86), 4-year (OR 0.53, 0.34–0.82), and 5-year mortality (OR 0.58, 0.37–0.91). Survival analysis demonstrated improved overall survival in the hepatology consult group (log-rank p = 0.048), while cumulative incidence of readmission did not differ significantly (Gray's p = 0.294). **Conclusion:** Hepatology consultation in cirrhotic patients with peritonitis is associated with greater disease severity and more intensive diagnostic and therapeutic management, yet linked to improved long-term survival. These findings suggest that specialized hepatology

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involvement may contribute to better longitudinal outcomes in this high-risk population.

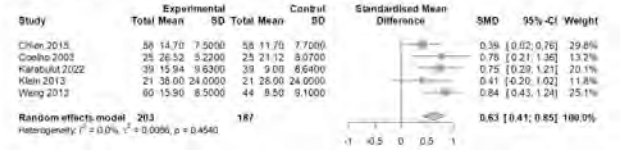
Disclosures: Kahler Doyle: Nothing to Disclose, Brayden Doyle: Nothing to Disclose, Viraj Gandhi: Nothing to Disclose, Mohammad Ashfaq: Nothing to Disclose.

★ 2236 | ◆ SEXUAL FUNCTION IN LIVER TRANSPLANT RECIPIENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

Yooyun Chung[1] Ilkay Ergenç[1] Tengfei Si[1] Alex Stagg[2] Michael Heneghan[1], [1]The Roger Williams Institute of Liver Studies, King's College London, London, SE5 9RS, UK, [2]Royal Free Hospital Medical Library, UCL Library, Culture, Collections & Open Science, Rowland Hill

Background: Sexual function (SF) is an integral part of quality of life (QOL) and is highly prevalent in patients with end-stage liver disease. Liver transplantation (LT) improves survival and QOL; however its impact on SF remains incompletely defined. This was a systematic review and meta-analysis evaluating SF outcomes following LT. **Methods:** A systematic search of MEDLINE, Embase and PsychINFO was conducted from inception to May 2026 in accordance with PRISMA 2020 guidelines. Studies evaluating SF in adult LT recipients were included. Meta-analysis was performed for studies reporting erectile function (EF) outcomes using the International Index of Erectile Function (IIEF). Standardized mean differences (SMDs) with 95% confidence intervals (CIs) were pooled using a random effects model. Narrative synthesis was performed for heterogeneous outcomes. **Results:** A total of 7289 records were identified with 48 studies included in the systematic review. Five studies involving 390 male participants (203 post-LT and 187 pre-LT) were eligible for meta-analysis (Figure 1). LT was associated with significant improvement in EF, with a pooled SMD 0.63 (95% CI 0.41-0.85, $p < 0.0001$). No significant heterogeneity was observed ($I2 = 0\%$, $p = 0.454$). Narrative synthesis indicated improvement across multiple domains including libido, sexual satisfaction and psychosocial wellbeing following LT. Restoration of endocrine function and improved overall health contributed to improved SF outcomes. However, persistent sexual dysfunction remained common and was associated with increasing age, metabolic risk factors, depression, anxiety and immunosuppression therapy. Female recipients demonstrated improvements in menstrual regularity and sexual satisfaction although data in women were limited. **Conclusion:** LT is associated with significant improvement in erectile function and broader sexual health outcomes. Despite overall improvement, persistent sexual dysfunction remains prevalent after transplantation. Routine standardised sexual health assessment should be incorporated into long-term post-transplant care pathways.

Figure 1. Forest plot of pooled effect estimate of studies assessing erectile function before (control) and after liver transplantation (experimental). Squares represent the effect estimate for each individual study, with the size of the square proportional to the weight of the study in the meta-analysis. Horizontal lines indicate the 95% confidence intervals. The diamond represents the pooled effect estimate.



Disclosures: Yooyun Chung: Nothing to Disclose, Ilkay Ergenç: Nothing to Disclose, Tengfei Si: Nothing to Disclose, Alex Stagg: Nothing to Disclose, Michael Heneghan: Advanz: Speaking and Teaching, Ipsen: Speaking and Teaching, Mirum: Consultant, Gilead: Speaking and Teaching.

2237 | ◆ INTER-HOSPITAL VARIATION IN CIRRHOSIS ICU MORTALITY: A MULTICENTER EICU ANALYSIS OF US CRITICAL CARE

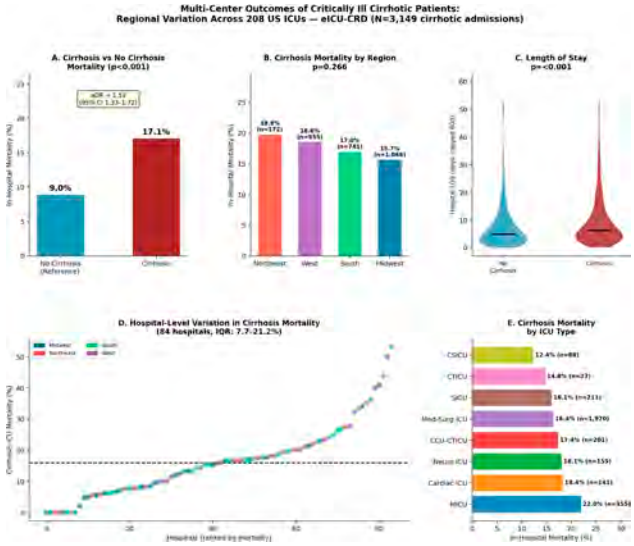
Innocent Lutaya[1] Vicki Oladoyin[1] Brian Xu[1] Shanelle Brodeur[1] Chima Amadi[1] Shaikhoon Mohammed[1] Christopher Fay[1] Henok Tafesse[1] Nicolas Bakinde[1] Emmanuel Marfo[1] Abisola Ajayi[1], [1]Morehouse School of Medicine

Background: Cirrhosis is associated with high ICU mortality, but the extent of inter-hospital variation in outcomes and the independent contribution of cirrhosis severity markers (hepatic failure co-diagnosis, APACHE IV scores) to mortality across diverse practice settings remains poorly understood uncharacterized in multi-center studies. **Methods:** We analyzed the eICU Collaborative Research Database v2.0 (eICU-CRD), comprising of 208 US hospitals and 164,573 adult ICU admissions. Cirrhosis was identified using the eICU APACHE IV admission diagnosis variable (apachePredVar.cirrhosis = 1). The primary outcome was in-hospital mortality. Multivariable logistic regression adjusted for hepatic failure co-diagnosis, APACHE IV score, age, sex, diabetes, and metastatic cancer. Inter-hospital variation in cirrhosis mortality was characterized by hospital-level mortality range, interquartile range (IQR), and Kruskal-Wallis test by region. **Results:** Cirrhosis was identified in 3,149 patients (1.91%). Cirrhosis patients had significantly higher in-hospital mortality (17.1% vs. 9.0%, $p < 0.001$; aOR

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1.51, 95% CI 1.33-1.72; p < 0.001). Concurrent hepatic failure was present in 51.3% of cirrhosis patients and independently reduced mortality (aOR 0.80, 95% CI 0.69-0.92; p = 0.002), likely reflecting a coding artifact (hepatic failure coded with cirrhosis vs. hepatic failure alone). Hospital-level mortality in cirrhosis ranged from 0-53.3% (IQR 7.7-21.2%), representing substantial inter-hospital variation. Region was not associated with mortality (Kruskal-Wallis p = 0.27). APACHE IV score was the strongest independent predictor of mortality (aOR 1.04 per unit increase; p < 0.001). **Conclusion:** Cirrhosis independently increases ICU mortality 1.5-fold across a 208-hospital US network after adjustment for APACHE IV severity. Marked inter-hospital variation (0-53% range) not explained by regional factors suggests substantial differences in care processes, case mix, or resource availability. These data provide a multi-center benchmarking framework for quality improvement initiatives in ICU management of cirrhosis.



Disclosures: Innocent Lutaya: Nothing to Disclose, Vicki Oladoyin: Nothing to Disclose, Brian Xu: Nothing to Disclose, Shanelle Brodeur: Nothing to Disclose, Chima Amadi: Nothing to Disclose, Shaikhoon Mohammed: Nothing to Disclose, Christopher Fay: Nothing to Disclose, Henok Tafesse: Nothing to Disclose, Nicolas Bakinde: Nothing to Disclose, Emmanuel marfo: Nothing to Disclose, Abisola Ajayi: Nothing to Disclose.

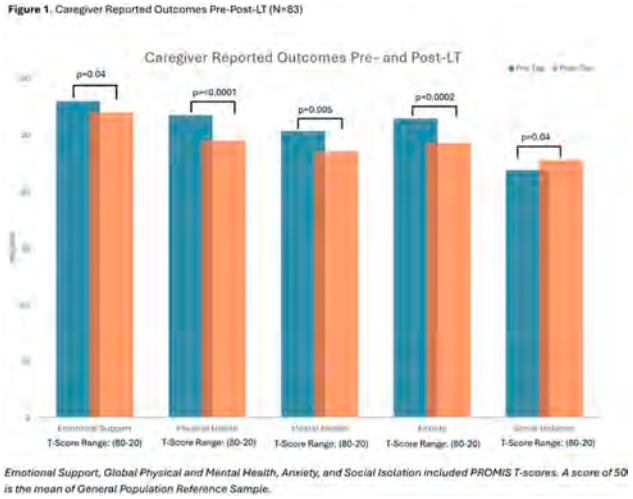
2238 | ◆ EARLY POST-LIVER TRANSPLANT CAREGIVER BURDEN AND PSYCHOSOCIAL OUTCOMES

Alvaro Noriega Ramirez[1] Meena Tadros[2] Dyanna Gregory[1] Arjmand Mufti[1] Madhukar Patel[1] Shannan Tujios[1] Mary Joy Tuquero[1] Samantha Kimbrough[1] Cheri Goldstein[1] Melissa Fogg[1] Brandy Brasfield[1] Derek Bartlett[1] Lisa VanWagner[1] Amit Singal[1] Sarah Lieber[1], [1]University of Texas Southwestern Medical Center, [2]University of Pennsylvania

Background: Caregivers of liver transplant recipients (LTRs) are essential to a successful patient recovery after liver transplant (LT). However, little is known about the burden of caregiver support and its impact on their quality of life. We aimed to investigate caregiver burden, psychosocial outcomes, and support pre- and post-LT. **Methods:** We conducted an interim analysis of a prospective cohort including LTRs and their caregiver at a large U.S. transplant center. LTRs and caregivers are enrolled at LT waitlist (baseline) and followed until 12 months post-LT. Sociodemographic, clinical, and caregiver reported variables were collected as well as: emotional/information support, global health, anxiety, and social isolation (PROMIS) and overall caregiver burden (Zarit Interview). We conducted multivariable linear regression to identify factors associated with higher post-LT caregiver burden and quality-of-life. **Results:** Among 83 caregivers, 75.9% were female and were the spouse/significant other (62.7%) of LTRs; 54.1 % were employed. At 6-months post-LT, 73.0% reported moderate to severe caregiver burden. Compared to pre-LT, caregivers reported decreased emotional support (p = 0.04), physical (p = < 0.0001) and mental (p = 0.005) quality-of-life, as well increased social isolation (p = 0.04) despite decreased anxiety (p = 0.0002) after LT (**Figure 1**). On multivariable modeling adjusted for covariates (caregiver age, sex, race, ethnicity, employment and LTR indication for LT, hospitalizations and inpatient LTE), caregivers of LTRs for alcohol related liver disease had lower post-LT anxiety (beta = -8.33; p = 0.001) and depression (beta = -9.09; p = < 0.0001) scores. Hispanic caregivers had higher post-LT informational (beta = 5.761; p = 0.02) and emotional support (beta = 5.76; p = 0.008), while Black caregivers reported higher emotional support post-LT (beta = 9.098; p = 0.04) compared to non-Hispanic Whites. **Conclusion:** Despite lower anxiety scores, caregivers report decreased emotional support, physical and mental quality-of-life post-LT. Increased caregiver burden and social isolation post-LT, especially among those employed. There may be more beneficial caregiver outcomes for ALD LTRs as well as differing emotional and informational support by race and ethnicity. These results highlight the crucial need to mitigate caregiver burden post-LT with interventions that promote physical and mental well-being, as well as support networks.

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2239 | ◆ IMPACT OF PALLIATIVE CARE INTERVENTION ON CAREGIVERS OF PATIENTS WITH ADVANCED CHRONIC LIVER DISEASES: A CLUSTER RANDOMIZED CONTROLLED TRIAL

Manisha Verma[1] Victor Navarro[2] Andrzej Kosinski[3] Michael Volk[4] Don Rockey[5] Gyorgy Baffy[6] Binu John[7] Richard Kalman[1] Alfred Barritt IV[8] Sofia Jakab[9] Mina Rakoski[10] Marina Serper[11] Eric Orman[12] Kristel Hunt[13] Marina Roytman[14] Nicholas Hoppmann[15] Christopher Woodrell[16] Ayse Aytaman[17] Elliot Tapper[18] Rohit Nathan[19] Maya Balakrishnan[20] Roniel Cabrera[21] Marie Bakitas[22] Tamar Taddei[23], [1]Thomas Jefferson University, [2]Jefferson Health System, [3]Duke University, [4]Baylor Scott&White Health, [5]MUSC, [6]VA Boston Healthcare System, [7]University of Miami and Miami VA, [8]UNC, [9]VA West Haven, [10]Loma Linda University, [11]University of Pennsylvania Health System, [12]Indiana University, [13]VA Bronx, [14]UCSF Fresno, [15]USC, [16]Icahn School of Medicine at Mount Sinai, [17]VA NY Harbor Healthcare System Brooklyn Campus, [18]University of Michigan Medical Center, [19]Einstein Medical Center, [20]Baylor College of Medicine, [21]University of Florida, [22]University of Alabama, Birmingham, [23]Yale University

Background: Caregivers of patients with advanced chronic liver disease (CLD) experience substantial burden and psychological distress, yet effective supportive interventions remain poorly defined. Palliative care (PC) may improve caregiver outcomes, although the comparative effectiveness of different PC delivery models is unknown. We compared the effectiveness of PC delivered by PC specialists (PC arm) versus trained hepatologists (Hep arm) on caregiver burden and related outcomes. **Methods:** This is the primary analysis of prespecified caregiver outcomes from the PAL-LIVER multicenter cluster RCT. Nineteen centers were randomized to PC delivered by 1) PC specialists (PC arm, 8 centers) or 2) trained hepatologists (Hep arm, 11 centers); conducted from 2019–2025. Hepatologists received training in PC tailored to CLD, after randomization. Caregivers were adults providing $\geq$10 hours/week of unpaid support and consistently involved in patient care and were enrolled separately from patients. Both arms followed a standardized 4-visit intervention addressing caregiver burden, disease education, and goals-of-care conversations.Caregiver outcomes were prespecified secondary outcomes in the parent trial. The primary outcome for this analysis was change in caregiver burden measured by the Zarit Burden Interview-12 (ZBI-12) at 3 months. Secondary outcomes included caregiver QoL (PROMIS-29) and caregiver-reported communication measures at 3 months. Higher score reflects higher domain assessed. Linear mixed models accounted for cluster randomization and adjusted for baseline ZBI-12 and randomization strata. **Results:** We enrolled 559 caregivers (PC arm 310, Hep arm 249). Most were female (77%), spouses (52%), college educated (68%), and employed (45%), with a mean age of 58 years (SD 14.2). Baseline caregiver burden was low [mean ZBI-12 score 9.3 (SD 8.3)].Change in ZBI-12 from baseline to 3 months did not differ between arms (Table). The PC arm had a small reduction in burden (-0.69, $P = 0.18$),

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while the Hep arm had a small increase (0.72, $P = 0.18$). Change in PROMIS-29 physical and mental health scores were similar between arms.Communication outcomes improved significantly in both groups. Care concordant with preferences scores improved in both arms, with greater improvement in the Hep arm (0.55, $P = 0.005$). Similarly, Goals of Care (GoC) conversations scores also improved in both groups, with greater improvement in the Hep arm (0.24, $P = 0.004$). **Conclusion:** In this RCT enrolling caregivers of patients with CLD, caregiver burden remained stable over 3 months in both groups, suggesting that integration of PC principles into hepatology care may mitigate short-term worsening. Hepatologist-delivered PC was associated with greater improvement in communication outcomes, possibly reflecting advantages in liver disease-specific communication, continuity, and integration of prognostic discussions into routine hepatology care.

Table: Demographics and Outcomes in the Two Comparative Models

Demographics	**PC arm (N= 310)**	**Hep arm (N=249)**			
Mean Age (SD)	58 (14.2)	58 (14.2)			
Females	79%	75%			
High School or less education	35%	29%			
Mean Duration of caregiving (years)	5.4 (8.9) years	5.0 (7.9) years			
Mean (SD) ZBI-12	9.8 (8.4)	9.8 (8.1)			
% High Burden (ZBI-12 >=20)	12%	12%			
Primary and Secondary Caregiver Outcomes *					
Outcome (change from baseline to 3 months) * *	**PC arm (Model 1) N= 296**		**Hep arm (Model 2) N= 240**		**Adjusted mean difference [Model 2 - Model 1] (95% CI)**	**P-value**
	Adjusted mean (95% CI)	P-value	Adjusted mean (95% CI)	P-value		
ZBI-12 total score (range 0-48, MCID 2-3 points)	-0.69 (-1.72, 0.33)	0.18	0.72 (-0.34, 1.79)	0.18	1.42 (-0.09, 2.93)	0.066
PROMIS domains						
PROMIS-29 Physical Health Summary score	0.19 (-0.43, 0.82)	0.54	0.18 (-0.47, 0.84)	0.59	-0.01 (-0.94, 0.92)	0.98
PROMIS-29 Mental Health Summary score	-0.10 (-1.14, 0.94)	0.85	-0.48 (-1.58, 0.61)	0.39	-0.38 (-1.94, 1.17)	0.63
Physical Function	0.10 (-0.62, 0.82)	0.79	0.24 (-0.54, 1.03)	0.54	0.15 (-0.96, 1.26)	0.80
Anxiety	-1.31 (-2.55, -0.10)	**0.034**	0.70 (-0.62, 2.02)	0.30	2.01 (0.14, 3.87)	0.035
Depression	0.08 (-1.09, 1.25)	0.89	0.633 (-0.64, 1.91)	0.33	0.55 (-1.22, 2.33)	0.54
Fatigue	1.58 (0.28, 2.88)	0.017	0.53 (-0.88,1.94)	0.46	-1.05 (-3.04, 0.94)	0.30
Sleep disturbance	-0.01 (-1.21, 1.20)	0.99	0.40 (-0.89, 1.69)	0.55	0.40 (-1.41, 2.21)	0.66
Social roles and activities	1.46 (0.10, 2.82)	0.035	0.28 (-1.19, 1.74)	0.71	-1.18 (-3.24, 0.87)	0.26
Pain Interference	0.70 (-0.47, 1.86)	0.24	0.72 (-0.50, 1.95)	0.25	0.03 (-1.71, 1.76)	0.98
Communication Measures						
CCP scale	0.32 (0.06, 0.58)	0.016	0.87 (0.61, 1.14)	<0.001	0.55 (0.17, 0.93)	**0.005**
GoC scale	0.21 (0.09, 0.32)	<0.001	0.45 (0.33, 0.57)	<0.001	0.24 (0.08, 0.41)	**0.004**

*Higher scores reflect higher caregiver burden and better communication; and better PROMIS domain.
** Negative value indicates an improvement in caregiver burden, anxiety, depression, fatigue, sleep disturbance, and pain interference. Positive value indicates improvement in physical function, summary scores, social roles, CCP (Care Concordant with preferences) and GoC (Goals of Care) scale.

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2240 | ◆ DEVELOPMENT AND VALIDATION OF A SYMPTOM-BASED PATIENT-REPORTED OUTCOME MEASURE FOR MASH: THE CLDQ-MASH SYMPTOM QUESTIONNAIRE (CLDQ-MASH-SQ)

Zobair Younossi[1] Maria Stepanova[1] Issah Younossi[1] Andrei Racila[1], [1]The Global NASH/MASH Council

Background: Metabolic dysfunction-associated steatohepatitis (MASH) is associated with a substantial symptom burden. However, no validated symptom-focused patient-reported outcome (PRO) instrument exists for this population. We aimed to develop and validate the MASH Symptom Questionnaire. **Methods:** We analyzed MASLD subjects from the Global NASH/MASH Registry (GNR) with clinical data and completed CLDQ-MASH instruments. For the new instrument development and preliminary validation, we used CLDQ-MASH items supplemented with symptom-related items from other generic instruments (Initial Development Cohort N = 2,066) and expert input. A list of 50 symptom-related items was identified. After removal of redundancy, 36 items were retained and evaluated using exploratory factor analysis. Standard pipeline for validation of a PRO instrument was applied. The instrument was validated again using another independent validation cohort from GNR (Independent Validation Cohort N = 2541). **Results:** In the development phase, 36 items were distributed in 8 symptom

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domains: Mental, Cognitive, Fatigue, Systemic, Abdominal, Health distress, Sleep Disturbance, and Peripheral symptoms domains. Seven of eight domains demonstrated Cronbach's alpha >0.80 (high internal consistency); the remaining Peripheral symptoms domain included diverse items. The domain scores significantly discriminated across histologic disease severity (early fibrosis vs. F2-F3 vs. cirrhosis), liver stiffness categories (<10 vs. 10-20 vs. >20 kPa) in both development and independent validation samples. The instrument discriminated well based on non-hepatic comorbidities (type 2 diabetes, hypertension, psychiatric, sleep, pruritus, clinically overt fatigue, GERD, other GI disorders). Similar strong validation properties were noted in the independent validation cohort. **Conclusion:** The 36-item, 8-domain CLDQ-MASH Symptom Questionnaire (CLDQ-MASH SQ) represents the first validated, disease-specific symptom questionnaire for patients with MASH showing good psychometric properties. With further external validation, the CLDQ-MASH-SQ has the potential to serve as a standardized tool in both clinical research and routine practice to comprehensively assess disease burden and treatment response.

Disclosures: Zobair Younossi: Zobair M. Younossi is a consultant or has received research: Consultant, madrigal: Grant/Research Support, Siemens: Research funding, GSK: Consultant, BI: Consultant, Sanofi: Research funding, Maria Stepanova: Nothing to Disclose, Issah Younossi: Nothing to Disclose, Andrei Racila: Nothing to Disclose.

2241 | ◆ PROMIS-29 DOMAINS AS PREDICTORS OF SURVIVAL AND DECOMPENSATIONS IN CIRRHOSIS

Lauren Kasmikha[1] Mounika Kanneganti[2] Sudheer Dhoop[1] Elliot Tapper[1], [1]University of Michigan Medical Center, [2]University of Michigan

Background: Patient reported outcomes (PROs) can reflect worsening in underlying disease prior to clinical progression of disease. The PROMIS-29 Profile questionnaire measures PROs and has distinct advantages in measuring health-related quality of life (HRQOL) in chronic liver disease. The prognostic value of PROMIS-29 measures in cirrhosis is unclear. **Methods:** This is a retrospective cohort study of adults with cirrhosis who completed the PROMIS-29 questionnaire between 6/1/23-6/30/25 at the University of Michigan Hospital, excluding those with prior liver transplants. PROPr summary health scores were calculated using PROMIS domain T-scores. Multivariable linear regression models were adjusted for demographics or disease burden (ascites, hepatic encephalopathy (HE), MELD score, modified Charlson Comorbidity Score (CCS)). Separate models were fit for each PROMIS-29 domain and PROPr score. Cox models assessed transplant-free survival, defined as death or transplant. Fine-Gray models assessed decompensation using subdistribution hazard ratios (sHR), and negative binomial models assessed ED visits and hospital days using incidence rate ratios (IRR). **Results:** Among 438 patients included, median follow-up time was 11 months; 37 died (8.4%) and 31 underwent transplant (7.1%). Patients were 55.3% male and 88.1% White, and alcohol accounted for 37% of cirrhosis etiology. 89.2% of patients had decompensated cirrhosis, with median MELD of 10 (IQR 8,13). After demographic adjustment, higher physical function (HR 0.92,95%CI 0.90-0.95) and social role participation (HR 0.93,95%CI 0.90-0.95) predicted better transplant-free survival, whereas fatigue predicted worse survival (HR 1.05,95%CI 1.03-1.07). After disease-burden adjustment, physical function (HR 0.97,95%CI 0.94-0.99) and social roles (HR 0.96,95%CI 0.93-0.98) remained significant. Adjusting for MELD and Charlson Comorbidity Score, physical function (sHR 0.94,95%CI 0.90-0.98), social roles (sHR 0.95,95%CI 0.92-0.98), and PROPr (sHR 0.70,95%CI 0.58-0.84) predicted lower HE risk, whereas sleep disturbance predicted higher risk (sHR 1.07,95%CI 1.02-1.11). After disease-burden adjustment, pain interference (sHR 0.94,95%CI 0.89-0.99) and cognitive function (sHR 0.94,95%CI 0.89-0.99) predicted SBP. Higher PROPr predicted fewer hospital days (IRR 0.76,95%CI 0.70-0.84) and ED visits (IRR 0.88,95%CI 0.82-0.95). **Conclusion:** PROMIS-29 domains and the summary PROPr measure are associated with transplant-free survival, decompensation, and healthcare use in cirrhosis. PROs may complement objective measures to identify high-risk patients who need additional support.

Table 1: Transplant-Free Survival Regression Analysis

	Unadjusted		Adjusted Model 1		Adjusted Model 2	
PROMIS domain T-scores for baseline questionnaire	HR (95% CI) for death/transplant	p-value	HR (95% CI) for death/transplant	p-value	HR (95% CI) for death/transplant	p-value
Physical function[2]	**0.93 (0.91-0.96)**	**<0.001**	**0.92 (0.90-0.95)**	**<0.001**	**0.97 (0.94-0.99)**	**0.016**
Anxiety[1]	1.02 (0.99-1.04)	0.152	1.02 (1.00-1.05)	0.053	1.02 (1.00-1.04)	0.102
Depression[1]	1.02 (1.00-1.05)	0.104	1.02 (1.00-1.05)	0.070	1.01 (1.01-0.99)	0.297
Fatigue[1]	**1.05 (1.02-1.07)**	**<0.001**	**1.05 (1.03-1.07)**	**<0.001**	**1.03 (1.01-1.05)**	**0.007**
Sleep Disturbance[1]	**1.03 (1.00-1.06)**	**0.047**	**1.03 (1.00-1.06)**	**0.027**	1.01 (0.98-1.04)	0.381
Ability to Participate in Social Roles and Activities[2]	**0.93 (0.91-0.96)**	**<0.001**	**0.93 (0.90-0.95)**	**<0.001**	**0.96 (0.93-0.98)**	**0.001**
Cognitive Function[2]	1.00 (0.97-1.02)	0.751	1.00 (0.97-1.02)	0.785	1.02 (0.99-1.05)	0.180
Pain Interference[1]	1.02 (0.99-1.04)	0.221	1.02 (0.99-1.04)	0.242	1.02 (0.99-1.04)	0.215
Pain Intensity[1]	1.05 (0.96-1.14)	0.305	1.04 (0.95-1.14)	0.363	1.02 (0.93-1.11)	0.706
PROPr **	**0.81 (0.71-0.91)**	**<0.001**	**0.80 (0.71-0.90)**	**<0.001**	0.91 (0.81-1.03)	0.126

*Model 1: adjusted for demographics (sex, gender, age, insurance status). Model 2: adjusted for disease burden (history of ascites, history of hepatic encephalopathy, MELD 3.0 score, modified Charlson Comorbidity score (non-liver comorbidity burden))

** PROMIS domain T-scores have a mean of 50 and standard deviation of 10. HR is interpreted per 1-pt increase in T-score for each domain, except for pain intensity (scale 0-10) and PROPr score (scale 0-1 with additional 0.1 unit rescale)

[1] higher T-score = worse health than average

[2] higher T-score = better health than average

Disclosures: Lauren Kasmikha: Nothing to Disclose, Mounika Kanneganti: Nothing to Disclose, Sudheer Dhoop: Nothing to Disclose, Elliot Tapper: Madrigal:

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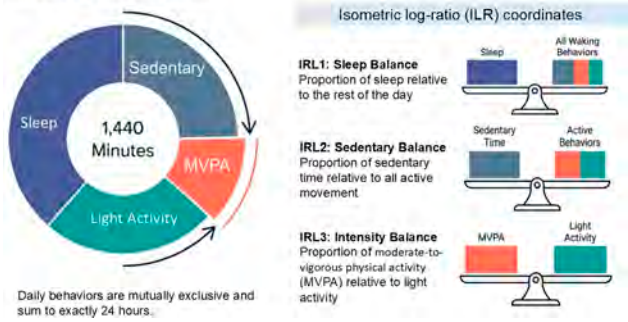
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2242 | ◆ REALLOCATING SEDENTARY TIME TO SLEEP IS ASSOCIATED WITH IMPROVED DISEASE SEVERITY IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD)

Lynn Gerber[1] James Paik[2] Markos Kalligeros[1] Ali Weinstein[1] Jonathen Stine[3] Shira Zelber-Sagi[4] Saleh Alqahtani[1] Kate Hallsworth[5] Elizabeth Pekas[1] Zobair Younossi[1], [1]The Global NASH/MASH Council, [2]Global NASH/MASH Council, [3]Penn State College of Medicine, Hershey, PA., USA, [4]The University of Haifa, [5]Newcastle University, UK

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is one of the leading causes of chronic liver disease worldwide. Current lifestyle recommendations address physical activity, sedentary behavior, and sleep as separate domains, even though time allocated to one behavior necessarily displaces time spent in another within the 24-hour day. Compositional data analysis (CoDA) accounts for this interdependence among movement behaviors; however, its relationship with liver stiffness measurement (LSM) (surrogate of disease severity) has not been evaluated in a nationally representative cohort of individuals with MASLD. **Methods:** Cross-sectional analysis of NHANES 2017–2018 including 889 adults with MASLD confirmed by vibration-controlled transient elastography (VCTE). Daily sleep, sedentary time, moderate-to-vigorous physical activity (MVPA), and other waking activities, summing to 1,440 minutes/day, were transformed into isometric log-ratio (ILR) coordinates and incorporated into survey-weighted regression models with log-transformed LSM, a surrogate marker of disease severity, as the outcome (Figure). Isotemporal substitution analyses estimated changes in LSM associated with reallocating 30 minutes between movement behaviors and were stratified according to alcohol use patterns. **Results:** Greater sedentary time relative to active behaviors was associated with 5.79% higher LSM (95% CI 1.14–10.66%; p = 0.027) after sociodemographic adjustment, attenuating after full cardiometabolic adjustment (3.73%; p = 0.086). Greater sleep relative to all other behaviors was independently associated with 15.55% lower LSM (95% CI −27.33% to −1.86%; p = 0.044), persisting after full adjustment (−14.38%, 95% CI −25.58% to −1.49%; p = 0.047). Reallocating 30 min/day of sedentary time to sleep yielded greater LSM reduction (−1.69%; p = 0.011) than reallocation to MVPA (−0.83%; p = 0.001), robust to obstructive sleep apnea and diet adjustment. Among former drinkers who carried the highest metabolic burden (type 2 diabetes 45%, hypertension 84%, obstructive sleep apnea 65%), sedentary-to-sleep reallocation was most beneficial (−2.24%; p = 0.005), while replacing sleep with MVPA paradoxically raised LSM (+2.57%; p = 0.021). Among low-income adults, sedentary-to-sleep yielded the largest effect (−3.09%; p < 0.001). **Conclusion:** Sleep is an independent metabolic determinant of disease severity, as assessed by LSM, in MASLD. Replacing sedentary time with sleep was associated with greater hepatic benefit than reallocating time to exercise, particularly among high-risk former drinkers and low-income adults. These findings support precision behavioral counseling in MASLD, whereby optimal daily movement and sleep targets may need to be individualized according to each patient's clinical and socioeconomic profile.

Figure. Compositional structure of 24-hour movement behaviors and corresponding isometric log-ratio coordinates



Disclosures: Lynn Gerber: Nothing to Disclose, James Paik: Nothing to Disclose, Markos Kalligeros: Nothing to Disclose, Ali Weinstein: Nothing to Disclose, Jonathen Stine: Nothing to Disclose, Shira Zelber-Sagi: Nothing to Disclose, Saleh Alqahtani: Nothing to Disclose, Kate Hallsworth: Nothing to Disclose, Elizabeth Pekas: Nothing to Disclose, Zobair Younossi: Zobair M. Younossi is a consultant or has received research: Consultant, madrigal: Grant/Research Support, Siemens: Research funding, GSK: Consultant, BI: Consultant, Sanofi: Research funding.

2243 | ◆ INCREASING HIGH-RISK ALCOHOL CONSUMPTION AMONG ADOLESCENTS, YOUNG ADULTS AND FEMALES OVER TIME MAY EXPLAIN INCREASING INCIDENT ALCOHOL-ASSOCIATED LIVER DISEASE

Courtney Campbell[1] Maya Djerboua[2] Kristel Leung[1] Sahar Saeed[1] Jennifer Flemming[3], [1]Queen's University, [2]ICES-Queen's, [3]Queen's University Cancer Research Institute

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Background: Severe alcohol-associated liver disease (ALD) is most rapidly increasing among adolescents and young adults (AYAs) and females and typically is a consequence of high-risk alcohol consumption. Yet, data suggest that the proportion of Canadians abstaining from alcohol is increasing and per capita consumption is decreasing. However, high-risk consumption trends remain to be characterized. This study aimed to describe age- and sex-specific high-risk alcohol consumption trends in Ontario, Canada. **Methods:** A retrospective population-based cohort of Canadian Community Health Survey (CCHS) respondents from Ontario aged 15-60 years from the 2003, 2005-2018 cross-sections were included. Self-reported alcohol consumption was categorized into groups to evaluate high-risk consumption: 1) daily and weekly standard drinks [1 drink = 14g alcohol]; 2) binge drinking frequency [>5 drinks for males and >4 drinks for females on one occasion] and; 3) monthly consumption frequency. Secular proportional changes in alcohol consumption over the study period were described by proportional changes according to age group (AYAs <40 vs. adults 40+) and sex. **Results:** 153,166 CCHS respondents were included (54% female, median age 39). From 2003 to 2018 (Figure), the proportion who participated in daily alcohol consumption increased among AYAs (33%), more so among females (74%) vs. males (21%) while daily consumption decreased among female and male adults. Further, weekly binge drinking increased by 45% among female AYAs and 131% for female adults yet decreased by -12% among male AYAs and -3% among male adults. For each category of weekly total drinks, female consumption rose (peaking at 27% for 8-14 drinks among female AYAs and 75% for >15 drinks among female adults). Among males, consumption only increased for 1-2 drinks among AYAs vs. 8-14 and >15 drinks among adults. Female adults similarly increased consumption among each total daily drinks category, while female AYAs increased all but the highest category (6+ drinks). Male AYAs only increased consumption of 6+ drinks while male adults only increased consumption of 4-6+ drinks, with all other consumption categories decreasing among males. **Conclusion:** High-risk alcohol consumption is rising over time among AYAs and females in Ontario in parallel with increasing incident ALD among these groups. These results suggest that increases in high-risk alcohol consumption could be driving these trends. Public health strategies to identify and provide intervention on those with high-risk use is a modifiable risk factor that could reverse severe ALD trends for future generations.

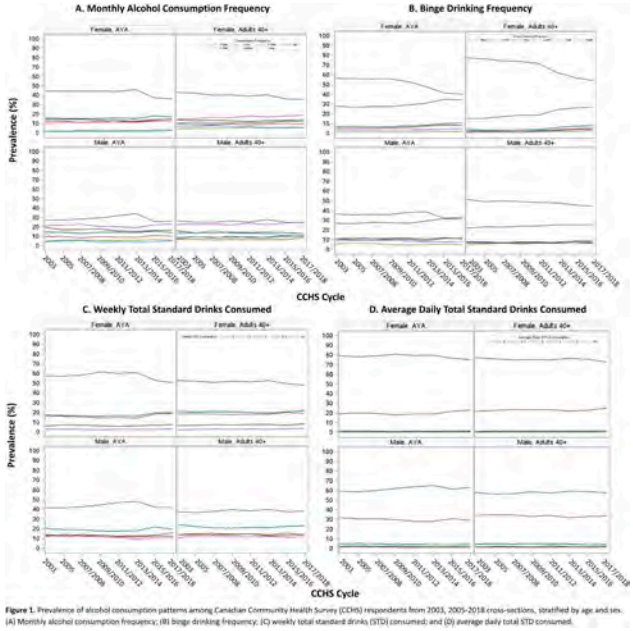


Figure 1. Prevalence of alcohol consumption patterns among Canadian Community Health Survey (CCHS) respondents from 2003, 2005-2018 cross-sections, stratified by age and sex. (A) Monthly alcohol consumption frequency; (B) binge drinking frequency; (C) weekly total standard drinks (STD) consumed; and (D) average daily total STD consumed.

Disclosures: Courtney Campbell: Nothing to Disclose, Maya Djerboua: Nothing to Disclose, Kristel Leung: Nothing to Disclose, Sahar Saeed: Novo Nordisk: Consultant, Jennifer Flemming: Nothing to Disclose.

2244 | SYMPTOM CLUSTERS AND 90-DAY HOSPITALIZATION RISK IN ADVANCED LIVER DISEASE

Brittany Bromfield[1] Elizabeth Aby[2] Melanie Hundt[3] Jonathan Rice[4] Mike Kriss[4] Kali Zhou[3] Lauren Nephew[5] Sarah Lieber[6] Alvaro Noriega Ramirez[6] Brett Fortune[7] Clara Tow[7] Paola Mejia[7] Deepika Devuni[8] Anita Krisharao[8] Shari Rogal[9] Stela Celaj[9] Alan Noll[10] Nathaly Cortez Bazan[11] Patricia Jones[12] Hersh Shroff[12] Krista Hunt[12] Areej Mazhar[13] Dempsey Hughes[13] Jackie Henson[14] Lindsay King[14] Thomas Leventhal[2] Enya Zhu[14] Grace Bizup[15] William Munroe[15] Lina Nurhussien[15] Nora Horick[15] Chengbo Zeng[16] Nneka Ufere[15], [1]Brigham and Women's hospital, [2]University of Minnesota, [3]University of Southern California, [4]University of Colorado, [5]Indiana University, [6]University of Texas Southwestern, [7]Montefiore Einstein Center for Transplantation, [8]University of Massachusetts, [9]University of Pittsburgh, [10]Tufts, [11]University of Miami, [12]University of North Carolina, [13]Northwestern University, [14]Duke University, [15]Massachusetts General Hospital, [16]Patient Reported Outcomes, Value and Experience (PROVE) Center, Department of Surgery

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Background: Patients with advanced liver disease (advLD) experience substantial multidimensional symptom burden associated with impaired quality of life and adverse clinical outcomes. Symptoms often occur in recognizable patterns, but whether these patterns identify patients at higher risk for near-term healthcare utilization beyond traditional clinical markers remains unclear. **Methods:** We conducted a secondary analysis of two prospective observational cohorts of patients with advLD. The first included adult outpatients with decompensated cirrhosis recruited from MGH between August 2018 and September 2022. The second included adult patients with advLD undergoing liver transplantation evaluation, recruited from 13 U.S. transplant centers between May 2023 and April 2024. Demographic and clinical characteristics were collected. Symptom burden was assessed using the revised Edmonton Symptom Assessment System (r-ESAS), a validated 10-item measure. Latent class analysis (LCA) identified empirically derived symptom clusters. Fine-Gray subdistribution hazard models, accounting for the competing risk of death, evaluated associations between symptom cluster membership and 90-day all-cause, unplanned, and liver-related hospitalization. Models were adjusted a priori for age, sex, race, ethnicity, ascites, hepatic encephalopathy, comorbidity burden, and MELD-Na score. **Results:** Among 584 patients included in the LCA, median age was 59 years, 59% were male, 52% had alcohol-related liver disease, and median MELD-Na score was 16. Four symptom clusters were identified: low burden (n = 151, 26%), tiredness/drowsiness (n = 224, 38%), SPPADE (high probability of anxiety, depression, impaired wellbeing, pain, tiredness, and drowsiness), (n = 88, 15%), and high burden (n = 121, 21%); defining symptom profiles are shown in the Table. Overall, 22% of patients were hospitalized within 90 days. Hospitalization rates were 19%, 21%, 17%, and 31% in the “low burden”, “tiredness and drowsiness”, “SPPADE”, and “high burden” clusters, respectively. Compared with the low burden cluster, the high burden cluster was associated with higher risk of all-cause hospitalization (SHR 2.09, 95% CI 1.24–3.51), unplanned hospitalization (SHR 2.47, 95% CI 1.42–4.31), and liver-related hospitalization (SHR 1.94, 95% CI 1.04–3.66). The tiredness/drowsiness and SPPADE clusters were not significantly associated with hospitalization risk. **Conclusion:** Among patients with advLD, membership in the high global symptom burden cluster was associated with increased risk of 90-day all-cause, unplanned, and liver-related hospitalization, independent of MELD-Na score and key decompensation features. These findings highlight the potential clinical value of routine multidimensional symptom screening as a complement to traditional risk assessment in hepatology practice.

Table. Symptom Clusters and 90-Day Hospitalization Risk in Advanced Liver Disease (N=584)

Symptom Cluster	Defining Symptom Profile	90-Day Hosp., % (n)	All-Cause SHR (95% CI)	Unplanned SHR (95% CI)	Liver-Related SHR (95% CI)
Low burden n=151 (26%)	Low endorsement across all 10 symptoms (all item probabilities <0.15)§	19% (28/151)	Reference	Reference	Reference
Tiredness and drowsiness n=224 (38%)	High tiredness and drowsiness; low endorsement of remaining symptoms	21% (46/224)	1.15 (0.72–1.84)	1.29 (0.78–2.13)	0.93 (0.44–1.47)
SPPADE n=88 (15%)	High probability of anxiety, depression, impaired wellbeing, tiredness, drowsiness, and pain	17% (15/88)	1.13 (0.59–2.17)	1.13 (0.55–2.33)	1.07 (0.48–2.39)
High burden n=121 (21%)	High endorsement across all 10 symptoms, including nausea, decreased appetite, and shortness of breath (most item probabilities >0.65)§	31% (38/121)	2.09 (1.24–3.51)‡	2.47 (1.42–4.31)‡	1.94 (1.04–3.66)‡

SHR, [illegible]; CI, confidence interval; Hosp., hospitalization; LCA, latent class analysis; and r-ESAS, revised Edmonton Symptom Assessment System.
* Subdistribution hazard ratios (95% CI) adjusted for age, sex, race, ethnicity, ascites, hepatic encephalopathy, comorbidity burden, and MELD-Na score. Low burden [illegible] reference group.
§ Endorsement reflects LCA-estimated probability of a positive response (≥4 on the 0–10 r-ESAS scale). Low burden: all item probabilities <0.15. High burden: [illegible].
‡ P<0.05 vs. low burden cluster.

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2246 | SCREENING FOR MASLD AMONG SUBJECTS WITH AND WITHOUT TYPE 2 DIABETES: IMPACT OF THE RECENT AGA PATHWAY UPDATE

Thuy-Duyen Nguyen[1] David Chascsa[2] Blanca Lizaola-Mayo[2] W. Ray Kim[2], [1]Mayo Clinic, [2]Mayo Clinic Arizona

Background: Effective screening for fibrotic MASLD remains an urgent public health priority. The 2026 updated AGA pathways suggest bypassing FIB-4 for direct elastography in high-risk (e.g. type 2 diabetes, T2DM) patients. Risk-based customization may make screening more complex and difficult to implement, whereas multivariable indices, such as the SAFE score, offer a more balanced alternative, integrating metabolic risk with laboratory parameters. **Methods:** National Health and Nutrition Examination Survey (NHANES) data from 2017-23 were used to evaluate the impact of the updated AGA pathway against (1) traditional FIB-4-first and (2) SAFE-based strategies (see Table). The updated AGA pathway was modeled using two allocation strategies: (1) allocating VCTE access proportionally between T2DM and non-T2DM patients and (2) prioritizing patients with T2DM. The high-risk screening population was identified based on updated AGA guidelines (adults with T2DM, obesity with one or more metabolic risk factors, or elevated aminotransferases). Significant liver fibrosis was defined as a median liver-stiffness measurement of $\geq$8.0 kPa. VCTE referral volume, diagnostic yield, and sensitivity were compared across the pathways. Finally, the pathways were compared with 3 scenarios with constrained VCTE capacities (top 5%, 10%, and 15% of the cohort). **Results:** The NHANES data estimated that the updated AGA screening criteria are met in 154.3 million US adults (95% CI, 143.1–165.4 million) in 2017–20 and 147.5 million (95% CI, 132.9 – 162.1 million) in 2021-23. In the Table, when elastography is available to all, the updated AGA pathways (including #1 and #2) achieved the highest sensitivity while using the most elastographies. The SAFE score approach was more efficient, with a higher positive predictive value and a lower number needed to screen than the updated pathways. In the scenarios where elastography is limited to 5%, 10%, or 15% of the eligible population, the SAFE approach maximized fibrosis detection across all utilization levels. The traditional FIB-4-first approach remained the least sensitive and efficient across all cohorts. **Conclusion:** The updated AGA pathway improves screening sensitivity by more than 50% compared to the traditional FIB-4-first method, but at the expense of a substantial increase in elastography utilization. In settings where elastography is constrained to a smaller proportion of the population, the SAFE score approach is most efficient.

Table 1. Comparison Between Pathways and Sensitivity of Significant Fibrosis (LSM ≥ 8 kPa) Detection

	2017– 2020								2021 – 2023							
Screening pathway	Traditional		Updated #1 (Proportional)		Updated #2 Prioritize T2DM		SAFE		Traditional		Updated #1 (Proportional)		Updated #2 Prioritize T2DM		SAFE	
T2DM	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Score criteria	High FIB-4[1]	High FIB-4[1]	Any FIB-4	High FIB-4[1]	Any FIB-4	N/A	SAFE ≥100	SAFE ≥100	High FIB-4[1]	High FIB-4[1]	Any FIB-4	High FIB-4[1]	Any FIB-4	N/A	SAFE ≥100	SAFE ≥100
No constraint in elastography resources																
% Elastography utilization	21.1%	13.2%	100%	13.2%	100%	0%	46.6%	7.2%	22.1%	14.2%	100%	14.2%	100%	0%	50.6%	9.5%
	14.8%		30.8%		20.1%		15.2%		15.8%		31.2%		19.8%		17.7%	
% of elastography with positive results	27.8%	8.1%	21.8%	8.1%	21.8%	-	30.1%	12.7%	32.4%	13.0%	24.8%	13.2%	24.8%	-	28.7%	19.8%
	13.6%		17.1%		21.8%		23.7%		18.4%		19.3%		23.0%		24.9%	
NNS	7.3 (5.3 – 9.2)		5.8 (4.8 – 6.9)		4.6 (3.7 – 5.4)		4.2 (3.4 – 5.0)		23.3% (19.6 – 27.0%)		48.5% (42.7 – 54.3%)		36.6% (31.0 – 42.3%)		35.4% (30.3 – 40.5%)	
Overall sensitivity (95% CI)	20.5% (15.0 – 27.4%)		53.1% (46.4 – 59.6%)		44.5% (39.2 – 49.7%)		36.1% (30.5 – 42.1%)		5.4 (4.3 – 6.7)		5.2 (4.5 – 5.9)		4.4 (3.8 – 4.9%)		4.0 (3.5 – 4.7)	
Sensitivity in scenarios with elastography resources constraints																
Elastography in 5%	6.9% (5.0 – 8.8%)		8.6% (7.5 – 9.7%)		11.0% (9.7 – 12.2%)		11.9% (10.4 – 13.4%)		7.4% (6.0 – 8.8%)		7.8% (6.8 – 8.7%)		9.2% (8.1 – 10.4%)		10.0% (8.6 – 11.4%)	
Elastography in 10%	13.8% (10.1 – 17.6%)		17.2% (15.1 – 19.4%)		21.9% (19.4 – 24.5%)		23.8% (20.8 – 26.8%)		14.8% (12.0 – 17.5%)		15.5% (13.7 – 17.4%)		18.5% (16.1 – 20.8%)		20.0% (17.2 – 27.8%)	
Elastography in 15%	20.5%[2] (15.0 – 27.4%)		25.8% (22.6 – 29.0%)		32.8% (29.1 – 36.8%)		35.7% (31.1 – 40.2%)		22.1% (18.1 – 26.1%)		23.3% (20.5 – 26.1%)		27.7% (24.2 – 31.3%)		30.0% (25.8 – 34.2%)	

[1]FIB-4 ≥ 2.0 if age ≥65 years, FIB-4 ≥1.3 otherwise.
[2]Data for the maximum proportion to be tested of 14.8% shown

Disclosures: Thuy-Duyen Nguyen: Nothing to Disclose, David Chascsa: Nothing to Disclose, Blanca Lizaola-Mayo: Nothing to Disclose, W. Ray Kim: Nothing to Disclose.

2247 | HEPATITIS B PATIENT-REPORTED OUTCOMES: MULTINATIONAL INSIGHTS ON QUALITY OF LIFE AND ANTIVIRAL ADHERENCE

Yasmin Ibrahim[1] Catherine Freeland[1] Chari Cohen[1], [1]Hepatitis B Foundation

Background: Quality of life (QoL) and treatment adherence are underexplored components of care for people living with hepatitis B (PLWHB). Patient-reported outcomes (PROs) remain largely absent from routine clinical management. This study (1) longitudinally evaluates hepatitis B–related QoL; (2) assesses rates of and variables associated with antiviral adherence; and (3) compares PROs and adherence between treatment-status cohorts. **Methods:** This global, longitudinal mixed-methods study recruited adults (18+) via convenience sampling for multilingual online surveys at baseline, 3- and 6-months. Validated instruments include HBQoL, PMAI-9, and CEAT-HBV alongside supplemental questions on treatment status, patient–provider communication, and care barriers. Analyses include descriptive statistics, multivariate logistic regression, and propensity score matching. **Results:** To date, 486 PLWHB have completed the baseline survey (mean age 42.1 years, 69.6% male) from 42 countries. 50.9% reported currently taking antiviral treatment, primarily tenofovir. Among treated participants, knowledge and adherence were high: 94.5% agreed/strongly agreed they understood why they were taking medication, 93.1% understood how to take it, and 86.2% reported taking medication daily as directed.

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76.1% described themselves as “quite”/“very” compliant with therapy; 84.4% expressed confidence that treatment was helping their hepatitis B. Fatigue or weakness was the most reported symptom (44.0%), and over half reported being “quite”/”extremely” concerned about liver morbidity and mortality. While most reported high medical care engagement, some (26.1%) rated the relationship with their doctor as “poor,” “somewhat poor,” or “fair”. Among participants not taking antiviral therapy, 63.7% were not engaged in any hepatitis B care. The most reported barriers were high medication/healthcare costs (37.4%), provider/medication inaccessibility (17.8% and 18.2%, respectively), and feeling healthy (17.8%). Willingness to initiate future treatment was high: 73.5% reported they would be “very willing” to start antiviral therapy if recommended and 74.4% indicated high confidence in taking a daily medication. Psychosocial burden remained substantial with concerns spanning stigma, anxiety, and long-term liver complications. **Conclusion:** This ongoing study represents one of the largest, multinational investigations of QoL and antiviral adherence among PLWHB. We elucidate QoL impact and adherence alongside systemic barriers/facilitators to adherence for future patient-centered interventions.

Disclosures: Yasmin Ibrahim: Roche/ Genentech: Speaking and Teaching, Vir Biotechnology: Speaking Honorarium paid to the Hepatitis B Foundation, Catherine Freeland: Nothing to Disclose, Chari Cohen: Vio Biotechnology: grant funds renumerated to Hepatitis B Foundation, Dynavax Technologies: grant funds renumerated to Hepatitis B Foundation, Gilead Sciences: grant funds renumerated to Hepatitis B Foundation, GSK: grant funds renumerated to Hepatitis B Foundation, Roche: grant funds renumerated to Hepatitis B Foundation, Gilead Sciences: funds renumerated to Hepatitis B Foundation, GSK: funds renumerated to Hepatitis B Foundation.

2248 | URINARY CANNABIS METABOLITES AND LIVER-RELATED OUTCOMES IN CIRRHOSIS: RESULTS FROM THE SOUTHERN LIVER HEALTHY STUDY (STRIVE)

Kaia Miller[1] Xintian Song[2] Eghosa Adodo[1] Marjorie Riggan[1] Alina Greene[3] Rachel Maguire[3] Lucas Li[1] Valerie Dartey-Hayford[1] Chukwuemeka Oko[4] Ashley Jowell[5] Andrew Moon[6] Joellen Schildkraut[2] Susan Murphy[1] Cathrine Hoyo[3] Cynthia Moylan[1], [1]Duke University, [2]Emory University, [3]North Carolina State University, [4]Duke University Hospital, [5]Duke University Medical Center, [6]University of North Carolina

Background: Cannabis use has become increasingly prevalent across the United States. Current studies suggest that cannabis use confers anti-inflammatory and anti-fibrotic benefits via modulation of hepatic endocannabinoid pathways, but its impact on the natural history of cirrhosis remains controversial. We aimed to determine whether cannabis use impacts disease outcomes in cirrhosis. **Methods:** We conducted a nested cross-sectional study of participants (pts) in the Southern Liver Health Study (STRIVE), a prospective multi-site study exploring environmental exposures in cirrhosis. We included pts aged 40-75 years with diagnosed cirrhosis and without hepatocellular carcinoma (HCC) at enrollment between 1/11/22 and 8/22/24 in North Carolina and Georgia. Pts were followed and medical records were abstracted for health history, including death, liver transplantation (LT), or diagnosis of HCC. The primary metabolite of cannabis (THC-COOH) was quantified from baseline urine using UPLC-MS/MS and reported as creatinine-normalized. The primary outcome was a composite of liver-related outcomes (LROs) including HCC, LT, or liver-related death. Fine-Gray subdistribution hazard models were used to estimate adjusted associations between cannabis exposure and LROs, controlling for site, age, sex, race, cigarette use, alcohol use, and diabetes. Proportional subdistribution hazard assumptions were confirmed using cumulative residual-based diagnostics and Kolmogorov–Smirnov type statistics. **Results:** 185 pts with cirrhosis and urine samples at baseline were included. 44 had detectable cannabis levels (**Table 1**). Over a median follow-up of 33 months, 58 LROs occurred, including 14 incident HCC, 15 LTs, and 29 liver-related deaths. 20 non-liver-related deaths occurred as competing events. The cumulative incidence of LROs did not differ significantly by cannabis exposure status (Gray’s test $p = 0.60$). However, cannabis-exposed pts exhibited a higher incidence of LROs within the first 1 year (23% vs. 16%), which attenuated by 2 years (25% vs. 24%) and crossed over by 3 years (27% vs. 29%). In adjusted models, cannabis exposure was not associated with LROs (sHR = 0.73, $p = 0.40$) while reported alcohol use was (sHR = 2.16, $p = 0.042$). When cannabis was modeled continuously using log-transformed THC-COOH concentration, higher concentrations showed a trend toward a protective effect (sHR per log-unit increase 0.90, $p = 0.091$). **Conclusion:** Nearly 25% of STRIVE pts with cirrhosis had detectable cannabis metabolites. Cannabis was not associated with future risk of LROs in this analysis, however findings suggest that cannabis metabolites may provide additional prognostic information in larger longitudinal cohorts. Larger future investigations in STRIVE will continue to explore this, as well as whether other environmental exposures interact

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with the impact of cannabis use on cirrhosis outcomes.

Table 1. Distribution of demographic and clinical characteristics.

	Overall N = 185[1]	No Liver-Related Outcomes N = 107[1]	HCC or Liver-Related Death or Liver Transplant N = 58[2]	Other death N = 20[1]	p-value[3]
Follow-up time (months)	33 (17)	45 (5)	14 (12)	20 (11)	<0.001
Site					0.3
Duke	121 (65%)	65 (61%)	39 (67%)	17 (85%)	
Emory	51 (28%)	34 (32%)	15 (26%)	2 (10%)	
UNC	13 (7.0%)	8 (7.5%)	4 (6.9%)	1 (5.0%)	
Region					0.13
Georgia	51 (28%)	34 (32%)	15 (26%)	2 (10%)	
North Carolina	134 (72%)	73 (68%)	43 (74%)	18 (90%)	
Detectable Cannabis (THC-COOH)	44 (24%)	27 (25%)	12 (21%)	5 (25%)	0.6
Detectable Cannabis (CBD)	17 (9.2%)	10 (9.3%)	6 (10%)	1 (5.0%)	>0.9
Age at enrollment	61 (9)	60 (9)	60 (9)	65 (8)	0.074
Sex, Male	95 (51%)	51 (48%)	32 (55%)	12 (60%)	0.5
Race					0.4
White	152 (82%)	85 (79%)	51 (88%)	16 (80%)	
Black	22 (12%)	13 (12%)	5 (8.6%)	4 (20%)	
Other	11 (5.9%)	9 (8.4%)	2 (3.4%)	0 (0%)	
BMI (kg/m^2)	31 (7)	30 (7)	32 (8)	31 (7)	0.5
Diabetes	85 (46%)	54 (50%)	22 (38%)	9 (45%)	0.3
Cigarette use, ever	27 (15%)	16 (15%)	6 (10%)	5 (25%)	0.3
Alcohol use, ever	132 (71%)	69 (64%)	47 (81%)	16 (80%)	0.053

[1]Mean (SD); n (%)
[2]Breakdown of events: HCC (n=14), Liver Transplant (n=15), Liver-Related Death (n=29)
[3]Kruskal-Wallis rank sum test; Fisher's exact test; Pearson's Chi-squared test
Abbreviations: UNC = University of North Carolina-Chapel Hill; CBD = cannabidiol; BMI = body mass index

Disclosures: Kaia Miller: Nothing to Disclose, Xintian Song: Nothing to Disclose, eghosa adodo: Nothing to Disclose, Marjorie Riggan: Nothing to Disclose, Alina Greene: Nothing to Disclose, Rachel Maguire: Nothing to Disclose, Lucas Li: Nothing to Disclose, Valerie Dartey-Hayford: Nothing to Disclose, Chukwuemeka Oko: Nothing to Disclose, Ashley Jowell: Nothing to Disclose, Andrew Moon: TARGET RWE: Consultant, DCN Diagnostics: Grant/Research Support, Intercept Pharmaceuticals: DSMB, IDEOlogy: Consultant, Eisai: Consultant, AstraZeneca: Consultant, Sirtex: Consultant, Madrigal: Grant/Research Support, Joellen Schildkraut: Nothing to Disclose, Susan Murphy: Nothing to Disclose, Cathrine Hoyo: Nothing to Disclose, Cynthia Moylan: GSK: Grant/Research Support, GSK: Grant/Research Support, Madrigal Pharmaceuticals: Grant/Research Support, Madrigal Pharmaceuticals: Grant/Research Support, Exact Sciences: Grant/Research Support, Exact Sciences: Grant/Research Support, Sirtex: Advisor, Sirtex: Advisor, NovoNordisk: Consultant, NovoNordisk: Consultant, GSK: Grant/Research Support, GSK: Grant/Research Support, Madrigal Pharmaceuticals: Grant/Research Support, Madrigal Pharmaceuticals: Grant/Research Support, Exact Sciences: Grant/Research Support, Exact Sciences: Grant/Research Support, Sirtex: Advisor, Sirtex: Advisor, NovoNordisk: Consultant, NovoNordisk: Consultant.

2249 | THE PREVALENCE, CAUSES, AND TEMPORAL TRENDS IN ALANINE AMINOTRANSFERASE ELEVATION AND CONCURRENT HEPATIC STEATOSIS AMONG U.S. ADULTS

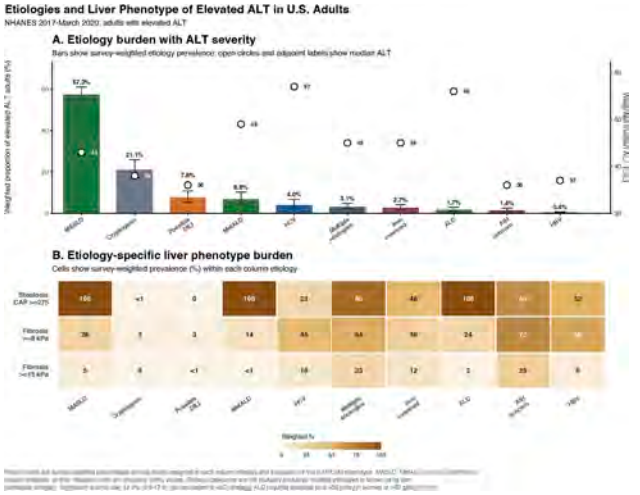
Timothy Davie[1] Jesse Fletcher[1] Kartik Dapke[2] Anna Strauss[1] Serena Brosten[1] Giovanni Roldan[3] Prowpanga Udompap[4], [1]Department of Medicine, University of Minnesota, [2]Department of Medicine, Saint Vincent Hospital, Worcester, MA, [3]Division of Gastroenterology, Hepatology and Nutrition, University of Minnesota, [4]Division of Gastroenterology, Minneapolis VA Medical Center

Background: Alanine aminotransferase (ALT) is the most commonly used liver enzyme for evaluating liver health. There is a lack of contemporary and historical data that estimates the prevalence of elevated ALT in the U.S population. We aim to provide a modern estimate of elevated ALT among U.S. adults, phenotype this population to identify specific underlying etiologies, and analyze national prevalence trends over a 20-year period. **Methods:** We performed a cross-sectional analysis using data from the National Health and Nutrition Examination Survey (NHANES) from 2003 to 2023 to evaluate the prevalence of U.S. adults with ALT elevation over the 20-year span. Adults aged ≥ 20 years with available ALT data were included. Elevated ALT was determined using standardized sex-specific thresholds of >33 U/L for men and >25 U/L for women. The specific etiology of ALT elevation was defined only for the participants in NHANES 2017-2020 given the availability of the data including vibration controlled transient elastography, medication, laboratory, and survey data. This allowed for classification into distinct categories: Metabolic Dysfunction Associated Steatotic Liver Disease (MASLD), MASLD with increased alcohol intake (MetALD), alcohol-associated liver disease, viral hepatitis (B or C), iron overload, suspected autoimmune hepatitis (AIH), or drug-induced liver injury (DILI). The participants without a clear etiology of ALT elevation were categorized as cryptogenic. **Results:** The proportion of participants with ALT elevation was downtrending from 24.4% in 2003-2004 to 18.4% in 2001-2023. Similar trends remained with stratification based on sex. When focusing on the most complete dataset from 2017 to 2020, 18.1% of participants, or approximately 40.8 million U.S. adults, had elevated ALT. Those with elevated ALT were more

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likely to be younger (49 vs 53 years), with elevated BMI (32 vs 30 kg/m^2). MASLD was the dominant etiology of ALT elevation (57.3%), followed by cryptogenic (21.1%), possible DILI(7.6%), and the rest shown in Figure 1A. Notably, hepatic steatosis (controlled attenuation parameters $\geq$275 dB/m) was a prominent feature across the entire etiologic spectrum, extending well beyond MASLD, MetALD, and ALD to affect high proportions of patients with hepatitis B infection (52%), AIH (69%), and multi-factorial liver diseases (86%) (Figure 1B). **Conclusion:** While the prevalence of elevated ALT gradually declined from 2003 to 2023, it remains high as nearly one out of five U.S. adults had elevated ALT. While MASLD is a primary driver, concurrent hepatic steatosis frequently overlaps with non-metabolic and non-alcoholic etiologies including but not limited to hepatitis B infection, AIH. Further research is warranted to granularly phenotype these diverse cohorts and clarify the clinical intersection between steatosis and secondary liver diseases.



Disclosures: Timothy Davie: Nothing to Disclose, Jesse Fletcher: Nothing to Disclose, Kartik Dapke: Nothing to Disclose, Anna Strauss: Nothing to Disclose, Serena Brosten: Nothing to Disclose, Giovanni Roldan: Nothing to Disclose, Prowpanga Udompap: Nothing to Disclose.

2250 | PSYCHOLOGICAL DISTRESS AMONG PATIENTS WITH DECOMPENSATED CIRRHOSIS AND THEIR CAREGIVERS: A LONGITUDINAL DYADIC COHORT STUDY

Brittany Bromfield[1] Grace Bizup[2] William Munroe[2] Maria Edelen[1] Chengbo Zeng[1] Nneka Ufere[3], [1]Brigham and Women's Hospital, [2]Massachusett's General Hospital, [3]Massachusetts General Hospital

Background: Patients with decompensated cirrhosis (DC) and their caregivers face high rates of psychological distress associated with poor clinical outcomes, yet are often studied in isolation rather than as an interdependent dyadic unit. Longitudinal dyadic data in hepatology remain limited. Prior cross-sectional work identified an association in which caregiver anxiety was linked to higher patient depression, but whether this association persists longitudinally remains unknown. **Methods:** We conducted a prospective cohort study of 127 patient-caregiver dyads enrolled at a single academic hepatology center from 8/2018 to 9/2022. Participants completed the validated Hospital Anxiety and Depression Scale (HADS) at baseline, 6, 12, and 24 weeks. We characterized the prevalence, co-prevalence, and longitudinal patterns of clinically significant anxiety and depression. Longitudinal associations between caregiver anxiety and patient depression were assessed using linear mixed-effects models, adjusting for age, sex, marital status, comorbidity burden, and Child-Pugh score. Sensitivity analyses used multiple imputation (MI), inverse probability weighting (IPW), and restricted follow-up windows to address approximately 50% attrition by week 24. **Results:** Among 127 dyads, patients had a median age of 60 years, 55% were male, median MELD-Na was 16, and 93% had Child-Pugh B/C cirrhosis; caregivers had a median age of 59 years, 62% were female, and 63% were spouses. Psychological distress was common and frequently co-prevalent: clinically significant anxiety was present in 48% of patients and 52% of caregivers, with both partners affected in 26% of dyads. Clinically significant depression was present in 41% of patients and 35% of caregivers, with both partners affected in 18% of dyads. Scores were stable across four timepoints; caregivers reported higher anxiety than patients through week 12, while patients reported higher depression at every timepoint. Across 24 weeks of follow-up, higher caregiver anxiety was associated with higher patient depression after adjustment (adjusted $\beta = 0.20$, 95% CI: 0.11-0.30). This association was consistent across IPW, MI, and shorter follow-up sensitivity analyses. **Conclusion:** Psychological distress was prevalent, co-prevalent, and longitudinally associated within patient-caregiver dyads affected by DC. The association between caregiver anxiety and patient depression persisted across analytic approaches despite substantial attrition, underscoring the importance of including caregivers in psychosocial assessment frameworks. These findings support consideration of dyadic screening and future trials evaluating whether caregiver-informed interventions may help improve psychological burden in advanced liver disease.

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Table. Association between caregiver anxiety and patient depression across analytic approaches and follow-up windows

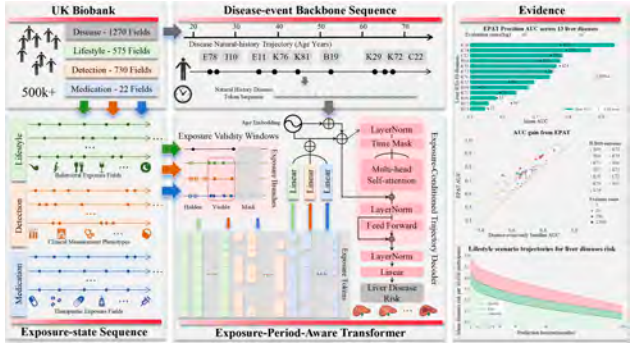
	Primary analysis (0–24 weeks)		Sensitivity analyses	
Analytic approach	Unadjusted β (95% CI)	Adjusted† β (95% CI)	0–6 weeks Adjusted β (95% CI)	9–12 weeks Adjusted β (95% CI)
Complete-case analysis	0.29 (0.18–0.40)	0.20 (0.11–0.29)	0.16 (0.04–0.28)	0.17 (0.07–0.27)
Multiple imputation	0.17 (0.07–0.27)	0.10 (0.02–0.19)	0.11 (0.01–0.22)	0.09 (0.00–0.18)
Inverse probability weighting	0.28 (0.17–0.39)	0.20 (0.10–0.30)	0.15 (0.03–0.27)	0.17 (0.07–0.28)

Disclosures: Brittany Bromfield: Nothing to Disclose, Grace Bizup: Nothing to Disclose, William Munroe: Nothing to Disclose, Maria Edelen: Nothing to Disclose, Chengbo Zeng: Nothing to Disclose, Nneka Ufere: Nothing to Disclose.

2251 | AGE-ALIGNED WHOLE-HEALTH DISEASE-TRAJECTORY MODELING IMPROVES LIVER DISEASE RISK PREDICTION

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Background: Liver disease risk reflects long-term interactions between prior diagnoses, lifestyle, clinical measurements and therapies, but these data have different temporal validity. Disease-event tokenization captures longitudinal natural-history structure, yet disease-only sequences omit important exposure and health-state information that shapes whole-health trajectories. Conversely, directly incorporating high-dimensional exposures into event sequences may overburden and dilute the disease event structure, while also introducing temporally invalid information. We therefore developed an Exposure-Period-Aware Transformer that aligns exposure information to age-indexed disease trajectories for liver risk prediction. **Methods:** Among 501,936 UK Biobank participants, we constructed a disease-event backbone sequence from longitudinal diagnostic histories and exposure-state sequences from lifestyle, clinical measurement and medication fields. The model encodes disease natural-history tokens using age embedding, while exposure branches are organized by predefined exposure validity windows so that only temporally eligible information contributes to prediction. Exposure representations are then projected into the disease-event backbone and processed by a time-masked multi-head self-attention decoder. We predicted 13 ICD-10 liver diseases across eight horizons from 1 to 120 months, compared performance with a disease-event-only baseline and evaluated healthy/unhealthy lifestyle scenarios. **Results:** Across 104 disease-horizon prediction cells, the main configuration achieved mean and median AUCs of 0.7175 and 0.7350; alcoholic liver disease was the best-performing outcome (AUC 0.9413). Relative to the disease-event-only baseline, mean AUC increased from 0.6464 to 0.7175, with improvements in 96 of 104 cells, including the 60- and 120-month horizons (+0.0772 and +0.0769). Ablation analyses supported the contribution of temporally aligned exposures: disabling exposure-branch inputs at inference reduced mean AUC by 0.0691, and training without these inputs reduced mean AUC by 0.0829. Bootstrap estimates supported robustness, with a macro-AUC 95% CI of 0.6859 to 0.7492 and both ablation contrasts excluding zero. In lifestyle scenario analyses, less healthy profiles increased disease risk by 17.0%, whereas healthier profiles reduced it by 11.8%; alcoholic liver disease showed the largest directional response (+79.2% and -34.7%). **Conclusion:** The Exposure-Period-Aware Transformer reframes liver risk prediction as age-indexed whole-health trajectory modeling. Age-aligned exposure integration improved performance over disease-event-only modeling and supported clinically plausible lifestyle responses, highlighting a promising framework for long-term liver disease risk prediction.



Disclosures: Muxue Liang: Nothing to Disclose, Ruoqian Li: Nothing to Disclose, Haibo Wang: Nothing to Disclose, You Wu: Nothing to Disclose.

2252 | ANCESTRY-SPECIFIC HSD17B13 PROTECTION AGAINST CIRRHOSIS: A MULTI-ANCESTRY WHOLE-GENOME ANALYSIS OF 414,830 ALL OF US PARTICIPANTS

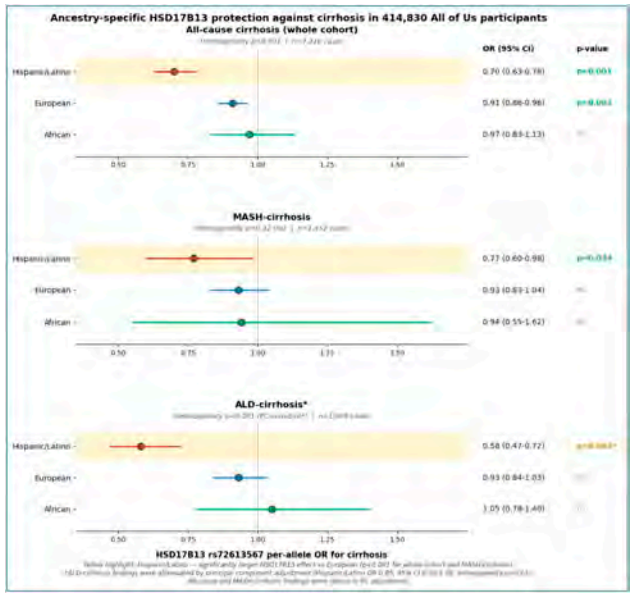
Hyunseok Kim[1] Derin Celtik[1] Walid Ayoub[1] Alexander Kuo[2] Paul Martin[2] Aarshi Vipani[2] Yun Wang[2] Yee Hui Yeo[2] Debiao Li[2] Stephen Pandol[2] Juan Pablo Arab[3] Suthat Liangpunsakul[4] Shelly Lu[2] JuDong Yang[2], [1]Cedars-Sinai Medical Center, [2]Cedars Sinai Medical

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Background: HSD17B13 loss-of-function variant rs72613567 is under therapeutic development for metabolic dysfunction-associated steatohepatitis (MASH) and alcohol-associated liver disease (ALD). Whether HSD17B13 effects differ across cirrhosis subtypes and ancestries has not been characterized at scale. **Methods:** Among 414,830 All of Us participants with whole-genome sequencing, we tested HSD17B13 rs72613567 per-allele effects on (1) all-cause cirrhosis (7,216 cases), (2) ALD-cirrhosis (heavy drinkers without viral hepatitis; 1,999 cases), and (3) MASH-cirrhosis (MASLD ICD + cardiometabolic criterion, no alcohol/viral hepatitis; 1,452 cases). Per-allele logistic regression adjusted for age, sex, BMI, and diabetes, stratified by genetically-determined ancestry (European [EUR], African [AFR], Admixed American [AMR; predominantly Hispanic/Latino]). Ancestry × HSD17B13 interaction was tested by likelihood ratio. **Results:** HSD17B13 effects differed significantly by ancestry (interaction $p < 0.001$ for all-cause cirrhosis), driven by larger effect in AMR vs EUR ($p < 0.001$). AMR participants showed the strongest protection: all-cause cirrhosis OR 0.70 (95% CI 0.63-0.78, $p < 0.001$) and MASH-cirrhosis OR 0.77 (0.60-0.98, $p = 0.034$), with directionally consistent ALD findings. EUR participants showed modest all-cause protection (OR 0.91, 0.86-0.96, $p < 0.001$) but no effect in MASH or ALD subsets. AFR participants showed no protection in any cohort (all-cause OR 0.97; ALD OR 1.05; MASH OR 0.94; all $p > 0.6$), despite $n = 83,064$, the largest HSD17B13 rs72613567 analysis in African-ancestry liver disease. Allele frequencies matched gnomAD (EUR 0.267; AMR 0.136; AFR 0.071), with the variant paradoxically least common in AMR, the ancestry with largest effect. In AMR, protection was observed across PNPLA3 G-carrier and non-carrier strata. ~6.8 million US Hispanic/Latino adults carry the protective allele. Findings were robust to principal component adjustment for the well-powered all-cause and MASH analyses. **Conclusion:** In the largest multi-ancestry WGS analysis of HSD17B13 in clinically-defined cirrhosis subtypes, we identify formally significant ancestry-specific effects: substantial protection in AMR, modest protection in EUR, and no detectable protection in AFR. For HSD17B13-targeted therapies in development for ALD and MASH, Hispanic/Latino patients may represent a priority population for ancestry-stratified therapeutic development.



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2253 | EFFECTS OF STATIN AND ASPIRIN ON RISK OF HEPATOCELLULAR CARCINOMA IN CHRONIC LIVER DISEASE: A POPULATION-BASED PROPENSITY-MATCHED COHORT STUDY

Arunkumar Krishnan[1] Diptasree Mukherjee[1] Carolin Schneider[2] Tatyana Kushner[3] Jörn Schattenberg[4] Nicola Pugliese[5] Christina Lindenmeyer[6] Amit Singal[7] Saleh Alqahtani[8], [1]Atrium Health, [2]RWTH Aachen University, [3]Weill Cornell Medicine, [4]Rheinland-Pfalz, [5]Humanitas Research Hospital, [6]Cleveland Clinic, [7]UT

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Background: Statins and aspirin have been proposed as chemopreventive agents against hepatocellular carcinoma (HCC), but their independent and combined associations remain uncertain due to confounding by indication. We evaluated the association between statin and aspirin exposure and incident HCC in a large real-world cohort of patients with chronic liver disease. **Methods:** We conducted a population-based propensity-matched retrospective cohort study using the TriNetX network. Adults with chronic liver disease (MASLD, viral hepatitis, alcoholic liver disease, autoimmune/cholestatic liver disease, cryptogenic cirrhosis) with at least 12 months of prior observation between January 1, 2016, and December 31, 2025, were included. Patients with prior HCC, other primary liver malignancy, or liver transplantation were excluded. Patients were classified into four exposure groups: neither statin nor aspirin; statin only; aspirin only; statin plus aspirin. Three pairwise 1: 1 propensity-matched comparisons were constructed versus the no-therapy group, with propensity scores incorporating demographics, liver disease etiology, non-invasive markers, cirrhosis status, comorbidities, renal function, and concurrent metformin and GLP-1RA use. The primary outcome was incident HCC, analyzed by Cox proportional hazards models. **Results:** Of 428,915 eligible patients, 132,480 statin-only, 47,360 aspirin-only, and 51,220 statin+aspirin users were each matched 1: 1 to no-therapy controls (all standardized mean differences < 0.1 after matching). Over a median follow-up of 4.8 years, statin monotherapy was associated with a significant reduction in HCC hazards (HR 0.55, 95% CI 0.47–0.64). Aspirin monotherapy showed a more modest protective association (HR 0.80, 95% CI 0.66–0.97). The combination of statin plus aspirin was associated with the greatest HCC risk reduction (HR, 0.40; 95% CI, 0.33–0.49). Subgroup analyses by liver disease etiology demonstrated the most pronounced statin-associated risk reduction in MASLD and viral hepatitis; a protective effect was preserved, though attenuated, in alcoholic liver disease and cirrhosis. In exploratory models additionally adjusting for time-updated cardiovascular medications, statin HRs remained stable, whereas the aspirin-only HR moved toward the null, suggesting that the aspirin association is more susceptible to residual confounding by concomitant therapies. Results were consistent in sensitivity analyses. **Conclusion:** Statin therapy was associated with a substantial reduction in HCC risk, while statin plus aspirin conferred the greatest observed benefit. The aspirin-only association was smaller and sensitive to residual confounding, suggesting a more fragile independent effect. These findings reinforce statins as a leading chemoprevention candidate in chronic liver disease and support selective, risk-stratified evaluation of adjunctive aspirin therapy.

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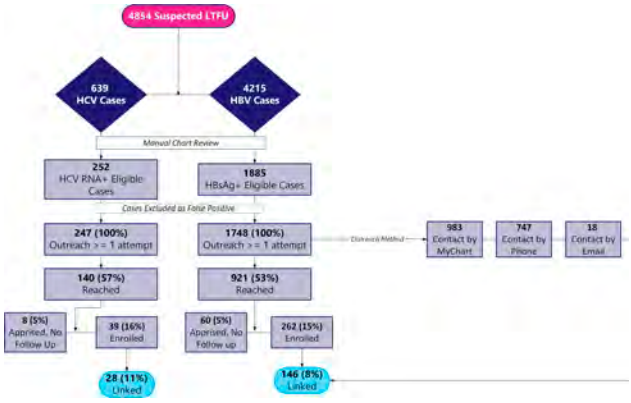
2254 | RELINKING PATIENTS WITH DIAGNOSED BUT UNTREATED HEPATITIS B AND C IN THE MOUNT SINAI HEALTH SYSTEM IN NYC

Tasnim Bhuiyan[1] Daemena Leocadio[1] Jihae Jeon[1] Francina Collado[1] Anna Mageras[1] Daryin Hummel[1] Lismeiry Paulino[1] Christopher Kim[1] Andrea Branch[2] Douglas Dieterich[1], [1]Icahn School of Medicine at Mount Sinai, [2]Icahn School of Medicine at Mount Sinai (ISMMS)

Background: We used digital phenotyping algorithms to find patients with chronic viral hepatitis (HBsAg+ and/or HCV RNA+) who might benefit from outreach. We aimed to provide linkage to care for patients who were not currently receiving it. **Methods:** Patient navigators (PNs) reviewed 4854 charts and excluded 2717 patients who were already in care or were otherwise ineligible (7/2024 to 4/2026). Exclusions included: a) Newly screened HBsAg+ and HCV RNA+ patients, b) Latest HCV RNA viral load negative, c) HBsAg+ but with an active prescription for HBV medication, or a visit to hepatology, gastroenterology, oncology, or infectious disease in the past 12 months, or receiving care from a PCP following AASLD guidelines for HBV management (including annual HCC surveillance), a suspected false positive test, or insurance coverage issues. At least three attempts were made to contact each of the remaining patients via multiple modalities. MyChart was used for initial outreach if available, otherwise phone and email were used. **Results:** Manual review showed that 252 HCV RNA+ patients were eligible for contact, 140 (55%) were reached; 39 (27%) expressed interest;

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28 (11%) were linked to care; 8 (5%) were apprised of their HCV status but were later lost to follow up (LTFU); and 2 (1%) declined linkage. Among 1885 HBsAg+ patients eligible for contact, 1748 were contacted. 983 were initially messaged via MyChart, 747 by phone, and 18 by e-mail. Among them, 921 (53%) were reached; 262 (15%) expressed interest; 146 (8%) were linked to care; and 60 (5%) were apprised of their HBsAg+ status but were LTFU after repeated attempts to link them. Linkage rates were similar for MyChart messaging and other methods (p-value 0.09). Patients between 41 to 65 years of age were more likely to express interest and to be linked to care (p = 0.029). PN findings of note: 1) MyChart messaging prior to phone outreach improved communication and trust because PNs could reference the message in their introduction, 2) PCP referrals with PN outreach boosted re-linkage, 3) Patients with normal liver enzymes and low viral loads preferred monitoring with their PCP rather than a specialist. **Conclusion:** In the decades since antiviral drugs for viral hepatitis became available, many patients have been engaged in care, but concerted efforts to reach the remaining patients remains are an important public health priority. In this project, 163 patients were re-linked; many additional patients were contacted and informed of treatment options. Our results highlight both the ability of a dedicated program to overcome barriers and the need for further innovation in the delivery of care.



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2255 | HEALTH-RELATED QUALITY OF LIFE IN AUTOIMMUNE HEPATITIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

Ilkay Ergenç[1] Jill Carlton[2] Yooyun Chung[3] Dermot Gleeson[4] Michael Heneghan[3], [1]King's College Hospital, [2]Sheffield Centre of Health and Related Research (SCHARR), University of Sheffield, Sheffield, United, [3]The Roger Williams Institute of Liver Studies, King's College Hospital, London, United Kingdom, [4]Liver Unit, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, United Kingdom

Background: Autoimmune hepatitis (AIH) is a chronic, liver condition that can impair health-related quality of life (HrQoL) through disease-related morbidity, treatment burden, and psychological impact. Biochemical remission alone may not adequately represent patient-perceived health status. This study aimed to systematically review the evidence on HrQoL in patients with AIH. **Methods:** A systematic search of MEDLINE, Embase, APA PsycInfo, and the Cochrane Library (1946–September 2025) was conducted using relevant medical subject headings (MeSH) terms. After deduplication, 1,668 records were identified. The review followed COSMIN 2.0 methodology for risk of bias assessment, evaluation of measurement properties, synthesis of results, and grading of evidence. Two reviewers independently screened records and 49 articles underwent full-text review. Twelve studies met inclusion criteria and were included in the quantitative synthesis. **Results:** Twelve studies involving 3,478 AIH patients (78.2% female) assessed PROMs including generic HRQoL (SF-12, SF-36, EQ-5D-5L), liver-specific HRQoL (CLDQ), anxiety/depression (GAD-2/7, PHQ-2/9), fatigue (FIS, CFQ), and somatic symptoms (SSS-8). Four studies included healthy controls (HC), four included disease controls, and four had no control group. The risk of bias assessment demonstrated substantial methodological limitations in structural validity, internal consistency, and measurement error. Across AIH cohorts, pooled scores were SF-12 physical component score (PCS) 46.12 (95% CI 45.44–46.80, I^2 0.0%, n = 985) and SF-12 mental component score (MCS) 47.32 (95% CI 45.46–49.18, I^2 61.6%, n = 985); SF-36 PCS 51.04 (95% CI 49.94–52.15, I^2 0.0%, n = 291) and SF-36 MCS 50.35 (95% CI 43.39–57.31, I^2 96.9%, n = 291). EQ-5D-5L (Index 0.84, 95% CI 0.77–0.92, I^2 97.7%; VAS 74.68, 95% CI 69.15–80.20, I^2 96.8%, n = 1,806), and HRQoL by CLDQ overall was 5.61 (95% CI 5.34–5.88, I^2 90.0%, n = 637). AIH was associated with lower scores than HCs: SF-12 PCS (−6.00; 95% CI: −7.77 to −4.23), SF-36 PCS (−2.50; 95% CI: −3.92 to −1.08), and SF-36 MCS (−7.73; 95% CI: −9.69 to −5.78). The CLDQ difference was −0.37 (95% CI: −1.05 to 0.32) with high

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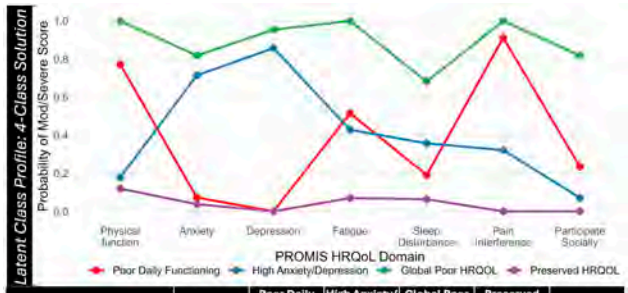
heterogeneity. **Conclusion:** Evidence regarding HRQoL in autoimmune hepatitis is constrained by methodological heterogeneity, reliance on diverse generic PROMs, lack of healthy controls, and substantial risk of bias. Although all studies reported HRQoL impairment across multiple domains, comparability and comprehensiveness remain inadequate.

Disclosures: Ilkay Ergenç: Nothing to Disclose, Jill Carlton: Nothing to Disclose, Yooyun Chung: Nothing to Disclose, Dermot Gleeson: Nothing to Disclose, Michael Heneghan: Advanz: Speaking and Teaching, Ipsen: Speaking and Teaching, Mirum: Consultant, Gilead: Speaking and Teaching.

2256 | DISTINCT HEALTH-RELATED QUALITY OF LIFE PROFILES ARE ASSOCIATED WITH SOCIAL VULNERABILITY, NOT LIVER DISEASE SEVERITY

Archita Desai[1] Miranda Stovall[1] Suhani Lodha[2] Lauren Boyer[1] Timothy Stump[1] Marwan Ghabril[1] Eric Orman[1] Naga Chalasani[1], [1]Indiana University, [2]Purdue University

Background: Patients with chronic liver disease (CLD) and cirrhosis experience substantial impairments in health-related quality of life (HRQOL). Whether distinct HRQOL phenotypes exist in those with liver disease remains poorly understood. We aimed to identify (1) unique HRQOL phenotypes and (2) characterize differences in demographic and clinical characteristics as well as patient reported needs. **Methods:** We performed a prospective study of adults with CLD/cirrhosis seen for routine hepatology care at an academic health center from 7/2024 to 4/2026. Participants were recruited by phone 1-2 weeks prior to their scheduled visit to complete surveys measuring HRQOL (PROMIS-29 v2.0), health related social needs (HRSN, Accountable Health Communities Screening Tool) and informational needs (Brief Health Literacy Scale, MyCirrhosisCoach, PROMIS Informational Support). Scores were interpreted using validated cutoffs. Latent class analysis was performed using categorized PROMIS-29 domain T-scores (mild-normal vs. moderate/severe symptoms) to identify distinct HRQOL phenotypes. Following class assignment, groups were compared across sociodemographic features, liver disease severity, comorbidity burden, and self-reported HRSN and informational needs. **Results:** In the study cohort of 280 individuals, 46% had cirrhosis (mean MELD 3.0: 10.1, SD 4.0), 50% had MASH, 14% had alcohol-associated liver disease (ALD) and 14% had viral hepatitis. A 4-class solution demonstrated the optimal statistical performance (model parsimony: BIC 1753, precision: entropy = 0.863, Figure) defining 4 phenotypes: (1) Poor Daily Functioning (25%), (2) High Anxiety/Depression (10%), (3) Global Poor HRQOL (8%), and (4) Preserved HRQOL (57%).Participants assigned to phenotypes without fully preserved HRQOL (classes 1-3) were younger, ($p = 0.049$), more often female ($p < 0.001$), had higher rates of high school or less education ($p = 0.040$), reported lower income ($p < 0.001$) and Medicaid insurance ($p < 0.001$, Figure). Other sociodemographic and clinical features were similar between classes including etiology of liver disease, rates of cirrhosis, MELD3.0 scores and Child-Pugh class. Classes 1-3 had poorer scores in many self-reported HRSN domains including housing ($p < 0.001$), food security ($p < 0.001$), transportation ($p = 0.017$), financial needs and utilities ($p < 0.001$). Higher informational needs were also associated with these classes including inadequate literacy ($p < 0.001$), low information support ($p < 0.001$) and medication obstacles ($p < 0.001$). **Conclusion:** Distinct HRQOL phenotypes exist among patients with CLD/cirrhosis. These phenotypes are associated with drivers of health disparity in liver disease such as health related informational and social needs but not liver disease severity. The phenotypes more directly inform how to best to bundle healthcare delivery interventions to improve patient-centered outcomes.



Variable	Overall N = 280[1]	Poor Daily Functioning N = 70^	High Anxiety/ Depression N = 29^	Global Poor HRQOL N = 22^	Preserved HRQOL N = 159^	p-value*
Age	55 (14)	56 (13)	49 (15)	52 (12)	56 (13)	0.049
Female*	188 (67%)	59 (84%)	19 (66%)	18 (82%)	92 (58%)	<0.001
Race*						0.872
Black	11 (4.1%)	4 (6.0%)	0 (0%)	1 (4.8%)	6 (3.9%)	
White	252 (93%)	61 (91%)	27 (96%)	20 (95%)	144 (94%)	
High school or less Education*	90 (32%)	26 (37%)	16 (55%)	7 (32%)	41 (26%)	0.014
Household Income ≤$50,000	103 (38%)	37 (55%)	15 (54%)	15 (71%)	36 (24%)	<0.001
Living with someone/partnered	189 (68%)	45 (64%)	18 (62%)	12 (55%)	114 (72%)	0.246
Health Insurance: Medicaid*	38 (14%)	13 (19%)	6 (21%)	9 (41%)	10 (6.4%)	<0.001
Charlson Total Points	5.38 (2.13)	5.53 (2.18)	4.66 (2.00)	4.86 (1.32)	5.51 (2.21)	0.104
Alcohol Related Liver Disease	39 (14%)	6 (8.6%)	4 (14%)	3 (14%)	26 (16%)	0.487
MASH	139 (50%)	37 (53%)	19 (66%)	12 (55%)	71 (45%)	0.174
Viral Hepatitis	39 (14%)	13 (19%)	4 (14%)	2 (9.1%)	20 (13%)	0.622
Autoimmune/Cholestatic	14 (5.0%)	2 (2.9%)	1 (3.4%)	2 (9.1%)	9 (5.7%)	0.632
Cirrhosis	127 (46%)	34 (49%)	11 (38%)	9 (41%)	73 (47%)	0.759
MELD 3.0	10.1 (4.0)	9.9 (3.5)	9.9 (4.2)	10.5 (3.4)	10.2 (4.2)	0.535
Child B/C	58 (24%)	14 (21%)	5 (19%)	6 (32%)	33 (25%)	0.705
Housing Needs	34 (11.7%)	9 (13.4%)	5 (17%)	9 (41%)	11 (6.9%)	<0.001
Food Insecurity	31 (12%)	9 (14.7%)	6 (25.2%)	12 (67%)	4 (2.6%)	<0.001
Transportation Needs	13 (4.6%)	3 (4.3%)	2 (6.9%)	4 (18%)	4 (2.5%)	0.017
Utilities Needs	17 (6.1%)	5 (7.1%)	4 (14%)	6 (27%)	2 (1.3%)	<0.001
Financial Needs	94 (33.7%)	32 (46.3%)	19 (65.4%)	18 (82%)	25 (16.3%)	<0.001
Disability Reported	83 (30%)	29 (42%)	17 (61%)	19 (90%)	18 (11.3%)	<0.001
Brief Health Literacy Score	13.33 (2.21)	12.99 (2.35)	12.62 (2.82)	11.32 (3.05)	13.89 (1.58)	<0.001
PROMIS Informational Support	57 (9)	56 (10)	53 (9)	47 (10)	59 (7)	<0.001
Medication Obstacles	108 (40%)	32 (47%)	14 (50%)	17 (81%)	45 (29%)	<0.001

*All categories not reported *Mean (SD); n (%) *Kruskal-Wallis rank sum test; Fisher's exact test

Disclosures: Archita Desai: Eli Lily: Consultant, Gilead: Grant/Research Support, Miranda Stovall: Nothing to Disclose, Suhani Lodha: Nothing to Disclose, Lauren Boyer: Nothing to Disclose, Timothy Stump: Nothing to Disclose, Marwan Ghabril: BioCryst: Consultant, Akero: Consultant, ABIM: Advisor, CymaBay: Consultant, Gilead: Consultant, MoonLake

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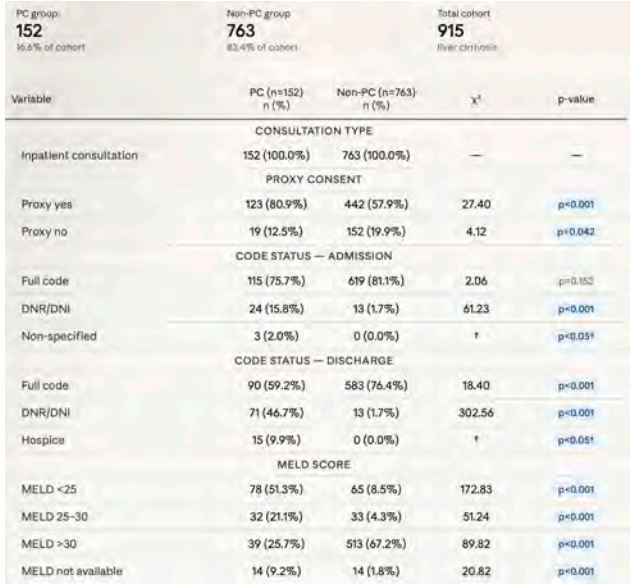
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2257 | PALLIATIVE CARE CONSULTATION IS ASSOCIATED WITH INCREASED END-OF-LIFE CARE TRANSITIONS IN A NON-TRANSPLANT CENTER COHORT WITH END STAGE LIVER DISEASE

Keila Carrera Mejias[1] Fernando Membreno[1] Genesis Camacho[1] James Castillo[1] Fernando Pena[1] Yashita Kakarlapudi[1], [1]DHR Health

Background: End stage liver disease (ESLD) is the advance phase of most liver disease and is character and is characterized by the complications of liver disease.Palliative care (PC) can provide at any stage of serious illness including patient receiving target curative treatment including organ transplants in patient liver cirrhosis a comprehensive support including advance care planning which address code status, proxy assignation and impact on hospital length stay. PC services have shown to be underutilized for such patient. A few studies have described the role of PC at a non-transplant tertiary center may help establish a standard of care in the management of patient with ESLD regards of transplant eligibility. **Methods:** We conduct a retrospective study analysis of adult (>18 years) patient with ESLD admitted to inpatient services at non transplant center in South Texas from 2020 to 2024. Patients were divided into groups based on the presence or absent of PC involvement. The primary outcome was inpatient transition to do not resuscitated (DNR) status. Secondary outcomes included transition to hospice care, cause of liver cirrhosis, length of stay (LOS). Categorical variables were compared using chi square or fisher's exact test. Odds ratio (OR) with 95% confidence of intervals (CL) were calculated for key outcomes. **Results:** Among 915 patients with liver cirrhosis, 152 (16.6%) received inpatient palliative care consultation. Patients in the palliative care group had significantly higher rates of DNR/DNI status at discharge compared to those without palliative care involvement (46.7% vs 1.7%, $p < 0.001$), as well as increased hospice utilization (9.9% vs 0%, $p < 0.001$). Full code status at discharge remained more common in the non-palliative group (76.4% vs 59.2%, $p < 0.001$). Notably, DNR/DNI status at admission was higher among patients who received palliative care (15.8% vs 1.7%, $p < 0.001$). Sex distribution was similar between groups (male: 57.7%) in the palliative care group vs 58.7% in the non-palliative group, $p = 0.90$). Patients receiving palliative care had 50-fold higher odds of DNR/DNI at discharge compared with non-PC patients. Palliative care is associated with an extremely strong increase in hospice referral, though precision is limited due to zero events in control group. **Conclusion:** Inpatient PC consultation in liver cirrhosis is associated with significant goals of care transitions including increased DNR/DNI designation, hospice utilization, and prolonged hospitalization reflecting the complexity of cases referred for PC. Notably, PC was consulted across a range of MELD scores, suggesting a role in decisional support and symptom management beyond the terminal phase. These findings support the systematic, early integration of palliative care into cirrhosis management to align treatment with patient-centered goals and potentially optimize resource utilization.



PC group: 152 (16.6% of cohort)	Non-PC group: 763 (83.4% of cohort)		Total cohort: 915 (liver cirrhosis)
Variable	PC (n=152) n (%)	Non-PC (n=763) n (%)	χ^2	p-value
CONSULTATION TYPE				
Inpatient consultation	152 (100.0%)	763 (100.0%)	—	—
PROXY CONSENT				
Proxy yes	123 (80.9%)	442 (57.9%)	27.40	p<0.001
Proxy no	19 (12.5%)	152 (19.9%)	4.12	p=0.042
CODE STATUS — ADMISSION				
Full code	115 (75.7%)	619 (81.1%)	2.06	p=0.152
DNR/DNI	24 (15.8%)	13 (1.7%)	61.23	p<0.001
Non-specified	3 (2.0%)	0 (0.0%)	†	p<0.05†
CODE STATUS — DISCHARGE				
Full code	90 (59.2%)	583 (76.4%)	18.40	p<0.001
DNR/DNI	71 (46.7%)	13 (1.7%)	302.56	p<0.001
Hospice	15 (9.9%)	0 (0.0%)	†	p<0.05†
MELD SCORE				
MELD <25	78 (51.3%)	65 (8.5%)	172.83	p<0.001
MELD 25–30	32 (21.1%)	33 (4.3%)	51.24	p<0.001
MELD >30	39 (25.7%)	513 (67.2%)	89.82	p<0.001
MELD not available	14 (9.2%)	14 (1.8%)	20.82	p<0.001

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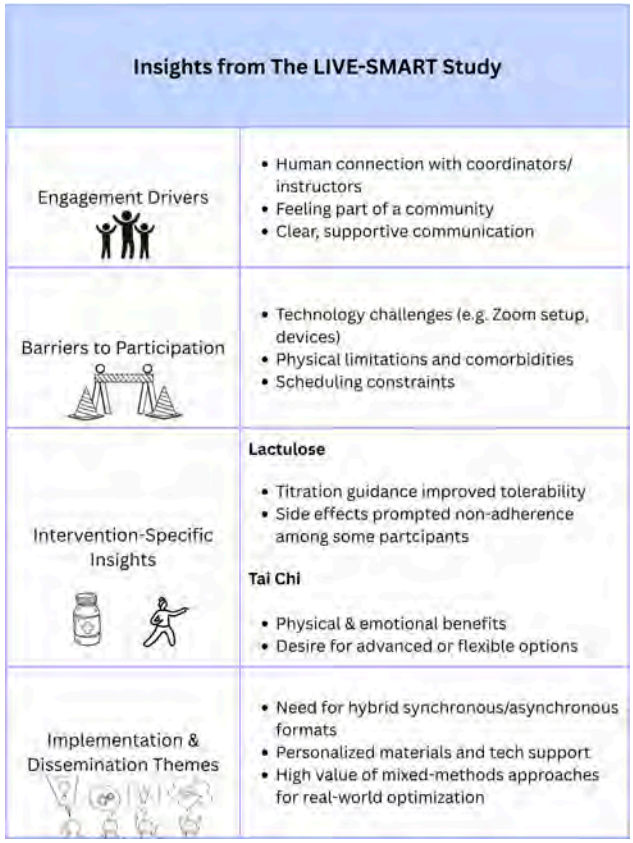
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2258 | BARRIERS AND FACILITATORS OF THE LIVE-SMART TRIAL TO REDUCE FALLS IN PATIENTS WITH CIRRHOSIS: A MIXED-METHODS STUDY

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Background: LIVE-SMART was a 24-week trial designed to evaluate lactulose and Tai-Chi as interventions to reduce falls in patients with cirrhosis. At the conclusion of the intervention period, a mixed-methods evaluation was conducted to assess protocol fidelity, perception of intervention characteristics, and barriers and facilitators to implementation. **Methods:** A 10-item study satisfaction survey was conducted at the conclusion of the interventions. Survey data and fidelity measures were analyzed using descriptive statistics. Factors associated with protocol fidelity were assessed via univariable logistic regression. Associations between socio-demographics, liver disease features, key comorbidities, medications, and study site were evaluated for dichotomous outcomes: 1) lactulose discontinuation, 2) unsuccessful Zoom video setup for TeleTai-Chi, and 3) low TeleTai-Chi attendance. Semi-structured interviews with patients and care partners were audio-recorded, transcribed and analyzed using NVivo 15. Two team members double-coded 20% of the transcripts (n = 7, inter-coder reliability K = 0.87) and resolved discrepancies through consensus. The remaining transcripts were independently coded (80%, n = 27). **Results:** Among 166 participants (72.1%) who completed the exit survey, overall satisfaction was high (Net Promoter Score = 51). Among TeleTai-Chi participants, 81% successfully completed Zoom setup; however, weekly attendance was low, with a median session attendance rate of 27.8% (IQR: 5.6%-72.2%). Among participants randomized to lactulose, 80% remained on therapy through study completion. Semi-structured interviews (n = 34) revealed positive experiences with participation in LIVE-SMART. Human connection with study coordinators, instructors, and fellow participants emerged as a major driver of study engagement and adherence. In contrast, logistical, physical, and technological barriers limited sustained participation in TeleTai-Chi. **Conclusion:** Mixed methods findings suggest that lactulose may be a feasible intervention for fall prevention when paired with structured dosing instructions. Remote Tai-Chi programs can be successfully implemented with adequate technological support, instructor training, and flexible participation options.



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2259 | NO HOPE TOO SMALL

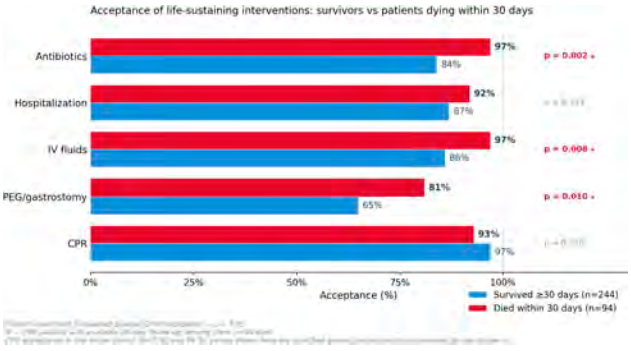
Daniel Jan Havaj[1] Karolina Sulejova[1] Daniela Zilincanova[2] Daniel Jan Havaj[2] Ivana Ihnatova[3] Svetlana Adamcova Selcanova[2] Lubomir Skladany[2], [1]University Hospital of F. D. Roosevelt, [2]University Hospital of F.D. Roosevelt, [3]Institute of Biology and Ecology, Faculty of Science, Pavol Jozef Safarik University in Kosice

Background: Patients with advanced chronic liver disease (ACLD) face high mortality and limited options

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outside liver transplantation (LT). Palliative care via advanced care planning (ACP) integration is recommended, yet patient readiness and its harmonisation with objective prognostic stratification remain poorly characterized. Therefore, we evaluated ACP against disease severity in a tertiary & liver transplant unit. **Methods:** This was a cirrhosis registry study (NCT 04767945). After structured best-case/worst-case prognostic communication, consecutive patients hospitalized with dACLD completed a nurse-administered 9-item ACP questionnaire (Slovak Warren/Wilson adaptation). Responses were analyzed against demographics, etiology, MELD, Child-Turcotte-Pugh (CTP), Liver Frailty Index, refractory ascites, and 30-/90-/365-day mortality using Fisher's exact test and multivariable logistic regression. **Results:** Among 778 patients (62 % male; 60 % alcohol-associated; 36 % frail), ACP items results were as follows. Pro-CPR preference was 94 % overall and 93 % of those who died within 30 days (n = 94). Antibiotics, hospitalization, and IV fluids were expected by 80-82 %, and nasogastric tube / PEG by 55-59 %. Patients dying within 30 days displayed a higher expectation rate than survivors: antibiotics 97 % vs 84 %, p = 0.002; IV fluids 97 % vs 86 %, p = 0.008; PEG 81 % vs 65 %, p = 0.010. MELD and CTP were not associated with CPR expectancy and place-of-care preference. Only 24 % of patients had a formalized legal proxy, inversely associated with frailty (21 % vs 28 %, p = 0.042) and refractory ascites (17 % vs 28 %, p = 0.012). Of 28 patients declining CPR, 64 % were women (vs 38 % in the cohort, p = 0.005). **Conclusion:** The worse the prognosis and symptom burden, the higher the expectations for life-sustaining interventions. ACLD patients are not prepared to forgo escalation even when the prognosis is poor. ACP and palliative care discussions should begin in earlier stages of ACLD.



Disclosures: Daniel Jan Havaj: Nothing to Disclose, Karolina Sulejova: Nothing to Disclose, Daniela Zilincanova: Nothing to Disclose, Daniel Jan Havaj: Nothing to Disclose, Ivana Ihnatova: Nothing to Disclose, Svetlana Adamcova Selcanova: Nothing to Disclose, Lubomir Skladany: Worwag: Speaking and Teaching, ProMed: Speaking and Teaching, Abbvie: Speaking and Teaching, Gilead: Speaking and Teaching, RegPharm: Speaking and Teaching, Astellas: Speaking and Teaching.

2260 | THE IMPACT OF PRACTICE VARIABILITY ON ENDOSCOPY TIMING FOR UPPER GI BLEEDING IN CIRRHOSIS INPATIENTS: INSIGHTS FROM A LARGE MULTI-CENTRE ONTARIO COHORT

Zuhal Mohmand[1] Surain Roberts[2] Matthew Wankiewicz[2] Sahar Saeed[1] Lauren Lapointe-Shaw[2] Siddhartha Srivastava[1] Michelle Ricci[1] Amol Verma[2] Fahad Razak[2] Florence Wong[2] Gideon Hirschfield[3] Jennifer Flemming[4] Kristel Leung[1], [1]Queen's University, [2]University of Toronto, [3]Toronto General Hospital, [4]Queen's University Cancer Research Institute

Background: Acute upper gastrointestinal bleeding (UGIB) is a life-threatening complication of decompensated cirrhosis. Guidelines recommend endoscopy within 12-24h of presentation, yet Canadian practice patterns and outcomes remain uncharacterized. **Methods:** We conducted a retrospective multicentre cohort study using administrative health data from 29 Ontario hospital medicine services (2016-2023). Adults with decompensated cirrhosis admitted from the ED with suspected UGIB who underwent inpatient upper endoscopy within 96h were included. Elective, palliative, acute care transfers, and data-incomplete admissions were excluded. Door-to-endoscopy time was divided into early (≤24h) vs. delayed (>24h). Standardized mean differences (SMD) were used for descriptives. Predictors of delay were identified using univariable and multivariable logistic regression, adjusted for patient and system factors. Outcomes were evaluated using Cox proportional hazards (in-hospital mortality), logistic regression (ICU admission, repeat endoscopy), and descriptives statistics (length of stay). **Results:** Among 3133 encounters, median age was 60 years (64.2% male). Alcohol (47.5%) and metabolic-associated liver disease (43.7%) were the most common cirrhosis etiologies. Median admission MELD-Na was 16. Median door-to-endoscopy time was 21.5h (IQR 13.4-35.0); 59.5% underwent endoscopy within 24h, while 40.5% after 24h. Early endoscopy was more common in patients transferred to ICU within 24h of admission (early: 26.8% vs. delayed: 10.3%, SMD 0.43) and those with confirmed variceal bleeds (56.9% vs. 43.4%, SMD 0.27). Repeat endoscopy was more common in the early group (14.5% vs. 10.7%, aOR 0.76, p = 0.023). Independent predictors of delay included weekend (aOR 2.13, 95% CI 1.80-2.53) and

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daytime arrival (aOR 1.89, 95%CI 1.61 – 2.17). Sex, liver disease etiology, HCC, and teaching hospital status were not independently associated with delay. Octreotide and ceftriaxone were prescribed in 69.8% and 69.2% of encounters, compared to pantoprazole at 86%. Delay was associated with longer hospital length of stay (median 5.3 vs. 4.6 days, $p < 0.001$), but not increased mortality after adjustment for patient- and system-level factors (aHR 0.87, 95% CI 0.65-1.16). **Conclusion:** In this large Canadian cohort, two-fifths of patients with decompensated cirrhosis presenting with UGIB underwent delayed endoscopy (>24h). Although higher acuity patients were more likely to undergo earlier endoscopy and were likely clinically sicker, 43.4% in the delayed endoscopy group were still confirmed to have variceal bleeds. Further investigation is warranted to better understand these observational findings and to inform hospital-level quality improvement initiatives aimed at reducing practice variability through standardized care pathways and optimized resource allocation.

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2261 | HOW RECOMMENDATIONS TAKE SHAPE: CO-CONSTRUCTING EARLY LIVER TRANSPLANT SELECTION IN COMMITTEE DELIBERATIONS

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Background: Selection for early liver transplant (ELT) in patients with alcohol-associated liver disease and < 6 months sobriety involves complex, multidisciplinary deliberation. While prior work has focused on clinical and psychosocial criteria, how decisions are collaboratively produced has not been extensively analyzed. **Methods:** We analyzed transcripts of transplant selection committee meetings across three transplant centers using a modified conversation analysis approach. Focusing on the factors that influence how recommendations are collaboratively constructed, elaborated, and resolved in real time, we examined how participants built on one another's contributions through sequences of implicit, hedged (e.g. "I think"), and explicit recommendations. We also examined how opinions evolved over the course of discussion and became accepted or contested, including instances in which concerns were raised but not incorporated into subsequent discussion. **Results:** A total of 49 ELT patients were presented at 26 full length meetings. Subsequent discussions about 8 of these patients were also evaluated. Decision-making unfolded as a dynamic, interactional process rather than a series of isolated recommendations. In some cases, participants collaboratively built toward a shared position through incremental contributions, with patient factors elaborated across speakers before the group reached consensus. In others, early explicit recommendations curtailed further debate, leading to rapid alignment with limited discussion. Implicit recommendations (indirect statements signaling concern or support) frequently employed by social work, psychiatry and addiction medicine often served as building blocks for subsequent recommendations but varied in their influence depending on whether they were taken up and developed by surgeons and hepatologists. Patterns of uptake varied by speaker role and clinical involvement, with contributions from surgeons and hepatologists often shaping subsequent discussion, particularly when they had evaluated the patient in person. This suggests that the incorporation of information and preferences into decision-making is selective and interactionally mediated. **Conclusion:** Transplant committee decisions are co-constructed through interactional sequences in which participants build, modify, and ratify recommendations during deliberation. Our findings show that decision-making depends not only on the information available, but also on how that information is taken up within group discussion. As deliberations unfold, implicit biases and power dynamics may shape which contributions are amplified, minimized, or incorporated into final recommendations. Making these processes more explicit may support reflective committee practice and promote greater transparency and equity in ELT decision-making.

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2262 | HIGH CO-MORBIDITY BURDEN AND RECURRENT HOSPITALIZATIONS ARE ASSOCIATED WITH ADVANCE DIRECTIVE DOCUMENTATION PRIOR TO TERMINAL HOSPITALIZATION IN PATIENTS WITH END-STAGE LIVER DISEASE

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Background: Despite the high levels of morbidity and mortality requiring significant resource utilization, patients with end-stage liver disease (ESLD) rarely undergo timely serious illness communication with goals of care (GOC) documentation. Our prior single center retrospective study found that only 28% of hospitalized patients with ESLD had a documented advance directive (AD). There is a gap in knowledge regarding the factors that support having a documented AD and its impact on terminal hospitalizations for patients with ESLD. The objective of this study was to describe the demographic and clinical features of patients with ESLD experiencing inpatient death and identify factors associated with AD documentation prior to terminal hospitalization. **Methods:** Single center, multi-hospital retrospective study with a standardized manual chart review. Inclusion criteria are adult patients with ESLD who experienced inpatient mortality at one of 8 central Texas hospitals from 2015–2025 with a documented AD. Demographics, clinical characteristics, AD type and timing, and inpatient end-of-life care were examined. Patients were stratified by AD timing (before vs. during terminal hospitalization). Continuous outcomes were modeled with ordinary least squares regression and binary outcomes (e.g., palliative care consultation, GOC discussion) with logistic regression. **Results:** Of 91 patients meeting criteria, mean age was 58 years with 62.6% males and 53.9% being non-White race and/or Hispanic ethnicity. Most (70.3%) patients did not have a domestic partner. Based on Charlson Comorbidity Index, 93.4% of patients had 1 or 2 co-morbidities present. Mean peak MELD 3.0 score

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was 30 and 82.4% of patients had an ICU admission during the terminal hospitalization. The mean terminal hospitalization length of stay was 11.8 days (SD 9.2) and ICU length of stay was 9.5 days (SD 9.1). 81.3% were full code at hospital admission and only 2.2% were full code at the time of death. AD documentation occurred during terminal hospitalization in 54% of patients. Only a health care power of attorney (HCPOA) was identified in 88% of patients. Pre-admission AD documentation was associated with higher comorbidity burden (OR 2.03, p = 0.057) and greater number of prior hospital admissions (5.0 vs 2.9, p < 0.001). HCPOA identification was associated with having a palliative care consultation and GOC discussion. Among 67 patients receiving both, 94% occurred on the same hospital day. **Conclusion:** Among patients with ESLD who experienced inpatient death with documented ADs, the majority were full code at admission and received aggressive care that included an average ICU admission that was 9.5 days and an average hospital stay of 12 days. AD documentation occurred most often during the terminal hospitalization and consisted primarily of HCPOA designation. Earlier AD documentation was associated with a greater number of prior hospital admissions and comorbidity burden. These findings support inpatient interventions that identify patients with ESLD earlier in the disease trajectory, even in the absence of significant co-morbidities and recurrent hospitalizations admissions, for serious illness communication and AD documentation.

Table 1: Demographic and clinical characteristics of the entire cohort

	Mean (SD)	Frequency N (%)
Demographics		
Age (years)	58.1 (12.1)	
Male		57 (62.6%)
Non-White race		15 (16.5%)
Hispanic ethnicity		34 (37.4%)
Married or domestic partner		27 (29.7%)
Clinical data		
Etiology		
Alcohol		51 (56.0%)
MASH		10 (15.4%)
Viral Hepatitis		10 (11.0%)
Other/Undocumented		27 (29.7%)
Peak MELD score	29.7 (8.8)	
Hepatic encephalopathy		42 (46.1%)
Number of co-morbidities		
1		69 (75.8%)
2		16 (17.6%)
3		5 (5.5%)
4		1 (1.1%)
AD documentation		
Power of attorney alone		78 (85.7%)
Timing		
Before hospitalization		41 (45.1%)
During hospitalization		50 (54.9%)
Hospital day of GOC conversation	6.1 (5.3)	
Hospital day of PC consult	6.3 (5.4)	
Full code at admission		74 (81.3%)
Full code at death		2 (2.2%)
Hospital utilization		
ICU admission		75 (82.4%)
Number hospitalizations during study period	3.9 (3.1)	
Terminal hospitalization LOS (days)	11.9	

Abbreviations: MASH - Metabolic dysfunction-associated steatohepatitis, GOC-Goals of care, LOS - Length of stay

Disclosures: Natalie Malluru: Nothing to Disclose, Nazan Aksan: Nothing to Disclose, Paul Mueller: Nothing to Disclose, Cristal Brown: GlaxoSmithKline: Speaking and Teaching.

2263 | AWARENESS OF LIVER DISEASE AMONG AT-RISK GROUPS

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Background: Despite low public awareness of liver disease, metabolic dysfunction-associated steatotic liver disease (MASLD) and its more progressive form, metabolic dysfunction-associated steatohepatitis (MASH), affect an estimated 30% or more of the general population. People living with MASLD-indicator conditions, e.g. obesity and type 2 diabetes (T2D), may not perceive themselves as being at risk for MASLD. Understanding these awareness gaps can generate valuable evidence to support health sector investments and help bridge critical shortfalls in public knowledge of these key public health threats. This study assesses awareness and evaluates concern regarding cardiometabolic and liver-related conditions among populations facing elevated risk. **Methods:** This cross-sectional study surveyed 3,010 adult residents of the United States via an online panel. Recruitment targeted individuals with a body mass index (BMI) greater than 30 or a self-reported diagnosis of diabetes. Respondents were matched to a sampling frame constructed from the 2023 American Community Survey (ACS) 1-year sample on the basis of gender, age, race, and education, and weighted using propensity score methods to adjust for selection bias, resulting in a final analytical sample of 1,000 adults. **Results:** Within the full sample, awareness of cirrhosis was highest (61%; n = 610), followed closely by fatty liver disease (60%). Recognition dropped markedly for more specific terminology, including NAFLD (36%), liver fibrosis (24%), MASLD (13%), and MASH (12%) (Table 1). Awareness was modestly higher across these terms among respondents with diabetes or prediabetes compared to those living with obesity alone. Individuals with indirect exposure to MASLD, such as knowing an affected parent, partner, or friend, also showed elevated awareness relative to the broader sample, though recognition of MASLD and MASH remained low across these factors. **Conclusion:** The higher awareness of fatty liver disease relative to MASLD and MASH likely reflects a lag in public and at-risk group knowledge of the names following the 2023

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nomenclature change from NAFLD. The strong recognition of cirrhosis may stem from its longstanding public association with alcohol-related harm and advanced disease severity. Given that MASLD is reversible in early stages, these awareness gaps underscore the need for targeted interventions to promote timely detection, encourage lifestyle modifications, and prevent progression to fibrosis, cirrhosis, and other serious complications.

Table 1. Familiarity with liver disease terms by sub-groups

Terms	Full sample (n=1,000)	BMI 30+ (n=804)	Living with type 2 diabetes or prediabetes (n=441)	Reported MASLD diagnosis (n=70)	Knowing Parent with MASLD (n=18)	Knowing Partner with MASLD (n=22)	Knowing Friend with MASLD (n=62)	Knowing Colleague with MASLD (n=9)
Liver cirrhosis	61%	59%	67%	85%	79%	70%	77%	77%
Fatty liver disease	60%	59%	64%	94%	91%	80%	92%	63%
Non-alcoholic fatty liver disease (NAFLD)	36%	36%	38%	80%	63%	62%	70%	47%
Liver fibrosis	24%	23%	26%	51%	48%	25%	52%	53%
Metabolic dysfunction-associated steatotic liver disease (MASLD)	13%	13%	15%	27%	40%	14%	64%	35%
Metabolic dysfunction-associated steatohepatitis (MASH)	12%	11%	15%	26%	29%	20%	34%	44%

Note: BMI: Body mass index

Disclosures: Trenton White: Nothing to Disclose, Leire Agirre-Garrido: Nothing to Disclose, Lila Neal: Nothing to Disclose, Sonal Kumar: Nothing to Disclose, Melina Manolas: Doximity: Social Media Content Provision, Health Monitor Network: Advisor, Roon: Stock options, Madrigal Pharmaceuticals: Consulting, Scott Isaacs: Nothing to Disclose, Jeffrey Lazarus: Nothing to Disclose.

2264 | TEMPORAL TRENDS AND DISPARITIES IN CHRONIC LIVER DISEASE-RELATED MORTALITY IN THE UNITED STATES, 2010-2023

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Background: Chronic liver disease (CLD) is a major cause of morbidity and mortality worldwide; however, population-based data on temporal trends in CLD-related mortality in the United States (U.S.) remain limited. We evaluated temporal changes in CLD-related mortality in the U.S. from 2010 to 2023 across subgroups stratified by age, sex, race and ethnicity, and urbanization status. **Methods:** We analyzed age-standardized mortality rates (ASMRs) for CLD-related deaths using data from the U.S. National Vital Statistics System available through the Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research (CDC WONDER) database among adults aged $\geq$ 25 years from 2010 to 2023. Joinpoint regression analyses were performed to estimate annual percentage changes (APCs) in mortality trends overall and across subgroups stratified by age, sex, race and ethnicity, and urbanization status. **Results:** Among 204,885 CLD-related deaths between 2010 and 2023, ASMRs (per 100,000 persons) rose from 17.07 to 22.02, with APC increased from 1.55% in 2010-2018 to 7.76% in 2018-2021, but decreased at -5.82% afterwards between 2021 and 2023, resulting in an average APC (AAPC) of 1.77% ($P < 0.001$) **(Table)** . Significant age-related differences in ASMR trends were noted, with the steepest increase observed among individuals aged $\geq$ 65 years (AAPC: 5.23%, $P < 0.001$) followed by those of individuals aged 25-44 years (AAPC: 4.73%, $P < 0.001$), while trends were stable among individuals aged 45-64 years (AAPC: -0.05%, $P = 0.923$). By sex, though males had higher ASMRs than females and ASMRs increased in both groups, the AAPC was higher in females than males (3.02% vs. 1.83%). ASMRs also increased among Non-Hispanic White individuals (AAPC: 2.71%, $P < 0.001$) and Non-Hispanic American Indian and Alaska Native individuals (AAPC: 3.73%, $P < 0.001$), but decreased among Non-Hispanic Asian or Pacific Islander individuals (AAPC: -1.42%, $P = 0.002$), while remaining stable among Hispanic and Non-Hispanic Black individuals (AAPC: 0.39%, $P = 0.324$ and -0.42%, $P = 0.402$, respectively). CLD-related ASMRs also varied across metropolitan categories, with the largest increase occurring in non-metropolitan areas (AAPC: 5.21%, $P < 0.001$). **Conclusion:** CLD-related mortality increased during 2010-2023, with notable disparities among the younger (25-44 year) and older ($\geq$ 65 year) individuals, the non-Hispanic Whites and Non-Hispanic American Indian and Alaska Native groups and non-metropolitan populations.

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Table. Age-standardized mortality rates (ASMRs) for chronic liver disease in the United States from 2010-2023, overall, by age, sex, race and ethnicity, and urbanization status

	Deaths (age-standardized rate per 100,000)				Average APC (95% CI)	*P* value
	2010	2015	2020	2023	2010-2023	
Overall	38257(17.07)	48733(19.89)	60138(23.55)	57757(22.02)	1.77(1.00-2.31)	<0.001
Age						
25-44 years	3839(4.96)	4580(5.76)	7700(9.30)	7559(8.82)	4.73(3.55-5.59)	<0.001
45-64 years	26085(31.27)	30477(34.23)	30860(34.64)	26469(30.07)	-0.05(-0.95 to 0.83)	0.923
≥65 years	8333(20.69)	13676(28.04)	21578(37.67)	23729(39.04)	5.23(4.67-5.97)	<0.001
Sex						
Female	11382(9.92)	15105(12.09)	20295(15.51)	20025(14.90)	3.02(2.14-3.65)	<0.001
Male	26875(24.90)	33628(28.43)	39843(32.32)	37732(29.70)	1.83(1.12-2.55)	<0.001
Race and ethnicity						
Non-Hispanic White	26125(16.04)	33171(19.40)	41365(23.98)	40122(23.20)	2.71(1.98-3.23)	<0.001
Non-Hispanic Black	4732(19.15)	5792(20.67)	6162(20.31)	5293(17.26)	-0.42(-1.49 to 0.61)	0.402
Non-Hispanic Asian or PI	1040(11.36)	1180(9.78)	1589(11.01)	1403(9.36)	-1.42(-2.30 to -0.54)	0.002
Non-Hispanic AI/AN	910(57.92)	1265(74.43)	1909(107.67)	1541(94.84)	3.73(2.08-4.91)	<0.001
Hispanic	5310(23.99)	7015(25.47)	8886(27.13)	8605(23.76)	0.39(-0.43 to 1.21)	0.324
Urbanization[a]						
Large and fringe metro	20044(16.74)	24644(18.51)	29141(20.81)	N/A	1.05(-0.10 to 2.21)	0.066
Small and medium metro	12289(18.20)	16164(22.08)	20245(26.44)	N/A	2.88(2.01-3.77)	<0.001
Non-metro	5924(16.55)	7925(21.32)	10752(28.87)	N/A	5.21(4.24-5.82)	<0.001

[a]Age-standardized mortality rate did not have data from 2021 to 2023 in urbanization categories. Metropolitan categories defined: large and fringe central metropolitan areas (>1 million people), small and medium metropolitan areas (between 50,000-249,999 to 250,000-999,999 people), and non-metropolitan areas (<50,000 people). APC, annual percentage change; CI, confidence interval; Non-Hispanic Asian or PI, Non-Hispanic Asian or Pacific Islander; Non-Hispanic AI/AN, non-Hispanic American Indian/Alaska Native; metro, metropolitan

Disclosures: Xinrong Zhang: Nothing to Disclose, Scott Barnett: Nothing to Disclose, Ramsey Cheung: Nothing to Disclose, Fanpu Ji: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Mindie Nguyen: Pfizer, Astra Zeneca, Aligos, GSK, Delfi, Innogen, Exact Sci: Grant/Research Support, GSK: Advisor.

2265 | INCREASING HIGH-RISK ALCOHOL CONSUMPTION TRANSITIONS AMONG CANADIAN YOUTH AND YOUNG ADULTS

Courtney Campbell[1] Maya Djerboua[2] Kristel Leung[1] Sahar Saeed[1] Jennifer Flemming[3], [1]Queen's University, [2]ICES-Queen's, [3]Queen's University Cancer Research Institute

Background: Severe alcohol associated liver disease (ALD) is rising among adolescents and young adults (AYAs) and is typically a consequence of high-risk alcohol consumption. Population-level self-reported alcohol use is often used to evaluate trends in consumption, yet it is unknown whether these discrete measurements are representative of an individual's consumption patterns over time. This study describes individual-level transitions in alcohol consumption by sex-specific ALD risk, stratified by age group. **Methods:** A population-level, retrospective cohort of Canadian Community Health Survey (CCHS) respondents from Ontario aged 15-60 years from the 2003, 2005-2018 cross-sections who had two survey responses were included. The transitions in alcohol consumption from no risk (0g/week alcohol), mild-moderate risk (up to 210g/week males and 140g/week females) or high-risk consumption (>210g/week males and >140g/week females) were defined. Consumption transitions between groups from the first to second survey were visualized as Sankey diagrams and stratified by age (AYAs <40 years vs. adults 40+ years). Proportional changes in each risk group between age-stratified surveys were calculated. **Results:** 1,786 individuals with two CCHS survey entries were included (41% AYAs, 56% female) with a median of 5.5 years between entries. A higher proportion of AYAs than adults transitioned between alcohol consumption categories (43.0% vs. 35.9%). Of those, 61% of AYAs *transitioned to a higher risk category* while 56% of adults *transitioned to a lower risk category*. Proportional changes in alcohol consumption between index and second survey among AYAs indicated substantial increases in the transition to mild-moderate (+24.1%) and high-risk (+6.7%) consumption, compared to a decrease in zero consumption (-17.6%). Conversely, zero alcohol consumption increased among adults (+9.1%) while mild-moderate (-9.0%) and high-risk (-1.1%) consumption decreased. **Conclusion:** After a median of 5.5 years between survey entries, nearly half of all AYA respondents transitioned to a different alcohol consumption risk category. Of those, over 60% transitioned to a higher risk category while the opposite was observed for adults. Limitations in the use of cross-sectional survey data to define alcohol exposure should be considered, and prospective documentation of alcohol consumption should be considered to explore the association between quantitative alcohol consumption and risk of ALD.

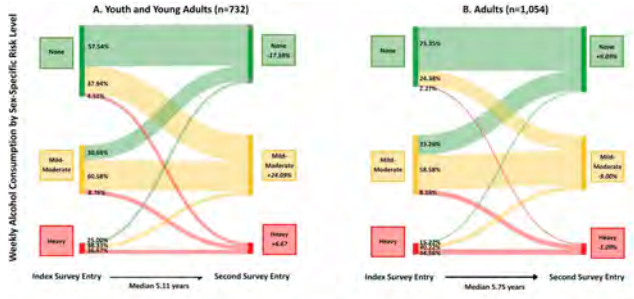


Figure. Age-Stratified Sankey Diagrams of Weekly Alcohol Consumption Transitions by Sex-Specific Liver Risk Level Among n=1,786 Individuals with Two Canadian Community Health Survey Entries Between 2003, 2005-2018.

Disclosures: Courtney Campbell: Nothing to Disclose, Maya Djerboua: Nothing to Disclose, Kristel Leung:

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Nothing to Disclose, Sahar Saeed: Novo Nordisk: Consultant, Jennifer Flemming: Nothing to Disclose.

2266 | IMPACT OF RESMETIROM ON HEALTH-RELATED QUALITY OF LIFE, WORK PRODUCTIVITY, AND DISEASE-SPECIFIC SYMPTOMS IN COMPENSATED MASH CIRRHOSIS

Zobair Younossi[1] Fatema Nader[2] Rebecca Taub[3] Andrei Racila[4] Maria Stepanova[1], [1]The Global NASH/MASH Council, [2]Center for Outcomes Research in Liver Diseases, CORLD, [3]Madrigal Pharmaceuticals, [4]The Center for Outcomes Research in Liver Disease

Background: Metabolic dysfunction-associated steatohepatitis (MASH) cirrhosis significantly impairs health-related quality of life (HRQL) with limited therapeutic options. This study evaluated the impact of resmetirom, a selective thyroid hormone receptor-β agonist, on HRQL work productivity and symptom burden in patients with compensated MASH cirrhosis. **Methods:** This post hoc analysis included 160 patients with compensated MASH cirrhosis from the MAESTRO-NAFLD-1 trial who completed HRQL assessments using the Liver Disease Quality of Life (LDQoL), Chronic Liver Disease Questionnaire-MASH (CLDQ-MASH), Chronic Liver Disease Questionnaire-MASH Symptom Questionnaire (CLDQ-MASH-SQ), and Work Productivity and Activity Impairment (WPAI) questionnaires. **Results:** At baseline, the most impaired HRQL and symptom domains were sleep- and fatigue-related. After 52 weeks of 80 mg resmetirom treatment, improvements were observed in CLDQ-MASH Worry (mean +0.30; $p = 0.001$) and LDQoL Health Distress (+3.44; $p = 0.051$) domains. Among patients with portal hypertension, improvements in both Health Distress and Worry scores were more pronounced. VCTE responders (relative decrease $\geq 25\%$) demonstrated improvement in bleeding gums and joint pain symptoms. **Conclusion:** Cirrhosis in MASH is associated with significant HRQL impairment and substantial symptom burden. Resmetirom treatment in these patients was associated with modest but significant improvements in mental health distress and worry domains, as well as specific symptom relief.
Disclosures: Zobair Younossi: Zobair M. Younossi is a consultant or has received research: Consultant, madrigal: Grant/Research Support, Siemens: Research funding, GSK: Consultant, BI: Consultant, Sanofi: Research funding, Fatema Nader: Nothing to Disclose, Rebecca Taub: Nothing to Disclose, Andrei Racila: Nothing to Disclose, Maria Stepanova: Nothing to Disclose.

2267 | MAPPING THE SOCIAL SUPPORT NETWORKS OF ADULTS LIVING WITH CHRONIC HEPATITIS B IN CALGARY, CANADA

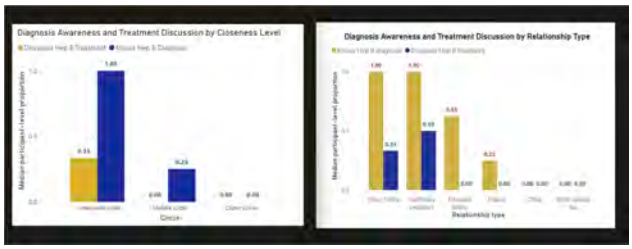
Md Irfan Hyder[1] Jenny Godley[2] Carla Coffin[3] Mayur Brahmania[4] Heidi Israelson[3] Danielle Tillie[3] Henry Nguyen[3] Folake Arinde[3] Pam Crotty[3] Tanvir C. Turin[5] Mark Swain[3], [1]Transdisciplinary Research Program, Faculty of Graduate studies, University of Calgary, [2]Department of Anthropology and Archaeology, Faculty of Arts, University of Calgary., [3]Department of Medicine, Cumming School of Medicine, University of Calgary., [4]Department of Medicine, Cumming School of Medicine, University of Calgary, [5]Department of Community Health Sciences, Cumming School of Medicine, University of Calgary.

Background: Chronic hepatitis B (CHB) requires long-term monitoring, treatment engagement, and support from personal networks. We report on a pilot study that gathered egocentric network data from patients receiving treatment at a CHB clinic to characterize the structure and composition of their support networks and to examine how these support networks might be activated to encourage treatment adherence. **Methods:** We conducted a descriptive egocentric social network analysis with 17 adults receiving CHB care at a Calgary liver clinic. We used Antonucci's hierarchical mapping method. Participants, treated as egos, were first asked to list "people who are important in your life right now." Each named person was treated as an alter and was placed by the participant into a hierarchical closeness map. The first level included people they felt very close to, talked to often, or relied on for support; the second level included people who were very important but not quite as close; and the third level included people who were still important but less involved in the patients' lives. Relationship types were coded as direct family, extended family, friends, work-related ties, healthcare providers, or other. For each alter, participants reported whether they discussed general health, whether the alter knew their CHB diagnosis, and whether they discussed CHB treatment/care with that alter. Counts were converted to participant-level proportions and summarized using medians and ranges. **Results:** Participants had a median age of 47 years (IQR: 41–53); 9 were female and 8 were male. They had lived in Canada for a median of 32 years (IQR: 19–44) and represented diverse ethnocultural backgrounds, commonly Chinese ($n = 8$) and Vietnamese ($n = 2$). Median network size was 11 alters per participant (IQR: 8–13; range: 4–25). The median participant placed 45.5% of their network in the innermost circle and 25.0% each in the middle and outer circles. Networks were mainly composed of direct family members and friends, representing 44.4% and

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28.6% of the median participant's network, respectively. Communication roles differed across networks. The median participant talked about general health with 33.3% of their network, while 50% knew about their CHB diagnosis and 18.2% discussed [MB3] CHB treatment/care. Diagnosis awareness was highest among innermost-circle and family ties: 100% of innermost-circle and direct-family ties knew the diagnosis, compared with 25% of middle-circle ties, 0% of outer-circle ties, 62.5% of extended-family ties, and 25% of friends. Treatment discussion was narrower, reported with 33.3% of innermost-circle ties and 33.3% of direct-family ties. **Conclusion:** CHB diagnosis awareness was broader than treatment discussion, suggesting that disclosure alone may not indicate treatment-related support. Network-informed questions may help identify trusted close or family ties who could support treatment engagement and long-term care.



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2268 | NEEDLE AND SYRINGE PROGRAM WITH OUTREACH TEAM ESSENTIAL IN MANAGING OUTBREAKS OF HEPATITIS B AND GROUP A STREPTOCOCCI AMONG PEOPLE WHO INJECT DRUGS

Marianne Alanko Blomé[1] Gülsen Özkaya Sahin[2] Magnus Paulsson[2] Johan Ringlander[3] Pernilla Isendahl[4], [1]Department of Infectious Diseases, Skåne University Hospital, Malmö and Lund University, [2]Division of Medical Microbiology, Department of Laboratory Medicine, Lund University, [3]Department of Clinical Microbiology, Sahlgrenska University Hospital, Gothenburg, Sweden, [4]Department of Infectious Diseases, Skåne University Hospital, Malmö, Sweden

Background: Early evaluations (1990-93) of the Malmö needle and syringe program (NSP), run by the Infectious disease department, found hepatitis B (HBV) incidence to be 11.7 seroconversions/100 person years at risk. Vaccination against HBV was introduced to all eligible participants in 1994. Coverage and efficacy have since been sufficient to prevent outbreaks. HBV incidence declined to 3.4/100 pyr in 1997-2005. No incident cases had been observed for the past decade – until the spring of 2025 when an incident, symptomatic case presented at the NSP, followed by others. Later in the same year, several cases of invasive group A streptococci (iGAS) were detected among people who inject drugs or lack stable housing. **Methods:** A team consisting of NSP staff (nurses, assistant nurses, ID physicians and social workers) implemented an outreach routine, regularly visiting low threshold centers providing counseling, testing, vaccination and contact tracing. Information was also distributed to other health care providers and arenas. Later, visits to night shelters for wound cultures and treatment with antibiotics aimed at GAS were added on. Whole genome sequencing (WGS) was used to verify transmission patterns. **Results:** Six incident, symptomatic cases of HBV were identified between February and June 2025. Contact tracing identified three more asymptomatic cases of ongoing HBV infection. One was a person with a chronic infection acquired in childhood. This patient has been identified as the source of transmission. Whole genome sequencing revealed identical viral strains for all cases. Almost all 25 contacts were reached, and via the low threshold shelters, around 40 more persons were tested for HBV, hiv and HCV and those susceptible for HBV have been offered vaccination. No cases of hiv were detected, while 3 previously unknown HCV cases were found and treated. In the end of november 2025 a patient presented with necrotizing fasciitis, followed by another case with a fatal outcome. Both had an usual strain of GAS, emm60, ST53. From december to march 2026

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ten more cases were detected. **Conclusion:** People who inject drugs and/or lack stable housing are under risk of viral and bacterial outbreaks. However, despite access to NSP and HBV vaccination, an outbreak of HBV may occur through introduction of a highly viremic patient with chronic HBV infection. Wound infections with GAS, predisposing for septic manifestations may also be easily transmitted. Through a warm alliance with the target population, the NSP outreach team could rapidly gain access to the persons at risk for primary and secondary prevention. Identical strains forming viral and bacterial clusters could be identified for both HBV and GAS by WGS.

Disclosures: Marianne Alanko Blomé: Gilead: Speaking and Teaching, Gülsen Özkaya Sahin: Nothing to Disclose, Magnus Paulsson: Nothing to Disclose, Johan Ringlander: Nothing to Disclose, Pernilla Isendahl: Nothing to Disclose.

2269 | ANALYSIS OF CLINICAL CHARACTERISTICS AND RELATED FACTORS OF GALLBLADDER POLYPS IN NORTHEAST CHINA

Hui Wang[1] Xiaoyu Wen[1], [1]The First Hospital of Jilin University

Background: The incidence of gallbladder polyps (GBP) is continuously increasing. This study aimed to analyze the clinical characteristics of the population with GBP in Northeast China and the factors influencing their formation and growth, to enhance public awareness of GBP, and to promote conservative management through lifestyle modifications and avoidance of relevant risk factors, thereby reducing unnecessary cholecystectomy and other surgical interventions. **Methods:** A total of 9,103 individuals with GBP who visited the Health Examination Center of the First Hospital of Jilin University from January 2022 to December 2024 were enrolled as the study group. A random sample of 15,767 individuals without GBP during the same period was selected as the control group. General data, physiological and biochemical indicators, and abdominal ultrasound reports were collected. Clinical characteristics were summarized, and factors associated with GBP formation and growth were analyzed through intergroup comparisons. **Results:** (1) The highest proportion of GBP subjects was in the 51–60 years age group (29.31%). Polyps sized 2.1–5.9 mm accounted for the majority (75.79%), and single polyps predominated (62.25%). (2) Male sex (OR = 1.338), age (OR = 1.014), elevated levels of TBiL (OR = 1.012), TBA (OR = 1.025), LDL-C (OR = 1.162), BUN (OR = 1.093), UA (OR = 1.001), HB (OR = 1.007), and PLT (OR = 1.001), as well as decreased HDL-C (OR = 0.539) and presence of fatty liver disease (OR = 1.152), were identified as independent factors associated with GBP formation. (3) Analysis across three groups stratified by GBP size ($\leq$2 mm, 2–6 mm, $\geq$6 mm) showed a progressive increase in the proportion of males, BMI, WC, ALT, GGT, TG, Cr, UA, HB, gallbladder wall roughness, fatty liver disease, overweight/obesity, central obesity, and hyperuricemia, while HDL-C levels progressively decreased. Analysis of groups based on changes in GBP size during the study period (increase >1 mm vs. no increase or increase $\leq$1 mm) revealed that AST, ALT, and GGT levels were higher in the former group. (4) Pathological results from the big data platform of the First Hospital of Jilin University for hospitalized patients with GBP who underwent cholecystectomy showed that cholesterol polyps were the dominant pathological type, while malignant or potentially malignant polyps accounted for a very low proportion. **Conclusion:** (1) The GBP population is predominantly aged 31–60 years, with polyp sizes mainly between 2.1–5.9 mm, and single polyps are the most common. (2) Sex, age, metabolic abnormalities, liver dysfunction, and inflammatory response may be factors associated with the formation and growth of GBP. (3) The majority of patients admitted with GBP and undergoing cholecystectomy are pathologically confirmed to have benign polyps without malignant potential. Rational control of surgical indications is recommended to reduce unnecessary cholecystectomies.

Figure 1. Pathological type distribution and proportional composition of surgically resected GBP-related lesions (2023 - 2025)

Pathologic type(n,%) / Year	Cholesterol polyp	Adenomyomatosis	Adenoma	ICPN	Adenocarcinoma
2025	663 (65.51)	227 (22.43)	94 (9.29)	11 (1.09)	17 (1.68)
2024	557 (70.15)	154 (19.40)	67 (8.44)	5 (0.63)	11 (1.39)
2023	432 (63.25)	156 (22.84)	61 (8.93)	19 (2.78)	15 (2.20)
Total	1652 (66.37)	537 (21.57)	222 (8.92)	35 (1.41)	43 (1.73)

Admission Diagnosis(n,%) / Pathologic type	Gallbladder malignant lesion	Gallstones	GBP	Hepatic malignant lesion
ICPN	15 (42.86)	8 (22.86)	10 (28.57)	2 (5.71)
Adenocarcinoma	17 (39.53)	20 (46.51)	5 (11.63)	1 (2.33)

Figure 2. Multivariate binary logistic regression analysis of factors related to GBP

Variable	β	S.E.	Wald	P	OR	95%CI
Age	0.014	0.001	111.854	<0.001	1.014	1.011-1.017
Gender	0.291	0.040	53.327	<0.001	1.338	1.237-1.446
ALT	-0.003	0.001	24.143	<0.001	0.997	0.995-0.998
GGT	0.000	0.000	0.417	0.518	1.000	0.999-1.001
TBiL	0.012	0.002	24.228	<0.001	1.012	1.007-1.016
TBA	0.025	0.005	24.862	<0.001	1.025	1.015-1.035
TG	-0.034	0.011	9.528	0.002	0.967	0.947-0.988
HDL-C	-0.618	0.056	120.677	<0.001	0.539	0.482-0.602
LDL-C	0.150	0.020	54.131	<0.001	1.162	1.117-1.210
FPG	-0.037	0.011	11.146	0.001	0.964	0.944-0.985
BUN	0.089	0.011	61.225	<0.001	1.093	1.069-1.118
Cr	-0.005	0.001	18.818	<0.001	0.995	0.993-0.997
UA	0.001	0.000	59.099	<0.001	1.001	1.001-1.002
HB	0.007	0.001	30.161	<0.001	1.007	1.004-1.009
PLT	0.001	0.000	34.035	<0.001	1.001	1.001-1.002
Fatty liver disease	0.141	0.032	19.181	<0.001	1.152	1.081-1.227
Gallstones	-0.063	0.060	1.101	0.294	0.939	0.835-1.056
Overweight/Obesity	-0.050	0.034	2.219	0.136	0.951	0.890-1.016

Disclosures: Hui Wang: Nothing to Disclose, Xiaoyu Wen: Nothing to Disclose.

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2270 | EVOLVING TREATMENT REGIMENS IN FATTY LIVER DISEASE: ANALYSIS OF GLP-1 AND RESMETIROM USE

Noha Abdelgelil[1] Anna Hefner[1] Mustafa Behan[2] Jutta Kurz[2] Tresha Elaine Ramonal[2] Karen Hoyt[3] Rachma Purnama[4] Lorrinda Gray-Davis[3] Michael Tunkelrott[4] Fatma Barakat[5] Emmanuel Gorospe[6] Deanna Oliver[1] Tarek Hassanein[1], [1]Southern California Liver Centers, [2]Amsety, [3]None, [4]Amsety LLC, [5]SCTI Research Foundation, [6]Burrell College of Osteopathic Medicine

Background: Management of fatty liver disease is rapidly evolving with new treatment options. Resmetirom is approved for the treatment of liver fibrosis. However, GLP-1 receptor agonists, originally approved for diabetes and weight loss, are also used in MASLD/MASH management. **Aim:** To evaluate how pts are prescribed GLP-1 receptor agonists and resmetirom in their management of fatty liver disease and how they're integrated into clinical care and lifestyle intervention. **Methods:** The Amsety database contains close to 450,000 individuals with MASLD/MASH in the US. This is an initial analysis of 83 respondents to a survey on the use of GLP-1 and/or resmetirom. The survey addresses treatment patterns, adherence, and patient-reported outcomes, including weight change, side effects, and perceived liver health. **Results:** Average age of respondents was 41 years and a BMI of 35.8. 39% were diagnosed with MASLD in the past 12 months, 39% within the past 1-3 years, and 19% within the past 3-5 years. Comorbidities included obesity (63%), hyperlipidemia (37%), and type 2 diabetes (29%). For disease monitoring, 37% reported being on an active treatment plan (prescribed medication, scheduled imaging, and regular liver-specific follow-ups) while 33% were on periodic monitoring (scheduled tests but no medication). Resmetirom and/or GLP-1 use: 13% received resmetirom. 58% received injectable semaglutide, 11% oral semaglutide, and 20% took tirzepatide. 35% have been on GLP-1 for 6-12 months at the time of completing the survey. Side effects included nausea/vomiting (48%), fatigue/weakness (41%), and gastrointestinal issues (36%). GLP-1 prescription: was mainly by Primary Care Providers (51.8%) and Gastroenterologists/Hepatologists (43.4%). 35% were prescribed GLP-1 for weight loss and 27% for liver health. Lifestyle modifications: Almost 50% made dietary and/or physical activity changes while on GLP-1. Outcomes: 36% lost 5% of body weight, 20% lost 5-10%, and 17% reported no weight loss/gain. After stopping GLP-1 medication, 35% maintained improved eating habits and weight while 25% returned to old eating habits. 34% and 22% of pts reported improvement or stability in liver fat and/or fibrosis according to their provider, respectively. **Conclusion:** GLP-1 medications show emerging use in fatty liver disease management, primarily for weight loss and metabolic comorbidities. Patient-reported outcomes indicate improvements in weight and dietary habits. Treatment patterns vary between primary and specialist care, with specialists more often tailoring therapy to underlying metabolic or liver-related indications. These therapies are a key component of care, but long-term benefit depends on continued treatment, lifestyle adherence, and clinical follow-up. GLP-1 use in combination with resmetirom needs to be better understood with a tailored management approach applied.

Disclosures: Noha Abdelgelil: Nothing to Disclose, Anna Hefner: Nothing to Disclose, Mustafa Behan: Nothing to Disclose, Jutta Kurz: Nothing to Disclose, Tresha Elaine Ramonal: Amsety GmbH: Employee, Karen Hoyt: Nothing to Disclose, Rachma Purnama: Amsety GmbH: Employee, Lorrinda Gray-Davis: Nothing to Disclose, Michael Tunkelrott: Nothing to Disclose, Fatma Barakat: Nothing to Disclose, Emmanuel Gorospe: Castle Biosciences: Employee, Deanna Oliver: Nothing to Disclose, Tarek Hassanein: AbbVie: Speaker and Research Support, Gilead: Speaker and Research Support, HepQuant Shunt: Advisor, Madrigal: Advisor and Research Support, Amgen: Grant/Research Support, Astra Zeneca: Grant/Research Support, Boehringer- Ingelheim: Grant/Research Support, COUR: Grant/Research Support, Escient: Grant/Research Support, Galectin: Grant/Research Support, Grifols: Grant/Research Support, Intercept: Grant/Research Support, Janssen: Grant/Research Support, Merck: Grant/Research Support, Mirum: Grant/Research Support, NeuroBo: Grant/Research Support, Novartis: Grant/Research Support, Novo Nordisk: Grant/Research Support, Pfizer: Grant/Research Support, Regeneron: Grant/Research Support, Salix Pharmaceuticals: Grant/Research Support, Takeda: Grant/Research Support, Akero: Grant/Research Support, Ipsen: Grant/Research Support, Kowa: Grant/Research Support, Bristol-Myers Squibb: Grant/Research Support, DURECT: Grant/Research Support, HepQuant: Grant/Research Support, Terns Pharmaceuticals: Grant/Research Support, Mallinckrodt: Speaker and Research Support, Eli Lilly: Grant/Research Support, PharmaIn: Grant/Research Support, Sonic incytes: Grant/Research Support, Tensor Bio: Grant/Research Support, 89Bio: Grant/Research Support, Terns Pharmaceuticals: Grant/Research Support, Nterica: Consultant, Atea: Grant/Research Support, Harbinger: Grant/Research Support, Sanofi-Aventis: Grant/Research Support, CurveBio: Grant/Research Support, AbbVie: Speaker and Research Support, Gilead: Speaker and Research Support, HepQuant Shunt: Advisor, Madrigal: Advisor and Research Support, Amgen: Grant/Research Support, Astra Zeneca: Grant/Research Support, Boehringer- Ingelheim: Grant/Research

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2271 | SPATIAL TRANSCRIPTOMIC ANALYSIS OF PORTAL INFLAMMATION DIFFERENTIATES ACTIVATED T CELL PEDIATRIC ACUTE LIVER FAILURE FROM AUTOIMMUNE HEPATITIS

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Background: Activated T-cell pediatric acute liver failure (TC-PALF) is the leading cause of acute liver failure in children in North America. Prior work from the PALF Immune Response Network (PALF-IRN) identified two TC-PALF endotypes defined by CD8+ T-cell Perforin1 (Prf) expression: High Prf and Normal Prf (NL Prf). High Prf cases show an interferon-gamma (IFN-γ)–positive CD8 tissue-resident memory transcriptional signature in peripheral blood. However, tissue-level T-cell–hepatic parenchymal interactions have not been well described. We used high-resolution spatial transcriptomics to map these interactions in liver biopsies. **Methods:** Formalin-fixed paraffin-embedded liver biopsies from PALF-IRN or Children's Hospital of Philadelphia were profiled by VisiumHD, 10x. Groups: TC-PALF High Prf (n = 8), TC-PALF NL Prf (n = 6), and seropositive acute fulminant autoimmune hepatitis (AIH, n = 3) were compared. Data were binned at 8×8 µm (≍1–2 cells/bin), clustered with Seurat, and annotated using Enrichr and histologic correlation in Loupe Browser software. Pseudo-bulk comparisons across annotated clusters used R (v4.4.0). To identify shared, biologically relevant programs, we filtered for differentially expressed genes present in >50% of cell populations and significantly upregulated in >75% of annotations. Uniform Manifold Approximation and Projection (UMAP) was used to visualize the data. **Results:** Seurat clustering revealed two transcriptionally distinct T-cell populations corresponding to microanatomic locations: portal and lobular (Fig. 1A). We focused on portal T cells, where comparable bins existed across TC-PALF High Prf, NL Prf and AIH. Compared with NL Prf, TC-PALF High Prf portal T cells were enriched for effector and cytolytic-related genes (KLRG1, SH2D1A/SAP, SRGN). Compared with AIH, TC-PALF High Prf showed enrichment for pathways mediating T-cell and monocyte recruitment (chemotaxis) and integrin–collagen interactions, whereas AIH was enriched for B-cell receptor signaling (Fig. 1B). Gene programs present in >75% of cell populations in TC-PALF High Prf versus AIH or NL Prf were dominated by T-cell proliferation and IFN signaling (Fig. 1C/D), indicating that both immune cell and parenchymal compartments in TC-PALF High Prf are responsive to IFN-γ. **Conclusion:** TC-PALF High Prf liver tissue displays a unique portal microenvironment characterized by cytotoxic T-cell effector signatures, chemokines promoting T-cell/monocyte recruitment,

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and enhanced integrin–extracellular matrix interactions. IFN signaling in TC-PALF High Prf is increased across immune and parenchymal cells. These spatially resolved features distinguish TC-PALF High Prf from NL Prf and AIH highlighting the importance of this cytokine in disease pathogenesis and provide key insights to disease biology.



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2272 | ◆ TGR5 INHIBITION DISRUPTS BILE ACID-DRIVEN IMMUNOSUPPRESSION IN CHOLANGIOCARCINOMA

Enis Hikmet Ozmert[1] Binbin Li[1] Hannah Stumpf[1] Jingchun Yang[1] Danielle Carlson[1] Jennifer Tomlinson[1] Rory Smoot[2] Sumera Ilyas[2], [1]Mayo Clinic, [2]Mayo Clinic Rochester

Background: Cholangiocarcinoma (CCA) is a lethal hepatobiliary malignancy where first line therapy (durvalumab + gemcitabine/cisplatin) provides marginal survival benefit. CCA exhibits a distinct tolerogenic tumor microenvironment (TME) shaped by elevated bile acid concentrations from obstructive cholestasis. TGR5 is a key receptor in bile acid signaling. We hypothesize that bile acids promote CCA progression via TGR5 signaling on myeloid cells, targetable with SBI-364, a novel potent small molecule TGR5 inhibitor. **Methods:** We generated a comprehensive single-cell RNA sequencing (scRNA-seq) atlas of human intrahepatic (iCCA) and perihilar (pCCA) cholangiocarcinoma to map TGR5 expression across TME populations. Monocyte-derived Kupffer cells (moKCs) emerged as the major TGR5 signaling hub and we performed CellChat analysis to identify its interactors within the TME. We evaluated SBI-364 (a small molecule inhibitor of TGR5 developed through a Sanford Burnham-Mayo Clinic collaboration) efficacy in syngeneic orthotopic models of iCCA and a novel pCCA model in C57BL/6J mice, with single-cell Flex profiling of treated tumors. Two patient-derived xenografts (PDXs) with divergent tumor TGR5 (GPBAR1) expression underwent treatment studies in NOD/SCID mice. Lastly, we analyzed the Mayo Tempus CCA cohort using CIBERSORTx to correlate our murine findings with patient data. **Results:** Human scRNA-seq revealed TGR5 expression was highly enriched in myeloid cells within a “moKC” population, across iCCA and pCCA. This population was also the most immunosuppressive myeloid cell population in the TME. CellChat analysis

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identified moKCs as a major outgoing signaling source to T cells across multiple tolerogenic pathways. SBI-364 significantly increased survival in orthotopic models when combined with gemcitabine/cisplatin and reduced tumor burden in murine iCCA and pCCA. In contrast, SBI-364 failed to inhibit tumor growth in both TGR5-high and TGR5-low PDXs in immunodeficient hosts, demonstrating that TGR5 blockade acts through immune-mediated mechanisms rather than tumor-intrinsic effects. Single-cell profiling of SBI-364 treated tumors demonstrated TME-wide reprogramming, including reduced moKC tolerogenic programs. In vitro, bile acids suppressed CD8+ T cell proliferation, which was abrogated by SBI-364 co-treatment. Clinically, elevated GPBAR1 expression in the Mayo Tempus cohort correlated with worse overall survival in both pCCA and iCCA, as well as with increased anti-inflammatory dendritic cell fractions. **Conclusion:** TGR5 inhibition reprograms the immunosuppressive myeloid-driven TME in CCA, reducing tumor burden by restoring effector T cell immunity. These findings establish TGR5 as a rational therapeutic target for overcoming immune evasion in cholangiocarcinoma and identify GPBAR1 expression as a candidate biomarker to guide patient selection for TGR5-directed therapy.

Disclosures: Enis Hikmet Ozmert: Nothing to Disclose, Binbin Li: Nothing to Disclose, Hannah Stumpf: Nothing to Disclose, Jingchun Yang: Nothing to Disclose, Danielle Carlson: Nothing to Disclose, Jennifer Tomlinson: Nothing to Disclose, Rory Smoot: Nothing to Disclose, Sumera Ilyas: Astrazeneca: Consultant.

2273 | D-GALACTOSAMINE/LPS ACUTE LIVER FAILURE RECAPITULATES EMERGENCY GRANULOPOIESIS LIKE SIGNATURES ACROSS THE BONE MARROW–SPLEEN–LIVER AXIS

Jessica Dieudonne[1] Alexandra Caron[1] Audrey Levy[1] Maryse Malysiak[1] Valerie Daix[1] Stephanie Ferreira[1] Jean-Marie Brusq[1] Zouher Majd[1] Bart Staels[2] Sakina Sayah Jeanne[1] Alessia Galgano[1], [1]Genfit, [2]University Lille 2

Background: Emergency granulopoiesis (EG) is an inflammation-driven disturbance of neutrophil homeostasis characterized by accelerated bone-marrow neutrophil production, release of immature neutrophils, and concomitant inhibition of lymphopoiesis. Recent transcriptomic studies have suggested EG signatures in patients with acutely decompensated cirrhosis progressing to Acute-on-Chronic Liver Failure (ACLF). Whether such EG-like features can be reproduced experimentally in liver failure models remains unknown. We therefore characterized whether the D-GalN/LPS acute liver failure (ALF) model reproduces EG hallmarks. **Methods:** Mice were challenged with D-GalN/LPS and euthanized 5.5 h post-challenge. Liver, spleen and bone marrow were harvested for flow cytometry using standardized gating to quantify total neutrophils, maturation status, activation features and T-, B- and NK-cell subsets were analyzed in parallel. Circulating NET-associated biomarkers were quantified in plasma by ELISA including H3R8Cit and total extracellular histone H3.1). H3R8Cit was assessed in controls ($n = 4$) and D-GalN/LPS mice at 3h ($n = 4$) and 5.5 h ($n = 4$) while H3.1 was measured in controls ($n = 11$) and D-GalN/LPS mice at 5.5 h ($n = 9$). **Results:** D-GalN/LPS induced a marked increase of total neutrophils in liver and spleen (approximatively 2-3-fold) together with a strong decrease of bone marrow neutrophils CD11b+/Ly6g+(-40-60%), highlighting a rapid mobilization of the steady-state pool toward peripheral organs. In liver and spleen, neutrophils displayed increased activation-associated features (CD62L+/CD101+ cells) and a shift toward immaturity (CD62L+/CD101- neutrophils), suggesting an early EG-like reprogramming during acute systemic inflammatory stress. Concomitantly, NK (CD45+/NK1.1+)- and B (CD45+/B220+)-cell markedly decreased, most prominently in the liver (50-70%), while total T-cell frequencies were preserved. Circulating NET-associated biomarkers increased following D-GalN/LPS challenge, with significantly higher H3R8Cit levels (H3R8Cit, ~2-fold vs controls; $p < 0.05$) and strong increase in total extracellular H3.1.(H3.1 vs controls, $p < 0.05$). **Conclusion:** The D-GalN/LPS model recapitulates EG-like features: bone marrow neutrophil release, peripheral neutrophil expansion of immature and activated neutrophils, associated with lymphocyte subset alteration, and finally NET-associated circulating markers. This in vivo model may enable the dissection of EG-associated mechanisms and support evaluation of neutrophil-targeted therapeutic approaches in acute liver diseases such as ALF, with potential relevance to AD/ACLF.

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2274 | ◆ ALCOHOL ENHANCES MYELOID-DERIVED SUPPRESSOR CELL EXPANSION THROUGH IRF3-DEPENDENT MECHANISMS AND THEREBY CONTRIBUTES TO IMMUNOSUPPRESSION

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Background: Alcohol-associated liver disease (ALD) is characterized by persistent inflammation and immune dysfunction. Myeloid-derived suppressor cells (MDSCs) have two types: monocytic-MDSCs (M-MDSCs) and granulocytic-MDSCs (G-MDSCs) that regulate immune responses, accumulate in the liver and may play a role in ALD. Interferon regulatory factor 3 (IRF3) is a key mediator of alcohol-induced inflammation, but its role in MDSC biology is unknown. We investigated the effects of alcohol and IRF3 signaling on MDSC differentiation and immunosuppressive function. **Methods:** Circulating blood of patients with severe alcohol-associated hepatitis (AH) and healthy controls were assessed by FACS for the frequency of G- and M-MDSCs. Mice received the NIAAA alcohol or control diet. In mice, bone marrow (BM)-derived MDSCs were generated from wild-type (WT) and IRF3 knockout (KO) mice using GM-CSF followed by LPS/IFN-γ stimulation. Cells were treated with alcohol in vitro and analyzed by flow cytometry for granulocytic (G-MDSCs; CD11b +Ly6G+) and monocytic MDSCs (M-MDSCs; CD11b +Ly6C+), IL10, Arg1, and phosphorylated IRF3 (pIRF3). Cytokine levels were measured by ELISA. T-cell suppressive function was assessed using CFSE-based proliferation assays. **Results:** We found a significant increase in the frequency of circulating G-MDSCs and M-MDSCs in AH patients compared to healthy controls (HC). A similar increase in G- and M-MDSCs was found in the livers of mice with AH compared to controls. Circulating levels of GM-CSF and IFN-gamma that are factors promoting MDSC generation were increased both in human AH subjects and AH mice compared to controls. In vitro, alcohol exposure of bone marrow progenitors significantly increased both G-MDSC and M-MDSC populations. Despite expansion of MDSCs, alcohol reduced IL10+ MDSCs and decreased IL6 and IL1β production, suggesting impaired functional activation. Alcohol-treated MDSCs demonstrated enhanced suppression of T-cell proliferation and reduced IFN-γ production compared to alcohol-naive MDSCs. Mechanistically, alcohol increased expression of phosphorylated IRF3 (pIRF3) predominantly in M-MDSCs. In IRF3 KO mice, alcohol-induced expansion of G-MDSCs was attenuated, accompanied by reduced Arg1 expression and diminished IL10+ M-MDSCs. Consistently, alcohol-treated IRF3-deficient MDSCs failed to suppress T-cell proliferation, indicating restoration of T-cell responses in the absence of IRF3 signaling. Furthermore, IRF3 deficiency significantly reduced alcohol-induced IL6 and IL1β production. These findings identify IRF3 as a critical regulator of alcohol-mediated MDSC expansion and suppressive function. **Conclusion:** Alcohol promotes MDSC expansion while impairing their inflammatory and immunoregulatory functions through IRF3-dependent mechanisms. IRF3 signaling is required for alcohol-induced MDSC-mediated suppression of T-cell proliferation and inflammatory cytokine production. These findings identify IRF3 as a key regulator of myeloid immune dysfunction in ALD and suggest that targeting IRF3-dependent pathways may restore immune function in alcohol-associated liver disease.

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★ 2275 | EOSINOPHILS PROMOTE CYTOTOXIC CD8+ T CELL RESPONSES IN AN IL-4-DEPENDENT MANNER

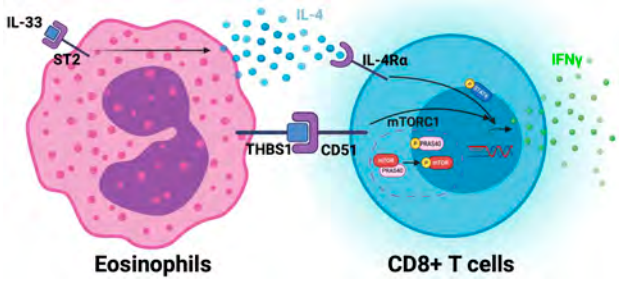
Yankai Wen[1], [1]University of Texas - Houston

Background: Hepatocellular carcinoma (HCC) is an aggressive malignancy with rising global incidence and mortality. Emerging evidence supports an anti-tumorigenic role of eosinophils during HCC progression. While eosinophils have increasingly been recognized as critical modulators of anti-tumor immunity, the molecular mechanisms through which eosinophils regulate CD8+ T cell activation remain elusive. **Methods:** In this study, we adopted a coculture system of bone marrow-derived eosinophils and splenocytes or purified splenic CD8+ T cells under various stimulatory conditions. CD8+ T cell activation was determined by measuring intracellular interferon (IFN)g and tumor necrosis factor (TNF)a levels via flow cytometry.

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Genetic knockout models, neutralizing antibodies, pharmacological inhibitors, trans-well assays, and reverse-phase protein assay were employed to dissect the mechanism. **Results:** We found that interleukin (IL)-33-activated eosinophils significantly enhanced CD8+ T cell activation, an effect dependent on eosinophil-derived IL-4 rather than IL-13. The data further revealed a cell-cell-contact-dependent mechanism involving the thrombospondin (THBS)1/CD51/mTORC1 signaling axis. This study demonstrates a two-pronged mechanism by which eosinophils enhance CD8+ T cell activation. On one hand, eosinophils secrete IL-4, which directly activates CD8+ T cells through STAT6 signaling. On the other hand, through cell-cell contact and engagement of the THBS1/CD51/mTORC1 signaling axis, eosinophils further amplify IL-4-induced CD8+ T cell activation. **Conclusion:** Collectively, these findings provide novel mechanistic insights into eosinophil-based therapeutic strategies for augmenting anti-tumor CD8+ T cell responses in HCC.



Disclosures: Yankai Wen: Nothing to Disclose.

2277 | DIET-INDUCED ALTERNATIVE MRNA SPLICING AS A KEY INITIATOR OF LIVER INFLAMMATION

Aizhan Surumbayeva[1] Sajjan Rajpoot[2] Michael Levin[3] Riley Williams[2] Yunyun Zhou[2] Siddharth Balachandran[2] Igor Astsaturov[2], [1]Fox Chase Cancer Center; Lewis Katz School of Medicine, Temple University, [2]Fox Chase Cancer Center, [3]College of Engineering, Temple University; Fox Chase Cancer Center

Background: The modern hypercaloric diet, rich in refined carbohydrates, is a major contributor to metabolic dysfunction-associated steatotic liver disease (MASLD). While it is well-known that a hypercaloric diet causes obesity and MASLD, about 30% of patients with MASLD develop metabolic syndrome-associated steatohepatitis (MASH) over time, which features advanced inflammation, steatosis, and hepatocyte damage. However, it remains unclear *what initially triggers this inflammation* and whether insulin could play a role in provoking an inflammatory response in the liver. **Methods:** Mice were fed a high-carbohydrate diet (HCD) or western diet (WD) and compared to fasted animals or mice on regular chow diet. Bulk RNA sequencing and alternative splicing analysis were performed on isolated hepatocytes. Immunofluorescence staining with antibodies against double-stranded RNA (dsRNA) was used to detect endogenous retroviral element (ERE)-derived dsRNA species in liver sections. Genetic knockouts (*Mavs*$^{-/-}$, *Ifnar1*$^{-/-}$) and pharmacological inhibitors of AKT and serine-arginine rich protein kinase 1 (SRPK1) were employed to interrogate pathway dependencies. Findings were validated in transcriptomic datasets from MASLD patients. **Results:** Feeding mice a HCD induces a type I interferon (IFN-I) response in hepatocytes and activates inflammatory signaling pathways in the liver. This IFN-I response is linked to infiltration of the liver with activated T cells and is absent in *Mavs* or *Ifnar1* knockout mice. Surprisingly, we discovered significantly increased alternative splicing events in the total transcriptomes of hepatocytes from mice on HCD. Notably, retained introns were most enriched in transcripts from HCD-fed hepatocytes and were predominantly found in genes regulated by insulin. Since retained introns contain EREs that tend to form double-stranded RNA (dsRNA), we demonstrated the presence of dsRNA through immunofluorescent staining of HCD-conditioned liver sections. Notably, mice fed a WD similarly exhibited aberrant splicing perturbations and dsRNA accumulation in hepatocytes, corroborating that these effects are a shared feature of obesogenic, hyperinsulinemic dietary conditions. Insulin may regulate alternative splicing in hepatocytes by inducing excessive phosphorylation of SR-family splicing factors. Blocking AKT or SRPK1 with selective inhibitors *in vivo* completely reversed the effects of HCD. Importantly, transcriptome analysis of patients with MASLD, compared to normal livers showed similarly increased alternative splicing and a dramatic rise in human ERE expression. We ***hypothesize*** that dsRNAs produced by chronic and excessive insulin signaling in hepatocytes are a key early trigger of liver inflammation. **Conclusion:** Our findings reveal a previously unrecognized mechanism and new therapeutic opportunities for preventing or treating MASLD and other inflammatory conditions related to obesity.

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2278 | CONTRIBUTION OF CYTOTOXIC NATURAL KILLER CELLS INFLAMMATION AND LIVER INJURY IN ALD

Shelene Mitchell[1] Emmanuel Boafo[1] Colin Varnet[1] Adam Kim[1], [1]UConn Health

Background: Alcohol-associated Hepatitis (AH) is a severe inflammatory disease with high short-term mortality. In AH, dysfunctional immune cells lead to uncontrolled inflammation and exacerbate hepatocellular damage. In the liver, cytotoxic lymphocytes like NK cells and CD8 T-cells detect and kill damaged cells, which should be protective, but they also produce a pro-inflammatory cytokines like interferon gamma (IFNG) that can contribute to liver inflammation. Previous work from our lab found that circulating NK-cells in AH are dysfunctional and lack Perforin (Prf1), a key factor in NK cell cytotoxic function. Less is known about the contribution of liver resident NK cells in alcohol-associated liver disease (ALD) and AH. **Methods:** Perforin knockout (Prf1-KO) mice were used to assess loss of cytotoxic function in NK cells in multiple chronic alcohol feeding models of ALD. Livers were collected for histology and multi-panel flow cytometry for detection of diverse immune populations. Additionally, we used a combination of publicly available single-cell RNA-seq and spatial RNA-seq datasets to assess the gene expression changes and tissue distribution of NK cells and CD8 T-cells in human ALD. **Results:** Prf1-KO mice have NK cells and CD8 T-cells with no ability to kill targeted cells, making these mice very sensitive to viral infections. Prf1-KO mice had similar levels of liver damage due to alcohol, as measured by ALT and AST, to wildtype controls in chronic 6% diet models and the NIAAA-model. qPCR and flow cytometry did not reveal increased inflammation in Prf1-KO mice. Except, in the NIAAA-model, Prf1-KO mice had significantly higher monocyte infiltration. Human RNA-seq studies reveal that liver resident NK cells are not reduced in ALD, but gene expression suggests decreased NK cell maturity. **Conclusion:** In recent years, NK cells have become a neglected cell type of study in the liver, despite being the second most common immune cell. Our studies reveal that NK-cell cytotoxic function does not contribute to or protect from alcohol in mouse models of ALD. These data suggest that NK cells can contribute to ALD by worsening inflammation, and cytotoxic functions. Future studies will focus on how NK-cells communicate to other important cells in ALD and AH, like monocytes, hepatocytes, and stellate cells.

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2279 | CELL INTRINSIC PROGRAMMED DEATH-LIGAND 1 (PD-L1) SIGNALING LIMITS LOW AFFINITY T CELL RESPONSES AND LIVER PATHOLOGY DURING ACUTE INFECTION WITH *LISTERIA MONOCYTOGENES*

Lucy Fry[1] Jessica Olivas-Corral[1] Jaime Shirley[1] David Orlicky[1] Beth Tamburini[1], [1]University of Colorado Anschutz medical campus

Background: Programmed Cell Death Protein-1 (PD-1)/Programmed Death-Ligand 1 (PD-L1) interactions act as an immune checkpoint. Upon PD-1 ligation, T cells undergo downregulation to prevent excessive tissue damage. During chronic infections such as hepatitis B or C, aberrant PD-1/PD-L1 signaling leads to T cell exhaustion. Interestingly, the intracellular PD-L1 domain has also been demonstrated to have immune regulatory functions, particularly in myeloid cells. *Listeria monocytogenes* (*Lm*) is a food-borne bacterial pathogen that rapidly localizes to the liver upon entry into the blood. Systemic administration of *Lm* elicits a well-characterized immune response that largely depends on myeloid cells for clearance, making this an ideal model to study tissue-specific responses that may be regulated by the PD-L1 intracellular domain. **Methods:** To determine how the PD-L1 intracellular domain regulates liver specific immune responses during infection, we utilized a novel mouse model containing mutations in the cytoplasmic tail of PD-L1 (*Pdl1*^{CyMt}), where signaling via the extracellular domain of PD-L1 remains intact. WT and *Pdl1*^{CyMt} mice were infected with *Lm, Lm* expressing Ovalbumin *(Lm-Ova),* or *Lm* expressing H2-Kb peptides of ovalbumin with altered amino acids (altered peptide ligands-*Lm-APL*) that bind MHC I equally but vary in their ability to stimulate ovalbumin specific TCR transgenic, OT-I, cells. We euthanized mice at numerous time-points following *Lm* infection and evaluated bacterial counts, serum cytokine levels, histologic analysis, tissue staining, and flow cytometry on liver tissue. **Results:** *Pdl1*^{CyMt} mice exhibit decreased inflammatory foci at day 7 post infection (p.i.) compared to control mice and increased endogenous CD8^{+} T cell cytokine production. Following OT-I CD8^{+} cell transfer and *Lm-APL* infection, we found that in *Pdl1*^{CyMt} mice, OT-I CD8^{+} T cells expanded more independent of the alterations in the peptide affinity for the T cell receptor, suggesting non-specific T cell activation, while also displaying a reduction in the inflammatory foci observed within the liver. These findings could be a result of increased myeloid cell populations in the *Pdl1*^{CyMt} mice at both early and late timepoints after infection. Intriguingly, *Pdl1*^{CyMt} mice exhibit enhanced bacteremia at day 7 when control mice have cleared the infection.

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Conclusion: These data suggest that the PD-L1 intracellular domain decreases the threshold of activation for lower affinity T cell responses and limits inflammatory foci associated with *Lm* infection and clearance. Additionally, these data suggest the intracellular domain of PD-L1 modulates myeloid cell dynamics in the liver, which may limit non-specific bystander T cell activation. Thus, in the *Pdl1*^{CyMt} mice aberrant myeloid cell activity could result in non-specific T cell responses that delay *Lm* clearance from the liver, defining a role for the intracellular domain of PD-L1 during infection.

Disclosures: Lucy Fry: Nothing to Disclose, Jessica Olivas-Corral: Nothing to Disclose, Jaime Shirley: Nothing to Disclose, David Orlicky: Lumen Biosciences: Grant/Research Support, Beth Tamburini: Nothing to Disclose.

2280 | ROLE OF PERMISSIVE CHROMATIN MODIFICATION IN THE DEVELOPMENTAL REGULATION OF THE HEPATOCYTE-SPECIFIC INNATE IMMUNE RESPONSE

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Background: Gene expression in mouse liver tissue undergoes a significant transition between postnatal day 3 (P3) and adulthood, shifting from a proliferative, neonatal state to a mature, metabolic, and detoxifying state. While P3 livers are characterized by high rates of cell expansion and metabolic adaptation, adult livers are defined by established hepatocyte zonation and mature drug metabolism. Hepatocytes, the major parenchymal cells in the liver, are responsible for a variety of cellular functions including carbohydrate, lipid and protein metabolism, detoxification and immune cell activation to maintain liver homeostasis. Recent studies show hepatocytes play a pivotal role in liver inflammation, however, the age-specific epigenetic modifications that orchestrate the interplay between the chromatin state and inflammatory gene expression are not well known. The objective of this study is to determine the nuclear association between H3k27ac, CBP/p300, and NFκB-p65 and acetylation changes of p65 binding site in the promoters of specific genes in p3 and adult hepatocytes. Further we assessed ATAC seq and bulk RNA seq in p3 and adult isolated hepatocytes to find out chromatin accessibility and gene expression. **Methods:** We isolated p3 and adult mice hepatocytes and used an assay for transposase-accessible chromatin using sequencing (ATAC-seq) combined with whole liver quantitative chromatin immunoprecipitation (ChIP) and bulk ribonucleic acid sequencing (RNA-seq) to provide a detailed description of gene expression. Promoter-associated histone modifications were investigated via ChIP qPCR at three transcriptionally relevant sites known for NFκB occupancy on the Tnf, cxcl2, ccl3, cxcl10, Il1rn, Icam1 and A20 promoters. Purified murine hepatocytes were treated with JQ1 (2.5μM x24h) and exposed to IL1b+IL6 (20 ng/mL each X 1h). mRNA was isolated followed by RT-qPCR for NFkB primary response genes (Cxcl2, Cxcl10, and Tnf) and several other genes were assessed. Each experiment was performed in triplicate. Results were statistically analyzed using t-test and significance defined as $p < 0.05$. **Results:** Quantitative ChIP using p65, CBP/p300 and h3k27ac antibodies give significantly more binding of NFkBp65 binding site on Tnf, cxcl2, ccl3, cxcl10, Il1rn, Icam1 and A20 promoters in adult liver when compared to p3. IgG was used as isotypic antibody control; normalized with 5% input (data represented as mean ± SEM,for three replicates). Chromatin accessibility was strongly linked to gene expression. To further understand the relations among variations in gene expression and chromatin accessibility, we performed integrated analysis of the ATAC-seq and RNA-seq from the isolated hepatocytes. Several genes transcriptional alterations linked to differentially accessible chromatin regions. Differentially expressed genes were related to immune responses to determine the relationship between chromatin accessibility and gene expression levels, we conducted RNA-seq using the p3 and adult hepatocytes samples. **Conclusion:** A growing amount of evidence has demonstrated stressed hepatocytes exert a pivotal role in the development of inflammation and fibrosis via cell-cell interactions during liver injury. In this study, we summarize the role of hepatocytes during development of their links to liver inflammation. Furthermore, we introduce a wide variety of proinflammatory signals carried by hepatocyte that can deliver the message to neighbor target cells and in the circulation to modulate immune response. Understanding of the molecular mechanisms involved in the regulation of hepatocytes damage, as well as role of hepatocyte in immune regulation may provide novel insights of dysregulated

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inflammation during neonatal development and identify new therapeutic targets for various liver diseases particularly sepsis

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2281 | P2Y2 PURINERGIC SIGNALING IS ESSENTIAL FOR THE EFFICIENT INDUCTION OF TLR4-MEDIATED MACROPHAGE ACTIVATION

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Background: P2Y2 purinergic receptor gene deletion protects mice from bacterial endotoxin and sepsis-associated liver injury and mortality. TLR4 activation of macrophages leads to nucleotide release, contributing to elevated nucleotide levels in the extracellular milieu. Extracelluar nucleotide-mediated activation of P2Y2 purinergic receptor signaling, via the activation of ERK-MAPK and NF-kB signaling and the induction of endoplasmic (ER) stress, has the potential to influence macrophage function. However, the functional significance of TLR4-mediated activation of P2Y2 signaling and its contribution to macrophage activation is currently unknown. Experiments were designed to test the **hypothesis** that extracellular nucleotide-mediated activation of P2Y2 purinergic signaling is necessary for the efficient induction of TLR4-mediated macrophage activation. **Methods:** BMDM (WT vs P2Y2-/- mice) were treated with LPS (100 ng/ml or 1.0 µg/ml, TLR4 agonist) for 0.5, 8, and 24 hr. BMDM (WT) were treated with AR-C118925 (100 µM, P2Y2 antagonist, 30 min) prior to LPS treatment. Total protein extracts were analyzed by Western blotting for the induction of phosphorylated and total p42/44-ERK (MAPK signaling), p65-NF-kB (NF-kB signaling), IRE1alpha, eIF2alpha, and GRP78 (ER Stress), and iNOS (pro-inflammatory polarization). The rank order of nucleotide agonist preference for the activation of ERK (5 min) and ER stress (24 hr) in BMDM (WT) was evaluated. Fold change was calculated based on the densitometric analysis of band intensity, and statistical significance was determined by unpaired Student's t-test ($p < 0.05$). **Results:** TLR4-mediated induction of p42/44-ERK and NF-kB signaling, ER stress, and pro-inflammatory iNOS protein expression were significantly attenuated in KO BMDM, as compared to WT controls [Fold change, FC: WT v P2Y2-/-; phos-ERK, 14.1 v 6.0; phos-NF-kB, 45.8 v 17.3; phos-IRE-1alpha, 19.9 v 8.9; phos-eIF2alpha, 12.6 v 1.3; Grp78, 4.9 v 0.7; iNOS: 11.2 v 4.4. $p < 0.05$]. P2Y2 antagonist treatment attenuated LPS-induced activation of ERK and NF-kB signaling [LPS v ARC118925+LPS, phos-ERK: 34.8 v 9.7; phos-NF-kB, 50.0 v 2.4] in the WT-BMDM. UTP (P2Y2 agonist) treatment showed the higher rank order potency for ERK activation in the WT BMDM [Veh v UTP, UDP, ATP, ATPgS, ADP: 3.3, 2.0, 1.4, 1.4, 1.1]. UTP-mediated induction of ERK (FC: phos-ERK: 2.8 v 1.6) and ER stress (phospho-IRE1alpha: 8.0 v 1.4; Grp78, 15.5 v 1.5) was attenuated in P2Y2-/- BMDM. **Conclusion:** Our findings, based on a combination of genetic and pharmacologic approaches, suggest that P2Y2 purinergic signaling is an essential co-determinant of TLR4-mediated macrophage activation. Considering the pathophysiologic role of macrophage-mediated hyperinflammation in the induction of liver injury in patients and animal models of sepsis, our findings highlight the potential for the development of novel therapeutics targeting P2Y2 purinergic receptors.

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2282 | RSPO2 DRIVES LIVER REGENERATION BUT FUELS FIBROTIC REMODELING

Bhupesh Singla[1] Ravi Varma Aithabathula[1] Frank Park[1] Srija Rairao[1] Bal Krishan Sharma[2], [1]The University of Tennessee Health Science Center, Memphis, TN, USA, [2]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

Background: The liver plays a central role in macronutrient metabolism and detoxification, and undergoes regeneration. Its regenerative ability is essential for functional recovery following liver resection and injury. However, the mechanisms regulating hepatic regeneration, injury, and fibrosis remain incompletely understood. Previously, we identified R-spondin 2 (RSPO2), a matricellular protein, as a key suppressor of diet-induced hepatic steatosis. The present study was designed to investigate the role of RSPO2 in hepatic regeneration, injury, and fibrosis. **Methods:** Multiple complementary mouse models, including 2/3 partial hepatectomy (PHx), acetaminophen (APAP)-induced liver injury, and carbon tetrachloride (CCl_4)-induced hepatic fibrosis, were utilized following AAV-mediated *Rspo2* overexpression in wild-type mice. Histochemical

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and molecular analyses were performed to determine metabolic zonation, injury, regeneration, and fibrosis in liver tissues. **Results:** *Rspo2*-AAV-injected mice exhibited a higher liver weight/body weight ratio at 3 and 6 days post-PHx compared with control AAV-administered mice, suggesting accelerated recovery of liver mass with *Rspo2* overexpression. Western blotting data demonstrated increased expression of proliferation markers, including PCNA and cyclin D1, at both time points in *Rspo2*-overexpressing mice. These changes were accompanied by reduced mRNA levels of pro-inflammatory molecules *Il1b*, *Il6*, and *Tnfa*. Additional immunostaining analyses revealed significantly elevated cyclin D1 and Ki67 expression in the periportal and mid zones, along with increased glutamine synthase staining in the pericentral zone, and a uniform distribution of Cyp1a2 throughout the liver lobule in *Rspo2*-AAV-injected mice. *Rspo2* overexpression also reduced APAP-induced pericentral hepatocyte apoptosis, as shown by decreased cleaved caspase-3 staining. Consistently, Western blotting experiments showed decreased expression of apoptosis signature proteins PARP and caspase 9 in *Rspo2*-overexpressing livers. Interestingly, *Rspo2* overexpression exacerbated CCl_4-induced hepatic fibrosis, as indicated by increased Sirius red- and Col1a1-positive areas. These results were further supported by elevated protein expression of Col1a1, TGFβ, vimentin, and αSMA in immunoblotting. Furthermore, *Rspo2*-AAV-injected mice treated with CCl_4 had augmented hepatic accumulation of F4/80-positive macrophages. **Conclusion:** These results reveal that RSPO2 exerts a dual role in liver pathophysiology by promoting hepatic regeneration and hepatoprotection while enhancing fibrotic remodeling. These findings identify RSPO2 as a potential therapeutic target for regulating liver regeneration, repair, and fibrosis.

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2283 | MYD88-DEPENDENT MITOCHONDRIAL OXIDATIVE DYSFUNCTION AND MALADAPTIVE METABOLIC RESPONSES DURING HYPERAMMONEMIA

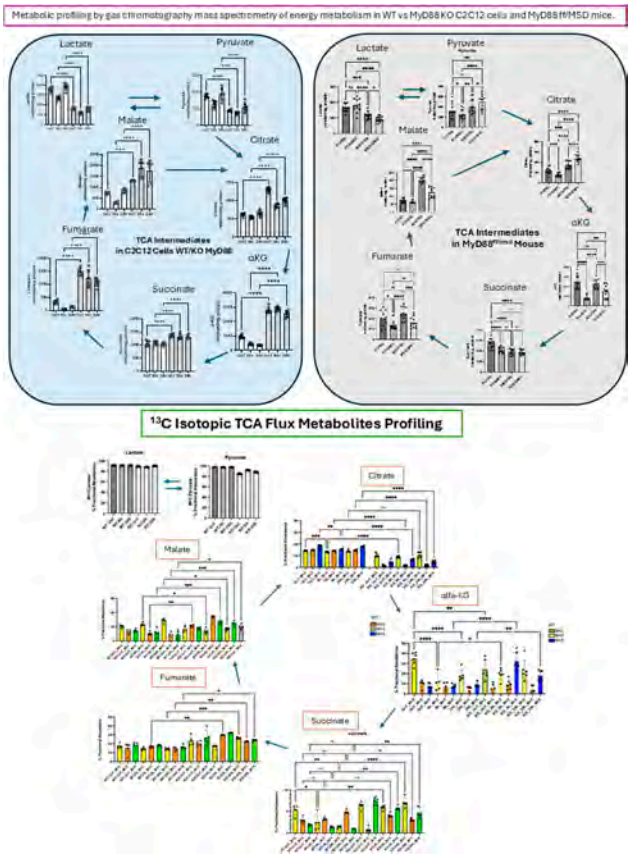
Seshu Vardhan Pothabathula[1] Saurabh Mishra[1] Annette Bellar[1] Pugazhendhi Kannan[1] Yana Sandlers[2] Takhar Kusumov[3] Nicole Welch[4] Srinivasan Dasarathy[4], [1]Lerner Research Institute, Cleveland Clinic, Cleveland, OH, [2]Department of Chemistry, Cleveland State University, OH., [3]Pharmaceutical Sciences, Northeast Ohio Medical University, OH, [4]Cleveland Clinic

Background: Myeloid differentiation primary response 88 (MyD88) is a canonical adaptor protein that mediates Toll-like receptor and interleukin-1 receptor signaling through NF-κB activation. During hyperammonemic stress response (HASR), MyD88 interacts with the ammonia transceptor RhBG with TLR-independent inflammatory signaling in skeletal muscle with consequent sarcopenia. We have identified decreased cellular ATP content due to mitochondrial oxidative dysfunction by metabolic perturbations, including cataplerosis of aKG during HASR. We hypothesized reversal of mitochondrial oxidative dysfunction, dysregulated protein homeostasis, and sarcopenia via non-canonical activation of MyD88. **Methods:** Studies were performed in differentiated murine C2C12 myotubes with wild-type or MyD88-knockout backgrounds and in C57BL/6 mice with muscle-specific MyD88 deletion ($MyD88^{msd}$) or floxed controls ($MyD88^{fl/fl}$) exposed to HAS. MyD88-interacting proteins were identified by LC/MS untargeted proteomics. Tricarboxylic acid (TCA) cycle metabolic perturbations were assessed using targeted GC-MS profiling and ^{13} C-isotope tracing to quantify isotopomer enrichment pool sizes of TCA-cycle intermediates over 6- and 24-hour intervals in $13C_6$ glucose enrichment for differentiated C2C12 cells. **Results:** MYD88-dependent mitochondrial oxidative dysfunction and adaptive metabolic responses were observed by proteomics and metabolomics profiling. LC/MS data showed MyD88 interacting with mitochondrial import proteins (TOM/SAM) and matrix-associated ATP synthase subunit ATP5PD. Total concentrations of TCA cycle intermediates in HAS-exposed mice (N = 12) revealed a highly significant increase in pyruvate, citrate, and α-ketoglutarate, within the $MyD88^{msd}$ group compared to $MyD88^{fl/fl}$ controls ($p < 0.0001$). In vitro differentiated C2C12 MyD88 KO showed there is a decrease in lactate and pyruvate concentrations in both untreated and AmAc-treated wild-type cells, whereas citrate and α-ketoglutarate showed a significant increase, recapitulating in vivo data. In vitro 13C6 glucose enrichment in WT/MyD88 KO groups showed equal fractional abundance of M+3 lactate and pyruvate in AmAc-treated cells. In MyD88 KO, the isotopologue distribution of α-ketoglutarate (M +2 and M+5) flux increased compared to WT untreated and AmAc treated cells ($p < 0.0001$). **Conclusion:** MyD88 functions as a non-canonical regulator of mitochondrial bioenergetics during hyperammonemic stress. Beyond its inflammatory adaptor role, MyD88 associates with mitochondrial protein-import machinery and contributes to impaired oxidative metabolism, disrupted TCA-cycle flux, and depletion of intermediary metabolites linked to sarcopenia. Targeting the MyD88-TOM complex interaction axis may represent a novel

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therapeutic strategy to preserve mitochondrial function and skeletal muscle.



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2284 | RIPK1 INHIBITION ATTENUATES NET RELEASE AND HAEMORRHAGIC LIVER INJURY IN D-GALACTOSAMINE/LPS MICE

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Background: Acute liver failure (ALF) is exhibiting severe immune dysregulation, and growing evidence implicating neutrophils and neutrophil extracellular traps (NETs) in liver injury. However, the upstream regulated cell-death pathways contributing to NET formation in liver failure remain incompletely defined. Because RIPK1 is a key regulator of immunogenic cell death in LPS-driven liver injury, making it a plausible candidate for linking inflammatory stress to NETosis. We investigated whether RIPK1 activity functionally contributes to NET release and liver pathology in the D-galactosamine/lipopolysaccharide (D-GalN/LPS) mouse model. **Methods:** ALF was induced in mice by D-GalN/LPS administration. RIPK1 was inhibited using Necrostatin-1S (Nec1S; 1-20 mg/kg). Neutrophil subsets distribution was analyzed by flow cytometry in liver, bone marrow, and spleen. Circulating markers of NET were assessed using immunoassays for extracellular histone H3.1 and citrullinated histone H3 (H3R8cit) (control n = 3; D-GalN/LPS n = 6). Liver injury biomarkers, histopathological features, systemic cytokines, and survival were evaluated. **Results:** D-GalN/LPS challenge induced marked neutrophil dysregulation and a robust (~5–10-fold) increase in circulating NET markers compared to controls. Nec1S administration did not significantly alter neutrophil subset distribution across examined tissues. In contrast, Nec1S treatment at 10 and 20 mg/kg led to an almost complete (>90%) suppression of circulating extracellular histone H3.1 and citrullinated histone H3 (H3R8cit). These findings support a functional link between RIPK1 activity and NET release in this model. NET marker suppression was associated with a dose-dependent reduction in liver injury biomarkers (ASAT, ALAT, TBA, TBIL) and marked attenuation of intrahepatic bleeding. Nec1S treatment was associated with a partial (~50%) survival benefit, with low effects on systemic cytokine release (IL-6, IL-1β, MCP-1). Despite effective NET release inhibition, liver injury and mortality were not fully prevented. **Conclusion:** RIPK1 inhibition with Nec-1S abrogates circulating NET-associated markers and attenuates haemorrhagic liver injury in the D-GalN/LPS model of ALF, resulting in improved liver function parameters and partial survival benefit. The incomplete survival rescue despite efficient suppression of NET-associated markers indicates the contribution of additional NET-independent pathogenic mechanisms. These results identify necroptosis and NETosis as a functionally relevant component of liver injury in acute liver Failure conditions settings and support further investigation of complementary injury pathways.

Disclosures: Jessica Dieudonne: Genfit: Employee, Alexandra Caron: Nothing to Disclose, Audrey Levy: Nothing to Disclose, Maryse Malysiak: Nothing to Disclose, Stephanie Ferreira: GENFIT: Employee, Jean-Marie Brusq: Nothing to Disclose, Zouher MAJD: Nothing to Disclose, Bart Staels: Genfit SA: Consultant, Sakina Sayah Jeanne: Nothing to Disclose, Valerie Daix: Nothing to Disclose, Alessia Galgano: Nothing to Disclose.

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2285 | HYPERAMMONEMIA IMPAIRS MITOCHONDRIAL QUALITY CONTROL THROUGH MYD88-DEPENDENT MECHANISMS IN SKELETAL MUSCLE

Saurabh Mishra[1] Seshu Pothabathula[1] Pugazhendhi Kannan[1] Vandana Agrawal[1] jamsine Cunnighan[1] Annette Bellar[1] Nicole Welch[1] Srinivasan Dasarathy[1], [1]Cleveland Clinic

Background: Hyperammonemia is a consistent abnormality in cirrhosis and contributes to sarcopenia and contractile dysfunction in chronic liver disease. Skeletal muscle mitochondrial oxidative dysfunction with cataplerosis of tricarboxylic acid cycle intermediates are recognized consequences of hyperammonemia and contribute to fatigue, decreased aerobic fitness, and dysregulated protein homeostasis. Whether impaired mitochondrial quality control (mitochondrial dynamics, biogenesis, and mitophagy) contributes to oxidative dysfunction during hyperammonemia is not known. We recently identified that myeloid differentiation primary response protein 88 (MyD88), a key adaptor of innate immune signaling, inhibits mitochondrial oxidative function in skeletal muscle. **Methods:** Studies were done in differentiated murine C2C12 wild type and CRISPR/Cas9-mediated knockout (KO) of MYD88 myotubes either untreated (unt) or treated with 10 mM ammonium acetate (AmAc) for 24h . Male and female C57/Bl6J hyperammonemic and control mice without/with muscle-specific deletion of MyD88 (MYD88msd) were infused with 2.5 mmol/kg/d of AmAc or vehicle (phosphate buffered saline-PBS) for 4 weeks . Mitochondrial quality control measures included biogenesis, dynamics, and mitophagy were studied by expression of proteins associated with mitochondrial biogenesis and dynamics, and mitophagy analyzed by immunoblotting of PINK1 with proteinase K protection assay. **Results:** Hyperammonemia significantly impaired mitochondrial biogenesis, as reduced expression of nuclear respiratory factor-1 (NRF-1), NRF-2, and mitochondrial transcription factor A (TFAM) in skeletal muscle and differentiated myotubes. These effects were reversed with MyD88 deletion in myotubes and skeletal muscle from Myd88msd mice during HAS, indicating a critical role for MyD88 in altering mitochondrial homeostasis. HAS affects the mitochondrial dynamics as mitochondrial fusion markers mitofusin1,2, OPA-1 were inhibited during HAS, while mitochondrial fission proteins Fis1, Mitochondrial fission factor (MFF) were increased in skeletal muscle tissue and myotubes, supporting alteration of mitochondrial dynamics during hyperammonemia while MyD88 deletion reversed the effect of HAS in in vitro with $Myd88^{KO}$ in $Myd88^{msd}$ mice against HAS. Proteinase K protection assay confirmed the accumulation of PINK-1 on the outer membrane as the PINK-1 was digested in the mitochondrial fraction with ammonia. compared to untreated mitochondria where PINK1 internalizes to inner membrane. **Conclusion:** Defects in mitochondrial quality control mechanisms during hyperammonemia are mediated via activation of Myd88. Use of muscle targeted MYD88 is a novel therapeutic approach to sarcopenia of cirrhosis.



Disclosures: Saurabh Mishra: Nothing to Disclose, Seshu Pothabathula: Nothing to Disclose, Pugazhendhi Kannan: Nothing to Disclose, Vandana Agrawal: Nothing to Disclose, jamsine Cunnighan: Nothing to Disclose, Annette Bellar: Nothing to Disclose, Nicole Welch: Nothing to Disclose, Srinivasan Dasarathy: Nothing to Disclose.

2286 | COVID-19 AS A NATURAL EXPERIMENT: IMMUNOSUPPRESSION PRESERVES LIVER FUNCTION WITHOUT INCREASING SYSTEMIC RISK IN AUTOIMMUNE HEPATITIS

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Background: The emergence of novel viruses, such as SARS-CoV-2, poses a challenge for patients with chronic autoimmune diseases who depend on lifelong immunosuppression (IS). For people with autoimmune hepatitis (AIH), the dilemma was whether to discontinue IS to reduce the risk of severe infection or continue it to avoid a potentially life-threatening flare or liver decompensation. To clarify this issue, we analyzed the largest population-based AIH cohort to understand how COVID-19 affected this immunosuppressed population and to guide the management of similar situations during future viral outbreaks. **Methods:** We analyzed 63,644 hospitalizations of patients with AIH, including 3,685 with COVID-19. Outcomes of interest included mortality, organ failure, respiratory compromise, thrombotic events, and liver-related

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complications. Although individuals with immunosuppressive medications were not captured, AIH patients are typically maintained on chronic steroid or antimetabolite therapy. As a result, this cohort provides a practical way to examine COVID-19 outcomes in a population that is characteristically immunosuppressed at baseline. **Results:** COVID-19 caused substantial systemic injury in patients with AIH, but it did not worsen liver-related complications. COVID-positive AIH patients had much higher mortality (12.7% vs. 4.2%; aOR 3.84, $p < 0.001$) and were far more likely to develop serious systemic problems, including shock (aOR 1.65), sepsis (aOR 1.73), mechanical ventilation (aOR 3.30), noninvasive ventilation (aOR 3.46), pulmonary embolism (aOR 2.28), and acute kidney injury (aOR 1.20). In contrast, liver-specific complications such as acute liver failure (aOR 0.76, $p = 0.003$) and ascites (aOR 0.63, $p = 0.001$) were actually less common in COVID-positive patients. These findings suggest that ongoing IS did not trigger hepatic deterioration during infection, and that the severe outcomes seen in this group were more likely driven by the systemic effects of COVID-19 rather than by their immunosuppressive therapy. **Conclusion:** The AIH–COVID-19 experience offers important lessons for managing chronic autoimmune diseases during future viral outbreaks. In our cohort, patients with AIH did not experience higher rates of liver-specific complications during infection, suggesting that maintaining IS may help protect against organ-specific failure, such as AIH flare or acute liver injury. These findings support a practical approach in which clinicians continue baseline IS to preserve autoimmune organ function while focusing preventive and therapeutic efforts on managing the systemic effects of viral illness. This perspective may help guide future care strategies for immunosuppressed autoimmune populations during emerging viral threats.

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2287 | BILIRUBIN TARGETS KEAP1 CYS513 TO DISSOCIATE KEAP1-IKKβ COMPLEX AND DRIVE HEPATIC INFLAMMATION VIA THE NF-κB PATHWAY

Yuping Yang[1] Caiyan Wang[1], [1]Guangzhou University of Chinese Medicine

Background: Aberrant accumulation of bilirubin is a critical pathological feature in liver diseases and is closely associated with hepatic inflammation and apoptosis. However, the molecular mechanisms by which bilirubin initiates inflammatory signaling remain poorly defined. This study aimed to elucidate the molecular mechanism linking bilirubin to inflammatory signaling. **Methods:** Mouse liver ductal organoids were used as the primary model to recapitulate hyperbilirubinemia-induced liver injury, complemented *in vivo* and *in vitro* systems (hyperbilirubinemia mouse models, primary hepatocytes, and human normal liver cells). Proximity labeling, NanoBiT, and Surface Plasmon Resonance analyses were performed to characterize the Keap1-IKKβ interaction. Structural biology, molecular dynamics simulations, and site-directed mutagenesis were applied to elucidate the underlying mechanism, followed by structure-based virtual screening targeting Keap1 Cys513 to identify potential modulators. **Results:** We demonstrate that bilirubin covalently modifies Kelch-like ECH-associated protein 1 (Keap1) at cysteine 513 (Cys513), disrupting the Keap1-IKKβ complex. This dissociation promotes IKKβ phosphorylation, induces nuclear translocation of p50/p65, and activates NF-κB-dependent inflammatory gene expression. Mechanistically, Cys513 modification induces conformational changes in Keap1, expands its binding pocket, and facilitates IKKβ release. Mutagenesis and structural analyses further confirm that Cys513 is a key regulatory node governing IKKβ activation and NF-κB signaling. Importantly, virtual screening identifies curcumin as a potent Cys513-targeting small molecule that restores the Keap1-IKKβ interaction, reverses bilirubin-induced conformational disruption, and significantly attenuates hyperbilirubinemia-induced liver injury. **Conclusion:** We identify a previously unrecognized bilirubin-Keap1 Cys513 axis that links hyperbilirubinemia to NF-κB-driven inflammation. Targeting Keap1 Cys513 represents a promising therapeutic strategy, and curcumin emerges as a potential lead compound. These findings establish Keap1 Cys513 as a druggable molecular switch with both mechanistic and translational significance in hyperbilirubinemia-associated liver diseases.

Disclosures: Yuping Yang: Nothing to Disclose, Caiyan Wang: Nothing to Disclose.

2288 | HISTOLOGIC PATTERNS AND OUTCOMES IN HEPATIC LARGE GRANULAR LYMPHOCYTE LEUKEMIA

Rachel Cruz Nieves[1] Madison Turner[1] Felicia Allard[1] Thomas Loughran[1] David Feith[1] Nicolas Intagliata[1] Jeffery Craig[1], [1]University of Virginia

Background: Large granular lymphocyte leukemia (LGLL) is a rare lymphoproliferative disorder of cytotoxic T cells or NK cells. Hepatic involvement is poorly characterized and may present as unexplained liver enzyme abnormalities in medically

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complex patients, posing a challenge for hepatologists. Potential associations between the extent and patterns of hepatic LGLL infiltration with liver function and clinical outcomes remain unknown. We aimed to characterize the clinicopathologic features and histologic patterns of hepatic LGLL infiltration. **Methods:** Retrospective cohort study of patients in the LGL Leukemia Registry at the University of Virginia. A total of 16 patients with biopsy-proven hepatic LGLL infiltration were included. Clinical, laboratory, imaging, histologic features, treatments, and outcomes were collected and analyzed. **Results:** The degree of LGLL infiltration in each liver biopsy (total n = 25) from 11 T-LGLL and 5 NK-LGLL patients was quantified as the average number of LGLL cells across three high-power fields and designated as either minimal (< 50/HPF, n = 6), moderate (50-100/HPF, n = 6) or extensive (> 100/HPF, n = 13). For each biopsy, the pattern(s) of inflammation (lobular, n = 23; portal, n = 17; both, n = 16) and other pathological changes (e.g., fibrosis, necrosis, etc.) were documented (Figure 1). Clinically, the most common indication for liver biopsy was elevated liver enzymes (LFTs) (13/16). Hepatology was involved in the care of 11/16 total patients. Median age at first biopsy was 54 years. Associated underlying diagnoses commonly associated with LGLL included immunodeficiency (25%), autoimmune diseases (56%), solid organ transplants (18%), and malignancy (3%). Laboratory evaluation demonstrated a predominantly mild mixed hepatocellular–cholestatic pattern, with median AST 65.6 U/L, ALT 58.5 U/L, total bilirubin 0.8 mg/dL and alkaline phosphatase 209 U/L. Treatment strategies varied and included methotrexate (7/16), prednisone (6/16), cyclophosphamide (4/16), and rituximab (1/16). Overall, 7 deaths occurred out of the total 16 patients. **Conclusion:** This study represents the first and largest description of liver pathology in patients with LGLL. In our cohort, patients frequently had coexisting autoimmune disease and immunodeficiency and commonly presented with elevated liver enzymes prompting hepatology evaluation and liver biopsy. Histopathology most often demonstrated lobular intrasinusoidal infiltration regardless of biologic subtype, although portal-based inflammation was observed in a subset of cases. Despite LGLL generally being considered an indolent disorder, mortality in this cohort was unexpectedly high, suggesting that hepatic involvement may identify a higher-risk population. Recognition of characteristic histologic patterns may improve the diagnostic evaluation and multidisciplinary management of patients with suspected hepatic LGLL.

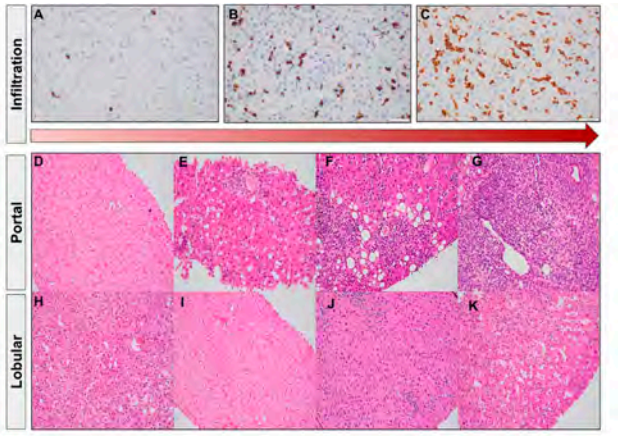


Figure 1: The degree of LGLL infiltration in each liver biopsy categorized as either minimal (A), moderate (B) or extensive (C) with the use of CD8 stains at 400X total magnification. Histologic sections of liver biopsies, assessed for both portal and lobular inflammation on a semiquantitative scale and categorized as no significant portal inflammation (D), mild portal inflammation (E), moderate portal inflammation (F) or severe portal inflammation (G). Similarly, lobular inflammation was categorized as no significant lobular inflammation (H), mild lobular inflammation (I), moderate lobular inflammation (J) or severe lobular inflammation (K). Photomicrographs D-K were taken of H&E slides at 200X.

Disclosures: Rachel Cruz Nieves: Nothing to Disclose, Madison Turner: Nothing to Disclose, Felicia Allard: Nothing to Disclose, Thomas Loughran: Nothing to Disclose, David Feith: Nothing to Disclose, Nicolas Intagliata: Nothing to Disclose, Jeffery Craig: Bayer: Expert Testimony, AstraZeneca: Advisor, Advanced Cell Diagnostics: Speaking and Teaching.

2289 | MYD88 IMPAIRS MITOCHONDRIAL TRANSLOCASE PROTEINS IN SKELETAL MUSCLE DURING HYPERAMMONEMIA

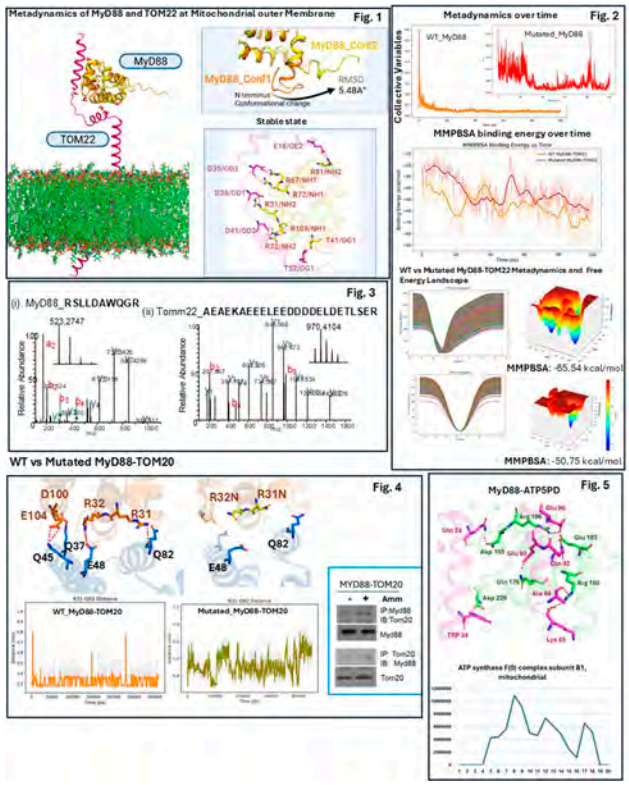
Srinivasan Dasarathy[1] Seshu Vardhan Pothabathula[2] Saurabh Mishra[2] Dhanachandra Khuraijam[3] Pugazhendhi Kannan[3] Annette Bellar[2] Nicole Welch[1] Jason A Mears[4] Sadashiva Karnik[2], [1]Cleveland Clinic, [2]Lerner Research Institute, Cleveland Clinic, Cleveland, OH, [3], Lerner Research Institute, Cleveland Clinic, Cleveland, OH, [4]School of Medicine, Case Western Reserve University, OH

Background: Myeloid differentiation primary response 88 (MyD88) is a canonical adaptor protein that mediates Toll-like receptor and interleukin-1 receptor signaling through NF-κB activation. During hyperammonemic stress (HAS), MyD88 interacts with the ammonia transceptor RhBG with TLR-independent

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inflammatory signaling in skeletal muscle with consequent sarcopenia (loss of muscle mass). We identified an unexpected role for MyD88 in mitochondrial oxidative dysfunction during HAS and sought to define the structural and metabolic basis of this effect. We hypothesized that hyperammonemia promotes MyD88 association with mitochondrial protein import and bioenergetic machinery, including TOM20, TOM22, and ATP5PD, thereby disrupting mitochondrial protein import functions. **Methods:** MyD88 interactions with mitochondrial membrane proteins were evaluated using AlphaFold3 modeling, HADDOCK molecular docking, Gromacs molecular dynamics, Molecular Mechanics Poisson-Boltzmann Surface Area (MMPBSA), and Free energy landscape. OpenMM-PLUMED meta-dynamics simulations were used for the MyD88 complex with TOM20, TOM22, and ATP5PD. During hyperammonemia, physical binding partners were evaluated by LC/MS proteomics and immunoprecipitation (IP) analysis. **Results:** Proteomics and targeted co-immunoprecipitation identified stress-induced MyD88 association with mitochondrial import proteins, including TOM20, TOM22, SAM50, TIM50, and the matrix-associated ATP synthase subunit ATP5PD. Metadynamics simulations reveal a significant conformational rearrangement of the MyD88 N-terminus when interacting with TOM22 by root mean square deviations (RMSD) of 5.48 Å for 200 ns. The interaction sites were TOM22 (D35, D38, D41, E18, T41, T52) and MyD88 (R31, R32, R67, R72, R81, R108). The Collective Variables (CV) were plotted for a 100 ns trajectory, which showed rapid initial convergence within the first 10–20 ns in WT/mutated proteins. The MMPBSA binding energy for WT is -65.54 kcal/mol, and for the mutated (-50.75 kcal/mol) complexes. MyD88 Fragment (RSLLDAWQGR) exhibited prominent sequence ions with a precursor mass-to-charge ratio m/z peak highlighted at 523.27. MyD88 R31 and R32 interact with D100, E104, Q37, E48, and Q82 on TOM20. IP anti-MyD88 reveals a significant increase in co-precipitated Tom20, ATP5PD, and proposed physical interaction with MyD88. MyD88-ATP5PD, followed by K85-R180, Q92-E183, E96-R196, Q24-D195, and A88-Q176 residues, were observed by molecular modelling and LC/MS. **Conclusion:** These findings identify MyD88 as a potential non-canonical regulator of mitochondrial function during (HASR). MyD88 interaction with TOM20, TOM22, and ATP5PD may cause mitochondrial oxidative stress and impair bioenergetics. Targeting this mitochondrial MyD88 interaction network may represent a novel strategy to preserve mitochondrial integrity under hyperammonemia conditions.



Disclosures: Srinivasan Dasarathy: Nothing to Disclose, Seshu Vardhan Pothabathula: Nothing to Disclose, Saurabh Mishra: Nothing to Disclose, Dhanachandra Khuraijam: Nothing to Disclose, Pugazhendhi Kannan: Nothing to Disclose, Annette Bellar: Nothing to Disclose, Nicole Welch: Nothing to Disclose, Jason A Mears: Nothing to Disclose, Sadashiva Karnik: Nothing to Disclose.

2290 | PAN-AUTOIMMUNE DISEASE SINGLE-CELL ANALYSIS IDENTIFIES MAIT CELLS MIGHT PLAY A ROLE IN INFLAMMATION-RELATED METABOLIC REGULATION

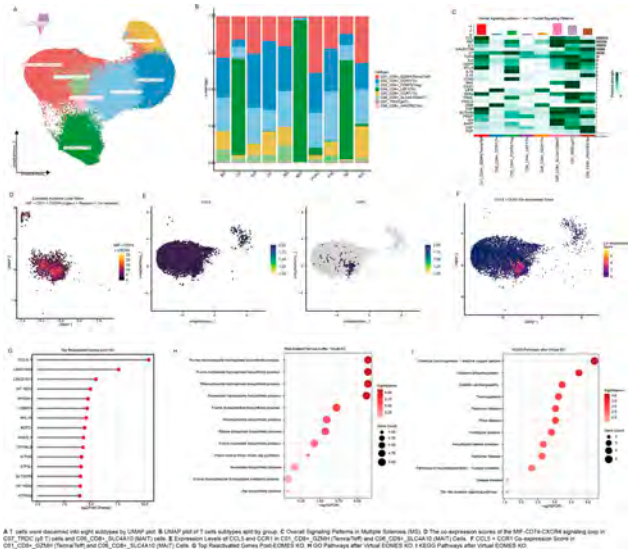
Jia-Wen Chen[1] Chao Cai[2] Mingqin Lu[2], [1]he First Affiliated Hospital of Wenzhou Medical University, [2]The First Affiliated Hospital of Wenzhou Medical University

Background: Autoimmune diseases (AID) exhibit diverse clinical phenotypes, yet the cellular communication logic and disease-specific regulatory mechanisms within their peripheral immune

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microenvironments lack systematic cross-disease understanding. By integrating large-scale, pan-immunity single-cell data (>600,000 cells), we systematically characterize disease-specific cell subpopulations and intercellular interactions to elucidate the key immune drivers of pathological inflammation. **Methods:** This study integrated single-cell transcriptome (scRNA-seq) data from 67 peripheral blood mononuclear cell (PBMC) samples across nine autoimmune diseases obtained from the GEO database, encompassing over 600,000 cells. Through systematic comparative analysis of transcriptomic features across diseases, we observed a unique expansion of MAIT cells within the immune microenvironment of multiple sclerosis (MS). Consequently, this study focused on MAIT cells within the MS cohort, employing CellChat for cellular communication analysis, SCENIC for the construction of regulatory networks to identify key transcription factors, and scTenifoldKnk for virtual knockout experiments to deeply investigate their pathological regulatory mechanisms. **Results:** CellChat analysis revealed that MAIT cells exhibit the most pronounced signaling intensity within the MS immune microenvironment, particularly involving the MIF and CCL pathways. Co-expression patterns suggest these cells form an autocrine MIF-CD74/CXCR4 loop, which may support their survival and sustained activation. Furthermore, high CCL5 and low CCR1 expression in MAIT cells points toward a paracrine function. Supported by pathway enrichment, we hypothesize that MAIT cells likely utilize CCL5 to recruit CCR1+ peripheral myeloid cells, potentially initiating T cell-myeloid crosstalk via downstream TNF signaling and driving inflammatory cascade amplification. Additionally, pySCENIC identified EOMES as a core transcription factor. scTenifoldKnk virtual knockout simulations indicate that EOMES ablation may induce metabolic reprogramming—shifting toward active purine synthesis and oxidative phosphorylation (OXPHOS)—alongside reactive oxygen species (ROS) accumulation. Consequently, EOMES appears critical for maintaining MAIT cell homeostasis, potentially limiting their neurotoxic pathogenic risk in MS. **Conclusion:** This study elucidates a dual pathogenic network orchestrated by MAIT cells in autoimmune disease, exemplified in multiple sclerosis, characterized by a MIF-mediated autocrine survival loop and a CCL5-mediated paracrine myeloid recruitment axis. Furthermore, we identified EOMES as a crucial "metabolic and inflammatory brake" that prevents MAIT cells from acquiring a pathogenic effector phenotype. Targeting the EOMES regulatory axis represents a promising novel therapeutic strategy for autoimmune diseases.



Disclosures: Jia-Wen Chen: Nothing to Disclose, Chao Cai: Nothing to Disclose, Mingqin Lu: Nothing to Disclose.

2291 | RHTPO PROTECTS LIVER CELL FUNCTION IN SEPSIS-INDUCED LIVER ORGANOIDS THROUGH BOTH DIRECT AND INDIRECT MECHANISMS

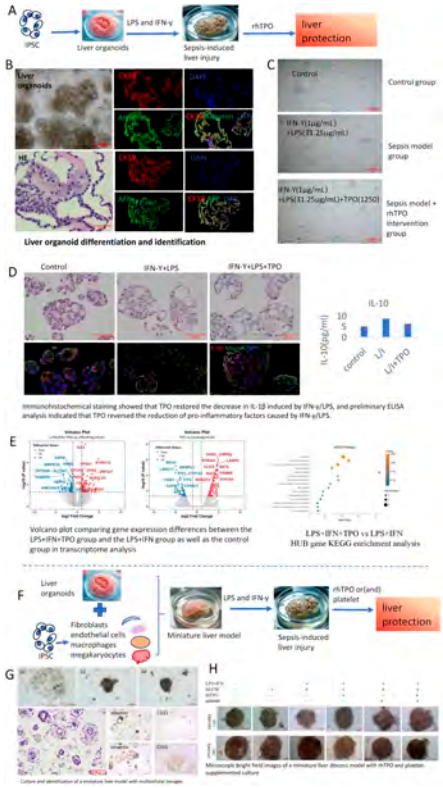
Lihua Shao[1] Minghao Fang[2], [1]HUST (Huazhong University of Science and Technology), [2]Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology

Background: Sepsis frequently induces acute liver dysfunction, exacerbating systemic inflammation and mortality. Existing models often fail to recapitulate sepsis pathology within the human liver microenvironment. Hepatic organoids reconstitute native hepatic composition, offering a humanized platform to study septic injury. Recombinant human thrombopoietin (rhTPO) exhibits tissue-protective properties, yet its role in septic liver injury remains undefined. We utilized induced pluripotent stem cell(iPSC)-derived hepatocyte-only and multicellular micro-hepatic organoids to investigate the hepatoprotective mechanisms of rhTPO. **Methods:** iPSCs were differentiated into hepatocyte-only organoids (Figure A) and validated via hematoxylin and eosin staining(HE staining)and immunohistochemistry (Figure B). A sepsis model was induced using LPS/IFN-γ, followed by rhTPO treatment and subsequent viability/liver function assays. Molecular mechanisms were identified through transcriptome sequencing, KEGG enrichment, and PPI analyses. Furthermore, a multicellular micro-liver model, co-cultured with fibroblasts, endothelial cells, macrophages, and megakaryocytes (Figure F), was validated using flow cytometry

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and functional assays (Figure G). In this model, the therapeutic effects of rhTPO and platelets were evaluated via TEM, cytokine profiling, single-cell sequencing, and viability assays . **Results:** rhTPO did not affect normal hepatocyte viability but significantly reversed LPS/IFN-γ-induced viability loss in organoids (Figures C and D). Transcriptomic analysis revealed that rhTPO significantly upregulated *IGF2*, with hub genes enriched in the p53 signaling pathway (Figure E). In the multicellular micro-liver model (Figure F), both rhTPO and platelet monotherapies mitigated septic injury (Figure H). Notably, combined treatment with rhTPO and platelets synergistically enhanced cell viability compared to either agent alone. Cell Counting Kit-8(CCK-8)assays confirmed this synergistic rescue, suggesting that rhTPO indirectly exerts hepatoprotection via platelet-mediated mechanisms. **Conclusion:** This study successfully established a humanized liver organoid and a multicellular micro-liver model to simulate sepsis-induced liver injury. We demonstrated that rhTPO effectively reverses LPS/IFN-γ-induced liver injury. Transcriptomic analysis indicates that this protective effect is associated with the upregulation of IGF2 and the p53 signaling pathway. Furthermore, the combination of rhTPO and platelets synergistically improves hepatocyte viability in the micro-liver model. These findings provide novel in vitro experimental evidence for the mechanistic investigation of sepsis-induced liver injury, suggesting that targeting the IGF2/p53 axis or leveraging platelet-based therapeutic strategies may represent promising interventions for clinical management.



Disclosures: Lihua Shao: Nothing to Disclose, Minghao Fang: Nothing to Disclose.

2292 | HEPATOBILIARY SAFETY OF TNF-ALPHA INHIBITOR THERAPY IN PRIMARY SCLEROSING CHOLANGITIS WITH INFLAMMATORY BOWEL DISEASE: A PROPENSITY-MATCHED COHORT STUDY USING THE TRINETX RESEARCH NETWORK

Osamah Salim[1] Mazen Elsheikh[2] Karim Adhem[2] Hamza Salim[3] Mohammad Mahdi[1] Sherry Fares[2] Youseph Karouni[2] Prasun Jalal[2], [1]Sam Houston State University College of Osteopathic Medicine, [2]Baylor College of Medicine, [3]University of Texas Medical Branch

Background: Primary sclerosing cholangitis (PSC) co-occurs with inflammatory bowel disease (IBD) in most western patients and carries substantial risk of biliary complications, liver failure, and cholangiocarcinoma. Tumor Necrosis Factor (TNF)-alpha inhibitors are widely used for IBD control in this population. A prior single-center study that explored the risks of TNF-alpha inhibitor therapy in patients with PSC (Kulkarni et al., 2021; n = 148) reported a 7-fold increase in acute cholangitis odds with TNF-alpha inhibitor therapy. To address this potential safety concern, we aimed to rigorously evaluate whether TNF-alpha inhibitor therapy is independently associated with acute cholangitis, ERCP utilization, or liver decompensation in a large, propensity-matched real-world cohort. **Methods:** We performed a retrospective propensity-matched cohort study using the TriNetX Research Network (112 U.S. healthcare organizations, data accessed April 27, 2026). Adults with PSC (ICD-10: K83.01) and IBD (K50/K51) were stratified into a TNF-alpha inhibitor cohort (infliximab, adalimumab, certolizumab pegol, or golimumab; n = 423 pre-match) and a control cohort (no TNF-alpha inhibitor exposure; n = 7,308 pre-match). After 1: 1 nearest-neighbor propensity score matching on age, sex, race, cirrhosis, portal hypertension, fatty liver disease, and chronic hepatitis, 420 matched pairs were retained (n = 840). Propensity score matching yielded robust baseline balance across the cohort covariates, with standardized mean differences tightly controlled post-match. **Results:** Rates of acute cholangitis were comparable with or without biologic exposure (20.8% vs. 20.5%; RR 1.02, 95% CI: 0.76–1.36; p = 0.921), and risk profiles remained similarly comparable regarding liver decompensation (HR 1.048, 95% CI: 0.702–1.564; p = 0.298). Notably, TNF-alpha

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inhibitor patients had a significantly lower mean number of ERCP instances (0.19 vs. 0.45; p = 0.006), with a trend toward reduced ERCP hazard (HR 0.668, 95% CI: 0.447–0.997; p = 0.060). **Conclusion:** In this propensity-matched real-world cohort of 840 PSC-IBD patients, TNF-alpha inhibitor therapy was not associated with increased hepatobiliary risk. A significant reduction in ERCP burden among TNF-alpha inhibitor-treated patients was observed, suggesting that effective IBD mucosal control may confer a protective effect by attenuating biliary bacterial seeding and reducing subsequent biliary interventions. These data do not support routine avoidance of TNF-alpha inhibitor agents on hepatobiliary safety grounds in PSC-IBD.

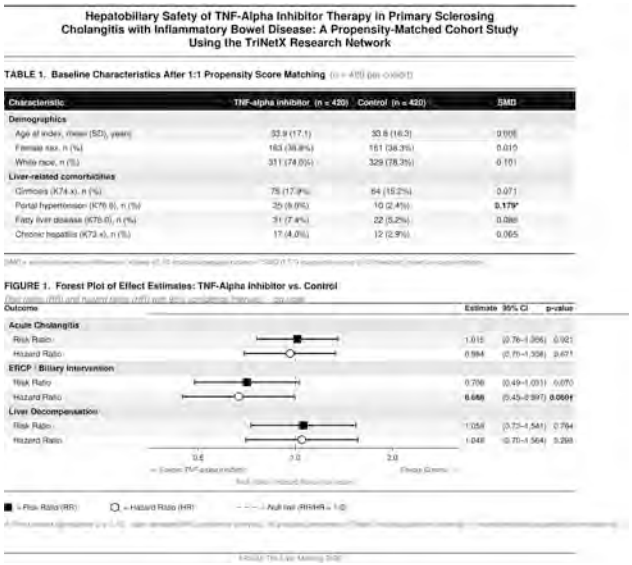

Hepatobiliary Safety of TNF-Alpha Inhibitor Therapy in Primary Sclerosing Cholangitis with Inflammatory Bowel Disease: A Propensity-Matched Cohort Study Using the TriNetX Research Network

TABLE 1. Baseline Characteristics After 1:1 Propensity Score Matching

Characteristic	TNF-alpha inhibitor (n = 420)	Control (n = 420)	SMD
Demographics			
Age at index, mean (SD), years	33.9 (17.1)	33.8 (16.3)	0.006
Female sex, n (%)	163 (38.8%)	161 (38.3%)	0.010
White race, n (%)	311 (74.0%)	329 (78.3%)	0.101
Liver-related comorbidities			
Cirrhosis (K74.x), n (%)	75 (17.9%)	64 (15.2%)	0.071
Portal hypertension (K76.6), n (%)	35 (8.0%)	10 (2.4%)	0.179*
Fatty liver disease (K76.0), n (%)	31 (7.4%)	22 (5.2%)	0.086
Chronic hepatitis (K73.x), n (%)	17 (4.0%)	12 (2.9%)	0.055

FIGURE 1. Forest Plot of Effect Estimates: TNF-Alpha Inhibitor vs. Control

Outcome	Estimate	95% CI	p-value
Acute Cholangitis			
Risk Ratio	1.015	(0.78–1.306)	0.921
Hazard Ratio	0.984	(0.70–1.358)	0.671
ERCP / Biliary Intervention			
Risk Ratio	0.706	(0.49–1.031)	0.070
Hazard Ratio	0.668	(0.45–0.997)	0.060†
Liver Decompensation			
Risk Ratio	1.054	(0.73–1.541)	0.784
Hazard Ratio	1.048	(0.70–1.564)	0.268

0.6 1.0 2.0

■ = Risk Ratio (RR) ◯ = Hazard Ratio (HR) – – – Null line (RR/HR = 1.0)

Disclosures: Osamah Salim: Nothing to Disclose, Mazen Elsheikh: Nothing to Disclose, Karim Adhem: Nothing to Disclose, Hamza Salim: Nothing to Disclose, Mohammad Mahdi: Nothing to Disclose, Sherry Fares: Nothing to Disclose, Youseph Karouni: Nothing to Disclose, Prasun Jalal: Madrigal, GSK, Mirum, Ipsen, Gilead, Genentech, Zydus: Grant/Research Support, Intercept, Genfit: Grant/Research Support.

2293 | WHEN AIH DOESN'T RESPOND AS EXPECTED: A CASE SERIES OF AIH–PBC AND AIH–PSC OVERLAP SYNDROMES

Clarimar Diaz Lopez[1] Rami Basmaci[2], [1]ECU Health Medical Center/Brody School of Medicine, [2]ECU Health Medical Center

Background: Autoimmune hepatitis (AIH) overlap syndromes with primary biliary cholangitis (PBC) or primary sclerosing cholangitis (PSC) are difficult to recognize early and often behave more aggressively than classic AIH. They may begin with routine elevations in liver enzymes but gradually evolve into cholestasis, bile duct injury, portal hypertension, or recurrent flares. Early identification is essential, as timely recognition can meaningfully change management and help prevent progression. **Methods:** Retrospective review of four patients (ages 21–57) evaluated at a tertiary academic center between 2023 and 2025 with serologic, radiologic, and histologic evidence of AIH–PBC or AIH–PSC overlap. Clinical presentation, autoimmune markers, MRCP findings, biopsy features, treatment course, and biochemical outcomes were analyzed. **Results:** Two female patients (57 and 41) demonstrated AIH–PBC overlap with AMA positivity, cholestatic enzyme elevation, and biopsies showing interface hepatitis with bile duct injury or duct loss. Both had persistent cholestasis despite prednisone and azathioprine; one improved partially with ursodiol, while the other developed refractory disease with azathioprine failure, 6-MP intolerance, and worsening cholestasis (ALP up to 900 U/L), requiring escalation to mycophenolate, seladelpar, and budesonide, with tacrolimus under consideration. Two male patients (21 and 23) demonstrated AIH–PSC overlap, each with recurrent hepatocellular flares and failure to achieve biochemical remission on corticosteroids and azathioprine. One developed intrahepatic ductal beading on MRCP, confirming PSC, and his biopsy (similar to the others) showed interface hepatitis with bile duct–centered injury, ductular reaction, and peri-ductal fibrosis; his course was complicated by thiopurine-induced pancreatitis. The other had biopsy-proven PSC overlap despite a normal MRCP, and cytopenias related to advanced liver disease prevented thiopurine use. Across all four cases, overlap syndromes showed aggressive behavior, often presenting with cirrhosis complications, esophageal varices, and steroid dependence. Delayed diagnosis was common due to early nonspecific or evolving biochemical features. **Conclusion:** Overlap syndromes can exhibit unpredictable and aggressive behavior. Autoimmune liver diseases are often nonspecific and easy to miss, mainly when abnormal liver enzymes are not thoroughly investigated. As a result, many patients are diagnosed only after features of end-stage liver disease are already present. Recognizing evolving cholestasis or a treatment response that does not follow the expected course should prompt earlier biopsy or MRCP to detect overlap disease. Achieving biochemical remission early is essential, as delayed remission has been clearly associated with increased mortality in AIH.

Disclosures: Clarimar Diaz Lopez: Nothing to Disclose, Rami Basmaci: Nothing to Disclose.

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2294 | ◆ BILE ACID UPTAKE ACTIVATES STAT SIGNALING AND IMPAIRS NATURAL KILLER CELLS IN METABOLIC DYSFUNCTION–ASSOCIATED STEATOHEPATITIS

Johnny Amer[1] Ahmad Salhab[2] Rifaat Safadi[1], [1]Hadassah Hebrew University Hospital, [2]Hadassah University

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) encompasses a spectrum of fatty liver diseases ranging from steatotic liver disease to metabolic dysfunction-associated steatohepatitis (MASH), and its prevalence is increasing worldwide due to the pandemic of obesity. Liver damage, such as cholestatic conditions in which bile secretion and flow are disturbed, is associated with impaired innate and adaptive immunity. NK cells play a crucial role in inhibiting liver fibrosis. However, how bile acids affect natural killer (NK) cells remains unknown. We aimed to assess the impact of bile acid concentration on NK cell functionality and identify the molecular and metabolic NK cell signaling pathways that influence liver fibrosis pathogenesis. To this end, we studied peripheral NK cells from patients with MASH, healthy donors, and a mouse model of MASH. **Methods: Results:** Sodium +/taurocholate cotransporting polypeptide (NTCP) expression was 2.5-fold higher in peripheral blood NK cells from MASH patients with advanced liver fibrosis than in those from early liver fibrosis patients and healthy donors. Greater taurocholic acid (TCA) uptake was observed in peripheral NK^{NTCP+} cells from the early and advanced liver fibrosis MASH patient groups than in NK^{NTCP-} cells from the same patients. It was associated with increased levels of exhaustion markers and decreased activity. Moreover, single-cell RNA sequencing and functional analyses demonstrated that $NTCP^{+}$ NK cells in advanced MASH adopt stress- and exhaustion-associated transcriptional programs with reduced translational activity, accompanied by increased STAT3 activation and diminished STAT1 signaling, highlighting their impaired cytotoxic function. Following STAT3 inhibition, $trNK^{NTCP+}$ cells presented significantly reduced NTCP expression, reduced NK cell exhaustion, and restored NK cell activity. In MASH mice, epigallocatechin gallate-mediated inhibition of NTCP expression reduced TCA uptake and attenuated liver fibrosis. Additionally, in immunodeficient liver fibrosis model mice, reconstitution with $trNK^{NTCP-}$ cells alleviated liver fibrosis, decreased proinflammatory and profibrotic cytokine levels, and ameliorated lipid homeostasis. **Conclusion:** Our findings suggest that enhancing immune responses by restoring NK cell activity through NTCP antagonism may offer a clinically beneficial strategy to prevent liver fibrosis in patients with metabolic disorders, autoimmune diseases, and chronic viral hepatitis.

Disclosures: Johnny Amer: Nothing to Disclose, Ahmad Salhab: Nothing to Disclose, Rifaat Safadi: Nothing to Disclose.

2295 | ◆ GENETIC POLYMORPHISMS ASSOCIATED WITH METABOLIC DYSFUNCTION–ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) AND ADVERSE CLINICAL OUTCOMES: A GLOBAL STUDY

Zobair Younossi[1] Leyla de Avila[1] Khalid AlNaamani[1] Cristiane Villela-Nogueira[1] Luca Valenti[2] Phunchai Charatcharoenwitthaya[1] Javier Crespo Garcia[1] Silvia Sookoian[3] Vincent Wong[4] Atsushi Nakajima[5] Yusuf Yilmaz[6] Claudia De Oliveira[1] Mario Pessoa[7] Anna Ludovica Fracanzani[8] Rosa Lombardi[9] Wah Kheong Chan[10] Adriaan Holleboom[1] Jian-Gao Fan[11] Andrea Siciliano[12] Giulia Periti[12] Francesco Malvestiti[12] Watcharin Wichapolchaiyakul[13] Paula Izrubieta[14] Carlos Pirola[15] Takashi Kobayashi[16] Shamsul Mohd Zain[17] Kirsi van Eekhout[18] James Estep[1] Brian Lam[1] Andrei Racila[19] Rui-Xu Yang[1] Ruinan Zhang[20] Saleh Alqahtani[21] Maria Stepanova[1], [1]The Global NASH/MASH Council, [2]Fondazione Ca' Granda OMP Milano, [3]CONICET, [4]The Chinese University of Hong Kong, [5]National Hospital Organization Yokohama Medical Center, [6]Recep Tayyip Erdoğan University, [7]University of São Paulo, [8]University of Milan, [9]University of the Study of Milan, [10]University of Malaya, [11]Xinhua Hospital Affiailted to Shanghai Jiaotong University School of Medicine, [12]Department of Pathophysiology and Transplantation, Università degli Studi di Milano, and Precisio, [13]Division of Gastroenterology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahid, [14]Gastroenterology and Hepatology Department, Marqués de Valdecilla University Hospital, Valdecilla, [15]CENITRES, UMAI-CONICET, [16]Department of Gastroenterology and Hepatology, Yokohama City University Graduate School of Medic, [17]The Pharmacogenomics Laboratory, Department of Pharmacology, Faculty of Medicine, Universiti Malaya, [18]Department of Vascular Medicine, Amsterdam University Medical Center, Amsterdam, Netherlands, [19]The Global NASH/MASH Council, [20]Department of Gastroenterology, Xinhua Hospital, Shanghai Jiao Tong University School of Medicine, [21]King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia

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Background: Genetic and environmental factors influence MASLD severity and progression. We evaluated associations between single nucleotide polymorphisms (SNPs) and advanced fibrosis and clinical outcomes in a multinational MASLD cohort. **Methods:** Adults with MASLD from 13 countries in the G-MASLD SNP subproject with genotyping data for four SNPs (rs738409 [*PNPLA3*], rs58542926 [*TM6SF2*], rs641738 [*MBOAT7*], rs62305723 [*HSD17B13*]) were included. Outcomes included presence of advanced fibrosis (F3–F4 or LSM $\geq$ 10 kPa) and time to clinical event (hepatic decompensation, HCC, transplantation, or death). **Results:** A total of 5,970 patients with MASLD were analyzed [mean ages 54 ± 13 years; 53% male; 67% obesity; 41% T2D; 63% hypertension; regions of enrollment - North America (30%), Europe (28%), Asia (26%), Latin America (11%), Middle East and North Africa (5%). The highest frequency of the minor allele (G) in rs738409 (*PNPLA3*) was observed in Latin America (72%), the lowest in North America (51%), while *MBOAT7* CC genotype predominated in Asia (49% vs. 30% in Europe and North America; pooled 35%). The *PNPLA3* C > G was independently associated with both histologic and LSM-defined advanced fibrosis. Advanced fibrosis prevalence increased with G allele dosage: histologic fibrosis 16% (CC), 24% (CG), 29% (GG); LSM-defined fibrosis 14%, 21%, 30%; respectively (all $p < 0.0001$). The *MBOAT7* C > T was associated with LSM-defined advanced fibrosis, with higher rates in TT versus CC/CT carriers (13% vs. 9%; $p = 0.0226$). TM6SF2 and HSD17B13 SNPs were not significantly associated with the outcomes ($p > 0.05$). In multivariate analysis adjusted for enrollment site, age, sex, obesity, and T2D status, *PNPLA3* variant independently predicted advanced histologic fibrosis (CG vs. CC: OR = 1.71, 95% CI: 1.35–2.18; GG vs. CC: OR = 2.61, 95% CI: 1.98–3.44; $p < 0.0001$). For LSM-defined advanced fibrosis, both *PNPLA3* GG (OR = 2.39, 95% CI: 1.58–3.62) and *MBOAT7* TT (OR = 1.91, 95% CI: 1.23–2.95) showed independent associations ($p < 0.01$). Regional subgroup analyses revealed that *PNPLA3* effects were consistent across regions. In contrast, the *MBOAT7* TT genotype association was present only in European patients (OR = 2.83; 95% CI: 1.41–5.70). In time-to-event analysis adjusted for region, age, sex, obesity, T2D, and hypertension, the *PNPLA3* GG genotype (vs. CC) was the only genetic modifier independently associated with increased risk of clinical event risk (adjusted HR = 2.46; 95% CI: 1.44–4.20, $p < 0.0001$). **Conclusion:** In this large, globally diverse MASLD cohort, *PNPLA3* rs738409 was consistently associated with advanced fibrosis and clinical events across regions, whereas the effect of *MBOAT7* rs641738 variant varied by geographic region.

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★ 2296 | ◆ ALDH2 DEFICIENCY BLUNTS SERUM ALT ELEVATION DESPITE ONGOING HEPATOCELLULAR INJURY BY ALCOHOL CONSUMPTION

Takuya Seike[1] Yi-Hsun Chen[2] I-Chen Wu[2] Taro Yamashita[1] Daria Mochly-Rosen[3], [1]Kanazawa University, [2]Kaohsiung Medical University Hospital, [3]Stanford University

Background: Serum alanine aminotransferase (ALT) is the most widely used biomarker of hepatocellular injury. However, whether genetic or metabolic factors alter the reliability of serum ALT as an indicator of liver injury remains unclear. Aldehyde dehydrogenase 2 (ALDH2) detoxifies acetaldehyde generated during ethanol metabolism, and the inactive ALDH2*2 variant (rs671), carried by approximately 560 million individuals worldwide, results in increased aldehyde stress after alcohol exposure. We investigated whether ALDH2 deficiency and alcohol consumption

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uncouple serum ALT levels from the hepatocellular injury. **Methods:** We analyzed biobank data from 91,743 participants to evaluate the interaction among ALDH2 genotype, alcohol consumption, and serum liver enzyme levels. Mechanistic studies were performed using ALDH2*2 knock-in mice acutely exposed to ethanol (1 g/kg) to determine whether ALDH2 deficiency alters hepatic injury responses and serum ALT dynamics. **Results:** After multivariable adjustment for age, body mass index (BMI), and γ-glutamyl transferase (GGT), alcohol consumption was associated with significantly lower serum ALT levels in both ALDH2*1/*1 carriers (normal enzymatic activity) and ALDH2*1/*2 carriers (reduced enzymatic activity), with decreases of 4.97 U/L and 7.56 U/L, respectively ($P < 0.001$). Stratified analyses according to BMI and GGT demonstrated that the reduction in ALT levels was most pronounced in individuals with BMI > 25 kg/m² and GGT > 50 U/L. Specifically, among non-drinkers, serum ALT levels were comparable regardless of ALDH2 genotype (48 U/L). In contrast, among drinkers, ALT levels were significantly lower in ALDH2*1/*1 carriers (37 U/L) and were further reduced in ALDH2*1/*2 carriers (29 U/L), whereas AST levels did not differ between groups.In ALDH2*1/*2 mice exposed to ethanol, accumulation of the lipid peroxidation product 4-hydroxynonenal was comparable to or greater than that observed in ethanol-treated wild-type mice. This was accompanied by enhanced MAPK activation, increased chemokine expression, and markedly aggravated histological necrosis. Despite evidence of liver injury, the elevation in serum ALT levels remained minimal in ALDH2*1/*2 mice. Furthermore, hepatic ALT mRNA and protein expression were both reduced in ethanol-treated ALDH2*1/*2 mice. **Conclusion:** ALDH2 deficiency suppresses hepatic ALT expression and blunts serum ALT elevation despite ongoing hepatocellular injury by alcohol consumption, thereby uncoupling serum ALT levels from the severity of alcohol-associated liver damage. These findings identify a genetically determined mechanism of biomarker underestimation and suggest that serum ALT levels may substantially underestimate liver injury in individuals carrying the ALDH2*2 variant.

Disclosures: Takuya Seike: Nothing to Disclose, Yi-Hsun Chen: Nothing to Disclose, I-Chen Wu: Nothing to Disclose, Taro Yamashita: Nothing to Disclose, Daria Mochly-Rosen: Nothing to Disclose.

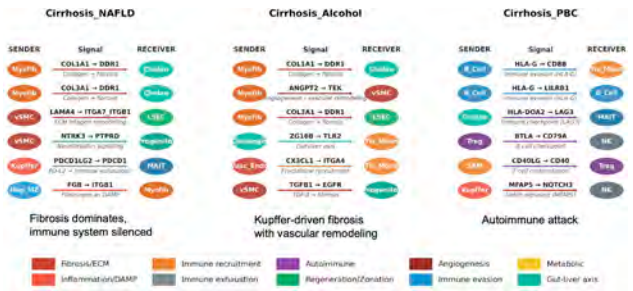
2297 | ◆ A MULTI-MODAL SINGLE-CELL AND SPATIAL ATLAS REVEALS PATHOLOGY-SPECIFIC IMMUNE DIVERGENCE IN HUMAN LIVER CIRRHOSIS

Diana Vucevic[1] Sumana Srinivasan[1] Shankar Subramaniam[1], [1]University of California San Diego

Background: Chronic liver disease progresses through steatosis, fibrosis, and cirrhosis, yet a comprehensive map of how this progression remodels cell types, cell states, zonation, and intercellular communication at single-cell and spatial resolution is lacking. Whether alcoholic, metabolic, and autoimmune cirrhosis follow divergent cellular trajectories has not been systematically compared. We built a multi-modal atlas integrating scRNA-seq (~150,000 cells), MERFISH (~310,000 cells), and Visium (17,573 spots) across healthy, NAFLD, MAFLD, and three cirrhosis etiologies (alcohol, NAFLD, PBC). **Methods:** scRNA-seq data (27 cell types) from four published cohorts were harmonized via Harmony, with all cirrhosis etiologies from a single dataset to eliminate batch confounding. Functional cell states were scored using literature-derived gene sets. Cell2location deconvolution mapped cell types onto Visium spots. Cell-cell communication (CCC) was analyzed via LIANA (five-method consensus). MERFISH provided independent spatial validation of cell state and compositional changes. **Results:** The disease cascade followed an ordered sequence. First, hepatocytes underwent lineage loss: lipid-laden states dominated in early disease (NAFLD/MAFLD), then gave way to senescent and ER-stress programs in cirrhosis. MERFISH mapping confirmed this transition spatially (Lipid_Laden 0.73x, Senescent 2.8x, ER_Stress 3.6x in fibrotic tissue). Hepatocyte zonation universally collapsed to midzone-only identity, with MERFISH mapping revealing loss of pericentral-periportal spatial complementarity. Second, the sinusoidal niche remodeled. LSEC capillarization was near-complete in cirrhosis (normal LSECs 48% to < 2%), and Visium deconvolution resolved Stellate_Activated and Signature_Fibrosis enrichment in fibrotic septa with Hepatocyte_Lipid_Laden in pericentral regions. Stellate activation was pathology-dependent (40% myofibroblast in alcoholic vs 18% in NAFLD cirrhosis). Third, the immune landscape diverged by pathology. Alcoholic cirrhosis preserved Kupffer cells (1.89x metabolic ratio) with compensatory SLC40A1 upregulation maintaining HAMP iron homeostasis, while metabolic cirrhosis showed Kupffer-to-SAM replacement and HAMP collapse. MERFISH mapping confirmed this shift in situ (Kupffer 0.31x, Monocyte 3.2x). CCC revealed that this divergence extended to signaling: SPP1-integrin remodeling and ZG16B-TLR2 gut-liver axis in alcoholic, collagen-DDR1 fibrogenesis in NAFLD, and HLA-G immune evasion with checkpoint activation (LAG3, BTLA) in PBC. **Conclusion:** Liver disease progression follows a conserved structural cascade, hepatocyte dedifferentiation, zonation collapse, sinusoidal remodeling, but branches into pathology-specific immune and communication programs at cirrhosis. These divergent architectures suggest antifibrotic strategies may need to be pathology tailored.

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Disclosures: Diana Vucevic: Nothing to Disclose, Sumana Srinivasan: Nothing to Disclose, Shankar Subramaniam: Nothing to Disclose.

2298 | ◆ ELEVATED LIVER ENZYMES UNDER CONTEMPORARY THRESHOLDS HIGHLIGHT A MISSING HEPATIC DIMENSION IN METABOLIC RISK ASSESSMENT

Chaojian He[1] Qingqiang Yi[2] Lei Zhao[3], [1]Rocky Vista University, [2]Tai'an Eighty-Eight Hospital, [3]Tai'an City Central Hospital

Background: The liver is the central orchestrator of systemic metabolism, yet no metabolic syndrome (MetS) criteria include liver enzymes. Notably, these stricter criteria, lower ALT thresholds (men >35, women >25 U/L) and age-/sex-specific GGT thresholds (men and women ≥45y: >38 U/L; women <45y: >27 U/L), have rarely been adopted in studies examining the association between liver enzymes and cumulative metabolic burden. Using a large Chinese cohort, we tested whether these contemporary thresholds associate with metabolic dysfunction, highlighting an overlooked hepatic dimension of metabolic risk assessment. **Methods:** We conducted a cross-sectional study of 13,335 consecutive participants from a health check-up center in Northern China. Metabolic burden score (MBS) (0-3) was defined as the number of metabolic abnormalities, including glucose, triglycerides, and HDL-C (ADA/IDF criteria). The primary outcome was elevated ALT/GGT (as defined in Background). Multivariable logistic regression assessed the independent association between MBS (continuous) and the outcome, adjusting for age, sex, BMI, and systolic blood pressure (SBP). Linear trend across increasing MBS categories was assessed. Age was modeled categorically (18-29, 30-39, 40-49, 50-59, ≥60 years). AUC was compared between a base model (age, sex, BMI, SBP) and a full model (base + MBS), using DeLong's test for paired ROC curves. An interaction term (MBS × sex) was tested. **Results:** Among 13,335 participants (mean age 44.5±12.9 years; 55.2% male), 29.7% met the composite outcome for ALT/GGT elevation. In the fully adjusted model, each 1-point increase in MBS was associated with higher odds of ALT/GGT elevation (adjusted OR = 1.63; 95% CI: 1.55-1.72; P < 0.001). A strong linear trend was observed across MBS categories (P for trend < 0.001). Age exhibited a non-linear association with the outcome, with the highest risk observed among individuals aged 40-49 years (OR = 2.96; 95% CI: 2.54-3.44) compared to those 18-29 years. A significant interaction was observed between MBS and sex (P for interaction = 0.032), indicating a stronger effect in men (sex-stratified ORs: men 1.71, women 1.49). Adding MBS significantly improved the AUC from 0.746 to 0.764 (P < 0.0001). **Conclusion:** Even using contemporary lower ALT/GGT thresholds that have rarely been applied in metabolic research, liver enzyme elevation was strongly, independently, and dose-dependently associated with cumulative metabolic burden. These findings suggest that the exclusion of liver biomarkers from current MetS frameworks may overlook an important hepatic manifestation of metabolic dysfunction. Incorporating contemporary ALT/GGT thresholds into metabolic risk stratification may facilitate earlier identification of individuals at increased metabolic risk.

Disclosures: Chaojian He: Nothing to Disclose, Qingqiang Yi: Nothing to Disclose, Lei Zhao: Nothing to Disclose.

2299 | ◆ ONCE-MONTHLY EFIMOSFERMIN ALFA IMPROVES NON-INVASIVE MARKERS OF FIBROSIS WITH AN ACCEPTABLE SAFETY PROFILE IN PARTICIPANTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS WITH MODERATE TO ADVANCED FIBROSIS OR COMPENSATED CIRRHOSIS (F2–4): RESULTS UP TO 52 WEEKS FROM AN OPEN-LABEL, PHASE 2 STUDY

Mazen Noureddin[1] Rohit Loomba[2] Janelle Lennie[3] Margaret James Koziel[4] Brenda Jeglinski[4] Matthew Bryant[4] Patricia Mendez[3] Stuart Kendrick[5] Anthony Lones[5] Victoria Woodham[6] Edoardo Lisi[5] Sumanta Mukherjee[3] Eric Lawitz[7], [1]Houston Methodist Hospital and Houston Research Institute, Houston, TX, USA, [2]University of California San Diego, San Diego, CA, USA, [3]GSK, Collegeville, PA, USA, [4]Boston Pharmaceuticals, Waltham, MA, USA, [5]GSK, Stevenage, UK, [6]GSK, London, UK, [7]Texas Liver

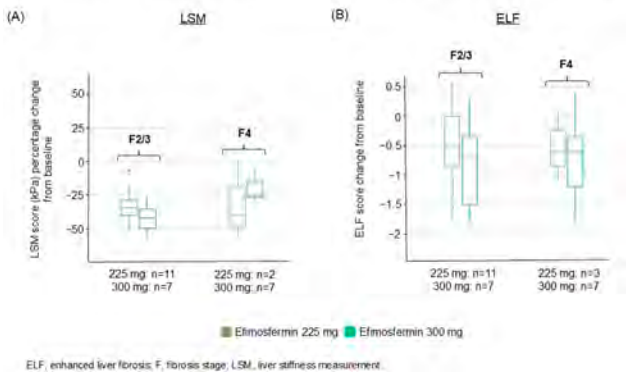
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Background: Efimosfermin alfa, a once-monthly (Q4W) FGF21 analog, led to improvements in fibrosis versus placebo at 24 weeks in participants (pts) with metabolic dysfunction-associated steatohepatitis (MASH) with stage 2/3 fibrosis (F2/3) in a Phase 2 study (NCT04880031). This analysis of a separate cohort of the Phase 2 study assessed changes in non-invasive tests (NITs) for fibrosis and safety of efimosfermin 225 mg and 300 mg in pts with F2–4 MASH. **Methods:** Pts willing/able to undergo liver biopsy with body mass index ≥ 25 kg/m^2, magnetic resonance imaging-proton density fat fraction (MRI-PDFF) $\geq 8\%$, vibration-controlled transient elastography liver stiffness measurement (LSM) ≥ 12.0–25.0 kPa, and enhanced liver fibrosis (ELF) ≥ 9.8 were included in this analysis. Pts with F1 at baseline were excluded from this analysis. In total, 24 pts had F2/3 (efimosfermin 225 mg: n = 13; 300 mg: n = 11) and 15 had F4 (efimosfermin 225 mg: n = 7; 300 mg: n = 8) at baseline. Changes in steatosis (MRI-PDFF) from baseline were assessed. Safety and changes in NITs for fibrosis improvement (LSM, ELF, and type III collagen pro-peptide [PRO-C3]) from baseline were assessed through 52 weeks. **Results:** Among all analyzed pts, mean (standard deviation [SD]) age was 60.6 years and 51.3% were female. For pts with F2/3 and F4, greater reductions in MRI-PDFF from baseline were observed with efimosfermin 300 mg (mean [SD] reductions of −58.5% [43.3; n = 7] and −71.1% [13.4; n = 6], respectively), versus 225 mg. Changes in LSM score from baseline were similar between pts with F2/3 and F4 and between doses (mean [SD] changes: F2/3 225 mg, −33.6% [13.6; n = 11]; F2/3 300 mg, −42.6% [11.6; n = 7]; F4 225 mg, −48.5% [11.7; n = 2]; F4 300 mg, −20.7% [10.4; n = 7]; **Figure**). Similar changes in ELF score from baseline were also observed across fibrosis stages (F2/3 versus F4) and dose groups (mean [SD] changes: F2/3 225 mg, −0.5 [0.665; n = 11]; F2/3 300 mg, −0.843 [0.789; n = 7]; F4 225 mg, −0.533 [0.603; n = 3]; F4 300 mg, −0.729 [0.81; n = 7]; **Figure**). For pts with F2/3 receiving efimosfermin 225 mg and 300 mg, mean (SD) changes in PRO-C3 from baseline were −19.5% (25.6; n = 11) and −24.8% (27.3; n = 7), respectively. For pts with F4 receiving efimosfermin 225 mg and 300 mg, mean (SD) changes in PRO-C3 from baseline were −21.8% (32.3; n = 3) and −23.5% (14.1; n = 7), respectively. Pharmacokinetics were similar between F2/3 and F4 pts at the same dose, with higher efimosfermin exposure observed with 300 mg versus 225 mg. No pts with F2/3 and 20% (n = 3) of pts with F4 had a serious adverse event; none were related to study treatment. **Conclusion:** Efimosfermin 225 mg and 300 mg demonstrated similar improvements in non-invasive markers of fibrosis and an acceptable, well-tolerated safety profile with comparable pharmacokinetics through 52 weeks in pts with F2–4 MASH. These results support continued evaluation of pts with advanced fibrosis and compensated cirrhosis in Phase 3 trials.

Figure. Distributions of change from baseline in (A) LSM score and (B) ELF score after 52 weeks of treatment



ELF, enhanced liver fibrosis; F, fibrosis stage; LSM, liver stiffness measurement.

Disclosures: Mazen Noureddin: Akero: Advisor, Alligos: Advisor, Altimmune: Advisor, AstraZeneca: Advisor, Boehringer Ingelheim: Advisor, Boston Pharma: Advisor, Cytodyn: Advisor, GSK: Advisor, Lilly: Advisor, Madrigal: Advisor, Merck: Advisor, Novo Nordisk: Advisor, Sagimet: Advisor, Terns: Advisor, Takeda: Advisor, Akero: Principal Investigator, Allergan: Principal Investigator, Altimmune: Principal Investigator, Boehringer Ingelheim: Principal Investigator, Bristol Myers Squibb: Principal Investigator, Boston Pharma: Principal Investigator, Conatus: Principal Investigator, Corcept: Principal Investigator, Galectin: Principal Investigator, Genfit: Principal Investigator, GSK: Principal Investigator, Kowa: Principal Investigator, Enanta: Principal Investigator, Madrigal: Principal Investigator, Lilly: Principal Investigator, Merck: Principal Investigator, Novartis: Principal Investigator, Novo Nordisk: Principal Investigator, Rivus: Principal Investigator, Shire: Principal Investigator, Takeda: Principal Investigator, Terns: Principal Investigator, Viking: Principal Investigator, Zydus: Principal Investigator, Rivus: Stock – privately held company, Cytodyn: Stock - publicly traded company, ChronWell: Stock – privately held company, Madrigal: Speakers bureau, Gilead Sciences: Principal Investigator, Akero: Consultant, Altimmune: Consultant, Alligos: Consultant, AstraZeneca: Consultant, BI: Consultant, Boston Pharma: Consultant, Curve bioscience: Consultant, Cytodyn: Consultant, GSK: Consultant, Histoindex: Consultant, Lilly: Consultant, Madrigal: Consultant, Merck: Consultant, Novo Nordisk: Consultant, Sagimet: Consultant, Terns: Consultant, Allergan: Grant/Research Support, Altimmune: Grant/Research Support, Akero: Grant/Research Support, BI: Grant/Research Support, BMS: Grant/Research Support, Boston Pharma: Grant/Research Support, Conatus: Grant/Research Support, Corcept: Grant/Research Support, Gilead: Grant/Research Support, Galectin: Grant/Research Support, Genfit: Grant/Research Support, GSK: Grant/Research Support, Kowa: Grant/Research Support, Enanta: Grant/Research Support, Madrigal: Grant/Research Support, Lilly: Grant/Research Support, Merck: Grant/Research Support, Novartis: Grant/Research Support, Novo Nordisk: Grant/Research Support, Rivus: Grant/Research

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2300 | ◆ DIABETESMASH INDEX FOR PREDICTING AT-RISK MASH AND LIVER-RELATED EVENTS IN TYPE 2 DIABETES

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Background: Metabolic dysfunction-associated steatohepatitis (MASH) is highly prevalent among individuals with type 2 diabetes (T2D) and significantly increases the risk of liver-related events. Individuals with at-risk MASH [MASH +NAS $\geq$ 4+F $\geq$ 2] are the main target population for emerging therapies. We aimed to develop and validate a non-invasive model to identify at-risk MASH and predicting long-term outcomes in adults with T2D. **Methods:** A multicenter biopsy-based derivation cohort from China (n = 525) was used for model development. External validation was conducted in an independent multicenter China DLIM-biopsy cohort (n = 423); three vibration-controlled transient elastography (VCTE)-based cohorts, including the China DLIM-VCTE cohort (n = 3,711), the Singapore cohort (n = 422), and the US NHANES cohort (n = 1,674); and the UK Biobank MRI cohort (n = 1,146). At-risk MASH was defined histologically in the derivation and biopsy-based validation cohorts, by the FibroScan-AST (FAST) score in the VCTE-based cohorts, and by proton density fat fraction and corrected T1 in the UK Biobank MRI cohort. Model performance was compared with the Fibrosis-4 index (FIB-4), non-alcoholic fatty liver disease fibrosis score (NFS), LiverRisk score, and AST-to-ALT ratio (AAR). In addition, the prognostic utility of the model for predicting liver-related events was evaluated in the UK Biobank cohort (n = 31,066). **Results:** The DiabetesMASH Index (DMI), incorporating age, AST, triglycerides, and high-density lipoprotein cholesterol, demonstrated robust discriminatory performance in the derivation and validation cohorts. The AUCs were 0.79 (95% CI 0.75-0.83), 0.75 (0.71-0.80), 0.91 (0.89-0.94), 0.88 (0.80-0.96), 0.90 (0.86-0.94), and 0.80 (0.73-0.86), respectively, outperforming the FIB-4, NFS, LiverRisk score, and AAR. Calibration analyses demonstrated good agreement between predicted and observed risks. The indeterminate zone comprised 35.8% of participants in the derivation cohort and 48.2%, 19.9%, 24.8%, 19.1%, and 74.3% across the validation cohorts. Furthermore, compared with the low-risk group, the intermediate- and high-risk groups had significantly increased risks of 10-year liver-related events, with multivariable-adjusted hazard ratios of 1.41 (95% CI 0.90-2.22) and 3.27 (95% CI 2.84-3.78), respectively. **Conclusion:** DMI is a validated, affordable, and accessible non-invasive tool for identifying at-risk MASH and stratifying the risk of liver-related events in individuals with T2D.

Disclosures: Yuping Chen: Nothing to Disclose, Bingtian Dong: Nothing to Disclose, Chuan Liu: Nothing to Disclose, Guo Han: Nothing to Disclose, Bicheng Ye: Nothing to Disclose, Jie Zhang: Nothing to Disclose, Zhen Li: Nothing to Disclose, Ming-Hua Zheng: Nothing to Disclose, Kaina Chen: Nothing to Disclose, Boon Bee George Goh: Nothing to Disclose, Xiao Liang: Nothing to Disclose, Airong Hu: Nothing to Disclose, Yiling Li: Nothing to Disclose, Qing-Lei Zeng: Nothing to Disclose, Yameng Sun: Nothing to Disclose, Wei Gou: Nothing to Disclose, Hua Bian: Nothing to Disclose, Chiwei Zhang: Nothing to Disclose, Xiaolin Wang: Nothing to Disclose, Yinqiu Zhang: Nothing to Disclose, Jiaojian Lv: Nothing to Disclose, Jie Shen: Nothing to Disclose, Xuan Liang: Nothing to Disclose, Xiqiao Zhou: Nothing to Disclose, Mingxing Huang: Nothing to Disclose, Qingge Zhang: Nothing to Disclose, Yan Wang: Nothing to Disclose, Xingguo Xiao: Nothing to Disclose, Yuehua Wang: Nothing to Disclose, Yuxia Qi: Nothing to Disclose, Yusen Zhou: Nothing to Disclose, Jing He: Nothing to Disclose, Taolong Zhou: Nothing to Disclose, Yan Wu: Nothing to Disclose, Weimin Jiang: Nothing to Disclose, Fengmei Wang: Nothing to Disclose, Tong Dang: Nothing to Disclose, Jing Du: Nothing to Disclose, Huimin Ying: Nothing to Disclose, Xuefeng Li: Nothing to Disclose, Yuwei Zhang: Nothing to Disclose, Ling Li: Nothing to Disclose, Zhe Dai: Nothing to Disclose, Xiaolong Qi: Nothing to Disclose, DiabetesLiver Integrated Management (DLIM) Consortium: Nothing to Disclose.

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2301 | ◆ GENETIC EVIDENCE LINKS OPA1-RELATED MITOCHONDRIAL QUALITY-CONTROL NETWORKS TO LIVER FIBROSIS IN MASLD

Xinting Yu[1] Shisong Rong[2] Pinzhu Huang[3] Yoshiko Nanki[4] Edward O'Neill[1] Enzo Cabrera[1] Jerry Cruz Rodriguez[1] Marla Sagatelian[1] Zaur Abilov[4] Chandra Shankar[4] Rene Gomez-Esquivel[1] Yuting Huang[5] Kawtar Al Khalloufi[6] Yury Popov[7], [1]University of South Florida, [2]Harvard Medical School, [3]Harvard University Medical School, [4]BIDMC, Harvard Medical School, [5]Mayo Clinic Florida, [6]Tampa General Hospital, [7]BIDMC Harvard Medical School

Background: Liver fibrosis is a major determinant of morbidity and mortality in metabolic dysfunction-associated steatotic liver disease (MASLD). Mitochondrial dysfunction is a hallmark of MASLD, and our prior work showed that damage-associated molecular pattern mitochondrial DNA (mtDNA), released from hepatocytes s activates hepatic stellate cells and promotes MASH fibrosis. In our prior large-scale Multi-trait GWAS - Multi-marker Analysis of GenoMic Annotation (MTAG-MAGMA) gene-based analyses of mitophagy, mitochondrial fusion, and mitochondrial fission pathways across datasets encompassing approximately 7 million individuals, *OPA1* emerged as a leading candidate linked to liver fibrosis. **Methods:** We performed gene-based association analyses of common and rare variants in genes encoding known OPA1 direct interactors (n = 27) and genes directly involved in OPA1-related pathways (n = 29). Common variants were evaluated using our MTAG-MAGMA pipeline applied to fibrosis-related GWAS summary statistics. Rare variants were assessed by in silico gene-based burden analyses using Genebass v0.13.0-43c83cc-202402232123 from UK Biobank data. Loss-of-function and missense variants were evaluated using SKAT-O, burden, and SKAT models for liver fibrosis and cirrhosis. To interrogate biological significance in vivo, we measured a circulating mtDNA using novel duplex ddPCR assay and assessed liver histology in mice with selective hepatocyte-specific OPA1 deletion and fibrotic MASH induced induced by 8 weeks of HF-CDAA diet. **Results:** In common-variant analyses, MIEF1, a mitochondrial fission-related gene, showed nominal association with liver fibrosis ($P <= 0.015$), as did CHCHD3, an OPA1 direct interactor ($P = 0.013$). Rare-variant burden analyses identified 16 OPA1-related genes with nominal associations with liver fibrosis or cirrhosis ($P <= 0.05$), including OPA1 ($P = 0.049$), MTCH2 ($P <= 0.004$), and 14 additional genes. In mice with MASH, hepatocyte-specific loss of OPA1 gene markedly increased circulating mtDNA after HF-CDAA diet feeding. OPA1 loss reduced overall liver steatosis and fibrosis. Intriguingly, OPA1 knockdown led to remarkable shift in scarring pattern from pericellular “chicken-wire” fibrosis to moderate interstitial fibrosis. **Conclusion:** OPA1 is a genetic and biological anchor linking mitochondrial quality-control pathways to MASLD fibrosis. These findings support OPA1-related mitochondrial dynamics and damage signaling as direct contributors to fibrotic liver disease, and provide a framework for functional studies and innovative therapies in MASLD.

Disclosures: Xinting Yu: Nothing to Disclose, Shisong Rong: OcuSciences, Inc.: Consultant, SunRegen Healthcare AG.: Consultant, C. Light Technologies: Consultant, Pinzhu Huang: Nothing to Disclose, Yoshiko Nanki: Nothing to Disclose, Edward O'Neill: Nothing to Disclose, Enzo Cabrera: Nothing to Disclose, Jerry Cruz Rodriguez: Nothing to Disclose, Marla Sagatelian: Nothing to Disclose, Zaur Abilov: Nothing to Disclose, Chandra Shankar: Nothing to Disclose, Rene Gomez-Esquivel: AMGEN: Independent Contractor, Yuting Huang: Nothing to Disclose, Kawtar Al Khalloufi: Nothing to Disclose, Yury Popov: Nothing to Disclose.

2302 | ◆ ELF TEST PREDICTS ADVANCED FIBROSIS AND FIBROSIS CHANGE IN CHILDREN WITH MASLD

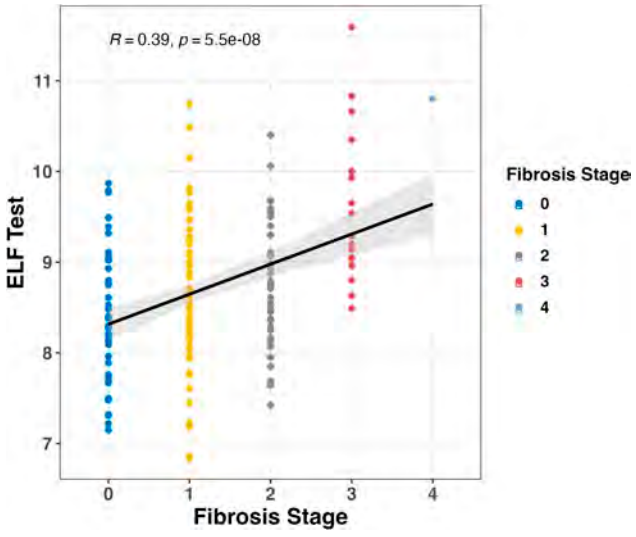
Adam Telega[1] Xinlian Zhang[1] Andrea Schreck[1] Raphael Yoo[1] Rush Chewning[1] Denise Malicki[1] Phillipp Hartmann[1], [1]University of California San Diego

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) affects 5-10% of children globally, and it is associated with severe comorbidities and long-term mortality. However, there is a paucity of reliable biomarkers that predict the degree of fibrosis in children with MASLD. Prior studies provided mixed results for the performance of the Enhanced liver fibrosis (ELF) test in pediatric nonalcoholic fatty liver disease (NAFLD) and lacked strict temporal association with biopsy. We aimed to validate the ELF test in pediatric MASLD after the recent change in terminology while anchoring it more closely in proximity to the biopsy. **Methods:** We prospectively enrolled 182 children with biopsy-confirmed MASLD and an ELF test within 30 days of biopsy as well as 20 healthy controls at an academic Children’s Hospital between 2023 and 2026. Analyses included t-tests, areas under the curve (AUCs), and Pearson correlations. **Results:**

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Children with MASLD had mean age 12.9 years, 79.1% were boys, mean body mass index was 33.5, mean NAFLD activity score (NAS) was 4.00, and fibrosis stages were F0 n = 45, F1 n = 73, F2 n = 45, F3 n = 18, and F4 n = 1. Mean ELF scores were significantly higher in patients with MASLD compared with controls (8.72 vs 8.32, p = 0.014). Amongst children with MASLD, the mean ELF scores of F1-F4 vs F0 were 8.82 vs 8.40 (p = 0.001), 9.03 for F2-F4 vs 8.55 for F0-F1 (p < 0.001), and 9.64 for F3-F4 vs 8.61 for F0-F2 (p < 0.001).The ELF scores correlated with fibrosis stage (R = 0.39, p < 0.001) (Figure). The ELF test had a higher AUC for detection of F1-F4, F2-F4, and F3-F4 than the basic biochemical markers ALT, AST, and GGT. It performed particularly well for detection of advanced fibrosis and outperformed ALT, AST, and GGT (AUC 0.82 with a threshold of 8.8; 0.74, 0.81, 0.73, respectively). Of note, an ELF score > 9.87 ruled in fibrosis (100% specificity/PPV), whereas an ELF score < 8.49 ruled out advanced fibrosis (100% sensitivity/NPV).Among 33 patients, repeat liver biopsy was performed a mean of 1 year and 5 months after the initial biopsy, with corresponding ELF scores obtained within 30 days of the second biopsy. Relative ELF change correlated with fibrosis stage change (R = 0.37, p = 0.036). ELF change predicted no fibrosis worsening (AUC 0.94, sensitivity 1.00, specificity 0.76), and improving ELF scores ruled out worsening of fibrosis. **Conclusion:** The ELF test correlates with fibrosis stage at baseline and its change predicts fibrosis response on repeat biopsy in children with MASLD. It may hence serve as a valuable noninvasive tool in clinical practice and clinical trials for pediatric MASLD.



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2303 | ◆ EXTERNAL VALIDATION OF LIQUIDTRANSFORMER IN MADRIGAL MASH PROGRAM: HEPTA'S AI-POWERED CELL-FREE DNA METHYLATION BIOMARKER OUTPERFORMS ALL EVALUATED BLOOD-BASED AND ELASTOGRAPHY MARKERS FOR DETECTING TREATMENT-ELIGIBLE MASH

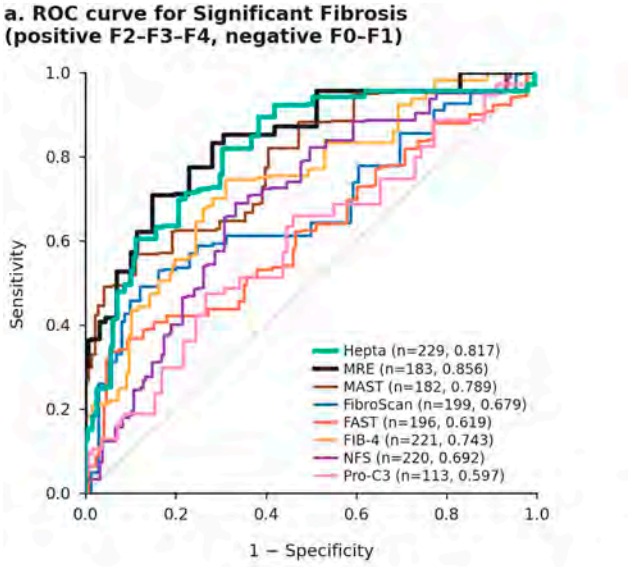
Rohit Loomba[1] Soheil Damangir[2] James Hennan[3] Manal Abdelmalek[4] Jörn Schattenberg[5] Chong Lu[2] Leila Bazargan[2] Suneil Hosmane[3] Hamed Amini[2] Rebecca Taub[3] Anna Mae Diehl[6], [1]University of California, San Diego, [2]Hepta Bio, Inc., [3]Madrigal Pharmaceuticals, [4]Mayo Clinic Rochester, [5]Saarland University Medical Center, [6]Duke University

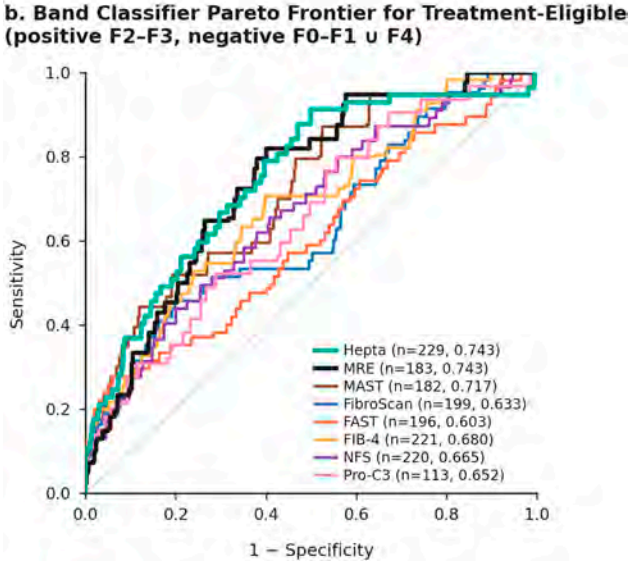
Background: The approval of resmetirom and semaglutide for MASH with moderate-to-advanced fibrosis (F2-F3) has made accurate, scalable identification of treatment-eligible patients a clinical priority. Existing NITs were largely developed to detect advanced fibrosis (F3-F4) and underperform at the F0/1-vs-F2 boundary that defines treatment eligibility. We previously developed LiquidTransformer, an AI-powered cell-free DNA (cfDNA) methylation technology, for non-invasive measurement of fibrosis and MASH. Here we report an independent validation of the test in the Madrigal MASH program and a head-to-head comparison against established NITs. **Methods:** LiquidTransformer was trained on a large biopsy-confirmed MASLD cohort, with no samples from the Madrigal MASH program used during training. Independent validation was performed on 229 biopsy-confirmed participants from the Madrigal MASH program. The primary endpoint was detection of significant fibrosis (F2+) and the secondary endpoint was detection of treatment eligible (F2-F3). Hepta was compared head-to-head against FAST, MAST, MRE, FibroScan/TE, Pro-C3 and FIB-4. Performance was measured using AUC for F2+ and Pareto frontier for F2-F3 classification. To make comparisons clinically interpretable, we reported case-mix-adjusted performance under two reference fibrosis-stage distributions: a general MASLD-population (Younossi 2016) and the LITMUS biomarker-validation cohort (Hardy 2023), alongside unweighted values. **Results:** Hepta's LiquidTransformer achieved an F2+ AUC of 0.85 (unweighted), 0.81 (MASLD-weighted), and 0.82 (LITMUS-weighted) on the Madrigal validation set. In all three weighting conditions, Hepta outperformed every blood- and TE-based NITs. Using LITMUS weighting Hepta outperformed FAST (AUC 0.62, Δ +0.20), MAST (0.79, Δ +0.04), FibroScan/TE (0.68, Δ +0.14), Pro-C3 (0.60, Δ +0.17) and FIB-4 (0.74, Δ +0.08). The only NIT with higher AUC was MRE (0.86, Δ −0.02), a specialized imaging modality available in a subset of Radiology centers. For treatment-eligible classification, Hepta's Pareto frontier equaled that of MRE and exceeded all other tests. Hepta's advantage over aforementioned NITs

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widened under realistic case-mix reweighting, reflecting robust discrimination at the clinically critical F1-vs-F2 boundary where conventional NITs lose performance. **Conclusion:** In an independent validation in the Madrigal MASH program, Hepta's LiquidTransformer accurately identified treatment-eligible patients and those with significant fibrosis and outperformed all evaluated blood-based and FibroScan (a type of TE system), including the composite scores FAST and MAST. Performance approached that of MRE for F2+ and matched MRE for treatment-eligible classification. These results support Hepta as a promising scalable blood-based approach for identifying treatment-eligible MASH patients.





Disclosures: Rohit Loomba: Eli Lilly and Company: Consultant, 89bio: Consultant, Aardvark Therapeutics: Consultant, Altimmune: Consultant, Alnylam/Regeneron: Consultant, Amgen: Consultant, Arrowhead Pharmaceuticals: Consultant, AstraZeneca: Consultant, Bristol Myers Squibb: Consultant, CohBar: Consultant, Eli Lilly: Consultant, Galmed Pharmaceuticals: Consultant, Gilead: Consultant, Glympse Bio: Consultant, Hightide: Consultant, Inipharma: Consultant, Intercept: Consultant, Inventiva: Consultant, Ionis: Consultant, Janssen, Inc.: Consultant, Madrigal Pharmaceuticals: Consultant, Merck, Metacrine, Inc.: Consultant, NGM Biopharmaceuticals: Consultant, Novartis: Consultant, Novo Nordisk: Consultant, Pfizer: Consultant, Sagimet Biosciences: Consultant, Terns Pharmaceuticals: Consultant, Theratechnologies and Viking Therapeutics: Consultant, 89bio: Stock options, Sagimet Biosciences: Stock options, Arrowhead Pharmaceuticals: Research grant, AstraZeneca: Research grant, Boehringer Ingelheim: Research grant, Bristol Myers Squibb: Research grant, Eli Lilly: Research grant, Galectin Therapeutics: Research grant, Galmed Pharmaceuticals: Research grant, Gilead: Research grant, Hanmi: Research grant, Intercept: Research grant, Inventiva: Research grant, Ionis: Research grant, Janssen, Inc.: Research grant, Madrigal Pharmaceuticals: Research grant, Merck: Research grant, NGM Biopharmaceuticals: Research grant, Novo Nordisk: Research grant, Pfizer: Research grant, Sonic Incytes: Research grant, Terns Pharmaceuticals: Research grant, LipoNexus, Inc.: Co-founder, Cascade Pharmaceuticals: Consultant, Eccogene: Consultant, HeptaBio: Consultant, Metavi: Consultant, Neurobo: Consultant, Novo Nordisk: Consultant, Sourcebio: Consultant, Roche: Consultant, Roche: Consultant, Takeda: Consultant, GSK: Grant/Research Support, Roche: Grant/Research Support, TensorBio: Grant/Research Support, Aarrowhead Pharmaceuticals: Consultant, Boehringer-Ingelheim: Consultant, Altimmune: Grant/Research Support, Eccogene: Grant/Research Support, Heptabio: Grant/Research Support, 89 bio: Grant/Research Support, Takeda: Grant/Research Support, Soheil Damangir: Nothing to Disclose, James Hennan: Nothing to Disclose, Manal Abdelmalek: 89Bio, Akero, Madrigal, Inventiva, Novo Nordisk, Intercept, Merck,: Advisor, Hanmi, Novo Nordisk: Consultant, Madrigal, Gilead, Inventiva, 89Bio, Akero, Hanmi: Grant/Research Support, Medscape; Clinical Care Options; Fishawack Inc, LLC; CLDF: Speaking and Teaching, Up-to-Date: Royalties or patent beneficiary, Prometheus: Advisor, Novo Nordisk: Consultant, Boehringer-Ingelheim: Grant/Research Support, Jörn Schattenberg: Akero: Consultant, 89Bio: Consultant, Boehringer Ingelheim: Consultant, Ipsen: Consultant, Inventiva Pharma: Consultant, Madrigal: Consultant, Northsea Therapeutics: Consultant, Novo Nordisk: Consultant, Roche: Consultant, Siemens Healthineers: Consultant, Boehringer Ingelheim: Advisor, AGED diagnostics: Stock – privately held company, Hepta Bio: Stock – privately held company, Novo Nordisk: Speaking and Teaching, Madrigal: Stock - publicly traded company,

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2304 | MASH PRECIS FIBROSIS SCORE: DEVELOPMENT, VALIDATION, AND HEAD-TO-HEAD COMPARISON WITH ELF FOR F2-F3 TREATMENT ELIGIBLE PATIENT SELECTION IN BIOPSY-PROVEN MASH

Rohit Loomba[1] Paul Pockros[2] Jessica Ho[3] John Whitaker[4] Manal Abdelmalek[5], [1]MASLD Research Center, University of California San Diego, [2]Scripps Clinic; Scripps Research Institute, [3]Prometheus Laboratories, [4]SoCal CompBio, [5]Mayo Clinic Rochester

Background: Approved therapies for metabolic dysfunction-associated steatohepatitis (MASH) currently target non-cirrhotic F2–F3 fibrosis, creating an urgent need for noninvasive tests (NITs) that reliably identify this population. The Enhanced Liver Fibrosis (ELF) score, an FDA-cleared serum-based NIT used to identify patients at risk for advanced fibrosis, has been incorporated into treatment algorithms; however, it was not designed for fibrosis staging and it generates indeterminate results in many patients at precisely the boundary where treatment eligibility is determined. We report the development, blinded multi-cohort validation, and head-to-head comparison of the MASH Precis fibrosis score, designed to improve classification accuracy and diagnostic yield, with ELF to support treatment eligibility decisions. **Methods:** The MASH Precis fibrosis score uses a five-biomarker panel [hyaluronic acid (HA), tissue inhibitor of metalloproteinases-1 (TIMP1), alpha-2-macroglobulin (A2MG), thrombospondin-2 (THBS2), vascular cell adhesion molecule-1 (VCAM1)] with ordinal logistic regression to estimate stage-specific probabilities across F0–F1, F2–F3, and F4, reported as a 0–100 fibrosis staging score. Thresholds were locked prior to validation. Training used 10,000-resamples and 10-fold cross-validation (n = 456). Validation used an independent blinded set (n = 450). ELF combines TIMP1, HA, and procollagen III N-terminal peptide (PIIINP) via linear regression, including a gray zone (7.7–9.8) where no classification is assigned per guidelines. **Results:** The MASH Precis fibrosis score demonstrated robust discrimination across fibrosis classes: training and validation AUCs were 0.905 and 0.871 (F0–F1 vs. rest), 0.818 and 0.782 (F2–F3 vs. rest), and 0.862 and 0.922 (F4 vs. rest) (Figure 1A-B). In head-to-head comparison, MASH Precis fibrosis score outperformed or trended higher than ELF on boundaries relevant to treatment selection: ruling out low-risk patients (AUC 0.871 vs. 0.802; $p < 0.001$) and detecting cirrhosis (AUC 0.922 vs. 0.888; $p = 0.131$). MASH Precis fibrosis score correctly classified 70.1% (164/234) of F0–F1, 56.7% (102/180) of F2–F3, and 77.8% (28/36) of F4 patients with 100% diagnostic yield (Figure 1C). ELF correctly classified 16.2%, 36.1%, and 41.7% across the same groups; gray zone results rendered 59.8% of patients unclassifiable, including 50.0% of F2–F3 cases, yielding an overall diagnostic yield of 40.2% (Figure 1D). **Conclusion:** The MASH Precis fibrosis score demonstrated robust multi-cohort validation and superior classification performance versus ELF across all fibrosis stages with 100% diagnostic yield. The high rate of indeterminate ELF results, particularly among F2–F3 patients, has direct implications for treatment eligibility. These findings support prospective evaluation of MASH Precis fibrosis score to guide treatment decision-making in MASH.

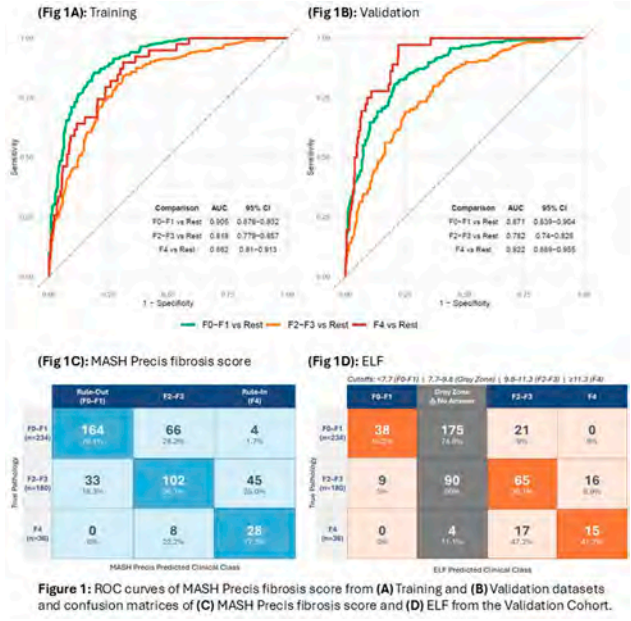


Figure 1: ROC curves of MASH Precis fibrosis score from **(A)** Training and **(B)** Validation datasets and confusion matrices of **(C)** MASH Precis fibrosis score and **(D)** ELF from the Validation Cohort.

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★ 2305 | ETHNIC DIFFERENCES IN NON-INVASIVE TESTS, DISEASE SEVERITY, AND CLINICAL OUTCOMES IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE: A LONGITUDINAL RETROSPECTIVE COHORT STUDY

Andre Jeyarajan[1] Chinmay Bera[2] Ravi Kiran[3] Maxwell Tong[4] Natalie Simonian[3] Leila Amiri[4] Nashla Hamdan[1] Keyur Patel[1], [1]University of Toronto, [2]University of Arkansas for Medical Sciences, [3]Toronto General Hospital, [4]University Health Network

Background: Non-invasive tests (NITs) are recommended to identify metabolic dysfunction-associated steatotic liver disease (MASLD) persons with advanced fibrosis (F3-4) at increased risk of liver-related outcomes. Although there are ethnic disparities in disease severity and outcomes, NITs were developed in predominantly White populations. Therefore, our aims were to characterize the performance of NITs in predicting advanced fibrosis and describe risk for MASLD severity and outcomes based on ethnicity. **Methods:** Retrospective study of a diverse ethnic cohort of 817 persons with biopsy-proven MASLD at a single Canadian tertiary-care centre. Ethnicity was self-reported and verified using machine learning models. NITs evaluated were FIB-4, NAFLD Fibrosis Score (NFS), liver stiffness measurement (LSM), Agile 3+, and MAFLD Fibrosis Score (MFS). **Results:** Race/ethnicity breakdown in the cohort was as follows: 434 (53.1%) White, 90 (11%) South Asian, 88 (10.8%) East Asian, 94 (11.5%) Southeast (SE) Asian, 61 (7.5%) Latin American, and 50 (6.1%) Other (27 Black, 22 Middle Eastern, and one Indigenous). Advanced fibrosis (F3-4) range was 31.8% (East Asians) to 56% (Whites). FIB-4 significantly outperformed for F3-4 in SE Asians compared to Whites and negative predictive value for FIB-4 was highest in East and SE Asians (Table 1). NFS, LSM, and Agile 3 + had poor sensitivity at validated thresholds for F3-4 in SE Asians (26-50%). Agile 3+ also had low sensitivity in Latin Americans (44%). LSM, Agile 3+, and MFS classified fewer indeterminates in Whites (Table 1). In prevalence modelling for F3-4, FIB-4 and MFS appeared to have stronger positive predictive value (PPV) at low (5%) prevalence in SE Asians compared to Whites (56% vs 25% and 47% vs 16%, respectively). LSM also had higher PPV at low prevalence in East Asians (48%) relative to Whites (24%). The recommended two-tier sequential approach using FIB-4 and LSM did not improve F3-4 classification rates in SE Asians (76% vs 83%), perhaps due to lower sensitivity of LSM at validated thresholds in this cohort. East Asian ethnicity was

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negatively associated with F3-4 at baseline compared to Whites (OR 0.52, p = 0.021). During mean follow-up up 5.0 +/- 5.1 years, both East (aHR 0.32, p = 0.05) and SE Asians (aHR 0.37, p = 0.006) had lower risks for hepatic decompensation compared to Whites. East Asians also had significantly lower all-cause mortality relative to Whites (aHR 0.24, p = 0.048). The rate of HCC and transplant were highest for South Asians (1.30 and 2.08 events per 100 person-years) while East Asians had the lowest rates of HCC and transplant (0.56 and 0.37 events per 100 person-years). **Conclusion:** There are ethnic differences in NIT sensitivity for F3-4 association with advanced MASLD fibrosis on biopsy and clinical outcomes. Further evaluation of NIT thresholds and liver-related events in low prevalence and underepresented ethnicities is warranted.

Table 1. Diagnostic performance of NITs in predicting advanced fibrosis using validated dual cut-offs.

		%					
NIT Ethnicity	AUROC	Sensitivity	Specificity	PPV	NPV	Indeterminate	Accuracy
FIB-4							
White	0.79	63	90	88	68	30	75
South Asian	0.80	61	92	85	75	29	78
East Asian	0.80	58	92	73	86**	19*	84
Southeast Asian	0.89**	50	98	91	83*	26	84
Latin American	0.81	64	96	94	71	21	79
Other	0.87	67	92	75	88	34	85
NFS							
White	0.80	59	94	92	70	40	77
South Asian	0.74	38	93	82	64	26*	68
East Asian	0.79	33	100	100	83	26*	84
Southeast Asian	0.87	26**	97	83	70	23**	72
Latin American	0.80	50	94	90	65	22*	72
Other	0.80	50	100	100	77	33	81
LSM							
White	0.85	78	87	89	75	14	82
South Asian	0.92	86	93	95	82	16	89
East Asian	0.87	65	96	92	81	24	84
Southeast Asian	0.75	50*	89	73	76	20	75
Latin American	0.86	67	91	92	63	12	76
Other	0.86	100	71	56	100	14	79
Agile 3+							
White	0.85	72	94	94	72	14	81
South Asian	0.85	67	94	93	70	14	79
East Asian	0.82	52	97	91	74	12	78
Southeast Asian	0.91	38**	97	86	76	13	77
Latin American	0.84	44*	100	100	55	9	67
Other	0.83	67	77	57	83	14	74
MFS							
White	0.81	79	78	85	70	18	78
South Asian	0.80	76	84	80	81	15	80
East Asian	0.83	57	94	80	84	15	83
Southeast Asian	0.87	58*	97*	93	74	15	79
Latin American	0.84	80	87	91	81	21	83
Other	0.86	91	72	67	93	15	79

* $p \leq 0.05$, ** $p \leq 0.01$, relative to White patients. Validated thresholds used to rule in and out advanced fibrosis: FIB-4 <1.3 to ≥2.67, NFS <-1.455 to ≥0.676, LSM <8 kPa to ≥12 kPa, MFS ≤14 to ≥15, and Agile 3+ <0.451 to ≥0.679.

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2306 | HEPATIC EXTRACELLULAR VESICLES FROM MASLD REPROGRAM HUMAN CARDIOMYOCYTE METABOLISM

Emeli Chatterjee[1], [1]Massachusetts General Hospital, Harvard Medical School.

Background: Metabolic dysfunction-associated steatic liver disease (MASLD) is a prevalent chronic liver condition epidemiologically linked to increased cardiovascular events and adverse cardiac remodeling. Extracellular vesicles (EVs) are candidate mediators of this inter-organ communication, transporting RNA species that reprogram distant cells. **Methods:** MASLD-relevant EVs were generated from a perfused multicellular human liver-on-chip model and characterized by size-exclusion chromatography, NTA, TEM, and immunoblotting. Small RNA sequencing prioritized RNAs by fold change, abundance, and predicted cardiac targets. Functional assays applied MASLD or control EVs to human induced pluripotent stem cell-derived cardiomyocytes, assessing uptake, lipid accumulation, mitochondrial morphology, transcriptomics, and metabolomics. **Results:** MASLD EVs selectively enriched microRNAs are predicted to target regulators of mitochondrial β-oxidation, glucose metabolism, and stress responses. MASLD EVs induced transcriptional repression of fatty acid transport/β-oxidation genes, lipid accumulation, and mitochondrial dysfunction in cardiomyocytes, accompanied by contractile disorganization. Metabolomics revealed elevated acylcarnitines and incomplete β-oxidation intermediates in treated cardiomyocytes, indicating impaired mitochondrial energetics. In MASLD ExoMap1 mice, hepatocyte EVs carried the prioritized RNA signature, and cardiac tissue exhibited concordant transcriptional remodeling, lipid deposition, and mild diastolic dysfunction. Inhibiting hepatic EV release attenuated cardiac abnormalities; enriching circulating EVs with these RNAs recapitulated the phenotype. **Conclusion:** MASLD-derived hepatic EVs convey a distinct RNA signature that reprograms cardiomyocyte metabolic and transcriptional networks, promoting lipid accumulation and mitochondrial dysfunction. This inter-organ communication axis identifies candidate biomarkers (e.g., EV-RNAs) and therapeutic targets for MASLD-related cardiac complications, highlighting the potential for EV-based diagnostics and RNA-targeted therapies to mitigate cardiovascular risk in MASLD patients

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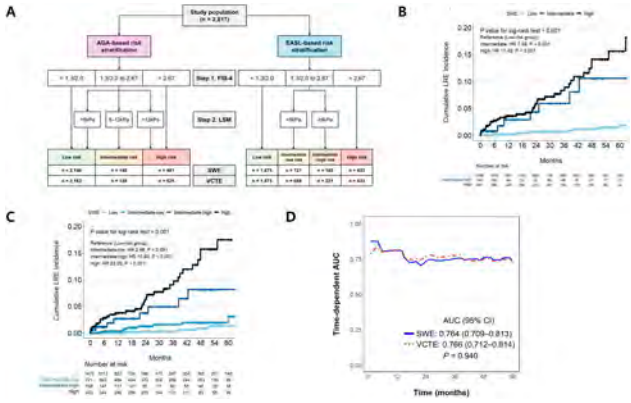
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2307 | SHEAR WAVE ELASTOGRAPHY PERFORMS COMPARABLY TO VIBRATION-CONTROLLED TRANSIENT ELASTOGRAPHY IN A FIB-4–BASED TWO-STEP RISK STRATIFICATION STRATEGY FOR MASLD

Soon Kyu Lee[1] Jaejun Lee[1] Soon Woo Nam[1] Jung Hyun Kwon[2], [1]College of Medicine, The Catholic University of Korea, [2]The Catholic University of Korea

Background: We compared the risk stratification performance of shear wave elastography (SWE) and vibration-controlled transient elastography (VCTE) using two-step algorithms proposed by the American Gastroenterological Association (AGA) and the European Association for the Study of the Liver (EASL). **Methods:** Patients with MASLD who underwent both VCTE and SWE during the same session between 2019 and 2025 were included. Risk stratification was performed using AGA- and EASL-based two-step approaches. The primary endpoint was liver-related events (LRE), defined as hepatocellular carcinoma (HCC), liver transplantation, liver-related death, and hepatic decompensation events. **Results:** Among 2,817 patients, 2,196, 140, and 481 were classified as low-, intermediate-, and high-risk, respectively, using the AGA algorithm with SWE, whereas 1,475, 721, 188, and 433 were classified as low-, intermediate-low, intermediate-high, and high-risk, respectively, using the EASL algorithm with SWE (Fig. A). Using the AGA-SWE algorithm, both intermediate- and high-risk groups showed increased risks of LREs compared with the low-risk group (hazard ratio [HR] 7.58 and 11.49, respectively) (Fig. B). The EASL-SWE algorithm also stratified LRE risk relative to the low-risk group, with higher HRs observed for the intermediate-low, intermediate-high, and high-risk groups (HR 2.98, 10.80, and 22.05, respectively) (Fig. C). The mean time-dependent area under the curve at 60 months was 0.764 and 0.766 for AGA-SWE and AGA-VCTE, respectively (Fig. D), and 0.785 for both EASL-SWE and EASL-VCTE, with no significant differences between SWE and VCTE in either algorithm. Moreover, SWE and VCTE demonstrated good concordance (Spearman's ρ = 0.713, p < 0.001). **Conclusion:** SWE-based two-step risk stratification showed predictive performance comparable to VCTE-based models in MASLD. These findings support SWE as a viable alternative for LSM within guideline-recommended two-step algorithms.



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2308 | FIB-4 AND APRI LINKED TO CARDIOMETABOLIC RISK AND MACE IN A REAL-WORLD TYPE 2 DIABETES COHORT

Melina Manolas[1] Sarah Barenbaum[1] Michele Yeung[1] Xiaoyue Ma[1] Sanaa Tejani[1] Sangeeta Kashyap[1], [1]Weill Cornell Medicine

Background: Metabolic dysfunction–associated steatotic liver disease (MASLD) is strongly linked with cardiovascular disease, the leading cause of mortality in affected individuals. Noninvasive fibrosis markers are increasingly used for risk stratification in type 2 diabetes mellitus (T2DM), but their prognostic significance for cardiovascular outcomes remains incompletely defined. We evaluated associations between fibrosis indices, cardiometabolic risk profiles, and major adverse cardiovascular events (MACE) in a large real-world T2DM cohort. **Methods:** We conducted a retrospective cohort study of 6,379 adults with T2DM at Weill Cornell Medicine. Fibrosis-4 (FIB-4) and AST-to-platelet ratio index (APRI) scores were calculated using temporally aligned AST, ALT, and platelet values. Age-adjusted FIB-4 categories (low, indeterminate, high) and APRI categories (<0.5, $0.5–<1.0$, ≥ 1.0) were applied. Because age is incorporated into FIB-4 and independently correlates with cardiovascular risk, APRI, which does not include age, was evaluated as an age-independent comparator. Outcomes included 4-component MACE (myocardial infarction, stroke, heart failure, or death). Multivariable logistic regression models adjusted for

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demographic and clinical covariates were used to assess associations with cardiovascular outcomes. **Results:** Higher FIB-4 identified a distinct high-risk phenotype. Patients with high FIB-4 were older (75.0 vs 65.7 years, $p < 0.001$), more frequently male, and had lower BMI despite greater multimorbidity, including higher rates of heart failure, atrial fibrillation, chronic kidney disease, and Charlson Comorbidity Index ≥ 4 (all $p < 0.001$, see Table 1). They also demonstrated lower use of SGLT2 inhibitors and GLP-1 receptor agonists (both $p < 0.001$).High FIB-4 was independently associated with increased odds of MACE (adjusted odds ratio [aOR] 1.53, 95% CI 1.25–1.86; $p < 0.001$), heart failure (aOR 1.56, 95% CI 1.28–1.89; $p < 0.001$), and mortality (aOR 1.45, 95% CI 1.09–1.92; $p = 0.011$). Indeterminate FIB-4 was also associated with heart failure (aOR 1.16, 95% CI 1.01–1.33; $p = 0.034$).To address potential age confounding within FIB-4, APRI was evaluated as an age-independent comparator. APRI ≥ 1.0 was associated with higher odds of MACE (aOR 1.56, 95% CI 1.01–2.41; $p = 0.048$), while APRI 0.5–<1.0 was associated with MACE, heart failure, and coronary artery disease. **Conclusion:** In patients with T2DM, elevated FIB-4 identifies a high-risk cardiometabolic phenotype with substantially increased cardiovascular risk. Similar findings observed with APRI suggest these associations are not solely driven by the age component embedded within FIB-4. Noninvasive fibrosis indices may serve as integrated prognostic tools for cardiovascular risk stratification in MASLD and T2DM.

Table 1: Baseline Characteristics by FIB-4 Category

Characteristic	Low FIB-4 (N=4057)	Indeterminate FIB-4 (N=1652)	High FIB-4 (N=670)	P value
Age, years	65.7 (11.3)	67.3 (10.8)	75.0 (9.7)	<0.001
Male sex	2141 (52.8)	1040 (63.0)	441 (65.8)	<0.001
BMI, kg/m²	31.2 (6.9)	30.3 (6.3)	28.3 (5.8)	<0.001
HbA1c ≤7.0%	1457 (48.3)	694 (57.5)	279 (56.7)	<0.001
SGLT2 inhibitor use	1498 (36.9)	572 (34.6)	190 (28.4)	<0.001
GLP-1 receptor agonist use	1339 (33.0)	492 (29.8)	109 (17.3)	<0.001
LDL cholesterol, mg/dL	96.8 (41.5)	90.3 (38.4)	81.4 (34.0)	<0.001
Triglycerides, mg/dL	169.8 (134.3)	158.6 (130.2)	146.5 (90.1)	<0.001
Heart failure	1046 (25.8)	501 (30.3)	274 (40.9)	<0.001
Atrial fibrillation	609 (15.0)	314 (19.0)	199 (29.7)	<0.001
Chronic kidney disease	1095 (27.0)	499 (30.2)	245 (36.6)	<0.001
Charlson Comorbidity Index ≥4	1871 (46.1)	830 (50.2)	391 (58.4)	<0.001

Abbreviations: BMI, body mass index; FIB-4, fibrosis-4 index; GLP-1, glucagon-like peptide-1; HbA1c, hemoglobin A1c; LDL, low-density lipoprotein; SGLT2, sodium-glucose cotransporter-2.

Values are presented as n (%) or mean (SD). FIB-4 categories were age-adjusted. P values reflect comparisons across FIB-4 strata.

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2309 | A NOVEL LARGE LANGUAGE MODEL TRAINED USING AASLD GUIDELINES CAN ACCURATELY DISTINGUISH SIGNIFICANT OR ADVANCED FIBROSIS AMONG ADULTS WITH MASLD/MASH USING ROUTINE CLINICAL DATA

Robert Wong[1] Anand Badarkhe[2] Parneet Kaur[2] Maytha Alshammari[3] Lakshmi Balasubramanian[2] Srinivas Thirunagari[2], [1]Stanford/VA Palo Alto Healthcare System, [2]Karyon Bio, [3]Kayon Bio

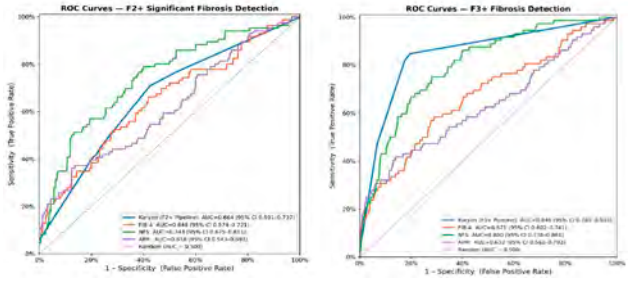
Background: Accessible non-invasive tools that accurately risk-stratify patients with significant fibrosis (F2+) or advanced fibrosis (F3+) in primary care settings is critical for streamlining metabolic dysfunction-associated steatotic liver disease/steatohepatitis (MASLD/MASH) clinical care pathways to GI/Liver specialty clinics, imaging-based fibrosis assessment (e.g. transient elastography), and linkage to approved therapies for MASH F2+. **Methods:** Using the 2017-2020 pre-pandemic National Health and Nutrition Examination Survey dataset, adults (age $\geq$ 20y) with MASLD/MASH who had available transient elastography data were categorized into significant fibrosis (liver stiffness measurement [LSM] $\geq$ 8.0kPa) or advanced fibrosis (LSM $\geq$ 9.5kPa). A large language model (Karyon) was trained using AASLD guidelines on MASLD/MASH and Noninvasive Liver Disease Assessment, and incorporated demographics (age, sex, ethnicity), anthropometric measurements, standard laboratory test results (e.g. complete blood count, comprehensive metabolic panel, lipid panel, hemoglobin A1c), and relevant risk factors (tobacco and alcohol use), to predict F2+ or F3+. Sensitivity, specificity, and area under the receiver operating curve (AUROC) of Karyon was compared against fibrosis-4 (FIB-4), AST to platelet ratio index (APRI), and NAFLD fibrosis score (NFS). **Results:** Among 2,585 adults with MASLD/MASH (48.7% men, mean age 50.0y, 34.0% non-Hispanic white, 24.4% African American, 23.4% Hispanic, 39.4% BMI $\geq$ 30kg/m^2, 12.7% diabetes, 43.9% hypertension), median LSM was 4.9 kPA, 5.3% with F2+, 2.9% with F3+. The sensitivity of Karyon for F2+ was 84.9% (95%CI 75.8-90.9), higher than FIB-4 (10.8%, 95%CI 5.6-10.0), APRI (17.4%, 95%CI 10.9-20.0), or NFS (20.9%, 95% CI 13.7-30.0), all $p < 0.01$. The sensitivity of Karyon for

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F2+ was higher in women vs. men (87.8% vs. 82.2%) and higher in older patients (age ≥ 60: 90.2% vs. 50.0% in age 18-39). The AUROC of Karyon for F2+ was 0.664 (95%CI 0.591-0.737), similar to NFS and FIB-4 (Figure). The sensitivity of Karyon for F3+ was 88.9% (95%CI 79.6-94.3), higher than FIB-4 (15.3%, 95%CI 8.8-20.0), APRI (5.6%, 95%CI 2.2-10.0), or NFS (26.4%, 95%CI 17.6-30.0), all $p < 0.01$. The sensitivity of Karyon for F3+ was similar in men vs. women (89.2% vs. 88.6%) and higher in older patients (age ≥ 60: 91.9% vs. 85.7% in age 18-39). The AUROC of Karyon for F3+ was 0.846 (95%CI 0.789-0.903), significantly higher than FIB-4 (AUROC 0.671, 95% CI0.602-0.741, $p < 0.01$). **Conclusion:** A novel large language model trained using AASLD guidelines shows promise in accurately risk-stratifying MASLD/MASH patients with significant or advanced fibrosis, which can be integrated into existing care pathways to improve the efficiency of the MASLD/MASH cascade of care. Refining the Karyon model with longitudinal data and liver biopsy confirmation of liver fibrosis stage will further enhance its performance and real-world utilization.

Figure. Performance characteristics of Karyon Model compared to FIB-4, APRI, and NFS in Accurately Risk Stratifying MASH with F2+ or MASH with F3+.



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2310 | ELF PREDICTS VCTE PROGRESSION AND REGRESSION AT 1 YEAR IN PATIENTS WITH ADVANCED FIBROSIS DUE TO MASH

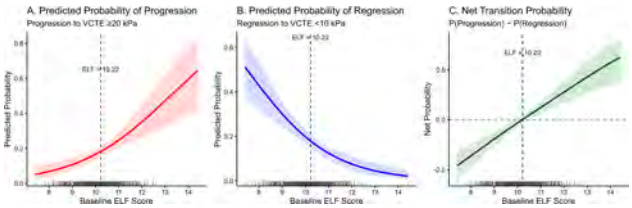
Matthew Gee[1] Jordan Feld[2] Keyur Patel[1], [1]University of Toronto, [2]Toronto General Hospital

Background: Metabolic dysfunction-associated steatohepatitis (MASH) is a leading cause of cirrhosis and liver-related mortality. Current clinical practice guidance from the AASLD and other societies recommends the use of non-invasive tests (NITs), including Enhanced Liver Fibrosis (ELF) and vibration-controlled transient elastography (VCTE), to identify patients at greatest risk of progression to cirrhosis and liver-related events, with widely used thresholds frequently implying clinical interchangeability between the two modalities. We previously demonstrated that baseline ELF predicts histologic fibrosis progression and regression at 1 year. In the current study, we evaluated whether baseline ELF similarly predicts VCTE-defined fibrosis progression and regression over 1 year. **Methods:** Data were pooled from 5 large placebo-controlled trials in patients with MASH and advanced fibrosis (NCT01672866, NCT01672879, NCT02462967, NCT03053050, NCT03053063). Patients with baseline VCTE ≥ 10 to < 20 kPa and available baseline ELF and 1-year VCTE were analyzed. Logistic regression estimated probabilities of progression at 1-year (VCTE ≥ 20 kPa) and regression (VCTE < 10 kPa) as a function of baseline ELF. Predicted and net transition probabilities were calculated across the ELF spectrum at the cohort mean baseline VCTE, with 95% CIs from 1000 bootstrap resamples. Odds ratios were used to assess associations between baseline ELF and VCTE progression/regression at 1 year. Rates of progression, regression, and mean ΔVCTE were calculated across ELF strata using established cutoffs: low (< 9.80), mid (≥ 9.80 to < 11.30), and high (≥ 11.30). Continuous ΔVCTE was modeled using least squares regression with baseline ELF, baseline VCTE, and their interaction. **Results:** 722 patients with F3&F4 MASH met inclusion criteria. 307 patients (43%) with VCTE ≥ 10 to < 20 kPa had discordant ELF scores (< 9.80 or ≥ 11.30). In logistic regression models, higher baseline ELF score was associated with increased odds of 1-year VCTE progression (OR 1.65, CI 1.32, 2.06), decreased regression odds (OR 0.57, CI: 0.46, 0.71), and a positive net transition toward progression, with progression and regression probabilities converging at ELF = 10.22 (see Figure). Across increasing ELF strata, progression rates increased (13.6% to 35.1%), regression rates decreased (30.4% to 8.8%), and mean ΔVCTE increased (−0.1 to +4.0 kPa). In a least squares linear regression model with an interaction term,

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baseline ELF was the strongest predictor of the direction of 1-year VCTE change. **Conclusion:** Baseline ELF identifies fibrotic activity associated with short-term VCTE change. These findings suggest that baseline discordance between ELF and VCTE may reflect active fibrotic remodeling rather than measurement disagreement, with VCTE primarily reflecting structural fibrosis burden and ELF capturing dynamic processes associated with future fibrosis transition.

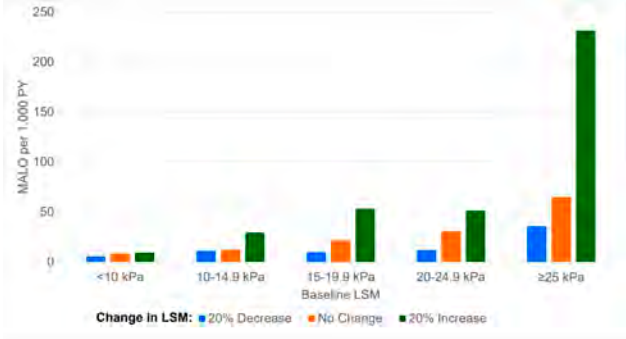


Disclosures: Matthew Gee: Siemens Healthineers: Employee, Jordan Feld: AbbVie: Advisor, Bluejay: Advisor, Gilead: Advisor, GlaxoSmithKline: Advisor, Precision Biosciences: Advisor, Arbutus: Advisor, Astra Zeneca: Advisor, Roche: Advisor, Vir: Advisor, Orphalan: Advisor, Pfizer: Advisor, Abbvie: Grant/Research Support, Gilead: Grant/Research Support, GlaxoSmithKline: Grant/Research Support, Atea: Advisor, Atea: Grant/Research Support, Roche: Grant/Research Support, Vir: Grant/Research Support, Mirum: Grant/Research Support, Mirum: Advisor, AusperBio: Advisor, Keyur Patel: Novo-Nordisk: Consultant, Gilead Sciences: Consultant, Merck: Consultant, Resalis: Advisor, Boehringer Ingelheim: Advisor, Inipharm: Advisor.

2311 | SERIAL LIVER STIFFNESS MEASUREMENT TRAJECTORIES AND INCIDENCE OF MAJOR ADVERSE LIVER OUTCOMES (MALO) IN

Binu John[1] Dustin Bastaich[2] Bassam Dahman[2], [1]University of Miami and Miami VA, [2]Virginia Commonwealth University

Background: Vibration-controlled transient elastography (VCTE) derived liver stiffness measurements (LSMs) are validated non-invasive tools for fibrosis assessment and risk stratification in metabolic dysfunction-associated steatotic liver disease (MASLD). While baseline LSM predicts major adverse liver outcomes (MALO), the independent prognostic significance of longitudinal LSM change, beyond baseline values alone, remains less well characterized. We examined MALO incidence rates stratified by the magnitude of change in LSM between serial VCTE assessments in a large in a North American cohort of patients with MASLD **Methods:** This retrospective cohort study utilized data from the VHA from January 2011 to November 2025. Adults with MASLD who underwent VCTE >10 valid measurements were eligible. Exclusion criteria included alternative liver disease etiologies, < 6 months of follow-up, or MALO within 6 months of VCTE. Serial LSM analysis required a follow-up VCTE between 6 months and 5 years with no intervening MALO. LSM trajectory was categorized as a ≥20% increase, <20% change (stable), or ≥20% decrease relative to baseline. MALO was defined as the composite of decompensation, HCC, liver transplantation, or liver-related death. Poisson regression estimated MALO incidence rates (IR) per 1,000 person-years (PY) with 95% confidence intervals, stratified by LSM category. **Results:** Of 29,823 patients with MASLD who underwent VCTE and met study criteria (median age 63 years (IQR = 18), 90.9% male), 7,241 were included in the analytic sample with a follow-up LSM between 6 months and 5 years with 18,196 person-years of follow-up from the second LSM. In the reference group of patients with stable LSM (<20% change), the MALO incidence increased progressively from LSM <10 kPa (IR 8.38, 95% CI 6.32-11.12), to 10-14.9 (12.16, 7.06-20.95), 15-19.9 (IR 21.54, 10.27-45.18), 20-24.9 (IR 30.80, 12.82-73.99), and ≥25 kPa (IR 64.80, 39.07-107.49). In comparison, MALO rates were lower across all categories in patients with a >20% decrease in LSM: from <10 kPa (IR 5.61, 3.49-9.02), 10-14.9 (IR 11.13, 7.01-17.66), 15-19.9 (IR 9.53, 4.28-21.20), 20-24.9 (IR 11.94, 4.48-31.82), and ≥25 kPa (IR 35.88, 23.15-55.61). MALO rates were highest in patients with a 20% increase in LSM, across all categories, increasing from LSM <10 kPa (IR 9.25, 6.61-12.95), to 10-14.9 (IR 29.17, 18.13-46.92), 15-19.9 (IR 53.11, 25.32-111.41), 20-24.9 (IR 51.36, 19.27-136.83), and ≥25 kPa (IR 231.36, 124.49-430.00). **Conclusion:** In this large national cohort, longitudinal LSM trajectory significantly modified MALO risk with a ≥20% LSM increase markedly increasing MALO incidence, particularly in patients with advanced fibrosis, while LSM improvement was associated with substantial risk reduction. These findings support serial VCTE monitoring as a dynamic, clinically actionable tool for risk stratification in MASLD.



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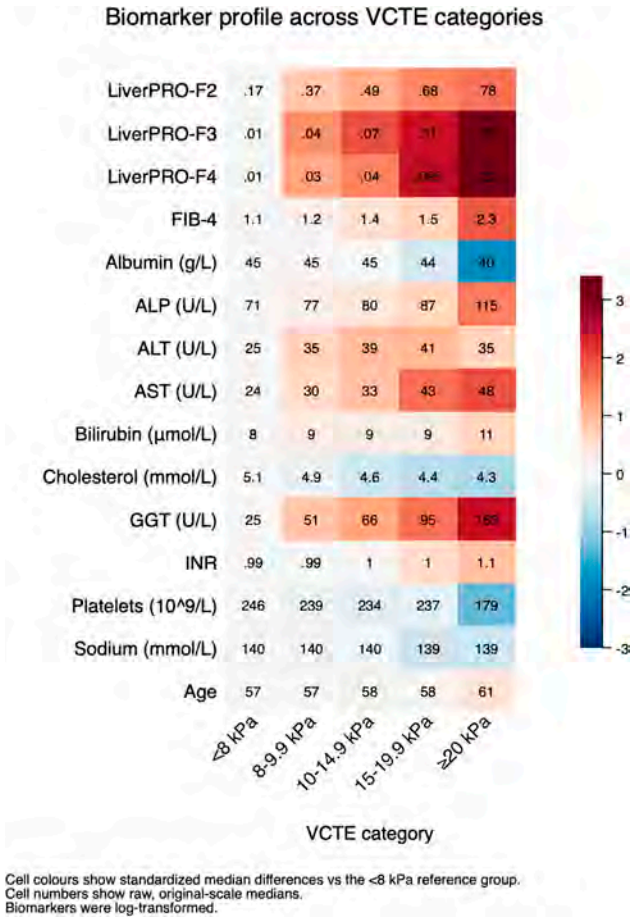
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2312 | LIVERPRO SCORES CAPTURE SUBTLE BIOLOGICAL DETERIORATION ACROSS INCREASING LIVER STIFFNESS IN STEATOTIC LIVER DISEASE

Maja Thiele[1] Julie Astono[1] Katrine Bech[2] Helle Schnefeld[2] Peter Andersen[2] Katrine Thorhauge[2] Stine Johansen[2] Ida Villesen[2] Sönke Detlefsen[3] Johanne Hansen[4] Camilla Hansen[2] Katrine Lindvig[1] Mads Israelsen[2] Aleksander Krag[2], [1]Evido Health, Copenhagen, Denmark, [2]Center for Liver Research, Department of Gastroenterology and Hepatology, Odense University Hospital, [3]Department of Clinical Research, University of Southern Denmark, Odense, Denmark, [4]Center for Liver Research, Department of Gastroenterology and Hepatology, Odense University Hospit

Background: Patients with steatotic liver disease (SLD) often have normal routine liver blood tests until decompensated cirrhosis. It remains unclear whether fibrosis progression causes incremental biochemical changes. We examined the association between increasing liver stiffness and biochemical biomarkers in asymptomatic individuals with SLD and assessed whether multivariable blood-based scores capture gradients across liver stiffness strata. **Methods:** We combined data from two single-centre cohorts of individuals at risk of SLD. All individuals underwent vibration-controlled transient elastography (VCTE), with liver biopsy offered in those with elevated VCTE. Participants were grouped into five VCTE strata based on proposed MASH therapy thresholds: low (<8 kPa), mildly elevated (8–9.9 kPa), moderate (10–14.9 kPa), high (15–19.9 kPa), and very high (≥ 20 kPa). Within strata, normalised median differences were calculated for age, 10 routine blood biomarkers, FIB-4, and LiverPRO relative to the low-VCTE group. LiverPRO is a medical device software estimating the risk of $\geq$F2, $\geq$F3 and F4 fibrosis. We visualised differences as heatmaps and validated findings in the NHANES cohort and in the biopsy-confirmed fibrosis subgroup. **Results:** We included 7,110 participants, 51% females, mean age 57 ± 8 years, BMI 29 ± 6 kg/m^2, 9% type 2 diabetes. 92% belonged to the low-VCTE group, while 3.0%, 2.6%, 0.6% and 1.7% had mildly elevated, moderate, high, or very high liver stiffness. Among 572 participants with liver biopsy, median VCTE was 9.6 kPa (IQR 6.7-16.4) and 29% had $\geq$ F3.All 10 biomarkers showed gradients across increasing VCTE. ALP, ALT, AST, and GGT changed in mildly elevated VCTE, whereas albumin, bilirubin, INR, platelets, and sodium changed at VCTE ≥ 15 kPa. Total cholesterol was inversely associated with VCTE from early strata onward, independent of lipid-lowering therapy. Despite these patterns, median biomarker values remained within conventional reference ranges across nearly all strata.Multivariable scores tracked VCTE significantly better than individual biomarkers. LiverPRO-F2 increased across all strata, while LiverPRO-F3 and LiverPRO-F4 showed greater separation in high and very high VCTE groups, consistent with model tuning. FIB-4 changed mainly at very high VCTE, and only 53-57% of participants had FIB-4 ≥ 1.30 in the moderate and high VCTE strata. We confirmed findings in the biopsy subgroup and NHANES cohort. **Conclusion:** Reference ranges and single routine blood tests are poorly suited to detect subtle fibrosis-associated biochemical changes. LiverPRO integrated biochemical deviations into a signal reflecting increasing liver stiffness and fibrosis stage more precisely than FIB-4. These findings support algorithmic interpretation of routine blood tests for earlier identification of patients with SLD eligible for therapy.



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to Disclose, Helle Schnefeld: Nothing to Disclose, Peter Andersen: Nothing to Disclose, Katrine Thorhauge: Nothing to Disclose, Stine Johansen: Nothing to Disclose, Ida Villesen: Nothing to Disclose, Sönke Detlefsen: Nothing to Disclose, Johanne Hansen: Nothing to Disclose, Camilla Hansen: Nothing to Disclose, Katrine Lindvig: Nothing to Disclose, Mads Israelsen: Nothing to Disclose, Aleksander Krag: Nothing to Disclose.

2313 | MASH RESOLUTION INDEX 2.0 PREDICTS FIBROSIS IMPROVEMENT IN PATIENTS TREATED WITH THE DGAT2 ANTISENSE OLIGONUCLEOTIDE ION224: POST HOC ANALYSIS OF THE RANDOMIZED PLACEBO-CONTROLLED ION224-CS2 PHASE 2B TRIAL

Rohit Loomba[1] Erin Morgan[2] Keyvan Yousefi[2] Dan Li[2] Sanjay Bhanot[2], [1]University of California, San Diego, [2]Ionis Pharmaceuticals, Inc

Background: Liver biopsy remains the gold standard for assessing treatment response in metabolic dysfunction–associated steatohepatitis (MASH). The challenges of an invasive and costly biopsy limit clinical development efficiency; thus, validating non-invasive predictive biomarkers of histologic response represents a major unmet need. The MASH Resolution Index (MASHResInd) is a validated biomarker composite of MRI-PDFF, ALT, and AST that detects histologic MASH resolution. ION224, a liver-targeted antisense inhibitor of DGAT2, previously showed meaningful histologic benefit in patients with MASH and fibrosis (ION224-CS2). We used this trial to evaluate MASHResInd as a predictor of treatment response. **Methods:** ION224-CS2 (NCT04932512) was a phase 2b, randomized, double-blind, placebo-controlled trial in adults with biopsy-confirmed MASH and fibrosis (F1–F3) treated with ION224 or placebo every 4 weeks for 49 weeks. MASHResInd was calculated using the published equation in participants with paired baseline and end-of-treatment (EOT) MRI-PDFF, ALT, AST, and liver biopsy (post hoc analysis set). Endpoints were MASH resolution without worsening of fibrosis and $\geq$1-stage fibrosis improvement without worsening of steatohepatitis. Univariable and **multivariable logistic regression** (adjusted for baseline MRI-PDFF, ALT, AST, BMI, age, and type 2 diabetes: MASHResInd 2.0) were used to estimate discrimination (area under the ROC curve [AUC]) and to define "rule-out" (~90% sensitivity) and "rule-in" (~90% specificity) cutpoints. **Results:** The post hoc analysis set (n = 111) had mean age 53 yr, BMI 37.7 kg/m², and 49.5% had type 2 diabetes. Baseline mean MRI-PDFF, ALT, and AST were 22.6%, 58.6 U/L, and 39.6 U/L, respectively; all improved by EOT as previously reported. For MASH resolution without worsening of fibrosis, MASHResInd showed excellent discrimination (multivariable AUC 0.81; 95% CI 0.72–0.90). A high-sensitivity "rule-out" threshold identified a large subgroup with negative predictive value (NPV) 93%, while a high-specificity "rule-in" threshold enriched for responders with positive predictive value (PPV) 67% and specificity 90%. For fibrosis improvement without worsening steatohepatitis, MASHResInd alone had AUC 0.64 (0.53–0.76), and after multivariable adjustment (MASHResInd 2.0) significantly improved to 0.71 (0.59–0.82) which is among the highest discriminative biomarkers for predicting fibrosis improvement. **Conclusion:** In ION224-CS2, MASHResInd 2.0 meaningfully improved discrimination for fibrosis improvement compared with the original index, while preserving excellent performance for MASH resolution. This is a major advancement in predicting fibrosis improvement in early MASH trials. Simple rule-out and rule-in cutpoints yielded high NPV and useful enrichment for responders, supporting MASHResInd as a valuable tool for patient selection and monitoring in future trials.

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2314 | THE MASH RESOLUTION INDEX FOR NON-INVASIVE DETECTION AND MONITORING OF MASH RESOLUTION: A SYSTEMATIC REVIEW AND POOLED ANALYSIS

Rahul Falodia[1] Ehsanullah Alokozay[2] Muhammad Junaid Azhar[3] Farhan Murtaza[4] Abdullah Imtiaz[5] Hamza Farooq Khan[6] Muhammad Ahmad Imran[3] Miriam Michael[3] Bacel Nseir[7] Wehbi Hanayni[6] Anand Deonarine[3], [1]All India Institute of Medical Sciences, Jodhpur, [2]Faculty of Medicine, Kandahar University, Kandahar, Afghanistan, [3]Howard University Hospital, [4]HCA Houston Healthcare/University of Houston Program, [5]Vassar Brothers Medical Center, [6]Corewell Health Dearborn, [7]HCA Houston healthcare/ University of Houston Program

Background: The MASH Resolution Index (MASHResInd) is a novel non-invasive score comprising baseline MRI-proton density fat fraction (MRI-PDFF), percentage change in MRI-PDFF, baseline alanine aminotransferase (ALT), change in ALT, and baseline aspartate aminotransferase (AST), developed to detect histological resolution of metabolic dysfunction-associated steatohepatitis (MASH) without worsening fibrosis. Despite its development in 2024, no synthesis of its diagnostic performance, comparative accuracy, and responsiveness to intervention exists. This systematic review and pooled analysis aimed to comprehensively evaluate the evidence for MASHResInd across pharmacological and non-pharmacological intervention settings. **Methods:** A systematic search of PubMed, Embase, and Cochrane databases was conducted through May 2026 using the terms "MASH Resolution Index," "MASHResInd," and related terms. Studies reporting diagnostic accuracy metrics or intervention-related changes in MASHResInd were included. Pooled sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated using a bivariate random-effects model. Comparative performance against the FibroScan-AST (FAST) score and individual non-invasive markers was assessed narratively. **Results:** Four studies comprising five independent cohorts (total n = 583 patients with biopsy-confirmed MASH) were included. Across two diagnostic cohorts (derivation n = 95; validation n = 163), MASHResInd achieved pooled AUCs of 0.81–0.83. At the rule-out cut-point (≤ -2.67), pooled NPV was 100% in the validation cohort, indicating high accuracy for excluding MASH resolution. At the rule-in cut-point (≥ -0.67), pooled PPV was 29%, reflecting the low prevalence of MASH resolution across cohorts (18–22%). In a head-to-head comparison (n = 160), MASHResInd significantly outperformed the FAST score (AUC 0.83 vs. 0.65; p = 0.001), with superior sensitivity, NPV, and positive likelihood ratio. In a pooled analysis of three aerobic exercise RCTs (n = 83), exercise training produced a significantly greater MASHResInd versus control (mean difference −0.66 units; p = 0.046), with 36% of exercising participants meeting the MASH resolution threshold versus 19% of controls (OR 2.2), representing the first evidence of MASHResInd responsiveness to a non-pharmacological intervention. **Conclusion:** MASHResInd demonstrates consistent and superior diagnostic accuracy for MASH resolution compared to existing non-invasive tests across independent pharmacological and exercise intervention cohorts. Its high NPV at the rule-out threshold supports its utility in sparing patients from unnecessary liver biopsies. Further validation in ethnically diverse cohorts, recently approved therapies, and long-term outcomes studies is warranted.

Disclosures: Rahul Falodia: Nothing to Disclose, Ehsanullah Alokozay: Nothing to Disclose, Muhammad Junaid Azhar: Nothing to Disclose, Farhan Murtaza: Nothing to Disclose, Abdullah Imtiaz: Nothing to Disclose, Hamza Farooq Khan: Nothing to Disclose, Muhammad Ahmad Imran: Nothing to Disclose, Miriam Michael: Nothing to Disclose, Bacel Nseir: Nothing to Disclose, Wehbi Hanayni: Nothing to Disclose, Anand Deonarine: Nothing to Disclose.

2315 | CREATININE-TO CYSTATIN-C RATIO (CCR) IS ASSOCIATED WITH ALL-CAUSE MORTALITY THROUGH MUSCLE PHENOTYPES AMONG ADULTS WITH SUSPECTED MASLD: A UK BIOBANK STUD

Melinda Wang[1] Dorothea Kent[1] Lisa Catalli[2] Giuseppe Cullaro[3] Mazen Nourredin[4] Naga Chalasani[5] Jennifer Lai[1], [1]UCSF, [2]University of California, San Francisco, [3]Columbia University, [4]Houston Methodist Hospital, [5]Indiana University Medical Center

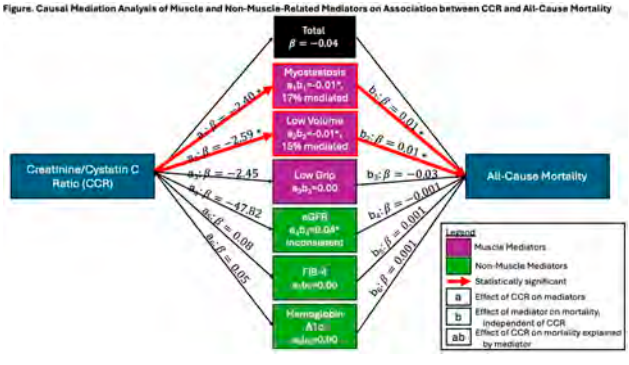
Background: Metabolic syndrome myopathy, defined as dysfunction in mass, quality, and function, is common among MASLD patients and associated with poor outcomes. CCR is a readily available laboratory index for muscle-related measures in the general population. We

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sought to evaluate the prognostic significance of CCR among MASLD patients and explore its relationship with muscle-related measures. **Methods:** Adults with suspected MASLD defined as Fatty Liver Index ≥ 60 with ≥ 1 cardiometabolic risk factor (CMRF) in UK Biobank. Baseline CCR was categorized into quartiles. A sub-cohort of patients who subsequently completed MRI was also identified. Logistic regression estimated adjusted prevalences of muscle-related measures: myosteatosis, low muscle volume, and low grip strength. Cox proportional hazards models examined CCR associations with all-cause mortality, adjusting for age, sex, BMI, diabetes, and FIB-4. Causal mediation analysis evaluated the relationship between muscle- and non-muscle-related measures (eGFR, FIB4, HbA1c) as mediators of the CCR-mortality relationship. **Results:** Of 134,321 MASLD participants, mean age was 57 (SD 8), 36% were women, and mean number of CMRFs was 4 (SD 1); 8,111 underwent subsequent abdominal MRI a median of 8 years (IQR 7–9) after baseline assessment. Patients with lower CCR were older (Q1: 59, Q2: 58, Q3: 57, Q4: 56 years), more likely women (Q1: 79%, Q2: 41%, Q3: 17%, Q4: 7%), and have greater CMRFs (Q1: 4.5, Q2: 4.3, Q3: 4.2, Q4: 4.0) ($p < 0.001$). Lower CCR was associated with higher adjusted prevalence of all muscle-related measures ($p < 0.001$). Higher CCR was also associated with decreased risk of all-cause mortality (aHR 0.87, 95%CI 0.85-0.88, p-value < 0.001). In causal mediation analyses, myosteatosis and low muscle volume each significantly mediated the CCR-mortality association, accounting for 17% (95%CI 4–55%, $p = 0.02$) and 15% (95%CI 1–58%, $p = 0.04$) of the total effect, respectively; low grip strength, and non-muscle-related measures were non-significant (Figure). **Conclusion:** Lower CCR is associated with worse metrics across all measures of metabolic syndrome myopathy and independently predicts all-cause mortality. This relationship appears to be, partially mediated through myosteatosis and low muscle volume. Future studies should assess the use of CCR as a laboratory-based tool to identify adults most vulnerable to metabolic syndrome myopathy who may benefit from targeted muscle-related therapy.

Figure. Causal Mediation Analysis of Muscle and Non-Muscle-Related Mediators on Association between CCR and All-Cause Mortality



Disclosures: Melinda Wang: Nothing to Disclose, Dorothea Kent: Nothing to Disclose, Lisa Catalli: Madrigal: Advisory board, Novo Nordisk: Advisor, Giuseppe Cullaro: Ocelot Bio: Consultant, Retro Sciences: Consultant, Ipsen: Consultant, Mazen Nourredin: Nothing to Disclose, Naga Chalasani: Madrigal, Eccogene, Insitro, Boston Pharma, Chugai: Consultant, Zydus, GSK, Akero, Plaint, Altimmune: Consultant, Exact Sciences: Grant/Research Support, NIH: Grant/Research Support, Heligenics: Board member, investor, Avant Sante: Board member, investor, Ipsen, Biomea Fusion, Pfizer, Merck: Consultant, Jennifer Lai: Nestle Nutrition Institute: Grant/Research Support, Novo Nordisk: Consultant, Genfit: Consultant, Boehringer Ingelheim: Advisor, Lipocine: Site PI, Gilead: Site PI, Insmed: Consultant, Cosmo: Advisor.

2316 | ADAPT AND VCTE SHOW COMPARABLE PERFORMANCE FOR IDENTIFYING PATIENTS ELIGIBLE FOR THERAPY (F2-F3), ADVANCED FIBROSIS (F3-F4), AND CIRRHOSIS (F4) IN PATIENTS LIVING WITH MASH

Ida Lønsmann Sorribes[1] Peder Frederiksen[1] Cecilie Bager[1] Mikkel Werge[2] Liv Hetland[2] Nina Kimer[2] Marie Louise Nautrup Therkelsen[3] Morten Karsdal[1] Diana Leeming[1] Lise Lotte Gluud[4], [1]Nordic Bioscience, [2]Gastro Unit, Copenhagen University Hospital, Amager and Hvidovre Hospital, Hvidovre, Denmark, [3]Novo Nordisk Foundation Center for Protein Research & Gastro Unit, Copenhagen University Hospital, [4]Department of Clinical Medicine, Copenhagen University & Gastro Unit, Copenhagen University Hospital

Background: Following the recent approval of pharmacological therapies for metabolic dysfunction–associated steatohepatitis (MASH), there is a need for reliable non-invasive tests (NITs) to accurately identify distinct liver fibrosis subgroups to optimize patient stratification and treatment decisions. In particular, therapy-eligible fibrosis (F2-F3), advanced fibrosis (F3-F4), and cirrhosis (F4) represent clinically important subgroups. We evaluated the diagnostic performance of two well-established NITs for fibrosis assessment—the PRO-C3–based ADAPT algorithm and vibration-controlled transient elastography (VCTE)—in a Danish prospective outpatient cohort. **Methods:** This specialized single-centre, high-risk cohort included 259 patients with histologically confirmed F0–F4 MASLD from the Copenhagen Cohort of MASLD (CoCoMASLD; > 1,000 participants), recruited at Hvidovre Hospital between 2017 and 2022. Among participants, 51 (19.7%) had F2 fibrosis, 40 had F3 (15.4%), and 48 (18.5%) had cirrhosis (F4). ADAPT® was calculated using Elecsys® (Roche) PRO-C3, platelet count, age, and diabetes status, and VCTE by FibroScan® (Echosens). FIB-4 and standard biochemical parameters were collected. Predefined cut-offs for F3-F4 were ≥ 11 for ADAPT and ≥ 12 kPa for VCTE; for F4 ≥ 11 for ADAPT and ≥ 15 kPa for VCTE; for F2–F3 it was9–11

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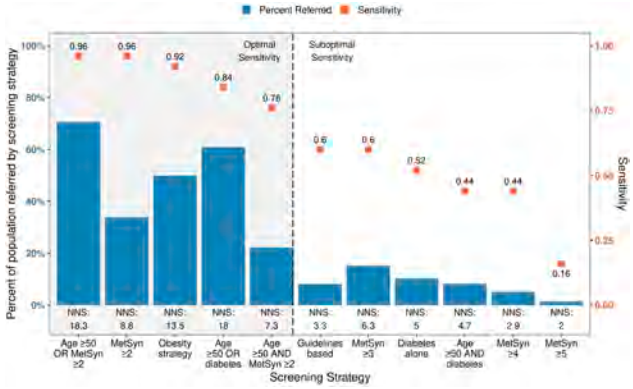
for ADAPT and 8–15 kPa for VCTE. Diagnostic performance was assessed by calculating AUROC, sensitivity, specificity, PPV, and NPV. **Results:** The cohort had a median age of 56 years (Q1–Q3: 43–64), 56.4% male, BMI 33.2 (29.4–38.1), and 41.3% had diabetes. Median AST was 48 U/L (34–63.2), ALT 69 U/L (40–98), PRO-C3 39.4 ng/mL (33–51), ADAPT 9 (7.8–10.9), and VCTE 10.3 kPa (7–15.4). For both fibrosis subgroups F3-F4/F4 alone, ADAPT and VCTE demonstrated strong diagnostic accuracy: AUROC 83/84% for ADAPT (sens 0.68/0.65, spec 0.85/0.86, PPV 70/51%, NPV 0.84/91%) and 88/88% for VCTE (sens 0.76/0.77, spec 0.83/0.84, PPV 70/52%, NPV 87/94%), with no statistically significant differences between tests (AUROC $p = 0.10/0.25$; sens $p = 0.23/0.18$, spec 0.75/0.64). While PPV was modest, limiting the ability to rule in cirrhosis (~50%), NPV was high (~91%) for ruling out. For F2–F3 fibrosis, diagnostic performance was lower: ADAPT sensitivity/spec 0.31/0.78, PPV 43%, NPV 68%; VCTE 0.61/0.67, PPV 50%, NPV 75%. Sensitivity was higher for VCTE ($p < 0.001$), whereas specificity was higher for ADAPT ($p = 0.017$). Both tests demonstrated modest rule-in capability, but some capability of ruling out F2–F3 patients (NPV 68-77%). **Conclusion:** ADAPT and VCTE performed similarly in detecting F2-F3, F3-F4, or F4 fibrosis, one being blood-based and the other imaging-based. These findings support the use of NITs for non-invasive fibrosis assessment independently of liver fibrosis subgroup.

Disclosures: Ida Lønsmann Sorribes: Nordic Bioscience: Employee, Peder Frederiksen: Nothing to Disclose, Cecilie Bager: Nothing to Disclose, Mikkel Werge: Nothing to Disclose, Liv Hetland: Nothing to Disclose, Nina Kimer: Nothing to Disclose, Marie Louise Nautrup Therkelsen: Nothing to Disclose, Morten Karsdal: Nothing to Disclose, Diana Leeming: Nordic Bioscience: Employee, Lise Lotte Gluud: Nothing to Disclose.

2317 | 40% OF FIBROTIC MASLD MISSED BY GUIDELINE-BASED SCREENING: COMPOSITE METABOLIC CRITERIA OPTIMIZE THE SENSITIVITY-EFFICIENCY TRADEOFF IN A PROSPECTIVE COMMUNITY COHORT

Alina Allen[1] Rachel Canning[2] Olivia Bobek[2] Maysa Eslami[2] Sudhakar Venkatesh[1] Joanne Benson[2] Meng Yin[2] Richard Ehman[1] Graham Rondell[2] Fang-Shu Ou[2], [1]Mayo Clinic Rochester, [2]Mayo Clinic

Background: Current guidelines recommend screening for fibrotic MASLD by identifying high-risk metabolic risk factors followed by FIB-4 scoring. Community-level performance of this strategy and evidence-based alternatives are poorly characterized. Prior comparisons focus on sensitivity alone, neglecting referral burden. We evaluated 12 screening strategies using a dual sensitivity-efficiency framework. **Methods:** This is a cross-sectional analysis of the TONES prospective community screening cohort (Olmsted County, MN). Between 2018-2026, all underwent MRI-PDFF and MRE for MASLD screening, irrespective of metabolic burden or age; liver biopsy was performed in participants with abnormal MRE and interpreted by one study pathologist blinded to imaging results. Fibrotic MASLD was defined by histologic fibrosis stage ≥ 2 or MRE LSM ≥ 3.1 kPa. MetSyn2 was defined as ≥ 2 metabolic syndrome components. Twelve strategies were evaluated for sensitivity, specificity, percent referred, and number-needed-to-screen (NNS). Strategies achieving $\geq 75\%$ sensitivity were ranked by NNS to identify optimal efficiency. **Results:** Among 621 adults (mean age 53 years; 56% women; 90% White; mean BMI 29.2 kg/m²; 10% diabetes), MASLD and fibrotic MASLD were present in 254/621 (41%) and 25/621 (4%) of the cohort, respectively; 13/25 (52%) of fibrotic MASLD had diabetes. The guideline-based strategy (metabolic risk factor identification followed by FIB-4 ≥ 1.3) achieved only 60% sensitivity, referred 8% of the population (NNS 3.3, Figure), and missed all 6 fibrotic MASLD cases under age 50. Among those with diabetes and fibrotic MASLD, 8/13 (62%) had normal AST and ALT, representing patients who would not undergo further evaluation in routine clinical practice. Strategies achieving $\geq 75\%$ sensitivity included MetSyn ≥ 2 (sensitivity 96%, NNS 8.8, 34% referred) and Age ≥ 50 AND MetSyn ≥ 2 (sensitivity 76%, NNS 7.3, 22% referred), both substantially outperforming current guidelines. **Conclusion:** Guideline-based FIB-4 screening misses 40% of community fibrotic MASLD, including all cases in adults under 50, and 62% of diabetic individuals with fibrotic MASLD. Composite metabolic criteria (MetSyn ≥ 2 alone or combined with age ≥ 50) represent the leading alternatives, offering superior sensitivity with acceptable referral burden; the optimal choice will depend on local referral capacity and acceptable sensitivity threshold. These data provide a framework for evidence-based guideline revision in community-level fibrotic MASLD screening.



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2318 | IMAGING-DEFINED MASLD WITH HISTOLOGICAL STEATOSIS GRADE S0: CAUSES AND CLINICAL IMPLICATIONS

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Background: Some patients diagnosed with MASLD by imaging show steatosis grade S0 on liver biopsy, creating a diagnostic gray zone. We investigated the frequency, causes, and clinical implications of this imaging-biopsy discordance. **Methods:** Steatosis 0 was defined as imaging-detected MASLD with biopsy-defined steatosis grade S0. We analyzed a global follow-up cohort of 3,273 biopsy-confirmed individuals

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from 16 centers to assess long-term outcomes and a paired-biopsy cohort of 1,865 patients from 40 centers to evaluate histologic evolution. Possible mechanisms were explored using MRI-PDFF assessment of segmental liver fat distribution, blinded re-reading of biopsy slides by multiple pathologists, and comparison of serial sections from the same tissue sample. **Results:** Among 3,273 individuals, 123 (3.8%) had steatosis 0. Of these, 36 (29.3%) had advanced fibrosis, consistent with burnt-out MASLD, and this subgroup accounted for all observed liver-related events; no liver-related events occurred in patients without advanced fibrosis during a median follow-up of 54 months. In the paired-biopsy cohort, 74 of 1,865 patients (4.0%) had steatosis 0 at baseline, and 69 of 74 (93.2%) remained within the S0-S1 range on follow-up biopsy. Among 516 patients assessed by MRI-PDFF, 42 showed at least one liver segment with PDFF-defined S0 despite overall MASLD, supporting heterogeneous fat distribution as a source of biopsy underestimation. Re-reading of 25 biopsy sections showed that 3-6 cases were reclassified from S0 to S1, and serial section analysis from 10 liver samples further demonstrated intra-sample variability. **Conclusion:** Imaging-defined MASLD with histological S0 is uncommon but clinically important. This phenotype reflects multiple mechanisms, including burnt-out MASLD, heterogeneous hepatic fat distribution, and pathologic sampling or reader variability. Fibrosis stage is critical for risk stratification: patients without advanced fibrosis appear low risk, whereas those with advanced fibrosis require closer attention.



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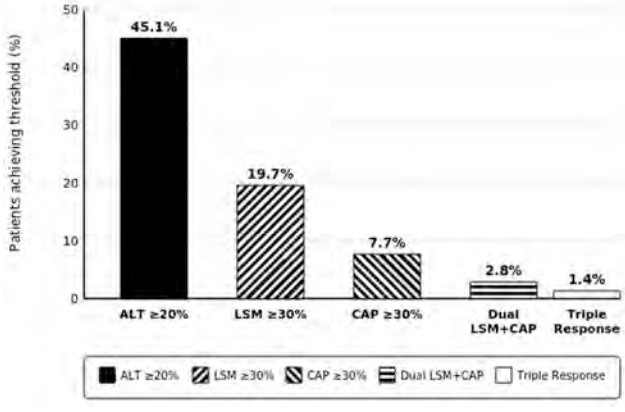
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2319 | SPONTANEOUS NON-INVASIVE TEST RESPONSE IN UNTREATED T2DM-MASLD: REAL-WORLD BENCHMARKS FOR MASH TRIAL INTERPRETATION

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Background: AASLD-endorsed NIT response thresholds, ≥30% relative reductions in liver stiffness measurement (LSM) and controlled attenuation parameter (CAP), and ≥20% ALT reduction are used for MASH pharmacotherapy monitoring. Spontaneous (placebo-equivalent) achievement of these thresholds in untreated type 2 diabetes (T2DM)–MASLD is poorly quantified. We measured one-year spontaneous response rates and their predictors to provide real-world benchmarks for trial interpretation. **Methods:** This was a retrospective analysis of 142 adults with T2DM-MASLD who had paired FibroScan-derived LSM and CAP, weight, and laboratory data at baseline and 1-year follow-up ±2 months. Patients on GLP-1 receptor agonists, SGLT2 inhibitors, and thiazolidinediones were excluded. Primary endpoints were spontaneous LSM ≥30% and CAP ≥30% relative reduction. Secondary endpoints included ALT ≥20% reduction, dual LSM+CAP response, triple LSM+CAP +ALT response, weight-stratified response, and predictors of LSM response using multivariable logistic regression. **Results:** The mean age was 54.7 ± 11.3 years, with 58.5% female; BMI was 33.1 ± 5.8 kg/m²; median baseline LSM was 5.9 kPa (IQR 4.2–9.4), and CAP was 306 dB/m (IQR 265–337). Spontaneous thresholds achievement were LSM ≥30% in 28/142 patients (19.7%; 95% CI, 13.4–26.8), and CAP ≥30% in 11/142 (7.7%; 95% CI, 3.5–12.7). Dual LSM+CAP response was uncommon (4/142; 2.8%; 95% CI, 0.7–5.6), and triple response occurred in 2/142 (1.4%). While, ALT r ≥20% response occurred in 64/142 patients (45.1%; 95% CI, 36.6–53.5) (Figure 1). LSM response was independently predicted by higher baseline LSM (advanced fibrosis ≥9.7 kPa: OR 6.92, 95% CI 2.56–18.74, $p < 0.001$) and inversely by hypertension (OR 0.30), but not by weight loss ($p = 0.203$). CAP response was weight-dependent (22.0% with ≥5% loss vs 0% if weight-stable, $p < 0.001$) and was predicted only by baseline BMI (OR 1.11, $p = 0.033$). In contrast, LSM response occurred in 15.6% of weight-stable patients and 29.3% of those losing ≥5% body weight. **Conclusion:** In T2DM-MASLD patients receiving no approved MASH-directed pharmacotherapy, spontaneous achievement of NIT response thresholds occurs at clinically meaningful rates, particularly for ALT and LSM. ALT responses largely reflect within-normal-range biochemical fluctuations rather than a true inflammatory signal. LSM improvement was strongly associated with baseline fibrosis severity rather than weight change, the CAP response, by contrast, required weight loss. These real-world background rates provide a benchmark for interpreting NIT-based endpoints in MASH trials and clinical practice, particularly in populations enriched for advanced fibrosis.

Figure 1. Prevalence of Spontaneous Achievement of AASLD-Endorsed NIT Response Thresholds in Untreated T2DM-MASLD (N=142)



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2320 | CLINICAL SUBTYPES OF COMPENSATED CIRRHOSIS IN METABOLIC DYSFUNCTION–ASSOCIATED STEATOHEPATITIS (MASH) IDENTIFIED BY UNSUPERVISED MACHINE LEARNING

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a heterogeneous condition driven by genetic, environmental, and metabolic factors. Although distinct phenotypes, such as insulin resistance–associated and lean MASLD, were described previously, differential risks of decompensation of the subgroups remain unclear. This study applies unsupervised machine learning to classify patients with compensated cirrhosis in metabolic dysfunction-associated steatohepatitis (MASH) and evaluate subgroup-specific risks of decompensation and hepatocellular carcinoma (HCC). **Methods:** We conducted a retrospective cohort study of adults with compensated MASH cirrhosis in the Mass General Brigham system (2005–2024). K-means clustering was performed to identify clinical phenotypes based on normalized clinical and laboratory variables within 3 months of cirrhosis diagnosis. The optimal cluster number was determined by the elbow method and Silhouette scores. Cox regression models were used to compare risks of decompensation and HCC across clusters. **Results:** Two clinically distinct clusters were identified among 636 MASH patients with compensated cirrhosis, with a median follow-up of 4.2 years. Cluster 1 (N = 547) was characterized by older age (mean age 60.8 vs. 53.5) and higher body mass index (BMI) (32.1 vs. 28.1 kg/m^2), whereas cluster 2 (N = 89) had higher liver enzymes (mean ALT 115.9 vs. 43.4 U/L), lower albumin level (3.5 vs. 4.1 g/dL), higher low-density lipoprotein (LDL) (91.8 vs. 87.8 mg/dL), and lower platelet count (154,400 vs. 176,700/μL) (Table 1). When compared to cluster 1, cluster 2 showed an increased risk of decompensation (HR 1.21, 95% CI 1.07–1.37), but a similar risk of HCC (HR 1.10, 95% CI 0.63-1.58). **Conclusion:** We identified two distinct clinical phenotypes of MASH patients with compensated cirrhosis: one characterized by older age and higher BMI, and the other by higher liver enzymes, lower albumin, higher LDL, and lower platelet. The second group had an increased risk of decompensation but a similar risk of HCC. These findings reveal distinct risk profiles within MASH, underscoring the need for tailored management strategies, and warrant validation in larger cohorts.

Table 1: Phenotype characteristics of two clusters of patients with compensated cirrhosis from metabolic dysfunction-associated steatotic liver disease (MASLD)

Cluster	1	2
N	547	89
Female, N (%)	253 (46.3%)	33 (37.1%)
Age, mean (SD), years	60.8 (10.7)	53.5 (11.9)
BMI, mean (SD), kg/m^2	32.1 (6.6)	28.1 (6.8)
AST, mean (SD), U/L	47.4 (23.1)	138.7 (82.6)
ALT, mean (SD), U/L	43.4 (26.2)	115.9 (101.4)
ALP, mean (SD), U/L	104.5 (43.2)	220.1 (136.1)
Total bilirubin, mean (SD), mg/dL	0.8 (0.5)	2.9 (4.3)
Albumin, mean (SD), g/dL	4.1 (0.4)	3.5 (0.7)
Creatine, mean (SD), mg/dL	0.9 (0.3)	0.8 (0.3)
Sodium, mean (SD), mEq/L	139.2 (2.5)	137.3 (2.8)
Hemoglobin A1c, mean (SD), %	6.5 (1.2)	6.2 (1.2)
HDL, mean (SD), mg/dL	50.2 (15.8)	49.7 (20.5)
LDL, mean (SD), mg/dL	87.8 (23.4)	91.8 (25.1)
Platelet, mean (SD), x10^3/μL	176.7 (72.7)	154.4 (88.9)
INR, mean (SD)	1.2 (0.2)	1.3 (0.3)

SD: standard deviation; BMI: body mass index; AST: aspartate transaminase; ALT: alanine transaminase; ALP: alkaline phosphatase; HDL: high-density lipoprotein; LDL: low-density lipoprotein; INR: international normalized ratio.

Disclosures: Peiyun Ni: Nothing to Disclose, Olga Demler: Nothing to Disclose.

2321 | PFHXS IS INVERSELY ASSOCIATED WITH HEPATIC FIBROSIS IN STEATOTIC LIVER DISEASE: A CROSS-SECTIONAL ANALYSIS OF NHANES 2017–2020

Jonathan Hong[1] Eduardo Reyes[1], [1]Mountain Area Health Education Center

Background: Per- and polyfluoroalkyl substances (PFAS) have consistently been associated wtih hepatotoxicity, with emerging evidence of sex-dependent effects on liver disease. However, the association between PFAS exposure and hepatic fibrosis across steatotic liver disease (SLD) subtypes defined by the 2023 multisociety nomenclature has not been examined. We evaluated the association between National Academies of Sciences, Engineering, and Medicine (NASEM) defined PFAS exposure and Vibration-Controlled Transient Elastography (VCTE) assessed fibrosis in Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) and Metabolic Dysfunction and Alcohol-Associated Liver Disease (MetALD). **Methods:** We analyzed NHANES 2017–March 2020 adults with VCTE-defined steatosis (CAP $\geq$275 dB/m), excluding viral hepatitis, pregnancy, and alcoholic liver disease (ALD) range alcohol use. MASLD and MetALD were classified per the 2023 Delphi consensus criteria. NASEM PFAS sum was calculated from seven serum analytes (PFOS, PFOA, PFHxS, PFNA, PFDA, PFUnDA, MeFOSAA). The primary outcome was liver stiffness measurement (LSM) $\geq$8 kPa. Survey-weighted logistic and linear regression assessed log-transformed NASEM sum with fibrosis outcomes, adjusting for age, sex, race/ethnicity, BMI, diabetes, and poverty-

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income ratio. Sex-stratified and individual PFAS component analyses were performed. **Results:** Among 3,444 adults with steatosis, 3,059 met MASLD and 151 met MetALD criteria. Complete PFAS data were available for 906 MASLD and 48 MetALD participants. Median NASEM sum was similar across subtypes (MASLD 8.5, MetALD 8.6 ng/mL). Overall, log-transformed NASEM sum was not associated with LSM $\geq$8 kPa (aOR 0.71, 95% CI 0.39–1.30; p = 0.245) or continuous LSM in MASLD (β −1.36 kPa, 95% CI −3.51 to 0.79; p = 0.193) or MetALD (β 0.08 kPa, 95% CI −0.72 to 0.88; p = 0.811). In sex-stratified analysis, the PFAS–fibrosis association was directionally stronger in males (aOR 0.59, 95% CI 0.26–1.35; p = 0.192) compared to females (aOR 0.90, 95% CI 0.21–3.98; p = 0.868), though neither reached significance. Among individual PFAS components, PFHxS was inversely associated with significant fibrosis (aOR 0.60, 95% CI 0.39–0.94; p = 0.029). No significant PFAS-by-SLD subtype interaction was observed (p = 0.483). **Conclusion:** In this early application of the NASEM PFAS framework to the 2023 SLD nomenclature, total PFAS exposure was not associated with VCTE-defined hepatic fibrosis in MASLD or MetALD. However, PFHxS was significantly and inversely associated with fibrosis, suggesting compound-specific effects that may be obscured by mixture-level analyses. PFHxS signal and sex-stratified trends warrant confirmation in larger, longitudinal cohorts with direct fibrosis assessment.
Disclosures: Jonathan Hong: Nothing to Disclose, Eduardo Reyes: Nothing to Disclose.

2322 | ENRICHMENT PANEL DESIGNED FOR THE STUDY OF CHRONIC LIVER DISEASE: TARGETED METHYLATION CFDNA ASSAY ENABLES COST-EFFECTIVE ULTRA-DEEP SEQUENCING FOR IDENTIFICATION OF TREATMENT-ELIGIBLE MASH PATIENTS

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Background: We previously reported LiquidTransformer (LT), an AI model on whole-methylome cell-free DNA (cfDNA) sequencing that outperforms guideline non-invasive tests (NITs) for detecting significant fibrosis (F2+), treatment-eligible fibrosis (F2-F3), and at-risk MASH. We designed a cfDNA methylation enrichment panel derived from LT for the study of metabolic diseases and chronic liver disease, with MASH diagnosis as the initial application. The compact footprint enables cost-effective ultra-deep sequencing. Here we test whether diagnostic performance is retained when the genome-wide footprint is reduced by more than two orders of magnitude. **Methods:** Panel regions were selected to capture disease related methylation signal, by integrating LT feature attributions with plasma and liver tissue methylation from training samples. The panel covers less than 1% of the genome. Panel content was compared at CpG and base-pair level to all major commercial methylation panels combined, including large methylome-wide research assays. Performance of three detections were assessed: significant fibrosis, treatment-eligible fibrosis, and at-risk MASH. For each task we cross-validated three variants across three independent cohorts (Duke MASLD Biobank, UMC Mainz, Akero SYNCHRONY), on samples held out from panel design: whole-methylome LT, the panel, and the panel subset overlapping commercial content. **Results:** Across all three tasks, the panel matched whole-methylome LT (AUC panel vs whole-methylome: F2+ 0.90 vs 0.90; F2–F3 0.77 vs 0.76; at-risk MASH 0.79 vs 0.78), with point estimates equivalent. The commercial-overlap subset showed substantially lower AUC across all tasks (F2+ 0.81, F2–F3 0.69, at-risk MASH 0.72), indicating that regions outside existing commercial panels carry substantial diagnostic signal. The majority of panel content, by CpG and base-pair, lay outside the combined coverage of all commercial methylation panels surveyed. **Conclusion:** A compact cfDNA methylation panel designed for chronic liver disease accurately diagnoses MASH and fibrosis across three cohorts. The performance depends on regions selected by LT that are absent from existing commercial methylation panels. Whole-methylome sequencing remains the discovery substrate; the targeted panel supports cost-effective ultra-deep cfDNA methylation profiling, translating validated diagnostic signals into a deployable assay and a scalable tool for broader chronic liver disease investigation.
Disclosures: Jörn Schattenberg: Akero: Consultant, 89Bio: Consultant, Boehringer Ingelheim: Consultant, Ipsen: Consultant, Inventiva Pharma: Consultant, Madrigal: Consultant, Northsea Therapeutics: Consultant, Novo Nordisk: Consultant, Roche: Consultant, Siemens Healthineers: Consultant, Boehringer Ingelheim: Advisor, AGED diagnostics: Stock – privately held company, Hepta Bio: Stock – privately held company, Novo Nordisk: Speaking and Teaching, Madrigal: Stock - publicly traded company, MedPublico GmbH: Speaking and Teaching, Eli Lilly: Advisor, Altimmune: Consultant, Astra Zeneca: Consultant, Gilead Science: Consultant,

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2323 | AI-ASSISTED ULTRASOUND FAT FRACTION OUTPERFORMS CONVENTIONAL ULTRASOUND MODELS FOR LIVER FAT QUANTIFICATION: A PROSPECTIVE STUDY USING MRI-PDFF AS THE REFERENCE STANDARD

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Background: Noninvasive quantification of hepatic steatosis is essential for diagnosing and monitoring MASLD. Although MR-PDFF is the most accurate noninvasive method, its use is limited by cost and availability. Ultrasound fat fraction Noninvasive quantification of hepatic steatosis is essential for diagnosing and monitoring MASLD. Although MR-PDFF is the most accurate noninvasive method, its use is limited by cost and availability. Ultrasound fat fraction (USFF) offers a low-cost, real-time point-of-care alternative, but has limited accuracy. In this study, we aim to assess the agreement of different models of USFF (DeepUSFF and conventional USFF) with MR-PDFF. **Methods:** This multicenter prospective study included patients from Stanford University, Springfield Clinic, and the University of Washington. Adults aged 18–75 years with MASLD confirmed by MR-PDFF were included. Patients with alternative causes of chronic liver disease were excluded. Ultrasound examinations were performed within 4 weeks of MR-PDFF.USFF was assessed using three models: (1) tissue attenuation imaging (TAI) alone, which measures ultrasound signal attenuation through liver tissue; (2) a multiparametric USFF (mUSFF) model combining TAI and tissue scatterer density; and (3) Deep-USFF, a deep learning–based AI model that analyzes raw radiofrequency ultrasound data to extract liver features and generate fat fraction estimates trained against MR-PDFF. Correlations with MR-PDFF were assessed using Pearson correlation coefficients, and agreement analyses were performed using Bland-Altman methods. **Results:** A total of 47 patients from three institutions were enrolled. The mean age was 58.7 years,

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the mean BMI was 33.8 kg/m², 65% were female, and 34% had diabetes.In pooled analysis, TAI-only and mUSFF demonstrated moderate correlation with MR-PDFF (TAI-R = 0.67; mUSFF R = 0.63). After applying DeepUSFF model, agreement has significantly improved (DeepUSFF R = 0.90). Site-specific analyses demonstrated similar findings. Bland-Altman analysis further confirmed the superiority of DeepUSFF compared with multiparametric [GN1] USFF. Deep-USFF demonstrated minimal bias relative to MR-PDFF (mean bias 0.11%) with narrower limits of agreement (−6.73% to 6.96%). In comparison, multiparametric USFF demonstrated greater variability and wider limits of agreement (mean bias −0.88%; −11.91% to 10.14%). **Conclusion:** Deep learning–assisted USFF estimation substantially improves agreement with MR-PDFF compared with conventional multiparametric USFF. DeepUSFF may represent a promising point-of-care noninvasive tool for steatosis assessment and longitudinal monitoring in MASLD.

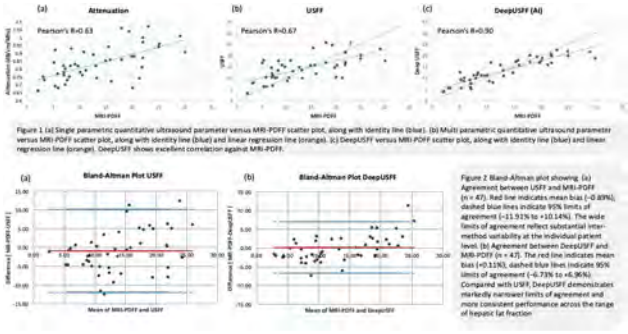


Figure 1. (a) Single parametric quantitative ultrasound parameter versus MRI-PDFF scatter plot, along with identity line (blue). (b) Multi parametric quantitative ultrasound parameter versus MRI-PDFF scatter plot, along with identity line (blue) and linear regression line (orange). (c) DeepUSFF versus MRI-PDFF scatter plot, along with identity line (blue) and linear regression line (orange). DeepUSFF shows excellent correlation against MRI-PDFF.

Figure 2 Bland-Altman plot showing. (a) Agreement between USFF and MRI-PDFF (n = 47). Red line indicates mean bias (−0.89%), dashed blue lines indicate 95% limits of agreement (−11.91% to +10.14%). The wide limits of agreement reflect substantial inter-method variability at the individual patient level. (b) Agreement between DeepUSFF and MRI-PDFF (n = 47). The red line indicates mean bias (+0.11%), dashed blue lines indicate 95% limits of agreement (−6.73% to +6.96%). Compared with USFF, DeepUSFF demonstrates markedly narrower limits of agreement and more consistent performance across the range of hepatic fat fraction

Disclosures: Negaur Iranpour: Nothing to Disclose, Amir Hossein Gougol: Nothing to Disclose, Gary Ng: Nothing to Disclose, Ronald Hidalgo: Samsung: Consultant, Samsung: Grant/Research Support, Manish Dhyani: Nothing to Disclose, Madhvi Yadav: Nothing to Disclose, Rotonya Carr: Merck: Grant/Research Support, Intercept: Consultant, Astra Zeneca: Consultant, Novo Nordisc: Consultant, Madrigal: Consultant, Boehringer: Advisor.

2324 | INTEGRATED CODING AND NON-CODING TRANSCRIPTOMICS IDENTIFY A TGFB1–E2F FIBROGENIC REGULATORY AXIS IN AFRICAN AMERICANS WITH MASLD

Tanmoy Mondal[1] Coleman Smith[2] Christopher Loffredo[3] Ruth Quartey[1] Charles Howell[4] Brent Korba[3] Zaki Sherif[1] Gail Nunlee-Bland[1] Leanna Rucker[3] Gemeyel Moses[1] Ghosh Ghosh[1], [1]Howard University, [2]Georgetown University Hospital, [3]Georgetown University, [4]Howard University College of Medicine

Background: The prevalence of MASLD in the US has risen to 30%. African Americans (AAs) demonstrate paradoxically lower MASLD prevalence despite higher metabolic risk burdens, suggesting the presence of distinct molecular regulatory mechanisms. Our previous transcriptomic studies identified dysregulation of T*GFB1* and *E2F*-associated signaling in AA MASLD patients. However, the contribution of non-coding RNA (ncRNA) networks regulating these pathways remains poorly characterized. This study integrated coding and non-coding whole-blood transcriptomic datasets to identify coordinated fibrogenic regulatory mechanisms in AA MASLD. **Methods:** Whole-blood transcriptomic datasets from AA MASLD participants and matched controls were integrated from two independent studies. The coding transcriptomic cohort included 23 MASLD and 24 controls, while the ncRNA cohort included 18 MASLD and 20 controls. MASLD was confirmed by imaging and/or liver biopsy, demonstrating hepatic steatosis with metabolic dysfunction. Global transcriptomics was performed using Affymetrix arrays, whereas miRNA/lncRNA profiling was performed using small RNA sequencing. Differential expressions, Ingenuity Pathway Analysis (IPA), canonical pathway (CP), upstream regulator, and network analyses were performed. Selected miRNAs were validated using qRT-PCR. **Results:** We identified hepatic fibrosis signaling as the top overlapping CP across both coding and ncRNA datasets. Coding transcriptomics demonstrated activation of TGFB1-centered fibrogenic networks associated with *hepatic stellate cell activation*, *IL-6 signaling*, and *hepatocellular carcinoma pathways*, while E2F-associated transcriptional programs were concurrently dysregulated within fibrosis- and cell cycle-related pathways. ncRNA transcriptomics identified 35 significantly dysregulated miRNAs and 28 ncRNAs in MASLD subjects. Among the most significant fibrosis-associated miRNAs, miR-218-5p, miR-370-3p, miR-1343-5p, miR-224-5p, and miR-193a-5p were consistently downregulated, whereas miR-206 was significantly upregulated. IPA integration demonstrated overlap between dysregulated miRNAs and pathways involving AMPK/TGFB signaling, epithelial–mesenchymal transition, and hepatic fibrosis/hepatic stellate cell activation. Additionally, dysregulated lncRNAs, including LINC01138, LINC00461, and SNHG29, were associated with proliferative signaling hubs involving *AKT*, *YAP1*, and *EZH2*. **Conclusion:** Integrated coding and ncRNA transcriptomics identified a coordinated TGFB1–E2F regulatory axis associated with hepatic fibrosis signaling in AA MASLD patients. Dysregulated miRNA and lncRNA networks appear to modulate key fibrogenic and proliferative pathways, supporting whole-blood transcriptomics as a minimally invasive platform for ancestry-informed biomarker discovery and mechanistic stratification in MASLD.

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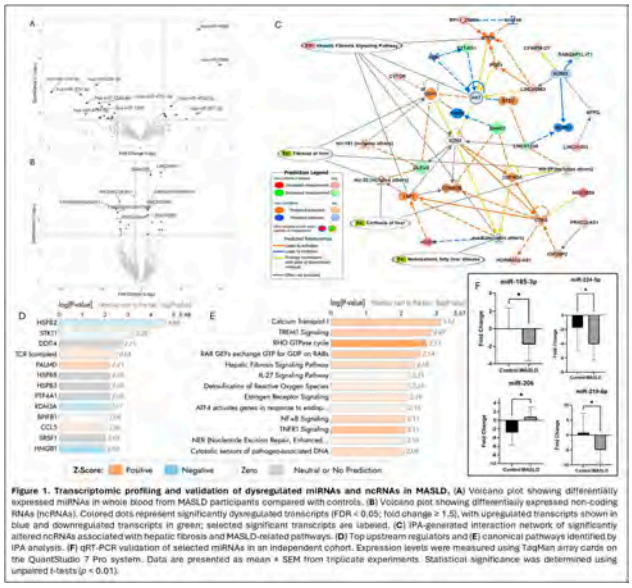


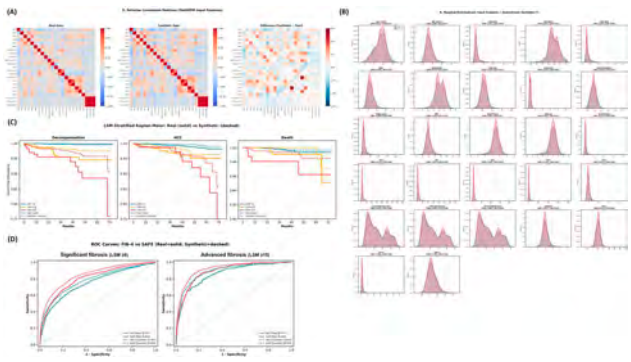
Figure 1. Transcriptomic profiling and validation of dysregulated miRNAs and ncRNAs in MASLD. (**A**) Volcano plot showing differentially expressed miRNAs in whole blood from MASLD participants compared with controls. (**B**) Volcano plot showing differentially expressed non-coding RNAs (ncRNAs). Colored dots represent significantly dysregulated transcripts (FDR < 0.05; fold change ≥ 1.5), with upregulated transcripts shown in blue and downregulated transcripts in green; selected significant transcripts are labeled. (**C**) IPA-generated interaction network of significantly altered ncRNAs associated with hepatic fibrosis and MASLD-related pathways. (**D**) Top upstream regulators and (**E**) canonical pathways identified by IPA analysis. (**F**) qRT-PCR validation of selected miRNAs in an independent cohort. Expression levels were measured using TaqMan array cards on the QuantStudio 7 Pro system. Data are presented as mean ± SEM from triplicate experiments. Statistical significance was determined using unpaired *t*-tests ($p < 0.01$).

Disclosures: Tanmoy Mondal: Nothing to Disclose, Coleman Smith: Nothing to Disclose, Christopher Loffredo: Nothing to Disclose, Ruth Quartey: Nothing to Disclose, Charles Howell: Nothing to Disclose, Brent Korba: Nothing to Disclose, Zaki Sherif: Nothing to Disclose, Gail Nunlee-Bland: Nothing to Disclose, Leanna Rucker: Nothing to Disclose, Gemeyel Moses: Nothing to Disclose, Ghosh Ghosh: Nothing to Disclose.

2325 | A PRIVACY-PRESERVING SYNTHETIC KOREAN MASLD COHORT PRESERVES FIBROSIS RISK STRATIFICATION AND NONINVASIVE TEST PERFORMANCE

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Background: SAFE has been proposed as an alternative to FIB-4 for MASLD risk stratification, but Asian validation is limited. Privacy-preserving synthetic data could enable international collaboration with patient-level data, but its ability to preserve clinical findings is uncertain. We evaluated whether TabDDPM-generated synthetic data could reproduce fibrosis risk stratification and comparative SAFE vs FIB-4 performance in a Korean MASLD FibroScan cohort. **Methods:** We applied MASLD criteria to a single-center Korean FibroScan cohort (n = 2,655; 23 continuous and 12 categorical baseline variables) and trained a TabDDPM model to generate 10,000 synthetic patients. Fidelity was assessed by standardized mean differences (SMD), Wasserstein distance, correlation preservation, and PCA/t-SNE/UMAP. Privacy was evaluated by exact-copy detection, distance-to-closest-record, k-anonymity, and re-identification risk. Clinical validity was tested by comparing FIB-4 and SAFE—neither used as model input—for advanced fibrosis (LSM ≥ 8 kPa) and cirrhosis (LSM ≥ 15 kPa), two-step screening pathways, and LSM-stratified Kaplan–Meier curves for decompensation, HCC, and death. **Results:** The synthetic cohort closely reproduced real-data distributions (mean |SMD| = 0.050, correlation preservation r = 0.974) (Figure A). Privacy was favorable: 0 exact copies, median k-anonymity = 31, re-identification risk 0.56%. Notably, downstream-derived variables not seen by the model (FIB-4, SAFE, LDL, globulin) matched real distributions (Figure B). LSM-stratified KM curves preserved dose-response gradients for decompensation, HCC, and death (log-rank $p < 0.001$), though absolute event rates were attenuated given low source event counts (Figure C). SAFE outperformed FIB-4 for significant fibrosis in both real (AUROC 0.804 vs 0.747) and synthetic data (0.844 vs 0.781), with similar superiority for advanced fibrosis (0.890 vs 0.857 real; 0.919 vs 0.892 synthetic) (Figure D). In two-step screening, SAFE ruled out more patients (65.6% real, 69.7% synthetic) than FIB-4 (51.3%, 50.4%) with higher diagnostic yield and specificity but lower sensitivity. **Conclusion:** In a Korean MASLD FibroScan cohort, TabDDPM-generated synthetic data preserved baseline distributions, multivariable correlation structure, privacy, and clinically meaningful fibrosis risk stratification, while reproducing SAFE's superior discrimination over FIB-4. These findings support synthetic Korean MASLD cohorts as privacy-preserving tools for international validation of noninvasive fibrosis algorithms; larger datasets are needed for rare-event outcome modeling.



Disclosures: Soon Kyu Lee: Nothing to Disclose, Jaejun Lee: Nothing to Disclose, SOON WOO NAM: Nothing to Disclose, Jung Hyun Kwon: Nothing to Disclose, W. Ray Kim: Nothing to Disclose, Joseph Ahn: Nothing to Disclose.

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2326 | MULTI-OMICS DEFINE DISTINCT FIBROGENIC REMODELING ENDOTYPES IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS

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Background: In Metabolic Dysfunction-Associated Steatohepatitis (MASH), progression to advanced fibrosis and cirrhosis occurs in some but not everyone, and fibrosis stage may not fully reflect fibrogenic activity. We identified inflammatory-enriched ("hot") and lower-inflammatory ("cold") fibrosis endotypes using AI-derived macrophage density. However, biologic profiles of these endotypes across fibrosis stages remain incompletely characterized.Aims: (1) To define subpopulations across fibrosis stages of MASH with distinct inflammatory-fibrogenic profiles using digital pathology, and (2) to identify the biological basis of these fibrosis-related endotypes. **Methods:** Quantitative digital pathology using LiverExplore (For Research Use Only. Not for use in diagnostic procedures; PathAI) was performed in 150 biopsy-confirmed MASH patients. Unsupervised clustering of LiverExplore features identified consensus inflammatory-fibrogenic subgroups. Conventional biomarkers, plasma proteomics (Olink), and metabolomics (Rubio) were analyzed using univariate, multivariable, and elastic net regression models adjusted for age, BMI, and sex. Top markers were prioritized by combined ranking and validated in an independent Virginia Commonwealth University transcriptomic cohort. **Results:** A total of 150 individuals with MASH spanning fibrosis stages F0–F4 (F0 = 14, F1 = 18, F2 = 56, F3 = 53, F4 = 7) underwent deep phenotyping; Masson's Trichrome staining was unevaluable in 2 cases. Consensus clustering identified active inflammatory ("hot", n = 32), intermediate mixed ("other", n = 60), and low inflammatory/metabolic ("cold", n = 58) fibrogenic endotypes (Fig. 1A). Hot fibrosis demonstrated higher PRO-C3, TSP2, ELF, fibrosis stage, liver stiffness, portal inflammation, and macrophage/neutrophil density. Cold fibrosis showed lower fibrosis stage, PRO-C3, and macrophage density, with enrichment for F0–F1 disease. Proteomics identified 155 proteins associated with hot fibrosis, enriched for immune activation, ECM remodeling, and inflammatory signaling. LY96 (TLR4 signaling) and MZB1 (plasma cell-associated ER chaperone) correlated with fibrosis and inflammatory features; LY96 was independently validated in the VCU cohort. Metabolomics demonstrated enrichment of taurine-conjugated bile acids in hot fibrosis, whereas cold fibrosis was enriched for ceramides and triglycerides, supporting a lower-inflammatory metabolic phenotype (Fig. 1B). **Conclusion:** Hot and cold fibrosis represent distinct fibrogenic rather than fixed histologic stages. Hot fibrosis reflects an inflammatory, injury-driven state, while cold fibrosis represents a metabolically driven, lower-inflammatory state. Multi-omics validation supports endotype-based patient selection beyond fibrosis stage alone to improve alignment between mechanism of action and therapeutic response in anti-fibrotic clinical development.

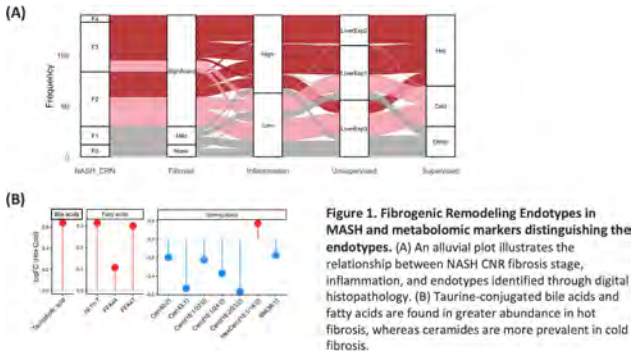


Figure 1. Fibrogenic Remodeling Endotypes in MASH and metabolomic markers distinguishing the endotypes. (A) An alluvial plot illustrates the relationship between NASH CNR fibrosis stage, inflammation, and endotypes identified through digital histopathology. (B) Taurine-conjugated bile acids and fatty acids are found in greater abundance in hot fibrosis, whereas ceramides are more prevalent in cold fibrosis.

Disclosures: Zoltan Derdak: Nothing to Disclose, Ying-Wooi Wan: Nothing to Disclose, Mingshi Gao: Nothing to Disclose, Stephen Hoang: PS Fertility: Consultant, Remedy Plan Inc.: Consultant, Banishree Saha: Nothing to Disclose, Cristina Alonso: Rubió Metabolomics, S.L.U.: Employee, Alejandro Montilla: Nothing to Disclose, Maria Martinez-Vives: Nothing to Disclose, Vandana Gupta: Nothing to Disclose, Lara Murray: Nothing to Disclose, Shima Nofallah: Nothing to Disclose, Guillaume Chhor: Nothing to Disclose, Dean Tai: Nothing to Disclose, Kutbuddin Akbary: HistoIndex Pte Ltd: Employee, Regina Lemus: Takeda Development Center Americas, Inc.: Employee, Andressa de Zawadzki: Nothing to Disclose, Diana Leeming: Nordic Bioscience: Employee, Morten Karsdal: Nothing to Disclose, Jennifer Sayne: Illumina, Inc.: Stock - publicly traded company, Quest Diagnostics: Stock - publicly traded company, Amon Asgharpour: Nothing to Disclose, Juan Pablo Arab: Nothing to Disclose, Vinayagam Arunachalam: Nothing to Disclose, Haakan Wennbo: Takeda: Employee, Paresh

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Thakker: Nothing to Disclose, Arun Sanyal: Nothing to Disclose.

2327 | HEPATOCYTE-SPECIFIC AND GLOBAL CIRCULATING EXTRACELLULAR VESICLE PROTEOMICS IDENTIFIES FIBROSIS-ASSOCIATED BIOMARKERS AND HEPATOCYTE-SPECIFIC METABOLIC SIGNATURES IN MASH

Saman Farahmand[1] Banishree Saha[2] Maria Paraskevopoulou[1] Sachin Kumar[1] Zoltan Derdak[1] Lauren Newman[3] Andrew Rowland[3] Paresh Thakker[1] hakaan wennbo[1] Alin Rai[4] David Greening[5], [1]Takeda Pharmaceutical, [2]Takeda Pharmaceuticals, [3]College of Medicine and Public Health, Flinders University, Australia, [4]Baker Department of Cardiovascular Research, La Trobe University, Melbourne, Victoria, Australia, [5]Baker Heart and Diabetes Institute, Melbourne, Victoria, Australia

Background: Metabolic dysfunction–associated steatohepatitis (MASH) poses a global health burden with few approved therapies. Liver biopsy remains the reference standard for fibrosis staging and treatment-response assessment, yet its invasiveness underscores the need for noninvasive biomarkers that track disease activity. Circulating extracellular vesicles (EVs) are candidates, as they are quantifiable in biofluids and carry cargo reflective of their cell of origin. Plasma EV proteomes respond to regulated metabolic processes in MASLD (DiStefano et al., 2024). Here, we extend this paradigm to a chronic fibrosis cohort by profiling paired global and hepatocyte-specific circulating EV proteomes across MASH fibrosis stages. **Methods:** Plasma was collected from healthy controls and clinically confirmed MASH patients (F2–F4) via academic/commercial biorepositories. Global EVs were isolated by density-based ultracentrifugation, and matched aliquots underwent ASGR1 immunoprecipitation for hepatocyte-derived EV enrichment (Newman et al., 2022). Particle concentration/size were measured by NTA, and proteomic profiling used SP3 with label-free DIA-MS. Proteins were mapped to a human liver snRNA-seq atlas for cell-of-origin assignment, followed by differential abundance and pathway enrichment analyses. **Results:** Across both workflows, we validated a conserved set of 182 hallmark circulating EV proteins—including ADAM10, STEAP3, and STX7—previously reported in plasma small EVs, supporting robust EV enrichment and proteome capture (Rai et al., Nature Cell Biology, 2025). In global EVs from MASH subjects versus controls, pathway analysis revealed dysregulated fibroinflammatory and metabolic pathways, including TGFβ signaling, complement signaling, bile acid metabolism, and coagulation. Global EVs from MASH patients were further enriched for disease-related proteins (e.g., BSG, ITGB1, LTBP1, P4HB, HSPD1) reflecting a dynamic crosstalk between hepatocytes, immune, and stromal compartments. ASGR1$^+$ EV particle concentration was positively associated with fibrosis stage and revealed distinct hepatocyte-derived signatures encompassing oxidative phosphorylation, fatty acid β-oxidation, cholesterol homeostasis and mTORC1 signaling. Top hepatocyte-specific biomarkers included PCSK9, LAMA2, LUM, CFB, and the hepatocyte-exclusive bile salt exporter ABCB11. **Conclusion:** Paired global and hepatocyte-specific EV proteomics support a noninvasive strategy to monitor metabolic, immune, and fibrotic processes driving MASH fibrosis progression. Global EVs captured broad inflammatory and profibrotic signaling, while ASGR1$^+$ hepatocyte derived EVs increased with fibrosis stage and revealed distinct hepatocellular dysfunction. Together, these findings highlight the added value of ASGR1$^+$ EVs in resolving hepatocyte-specific disease biology beyond bulk circulating EV analyses.

Disclosures: Saman Farahmand: Nothing to Disclose, Banishree Saha: Nothing to Disclose, Maria Paraskevopoulou: Nothing to Disclose, Sachin Kumar: Nothing to Disclose, Zoltan Derdak: Nothing to Disclose, Lauren Newman: Nothing to Disclose, Andrew Rowland: Nothing to Disclose, Paresh Thakker: Nothing to Disclose, hakaan wennbo: Nothing to Disclose, alin rai: Nothing to Disclose, david greening: Nothing to Disclose.

2328 | MISSING THE MARK: CHALLENGES IN SCREENING FOR METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS IN PEOPLE UNDER 40

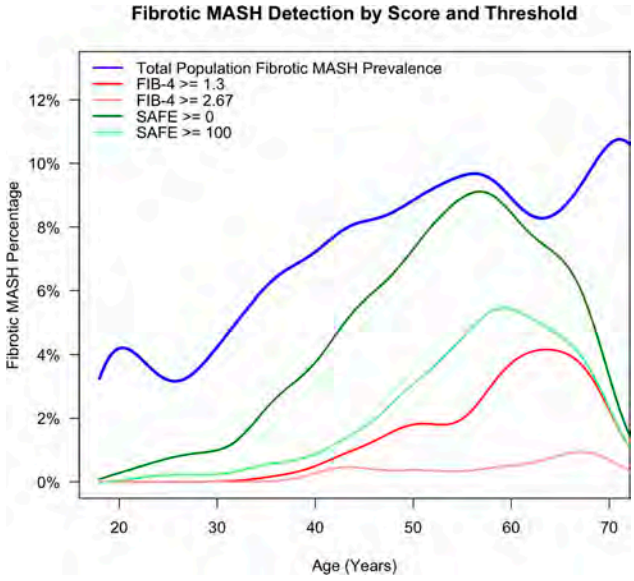
Thuy-Duyen Nguyen[1] W. Ray Kim[2], [1]Mayo Clinic, [2]Mayo Clinic Arizona

Background: Young adults with metabolic dysfunction-associated steatohepatitis (MASH) represent the highest lifetime-risk group for liver-related complications, standing to benefit most from currently available interventions. Screening for early MASH in this group is challenging because the prevalence of fibrosis is low and the performance of non-invasive markers remains poorly characterized. We evaluated age-stratified performance of the FIB-4 index in a U.S. population sample, in comparison to the SAFE score, a multivariable score that includes metabolic parameters, including diabetes and body mass index. **Methods:** Using National Health and Nutrition Examination Survey (NHANES) 2017–2023 data, we measured the prevalence of fibrotic MASH, defined as a liver stiffness measurement (LSM) $\geq$ 8.0 kPa with a controlled attenuation parameter (CAP) $\geq$ 275 dB/m or LSM $\geq$ 15.0 kPa regardless of CAP by vibration-controlled transient elastography (VCTE). Among the survey

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respondents, at-risk individuals were identified by the presence of obesity/overweight, prediabetes/Type 2 diabetes, or ≥ 2 cardiometabolic risk factors. We evaluated the diagnostic performance of FIB-4 with thresholds of 1.3 and 2.67, and SAFE with thresholds of 0 and 100, for identifying fibrotic MASH across age strata from 20 to 70. **Results:** Among the at-risk subjects in NHANES 2017–2023, projecting to 84 million US civilian adults, the prevalence of fibrotic MASH was 8.2%. The prevalence was lower in the 20–29 and 30–39-year-old strata with fibrotic MASH found in 5.1% and 7.5%, respectively. In Figure 1, FIB-4 ≥1.3 identified 0% of cases in the 20–29-year-old group and 1.7% in the 30–39-year-old group. The traditional 'rule-in' threshold of SAFE, namely >100, demonstrated better sensitivity at 5.4% in the 20–29 year-old group and 7.3% in the 30–39 year-old group. The SAFE score ≥0 threshold further increased the sensitivity to 22.0% and 31.6% in the corresponding age groups. For the AUROC analysis, SAFE consistently outperformed FIB-4 across all age strata (0.725–0.768 vs 0.503–0.573), with the largest performance gap in individuals <40 years. Specifically, in the 20–29 age group, the SAFE AUROC was 0.738 [95% CI: 0.620–0.856] compared to a FIB-4 AUROC of 0.556 [95% CI: 0.424–0.688], while in the 30–39 age group, the SAFE AUROC was 0.725 [95% CI: 0.654–0.796] compared to 0.528 [95% CI: 0.435–0.620] for FIB-4. Sensitivity analysis using LSM > 10 yielded similar results. **Conclusion:** In this important age group under 40 years, a group with high lifetime risk, the current FIB-4–based screening strategies are ineffective for identifying fibrotic MASH. Alternative approaches incorporating metabolic parameters, such as the SAFE score, demonstrate improved performance but may require age-specific optimization. These findings highlight a critical gap in early detection and the need for tailored screening strategies in younger populations.



Disclosures: Thuy-Duyen Nguyen: Nothing to Disclose, W. Ray Kim: Nothing to Disclose.

2329 | CT1 IS A VIABLE, SCALABLE NIT IN THE SECOND STEP OF THE MASLD SCREENING CARE PATHWAY

Niharika Samala[1] Kento Imajo[2] Atsushi Nakajima[3] Masato Yoneda[4] Adriaan Holleboom[5] Stephen Harrison[6] Winston Dunn[7] Dan Yock Young[8] Mark Mutiah[8] Mazen Noureddin[9], [1]Indiana University School of Medicine, Indianapolis, Indiana, USA, [2]Shin-yurigaoka General Hospital, Kawasaki, Japan, [3]National Hospital Organization Yokohama Medical Center, Japan, [4]Yokohama City University Graduate School of Medicine, Yokohama, Japan, [5]Amsterdam UMC, Amsterdam, The Netherlands., [6]Summit Clinical Research, San Antonio, Texas, USA, [7]University of Kansas Medical Center, Kansas, USA, [8]National University of Singapore, Singapore, [9]Houston Methodist Hospital, Houston, Texas, USA

Background: Current practice guidance suggest screening individuals at risk of metabolic dysfunction-associated steatohepatitis (MASH) using two-step sequential noninvasive tests (NIT) to identify MASH patients with significant disease for referral to specialist care. However, compliance to the MASH screening pathway is sub-optimal, partly due to limited access to NITs. We evaluated sequential screening strategies starting with FIB-4, followed by either vibration controlled transient elastography (VCTE) or corrected T1 (cT1), for the identification of at-risk MASH (treatment eligible MASH). **Methods:** We conducted a pooled analysis using data from individuals with biopsy-proven MASLD enrolled in four observational studies (conducted in United States, The Netherlands, Japan, and Singapore) alongside standard clinical assessment. Accurate risk stratification for those with biopsy confirmed at-risk MASH was assessed for FIB-4 <1.3 (or < 2 for ≥65 years) and 1.3-2.67 (or 2.0-2.67 for ≥65 years), VCTE ≥8kPa and cT1 ≥800ms, individually and applied sequentially. Diagnostic accuracy statistics were reported to allow different pathways to be compared. **Results:** Among 578 individuals included in the analysis (41% female; median age: 56 [50, 63] years; median BMI: 31 [28, 34] kg/m^2 ; 46% type 2 diabetes), 57% had MASH, 34% at-risk MASH and 31% had advanced fibrosis on biopsy. In those with intermediate FIB-4 (n = 155), 68% had MASH, 48% had at-risk MASH on biopsy. The two-step stratification with either VCTE (sensitivity: 55% ; specificity: 82%) or cT1 (sensitivity: 58%; specificity: 83%) in intermediate FIB-4 performed comparably in identifying at-risk MASH. In the intermediate-risk FIB-4 group, adding cT1 ≥800ms

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as third step after VCTE (8-12kPa), only marginally increased specificity (86%), while lowering sensitivity (53%) compared to using cT1 ≥ 800ms alone as the second step. Notably, in those with low FIB-4 (< 1.3, or < 2; n = 346), 48% had MASH and 22% had at-risk MASH on biopsy. Even in this low-risk group cT1 ≥ 800 ms identified 83% of those with at-risk MASH. **Conclusion:** In the MASH screening pathway, cT1 is a viable and scalable alternative to VCTE as the second step NIT. Our study results suggest that cT1, an MRI adaptable technology, could potentially increase patient access to MASH screening in non-urban settings without access to VCTE.

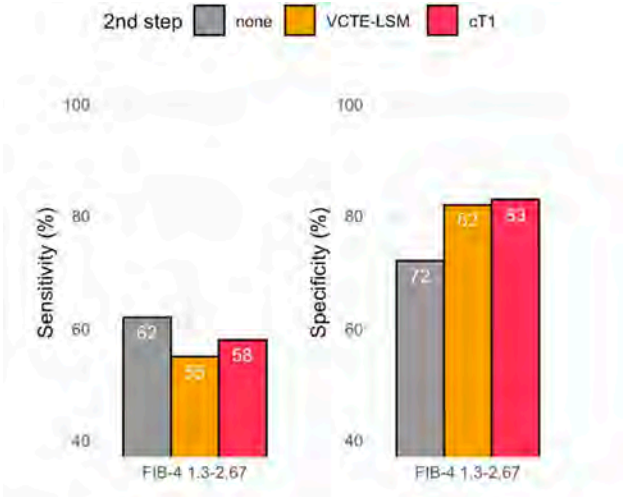


Figure. The sensitivity (left) and specificity (right) of the two-step risk stratification strategies, starting with FIB-4, followed by either VCTE-LSM (≥8kPa) or cT1 (≥800ms) as the second tests.

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2330 | REDUCING CV RISK IN PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS INDEPENDENT OF BASELINE BASED ON LP(A) AND LDL LOWERING BY RESMETIROM

Meena Bansal[1] Rebecca Taub[2] Dominic Labriola[2] David Soergel[2] Yestle Kim[2] Naim Alkhouri[3] Mazen Noureddin[4] Seth Baum[5] Rohit Loomba[6], [1]Icahn School of Medicine at Mount Sinai (ISMMS), [2]Madrigal Pharmaceuticals, [3]Summit Clinical Research, [4]Houston Methodist Hospital, [5]Florida Atlantic University, [6]University of California, San Diego

Background: Patients with metabolic dysfunction-associated steatohepatitis (MASH) have high cardiovascular morbidity and mortality. Resmetirom, a selective thyroid hormone receptor-beta agonist, is approved for treatment of patients with noncirrhotic MASH with moderate to advanced liver fibrosis. Resmetirom reduces atherogenic lipids and lipoproteins. In a secondary analysis of the Phase 3 MAESTRO-NASH clinical trial, the effects of resmetirom over 52 weeks on MASH efficacy parameters, atherogenic lipids, lipoproteins, and safety were evaluated according to baseline statin use. **Methods:** Data from the MAESTRO-NASH and MAESTRO-NAFLD-1 trials were analyzed. Analyses assessed MASH and lipid responses, shift in LDL and lipoprotein(a) [Lp(a)] risk profiles, and standard safety assessments including serial liver enzymes and adverse events according to baseline statin use. **Results:** Approximately half (n = 473; 49%) of MAESTRO-NASH participants were on statins at baseline. Atorvastatin was the most commonly used statin (47.1%), and 26.9% of statin-treated patients were receiving high-intensity statin therapy. Baseline characteristics were generally similar across statin subgroups; however, a greater proportion of patients receiving statins, compared with those not receiving statins, had diabetes (79.5% vs 55.0%), dyslipidaemia (100% vs 43.8%), and advanced fibrosis (F3: 64.3% vs 56.6%) at baseline. The dual primary endpoints remained directionally consistent with the overall MAESTRO-NASH results and were nominally statistically significant for both resmetirom 80 mg and 100 mg versus placebo, regardless of baseline statin use.A numerically greater reduction in liver fat as measured by MRI-PDFF at Week 52 was also observed with resmetirom compared with placebo irrespective of baseline statin use. At Week 24, placebo-corrected reductions were observed for LDL-C, ApoB, TGs, and Lp(a) across statin and non-statin subgroups. In patients on statins 44.4% with LDL-C $\geq$ 70 mg/dL at baseline shifted to LDL-C < 70 mg/dl with 100 mg resmetirom; 36.3% and 37.5% with Lp(a) $\geq$ 30 or $\geq$ 50 mg/dL at baseline shifted to < 30 or < 50 mg/dL with 100 mg resmetirom. Patients in the highest CV risk quartile of baseline Lp(a) showed significant reductions in Lp(a) with resmetirom independent of statin use (Figure). **Conclusion:** Independent of statin use, treatment with resmetirom was efficacious at multiple MASH endpoints and improved lipid profiles for LDL-C, ApoB and Lp(a).

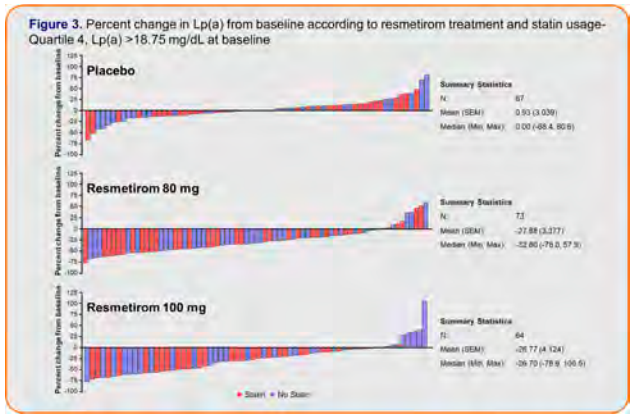


Figure 3. Percent change in Lp(a) from baseline according to resmetirom treatment and statin usage-Quartile 4, Lp(a) >18.75 mg/dL at baseline

Disclosures: Meena Bansal: Madrigal: Advisor, Fibronostics: Advisor, NOVO Nordisk: Advisor, GSK: Advisor, Merck: Advisor, Boeheringer-Ingelheim: Advisor, Boston Pharma: Advisor, The Kinetix Group: Advisor, Corcept: Advisor, Rebecca Taub: Nothing to Disclose, Dominic Labriola: Nothing to Disclose, David Soergel: Nothing to Disclose, Yestle Kim: Nothing to Disclose, Naim Alkhouri: Madrigal: Speaking and Teaching, Novo Nordisk: Consulting, Novo Nordisk: Grant/Research Support, Corcept: Grant/Research Support, Echosens: Speaking and Teaching, Perspectum: Consultant, Cima: Consultant, Fibronostics: Consultant, 89Bio: Grant/Research Support, Inventiva: Grant/Research Support, Merck: Grant/Research Support, Pfizer: Grant/Research Support, Ipsen: Speaking and Teaching, Intercept: Speaking and Teaching, Madrigal: Consulting, Research Funding, Novo Nordisk: Consulting, Research Funding, Inventiva: Research Funding, Boehringer Ingelheim: Consulting, Research Funding, Corcept: Research Funding, Ipsen: Consulting, Research Funding, Gliead: Consulting, Research Funding, Speaking, Perspectum: Consulting, Research Funding, Cima: Advisor, 89Bio: Consulting, Research Funding, Arbutus: Grant/Research Support, GSK: Grant/Research Support, Regeneron: Grant/Research Support, AstraZeneka: Grant/Research Support, Madrigal: Grant/Research Support, Akero: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Eli Lilly: Grant/Research Support, Gilead: Grant/Research Support, Galectin: Grant/Research Support, Boston Pharma: Grant/Research Support, Mazen Noureddin: Akero: Advisor, Alligos: Advisor, Altimmune: Advisor, AstraZeneca: Advisor, Boehringer Ingelheim: Advisor, Boston Pharma: Advisor, Cytodyn: Advisor, GSK: Advisor, Lilly: Advisor, Madrigal: Advisor,

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2331 | SCALE-MASLD: SCALING CARE PATHWAYS FOR ADVANCED LIVER ENGAGEMENT IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

Rena Fox[1] Kenneth Cusi[2] Sun Kim[1] Diana Barb[2] Anu Sharma[2] Gopanandan Parthasarathy[1] Varalakshmi Niranjan[1] Bilal Hameed[3] Radha Pachpor[4] Kristi Cohn[4] Paul Kwo[5], [1]Stanford University School of Medicine, Stanford, CA, [2]University of Florida, [3]University of California San Francisco, San Francisco, CA, [4]Petauri Kinect, [5]Stanford University Medical Center

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) affects approximately 38% of the global adult population, including 60-70% of individuals with type 2 diabetes and 70-80% with obesity, yet it remains underdiagnosed. While guidelines recommend screening for MASLD related fibrosis in high-risk populations, implementation in routine clinical practice remains limited. Electronic health record (EHR) enabled MASLD pathways are needed to streamline screening, risk stratification, and diagnosis, particularly in primary care where clinical demands compete for early identification and management. **Methods:** Building upon the framework established in a previous study involving four health systems, this pilot project scales EHR-enabled MASLD care pathway interventions to an additional six institutions: University of Florida, Stanford University, University of California, San Francisco, Duke Health, Methodist, and Northwestern University. Table 1 depicts interventions deployed. Targeted education was delivered to participating clinicians. Performance was evaluated using a common data framework measuring baseline (2-6 months) and intervention (6-12 months) time frames. **Results:** Preliminary data from three of the six health systems identified 6,283 patients seen in participating primary care and endocrinology clinics. Among the 6,283 patients seen at baseline, 63.3% (3,976) had labs available for FIB-4 calculation and were eligible for fibrosis screening. Of the 3,976 patients with available labs, 18% (723) met criteria for secondary assessment (i.e., FIB-4 $\geq$1.3). Of the 723 patients, 28.2% (204) were referred for secondary assessment (VCTE and/or hepatology referral), and 13.6% (99) completed VCTE and/or hepatology referral.Preliminary follow-up data from two of the six health systems identified 11,159 patients seen in participating clinics. Of the 11,159 patients seen over the follow-up period (ranging from 4-12 months), 46% (5,145) had labs available for FIB-4 calculation and were eligible for fibrosis screening. Of the 5,145 patients with available labs, 14.8% (763) met criteria for secondary assessment (i.e., FIB-4 $\geq$1.3). Of the 763 patients, 20.4% (156) were referred for secondary assessment (VCTE and/or hepatology referral), and 21.2% (162) completed VCTE and/or hepatology referral.Data collection underway at 5 of 6 systems. **Conclusion:** Baseline data highlights major gaps in MASLD fibrosis assessment in high-risk patients. Further data collection is needed to evaluate the impact of the EHR-enabled interventions on MASLD fibrosis assessment. However, early data suggest modest improvements in follow-up rate of referral to secondary diagnostics.

Table 1:

Institution	University of Florida	UCSF	Stanford University
Target population	DM only	DM and/or Obesity	DM only
Care setting	Internal Medicine and Endocrinology	Internal Medicine	Primary care
Intervention	System-initiated Care Path[1]	Back-end FIB-4 Calculation[2]	Clinician-activated Age Adjusted FIB-4 SmartPhrase[3]
Total, no. of clinicians	57	115	30

Intervention definitions:

1. System-initiated: EPIC clinical care path infrastructure using silent Our Practice Advisories (OPAs) and reminders to prompt FIB-4 screening at the point of care.

2. Back-end: Retrospective FIB-4 calculation across patient panels with outreach for high and intermediate risk patients.

3. Clinician-activated: An age-adjusted FIB-4 SmartPhrase that facilitates real-time calculation of the FIB-4 score, alongside interpretation and recommendations for subsequent actions.

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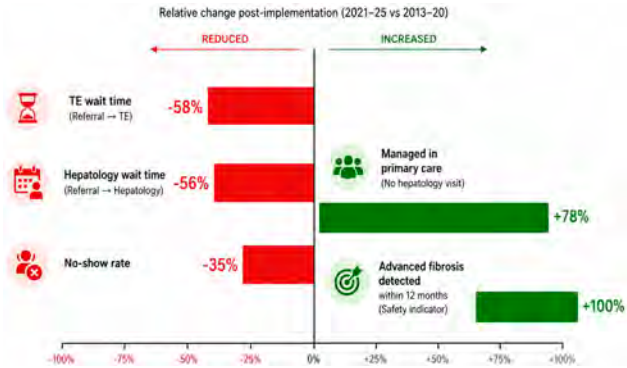
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BioSciences: Consultant, Tune Therapeutics: Consultant, Mirum: Consultant, Target Registries: Advisor, Takeda: Advisor, Lygenesis: Advisor, Ausper Bio: Advisor.

2332 | NON-INVASIVE TWO-STEP TRIAGE IMPROVES ACCESS TO HEPATOLOGY CARE AND ACCELERATES DETECTION OF ADVANCED LIVER FIBROSIS IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE: A TERTIARY CARE PROGRAM EVALUATION

Yasamin Farbod[1] Neha Sharma[1] France Martineau[1] Dana Kablawi[2] Philip Wong[1] Xun Zhao[1] Marc Deschenes[1] Tianyan Chen[1] Sahar Saeed[3] Amine Benmassaoud[1] Giada Sebastiani[2], [1]McGill University Health Centre, [2]McGill University, [3]Queen's University

Background: The growing burden of metabolic dysfunction-associated steatotic liver disease (MASLD) is placing increasing pressure on hepatology services. Although transient elastography (TE; FibroScan®) is recommended as a first-line non-invasive fibrosis assessment tool, limited access to TE and specialist consultation remains a major barrier to timely care. In 2021, our tertiary hepatology program implemented a biomarker-guided, TE-confirmed two-step triage pathway to optimize resource allocation by prioritizing high-risk patients while safely retaining low-risk patients in primary care. We evaluated the impact of this model on access to TE and hepatology services, referral efficiency, referral efficiency, and early detection of advanced fibrosis. **Methods:** We conducted a quasi-experimental study including all consecutive referrals for liver assessment between 2013-2020 (pre-implementation) and 2021-2025 (post-implementation). The triage algorithm used age-adjusted FIB-4 cut-offs as the first tier (low risk: <1.3 if <65 years or <2.0 if ≥ 65 years), with non-low-risk patients proceeding to TE for fibrosis confirmation. Primary outcomes were time from referral to TE and time from referral to hepatology consultation. Secondary outcomes included the proportion of patients managed without in-person hepatology consultation, hepatology no-show rate, and detection of advanced fibrosis ($\geq$ F3) within 12 months of referral as a safety indicator. **Results:** Among 3,953 patients with MASLD who underwent TE (mean age 62; 73% male), 1,750 (44.3%) were pre- and 2,203 (55.7%) post-implementation. Following implementation of the two-step triage pathway, mean time from referral to TE decreased from 13.2 to 5.5 months (absolute reduction −7.7 months; 95% CI -8.9, -6.5). Mean time from referral to hepatology consultation decreased from 30 to 13.2 months (absolute reduction −16.8 months; 95% CI -18.5, -15). The proportion of referrals managed without hepatology consultation increased from 45% to 80%, while hepatology no-show rates declined from 23% to 15%. As a safety signal, the proportion of patients diagnosed with advanced fibrosis within 12 months of referral doubled from 10% to 20%, consistent with improved prioritization and earlier identification of higher-risk patients. Relative changes for all outcomes are reported in the Figure. **Conclusion:** Implementation of a biomarker-guided, TE-confirmed two-step triage pathway substantially reduced delays in access to liver care, improved referral efficiency, and accelerated detection of advanced fibrosis in patients with MASLD. These real-world findings support scalable, cost-neutral strategies to decongest hepatology services and improve equitable access to specialized liver care in the context of population-level management of the growing MASLD epidemic.



Disclosures: Yasamin Farbod: Nothing to Disclose, Neha Sharma: Nothing to Disclose, France Martineau: Nothing to Disclose, Dana Kablawi: Nothing to Disclose, Philip Wong: Nothing to Disclose, Xun Zhao: Nothing to Disclose, Marc Deschenes: Nothing to Disclose, Tianyan Chen: Nothing to Disclose, Sahar Saeed: Novo Nordisk: Consultant, Amine Benmassaoud: Nothing to Disclose, Giada Sebastiani: Novo Nordisk: Consultant, Abbvie: Speaking and Teaching, Merck: Consultant, Gilead: Speaking and Teaching, Eli Lilly: Consultant, GSK: Advisor, Novo Nordisk: Consultant, Novo Nordisk: Grant/Research Support, Lupin: Speaking and Teaching, Gilead: Advisor, Boheringer Ingelheim: Speaking and Teaching, Echosens: Advisor.

2333 | TITLE: SERUM ECM BIOMARKERS DISCRIMINATE MASH FIBROSIS AND DISEASE ACTIVITY: MULTI-OMICS PROTEOMIC CORRELATES IN A JAPANESE COHORT

Ruixue Hou[1] Ali Ebrahimi[2] Vandana Gupta[2] Hiroaki Yashiro[2] Jen-Chieh Chuang[1] Zoltan Derdak[1] Saman Farahmand[2] Shinichi Aishima[3] Hideyuki Hyogo[4] Yuichiro Eguchi[5] Eisuke Murakami[6] Masato Yoneda[7]

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Background: Background & Aims: Non-invasive biomarkers that accurately stage hepatic fibrosis and quantify disease activity remain an unmet need in MASH. Serum ECM biomarkers reflecting collagen synthesis and degradation are mechanistically plausible candidates, but integration with multi-modal molecular and tissue-level data from the same cohort remains limited. We evaluated the discriminative performance of serum ECM biomarkers and characterized their proteomic correlates in a Japanese MASH cohort with multi-omics data. **Methods:** Serum ECM biomarkers were profiled in a Japanese biopsy-confirmed MASH cohort (F0–F4; n = 242). The panel included markers of fibrolysis (C4M, CTX-III), fibrogenesis/matrix turnover (PRO-C3, PRO-C4, PRO-C5, PRO-C6), perisinusoidal fibrosis (PRO-C8, PRO-C18L), and fibrosis-associated markers including TSP-2, C6Mα3, ELF, HA, PIIINP, and TIMP-1. Fibrosis- and NAS-based endpoints (significant fibrosis ($F \geq 2$), advanced fibrosis ($F \geq 3$), NAS group (NAS < 4, NAS > = 4), Active MASH with Significant Fibrosis (FibStage > = 2 & NAS > = 4), Active MASH with Advanced Fibrosis (FibStage > = 3 & NAS > = 4)) were assessed by ROC-based univariate analysis. Multivariate elastic net models were generated using the ECM panel alone or combined with FIB-4, AST, and ALT. Serum ECM biomarkers were correlated with SomaScan serum proteomics (11K proteins) by Spearman correlation, followed by Reactome over-representation analysis. Correlated proteins were integrated with single nucleus RNA-sequencing (sNuc-seq) data from patients with MASH to map potential liver source cells. **Results:** TSP-2 and PRO-C3 were the top-performing biomarkers, positively associated with all five disease-state variables, with AUCs ranging from 0.73–0.88 and 0.68–0.73, respectively. C4M and C6Mα3 were inversely associated with fibrosis and active MASH, whereas PRO-C6 and CTX-III showed no significant associations. TSP-2 was retained across all multivariate models, but no model outperformed univariate TSP-2. TSP-2 and PRO-C3 correlated with 255 and 1348 SomaScan serum proteins enriched for ECM remodeling, collagen formation/degradation, and fibrogenesis pathways, with THBS2, ADAMTSL2, C7, and COL5A1 among the strongest correlates. These proteins were enriched in the liver mesenchyme and validated in independent multi-omics MASH datasets, anchoring the serum ECM signal in fibrogenic biology. Inversely associated markers were linked to inflammatory and immune pathways. **Conclusion:** In a Japanese MASH cohort, TSP-2 and PRO-C3 were the most informative serum ECM biomarkers for fibrosis staging and disease activity and were strongly anchored to molecular and cellular signatures, supporting their prioritization for prospective validation.

Disclosures: Ruixue Hou: Takeda Pharmaceuticals: Employee, Ali Ebrahimi: Nothing to Disclose, Vandana Gupta: Nothing to Disclose, Hiroaki Yashiro: Takeda Pharmaceuticals: Employee, Jen-Chieh Chuang: Nothing to Disclose, Zoltan Derdak: Nothing to Disclose, Saman Farahmand: Nothing to Disclose, Shinichi Aishima: Nothing to Disclose, Hideyuki Hyogo: Nothing to Disclose, Yuichiro Eguchi: Nothing to Disclose, Eisuke Murakami: Nothing to Disclose, Masato Yoneda: Nothing to Disclose, Haakan Wennbo: Takeda: Employee, Paresh Thakker: Nothing to Disclose, Bernard Allan: Nothing to Disclose, Hirokazu Takahashi: Sysmex: Grant/Research Support, Novo Nordisk: Speaking and Teaching, Taisho: Speaking and Teaching, Takeda: Grant/Research Support, Lilly: Speaking and Teaching, Boehringer Ingelheim: Speaking and Teaching, Atsushi Nakajima: Nothing to Disclose, Maria Paraskevopoulou: Nothing to Disclose, Banishree Saha: Nothing to Disclose.

2334 | REAL-WORLD PERFORMANCE OF ULTRASOUND FOR CIRRHOSIS DETECTION: SIGNIFICANT OVERDIAGNOSIS COMPARED TO MAGNETIC RESONANCE ELASTOGRAPHY

Morgan Ford[1] Garrett Coleman[1] William Southall[1] Jad Allam Saab[1] Elizabeth Statham[1] Fernando Bril[1] Meagan Gray[1], [1]University of Alabama at Birmingham

Background: Ultrasound (US) is commonly ordered as an initial evaluation in patients with liver disease because it is inexpensive and easily accessible in clinical practice. Prior studies assessing the diagnostic accuracy of US for cirrhosis were largely performed in higher prevalence populations. We evaluated the accuracy of US compared with magnetic resonance imaging (MRE) for detection of cirrhosis in a low prevalence population. **Methods:** This was a retrospective analysis of real-world patients who underwent both liver US and MRE within one year of each other. Cirrhosis on US was defined by radiology reports describing the liver as “nodular” or “cirrhotic.” MRE-defined cirrhosis was defined as liver stiffness ≥ 5 kPa. **Results:** A total of 521 patients were included (54 ± 13 years; 55.3% female; 75.0%

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White, 16.4% African American, and 8.6% other). The predominant liver disease etiologies were metabolic dysfunction-associated steatotic liver disease (MASLD, 69.7%) and metabolic and alcohol-related liver disease (Met-ALD, 9.4%). Mean BMI was 33.5 ± 6.9 kg/m2. Diabetes was present in 23.6% of patients, with mean hemoglobin A1C of 6.1 ± 1.2%. Cirrhosis prevalence by MRE was 6.3% (n = 33). US identified cirrhosis in 120 patients, of whom 25 had confirmed cirrhosis on MRE and 95 did not. Among 401 patients without cirrhosis on US, 8 had cirrhosis on MRE and 393 did not. Compared with MRE, US demonstrated a sensitivity of 75.8%, specificity of 80.5%, positive predictive value of 20.8%, and negative predictive value of 98.0%. **Conclusion:** Ultrasound demonstrated moderate sensitivity and specificity but poor positive predictive value for detection of cirrhosis compared with MRE in this MASLD-predominant cohort. Nearly 4 out of 5 patients identified as cirrhotic on ultrasound did not meet MRE criteria for cirrhosis. Because ultrasound findings frequently influence cirrhosis labeling, surveillance strategies, and clinical management in real-world practice, these findings have important implications for patient care. Consistent with prior reports, our findings suggest US may function better as a rule-out rather than rule-in test for cirrhosis in MASLD populations. The markedly low PPV observed in this low-prevalence cohort highlights the influence of disease prevalence on diagnostic utility. Confirmatory fibrosis assessment with elastography-based modalities may be warranted in patients with ultrasound findings suggestive of cirrhosis.

Disclosures: Morgan Ford: Nothing to Disclose, Garrett Coleman: Nothing to Disclose, William Southall: Nothing to Disclose, Jad Allam Saab: Nothing to Disclose, Elizabeth Statham: Nothing to Disclose, Fernando Bril: NovoNordisk: Consultant, NovoNordisk: Speaking and Teaching, Boehringer Ingelheim: Consultant, Madrigal: Consultant, Boehringer-Ingelheim: Speaking and Teaching, Meagan Gray: NovoNordisk: Consultant, Madrigal Pharmaceuticals: Consultant, Intercept Pharmaceuticals: Consultant, Boehringer Ingelheim: Consultant.

2335 | INTENTIONAL CALCULATION OF FIB-4 BY PRIMARY CARE PROVIDERS PREDICTS HEPATOLOGY SPECIALTY CARE REFERRAL

Alejandra Meza[1] Jonathan Dranoff[2], [1]Yale School of Medicine, [2]Yale University

Background: Chronic liver disease affects over 1.5 billion people worldwide, with Metabolic dysfunction-Associated Steatotic Liver Disease (MASLD) as the leading cause. The Fibrosis-4 (FIB-4) Index is a low-cost, validated tool for risk stratification of patients with MASLD and other chronic liver diseases. FIB-4 ≥ 1.3 should prompt elastography or hepatology referral. However, this score remains underutilized, and appropriate follow-up is suboptimal. This project aimed to evaluate both the rates of appropriate follow-up after identification of an elevated FIB-4 score and the extent of provider utilization of the FIB-4 score in clinical practice. **Methods:** We conducted a retrospective cross-sectional study of adult patients (≥ 18 years) seen at Fair Haven Community Health Care (New Haven, CT) over the past two years. Patients with available AST, ALT, and platelet counts were included to calculate FIB-4 scores; those with FIB-4 ≥ 1.3 formed the study cohort. Data were extracted from the electronic medical record. Descriptive statistics were used to characterize the cohort. Group comparisons were performed using Chi-square or Fisher's exact test for categorical variables and t-test or Mann–Whitney U for continuous variables. Predictors of failure to receive elastography or hepatology referral were assessed using multivariable logistic regression. Statistical significance was defined as $p < 0.05$. **Results:** Among 781 patients with FIB-4 ≥ 1.3, only 11.8% underwent elastography or hepatology referral. While most patients had FIB-4 scores between 1.3-2.67, referral rates were substantially higher in those with FIB-4 ≥ 2.67 (37.6% vs 8.3%). Provider calculation of FIB-4 occurred in only 9% of cases but was strongly associated with referral in both univariable (OR = 9.1, 95% CI 5.1-16.1; $p < 0.0001$) and multivariable analysis (OR = 13.3, 95% CI 6.83-26.2; $p < 0.001$). Cirrhosis was the strongest predictor of referral (multivariable OR = 54.4, 95% CI 22.2-146; $p < 0.001$). Elevated LDL cholesterol was associated with lower odds of evaluation (OR = 0.29, 95% CI 0.09-0.81; p = 0.03). Other studied factors were not independently associated with referral. **Conclusion:** Despite elevated FIB-4 scores, the vast majority of high-risk patients did not receive elastography or hepatology referral, highlighting a major care gap. Provider calculation of FIB-4 emerged as a strong predictor of referral, suggesting that improving provider recognition and integration of noninvasive fibrosis assessment may represent an important target for quality improvement interventions.

Table 1. Univariable and Multivariable analysis

	Univariable			Multivariable		
Variable	OR	95% CI	p-value	OR	95% CI	p-value
Age*	0.97	0.95-0.99	0.0002	0.98	0.95-1.01	0.11
FIB-4 ≥2.67	6.68	4.04-11	<0.0001	1.42	0.44-4.05	0.5
FIB-4*	1.82	1.55-2.18	<0.0001	1.19	0.9-1.67	0.3
Diagnosis of cirrhosis	52.2	25.6-116	<0.0001	54.4	22.2-146	<0.001
High LDL-C	0.34	0.13-0.73	0.004	0.29	0.09-0.81	0.03
Calculated score	9.1	5.1-16.1	<0.0001	13.3	6.83-26.2	<0.001

*By year/unit increase

Disclosures: Alejandra Meza: Nothing to Disclose, Jonathan Dranoff: Nothing to Disclose.

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2336 | STRATEGIES TO PRIORITIZE TREATMENT FOR METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) PATIENTS WITH HISTOLOGICALLY CONFIRMED SIGNIFICANT FIBROSIS: FINDINGS FROM THE HEPAMET REGISTRY

Douglas Maya-Miles[1] Javier Crespo[2] Rocio Aller[3] Luis Ibañez-Samaniego[4] Rosa Martín Mateos[5] Jose Luis Calleja[6] Juan M. Pericas[7] Judith Gómez-Camarero[8] Mercedes Latorre[9] Isabel Graupera[10] Desamparados Escudero-Garcia[11] Rosa Maria Morillas[12] Salvador Benlloch[13] Juan Turnes[14] Maria Poca[15] Rubén Francés[16] Raul Andrade[17] Antonio Olveira[18] José Miguel Rosales[19] Conrado Fernández Rodríguez[20] Vanesa Bernal-Monterde[21] Águeda González-Rodríguez[22] Raquel Latorre Martinez[23] Rocio Gallego-Duran[24] Ruben Diez Rodríguez[25] Manuel Hernández Guerra de Aguilar[26] Paloma Carrillo Fernández[27] Carmen Carnicero[28] Paula Iruzubieta[29] Laura Suarez López[30] Manuel Romero-Gómez[31] Javier Ampuero Herrojo[32], [1]Institute of Biomedicine of Seville, [2]Hospital Universitario Marqués de Valdecilla, Santander, Spain, [3]Hospital Clínico Universitario de Valladolid, [4]Hospital General Universitario Gregorio Marañón, [5]Hospital Universitario Ramón y Cajal, [6]Hospital Universitario Puerta de Hierro, [7]Liver Unit, Vall d'Hebron University Hospital Campus, VHIR, [8]Hospital Universitario de Burgos, [9]Consorcio Hospital General Universitario de Valencia, [10]Liver Unit. Hospital Clínic. Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), [11]Hospital Clínico Universitario de Valencia, [12]Hospital Germans Trias i Pujol, Badalona, [13]Hospital Universitari i Politècnic La Fe/ Hospital Arnau de Vilanova, [14]19. Complejo Hospitalario Universitario de Pontevedra & IIS Galicia Sur, [15]Hospital de la Santa Creu i San Pau, Barcelona, [16]Hospital General Universitario de Alicante, [17]UNIVERSIDAD DE MÁLAGA, [18]La Paz University Hospital, Madrid, Spain, [19]Agencia Sanitaria Costa del Sol, Marbella, [20]25. Hospital Universitario Fundación de Alcorcón, Universidad Rey Juan Carlos, [21]Hospital Universitario Miguel Servet, Zaragoza, [22]Hospital Universitario Santa Cristina, Madrid, [23]Hospital Son Llatzer, Palma de Mallorca/Hospital Universitario Infanta Elena de Madrid, [24]Ibis- Biomedicine Institute of Sevilla, [25]Hospital de León, León, [26]Hospital Universitario de Canarias, Tenerife, [27]SeLiver group, Instituto de Biomedicina de Sevilla, Hospital Universitario Virgen del Rocío, [28]Institute of Health Sciences of Castilla y Leon (IECSCYL), 42002 Soria, [29]Hospital Universitario Marqués de Valdecilla/IDIVAL, Santander, [30]Liver Unit. Hospital General Universitario Gregorio Marañón., [31]Virgen del Rocio University Hospital, [32]Virgen del rocío University Hospital, Seville, Spain

Background: Treatment for MASLD is currently indicated for non-cirrhotic patients with histologically confirmed significant fibrosis. This study aimed to identify factors able to discriminate which of these patients are more likely to progress to cirrhosis or decompensation during follow-up. **Methods:** 752 histologically confirmed F2-F3 MASLD patients from the HEPAMET registry were included. Anthropometric, biochemical, and metabolic parameters were analyzed to identify predictors in uni- and multivariate analyses including or not histological readouts. Patients were classified as progressors when cirrhosis or liver decompensation were reported during follow-up. Biopsy, ultrasound, or transient elastography were used to defined cirrhosis. Liver decompensation with the occurrence of one or more major complications of liver disease (ascites, hepatic encephalopathy, gastrointestinal bleeding, or bacterial infection) during follow-up. **Results:** Mean age was 55.5 ± 11.4 years and mean BMI 34.8 ± 7.9 kg/cm^2 (69.2% obese); 51.7% were men. Type-2 Diabetes Mellitus (T2DM) was present in 57.2% of patients. MASH in 56.2% and fibrosis stages were F2 46.5% and F3 53.5%. Mean follow-up was 6.28 ± 4.4 years. Progression to cirrhosis or decompensation occurred in 17.7%. Cox regressions indicated positive associations between progression and advanced fibrosis, T2DM, AST, GGT, glucose and bilirubin, while inverse associations to MASH, ballooning, inflammation cholesterol, albumin and platelets. T2DM, age, GGT and platelets together with the prevalence of advanced fibrosis remained significant after multivariate correction and were integrated in a histology (right model) and histology-free scores (left model). Both of them showed a good prognostic ability to identify patients more likely to progress to cirrhosis or develop liver related complications (Figure 1). **Conclusion:** Age, GGT, platelets and T2DM can be useful and combined or not to liver fibrosis stage to estimate the risk of progression and prioritize which patients should first receive treatment for MASLD.

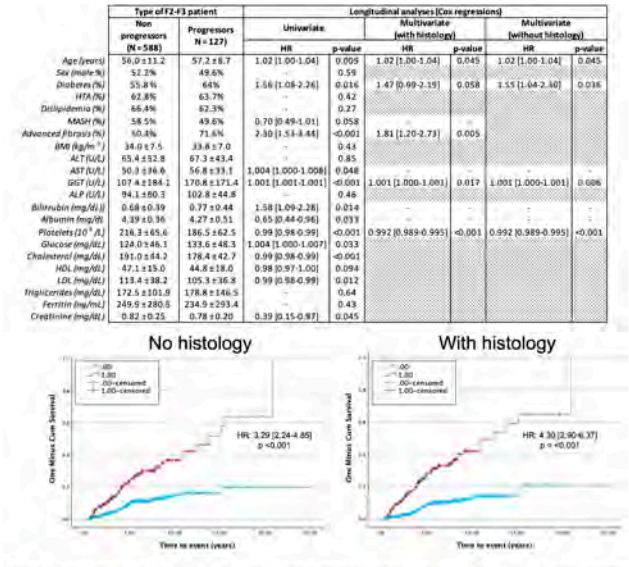


Figure 1: upper panel: Summary results of descriptive statistics and Cox regression analyses. Lower graphs. Kaplan Meyer results obtained for predictor models integrating or not histological features.

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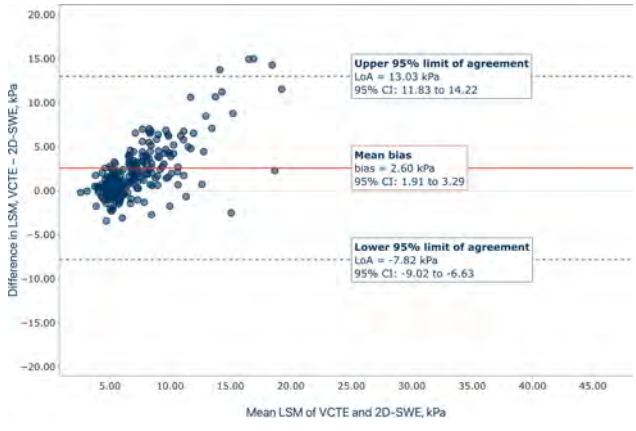
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Disclosures: Douglas Maya-Miles: Nothing to Disclose, Javier Crespo: Nothing to Disclose, rocio aller: Nothing to Disclose, Luis Ibañez-Samaniego: Nothing to Disclose, Rosa Martín Mateos: Nothing to Disclose, Jose Luis Calleja: Nothing to Disclose, Juan M. Pericas: Nothing to Disclose, Judith Gómez-Camarero: Nothing to Disclose, Mercedes Latorre: Nothing to Disclose, ISABEL GRAUPERA: Nothing to Disclose, Desamparados Escudero-Garcia: Nothing to Disclose, Rosa Maria Morillas: Nothing to Disclose, Salvador Benlloch: Nothing to Disclose, Juan Turnes: Nothing to Disclose, Maria Poca: Nothing to Disclose, Rubén Francés: Nothing to Disclose, Raul Andrade: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Antonio Olveira: Roche: Grant/Research Support, Canon: Speaking and Teaching, Gilead: Grant/Research Support, Ipsen: Speaking and Teaching, Madrigal: Speaking and Teaching, Novo Nordisk: Speaking and Teaching, Boehringer-Ingelheim: Speaking and Teaching, José Miguel Rosales: Nothing to Disclose, Conrado Fernández Rodríguez: Nothing to Disclose, Vanesa Bernal-Monterde: Nothing to Disclose, Águeda González-Rodríguez: Nothing to Disclose, RAQUEL LATORRE MARTINEZ: Nothing to Disclose, Rocio Gallego-Duran: Nothing to Disclose, Ruben Diez Rodríguez: Nothing to Disclose, Manuel Hernández Guerra de Aguilar: Nothing to Disclose, Paloma Carrillo Fernández: Nothing to Disclose, Carmen Carnicero: Nothing to Disclose, Paula Iruzubieta: Nothing to Disclose, Laura Suarez López: Nothing to Disclose, Manuel Romero-Gómez: Nothing to Disclose, Javier Ampuero Herrojo: Nothing to Disclose.

2337 | AGREEMENT BETWEEN VCTE AND 2D-SWE FOR LIVER FIBROSIS ASSESSMENT IN MASLD: EVIDENCE AGAINST INTERCHANGEABILITY

Vasily Isakov[1] Alexei Goncharov[1] Murad Israpilov[2], [1]Federal Research Center of Nutrition, Biotechnology & Food Safety, [2]Federal Research Ceter of Nutrition, Biotechnology & Food Safety

Background: Liver stiffness measurement (LSM) is widely used for non-invasive fibrosis assessment in metabolic dysfunction-associated steatotic liver disease (MASLD), but values obtained using different elastography technologies may not be interchangeable. We evaluated agreement between vibration-controlled transient elastography (VCTE; FibroScan 530) and two-dimensional shear wave elastography (2D-SWE; LOGIQ E9) in patients with MASLD and explored factors associated with inter-method discrepancy. **Methods:** We analyzed 228 adults with MASLD examined from 2024 to 2026. All participants underwent fasting VCTE and 2D-SWE performed by different blinded operators. Agreement was assessed using Bland–Altman analysis, intraclass correlation coefficient (ICC), F0–F4 reclassification tables, and weighted Cohen's kappa. Restricted cubic spline models were used to examine whether absolute inter-method differences were associated with waist circumference and VCTE measurement variability. **Results:** Agreement between VCTE and 2D-SWE was only moderate. The ICC was 0.436 (95% CI, 0.383–0.582). Bland–Altman analysis demonstrated systematic positive bias for VCTE versus 2D-SWE, with a mean difference of 2.60 kPa and wide limits of agreement from −7.82 to 13.03 kPa (Figure). The discrepancy increased as mean LSM increased, indicating proportional bias ($\beta = 1.037$; $p < 0.001$). Complete F0–F4 stage agreement was observed in 107/228 patients (46.9%). Agreement was highest at the extremes, F0 (72.3%) and F4 (64.7%), but substantially lower in intermediate stages F1–F3 (20.0%–35.7%). Weighted Cohen's kappa was 0.645 (95% CI, 0.554–0.723). Reclassification was asymmetric: 2D-SWE more frequently assigned patients to a lower fibrosis category than VCTE. Larger waist circumference and higher VCTE variability were associated with greater absolute inter-method discrepancy; the waist-circumference association was significant ($p = 0.002$), with marked divergence beyond approximately 110 cm. **Conclusion:** In patients with MASLD, VCTE and 2D-SWE showed moderate categorical agreement but poor individual-level interchangeability, particularly across intermediate fibrosis stages where clinical decisions are most uncertain. Severe abdominal adiposity and VCTE variability appear to amplify method-dependent differences. These findings support using the same elastography modality and device for longitudinal monitoring and caution against direct substitution of 2D-SWE for VCTE-derived fibrosis thresholds without device-specific validation.



Disclosures: Vasily Isakov: Nothing to Disclose, Alexei Goncharov: Nothing to Disclose, Murad Israpilov: Nothing to Disclose.

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2338 | TRANSITIONING MASH DRUG DEVELOPMENT FROM PHASE 1 TO PHASE 2: THE EVOLVING ROLE OF NON-INVASIVE ENDPOINTS

Judith Hey-Hadavi[1] Sigrunn Blacoe[1] Casey Ustick[1] Frederic Flandrin[1] Andrew Kuhlman[1], [1]Worldwide Clinical Trials

Background: Noninvasive tests (NITs) are increasingly integrated for metabolic dysfunction-associated steatohepatitis (MASH) drug development to inform proof-of-mechanism (PoM), dose selection, and early efficacy assessment. This is driven by the limitations of liver biopsy. However, comparative performance of imaging, serum, and composite biomarkers across therapeutic classes remains incompletely characterized. This review evaluated the utility of NITs in early interventional studies of MASLD/MASH therapies. **Methods:** Peer-reviewed publications, abstracts, ClinicalTrials.gov postings, and publicly available company reports through May, 2026 were screened. Interventional clinical studies in MASLD/MASH with a defined mechanism of action and quantifiable NIT endpoints were included. Observational studies, lifestyle interventions, and studies without measurable biomarker or imaging outcomes were excluded. 14 representative studies in multiple therapeutic classes were analyzed, including THR-β agonists, FGF analogs, GLP-1–based therapies, FXR agonists, ACC inhibitors, and other metabolic or fibrosis-directed agents. **Results:** MRI-proton density fat fraction (MRI-PDFF) consistently demonstrated the strongest evidence for detecting early clinical activity, distinguishing dose-response relationships, and supporting early efficacy assessment across therapeutic classes. Relative MRI-PDFF reductions ≥30% were repeatedly associated with later histologic response. Imaging-based endpoints generally surpassed serum biomarkers for short-term dose and exposure-response characterization. Across programs, steatosis-oriented endpoints changed earlier and more consistently than fibrosis-oriented NITs, while stiffness measures such as MRE and VCTE demonstrated slower and/or weaker short-term responsiveness. Fibrogenesis markers incl. ELF and PRO-C3 showed encouraging supportive utility, particularly when interpreted alongside imaging biomarkers. Several studies suggested that combining imaging, serum biomarkers, and composite measures may provide more clinically informative assessment than reliance on single endpoint modality. FAST score showed emerging value for corroborating histologic improvement in post hoc analyses. (See table 1) **Conclusion:** Among currently studied NITs, MRI-PDFF is the most robust in early phase MASH drug development, particularly for PoM evaluation, dose selection, and early efficacy detection. Fibrosis-oriented biomarkers may provide complementary information but are less sensitive in short trial durations. The findings support a multimodal NIT strategy of imaging, serum biomarkers, and composite indices to improve interpretation of pharmacodynamic and early efficacy signals in MASH studies. Continued NIT standardization, validation and innovation are essential to accelerate early development decisions and ultimately patient's care.



Category	NIT / Biomarker	Pathology	Proof-of-Mechanism (PoM) use	Dose / Exposure–Response	Early Efficacy Signal	Temporal Response	Key Strengths	Limitations
Serum Biomarkers	ALT, AST	Hepatocellular injury	Moderate – reflects liver injury and activity	Moderate (broke dose-dependent changes)	Supportive, indirect	Rapid (weeks)	Widely available, dynamic, low cost	Limited specificity for MASH inflammation
	CK-18	Apoptosis	Variable – inconsistent signal	Limited	Weak/inconsistent	Variable	Mechanistic relevance to cell death	Poor standardization, high variability
	PRO-C3	Fibrogenesis	Moderate – early signal anti-fibrotic activity	Limited–moderate	Emerging predictive value	Slow	Specific to collagen formation	Small early changes, less sensitive short-term
Composite Scores	Fibrosis-4 (FIB-4)	Fibrosis risk	Low for PoM	Limited	Low (short-term)	Slow	Simple, widely used, cost effective	Insensitive to short-term change
	Enhanced Liver Fibrosis (ELF) score	Fibrogenesis	Moderate	Limited	Moderate (longer-term)	Slow	Reflects ECM remodeling	Modest early changes
	Fibroscan-AST (FAST) score	Steatosis + inflammation + fibrosis	Limited as PD marker	Limited	Moderate (not synchronous)	Moderate	Identifies "at-risk MASH" (F2–F3)	Limited validation for dynamic response
Imaging Biomarkers	MRI-PDFF	Hepatic steatosis	High – robust PoM marker	High – detects dose response	Strong predictor (≥30% reduction linked to histologic response)	Rapid (4-12 weeks)	Highly sensitive, reproducible	Focuses on fat, not fibrosis directly
	Magnetic Resonance Elastography (MRE)	Fibrosis (& fibrosis)	Moderate	Limited (short-term)	Moderate (long-term)	Slow	High sensitivity for fibrosis	Cost, accessibility constraints
	VCTE (FibroScan)	Fibrosis (& fibrosis)	Low–moderate	Limited	Limited	Slow	Widely available non-invasive, FDA accepted letter intent	Less sensitive than MRE, variability
	Iron-corrected T1 (cT1)	Inflammation + Fibrosis	Moderate	Moderate	Emerging predictive value	Moderate	Monitoring and risk stratification	Less standardized, fewer datasets than MRI-PDFF

Disclosures: Judith Hey-Hadavi: Pfizer Inc: employee, Worldwide Clinical Trials: CRO, Sigrunn Blacoe: Nothing to Disclose, Casey Ustick: Nothing to Disclose, Frederic Flandrin: Nothing to Disclose, Andrew Kuhlman: Nothing to Disclose.

2339 | UTILITY OF VIBRATION-CONTROLLED TRANSIENT ELASTOGRAPHY IN PATIENTS WITH ELEVATED BMI: BIOPSY-VALIDATED ASSESSMENT OF BMI-DEPENDENT DISCORDANCE WITH FIB-4

Neharika Bandaru[1] Allen Luo[1] Chester Hui[1] Kali Zhou[1] Emilie Mitten[2] Marvin Ryou[3] Thomas Wang[1], [1]Keck School of Medicine of USC, [2]Brigham and Women's Hospital, Massachusetts General Hospital, [3]Brigham and Women's Hospital

Background: Vibration-controlled transient elastography (VCTE) and Fibrosis-4 index (FIB-4) are commonly used noninvasive tools for fibrosis risk stratification in metabolic dysfunction-associated steatotic liver disease (MASLD). Although FIB-4 has shown stable performance across body mass index (BMI) classes, obesity may reduce the diagnostic accuracy of VCTE. We aimed to (1) evaluate the relationship between BMI and discordance between FIB-4 and VCTE results and (2) determine which modality more accurately predicts advanced fibrosis when discordance is present. **Methods:** We performed a retrospective multicenter study across three healthcare systems from 2016 to 2025, including

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adults aged ≥18 years old. Adults with biopsy-proven MASLD, VCTE, laboratory testing within 1 year were included. Patients with alternative liver disease etiologies or ≥10% total body weight loss between testing and biopsy were excluded. Patients were stratified by BMI (<30, 30–34.9, 35–39.9, and ≥40 kg/m²). FIB-4 and VCTE thresholds for advanced fibrosis were defined according to AASLD guidance (<1.3 low risk and >2.67 high risk for FIB-4; <8 kPa low risk and >12 kPa high risk for VCTE). Diagnostic performance for advanced fibrosis was assessed using AUROC analysis across BMI categories. Discordance was defined as low-risk FIB-4 with high-risk VCTE or high-risk FIB-4 with low-risk VCTE. **Results:** A total of 597 patients were included, of whom 188 (31.5%) had biopsy-confirmed advanced fibrosis (F3+). Overall, VCTE and FIB-4 showed similar diagnostic accuracy for advanced fibrosis (AUROC 0.774 vs 0.734, p = 0.17). There was a trend towards lower diagnostic accuracy with FIB-4 across all BMI categories, reaching statistical significance only in patients with BMI <30 kg/m² (0.826 vs 0.713, p = 0.0069). Rates of discordance between FIB-4 and VCTE increased with BMI and were driven predominantly by low FIB-4/high VCTE discordance. Specifically, low FIB-4/high VCTE discordance increased from 4.2% in patients with BMI <30 kg/m² to 30.5% in patients with BMI ≥40 kg/m² (p < 0.0001). In these discordant cases, FIB-4 correctly predicted fibrosis stage in 81.3% of patients with BMI ≥40 kg/m². The reverse discordance pattern (high FIB-4/low VCTE) was uncommon, with no cases among those with BMI ≥40 kg/m². For patients with BMI <30 kg/m², VCTE was more accurate for the reverse discordance pattern (83.3%, p = 0.02). **Conclusion:** Increasing BMI was associated with greater discordance between FIB-4 and VCTE assessment of advanced fibrosis risk in MASLD. In patients with BMI ≥40 kg/m², discordance most often occurred with high-risk VCTE but low-risk FIB-4 results, with biopsy more frequently supporting FIB-4 classification. These findings suggest standard VCTE thresholds may overestimate advanced fibrosis in severe obesity and that BMI-adjusted interpretation may improve risk stratification.

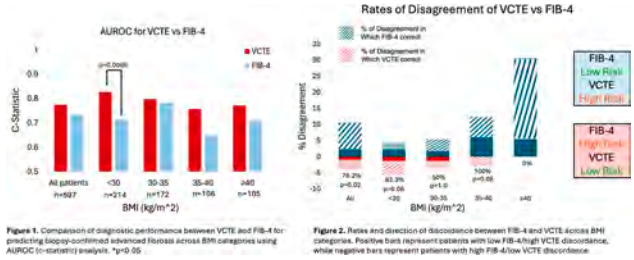


Figure 1. Comparison of diagnostic performance between VCTE and FIB-4 for predicting biopsy-confirmed advanced fibrosis across BMI categories using AUROC (c-statistic) analysis. *p<0.05

Figure 2. Rates and direction of discordance between FIB-4 and VCTE across BMI categories. Positive bars represent patients with low FIB-4/high VCTE discordance, while negative bars represent patients with high FIB-4/low VCTE discordance.

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2340 | ELEVATED SERUM URIC ACID ENHANCES THE ASSOCIATION BETWEEN CARDIOMETABOLIC RISK FACTORS AND SIGNIFICANT LIVER FIBROSIS: A NHANES ANALYSIS 2021-2023

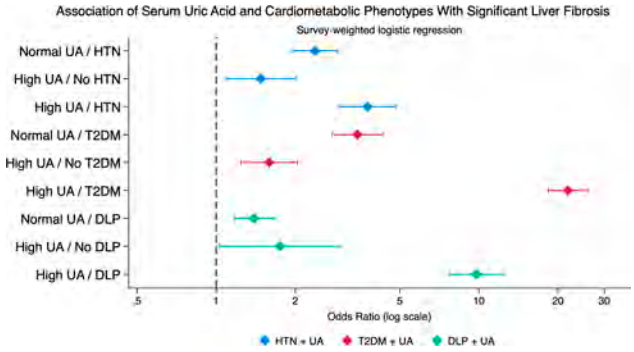
Angela Sato Espinoza[1] Ruchita Jadhav[1] Manaal Babar[1] Javier Diaz Ferrer[2], [1]Sinai Hospital of Baltimore, [2]Hospital Rebagliati Martins

Background: Metabolic dysfunction–associated steatotic liver disease (MASLD) is the most common chronic liver disease worldwide. Cardiometabolic risk factors are well-established as independent drivers of MASLD and progression to liver fibrosis. In addition to these metabolic risk factors, elevated serum uric acid has also emerged as a potential independent contributor to MASLD. However, limited studies have evaluated the combined impact of elevated serum uric acid and cardiometabolic risk factors. We aimed to evaluate the association between elevated serum uric acid, cardiometabolic risk factors, and significant liver fibrosis among U.S. adults. **Methods:** We used NHANES 2021-2023 data to identify individuals aged 18 years and older. Type 2 Diabetes (T2DM) was defined with HbA1C ≥6.5%, while no diabetes as HbA1C <6.5%. Hypertension (HTN) status was determined from survey questionnaire responses. Dyslipidemia (DLP) was defined as HDL <50mg/dL for females, <40 mg/dL for males, and/or triglycerides >150 mg/dL for both sexes. Significant fibrosis was defined as a liver stiffness measurement (LSM) > 8kPa, and no significant fibrosis as LSM ≤8 kPa. High uric acid was defined as >6 mg/dL for females and >7 mg/dL for males. We classified cardiometabolic phenotypes based on serum uric acid (UA) level and the presence or absence of metabolic comorbidities. **Results:** We included 11,933 individuals in our analysis. The combination of elevated serum uric acid and cardiometabolic risk factors was associated with higher odds of significant liver fibrosis. The T2DM phenotype with elevated UA had the strongest association with significant fibrosis, with nearly 22-fold higher odds of significant fibrosis (OR 21.80, 95% CI 18.35–25.89, p < 0.001). T2DM with normal UA was significantly associated with fibrosis (OR 3.44, 95% CI 2.76–4.29, p < 0.001), while elevated UA without T2DM showed a modest association (OR 1.59, 95% CI 1.24–2.04, p = 0.001). In the HTN phenotype, the highest risk for

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significant fibrosis was observed with both elevated UA and HTN (OR 3.76, 95% CI 2.94-4.82, p < 0.001), compared with HTN and normal UA (OR 2.38, 95% CI 1.95–2.90, p < 0.001) and elevated UA without HTN (OR 1.48, 95% CI 1.09–2.00, p = 0.015). In the DLP phenotype, the highest risk for significant fibrosis was in elevated UA and dyslipidemia (OR 9.78, 95% CI 7.70–12.42, p < 0.001), compared with DLP and normal UA (OR 1.40, 95% CI 1.17–1.66, p = 0.001), and elevated UA without DLP (OR 1.75, 95% CI 1.03–2.97, p = 0.040) (Figure 1). **Conclusion:** Elevated uric acid appeared to amplify the risk of significant fibrosis in the presence of cardiometabolic risk factors, particularly among individuals with diabetes. These findings suggest that serum uric acid could serve as an additional marker to improve risk stratification for significant liver fibrosis in individuals with cardiometabolic diseases.



Disclosures: Angela Sato Espinoza: Nothing to Disclose, Ruchita Jadhav: Nothing to Disclose, Manaal Babar: Nothing to Disclose, JAVIER DIAZ FERRER: Nothing to Disclose.

2341 | MULTIMODAL DISCOVERY AND CLINICAL VALIDATION OF CIRCULATING FIBROSIS BIOMARKERS IN MASH

Elisabeth Galsgaard[1] Gianluca Mazzoni[1] Lea Harder[1] Marie Louise Therkelsen[1] Annabelle Hoegl[1] Mads Grønborg[1] April Hartley[1] Steen Ladelund[1] Anouk Oldenburger[1] Diana Samodova-Sommer[1] Christian Madsen[1] Dres Damgaard[1] Naba Al-Sari[1] Morten Fog-Tonnesen[1] Lise Lotte Gluud[2] Michelle Long[1] Trine Pagh Ludvigsen[1], [1]Novo Nordisk, [2]Copenhagen University Hospital Copenhagen Hvidovre

Background: Omics platforms offer a new frontier for characterising the molecular heterogeneity of hepatic fibrosis in metabolic dysfunction-associated steatohepatitis (MASH), yet the field has not delivered clinically actionable tools. Most omics-based fibrosis studies rely on single-platform approaches, small sample sizes, and lack independent external validation. **Methods:** We conducted a cross-validated biomarker study anchored in a *discovery cohort* Copenhagen Cohort of MASLD (CoCoM) with paired liver and plasma multi-omics and systematically evaluated candidate fibrosis BMs across complementary independent resources. *Genetic support*: Summary-level Mendelian randomization using published genome-wide association studies (GWAS) for metabolic dysfunction-associated steatotic liver disease (MASLD), MASH, and cirrhosis as exposures and proteomics from UK Biobank (UKB, Olink) and DECODE (SomaScan, SomaLogic) for outcomes. *Preclinical study*: Disease progression and antifibrotic treatment effect in rat choline-deficient high-fat diet (CDHFD) study with hepatic liquid chromatography-mass spectrometry (LC-MS) proteomics and transcriptomics. *Validation cohorts*: Semaglutide MASH phase 2 randomized controlled trials (RCTs) with serum SomaScan proteomics at baseline or pre-screening visits. *Clinical feasibility*: Evaluation of immuneassays and recombinant proteins from commercial suppliers. *Statistical analysis*: see table. **Results:** Plasma SomaScan and LC-MS proteomics analyses in the *discovery* cohort identified 43 circulating biomarkers linked to MASH fibrosis stage, strongly correlated with their encoding transcript expression levels in liver biopsy samples. Genetic analysis provided support for 21 of the 43 candidate BMs showing that MASH was driving the observed change in circulating levels. BM candidates were evaluated in i) longitudinal analysis of CDHFD data correlating BM changes in hepatic protein and gene expression levels with disease progression, ii) BM modulation by pharmacological intervention with ALK5 inhibitor in the pre-clinical study, iii) RCTs for validation of association of circulating BM levels with fibrosis stages, and iv) availability of BM immunoassay from trusted vendors. We ranked the identified proteins and present the top 4 candidate BMs: C7 Complement Factor, IGF-1 Binding Protein 7 (IGFBP7), Tissue Inhibitor of Metalloproteinases 1 (TIMP1), and ADAMTS-like 2 (ADAMTSL2). **Conclusion:** This study identified biologically anchored, clinically feasible candidate fibrosis BMs ready for prospective analytical validation and qualification. Several candidate BMs have been previously identified, further validating this approach. If confirmed in larger independent cohorts, these proteins, individually or as a composite panel, have the potential to

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advance non-invasive fibrosis assessment.



Study	Datasets and statistical analysis		C7		IGFBP7		TIMP1		ADAMTSL2	
MASLD cohort study	Plasma SomaScan	MASH F0-F4 stages at baseline (ordinal regression)	1,5	4,70E-06	1,5	4,90E-09	1,1	3,40E-06	1,4	4,4E-07
	Plasma LCMS		1,6	1,60E-12	1,5	9,30E-12	1,2	6,50E-10	1,4	3,90E-11
	Plasma SomaScan	Paired liver RNAseq (correlation)	0,66	9,09E-06	0,58	7,95E-05	0,68	2,16E-08	0,56	2,79E-04
	Plasma LCMS		0,70	~0	0,43	4,35E-03	0,56	2,80E-07	0,56	3,83E-07
Semaglutide MASH RCTs	Serum SomaScan	MASH F1-F3 stages at baseline (ANOVA)	3,04E-06		7,02E-05		1,03E-04		3,12E-17	
		MASH F0-F4 stages at screening (Kruskal-Wallis rank sum test)	2,54E-09		1,04e-9		3,15E-05		1,64e-4	
Preclinical CDHFD study	Liver CMS	CDHFD 4 vs 12 weeks (pair-wise comparison)	4w: 9,57 12w: 11,41	2,18E-07	4w: 13,38 12w: 14,54	7,72E-06	NA	NA	4w: 11,67 12w: 13,72	1,03E-09
		ALK5i vs vehicle at 12 weeks (pair-wise comparison)	-0,78	9,10E-03	-0,76	8,99E-04	NA	NA	-0,97	1,11E-02
	Liver RNAseq	CDHFD vs chow at 12 weeks (pair-wise comparison)	-3,44	2,98E-20	-1,98	6,15E-28	-3,72	1,24E-52	-2,83	1,24E-23
		Decrease ALK5i vs vehicle at 12 weeks (pair-wise comparison)	≤ 0,0001		≤ 0,0001		≤ 0,0001		≤ 0,0001	
GWAS	Serum Olink and SomaScan	Traits	MASLD, MASH, cirrhosis		MASLD, MASH, cirrhosis, cT1		MASLD, MASH, cirrhosis		MASLD, MASH, cirrhosis, PDFF	

Disclosures: Elisabeth Galsgaard: Nothing to Disclose, Gianluca Mazzoni: Nothing to Disclose, Lea Harder: Nothing to Disclose, Marie Louise Therkelsen: Nothing to Disclose, Annabelle Hoegl: Nothing to Disclose, Mads Grønborg: Nothing to Disclose, April Hartley: Nothing to Disclose, Steen Ladelund: Nothing to Disclose, Anouk Oldenburger: Novo Nordisk: Employee, Diana Samodova-Sommer: Nothing to Disclose, Christian Madsen: Nothing to Disclose, Dres Damgaard: Novo Nordisk: Employee, Naba Al-Sari: Nothing to Disclose, Morten Fog-Tonnesen: Nothing to Disclose, Lise Lotte Gluud: Nothing to Disclose, Michelle Long: Nothing to Disclose, Trine Pagh Ludvigsen: Nothing to Disclose.

2342 | PORTAL HYPERTENSIVE COMPLICATIONS IN PATIENTS WITH MASLD AND ALPHA-1 ANTITRYPSIN DEFICIENCY

Madeha Irfan[1] Talal Bhatti[1] Sajid Jalil[2] Ashwani Singal[3] Ahmed Ibrahim[4] Shahzad Ashraf[5] Sanjaya Satapathy[1], [1]Northwell Health, [2]Stanford University, [3]University of Louisville, [4]San Joaquin General hospital, [5]Prime Medical and Dental college

Background and Aims: Portal hypertension represents a major driver of morbidity and transition to decompensated liver disease in patients with metabolic dysfunction-associated steatotic liver disease (MASLD). Alpha-1 Antitrypsin Deficiency (A1ATD) is associated with progressive hepatic fibrosis and cirrhosis; however, its impact on portal hypertension-related complications in MASLD remains poorly characterized. This study evaluated the association between concomitant A1ATD and clinically significant portal hypertensive outcomes in patients with MASLD. **Methods:** A retrospective cohort study was conducted using the TriNetX US Collaborative Network comprising 66 healthcare organizations. Adult patients with MASLD diagnosed between January 1, 2005, and May 21, 2021, were identified and stratified according to the presence (A1+) or absence (A1−) of A1ATD. Patients with competing chronic liver diseases were excluded. Following 1: 1 propensity score matching, 2,122 patients were included in each cohort. Primary outcomes included variceal hemorrhage, ascites, and hepatic encephalopathy (HE). Secondary outcomes included spontaneous bacterial peritonitis (SBP) and hepatorenal syndrome (HRS). Relative risks (RRs), Kaplan–Meier analyses, and hazard ratios (HRs) were evaluated. **Results:** Among 4,244 propensity score-matched patients, A1ATD was associated with significantly increased portal hypertension-related morbidity. Patients with A1ATD demonstrated higher risks of variceal hemorrhage (2.3% vs. 1.1%; RR 1.97, 95% CI 1.21–3.20; $p = 0.006$), ascites (8.2% vs. 4.9%; RR 1.68, 95% CI 1.31–2.16; $p < 0.001$), and HE (10.7% vs. 7.0%; RR 1.53, 95% CI 1.24–1.88; $p < 0.001$). A1ATD was additionally associated with increased risks of SBP (2.0% vs. 0.7%; RR 3.04, 95% CI 1.67–5.56; $p < 0.001$) and HRS (2.6% vs. 1.2%; RR 2.22, 95% CI 1.39–3.55; $p = 0.001$). Detailed outcomes are summarized in Table 1. **Conclusion:** In this large propensity score-matched cohort, concomitant A1ATD was associated with significantly increased risks of portal hypertensive complications and downstream systemic sequelae in patients with MASLD. These findings identify A1ATD as an important risk modifier requiring earlier recognition and closer clinical surveillance.

Table 1. Portal Hypertensive Outcomes in Propensity Score-Matched Cohorts

Outcome	MASLD + A1ATD	MASLD Alone	RR (95% CI)	P value
Variceal hemorrhage	2.3%	1.1%	1.97 (1.21–3.20)	0.006
Ascites	8.2%	4.9%	1.68 (1.31–2.16)	<0.001
Hepatic encephalopathy	10.7%	7.0%	1.53 (1.24–1.88)	<0.001
Spontaneous bacterial peritonitis	2.0%	0.7%	3.04 (1.67–5.56)	<0.001
Hepatorenal syndrome	2.6%	1.2%	2.22 (1.39–3.55)	0.001

Keywords: MASLD; Alpha-1 Antitrypsin Deficiency; Portal Hypertension; Hepatic Encephalopathy; Ascites; TriNetX.

Disclosures: MADEHA IRFAN: Nothing to Disclose, Talal Bhatti: Nothing to Disclose, Sajid Jalil: Nothing to Disclose, Ashwani Singal: Madrigal: Speaking and Teaching, Pleiogenix: Stock – privately held company, Pleiogenix: Consultant, CLD Foundation: Advisor, Medical Speaker's Network: Speaking and Teaching,

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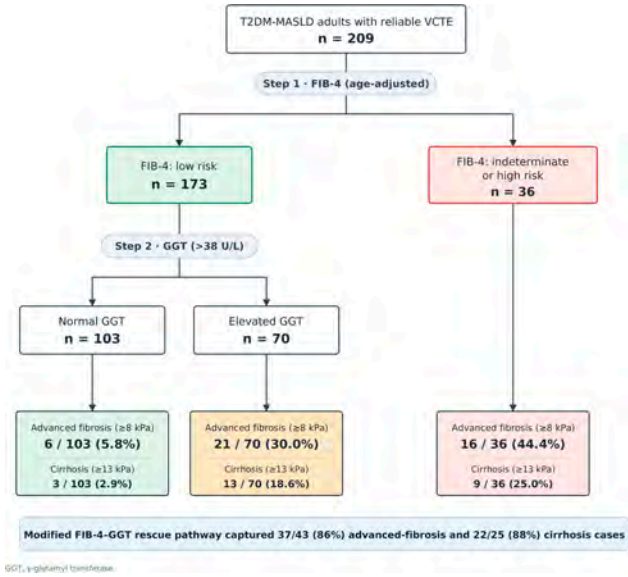
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2343 | THE FIB-4 BLIND SPOT: ELEVATED GGT IDENTIFIES VCTE-DEFINED ADVANCED FIBROSIS MISSED BY CONVENTIONAL FIB-4 RISK STRATIFICATION IN T2DM-ASSOCIATED MASLD

Mona Ismail[1], [1]Imam Abdulrahman Bin Faisal University

Background: The Fibrosis-4 index (FIB-4) is a first-line non-invasive test for fibrosis risk stratification in MASLD. Patients classified as low risk may not undergo further assessment. We evaluated whether elevated gamma-glutamyl transferase (GGT) identifies VCTE-defined advanced fibrosis among patients classified as low-risk FIB-4. **Methods:** We retrospectively studied 209 adults with T2DM-associated MASLD who underwent reliable VCTE at a tertiary university hospital. MASLD was defined by controlled attenuation parameter ≥247 dB/m with sonographic steatosis. Elevated GGT was defined a priori as >38 U/L. Guideline-recommended age-adjusted FIB-4 thresholds were applied. The primary outcome was VCTE-defined advanced fibrosis (liver stiffness measurement [LSM] ≥8.0 kPa); cirrhosis (LSM ≥13.0 kPa) was secondary. Patients were categorized by FIB-4 risk status and GGT level. A modified FIB-4–GGT pathway flagged patients with indeterminate/high-risk FIB-4 or elevated GGT despite low-risk FIB-4. **Results:** Overall, 43/209 (20.6%) had advanced fibrosis and 25/209 (12.0%) had cirrhosis. FIB-4 classified 173/209 patients (82.8%) as low risk, including 27/43 with advanced fibrosis (62.8%) and 16/25 with cirrhosis (64.0%). Within the low-risk FIB-4 group, advanced fibrosis was more prevalent with elevated versus normal GGT (21/70 [30.0%] vs 6/103 [5.8%]), as was cirrhosis (13/70 [18.6%] vs 3/103 [2.9%]). This pattern persisted among patients with normal aminotransferases (advanced fibrosis: 9/29 [31.0%] vs 4/79 [5.1%]). Among low-risk FIB-4 patients, elevated GGT was present in 21/27 (77.8%) advanced fibrosis cases and 13/16 (81.3%) cirrhosis cases. Adding GGT to FIB-4 captured 37/43 (86.0%) advanced fibrosis and 22/25 (88.0%) cirrhosis cases, versus 16/43 (37.2%) and 9/25 (36.0%) with FIB-4 alone **(Figure 1). Conclusion:** In T2DM-associated MASLD, most patients with VCTE-defined advanced fibrosis or cirrhosis were classified as low risk by FIB-4. Elevated GGT identified a higher-risk subgroup within the low-risk FIB-4 group, including patients with normal aminotransferases, and captured most cases missed by FIB-4 alone. GGT may complement FIB-4 in fibrosis risk stratification, warranting prospective validation within risk-stratification pathways.



Disclosures: Mona Ismail: Nothing to Disclose.

2344 | METABOLIC THRESHOLD PATTERN OF OBESITY AND LIVER FIBROSIS SEVERITY IN A NATIONALLY REPRESENTATIVE U.S. COHORT

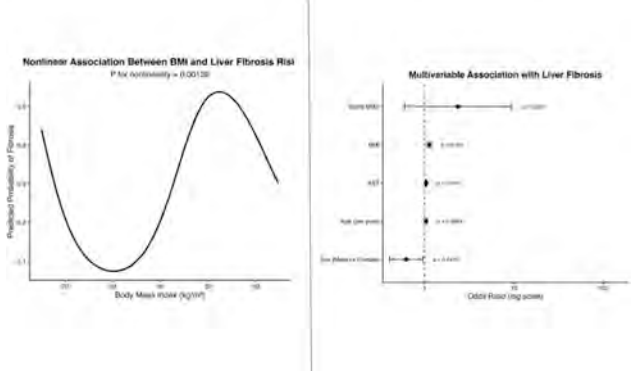
Narissa Nursjamsi[1] Prateeka Kodali[2] Elsa Sasongko[3] Kesava Achuta[4] Pranay Gupta[1] Sujata Kambhatla[1], [1]garden city hospital/msucom, [2]Sichuan University, Chengdu, China, [3]Faculty of Medicine, Universitas Padjadjaran, [4]garden city hospital/ msucom

Background: BMI has been linked to hepatic fibrosis, although the relationship may not be strictly linear, particularly in severe obesity. In addition, shared metabolic and inflammatory pathways have raised interest in the potential association between bone mineral density (BMD) and liver fibrosis, though existing evidence remains inconsistent. Using the NHANES cohort, we

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evaluated the association between BMI and liver fibrosis severity and explored nonlinear BMI effects and potential interaction with BMD. **Methods:** This cross-sectional analysis was conducted using the NHANES 2017-2020 cycles. Data collected included participant demographics, CBC, HbA1c, hepatic function panel, lumbar spine DXA, controlled attenuation parameter (CAP), and vibration-controlled transient elastography. The dataset was merged using participant unique identifier SEQN. Prticipants with missing DXA, BMI, or other survey design variables were excluded. All analyses incorporated NHANES complex survey design variables (sampling weights, strata, and clusters). Multivariable logistic regression was used to evaluate independent variables associated with liver fibrosis. Restricted cubic spline modeling was used to assess associations between BMI and fibrosis. **Results:** The final analytic cohort included 1918 participants, predominantly older adults due to lumbar spine DXA availability. BMI was broadly distributed falling within 20-40 with highest fibrosis prevalence observed among participants with BMI $\geq$35. Restricted cubic spline analysis showed a significant nonlinear association between BMI and liver fibrosis (P for nonlinearity = 0.00139) with disproportionate increase in fibrosis risk beginning in the obese range, suggesting a threshold-dependent metabolic relationship rather than a linear dose-response relationship. In multivariable survey-weighted analysis, BMI and AST were independently associated with increased odds of liver fibrosis. BMI (OR 1.14 and 1.07 respectively with both p < 0.001), followed by age (OR 1.03; p = 0.0354). Sex independently associated with liver fibrosis (OR 0.60, p = 0.0416) . Spine BMD did not show association with odds of liver fibrosis (OR 2.04; p = 0.235). **Conclusion:** BMI was non linearly associated with liver fibrosis, with disproportionately higher risk in severe obesity. AST remained the strongest predictor, while BMD was not associated. These findings support earlier fibrosis surveillance and risk stratification in patients with high BMI.



Disclosures: narissa nursjamsi: Nothing to Disclose, Prateeka Kodali: Nothing to Disclose, elsa sasongko: Nothing to Disclose, kesava achuta: Nothing to Disclose, pranay gupta: Nothing to Disclose, sujata kambhatla: Nothing to Disclose.

2345 | PERFORMANCE OF NON-INVASIVE TESTS FOR PREDICTING FIBROSIS SEVERITY IN A MULTI-CENTER LATIN AMERICAN STEATOTIC LIVER DISEASE COHORT

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Background: Latin America faces a growing burden of steatotic liver disease (SLD), yet previous assessments of most non-invasive tests (NITs) for fibrosis risk stratification have demonstrated poor performance in this population, particularly in retrospective cohorts. We aimed to compare the performance of commonly used serum-based and laboratory-derived NITs for predicting fibrosis in a well-characterized multinational Latin American SLD cohort. **Methods:** Cross-sectional analysis of prospectively enrolled adults with steatotic liver disease (SLD) at 16 tertiary centers across seven countries (Argentina, Brazil, Chile, Colombia, Dominican Republic, Mexico, and Peru). Fibrosis severity was assessed using liver biopsy, vibration-controlled transient elastography (VCTE), or clinical diagnosis of cirrhosis. Evaluated NITs included composite fibrosis indices, such as FIB-4, MAF-5, APRI, GGT-to-platelet ratio (GPR), and AST/ALT ratio, as well as individual laboratory markers such as AST, ALT, GGT, and platelet count. Diagnostic performance was assessed using AUROC, sensitivity, and specificity analyses, as well as logistic regression models. **Results:** The cohort included 923 participants (85.1% MASLD, 6.0% MetALD, and 8.9% ALD). The median age was 62 [52–69] years, and 56.6% were women. Significant and advanced fibrosis were present in 45.9% and 35.5% of participants, respectively. Among composite fibrosis index NITs, FIB-4 demonstrated the strongest discriminatory performance for significant fibrosis (AUROC: 0.723, 95% CI: 0.685–0.761) and advanced fibrosis (AUROC: 0.707, 95% CI: 0.669–0.745), followed closely by APRI (AUROC: 0.719, 95% CI: 0.679–0.758; and 0.704, 95% CI: 0.666–0.742, respectively). Platelet count also demonstrated strong discrimination across fibrosis stages (AUROC: 0.720, 95% CI: 0.683–0.757 and 0.726, 95% CI: 0.680–0.762, respectively). Compared with the lowest-risk category, FIB-4 >2.67 was associated with markedly increased odds of significant fibrosis (OR: 13.05, 95% CI: 7.03–24.23) and advanced fibrosis (OR: 13.45, 95% CI: 8.03–22.52). Platelet count $<150\times10^9$ /L was similarly associated with substantially increased odds of significant fibrosis (OR: 23.05, 95% CI: 10.56–50.33) and advanced fibrosis (OR: 15.89, 95% CI: 9.04–27.95). **Conclusion:** In this multinational Latin American SLD cohort, FIB-4 and APRI demonstrated the strongest performance among serum-based NITs for predicting fibrosis severity. Platelet count alone also showed strong discriminatory ability and robust associations with fibrosis progression. These findings support the utility of inexpensive and widely accessible NITs for fibrosis risk stratification in Latin American populations with SLD (Fondecyt #1241450).

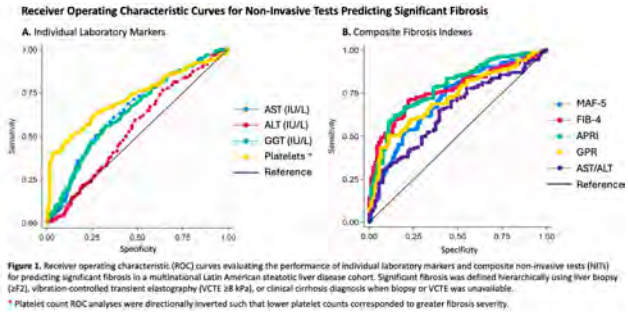


Figure 1. Receiver operating characteristic (ROC) curves evaluating the performance of individual laboratory markers and composite non-invasive tests (NITs) for predicting significant fibrosis in a multinational Latin American steatotic liver disease cohort. Significant fibrosis was defined hierarchically using liver biopsy (≥F2), vibration-controlled transient elastography (VCTE ≥8 kPa), or clinical cirrhosis diagnosis when biopsy or VCTE was unavailable.
* Platelet count ROC analyses were directionally inverted such that lower platelet counts corresponded to greater fibrosis severity.

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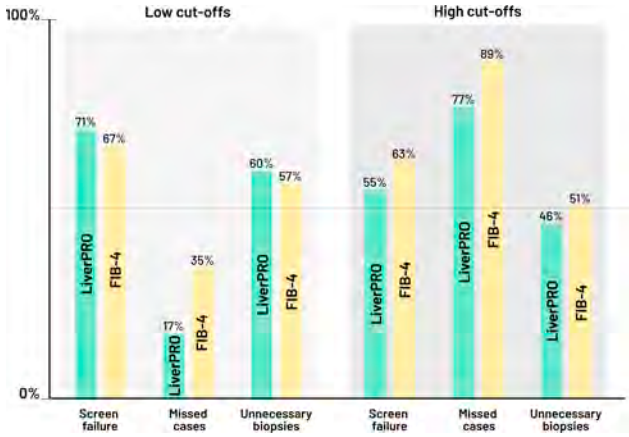
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Daniza Alexandra Contreras: Nothing to Disclose, Daniela Simian Marin: Nothing to Disclose, Juan Roblero: Nothing to Disclose, Pamlea Gill Galleguillos: Nothing to Disclose, Arun Sanyal: Nothing to Disclose, Juan Pablo Arab: Nothing to Disclose, Luis Díaz: Nothing to Disclose, Marco Arrese: Nothing to Disclose.

2346 | OPTIMIZING MASH CLINICAL TRIAL SCREENING USING LIVERPRO: ANALYSIS OF THE PHASE 2B EMMINENCE TRIAL

Julie Astono[1] Katrine Lindvig[1] Jerry Colca[2] Maja Thiele[1], [1]Evido Health, [2]Western Michigan University

Background: Efficient identification of patients eligible for clinical trials in metabolic dysfunction-associated steatohepatitis (MASH) is difficult with screen failure rates (SFR) often exceeding 80%. Non-invasive tests like FIB-4 can reduce biopsies but may miss eligible patients due to low sensitivity. We evaluated the potential of LiverPRO, a novel flexible blood-based medical device software for detecting liver fibrosis, to optimize screening compared with FIB-4. We conducted a retrospective analysis of the phase 2b EMMINENCE trial of the insulin sensitizer MSDC-0602K, which was handicaped by recruitment strategy and showed statistical histological benefit only on post-hoc analysis. **Methods:** We modeled four screening pathways using data from the EMMINENCE trial: (a-b) LiverPRO at cut-offs 0.25 and 0.65, (c-d) FIB-4 at cut-offs 1.3 and 2.67. Our primary outcome was SFR, secondary outcomes were proportion of unnecessary biopsies and missed eligible cases. The target of this analysis was enrollment with eligibility criteria commonly used in recent MASH trials: fibrosis stage $\geq$ F2 + non-alcoholic fatty liver disease activity score $\geq$ 4 with at least one in each component; steatosis, ballooning and inflammation, reflecting recruitment to both pre-cirrhosis and cirrhosis trials. **Results:** The EMMINENCE trial screened 1,090 individuals and performed liver biopsy in the 725 with aspartate aminotransferase $\geq$ 20 U/L, controlled attenuation parameter $\geq$ 270 dB/m and liver stiffness measurement $\geq$ 8.5 kPa. Of those, 222 (31%) met the target. The LiverPRO $\geq$ 0.25 pathway identified 628/1,090 individuals, of whom 460 had a biopsy, and 184 met target yielding a SFR of 71%. FIB-4 $\geq$ 1.3 yielded a slightly lower SFR of 67%. However, FIB-4 missed 35% of cases compared with 17% for LiverPRO, a relative reduction of 51%. The rate of unnecessary biopsies remained comparable: LiverPRO 60% and FIB-4 57%. At higher thresholds, LiverPRO $\geq$ 0.65 achieved the lowest SFR of 55%, while FIB-4 $\geq$ 2.67 had a slightly higher SFR of 63%, although at the expense of missed cases. LiverPRO missed 77%, while FIB-4 missed 89%. Unnecessary biopsy rates were 46% for LiverPRO and 51% for FIB-4. The AUROCs were 0.702 (95% CI: 0.661–0.742) for LiverPRO and 0.689 (95% CI: 0.648–0.730) for FIB-4. **Conclusion:** LiverPRO captures a greater proportion of eligible patients than FIB-4 without markedly increasing the unnecessary liver biopsies, suggesting that LiverPRO can enhance recruitment efficiency. Stricter screening thresholds reduce screen failures at the expense of more missed cases. The high screening thresholds can be used if sites are able to widen the screening funnel to achieve the required enrollment. LiverPRO's flexible design supports large-scale screening. This screening strategy will facilitate the recruitment and conduct of Phase 3 registration studies.



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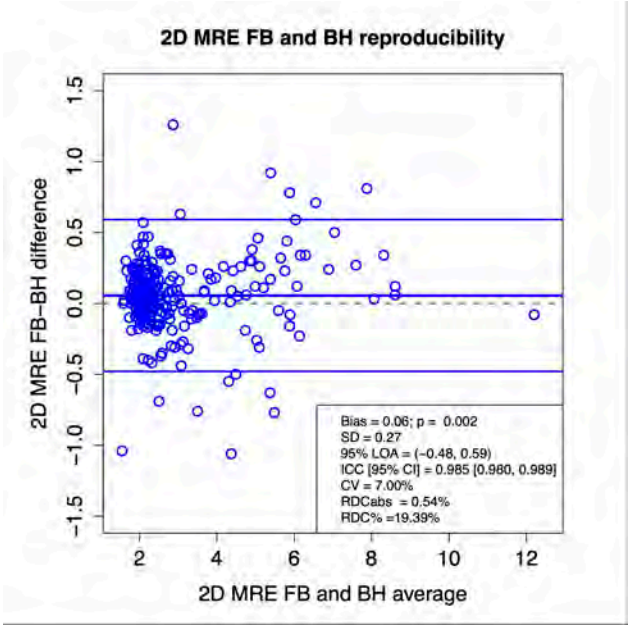
2347 | REPRODUCIBILITY BETWEEN AND REPEATABILITY OF FREE-BREATHING AND BREATH-HOLD 2D SE-EPI MRE FOR QUANTIFYING LIVER STIFFNESS

Gage Tanzman[1] Lael Ceriani[1] Nicholas Tripathi[1] Tanya Wolfson[1] Gavin Hamilton[1] Mary Dalupang[1] Egbert Madamba[1] Michael Middleton[1] Richard Ehman[2] Kevin Glaser[2] Yuan Le[2] Jiahui Li[2] Meng Yin[3] Yesenia Covarrubias[1] Mustafa Bashir[4] Scott Reeder[5] Bachir Taouli[6] Rohit Loomba[1] Claude Sirlin[1], [1]University of California, San Diego, [2]Mayo Clinic Rochester, [3]Mayo Clinic, [4]Duke University, [5]University of Wisconsin, Madison, [6]Icahn School of Medicine at Mount Sinai (ISMMS)

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Background: Free-breathing (FB) 2D spin-echo EPI (SE-EPI) magnetic resonance elastography (MRE) is an ~40-s investigational alternative to conventional ~16-s breath-hold (BH) 2D SE-EPI MRE. It uses the same 4-slice pulse sequence design but reduces the TR from ~1600ms to ~450ms, increases the number of phase offsets from 4 to 40, and uses temporal averaging. This increases the sampling efficiency, maintains the signal-to-noise ratio (SNR), reduces motion artifacts, and can be used when patients have difficulty suspending respiration. We sought to assess reproducibility between and repeatability of FB and BH 2D MRE for quantifying liver stiffness (LS) in adults with chronic liver disease (CLD). **Methods:** This prospective, single-center study enrolled adults with known or suspected CLD who received same-day FB and BH 2D SE-EPI MRE exams, a subset of whom had repeat exams after repositioning. Images were acquired at 60Hz on a GE 3T system with a 420-mm field-of-view reconstructed to a 256x256 final matrix. Expert analysts placed regions of interest (ROIs) in areas of planar wave propagation and recorded LS and cumulative ROI size (cROI). Exams were scored successful if cROI $\geq$ 700 pixels (Px). Success rate (SR) of each method was calculated. cROI (paired t-test) and SR (McNemar's test) were compared between methods. Inter-method reproducibility (all participants) and intra-method repeatability (of repeated exams) for quantifying LS were assessed by Bland-Altman analysis, yielding bias and its p-value, limits of agreement (LoA), proportional reproducibility (RDC %) or repeatability (RC%) coefficient, and intraclass correlation coefficient (ICC) with 95% confidence intervals (CIs). RC% were compared between methods using nonparametric bootstrap. **Results:** This study included 256 participants (136 female; mean age 56 ± 13 yrs; mean body mass index 31 ± 6 kg/m^2), 15 of whom had repeated exams. Median (range) cROIs were 4,349 (863-11,644) Px for FB and 4,398 (781-11,038) Px for BH 2D MRE (p = 0.366). The SR of FB (94%) and BH (95%) 2D MRE were also similar (p = 0.387). In 236 participants, both methods were successful. In these, mean LS (range) was 3.1 (1.0-12.2) kPa for FB and 3.0 (1.5-12.2) kPa for BH 2D MRE. Bias (p-value), LoA, RDC%, and ICC (95% CI) were 0.06 kPa (p = 0.002), (-0.5 kPa, 0.6 kPa), 19.4%, and 0.985 (0.980, 0.989), respectively. The difference in RC% for FB (8.3%) and BH (14.6%) 2D MRE was -6.3% (p = 0.013). **Conclusion:** In adults with CLD imaged at 3T, FB 2D MRE agreed with and had better repeatability than BH 2D MRE, with precision metrics akin to test-retest repeatability of BH 2D MRE in prior studies and negligible bias. FB 2D MRE is feasible as a repeatable alternative to BH 2D MRE.



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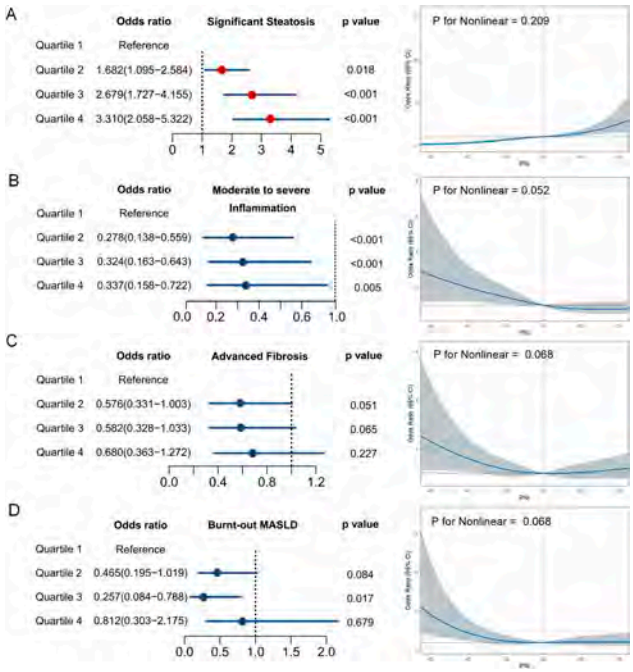
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2348 | ASSOCIATION OF PROGNOSTIC NUTRITIONAL INDEX WITH HISTOLOGICAL STAGE AND MORTALITY IN PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

Yixuan Zhu[1] Jie Li[2], [1]Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University, [2]Nanjing Drum Tower Hospital

Background: Nutritional–metabolic dysregulation is a central driver of metabolic dysfunction–associated steatotic liver disease (MASLD), yet quantitative assessment of nutritional status remains limited.This study aimed to investigate the associations between the prognostic nutritional index (PNI), an indicator of nutritional reserve, immune competence, and systemic inflammation, with histological severity and mortality in MASLD. **Methods:** This study included four population-based cohorts: two cross-sectional cohorts, the liver biopsy cohort and the vibration-controlled transient elastography (VCTE; FibroScan) cohort from 7 medical centers across China from 2004 to 2024, and two longitudinal cohorts, the National Health and Nutrition Examination Survey (NHANES) III cohort from the United States and the UK Biobank cohort from the United Kingdom. Logistic regression and restricted cubic splines were used to investigate the association between PNI levels and significant steatosis, moderate-to-severe inflammation and advanced fibrosis.The relationship between PNI and all-cause and cardiovascular-related mortality were subsequently assessed by cox and competing risk models in two follow-up cohorts. **Results:** We included 969 biopsy-proven and 1,967 VCTE-based Chinese MASLD patients. In the biopsy cohort, PNI showed a biphasic pattern across disease stages, initially rising and subsequently declining, with the inflection point corresponding to the onset of moderate-to-severe inflammation or advanced fibrosis. Higher PNI was independently and linearly associated with significant steatosis (P for nonlinear = 0.209), whereas lower PNI was linearly associated with moderate-to-severe inflammation, advanced fibrosis, and "burnt-out" MASLD (all P for nonlinear > 0.05), with these associations particularly evident in individuals aged ≥ 45 years.Findings were replicated in the VCTE cohort. In two longitudinal cohorts, lower PNI was associated with higher risks of all-cause, cardiovascular, and liver-related mortality, with a pronounced increase in risk observed in the lowest PNI category. **Conclusion:** PNI reflects histological disease phenotype and may serve as an independent prognostic marker. PNI may be a helpful tool to monitoring nutritional status and improve risk stratification in individuals with MASLD.



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Disclosures: Yixuan Zhu: Nothing to Disclose, Jie Li: Nothing to Disclose.

2349 | DIFFERENTIAL CANCER RISKS AND NONINVASIVE PREDICTORS IN MASLD, METALD, AND ALD: A LONGITUDINAL ANALYSIS

Hana Park[1] Ji Young Lee[2] Ja Eun Koo[2] Jong Soo Lee[2] Sungwon Park[2] Hye Won Park[2] Hye-Sook Chang[2] Hong-Kyu Kim[2] Jaewon Choe[2] Ju Hyun Shim[2], [1]Konkuk University School of Medicine, [2]Asan Medical Center

Background: The recently proposed classification of steatotic liver disease (SLD) includes metabolic dysfunction–associated steatotic liver disease (MASLD), MASLD with increased alcohol intake (MetALD), and alcohol-related liver disease (ALD). However, differences in long-term cancer risk across these phenotypes remain incompletely characterized. This study investigated cancer incidence across SLD subgroups. **Methods:** This longitudinal cohort study included 43,994 adults who underwent health check-ups between 2010 and 2011. Liver steatosis was diagnosed by ultrasonography. The predictive potential of the Fibrosis-4 Index (FIB-4) and the Steatosis-Associated Fibrosis Estimator (SAFE) score for cancer incidence was evaluated. **Results:** During a median follow-up period of 10.5 years (398,202 person-years), 3,169 cancers were documented (7.2%; 796.4 per 100,000 person-years). Compared with individuals without SLD, overall cancer risk was elevated in ALD (IRR 1.38, 95% CI 1.08–1.79) but not in MASLD or MetALD. Hepatocellular carcinoma risk was increased across all SLD groups. ALD was associated with an elevated risk of esophageal cancer (IRR 3.69) and stomach cancer (IRR 1.81), while MetALD was associated with an increased risk of stomach cancer (IRR 1.61). MASLD in women showed elevated risks of overall (IRR 1.19) and gynecological cancers (IRR 1.49). FIB-4 and SAFE scores demonstrated dose-response associations with cancer risk in all SLD subgroups. **Conclusion:** Cancer risk profiles differ across MASLD, MetALD, and ALD, with alcohol-related phenotypes showing the highest cancer burden. Noninvasive fibrosis indices such as FIB-4 and SAFE can stratify cancer risk and inform tailored surveillance strategies in patients with SLD.

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2350 | A PROGNOSTIC COMPARISON OF SIMPLE BLOOD TESTS FOR THE FIRST-LINE STRATIFICATION OF THE SEVERITY OF STEATOTIC LIVER DISEASE

Jerome Boursier[1] Adrien Lannes[2] Isabelle Fouchard[2] Frederic Oberti[2] Marine Roux[1], [1]Angers University, [2]Angers University Hospital

Background: The new blood tests Liver Risk Score (LRS), SAFE, MAF-5 and eLIFT are potential alternatives to the recommended FIB-4 for identifying at-risk patients in steatotic liver disease (SLD). Diagnostic studies that compared these simple non-invasive tests (NITs) used liver stiffness as the reference, which is only a surrogate of SLD severity. Here, we aimed: i) to determine which simple NITs best rule out patients at low liver risk in a longitudinal study with hard outcomes as the endpoint; and ii) to evaluate whether accuracy in diagnosing liver stiffness translates into prognostic accuracy. **Methods:** The ARPPEGE Registry aggregates data from all patients who have been managed at our Hepatology Department since 2004. From the Registry, we selected patients with SLD (MASLD or excessive alcohol consumption) who had data for NITs calculation, and who had no history of liver-related events (LRE) before or within 3 months after baseline. Eight simple NITs were evaluated (rule-out threshold): FIB-4 (< 1.30), APRI (≤ 0.5), NAFLD Fibrosis Score (NFS; < -1.455), Forns Index (FI; < 4.2), LRS (< 6), MAF-5 (< 0), SAFE (< 0), eLIFT (< 8). The study endpoint was LRE defined as cirrhosis complication or hepatocellular carcinoma. Discrimination for LRE was evaluated using integrated area under the receiver-operating characteristics (iAUC). **Results:** 2,682 patients were included (MASLD: n = 1,557; alcohol: n = 1,125). 350 LRE occurred during the median 5.9 years follow-up [IQR: 3.4-10.3], including 259 cirrhosis decompensations and 91 HCC. iAUC for LRE prediction was 81.8 [95%CI: 81.1-82.5] for eLIFT, FIB-4: 81.0 [80.2-81.8], SAFE: 80.7 [79.9-81.4], FI: 80.2 [79.4-81.0], LRS: 76.6 [75.8-77.4], APRI: 75.4 [74.6-76.3], NFS: 75.0 [74.2-75.9], MAF-5: 68.3 [67.4-69.2]. Using rule out threshold, the best balance between rate of patients in the low-risk group and sensitivity for LRE was achieved with eLIFT (low risk: 42%/sensitivity: 89%), FIB-4 (41%/89%), and LRS (30%/93%). SAFE, MAF-5 and FI provided better sensitivity (94-97%), but lower rate of low-risk patients (17-22%). Sensitivity for LRE was the lowest with NFS (81%) and APRI (66%). The iAUCs in the alcohol group (MAF-5: 67.8 to eLIFT:

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76.1) were lower than those in the MASLD group (APRI: 74.9 to SAFE: 86.4), but the NITs ranking remained similar between the two aetiologies. Finally, higher accuracy in diagnosing elevated liver stiffness (≥ 8, ≥ 10, ≥ 12 kPa) did not translate into better prognostic accuracy in the MASLD group. Especially, MAF-5 ranked among the top two tests for diagnostic accuracy, even though it has the lowest iAUC (prognosis) along with APRI. Conversely, FIB-4 provided one of the lowest diagnostic accuracies, yet it had the second highest iAUC. **Conclusion:** New simple blood tests do not provide better prognostic accuracy than FIB-4 in SLD. Diagnostic studies should be completed by prognostic evaluation to definitively determine which NITs are the most appropriate for clinical practice.

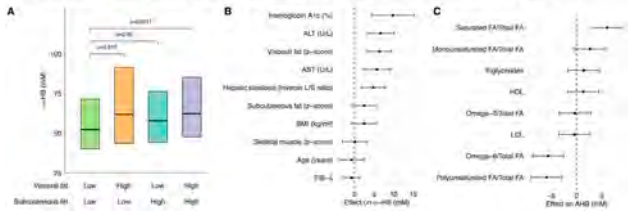
Disclosures: Jerome Boursier: echosens: Consultant, Inventiva: Consultant, Siemens: Consultant, Pfizer: Advisor, Novonordisk: Consultant, Gilead: Royalties or patent beneficiary, Siemens: Independent Contractor, Lilly: Consultant, Adrien Lannes: Nothing to Disclose, Isabelle Fouchard: Nothing to Disclose, Frederic Oberti: Nothing to Disclose, Marine Roux: Nothing to Disclose.

2351 | α-HYDROXYBUTYRATE, A CIRCULATING MARKER OF HEPATIC REDUCTIVE STRESS, PREDICTS HEPATIC STEATOSIS, VISCERAL FAT AND ATHEROGENIC RISK IN A LARGE, MULTICENTER COHORT

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Background: Hepatic reductive stress, defined by increased hepatic NADH/NAD$^+$, is mechanistically implicated in steatotic liver disease pathogenesis, insulin resistance, and dyslipidemia, and is reflected by the circulating biomarker α-hydroxybutyrate (α-HB). Biobank-based phenotyping enables integrated analysis of hepatic steatosis, body composition, and metabolomics to characterize reductive stress-associated disease in humans at scale. **Methods:** We identified adults in the Mass General Brigham Biobank with an abdominal CT scan within one year of biospecimen collection. Demographic and clinical data were from the time of imaging. Body composition features, including visceral fat, subcutaneous fat, and skeletal muscle area, were extracted using automated machine-learning algorithms and reported using z-scores relative to the corresponding demographics ("high" is $z > 0$, "low" is $z < 0$). Hepatic steatosis was quantified using the liver-to-spleen attenuation (L/S) ratio. Metabolomic profiling was performed using Nightingale Health nuclear magnetic resonance spectroscopy. α-HB was measured using the XpressGT kit. **Results:** Among 499 patients, median age was 62.1 (interquartile range 51.7-70.4) years and 45% were female. α-HB did not differ between body mass index (BMI) >30 vs. <25 kg/m^2 (60.3 vs. 56.2 mM; $p = 0.14$) or high vs. low skeletal muscle (56.4 vs. 58.4 mM; $p = 0.82$), but was increased in severe vs. mild-to-no steatosis (63.1 vs. 56.1 mM; $p = 0.026$), high vs. low subcutaneous fat (61.1 vs. 55.4 mM; $p = 0.019$), and high vs. low visceral fat (62.3 vs. 54.3 mM; $p = 2.6e\text{-}4$). Visceral and subcutaneous fat were correlated ($R^2 = 0.47$), with visceral fat primarily driving the increases in α-HB (**Figure 1A**). α-HB correlated with A1c, transaminases, visceral fat, and degree of hepatic steatosis in univariable regression (**Figure 1B**). In multivariable regression of body composition metrics, increased α-HB was independently associated with higher visceral fat ($\beta = 11.50$, $p = 8.7e\text{-}6$), but not subcutaneous fat ($\beta = -6.28$, $p = 0.065$), skeletal muscle ($\beta = 0.63$, $p = 0.78$), or BMI ($\beta = -0.09$, $p = 0.88$). Examining broad metabolomic profiling, α-HB was associated with the metabolically unfavorable saturated/total fatty acid ratio (**Figure 1C**). α-HB was inversely associated with the polyunsaturated/total fatty acid ratio and the omega-6/total fatty acid ratio, metabolic biomarkers associated with cardiovascular health. **Conclusion:** Consistent with mechanistic insights from preclinical studies, circulating α-HB reflects metabolically deleterious fat distribution—particularly visceral adiposity—rather than overall adiposity, as well as hepatic steatosis and atherogenic metabolic profiles. These data support the role of α-HB as a biomarker of steatotic liver disease and metabolic dysfunction.

Figure 1. (A) α-HB compared by visceral and subcutaneous fat ("high" is z-score >0, "low" is z-score <0). (B) Univariable regression between α-HB and select clinical variables and (C) metabolites (predictors are per 1 standard deviation; FA, fatty acids).



Disclosures: Wesley Dixon: Nothing to Disclose, Joseph Bonventre: Crinetics: Consultant, Dynamicure: Consultant, Dyne: Consultant, Mitsubishi Tanabe: Consultant, Sarepta: Consultant, Pacific Biosciences: Stock - publicly traded company, Autonomous Medical Devices: Stock – privately held company, Theravance: Stock - publicly traded company, Cascade Medical Devices: Stock – privately held company, Otsuka: Consultant, Pfizer: Consultant, Monogram: Consultant, MediBeacon: Stock – privately held company, Oisin:

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Stock – privately held company, Wearable Artificial Organs: Grant/Research Support, ROKIT: Grant/Research Support, Ayumi Takakura: Nothing to Disclose, Esperance Schaefer: Nothing to Disclose, Russell Goodman: Nothing to Disclose.

2352 | DEVELOPMENT AND VALIDATION OF M-SLD, A BIOPSY-ANCHORED NO-WAIST NONINVASIVE MODEL FOR STEATOTIC LIVER DISEASE

Hyo Jin Nam[1] Hae Young Kim[1] Sung Won Chung[1] Byungchul Cho[1] Won-Mook Choi[1] Jonggi Choi[2] Danbi Lee[1] Ju Hyun Shim[1] Seung Soo Lee[1] Kang Mo Kim[1] Young Suk Lim[1] Han Chu Lee[1], [1]Asan Medical Center, [2]University of Ulsan, Asan Medical Center

Background: FLI is widely used to estimate hepatic steatosis, but most validation studies have relied on ultrasonography rather than histology. We aimed to develop and validate M-SLD, a biopsy-anchored no-waist noninvasive model for steatotic liver disease, compare it with FLI, and externally validate the model in a large ultrasound screening cohort. **Methods:** We conducted a retrospective cross-sectional diagnostic accuracy study. The pathology source cohort included 3,062 patients with biopsy-based steatosis assessment; 363 without alcohol intake data were excluded from the main analysis, leaving 2,699 patients for temporal derivation (n = 1,787) and validation (n = 912). The primary endpoint was biopsy-defined steatosis ≥ S1. M-SLD was developed using ordinary multivariable logistic regression with age, sex, BMI, ln(TG), ln(GGT), ln(ALT), HDL, and diabetes. External validation used an ultrasound-defined health-screening cohort. **Results:** M-SLD outperformed FLI in both derivation (AUROC 0.772 vs 0.710; $p < 0.001$) and validation (0.760 vs 0.683; $p < 0.001$) cohorts. A rule-out threshold of 0.235 yielded validation sensitivity 89.7% and NPV 84.9%, whereas a rule-in threshold of 0.585 yielded validation specificity 88.3%. In the external ultrasound cohort (n = 120,785), M-SLD modestly but significantly outperformed FLI (AUROC 0.873 vs 0.865; $p < 0.001$). Retaining anti-HBc IgG-positive individuals in a sensitivity cohort yielded similar results (0.855 vs 0.849; $p < 0.001$). **Conclusion:** M-SLD is a biopsy-anchored, no-waist noninvasive model that improves upon FLI and provides clinically interpretable rule-out and rule-in thresholds for screening-oriented use.

Disclosures: Hyo Jin Nam: Nothing to Disclose, Hae Young Kim: Nothing to Disclose, SUNG WON CHUNG: Nothing to Disclose, Byungchul Cho: Nothing to Disclose, Won-Mook Choi: Gilead Sciences: Speaking and Teaching, AbbVie: Speaking and Teaching, Roche: Consultant, Boehringer Ingelheim: Advisor, GSK: Consultant, Eisai: Speaking and Teaching, AstraZeneka: Speaking and Teaching, Jonggi Choi: Nothing to Disclose, Nothing to Disclose, Danbi Lee: Nothing to Disclose, Ju Hyun Shim: Nothing to Disclose, Seung Soo Lee: Nothing to Disclose, Kang Mo Kim: Nothing to Disclose, Young Suk Lim: Gilead Sciences: Grant/Research Support, Han Chu Lee: Roche: Grant/Research Support, BMS: Grant/Research Support, Astrazeneca: Grant/Research Support, Merck: Grant/Research Support.

2353 | COMBINATORIAL MODELS OF BIOMARKER PANELS REFLECTING ACTIVITY VERSUS FIBROSIS ALLOW IDENTIFICATION OF MASLD SUB-PHENOTYPES WITH HIGH PRECISION

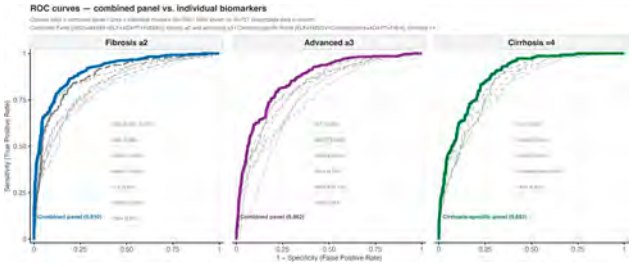
Gamze Bulut[1] Rohit Loomba[2] Ekaterina Smirnova[1] Katherine Yates[3] Anthony Samir[4] Claude Sirlin[5] Sarah Sherlock[6] Patricia Grebenstein[7] Tania Kamphaus[8] Anna Mae Diehl[9] Kris Kowdley[10] Brent Neuschwander-Tetri[11] David Kleiner[12] Bryce Hatfield[1] Roberto Calle[13] Arun Sanyal[1], [1]Virginia Commonwealth University, [2]University of California, San Diego, [3]Johns Hopkins University, [4]Harvard University Medical School, [5]University of California San Diego, [6]Pfizer, [7]FNIH, [8]NIH, [9]Duke University, [10]Liver Institute Northwest, [11]San Louis University, [12]National Cancer Institute, Bethesda, [13]GSK

Background: None of the currently available circulating biomarker panels identify all key specific phenotypes with high precision. Further, even for specific phenotypes, there is a steep decline in specificity at high sensitivity and vice versa reducing precision. **Aims:** To develop and validate a combinatorial approach leveraging biomarkers reflecting different aspects of disease biology and histology to identify MASH with clinically significant (≥ stage 2), advanced (≥ stage 3) fibrosis or cirrhosis (stage 4). **Methods:** A prespecified analysis of the NIMBLE cohort, a subset of the NIDDK NASH CRN study population, with complete cases of data (n = 764) including NIS2+™, MASEF, ADAPT, ELF, Fibrometer-V 3rd Gen (FM3GV), PROC3-6 and FIB-4 was performed. Non-negative matrix factorization identified biomarkers along 3-factors reflecting disease activity, fibrosis stage and demographic/clinical parameters. Biomarkers were included in the model based on natural elbow in Pearson |r| ranking and individual AUROC ≥ 0.80. Ridge-regression was trained using threshold-specific panels 10x5 repeated stratified cross-validation with stacked out of fold predictions providing stable AUROC estimates. **Results:** For at risk MASH (MASH + NAS ≥ 4 + fibrosis stage ≥ 2), the 5-biomarker model (NIS2+™ + MASEF + ELF + ADAPT + FM3GV), referred to as "combined

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panel", outperformed (AUROC 0.91, Sens = 86.4%, Spec = 80.9%, PPV = 91.0%, NPV = 72.6%) all of the individual panels including NIS2^{+TM} which had the best AUROC 0.86 for this context of use. Combined panel also performed well for MASH with ≥ stage 3 fibrosis (AUROC = 0.863; Sens = 80.8%, Spec = 77.2%, PPV = 73.4%, NPV = 83.8%) with threshold-specific selection (ELF+ADAPT+FM3GV) offering no meaningful gain (AUROC = 0.859; SD = 0.030). For stage 4 (prevalence = 18.8%), a cirrhosis-specific panel [ELF+FM3GV+CirrhosisScore+ ADAPT+FIB-4] outperformed the combined panel (AUROC = 0.883 vs 0.879), yielding NPV = 96.2% — correctly ruling out cirrhosis in 96% of predicted-negative cases (FN = 18/144). Ridge coefficient analysis revealed divergent biomarker weights across phenotypes: NIS2+^{TM} dominated ≥ stage 2 prediction but not for cirrhosis, while ELF strengthened monotonically from stage 2, to 3 to 4, confirming that a single model does not optimally serve all clinical purposes. **Conclusion:** Optimization of a combinatorial biomarker panel leveraging the ability of different biomarkers to reflect different aspects of MASLD allows identification of its key phenotypes for each stage with higher precision.



Disclosures: Gamze Bulut: Nothing to Disclose, Rohit Loomba: Eli Lilly and Company: Consultant, 89bio: Consultant, Aardvark Therapeutics: Consultant, Altimmune: Consultant, Alnylam/Regeneron: Consultant, Amgen: Consultant, Arrowhead Pharmaceuticals: Consultant, AstraZeneca: Consultant, Bristol Myers Squibb: Consultant, CohBar: Consultant, Eli Lilly: Consultant, Galmed Pharmaceuticals: Consultant, Gilead: Consultant, Glympse Bio: Consultant, Hightide: Consultant, Inipharma: Consultant, Intercept: Consultant, Inventiva: Consultant, Ionis: Consultant, Janssen, Inc.: Consultant, Madrigal Pharmaceuticals: Consultant, Merck, Metacrine, Inc.: Consultant, NGM Biopharmaceuticals: Consultant, Novartis: Consultant, Novo Nordisk: Consultant, Pfizer: Consultant, Sagimet Biosciences: Consultant, Terns Pharmaceuticals: Consultant, Theratechnologies and Viking Therapeutics: Consultant, 89bio: Stock options, Sagimet Biosciences: Stock options, Arrowhead Pharmaceuticals: Research grant, AstraZeneca: Research grant, Boehringer Ingelheim: Research grant, Bristol Myers Squibb: Research grant, Eli Lilly: Research grant, Galectin Therapeutics: Research grant, Galmed Pharmaceuticals: Research grant, Gilead: Research grant, Hanmi: Research grant, Intercept: Research grant, Inventiva: Research grant, Ionis: Research grant, Janssen, Inc.: Research grant, Madrigal Pharmaceuticals: Research grant, Merck: Research grant, NGM Biopharmaceuticals: Research grant, Novo Nordisk: Research grant, Pfizer: Research grant, Sonic Incytes: Research grant, Terns Pharmaceuticals: Research grant, LipoNexus, Inc.: Co-founder, Cascade Pharmaceuticals: Consultant, Eccogene: Consultant, HeptaBio: Consultant, Metavi: Consultant, Neurobo: Consultant, Novo Nordisk: Consultant, Sourcebio: Consultant, Roche: Consultant, Roche: Consultant, Takeda: Consultant, GSK: Grant/Research Support, Roche: Grant/Research Support, TensorBio: Grant/Research Support, Aarrowhead Pharmaceuticals: Consultant, Boehringer-Ingelheim: Consultant, Altimmune: Grant/Research Support, Eccogene: Grant/Research Support, Heptabio: Grant/Research Support, 89 bio: Grant/Research Support, Takeda: Grant/Research Support, Ekaterina Smirnova: Nothing to Disclose, Katherine Yates: Nothing to Disclose, Anthony Samir: Nothing to Disclose, Claude Sirlin: Bayer: Grant/Research Support, GE Healthcare: Grant/Research Support, Pfizer: Grant/Research Support, Siemens: Grant/Research Support, Butterfly: Grant/Research Support, AMRA: Grant/Research Support, Perspectum: Grant/Research Support, OrsoBio: Independent Contractor, Prosciento: Independent Contractor, Velocity: Independent Contractor, Bayer: Consultant, Boehringer-Ingelheim: Consultant, Ascelia: Consultant, Livivos: Advisor, Livivos: Executive role, Wolters Kluwer: Royalties or patent beneficiary, HealthPro Match: Speaking and Teaching, Foundation for Care Management: Speaking and Teaching, Sarah Sherlock: Nothing to Disclose, Patricia Grebenstein: Nothing to Disclose, TANIA KAMPHAUS: Nothing to Disclose, Anna Mae Diehl: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Kris Kowdley: Nothing to Disclose, Brent Neuschwander-Tetri: Abbvie: Consultant, Akero: Consultant, Aligos: Consultant, Arrowhead: Consultant, GSK: Consultant, Hepion: Consultant, Histoindex: Consultant, Madrigal: Consultant, Merck: Consultant, Mirum: Consultant, Sagimet: Consultant, Senseion: Consultant, HepGene: Stock – privately held company, HeptaBio: Consultant, Pliant: Consultant, David Kleiner: Nothing to Disclose, Bryce Hatfield: Nothing to Disclose, Roberto Calle: GSK: Employee, Regeneron: Employee, Arun Sanyal: Nothing to Disclose.

2354 | NORMAL ALANINE AMINOTRANSFERASE LEVELS UNDERESTIMATE THE BURDEN OF STEATOTIC LIVER DISEASE AND FIBROSIS IN US ADULTS: A CROSS-SECTIONAL ANALYSIS

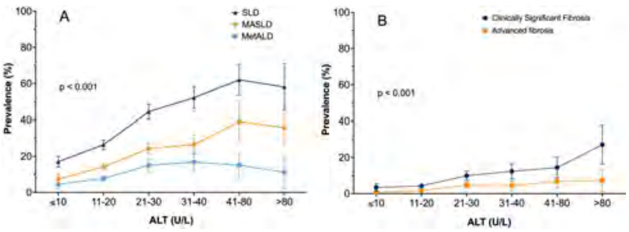
Jad Allam Saab[1] Paul Nietert[2] Don Rockey[2], [1]The University of Alabama at Birmingham, [2]Medical University of South Carolina

Background: Despite the wide use of serum alanine aminotransferase (ALT) in screening and evaluating

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liver disease, the definition of a normal ALT has long been debated. **Methods:** A cross-sectional analysis of the National Health and Nutrition Examination Survey (NHANES) from 2021-2023 was performed. A total of 5,245 US adults ≥18 years with available liver elastography, ALT, and BMI data were included. Steatotic liver disease (SLD) was defined by a controlled attenuation parameter of ≥285 dB/m. Metabolic dysfunction-associated steatotic liver disease (MASLD) was defined as SLD with ≥1 cardiometabolic risk factor and no or light alcohol use, whereas metabolic dysfunction and alcohol-associated liver disease (MetALD) was defined as SLD with ≥1 cardiometabolic risk factor and moderate alcohol use. Serum ALT levels were stratified into the following categories: ≤10, 11-20, 21-30, 31-40, 41-80, and >80 U/L. Our outcomes included the prevalence of SLD, MASLD, MetALD, clinically significant and advanced fibrosis across these distinct ALT strata, as well as the association between every 10 U/L increment in ALT and each outcome in multivariable logistic regression. **Results:** Of 5,245 adults, SLD prevalence increased stepwise from 17% at ALT ≤10 U/L to 26% at ALT 11-20 U/L, 44% at 21-30 U/L, and 52% at 31-40 U/L ($p < 0.001$) (**Figure A**). MASLD and MetALD followed similar graded patterns (both $p < 0.001$). Clinically significant fibrosis increased from 3% at ALT ≤10 U/L to 10% at ALT 21-30 U/L, and 12% at ALT 31-40 U/L, with similar increases in advanced fibrosis (both $p < 0.001$) (**Figure B**). After multivariable adjustments for age, sex, race/ethnicity, and BMI, each 10 U/L increase in ALT was associated with 24% greater odds of SLD (aOR, 1.24 [CI, 1.17 to 1.32]), 18% greater odds of MASLD (aOR, 1.18 [CI, 1.13 to 1.26]), 18% greater odds of clinically significant fibrosis (aOR, 1.18 [CI, 1.08 to 1.29]), and 13% greater odds of advanced fibrosis (aOR, 1.13 [CI, 1.00 to 1.24]). **Conclusion:** A significant burden of SLD, MASLD, MetALD, and hepatic fibrosis exists at ALT values commonly considered normal, including at levels 11-30 IU/L, suggesting current reference ranges may be too high to reliably exclude liver disease. We suggest that ALT should be interpreted alongside metabolic risk factors rather than as a standalone threshold.



Disclosures: Jad Allam Saab: Nothing to Disclose, Paul Nietert: Nothing to Disclose, Don Rockey: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose.

2355 | METABOLOME ANALYSIS REVEALED RED FLAG SIGNATURES FOR THE IDENTIFICATION OF MASLD RISK ACROSS PATIENTS WITH DYSMETABOLIC TRAITS

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Background: Adolescents and adults with dysmetabolic traits can either develop MASLD or show no evidence of fatty liver despite comparable cardiometabolic burden. However, it is still unclear whether patients with MASLD exhibit a specific circulating metabolic fingerprint compared to non-MASLD dysmetabolic subjects. Therefore, we aimed to analyze the serum metabolomic profile in a dysmetabolic cohort (n = 383), including adolescents with MASLD (n = 100, A-MASLD), adults with biopsy-proven (n = 95, B-MASLD) or non-invasive MASLD (n = 88, NI-MASLD) diagnosis, and a control group of dyslipidemic patients (n = 100, Dys) without MASLD. **Methods:** Targeted metabolomics (TM) was performed by UHPLC and analyzed through MetaboAnalyst 6.0. **Results:** Serum TM analysis revealed two main hierarchical clusters across dysmetabolic patients, highlighting that A/B-MASLD and NI-MASLD/Dys showed a similar metabolic pattern, respectively. In particular, ∼100 species were dysregulated (adjusted $p < 0.05$ FDR) in A/B-MASLD *vs* NI-MASLD/Dys patients. Among them, 64 metabolites were shared between the A/B-MASLD groups, suggestive of a conserved signature across pediatric and adult biopsied cases potentially due to a comparable rate of severe disease. To discover candidate MASLD-specific biomarkers, we performed the intersection analysis of differentially abundant species across the 4 groups. Sixteen metabolites were consistently altered in all MASLD patients (A-, B-, NI-MASLD) vs Dys. Two of them, glutamic acid and phosphatidylcholine (PC) O-40: 6, accurately discriminated MASLD from non-MASLD with 94% AUC (sens: 95%, spec: 88%), remaining stable after 10-fold cross-validation. Next, in the attempt to identify compounds with potential prognostic value, we stratified the dysmetabolic cohort according to MASLD severity. Nine metabolites were mainly dysregulated in severe disease vs controls (Dys). At multivariate and cross-validation analyses, a 5-metabolite model (Decanoylcarnitine, Ocatnoylcarnitine, Leucine, LysoPC 18: 2,

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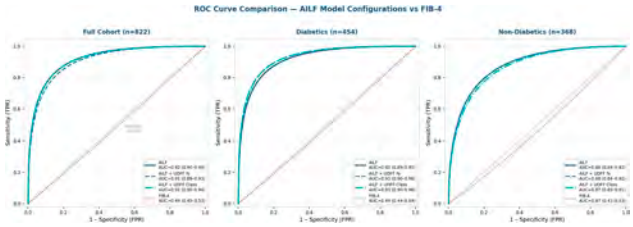
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SM 41: 2) achieved the best performance in distinguishing between severe MASLD vs controls (AUC 93%; sens: 87%; spec: 88%). **Conclusion:** Serum TM analysis captured a specific circulating profile shared across young and adult MASLD patients, possibly linked to an advanced clinical phenotype, which may be a red flag for cardiometabolic complications in pediatric cases. Furthermore, we disclosed 2 compounds specific for MASLD and 5-metabolites highly predictive of severe MASLD.
Disclosures: Miriam Longo: Nothing to Disclose.

2356 | CLINICAL UTILITY OF AN AI-BASED MODEL INCLUDING ULTRASOUND DERIVED FAT FRACTION FOR RISK STRATIFICATION OF ADVANCED FIBROSIS IN MASLD ACROSS METABOLIC PHENOTYPES

Ipshita Gupta[1] Sujoy Kar[2] Yassin Labyed[1] Akash Roy[2] Sudhakar Kattoju[2] Arati Gurung[1] Dhivya Josphin[2], [1]Siemens Healthineers, [2]Apollo Hospitals

Background: Non-invasive detection of advanced fibrosis in metabolic dysfunction-associated steatotic liver disease (MASLD) remains suboptimal, particularly in metabolically heterogeneous populations. We evaluated the clinical utility of an artificial intelligence-based liver fibrosis (AILF) model and its performance across diabetic and non-diabetic subgroups. **Methods:** A total of 822 patients with suspected MASLD were included, comprising 454 diabetics and 368 non-diabetics. The AILF model integrated clinical variables, laboratory markers, medication history, and quantitative ultrasound parameters including ultrasound-derived fat fraction (UDFF) and used automated point shear-wave elastography (Auto pSWE) as the reference. **Results:** In diabetic subjects (n = 454), baseline AILF achieved an AUROC of 0.92, accuracy of 83%, sensitivity of 76%, specificity of 89%, and MCC of 0.66. Addition of continuous UDFF percentage improved AUROC to 0.93, while categorical UDFF integration also achieved an AUROC of 0.93 with sensitivity improving from 76% to 78% and specificity maintained at 87%.In non-diabetic subjects (n = 368), baseline AILF achieved an AUROC of 0.88, accuracy of 86%, specificity of 91%, and MCC of 0.69. Integration of continuous UDFF percentage maintained AUROC at 0.88 while improving specificity to 93% and precision to 85%. Addition of categorical UDFF achieved accuracy of 86%, specificity of 92%, F1 score of 0.81, and improved MCC to 0.71, representing the strongest overall balanced performance within the non-diabetic cohort. Across the overall cohort, AILF and AILF+UDFF class showed AUROCs of 0.92, while AILF+UDFF percentage showed an AUROC of 0.91. DeLong analysis demonstrated significant superiority of all AILF configurations over FIB-4 (all $p < 0.0001$), with no significant difference between AILF variants ($p > 0.35$). In diabetics, both AILF+UDFF percentage and AILF+UDFF class achieved AUROCs of 0.93 compared with 0.92 for baseline AILF, while in non-diabetics AILF and AILF +UDFF percentage showed AUROCs of 0.88 and AILF +UDFF class achieved 0.87. No significant within-model DeLong differences were observed in diabetic or non-diabetic subgroups. **Conclusion:** Integration of multiparametric ultrasound biomarkers may enable scalable, non-invasive risk stratification and support improved clinical decision-making for liver fibrosis assessment. The observed improvement in diabetic cohorts suggests that incorporation of quantitative liver fat biomarkers may be particularly valuable in metabolically high-risk populations where fibrosis progression risk is elevated and early detection is clinically important. In non-diabetic patients, UDFF integration improved specificity and overall classification balance, supporting its role in reducing false-positive fibrosis classification while maintaining diagnostic robustness.



Disclosures: Ipshita Gupta: Siemens Healthineers: Employee, Sujoy Kar: Nothing to Disclose, Yassin Labyed: Nothing to Disclose, Akash Roy: Nothing to Disclose, Sudhakar Kattoju: Nothing to Disclose, Arati Gurung: Nothing to Disclose, Dhivya Josphin: Nothing to Disclose.

2357 | IN F0-F3 MASH, ≥5% WEIGHT LOSS (WL) SIGNIFICANTLY LOWERS VCTE AND ELF INDEPENDENT OF BIOPSY FIBROSIS IMPROVEMENT; RESMETIROM (RES) AND NOT PLACEBO (PBO) REDUCTION OF ELF AND VCTE ARE ASSOCIATED WITH BIOPSY IMPROVEMENT OF FIBROSIS, INDEPENDENT OF WL

Rohit Loomba[1] Quentin Anstee[2] Rebecca Taub[3] Dominic Labriola[3] Robin Mogg[3] Suneil Hosmane[3] Jörn Schattenberg[4] Vlad Ratziu[5], [1]San Diego School of Medicine, [2]Anstee Medical Services Ltd, [3]Madrigal Pharmaceuticals, [4]Saarland University Medical Center, [5]Service D' Hepatogastroenterologie (FR)

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Background: Changes in liver stiffness (VCTE) and ELF are proposed as surrogate endpoints for fibrosis response in MASH. Weight loss (WL) reduces liver stiffness and collagen markers in F0-F1 pts who have obesity/metabolic risk in whom serum markers of fibrosis may be elevated. In Res and Pbo pts, the impact of ≥5% WL on VCTE and ELF and association with biopsy fibrosis improvement (FI) was examined in F0-F1+F2-F3 MASH from MAESTRO program. **Methods:** Baseline (BL) and Week 52 (W52) VCTE+ELF components were determined in MAESTRO-NASH (NCT03900429) and MAESTRO-NAFLD-1 (NCT04197479). Logistic regression models explored associations between Res or Pbo changes (absolute difference for ELF, difference of log transformed for VCTE), weight change (≥5% vs < 5% WL) and biopsy FI. **Results:** In F0-F1, Res did not significantly reduce ELF v. Pbo. Approximately 14% pts w/F0-F1 had ≥ 5% WL at W52; ELF showed greater reduction in those with ≥5 % WL, with the P3NP component showing the greatest reduction in pts with WL, independent of treatment. P3NP is the major fibrogenesis biomarker in ELF. Baseline F0-F1 VCTE was mean 7.4 kPa, median 6.5 kPa. Res did not significantly reduce VCTE compared with Pbo in F0-F1 pts. VCTE was significantly reduced in ≥5 % WL vs. < 5% WL independent of treatment. In F2-F3, mean baseline ELF score was 9.8. At W52, 17% and 22% (80 and 100 mg Res) v. 12% (Pbo) had ≥ 5% WL. Absolute changes in ELF were evaluated using observed and modeled data from 758 F2-F3 pts (MAESTRO-NASH) with paired fibrosis, weight, and ELF data. There were independent associations of WL and FI with changes in ELF, and associations of change in ELF with WL were more pronounced than associations of change in ELF with FI; most noticeable effects were observed in the F3 pts. ≥5% WL on ELF attenuated a relationship between ELF and FI in Res and Pbo patients with <5% WL. Change in ELF with FI was more pronounced in <5% WL vs. ≥5% WL. Changes in ELF were strongly associated with FI only in F3 pts with < 5% WL. In F2-F3 baseline VCTE was 13.3 kPa. Relative changes in VCTE were evaluated using observed and modeled data from a cohort of 724 F2-F3 pts (MAESTRO-NASH) with paired fibrosis, weight, and VCTE data. There were independent associations of WL and FI with changes in VCTE, and associations of change in VCTE with WL were more pronounced than associations of change in VCTE with FI. The association of VCTE with FI was pronounced in < 5% WL vs. ≥ 5% WL in both res and pbo pts. Change in liver stiffness by VCTE predicted FI on biopsy in F2-F3 without WL. **Conclusion:** In patients with F2-F3 MASH, weight loss ≥5% and fibrosis improvement independently associated with reductions in VCTE and ELF. Fibrosis improvement was clearly associated with VCTE and ELF reduction in patients without weight loss treated with resmetirom or placebo. Confounding effects of weight loss on ELF and VCTE, independent of histologic fibrosis improvement, should be considered when evaluating MASH treatments.

Disclosures: Rohit Loomba: Eli Lilly and Company: Consultant, 89bio: Consultant, Aardvark Therapeutics: Consultant, Altimmune: Consultant, Alnylam/Regeneron: Consultant, Amgen: Consultant, Arrowhead Pharmaceuticals: Consultant, AstraZeneca: Consultant, Bristol Myers Squibb: Consultant, CohBar: Consultant, Eli Lilly: Consultant, Galmed Pharmaceuticals: Consultant, Gilead: Consultant, Glympse Bio: Consultant, Hightide: Consultant, Inipharma: Consultant, Intercept: Consultant, Inventiva: Consultant, Ionis: Consultant, Janssen, Inc.: Consultant, Madrigal Pharmaceuticals: Consultant, Merck, Metacrine, Inc.: Consultant, NGM Biopharmaceuticals: Consultant, Novartis: Consultant, Novo Nordisk: Consultant, Pfizer: Consultant, Sagimet Biosciences: Consultant, Terns Pharmaceuticals: Consultant, Theratechnologies and Viking Therapeutics: Consultant, 89bio: Stock options, Sagimet Biosciences: Stock options, Arrowhead Pharmaceuticals: Research grant, AstraZeneca: Research grant, Boehringer Ingelheim: Research grant, Bristol Myers Squibb: Research grant, Eli Lilly: Research grant, Galectin Therapeutics: Research grant, Galmed Pharmaceuticals: Research grant, Gilead: Research grant, Hanmi: Research grant, Intercept: Research grant, Inventiva: Research grant, Ionis: Research grant, Janssen, Inc.: Research grant, Madrigal Pharmaceuticals: Research grant, Merck: Research grant, NGM Biopharmaceuticals: Research grant, Novo Nordisk: Research grant, Pfizer: Research grant, Sonic Incytes: Research grant, Terns Pharmaceuticals: Research grant, LipoNexus, Inc.: Co-founder, Cascade Pharmaceuticals: Consultant, Eccogene: Consultant, HeptaBio: Consultant, Metavi: Consultant, Neurobo: Consultant, Novo Nordisk: Consultant, Sourcebio: Consultant, Roche: Consultant, Roche: Consultant, Takeda: Consultant, GSK: Grant/Research Support, Roche: Grant/Research Support, TensorBio: Grant/Research Support, Aarrowhead Pharmaceuticals: Consultant, Boehringer-Ingelheim: Consultant, Altimmune: Grant/Research Support, Eccogene: Grant/Research Support, Heptabio: Grant/Research Support, 89 bio: Grant/Research Support, Takeda: Grant/Research Support, Quentin Anstee: AstraZeneca, Boehringer Ingelheim, Intercept.: Grant/Research Support, Alimentiv, Akero, AstraZeneca, Axcella, 89Bio: Consultant, Boehringer Ingelheim, Bristol Myers Squibb, Corcept: Consultant, Enyo Pharma, Galmed, Genfit, Genentech, Gilead, GlaxoSmithKl: Consultant, Hanmi, HistoIndex, Intercept, Inventiva, Ionis, IQVIA, Janss: Consultant, Madrigal, Medpace, Merck, Metadeq, NGMBio, North Sea T: Consultant, Novartis, Novo Nordisk, PathAI, Pfizer, Pharmanest: Consultant, Poxel, Prosciento, Resolution Therapeutics, Roche,: Consultant, Ridgeline Therapeutics, RTI, Shionogi, Terns: Consultant, Fishawack,

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2358 | DIAGNOSTIC ACCURACY OF THE METABOLOMICS-ADVANCED STEATOHEPATITIS FIBROSIS (MASEF) SCORE FOR THE IDENTIFICATION OF AT-RISK MASH: A BIVARIATE RANDOM-EFFECTS META-ANALYSIS

Rahul Falodia[1] Ehsanullah Alokozay[2] Farhan Murtaza[3] Muhammad Junaid Azhar[4] Rameen Khalid[5] Abdul Wahab Ali[5] Muhammad Ikram[6] Waqas Anwar[7] Muhammad Hammad ul Hassan[8] Ahmed Ibrahim[9] Anand Deonarine[4] Miriam Michael[4] Bacel Nseir[3], [1]All India Institute of Medical Sciences, Jodhpur, [2]Faculty of Medicine, Kandahar University, Kandahar, Afghanistan, [3]HCA Houston Healthcare/ University of Houston Program, [4]Howard University Hospital, [5]Rawalpindi Medical University, [6]Allama Iqbal Memorial Teaching Hospital, Sialkot, [7]Wyckoff Heights Medical Center, [8]South Brooklyn Health NY, [9]University of Buffalo, Catholic Health System

Background: Non-invasive identification of "at-risk" metabolic dysfunction-associated steatohepatitis (MASH) defined histologically as MASH with a NAFLD Activity Score (NAS) >4 and significant fibrosis (> F2) is critical for clinical trial enrichment and targeted therapeutic strategies. The Metabolomics-Advanced Steatohepatitis Fibrosis (MASEF) score is a novel serum panel combining 12 lipid species with clinical parameters (BMI, AST, ALT). We performed a systematic review and diagnostic test accuracy (DTA) meta-analysis to determine the pooled global efficacy of the MASEF score at its standard clinical threshold of 0.33. **Methods:** Public databases were systematically screened to identify clinical verification datasets reporting diagnostic boundaries for the MASEF score. Raw 2x2 diagnostic frequencies (true positives, false positives, false negatives, true negatives) were extracted or mathematically reconstructed. To account for the inherent correlation between diagnostic parameters, a rigorous bivariate random-effects meta-analysis (Reitsma linear mixed-effects model) was executed using the mada engine in R. The primary model (Model A) strictly included cohorts utilizing histological liver biopsy as the reference standard. An exploratory sensitivity model (Model B) integrated additional cohorts using non-invasive clinical routing frameworks. **Results:** Four unique validation cohorts across three independent data publications encompassing 1,584 total subjects were modeled. In the primary biopsy-confirmed framework (Model A; 3 cohorts, n = 1,479), the bivariate model demonstrated a pooled sensitivity of 75.4% (95% CI: 67.8%–81.7%) and a pooled specificity of 68.3% (95% CI: 60.4%–75.2%), with a summary Area Under the Curve (AUC) of 0.779. Between-study heterogeneity for both sensitivity and false positive rates was exceptionally low (I^2 = 0%). In the all-inclusive sensitivity analysis (Model B; 4 cohorts, n = 1,584), diagnostic robustness remained stable, yielding a pooled sensitivity of 73.1% (95% CI: 64.6%–80.2%), a pooled specificity of 70.7% (95% CI: 62.9%–77.5%), and an overall AUC of 0.778 (I^2 = 0%). **Conclusion:** The MASEF score demonstrates high diagnostic reproducibility and zero statistical heterogeneity across international cohorts. Operating with a stable summary AUC of ~0.78, this blood-based metabolomic profile provides a highly reliable, reproducible non-invasive pathway to rule out or triage at-risk MASH, successfully minimizing reliance on secondary tissue histology or expensive specialized elastography inside clinical trial validation screens and frontline specialty clinics.

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2359 | MACHINE LEARNING ENABLED RISK STRATIFICATION IN MASLD: A NON-INVASIVE DECISION SUPPORT TOOL FOR EARLIER IDENTIFICATION AND REFERRAL FOR INTERVENTION

James Rickard[1] Jorg Taubel[2] Edward Jackson[2] Ulrike Lorch[2] Charlene Cheong[3], [1]Richmond Research Institute, [2]Richmond Pharmacology, [3]Richmond Research Institute

Background: Metabolic associated steatotic liver disease (MASLD) affects approximately one in three of the global adult population, and ranges in severity from benign fatty liver infiltration to hepatitis and cirrhosis. With growing rates of MASLD there is a need to identify patients earlier in the clinical pathway for

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appropriate referral and intervention. This will require additional tools to complement existing early assessment points in the clinical pathway, utilising routinely available clinical assessments only. Earlier identification and triaging of patients between low, medium and higher clinical risk will aid those in greater need earlier. We set out to develop a tool using Machine Learning approaches to support this opportunity of earlier identification. **Methods:** An observational cross-sectional study of 2081 volunteers aged 18-90 years was conducted (NCT04873258). The dataset was split into training, validation and test (60/20/20%). Two Random Forest (RF) binary classifiers were independently trained using two separate MASLD case definitions as defined by Fibroscan measurements (RF1: CAP $\geq$ 248 dB/m; RF2: CAP > 290 dB/m. RF1 was optimised as a high-sensitivity rule-out model to identify individuals unlikely to have MASLD, while RF2 was optimised as a high-specificity rule-in model to identify highly likely MASLD cases. Predicted probabilities from both models were subsequently combined into a threshold-based triage model to classify participants into low CAP < 248, medium > 248 & < 290 and high > 290dB/m groups. Thresholds were optimised on the validation dataset (negative predictive value (NPV) $\geq$ 95% and sensitivity $\geq$ 95% for the rule-out classification; positive predictive value (PPV) $\geq$ 90% and specificity $\geq$ 90% for the rule-in classification). Final triage model performance was evaluated on the independent test dataset. **Results:** The final RF models utilised age, weight, waist-to-height ratio, BMI, waist circumference, ALT, GGT and HbA1c for MASLD prediction. RF1 achieved sensitivity (0.890) and AUROC (0.887), while RF2 achieved specificity (0.788) and AUROC (0.879). The combined threshold-based triage model classified participants into low, medium and high-risk MASLD categories. The low-risk group achieved high NPV (0.940 [95% CI 0.903-0.975]) and sensitivity (0.951 [95% CI 0.919-0.978]), while the high-risk group achieved high PPV (0.900 [95% CI 0.750-1.00]) and specificity (0.993 [95% CI 0.982-1.00]). **Conclusion:** The proposed dual RF triage model demonstrated promising performance for non-invasive MASLD identification and triage, utilising simple test parameters. This three-classification framework minimises misclassifications by allocating uncertain cases into the medium category while achieving high NPV for < 248dB/m and high PPV in > 290dB/m classifications. We now plan to pilot this tool in primary care settings in the UK.

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2360 | GENETIC VARIANT BURDEN IN LEAN MASLD: A LARGE MULTI-COHORT EXOME SEQUENCING STUDY

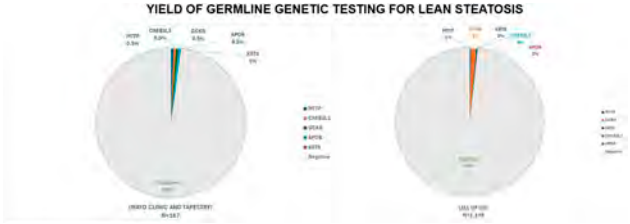
Jee Won Shin[1] Kirk Wangensteen[2] Samuel Antwi[2] Hunter Miller[2] Karina Sato-Espinoza[2] Filippo Pinto e Vairo[2] Jun Ma[2], [1]Mayo Clniic, [2]Mayo Clinic

Background: Metabolic dysfunction–associated steatotic liver disease (MASLD) affects ~25–30% of adults worldwide. Lean steatosis is a distinct subgroup associated with increased fibrosis and mortality, yet its biological drivers remain unclear. We previously showed enrichment of common *PNPLA3* risk alleles in lean individuals with steatosis. Small studies also suggest rare loss-of-function (LoF) variants in other genes may contribute to lean steatosis risk. To better define its genetic architecture, we analyzed clinical and exome sequencing data from > 100,000 Mayo Clinic biobank participants and > 400,000 All of Us Research Program participants. **Methods:** We analyzed whole-exome sequencing and clinical data from the Mayo Clinic Biobank, Tapestry Study, and the All of Us Research Program. Lean steatosis cases were defined by diagnosis codes in individuals with BMI $\leq$ 25 kg/m². Mayo Clinic participants underwent detailed chart review. Joint variant calling was performed for 458 liver disease-associated genes. Rare variants were defined as minor allele frequency $\leq$ 1%. Gene-based LoF burden testing used REGENIE adjusted for age, sex, and ancestry principal components; significance was assessed by nominal p values and false discovery rate (FDR). **Results:** The Mayo Clinic cohort included 188 lean cases with steatosis and 694 lean controls. No gene reached FDR significance. Nominal LoF enrichment was observed for *AGL* (OR 12.4 [2.65,58.3]; p < 0.01]), *PEX11B* (OR 29.8 [1.52,585], p < 0.05), *ABCG8* (OR 17.0 [1.30, 222], p < 0.05), *TSFM* (OR 14.7 [1.02, 211], p < 0.05), and *SKIC3* (OR 25.7 [1.31, 502]; p < 0.05). Replication in All of Us (1,178 cases and 15,095 controls) identified only *PEX11B* (OR 8.0 [1.34, 47.6]; p < 0.05) as associated with steatosis. Among 34 genes reported to be associated with steatotic liver disease in OMIM or Pubmed 29 were autosomal recessive, and no patients had biallelic variants. Among the 5 autosomal dominant genes, there was one carrier for *CREB3L3*, *GCKR*, *APOB*, and *MTTP* among cases, and none for *KRT8*. Overall, 4/187 (2.1%) Mayo cases had a potential monogenic explanation. In All of Us, 21/1,178 (1.78%) lean steatosis cases carried LoF variants in autosomal dominant steatosis genes, with enrichment for *MTTP* (OR 6.13 [1.66,22.6]; p < 0.05) and *KRT8* (OR 7.98 [1.50,42.5]; p < 0.05). **Conclusion:** Rare LoF variants showed nominal associations with lean steatosis, with replication only for *PEX11B* across two large biobanks. The predominance of single

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variants in recessive genes and absence of biallelic variants argue against haploinsufficiency as a disease mechanism. These findings suggest lean steatosis is more likely driven by complex/polygenic architecture or other host/environmental factors than by monogenic disorders. Genetic testing in lean patients with steatosis will likely have low yield without additional distinguishing clinical, host, or environmental features.



Disclosures: Jee Won Shin: Nothing to Disclose, Kirk Wangensteen: Nothing to Disclose, Samuel Antwi: Nothing to Disclose, Hunter Miller: Nothing to Disclose, Karina Sato-Espinoza: Nothing to Disclose, Filippo Pinto e Vairo: Nothing to Disclose, Jun Ma: Nothing to Disclose.

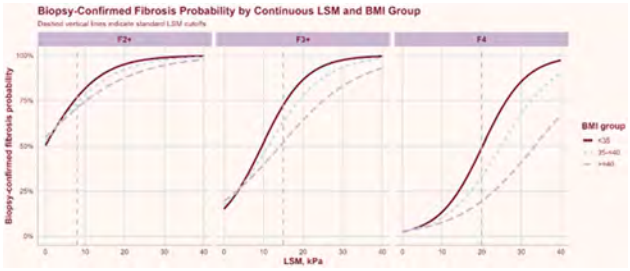
2361 | REFINING VCTE CUTOFFS IN PATIENTS WITH HIGH BMI: A SIMPLE ADJUSTMENT REDUCES FALSE POSITIVES FOR IDENTIFYING F3–F4 FIBROSIS FOR CLINICAL TRIALS

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Background: VCTE is increasingly utilized to identify patients with advanced fibrosis in both trial and clinical settings. However, high BMI alters the relationship between LSM and fibrosis risk. As a result, reliance on these measures alone may overstage fibrosis compared with biopsy, with important implications for patients selection and trial enrichment. The purpose of this study is to identify whether a correction algorithm can improve the performance of LSM in identifying patients with F2+, F3+, and F4 among patients with high BMI. **Methods:** Patients with available biopsy, VCTE, and BMI data were identified from a multicenter database of patients (n = 24491) screened for inclusion in MASH clinical trials, split into development (internal network centers) and external validation (external network centers) cohorts. Separate analyses were performed for F2+, F3+, and F4. Logistic regression was used to model fibrosis stage with LSM, BMI, and an LSM x BMI interaction term were used to assess BMI effects on fibrosis prediction. Multiple BMI-adjusted LSM thresholds were evaluated across BMI categories using standard highly specific cut offs commonly used in clinical trials of 8 kPa (F2+), 15 kPa (F3+), and 20 kPa (F4). Performance was assessed using sensitivity, specificity, and Youden index. **Results:** Of the 4549 patients with biopsy, BMI, and VCTE data, 2165 were included in the development cohort and 2,384 were included in the validation cohort. The LSM x BMI interaction term was statistically significant for F2+, F3+, and F4 in both cohorts (all $p < 0.05$). A BMI-adjusted strategy improved specificity and reduced false positives across fibrosis stages. For F2+, specificity increased from 18.9% to 45.4%, with corresponding reductions in false positives, although sensitivity declined from 92.0% to 79.0%. For F3+, specificity increased from 83.3% to 88.6%, with a 32% reduction in false positives, while sensitivity decreased from 46.5% to 40.1%. For F4, while sensitivity decreased from 45.0% to 39.7% specificity increased from 89.8% to 93.4%, with a 35% reduction in false positives. Adding 2 kPa in patients with BMI 35- < 40 and 4 kPa in patients with BMI ≥ 40 yielded the highest Youden index in both F3/F4 and F4 patients. **Conclusion:** Adjusting LSM by +2 kPa in patients with BMI 35- < 40 and +4 kPa in patients with BMI ≥ 40 kg/m2 increases the performance of VCTE in identifying patients with F2, F3 and F4 fibrosis.

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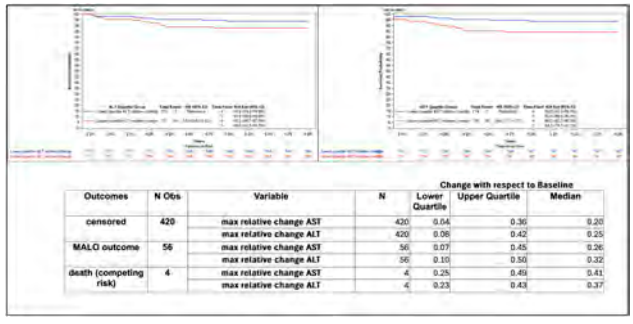
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2362 | AST AND ALT FLARES AS A RISK FACTOR FOR PROGRESSION TO MAJOR ADVERSE LIVER OUTCOMES IN CLINICALLY COMPENSATED INDIVIDUALS WITH MASLD AT INTERMEDIATE RISK OF MORTALITY

Vinay Jahagirdar[1] Breda Munoz-Hernandez[2] Julie Crawford[3] Philip Newsome[4] Brent Neuschwander-Tetri[5] A. Sidney Barritt[6] Michael Fried[3] Arun Sanyal[1], [1]Virginia Commonwealth University, Richmond, VA, [2]Headwater Science, Durham, NC, [3]Pedestal Health, Durham, NC, [4]Foundation for Liver Research and King's College Hospital; University of Birmingham, [5]Saint Louis University, St. Louis, MO, [6]University of North Carolina, Chapel Hill, NC

Background: Liver enzymes fluctuate over time in MASLD, but whether these fluctuations drive disease progression and predict major adverse liver outcomes (MALO) is unclear. We assessed the association between AST and ALT fluctuations and subsequent MALO risk in a predominantly non-cirrhotic population with clinically compensated MASLD. **Methods:** We performed a retrospective analysis of adults enrolled in the prospective, multicenter TARGET-NASH registry. Patients with FIB-4 1.3-2.6 were selected to enrich for outcome risk while minimizing confounding by advanced cirrhosis. Individuals with baseline AST or ALT >60 U/L were excluded. Liver enzymes obtained through routine care from enrolment through year 3 were analyzed as predictors of MALO between years 3 and 5. Fine-Gray competing risk and Kaplan-Meier analyses compared outcome risk between patients in the lowest versus highest quartile of relative AST or ALT change from baseline. **Results:** A total of 687 individuals were evaluated. Mean baseline FIB-4 was 1.8 (SD 0.35); 41% had type 2 diabetes and 79% had hypertension. Liver stiffness was available in 111 patients, with mean 10.9 kPa (SD 8.5). From enrollment to year 3, AST and ALT fluctuated widely, with median relative changes of 26% and 20%, respectively. These fluctuations were not explained by documented acute events, medication changes, or reported alcohol use, and returned to baseline without intervention. From years 3 to 5, 56 individuals developed MALO and 4 died. Baseline parameters did not predict outcomes. Patients who developed MALO demonstrated greater enzyme excursions from baseline than those without MALO, with mean AST rising 36% versus 30% ($p = 0.02$) and mean ALT rising 42% versus 36% ($p = 0.055$) from baseline. Compared with the lowest quartile, the highest quartile of AST relative change was associated with higher MALO risk, with 5-year MALO-free survival of 85% vs 94% and HR 2.66 (95% CI 1.11–6.37). The highest quartile of ALT relative change showed a nonsignificant trend toward lower 5-year MALO-free survival, 88% vs 94%, HR 2.03 (0.82–5.02). **Conclusion:** AST and ALT fluctuate widely over time in clinically compensated MASLD. A relative AST or ALT increase of approximately 50% from baseline identified patients with higher subsequent MALO risk, with the strongest association for AST. Aminotransferase flares may represent a clinically relevant risk marker for progression, although under-reported alcohol use requires further study.



Outcomes	N Obs	Variable	N	Change with respect to Baseline: Lower Quartile	Upper Quartile	Median
censored	420	max relative change AST	420	0.04	0.36	0.20
		max relative change ALT	420	0.08	0.42	0.25
MALO outcome	56	max relative change AST	56	0.07	0.45	0.26
		max relative change ALT	56	0.10	0.50	0.32
death (competing risk)	4	max relative change AST	4	0.25	0.49	0.41
		max relative change ALT	4	0.23	0.43	0.37

Disclosures: Vinay Jahagirdar: Nothing to Disclose, Breda Munoz-Hernandez: Nothing to Disclose, Julie Crawford: Nothing to Disclose, Philip Newsome: Novo Nordisk: Consultant, B Ingelheim: Consultant, Madrigal: Consultant, 89 Bio: Consultant, Sagimet: Consultant, Echosens: Speaking and Teaching, Abbott: Speaking

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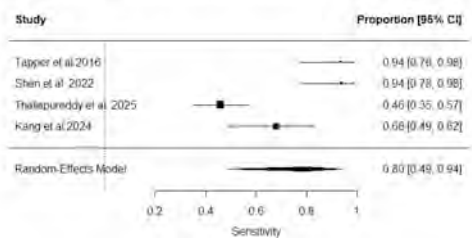
and Teaching, Akero: Consultant, Inventiva: Consultant, Brent Neuschwander-Tetri: Nothing to Disclose, A. Sidney Barritt: Nothing to Disclose, Michael Fried: Nothing to Disclose, Arun Sanyal: Nothing to Disclose.

2363 | SEQUENTIAL NON-INVASIVE FIBROSIS PATHWAYS FOR ADVANCED FIBROSIS IN MASLD: A SYSTEMATIC REVIEW AND META-ANALYSIS USING AN INTENTION-TO-DIAGNOSE FRAMEWORK

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Background: Accurate identification of advanced fibrosis in metabolic dysfunction-associated steatotic liver disease (MASLD) remains essential for risk stratification and clinical management. Sequential non-invasive fibrosis pathways incorporating serum biomarkers and elastography have emerged as alternatives to liver biopsy. However, real-world diagnostic performance remains incompletely characterized due to exclusion of indeterminate and failed tests in many studies. This study aims to evaluate the diagnostic accuracy and clinical performance of sequential non-invasive fibrosis pathways for detecting advanced fibrosis in MASLD using an intention-to-diagnose (ITD) framework. **Methods:** A systematic review was conducted according to PRISMA 2020 guidelines. PubMed, Embase, Scopus, Web of Science, and Cochrane Library databases were searched for U.S.-based studies published between 2010 and 2025 evaluating sequential non-invasive fibrosis testing pathways in adults with MASLD. Studies assessing serum-based indices, vibration-controlled transient elastography (VCTE), enhanced liver fibrosis (ELF), and related sequential approaches were included. For quantitative synthesis, studies were required to provide biopsy-confirmed advanced fibrosis (F3-F4) and reconstructable diagnostic contingency data. Diagnostic contigency data were reconstructed into 2×2 tables and analyzed using a bivariate random-effects model with restricted maximum likelihood estimation. **Results:** Twenty-five studies met criteria for qualitative synthesis, and four biopsy-based cohort studies comprising 619 patients were included in quantitative meta-analysis. Pooled sensitivity and specificity of VCTE for detecting advanced fibrosis were 0.80 (95% CI, 0.48-0.94) and 0.79 (95% CI, 0.68-0.87), respectively. The false-positive rate was 0.21 (95% CI, 0.13-0.32), and the area under the receiver operating characteristic curve was 0.84, supporting good discriminatory performance. Moderate heterogeneity was observed (I^2 = 65.4%). Sequential strategies combining Fibrosis-4 Index (FIB-4), NAFLD Fibrosis Score (NFS), ELF, and VCTE improved risk stratification while reducing unnecessary biopsy and specialty referral across included studies. **Conclusion:** Sequential non-invasive fibrosis pathways demonstrate clinically meaningful utility for identifying advanced fibrosis in MASLD. Application of an ITD framework provides more clinically relevant estimates of diagnostic performance by incorporating indeterminate and failed tests into analysis. Integration of serum biomarkers with elastography-based approaches may support structured, clinically applicable fibrosis risk stratification and reduce reliance on liver biopsy in routine clinical practice.

Figure 1: Forest Plot of sensitivity of VCTE for Advanced Fibrosis Detection in MASLD



Disclosures: Abidemi Akinrinmade: Nothing to Disclose, Bright Nwatamole: Nothing to Disclose, Olanrewaju Adeniran: Nothing to Disclose, Olutomiwa Omokore: Nothing to Disclose, Savio John: Nothing to Disclose.

2364 | AUTOMATED FIB-4 INTEGRATION INTO THE ELECTRONIC HEALTH RECORD ENHANCES MASLD RISK ASSESSMENT

Theodore Feldman[1] Brittany Bromfield[2] Jeremy Chimene-Weiss[3] Gregory Gheewalla[4] Emilie Mitten[2] Nathanael Fillmore[1] Nhan Do[1] Gyorgy Baffy[1], [1]VA Boston Healthcare System, [2]Brigham and Women's Hospital, [3]Boston University Medical Center, [4]Boston Medical Center

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is underrecognized in patients with diabetes despite increased risk for advanced liver disease. In 2020, our VA medical center implemented automated reporting of the fibrosis-4 (FIB-4) index within the electronic health record (EHR), integrating this noninvasive fibrosis assessment tool into the comprehensive metabolic panel. We evaluated the impact of this intervention on referral practices.

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Preliminary findings were presented previously. **Methods:** Patients with diabetes (HbA1c >6.5% on ≥1 occasion) seen in primary care clinics between 2010-2025 were identified. Patients were categorized into low (<1.3), intermediate (1.3-2.67), and high (>2.67) FIB-4 groups. Annual GI consults were reviewed to compare referral patterns in 2010-2019 and 2020-2025. Temporal trends were analyzed using interrupted time series and piecewise linear regression. **Results:** A total of 21,274 unique patients with diabetes were identified, with an average annual cohort size of 10,730. The median annual proportion with sufficient laboratory data for FIB-4 calculation was 45.0% (range, 37.0%-53.3%). Among these, 36.2% (26.8%-39.8%), 51% (48.9%-55.9%), and 12.7% (11.2%-17.3%) were categorized as low-, intermediate-, and high-risk, respectively, without significant annual variation. Annual outpatient GI consult volumes ranged from 614-1,090 (6.8%-9.5% of patients, NS), with annual liver-related referrals accounting for a median of 10.3% (8.5%-15.4%, NS). Referral patterns changed substantially during the study period. Hepatitis C-related referrals declined markedly (50.8%-2.2%, $p<0.001$), consistent with widespread antiviral treatment before 2020. Referrals prompted by abnormal liver tests showed no significant temporal change (range, 18.3%-38.5% of liver-related consults, NS), whereas MASLD/NAFLD-related ICD-9/10 codes emerged as a major referral indication (0.0%-42.0%, $p<0.001$). Annual rates of referrals among patients with elevated FIB-4 values that could already be calculated prior to liver-related referral did not change significantly (median, 54.8%; range, 44.8%-64.7%; NS), suggesting that lower MASLD-related referral rates before automated reporting were not primarily due to unavailable laboratory data. **Conclusion:** Automated inclusion of FIB-4 in the EHR may influence referral behavior and facilitate recognition of patients with diabetes at risk for advanced liver disease. However, peak annual referral rates represented only 5.1% and 22.3% of patients with intermediate and high FIB-4 scores, respectively, without significant positive trends over time. These findings highlight persistent gaps in MASLD risk assessment and the need for additional strategies to improve screening, clinician awareness, and risk stratification.
Disclosures: Theodore Feldman: Gilead Sciences: Stock - publicly traded company, Astrazeneca PLC: Stock - publicly traded company, Moderna: Stock - publicly traded company, Merck: Stock - publicly traded company, AbbVie: Stock - publicly traded company, Brittany Bromfield: Nothing to Disclose, Jeremy Chimene-Weiss: Nothing to Disclose, Gregory Gheewalla: Nothing to Disclose, Emilie Mitten: Nothing to Disclose, Nathanael Fillmore: Nothing to Disclose, Nhan Do: Nothing to Disclose, Gyorgy Baffy: Novo Nordisk: Consultant.

2365 | RECALIBRATING ELF AGAINST MRE IN MASH: TOWARD A DATA-DERIVED THRESHOLD FOR TREATMENT-ELIGIBLE FIBROSIS

Cecilia Katzenstein[1] Anna Mageras[2] Mark Miller[2] Victor Llanes[2] Xiaotao Zhang[1] Meena Bansal[3], [1]Icahn School of Medicine at Mount Sinai, [2]Icahn School of Medicine at Mount Sinai, New York, United States, [3]Icahn School of Medicine at Mount Sinai (ISMMS)

Background: The Enhanced Liver Fibrosis (ELF) test is FDA-approved for prognostication but is increasingly proposed for fibrosis risk stratification in MASH, where identifying treatment-eligible patients is now a clinical priority given approved MASH therapies. As an operator-independent, blood-based test, ELF shows promise as second-line testing in FIB-4 pathways where elastography is unavailable or unreliable. Recent guidance has incorporated lower ELF values than the standard 9.8 (AGA ≥9.2 for significant fibrosis; AASLD 9.2–10.5 for treatment-eligible F2–F3 disease), though cutoffs have historically been derived from biopsy-anchored prognostic cohorts. ELF has not been benchmarked against magnetic resonance elastography (MRE), the reference standard used in many academic medical centers. **Methods:** We conducted a prospective study of 200 consecutive patients evaluated for MASH at a tertiary center, all with ELF, vibration-controlled transient elastography (VCTE), and MRE. Significant fibrosis was defined as MRE ≥3.1 kPa and cirrhosis as ≥5.0 kPa. Discrimination was assessed by AUC (DeLong). Optimal thresholds were derived by the Youden index with 1,000-replication bootstrap validation. Predictive values were extrapolated across significant-fibrosis prevalence scenarios (5–49%) within the FIB-4 >1.3 pathway using Bayes theorem. **Results:** ELF and VCTE showed comparable discrimination for significant fibrosis (AUC 0.75 vs 0.78, $p=0.51$). The Youden-optimal ELF threshold was 9.42 in the full cohort, 9.58 in the FIB-4 >1.3 subgroup, and 9.60 in the indeterminate FIB-4 subgroup, consistently below the standard 9.8. Bootstrap validation confirmed negligible optimism (full-cohort bias-corrected 95% CI 0.68–0.82). Within the FIB-4 >1.3 pathway, ELF ≥9.5 and VCTE ≥8.0 kPa had identical sensitivity (79.4%) and referred a near-identical number of patients (71 vs 68). Across prevalence scenarios representative of non-hepatology settings (10–20%), ELF ≥9.5 and VCTE ≥8.0 kPa yielded closely matched negative predictive value (92–97%). **Conclusion:** This prospective MRE-anchored derivation places the optimal ELF threshold for significant fibrosis near 9.5. The value sits below the manufacturer cutoff, lies within the AASLD treatment-eligibility

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range, and falls within the narrow 9.37–9.6 range of data-derived thresholds from biopsy- and composite-reference cohorts. At this threshold ELF performs comparably to VCTE within FIB-4 pathways, and a negative result appears to reliably exclude significant fibrosis at non-hepatology prevalence, allowing patients to be managed without referral or elastography where access is limited.

Recalibrating the ELF threshold against MRE in MASH (n=200)

A MRE-anchored optimal ELF thresholds vs the standard cutoff

Population (n)	Reference standard	Optimal ELF threshold
Full cohort (200)	MRE	9.42
FIB-4 >1.3 (109)	MRE	9.58
Indeterminate FIB-4, 1.3–2.67 (78)	MRE	9.60
Manufacturer / standard cutoff	Biopsy-anchored prognostic	9.8

Youden-optimal thresholds (1,000-replication bootstrap-validated; full-cohort bias-corrected 95% CI 0.68–0.82). All three MRE-anchored optima fall below the manufacturer cutoff of 9.8 and cluster with data-derived optima reported from independent biopsy and composite-reference cohorts (range 9.37–9.6), suggesting a reproducible optimal ELF range near 9.5 across differing reference standards.

B Predictive values across modeled prevalence, FIB-4 >1.3 pathway

Significant fibrosis prevalence	ELF ≥9.5 PPV / NPV (%)	VCTE ≥8.0 kPa PPV / NPV (%)
5%	9.1 / 98.2	10.9 / 98.4
10%	17.5 / 96.2	20.6 / 96.6
15%	25.2 / 94.1	29.1 / 94.8
20%	32.4 / 91.9	36.8 / 92.8
30%	45.1 / 86.9	49.9 / 88.2
49% (observed cohort)	64.8 / 74.7	69.1 / 76.9

Bayes extrapolation applying observed FIB-4 >1.3 pathway operating characteristics (ELF ≥9.5: sensitivity 79.4%, specificity 58.5%; VCTE ≥8.0 kPa: sensitivity 79.4%, specificity 65.3%). Across non-hepatology prevalence (10–20%), ELF and VCTE yield closely matched negative predictive value; the highlighted 15% row is representative of endocrinology and diabetology populations.

Disclosures: Cecilia Katzenstein: Nothing to Disclose, Anna Mageras: The Kinetix Group: Advisor, Novo Nordisk: Advisor, Gilead Sciences: Grant/Research Support, Gilead Sciences: Advisor, Mark Miller: Nothing to Disclose, Victor Llanes: Nothing to Disclose, Xiaotao Zhang: Nothing to Disclose, Meena Bansal: Madrigal: Advisor, Fibronostics: Advisor, NOVO Nordisk: Advisor, GSK: Advisor, Merck: Advisor, Boeheringer-Ingelheim: Advisor, Boston Pharma: Advisor, The Kinetix Group: Advisor, Corcept: Advisor.

2366 | IMPACT OF OBESITY ON CONTROLLED ATTENUATION PARAMETER PERFORMANCE IN PATIENTS EVALUATED FOR METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD)

Chester Hui[1] Allen Luo[1] Neharika Bandaru[1] Kali Zhou[1] Emilie Mitten[2] Marvin Ryou[2] Thomas Wang[1], [1]Keck School of Medicine of USC, [2]Brigham and Women's Hospital, Massachusetts General Hospital

Background: Controlled attenuation parameter (CAP) obtained during vibration-controlled transient elastography (VCTE) is a widely used noninvasive measure of hepatic steatosis in metabolic dysfunction-associated steatotic liver disease (MASLD). Recent studies suggest these thresholds may overestimate steatosis severity in patients with obesity and propose substantially higher CAP cutoffs in patients with body mass index (BMI) > 30 kg/m². We aimed to further evaluate the impact of elevated BMI on CAP performance and propose BMI-stratified CAP thresholds. **Methods:** We performed a retrospective multi-center cohort study of adults with biopsy-proven MASLD who underwent VCTE with CAP assessment within 12 months of the liver biopsy between 2016 and 2025. Three academic centers were included. CAP measurements, liver stiffness measurement, probe type, fibrosis stage, diabetes status, and BMI were obtained. Histologic steatosis was graded as S0 (< 5%), S1 (5–33%), S2 (34–66%), and S3 (> 66%). Patients were stratified by BMI category: < 30, 30 to < 40, and ≥ 40 kg/m². Diagnostic performance of CAP for predicting S1, S2, and S3 steatosis was assessed using area under the receiver operating characteristic (AUROC) analysis. Optimal CAP thresholds for BMI subgroups were derived using the Youden Index, with calculation of AUROC, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). **Results:** Out of 597 patients who underwent VCTE, 557 had a CAP score available. 94 patients had no steatosis (S0), 202 had S1 grade, 169 had S2 grade, and 92 had S3 grade on biopsy. CAP diagnostic performance for S1 steatosis on biopsy was preserved as BMI increased (AUROC 0.749 and 0.749 for BMI < 30 and ≥ 40, respectively) (Figure 1). However, performance declined for S2 (AUROC 0.811 to 0.710) and S3 (AUROC 0.740 to 0.597) as BMI increased. CAP performance for S3 for BMI ≥ 40 did not significantly perform better than reference (p = 0.28), thus, Youden index was not measured for S3. Patients with BMI 30 to < 40 demonstrated significantly reduced discrimination for S2 and S3 steatosis compared with BMI < 30 (p = 0.03 for both). Optimal CAP thresholds increased with BMI across all steatosis grades, from 283 to 324 dB/m for S1 and from 302 to 330 dB/m for S2 (Figure 2). PPV declined as steatosis grading increased and was significantly lower for S3 steatosis across all BMI strata, ranging from 22-30%. **Conclusion:** Our study suggests that BMI impacts CAP performance and optimal thresholds for hepatic steatosis grading in MASLD. While performance for S1 steatosis is relatively preserved regardless of BMI,

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discrimination for more severe steatosis declines with increasing BMI. These findings may support the use of BMI-stratified CAP thresholds or alternative testing in patients with obesity if grading of hepatic steatosis is desired.

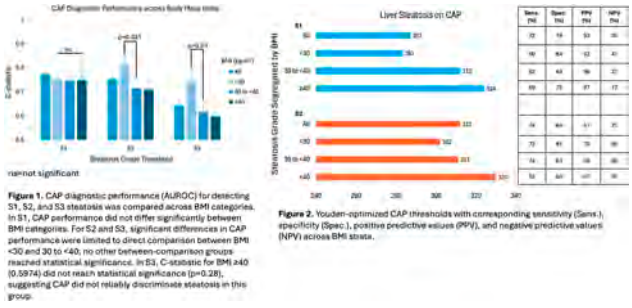


Figure 1. CAP diagnostic performance (AUROC) for detecting S1, S2, and S3 steatosis was compared across BMI categories. In S1, CAP performance did not differ significantly between BMI categories. For S2 and S3, significant differences in CAP performance were limited to direct comparison between BMI <30 and 30 to <40; no other between-comparison groups reached statistical significance. In S3, C-statistic for BMI ≥40 (0.5974) did not reach statistical significance (p=0.28), suggesting CAP did not reliably discriminate steatosis in this group.

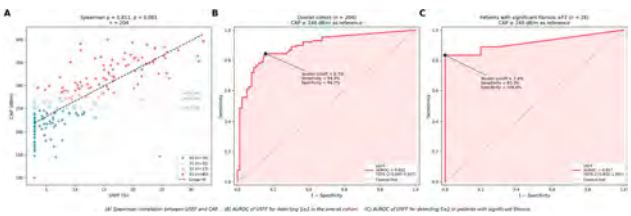
Figure 2. Youden-optimized CAP thresholds with corresponding sensitivity (Sens.), specificity (Spec.), positive predictive values (PPV), and negative predictive values (NPV) across BMI strata.

Disclosures: Chester Hui: Nothing to Disclose, Allen Luo: Nothing to Disclose, Neharika Bandaru: Nothing to Disclose, Kali Zhou: Gilead Sciences Inc: Grant/Research Support, Merck: Grant/Research Support, Emilie Mitten: Nothing to Disclose, Marvin Ryou: Nothing to Disclose, Thomas Wang: Nothing to Disclose.

2367 | COMPARATIVE PERFORMANCE OF ULTRASOUND-DERIVED FAT FRACTION (USFF - COMBINING TISSUE ATTENUATION AND TISSUE SCATTER DISTRIBUTION IMAGING) VERSUS CONTROLLED ATTENUATION PARAMETER (CAP) FOR HEPATIC STEATOSIS ASSESSMENT IN A REAL-WORLD COHORT

Joao Marcello de Araujo-Neto[1] Flavia Fernandes[2] Priscila Flores[3] Juliana Baptista Piedade-Barrocas[2] Vania Cristina de Sant`Anna R. Nunnes[1] Larissa Miranda[1] Melina Torres[1] Mauren Machado[4] Claudia Oliveira[5], [1]Federal University of Rio de Janeiro, [2]Hospital Federal de Bonsucesso, [3]UNIVERSIDADE FEDERAL FLUMINENSE, [4]Federal Universisty of Rio de Janeiro, [5]University of Sao Paulo School of Medicine

Background: Ultrasound-derived Fat Fraction (USFF) is a novel quantitative ultrasound technique that combines attenuation and backscatter coefficient measurements to estimate hepatic fat content, with the integration of both parameters potentially improving diagnostic accuracy. Data on its performance remain scarce. This study aims to compare USFF with the Controlled Attenuation Parameter (CAP), the most widely used point-of-care tool for hepatic steatosis quantification in clinical practice, in a real-life cohort. **Methods:** In this single-centre cross-sectional study, 442 consecutive adults were prospectively assessed with same-day transient elastography stiffness (Fibroscan), CAP and Ultrasound-derived Fat Fraction (Samsung RS85). USFF and CAP were measured in 204 patients. CAP-based steatosis grades followed the Karlas thresholds (S0 <248, S1 $248–<268$, S2 $268–<280$, S3 ≥ 280 dB/m). Significative fibrosis (F2) was considered $\geq$ 7kPa on trnasient elastography. Statistical tests were non-parametric throughout. **Results:** In the paired USFF and CAP cohort (n = 204), median age was 56 years (45–65), 51% were male, and CAP-defined steatosis grades were S0: 37.3%, S1: 17.2%, S2: 6.4%, and S3: 39.2%. USFF correlated strongly with CAP (Spearman ρ = 0.811, p < 0.001). USFF yielded AUROCs of **0.892 (95% CI 0.843–0.933)** for detecting any steatosis ($\geq$S1), **0.927 (0.888–0.958)** for $\geq$S2, and **0.919 (0.878–0.954)** for $\geq$S3, with Youden-optimal cutoffs of **6.7%, 8.1%, and 10.0%**, respectively. Sensitivity was **84.4%, 90.3%, and 86.3%**, and specificity was **84.2%, 81.1%, and 83.9%** for $\geq$S1, $\geq$S2, and $\geq$S3, respectively. The prevalence of significant fibrosis ($\geq$F2) by vibration-controlled transient elastography was 13.7%. Subgroup analysis by fibrosis stage (F0/F1 vs $\geq$F2) showed preserved USFF performance: AUROCs in F0/F1 (n = 176) were **0.89, 0.92, and 0.91**, versus **0.92, 0.97, and 0.97** in $\geq$F2 (n = 28), suggesting that hepatic fibrosis did not impair USFF accuracy. USFF was also compared with tradicional B-mode visual grading of steatosis. USFF correlated strongly with B-mode grading (Spearman ρ = 0.837, p < 0.001) and showed a clear dose-response: median USFF values were **3.0%, 7.7%, 13.0%, and 20.9%** for absent, mild, moderate, and severe steatosis, respectively (p < 0.001). AUROCs for detecting $\geq$S1, $\geq$S2, and $\geq$S3 were **0.92 (95% CI 0.88–0.96)**, **0.94 (0.90–0.97)**, and **0.94 (0.90–0.97)**, with Youden-optimal cutoffs of **7.3%, 9.0%, and 15.6%**, respectively. **Conclusion:** USFF demonstrated strong correlation with CAP and excellent agreement with visual B-mode steatosis grading, achieving high diagnostic accuracy for the detection and grading of hepatic steatosis in a real-life cohort, with consistent performance across fibrosis stage, sex, and age subgroups. These findings support USFF as a reliable, B-mode integrated alternative for non-invasive quantification of liver fat in routine clinical practice.



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2368 | ROBUST REPRODUCIBILITY OF LOCAL VERSUS CENTRAL MAGNETIC RESONANCE ELASTOGRAPHY READS ACROSS FIBROSIS STAGES AND BMI IN MASLD: AN INTERNATIONAL, PROSPECTIVE GOLDMINE STUDY

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Background: Magnetic resonance elastography (MRE) is the most accurate non-invasive imaging biomarker for hepatic fibrosis assessment in metabolic dysfunction-associated steatotic liver disease (MASLD). However, variability between local and centralized expert reads remains a critical knowledge gap for deployment in multicenter clinical trials and real-world practice. The aim of this study was to assess the reproducibility of local versus centralized MRE liver stiffness measurements (LSM) in a prospective multicenter cohort of adults with biopsy-confirmed MASLD. **Methods:** GOLDMINE is a prospective, multicenter, international, operator-blinded cohort study of adults with MASLD undergoing contemporaneous liver biopsy and MRE. Liver biopsies were scored by one expert liver pathologist blinded to clinical data using the NASH CRN histologic scoring system. LSM by MRE was analyzed 1) manually by an expert analyst locally and 2) centrally using an automated method (Hepatogram plus+, Resoundant, Inc) with expert analyst review. Reproducibility was assessed using intraclass correlation coefficient (ICC), within-subject coefficient of variation (wCV), repeatability coefficient (RDC%), Bland-Altman analysis, and Spearman correlation. Diagnostic accuracy for advanced fibrosis on central biopsy read (stage $\geq$3) was assessed by receiver operating characteristic (ROC) analyses. **Results:** A total of 293 adults with biopsy-proven MASLD were included; 59% were female, with a mean age 53.9 ($\pm$ 12.8 years) and BMI 31.7 ($\pm$ 4.9 kg/m^2). The distribution of fibrosis stage on central liver biopsy read was: stage 0 = 33% (N 89), 1 = 23% (N 63), 2 = 17% (N 45), 3 = 16% (N 43), 4 = 11% (N 29). Local and central MRE LSM demonstrated excellent reproducibility: ICC 0.97 (95% CI: 0.96-0.98), wCV 6.45%, RDC 17.89%, Bland-Altman bias 0.10 kPa with limits of agreement (-0.45; 0.67) kPa and Spearman correlation coefficient 0.97 (95% CI: 0.96-0.98) (**Table, Figure 1a**). Reproducibility was consistent across fibrosis stages and BMI subgroups. The AUROC to diagnose advanced fibrosis was 0.90 (95% CI 0.86–0.94) for the local MRE read versus 0.89 (95% CI 0.85–0.94) for the central read (Delong p = 0.27 indicating no significant difference between AUROCs) **(Figure 1b). Conclusion:** In this prospective, international multicenter cohort of adults with biopsy-confirmed MASLD, local and centralized MRE LSM demonstrated excellent reproducibility with minimal systematic bias across the full spectrum of fibrosis stages and BMI. These findings support the interchangeability of local and centralized MRE reads in multicenter MASLD trials and clinical practice, strengthening the utility of MRE as a scalable imaging biomarker across diverse international settings.

Table. Reproducibility Assessments for Local Versus Central MRE Reads

Subgroup	N	wCV (%)	RDC% (95% CI)	ICC (95% CI)	Bias (kPa)	Abs. Rel. Bias (%)	Rho (95% CI)
Overall cohort	293	6.45	17.89 (15.19, 20.89)	0.97 (0.96, 0.98)	0.10	6.47	0.97 (0.96, 0.98)
MRE LSM — by central liver biopsy fibrosis stage							
F0–F1	152	6.10	16.91 (13.91, 20.11)	0.91 (0.87, 0.94)	0.07	6.19	0.92 (0.89, 0.94)
F2	45	6.40	17.73 (12.23, 23.58)	0.97 (0.94, 0.99)	0.12	6.80	0.94 (0.89, 0.97)
F3–F4	72	7.12	19.74 (12.80, 29.02)	0.96 (0.91, 0.98)	0.18	6.74	0.95 (0.92, 0.97)
MRE LSM — by BMI							
BMI < 30 kg/m²	106	5.32	14.75 (12.72, 16.96)	0.99 (0.98, 0.99)	0.09	5.92	0.97 (0.96, 0.98)
BMI ≥ 30 kg/m²	187	7.02	19.44 (15.64, 23.66)	0.96 (0.94, 0.97)	0.12	6.79	0.96 (0.95, 0.97)

Figure1a. Bland Altman Analysis of Local vs Central MRE reads

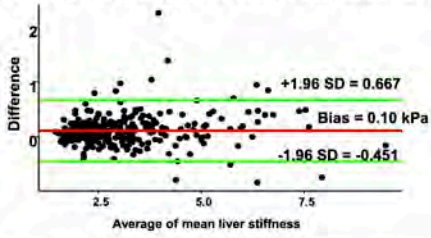
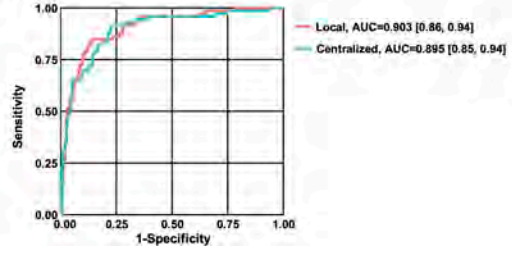


Figure 1b. AUROC for diagnosis of advanced fibrosis compared to liver biopsy using local versus central MRE read



Disclosures: Monica Tincopa: Nothing to Disclose, Nothing to Disclose, Suzanne Sharpton: Takeda Pharmaceuticals: Advisor, AstraZeneca: Grant/Research Support,

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2369 | LYSO- PHOSPHATIDYL ETHANOLAMINE (LYSOPE) MEDIATES THE EFFECT OF OBETICHOLIC ACID (OCA) IN INDIVIDUALS WITH NON-CIRRHOTIC METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH) WITH FIBROSIS: RESULTS OF METABOLOMICS IN THE FLINT STUDY

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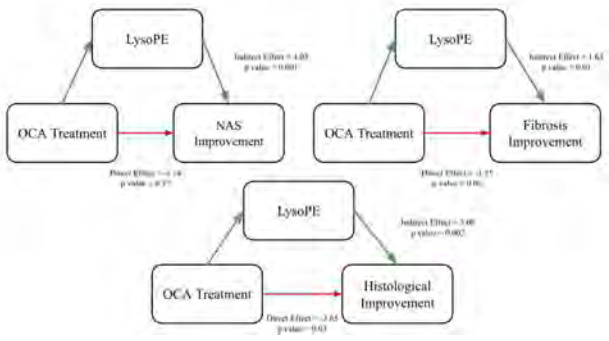
Background: Metabolic dysfunction-associated steatohepatitis (MASH) has limited treatment options, and the molecular mechanisms underlying therapeutic response remain insufficiently understood. Using data from the Farnesoid X Receptor (FXR) Ligand, obeticholic acid (OCA) in MASH Treatment (FLINT) trial, we wanted to understand metabolic underpinnings of response to FXR-agonists. **Methods:** Serum samples from 192 participants from FLINT-trial, including 99 in OCA and 93 in placebo arms were analyzed. Samples from weeks 0, 36, and 72 were analyzed to investigate the dynamic metabolomic pathways mediating the impact of FXR-agonism on histologic outcomes. Outcomes evaluated included MASH histologic improvement by FLINT-trial (reduction in MASLD activity Score (MAS) by ≥ 2 points without worsening fibrosis), any improvement in -MAS and, -fibrosis. A trajectory-based longitudinal causal mediation framework analysis was performed to summarize complex temporal mediator profiles using subject specific slopes. FDR < 0.05 was deemed significant. **Results:** The mean age of the cohort was 51.5 years, 67% were females, and 76% had obesity. A total of 13,893 metabolites across 566 samples were identified, of which slope of change in concentrations of 169 metabolites were significantly associated with the OCA treatment over duration of the study. Of the 169 metabolites, lyso-phosphatidyl ethanolamine (lysoPE), an important metabolite of glycerophospholipid metabolism, was identified as a key mediator of response to OCA, with significant indirect effects on all three histologic outcomes. The effect of OCA on MASH histologic improvement was primarily mediated through lysoPE (indirect effect: 5.08, $p = 0.002$), despite a negative direct (non-metabolomic) effect of OCA (-3.65, $p = 0.03$). LysoPE also mediated the effect of OCA on both MAS improvement (indirect

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effect: 4.03, p = 0.001) and fibrosis improvement (indirect effect: 1.63, p = 0.01), with no direct (non-metabolomic) effect. (Figure 1) LysoPE enriched glutathione, amino-acid and carnitine metabolism pathways. **Conclusion:** Longitudinal causal mediation analysis of metabolomics in the FLINT trial identified lysoPE as a key mediator of response to FXR-agonism. Our results show that early metabolomic changes during treatment with FXR-agonists class of medications, and possibly other classes of medications as well, in clinical trials could help identify patients who might be most likely to benefit from continuing therapy.

Figure 1: Indirect and Direct Effects of Treatment on Clinical Outcomes in the Trajectory-Based Longitudinal Causal Mediation Analyses



Disclosures: Niharika Samala: Novo Nordisk: Consultant, Madrigal: Advisor, Petauri Kinect: Grant/Research Support, Eli Lilly: Grant/Research Support, Regeneron: Grant/Research Support, GSK: Grant/Research Support, Xincheng Li: Nothing to Disclose, Matthew Smith: Nothing to Disclose, Wanyu Zhang: Nothing to Disclose, Maiying Kong: Nothing to Disclose, David Hein: Nothing to Disclose, Dean Jones: Nothing to Disclose, Jianzhu Luo: Nothing to Disclose, Hongmei Zhang: Nothing to Disclose, Naga Chalasani: Madrigal, Eccogene, Insitro, Boston Pharma, Chugai: Consultant, Zydus, GSK, Akero, Plaint, Altimmune: Consultant, Exact Sciences: Grant/Research Support, NIH: Grant/Research Support, Heligenics: Board member, investor, Avant Sante: Board member, investor, Ipsen, Biomea Fusion, Pfizer, Merck: Consultant, Matthew Cave: Nothing to Disclose.

2370 | PERFORMANCE OF THE FATTY LIVER INDEX AND HEPATIC STEATOSIS INDEX FOR IDENTIFYING METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE IN A SAUDI COHORT: THE GENESIS STUDY

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Background: Non-invasive scores are widely used to case-find metabolic dysfunction-associated steatotic liver disease (MASLD) in primary care and endocrinology settings, but data from Middle Eastern populations remain limited. We evaluated the Fatty Liver Index (FLI) and Hepatic Steatosis Index (HSI) against vibration-controlled transient elastography (VCTE)-defined MASLD in the Saudi GENESIS cohort. **Methods:** We analyzed baseline data from GENESIS, a prospective, population-based study conducted across seven primary care centers in Saudi Arabia between March 2024 and June 2025. MASLD was defined as hepatic steatosis on VCTE (controlled attenuation parameter ≥ 268 decibels per metre) plus at least one of the five cardiometabolic risk factors per the 2023 multisociety Delphi consensus. We calculated FLI and HSI using published formulas. We assessed discrimination using the area under the receiver operating characteristic curve (AUC). We reported sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy at the lower cutoff threshold (< 30 for both scores) and the rule-in cutoffs (FLI ≥ 60; HSI ≥ 36) with Wilson 95% confidence intervals (CIs). **Results:** MASLD was present in 1,111 of 2,979 participants (37.3%) based on VCTE. FLI showed numerically higher discrimination than HSI (AUC, 0.806 [95% CI 0.791–0.822] vs. 0.788 [95% CI 0.771–0.805]. At the rule-out cutoff, HSI had higher sensitivity and NPV than FLI (99.5% and 98.1% vs. 92.4% and 91.5%) but lower specificity (15.6% vs. 49.2%). At the rule-in cutoff, FLI had higher specificity, PPV, and accuracy than HSI (76.5%, 64.1%, and 73.9% vs. 49.7%, 51.4%, and 64.5%). **Conclusion:** FLI demonstrated numerically higher overall discrimination and better rule-in performance than HSI for identifying MASLD in this Saudi population-based cohort. HSI provided near-complete rule-out sensitivity but had limited rule-in utility at published cutoffs, supporting population-specific recalibration before clinical implementation in Saudi primary care.

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Table 1. Diagnostic performance of Fatty Liver Index and the Hepatic Steatosis Index for metabolic dysfunction-associated steatotic liver disease in the GENESIS cohort (n = 2,979).

Score, Cutoff	AUC (95% CI)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	Accuracy, % (95% CI)
FLI <30 (rule-out)	0.806 (0.791–0.822)	92.4 (90.7–93.9)	49.2 (46.9–51.6)	52.3 (50.1–54.6)	91.5 (89.6–93.1)	65.5 (63.7–67.2)
FLI ≥60 (rule-in)	0.806 (0.791–0.822)	69.4 (66.6–72.1)	76.5 (74.5–78.5)	64.1 (61.3–66.8)	80.6 (78.6–82.4)	73.9 (72.2–75.4)
HSI <30 (rule-out)	0.788 (0.771–0.805)	99.5 (98.8–99.8)	15.6 (14.0–17.4)	41.3 (39.3–43.3)	98.1 (95.7–99.2)	47.0 (45.1–48.8)
his ≥36 (rule-in)	0.788 (0.771–0.805)	89.2 (87.1–91.0)	49.7 (47.3–52.1)	51.4 (49.1–53.7)	88.5 (86.3–90.4)	64.5 (62.6–66.2)

Abbreviations: AUC, area under the receiver operating characteristic curve; CI, confidence interval; FLI, Fatty Liver Index; HSI, Hepatic Steatosis Index; NPV, negative predictive value; PPV, positive predictive value.

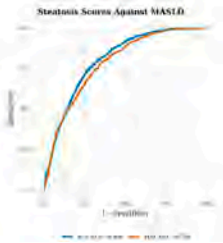


Figure 1. Receiver operating characteristic curves for the Fatty Liver Index (FLI) and the Hepatic Steatosis Index (HSI) against metabolic dysfunction-associated steatotic liver disease in the GENESIS cohort. The diagonal dashed line represents non-informative discrimination.

Abbreviations: AUC, area under the receiver operating characteristic curve; FLI, Fatty Liver Index; HSI, Hepatic Steatosis Index; MASLD, metabolic dysfunction-associated steatotic liver disease; ROC, receiver operating characteristic.

Disclosures: Saleh Alqahtani: Nothing to Disclose, Shadan AlMuhaidib: Nothing to Disclose, Faisal Sanai: Nothing to Disclose, Bandar Al-Judaibi: Nothing to Disclose, Feras Altunusi: Nothing to Disclose, Basmah Khoja: Nothing to Disclose, Sahar Alnasrallah: Nothing to Disclose, Abdulraheem Bayameen: Nothing to Disclose, Abdullah Alharthi: Nothing to Disclose, Mona Ismail: Nothing to Disclose, Mohammed Alghamdi: Nothing to Disclose, Khalid Alswat: Nothing to Disclose, Waleed Alhazzani: Nothing to Disclose.

2371 | IMPACT OF OBESITY ON VIBRATION-CONTROLLED TRANSIENT ELASTOGRAPHY PERFORMANCE IN PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD)

Allen Luo[1] Chester Hui[1] Neharika Bandaru[1] Kali Zhou[1] Emilie Mitten[2] Marvin Ryou[2] Thomas Wang[1], [1]Keck School of Medicine of USC, [2]Brigham and Women's Hospital, Massachusetts General Hospital

Background: Vibration-controlled transient elastography (VCTE) is a validated noninvasive tool for liver fibrosis assessment in MASLD, with AASLD guidance endorsing liver stiffness measurement (LSM) thresholds of < 8 kPa and > 12 kPa to rule in and rule out advanced fibrosis in MASLD, respectively, and < 10 kPa and ≥ 15 kPa for advanced chronic liver disease (ACLD). Whether these thresholds perform equally across BMI categories remains uncertain, as increasing abdominal adiposity may attenuate probe signal transmission. We aimed to evaluate BMI-stratified VCTE performance in predicting liver fibrosis stages. **Methods:** We performed a retrospective cohort study of adults with biopsy-proven MASLD who underwent VCTE within 12 months of liver biopsy from 2016-2025 at three academic centers. LSM (kPa) and fibrosis stage (NASH CRN) on biopsy were obtained. Patients were stratified by BMI at time of biopsy: < 30, 30-40, and ≥ 40 kg/m². LSM performance for various fibrosis stages (F2-F4) was assessed by area under the receiver operating characteristic (AUROC) analysis. Optimal thresholds were derived using the Youden Index. Evaluation of existing AASLD thresholds for advanced fibrosis and ACLD were performed with BMI stratification. **Results:** 597 patients were included, including 188 (31.5%) with advanced fibrosis (F3) and 76 (12.7%) with ACLD (F4) on liver biopsy. VCTE overall performance for predicting liver fibrosis stages (F2-F4) was moderate (AUROC 0.75-0.77), with decreasing accuracy as BMI increased (not statistically significant) [Figure 1]. Youden-derived optimal thresholds were highest for patients with BMI ≥ 40 [Figure 2]. Rule-out performance of VCTE remained robust. Across all BMI categories, LSM of < 8 kPa demonstrated a negative predictive value (NPV) of 86-91% for advanced fibrosis and LSM of < 10 kPa had NPV 93-100% for ACLD. In contrast, rule-in performance of VCTE deteriorated with increasing BMI. Positive predictive value (PPV) for LSM > 12 kPa in predicting advanced fibrosis decreased from 73.3% in patients with BMI < 30 to 38.5% for BMI ≥ 40 (p = 0.0003) [Figure 3]. PPV for LSM ≥ 15 kPa in predicting ACLD declined similarly from 38.3% in BMI < 30 to 17.5% in BMI ≥ 40 (p = 0.0362). PPV in predicting ACLD at higher CSPH thresholds (LSM ≥ 20 kPa with PLT < 150K and LSM ≥ 25 kPa) also remained poor despite higher cutoff values. **Conclusion:** Higher BMI substantially impacts VCTE diagnostic performance in patients with MASLD. While rule-out thresholds for cirrhosis and CSPH retain excellent NPV across all BMI categories, rule-in performance declined as BMI increases, suggesting obesity-associated inflation of LSM and increased risk of false positives. BMI-stratified VCTE thresholds or alternative testing may improve fibrosis risk stratification in patients with obesity.

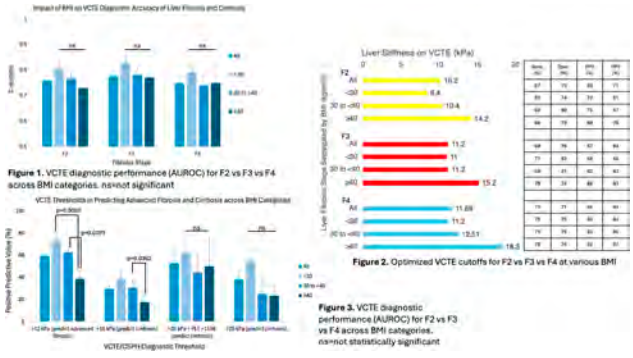


Figure 1. VCTE diagnostic performance (AUROC) for F2 vs F3 vs F4 across BMI categories. ns=not significant

Figure 2. Optimized VCTE cutoffs for F2 vs F3 vs F4 at various BMI

Figure 3. VCTE diagnostic performance (AUROC) for F2 vs F3 vs F4 across BMI categories. ns=not statistically significant

Disclosures: Allen Luo: Nothing to Disclose, Chester Hui: Nothing to Disclose, Neharika Bandaru: Nothing to

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2372 | PROSPECTIVE REAL-WORLD MASH SCREENING IN PRIMARY CARE YIELDS HIGH PREVALENCE OF SIGNIFICANT FIBROSIS AND IDENTIFIES HIGH-RISK METABOLIC PHENOTYPES

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Background: Metabolic dysfunction-associated steatohepatitis (MASH) is a leading cause of advanced chronic liver disease, yet fibrosis screening remains underutilized in primary care, resulting in underdiagnosis of significant fibrosis. We evaluated the prevalence and predictors of significant fibrosis among primary care patients with metabolic dysfunction-associated steatotic liver disease (MASLD) risk factors undergoing prospective FIB-4–based screening. **Methods:** We conducted a prospective pragmatic implementation trial in a large primary care network with ~60,000 annual visits. Adults with type 2 diabetes mellitus (DM), obesity, or both were identified through the electronic medical record (EMR); patients with viral hepatitis or alcohol use disorder were excluded. Annual FIB-4 score from 2019-2023 were calculated and age-adjusted for fibrosis assessment. Primary care providers (PCPs) received standardized EMR recommendations for vibration-controlled transient elastography (VCTE). Significant fibrosis was defined as F2–4 on VCTE. Multivariable logistic regression identified factors associated with significant fibrosis. **Results:** Among 7,014 patients with DM and/or obesity, 3,835 patients aged 30-75 had at least one calculable FIB-4. Of these, 3,232 (84%) were low-risk and 603 (16%) had indeterminate- or high-risk FIB-4. PCPs were contacted for 453 patients; 32 had prior VCTE through a pilot study and 55 through usual care. Overall, 211 patients completed fibrosis assessment and 208 had available VCTE results. The majority were male (61%) with mean age of 62 years, and race/ethnicity included 36% white, 29% Asians, 16% Latinx and 12% Black patients. Metabolic phenotypes included obesity alone (41%), DM alone (30%) and both obesity/DM (29%). Most patients had indeterminate-risk (81%) while 19% had high-risk FIB-4. Overall, 65 of 208 (31%) patients had significant fibrosis with F2-4 fibrosis. On multivariable analysis, high-risk FIB-4 (aOR 2.52, 95%CI 1.04-6.08), DM (aOR 2.71, 95%CI 1.23-5.98), and higher BMI (aOR 1.17, 95%CI 1.09-1.27) were independently associated with significant fibrosis after adjusting for age, sex, race/ethnicity, metabolic factors including hypertension and hyperlipidemia. Combined obesity and DM was also independently associated with significant fibrosis (aOR 2.99, 95% CI 1.30-6.86) when adjusting for similar factors as above. **Conclusion:** In this prospective real-world primary care MASH screening trial, nearly one-third of patients with elevated FIB-4 had significant fibrosis on secondary assessment. Furthermore, combined DM and obesity conferred approximately three-fold higher odds of significant fibrosis compared with either condition alone, highlighting a particularly high-risk metabolic phenotype. These findings support the call for FIB-4-based screening in primary care to improve identification of patients with MASH and progressive liver disease.

Table 1. Univariable and multivariable analysis of F2-4 fibrosis among primary care patients with elevated FIB-4 undergoing VCTE

	Univariable		Multivariable	
Variable	OR	95% CI	OR	95% CI
Age (continuous)	1.04	0.99-1.08	**1.06**	**1.01-1.11**
Male sex (ref. Female)	1.25	0.67-2.29	1.31	0.63-2.73
Race/Ethnicity (ref. White)				
Black	0.34	0.10-1.08	**0.26**	**0.07-0.98**
Latinx	1.54	0.67-3.55	2.60	0.99-6.86
Asian	0.69	0.33-1.45	1.40	0.55-3.55
Other	0.82	0.23-2.92	1.23	0.29-5.15
DM (ref. No DM)	1.54	0.84-2.83	**2.71**	**1.23-5.98**
Hypertension ICD	2.33	1.1-4.87	1.17	0.46-2.97
Hyperlipidemia ICD	1.59	0.75-3.38	1.26	0.52-3.03
BMI (continuous)	1.08	1.02-1.14	**1.17**	**1.09-1.27**
ALT>31	2.21	1.12-4.37	2.05	0.92-4.57
High FIB-4 (ref. Indeterminate)	2.22	1.09-4.54	**2.52**	**1.04-6.08**

Disclosures: Janet Chu: Nothing to Disclose, Nghiem Ha: Nothing to Disclose, Max Goldman: Nothing to Disclose, Bilal Hameed: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Maria Tolentino: Nothing to Disclose, Mohsen Merati: Nothing to Disclose, Mandana Khalili: gilead sciences: Grant/Research Support, GSK pharmaceuticals: Consultant, Intercept pharmaceuticals: Grant/Research Support, Gilead Sciences Inc: Consultant, Resolution Therapeutics: Consultant, Rena Fox: Novo Nordisk, Inc: Grant/Research Support, Novo Nordisk, Inc: Advisor, Gilead Sciences, Inc.: Grant/Research Support, Abbott: Consultant, Boehringer Ingelheim, Inc: Advisor.

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2373 | IMPACT OF CONCOMITANT ALPHA-1 ANTITRYPSIN DEFICIENCY ON CLINICAL OUTCOMES IN PATIENTS WITH MASLD: A PROPENSITY SCORE-MATCHED COHORT STUDY

Madeha Irfan[1] Talal Bhatti[1] Sajid Jalil[2] Ahmed Ibrahim[3] Ashwani Singal[4] Sanjaya Satapathy[5] Shahzad Ashraf[6], [1]Northwell Health, [2]Stanford University, [3]San Joaquin General Hospital, [4]University of Louisville, [5]Northshore University Hospital/Northwell Health, [6]Prime medical and Dental health

Background: Background and Aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a leading cause of chronic liver disease worldwide. Alpha-1 Antitrypsin Deficiency (A1ATD) is associated with progressive hepatic fibrosis and cirrhosis; however, its impact in MASLD remains incompletely characterized. This study evaluated hepatic decompensation, liver transplantation (LT), and mortality outcomes associated with concomitant A1ATD in patients with MASLD. **Methods:** A retrospective cohort study was performed using the TriNetX US Collaborative Network comprising 66 healthcare organizations. Adult patients with MASLD diagnosed between January 1, 2005, and May 21, 2021, were identified using ICD codes and stratified according to the presence or absence of concomitant A1ATD. Patients with competing chronic liver diseases were excluded. Following 1: 1 propensity score matching, 2,122 patients were included in each cohort (Table 1). Outcomes assessed included hepatic decompensation, hepatocellular carcinoma (HCC), LT, and all-cause mortality. **Results:** MASLD patients with concomitant A1ATD demonstrated higher cumulative risk of hepatic decompensation compared with MASLD alone (11.7% vs. 7.6%; RR 1.54, 95% CI 1.25–1.89; $p < 0.001$). Portal hypertensive complications were more frequent among patients with concomitant A1ATD, including ascites (8.2% vs. 4.9%; RR 1.68, 95% CI 1.31–2.16; $p < 0.001$), variceal hemorrhage (2.3% vs. 1.1%; RR 1.97, 95% CI 1.21–3.20; $p = 0.006$), and hepatic encephalopathy (10.7% vs. 7.0%; RR 1.53, 95% CI 1.24–1.88; $p < 0.001$). Concomitant A1ATD was additionally associated with increased risks of hepatorenal syndrome (2.6% vs. 1.2%; RR 2.22, 95% CI 1.39–3.55; $p = 0.001$) and spontaneous bacterial peritonitis (2.0% vs. 0.7%; RR 3.04, 95% CI 1.67–5.56; $p < 0.001$). LT rates were markedly higher among patients with concomitant A1ATD (5.0% vs. 1.6%; RR 3.12, 95% CI 2.13–4.58; $p < 0.001$). Mortality was significantly higher among patients with concomitant A1ATD (14.4% vs. 11.5%; RR 1.25, 95% CI 1.07–1.46; $p = 0.006$), whereas HCC incidence did not significantly differ between groups (2.2% vs. 1.5%; RR 1.48, 95% CI 0.94–2.33; $p = 0.085$). **Conclusion:** Concomitant A1ATD was associated with increased risks of hepatic decompensation, portal hypertensive complications, and LT in patients with MASLD.

Table 1. Baseline Characteristics of Propensity Score-Matched Cohorts

Characteristic	MASLD + A1ATD (n=2,122)	MASLD Alone (n=2,122)	SMD
Age, mean ± SD (years)	51.5 ± 17.6	52.5 ± 17.2	0.056
Female sex, n (%)	1,130 (53.3%)	1,140 (53.7%)	0.009
White race, n (%)	1,925 (90.7%)	1,915 (90.2%)	0.016
Hispanic ethnicity, n (%)	104 (4.9%)	98 (4.6%)	0.013
Type 2 diabetes mellitus, n (%)	398 (18.8%)	412 (19.4%)	0.017
Hypertension, n (%)	685 (32.3%)	720 (33.9%)	0.035
Hyperlipidemia, n (%)	467 (22.0%)	486 (22.9%)	0.021
Chronic kidney disease, n (%)	159 (7.5%)	156 (7.4%)	0.005
Fibrosis/cirrhosis, n (%)	363 (17.1%)	368 (17.3%)	0.006
Overweight/obesity, n (%)	491 (23.1%)	485 (22.9%)	0.007
Albumin, mean ± SD (g/dL)	4.0 ± 0.7	4.0 ± 0.7	0.053
INR, mean ± SD	1.2 ± 0.5	1.2 ± 0.5	0.016
Total bilirubin, mean ± SD (mg/dL)	1.0 ± 1.9	0.8 ± 1.2	0.114
Platelet count, mean ± SD ($\times 10^3/\mu L$)	230.5 ± 100.3	235.5 ± 102.3	0.049
Creatinine, mean ± SD (mg/dL)	1.0 ± 0.7	1.0 ± 0.6	0.027
BMI, mean ± SD (kg/m^2)	32.8 ± 7.7	33.5 ± 8.0	0.098

Disclosures: MADEHA IRFAN: Nothing to Disclose, Talal Bhatti: Nothing to Disclose, Sajid Jalil: Nothing to Disclose, Ahmed Ibrahim: Nothing to Disclose, Ashwani Singal: Madrigal: Speaking and Teaching, Pleiogenix: Stock – privately held company, Pleiogenix: Consultant, CLD Foundation: Advisor, Medical Speaker's Network: Speaking and Teaching, Up-to-Date: Royalties or patent beneficiary, Medscape: Speaking and Teaching, University of Louisville School of Medicine: Employee, NIAAA: Grant/Research Support, Gastro Endo News: Executive role, Durect: Advisor, University of Louisville Health: Other, Sanjaya Satapathy: Gilead Sciences: Grant/Research Support, Durect Pharma: Grant/Research Support, Fibronostics: Grant/Research Support, Novartis: Grant/Research Support, Zydus Pharma: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Intercept Pharma: Grant/Research Support, AKERO: Grant/Research Support, Altimmune: Grant/Research Support, IPSEN: Grant/Research Support, Madrigal: Grant/Research Support, Shahzad Ashraf: Nothing to Disclose.

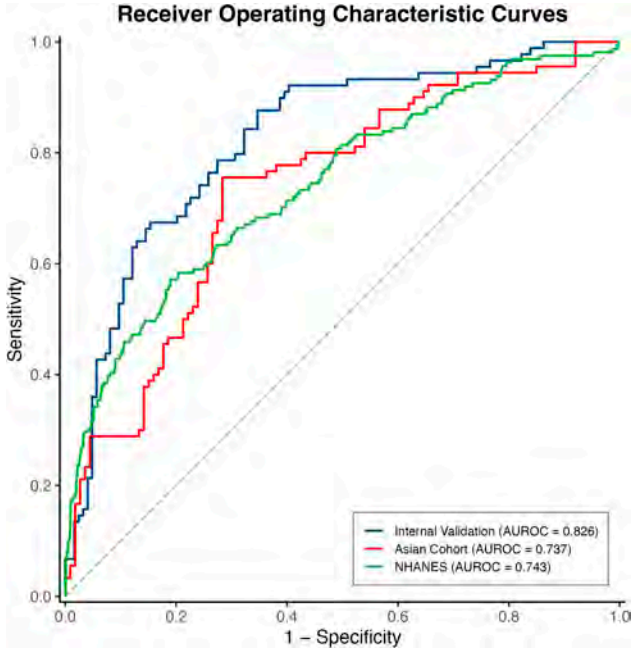
2374 | A SIMPLE MODEL TO PREDICT ADVANCED FIBROSIS IN MASLD PATIENTS WITH INDETERMINATE FIB-4

Laith Alomari[1] Zaid Al-Fakhouri[2] Ahmad Al-Riyalat[1] Daniel Simadibrata[2] Ghideon Ezaz[1], [1]Jefferson Einstein Philadelphia Hospital, Thomas Jefferson University, Philadelphia, PA, [2]The MetroHealth System, Case Western Reserve University, Cleveland, OH

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Background: The Fibrosis-4 (FIB-4) index is recommended as a first-line screening tool for advanced fibrosis in patients with metabolic dysfunction-associated steatotic liver disease (MASLD). However, 25–35% of patients fall in the indeterminate range (1.3–2.67), where FIB-4 provides limited guidance. We developed and validated a simple, laboratory-based model to further stratify fibrosis risk in this population. **Methods:** Using a biopsy-proven MASLD cohort (n = 1,810; 608 indeterminate), we developed an L2-regularized logistic regression model using recursive feature elimination. Eight clinical and laboratory variables were selected from 24 candidates. The model was internally validated in a held-out subset (n = 213) and externally validated in a multi-center Asian cohort from China and Malaysia (n = 203 indeterminate). Generalizability was assessed in the National Health and Nutrition Examination Survey (NHANES) 2017–2020 (n = 1,503 indeterminate). **Results:** In internal validation, the model achieved an area under the receiver operating characteristic curve (AUROC) of 0.826 (95% CI, 0.762–0.880). External validation in the Asian cohort demonstrated preserved discrimination (AUROC 0.737, 95% CI 0.668–0.801). In NHANES, the model maintained good discrimination (AUROC 0.743, 95% CI 0.698–0.788). At a rule-out threshold of 0.256, sensitivity was 94.4% with negative predictive value of 88.1% in internal validation. Subgroup analyses demonstrated consistent performance across age groups, BMI categories, and diabetes status. **Conclusion:** A simple, interpretable model using routine laboratory values can provide additional risk stratification for patients with indeterminate FIB-4 scores. Prospective validation in primary care settings is warranted.



Disclosures: Laith Alomari: Nothing to Disclose, Zaid Al-Fakhouri: Nothing to Disclose, Ahmad Al-Riyalat: Nothing to Disclose, Daniel Simadibrata: Nothing to Disclose, Ghideon Ezaz: Nothing to Disclose.

2375 | CLIPS (CROHN'S LIVER FIBROSIS PREDICTION SCORE): A NON-INVASIVE RISK SCORE FOR SIGNIFICANT LIVER FIBROSIS IN CROHN'S DISEASE. DEVELOPMENT AND EXTERNAL VALIDATION

Maria Teresa Arias-Loste[1] Coral Rivas-Rivas[1] Sandra García-Mateo[2] Samuel Martinez-Dominguez[2] Maria del Henar Ruiz Saez[1] Inmaculada Sánchez-Ojeda[1] sergio García-Mateo[2] Monserrat Rivero[1] Maria Escuin[2] Maria Jose Garcia[1] Beatriz Gallego[2] Angela Puente[1] Jose Ignacio Fortea[1] Juan Carlos Rodriguez-Duque[3] Carla Gargallo[2] Antonio Cuadrado[1] Fernando Gomollon[2], [1]Clinical and Translational Research Group in Digestive Diseases, IDIVAL. Santander. Spain, [2]Hospital Clínico Universitario Lozano Blesa. Instituto Investigación Sanitaria de Aragon. CIBERehd, [3]Clinical and Translational Research Group in Digestive Diseases, IDIVAL

Background: Crohn's disease (CD) confers an independent fibrogenic risk beyond classic metabolic factors, yet available non-invasive fibrosis scores (FIB-4, NAFLD Fibrosis Score) were developed in metabolic populations and show suboptimal performance in CD. We developed and externally validated CLIPS, a novel non-invasive risk score for significant liver fibrosis in CD, applicable regardless of concomitant steatotic liver disease (SLD). **Methods:** CLIPS was developed in 390 consecutive CD patients undergoing vibration-controlled transient elastography (VCTE) at Hospital Universitario Marqués de Valdecilla (Santander, Spain). Patients with chronic liver disease outside the SLD spectrum were excluded. Significant fibrosis was defined as liver stiffness $\geq$8 kPa. Penalised Firth logistic regression with FDR-corrected variable selection was used; internal validation employed 200-iteration bootstrap resampling. External validation was performed in 347 independent CD patients from Hospital Clínico Universitario Lozano Blesa (Zaragoza, Spain), applying identical exclusion criteria. **Results:** Significant fibrosis prevalence was 13.1% in the development cohort and 9.5% in the validation cohort; one-third of fibrosis cases in each cohort occurred without concomitant SLD, highlighting a non-metabolic fibrogenic pathway in CD. CLIPS incorporates nine routinely available variables, with leucocyte count (OR 0.678; p < 0.001) and GGT (OR 1.017; p = 0.003) as primary independent predictors. Bootstrap-validated AUROC was 0.798 (95% CI 0.741–0.862), with good calibration (Hosmer-Lemeshow p = 0.272; Brier score 0.094), significantly outperforming

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FIB-4 (AUROC 0.652) and NFS (AUROC 0.660) (DeLong $p < 0.05$ for both). External validation AUROC was 0.729 (95% CI 0.616–0.843), with a Youden-optimal threshold virtually identical to development ($p \geq 0.163$ vs. $p \geq 0.162$). A dual-threshold approach yielded a low-risk zone (NPV 96.0%/95.4% in development/validation cohorts) and a high-risk zone with equivalent sensitivity (64.6% vs. 67.7%), with statistically comparable risk stratum distribution across cohorts. **Conclusion:** CLIPS is a well-calibrated, externally validated non-invasive tool for significant liver fibrosis risk stratification in CD, outperforming metabolic-population scores. Its dual-threshold design enables clinical rule-out of fibrosis with high NPV and identification of patients warranting elastography referral, regardless of SLD status, addressing a critical gap in the hepatological follow-up of CD patients.

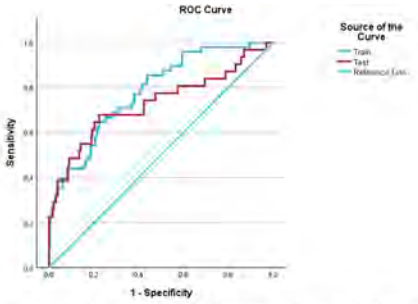


Figure. *Superimposed CLIPS ROC curves for the development (Train; AUROC 0.798) and validation (Test; AUROC 0.729) cohorts. CCLIPS: Crohn's Liver fibrosis Prediction Score.*

Disclosures: Maria Teresa Arias-Loste: Nothing to Disclose, Coral Rivas-Rivas: Nothing to Disclose, Sandra García-Mateo: Nothing to Disclose, Samuel Martinez-Dominguez: Nothing to Disclose, Maria del Henar Ruiz Saez: Nothing to Disclose, Inmaculada Sánchez-Ojeda: Nothing to Disclose, sergio García-Mateo: Nothing to Disclose, Monserrat Rivero: Nothing to Disclose, Maria Escuin: Nothing to Disclose, Maria Jose Garcia: Nothing to Disclose, Beatriz Gallego: Nothing to Disclose, Angela Puente: Nothing to Disclose, Jose Ignacio Fortea: Grifols: Speaking and Teaching, Juan Carlos Rodriguez-Duque: Nothing to Disclose, Carla Gargallo: Nothing to Disclose, Antonio Cuadrado: Nothing to Disclose, Fernando Gomollon: Abbvie: Speaking and Teaching, Johnson and Johnson: Speaking and Teaching, Lilly: Speaking and Teaching.

2376 | REAL-WORLD PERFORMANCE OF FIB-4 USING MRE AS REFERENCE STANDARD IS NOT AFFECTED BY BMI OR HEMOGLOBIN A1C

Garrett Coleman[1] Morgan Ford[1] William Southall[1] Elizabeth Statham[1] Jad Allam Saab[1] Meagan Gray[1] Fernando Bril[1], [1]The University of Alabama at Birmingham

Background: The fibrosis-4-score (FIB-4) is a widely used non-invasive test to screen for patients at risk of clinically significant fibrosis. Recent data suggests that FIB-4 may underestimate clinically significant fibrosis in patients with diabetes and/or obesity. The implications of these findings are concerning as metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common cause of newly diagnosed cirrhosis in the United States. Using magnetic resonance elastography (MRE) as the gold standard, we compared real-world performance of FIB-4 across various BMI and A1c ranges at our tertiary center. **Methods:** Patients seen between April 2018 and September 2025 at the University of Alabama at Birmingham with MRE and FIB-4 data available were included in this study ($n = 521$). Laboratory values within 6 months of MRE were used to calculate FIB-4. Standard areas under receiver operator curve (AUROC) were calculated for BMI groups ($< 30 kg/m^2$, 30-40kg/m^2, and $> 40 kg/m^2$) and A1c categories ($< 6\%$, 6-8%, and $> 8\%$) to assess FIB-4 performance in detecting clinically significant fibrosis, defined as ≥ 3.14 kilopascals (kPa) on MRE. **Results:** A total of 521 patients were included (54 ± 13 years; 55.3% female; 75.0% White, 16.4% African American, and 8.6% other; BMI: 33.5 ± 6.9 kg/m^2; 23.6% with diabetes, and hemoglobin A1C $6.1 \pm 1.2\%$). The predominant liver disease etiologies were MASLD (69.7%) and metabolic and alcohol-related liver disease (Met-ALD, 9.4%), and 120 (23.0%) had clinically significant fibrosis. The performance of FIB-4 to detect clinically significant fibrosis in patients with diabetes was 0.71 (0.61-0.82) vs. 0.76 (0.70-0.81) in individuals without diabetes, $p = 0.48$. FIB-4 performance was also similar in all A1c subgroups ($< 6.0\%$: 0.77 [0.70-0.84], 6-8%: 0.71 [0.61-0.81], and $> 8\%$: 0.84 [0.67-1.00], $p = 0.41$). This was also true when limiting the analysis to only patients with diabetes ($p = 0.47$). FIB-4 also performed similarly across BMI groups (< 30: 0.78 [0.70-0.86], 30-40: 0.70 [0.62-0.78], and > 40: 0.81 [0.70-0.93], $p = 0.21$). Performance of FIB-4 across groups remained similar when limiting the analysis to patients with MASLD. **Conclusion:** Overall, FIB-4 performed similarly across A1c and BMI groups to detect clinically significant fibrosis using MRE as a reference standard. Despite reports that FIB-4 may underperform in individuals with diabetes, this does not seem to be driven by hyperglycemia or increased adiposity. FIB-4 remains a useful non-invasive diagnostic tool to assess for clinically significant fibrosis.

Disclosures: Garrett Coleman: Nothing to Disclose, Morgan Ford: Nothing to Disclose, William Southall: Nothing to Disclose, Elizabeth Statham: Nothing to Disclose, Jad Allam Saab: Nothing to Disclose, Meagan Gray: NovoNordisk: Consultant, Madrigal Pharmaceuticals: Consultant, Intercept Pharmaceuticals: Consultant, Boehringer Ingelheim: Consultant, Fernando Bril:

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2377 | RELIANCE ON THE FIB-4 INDEX DEPRIVES PATIENTS WITH F2 FIBROSIS FROM PHARMACOTHERAPEUTIC OPPORTUNITIES: EVIDENCE FROM A 5,000 SUBJECT COHORT STUDY

Natalie Vellutini[1] Dameia Brewster[1] Qingxia Chen[1] Jackson Resser[1] Ashley Spann[1] Manhal Izzy[1], [1]Vanderbilt University Medical Center

Background: The FIB-4 index is a noninvasive liver disease assessment that was initially developed to predict advanced hepatic fibrosis and cirrhosis (i.e., stage F3-4). Multiple society guidelines continue to recommend the FIB-4 index as the first line screening test. However, now that recently approved pharmacotherapies for metabolic-associated liver disease (MASLD) are initiated at the F2 stage, it is critical to investigate if continued reliance on FIB-4 may inappropriately exclude F2 patients from opportunities for treatment. Our aim is to assess the prevalence and predictors of FIB-4 misclassification rates in patients with elastography-proven F2 in real-world clinical settings. **Methods:** We conducted a single center retrospective analysis of patients undergoing transient elastography (TE) and/or MRI elastography (MRE) with concurrently available FIB-4 data between 01/01/2018 – 12/31/2025. Liver transplant recipients and those with poor quality elastography studies were excluded. The normalcy cutoff for FIB-4 index was 1.3 for patients age < 65 and 2.0 for patients age ≥ 65. Transient elastography and MRI elastography cutoffs for F0 - F4 were based on current society guidelines. We evaluated the misclassification rate of the FIB-4 index compared to the respective elastography assessment and applied generalized linear regression modeling to compare likelihood of misclassification, adjusted for relevant clinical characteristics. **Results:** The study included 5045 patients with 5292 elastography studies ([TE] = 3997 and [MRE] = 1295). Of those classified as F2 by elastography study, 312/747 (41.8%) in the TE group and 37/110 (33.6%) in the MRE group were misclassified as having a normal FIB-4. Patients without a diagnosis of diabetes (OR: 1.39 [1.01, 1.92]), patients of a race other than non-Hispanic white (OR: 1.73 [1.10, 2.77]), and patients having BMI above 25.3 (OR: 1.06 [1.03, 1.09]) were associated with higher odds of this misclassification event (F2 patient/normal FIB-4) relative to patients with diabetes, non-Hispanic whites, and having one unit lesser BMI, respectively. **Conclusion:** In this large study cohort, patients with clinically significant fibrosis were frequently misclassified with a normal FIB-4 score. In practice, this inappropriately normal FIB-4 score could lead to missed opportunities for advanced care such as initiation of pharmacotherapy in eligible patients with MASLD. Further refinement of this model with improved sub-group (DM, BMI, race/ethnicity) predictive accuracy is critically needed.

Disclosures: Natalie Vellutini: Nothing to Disclose, Dameia Brewster: Nothing to Disclose, Qingxia Chen: Nothing to Disclose, Jackson Resser: Nothing to Disclose, Ashley Spann: Bristol Myers Squibb Foundation: Grant/Research Support, Novo Nordisk: Consultant, Madrigal Pharmaceuticals: Consultant, Manhal Izzy: Mallinckrodt: Speaking and Teaching, Madrigal: Advisor, Natera: Advisor, Mirum: Advisor.

2378 | ENVIRONMENTAL VOLATOMIC SIGNATURES ASSOCIATED WITH LEAN MASLD IDENTIFIED THROUGH EXPLAINABLE AI

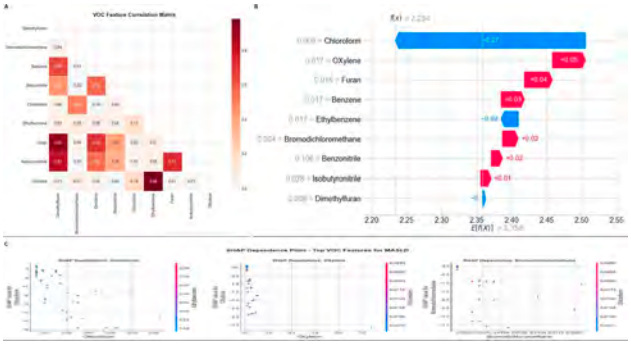
Sarpong Boateng[1] Guy loic Nguefang Tchoukeu[2] Khaled Halwani[3] Chimezirim Ezeano[4] Yazan Al-ajlouni[5] Eunice Omeludike[6] Ihunanya Kanu[7] Basile Njei[8], [1]Yale New Haven Health, [2]Texas Tech University Health Science Center, Permian Basin, [3]Yale University School of Medicine, [4]Advocate Aurora Healthcare, [5]Montefiore Medical Center, [6]Piedmont Athens Regional Medical Center, [7]Baptist Memorial Hospital- Golden Triangle, [8]Yale University

Background: Lean metabolic dysfunction-associated steatotic liver disease (MASLD) affects up to 20% of individuals with normal body mass index, yet its environmental determinants remain poorly characterized. Volatile organic compounds (VOCs), including disinfection byproducts and petroleum-derived toxicants, possess hepatotoxic properties and may contribute to liver injury through mechanisms independent of adiposity, representing a potentially underrecognized etiologic pathway in lean MASLD. **Methods:** We performed a cross-sectional analysis of lean adults (BMI < 25 kg/m²) in the NHANES 2017–March 2020 dataset with whole-blood measurements of nine VOCs and transient elastography data. MASLD was defined using steatosis and consensus metabolic criteria, while advanced fibrosis was defined as liver stiffness ≥ 8.6 kPa. Explainable machine learning with SHapley Additive exPlanations (SHAP) was applied to identify VOCs associated with MASLD and characterize exposure-response patterns across the volatomic profile. **Results:** Among 860 lean adults, 77 (9.0%) had MASLD and 14 (1.6%) had advanced fibrosis. Participants with MASLD were older (median 62 vs. 52 years) and had

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higher prevalences of metabolic syndrome, diabetes, and hypertension (all $p < 0.001$). Chloroform emerged as the dominant VOC associated with MASLD (mean absolute SHAP 0.82), followed by o-xylene (0.29), bromodichloromethane (0.23), benzene (0.20), and furan (0.17). Notably, chloroform demonstrated weak intercorrelation with other VOCs, supporting an independent environmental exposure signal rather than shared-source clustering. SHAP analyses revealed complex nonlinear exposure-response relationships at low VOC concentrations. Advanced fibrosis analyses were substantially underpowered and should be considered hypothesis-generating. **Conclusion:** In a nationally representative cohort of lean adults, blood volatomic profiling identified distinct systemic VOC signatures associated with MASLD, dominated by chloroform, a water disinfection byproduct whose CYP2E1-mediated bioactivation generates phosgene and depletes hepatic glutathione. These findings support environmental toxicant exposure as a plausible mechanistic contributor to lean MASLD independent of classical adiposity-driven metabolic pathways. Explainable AI enabled transparent characterization of complex environmental exposure patterns and highlights the emerging potential of volatomics for environmental biomarker discovery in hepatology.



Disclosures: Sarpong Boateng: Nothing to Disclose, GUY LOIC NGUEFANG TCHOUKEU: Nothing to Disclose, Khaled Halwani: Nothing to Disclose, chimezirim ezeano: Nothing to Disclose, Yazan Al-ajlouni: Nothing to Disclose, Eunice Omeludike: Nothing to Disclose, Ihunanya Kanu: Nothing to Disclose, Basile Njei: Nothing to Disclose.

2379 | FIB-4 DISCORDANCE WITH VCTE-DEFINED FIBROSIS RISK AMONG NON-HISPANIC ASIAN ADULTS

Jonathan Hong[1] Adrian Singson[1], [1]Mountain Area Health Education Center

Background: Non-Hispanic Asian(NHA) adults may develop MASLD and fibrosis risk at lower BMI levels than non-Hispanic White(NHW) adults, suggesting that conventional fibrosis screening may miss liver disease. FIB-4 is widely used for fibrosis risk stratification, but its performance across NHA ethnicity-specific BMI categories is not well studied. **Methods:** We analyzed adults ≥ 18 years in NHANES 2017–March 2020 with valid FibroScan liver stiffness measurement (LSM), AST, ALT, and platelet counts. Participants with significant alcohol use, hepatitis B/C, or pregnancy were excluded. Elevated liver stiffness was defined as LSM ≥ 8 kPa and low risk FIB-4 as < 1.3. Asian specific BMI categories were applied to NHA adults (lean < 23, overweight 23–27.5, and obese ≥ 27.5). Standard BMI categories were applied to NHW adults. The primary outcome was low risk FIB-4 despite LSM ≥ 8 kPa. Descriptive analyses focused on NHA adults, with comparison between NHA ethnicity specific overweight and NHW standard overweight. Regression models evaluated FIB-4/LSM discordance by ethnicity-specific BMI category, adjusting for age and sex. **Results:** Among 875 NHA adults of 7,006 adults, mean age was 45.4 years, 46.6% were male, and mean BMI was 25.9 kg/m². 6.5% of NHA adults had LSM ≥ 8 kPa, of whom nearly two-thirds had low-risk FIB-4, corresponding to an overall FIB-4/LSM discordance prevalence of 4.4%. Discordance increased across Asian-specific BMI categories (lean 0.7%; overweight: 3.3%; obese: 9.2%). Among ethnicity-specific overweight adults, NHA had lower mean BMI than NHW adults but higher prevalence of LSM ≥ 8 kPa (6.1% vs. 3.4%). Among those with LSM ≥ 8 kPa, low risk FIB-4 was present in 54.9% of NHA adults with BMI 23–27.5, 50.7% of NHA adults with BMI 25–29.9, and 28.6% of NHW adults with BMI 25–29.9. In age/sex adjusted models, ethnicity-specific overweight NHA adults had higher odds of discordance than standard overweight NHW (OR 3.31, 95% CI 1.00–10.94, $p = 0.049$). In a separate interaction model, a significant NHA × overweight interaction (OR 9.84, 95% CI 1.11–87.51, $p = 0.041$) indicated that the lean-to-overweight transition was associated with a disproportionately larger increase in discordance for NHA than NHW adults. **Conclusion:** NHA adults with Asian-specific overweight BMI thresholds had higher FIB-4/LSM discordance than NHW adults, with more than half of overweight NHA adults with elevated liver stiffness classified as low risk by FIB-4. FIB-4 was originally derived in HCV/HIV-coinfected cohorts with limited racial and ethnic diversity and subsequently validated predominantly in Western populations. These findings highlight how fibrosis screening tools derived predominantly from non-Asian populations may systematically under-detect disease in NHA adults. Earlier VCTE referral for overweight NHA adults should be considered in MASLD screening pathways.

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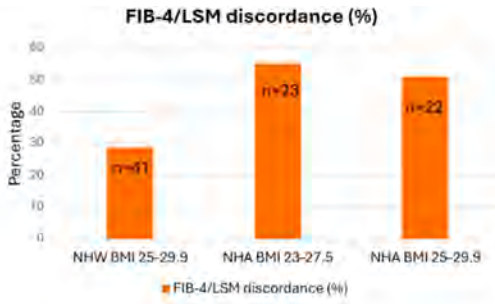


Figure 1: Conditional FIB-4 discordance rate (Among adults with LSM ≥8 kPa, % of adults who had low-risk FIB-4) across three comparison groups: NHW overweight (BMI 25–29.9), NHA ethnicity-specific overweight (BMI 23–27.5), and NHA standard overweight (BMI 25–29.9). Number of LSM ≥8 kPa for each group noted in the figure.

Disclosures: Jonathan Hong: Nothing to Disclose, Adrian Singson: Nothing to Disclose.

2380 | PREDICTING 7-YEAR OUTCOMES IN CHRONIC LIVER DISEASE: A COMPARISON OF L1-DERIVED AND WHOLE-BODY MRI MUSCLE METRICS

Wile Balkhed[1] Mattias Ekstedt[1] Olof Dahlqvist Leinhard[2] Shan Cai[1] Simone Ignatova[3] Peter Lundberg[1] Nils Dahlström[1] Stergios Kechagias[1] Mikael Forsgren[2] Patrik Nasr[1], [1]Linkoping University, [2]AMRA Medical AB, [3]Region Östergötland

Background: While patients with advanced liver disease are at risk of sarcopenia, no practical established imaging-based screening method exists. In this study we validated liver MRI-derived L1-level body composition assessment against whole-body MRI body composition assessment and investigated the prognostic value of these measurements for adverse clinical outcomes. **Methods:** Patients with suspected chronic liver disease with clinical indication for liver biopsy underwent a same-day liver MRI. In half of the cohort whole-body MRI was also performed. MRI measurements used AMRA® Researcher. Liver MRI body composition was assessed from the craniocaudal extent of the L1 vertebral level, including fat-free erector spinae muscle volume indexed to height (L1-ESMI), muscle fat infiltration (L1-MFI) and visceral adipose tissue indexed to height (L1-VATI). Whole-body MRI assessed the thighs for total fat-free muscle volume (FFMV), mean MFI, and total abdominal VAT volume. Z-FFMV and Z-VAT were sex- and BMI standardized Z-scores; sex-adjusted MFI was reported in percentage points (pp). Low FFMV was defined as Z-FFMV $<25^{th}$ percentile, and high MFI as $>75^{th}$ sex-specific percentile from a UK Biobank reference population. A retrospective follow-up review of patient records was performed $\geq$1 year after baseline visit to screen for adverse outcomes, including all-cause mortality, major adverse cardiovascular events (MACE) and major adverse liver-related outcomes (MALO). **Results:** 161 participants were included (whole-body MRI n = 80) with mean age of 55 ± 14 years and BMI 28.5 ± 5.2 kg/m^2 . The most common etiology was MASLD (47%), and 29% had advanced fibrosis. L1 muscle volume, L1-MFI and L1-VAT had strong correlation with thigh FFMV (R^2 = 0.75), MFI (R^2 = 0.54) and total VAT (R^2 = 0.89), all P < 0.001. During a mean follow-up time of 7.0 yrs 35 adverse events were captured (MALO n = 18; MACE n = 13, deaths n = 4). Mean follow-up time in whole-body MRI subgroup was 4.7 years and 15 events were recorded. Cox proportional hazards regression analysis found no correlation between L1-level body composition variables and risk of adverse event in follow-up. Meanwhile lower Z-FFMV (per SD increase; cHR 0.53, 95% CI 0.34–0.84, P < 0.01) and higher sex-adjusted MFI (pp) (cHR 1.20 95% CI 1.04–1.38, P < 0.05) and Z-VAT (SD) (cHR 1.55, 95% CI 1.05–2.29, P < 0.05) increased risk. Presence of high MFI also increased risk (cHR 3.52, 95% CI 1.27–9.77, P < 0.05) while no associations were shown for low Z-FFMV. Adjusting for age and baseline fibrosis stage, only lower Z-FFMV (SD) (aHR 0.58, 95% CI 0.36–0.97, P < 0.05) and presence of high MFI (aHR 3.33, 95% CI 1.07–10.34, P < 0.05) remained significant. **Conclusion:** L1-derived body composition from liver MRI has strong anatomic correlation to whole body MRI body composition, but lacks in prognostic accuracy, whereas lower thigh Z-FFMV and presence of high thigh MFI were independent predictors of adverse events in longitudinal follow-up.

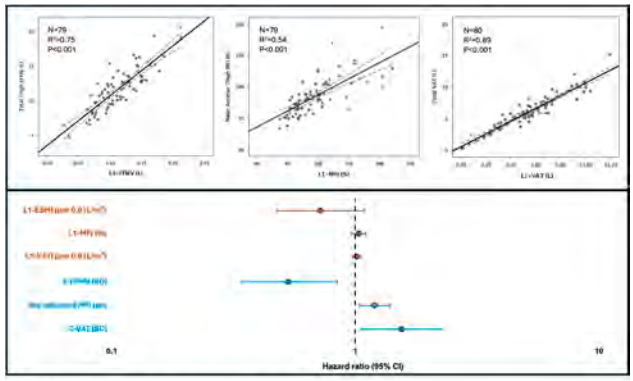


Figure 1. Validation and prognostic performance of L1-derived body composition markers

Panel A: Associations between L1-derived and whole-body MRI measures with fitted linear regression and 95% CI.
Panel B: Crude hazard ratios (95% CI) from Cox regression for MACE, MALO, or death. L1-derived measures were analyzed in 161 participants (35 events; mean follow-up 7.0 years) and whole-body MRI measures in 80 participants (15 events; mean follow-up 4.7 years).

FFMV, fat-free muscle volume; MFI, muscle fat infiltration; VAT, visceral adipose tissue; ESMI, erector spinae muscle index; VATI, visceral adipose tissue index

Disclosures: Wile Balkhed: Nothing to Disclose, Mattias Ekstedt: Nothing to Disclose, Olof Dahlqvist Leinhard: Nothing to Disclose, Shan Cai: Nothing to Disclose, Simone Ignatova: Nothing to Disclose, Peter Lundberg: Nothing to Disclose, Nils Dahlström: Nothing

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to Disclose, Stergios Kechagias: Nothing to Disclose, Mikael Forsgren: AMRA Medical AB: Employee, AMRA Medical AB: Stock – privately held company, Patrik Nasr: Boehringer Ingelheim: Advisor, Novo Nordisk: Consultant.

2381 | DIAGNOSTIC UTILITY OF AN AUTOMATED PLASMA CARBOXYLESTERASE 1 ASSAY FOR HEPATIC STEATOSIS: A COMPARATIVE STUDY BETWEEN SCREENING AND CHRONIC HEPATITIS B COHORTS

Shingo Tanaka[1] Makito Tanaka[1] Kayoko Ochi[2] Ryo Kobayashi[2] Ryosei Murai[2] Satoshi Takahashi[1], [1]Sapporo Medical University, [2]Sapporo Medical University Hospital

Background: Steatotic liver disease (SLD) is a global health priority, increasing the demand for non-invasive biomarkers. Carboxylesterase 1 (CES1) is a key hepatic enzyme in lipid metabolism. We previously established a high-throughput automated ELISA platform for plasma CES1 and validated its excellent analytical stability, confirming its readiness for clinical research. However, its diagnostic performance across different clinical backgrounds remains to be fully elucidated. This study compared the diagnostic utility of plasma CES1 for hepatic steatosis between a screening outpatient cohort and a chronic hepatitis B (CHB) cohort. **Methods:** We analyzed two distinct cohorts who underwent same-day blood sampling and abdominal ultrasonography: (1) a screening cohort of 212 outpatients (excluding advanced fibrosis and significant alcohol consumption) and (2) a CHB cohort of 108 patients. Plasma CES1 levels were measured using our automated ELISA platform. Hepatic steatosis was quantified using ultrasound-derived attenuation imaging (Aplio i700, Canon Medical Systems) to determine the attenuation coefficient (AC; cutoff $\geq$ 0.66 dB/cm/MHz). Clinical profiles associated with diagnostic discordance (false-negative and false-positive) between AC and CES1 were also evaluated. **Results:** In both cohorts, plasma CES1 levels consistently demonstrated significant positive correlations (all $r \geq 0.3$, $P < 0.001$) with metabolic markers, liver injury indicators, and ultrasound parameters: BMI ($r = 0.469$ in screening, 0.409 in CHB), ALT ($r = 0.578$, 0.341), GGT ($r = 0.442$, 0.337), hepatorenal index ($r = 0.607$, 0.390), and AC ($r = 0.692$, 0.483). ROC analysis for diagnosing steatosis yielded an AUC of 0.87 in the screening cohort and 0.80 in the CHB cohort, indicating slightly higher diagnostic performance in the screening population. Although clinical characteristics of false-negative and false-positive cases were thoroughly analyzed in each cohort, no common contributing factors for diagnostic discordance were identified between the two groups. **Conclusion:** Plasma CES1 holds promise as a reliable, non-invasive biomarker for hepatic steatosis across distinct clinical settings. Despite minor variations in diagnostic performance between the cohorts, plasma CES1 consistently reflected hepatic fat accumulation. These findings highlight its clinical utility and warrant further large-scale, multi-etiology studies to confirm its generalizability.

Disclosures: Shingo Tanaka: Nothing to Disclose, Makito Tanaka: Nothing to Disclose, Kayoko Ochi: Nothing to Disclose, Ryo Kobayashi: Nothing to Disclose, Ryosei Murai: Nothing to Disclose, Satoshi Takahashi: Nothing to Disclose.

2382 | RANKING FIBROSIS BIOMARKERS IN STEATOTIC LIVER DISEASE: A MACHINE LEARNING APPROACH

Cristiane Tovo[1] Juliana Czermainski[1] Maria Goyer[2] Luis Ferreira[1] Randhall Carteri[3], [1]Federal University of Health Sciences of Porto Alegre (UFCSPA), Porto Alegre, Brazil, [2]Federal University of Health Sciences of Porto Alegre (UFCSPA), Porto Alegre, Brazil., [3]CESUCA University Center, Cachoeirinha, Brazil

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the major leading causes of chronic liver disease worldwide, and noninvasive fibrosis detection remains a challenge. Machine learning (ML), emerge as an alternative to improve well-established scores and features. This study aimed to evaluate ML algorithms for fibrosis prediction and rank the most relevant biomarkers associated with fibrosis in MASLD patients using routine clinical and laboratory data. **Methods:** Transversal study, with data were obtained from the National Health and Nutrition Examination Survey (NHANES) 2017–2020 cycle. All adults with hepatic steatosis (controlled attenuation parameter- CAP >275) were included. Fibrosis was defined by transient elastography (TE) $\geq$ 8 kPa. Machine learning models were developed using demographic, anthropometric, and blood biomarker data. Data preprocessing included normalization, 70: 30 train-test split, and SMOTE balancing. The evaluated classifiers included Logistic Regression, Random Forest, XGBoost, LightGBM, Extra Trees, AdaBoost, Gaussian Naive Bayes, Decision Tree, and Support Vector Classifier with K-Fold cross-validation. Performance was assessed using F1-score, accuracy, AUC-ROC, and AUC-PR. **Results:** 2,474 participants were included , being 1,970 without fibrosis (79.6%) and 504 with fibrosis (20.4%). The group with fibrosis showed

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significantly increased body mass index (BMI) (38.6kg/m² vs 32.6kg/m²; p < 0.001), and higher rates of severe obesity (37.1% vs 12.5%; p = 0.001), type 2 diabetes mellitus (29.2% vs 14.4%; p = 0.001), low HDL cholesterol (47.8% vs 39.9%; p = 0.001), and higher waist circumference - WC (121cm vs 108cm; p < 0.001). Several biomarkers also differed significantly between groups, all with higher levels in fibrosis group. Logistic Regression analyzing the whole blood panel demonstrated the best overall performance, achieving F1-score = 0.50 ± 0.03, AUC-PR = 0.52 ± 0.04, and AUC-ROC = 0.78 ± 0.02. . WC and BMI were identified as the strongest overall predictors of fibrosis, followed by AST, GGT, total bilirubin and age. Using only the five highest-ranked biomarkers, has been noted an improved predictive performance (F1-score = 0.51 ± 0.03; AUC-ROC = 0.79 ± 0.02). A predictive equation was developed incorporating hemoglobin, BMI, age, AST, and GGT. The new equation is as follows: (0.098 × Haemoglobin) + (0.899 × BMI) + (0.452 × AGE) + (0.398 × AST + (0.238 × GGT) + (-1.641). **Conclusion:** ML models using routine blood biomarkers and anthropometric measurements can effectively identify fibrosis in MASLD patients, using less biomarkers than a complete blood work. This approach may contribute to scalable, low-cost, and noninvasive fibrosis screening strategies in clinical practice.

Disclosures: Cristiane Tovo: Nothing to Disclose, Juliana Czermainski: Nothing to Disclose, Maria Goyer: Nothing to Disclose, Luis Ferreira: Nothing to Disclose, Randhall Carteri: Nothing to Disclose.

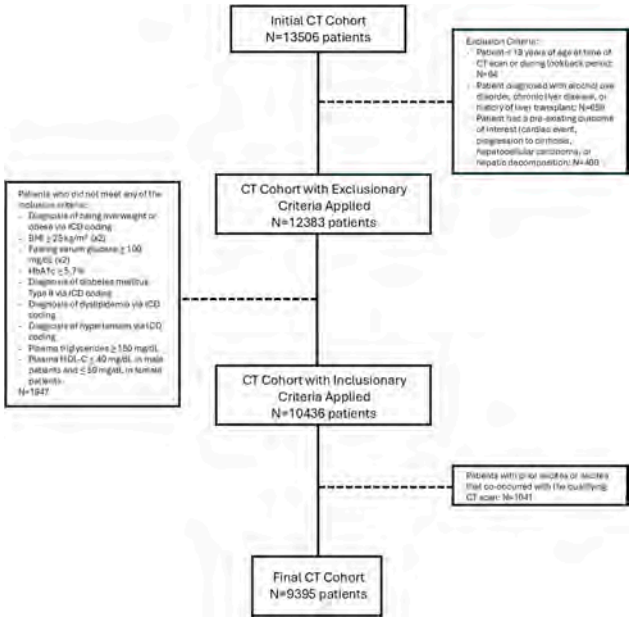
2383 | OPPORTUNISTIC CT IDENTIFIES A SIGNIFICANT POPULATION OF CLINICALLY UNRECOGNIZED STEATOTIC LIVER DISEASE IN CARDIOMETABOLIC AT-RISK PATIENTS

Vignesh Rajasekaran[1] Asad Aali[2] Alexandria Jensen[3] Allison Kwong[4] Andrew Johnston[5] Ates Fettahoglu[2] Hye Na[5] Luyao Shen[5] Taiyo Shimizu[5] Luke Yoon[5] David Svec[6] Robert Boutin[5] Jason Hom[6] Akshay Chaudhari[2] Laura Derry[6], [1]Stanford University Department of Internal Medicine, [2]Stanford University, Department of Biophysics, [3]Stanford University, Quantitative Sciences Unit, [4]Stanford University, Department of Gastroenterology and Hepatology, [5]Stanford University, Department of Radiology, [6]Stanford University, Department of Hospital Medicine

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) - hepatic steatosis with at least one cardiometabolic risk factor - is the most common form of steatotic liver disease (SLD) and is a leading cause of chronic liver disease globally, yet it remains substantially underdiagnosed. We previously showed that Comp2Comp, a validated deep-learning algorithm, identifies hepatic steatosis on contrast-enhanced CT more often than radiology reports or ICD-coding. We aimed to determine how often patients with ≥1 cardiometabolic risk factor for MASLD lack formal clinical recognition and to characterize their demographic, metabolic, and fibrosis risk profile. **Methods:** We conducted a retrospective cohort study of adults ≥18 years old who had ≥ 1 cardiometabolic risk factor for MASLD (2023 multisociety consensus) in the three years preceding the qualifying CT and underwent contrast-enhanced or non-contrast abdominal CT at a multisite academic health system (2013–2018, 2021–2024). Patients were classified into one of two groups: (1) ICD-coded SLD prior to or within 30 days of the qualifying CT scan (clinically recognized [CR]) or (2) incidentally detected SLD by radiology report or Comp2Comp deep-learning algorithm without ICD-coding (clinically unrecognized [CU]). Patients with ICD-9 or ICD-10 diagnosis codes for other chronic liver disease (including cirrhosis), alcohol use disorder, prior hepatic decompensation (ascites, hepatic encephalopathy, variceal bleed), prior hepatocellular carcinoma, liver transplant, or a cardiovascular event within 30 days of the qualifying CT were excluded. **Results:** Of 13,506 patients with a qualifying abdominal CT, 9,395 had ≥1 cardiometabolic risk factor. Among these, 2,361 had identified SLD by ICD-coding, radiology report, or Comp2Comp. Of those, 553 (23.4%) were clinically recognized (CR) and 1,808 (76.6%) were clinically unrecognized (CU). Compared with CR patients, CU patients were older (mean 64.5 vs 59.6 yr) and had a lower burden of metabolic comorbidities (type 2 diabetes 22.3% vs 32.7%; obesity 22.1% vs 41.8%; OSA 16.2% vs 26.4%; all p < 0.001). Among CU patients with available FIB-4, 36.9% had indeterminate-or-higher fibrosis risk (≥1.3) and 2.9% met the high-risk threshold (>3.25). FIB-4 was unable to be calculated in 23.7% of CU vs 12.8% of CR patients. **Conclusion:** Even among patients who unambiguously met MASLD criteria, approximately three of four were clinically unrecognized, including many with existing fibrosis risk. The high rate of unavailable FIB-4 assessment in the unrecognized cohort exposes a potential gap in liver risk stratification. Integrating opportunistic CT with a deep-learning algorithm into clinical pathways may identify a large, at-risk population not captured by conventional screening and detection pathways.

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2384 | AI-ASSISTED OCULAR PHENOTYPING FOR LIVER–METABOLIC RISK STRATIFICATION: A REAL-WORLD EXPLAINABLE FRAMEWORK FOR PRECISION HEPATOLOGY

Fangpin Huang[1] Yichen Peng[1], [1]Chengdu University of TCM, China

Background: Metabolically-dysfunction-associated steatotic liver disease (MASLD) is closely linked to systemic cardiometabolic dysfunction, yet scalable non-invasive screening strategies remain limited. Ocular phenotyping enables direct assessment of microvascular and tissue-level alterations and may reflect broader metabolic abnormalities. Although artificial intelligence (AI)-assisted ocular analysis has shown diagnostic potential, its application in hepatology remains limited by concerns regarding confounding and interpretability. This study evaluated whether real-world ocular diagnostic patterns could support liver-metabolic risk stratification. **Methods:** A structured clinical dataset comprising 350 patients, 512 visits, and 2,054 diagnostic observations across 52 disease categories was analyzed. Diagnoses were grouped into liver/hepatobiliary, metabolic/endocrine, cardiovascular, renal, and neurologic domains. Co-occurrence mapping was used to assess systemic clustering. In parallel, a conceptual explainable artificial intelligence (XAI) framework integrating saliency mapping, counterfactual auditing, and confounder isolation was developed to outline interpretable ocular AI pipelines. **Results:** Among 350 patients, 21.7% had liver/hepatobiliary findings, 58.3% had metabolic/endocrine diagnoses, and 74.9% had cardiovascular conditions. Marked overlap was observed among hepatic, metabolic, and cardiometabolic disease domains. Repeated visit-level observations revealed persistent disease co-expression rather than isolated organ-specific manifestations. The convergence of metabolic, cardiovascular, and hepatic categories suggests that ocular biomarkers may capture systemic signatures relevant to MASLD risk. Variability in disease burden across visits also highlighted potential confounding effects, supporting the need for explainable and fairness-aware AI models. **Conclusion:** This real-world ocular phenotyping study identified substantial co-occurrence among liver/hepatobiliary, metabolic/endocrine, and cardiovascular diseases, suggesting that ocular phenotypes may reflect cardiometabolic burden associated with MASLD. Clinical co-occurrence analysis was integrated into a conceptual XAI framework, providing an interpretable approach for AI-assisted ocular risk stratification in hepatology. These findings support the eye as a scalable, non-invasive biomarker platform for precision liver-metabolic medicine. Prospective multicenter validation and standardized ocular imaging workflows are needed to further evaluate the clinical applicability of AI-assisted ocular biomarkers for MASLD screening and risk stratification.



Disclosures: Fangpin Huang: Nothing to Disclose, Yichen Peng: Nothing to Disclose.

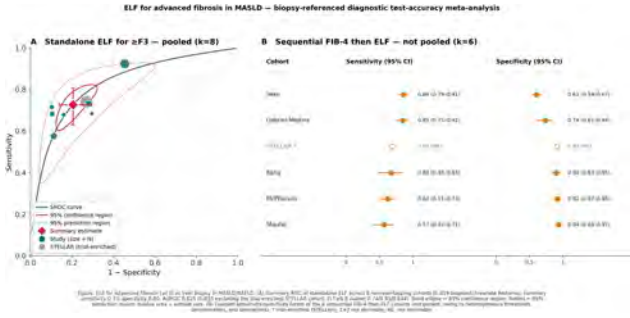
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2385 | ENHANCED LIVER FIBROSIS (ELF) TEST FOR ADVANCED FIBROSIS IN MASLD: A BIOPSY-REFERENCED DIAGNOSTIC TEST-ACCURACY META-ANALYSIS

Gabriel Prusch Fernandes[1] Hamza Sadhra[1] Advait Suvarnakar[1] Eliabe Abreu[2] Diego Drumond Westgeest e Sousa[2] Kamalpreet Hara[2] Douglas Simonetto[2], [1]Montefiore Einstein, [2]Mayo Clinic Rochester

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) has become the leading chronic liver disease, and advanced fibrosis (≥F3) drives liver-related outcomes and pharmacologic treatment eligibility. Guidelines recommend a two-step case-finding pathway: FIB-4 first, then a second test such as the Enhanced Liver Fibrosis (ELF) test, to reduce unnecessary referral. How accurately ELF detects ≥F3 across contemporary biopsy-referenced MASLD cohorts remains uncertain, and no prior systematic review has synthesized the biopsy-referenced sequential FIB-4-then-ELF pathway. **Methods:** We conducted a PRISMA-DTA systematic review of studies evaluating ELF against liver biopsy for advanced fibrosis (≥F3) in MASLD/NAFLD across PubMed, Embase, Cochrane Library, and Web of Science databases. From 868 records, 31 studies were eligible for review; 9 distinct studies reported extractable biopsy-referenced 2x2 data at ≥F3 and entered the meta-analysis, contributing 8 standalone-ELF cohorts and 6 sequential FIB-4-then-ELF cohorts (5 studies contributed to both pools). We pooled standalone ELF accuracy with a bivariate (Reitsma) model and prespecified sensitivity analyses; the sequential FIB-4-then-ELF pathway was summarized as a forest plot. Analyses used R (mada). **Results:** The 8 standalone-pool cohorts included 6,019 biopsied participants (≥F3 prevalence 18–71%; cross-sectional diagnostic cohorts and one trial-screening cohort). Pooled standalone ELF for ≥F3 had sensitivity 0.73 (95% CI, 0.63–0.81) and specificity 0.80 (95% CI, 0.70–0.86), with summary ROC AUC 0.825; the estimate stayed stable on leave-one-out analysis, in the ELF≥9.8 subset (5 cohorts: sensitivity 0.74, specificity 0.81, AUC 0.844), and after excluding a trial-enriched cohort (AUC 0.833). Across the 6 sequential FIB-4-then-ELF cohorts, sensitivity ranged 0.57–0.86 and specificity 0.61–0.94, with the second ELF step tending to favor specificity. We did not pool these because thresholds, denominators, and derivations differed and the bivariate fit was unstable. Most other included studies reported ELF only as an AUROC or at stages other than ≥F3, leaving too few data to pool the pathway. **Conclusion:** ELF accurately identifies advanced fibrosis in MASLD and, applied as a confirmatory second step, raises specificity to reduce unnecessary referral. Evidence on the sequential pathway remains heterogeneous and sparsely reported. Standardized reporting and prospective validation are needed before the two-step pathway can be pooled or recommended.



Disclosures: Gabriel Prusch Fernandes: Nothing to Disclose, Hamza Sadhra: Nothing to Disclose, Advait Suvarnakar: Nothing to Disclose, Eliabe Abreu: Nothing to Disclose, Diego Drumond Westgeest e Sousa: Nothing to Disclose, Kamalpreet Hara: Nothing to Disclose, Douglas Simonetto: Mallinckrodt: Consultant, BioVie: Consultant, Resolution Therapeutics: Consultant, Evive: Consultant, Iota: Consultant, Novo Nordisk: Consultant, Astra Zeneca: Consultant.

2386 | OBESITY-ASSOCIATED ATTENUATION OF THE BAVENO VII LSM RULE-IN THRESHOLD FOR CLINICALLY SIGNIFICANT PORTAL HYPERTENSION IN MASLD: A SYSTEMATIC REVIEW AND META-ANALYSIS

Rubab Fatimaa[1] Rida Fatima[2], [1]Fatima Jinnah Medical University, [2]Shaukat Khanum Memorial Hospital

Background: Clinically significant portal hypertension (CSPH; HVPG ≥10 mmHg) identifies patients with compensated advanced chronic liver disease (cACLD) at high risk for decompensation. Baveno VII liver stiffness measurement (LSM) thresholds and ANTICIPATE-NASH are increasingly used as HVPG surrogates; however, most fixed CSPH thresholds were derived largely from viral hepatitis and alcohol-related cACLD cohorts. In MASLD, obesity may independently elevate LSM and reduce the reliability of fixed thresholds. We evaluated the accuracy of non-invasive tests (NITs) for CSPH in MASLD-cACLD, stratified by obesity, and compared fixed Baveno VII thresholds with BMI-integrated ANTICIPATE-NASH. **Methods:** PubMed, Embase, and Cochrane were searched from inception through April 2026 per PRISMA. Eligible studies included adults with MASLD/NAFLD/NASH-related cACLD and HVPG as the reference standard. Extractable NIT metrics included sensitivity, specificity, AUC, PPV, or NPV. Two reviewers independently screened studies, extracted data, and assessed bias using QUADAS-2. When available, 2×2 tables were

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extracted or reconstructed. Prespecified Baveno VII thresholds were prioritized. Bivariate random-effects models pooled sensitivity, specificity, and diagnostic odds ratios. Obesity (BMI ≥30 vs <30 kg/m²) was the primary subgroup. Sensitivity analyses evaluated threshold effects, cohort overlap, and heterogeneity. Duplicate populations were excluded where applicable. **Results:** Six studies contributed data from seven independent cohorts (N = 1,284); CSPH prevalence ranged from 39% to 74%. For Baveno VII rule-in (LSM ≥25 kPa), PPV was ~91% in non-obese MASLD but ~63–67% in obese MASLD, an estimated 24–29 percentage-point reduction. Baveno VII rule-out (LSM ≤15 kPa plus platelets ≥150×10⁹/L) maintained high NPV among patients meeting rule-out criteria across BMI strata: 99% (95% CI 97–100%). In obese MASLD, ANTICIPATE-NASH showed higher discrimination than LSM alone: AUC 0.83 (95% CI 0.80–0.85) vs 0.69 (95% CI 0.62–0.76). An ANTICIPATE-NASH probability threshold ≥75% yielded PPV 83%, compared with ~63–67% for fixed LSM rule-in. LSM-alone estimates showed substantial heterogeneity (I^2 > 55%; up to 82% for specificity), whereas ANTICIPATE-NASH showed low heterogeneity (I^2 < 10%). Available 100-Hz spleen stiffness measurement data suggested high accuracy (AUC 0.95) and grey-zone reduction from 60% to 15–20%, but were limited to one MAFLD cohort. **Conclusion:** In MASLD-cACLD, obesity attenuates Baveno VII LSM rule-in performance while preserving rule-out reliability among patients meeting rule-out criteria. BMI-integrated models such as ANTICIPATE-NASH may improve CSPH probability estimation in obese MASLD. Spleen stiffness is promising but needs external validation. These findings support BMI-calibrated, phenotype-specific interpretation of NITs rather than reliance on fixed LSM thresholds alone.

Test / Threshold	Key Result	Context
Baveno VII Rule-In (LSM ≥25 kPa)	PPV ~91% → ~63–67%	~24–29 pp reduction; non-obese vs obese MASLD
Baveno VII Rule-Out (LSM ≤15 + PLT ≥150)	NPV 99% (95% CI 97–100%)	Among patients meeting rule-out criteria; preserved across BMI strata
ANTICIPATE-NASH Pooled AUC	0.83 (95% CI 0.80–0.85)	vs LSM alone in obese: 0.69 (95% CI 0.62–0.76)
ANTICIPATE-NASH ≥75% threshold	PPV 83% in obese MASLD	Supported by prior IPD analysis; vs ~63–67% fixed LSM
SSM 100-Hz VCTE (AUC 0.95)	Grey zone: 60% → 15–20%	Single MAFLD cohort (N=60); external validation needed

Disclosures: Rubab Fatimaa: Nothing to Disclose, Rida Fatima: Nothing to Disclose.

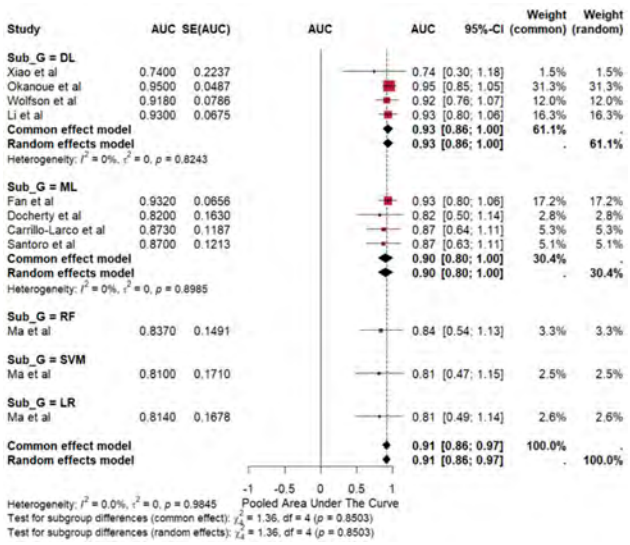
2387 | DIAGNOSTIC ACCURACY OF ARTIFICIAL INTELLIGENCE-BASED MODELS FOR LIVER FIBROSIS ASSESSMENT IN MASLD: A SYSTEMATIC REVIEW AND META-ANALYSIS

Raja Chandra Chakinala[1] Era Gupta[1] Aryan Gupta[2] Omar Oudit[3] Harmanjeet Singh[4] Gautam Maddineni[5] Aakash Desai[6] Chaitanya Chandrala[7], [1]Guthrie/Robert Packer Hospital, PA, USA, [2]Bangalore Medical College and Research Institute, India, [3]Brookdale University Hospital Medical Center, NY, USA, [4]Mahatma Gandhi Memorial Medical College, India, [5]Creighton University, NE, USA, [6]Allegheny Health Network, PA, USA, [7]Guthrie/Robert Packer Hospital,PA,USA

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a major cause of chronic liver disease and can progress to advanced fibrosis, cirrhosis, and liver-related complications. Accurate fibrosis assessment is important for prognostication and disease monitoring; however, liver biopsy is invasive and unsuitable for large-scale screening. Artificial intelligence (AI)-based models have emerged as promising noninvasive tools for fibrosis detection in MASLD. We performed a systematic review and meta-analysis evaluating the diagnostic accuracy of AI-based approaches for liver fibrosis assessment in MASLD. **Methods:** This review was conducted in accordance with PRISMA guidelines. PubMed, Google Scholar, and ScienceDirect were systematically searched using a comprehensive search strategy. Studies evaluating AI-based models for fibrosis detection in MASLD and reporting area under the receiver operating characteristic curve (AUC) values were included. Pooled AUC values were calculated using inverse-variance random-effects models. Subgroup analyses comparing deep learning (DL) approaches and traditional machine learning methods, including random forest (RF), support vector machine (SVM), and logistic regression (LR), were performed. Statistical heterogeneity was assessed using the I^2 statistic. Data were analyzed in RStudio using the meta, metadata, and metafor packages. **Results:** Eleven studies were included in the final analysis. The pooled AUC for AI-based fibrosis detection models was 0.91 (95% CI 0.86–0.97), demonstrating high overall diagnostic accuracy. DL models demonstrated the highest pooled AUC (0.93), followed by ML models (0.90). RF, SVM, and LR approaches demonstrated pooled AUCs of 0.84, 0.81, and 0.81, respectively. Okanoue et al. reported the highest-performing DL algorithm among included studies. No significant interstudy heterogeneity was observed (I^2 = 0%), and subgroup analyses demonstrated comparable diagnostic performance across AI model categories. **Conclusion:** AI-based models demonstrate high diagnostic accuracy for liver fibrosis assessment in MASLD and may serve as promising noninvasive tools for fibrosis risk stratification. Further large-scale prospective studies with standardized external validation frameworks are needed to support routine clinical implementation.

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2389 | EVALUATION OF ALBUMIN-DERIVED RATIOS IN PREDICTING 30-DAY MORBIDITY AND MORTALITY IN HBV- AND MASLD-RELATED CIRRHOSIS: A COMPARATIVE ANALYSIS WITH MELD 3.0

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Background: Liver cirrhosis due to HBV or MASLD remains a major global health concern with high short-term mortality. While MELD-based scoring systems are widely utilized for prognostic assessment, albumin-derived biochemical ratios have recently emerged as promising supplementary markers. This study aimed to evaluate the predictive value of albumin-derived ratios—particularly blood urea nitrogen-to-albumin ratio (BAR) and red cell distribution width-to-albumin ratio (RAR)—in comparison with the MELD 3.0 score for 30-day and 60-day mortality in patients with HBV- or MASLD-related decompensated cirrhosis. **Methods:** This retrospective cohort study included 210 patients who were hospitalized with HBV- or MASLD-related decompensated cirrhosis between April 2019 and April 2024. Clinical, demographic and laboratory data were systematically retrieved from institutional medical records. MELD 3.0 scores and albumin-derived ratios were calculated for each patient. Receiver operating characteristic (ROC) curve and logistic regression analyses were conducted to assess independent predictors and discriminatory performance. **Results:** The 30-day and 60-day mortality rates were 32.9% and 40.0%, respectively. In multivariate analyses, MELD 3.0 (OR = 1.098, p = 0.023), BAR (OR = 1.057, p = 0.018), RAR (OR = 1.295, p = 0.046) were independent predictors of 30-day mortality. BAR showed the highest predictive power with an AUC of 0.834, followed by MELD 3.0 (AUC = 0.805) and RAR (AUC = 0.766). A combined predictive model incorporating MELD 3.0, BAR, and RAR yielded an AUC of 0.857, with 82.6% sensitivity and 75.5% specificity. **Conclusion:** BAR and RAR are strong, independent predictors of short-term mortality in decompensated cirrhotic patients, with prognostic utility beyond the MELD 3.0 score. The integration of albumin-derived ratios into existing models enhances risk stratification and may contribute to more personalized management strategies in HBV- and MASLD-related cirrhosis.

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2390 | MODERATE ALCOHOL CONSUMPTION AND LIVER-RELATED EVENTS IN MASLD: THRESHOLDS AND LONGITUDINAL EFFECTS

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Background: Although several studies have suggested potential health benefits of low-volume alcohol consumption, findings remain controversial, particularly in patients with liver disease. This nationwide study investigated the association between varying alcohol intake levels and the risk of liver-related events (LREs) in individuals with steatotic liver disease (SLD). **Methods:** We analyzed data from 2,951,003 adults aged 40–64 years in the Korean National Health Insurance Service database who underwent health examinations between 2009 and 2010. Hepatic steatosis was defined by a Fatty Liver Index ≥30, and SLD was classified according to established criteria. Alcohol intake was categorized as none, very low (1–49 g/week), low (50–99 g/week), moderate (100–139 g/week in women, 100–200 g/week in men), high (140–350

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g/week in women, 210–420 g/week in men), and heavy (>350 g/week in women, >420 g/week in men). We evaluated the impact of baseline alcohol intake and 4-year longitudinal changes in consumption on long-term LRE risk among individuals with SLD. **Results:** During a median follow-up of 14 years, incidence rates of LREs per 100,000 person-years were 132.7 in the non-SLD group and 493.7, 435.7, 439.8, and 446.8 in MASLD groups with no, very-low, low, and moderate alcohol intake, respectively. Compared with the MASLD group with none-to-low alcohol intake (0–99 g/week), moderate alcohol intake was associated with a significantly increased risk of LREs in both multivariable-adjusted (adjusted sub-distribution hazard ratio [aSHR] = 1.035; 95% CI 1.011–1.059; P = 0.003) and IPTW-adjusted models (aSHR = 1.071; 95% CI 1.057–1.084; P < 0.001). Sex-specific analyses showed a lower risk threshold in women than in men. In men, significant risk elevation was observed only at moderate intake (aSHR = 1.036; 95% CI 1.009–1.064; P = 0.009), whereas women demonstrated increased risk beginning at low-volume intake (aSHR = 1.093; 95% CI 1.022–1.169; P = 0.009) and continuing at moderate intake (aSHR = 1.122; 95% CI 0.997–1.264; P = 0.057). Longitudinal analysis showed that progression to moderate alcohol intake was associated with higher LRE risk than sustained low-volume drinking (HR 1.393–1.509 for progression to moderate intake vs. HR 1.141–1.295 for maintaining or shifting within the low-volume range). Among individuals initially in the moderate alcohol group, LRE risk remained similarly high regardless of whether alcohol intake decreased or remained unchanged (HR 1.290–1.450 for reduction to low-volume vs. HR 1.312 for maintaining moderate volume). **Conclusion:** In this nationwide cohort, moderate alcohol intake was associated with increased LRE risk in individuals with MASLD, with a lower risk threshold in women. Longitudinal increases in alcohol intake were also associated with higher risk.

Risk of liver-related events
(vs. MASLD without any alcohol group)

Population group	Events	Person-yrs	IR	Hazard ratio (95% confidence interval)					
				Model 1		Model 2		Model 3	
Liver-related event									
MASLD without any alcohol	28,979	5,960,918	493.7	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)
MASLD with very-low alcohol	5,725	1,313,837	435.7	0.93	(0.90–0.95)	0.97	(0.94–1.00)	0.99	(0.97–1.02)
MASLD with low alcohol	7,920	1,800,102	439.8	0.94	(0.91–0.96)	0.99	(0.97–1.02)	1.00	(0.98–1.03)
MASLD with moderate alcohol	10,716	2,398,626	446.8	0.95	(0.93–0.97)	1.03	(1.01–1.06)	1.04	(1.01–1.06)

*Incidence rate per 100,000 person-years
Model 1: unadjusted
Model 2: adjusted for age and sex.
Model 3: adjusted for age, sex, household income quartile, residential area, Charlson comorbidity index, tobacco smoking, physical activity level, type 2 diabetes mellitus, hypertension, dyslipidemia, and eGFR.
MASLD, metabolic dysfunction-associated steatotic liver disease; IR, incident rate.

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2391 | DEVELOPMENT OF A CLINICALLY SCALABLE CIRCULATING MICRORNA ASSAY FOR LIVER FIBROSIS STAGING IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH)

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) affects 30–35% of U.S. adults and can progress to metabolic dysfunction-associated steatohepatitis (MASH), fibrosis, cirrhosis, and liver failure. Liver biopsy is the gold standard for fibrosis staging but is invasive and costly. Current noninvasive methods have limitations in accuracy and accessibility. Circulating microRNAs (miRNAs) are promising biomarkers due to their stability and role in liver fibrogenesis. We developed a multiplex circulating miRNA assay using a proprietary one-step RT-qPCR workflow for noninvasive fibrosis assessment in MASH patients. **Methods:** A proprietary one-step RT-qPCR workflow was developed for multiplex circulating miRNA detection targeting miR-34a, miR-99a, miR-192, miR-223, miR-122, and endogenous control miR-23a. Analytical performance, including quantification range, sensitivity, and specificity, was evaluated using synthetic miRNA mimics. Plasma samples were collected from obesity controls without MASLD/MASH, MASLD patients, and MASH patients with different fibrosis stages. A total of 200 µL plasma per patient was used for miRNA isolation and RT-qPCR analysis. Relative miRNA expression was normalized to miR-23a. Algorithms were developed to differentiate low fibrosis (F0/F1) from moderate-to-advanced fibrosis (F2+) MASH patients and to distinguish MASLD from MASH. Clinical performance was evaluated using leave-one-out cross-validation (LOOCV). **Results:** Analytical validation demonstrated robust performance for all targeted miRNAs suitable for clinical use. Twenty-three patients were included: 3 obesity controls, 7 MASLD patients, 7 MASH F0/F1 patients, and 6 MASH F2+ patients. Differential expression patterns of miR-34a, miR-99a, miR-192, miR-223, and miR-122 were observed among groups. Using LOOCV, the multiplex miRNA model distinguished MASH F0/F1 from F2+ patients with 92.3% accuracy (95% CI: 0.64–0.998), 87.5% positive predictive value, and 100% negative predictive value. Significant correlations were observed between transient elastography liver stiffness measurements and circulating miRNA levels, including miR-34a (r = -0.71), miR-122 (r = -0.65), and miR-192 (r = -0.57). **Conclusion:** This preliminary study demonstrates the potential utility of a multiplex circulating miRNA RT-qPCR assay for noninvasive liver fibrosis staging in MASH patients. The assay showed robust analytical performance and promising discrimination between early-stage and clinically significant fibrosis. Correlations between circulating miRNAs and liver stiffness

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measurements further support the biological relevance of these biomarkers. These findings support continued clinical validation of this scalable, low-cost miRNA-based assay for fibrosis risk stratification and patient monitoring in MASLD/MASH.

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2392 | WAIST-TO-HEIGHT RATIO OUTPERFORMS BMI IN IDENTIFYING HEPATIC AND METABOLIC COMORBIDITIES AND PREDICTING DISEASE COURSE IN CROHN'S DISEASE

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD), metabolic syndrome (MS), and liver fibrosis are increasingly recognized comorbidities in Crohn's disease (CD). Body mass index (BMI) fails to adequately capture central adiposity, potentially underestimating hepatic and metabolic risk. Waist-to-height ratio (WHtR) is a simple anthropometric marker of central adiposity, but its utility for identifying liver-related and metabolic comorbidities and predicting CD course remains unexplored. **Methods:** Prospective multicenter cohort study including CD patients in clinical remission from two Spanish tertiary hospitals. Baseline BMI, WHtR, and prevalence of MASLD (CAP > 248 dB/m plus ≥ 1 metabolic criterion), MS (NCEP-ATP3), and significant liver fibrosis (liver stiffness > 8 kPa) were assessed. Relapses, steroid use, and treatment modifications were recorded over follow-up. **Results:** A total of 641 CD patients were included (median follow-up 36 months). MASLD was present in 41.2%, MS in 21.5%, and significant liver fibrosis risk in 10.9%. WHtR ≥ 0.50 was detected in 74.6% of patients, including > 50% of those with normal BMI. WHtR demonstrated markedly higher sensitivity than BMI for detecting MASLD (96.2% vs. 85.6%; p < 0.001), MS (99.2% vs. 86.2%; p < 0.001), and significant liver fibrosis (84.2% vs. 68.5%; p < 0.001). Regarding disease course, elevated WHtR was independently associated with increased risk of relapse (aHR 1.518; 95%CI 1.004–2.296), steroid use (aHR 1.774; 95%CI 1.004–3.136), and treatment modification (aHR 1.674; 95%CI 1.111–2.523), whereas BMI showed no significant associations. **Conclusion:** WHtR outperforms BMI in identifying hepatic and metabolic comorbidities in CD, and independently predicts adverse disease course. Its routine use may improve risk stratification and facilitate early detection of metabolically vulnerable patients, including those misclassified by BMI.

Comorbidities	BMI ≥30 Crohn's disease	WHtR ≥ 0.5 Crohn's disease	P value
MASLD			
Sensitivity	85.6%	96.2%	
Specificity	71.3%	39%	**<0.001**
NLR	-1.18	-2.44	
MS			
Sensitivity	86.2%	99.2%	
Specificity	57.2%	32%	**<0.001**
NLR	-1.47	-3.06	
Significant liver fibrosis			
Sensitivity	68.5%	84.2%	**<0.001**
Specificity	50%	27%	
NLR	-1.35	-3.08	

BMI, body mass index. MASLD, Metabolic dysfunction associated Steatotic liver disease. NLR: negative likelihood ratio, MS, metabolic syndrome. WHtR, waist-to-height ratio. P value from McNemar's test indicates the comparison of diagnostic ability between the two tests. *p* values in bold indicate statistical significance: $p < 0.05$.

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2393 | SOLUBLE TREM2 PREDICTS POST-TRANSPLANT MASH RECURRENCE AND REFLECTS SCAR-ASSOCIATED MACROPHAGE EXPANSION RATHER THAN ENHANCED PROTEOLYTIC SHEDDING

Zhihao Li[1] Kai-Philipp Seeger[1] Xingxing Zhu[1] Yawen Dong[1] David Pereyra[1] Byron Smith[1] Tayyab Diwan[1] Kymberly Watt[1] Timucin Taner[1] Patrick Starlinger[1] Hu

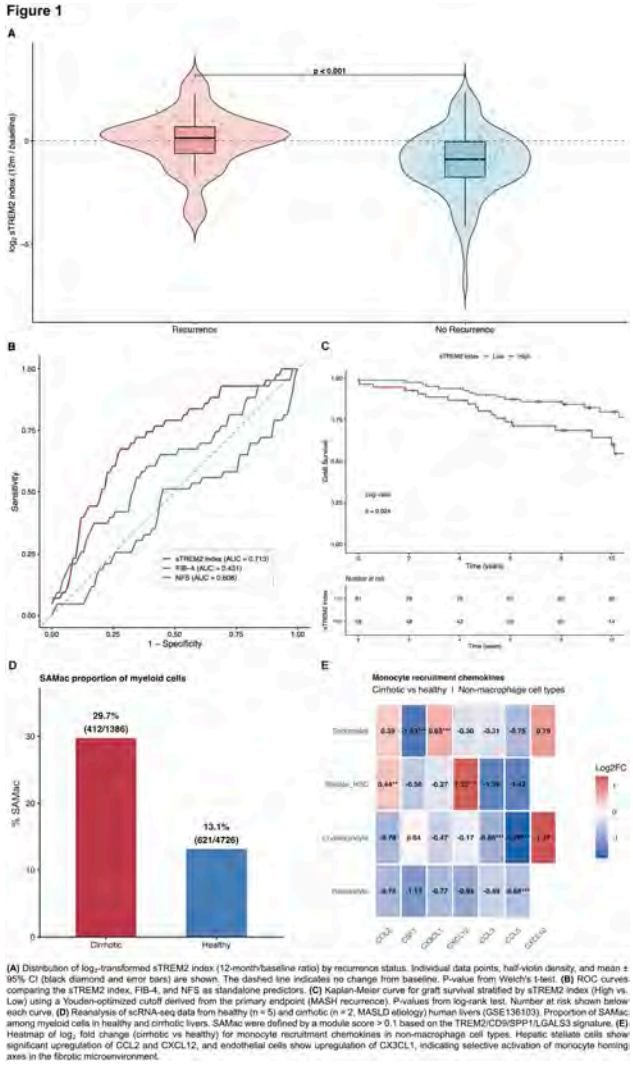
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Background: Metabolic dysfunction-associated steatohepatitis (MASH) recurs in up to 25% of liver transplant (LT) recipients, yet reliable predictors are lacking. Soluble triggering receptor expressed on myeloid cells 2 (sTREM2) correlates with MASLD severity, but whether its elevation reflects ADAM10/17-mediated proteolytic shedding or scar-associated macrophage (SAMac) expansion is unresolved. We evaluated a longitudinal sTREM2 index as a biomarker for post-LT MASH recurrence and integrated single-cell and proteomic data to define the underlying mechanism. **Methods:** Consecutive adult LT recipients with MASH at Mayo Clinic Rochester (2010–2022) with stored plasma were included. sTREM2 was measured at baseline, 4 and 12 months by ELISA, and the sTREM2 index (12-month/baseline ratio) was tested against FIB-4 and NFS for predicting 3-year MASH recurrence, defined as MRE liver stiffness ≥ 3 kPa. Logistic and Cox models were adjusted for recipient age, BMI, and diabetes. To define cellular mechanism, we re-analyzed human liver scRNA-seq (GSE136103; 45,328 cells, 8 populations) and two independent liver proteomics cohorts spanning the MASLD spectrum. **Results:** Of 140 recipients (median age 60, BMI 31.8, 63.6% diabetes), 43 (30.7%) developed MASH recurrence. sTREM2 declined uniformly at 4 months, then rebounded to near-baseline in the recurrence group (median index 1.10) versus remaining suppressed in non-recurrence (0.54; $p < 0.001$). The sTREM2 index discriminated recurrence with AUC 0.713, outperforming FIB-4 (0.431; DeLong $p < 0.001$) and NFS (0.608; $p = 0.074$); adjusted OR 1.68 (95% CI 1.17–2.42; $p = 0.005$, Fig.1A&B). Adding the index to a clinical base raised AUC from 0.543 to 0.722 ($p = 0.002$). The index was also independently associated with post-transplant diabetes (aOR 1.45; $p = 0.011$), and a Youden-dichotomized high index predicted worse graft survival (log-rank $p = 0.024$, Fig.1C). Mechanistically, scRNA-seq revealed a 2.3-fold expansion of TREM2-high SAMac in cirrhotic livers with per-cell TREM2 upregulation ($\log_2FC = 1.54$, Fig.1D), while ADAM10/ADAM17 were unchanged across 8 cell types — confirmed at the protein level in both proteomics cohorts. Cell-cycle distribution was unchanged ($p = 0.399$), excluding proliferation; instead, stellate (CCL2/CXCL12) and endothelial (CX3CL1) chemokine axes were upregulated (Fig.1E), identifying monocyte recruitment as the driver of SAMac accumulation, with recruited cells reprogrammed toward oxidative phosphorylation and lipid handling. **Conclusion:** The sTREM2 index is a novel non-invasive biomarker for post-transplant MASH recurrence outperforming conventional fibrosis indices. Elevated circulating sTREM2 reflects chemokine-driven SAMac recruitment rather than enhanced proteolytic shedding. This positions sTREM2 as an actionable post-LT surveillance tool and the CCL2/CXCL12/CX3CL1 axes as therapeutic targets.

Figure 1



(A) Distribution of $\log_2$-transformed sTREM2 index (12-month/baseline ratio) by recurrence status. Individual data points, half-violin density, and mean ± 95% CI (black diamond and error bars) are shown. The dashed line indicates no change from baseline. P-value from Welch's t-test. (B) ROC curves comparing the sTREM2 index, FIB-4, and NFS as standalone predictors. (C) Kaplan-Meier curve for graft survival stratified by sTREM2 index (High vs. Low) using a Youden-optimized cutoff derived from the primary endpoint (MASH recurrence). P-values from log-rank test. Number at risk shown below each curve. (D) Reanalysis of scRNA-seq data from healthy (n = 5) and cirrhotic (n = 2, MASLD etiology) human livers (GSE136103). Proportion of SAMac among myeloid cells in healthy and cirrhotic livers. SAMac were defined by a module score > 0.1 based on the TREM2/CD9/SPP1/LGALS3 signature. (E) Heatmap of $\log_2$ fold change (cirrhotic vs healthy) for monocyte recruitment chemokines in non-macrophage cell types. Hepatic stellate cells show significant upregulation of CCL2 and CXCL12, and endothelial cells show upregulation of CX3CL1, indicating selective activation of monocyte homing axes in the fibrotic microenvironment.

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2394 | POC-HRM: A POINT-OF-CARE HIGH-RISK MASLD MACHINE LEARNING FRAMEWORK FOR RISK STRATIFICATION AND ENRICHMENT FOR SYNERGY OUTCOMES TRIAL SCREENING

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Background: The SYNERGY Outcomes trial targets patients with high-risk MASLD (HRM) defined by elevated LSM and ELF score. Identifying eligible patients remains challenging because VCTE and ELF testing are costly, not universally available, and frequently result in screen failure. We aimed to develop a point-of-care machine (POC) learning framework using routinely available laboratory and clinical variables to stratify patients into lower- and higher-probability groups for SYNERGY Outcomes eligibility prior to VCTE and ELF testing. **Methods:** HRM was defined according to SYNERGY Outcomes inclusion criteria. The derivation cohort included a multi-center cohort of 5249 patients, of whom 1459 (27.8%) met HRM criteria. The external validation cohort included 4336 patients from non-overlapping centers, of whom 1287 (29.7%) met criteria. Extreme gradient boosting machine learning models predicted lower- and higher-risk MASLD phenotypes using routinely available clinical and laboratory variables. SHAP analysis ranked variable importance and identified reduced point-of-care models. Optimized probability thresholds were selected using the Youden index. **Results:** SHAP analysis identified platelet count, GGT, AST, ALT, globulin, hemoglobin A1c, age, height, and weight as the top-ranking variables. The POC-HRM rule-in model demonstrated an AUC of 0.766 (95% CI 0.752-0.780) in external validation, outperforming SAFE at 0.750 (95% CI 0.736-0.765) and FIB-4 at 0.731 (95% CI 0.717-0.746). At the optimized threshold, sensitivity was 68.5% and NPV was 70.4%, compared with 63.8% and 67.8% for SAFE, and 63.9% and 66.9% for FIB-4, at a cutpoint of 1.25 and 107 respectively. The rule-out model demonstrated an AUC of 0.792 (95% CI 0.775-0.809), outperforming SAFE (0.777; 95% CI 0.760-0.794) and FIB-4 (0.763; 95% CI 0.746-0.781). At the optimized threshold, specificity was 75.4% and PPV was 44.4%, compared with 73.7% and 42.7% for SAFE, and 73.4% and 42.0% for FIB-4, at a cutpoint 1.49 and 132, respectively. **Conclusion:** A POC machine learning framework using routinely available laboratory and clinical variables successfully stratified patients into rule-in and rule-out groups for SYNERGY Outcomes eligibility prior to VCTE and ELF testing. Compared with SAFE and FIB-4, the framework demonstrated improved exclusion performance in lower-risk patients and superior enrichment capability in higher-risk patients. This strategy may improve screening efficiency using variables readily available in routine clinical practice.

Model	Threshold	AUC	95% CI Lower	95% CI Upper	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Rule-in Threshold								
POC-HRM	0.406	0.766	0.752	0.780	68.5	71.3	69.4	70.4
FIB4	1.25	0.731	0.717	0.746	63.9	69.2	66.4	66.9
SAFE	107	0.750	0.736	0.765	63.8	72.5	68.8	67.8
Rule-out Threshold								
POC-HRM	0.226	0.792	0.775	0.809	69.0	75.4	44.4	89.5
FIB4	1.49	0.763	0.746	0.781	67.5	73.4	42.0	88.8
SAFE	132	0.777	0.760	0.794	68.5	73.7	42.7	89.1

AUC = Area Under the Receiver Operating Characteristic Curve; CI = Confidence Interval; PPV = Positive Predictive Value; NPV = Negative Predictive Value.

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89Bio: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Boston Pharmaceuticals: Grant/Research Support, Boston Pharmaceuticals: Grant/Research Support, Eli Lilly: Grant/Research Support, Eli Lilly: Grant/Research Support, Helio Health: Grant/Research Support, Helio Health: Grant/Research Support, Inventiva: Grant/Research Support, Inventiva: Grant/Research Support, Madrigal Pharmaceuticals: Grant/Research Support, Madrigal Pharmaceuticals: Grant/Research Support, Madrigal Pharmaceuticals: Speaking and Teaching, Madrigal Pharmaceuticals: Speaking and Teaching, Merck: Grant/Research Support, Merck: Grant/Research Support, Novo Nordisk: Grant/Research Support, Novo Nordisk: Grant/Research Support, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Galectin Therapeutics: Grant/Research Support, Galectin Therapeutics: Grant/Research Support, Hepion Pharmaceuticals: Grant/Research Support, Hepion Pharmaceuticals: Grant/Research Support, GlaxoSmithKline: Grant/Research Support, GlaxoSmithKline: Grant/Research Support, Corcept Therapeutics: Grant/Research Support, Corcept Therapeutics: Grant/Research Support, Boehringer Ingelheim: Consultant, Boehringer Ingelheim: Consultant, Novo Nordisk: Speaking and Teaching, Novo Nordisk: Speaking and Teaching, Genentech Roche: Grant/Research Support, LiverRight: Advisor, Hinova Pharmaceuticals: Consultant, Rohit Puskoor: Nothing to Disclose, David Huang: Nothing to Disclose, Nirupama Esther Jerome: Nothing to Disclose, John Poulos: Nothing to Disclose, Alaa Abousaif: Nothing to Disclose, Aasim Sheikh: Nothing to Disclose, Alma Laura Ladrón de Guevara: Eli Lilly and company: Grant/Research Support, Galectin Therapeutics: Grant/Research Support, AStra Zeneca: Grant/Research Support, Inventiva Pharma: Grant/Research Support, Cymabay Therapeutics: Grant/Research Support, Akero Therapeutics: Grant/Research Support, Novonordisk: Grant/Research Support, MSD: Grant/Research Support, Cymabay: Grant/Research Support, GSK: Grant/Research Support, Madrigal Pharmaceuticals: Grant/Research Support, Roche: Grant/Research Support, Marcelo Kugelmas: Nothing to Disclose, Mousab Tabbaa: Nothing to Disclose, Sam Moussa: Nothing to Disclose, Vlad Ratziu: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Meena Bansal: Madrigal: Advisor, Fibronostics: Advisor, NOVO Nordisk: Advisor, GSK: Advisor, Merck: Advisor, Boeheringer-Ingelheim: Advisor, Boston Pharma: Advisor, The Kinetix Group: Advisor, Corcept: Advisor, Jörn Schattenberg: Akero: Consultant, 89Bio: Consultant, Boehringer Ingelheim: Consultant, Ipsen: Consultant, Inventiva Pharma: Consultant, Madrigal: Consultant, Northsea Therapeutics: Consultant, Novo Nordisk: Consultant, Roche: Consultant, Siemens Healthineers: Consultant, Boehringer Ingelheim: Advisor, AGED diagnostics: Stock – privately held company, Hepta Bio: Stock – privately held company, Novo Nordisk: Speaking and Teaching, Madrigal: Stock - publicly traded company, MedPublico GmbH: Speaking and Teaching, Eli Lilly: Advisor, Altimmune: Consultant, Astra Zeneca: Consultant, Gilead Science: Consultant, Merck: Consultant, MSD Sharp & Dohme GmbH: Consultant, AbbVie: Advisor, Mazen Noureddin: Nothing to Disclose.

2395 | RISK STRATIFICATION OF MASLD IN PATIENTS WITH BMI ≥40: PERFORMANCE OF FIB-4 AND VCTE WITHIN THE 2026 AGA CLINICAL CARE PATHWAY

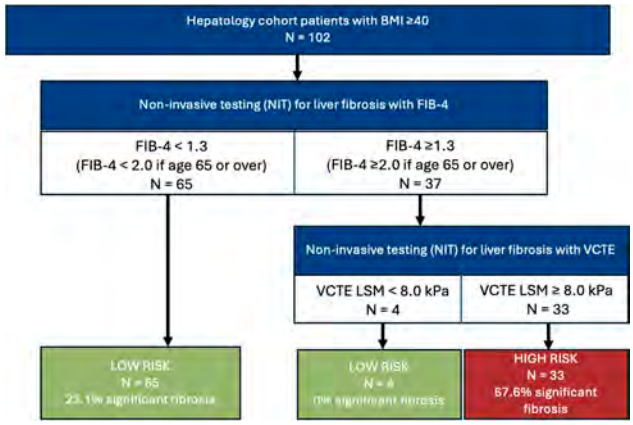
Abigail Tami[1] Fady Gendy[1] Mustafa Shah[1] G. Craig Wood[1] Meredith Lewis[1] Andrea Berger[1] Samantha Service[1] Christopher Still[1] Alberto Unzueta[1], [1]Geisinger Medical Center

Background: Non-invasive liver disease assessments (NILDA) such as FIB-4 and vibration

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controlled transient elastography (VCTE) are useful in the risk stratification in MASLD. In individuals with BMI ≥ 40, the accuracy of FIB-4 and VCTE in predicting significant fibrosis has not been completely characterized. This study evaluates the performance of FIB-4 and VCTE within the 2026 AGA multi-step MASLD clinical care pathway in two obesity class III cohorts using liver biopsy as the reference standard. **Methods:** This retrospective study utilized two institutional data registries composed of all patients who underwent liver biopsy between 2016-2021. The study included those with BMI ≥ 40 kg/m^2 who either had a wedge liver biopsy at the time of bariatric surgery (bariatric cohort) or were referred to hepatology clinic (hepatology cohort). Patients with alternate liver disease etiologies were excluded. Among those with FIB-4 data across both cohorts, the prevalence of significant fibrosis (≥ F2 fibrosis) was outlined in those labeled as low- and high- risk by the initial steps of the AGA clinical care pathway. In hepatology patients with both FIB-4 and VCTE data, the multi-step approach of the pathway was applied and validated. **Results:** A total of 1,495 patients (mean BMI 47.4 kg/m²) were included, and 1,402 (93.8%) patients had FIB-4 values. Most patients were female (77.2%) with a mean age of 43.8 ± 11.9 years. Within the bariatric cohort, 112 (10.0%) patients had a high- risk FIB-4 (≥ 1.3 or ≥ 2.0 for Age > 65), and significant fibrosis (≥ F2) was present in 90 (8.0%) of patients based on liver biopsy. Within the hepatology cohort, 92 (32.9%) patients had a high- risk FIB-4, and significant fibrosis was present in 104 patients (37.1%). Within the bariatric cohort, 94.5% of patients with a low-risk FIB-4 (< 1.3) had no fibrosis on liver biopsy, compared to 73.4% in the hepatology cohort. Multi-step risk stratification in the clinical care pathway was applied among hepatology referred patients with both FIB-4 and VCTE data (N = 102). Using FIB-4 alone, 65 patients were labeled as low-risk, with 23.1% having ≥ F2 fibrosis on their liver biopsy. After applying both FIB-4 and VCTE, none of the low-risk patients had ≥ F2 fibrosis. In the high-risk group, 67.6% had ≥ F2 fibrosis histologically. **Conclusion:** In patients with BMI ≥ 40, FIB-4 performance varied by clinical setting. Using liver biopsy data, a low-risk FIB-4 < 1.3 correctly identified a higher proportion of those in the bariatric cohort, which may better represent a primary care population. Among those referred to hepatology care, a high percentage of misclassification was observed in the application of the AGA multi-step MASLD clinical care pathway. These results further support an expanded combination of NILDA in populations with a higher pre-test probability of significant fibrosis.



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2396 | INTEGRATING AN ENHANCED LIVER FIBROSIS (ELF)-BASED RISK STRATIFICATION PATHWAY FOR AT-RISK MASH FIBROSIS IN DIABETES CLINICS: A FEASIBILITY PILOT

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Background: Patients with type 2 diabetes (T2D) are at risk for metabolic dysfunction-associated steatohepatitis (MASH), advanced fibrosis, cirrhosis, and liver cancer. There is consensus among multiple societies to screen for at-risk MASH (i.e., MASH and ≥ F2 liver fibrosis) in all with T2D. The first step in screening is calculating a FIB-4 score, followed by transient elastography (TE) or serum Enhanced Liver Fibrosis (ELF) test in those with FIB-4 ≥1.3. ELF is a blood test that can be easily drawn alongside other labs as part of routine T2D care. The goal of this pilot was to examine the feasibility of integrating an ELF-based care pathway in T2D clinics to identify at-risk MASH. **Methods:** We conducted a prospective feasibility pilot with 3 Endocrinologists across 3 clinics at a tertiary care center. Each Endocrinologist was educated about at-risk MASH and the use of ELF. They were asked to implement an ELF-based care pathway in their T2D practice between 10/2024 and 10/2025. The protocol consisted of an initial FIB-4 calculation followed by an ELF test if FIB-4 was ≥ 1.3 (or ≥ 2.0 if ≥ 65 years of age). Hepatology referral was recommended for ELF ≥ 9.5.

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Feasibility and outcome data were collected. **Results:** Analysis includes 33 patients with T2D for whom the ELF-based care pathway was implemented. Demographics are described in Table 1. Median age was 66 years (IQR 55, 71), 51% were female, 6% were Latino/a, 67% White, and 30% Black. Median HbA1c was 7.6% (IQR 6.8, 8.6), median FIB-4 was 1.8 (IQR 1.5, 2.6), and 36% were on GLP-1 receptor agonist therapy. Deviation from the care pathway occurred twice; in both cases, referral to Hepatology was placed despite ELF < 9.5. The majority of the patients (n = 31/33, 94%) had ELF drawn within 1 day. The median ELF value was 9.9 (IQR 9.3, 10.6). Two-thirds (n = 22/33, 67%) were referred to Hepatology. Median time from ELF result to referral was 8 days (IQR 3, 26). Of the 22 referrals, 13 completed Hepatology evaluation, 7 had future appointments, and 4 remained unscheduled. Of the 10 who saw Hepatology and underwent TE or MR elastography (MRE), 4 had cirrhosis (F4), 2 had significant fibrosis (F2/F3), and 4 had minimal fibrosis (< F2). **Conclusion:** Our ELF-based care pathway for identifying at-risk MASH was feasible to implement in Endocrinology clinics and resulted in high-quality Hepatology referrals. Among patients with indeterminate FIB-4 scores (> 1.3) who were evaluated by Hepatology, 60% were identified as having at-risk MASH or cirrhosis, highlighting the clinical utility of this approach for detecting advanced liver disease that may otherwise remain underrecognized. Comparison to a matched control cohort of patients managed by endocrinologists not participating in the ELF stratification initiative is ongoing.

Table 1: Patient Demographics

N (%), or median (Q1, Q3)	
Age, years	66.0 (55.0, 71.0)
Race	
White	22 (66.7%)
Black or African American	10 (30.3%)
Asian	0 (0.0%)
Other, including more than one race	1 (3.0%)
Ethnicity	
Hispanic or Latino	2 (6.1%)
Non-Hispanic or Latino	30 (90.9%)
Unknown	1 (3.0%)
Sex	
Male	16 (48.5%)
Female	17 (51.5%)
BMI (kg/m^2)	31.7 (27.0, 37.5)
Comorbidities	
Hypertension	28 (84.9%)
Hyperlipidemia	25 (75.8%)
OSA	13 (39.4%)
CKD	10 (30.3%)
HFrEF	5 (15.2%)
PAD	3 (9.1%)
CVA	1 (3.0%)
Smoking Status	
Current Smoker	4 (12.1%)
Former Smoker	13 (39.4%)
Never Smoker	16 (48.5%)

OSA=Obstructive Sleep Apnea; CKD=Chronic Kidney Disease, HFrEF = Heart Failure with Reduced Ejection Fraction, PAD = Peripheral Artery Disease, CVA= Cerebrovascular Accident

Table 1: Demographic data for patients participating in the ELF-based care pathway. N=33.

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2397 | PERFORMANCE OF MAF-5 SCORE IN THE DIAGNOSIS OF ADVANCED FIBROSIS IN PATIENTS WITH MASLD: A MULTICENTRIC OBSERVATIONAL RETROSPECTIVE BRAZILIAN COHORT

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Background: MASLD may progress to advanced fibrosis and cirrhosis, the stage of liver fibrosis (LF) being the main determinant of liver-related clinical outcomes in MASLD. Aiming to overcome the limitations of noninvasive tests for LF assessment, the Metabolic Dysfunction–Associated Fibrosis 5 (MAF-5) score was developed. This study aims to evaluate the accuracy of MAF-5 score in patients with MASLD in a Brazilian multicenter cohort. **Methods:** This was a multicenter, cross-sectional, retrospective study conducted at 10 referral centers in Hepatology across Brazil. Individuals older than 18 years, with diagnosis of biopsy-confirmed MASLD, and complete data for calculation of MAF-5 were included. The primary outcome was to evaluate the performance of the MAF-5 score in the assessment of LF in individuals with MASLD. MAF-5 score was calculated as follows, and classified as low (<0), intermediate (0–1), and high risk (>1) for LF. MAF-5 = $-11.3674 + WC \times 0.0282 - BMI \times 0.1761 + WC \times BMI \times 0.0019 + 2.0762$ (if T2DM) + $\ln(AST) \times 2.9207 -$ platelets $\times 0.0059$ Diagnostic performance was evaluated by AUROC. A p-value <0.05 was considered statistically significant, while an AUROC >0.7 was considered adequate. **Results:** The sample consisted of 1,115 individuals, with a mean age of 47.99 ± 18.7 years, predominantly women (n = 813; 72.9%). A high prevalence of comorbidities was observed, including diabetes mellitus (n = 454; 40.7%) and systemic arterial hypertension (n = 586; 52.6%). Liver biopsy showed that 511 patients (45.8%) had no fibrosis (F0), whereas 604 (54.2%) presented some degree of fibrosis: 350 (31.4%) with F1, 93 (8.3%) with F2, 110 (9.9%) with F3, and 51 (4.6%) with F4. The performance analyses of the MAF-5 score under different scenarios are presented in Table 1. Statistical significance was found when advanced fibrosis (F3 and F4) or cirrhosis (F4) were considered as outcome variables (p = 0.002 and p = 0.013, respectively), although with low AUROC values (0.574 and 0.589, respectively). When the sample was stratified according to the presence of grade II obesity (BMI ≥ 35) or not, all p-values were statistically significant. MAF-5 score performed better in groups with BMI <35 across all fibrosis stages (F1 to F3). Among cirrhotic patients (F4), the score performed better in individuals with obesity grade II.When the population was stratified into older (age $\geq$ 60 years) people or not, a moderate predictive performance for advanced fibrosis (F3–F4; AUROC = 0.778; p < 0.001) and high predictive performance for cirrhosis (F4; AUROC = 0.856; p < 0.001) was observed only in the older people group. **Conclusion:** In this sample, MAF-5 showed better performance for the diagnosis of advanced fibrosis (F3-F4) and cirrhosis (F4) in older population. Also, there was a tendency of good performance, with statistical relevance, when the sample were divided in above or below BMI 35Kg/m².

Table 1. Areas under the ROC Curve for different Scenarios

Grouping	State Variable	AUROC	p-value	CI 95% Lower limit	CI 95% Upper limit
Total Sample n=1,115 (100%)	F1-F4	0.496	0.811	0.461	0.531
	F2-F4	0.533	0.110	0.490	0.575
	F3-F4	0.574	**0.002***	0.525	0.623
	F4	0.589	**0.013***	0.514	0.663
BMI <35 n=388 (34.8%)	F1-F4	0.628	**<0.001***	0.563	0.693
	F2-F4	0.622	**<0.001***	0.565	0.680
	F3-F4	0.636	**<0.001***	0.570	0.701
	F4	0.619	**0.016***	0.516	0.723
BMI ≥35 n=727 (65.2%)	F1-F4	0.561	**0.008***	0.516	0.606
	F2-F4	0.602	**0.001***	0.539	0.666
	F3-F4	0.624	**0.001***	0.551	0.696
	F4	0.631	**0.012***	0.525	0.738
Adult (age <60 y/o) n=835 (74.9%)	F1-F4	0.478	0.284	0.437	0.518
	F2-F4	0.509	0.683	0.464	0.555
	F3-F4	0.543	0.095	0.490	0.597
	F4	0.552	0.184	0.470	0.633
Older people (age ≥60 y/o) n=280 (25.1%)	F1-F4	0.556	0.126	0.484	0.629
	F2-F4	0.688	**<0.001***	0.591	0.785
	F3-F4	**0.778**[1]	**<0.001***	0.679	0.877
	F4	**0.856**[2]	**<0.001***	0.794	0.918

Where: AUROC: Area Under the Receiver Operating Characteristic; p-value: statistical significance stablished when; *: p≤0.05; CI: confidence interval of 95%; #BMI: Body mass index; y/o: years old; [1] Moderate predictive performance (AUROC ≥0.7); [2] High predictive performance (AUROC ≥0.8).

Disclosures: Cristiane Tovo: Nothing to Disclose, Carolina Dornelles: Nothing to Disclose, Flavia Fernandes: Nothing to Disclose, Cristiane Villela-Nogueira: Nothing to Disclose, Claudia Oliveira: Nothing to Disclose, Nothing to Disclose, Helma Cotrim: Nothing to Disclose, Nathalie Leite: Nothing to Disclose, Edison Parise: Nothing to Disclose, Claudia Ivantes: Nothing to Disclose, Mário Alvares-da-Silva: Nothing to Disclose, Celso Didoné Filho: Nothing to Disclose, Mario Pessoa: Nothing to Disclose, Leila Pereira: Nothing to Disclose, Julia Vieira: Nothing to Disclose, Natalia Wajsbrot: Nothing to Disclose, Patricia Zitelli: Nothing to Disclose, Sebastião Duarte: Nothing to Disclose, Ana Lucia Salgado: Nothing to Disclose, Giulia Arima: Nothing to Disclose, Juliana Macedo: Nothing to Disclose, Luis Ferreira: Nothing to Disclose.

2398 | DISEASE SEVERITY INDEX DETECTS DYNAMIC CHANGES IN LIVER FUNCTION ACROSS THERAPEUTIC INTERVENTIONS AND LIVER DISEASE ETIOLOGIES

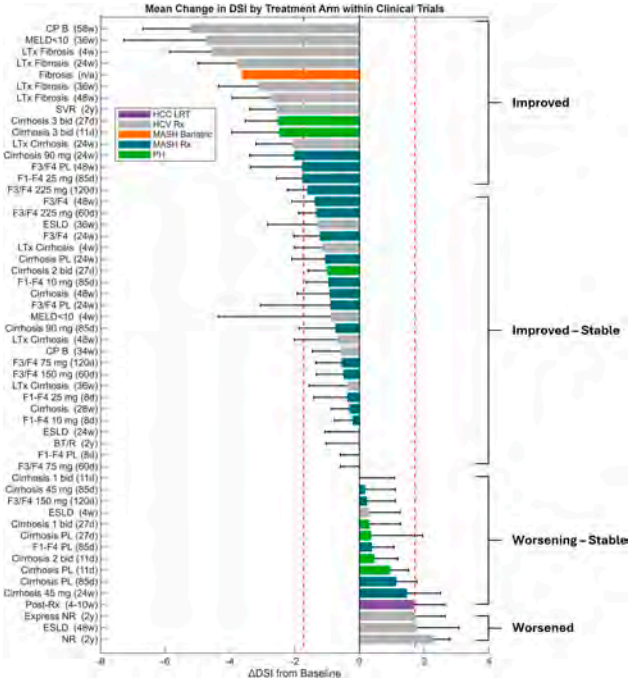
Eric Lawitz[1] Michael McRae[2] Joanne Imperial[3] Gregory Everson[4], [1]The Texas Liver Institute, [2]Custom DX Solutions LLC, [3]HepQuant LLC, [4]HepQuant

Background: Responsiveness to therapeutic intervention across diverse disease etiologies has not been systematically characterized. The Disease Severity Index (DSI) is a measure of global liver disease severity from 0 (healthy) to 50 (severe

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dysfunction) derived from the noninvasive oral cholate challenge test (OCCT). This analysis evaluated the changes in DSI relative to baseline in response to therapeutic interventions. **Methods:** Data from 14 clinical trials were analyzed, comprising 1258 tests from 473 subjects. The OCCT involved oral administration of deuterium-labelled (d4-) cholate, blood sampling at 20 and 60 minutes, and quantification of the d4-cholate by LC-MS/MS. Test parameters, including DSI, were calculated for each subject. The minimum detectable difference (MDD), which is the smallest difference between treatment and control group that can be detected with statistical significance, was ±1.7 for DSI based on prior within-individual reproducibility studies (McRae et al. 2024). For each treatment arm, the mean change from baseline in DSI (ΔDSI) was calculated. Treatment response was categorized relative to the MDD as improved ($\Delta DSI \leq -1.7$), stable/improved ($-1.7 < \Delta DSI \leq 0$), stable/worsened ($0 < \Delta DSI \leq 1.7$), or worsened ($\Delta DSI > 1.7$). **Results:** The trials represented primarily subjects with HCV and MASH and represented a broad spectrum of disease severity, ranging from fibrosis to cirrhosis to end-stage liver disease (ESLD) (Figure). Among 54 treatment groups, 14 (26%) improved, 25 (46%) were stable/improved, 12 (22%) were stable/worsened, and 3 (6%) worsened. The largest improvements in liver function occurred in HCV treatment arms receiving antiviral therapy, consistent with viral eradication. Substantial improvement was also observed in subjects with fibrotic MASH who underwent bariatric surgery (ΔDSI −3.6). The OCCT detected rapid functional improvement within 27 days in subjects with Child-Pugh A cirrhosis treated with the highest dose of avenciguat, a soluble guanylate cyclase activator for treatment of portal hypertension (3 mg twice daily; ΔDSI −2.5). Among MASH treatment cohorts, 19 of 24 (79%) were improved or stable/improved. Hepatotoxicity (ΔDSI of +1.7) was observed in patients undergoing locoregional therapy for hepatocellular carcinoma (HCC). Worsening DSI was observed in antiviral nonresponders (NR) and patients with ESLD prior to liver transplantation. **Conclusion:** DSI is a dynamic, sensitive indicator of liver function that detects both improvement and worsening across diverse liver disease etiologies, severities, and therapeutic modalities. Incorporation of DSI into clinical trials as a continuous functional endpoint may enable earlier detection of treatment response, support adaptive trial designs, and reduce required sample sizes by providing a quantitative functional endpoint.



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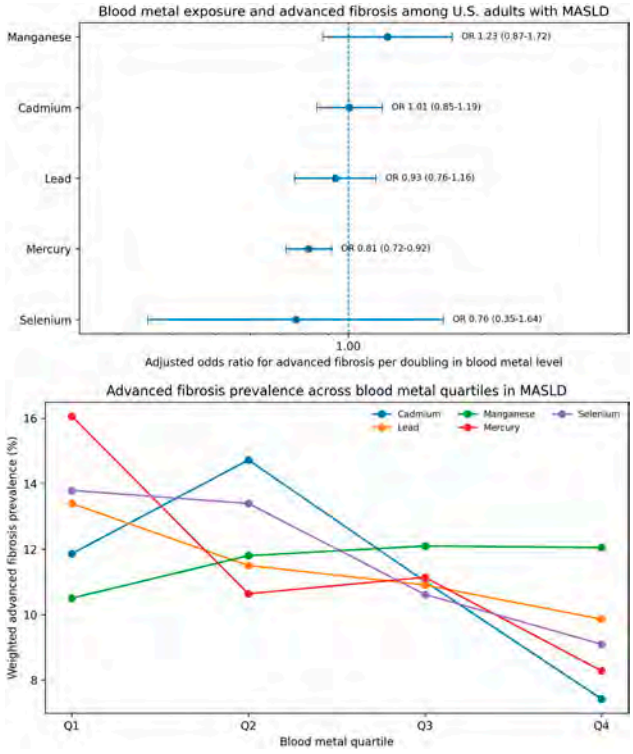
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Consultant, Corcept Therapeutics: Grant/Research Support, Astrazeneca: Consultant, inventiva: Consultant, Michael McRae: HepQuant, LLC: Independent Contractor, Joanne Imperial: Nothing to Disclose, Gregory Everson: Nothing to Disclose.

2399 | BLOOD METAL EXPOSURE AND ADVANCED FIBROSIS IN MASLD: NATIONAL EVIDENCE FROM NHANES 2017–MARCH 2020

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Background: Environmental metal exposure may influence metabolic dysfunction and liver injury, but its association with advanced fibrosis in MASLD remains unclear. We examined blood metal exposure and VCTE-defined advanced fibrosis among U.S. adults with MASLD. **Methods:** We analyzed NHANES 2017–March 2020 adults aged ≥20 years with valid VCTE and blood metal data. MASLD was defined as CAP ≥285 dB/m plus ≥1 cardiometabolic risk factor, excluding heavy alcohol use and hepatitis C. Advanced fibrosis was defined as LSM ≥9.7 kPa. Blood lead, cadmium, mercury, selenium, and manganese were assessed by quartiles and log2-transformed continuous levels. Survey-weighted logistic regression adjusted for demographics, socioeconomic factors, BMI, diabetes/prediabetes, hypertension, smoking, and alcohol intake. **Results:** Among adults with MASLD and blood metal data, the final analytic sample included 2,382 participants, representing 66.2 million U.S. adults. VCTE-defined advanced fibrosis was present in 11.6%, corresponding to approximately 7.7 million U.S. adults. Across quartiles, advanced fibrosis prevalence did not show a positive dose-response pattern for lead, cadmium, selenium, or manganese. For mercury, advanced fibrosis prevalence decreased from 16.1% in Q1 to 8.3% in Q4. In fully adjusted models, each doubling in blood mercury was associated with lower odds of advanced fibrosis, OR 0.81, 95% CI 0.72–0.92, p = 0.0007. Lead was not significantly associated with advanced fibrosis, OR 0.93, 95% CI 0.76–1.16, p = 0.53. Cadmium showed no independent association, OR 1.01, 95% CI 0.85–1.19, p = 0.95. Selenium was also not significant, OR 0.76, 95% CI 0.35–1.64, p = 0.48, and manganese showed a non-significant positive association, OR 1.23, 95% CI 0.87–1.72, p = 0.24. These findings suggest that among measured blood metals, mercury demonstrated the strongest exposure–fibrosis signal, whereas other metals were not independently associated with advanced fibrosis after multivariable adjustment. **Conclusion:** In this nationally representative VCTE-based analysis of U.S. adults with MASLD, lead, cadmium, selenium, and manganese were not independently associated with advanced fibrosis. Higher blood mercury was associated with lower observed fibrosis odds, likely reflecting dietary, seafood-related, or socioeconomic exposure patterns rather than direct biological protection. Environmental exposure profiles in MASLD should be interpreted alongside metabolic and social determinants of fibrosis risk.



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2400 | REPRODUCIBILITY BETWEEN FREE-BREATHING AND BREATH-HOLD 3D MRE AT 60HZ FOR QUANTIFYING LIVER STIFFNESS

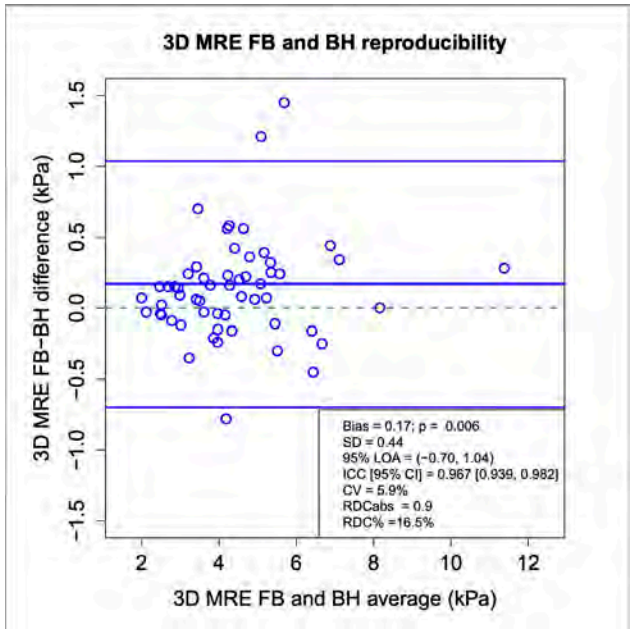
Gage Tanzman[1] Lael Ceriani[1] Nicholas Tripathi[1] Tanya Wolfson[1] Gavin Hamilton[1] Mary Dalupang[1] Egbert

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Background: 3D magnetic resonance elastography (MRE) analyzes wave motion in three dimensions, theoretically enabling more accurate and precise liver stiffness (LS) quantification than 2D MRE. Free-breathing (FB) 3D spin-echo EPI (SE-EPI) MRE is an ~3: 50 min investigational alternative to conventional breath-hold (BH) 3D SE-EPI MRE, which can take over 4 minutes to acquire due to its six separate required breath-holds with pauses between. FB 3D MRE uses the same 32-slice pulse sequence design at 60Hz as BH 3D MRE but increases the TR from ~1600ms to ~3200ms, increases the number of phase offsets from 3 to 12, and uses temporal averaging. This increases the signal-to-noise ratio (SNR), reduces motion artifacts, and can be used when patients have difficulty suspending respiration. We sought to assess reproducibility between FB 3D MRE and BH 3D MRE for quantifying LS at 3T in adults with chronic liver disease (CLD). **Methods:** This prospective, single-center study enrolled adults with known or suspected CLD who received same-day FB and BH 3D SE-EPI MRE exams. Images were acquired at 60Hz on a GE 3T system with a 448-mm field-of-view reconstructed to a 128x128 final matrix. Expert analysts placed regions of interest (ROIs) on 4 of 32 slices, centered in the liver and approximately 10mm apart, in areas of planar wave propagation and recorded LS and cumulative ROI size (cROI). Exams were scored successful if cROI $\geq$ 300 pixels (Px). Success rate (SR) of each method was calculated. cROI (paired t-test) and SR (McNemar's test) were compared between methods. Inter-method reproducibility for quantifying LS was assessed by Bland-Altman analysis, yielding bias and its significance, limits of agreement (LoA), proportional reproducibility coefficient (RDC%), and intraclass correlation coefficient (ICC) with 95% confidence intervals (CIs). **Results:** This study included 62 participants (34 female; mean age 59 ± 12 yrs; mean body mass index 30 ± 6 kg/m^2). Median (range) cROIs were 3,201 (553-10,210) Px for FB 3D MRE and 2,611 (494-5,716) Px for BH 3D MRE ($p = 0.003$). The SR of FB (98%) and BH (94%) 3D MRE were similar ($p = 0.371$). In 57 participants, both methods were successful. In these, mean LS (range) was 4.6 (2.0-11.7) kPa for FB 3D MRE and 4.4 (2.0-11.2) kPa for BH 3D MRE. Bias (p-value), LoA, RDC%, and ICC (95% CI) were: 0.2 kPa ($p = 0.006$), (-0.7 kPa, 1.0 kPa), 16.5%, and 0.967 (0.939, 0.982), respectively. **Conclusion:** In adults imaged at 3T, FB 3D MRE agreed with BH 3D MRE for quantification of LS, with precision metrics akin to test-retest repeatability of BH 3D-MRE in prior studies, larger cROIs, and negligible bias. FB 3D MRE provides an attractive alternative to BH 3D MRE, especially for those who have difficulty suspending respiration.



Disclosures: Gage Tanzman: Nothing to Disclose, Lael Ceriani: Nothing to Disclose, Nicholas Tripathi: Nothing to Disclose, Tanya Wolfson: Nothing to Disclose, Gavin Hamilton: Nothing to Disclose, Mary Dalupang: Nothing to Disclose, Egbert Madamba: Nothing to Disclose, Michael Middleton: Nothing to Disclose, Richard Ehman: Resoundant Inc.: Royalties or patent beneficiary, Resoundant Inc.: Stock – privately held company, Resoundant: Uncompensated role assigned by my employer, Mayo Clinic, Kevin Glaser: Nothing to Disclose, Yuan Le: Nothing to Disclose, Jiahui Li: Nothing to Disclose, Meng Yin: Resoundant, Inc.: Stock – privately held company, Yesenia Covarrubias: Nothing to Disclose, Mustafa Bashir: Rectify Pharma: Consultant, Siemens Healthineers: Grant/Research Support, Bayer Healthcare: Grant/Research Support, Madrigal Pharmaceuticals: Grant/Research Support, Corcept Therapeutics: Grant/Research Support, Carmot Therapeutics: Grant/Research Support, United Therapeutics: Consultant, GE Healthcare: Consultant, RapidAI: Consultant, NGM Bio: Grant/Research Support, Opko Health: Grant/Research Support, Scott Reeder: Nothing to Disclose, Bachir Taouli: Nothing to Disclose, Rohit Loomba: Eli Lilly and Company: Consultant, 89bio: Consultant, Aardvark Therapeutics: Consultant, Altimmune: Consultant, Alnylam/Regeneron: Consultant, Amgen: Consultant, Arrowhead Pharmaceuticals: Consultant, AstraZeneca: Consultant, Bristol Myers Squibb: Consultant, CohBar: Consultant, Eli Lilly: Consultant, Galmed Pharmaceuticals: Consultant, Gilead: Consultant, Glympse Bio: Consultant, Hightide: Consultant, Inipharma: Consultant, Intercept: Consultant, Inventiva: Consultant, Ionis: Consultant, Janssen, Inc.: Consultant, Madrigal Pharmaceuticals: Consultant, Merck, Metacrine, Inc.:

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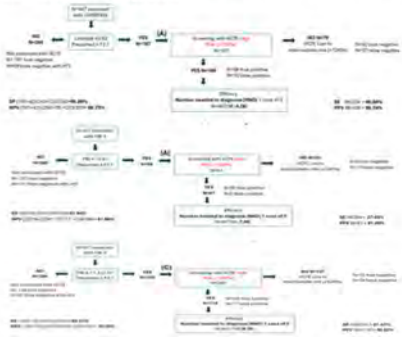
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2401 | LIVERFAST IN SEQUENTIAL COMBINATION WITH VIBRATION CONTROLLED TRANSIENT ELASTOGRAPHY (VCTE) OUTPERFORMS FIB-4 AND VCTE FOR IDENTIFYING ADVANCED FIBROSIS (≥F3) IN PATIENTS WITH MASLD

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Background: AASLD clinical practice guidelines recommends FIB-4 followed by VCTE for the detection of ≥F3 stages. LIVERFAST (Fibronostics U.S.,Inc., New Orleans, US) is a novel blood-based test reimbursed in US to identify liver fibrosis. The study aimed to compare the performance, efficacy of LIVERFAST and FIB-4, sequentially with VCTE, and to assess the and need to VCTE referral for the identification of ≥F3 fibrosis in the overall MASLD population and in the subgroup of patients with type 2 diabetes (T2DM). **Methods:** Cross-sectional retrospective study including MASLD patients from a tertiary hepatology center with contemporary LIVERFAST, FIB-4, VCTE, and liver biopsy within 6-month. Performances were assessed using sensitivity, specificity, PPV, NPV, and number needed to diagnose (NND), number of refferals for a second assessment. VCTE with IQR < 30% of median value, 10 valid measurements and success rate ≥ 60% were included. The following cutoffs have been tested for VCTE, 8 and 12 kPa, for FIB-4 2.67 and 1.3 and for LIVERFAST 0.52. **Results:** LIVERFAST outperformed FIB-4 for identifying ≥F3 fibrosis, showing almost twice higher sensitivity and higher NPV at the rule-in FIB-4 cut-off (>2.67) and higher specificity and PPV at the recommended rule-out cut-off (≥1.3 [2.0]). The combination LIVERFASt and VCTE achieved higher PPV (90.4%) than FIB-4 and VCTE (76%) with similar NPV. LIVERFASt identified almost twice more of ≥F3 cases as FIB-4 at the rule-out >2.67 cut-off, NNDs 4.56 vs 7.98, respectively. LIVERFAST identified a similar number of ≥F3 cases as FIB-4 at the recommended rule-out ≥1.3 [2.0] cut-off with a lower number of required VCTEs referrals of 187 vs 243 ($p < 0.001$), respectively. Similar results have been observed in the T2DM subanalysis with a with a lower number of required VCTEs referrals of 118 vs 146 ($p < 0.01$), respectively. **Conclusion:** LIVERFASt outperformed FIB-4 and its integration into MASLD pathways may enhance screening efficiency, including in high-risk T2DM patients.

Figure 1. Sequential approach with LIVERFAST ≥F3, FIB-4 >2.67 cut-off and recommended FIB-4≥1.3 (2) followed by VCTE >12 KPa, high risk for ≥F3 in the overall population.



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2402 | INDIVIDUALS UNDERGOING JOINT REPLACEMENT ARE AT RISK FOR UNRECOGNIZED ADVANCED LIVER DISEASE

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Background: Cirrhosis makes joint replacement surgery riskier due to an increased risk for complications. Chronic liver disease (CLD) is common in the United States with metabolic dysfunction associated steatotic liver disease (MASLD) affecting 1 out of every 3 adults and more than 80% of adults living with type 2 diabetes. Most people with CLD are unaware that they are at risk for liver disease and up to 75% of people with liver cirrhosis are unaware of their condition. Older adults with metabolic disease are at highest risk for advanced disease from MASLD and are also impacted by osteoarthritis leading to evaluation for joint replacement. Non-invasive tools such as FIB4 can be used to identify people at risk for advanced liver disease, even when they are unaware of their risk. A FIB4 score > 2.67 is associated with risk for advanced liver disease and > 3.25 has a positive predictive value of 65% for advanced fibrosis. Primary aim is to evaluate for unrecognized advanced liver disease in a population of individuals undergoing joint surgery. Secondary aim to see if this impacts perioperative outcome. **Methods:** Retrospective chart review of patients undergoing joint replacement surgery over a 12-month period with at least 6 months post-surgical follow-up. Data collection will include demographics (age, sex), comorbid conditions (T2DM, HTN, Liver disease), BMI, and preoperative blood work (CBC, CMP) to allow calculation of FIB4. Post-operative outcomes will be assessed, including infection and dislocation. **Results:** 403 consecutive total joint patients were reviewed. No patient had known cirrhosis. 12 were eliminated for inadequate labs to calculate FIB4. Avg Age 69 (58-81), 61% TKI (total knee implant), 39% THI (total hip implant), 52% male, Avg BMI 33.9 (28-39), 30% T2DM, 62% HTN. 25% had a calculated FIB4 > 2.67 and 8% with FIB4 > 3.25. There were no post-operative dislocations or joint infections. Elevated FIB4 did not correlate with T2DM. **Conclusion:** In this population of individuals enriched with risk factors for MASLD, 25% had a FIB4 that suggested they were at high risk for advanced liver disease and 8% with a score concerning for very high risk. Not only is this an opportunity to identify patients at risk for surgical complications it is also an excellent opportunity to identify individuals at risk for liver related morbidity and mortality.

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2403 | ULTRASOUND-DERIVED FAT FRACTION (UDFF) AND AUTOMATED POINT SHEAR WAVE ELASTOGRAPHY (AUTO PSWE) FOR NON-INVASIVE STEATOSIS QUANTIFICATION AND LIVER FIBROSIS STAGING

Christian Sebesta[1] Nina Dominik[1] Georg Kramer[1] Benedikt Hofer[1] Paul Thöne[1] Marlene Hintersteininger[1] Mathias Jachs[1] Lukas Hartl[1] Lorenz Balcar[1] Philipp Schwabl[1] Benedikt Simbrunner[1] Georg Semmler[1] Michael Trauner[1] Mattias Mandorfer[1] David Bauer[1] Thomas Reiberger[1], [1]Medical University of Vienna

Background: Modern ultrasound platforms allow the measurement of liver stiffness (LSM) and hepatic

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steatosis quantification such as by ultrasound derived fat fraction (UDFF). Validating these ultrasound-based parameters against vibration controlled transient elastography (VCTE), the current non-invasive reference standard may support their implementation in routine clinical practice. **Methods:** In this prospective study, patients with suspected liver disease underwent same-day non-invasive assessment on two elastography platforms. LSM was measured by Auto point shear wave elastography (auto pSWE) on a Siemens ACUSON Sequoia system, which also enabled acquisition of UDFF. Participants additionally underwent LSM by VCTE with continuous controlled attenuation parameter (cCAP). VCTE-derived LSM thresholds of ≥15 kPa and ≥25 kPa were used to define advanced chronic liver disease (ACLD) and clinically significant portal hypertension (CSPH), respectively. Steatosis grades were defined according to cCAP thresholds, with ≥S1 steatosis defined as cCAP ≥248 dB/m and severe steatosis (≥S3) as cCAP ≥280 dB/m. **Results:** The study included 111 patients with suspected liver disease. Median age was 51 years, 76% were male, and the most common etiology was steatotic liver disease (46%). Overall, 49 patients (44%) fulfilled criteria for ACLD and 25 (23%) for CSPH. Median VCTE-LSM was 9 kPa, while median Auto pSWE-LSM was 6 kPa. Median cCAP was 250 dB/m. Any steatosis (≥S1) was present in 49 patients (51%), and S3 steatosis in 33 patients (34%). Median UDFF was 6%. UDFF showed a moderate correlation with cCAP ($r = 0.50$, $p < 0.001$) and provided moderate diagnostic performance for steatosis staging, with AUCs of 0.79 for ≥S1 and 0.83 for S3 steatosis. Optimized UDFF thresholds for excluding ≥S1 steatosis were at <5% (NPV 88%), for identifying S3 at >15% (PPV 70%).Auto pSWE-LSM demonstrated a strong correlation with VCTE-LSM ($r = 0.76$, $p < 0.001$). However, Bland–Altman analysis indicated a systematic underestimation of LSM by Auto pSWE compared to VCTE, with a mean bias of −10.5 kPa and greater divergence at higher VCTE-LSM values. For liver disease staging, Auto pSWE-LSM showed good discrimination for ACLD (AUC 0.79, 95% CI 0.70–0.88) and excellent discrimination for CSPH (AUC 0.87, 95% CI 0.77–0.96). Optimized cutoffs supported the use of Auto pSWE-LSM <4.0 kPa to rule out ACLD (NPV 79%) and >10.3 kPa to rule in CSPH (PPV 65%). Incorporating platelet count further improved diagnostic performance, increasing the AUC to 0.88 for ACLD and 0.94 for CSPH. **Conclusion:** UDFF demonstrated good performance for hepatic steatosis quantification, with values <5% excluding any steaotosis (≤S1) and >15% identifying severe steatosis (≥S3). Auto pSWE yielded systematically lower LSM values than VCTE especially at higher VCTE-LSM strata, thus, further studies investigating the value of Auto pSWE-LSM for non-invasive ACLD and CSPH assessment are needed.

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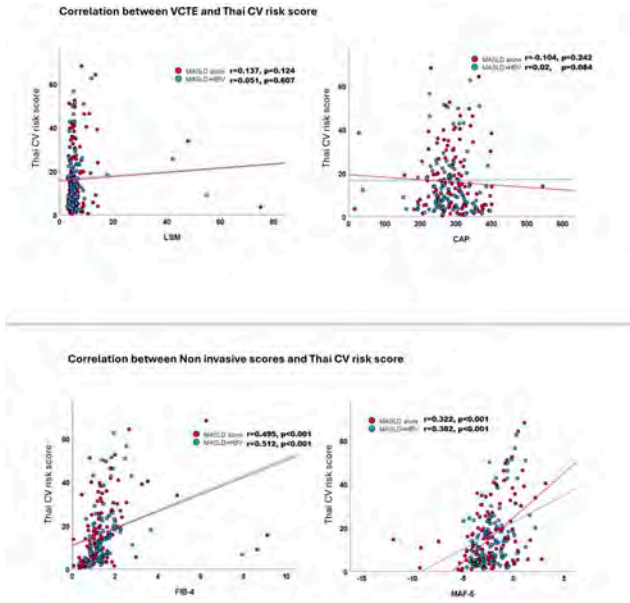
2404 | CORRELATION BETWEEN LIVER ELASTOGRAPHY AND THAI CARDIOVASCULAR RISK IN PATIENTS WITH MASLD WITH OR WITHOUT CHRONIC HBV INFECTION

Itsara Bunupuradah[1], [1]Faculty of Medicine Ramathibodi Hospital, Mahidol University

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is strongly associated with increased cardiovascular (CV) risk, which is a leading cause of mortality. Conversely, chronic hepatitis B (CHB) infection alters hepatic lipid metabolism and may have a protective effect against atherosclerosis. This study aimed to evaluate the correlation between vibration-controlled transient elastography (VCTE) parameters (LSM and CAP), non-invasive fibrosis scores (FIB-4 and MAF-5), and the Thai CV risk score in MASLD patients with or without CHB. **Methods:** A retrospective cross-sectional study was conducted at Ramathibodi Hospital between January 2023 and December 2024, including 234 MASLD patients aged 35–70 years (128 with MASLD alone and 106 with MASLD plus CHB). All patients underwent VCTE and 10-year Thai CV risk score assessment. Patients with HCV infection, HIV infection, significant alcohol use, or established ASCVD were excluded. Data were analyzed using Spearman's rank correlation and multivariable logistic regression. **Results:** Most patients in both groups presented with early-stage fibrosis (predominantly F1). Compared with the MASLD-alone group, the MASLD plus CHB group had significantly lower BMI (27.8 vs 26.3 kg/m², $p = 0.029$), lower prevalence of hypertension (53.9% vs 39.6%, $p = 0.025$), and lower CAP values (292 vs 274 dB/m, $p = 0.031$). VCTE parameters (LSM and CAP) demonstrated no significant correlation with the Thai CV risk score in either group. Conversely, non-invasive fibrosis scores (FIB-4 and MAF-5) showed significant positive correlations with the Thai CV risk score (all $p < 0.001$). Multivariable analysis identified higher HbA1c (adjusted OR 1.54, $p = 0.019$) and reduced renal function (CKD stage ≥ 2; adjusted OR 4.10, $p < 0.001$) as independent predictors of intermediate-to-very-high Thai CV risk score. **Conclusion:** VCTE parameters (LSM and CAP) were not correlated with the Thai CV risk score in this MASLD cohort with predominantly early-stage fibrosis. However, non-invasive fibrosis scores (FIB-4 and MAF-5) were significantly correlated with Thai CV risk score. These findings suggest that VCTE alone may not adequately reflect cardiovascular risk score in early-stage fibrosis, highlighting the importance of comprehensive multimodal assessment.



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2405 | HEPASCORE ALONE MATCHES A TWO-STEP FIB-4 AND FIBROSCAN ALGORITHM FOR DETECTION OF SIGNIFICANT FIBROSIS IN METABOLIC ASSOCIATED STEATOTIC LIVER DISEASE: IMPLICATIONS FOR COMMUNITY SCREENING

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Background: Current guidelines recommend sequential non-invasive testing with FIB-4 followed by liver stiffness measurement (LSM) by Fibroscan to screen for significant hepatic fibrosis (F2–F4) in metabolic associated steatotic liver disease (MASLD). We compared the diagnostic accuracy of Hepascore, a composite serum biomarker for hepatic fibrosis, against FIB-4 combined with Fibroscan for identifying significant fibrosis on liver biopsy. **Methods:** A retrospective analysis of 101 patients with biopsy-proven

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MASLD using NASH CRN fibrosis staging as the reference standard was performed. Four triage pathways were compared: Pathway A (FIB4 ≥1.3 → LSM ≥8 kPa; guideline-recommended), Pathway B (Hepascore >0.6 → LSM ≥8 kPa), Pathway C (Hepascore >0.5 → LSM ≥8 kPa), and Pathway D (Hepascore >0.5 alone). AUROC of FIB-4, Hepascore and LSM for F2–F4 fibrosis prediction were compared by DeLong's method. The diagnostic performance of each pathway was compared with referral rates compared using McNemar's test. **Results:** The cohort had a mean age 53 ± 12 years, 60% were female with a mean BMI of 37 ± 8 kg/m². Significant fibrosis (F2–F4) was present in 45.5% (46/101). All three markers demonstrated equivalent discriminative ability: AUROC 0.804 (95% CI 0.718–0.891) for Hepascore, 0.793 (0.705–0.880) for LSM, and 0.788 (0.701–0.874) for FIB4 (all comparisons p > 0.05). Despite equivalent AUROCs, all Hepascore pathways demonstrated lower false positive rates (6–11% vs 16%) and higher PPV (82–86% vs 76%) than Pathway A. Pathways B and C required fewer Fibroscans than Pathway A (21 and 28 vs 38; p = 0.001 and p = 0.04), though with lower sensitivity (39–52% vs 63%). Pathway D referred an equivalent number as Pathway A (34 vs 38; p = 0.46) with superior specificity (89% vs 84%), higher PPV (82% vs 76%), lower false positive rate (11% vs 16%), and similar sensitivity (61% vs 63%) without requiring Fibroscan (**Table 1)** . **Conclusion:** Hepascore, FIB-4, and LSM demonstrated equivalent overall discriminative ability by AUROC, however Hepascore >0.5 alone showed similar diagnostic performance to the two-step FIB-4 and Fibroscan algorithm with slightly better predictive ability and no Fibroscan requirement. Hepascore based screening may reduce community Fibroscan demand and identify MASLD patients with significant fibrosis requiring treatment where Fibroscan is not available.

Table 1 — Diagnostic performance of referral pathways for significant fibrosis detection in MASLD (n = 101)

	Pathway A FIB4 ≥1.3 → LSM ≥8	Pathway B Hepascore >0.6 → LSM ≥8	Pathway C Hepascore >0.5 → LSM ≥8	Pathway D Hepascore >0.5 alone
Referral rate				
Referral rate	38 (37.6%)	21 (20.8%)	28 (27.7%)	34 (33.7%)
vs Pathway A	—	p = 0.001	p = 0.041	p = 0.465
Diagnostic performance				
Sensitivity	63.0%	39.1%	52.2%	60.9%
Specificity	83.6%	94.5%	92.7%	89.1%
Accuracy	74.3%	69%	74.3%	76%
PPV	76.3%	85.7%	85.7%	82.4%
NPV	73.0%	65.0%	69.9%	73.1%
FPR	16.4%	5.5%	7.3%	10.9%
FNR	37.0%	60.9%	47.8%	39.1%
FIBROSCAN scans required	38	21	28	0

Pathway A = guideline-recommended pathway (FIB4 ≥1.3 → LSM ≥8 kPa). Pathway B = Hepascore >0.6 → LSM ≥8 kPa. Pathway C = Hepascore >0.5 → LSM ≥8 kPa. Pathway D = Hepascore >0.5 alone (no FIBROSCAN required). McNemar p-value shown vs Pathway A. FPR = false positive rate;

Disclosures: Dewruwan Gammanpila: Nothing to Disclose, Angus Jeffrey: Nothing to Disclose, Chloe Attree: Nothing to Disclose, Michael Wallace: Nothing to Disclose, George Garas: Nothing to Disclose, Zhengyi Wang: Nothing to Disclose, Gerry MacQuillan: Nothing to Disclose, Gary Jeffrey: Nothing to Disclose, Leon Adams: Novo Nordisk: Advisor, SCL Behring: Advisor, Dr Falk: Speaking and Teaching, Novo Nordisk: Grant/Research Support, Boehringer Ingelheim: Speaking and Teaching.

2406 | DISPOSITION OF THE EXOGENOUS BIOMARKER EZETIMIBE-GLUCURONIDE EFFECTIVELY IDENTIFIES MASH

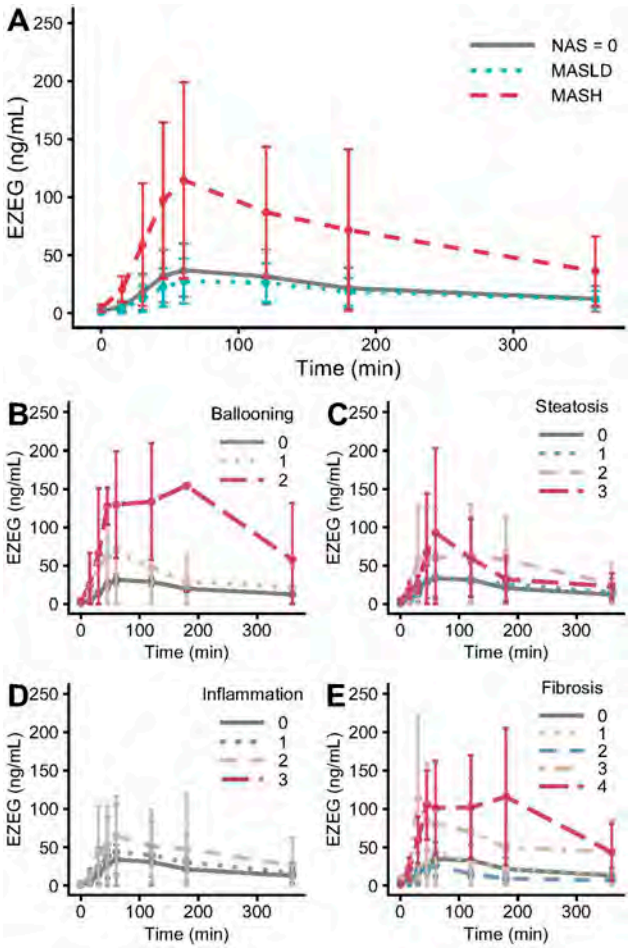
Geoffrey Block[1] Dominique Farrera[2] Kayla Frost[2] Joseph Jilek[2] Raxton Sample[2] Jailyn Isu[2] Mina Alaaldin[2] Paige Linberg[2] Max Maloney[2] David Rodrigues[3] Emi Yamaguchi[3] Ryu Sangwoo[3] Yi-An Bi[3] Mark West[3] Sumathy Mathialagan[3] Sarah Lazzaro[3] Brooke Rabe[4] Aiden-Hung Nguyen[5] Katherine Ho[6] Susie Messenger[6] Ahmad Omid Rahimi[6] Ryan Kian Aknbari[6] Carolina Säll[7] Walter Klimecki[2] Mary Paine[5] Stephen Wright[8] Dean Billheimer[6] Iman Ghaderi[6] Nathan Cherrington[2], [1]Boyer Liver Institute, College of Medicine, University of Arizona-Tucson, [2]College of Pharmacy, University of Arizona, Tucson, AZ, [3]Pfizer Inc., Groton, CT 06340, USA, [4]BIO5 Insitute, University of Arizona, Tucson, AZ, [5]College of Pharmacy and Pharmaceutical Sciences, Washington State University, Spokane, WA 99202, [6]College of Medicine, University of Arizona, Tucson, AZ, [7]Novo Nordisk A/S, 2760 Måløv, Denmark, [8]Mel and Enid Zuckerman College of Public Health, University of Arizona, Tucson, AZ

Background: Metabolic dysfunction-associated steatohepatitis (MASH) is a progressive liver disease with an urgent need for reliable, noninvasive biomarkers that can serve as reasonably likely surrogate endpoints, as diagnosis remains limited by the invasiveness of liver biopsy and the limited accuracy of existing noninvasive tests. MASH disrupts hepatic and renal transporter expression and function (OATP1B1, MRP2, MRP3), leading to increased systemic retention of drug substrates. Because ezetimibe-glucuronide (EZEG) is a substrate of transporters altered in MASH, we evaluated whether EZEG could serve as a noninvasive, mechanism-based exogenous diagnostic function test. **Methods:** Subjects at risk for MASLD, with normal renal function, underwent liver biopsy to confirm SLD (N = 52) and enrolled in this hIRB-approved study. Following p.o. administration of a 1 mg subtherapeutic dose of ezetimibe (EZE), plasma and urine EZEG concentrations were quantified by LC-MS/MS. The pathology reader was blinded to EZEG results. Patients were classified as MASLD (NAFLD Activity Score [NAS] ≤3 or NAS = 4 without ballooning) or MASH (NAS ≥5 or NAS = 4 with ballooning, N = 10). **Results:** At 60 minutes post-dose, patients with MASH exhibited significantly elevated plasma EZEG concentrations relative to MASLD individuals and biopsied subjects with NAS = 0, with a geometric mean ratio of 3.44 (95% CI: 1.63–7.25, p = 0.004) (Figure, Panel A). Excluding patients with cirrhosis

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(fibrosis score = 4) did not materially alter these findings. Plasma EZEG demonstrated strong diagnostic discrimination for MASH, with an area under the receiver operating characteristic curve (AUROC) of 0.82 (95% CI: 0.64–1.00). Renal clearance of EZEG did not vary significantly across NAS scores. EZEG levels by NAS component scores and fibrosis scores are shown (Figure, Panel B-E), consistent with altered EZEG levels driven by hepatocyte cytosolic dysfunction/disruption. **Conclusion:** These findings support the concept that MASH-associated transporter dysfunction leads to systemic EZEG accumulation and suggest that plasma EZEG may serve as a promising mechanism-based, noninvasive diagnostic function test for disease detection and stratification.



Disclosures: Geoffrey Block: Nothing to Disclose, Dominique Farrera: Nothing to Disclose, Kayla Frost: Nothing to Disclose, Joseph Jilek: Nothing to Disclose, Raxton Sample: Nothing to Disclose, Jailyn Isu: Nothing to Disclose, Mina Alaaldin: Nothing to Disclose, Paige Linberg: Nothing to Disclose, Max Maloney: Nothing to Disclose, David Rodrigues: Nothing to Disclose, Emi Yamaguchi: Nothing to Disclose, Ryu Sangwoo: Nothing to Disclose, Yi-An Bi: Nothing to Disclose, Mark West: Nothing to Disclose, Sumathy Mathialagan: Nothing to Disclose, Sarah Lazzaro: Nothing to Disclose, Brooke Rabe: Nothing to Disclose, Aiden-Hung Nguyen: Nothing to Disclose, Katherine Ho: Nothing to Disclose, Susie Messenger: Nothing to Disclose, Ahmad Omid Rahimi: Nothing to Disclose, Ryan Kian Aknbari: Nothing to Disclose, Carolina Säll: Novo Nordisk: Employee and stock holder, Walter Klimecki: Nothing to Disclose, Mary Paine: Nothing to Disclose, Stephen Wright: Nothing to Disclose, Dean Billheimer: Nothing to Disclose, Iman Ghaderi: Nothing to Disclose, Nathan Cherrington: Nothing to Disclose.

2407 | EFFECTS OF GLP-1 ON LIVER TISSUE AND PLASMA LIPIDS AMONG PATIENTS WITH MASLD

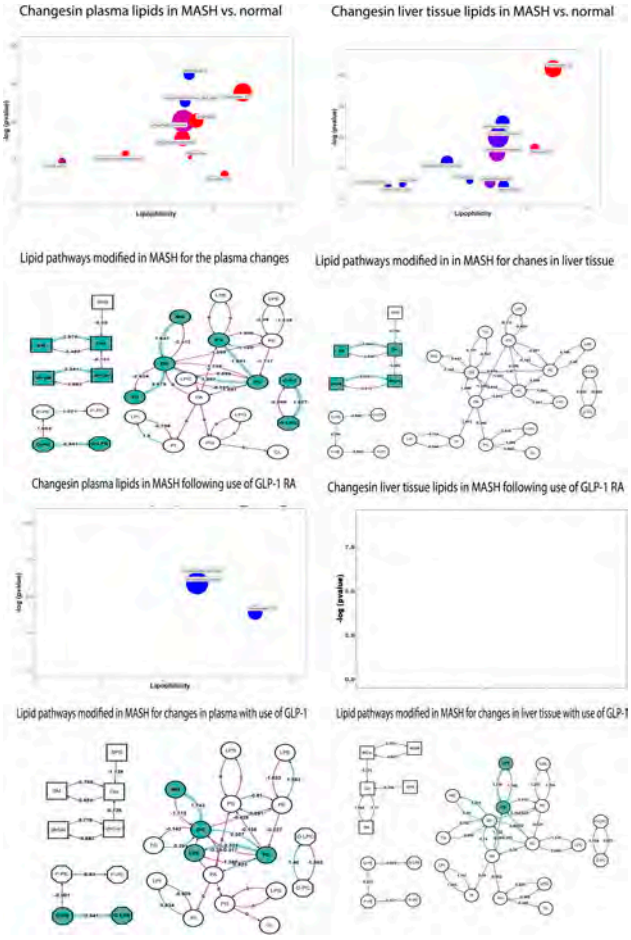
Achuthan Sourianarayanane[1] Christopher Brydges[2], [1]Medical College of Wisconsin, [2]Duke's University

Background: Glucagon-like peptide 1 (GLP-1) receptor agonists (RA) are increasingly used to manage diabetes, obesity, and metabolic dysfunction-associated steatotic liver disease (MASLD). Studies have shown that GLP-1 RA use improves plasma lipid profiles, metabolic dysfunction, and histological features of MASLD. The changes in liver tissue lipids following GLP-1 RA use in patients with MASLD are unknown. This study assesses relative changes in liver tissue lipids using GLP-1 RA. It also correlates) plasma markers in these patients. **Methods:** We collected liver tissue and plasma/serum at the time of liver biopsy for histological diagnosis and stored them at -80°C in our biobank. We performed untargeted multiomics on samples from both liver tissue and plasma, including lipid analysis. Serum from these patients was analyzed for a panel of adipokines, cardiovascular disease markers, metabolic hormones, and inflammatory markers. We had three study groups: MASLD without metabolic dysfunction-associated steatohepatitis (MASH) [n = 10], MASH (n = 17), and controls (n = 18). Nearly 50% of patients with MASLD had been on a GLP-1 RA for more than six months. **Results:** Patients with MASH, compared with controls, had increased levels of unsaturated and saturated triglycerides (TG) and reduced levels of plasmalogens in both plasma and liver tissue. Different phosphoethanolamine and phosphatidylcholine species showed increases and decreases in both compartments. Patients who used GLP-1 RA showed reductions in unsaturated TG, phosphoethanolamine, and phosphatidylcholine in plasma, but no differences were observed in liver tissue for any lipid group (as shown in the Figure). Similar differences were observed between plasma and liver tissue in lipid group changes with GLP-1 RA use among patients with MASLD without MASH (data not shown). The

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lipid pathways modified in these conditions also differed. Among the three study groups, MASLD without MASH and MASH showed statistically significant reductions in serum adiponectin and sVCAM and increases in PAI-1, IL8, MCP-1, GIP, and leptin levels compared with controls. Following GLP-1 RA use in patients with MASLD, reductions in PAI-1 and increases in GIP and PP were observed, with no change in serum GLP-1 levels. (data not shown). **Conclusion:** Compared with controls, patients with MASLD and MASH have altered lipid profiles in both plasma and liver tissue. They also had changes in adipokines, cardiovascular disease markers, and metabolic hormones. GLP-1 RA alters plasma lipid profiles; however, its effects on liver tissue in MASH were not observed. The changes observed following GLP-1 RA do not appear to reverse the lipid profile seen in MASH towards the control. There were also changes in adipokines and metabolic hormones in GLP-1 RA. The beneficial histological effects observed in MASH following GLP-1 RA may result from mechanisms other than lipid improvements.



Disclosures: Achuthan Sourianarayanane: Nothing to Disclose, Christopher Brydges: Nothing to Disclose.

2408 | IMPROVING RECOGNITION OF LIVER DISEASE IN PRIMARY CARE RESIDENT CLINICS USING FIB-4 EDUCATION: A PRE/POST COMPARISON ACROSS TRAINING LEVELS

Husam Mikati[1] Mirjana Grocic[1] Matthew Ambrosio[2] Richard Sterling[1], [1]Virginia Commonwealth University Health System, [2]Virginia Commonwealth Univertisy

Background: Hepatitis C virus (HCV) and metabolic-dysfunction associated steatohepatitis (MASLD) are frequently under-recognized and under-managed by primary care providers (PCP). FIB-4, is a simple validated tool used to evaluate MASLD. Within our Veterans Affairs (VA) Hospital, FIB-4 is automatically calculated with routine labs, while at VCU calculation is done through a dot phrase in the electronic health record (EHR) that, however, is not included in most notes. We hypothesized that, irrespective of site of care, a brief educational intervention on FIB-4 will improve diagnostic workup and hepatology referrals. **Methods:** Resident PCP clinics were identified at VCU and the VA. Demographic, clinical and laboratory data from each EHR were extracted over a 4-week period on all eligible patients (pts) along with post-graduate year (PGY) of the trainee (1-3). Then, a single, 30-minute standardized educational session was embedded in routine resident teaching that highlighted knowledge of FIB-4, how to calculate it, how to interpret it, its limitations, and suggested follow up actions based on that. Data were collected again 4 weeks after the education session across each hospital system. Univariate and multivariate mixed-effects model analyses was used to determine the effects of the training while adjusting for covariates. **Results:** Between both sites, 1104 pts were included: 522 VA and 582 VCU. Mean age was 60, 34% female, 36% White, no HCV testing in 19%, 27% had type 2 diabetes (T2DM), 67% had hypertension (HTN), 28% had increased triglycerides (TG), and 52% were obese with differences between the clinic sites (Table). There were marked differences in documented FIB-4: 88% at the VA and 26% at VCU ($p < .001$) and highest among PGY3 (41%) and lowest PGY1 (29%). Among those with FIB-4, scores > 1.3 were observed more at the VA compared to VCU (32% vs 17%; $p < .001$). Among those with FIB-4 > 1.3, hepatology referrals were low (7.1% at the VA and 11% at VCU). After the educational session, FIB-4 documentation increased at the VA clinic while decreased at VCU with no difference by PGY level or presence of metabolic features (Figure). Overall, training did not significantly increase or decrease

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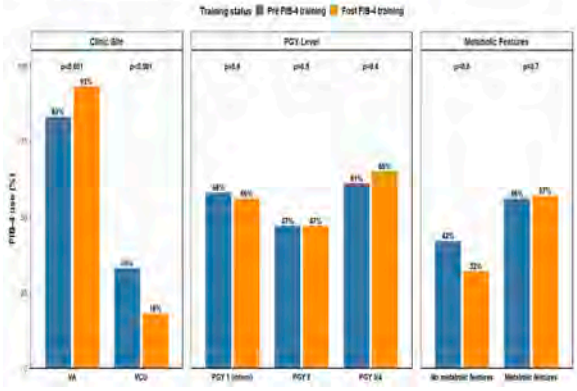
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the likelihood of FIB-4 use in those without or without metabolic features. Multivariate regression identified VA site ($p < .001$), PGY level ($p = .038$), and HCV positive test ($p = .001$) as predictors of documenting FIB-4 while age, sex, race, T2DM, HTN, and obesity were not. Among those with FIB-4 > 1.3 or HCV positive, 30% were referred to hepatology. **Conclusion:** Despite an EMR that automatically calculates FIB-4 when relevant variables are available (VA), referral to hepatology is low in those with FIB-4 > 1.3. Additionally, with the use of a dot phase (VCU), documenting FIB-4 remained low even after education on its use and importance. Therefore, additional strategies to educate PCPs on recognizing liver disease are needed.

Table 1. Composite Data Evaluating Differences Between Resident Clinic Site and Training Level.

Characteristic	Overall (N = 1,104)	VA N=522	VCU N=582	P-value
No FIB-4 done	489 (44%)	60 (12%)	429 (74%)	
FIB-4 Included	612 (56%)	461 (88%)	151 (26%)	0.081
No Hepatology Referral (FIB-4 >1.3)	359 (35%)	140 (30%)	219 (39%)	0.019
Referral not indicated (FIB-4 < 1.3, no HCV, normal ALT)	578 (56%)	291(63%)	287(51%)	0.331
Referral indicated and Ordered (FIB-4 > 1.3	95 (9.2%)	33 (7.1%)	62(11%)	<0.001
Characteristic	**Overall N=1,102**	**FIB-4 Not Included N=490**	**FIB-4 Included N=612**	**P-value**
PGY-1	307 (28%)	132 (27%)	175 (29%)	<0.001
PGY-2	400 (36%)	212 (43%)	188 (31%)	<0.001
PGY 3/4	394 (36%)	146 (30%)	248 (41%)	<0.001

Figure 1. Effect of Educational Intervention on FIB-4 Use



Disclosures: Husam Mikati: Nothing to Disclose, Mirjana Grocic: Nothing to Disclose, Matthew Ambrosio: Nothing to Disclose, Richard Sterling: ABIM: GI Specialty Board, Abbott: Grant/Research Support, GSK: Grant/Research Support, HCV Vax: Grant/Research Support, Gilead: Grant/Research Support, Zydus: Grant/Research Support, Vertex: Consultant, Madrigal: Advisor, Gigagen: Grant/Research Support, Atea: Grant/Research Support, Cima Science: Consultant, Celaris: Consultant, GSK: Advisor.

2409 | DIFFERENTIAL PLACEBO-ASSOCIATED LONGITUDINAL CHANGES IN NONINVASIVE FIBROSIS BIOMARKERS IN F2-F4 MASH: A SYSTEMATIC LITERATURE REVIEW AND META-ANALYSIS

Mazen Noureddin[1] Alma Laura Ladrón de Guevara[2] Sarah Williams[3] Valentina D'Arienzo[3] Steven Levitte[4] Jorge Alfonso Ross Terres[4] KT Park[4], [1]Houston Research Institute and Houston Methodist Hospital, [2]Roma Gastroenterology Research Center, [3]F. Hoffmann-La Roche Ltd, [4]Genentech, Inc.

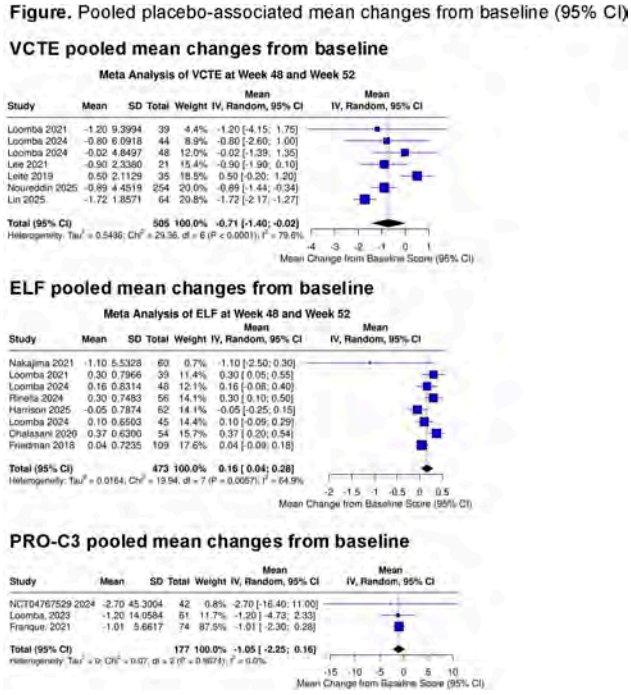
Background: Noninvasive biomarkers are increasingly used to assess disease activity and fibrosis progression in metabolic dysfunction–associated steatohepatitis (MASH). However, longitudinal placebo-associated changes in these biomarkers remain poorly characterized despite increasing use in endpoint assessment and treatment-effect interpretation in clinical trials. We conducted a systematic literature review and meta-analysis to evaluate placebo-associated changes in noninvasive tests, including enhanced liver fibrosis (ELF), vibration-controlled transient elastography (VCTE), N-terminal pro-peptide of type III collagen (PRO-C3) and MRI iron-corrected T1 (MRI-cT1) in randomized controlled trials in patients with F2-F4 MASH. **Methods:** A systematic search of MEDLINE, Embase, CENTRAL and ClinicalTrials.gov and AI-assisted supplementary full-text searches were conducted to identify relevant trials published within the last 10 years. Placebo-arm data for ELF, VCTE liver stiffness, PRO-C3 and MRI-cT1 were extracted from eligible studies. Random-effects meta-analyses were performed using studies reporting approximately 1-year follow-up data for changes from baseline in ELF and VCTE (48-52 weeks) and PRO-C3 (24 weeks); MRI-cT1 data were insufficient for meta-analysis. Heterogeneity was assessed by visually inspecting the forest plots, χ^2 values and I^2 statistics. **Results:** A total of 3459 records were screened; 84 records from 75 unique studies were included. Biomarker data were reported in 40 records for ELF, 37 for VCTE, 26 for PRO-C3 and 12 for MRI-cT1. A total of 15 studies were included in the meta-analyses; the majority evaluated predominantly F2-F3 populations. Meta-analysis demonstrated modest placebo-associated longitudinal changes across biomarkers. Placebo-treated patients demonstrated a pooled mean increase in ELF of 0.16 (95% CI, 0.04 to 0.28; I^2 = 64.9%; n = 473). In contrast, pooled mean changes demonstrated slight reductions in VCTE liver stiffness (−0.71; 95% CI, −1.40 to −0.02; I^2 = 79.6%; n = 505) and PRO-C3 (−1.05; 95% CI, −2.25 to 0.16; I^2 = 0; n = 177). Biomarker-specific differences in directionality and heterogeneity were observed across modalities. **Conclusion:** Placebo-

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associated longitudinal changes in noninvasive fibrosis biomarkers in F2-F4 MASH trials were generally modest over approximately 1 year. ELF demonstrated a small but consistent increase over time, whereas VCTE and PRO-C3 showed reduced placebo-associated biomarker values. These findings consider the specific characteristics of this patient cohort and help contextualize the limited scope of the changes recorded. These findings also provide important context for interpretation of biomarker endpoints in MASH clinical trials. Understanding biomarker variability and placebo dynamics may help inform endpoint interpretation and future MASH trial design.

Figure. Pooled placebo-associated mean changes from baseline (95% CI)



Disclosures: Mazen Noureddin: Akero: Advisor, Alligos: Advisor, Altimmune: Advisor, AstraZeneca: Advisor, Boehringer Ingelheim: Advisor, Boston Pharma: Advisor, Cytodyn: Advisor, GSK: Advisor, Lilly: Advisor, Madrigal: Advisor, Merck: Advisor, Novo Nordisk: Advisor, Sagimet: Advisor, Terns: Advisor, Takeda: Advisor, Akero: Principal Investigator, Allergan: Principal Investigator, Altimmune: Principal Investigator, Boehringer Ingelheim: Principal Investigator, Bristol Myers Squibb: Principal Investigator, Boston Pharma: Principal Investigator, Conatus: Principal Investigator, Corcept: Principal Investigator, Galectin: Principal Investigator, Genfit: Principal Investigator, GSK: Principal Investigator, Kowa: Principal Investigator, Enanta: Principal Investigator, Madrigal: Principal Investigator, Lilly: Principal Investigator, Merck: Principal Investigator, Novartis: Principal Investigator, Novo Nordisk: Principal Investigator, Rivus: Principal Investigator, Shire: Principal Investigator, Takeda: Principal Investigator, Terns: Principal Investigator, Viking: Principal Investigator, Zydus: Principal Investigator, Rivus: Stock – privately held company, Cytodyn: Stock - publicly traded company, ChronWell: Stock – privately held company, Madrigal: Speakers bureau, Gilead Sciences: Principal Investigator, Akero: Consultant, Altimmune: Consultant, Alligos: Consultant, AstraZeneca: Consultant, BI: Consultant, Boston Pharma: Consultant, Curve bioscience: Consultant, Cytodyn: Consultant, GSK: Consultant, Histoindex: Consultant, Lilly: Consultant, Madrigal: Consultant, Merck: Consultant, Novo Nordisk: Consultant, Sagimet: Consultant, Terns: Consultant, Allergan: Grant/Research Support, Altimmune: Grant/Research Support, Akero: Grant/Research Support, BI: Grant/Research Support, BMS: Grant/Research Support, Boston Pharma: Grant/Research Support, Conatus: Grant/Research Support, Corcept: Grant/Research Support, Gilead: Grant/Research Support, Galectin: Grant/Research Support, Genfit: Grant/Research Support, GSK: Grant/Research Support, Kowa: Grant/Research Support, Enanta: Grant/Research Support, Madrigal: Grant/Research Support, Lilly: Grant/Research Support, Merck: Grant/Research Support, Novartis: Grant/Research Support, Novo Nordisk: Grant/Research Support, Rivus: Grant/Research Support, Shire: Grant/Research Support, Takeda: Grant/Research Support, Terns: Grant/Research Support, Viking: Grant/Research Support, Akero: Stock - publicly traded company, Zydus: Grant/Research Support, Takeda: Consultant, Madrigal: Speaking and Teaching, Novo Nordisk: Speaking and Teaching, HepaNova: Consultant, Daiichi Sankyo: Advisor, Daiichi Sankyo: Consultant, Curve Bioscience: Advisor, Curve Bioscience: Consultant, HepaNova: Advisor, HepaTx: Advisor, HepaTx: Consultant, HepaTx: Stock - publicly traded company, HepaTx: Stock - publicly traded company, HepaNova: Stock - publicly traded company, Histoindex: Advisor, Histoindex: Consultant, Kryia: Advisor, Kryia: Consultant, Kryia: Stock - publicly traded company, Neuraly: Advisor, Neuraly: Consultant, Novo Nordisk,: Consultant, OPKO: Advisor, OPKO: Consultant, OPKO: Stock - publicly traded company, OPKO: Stock - publicly traded company, OPKO: Stock - publicly traded company, Rivus: Advisor, Rivus: Consultant, Rivus: Stock - publicly traded company, Alma Laura Ladrón de Guevara: Eli Lilly and company: Grant/Research Support, Galectin Therapeutics: Grant/Research Support, AStra Zeneca: Grant/Research Support, Inventiva Pharma: Grant/Research Support, Cymabay Therapeutics: Grant/Research Support, Akero Therapeutics: Grant/Research Support, Novonordisk: Grant/Research Support, MSD: Grant/Research Support, Cymabay: Grant/Research Support, GSK: Grant/Research Support, Madrigal Pharmaceuticals: Grant/Research Support, Roche: Grant/Research Support, Sarah Williams: Nothing to

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Disclose, Valentina D'Arienzo: Nothing to Disclose, Steven Levitte: Nothing to Disclose, Jorge Alfonso Ross Terres: Nothing to Disclose, KT Park: Nothing to Disclose.

2410 | OPTIMIZING ELASTOGRAPHY REFERRAL IN MASLD SCREENING USING ROUTINELY AVAILABLE HEALTH CHECK-UP DATA

Jung Pyo Hong[1] Jaehong Jeong[2] Dong Yun Kim[2] Jae Seung Lee[2] Mi Na Kim[2] Beom Kyung Kim[2] Jeong Eun Song[3] Hyun Chin Cho[1] Jun Yong Park[2] Do Young Kim[2] Sang Hoon Ahn[2] Hye Won Lee[2] Seung Up Kim[2], [1]Gyeongsang National University College of Medicine, [2]Yonsei University College of Medicine, [3]Daegu Catholic University School of Medicine

Background: Liver fibrosis stage determines the risk of liver-related mortality in metabolic dysfunction-associated steatotic liver disease (MASLD). We developed and validated a machine learning-based triage algorithm using health check-up data to identify patients with MASLD warranting specialized vibration-controlled transient elastography (VCTE) referral. **Methods:** We retrospectively analyzed 4,212 patients with MASLD from a health check-up cohort (2012–2020). The prevalence of significant (liver stiffness [LS] > 7.0 kPa) and advanced fibrosis (LS ≥ 8.0 kPa) was 2.6% and 1.4%, respectively. We trained a Balanced Random Forest model using 24 anthropometric and laboratory variables. The cohort was partitioned into training (70%, n = 2,948), internal testing (20%, n = 842), and independent validation (10%, n = 422) sets. **Results:** In the independent validation cohort, the Balanced Random Forest model achieved an area under the receiver operating characteristic curve (AUROC) of 0.658 (95% confidence interval [CI], 0.599–0.717, P = 0.037) for predicting significant fibrosis (sensitivity 63.6%, specificity 85.9%, and negative predictive value [NPV] of 98.9%) and 0.709 (95% CI, 0.650–0.768, P = 0.040) for predicting advanced fibrosis (sensitivity 66.7%, specificity 82.5%, and NPV 99.4%), respectively. SHAP analysis further identified body mass index, gamma-glutamyl transferase, platelet count, and waist circumference as the primary predictive features. Decision curve analysis demonstrated a higher clinical net benefit than the FIB-4 index across clinically relevant threshold probabilities. **Conclusion:** A machine learning model trained on health check-up data provides an effective zero-cost triage step for identifying patients with MASLD at high risk for significant and advanced fibrosis, optimizing referral decisions in low-prevalence screening settings.

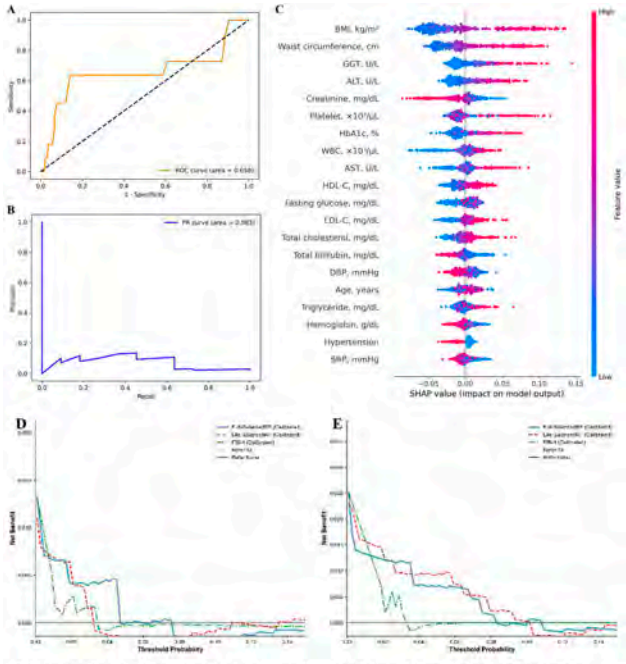


Figure 1. Predictive performance, feature interpretability, and clinical utility of the Balanced Random Forest m odel in the validation cohort (n=422). **(A)** ROC curve and **(B)** precision-recall curve for significant fibrosis (liv er stiffness >7.0 kPa). **(C)** SHAP summary plot showing the magnitude and direction of each feature's contribut ion to the model output; red indicates high feature values and blue indicates low values. **(D, E)** Decision curve analysis comparing the full (24-feature) and parsimonious (8-feature) Balanced Random Forest models with the FIB-4 index for predicting **(D)** significant and **(E)** advanced fibrosis (liver stiffness ≥8.0 kPa). Calibrated proba bilities were used to account for class imbalance. SHAP, SHapley Additive exPlanations; ROC, receiver operat

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★ 2411 | SERUM AND HEPATIC LIPIDOMICS ANALYSES IN PATIENTS WITH MASLD IDENTIFY GLYCEROL TRIPALMITATE AS A BIOMARKER ELEVATED IN MASH

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Background: The prevalence of metabolic dysfunction–associated steatotic liver disease (MASLD) has been rising in parallel with obesity. Approximately 10–20% of patients with MASLD progress to metabolic dysfunction–associated steatohepatitis (MASH), which has a higher risk of fibrosis. The primary pathophysiology of MASLD involves the accumulation of triglycerides (TGs) in the liver due to excessive lipid intake. Although noninvasive biomarkers have increasingly been explored for

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predicting MASH without liver biopsy, reliable diagnostic approaches remain insufficiently established. Moreover, the lipid species that accumulate in the liver or are detectable in the circulation in MASH have not been fully characterized. This study aimed to identify serum lipid biomarkers capable of differentiating MASL from MASH. **Methods:** We performed liver and serum LC-MS-based lipidomics analyses in patients with biopsy-confirmed MASL (n = 39) and MASH (n = 38), with the latter defined by the presence of ballooning and inflammation. Healthy controls without liver disease (n = 50) underwent serum analysis only. Correlation of glycerol tripalmitate, TG (16: 0/16: 0/16: 0) with clinical parameters were tested. ROC analysis was performed for assessing the accuracy of predicting MASL and MASH. **Results:** A total of 101 and 90 lipid species were detected in liver tissue and serum, respectively, with 89 TGs identified in both. TGs exhibiting positive correlations between liver and serum levels were enriched with those containing C16: 0 (palmitic acid). Notably, TG (16: 0/16: 0/16: 0), glycerol tripalmitate, showed a strong positive correlation between liver and serum concentrations ($\rho = 0.70$). TG (16: 0/16: 0/16: 0) was significantly elevated in MASH compared with MASL in both liver (1.148 vs. 0.6011, $p < 0.001$) and serum (4.577 vs. 2.374, $p = 0.009$). Serum TG (16: 0/16: 0/16: 0) levels significantly correlated with AST, ALT, body weight, triglyceride, HbA1c, HDL cholesterol, HOMA-IR, and FIB-4 index. A predictive model combining serum TG (16: 0/16: 0/16: 0) and AST yielded an AUC of 0.8441 in ROC analysis. **Conclusion:** Serum TG (16: 0/16: 0/16: 0) correlated with its liver levels, significantly increased in MASH, and was associated with metabolic parameters of insulin resistance. This lipid species may serve as a promising non-invasive biomarker for distinguishing MASH from MASL, reflecting key pathological features of MASLD.

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2412 | ICAM1 AS A STRONG PREDICTOR OF HISTOLOGICAL SEVERITY IN MASLD: PRELIMINARY RESULTS OF THE UNMASK STUDY

Carola Zurita Palomo[1] José Manuel Reales Guirado[2] María Vázquez Bazo[2] Luis Calzadilla Bertot[1] Douglas Maya Miles[3] Isabel Fernández Lizaranzu[1] Miguel Ángel Fernández-Gómez[4] Paloma Carrillo Fernández[1] Vanessa García Fernández[1] Sheila Gato Zambrano[1] Ángela Rojas[1] Javier Ampuero Herrojo[5] Javier Cubero[6] Jordi Gracia Sancho[7] Rui Castro[8] Rubén Francés[9] Luca Miele[10] Yasemin Balaban[11] Franz Martín Bermudo[12] Rocío Gallego Durán[13] Manuel Romero Gómez[5], [1]1. SeLiver Group, IBiS/CSIC/HUVR/US, Seville, Spain; 2. CIBEREHD, Spain., [2]1. SeLiver Group, IBiS/CSIC/HUVR/US, Seville, Spain., [3]1. SeLiver Group, IBiS/CSIC/HUVR/US, 3.Department of Physiology, US, Seville, Spain; 2. CIBEREHD., [4]4. Sports Activity Service, University of Sevilla, Sevilla, Spain., [5]1. SeLiver Group, IBiS/CSIC/HUVR/US; 5. Digestive Diseases Unit, HUVR, Seville, Spain; 2. CIBEREHD., [6]6. Dept. of Immunology, Ophthalmology and ENT, Faculty of Medicine, UCM, Madrid; 2. CIBEREHD, Spain., [7]7. Liver Vascular Biology Research Group, IDIBAPS Biomedical Research Institute; 2. CIBEREHD, Spain., [8]8. Research Institute for Medicines (iMed.ULisboa), Faculty of Pharmacy, Universidade de Lisboa., [9]9. Hepatic and Intestinal Immunobiology Group. Instituto IDIBE, UMH, Alicante, Spain; 2. CIBEREHD., [10]10. Department of Translational Medicine and Surgery, Università Cattolica del Sacro Cuore, Italy., [11]11. Department of Gastroenterology, Hacettepe University Faculty of Medicine, Turkey., [12]12. CABIMER- UPO-US-CSIC, Sevilla, Spain; 13. CIBERDEM, Spain., [13]1. SeLiver Group, IBiS/CSIC/HUVR/US; 14. Department of Medicine, US, Seville, Spain; 2. CIBEREHD.

Background: The aim of this study was to evaluate the clinical utility and predictive capacity of a panel of soluble, tissue and genetic biomarkers in relation to histological severity in a cohort of MASLD patients. **Methods:** A total of 229 patients with biopsy-proven MASLD were included as part of the UNMASK Project (EPPERMED2024-496). Serum levels of ICAM1, vWF, CK-18, FGF21 and NRF2 were quantified by ELISA. Activation and nuclear translocation of phosphorylated NRF2 (pNRF2) in liver tissue were analyzed by immunohistochemistry (IHC). Genotyping of SNPs located in the *PNPLA3* (rs738409), *IL28B* (rs8099917), *FGF21* (rs838133), CPS1 (rs1047891) and *TLR9* (rs5743836) genes was performed by PCR. **Results:** Regarding serum biomarkers, ICAM1 levels showed a significant positive correlation with NAS Score ($r = 0.429$; $p < 0.0001$) and fibrosis stage ($r = 0.376$; $p < 0.0001$), with significantly higher concentrations in patients with MASH compared to those with simple steatosis (468.8 ± 230.3 *vs.* 362 ± 107.4 ng/mL; $p < 0.0001$) and significant fibrosis patients (515.9 ± 263.2 vs. 384.2 ± 132.6 ng/mL; $p < 0.0001$). Likewise, FGF21 was found to be increased in MASH vs. steatosis (552.1 ± 442,9 vs. 374.9 ± 341.9 pg/mL; $p = 0.008$). Finally, both vWF and FGF21 levels were further found to be increased in significant fibrosis ($\geq$ F2) (vWF: 1905.6 ± 937.8 *vs.* 2317.1 ± 788.5 mIU/mL; $p = 0.004$ and FGF21 420.1 ± 370.3 *vs.* 562.7 ± 457.3 pg/mL; $p = 0.040$). CK-18 and NRF2 levels did not reach statistical significance. Quantification of hepatic pNRF2 revealed a

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significant increase in patients with advanced fibrosis compared with those with mild fibrosis (F3–F4: 90.1 ± 9.03 vs. F0–F2: 65.7 ± 15.9 positive cells; p = 0.025). As previously reported, GG genotype of *PNPLA3* was associated with a more aggressive phenotype characterized by higher rates of steatosis (p = 0.001), inflammation (p = 0.011), hepatocellular ballooning (p = 0.021), MASH (p = 0.001), and liver fibrosis (p = 0.008). Furthermore, the T allele of *IL28B* was significantly associated with a higher prevalence of MASH (p = 0.015), while the AA genotype of *FGF21* was associated with a higher proportion of hepatocellular ballooning (p = 0.005). After multivariate analyses, ICAM1 remained as an independent predictor of both MASH (OR = 1.005 [CI 95% 1.001-1.009]; p = 0.007) and significant fibrosis (OR = 1.007 [CI 95% 1.004-1.010]; p < 0.0001). Finally, the combined model based on ICAM1 levels and age demonstrated the best non-invasive diagnostic performance for predicting significant liver fibrosis, achieving an AUROC of 0.78 (CI95% 0.69-0.86; p < 0.0001). **Conclusion:** The integration of soluble biomarkers such as FGF21 enables the effective prediction of histological severity in MASLD. In particular, a combined model based on age and circulating ICAM1 levels appears to be a promising non-invasive strategy for assessing the risk of significant liver fibrosis. Acknowledgments: UNMASK EPPERMED CÓDIGO AND ISCIII PI24/02008.

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2413 | AUTOMATED AI-BASED QUANTITATIVE FIBROSIS STAGING TO SUPPORT IDENTIFICATION OF MASH PATIENTS ELIGIBLE FOR APPROVED THERAPIES

Yukti Choudhury[1] Daniel Tan[1] Serene Lek[1] Desiree Abdurrachim[2] Asad Abu Bakar Ali[2] Naim Alkhouri[3], [1]HistoIndex Pte Ltd, [2]MSD, Singapore, [3]Summit Clinical Research

Background: Approved pharmacotherapies are available for the treatment of adults with metabolic dysfunction-associated steatohepatitis (MASH) and F2–F3 fibrosis. However, selection algorithms based on non-invasive tests (NITs) often fail to accurately identify the treatment-eligible population defined by histological criteria, and these NIT-based criteria identify a large target population, placing a financial burden on the healthcare system. This may be alleviated by direct liver biopsy evaluation in select cases. This study aimed to evaluate FibroSIGHT™ Plus, a fully automated artificial intelligence (AI)-based fibrosis scoring tool for MASH liver biopsies, and compared its performance to fibrosis staging using standard methods by community pathologists. **Methods:** A total of 75 MASH liver biopsies from a retrospective cohort from Mount Sinai were selected across a range of fibrosis stages (F0-F4) and their Masson's trichrome stained images were reviewed by three expert hepatopathologists. The median score for each biopsy was used to assign a reference NASH-CRN fibrosis stage as ground truth. Three community pathologists also reviewed the same images and assigned fibrosis stages to each case. An adjacent unstained section from each of the biopsies underwent second harmonic generation (SHG) imaging and analysis with FibroSIGHT™ Plus to generate continuous qFibrosis® scores and qFibrosis® stage assignments. Concordance of community pathologists' staging and qFibrosis® staging with the reference stages was assessed. **Results:** Among pathologists, inter-reader agreement differed by experience – exact stage agreement by all three experts across 75 cases was observed in 65.33% of cases vs. only 26.67% for three community pathologists. qFibrosis® continuous scores correlated well with reference stage (Spearman's r = 0.84, p < 0.001). Overall, qFibrosis® stage was concordant with reference stage in 58.67% of cases, whereas the average concordance of community pathologists staging compared to reference stage was 53.33% ± 3.52. In F2/F3 (treatment-eligible) cases (n = 38), qFibrosis® stage concordance exceeded community pathologists (60.53% vs. 51.75% ± 3.04%). **Conclusion:** The automated fibrosis assessment tool, FibroSIGHT™ Plus, had higher concordance with expert-assigned reference fibrosis staging than community pathologists, particularly in the treatment-eligible population. FibroSIGHT™ Plus may serve as a decision-support tool to provide more consistent fibrosis staging for treatment selection, particularly in resource-constrained settings with large MASH populations.

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2414 | DEVELOPMENT AND VALIDATION OF A NON-INVASIVE SCORE FOR SEVERE MASH BASED ON ROUTINE SEROLOGICAL MAKERS: THE SEVERE METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS SCORE (SMASH)

Miaoyang Chen[1] Shasha Li[2] Jialuo Wang[1] Hongli Liu[1] Yongfeng Yang[1], [1]The Second Hospital of Nanjing, [2]Nanjing University

Background: Early diagnosis of severe metabolic dysfunction-associated steatohepatitis (MASH) patients deserves high priority, given their increased disease progression risk. We developed and validated a non-invasive score to identify severe MASH. **Methods:** Liver biopsy-proven metabolic dysfunction-associated steatotic liver disease (MASLD) patients were randomly allocated to the training and validation set at a 7: 3 ratio. We utilized the least absolute shrinkage and selection operator and multivariate logistic regression to selected variables and construct a model, termed the SMASH (severe metabolic dysfunction-associated steatohepatitis) score. SHapley Additive exPlanations was employed to measure feature importance. Finally, a nomogram was adopted to visualize the model. The performance of the SMASH score was assessed by area under curve (AUC), calibration curve, and decision curve analysis. Also, we further compared the SMASH score with fibrosis-4 (FIB-4), FibroScan-aspartate aminotransferase (FAST) and aspartate aminotransferase-alanine aminotransferase ratio (AAR). **Results:** The age, overweight, hyperuricemia, platelet, aspartate aminotransferase, gamma-glutamyl transferase, and phosphorus were independent predictors of severe MASH. The diagnostic performance of the SMASH score demonstrated an AUC, sensitivity, specificity, and positive and negative predictive values of 0.840, 0.812, 0.709, 0.876, and 0.598 in the training set, and 0.781, 0.714, 0.750, 0.879, and 0.508 in the validation set. Compared to FIB-4 and AAR, the SMASH score exhibited a superior performance. Compared to FAST, the SMASH score showed comparable diagnostic efficacy but fewer patients with indeterminate scores. **Conclusion:** This non-invasive SMASH score has an excellent performance in severe MASH identification and enables risk stratification and timely intervention among MASLD patients.

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2415 | EVALUATING THE IMPACT OF NIS2+® ON REFERRALS OF PATIENTS WITH AT-RISK MASH

Amreen Dinani[1] Chukwuemeka Oko[2] Mark Miller[3] Victor Llanes[3] Margery Connelly[4] Kendrick Basso[4] Kristi Cohn[5] Andrea Econome[5] Kristen Shea[5] Meena Bansal[6], [1]Duke University School of Medicine, [2]Duke University Hospital, [3]Icahn School of Medicine at Mount Sinai, [4]Labcorp, [5]MASHNET, [6]Icahn School of Medicine at Mount Sinai (ISMMS)

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) poses a global threat, with at least 38% of the global adult population impacted. Diabetes has been identified as an at-risk population for MASLD, fibrotic metabolic dysfunction-associated steatohepatitis (MASH) and progressive disease. The performance of noninvasive liver disease assessments (NILDAs), such as FIB-4, is sub-optimal in patients with diabetes and ages 65 years and older. NIS2+® is a serum-based non-invasive diagnostic to detect patients with at-risk MASH, or patients with a MASLD Activity Score (MAS) ≥ 4 and at least stage 2 fibrosis ($\geq$ F2 fibrosis). The aim of this study is to assess the accuracy of NIS2+® as a first-line test to risk stratify individuals with metabolic risk factors (e.g., diabetes) for fibrotic MASH. **Methods:** A prospective study is underway to evaluate the impact of NIS2+® on referrals for at-risk MASH patients to hepatology at two tertiary care clinics. Patients meeting enrollment criteria, defined as patients ≥ 18 years with metabolic risk factors (e.g., diabetes), are randomly assigned to two cohorts:

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Cohort 1 receives standard of care only (NIS2+® results blinded), and Cohort 2 receives standard of care with NIS2+® results communicated to the endocrinologists overseeing patients' care. **Results:** To date, 268 patients with metabolic risk factors have been enrolled in the study; 46.3% (124) were assigned to cohort 1 (blinded), and 53.7% (144) were assigned to cohort 2 (non-blinded). 61.9% (166) were female, 37.3% (100) were male, 0.7% (2) were MtF; 44.0% (118) patients self-reported as White, 41.0% (110) Black, 6.7% (18) Asian, and 8.2% (22) did not disclose their race. 10.1% (27) were Hispanic or Latino. 74.3% (199) of enrolled patients were living with diabetes, and 31.0% (83) of enrolled patients were <35 years or ≥ 65 years. 55.6% (149) of enrolled patients had FIB-4s that were low risk (<1.3), 23.5% (63) were intermediate risk (1.3 – 2.66 if <65, 2.0 – 2.66 if ≥ 65), 3.7% (10) were high risk (≥ 2.67 if <65, ≥ 2.0 if ≥ 65), and 17.2% (46) had no data. 45.1% (121) of patients with NIS2+® scores were low risk (<0.46), 12.7% (34) were intermediate risk (0.46 – 0.67), and 8.6% (23) were high risk (≥ 0.68). Of those with available referral data (166), patients in cohort 2 (non-blinded) were 3.5 times more likely to be referred to hepatology than those in cohort 1 (blinded), and 5 patients with a low FIB-4 score and high-risk NIS2+ score were referred (80% of which were from cohort 2). **Conclusion:** While early data suggests NIS2+® is effective at improving referrals for patients with at-risk MASH, additional data is needed to demonstrate trends across a larger study population.

Referrals by Cohort

Cohort 1 (Blinded)	Referred = Yes (6)		Referred = No (82)	
	n	% Total with Referral Data (166)	n	% Total with Referral Data (166)
Low Risk (NIS2+ < 0.46)	2	1.2%	48	28.9%
Medium Risk (0.46 ≤ NIS2+ ≤ 0.68)	1	0.6%	15	9.0%
High Risk (NIS2+ > 0.68)	2	1.2%	9	5.4%
ND (No Data / missing NIS2+)	1	0.6%	10	6.0%
Subtotal	**6**	**3.6%**	**82**	**49.4%**

Cohort 2 (Non-Blinded)	Referred = Yes (16)		Referred = No (62)	
	n	% Total with Referral Data (166)	n	% Total with Referral Data (166)
Low Risk (NIS2+ < 0.46)	3	1.8%	46.00	27.7%
Medium Risk (0.46 ≤ NIS2+ ≤ 0.68)	4	2.4%	14.00	8.4%
High Risk (NIS2+ > 0.68)	9	5.4%	2.00	1.2%
ND (No Data / missing NIS2+)	0	0.0%	0.00	0.0%
Subtotal	**16**	**9.6%**	**62**	**37.3%**

Disclosures: Amreen Dinani: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Chukwuemeka Oko: Nothing to Disclose, Mark Miller: Nothing to Disclose, Victor Llanes: Nothing to Disclose, Margery Connelly: Labcorp: Employee, Kendrick Basso: Labcorp: Employee, Kristi Cohn: Nothing to Disclose, Andrea Econome: Nothing to Disclose, Kristen Shea: Nothing to Disclose, Meena Bansal: Madrigal: Advisor, Fibronostics: Advisor, NOVO Nordisk: Advisor, GSK: Advisor, Merck: Advisor, Boeheringer-Ingelheim: Advisor, Boston Pharma: Advisor, The Kinetix Group: Advisor, Corcept: Advisor.

2416 | METABOLIC ASSOCIATION BETWEEN TRIGLYCERIDE-TO-HIGH-DENSITY LIPOPROTEIN CHOLESTEROL RATIO AND FATTY LIVER DISEASE AND LIVER FIBROSIS IN PARTICIPANTS FROM AN OBSERVATIONAL STUDY

Amin Yarahmadi[1] Ulrike Lorch[1] Jorg Taubel[1] Edward Jackson[1] James Rickard[2], [1]Richmond Pharmacology, [2]Richmond Research Institute

Background: The triglyceride-to-high-density lipoprotein cholesterol (TG/HDL-C) ratio has emerged as a potential marker of metabolic dysfunction and cardiovascular risk. This study investigated the association between TG/HDL-C ratio, metabolic dysfunction-associated steatotic liver disease (MASLD), and liver fibrosis in participants enrolled in study (NCT04873258). **Methods:** This cross-sectional study included 1,544 participants from the observational study. Demographic, laboratory, and transient elastography data were analysed to evaluate the triglyceride-to-high-density lipoprotein cholesterol (TG/HDL-C) ratio as a potential risk factor for metabolic dysfunction-associated steatotic liver disease (MASLD). TG/HDL-C ratio was calculated from serum triglyceride and HDL cholesterol levels. MASLD was defined as controlled attenuation parameter (CAP) ≥ 274 dB/m, and significant liver fibrosis as liver stiffness measurement (LSM) ≥ 8.2 kPa. Participants were stratified by TG/HDL-C quartiles. Associations with MASLD and liver fibrosis were assessed using multivariable logistic regression adjusted for age, sex, and ethnicity. Nonlinear relationships were evaluated using restricted cubic spline models. **Results:** Higher TG/HDL-C ratios were positively associated with increased prevalence of MASLD. After adjustment for potential confounding clinical variables, participants in the highest TG/HDL-C quartile had significantly greater odds of MASLD compared with those in the lowest quartile (OR 13.1, 95% CI 7.59–22.4; $p < 0.001$). A nonlinear relationship between TG/HDL-C ratio and MASLD was identified using smoothed curve fitting models. In contrast, although an initial association between TG/HDL-C ratio and liver fibrosis was observed, this relationship was not statistically significant after adjustment for confounders ($p = 0.025$), and no nonlinear association was identified. These findings are consistent with the existing literature and support the homogeneity and external validity of participant recruitment within this observational cohort. **Conclusion:** Elevated TG/HDL-C ratio was strongly associated with MASLD prevalence in this cohort and

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may represent a useful non-invasive biomarker for identifying individuals at increased risk of MASLD. These findings are consistent with the existing literature and support the homogeneity and external validity of participant recruitment within this observational cohort. Future analyses will incorporate additional established risk factors, including smoking status and educational attainment, to further refine risk prediction models.

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2417 | METABOLOMIC AND LIPIDOMIC SIGNATURES OF STEATOTIC LIVER DISEASE IN PREGNANCY FROM THE PROSPECTIVE FATTY LIVER IN PREGNANCY COHORT

Himel Mallick[1] Cecilia Katzenstein[2] Amy Deik[3] Nina Rodriguez[2] Jeanette Rios[2] Rhoda Sperling[2] Norah Terrault[4] Lauren Alpert[2] Baran Ersoy[5] Keith Sigel[2] Tatyana Kushner[5], [1]Cornell University, [2]Icahn School of Medicine at Mount Sinai, [3]Broad Institute, [4]University of Southern California, [5]Weill Cornell Medicine

Background: The prevalence of steatotic liver disease (SLD) in pregnancy has tripled over the past decade and is associated with adverse pregnancy outcomes. In non-pregnant populations, SLD is characterized by circulating lipid signatures including elevated triacylglycerols, diacylglycerols, sphingolipids, and sterols as well as phosphatidylethanolamine remodeling. We aimed to characterize circulating metabolomic and lipidomic signatures associated with SLD and identify pregnancy-specific SLD signatures. **Methods:** The Fatty Liver in Pregnancy (FLIP) cohort is a prospective cohort in which pregnant patients were evaluated for SLD using ultrasound and transient elastography. Hybrid nontargeted metabolomic profiling was performed in a subcohort using four LC-MS platforms that combined complementary chromatography modalities with either positive or negative ion mode MS: C8-pos, C18-neg, HILIC-pos, and HILIC-neg. The combined analyses yielded profiles of 1,136 identified plasma metabolites and lipids. Associations between SLD and metabolites were assessed using multivariable linear models with BMI adjustment. Log fold changes (LFCs) were evaluated and P-values were FDR-adjusted. **Results:** Among 154 participants, 35 (22.7%) had SLD. Participants were predominantly Hispanic/Latina (56%) and Medicaid-insured (86%), with median age 29 years (IQR, 25-33) and pre-pregnancy BMI 29.3 kg/m² (IQR, 26.5-33.2); 90% had BMI $\geq$25 kg/m². Across 1,136 measured metabolite features, 165 (14.5%) differed between SLD and non-SLD participants (n = 119) after BMI adjustment at FDR-adjusted P < 0.05, with 149 elevated and 18 reduced metabolites, establishing a largely BMI-independent signature. Differences were dominated by elevations in triacylglycerols (n = 74; e.g., TG 38: 2 LFC = 1.76; TG 40: 3 LFC = 1.74) and diacylglycerols (n = 20; e.g., DG 32: 2 LFC = 1.29). Phosphatidylethanolamines (n = 20), phosphatidylcholines (n = 14), ceramides (n = 6), and lysophosphatidylethanolamines (n = 4) were also elevated. In contrast, medium- and long-chain acylcarnitines (n = 13; e.g., CAR 14: 3 LFC = -1.02; CAR 16: 4 LFC = -0.76) and polyunsaturated cholesterol esters (n = 3; e.g., CE 22: 4 LFC = -0.73; CE 19: 4 LFC = -0.66) were reduced, differing from non-pregnancy MASLD, where cholesterol esters are typically elevated (**Fig. 1**). **Conclusion:** SLD in pregnancy exhibits a robust, BMI-independent plasma lipidomic signature characterized by elevated triacylglycerols, diacylglycerols, phosphatidylethanolamines, and ceramides, largely concordant with non-pregnancy MASLD, but with pregnancy-specific reductions in acylcarnitines and polyunsaturated cholesterol esters that may reflect altered β-oxidation and PUFA flux during gestation. These findings support circulating metabolite profiling as a tractable approach for identifying and characterizing SLD in pregnancy and suggest potential mechanisms linking SLD to adverse pregnancy outcomes.

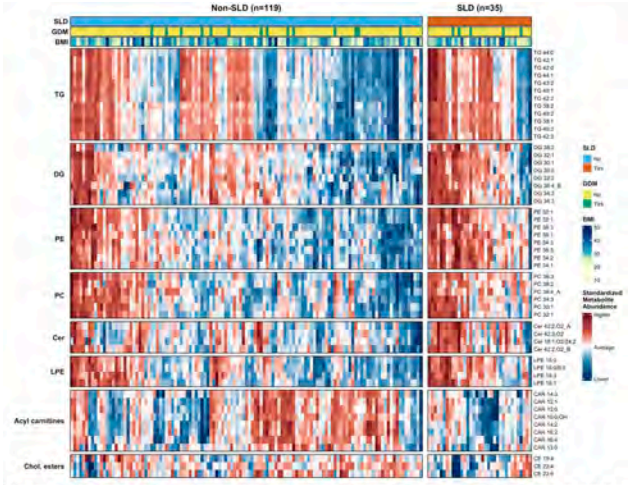


Figure 1. Heatmap of 53 plasma lipid species differentially abundant between pregnant individuals with (n=35) and without (n=119) SLD, selected from 165 features significant after BMI adjustment (MaAsLin2, FDR-adjusted P <0.05; 149 elevated, 18 reduced). Rows are clustered within lipid subclass; columns within SLD group. Cell color reflects standardized metabolite abundance (red, higher; blue, lower). Triacylglycerols, diacylglycerols, phosphatidylethanolamines, phosphatidylcholines, ceramides, and lysophosphatidylethanolamines were uniformly elevated in SLD; acylcarnitines and polyunsaturated cholesterol esters were reduced.

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2418 | GAPS IN LABORATORY TESTING FOR FIB-4 SCREENING AMONG HIGH-RISK PATIENTS IN RESIDENCY-AFFILIATED PRIMARY CARE CLINIC

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Background: The primary care setting is an important site for screening for metabolic dysfunction-associated steatotic liver disease (MASLD). The most recent American Diabetes Association (ADA) guidelines now recommend FIB-4 screening every 1-2 years for patients with risk factors for MASLD, including prediabetes, diabetes, and obesity. However, uptake of the FIB-4 score for MASLD screening in primary care practice remains unclear. We undertook a quality-improvement initiative at an internal medicine residency-affiliated primary care clinic to improve FIB-4 screening rates. This study characterizes the eligible patient population and identifiespatient characteristics associated with the absence of laboratory testing needed for FIB-4-based screening. **Methods:** Among the 8,453 patients seen in the past year at the primary care clinic, 5,469 had a diagnosis of prediabetes, diabetes, or obesity and thus were identified as eligible for FIB-4 screening. Among those eligible patients, we looked to see if they had an AST, ALT, and platelet count, which are needed to calculate a FIB-4, drawn during their time in the clinic. We also collected data on patient characteristics including age, sex, BMI, race, insurance type, most recent A1c, and presence of diabetes or obesity. We compared categorical variables using Chi-square and continuous variables using t-tests (GraphPad Software). **Results:** Among the clinic patients eligible for FIB-4 screening, the mean age was 52.8, more than half were male (53.1%), the mean BMI was 33, and most had some form of insurance (87.8%). Most eligible patients had an AST, ALT, and platelet count completed (88.3%). Patients who had completed screening labs had an older mean age than those did not have labs completed (54.2 years old vs

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42.6 years old, p < 0.01) and had a higher mean A1C (6.59 vs 5.96, p < 0.01) (Table 1). Higher proportions of patients who had completed screening labs had a diagnosis of diabetes compared with those who did not have labs completed(27.7% vs 8.9%, p < 0.01). **Conclusion:** The first step to screening high-risk patients for MASLD is to draw the labs needed to calculate a FIB-4. In our clinic, more than one in ten high-risk patients did not have an AST, ALT, and platelet count on file. The current study suggests that primary care patients who appear healthier (i.e., younger, well-controlled diabetes) may be a population at risk of being overlooked for MASLD screening despite meeting recommendations. We plan to use these findings to implement quality improvement initiatives aimed at clinician education on MASLD risk factors and at increasing uptake of screening guidelines.

Table 1 Patient Characteristics Associated with FIB-4 Screening Completion

	Screening Completed (n = 4830)	Screening Incomplete (n = 639)	P-value
Age	54.2 (16.1)	42.6 (14.8)	**<0.01**
Sex			
M =	2558 (53.0%)	348 (54.5%)	0.818
F =	2272 (47.0%)	291 (45.5%)	
BMI	33.4 (7.51)	33.5 (5.75)	0.746
Race			
White/Caucasian =	1378 (28.5%)	208 (32.5%)	0.465
Black =	1159 (24.0%)	114 (17.5%)	
Other =	2293 (47.5%)	317 (49.6%)	
Insurance			
None =	621 (12.9%)	97 (15.2%)	0.659
Public =	1857 (38.5%)	213 (33.3%)	
Private =	2352 (48.6%)	329 (51.5%)	
Last A1C	6.59 (1.82)	5.96 (1.33)	**<0.01**
Diabetes			
None/Prediabetes =	3490 (72.3%)	582 (91.1%)	**<0.01**
Formal =	1340 (27.7%)	57 (8.9%)	
BMI Category			
Obese/Class 3	3124 (64.7%)	354 (55.4%)	0.120
Not Obese	1706 (35.3%)	285 (44.6%)	

Disclosures: Alex Chang: Nothing to Disclose, Kimberly Ho: Nothing to Disclose, Julio Blasco Jimenez: Nothing to Disclose, Alex Friefeld: Nothing to Disclose, Timothy Greenfield: Nothing to Disclose, Paige McLean Diaz: Nothing to Disclose, Rebekah Gardner: Nothing to Disclose.

2419 | URIC ACID-TO-HIGH-DENSITY LIPOPROTEIN CHOLESTEROL RATIO IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS OF ASSOCIATION AND DIAGNOSTIC ACCURACY

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most prevalent chronic liver disease worldwide. The uric acid-to-high-density lipoprotein cholesterol ratio (UHR) is an inexpensive metabolic-inflammatory biomarker that may reflect both hyperuricemia and impaired lipid metabolism. We evaluated the association between UHR and prevalent MASLD and assessed its diagnostic accuracy. **Methods:** We performed a systematic review and meta-analysis of observational studies assessing UHR in adults with prevalent NAFLD, MASLD, or MAFLD. For association analysis, adjusted odds ratios (ORs) comparing the highest versus lowest UHR categories were pooled using a random-effects model. Diagnostic accuracy was assessed using a bivariate model, with pooled sensitivity, specificity, likelihood ratios, diagnostic odds ratio (DOR), and hierarchical summary receiver operating characteristic (HSROC) area under the curve (AUC). **Results:** Fourteen studies involving 79,805 patients were included in the systematic review; nine studies (20,936 patients) were eligible for the association meta-analysis and eight studies contributed to the diagnostic accuracy analysis. In the categorical association analysis, individuals in the highest UHR category had significantly higher odds of prevalent MASLD compared with those in the lowest category (OR 2.33, 95% CI 1.70–3.21; $I^2 = 57.5\%$). The prediction interval included the null (0.88–6.17). In diagnostic accuracy analysis, pooled sensitivity was 0.68 (95% CI 0.63–0.74), pooled specificity was 0.61 (95% CI 0.56–0.66), and DOR was 3.40 (95% CI 3.06–3.78). The HSROC AUC was 0.69 (95% CI 0.68–0.71), indicating modest discriminative performance. Deeks' test did not suggest significant publication bias. **Conclusion:** Higher UHR is significantly associated with prevalent MASLD and may serve as a simple, low-cost marker for metabolic risk stratification. However, its standalone diagnostic accuracy is modest (AUC 0.69), suggesting that UHR should complement rather than replace established diagnostic approaches. Prospective studies using standardized UHR cutoffs are needed before routine clinical application.

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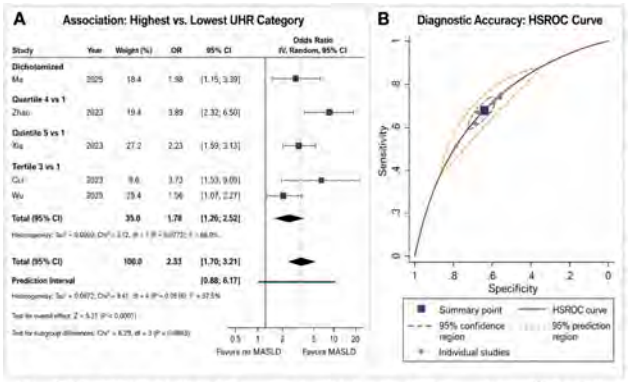


Figure 1. (A) Forest plot of adjusted odds ratios for the association between highest versus lowest UHR category and prevalent MASLD, stratified by comparison scale. Diamond represents the pooled random-effects estimate; green bar indicates the 95% prediction interval. (B) Hierarchical summary receiver operating characteristic (HSROC) curve for UHR as a diagnostic marker for MASLD. The summary operating point (square) represents pooled sensitivity and specificity; dashed ellipses represent 95% confidence and prediction regions.

Disclosures: Yazan Alnairah: Nothing to Disclose, EzzElDien A. Ibrahim: Nothing to Disclose, Abdallfatah Abdallfatah: Nothing to Disclose, Mostafa Adel T. Mahmoud: Nothing to Disclose, Ahmed Kertam: Nothing to Disclose, Yasmin Aly: Nothing to Disclose, Abdelrahman A. Hashem: Nothing to Disclose, Nourhan Hatem: Nothing to Disclose, Mohamed R. Murad: Nothing to Disclose, Oshaz Fatima: Nothing to Disclose, Omar Medhat Abdelaziz Farag: Nothing to Disclose, Mustafa Gandhi: Nothing to Disclose, Islam Mohamed: Nothing to Disclose, Ashraf Almomani: Nothing to Disclose.

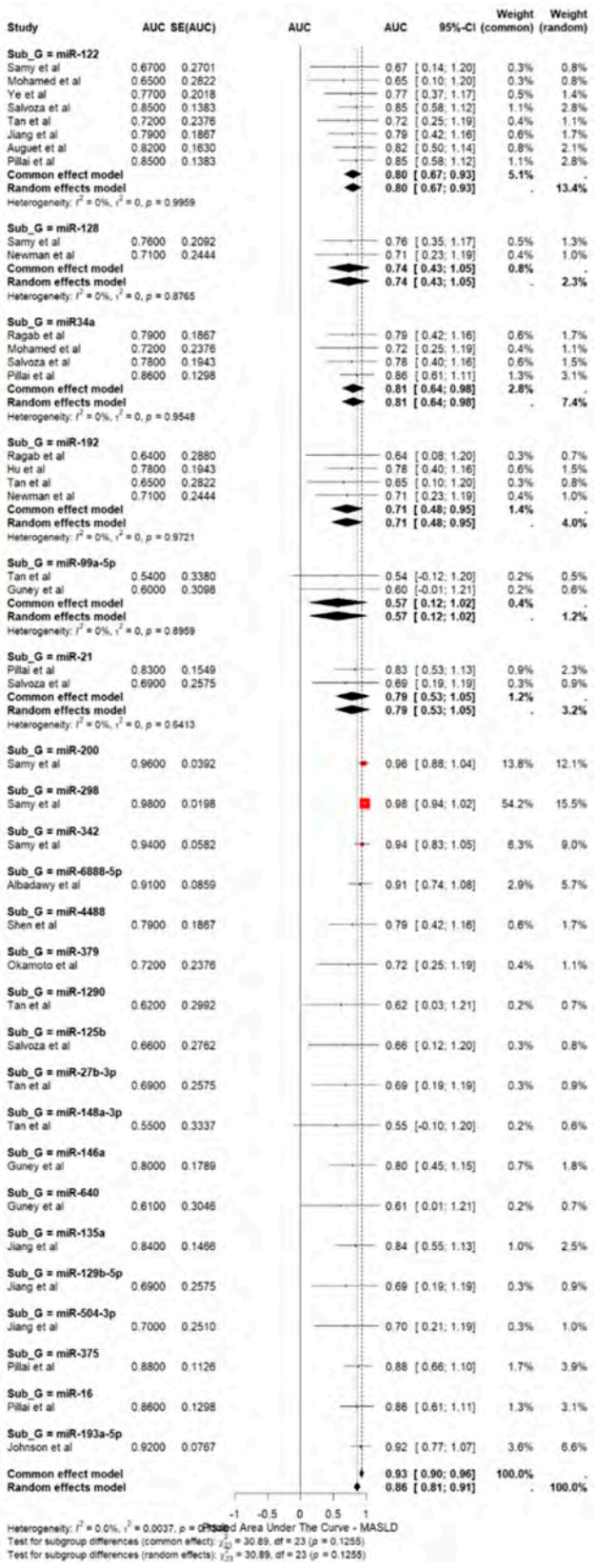
2420 | CIRCULATING MICRORNAS AS DIAGNOSTIC BIOMARKERS ACROSS THE MASLD DISEASE SPECTRUM: A SYSTEMATIC REVIEW AND META-ANALYSIS

Aryan Gupta[1] Era Gupta[2] Omar Oudit[3] Priyanshi Mehulkumar Gandhi[4] Rewanth Katamreddy[5] Pius Ojemolon[6] Dushyant Singh Dahiya[7] Aakash Desai[8], [1]Bangalore Medical College and Research Institute, India, [2]Guthrie/ Robert Packer Hospital, PA, USA, [3]Brookdale University Hospital Medical Centre, NY, USA, [4]Government Medical Colege, Surat, India, [5]Guthrie/Robert Packer Hospital, PA, USA, [6]Emory University School Of Medicine, GA, USA, [7]The University Of Kansas School Of Medicine, Kansas, USA, [8]Allegheny Health Network, PA, USA

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) encompasses a spectrum from hepatic steatosis to metabolic dysfunction-associated steatohepatitis (MASH) and hepatocellular carcinoma (HCC). As MASLD is a leading etiology of non-viral HCC, circulating miRNAs were evaluated across the full disease spectrum. Circulating microRNAs (miRNAs), extracted from serum or plasma via liquid biopsy, have emerged as promising minimally invasive biomarkers given their role in hepatic inflammation, lipid metabolism, and fibrogenesis. We performed a systematic review and meta-analysis evaluating their diagnostic utility in MASLD, MASH, and MASLD-associated HCC. **Methods:** This review followed PRISMA guidelines. PubMed, Google Scholar, and ScienceDirect were searched for studies evaluating circulating miRNAs extracted from serum or plasma as liquid biopsy-derived biomarkers in MASLD, MASH, and HCC. Studies reporting AUC were included. Subgroup analyses were performed by disease stage (MASLD, MASH, and HCC) and by individual miRNA profile. Data were analyzed using Meta, Metadata, and Metafor packages in R Studio using a common effects model. **Results:** Twenty-two studies were included. For MASLD, miR-298 (AUC 0.98 [0.94-1.02, 95% CI]), miR-200 (AUC 0.96 [0.88-1.04, 95% CI]), and miR-342 (AUC 0.94 [0.83-1.05, 95% CI]) demonstrated the highest individual diagnostic accuracy. The best-performing panel combined changes in hepatic fat content, total cholesterol, triglycerides, miR-15b-3p, and BMI (AUC 0.89 [0.85-0.93, 95% CI]). For MASH, miR-200, miR-298, and miR-342 achieved near-perfect AUCs of 0.99 [0.97-1.01, 95% CI], while the panel of miR-21-5p, miR-151a-3p, miR-192-5p, and miR-4449 achieved AUC 0.99 [0.98-1.00, 95% CI]. For MASLD-associated HCC, miR-214 showed the highest individual AUC at 0.88 [0.66-1.100, 95% CI], while a panel of miR-34a, miR-221, miR-16, miR-23-3p, miR-122-5p, miR-198, and miR-199a-3p achieved AUC 0.99 [0.98-1.00, 95% CI]. Overall pooled AUCs were 0.86 [0.81-0.91, 95% CI] for MASLD, 0.99[0.98-1.00, 95% CI] for MASH, and 0.760 [0.64-0.88, 95% CI] for HCC. **Conclusion:** Circulating microRNAs show promising diagnostic utility in MASLD, MASH and HCC and may serve as minimally invasive biomarkers for disease detection. However, variability in profiling techniques and validation approaches limits current clinical translation. Standardized large-scale prospective studies are needed to confirm their role in routine hepatology evaluation.

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Disclosures: Aryan Gupta: Nothing to Disclose, Era Gupta: Nothing to Disclose, Omar Oudit: Nothing to Disclose, Priyanshi Mehulkumar Gandhi: Nothing to Disclose, Rewanth Katamreddy: Nothing to Disclose, Pius Ojemolon: Nothing to Disclose, Dushyant Singh Dahiya: Nothing to Disclose, Aakash Desai: Nothing to Disclose.

2421 | PREVALENCE OF STEATOTIC LIVER DISEASE AMONG COMMUNITY-DWELLING ADULTS ASSESSED BY MAGNETIC RESONANCE IMAGING–PROTON DENSITY FAT FRACTION

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Background: Steatotic liver disease (SLD) is a common chronic liver condition in China. However, there is limited epidemiological data based on MRI-PDFF, the non-invasive gold standard. This study aims to assess the prevalence of SLD using MRI-PDFF and to analyze the distribution of its subtypes and associated metabolic risk factors. **Methods:** This cross-sectional study enrolled patients who underwent abdominal MRI at a tertiary hospital between March and November 2025. After applying inclusion and exclusion criteria, 1,414 patients were ultimately included. SLD was diagnosed based on MRI-PDFF $\geq$5%. According to the 2023 AASLD-EASL-ALEH consensus, SLD was subclassified into metabolic dysfunction-associated steatotic liver disease (MASLD), metabolic dysfunction and alcohol-related steatotic liver disease (MetALD), alcohol-related liver disease (ALD), and cryptogenic SLD. Demographic and metabolic data were collected. Prevalence by sex, age, and metabolic comorbidities was analyzed, and logistic regression was performed. **Results:** Among the 1,414 participants (mean age 48.9 ± 13.6 years; mean BMI 25.6 ± 3.7 kg/m²), 817 (57.8%) had SLD. Of these 817 SLD cases, MASLD accounted for 83.0%, MetALD 8.2%, ALD 7.1%, and cryptogenic SLD 1.7%. SLD prevalence was higher in men than in women (71.9% vs. 45.4%). Prevalence among individuals with metabolic syndrome, obesity, and diabetes was 86.5%, 85.8%, and 72.9%, respectively. Multivariable logistic regression showed that age (OR = 1.015, 95%CI 1.004–1.026), BMI (OR = 1.236, 95%CI 1.177–1.302), triglycerides (OR = 2.365, 95%CI 1.898–2.984), HOMA-IR (OR = 1.169, 95%CI 1.068–1.285), and GGT (OR = 1.013, 95%CI 1.006–1.022) were independent risk factors for SLD (all $P < 0.05$). **Conclusion:** Among community-dwelling

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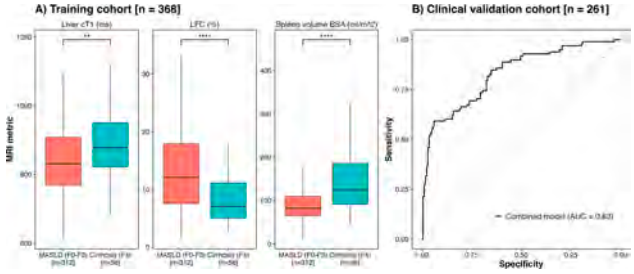
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adults in this study, the MRI-PDFF-based prevalence of SLD was 57.8%, with MASLD being the predominant subtype. SLD was closely associated with metabolic abnormalities. Age, BMI, TG, HOMA-IR, and GGT were identified as independent risk factors, supporting early screening and intervention.
Disclosures: Ruyu Liu: Nothing to Disclose, Kaiyue Zhao: Nothing to Disclose.

2422 | MULTIPARAMETRIC MRI BASED RISK MODEL HAS STRONG DIAGNOSTIC ACCURACY AT DETECTING LIVER CIRRHOSIS

Charlie Diamond[1] Michele Pansini[1] Yi-Chun Wang[1] Masato Yoneda[2] Atsushi Nakajima[2] Kento Imajo[3] Mark Muthiah[4] Dan Yock Young[4] ELEGANCE Consortium[5] Pierce Chow[6] Andrea Dennis[1], [1]Perspectum, [2]Yokohama City University School of Medicine Graduate School of Medicine, [3]Shin Yurigaoka General Hospital, [4]Yong Loo Lin School of Medicine, [5]NA, [6]Singapore General Hospital and National Cancer Centre Singapore

Background: Non-invasive assessment of liver fibrosis and cirrhosis is crucial in patients with metabolic dysfunction-associated steatotic liver disease (MASLD). MRI-derived iron-corrected T1 (cT1) correlates with fibrosis, whilst liver fat content (LFC) correlates with steatosis and declines in advanced fibrosis. Increasing spleen volume can occur in cirrhosis, reflecting portal hypertension. Combining these metrics may improve identification of patients with cirrhosis compared to individual metrics alone. **Methods:** We combined data from 368 individuals with biopsy-confirmed MASLD, collected from 2 observational studies in Japan and Singapore (histology training cohort) and 261 individuals with clinically diagnosed MASLD from a separate study in Singapore (clinical validation cohort).In the training cohort (mean age 54 years, 55% male, mean BMI 30 kg/m²) 56 individuals (15%) had histological cirrhosis (F4). In the validation cohort (mean age 62 years, 56% male, mean BMI 26 kg/m²) 98 individuals (38%) had a clinical diagnosis of cirrhosis. All underwent standardised cT1, LFC and spleen volume (body surface area adjusted) measurements by MRI. A multivariate logistic regression model was developed in the training cohort to identify cirrhosis. The model was then applied to the validation cohort, where diagnostic accuracy for cirrhosis was assessed by area under the receiver operating characteristic curve (AUC). **Results:** In the training data, mean cT1 and spleen volume (BSA) were significantly higher in individuals with cirrhosis (889 vs. 842ms and 147 vs. 91 ml/m², both $p < 0.01$), while LFC was significantly lower (9% vs. 13%; $p < 0.001$). Used independently, cT1, LFC and spleen volume identified F4 with AUCs of 0.64, 0.69 and 0.72, respectively. The combination risk score substantially improved diagnostic accuracy for identifying F4 in the training data (AUC 0.86 [0.81-0.91]). When applied to the independent clinical validation cohort, the performance was maintained (0.83 [0.78-0.89]). **Conclusion:** Non-invasive multiparametric MRI combining of liver disease activity, liver fat and spleen volume can detect cirrhosis with excellent accuracy in MASLD and may have potential applications in enrichment or stratification of clinical trial populations.



Disclosures: Charlie Diamond: Perspectum Ltd: Employee, Michele Pansini: Nothing to Disclose, Yi-Chun Wang: Perspectum Ltd: Employee, Masato Yoneda: Nothing to Disclose, Atsushi Nakajima: Nothing to Disclose, Kento Imajo: Nothing to Disclose, Mark Muthiah: Nothing to Disclose, Dan Yock Young: Nothing to Disclose, ELEGANCE Consortium: Nothing to Disclose, Pierce Chow: Roche: Consultant, Pfizer: Advisor, Perspectum: Advisor, AVATAMED: Stock – privately held company, SIRTEX Medical: Speaking and Teaching, Astrazeneca: Advisor, IQVIA: Consultant, MIRXES: Grant/Research Support, Perspectum: Grant/Research Support, AMILI: Grant/Research Support, Stratificare: Grant/Research Support, Roche: Grant/Research Support, SIRTEX Medical: Grant/Research Support, Siemens: Speaking and Teaching, Andrea Dennis: Nothing to Disclose.

2423 | BODY MASS INDEX OUTPERFORMS WAIST CIRCUMFERENCE FOR IDENTIFYING HIGH-RISK OBSTRUCTIVE SLEEP APNEA IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE: A RECEIVER OPERATING CHARACTERISTIC ANALYSIS

Waleed Alhazzani[1] Shadan AlMuhaidib[1] Faisal Abaalkhail[2] Haifa Alotaibi[1] Saleh Alessy[2] Feras Altunisi[1] Waleed Alomaim[2] Abdullah Alharthi[3] Fahad Alkhayal[3] Walid Alkeridy[4] Badr Almutairi[3] Moawad Alotaibi[3] Basmah Khoja[2] Saleh Alqahtani[5], [1]Ministry of Defense Health Services, Riyadh, Saudi Arabia, [2]King

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Background: Polysomnography is resource-intensive and rarely accessible during routine hepatology consultations. A simple anthropometric rule to identify which patients with metabolic dysfunction-associated steatotic liver disease (MASLD) merit further obstructive sleep apnea (OSA) evaluation has not been established. We aimed to evaluate body mass index (BMI) and waist circumference (WC) thresholds for identifying Berlin Questionnaire-defined high risk for OSA among adults with MASLD. **Methods:** Within the GENESIS prospective cohort, adults with MASLD (hepatic steatosis on VCTE defined by controlled attenuation parameter [CAP] $\geq$268 dB/m plus $\geq$1 of the 5 cardiometabolic risk factors per the 2023 multisociety Delphi consensus) and complete Berlin Questionnaire data were analyzed. High-risk OSA was defined per the standard Berlin Questionnaire scoring (positive in $\geq$2 of the 3 categories: (Snoring/witnessed apneas, daytime sleepiness, and hypertension/obesity risk factors). Analyses were restricted to complete cases with available BMI and WC measurements. Receiver operating characteristic (ROC) analysis assessed the discrimination of BMI and WC for high-risk OSA. The Youden index identified optimal cutoffs; area under the curve (AUC), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were computed. Because BMI contributes to Berlin Questionnaire classification, BMI-based discrimination was interpreted as a pragmatic triage assessment rather than independent diagnostic validation. **Results:** Among 1,107 participants with MASLD (mean age 46.1 ± 13.0 years; 58.2% male), 410 (37.0%) screened as high risk for OSA. BMI discriminated high-risk OSA better than WC overall (BMI AUC, 0.675; 95% CI, 0.644–0.707 vs WC AUC, 0.646; 95% CI, 0.613–0.679). At the Youden-optimal cutoff of 30 kg/m², BMI achieved a sensitivity of 83.7%, specificity of 49.4%, PPV of 49.2%, NPV of 83.8%, and a Youden index of 0.332. The Youden-optimal WC cutoff (102.5 cm) traded sensitivity for specificity (sensitivity, 64.9%; specificity, 58.7%; PPV, 48.0%; NPV, 74.0%; Youden index, 0.236). **Conclusion:** A BMI threshold of 30 kg/m², already routinely measured in hepatology practice, identifies the majority of patients with MASLD at high risk for OSA while reliably excluding low-risk individuals. Embedding this single-variable rule into MASLD clinical workflows may enable evidence-based, scalable OSA case-finding without additional equipment or cost. Because BMI is already part of Berlin Questionnaire scoring, BMI $\geq$30 kg/m² should not be interpreted as a new diagnostic rule. Rather, it may provide a simple clinic-based trigger to prioritize MASLD patients for formal sleep evaluation, pending prospective validation with formal sleep testing.

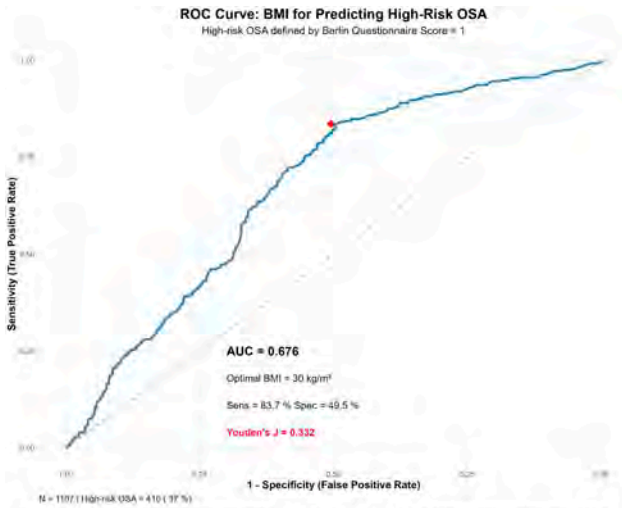


Figure 1. Receiver operating characteristic curve for body mass index predicting high-risk obstructive sleep apnea, defined per the standard Berlin Questionnaire scoring (positive in ≥2 of the 3 categories).

AUC 0.675 (95% CI 0.644–0.707). Optimal cutoff 30 kg/m²: sensitivity 83.7%, specificity 49.4%, Youden index 0.332. AUC, area under the curve; CI, confidence interval.

Disclosures: Waleed Alhazzani: Nothing to Disclose, Shadan AlMuhaidib: Nothing to Disclose, Faisal Abaalkhail: Nothing to Disclose, Haifa Alotaibi: Nothing to Disclose, Saleh Alessy: Nothing to Disclose, Feras Altunisi: Nothing to Disclose, Waleed Alomaim: Nothing to Disclose, Abdullah Alharthi: Nothing to Disclose, Fahad Alkhayal: Nothing to Disclose, Walid Alkeridy: Nothing to Disclose, Badr Almutairi: Nothing to Disclose, Moawad Alotaibi: Nothing to Disclose, Basmah Khoja: Nothing to Disclose, Saleh Alqahtani: Nothing to Disclose.

2424 | BEYOND ADDITIVE SCORES: A MULTIPLICATIVE LSM × CAP INTERACTION DEFINES AN ETIOLOGY-SPECIFIC PIVOT POINT THAT REFRAMES DIAGNOSTIC THRESHOLDS FOR ADVANCED FIBROSIS (F$\geq$3) IN THE ERA OF RESMETIROM

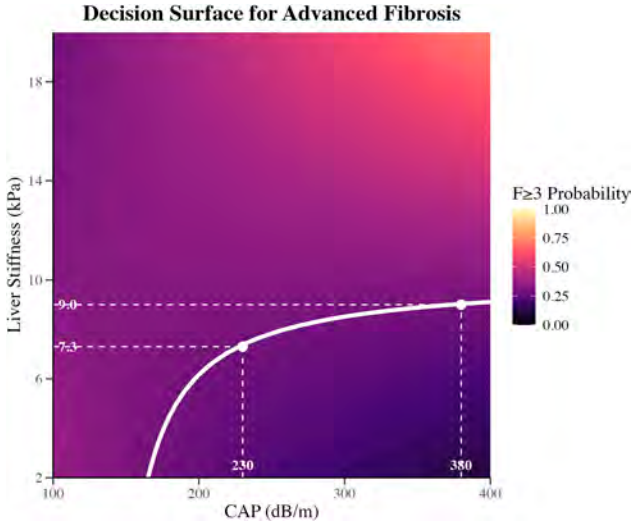
Lucia Parlati[1] Clemence Moreau[2] Jerome Boursier[2] Marc De Saint Loup[2] Vincent Mallet[1], [1]AP-HP.Centre Université Paris Centre, Groupe Hospitalier Cochin Port Royal, [2]Angers University Hospital

Background: The advent of targeted antifibrotic therapies (e.g., resmetirom) demands precise non-invasive identification of MASLD patients with advanced fibrosis (F$\geq$3). FibroScan-based scores currently combine liver stiffness (LSM) and controlled attenuation parameter (CAP) additively, assuming independent effects. We tested whether a multiplicative LSM×CAP interaction captures a MASLD-specific signal justifying dynamic, CAP-dependent thresholds. **Methods:** We analyzed 502

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biopsy-referenced MASLD patients (median age 61 years, 62% male, 57% diabetic; 177 [35%] $F \geq 3$) and 151 controls (alcohol-associated, HCV, HBV). Firth-penalized logistic regression with a mean-centered LSM×CAP interaction was fitted per etiology to ensure robust estimation. The composite score was compared to FAST and AGILE4 (DeLong test) with 5-fold cross-validated AUC. **Results:** LSM was strongly elevated in $F \geq 3$ (mean 15.1 vs 8.6 kPa), whereas CAP barely differed (322 vs 317 dB/m). Centered on cohort means, LSM independently predicted $F \geq 3$ ($\beta = +1.11$, $p < 10^{-15}$); CAP alone did not ($\beta = +0.04$, $p = 0.83$). Their multiplicative interaction was highly significant ($\beta\_int = +0.57$ [95% CI: 0.27–0.94], $p = 0.0008$) and reversed in ALD ($\beta\_int = -1.39$, $p = 0.064$), establishing MASLD specificity. This interaction generates a unique pivot at LSM = 10.2 kPa, defining two phenotypes. Below this pivot, steatosis masks true fibrosis risk. Clinically, a raw 9.0 kPa reading at a CAP of 380 dB/m carries the identical biological $F \geq 3$ risk (30%) as a 7.3 kPa reading at a CAP of 230 dB/m (**Figure**). Additive scores ignore this interference, driving the massive over-staging of steatotic patients. Conversely, above the 10.2 kPa pivot, steatosis synergistically amplifies the diagnostic signal, locking in active MASH fibrogenesis. Applying this dynamic threshold achieved 76% sensitivity and 84% NPV. Cross-validated AUC was 0.80, significantly exceeding FAST (0.76; $p = 0.005$) and comparable to AGILE3+ (0.83; $p = 0.18$) AGILE4 (0.83; $p = 0.19$), without any blood test. **Conclusion:** The LSM×CAP interaction enables a blood-test-free, point-of-care diagnostic tool for MASLD. It defines two phenotypes pivoting around LSM ≍ 10.2 kPa: below, steatosis acts as a signal moderator; above, it accelerates MASH-driven fibrosis. CAP-dependent upward adjustment of LSM cut-offs prevents over-staging highly steatotic patients—directly relevant for resmetirom candidate selection. The interaction's reversal in ALD underscores a distinct biomechanical reality.



Disclosures: Lucia Parlati: Nothing to Disclose, Clemence Moreau: Nothing to Disclose, Jerome Boursier: echosens: Consultant, Inventiva: Consultant, Siemens: Consultant, Pfizer: Advisor, Novonordisk: Consultant, Gilead: Royalties or patent beneficiary, Siemens: Independent Contractor, Lilly: Consultant, Marc De Saint Loup: Nothing to Disclose, Vincent MALLET: Nothing to Disclose.

2425 | POINT-OF-CARE MR-PDFF™ DEVICE ACCURATELY STAGES HEPATIC STEATOSIS IN SLD

Muhammad Sheikh[1] Jerry Mabary[2], [1]Fresno Clinical Research Center, [2]Livivos

Background: MRI-PDFF is the reference standard for noninvasive quantification of hepatic steatosis in MASLD and MASH, but use is constrained by cost and limited access. With the approval of multiple at-risk MASH therapeutics, point-of-care PDFF-based steatosis quantification may improve disease management. The LiverScope® device (Livivos, Inc.) is a point-of-care steatosis assessment system that employs magnetic resonance proton density fat fraction (MR-PDFF™) technology. In this study, we evaluated the accuracy of LiverScope-derived MR-PDFF™ for steatosis staging, using MRI-PDFF as the reference standard. LiverScope MR-PDFF™ sensitivity and specificity for MASLD and MASH prediction were determined using published MRI-PDFF thresholds. **Methods:** Hepatic steatosis was evaluated in 36 subjects who underwent paired same-day MRI-PDFF and LiverScope-based MR-PDFF™ assessments in the fasted state. LiverScope MR-PDFF™ data were acquired by trained operators at Fresno Clinical Research Center who were blinded to MRI-PDFF results. MRI-PDFF was performed at California Imaging Center using a GE 1.5T scanner and analyzed centrally with Perspectum MultiScan to quantify hepatic PDFF. LiverScope-derived MR-PDFF™ sensitivity and specificity for MASLD and MASH were calculated using published MRI-PDFF thresholds[1] from Panagiotopoulos et al of 4.4% and 6.9%, respectively, with MRI-PDFF determined PDFF as the reference standard. **Results:** Using MRI-PDFF as the reference standard and Panagiotopoulos et al MRI-PDFF thresholds of 4.4% for MASLD and 6.9% for MASH,1 LiverScope-derived MR-PDFF™ achieved a sensitivity of 1.0 for both MASLD and MASH, and a specificity of 0.62 and 0.93, respectively (Figure 1). In this cohort, LiverScope MR-PDFF™ did not miss any MRI-PDFF–defined cases of MASLD or MASH. (Figure 1). Figure 1. MASLD-MASH Staging Prediction Accuracy using same-day MRI-PDFF reference standard and published Panagiotopoulos et al thresholds. **Conclusion:**

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The LiverScope device predicted MRI-PDFF-defined MASLD, and MASH with high sensitivity using point-of-care MR-PDFF™ technology. These findings support a potential future role for point-of-care MR-PDFF™ in MASLD and MASH disease management, pending validation in larger, multisite studies. 1. Proton Density Fat Fraction for Diagnosis of MASLD; Panagiotopoulos et al; Hepatology. 2026;83: 127–141. Caution: LiverScope is an investigational device limited by federal law to investigational use.

		MR-PDFF™ Staging Performance	
Steatosis Stage	MRI-PDFF Cut-Off[1]	Sensitivity	Specificity
MASLD	≥ 4.4%	1.0	0.62
MASH	≥ 6.9%	1.0	0.93

Disclosures: Muhammad Sheikh: Nothing to Disclose, Jerry Mabary: Nothing to Disclose.

2426 | CARDIOMETABOLIC RISK FACTORS ASSOCIATED WITH AT-RISK MASLD: A MULTI-CENTER PROSPECTIVE COHORT STUDY

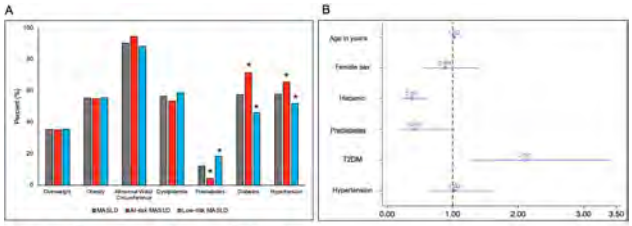
Kaleb Tesfai[1] Nikhil Kalita[1] Francisco Idalsoaga[2] Mario Pessoa[3] Claudia Oliveira[4] Patricia Ziteli[3] Scherezada loza[5] Ezequiel Ridruejo[6] Mirta Peralta[7] César Castro[8] Jorge Garavito[8] Rommel Huailla[8] Gustavo Ayares Campos[9] Nancy Solis[9] Maria Orellana[9] Francisco Barrera[9] Sebastian Marciano[10] Adrián Gadano[10] Jorge Martínez[10] Maria Jose Acosta[10] Martin Tagle[11] Hugo Cedron[11] Ismael Yepes[12] Dalis Pérez[12] MaríaFernanda SaavedraChacón[13] Samuel Perez[14] Ignacio García-Juárez[15] Orfanel Sebastian Pineda-Arzat[15] Liz Toapanta-Yanchapaxi[16] Aline Sorribas[17] Manuel Mendizabal[18] Lorena Castro Solari[19] Loreto Aguilar Barría[20] Samantha Wu[21] Catalina Roa[21] Fabiana Nina[22] Estefanía Liza Baca[23] Javier Diaz Ferrer[23] Roberto Pérez Ravier[24] Maria Martinez[24] Natalie Vilcinskas[24] Daniza Alexandra Contreras[25] Daniela Simian[26] Juan Roblero[27] Pamela Gil[24] Arun Sanyal[28] Juan Pablo Arab[28] Luis Díaz[29] Marco Arrese[29], [1]University of California San Diego, [2]Pontificia Universidad, [3]Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, [4]University of Sao Paulo School of Medicine, [5]Hospital Juárez de México, [6]Centro de Educación Médica e Investigaciones Clínicas Norberto Quirno "CEMIC, [7]Hospital Francisco J Muñiz, Ciudad Autónoma de Buenos Aires, [8]Hospital Nacional Arzobispo Loayza, [9]Pontificia Universidad Católica de Chile, [10]Hospital Italiano de Buenos Aires, [11]Clínica Anglo Americana, San Isidro, [12]Universidad de Cartagena, [13]Servicio de Hepatología Clínica y Medicina Interna, Clínica CES, Medellín, Colombia., [14]Servicio de Hepatología Clínica y Medicina Interna, Clínica CES, Medellín, Colombia, [15]Department of GastroenterologyNational Institute of Medical Sciences and Nutrition Salvador Zubirán, [16]Department of Gastroenterology,National Institute of Medical Sciences and Nutrition Salvador Zubirán, [17]Unidad de Hígado y Trasplante Hepático, Hospital Universitario Austral, Pilar, Provincia de Buenos, [18]Hospital Universitario Austral, [19]Centro de Enfermedades Digestivas, Clínica Universidad de los Andes, Santiago, Chile., [20]Centro de Investigación e Innovación Biomédica, Universidad de los Andes, Santiago, Chile., [21]Escuela de Medicina, Universidad de los Andes, Santiago, Chile., [22]Escuela de Medicina, Universidad del Alba, Santiago, Chile., [23]Hospital Nacional Edgardo Rebagliati Martins, Jesús María, Lima, Perú., [24]Liver Unit, Hospital Central de Mendoza, Mendoza, Argentina., [25]National Institute of Diabetes, Nutrition, and Endocrinology (INDEN), Santo Domingo, Dominican Repub, [26]Sección de Gastroenterología, Departamento de Medicina Interna,Hospital Clínico Universidad de Chile, [27]University of Chile, [28]Virginia Commonwealth University, [29]Pontificia Universidad Católica de Chile, Santiago, Chile

Background: Although MASLD diagnosis is based on the presence of at least one cardiometabolic risk factor (CMRF), the role of individual CMRFs in the diagnosis and severity of MASLD has been poorly characterized. Thus, we aimed to identify the most relevant CMRFs for diagnosing MASLD and predicting at-risk MASLD in a well-characterized multinational cohort. **Methods:** We conducted a cross-sectional analysis of prospectively enrolled adults with MASLD at 16 tertiary centers in seven countries (Argentina, Brazil, Chile, Colombia, the Dominican Republic, Mexico, and Peru). At-risk MASLD was defined as the presence of MASLD and ≥ F2 on biopsy or a FAST score ≥ 0.67, if liver biopsy was not available. Analyses included a logistic regression model adjusted for age, sex, Hispanic ethnicity, and CMRFs. **Results:** The cohort comprised of 408 participants; 67.8% were female and 30.2% were Hispanic. The prevalence of at-risk MASLD was 44.9%. The median [IQR] age and body mass index (BMI) were 65 [55–72] years and 30.4 [27.4–34.0] kg/m², respectively. Compared with low-risk MASLD, participants with at-risk MASLD had a significantly greater prevalence of type 2 diabetes (T2D) (71.4% vs. 45.9%, $p < 0.001$) and hypertension (65.4% vs. 51.8%, $p = 0.006$), while a significantly lower prevalence of prediabetes, 4.4% vs. 18.6%, $p < 0.001$. There were no differences in the prevalence of other CMRFs between

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those with at-risk MASLD and low-risk MASLD: overweight, 34.9% vs. 35.5%, p = 0.902; obesity, 54.9% vs. 55.5%, p = 0.906; abnormal waist circumference, 94.6% vs. 88.3%, p = 0.176; dyslipidemia, 53.4% vs. 58.8% p = 0.275 (**Figure A**). In multivariable logistic regression, only T2D (OR 2.10; 95% CI 1.29–3.41; p = 0.003) remained a significant CMRF predictor of at-risk MASLD (**Figure B**). **Conclusion:** In a multicenter Latin American prospective cohort study, abnormal waist circumference was present in 9 of 10 patients, while type 2 diabetes was the only CMRF that predicted increased odds of at-risk MASLD. While patients with MASLD may present with multiple cardiometabolic risk factors, the presence of increased adiposity and dysglycemia should be considered major diagnostic criteria for MASLD (FONDECYT 1241450).



A) Prevalence of different cardiometabolic risk factors across MASLD risk subtype
B) Multivariable adjusted odds ratio of cardiometabolic risk factors, significant on univariate analysis, predicting odds of at-risk MASLD

Disclosures: Kaleb Tesfai: Nothing to Disclose, Nikhil Kalita: Nothing to Disclose, Francisco Idalsoaga: Nothing to Disclose, Mario Pessoa: Nothing to Disclose, Claudia Oliveira: Nothing to Disclose, Nothing to Disclose, Patricia Ziteli: Nothing to Disclose, scherezada loza: Nothing to Disclose, Ezequiel Ridruejo: Nothing to Disclose, mirta peralta: Nothing to Disclose, César Castro: Nothing to Disclose, Jorge Garavito: Nothing to Disclose, Rommel Huailla: Nothing to Disclose, Gustavo Ayares Campos: Nothing to Disclose, Nancy Solis: Nothing to Disclose, Maria Orellana: Nothing to Disclose, Francisco Barrera: Nothing to Disclose, Sebastian Marciano: Nothing to Disclose, Adrián Gadano: Nothing to Disclose, Jorge Martínez: Nothing to Disclose, Maria Jose Acosta: Nothing to Disclose, Martin Tagle: Nothing to Disclose, Hugo Cedron: Nothing to Disclose, Ismael Yepes: Nothing to Disclose, Dalis Pérez: Nothing to Disclose, María-Fernanda SaavedraChacón: Nothing to Disclose, Samuel Perez: Nothing to Disclose, Ignacio García-Juárez: Nothing to Disclose, Orfanel Sebastian Pineda-Arzat: Nothing to Disclose, Liz Toapanta-Yanchapaxi: Nothing to Disclose, Aline Sorribas: Nothing to Disclose, Manuel Mendizabal: Gilead: Speaking and Teaching, Biosidus: Speaking and Teaching, Gador: Speaking and Teaching, Knight: Speaking and Teaching, Novo Nordisk: Advisor, Lorena Castro Solari: Nothing to Disclose, Loreto Aguilar Barría: Nothing to Disclose, Samantha Wu: Nothing to Disclose, Catalina Roa: Nothing to Disclose, Fabiana Nina: Nothing to Disclose, Estefanía Liza Baca: Nothing to Disclose, JAVIER DIAZ FERRER: Nothing to Disclose, Roberto Pérez Ravier: Nothing to Disclose, Maria Martinez: Nothing to Disclose, Natalie Vilcinskas: Nothing to Disclose, Nothing to Disclose, Daniza Alexandra Contreras: Nothing to Disclose, Daniela Simian: Nothing to Disclose, Juan Roblero: Nothing to Disclose, Pamela Gil: Nothing to Disclose, Arun Sanyal: Nothing to Disclose, Nothing to Disclose.

2427 | BIOLOGICAL AGE ACCELERATION FROM ROUTINE LABS CLASSIFIES ELASTOGRAPHY-MEASURED LIVER FIBROSIS AND DETECTS DISEASE MISSED BY FIB-4: A SURVEY-WEIGHTED NHANES ANALYSIS

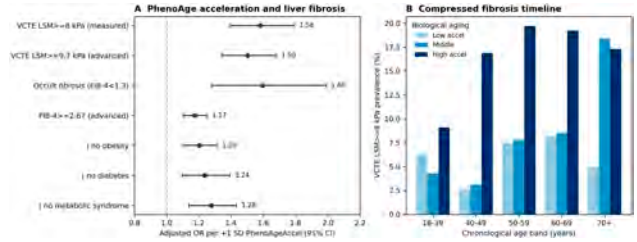
Harika Dadigiri Srinivas Venkatanarayanan[1] Jeril Lasington[2] Anas Al Mardini[3] Venkatesh Gondhi[2] Vinod Nookala[2], [1]UCF, [2]NYMC Saint Clare's and Saint Marys's Hospital, [3]NYMC, St Clare St Mary hospital

Background: Fibrosis stage drives mortality in chronic liver disease, yet routine risk tools (FIB-4) are age-centric and miss early disease. DNA-methylation aging clocks predict liver outcomes but need costly methylation absent from population data. Whether lab-derived phenotypic age acceleration (PhenoAgeAccel), computable from routine bloodwork, classifies liver fibrosis and adds to FIB-4 is unknown. **Methods:** ross-sectional NHANES 2005-2018 (5 cycles with C-reactive protein). Levine PhenoAge was computed from 9 routine labs; PhenoAgeAccel = residual of PhenoAge on chronological age. Primary outcome: vibration-controlled transient elastography (VCTE/FibroScan, 2017-2018) liver stiffness (LSM) > = 8 and > = 9.7 kPa (reliable scans only). Secondary: FIB-4 > = 2.67. Survey-weighted logistic regression with Taylor-linearised SE adjusted for age, sex, race/ethnicity, income, smoking, and alcohol; a metabolic model added BMI, diabetes, and hypertension. Sensitivity analyses used a non-hepatic PhenoAge (excluding hepatic markers), multiple imputation, and serology-based viral hepatitis exclusion. AI (ChatGPT/Claude) aided language only; all analysis and conclusions are the authors'. De-identified public data; IRB-exempt (45 CFR 46). **Results:** 26,771 adults had computable FIB-4 (representing ~216 million US adults); 4,461 had reliable VCTE. Per +1 SD PhenoAgeAccel, adjusted odds of measured fibrosis rose: LSM > = 8 kPa OR 1.58 (95% CI 1.39-1.79); LSM > = 9.7 OR 1.50 (1.34-1.68); FIB-4 > = 2.67 OR 1.17 (1.10-1.25); all p < 0.001 (p-trend < 0.001). Among low-risk adults (FIB-4 < 1.3), 7.5% had occult VCTE fibrosis; PhenoAgeAccel flagged it (OR 1.60, 1.28-1.99) and improved discrimination over FIB-4 (AUROC 0.60 to 0.68; delta-AUROC 0.081, 0.040-0.132; IDI 0.029). The FIB-4 > = 2.67 association was strongest in metabolically low-risk strata (no metabolic syndrome OR 1.28; no diabetes 1.24). Biologically older adults aged 40-49 had

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higher fibrosis prevalence (16.9%) than biologically younger adults aged > = 60 (5-8%). Inflammation (CRP) and glucose dominated component drivers; PhenoAgeAccel stayed associated beyond RDW and CRP (OR 1.41). Findings were unchanged with non-hepatic PhenoAge (OR 1.55) and multiple imputation. PhenoAgeAccel independently predicted all-cause mortality (HR 1.44 per SD; 2,731 deaths). Adjusting for BMI and diabetes attenuated the VCTE association, indicating partial metabolic mediation. **Conclusion:** Routine-laboratory biological age acceleration classifies gold-standard, elastography-measured liver fibrosis, detects fibrosis missed by FIB-4, and is strongest in metabolically low-risk adults, identifying aging as a fibrosis risk axis beyond traditional metabolic factors. PhenoAgeAccel is a free, scalable adjunct to FIB-4 for fibrosis risk stratification.



Disclosures: Harika Dadigiri: Nothing to Disclose, srinivas Venkatanarayanan: Nothing to Disclose, Jeril Lasington: Nothing to Disclose, Anas Al Mardini: Nothing to Disclose, Venkatesh Gondhi: Nothing to Disclose, vinod Nookala: Nothing to Disclose Juan Pablo Arab: Nothing to Disclose, Luis Díaz: Nothing to Disclose, Marco Arrese: Nothing to Disclose.

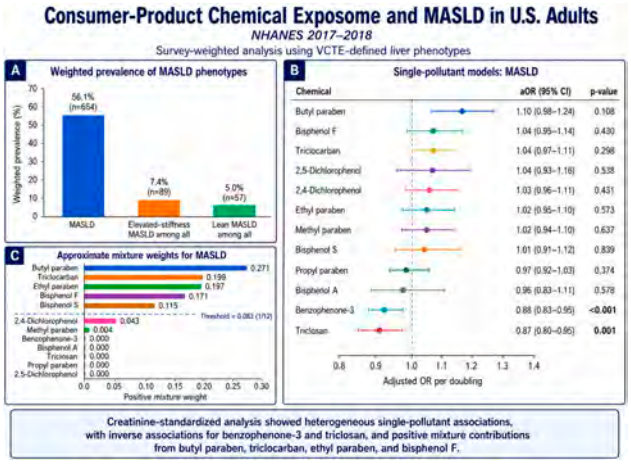
2428 | THE PERSONAL CARE CHEMICAL EXPOSOME AND MASLD IN U.S. ADULTS: A MULTI-POLLUTANT NHANES 2017–2018 ANALYSIS USING VCTE-DEFINED LIVER PHENOTYPES

Jagadish Koyi[1] Mounika Kotte[2] Digantkumar Patel[3] Pragathi Munnangi[4] Sri Ram Charan Gundapaneni[5] Serene Sara John[6] Hardik Dineshbhai Desai[7], [1]Integris Health, Oklahoma City, Oklahoma. USA. 73112, [2]Prime south consortium, Weslaco, Texas, USA,78596, [3]Springfield Clinic, Springfield, IL, USA, [4]BronxCare Health System , Bronx , New York - 10457, [5]UCF/HCA Florida Ocala Hospital, Ocala, Florida, United States, 34471, [6]Detroit medical center, Detroit, Michigan, 48201, [7]AB Plus Multispecialty Hospital, Ahmedabad, Gujarat, India

Background: Personal care and consumer-product chemicals (phenols, parabens, bisphenols, antimicrobials) are widely detected in the general population and may contribute to metabolic liver injury. However, their single-pollutant and combined mixture-level associations with metabolic dysfunction-associated steatotic liver disease (MASLD) particularly elevated-stiffness and lean MASLD phenotypes—remain insufficiently characterized. **Methods:** We analyzed adults aged ≥18 years from the National Health and Nutrition Examination Survey (NHANES) 2017–2018 with valid vibration-controlled transient elastography (VCTE), urinary phenol/paraben measurements, urinary creatinine, and eligible survey weights. Participants with viral hepatitis, significant alcohol intake, pregnancy, invalid VCTE examinations, or missing covariates were excluded. MASLD was defined as controlled attenuation parameter (CAP) ≥248 dB/m with ≥1 cardiometabolic risk factor. Elevated-stiffness MASLD was defined as MASLD with liver stiffness measurement (LSM) ≥8.0 kPa, and lean MASLD as MASLD with body mass index (BMI) <25 kg/m². Survey-weighted logistic regression estimated adjusted odds ratios (aORs) per doubling of creatinine-standardized urinary chemical concentration. **Results:** Among 1,132 adults, the weighted prevalence of MASLD was 56.1%, elevated-stiffness MASLD was 7.4%, and lean MASLD was 5.0%. In single-pollutant models, benzophenone-3 was inversely associated with MASLD (aOR 0.88 per doubling; 95% confidence interval [CI] 0.83–0.95; p < 0.001), as was triclosan (aOR 0.87; 95% CI 0.80–0.95; p = 0.001). Butyl paraben showed a positive but nonsignificant association with overall MASLD (aOR 1.10; 95% CI 0.98–1.24; p = 0.108), but was significantly associated with lean MASLD (aOR 1.31; 95% CI 1.07–1.62; p = 0.009). For elevated-stiffness MASLD, methyl paraben (aOR 1.22; 95% CI 1.06–1.40; p = 0.005) and propyl paraben (aOR 1.13; 95% CI 1.01–1.25; p = 0.025) were significantly associated with higher odds. Approximate mixture models demonstrated significant positive cumulative associations with MASLD (mixture odds ratio [OR] 2.03; 95% CI 1.26–3.27; p = 0.004), elevated-stiffness MASLD (mixture OR 3.99; 95% CI 1.57–10.14; p = 0.004), and lean MASLD (mixture OR 9.54; 95% CI 2.09–43.48; p = 0.004). The leading positive contributors to the MASLD mixture index were butyl paraben, triclocarban, ethyl paraben, bisphenol F, and bisphenol S. **Conclusion:** In this nationally representative NHANES analysis, creatinine-standardized consumer-product chemical mixtures were significantly associated with MASLD phenotypes, with particularly strong signals for elevated-stiffness and lean MASLD. Individual chemicals showed heterogeneous associations, including inverse associations for benzophenone-3 and triclosan with overall MASLD and positive paraben-related associations with elevated-stiffness or lean MASLD.

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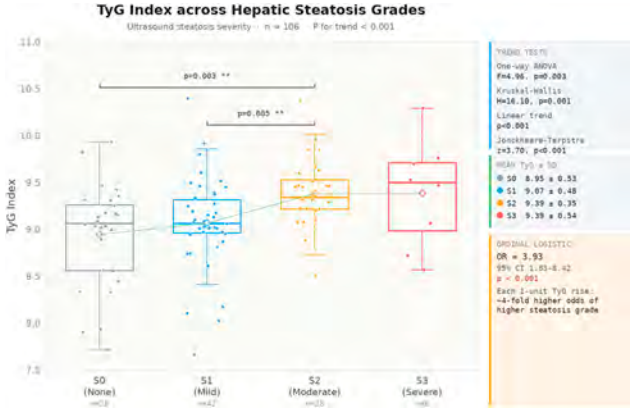


Disclosures: Jagadish Koyi: Nothing to Disclose, Mounika Kotte: Nothing to Disclose, Digantkumar Patel: Nothing to Disclose, Pragathi Munnangi: Nothing to Disclose, Sri Ram Charan Gundapaneni: Nothing to Disclose, Serene Sara John: Nothing to Disclose, Hardik Dineshbhai Desai: Nothing to Disclose.

2429 | THE TRIGLYCERIDE-GLUCOSE (TYG) INDEX AS A NON-INVASIVE BIOMARKER OF MASLD AND HEPATIC STEATOSIS SEVERITY IN A SOUTH ASIAN COHORT

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) spans a spectrum from simple steatosis to fibrosis. Existing diagnostic tools, including FibroScan and biopsy, are resource-intensive, limiting screening in low-resource settings. The triglyceride-glucose (TyG) index, a validated surrogate of insulin resistance, has emerged as a potential non-invasive biomarker of metabolic liver disease. We aimed to evaluate the diagnostic utility of the TyG index for MASLD and its relationship with the degree of hepatic steatosis severity. **Methods:** This cross-sectional study enrolled 106 adults at a tertiary care centre in northern India. The TyG index was calculated as ln(TG [mg/dL] × FBG [mg/dL] / 2). Hepatic steatosis was graded on ultrasound as S0 (none) to S3 (severe), and patients were classified into MASLD (n = 52) and non-MASLD (n = 54) groups per the 2023 multi-society Delphi consensus criteria. TyG across steatosis grades was compared using ANOVA, Kruskal-Wallis, and trend tests. Ordinal logistic regression evaluated the relationship between TyG and steatosis severity. ROC analysis, multivariable logistic regression, and Pearson/Spearman correlation were performed to identify the independent predictors and discriminative performance of TyG for MASLD. **Results:** TyG increased progressively across steatosis grades: S0 8.95 ± 0.53, S1 9.07 ± 0.48, S2 9.39 ± 0.35, S3 9.39 ± 0.54 (ANOVA $p = 0.003$; Kruskal-Wallis $p = 0.001$; P for trend < 0.001; Spearman $\rho = 0.354$, $p < 0.001$). On ordinal logistic regression, each 1-unit rise in TyG was associated with a 4-fold higher odds of a higher steatosis grade (OR = 3.93, 95% CI 1.83–8.42, $p < 0.001$), unchanged after age/sex adjustment. On multivariable logistic regression adjusting for hypertension, BMI, and HbA1c, TyG was the strongest independent predictor of MASLD (adjusted OR = 13.28, 95% CI 3.24–54.46, $p = 0.0003$); hypertension was the only other significant predictor (aOR = 5.77, $p = 0.0004$). Model fit was good (Nagelkerke $R^2 = 0.418$; Hosmer-Lemeshow $p = 0.494$). ROC analysis demonstrated good discriminative performance of TyG for MASLD (AUC 0.769, 95% CI 0.674–0.855, $p < 0.001$), with an optimal cut-off of 9.063 yielding sensitivity 86.5%, specificity 59.3%, NPV 82.1%, and accuracy 72.6%. **Conclusion:** TyG is significantly and independently associated with hepatic steatosis severity and is the strongest independent predictor of MASLD on multivariable analysis. TyG demonstrated good discriminative performance for MASLD (AUC 0.769) and, at a cut-off of 9.063, showed high sensitivity and NPV. These findings support its potential utility as a simple, non-invasive biomarker for MASLD screening and risk stratification in South Asian populations. External validation in larger, ethnically diverse cohorts is warranted.



Disclosures: Mihika Aggarwal: Nothing to Disclose, Akash Rawat: Nothing to Disclose, Drishtdeum Malik: Nothing to Disclose.

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2430 | CORRELATION OF FIB-4 INDEX WITH LIVER STIFFNESS MEASUREMENT ON VIBRATION-CONTROLLED TRANSIENT ELASTOGRAPHY IN PATIENTS WITH MASLD IN A SAFETY-NET HOSPITAL

Kathryn Thompson[1] Dominique Mosley[1] Lesley Miller[1], [1]Emory University School of Medicine

Background: The Fibrosis-4 (FIB-4) index is a validated non-invasive liver fibrosis assessment with high negative predictive value to rule out advanced fibrosis. The AASLD recommends using the FIB-4 index to stratify patients with MASLD to determine the need for further work-up and treatment. However, data suggests that the FIB-4 index may not be as reliable among subgroups of age and race. The aim of this study was to compare FIB-4 scores with liver stiffness measurement (LSM) on vibration-controlled transient elastography (VCTE) in patients with MASLD to determine if the FIB-4 index reliably predicts advanced fibrosis in this diverse, underserved patient population. **Methods:** A retrospective cohort analysis was conducted in 305 patients with MASLD who underwent VCTE from 01/01/2018-03/31/2024 at Grady Memorial Hospital in Atlanta, Georgia. Demographic, laboratory, and VCTE data were reviewed. Mean FIB-4 indices were calculated for all patients who had VCTE exams. We compared FIB-4 indices to LSM on VCTE to evaluate differences in FIB-4 indices based on sex, race/ethnicity (Other/Hispanic/Latino, Black/African American (AA), White/Caucasian), and age (< 40 y/o, 40-49 y/o, 50-59 y/o, 60-69 y/o, ≥ 70 y/o). **Results:** For all patients, the mean FIB-4 index increased with LSM on VCTE: 1.17 for F0-F1, 1.34 for F2, 1.66 for F3, and 2.82 for F4. Females had higher mean FIB-4 indices for F2 and F3 fibrosis compared to males (1.38 and 1.83 vs. 1.26 and 1.28) but males had a higher mean FIB-4 index for F4 fibrosis (3.26 vs. 2.50). Hispanic and White patients had similar rises in mean FIB-4 indices by LSM while AA patients had overall lower mean FIB-4 indices, especially for F3 and F4 fibrosis (1.32 and 2.57). Younger patients < 40 y/o had lower mean FIB-4 indices with highest mean FIB-4 index of 1.21 correlating with F3 fibrosis. On the contrary, older patients ≥ 70 y/o had higher mean FIB-4 indices, including for F0-F1 and F2 fibrosis (1.61 and 2.44). **Conclusion:** Overall, FIB-4 indices correlated with LSM but there were key differences in FIB-4 by gender, race, and age. Males had less FIB-4 elevation by LSM compared to females and even with F3 fibrosis, their mean FIB-4 index < 1.3 would have precluded secondary risk assessment for advanced fibrosis. Further, lower mean FIB-4 indices across all LSM in AA patients suggests that the severity of liver fibrosis is underpredicted with the FIB-4 index among AA patients in our study. Lastly, lower mean FIB-4 indices for younger patients and higher mean FIB-4 indices for older patients do not correlate with LSM. This aligns with current data that suggests the FIB-4 index is not as accurate in younger and older populations as alternative non-invasive fibrosis assessments to the FIB-4 index are recommended in younger patients and higher FIB-4 index thresholds are recommended in older patients.

FIB-4 (mean) by liver stiffness measurement (kPa)	F0-F1 (≤7.0 kPa)- minimal to mild fibrosis: 1.17 F2 (>7 kPa)- moderate fibrosis: 1.34 F3 (≥10 kPa)- advanced fibrosis: 1.66 F4 (≥14 kPa)- cirrhosis: 2.82
FIB-4 (mean) by liver stiffness measurement (kPa) based on gender	**Female (n=210):** F0-F1 (≤7.0 kPa)- minimal to mild fibrosis: 1.16 F2 (>7 kPa)- moderate fibrosis: 1.38 F3 (≥10 kPa)- advanced fibrosis: 1.83 F4 (≥14 kPa)- cirrhosis: 2.50 **Male (n=95):** F0-F1 (≤7.0 kPa)- minimal to mild fibrosis: 1.18 F2 (>7 kPa)- moderate fibrosis: 1.26 F3 (≥10 kPa)- advanced fibrosis: 1.28 F4 (≥14 kPa)- cirrhosis: 3.26
FIB-4 (mean) by liver stiffness measurement (kPa) based on race	**Other/Hispanic/Latino (n=143):** F0-F1 (≤7.0 kPa)- minimal to mild fibrosis: 1.09 F2 (>7 kPa)- moderate fibrosis: 1.17 F3 (≥10 kPa)- advanced fibrosis: 1.59 F4 (≥14 kPa)- cirrhosis: 3.04 **Black/African American (n=125):** F0-F1 (≤7.0 kPa)- minimal to mild fibrosis: 1.27 F2 (>7 kPa)- moderate fibrosis: 1.56 F3 (≥10 kPa)- advanced fibrosis: 1.32 F4 (≥14 kPa)- cirrhosis: 2.57 **White/Caucasian (n=27):** F0-F1 (≤7.0 kPa)- minimal to mild fibrosis: 1.27 F2 (>7 kPa)- moderate fibrosis: 1.19 F3 (≥10 kPa)- advanced fibrosis: 1.66 F4 (≥14 kPa)- cirrhosis: 2.96
FIB-4 (mean) by liver stiffness measurement (kPa) based on age	**<40 years-old (n=46):** F0-F1 (≤7.0 kPa)- minimal to mild fibrosis: 0.64 F2 (>7 kPa)- moderate fibrosis: 0.62 F3 (≥10 kPa)- advanced fibrosis: 1.21 F4 (≥14 kPa)- cirrhosis: 1.03 **40-49.99 years-old (n=83):** F0-F1 (≤7.0 kPa)- minimal to mild fibrosis: 1.21 F2 (>7 kPa)- moderate fibrosis: 1.03 F3 (≥10 kPa)- advanced fibrosis: 2.21 F4 (≥14 kPa)- cirrhosis: 2.47 **50-59.99 years-old (n=87):** F0-F1 (≤7.0 kPa)- minimal to mild fibrosis: 1.16 F2 (>7 kPa)- moderate fibrosis: 1.86 F3 (≥10 kPa)- advanced fibrosis: 1.10 F4 (≥14 kPa)- cirrhosis: 2.33 **60-69.99 years-old (n=68):** F0-F1 (≤7.0 kPa)- minimal to mild fibrosis: 1.50 F2 (>7 kPa)- moderate fibrosis: 1.54 F3 (≥10 kPa)- advanced fibrosis: 1.32 F4 (≥14 kPa)- cirrhosis: 3.43 **≥70 years-old (n=13):** F0-F1 (≤7.0 kPa)- minimal to mild fibrosis: 1.61 F2 (>7 kPa)- moderate fibrosis: 2.44 F3 (≥10 kPa)- advanced fibrosis: 2.76 F4 (≥14 kPa)- cirrhosis: 3.09

Table 1. Mean Fibrosis-4 indices (FIB-4) by liver stiffness measurement on vibration-controlled transient elastography based on gender, race, and age

Disclosures: Kathryn Thompson: Nothing to Disclose, Dominique Mosley: Nothing to Disclose, Lesley Miller: Gilead Sciences: Grant/Research Support, Cepheid: Grant/Research Support, AbbVie: Advisor.

2431 | DEVELOPMENT OF PREDICTIVE MODELS FOR HEPATOCELLULAR CARCINOMA IN CIRRHOTIC AND NON-CIRRHOTIC METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is an increasingly important cause of hepatocellular carcinoma (HCC). Current HCC surveillance is largely cirrhosis-based. However, approximately 39% of MASLD-HCC cases occur in non-cirrhotic patients. We aimed to identify factors associated with HCC in a North-West London MASLD population, and to derive HCC risk

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prediction models for overall and non-cirrhotic MASLD. **Methods:** We included consecutive MASLD patients with HCC, seen between 1st January 2014 and 31st December 2025 at Imperial College NHS Trust, London. Collected data included demographic, clinical, and biochemical factors 12-18 months before HCC diagnosis. A cohort of MASLD patients without HCC was age-matched. Univariate and multivariate binary logistic regression analyses were used to identify factors associated with HCC. Four prediction models were derived from age-matched and unmatched MASLD cohorts, including non-cirrhotic subcohorts, using 70: 30 derivation-validation splits. Model discrimination was assessed using area under the receiver operating characteristic curve (AUROC). **Results:** There were 219 HCC cases and 219 age-matched controls. Residual age imbalance persisted between these two cohorts. Sensitivity analyses used the full, unmatched control cohort of 656. HCC patients were more frequently male, older, and were more likely to have higher FIB-4 and cirrhosis, and MetALD. MASLD models incorporated combinations of male sex, age, cirrhosis, MetALD, statin use, and type 2 diabetes mellitus, while non-cirrhotic MASLD models incorporated male sex, age, MetALD, statin use, and platelet count. In sensitivity analysis of the age-matched non-cirrhotic MASLD cohort, higher FIB-4 was associated with HCC. The age-matched MASLD and non-cirrhotic MASLD models demonstrated AUROCs of 0.809 and 0.755, respectively, for predicting HCC in 12 months. The corresponding sensitivity analysis models demonstrated higher AUROCs of 0.901 and 0.884, respectively. **Conclusion:** We derived MASLD-HCC risk models using routinely available clinical variables, with acceptable-to-excellent discrimination in both overall and non-cirrhotic MASLD. These findings could support risk-based stratification studies beyond cirrhosis for identifying MASLD patients who may benefit from HCC surveillance.
Disclosures: Daniel Sanmuganathan: Nothing to Disclose, Prerana Vatsavayi: Nothing to Disclose, Michael Yee: Nothing to Disclose, Fernando Iorra: Nothing to Disclose, Shahid Khan: Nothing to Disclose, Mark Thursz: GSK: Consultant, Resolution Tx: Consultant, Intercept: Consultant, Galecto: Consultant, Durect: Consultant, Pinelopi Manousou: Nothing to Disclose.

2432 | DISCRIMINATIVE PERFORMANCE OF THE PREVENT CVD AND ASCVD RISK SCORE FOR HEPATIC STEATOSIS AND FIBROSIS COMPARED WITH FIB-4 SCORE

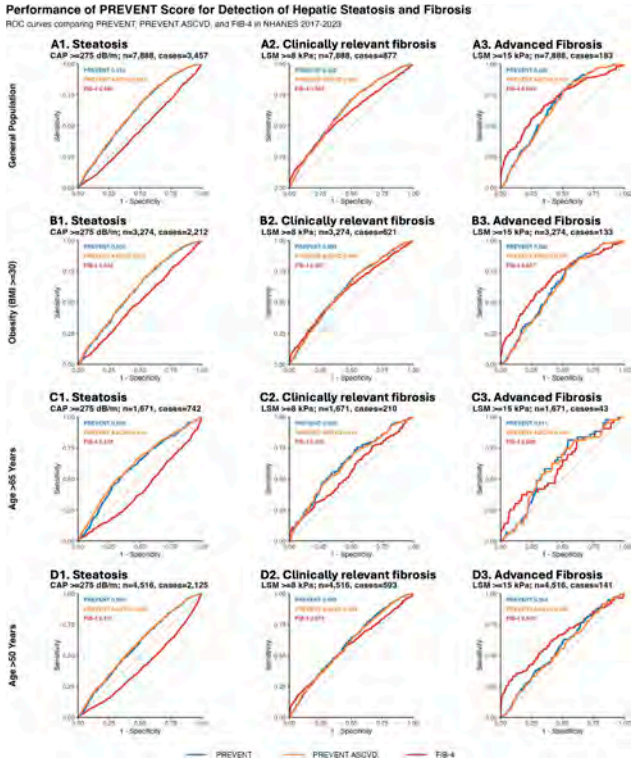
Anna Strauss[1] Timothy Davie[1] Jesse Fletcher[1] Kartik Dapke[2] Serena Brosten[1] Giovanni Roldan[3] Prowpanga Udompap[4], [1]Department of Medicine, University of Minnesota, [2]Department of Medicine, Saint Vincent Hospital, Worcester, MA, [3]Division of Gastroenterology, Hepatology and Nutrition, University of Minnesota, [4]Division of Gastroenterology, Minneapolis VA Medical Center

Background: PREVENT CVD and ASCVD equations are designed to predict cardiovascular risk. Their component variables closely mirror the cardiometabolic drivers of metabolic dysfunction-associated steatotic liver disease (MASLD). Given its widespread use in primary care, PREVENT CVD and/or ASCVD could serve as an opportunistic tool to increase MASLD awareness and enhance risk stratification alongside the recommended FIB-4 index. We evaluated the discriminative performance of PREVENT for hepatic steatosis (HS) and fibrosis in a nationally representative cohort. **Methods:** Using the data from National Health and Nutrition Examination Survey (NHANES) 2017–2023, adults aged 30 to 79 were included. PREVENT CVD, PREVENT ASCVD, and FIB-4 scores were calculated. HS was defined as controlled attenuation parameter $\geq$275 dB/m, clinically relevant fibrosis (CRF) as liver stiffness measurement (LSM) $\geq$8 kPa, and advanced fibrosis (AF) as LSM $\geq$15 kPa. Diagnostic performance was assessed using AUROC analyses, sensitivity, and specificity. Subgroup analyses included BMI $\geq$30 and age $\geq$50 and $\geq$65 years. Multivariable logistic regression estimated odds ratios per 5% PREVENT increment within cardiometabolic subgroups. **Results:** Among 8,969 adults representing 148.6 million (M) U.S. adults (mean age 52.2 years; 50.4% women; mean BMI 29.8 kg/m^2), 7,888 had complete data: 3,457 with HS, 877 with CRF, and 183 with AF. For detection of HS, PREVENT CVD and ASCVD outperformed FIB-4 in the overall cohort (AUROC: 0.616 and 0.622 vs. 0.468), especially among adults aged $\geq$65 years (0.599 and 0.616 vs. 0.418). For CRF, PREVENT CVD demonstrated moderate discrimination superior to FIB-4 in the overall cohort (0.632 vs. 0.592), obesity subgroup (0.609 vs. 0.557), and adults aged $\geq$65 years (0.626 vs. 0.555). For AF, FIB-4 had the highest discrimination in the overall cohort (0.699), compared to PREVENT CVD and ASCVD (0.663, 0.654). At PREVENT CVD thresholds of $\geq$10% and $\geq$20%, specificity for CRF was 80.6% and 95.3%, respectively. Also, each 5-percentage-point PREVENT CVD increase was associated with higher odds of AF in obesity (OR 1.29; $p<0.001$), hypertension (OR 1.18; $p=0.006$), and ALT >40 U/L (OR 1.62; $p=0.003$), but not diabetes (OR 1.07; $p=0.48$). **Conclusion:** The PREVENT CVD and ASCVD risk scores outperform the FIB-4 index in predicting HS and demonstrates comparable or modestly superior discrimination for CRF, particularly in older adults and those with obesity. FIB-4 retained an advantage for AF. Because PREVENT CVD and ASCVD risk scores are already established in primary care cardiovascular workflows, an elevated score may serve as an opportunistic signal

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to prompt hepatic evaluation and risk stratification.



Disclosures: Anna Strauss: Nothing to Disclose, Timothy Davie: Nothing to Disclose, Jesse Fletcher: Nothing to Disclose, Kartik Dapke: Nothing to Disclose, Serena Brosten: Nothing to Disclose, Giovanni Roldan: Nothing to Disclose, Prowpanga Udompap: Nothing to Disclose.

2433 | TREATED HYPOTHYROIDISM AS A DISEASE MODIFIER IN MASLD: HEPATIC PROGRESSION, DECOMPENSATION, AND MORTALITY IN A PROPENSITY SCORE–MATCHED COHORT ANALYSIS

Archana Salek[1] Jashanveer Johal[1] Bianca Patel[1] Mahmoud Al-Bataineh[1] Brandon Cunha[1] Abdallah Hussein[1] Jason Hyman[2] Yecheskel Schneider[1], [1]Virtua Health, [2]Einstein Medical Center, Philadelphia

Background: Hypothyroidism impairs hepatic fatty acid oxidation and promotes lipogenesis through reduced thyroid hormone receptor-β (THRβ) signaling, the same pathway targeted by resmetirom in MASLD. However, the independent effect of hypothyroidism on MASLD progression remains poorly defined, confounded by coexisting metabolic disease. We evaluated whether treated hypothyroidism is associated with accelerated hepatic progression in MASLD. **Methods:** We performed a propensity score–matched retrospective cohort study using the TriNetX Global Collaborative Network (191.9 million patients). Cohort 1 included adults with MASLD (K76.0/K75.81) and hypothyroidism (E03.8, E03.9, or E06.3) treated with levothyroxine after MASLD diagnosis. Cohort 2 included MASLD patients without thyroid disease. Patients with prior cirrhosis, hepatocellular carcinoma (HCC), chronic viral hepatitis, alcoholic liver disease, or thyroid malignancy were excluded. After 1: 1 propensity matching, 14,039 patients remained in each cohort with 6–60 months follow-up. Outcomes included incident cirrhosis, ascites, hepatic encephalopathy (HE), HCC, AST/ALT normalization, inpatient utilization, and all-cause mortality. **Results:** Treated hypothyroidism was associated with increased risk of incident cirrhosis (HR 1.62, 95% CI 1.30–2.04; $p < 0.001$), with cirrhosis-free survival of 93.4% in the hypothyroid cohort versus 97.1% in control cohort at study end, ascites (HR 1.31, 95% CI 1.09–1.59; $p = 0.005$), and HE (HR 1.50, 95% CI 1.01–2.23; $p = 0.045$). HCC incidence trended higher but was not significant (HR 1.44, 95% CI 0.66–3.11; $p = 0.35$). AST/ALT normalization was delayed in the hypothyroid cohort (HR 1.22, 95% CI 1.07–1.40; $p = 0.004$), with median time to normalization of 1,627 versus 1,219 days. All-cause mortality was higher in the hypothyroid cohort (5.5% vs. 4.4%; HR 1.53, 95% CI 1.37–1.70; $p < 0.001$). Despite worse hepatic outcomes, inpatient encounter burden was lower in the hypothyroid cohort. **Conclusion:** In this large propensity-matched real-world study, treated hypothyroidism was independently associated with accelerated hepatic progression in MASLD, including higher rates of cirrhosis, hepatic decompensation, delayed biochemical recovery, and increased mortality despite levothyroxine therapy. Persistent hepatic risk despite levothyroxine therapy suggests thyroid hormone replacement alone may not fully reverse THRβ-mediated hepatic dysregulation in MASLD. These findings support hypothyroidism as an independent modifier of MASLD progression and reinforce the clinical relevance of THRβ signaling in MASLD pathogenesis and emerging targeted therapies.

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2434 | IDENTIFICATION OF BIOMARKERS IN HUMAN PLASMA EXOSOMES WITH RELEVANCE TO METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD)

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH) are common chronic liver diseases characterized by liver steatosis, inflammation, and fibrosis. There are limited non-invasive biomarkers available for early diagnosis or tracking the disease progression towards fibrosis and hepatocellular carcinoma. In this study, we have characterized biomarkers from plasma samples in MASLD/MASH patients. **Methods:** The individuals were segregated into 5 groups based on disease prognosis assessed by Vibration-Controlled Transient Elastography (VCTE) or Fibroscan: Healthy control (N), fibrosis stage 0-1 (F1), fibrosis stage 2 (F2), fibrosis stage 3 (F3), and fibrosis stage 4 (F4). Each group had 5 samples, with mean ages of 35, 59.8, 52.8, 51.8, and 67.6 years. The plasma was separated from whole blood, and exosomes were isolated by ultracentrifugation. Exosomal miRNAs were isolated and sequenced, and exosomal proteins were analyzed by non-targeted proteomics. Highly significant miRNAs and proteins were identified. The data were analyzed statistically by one-way ANOVA. **Results:** miRNA studies revealed that miR-126-5p, miR-99b-5p, and miR-361-5p were reduced in the F1–F4 groups compared with the N group. miR-1307-3p, miR-3138, and miR-30C-1-3p levels were induced in the F3 group compared to normal, early, and late stages of fibrosis. miR-339-3p levels were increased in the F3 group compared to F1 or F2 groups. In the proteomics studies, ficolin-3 (FCN3) and inter-alpha-trypsin inhibitor heavy chain H4 (ITIH4) were elevated in the F2 group compared with the normal, early, and late fibrosis stages. Smooth muscle alpha actin (ACTG2) and beta actin (ACTB) were prominently increased in the F1 group compared to the normal group and declined gradually towards later stages of fibrosis (F3, F4 groups). **Conclusion:** Our studies have identified a few miRNAs that are changed in MASLD/MASH. In particular, plasma miR-1307-3p, miR-3138, and miR-30C-1-3p are increased in the F3 group. Also, plasma exosomal proteins FCN3 and ITIH4 are increased in the F2 group. These miRNA and protein markers may have potential for non-invasive diagnosis of MASH and tracking fibrotic stages in MASLD. Further studies will help determine the significance of the changes in these biomarkers.

	Normal (N)	Fibrosis stage – 1 (F1)	Fibrosis stage – 2 (F2)	Fibrosis stage – 3 (F3)	Fibrosis stage – 4 (F4)	p value
age	35 (±7.26)	59.8 (±13.71)	52.8 (±5.11)	51.8 (±19.67)	67.6 (±8.87)	
miRNAs (counts from miRNA analysis)						
miR-126-5p	51572.80 (±1882.61)	9021.13 (±1259.63)	6804.49 (±1130.85)	6573.52 (±2249.73)	6115.71 (±1418.31)	N vs F2, N vs F3, N vs F4 ($p \leq 0.001$); F1 vs F4 ($p \leq 0.001$)
miR-99b-5p	243.97 (±105.29)	108.94 (±115.56)	115.56 (±34.38)	39.73 (±40.93)	69.95 (±53.42)	N vs F3 ($p \leq 0.005$); F1 vs F4 ($p \leq 0.05$)
miR-361-5p	180.84 (±112.07)	68.57 (±42.68)	58.41 (±53.86)	59.06 (±42.47)	46.56 (±44.82)	N vs F2, N vs F4 ($p \leq 0.05$)
miR-1307-3p	77.11 (±77.51)	258.57 (±98.67)	241.17 (±99.80)	364.88 (±227.65)	162.14 (±172.06)	N vs F3 ($p \leq 0.05$)
miR-3138	0 (±0)	7.914 (±17.69)	0 (±0)	28.26 (±24.82)	0 (±0)	N vs F3, F2 vs F3, F3 vs F4 ($p \leq 0.05$)
miR-30C-1-3p	11.38 (±25.45)	12.21 (±18.48)	0.42 (±0.89)	58.51 (±36.51)	24.44 (±35.13)	F2 vs F3 ($p \leq 0.05$)
Proteins (spectral counts from proteomics)						
FCN3	15.51 (±9.72)	6.92 (±3.51)	39.59 (±34.59)	12.00 (±6.06)	13.60 (±6.64)	F1 vs F2 ($p \leq 0.005$); N vs F2, F2 vs F3, F3 vs F4 ($p \leq 0.05$)
ACTB	3.43 (±3.50)	30.90 (±27.39)	9.00 (±3.23)	3.19 (±1.75)	4.23 (±3.05)	N vs F1, F1 vs F2, F1 vs F4 ($p \leq 0.05$)
ACTG2	2.81 (±1.64)	19.75 (±15.46)	9.04 (±3.53)	5.89 (±1.80)	3.80 (±2.19)	N vs F1, F1 vs F3, F1 vs F4 ($p \leq 0.05$)
ITIH4	2.94 (±1.49)	2.07 (±1.92)	5.70 (±2.76)	1.16 (±0.75)	1.10 (±1.24)	F1 vs F2 ($p \leq 0.05$); F2 vs F3, F2 vs F4 ($p \leq 0.005$)

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2435 | BRIDGING THE DIAGNOSTIC GAP IN MASH: REAL-WORLD EVIDENCE OF UNDERDIAGNOSIS IN THE US

Jörn Schattenberg[1] Zuleika Aponte Torres[2] Lu Zhang[2] Katrine Prier Lindvig[3] Mireia Raluy[4] Mark Yates[4] Faizan Mazhar[4] Claudio Sartini[2] Zobair Younossi[5], [1]Saarland University Medical Center Homburg, [2]Boehringer Ingelheim, [3]Evido Health, [4]Thermo Fisher Scientific, [5]The Global NASH/MASH Council

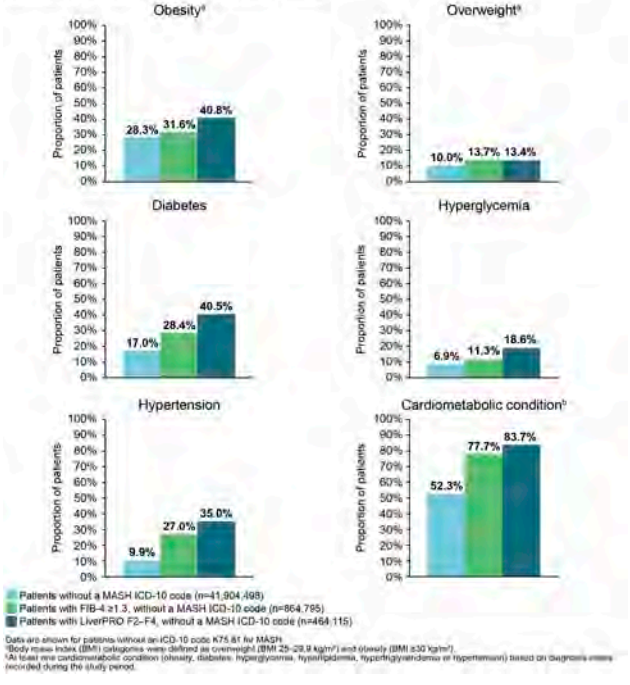
Background: Low prevalence of metabolic dysfunction–associated steatohepatitis (MASH) International Classification of Diseases (ICD-10) codes in real-world administrative claims databases indicate its burden may be inadequately captured, particularly with respect to fibrosis stage. Non-invasive test (NIT) screening tools such as Fibrosis-4 Index (FIB-4) and LiverPRO use routinely collected lab and patient data to assess fibrosis risk and may enable risk stratification in people at risk for developing MASH. **Methods:** This retrospective observational study used electronic health record and claims data from the Optum® Market Clarity (OMC) US database (January 1, 2021–December 31, 2023). Adults aged $\geq$18 years, with $\geq$1 healthcare encounter during the study period were included; those with non-MASH liver disease etiologies were excluded. Patients were classified as diagnosed with MASH (ICD-10 code K75.81) or at risk for MASH using combinations of the ICD-10 code for metabolic dysfunction–associated steatotic liver diseases (MASLD [K76.0]); FIB-4 scores $\geq$1.3 estimating moderate-to-advanced liver fibrosis risk; and/or LiverPRO-defined F2–4 fibrosis risk. NITs, age and same-day lab

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measurements were required for calculations. Suspected metabolic syndrome (MetS) was defined as presence of ≥3 cardiometabolic conditions (obesity, diabetes, hyperglycemia, hyperlipidemia, hypertriglyceridemia, hypertension), based on ICD-10 codes during the study period. **Results:** Of 42,596,381 patients in the study population, 3,409,957 (8%) and 4,734,642 (11%) had sufficient data to calculate FIB-4 and LiverPRO, respectively. Among these, 814,276 (24%) had FIB-4 ≥1.3 and no MASLD/MASH codes, and 422,608 (9%) had LiverPRO-defined F2–4 fibrosis without MASLD/MASH codes, indicating a substantial population with elevated fibrosis risk but no recorded diagnosis. Among patients with a MASLD or MASH code, 3% and 46% respectively, had FIB-4 ≥1.3; rates of suspected MetS were 72% and 86%. Among patients without MASLD/MASH codes, 43% and 55% of those with FIB-4 ≥1.3 and LiverPRO F2–4, respectively, had suspected MetS. In patients without a MASH code, conditions associated with MASH risk were more prevalent in those with signs of fibrosis by FIB-4 or LiverPRO (Figure). Advanced evaluation procedures were infrequently used among patients at risk for MASH, despite a high burden of cardiometabolic conditions. **Conclusion:** Real-world data indicate a substantial gap between MASH diagnoses and fibrosis risk identified using NITs, suggesting underdiagnosis in routine clinical practice. A sizeable proportion of patients without MASLD/MASH codes showed elevated fibrosis risk by NITs, many of whom had cardiometabolic conditions consistent with MASH risk. Targeted use of NIT screening in patients with metabolic risk factors or MASLD may improve identification of patients at risk for MASH, though broader application is limited by data availability.

Prevalence of cardiometabolic conditions indicative of MASH risk among patients without a MASH ICD-10 code



Data are shown for patients without an ICD-10 code K75.81 for MASH.
[a]Body mass index (BMI) categories were defined as overweight (BMI 25–29.9 kg/m²) and obesity (BMI ≥30 kg/m²).
[b]At least one cardiometabolic condition (obesity, diabetes, hyperglycemia, hyperlipidemia, hypertriglyceridemia or hypertension) based on diagnosis codes recorded during the study period.

Disclosures: Jörn Schattenberg: Akero: Consultant, 89Bio: Consultant, Boehringer Ingelheim: Consultant, Ipsen: Consultant, Inventiva Pharma: Consultant, Madrigal: Consultant, Northsea Therapeutics: Consultant, Novo Nordisk: Consultant, Roche: Consultant, Siemens Healthineers: Consultant, Boehringer Ingelheim: Advisor, AGED diagnostics: Stock – privately held company, Hepta Bio: Stock – privately held company, Novo Nordisk: Speaking and Teaching, Madrigal: Stock - publicly traded company, MedPublico GmbH: Speaking and Teaching, Eli Lilly: Advisor, Altimmune: Consultant, Astra Zeneca: Consultant, Gilead Science: Consultant, Merck: Consultant, MSD Sharp & Dohme GmbH: Consultant, AbbVie: Advisor, Zuleika Aponte Torres: Boehringer Ingelheim: Employee, Lu Zhang: Nothing to Disclose, Katrine Prier Lindvig: Nothing to Disclose, Mireia Raluy: Nothing to Disclose, Mark Yates: Nothing to Disclose, Faizan Mazhar: Nothing to Disclose, Claudio Sartini: Nothing to Disclose, Zobair Younossi: Zobair M. Younossi is a consultant or has received research: Consultant, madrigal: Grant/Research Support, Siemens: Research funding, GSK: Consultant, BI: Consultant, Sanofi: Research funding.

2436 | NIMIT-AI: A LONGITUDINAL DEEP LEARNING FRAMEWORK FOR NON-INVASIVE MASLD FIBROSIS TRIAGE USING ROUTINE ELECTRONIC HEALTH RECORD TRAJECTORIES

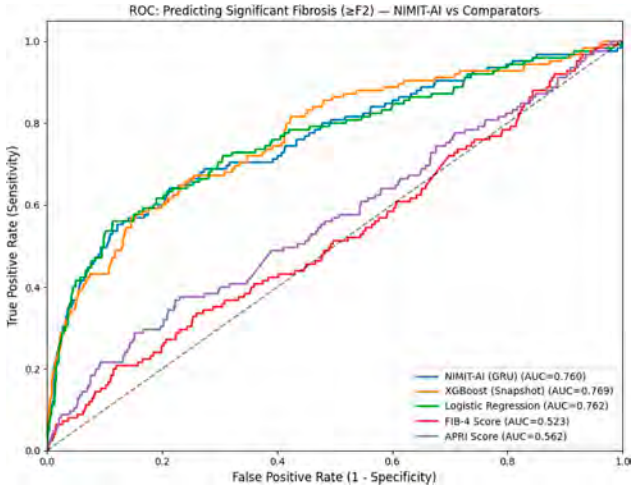
Teerachod Suwanwilaikul[1] Tawesak Tanwandee[2] Supot Nimanong[2], [1]Faculty of Medicine Siriraj Hospital, Mahidol University, [2]Siriraj Hospital/Mahidol University

Background: Every year, thousands of patients with MASLD leave outpatient clinics without a clear fibrosis verdict because the triage tools we use cannot read it properly. Current triage relies on FIB-4, static serum indices with positive predictive values of 20 to 60% that regularly fail to justify definitive management without confirmatory elastography. More fundamentally, FIB-4 requires a full laboratory set at every visit; a single missing platelet count or transaminase renders the score uncomputable. This is a failure that recurs routinely in clinical practice. We developed NIMIT-AI (Neural Inference for Metabolic-liver Integrated Trajectories), a GRU-based deep learning model that learns fibrosis risk from serial routine laboratory results from years of follow-up, enabling reliable one-step triage without elastography dependence. **Methods:** NIMIT-AI was trained on three consecutive CDC NHANES cycles (2013 to 2018; n = 5,651 elastography-labelled adults). Fibrosis was staged per 2024 EASL and Baveno VII thresholds: F0–F1 (<7.0 kPa), F2 (8.0 to 10.0 kPa), and F3–F4 cACLD (≥10.0 kPa), with a 1.0 kPa

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censoring buffer applied during training to sharpen inter-class separation. Inputs comprised 18 features across four clinical domains: hepatology laboratories (AST, ALT, GGT, platelets, albumin, total bilirubin), metabolic markers (HbA1c, BMI, lipid panel), comorbidities (T2DM, CKD, OSA), and medication exposures (SGLT2i, GLP-1RA, statins). Binary input masking distinguished true missing values from observed zeros, preserving model integrity under real-world data sparsity and irregular follow-up intervals, allowing our model to operate natively on incomplete visit records without imputation. Performance was benchmarked against FIB-4, APRI, XGBoost, and logistic regression for identification of significant fibrosis ($F \geq 2$). **Results:** NIMIT-AI achieved AUROC 0.76 for significant fibrosis ($F \geq 2$), outperforming FIB-4 (0.52) and APRI (0.56), with a sensitivity of 81% compared to 69% for FIB-4. Discrimination for cACLD (F3–F4) from earlier fibrosis stages reached AUROC 0.78. SHAP analysis identified longitudinal AST-to-platelet dynamics and declining albumin trajectory as the strongest predictors of stage transition, findings consistent with established portal hypertension physiology. **Conclusion:** NIMIT-AI offers a practical and scalable one-step triage alternative for MASLD that outperforms conventional non-invasive indices, with particular relevance in resource-constrained settings where elastography access remains limited. Critically, unlike FIB-4, which yields no output whenever a required value is absent, NIMIT-AI processes incomplete records by design, ensuring every clinical encounter contributes to risk estimation rather than being discarded. This native tolerance for missing data makes it directly compatible with real-world EHR practice.



Disclosures: Teerachod Suwanwilaikul: Nothing to Disclose, Tawesak Tanwandee: Roche: Grant/Research Support, MSD: Grant/Research Support, Altimune: Grant/Research Support, Gilead: Grant/Research Support, Vir Biotech: Grant/Research Support, Supot Nimanong: Nothing to Disclose.

★ 2437 | HIGH PREVALENCE AND SUBOPTIMAL FIB-4 SENSITIVITY SUPPORT DIRECT VCTE REFERRAL FOR DIABETIC PATIENTS WITH MASLD

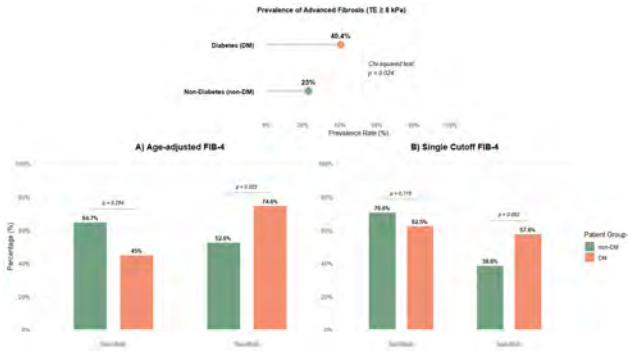
Pimsiri Sripongpun[1] Chitchai Rattananukrom[2] Huttakan Navadurong[3] Kessarin Thanapirom[4] Kanokwan Pinyopornpanish[5] Supot Nimanong[6] Apichat Kaewdech[1] Sakkarin Chirapongsathorn[7] Chalermrat Bunchorntavakul[8] Chanunta Hongthanakorn[9] Sith Siramolpiwat[10] Abhasnee Sobhonslidsuk[11] Sarita Ratana-Amornpin[11] Watcharasak Chotiyaputta[6] Sombat Treeprasertsuk[4] Teerha Piratvisuth[1], [1]Prince of Songkla University, [2]Khon Kaen University, [3]Navamindradhiraj University, [4]Chulalongkorn University, [5]Chiang Mai University, [6]Siriraj Hospital, [7]Phramongkutklao Hospital and College of Medicine, [8]Rajavithi Hospital, [9]Bhumibol Adulyadej Hospital, [10]Thammasart University, [11]Ramathibodi Hospital

Background: Current guidelines recommend screening for advanced fibrosis (AF) in patients at risk of metabolic dysfunction-associated steatotic liver disease (MASLD) using an age-adjusted FIB-4, followed by vibration-controlled transient elastography (VCTE) for those above the threshold. Conversely, the recent AGA clinical care pathway suggests direct VCTE referral for patients with diabetes (DM) due to a higher baseline risk. The applicability of this direct-referral strategy remains to be validated. This study evaluated advanced fibrosis prevalence and compared age-adjusted versus single-cutoff FIB-4 strategies among Thai MASLD patients with and without DM. **Methods:** This study is a preliminary analysis of the ongoing, multicenter Gastroenterological Association of Thailand (GAT) Fibroscan registry, focusing on patients who underwent VCTE for MASLD across six tertiary academic centers between 2016 and 2026. Those with unreliable VCTE results or aminotransferase levels >200 IU/mL were excluded. Advanced fibrosis (AF) was defined as a liver stiffness measurement ≥ 8 kPa. Two FIB-4 triage strategies were evaluated: a single-cutoff approach (FIB-4 >1.3 across all ages) and an age-adjusted strategy (FIB-4 >1.3 for patients <65 years and >2.0 for those ≥ 65 years). **Results:** Of 359 patients evaluated, 302 were eligible. The prevalence of AF was significantly higher in the DM than the non-DM group (35.7% vs. 19.8%, $p = 0.006$). In a subset of 173 patients (99 DM, 74 non-DM) with concurrent laboratory data to calculate FIB-4, the AF prevalence was 40.4% vs. 23.0% ($p = 0.024$). In this subset, the age-adjusted FIB-4 strategy demonstrated

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lower sensitivity (45.0% vs. 64.7%, p = 0.284) but significantly higher specificity (74.6% vs. 52.6%, p = 0.023) in patients with DM compared to non-DM. Conversely, the single-cutoff approach yielded comparable sensitivity between groups (62.5% vs. 70.6%, p = 0.778), with a trend toward higher specificity in the DM cohort as shown in Figure. Notably, both strategies, particularly the age-adjusted approach, missed a substantial proportion of AF cases in patients with DM due to compromised sensitivity. **Conclusion:** Thai MASLD patients with DM exhibit a notably high prevalence of AF. Both FIB-4 strategies demonstrate suboptimal sensitivity in the diabetic cohort, potentially underestimating the true disease burden. These findings corroborate the AGA pathway suggesting that direct VCTE assessment may optimize case-finding in DM. However, caution is warranted as this registry-based cohort inherits potential selection bias by including only patients referred for VCTE. Further validation in primary care cohorts is required. Notably, recruitment for this multi-center registry remains active, with a larger sample size anticipated for future definitive validation.



Disclosures: Pimsiri Sripongpun: Novo Nordisk: Speaking and Teaching, Takeda: Speaking and Teaching, Nestle: Speaking and Teaching, Zuellig Pharma: Speaking and Teaching, Thai Meiji: Speaking and Teaching, Thai Otsuka: Speaking and Teaching, Chitchai Rattananukrom: Nothing to Disclose, Huttakan Navadurong: Nothing to Disclose, Kessarin Thanapirom: Nothing to Disclose, Kanokwan Pinyopornpanish: Nothing to Disclose, Supot Nimanong: Nothing to Disclose, Apichat Kaewdech: Nothing to Disclose, Sakkarin Chirapongsathorn: Nothing to Disclose, Chalermrat Bunchorntavakul: Nothing to Disclose, Chanunta Hongthanakorn: Nothing to Disclose, Sith Siramolpiwat: Nothing to Disclose, Abhasnee Sobhonslidsuk: Nothing to Disclose, Sarita Ratana-Amornpin: Nothing to Disclose, Watcharasak Chotiyaputta: Nothing to Disclose, Sombat Treeprasertsuk: Nothing to Disclose, Teerha Piratvisuth: Nothing to Disclose.

2438 | LOW-RISK ADVANCED FIBROSIS BY TRANSIENT VIBRATION ELASTOGRAPHY (TVE FIBROSCAN 502 ≤ 8 KPAS) SCORE COMPARED TO FIB-4 SCORE, 2D-SHEARWAVE ELASTOGRAPHY SUPERSONIC (2D-SWE) AND LIVER BIOPSY: REAL WORD DATA WITH SOBERING RESULTS

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Background: AASLD Guidelines have been published 2024 (1) concerning the estimate of fibrosis severity based on the combination of blood based fibrosis using FIB-4 or NFS scores along with LSM with TVE. Blood bases fibrosis scores generate three groups of pts; low, intermediate, and high risk, and along with TVE LSM score, predict actual liver fibrosis. LSM TVE ≤ 8 are predictive of non-advanced fibrosis, and when used in conjunction with FIB-4 score predicts either F0-F1 fibrosis or requires follow up versus liver biopsy (1). Fibroscan LSM measurements do not allow real time US and concurrent TVE imaging. 2D-SWE allows for real time, concurrent US imaging and a 2D-SWE image that the operator can readily accept or reject using Q-Box tool to ensure all data is at least 90% reliable. Due to the ability of SSI to generate SWE with reliable data, we speculated that this would lead to improved concurrence of FIB-4 risk stratrification to LSM and liver biopsy. **Methods:** Retropsective review of consecutive pts that underwent outpt in office FIBROSCAN 502 TVE followed immediately by SSI 2D-SWE from 10/10/2023 to 05/17/2026. Pts were excluded if TVE was unattainable or unreliable (IQR/M > 30%). Pts who underwent multiple studies during the review are included only once (their first US imaging exam). Demographic data (age, gender, BMI), PMH (HTN, DM, ETOH intake, Smoking Hx, Hepatitis C/B status), Lab data (ast/alt, albumin, Plt Ct) within 90 days of US exam and prior CT/MRI/US imaging was recorded. Only pts with low risk TVE LSM ≤ 8 are included in this analysis to determine the accuracy TVE LSM at truly predicting F01-F1 fibrosis. Low risk TVE LSM measurements were compared to FIB-4 risk groups (low ≤ 1.3, intermediate > 1.3 to 2.67, and high > 2.67), SSI 2D-SWE LSM [with ≤ 7.1 kPas used for F0-F1 fibrosis cutoff (3)], and liver biopsy. **Results:** A total of 602 pts were seen over the study period. 250 had TVE ≤ 8 kPas, their mean age 58.4+/-9.5 yrs, 92 male: 158 females, BMI mean 30.7+/-5.3, DM Type 2 73, Type 1 2, HTN 107. FIB-4 low risk group was 55 pts, intermediate 27, high risk 14 and not obtained 154. 2D-SWE was not done in 5 pts. Recent Liver Bx were obtained in 30 pts. Of the 55 patients in the low risk TVE

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group and with low risk FIB-4 scores, SWE agreed with F0-F1 fibrosis in 83.6%. In the FIB-4 intermediate group, SWE concurrence noted in 77.8%, in the high-risk FIB-4 group, SWE concurrence in only 35.7%, and for the not done FIB-4 patients 70.8%. In only 14/30 (46.7%) pts, the liver bx F0-F1 severity concured with a TVE ≤ 8 kPas score. 16 pts overall in the low risk TVE group had a liver bx showing ≥ F2 fibrosis: 10 F2, 2 F3, and 4 F4 fibrosis. 6/6 (100%) of the pts with F3 or F4 fibrosis were properly predicted as having advanced fibrosis by 2D-SWE and 70% (7/10) for F2. **Conclusion:** Fibroscan 502 TVE scores ≤ 8 that are not in concurrence a low risk FIB-4 score warrants further investigation with a more accurate fibrosis severity overall generated from SSI 2D-SWE evaluation which was confirmed by liver bx data.

Disclosures: Allan Weston: Nothing to Disclose, Kimberly Wood: Nothing to Disclose, Jennifer Rickman: Nothing to Disclose.

2439 | UNSUPERVISED CLINICAL CLUSTERING IDENTIFIES A GUT–LIVER IGA IMMUNE CLUSTER WITH HIGH RISK OF LIVER-RELATED EVENTS IN MASLD

Takefumi Kimura[1] Shun-Ichi Wakabayashi[1] Takuro Uchida[2] Naoki Tanaka[1], [1]Shinshu University School of Medicine, [2]Oita University

Background: MASLD is clinically heterogeneous, and fibrosis stage alone does not fully explain liver-related event (LRE) risk. We aimed to use unsupervised clinical clustering to identify prognostically relevant MASLD clusters and characterize IgA-associated immune mechanisms linked to disease progression. **Methods:** We performed unsupervised clustering using 51 baseline clinical and biochemical variables in a biopsy-proven MASLD discovery cohort (n = 349). Histological variables and outcome data were excluded from clustering. Cluster reproducibility was assessed by applying the same clustering framework to an independent multicenter validation cohort (n = 272), and phenotypic validation was performed in an internal VCTE cohort (n = 287). LREs were defined as hepatocellular carcinoma, grade ≥ II hepatic encephalopathy, ascites requiring hospitalization, or varices requiring intervention. IgA-related mechanisms were investigated using hepatic qPCR, spatial transcriptomics, single-cell RNA sequencing, liver and colonic immunohistochemistry, serum IgA subclass analyses, and serum EndoCAb IgG. **Results:** Variational Bayesian Gaussian mixture modeling identified four clinically distinct MASLD clusters. Among them, Cluster 2 showed the highest 5-year cumulative incidence of LREs (24.0%; 95% CI, 14.8%–37.4%; P < 0.001) and was characterized by elevated serum IgA and hyaluronic acid levels, reduced platelet count, and a high fibrosis burden. Cluster 2 was strongly associated with LRE risk (HR 15.96, 95% CI 4.20–60.68; P < 0.001). Serum IgA increased stepwise with fibrosis stage (P = 0.0001), correlated with liver stiffness in the VCTE cohort (r = 0.444; P < 0.0001), and a cutoff of 318 mg/dL independently predicted LREs after adjustment for advanced fibrosis (HR 3.17, 95% CI 1.27–7.91; P = 0.013). The IgA-enriched cluster and the prognostic relevance of IgA were reproduced in the external multicenter validation cohort (P = 0.039). Patients with both elevated IgA and advanced fibrosis had the highest 10-year cumulative LRE incidence (48%; P < 0.0001). Mechanistically, colonic immunohistochemistry demonstrated increased IgA-positive cells in the mucosa and submucosa of MASLD patients with advanced fibrosis, and serum IgA correlated with EndoCAb IgG, supporting a link between gut barrier dysfunction and systemic IgA activation. Hepatic IGHA1 expression correlated with EndoCAb IgG and increased with fibrosis stage, suggesting coordinated intestinal and intrahepatic IgA-associated immune activation. Spatial transcriptomics and immunohistochemistry demonstrated portal enrichment of IGHA1/IgA-positive B-lineage cells, with spatial concordance between IGHA1-enriched spots and IgA-positive cell–rich portal regions. Single-cell RNA sequencing localized IGHA1 expression predominantly to B-lineage/plasma cells. IGHA1-high spatial niches were enriched for pathways related to B-cell receptor signaling, Fc receptor-associated signaling molecules, extracellular matrix organization, hepatic stellate cell activation, fibrogenesis, and vascular remodeling. **Conclusion:** Unsupervised clinical clustering identified a reproducible IgA-enriched MASLD cluster with high LRE risk. Serum IgA may support cluster-based risk stratification, while gut–liver IgA activation may link barrier dysfunction, immune–fibrotic remodeling, vascular remodeling, and LRE development.

Disclosures: Takefumi Kimura: Nothing to Disclose, Shun-Ichi Wakabayashi: Nothing to Disclose, Takuro Uchida: Nothing to Disclose, Naoki Tanaka: Nothing to Disclose.

2440 | CORRELATION OF ULTRASOUND-DERIVED FAT FRACTION WITH HISTOLOGIC AND NON-INVASIVE BIOMARKERS IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

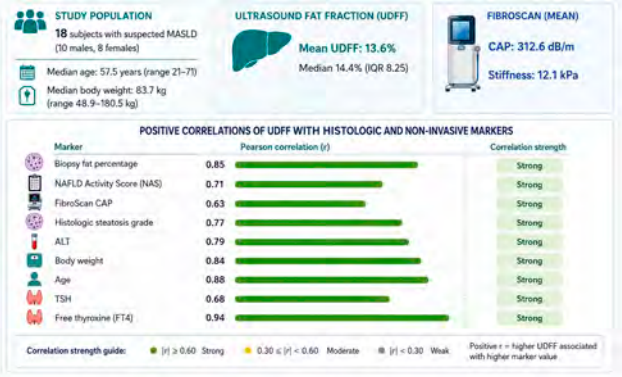
Ipshita Gupta[1] Dan Young[2] Arati Gurung[1] Yassin Labyed[1], [1]Siemens Healthineers, [2]National University Hospital Singapore

Background: Accurate non-invasive quantification of hepatic steatosis remains an unmet need in metabolic dysfunction-associated steatotic liver disease (MASLD). Ultrasound-derived fat fraction (UDFF) is an emerging quantitative ultrasound biomarker with

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potential utility for steatosis assessment and disease monitoring. This study evaluated the relationship between UDFF and histologic, elastographic, and biochemical markers of liver disease severity. **Methods:** Adults with suspected MASLD underwent multimodal clinical evaluation including quantitative ultrasound, FibroScan, laboratory assessment, and liver histology where available. Quantitative ultrasound parameters included UDFF (%). Correlation analysis was performed between UDFF, stiffness parameters, histologic findings, and biochemical markers using Pearson correlation coefficients. Strong correlations were defined as $|r| \geq 0.60$. **Results:** Eighteen subjects with suspected MASLD (10 males, 8 females) were recruited. Median age at enrolment was 57.5 years (range 21–71 years) and median body weight was 83.7 kg (range 48.9–180.5 kg). Mean UDFF was 13.6% (median 14.4%, IQR 8.25), while mean FibroScan CAP was 312.6 dB/m and mean FibroScan stiffness was 12.1 kPa. UDFF demonstrated strong positive correlations with histologic and non-invasive steatosis markers, including biopsy fat percentage ($r = 0.85$), NAFLD Activity Score (NAS) ($r = 0.71$), FibroScan CAP ($r = 0.63$), and histologic steatosis grade ($r = 0.77$). UDFF also correlated positively with ALT ($r = 0.79$), body weight ($r = 0.84$), age ($r = 0.88$), TSH ($r = 0.68$), and free thyroxine/FT4 ($r = 0.94$). **Conclusion:** UDFF demonstrated strong concordance with biopsy-derived fat quantification, FibroScan CAP, NAS, and histologic steatosis grade, supporting its role as a promising non-invasive biomarker for hepatic steatosis assessment in MASLD. Quantitative ultrasound biomarkers may provide clinically useful information for disease stratification and longitudinal monitoring while reducing dependence on invasive liver biopsy.



Disclosures: Ipshita Gupta: Siemens Healthineers: Employee, Dan Young: Nothing to Disclose, Arati Gurung: Nothing to Disclose, Yassin Labyed: Nothing to Disclose.

2441 | HETEROGENEITY OF DIFFUSE LIVER STEATOSIS IN PATIENTS WITH METABOLIC ASSOCIATED STEATOHEPATITIS (MASH) OR ALCOHOL LIVER DISEASE (ALD)

Renaud Winzenrieth[1] Juliette Foucher[2] Nora Fruilo[3] Adèle Delamarre[2] Benoit Recur[1] Paul Hermabessière[2], [1]SoQut-Imaging, Begles, France, [2]Hepatology, Hôpital Haut-Lévêque, Pessac, France, [3]Digestive Imaging, Hôpital Haut-Lévêque, Pessac, France

Background: Magnetic resonance imaging (MRI) is a simple, noninvasive and accurate modality for detecting and quantifying liver fat. Among MRI existing methods, chemical shift-encoded MRI (CSE-MRI) is a method of choice and allows simultaneous liver fat and iron content estimations through PDFF and R2* measurements. Steatosis in the liver is generally diffuse, but it can also be focal. However, even when diffuse, this fat accumulation may also be distributed heterogeneously within the liver. This study aims to assess fat heterogeneity distribution in patient suffering from MASH or ALD with diffuse steatosis. **Methods:** We retrospectively analyzed 53 patients suffering from MASH ($n = 43$) and ALD ($n = 10$). These patients underwent a 1.5T MRI with CSE-MRI acquisition between April 2024 and June 2025 and had a retrospective delay of 6-month between MRI and blood tests and Fibroscan®. PDFF values and distributions of each entire patient's liver were automatically computed using EliBio® software (SoQut-imaging, France). PDFF value of each patient's liver voxel were categorized as normal ($< 5.75\%$), stage1 (5.75-15%), stage 2(15-30%) or stage 3 ($\geq 30\%$). Related liver volume (expressed in % of the total liver volume) per category was also assessed. Patient's steatosis was also evaluated using Fibroscan's Controlled Attenuation Parameter (CAP) considering the following thresholds: normal (150-238 dB/m), stage 1(238-260 dB/m), stage 2 (260-290 dB/m) and stage 3(≥ 290 dB/m). **Results:** In overall, 45% of the patients had normal PDFF-steatosis while 30% had stage 1, 23% had stage 2 and 2% had stage 3. In comparison, 10% of the patients had normal CAP-steatosis while 35% had stage 1, 19% had stage 2 and 37% had stage 3. A poor agreement exists between CAP and PDFF staging (Kappa = 0.19). Of the 53 patient livers, the majority showed at least three grades of steatosis (58%) within the entire liver volume, while 40% showed two grades. Only one patient showed a single grade of steatosis. In 14 of the 43 MASH patients, more than 30% of the liver volume (32 to 58%) showed a one-grade worsening compared to their average based staging. Only 2 out of 10 ALD patients exhibited this one-grade worsening. Variability of PDFF Standard deviation in ALD patients was more

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homogeneous (0.17-2.02) than the one from MASH patients (0.18-6.2). **Conclusion:** Almost all patients with diffuse hepatic steatosis exhibit a heterogeneous accumulation of fat within the liver. This heterogeneity can lead to misclassification of the severity of steatosis in the patient, resulting in an underestimation of the stage of steatosis in 16 out of 53 patients in whom more than 30% of the liver volume showed a one-grade worsening compared to their average based staging of the entire liver. Patients with MASH had a more heterogeneous fat accumulation than those with ALD, suggesting a different mechanism of hepatic fat accumulation.

Disclosures: Renaud WINZENRIETH: SoQut-Imaging: Employee, Hekat Fluidics: Employee, Molzym GmbH: Employee, 3D-SHAPER MEDICAL SL: Consultant, Juliette Foucher: abbvie: Speaking and Teaching, GSK: Consultant, gilead: Speaking and Teaching, boehringer ingelheim: Consultant, VIi: Speaking and Teaching, Nora Fruilo: Nothing to Disclose, Adèle Delamarre: Nothing to Disclose, Benoit Recur: Nothing to Disclose, Paul Hermabessière: Nothing to Disclose.

2442 | LONGITUDINAL EVOLUTION OF STEATOTIC LIVER DISEASE SUBTYPES IN YOUNG BRAZILIANADULTS: A PROSPECTIVE COHORT STUDY USING TRANSIENT ELASTOGRAPHY

Fabiana Silva[1] Ana Cardoso[2] Katia Bloch[1] Nathalie Leite[3] Cristiane Villela-Nogueira[2], [1]School of Medicine, Universidade Federal do Rio de Janeiro, [2]School of Medicine, Hepatology Division , Universidade Federal do Rio de Janeiro, [3]Hepatology Division, Universidade Federal do Rio de Janiero

Background: Steatotic liver disease (SLD) has been recently redefined according to subcategories such as metabolic dysfunction-associated steatotic liver disease (MASLD), metabolic dysfunction-associated alcohol-related liver disease (MetALD), and alcohol-related liver disease (ALD). Longitudinal data in young adults remain limited. Our aim was to evaluate the prevalence and longitudinal evolution of steatotic liver disease (SLD) subtypes in young adults, as well as their association with cardiometabolic risk factors. **Methods:** This longitudinal study included a subcohort of young adults evaluated in 2018 (BL) and reassessed in 2024-2025 (FU) regarding anthropometric data, cardiometabolic factors, FINDRISC score and elastography with CAP (Fibroscan®, Echosens,Fr). SLD was defined by controlled attenuation parameter (CAP) $\geq$ 248 dB/m. Additionally, in both periods, steatosis subtypes were defined. **Results:** At BL, 123 individuals were evaluated (age 19.5 ± 1.5 years; 68.3% female), with SLD prevalence of 21.9%. Among these, 52% were MASLD, 33% MetALD, and 15% ALD. Individuals with steatosis had higher BMI. and waist circumference (all $p < 0.001$). After 64.5 (62-66), months 50 individuals were re assessed. SLD increased to 26% (MASLD 77%, MetALD 23% and ALD 0%), with significant increases in BMI, waist circumference, and systolic blood pressure (all $p < 0.001$). During follow-up, 4% developed type-2 diabetes and 44% worsened FINDRISC score by ≥ 1 category. **Conclusion:** SLD and cardiometabolic factors are highly prevalent in young adults, specially MASLD subtype. SLD presents a dynamic profile over time and needs constant reassessment in this population. Increasing awareness of MASLD in this population is essential to promote lifestyle interventions aimed at reducing long-term cardiometabolic and liver-related outcomes.

Disclosures: Fabiana Silva: Nothing to Disclose, Ana Cardoso: Nothing to Disclose, Katia Bloch: Nothing to Disclose, Nathalie Leite: Nothing to Disclose, Cristiane Villela-Nogueira: Nothing to Disclose.

2443 | MULTI-ORGAN MRI REVEALS HIGH BURDEN OF HEPATIC AND CARDIAC ABNORMALITIES IN HYPERTENSIVE ADULTS WITH AND WITHOUT TYPE 2 DIABETES

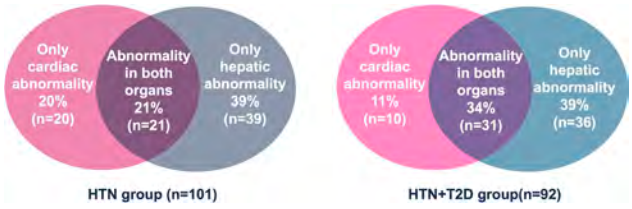
Yameng Deng[1] Edward Jackson[1] Jennifer Bryant[2] Yiying Han[2] Aisyah Binte Latib[2] Thu-Thao Le[2] Andrea Dennis[3] Helena Thomaides Brears[1] Masliza Mahmod[1] Calvin Chin[2], [1]Perspectum Ltd, [2]National Heart Centre Singapore, [3]Perspectum

Background: Cardiac and hepatic abnormalities independently predict adverse cardiovascular outcomes, yet their relationship in hypertension (HTN) remains poorly characterised. We used quantitative multi-organ magnetic resonance imaging (MRI) to characterise cardiac and hepatic phenotypes in adults with HTN, with and without type 2 diabetes (T2D). **Methods:** The REMODEL study (NCT 02670031) evaluates cardiometabolic disease in adults with HTN recruited from outpatient and primary care settings in Singapore. 193 participants underwent blood biomarker assessment and multi-organ MRI to measure cardiac structure and function, including left ventricular ejection fraction (LVEF), global longitudinal strain (GLS), LV mass index (LVMi), maximal wall thickness (LVWT), and late gadolinium enhancement (LGE), extracellular volume (ECV), alongside liver fat content (LFC) and disease activity assessed by iron-corrected T1 (cT1). Baseline comparisons were performed between HTN alone ($n = 101$) and HTN+T2D ($n = 92$). A subgroup of 51 participants underwent repeat MRI after 5 ± 2 years

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and correlations between relative weight change and MRI biomarkers changes were evaluated. MRI phenotypes were hepatic (MASLD (LFC ≥ 5 %) and MASH (MASLD and cT1 ≥ 800 ms)) and cardiac (any of: reduced LVEF, elevated LVMi, elevated LV mass-to-volume ratio, left atrial enlargement or presence of LGE). **Results:** At baseline, groups were well matched for BMI and sex (obesity prevalence 33% vs 46%, p = 0.14; female sex 63% vs 52%, p = 0.14), although participants with HTN+T2D were older (62 vs 56 years, p < 0.001). Both groups showed a high burden of MRI-defined MASLD (73% with T2D vs 59% without, p = 0.05) and MASH (29% vs 27%, p = 0.7). NT-proBNP ≥400 pg/mL in only 6% with HTN+T2D and 3% without T2D (p = 0.5). Median LVEF of 59% in both groups (p = 0.5). However, HTN+T2D group demonstrated lower LV stroke volume (69 vs 81 mL, p < 0.001), impaired GLS (-16% vs -17%, p = 0.034), higher ECV (26.3% vs 25.1%, p = 0.049), and greater non-ischaemic fibrosis burden on LGE imaging (34% vs 26%), despite limited differences in LVMi, LVWT, and left atrial size. The prevalence of MRI phenotypes in both organs was higher with T2D (34% vs 21%, p = 0.04). Despite this, hepatic and cardiac phenotypes showed limited association. In the follow-up subgroup, relative weight change correlated with changes in LFC (r = 0.62, p < 0.001) and cT1 (r = 0.47, p < 0.001), whereas changes in cardiac MRI measures showed limited association with weight change. **Conclusion:** In adults with hypertension and T2D there was a high burden of adverse hepatic and cardiac MRI phenotypes that were not tightly coupled. This suggests shared metabolic drivers for disease in the liver and heart but heterogeneous organ expression, supporting the value of multi-organ imaging in characterisation of such organ-specific manifestations.



Disclosures: Yameng Deng: Perspectum Ltd: Employee, Edward Jackson: Perspectum Ltd.: Employee, Owlstone Medical Ltd: Employee, Richmond Pharmacology: Employee, Perspectum Ltd.: Employee, Jennifer Bryant: Nothing to Disclose, Yiying Han: Nothing to Disclose, Aisyah Binte Latib: Nothing to Disclose, Thu-Thao Le: Nothing to Disclose, Andrea Dennis: Nothing to Disclose, Helena Thomaides Brears: Perspectum: Employee, Perspectum: Stock – privately held company, Masliza Mahmod: Perspectum Ltd: Employee, Calvin Chin: Nothing to Disclose.

2444 | SEQUENTIAL TESTING REFINES THE DIAGNOSIS OF SIGNIFICANT FIBROSIS IN GRAY-ZONE VCTE AND ELF BUT IS UNNECESSARY FOR HIGH-RISK SINGLE CUT-POINTS IN MASLD

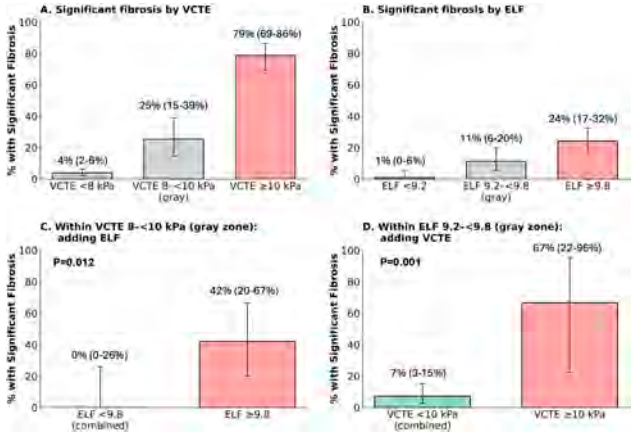
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Background: Non-invasive tests (NITs), including vibration-controlled transient elastography (VCTE) and the Enhanced Liver Fibrosis (ELF) score, are widely used to identify significant fibrosis in metabolic dysfunction–associated steatotic liver disease (MASLD), but whether single high cut-points suffice and whether gray-zone results benefit from a concordant second test is unclear. Using magnetic resonance elastography (MRE) as the reference standard for significant fibrosis, we evaluated diagnostic performance of VCTE and ELF and the incremental value of concordance. **Methods:** Adults at-risk for or with MASLD enrolled in a prospective cohort underwent same-visit VCTE, MRE, ELF, and labs. Significant fibrosis was defined as MRE ≥3.3 kPa. We computed prevalence of significant fibrosis within each NIT stratum at **low** (VCTE < 8kPa, ELF < 9.2), **gray** (VCTE 8–<10 kPa, ELF 9.2–<9.8) and **high** (VCTE ≥10 kPa, ELF ≥9.8) cut-points. Within each gray zone we further stratified by sequential use of the other NIT. **Results:** Among 858 adults with MRE (68% MASLD; median age 59 years, 61% female, 38% Hispanic, 59% T2DM), 156 (18%) had significant fibrosis (MRE ≥3.3 kPa). Among 555 with both VCTE and MRE, the prevalence of significant fibrosis by VCTE category was: **low** (VCTE < 8kPa): 4.0% (95% CI: 2.3–6.4%); **gray** (VCTE 8–<10kPa): 25.5% (95% CI: 14.7–39.0%); and **high** (VCTE ≥10kPa): 78.8% (95% CI: 69.4–86.4%). The prevalence of significant fibrosis by ELF category (n = 315) was: **low** (ELF <9.2): 1.1% (95% CI: 0–5.7%); **gray** (ELF 9.2–<9.8): 11.4% (95% CI: 5.6–19.9%); and **high** (ELF ≥9.8): 24.2% (95% CI: 17.2–32.5%). High single cut-points performed well alone: VCTE ≥10 kPa: sensitivity 72%, specificity 95%, PPV 79%, NPV 93% and ELF ≥9.8: sensitivity 74%, specificity 63%, PPV 24%, NPV 94%. Concordance added little to VCTE ≥10 (PPV 79% alone vs 81% concordant with ELF ≥9.8). Concordance substantially refined diagnosis within gray zones. Within gray zone VCTE adding ELF ≥9.8 increased the prevalence of significant fibrosis to 42.1% (20.3–66.5%) vs 0% (0–26%) for ELF <9.8, P = 0.012. Within gray zone ELF adding VCTE ≥10 kPa increased the prevalence of significant fibrosis to 66.7% (22.3–95.7%) vs 7.3% (2.7–15.2%) for VCTE <10 kPa, P = 0.001. **Conclusion:** In adults with

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MASLD, single high-risk cut-points, particularly VCTE ≥ 10 kPa, have high PPV for significant fibrosis and do not require a concordant second NIT. In contrast, gray-zone VCTE (8–< 10 kPa) and gray-zone ELF (9.2–< 9.8) benefit from a concordant second test, supporting a strategy of acting on high single-NIT cut-points alone, and reserving sequential testing for gray-zone results.



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2445 | INVESTIGATING PRIMARY CARE MANAGEMENT OF PATIENTS WITH LIVER STEATOSIS ON ABDOMINAL IMAGING, STRATIFIED BY RISK FOR ADVANCED FIBROSIS

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Background: Liver steatosis identified on imaging is often an incidental finding but can be an early clue to suspect a patient has metabolic dysfunction-associated steatotic liver disease (MASLD). Primary care doctors are regularly tasked with the initial evaluation of these patients. International guidelines suggest utilizing non-invasive tests like FIB-4 to stratify these patients by their advanced fibrosis risk and guide referral, evaluation, and management. The purpose of this study was to evaluate if the presence of hepatic steatosis on abdominal imaging led to augmented evaluation for advanced liver fibrosis in the primary care setting. **Methods:** We conducted a retrospective cohort study of 43,661 patients aged 35-70 years with a calculable FIB-4 score. Patients were seen between January 2018 and April 2026 at one of 28 primary care clinics within a large urban academic health system. Natural language processing on MDCLONE kiosk analytic software was used to analyze abdominal CT and ultrasound reports for mention of “steatosis”, “fatty”, or “echogenic”. In total, 2,470 patients with these liver imaging findings were included in the study. MDCLONE software also identified demographics, medication use, hepatology visits, fibrosis testing, and metabolic risk factors. We examined these variables across 3 tiers of FIB-4 using ANOVA and chi-squared testing. **Results:** Of 2,470 patients with evidence of hepatic steatosis on imaging, 70% were low risk, 21% moderate risk, and 9% high risk for advanced fibrosis based on FIB-4.

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Demographics, laboratory values, and clinical management varied significantly across fibrosis categories (Table 1). The prevalence of diabetes was highest among patients in the highest risk fibrosis group ($p < 0.001$, 38%). Vibration controlled elastography score correlated with increasing FIB-4 culminating in mean 11.99 kPa in the high risk group. There was no difference in hepatology visits nor completed liver stiffness testing between fibrosis risk groups ($p = 0.37$, $p = 0.67$, respectively). The percentage of patients prescribed GLP-1 medications paradoxically decreased with higher FIB-4 ($p < 0.001$). Among high risk patients, the presence of steatosis on imaging did not increase the frequency of hepatology visits ($p = 0.75$). **Conclusion:** The majority of primary care patients with high risk for liver fibrosis and evidence of steatosis on imaging are not undergoing AASLD guideline-suggested management. Despite evidence of liver steatosis on imaging, overall 75% of high-risk FIB-4 patients have not had liver stiffness assessed nor been seen in hepatology. Targeted system-wide intervention is clearly needed to improve MASLD evaluation, referral, and management in the populations most at risk.

Table 1: Characteristics and management of primary care patients noted to have steatosis on imaging stratified by fibrosis risk categories

Parameters (Results are n (%) or mean (SD))	FIB-4 Category			P-value
	Low-risk FIB-4 < 1.3 if < 65 y FIB-4 < 2.0 if ≥ 65 y N=1,720	Intermediate-risk FIB-4: 1.3 - 2.66 if < 65 y FIB-4: 2.0 - 2.66 if ≥ 65 y N=534	High-risk FIB-4 ≥ 2.67 N=216	
Demographics				
Female	964 (56%)	254 (46%)	101 (47%)	<0.001
White race	723 (42%)	220 (41%)	70 (32%)	0.030
Black race	654 (38%)	242 (45%)	120 (56%)	<0.001
Age, years	50.2 (9.4)	56.8 (7.9)	59.0 (9.6)	<0.001
BMI, kg/m^2	32.9 (7.7)	31.4 (7.4)	28.9 (7.9)	<0.001
Laboratory Results				
Diabetes	434 (25%)	167 (31%)	82 (38%)	<0.001
ALT, IU/L	35 (22)	46 (40)	57 (49)	<0.001
AST, IU/L	27 (11)	44 (28)	89 (60)	<0.001
Alk Phos, IU/L	87 (72)	102 (77)	148 (152)	<0.001
LDL, mg/dL	105 (38)	94 (38)	82 (45)	<0.001
Triglycerides, mg/dL	133 (100)	141 (125)	131 (166)	0.292
Albumin, g/dL	4.3 (0.4)	4.2 (0.6)	3.7 (0.8)	<0.001
Ferritin, ng/mL	253 (407)	568 (888)	1954 (7098)	<0.001
Platelets, G/L	293 (62)	216 (53)	168 (65)	<0.001
INR	1 (0.2)	1.1 (0.3)	1.3 (0.4)	<0.001
Management				
Presence of liver stiffness testing (VCTE or MRE)	279 (16%)	84 (16%)	30 (14%)	0.671
Liver stiffness, kPa	5.63 (3.0)	8.09 (5.6)	11.99 (11.0)	<0.001
Hepatology visit	220 (13%)	72 (13%)	35 (16%)	0.371
GLP1-RA use	532 (31%)	116 (22%)	25 (12%)	<0.001
SGLT2i use	136 (8%)	64 (12%)	28 (13%)	0.002

Disclosures: Rahul Sandella: Nothing to Disclose, Hee Yeon Kim: Nothing to Disclose, Christopher Kasia: Nothing to Disclose, Andrew Davis: Nothing to Disclose, Mary Rinella: akero: Consultant, akero: Consultant, 89Bio: Consultant, 89Bio: Consultant, Boehringer Ingelheim: Consultant, Boehringer Ingelheim: Consultant, Cytodyn: Consultant, Cytodyn: Consultant, Echosens: Consultant, Echosens: Consultant, Histoindex: Consultant, Histoindex: Consultant, Intercept: Consultant, Intercept: Consultant, Madrigal: Consultant, Madrigal: Consultant, GSK: Consultant, GSK: Consultant, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Eli Lilly: Consultant, Eli Lilly: Consultant, Takeda: Consultant, Takeda: Consultant, Sagimet: Consultant, Sagimet: Consultant, Sonic Incytes: Consultant, Sonic Incytes: Consultant, NGM Bio: Consultant, NGM Bio: Consultant, Regeneron: Consultant, Boston Pharma: Consultant, Eccogene: Consultant, Inventiva: Consultant, Sagimet: Consultant, Madrigal: Consultant, akero: Consultant, akero: Consultant, 89Bio: Consultant, 89Bio: Consultant, Boehringer Ingelheim: Consultant, Boehringer Ingelheim: Consultant, Cytodyn: Consultant, Cytodyn: Consultant, Echosens: Consultant, Echosens: Consultant, Histoindex: Consultant, Histoindex: Consultant, Intercept: Consultant, Intercept: Consultant, Madrigal: Consultant, Madrigal: Consultant, GSK: Consultant, GSK: Consultant, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Eli Lilly: Consultant, Eli Lilly: Consultant, Takeda: Consultant, Takeda: Consultant, Sagimet: Consultant, Sagimet: Consultant, Sonic Incytes: Consultant, Sonic Incytes: Consultant, NGM Bio: Consultant, NGM Bio: Consultant, Regeneron: Consultant, Boston Pharma: Consultant, Eccogene: Consultant, Inventiva: Consultant, Sagimet: Consultant, Madrigal: Consultant.

2446 | COMBINING BODY ROUNDNESS INDEX WITH FIB-4 IMPROVES FIBROSIS TRIAGE IN MASLD: A VCTE-CONFIRMED CROSS-SECTIONAL STUDY

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Background: The Body Roundness Index (BRI) is a simple anthropometric measure that has shown value in detecting hepatic steatosis. However, its value in predicting clinically significant fibrosis in metabolic dysfunction-associated steatotic liver disease (MASLD) is unknown. This study evaluated: (I) BRI performance for liver stiffness measurement (LSM) ≥ 8 kPa in a vibration-controlled transient elastography (VCTE)-confirmed MASLD cohort; (II) whether BRI+FIB-4 improves fibrosis prediction over individual non-invasive scores; and (III) the correlation between BRI and the FAST score. **Methods:** This single-centre, cross-sectional study included 58 adults with VCTE-confirmed MASLD. Patients were classified according to the following kPa thresholds: < 8 ($n = 17$), 8–12 ($n = 24$), and > 12 kPa ($n = 17$). BRI was calculated from waist circumference and height. Kruskal–Wallis, Mann–Whitney U, Spearman correlation, logistic regression, and ROC analyses were performed. **Results:** BRI was numerically higher in the kPa ≥ 8 group (5.60 vs. 4.63, $p = 0.063$). BRI did not correlate with LSM ($r = 0.116$, $p = 0.384$) or FAST score ($r = 0.155$, $p = 0.245$). Neither BRI (AUC = 0.656, $p = 0.063$) nor FIB-4 (AUC = 0.664, $p = 0.051$) achieved significant individual ROC performance. The BRI+FIB-4 combined model achieved AUC =

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0.726 (95% CI 0.579–0.873, p = 0.007), outperforming all individual blood-based scores. **Conclusion:** BRI alone was not a significant predictor of fibrosis severity and FAST-defined Metabolic Dysfunction-Associated Steatohepatitis (MASH) activity in this cohort. However, Its combination with FIB-4 improved the discrimination of significant fibrosis. and may be useful as a simple triage approach, especially in patients with intermediate LSM values.

Figure 2. Receiver Operating Characteristic (ROC) Curve Analysis of Blood-Based Fibrosis Scores and BRI + FIB-4 Combined Score for Prediction of Liver Stiffness ≥ 8 kPa

Area under the curve (AUC) comparison across individual and combined indices



AUC = area under the curve; CI = confidence interval; BRI = Body Roundness Index; FIB-4 = Fibrosis-4 Index; APRI = AST-to-Platelet Ratio Index; NFS = NAFLD Fibrosis Score; BARD = BMI, AST/ALT ratio, Diabetes score. ROC curves are estimated from reported AUC values using a parametric approximation. While BRI and FIB-4 individually did not reach statistical significance (p > 0.05), their combined score achieved significant discriminative performance (AUC = 0.726, p = 0.007). * Statistically significant at p < 0.05.

Disclosures: Dogan Can Gavcar: Nothing to Disclose, Nilay Danis: Nothing to Disclose.

2447 | COMPARATIVE PERFORMANCE OF NONINVASIVE TESTS FOR HISTOLOGIC SEVERITY IN A NORTH TEXAS TERTIARY COHORT WITH MASH

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Background: Liver biopsy remains the standard for assessment of disease severity in metabolic dysfunction-associated steatohepatitis (MASH), but non-invasive tests (NITs) are increasingly used in routine care. Real world comparative data evaluating how commonly used NITs relate to histologic severity remain limited. We evaluated the performance of serum and elastography based NITs against biopsy severity in a tertiary MASH cohort. **Methods:** We performed a retrospective analysis of 450 adults with MASH from a North Texas tertiary care cohort. Histologic severity was assessed using Brunt severity and NAFLD activity score (NAS). Available NITs included Fibrosis-4 (Fib-4), FibroScan liver stiffness measurement (kPa), controlled attenuation parameter (CAP), FibroScan fibrosis stage, FibroSure fibrosis stage, FibroSure NASH grade, enhanced liver fibrosis (ELF), and initial LIVERFASt fibrosis, steatosis, and activity scores. Continuous variables underwent variable specific outlier trimming using a 3×IQR Tukey approach. Associations between NITs and histologic severity were assessed using Spearman rank correlation. Receiver operating characteristic (ROC) analysis was performed for advanced Brunt severity. **Results:** Liver biopsy was available in 272/450 patients (61.1%). Among biopsy linked analyses, Brunt severity correlated with NAS (rho = 0.313, p < 0.001), baseline FibroScan kPa (rho = 0.312, n = 111, p = 0.0013), Fib-4 (rho = 0.210, n = 224, p = 0.0015), FibroSure NASH grade (rho = 0.351, n = 67, p = 0.003), and FibroScan fibrosis stage (rho = 0.255, n = 104, p = 0.008). CAP did not significantly correlate with Brunt severity. For advanced Brunt severity, FibroSure fibrosis stage showed the highest discriminatory performance among available NITs (AUC 0.709), followed by baseline FibroScan kPa (AUC 0.693) and Fib-4 (AUC 0.620), while CAP showed no meaningful discrimination (AUC 0.494). Correlations involving ELF and LIVERFASt were limited by smaller sample sizes and did not demonstrate robust histologic association in the available subsets. **Conclusion:** In this North Texas tertiary MASH cohort, FibroSure fibrosis stage and FibroScan liver stiffness showed the strongest overall performance for histologic severity, while Fib-4 demonstrated a more modest but still significant association with biopsy-based disease severity. CAP showed limited histologic discrimination in this cohort. These findings suggest that fibrosis-oriented NITs more closely reflect biopsy severity than steatosis focused measures in real-world MASH practice.

Noninvasive test	Biopsy linked n	Spearman rho vs Brunt severity	p-value	AUC for advanced Brunt severity
FibroSure fibrosis stage	73	0.285	0.0147	0.709
Baseline FibroScan kPa	103	0.312	0.0013	0.693
Fib-4	224	0.210	0.0015	0.620
FibroSure NASH grade	68	0.351	0.0033	0.647
FibroScan fibrosis stage	108	0.255	0.0077	0.685
CAP	98	-0.070	0.492	0.494

Table 1. Comparative performance of noninvasive tests for histologic severity in a North Texas tertiary MASH cohort.

Disclosures: Jeevin Sandhu: Nothing to Disclose, Zixin Zeng: Nothing to Disclose, Simran Joshi: Nothing to Disclose, Kinnari Modi: Nothing to Disclose, Ashwini Mehta: Nothing to Disclose, Mangesh Pagadala: Nothing to Disclose, Parvez Mantry: Nothing to Disclose.

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2448 | ASSOCIATION OF NONINVASIVE PARAMETERS WITH HISTOLOGICAL SCORES AND A DIAGNOSTIC MODEL FOR MASH IN BIOPSY-CONFIRMED MASLD

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is highly prevalent, yet noninvasive identification of metabolic dysfunction-associated steatohepatitis (MASH) and advanced fibrosis remains challenging. We aimed to evaluate the association of clinical and noninvasive parameters with liver histology and develop a practical MASH prediction model in a biopsy-confirmed MASLD cohort. **Methods:** This retrospective study included 106 patients with biopsy-confirmed MASLD from 2018 to 2026. Clinical data were collected, including demographic and medical history, blood routine, serum biochemical indicators, urine routine, abdominal imaging, liver controlled attenuation parameter (CAP), liver stiffness value (LSM), FIB-4, MASLD fibrosis score (NFS). Histological steatosis, ballooning, lobular inflammation, NAFLD activity score (NAS), and fibrosis stage were scored. Ordinal logistic regression was used to identify independent factors for each histological component. Binary logistic regression was used to construct a diagnostic model for definite MASH (histologically defined by steatosis, lobular inflammation, and ballooning, with NAS $\geq$ 5) and high-risk MASH (definite MASH + significant fibrosis F $\geq$ 2). Model performance was assessed by AUROC. **Results:** On multivariate ordinal analysis, ALT (OR 1.013, P = 0.024) and CAP (OR 1.018, P = 0.013) were independent risk factors for steatosis grade. Age (OR 1.095, P = 0.005) and negative urine glucose (OR 0.095, P = 0.041) were independently associated with ballooning grade. Fasting glucose, ALT, CAP, and LSM were independently associated with NAS total score (all P < 0.05). For fibrosis stage, platelet count (OR 0.995, P = 0.023) was a protective factor and LSM (OR 1.134, P < 0.001) a risk factor. Male sex was independently protective against severe MASLD (OR 0.324, P = 0.026), while LSM remained a risk factor (OR 1.120, P = 0.005). FIB-4 correlated better with fibrosis stage than NFS (r_s = 0.338 vs 0.241). For MASH diagnosis, the model combining CAP and LSM achieved an AUROC of 0.742 (sensitivity 93.1%, specificity 51.1%). For high-risk MASH, LSM alone yielded an AUROC of 0.814 (optimal cutoff 9.45 kPa, sensitivity 82.4%, specificity 69.2%). Both models demonstrated good calibration and clinical net benefit. **Conclusion:** LSM and CAP are core noninvasive indicators reflecting histological injury in MASLD. Abnormal liver function effectively indicates disease activity. FIB-4 is superior to NFS for fibrosis assessment. The proposed MASH and high-risk MASH models show good discrimination and clinical utility, supporting their use for early screening and risk stratification in clinical practice.
Disclosures: Sidan Fu: Nothing to Disclose, Ke Yang: Nothing to Disclose, Li Liu: Nothing to Disclose, Yu Lei: Nothing to Disclose.

2449 | CAP SCORE VARIATION ACROSS CARDIOMETABOLIC AND RACIAL SUBGROUPS IN A U.S. MASLD COHORT: DOES RACE MODIFY THE METABOLIC LIVER DISEASE BURDEN?

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Background: FibroScan Vibration Controlled Transient Elastography (VCTE) has emerged as a noninvasive, cost-effective alternative to liver biopsy for quantifying hepatic fibrosis and steatosis in metabolic dysfunction associated steatotic liver disease (MASLD)/metabolic dysfunction-associated steatohepatitis (MASH), simultaneously measuring liver stiffness (LSM) and the Controlled Attenuation Parameter (CAP). Existing studies of CAP in relation to cardiometabolic comorbidity have been conducted predominantly in non-U.S. cohorts with limited racial and ethnic diversity, leaving unanswered whether insulin-resistance-defining conditions (IR-defining) differentially affect steatosis severity across race and ethnicity groups. **Methods:** Patients with a diagnosis of MASLD/MASH were selected from the Pedestal Health multi-center EHR-derived database, and VCTE test results between first ICD diagnosis code up to July 31, 2025 were extracted using artificial intelligence/ large language models (LLMs). LLM accuracy was benchmarked against human abstraction performance, both measured against a reference standard. Adults with at least one VCTE test following the first MASLD/MASH diagnosis code were included. Annual VCTE testing volume was tracked over time. Hepatic steatosis severity

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by CAP score was stratified by LSM-defined fibrosis stage (F0–F1 <8 kPa, F2 8–10 kPa, F3–F4 ≥10 kPa), race/ethnicity, and cardiometabolic condition type (IR-defining [obesity and/or T2DM] vs. non-IR-defining [hypertension and/or dyslipidemia only]). To evaluate whether race/ethnicity modifies the association between IR-defining cardiometabolic conditions and CAP score, we fit an unadjusted linear regression model with a multiplicative interaction term. **Results:** In a test set of 357 patients, the LLM had slightly lower completeness for VCTE test date relative to human abstraction (84% vs. 94%). LLM accuracy for extracting the correct VCTE test date (+/- 15 days), LSM result and CAP score was on par with human performance (within 4% of human accuracy). In a cohort of 3383 MASH/MASLD patients, testing volume increased from 454 tests in 2021 to 1278 tests in 2024. Stratified analyses found lower CAP scores among patients with minimal fibrosis (F0-F1), Non-Hispanic Black (vs. White), and patients without IR-defining comorbidities (Table 1). The interaction between race and insulin-resistance-defining cardiometabolic conditions was non-significant. **Conclusion:** FibroScan use is increasing in clinical practice. AI is a viable tool for extracting LSM and CAP values from unstructured text in the EHR for real world research. CAP score distributions across subgroups were broadly consistent with clinical expectations. The relationship between IR-defining condition and hepatic steatosis severity persisted across race/ethnicity groups in the study population.

Table 1. CAP Distribution by Subgroup

Subgroup	CAP Score median, (IQR)
F0-F1 (No/Minimal)	285 (244, 323)
F2 (Intermediate)	303 (267, 340)
F3-F4 (Advanced)	306 (266, 343)
IR-defining (Obesity and/or T2DM)	298 (259, 334)
Not IR-defining	272 (233, 309)
NH White	294 (254, 332)
NH Black	288 (244, 321)
Hispanic	289 (251, 322)
Other	296 (258, 334)

Disclosures: Alfred Barritt IV: Nothing to Disclose, Melissa Estevez: Nothing to Disclose, Nate Nussbaum: Nothing to Disclose, Sriram Krishnan: Nothing to Disclose, Laney Bowden: Nothing to Disclose, Elizabeth Verna: Nothing to Disclose, Coleman Smith: Nothing to Disclose, TARGET-LD investigators: Nothing to Disclose, Michael Fried: Nothing to Disclose.

2450 | STEATOSIS BURDEN AND SEVERE OBESITY ARE ASSOCIATED WITH FIBROSCAN–BIOPSY DISCORDANCE IN MASLD

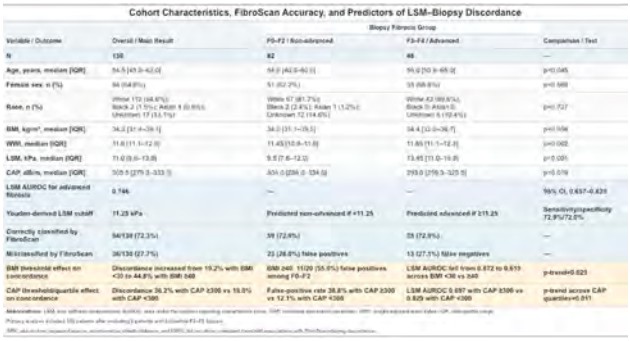
Krishna Venkata[1] Hussein Harb[1] Fabian Rodas[1] Eric Lawitz[1], [1]Texas Liver Institute

Background: Liver stiffness measurement (LSM) by FibroScan may over-stage fibrosis in some patients with metabolic dysfunction–associated steatotic liver disease (MASLD), but factors contributing to FibroScan–biopsy discordance are not well defined. We evaluated the performance of LSM for biopsy-confirmed advanced fibrosis in MASLD and examined whether adiposity, steatosis burden, ultrasound body-habitus measures, or measurement reliability were associated with discordance. **Methods:** We prospectively analyzed patients with MASLD who underwent paired FibroScan and liver biopsy. Advanced fibrosis was defined as METAVIR F3–F4 and non-advanced fibrosis as F0–F2; borderline F2–F3 cases were excluded. LSM discrimination for advanced fibrosis was assessed using AUROC and a Youden-derived cutoff. Discordance was defined as disagreement between LSM-predicted and biopsy-confirmed advanced fibrosis. Candidate predictors included controlled attenuation parameter (CAP), body mass index (BMI), weight-adjusted waist circumference index (WWI), skin-to-liver capsule distance, skin-to-rectus sheath distance, and LSM IQR%. **Results:** The MASLD cohort included 130 patients: 82 with non-advanced fibrosis and 48 with advanced fibrosis. LSM demonstrated moderate discrimination for advanced fibrosis (AUROC 0.746; 95% CI, 0.657–0.835), with an optimal cutoff of 11.25 kPa. Overall, 94 patients were correctly classified and 36 (27.7%) were discordant. Discordance was driven predominantly by false-positive LSM overestimation. Compared with concordant patients, discordant patients had higher CAP values and BMI ≥40 kg/m², whereas WWI and ultrasound-depth measures were not significantly different. Discordance increased across BMI categories, reaching 44.8% among patients with BMI ≥40 kg/m², where LSM discrimination was lowest. Discordance was also higher among patients with CAP ≥300 dB/m. Across ordered strata, discordance increased with both BMI category and CAP quartile, but not with WWI, skin-to-liver distance, skin-to-rectus distance, or IQR%. In parsimonious multivariable models, CAP remained independently associated with discordance after adjustment for WWI and ultrasound-depth measures, whereas the association between BMI and discordance attenuated after CAP adjustment. **Conclusion:** In this biopsy-paired MASLD cohort, FibroScan LSM showed moderate accuracy for advanced fibrosis, but more than one-quarter of patients were discordantly

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classified. Discordance was driven mainly by false-positive LSM overestimation and was most consistently associated with higher CAP and severe obesity. WWI and ultrasound body-habitus measures provided limited additional explanatory value. Elevated LSM values in patients with MASLD, particularly those with marked steatosis or class III obesity, may warrant confirmatory testing before upstaging fibrosis severity.



Cohort Characteristics, FibroScan Accuracy, and Predictors of LSM–Biopsy Discordance

		Biopsy Fibrosis Group		
Variable / Outcome	Overall / Main Result	F0–F2 / Non-advanced	F3–F4 / Advanced	Comparison / Test
N	130	82	48	—
Age, years, median [IQR]	54.5 [45.0–62.0]	54.0 [42.0–60.0]	55.0 [50.0–65.0]	p=0.045
Female sex, n (%)	84 (64.6%)	51 (62.2%)	33 (68.8%)	p=0.568
Race, n (%)	White 72 (55.4%); Black 2 (1.5%); Asian 1 (0.8%); Unknown 17 (13.1%)	White 67 (81.7%); Black 2 (2.4%); Asian 1 (1.2%); Unknown 12 (14.6%)	White 42 (100.0%); Black 0; Asian 0; Unknown 6 (12.5%)	p=0.727
BMI, kg/m², median [IQR]	34.2 [31.4–39.1]	34.0 [31.1–39.5]	34.4 [32.0–36.7]	p=0.936
WWI, median [IQR]	11.8 [11.1–12.5]	11.45 [10.8–11.8]	11.85 [11.1–12.5]	p=0.002
LSM, kPa, median [IQR]	11.0 [9.0–13.8]	9.5 [7.6–12.2]	13.45 [11.0–16.8]	p<0.001
CAP, dB/m, median [IQR]	325.5 [275.3–333.1]	304.0 [284.0–334.5]	293.0 [256.3–325.5]	p=0.016
LSM AUROC for advanced fibrosis	0.746	—	—	95% CI, 0.657–0.835
Youden-derived LSM cutoff	11.25 kPa	Predicted non-advanced if <11.25	Predicted advanced if ≥11.25	Sensitivity/specificity 72.9%/72.0%
Correctly classified by FibroScan	94/130 (72.3%)	59 (72.0%)	35 (72.9%)	—
Misclassified by FibroScan	36/130 (27.7%)	23 (28.0%) false positives	13 (27.1%) false negatives	—
BMI threshold effect on concordance	Discordance increased from 15.2% with BMI <30 to 44.8% with BMI ≥40	BMI ≥40: 11/20 (55.0%) false positives among F0–F2	LSM AUROC fell from 0.872 to 0.619 across BMI <30 vs ≥40	p-trend=0.023
CAP threshold/quartile effect on concordance	Discordance 36.2% with CAP ≥306 vs 19.0% with CAP <306	False-positive rate 38.8% with CAP ≥306 vs 12.1% with CAP <306	LSM AUROC 0.897 with CAP ≥306 vs 0.829 with CAP <306	p-trend across CAP quartiles=0.041

Abbreviations: LSM, liver stiffness measurement; AUROC, area under the receiver operating characteristic curve; CAP, controlled attenuation parameter; BMI, body mass index; CI, confidence interval; IQR, interquartile range.

Primary analysis included 130 patients after excluding 5 patients with Columbia F1–F3 biopsies.

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2451 | AST-ASSOCIATED INFLAMMATORY ACTIVITY CONTRIBUTES TO DISCORDANT FIBROSIS ESTIMATION IN SUSPECTED MASH POPULATION

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Background: Transient elastography–derived liver stiffness measurement (LSM) is widely used to noninvasively stage fibrosis in metabolic dysfunction–associated steatohepatitis (MASH), though hepatocellular injury and inflammation may elevate LSM independent of fibrosis. While this effect is recognized in other liver diseases, its significance and relevant transaminase thresholds in MASH remain unclear. We aimed to determine whether transaminase elevation independently increases FibroScan LSM in suspected MASH and identify AST and ALT thresholds at which inflammation significantly confounds interpretation. **Methods:** 162 patients with suspected MASH (elevated transaminases and/or imaging steatosis/fibrosis) who underwent FibroScan prior to liver biopsy were analyzed. Multivariable linear regression assessed associations between continuous transaminase elevations and liver stiffness measurement (LSM), adjusting for age, sex, BMI, fibrosis stage, and steatosis grade. Sensitivity analyses evaluated AST thresholds of 50/60/70/80/85/90 IU/L and ALT thresholds of 80/90/100 IU/L. Analyses were repeated excluding F4 patients to isolate inflammation-related effects in F0 to F3 disease (n = 126). Fibrosis overestimation was defined as LSM-predicted stage exceeding histology, with cutoffs of 7/8.5/10.5/14 kPa for F1/F2/F3/F4. Multivariable logistic regression evaluated associations between AST elevation and fibrosis overestimation while controlling demographic and histologic factors. **Results:** In the full F0 to F4 cohort, neither continuous nor threshold transaminase values were independently associated with liver stiffness after adjustment. After excluding cirrhosis (F4), higher AST thresholds (AST $\geq$ 60, 70, 80, 85) showed a stepwise association with increased LSM, whereas AST $\geq$50 and $\geq$90 were not significant. Continuous AST was also significantly associated with LSM in this subgroup; however, ALT thresholds and continuous ALT were not significant. Higher AST thresholds were

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associated with increased odds of fibrosis overestimation, with significant effects at AST ≥80 and ≥85. Lower AST thresholds and continuous AST values were not significant predictors of overestimation. **Conclusion:** AST elevation independently increases liver stiffness measurements in noncirrhotic MASH, with AST ≥80 IU/L associated with approximately 3.0 kPa higher LSM and increased risk of fibrosis overestimation. The non-significant result at AST ≥90 likely reflects limited power (n = 7) rather than a true threshold ceiling. This effect was greatest in F0 to F3 disease, suggesting inflammation contributes more to LSM at lower fibrosis stages. ALT was not associated with increased LSM. In patients with AST ≥80, FibroScan results should be interpreted with caution and may warrant repeat measurement after transaminase normalization.

Multivariable Linear Regression (F0-F4 pop.) (Table 1)

Total n	AST Threshold	n(≥Threshold)	p-value	Coefficient (β)	95% Confidence Interval	
162	Continuous	NA	0.2447	0.0264	-0.0183	0.0711
	≥50	68	0.6238	0.5844	-1.7642	2.9330
	≥60	47	0.4867	0.8858	-1.6236	3.3951
	≥70	30	0.1474	2.1412	-0.7640	5.0464
	≥80	21	0.4593	1.2326	-2.0499	4.5151
	≥85	16	0.2399	2.2072	-1.4887	5.9030
	≥90	11	0.5322	1.3791	-2.9728	5.7309
	ALT Threshold					
	Continuous	NA	0.78216	-0.00521	-0.04236	0.03194
	≥80	23	0.1095	-2.6463	-5.8935	0.6010
	≥90	20	0.1312	-2.6238	-6.0393	0.7916
	≥100	11	0.3541	-2.0499	-6.4065	2.3067

Multivariable Linear Regression (F0-F3 pop.) (Table 2)

Total n	AST Threshold	n(≥Threshold)	p-value	Coefficient (β)	95% Confidence Interval	
126	Continuous	NA	**0.0029**	0.0569	0.0198	0.0940
	≥50	53	0.3050	1.0117	-0.9328	2.9563
	≥60	39	**0.0432**	2.1099	0.0658	4.1540
	≥70	24	**0.0287**	2.6041	0.2750	4.9331
	≥80	16	**0.0309**	2.8997	0.2703	5.5290
	≥85	12	**0.0124**	3.7775	0.8306	6.7244
	≥90	7	0.1112	3.0772	-0.7194	6.8738
	ALT Threshold					
	Continuous	NA	0.0609	0.0288	-0.0013	0.0590
	≥80	18	0.9307	0.1169	-2.5384	2.7722
	≥90	17	0.8314	-0.6587	-3.3701	2.0527
	≥100	8	0.7464	0.6013	-3.0724	4.2751

Multivariable Logistic Regression (F0-F3 pop.) (Table 3)

Total n	AST Threshold	n (≥Threshold)	Odds Ratio	p-value	95% Confidence Interval	
126	Continuous	NA	1.0159	0.1034	0.9968	1.0353
	≥50	53	1.4231	0.4135	0.6109	3.3155
	≥60	39	1.5463	0.3452	0.6255	3.8226
	≥70	24	2.6375	0.0724	0.9155	7.5985
	≥80	16	3.7296	**0.0396**	1.0647	13.064
	≥85	12	5.731	**0.0247**	1.2492	26.2926
	≥90	7	2.0488	0.7562	0.3807	11.0277

Disclosures: Joseph Scaravalle: Nothing to Disclose, Nicholas Kruzdlo: Nothing to Disclose, Stephanie Oliveros-Diaz: Nothing to Disclose, Elisabeth Verwest: Nothing to Disclose, Lily Lu: Nothing to Disclose, Kirsten Hobson: Nothing to Disclose, Cameron Rolph: Nothing to Disclose, Isabelle Crotsley: Nothing to Disclose, Raymond Bell: Nothing to Disclose, Yovanni Rosario: Nothing to Disclose, Guy Neff: Nothing to Disclose.

2452 | LIVERSCAN VS. MRI: A PILOT STUDY OF A NOVEL PORTABLE VCTE DEVICE

Zhuoru Jiang[1] Zihao Huang[2] Yongping Zheng[2] Jie Li[1], [1]Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University, [2]The Hong Kong Polytechnic University

Background: Vibration-controlled transient elastography (VCTE) is widely used for liver fibrosis assessment. While the diagnostic accuracy of standard VCTE, particularly Fibroscan, has been extensively compared to magnetic resonance elastography (MRE), Liverscan is a novel, portable, phased array transducer-based VCTE system whose diagnostic performance remains to be rigorously validated. This study aimed to perform a head-to-head comparison between this novel portable VCTE device vs. the MRE for liver stiffness measurement and Liverscan-derived multi-domain attenuation parameter (MAP) vs. MRI-proton density fat fraction (PDFF) for fat measurement, specifically investigating physiological factors driving measurement discordance. **Methods:** We performed a cross-sectional analysis of 81 participants, including 49 metabolic dysfunction-associated steatotic liver disease (MASLD) patients and 32 healthy controls (HC), who underwent concurrent liver stiffness measurement (LSM) using the portable Liverscan (Eieling Technology Limited, Hong Kong, China) and MRE (uPMR 790, United Image, Shanghai, China). Liver fat quantification was also compared between the Liverscan-derived MAP and MRI-PDFF. Agreement was assessed using Spearman's correlation. **Results:** The correlation between LSM by Liverscan and MRE was significant (r_s = 0.62, $p < 0.001$). Similarly, liver fat quantification demonstrated strong concordance with MRI-PDFF (r_s = 0.84, $p < 0.001$). Importantly, this diagnostic performance was sustained in the MASLD subgroup, where LiverScan maintained significant correlations with MRE for stiffness (r_s = 0.69, $p < 0.001$) and with MRI-PDFF for fat quantification (r_s = 0.66, $p < 0.001$). **Conclusion:** Liverscan demonstrates robust diagnostic concordance with MRE and MRI-PDFF, providing a reliable point-of-care solution for the simultaneous assessment of liver fibrosis and steatosis. However, due to the limited sample size and heterogeneous etiologies of participants, the results are preliminary and inconclusive. Future research should compare the diagnostic accuracy of MRI-based techniques against Liverscan for the diagnosis of liver fibrosis and steatosis using histology as the reference standard.

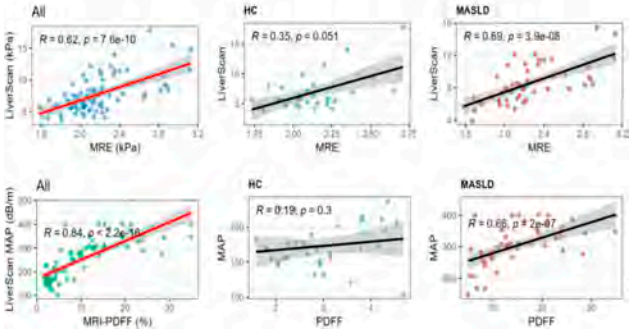
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Table 1. Characteristics of participants.
Abbreviations: BMI=body mass index; MRE=magnetic resonance elastography; PDFF=MRI-proton density fat fraction; LSM=liver stiffness measurement; MAP=multi-domain attenuation parameter.

	HC (n=32)	MASLD (n=49)	p value	Effect size
Male Sex (%)	9 (28.1)	35 (71.4)	<0.001	0.961
Age	31.00 [26.75, 35.50]	31.00 [28.00, 38.00]	0.824	0.031
Height (cm)	165.00 [160.75, 170.50]	175.00 [166.00, 178.00]	0.001	0.862
Weight (kg)	65.06 (9.83)	87.22 (13.34)	<0.001	1.891
BMI (kg/m²)	23.45 (3.16)	29.14 (3.61)	<0.001	1.678
MRE (kPa)	2.08 [1.97, 2.22]	2.19 [2.02, 2.44]	0.097	0.452
PDFF (%)	2.89 [2.25, 3.79]	13.00 [9.38, 19.32]	<0.001	2.222
USE-LSM (kPa)	5.80 [5.05, 7.32]	8.30 [6.70, 10.10]	<0.001	0.659
MAP (dB/m)	170.00 [154.25, 196.50]	304.00 [273.00, 348.00]	<0.001	2.605

Figure 1. Diagnostic concordance of liver stiffness and liver fat content between Liverscan and MRI.
Upper line: Concordance of liver stiffness between Liverscan and MRE.
Lower line: Concordance of liver fat content between Liverscan and MRI-PDFF.



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2453 | ARTIFICIAL INTELLIGENCE-BASED PREDICTION OF HEPATOCELLULAR CARCINOMA IN INDIVIDUALS WITHOUT HBV OR HCV INFECTION IN THE MASLD ERA

Young Seok Kim[1], [1]Soon Chun Hyang University

Background: Current surveillance guidelines for hepatocellular carcinoma (HCC) focus on individuals with liver cirrhosis or viral hepatitis. This study aimed to develop an artificial intelligence (AI)-based model to predict HCC risk in individuals without viral hepatitis. **Methods:** Using the South Korean National Health Insurance Service (NHIS) database, we retrospectively analyzed 7,961,075 individuals aged 20 to 79 years who underwent health screening in 2017 and were followed through 2023. Twelve AI models, including deep learning and machine learning algorithms, were trained and validated using a 7: 3 split. **Results:** The Multi-Head Attention with Deep Neural Network (MHA_DNN) model demonstrated the highest predictive performance (AUC 0.9385, 95% confidence interval [CI]: 0.9312–0.9455) and was selected as the final model. Risk stratification based on predicted probabilities showed a significantly higher incidence of HCC in the High and Extremely High-Risk groups compared to the Low-Risk group (hazard ratio [HR] 11.08 and 91.09, respectively; both $P < 0.001$). SHAP analysis identified the fatty liver index (FLI) and triglyceride (TG) as key factors for predicting HCC. In individuals with FLI < 60, TG ≥ 150 mg/dL was a significant risk factor for HCC (HR 1.14, 95% CI 1.04–1.25), whereas in those with FLI ≥ 60, higher TG levels were associated with a markedly reduced HCC risk (HR 0.27, 95% CI 0.25–0.29). **Conclusion:** We developed a robust AI model for predicting HCC risk in an HBV/HCV-negative general population. FLI and TG emerged as major predictors, supporting the use of metabolic indicators for personalized surveillance in the era of MASLD.
Disclosures: Young Seok Kim: Nothing to Disclose.

2454 | ◆ PREVALENCE OF LIVER FIBROSIS AND STEATOTIC LIVER DISEASE IN COMMUNITY-DWELLING ADULTS (THE LIVERHEALTH PROJECT): A PROSPECTIVE, MULTICENTRE STUDY IN CHINA

Shanghao Liu[1] Xibin Liu[2] Jianxiang Song[3] Yilin Zhang[1] Hui Shi[4] Erdan Huang[5] Lan Ma[6] Yuxia Qi[7] Yang Bo[8] Ruyu Liu[9] Yijun Tang[10] JianSong Ji[3] Puqiang Liu[11] Yan Yang[12] Qing He[13] Wenjuan Wang[14] Huizhen Fan[15] Qiang Yan[16] Xiao Liang[17] Hui Yang[18] Kunyu Ke[19] Xiongwei He[20] Yanhong Liu[21] Wen Kang[22] Chaoyong Wang[23] Haiying Feng[2] Zhiyong Li[24] Caihong Gu[4] Liping Wang[6] Jie Liu[7] Jing Wang[8] Kai Hu[9] Zhongji Meng[10] Lili Ye[25] Jianping Zhang[11] Yinyu Gao[12] Jianquan Wu[26] Xiufeng Zhang[27] Fengjuan Chen[13] Guo Zhang[14] Jianwen Sheng[15] Zhaowei Tong[28] Yongfen Zhu[29] Yajuan Zhao[18] Junchao Zhang[19] Jiangwen Liu[20] Lidong Xu[21] Jing Huang[30] Yani Shi[23] Xinrong Zhang[31] Xinyu Zhao[32] Vincent Wai-Sun Wong[33] Wenhong Zhang[34] Gao-Jun Teng[1] Aleksander Krag[35] Pere Gines[36] Xiaolong Qi[1], [1]Zhongda Hospital, School of Medicine, Southeast University, [2]People's Hospital of Huanghua, [3]Affiliated Yancheng Hospital, School of Medicine, Southeast University, [4]The First Affiliated Hospital of Kangda College of Nanjing Medical University, [5]China national health development research center, [6]Bozhou People's Hospital, [7]Qingdao Public Health Clinical Center, [8]General Hospital of

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Background: Chronic liver disease (CLD) is rapidly increasing worldwide, largely driven by the growing epidemics of obesity, diabetes, and alcohol consumption. China, which has the world's largest population affected by these conditions, lacks prospective, community-based data to estimate the true burden of CLD. We aimed to determine the prevalence of liver fibrosis and steatotic liver disease (SLD) and identify their associated factors among community-dwelling adults in China. **Methods:** This prospective, community-based, investigator-initiated cohort study (the LiverHealth project) was conducted at 18 sites across 13 provincial-level administrative regions in China between September 2024 and January 2026. Participants were recruited from the general community rather than through clinical referrals or health check-ups, guided by local age- and sex-specific population distributions to enhance representativeness. Adults aged 18 years or older underwent vibration-controlled transient elastography. The primary outcome was the prevalence of significant fibrosis (liver stiffness measurement [LSM] $\geq$ 8 kPa). Secondary outcomes included the prevalence of advanced fibrosis (LSM $\geq$ 12 kPa), SLD (controlled attenuation parameter $\geq$ 248 dB/m), and SLD spectrum —metabolic dysfunction-associated steatotic liver disease (MASLD), metabolic and alcohol related/associated liver disease (MetALD), and alcohol-associated/related liver disease (ALD). Factors associated with fibrosis and SLD were assessed using mixed-effects logistic regression. **Results:** Of 25805 community-dwelling adults enrolled (median age 51.0 years; 44.9% men), 4.4% had significant fibrosis and 0.8% had advanced fibrosis. SLD was present in 43.7% of participants, with MASLD in 39.4%, MetALD in 2.0%, and ALD in 1.6%. The highest prevalences of significant fibrosis were observed in individuals with obesity (10.6%) and diabetes (10.4%). In multivariable analyses, male sex, older age, overweight or obesity, central obesity, prediabetes or diabetes, hypertension, dyslipidaemia, and an increasing number of cardiometabolic risk factors were independently associated with both steatosis and fibrosis. Heavy alcohol consumption was independently associated with significant fibrosis and was consistently linked to higher fibrosis prevalence across all cardiometabolic and chronic viral hepatitis subgroups, with no significant interaction between alcohol and any individual risk factor (all $p > 0.05$; Figure 1). **Conclusion:** Liver fibrosis and SLD are highly prevalent in community-dwelling Chinese adults, driven by metabolic factors and alcohol consumption. The 4.4% prevalence of significant fibrosis corresponds to nearly 49 million adults in China. Identifying these individuals at an early stage offers a critical opportunity to deliver targeted interventions and curb the progression to cirrhosis and hepatocellular carcinoma.

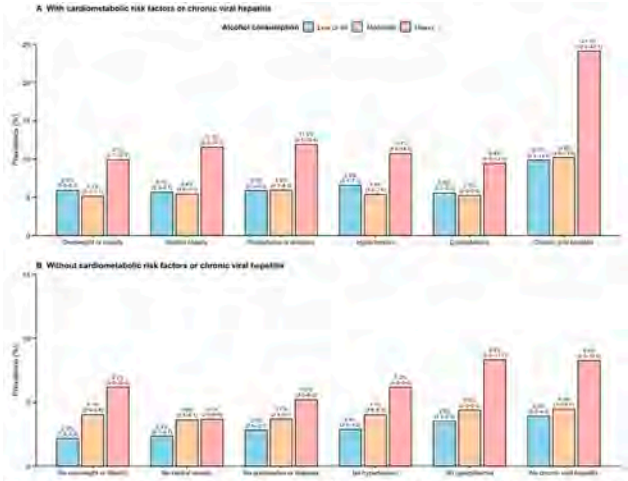


Figure 1. Prevalence of significant fibrosis (LSM ≥8 kPa) by alcohol consumption across cardiometabolic and chronic viral hepatitis subgroups

(A) Prevalence of significant fibrosis by alcohol consumption category among individuals with each cardiometabolic risk factor or chronic viral hepatitis. (B) Prevalence of significant fibrosis by alcohol consumption category among individuals without each cardiometabolic risk factor or chronic viral hepatitis. Data are presented as % (95% CI). Alcohol consumption was categorized as low or no (≤30 g/day for men and ≤20 g/day for women), moderate (>30-60 g/day for men and >20-50 g/day for women), and heavy (>60 g/day for men and >50 g/day for women), corresponding to MASLD, MetALD, and ALD criteria in the multi-society nomenclature, respectively. LSM=liver stiffness measurement. CI=confidence interval. MASLD=metabolic dysfunction-associated steatotic liver disease. MetALD=metabolic and alcohol related/associated liver disease. ALD=alcohol-associated/related liver disease.

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to Disclose, Yan Yang: Nothing to Disclose, Qing He: Nothing to Disclose, Wenjuan Wang: Nothing to Disclose, Huizhen Fan: Nothing to Disclose, Qiang Yan: Nothing to Disclose, Xiao Liang: Nothing to Disclose, Hui Yang: Nothing to Disclose, Kunyu Ke: Nothing to Disclose, Xiongwei He: Nothing to Disclose, Yanhong Liu: Nothing to Disclose, Wen Kang: Nothing to Disclose, Chaoyong Wang: Nothing to Disclose, Haiying Feng: Nothing to Disclose, Zhiyong Li: Nothing to Disclose, Caihong Gu: Nothing to Disclose, Liping Wang: Nothing to Disclose, Jie Liu: Nothing to Disclose, Jing Wang: Nothing to Disclose, Kai Hu: Nothing to Disclose, Zhongji Meng: Nothing to Disclose, Lili Ye: Nothing to Disclose, Jianping Zhang: Nothing to Disclose, Yinyu Gao: Nothing to Disclose, Jianquan Wu: Nothing to Disclose, Xiufeng Zhang: Nothing to Disclose, Fengjuan Chen: Nothing to Disclose, Guo Zhang: Nothing to Disclose, Jianwen Sheng: Nothing to Disclose, Zhaowei Tong: Nothing to Disclose, Yongfen Zhu: Nothing to Disclose, Yajuan Zhao: Nothing to Disclose, Junchao Zhang: Nothing to Disclose, Jiangwen Liu: Nothing to Disclose, Lidong Xu: Nothing to Disclose, Jing Huang: Nothing to Disclose, Yani Shi: Nothing to Disclose, Xinrong Zhang: Nothing to Disclose, Xinyu Zhao: Nothing to Disclose, Vincent Wai-Sun Wong: Nothing to Disclose, Wenhong Zhang: Nothing to Disclose, Gao-Jun Teng: Nothing to Disclose, Aleksander Krag: Nothing to Disclose, Pere Gines: Gilead & Grifols: Grant/Research Support, SeaBeLife, Merck, Sharp and Dohme (MSD), Ocelot Bio, Roche Diagnostics Intern, Boehringer Ingelheim: Advisor, Gilead, RallyBio, Behring: Advisor, Pfizer: Speaking and Teaching, Astra Zeneca: Advisor, Sysmex: Advisor, Grifols: Speaking and Teaching, Xiaolong Qi: Nothing to Disclose.

2455 | ◆ TRANSITION FROM CHRONIC VIRAL HEPATITIS TO METABOLIC PREDOMINANCE IN LIVER FIBROSIS IN CHINA: A PROSPECTIVE COMMUNITY-BASED STUDY

Shanghao Liu[1] Yilin Zhang[1] Xibin Liu[2] Lan Ma[3] Yuxia Qi[4] Yang Bo[5] Ruyu Liu[6] Yijun Tang[7] Yan Yang[8] Guo Zhang[9] Huizhen Fan[10] Tingting Bian[11] Xiao Liang[12] Hui Yang[13] Kunyu Ke[14] Haiying Feng[2] Yiwei Shen[1] Diya Lu[3] Kun Xu[4] Jing Wang[5] Chuanchun Mao[6] Zhongji Meng[7] Junhong Yang[8] Wenjuan Wang[9] Jianwen Sheng[10] Zhaowei Tong[11] Yongfen Zhu[12] Yajuan Zhao[13] Junchao Zhang[14] Wenhong Zhang[14] Gao-Jun Teng[1] Aleksander Krag[15] Xiaolong Qi[1], [1]Zhongda Hospital, School of Medicine, Southeast University, [2]People's Hospital of Huanghua, [3]Bozhou People's Hospital, [4]Qingdao Public Health Clinical Center, [5]General Hospital of Ningxia Medical University, [6]Beijing Ditan Hospital, Xuzhou Hospital, Capital Medical University, [7]Taihe Hospital, Hubei University of Medicine, [8]Baiyin Central Hospital, [9]Guangxi Hospital Division of The First Affiliated Hospital, Sun Yat-sen University, [10]Yichun People's Hospital, [11]Huzhou Central Hospital, Affiliated Central Hospital, Huzhou University, [12]Sir Run-Run Shaw Hospital, Zhejiang University School of Medicine, [13]The Second Affiliated Hospital of Guangzhou Medical University, [14]Mengchao Hepatobiliary Hospital of Fujian Medical University, [15]Odense University Hospital

Background: Chronic viral hepatitis has historically been the dominant cause of chronic liver disease in China. However, rapid increases in metabolic dysfunction and alcohol consumption, alongside declining viral hepatitis prevalence, may be reshaping the aetiological landscape of liver fibrosis. Robust population-based evidence quantifying this transition remains limited. We aimed to characterise the contemporary aetiological distribution of liver fibrosis in China, with a focus on the relative contributions of metabolic dysfunction, chronic viral hepatitis, and harmful alcohol consumption. **Methods:** In this large, prospective, community-based cohort study (the LiverHealth project), adults aged ≥18 years were recruited across 13 sites in 12 provincial-level administrative regions in China between December 2024 and January 2026. All participants underwent standardised serological testing for hepatitis B virus and hepatitis C virus, structured assessment of alcohol consumption, comprehensive metabolic dysfunction evaluation, and vibration-controlled transient elastography for liver fibrosis assessment. Participants were classified into four mutually exclusive aetiological groups using a hierarchical framework: chronic viral hepatitis, harmful alcohol consumption, metabolic dysfunction, and no major aetiological factor identified. The primary outcome was the aetiological distribution of significant fibrosis (liver stiffness measurement ≥8 kPa). **Results:** We enrolled 17610 participants (median age 50.0 years; 43.2% male). Metabolic dysfunction accounted for the largest proportion of significant fibrosis cases (69.5%, 95% CI 65.9-72.8), substantially exceeding the contributions of chronic viral hepatitis (14.0%, 11.6-16.8) and harmful alcohol consumption (13.3%, 10.9-16.0). The relative contribution of metabolic dysfunction was greater in women and older adults, whereas harmful alcohol consumption contributed more in men and younger individuals (Figure 1). Across all aetiological groups, obesity (adjusted odds ratios 3.41-5.44), severe central obesity (3.58-6.54), and diabetes (2.26-4.67) were independently associated with significant fibrosis. Coexistence of metabolic dysfunction markedly increased fibrosis prevalence among individuals with chronic viral hepatitis or harmful alcohol consumption. **Conclusion:** Metabolic dysfunction has emerged as the predominant driver of liver fibrosis in China. Metabolic risk factors—particularly obesity and diabetes—consistently increase fibrosis risk across underlying aetiologies. These findings underscore the need for integrated

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metabolic health strategies and support the incorporation of liver fibrosis screening into community-based chronic disease management programmes to prevent progression to cirrhosis and hepatocellular carcinoma.

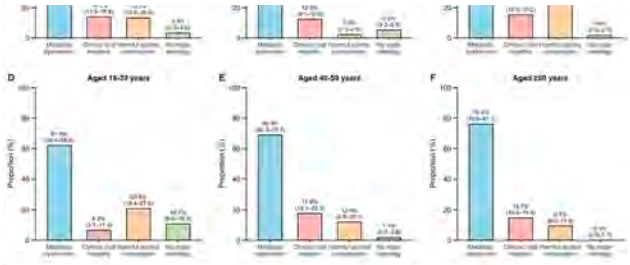


Figure 1. Aetiological distribution of significant fibrosis (LSM ≥8 kPa) overall and by sex and age

(A) Overall population; (B) female; (C) male; (D) participants aged 18-39 years; (E) participants aged 40-59 years; (F) participants aged ≥60 years. Aetiological groups were classified into four mutually exclusive categories—chronic viral hepatitis, harmful alcohol consumption, metabolic dysfunction, and no major aetiological factor—using a hierarchical framework (see Methods). LSM=liver stiffness measurement.

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2456 | ◆ HOW ARE PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH) MANAGED IN THE REAL WORLD? A DESCRIPTIVE ANALYSIS OF DIAGNOSTIC TESTING, TREATMENT, AND MONITORING IN US ADMINISTRATIVE CLAIMS

Christopher Bell[1] Guillaume Germain[2] Hannah Mei[3] Patricia Juliao[4] Patrick Gravelle[2] Sophie Ma[2] Jessica Abou Shaar[2] François Laliberté[2], [1]GSK, Durham, NC, USA, [2]Groupe d'analyse SRI, Montréal, QC, Canada, [3]GSK, Collegeville, PA, USA, [4]GSK, Philadephia, PA, USA

Background: Metabolic dysfunction-associated steatohepatitis (MASH) affects ~17 million US adults, yet <5% carry a coded diagnosis. Fibrosis stage predicts liver-related events and mortality, and fibrosis regression assessed by non-invasive tests (NITs) is a key predictor of clinical benefit. Guidelines recommend at-risk patient identification, diagnosis, NIT-based fibrosis staging, specialist referral, treatment, and ongoing fibrosis monitoring, yet real-world pathway completion is limited. We conducted a retrospective analysis to characterize patients with MASH and assess diagnostic, treatment, and monitoring patterns. **Methods:** This retrospective cohort study used claims from Komodo Health Research Database (>230 million US patients). Adults with MASH (K75.81; ≥1 inpatient or ≥2 outpatient claims) or a resmetirom claim without a MASH diagnosis were identified (Jan 2017 to July 2025). Index date was the earliest qualifying diagnosis/pharmacy claim. Cohorts included incident (no MASH claim 12 months pre-index) and prevalent (prior MASH claim) patients. At least 12 months of continuous enrollment pre- and post-index were required, and patients with non-MASH liver disease were excluded. Outcomes included demographics, comorbidities, medication history, diagnostic testing, specialist visits, treatment, and costs (2025 US$). **Results:** In total, 108,856 adults were included (incident: 78.5%; prevalent: 21.5%). Mean (SD) age was 55.8 (13.7) years, 55.2% of patients were female and 55.7% were commercially insured. Comorbidities included hypertension (61.8%), hyperlipidemia (54.6%), type 2 diabetes (43.2%), obesity (40.8%), and cirrhosis (12.4%) (Table). Fibrosis-specific testing was low in the observation period: VCTE (7.2%), MRE (0.5%), and liver biopsy (4.6%). While components of serum-based fibrosis scores were identifiable, full panel completion was limited: (FIB-4: 20.8%; APRI: 21.1%; Agile 3+/4: 25.1%; NFS: 17.8%; ELF: 0.1%). General metabolic testing was common (comprehensive metabolic panel: 82.8%), suggesting patients were metabolically monitored but rarely fibrosis assessed. Overall, 36.4% of patients saw a gastroenterologist and 3.7% saw a hepatologist post-index, an increase from pre-index levels. MASH-directed pharmacotherapy was rare (resmetirom: 0.1%; semaglutide: 6.9%; note: study period largely preceded MASH-specific approval). Mean (SD) total costs were $24,735 ($44,651), rising to $43,976 ($68,680) with cirrhosis — a 78% increase. **Conclusion:** In >100,000 US patients with MASH, there was limited fibrosis-specific testing, specialist visits, and use of MASH-specific therapy, indicating gaps in care. As therapies with direct antifibrotic mechanisms become available, closing these gaps will ensure patients are staged, treated, and managed according to fibrosis-direct goals.

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Table Patient characteristics and healthcare utilization patterns

	MASH Cohort N=108,856 (100%)	Incident MASH n=85,402 (78.5%)	Prevalent MASH n=23,454 (21.5%)
Demographic/characteristic (pre-index)			
Age, mean (SD), years	55.8 (13.7)	55.4 (13.7)	57.4 (13.3)
Female, (%)	55.2	54.8	56.4
Commercially insured, (%)	55.7	57.7	48.3
Comorbidities, (%)			
Hypertension	61.8	59.7	69.3
Hyperlipidemia	54.8	52.0	63.8
T2DM	43.2	40.8	51.7
Obesity	40.8	39.5	45.7
CVD	18.1	17.7	19.7
Cirrhosis	12.4	11.0	17.6
Quan-CCI, mean (SD)	1.51 (1.7)	1.45 (1.6)	1.71 (1.8)
Prescriptions (select), (%)			
CVD	66.1	64.8	70.7
Biguanides	29.3	27.9	34.3
GLP-1 RA	10.6	10.2	12.1
Diagnostic testing patterns (pre-index / post-index), (%)			
CMP	77.4 / 82.8	76.0 / 82.5	82.5 / 84.2
Hepatic function panel	16.6 / 19.7	15.7 / 19.7	20.0 / 19.7
Abdominal ultrasound	28.4 / 26.4	28.6 / 26.6	27.5 / 25.7
Gastroesophageal varices screening	11.8 / 15.9	11.1 / 16.2	14.1 / 14.5
AFP	5.6 / 9.9	4.2 / 9.1	10.9 / 12.5
Elastography - VCTE	4.5 / 7.2	4.2 / 7.6	5.5 / 5.6
Elastography - MRE	0.2 / 0.5	0.2 / 0.5	0.2 / 0.3
Liver biopsy	1.4 / 4.6	1.0 / 5.3	2.7 / 1.7
Scores (pre-index / post-index), (%)			
FIB-4	17.8 / 20.8	-	-
APRI	18.1 / 21.1	-	-
Agile 3+/4	21.5 / 25.1	-	-
NFS	15.0 / 17.8	-	-
ELF	0.04 / 0.1	-	-
MASH-directed pharmacotherapy (pre-index / post-index), (%)			
Resmetirom	0.0 / 0.1	-	-
Semaglutide	4.0 / 6.9	-	-
Specialist visit (pre-index / post-index), (%)			
Cardiologist	28.0 / 32.4	27.9 / 32.5	28.6 / 32.0
Gastroenterologist	26.9 / 36.4	24.7 / 36.6	34.7 / 35.6
Hepatologist	1.9 / 3.7	1.3 / 3.5	3.9 / 4.4
Endocrinologist	9.7 / 11.4	9.0 / 11.0	12.2 / 12.8

AFP, alpha-fetoprotein; APRI, aminotransferase to platelet ratio index; CMP, comprehensive metabolic panel; CVD, cardiovascular disease; ELF, enhanced liver fibrosis; FIB-4, Fibrosis-4; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HCP, healthcare practitioner; MASH, metabolic dysfunction-associated steatohepatitis; MRE, magnetic resonance elastography; NFS, non-alcoholic fatty liver disease fibrosis score; Quan-CCI, Quan-Charlson comorbidity index; SD, standard deviation; T2DM, type 2 diabetes mellitus; VCTE, vibration-controlled transient elastography

Disclosures: Christopher Bell: Nothing to Disclose, Guillaume Germain: Nothing to Disclose, Hannah Mei: GSK: Independent Contractor, Patricia Juliao: Nothing to Disclose, Patrick Gravelle: Nothing to Disclose, Sophie Ma: Nothing to Disclose, Jessica Abou Shaar: Nothing to Disclose, François Laliberté: Nothing to Disclose.

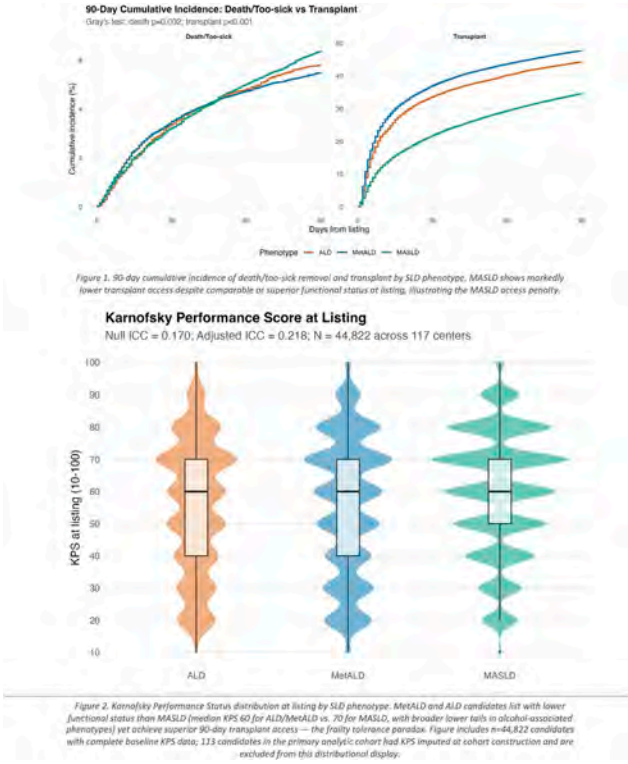
2457 | ◆ THE MASLD ACCESS PENALTY: FRAILTY TOLERANCE AND 90-DAY WAITLIST OUTCOMES ACROSS STEATOTIC LIVER DISEASE PHENOTYPES IN 44,935 UNOS CANDIDATES

Islam Mohamed[1] Mohamed Nadeem[2] Basil Jalamneh[2] Mohamad Ali Ibrahim[3] Prasun Jalal[3], [1]The Cleveland Clinic Foundation-Fairview hospital, [2]Cleveland Clinic Foundation, [3]Baylor College of Medicine

Background: Karnofsky Performance Status (KPS) is the only frailty surrogate collected nationally in UNOS, yet whether the transplant system applies consistent functional thresholds across steatotic liver disease (SLD) phenotypes and whether the prognostic weight of functional impairment differs by etiology is unknown. We hypothesized that frailty tolerance at listing would vary across ALD, MetALD, and MASLD, with differential consequences for waitlist mortality and transplant access. **Methods:** We analyzed OPTN/UNOS STAR data (2017–2023), classifying 44,935 adults at 117 centers as ALD (n = 7,319), MetALD (n = 20,494), or MASLD (n = 17,122) using the validated SLD algorithm. Center-level KPS clustering was quantified by ICC from a multilevel mixed-effects model; Spiegelhalter over-dispersion-adjusted funnel plots identified outlier centers. 90-day waitlist death/too-sick removal and transplant were modeled as competing risks using Fine-Gray regression adjusted for MELD-Na, demographics, and insurance. Phenotype-stratified Fine-Gray models examined whether outcome associations differed by etiology; a multilevel cause-specific Cox model decomposed patient vs. centers contributions to observed disparities. **Results:** KPS at listing was lower in MetALD (55.5 ± 21.6) and ALD (55.3 ± 20.7) than MASLD (59.6 ± 19.5; $p < 0.001$), despite higher MELD in MetALD (23.4) and ALD (22.8) versus MASLD (19.1). Center membership explained 21.8% of KPS variance after case-mix adjustment (ICC = 0.218). Medicare and Medicaid patients listed with 2.6–2.7 fewer KPS points than privately insured patients, independent of disease severity ($p < 0.001$). Despite lower KPS and higher MELD at listing, MetALD achieved the highest 90-day transplant access (47.8%) and lowest mortality (5.5%), while MASLD with the best KPS at listing had the lowest access (34.7%) and highest mortality (6.4%; Gray's $p < 0.001$). In adjusted models, MetALD carried significantly lower mortality than MASLD (sHR 0.79, 95% CI 0.71–0.87); ALD did not differ significantly (sHR 0.94). Hispanic candidates had 23% lower transplant access (sHR 0.77) and Black candidates 25% higher mortality (sHR 1.25), independent of phenotype. Black and Medicare mortality disparities were fully robust to center clustering, reflecting patient-level inequities. Hispanic transplant and Medicaid access disparities were largely explained by where patients listed. **Conclusion:** MetALD and ALD candidates list with worse functional status yet achieve superior waitlist outcomes compared to MASLD, demonstrating that the transplant system is more tolerant of functional impairment in ALD. MASLD candidates face a systematic access penalty: a paradox of withheld urgency despite relatively preserved KPS. Center-level KPS variation is clinically meaningful and contributing independently to insurance-based listing disparities across the SLD spectrum.

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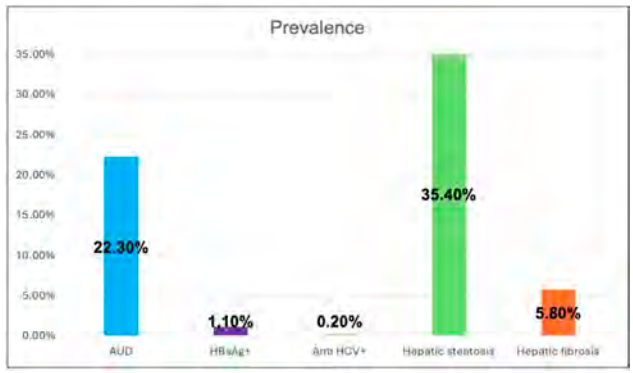


Disclosures: Islam Mohamed: Nothing to Disclose, Mohamed Nadeem: Nothing to Disclose, Basil Jalamneh: Nothing to Disclose, Mohamad Ali Ibrahim: Nothing to Disclose, Prasun Jalal: Mallinckrodt Pharmaceuticals: Advisor, Madrigal: Grant/Research Support, Ipsen: Grant/Research Support, mirum: Advisor.

2458 | ◆ ALCOHOL USE DISORDER AND STEATOTIC LIVER DISEASE ARE COMMON IN RURAL INDIA-A CROSS SECTIONAL POPULATION-BASED STUDY

Anand Kulkarni[1] Sridevi Prasanna[2] Keerthi Bandi[3] Murali Mohan Reddy Gopireddy[2] Shailaja Tetali[3] Rachana Domudala[2] Rohit Kumar[2] Sasikala Mitnala[4] Padaki Nagaraja Rao[2] K Rajender Reddy[5] Nageshwar Reddy[2], [1]Asian Institute of Gastroenterology, [2]AIG Hospitals, [3]Indian Institute of Public Health, [4]AHF, [5]University of Pennsylvania

Background: At a population level, few studies have assessed the prevalence of metabolic dysfunction-associated liver disease (MASLD), while the impact of alcohol use has not been well addressed worldwide. It is also common to consider that all patients with SLD in the community are related to MASLD, and the impact of alcohol use on SLD has not been evaluated with validated methods. We aimed to assess the prevalence of alcohol use disorder (AUD) and its impact on SLD, and hepatic fibrosis, in rural India. **Methods:** A cross-sectional community based study was conducted and adults were screened for AUD using AUD identification test (AUDIT) in 77 villages in rural Southern India. Demographic, clinical, and behavioural assessments, along with vibration-controlled transient elastography (FibroScan by Echosens, Paris), biochemical tests, and viral marker tests were performed. The objectives were to assess the prevalence of AUD, SLD and hepatic fibrosis, and to identify factors associated with AUD and fibrosis. **Results:** Among 4,281 participants (age: 54.42 ± 14.37 years; Women: 51.7%; BMI: 24.80 ± 4.72 kg/m^2 ; overweight/obese: 63.2%; diabetes mellitus: 18.3%; hypertension: 30.7%) with complete data, AUD was identified in 22.3% (95% CI, 21.0–23.5) with hazardous, harmful, and dependent alcohol use observed in 21.1%, 0.8%, and 0.3%, respectively. The median controlled attenuation parameter (CAP) was 228 (IQR 68 db/m) and median liver stiffness measurement (LSM) was 4.9 (IQR, 1.8 kPa). 35.4% (95%CI, 34-36.9) had hepatic steatosis (CAP > 248 dB/m) and 5.8% (95%CI, 5.2-6.6) had fibrosis (LSM > 8.2 kPa). HBsAg was positive in 1.1% (95% CI, 0.9-1.5) and anti HCV in 0.2% (95% CI, 0.1-0.4). Among individuals with steatosis (n = 1517), MASLD was the predominant subtype (70.1%), followed by MetALD (22.3%), cryptogenic (5.6%), and ALD (1.2%). Adjusted analysis showed significantly higher odds of AUD among individuals aged 31–45 years (aOR: 2.53; p = 0.021), men (aOR: 3.29; p < 0.001), and those with lower educational status. Diabetes mellitus (aOR: 1.77), AUD (aOR: 1.50), and hepatic steatosis (aOR: 2.87) were independently associated with Hepatic fibrosis (^{3}F2). **Conclusion:** AUD is highly prevalent in rural India and is associated with high rates of SLD. Its significant association, along with diabetes, with hepatic fibrosis highlights the need for integrated community-based screening and targeted interventions to reduce burden of ALD/MetALD.



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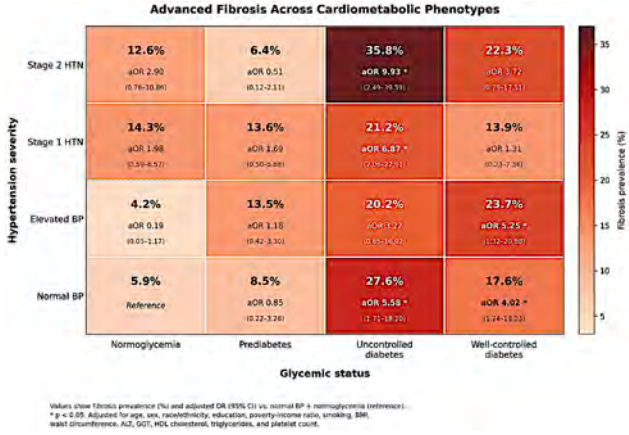
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2459 | ◆ INDEPENDENT AND JOINT ASSOCIATIONS OF HYPERTENSION SEVERITY AND GLYCEMIC DYSFUNCTION WITH ADVANCED LIVER FIBROSIS IN U.S. ADULTS WITH MASLD: NHANES 2017–2023

Ridwan Lawal[1] Sarpong Boateng[2] Guy Loic Nguefang Tchoukeu[3] Cherechi Nwabueze[4] Bright Nwatamole[5] Mayowa Adefuye[6] Chimezirim Ezeano[7] Ihunanya Kanu[8] Eunice Omeludike[9] Basile Njei[10], [1]University of Texas Rio Grande Valley, [2]Yale New Haven Health, Bridgeport Hospital, [3]Texas Tech University Health Science Center, Permian Basin, [4]John H. Stroger Jr. Hospital of Cook County, [5]Zucker School of Medicine at Hofstra/Northwell at Vassar Brothers Medical Center, [6]Bridgeport hospital, Bridgeport CT, [7]Advocate Aurora Healthcare, [8]Baptist Memorial Hospital- Golden Triangle, [9]Piedmont Athens Regional Medical Center, [10]Yale University

Background: Metabolic dysfunction–associated steatotic liver disease (MASLD) is closely linked to cardiometabolic comorbidities, including hypertension and dysglycemia. However, the independent and combined contributions of hypertension severity and glycemic dysfunction to advanced liver fibrosis remain incompletely characterized in contemporary U.S. populations. We evaluated the associations of hypertension severity and glycemic status with advanced liver fibrosis among U.S. adults with MASLD. **Methods:** We analyzed adults with MASLD from NHANES 2017–2023 using survey-weighted analyses. Hypertension severity was categorized per ACC/AHA criteria (normal, elevated, stage 1, stage 2). Glycemic status was classified as normoglycemia, prediabetes, well-controlled diabetes (HbA1c $<7\%$), and uncontrolled diabetes (HbA1c $\geq 7\%$). Advanced liver fibrosis was primarily defined by vibration-controlled transient elastography liver stiffness measurement (LSM) ≥ 10 kPa. Secondary analyses evaluated continuous liver stiffness and alternative fibrosis thresholds. Multivariable survey-weighted logistic and linear regression models adjusted for demographic, socioeconomic, lifestyle, and metabolic factors. Trend analyses across hypertension and glycemic severity categories were performed. **Results:** Among 67.7 million weighted U.S. adults with MASLD, advanced fibrosis prevalence increased progressively across worsening cardiometabolic phenotypes, from 5.9% among normotensive normoglycemic individuals to 35.8% among those with stage 2 hypertension and uncontrolled diabetes. Compared with the reference phenotype (normal blood pressure plus normoglycemia), uncontrolled diabetes demonstrated the strongest associations: normal blood pressure plus uncontrolled diabetes (aOR 5.58, 95% CI 1.71–18.20), stage 1 hypertension plus uncontrolled diabetes (aOR 6.87, 95% CI 2.06–22.91), and stage 2 hypertension plus uncontrolled diabetes (aOR 9.93, 95% CI 2.49–39.59). Increasing hypertension severity (p-trend $= 0.026$) and glycemic severity (p-trend < 0.001) were independently associated with advanced fibrosis. Continuous liver stiffness analyses were consistent, with the highest burden among participants with stage 2 hypertension and uncontrolled diabetes ($\beta = 0.40$, $p < 0.001$). No significant multiplicative interaction was observed (p-interaction $= 0.15$), suggesting additive cardiometabolic effects. **Conclusion:** Among U.S. adults with MASLD, worsening hypertension severity and glycemic dysfunction were independently associated with progressively higher advanced liver fibrosis burden, with uncontrolled diabetes demonstrating the strongest associations. These findings highlight the cumulative impact of cardiometabolic dysfunction in MASLD and support integrated cardiometabolic risk stratification and aggressive metabolic optimization in high-risk populations.



Disclosures: Ridwan Lawal: Nothing to Disclose, Sarpong Boateng: Nothing to Disclose, GUY LOIC NGUEFANG TCHOUKEU: Nothing to Disclose, Cherechi Nwabueze: Nothing to Disclose, Bright Nwatamole: Nothing to Disclose, Mayowa Adefuye: Nothing to Disclose, chimezirim ezeano: Nothing to Disclose, Ihunanya Kanu: Nothing to Disclose, Eunice Omeludike: Nothing to Disclose, Basile Njei: Nothing to Disclose.

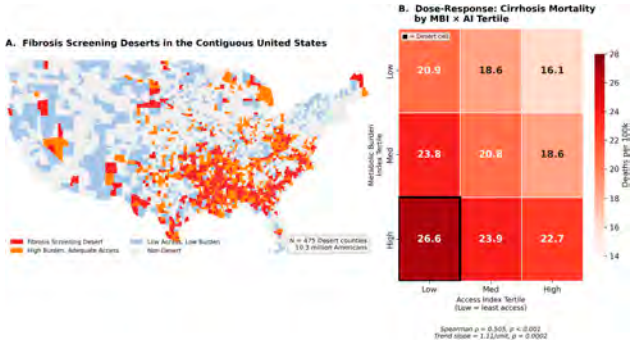
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2460 | ◆ FIBROSIS SCREENING DESERTS: A NATIONAL COUNTY-LEVEL ANALYSIS OF METABOLIC BURDEN, HEPATOLOGY ACCESS, AND CIRRHOSIS MORTALITY

Harika Dadigiri[1] Srinivas Venkatanarayanan[2] Jeril Lasington[3] Anas Mardini[3] Venaktesh Gondhi[3] Edward Barbarito[4], [1]New York Medical college Saint Clare's and Saint Mary's Hospital, [2]UCF, [3]NYMC Saint Clare's and Saint Mary's Hospital, [4]Saint Clare's Health

Background: Although MASLD affects approximately 38% of U.S. adults, advanced fibrosis remains largely undetected. Prior studies have linked upstream determinants to preventable MASLD mortality, but no national framework has defined counties where metabolic risk overlaps with limited hepatology screening capacity. We operationalised and mapped "Fibrosis Screening Deserts" and evaluated their association with cirrhosis mortality at the county level. **Methods:** We performed an ecological study of 3,134 U.S. counties using CDC PLACES, HRSA AHRF, SVI, USDA RUCC, HME GHDX, SAHIE, and OPTN data. A Metabolic Burden Index combined obesity, diabetes, and hypertension using Z-scores (Cronbach's a = 0,85), while an Access Index combined GI density, inverse HPSA status, and SVI Theme 4 using percentile ranks, given zero gastroenterologists in 69% of counties. Deserts were defined as top-tertile MBI plus bottom-tertile AI. Primary outcome was 2017-2019 IHME age-adjusted cirrhosis mortality. Multivariable OLS with HC SE adjusted for socioeconomic, demographic, rurality, insurance, transplant-distance, and state effects; multiple sensitivity analyses were performed. **Results:** Of 3,134 counties, 478 (15.3%) met Desert criteria, encompassing 10.3 million Americans. Desert counties were predominantly rural (82%) with mean non-Hispanic Black proportion of 22.5% vs. 6.4%. Among Desert counties, 97% had zero gastroenterologists (0.1 vs. 1.7 per 100,000). Obesity (42.1% vs. 36.5%), diabetes (17.2% vs. 13.0%), and unadjusted cirrhosis mortality (26.6 vs. 20.4 per 100,000) were higher in Deserts (all $p < 0.001$). In adjusted analyses, Desert status was associated with 2.53 excess cirrhosis deaths per 100,000/year (95% CI 1.53–3.52, $p < 0.001$), corresponding to ~260 preventable deaths annually (PAF 0.43%). A 66% dose-response gradient spanned MBI-by-AI tertiles (16.1 to 26.6 per 100,000; Spearman $\rho = 0.505$, $p < 0.001$). Desert status showed spatial concordance with cirrhosis mortality (bivariate Moran's $I = 0.163$, $p = 0.001$). Adjusted liver-specific excess (+12.4%) was three times non-liver excess (+4.1%); external-cause mortality was null in the 12-covariate model ($\beta = 0.01$, $p = 0.996$), confirming a liver-specific mechanism. The E-value was 1.93 (lower CI bound 1.36). Results were robust across eight specifications ($\beta = 0.84$–2.53, all $p < 0.05$). **Conclusion:** Fibrosis screening deserts affect 10.3 million Americans in the rural South and Appalachia, disproportionately burden minority populations, and are independently associated with 2.53 excess cirrhosis deaths/100,000/year. Based on the published cost-effectiveness of community FIB-4 to VCTE screening ($78,647/QALY; Park 2025), targeted community screening with telemedicine hepatology in desert counties is a cost-effective policy intervention.



Disclosures: Harika Dadigiri: Nothing to Disclose, Srinivas Venkatanarayanan: Nothing to Disclose, Jeril Lasington: Nothing to Disclose, Anas Mardini: Nothing to Disclose, Venaktesh Gondhi: Nothing to Disclose, Edward Barbarito: Nothing to Disclose.

2461 | ◆ REAL-WORLD COMPARATIVE EFFECTIVENESS OF SEMAGLUTIDE VERSUS RESMETIROM ON LIVER ENZYMES AND CARDIOMETABOLIC MARKERS IN PATIENTS WITH MASH

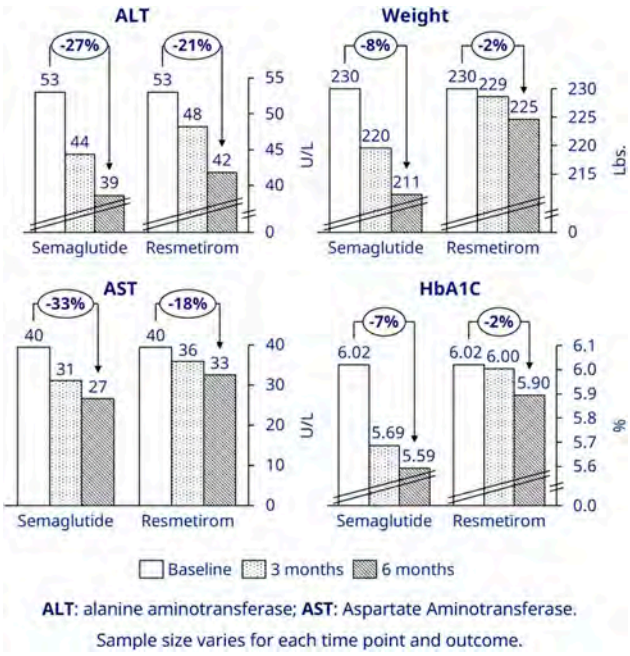
Prachi Arora[1] David Shi[1] Abdalla Aly[1] Husam Albarmawi[1] Maximilian Kurt Jara[2] Eric Lawitz[3], [1]Novo Nordisk, [2]Novo Nordisk Inc., [3]Texas Liver Institute, University of Texas Health San Antonio

Background: Semaglutide and resmetirom received FDA conditional approval for the treatment of metabolic dysfunction associated steatohepatitis (MASH) with F2-F3 fibrosis. Real-world evidence comparing both agents is limited. This study compared the effectiveness of semaglutide versus resmetirom on liver enzymes and cardiometabolic markers in patients with MASH. **Methods:** This observational retrospective cohort study used EMR data from 30 health systems in the Truveta data (June 2021–March 2026). Adults with MASH diagnosis who initiated semaglutide injection or resmetirom were identified (index date was the first dispensation of either agent). Patients were followed until death, disenrollment, discontinuation/switching, or end of study. Patients with evidence of cirrhosis or other chronic liver diseases were excluded. Changes from baseline in ALT, AST, weight, and HbA1C were assessed at 1, 3, 6, and 12 months. To

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reduce confounding, inverse probability of treatment weighted generalized estimating equations were used to estimate changes at 3 and 6 months. Models were adjusted for baseline outcome, age, sex, race, ethnicity, baseline BMI, comorbidities (hypertension, hyperlipidaemia, type 2 diabetes, heart failure and atherosclerotic cardiovascular disease), and prescription drug use. For all analysis, persistence to treatment (45-day gap allowed) was required for each time point. A subgroup with abnormal baseline ALT (>33 U/L for males and >25 U/L for females) was also analyzed. **Results:** The study included 2,873 and 2,285 patients treated with semaglutide and resmetirom, respectively. Semaglutide cohort was younger (48 vs 59 years), more frequently female (67% vs 58%), had higher BMI (39 vs 34 Kg/m^2), higher baseline weight (243 vs 218 lbs.), had more frequently hypertension (51% vs 45%), hyperlipidemia (60% vs 44%), lower baseline ALT (51 vs 58 U/L), AST (33 vs 43 U/L), and HbA1C (5.63 vs 6.63%); (all $P<0.05$). In unadjusted analyses, semaglutide cohort showed greater 1-month reductions in ALT (-6.0 vs +5.4 U/L) and AST (-4.5 vs +4.0 U/L) and greater 6- and 12-month reductions in weight (-20.2 vs -3.6 lbs., -31.6 vs -4.1 lbs.), and HbA1C (-0.36 vs -0.09%, -0.4 vs -0.2%); (all $P<0.05$). In adjusted analyses, semaglutide cohort had significantly greater reductions in ALT, AST, weight, and HbA1C at 3 and 6 months (Figure). Similar relative reductions were observed in the sub-group analysis. **Conclusion:** Patients treated with semaglutide achieved significantly greater reductions in ALT, AST, weight, and HbA1C compared to patients treated with resmetirom.



ALT: alanine aminotransferase; **AST**: Aspartate Aminotransferase.
Sample size varies for each time point and outcome.

Disclosures: Prachi Arora: Novo Nordisk, Inc: Employee, David Shi: Nothing to Disclose, Abdalla Aly: Novo Nordisk Incorporated: Employee, Novo Nordisk Incorporated: Stock - publicly traded company, Husam Albarmawi: Novo Nordisk Inc.: Employee, Novo Nordisk Inc.: Stock - publicly traded company, Genentech Inc.: Employee, Genentech Inc.: Stock - publicly traded company, Maximilian Kurt Jara: Nothing to Disclose, Eric Lawitz: 89Bio: Grant/Research Support, Akero Therapeutics: Grant/Research Support, Astrazeneca: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Bristol-Myers Squibb: Grant/Research Support, Cour Pharmaceuticals: Grant/Research Support, Cymabay Therapeutics: Grant/Research Support, Eli Lilly and Company: Grant/Research Support, Galectin Therapeutics: Grant/Research Support, Gilead Sciences: Grant/Research Support, GlaxoSmithKline: Grant/Research Support, Hanmi Pharmaceuticals: Grant/Research Support, Hightide Biopharma: Grant/Research Support, Intercept Pharmaceuticals: Grant/Research Support, Inventiva: Grant/Research Support, Ipsen: Grant/Research Support, Madrigal Pharmaceuticals: Grant/Research Support, Merck & Co: Grant/Research Support, NGM Biopharmaceuticals: Grant/Research Support, Novartis: Grant/Research Support, Novo Nordisk Inc: Grant/Research Support, Regeneron: Grant/Research Support, Sagimet Biosciences: Grant/Research Support, Takeda: Grant/Research Support, Terns Pharmaceuticals: Grant/Research Support, Viking Therapeutics: Grant/Research Support, Zydus Pharmaceuticals: Grant/Research Support, Gilead Sciences: Speaking and Teaching, Abbvie: Speaking and Teaching, Intercept: Speaking and Teaching, Madrigal Pharmaceuticals: Speaking and Teaching, 89Bio: Consultant, Boehringer Ingelheim: Consultant, Merck & Co: Consultant, Novo Nordisk Inc: Consultant, Organovo: Consultant, Regeneron: Grant/Research Support, Sagimet Biosciences: Consultant, Corcept Therapeutics: Consultant, Corcept Therapeutics: Grant/Research Support, Astrazeneca: Consultant, inventiva: Consultant.

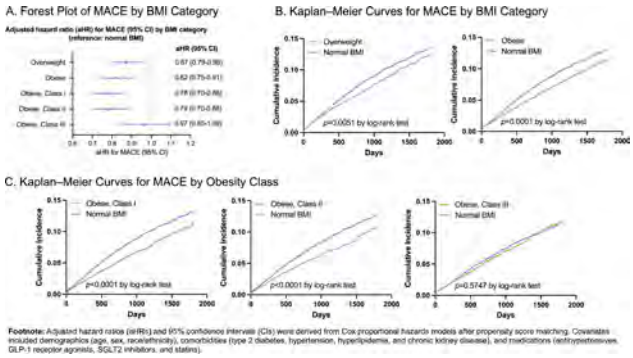
2462 | ◆ LEAN MASLD IS NOT BENIGN: HIGHER CARDIOVASCULAR RISK COMPARED WITH OVERWEIGHT AND OBESITY

Sainan Li[1] Shannan Tujios[1] Maddie Kubiliun[2] Rita Lepe[3] Lafaine Grant[1] Sarah Lieber[1] Ludovic Saba[4] Michel Toutoungy[1] Janvi Patel[1] Lisa VanWagner[1], [1]University of Texas Southwestern Medical Center, [2]UT Southwestern, [3]UTSW Medical Center, [4]UT Southwestern Medical Center

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Background: Metabolic dysfunction–associated steatotic liver disease (MASLD) is strongly linked to cardiovascular disease (CVD), the leading cause of mortality in this population. While obesity is a known risk factor, individuals with MASLD and normal body mass index (BMI) may exhibit adverse cardiometabolic phenotypes. Comparative real-world data across BMI categories in non-cirrhotic MASLD are limited. **Methods:** We conducted a retrospective cohort study using the TriNetX Research Network (3/2006– 3/2026), a federated database of de-identified electronic health records from multiple healthcare systems. Adults (≥18 years) with MASLD, identified using ICD codes K75.81 and K76.0, and available BMI were included. BMI was categorized as normal (18.5–24.9 kg/m2), overweight (25.0–29.9 kg/m2), or obesity (≥30.0 kg/m2), with obesity further stratified as class I (30.0–34.9 kg/m2), class II (35.0–39.9 kg/m2), and class III (≥40.0 kg/m2). The index date was the first MASLD diagnosis with documented BMI. Persons with cirrhosis (baseline or incident), hepatocellular carcinoma, other chronic liver diseases, or prior cardiovascular events were excluded. The primary outcome was incident major adverse cardiovascular events (MACE: myocardial infarction, ischemic stroke, heart failure, or cardiovascular mortality). Propensity score matching balanced demographics, comorbidities, and cardiometabolic therapies. Kaplan–Meier and Cox models were used to assess MACE. **Results:** After matching, 14,051 persons with non-cirrhotic MASLD were included in the normal vs. overweight cohort and 12,926 in the normal vs. obese cohort. Over ~2.5 years (35,100 and 32,300 person-years), MACE occurred in 7.9% vs. 7.1% (normal vs. overweight) and 7.7% vs. 6.9% (normal vs. obesity). Overweight and obesity were associated with lower MACE risk compared with normal BMI (overweight: aHR 0.87, 95% CI 0.79–0.96; obese: aHR 0.82, 95% CI 0.75–0.91). This association persisted for class I–II obesity but not class III obesity (Figure 1A). Kaplan–Meier analyses showed higher cumulative MACE incidence in normal BMI versus overweight and class I–II obesity (all $p < 0.01$, Figure 1B), with no difference for class III obesity ($p = 0.57$, Figure 1C). **Conclusion:** In non-cirrhotic MASLD, overweight and class I–II obesity were associated with lower MACE compared with normal BMI, with no apparent benefit in class III obesity. These findings highlight substantial heterogeneity in cardiometabolic risk across BMI categories. Importantly, MASLD with normal BMI ("lean MASLD") appears to represent a distinct phenotype with disproportionate cardiovascular risk, underscoring the limitations of BMI-based risk assessment and the need for improved cardiometabolic risk stratification in this population.



Disclosures: Sainan Li: Nothing to Disclose, Shannan Tujios: Nothing to Disclose, Maddie Kubiliun: Nothing to Disclose, Rita Lepe: Nothing to Disclose, Lafaine Grant: Nothing to Disclose, Sarah Lieber: Nothing to Disclose, Ludovic Saba: Nothing to Disclose, Michel Toutoungy: Nothing to Disclose, Janvi Patel: Nothing to Disclose, Lisa VanWagner: W.L. Gore & Associates: Grant/Research Support, Akero: Grant/Research Support, Madrigal: Grant/Research Support, Gerson Lehrman Group: Consultant, Madrigal: Advisor, Slingshot Insights: Consultant, Antheneum Partners: Consultant, Gerson Lehrman Group: Consultant, Alpha Insights: Consultant, Slingshot Insights: Consultant, Madrigal Pharmaceuticals: Grant/Research Support, W.L. Gore & Associates: Grant/Research Support, BD: Grant/Research Support, Medicolegal consulting: Consultant.

2463 | ◆ PROTEOMIC INSIGHTS INTO THE BIDIRECTIONAL ASSOCIATION BETWEEN LUNG FUNCTION AND MASLD: EVIDENCE FROM MULTI-COHORT STUDIES

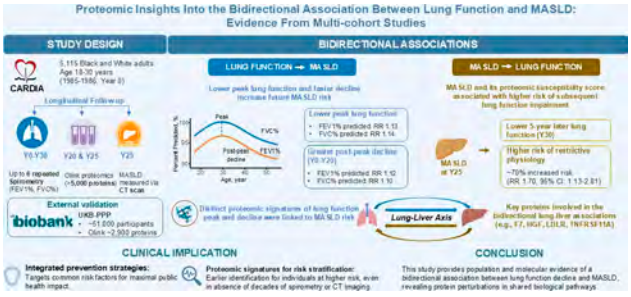
Yun Chen[1] Longgang Zhao[2] Bharat Thyagarajan[3] Ravi Kalhan[4] George Washko[5] Jing Li[6] Raúl San José Estépar[5] Alexander Arynchyn[6] David Jacobs[7] Lifang Hou[8] Xuehong Zhang[2], [1]Yale School of Nursing, [2]Yale University, [3]University of Minnesota, [4]Feinberg School of Medicine, Northwestern University, [5]Brigham and Women's Hospital, [6]The University of Alabama at Birmingham, School of Medicine, [7]School of Public Health, University of Minnesota, [8]Northwestern University Feinberg School of Medicine

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is highly prevalent among individuals with impaired lung function, and the association may be bidirectional. However, prospective evidence is limited. We aimed to investigate these relationships at both population and molecular levels. **Methods:** In CARDIA cohort, 5115 participants aged

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18 to 30 years were enrolled in 1985-1986 (Year 0, Y0). Forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) were repeatedly measured via spirometry from young adulthood through middle age (Y0 to Y30). MASLD was measured using CT at Y25. Proteomic signatures for lung function and MASLD were constructed using elastic net regression based on profiling at Y20 and Y25. Bidirectional associations between lung function, protein signatures, and MASLD were estimated using Poisson and linear regression, with Mendelian randomization (MR) to evaluate potential causality. Proteomic results were validated in the UK Biobank Pharma Proteomics Project (UKB-PPP). **Results:** In CARDIA, lower peak FEV1% and FVC% predicted, and accelerated post-peak declines over 20 years (Y0 to Y20), were associated with higher MASLD risk (relative risks per SD: 1.10 to 1.14). Distinct proteomic signatures correlated with peak lung function and post-peak decline, showing strong independent associations with MASLD across both CARDIA and UKB-PPP. MR analyses supported a link between genetic predicted lung functions to MASLD. Conversely, MASLD at Y25 was associated with lower lung function 5-years later and a 70% higher risk of restrictive respiratory physiology. MASLD-related proteomic susceptibility score was also independently associated with lung function traits and restrictive physiology in both CARDIA and UKB-PPP. Key proteins (e.g., HGF, LDLR, F7, TNFRSF11A) were identified involving in the bidirectional associations. **Conclusion:** This study provides population and molecular evidence of a bidirectional association between lung function decline and MASLD, revealing protein perturbations in shared biological pathways. Proteomic signatures demonstrated potential clinical utility for risk stratification and early prevention in both conditions, even in the absence of decades of spirometry or CT.



Disclosures: Yun Chen: Nothing to Disclose, Longgang Zhao: Nothing to Disclose, Bharat Thyagarajan: Nothing to Disclose, Ravi Kalhan: Nothing to Disclose, George Washko: Nothing to Disclose, Jing Li: Nothing to Disclose, Raúl San José Estépar: Nothing to Disclose, Alexander Arynchyn: Nothing to Disclose, David Jacobs: Nothing to Disclose, Lifang Hou: Nothing to Disclose, Xuehong Zhang: Nothing to Disclose.

2464 | ◆ THE RISK OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE AND ADVANCED HEPATIC FIBROSIS IN ADULTS WITH INFLAMMATORY BOWEL DISEASE: A MULTICENTER REAL-WORLD DATABASE STUDY

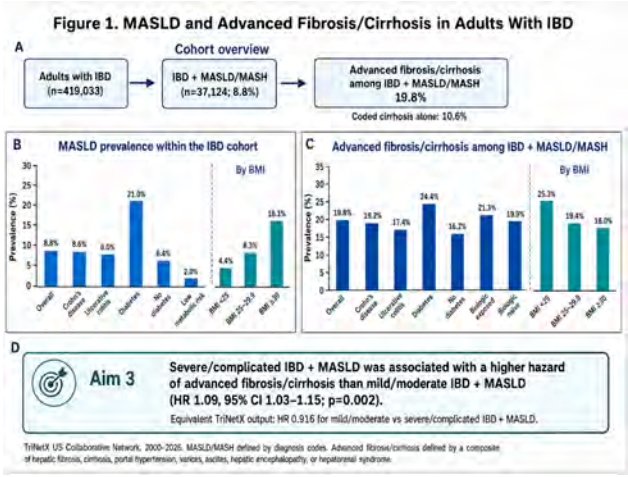
Stefanie Gallagher[1] Brandon Havranek[2] Leanna Rucker[1] Navya Pendyala[1] Ali Awadalla[2] Dina Halegoua-De Marzio[1], [1]Thomas Jefferson University Hospital, [2]Sidney Kimmel Medical College

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is increasingly recognized in patients with inflammatory bowel disease (IBD), yet its real-world prevalence and association with advanced hepatic fibrosis/cirrhosis remain incompletely defined. This study examined the burden of MASLD and advanced fibrosis/cirrhosis among adults with IBD in a large multicenter cohort. **Methods:** A retrospective cohort study was performed using the TriNetX US Collaborative Network. From January 1, 2000 to April 14, 2026, adults with IBD were identified using ICD-10-CM codes for Crohn's disease or ulcerative colitis. MASLD/MASH was defined using diagnosis codes for fatty liver or nonalcoholic steatohepatitis. Patients with competing chronic liver diseases or prior liver transplant were excluded. Advanced fibrosis/cirrhosis was defined using a composite of diagnosis codes for hepatic fibrosis, cirrhosis, and complications of portal hypertension. Prevalence estimates were calculated overall and across subgroups. Severe/complicated IBD was defined by complication codes including obstruction, fistula, abscess, or rectal bleeding. Cox proportional hazards modeling was used to evaluate the association between severe/complicated IBD and incident of advanced fibrosis/cirrhosis among patients with IBD and MASLD. **Results:** Among 419,033 adults with IBD, 37,124 had MASLD corresponding to an overall prevalence of 8.8%. MASLD prevalence increased with body mass index, from 4.4% in patients with BMI < 25 kg/m² to 8.3% with BMI 25–29.9 kg/m² and 16.1% with BMI ≥ 30 kg/m². In a low-metabolic-risk subgroup

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defined by BMI < 25 kg/m² and absence of diabetes, hypertension, and dyslipidemia, MASLD prevalence decreased to 2%. Among patients with IBD and MASLD, 19.8% had advanced fibrosis/cirrhosis by composite definition, while coded cirrhosis alone was present in 10.6%. Advanced fibrosis/cirrhosis was similar in Crohn's disease and ulcerative colitis, occurring in 19.2% and 17.4% respectively. Notably, fibrosis/cirrhosis prevalence was highest among patients with BMI < 25 kg/m² (25.3%) compared with BMI 25–29.9 kg/m² (19.4%) and BMI ≥ 30 kg/m² (18.0%). Exposure to biologics resulted in an increased prevalence of fibrosis/cirrhosis. In a Cox analysis, mild/moderate IBD + MASLD was associated with lower hazard of advanced fibrosis/cirrhosis compared with severe/complicated IBD + MASLD, HR 0.916, 95% CI 0.866–0.968, p = 0.002. **Conclusion:** In this real-world IBD cohort, nearly 1 in 5 patients with IBD and MASLD had advanced fibrosis/cirrhosis. Severe/complicated IBD was independently associated with higher hazard of fibrosis/cirrhosis, suggesting that inflammatory disease burden contributes to liver disease progression in patients with MASLD. These findings support targeted MASLD screening and fibrosis risk assessment in patients with IBD and complicated intestinal disease, including those with normal BMI.



Disclosures: Stefanie Gallagher: Nothing to Disclose, Brandon Havranek: Nothing to Disclose, Leanna Rucker: Nothing to Disclose, Navya Pendyala: Nothing to Disclose, Ali Awadalla: Nothing to Disclose, Dina Halegoua-De Marzio: Novo Nordisk: Advisor, Galectin: Grant/Research Support, Madigral: Advisor, Novo Nordisk: Grant/Research Support, Madigral: Advisor, Viking: Grant/Research Support, Akero: Grant/Research Support, Intercept: Grant/Research Support, 89Bio: Grant/Research Support.

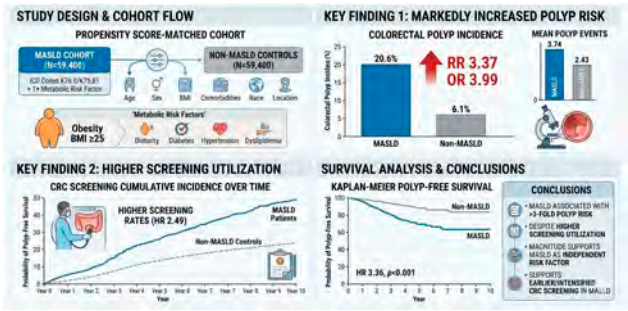
2465 | ◆ MASLD IS ASSOCIATED WITH MARKEDLY INCREASED RISK OF COLORECTAL POLYPS DESPITE HIGHER COLORECTAL CANCER SCREENING UTILIZATION

Lina AlQirem[1] Ragesh Thandassery[1], [1]The University of Arkansas for Medical Sciences

Background: The relationship between MASLD and colorectal neoplasia remains underrecognized, particularly in the context of standard colorectal cancer screening practices. **Methods:** We conducted retrospective propensity score-matched cohort analysis using TriNetX, a global federated health research network of de-identified electronic medical records. A total of 59,400 MASLD patients and 59,400 non-MASLD matched controls were identified between January 2010 and December 2012 and were followed longitudinally through December 2025. Those with prior extrahepatic malignancy and other causes of hepatic steatosis, including alcohol use disorder, chronic hepatitis C infection, celiac disease, hemochromatosis, and long-term use of steatosis-associated medications (systemic corticosteroids, methotrexate, tamoxifen, or amiodarone) were excluded. Propensity score 1: 1 matching was based on age and baseline characteristics with standardized mean differences < 0.1. Outcomes included colorectal polyp incidence and CRC screening utilization, Risk Ratios (RR), and hazard ratios (HR), with Kaplan-Meier analysis for time-to-event outcomes. **Results:** MASLD was associated with significantly higher risk of colorectal polyps (20.6% vs 6.1%; RR 3.37, 95% CI 3.26-3.50; OR 3.99; p < 0.001). Time-to-event analysis demonstrated increased hazard (HR 3.36, p < 0.001) and reduced polyp-free survival (65.2% vs 85.0%). MASLD patients also had more frequent polyp events (mean 3.74 vs 2.43; p < 0.001). CRC screening was more common in MASLD patients (29.2% vs 12.3%; RR 2.38; p < 0.001), with higher screening rates over time (HR 2.49, p < 0.001), however this did not offset the increased polyp burden. **Conclusion:** MASLD is associated with a three fold increased risk of colorectal polyps despite higher screening rates. While increased screening may contribute to higher polyp detection, the magnitude of association and increased polyp burden support MASLD as an independent risk factor for colorectal neoplasia. This supports consideration of earlier or intensified CRC screening in this population.

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Disclosures: Lina AlQirem: Nothing to Disclose, Ragesh Thandassery: Nothing to Disclose.

2466 | ◆ SEX-SPECIFIC AND ADIPOSITY-DEPENDENT ASSOCIATIONS BETWEEN SOCIAL JETLAG AND MASLD: A NATIONWIDE CROSS-SECTIONAL STUDY

Xiaosheng Tao[1] Xinyuan He[1] Zhiluo Yang[1] Xindi Huang[1] Yuzhen Zhao[1] Qiaoman Fei[1] Dou Qu[1] Yue Zhang[1] Enrui Xie[1] Fanpu Ji[1], [1]the Second Affiliated Hospital of Xi'an Jiaotong University

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) affects approximately 30% of adults around the world, frequently progressing to cirrhosis, hepatocellular carcinoma, and broader cardiometabolic diseases. Social jetlag (SJL), defined as the discrepancy in mid-sleep time between workdays and free days, reflects chronic circadian disruption and has been associated with insulin resistance and hepatic steatosis. However, its specific impact on MASLD risk and phenotypic susceptibilities remains unclear. Our study aimed to evaluate the independent association between SJL and MASLD, exploring susceptibility patterns by sex and body mass index (BMI). We hypothesise that elevated SJL independently increases MASLD risk, particularly in females and individuals with higher adiposity. **Methods:** From 15,560 NHANES participants, 7,049 were included after excluding those aged < 12 or > 70, heavy alcohol use, and missing data. SJL was quantified as the absolute difference in mid-sleep times between free days and workdays. MASLD was defined as Controlled Attenuation Parameter (CAP) ≥ 288 dB/m with ≥ 1 cardiometabolic risk factor, stratified as lean or obese by BMI status. Weighted multivariable logistic regression, progressively adjusting for demographic, lifestyle, and biochemical covariates, was utilised to evaluate the SJL-MASLD association, and tested effect modification by sex and BMI. **Results:** Among 7,049 participants (33.0% MASLD prevalence), the overall mean SJL was 1.56 ± 2.63 hours, with significantly higher levels observed in the MASLD group ($p < 0.05$). Compared to the lowest quartile (Q1), individuals in Q4 independently exhibited a 43% increased risk of MASLD (OR = 1.43, p = 0.031) in the fully adjusted model. Subgroup analyses revealed pronounced risks in overweight/obese individuals (BMI interaction p = 0.026) and non-diabetic cohorts. Crucially, sex-stratified analyses uncovered a profound sex-specific susceptibility; females in the highest SJL quartile exhibited a two-fold increased MASLD risk (OR = 2.07, p = 0.002) following comprehensive adjustment, whereas no significant association occurred in males. High SJL thus emerges as a potent, female-specific independent driver of MASLD. **Conclusion:** SJL is an independent MASLD risk factor, with particularly heightened vulnerability in females and those with excess adiposity, highlighting circadian–endocrine–metabolic interplay. Consequently, targeted sleep-wake interventions should be prioritised as fundamental preventive and therapeutic strategies for these highly vulnerable populations.

Table Subgroup Multiple regression analysis (Female)

Variable Social Jetlag (Quartiles)	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)	Model 4 OR (95% CI)
Females (N=3,641)				
Q1 (Lowest)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2	1.05 (0.84, 1.31) P=0.682	1.12 (0.87, 1.43) P=0.379	1.10 (0.84, 1.45) P=0.485	1.22 (0.80, 1.87) P=0.355
Q3	**1.32 (1.05, 1.65) P=0.017***	**1.42 (1.11, 1.82) P=0.006****	**1.44 (1.09, 1.91) P=0.01***	1.53 (0.99, 2.38) P=0.055
Q4 (Highest)	**1.39 (1.10, 1.76) P=0.007****	**1.52 (1.17, 1.99) P=0.002****	**1.48 (1.10, 1.99) P=0.01***	**2.07 (1.32, 3.26) P=0.002****

Model 1: Adjusted for Age, Race/Ethnicity.
Model 2: Model 1 + Smoking status, Education level, Marital status, and Family Income (PIR).
Model 3: Model 2 + BMI.
Model 4: Model 3 + ALT, AST, TG, HDL, LDL, Glucose, Hb1Ac, GGT.
* P < 0.05, ** P < 0.01.

Disclosures: Xiaosheng Tao: Nothing to Disclose, Xinyuan He: Nothing to Disclose, Zhiluo Yang: Nothing to Disclose, Xindi Huang: Nothing to Disclose, Yuzhen Zhao: Nothing to Disclose, Qiaoman Fei: Nothing to Disclose, Dou Qu: Nothing to Disclose, Yue Zhang: Nothing to Disclose, Enrui Xie: Nothing to Disclose, Fanpu Ji: Nothing to Disclose.

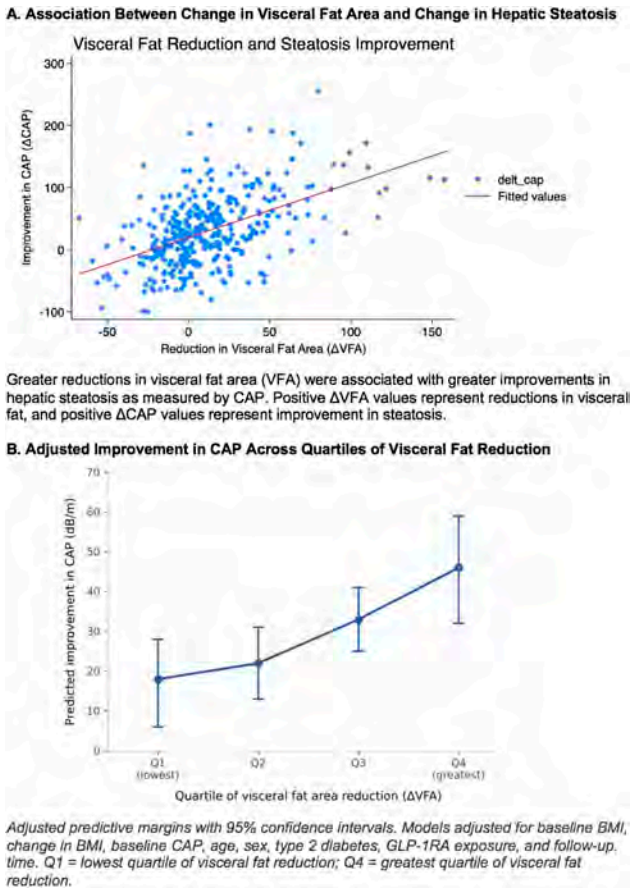
2467 | ◆ REDUCTION IN VISCERAL FAT PREDICTS IMPROVEMENT IN HEPATIC STEATOSIS INDEPENDENT OF WEIGHT LOSS IN MASLD

Ani Bernardi[1] Sophie Silbert[1] Adam Buckholz[1] Sonal Kumar[1] Melina Manolas[2], [1]Weill Cornell Medicine, [2]Weill Cornell

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Background: Visceral adiposity is strongly linked to hepatic steatosis in metabolic dysfunction-associated steatotic liver disease (MASLD), but it remains less clearly defined whether reductions in visceral fat improve steatosis independent of overall weight loss. We evaluated whether change in visceral fat area (VFA) predicts change in controlled attenuation parameter (CAP) independent of body weight change. **Methods:** We performed a retrospective longitudinal study of adults with MASLD who underwent paired FibroScan and InBody assessments. Change in CAP (ΔCAP) was the primary outcome and change in VFA (ΔVFA) was the primary exposure. Multivariable linear regression models evaluated associations between ΔVFA and ΔCAP adjusting for baseline BMI, change in BMI, baseline CAP, age, sex, type 2 diabetes (T2D), GLP-1RA exposure, and follow-up time. Secondary analyses evaluated additional body composition markers and odds of steatosis improvement. Predictive margins across quartiles of ΔVFA were also assessed. **Results:** A total of 352 patients with paired FibroScan and InBody measurements were included; 59.4% were women, 31.0% had T2D, and 51.9% had GLP-1RA exposure. Mean age was 51.0 ± 13.0 years and baseline CAP was 307.1 ± 40.6 dB/m. Over a mean follow-up period of 723 days, mean BMI decreased from 33.3 to 31.6 kg/m², CAP from 307.8 to 278.9 dB/m, and VFA from 181.1 to 169.5 cm². Reduction in VFA was independently associated with improvement in hepatic steatosis based on CAP after adjustment for baseline BMI, change in BMI, age, sex, T2D, and GLP-1RA exposure ($\beta = 0.49$, $p = 0.001$) and remained significant after adjusting for follow-up time. Similar associations were observed for change in % body fat and truncal fat mass, whereas changes in skeletal muscle indices were not associated with CAP improvement. The association between ΔVFA and ΔCAP did not differ by sex, menopausal-age subgroup among women, or T2D status. While there was no statistically significant interaction,T2D appeared to attenuate the BMI response. GLP-1RA exposure significantly attenuated the relationship between VFA reduction and CAP improvement (interaction $p = 0.027$), suggesting that steatosis improvement among GLP-1RA users may occur through mechanisms beyond visceral fat reduction alone. Adjusted for BMI change, resolution of elevated VFA was associated with higher dCAP (+27.1 dB/m, $p = 0.008$). **Conclusion:** Reduction in visceral adiposity predicted improvement in hepatic steatosis independent of overall weight loss in MASLD. This association was consistent across sex and diabetes subgroups, while GLP-1RA exposure attenuated the relationship between visceral fat reduction and CAP improvement. Visceral adiposity may represent a clinically meaningful therapeutic target beyond BMI reduction alone in MASLD.



Disclosures: Ani Bernardi: Nothing to Disclose, Sophie Silbert: Nothing to Disclose, Adam Buckholz: Tortugas Neurosciences: Consultant, Sonal Kumar: Nothing to Disclose, Melina Manolas: Doximity: Social Media Content Provision, Health Monitor Network: Advisor, Roon: Stock options, Madrigal Pharmaceuticals: Consulting.

2468 | CHOLANGIOCARCINOMA: INCIDENCE, METASTATIC PATTERNS, AND SURVIVAL OUTCOMES IN PATIENTS WITH AND WITHOUT MASLD: A PROPENSITY SCORE–MATCHED ANALYSIS

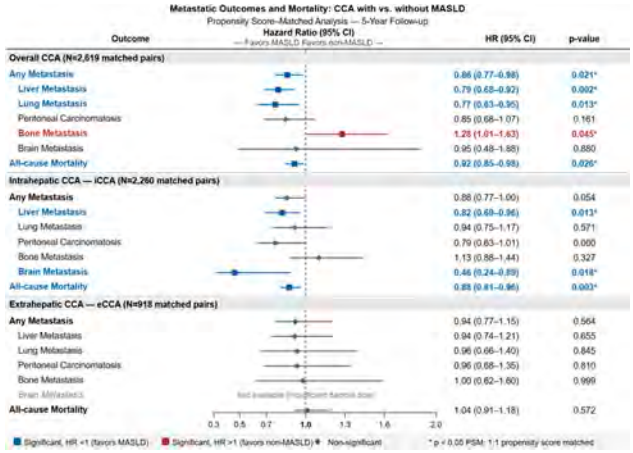
Guy Loic Nguefang[1] Sarpong Boateng[2] Ridwan Lawal[3] Yussif Issaka[2] Joel Gabin Konlack Mekontso[4] Armand Ngassam[5] Chimezirim Ezeano[6] Basile Njei[7], [1]Texas Tech University Health Sciences Center, [2]Yale New Haven Health, Bridgeport Hospital, [3]University of Texas Rio Grande Valley, [4]New York City Health Hospitals, South Brooklyn Health, [5]Sovah Health, [6]Advocate Aurora Healthcare, [7]Yale University

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) has been implicated in hepatobiliary carcinogenesis; however, its

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association with cholangiocarcinoma (CCA) incidence and metastatic patterns remains poorly characterized. We aimed to investigate the relationship between MASLD and CCA incidence, site-specific metastatic patterns, and overall mortality. **Methods:** We conducted a retrospective cohort study using the TriNetX database from January 2009 to May 2026. Adults older than 18 years with at least one metabolic risk factor were included and subsequently divided into two cohorts: MASLD and non-MASLD. Individuals with alcoholic liver disease, autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis, and malignancy were excluded. The incidence of CCA was then analyzed in both cohorts. Additionally, a 1: 1 propensity score–matched (PSM) analysis was performed, with covariates including age, sex, BMI, comorbidities, alcohol use, and tobacco use, to compare site-specific metastatic patterns among CCA patients with and without MASLD. Sensitivity analyses were conducted separately for patients with intrahepatic (iCCA) and extrahepatic (eCCA). The index date was defined as the date of CCA diagnosis, with a follow-up period of 5 years. Time-to-event analysis was performed using Cox proportional hazards regression to generate hazard ratios (HR) with 95% confidence intervals (CI). **Results:** A total of 12,677 patients with MASLD and 24,805 without MASLD were included. Patients with MASLD demonstrated a higher crude CCA incidence compared to non-MASLD patients (241 vs. 85 per 100,000 persons). When stratified by subtype, iCCA incidence was higher in the MASLD cohort (241 vs. 69 per 100,000 persons), as was eCCA incidence (80 vs. 40 per 100,000 persons). We matched 2,619 patients in both the MASLD and non-MASLD CCA cohorts. MASLD was associated with a significantly lower risk of overall metastasis (HR 0.87, 95% CI 0.77–0.98), but a significantly higher risk of bone metastasis (HR 1.28, 95% CI 1.01–1.63). All-cause mortality was also significantly lower in the MASLD group compared to non-MASLD (HR 0.92, 95% CI 0.85–0.98). In the iCCA subgroup, MASLD was associated with significantly reduced risks of liver metastasis (HR 0.82, $p = 0.013$), brain metastasis (HR 0.46, 95% CI 0.24–0.89, $p = 0.018$), and mortality (HR 0.88, $p = 0.003$). In contrast, among eCCA patients, no statistically significant differences in metastatic outcomes or mortality were observed. **Conclusion:** The incidence of CCA is higher in MASLD. Paradoxically, MASLD confers a more favorable metastatic profile and survival. The unexpected increase in bone metastasis risk warrants further investigation. These findings underscore the biological heterogeneity between CCA subtypes and have implications for risk stratification, surveillance, and prognostication in patients with MASLD.



Disclosures: GUY LOIC NGUEFANG: Nothing to Disclose, Sarpong Boateng: Nothing to Disclose, Ridwan Lawal: Nothing to Disclose, Yussif Issaka: Nothing to Disclose, Nothing to Disclose, Joel Gabin Konlack Mekontso: Nothing to Disclose, Armand Ngassam: Nothing to Disclose, chimezirim ezeano: Nothing to Disclose, Basile Njei: Nothing to Disclose.

2469 | ESTIMATION OF CARDIOVASCULAR EVENT PREVENTION WITH SEMAGLUTIDE THERAPY IN PATIENTS WITH HIGH-RISK TYPE 2 DIABETES AND MASLD

Alex Chang[1] JF Monteiro[1] Kimberly Ho[1] Sahas Chandragiri[1] Paige Mclean DIaz[1] Kittichai Promrat[2], [1]Brown University, [2]Brown University School of Medicine

Background: The SOUL trial is a large randomized controlled trial demonstrating lower risk of major adverse cardiovascular events (MACE) for patients with high-risk type 2 diabetes treated with oral semaglutide. The current study identifies the proportion of the US population with co-morbid MASLD and

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high-risk type 2 diabetes and uses data from the SOUL trial to project MACE that can be prevented through prescribing semaglutide to patients with dual indications. **Methods:** The current study utilizes the 2017 – 2020 US NHANES survey. Patients eligible for semaglutide therapy for MASLD were identified by including those with FIB-4 > 1.3 and a transient elastography with liver stiffness of kPa > 8 and < 15. Patients with other etiologies of liver disease were excluded. We then identified those with co-morbid high-risk Type 2 diabetes patients defined by the inclusion criteria for the SOUL trial: 50 years of age or older, an A1C of 6.5 to 10.0%, and diagnosis of coronary artery disease, cerebrovascular disease, or chronic kidney disease. We set the incidence rate of MACE in these patients to be equal to the incidence observed in the placebo arm of the SOUL trial (668 events out of 4825 patients, or 13.8%). With this incidence rate, we estimated the number of MACE events and used the hazard ratio in the treatment arm of the SOUL trial to calculate the number of MACE that could be prevented over 54 months. **Results:** Applying sampling weights, approximately 3,091,327 individuals with MASLD in the US are estimated to be eligible for semaglutide (**Table 1**). Of the patients eligible for semaglutide, 10% or 307,701 patients are further characterized as having high-risk Type 2 diabetes and thus may benefit from risk reduction in MACE. The number of patients increases to 360,666 if utilizing a higher stiffness cutoff for semaglutide eligibility. The characteristics of the patients who may benefit from MACE reduction are described in **Table 2**.The projected number of MACE prevented in the United States if 100% of patients eligible for semaglutide therapy for MASLD were placed on the therapy is 5,945 (95% CI: 1,699 - 9,766) events. This would increase to 6,968 (95% CI: 1,991 - 11,448) events if semaglutide were prescribed up to stiffness threshold of kPA < 20. Reduction in secondary outcomes such as fatal or nonfatal MI or coronary revascularization as well as variation in adverse events prevented according to percentage of population prescribed is summarized in **Figure 1** . **Conclusion:** In patients with MASLD and high-risk type 2 diabetes, treatment with semaglutide may have favorable effects not only on liver fibrosis but also cardiovascular event reduction. The current guidelines indicate that treatment of MASLD for patients with liver stiffness between 15 to 20 should be an individualized decision. In these patients, consideration of comorbid conditions may be useful for individualized decision making when discussing treatment options for MASLD.

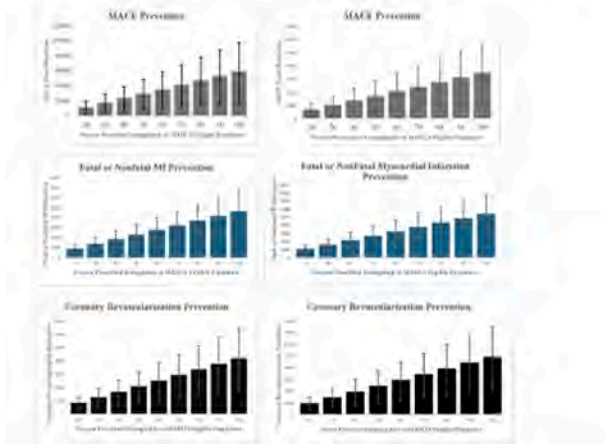
Table 1 Characteristics of Patients in the United States Eligible for Semaglutide Therapy for MASLD

	Eligible for Semaglutide for MASLD Fibrosis (upper kPA cutoff < 15), unweighted (n = 138)	Eligible for Semaglutide for MASLD Fibrosis (upper kPA cutoff < 15), Weighted (n = 3,091327)	Eligible for Semaglutide for MASLD Fibrosis (upper kPA cutoff < 20), Unweighted (n = 161)	Eligible for Semaglutide for MASLD Fibrosis (upper kPA cutoff < 20), Weighted (n = 3,556,242)
Age	67.6 (10.1)	68.6 (11.6)	67.7 (10.3)	67.0 (1.3)
Sex				
Female (n%) =	57 (41.3%)	1264032 (40.9%)	64 (39.8%)	1461225 (39.5%)
Race/Ethnicity				
White =	58 (42.0%)	2095963 (67.8%)	70 (43.5%)	2379679 (66.9%)
Black =	34 (24.6%)	290870 (9.4%)	35 (21.7%)	302700 (8.5%)
Asian =	7 (5.1%)	85336 (2.8%)	8 (5.0%)	95365 (2.7%)
Other =	6 (4.4%)	180627 (5.8%)	8 (5.0%)	236983 (6.7%)
Mexican American =	21 (15.2%)	270549 (8.8%)	27 (16.8%)	346058 (9.7%)
Other Hispanic =	12 (8.7%)	168579 (5.5%)	13 (8.1%)	195474 (5.5%)
BMI	34.5 (7.7)	33.9 (1.0)	34.4 (7.4)	33.9 (1.0)

Table 2 Characteristics of Patients Eligible for Semaglutide Therapy and Meeting Inclusion Criteria for the SOUL trial

	SOUL Trial Placebo Arm (n = 4825)	Eligible Semaglutide (kPA cutoff < 15) with High Risk Diabetes, unweighted (n = 10)	Eligible Semaglutide (lower cutoff) with High-Risk Diabetes, weighted (n = 307701)	Eligible Semaglutide (kPA cutoff < 20) with High Risk Diabetes, unweighted (n = 14)	Eligible Semaglutide (lower cutoff) with High-Risk Diabetes, weighted (n = 360666)
Age (SD)	66.1 (7.5)	66.1 (10.2)	67.0 (1.3)	70.7 (9.8)	67.0 (1.3)
Sex					
Female (n, %)	1376 (28.5%)	3 (30%)	78516 (25.5%)	3 (21.4%)	78516 (21.8%)
Race/Ethnicity					
White =	3327 (69%)	5 (50%)	274350 (89%)	7 (50%)	304273 (84%)
Black =	124 (2.6%)	4 (40%)	27176 (8.8%)	4 (40%)	27176 (7.5%)
Asian =	1134 (23.5%)	0 (0%)	0 (0%)	1 (7%)	10029 (2.8%)
Other =	185 (3.8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Hispanic Ethnic Group =	DNI	1 (10%)	6195 (2.0%)	2 (14%)	19168 (5.3%)
BMI	31.0 (5.7)	36.4 (6.4)	33.9 (1.0)	34.8 (6.0)	33.9 (1.0)

Figure 1 Left Events Prevented using stiffness threshold kPa < 15 **Right** Events Prevented using stiffness threshold kPa < 20



Disclosures: Alex Chang: Nothing to Disclose, JF Monteiro: Nothing to Disclose, Kimberly Ho: Nothing to Disclose, Sahas Chandragiri: Nothing to Disclose, Paige Mclean DIaz: Nothing to Disclose, Kittichai Promrat: Nothing to Disclose.

2470 | METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH) IN TYPE 2 DIABETES (T2D) ACROSS NINE COUNTRIES: ECONOMIC BURDEN AND REAL-WORLD IMPLEMENTATION IMPACT (2025–2045)

Zobair Younossi[1] Frank Tacke[1] Patrizia Burra[1] Cristiane Villela-Nogueira[2] Javier Crespo Garcia[1] Elisabetta Bugianesi[1] Hirokazu Takahashi[1] Yuichiro Eguchi[1] Mario Pessoa[3] Claudia Oliveira[4] Michael Roden[1] Cyrielle Caussy[1] Amalia Gastaldelli[1] Fernando Bril[1] Jeremy Tomlinson[1] Paul Brennan[1] Manuel Romero-Gómez[1] Takumi Kawaguchi[5] Jerome

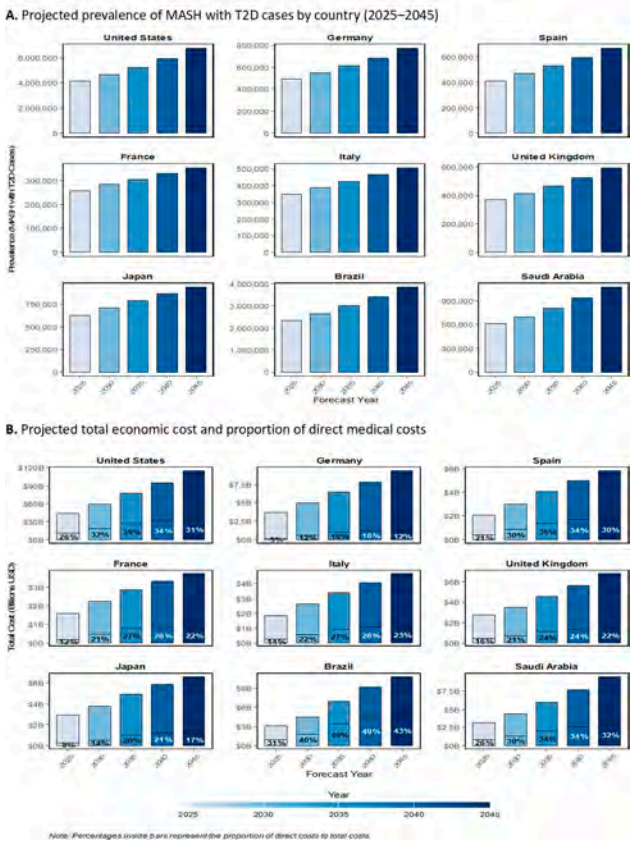
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Boursier[6] Faisal Abaalkhail[7] Ahmed Al-jedai[1] Hussain Abdulrahman Al-Omar[1] Maria Stepanova[1] Fatema Nader[1] Markos Kalligeros[1] Laurent Castera[8] Saleh Alqahtani[1] James Paik[9], [1]The Global NASH/MASH Council, [2]Universidade Federal do Rio de Janeiro, [3]University of São Paulo, [4]University of Sao Paulo School of Medicine, [5]Kurume University School of Medicine, [6]Angers University, [7]KING FAISAL SPECIALIST HOSPITAL, [8]Hopital Beaujon, [9]Global NASH/MASH Council

Background: T2D is the dominant metabolic driver of progression in MASH. The long-term clinical and economic consequences of MASH with T2D and the population-level impact of pharmacotherapy under real-world conditions remain poorly characterized across diverse health systems. **Methods:** An age-stratified Markov model projected clinical and economic outcomes of MASH with T2D from 2025 to 2045 across nine countries (US, Germany, Spain, France, Italy, UK, Japan, Brazil and Saudi Arabia), incorporating fibrosis progression, decompensated cirrhosis (DCC), hepatocellular carcinoma, liver transplantation, cause-specific mortality, and QALYs. Base-case pharmacotherapy included semaglutide or resmetirom for MASH with F2 to F3 using country-specific effective treatment exposure, defined as the sequential product of coverage, diagnosis and eligibility, adherence, and persistence. An optimized scenario introduced a next-generation MASH drugs starting in 2031. **Results:** By 2045, By 2045, MASH with T2D prevalence is projected to reach 6.75 million in the US (63% increase), 3.91 million in Brazil, and 1.07 million in Saudi Arabia (Figure). US annual costs are estimated to rise from $43.45 billion to $115.00 billion (165% increase), with indirect costs representing 75% of the total economic burden. Despite nominal treatment coverage of 65% for semaglutide and 43% for resmetirom, effective exposure remains approximately 30% and 20%, respectively, due to attrition across diagnosis, eligibility, adherence, and persistence phases. Base pharmacotherapy averts 12,696 liver-related deaths, 63,879 cardiovascular deaths, and 243,760 disability-adjusted life-years. An optimized treatment scenario amplifies these outcomes 3.5–4.0-fold: advanced fibrosis avoided increases from 3.4% to 13.8%, liver-related deaths averted from 12,696 to 44,897, and quality-adjusted life-years gained from 72,407 to 251,585. These findings underscore both the urgent need to address MASH-T2D and the substantial value of interventions that improve treatment engagement and persistence. **Conclusion:** MASH with T2D will impose a rapidly escalating global burden through 2045. Population-level impact is constrained primarily by implementation efficiency rather than therapeutic efficacy. Systematic risk stratification, earlier diagnosis, and integrated metabolic-hepatic care pathways can amplify disease burden reduction 4-fold, delivering substantially greater benefits than incremental pharmaceutical innovation alone.

Figure. Projected Clinical and Economic Burden of MASH With Type 2 Diabetes, 2025-2045.



Disclosures: Zobair Younossi: Zobair M. Younossi is a consultant or has received research: Consultant, madrigal: Grant/Research Support, Siemens: Research funding, GSK: Consultant, BI: Consultant, Sanofi: Research funding, Frank Tacke: Gilead: Grant/Research Support, MSD: Grant/Research Support, AstraZeneca: Grant/Research Support, Agomab: Grant/Research Support, NovoNordisk, Boehringer, Gilead, MSD, GSK: Consultant, Pfizer, Sanofi: Advisor, Madrigal, Mirum, Ipsen: Consultant, Sanofi: Advisor, Falk: Speaking and Teaching, Patrizia Burra: Nothing to Disclose, Cristiane Villela-Nogueira: Nothing to Disclose, Javier Crespo Garcia: Nothing to Disclose, Elisabetta Bugianesi: Nothing to Disclose, Hirokazu Takahashi: Nothing to Disclose, Yuichiro Eguchi: Nothing to Disclose, Mario Pessoa: Nothing to Disclose, Nothing to Disclose, Claudia Oliveira: Nothing to Disclose, Nothing to Disclose, Michael Roden: Astra Zeneca: Speaking and Teaching, Echosens: Advisor, Boehringer Ingelheim: Grant/Research Support, Madrigal: Speaking and Teaching, MSD: Speaking and Teaching, Lilly: Advisor, Novo Nordisk: Advisor, Synlab: Speaking and Teaching, Cyrielle Caussy: Nothing to

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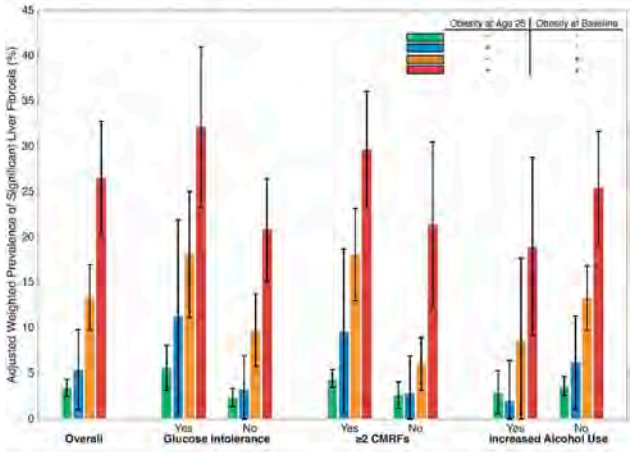
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2471 | A HISTORY OF EARLY ADULTHOOD OBESITY IS ASSOCIATED WITH LIVER FIBROSIS BEYOND CURRENT OBESITY STATUS: A NATIONAL CROSS-SECTIONAL STUDY

Yinan Su[1] Jennifer Dodge[1] Brian Lee[1], [1]University of Southern California Keck School of Medicine

Background: Obesity has doubled in young adults in the US over the past 30 years. Fibrosis risk is typically assessed from current obesity, but whether a history of early adulthood obesity adds risk information beyond current obesity status is understudied. **Methods:** We performed a cross-sectional study using the National Health and Nutrition Examination Survey 2017-2020, including adults aged ≥27 with weight history and valid vibration-controlled transient elastography (VCTE) data. Significant liver fibrosis was liver-stiffness ≥8 kPa by VCTE. Obesity (BMI ≥30 or ≥27.5 kg/m^2 for Asians) at age 25 and at baseline (survey time) defined four obesity history groups: never obese (neither timepoint), remitted (age 25 only), incident (baseline only), and persistent (both age 25 and baseline). Survey-weighted multivariable logistic regression (adjusted for age, sex, education, increased alcohol) estimated significant liver fibrosis prevalence and its association with obesity history group overall and across risk-factor strata (glucose intolerance, ≥2 cardiometabolic risk factors [CMRFs], increased alcohol). **Results:** Among 5,608 (mean age 51.6, 51.3% female), 2,945 (52.5% [95%CI 51.2-53.8%]) were never obese, 156 (2.8% [2.4-3.2%]) remitted, 1,843 (32.9% [31.6-34.1%]) incident, and 664 (11.8% [11.0-12.7%]) persistent. Adjusted weighted prevalence of significant liver fibrosis was highest in the persistent group (26.6% [20.4-32.8%]), followed by incident (13.4% [9.8-17.0%]), remitted (5.4% [1.0-9.8%]), and never obese (3.5% [2.5-4.4%]). Among adults with current obesity, prevalence was nearly 2-fold higher in the persistent vs incident group, whereas the remitted group approximated never-obese individuals. Persistent obesity was associated with significant liver fibrosis vs never obese, overall (aOR 10.69 [6.42-17.80]) and within every stratification. Persistent obesity carried the highest fibrosis prevalence among those with glucose intolerance (32.2% [23.4-41.0%]) or ≥2 CMRFs (29.7% [23.3-36.1%]); the remitted group carried the lowest among those without glucose intolerance (3.3% [0.0-6.9%]) or ≥2 CMRFs (2.9% [0.0-6.9%]). **Conclusion:** Liver fibrosis prevalence varied by obesity history, not current obesity status alone. Among currently obese adults, prevalence was 2-fold higher in those obese since early adulthood, while the remitted group had a prevalence similar to never-obese individuals. Obesity history may identify high-risk adults not captured by current BMI; longitudinal studies are needed to determine whether preventing or reversing early adulthood obesity reduces liver fibrosis.

Figure. Adjusted weighted prevalence of significant liver fibrosis (LSM ≥8kPa) by obesity history group and stratified by risk factors.



Adjusted weighted prevalence of significant liver fibrosis (LSM ≥8 kPa) % (95% CI)

Obesity at: Age 25 / Baseline	Never obese: Without obesity / Without obesity	Remitted obesity: With obesity / Without obesity	Incident obesity: Without obesity / With obesity	Persistent obesity: With obesity / With obesity
Overall[a] (N=5,608)	3.5 (2.5-4.4)	5.4 (1.0-9.8)	13.4 (9.8-17.0)	26.6 (20.4-32.8)
Glucose intolerance				
Yes[a] (n=2,284)	5.6 (3.2-8.1)	11.3 (0.6-21.9)	18.1 (11.1-25.1)	32.2 (23.4-41.0)
No[a] (n=3,324)	2.4 (1.4-3.4)	3.3 (0.0-6.9)	9.7 (5.7-13.8)	20.9 (15.2-26.5)
≥2 CMRFs				
Yes[a] (n=3,077)	4.4 (3.5-5.4)	9.6 (0.6-18.7)	18.1 (13.0-23.2)	29.7 (23.3-36.1)
No[a] (n=2,531)	2.7 (1.2-4.1)	2.9 (0.0-6.9)	6.1 (3.2-9.0)	21.4 (12.3-30.5)
Increased alcohol use				
Yes[b] (n=374)	2.9 (0.6-5.3)	2.0 (0.0-6.4)	8.6 (0.0-17.7)	19.0 (9.2-28.8)
No[b] (n=5,234)	3.6 (2.6-4.7)	6.2 (1.1-11.3)	13.3 (9.7-16.9)	25.5 (19.2-31.7)

[a]Adjusted for age, sex, educational attainment, and increased alcohol use.
[b]Adjusted for age, sex, educational attainment, and glucose intolerance.
LSM: liver-stiffness measurement; CMRF: cardiometabolic risk factor.

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2472 | GENETIC RISK STRATIFICATION AND MODIFIABLE LIFESTYLE FACTORS IN METABOLIC DYSFUNCTION–ASSOCIATED STEATOTIC LIVER DISEASE

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Background: Metabolic dysfunction–associated steatotic liver disease (MASLD) is the most prevalent chronic liver disease worldwide and results from complex interactions between inherited susceptibility and modifiable lifestyle factors. While polygenic risk scores (PRS) capture cumulative inherited risk, how inherited susceptibility and lifestyle behaviors jointly influence MASLD remains incompletely understood, particularly in Asian populations. **Methods:** We conducted a population-based study using Taiwan Biobank data. A multi-trait PRS was derived in a PRS derivation population (n = 81,452) using genome-wide association summary statistics for eight cardiometabolic traits and constructed using PRS-CS. The PRS was subsequently applied to an analytical population (n = 15,951) with imaging-defined MASLD. Lifestyle behaviors, including physical activity, smoking, and dietary behaviors, were assessed using structured questionnaires. Logistic regression models were used to evaluate independent and joint associations between PRS, lifestyle factors, and MASLD. **Results:** Higher multi-trait PRS was significantly associated with increased MASLD risk, with adjusted odds ratios (ORs) of 1.19 (95% CI 1.09–1.31) and 1.55 (95% CI 1.39–1.73) for intermediate and high PRS categories, respectively, compared with the lowest category. Higher physical activity was independently associated with lower MASLD risk (adjusted OR 0.80, 95% CI 0.74–0.86), and healthier dietary patterns were also inversely associated with MASLD, whereas cigarette smoking was associated with increased risk. Favorable lifestyle behaviors were consistently associated with lower odds of MASLD across all levels of inherited susceptibility, including among individuals with elevated PRS. No significant gene–lifestyle interactions were observed. **Conclusion:** Inherited susceptibility and modifiable lifestyle factors independently contribute to MASLD risk. Favorable lifestyle behaviors were associated with lower MASLD risk even among individuals with elevated inherited susceptibility, supporting lifestyle intervention as a key strategy for MASLD prevention and precision prevention approaches.

Disclosures: Mei-Hsuan Lee: Nothing to Disclose, Yan-Lin You: Nothing to Disclose, Xia-Rong Liu: Nothing to Disclose, Szu-Ching Yin: Nothing to Disclose, Yen-Feng Lin: Nothing to Disclose, Ming-Lung Yu: Abbvie, Gilead and Roche diagnostics.: Grant/Research Support, Abbott, Abbvie, Gilead, Roche and Roche diagnostics: Consultant, Abbvie, BMS, Gilead, Roche and Roche diagnostics: Speaking and Teaching, Chien-Jen Chen: Nothing to Disclose.

2473 | SEMAGLUTIDE 2.4 MG AND THE CHANGES IN LIVER ENZYMES AND CARDIOMETABOLIC MARKERS IN PATIENTS WITH MASH: A DESCRIPTIVE REAL-WORLD DATA STUDY

Husam Albarmawi[1] David Shi[1] Abdalla Aly[2] Katie Brown[3] Katherine Gilbert[3] Sunny Guin[3] Benjamin Hong[3] Maximilian Kurt Jara[4] Amy Wu[3] Eric Lawitz[5], [1]Novo Nordisk Inc., USA, [2]Novo Nordisk, [3]Truveta, USA, [4]Novo Nordisk Inc., [5]The Texas Liver Institute, USA

Background: Semaglutide 2.4 mg received an accelerated US Food and Drug Administration approval in 2025 for the treatment of noncirrhotic metabolic dysfunction-associated steatohepatitis (MASH) with moderate to advanced liver fibrosis in adults. Real-world evidence on the impact of semaglutide on MASH remains limited. **Methods:** This retrospective cohort analysis utilized de-identified electronic health records from Truveta Data. Patients with a MASH diagnosis were identified between June 2021 and March 2026. We compared patients who initiated semaglutide and those who did not. The index date was semaglutide first dispensing date for the semaglutide group. For the no-semaglutide group, it was randomly assigned to match the distribution of semaglutide index dates. Patients with cirrhosis or other liver disease etiologies were excluded, as were those treated with other glucagon-like peptide-1 agonists or resmetirom. Within each group, we reported mean absolute and percent changes in liver enzymes (alanine aminotransferase [ALT]; aspartate aminotransferase [AST]) and cardiometabolic markers at 3, 6, and 12 months post-index. Liver enzyme changes were also reported in a subgroup with elevated baseline ALT (> 25 U/L in women; > 35 U/L in men). **Results:** We identified 2,479 patients in the semaglutide group and 70,702 in the no-semaglutide group. Patients receiving semaglutide were younger (mean age: 48 vs 54 years), more often female (67% vs 59%), and had higher body mass index (mean: 39 vs 34 kg/m^2). Cardiometabolic conditions

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were similar between groups, except for type 2 diabetes, which was less common in the semaglutide group (8% vs 28%). Among patients with paired baseline and 1-year laboratory measurements in the semaglutide group, ALT decreased by 16 U/L (33%; mean at baseline = 48 U/L; N = 99; $P < 0.01$) and AST decreased by 10 U/L (29%; baseline = 33 U/L; N = 99; $P < 0.01$). HbA1c decreased by 0.46 percentage points (8%; baseline = 5.7%; N = 56; $P < 0.01$). Body weight decreased by 30 lb. (12%; baseline = 247 lb.; N = 267; $P < 0.01$). In the no-semaglutide group, ALT decreased by 4 U/L (9%; baseline = 46 U/L; N = 10653; $P < 0.01$), AST decreased by 2 U/L (6%; baseline = 34 U/L; N = 10620; $P < 0.01$), HbA1c decreased by 0.09 percentage points (1%; baseline = 6.7%; N = 7063; $P < 0.01$), and body weight decreased by 2 lb. (1%; baseline = 214 lb.; N = 23689; $P < 0.01$). In the subgroup with elevated baseline ALT, mean ALT reduction was 26 U/L (42%; baseline = 62 U/L; N = 66; $P < 0.01$) in the semaglutide group and 10 U/L (17%; baseline = 62 U/L; N = 6524; $P < 0.01$) in the no-semaglutide group. Changes at 3, 6, and 12 months among patients with available data are shown in the table. **Conclusion:** These real-world findings are directionally consistent with those observed in the ESSENCE trial and support the use of semaglutide as a disease modifying option in routine MASH care. Improvements in liver enzymes were more pronounced in those with elevated baseline ALT.

Changes in liver enzymes and cardiometabolic markers among patients with available data at 3, 6 and 12 months post-index

	Mean change at 3 months		Mean change at 6 months		Mean change at 12 months	
Marker	Semaglutide	No semaglutide	Semaglutide	No semaglutide	Semaglutide	No semaglutide
ALT (U/L)	-7 (-13%)	-3 (-7%)	-11 (-20%)	-3 (-7%)	-16 (-33%)	-4 (-9%)
AST (U/L)	-5 (-14%)	-1 (-4%)	-7 (-21%)	-2 (-5%)	-10 (-29%)	-2 (-6%)
Weight (lb.)	-10 (-4%)	-1 (-1%)	-20 (-8%)	-2 (-1%)	-30 (-12%)	-2 (-1%)
HbA1c (percentage points)	-0.29 (-5%)	-0.14 (-2%)	-0.42 (-7%)	-0.06 (-1%)	-0.46 (-8%)	-0.09 (-1%)
	Subgroups with elevated ALT (>25 in women and >35 in men) at baseline					
ALT (U/L)	-11 (-16%)	-8 (-13%)	-16 (-25%)	-9 (-14%)	-26 (-42%)	-10 (-17%)
AST (U/L)	-7 (-18%)	-4 (-9%)	-10 (-26%)	-4 (-10%)	-15 (-38%)	-5 (-12%)

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2474 | PEDIATRIC MALSD AND EARLY ONSET OBESITY: INVESTIGATING A GENETIC SIGNATURE

Anna Pitts[1] Sara Hassan[1], [1]University of Texas Southwestern Medical Center

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common chronic liver disease in children, yet pathogenic drivers of hepatic steatosis in very young children remain incompletely understood. Early onset obesity (onset prior to age 5) is increasingly recognized as a distinct entity often reflecting underlying monogenic or syndromic causes. We describe a single-center cohort of children and adolescents with MASLD or steatohepatitis (MASH) and early-onset obesity, evaluated with targeted genetic testing to determine the prevalence of monogenic and syndromic causes in this population. **Methods:** We performed a retrospective analysis of a prospectively maintained cohort from a single-center pediatric hepatology clinic over 12 months. Patients were eligible if they developed obesity onset prior to age 5 and imaging (ultrasound or MRI with hepatic steatosis, a controlled attenuation parameter (CAP) $\geq$ 248 dB/m on vibration-controlled transient elastography (FibroScan)) or biopsy-confirmed MASLD. Of the forty-seven patients initially

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identified; 4 were excluded (3 with suspected autoimmune hepatitis, 1 without steatosis at our center), yielding 43 patients. All 43 patients underwent genetic testing using a next-generation sequencing panel covering genes associated with monogenic obesity, ciliopathies, and related metabolic disorders. For each identified variant, mode of inheritance (MOI) and in silico missense pathogenicity predictions were recorded clinical data extracted from the electronic medical record included demographics, anthropometrics, alanine aminotransferase (ALT), fasting lipid panel, hemoglobin A1c (HbA1c), vitamin D, FibroScan (CAP and LSM), comorbidities, and medications. Liver stiffness measurement (LSM), was assessed via FibroScan, with a threshold of ≥ 7 kPa used to indicate clinically significant fibrosis. Descriptive statistics were calculated. **Results: Demographics** : The cohort (n = 43) included 23 males (53%) with a median age of 12 years (range 4-18). The cohort was predominantly Hispanic (79%). Mean BMI was 145% of the 95th percentile; 60% had Class III obesity. Hypertension was present in 37% and obstructive sleep apnea in 23%. Median ALT was 63 U/L (range 10-554). Among those with available FibroScan data, (n = 19), mean CAP was 289 dB/m, consistent with moderate-to-severe hepatic steatosis. The median LSM was 7.1 kPa (n = 24), including those children with MR Elastography (n = 5). Four patients underwent liver biopsy, all demonstrating histologic steatohepatitis; two had fibrosis. **Genetic testing** : Of 43 patients, 40 had interpretable genetic results (2 pending, 1 quality control failure). Of these, 30 (75%) had at least one pathogenic or likely pathogenic variant: 14 patients (47%) had a single gene variant, 9 (30%) had two, and 7 (23%) had three or more. Ten patients (25%) were negative. Sixteen of the 30 (53%) carried variants in genes with established obesity or metabolic associations. The most enriched pathway was ciliopathy-associated (with a second prominent cluster involving semaphorin). Autosomal recessive inheritance predominated (20 patients); 8 had autosomal dominant or mixed variants. In silico predictions showed damaging/pathogenic results in 4 patients, conflicting in 22, and tolerated/uncertain in 4. These are represented in Table 2. **Conclusion:** In this descriptive cohort of children with very early onset obesity and MASLD, 75% of patients harbored at least one pathogenic or likely pathogenic variant, and more than half carried variants in two or more genes. The predominance of ciliopathy genes and genes with established obesity associations suggests that MASLD coupled with early onset obesity may represent a genetically distinct entity in which disrupted cilia function, hypothalamic satiety signaling, and metabolic regulation lead to hepatic steatosis at an unusually young age. These in conjunction with gestational exposures such as maternal pre-pregnancy obesity and environmental exposures likely impact weight in early life. While direct comparison to typical MASLD in youth was beyond the scope of this study, these findings are consistent with a genetic landscape that may differ from the one described in older cohorts. This study suggests that routine testing with rare obesity gene panels may be warranted in children with MASLD presenting with obesity before 5 years of age. Larger prospective studies are needed to validate these findings, better define associations between genetic subtypes, histologic severity, and disease progression, and explore potential implications for targeted therapeutic strategies.

Table 2. Genetic testing results (n = 40 with interpretable results)
Values are n (%) unless otherwise indicated. Three patients excluded from denominator: 2 results pending, 1 quality-control failure.

Variable	Value
Overall yield	
Pathogenic or likely pathogenic variant(s) identified	30 (75)
Negative	10 (25)
Variant burden among positive cases (n = 30)	
1 variant	14 (47)
2 variants	9 (30)
≥3 variants	7 (23)
Genes with established obesity or metabolic associations (n = 30)	
At least one such variant	16 (53)
Genes identified	MC4R, PCSK1, ALMS1, BBS1, BBS5, BBS10, MAGEL2, SIM1, SH2B1, MKKS, KSR2
Pathway enrichment	
Ciliopathy-associated genes	ALMS1, CEP290, RPGRIP1L, INPP5E, IFT172, MKKS, NPHP1, SDCCAG8, VPS13B
Semaphorin / axon guidance genes	SEMA3A, SEMA3C, SEMA3D, SEMA3G, PLXNA1, PLXNA2, PLXNA3, NRP1
Mode of inheritance (n = 40)	
Autosomal recessive	20 (50)
Autosomal dominant or mixed AR/AD	8 (20)
Indeterminate	2 (5)
Negative	10 (25)
In silico pathogenicity predictions (n = 30)	
Damaging / pathogenic (SIFT, PolyPhen-2, CADD concordant)	4 (13)
Conflicting	22 (73)
Tolerated / uncertain	4 (13)

AR = autosomal recessive; AD = autosomal dominant. In silico predictions recorded per variant using SIFT, PolyPhen-2, and CADD scores.

Disclosures: Anna Pitts: Nothing to Disclose, Sara Hassan: Ipsen: Consultant.

2475 | STATIN USE AND LIVER-RELATED OUTCOMES IN PATIENTS WITH DIABETES-ASSOCIATED MASLD: A NATIONWIDE COHORT STUDY WITH GENETIC RISK ANALYSIS

Hyein Han[1] Moon Haeng Hur[2] Hyunjae Shin[2] Sungho Won[1] Yun Bin Lee[2] Eun Ju Cho[3] Jeong-Hoon Lee[2] Su Jong Yu[2] Jung-Hwan Yoon[2] Yoon Jun Kim[2], [1]Seoul National University, [2]Seoul National University College of Medicine, [3]Seoul National University Hospital

Background: Patients with metabolic dysfunction-associated steatotic liver disease (MASLD) and diabetes mellitus (DM) are at high risk of liver-related outcomes (LROs), including hepatocellular carcinoma

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(HCC) and cirrhosis decompensation. Although statins may have hepatoprotective effects beyond lipid lowering, their role in DM-MASLD remains insufficiently defined. We aimed to evaluate the association between statin use and LROs in patients with DM-MASLD using the Korean National Health Insurance Service database, complemented by Mendelian randomization (MR) analysis. **Methods:** We conducted a nationwide retrospective cohort study of adults who underwent national health screening between 2009 and 2013 and met the criteria for DM-MASLD. A 3-year landmark design was used to classify statin users, defined as those with a cumulative defined daily dose ≥ 30 during the landmark period. Baseline characteristics were balanced using inverse probability of treatment weighting (IPTW) and 1:1 propensity score matching (PSM). The primary outcome was a composite LRO, comprising HCC, liver transplantation, decompensated cirrhosis, and liver-related death. Additional analyses included time-varying Cox models and target trial emulation (TTE). To support causal inference, 2-sample MR was performed using HMGCR cis-locus genetic variants as proxies for HMG-CoA reductase inhibition and cirrhosis-related outcomes from the FinnGen R12 cohort. **Results:** Among 171,580 patients with DM-MASLD, 63,553 were statin users and 108,027 were non-users. After IPTW, baseline characteristics were well balanced. Statin use was associated with significantly lower risks of the composite LRO (adjusted hazard ratio [aHR], 0.85; 95% confidence interval [CI], 0.78–0.92; $p < 0.001$), HCC (aHR, 0.79; 95% CI, 0.67–0.92; $p = 0.002$), and decompensated cirrhosis (aHR, 0.78; 95% CI, 0.71–0.87; $p < 0.001$). These associations were consistent in PSM and time-varying Cox analyses. In TTE, statin use was also associated with reduced risks of LRO (pooled odds ratio [OR], 0.85; 95% CI, 0.80–0.90) and HCC (pooled OR, 0.80; 95% CI, 0.71–0.90). Among statin subtypes, lipophilic statin use showed a more pronounced protective association across all outcomes compared to hydrophilic statin. In MR analysis, genetically proxied HMG-CoA reductase inhibition was associated with reduced risks of cirrhosis (OR, 0.60; 95% CI, 0.42–0.85; $p = 0.004$), and the fibrosis/cirrhosis composite outcome (OR, 0.56; 95% CI, 0.34–0.92; $p = 0.021$), with directionally consistent results across sensitivity analyses. **Conclusion:** In this study, statin use was associated with lower risks of LRO, and complementary MR findings supported a potential causal role of HMG-CoA reductase inhibition in reducing cirrhosis-related risk. These results suggest that statins may have a chemopreventive role in liver disease progression among patients with DM-MASLD, warranting prospective validation.

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2476 | LEVERAGING REAL-WORLD DATA AND NLP TO IDENTIFY AT RISK METABOLIC DYSFUNCTION ASSOCIATED STEATOHEPATITIS IN THE GENERAL POPULATION

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Background: Metabolic Dysfunction Associated Steatotic Liver Disease (MASLD) affects approximately 25% of the global population. Its progressive form, Metabolic Dysfunction-Associated Steatohepatitis (MASH), is associated with cirrhosis and hepatocellular carcinoma. Yet MASLD screening remains inconsistent, EHR documentation is incomplete, and emerging therapies have made identifying undiagnosed or under-documented cases increasingly important. This study aimed to leverage real-world data (RWD) and develop an advanced natural language processing (NLP) model to identify patients with at-risk MASH through radiology reports and laboratory test results. **Methods:** This retrospective study analyzed de-identified EHR, laboratory, and radiology data from a partnering hospital accessed and harmonized using Briya AIRE. The study cohort included patients who underwent abdominal ultrasound between 2020 and 2024. An NLP model was developed to identify signs of fatty liver in ultrasound reports using commonly documented clinical terminology. Patients were then stratified by MASH risk using Fibrosis-4 (FIB-4) scores. To enhance fibrosis risk detection, an additional NLP-derived "Fibrosis Score" was generated from ultrasound report features, including spleen size, liver morphology and dimensions, ascites, varices, and other radiological indicators, and integrated with FIB-4 results to classify patients into high- and low-risk groups. **Results:** The analysis included 28,795 radiology reports from 20,422 unique patients. NLP-based analysis identified 4,036 additional patients with confirmed fatty liver disease, increasing the relevant study population by 360%, from 1,122 to 5,158 patients. Only 22% of MASLD patients had a documented diagnosis in structured EHR fields, while 85% had evidence of fatty liver in ultrasound reports; 78% were identified exclusively through unstructured ultrasound data, and 7% were identified by both ICD-10 codes and ultrasound analysis. Among 20,422 patients, 13,368 available FIB-4 scores were identified, including 9,279 within three months of the reference ultrasound date. Of these, 4,368 patients had

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scores above the at-risk threshold. External validation demonstrated high NLP performance, achieving precision of 0.94 and recall of 0.97 for fatty liver detection, and precision of 0.77 and recall of 0.94 for fibrosis signs among patients with fatty liver. **Conclusion:** This RWD-driven NLP approach significantly improved identification of under-documented fatty liver disease and enabled risk stratification for at-risk MASH using existing clinical data, facilitating earlier detection, monitoring, and intervention for patients at risk of progressive liver disease.

Disclosures: April Chan: Nothing to Disclose, Or Shaked: Nothing to Disclose, Talia Tron: Nothing to Disclose, Gadi Lalazar: Nothing to Disclose.

2477 | REAL-WORLD LIVER STIFFNESS TRAJECTORIES IDENTIFY GLYCEMIC CONTROL AS AN IMPORTANT PREDICTOR OF RAPID FIBROSIS PROGRESSION IN A DIVERSE URBAN MASLD POPULATION

Adeeba Tak[1] Yulu He[1] Maryfe Coronel Novoa[1] Mark Miller[1] Victor Llanes[1] Asher Leviton[1] Francecs Lee[1] Ryan Walker[1] Dania Valvi[1] Scott Friedman[1] Meena Bansal[2] Xiaotao Zhang[1], [1]Icahn School of Medicine at Mount Sinai, [2]Icahn School of Medicine at Mount Sinai (ISMMS)

Background: MASLD is the most common chronic liver disease worldwide and is increasing in parallel with obesity and type 2 diabetes. However, real-world longitudinal data on liver stiffness trajectories, a noninvasive surrogate of fibrosis dynamics, remain limited in diverse MASLD populations. We used serial VCTE measurements to characterize liver stiffness regression and progression and identify baseline factors associated with rapid progression. **Methods:** Adults with MASLD and paired baseline/follow-up VCTE ≥6 months apart were included (n=505). Annualized LSM percent change was calculated as the percent change in LSM between baseline and follow-up, divided by the interval between measurements in years. This was classified into six predefined trajectories ranging from marked regression (≥30% decrease) to rapid progression (≥30% increase). Rapid-progression rates were compared across demographic, cardiometabolic, and medication-use strata, and baseline predictors of rapid progression were evaluated using logistic regression. **Results:** The cohort was 55.6% female, mean age was 55.5 years (SD 13.8), 50.7% Hispanic, 37.0% diabetic, 58.2% had obesity, and 39.2% had documented GLP-1 RA or dual GLP-1/GIP agonist exposure (active at baseline and/or initiated during follow-up). Median baseline LSM was 7.5 kPa (IQR 4.7-9.6). Over a median follow-up of 23.7 months (IQR 14.6-31.7), 54.2% regressed (rapid 8.3%, moderate 26.5%, slight 19.4%), while 45.7% progressed (slight 18.4%, moderate 16.8%, rapid 10.5%). Rapid progression (n=53) was similar by age, sex, and ethnicity. Progressors were mainly characterized by cardiometabolic burden. In univariate logistic regression, rapid progression was associated with diabetes (OR 1.87, 95% CI 1.05-3.33), higher HbA1c (OR 1.23 per 1 percentage-point increase 95% CI 1.04-1.43), metformin (OR 2.12, 95% CI 1.18-3.80), statin (OR 1.86, 95% CI 1.04-3.39), and aspirin use (OR 2.48, 95% CI 1.29-4.60). In multivariable analysis, only HbA1c remained independently associated with rapid progression (aOR 1.21 per 1 percentage-point increase, 95% CI 1.01-1.46). Rapid regressors had significantly lower baseline HbA1c than rapid progressors in a symmetric head-to-head contrast (mean 6.1% vs 6.9%, p=0.018), confirming a bidirectional HbA1c-trajectory association. **Conclusion:** About 1 out of 10 patients experienced rapid progression. Rapid progression was more prevalent among patients with diabetes and higher HbA1c, while the lowest HbA1c concentrated among rapid regressors, identifying dysregulated glycemic control as a bidirectional signal of liver stiffness trajectory. Findings motivate routine longitudinal VCTE monitoring and suggest glycemic optimization as a modifiable target. Future work should incorporate physical activity, dietary quality, and fasting plasma glucose to refine the cardiometabolic signal.

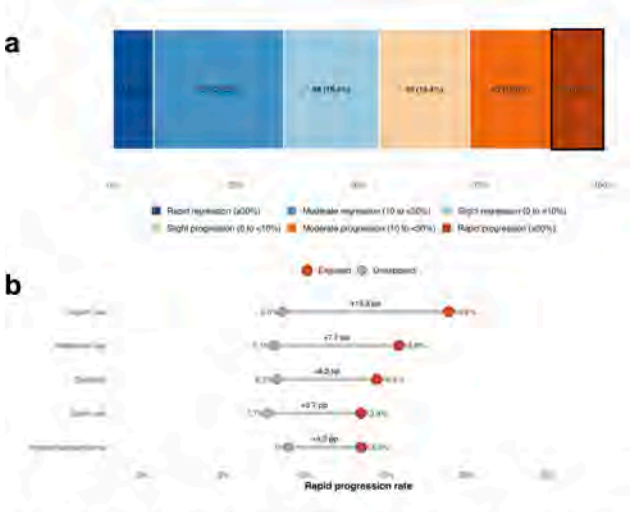


Figure 1. Liver stiffness trajectories and cardiometabolic predictors of rapid progression in a diverse urban MASLD cohort. Mount Sinai MASLD Registry; adults with paired baseline and follow-up VCTE ≥6 months apart (n=505; median follow-up 23.7 months). Rapid progression defined as ≥30% annualized LSM increase. **(a)** Distribution of annualized LSM percent change across six categories from rapid regression (≥30% decrease) to rapid progression (≥30% increase); 54.2% regressed and 45.7% progressed, with rapid progression in 10.5%. **(b)** Rapid progression rates stratified by cardiometabolic burden and medication exposure (exposed vs unexposed). On univariable analysis, progression was associated with diabetes, HbA1c, and metformin, statin, and aspirin use; only HbA1c remained independent on multivariable analysis (aOR 1.21 per 1-percentage-point, p=0.039).

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2478 | LLM-ASSISTED PHENOTYPING REVEALS MULTILEVEL PREDICTORS OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) PROGRESSION IN A LARGE PRIMARY CARE COHORT

Janet Chu[1] Aryana Far[1] Mindy DeRouen[2] Alyssa Cortella[1] Alison Canchola[1] Pushkar Inamdar[1] Salma Shariff-Marco[1] Jin Ge[1], [1]University of California, San Francisco, [2]New Mexico State University

Background: Identifying multilevel predictors (individual, healthcare system, and neighborhood) of MASLD progression is critical for risk stratification and sub-specialty referral for high-risk patients. Structured electronic health record (EHR) data underdiagnoses MASLD, misclassifies disease severity, and omits progression events, which are found in unstructured data such as clinical, radiology, and pathology notes. Large language model (LLM)-assisted natural language processing (NLP) extracts and analyzes unstructured text, thereby improving accurate ascertainment of MASLD and multilevel predictors of progression. **Methods:** We included adults 18+ years old with 1+ primary care visit and diagnosis of steatosis between 2019-2024 at UCSF; those with other etiologies of liver disease were excluded. We extracted structured data (sociodemographic characteristics; vital signs; diagnostic codes; medications; labs) and used a PHI-protected implementation of GPT-5.2 to apply NLP on unstructured data (clinical, Vibration-Controlled Transient Elastography, radiology, and pathology notes) for evidence of steatosis, fibrosis, cirrhosis, or hepatocellular carcinoma (HCC). Area Deprivation Indices (ADI) were defined using patient ZIP codes. First MASLD progression event (outcome) was defined as incident F2 fibrosis, cirrhosis, or HCC based on ICD code or unstructured data. Patients were censored at first progression event, death, or study end date. We used multivariable LASSO-Cox proportional hazards regression adjusted for clustering by area code to determine multilevel factors associated with first MASLD progression. **Results:** Of 5,585 primary care patients found to have steatosis, 62% (N = 3,456) were only identified through LLM-assisted NLP (i.e. without an ICD code (K76.0 or K78.51)). A progression event was identified for 16% (N = 881; median time to event = 885 days (IQR 360-1289)); the majority (62%) were identified through NLP. Among patients with progression events, 557 had F2 fibrosis or more, 392 cirrhosis, and 35 HCC. In multivariable analyses adjusted for number of inpatient days and outpatient visits, age (HR 1.01; 95%CI 1.00-1.01), hypertension (HR 1.20; 95%CI 1.02-1.42), and higher ADI (HR 1.04; 95%CI 1.00-1.08) were associated with progression. BMI was inversely associated with progression (HR 0.99; 95%CI 0.98-1.00). **Conclusion:** LLM-assisted NLP captured 62% of MASLD cases and 62% of progression events lacking ICD codes, highlighting critical EHR data gaps. Older age, hypertension, greater healthcare utilization, and socioeconomic disadvantage were associated with disease progression; the inverse BMI association warrants further investigation. Future studies should incorporate additional neighborhood-level variables, including measures of healthcare access, environmental exposures, and food environment, to better characterize contextual drivers of MASLD progression.

Disclosures: Janet Chu: Nothing to Disclose, Aryana Far: Nothing to Disclose, Mindy DeRouen: Nothing to Disclose, Alyssa Cortella: Nothing to Disclose, Alison Canchola: Nothing to Disclose, Pushkar Inamdar: Nothing to Disclose, Salma Shariff-Marco: Nothing to Disclose, Jin Ge: Merck and Co: Grant/Research Support, Iota Biosciences/Astellas Pharmaceuticals: Consultant, Madrigal Pharamaceuticals: Consultant, Gilead Sciences: Consultant.

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2479 | COMPARABLE FIBROSIS BURDEN IN MASLD AND METALD DESPITE DIFFERENCES IN CARDIOMETABOLIC RISK: A NATIONALLY REPRESENTATIVE NHANES ANALYSIS 2021-2023

Saad Nadeem[1] David Victor[2] Sudha Kodali[2] Tamneet Basra[2] Michelle Jones-Pauley[2] Mohammad Siddiqui[3] R. Mark Ghobrial[4] Mazen Noureddin[2] Kavish Patidar[2], [1]Texas A&M College of Medicine, [2]Houston Methodist Hospital, [3]Virginia Commonwealth University, [4]Houston Methodist JC Walter Transplant Center

Background: The 2023 multi-society nomenclature introduced metabolic dysfunction and alcohol associated liver disease (MetALD). Although MetALD is often conceptualized as an overlap phenotype between metabolic dysfunction-associated steatotic liver disease (MASLD) and alcohol associated liver disease, its fibrosis burden and relationship to cardiometabolic risk factor (CMRF) burden remain unclear in nationally representative data. We compared fibrosis prevalence in MASLD versus MetALD and tested whether the association between CMRF burden and fibrosis differs by steatotic liver disease (SLD) subtype. **Methods:** We analyzed adults aged ≥20 years in the NHANES 2021–2023 with a transient elastography (n = 5,327; weighted N = 217.7 million U.S. adults). SLD was defined as a controlled attenuation parameter ≥285 dB/m. Applying 2023 AASLD-EASL-ALEH criteria, participants with ≥1 CMRF were classified as MASLD if alcohol intake was ≤210 g/wk in men, ≤140 g/wk in women and MetALD if alcohol intake was 211–420 g/wk in men and 141–350 g/wk in women. Fibrosis defined as ≥8.0 (≥F2) and ≥11.7 kPa (≥F3). Multivariable logistic regression with primary sampling unit-clustered standard errors tested SLD subtype × CMRF interaction, adjusting for age, sex, and race/ethnicity. **Results:** Prevalence was 30.9% (95% CI 29.0–32.8) for MASLD and 2.2% (1.8–2.6) for MetALD. Fibrosis prevalence was similar between groups (≥F2: 24.2% vs. 24.8%; ≥F3: 10.8% vs. 9.4%) despite comparable CMRF burden (median 3 [IQR 2–4]) and higher alcohol intake in MetALD. In MASLD, ≥F2 fibrosis increased stepwise across 1–2, 3, and 4–5 CMRFs (16.7% → 26.7% → 28.9%), whereas in MetALD it was highest at 1–2 CMRFs (33.1%) and lower at higher CMRF counts (19.3% and 19.6%). Each additional CMRF increased odds of ≥F2 (OR 1.28; 95% CI 1.15–1.41; p < 0.001) and ≥F3 fibrosis (OR 1.36; 95% CI 1.20–1.54; p < 0.001). The subtype × CMRF interaction suggested a weaker association in MetALD but was not statistically significant (OR 0.70; 95% CI 0.45–1.07; p = 0.098) (Figure 1). **Conclusion:** In this U.S. sample, MetALD affected 2% and had a similar fibrosis burden to that of MASLD, despite lower CMRF burden. Unlike MASLD, fibrosis in MetALD did not track with higher CMRF burden, suggesting that moderate alcohol intake may identify a distinct fibrosis-risk phenotype not captured by MALD-centric risk stratification. These findings support fibrosis assessment in moderate drinkers with SLD, even with modest CMRF burden.

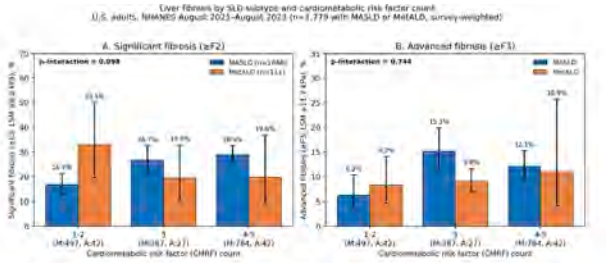


Figure 1. Weighted prevalence of significant (≥F2, panel A) and advanced (≥F3, panel B) fibrosis by cardiometabolic risk factor (CMRF) count, stratified by SLD subtype (MASLD vs. MetALD). Error bars: 95% confidence intervals. p-interaction values from multivariable logistic regression adjusting for age, sex, and race/ethnicity, with PSU-clustered robust SEs. Bracketed labels show unweighted sub-sample sizes (M = MASLD, A = MetALD).

Disclosures: Saad Nadeem: Nothing to Disclose, David Victor: Intercept: Speaker, and Advisor, Gilead: Speaking and Teaching, Madrigal: Speaker, BMS: Stock - publicly traded company, Pfizer: Stock - publicly traded company, Sudha Kodali: Nothing to Disclose, Tamneet Basra: Nothing to Disclose, Michelle Jones-Pauley: Nothing to Disclose, Mohammad Siddiqui: NovoNordisk: Grant/Research Support, 89Bio: Consultant, Sagimet: DSMB, R. Mark Ghobrial: Nothing to Disclose, Mazen Noureddin: Akero: Advisor, Alligos: Advisor, Altimmune: Advisor, AstraZeneca: Advisor, Boehringer Ingelheim: Advisor, Boston Pharma: Advisor, Cytodyn: Advisor, GSK: Advisor, Lilly: Advisor, Madrigal: Advisor, Merck: Advisor, Novo Nordisk: Advisor, Sagimet: Advisor, Terns: Advisor, Takeda: Advisor, Akero: Principal Investigator, Allergan: Principal Investigator, Altimmune: Principal Investigator, Boehringer Ingelheim: Principal Investigator, Bristol Myers Squibb: Principal Investigator, Boston Pharma: Principal Investigator, Conatus: Principal Investigator, Corcept: Principal Investigator, Galectin: Principal Investigator, Genfit: Principal Investigator, GSK: Principal Investigator, Kowa: Principal Investigator, Enanta: Principal Investigator, Madrigal: Principal Investigator, Lilly: Principal Investigator, Merck: Principal Investigator, Novartis: Principal Investigator, Novo Nordisk: Principal Investigator, Rivus: Principal Investigator, Shire: Principal Investigator, Takeda: Principal

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2480 | IMPLEMENTATION OF A PATIENT-CENTERED MOBILE FIB-4 APPLICATION FOR FIBROSIS RISK STRATIFICATION AND HEPATOLOGY REFERRAL IN TYPE 2 DIABETES

Tung-Hung Su[1] Chih-Yuan Wang[2] Tien-Jyun Chang[2] Chia-Hung Lin[2] Hung-Yuan Li[2] Jin-Ying Lu[2] Yi-Cheng Chang[2] Wan-Chen Wu[2] Feng-Jung Nien[3] Shyang-Rong Shih[2] Chia-Wen Lu[4] I-Weng Yen[2] Chyi-Feng Jan[4] Jia-Horng Kao[2], [1]National Taiwan University Hospital, [2]Department of Internal Medicine, National Taiwan University Hospital, [3]Department of General Medicine, National Taiwan University Cancer Center, [4]Department of Family Medicine, National Taiwan University Hospital

Background: Patients with type 2 diabetes mellitus (T2DM) are at increased risk of liver fibrosis. Current guidelines recommend hepatology referral for patients with FIB-4 > 2.67, but such referrals remain suboptimal. We evaluated whether a patient-centered mobile FIB-4 application could facilitate fibrosis risk stratification and hepatology referral. **Methods:** We developed a mobile phone-based FIB-4 application that automatically calculates the FIB-4 score from electronic medical records and provides management recommendations based on risk categories (< 1.3, 1.3–2.67, and > 2.67). In this prospective cluster-randomized trial (NCT06694974), endocrinologists and family medicine physicians were randomized to either the FIB-4 App group or standard care group, and their enrolled patients were assigned accordingly. Adults with T2DM aged 35–65 years were included. Patients in the FIB-4 App group received education on accessing their FIB-4 results through the App after 3-month follow-up laboratory testing and were encouraged to remind their physicians of recommended management based on the FIB-4 guidance. The primary endpoint was hepatology referral among patients with FIB-4 > 2.67. Secondary endpoints included vibration-controlled transient elastography (VCTE) utilization and prevalence of metabolic dysfunction-associated steatotic liver disease. **Results:** A total of 561 patients were enrolled (FIB-4 App group, n = 281; standard care group, n = 280). Median age was 58 years, 53% were male, median BMI was 26.3 kg/m², and median HbA1c was 6.9%. Overall, 77.4%, 21.4%, and 1.2% had FIB-4 < 1.3, 1.3-2.67, and > 2.67, respectively. Among patients with FIB-4 > 2.67,

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hepatology referral occurred in neither the standard care group (0/4) nor the FIB-4 App group (0/3). Referral rates were 2.5% (3/120) in the intermediate-risk group and 0% (0/434) in the low-risk group. Nineteen patients underwent VCTE with a median liver stiffness of 4.7 kPa (IQR 4.3–5.6). Two patients had liver stiffness >8 kPa, with corresponding FIB-4 values of 1.05 and 2.12. Correlation between FIB-4 and liver stiffness was weak (Spearman's rho = 0.20, $p = 0.419$). Among patients undergoing abdominal ultrasound, 71% (29/41) had steatotic liver disease, and 24% fulfilled criteria for metabolic dysfunction-associated steatohepatitis. In the FIB-4 App group, 83% completed the satisfaction survey, with a median satisfaction score of 10 (IQR 8–10). Patients appreciated the convenience of self-monitoring, although elderly users reported technical difficulties and frequently forgot to review their FIB-4 results. **Conclusion:** Only 1.2% of patients with T2DM younger than 65 years had FIB-4 >2.67. Although this patient-initiated FIB-4 referral reminder system was feasible and well accepted, hepatology referral rates remained extremely low. Greater awareness and implementation efforts are needed among both physicians and patients.

Disclosures: Tung-Hung Su: Gilead Sciences: Consultant, AbbVie: Speaking and Teaching, Bristol-Myers Squibb: Speaking and Teaching, Gilead Sciences: Speaking and Teaching, Merck Sharp and Dohme: Speaking and Teaching, Roche: Speaking and Teaching, Sysmex: Speaking and Teaching, Eisai: Speaking and Teaching, Abbott: Speaking and Teaching, Chih-Yuan Wang: Nothing to Disclose, Tien-Jyun Chang: Nothing to Disclose, Chia-Hung Lin: Nothing to Disclose, Hung-Yuan Li: Nothing to Disclose, Jin-Ying Lu: Nothing to Disclose, Yi-Cheng Chang: Nothing to Disclose, Wan-Chen Wu: Nothing to Disclose, Feng-Jung Nien: Nothing to Disclose, Shyang-Rong Shih: Nothing to Disclose, Chia-Wen Lu: Nothing to Disclose, I-Weng Yen: Nothing to Disclose, Chyi-Feng Jan: Nothing to Disclose, Jia-Horng Kao: Nothing to Disclose.

2481 | ASSOCIATION BETWEEN VITAMIN E AND METABOLIC DYSFUNCTION–ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) PREVALENCE, STEATOSIS SEVERITY, AND FIBROSIS SEVERITY: A CROSS-SECTIONAL ANALYSIS OF NHANES 2017–2018

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Background: Vitamin E has antioxidant and anti-inflammatory properties relevant to pathogenesis of metabolic dysfunction–associated steatotic liver disease (MASLD), and supplementation is recommended for select patients with biopsy-proven metabolic dysfunction–associated steatohepatitis (MASH). However, population-level data evaluating serum vitamin E and MASLD outcomes remain limited. Prior studies largely relied on dietary intake and older NAFLD definitions without separately assessing steatosis and fibrosis severity. Because α-tocopherol circulates bound to lipoproteins, lipid adjustment is important for accurate assessment. We evaluated the association between lipid-adjusted serum vitamin E and MASLD prevalence, severe steatosis, and clinically significant fibrosis in U.S. adults. **Methods:** Adults aged ≥ 18 years from NHANES 2017–2018 with serum α-tocopherol, lipid panel, and transient elastography (TE) data were included. Lipid-adjusted vitamin E was calculated as α-tocopherol/(total cholesterol + triglycerides), and participants were categorized into weighted quartiles (Q4 highest = reference). MASLD was defined as CAP ≥ 274 dB/m with ≥ 1 cardiometabolic risk factor and no significant alcohol use or viral hepatitis. Severe steatosis was defined as CAP ≥ 302 dB/m and significant fibrosis as TE ≥ 8 kPa among participants with MASLD. Multivariable logistic regression models adjusted for demographics, socioeconomic factors, smoking, and physical activity. Exploratory models additionally adjusted for BMI, diabetes, hypertension, and dyslipidemia. **Results:** Among 5,036 participants (mean age 47.3 years; 51.8% female), those in the lowest vitamin E quartile (Q1) versus highest (Q4) were younger (42.8 vs. 53.6 years), more likely male (59.9% vs. 36.1%), and had higher BMI (32.3 vs. 27.3 kg/m²; all $p < 0.001$). A stepwise increase ALT (19.7 to 28.2 U/L) was observed from Q4 to Q1 ($p < 0.001$). After adjustment for sociodemographic and lifestyle factors, Q1 was associated with higher odds of MASLD (adjusted OR [aOR] 5.17, 95% CI 4.07–6.57), severe steatosis (aOR 5.29, 95% CI 3.66–7.63), and significant fibrosis (aOR 1.65, 95% CI 1.12–2.41) versus Q4, with a dose-response relationship across quartiles for MASLD and steatosis. After additional metabolic adjustment, associations remained significant for MASLD (aOR 2.40, 95% CI 1.74–3.32) and severe steatosis (aOR 2.38, 95% CI 1.48–3.84), while the fibrosis association was attenuated. **Conclusion:** Lower lipid-adjusted serum vitamin E levels were independently associated with MASLD prevalence and steatosis severity, but not fibrosis after metabolic adjustment. These findings support a potential role for vitamin E in early MASLD

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pathogenesis and highlight the importance of lipid-adjusted measurement in population-based studies. Future studies are needed to determine whether targeted supplementation can alter the natural history of disease progression.

Table. Association Between Lipid-Adjusted Vitamin E Quartiles and Liver Disease Outcomes in NHANES 2017–2018

	Unadjusted OR (95% CI)	Primary Adjusted OR (95% CI)*	Exploratory Metabolic OR (95% CI)†
MASLD Prevalence			
Q4 Highest	Reference	Reference	Reference
Q3	1.63 (1.29–2.05)	1.86 (1.48–2.34)	1.50 (1.15–1.97)
Q2	2.38 (1.71–3.30)	3.06 (2.22–4.22)	1.81 (1.26–2.60)
Q1 Lowest	3.86 (3.06–4.89)	5.17 (4.07–6.57)	2.40 (1.74–3.32)
Severe steatosis (CAP ≥302 dB/m) among MASLD			
Q4 Highest	Reference	Reference	Reference
Q3	1.32 (0.99–1.76)	1.65 (1.21–2.25)	1.34 (0.95–1.88)
Q2	2.20 (1.70–2.84)	2.75 (1.95–3.89)	1.61 (1.06–2.46)
Q1 Lowest	3.87 (2.79–5.36)	5.29 (3.66–7.63)	2.38 (1.48–3.84)
Clinically Significant fibrosis (TE≥8 kPa) among MASLD			
Q4 Highest	Reference	Reference	Reference
Q3	0.86 (0.55–1.36)	0.85 (0.53–1.37)	0.74 (0.44–1.23)
Q2	1.41 (0.82–2.43)	1.28 (0.73–2.25)	0.94 (0.49–1.82)
Q1 Lowest	1.53 (1.10–2.13)	1.65 (1.12–2.41)	1.06 (0.63–1.78)

* Primary adjusted models were adjusted for age, sex, race/ethnicity, education level, poverty-income ratio, smoking status, and physical activity.

† Exploratory metabolic models were additionally adjusted for body mass index, diabetes, hypertension, and dyslipidemia.

Lipid-adjusted vitamin E was calculated as serum α-tocopherol divided by the sum of total cholesterol and triglycerides.

Disclosures: Nishat Anjum Shaik: Nothing to Disclose, Mohammed Rifat Shaik: Nothing to Disclose, Kamran Qureshi: Nothing to Disclose.

2482 | ASSOCIATION BETWEEN GLP-1 RECEPTOR AGONIST USE AND MORTALITY IN TYPE 2 DIABETES AND DECOMPENSATED CIRRHOSIS

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Background: Glucagon-like peptide-1 receptor agonist (GLP-1) use is associated with reduced decompensation risk in compensated cirrhosis. This study examined if patients with type 2 diabetes (T2DM) and decompensated cirrhosis (DC) may also benefit from GLP-1 use. **Methods:** We conducted a retrospective cohort study using TriNetX Global Network data (2015-2023), including adults with T2DM, subsequent cirrhosis, and ≥ 1 decompensation event (DE). Patients with prior liver transplant (LT) or hepatocellular carcinoma were excluded. The primary exposure was continuous GLP-1 use (study group) or oral antidiabetic/insulin use without GLP-1 (control group) maintained through first DE, defined as ≥ 1 exposure instance in each interval: 6-12 months before, 0-6 months before, 0-6 months after, and 6-12 months after first DE. Propensity score matching (PSM) balanced cohorts by age, sex, race, ethnicity, LT waitlist status, HbA1c, creatinine, albumin, total bilirubin, sodium, and INR. Logistic regression and survival analyses assessed 3-year outcomes. Secondary analyses compared 3-year outcomes in patients initiating GLP-1 therapy after first DE vs. controls, and 5-year outcomes in those using GLP-1s both before and after first DE vs. initiation after first DE. **Results:** A total of 1,906 patients were identified: 157 with GLP-1 use and 1,749 without. PSM yielded 154 matched pairs (MP) with a mean age of 61 years (±11). Among patients with GLP-1 use before first DE, 14.8% died within 3 years compared to 32.5% of controls, representing a 50% lower hazard of mortality (HR 0.50, 95% CI 0.30-0.84). Groups were comparable in inpatient encounters (GLP-1: 4.2±9.0 vs. controls: 9.4±36.9, p=0.09) and HbA1c (6.9±1.5 vs 7.2±1.6, p=0.08). In secondary analyses, patients initiated on a GLP-1 after first DE (75 MP) also demonstrated lower mortality compared to controls (HR 0.43, 95% CI 0.21-0.86). There were no significant differences in inpatient utilization (7.2±12.9 vs. 6.5±10.7, p=0.72) or HbA1c (7.0±1.8 vs. 7.2±1.8, p=0.45). Mortality did not differ significantly in those who initiated GLP-1 use before vs. after first DE (HR 0.78, 95% CI 0.36-1.66). **Conclusion:** In patients with T2DM and cirrhosis, GLP-1 use at time of first DE was associated with significantly lower 3-year mortality compared to controls. This benefit appeared independent of glycemic control and inpatient healthcare utilization, suggesting that the observed survival advantage was not attributable to baseline differences in disease severity between groups.

Table 1: GLP-1 associated outcomes in patients with type 2 diabetes and decompensated cirrhosis

	GLP-1 before + after DE vs control HR (95% CI)			GLP-1 only after DE vs control HR (95% CI)			GLP-1 before + after DE vs only after DE HR (95% CI)		
Death	0.50 (0.30-0.84)*			0.43 (0.21-0.85)*			0.78 (0.36-1.66)		
	GLP-1 Avg ± SD	Control Avg ± SD	P-value	GLP-1 Avg ± SD	Control Avg ± SD	P-value	GLP-1 (before + after) Avg ± SD	GLP-1 (only after) Avg ± SD	P-value
HbA1c	6.9±1.5	7.2±1.6	0.08	7.0±1.8	7.2±1.8	0.45	7.1±1.3	7.1±1.9	0.95
Inpatient encounters	4.2±9.0	9.4±36.9	0.09	7.2±12.9	6.5±10.7	0.72	4.4±6.9	7.8±12.9	0.055

*=statistically significant
CI: confidence interval; GLP-1: glucagon-like peptide-1 receptor agonist; HbA1c: hemoglobin A1c; HR: hazard ratio

Disclosures: Kai-Lou Yue: Nothing to Disclose, Charanpreet Sasan: Nothing to Disclose, Taylor Seacor: Nothing to Disclose, Anita Krishnarao: Madrigal Pharmaceuticals: Advisory Board.

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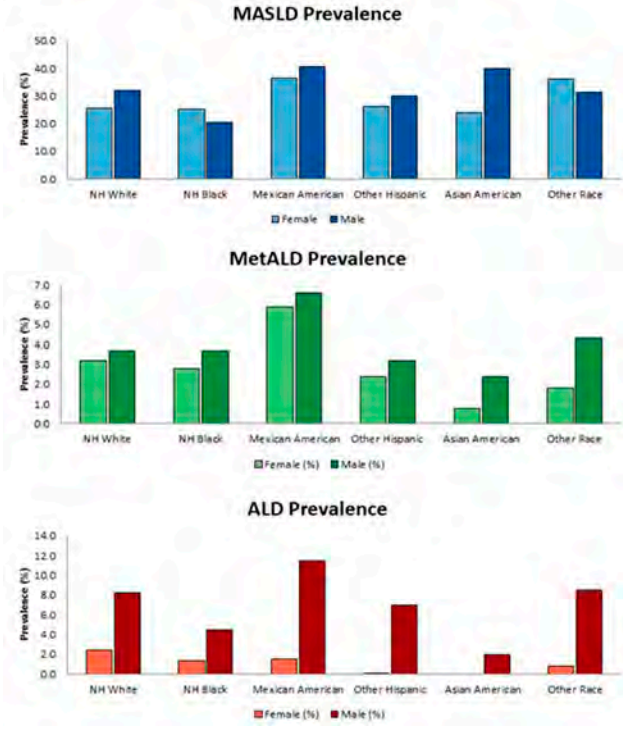
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2483 | RACIAL AND ETHNIC DISPARITIES IN STEATOTIC LIVER DISEASE (SLD) SUBTYPES USING A NOVEL ALCOHOL-CORRECTED CLASSIFICATION

Zobair Younossi[1] Markos Kalligeros[1] Annette Paik[1] Khalid AlNaamani[1] Waleed Alhazzani[1] Shadan AlMuhaidib[1] Basmah Khoja[1] Saleh Alqahtani[1] James Paik[2], [1]The Global NASH/MASH Council, [2]Global NASH/MASH Council

Background: Prior estimates of SLD subtypes relied on uncorrected self-reported alcohol intake, underestimating ALD and MetALD prevalence and risking misclassification, a paradox given that ALD is the most common cause of cirrhosis. A recently validated, sex- and frequency-specific alcohol correction algorithm, calibrated to national per-capita consumption, now enables accurate SLD subtype classification. We characterized SLD burden across racial, ethnic, and sex groups and identified drivers of racial and ethnic disparities. **Methods:** NHANES 2017–2020 adults aged ≥18 years with vibration-controlled transient elastography (n = 8,226) were analyzed. Steatosis was defined by controlled attenuation parameter (CAP ≥280 dB/m). MASLD, MetALD, and ALD were classified per multi-society nomenclature using alcohol-corrected intake. Prevalence of each subtype was estimated according to gender and race/ethnicity. Survey-weighted Oaxaca-Blinder decomposition partitioned racial/ethnic SLD subtype prevalence gaps into metabolic, corrected alcohol, demographic, and unexplained components. **Results:** Of 8,226 participants (mean age 47.5 years; 48.6% male; 63.5% Non-Hispanic (NH) White; 15.6% T2D; 42.6% obesity), alcohol-corrected prevalence of MALD, MetALD, and ALD was 29.2%, 3.5%, and 4.7%. Mexican Americans showed the highest prevalence in MASLD (38.5%), MetALD (6.2%) and ALD (6.7%), while Asian Americans had the lowest in MetALD (1.6%) and ALD (1.0%) **(Figure)** . NH Black adults had the lowest MASLD prevalence (23.2%) despite the highest rates for obesity/T2D/hypertension (49.9%/17.7%/58.7%), representing metabolic dissociation. Males had higher ALD than females across all racial groups (7.7% vs 1.9%; 4.1-fold), most pronounced in Mexican American males (11.5% vs females 1.5%; 7.7-fold). NH Black males showed a reverse pattern for MASLD (prevalence in males 20.5% vs females 25.3%). Oaxaca-Blinder decomposition revealed that 13.2 percentage-point Mexican American-White MASLD gap was not explained by metabolic risk factors, suggesting biological or genetic susceptibility beyond conventional cardiometabolic pathways. MetALD and ALD disparities were similarly unexplained. For ALD, alcohol-corrected intake was the single largest explaining factor (14.7% of the gap), a contribution undetectable without correction for underreporting. **Conclusion:** A validated alcohol correction reveals substantial racial and sex disparities in SLD subtypes. The disproportionate MASLD burden in Mexican Americans persists despite metabolic risk adjustment, suggesting genetic or other unmeasured factors as potential drivers. Corrected alcohol intake resolves the ALD paradox, highlighting the critical importance of accurate alcohol ascertainment in liver disease equity research.

Figure. Alcohol-corrected MASLD prevalence by race/ethnicity and sex



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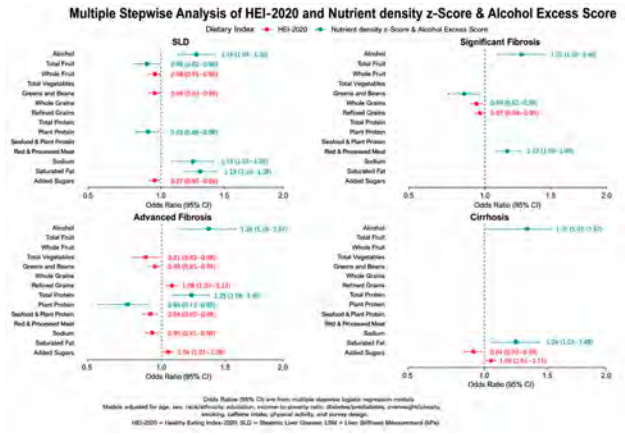
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2484 | US DIETARY HEALTH CARE POLICIES 2025–30 MAY BE DETRIMENTAL TO LIVER HEALTH

Nicholas Dunn[1] Sheel Patel[2] Luis Antonio Diaz[3] Robert Wong[4] Juan Pablo Arab[5] Shira Zelber-Sagi[6] Aleksander Krag[7] Zobair Younossi[8] Naim Alkhouri[9] Mazen Noureddin[10] Ashwani Singal[11], [1]University of Missouri-Kansas City School of Medicine, [2]Department of Medicine, University of Louisville School of Medicine, KY, USA, [3]Pontificia Universidad Católica de Chile, [4]Stanford/VA Palo Alto Healthcare System, [5]Virginia Commonwealth University, [6]The University of Haifa, [7]University of Southern Denmark, [8]The Global NASH/MASH Council, [9]Summit Clinical Research, [10]Houston Methodist Hospital, [11]University of Louisville

Background: The 2025–2030 Dietary Guidelines for Americans (DGA-2025) introduced major changes in dietary recommendations, including greater emphasis on total protein intake, de-emphasis of seafood and plant-based proteins, and removal of explicit alcohol guidance. We evaluated associations between individual dietary components and steatotic liver disease (SLD), fibrosis, and cirrhosis in U.S. adults using NHANES 2017–2023. **Methods:** We analyzed 10,944 adults from NHANES 2017–2023 with dietary recall and vibration-controlled transient elastography (VCTE). Dietary exposures included Healthy Eating Index-2020 (HEI-2020) component scores and energy-adjusted nutrient-density z-scores reflecting DGA-2025-aligned food groups. Outcomes included SLD (CAP $\geq$274 dB/m with cardiometabolic risk factor), significant fibrosis (LSM $\geq$8 kPa), advanced fibrosis ($\geq$10 kPa), and cirrhosis ($\geq$15 kPa). Survey-weighted multivariable logistic regression and stepwise models adjusted for demographic, metabolic, and lifestyle factors. **Results:** The weighted prevalence of SLD, significant fibrosis, advanced fibrosis, and cirrhosis was 40.0%, 10.1%, 5.8%, and 2.2%, respectively. Higher intake of total and whole fruit, vegetables, greens and beans, whole grains, and seafood/plant protein was associated with lower odds of SLD and fibrosis. In contrast, higher intake of red/processed meat, sodium, saturated fat, added sugars, and total protein was associated with greater liver disease burden. Whole grains were independently protective for significant and advanced fibrosis, whereas higher total protein intake was independently associated with advanced fibrosis. Greater adherence to prior DGA-2020 alcohol recommendations was associated with lower prevalence of significant fibrosis, advanced fibrosis, and cirrhosis. Protective dietary components, including greens and beans, seafood/plant protein, and alcohol restriction, were absent or de-emphasized in DGA-2025. **Conclusion:** In a nationally representative U.S. cohort, multiple dietary components promoted or omitted in DGA-2025 were significantly associated with SLD and fibrosis outcomes. Emphasis on total protein intake without consideration of protein source, alongside reduced emphasis on plant-based proteins and omission of alcohol guidance, may conflict with liver health–associated dietary patterns. These findings support a more liver-focused, source-specific nutritional framework for future dietary recommendations.



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2485 | SUBTYPE-AWARE EXPLAINABLE MACHINE LEARNING MODELS FOR PREDICTING RAPID PROGRESSION TO SEVERE LIVER DISEASE IN MASLD

Shulan Tian[1] Huihuang Yan[1] Tahmina Priya[1] Vincent Chen[2] Andres Acosta[3] Tara Haynes[1] Hugues Sicotte[1] Anthony Batzler[1] Shannon McDonnell[1] Kirk

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Wangensteen[1] Alina Allen[3] Konstantinos Lazaridis[1] Eric Klee[1], [1]Mayo Clinic, [2]University of Michigan, [3]Mayo Clinic Rochester

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common chronic liver disease worldwide. While fibrosis progression is typically slow, a substantial subset of patients advances rapidly to severe liver disease (SLD). For which the major drivers remain poorly understood. Current non-invasive tests such as FIB-4 were developed primarily to detect advanced fibrosis; yet nearly half of patients who later develop liver-related events do not have elevated FIB-4, and about one-third to half of hepatocellular carcinoma cases in MASLD occur in the absence of cirrhosis. The multifactorial nature and long asymptomatic phase in MASLD represent major challenges for accurate risk prediction. **Methods:** We identified subtypes using latent class analysis (LCA) and 9 clinical variables (Fig. 1) in a MASLD cohort (n = 4,623) from Mayo Clinic Biobank. Genetic and metabolic profiles were used to define subtype-specific signatures. To enable accurate time-to-event analyses, we developed a composite algorithm to define the earliest MASLD index date by integrating ICD-coded diagnoses, elevated ALT, and metabolic comorbidities. We developed subtype-aware, interpretable machine learning (ML) models to predict 5-year risk of SLD. SHAP analysis was applied to identify key features of progression. **Results:** LCA identified 5 subtypes that broadly segregated into cardiometabolic-dominant and liver-centric phenotypes (Fig. 2). The former was marked by high prevalence of obesity and type 2 diabetes while the latter were enriched for hepatic genetic variants and showed higher prevalence of SLD. Notably, patients in liver-centric subgroup had 25% higher proportion of patients progressing to SLD and nearly twice as many fast progressors (within 0.5–3 years) vs. cardiometabolic-dominant subgroup (Fig. 3) . Subtype-specific ML models substantially outperformed model trained on the full cohort, achieving AUCs of 0.95 in the liver-centric and 0.87 in the cardiometabolic-dominant subgroup, vs. 0.76 overall (Fig. 4). SHAP analysis revealed that the liver-centric subgroup was dominated by AST, whereas the cardiometabolic-dominant subgroup was more strongly influenced by metabolic and renal markers, including average BMI, HDL cholesterol, and creatinine. Notably, sex ranked among the top predictors in the cardiometabolic-dominant subgroup but had minimal importance in the liver-centric subgroup and the full cohort model (Fig. 4). **Conclusion:** Our subtype-aware ML modeling framework demonstrates that phenotypic subgroups in MASLD are driven by distinct sets of clinical predictors. By explicitly accounting for this heterogeneity in subtype-specific modeling, we achieved substantially better predictive performance compared with conventional population-level approaches. These findings support the incorporation of mechanistically defined subtypes to enhance risk prediction in MASLD.

Supplemental Figures:

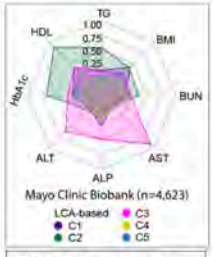


Figure 1: Proportion of patients in the highest category across 8 variables. TG, triglyceride.

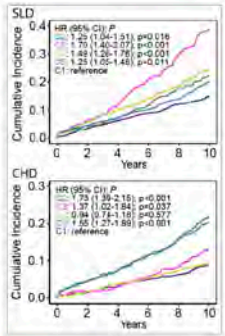


Figure 2: Cumulative incidence of SLD and CHD across subtypes in the Mayo Biobank cohort (n=4,623). Hazard Ratio (95% Confidence Interval) and p value were calculated using Cox proportional hazards regression model, adjusted by age. SLD, severe liver disease; CHD, coronary heart disease.

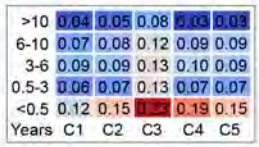


Figure 3: Proportion of patients progressing to SLD at discrete time frames, separated by subtype, in the Mayo Biobank cohort (n=4,623). Time-to-event was estimated from the index date to the first incidence of an SLD event.

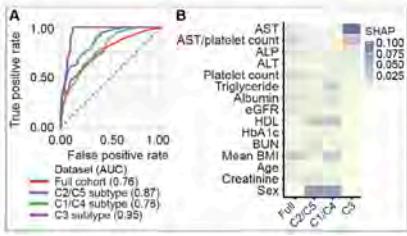


Figure4: Performance of ML models in predicting SLD **(A)** and top features **(B)**. The dashed gray diagonal line in (**A**) represents random chance. Important features are based on SHAP values, with a higher value indicating more importance. SHAP, SHapley Additive exPlanations.

Disclosures: Shulan Tian: Nothing to Disclose, Huihuang Yan: Nothing to Disclose, Tahmina Priya: Nothing to Disclose, Vincent Chen: AstraZeneca: site PI on industry-sponsored trial, Ipsen: site co-I on industry-sponsored trial, Kowa: site co-I on industry-sponsored trial, Madrigal: Grant/Research Support, GSK: Site PI for clinical trial, CSL: Site PI for clinical trial, Andres Acosta: Nothing to Disclose, Tara Haynes: Nothing to Disclose, Hugues Sicotte: Nothing to Disclose, Anthony Batzler: Nothing to Disclose, Shannon McDonnell: Nothing to Disclose, Kirk Wangensteen: Nothing to Disclose, Alina Allen: Novo Nordisk: Grant/Research Support, Novo Nordisk: Advisor, Target Pharma: Grant/Research Support, Boehringer Ingelheim: Advisor, Madrigal: Advisor, GSK: Advisor, Oncoustics: Grant/Research Support, Escopics: Grant/Research Support, Astra Zeneca: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Madrigal: Grant/Research Support, Siemens:

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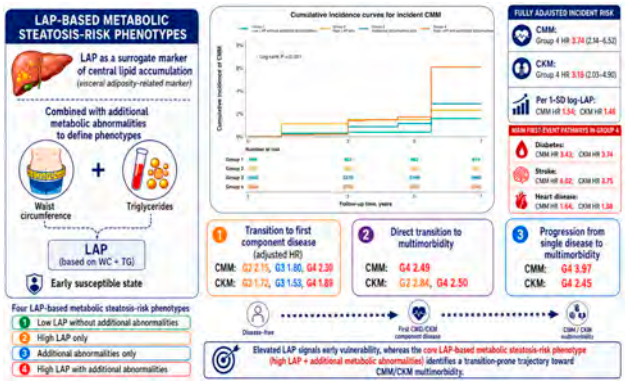
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2486 | LAP-BASED METABOLIC STEATOSIS-RISK PHENOTYPES AND CARDIOMETABOLIC MULTIMORBIDITY TRAJECTORIES AMONG MIDDLE-AGED AND OLDER CHINESE ADULTS

Bowen Qin[1] Xinyuan He[1] Sikai Qiu[2] Qian Wang[1] Qiaoman Fei[1] Zhiluo Yang[1] Ruiyuan Zhang[1] Yajing Bo[1] Mingzhu Liu[1] Qi Shang[1] Yi Liu[1] Haidan Shi[1] Fanpu Ji[1], [1]The Second Affiliated Hospital of Xi'an Jiaotong University, [2]The First Affiliated Hospital of Xi'an Jiaotong University

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a manifestation of systemic metabolic impairment and is closely linked to cardiometabolic complications. In community-based cohorts where liver imaging is often unavailable, simple and reliable markers are needed to identify steatosis-related metabolic risk. The lipid accumulation product (LAP), derived from waist circumference and triglycerides, may reflect central lipid accumulation, but whether elevated LAP, alone or in combination with additional non-LAP metabolic abnormalities, predicts cardiometabolic disease onset and subsequent progression to cardiometabolic multimorbidity (CMM) remains unclear. **Methods:** We used China Health and Retirement Longitudinal Study data from 2011, 2013, 2015, and 2018. The primary analysis included 6,559 adults aged $\geq$45 years free of diabetes, heart disease, and stroke at baseline. Additional non-LAP metabolic abnormalities were defined as $\geq$1 of the following: prediabetes, elevated blood pressure, or low HDL-C. Participants were classified into four phenotypes: low LAP without additional abnormalities, high LAP only, additional abnormalities only, and high LAP with additional abnormalities. Incident CMM was defined as at least two conditions among diabetes, heart disease, and stroke. Cox models estimated hazard ratios (HRs). Multi-state models evaluated transitions from no disease to single disease, direct transition to CMM, and progression from single disease to CMM. First-event and sensitivity analyses were performed. **Results:** During follow-up, 246 participants developed CMM. In phenotype-based Cox analysis, high LAP with additional abnormalities had the highest CMM risk versus low LAP without additional abnormalities (HR 3.74, 95% CI 2.14–6.52), whereas no statistically significant associations were observed for high LAP only or additional abnormalities only. In multi-state models, all abnormal phenotypes were associated with transition to a first cardiometabolic disease. However, only high LAP with additional abnormalities was consistently associated with direct transition to CMM (HR 2.49, 95% CI 1.23–5.03) and progression from single disease to CMM (HR 3.97, 95% CI 1.44–10.94). First-event analysis further showed that this phenotype was associated with higher risks of first-onset diabetes, heart disease, stroke, and direct CMM, suggesting that its link to multimorbidity was not driven by a single disease pathway. Findings were robust in sensitivity analyses and remained consistent when chronic kidney disease was included. **Conclusion:** Elevated LAP may capture early cardiometabolic disease onset, whereas high LAP with additional abnormalities identifies individuals prone to progression from single disease to multimorbidity. This LAP-based phenotype offers a simple tool for cardiometabolic risk stratification when liver imaging is unavailable.



Disclosures: Bowen Qin: Nothing to Disclose, Xinyuan He: Nothing to Disclose, Sikai Qiu: Nothing to Disclose, Qian Wang: Nothing to Disclose, Qiaoman Fei: Nothing to Disclose, Zhiluo Yang: Nothing to Disclose, Ruiyuan Zhang: Nothing to Disclose, Yajing Bo: Nothing to Disclose, Mingzhu Liu: Nothing to Disclose, Qi Shang: Nothing to Disclose, Yi Liu: Nothing to Disclose, Haidan Shi: Nothing to Disclose, Fanpu Ji: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose.

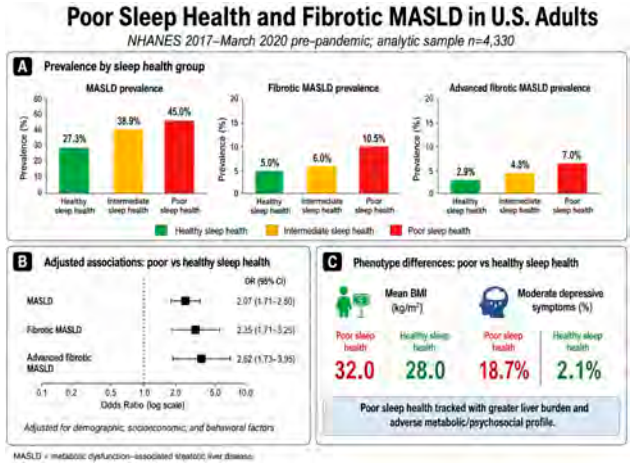
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2487 | POOR SLEEP HEALTH IDENTIFIES A HIGH-BURDEN FIBROTIC MASLD PHENOTYPE IN U.S. ADULTS: A NATIONAL NHANES VCTE ANALYSIS

Mounika Kotte[1] Digantkumar Patel[2] Jagadish Koyi[3] Serene Sara John[4] Sri Ram Charan Gundapaneni[5] Pragathi Munnangi[6] Hardik Dineshbhai Desai[7], [1]Prime south consortium, [2]Springfield Clinic, Springfield, IL, USA, [3]Integris Health, Oklahoma City, Oklahoma. USA. 73112, [4]Detroit medical center, Detroit, Michigan, 48201, [5]UCF/HCA Florida Ocala Hospital, Ocala, Florida, United States, 34471, [6]BronxCare Health System , Bronx , New York - 10457, [7]AB Plus Multispecialty Hospital

Background: Poor sleep health is linked to cardiometabolic dysfunction, but its association with fibrotic metabolic dysfunction–associated steatotic liver disease remains unclear. We examined sleep health phenotypes and vibration-controlled transient elastography (VCTE)-defined fibrotic MASLD among U.S. adults. **Methods:** We analyzed National Health and Nutrition Examination Survey 2017–March 2020 adults aged ≥20 years with valid VCTE and sleep data, excluding heavy alcohol use and hepatitis C. Poor sleep health was defined using a composite of abnormal sleep duration, frequent snoring, sleep apnea symptoms, physician-reported trouble sleeping, and frequent daytime sleepiness. MASLD was defined as controlled attenuation parameter ≥285 dB/m plus ≥1 cardiometabolic risk factor. Fibrotic MASLD was defined as MASLD with liver stiffness measurement (LSM) ≥8.0 kPa, and advanced fibrotic MASLD as MASLD with LSM ≥9.7 kPa. Survey-weighted prevalence and logistic regression models were used. **Results:** The analytic sample included 4,330 adults, representing 125.6 million U.S. adults. MASLD prevalence increased from 27.3% in adults with healthy sleep health to 38.9% with intermediate sleep health and 45.0% with poor sleep health. Fibrotic MASLD prevalence increased from 5.0% to 6.0% and 10.5%, while advanced fibrotic MASLD increased from 2.9% to 4.8% and 7.0%, respectively. Compared with healthy sleep health, poor sleep health was associated with higher mean body mass index, 32.0 vs 28.0 kg/m², and higher moderate depressive symptoms, 18.7% vs 2.1%. In demographic, socioeconomic, and behavioral adjusted models, poor sleep health was associated with higher odds of MASLD, OR 2.07, 95% CI 1.71–2.50, p < 0.001, fibrotic MASLD, OR 2.35, 95% CI 1.71–3.25, p < 0.001, and advanced fibrotic MASLD, OR 2.62, 95% CI 1.73–3.95, p < 0.001. After additional adjustment for body mass index, diabetes/prediabetes, hypertension, and dyslipidemia, associations were attenuated, suggesting partial mediation through metabolic dysfunction. **Conclusion:** Poor sleep health identifies a high-burden phenotype with substantially higher MASLD, fibrotic MASLD, and advanced fibrotic MASLD prevalence. These findings support sleep health as a modifiable risk marker that may improve population-level liver disease risk stratification beyond traditional metabolic factors alone.



Disclosures: Mounika Kotte: Nothing to Disclose, Digantkumar Patel: Nothing to Disclose, Jagadish Koyi: Nothing to Disclose, Serene Sara John: Nothing to Disclose, Sri Ram Charan Gundapaneni: Nothing to Disclose, Pragathi Munnangi: Nothing to Disclose, Hardik Dineshbhai Desai: Nothing to Disclose.

2488 | PROGNOSTIC VALUE OF ALKALINE PHOSPHATASE IN PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE AND TYPE 2 DIABETES

Cristiane Villela-Nogueira[1] Nathalie Leite[2] Mariana de Almeida[1] Ana Carolina Cardoso[3] Natalia Balassiano Wajsbrot[1] Claudia MAria Equi[1] Claudia Regina Cardoso[1] Gil Salles[1], [1]Universidade Federal do Rio de Janeiro, [2]Universidade do Rio de Janeiro, [3]Universidaed Federal do Rio de Janeiro

Background: The role of elevated alkaline phosphatase levels in liver fibrosis staging and in the prognosis of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) in patients with type 2 diabetes mellitus (T2DM) has not yet been well established. The aim was to evaluate the association between elevated alkaline phosphatase levels and the presence of moderate/advanced fibrosis assessed by histology

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and/or transient liver elastography (TE), and to determine its impact on liver-related outcomes in a cohort of patients with MASLD and T2DM. **Methods:** Individuals aged ≥18 years with MASLD and T2DM followed at a tertiary hospital were included. Anthropometric measurements, clinical variables, laboratory tests, PNPLA3 and TM6SF2 genotyping, as well as fibrosis staging by liver biopsy or TE, were evaluated. Moderate/advanced fibrosis was defined as F2–F4 on histology and/or liver stiffness ≥8 kPa measured by VCTE (FibroScan®). During follow-up, liver-related outcomes (ascites, encephalopathy, variceal bleeding, and hepatocellular carcinoma [HCC]) were recorded. Follow-up duration was defined as the interval between baseline alkaline phosphatase (ALP) levels and the last clinical visit or the occurrence of outcomes. **Results:** A total of 456 patients were included, of whom 66% were women, with a mean age of 62 ± 10 years and BMI of 31 ± 5 kg/m². At baseline, 63 (14%) had elevated ALP levels, and 174 (38%) had moderate/advanced fibrosis. Compared with patients with normal ALP levels, those with elevated ALP levels more frequently had moderate/advanced fibrosis (57% vs. 35%, $p = 0.001$). In multivariate logistic regression analysis, moderate/advanced fibrosis was independently associated with elevated ALP levels in a model including age, sex, BMI, smoking status, alcohol intake, type of diabetes treatment and glycemic control, and the presence of PNPLA3 and/or TM6SF2 risk alleles (OR 2.71; 95% CI 1.42–5.17; $p = 0.003$).During follow-up over a median period of 69 (52–85) months, 21 patients developed liver-related outcomes. Kaplan–Meier curves showed a significantly higher cumulative incidence of outcomes among patients with elevated versus normal ALP levels (log-rank $p < 0.001$). In Cox regression analysis, elevated baseline ALP levels were independently associated with the occurrence of liver-related outcomes in a model including age, sex, BMI, smoking status, alcohol intake, type of diabetes treatment and glycemic control, and the presence of PNPLA3 and/or TM6SF2 risk alleles (HR 7.31; 95% CI 2.74–19.53; $p < 0.001$). **Conclusion:** Elevated ALP levels are associated with moderate/advanced fibrosis and may predict the risk of clinically significant liver-related outcomes in our cohort of patients with T2DM and MASLD. Further studies are needed to identify the underlying mechanisms and the impact of this presentation pattern on the diagnostic and prognostic approach in this specific subgroup of patients.

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2489 | COMPARATIVE EFFECTIVENESS OF GLP-1 RECEPTOR AGONISTS VERSUS OTHER ANTIDIABETIC THERAPIES ON LIVER OUTCOMES IN PATIENTS WITH MASLD AND TYPE 2 DIABETES: A PROPENSITY-MATCHED REAL-WORLD STUDY

Arunkumar Krishnan[1] Diptasree Mukherjee[1] Naim Alkhouri[2] Tatyana Kushner[3] Doan Dao[4] Nicola Pugliese[5] Jörn Schattenberg[6] Christina Lindenmeyer[7] Saleh Alqahtani[8], [1]Atrium Health, [2]Summit Clinical Research, [3]Weill Cornell Medical College, [4]Massachusetts General Hospital, [5]Humanitas Research Hospital, [6]Rheinland-Pfalz, [7]Cleveland Clinic, [8]King Faisal Specialist Hospital & Research Centre

Background: Metabolic dysfunction–associated steatotic liver disease (MASLD) in individuals with type 2 diabetes (T2D) is associated with an elevated risk of advanced chronic liver disease, hepatocellular carcinoma (HCC), and all-cause mortality. Although GLP-1 receptor agonists (GLP-1RAs) can improve metabolic parameters and promote weight loss, their comparative effectiveness for liver-related outcomes versus other glucose-lowering classes remains poorly defined. We compared liver outcomes following GLP-1RA initiation with those of other antidiabetic therapies in patients with MASLD and T2D. **Methods:** We conducted a new-user, active-comparator cohort study within a global federated electronic health record network. Adults ≥18 years with MASLD and T2D and ≥12 months of prior observation were identified. GLP-1RA initiators (≥2 prescriptions within 6 months) were each compared with initiators of each comparator class in four separate 1: 1 propensity-matched trials, with the index date set at the first prescription. Patients with prior HCC, other primary liver cancer, or liver transplantation were excluded. Propensity scores balanced demographics, BMI, HbA1c, comorbidity burden, causes of liver disease, and medications. The primary outcome was incident HCC; secondary outcomes were hepatic decompensation (composite of ascites, variceal bleeding, or hepatic encephalopathy) and all-cause mortality. Time-to-event analyses used Cox proportional hazards models. **Results:** Prior to matching, GLP-1RA initiators

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(n = 198764) were younger, had higher BMI, and had a greater comorbidity burden than comparator initiators (several standardized mean differences [SMDs] > 0.1); all SMDs were < 0.1 after matching. GLP-1RA initiation was associated with lower hazards of incident HCC versus insulin (HR 0.25, 95% CI 0.18–0.34) and sulfonylureas (0.45, 0.28–0.72), a nonsignificant reduction versus metformin (HR 0.70, 095% CI .42–1.15), and no significant difference versus DPP-4 inhibitors (0.98, 0.75–1.27). For hepatic decompensation, GLP-1RA initiation was associated with lower HRs than all comparators: insulin (0.60, 0.52–0.70), sulfonylureas (0.72, 0.59–0.89), metformin (0.82, 0.68–0.99), and DPP-4 inhibitors (0.86, 0.74–0.99). All-cause mortality findings followed a similar gradient (HR 0.32, 95% CI 0.21–0.43). Effect directions were consistent across subgroups defined by cirrhosis status, with attenuation but persistence of benefit in patients with established cirrhosis. **Conclusion:** GLP-1RA initiation was associated with lower hazards of incident HCC and hepatic decompensation compared with insulin or sulfonylureas, a smaller reduction than with metformin, and no difference in HCC versus DPP-4 inhibitors. The gradient of effect across comparator classes suggests that the apparent benefit is partly dependent on the reference group, raising the possibility of residual confounding by indication.

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2490 | ASSOCIATION BETWEEN CANNABIS USE AND CLINICAL OUTCOMES IN METABOLIC DYSFUNCTION–ASSOCIATED STEATOTIC LIVER DISEASE: INSIGHTS FROM A LARGE TRINETX ANALYSIS

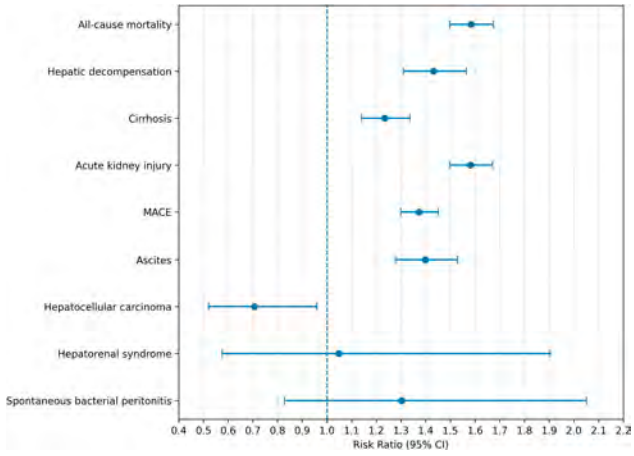
Muhamad Oum[1] Ahmed Ibrahim[2] Sammy Saab[3], [1]Saint Agnes Medical Center, [2]San Joaquin General Hospital, [3]University of California, Los Angeles

Background: Cannabis use has been associated with increased risks of major adverse cardiovascular events, including myocardial infarction, stroke, arrhythmias, and cardiovascular mortality; however, its impact on liver disease remains poorly understood. We aimed to evaluate the association between cannabis use and liver-related and systemic outcomes among patients with metabolic dysfunction–associated steatotic liver disease (MASLD). **Methods:** We conducted a retrospective cohort study using the TriNetX US Collaborative Network. Adult patients with MASLD identified using ICD-10 code were included. Patients with alcoholic liver disease, viral hepatitis, autoimmune hepatitis, primary biliary cholangitis, and primary sclerosing cholangitis were excluded. Cannabis users were identified using ICD-10 codes for cannabis abuse, dependence, or unspecified cannabis use and compared with nonusers. Propensity score matching was performed 1: 1 adjusting for demographics and major comorbidities including diabetes mellitus, hypertension, hyperlipidemia, nicotine dependence, albumin, and international normalized ratio (INR). Outcomes included all-cause mortality, hepatic decompensation, cirrhosis, hepatocellular carcinoma (HCC), acute kidney injury (AKI), major adverse cardiovascular events (MACE), ascites, hepatorenal syndrome (HRS), and spontaneous bacterial peritonitis (SBP). MACE was defined as myocardial infarction, cerebrovascular accident, and heart failure. **Results:** A total of 31,120 cannabis users and 1,730,942 nonusers with MASLD were identified. Before propensity score matching, cannabis users were younger (mean age 44.4 vs 52.0 years), more likely to be male (55.2% vs 45.3%), and less likely to be Hispanic (11.7% vs 13.9%) compared with nonusers. After propensity score matching, 31,115 patients remained in each cohort, with all

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standardized mean differences below 0.1. Cannabis users demonstrated significantly increased risks of all-cause mortality (RR 1.58, 95% CI 1.50–1.68), hepatic decompensation (RR 1.43, 95% CI 1.31–1.56), cirrhosis (RR 1.23, 95% CI 1.14–1.34), AKI (RR 1.58, 95% CI 1.50–1.67), MACE (RR 1.37, 95% CI 1.30–1.45), and ascites (RR 1.40, 95% CI 1.28–1.53) compared with nonusers. Cannabis users had a lower risk of HCC (RR 0.71, 95% CI 0.52–0.96). No significant differences were observed in HRS or SBP. **Conclusion:** Among patients with MASLD, cannabis use was associated with significantly increased risks of hepatic decompensation, cirrhosis, AKI, cardiovascular events, ascites, and all-cause mortality. These findings suggest cannabis use may adversely affect disease progression and outcomes in MASLD. More comprehensive prospective studies are needed to further evaluate the relationship between cannabis use and chronic liver disease progression.



Disclosures: Muhamad Oum: Nothing to Disclose, Ahmed Ibrahim: Nothing to Disclose, Sammy Saab: AbbVie: Speaking and Teaching, gilead: speaker, salix: consultant, takeda: Speaking and Teaching, madrigal: consultant, mallinckrodt: Speaking and Teaching, Sequana: Advisor, ipsen: Advisor, novo nordisk: Speaking and Teaching.

2491 | PROJECTIONS OF MASLD BURDEN AND IMPACT OF GLP-1/GIP RECEPTOR AGONIST UTILIZATION AMONG U.S. ADULTS WITH TYPE 2 DIABETES: A MICROSIMULATION ANALYSIS

Ha Tran[1] Phuc Le[2] Olajide Adekunle[2] Naim Alkhouri[3] William Herman[4] Michael Rothberg[2] Srinivasan Dasarathy[2], [1]Cleveland Clinic Foundation, [2]Cleveland Clinic, [3]Summit Clinical Research, [4]University of Michigan

Background: Type 2 diabetes (T2D) accelerates the progression of metabolic dysfunction-associated steatotic liver disease (MASLD) to advanced liver-related complications. We projected the future burden of MASLD among U.S. adults with T2D through 2050 and quantified the potential impact of glucagon-like peptide-1 (GLP-1) and dual GLP-1/glucose-dependent insulinotropic polypeptide (GIP) receptor agonists (RAs) on hepatic outcomes. **Methods:** We developed an agent-based state transition microsimulation model of MASLD progression among U.S. adults with T2D. The model comprised 14 health states with annual cycles over a lifetime horizon and incorporated use of pioglitazone, semaglutide, liraglutide, and tirzepatide—medications with beneficial impacts on liver outcomes. Treatment effects on MASLD progression were derived from randomized clinical trials, while treatment uptake trends were informed by population-based surveys and Epic Cosmos data. In the base-case analysis, GLP-1/GIP RA use was assumed to increase at the rate observed before 2025 until reaching a 50% overall uptake, after which it remained stable. We also explored two scenarios: accelerated uptake, in which use after 2025 increased at twice the base-case rate until reaching 100% overall uptake (best-case), and stagnant uptake, in which future use remained at the 2025 level of 22% (worst-case). **Results:** Model prediction between 2000 and 2024 aligned well with observed epidemiologic data. In the base-case analysis, MASLD cases in patients with T2D rose from 27.3 million (65.5%) in 2025 to 39.7 million (71.8%) in 2050. Over the same period, metabolic dysfunction-associated steatohepatitis cases increased from 12.4 to 16.4 million. Although the prevalence of advanced fibrosis ($F \geq F2$) decreased from 42.8% to 37.8%, the number of decompensated cirrhosis cases increased by 48.7%, from 362,100 to 538,400. Annual hepatocellular carcinoma (HCC) cases, liver transplants (LTs), and liver-related deaths also increased by 17.3%, 59.7%, and 64.6%, respectively. Compared with the base-case analysis, accelerate uptake of GLP-1/GIP RAs reduced HCC cases by 13.7%, LTs by 15.3%, and death by 11.9%, although these reductions did not occur until 2030. Conversely, stagnant uptake increased cumulative HCC cases, LTs, and liver-related deaths by 9.1%, 12.8%, and 7.3%, respectively, relative to the base-case analysis. **Conclusion:** MASLD burden among U.S. adults with T2D is projected to increase substantially over the next 25 years, even under an assumption of 50% uptake of GLP-1/GIP receptor agonists. Expanded GLP-1 and GLP-1/GIP access may reduce future liver-related complications, but the delayed benefit highlights the importance of early adoption.

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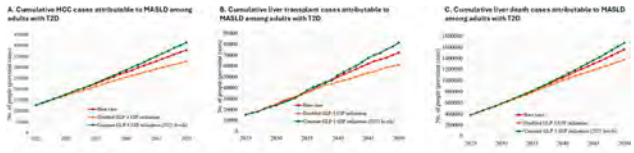


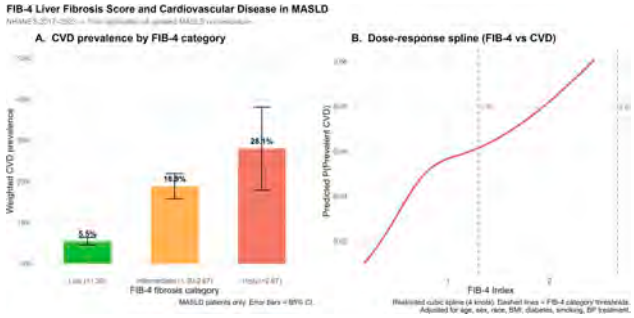
Figure. Cumulative MASLD-Related Clinical Events from 2025 to 2050 Under Three Drug Utilization Scenarios. Cumulative cases of (A) hepatocellular carcinoma, (B) liver transplantation, and (C) liver-related death attributable to MASLD among U.S. adults with T2D are shown for the base-case (utilization increasing linearly to 50% by 2050), doubled GLP-1/GIP utilization (twice the base-case rate), and constant GLP-1/GIP utilization scenarios (held at 2025 levels). The three scenarios showed meaningful divergence over time, with differences driven by the effect of treatment on fibrosis progression and MASH resolution rather than MASLD prevalence. Abbreviations: HCC = hepatocellular carcinoma; MASLD = metabolic dysfunction–associated steatotic liver disease; T2D = type 2 diabetes.

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2492 | LIVER FIBROSIS QUANTIFIED BY FIB-4 IMPROVES CARDIOVASCULAR RISK CLASSIFICATION BEYOND THE AHA PREVENT SCORE IN ADULTS WITH MASLD: NHANES 2017–2023

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD), the 2023 multi-society renamed successor to NAFLD, affects over half of U.S. adults and is increasingly recognized as a cardiometabolic condition. The FIB-4 index calculable from routine biochemistry (age, AST, platelets, ALT) stratifies MASLD severity by hepatic fibrosis stage. Whether FIB-4 improves CVD risk classification beyond the AHA PREVENT score in a contemporary nationally representative MASLD population has not been evaluated. **Methods:** We analyzed NHANES 2017–2023 (n = 9,962 adults ≥18 years). MASLD was defined per 2023 multi-society consensus using Hepatic Steatosis Index proxy plus ≥1 cardiometabolic risk factor. FIB-4 was categorized as Low (<1.30), Intermediate (1.30–2.67), or High (>2.67). Prevalent CVD (self-reported MI, stroke, or heart failure) was the primary outcome. Survey-weighted logistic regression and restricted cubic splines (4 knots) modeled FIB-4–CVD associations. Net reclassification improvement (NRI) and integrated discrimination improvement (IDI) tested incremental value of FIB-4 beyond PREVENT. **Results:** MASLD prevalence was 52.5%. Among 5,167 MASLD patients, CVD prevalence increased markedly across FIB-4 categories: Low 5.5%, Intermediate 18.9%, High 28.1%. In adjusted models, High FIB-4 was associated with 65% higher odds of CVD vs. Low FIB-4 (OR 1.65, 95% CI 0.89–3.08), with a significant nonlinear dose-response (p for nonlinearity <0.0001). FIB-4 significantly improved CVD risk classification beyond PREVENT alone: categorical NRI 0.081 (95% CI 0.032–0.131, p = 0.001), continuous NRI 0.509 (p<0.001), IDI 0.027 (p<0.001). Diabetes (OR 2.62), smoking (OR 2.54), and BP treatment (OR 1.45) were the strongest independent CVD predictors. **Conclusion:** In the first nationally representative analysis applying updated MASLD nomenclature, FIB-4 liver fibrosis staging significantly improves 10-year CVD risk classification beyond the AHA PREVENT score. These findings support FIB-4 as a low-cost hepato-cardiac risk enhancer warranting consideration in the cardiovascular evaluation of the 52% of U.S. adults meeting MASLD criteria.



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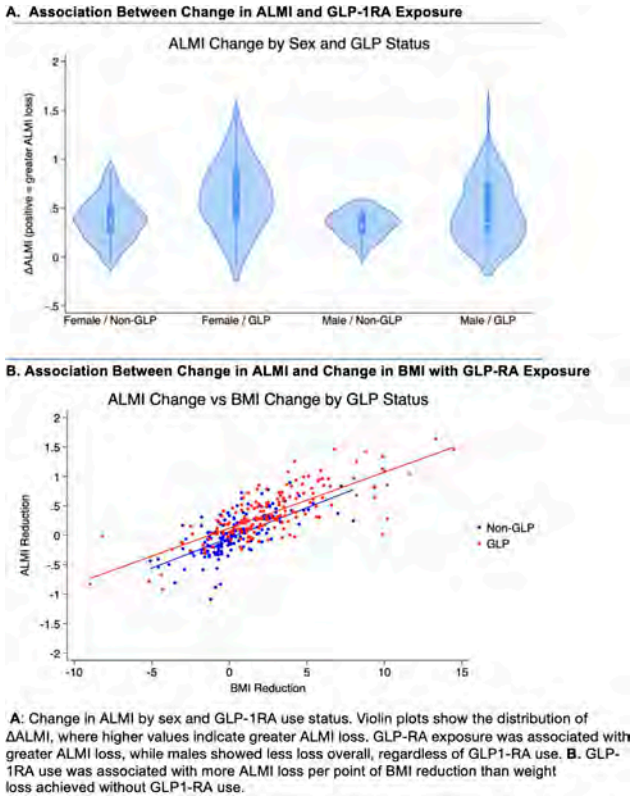
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2493 | GLP-1RA USE IS ASSOCIATED WITH GREATER APPENDICULAR LEAN MASS DECLINE IN PATIENTS WITH MASLD ACHIEVING SIGNIFICANT WEIGHT LOSS

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Background: Glucagon-like-peptide-1 receptor agonists (GLP-1RAs) produce weight loss through reductions in both fat and muscle mass. While they are increasingly prescribed in patients with metabolic dysfunction-associated steatotic liver disease (MASLD) to treat its metabolic comorbidities, given the elevated risk of sarcopenia in MASLD and its advanced form steatohepatitis (MASH), GLP-1 agonism effects on body composition warrants investigation. We examined longitudinal changes in body composition among patients with MASLD, with particular attention to factors that may modify lean mass change during weight loss. **Methods:** We conducted a retrospective longitudinal study of patients with MASLD who had paired Fibroscan and InBody assessments. Change in Appendicular Lean Mass Index (ΔALMI) was the primary outcome and any GLP-1RA use was the primary exposure. Multivariable linear regression analysis evaluated the relationships between baseline ALMI, change in BMI, age, diabetes status, fibrosis stage, and sex. A sensitivity analysis was performed restricted to those who had a minimum of 5% total body weight loss (TBWL). **Results:** A total of 352 patients with paired Fibroscan and InBody scans for body impedancea analysis were included; 59.4% were women, 31.0% had T2D, and 51.9% had any GLP-1 exposure. The mean age was 51 years, the mean baseline ALMI was 8.06 (8.91 M, 7.48 F), and the mean follow up time was 23.7 months. Mean BMI decreased from 33.3 to 31.6 kg/m², mean TBWL was 4.53%, and mean ΔALMI was – 0.19. Among individuals achieving ≥ 5% TBWL, GLP-1RA use was independently associated with greater ALMI decline after adjustment for baseline ALMI, BMI reduction, age, T2D status, and fibrosis stage (β = +0.11, p = 0.023), with no evidence of sex interaction. GLP-1RA users also experienced greater ALMI loss per unit BMI reduction than those who lost weight without GLP-1RA therapy (0.57 vs 0.27 per BMI point, p < 0.01). Male sex was independently associated with less ALMI decline than female sex (β = −0.24, p < 0.001). In exploratory sex-stratified analyses, GLP-1 use remained significantly associated with greater ALMI decline among women (β = +0.088, p = 0.025), with a similar but non-significant directional trend observed in men (β = +0.17, p = 0.076). **Conclusion:** In patients with MASLD achieving at least 5% TBWL, GLP-1RA exposure was independently associated with greater ALMI decline, including greater ALMI loss per unit of BMI reduction. Although women exposed to GLP-1RAs demonstrated a greater ALMI loss than men, there was no significant sex interaction. These findings suggest that muscle preservation strategies may be important during GLP-1R-associated weight loss in MASLD. Incorporating body impedance analysis into MASLD care may help contextualize guideline-recommended 5–7% TBWL by distinguishing favorable fat loss from potentially clinically relevant lean mass loss during treatment.



A: Change in ALMI by sex and GLP-1RA use status. Violin plots show the distribution of ΔALMI, where higher values indicate greater ALMI loss. GLP-RA exposure was associated with greater ALMI loss, while males showed less loss overall, regardless of GLP1-RA use. **B**. GLP-1RA use was associated with more ALMI loss per point of BMI reduction than weight loss achieved without GLP1-RA use.

Disclosures: Sophie Silbert: Nothing to Disclose, Melina Manolas: Doximity: Social Media Content Provision, Health Monitor Network: Advisor, Roon: Stock options, Madrigal Pharmaceuticals: Consulting, Ani Bernardi: Nothing to Disclose, Adam Buckholz: Tortugas Neurosciences: Consultant, Sonal Kumar: Nothing to Disclose.

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2494 | COMMON VARIANTS ASSOCIATED WITH LIPODYSTROPHY INFLUENCE MASLD SUSCEPTIBILITY BUT NOT ITS HISTOLOGICAL SEVERITY

Jingyi Tan[1] Tae-Hwi Schwantes-An[2] Xiuqing Guo[1] Callie Zaborenko[2] Cristian Sanchez-Torres[3] Marco Abreu[2] Jie Yao[1] Samer Gawrieh[2] Jerome Rotter[1] Naga Chalasani[4] Kashyap Patel[5] Rebecca Brown[6] Miriam Vos[7], [1]Lundquist Institute, [2]Indiana University, [3]Emory University, [4]Indiana University Medical Center, [5]University of Exeter Medical School, [6]National Institute of Diabetes and Digestive and Kidney Diseases, [7]Michigan State University, Helen DeVos Children's Hospital

Background: Lipodystrophy is characterized by altered adipose tissue distribution and severe metabolic dysfunction, features that overlap with MASLD and MASH. However, the relationship between genetic risks for lipodystrophy and MASLD and MASH is not well understood. We therefore examined the relationship between a lipodystrophy polygenic risk score (PRS) and MASLD and its histological severity in adults using several well-characterized datasets. **Methods:** We interrogated the weighted lipodystrophy PRS, which consisted of 53 SNPs without *PNPLA3*. First, we examined the relationship between lipodystrophy PRS and MASLD by comparing the NASH CRN adult participants (1,791 European and 358 Hispanic MASLD) and steatosis-free adult controls from MESA (2,002 European and 1,044 Hispanic). Second, within the NASH CRN adult cohort (N = 2149), we evaluated the association between PRS and histologic severity measures, including advanced fibrosis (AF) and NAS $\geq$ 4. We replicated our finding in the Indiana Biobank Liver cohort, including adults with MASLD (N = 342) and without liver disease (N = 3,245). **Results:** In individuals of European ancestry from the NASH CRN and MESA, lipodystrophy PRS was significantly associated with MASLD risk. Individuals in the 4th PRS quartile had an odds ratio (OR) of 1.69 (95% CI 1.37-2.08; p = 6.69e^{-07}) compared with those in the 1st quartile. The 2nd and 3rd quartiles showed significant but smaller ORs (Table 1). Among Hispanic participants, higher quartiles showed a statistically significant association with MASLD, although the OR point estimates were increased risk for MASLD (Table 1). The association in European-ancestry individuals was replicated in the Indiana Biobank Liver cohort, where each SD increase in the PRS was associated with an OR of 1.12 (95% CI 1.01-1.26; p = 0.04). In comparison between NASH CRN and MESA European participants, the OR for MASLD was 1.23 (1.14-1.32, p = 4.66e^{-08}) for each SD increase. However, there was no significant association between PRS and histologic severity within the NASH CRN. **Conclusion:** Lipodystrophy PRS is associated with MASLD risk in two large, independent cohorts, supporting a shared genetic basis between lipodystrophy and MASLD involving common variants, independent of PNPLA3. The lack of association between the PRS and the histologic severity suggests that common variants associated with lipodystrophy influence disease susceptibility rather than progression.

Table 1. Relationship between lipodystrophy PRS by quartiles and the risk for MASLD: Comparison between adults with MASLD in the NASH CRN vs adults without steatosis in the MESA

Phenotype-Group	Quartile	OR (95% C.I.)	P-value
NASH CRN MASLD vs MESA Controls Without Steatosis: European	1	Ref	
	2	1.27 (1.03-1.56)	2.35E-02
	3	1.45 (1.18-1.78)	3.86E-04
	4	1.69 (1.37-2.08)	6.69E-07
NASH CRN MASLD vs MESA Controls Without Steatosis: Hispanic	1	Ref	
	2	1.37 (0.90-2.09)	1.41E-01
	3	1.26 (0.83-1.91)	2.79E-01
	4	1.41 (0.93-2.15)	1.04E-01

Disclosures: Jingyi Tan: Nothing to Disclose, Tae-Hwi Schwantes-An: Nothing to Disclose, Xiuqing Guo: Nothing to Disclose, Callie Zaborenko: Eli Lilly: Stock - publicly traded company, Cristian Sanchez-Torres: Nothing to Disclose, Marco Abreu: Nothing to Disclose, Jie Yao: Nothing to Disclose, Samer Gawrieh: Transmedics: Consultant, pfizer: Consultant, kowa: Consultant, spruce: Consultant, viking: Grant/Research Support, zydus: Grant/Research Support, dsm: Grant/Research Support, Sonicincytes: Grant/Research Support, Novo Nordisk: Consultant, GSK: Consultant, Jerome Rotter: Nothing to Disclose, Naga Chalasani: Madrigal, Eccogene, Insitro, Boston Pharma, Chugai: Consultant, Zydus, GSK, Akero, Plaint, Altimmune: Consultant, Exact Sciences: Grant/Research Support, NIH: Grant/Research Support, Heligenics: Board member, investor, Avant Sante: Board member, investor, Ipsen, Biomea Fusion, Pfizer, Merck: Consultant, Kashyap Patel: Nothing to Disclose, Rebecca Brown: Pfizer: Grant/Research Support, Marea: Grant/Research Support, Regeneron: Grant/Research Support, Chiesi: Grant/Research Support, Miriam Vos: Boehringer Ingelheim: Consultant, Madrigal: Consultant, Eli Lilly: Consultant, Inventiva: Consultant, Alberio: Consultant, Target Real World Evidence: Advisor, Thiogenesis: Advisor, Tern Pharmaceuticals: Stock - publicly traded company, Dexcom: Grant/Research Support, Sonic Incytes Medical Corp: Grant/Research Support, Prosciento: Advisor, Regeneron: Consultant.

2495 | REAL-WORLD WEIGHT LOSS STRATEGIES AND OUTCOMES IN A MULTIDISCIPLINARY MASLD CLINIC FROM 2018 TO 2025

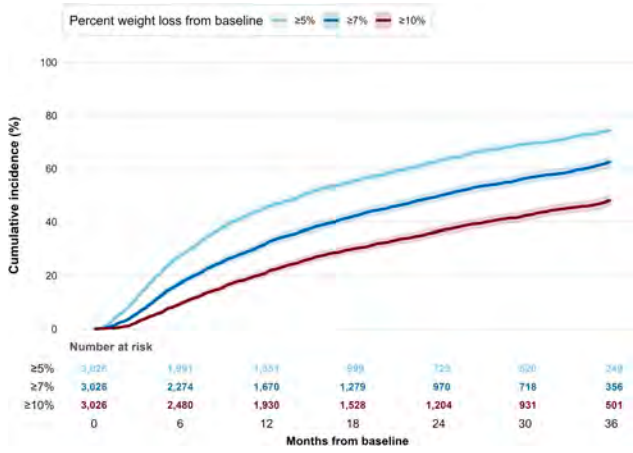
Zoe Zimmerman[1] Saumya Srivastava[1] Yanhong Deng[2] Ysabel Ilagan-Ying[1] Emmanuel Yeboah[1] Fangyong Li[2]

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Wajahat Mehal[1] Bubu Banini[1], [1]Yale School of Medicine, [2]Yale School of Public Health

Background: Weight loss is a cornerstone of metabolic dysfunction-associated steatotic liver disease (MASLD) management; ≥5% total body weight loss typically reduces hepatic steatosis, ≥7% may improve steatohepatitis, and ≥10% may improve fibrosis. Although multiple weight loss strategies are available for patients with MASLD, real-world data on their use and effectiveness remain limited. In this study, we characterize patients seen in a multidisciplinary, MASLD clinic over a 7-year period and describe weight loss strategy uptake and longitudinal outcomes. **Methods:** This is a single-center, retrospective cohort study of adult patients evaluated at a multidisciplinary, MASLD clinic between May 2018 and November 2025. Demographic, clinical, laboratory, imaging, prescription, and clinic visit data were extracted from the electronic medical record. Time to achieve ≥5%, ≥7%, and ≥10% weight loss was estimated using Kaplan–Meier (KM) methods, and percent of cohort achieving these weight loss thresholds at 24 months was assessed. Within-patient longitudinal changes in ALT, as well as fibrosis (liver stiffness measurement, LSM) and steatosis (controlled attenuation parameter, CAP) measured by vibration-controlled transient elastography (VCTE), were evaluated using the Wilcoxon signed-rank test. **Results:** A total of 3,026 adult patients were evaluated with mean baseline age 53 years, mean BMI 36 kg/m², median ALT 41 IU/L, median LSM 6.4 kPa, and median CAP 304 dB/m. Over an average follow-up period of 3 years, 762 patients (25%) utilized no strategies aside from lifestyle counseling received during clinic appointment; 1,369 (45%) utilized 1 strategy; and 791 (26%) and 104 (4%) utilized 2 and ≥3 strategies, respectively. Anti-obesity pharmacotherapy was the most used strategy (65% of cohort), followed by nutrition consultation (38%), bariatric surgery (3%), and meal replacement program (2%). KM estimates of time to achieve weight loss thresholds are shown in the figure. Achievement of ≥5%, ≥7%, and ≥10% weight loss by 24 months was 63.1% (95% CI 61.1-64.9%), 49.8% (95% CI 47.8-51.8%), and 36.8% (95% CI 34.8-38.7%), respectively. Median ALT improved within 24 months in 828 patients with elevated ALT at baseline (49 versus 35 IU/L; $p < 0.001$). Within 24 months, significant improvements were noted also for median LSM (6.7 versus 5.8 kPa; $p < 0.001$; $n = 262$) and median CAP (310 versus 279 dB/m; $p < 0.001$; $n = 222$) compared to baseline. **Conclusion:** In a large cohort of patients with MASLD undergoing multidisciplinary management, most patients utilized one or more weight loss interventions and achieved clinically meaningful weight loss thresholds. Importantly, improvement in liver status as demonstrated by a decrease in ALT, steatosis, and fibrosis were noted. These findings underscore the utility and effectiveness of multidisciplinary MASLD care in the real-world setting.



Disclosures: Zoe Zimmerman: Nothing to Disclose, Saumya Srivastava: Nothing to Disclose, Yanhong Deng: Nothing to Disclose, Ysabel Ilagan-Ying: Nothing to Disclose, Emmanuel Yeboah: Nothing to Disclose, Fangyong Li: Nothing to Disclose, Wajahat Mehal: Nothing to Disclose, Bubu Banini: Nothing to Disclose.

2496 | LONGITUDINAL MUSCLE LOSS CONFERS AN INCREASED RISK OF CARDIOVASCULAR OUTCOMES AND ALL-CAUSE

Siru Wu[1] Xiao Han[1] Chenglin Sun[1] Hanshu Liu[1] Yankun Gao[1] Shuyan Chen[1] Yameng Sun[1] Hong You[2], [1]Liver Research Center, Beijing Friendship Hospital, Capital Medical University, [2]Capital Medical University

Background: Low baseline muscle mass is associated with increased cardiovascular risk in patients with metabolic dysfunction-associated steatotic liver disease (MASLD). However, the prognostic significance of dynamic muscle mass changes over time remains poorly defined. We aimed to investigate whether longitudinal changes in muscle mass and the rate of depletion are associated with incident cardiovascular disease (CVD) and all-cause mortality in MASLD. **Methods:** We analyzed prospective data from 5,761 MASLD individuals free of CVD at baseline from the China Health and Retirement Longitudinal Study (CHARLS). MASLD was defined using TyG-WC criteria. Muscle mass was assessed using appendicular skeletal muscle mass / body weight (ASM/BW). Dynamic muscle change was quantified as the percentage change in ASM/BW (ΔASM/BW%), with categorical muscle loss defined as the lowest tertile (<33.3%) of this distribution. Primary endpoints included incident CVD (physician-diagnosed heart disease or stroke) and all-cause mortality. Risk

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associations were quantified using Bayesian joint modeling (JMbayes2) and time-dependent Cox regression. **Results:** Over a median follow-up of 84 months among 4,848 included individuals who completed at least two muscle mass assessments, 944 (19.5%) incident CVD cases and 378 (7.8%) all-cause deaths occurred. An accelerated annualized rate of ASM/BW depletion (slope) was significantly associated with incident CVD in the age- and sex-adjusted model (HR = 9.17, 95% CI: 1.90–58.84, $P = 0.004$) and with all-cause mortality upon further adjustment for metabolic comorbidities (HR = 7.85, 95% CI: 1.13–43.00, $P = 0.027$), as evaluated via Bayesian joint modeling. Conversely, higher longitudinal ASM/BW values over time were inversely associated with risks of CVD (HR = 0.81, 95% CI: 0.71–0.93, $P < 0.001$) and mortality (HR = 0.70, 95% CI: 0.54–0.93, $P = 0.007$) in the corresponding models. For clinical risk stratification, categorical muscle loss independently elevated overall CVD risk (aHR = 1.55, 95% CI: 1.11–2.18, $P = 0.011$) in time-dependent Cox regression. This association was primarily driven by heart disease rather than stroke, with the heart disease risk being particularly pronounced among male patients (aHR = 3.53, 95% CI: 1.63–7.61, $P = 0.001$) and overweight/obese individuals (aHR = 3.10, 95% CI: 1.66–5.80, $P < 0.001$). **Conclusion:** Dynamic ASM/BW status is significantly associated with the risk of cardiovascular progression and mortality in MASLD. Specifically, the annualized rate of muscle depletion (slope) provides incremental prognostic value over static measurements, particularly exhibiting a robust independent association with all-cause mortality. These findings support that integrating long-term monitoring of individualized muscle trajectories into the management of MASLD is essential for optimizing cardiovascular risk stratification and improving patient survival.

Disclosures: Siru Wu: Nothing to Disclose, Xiao Han: Nothing to Disclose, Chenglin Sun: Nothing to Disclose, Hanshu Liu: Nothing to Disclose, Yankun Gao: Nothing to Disclose, Shuyan Chen: Nothing to Disclose, Yameng Sun: Nothing to Disclose, Hong You: Nothing to Disclose.

2497 | WAIST-TO-HIP RATIO IMPROVES IDENTIFICATION OF LIVER FIBROSIS BEYOND BMI IN A NATIONAL NHANES ELASTOGRAPHY COHORT

Navin Prasad[1], [1]*Presbyterian Hospital*

Background: Body mass index (BMI) is widely used for metabolic dysfunction–associated steatotic liver disease (MASLD) risk stratification but incompletely reflects visceral adiposity, a major driver of hepatic fibrogenesis. We evaluated whether waist-to-hip ratio (WHR), a marker of central adiposity, improves identification of liver fibrosis beyond BMI in a nationally representative U.S. cohort. **Methods:** We performed a cross-sectional analysis of adults aged ≥ 18 years with transient elastography data from the National Health and Nutrition Examination Survey (NHANES) 2017–March 2020 and 2021–2023 cycles. Significant liver fibrosis risk was defined as liver stiffness measurement ≥ 8 kPa. WHR was calculated using measured waist and hip circumferences and categorized into quartiles. Survey-weighted logistic regression evaluated associations between WHR and fibrosis after adjustment for BMI, age, and sex. Predictive discrimination was assessed using survey-weighted receiver operating characteristic (ROC) analysis. **Results:** Among 13,190 adults, the weighted prevalence of significant liver fibrosis risk was 10.4%. Fibrosis prevalence increased progressively across WHR quartiles from 3.7% in the lowest quartile to 19.7% in the highest quartile (p-trend < 0.001). In multivariable analysis adjusting for BMI, age, and sex, individuals in the highest WHR quartile had significantly increased odds of fibrosis compared with the lowest quartile (OR 2.02, p = 0.001). BMI also remained independently associated with fibrosis risk (OR 1.13 per unit increase, p < 0.001). WHR provided incremental improvement in fibrosis discrimination beyond BMI alone (AUC 0.758 vs 0.750, $p = 6.1\times10^{-6}$). Stratified analyses demonstrated substantial heterogeneity in fibrosis prevalence across WHR quartiles within BMI categories, with the highest prevalence observed among individuals with BMI ≥ 35 and WHR Q4 (37.8%). **Conclusion:** WHR independently identifies increased liver fibrosis risk beyond BMI and provides incremental improvement in fibrosis risk discrimination in a nationally representative U.S. population. Central adiposity measures may help identify high-risk individuals with MASLD who could be underrecognized using BMI-based screening approaches alone.

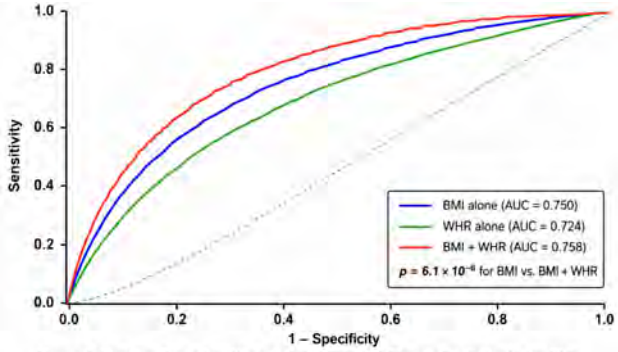


Figure 4. Receiver Operating Characteristic Curves for Fibrosis Prediction Using BMI, WHR, and Combined Models.
ROC curves comparing BMI alone, WHR alone, and combined BMI + WHR models for prediction of liver stiffness ≥8 kPa. Addition of WHR to BMI improved discrimination compared with BMI alone (AUC 0.758 vs 0.750; p = 6.1 × 10⁻⁶).

Disclosures: Navin Prasad: Nothing to Disclose.

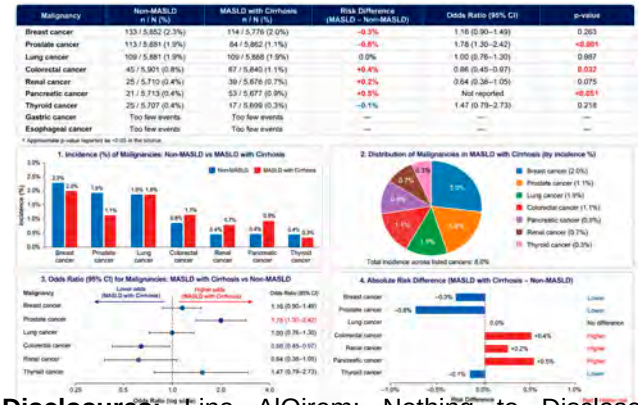
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2498 | RISK OF EXTRAHEPATIC MALIGNANCIES IN PATIENTS WITH MASLD WITH AND WITHOUT CIRRHOSIS: A PROPENSITY-MATCHED COHORT STUDY

Lina AlQirem[1] Ragesh Thandassery[1], [1]The University of Arkansas for Medical Sciences

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is considered to have increased risk of extrahepatic malignancies; however, the impact of cirrhosis on this risk remains poorly understood. We aimed to evaluate the incidence of extrahepatic malignancies among patients with MASLD with and without cirrhosis compared to matched non-MASLD controls. **Methods:** We conducted a retrospective cohort study using the TriNetX global research network of de-identified electronic health records. Patients with MASLD (with and without cirrhosis) were compared to non-MASLD controls and stratified by cirrhosis status. Those with prior diagnosis of extrahepatic malignancy and other causes of hepatic steatosis, including alcohol use disorder, chronic hepatitis C infection, celiac disease, hemochromatosis, and steatosis-associated medications (systemic corticosteroids, methotrexate, tamoxifen, or amiodarone) were excluded. Before propensity score matching, 19,444,137 non-MASLD patients and 5,716 MASLD patients with cirrhosis were identified between the years 2010 and 2012; after 1: 1 matching, 5,716 pairs remained. For MASLD without cirrhosis, 55,270 matched pairs were included. Matching was based on age and baseline characteristics with standardized mean differences <0.1. Risk ratios (RR) and hazard ratios (HR) were calculated, with Kaplan-Meier analysis for time-to-event outcomes. **Results:** Among 5,716 matched pairs (mean age 57.9 ± 12.5 years), MASLD with cirrhosis was associated with increased risk of colorectal cancer (1.1% vs 0.8%; RR 1.50, $p=0.032$; HR 1.79, $p=0.002$), pancreatic cancer (0.9% vs 0.4%; RR 2.25, $p<0.01$; HR ~1.78, $p<0.05$), and renal cancer (0.7% vs 0.4%; HR 1.78, $p=0.023$). Breast, lung, and thyroid cancers were not significantly different. Prostate cancer showed lower cumulative incidence (1.1% vs 1.9%; RR 0.57, $p<0.001$) but higher hazard over time (HR 1.44, $p=0.021$), suggesting likely delayed diagnosis. In a larger cohort of 55,270 matched pairs, MASLD without cirrhosis was associated with increased risk of breast (2.4% vs 1.9%), lung (1.8% vs 1.4%), colorectal (1.0% vs 0.6%), renal (0.9% vs 0.4%), and pancreatic cancer (0.7% vs 0.3%) (all $p<0.001$), with consistently higher hazards over time. **Conclusion:** MASLD is associated with increased risk of extrahepatic malignancies even without cirrhosis, with further increased risk in colorectal and pancreatic cancers with cirrhosis. These findings support heightened cancer awareness and tailored surveillance strategies in MASLD.



Disclosures: Lina AlQirem: Nothing to Disclose, Ragesh Thandassery: Nothing to Disclose.

2499 | METABOLIC SIGNATURES SHAPE HEPATOCELLULAR CARCINOMA RISK AND TRAJECTORIES IN MASLD PATIENTS WITH ADVANCED FIBROSIS

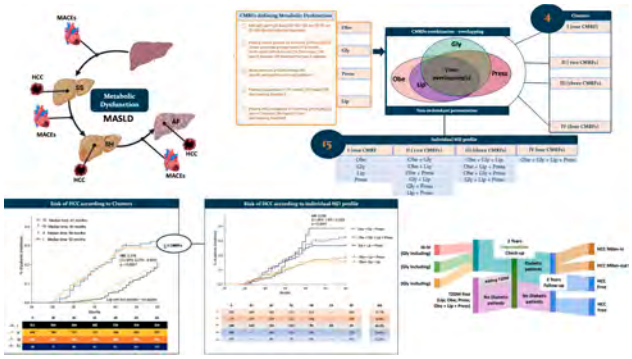
Mario Romeo[1] Marcello Dallio[1] Carmine Napolitano[1] Fiammetta Di Nardo[1] Paolo Vaia[1] Claudio Basile[1] Luigi Di Puorto[1] Mattia Indipendente[1] Marco Niosi[1] Luigi Maria Vitale[1] Alessandro Federico[1], [1]Hepatogastroenterology Division, University of Campania Luigi Vanvitelli, 80138, Naples

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is an increasingly prevalent cause of hepatocellular carcinoma (HCC) (**Figure**). While individual cardiometabolic risk factors (CMRFs) such as obesity, type 2 diabetes mellitus (T2DM), hypertension, and dyslipidemia have been linked to HCC, the impact of their cumulative burden and specific combinations on HCC trajectories in patients with advanced fibrosis (AF) remains poorly defined. We aimed to assess HCC risk according to distinct metabolic dysfunction (MD) profiles in a large Italian cohort of MASLD-AF patients. **Methods:** We retrospectively analyzed 1,921 consecutive patients with MASLD and advanced fibrosis (F3-F4) undergoing semiannual ultrasound-based surveillance at a tertiary referral center network. MD was defined by the presence of four CMRFs: obesity, T2DM, hypertension, and dyslipidemia. Patients were stratified into four clusters according to the number of CMRFs (I, II, III, or IV) and into specific nonredundant metabolic profiles (n.15) based on all possible combinations (**Figure**). The primary endpoint was incident HCC. Secondary endpoints included HCC beyond Milan criteria at first diagnosis and the impact of incident T2DM during follow-up. **Results:** Patients were distributed across

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metabolic burden clusters as follows: Cluster I (1 CMRF), n = 311; Cluster II (2 CMRFs), n = 840; Cluster III (3 CMRFs), n = 680; and Cluster IV (4 CMRFs), n = 90. HCC risk significantly increased across clusters, with the highest incidence observed in patients with ≥ 3 CMRFs. Patients with ≥ 3 CMRFs were more likely to present with HCC and with HCC beyond Milan criteria at first diagnosis (OR 2.46; p = 0.016; OR: 1.54, p = 0.035). Within Cluster III, the obesity-diabetes-hypertension profile showed the highest risk of both overall HCC and Milan-out HCC (**Figure**). In multivariable competing-risk analysis, the presence of ≥ 3 CMRFs (Clusters III-IV) was independently associated with HCC development (HR 2.05, 95% CI 1.42-2.96; p < 0.0001), together with age (HR 1.03 per year, 95% CI 1.01-1.05; p = 0.004) and baseline T2DM (HR 1.82, 95% CI 1.30-2.54; p < 0.0001). In dynamic analyses, restricted to patients free of diabetes at baseline, incident diabetes during follow-up markedly modified HCC trajectories, accounting for most of the association between cumulative metabolic burden and cancer risk (risk attenuation 82% after mediation modelling). **Conclusion:** In MASLD patients with AF, HCC risk is driven by distinct cardiometabolic signatures rather than by the mere presence of MD. The coexistence of obesity, T2DM, and hypertension identifies a particularly high-risk phenotype, while incident T2DM acts as a disease-modifying event that largely mediates the relationship between metabolic burden and HCC. These findings support precision surveillance strategies based on individualized metabolic profiling.



Disclosures: Mario Romeo: Nothing to Disclose, Marcello Dallio: Nothing to Disclose, Carmine Napolitano: Nothing to Disclose, Fiammetta Di Nardo: Nothing to Disclose, Paolo Vaia: Nothing to Disclose, Claudio Basile: Nothing to Disclose, Luigi Di Puorto: Nothing to Disclose, Mattia Indipendente: Nothing to Disclose, Marco Niosi: Nothing to Disclose, Luigi Maria Vitale: Nothing to Disclose, Alessandro Federico: Nothing to Disclose.

2500 | ONE SIZE DOES NOT FIT ALL: HIGHER STARTING BMI AND LOWER APPENDICULAR LEAN MASS ATTENUATE STEATOSIS IMPROVEMENT BY TRANSIENT ELASTOGRAPHY AFTER WEIGHT LOSS

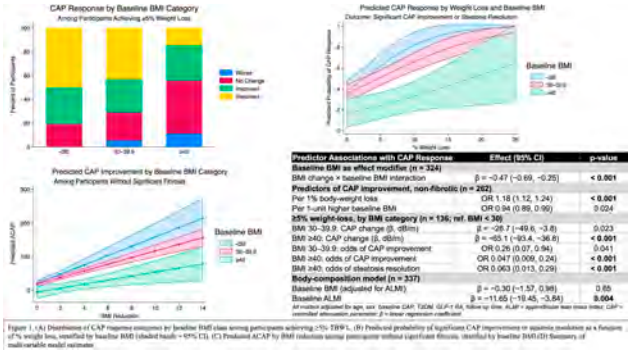
Alec Chang[1] Sophie Silbert[1] Ani Bernardi[1] Carolyn Newberry[1] Reem Sharaiha[1] Sonal Kumar[1] Melina Manolas[1] Adam Buckholz[1], [1]NewYork-Presbyterian/ Weill Cornell Medical Center

Background: MASLD is the leading chronic liver disease worldwide, and weight loss remains the cornerstone treatment for hepatic steatosis. Guidelines recommend ≥ 5% total body weight loss (TBWL) for steatosis improvement in non-fibrotic disease, yet whether this threshold produces comparable controlled attenuation parameter (CAP) reductions across BMI classes is unclear. We hypothesized that higher baseline BMI attenuates CAP response to weight loss. **Methods:** We retrospectively studied adults with MASLD (CAP > 238 dB/m) who underwent paired FibroScan and Body Impedance Analysis, excluding patients with liver stiffness ≥ 15 kPa, suggestive of F4-range fibrosis. Multivariable linear regression assessed the association between ΔBMI and ΔCAP, adjusted for baseline BMI and CAP, age, sex, type 2 diabetes (T2D), and GLP-1 receptor agonist (GLP1-RA) use. Logistic regression evaluated CAP improvement (> 30-point reduction) and steatosis resolution (CAP < 238 dB/m). Among patients achieving ≥ 5% TBWL, CAP outcomes were compared across BMI categories (< 30, 30–39.9, ≥ 40 kg/m²). Sensitivity analyses incorporated baseline appendicular lean mass index (ALMI) to evaluate whether body composition explained the BMI effect. **Results:** Of 337 subjects with mean age 51.0 years and follow-up 24 months, 59.4% were female, 30.0% had T2D, and 51.2% GLP-1RA use, 42.4% achieved ≥ 5% TBWL. Mean baseline CAP was 305.9 dB/m, median kPa 6.1, and 281 lacked clinically meaningful fibrosis (kPa < 8). Greater BMI reduction was associated with greater CAP improvement (p < 0.001), but this effect diminished with higher baseline BMI (interaction β = −0.47, p < 0.001; nonfibrotic sensitivity analysis β = −0.49, p = 0.003). Among nonfibrotic participants, each 1% TBWL increased the odds of CAP improvement by 18% (OR 1.18, 95% CI 1.12–1.24, p < 0.001), while each 1-unit higher baseline BMI reduced the odds by 6% (OR 0.94, p = 0.024). Among those achieving ≥ 5% TBWL, BMI 30–39.9 and ≥ 40 had 27- and 65-dB/m smaller ΔCAP, respectively, versus BMI < 30. Class III obesity (BMI ≥ 40) had significantly lower odds of CAP improvement (OR 0.047, p < 0.001) and steatosis resolution (OR 0.063, p < 0.001). A mediation analysis identified baseline ALMI as a significant mediator of BMI to ΔCAP association, with the direct effect of BMI attenuated to non-significance (β = −0.30, p = 0.65), while

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ALMI independently predicted CAP response (β = −11.65, p = 0.004). **Conclusion:** In this real-world MASLD cohort, CAP improvement with BMI reduction was progressively blunted at higher baseline BMI, independent of clinical predictors. Class III obesity was associated with markedly reduced odds of steatosis improvement even after ≥5% TBWL, and attenuation of the BMI effect by ALMI suggests that body composition phenotype may underlie differences in steatosis responsiveness. These findings support establishing BMI- and body composition–informed weight loss targets in MASLD management and future studies.



Disclosures: Alec Chang: Nothing to Disclose, Sophie Silbert: Nothing to Disclose, Ani Bernardi: Nothing to Disclose, Carolyn Newberry: Eli Lilly & Company: Consultant, Reem Sharaiha: Nothing to Disclose, Sonal Kumar: Nothing to Disclose, Melina Manolas: Nothing to Disclose, Adam Buckholz: Tortugas Neurosciences: Consultant.

2501 | PREDICTION OF MAJOR ADVERSE LIVER OUTCOMES (MALOS) BY THE TWO-STEP ALGORITHM FOR METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) BASED ON AMERICAN DIABETES ASSOCIATION (ADA)-PROPOSED AT-RISK POPULATION: A MULTINATIONAL COHORT STUDY

Jimmy Che-To Lai[1] Grace Wong[1] Huapeng Lin[2] Emmanuel Tsochatzis[3] Mirko Zoncapè[3] Salvatore Petta[4] Elisabetta Bugianesi[5] Masato Yoneda[6] Ming-Hua Zheng[7] Javier Crespo[8] Paula Iruzubieta[8] Jerome Boursier[9] Jose Luis Calleja[10] Boon Bee George Goh[11] Eugene Wong[12] Wah-Kheong Chan[13] Rocio Gallego-Durán[14] Arun J Sanyal[15] Victor de Ledinghen[16] Philip Newsome[17] Jian-Gao Fan[18] Laurent Castera[19] Grazia Pennisi[4] Angelo Armandi[5] Kamela Gijni[5] Atsushi Nakajima[6] Wen-Yue Liu[7] Ming-Hua Zheng[7] Ying Shang[20] Marc De Saint Loup[9] Elba Llop[10] Kevin Kim Jun Teh[11] Carmen Lara Romero[14] Racio Macias[10] Amon Asgharpour[15] Sara Mahgoub[21] Adrien Lannes[9] Manuel Romero-Gómez[22] Seung Up Kim[23] Vincent Wong[1] Terry Cheuk-Fung Yip[1] Hye Won Lee[23], [1]The Chinese University of Hong Kong, [2]Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, [3]Royal Free Hospital and UCL, [4]University of Palermo, [5]University of Torino, [6]Yokohama City University Graduate School of Medicine,, [7]The First Affiliated Hospital of Wenzhou Medical University, [8]Marqués de Valdecilla University Hospital, [9]Angers University, [10]Universidad Autonoma de Madrid, [11]Singapore General Hospital, [12]Changi General Hospital, [13]University of Malaya, [14]University of Seville, [15]Virginia Commonwealth University School of Medicine, [16]Echosens, [17]King's College London, [18]Xinhua Hospital Affiailted to Shanghai Jiaotong University School of Medicine, [19]Université Paris Cité, [20]Karolinska Institutet, [21]University Hospitals Birmingham NHS Foundation Trust and University of Birmingham, [22]Virgen del Rocio University Hospital, [23]Yonsei University College of Medicine

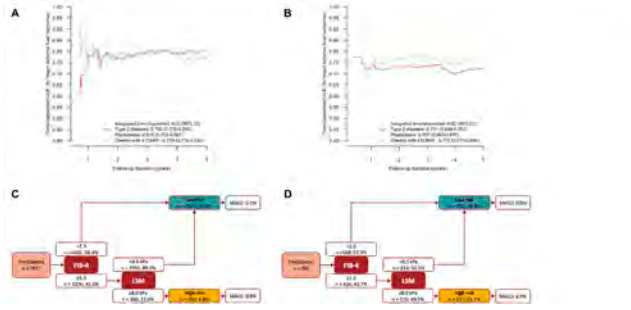
Background: Building on the two-step algorithms for MASLD introduced by liver societies, ADA endorsed a simplified pathway using FIB-4 at a single cutoff of 1.3, followed by vibration-controlled transient elastography (VCTE) at a liver stiffness measurement (LSM) cutoff of 8.0 kPa for fibrosis risk stratification. The ADA-defined at-risk population also extends to prediabetes, which is broader than type 2 diabetes (T2D) and obesity with ≥1 cardiometabolic risk factor (CMRF) as in other guidelines. However, the prognostic performance of this algorithm across these metabolic risk groups, particularly among individuals with prediabetes, remains uncertain. We validated this algorithm across ADA-defined at-risk populations. **Methods:** We analyzed two VCTE-based multicenter cohorts in different clinical settings: the V-LINK cohort comprising tertiary-care patients with chronic liver disease and health screening subjects in Korea, and the international VCTE-Prognosis cohort of patients with MASLD from 16 tertiary centers in the US, Europe, and Asia. The primary outcome was MALOs, defined as hepatic decompensation, hepatocellular carcinoma, liver transplantation, and/or liver-related death. **Results:** Of 26,362 adults in V-LINK, 8,365 (31.7%) had T2D, 7,877 (29.9%) had prediabetes, and 6,980 (26.5%) had obesity with ≥1 CMRF. Corresponding numbers among 4,680 adults in VCTE-Prognosis were 1,644 (35.1%), 992 (21.2%), and 1,987 (42.5%), respectively. During median follow-up of 5.0 and 4.2 years, MALOs occurred in 85 (1.0%), 35 (0.4%), and 66 (0.9%) patients with T2D, prediabetes, and obesity with ≥1 CMRF in V-LINK, and in 76 (4.6%), 16 (1.6%), and 62 (3.1%) patients in VCTE-Prognosis, respectively. Integrated time-dependent AUCs for MALO prediction demonstrated good discrimination across cohorts and metabolic risk groups, ranging from 0.78 to 0.82 in V-LINK and 0.73 to 0.79 in VCTE-Prognosis (Fig 1A,B). In V-LINK, the two-step

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algorithm classified 11.5%, 10.6%, and 4.6% of patients with T2D, obesity with ≥1 CMRF, and prediabetes as high risk, respectively; in VCTE-Prognosis, these proportions were 44.5%, 34.0%, and 21.1%, respectively. Across T2D, prediabetes, and obesity with ≥1 CMRF, high-risk patients had consistently higher 5-year cumulative MALO incidence than low-risk patients in both V-LINK (7.1%-8.0% vs 0.2%-0.5%) and VCTE-Prognosis (8.9%-11.8% vs 0.6%-1.6%). Prediabetes had the lowest high-risk yield in both cohorts. Among patients with prediabetes and FIB-4 ≥1.3, second-step LSM reclassified a large proportion as low risk, with LSM <8.0 kPa in 89.0% of V-LINK and 50.5% of VCTE-Prognosis patients (Fig 1C,D). **Conclusion:** The ADA two-step algorithm effectively stratified MALO risk stratification across T2D, prediabetes, and obesity with ≥1 CMRF in distinct clinical settings. False-positive referrals are common in prediabetes, limiting the utility of two-step algorithm.

Figure 1. Performance of the ADA two-step algorithm for MALO across metabolic risk groups. (A) Time-dependent AUROC for MALO by the two-step algorithm among patients with T2D, prediabetes and obesity with ≥1 CMRF in V-LINK cohort, (B) Time-dependent AUROC for MALO by the two-step algorithm among patients with T2D, prediabetes and obesity with ≥1 CMRF in VCTE-Prognosis cohort, (C) Categorisation of patients with prediabetes by two-step algorithm in V-LINK cohort, (D) Categorisation of patients with prediabetes by two-step algorithm in VCTE-Prognosis cohort.



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2502 | DO HISPANIC PATIENTS WITH METABOLIC DYSFUNCTION–ASSOCIATED STEATOTIC LIVER DISEASE HAVE WORSE OUTCOMES? A LARGE PROPENSITY SCORE–MATCHED STUDY

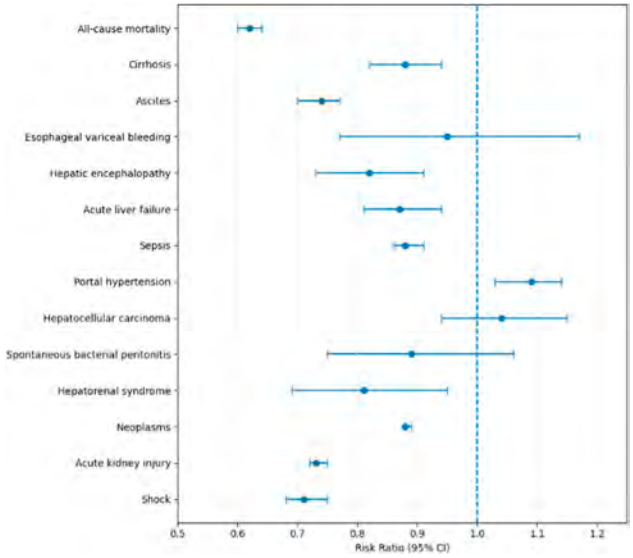
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Background: Metabolic dysfunction–associated steatotic liver disease (MASLD) disproportionately affects Hispanic populations and has been associated with worse liver-related outcomes and mortality. However,

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it remains unclear whether Hispanic ethnicity independently contributes to adverse outcomes after controlling for associated metabolic and systemic comorbidities. We aimed to compare liver-related and systemic outcomes between Hispanic and non-Hispanic patients with MASLD using a large multicenter propensity score–matched analysis. **Methods:** We conducted a retrospective cohort study using the TriNetX US multicenter electronic health records network. Adult patients with MASLD were identified using ICD-10 code K76.0. Patients with preexisting advanced liver disease, including cirrhosis, ascites, esophageal varices with bleeding, hepatic encephalopathy, and acute liver failure, were excluded. Hispanic patients with MASLD were compared with non-Hispanic patients with MASLD. Propensity score matching was performed 1: 1 adjusting for demographics and major comorbidities. Outcomes assessed within 1 year included all-cause mortality, cirrhosis, ascites, hepatic encephalopathy, acute liver failure, portal hypertension, hepatocellular carcinoma, spontaneous bacterial peritonitis, hepatorenal syndrome, acute kidney injury, sepsis, shock, and neoplasms. **Results:** A total of 254,107 Hispanic patients and 1,278,495 non-Hispanic patients with MASLD were identified. After matching, 226,088 patients remained in each cohort, with all standardized mean differences below 0.1. Hispanic patients demonstrated significantly lower risks of all-cause mortality (RR 0.62, 95% CI 0.60–0.64), cirrhosis (RR 0.88, 95% CI 0.82–0.94), ascites (RR 0.74, 95% CI 0.70–0.77), hepatic encephalopathy (RR 0.82, 95% CI 0.73–0.91), acute liver failure (RR 0.87, 95% CI 0.81–0.94), sepsis (RR 0.88, 95% CI 0.86–0.91), acute kidney injury (RR 0.73, 95% CI 0.72–0.75), shock (RR 0.71, 95% CI 0.68–0.75), hepatorenal syndrome (RR 0.81, 95% CI 0.69–0.95), and neoplasms (RR 0.88, 95% CI 0.88–0.89). Portal hypertension was more common among Hispanic patients (RR 1.09, 95% CI 1.03–1.14). No significant differences were observed in hepatocellular carcinoma, spontaneous bacterial peritonitis, or esophageal variceal bleeding. **Conclusion:** After rigorous propensity score matching, Hispanic patients with MASLD demonstrated lower risks of all-cause mortality and multiple liver-related complications compared with non-Hispanic patients. These findings suggest that previously reported disparities in MASLD outcomes among Hispanic populations may be driven predominantly by associated cardiometabolic and socioeconomic factors rather than ethnicity alone. Importantly, MASLD remained associated with substantial morbidity across all populations once established, regardless of ethnicity.



Disclosures: Muhamad Oum: Nothing to Disclose, Osama Alshakhatreh: Nothing to Disclose, Gokul Karthikeyan: Nothing to Disclose, Sammy Saab: AbbVie: Speaking and Teaching, gilead: speaker, salix: consultant, takeda: Speaking and Teaching, madrigal: consultant, mallinckrodt: Speaking and Teaching, Sequana: Advisor, ipsen: Advisor, novo nordisk: Speaking and Teaching.

2503 | CRYPTOGENIC STEATOTIC LIVER DISEASE IS RARE BUT NOT FULLY BENIGN: A VCTE-BASED CLINICAL AND BODY COMPOSITION STUDY

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Background: The 2023 steatotic liver disease nomenclature introduced cryptogenic steatotic liver disease (CSLD), defined by hepatic steatosis without cardiometabolic criteria, alcohol-related liver disease, or other identifiable causes. Its prevalence and phenotype remain poorly characterized. **Methods:** We retrospectively analyzed 4,673 adults who underwent vibration-controlled transient elastography with controlled attenuation parameter (CAP) assessment at a tertiary nutrition clinic. Steatosis was defined as CAP $\geq$ 248 dB/m; liver stiffness measurement was used for fibrosis staging. Patients with viral, autoimmune, cholestatic,

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genetic, drug-related, alcohol-related, postsurgical, or other secondary causes of steatosis were excluded. CSLD was diagnosed when steatosis was present but no cardiometabolic criterion was met. MASLD patients and healthy controls without steatosis, fibrosis, or cardiometabolic criteria were comparator groups. Body composition was assessed by bioimpedance analysis. **Results:** Among 2,643 patients with hepatic steatosis, CSLD was identified in 22 patients (0.8%), whereas MASLD accounted for 2,389 cases (90.4%). Compared with MASLD, CSLD showed a milder hepatic phenotype: severe steatosis (S3) was less frequent (27.3% vs 67.6%; $p < 0.001$), and significant-to-advanced fibrosis (F2–F4) was uncommon (9.1% vs 29.3%; $p = 0.02$), with no CSLD patient classified as F3–F4. Compared with healthy controls ($n = 266$), CSLD patients had higher BMI despite normal-range values (24.1 [22.1–24.5] vs 22.4 [20.7–23.7] kg/m²; $p = 0.008$), driven mainly by greater fat mass (19.0 [16.6–26.7] vs 16.4 [12.2–20.5] kg; $p = 0.03$) and higher visceral fat area. In contrast, sex distribution, age, triglycerides, LDL cholesterol, total cholesterol, fasting glucose, HbA1c, HOMA-IR, ALT, and AST did not differ significantly between CSLD and controls. **Conclusion:** In this VCTE-based cohort, CSLD was rare, representing < 1% of patients with hepatic steatosis. CSLD was hepatically and metabolically milder than MASLD but was not fully identical to health, showing increased adiposity despite normal BMI and preserved routine metabolic markers. These findings suggest that "benign" steatosis is uncommon and that incidentally detected steatosis should prompt structured cardiometabolic and fibrosis assessment.

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2504 | RECREATIONAL PHYSICAL ACTIVITY AND METABOLIC DYSFUNCTION–ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) PREVALENCE, STEATOSIS SEVERITY, AND FIBROSIS SEVERITY: A CROSS-SECTIONAL ANALYSIS OF NHANES 2017–2018

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Background: Physical activity is a cornerstone of lifestyle management for metabolic dysfunction-associated steatotic liver disease (MASLD). However, population-level data evaluating the association between recreational physical activity and MASLD-related outcomes remain limited. We examined the association between recreational physical activity and MASLD prevalence, steatosis severity, and fibrosis severity in a nationally representative cohort of U.S. adults. **Methods:** This cross-sectional study used NHANES 2017–2018 data from adults aged ≥ 18 years with complete recreational physical activity and transient elastography (TE) data. Recreational activity was quantified as weekly metabolic equivalent (MET)-minutes from self-reported moderate- and vigorous-intensity recreational activities and categorized into weighted quartiles (Q1 = reference). MASLD was defined as controlled attenuation parameter (CAP) ≥ 274 dB/m with ≥ 1 cardiometabolic risk factor in the absence of significant alcohol use or viral hepatitis. Severe steatosis was defined as CAP ≥ 302 dB/m, and clinically significant fibrosis as TE ≥ 8 kPa among participants with MASLD. Survey-weighted logistic regression models included unadjusted, primary adjusted (age, sex, race/ethnicity, education, poverty-income ratio, smoking), and exploratory metabolic models (additionally adjusted for BMI, diabetes, hypertension, and dyslipidemia). **Results:** A total of 5,848 participants were included (mean age 49.9 years; 51.5% female). Compared with participants in the lowest recreational activity quartile (Q1), those in the highest quartile (Q4) were younger (41.7 vs 53.6 years), more likely male (57.9% vs 46.4%), had lower BMI (28.5 vs 30.4 kg/m²), and had lower prevalence of diabetes (9.8% vs 23.6%), hypertension (23.6% vs 42.3%), and dyslipidemia (39.3% vs 56.2%) (all $p < 0.001$). In the primary adjusted model, Q4 recreational activity was independently associated with lower odds of MASLD (OR 0.44, 95% CI 0.36–0.54) and severe steatosis (OR 0.45, 95% CI 0.32–0.63) using Q1 as reference. In exploratory metabolic models, associations were attenuated but remained significant for MASLD (OR 0.69, 95% CI 0.56–0.84) and severe steatosis (OR 0.75, 95% CI 0.58–0.97). There was no significant difference in clinically significant fibrosis in Q2, Q3, or Q4 compared to Q1 across all models. **Conclusion:** Higher recreational physical activity was independently associated with lower MASLD prevalence and lower steatosis severity, but not with significant fibrosis. The concentration of benefit within the highest activity quartile suggests a potential threshold effect, whereby substantial recreational activity may be required for hepatoprotection. These findings reinforce current lifestyle recommendations and support targeted interventions to promote higher-intensity recreational physical activity among adults with MASLD.

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Table. Association Between Recreational Physical Activity Quartiles and Liver Disease Outcomes in NHANES 2017–2018

Outcome / Exposure	Unadjusted OR (95% CI)	Primary Adjusted OR (95% CI)*	Exploratory Metabolic OR (95% CI)†
MASLD			
Q1 Lowest	Reference	Reference	Reference
Q2	0.86 (0.65–1.13)	0.87 (0.66–1.13)	0.96 (0.69–1.33)
Q3	0.78 (0.60–1.03)	0.76 (0.58–1.00)	0.93 (0.67–1.29)
Q4 Highest	0.47 (0.39–0.56)	0.44 (0.36–0.54)	0.69 (0.56–0.84)
Severe steatosis (CAP ≥302 dB/m)			
Q1 Lowest	Reference	Reference	Reference
Q2	0.99 (0.78–1.26)	1.05 (0.83–1.34)	1.21 (0.92–1.59)
Q3	0.79 (0.59–1.06)	0.82 (0.60–1.12)	1.11 (0.82–1.50)
Q4 Highest	0.45 (0.34–0.61)	0.45 (0.32–0.63)	0.75 (0.58–0.97)
Clinically significant fibrosis (LSM ≥8 kPa) among MASLD			
Q1 Lowest	Reference	Reference	Reference
Q2	0.86 (0.64–1.17)	0.95 (0.71–1.27)	1.10 (0.67–1.79)
Q3	0.90 (0.67–1.20)	0.91 (0.64–1.30)	1.30 (0.86–1.97)
Q4 Highest	0.54 (0.28–1.04)	0.67 (0.37–1.24)	1.12 (0.60–2.11)

Footnotes

* Primary adjusted models were adjusted for age, sex, race/ethnicity, education level, poverty-income ratio, and smoking status.

† Exploratory metabolic models were additionally adjusted for body mass index, diabetes, hypertension, and dyslipidemia.

Recreational physical activity was calculated using self-reported moderate and vigorous recreational activities and converted into weekly metabolic equivalent (MET)-minutes according to NHANES physical activity guidelines.

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2505 | GLYCEMIC TRAJECTORIES MODIFY LONG-TERM OUTCOMES IN METABOLIC STEATOTIC LIVER DISEASE

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Background: Background and Aims: The impact of evolving glycemic status over time in metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction and alcohol-related liver disease (MetALD) remains uncertain. We aimed to investigate the influence of 2-year fasting plasma glucose (FPG) trajectories on major cardiovascular events (MACE), all-cause mortality, and liver-related events (LREs) in MASLD and MetALD. **Methods:** This cohort study recruited 269,128 adults with MASLD or MetALD who underwent biennial health examinations in 2012 and 2014 from the Korean National Health Insurance Service database. The patients were classified into normal fasting glucose (NFG), impaired fasting glucose (IFG), and diabetic fasting glucose (DFG). The category transitions in 2 years labeled them as improvers, sustainers, or worseners. Competing-risk Fine–Gray models yielded adjusted subdistribution hazard ratios (aSHRs). **Results:** Over 7.3 years, 10,695 MACE, 6,310 deaths, and 6,529 LREs occurred. Relative to IFG-sustainers, IFG-worseners showed a higher risk of MACE (aSHR 1.22; 95% confidence interval [CI], 1.11–1.34). DFG-improvers experienced a lower risk of MACE than DFG-sustainers (aSHR 0.85; 95% CI, 0.77–0.94). NFG worseners and IFG worseners exhibited increased risk of all-cause mortality (aSHR 1.16; 95% CI, 1.07–1.26 and aSHR 1.30; 95% CI, 1.16–1.46, respectively). Glycemic change did not significantly influence LREs. Findings persisted in sensitivity analyses using ≥6 mg/dL and ≥10 mg/dL for thresholds. **Conclusion:** In metabolic steatotic liver disease (SLD), worsening glycemia augments cardiovascular and mortality risks, whereas improvement from FPG levels mitigates MACE risk. Vigilant and proactive glycemic management should be integral to the care of metabolic SLD.

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2506 | SARCOPENIC OBESITY AND LONG-TERM RISKS OF LIVER-RELATED OUTCOMES AND ALL-CAUSE MORTALITY: A PROSPECTIVE COHORT STUDY

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Background: Sarcopenic obesity (SO), defined as the coexistence of sarcopenia and obesity, is a high-risk phenotype associated with adverse metabolic and hepatic outcomes. Although cross-sectional studies have suggested an association between SO and metabolic dysfunction-associated steatotic liver disease (MASLD), the impact of SO on the long-term outcomes of patients with MASLD remains poorly characterized. Therefore, we investigated the associations of sarcopenia-obesity phenotypes with all-cause mortality, cirrhosis, and hepatocellular carcinoma (HCC) in a prospective cohort study. **Methods:** Participants were categorized into non-obesity, obesity

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alone, and SO using data from UK Biobank. Sarcopenia was defined according to the European Working Group on Sarcopenia in Older People criteria: low handgrip strength (< 27 kg for men, < 16 kg for women) and/or low skeletal muscle index (< 7.0 kg/m² for men, < 5.5 kg/m² for women). Obesity was defined as body mass index ≥ 30 kg/m² for non-Asian participants, and ≥ 25 kg/m² for non-Hispanic Asian individuals. Cox proportional hazards models were used to estimate adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) for all-cause mortality, cirrhosis, and HCC. **Results:** A total of 457,708 eligible participants were included. Median age was 58 years, and 45.7% were male. Participants were categorized into non-obesity (n = 346,744), obesity alone (n = 103,904), and SO (n = 7,060). Compared with the non-obese group, those with SO were older, more likely to be female, and had a higher burden of cardiometabolic risk factors, including type 2 diabetes, hypertension, and dyslipidemia (all p < 0.001). During follow-up, 48,943 deaths, 2,768 cases of cirrhosis, and 488 cases of HCC were recorded. In fully adjusted models, SO was associated with significantly higher risks of all-cause mortality (aHR 1.66, 95% CI: 1.57-1.74, p < 0.001), cirrhosis (aHR 2.69, 95% CI: 2.25-3.23, p < 0.001), and HCC (aHR 2.37, 95% CI: 1.52-3.68, p < 0.001). These associations were consistently stronger for SO than obesity alone. Subgroup analyses showed that the increased risks of all-cause mortality and liver outcomes associated with SO were broadly consistent across age, sex, and racial subgroups. **Conclusion:** In this prospective cohort study, SO was independently associated with higher risks of all-cause mortality, cirrhosis, and HCC, with stronger effects than obesity alone. These findings identify SO as a high-risk phenotype warranting targeted monitoring and intervention.

Table. Associations between obesity and sarcopenia status and all-cause mortality, liver cirrhosis and hepatocellular carcinoma in UK Biobank.

All-cause mortality		HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
No obesity	33687/346744	ref		ref		ref	
Only obesity	13627/103904	1.36 (1.33, 1.39)	<0.001	1.27 (1.25, 1.29)	<0.001	1.16 (1.14, 1.19)	<0.001
Obesity + sarcopenia	1629/7060	2.12 (2.02, 2.22)	<0.001	2.45 (2.33, 2.57)	<0.001	1.66 (1.57, 1.74)	<0.001
Liver Cirrhosis		HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
No obesity	1545/346744	ref		ref		ref	
Only obesity	1082/103904	2.28 (2.11, 2.46)	<0.001	2.17 (2.00, 2.34)	<0.001	1.72 (1.57, 1.88)	<0.001
Obesity + sarcopenia	141/7060	4.34 (3.65, 5.16)	<0.001	3.98 (3.34, 4.74)	<0.001	2.69 (2.25, 3.23)	<0.001
Hepatocellular carcinoma		HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
No obesity	246/346744	ref		ref		ref	
Only obesity	217/103904	2.85 (2.37, 3.42)	<0.001	2.74 (2.28, 3.29)	<0.001	2.00 (1.64, 2.45)	<0.001
Obesity + sarcopenia	25/7060	4.35 (2.88, 6.57)	<0.001	4.04 (2.66, 6.13)	<0.001	2.37 (1.52, 3.68)	<0.001

Model 1 was adjusted for age, sex.
Model 2 was adjusted for covariates in model 1 plus race, education, smoking and drinking status.
Model 3 was adjusted for covariates in model 2 plus T2DM, hypertension, hyperlipidemia, ALT, AST, TG, TC.
T2DM: Type 2 diabetes mellitus; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; TG: Triglycerides; TC: Total cholesterol

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2507 | HIGH RISK OF UNDIAGNOSED ADVANCED LIVER DISEASE LEADING TO HEPATIC DECOMPENSATION IN PATIENTS WITH DIABETES MELLITUS DESPITE ENGAGEMENT IN AMBULATORY CARE

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Background: Patients with diabetes mellitus (DM) are at high risk for the development of metabolic-associated steatotic liver disease (MASLD) which may be asymptomatic and without significant laboratory abnormalities even in the presence of advanced fibrosis. The purpose of this study was to identify and describe patients whose first diagnosis of advanced liver disease was at the time of liver decompensation ("late diagnosis") despite participation in outpatient care. **Methods:** A retrospective review of a large, single, urban health system's validated Diabetes Registry (Nathani et al., 2026) was performed from 2000-2025. Inclusion criteria were registry patients with an ambulatory visit to primary care or endocrinology from 2023-2024. Hepatic decompensation was defined as: diagnosis code for hepatic encephalopathy (HE), variceal bleeding (EVB), ascites, liver failure, hepatorenal syndrome, or hepatocellular carcinoma; prescription for lactulose or rifaximin (HE); prescription for furosemide with spironolactone (ascites); procedure code for paracentesis (ascites), variceal band ligation (EVB), or transjugular intrahepatic portosystemic shunt (TIPS)/surgical shunt (shunt). Known diagnosis of advanced liver disease was defined as a diagnosis of cirrhosis, referral to hepatology, or visit in hepatology clinic predating first decompensating event (hepatology and gastroenterology are separate in our health system). **Results:** 3768 patients (50% female, 25.6% White) had liver decompensation. Most common decompensating events were HE, ascites, and HCC. 3015 patients had late diagnosis (Table 1). 1923 (64%) had lab data within 1 year of decompensation allowing for Fibrosis-4 liver index for fibrosis (FIB-4) risk stratification. Patients with late diagnosis had fewer mean number of outpatient encounters across specialties prior to decompensation compared to those with known liver disease (7.5 vs. 12.2, p < 0.01). Of patients with available FIB-4 scores (the majority of patients), most were high or indeterminate, and most were female (52.4% vs 47.6% chi-squared p < 0.01). There were no other significant differences in demographics between patients who had available FIB-4 data compared to those who did not. **Conclusion:** These findings suggest a missed opportunity for linkage to hepatology despite engagement in ambulatory care, often with multiple specialists. Simple FIB-4 calculation

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could highlight those requiring further secondary risk assessment such as vibration-controlled transient elastography, Enhanced Liver Fibrosis testing, or magnetic resonance elastography. It is critical to identify patients during the compensated cirrhosis phase when targeted preventive measures may be employed to avoid decompensation and the associated high costs that come with urgent hospitalization. Careful attention to hepatic end-organ damage is needed as part of regular DM healthcare maintenance and screening.

Table. Decompensated patients: demographics and pre-decompensation care

	LATE DIAGNOSIS (n=3015)		KNOWN ADVANCED LIVER DISEASE (n=753)		
	n	Percent	n	Percent	Chi-squared P
First Decompensation					**<0.001**
HE	1774	58.8%	329	43.7%	
Ascites	1043	34.6%	255	33.9%	
HCC	113	3.7%	94	12.5%	
EVB	69	2.3%	74	9.8%	
Liver Failure	15	0.5%	1	0.1%	
HRS	1	0.0%	0	0.0%	
Female	1521	50.4%	372	49.4%	0.61
Race/Ethnicity					**<0.001**
White	820	27.2%	148	19.7%	
Non-White	2195	72.8%	605	80.3%	
Primary Language					0.36
English	2497	82.8%	612	81.3%	
Other	518	17.2%	140	18.6%	
Primary Insurance					0.68
Medicaid/Medicare	2126	70.5%	519	68.9%	
Private	725	24.0%	192	25.5%	
Other	160	5.3%	41	5.4%	
FIB-4 within 1 year of decompensation					**<0.001**
Low (<1.30)	834	27.7%	156	20.7%	
Indeterminate	839	27.8%	242	32.1%	
High (>2.67)	250	8.3%	276	36.7%	
Unavailable	1092	36.2%	79	10.5%	
Outpatient visits					
Primary Care	1584	52.47%	557	74.0%	**<0.001**
Gastroenterology	60	1.99%	50	6.82%	**<0.001**
Cardiology	194	6.43%	44	5.88%	0.55
Endocrinology	94	3.12%	33	4.41%	0.09

HE: hepatic encephalopathy, HCC: hepatocellular carcinoma, EVB: esophageal variceal bleed, HRS: hepatorenal syndrome

Disclosures: Emily Leven: Nothing to Disclose, Anna Mageras: The Kinetix Group: Advisor, Novo Nordisk: Advisor, Gilead Sciences: Grant/Research Support, Gilead Sciences: Advisor, Xiaotao Zhang: Nothing to Disclose, Meena Bansal: Madrigal: Advisor, Fibronostics: Advisor, NOVO Nordisk: Advisor, GSK: Advisor, Merck: Advisor, Boeheringer-Ingelheim: Advisor, Boston Pharma: Advisor, The Kinetix Group: Advisor, Corcept: Advisor.

2508 | WAITLIST OUTCOMES FOR CANDIDATES WITH MASH AND LOW MELD SCORES COMPARED WITH VIRAL HEPATITIS

Eman Chaudhry[1] Catherine Kelty[2] Ralph Quillin[2] Christine Haugen[2] Khurram Bari[2], [1]Northeast Ohio Medical University, [2]University of Cincinnati

Background: MELD-based allocation prioritizes liver transplant candidates using laboratory markers but does not capture metabolic burden, frailty, or portal hypertensive complications. We evaluated whether candidates with metabolic dysfunction-associated steatohepatitis (MASH) have worse waitlist outcomes than candidates with viral hepatitis, focusing on low MELD, where non-liver factors may be underrecognized. **Methods:** We performed a retrospective cohort study using Scientific Registry of Transplant Recipients data of adult liver-only waitlist candidates listed between Feb 1, 2016 and Jan 31, 2023 (MELD 1.0 to ensure adequate follow up and cohort size). Etiology was defined using candidate diagnosis codes for MASH and viral hepatitis. Candidates with prior liver transplant or hepatocellular carcinoma exception were excluded and stratified by MELD at listing: < 15, 15-20, and 21-30. The primary outcome was waitlist removal due to deterioration/death. Secondary outcomes included 90-day and 1-year removal, time to transplant, and MELD change from listing to transplant/removal. Time to deterioration/death was assessed by Kaplan-Meier analysis. MELD > 30 was excluded from this analysis because severe hepatic dysfunction and short wait times may obscure non-liver contributors to waitlist risk. **Results:** The cohort included 24,280 candidates with MELD < 30: 11,850 with MELD < 15, 7,496 with MELD 15-20, and 4,934 with MELD 21-30. In MELD < 15, candidates with MASH had higher BMI (31 vs 28, $p < 0.001$), higher initial MELD (12 vs 10, $p < 0.001$), lower albumin (3 vs 4, $p < 0.001$), and more moderate ascites (25.1% vs 11.5%, $p < 0.001$) compared with candidates with viral hepatitis (Table 1). In MELD 15-20 and 21-30, MASH was associated with higher BMI and more moderate ascites (37.3% MASH vs. viral hepatitis: 31.2%; 49.0% vs 41.7%, both $p < 0.001$). For MELD < 15, overall removal due to deterioration/death was higher with MASH (20.6% vs 18.5%, $p = 0.003$), while 90-day (2.1% vs 2.0%, $p = 0.658$) and 1-year removal (9.4% vs 10.5%, $p = 0.058$) were not different. Candidates with MASH had shorter time to transplant (226 vs 255 days, $p < 0.001$) and greater MELD increase (2 vs 1, $p < 0.001$), while time to deterioration/death did not differ (306 vs 292 days, $p = 0.747$). MASH was associated with significantly shorter time to waitlist deterioration or death across MELD 15–20 (152 vs 169 days, $p = 0.016$) and 21–30 (36 vs 51 days, $p < 0.001$) compared to viral hepatitis. Kaplan-Meier curves showed increased removal with MASH in MELD 15-20 at 1 year, 3 years, and anytime, and in MELD 21-30 at all assessed time points. **Conclusion:** Among candidates with MELD < 15, MASH was associated with greater metabolic/portal hypertensive burden, higher removal due to deterioration/death, and greater MELD progression. When combined with findings in MELD 15-20 and 21-30 cohorts, these data suggest MELD may incompletely capture MASH risk before

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severe liver dysfunction dominates waitlist outcomes.

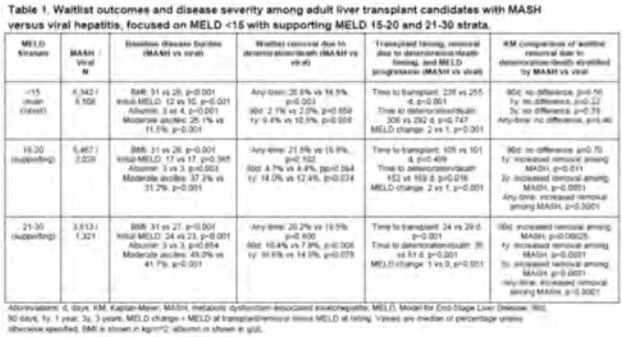


Table 1. Waitlist outcomes and disease severity among adult liver transplant candidates with MASH versus viral hepatitis, focused on MELD <15 with supporting MELD 15-20 and 21-30 strata.

MELD Strata	MASH / Viral N	Baseline disease burden (MASH vs viral)	Waitlist removal due to deterioration/death (MASH vs viral)	Transplant timing, removal due to deterioration/death, and MELD progression (MASH vs viral)	KM comparison of waitlist removal due to deterioration/death stratified by MASH vs viral
<15 (main cohort)	6,942 / 5,508	BMI: 31 vs 28; p<0.001 Initial MELD: 12 vs 10; p<0.001 Albumin: 3 vs 4; p<0.001 Moderate ascites: 25.1% vs 11.5%; p<0.001	Any-time: 20.6% vs 16.5%; p<0.003 90d: 2.1% vs 2.0%; p=0.659 1y: 9.4% vs 10.5%; p=0.056	Time to transplant: 226 vs 255 d; p<0.001 Time to deterioration/death: 306 vs 292 d; p=0.747 MELD change: 2 vs 1; p<0.001	90d: no difference; p=0.16 1y: no difference; p=0.22 3y: no difference; p=0.76 Any-time: no difference; p=0.46
15-20 (supporting)	5,467 / 3,029	BMI: 31 vs 28; p<0.001 Initial MELD: 17 vs 17; p=0.365 Albumin: 3 vs 3; p=0.003 Moderate ascites: 37.3% vs 31.2%; p<0.001	Any-time: 21.5% vs 19.9%; p=0.102 90d: 4.7% vs 4.4%; pp=0.364 1y: 14.0% vs 12.4%; p=0.074	Time to transplant: 105 vs 101 d; p=0.409 Time to deterioration/death: 152 vs 169 d; p=0.016 MELD change: 2 vs 1; p<0.001	90d: no difference; p=0.70 1y: increased removal among MASH; p<0.011 3y: increased removal among MASH; p<0.0001 Any-time: increased removal among MASH; p<0.0001
21-30 (supporting)	3,613 / 1,321	BMI: 31 vs 27; p<0.001 Initial MELD: 24 vs 23; p<0.001 Albumin: 3 vs 3; p=0.654 Moderate ascites: 49.0% vs 41.7%; p<0.001	Any-time: 20.2% vs 19.5%; p=0.600 90d: 10.4% vs 7.9%; p=0.006 1y: 19.6% vs 14.3%; p=0.079	Time to transplant: 24 vs 29 d; p<0.001 Time to deterioration/death: 39 vs 51 d; p<0.001 MELD change: 3 vs 0; p<0.001	90d: increased removal among MASH; p=0.00025 1y: increased removal among MASH; p<0.0001 3y: increased removal among MASH; p<0.0001 Any-time: increased removal among MASH; p<0.0001

Abbreviations: d, days; KM, Kaplan-Meier; MASH, metabolic dysfunction-associated steatohepatitis; MELD, Model for End-Stage Liver Disease; 90d, 90 days; 1y, 1 year; 3y, 3 years; MELD change = MELD at transplant/removal minus MELD at listing. Values are median or percentage unless otherwise specified; BMI is shown in kg/m^2; albumin is shown in g/dL.

Disclosures: Eman Chaudhry: Nothing to Disclose, Catherine Kelty: Nothing to Disclose, Ralph Quillin: Nothing to Disclose, Christine Haugen: Nothing to Disclose, KHURRAM BARI: Madrigal: Advisor, Mallinckrodt: Speaking and Teaching.

2509 | DOES INFLAMMATION IN LIVER BIOPSY REALLY MATTER IN CLINICAL OUTCOMES OF PEOPLE WITH METABOLIC DYSFUNCTION–ASSOCIATED STEATOTIC LIVER DISEASE (MASLD)?

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Background: Fibrosis stage has been established as the strongest predictor of liver-related and all-cause mortality in MASLD. Yet the independent prognostic contributions of metabolic dysfunction-associated steatohepatitis (MASH), lobular inflammation, and hepatocyte ballooning, particularly for clinical outcomes, remain controversial. **Methods:** We conducted a retrospective longitudinal cohort study of 396 adults with biopsy-proven MASLD across Imperial College Healthcare NHS Trust (2003–2026). Histological features were scored using the NASH CRN system. Outcomes comprised composite liver-related events (incident cirrhosis, hepatic decompensation, hepatocellular carcinoma), major adverse cardiovascular events (MACE), all-cause mortality, extrahepatic malignancy, and a major composite endpoint aggregating the first three. Multivariable Cox proportional hazards regression, adjusted for baseline age and type 2 diabetes mellitus (T2DM), were performed. **Results:** Over a median (IQR) follow-up of 60.0 (40.5–84.0) months, the cohort (mean age 50.7 years; 55.1% T2DM; 57.3% stage F3/F4 at baseline) experienced 21 liver-related events, 14 cardiovascular events, 19 extrahepatic malignancies, and 15 deaths. Advanced fibrosis (F3–F4) independently predicted liver-related events (adjusted hazard ratio [aHR] 1.96 [95% confidence interval (CI): 1.13–3.40], p = 0.016) and the major composite outcome (aHR 2.84 [95% CI: 1.22–6.64], p = 0.016). MASH independently predicted liver-related events when adjusted for age and T2DM alone (aHR 3.08 [95% CI: 1.22–7.73], p = 0.017); however, when fibrosis was entered simultaneously, MASH was attenuated to non-significance (HR 2.41 [95% CI: 0.96–6.09], p = 0.062), with fibrosis dominating (HR 6.60 [95% CI: 1.53–28.60], p = 0.012). Neither lobular inflammation (grades 2–3 vs 0–1) nor hepatocyte ballooning (grades 1–2 vs 0) independently predicted any outcome. No histological feature predicted cardiovascular events, extrahepatic malignancy, or all-cause mortality after multivariable adjustment. **Conclusion:** Fibrosis stage is the only histological feature to independently predict both liver-specific and global composite outcomes in this MASLD cohort. MASH provides no additional prognostic information once fibrosis is accounted for. These findings challenge the use of MASH resolution as a standalone surrogate endpoint in clinical trials and support fibrosis regression as the primary therapeutic target in MASLD.

Table 1. Univariable and multivariable histological predictors of liver-related and systemic outcomes. Standard multivariable Cox proportional hazards models were adjusted for baseline age and type 2 diabetes mellitus. To assess independent prognostic utility, an additional simultaneous model evaluated advanced fibrosis and definitive MASH as competing covariates. Significant p-values (<0.05) are bolded. *Liver-related events*: composite of incident cirrhosis, hepatocellular carcinoma, or hepatic decompensation. *Major composite outcome*: composite of liver-related events, cardiovascular events, and all-cause mortality.

Outcome category	Histological predictor	Univariable HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Liver-related evenis	Advanced fibrosis (F3–F4)	1.84 (1.16–2.91)	**0.010**	1.96 (1.13–3.40)	**0.016**
	Definitive MASH (NAS ≥5)	2.94 (1.17–7.39)	**0.021**	3.08 (1.22–7.73)	**0.017**
	Lobular inflammation (grades 2–3)	1.39 (0.50–3.89)	0.530	1.43 (0.52–3.92)	0.484
	Hepatocyte ballooning (grades 1–2)	3.58 (0.48–26.83)	0.214	3.22 (0.43–24.19)	0.255
Cardiovascular events	Advanced fibrosis (F3–F4)	1.12 (0.76–1.67)	0.563	0.89 (0.55–1.41)	0.612
	Definitive MASH (NAS ≥5)	0.63 (0.19–2.02)	0.442	0.68 (0.21–2.16)	0.513
	Lobular inflammation (grades 2–3)	0.81 (0.18–3.63)	0.785	0.75 (0.17–3.38)	0.711
	Hepatocyte ballooning (grades 1–2)	26.53 (0.05–12130)	0.204	2.02 (0.26–15.52)	0.498
All-cause mortality	Advanced fibrosis (F3–F4)	1.93 (1.09–3.41)	**0.024**	1.63 (0.86–3.10)	0.134
	Definitive MASH (NAS ≥5)	2.02 (0.71–5.73)	0.187	2.08 (0.72–5.99)	0.174
	Lobular inflammation (grades 2–3)	1.14 (0.32–4.05)	0.845	1.13 (0.32–4.04)	0.846
	Hepatocyte ballooning (grades 1–2)	2.36 (0.30–18.15)	0.407	3.22 (0.42–24.19)	0.255
Other malignancy	Advanced fibrosis (F3–F4)	1.12 (0.75–1.67)	0.563	0.96 (0.62–1.47)	0.836
	Definitive MASH (NAS ≥5)	0.97 (0.37–2.51)	0.959	1.11 (0.43–2.88)	0.824
	Lobular inflammation (grades 2–3)	1.03 (0.30–3.57)	0.957	0.90 (0.26–3.11)	0.865
	Hepatocyte ballooning (grades 1–2)	1.60 (0.36–6.99)	0.528	1.39 (0.31–6.03)	0.665
Major composite outcome	Advanced fibrosis (F3–F4)	3.93 (1.74–8.87)	**<0.001**	2.84 (1.22–6.64)	**0.016**
	Definitive MASH (NAS ≥5)	1.70 (0.93–3.12)	0.087	1.80 (0.98–3.31)	0.060
	Lobular inflammation (grades 2–3)	1.30 (0.62–2.72)	0.487	1.22 (0.58–2.55)	0.598
	Hepatocyte ballooning (grades 1–2)	3.97 (0.96–16.44)	0.057	3.55 (0.86–14.71)	0.081
Liver-related events (adjusted for MASH and fibrosis)	Advanced fibrosis (F3–F4)	—	—	6.60 (1.53–28.60)	**0.012**
	Definitive MASH (NAS ≥5)	—	—	2.41 (0.96–6.09)	0.062

Disclosures: Khadija Qazi: Nothing to Disclose, Pinelopi Manousou: Nothing to Disclose, Michael Yee: Nothing to Disclose, Maria Kalafateli: Nothing to Disclose, Mark Thursz: GSK: Consultant, Resolution Tx: Consultant, Intercept: Consultant, Galecto: Consultant, Durect: Consultant, Rob Goldin: Nothing to Disclose, Fernando Iorra: Nothing to Disclose.

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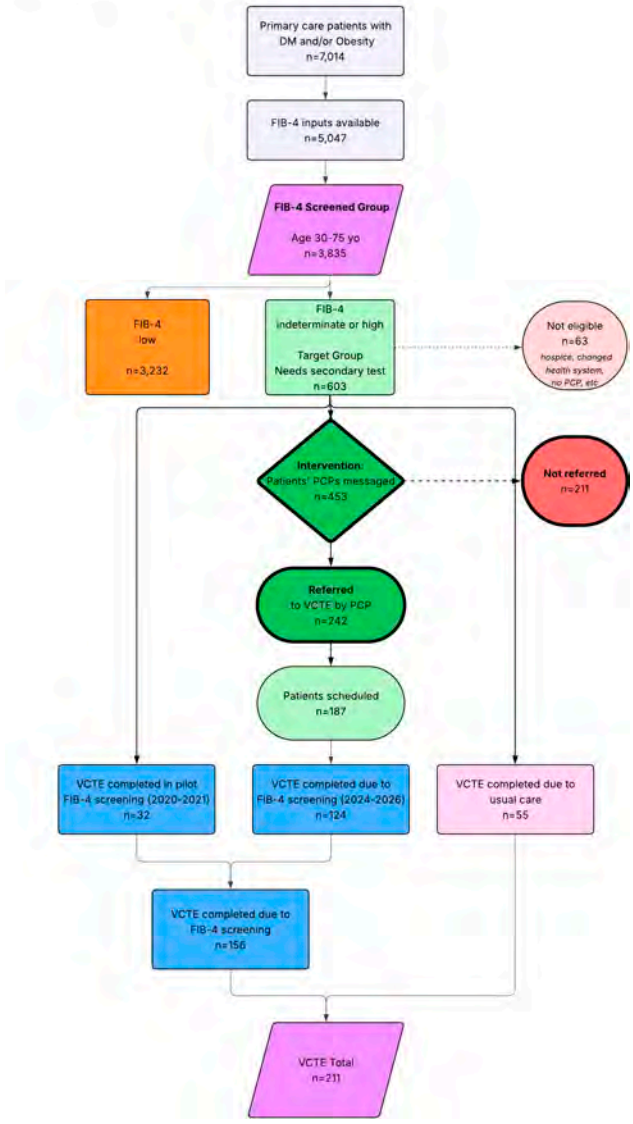
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2510 | PRIMARY CARE UPTAKE OF MASH SCREENING AND PREDICTORS OF REFERRAL FOR SECONDARY FIBROSIS TESTING AFTER ELEVATED FIB-4

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Background: Metabolic dysfunction–associated steatotic liver disease (MASLD) screening pathways rely on a stepwise approach using the fibrosis-4 index (FIB-4) followed by vibration-controlled transient elastography (VCTE) or blood-based risk scores. However, little is known about how primary care providers (PCPs) respond to elevated FIB-4 results, particularly among patients with obesity and/or type 2 diabetes mellitus (DM). We aimed to evaluate VCTE referral patterns by PCPs and identify factors associated with referral behavior across metabolic risk phenotypes. **Methods:** We conducted a prospective pragmatic implementation trial of screening for MASLD with significant fibrosis among primary care patients with obesity and/or DM during 2024-2026. We calculated FIB-4s with existing laboratory inputs. Using the most recent FIB-4 and age-based cutoffs, for patients with indeterminate- or high FIB-4s, we prompted their PCP to refer for VCTE as a second-step fibrosis assessment. PCPs opted whether to refer each patient. Descriptive statistics were used to compare characteristics of referred versus non-referred patients. Univariable and multivariable logistic regression analyses were performed to identify factors associated with referral patterns. **Results:** Among 453 patients, the majority were male (58%) with mean age 64 ± 8 years and mean BMI of 31.0 ± 6.3 kg/m^2 . They were diverse with 40% White, 27% Asian, 15% Black, and 11% Hispanic. Metabolic risk factors included 54% DM, 69% hypertension, 75% hyperlipidemia, and 34% obstructive sleep apnea. The overall referral rate was 53%; by FIB-4 category, the rate was 56% among indeterminate-risk and 44% among high-risk. Referral rates were similar for those with obesity without DM (53%) and DM without obesity (52%), and somewhat higher for DM with obesity (59%). There were no significant differences at baseline among those referred vs non-referred including age, sex, ethnicity/race, insurance status, BMI, mean HbA1c, mean ALT, frequency of primary care visits, or FIB-4 category. On univariable and multivariable logistic regression, adjusted for age, sex, BMI, and metabolic risk factors, neither elevated ALT, HbA1c, nor FIB-4 category was significantly associated with referral, though DM with or without obesity, compared to obesity alone, approached significance (OR 1.51, 95% CI 0.99-2.32). **Conclusion:** In this prospective implementation trial of MASLD- fibrosis screening, PCPs referred just over half of patients to VCTE. Importantly, we found PCP referrals were not associated with FIB-4, suggesting that the decision to refer may be driven by other patient and/or provider-related factors rather than objective liver-related measurements. These data point to important gaps between screening recommendations and real-world practices and support the need for greater PCP education and PCP-focused guidelines for the use of standardized MASLD referral pathways in primary care.

Figure 1. Uptake of MASH Screening in Primary Care



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2511 | THE PREVENT CARDIOVASCULAR RISK SCORE AS AN OPPORTUNISTIC TOOL TO IDENTIFY UNDERRECOGNIZED MASLD AND FIBROSIS IN PRIMARY CARE: AN ANALYSIS FROM NHANES 2017-2023

Jesse Fletcher[1] Timothy Davie[1] Serena Brosten[1] Kartik Dapke[2] Anna Strauss[1] Giovanni Roldan[3] Prowpanga Udompap[4], [1]Department of Medicine, University of Minnesota, [2]Department of Medicine, Saint Vincent Hospital, Worcester, MA, [3]Division of Gastroenterology, Hepatology and Nutrition, University of Minnesota, [4]Division of Gastroenterology, Minneapolis VA Medical Center

Background: The PREVENT equations are widely utilized in primary care to predict cardiovascular risk. Because their component variables closely mirror the cardiometabolic drivers of metabolic dysfunction-associated steatotic liver disease (MASLD), these equations could serve as a pragmatic tool to simultaneously increase disease awareness and enhance risk stratification. We hypothesized that the prevalence of hepatic steatosis and significant fibrosis increases step-wise with rising PREVENT cardiovascular risk scores. **Methods:** Using National Health and Nutrition Examination Survey (NHANES) data from 2017–March 2020 and August 2021–August 2023, we included adults aged 30–79 years with valid vibration-controlled transient elastography and complete data required for the PREVENT total cardiovascular disease (CVD) equation. Ten-year cardiovascular risk was categorized as $<5\%$, 5% to $<10\%$, 10% to $<20\%$, and $\geq 20\%$. Outcomes evaluated across strata included hepatic steatosis (HS; defined by controlled attenuation parameter or CAP ≥ 275 dB/m), clinically relevant fibrosis (≥ 8 kPa), advanced fibrosis (≥ 15 kPa), self-reported CVD, and liver disease awareness. Survey-weighted prevalences and Rao-Scott p-values were estimated. **Results:** Among 8,969 participants (representing approximately 148 million U.S. adults), increasing 10-year PREVENT CVD risk scores ($<5\%$, 5 to $<10\%$, 10 to $<20\%$, and $\geq 20\%$) correlated step-wise with higher rates of hepatic steatosis (37.2% to 59.3%) and clinically relevant fibrosis (LSM ≥ 8 kPa; 7.2% to 21.3%; $p<0.001$). Despite this rising disease burden, liver disease awareness was profoundly deficient and decoupled from clinical risk. Among individuals with objective hepatic steatosis, awareness never exceeded 10.2% in any stratum (ranging from 4.4% to 9.1%; $p<0.001$). Crucially, even among those with clinically relevant fibrosis (LSM ≥ 8 kPa), awareness remained alarmingly low, peaking at just 21.4% in the 10 to $<20\%$ risk group and dropping to 14.3% in the highest-risk stratum ($p=0.006$). Conversely, self-reported CVD awareness scaled appropriately across the same strata (2.8% to 34.7%, $p<0.001$) (Table 1). **Conclusion:** Elevated PREVENT CVD risk scores are strongly associated with a high prevalence of hepatic steatosis and clinically relevant fibrosis in the U.S. population. Despite this substantial disease burden, patient awareness of liver disease remains dismal across all risk strata. Because the PREVENT equation is already an established staple in primary care clinics, leveraging it to identify patients at risk for MASLD and those at risk of disease progression represents a highly feasible opportunity to improve early detection, increase clinical awareness, and optimize metabolic care.

Table 1: Characteristics and disease awarness of NHANES participants in each PREVENT CVD risk group

Characteristic	PREVENT CVD RISK				P value
	<5%	5–<10%	10–<20%	≥20%	
Unweighted n	4,262	1,816	1,947	924	
Weighted N (in millions; M)	83.7	28.3	25.8	10.9	
Age, years	43.3 (42.9–43.6)	56.5 (57.6–59.2)	66.1 (65.6–66.6)	71.5 (70.9–72.0)	<0.001
BMI, kg/m^2	29.5 (29.2–29.8)	30.3 (29.8–30.9)	30.3 (29.9–30.8)	30.5 (30.0–31.0)	<0.001
Female sex	54.5% (52.6–56.4)	48.7% (45.6–51.8)	43.5% (40.7–46.4)	38.8% (34.5–43.3)	<0.001
Liver Disease Severity					
Steatosis (CAP ≥275 dB/m)	37.2% (35.5–38.9)	54.8% (51.0–58.5)	54.5% (51.1–57.7)	59.3% (55.5–63.0)	<0.001
FIB-4 high risk (>2.67)	0.6% (0.4–0.9)	3.0% (2.2–4.1)	3.7% (2.8–4.8)	7.5% (6.0–9.3)	<0.001
SAFE high risk (≥100)	2.6% (2.0–3.2)	13.9% (11.7–16.5)	26.2% (25.7–30.9)	53.7% (49.3–58.1)	<0.001
Fibrosis (LSM ≥8 kPa)	7.2% (6.2–8.3)	14.3% (11.7–17.2)	18.2% (12.6–18.2)	21.3% (17.5–25.7)	<0.001
Advanced fibrosis (LSM ≥15 kPa)	1.3% (0.8–1.8)	3.6% (2.5–5.2)	3.4% (2.5–4.5)	8.2% (4.5–8.0)	<0.001
Disease Awareness — Overall Participants Included					
CVD awareness	2.8% (2.3–3.4)	9.5% (7.6–11.9)	16.5% (16.0–21.2)	34.7% (29.9–39.9)	<0.001
Liver disease awareness	3.6% (2.8–4.6)	7.8% (6.0–10.1)	8.4% (6.9–10.2)	9.7% (6.3–11.8)	<0.001
Disease Awareness — Among Those with Steatosis					
CVD awareness	3.4% (2.1–5.3)	10.2% (7.1–14.5)	20.6% (17.4–24.3)	34.8% (29.1–40.9)	<0.001
Liver disease awareness	4.4% (3.3–5.9)	9.4% (6.8–12.9)	10.2% (8.1–12.7)	9.1% (6.3–13.0)	<0.001
Disease Awareness — Among Those with Fibrosis ≥8 kPa					
CVD awareness	4.4% (2.2–8.8)	9.0% (6.1–13.1)	20.2% (14.5–27.4)	41.1% (32.4–50.4)	<0.001
Liver disease awareness	7.5% (5.1–10.9)	19.0% (11.7–29.3)	21.4% (14.6–30.1)	14.3% (9.3–21.3)	0.006

Abbreviations: CAP = Controlled Attenuation Parameter; SAFE = Steatosis-Associated Fibrosis Estimator; FIB-4 = Fibrosis-4 Index; LSM = Liver Stiffness Measurement; T2DM = Type 2 Diabetes Mellitus; CVD = Cardiovascular Disease; CI = Confidence Interval.

Disclosures: Jesse Fletcher: Nothing to Disclose, Timothy Davie: Nothing to Disclose, Serena Brosten: Nothing to Disclose, Kartik Dapke: Nothing to Disclose, Anna Strauss: Nothing to Disclose, Giovanni Roldan: Nothing to Disclose, Prowpanga Udompap: Nothing to Disclose.

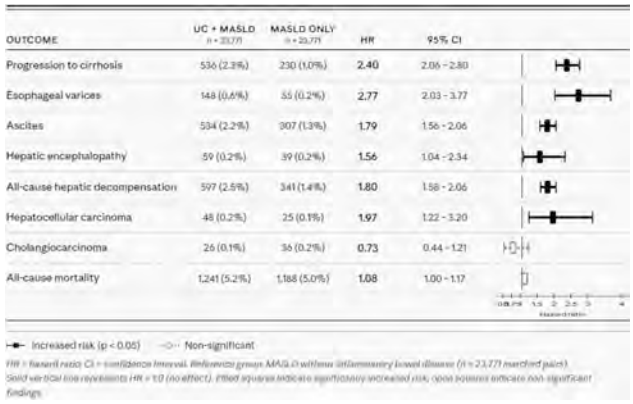
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2512 | ULCERATIVE COLITIS IS ASSOCIATED WITH WORSE LIVER-RELATED OUTCOMES IN PATIENTS WITH MASLD: A PROPENSITY-MATCHED REAL-WORLD COHORT STUDY

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Background: Extraintestinal hepatic manifestations occur in up to 30–50% of patients with inflammatory bowel disease (IBD), driven by gut dysbiosis, intestinal permeability, portal endotoxemia, and chronic systemic inflammation. Among these, MASLD has emerged as a significant hepatic comorbidity. The clinical hepatic behavior of MASLD in the setting of concurrent UC remains poorly understood. We therefore conducted a large real-world cohort study to determine whether concomitant UC independently worsens liver-related outcomes in patients with established MASLD, excluding those with PSC. **Methods:** We performed a retrospective propensity score–matched (1: 1) cohort study using the TriNetX Research Network, a large multicenter federated EHR database. Adult patients with MASLD and concomitant UC were matched to MASLD patients without IBD. Patients with Crohn's disease, pre-existing cirrhosis or hepatic decompensation, hepatocellular carcinoma, liver transplantation, viral hepatitis, autoimmune or alcoholic liver disease, or other chronic liver conditions were excluded. Follow-up = 5 years. The primary outcome was progression to cirrhosis; secondary outcomes included ascites, esophageal varices, hepatic encephalopathy, hepatocellular carcinoma (HCC), cholangiocarcinoma, composite hepatic decompensation, and all-cause mortality. Propensity score matching balanced baseline demographic, metabolic, cardiovascular, medication, and laboratory variables. Kaplan-Meier survival analyses with log-rank testing were used to estimate time-to-event outcomes, and hazard ratios (HRs) with 95% confidence intervals (CIs) were reported. **Results:** After propensity score matching, 23,771 patients were retained in each cohort. MASLD +UC was associated with significantly higher risks of cirrhosis progression (HR 2.40, 95% CI 2.06–2.80; $p < 0.001$), esophageal varices, ascites, hepatic encephalopathy, HCC (HR 1.97, 95% CI 1.22–3.20; $p = 0.005$), and composite hepatic decompensation (HR 1.80, 95% CI 1.58–2.06; $p < 0.001$). Cholangiocarcinoma risk did not differ between groups. All-cause mortality was numerically higher in the UC cohort but did not reach statistical significance. Figure-1. **Conclusion:** In this large propensity-matched real-world study, concomitant UC independently conferred substantially elevated risks of cirrhosis, hepatic decompensation, esophageal varices, ascites, hepatic encephalopathy, and HCC among patients with MASLD, even in the absence of PSC. The MASLD-UC overlap represents a distinct high-risk hepatic phenotype that warrants systematic fibrosis screening, heightened hepatic surveillance, and proactive multidisciplinary care. The nearly twofold increased risk of HCC in MASLD-UC patients without PSC represents a clinically significant signal. Whether this excess risk arises independently of cirrhosis remains an unanswered question that warrants prospective validation.



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2513 | EPIDEMIOLOGIC TRENDS IN CIRRHOSIS AND METABOLIC SYNDROME MORTALITY AMONG ADULTS AGED ≥65 YEARS: A NATIONWIDE ANALYSIS, 1999–2024

Bland Ahmed[1] Mahrukh Mahrukh[2] Zainab Attiq[2] Shehryar Rasheed Sohail[3] Arishman Yasin Chaudhary[2] Palwasha Farooqi[1] Ehsanullah Alokozay[4], [1]Desert Regional Medical Center, Palm Springs, Ca, USA, [2]University Medical and Dental College, University of Faisalabad, Faisalabad, Pakistan, [3]Jinnah Sindh Medical University, [4]Faculty of Medicine, Kandahar University, Kandahar, Afghanistan

Background: Metabolic Syndrome (MetS) has become a significant contributor to chronic liver disease, with cirrhosis being its most severe outcome. In individuals aged 65 and older, metabolic syndrome hastens the progression of hepatic fibrosis due to insulin resistance, altered lipid levels, and the accumulation of visceral fat, ultimately increasing

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cirrhosis related mortality. This study aims to analyze long-term mortality trends due to cirrhosis and MetS among older adults. **Methods:** This retrospective study utilized data from the CDC WONDER Multiple Cause of Mortality database from 1999 to 2024 among older adults (>65 years) using ICD-10 codes K74.0-K74.6 for cirrhosis and I10, E10–E14, E66, E78, E88 for MetS. Age-adjusted mortality rates (AAMR) per 100,000 population were calculated. Joinpoint regression analysis was used to calculate annual percent changes (APC) and average annual percent changes (AAPC), with $p < 0.05$ considered significant. **Results:** From 1999-2024, a total of 115,056 deaths were recorded due to cirrhosis and MetS among older adults. The AAMR rose from 6.53 in 1999 to 16.9 in 2024 (AAPC: 3.75; 95% CI: 3.54 to 4.09). Throughout the study period, Men (AAPC: 4.10; 95% CI: 3.81 to 4.46) consistently had higher mortality trend than Women (AAPC: 3.47; 95% CI: 3.21 to 3.85). All age groups showed notable long-term changes, but the most pronounced increase was shown by 85+ age cohort (AAPC: 5.20; 95% CI: 4.88 to 5.59). Regionally, highest mortality rate was shown by the South region (AAPC: 4.48; 95% CI: 4.21 to 4.77), followed by the West region (AAPC: 3.58; 95% CI: 3.18 to 3.99). Racial analysis showed that the White individuals had the greatest mortality burden (AAPC: 4.02; 95% CI: 3.82 to 4.33). Although both urban and rural areas showed rising trends, rural areas (AAPC: 4.21; 95% CI: 3.79 to 4.72) had greater mortality burden than urban areas (AAPC: 3.13; 95% CI: 2.81 to 3.56). **Conclusion:** Deaths due to cirrhosis and metabolic syndrome rose among older adults throughout the study span. Notably, significant demographic and geographical differences persist. Fluctuations in mortality rates highlight the need for targeted prevention approach and equitable access to healthcare for the most at-risk populations.

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2514 | NATURAL HISTORY OF MASLD IN LATIN AMERICA: CIRRHOSIS INCIDENCE AND PREDICTORS OF PROGRESSION IN A MULTINATIONAL COHORT

Ximena Parraga[1] Denisse Rubio Cruz[2] Leandro Sierra[3] Paula Huerta[4] Kriti Soni[1] Stephen Hoang[1] S. Fisher Rhoads[1] Ezequiel Ridruejo[5] Sebastian Marciano[6] Jorge Martínez[6] Maria Jose Acosta[6] Adrian Gadano[6] Cristiane Villela-Nogueira[7] Ana Carolina Cardoso[7] Natalia Balassiano Wajsbrot[7] Nathalie Leite[7] Gil Salles[7] Claudia Cardoso[7] Claudia Couto[8] Guilherme Grossi Cancado[9] Rafael Theodoro[10] Mísia Joyner de Sousa Dias Mo[11] Igor Lima Ferraz[12] Roberta Araújo[12] Claudia Oliveira[13] Mario Pessoa[12] Natalia Baeza[14] Francisco Idalsoaga[14] Gustavo Ayares[14] Marco Arrese[14] MaríaFernanda SaavedraChacón[15] Katherine Marrugo[16] Alonso Vera Torres[16] Juan Diego Torres[16] Valentina Mejía Valdés[16] Daniza Alexandra Contreras[17] José Antonio Velarde-Ruiz Velasco[18] Graciela Castro-Narro[19] Eira Cerda Reyes[20] Stefanny Cornejo Henández[20] Luis Díaz[14] Juan Pablo Arab[1], [1]Virginia Commonwealth University, [2]Lahey hospital, Virginia Commonwealth University, [3]Cleveland Clinic, [4]Los Angeles Hospital, Chile, [5]Centro de Educación Médica e Investigaciones Clínicas Norberto Quirno "CEMIC, [6]Hospital Italiano de Buenos Aires, [7]Universidade Federal do Rio de Janeiro, [8]Federal University of Minas Gerais, [9]Universidade Federal de Minas Gerais, [10]rafaeltheodoro.f@gmail.com, [11]misiajoyner@hotmail.com, [12]Universidade de São Paulo, [13]University of Sao Paulo School of Medicine, [14]Pontificia Universidad Católica de Chile, [15]Clínica CES, [16]Fundación Santa Fe de Bogotá, [17]Instituto Nacional de Diabetes, Endocrinología y Nutrición (INDEN), [18]Hospital Civil de Guadalajara, [19]Hospital Médica Sur, Ciudad de México. Instituto Nacional de Ciencias Médicas y Nutrición, [20]Central Military Hospital

Background: Latin America carries a substantial burden of MASLD; however, data describing its natural history remain scarce. Most existing cohort studies derive from North America, Europe, and Asia, limiting the applicability of risk stratification models to Latin American populations. We characterized cirrhosis incidence and its predictors in a large multinational Latin American MASLD cohort. **Methods:** We conducted a retrospective cohort study of adults with MASLD across six Latin American countries (n = 1,529), (Brazil, Argentina, Chile, Colombia, Dominican Republic, and Mexico). Patients with baseline cirrhosis were excluded from incidence analyses yielding a remaining analytic cohort of n = 1,341. Baseline fibrosis was staged by liver biopsy, VCTE, or FIB-4. Cirrhosis incidence rates were estimated per 100 person-years, and Cox proportional hazards models identified independent predictors of progression. **Results:** We included 1,529 participants (mean age 56.2 ± 12.9 years and 62% female), with a mean follow-up of 3.7 years. The mean body mass index was 32.2 ± 6.0 kg/m2, 61% had type 2 diabetes, 59% hypertension, and 61% hyperlipidemia. Cohort characteristics differed significantly across countries (all $p < 0.001$); type 2

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diabetes prevalence ranged from 23% (Colombia) to 87% (Brazil), hypertension from 29% (Chile) to 80% (Brazil), and mean follow-up from 0.2 years (Dominican Republic) to 5.5 years (Brazil and Chile). At baseline, 76% had non-advanced fibrosis (F0–F2) and 12% advanced fibrosis (F3). Overall, cirrhosis incidence showed marked variation by country (Brazil 1.1, Argentina 2.2, Chile 1.3, Colombia 3.8, Mexico 0.9 per 100 PY). Advanced baseline fibrosis (F3) carried a 3-fold higher incidence rate versus non-advanced disease (4.4 vs. 1.0 per 100 PY). On multivariable Cox analysis, older age (HR 1.06/year, 95% CI 1.04–1.08; $p < 0.001$) was independently associated with cirrhosis development, while hyperlipidemia (HR 0.37, 95% CI 0.21–0.66; $p < 0.001$) was associated with a lower risk. **Conclusion:** In this first large multinational Latin American MASLD cohort, cirrhosis incidence varied markedly across countries, and advanced baseline fibrosis identified a high-risk subgroup with significantly greater progression rates. The protective association of hyperlipidemia warrants further investigation, as it may reflect statin use or metabolic phenotype differences. These findings support the need for region-specific fibrosis-based risk stratification in Latin American MASLD populations.

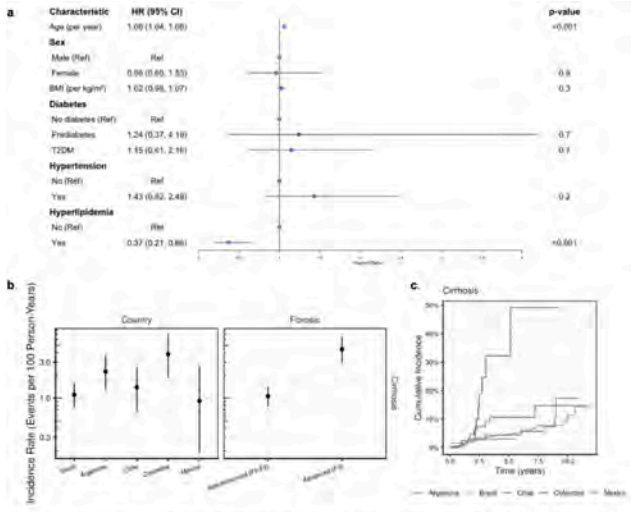


Figure 1a. Cox Proportional Hazards Analysis of Factors Associated with Incident Cirrhosis; **b.** Incidence Rates of Progression to Cirrhosis by Country and Baseline Fibrosis Stage; **c.** Cumulative Incidence of Cirrhosis by Country.

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2515 | FROM PRESCRIPTION TO DISPENSE: PRIMARY ADHERENCE TO RESMETIROM IN REAL-WORLD CLINICAL PRACTICE

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Background: Resmetirom is the first approved pharmacotherapy for adults with noncirrhotic metabolic dysfunction-associated steatohepatitis and moderate-to-advanced liver fibrosis. However, little is known about whether patients who are prescribed resmetirom successfully obtain the medication in routine clinical practice or which factors are associated with primary adherence. **Methods:** We conducted a retrospective cohort study using Epic Cosmos data. Adults aged ≥ 18 years with a new resmetirom prescription between April 1, 2024 and March 1, 2026 and ≥ 30 days of follow-up were included. The index date was the first observed prescription after a 183-day washout period without prior resmetirom prescription or dispense. Primary adherence was defined as ≥ 1 resmetirom dispense within 30 days after the index date. We estimated prevalence of adherence and median time from prescription to first dispense. Multivariable logistic

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regression was used to identify factors associated with adherence. **Results:** Of the 10,591 patients with a new resmetirom prescription (mean age, 57.9 years, 59.4% female, 58.3% White), 6,453 (60.9%) filled it during the study period. Of them, 64.7% (n = 4,172), 78.5% (n = 5,066), and 84.6% (n = 5,457) did so within 30, 60, and 90 days respectively. Median time from prescription to first dispense was 18 days (IQR, 7-49). More than 10% of patients had a liver biopsy at baseline. Primary adherence was highest in Asian patients (47.5%) and Medicare beneficiaries (43.2%). In adjusted analysis, Asian race (vs White; adjusted odds ratio [aOR], 1.39; 95% CI, 1.11-1.74), Medicare insurance (vs private; aOR, 1.16; 95% CI, 1.04-1.29), and having liver biopsy (aOR, 1.18; 95% CI, 1.04-1.34) were positively associated with adherence. Patients who used GLP-1, SGLT-2i, statin, and hypertensive medications also had increased odds of adherence. In contrast, Hispanic ethnicity (aOR, 0.86; 95% CI, 0.75-0.98), Medicaid insurance (aOR, 0.73; 95% CI, 0.54-0.97), type 2 diabetes (aOR, 0.86; 95% CI,0.79-0.95), and clopidogrel use (aOR, 0.76; 95% CI, 0.58-0.98) were negatively associated with adherence. **Conclusion:** In this large real-world study, fewer than 4 in 10 patients prescribed resmetirom filled the prescription within 30 days, with notable differences by race, ethnicity and insurance. These findings provide early evidence on access to resmetirom in clinical practice and identify patient and prescribing factors associated with successful medication initiation.

Disclosures: Phuc Le: Nothing to Disclose, Naim Alkhouri: Madrigal: Speaking and Teaching, Novo Nordisk: Consulting, Novo Nordisk: Grant/Research Support, Corcept: Grant/Research Support, Echosens: Speaking and Teaching, Perspectum: Consultant, Cima: Consultant, Fibronostics: Consultant, 89Bio: Grant/Research Support, Inventiva: Grant/Research Support, Merck: Grant/Research Support, Pfizer: Grant/Research Support, Ipsen: Speaking and Teaching, Intercept: Speaking and Teaching, Madrigal: Consulting, Research Funding, Novo Nordisk: Consulting, Research Funding, Inventiva: Research Funding, Boehringer Ingelheim: Consulting, Research Funding, Corcept: Research Funding, Ipsen: Consulting, Research Funding, Gliead: Consulting, Research Funding, Speaking, Perspectum: Consulting, Research Funding, Cima: Advisor, 89Bio: Consulting, Research Funding, Arbutus: Grant/Research Support, GSK: Grant/Research Support, Regeneron: Grant/Research Support, AstraZeneka: Grant/Research Support, Madrigal: Grant/Research Support, Akero: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Eli Lilly: Grant/Research Support, Gilead: Grant/Research Support, Galectin: Grant/Research Support, Boston Pharma: Grant/Research Support, Ha Tran: Nothing to Disclose, Hamlet Gasoyan: Nothing to Disclose, Michael Rothberg: Moderna: Stock - publicly traded company.

2516 | WEIGHT CHANGE, NOT STATIN USE OR GLYCEMIC CONTROL, DRIVES FIBROSIS TRAJECTORY IN MASLD: A REAL-WORLD COHORT STUDY

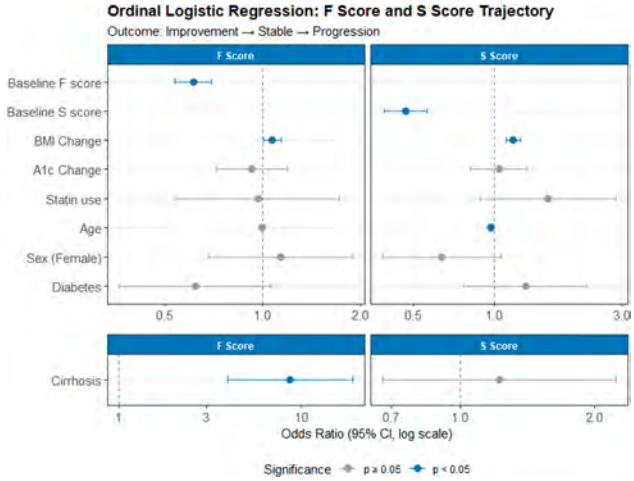
Anju Pradeep[1] Fnu Rashi[2] James Mo[1] Allen Chehimi[3] Sadie Knill[1] Aastha Bahl[3] Xuan Ma[1] Syed-Mohammed Jafri[4], [1]Henry Ford Health, [2]Henry Ford Macomb, [3]Michigan State University, [4]Henry Ford Health System

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is one of the most common causes of chronic liver disease globally. More data is needed to determine if weight change outweighs pharmacologic metabolic interventions in determining fibrosis trajectory in real world practice. We evaluated whether statin use, glycemic control, and BMI change independently predicted fibrosis outcomes in a real-world MASLD cohort. **Methods:** We conducted a retrospective cohort study of adults with MASLD evaluated at Henry Ford Health from January 2019 to December 2024. Patients with ≥ 2 FibroScan assessments ≥ 12 months apart comprised Cohort A (n = 317); those with ≥ 2 FIB-4 measurements comprised Cohort B (n = 288). Fibrosis trajectory was classified as improvement, stable, or progression. Multivariable linear regression modeled continuous changes in kPa, CAP, and FIB-4. Ordinal and binary logistic regression and linear mixed-effects models (LMM) assessed predictors of fibrosis trajectory, adjusting for age, sex, diabetes, cirrhosis, and time-matched metabolic variables. **Results:** Mean age was 58 years (51% female, mean BMI of 35.7 kg/m^2); 53% had diabetes, 23% had cirrhosis at baseline. By FibroScan, mean kPa declined from 10.5 to 8.3 (Δ −2.3 kPa). On F score trajectory, 52.8% improved, 30.7% were stable, and 16.5% progressed. On multivariable analysis, BMI change was independently associated with fibrosis trajectory on ordinal F score analysis (OR 1.07, 95% CI 1.01-1.14, $p = 0.034$) and was the dominant predictor of steatosis progression by ordinal S score (OR 1.18, 95% CI 1.11-1.26, $p < 0.001$). Baseline cirrhosis markedly amplified fibrosis progression risk on both binary (OR 4.64, 95% CI 1.79-12.6, $p = 0.002$) and ordinal F score models (OR 8.65, 95% CI 4.01-19.6, $p < 0.001$) but was not associated with steatosis trajectory. Statin use and HbA1c change were not independently associated with any outcome (all $p > 0.1$). LMM confirmed BMI as the dominant time-varying predictor of kPa (β 0.18, $p = 0.009$) and CAP (β 2.2, $p < 0.001$), but not FIB-4 (β 0.00, $p = 0.6$). Despite 92% of patients meeting GLP-1 receptor agonist

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therapy eligibility criteria, only 48% were initiated during follow-up. **Conclusion:** In this real-world MASLD cohort, BMI change was the dominant modifiable predictor of both fibrosis and steatosis trajectory, while statin use and glycemic control did not independently predict outcomes. Baseline cirrhosis markedly amplified progression risk irrespective of BMI change or pharmacologic therapy but did not influence steatosis trajectory. Critically, BMI predicted FibroScan-derived fibrosis and steatosis measures, but not FIB-4 change, underscoring FIB-4's limitations as a dynamic monitoring tool in MASLD. Weight management remains the critical therapeutic target, with an urgent need to close the substantial GLP-1 treatment gap in this population.



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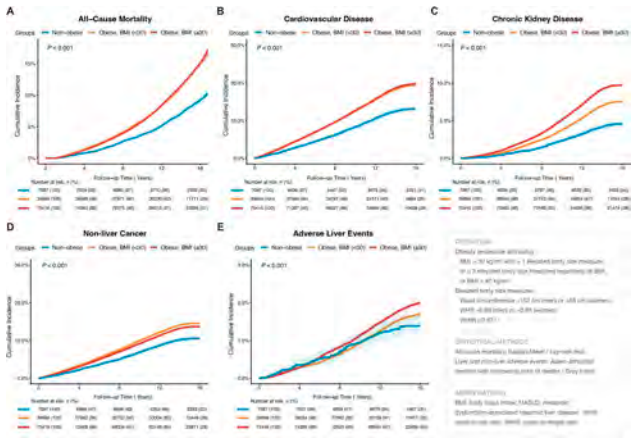
2517 | UPDATED OBESITY DEFINITION RECLASSIFIES INDIVIDUALS WITH MASLD AT RISK OF MORTALITY AND ADVERSE NONLIVER OUTCOMES

Xiaohan Qian[1] Ruoqi Zhou[2] Haotian Zhang[2] Mindie Nguyen[1] Yu Shi[2], [1]Stanford University Medical Center, [2]The First Affiliated Hospital, Zhejiang University School of Medicine

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) occurs across body mass index (BMI) categories, yet BMI inadequately captures visceral adiposity, limiting precise subtyping. An updated obesity definition incorporating waist circumference (WC), waist-to-hip ratio (WHR), and waist-to-height ratio (WHtR) beyond BMI has been proposed, but its prognostic significance in MASLD remains under-evaluated. **Methods:** This prospective cohort study included 122,202 participants with MASLD identified from the UK Biobank (2006–2010), classified as nonobese or obese by updated criteria (BMI $\geq$ 30 kg/m² with $\geq$ 1 elevated body size measure; $\geq$ 2 elevated body size measures regardless of BMI; or BMI $\geq$ 40 kg/m²; with elevated body size defined as WC > 102/88 cm [men/women], WHR > 0.90/0.85 [men/women], or WHtR $\geq$ 0.50. We stratified the obese group further by BMI cutoff of 30 kg/m²). We evaluated all-cause mortality, adverse liver (hepatocellular carcinoma, decompensated cirrhosis, liver transplantation, liver-related death) and nonliver (CVD, CKD and nonliver cancers) events. Subgroup analyses explored effect modification by age, sex, race, diabetes, cardiometabolic risks (CMRF), and FIB-4. Sensitivity analyses included Fine-Gray models and additional adjustments for FIB-4 and alcohol consumption, and exclusions for baseline adverse liver events, prior bariatric surgery, or anti-obesity medication use. **Results:** Updated obesity criteria reclassified 39,699 individuals (32.5%: 31.2% with BMI 25–29.9 kg/m²; 1.2% with BMI < 25 kg/m²) as obese. All-cause mortality per 1,000 person-years (PY) was lowest in nonobese but similar between the obese BMI < 30 kg/m² and $\geq$ 30 kg/m² groups (5.9, 9.6, 9.7). Similar patterns were observed for CVD (9.2, 14.2, 14.4), CKD (3.0, 5.1, 6.7), and nonliver cancers (9.8, 13.7, 12.1), but not for adverse liver events (0.8, 1.0, 1.2, respectively, all $P < 0.001$; Figure 1). In multivariable Cox models, compared to nonobese participants, both obese groups had higher risks of all-cause mortality (BMI < 30 kg/m²: aHR 1.13 [1.04–1.23]; BMI $\geq$ 30 kg/m²: aHR 1.25 [1.16–1.36]) and nonliver events (aHR 1.12 [1.05–1.20]; 1.24 [1.16–1.32] for CVD; 1.14 [1.01–1.28]; 1.39 [1.24–1.56] for CKD and 1.15 [1.07–1.23]; 1.14 [1.07–1.22] for nonliver cancers, respectively), though not adverse liver events (aHR 0.97 [0.77–1.22]; 1.10 [0.88–1.37]). Findings were largely consistent across subgroup and sensitivity analyses. **Conclusion:** Updated obesity criteria reclassified a substantial proportion (32.5%) of individuals with MASLD with BMI < 30 kg/m² as obese. The findings of higher rates of CVD, CKD, nonliver cancers and all-cause mortality in the newly classified obese individuals with MASLD as compared to the nonobese group lend support to the validity of the updated criteria. Its clinical application can help identify higher risk phenotype for monitoring and treatment.

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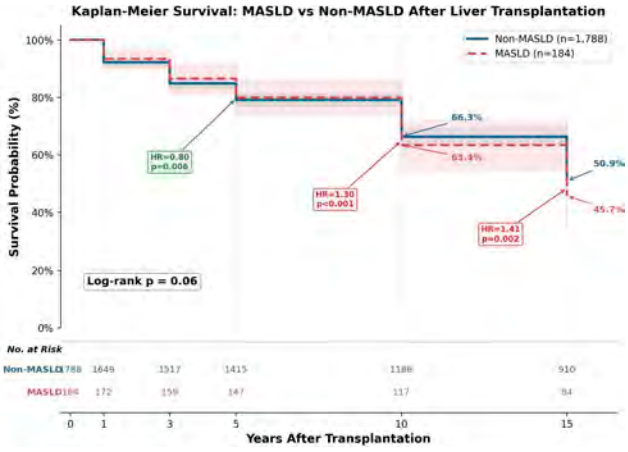


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2518 | ACCELERATED LATE MORTALITY AFTER LIVER TRANSPLANTATION FOR MASLD: TIME-VARYING HAZARD DRIVEN BY PROGRESSIVE DIABETIC BURDEN

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Background: Short-term post liver transplantation (LT) survival in metabolic dysfunction-associated steatotic liver disease (MASLD) recipients is comparable to other etiologies, but late mortality may increase as metabolic comorbidities, particularly diabetes, accumulate over time. We hypothesized that MASLD recipients exhibit accelerated late mortality due to progressive metabolic risk. **Methods:** We retrospectively studied adult first-time, single-organ LT recipients at a single academic transplant center from 2002–2016. The primary outcome was all-cause post-LT mortality. Piecewise Cox proportional hazards models were constructed at prespecified 5-, 10-, and 15-year cutpoints with covariate–time interaction terms to detect non-proportional hazards, and were fit for 0–10 year and >10-year intervals to identify temporal predictor transitions. Kaplan-Meier survival analysis with log-rank testing was performed. Claude (Anthropic) was used to assist with Python code development for data analysis; data analyses, result interpretation and conclusions were performed and verified by the investigators. **Results:** Among 1,972 LT recipients (184 MASLD, 1,788 non-MASLD) with a median follow-up of 11.1 years (maximum 23 years), MASLD recipients were significantly older, had higher BMI, and had more diabetes ($p < 0.001$). Overall Kaplan-Meier survival did not significantly differ (log-rank $p = 0.06$), masking an important late divergence (15-year survival: 44.1% vs. 50.9%). Piecewise analysis revealed a dynamic, non-linear hazard trajectory: mortality risk decreased after 5 years (HR 0.80, 95% CI 0.69–0.94, $p = 0.006$), then significantly increased after 10 years (HR 1.30, 95% CI 1.13–1.50, $p < 0.001$) and 15 years (HR 1.41, 95% CI 1.14–1.75, $p = 0.002$). Diabetes was the only covariate demonstrating significant time-interaction at all cutpoints, with a progressively strengthening deleterious effect (interaction HR: 1.31, $p = 0.029$ at 5 years; 1.34, $p = 0.028$ at 10 years; 1.75, $p = 0.006$ at 15 years). Period-specific models revealed a predictor transition: creatinine (HR 1.18, $p = 0.002$) and MELD (HR 0.98, $p = 0.002$) dominated 0–10 year mortality, whereas recipient age (HR 1.06, $p < 0.001$), BMI (HR 1.03, $p = 0.005$), and donor age (HR 1.01, $p = 0.019$) emerged as significant predictors beyond 10 years. **Conclusion:** This study demonstrates that post-LT mortality follows a non-linear, time-varying trajectory in which MASLD recipients experience accelerated late mortality linked to the progressive impact of diabetes. Standard analyses may miss this temporal shift. These findings support long-term metabolic surveillance extending beyond the first post-transplant decade and incorporation of time-varying risk into post-LT care models to improve late outcomes.



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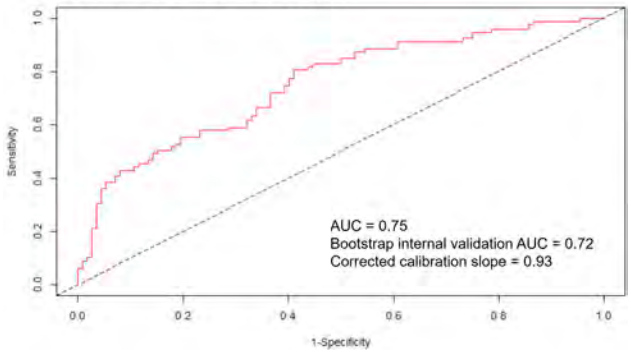
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2519 | AT-RISK FIBROSIS IS ASSOCIATED WITH ELEVATED CARDIOVASCULAR RISK IN MASLD: DEVELOPMENT AND INTERNAL VALIDATION OF A 5-YEAR RISK PREDICTION MODEL

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Background: Cardiovascular disease (CVD) is a leading cause of mortality in metabolic dysfunction–associated steatotic liver disease (MASLD). However, the relative contribution of MASLD disease characteristics to CVD risk remains uncertain, and existing CVD prediction models have suboptimal performance in MASLD. In patients with biopsy-proven MASLD in a hospital network-based cohort, we evaluated the associations of steatohepatitis and at-risk fibrosis (≥F2) with incident CVD and developed a 5-year CVD risk prediction model in patients with MASLD and at-risk fibrosis. **Methods:** We identified all adults with biopsy-confirmed MASLD and without baseline CVD in the Mass General Brigham health network, between 1999 and 2021, using a validated natural language processing algorithm. Cox proportional hazards models were used to evaluate the association between histologic steatohepatitis and at-risk fibrosis (≥F2) with incident CVD events (composite of hospitalization for myocardial infarction, heart failure, cerebrovascular disease, and peripheral vascular disease) as defined by ICD codes. Covariates included age, sex, diabetes, hypertension, aspirin use, statin use, insulin use, and smoking status. A 5-year CVD risk prediction model was then developed among patients with at-risk fibrosis using multivariable logistic regression and internally validated with bootstrap resampling. Model performance was assessed using area under the receiver operating characteristic curve (AUC) and calibration analyses. **Results:** A total of 1624 patients with biopsy-proven MASLD were identified, including 861 with steatohepatitis and 320 with at-risk fibrosis. There were 359 CVD events and a median follow-up of 3.3 years. In age-adjusted models, both steatohepatitis (aHR 1.22; 95% CI, 0.99-1.51; P = 0.06) and at-risk fibrosis (aHR 1.55; 95% CI, 1.23-1.96; P < .001) were associated with incident CVD. After multivariable adjustment, steatohepatitis was no longer associated with CVD risk, whereas at-risk fibrosis remained associated with incident CVD (aHR 1.43; 95% CI, 1.12-1.81; P = 0.003). The association of at-risk fibrosis and CVD strengthened after further adjustment for steatohepatitis (aHR, 1.51; 95% CI, 1.17-1.95; P = 0.001). A 5-year CVD risk prediction model containing the aforementioned covariates plus AST and ALT was tested in MASLD patients with at-risk fibrosis; the model demonstrated good discrimination (AUC 0.75) with bootstrap internal validation AUC of 0.72 and optimism-corrected calibration slope of 0.927. **Conclusion:** Among patients with biopsy-proven MASLD, at-risk fibrosis, but not steatohepatitis, was associated with future CVD events. A 5-year CVD risk prediction model in patients with MASLD and at-risk fibrosis demonstrated acceptable discrimination and calibration, supporting its potential utility for CVD risk stratification in this population. External validation is needed to confirm these findings.

Figure 1: Time-Dependent ROC Curve of 5-year CVD Risk Prediction Model in MASLD with At-Risk Fibrosis



Disclosures: Robert Wilechansky: Nothing to Disclose, Prasanna Challa: Nothing to Disclose, Marc Sherman: Nothing to Disclose, Tracey Simon: Nothing to Disclose.

2520 | ASSOCIATION OF STEATOTIC LIVER DISEASE WITH PERINATAL OUTCOMES: A SYSTEMATIC REVIEW AND META-ANALYSIS OF 75 MILLION PREGNANT INDIVIDUALS

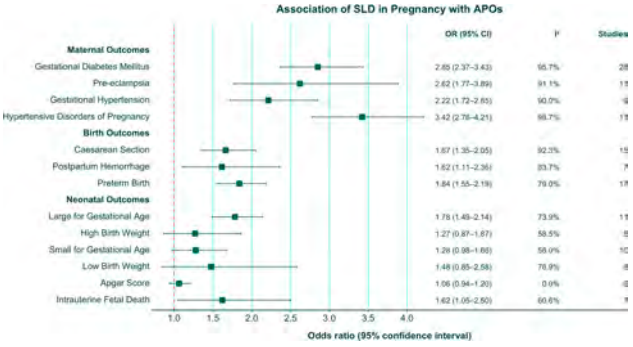
Jacqueline Slobin[1] Nina Rodriguez[1] Cecilia Katzenstein[1] Nadejda Capatina[2] Caroline Ovadia[3] Tatyana Kushner[4], [1]Icahn School of Medicine at Mount Sinai, [2]Guy's and St Thomas' NHS Foundation Trust, London, UK, [3]University of Edinburgh, Edinburgh, Scotland, UK, [4]Weill Cornell Medicine

Background: The prevalence of steatotic liver disease (SLD) in pregnancy has tripled over the past decade, affecting up to 18% of pregnant individuals. Prior studies report varied associations between SLD and adverse pregnancy outcomes (APOs). **Methods:** We conducted a systematic review and meta-analysis querying PubMed, Embase, and Web of Science for studies reporting APOs in individuals with SLD. Two independent reviewers screened titles and abstracts, full texts, and extracted data. Pooled prevalence and odds ratios

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(ORs) with 95% confidence intervals (CI) were calculated using random-effects models in R 4.6.0. **Results:** Thirty-one studies with 75 million pregnant individuals and 105,185 SLD cases were included. In 18 studies reporting prevalence, the pooled prevalence of SLD was 14.6% (95% CI: 11.0% – 19.0%). SLD was diagnosed by ultrasound (17), ICD codes (5), Hepatic Steatosis Index (5), Fibroscan (3), biopsy (1), and Fatty Liver Index (2). Studies were conducted in Asia (19), North America (5), Europe (4), Australia (2), and Africa (1). SLD was significantly associated with hypertensive disorders of pregnancy (OR 3.42, 95% CI 2.77–4.22), gestational diabetes (OR 2.85, 95% CI 2.38–3.41), preeclampsia (OR 2.62, 95% CI 1.81–3.80), and gestational hypertension (OR 2.22, 95% CI 1.78 – 2.75). Additionally, SLD was associated with cesarean delivery, postpartum hemorrhage, and preterm birth <37 weeks. Among neonatal outcomes, SLD was associated with large for gestational age, small for gestational age, and intrauterine fetal demise, but not low birth weight, high birth weight, or Apgar <7 at 5 minutes (Figure). In subgroup analyses of studies that diagnosed SLD with ultrasound or Fibroscan, associations with intrauterine fetal demise, small for gestational age, and postpartum hemorrhage were no longer significant, and the association with preeclampsia was attenuated. Associations with gestational diabetes (OR 2.92), preeclampsia (OR 3.01), and gestational hypertension (OR 2.79) were strongest in Asian cohorts. **Conclusion:** SLD in pregnancy was associated with increased risk of several APOs, with strongest associations for maternal outcomes and more variable findings for neonatal outcomes. These findings highlight the importance of screening for early gestational diabetes, potential aspirin use to decrease risk of associated preeclampsia, and counseling patients on elevated risk of APOs. Future directions are focused on completing an individual participant data meta-analysis to identify subgroups of patients with SLD at highest risk of APOs.



Disclosures: Jacqueline Slobin: Nothing to Disclose, Nina Rodriguez: Nothing to Disclose, Cecilia Katzenstein: Nothing to Disclose, Nadejda Capatina: Nothing to Disclose, Caroline Ovadia: Nothing to Disclose, Tatyana Kushner: Gilead: Grant/Research Support, Gilead: Advisor, GSK: Advisor, Eiger: Advisor, GSK: Consultant, Madrigal: Advisor, Ipsen: Advisor, Mirum: Advisor, Mirum: Grant/Research Support, Ipsen: Grant/Research Support.

2521 | METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE AND INCREASED CARDIOVASCULAR MORBIDITY IN ATRIAL FIBRILLATION

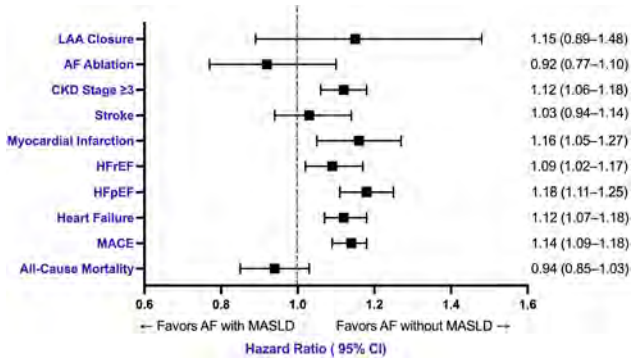
Pojsakorn Danpanichkul[1] Yanfang Pang[2] Nithila Sivakumar[1] Primrose Tothanarungroj[3] Ahmad Anouti[4] Matheus Henrique Gonçalves de Souza[5] Kwanjit Duangsonk[3] Omar Mousa[6] Thomas Cotter[7] Donghee Kim[8] Suthat Liangpunsakul[9] Chayakrit Krittanawong[10] Mazen Noureddin[11], [1]Texas Tech University Health Sciences Center, [2]Affiliated Hosp of Youjiang Medical University, Chiang Mai University, [3]Chiang Mai University, [4]University of Texas Southwestern, [5]Federal University of Rio de Janeiro, [6]Mayo Clinic, [7]Evidentis Clinical Research, [8]Stanford University School of Medicine, [9]Indiana University School of Medicine, Roudebush Veterans Administration Medical Center, [10]HumanX, [11]Houston Methodist Hospital, Houston Research Institute

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is associated with incident atrial fibrillation (AF), but its prognostic impact in patients with established AF is unclear. We evaluated whether concomitant MASLD is linked to adverse clinical outcomes in this population. **Methods:** We conducted a retrospective cohort study using the TriNetX Research Network. Adult patients with AF were classified as AF with or without MASLD. Cohorts were 1: 1 propensity score-matched for demographic, clinical, and laboratory variables. Outcomes were assessed over 3 years using Kaplan–Meier methods and Cox proportional hazards models to estimate hazard ratios (HRs) with 95% confidence intervals (CIs). **Results:** After matching, 19,154 patients were included (9,577 per group) with balanced baseline characteristics. All-cause mortality was similar between groups (HR 0.94, 95% CI 0.85–1.03). MASLD was associated with higher risk of major adverse cardiovascular events (MACE; HR 1.14, 95% CI 1.09–1.18), heart failure (HR 1.12, 95% CI 1.07–1.18), including HFpEF (HR 1.18, 95% CI 1.11–1.25) and HFrEF (HR 1.09, 95% CI 1.02–1.17), and myocardial infarction (HR 1.16, 95% CI 1.05–1.27). Stroke risk was similar (HR 1.03, 95% CI 0.94–1.14). MASLD was also associated with increased incidence of CKD stage ≥3 (HR 1.12, 95% CI 1.06–1.18). **Conclusion:** Among patients with established AF, concomitant MASLD is associated with higher risks of MACE, heart failure, myocardial

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infarction, and CKD progression, without increased all-cause mortality or stroke. These findings highlight MASLD as a clinically relevant modifier of cardiometabolic risk and support integrated cardio-hepatic risk management.



Disclosures: Pojsakorn Danpanichkul: Nothing to Disclose, Yanfang Pang: Nothing to Disclose, Nithila Sivakumar: Nothing to Disclose, Primrose Tothanarungroj: Nothing to Disclose, Ahmad Anouti: Nothing to Disclose, Matheus Henrique Gonçalves de Souza: Nothing to Disclose, Kwanjit Duangsonk: Nothing to Disclose, Omar Mousa: Nothing to Disclose, Thomas Cotter: Nothing to Disclose, Donghee Kim: Nothing to Disclose, Suthat Liangpunsakul: Durect Corporation: Consultant, Surrozen: Consultant, Korro Bio: Consultant, Durect Corporation: Consultant, Dimension Bio: Consultant, Chayakrit Krittanawong: Nothing to Disclose, Mazen Noureddin: Akero: Advisor, Alligos: Advisor, Altimmune: Advisor, AstraZeneca: Advisor, Boehringer Ingelheim: Advisor, Boston Pharma: Advisor, Cytodyn: Advisor, GSK: Advisor, Lilly: Advisor, Madrigal: Advisor, Merck: Advisor, Novo Nordisk: Advisor, Sagimet: Advisor, Terns: Advisor, Takeda: Advisor, Akero: Principal Investigator, Allergan: Principal Investigator, Altimmune: Principal Investigator, Boehringer Ingelheim: Principal Investigator, Bristol Myers Squibb: Principal Investigator, Boston Pharma: Principal Investigator, Conatus: Principal Investigator, Corcept: Principal Investigator, Galectin: Principal Investigator, Genfit: Principal Investigator, GSK: Principal Investigator, Kowa: Principal Investigator, Enanta: Principal Investigator, Madrigal: Principal Investigator, Lilly: Principal Investigator, Merck: Principal Investigator, Novartis: Principal Investigator, Novo Nordisk: Principal Investigator, Rivus: Principal Investigator, Shire: Principal Investigator, Takeda: Principal Investigator, Terns: Principal Investigator, Viking: Principal Investigator, Zydus: Principal Investigator, Rivus: Stock – privately held company, Cytodyn: Stock - publicly traded company, ChronWell: Stock – privately held company, Madrigal: Speakers bureau, Gilead Sciences: Principal Investigator, Akero: Consultant, Altimmune: Consultant, Alligos: Consultant, AstraZeneca: Consultant, BI: Consultant, Boston Pharma: Consultant, Curve bioscience: Consultant, Cytodyn: Consultant, GSK: Consultant, Histoindex: Consultant, Lilly: Consultant, Madrigal: Consultant, Merck: Consultant, Novo Nordisk: Consultant, Sagimet: Consultant, Terns: Consultant, Allergan: Grant/Research Support, Altimmune: Grant/Research Support, Akero: Grant/Research Support, BI: Grant/Research Support, BMS: Grant/Research Support, Boston Pharma: Grant/Research Support, Conatus: Grant/Research Support, Corcept: Grant/Research Support, Gilead: Grant/Research Support, Galectin: Grant/Research Support, Genfit: Grant/Research Support, GSK: Grant/Research Support, Kowa: Grant/Research Support, Enanta: Grant/Research Support, Madrigal: Grant/Research Support, Lilly: Grant/Research Support, Merck: Grant/Research Support, Novartis: Grant/Research Support, Novo Nordisk: Grant/Research Support, Rivus: Grant/Research Support, Shire: Grant/Research Support, Takeda: Grant/Research Support, Terns: Grant/Research Support, Viking: Grant/Research Support, Akero: Stock - publicly traded company, Zydus: Grant/Research Support, Takeda: Consultant, Madrigal: Speaking and Teaching, Novo Nordisk: Speaking and Teaching, HepaNova: Consultant, Daiichi Sankyo: Advisor, Daiichi Sankyo: Consultant, Curve Bioscience: Advisor, Curve Bioscience: Consultant, HepaNova: Advisor, HepaTx: Advisor, HepaTx: Consultant, HepaTx: Stock - publicly traded company, HepaTx: Stock - publicly traded company, HepaNova: Stock - publicly traded company, Histoindex: Advisor, Histoindex: Consultant, Kryia: Advisor, Kryia: Consultant, Kryia: Stock - publicly traded company, Neuraly: Advisor, Neuraly: Consultant, Novo Nordisk,: Consultant, OPKO: Advisor, OPKO: Consultant, OPKO: Stock - publicly traded company, OPKO: Stock - publicly traded company, OPKO: Stock - publicly traded company, Rivus: Advisor, Rivus: Consultant, Rivus: Stock - publicly traded company.

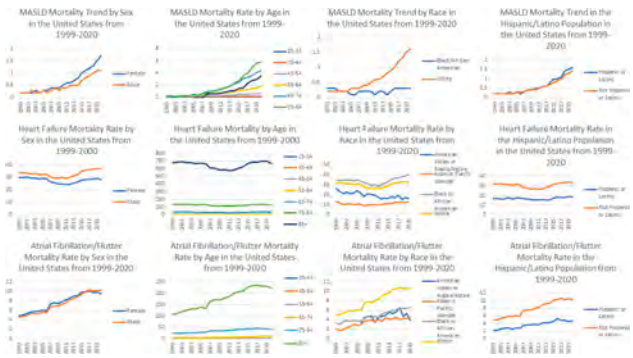
2522 | TRENDS IN MORTALITY FROM METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE, HEART FAILURE, AND ATRIAL FIBRILLATION IN THE UNITED STATES FROM 1999-2020

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD), heart failure (HF), and atrial fibrillation (AFib) are major contributors to morbidity and mortality in the United States, with growing evidence of shared cardiometabolic pathways linking these conditions. Despite this, population-level mortality trends and demographic disparities across all three diagnoses remain incompletely characterized. This study examined temporal patterns in MASLD, HF, and AFib mortality in the US from 1999 to 2020, with a focus on variation by sex, age, race, and Hispanic ethnicity. **Methods:** Death certificate data were obtained from the CDC Wide-Ranging Online Data for Epidemiological Research (CDC WONDER) database, which compiles underlying cause of death records for the US population from 1999 to 2020. MASLD-related deaths were captured using ICD-10 code K76.0 (fatty change of liver, not elsewhere classified). HF-related deaths were identified using ICD-10 code I50 (heart failure), and AFib-related deaths using code I48 (atrial fibrillation and flutter). Age-adjusted mortality rates (AAMRs) per 100,000 population, standardized to the year 2000 US population, were calculated stratified by race and sex. Crude mortality rates were used for age-group comparisons, and linear regression assessed temporal trends. **Results:** MASLD and AFib mortality rose consistently over the study period. HF mortality declined from 1999 through ~2012 before rebounding through 2020. Men had higher AAMRs for HF (36.9 vs. 28.0) and AFib (10.2 vs. 9.5) in 2020, while women had a higher MASLD AAMR (1.7 vs. 1.1). The 85+ age group recorded the highest crude rates for HF (663.9) and AFib (222.0); MASLD mortality peaked in the 75–84 group (5.8). Hispanic patients had modestly higher MASLD mortality (AAMR 1.6 vs. 1.4) but substantially lower HF (18.8 vs. 33.2) and AFib (4.7 vs. 10.3) rates compared to non-Hispanic patients. Black or African American patients had the highest AAMRs for HF (40.1) and AFib (6.7), while White patients had the highest MASLD AAMR (1.6). Asian or Pacific Islander patients had the lowest AAMRs across all three conditions. **Conclusion:** MASLD and AFib mortality rose substantially from 1999 to 2020, while HF exhibited a distinctive biphasic pattern. Pronounced disparities by sex, age, race, and Hispanic ethnicity were observed across all three conditions, underscoring the uneven distribution of cardiometabolic disease burden in the US population. The concurrent rise in MASLD mortality alongside persistent cardiovascular mortality from HF and AFib points to shared upstream risk factors and suggests that condition-specific management approaches may be insufficient. Coordinated strategies targeting the cardiometabolic continuum, with deliberate focus on groups bearing the greatest burden, are needed to address these converging trends.



Disclosures: Ahamed Lazim Vattoth: Nothing to Disclose, Adnan Said: Mallinckrodt: Speaking and Teaching, Madrigal Pharmaceuticals: Speaking and Teaching, Novo Nordisk: Speaking and Teaching, GIlead: Speaking and Teaching, Delcath: Consultant.

2523 | BEYOND FIB-4: A NON-FASTING MACHINE-LEARNING STRATEGY FOR FIRST-LINE TRIAGE OF SIGNIFICANT LIVER FIBROSIS

David Guardamino Ojeda[1] Marco Guardamino Ojeda[2] Marco Montoya Flores[3] Renato Luque[4] Samuel Lagos[2], [1]University of Miami / Jackson Memorial Hospital, [2]Universidad Nacional Mayor de San Marcos, [3]Universidad Peruana Cayetano Heredia, [4]Universidad Cientifica del Sur

Background: Scalable fibrosis risk stratification requires tools that are accurate, broadly applicable, and feasible without specialized testing conditions. Conventional first-line noninvasive fibrosis scores such as FIB-4 and APRI are easy to calculate but may have limited discrimination for fibrosis triage. We aimed to determine whether machine learning applied to routine clinical data could improve identification of significant liver fibrosis and support a practical non-fasting triage strategy. **Methods:** We analyzed adults from NHANES 2017–2023 with valid vibration-controlled transient elastography (VCTE). Significant fibrosis was defined as liver stiffness measurement (LSM) $\geq$7.0 kPa. Two predictive frameworks were developed: a universal non-fasting model using routine clinical variables and an extended fasting model including fasting glucose, insulin, HOMA-IR, LDL cholesterol, and triglycerides. XGBoost, Random Forest, and LASSO were trained using stratified 70/30 train-test splits and compared against FIB-4 and APRI in held-out test sets. We further assessed variable importance, decision-curve performance, calibration, and threshold-based triage characteristics. **Results:** The universal and extended cohorts included 10,900 and 6,363 participants, respectively,

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with significant fibrosis prevalence of 17.5% in both. Across both cohorts, machine-learning models consistently outperformed conventional fibrosis scores. In the universal cohort, XGBoost achieved the highest discrimination (AUC 0.784, 95% CI 0.763–0.806), followed by Random Forest (0.774) and LASSO (0.772), versus 0.599 for FIB-4 and 0.608 for APRI. In the fasting cohort, XGBoost again performed best (AUC 0.786, 95% CI 0.757–0.814), with near-identical performance relative to the universal model (ΔAUC = 0.002), indicating minimal incremental value from fasting biomarkers. Waist circumference and BMI were the dominant predictors, accounting for 46.4% of total XGBoost gain in the universal model. Decision-curve analysis showed that XGBoost provided the highest and most consistent net benefit across clinically relevant threshold probabilities. Threshold analysis identified a rule-out cutoff of 0.26 (sensitivity 91.2%, NPV 95.3%) and a rule-in cutoff of 0.66 (specificity 90.1%, PPV 49.2%), stratifying the test set into low-risk (32.9%; fibrosis rate 4.7%), indeterminate (51.0%; 15.7%), and high-risk (16.1%; 49.2%) groups. **Conclusion:** Machine learning applied to routine non-fasting clinical variables enables a pragmatic, population-level triage strategy for significant fibrosis that substantially outperforms conventional serum scores. The negligible performance gain from fasting biomarkers suggests that scalable first-line fibrosis triage may be achievable without fasting requirements, supporting staged downstream evaluation with elastography or adjunctive biomarker testing.



Disclosures: David Guardamino Ojeda: Nothing to Disclose, Marco Guardamino Ojeda: Nothing to Disclose, Marco Montoya Flores: Nothing to Disclose, Renato Luque: Nothing to Disclose, Samuel Lagos: Nothing to Disclose.

2525 | ASSOCIATION BETWEEN HEPATIC FIBROSIS AND CARDIOVASCULAR RISK BASED ON PREVENT RISK SCORE IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

Mohsen Merati[1] Janet Chu[2] Rena Fox[2] Max Goldman[3] Bilal Hameed[4] Mandana Khalili[2] Maria Tolentino[4] Nghiem Ha[2], [1]Sutter Health / University of California San Francisco, [2]University of California, San Francisco, [3]Kaiser Permanente, [4]University of California San Francisco (UCSF)

Background: Cardiovascular disease (CVD) remains the leading cause of mortality in metabolic dysfunction-associated steatotic liver disease (MASLD), underscoring the need for integrated cardiometabolic risk assessment. The American Heart Association recently introduced the PREVENT score as a tool for estimating CVD risk; however, its relationship with hepatic fibrosis and/or steatosis has not been well characterized. We aimed to evaluate the association between PREVENT risk categories and hepatic fibrosis and steatosis among patients with MASLD. **Methods:** We conducted a retrospective study of adult primary care patients with MASLD who had indeterminate or high-risk FIB-4 scores on initial screening and subsequently underwent vibration-controlled transient elastography (VCTE), with available PREVENT risk scores, between 2021 and 2026. PREVENT risk scores were calculated using clinical and laboratory values within 6 months of VCTE. PREVENT risk was categorized as low/intermediate (< 10%), high (10-20%), and very high (> 20%). Clinical and metabolic characteristics were compared across PREVENT risk groups (Table). Associations between PREVENT risk categories and liver fibrosis or steatosis were separately evaluated using univariable and multivariable logistic regression. **Results:** Among 96 patients, 52% were male with median age 66 years (59-73). Compared with patients with low/intermediate PREVENT risk, those with high/very high PREVENT risk were older ($p < 0.001$) and demonstrated greater MASLD severity, including greater FIB-4 scores (1.87 vs 1.50, $p = 0.03$), more severe CAP scores (274 vs 238, $p = 0.003$), and higher liver stiffness (6.3 vs 4.6 kPa, $p = 0.007$). Patients with high/very high PREVENT risk scores also had less favorable metabolic profiles, with significantly greater prevalence of hypertension (87% vs. 31%, $p < 0.001$), diabetes mellitus (69% vs. 35%, $p = 0.003$), and hyperlipidemia (89% vs. 58%, $p = 0.006$). In multivariable logistic regression adjusted for age, sex, body mass index, diabetes, and hyperlipidemia, higher PREVENT categories remained independently associated with advanced fibrosis (aOR 6.12, 95% CI 1.25-41.47) and severe steatosis (aOR 3.93, 95%CI 1.36-13.00) (Table). **Conclusion:** In patients with MASLD, higher PREVENT cardiovascular risk categories were independently associated with more advanced fibrosis stage and severe steatosis. These findings support the close interplay between hepatic and cardiovascular risk and highlight the potential value of integrating PREVENT and liver fibrosis assessment into MASLD screening and management strategies to identify high-risk patients who may benefit from earlier intervention and multidisciplinary care.

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Table. (a) Multivariable logistic regression analyses assessing the association of PREVENT with advanced fibrosis and severe steatosis. (b) Comparison of clinical characteristics by PREVENT risk category.

(a) Multivariable Logistic Regression Models for Advanced Fibrosis and Severe Steatosis

	Model for Advanced Fibrosis (F≥2)		Model for Severe Steatosis (CAP ≥300 dB/m)	
	OR	95% CI	OR	95% CI
Age (year)	0.92	0.81-1.05	0.98	0.89-1.08
Male sex	0.66	0.12-3.31	1.45	0.48-4.66
BMI (kg/m2)	**1.18**	**1.06-1.36**	**1.19**	**1.08-1.32**
T2DM (yes/no)	1.52	0.19-13.54	1.58	0.46-5.84
HLD (yes/no)	0.20	0.03-1.37	0.50	0.12-1.96
PREVENT category	**6.12**	**1.25-41.47**	**3.93**	**1.36-13.00**

(b)

		Overall	PREVENT Score (Categories) Low/Intermediate	High/Very High	*P*-value
		n=96	n=26	n=70	
Age (years)		66 (59-73)	60 (57-63)	68 (66-69)	**<0.001**
Sex (male, %)		50 (52%)	12 (46%)	38 (54%)	0.48
BMI (kg/m²)		30.6 (23.8-37.4)	28.9 (26.3-31.6)	31.2 (29.6-32.8)	0.14
Fibrosis Assessment					
CAP score (dB/m)		264 (202-326)	238 (220-256)	274 (258-290)	**0.003**
CAP categories (n, %)	Mild (237- 259)	47 (49%)	15 (58%)	32 (46%)	0.46
	Moderate (260-299)	22 (23%)	6 (23%)	16 (23%)	
	Severe (≥300)	27 (28%)	5 (20%)	22 (31%)	
Liver stiffness (kPa)		5.8 (1.6-10)	4.6 (4.0-5.1)	6.3 (5.2-7.4)	**0.007**
Fibrosis stages (n, %)	F1 (<8)	86 (90%)	22 (85%)	64 (91%)	0.45
	F≥2 (≥8)	10 (10%)	4 (15%)	6 (9%)	
FIB-4 at VCTE appointment		1.77 (1.59-1.94)	1.50 (1.22-1.77)	1.87 (1.66-2.09)	**0.03**
FIB-4 at initial cohort screening		1.92 (1.79-2.06)	1.79 (1.63-1.94)	1.98 (1.80-2.16)	0.11
Metabolic Assessment					
Total Cholesterol (mg/dL)		157 (117-197)	171 (155-186)	153 (143-162)	0.05
Consistently elevated Cholesterol within the last five years		30 (31%)	9 (35%)	21 (30%)	0.68
HDL (mg/dL)		49 (35-63)	58 (52-64)	45 (43-48)	**<0.001**
Consistently low HDL within the last five years		41 (43%)	5 (19%)	36 (51%)	**0.002**
Triglycerides (mg/dL)		128 (75)	102 (83-120)	138 (119-158)	**0.006**
Consistently elevated TG within the last five years		30 (32%)	4 (15%)	27 (39%)	**0.02**
Hypertension (on medication)		70 (72%)	8 (31%)	61 (87%)	**<0.001**
Diabetes mellitus (on medication)		57 (59%)	9 (35%)	48 (69%)	**0.003**
Hyperlipidemia (on medication)		77 (80%)	15 (58%)	62 (89%)	**0.006**
Incretin-based therapy		38 (40%)	8 (31%)	31 (44%)	0.23
Cardiovascular Risk Assessment					
PREVENT risk score (%)		15.9 (7.0-24.8)	6.6 (5.7-7.6)	19.4 (17.5-21.2)	**<0.001**
ASCVD risk score (%)		8.6 (3.7-13.5)	3.8 (3.3-4.4)	10.3 (9.2-11.4)	**<0.001**

Disclosures: Mohsen Merati: Nothing to Disclose, Janet Chu: Nothing to Disclose, Rena Fox: Novo Nordisk, Inc: Grant/Research Support, Novo Nordisk, Inc: Advisor, Gilead Sciences, Inc.: Grant/Research Support, Abbott: Consultant, Boehringer Ingelheim, Inc: Advisor, Max Goldman: Nothing to Disclose, Bilal Hameed: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Mandana Khalili: gilead sciences: Grant/Research Support, GSK pharmaceuticals: Consultant, Intercept pharmaceuticals: Grant/Research Support, Gilead Sciences Inc: Consultant, Resolution Therapeutics: Consultant, Maria Tolentino: Nothing to Disclose, Nghiem Ha: Nothing to Disclose.

2526 | ACT ON MASH – US DATA: A SURVEY OF AWARENESS, UNDERSTANDING, AND PERCEPTIONS OF MASLD AND MASH AMONG HEALTHCARE PROFESSIONALS

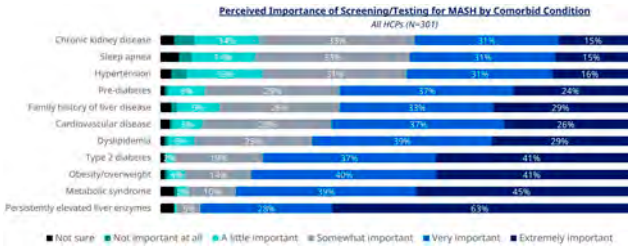
Husam Albarmawi[1] Nathalie Marcela Eklöf[2] Maximilian Kurt Jara[3] Jeff McIntyre[4] Marco Petti[1] Lauren Nephew[5], [1]Novo Nordisk Inc., USA, [2]Novo Nordisk, Denmark, [3]Novo Nordisk Inc., [4]Patient Advocate, Washington DC, USA, [5]Indiana University

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is highly prevalent in the United States (US); however, research remains limited regarding healthcare professionals' (HCPs) awareness, knowledge, and perceptions of MASLD and metabolic dysfunction-associated steatohepatitis (MASH), and the associations between these conditions and cardiometabolic comorbidities. **Methods:** In 2025, an online cross-sectional survey was conducted with healthcare professionals (HCPs) in multiple countries. This analysis includes data from respondents in the US only. HCPs were recruited through online panels and comprised gastroenterologists, hepatologists, endocrinologists, cardiologists, obesity specialists, primary care physicians, radiologists, and nurse practitioners/physician assistants (NPs/PAs). **Results:** In the US sample, 301 HCPs completed the survey. Respondents reported a mean of 19 years in clinical practice, and most worked in outpatient (72%) or hospital settings (24%). Most HCPs reported being "very" or "extremely" knowledgeable about MASLD (68%) and MASH (69%), with the highest ratings among gastroenterologists and hepatologists and the lowest among cardiologists. 56% of HCPs were "very" or "extremely" confident in identifying people at risk of MASH, ranging from 32% for radiologists to 95% for hepatologists. Agreement was high that MASH and MASLD increase the risk of cardiovascular events (88%) and that early diagnosis and management improve health outcomes (90%). Only 35% of HCPs reported changing MASH screening approach in the past year

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due to guidelines. Hepatologists, endocrinologists, and gastroenterologists were the most likely to include Fibrosis-4 (FIB-4) as part of their testing for MASH (65-74%) while cardiologists, NPs/PAs, and PCPs were the least likely (30-45%). HCPs estimated that nearly half of MASLD (49%) and MASH (46%) diagnoses followed incidental findings that first raised suspicion of steatotic liver disease. Following incidental detection of MASH or MASLD, the most common actions taken by HCPs were initiating lifestyle counseling related to diet or exercise (70%) and initiating non-invasive laboratory testing (70%). Radiologists reported incidental findings of MASLD and MASH in 25% and 17% of scans evaluated in a typical month, respectively. Perceived importance of screening patients with cardiometabolic conditions for MASH varied by condition; results are shown in the Figure. Finally, 30% reported that fear of stigmatizing patients with obesity was a barrier to screening. **Conclusion:** US HCPs reported strong knowledge of MASLD and MASH. However, variability in identifying people at risk of MASH, gaps in guideline-informed screening, and the high rate of incidental detection of MASLD and MASH highlight opportunities to strengthen health-professional education.



Disclosures: Husam Albarmawi: Novo Nordisk Inc.: Employee, Novo Nordisk Inc.: Stock - publicly traded company, Genentech Inc.: Employee, Genentech Inc.: Stock - publicly traded company, Nathalie Marcela Eklöf: Nothing to Disclose, Maximilian Kurt Jara: Nothing to Disclose, Jeff McIntyre: Nothing to Disclose, Marco Petti: Nothing to Disclose, Lauren Nephew: NovoNordisk: Consultant, NovoNordisk: Consultant, NovoNordisk: Consultant, NovoNordisk: Consultant.

2527 | METABOLIC-ASSOCIATED STEATOTIC LIVER DISEASE IN POLYCYSTIC OVARY SYNDROME AND LONG-TERM ADVERSE OUTCOMES: A PROPENSITY SCORE-MATCHED RETROSPECTIVE COHORT STUDY

Mythily Rao Ponaganti[1] Moksha Prasoona Avvaru[2] Ronald Blanco Montecino[1] Dharani Kunireddi[3] Suresh Kumar Nayudu[1] Naga Praneeth Vakkalagadda[4], [1]SBH Health System, [2]Harnett Health, [3]Clemson University, [4]University of Alabama at Birmingham

Background: Polycystic ovary syndrome (PCOS) and metabolic-associated steatotic liver disease (MASLD) frequently coexist in young women and share common pathophysiologic mechanisms. While both conditions independently have an elevated cardiometabolic risk, the long-term outcomes in PCOS women with MASLD are scarcely reported. We aimed to evaluate cardio-metabolic outcomes of MASLD and PCOS compared to PCOS alone. **Methods:** A retrospective cohort study was conducted using the TriNetX Global Collaborative Network. Women aged 18–50 years with a diagnosis of PCOS were identified and divided into two cohorts based on presence or absence of MASLD. Patients with pre-existing cardiovascular disease were excluded from both cohorts. Propensity score matching (1: 1) was performed to balance baseline characteristic and comorbidities. Outcomes of interest included Diabetes Mellitus [DM], Chronic Kidney Disease [CKD], Myocardial Infarction [MI], Cardiovascular revascularization procedures, ischemic stroke and all-cause mortality, assessed at 3-year, 5-year, and anytime follow-up intervals. Hazard ratios (HR) with 95% confidence intervals (CI) were calculated using Kaplan-Meier survival analysis. **Results:** After propensity score matching, 43,049 PCOS females with and without MASLD in each cohort were included for analyses. The PCOS + MASLD cohort had a mean age of 30.8 ± 8.0 years compared to 28.0 ± 7.2 years in the PCOS-only cohort with predominantly non hispanic [65% vs 60%] and white population [69% vs 58%] in both cohorts respectively. In PCOS females with MASLD the risk of incident DM was approximately doubled at all the follow up time points (HR 1.95-2.02) as shown in table1. Similarly, CKD risk was consistently elevated (HR 1.79-1.82) across all follow-up intervals whereas risk of ischemic stroke was significant starting at 5 years and over the entire follow-up period with a non-significant trend observed at 3 years. Notably, no cases of myocardial infarction or cardiac revascularization were observed in either cohort at any time point during follow-up but all-cause mortality was nearly twofold higher at 3 years and remained significantly elevated at 5 years and over the entire follow-up period. **Conclusion:** The presence of MASLD with PCOS significantly increased risks of DM, CKD, stroke and all-cause mortality compared to PCOS alone. On the other hand the absence of MI and cardiac revascularization events in this young, premenopausal female population suggests that the cardiovascular burden of MASLD in PCOS may initially manifest through cerebrovascular and metabolic pathways rather than acute coronary events. These findings highlight the importance of early identification and management of MASLD in women with PCOS to mitigate long-term risk and mortality.

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Table 1 showing outcomes in PCOS patients with and without MASLD

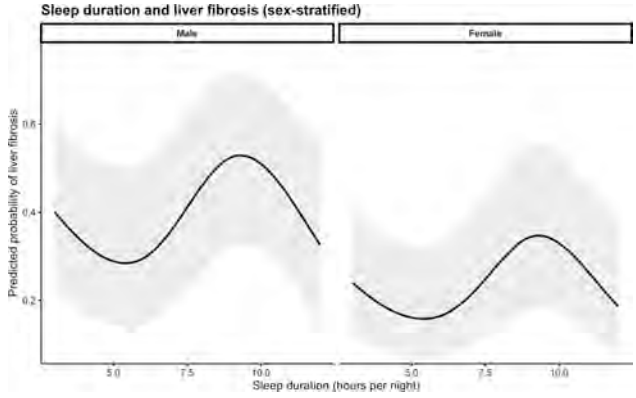
Outcome	Follow-up	HR (95% CI)	OR (95% CI)	p-value
Ischemic Stroke	3 Years	1.397 (0.982–1.986)	1.483 (1.043–2.108)	0.062
	5 Years	1.549 (1.138–2.108)	1.649 (1.211–2.245)	0.005
	Anytime	1.574 (1.201–2.062)	1.596 (1.218–2.091)	0.001
Diabetes Mellitus	3 Years	2.003 (1.888–2.125)	2.185 (2.056–2.322)	0.001
	5 Years	2.020 (1.916–2.131)	2.217 (2.098–2.343)	0.001
	Anytime	2.108 (2.009–2.212)	2.234 (2.124–2.349)	0.001
CKD	3 Years	1.819 (1.516–2.183)	1.934 (1.611–2.322)	0.001
	5 Years	1.814 (1.550–2.121)	1.932 (1.651–2.261)	0.001
	Anytime	1.789 (1.565–2.045)	1.806 (1.579–2.065)	0.001
All-Cause Mortality	3 Years	1.924 (1.495–2.476)	2.038 (1.583–2.625)	0.001
	5 Years	1.699 (1.371–2.105)	1.805 (1.456–2.238)	0.001
	Anytime	1.588 (1.318–1.913)	1.616 (1.341–1.947)	0.001

Disclosures: Mythily Rao Ponaganti: Nothing to Disclose, Moksha Prasoona Avvaru: Nothing to Disclose, Ronald Blanco Montecino: Nothing to Disclose, Dharani Kunireddi: Nothing to Disclose, Suresh Kumar Nayudu: Nothing to Disclose, Naga Praneeth Vakkalagadda: Nothing to Disclose.

2528 | SEX- AND BMI-MODIFIED NONLINEAR ASSOCIATION BETWEEN SLEEP DURATION AND LIVER FIBROSIS

Nazli Begum Ozturk[1] Matthew Solway[2] Ahmet Gurakar[3], [1]St. Louis University, [2]Henry Ford Hospital, [3]Johns Hopkins University

Background: Sleep duration is increasingly recognized as a modifiable determinant of metabolic dysfunction and systemic inflammation, both closely linked to chronic liver disease. However, population-level data evaluating its relationship with liver fibrosis and potential effect modification by demographic and metabolic factors remain limited. We examined the association between sleep duration and liver fibrosis in a nationally representative U.S. cohort. **Methods:** We analyzed 4653 adults from the National Health and Nutrition Examination Survey (NHANES). Survey-weighted generalized linear models accounting for complex sampling were used to evaluate associations with liver fibrosis. Sleep duration was modeled using restricted cubic splines (df = 3) to capture nonlinear effects. Multivariable models adjusted for age, sex, race/ethnicity, body mass index (BMI), diabetes, hypertension, alcohol use, smoking status, education, and poverty-income ratio (PIR). Effect modification by sex and BMI was assessed using interaction terms with Wald F-tests. A secondary analysis evaluated fibrosis severity as a continuous outcome. **Results:** In multivariable-adjusted models, metabolic risk factors were strongly associated with fibrosis. BMI was significantly associated with fibrosis (OR 1.13 per kg/m², 95% CI 1.10–1.16, $p < 0.001$), as was diabetes (OR 2.46, 95% CI 1.71–3.54, $p < 0.001$). Female sex was associated with lower odds of fibrosis compared with males (OR 0.48, 95% CI 0.32–0.72, $p = 0.001$). Higher socioeconomic status was inversely associated with fibrosis (PIR OR 0.88, 95% CI 0.78–0.99, $p = 0.038$). Sleep duration was not linearly associated with fibrosis (OR 0.98 per hour, 95% CI 0.95–1.02, $p = 0.29$). However, spline modeling demonstrated a nonlinear (U-shaped) association, with increased predicted fibrosis risk at both short and long sleep durations. There was significant effect modification by sex (Wald F = 7.07, p = 0.026) and BMI (Wald F = 8.01, p = 0.020), indicating that the association between sleep duration and fibrosis varies across demographic and metabolic subgroups. In secondary analysis, fibrosis severity was not significantly associated with sleep duration (β = -0.0004, $p = 0.74$), but remained strongly associated with BMI ($p < 0.001$) and diabetes ($p < 0.001$). Alcohol use, smoking status, hypertension, and education level were not independently associated with fibrosis after adjustment. **Conclusion:** In a nationally representative cohort of U.S. adults, sleep duration demonstrates a nonlinear association with liver fibrosis, with significant modification by both sex and BMI. While metabolic risk factors remain the dominant drivers of fibrosis, these findings highlight sleep as a potential behavioral correlate of liver disease risk, particularly in metabolically high-risk populations.



Disclosures: Nazli Begum Ozturk: Nothing to Disclose, Matthew Solway: Nothing to Disclose, Ahmet Gurakar:

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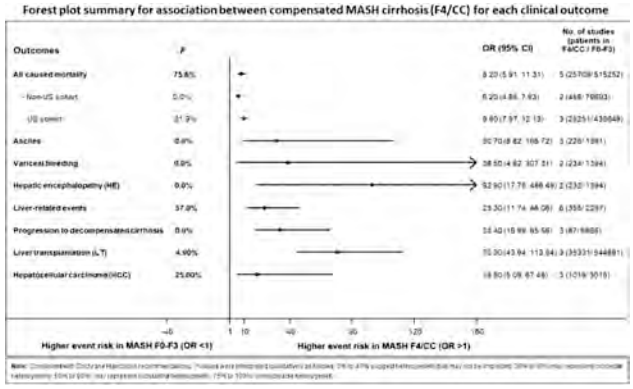
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DURECT: Grant/Research Support, Orphalan: Advisor, ETON: Advisor.

2529 | CLINICAL OUTCOMES IN MASH WITH COMPENSATED CIRRHOSIS: A SYSTEMATIC REVIEW AND META-ANALYSIS OF REAL-WORLD DATA

Ratree Sawangjit[1] Alexandre Watanabe[2] Saranrat Sadoyu[3] Jirawan Viengthoun[4] Muhammed Rashid[5] Prakash Navaratnam[6] Gail Fernandes[2] Yuzhi Xi[2] Zobair Younossi[7] Nathorn Chaiyakunapruk[5], [1]CTEBs RU, Faculty of Pharmacy, Mahasarakham University, Thailand, [2]Merck & Co., Inc., [3]Pakchongnana Hospital, Nakhon Ratchasima, Thailand, [4]Faculty of Pharmacy, Siam University, Thailand, [5]College of Pharmacy, University of Utah, Salt Lake City, Utah, USA, [6]DataMed solution, USA, [7]The Global NASH/MASH Council

Background: Metabolic dysfunction-associated steatohepatitis (MASH) with advanced fibrosis and compensated cirrhosis is a critical disease stage with substantial complications. However, real-world evidence on outcomes remain fragmented. This study aimed to synthesize evidence on clinical outcomes among adults with MASH and advanced fibrosis in real-world settings. **Methods:** A systematic literature review following PRISMA guidelines was conducted in PubMed, Embase, and Web of Science from inception to September 2025 (PROSPERO CRD420251168041). Observational studies evaluating risk of liver events and mortality among adults with MASH and advanced fibrosis (F3-F4) were included. Outcomes included all-cause mortality, hepatic decompensation events, and severe liver-related complications. Two reviewers independently reviewed studies and extracted the data. Random-effects meta-analyses generated odds ratios (ORs) with 95% confidence intervals (CIs). Heterogeneity was assessed using I^2 statistics and Cochran's chi-squared tests. **Results:** Thirteen cohort studies (733,561 participants) were included in the meta-analysis of compensated cirrhosis (F4/CC). All results are presented in Figure 1. Compared with non-cirrhotic (F0–F3), adults with F4/CC had significantly increased risks of all-cause mortality (OR 8.2; 95%CI: 5.9-11.3), with stronger association in US cohorts (OR 9.8; 95%CI: 7.9-12.1;). MASH with F4/CC was associated with a substantially higher risk of hepatic decompensation, including ascites (OR 30.7; 95%CI: 8.82-106.72), variceal bleeding (OR 38.5; 95%CI: 4.82-307.31), and hepatic encephalopathy (OR 92.9; 95%CI: 17.75-486.49). Consistent findings were observed in studies using composite measures of decompensation, including liver-related events (OR 23.3; 95%CI 11.7–46.1) and progression to decompensated cirrhosis (OR 33.4; 95%CI 17.0–65.6). Additionally, MASH F4/CC was associated with increased risks of severe liver-related complications, including liver transplantation (OR 70.3; 95%CI: 43.9-112.5) and hepatocellular carcinoma (OR 18.5; 95%CI: 5.1-67.5). However, these findings should be interpreted with caution because the number of studies directly comparing non-cirrhotic MASH with F4/CC was limited. **Conclusion:** In real-world practice, adults with F4/compensated MASH cirrhosis experience markedly increased risks of mortality, hepatic decompensation, and severe liver-related complications compared with non-cirrhotic populations. These patients have 8 times higher risk of mortality,23 times higher risk of liver events and 18 times higher risk of HCC. These findings highlight the importance of disease screening, the need for effective approved therapies for adults with compensated cirrhosis, and the need for further research into clinical outcomes and healthcare burden in this population.



Disclosures: Ratree Sawangjit: Nothing to Disclose, Alexandre Watanabe: Merck & Co., Inc.: Employee, Saranrat Sadoyu: Nothing to Disclose, Jirawan Viengthoun: Nothing to Disclose, Muhammed Rashid: Nothing to Disclose, Prakash Navaratnam: ALK Abello: Independent Contractor, Merck & Co: Independent Contractor, Stemline Therapeutics: Independent Contractor, Gail Fernandes: Merck & Co., Inc: Employee, Merck & Co., Inc: Stock - publicly traded company, Yuzhi Xi: Nothing to Disclose, Zobair Younossi: Zobair M. Younossi is a consultant or has received research: Consultant, madrigal: Grant/Research Support, Siemens: Research funding, GSK: Consultant, BI: Consultant, Sanofi: Research funding, Nathorn Chaiyakunapruk: Nothing to Disclose.

2530 | REAL-WORLD MEDICATION ADHERENCE AND PERSISTENCE TO RESMETIROM IN PATIENTS WITH MASH

Joaquim Fernandes[1] Raman Kumar[1] Sheila Thomas[1] Nipun Atreja[2] Blake Thomas[2] Francis Lobo[2], [1]CVS Healthspire Life Sciences Solutions, [2]Madrigal Pharmaceuticals

Background: Metabolic dysfunction–associated steatohepatitis (MASH), previously referred to as NASH/NAFLD, is a progressive liver disease with limited approved

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therapies and a growing clinical burden. In March 2024, resmetirom, a selective thyroid hormone receptor beta (THR-β) agonist, became the first FDA-approved liver-directed treatment for MASH. Given its recent introduction into clinical practice, evaluating real-world treatment patterns—particularly adherence and persistence—is critical to understanding its effectiveness and optimizing patient outcomes. **Methods:** This retrospective cohort study utilized large specialty and retail pharmacy fill data for resmetirom between March 14, 2024 and April 30, 2026. Inclusion criteria were patients (aged ≥18 years) with at least 2 prescription fills for resmetirom consistent with standard medication measures used to assess treatment compliance. Patients were considered persistent if they were actively filling resmetirom scripts at 6- and 12-months post initiation with a permissible 60/90-day fill grace period. Adherence was measured using a proportion of days covered (PDC), calculated from the first dispensation for 6 and 12 months. **Results:** At 6 months, 11,469 patients were assessed (mean age, 57.5 years; 56.1% female). Persistence was 89.4% and 94.5% using 60- and 90-day grace periods, respectively, with a mean PDC of 85.6% (75.9% meeting PDC ≥80%). At 12 months, 6,898 patients were assessed (mean age, 57.1 years; 56.4% female). Persistence was 72.4% and 75.8%, with a mean PDC of 76.4% (61.7% meeting PDC ≥80%). **Conclusion:** In this large real-world cohort of patients with MASH, adherence and persistence to resmetirom were high at 6 months and 12 months as indicated by both persistence and PDCs. Findings indicate the need for continued monitoring and the need for targeted strategies to sustain long-term treatment use and optimize clinical outcomes. Further research is warranted to identify factors influencing long-term persistence and to evaluate the clinical outcomes associated with high adherence to resmetirom.Sponsorships: Madrigal Pharmaceuticals.

Disclosures: Joaquim Fernandes: CVS Health: Employee, Novavax: Stock - publicly traded company, AstraZeneca: Stock - publicly traded company, Insmead: Stock - publicly traded company, Raman Kumar: Nothing to Disclose, Sheila Thomas: Jazz Pharmaceuticals: Former employee, Nipun Atreja: madrigal pharmaceuticals: Employee, Blake Thomas: Madrigal Pharmaceuticals: Employee, Francis Lobo: Nothing to Disclose.

2531 | HIDDEN BURDEN OF METABOLIC DYSFUNCTION–ASSOCIATED STEATOTIC LIVER DISEASE IN CARIBBEAN POPULATIONS: A SYSTEMATIC REVIEW AND META-ANALYSIS

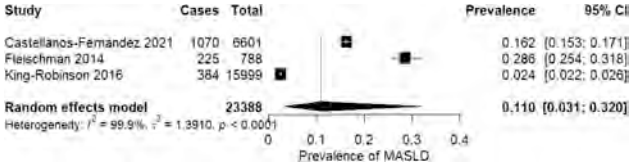
Francesca Farina[1] Aurgho Datta[1] Adam Hassan[1] Thierry Fotsing Tadjo[1] Genevieve Gore[2] Jihoon Lim[3] Felice Cinque[4] Sherrydene Barrett[5] Harold Munnings[6] Trevor Murphy[7] Giada Sebastiani[2], [1]McGill University Health Centre, [2]McGill University, [3]Research Institute of the McGill University Health Centre, [4]University of Milan, [5]University Hospital of the West Indies (UHWI), [6]The Centre for Digestive Health, Bahamas, [7]University of the West Indies

Background: Caribbean populations face a disproportionately high burden of obesity, diabetes, and other cardiometabolic risk factors, along with potential genetic susceptibility, all strongly associated with metabolic dysfunction-associated steatotic liver disease (MASLD). However, the epidemiology of MASLD in this region remains poorly defined, with fragmented data across island nations and limited access to contemporary diagnostic tools. We conducted a systematic review and meta-analysis to estimate the prevalence of MASLD in Caribbean populations and characterize associated metabolic comorbidities. **Methods:** We systematically searched studies reporting MASLD prevalence and metabolic risk factors in Caribbean populations. Among 4,425 records screened, 11 studies met inclusion criteria and were included in the final meta-analysis. Pooled prevalence estimates with 95% confidence intervals (CI) were calculated using random-effects models. MASLD prevalence was derived from studies reporting hepatic steatosis prevalence, while metabolic comorbidities were pooled from all eligible studies reporting risk factor data among individuals with MASLD. Between-study heterogeneity was assessed using the I^2 statistic. **Results:** MASLD prevalence was estimated from three studies including 2,088 individuals, yielding a pooled prevalence of 11.0% (95% CI 3.1%–32.0%) with marked heterogeneity ($I^2 = 99.9\%$). Diagnostic approaches varied substantially and included abdominal ultrasound, computed tomography, and liver biopsy in selected cohorts. Among 23,388 individuals with MASLD, metabolic comorbidities were highly prevalent: obesity 48.0% (95% CI 33.9%–62.3%; $I^2 = 85.9\%$), hypertriglyceridemia 55.9% (95% CI 31.1%–78.0%; $I^2 = 93.2\%$), dyslipidemia 43.1% (95% CI 21.2%–68.2%; $I^2 = 95.0\%$), hypertension 32.5% (95% CI 18.1%–51.2%; $I^2 = 91.0\%$), and type 2 diabetes 25.6% (95% CI 15.3%–39.6%; $I^2 = 92.4\%$). Liver biochemistry was sparsely reported, with only three studies (n = 180) contributing data on aminotransferases. Pooled mean ALT was 50.4 U/L (95% CI 14.6–173.9; $I^2 = 99.0\%$) and AST 44.4 U/L (95% CI 11.9–165.4; $I^2 = 99.4\%$). **Conclusion:** Despite a high burden of obesity, diabetes, and other cardiometabolic risk factors, reported MASLD prevalence in Caribbean populations remains substantially lower than global estimates, strongly suggesting under-recognition and underdiagnosis. This discrepancy likely reflects reliance on older studies, heterogeneous and insensitive diagnostic methods, and limited

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access to contemporary non-invasive liver assessment. These findings highlight a major unmet public health need and underscore the urgency of standardized MASLD definitions, contemporary population-based epidemiological studies, and integrated liver-metabolic care pathways tailored to Caribbean populations.



Disclosures: Francesca Farina: Nothing to Disclose, Aurgho Datta: Nothing to Disclose, Adam Hassan: Nothing to Disclose, Thierry Fotsing Tadjo: Nothing to Disclose, Genevieve Gore: Nothing to Disclose, Jihoon Lim: Nothing to Disclose, Felice Cinque: Nothing to Disclose, Sherrydene Barrett: Nothing to Disclose, Harold Munnings: Nothing to Disclose, Trevor Murphy: Nothing to Disclose, Giada Sebastiani: Novo Nordisk: Consultant, Abbvie: Speaking and Teaching, Merck: Consultant, Gilead: Speaking and Teaching, Eli Lilly: Consultant, GSK: Advisor, Novo Nordisk: Consultant, Novo Nordisk: Grant/Research Support, Lupin: Speaking and Teaching, Gilead: Advisor, Boheringer Ingelheim: Speaking and Teaching, Echosens: Advisor.

2532 | RECLASSIFYING OBESITY USING THE LANCET COMMISSION FRAMEWORK RESOLVES THE OBESITY-CARDIOVASCULAR MORTALITY PARADOX IN MASLD

Guy Loic Nguefang[1] Sarpong Boateng[2] Christian Akem Dimala[3] Solomon Gyabaah[4] Yazan Al Ajlouni[5] chimezirim ezeano[6] Khaled Halwani Halwani[7] Ulrick Sidney Kanmounye[8] Nso Nso[9] Basile Njei[10], [1]Texas Tech University Health Sciences Center, [2]Yale New Haven Health, Bridgeport Hospital, [3]University of Texas Southwestern Medical Center, [4]Komfo Anokye Teaching Hospital, [5]Montefiore Medical Center/Albert Einstein College of Medicine, [6]Advocate Aurora Healthcare, [7]Yale University School of Medicine, [8]Research Department, Association of Future African Neurosurgeons, [9]Division of Cardiology, University of Chicago, [10]Yale University

Background: In MASLD, lower BMI has been paradoxically associated with higher cardiovascular (CVD) mortality (obesity paradox). This reflects BMI's inability to distinguish sarcopenia and visceral adiposity from metabolically healthy obesity. We evaluated whether the 2025 Lancet Commission obesity framework resolves this paradox in a nationally representative U.S. MASLD cohort. **Methods:** Adults with MASLD were identified from NHANES III (1988–1994), linked to National Death Index mortality data through December 2019. MASLD required hepatic steatosis on ultrasound plus ≥1 cardiometabolic criterion. Participants were classified by traditional BMI categories and the Lancet framework: Non-Obese (BMI < 30), Preclinical Obesity (BMI ≥ 30, no obesity-related complications), and Clinical Obesity (BMI ≥ 30 plus ≥ 1 complication: hypertension, type 2 diabetes, renal dysfunction, ECG abnormality, or functional limitation). Complex-survey-weighted Cox proportional hazards models estimated adjusted HRs for CVD mortality. Subgroup analyses by sex and age (<65 vs. ≥65 years) and Fine-Gray competing risks regression were performed. **Results:** A total of 1721 participants (weighted 13 million US adults) met MASLD criteria. Using the Lancet framework, we identified 60.3% non-obese, 11.3% preclinical obesity, and 28.4% clinical obesity. Clinical obesity carried the highest burden of comorbidity: hypertension (22.8%), diabetes (27.7%), and functional limitations (47.1%). Over 30.5 years, 1,720 deaths and 1,089 CVD deaths occurred. Traditional BMI categories were not associated with cardiovascular mortality, and overweight showed a non-significant trend toward lower risk (HR 0.82; 95% CI 0.66-1.01; p = 0.062). With the Lancet framework, clinical obesity independently predicted 27% higher CVD mortality vs. non-obese (HR 1.27; 95% CI 1.00–1.60; p = 0.048), while preclinical obesity had neutral risk (HR 1.01; 95% CI 0.80-1.27; p = 0.95). Among adults <65 years, clinical obesity conferred a 38% higher CVD mortality risk (HR 1.38; 95% CI 1.10–1.74; p = 0.006). After competing risks analysis, the association between clinical obesity and CVD mortality was attenuated (HR 1.06; 95% CI 0.92–1.23; p = 0.399). Fine-Gray competing risks regression accounting for non-CVD deaths attenuated the clinical obesity-CVD mortality association (HR 1.06; 95% CI 0.92–1.23; p = 0.399). **Conclusion:** Staging obesity using the Lancet Commission framework attenuates the obesity-CVD mortality paradox in MASLD and identifies clinical obesity as a high-risk phenotype. Cardiovascular risk appears to be driven by obesity-related complications and metabolic dysfunction rather than BMI categories. These findings underscore the importance of transitioning from anthropometry-focused paradigms to complication-focused obesity staging to improve CVD risk stratification in MASLD.

Table Head-to-head comparison: traditional BMI vs. Lancet obesity framework on CVD mortality
Fully adjusted Cox proportional hazards models†

Predictor	Adjusted HR (95% CI)	P-value
Model A — Traditional BMI categories		
Normal weight (reference)	1.00	—
Overweight	0.82 (0.66–1.01)	0.062
Class I obesity	0.94 (0.72–1.22)	0.616
Class II obesity	1.36 (0.97–1.91)	0.071
Class III obesity	1.37 (0.92–2.05)	0.119
Model B — Lancet obesity framework		
Non-obese (reference)	1.00	—
Preclinical obesity	1.01 (0.80–1.27)	0.950
Clinical obesity	1.27 (1.00–1.60)*	0.048*

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2533 | LIMITED ADOPTION OF MET-ALD AS A DIAGNOSIS FOR LIVER TRANSPLANTATION

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Background: Metabolic and alcohol-related liver disease (Met-ALD) was formally introduced in 2023 with the intention of highlighting a clinically distinct subgroup of individuals with steatotic liver disease (SLD), at the intersection of metabolic dysfunction-associated steatotic liver disease (MASLD) and alcohol-related liver disease (ALD). In 2024, the diagnosis of Met-ALD was incorporated into the UNOS registry to better understand outcomes in this subpopulation. In addition, NASH was re-categorized to MASH. In this study, we seek to examine the use of Met-ALD as a primary diagnosis code since its implementation. **Methods:** We analyzed the UNOS transplant registry to review adult liver registrations and transplants 1 year before (pre-diagnosis update) and after (post-diagnosis update) the inclusion of Met-ALD as a diagnosis code on 10/10/2024. Demographic data, primary and secondary diagnosis at time of listing and transplant, and cardiometabolic risk factors including body mass index (BMI) and presence of diabetes were collected. We compared two scenarios: (1) the actual use of the Met-ALD diagnosis with (2) a previously validated estimate of Met-ALD (henceforth called Met-ALD*, *Hepatology* 2025). Met-ALD* was defined by (1) a primary diagnosis of MASH and secondary diagnosis of ALD (or vice versa), or (2) a diagnosis of ALD with diabetes or obesity, adjusted for the severity of ascites. **Results:** During the study period, there were a total of 29,927 new registrations (14,569 before, 15,358 after the diagnosis update) and 22,313 transplants (10,780 before, 11,533 after the diagnosis update). Met-ALD was the primary diagnosis for 4.5% (N = 687) of registrations and 3.9% (N = 419) of transplants. However, using the surrogate definitions (Met-ALD*), 18.5% (N = 2,844) of registrations and 18.4% (N = 2,117) of transplants during the same period were estimated to have Met-ALD* (*Figure 1*). Median MELD of registrations and transplants was higher in the Met-ALD* population (23 and 27, respectively) than the observed Met-ALD population (21 and 26, respectively). The Met-ALD* group included a higher proportion of men and individuals with diabetes than the Met-ALD group. **Conclusion:** In the year following its incorporation into the UNOS registry, Met-ALD has been underutilized as a primary diagnosis for registration or transplantation. The estimated prevalence of Met-ALD among transplant candidates and recipients is significantly higher than the observed use of Met-ALD as a diagnosis. Met-ALD may be underrecognized in men and patients with diabetes. The lower-than-expected usage of the Met-ALD diagnosis may be due to (1) limited awareness of the updated diagnosis codes and (2) the challenge of accurately distinguishing among MASLD, Met-ALD, and ALD in the context of cirrhosis. The transplant community would benefit from increased education and awareness regarding the diagnosis of Met-ALD.

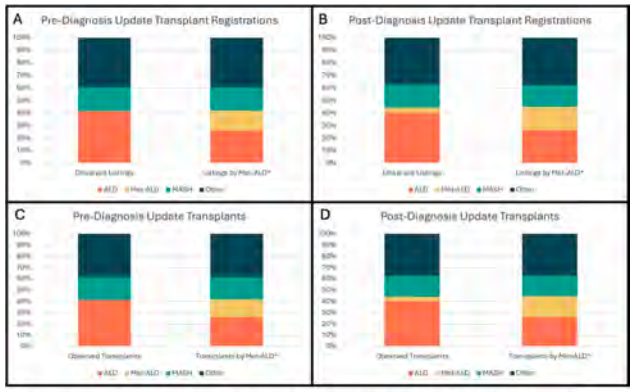


Figure 1: Comparison of percentages of transplant registrations and transplants in the pre- and post-diagnosis update (addition of Met-ALD as a diagnosis code) periods. Met-ALD* represents the use of a previously validated estimate of the Met-ALD diagnosis.

Disclosures: Previn Ganesan: Nothing to Disclose, Scott Biggins: Nothing to Disclose, Kymberly Watt: Madrigal: Stock - publicly traded company, Viking: Stock - publicly traded company, Novo Nordisk: Speaking and Teaching, Neil Shah: GSK: Consultant, GSK: Consultant, Ipsen: Consultant, Ipsen: Consultant, GSK: Consultant, GSK: Consultant, Ipsen: Consultant, Ipsen: Consultant, Allison Kwong: Nothing to Disclose.

2534 | THE MULTI-DOMAIN FRAMEWORK OF METABOLIC SYNDROME MYOPATHY IDENTIFIES WORSE HEALTH-RELATED QUALITY OF LIFE (HRQOL) AMONG PATIENTS WITH MASLD

Melinda Wang[1] Dorothea Kent[1] Fawzy Barry[1] Lisa Catalli[2] Jennifer Lai[1], [1]UCSF, [2]University of California, San Francisco

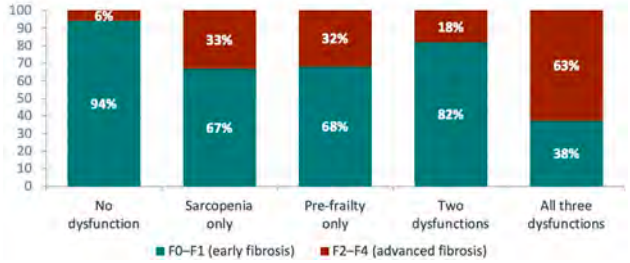
Background: Metabolic syndrome myopathy, dysfunction in three domains: muscle mass, quality, and function, is common among MASLD patients. Risk factors associated with metabolic syndrome myopathy may

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identify vulnerable patients who may benefit from targeted intervention. We aimed to characterize phenotypes of metabolic syndrome myopathy and evaluate its relationship with HrQoL. **Methods:** Adults with MASLD by ICD-10 code were enrolled in the single-center prospective cohort between October 2025 and May 2026. All participants underwent fibroscan (stiffness and CAP), bioelectrical impedance analysis (BIA; Quantum VII, RJL Systems), Liver Frailty Index (LFI), and patient-reported outcomes including PROMIS-29 and Duke Activity Status Index (DASI). Dietary quality was assessed by ASA24 or DietID® and scored using the Healthy Eating Index (HEI-2020). Metabolic syndrome myopathy domains were defined as: sarcopenia (skeletal muscle index $<9.2 kg/m^2$ in men, <7.4 kg/m^2 in women), myosteatosis (phase angle <5.6 for men, <5.4 for women), and/or physical pre-frailty (LFI ≥ 3.2). Binary covariates were defined as advanced fibrosis (F0-F1 vs F2-F4 by fibroscan), adequate exercise capacity (DASI ≥ 34 vs <34) and good dietary quality (HEI2020 ≥ 80 vs <80). Mann-Whitney U tests assessed number of domain dysfunctions across binary exposures. Multivariable logistic regression analyzed odds of worse general health by phenotype. **Results:** Among 100 adults, median age was 54 (IQR 46-62), 48% were women, 36% were non-White, 70 (75%) had adequate exercise capacity, 28 (38%) had good dietary quality, and 76% had F0-F1 fibrosis; 45% had sarcopenia, 49% were pre-frail, and 16% had myosteatosis. Overall, 40% met criteria for dysfunction in one domain, 22% in two, and 9% in all three domains. Phenotype distribution differed significantly by fibrosis group ($p=0.005$, Figure A). Each additional domain dysfunction was associated with 2.20 times greater odds of poor general health (OR 2.20, 95%CI 1.11-4.35, $p=0.02$). **Conclusion:** Dysfunction in domains of metabolic syndrome myopathy demonstrate variability across fibrosis stages and are associated with worse HrQoL. The multidomain metabolic syndrome myopathy framework identifies MASLD patients with worse HrQoL and should be used when assessing muscle health among adults with MASLD.

Figure. Metabolic Syndrome Myopathy Phenotype by Domain Dysfunction by fibrosis stage



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2535 | ASSOCIATION BETWEEN FOOD INSECURITY AND METABOLIC DYSFUNCTION–ASSOCIATED STEATOTIC LIVER DISEASE (MASLD)

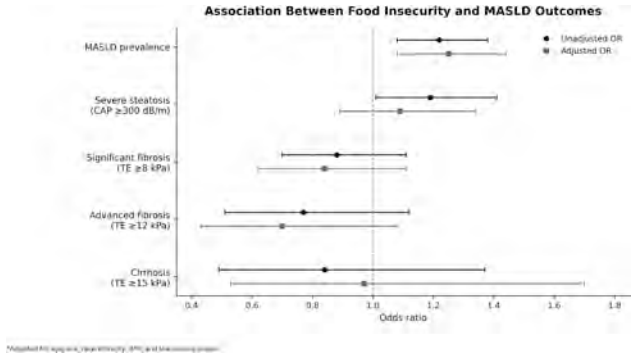
Nishat Anjum Shaik[1] Mohammed Rifat Shaik[2] Vincenzo Cardinale[3] Lewis Frey[3] Wing-Kin Syn[4], [1]SSM Health/Saint Louis University, [2]National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, [3]Division of Gastroenterology, Department of Internal Medicine, SSM Health/Saint Louis University, [4]Saint Louis University School of Medicine

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) affects over one-third of U.S. adults and is projected to become the leading indication for liver transplantation. Food insecurity affects ~12.8% of U.S. households and promotes reliance on energy-dense, nutrient-poor diets that contribute to visceral adiposity and insulin resistance. Prior studies linking food insecurity to MASLD have largely relied on serological fibrosis indices but its independent contribution across the full disease spectrum from steatosis to fibrosis remains unclear. We aimed to determine whether food insecurity is independently associated with MASLD prevalence, severe steatosis, and liver fibrosis severity among U.S. adults. **Methods:** We conducted a cross-sectional analysis of adults aged ≥ 18 years from NHANES 2017–2020 with complete transient elastography (TE) and food security data. MASLD was defined as controlled attenuation parameter (CAP) ≥ 263 dB/m with at least one cardiometabolic risk factor and no other chronic liver disease etiology. Food insecurity was assessed using the USDA Household Food Security Survey Module. Primary outcomes were MASLD prevalence, severe steatosis (CAP ≥ 300 dB/m), and elevated liver stiffness at multiple thresholds (LSM ≥ 8, ≥ 12, and ≥ 15 kPa). Multivariable logistic regression models adjusted for age, sex, race/ethnicity, BMI, and low-income status. **Results:** Among 3,459 eligible adults, 804 (23.2%) were food insecure. Food-insecure adults were younger (48.8 vs. 53.4 years, $p<0.001$), more likely female (53.1% vs. 46.5%, $p=0.001$), had higher BMI (34.9 vs. 33.2 kg/m², $p<0.001$), and were more likely to have low income (60.9% vs. 22.4%, $p<0.001$). Food insecurity was independently associated with MASLD prevalence after adjustment for age, sex, race/ethnicity, and low-income status (OR 1.25, 95% CI 1.08–1.44, $p=0.003$). Among adults with MASLD, food insecurity was associated with severe steatosis in unadjusted analysis (OR 1.19, 95% CI

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1.01–1.41, p = 0.040), but this was attenuated after adjustment (OR 1.09, 95% CI 0.89–1.34, p = 0.415). Food insecurity was not associated with elevated liver stiffness at any threshold: TE ≥ 8 kPa (adjusted OR 0.84, 95% CI 0.62–1.11), TE ≥ 12 kPa (adjusted OR 0.70, 95% CI 0.43–1.08), or TE ≥ 15 kPa (adjusted OR 0.97, 95% CI 0.53–1.70). Sensitivity analyses using an alternative MASLD definition (CAP ≥ 248 dB/m) yielded consistent results. **Conclusion:** Food insecurity is independently associated with MASLD prevalence and demonstrates a signal toward increased steatosis severity but is not independently associated with liver fibrosis. These findings suggest that food insecurity primarily drives MASLD burden through adiposity and dietary quality rather than directly promoting fibrosis progression. Food insecurity may represent a modifiable upstream determinant of MASLD, supporting integration of food security screening into hepatology practice.



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2536 | THE MASH CIRRHOSIS EVIDENCE GAP: A DECADE-LONG CLINICALTRIALS.GOV ANALYSIS

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Background: Despite FDA approvals of resmetirom and semaglutide, both medications are available only to adults with noncirrhotic MASH and significant fibrosis (F2-F3). MASH cirrhosis patients, who carry the highest liver-related morbidity and mortality, lack approved treatments due to this evidence gap. It is unclear whether this gap reflects systematic underrepresentation in the MASH trial pipeline. We evaluated the inclusion of patients with cirrhosis across a decade of MASH drug trials. **Methods:** We queried ClinicalTrials.gov for trials initiated from 2015 to 2025 that referenced MASH, MASLD, NASH, or NAFLD. Eligibility criteria and title were programmatically classified as cirrhosis-targeted, cirrhosis-allowed, F2–F3 only, cirrhosis-excluded (explicit exclusion of cirrhosis, Child-Pugh B/C, decompensation, or portal hypertension), or unspecified. Compared with 2015–2023, trends in 2024–2025 were analyzed by start year, phase, mechanism, and sponsor type. **Results:** Among 470 MASH trials enrolling 75,677 participants, only 28 (6.0%) targeted cirrhosis, while 236 (50.2%) explicitly excluded cirrhosis, and 15 (3.2%) restricted enrollments to F2-F3. In the post-resmetirom era, cirrhosis-targeted trials remained low (annual range: 1.7-16.1%), while the proportion of patients explicitly excluded for cirrhosis increased (69.9% vs. 49.9%) (Figures A and B). Despite 47 Phase 3 trials, only 5 (10.6%) targeted cirrhosis and 27 (57.4%) excluded it. Trials targeting cirrhosis accounted for 10.6% of total planned enrollment (8,021/75,677). Exclusion was most pronounced among PPAR agonists (0% cirrhosis-targeted), GLP-1 RAs (4%), SGLT2 inhibitors (7%), and GLP-1/glucagon dual agonists (10%); antifibrotic biologics (50%), FGF21 analogs (42%), and ACC inhibitors (36%) had higher cirrhosis expression (Figure C). Industry sponsored 61.1% of trials; 12.6% were terminated/withdrawn. **Conclusion:** Despite rapid therapeutic progress in noncirrhotic MASH, patients with MASH cirrhosis remain largely excluded from drug development. Across 470 interventional trials, cirrhosis-targeted studies represented only 6% of trials and 11% of planned enrollment, with exclusion increasing after the first MASH approval. These findings identify a widening therapeutic evidence gap and support urgent regulatory, sponsor, and protocol-design strategies to responsibly extend MASH therapeutics to compensated cirrhosis, with carefully designed pathways for decompensated populations.

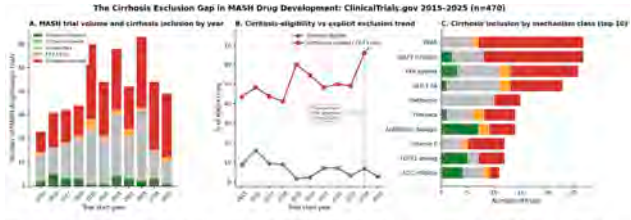


Figure 1. The cirrhosis exclusion gap in MASH drug development (ClinicalTrials.gov, 2015–2025; n=470). (A) Stacked trial volume by start year. (B) Annual % of trials that are cirrhosis-eligible (green) versus explicitly cirrhosis-excluded or F2–F3 only (red); dashed line marks resmetirom FDA approval (Mar 2024). (C) Cirrhosis-inclusion bucket within the top 10 mechanism classes. Classification performed via programmatic parsing of eligibility-criteria text, condition tags, and study titles.

Disclosures: Saad Nadeem: Nothing to Disclose, David Victor: Intercept: Speaker, and Advisor, Gilead: Speaking and Teaching, Madrigal: Speaker, BMS: Stock - publicly traded company, Pfizer: Stock - publicly traded company,

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2537 | IMPACT OF MACE EXPOSURE AND GLP-1 USE ON NON-CIRRHOTIC HCC DEVELOPMENT IN MASLD

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a risk factor for hepatocellular carcinoma (HCC) in non-cirrhotic individuals. This study examined major adverse cardiovascular events (MACE) as a risk factor for HCC, along with the differential impact of glucagon-like peptide-1 receptor agonists (GLP-1) on HCC risk by MACE status in this population. **Methods:** Data from the TriNetX Global Network from 1/1/2005 to 12/31/2025 were used. We included adults with hepatic steatosis and ≥ 1 MASLD-associated cardiometabolic risk factor (e.g. hypertension, type 2 diabetes, hyperlipidemia, or obesity) as a surrogate definition for MASLD. Study group inclusion required patients to also have ≥ 1 MACE, defined as acute myocardial infarction, heart failure, cerebral infarction, or unstable angina. Patients with viral hepatitis, cirrhosis, alcohol use disorder, or prior HCC were excluded. Cox regression identified risk factors for HCC, adjusting for age, sex, race, ethnicity, body mass index (BMI), hemoglobin A1c (HbA1c), low-density lipoprotein (LDL), aspartate aminotransferase (AST), and nicotine dependence. Secondary analyses assessed the association between ≥ 1 instance of GLP-1 use and HCC risk stratified by MACE status. **Results:** A total of 1,481,092 patients with non-cirrhotic MASLD were identified: 276,469 with MACE and 1,204,623 without MACE. The presence of MACE was associated with two-fold higher hazard of

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developing HCC (HR 2.20, 95% CI 1.92-2.52) compared to those without MACE. Male sex (HR 1.70, 95% CI 1.51-1.91) and increasing age per year (HR 1.05, 95% CI 1.05-1.06) were independently associated with higher HCC risk. White race (HR 0.38, 95% CI 0.34-0.43) was associated with lower HCC risk. In secondary analyses of non-cirrhotic MASLD patients without MACE, GLP-1 users (n = 79,254) had a lower hazard of HCC than non-users (n = 946,957; HR 0.44, 95% CI 0.26-0.75). In patients with MACE, GLP-1 use (n = 7,038) was associated with a lower but non-significant hazard of HCC compared to controls (n = 173,885; HR 0.15, 95% CI 0.02-1.11). **Conclusion:** In patients with non-cirrhotic MASLD, MACE was an independent predictor of HCC development. While GLP-1 exposure was associated with lower HCC risk in patients without MACE, this association attenuated among patients with MACE. These findings suggest a potential HCC-related benefit to GLP-1 initiation in MASLD at earlier stages of cardiometabolic disease.

Table 1: Cox regression analysis of HCC risk factors and the differential impact of GLP-1s by MACE status in non-cirrhotic MASLD

	Non-Cirrhotic MASLD *MACE vs. No MACE*			Non-Cirrhotic MASLD without MACE *GLP-1 vs no GLP-1*			Non-cirrhotic MASLD with MACE *GLP-1 vs no GLP-1*		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Cohort membership	**2.20**	**1.92-2.52**	**<0.01**	**0.44**	**0.26–0.75**	**<0.01**	0.15	0.02–1.11	0.06
Male sex	**1.70**	**1.51-1.91**	**<0.01**	**1.73**	**1.48–2.03**	**<0.01**	**1.96**	**1.47–2.60**	**<0.01**
Age at index	**1.06**	**1.05-1.06**	**<0.01**	**1.04**	**1.04–1.05**	**<0.01**	**1.04**	**1.03–1.05**	**<0.01**
White race	**0.38**	**0.34-0.43**	**<0.01**	**0.73**	**0.61–0.86**	**<0.01**	0.76	0.56–1.03	0.07
Hispanic/ Latino	0.81	0.64-1.07	0.17	1.11	0.85–1.45	0.44	0.99	0.55–1.78	0.96
BMI	**0.98**	**0.97-0.99**	**<0.01**	**0.98**	**0.96–0.99**	**<0.01**	0.99	0.97–1.02	0.50
Nicotine dependence	0.98	0.64-1.50	0.93	1.11	0.71–1.74	0.64	0.91	0.55–1.50	0.79
HbA1C	1.01	0.94-1.08	0.80	1.08	1.00–1.18	0.06	**1.16**	**1.04–1.30**	**<0.01**
LDL	**1.01**	**1.00-1.01**	**<0.01**	1.00	1.00–1.00	0.60	1.00	0.99–1.00	0.53
AST	1.00	1.00-1.00	0.16	-	-	-	-	-	-

AST: aspartate aminotransferase; BMI: body mass index; CI: confidence interval; GLP-1: glucagon-like peptide-1 receptor agonist; HbA1c: hemoglobin A1c; HCC: hepatocellular carcinoma; HR: hazard ratio; LDL: low-density lipoprotein; MACE: major adverse cardiovascular events; MASLD: metabolic dysfunction-associated steatotic liver disease

Disclosures: Kai-Lou Yue: Nothing to Disclose, Charanpreet Sasan: Nothing to Disclose, Taylor Seacor: Nothing to Disclose, Anita Krishnarao: Madrigal Pharmaceuticals: Advisory Board.

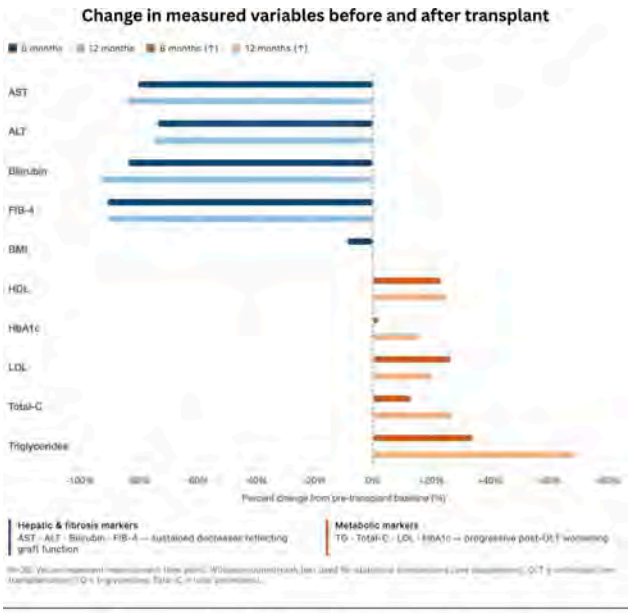
2538 | RECURRENT MASLD AFTER ORTHOTOPIC LIVER TRANSPLANTATION: IDENTIFYING CARE GAPS TO GUIDE STRUCTURED FOLLOW-UP

Hamsika Moparty[1] Rohan Karkra[1] Lucie Pham[1] Nishanth Moparty[2] Annie Xu[1] Anika Makol[1] Shivani Patel[1] Zaid Tafesh[1] Paul Gaglio[3], [1]Rutgers New Jersey Medical School, [2]Bhaskar Medical College, NTR University, [3]Rutgers NJ Medical School

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) has become one of the leading indications for liver transplantation. However, recurrence or new onset of MASLD after transplant is increasingly recognized but poorly studied. There is a growing need for a standardized post-transplant approach to monitor metabolic risk factors, incorporate regular non-invasive fibrosis assessment, and coordinate multidisciplinary care. This quality improvement project aims to better define recurrence patterns, identify care gaps, and use these data to design a structured follow-up pathway. **Methods:** A single-center retrospective chart review was conducted on all orthotopic adult liver transplant recipients over the past 10 years who had MASLD as an indication for transplant. Demographic, metabolic, serologic, histological, and imaging data were extracted at pre-transplant baseline, at 6- and 12-month, and 1-, 3- and 5- years post-OLT time points. Key outcomes included MASLD recurrence, Fib-4 risk stratification, non-invasive fibrosis testing rates, metabolic markers, weight management referral practices, and use of novel pharmacotherapies. **Results:** We searched hospital records to identify patients who received an orthotopic liver transplant between 2015 and 2025 for the primary indication of MASLD cirrhosis. We describe a cohort of 26 patients. Mean age was 60.3 ± 9.2 years and 61.5% were male. Patients had a high pre-transplant metabolic burden, including hypertension (65.4%), diabetes (53.8%), hyperlipidemia (46.2%), and obesity (36% with BMI > 30 kg/m²). Mean MELD score was 26.9 ± 9.1. Explant pathology showed cirrhosis in 60% and hepatocellular carcinoma in 20%.Post-transplant liver enzymes and bilirubin normalized by 6 months, but metabolic parameters increased over time. Mean triglycerides rose from 114.7 to 172.9 mg/dL, total cholesterol from 129.3 to 165.7 mg/dL, and HbA1c from 5.4% to 6.3% by 12 months. The proportion of patients with BMI > 30 kg/m² increased from 36% pre-transplant to 56.2% at 12 months. Recurrent MASLD was identified in 3 patients (11.5%) at a mean follow-up of 4.1 years. FibroScan or FibroSure was performed in only 1 patient (3.8%) at each time point, and among patients with BMI > 30 kg/m², 55.6%, only 7.7% of patients received GLP-1 receptor agonists. **Conclusion:** Orthotopic Liver transplant recipients with MASLD demonstrated worsening metabolic risk factors over time despite stable graft function, indicating that the risks for metabolic syndrome continued post-transplant. These findings highlight the importance of developing a structured post-transplant MASLD surveillance protocol with routine metabolic monitoring, Fib-4 assessment, non-invasive fibrosis testing, and multidisciplinary management to support early identification and treatment of recurrent disease.

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Structured Post-OLT MASLD Surveillance Protocol

Timepoint	Recommended Evaluation
6 months	Weight/BMI, blood pressure, HbA1c, lipid panel, liver enzymes, FIB-4 calculation ± FibroSure; consider TTE in high cardiovascular-risk patients
12 months	FibroScan or ultrasound elastography ± ELF/FibroSure, repeat metabolic profile, cardiology follow-up/TTE if indicated
Annually thereafter	Repeat above fibrosis and metabolic assessment; nutrition, endocrinology, and bariatric referral if criteria met
As indicated	GLP-1 receptor agonists, obesity pharmacotherapy, or bariatric intervention

Disclosures: Hamsika Moparty: Nothing to Disclose, Rohan Karkra: Nothing to Disclose, Lucie Pham: Nothing to Disclose, Nishanth Moparty: Nothing to Disclose, Annie Xu: Nothing to Disclose, Anika Makol: Nothing to Disclose, Shivani Patel: Nothing to Disclose, Zaid Tafesh: Nothing to Disclose, Paul Gaglio: Nothing to Disclose.

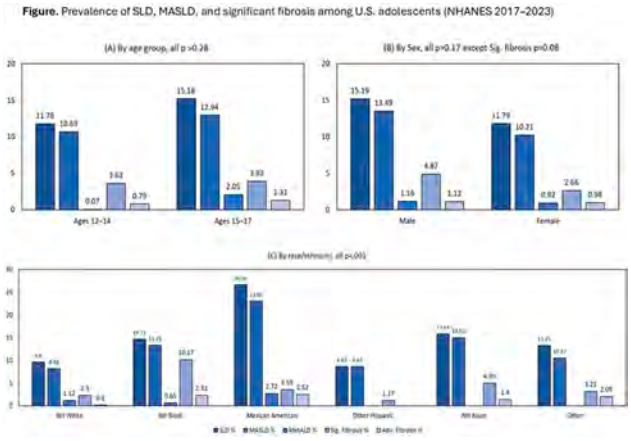
2539 | STEATOTIC LIVER DISEASE (SLD) SUBTYPES AMONG ADOLESCENTS IN THE UNITED STATES: A NATIONALLY REPRESENTATIVE STUDY

Zobair Younossi[1] Annette Paik[1] Fatema Nader[2] Andrei Racila[1] James Paik[3], [1]The Global NASH/MASH Council, [2]Center for Outcomes Research in Liver Diseases, CORLD, [3]Global NASH/MASH Council

Background: SLD is common cause of liver disease in the U.S., yet its burden among adolescents is poorly characterized due to limited alcohol exposure data. This study used the National Health and Nutrition Examination Survey (NHANES) to estimate the prevalence of SLD and its subtypes among U.S. adolescents **Methods:** NHANES 2017–2023 participants aged 12–17 years with controlled attenuation parameter (CAP) and liver stiffness measurement (LSM) data and no other liver diseases were analyzed. SLD was defined as CAP $\geq$280 dB/m. Significant fibrosis (SF) and advanced fibrosis (AF) were defined as LSM $\geq$8.0 and $\geq$12.0 kPa. Obesity was defined using CDC 2000 BMI-for-age percentiles. Cardiometabolic risk (CMR) factors were adapted for pediatric populations. Participants were classified by past-30-day alcohol use as: no exposure (never drank), low (experimental or 1–2 days per month, no binge episodes), moderate (2-5 days per month and no binge episodes), or high-risk (>5 days or 1-5 binge episode per month) and severe (>5 days and >5 episodes of binge per month). Metabolic-associated fatty liver disease (MASLD) was defined as SLD with no/low alcohol exposure plus $\geq$1 CMRs; metabolic dysfunction-associated alcoholic liver disease (MetALD) as SLD with moderate/high-risk plus $\geq$1 CMRs and alcohol associated liver disease (ALD) was SLD with severe alcohol use. **Results:** Among 1,775 adolescents (mean age 14.5 years; 52.1% male; 46.7% White; 24.7% with obesity; 2.4% with hypertension; 0.6% with type 2 diabetes(T2D), weighted prevalence of SLD in this group was 13.5% [11.8% for (MASLD), 1.1% for MetALD, 0% for ALD, 3.8% for SF, and 1.1% for AF]. Prevalence of MASLD and MetALD differed by age group (12–15 vs. 15–17 years): 10.7% vs 12.9% and 0.07% vs. 2.05% [Figure A]. Boys had higher prevalence of all SLDs than girls [Figure B]. Mexican American adolescents had the highest prevalence of SLD and MASLD (p = 0.0001), while Non-Hispanic Black adolescents had the highest prevalence of SF (p = 0.0008; Figure C). In socioeconomic-adjusted models, low household income was independently associated with MASLD (OR 1.85, 95% CI 1.03–3.30). In fully adjusted model, obesity (OR 15.90, 95% CI 6.54–38.64), T2D (OR 4.69, 95% CI 1.28–17.16), and hypertension (OR 3.43, 95% CI 1.04–11.34) were independently associated with MASLD. Across all adolescents, obesity (β = 0.095, p = 0.002) and hypertension (β = 0.130, p = 0.023) were independently associated with higher LSM. Among adolescents with SLD, hypertension was the only independent clinical correlate of higher LSM (β = 0.193, p = 0.018). **Conclusion:** Steatotic liver disease affects approximately 1 in 8 U.S. adolescents, with substantial racial/ethnic disparities. MASLD is the predominant subtype of SLD, while MetALD represents a small but important subset. Among adolescents with SLD, hypertension was the strongest independent clinical correlate of liver stiffness, warranting longitudinal investigation.

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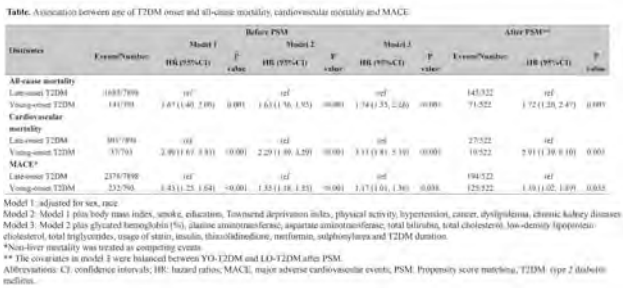


Disclosures: Zobair Younossi: Zobair M. Younossi is a consultant or has received research: Consultant, madrigal: Grant/Research Support, Siemens: Research funding, GSK: Consultant, BI: Consultant, Sanofi: Research funding, Annette Paik: Nothing to Disclose, Fatema Nader: Nothing to Disclose, Andrei Racila: Nothing to Disclose, James Paik: Nothing to Disclose.

★2540 | CARDIOVASCULAR AND MORTALITY RISKS IN YOUNG-ONSET VERSUS LATE-ONSET TYPE 2 DIABETES AMONG PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

Xinrong Zhang[1] Ruoqi Zhou[2] Yuankai Wu[1] Zilong Lu[1] Haotian Zhang[2] Yuhua Hao[1] Fanpu Ji[3] Rongtao Lai[4] Vincent Wai-Sun Wong[5] Yu Shi[2], [1]Sun Yat-sen University, [2]The First Affiliated Hospital, Zhejiang University School of Medicine, [3]Xi'an Jiaotong University, [4]Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, [5]The Chinese University of Hong Kong

Background: The concurrent rise in type 2 diabetes mellitus (T2DM) and metabolic dysfunction-associated steatotic liver disease (MASLD) represents a major public health challenge. Young-onset T2DM (YO-T2DM) is associated with a more aggressive disease phenotype and higher complication risks than late-onset T2DM (LO-T2DM). However, whether this excess risk persists among T2DM patients with coexisting MASLD, who are already at elevated risk for adverse outcomes, remains unclear. In addition, data directly comparing major adverse cardiovascular events (MACE) and mortality between YO- and LO-T2DM in patients with MASLD are limited. **Methods:** Participants with MASLD (defined by Fatty Liver Index >60 plus at least one cardiometabolic risk factor, excluding excessive alcohol use and other liver diseases) and coexisting T2DM were identified from the UK Biobank. YO-T2DM was defined as T2DM diagnosed before 40 years of age, whereas all other cases were classified as LO-T2DM. The primary outcomes were all-cause mortality, cardiovascular mortality, and MACE. We estimated these associations by age-scaling Cox proportional hazards models with stepwise adjustment for demographics, T2DM duration, comorbidities, laboratory indicators and medication use. Propensity score matching (PSM) and restricted cubic splines (RCS) were conducted to validate the findings. **Results:** A total of 8,691 MASLD patients were included, comprising 7,898 with LO-T2DM and 793 with YO-T2DM. Compared to the LO-T2DM group, MASLD patients with YO-T2DM exhibited higher risks of adverse outcomes after full adjustment for covariates, including a 1.74-fold increased risk for all-cause mortality, a 3.13-fold increased risk for cardiovascular mortality, and a 1.17-fold increased risk for MACE (**Table**). These significant elevated risks in the YO-T2DM population were consistently observed after PSM analyses. Furthermore, the RCS analysis supported an inverse association between age at T2DM diagnosis and adverse outcomes among patients with MASLD. **Conclusion:** In this large prospective cohort of MASLD patients, YO-T2DM was associated with higher risks of all-cause mortality, cardiovascular mortality, and MACE than LO-T2DM. These results support YO-T2DM as a high-risk phenotype in MASLD, emphasizing the need for early and intensive cardiovascular risk management.



Disclosures: Xinrong Zhang: Nothing to Disclose, Ruoqi Zhou: Nothing to Disclose, Yuankai Wu: Nothing to Disclose, Zilong Lu: Nothing to Disclose, Haotian Zhang: Nothing to Disclose, Yuhua Hao: Nothing to Disclose, Fanpu Ji: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Rongtao Lai: Nothing to Disclose, Vincent Wai-Sun Wong: Nothing to Disclose, Yu Shi: Nothing to Disclose.

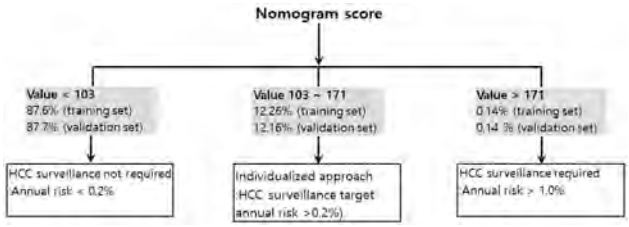
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2541 | RISK OF HEPATOCELLULAR CARCINOMA IN ELDERLY PATIENTS WITH METABOLIC DYSFUNCTION–ASSOCIATED STEATOTIC LIVER DISEASE AND PROPOSAL OF AN EFFECTIVE NATIONWIDE SURVEILLANCE STRATEGY

Young Eun Chon[1] Kyung-Do Han[2] Ju-Yeong Park[3] Beom Kyung Kim[4], [1]CHA University, [2]Department of Statistics and Actuarial Science, Soongsil University, [3]Department of Statistics and Actuarial Science, Soongsil University, Seoul, Republic of Korea, [4]Yonsei University College of Medicine, Seoul, Republic of Korea

Background: Metabolic dysfunction–associated steatotic liver disease (MASLD) is increasingly prevalent among aging populations. We evaluated hepatocellular carcinoma (HCC) risk across MASLD spectrum in this population and developed a nomogram to guide optimized surveillance. **Methods:** Using a nationwide South Korean database, we identified participants aged ≥75 years undergoing health screening between 2012 and 2015. Steatotic liver disease (SLD) was classified as MASLD, MetALD (MASLD with increased alcohol intake), or alcohol-associated liver disease (ALD). Competing-risk regression for HCC risk was used to estimate adjusted subdistribution hazard ratios (a-sHRs) by SLD subtype, using Fine–Gray models. **Results:** Among 1,088,314 participants, 34.3% had SLD (351,583 MASLD; 11,586 MetALD; 9,619 ALD). The overall 5-year HCC incidence in SLD group (0.769%) was higher, compared to non-SLD group (0.334%). It increased stepwise from MASLD (0.687%) to MetALD (1.856%) and ALD (2.443%): a-sHRs of 1.93, 2.99, and 4.35, respectively. Stratified analyses consistently demonstrated the same pattern. A nomogram incorporating age, sex, smoking, diabetes, statin use, SLD subtype, gamma-glutamyl transferase, body mass index, liver cirrhosis, and aspartate transaminase/alanine transaminase ratio was developed, with good discriminative ability. Scores < 103 (87.7% of participants) corresponded to annual HCC risk < 0.2%, suggesting exemption from HCC screening, whereas scores > 171 (0.14%) corresponded to annual risk > 1%, indicating the need for continuous screening. **Conclusion:** Elderly individuals with MASLD spectrum exhibit a significant HCC risk, with higher risk in MetALD and ALD groups. Given the very small proportion who require HCC screening, our nomogram serves as a practical tool for community-based risk stratification and optimized surveillance.



Disclosures: Young Eun Chon: Nothing to Disclose, Kyung-Do Han: Nothing to Disclose, Ju-Yeong Park: Nothing to Disclose, Beom Kyung Kim: Nothing to Disclose.

2542 | A VIRULENCE–HOST GENE INTERACTION BETWEEN HELICOBACTER PYLORI CAGA AND NOD1 IS ASSOCIATED WITH MASLD SEVERITY

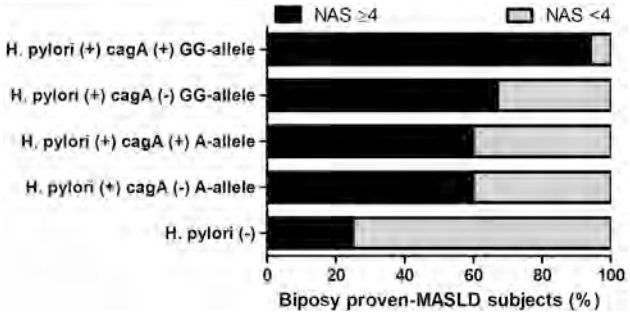
Fernando Barreyro[1] Facundo Maiorana[1] Maria Virginia Caronia[2] Soraya Acardi[3] Georgina Veron[4] Pedro Zapata[1], [1]Instituto de Biotecnología de Misiones (InBioMis). Universidad Nacional de Misiones, [2]Instituto de Biotecnología de Misiones (InBioMis). Universidad Nacional de Misiones, [3]Fundación HA Barceló, Instituto Universitario en Ciencias de la Salud., [4]Fundación HA Barceló, Instituto Universitario en Ciencias de la Salud

Background: Helicobacter pylori (Hp) is increasingly recognized as a gut exposome factor that may amplify metabolic inflammation and liver injury in metabolic dysfunction-associated steatotic liver disease (MASLD). We assessed whether the Hp virulence gene *cagA* and the host innate-immunity sensor NOD1 rs2075820 were associated with MASLD severity. **Methods:** In this prospective study conducted in northeast Argentina (2021–2024), 494 adults with Rome-IV functional dyspepsia underwent upper endoscopy. Clinical, biochemical, ultrasound, FIB-4, liver stiffness measurement (LSM) by vibration-controlled transient elastography, gastric biopsies, Hp *cagA* status, and NOD1 rs2075820 genotype were evaluated. A second retrospective cohort included 127 patients with biopsy-proven MASLD who underwent gastroscopy with gastric biopsies. Comparisons used chi-square testing, ANOVA with Tukey post hoc analysis, and logistic regression. *$p < 0.05$. **Results:** The cohort included 60% women, with mean age 49 ± 13 years and BMI 27.9 ± 13.1 kg/m². MASLD was present in 209 subjects (42%) and active Hp infection in 51%. Hp positivity was associated with higher BMI and MASLD prevalence (52% vs 32%,*), whereas T2D, dyslipidemia, and

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hypertension did not differ by Hp status. In MASLD subgroup, Hp+ with cagA+ strain was associated with higher AST (Hp- 25 ± 11, Hp+/cagA- 28 ± 13, Hp +/cagA+ 33 ± 14*), FIB-4 (Hp- 1 ± 0.5, Hp+/cagA- 1.4 ± 0.9, Hp+/cagA+ 1.5 ± 0.8*), and LSM (Hp- 5.7 ± 2.8, Hp+/cagA- 6.9 ± 5.8, Hp+/cagA+ 7.8 ± 5.2*), but not with ALT and GGT. Notably, carriers of cagA+/NOD1GG allelic combination were associated with higher FIB-4 (Hp- 1 ± 0.5, cagA-/A-allele 1.1 ± 0.7, cagA+/A-allele1.3 ± 0.6, cagA+/GG-allele 1.5 ± 0.6*), and LSM (Hp- 5.7 ± 2.9, cagA-/A-allele 5.6 ± 3.1, cagA+/A-allele 6.2 ± 2.16, cagA+/GG-allele 8.5 ± 3.6*). Indeed, more proportion of patients with cagA+/GG-allele combination (Hp- 15%, cagA-/A-allele 11%, cagA+/A-allele 29%, cagA+/GG-allele 41%*) were observed with the LSM cut-off for high-risk of significant/advanced- fibrosis (≥8kPa). Hp *cagA*+/NOD1 GG carriers had increased odds of LSM ≥8 kPa (OR 3.99; 95% CI, 1.6–10.0), remaining significant after adjustment for age, T2D, BMI, dyslipidemia, and hypertension (adjusted OR 4.98; 95% CI, 1.9–13.5). In biopsy-proven MASLD, Hp *cagA*+/NOD1 GG was associated with higher NAS, fibrosis stage, and MASH prevalence. The odds of MASH were increased in Hp *cagA*+/NOD1 GG carriers (OR 48.0; 95% CI, 8.7–393.0), remaining significant after multivariable adjustment (adjusted OR 36.4; 95% CI, 6.2–400.3). **Conclusion:** Hp infection, particularly *cagA*+ strains, was associated with greater MASLD severity. The Hp *cagA*+/NOD1 GG combination independently identified patients at higher risk of significant/advanced fibrosis by LSM and biopsy-confirmed MASH, supporting a potential virulence–host gene interaction that may exacerbate liver injury in MASLD.



Disclosures: Fernando Barreyro: Nothing to Disclose, Facundo Maiorana: Nothing to Disclose, Maria Virginia Caronia: Nothing to Disclose, Soraya Acardi: Nothing to Disclose, Georgina Veron: Nothing to Disclose, Pedro Zapata: Nothing to Disclose.

2543 | NORMAL BMI, HIDDEN LIVER RISK: METABOLICALLY OBESE NORMAL-WEIGHT PHENOTYPE AND FIBROTIC LIVER DISEASE IN U.S. ADULTS

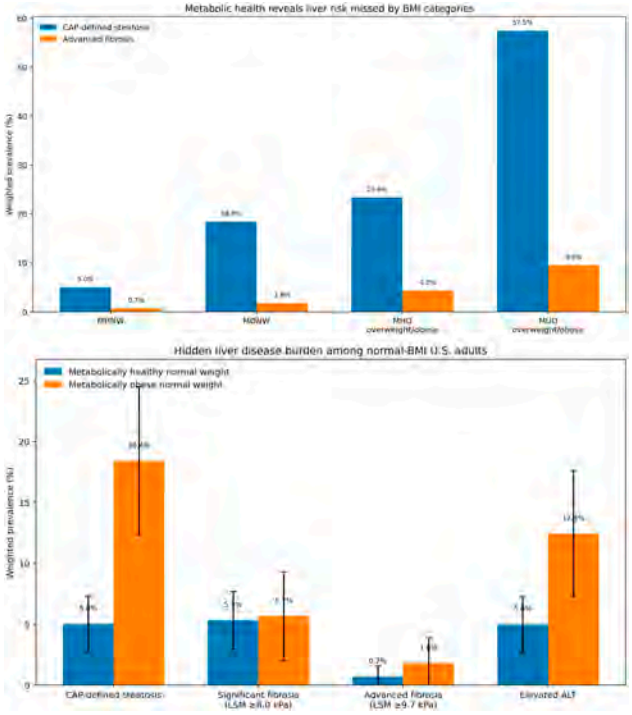
Madhu babu Adusumilli[1] Serene Sara John[2] Sri Ram Charan Gundapaneni[3] Pragathi Munnangi[4] Mounika Kotte[5] Jagadish Koyi[6] Hardik Dineshbhai Desai[7], [1]HCA Ocala hospital/ UCF, [2]detroit medical center, [3]University of Central Florida, HCA Healthcare GME, [4]BronxCare Health System, [5]Prime South Consoritum, Texas, [6]Integris Health, Oklahama, [7]AB Plus speciality hospital, Ahmedabad, India

Background: Normal body mass index (BMI) may obscure clinically important metabolic dysfunction and liver disease risk. We examined whether the metabolically obese normal-weight (MONW) phenotype is associated with vibration-controlled transient elastography (VCTE)-defined steatosis and fibrosis among U.S. adults. **Methods:** We analyzed National Health and Nutrition Examination Survey (NHANES) 2017–March 2020 adults aged ≥20 years with valid VCTE and BMI data, excluding underweight adults, heavy alcohol use, and hepatitis C. Normal BMI was defined as 18.5–24.9 kg/m². MONW was defined as normal BMI plus ≥2 metabolic abnormalities, including central adiposity, dysglycemia, hypertension, hypertriglyceridemia, or low high-density lipoprotein cholesterol. Outcomes included controlled attenuation parameter (CAP)-defined steatosis, liver stiffness measurement (LSM)-defined significant fibrosis, advanced fibrosis, and elevated alanine aminotransferase (ALT). Survey-weighted prevalence estimates and logistic regression models were used. **Results:** The analytic sample included 5,045 adults, representing 135.0 million U.S. adults. Among normal-BMI adults, 26.8% had MONW, representing 9.2 million adults. Compared with metabolically healthy normal-weight adults, MONW adults were older, 61.2 vs 43.8 years, had higher waist circumference, 85.1 vs 79.1 cm, and higher mean metabolic abnormality count, 2.42 vs 0.45. CAP-defined steatosis was 18.4% in MONW versus 5.0% in metabolically healthy normal-weight adults. Elevated ALT was 12.4% vs 5.0%, significant fibrosis was 5.7% vs 5.3%, and advanced fibrosis was 1.8% vs 0.7%. In age/sex-adjusted models, MONW was associated with higher odds of steatosis, odds ratio (OR) 3.09, 95% confidence interval (CI) 1.96–4.86, $p < 0.001$, and elevated ALT, OR 2.86, 95% CI 1.64–5.01, $p < 0.001$. In extended models adjusting for socioeconomic, behavioral, sleep, depression, and insurance factors, MONW remained associated with steatosis, OR 4.34, 95% CI 2.01–9.37, $p < 0.001$, significant fibrosis, OR 3.20, 95% CI

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1.39–7.36, p = 0.006, and showed a strong trend toward advanced fibrosis, OR 5.67, 95% CI 0.82–39.07, p = 0.078. **Conclusion:** More than 1 in 4 normal-BMI U.S. adults had a metabolically obese phenotype. MONW identified a hidden high-risk group with substantially higher steatosis, elevated ALT, and fibrosis signal despite normal BMI. These findings support metabolic-risk-based liver screening beyond BMI alone.



Disclosures: Madhu babu Adusumilli: Nothing to Disclose, Serene Sara John: Nothing to Disclose, Sri Ram Charan Gundapaneni: Nothing to Disclose, Pragathi Munnangi: Nothing to Disclose, Mounika Kotte: Nothing to Disclose, Jagadish Koyi: Nothing to Disclose, Hardik Dineshbhai Desai: Nothing to Disclose.

2544 | IMPACT OF DIETARY PROFILE AND BODY COMPOSITION ON RISK OF FIBROSIS IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

Ozge Ozgur[1] Renwei Wang[1] Jian-Min Yuan[1] Jaideep Behari[1], [1]University of Pittsburgh Medical Center

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) affects more than 30% of adults worldwide and is associated with significant liver-related morbidity and mortality. Although MASLD is closely linked to metabolic dysfunction, the independent effects of anthropometric, demographic, and dietary factors on fibrosis severity remain incompletely understood. We aimed to determine the impact of body composition and nutritional variables associated with risk of liver fibrosis in patients with MASLD. **Methods:** Patients with MASLD were prospectively enrolled from a tertiary care clinic in the United States. Clinical history was obtained from electronic health records, body composition determined by bioimpedance analyzer, liver stiffness measurement by Transient Elastography, and dietary history by the validated ASA24 and DHQ3 questionnaire. We performed univariate and multivariate analyses evaluating associations between clinical, demographic, anthropometric, and dietary variables with fibrosis stage, treated as an ordinal outcome (stages 1-3). Fibrosis stage was analyzed as an ordinal outcome variable (stages 1-3), with corresponding mean liver stiffness measurements of 5.5 kPa for stage 1, 9.2 kPa for stage 2, and 22.4 kPa for stage 3. Variables significant in univariate analysis were entered into a stepwise generalized linear model selection procedure to identify independent predictors of fibrosis. Model performance was assessed using adjusted R-square and analysis of variance metrics. **Results:** Among 583 participants included in the analysis, six variables were independently associated with increasing fibrosis stage in the final multivariate model. Type 2 diabetes mellitus (T2DM) demonstrated a significant positive association with higher stage severity. Increased waist circumference and older age were also independently associated with advanced stage. Male sex was associated with higher fibrosis stage compared with female sex. Dietary composition was significantly associated with fibrosis stage. Lower protein-to-carbohydrate ratio intake and lower total dietary protein intake were independently associated with increasing stage severity. The final model demonstrated moderate explanatory capacity (R^2 = 0.18, adjusted R^2 = 0.17; F = 15.81, p < 0.001). **Conclusion:** Higher fibrosis stage in MASLD was independently associated with metabolic risk factors, central adiposity, demographic characteristics, and dietary composition. Our findings highlight the potential contribution of nutritional composition in fibrosis progression and may help guide future dietary and risk stratification strategies in MASLD.

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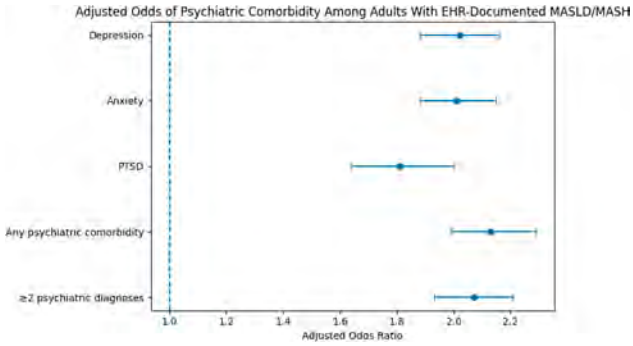
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Institutional research contract, Akero: Institutional research contract, Madrigal: Grant/Research Support.

2545 | DEPRESSION, ANXIETY, AND PTSD BURDEN AMONG ADULTS WITH EHR-DOCUMENTED MASLD IN THE ALL OF US RESEARCH PROGRAM

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Background: The gut-brain-liver axis suggests bidirectional links between psychiatric health and metabolic dysfunction-associated steatotic liver disease (MASLD). However, the burden of psychiatric comorbidity among adults with MASLD remains incompletely characterized in diverse U.S. populations. We examined the prevalence and adjusted odds of depression, anxiety, and post-traumatic stress disorder (PTSD) among adults with EHR-documented MASLD/MASH in the All of Us Research Program. **Methods:** We conducted a cross-sectional analysis of adults aged ≥18 years with EHR data in the All of Us Controlled Tier Dataset v8. EHR-documented MASLD/MASH was identified using diagnosis concepts for nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, and NASH-related cirrhosis, excluding alcoholic fatty liver and acute fatty liver of pregnancy. Psychiatric comorbidities were identified using EHR diagnosis concepts for depression, anxiety, and PTSD. Psychiatric multimorbidity was defined as ≥2 psychiatric diagnoses. Multivariable logistic regression estimated adjusted odds of psychiatric outcomes among adults with MASLD/MASH compared with those without MASLD/MASH, adjusting for age, BMI, sex at birth, race/ethnicity, and type 2 diabetes. Sex-stratified models evaluated associations with any psychiatric comorbidity. Analyses were performed using Python in Jupyter Notebook. **Results:** Among 388,424 adults with EHR data, 3,700 had EHR-documented MASLD/MASH. Depression was present in 53.92% of adults with MASLD/MASH versus 27.12% without MASLD/MASH, anxiety in 49.51% versus 25.61%, PTSD in 12.97% versus 5.39%, and any psychiatric comorbidity in 64.41% versus 36.04%. Psychiatric multimorbidity was also higher in MASLD/MASH, with 41.84% having ≥2 psychiatric diagnoses compared with 18.62% without MASLD/MASH. After adjustment for age, BMI, sex at birth, race/ethnicity, and type 2 diabetes, MASLD/MASH remained associated with higher odds of depression (aOR 2.02, 95% CI 1.88–2.16), anxiety (aOR 2.01, 95% CI 1.88–2.15), PTSD (aOR 1.81, 95% CI 1.64–2.00), any psychiatric comorbidity (aOR 2.13, 95% CI 1.99–2.29), and ≥2 psychiatric diagnoses (aOR 2.07, 95% CI 1.93–2.21). Sex-stratified models showed persistent associations in females (aOR 2.18, 95% CI 1.99–2.40) and males (aOR 2.08, 95% CI 1.86–2.32). **Conclusion:** Adults with EHR-documented MASLD/MASH had a substantially higher burden of depression, anxiety, PTSD, and psychiatric multimorbidity, with associations persisting after adjustment for metabolic and demographic factors. These findings highlight the need to integrate mental health screening and support into MASLD care, supporting a more integrated, multidisciplinary MASLD care model.



Disclosures: Ihunanya Kanu: Nothing to Disclose, Sarpong Boateng: Nothing to Disclose, chimezirim ezeano: Nothing to Disclose, Bolaji Ayinde: Nothing to Disclose, Olamide Asifat: Nothing to Disclose, Joshua Kalu: Nothing to Disclose, Nothing to Disclose, Richard Heard: Nothing to Disclose.

2546 | CLINICOPATHOLOGICAL CHARACTERISTICS AND RISK FACTORS FOR ADVANCED LIVER FIBROSIS IN PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED FATTY LIVER DISEASE

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Background: To investigate the clinical pathological features and the possible influencing factors of advanced liver fibrosis in patients with metabolic dysfunction-associated fatty liver disease (MAFLD), in order to provide guidance for clinical diagnosis and treatment. **Methods:** A total of 222 patients

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diagnosed with MAFLD based on pathological and clinical characteristics from January 2019 to December 2024 were enrolled as study subjects. MASH and liver fibrosis (F) were assessed using the SAF scoring system within the FLIP algorithm (SAF/FLIP). Patients were stratified into groups without or with advanced fibrosis (less than F3 vs. F3 or more), as well as into F3 and F4 subgroups. Propensity score matching (PSM) was performed at a 1: 1 ratio to balance baseline characteristics between the two groups. **Results:** Based on the SAF/FLIP scoring, MASH was diagnosed in 204 patients (91.89%). The numbers of patients with less than F3 and F3 or more were 159 and 63, respectively. A total of 162 patients had 2 or more MetS components. After PSM, 126 patients (63 pairs) were included in the final analysis. Compared with the F3 or more group, the less than F3 group had lower age, SAF/FLIP score, levels of GLB, AST, AST/ALT ratio, ADA, INR, APRI, and FIB-4. The less than F3 group had lower proportions of hypertension, hyperglycemia, 2 MetS components or more, and MASH, as well as lower mean Ridit values for hepatocellular ballooning and inflammation activity. All these indicators showed a positive correlation with advanced fibrosis. Conversely, levels of ALB, ALB-to-GLB ratio, and PLT were significantly higher in the less than F3 group than in the F3 or higher group, and showed a negative correlation with advanced fibrosis. A interaction was observed between the hepatic steatosis score and the hepatocellular ballooning score. Compared with the F3 subgroup, the F4 subgroup had significantly higher age, AST/ALT, INR, and FIB-4, but significantly lower ALT, total cholesterol, low-density lipoprotein cholesterol, and PLT (all P less than 0.05). Pathological factors independently associated with advanced fibrosis were hepatocellular ballooning and inflammation activity. Clinical factors independently associated with advanced fibrosis were hypertension components, ADA, PLT , and 2 MetS components or more. During follow-up, patients with advanced fibrosis had an increased risk of developing cirrhosis. **Conclusion:** Among hospitalized patients with MAFLD, 28.38% present with advanced liver fibrosis. Patients with cirrhosis exhibit lower levels of ALT, total cholesterol, and low-density lipoprotein cholesterol. A negative interaction exists between hepatic steatosis and hepatocellular ballooning, partially counteracting the pro-fibrotic effect of the latter. Multidimensional parameters integrating ADA, PLT, metabolic components, and pathological characteristics may inform stratified intervention strategies for advanced fibrosis.

Table 1 Logistic regression analysis of risk factors for advanced fibrosis

Risk factor	univariate		multivariate			
			Model 1/model 2		Model 3/model 4	
	OR (95% CI)	*P*-value	*OR (95% CI)*	*P*-value	*OR (95% CI)*	*P*-value
Age	1.061(1.030 ~ 1.093)	<0.001				
hyperglycemia component	2.330(1.136 ~ 4.775)	0.021				
hypertension component	5.375(2.509 ~ 11.513)	<0.001	4.913(1.913 ~ 12.618)	<0.001	3.803(1.557 ~ 9.286)	0.003
≥2 MetS components	6.224(2.178 ~ 17.790)	0.001			4.065(1.145 ~ 14.433)	0.030
Ballooning score	5.463(2.633 ~ 11.338)	<0.001	4.531(1.769 ~ 11.603)	0.002		
Lobular inflammation score	4.111(1.889 ~8.946)	<0.001	3.234(1.104 ~ 9.474)	0.032		
SAF/FLIP score	1.709(1.263 ~ 2.311)	0.001				
ALB	0.864(0.782 ~ 0.955)	0.004				
GLB	1.104(1.023 ~ 1.193)	0.011				
AGR	0.082(0.021 ~ 0.324)	<0.001				
AST/ALT	1.754(1.011 ~ 3.045)	0.046				
ADA	1.237(1.114 ~ 1.373)	<0.001	1.144(1.018 ~ 1.286)	0.024	1.211(1.085 ~ 1.352)	0.001
PLT	0.988(0.982 ~ 0.994)	<0.001	0.991(0.983 ~ .998)	0.018		
INR	1.861(1.189 ~ 2.913)	0.007				
APRI	2.431(1.311 ~ 4.509)	0.005				
FIB-4	1.438(1.148 ~ 1.801)	0.002				

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2547 | IMPACT OF CLINICAL AND GENETIC FACTORS ON CARDIOVASCULAR RISK IN MASLD

Tomomi Kogiso[1] Yuri Ogasawara[1] Makiko Taniai[1] Yousuke Nakai[1], [1]Tokyo Women's Medical University

Background: Cardiovascular disease (CVD) is an important extrahepatic complication in patients with metabolic dysfunction–associated steatotic liver disease (MASLD). However, the contribution of genetic background to CVD risk in MASLD remains unclear. We investigated clinical and genetic predictors of CVD events in patients with MASLD. **Methods:** We retrospectively analyzed 345 patients (178 men; median age, 54 years) clinicopathologically diagnosed with MASLD at our institution between 1990 and 2018. Twenty-six patients (7.5%) had CVD events, including 17 incident cases during follow-up. Clinical characteristics, laboratory findings, liver histology, and single nucleotide polymorphisms associated with MASLD progression, including patatin-like phospholipase domain-containing protein 3 (PNPLA3), hydroxysteroid 17-beta dehydrogenase 13 (HSD17B13), glucagon-like peptide-1 receptor (GLP1R), and glucokinase regulatory protein (GCKR), were evaluated. A joint genetic risk score (GRS) was calculated from the cumulative number of risk alleles of these variants to assess their

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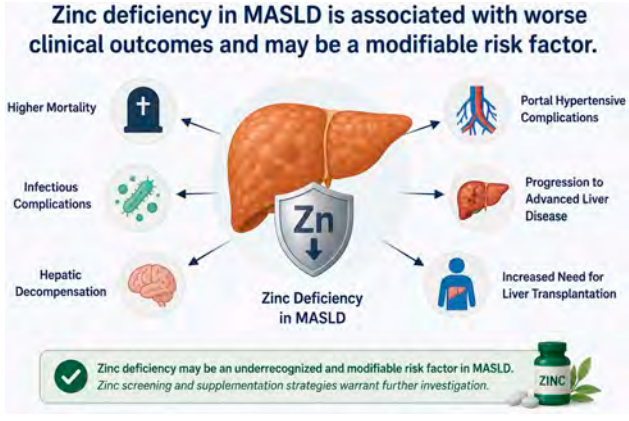
combined impact on CVD risk. **Results:** Patients with CVD events were significantly older than those without events (median age: 67 vs. 53 years). Obesity (BMI $\geq$ 23 kg/m²) was less frequent in patients with CVD events (73.1% vs. 88.1%), whereas hypertension (88.5% vs. 51.7%) was significantly more prevalent, and dyslipidemia tended to be more common (84.6% vs. 66.5%). There were no significant differences in sex or fibrosis stage between the groups. Serum total bilirubin (0.6 vs. 0.7 mg/dL, p = 0.03), albumin (4.1 vs. 4.4 g/dL, p < 0.01), and platelet count (18.0 vs. 20.3 $\times 10^4$/μL, p = 0.01) were significantly lower in patients with CVD events. Multivariate analysis identified older age (odds ratio [OR] 1.04, p = 0.009) and hypertension (OR 4.06, p = 0.040) as independent clinical predictors of CVD events. In genetic analyses, PNPLA3 was positively associated with CVD risk (OR 1.97, p = 0.007), whereas HSD17B13 showed a protective association (OR 0.39, p = 0.023). Furthermore, age, hypertension, and GRS remained independently associated with CVD events. **Conclusion:** Older age and hypertension are major determinants of CVD events in MASLD. Genetic susceptibility, particularly PNPLA3 and HSD17B13 variants, may further influence cardiovascular risk. Combined clinical and genetic risk assessment may help identify high-risk patients requiring intensive cardiovascular surveillance and management.

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2548 | ZINC DEFICIENCY AND ADVERSE CLINICAL OUTCOMES IN MASLD: A LARGE MULTICENTER PROPENSITY-MATCHED ANALYSIS

Adham Obeidat[1] Nour Mansour[2] Ahmad Alqam[2] Christopher Chang[2], [1]Presbyterian Medical Group, [2]University of New Mexico

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is commonly associated with micronutrient deficiencies that may contribute to hepatic decompensation and systemic complications. Zinc plays an important role in ammonia metabolism, oxidative stress regulation, immune function, and hepatocellular repair. However, large-scale data evaluating the clinical impact of zinc deficiency in MASLD are limited. We aimed to assess the association between zinc deficiency and adverse clinical outcomes among patients with MASLD using a large multicenter database. **Methods:** We performed a retrospective cohort study using the TriNetX Research Network. Adult patients with MASLD were identified and stratified by the presence or absence of zinc deficiency. Propensity score matching was conducted for demographics and baseline comorbidities. Primary outcomes included all-cause mortality and liver-related complications. Secondary outcomes included sepsis, spontaneous bacterial peritonitis (SBP), portal hypertension, esophageal varices, hepatic encephalopathy, variceal bleeding, acute liver failure, cirrhosis, and liver transplantation. Outcomes were reported as odds ratios (ORs) with 95% confidence intervals (CIs). **Results:** Following propensity score matching, 6,263 patients with MASLD and zinc deficiency were matched to 6,263 MASLD patients without zinc deficiency. Zinc deficiency was independently associated with increased odds of mortality (OR 1.41, 95% CI 1.19–1.67; P < 0.001), sepsis (OR 2.07, 95% CI 1.87–2.29; P < 0.001), spontaneous bacterial peritonitis (OR 1.83, 95% CI 1.38–2.43; P < 0.001), cirrhosis (OR 1.62, 95% CI 1.47–1.79; P < 0.001), portal hypertension (OR 1.57, 95% CI 1.39–1.77; P < 0.001), esophageal varices (OR 1.51, 95% CI 1.35–1.69; P < 0.001), hepatic encephalopathy (OR 1.69, 95% CI 1.46–1.95; P < 0.001), variceal bleeding (OR 1.61, 95% CI 1.23–2.11; P < 0.001), and acute liver failure (OR 1.74, 95% CI 1.41–2.15; P < 0.001). In addition, patients with zinc deficiency had higher odds of liver transplantation (OR 1.56, 95% CI 1.11–2.18; P = 0.009). **Conclusion:** In this large multicenter propensity-matched analysis, zinc deficiency was associated with increased mortality, infectious complications, portal hypertensive complications, hepatic decompensation, and liver transplantation among patients with MASLD. To our knowledge, this is among the first large-scale real-world studies demonstrating the adverse clinical impact of zinc deficiency in MASLD. These findings suggest that zinc deficiency may represent an underrecognized and potentially modifiable risk factor in this population, warranting further investigation into zinc screening and supplementation strategies.



Disclosures: Adham Obeidat: Nothing to Disclose, Nour Mansour: Nothing to Disclose, Ahmad Alqam:

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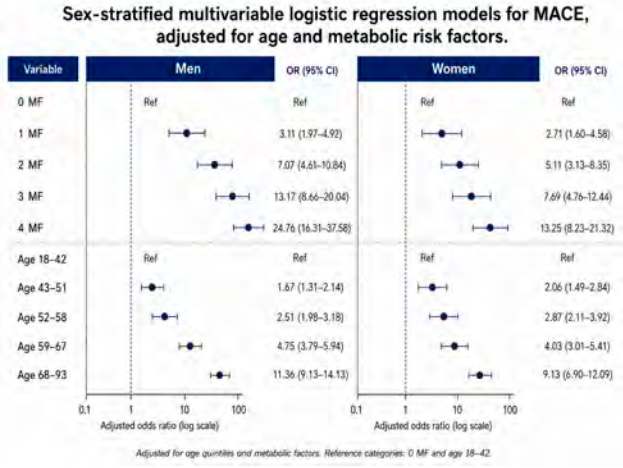
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Nothing to Disclose, Christopher Chang: Nothing to Disclose.

2549 | ARTIFICIAL INTELLIGENCE–BASED IDENTIFICATION OF MASLD IN CLINICAL PRACTICE: DIFFERENTIAL HEPATIC AND CARDIOVASCULAR RISK ACROSS INCREASING METABOLIC FACTOR LOAD

Manuel Mendizabal[1] Magdalena Princz[1] Federico Piñero[1] Amparo Gabrielli[1] Luciano Olguin[1] Pablo Bizzotto[1] Matias Cortiñas[1] Jimena Flores[1] Josefina Pages[1] Marcello Silva[1] Juan Pablo Arab[2], [1]Hospital Universitario Austral, [2]Virginia Commonwealth University

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) remains underrecognized in clinical practice. We aimed to use artificial intelligence (AI) applied to electronic health records (EHRs) to identify adults with MASLD and assess the effect of metabolic factors (MFs) on major hepatic (MAHE) and cardiovascular events (MACE). **Methods:** We performed a cross-sectional study using EHR data from 2015–2025 applying non-probability sampling using an AI strategy integrating natural language processing and structured variables to identify adults with hepatic steatosis. Metabolic factors included obesity, diabetes, hypertension, and dyslipidemia. MAHE comprised cirrhosis, ascites, hepatic encephalopathy, variceal bleeding, hepatocellular carcinoma, and liver transplantation. MACE included myocardial infarction, heart failure, peripheral arterial disease, and stroke. Multivariable logistic regression models were used to estimate the effect of MFs on MAHE and MACE adjusted for age quintiles and sex. Model performance was evaluated by calibration and discrimination. **Results:** Among 627,274 EHRs screened, 486,774 (77.6%) corresponded to adults, and 42,594 (8.8%) had steatosis. After excluding 1,694 (4.0%) patients with alcohol use disorder, 40,900 (8.4%) had steatotic liver disease and 36,993 (7.6%) fulfilled MASLD criteria. In the the MASLD cohort, dyslipidemia, diabetes, hypertension, and obesity were present in 61.4%, 60.5%, 56.2%, and 52.1%, respectively. Overall, MAHE and MACE occurred in 1,291 (3.2%) and 3,895 patients (9.5%); respectively. In the hepatic model, MAHE were associated with the presence of 2 MFs (OR 1.43, 95% CI 1.13–1.82) and 3 MFs (OR 1.35, 95% CI 1.07–1.70), adjusted for age quintiles (OR 6.55, 95% CI 5.25–8.18. MACE showed a stronger stepwise association with metabolic burden (Table), with sex acting as an effect modifier. For 4 MFs, the was OR 24.76 (95% CI 16.31–37.58) for men and OR 13.25 (95% CI 8.23–21.32) for women. Among individual factors, diabetes was associated with markedly higher odds of MAHE (OR 2.31, 95% CI 2.02–2.63), whereas dyslipidemia was associated with substantially higher odds of MACE in both men (OR 7.70, 95% CI 6.69–8.86) and women (OR 4.18, 95% CI 3.56–4.92). **Conclusion:** AI-enabled EHR screening identified a large MASLD population. Increasing MF burden was modestly associated with MAHE but showed a stronger sex-specific association with MACE. Prospective longitudinal studies are needed to confirm these findings.



Disclosures: Manuel Mendizabal: Gilead: Speaking and Teaching, Biosidus: Speaking and Teaching, Gador: Speaking and Teaching, Knight: Speaking and Teaching, Novo Nordisk: Advisor, Magdalena Princz: Nothing to Disclose, FEDERICO PIÑERO: Nothing to Disclose, Amparo Gabrielli: Nothing to Disclose, Luciano Olguin: Nothing to Disclose, Pablo Bizzotto: Nothing to Disclose, Matias Cortiñas: Nothing to Disclose, Jimena Flores: Nothing to Disclose, Josefina Pages: Nothing to Disclose, Marcello Silva: Nothing to Disclose, Juan Pablo Arab: Nothing to Disclose.

2550 | BRIDGING MASLD CARE GAPS THROUGH COMMUNITY-BASED PROVIDER EDUCATION

Lesley Miller[1] Aarshi Vipani[2] Natasha Travis[1] Sarah Koumtouzoua[1] Carol Pashman Derman[3] Sarah Gallant[4] Kristi Cohn[5] Walid Ayoub[2], [1]Emory University School of Medicine, [2]Cedars-Sinai Medical Center, [3]MedicusCME, [4]Petauri Kinect |MASHNET, [5]Petauri Kinect | MASHNET

Background: Despite the rising prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated

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steatohepatitis (MASH), over 50% of at-risk adults remain unscreened. Delayed diagnosis increases patient and health system burden, particularly in advanced stages, while knowledge gaps among providers limit opportunities for early intervention. Community-based provider educational resources are needed to improve MASLD care delivery. **Methods:** Two live, in-person MASLD community education workshops were conducted in Los Angeles (February 2026) and Atlanta (March 2026). Invitees included physicians, advanced practice providers, and extended care team members specializing in primary care, gastroenterology, hepatology, endocrinology, nutrition, and social work. Outreach targeted providers affiliated with federally qualified health centers, health systems, and independent practices within a 25-mile radius of each workshop venue. The curriculum combined a didactic lecture on MASLD prevalence, risk factors, screening, test interpretation, and management approaches with interactive case discussions. **Results:** Of the 20 attendees, 16 completed pre- and post-session surveys. Most were in practice for $\geq$11 years (62.5%), and 50% held MD or DO licensure. Primary care (25%) and hepatology (25%) were the most represented specialties. Baseline care pathway utilization was limited, with 69.2% reporting unfamiliarity with or an institutional absence of systemized protocols. However, 93.75% indicated the session influenced their clinical practice. Open-response data highlighted intended actions within 30 days, including increased MASLD screening for high-risk patients using Fibrosis-4 (FIB-4) and prioritization of continued MASLD education and best practice sharing. Additional planned changes included greater focus on preventative care, such as patient education and nutrition counseling. Participants demonstrated improved confidence across multiple areas, including a 60% increase in ability to identify risk factors, 75% in recognizing early-stage MASLD, and 100% in counseling patients on risk factors, diagnostics, and treatment options. All participants reported the workshop achieved its learning objectives. Beyond providing education, these sessions also helped inform future programming, with attendees emphasizing the need for broader community-based interventions for both patients and providers. **Conclusion:** Expanded community-based education is needed to improve awareness and adoption of MASLD screening and management best practices. Educational initiatives should prioritize interactive, case-based learning to enhance engagement and facilitate practical application. Future programs may amplify their impact through earlier outreach and proactive scheduling to reduce conflicts with local competing events and maximize attendance.

Disclosures: Lesley Miller: Gilead Sciences: Grant/Research Support, AbbVie: Advisor, Aarshi Vipani: Nothing to Disclose, Natasha Travis: Nothing to Disclose, Sarah Koumtouzoua: Nothing to Disclose, Carol Pashman Derman: Nothing to Disclose, Sarah Gallant: Petauri Kinect: Employee, Kristi Cohn: Nothing to Disclose, Walid Ayoub: Gilead, Ipsen, Mirum, GSK, 89bio, Madrigal, Genfit, Zydus: Grant/Research Support, perspectum: Advisor, Gilead, Ipsen, Madrigal, NovoNordick: Speaking and Teaching.

2551 | FIBRO-INFLAMMATORY LIVER INJURY, NOT STEATOSIS, PREDICTS INCIDENT COMPOSITE NEUROPSYCHIATRIC EVENTS AND MORTALITY IN THE UK BIOBANK

Tsubasa Tsutsumi[1] Wen Hui Lim[2] Darren Jun Hao Tan[2] Jing Kai Tioh[3] Damien Chua[4] Hun Jee Choe[5] Ryan YanZhe Lim[3] Mirudhula Gnanavelou[3] Jordan Jun Yi Low[3] Benjamin YQ Tan[3] Hirokazu Takahashi[6] Huang Wei Ting[7] Mamas A. Mamas[8] Anurug Methra[9] Mei Chin Lim[2] Cheng Han Ng[2] Mark Muthiah[3],
[1]Kurume University Scool of Medicine, [2]National University Hospital, [3]National University of Singapore, [4]Nanyang Technological University, [5]Hallym University Dongtan Sacred Heart Hospital, [6]Saga University, [7]National Heart Centre Singapore, [8]Keele University, [9]Emory University School of Medicine

Background: Steatotic liver disease may be linked to neuropsychiatric outcomes, but the relevant liver MRI signal remains uncertain. Iron-corrected T1 (cT1) reflects fibro-inflammatory liver injury, whereas proton density fat fraction (PDFF) quantifies hepatic fat. We examined associations of cT1 and PDFF with incident neuropsychiatric events and mortality and assessed whether combined liver-brain MRI phenotyping identifies a higher-risk subgroup. **Methods:** This prospective UK Biobank study included 29,344 participants with liver MRI measures of cT1 and PDFF and brain MRI quantification of white matter hyperintensity (WMH) volume. Participants were classified into four imaging phenotypes according to liver imaging impairment (cT1 $\geq$800 ms) and high WMH burden, defined as age-adjusted WMH volume >80th percentile. Cause-specific Cox models estimated risks of composite neuropsychiatric events, defined as stroke, dementia, or late-life depression, liver events, and all-cause mortality. Models were adjusted for age, sex, diabetes, hypertension, dyslipidemia, smoking, alcohol intake, education, and deprivation index. **Results:** Over a median follow-up of 5.7 years, 530 neuropsychiatric events, 231 liver events, and 631 deaths occurred. Higher cT1 per 100 ms was associated with neuropsychiatric events (HR 1.31, 95% CI 1.04–1.65), liver events (HR 2.36, 1.77–3.15), and mortality (HR 1.29, 1.04–1.60). PDFF was not associated with neuropsychiatric events (HR 1.00, 0.98–1.03) or mortality (HR 1.00, 0.97–1.03),

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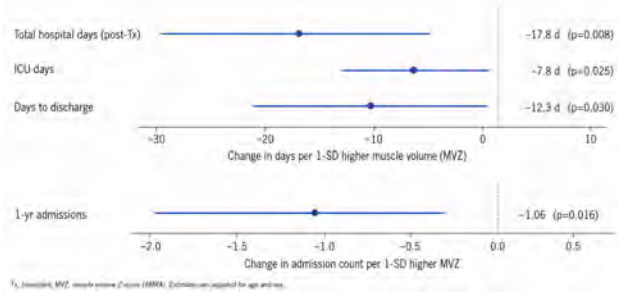
but was associated with liver events (HR 1.09, 1.07–1.12). Log-transformed WMH volume was associated with neuropsychiatric events (HR 1.26, 1.08–1.48) and mortality (HR 1.17, 1.01–1.35). Participants with both liver and brain imaging impairment had the highest risk estimates for neuropsychiatric events (HR 2.30, 1.00–5.29) and liver events (HR 7.13, 3.32–15.33) compared with participants without either imaging impairment. In the prespecified MASLD subgroup, markedly elevated cT1 ($\geq$875 ms) was associated with neuropsychiatric events (HR 4.48, 1.55–12.98) and liver events (HR 6.11, 2.03–18.36). **Conclusion:** Higher cT1 was associated with incident neuropsychiatric events, liver events, and mortality, while PDFF was associated only with liver events. The combined cT1-WMH phenotype identified the highest-risk imaging group. In this cohort, cT1 was more closely associated with extrahepatic outcomes than PDFF.

Disclosures: Tsubasa Tsutsumi: Madrigal: Consultant, Wen Hui Lim: Nothing to Disclose, Darren Jun Hao Tan: Nothing to Disclose, Jing Kai Tioh: Nothing to Disclose, Damien Chua: Nothing to Disclose, Hun Jee Choe: Nothing to Disclose, Ryan YanZhe Lim: Nothing to Disclose, Mirudhula Gnanavelou: Nothing to Disclose, Jordan Jun Yi Low: Nothing to Disclose, Benjamin YQ Tan: Nothing to Disclose, Hirokazu Takahashi: Sysmex: Grant/Research Support, Novo Nordisk: Speaking and Teaching, Taisho: Speaking and Teaching, Takeda: Grant/Research Support, Lilly: Speaking and Teaching, Boehringer Ingelheim: Speaking and Teaching, Huang Wei Ting: Nothing to Disclose, Mamas A. Mamas: Nothing to Disclose, Anurug Methra: Nothing to Disclose, Mei Chin Lim: Nothing to Disclose, Cheng Han Ng: Nothing to Disclose, Mark Muthiah: Nothing to Disclose.

2552 | LOWER MRI-DERIVED MUSCLE VOLUME Z-SCORE IS ASSOCIATED WITH GREATER POST-TRANSPLANT HOSPITAL BURDEN IN PATIENTS WITH CIRRHOSIS EVALUATED FOR LIVER TRANSPLANTATION

Tsubasa Tsutsumi[1] Mary Rinella[2] Omar Jamil[2], [1]Kurume University Scool of Medicine, [2]The University of Chicago

Background: Few markers anticipate post-transplant hospital burden in patients with cirrhosis undergoing liver transplantation. Body-composition assessment in cirrhosis remains inconsistent, but may provide markers relevant to post-transplant recovery. The AMRA(R) Profiler 4 MAsS Scan provides automated fat-water-separated whole-body MRI measures of muscle volume, muscle fat infiltration, adipose tissue, and liver fat. We examined whether AMRA-derived muscle volume Z-score (MVZ) provides MELD-independent information associated with post-transplant hospital burden. **Methods:** We studied a single-center retrospective cohort of 55 patients with cirrhosis evaluated for liver transplantation (LT), including 18 LT recipients and 37 non-LT patients. AMRA-derived metrics were MVZ (sex and BMI adjusted), muscle fat infiltration (MFI; sex adjusted), and liver fat. Associations between AMRA metrics and MELD 3.0 were assessed by Spearman correlation and across transplant status. In LT recipients, post-transplant hospital days, ICU days, days to discharge, and 1-year admissions were analyzed using age- and sex-adjusted linear models. **Results:** Median age was 64 years, 36% were female, and median MELD was 10. MELD was higher in LT recipients than non-LT patients (median 13 vs 9; $p = 0.024$). MVZ and MFI were essentially uncorrelated with MELD (rho −0.04 and −0.02) and did not differ by transplant status (MVZ $p = 0.49$; MFI $p = 0.99$). In contrast, liver fat was inversely correlated with MELD (rho −0.57; $p < 0.001$). Among LT recipients, each 1-SD higher MVZ was associated with fewer post-transplant hospital days (−17.8; $p = 0.008$), ICU days (−7.8; $p = 0.025$), days to discharge (−12.3; $p = 0.030$), and 1-year re-admissions (−1.06; $p = 0.016$) in age- and sex-adjusted models. In parallel age/sex-adjusted models, MELD was not associated with these outcomes (all $p \geq 0.36$). MFI and general-population adverse-muscle-composition thresholds did not separate these post-transplant outcomes. **Conclusion:** Among LT recipients, pre-transplant AMRA (R) Profiler 4 MAsS Scan-derived MVZ was associated with post-transplant hospitalization and ICU burden not captured by MELD. These findings support MRI-derived muscle volume as a potential prognosticator of post-transplant course. These exploratory findings warrant validation in larger multicenter cohorts.



Disclosures: Tsubasa Tsutsumi: Madrigal: Consultant, Mary Rinella: akero: Consultant, akero: Consultant, 89Bio: Consultant, 89Bio: Consultant, Boehringer Ingelheim: Consultant, Boehringer Ingelheim: Consultant, Cytodyn: Consultant, Cytodyn: Consultant, Echosens: Consultant, Echosens: Consultant, Histoindex: Consultant, Histoindex: Consultant, Intercept:

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2553 | LIVER FAT IN RELATION TO PROGNOSTIC OUTCOMES OF COLORECTAL CANCER: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Liver steatosis is a prevalent liver condition which shares risk factors with colorectal cancer (CRC), such as body fatness and having a Western lifestyle. Several studies have investigated the role of liver steatosis in CRC recurrence, metastasis, and mortality, but study results are inconsistent and large between-study heterogeneity exists. Here, we summarized and analysed all available literature on liver steatosis in relation to prognostic outcomes of CRC to explain between-study heterogeneity. **Methods:** We systematically searched PubMed, Scopus and Web of Science databases using Medical Subject Headings and free-text words. The search was conducted on 11 February 2026 and relevant prognostic outcomes included cancer recurrence, cancer metastasis, synchronous liver metastases, metachronous liver metastases, disease-free survival (DFS), overall survival (OS), and cancer-specific survival (CSS). If sufficient ($n \geq 3$) studies reported risk estimates on the respective prognostic outcome, we conducted meta-analyses with random-effects models, Quality of the included studies was assessed with the Newcastle-Ottawa Scale. **Results:** In total, 33 studies were identified for the systematic review, of which 17 studies were included in the meta-analyses. Liver steatosis at time of cancer diagnosis was associated with a higher risk of metachronous metastases ($n = 4$ studies, pooled hazard ratio [HR] 1.65, 95% confidence interval [CI] 1.14-2.37, I^2 = 64%) and worse DFS ($n = 7$, HR 1.22, 95%CI 1.02-1.47, I^2 = 65%). Liver steatosis was not associated with OS ($n = 8$, HR 0.86, 95%CI 0.66-1.12, I^2 = 82%), nor CSS ($n = 5$, HR 1.02, 95%CI 0.79-1.32, I^2 = 84%). Results remained consistent when restricting meta-analyses to studies that solely investigated metastatic cancer ($n = 4$ and 5 studies for DFS and OS, respectively). Further subgroup analyses based on cancer stage or tumour location were not possible ($n < 3$ studies per subgroup). **Conclusion:** Liver steatosis at time of diagnosis was associated with higher risk of liver metastases during follow-up and poorer DFS in patients with all stages of CRC. Future studies should consider exploring relevant subgroups based on primary tumour location and cancer stage.
Disclosures: Deborah Ophoff: Nothing to Disclose, Nienke Zwart: Nothing to Disclose, Moniek van Zutphen: Nothing to Disclose, Daniel Bos: Nothing to Disclose, N. Tjarda van Heek: Nothing to Disclose, Johannes de Wilt: Nothing to Disclose, Harm Westdorp: Nothing to Disclose, Edward Giovannucci: Nothing to Disclose, Ellen Kampman: Nothing to Disclose, Dieuwertje Kok: Nothing to Disclose.

2554 | THE INTERPLAY OF ALCOHOL USE PATTERNS AND CARDIOMETABOLIC RISK FACTORS ON FIBROSIS IN STEATOTIC LIVER DISEASE

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Background: Alcohol use and metabolic syndrome are the two leading causes of steatotic liver disease (SLD). Recently, there has been increasing recognition of the complexity of interplay of these risk factors. However, further research is needed to tease out the interactions of these risk factors, with recent studies pointing to insulin resistance as particularly significant cardiometabolic risk factor CMRF, and alcohol use as contributing to fibrosis risk even among patients with MASLD. These findings raise questions pertaining to the optimal threshold for alcohol use in defining the subtype of SLD as well as the impact of alcohol use patterns. Similarly, the relative impact of CMRF on SLD requires exploration, in terms of the impact of increasing number of cardiometabolic risk factors, control of these risk factors, and whether specific risk factors, particularly type 2 diabetes, have a greater impact on fibrosis. **Methods:** We preformed a population-based study using the NHANES database, using data from transient elastography (FibroScan) and survey questions to examine fibrosis, alcohol use patterns, and CMRF. We included patients >18 years of age with the presence of valid elastography and steatotic liver disease, and excluded patients with HBSag+, HCV RNA+, Ferritin>300 and Tsat>45%. We used descriptive statistics with mean and standard deviation (SD) for normally distributed continuous variables, medians and interquartile range (IQR) for non-normally distributed continuous variables, and frequency (percentage) for categorical variables. We used ANOVA test to compare the degree of fibrosis between groups if normally distributed and the Kruskal-Wallis test if non-normally distributed. A p-value of 0.05 defined significance. **Results:** Of 4073 patients, 915 had no drinking, 2066 moderate, 609 heavy, and 208 high-intensity. Fibrosis score was significantly impacted by the number of CMRF and by presence of diabetes, at all levels of alcohol use. However, the impact of additional CMRF in patients with diabetes was not significant. Of 3721 patients with MASLD by AASLD criteria, 591 had heavy drinking by NIAAA criteria, and 205 had high-intensity drinking by NIAAA criteria. Drinking patterns had a statistically significant effect on fibrosis within the MASLD group, but there was no clear dose-dependent effect. **Conclusion:** Alcohol use patterns and CMRF coexist and contribute to fibrosis risk in SLD. The presence and control of diabetes was the most significant CMRF across alcohol use levels. A significant number of patients with classified as MASLD display high-risk alcohol use by NIAAA criteria. While drinking patterns had a statistically significant impact on fibrosis in patients with MASLD, the clinical impact is less clear.

Impact of DM2 on fibrosis, stratified by alcohol use

	No drinking	Moderate drinking	Heavy drinking	High-intensity drinking
Poorly controlled DM2 (A1c>7)	6.4 (4.9–8.9), n=154	6.2 (5–8.3), n=218	6.1 (4.8–9.1), n=58	7.6 (6.2–10.7), n=20
Well-controlled DM2 (A1c<7)	6 (4.9–7.4), n=176	6 (4.8–8.4), n=251	5.7 (4.3–7.7), n=62	6.4 (4.5–8.1), n=20
No DM2	5.4 (4.3–6.5), n=585	5.1 (4.2–5.3), n=1597	5 (4.1–6.2), n=643	5.4 (4.4–6.5), n=289
P value	<0.05	<0.05	<0.05	<0.05

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2555 | PREVALENCE, DEMOGRAPHIC PROFILE AND ETIOLOGY OF LIVER DISEASE IN WOMEN WITH NEWLY DIAGNOSED BREAST CANCER: A RETROSPECTIVE COHORT STUDY

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Background: Breast cancer is the most frequent cancer among women globally and is increasingly linked to metabolic and hepatic comorbidities that can negatively impact therapeutic outcomes. Baseline hepatic dysfunction in newly diagnosed breast cancer patients can be due to viral hepatitis, alcohol-related liver injury, metabolic dysfunction-associated steatotic liver disease (MASLD), or hepatic metastases. Systemic breast cancer therapies possess significant hepatotoxic potential. Pre-existing hepatic abnormalities may increase toxicity from treatment, result in dose modifications and impair therapeutic efficacy . Thus, at the critical clinical intersection of oncology and hepatology, comprehensive baseline hepatic and metabolic phenotyping of treatment-naïve breast cancer patients. **Methods:** This was a retrospective cohort study of treatment-naive women with breast cancer who were registered at a tertiary oncology referral center between January 2020 and December 2024. Clinical, biochemical and radiological data were obtained from the electronic medical records. Available baseline assessments included liver function tests (LFTs), abdominal ultrasound, viral serology and metabolic comorbidities. Statistical analysis was done by SPSS version 16. **Results:** A total of 4394 women with a new breast cancer diagnosis were included. The median age was 53 years (range 21-89 years). Baseline viral screening (HBsAg, Anti-HCV and HIV) was negative in 99.7% of patients tested. MASLD was defined as imaging-proven hepatic steatosis with one or more

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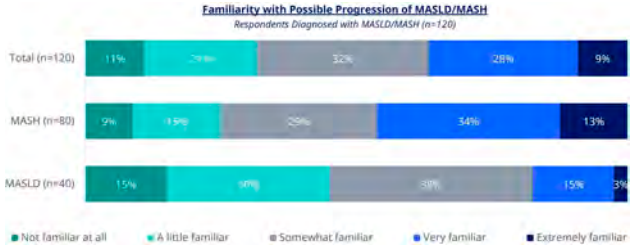
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cardiometabolic risk factors. Hepatic steatosis was found in 41.2% (n = 1,488) of the 3,612 patients who underwent baseline abdominal ultrasonography. 40.2% (n = 1,452) met criteria for MASLD. Among patients with hepatic steatosis, 97.6% met criteria for MASLD, while 2.4% (n = 36) had isolated steatosis without identifiable metabolic risk factors. Out of (4,046) tested patients, 20.37% (n = 824) had abnormal baseline LFTs, consisting of 16.26% (n = 658) with isolated transaminitis, 2.20% (n = 89) with isolated increased ALP, and 1.90% (n = 77) with both abnormalities. Other hepatobiliary abnormalities were cholelithiasis in 5.8% (n = 211), hepatic cysts in 2.1% (n = 76), radiologically evident liver metastases in 1.2% (n = 45) and 16 patients had cirrhosis (0.44%) prior to initiation of oncological therapy. **Conclusion:** Women with newly diagnosed breast cancer have a high prevalence of baseline hepatic abnormalities, with MASLD as the leading cause. These findings underscore the need for complete baseline hepatic evaluation before initiating potentially hepatotoxic systemic or radiation therapy. Early detection of MASLD and other liver abnormalities may help with risk stratification, treatment plan optimization, proactive hepatology referral, and optimization of oncologic outcomes.
Disclosures: Sujatha Lakshminarayanan: Nothing to Disclose, Thirumoorthi Natarajan: Nothing to Disclose.

2556 | ACT ON MASH – US DATA: A SURVEY OF AWARENESS, UNDERSTANDING, AND PERCEPTIONS OF MASLD AND MASH AMONG PEOPLE LIVING WITH MASLD/MASH OR AT RISK FOR MASH

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) affects about 1 in 3 people in the US; yet, the experiences and views of those living with, or at risk for, MASLD have been insufficiently described. This study evaluated the awareness, knowledge, and perceptions of MASLD and metabolic dysfunction–associated steatohepatitis (MASH) among people diagnosed with, or at risk for, MASLD/MASH. **Methods:** In 2025, we conducted an online cross-sectional survey of people diagnosed with, or at risk for, MASLD/MASH in multiple countries. This analysis includes data from respondents in the US. The survey was developed by a multidisciplinary team, including a patient advocacy representative. "At risk" was defined as having ≥1 cardiometabolic risk factor or elevated liver enzymes but no MASLD/MASH diagnosis. Recruitment was conducted via online panels, targeted outreach, and social media. **Results:** 160 respondents completed the survey: 40 with MASLD, 80 with MASH, and 40 at risk for MASLD/MASH. The mean age of the respondents was 50 years. 19% were of Hispanic ethnicity and 58% were females. The most common cardiometabolic comorbidities among respondents with MASLD were: obesity/overweight (78%), hypertension (60%), and sleep apnea (48%); among those with MASH: obesity/overweight (61%), hypertension (46%), type 2 diabetes (39%), and dyslipidemia (39%); and among those at risk for MASH: obesity/overweight (63%), hypertension (60%), and type 2 diabetes (43%). The reported time between initial testing and diagnosis of liver disease averaged 22 months for respondents with MASH and 24 months for those with MASLD. Perceived timeliness of MASLD/MASH diagnosis was common (69%). Few respondents reported being "very" or "extremely" familiar with disease progression (MASLD, 18%; MASH, 47%; Figure). 53% of all respondents have not had their healthcare provider (HCP) discuss MASLD/MASH risk factors prior to diagnosis. Among at-risk respondents, 60% were aware of being at risk for MASLD/MASH, and only 33% reported having received screening. Among at-risk respondents who had not received screening, 67% reported that an HCP had not recommended screening. Overall, 30% of at-risk respondents reported no intention of asking an HCP for liver disease screening. 47% of all respondents with MASLD/MASH and those at-risk for MASH who received screening reported that primary care physicians were the first to recommend screening for liver disease. 55% of respondents agreed or strongly agreed that liver disease is associated with stigma. **Conclusion:** US respondents reported gaps in familiarity with MASLD/MASH progression and low screening uptake among those at risk for MASH. The low screening uptake and the presence of perceived stigma underscore the need for patient-focused education and strengthened patient-HCP communication to support earlier screening and improve patients' awareness of MASLD/MASH.



Disclosures: Husam Albarmawi: Novo Nordisk Inc.: Employee, Novo Nordisk Inc.: Stock - publicly traded company, Genentech Inc.: Employee, Genentech Inc.: Stock - publicly traded company, Nathalie Marcela Eklöf: Nothing to Disclose, Maximilian Kurt Jara: Nothing to Disclose, Jeff McIntyre: Nothing to Disclose, Marco Petti: Nothing to Disclose, Lauren Nephew:

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2557 | AUDIT-C SCORE IN PATIENTS WITH MASLD AND ADVANCED LIVER FIBROSIS-ANALYSIS OF A LARGE REGIONAL VETERANS AFFAIRS COHORT

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Background: Alcohol use is frequently observed in patients with metabolic dysfunction-associated steatotic liver disease (MASLD), even when criteria for MetALD are not met. We sought to determine whether alcohol use, as identified by Alcohol Use Disorders Identification Test-Consumption (AUDIT-C) scores, was associated with liver fibrosis burden, cardiovascular risk, and preventive care utilization in a regional (South-Central) Veterans Affairs MASLD cohort. **Methods:** In this retrospective primary care cohort, we identified 315,578 veterans with MASLD for fiscal year 2024, excluding those with significant alcohol use (< 30g/day for men and < 20g/day for women). Veterans with BMI above 30 (37.1%) and advanced liver fibrosis (3.3%) were included; decompensated cirrhosis was excluded. Advanced fibrosis was defined by Fibrosis-4 (FIB-4) > 2.67, with age capped at 65. AUDIT-C scores ≥ 4 for men and ≥ 3 for women were classified as positive screens. Scores < 8 were classified as low and ≥ 8 as high. **Results:** Of the 4,107 veterans meeting inclusion criteria, 97.3% had AUDIT-C scores recorded. Median age was 67 years (IQR 61–72), 94.6% male, 72.4% Caucasian (17.9% African American). AUDIT-C screens were positive in 1.6% of men and 8.1% of women; 140 (3.5%) had high and 3,855 (96.5%) had low scores (58.3% scored 0). Veterans with positive AUDIT-C scores were younger and less often above 65 years (73.2% vs 91.0%, p < 0.001). Positive AUDIT-C screening was associated with significantly greater liver fibrosis burden, including higher median FIB-4 scores [3.7 (IQR 3.1– 4.9) vs 3.2 (2.8 – 4.1), p = 0.004] and NAFLD Fibrosis Scores [1.89 (1.14–2.71) vs 1.39 (0.84–2.05), p = 0.008]. Incremental rise in ALT compared with the previous year (2023) was more common among positive screens (54.9% vs 32.2%, p = 0.001). Despite greater liver disease severity, positive AUDIT-C patients demonstrated lower use of preventive cardiometabolic therapies and services. They were less likely to attend weight loss clinics (12.7% vs 24.6%, p = 0.028) and receive statin therapy (43.7% vs 62.4%, p = 0.004). Among patients with high ASCVD risk (> 20%), positive screens remained less likely to receive statins (54.2% vs 78.0%, p = 0.014). AUD pharmacotherapy use was higher among positive screens (5.6% vs 0.7%, p = 0.011), though overall utilization remained low. In secondary analyses, high (≥ 8) versus low (< 8), high AUDIT-C scores were associated with higher median FIB-4 (3.5 vs 3.3, p = 0.013) and NAFLD Fibrosis Scores (1.76 vs 1.42, p = 0.021). **Conclusion:** Positive AUDIT-C screening among veterans with MASLD was associated with increased liver fibrosis and biochemical liver injury, yet reduced utilization of cardiovascular preventive therapies and weight management services. These findings highlight a significant care gap and support the integration of alcohol-focused interventions and cardiometabolic risk reduction strategies in veterans with MASLD.

Table 1. Clinical, liver fibrosis, and cardiometabolic characteristics by AUDIT-C screening status in veterans with MASLD

Variable	Negative AUDIT-C Screen	Positive AUDIT-C Screen	p value
Age >65 years	87.3%	12.7%	<0.001
Median FIB-4 score (IQR)	3.2 (2.8–4.1)	3.7 (3.1–4.9)	0.004
Median NAFLD Fibrosis Score (IQR)	1.39 (0.84–2.05)	1.89 (1.14–2.71)	0.008
Elevated AST in prior 1 year	30.2%	52.1%	0.001
Elevated ALT in prior 1 year	32.2%	54.9%	<0.001
NSBB use	18.2%	9.9%	0.08
GI/liver follow-up	54.2%	43.7	0.11
High ASCVD risk (>20%)	54.7%	33.8%	0.002
Type 2 diabetes among high ASCVD risk patients	72.9%	45.8%	0.009
Elevated HbA1c among high ASCVD risk patients	45.8%	25.0%	0.048
Statin use, overall	62.4%	43.7%	0.004
Weight loss clinic attendance[1]	24.6%	12.7%	0.028
Weight loss medication use	10.5%	4.2%	0.11
Nutrition follow-up	35.4%	25.4%	0.12
Use of medications associated with weight gain	38.1%	25.4%	0.047
AUD diagnosis	29.3%	5.6%	0.011

Abbreviations: AUDIT-C, Alcohol Use Disorders Identification Test–Consumption; FIB-4, Fibrosis-4; NAFLD, nonalcoholic fatty liver disease; AST, aspartate aminotransferase; ALT, alanine aminotransferase; NSBB, nonselective beta-blocker; ASCVD, atherosclerotic cardiovascular disease; HbA1c, hemoglobin A1c; AUD, alcohol use disorder.
[1] MOVE clinic (VA weight management program).

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2558 | COFFEE BUT NOT SUGAR-SWEETENED BEVERAGES IS ASSOCIATED WITH LOWER FIBROSIS RISK IN METABOLIC LIVER DISEASE: SYNERGY WITH ALCOHOL CONSUMPTION

Sebastian Niezen[1] Markos Kalligeros[1] Manaav Mehta[2] Elliot Tapper[3], [1]Beth Israel Deaconess Medical Center, [2]University of Massachusetts Medical School, [3]University of Michigan Medical Center

Background: Coffee consumption has been associated with reduced liver fibrosis, though data in metabolic dysfunction–associated steatotic liver disease (MASLD) and metabolic dysfunction–associated alcohol-related liver

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disease (MetALD) remain limited. We evaluated the association of coffee and sugar-sweetened beverage (SSB) intake with advanced fibrosis in a nationally representative cohort. **Methods:** We performed a cross-sectional analysis of adults from NHANES 2021–2023. Advanced fibrosis was defined as liver stiffness measurement (LSM) ≥10 kPa. Coffee and SSB intake were categorized as 0, >0–1, >1–3, and >3 cups/day. Survey-weighted logistic regression models were adjusted for demographic, metabolic, and behavioral covariates. Trend analyses assessed dose-response relationships using ordinal exposure modeling. Interaction models evaluated effect modification by continuous alcohol consumption. Exploratory stratified analyses by alcohol use category and a sensitivity analysis restricted to MASLD only (excluding MetALD) were performed. **Results:** The study included 245,061,169 weighted participants (median age 48 years; 52% female). Steatosis was present in 36% (88.2 million) and advanced fibrosis in 8.0% (19.6 million) of US adults. MASLD and MetALD accounted for 24% (58.8 million) and 1.9% (4.7 million) of the population, respectively. In adjusted analyses, moderate coffee intake (>1–3 cups/day) was associated with lower odds of advanced fibrosis (OR 0.62, 95% CI 0.41–0.95, p = 0.043). Trend analysis demonstrated a significant inverse dose-response relationship for coffee intake (OR 0.84 per category increase, 95% CI 0.75–0.95, p = 0.012). SSB intake was not significantly associated with advanced fibrosis across any category, and no significant dose-response trend was identified (OR 0.93, 95% CI 0.77–1.11, p = 0.406). Formal coffee with alcohol interaction testing did not identify significant effect modification (all p > 0.48). In exploratory stratified analyses by alcohol use, the protective association of moderate coffee intake appeared most pronounced among moderate drinkers (OR 0.20, 95% CI 0.05–0.76, p = 0.032), though this should be interpreted cautiously given limited subgroup power and a non-significant formal interaction test. Sensitivity analyses restricted to MASLD only yielded directionally consistent results. **Conclusion:** Moderate coffee intake was associated with significantly lower odds of advanced fibrosis among adults with MASLD and MetALD, with evidence of a graded dose-response relationship. SSBintake was not independently associated with fibrosis risk, and the coffee-fibrosis association appeared independent of alcohol consumption.



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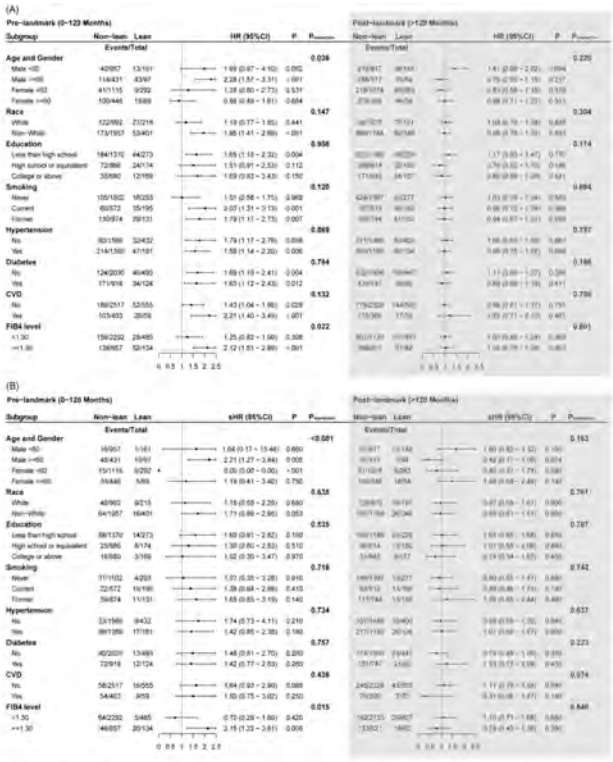
2559 | LONG-TERM SURVIVAL OUTCOMES IN LEAN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE: A COHORT ANALYSIS

Yajing Bo[1] Enrui Xie[1] Xiao Yuan[1] Xinyuan He[1] Zhiluo Yang[1] Xin Liu[1] Qi Shang[1] Xinrong Zhang[2] Yee Hui Yeo[3] Fanpu Ji[1], [1]The Second Affiliated Hospital of Xi'an Jiaotong University, [2]Sun Yat-sen University, [3]Cedars-Sinai Medical Center

Background: The long-term prognosis of lean metabolic dysfunction-associated steatotic liver disease (MASLD) remains controversial, and its specific associations with all-cause and cardiovascular mortality have not been fully elucidated. **Methods:** Data from 3568 participants with MASLD in the Third National Health and Nutrition Examination Survey ((NHANES III) were analyzed. Cox proportional hazard models and Fine-Gray competing-risk models were used to assess all-cause and cardiovascular mortality, respectively. A 10-year landmark analysis was performed to evaluate stage-specific mortality risks. Restricted cubic spline analyses examined dose-response associations between body mass index (BMI) and early all-cause mortality. Subgroup analyses were conducted to identify high-risk populations. **Results:** Over a median follow-up of 27.7 years, lean MASLD was independently associated with an increased risk of early all-cause mortality within 0-120 months (adjusted hazard ratio [HR], 1.68; 95% confidence interval [CI], 1.29-2.20), whereas this association was no longer significant after 120 months (adjusted HR 1.04, 95%CI 0.87-1.25). No significant association between lean MASLD and cardiovascular mortality was observed during either period. RCS analysis demonstrated a nonlinear U-shaped association between BMI and early all-cause mortality, with an inflection point at 29.5 kg/m². The increased early mortality risk was most pronounced among males aged ≥ 60 years and participants with a baseline FIB-4 index ≥ 1.30. **Conclusion:** Lean MASLD was associated with increased early all-cause mortality and demonstrated a U-shaped relationship with BMI and mortality risk. Males aged ≥ 60 years and patients with FIB-4 ≥ 1.30 may represent high-risk phenotypes requiring closer clinical monitoring.

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Stratified analysis of lean MASLD and mortality. A: All-cause mortality; B: Cardiovascular mortality. The model was adjusted for age, sex, race, education, poverty income ratio, smoking, diabetes, CVD, hypertension, and FIB-4.

Disclosures: Yajing Bo: Nothing to Disclose, Enrui Xie: Nothing to Disclose, Xiao Yuan: Nothing to Disclose, Xinyuan He: Nothing to Disclose, Zhiluo Yang: Nothing to Disclose, Xin Liu: Nothing to Disclose, Qi Shang: Nothing to Disclose, Xinrong Zhang: Nothing to Disclose, Yee Hui Yeo: Nothing to Disclose, Fanpu Ji: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose.

2561 | METABOLIC DYSFUNCTION–ASSOCIATED STEATOTIC LIVER DISEASE: HISTOLOGICAL SPECTRUM IN LEAN VERSUS OVERWEIGHT, AND PATIENTS WITH OBESITY

Helma Cotrim[1] Luiz Antonio de-Freitas[2] Antonio Ricardo Antonio Ricardo Andrade[2] Ana Cristina Ana Cristina Landin[2] Neilson Souza[2], [1]Medicine School-Universidade Federal Da Bahia - Brazil, [2]Federal University of Bahia -Brazil

Background and Aim: MASLD is a global health challenge. Although strongly linked to obesity, lean MASLD represents a distinct and underrecognized phenotype. Aim: to compare histological severity and non-invasive fibrosis assessment across lean, overweight, and patients with obesity. **Methods:** In this cross-sectional study, 133 patients with biopsy-proven MASLD/MASH were categorized as lean (n = 30), overweight (n = 59), and patients with obesity (n = 44) (Fig 1-A). Clinical variables, as well as non-invasive scores (e.g., FIB-4), were analyzed. Liver biopsies were assessed using the Kleiner classification and the NAFLD Activity Score (NAS). Multivariate logistic regression was performed to identify predictors of significant fibrosis ($\geq$F2) and steatohepatitis (NAS$\geq$3). Spearman correlation analysis was used to assess the relationship between histological, metabolic, and non-invasive markers. The diagnostic accuracy of FIB-4 for significant ($\geq$F2) and advanced fibrosis ($\geq$F3) was evaluated using receiver operating characteristic (ROC) curves. **Results:** Lean patients had a significantly lower prevalence of type 2 diabetes (DM2) (30.0% vs. 61.0% and 68.2%) and metabolic syndrome (13.3% vs. 42.4% and 54.5%) than overweight and patients with obesity ($p < 0.05$). Despite this more favorable metabolic profile, histological severity was comparable across BMI categories. Significant fibrosis ($\geq$ F2) was observed in 50.0% of lean, 49.1% of overweight, and 43.2% of patients with obesity ($p = 0.931$). Rates of steatohepatitis were also similar among groups ($p = 0.723$). In multivariate analysis, DM2 was the only independent predictor of significant fibrosis (OR: 4.01; 95% CI: 1.52–10.59; p = 0.005), whereas BMI categories were not associated with fibrosis ($p > 0.25$) or steatohepatitis ($p > 0.20$). Correlation analysis showed a negligible relationship between BMI and fibrosis stage (rho = -0.04). FIB-4 performed better in lean patients for significant ($\geq$F2; AUC: 0.822 vs. 0.743 and 0.695) and advanced fibrosis ($\geq$F3; AUC: 0.954 vs. 0.676 and 0.856) than in overweight and patients with obesity (Fig 1 B, C, D, E, F). **Conclusion:** Lean MASLD patients, in this sample, presented histological severity comparable to that observed in overweight and obesity patients, despite a lower burden of metabolic comorbidities. DM2, rather than BMI, appears to be the main driver of fibrosis progression. The high diagnostic accuracy of FIB-4 in lean patients demonstrated the need for vigilant fibrosis screening even in non-obese individuals with metabolic risk factors.

Disclosures: Helma Cotrim: Nothing to Disclose, Luiz Antonio de-Freitas: Nothing to Disclose, Antonio Ricardo Antonio Ricardo Andrade: Nothing to Disclose, Ana Cristina Ana Cristina Landin: Nothing to Disclose, Neilson Souza: Nothing to Disclose.

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2562 | ALCOHOL-USE TRAJECTORIES AND MAJOR ADVERSE LIVER OUTCOMES IN METALD: A NATIONWIDE LONGITUDINAL COHORT STUDY

Eileen Yoon[1] Hyo Young Lee[2] Sang Bong Ahn[3] Mimi Kim[4] Bo-Kyeong Kang[5] Dae Won Jun[2], [1]Department of Internal Medicine, Hanyang University College of Medicine, [2]Department of Internal Medicine, Hanyang University, [3]Department of Internal Medicine, Nowon Eulji Medical Center, Eulji University, [4]Department of Radiology, Hanyang University College of Medicine, [5]Department of Radiology, Hanyang University College of Medicine

Background: Alcohol contributes to the progression of steatotic liver disease. However, in individuals with MetALD, the impact of changes in drinking behavior on disease progression remains unclear. We investigated whether longitudinal changes in alcohol consumption were associated with the risk of major adverse liver outcomes in people with MetALD. **Methods:** Data were obtained from the Korean National Health Screening Program. Adults with MetALD who completed three screening examinations (2009–2010, 2011–2012, and 2013–2014) were included (n = 58,434). Participants were categorized by alcohol consumption trajectories: Group 1 (sustained consumption), Group 2 (fluctuating consumption), and Group 3 (consistent reduction). The primary outcome was major adverse liver outcomes. Changes in cardiometabolic risk factors from baseline to the last examination were also evaluated. **Results:** Over a median follow-up of 8.1 years, 33.2% of participants were classified as Group 1, 34.8% as Group 2, and 32.0% as Group 3. After multivariable adjustment, Group 3 had a lower risk of major adverse liver outcomes than Group 1 (adjusted HR, 0.84; P = 0.032). For liver-related mortality, risk was lower in Group 2 (adjusted HR, 0.73; P = 0.023) and Group 3 (adjusted HR, 0.65; P = 0.004). Consistent alcohol reduction was accompanied by greater resolution of hypertriglyceridemia and hypertension compared with sustained consumption. **Conclusion:** Alcohol use in MetALD is highly dynamic, and hepatic risk is better captured using longitudinal drinking trajectories. Sustained alcohol reduction appears to confer cardiometabolic benefits, largely through improvements in hypertriglyceridemia and hypertension.

Disclosures: Eileen Yoon: Nothing to Disclose, Hyo Young Lee: Nothing to Disclose, Sang Bong Ahn: Nothing to Disclose, Mimi Kim: Nothing to Disclose, Bo-Kyeong Kang: Nothing to Disclose, Dae Won Jun: Nothing to Disclose.

2563 | WHEN BILE MEETS FAT, THE HEART PAYS: COEXISTING PRIMARY BILIARY CHOLANGITIS AMPLIFIES MYOCARDIAL INFARCTION AND HEART FAILURE RISK IN MASLD

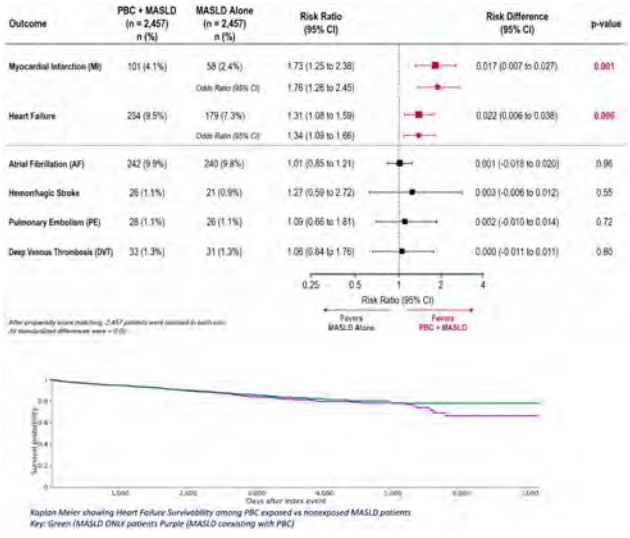
Emeka Stanley Obi[1] Adedeji Adenusi[2] Chimezirim Ezeano[3] Gedion Amdetsion[4] Olamide Asifat[5] Winifred Iklaki[6] Onyinye Ugonabo[7] Basile Njei[8], [1]Brookdale University Hospital and Medical Center, [2]Interfaith Medical Center, [3]Advocate Aurora Healthcare, [4]John H Stroger Hospital of Cook County, [5]Georgia Southern University, [6]University of Missouri Columbia Hospital, [7]Zucker School of Medicine Northwell, [8]Yale University

Background: MASLD is the leading chronic liver disease worldwide, and cardiovascular disease drives most mortality in this population. Primary biliary cholangitis (PBC) produces atherogenic dyslipidemia, autoimmune inflammation, and endothelial dysfunction. The two conditions increasingly coexist, yet the cardiovascular consequences remain poorly defined, and guidelines offer limited direction on cardiac risk in this overlap. Current AASLD and EASL guidance on PBC concentrates on hepatic progression and pruritus, with limited recommendations on extrahepatic cardiovascular risk stratification when MASLD is also present. **Methods:** We conducted a retrospective cohort study using the TriNetX Global Collaborative Network (172 healthcare organizations). Adults aged 18 years and older with MASLD/MASH (ICD10CM K76.0 or K75.81) were identified. Adults with MASLD/MASH (ICD10CM K76.0, K75.81) were stratified by presence (exposure) or absence (control) of PBC (K74.3). Patients with competing liver diseases; alcoholic liver disease, viral hepatitis B or C, hepatic fibrosis, Wilson disease, toxic hepatitis, liver transplantation, or alcohol abuse were excluded. Outcomes included acute myocardial infarction (MI), atrial fibrillation (AF), heart failure (HF), hemorrhagic stroke, pulmonary embolism (PE), and deep venous thrombosis (DVT). Propensity score matching (1: 1) balanced age, sex, race, ethnicity, hypertensive disease, and other cardiometabolic cormobidities. Risk analyses excluded patients with the outcome prior to the time window. Kaplan Meier survival with log rank testing and hazard ratios were computed. **Results:** After matching, 2,457 patients were retained per cohort with all standardized differences below 0.02. Coexisting PBC conferred a significantly higher risk of MI (4.1% vs 2.4%; RR 1.73, 95% CI 1.25 to 2.38; p = 0.001) and heart failure (9.5% vs 7.3%; RR 1.31, 95% CI 1.08 to 1.59; p = 0.006). No significant differences emerged for AF (RR 1.01), hemorrhagic stroke (RR 1.27), PE (RR 1.09), or DVT

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(RR 1.06). Heart failure free survival at the end of the window was 66.4% in the PBC group versus 78.0% in controls. **Conclusion:** Coexisting PBC was associated with a 73% relative increase in MI, a 31% relative increase in heart failure an reduced heart failure survivability among adults with MASLD. The selective rise in cardiac events without a parallel rise in thromboembolic or cerebrovascular events suggests mechanisms rooted in cholestasis driven dyslipidemia, chronic autoimmune inflammation, and altered bile acid signaling rather than a generalized procoagulant state, and points towards coronary and myocardial vulnerability. The PBC and MASLD overlap should be recognized as a high cardiac risk phenotype warranting structured cardiovascular surveillance and lipid optimization in routine PBC care. Some limitations include reliance on administrative coding, absence of data on fibrosis stage, and UDCA use.



Kaplan Meier showing Heart Failure Survivability among PBC exposed vs nonexposed MASLD patients
Key: Green (MASLD ONLY patients Purple (MASLD coexisting with PBC)

Disclosures: Emeka Stanley Obi: Nothing to Disclose, Adedeji Adenusi: Nothing to Disclose, chimezirim ezeano: Nothing to Disclose, Gedion Amdetsion: Nothing to Disclose, Olamide Asifat: Nothing to Disclose, Winifred Iklaki: Nothing to Disclose, Onyinye Ugonabo: Nothing to Disclose, Nothing to Disclose, Basile Njei: Nothing to Disclose.

2564 | LOW USE OF GLP-1 RECEPTOR AGONISTS AMONG U.S. ADULTS WITH OBESITY OR TYPE 2 DIABETES ACROSS LIVER DISEASE RISK MARKERS, NHANES 2005–MARCH 2020

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Background: Glucagon-like peptide-1 receptor agonists (GLP-1RAs) provide glucose-lowering, cardiometabolic, anti-obesity and liver-protective benefits, with expanded indications for metabolic dysfunction-associated steatohepatitis (MASH). They are highly relevant for patients with obesity, type 2 diabetes (T2D), and metabolic dysfunction-associated steatotic liver disease (MASLD). Anti-obesity medication uptake was historically low before the modern GLP-1RA era, limited by patient access and clinician prescribing barriers. It remains unclear whether early GLP-1RA use aligned with cardiometabolic and liver risk or concentrated in populations with better economic and insurance access. This study evaluated GLP-1RA utilization trends in US adults using National Health and Nutrition Examination Survey (NHANES) data from 2005 to 2020. **Methods:** NHANES participants were divided into two eras: 2005–2014 and 2015–March 2020, corresponding to pre- and post-obesity indication expansion of GLP-1RAs.Three cohorts were analyzed: body mass index (BMI) $\geq$30 kg/m²; BMI $\geq$27 kg/m² with at least one weight-related comorbidity; and adults with T2D. MASLD was defined by the Fatty Liver Index, and liver fibrosis risk was stratified by FIB-4 using a cutoff of 1.3. Demographics, poverty-income ratio (PIR), insurance status, MASLD and FIB-4 levels were compared by GLP-1RA use. T-test, chi-square and Fisher's exact test were used for analysis. **Results:** GLP-1RA utilization nearly tripled across eras but remained low in all cohorts. From 2005–2014 to 2015–2020, use increased from 0.4% to 1.2% in adults with BMI $\geq$30 kg/m², 0.4% to 1.2% in those with BMI $\geq$27 kg/m² plus comorbidities, and 0.9% to 3.1% in adults with T2D. In 2015–2020, GLP-1RA users were older in obesity and overweight-comorbidity groups, while sex showed no association with medication uptake. Higher PIR and private insurance were consistently linked to greater GLP-1RA use. GLP-1RA uptake was numerically higher in participants with MASLD without statistical significance. Adults with elevated FIB-4 index had no preferential GLP-1RA prescription; T2D patients with FIB-4 $\geq$1.3 even showed lower utilization than those with lower fibrosis risk. **Conclusion:** GLP-1RAs were substantially underused among US adults with obesity, T2D and liver-risk markers during 2005–2020. Early GLP-1RA adoption was driven more by socioeconomic affordability and insurance coverage than by liver and fibrosis risk stratification. Limited historical indications, cost barriers and clinician prescribing reluctance contributed to low real-world uptake. Expanded GLP-1RA application should prioritize patients with the highest metabolic and hepatic burden to mitigate access disparities.

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Disclosures: Cheng Han: Nothing to Disclose, Maddie Kubiliun: Nothing to Disclose, Wei Zhao: Nothing to Disclose.

2565 | CLINICAL OUTCOMES BY DIABETES STATUS IN BIOPSY-PROVEN MASLD AND METALD: MULTICENTER PROSPECTIVE COHORT STUDY

Won Kim[1] Gi-Ae Kim[2] Bo Kyung; Koo[1], [1]Seoul National University College of Medicine, [2]Kyung Hee University School of Medicine

Background: Although type 2 diabetes (T2D) is associated with adverse clinical outcomes in metabolic dysfunction-associated steatotic liver disease (MASLD), this association has not been well established in biopsy-based studies. We aimed to investigate the risk of clinical outcomes according to T2D status in biopsy-proven MASLD and metabolic dysfunction and alcohol-related liver disease (MetALD). **Methods:** This multicenter prospective cohort study recruited patients with biopsy-proven MASLD and MetALD from eight tertiary hospitals in Korea between 2010 and 2023. The risks of all-cause mortality, cardiovascular disease (CVD), liver-related events (LREs), and extrahepatic malignancies were investigated. Adjusted subdistribution hazard ratios (aSHRs) were calculated using Fine–Gray models accounting for competing risks. **Results:** Among 1,871 patients, 910 (48.7%) had T2D. Patients with T2D exhibited a higher prevalence of significant fibrosis (54.1% vs 33.6%) and metabolic dysfunction-associated steatohepatitis (MASH) or metabolic dysfunction and alcohol-associated steatohepatitis (MetASH) (65.9% vs 52.5%; all $p < 0.001$). In inverse probability of treatment weighting analysis, T2D was associated with increased risks of all-cause mortality (aSHR, 2.06; 95% CI, 1.39−3.05; $p < 0.001$), CVD (aSHR, 1.91; 95% CI, 1.20−3.05; $p = 0.007$), and LREs (aSHR, 1.76; 95% CI, 1.14−2.70; $p = 0.010$) compared to those without T2D. In subgroup analysis of patients with T2D, those with MASH/MetASH or at-risk MASH/MetASH had higher risks of all-cause mortality and LREs, whereas no significant differences in CVD risk were observed. **Conclusion:** T2D is associated with substantially higher risks of all-cause mortality, CVD, and LREs in MASLD and MetALD. Tailored management strategies accounting for T2D status are warranted in MASLD and MetALD.

Disclosures: Won Kim: Nothing to Disclose, Gi-Ae Kim: Nothing to Disclose, Bo Kyung; Koo: Nothing to Disclose.

2566 | MORTALITY DISPARITIES FOLLOW THE PATIENT; ACCESS DISPARITIES FOLLOW THE CENTER: DECOMPOSING WAITLIST EQUITY ACROSS STEATOTIC LIVER DISEASE PHENOTYPES IN 44,935 CANDIDATES

Islam Mohamed[1] Mohamed Nadeem[2] Basil Jalamneh[2] Shilpa Junna[2], [1]The Cleveland Clinic Foundation-Fairview hospital, [2]Cleveland Clinic Foundation

Background: The 2023 Delphi consensus defined MetALD as a distinct steatotic liver disease (SLD) phenotype, yet its waitlist prognosis relative to ALD and MASLD remains uncharacterized at scale. Karnofsky Performance Status (KPS), the sole frailty surrogate in UNOS, varies substantially by center but whether this variation contributes to inequitable waitlist outcomes across SLD phenotypes is unknown. **Methods:** We analyzed OPTN/UNOS STAR data (2017–2023), classifying 44,935 adults at 117 centers as ALD (n = 7,319), MetALD (n = 20,494), or MASLD (n = 17,122) using the validated SLD algorithm. Center-level KPS clustering was quantified by intraclass correlation coefficient (ICC) from a multilevel mixed-effects model; outlier centers were identified by Spiegelhalter overdispersion-adjusted funnel plots. Ninety-day waitlist death/too-sick removal and transplant were modeled as competing risks using Fine-Gray regression, adjusted for listing year, MELD-Na, age, sex, race/ethnicity, insurance, ascites, and encephalopathy. A multilevel cause-specific Cox model with random center intercepts then tested whether equity disparities were attenuated after accounting for center clustering. **Results:** Center membership explained 21.8% of KPS variance after case-mix adjustment (null ICC = 0.170; adjusted ICC = 0.218); Spiegelhalter correction identified 4/117 (3.4%) genuine outlier centers versus 74 by naive count. Medicare and Medicaid patients listed with 2.6–2.7 fewer KPS points than privately insured patients ($p < 0.001$), independent of MELD and disease severity. Ninety-day transplant access was lowest for MASLD (34.7%), intermediate for ALD (44.4%), and highest for MetALD (47.8%; Gray's $p < 0.001$). In adjusted competing risks models, MetALD had significantly lower 90-day mortality than MASLD (sHR 0.79, 95% CI 0.71–0.87). Black patients faced 25% higher mortality (sHR 1.25, 95% CI 1.04–1.52) and Hispanic patients 23% lower transplant access (sHR 0.77, 95% CI 0.74–0.81). Black mortality (sHR 1.25 to 1.25) and Medicare mortality disparities (sHR 1.34 to 1.30) were fully robust to center adjustment, reflecting patient-level inequities. Hispanic mortality (1.17 to 1.05, $p = 0.37$)

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and Medicaid transplant disparities (0.90 to 0.99, p = 0.75) were substantially attenuated largely explained by where patients listed. Center random-effect SDs were twice as large for transplant access as for mortality (0.57 vs. 0.24). **Conclusion:** MASLD carries the greatest access disadvantage despite lower MELD severity at listing. Mortality disparities for Black and Medicare patients persist after center adjustment and represent patient-level inequities requiring systemic intervention. Access disparities for Hispanic and Medicaid patients are largely geographic, identifying high-disparity centers as tractable targets for equity-focused quality improvement.

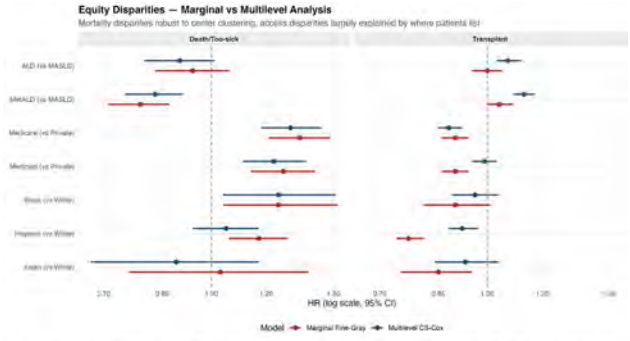


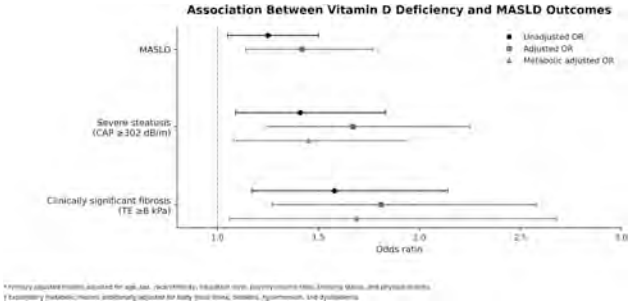
Figure 1. Equity disparities — marginal Fine-Gray vs. multilevel cause-specific Cox. Mortality disparities for Black and Medicare patients are robust to center adjustment; access disparities for Hispanic and Medicaid patients are largely attenuated, reflecting center-level geographic clustering.

Disclosures: Islam Mohamed: Nothing to Disclose, Mohamed Nadeem: Nothing to Disclose, Basil Jalamneh: Nothing to Disclose, Shilpa Junna: Nothing to Disclose.

2567 | VITAMIN D DEFICIENCY IS ASSOCIATED WITH METABOLIC DYSFUNCTION–ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) PREVALENCE, STEATOSIS SEVERITY, AND SIGNIFICANT FIBROSIS: A NATIONAL POPULATION-BASED STUDY

Nishat Anjum Shaik[1] Mohammed Rifat Shaik[2] Kamran Qureshi[3], [1]SSM Health/Saint Louis University, [2]National Institutes of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, [3]Saint Louis University

Background: Vitamin D deficiency has been implicated in pathogenesis of metabolic dysfunction–associated steatotic liver disease (MASLD) through effects on insulin resistance, lipid metabolism, and inflammatory pathways. Prior studies evaluating this relationship used older NAFLD/MAFLD definitions with inconsistent findings, and most assessed steatotic liver disease as a binary outcome without separately evaluating steatosis and fibrosis severity under the current MASLD nomenclature. We aimed to evaluate the association of vitamin D deficiency with MASLD prevalence, severe steatosis, and significant fibrosis in a nationally representative U.S. cohort. **Methods:** We conducted a cross-sectional analysis of adults aged ≥ 18 years from NHANES 2017–2018 with serum 25-hydroxyvitamin D and transient elastography (TE) data. Vitamin D deficiency was defined as serum 25-hydroxyvitamin D < 20 ng/mL. MASLD was defined as controlled attenuation parameter (CAP) ≥ 274 dB/m with ≥ 1 cardiometabolic risk factor, in the absence of excess alcohol use or viral hepatitis. Severe steatosis was defined as CAP ≥ 302 dB/m and significant fibrosis was defined as TE ≥ 8 kPa. Multivariable logistic regression models were used to evaluate associations between vitamin D deficiency and MASLD outcomes. Models were sequentially adjusted for demographics, socioeconomic factors, smoking, physical activity. An exploratory model additionally adjusted for body mass index (BMI), diabetes, hypertension, and dyslipidemia. **Results:** Among 5,225 participants, 1,542 (29.5%) had vitamin D deficiency. Compared with non-deficient participants, vitamin D deficient ones were younger (40.8 vs 49.4 years, p < 0.001), had higher BMI (31.0 vs 29.4 kg/m², p < 0.001), lower HDL (50.8 vs 54.3 mg/dL, p < 0.001), and were more likely to be Black (26.3% vs 6.4%) or Hispanic (26.2% vs 13.5%). Vitamin D deficiency was associated with higher MASLD prevalence on both unadjusted (OR 1.25, 95% CI: 1.05–1.50) and adjusted analyses (adjusted OR [aOR] 1.42, 95% CI: 1.14–1.77). Among those with MASLD, vitamin D deficiency was also associated with severe steatosis (unadjusted OR 1.41, 95% CI: 1.09–1.83; aOR 1.67, 95% CI: 1.24–2.25) and significant fibrosis (unadjusted OR 1.58, 95% CI: 1.17–2.14; aOR 1.81, 95% CI: 1.27–2.58). These associations were attenuated but persisted after additional adjustment for metabolic factors for both severe steatosis (aOR 1.45, 95% CI: 1.08–1.94) and significant fibrosis (aOR 1.69, 95% CI: 1.06–2.68) in exploratory analyses. **Conclusion:** Vitamin D deficiency is associated with MASLD prevalence, severe steatosis, and significant fibrosis. Partial attenuation after metabolic adjustment suggests that the associations may be mediated, in part, through metabolic pathways. These findings support vitamin D deficiency as a potential modifiable risk factor for MASLD and its severity, warranting further evaluation in prospective and interventional studies.



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Disclosures: Nishat Anjum Shaik: Nothing to Disclose, Mohammed Rifat Shaik: Nothing to Disclose, Kamran Qureshi: Nothing to Disclose.

2568 | LEAN VERSUS NON-LEAN MASLD: FIBROSIS BURDEN, CARDIOMETABOLIC PROFILE, AND TEMPORAL TRENDS IN NHANES 2017–2023

Aleena Mujahid[1] Fatima Rajab[2] Mukarram Farooq[3] Ahmad Jalil[4] Haris Yaseen[5] Asim Elahi[1], [1]Harlingen Medical Center, [2]Baptist Hospitals of Southeast Texas, [3]South Texas Health System GME Consortium, [4]BAPTIST MEMORIAL HOSPITAL, [5]University at Buffalo

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) in lean individuals (BMI < 25 kg/m², or < 23 for Asians) is an emerging phenotype with unclear fibrosis risk and awareness. We compared liver fibrosis burden, undiagnosed rates, cardiometabolic profile, and temporal trends between Lean and Non-Lean MASLD using recent NHANES data. **Methods:** We conducted a cross-sectional analysis of NHANES 2017-2023 adults (≥ 18 years) with valid vibration-controlled transient elastography. MASLD defined as CAP ≥ 263 dB/m plus ≥ 1 cardiometabolic risk factor, excluding heavy alcohol and viral hepatitis. Lean defined as BMI < 25 (< 23 for Asians). Survey-weighted analysis compared mean liver stiffness (LSM), significant fibrosis (≥ 8.6 kPa), undiagnosed status, cardiometabolic risk factors, and temporal trends. Multivariable logistic regression with Lean MASLD as reference calculated adjusted odds ratios (aOR). Sensitivity analysis used CAP ≥ 285 dB/m. **Results:** Among 4,938 MASLD participants (weighted N ~159.5 million US adults), Lean MASLD patients (6.9%) had significantly lower mean LSM (5.06 vs 7.18 kPa, p < 0.001) and lower significant fibrosis prevalence (5.3% vs 16.4%, p < 0.001). Alarmingly, 98.3% of Lean MASLD and 99.1% of Non-Lean MASLD were undiagnosed. Cardiometabolically, Lean MASLD had lower dyslipidemia (27.3% vs 39.9%, p < 0.001), but similar rates of diabetes (22.5% vs 23.9%, p = 0.658), hypertension (37.7% vs 42.6%, p = 0.103), and prediabetes (49.0% vs 46.1%, p = 0.438). After multivariable adjustment, Lean MASLD was associated with significantly lower odds of significant fibrosis (aOR = 0.30, 95% CI: 0.18-0.49, p < 0.001). Female sex was protective (aOR = 0.74, 95% CI: 0.60-0.92, p = 0.008). Diabetes (aOR = 2.63) and hypertension (aOR = 1.63) were independent risk factors (both p < 0.001). Sensitivity analysis using CAP ≥ 285 dB/m confirmed findings. Temporal trend analysis showed no significant change in Lean MASLD proportion from pre-pandemic to post-pandemic (6.65% vs 7.22%, p = 0.637). **Conclusion:** Lean MASLD affects an estimated 11.1 million U.S. adults and is associated with substantially lower liver fibrosis burden compared with Non-Lean MASLD (70% lower adjusted odds). However, the very high proportion of undiagnosed disease across both phenotypes highlights an important gap in awareness and detection. These findings support consideration of fibrosis risk assessment in individuals with metabolic risk factors, including diabetes and hypertension, regardless of BMI status.

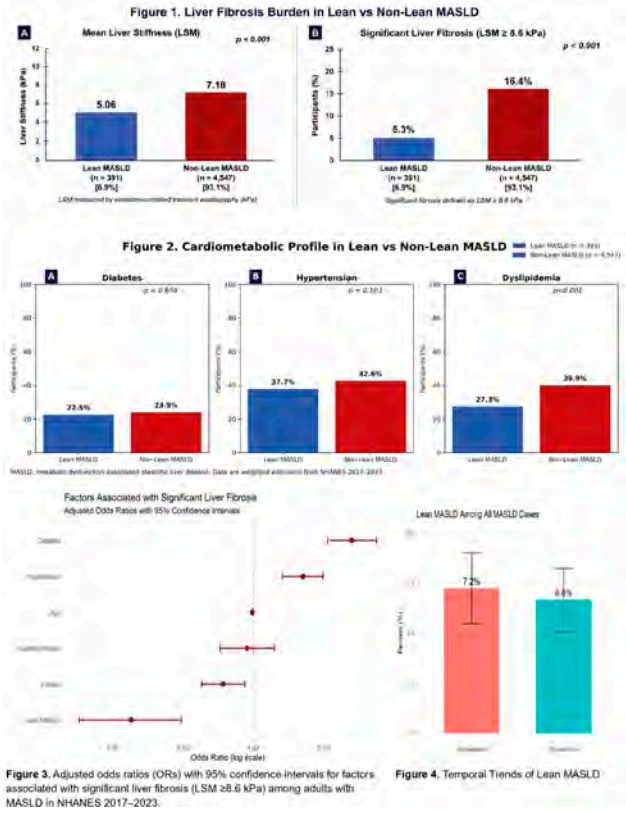


Figure 3. Adjusted odds ratios (ORs) with 95% confidence intervals for factors associated with significant liver fibrosis (LSM ≥8.6 kPa) among adults with MASLD in NHANES 2017–2023.

Figure 4. Temporal Trends of Lean MASLD

Disclosures: Aleena Mujahid: Nothing to Disclose, Fatima Rajab: Nothing to Disclose, Mukarram Farooq: Nothing to Disclose, Ahmad Jalil: Nothing to Disclose, Haris Yaseen: Nothing to Disclose, Asim Elahi: Nothing to Disclose.

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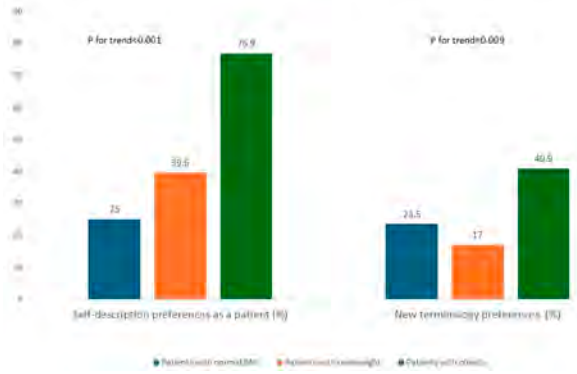
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2569 | BRIDGING THE GAP BETWEEN MASLD TERMINOLOGY AND PATIENT PREFERENCES: A MULTINATIONAL SURVEY

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Background: The nomenclature for metabolic dysfunction-associated steatotic liver disease (MASLD) changed in 2023, yet little is known about patients' preferences for the new terminology and self-identification. This study evaluated terminology and self-description preferences among individuals with self-reported MASLD/ nonalcoholic fatty liver disease (NAFLD). **Methods:** A 15-question survey was disseminated in English (United States, United Kingdom, Canada), Spanish (Spain, Mexico), and Arabic (Egypt, Bahrain, Saudi Arabia) speaking countries through liver patient associations and hospitals. Only individuals who indicated a self-diagnosis of MASLD/NAFLD were eligible to participate. Individuals were asked to choose how they preferred to be identified (person/patient/no preference) and which term they preferred for their liver condition. Terms were classified as old (fatty liver/fatty liver disease/NAFLD), new (steatotic liver, steatotic liver disease/MASLD), or no preference. Demographic and anthropometric data were collected. Body mass index (BMI) was calculated and classified as normal (<25), overweight (25–29.99), or obesity (≥ 30). **Results:** From 420 individuals who started the survey, 58.8% (n = 247) had a self-reported MASLD/NAFLD diagnosis. Of those, 157 individuals were eligible and included in the analysis. Overall, 46.5% were women, the mean age was 48.8 years (SD = 13.4), and the mean BMI was 31.5 Kg/m² (9.1). Participants were from English (20.4%), Spanish (53.5%), and Arabic-speaking (26.1%) countries. Most individuals (51.6%) preferred to self-describe as a patient. Individuals preferring the term "patient" (compare to person) were significantly younger [47.2 (14.4) vs 51.2 (11.2), P = 0.034], had higher BMI [34.3 (10.8) vs 28.3 (4.4), P < 0.001], were more likely to be men (62.0% vs 37.7%, P = 0.004), and more likely to be from Arabic-speaking countries (46.9% vs 1.6%, P < 0.001). Most participants (36.9%) preferred the old terminology, while 31.6% preferred the new terminology, and 30.3% had no clear preference. Women and participants from English-speaking countries demonstrated a higher preference for the new terminology. A dose-response relationship was observed across BMI categories, with preferences for both the new terminology and self-identification as a patient increasing with higher BMI; these preferences were highest among individuals with obesity **(Figure 1). Conclusion:** A substantial gap exists between the recently adopted MASLD nomenclature and individuals' preferred terminology, with most participants favoring the former terminology. Preferences varied across demographic and cultural groups, suggesting that terminology is linked to individuals' identities and contexts. These findings highlight the need for patient-centered and culturally sensitive implementation strategies, incorporating patient perspectives to improve acceptance and engagement.

Figure 1. Patients' preferences across BMI categories



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Roon: Stock options, Madrigal Pharmaceuticals: Consulting, Vanessa Vilas-Riotorto: Nothing to Disclose, Anish Arora: Nothing to Disclose, Paul Brennan: Nothing to Disclose, Didac Mauricio: Nothing to Disclose, Damien Leith: Nothing to Disclose, Yumar Hidalgo: Nothing to Disclose, Veronika Vsetickova: Nothing to Disclose, José Willemse: Nothing to Disclose, Michael Betel: Nothing to Disclose, Faisal Alnase: Nothing to Disclose, Mohamed El-Kassas: Nothing to Disclose, Jeffrey Lazarus: Nothing to Disclose.

2570 | COMPARING AT-RISK POPULATION FOR MASLD SCREENING ACCORDING TO INTERNATIONAL GUIDELINE IN COMMUNITY-BASED COHORTS

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Background: Current guidelines provide heterogeneous definitions of the 'at-risk population' for metabolic dysfunction-associated steatotic liver disease (MASLD), resulting in substantial variability in screening eligibility. This study aimed to compare the "at-risk populations" requiring MASLD screening as defined by the five major guidelines, and to evaluate the burden of hepatic fibrosis and long-term outcomes according to key risk factors. **Methods:** We analyzed four community base cross-sectional cohorts (Korean MRE [N = 9,506], V-LINK health screening [N = 12,341], Japanese VCTE [N = 2,512], and US NHANES VCTE [N = 5,707]), and one hospital-based longitudinal cohort (V-LINK MASLD [N = 26,595]). We compared the fibrosis burden across different guideline-based 'at-risk population' for MASLD in the four community-based cohorts, and assessed their longitudinal prognostic performance for major adverse liver outcomes (MALO) in the hospital-based cohort. **Results:** Across the five guideline-based definitions, the proportion of individuals classified as the MASLD at-risk population varied substantially across the four community-based cohorts, ranging from 58.5% to 87.7%. In the US NHANES cohort, only 42.1% of individuals were consistently identified across all five guidelines. The overlap between the AASLD and EASL definitions was 68.7%, whereas the lowest concordance was observed between APASL and ADA, with only 59.8% of individuals overlapping. Despite this heterogeneity, four common risk factors were consistently associated with a high burden of significant hepatic fibrosis across the guidelines: imaging-defined steatosis, elevated ALT (> 40 U/L), type 2 diabetes, and obesity with additional cardiometabolic risk factors. Individuals with all four common risk factors also consistently showed a higher risk of MALOs in the longitudinal hospital-based cohort. **Conclusion:** The current five definitions of the 'at-risk population' for MASLD show substantial heterogeneity. Presence of four common risk factors across guidelines consistently identified individuals with a greater burden of hepatic fibrosis and a higher risk of MALOs.

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2571 | LONGITUDINAL ALT MAINTANACE AND LIVER-RELATED EVENTS IN MASLD: A NATIONWIDE HEALTH-CHECKUP COHORT STUDY

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Background: ALT is routinely measured in checkups, but its value as a longitudinal surrogate of disease control in metabolic dysfunction-associated steatotic liver disease (MASLD) is uncertain. As biopsy and elastography are often unavailable outside specialist settings, a simple repeated biomarker linked to outcomes is needed. We aimed to determine whether the proportion of follow-up time with ALT < 30 U/L was associated with liver-related events (LREs) in a large Japanese MASLD cohort. **Methods:** Retrospective cohort study using Japanese claims database, linking claims with annual checkup data from Japanese employer-based insurance societies. Among 8,425,681 individuals, steatotic liver disease was defined by fatty liver index ≥ 60 or a fatty-liver diagnosis; after excluding other chronic liver diseases or prior LREs and restricting to MASLD, 1,362,475 were analyzed after multiple imputation (m = 20). The exposure was the proportion of follow-up time with ALT < 30 U/L; ALT ≥ 30 U/L was modeled as a time-varying covariate. The outcome was the first LRE (HCC, esophageal varices, hepatic ascites, hepatic encephalopathy). Cox models were adjusted for age, sex,

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smoking, diabetes, hypertension, and dyslipidemia, with estimates pooled by Rubin's rules. Three-year landmark Kaplan–Meier analyses across five categories (0%, 1–32%, 33–65%, 66–99%, 100%) used Holm-adjusted log-rank tests. **Results:** The MASLD cohort comprised 1,362,475 individuals (median follow-up 5.2 years, IQR 4.1–7.0), with 888 incident LREs. In the adjusted time-dependent Cox model, ALT ≥ 30 U/L was associated with markedly higher LRE risk (HR 2.27, 95% CI 1.96–2.62; $p < 0.001$), independent of age, sex, smoking, diabetes, hypertension, and dyslipidemia, with good discrimination (C-index 0.82). In the 3-year landmark analysis, 3-year LRE incidence decreased monotonically with greater proportion of time with ALT < 30 U/L, from 0.08% in the 0% group to 0.03% in the 100% group response between sustained ALT control and lower liver event risk. **Conclusion:** In a nationwide MASLD cohort, a higher proportion of follow-up time with ALT < 30 U/L was strongly and consistently associated with lower LRE incidence, with a clear dose–response across time-in-target. Longitudinal ALT control is a simple, routinely available metric to identify MASLD patients at higher risk of liver complications in non-specialist settings.

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2572 | SEVERITY-GRADED CARDIOMETABOLIC AND HEPATIC BURDEN IN HEPATIC STEATOSIS: FINDINGS FROM THE PROSPECTIVE, POPULATION-BASED VCTE COHORT OF 2,979 SAUDI ADULTS (GENESIS STUDY)

Saleh Alqahtani[1] Shadan AlMuhaidib[2] Basmah Khoja[3] Mohammed Alghamdi[4] Haifa Otaibi[2] Mariam Seria[4] Layan Alsubki[5] Alwaleed Almojel[4] Nayef Alshabyli[6] Mohammed Aldrees[6] Alanood Aladel[7] Tatyana Kushner[8] Faisal Sanai[9] Waleed Alhazzani[2], [1]King Faisal Specialist Hospital & Research Center, [2]Research and Innovation Institute, Ministry of Defense Health Services, Riyadh, Saudi Arabia, [3]King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia, [4]King Fahad Military Medical Complex, Dhahran, Saudi Arabia, [5]King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia, [6]Prince Sultan Military Medical City, Riyadh, Saudi Arabia, [7]King Saud University, Riyadh, Saudi Arabia, [8]Weill Cornell Medicine, New York, NY, USA, [9]King Abdulaziz Medical City, King Abdullah International Medical Research Center, Jeddah, KSA

Background: Metabolic dysfunction–associated steatotic liver disease (MASLD) is the most common chronic liver disease worldwide, yet population-level data linking the severity of hepatic steatosis to metabolic and comorbid burden remain scarce in the Middle East. We aimed to characterize the gradient of cardiometabolic, hepatic, and comorbid markers across controlled attenuation parameter (CAP)–defined steatosis grades in a Saudi population-based cohort. **Methods:** We analyzed baseline data from the prospective, population-based GENESIS study conducted across seven Saudi primary care centers between March 2024 and June 2025. Adults underwent clinical assessment, laboratory testing, and vibration-controlled transient elastography using the SmartExam protocol on FibroScan Mini +430 (Echosens). Participants were classified by CAP into no steatosis (< 248 dB/m), mild (248–267), moderate (268–279), and severe (≥ 280 dB/m). Anthropometric, biochemical, and comorbidity measures were compared across groups using chi-square, one-way ANOVA, or Kruskal-Wallis tests. **Results:** Of 2,979 participants (mean age 41.9 ± 13.3 years; 49.7% men), 1,508 (50.6%) had no steatosis, 347 (11.6%) mild, 202 (6.8%) moderate, and 922 (30.9%) severe steatosis. Across the four CAP grades, group medians increased for body mass index (BMI) 26.4 to 31.9 kg/m², glycated hemoglobin (HbA1c) 5.5% to 5.9%, alanine aminotransferase (ALT) 15 to 24 U/L, gamma-glutamyl transferase (GGT) 16 to 28 U/L, and triglycerides 0.9 to 1.4 mmol/L, with mean waist circumference increasing from 87.4 ± 14.0 to 104.1 ± 14.0 cm (all $P < 0.001$). Comorbidity prevalence followed a similar gradient: diabetes 10.7% to 35.1%, hypertension 9.0% to 23.2%, and dyslipidemia 18.3% to 35.9% (all $P < 0.001$). Overall, 1,471 (49.4%) had hepatic steatosis on VCTE, and 1,111 met MASLD criteria, yielding a crude prevalence of 37.3% (95% confidence interval [CI] 35.6–39.0) and an age- and sex-adjusted prevalence of 34.2% (95% CI 32.5–35.9). Significant liver fibrosis (liver stiffness measurement ≥ 8 kPa) was identified in 57 participants (1.9%) overall, including 48 participants with MASLD (4.3% of the MASLD group). **Conclusion:** Hepatic

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steatosis affects nearly half of Saudi adults, with CAP-defined severity tracking stepwise with cardiometabolic dysfunction and comorbidity. These findings provide the first prospective, population-level estimates of steatosis severity at a country level in Saudi Arabia and support scalable VCTE-based risk stratification in primary care.

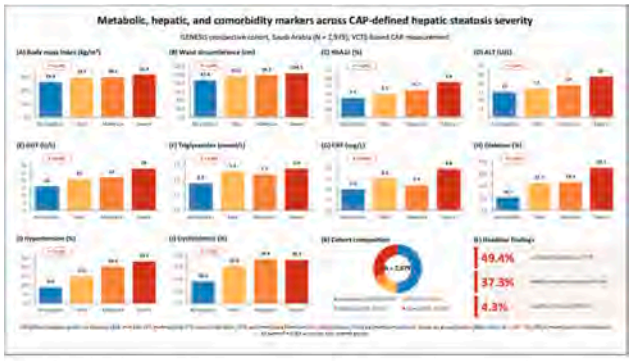


Figure 1. Metabolic, hepatic, and comorbidity markers across controlled attenuation parameter (CAP)–defined hepatic steatosis severity.
GENESIS prospective cohort, Saudi Arabia (N = 2,979). Panels (A)–(J) show stepwise increases in body mass index (BMI), waist circumference, glycated hemoglobin (HbA1c), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), triglycerides, C-reactive protein (CRP), diabetes, hypertension, and dyslipidemia across the four CAP-defined steatosis grades (all $P < 0.001$). Panel (K) shows cohort composition; panel (L) summarises headline epidemiological findings, including metabolic dysfunction–associated steatotic liver disease (MASLD) prevalence. CAP-defined steatosis grades: no steatosis <248, mild 248–267, moderate 268–279, severe ≥280 dB/m. Vibration-controlled transient elastography (VCTE) performed using the SmartExam protocol on FibroScan Mini +430 (Echosens). Continuous values are group medians (BMI, HbA1c, ALT, GGT, triglycerides, CRP) or means (waist circumference).

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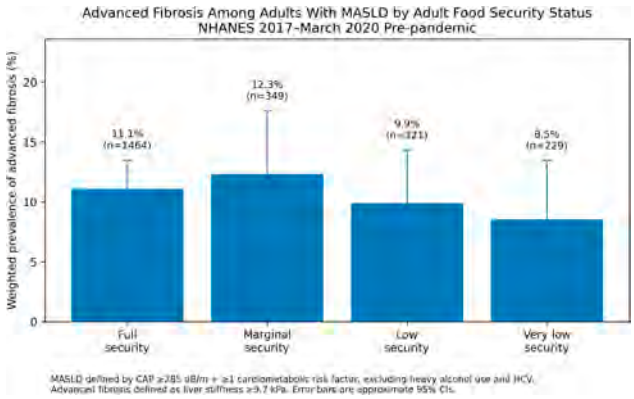
2573 | SOCIAL VULNERABILITY AND SILENT FIBROSIS RISK IN MASLD: A NATIONAL NHANES VCTE ANALYSIS OF FOOD INSECURITY

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Background: Food insecurity is a major social determinant of cardiometabolic health, but its association with advanced hepatic fibrosis in metabolic dysfunction–associated steatotic liver disease remains unclear. We examined the national burden of food insecurity and its relationship with VCTE-defined advanced fibrosis among U.S. adults with MASLD. **Methods:** We analyzed NHANES 2017–March 2020 pre-pandemic adults aged ≥20 years with valid transient elastography. MASLD was defined as CAP ≥285 dB/m plus ≥1 cardiometabolic risk factor, excluding heavy alcohol use and hepatitis C. Food insecurity was assessed using the NHANES Food Security Questionnaire. Advanced fibrosis was defined as liver stiffness measurement ≥9.7 kPa. Survey-weighted prevalence estimates and logistic regression models were used. **Results:** Among 15,560 NHANES participants, 9,232 were adults, 7,395 had valid VCTE, 2,748 had CAP-defined steatosis, and 2,506 met MASLD criteria. The final analytic sample included 2,363 adults with MASLD and food security data, representing 66.3 million U.S. adults. Overall, 16.7% were food insecure, representing 11.1 million adults. Advanced fibrosis was present in 10.9%, corresponding to 7.2 million adults. Advanced fibrosis prevalence was 11.1% with full food security, 12.3% with marginal, 9.9% with low, and 8.5% with very low food security. When grouped, advanced fibrosis prevalence was 11.3% among food-secure/marginally secure adults versus 9.3% among food-insecure adults. Food-insecure adults with MASLD were younger than food-secure/marginally secure adults, with mean age 45.2 versus 52.0 years, had higher BMI, 35.7 versus 33.8 kg/m², and lower income-to-poverty ratio, 1.48 versus 3.45. Food insecurity was not associated with higher odds of advanced fibrosis in unadjusted analysis, OR 0.81, 95% CI 0.52–1.26, $p = 0.34$, or age/sex-adjusted analysis, OR 0.85, 95% CI 0.54–1.35, $p = 0.50$. In the fully adjusted model, food insecurity showed lower observed odds of advanced fibrosis, OR 0.56, 95% CI 0.32–1.00, $p = 0.049$, likely reflecting age and demographic structure rather than biological protection. **Conclusion:** Nearly 1 in 6 U.S. adults with MASLD experienced food insecurity. Food insecurity was not associated with higher advanced fibrosis prevalence; instead, affected adults represented a younger, higher-BMI, economically disadvantaged MASLD phenotype. These findings support fibrosis risk stratification that integrates social vulnerability with age, metabolic severity, and elastography-based assessment.

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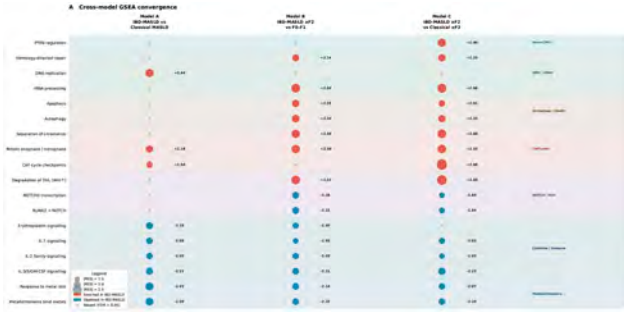


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2574 | IBD IMPRINTS A PRO-TUMORIGENIC HEPATIC TRANSCRIPTOMIC SIGNATURE IN MASLD THAT PRECEDES AND IS AMPLIFIED BY FIBROSIS: A MULTICENTRE CLINICAL AND MOLECULAR STUDY

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Background: IBD confers excess cancer risk through disease-intrinsic and treatment-related mechanisms. MASLD is independently more prevalent in IBD and associated with extrahepatic malignancy. Whether IBD imprints a distinct oncogenic hepatic transcriptomic programme in MASLD and whether this translates into measurable clinical cancer risk remains undefined. **Methods:** Hepatic transcriptomics (limma-voom; GSEA; GEO: GSE268273) were analysed across three complementary pairwise models: IBD-MASLD vs. classical MASLD (Model A; n = 42 vs. 40, adj. BMI/sex/fibrosis); IBD-MASLD F ≥ 2 vs. F0-F1 (Model B; n = 7 vs. 35, adj. BMI/sex); and IBD-MASLD F ≥ 2 vs. classical MASLD F ≥ 2 (Model C; n = 7 vs. 16, adj. BMI/sex). For clinical validation, 1,508 IBD patients (712 CD, 796 UC) underwent prospective hepatic assessment by transient elastography at two Spanish tertiary centres. At-risk MASLD was defined as CAP ≥ 248 dB/m and LSM > 8 kPa. Cancer history was ascertained retrospectively and associations examined by logistic and Firth penalised regression adjusted for age and sex. **Results:** Transcriptomics identified a convergent pro-tumorigenic signature across all three models: coordinate suppression of the metallothionein tumour-suppressor cluster (MT1H, MT1M, MT1F, MT1G; $\log_2$FC up to −3.56 in Model C), upregulation of oncogenic drivers (IGFBP2, GDF15, MYC, SOX4, RRM2, SPP1), and collapse of the cytotoxic immune programme (PRF1, GNLY, EOMES, IL2RB). GSEA confirmed enrichment of cell cycle, Wnt/DVL degradation, and DNA replication pathways alongside depletion of metallothionein and cytokine-immune gene sets in all three models. This signature was detectable in non-fibrotic IBD-MASLD and progressively amplified with fibrosis advancement, with PTEN regulation uniquely enriched in Model C (NES +2.46). In the clinical cohort, only at-risk SLD and at-risk MASLD were significantly associated with digestive cancer prevalence (3.6% and 4.1% vs. 0.6% in the respective reference groups; p < 0.001). At-risk MASLD independently predicted digestive cancer (Firth OR 4.93, 95%CI 1.24–19.71; p = 0.024), and WHtR independently predicted digestive cancer risk as a continuous variable (Firth OR 3,761; p = 0.013) and overall cancer when dichotomised (OR 2.09; p = 0.006). **Conclusion:** IBD imprints a fibrosis-potentiated but fibrosis-independent pro-tumorigenic hepatic programme in MASLD, clinically translated into an independent digestive cancer risk emerging at the threshold of significant fibrosis and further amplified by visceral adiposity. These findings support systematic hepatic and anthropometric assessment in IBD as a cancer risk stratification strategy.



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2575 | NEUROBEHAVIORAL BURDEN IN MASLD: PAIN-RELATED CONDITIONS, PSYCHIATRIC DISEASE, AND OPIOID USE DISORDER

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Background: MASLD is increasingly recognized as a multisystem disease extending beyond hepatic and metabolic complications. Pain-related conditions, psychiatric disease, and opioid use disorder may share behavioral, inflammatory, and neurobiological pathways that worsen quality of life and care complexity, yet their combined burden in MASLD remains poorly characterized. We examined pain-related conditions, psychiatric comorbidity, opioid use disorder, and overlapping neurobehavioral phenotypes among adults with EHR-documented MASLD/MASH in the All of Us Research Program. **Methods:** We conducted a cross-sectional analysis of adults $\geq$18 years with EHR data in the All of Us Controlled Tier Dataset v8. EHR-documented MASLD/MASH was identified using diagnosis concepts for nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, and NASH-related cirrhosis, excluding alcoholic fatty liver and acute fatty liver of pregnancy. Pain-related conditions included chronic pain, back pain, fibromyalgia, neuropathic pain, arthritis, and osteoarthritis. Psychiatric comorbidity included depression, anxiety, and PTSD; opioid use disorder was identified using EHR diagnosis concepts. Composite phenotypes included pain-psychiatric and pain-psychiatric-OUD overlap. Multivariable logistic regression estimated adjusted odds of each outcome among adults with versus without MASLD/MASH, adjusting for age, BMI, sex at birth, race/ethnicity, and type 2 diabetes. Multinomial logistic regression assessed graded neurobehavioral burden across pain-related conditions, psychiatric comorbidity, and OUD. Analyses were performed using Python in Jupyter Notebook. **Results:** Among 388,424 adults with EHR data, 3,700 had EHR-documented MASLD/MASH. Pain-related conditions were present in 78.78% of adults with MASLD/MASH versus 45.59% without MASLD/MASH, opioid use disorder in 6.65% versus 3.62%, pain-psychiatric overlap in 55.11% versus 24.37%, and pain-psychiatric-OUD overlap in 5.89% versus 2.22%. After adjustment for age, BMI, sex at birth, race/ethnicity, and type 2 diabetes, MASLD/MASH was associated with higher odds of pain-related conditions (aOR 2.70, 95% CI 2.48–2.94), opioid use disorder (aOR 1.59, 95% CI 1.39–1.81), pain-psychiatric overlap (aOR 2.32, 95% CI 2.16–2.48), and pain-psychiatric-OUD overlap (aOR 1.82, 95% CI 1.58–2.11). A graded burden pattern was observed: compared with no neurobehavioral conditions, MASLD/MASH was associated with progressively higher adjusted odds of 1 condition (aOR 2.45, 95% CI 2.19–2.75), 2 conditions (aOR 4.09, 95% CI 3.67–4.57), and 3 conditions (aOR 4.86, 95% CI 4.10–5.77). **Conclusion:** Adults with EHR-documented MASLD/MASH had higher burdens of pain-related conditions, opioid use disorder, and overlapping pain-psychiatric phenotypes. These findings support integrating pain, mental health, and opioid-risk assessment into MASLD care.

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2576 | IMPROVING EARLY DETECTION: A QUALITY IMPROVEMENT INITIATIVE FOR METABOLICALLY-DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD)SCREENING IN AT-RISK POPULATIONS IN A RURAL ACADEMIC MEDICAL CENTER

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Background: MASLD affects up to 38% of adults globally and approximately 70% of patients with type 2 diabetes mellitus, with a substantial proportion progressing to MASH and advanced fibrosis. Despite guideline recommendations for fibrosis screening using the FIB-4 index, implementation gaps remain significant - particularly in rural academic centers where access to hepatology is limited and competing clinical priorities are high. Guthrie Robert Packer Hospital (GRPH), a rural academic medical center in Sayre, Pennsylvania, identified a critical gap in MASLD screening among its internal medicine resident patient panel. **Methods:** A prospective QI study with retrospective chart review was conducted using Epic EHR data from GPRH's Internal Medicine Clinic. A 755-patient at-risk cohort was identified - adults aged 35-85 meeting ≥ 1 inclusion criterion: Type II DM, BMI ≥ 30 kg/m², ≥ 2 metabolic risk factors, incidental hepatic steatosis on imaging, first-degree relative with MASH cirrhosis, or known MASLD without prior NIT in the prior 2 years. Patients with known advanced fibrosis under active hepatology care, decompensated cirrhosis, HCC, pregnancy, or solid organ transplant were excluded. The multi-component intervention included resident education on current MASLD screening guidelines, instruction on FIB-4 calculation on EHR using a developed 'dot-phrase', a four-step MASLD screening flowsheet, and monthly individualized performance feedback to residents. The study interval was from October 1, 2025, to December 30, 2025. The primary aim was to increase the screening rate among eligible at-risk patients from baseline by $\geq 5.0\%$. Outcomes were assessed descriptively; no inferential statistical testing was performed, given the QI design. **Results:** The cohort was 55% (n = 416) male and 97% (n = 736) White, with a mean age of 64 years. Clinically, 75% had hypertension, 92% had ≥ 2 metabolic risk factors, 25% had a known MASLD diagnosis, and 14% were on GLP-1 therapy. At baseline, 0% (n = 0) of these 755 patients had screening or risk stratification in the prior 2 years. During the study period, 36% (n = 273) had a clinical encounter. Of these, 21% (n = 57) had risk stratification with documented FIB-4 scores - 7.55% of the total cohort, exceeding the primary $\geq 5.0\%$ target. Risk stratification: 67% low risk, 25% intermediate, 9% high risk. Of 14 intermediate-risk patients, 57% (n = 8) underwent ultrasound elastography, markedly exceeding the secondary $\geq 5.0\%$ target. Of 5 high-risk patients, 40% (n = 2) completed a MASLD-related GI visit. **Conclusion:** The structured QI initiative exceeded both MASLD screening targets within the first quarter at a rural academic center, demonstrating that education, clinical decision support tools, and performance feedback can rapidly improve FIB-4 implementation. Workflow automation via Epic OurPractice Advisory integration and expansion of this model to non-resident panels are the next steps.

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2577 | PANCREATECTOMY AND RISK OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE: A PROPENSITY SCORE-MATCHED MULTICENTER COHORT STUDY

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Background: Patients with chronic pancreatitis or pancreatic cancer may ultimately require pancreatectomy, but its long-term impact on liver health is underexplored. Resection-induced exocrine/endocrine insufficiency, diabetes, and altered lipid metabolism may predispose patients to metabolic dysfunction-associated steatotic liver disease (MASLD). We evaluated the risk of MASLD and liver-related complications after pancreatectomy using a large multicenter database. **Methods:** We queried the TriNetX US Collaborative Network to identify adults (≥ 18 years) with chronic pancreatitis or pancreatic cancer who underwent pancreatectomy (study cohort) or did not (control cohort). MASLD was defined by ICD-10-CM codes for hepatic steatosis with ≥ 1 cardiometabolic risk factor (obesity, type 2 diabetes, hypertension, or hyperlipidemia), aligning with the Delphi consensus. Patients with pre-existing or competing chronic liver diseases (alcoholic, viral, autoimmune, or baseline cirrhosis) were excluded. Propensity score matching (PSM, 1: 1) was applied to balance baseline covariates (demographics, metabolic factors, comorbidities). Outcomes included new-onset MASLD, metabolic dysfunction-associated steatohepatitis (MASH), liver cirrhosis, and a composite liver outcome (cirrhosis, portal hypertension, varices, ascites, encephalopathy, hepatorenal syndrome) over a 5-year follow-up. Results were reported as adjusted odds ratios (aORs) with 95% confidence intervals (CIs). **Results:** Before matching, 11,802 pancreatectomy and 413,201 control patients were identified. After 1: 1 PSM, 10,577 patients remained in each cohort with well-balanced characteristics. Over 5-year follow-up,

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pancreatectomy was associated with significantly higher odds of MASLD (9.1% vs. 5.8%; aOR 1.62, 95% CI 1.45–1.79, p < 0.001) and composite liver outcomes (9.5% vs. 6.3%; aOR 1.57, 95% CI 1.42–1.74, p < 0.001). The incidence of MASH (0.4% vs. 0.4%; aOR 1.02, 95% CI 0.68–1.54, p = 0.92) and liver cirrhosis (0.5% vs. 0.3%; aOR 1.50, 95% CI 0.97–2.32, p = 0.07) did not differ significantly between cohorts. **Conclusion:** In this multicenter cohort study, pancreatectomy was associated with higher odds of MASLD and composite liver complications, without a clear increase in MASH or cirrhosis. These findings identify pancreatic resection as a high-risk setting for metabolic liver disease, supporting longitudinal hepatic surveillance and metabolic management post-resection.

Table 1. Baseline characteristics of patients with chronic pancreatitis or pancreatic cancer with and without pancreatectomy before and after propensity score matching.

Variables	Before PSM			After PSM		
	Pancreatectomy	No pancreatectomy	P-value	Pancreatectomy	No pancreatectomy	P-value
Number of patients	11,802	371,655	–	10,577	10,577	–
Age (yrs, mean ± SD)	64.0 ± 12.1	60.4 ± 14.9	<0.001	63.9 ± 12.1	64.4 ± 13.0	0.003
Race/ethlnicity, n (%)						
White	9,332 (80.1)	198,797 (55.7)	<0.001	8,356 (79.0)	8,411 (79.5)	0.351
African American	1,118 (9.6)	37,012 (10.4)	0.008	1,036 (9.8)	1,053 (10.0)	0.695
Asian	321 (2.8)	12,656 (3.5)	<0.001	320 (3.0)	353 (3.3)	0.196
Hispanic	616 (5.3)	15,683 (4.4)	<0.001	567 (5.4)	589 (5.6)	0.506
Gender, n (%)						
Female	5,824 (50.0)	172,375 (48.3)	<0.001	5,265 (49.8)	5,216 (49.3)	0.500
Male	5,820 (50.0)	184,625 (51.7)	<0.001	5,312 (50.2)	5,360 (50.7)	0.509
Comorbidities , n (%)						
Obesity	1,989 (17.1)	32,903 (9.2)	<0.001	1,730 (16.4)	1,807 (17.1)	0.156
Type 2 DM	3,604 (31.0)	59,246 (16.6)	<0.001	3,071 (29.0)	2,932 (27.7)	0.034
Hypertension	6,275 (53.9)	102,463 (28.7)	<0.001	5,449 (51.5)	5,668 (53.6)	0.003
Hyperlipidemia	4,318 (37.1)	63,791 (17.9)	<0.001	3,731 (35.3)	3,773 (35.7)	0.546
Metabolic syndrome	69 (0.6)	1,499 (0.4)	0.005	62 (0.6)	56 (0.5)	0.580
Coronary artery diseases	2,069 (17.8)	41,641 (11.7)	<0.001	1,868 (17.7)	1,953 (18.5)	0.129
CKD	868 (7.5)	23,616 (6.6)	<0.001	831 (7.9)	947 (9.0)	0.004
Tobacco use	446 (3.8)	9,449 (2.6)	<0.001	392 (3.7)	424 (4.0)	0.253
Malignant neoplasm of pancreas	8,288 (71.2)	108 (0.0)	<0.001	7,408 (70.0)	56 (0.5)	<0.001

PSM: propensity score matching; DM: diabetes mellitus; CKD: chronic kidney disease; SD: standard deviation.

Table 2. Liver-related outcomes in patients undergoing pancreatectomy versus no pancreatectomy.

Outcome, n (%)	Pancreatectomy (N = 10,577)	No pancreatectomy (N = 10,577)	aOR (95% CI)	P-value
MASLD	959 (9.1)	615 (5.8)	1.62 (1.45–1.79)	<0.001
MASH	47 (0.4)	46 (0.4)	1.02 (0.68–1.54)	0.92
Liver cirrhosis	51 (0.5)	34 (0.3)	1.50 (0.97–2.32)	0.07
Composite liver outcome*	1,007 (9.5)	663 (6.3)	1.57 (1.42–1.74)	<0.001

*Composite outcome includes MASLD, MASH, liver fibrosis and cirrhosis, portal hypertension, esophageal varices, ascites, hepatic encephalopathy, and hepatorenal syndrome.

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2578 | FIRST PROSPECTIVE COUNTRY-LEVEL PREVALENCE OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE AND SIGNIFICANT FIBROSIS IN THE MIDDLE EAST: FINDINGS FROM SAUDI ARABIA&RSQUO;S GENESIS POPULATION-BASED COHOR

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common chronic liver disease worldwide, yet most population-level estimates are derived from Western or East Asian cohorts. Country-level, prospectively collected, vibration-controlled transient elastography (VCTE)-based estimates from the Middle East are largely absent and are needed to inform global burden modeling and screening policy. We aimed to estimate the national prevalence of MASLD and significant fibrosis and identify independent cardiometabolic and sleep-related predictors in Saudi adults. **Methods:** GENESIS is a prospective, national population-based cohort recruiting adults through community-based sampling across Saudi Arabia. All participants underwent VCTE (FibroScan) for controlled attenuation parameter (CAP) and liver stiffness measurement (LSM). MASLD was defined as hepatic steatosis on VCTE (CAP ≥ 268 dB/m) plus ≥ 1 of the 5 cardiometabolic risk factors per the 2023 multisociety Delphi consensus. Significant fibrosis was defined by LSM ≥ 8.0 kPa. High-risk

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obstructive sleep apnea (OSA) was assessed using the Berlin Questionnaire. Prevalence estimates were age- and sex-standardized to the 2022 national census. Independent associations were assessed by multivariable logistic regression. **Results:** Among 2,979 adults with valid VCTE measurements, MASLD was identified in 1,111 (crude prevalence 37.3%; age- and sex-adjusted 34.2%, 95% confidence interval [CI] 32.5–35.9). Significant fibrosis was present in 48 participants with MASLD (4.3%). Diabetes (adjusted odds ratio [OR] 1.80), waist circumference (adjusted OR 1.35 per 5 cm), and high-risk OSA (adjusted OR 1.47) were independently associated with MASLD. Among participants with MASLD, diabetes (adjusted OR 4.41), male sex (adjusted OR 2.83), and waist circumference (adjusted OR 1.24 per 5 cm) were independently associated with significant fibrosis. **Conclusion:** In this first prospective country-level Middle Eastern cohort, MASLD was identified in 1 in 3 adults and significant fibrosis in 1 in 23 adults with MASLD. Diabetes and central adiposity were independently associated with both MASLD presence and significant fibrosis, while high-risk OSA was independently associated with MASLD presence. These findings support urgent integration of MASLD and fibrosis screening into high-yield clinical settings, particularly diabetes and obesity care, and provide a model for generating standardized VCTE-based burden estimates across the Middle East.

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★ 2579 | DYNAMIC CHANGES IN STEATOTIC LIVER DISEASE SUBTYPE CLASSIFICATION AND PREDICTORS OF ADVANCED FIBROSIS IN LATIN AMERICA

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Background: Latin America is underrepresented in prospective steatotic liver disease (SLD) studies despite a high metabolic burden. This multinational study aims to identify the risk of advanced fibrosis across the SLD subtypes in Latin America. **Methods:** Cross-sectional analysis of prospectively enrolled adults with SLD (2023 criteria) at 16 tertiary centers in seven countries (Argentina, Brazil, Chile, Colombia, Dominican Republic, Mexico, and Peru) between 2024 and 2026. We performed standardized interviews and assessed fibrosis using liver biopsy or vibration-controlled transient elastography (VCTE) when biopsy was unavailable (advanced fibrosis: biopsy $\geq$F3 or VCTE $\geq$12 kPa). Predictors of advanced fibrosis were examined using binary logistic regression, including age, sex, ethnicity, body mass index (BMI), type 2 diabetes mellitus (T2DM), physical activity, and SLD subtype. **Results:** We included 914 participants (median age 62 [52–69] years; 56.6% women; 57.0% self-reported Hispanic ethnicity). The median BMI was 30.3 [27.3–34.0] kg/m^2, and 46.4% had T2DM. Based on registry diagnoses, 86.2% had MASLD, 5.4% MetALD, and 8.4% ALD. At enrollment, 87.8% with prior MetALD reported alcohol intake within the MASLD alcohol range, while 50.7% and 46.5% with prior ALD were within the MASLD and MetALD alcohol ranges, respectively (**Figure A**). Only 1.3% presumed MASLD cases were recategorized as MetALD or ALD, and

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6.0% MetALD cases as ALD. Prevalence of advanced fibrosis was 35.5%. In the adjusted model, age (aOR 1.05, 95% CI 1.03–1.07; p < 0.0001), T2DM (aOR 3.65, 95% CI 2.32–5.74; p < 0.0001), MetALD (reference MASLD; aOR 2.72, 95% CI 1.32–5.58; p = 0.007) and ALD (reference MASLD; aOR 21.33, 95% CI 9.02–50.44; p < 0.0001) were independently associated with higher odds of advanced fibrosis, whereas those who walked >10,000 daily steps had lower odds (reference 1,000–5,000 daily steps; aOR 0.06, 95% CI 0.01–0.35; p = 0.002) (**Figure B**). **Conclusion:** In this multicenter Latin American SLD cohort, advanced fibrosis was common and mainly associated with alcohol intake (MetALD and ALD), T2DM, and older age, while physical activity was protective. The frequent discrepancy between self-reported alcohol intake at enrollment and registry-based historical diagnoses highlights the need for longitudinal ascertainment of prior alcohol exposure to improve SLD subtype classification and clinical decision-making (FONDECYT 1241450).

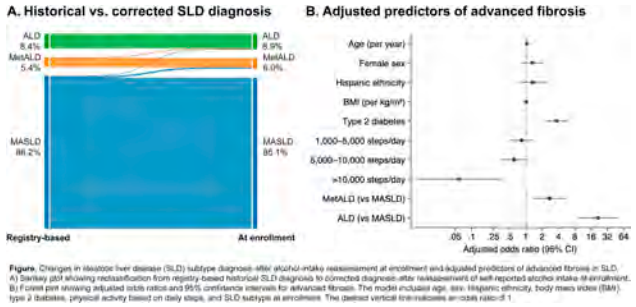


Figure. Changes in steatotic liver disease (SLD) subtype diagnosis after alcohol-intake reassessment at enrollment and adjusted predictors of advanced fibrosis in SLD. A) Sankey plot showing reclassification from registry-based historical SLD diagnosis to corrected diagnosis after reassessment of self-reported alcohol intake at enrollment. B) Forest plot showing adjusted odds ratios and 95% confidence intervals for advanced fibrosis. The model included age, sex, Hispanic ethnicity, body mass index (BMI), type 2 diabetes, physical activity based on daily steps, and SLD subtype at enrollment. The dashed vertical line indicates an odds ratio of 1.

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2580 | PREVALENCE AND PREDICTORS OF LEAN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE AMONG ADULTS: A CROSS-SECTIONAL STUDY USING VIBRATION-CONTROLLED TRANSIENT ELASTOGRAPHY AND METABOLIC PHENOTYPING

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a leading global cause of chronic liver disease and is increasingly recognized among individuals without obesity. Lean MASLD may be particularly relevant in Middle East and North Africa (MENA) populations, where cardiometabolic risk and ethnicity-specific body composition may modify liver fat and fibrosis risk at lower BMI thresholds. However, regional data on lean MASLD remain limited. We aimed to characterize the prevalence, metabolic phenotype, fibrosis burden, and independent predictors of lean MASLD among adults undergoing vibration-controlled transient elastography (VCTE) in Bahrain. **Methods:** We conducted a cross-sectional study of consecutive adults (≥18 y) referred for VCTE (FibroScan) at Bahrain Government Hospitals from Jan 2024–Feb 2026. Exclusions included viral hepatitis, excess alcohol use, autoimmune/metabolic liver disease, decompensated cirrhosis, pregnancy, or prior LT. Steatosis was defined as CAP ≥275 dB/m; MASLD per 2023 Delphi criteria. Lean BMI was defined using ethnicity-specific cutoffs: <25 kg/m² for Arab/Caucasian and <23 kg/m² for South Asian adults. Fibrosis was assessed by LSM: <8, 8–12, and >12 kPa for no

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significant, significant, and advanced fibrosis, respectively. Multivariable logistic regression identified predictors of lean MASLD. **Results:** Among 412 adults, mean age was 46.2 ± 12.8 years, 54.7% were male, 61.3% Bahraini, and 26.2% South Asian. Overall MASLD prevalence was 68.4% (282/412). By BMI category, MASLD was present in 19.2% of lean, 63.9% of overweight, and 87.6% of obese participants ($p < 0.001$); lean MASLD accounted for 3.4% of the total cohort. Lean MASLD patients had higher waist circumference than lean non-MASLD participants (86.4 ± 7.2 vs. 78.1 cm, $p < 0.001$), while CAP was lower than in non-lean MASLD (298 ± 24 vs. 326 ± 38 dB/m, $p = 0.001$). Despite lower steatosis burden, fibrosis estimates were comparable between lean and non-lean MASLD: LSM ≥ 8 kPa (21.4% vs. 28.1%, $p = 0.60$), LSM > 12 kPa (7.1% vs. 11.6%, $p = 0.61$), and FIB-4 (1.18 ± 0.62 vs. 1.24 ± 0.74, $p = 0.68$). ALT was normal in 71.4% of lean MASLD patients. South Asians had higher lean MASLD prevalence than Bahrainis (5.6% vs. 2.4%, $p = 0.04$), despite lower BMI. Independent predictors of lean MASLD were waist circumference ≥ 85 cm (aOR 3.42, $p = 0.004$), South Asian ethnicity (aOR 2.68, $p = 0.02$), and triglycerides ≥ 150 mg/dL (aOR 2.24, $p = 0.04$). **Conclusion:** Lean MASLD affected nearly one in five lean adults in this study and was often associated with normal ALT. Despite lower steatosis burden, fibrosis estimates were comparable to non-lean MASLD. South Asian ethnicity, increased waist circumference, and hypertriglyceridemia independently predicted lean MASLD, supporting ethnicity-sensitive screening strategies that incorporate central adiposity rather than BMI alone.

Disclosures: Noor Albusta: Nothing to Disclose, Ahmed Ali: Nothing to Disclose, Mohamed Hasan: Nothing to Disclose.

2581 | DECOMPENSATED LIVER DISEASE IN MASLD: WHO IS AT RISK IN A LARGE MULTI-ETHNIC US COHORT, AND DEVELOPMENT OF A 3-YEAR RISK SCORE

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Background: Despite increasing incidence of metabolic dysfunction–associated steatotic liver disease (MASLD), data on incidence and risk factors for liver decompensation are limited, particularly in multi-ethnic populations. The development of a risk score in a large, multi-ethnic US population would allow identification of patients at highest risk for decompensation early and inform targeted interventions to reduce disease progression. **Methods:** Within a cohort of 884950 adult Kaiser Permanente patients identified with MASLD from 1/2009 to 1/2019 using a validated MASLD prediction algorithm (diagnosis codes, radiology reports and the Dallas Steatosis Index (DSI)), we identified compensated advanced chronic liver disease (cACLD) between 1/2014 to 12/2021 based on at least one of: ICD 9/10 diagnosis of cirrhosis or F3 MASLD FIB4 score > 2.67 Transient elastography score > 10Kpa Hepatic decompensation was identified by ICD 9 codes for complications of cirrhosis, radiographic ascites, CPT codes for liver transplantation, endoscopy with variceal banding and paracentesis. Patients with < 1 year of membership prior and < 3 years of membership after cohort entry were excluded. Incidence of decompensation was calculated. We will develop a predictive score for decompensation using multivariable logistic regression using demographic and clinical data. Model performance will be evaluated using receiver operating characteristic (ROC) curves (C-statistic), sensitivity, specificity, positive predictive values, and number needed to evaluate across risk thresholds. **Results:** Among 884950 adults with MASLD, 93466 patients (11%) were identified with cACLD based on one or more of the following: ICD 9/10 diagnosis of cirrhosis (N = 4599) and F3 fibrosis MASLD (N = 152); FIB4 > 2.67 (N = 91727); Transient elastography score > 10Kpa (N = 1387). Mean (SD) age of the cohort was 66(12), with 51% women. Decompensation within one year of cohort entry was identified in 11114 patients (1.3%), with ICD 9/10 diagnosis of decompensation (N = 3241), Bilirubin > 2 mg/dl (N = 7102), CPT codes for paracentesis or variceal banding (N = 762), and liver transplantation (N = 9), and excluded from further analysis . A total of 54459 patients with cACLD and no prior decompensation were included for analysis of incidence of decompensation and development of the 3-year risk score, results of which will be presented. **Conclusion:** cACLD is found in approximately 11% of patients with MASLD in this large multi-ethnic US cohort, and is underdiagnosed, with only 4.8% identified by ICD 9/10 codes. Prevalent decompensation occurred in 1.3% of patients, with bilirubin > 2mg/dL as the most common marker. These findings highlight a large, high-risk population with unmet diagnostic need and support the development of a 3-year risk prediction tool to enable proactive risk-stratified care in MASLD. Additional results on incident decompensation and model performance will be presented.

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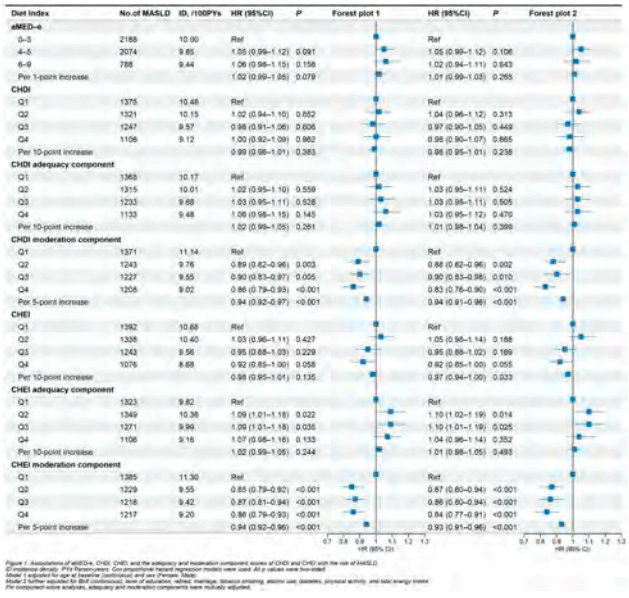


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2582 | DIETARY PATTERNS, ADEQUACY AND MODERATION COMPONENTS, AND RISK OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE: FINDINGS FROM THE SHANGHAI SUBURBAN ADULT COHORT AND BIOBANK

Jiayi Xu[1] Xing Liu[1] Yiling Wu[2] Chunze Xu[2] Bo Chen[1] Jing Li[2] Wei Wang[3] Qin Wang[4] Xiedong Xu[5] Na He[1] Yonggen Jiang[2] Genming Zhao[1], [1]Department of Epidemiology, School of Public Health, Fudan University, Shanghai, China, [2]Songjiang District Center for Disease Control and Prevention, Shanghai, China, [3]Xinqiao Community Health Service Center, Songjiang District, Shanghai, China, [4]Sheshan Community Health Service Center, Songjiang District, Shanghai, China, [5]Maogang Community Health Service Center, Songjiang District, Shanghai, China

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a growing health burden closely related to dietary behaviors. This study aims to compare how different dietary patterns are related to the risk of MASLD in a Chinese population and to further examine whether adequacy and moderation components of diet-quality indices were differentially associated with MASLD risk. **Methods:** Participants free of MASLD at baseline were included from the Shanghai Suburban Adult Cohort and Biobank (SSACB) established since 2016 and followed-up until 2024. MASLD was diagnosed via ultrasonography with evaluation of cardiometabolic risk factors. Dietary intake was assessed using a validated food frequency questionnaire (FFQ). Adherence scores were calculated for the energy-standardized alternative Mediterranean Diet (aMED-e), the Chinese Healthy Diet Index (CHDI), and the Chinese Healthy Eating Index (CHEI). CHDI and CHEI were further separated into adequacy component scores, reflecting intake of recommended foods, and moderation component scores, reflecting limited intake of unfavorable dietary components. The aMED-e score was categorized into three groups: 0–3, 4–5, and 6–9 points, whereas CHDI and CHEI scores were categorized into quartiles. Multivariable Cox proportional hazards models were used to estimate hazard ratios and 95% confidence intervals. **Results:** A total of 11,358 participants were included, of whom 5,049 developed MASLD during a median follow-up of 4.28 years. Each 10-point increase in CHEI score was associated with a 3% lower risk of MASLD (HR = 0.97, 95% CI: 0.94–1.00, P = 0.033), while no significant association was observed for aMED-e (6–9 vs 0–3: HR = 1.02, 95% CI: 0.94–1.11) or CHDI (Q4 vs Q1: HR = 0.98, 95% CI: 0.90–1.07). Adequacy component scores of CHDI showed no association with MASLD risk (Q4 vs Q1: HR = 1.03, 95% CI: 0.95–1.12), while higher moderation component scores of CHDI were associated with lower MASLD risk (Q4 vs Q1: HR = 0.83, 95% CI: 0.76–0.90). For the adequacy component score of CHEI, modestly higher risks were observed in the intermediate quartiles, but the association was not statistically significant in the highest quartile (Q2 vs Q1: HR = 1.10, 95% CI: 1.02–1.19, Q3 vs Q1: HR = 1.10, 95% CI: 1.01–1.19, Q4 vs Q1: HR = 1.04, 95% CI: 0.96–1.14). Higher moderation component scores of CHEI were associated with lower MASLD risk (Q4 vs Q1: HR = 0.84, 95% CI: 0.77–0.91). Stratified analyses revealed that some heterogeneity was observed by sex, age, smoking, and alcohol consumption ($P_{heterogeneity}$ < 0.05). **Conclusion:** The moderation component scores of both CHDI and CHEI were inversely associated with the risk of MASLD in Chinese adults. These findings suggest that greater emphasis needed to be placed on limiting unfavorable dietary components rather than simply increasing recommended foods for MASLD prevention in Chinese population.



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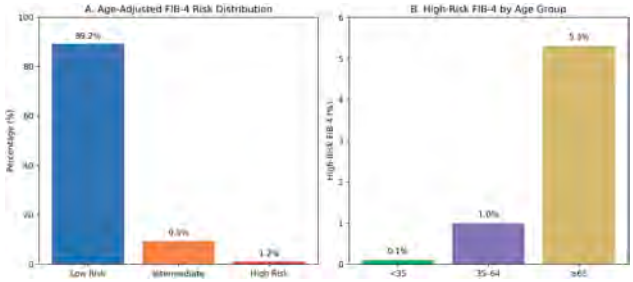
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2583 | PREVALENCE AND METABOLIC PREDICTORS OF ADVANCED LIVER FIBROSIS USING AGE-ADJUSTED FIB-4 IN A REAL-WORLD COHORT OF MORE THAN 51,000 PRIMARY CARE PATIENTS

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Background: Chronic liver disease remains underdiagnosed in primary care despite liver fibrosis being the strongest predictor of liver-related morbidity and mortality. Metabolic dysfunction-associated steatotic liver disease (MASLD) is strongly associated with obesity, diabetes mellitus, hypertension, and dyslipidemia and represents a growing public health burden worldwide. The Fibrosis-4 (FIB-4) index is a simple non-invasive tool derived from routinely available laboratory parameters that enables large-scale fibrosis risk stratification in primary care populations. **Methods:** This retrospective cross-sectional study evaluated primary care patients in the western region of Saudi Arabia with complete laboratory data enabling FIB-4 calculation. Patients with marked transaminitis (AST or ALT >400 U/L) or severe thrombocytopenia (platelet count $<100\times10^9$/L) were excluded to minimize overestimation of fibrosis risk unrelated to chronic liver disease. Age-adjusted FIB-4 thresholds were applied according to AASLD guidance. Metabolic risk was defined as the presence of one or more of the following: overweight/obesity, diabetes mellitus, hypertension, or dyslipidemia. Associations between fibrosis risk and metabolic factors were analyzed using subgroup and comparative statistical analyses. **Results:** A total of 51,445 patients met inclusion criteria. Using age-adjusted FIB-4 thresholds, 45,913 (89.2%) patients were classified as low risk, 4,892 (9.5%) as intermediate risk, and 640 (1.2%) as high risk for advanced fibrosis (Figure below). Patients with one or more metabolic risk factors demonstrated a higher prevalence of high-risk FIB-4 compared with metabolically healthy individuals (1.62% vs 0.80%, OR 2.31, 95% CI 1.73–3.08; $p<0.001$). Age-stratified analysis demonstrated increasing prevalence of high-risk FIB-4 with advancing age (<35 years: 0.1%, 35–64 years: 1.0%, ≥65 years: 5.3%; $p<0.001$) (Figure below). Intermediate-risk FIB-4 prevalence was also highest among patients aged ≥65 years (42.0%). High-risk FIB-4 prevalence by BMI category was 1.67% in overweight patients, 1.62% in normal BMI, 1.39% in obesity class I, 1.31% in obesity class II, and 1.19% in obesity class III patients. **Conclusion:** In this large real-world primary care cohort, approximately 10% of patients demonstrated intermediate or high-risk age-adjusted FIB-4 scores suggestive of clinically significant fibrosis risk. Metabolic dysfunction was strongly associated with advanced fibrosis risk, while severe obesity alone was not independently associated with higher fibrosis prevalence after age adjustment. These findings support implementation of non-invasive fibrosis screening strategies in primary care populations with metabolic disease and highlight the importance of age-adjusted FIB-4 interpretation in fibrosis risk assessment.



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2584 | REAL-WORLD OBSERVATIONAL CROSS-SECTIONAL DATA ON A LARGE DIVERSE PATIENT GROUP WITH MASLD FROM A SINGLE HEPATOLOGY CLINIC IN SOUTHERN CALIFORNIA: HISPANIC/LATINO PRESENT WITH GREATER METABOLIC BURDEN, ADVANCED FIBROSIS, AND CIRRHOSIS

Sabrina Alff[1] Torie Oishi[1] Orlinda Ventura[1] Daniel Joseph[1] Irene Arevalo[1] Edward Mena[2] Michel

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Mendler[1], [1]California Liver Research Institute, [2]California Liver Reasearch Instituite

Background: Racial and ethnic disparities in MASLD severity reflect differences in socioeconomics, lifestyle, and metabolic syndrome (MS). This study examined these in a large, diverse cohort in a non-academic hepatology clinic in Los Angeles County (LAC). **Methods:** A retrospective cross-sectional study of MASLD patients diagnosed by AASLD criteria, capturing a data within the first 6 months of initial presentation. MASLD was diagnosed with steatosis on CAP or other imaging, at least one metabolic syndrome (MS) component, with no other liver comorbidities. Fibrosis assessed by VCTE (kPa) and cirrhosis by usual imaging criteria. Continuous variables expressed as mean ± SD compared by t-test/ANOVA; categorical variables by chi-square; multivariate analyses by nominal logistic stepwise modeling. Significance: $p < 0.05$. **Results:** 2,488 patients seen between 2008-2023; mean age 53.1 ± 14.0y, 61.5% female, 64.2% married. Of the 1,811 who self-identified race, 38.7% were Caucasian, 1.9% Black, 19.1% Asian, and 40.3% other-Non-Caucasian. Of 1,981 who self-identified ethnicity, 55.7% were Hispanic/Latino (HL) and 44.3% were Non-Hispanic/Latino (NHL). Mean Area Deprivation Index (ADI; 1-10, least to most disadvantaged) was 4.6 ± 1.9: 30.0% ADI 1-3, 53.1% ADI 4-6, 16.9% ADI 7-10. 14.3% reported minimal/occasional alcohol use. Mean BMI was 32.1 ± 6.3 *kg*/m^2 : 9.4% lean, 31.9% overweight, 58.7% obese. 41.2% had DM2, 44.3% dyslipidemia, 46.3% HTN. Those with MS data: 29.7% had 1, 29.6% had 2, 26.5% had 3, and 14.2% had 4 components. 11.9% had cirrhosis; 85.3% had an ultrasound/imaging confirmation of MASLD. VCTE and CAP (n = 1,376): mean kPa 9.0 ± 6.6, CAP 318 ± 44 dB/m; IQR 13.5 ± 6.0. Mean HbA1c 6.6 ± 1.5%, platelets 251.8 ± 77.3x10^3 /µL, AST 46.1 ± 37.0 U/L, ALT 65.0 ± 53.1 U/L, ALP 89.6 ± 40.2 U/L, and AST/ALT ratio 0.83 ± 0.39. 73.7% had follow-up visits with a mean follow-up of 2.6 ± 3.2 years. As compared to NHL, HL had significantly higher BMI ($p < 0.0001$), rates of DM2 ($p = 0.0012$), greater numbers of MS components ($p = 0.0010$), greater socioeconomic deprivation ($p < 0.0001$), higher significant fibrosis [kPa ≥ 8 (≥ F2), $p = 0.0006$], and cirrhosis (15.0% vs 10.2%, $p = 0.0014$). On multivariate analysis: BMI, ALP, and HbA1c were independently associated with significant steatosis grade (S2+, AUC = 0.68); BMI, diabetes, age, CAP steatosis grade, and HL ethnicity were independently associated with significant fibrosis (kPa ≥ 8, AUC = 0.73); and low platelets, older age, elevated ALP, elevated HbA1c, and higher BMI with cirrhosis (AUC = 0.80). **Conclusion:** In this diverse Southern California MASLD cross-sectional group at initial diagnosis, as compared to NHL, HL patients presented with higher BMI, greater number of MS components, increased socioeconomic disparities, and higher degree of fatty liver, fibrosis and cirrhosis.

Disclosures: Sabrina Alff: Nothing to Disclose, Torie Oishi: Nothing to Disclose, Orlinda Ventura: Nothing to Disclose, Daniel Joseph: Nothing to Disclose, Irene Arevalo: Nothing to Disclose, Edward Mena: Nothing to Disclose, Michel Mendler: Nothing to Disclose.

2585 | EARLY MOBILITY IMPAIRMENT AS A FUNCTIONAL PHENOTYPE OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

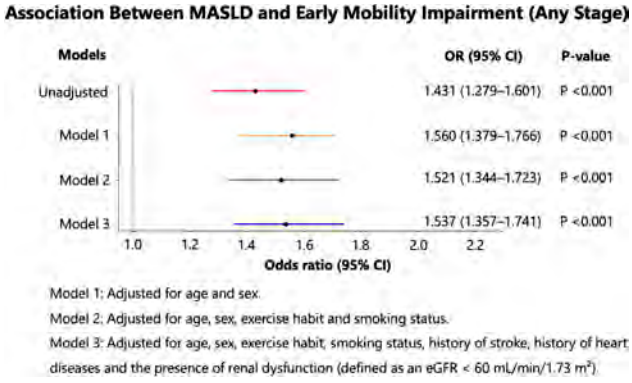
Shinya Yokoyama[1] Takashi Honda[1] yoji ishizu[1] Norihiro Imai[2] Takanori Ito[1] Kenta Yamamoto[1] Tetsuhito Kojima[3] Naoyoshi Kariya[3] Hiroki Kawashima[1], [1]Nagoya University, [2]Nagoya University Graduate School of Medicine, [3]Aichi Health Promotion Foundation

Background: Metabolic dysfunction–associated steatotic liver disease (MASLD) is increasingly recognized as a systemic cardiometabolic disorder with clinically relevant extrahepatic manifestations. However, its association with early functional decline remains unclear. Early mobility impairment may represent an early musculoskeletal phenotype of metabolic dysfunction before overt frailty, sarcopenia, or disability. We examined the association between MASLD and early mobility impairment in a large health examination cohort. **Methods:** This retrospective cross-sectional study included 7,776 adults who underwent health examinations between April 2018 and March 2025. MASLD was defined as ultrasonographic liver steatosis with cardiometabolic risk factors and alcohol intake below prespecified thresholds. Early mobility impairment was assessed using an established, standardized, equipment-free mobility-assessment battery consisting of the stand-up test, two-step test, and 25-question Geriatric Locomotive Function Scale. Participants were classified into stages 0–3 according to mobility impairment severity. Multivariable logistic regression was performed with adjustment for demographic, lifestyle, and comorbidity factors. **Results:** MASLD was present in 27.5% of participants. Early mobility impairment was more prevalent in individuals with MASLD than in those without (29.4% vs. 22.5%, $P < 0.001$). Early mobility impairment was independently associated with MASLD (adjusted odds ratio [OR] 1.537, 95% confidence interval [CI] 1.357–1.741, $P < 0.001$). A graded association was observed, with each one-stage increase in early mobility impairment being associated with higher odds of MASLD (adjusted OR 1.336, 95% CI 1.216–1.468, $P < 0.001$). This association was significant in participants aged <

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65 years (OR 1.712, 95% CI 1.488–1.969) but not in those aged ≥ 65 years (OR 1.217, 95% CI 0.922–1.606; P for interaction = 0.0097). Among the three components of early mobility impairment, the two-step test showed the largest effect size (OR 1.759, 95% CI 1.437–2.152, P < 0.001). Obesity was consistently associated with early mobility impairment regardless of MASLD status, whereas hypertension showed an additional association with early mobility impairment only in the MASLD group. **Conclusion:** MASLD was independently associated with early mobility impairment, particularly in adults younger than 65 years. These findings suggest that simple mobility assessment may capture a clinically relevant extrahepatic phenotype at the metabolic–musculoskeletal interface and help identify individuals with MASLD who are vulnerable to early functional decline before overt frailty or disability. Incorporating mobility assessment into routine metabolic health screening may support earlier risk stratification and preventive intervention.



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2586 | ROLE OF LATINO ETHNICITY IN POST-LIVER TRANSPLANT AND CARDIOMETABOLIC OUTCOMES FOR MASH

John Elsanadi[1] Jason Pan[1] Katherine Meneses[1] Mark Ebaid[1] Angshuman Saha[1] Sammy Saab[1], [1]David Geffen School of Medicine at UCLA

Background: Metabolic dysfunction-associated steatohepatitis (MASH) has become a leading indication for liver transplantation (LT). Emerging data suggests metabolic syndrome in LT recipients for MASH is substantial (Chan et al., 2025). Latino populations bear a disproportionate burden of MASH (Cumpian et al., 2025). However, granular data regarding post-LT outcomes is limited. We examined whether Latino ethnicity is associated with differences in cardiometabolic outcomes post-LT for MASH. **Methods:** This single-center retrospective study evaluated medical records of patients with MASH over 18 years of age who underwent LT between 2014 to 2024, noting pre-, post-LT outcomes and diagnoses including coronary artery disease (CAD), obesity, diabetes mellitus (DM), hypertension (HTN), hyperlipidemia (HLD). **Results:** Between 2014 to 2024, 332 patients at our center underwent LT for MASH, including 211 Latino recipients (63.6%) and 121 non-Latino recipients (36.4%). Latino recipients had lower median household income ($86,195 vs $103,803, p < 0.001) and greater possession of public insurance (69.2% vs 55.4%, p = 0.043) compared to non-Latinos. Pre-LT, Latino and non-Latino patients had significant differences in obesity (51.2% vs 38%, p = 0.028) and CAD (24.6% vs 36.4%, p = 0.032). Post-LT, the prevalence of obesity decreased in Latino patients and increased in non-Latino patients, while CAD increased in Latino patients. Subsequently, Latino and non-Latino patients had no significant post-LT differences in obesity (45.5% vs 43.0%, p = 0.741), DM (66.7% vs 57.0%, p = 0.102), HLD (58.1% vs 53.7%, p = 0.51), HTN (71.0% vs 77.7%, p = 0.228), CAD (33.2% vs 35.5%, p = 0.751). Post-LT, Latino and non-Latino patients had similar 1-year post-LT survival (92.9% vs 90%, p = 0.489), retransplant rates (2.4% vs 0.8%, p = 0.557), liver rejection (19.9% vs 17.4%, p = 0.656), median time to death (1.27 vs 2.23 years, p = 0.773). Kidney transplantation was more common among non-Latino recipients (14.2% vs 23.1%, p = 0.056). Only 19% of the post-LT population has had transient elastography with reassuring results: mean liver stiffness of 8.0 kPa (StD: 9.6) and CAP 270.7 db/m (StD: 53.3). **Conclusion:** Latino recipients represented nearly two-thirds of patients undergoing liver transplantation for MASH and achieved post-transplant cardiometabolic outcomes and survival rates comparable to those of non-Latino recipients despite greater socioeconomic disadvantage and a higher occurrence of pretransplant obesity. Persistent cardiometabolic dysfunction remained highly prevalent in both groups, and cardiovascular and cerebrovascular events were the leading documented case of death. Development of targeted surveillance and interventions pre-LT (prevention of obesity in Latino and early identification of CAD in non-Latino patients) may improve care consistency and long-term outcomes as MASH-related transplantation grows.

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Disclosures: John Elsanadi: Nothing to Disclose, Jason Pan: Nothing to Disclose, Katherine Meneses: Nothing to Disclose, Mark Ebaid: Nothing to Disclose, Angshuman Saha: Nothing to Disclose, Sammy Saab: AbbVie: Speaking and Teaching, gilead: speaker, salix: consultant, takeda: Speaking and Teaching, madrigal: consultant, mallinckrodt: Speaking and Teaching, Sequana: Advisor, ipsen: Advisor, novo nordisk: Speaking and Teaching.

2587 | LEAN PHENOTYPE IN METALD AND ALD WAS ASSOCIATED WITH ADVERSE OUTCOMES ACROSS EAST ASIAN COHORTS: EAST ASIA LIVER ALLIANCE (EALA)

Norihiro Imai[1] Hanah Lee[2] Young-Sun Lee[3] Shang-Chin Huang[4] Kai-Chi Chang[5] Shih-Chieh Chien[6] Shun-Ichi Wakabayashi[7] Takefumi Kimura[8] Nobuharu Tamaki[9] Seung Up Kim[10] Sang Gyune Kim[11] Dae Won Jun[12] Soo Young Park[13] Tung-Hung Su[5] Jia-Horng Kao[5] W. Ray Kim[14] Takumi Kawaguchi[15] Jee-Fu Huang[16] Ming-Lung Yu[17] Young Suk Lim[18] Tetsuo Takehara[19], [1]Nagoya University Graduate School of Medicine, [2]Chung-Ang University College of Medicine, [3]Korea University College of Medicine, [4]National Taiwan University, [5]National Taiwan University Hospital, [6]National Cheng Kung University Hospital, [7]Shinshu University School of Medicine, [8]Shinshu University, [9]Musashino Red Cross Hospital, [10]Yonsei University College of Medicine, [11]Mayo Clinic Rochester, [12]Hanyang University College of Medicine, [13]Kyungpook National University, [14]Mayo Clinic Arizona, [15]Kurume University School of Medicine, [16]Kaohsiung Medical University Hospital, [17]Kaohsiung Medical University/ Kaohsiung Medical University Hospital, [18]University of Ulsan College of Medicine, [19]Kansai Rosai Hospital

Background: Body mass index (BMI), in particular lean, is a fundamental clinical parameter in steatotic liver disease (SLD). However, metabolic dysfunction–associated steatotic liver disease with increased alcohol intake (MetALD) and alcohol-associated liver disease (ALD) are currently subclassified primarily based on alcohol consumption. This study aimed to investigate the clinical characteristics of MetALD and ALD, focusing on the lean phenotype. **Methods:** We analyzed three independent cohorts: a Japanese health checkup-based MetALD cohort (N = 108,494), a Korean multicenter hospital-based MetALD cohort (V-LINK, N = 35,087), and a Taiwanese hospital-based ALD cohort (N = 1,352). Patients with MetALD and ALD were subclassified by BMI as lean (BMI < 23 kg/m²) or non-lean (BMI ≥ 23 kg/m²). **Results: :** (1) **In the Japanese health checkup-based cohort**, patients with lean MetALD were significantly older, consumed less alcohol, and had fewer cardiometabolic risk factors than those with non-lean MetALD (all $P < 0.01$). Despite this, the lean group exhibited significantly higher liver injury markers, including FIB-4 index (1.52 vs. 1.29, $P < 0.01$). Moreover, the cumulative incidence of liver-related events (LRE) was significantly higher in lean MetALD than in non-lean MetALD (5-year incidence: 0.18% vs. 0.09%, respectively, $P = 0.011$). Notably, no significant difference was observed in the cumulative incidence of 3-point major adverse cardiovascular events between the two groups (5-year incidence: 0.4% vs. 0.5%, respectively, $P = 0.39$). (2) **In the Korean multicenter hospital-based cohort,** BMI-based subclassification revealed distinct clinical phenotypes consistent with those observed in the Japanese health checkup cohort, including a significantly higher FIB-4 index in lean MetALD (3.46 vs. 1.69, $P < 0.01$). The cumulative incidence of LRE was also significantly higher in lean MetALD than in non-lean MetALD (5-year incidence: 21% vs. 7%, respectively, $P < 0.001$). Furthermore, multivariable analysis adjusting for age and sex showed that lean status was an independent risk factor for LRE (hazard ratio 2.75, $P < 0.001$). (3) **In the Taiwanese hospital-based ALD cohort**, with a median follow-up duration of 6.9 years and 501 deaths, lean patients with ALD had a worse prognosis after multivariable adjustment for age, sex, cirrhosis, alanine aminotransferase level, diabetes mellitus, and other metabolic comorbidities (hazard ratio 1.45, $P < 0.001$). **Conclusion:** This study provides robust evidence from three independent East Asian cohorts that the lean phenotype in MetALD and ALD was associated with adverse outcomes.

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Teaching, Gilead: Speaking and Teaching, Sysmex: Speaking and Teaching, Novo Nordisk: Consultant, Berlinger-Ingelheim: Consultant, Ming-Lung Yu: Abbvie, Gilead and Roche diagnostics.: Grant/Research Support, Abbott, Abbvie, Gilead, Roche and Roche diagnostics: Consultant, Abbvie, BMS, Gilead, Roche and Roche diagnostics: Speaking and Teaching, Young Suk Lim: Gilead Sciences: Grant/Research Support, Tetsuo Takehara: Nothing to Disclose.

2588 | IMPACT OF ORTHOPEDIC CONDITIONS ON BMI TRAJECTORIES IN VETERANS WITH MASLD UNDERGOING LIFESTYLE-BASED WEIGHT MANAGEMENT

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a leading cause of liver disease globally. Lifestyle modification to achieve clinically significant weight loss remains first-line therapy, with >7-10% weight loss associated with histologic improvement. However, prior studies of MOVE!, a nationally implemented Veterans Health Administration (VHA) lifestyle-based weight management program, have shown limited efficacy. Patients with orthopedic injuries may benefit even less from lifestyle interventions due to impaired mobility and reduced activity. We therefore investigated body mass index (BMI) trajectories for VHA patients with MASLD enrolled in MOVE! according to the presence and type of orthopedic conditions. **Methods:** This was a retrospective cohort study of US VHA patients with MASLD and BMI $\geq$35kg/m^2 enrolled in MOVE! between 2008 and 2022 without prior bariatric surgery or glucagon-like peptide-1 receptor agonist (GLP-1RA) use. Baseline demographic, BMI, comorbidity, and laboratory data were obtained. Using a validated algorithm based on diagnosis codes, orthopedic conditions (primary exposure) were categorized as: (1) emergent or urgent (e.g. dislocations, fractures) and (2) nonurgent (e.g. sprains, osteoarthritis). Multivariable Cox regression was used to evaluate risk of both 10% BMI reduction and 10% BMI gain in patients with or without orthopedic injury. Patients were right-censored at GLP-1RA initiation, bariatric surgery, or maximum follow-up, up to 18 years. **Results:** Of the 115,550 patients meeting inclusion criteria, 345 had emergent or urgent orthopedic injury, 12,694 had nonurgent orthopedic injury, and 102,511 control patients had no orthopedic injury. The emergent or urgent patients had higher rates of cardiovascular and thromboembolic comorbidities compared to nonurgent and control patients, including coronary artery disease (20% vs 15% vs 15%, p = 0.009), deep vein thrombosis (4.9% vs 2.2% vs 1.7%, p < 0.001), and pulmonary embolism (2.0% vs 1.5% vs 1.3%, p = 0.020). Overall, 9.5% of patients had 10% BMI gain and 27.1% achieved 10% BMI loss. The adjusted hazard ratios for 10% BMI gain were 1.58 (95% confidence interval [CI]: 1.27 to 1.97, p < 0.001) for the emergent or urgent group and 1.16 (95% CI: 1.11 to 1.22, p < 0.001) for the nonurgent group, relative to the control group. Figure 1 shows BMI trajectories and adjusted Cox survival curves for 10% BMI gain. Adjusted hazard ratios for 10% BMI loss were similar for patients with and without orthopedic injury (p > 0.05). **Conclusion:** Orthopedic conditions, particularly emergent or urgent injuries, were associated with significantly increased risk of clinically meaningful BMI gain among VHA patients with MASLD participating in MOVE!. These findings suggest that patients with orthopedic conditions may benefit from earlier consideration of more intensive weight loss interventions, such as GLP-1RAs or bariatric surgery.

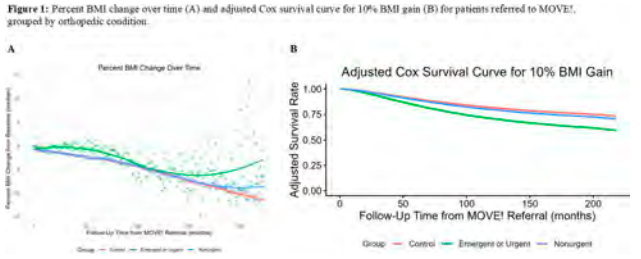


Figure 1: Percent BMI change over time (A) and adjusted Cox survival curve for 10% BMI gain (B) for patients referred to MOVE!, grouped by orthopedic condition.

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2589 | ASSOCIATION BETWEEN THE LIFE'S ESSENTIAL 8 SCORE AND MASLD: A CROSS-SECTIONAL STUDY AMONG COMMUNITY RESIDENTS IN SHANGHAI

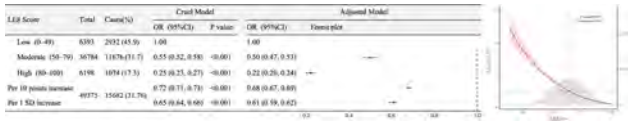
Qi Zhang[1] Xing Liu[1], [1]Fudan University

Background: To investigate the association between the Life's Essential 8 (LE8) score and metabolic

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dysfunction-associated steatotic liver disease (MASLD) among community residents in Shanghai, and to provide evidence for MASLD prevention through lifestyle interventions. **Methods:** This study was based on baseline data collected from 2016 to 2019 in the Shanghai Suburban Adult Cohort and Biobank (SSACB) and included adults aged from 20 to 74. Demographic characteristics and lifestyle factors were collected by standardized questionnaires. MASLD was defined as the presence of hepatic steatosis identified by abdominal ultrasonography in individuals with at least one of five cardiometabolic risk factors, after exclusion of excessive alcohol consumption and other chronic liver diseases. The LE8 score was calculated based on the scoring algorithm proposed by the American Heart Association (AHA), with localized adaptations for Chinese population.The total LE8 score was calculated as the arithmetic mean of the eight component scores, ranging from 0 to 100, and was further categorized into low (0–49 points), moderate (50–79 points), and high cardiovascular health (80–100 points).Multivariable logistic regression models and restricted cubic spline (RCS) models were constructed after adjustment for confounders to assess the association between the LE8 score and the prevalence of MASLD. Stratified analyses were further performed according to demographic characteristics. **Results:** A total of 49,375 individuals were included in the study, and 15682 (30.8%) participants were determined to have MASLD. The mean LE8 score was significantly lower among participants with MASLD than among those without MASLD (60.8 ± 12.4 vs. 66.2 ± 12.8, P < 0.001). According to CVH categories, 6,393 (12.9%) ,36,784 (74.5%) and 6,198 (12.6%) participants were respectively classified into the low,moderate and high CVH group. Multivariable logistic regression models shows that compared with participants in the low CVH group, those in the moderate and high CVH groups had a 50% (OR = 0.50, 95% CI: 0.47–0.53; P < 0.001) and 78% (OR = 0.22, 95% CI: 0.20–0.24) lower odds of MASLD, respectively. Each 10-point increase in LE8 score was associated with a 32% lower odds of MASLD (OR = 0.68, 95% CI: 0.67–0.69). Stratified analyses showed that the inverse association between LE8 score and MASLD was more pronounced among women (OR = 0.62, 95% CI: 0.61–0.63), younger participants aged 20–39 years (OR = 0.62, 95% CI: 0.58–0.66) and participants with college education or above (OR = 0.66, 95% CI: 0.62–0.71). RCS analysis results suggested a significant nonlinear inverse association between LE8 score and MASLD risk (P for overall < 0.001, P for nonlinearity < 0.001). **Conclusion:** A higher LE8 score is significantly associated with a lower prevalence of MASLD. Maintaining a healthy lifestyle may help prevent MASLD.



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2590 | COMPARATIVE EFFECTIVENESS OF FACTOR XA INHIBITORS AND WARFARIN ON HEPATIC OUTCOMES IN MASLD

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most prevalent chronic liver disease in the U.S. and frequently coexists with conditions requiring anticoagulation. Preclinical studies suggest that Factor Xa inhibitors (FXai) may confer hepatoprotective benefits through antifibrotic and anti-inflammatory mechanisms, yet clinical evidence is limited. We explored whether FXai use, compared with warfarin, is associated with differences in hepatic complications in pre-cirrhotic MASLD. **Methods:** Using the NIH's *All of Us* Research Program (Controlled Tier v8), we conducted a target trial emulation comparing adults with MASLD and type 2 diabetes (T2DM) who initiated FXai (apixaban and rivaroxaban) versus warfarin from 2013-2023. Participants with HBV, HCV, alcohol-associated liver disease, HIV, organ transplant, FIB-4 $\geq$2.67, or primary outcome components were excluded. The primary analysis used pooled inverse probability of treatment weighting (IPTW) at a 2-year MASLD ascertainment window, fitting a propensity score (PS) on 31 unique covariates with a weighted Cox model adjusting for calendar year. Sensitivity analyses included per-trial-year IPTW and 1: 1 PS matching. Analyses were replicated across 0-, 1-, and 3-year ascertainment windows. Cox models added imbalanced covariates (|SMD|$\geq$0.1) as adjustments. The primary outcome was a composite of incident cirrhosis, hepatic decompensation (esophageal varices, ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, hepatorenal syndrome), hepatocellular carcinoma, or liver transplantation. Intention-to-treat (ITT) and per-protocol (PP) hazard ratios used multiple imputation (m = 20; Rubin's rules). Incident fracture was a negative control outcome. **Results:** In the primary pooled IPTW analysis at

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the 2-year ascertainment window (median N = 738, 88 ITT/43 PP events across 20 imputations), FXai was associated with a lower but non-significant ITT hazard (HR 0.74, 95% CI 0.43-1.29, p = 0.29) and a significantly lower PP hazard (HR 0.39, 95% CI 0.19-0.81, p = 0.01). The PP signal was consistent across all windows, reaching significance at 1-year (p = 0.02) and 3-year (p = 0.03). Per-trial-year IPTW ITT was directionally consistent (HR 0.83, 95% CI 0.42-1.62, p = 0.58) and PP reached significance (HR 0.34, 95% CI 0.13-0.88, p = 0.03). Per-trial-year PS-matched ITT (HR 0.66, 95% CI 0.27-1.60, p = 0.36) and PP (HR 0.30, 95% CI 0.06-1.61, p = 0.16) were directionally consistent. Negative control analysis supported absence of residual confounding. **Conclusion:** In this target trial emulation, FXai use was associated with fewer hepatic complications than warfarin under per-protocol follow-up in pre-cirrhotic MASLD with T2DM. The protective signal was directionally consistent across multiple analyses, although limited by small event counts. These hypothesis-generating findings warrant validation in prospective cohorts.

Disclosures: Erik Almazan: Nothing to Disclose, Jonggi Choi: Nothing to Disclose, Tushar Kamath: Nothing to Disclose, Vy Nguyen: Nothing to Disclose, Eric Przybyszewski: Nothing to Disclose, Jiunn Song: Nothing to Disclose, Allison Carroll: Nothing to Disclose, Megan Michta: Nothing to Disclose, Tracey Simon: Nothing to Disclose, Raymond Chung: GSK: Grant/Research Support, Salix: Grant/Research Support, GSK: Consultant, Precision Biosciences: Consultant, Boehringer: Grant/Research Support, BMS: Grant/Research Support, Aligos: Grant/Research Support, Curve: Grant/Research Support.

2591 | ORAL CONTRACEPTIVE USE AND RISK OF STEATOTIC LIVER DISEASE IN WOMEN: A TRINETX GLOBAL COLLABORATIVE NETWORK STUDY

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Background: Steatotic liver disease (SLD) is a major contributor to the burden of chronic liver disease. Oral contraceptive pills (OCPs) comprise 22% of all contraceptive use in the United States. Despite widespread hormonal contraceptive exposure among reproductive-age women, data evaluating the relationship between contraceptive formulations and liver-related outcomes are limited. **Methods:** A retrospective cohort study was conducted using the TriNetX Global Collaborative Network, including females aged 10-40 years between January 2010 and January 2020. Exposure cohorts included combined OCP (COCP) users and progestin-only contraceptive users. Comparator cohorts consisted of females taking multivitamins without documented OCP exposure. Propensity score matching was performed for demographic factors, metabolic risk factors, liver disease risk factors, and medications. Outcomes assessed over 5 years included steatotic liver disease (SLD), MASLD, ALD, cirrhosis, and MALOs. Kaplan-Meier survival analyses were used to estimate hazard ratios (HRs). Similar analyses were performed to compare various contraceptives. **Results:** A total of 10,633 COCP users and 43,481 progestin-only contraceptive users were identified. Both COCP and progestin-only cohorts demonstrated lower observed hazards of SLD (HR 0.57, 95% CI 0.45-0.75, p < 0.001) and MASLD (HR 0.49, 95% CI 0.38-0.63, p < 0.001) compared with matched controls (Table 1). The progestin-only cohort also demonstrated lower hazard ratios for SLD and MASLD compared with the IUD cohort. No significant associations were identified when various contraceptives were compared (Table 2). **Conclusion:** Hormonal contraceptive use was associated with lower observed hazards of incident SLD and MASLD over 5 years, with no significant association with ALD, cirrhosis, or MALO. These findings suggest a potential protective metabolic or anti-inflammatory association, though residual confounding and detection bias remain important limitations. The absence of differences in cirrhosis or MALO may be attributable to the young study population, the limited duration of liver injury, and endogenous estrogen-mediated protection against MASLD in premenopausal women.

Outcome	Combined Oral Contraceptives vs multivitamin (HR (95% CI), p-value) N=10,633 in group	Progestin-Only vs multivitamin (HR (95% CI), p-value) N=43,481 in each group
SLD	0.57 (0.45-0.75), 0.0001	0.81 (0.68-0.96), 0.02
MASLD	0.49 (0.38-0.63), 0.0001	0.83 (0.69-0.98), 0.04
ALD	-	0.55 (0.28-1.09), 0.08
Cirrhosis	-	0.78 (0.41-1.49), 0.46
MALO	1.18 (0.96-1.45), 0.12	0.97 (0.86-1.09), 0.64

Table 1

Outcome	Progestin-Only vs Depot N=6,247 in each group	Progestin-Only vs Nexplanon N=1,658 in each group	Progestin vs IUD N=8,942 in each group	Depot vs Nexplanon N=1,617 in each group	Depot vs IUD N=4,682 in each group
SLD	0.67 (0.43-1.06), 0.08	0.49 (0.26-0.94), 0.03	0.5 (0.38-0.67), 0.0001	0.87 (0.50-1.52), 0.63	0.84 (0.56-1.26), 0.40
MASLD	0.68 (0.44-1.06), 0.09	0.49 (0.26-0.94), 0.03	0.4 (0.31-0.54), 0.0001	0.87 (0.50-1.52), 0.63	0.71 (0.48-1.04), 0.08
ALD	-	-	-	-	-
Cirrhosis	-	-	-	-	-
MALO	1.03 (0.78-1.37), 0.83	1.40 (0.77-2.53), 0.26	0.74 (0.58-0.94), 0.01	1.30 (0.68-2.50), 0.42	0.89 (0.66-1.21), 0.47

Table 2

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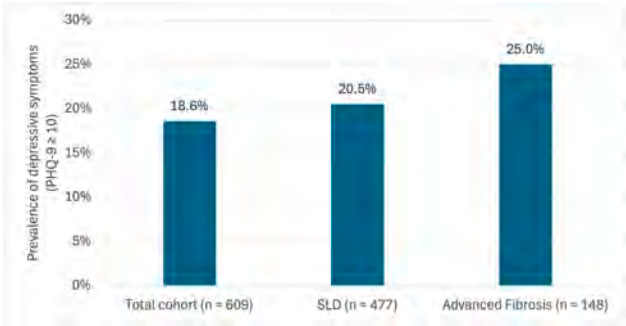
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2592 | ADVANCED FIBROSIS IS AN INDEPENDENT RISK FACTOR FOR DEPRESSIVE SYMPTOMS IN STEATOTIC LIVER DISEASE

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Background: Depressive symptoms contribute substantially to the global disease burden and are increasingly recognized in metabolic disorders. However, their association with steatotic liver disease (SLD) and fibrosis remains incompletely characterized. This study aimed to assess the prevalence and predictors of depressive symptoms in individuals with SLD. **Methods:** In this prospectively enrolling bicentric cohort study, adults with confirmed or suspected SLD based on cardiometabolic risk factors (CMRF) were recruited from hepatology outpatient clinics at the university medical centers of Mainz and Homburg, Germany. Demographics, CMRF (overweight/obesity, dysglycemia, hypertension, hypertriglyceridemia, low HDL cholesterol) and alcohol intake were recorded. Hepatic steatosis and advanced fibrosis were assessed by transient elastography using controlled attenuation parameter (CAP; ≥ 275 dB/m for SLD) and liver stiffness measurement (LSM; ≥ 10 kPa for advanced fibrosis). Depressive symptoms were evaluated using the Patient Health Questionnaire-9 (PHQ-9; cutoff ≥ 10). Univariable and multivariable logistic regression analyses were performed to identify predictors of depressive symptoms in patients with SLD. **Results:** Among 609 participants (47.8% female, mean age 55.4 ± 13.5 years), the prevalence of depressive symptoms was 18.6% with a mean PHQ-9 score of 5.7 ± 4.7. Female sex, BMI ≥ 35 kg/m^2, and SLD were significantly more prevalent in participants with depressive symptoms compared to those without. Mean BMI was 33.6 ± 7.8 kg/m^2, with 64.2% being obese. 72.7% and 52.7% of participants had ≥ 3 and ≥ 4 CMRF, respectively. SLD was present in 477 (78.3%) participants (mean CAP 305.0 ± 49.2 dB/m), comprising MASLD (n = 454, 74.5%), MetALD (n = 17, 2.8%) and ALD (n = 5, 0.8%). Advanced fibrosis was identified in 148 (24.3%) participants. The prevalence of depressive symptoms increased with disease severity, reaching 20.5% in SLD and 25.0% in advanced fibrosis (Fig. 1). In multivariable regression analysis, female sex (odds ratio [OR] 2.16, 95% confidence interval [CI] 1.34–3.47), advanced fibrosis (OR 1.90, 95% CI 1.15–3.14), and ≥ 4 CMRF (OR 1.88, 95% CI 1.15–3.06) were independently associated with depressive symptoms in participants with SLD after adjustment for age and sex. **Conclusion:** Depressive symptoms are common in individuals with SLD. Female sex, advanced fibrosis and a high burden of CMRF are independently associated with depressive symptoms, highlighting the need for mental health screening and management in SLD care.



Disclosures: Alexander Barton: Nothing to Disclose, Stella Thielmann: Nothing to Disclose, Leonard Kaps: Nothing to Disclose, Lisa Riescher: Nothing to Disclose, Saleh Alqahtani: Nothing to Disclose, Christian Labenz: Nothing to Disclose, Joern M. Schattenberg: Nothing to Disclose, Maurice Michel: Nothing to Disclose.

2593 | PREVALENCE AND INDEPENDENT PREDICTORS OF HIGH-RISK OBSTRUCTIVE SLEEP APNEA IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE: FINDINGS FROM THE GENESIS POPULATION-BASED COHORT

Waleed Alhazzani[1] Basmah Khoja[2] Faisal Sanai[3] Samar Alqussayer[1] Faisal Abaalkhail[2] Waleed Alomaim[2] Haifa Alotaibi[1] Mohammed Alghamdi[4] Layan Alsubki[2] Hani Tamim[5] Shadan AlMuhaidib[1] Saleh Alqahtani[6]

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Background: Obstructive sleep apnea (OSA) and metabolic dysfunction-associated steatotic liver disease (MASLD) share metabolic drivers, but population-level estimates of OSA risk within MASLD cohorts are scarce, with most prior data derived from sleep-clinic or biopsy-based samples. Identifying the independent predictors of high-risk OSA in MASLD is needed to guide targeted screening. We aimed to estimate the prevalence of high risk for OSA and identify independent predictors among adults with vibration-controlled transient elastography (VCTE)-defined MASLD. **Methods:** GENESIS is a prospective, national population-based cohort with VCTE phenotyping. MASLD was defined as hepatic steatosis on VCTE (controlled attenuation parameter [CAP] $\geq$ 268 dB/m) plus at least one of the 5 cardiometabolic risk factors per the 2023 multisociety Delphi consensus. The Berlin Questionnaire stratified participants into high-risk and low-risk OSA groups per its standard scoring (positive in $\geq$ 2 of the 3 categories: snoring, daytime sleepiness/fatigue, and hypertension or obesity). Multivariable logistic regression identified independent predictors of high-risk OSA, adjusting for age, sex, waist circumference, weekday sleep duration, and physical activity by the International Physical Activity Questionnaire (IPAQ). **Results:** Among 1,111 adults with MASLD (mean age 46.1 ± 13.0 years; 58.2% male), 411 (37.0%) screened high-risk for OSA. On multivariable logistic regression, three factors were independently associated with high-risk OSA: waist circumference (WC; odds ratio [OR] 1.21 per 5 cm; 95% confidence interval [CI] 1.15–1.27; $p < 0.001$), weekday sleep duration (OR 0.84 per additional hour; 95% CI 0.76–0.93; $p < 0.001$), and physical activity by the International Physical Activity Questionnaire (IPAQ; OR 0.71 per category increase; 95% CI 0.54–0.93; $p = 0.01$). Age (OR 1.03 per 10 years; 95% CI 0.93–1.14; $p = 0.55$) and male sex (OR 0.90; 95% CI 0.69–1.18; $p = 0.46$) were not independently associated. **Conclusion:** More than one in three adults with MASLD screened high risk for OSA, representing a substantial undiagnosed population-level burden. Central adiposity, shorter weekday sleep duration, and lower physical activity independently identify patients who may benefit from sleep evaluation. These findings support embedding a brief OSA screen, incorporating waist circumference, sleep duration, and physical activity, into routine MASLD hepatology workflows as part of an integrated cardiometabolic-hepatic-sleep care pathway.

Predictor	Adjusted OR (95% CI)	p value
Waist circumference (per 5 cm)	1.21 (1.15–1.27)	<0.001
Physical activity, IPAQ level	0.71 (0.54–0.93)	0.01
Weekday sleep duration (per hour)	0.84 (0.76–0.93)	<0.001
Age (per 10 years)	1.03 (0.93–1.14)	0.55
Male sex	0.90 (0.69–1.18)	0.46

Table 1. Independent predictors of high-risk obstructive sleep apnea in the metabolic dysfunction-associated steatotic liver disease subcohort (multivariable logistic regression, n=1,111). CI, confidence interval; IPAQ, International Physical Activity Questionnaire; OR, odds ratio.

Disclosures: Waleed Alhazzani: Nothing to Disclose, Basmah Khoja: Nothing to Disclose, Faisal Sanai: Nothing to Disclose, Samar Alqussayer: Nothing to Disclose, Faisal Abaalkhail: Nothing to Disclose, Waleed Alomaim: Nothing to Disclose, Haifa Alotaibi: Nothing to Disclose, Mohammed Alghamdi: Nothing to Disclose, Layan Alsubki: Nothing to Disclose, Hani Tamim: Nothing to Disclose, Shadan AlMuhaidib: Nothing to Disclose, Saleh Alqahtani: Nothing to Disclose.

2594 | HIGH-RISK OBSTRUCTIVE SLEEP APNEA IS ASSOCIATED WITH SUBSTANTIALLY LOWER HEALTH-RELATED QUALITY OF LIFE IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE: 36-ITEM SHORT FORM HEALTH SURVEY FINDINGS FROM THE GENESIS COHORT

Waleed Alhazzani[1] Hani Tamim[2] Samar Alqussayer[1] Shadan AlMuhaidib[1] Haifa Alotaibi[1] Faisal Abaalkhail[3] Basmah Khoja[3] Ahmad Almalky[4] May Alzahrani[5] Bandar Al-Judaibi[3] Amr Arafat[1] Saleh Alqahtani[6], [1]Ministry of Defense Health Services, Riyadh, Saudi Arabia, [2]Alfaisal University, Riyadh, Saudi Arabia, [3]King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia, [4]Prince Sultan Military Medical City, Riyadh, Saudi Arabia, [5]King Faisal Specialist Hospital and Research Center, Jeddah, Saudi Arabia, [6]King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia

Background: Patient-reported outcomes are now central endpoints in metabolic dysfunction-associated steatotic liver disease (MASLD) clinical care and drug development, yet the contribution of common comorbidities to quality-of-life impairment is underexplored. Obstructive sleep apnea (OSA) frequently coexists with MASLD, and the magnitude of any associated quality-of-life impact has not been quantified at the population level. We aimed to evaluate the association between high risk for OSA and health-related quality of life among adults with vibration-controlled transient elastography (VCTE)-defined MASLD in the GENESIS cohort. **Methods:** Within the GENESIS prospective population-based cohort, adults with VCTE-defined MASLD completed the 36-Item Short Form Health Survey (SF-36) and the Berlin Questionnaire. The SF-36 is a validated generic health-related quality-of-life instrument comprising 8 domains that aggregate into two summary measures, the Physical Component Summary (PCS) and the Mental Component Summary (MCS); scores range from 0 to 100, with higher scores indicating better health. PCS and MCS were compared between high-risk and low-

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risk OSA groups using Student's t-test or the Mann-Whitney U test as appropriate. **Results:** Of 1,111 adults with MASLD (mean age 46.1 ± 13.0 years; 58.2% male), 411 (37.0%) screened high-risk for OSA and 700 (63.0%) screened low-risk. Both SF-36 summary scores were lower in the high-risk group: PCS 75.5 ± 18.7 vs 82.1 ± 15.5 (mean difference 6.6 points; $p < 0.001$) and MCS 73.3 ± 18.8 vs 82.6 ± 14.5 (mean difference 9.3 points; $p < 0.001$). **Conclusion:** High-risk OSA in MASLD is associated with substantially lower health-related quality of life across both the physical and mental component summaries of the SF-36, with the mental component showing the larger absolute gap. These findings support routine quality-of-life screening as a low-burden way to identify patients with MASLD who may benefit from sleep evaluation.

SF-36 summary score	High-risk OSA (n=411)	Low-risk OSA (n=700)	Mean difference	p value
Physical Component Summary	75.5 ± 18.7	82.1 ± 15.5	6.6	<0.001
Mental Component Summary	73.3 ± 18.8	82.6 ± 14.5	9.3	<0.001

Table 1. SF-36 Physical and Mental Component Summary scores by obstructive sleep apnea risk group, presented as mean ± standard deviation. OSA, obstructive sleep apnea; SF-36, 36-Item Short Form Health Survey.

Disclosures: Waleed Alhazzani: Nothing to Disclose, Hani Tamim: Nothing to Disclose, Samar Alqussayer: Nothing to Disclose, Shadan AlMuhaidib: Nothing to Disclose, Haifa Alotaibi: Nothing to Disclose, Faisal Abaalkhail: Nothing to Disclose, Basmah Khoja: Nothing to Disclose, Ahmad Almalky: Nothing to Disclose, May Alzahrani: Nothing to Disclose, Bandar Al-Judaibi: Nothing to Disclose, Amr Arafat: Nothing to Disclose, Saleh Alqahtani: Nothing to Disclose.

2595 | ADDRESSING UNDERDIAGNOSIS OF MASLD IN PRIMARY CARE: A QUALITY IMPROVEMENT EDUCATIONAL INTERVENTION USING AN AI-DRIVEN EMR ALGORITHM

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) affects nearly 30% of adults and is a rapidly growing indication for liver transplantation. Despite its prevalence, MASLD frequently remains underdiagnosed, with many cases identified incidentally on imaging. We developed an AI algorithm to identify patients meeting MASLD criteria within the EMR and found that only half carried a formal diagnosis, with even fewer undergoing fibrosis risk stratification. We subsequently conducted a QI educational intervention to improve primary care provider (PCP) recognition and management of MASLD. **Methods:** We performed a pre-post QI study evaluating the impact of a PCP educational intervention on paired MALSD patients identified by an AI algorithm. Eligible patients met MASLD criteria without a MASLD-related ICD diagnosis. Corresponding PCPs received an Epic-messaged educational "one-sheet" outlining guideline-based MASLD management recommendations. Outcomes assessed at baseline, 6 months, and 12 months included documented MASLD diagnosis, fibrosis risk stratification with FIB-4, referrals for elastography and Hepatology, screening for diabetes mellitus (DM), hyperlipidemia (HLD), and chronic kidney disease (CKD), and lifestyle counseling documentation. **Results:** The intervention was distributed to 259 PCPs, with a 24% response rate ($n = 61$). One patient died before follow up, leaving 60 paired patients for analysis. Formal MASLD diagnosis increased from 5% at baseline to 10% at 12 months ($p = 0.25$), while informal documentation remained unchanged at 11.7%. FIB-4 assessment rates remained low following intervention (6.7% at baseline, 5% at 6 months, and 3.3% at 12 months). Among intermediate risk patients (FIB-4 score ≥ 1.3; $n = 11$), only 1 was referred for elastography at 6-months, with no referrals at 12 months. The single high-risk patient had already been referred to Hepatology prior to intervention. Screening for MASLD-associated comorbidities improved following intervention. Approximately 50% of patients underwent DM and HLD screening at baseline, while only 8% underwent CKD screening. CKD screening increased to 35% at 6 months and 47% at 12 months. Lifestyle counseling documentation increased from 8% to 13% between 6 and 12 month follow up. However, only 28% and 40% of patients completed PCP follow up visits during the 6 and 12 month periods, limiting opportunities for longitudinal reassessment and intervention implementation. **Conclusion:** Our QI intervention highlights persistent underdiagnosis of MASLD and gaps in fibrosis risk stratification within primary care. Although modest improvements were observed in disease recognition, comorbidity screening, and lifestyle counseling, rates of FIB-4 documentation and referral for secondary fibrosis assessment remained low. These findings support the need for continued educational and EMR-based interventions to improve guideline-concordant MASLD management in primary care.

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Outcome	Baseline	6 Months	12 Months
Formal MASLD Diagnosis	3 (5%)	3 (5%)	6 (10%)
Informal MASLD Diagnosis	8 (13.3%)	7 (11.7%)	7 (11.7%)
FIB-4 Assessment	4 (6.7%)	3 (5%)	2 (3.3%)
Intermediate-risk, referral for elastography†	0	1 (1.67%)	0
High-risk, referral to Hepatology‡	1 (1.67%)	1 (1.67%)	0
Diabetes Mellitus screening	31 (51.7%)	10 (16.7%)	9 (15%)
HLD Screening	35 (58.3%)	9 (15%)	8 (13.3%)
CKD Screening	49 (81.7%)	21 (35%)	28 (46.7%)
Lifestyle Counseling	-	5 (8.3%)	8 (13.3%)
PCP Follow Up	-	17 (28%)	24 (40%)

* Represents 3 new formal MASLD diagnoses during follow-up (McNemar p=0.25)
† Intermediate-risk defined as calculated FIB-4 >1.3 (n=11)
‡ High-risk FIB-4 cohort included 1 patient.

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2596 | HIGHER TESTOSTERONE LEVELS ARE ASSOCIATED WITH ALT LEVELS AND STEATOSIS SEVERITY IN WOMEN WITH MASLD AND POLYENDOCRINE METABOLIC OVARIAN SYNDROME (PMOS)

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Background: Polyendocrine metabolic ovarian syndrome (PMOS), formerly known as Polycystic Ovary Syndrome, is a risk factor for presence and severity of metabolic dysfunction-associated steatotic liver disease (MASLD). Whether higher androgens drive this risk, beyond established metabolic comorbidities, is not known. **Methods:** In this two-site prospective cohort study of reproductive-aged women with MASLD and PMOS, we evaluated the cross-sectional association of baseline androgen levels with severity of MASLD. Outcome measures included serum ALT, and steatosis and fibrosis assessment by transient elastography-controlled attenuation parameter (TE-CAP). Standardized protocols were employed to obtain socio-demographics, anthropomorphic measures, fasting metabolic labs, liver tests, and androgen levels. Linear and logistic regressions were used to evaluate the association of free testosterone (free T) with study outcomes, adjusting for potential confounding conditions, while ROC-analyses and Youden indices were used to identify optimal free T thresholds for predicting study outcomes. **Results:** Among 102 participants with MASLD and PMOS, median age was 31 years (IQR 28-35); 48.5% were White, 19.8% Asian, and 31.7% Hispanic. Median body mass index (BMI) was 35.0 kg/m^2 (31.5-40.2), median HOMA-IR was 3.5 (2.5-5.6), and median free T was 0.71 ng/dL (0.35-1.12). Dyslipidemia, hypertension, and type 2 diabetes mellitus were present in 30.4%, 20.6%, and 13.7%, respectively. Stable GLP-1 receptor agonist use ($\geq$ 3 months) occured in 18.6%. Median ALT was 37.0 U/L (20.0- 60.0) with 32.4% having ALT $\geq$ 50.0 U/L. Median CAP score was 313 dB/m (283-346) and 56.9% had severe steatosis (CAP $\geq$ 300 dB/m). Median fibrosis score was 5.6kPa (4.9-7.6), and 20.4% had fibrosis (kPa $\geq$ 8.0).On univariate analysis, free T was associated with higher ALT (back-transformed β coefficient = 1.6, 95% CI 1.2-2.0, p < 0.001), ALT levels $\geq$ 50.0 U/L (OR 2.6, 95% CI 1.3-5.5, p = 0.01), higher CAP scores (β = 14.7, 95% CI 2.2-,27.2, p = 0.02), and severe steatosis (OR 3.9, 95% CI 1.6,9.9, p = 0.004), while the association with fibrosis severity did not reach statistical significance (β = 1.1, 95% CI 1.0-1.3, p = 0.06). After adjustment for BMI and HOMA-IR, free T remained associated with higher ALT levels (β = 1.4, 95% CI 1.1-1.8, p = 0.004), ALT $\geq$ 50 (AOR 2.6, 95% CI 1.2-5.7, p = 0.02) and presence of severe steatosis (AOR 3.3, 95% CI 1.2-8.8, p = 0.02). On ROC-analyses, the optimal free T thresholds for predicting elevated ALT was 0.69 ng/dL (AUROC = 0.66) and for predicting severe steatosis was 0.85 ng/dL (AUROC = 0.70) (Figure). **Conclusion:** In this cohort of reproductive-aged women with MASLD and PMOS, free testosterone levels were associated with higher ALT levels and severe steatosis. These data support the role of testosterone in promoting worsening MASLD, and the need to consider hormonal modulation as a potential novel therapeutic mechanism for MASLD treatment in women with PMOS.

Figure: Free Testosterone Thresholds and Risk for MASLD-Related Outcomes in Women with PMOS (n=102)

Outcome	AUROC (95% CI)	Optimal Free T Threshold*	Sensitivity	Specificity	Youden Index
ALT ≥ 50 U/L	0.66 (0.54-0.78)	0.69	0.73	0.60	0.327
Severe Steatosis (CAP > 300 dB/m)	0.70 (0.59-0.80)	0.85	0.50	0.87	0.367

*selected using the maximum Youden index

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2598 | DISCORDANCE BETWEEN ILLNESS PERCEPTIONS AND REAL-WORLD DIETARY BEHAVIORS IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE: A MIXED-METHODS EXPLORATORY ANALYSIS

Sangmin Lee[1] Mohammad Khan[1], [1]University of Western Ontario

Background: Dietary behavior is central to metabolic dysfunction-associated steatotic liver disease (MASLD) management, yet patients' illness perceptions and self-reported barriers may not align with real-world dietary practices. Examining this discordance at baseline using a mixed-methods approach may better capture the complexity underlying dietary adherence and change in MASLD. **Methods:** As part of a multidisciplinary MASH Clinic, 122 adult patients completed a baseline screening questionnaire and a 3-day food diary (2 weekdays, 1 weekend) prior to their first visit. The questionnaire assessed illness perception, dietary self-efficacy, and perceived barriers using a 7-point Likert scale (collapsed to Agree/Neutral/Disagree categories). Food diaries underwent direct content analysis in NVivo across 13 dietary domains, coded semi-quantitatively as Never, Occasional (1-2 instances), or Frequent (≥ 3 instances). Pilot analysis of the first 60 consecutive patients is presented. Limitations of social desirability and recall bias are acknowledged. **Results:** Participants had a mean age of 52 years, and 61.7% (n = 37)

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were female. Frequent refined carbohydrate intake was observed in 72% of patients, while whole grain consumption was absent in 37%. Integrative analysis revealed substantial discordance across multiple domains. Among patients reporting a complete understanding of MASLD, frequent refined carbohydrate intake was universal (100%), suggesting disease knowledge alone does not translate into healthier dietary behaviors. Patients expressing low illness concern demonstrated lower lean protein (20% vs. 68%) and vegetable intake (60% vs. 77%) compared to those expressing concern. Among patients reporting no personal habits requiring change, 83% had frequent refined carbohydrate and/or high-sugar snack consumption. Patient reporting uncertainty about healthy eating (32%) did not demonstrate worse dietary patterns than confident peers, indicating knowledge gaps alone do not drive poor behavior. Symptoms of depression and anxiety were endorsed by 33% and 35% of patients, respectively, and were associated with greater meal irregularity compared to those not reporting symptoms (35% vs. 10%). **Conclusion:** Significant discordance exists between illness perceptions and real-world dietary behaviors in MASLD. Disease knowledge and perceived access to healthy living resources alone may be insufficient to drive behavioral change. Meanwhile illness perception and psychological factors appear to be more strongly associated with maladaptive dietary patterns. These findings underscore the need for integrating psychological and behavioral frameworks into multidisciplinary MASLD clinics alongside nutritional and exercise counselling.
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2599 | THE IMPACT OF DIET AND ALCOHOL CONSUMPTION ON RISK OF STEATOTIC LIVER DISEAS

Kazuya Miyamoto[1] Zhengyi Wang[2] Luis Calzadilla Bertot[3] Oyekoya Ayonrinde[2] John Olynyk[4] Therese O'Sullivan[5] Trevor Mori[2] Lawrence Beilin[2] Leon Adams[2], [1]Okayama University, [2]University of Western Australia, [3]University of Sevilla, [4]Curtin University, [5]Edith Cowan University

Background: Diet and alcohol are both purported drivers of steatotic liver disease (SLD) however their relative impact and interaction is poorly understood. We assessed the impact and interacting effects of dietary components and alcohol consumption on the risk of SLD. **Methods:** Participants of the community based Raine Study cohort underwent assessment at age 27 years including anthropometrics, fasting serum biochemistry, *PNPLA3* genotyping and liver fat quantification by magnetic resonance imaging. SLD was defined using a biopsy validated volumetric fat fraction cut-off of $>3.55\%$. Habitual dietary intake and weekly alcohol consumption was assessed using a validated food frequency questionnaire. **Results:** Overall, 111/710 (15.6%) had SLD (55% male, average age 26.7 years). Those with SLD had higher body mass index, waist circumference, blood pressure, serum liver enzymes, fasting glucose and serum triglycerides when compared with those without SLD (all $p<0.01$). Dietary intake of total fat, saturated fat, carbohydrate, sugars, and starch did not differ by SLD status ($p>0.05$ for all). However, participants with SLD compared to those without reported lower long-chain omega-3 fatty acids (O-3FA) (median 238 vs 290 mg/day; $p<0.001$), lower dietary fibre (19.6 vs 22.7 gm/day; $p=0.002$) and lower caffeine intake (236 vs 501 gm/day; $p=0.057$). Following adjustment for sex, alcohol, caloric intake, physical activity, BMI and *PNPLA3* genotype, a protective association for SLD was observed with increasing O-3FA intake (OR 0.57, 95% CI 0.39-0.81) and caffeine (OR 0.73, 95% CI 0.55-0.96). Average weekly alcohol intake did not differ significantly between those with and without SLD (median 27 vs 52 g/week; $p=0.2$). The proportion exceeding sex-specific thresholds (≥ 20 g/day in females or ≥ 30 g/day in males) was also similar between groups (18.0% vs 15.2%; $p=0.4$). Significant interactions between alcohol and dietary O-3FA and fibre existed ($P<0.05$ for both). Among low alcohol users (<50 grams/wk), no significant associations between dietary components and SLD were seen. Among higher alcohol users (≥ 50 g/week), higher O-3FA and dietary fibre intake were independently associated with lower odds of SLD (O-3FA adjusted OR 0.45; 95% CI 0.22–0.93; fiber adjusted OR 0.36; 95% CI 0.17–0.75). **Conclusion:** Dietary intake of omega-3 fatty acids and caffeine may reduce the risk of SLD. Alcohol consumption modifies the protective association of omega-3 fatty acids and fibre on SLD.
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Advisor, SCL Behring: Advisor, Dr Falk: Speaking and Teaching, Novo Nordisk: Grant/Research Support, Boehringer Ingelheim: Speaking and Teaching.

2600 | MASLD IS ASSOCIATED WITH RENAL DYSFUNCTION INDEPENDENT OF DIABETES AND HYPERTENSION: A REAL-WORLD COHORT STUDY USING TRINETX

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is increasingly recognized as a systemic disease. While chronic kidney disease (CKD) is common in MASLD patients, most studies have focused on populations with coexisting diabetes and hypertension. We aimed to investigate whether MASLD is associated with an increased risk of new incident renal dysfunction in patients without diabetes or hypertension. **Methods:** We used the TriNetX database, which includes 120,102,956 patients from 67 US health care organizations. We examined adult patients ($\geq$18 years) diagnosed with MASLD (2010-2020), to allow for a minimum follow-up of 5 years. A 1:1 propensity score matching (PSM) was used to compare patients with MASLD to those without MASLD (control group). Patients with coexisting diabetes mellitus, hypertension, viral hepatitis, autoimmune liver disease, alcohol-related liver disease, liver/kidney transplant, or any of the outcomes of interest at baseline (acute kidney injury (AKI), chronic kidney disease (CKD), proteinuria) were excluded from both groups. Patients' demographics, clinical data, and outcomes were studied using ICD codes as follows: MASLD (K76.8), CKD (N18), AKI (N17), and proteinuria (R80). The primary outcome was incident AKI. Secondary outcomes included new-onset CKD, albuminuria/proteinuria, renal dialysis procedures, and/or major adverse cardiac outcomes (MACE; combined stroke, heart failure, and ischemic heart disease). Data were collected and analyzed using TriNetX Analytics Platform built-in functions (R, version 4.0, including HRs and their associated 95% CIs). **Results:** A total of 72,922 patients with MASLD, but without diabetes or hypertension, were identified and matched at a 1:1 ratio to non-MASLD controls. Before matching, patients with MASLD were generally younger (42 yrs vs 45 yrs), similar female percentages (60% vs 60%), and predominantly White individuals (73% vs 64%) compared to those without MASLD. After matching, each group had 72,922 patients (mean [SD] age, 42 [14] years; 61% women) and was evenly matched from a clinical standpoint. Among 72,922 MASLD patients, 14% developed incident AKI compared to 7% in the non-MASLD group (OR: 2.16, 95%CI: 2.08 -2.24; p < 0.001, **Table**). Rates of new incident albuminuria/proteinuria and CKD diagnoses were also higher in the MASLD group (OR: 1.79, 95% CI: 1.60-2.02, p < 0.001; OR: 2.18, 95% CI: 2.09-2.27, p < 0.001, **Table**). MACE was also observed more frequently in the MASLD group (OR: 2.42, 95% CI: 2.32-2.68, p < 0.001) compared to the non-MASLD group. However, there were no differences in the incidence of renal dialysis procedures between both groups (**Table**). **Conclusion:** MASLD is independently associated with an increased risk of renal dysfunction even in the absence of diabetes or hypertension. These findings highlight that routine renal monitoring in MASLD individuals might be beneficial.

Clinical outcomes

Outcome (%)	Non-MASLD group N= 72,922	MASLD group N= 72,922	OR (95% CI)	P value
New onset AKI*	7.0%	14.0%	2.16 (2.08 -2.24	<0.001
New onset albuminuria/proteinuria	0.6%	1.1%	1.79 (1.60 -2.02)	<0.001
New onset CKD**	5.7%	11.6%	2.18 (2.09 -2.27)	<0.001
New onset dialysis	0.2%	0.1%	0.88 (0.68-1.17)	0.4
MACE	3.6%	8.8%	2.42 (2.32-2.68)	<0.001

Abbreviations: CKD: chronic kidney disease; AKI: acute kidney injury; MACE: major adverse cardiac events.
*Defined by ICD-10 code diagnosis of AKI or creatinine >1.5mg/dL
**Defined by ICD-10 diagnosis of CKD or eGFR < 60 mL/min/1.73 m^2.
***Defined by a combination of heart failure, stroke, or ischemic heart disease.

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2601 | COMPARING TRENDS OF ASSOCIATIONS OF SOCIODEMOGRAPHIC AND LIFESTYLE FACTORS WITH STEATOTIC LIVER DISEASE IN THE POST-PANDEMIC ERA, DOES THE RISK REMAIN THE SAME?

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Background: Sociodemographic and behavioral risk factors are reported to be closely linked to steatotic liver disease (SLD). However, data on changing trends of association with SLD since the pandemic remain limited. The current study aims to evaluate whether the association between certain sociodemographic and lifestyle factors with SLD has changed overtime in postpandemic era. **Methods:** We conducted a cross-sectional observational study using National Health and Nutrition Examination Survey (NHANES) data. Data on sociodemographic and behavioral factors were extracted from pre-pandemic (2017-2020) and post-pandemic (2021-2023)cycles. Primary outcome was SLD, defined as Controlled Attenuation Parameter (CAP) score $\geq$ 268 dB/m. Data missing at random were handled using Multiple Imputations Chain Equation method. Univariate regression models were used to assess prevalence, and multivariate models to evaluate associations with SLD in each cycle. The associations between cycles were compared as a ratio of adjusted odds ratios, and effect modification by time was used for statistical significance. A two-tailed p-value <0.05 was set as significant. **Results:** Among baseline characteristics in each cycle, majority of participants,(n = 6820 in pre- and n = 4607 in post-pandemic), were White males, employed, non-smokers, light to moderate drinkers, and obese. In each cycle, SLD group (52% in pre- and 55% in post-pandemic) were observed to have a higher risk profile, i.e., belonged to middle-income and lower education groups, were obese, having medical co-morbidities and no mental health follow-ups compared to controls. In the adjusted analysis, among sociodemographic factors, being unmarried was significantly associated with lower odds of SLD ($_a$OR; 0.69 [0.57-0.83]) in pre- and ($_a$OR; 0.75 [0.59-0.96]) in post-pandemic time and association remained significantly stronger (ratio;1.08 [p <0.001]) comparing time. People with no mental health follow-ups had a higher risk of SLD ($_a$OR; 1.05[0.82-1.33]) in post-pandemic era, but no significant evidence of effect modification by time (ratio; 1.31[p >0.99]) was observed. Among lifestyle factors, in both cycles, moderate and higher levels physical activity had significantly lowererd risk of SLD compared to reference groups and association remained stronger for both levels but was only significant for higher levels (ratio; 1.5 [p 0.006]) comparing time. Among dietary factors, a low fiber diet was associated with a higher risk of SLD in both eras but was significant in post-pandemic era. Comparing time, the association remained stronger but findings were not significant [Table 1]. **Conclusion:** Current study shows persistent positive associations of certain sociodemographic and lifestyle factors with SLD since pandemic and highlights importance of integrating these key drivers in decision making to provide comprehensive multidisciplinary care to SLD patients.

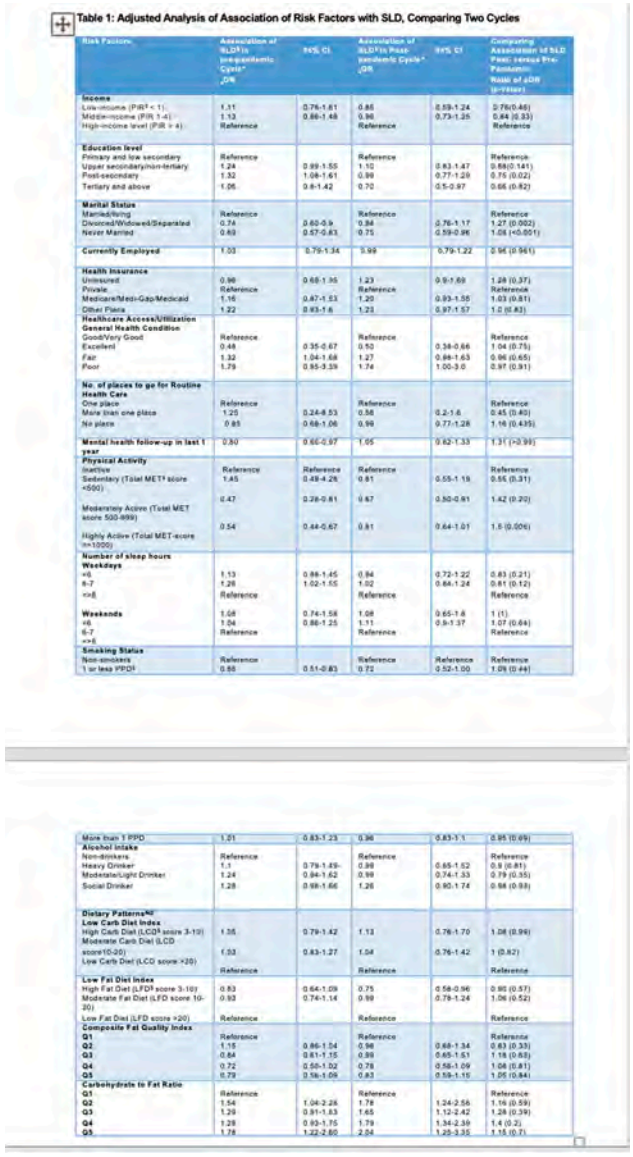


Table 1: Adjusted Analysis of Association of Risk Factors with SLD, Comparing Two Cycles

Risk Factors	Association of SLD[a] in pre-pandemic Cycle* (OR	95% CI	Association of SLD[a] in Post-pandemic Cycle* (OR	95% CI	Comparing Association of SLD Post- versus Pre-Pandemic- Ratio of aOR (p-Value)
Income					
Low-income (PIR[b] < 1)	1.31	0.76-1.61	0.85	0.59-1.24	0.76(0.46)
Middle-income (PIR 1-4)	1.13	0.86-1.48	0.96	0.73-1.25	0.84 (0.33)
High-income level (PIR > 4)	Reference		Reference		Reference
Education level					
Primary and low secondary	Reference		Reference		Reference
Upper secondary/non-tertiary	1.24	0.89-1.55	1.10	0.83-1.47	0.88(0.141)
Post-secondary	1.32	1.08-1.61	0.99	0.77-1.29	0.75 (0.02)
Tertiary and above	1.06	0.8-1.42	0.70	0.5-0.97	0.66 (0.62)
Marital Status					
Married/living	Reference		Reference		Reference
Divorced/Widowed/Separated	0.74	0.60-0.9	0.84	0.76-1.17	1.27 (0.002)
Never Married	0.69	0.57-0.83	0.75	0.59-0.96	1.08 (<0.001)
Currently Employed	1.03	0.79-1.34	0.99	0.79-1.22	0.96 (0.961)
Health Insurance					
Uninsured	0.96	0.68-1.36	1.23	0.9-1.69	1.28 (0.37)
Private	Reference		Reference		Reference
Medicare/Medi-Gap/Medicaid	1.16	0.87-1.53	1.20	0.93-1.55	1.03 (0.81)
Other Plans	1.22	0.83-1.6	1.23	0.97-1.57	1.0 (0.83)
Healthcare Access/Utilization					
General Health Condition					
Good/Very Good	Reference		Reference		Reference
Excellent	0.48	0.35-0.67	0.50	0.34-0.66	1.04 (0.75)
Fair	1.32	1.04-1.68	1.27	0.98-1.63	0.96 (0.65)
Poor	1.79	0.95-3.39	1.74	1.00-3.0	0.97 (0.91)
No. of places to go for Routine Health Care					
One place	Reference		Reference		Reference
More than one place	1.25	0.24-6.53	0.58	0.2-1.6	0.45 (0.40)
No place	0.85	0.68-1.06	0.99	0.77-1.28	1.16 (0.435)
Mental health follow-up in last 1 year	0.80	0.66-0.97	1.05	0.82-1.33	1.31 (>0.99)
Physical Activity					
Inactive	Reference	Reference	Reference		Reference
Sedentary (Total MET[1] score <500)	1.45	0.49-4.26	0.81	0.55-1.19	0.55 (0.31)
Moderately Active (Total MET score 500-999)	0.47	0.28-0.81	0.67	0.50-0.91	1.42 (0.20)
Highly Active (Total MET-score >=1000)	0.54	0.44-0.67	0.81	0.64-1.01	1.5 (0.006)
Number of sleep hours					
Weekdays					
<6	1.13	0.88-1.45	0.94	0.72-1.22	0.83 (0.21)
6-7	1.28	1.02-1.55	1.02	0.84-1.24	0.81 (0.12)
>=8	Reference		Reference		Reference
Weekends					
<6	1.08	0.74-1.58	1.08	0.65-1.8	1 (1)
6-7	1.04	0.86-1.25	1.11	0.9-1.37	1.07 (0.64)
>=8	Reference		Reference		Reference
Smoking Status					
Non-smokers	Reference		Reference		Reference
1 or less PPD[2]	0.66	0.51-0.83	0.72	0.52-1.00	1.09 (0.44)
More than 1 PPD	1.21	0.83-1.23	0.96	0.83-1.1	0.95 (0.09)
Alcohol intake					
Non-drinkers	Reference		Reference		Reference
Heavy Drinker	1.1	0.79-1.49	0.99	0.65-1.52	0.9 (0.81)
Moderate/Light Drinker	1.24	0.94-1.62	0.99	0.74-1.33	0.79 (0.35)
Social Drinker	1.28	0.98-1.66	1.26	0.90-1.74	0.98 (0.93)
Dietary Patterns[#]					
Low Carb Diet Index					
High Carb Diet (LCD[3] score 3-10)	1.35	0.79-1.42	1.13	0.76-1.70	1.08 (0.99)
Moderate Carb Diet (LCD score10-20)	1.53	0.83-1.27	1.04	0.76-1.42	1 (0.82)
Low Carb Diet (LCD score >20)	Reference		Reference		Reference
Low Fat Diet Index					
High Fat Diet (LFD[4] score 3-10)	0.83	0.64-1.09	0.75	0.58-0.96	0.95 (0.57)
Moderate Fat Diet (LFD score 10-20)	0.93	0.74-1.14	0.99	0.79-1.24	1.06 (0.52)
Low Fat Diet (LFD score >20)	Reference		Reference		Reference
Composite Fat Quality Index					
Q1	Reference		Reference		Reference
Q2	1.15	0.86-1.54	0.98	0.68-1.34	0.83 (0.33)
Q3	0.84	0.61-1.15	0.89	0.65-1.51	1.18 (0.63)
Q4	0.72	0.50-1.02	0.78	0.58-1.09	1.04 (0.81)
Q5	0.79	0.56-1.09	0.83	0.59-1.15	1.05 (0.84)
Carbohydrate to Fat Ratio					
Q1	Reference		Reference		Reference
Q2	1.54	1.04-2.26	1.78	1.24-2.56	1.16 (0.59)
Q3	1.29	0.91-1.83	1.65	1.12-2.42	1.28 (0.39)
Q4	1.28	0.93-1.75	1.79	1.34-2.39	1.4 (0.2)
Q5	1.78	1.22-2.60	2.04	1.29-3.25	1.15 (0.7)

Disclosures: Iqra Arshad: Nothing to Disclose, Xinyuan Zhang: Nothing to Disclose.

2602 | GLP-1 RECEPTOR AGONISTS REDUCE CARDIOVASCULAR AND RENAL EVENTS IN NON-OBESE, NON-DIABETIC MASLD: A PROPENSITY SCORE-MATCHED COHORT STUDY

Anh Thu Nguyen[1] Yahya Hamad[1] Riddhi Prateek[1] Daanish Imam[1] Harish Gopalakrishna[2] Gurinder Luthra[1], [1]University of Texas Medical Branch, [2]UTMB

Background: Non-obese individuals account for up to 30% of metabolic dysfunction-associated

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steatotic liver disease (MASLD) cases but are often excluded from GLP-1 receptor agonist (GLP-1 RA) efficacy studies. While GLP-1 RAs demonstrate many benefits in general MASLD populations, their therapeutic role in non-obese, non-diabetic MASLD remains undefined. We evaluated the association between sustained GLP-1 RA use and clinical outcomes in this understudied population. **Methods:** We conducted a retrospective cohort study using the TriNetX federated electronic health records network. Non-obese MASLD patients (BMI ≤ 27 kg/m², ICD-10 K76.0 or K75.81, ≥ 1 cardiometabolic risk factor) in non-diabetics were identified. Exclusions were alternative liver disease, baseline cirrhosis, decompensation, bariatric surgery, or prior transplant. Exposed patients had sustained GLP-1 RA use (second prescription ≥ 3 months after first, initiated within 3 months of diagnosis). 1: 1 propensity score matching included demographics, comorbidities, medications, and labs. Outcomes included major adverse cardiovascular events (MACE), major adverse liver outcomes (MALO), acute kidney injury (AKI), and atrial fibrillation/flutter (afib). Cox models estimated hazard ratios over 5 years. Sensitivity analyses excluded baseline metformin, substance use disorders, and tirzepatide. **Results:** After 1: 1 PSM (n = 1,261/arm), GLP-1 RA use was associated with significant reductions in MACE (HR 0.54, p = 0.010), heart failure (HR 0.34, p < 0.001), AKI (HR 0.46, p = 0.005), and afib (HR 0.64, p = 0.033). (Table 1) MALO did not differ significantly. Benefits persisted after metformin exclusion and were directionally consistent after tirzepatide exclusion. In a broader non-diabetic MASLD cohort (n = 23,983/arm), significant reductions were seen across all endpoints. **Conclusion:** GLP-1 RA use was associated with reductions in MACE (46%), heart failure (66%), AKI (54%), and afib (36%) in non-obese nondiabetic MASLD patients, independent of metformin and consistent after tirzepatide exclusion, supporting a class effect. MALO showed no significant difference (HR 1.16, p = 0.67) versus 83% reduction in broader non-diabetics, likely due to 1) small sample size, 2) lower baseline severity in non-obese patients, and 3) distinct pathophysiology. Despite comprising 30% of MASLD cases, non-obese patients remain excluded from landmark trials [5]. These findings support prospective trials and guideline consideration of GLP-1 RAs for cardiorenal risk reduction in non-obese MASLD.

Characteristic/Outcome	Sustained GLP-1 RA	No GLP-1 RA	HR (95% CI) or Std Diff
Baseline Characteristics			
Age at index (years), mean ± SD	52.7 ± 12.4	52.9 ± 14.9	0.010
Female, n (%)	898 (71.2%)	902 (71.5%)	0.007
BMI (kg/m²), mean ± SD	28.8 ± 4.2	27.4 ± 4.0	0.351
HbA1c (%), mean ± SD	5.5 ± 0.4	5.5 ± 0.5	0.053
Hypertension, n (%)	672 (53.3%)	649 (51.5%)	0.037
Dyslipidemia, n (%)	976 (77.4%)	998 (79.1%)	0.042
FIB-4 Components ‡			
AST (U/L), mean ± SD	36.3 ± 32.5	32.8 ± 35.6	0.103
ALT (U/L), mean ± SD	47.3 ± 43.4	41.5 ± 51.0	0.122
Platelets (×10⁹/L), mean ± SD	266 ± 68.8	266 ± 72.8	0.008
Clinical Outcomes	**n (%)**	**n (%)**	**p-value**
MACE*	27 (2.14%)	45 (3.57%)	**0.54 (0.33–0.87) p=0.010**
Heart Failure	17 (1.35%)	46 (3.65%)	**0.34 (0.19–0.59) p<0.001**
Acute Kidney Injury	18 (1.43%)	35 (2.78%)	**0.46 (0.26–0.81) p=0.005**
Atrial Fibrillation/Flutter	38 (3.01%)	54 (4.28%)	**0.64 (0.42–0.97) p=0.033**
MALO†	19 (1.51%)	15 (1.19%)	1.16 (0.59–2.28) p=0.67
All-Cause Mortality	<10	<10	Insufficient events

Disclosures: Anh Thu Nguyen: Nothing to Disclose, Yahya Hamad: Nothing to Disclose, Riddhi Prateek: Nothing to Disclose, Daanish Imam: Nothing to Disclose, Harish Gopalakrishna: Nothing to Disclose, Gurinder Luthra: Nothing to Disclose.

2603 | DISTINCT CARDIOVASCULAR PHENOTYPES AND OUTCOMES IN HCV AND MASLD ACROSS FIBROSIS STAGES: A NHANES 2007–2016 ANALYSIS

Fatima Rajab[1] Aleena Mujahid[2] Barsha Baral[3] Ahmad Jalil[3] Umaiza Ihsan[4], [1]Baptist Hospitals of Southeast Texas, [2]Harlingen Medical Center, [3]BAPTIST MEMORIAL HOSPITAL, [4]King Edward Medical University

Background: Hepatitis C virus (HCV) infection and metabolic dysfunction-associated steatotic liver disease (MASLD) are both associated with increased cardiovascular disease (CVD) burden. However, differences in cardiovascular risk patterns between viral and

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metabolic liver disease across fibrosis stages remain incompletely understood. **Methods:** We performed a cross-sectional analysis of adults with HCV or MASLD from NHANES 2007–2016 linked to mortality data. MASLD was identified using the Hepatic Steatosis Index (HSI), and advanced fibrosis was defined using FIB-4 criteria (FIB-4 >2.67). Stage-matched analyses compared HCV and MASLD phenotypes among participants with and without advanced fibrosis. Survey-weighted multivariable logistic and Cox regression models adjusted for age, sex, BMI, diabetes, hypertension, and smoking were used to evaluate cardiovascular morbidity, all-cause mortality, and cardiovascular mortality. Exploratory analyses examined coronary artery disease (CAD), myocardial infarction (MI), stroke, and congestive heart failure (CHF). **Results:** The study included 4,431 participants, including 4,008 with MASLD and 423 with HCV. HCV-related advanced fibrosis demonstrated marked male predominance (77.1% male) with balanced distribution in MASLD group. Among participants without advanced fibrosis, HCV was associated with higher cardiovascular morbidity compared with MASLD (adjusted OR 2.41, 95% CI 1.51–3.84) and higher all-cause mortality (adjusted HR 3.36, 95% CI 2.12–5.31), while cardiovascular mortality was numerically higher but not statistically significant (adjusted HR 2.33, 95% CI 0.86–6.28). Among participants with advanced fibrosis, cardiovascular morbidity (adjusted OR 0.52, 95% CI 0.14–1.91) and cardiovascular mortality (adjusted HR 1.50, 95% CI 0.39–5.71) were comparable between HCV and MASLD, while all-cause mortality was numerically higher in HCV fibrosis (adjusted HR 1.96, 95% CI 0.90–4.31). Phenotype-specific analyses demonstrated differing cardiovascular patterns. Compared with MASLD without advanced fibrosis, HCV without advanced fibrosis was associated with higher stroke (adjusted OR 2.08, 95% CI 1.18–3.53) and CHF burden (adjusted OR 2.84, 95% CI 1.58–4.90), whereas CAD and MI burden were not increased. In advanced fibrosis, MASLD demonstrated a relatively stronger CAD phenotype, with lower CAD prevalence observed in HCV fibrosis (adjusted OR 0.24, 95% CI 0.07–0.79). **Conclusion:** HCV and MASLD may demonstrate distinct cardiovascular phenotypes across fibrosis stages. HCV was associated with increased cardiovascular morbidity and all-cause mortality even without advanced fibrosis, whereas MASLD-related fibrosis appeared more closely associated with atherosclerotic CAD burden. These findings suggest differing cardiovascular risk profiles between viral and metabolic liver disease.

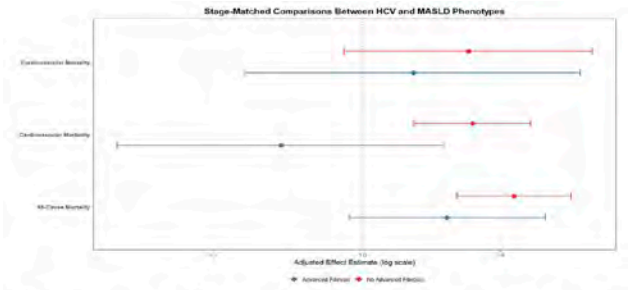


Figure 1. Forest Plot of Stage-Matched Cardiovascular Morbidity, Cardiovascular Mortality, and All-Cause Mortality in HCV and MASLD

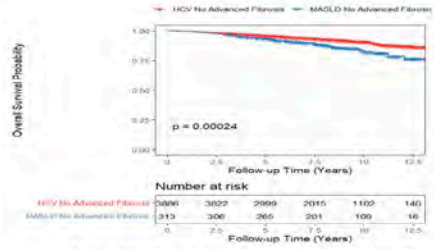


Figure 2. Kaplan-Meier Curves for Overall Survival in Non-Fibrotic HCV and MASLD

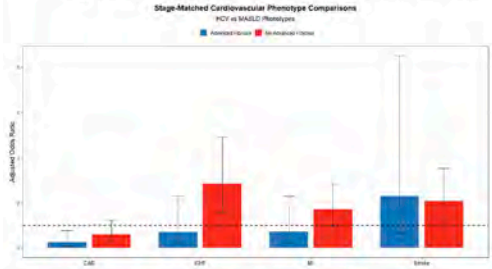


Figure 3. Stage-Matched Comparisons of Cardiovascular Phenotypes Between HCV and MASLD

Disclosures: Fatima Rajab: Nothing to Disclose, Aleena Mujahid: Nothing to Disclose, Barsha Baral: Nothing to Disclose, Ahmad Jalil: Nothing to Disclose, Umaiza Ihsan: Nothing to Disclose.

2604 | A COHORT STUDY ON THE ASSOCIATION OF PHYSICAL ACTIVITY LEVEL WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE BASED ON THE SHANGHAI SUBURBAN ADULT COHORT AND BIOBANK (SSACB)

Xinyu Hu[1], [1]Fudan University

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is highly prevalent worldwide. Physical activity (PA) may protect

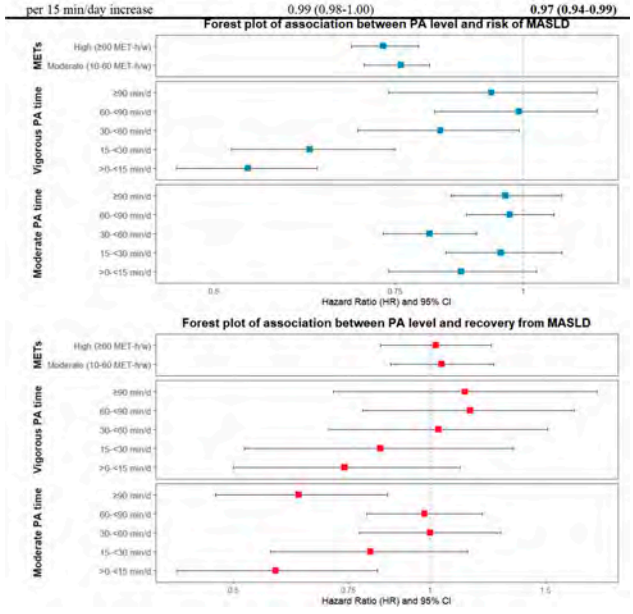
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against MASLD, but evidence from large Chinese cohorts is limited, and its role in disease recovery remains unclear. We prospectively evaluated the associations of PA with MASLD in a Chinese community-based cohort. **Methods:** This study was based on the Shanghai Suburban Adult Cohort and Biobank (SSACB). A total of 47,472 participants without MASLD at baseline and 10,799 participants with MASLD at baseline were included. Baseline PA information was collected using a physical activity questionnaire. Participants without MASLD at baseline were followed for new-onset MASLD, while those with MASLD at baseline were followed for recovery from MASLD. Multivariable Cox proportional hazards regression models were used to analyze the association between PA level and MASLD, and stratified analyses were performed across different subgroups. **Results:** In the incidence cohort, higher total PA was significantly associated with lower MASLD risk. Compared to the lowest tertile ($\leq$10 MET-h/w), the highest tertile ($\geq$60 MET-h/w) had a 27% lower risk (HR = 0.73, 95%CI: 0.68-0.79; P-trend < 0.001). Each 10 MET-h/w increment reduced risk by 2% (HR = 0.98, 95%CI: 0.97-0.98). Threshold effects were observed: 15-30 min/week of vigorous PA(VPA) gave the greatest benefit (HR = 0.62, 95%CI: 0.52-0.75), and 30-60 min/week of moderate PA(MPA) significantly reduced risk (HR = 0.81, 95%CI: 0.73-0.90), with no further benefit beyond 60 min/week. Stratified analyses showed no significant interactions (all P $\geq$ 0.05). In the recovery cohort, total PA was not significantly associated with MASLD recovery. Unexpectedly, MPA time was inversely associated with recovery: compared to no MPA, 0-15 min/day (HR = 0.58, 95%CI: 0.41-0.83) and $\geq$90 min/day (HR = 0.63, 95%CI: 0.47-0.86) showed lower likelihood of recovery (P-trend = 0.016). However, in patients with diabetes, higher PA levels tended to promote recovery (MPA: HR = 1.61, 95%CI: 1.00-2.60; VPA: HR = 1.66, 95%CI: 1.01-2.73; P-interaction = 0.149). **Conclusion:** PA level is an independent protective factor for the onset of MASLD, with a clear dose-response relationship and a threshold effect. The association between PA level and MASLD recovery was not confirmed in this study. It is recommended that the general population engage in at least 150 minutes of moderate-to-vigorous PA per week to prevent MASLD, while exercise interventions for patients with MASLD should be individually tailored.

Table Cox regression analysis of the association between physical activity level and MASLD.

	Incidence Cohort(N=47472)		Recovery Cohort(N=10799)	
	MASLD(%)	HR (95%CI)	recovery (%)	HR (95%CI)
METs				
Low, ≤10MET-h/w	28.2	reference	30.4	reference
Median,10–60 MET-h/w	23.2	0.76 (0.70-0.81)	27	1.04 (0.87-1.25)
High,≥60 MET-h/w	25.3	0.73 (0.68-0.79)	26.7	1.02 (0.84-1.24)
P trend		<0.001		0.983
per 10MET-h/w increase		0.98 (0.97-0.98)		1.00 (0.98-1.01)
Vigorous PA time, h/d				
0 min/day	25.2	reference	27.1	reference
>0-<15 min/day	26.5	0.54 (0.46-0.63)	29.8	0.74 (0.50-1.11)
15-<30 min/day	22.5	0.62 (0.52-0.75)	26.5	0.84 (0.52-1.34)
30-<60 min/day	19.7	0.83 (0.69-0.99)	30.7	1.03 (0.70-1.51)
60-<90 min/day	28.1	0.99 (0.82-1.18)	29	1.15 (0.79-1.66)
>=90 min/day	22.9	0.93 (0.74-1.18)	31.6	1.13 (0.71-1.80)
P trend		<0.001		0.703
per 15 min/day increase		0.97 (0.95-0.99)		1.01 (0.97-1.06)
Moderate PA time, h/d				
0 min/day	24.9	reference	27.2	reference
>0-<15 min/day	19.6	0.87 (0.74-1.03)	31.4	**0.58 (0.41-0.83)**
15-<30 min/day	25.6	0.95 (0.84-1.09)	26.7	0.81 (0.57-1.14)
30-<60 min/day	23.3	0.81 (0.73-0.90)	26.9	1.00 (0.78-1.28)
60-<90 min/day	29.7	0.97 (0.88-1.07)	29.8	0.98 (0.80-1.20)
>=90 min/day	27.4	0.96 (0.85-1.09)	23.4	**0.63 (0.47-0.86)**
P trend		0.026		**0.016**
per 15 min/day increase		0.99 (0.98-1.00)		**0.97 (0.94-0.99)**



Disclosures: Xinyu Hu: Nothing to Disclose.

2605 | RISK OF GERD IN PATIENTS WITH MASLD: A RETROSPECTIVE CASE-CONTROL STUDY BASED ON CLINICAL ENDOSCOPY DATA AND MULTI-OMICS ANALYSIS

Nan Li[1] CongCong Wang[1] Yulin Li[1] Zhiyu Ji[1] Changjiang Qin[1], [1]Huai He Hospital of Henan University

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Background: Metabolic associated fatty liver disease (MASLD) and gastroesophageal reflux disease (GERD) share obesity and high-fat diet as common risk factors. However, high-quality large-sample evidence using gastroscopy to confirm their association remains limited, and shared pathogenic mechanisms are unclear. This study aims to analyze the association between MASLD and GERD using real-world clinical data. It also integrates multi-omics analysis to explore shared molecular pathways to guide gastrointestinal health monitoring in MASLD patients. **Methods:** This study integrates a retrospective case-control study with bioinformatic analysis. Adult patients who visited the Department of General Surgery at Huaihe Hospital Affiliated with Henan University from April 2025 to April 2026 were included. Patients were divided into the MASLD group and the non-MASLD group. All patients underwent gastroscopy and liver imaging examinations. After comparing the clinical characteristics of the two groups, univariate and multivariate logistic regression analyses were performed to identify the risk factors for GERD in MASLD patients. Expression profiles of MASLD (GSE89632) and GERD (GSE148381) were obtained from the GEO database. Common differentially expressed genes (DEGs) were selected to construct a PPI network. Finally, enrichment analyses were performed to explore the shared gene functions and pathways between MASLD and GERD. **Results:** This study ultimately included 156 patients with MASLD and 317 without MASLD patients for analysis. The prevalence of GERD in the MASLD group was 45.5%, significantly higher than the 31.2% in the non-MASLD group (p = 0.002). Additionally, the MASLD group was younger (median age 49 vs. 57, p < 0.001), had a higher proportion of males (52.6% vs. 42.3%, p = 0.035), and exhibited significantly higher levels of metabolic-related indicators, such as BMI, transaminase, and uric acid, compared to the non-MASLD group. The unadjusted regression model showed that MASLD was associated with an increased risk of GERD. After adjusting for age, gender, blood pressure, BMI, and uric acid, this association remained (OR = 1.62, 95% CI: 1.01-2.60, p = 0.047). This study identified 20 common differentially expressed genes (DEGs). Among these, MYH11, ACTG2, and VCAN emerged as the top three hub genes. The functional enrichment of the common DEGs was associated with muscle cell differentiation, myosin filament, and vascular smooth muscle contraction. **Conclusion:** MASLD increased the risk of GERD by 62%. Metabolic factors and vascular smooth muscle contraction may collectively mediate this association. The findings of this study underscore the importance of standardized gastroscopy in MASLD patients, offering evidence to refine clinical management strategies for comorbidities.

Table 1: Characteristics of participants enrolled in study.

Variables[a]	Overall N = 473	Non-MASLD N = 317	MASLD N = 156	P-value[b]
Age - Years	55 (44, 65)	57 (47, 68)	49 (40, 60)	<0.001
Sex - (%)				0.035
Female	257 (54.3%)	183 (57.7%)	74 (47.4%)	
Male	216 (45.7%)	134 (42.3%)	82 (52.6%)	
Systolic pressure	125 (120, 132)	125 (120, 131)	126 (120, 139)	0.055
Diastolic pressure	76 (70, 80)	75 (70, 80)	79 (71, 87)	<0.001
BMI - kg/m²	24.6±2.4	23.7±2.1	26.8±2.6	<0.001
ALT - U/L	22 (17, 31)	19 (15, 25)	30 (21, 44)	<0.001
AST - U/L	24 (20, 29)	23 (20, 27)	27 (22, 34)	<0.001
ALB - g/L	42.3 (39.9, 44.3)	42.0 (39.8, 43.9)	42.9 (40.6, 44.8)	0.003
GGT - U/L	22 (16, 34)	19 (14, 28)	31 (22, 46)	<0.001
UA - umol/L	273 (222, 343)	257 (211, 317)	325 (253, 390)	<0.001
AFP - ng/mL	3.25 (2.51, 3.91)	3.14 (2.46, 3.74)	3.40 (2.75, 4.40)	<0.001
PLT - ×10⁹/L	244 (205, 289)	238 (199, 284)	257 (218, 299)	0.003
WBC - ×10⁹/L	5.98 (4.91, 7.30)	5.87 (4.83, 7.04)	6.18 (5.08, 7.65)	0.035
HGB - g/L	136 (124, 148)	133 (121, 145)	142 (132, 153)	<0.001
GERD - (%)				0.002
No	303 (64.1%)	218 (68.8%)	85 (54.5%)	
Yes	170 (35.9%)	99 (31.2%)	71 (45.5%)	

[a]Variables are presented as median (IQR), mean ± SD or No. (%).
[b]Wilcoxonrank test, Chi-square independence test

Figure 1: Association between MASLD and GERD.

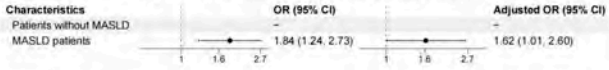
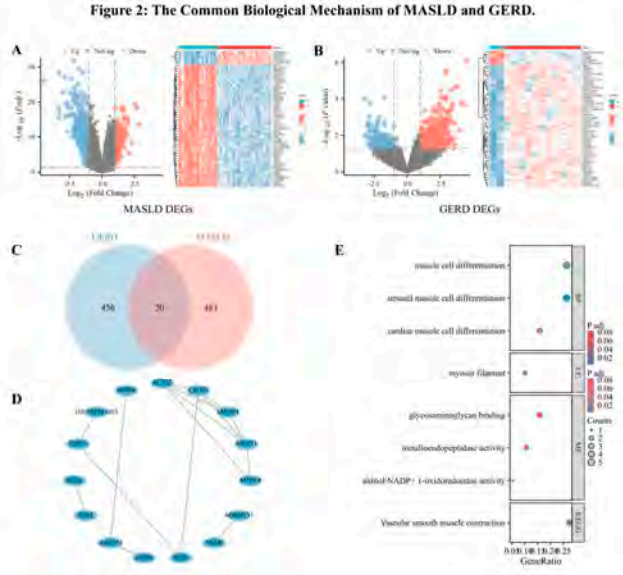


Figure 2: The Common Biological Mechanism of MASLD and GERD.



Disclosures: Nan Li: Nothing to Disclose, CongCong Wang: Nothing to Disclose, Yulin Li: Nothing to Disclose, Zhiyu Ji: Nothing to Disclose, Changjiang Qin: Nothing to Disclose.

2606 | ASSOCIATION OF FIBROSIS-OBESITY PHENOTYPES WITH ALL-CAUSE MORTALITY AMONG U.S. ADULTS

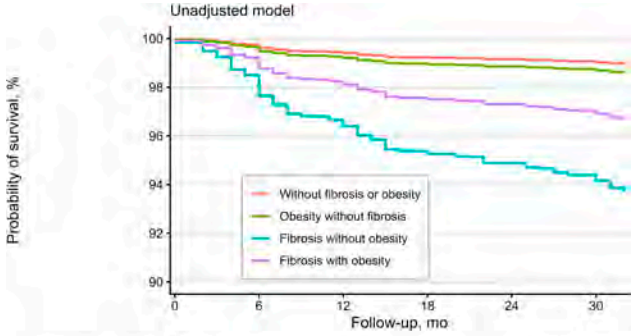
Zilong Lu[1] Yuankai Wu[2] Yu Shi[3] Vincent Wai-Sun Wong[4] Xinrong Zhang[1], [1]School of Public Health, Sun Yat-sen University, [2]Department of Infectious Diseases, Third Affiliated Hospital of Sun Yat-sen University, [3]Zhejiang University School of Medicine,

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Background: With epidemic of obesity, the burden of metabolic dysfunction-associated steatotic liver disease is increasing worldwide. Its more active histological phenotype, metabolic dysfunction-associated steatohepatitis, may progress to advanced liver fibrosis, cirrhosis and even mortality. However, whether coexisting fibrosis and obesity confer increased short-term mortality risk in the general population remains unclear. Therefore, we evaluated the associations between fibrosis–obesity phenotypes and all-cause mortality among U.S. adults. **Methods:** Adult participants with complete vibration-controlled transient elastography data were identified from the 2017-2018 National Health and Nutrition Examination Survey and linked to mortality data from the National Death Index through December 31, 2019. Advanced fibrosis was defined as liver stiffness measurement (LSM) $\geq$9.7 kPa. Obesity was defined as body mass index (BMI) $\geq$30 kg/m² for non-Asian participants and BMI $\geq$25 kg/m² for Asian participants. Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause mortality. **Results:** A total of 4,174 adults were included, with 62 deaths during follow-up. Individuals with both fibrosis and obesity exhibited a more adverse metabolic and cardiometabolic profiles than those without either fibrosis or obesity. Compared with participants without advanced fibrosis or obesity, advanced fibrosis without obesity was associated with markedly higher risk of all-cause mortality (HR, 6.15; 95% CI, 1.50-25.19), as was advanced fibrosis with obesity (HR, 3.20; 95% CI, 1.10-9.33), whereas obesity alone was not associated with mortality. After adjustment for age, sex, and race, the association for advanced fibrosis without obesity was attenuated (HR, 2.45; 95% CI, 0.61-9.77), while advanced fibrosis with obesity remained significantly associated with increased mortality risk (HR, 3.10; 95% CI, 1.03-9.31). Among participants with obesity, fibrosis stage was not significantly associated with mortality. Restricted cubic spline analyses showed no significant association between LSM and all-cause mortality. **Conclusion:** In this national study, the coexistence of fibrosis and obesity was associated with increased mortality risk, suggesting that fibrosis burden in individuals with obesity may help identify those at elevated short-term mortality risk.



No. at risk

Without fibrosis or obesity	2259	2251	2238	1648	1140	611
Obesity without fibrosis	1694	1689	1680	1257	861	452
Fibrosis without obesity	43	43	40	30	20	10
Fibrosis with obesity	178	175	174	133	96	53
	0	6	12	18	24	30

Unadjusted model

Group	HR (95% CI)	P value
Without fibrosis or obesity	Ref	
Obesity without fibrosis	1.35 (0.56, 3.25)	0.510
Fibrosis without obesity	6.15 (1.50, 25.19)	0.012
Fibrosis with obesity	3.20 (1.10, 9.33)	0.033

Adjusted for age, sex, and race

Group	HR (95% CI)	P value
Without fibrosis or obesity	Ref	
Obesity without fibrosis	1.35 (0.54, 3.37)	0.515
Fibrosis without obesity	2.45 (0.61, 9.77)	0.204
Fibrosis with obesity	3.10 (1.03, 9.31)	0.044

Disclosures: Zilong Lu: Nothing to Disclose, Yuankai Wu: Nothing to Disclose, Yu Shi: Nothing to Disclose, Vincent Wai-Sun Wong: Nothing to Disclose, Xinrong Zhang: Nothing to Disclose.

2607 | MACHINE LEARNING–BASED PREDICTION OF SIGNIFICANT FIBROSIS IN METABOLIC DYSFUNCTION–ASSOCIATED STEATOTIC LIVER DISEASE IN TAIWAN

Chia-Yen Dai[1] Tzu-Chun Lin[1] Yu- Wei Wei[2] Po-Cheng Liang[2] Tyng-yuan Jang[2] Chih-Wen Wang[2] Ming-Lun Yeh[2] Jee-Fu Huang[3] Chung-Feng Huang[2] Wan-Long Chuang[2] Ming-Lung Yu[4], [1]Kaohsiung Medical University Hospital, Kaohsiung Medical University, [2]Kaohsiung Medical University Hospital, Kaohsiung Medical University, [3]Kaohsiung Medical University Hospital, [4]Kaohsiung Medical University/ Kaohsiung Medical University Hospital

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a growing global health burden and a leading cause of chronic liver disease. Liver fibrosis is the strongest predictor of complications and liver-related mortality; however, early identification of significant fibrosis remains challenging. This study

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aimed to develop and validate machine learning (ML) models for predicting significant fibrosis in MASLD using routinely available clinical variables and to improve model interpretability using explainable artificial intelligence. **Methods:** A total of 2,825 participants with FibroScan-confirmed MASLD were retrospectively enrolled. The cohort was randomly divided into training (80%, n = 2,260) and testing (20%, n = 565) datasets. Demographic, anthropometric, metabolic, and biochemical variables were analyzed, including age, sex, body mass index (BMI), waist circumference, liver enzymes, fasting plasma glucose, lipid profiles, and platelet count. Five supervised ML algorithms-Logistic Regression, Random Forest, CatBoost, Elastic Net, and XGBoost-were developed and evaluated using accuracy, precision, recall, F1-score, receiver operating characteristic area under the curve (AUROC), and precision-recall (PR) curve analysis. Model robustness was assessed using 1,000 bootstrap resampling iterations. SHapley Additive exPlanations (SHAP) analysis was applied to the best-performing model to identify key predictors and nonlinear threshold effects. **Results:** Among all models, CatBoost demonstrated the best predictive performance. In the training dataset, CatBoost achieved an AUROC of 0.93, compared with 0.91 for Random Forest and XGBoost and approximately 0.88 for Logistic Regression and Elastic Net. In the testing dataset, CatBoost maintained superior discrimination with an AUROC of 0.90, indicating strong generalizability and minimal overfitting. CatBoost also achieved the highest PR AUC values in both training (0.64) and testing (0.52) datasets, along with the highest testing accuracy (0.835), precision (0.355), and F1-score (0.486). Bootstrapping confirmed significantly superior model performance compared with other algorithms ($p < 0.001$). SHAP analysis identified aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), BMI, alanine aminotransferase (ALT), platelet count, and waist circumference as the most influential predictors of significant fibrosis. **Conclusion:** ML models, particularly CatBoost, demonstrated high accuracy and robustness for predicting significant fibrosis in MASLD using routinely available clinical data. Integration of SHAP analysis enhanced model interpretability and identified clinically meaningful predictors and threshold effects. These findings support the potential application of explainable ML models as scalable, non-invasive tools for fibrosis risk stratification and early clinical intervention in MASLD.
Disclosures: Chia-Yen Dai: Nothing to Disclose, Tzu-Chun Lin: Nothing to Disclose, Yu- Wei Wei: Nothing to Disclose, Po-Cheng Liang: Nothing to Disclose, Tyng-yuan Jang: Nothing to Disclose, Chih-Wen Wang: Nothing to Disclose, Ming-Lun Yeh: Nothing to Disclose, Jee-Fu Huang: Roche: Consultant, Gilead: Consultant, Sysmex: Consultant, Aligos: Consultant, Abbvie: Speaking and Teaching, Gilead: Speaking and Teaching, Sysmex: Speaking and Teaching, Novo Nordisk: Consultant, Berlinger-Ingelheim: Consultant, Chung-Feng Huang: Nothing to Disclose, Wan-Long Chuang: Gilead: Speaking and Teaching, AbbVie: Speaking and Teaching, BMS: Speaking and Teaching, Vaccitech: Consultant, PharmaEssentia: Consultant, GSK: Consultant, Ming-Lung Yu: Abbvie, Gilead and Roche diagnostics.: Grant/Research Support, Abbott, Abbvie, Gilead, Roche and Roche diagnostics: Consultant, Abbvie, BMS, Gilead, Roche and Roche diagnostics: Speaking and Teaching.

2608 | THE HASHIMOTO MIRAGE: WHY AUTOIMMUNE THYROIDITIS LOOKS PROTECTIVE AGAINST MASLD IN TYPE 2 DIABETES

Emeka Stanley Obi[1] Uwakmfonabasi Umoudoh[2] Adedeji Adenusi[3] Gedion Amdetsion[4] Abdulrahman Atasi[1] Chimezirim Ezeano[5] Somtochukwu Abazu[6] Abidemi Akinrinmade[7] Joshua Kalu[8], [1]Brookdale University Hospital and Medical Center, [2]NYCHHC/Lincoln Medical Center, [3]Interfaith Medical Center, [4]John H Stroger Hospital of Cook County, [5]Advocate Aurora Healthcare, [6]Howard University Hospital, [7]SUNY Upstate University, [8]Suny Downstate Medical Center

Background: Thyroid hormone signaling drives hepatic lipid metabolism, validated by resmetirom's MASH approval. Prior work links hypothyroidism to MASLD, but whether the autoimmune process of Hashimoto's thyroiditis (AT) confers independent hepatic or cardiometabolic risk, separate from hormone deficiency, is untested. We examined this in type 2 diabetes (T2DM), restricting both arms to patients not on levothyroxine to isolate the immune from the treated hypothyroid phenotype. **Methods:** Retrospective propensity matched cohort study using the TriNetX US Collaborative Network (65 HCOs). Adults ≥ 18 with T2DM in the prior 5 years were included; Cohort 1 had coexisting AT, Cohort 2 did not. Both excluded levothyroxine use, hyperthyroidism, T1DM, viral hepatitis, hemochromatosis, and Wilson's disease. 1: 1 propensity score matching balanced age, sex, race, BMI, hypertension, hyperlipidemia, obesity, tobacco or alcohol use, CKD, and OSA. Incident MASLD, MASH, cirrhosis, MI, and ischemic stroke were assessed ≥ 180 days after index via risk ratios (RR) and Cox hazard ratios (HR). **Results:** After matching, 9,192 patients per cohort (mean age 59.5; 81% female; post PSM Standardized Mean Difference < 0.10 except BMI 0.139). The AT cohort had lower incidence of MASLD (3.2% vs 4.3%; RR 0.74 [0.63–0.87], $p < 0.001$; HR 1.02, $p = 0.86$), MASH (0.58% vs 0.88%; RR 0.67 [0.47–0.94], $p = 0.021$; HR 0.94, $p = 0.72$), cirrhosis

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(0.97% vs 1.63%; RR 0.59 [0.46–0.77], p < 0.001; HR 0.65 [0.43–0.96], p = 0.029), acute MI (0.92% vs 2.06%; RR 0.45 [0.34–0.58], p < 0.001; HR 0.62 [0.48–0.81], p < 0.001), and ischemic stroke (1.24% vs 1.86%; RR 0.67 [0.53–0.85], p = 0.001; HR 0.98, p = 0.86). Prevalent MASLD before the window was more frequent in the AT cohort (1,451 vs 1,099), indicating depletion of susceptibles. **Conclusion:** Among diabetic adults not on levothyroxine, AT was associated with 26% lower MASLD, 33% lower MASH, 41% lower cirrhosis, 55% lower MI, and 33% lower ischemic stroke incidence, with the strongest signals, significant on both risk and survival analyses, for cirrhosis and acute MI. AT patients are surveilled more intensively, so steatotic and cardiometabolic disease is detected earlier and depleted from the at-risk pool. Excluding levothyroxine strips out the metabolically sickest AT patients, leaving an inherently healthier, euthyroid subgroup in the exposed arm. Intensified cardiometabolic care from chronic endocrine follow-up may accelerate diagnosis and treatment of dyslipidemia and hypertension, lowering downstream MI and cirrhosis risk independent of any thyroid mechanism. Possible immunometabolic crosstalk between thyroid, gut, and liver, together with the above explains AT without levothyroxine in T2DM as a lower risk cardiometabolic phenotype. Confirmatory analyses should incorporate anti-TPO titers, lab-confirmed euthyroid status, FIB-4 trajectories, and active-comparator designs against non-autoimmune euthyroid populations.

Disclosures: Emeka Stanley Obi: Nothing to Disclose, Uwakmfonabasi Umoudoh: Nothing to Disclose, Adedeji Adenusi: Nothing to Disclose, Gedion Amdetsion: Nothing to Disclose, Abdulrahman Atasi: Nothing to Disclose, chimezirim ezeano: Nothing to Disclose, Somtochukwu Abazu: Nothing to Disclose, Abidemi Akinrinmade: Nothing to Disclose, Joshua Kalu: Nothing to Disclose, Nothing to Disclose.

2609 | INTERMITTENT HYPOXIA AND CIRRHOSIS RISK IN MASLD-OSA OVERLAP: A PROPENSITY-MATCHED STUDY

Ihunanya Kanu[1] Chimezirim Ezeano[2] Cherechi Nwabueze[3] Nzubechukwu Okeke[4] Eunice Omeludike[5] Emeka Stanley Obi[6] Richard Heard[7], [1]Baptist Memorial Hospital- Golden Triangle, [2]Advocate Aurora Healthcare, [3]John H. Stroger Jr. Hospital of Cook County, [4]Zucker School of Medicine at Hofstra/Northwell at Vassar Brothers Medical Center, [5]Piedmont Athens Regional Medical Center, [6]Brookdale University Hospital and Medical Center, [7]Baptist Memorial Hospital - Golden Triangle

Background: Obstructive sleep apnea (OSA) and metabolic dysfunction-associated steatotic liver disease (MASLD) commonly coexist, with intermittent hypoxia implicated in hepatic inflammation and fibrogenesis. Although continuous positive airway pressure (CPAP) is the cornerstone of OSA management, its association with liver-related outcomes in MASLD-OSA overlap remains poorly characterized. We evaluated the association between documented CPAP exposure and incident cirrhosis in a large propensity-matched cohort derived from a federated electronic health record network. **Methods:** We conducted a retrospective propensity score-matched cohort study using the TriNetX Global Collaborative Network, including 16 U.S. healthcare systems. Adults aged ≥ 18 years with diagnostic codes for MASLD/MASH and OSA were identified. Patients with competing liver diseases, prior liver transplantation, or central sleep apnea were excluded. The exposed cohort included patients with ≥ 1 documented CPAP procedure or durable medical equipment code, while the comparator cohort had OSA without CPAP codes. Cohorts were propensity score matched 1: 1 on demographics and cardiometabolic comorbidities, yielding 844 patients per group. The primary outcome was incident cirrhosis, defined by de novo diagnostic codes. Risk differences, risk ratios, odds ratios, Kaplan-Meier curves with log-rank testing, and Cox proportional hazards models were used to compare outcomes. **Results:** Before matching, 845 CPAP-exposed and 88,382 unexposed patients were identified. After 1: 1 propensity score matching, 844 patients remained in each cohort. Mean follow-up was 1,415.9 ± 1,219.2 days in the CPAP cohort and 1,680.2 ± 1,346.6 days in the untreated cohort. Incident cirrhosis occurred more frequently in the CPAP cohort than in the untreated cohort, 56/780 (7.2%) vs 36/815 (4.4%), respectively, corresponding to a risk difference of 2.8% (95% CI, 0.5–5.1; p = 0.018), risk ratio of 1.63 (95% CI, 1.08–2.44), and odds ratio of 1.67 (95% CI, 1.09–2.58). Kaplan-Meier analysis similarly showed higher cumulative incidence of cirrhosis among CPAP-exposed patients, with a log-rank p = 0.005 and hazard ratio of 1.82 (95% CI, 1.19–2.78; p = 0.009). Cirrhosis-coded encounters were also higher in the CPAP cohort, 0.742 ± 4.727 vs 0.240 ± 2.146; p = 0.006. **Conclusion:** Documented CPAP exposure was associated with higher observed cirrhosis risk among adults with MASLD and OSA, likely reflecting unmeasured confounding by OSA severity, indication bias, and differential healthcare utilization. These findings underscore the need for prospective studies incorporating OSA severity metrics, CPAP adherence data, and longitudinal liver biomarkers and fibrosis measures before concluding that CPAP modifies MASLD progression.

Disclosures: Ihunanya Kanu: Nothing to Disclose, chimezirim ezeano: Nothing to Disclose, Cherechi

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Nwabueze: Nothing to Disclose, Nzubechukwu Okeke: Nothing to Disclose, Eunice Omeludike: Nothing to Disclose, Emeka Stanley Obi: Nothing to Disclose, Richard Heard: Nothing to Disclose.

2610 | ASSOCIATION BETWEEN NON-ALCOHOLIC FATTY LIVER DISEASE, METABOLIC SYNDROME, AND STROKE SUBTYPE: A HOSPITAL-BASED OBSERVATIONAL STUDY

Ajay Jain[1] Vishwa Gupta[2] Suchita Jain[3] Shohini Sircar[4] Sudhanshu Yadav[4], [1]Shalby Hospital, [2]All India Institute of Medical Sciences, [3]Sri Aurobindo Institute of Medical Sciences, [4]Shalby Institute of Gastroenterology

Background: NAFLD is often regarded as the hepatic manifestation of metabolic syndrome, with both conditions sharing pathophysiological links to cerebrovascular disease. However, whether NAFLD independently associates with stroke type and metabolic syndrome in Indian patients remains unexplored. We aimed to determine the prevalence of NAFLD in hospitalized stroke patients. **Methods:** This cross-sectional, observational study enrolled 110 acute stroke patients (age > 30 years) admitted to the Department of Neurology from April 2023 to August 2024. NAFLD was diagnosed by abdominal ultrasonography (USG) based on increased hepatic echogenicity after exclusion of secondary causes and significant alcohol use. The NAFLD fibrosis score (NFS) was computed to estimate fibrosis severity. Laboratory investigations included liver function tests (LFT), lipid profile, and fasting blood glucose. Metabolic syndrome was assessed using established criteria. Statistical analysis was performed using SPSS v25.0. **Results:** Of 110 patients (76.4% male; mean age 62.6 +/- 9.9 years), 89 (80.9%) had ischemic and 21 (19.1%) hemorrhagic stroke. On USG, 57 patients (51.8%) had fatty liver - grade I in 31.8%, grade II in 15.5%, and grade III in 4.5%. By NFS, 42.7% had no/mild fibrosis (F0-F2), 10% had significant fibrosis (F3-F4), and 47.3% were indeterminate. Hypertension (68.2%), overweight/obesity (61.8%), and diabetes mellitus (46.4%) were the most prevalent comorbidities. Metabolic syndrome was present in 50% of subjects. Serum albumin was significantly lower in NAFLD patients compared to those without NAFLD (p = 0.006). No statistically significant association was found between NAFLD and type of stroke, age, BMI, or metabolic syndrome. **Conclusion:** NAFLD was highly prevalent (51.8%) among stroke patients in this central Indian cohort. These findings underscore the need for routine screening of liver disease in stroke populations to guide comprehensive cardiometabolic management.

Disclosures: Ajay Jain: Nothing to Disclose, Vishwa Gupta: Nothing to Disclose, Suchita Jain: Nothing to Disclose, Shohini Sircar: Nothing to Disclose, Sudhanshu Yadav: Nothing to Disclose.

2611 | PREGNANCY OUTCOMES IN PATIENTS WITH MASLD FOLLOWING ROUX-EN-Y GASTRIC BYPASS: A PROPENSITY SCORE-MATCHED TRINETX ANALYSIS

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is increasingly prevalent among women of reproductive age and is associated with adverse maternal and pregnancy outcomes. Roux-en-Y gastric bypass (RYGB) improves obesity-related metabolic dysfunction and MASLD severity; however, pregnancy outcomes among patients with MASLD following bariatric surgery remain incompletely characterized. **Methods:** We performed a retrospective cohort study using the TriNetX Research Network database from 2005 to 2026. Pregnant patients with MASLD and prior RYGB were identified and compared to pregnant patients with MASLD without prior bariatric surgery. The index event was defined as a pregnancy diagnosis. MASLD diagnosis and RYGB were required to occur at least 6 months prior to the index event. Outcomes were assessed within 300 days following the index date and included hypertensive disorders of pregnancy, gestational metabolic complications, hemorrhagic complications, obstetric complications, severe maternal morbidity, and cesarean delivery. We performed 1: 1 propensity score matching using demographics and metabolic comorbidities including age, race, obesity, and type 2 diabetes mellitus. Multivariable Cox proportional

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hazards regression was subsequently performed to generate adjusted hazard ratios (aHRs) for maternal and obstetric outcomes. **Results:** A total of 23,360 pregnant patients with MASLD without bariatric surgery and 2,339 pregnant patients with MASLD and prior RYGB were identified. After propensity score matching, 2,334 patients remained in each cohort with balanced baseline characteristics and no significant differences in demographics or major metabolic comorbidities ($p > 0.05$). On multivariable regression analysis, prior RYGB remained independently associated with lower hazards of pre-eclampsia (aHR 0.55, 95% CI 0.47–0.65), gestational hypertension (aHR 0.75, 95% CI 0.66–0.86), gestational diabetes mellitus (aHR 0.53, 95% CI 0.47–0.58), postpartum hemorrhage (aHR 0.74, 95% CI 0.60–0.90), polyhydramnios (aHR 0.77, 95% CI 0.62–0.96), and cesarean delivery (aHR 0.85, 95% CI 0.77–0.95) (all $p < 0.05$). No significant adjusted differences were observed for premature rupture of membranes, preterm labor, antepartum hemorrhage, or severe obstetric complications. **Conclusion:** Among pregnant patients with MASLD, prior RYGB was associated with significantly lower risks of several adverse maternal and metabolic pregnancy outcomes, including hypertensive disorders of pregnancy, gestational diabetes, postpartum hemorrhage, and cesarean delivery. These findings suggest bariatric surgery may provide maternal benefits in this high-risk population. Prospective studies are needed to further evaluate maternal and fetal outcomes following bariatric surgery in patients with MASLD.

Table 1. Adjusted Maternal and Obstetric Outcomes Following Prior RYGB in Pregnant Patients with MASLD

Outcome	Adjusted Hazard Ratio	95% CI	P-value
Pre-eclampsia	0.55	0.47–0.65	<0.0001
Gestational HTN	0.75	0.66–0.86	<0.0001
Gestational DM	0.53	0.47–0.58	<0.0001
Preterm labor	1.10	0.93–1.31	0.2684
Postpartum hemorrhage	0.74	0.60–0.90	0.0032
Antepartum hemorrhage	1.16	0.99–1.36	0.0712
Polyhydramnios	0.77	0.62–0.96	0.0209
Severe maternal morbidity¥	0.78	0.46–1.33	0.3652
Cesarean delivery	0.85	0.77–0.95	0.0042
PROM	0.96	0.80–1.16	0.7031

¥A composite of outcomes: Peripartum cardiomyopathy, postpartum acute kidney failure, obstetric thromboembolism, amniotic fluid embolism

Disclosures: Sherifatu Abu: Nothing to Disclose, Kailyn Brown: Nothing to Disclose, Shama Antala: Nothing to Disclose, Mitali Sarkar: Nothing to Disclose, Yedidya Saiman: Nothing to Disclose, Kimberly Forde: Nothing to Disclose.

2612 | IMPROVING FIB-4-BASED MASLD FIBROSIS RISK ASSESSMENT AND DOWNSTREAM MANAGEMENT IN A RESIDENT PRIMARY CARE CLINIC

Tomas Correa-Gaviria[1] Maitri Patel[1] Jonathan Dranoff[1] Mario Ochoa Prieto[1], [1]Yale University

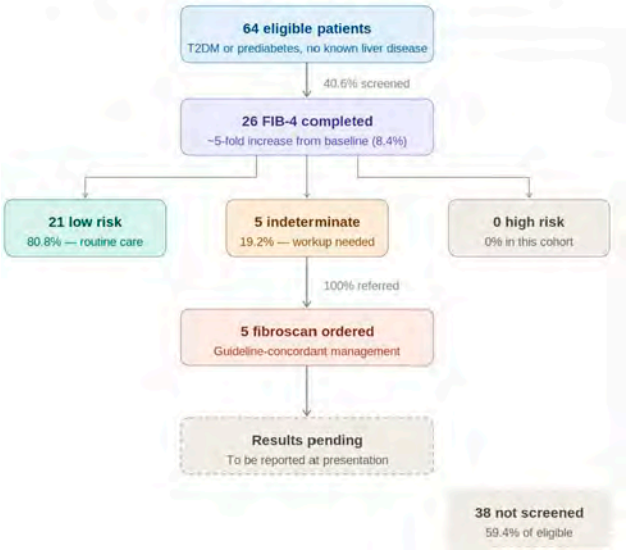
Background: MASLD affects up to 70% of patients with type 2 diabetes (T2DM) and disproportionately impacts underserved populations. The FIB-4 index is recommended as a first-line fibrosis tool but remains underutilized in primary care. We evaluated baseline FIB-4 use in a resident continuity clinic and assessed the impact of a multifaceted intervention on screening rates and downstream management. **Methods:** We conducted a single-center quality improvement initiative in a resident clinic embedded within a Federally Qualified Health Center. Eligible patients were adults with T2DM and without a prior diagnosis of liver disease. Baseline FIB-4 documentation was assessed retrospectively before January 2026. Resident surveys assessed barriers and knowledge gaps. Interventions included resident and preceptor education, an Epic SmartPhrase with automated FIB-4 calculation and interpretation guidance, and clinic-based visual reminders. The primary outcome was patient-level FIB-4 documentation; secondary outcomes included risk classification and guideline-concordant management. Outcomes were tracked prospectively from January through May 2026. **Results:** At baseline, FIB-4 was documented in 13/154 eligible patients (8.4%). Pre-intervention surveys identified uncertainty in FIB-4 interpretation and competing clinical priorities as major barriers. Post-intervention, 64 eligible patients were identified. FIB-4 was completed in 26 patients (40.6%), representing a ~5-fold increase from baseline. Risk stratification revealed 21 low-risk (80.8%) and 5 indeterminate (19.2%) results; no patients were classified as high-risk. All 5 patients with indeterminate FIB-4 had a guideline-concordant fibroscan ordered (100%). Fibroscan results are pending and will be reported at the time of presentation. **Conclusion:** A multifaceted EMR-integrated intervention significantly improved FIB-4-based fibrosis screening rates in a safety-net primary care clinic serving a high-risk, underserved population. The cascade of care identified patients with potentially unrecognized advanced fibrosis, underscoring the real-world clinical impact of systematic screening in this population. Persistent gaps between risk identification and completion of secondary evaluation highlight the ongoing need for continued workflow

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integration and EMR automation to sustain and expand these gains.

Figure 1. FIB-4 Screening Cascade — Post-Intervention



Disclosures: Tomas Correa-Gaviria: Nothing to Disclose, Maitri Patel: Nothing to Disclose, Jonathan Dranoff: Nothing to Disclose, Mario Ochoa Prieto: Nothing to Disclose.

2613 | TEMPORAL TRENDS IN MORTALITY DUE TO LIVER DISEASES AND COMORBID METABOLIC SYNDROME IN OLDER ADULTS IN THE UNITED STATES: CDC WONDER ANALYSIS (1999–2024)

Bland Ahmed[1] Mahrukh Mahrukh[2] Shehryar Rasheed Sohail[3] Hajra Umar Jaspal[4] Zainab Attiq[2] Arooj Ihsan Ullah[5] Palwasha Farooqi[6] Ehsanullah Alokozay[7], [1]Desert Regional Medical Center, [2]University Medical and Dental College, University of Faisalabad, Faisalabad, Pakistan, [3]Jinnah Sindh Medical University, [4]University College of Medicine and Dentistry (UCMD), The University of Lahore, Lahore, Pakistan, [5]FJMU lahore, [6]Desert Regional Medical Center, Palm Springs, Ca, USA, [7]Faculty of Medicine, Kandahar University, Kandahar, Afghanistan

Background: Liver diseases share pathophysiological mechanisms with metabolic syndrome, including chronic inflammation and insulin resistance. These conditions frequently co-occur in older adults (≥65 years) and may synergistically increase mortality risk. This study examined national mortality trends in concomitant liver diseases and metabolic syndrome among older U.S. adults from 1999 through 2024. **Methods:** A retrospective, population-based analysis was performed using the CDC WONDER Multiple Cause of Death database. Deaths with ICD-10 codes for liver diseases (K70–K76) and metabolic syndrome (Diabetes: E10–E14; Obesity: E66.0–66.2, E66.8–66.9; Hyperlipidemia and plasma protein metabolism disorders: E78, E88.0–88.3, E88.8–88.9; Essential hypertension: I10) were included. Age-adjusted mortality rates (AAMRs) were calculated per 100,000 population. Joinpoint regression was used to assess temporal trends. Analyses were stratified by sex, age group, race/ethnicity, census region, and urbanization. **Results:** Between 1999 and 2024, the overall AAMR for liver diseases with metabolic syndrome increased significantly from 11.92 to 29.27 per 100,000 (AAPC: +3.61%; 95% CI: 3.37–3.93). Sex-stratified analysis showed higher long-term increases in men (AAPC: +3.87%; 95% CI: 3.60–4.24) compared to women (AAPC: +3.20%; 95% CI: 2.95–3.58). Age-specific analysis revealed the sharpest increase among the 85 + years cohort (AAPC: +4.73%; 95% CI: 4.28–5.29), with notable acceleration after 2018 (APC: +16.23%). Regional analysis showed that the South recorded the largest long-term increase (AAPC: 4.17%; 95% CI: 3.96–4.40), while the Midwest showed the steepest rise between 2018 and 2021 (APC: 14.13%). Compared to urban areas, rural populations had a higher and more persistent rise in mortality (AAPC: +3.82%; 95% CI: 3.46–4.24). By race/ethnicity, White adults showed the highest long-term increase (AAPC: +3.97%; 95% CI: 3.75–4.23), followed by American Indian or Alaska Native adults (AAPC: +2.85%; 95% CI: 1.96–4.27). Black or African American adults showed a sharp short-term rise from 2016–2022 (APC: +10.76%). **Conclusion:** From 1999 to 2024, mortality among older adults with concurrent liver diseases and metabolic syndrome increased substantially, with pronounced acceleration after 2018. Older men (85+ years), rural residents, and White populations experienced the highest mortality burden. These data highlight the growing intersection of liver diseases and metabolic syndrome as a determinant of mortality in older adults, underscoring the need for integrated metabolic and hepatologic management in aging populations.

Disclosures: BLAND AHMED: Nothing to Disclose, Mahrukh Mahrukh: Nothing to Disclose, Shehryar Rasheed Sohail: Nothing to Disclose, Hajra Umar Jaspal: Nothing to Disclose, Zainab Attiq: Nothing to Disclose, Arooj Ihsan Ullah: Nothing to Disclose,

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Palwasha Farooqi: Nothing to Disclose, Ehsanullah Alokozay: Nothing to Disclose.

2614 | HEPATOLOGY REFERRAL TIMING IN MASLD-ASSOCIATED DECOMPENSATED CIRRHOSIS: A RETROSPECTIVE COHORT STUDY

Maitri Patel[1] Saumya Srivastava[1] Bubu Banini[1], [1]Yale University

Background: Decompensated cirrhosis is a leading cause of liver-related morbidity and mortality, with metabolic dysfunction-associated steatotic liver disease (MASLD) emerging as one of its fastest-growing etiologies. Patients who progress to decompensation face high short-term mortality and require timely, coordinated specialty care, yet access to hepatology services remains variable and infrequently studied. We aimed to evaluate referral patterns and the association between time-to-care and mortality amongst a sample of patients with decompensated MASLD cirrhosis to better characterize whether longer time-to-care contributes to worse outcomes. **Methods:** We performed a retrospective cohort study of patients with decompensated cirrhosis who were seen in a tertiary care fatty liver disease clinic between 2018-2022. Demographic, referral, and clinical outcomes data were abstracted from the electronic medical records. Time intervals were calculated between the diagnosis of cirrhosis, gastroenterology (GI)/hepatology referral, first outpatient GI visit, first hepatology visit, and mortality. Descriptive statistics were calculated and presented as medians and interquartile ranges (IQR). Kaplan-Meier curves were developed to evaluate this association between delays in hepatology care and time to mortality. **Results:** Of the 1,028 patients evaluated in the fatty liver disease clinic during this time period, 65 patients (6.3%) had decompensated cirrhosis. Mean age at the first hepatology visit was 57.1 years (median 58.8 years, IQR 48.1–65.8) and 35 (53.8%) were men. Primary care providers placed the largest proportion of referrals (38.5%), followed by GI/hepatology providers (33.8%), other specialists (15.4%), and hospitalists (10.8%). The median time from cirrhosis diagnosis to GI evaluation was 0 days (IQR -99–46), compared to 112 days (IQR 8–694) for hepatology evaluation. From referral time to initial clinic visit, wait times were also higher for hepatology visits (median 36 days; IQR 12-53) compared to gastroenterology (median 16 days; IQR 10-22). Notably, 24 of 65 patients (36.9%) experienced a decompensation event prior to hepatology referral placement. A total of 23 patients (35.4%) died during follow-up. Among deceased patients, median time from first hepatology visit to death was 907 days (IQR 328–2,034). **Conclusion:** Among patients with decompensated MASLD cirrhosis, over one-third experienced decompensation prior to referral placement. This pattern suggests that patients may be entering specialty care late in the disease course, potentially limiting opportunities for preventive interventions, surveillance, and transplant evaluation. Health-system strategies focused on earlier cirrhosis recognition and expedited hepatology referral pathways warrant further investigation, especially within primary care, where the majority of patients with MASLD are initially evaluated.

Disclosures: Maitri Patel: Nothing to Disclose, Saumya Srivastava: Nothing to Disclose, Bubu Banini: Nothing to Disclose.

2615 | NON-CIRRHOTIC METABOLIC DYSFUNCTION–ASSOCIATED STEATOTIC LIVER DISEASE AND INPATIENT OUTCOMES AMONG ADULTS HOSPITALIZED FOR INFLAMMATORY BOWEL DISEASE FLARES: A NATIONWIDE ANALYSIS

Cherechi Nwabueze[1] Eunice Omeludike[2] Chimezirim Ezeano[3] Yetunde Akande[1] Ihunanya Kanu[4] Nzubechukwu Okeke[5] Ridwan Lawal[6] Ifelunwa Osanakpo[7], [1]John H. Stroger Jr. Hospital of Cook County, [2]Piedmont Athens Regional Medical Center, [3]Advocate Aurora Healthcare, [4]Baptist Memorial Hospital- Golden Triangle, [5]Zucker School of Medicine at Hofstra/Northwell at Vassar Brothers Medical Center, [6]University of Texas Rio Grande Valley, [7]Carle Foundation Hospital

Background: The gut–liver axis plays a central role in regulating immune responses and systemic inflammation. Metabolic dysfunction–associated steatotic liver disease (MASLD) and inflammatory bowel disease (IBD) frequently coexist and share overlapping inflammatory and metabolic pathways, however, the impact of pre-existing MASLD on outcomes during IBD flares remains unclear. We evaluated the association between non-cirrhotic MASLD and inpatient outcomes among adults hospitalized for IBD flares using a nationwide U.S. cohort. **Methods:** A retrospective cohort analysis of the National Inpatient Sample (2016–2022) was conducted. Adult hospitalizations with a primary diagnosis of IBD flare were identified using ICD-10-

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CM codes; those with pre-existing non-cirrhotic MASLD comprised the exposure group. Survey-weighted analyses generated national estimates. Multivariable logistic and linear regression models adjusted for demographics, hospital characteristics, IBD subtype, cardiometabolic comorbidities, and overall comorbidity burden were used to evaluate mortality, complications, healthcare utilization, and discharge outcomes. **Results:** Among 121,176 hospitalizations for primary IBD flares (weighted estimate: 605,880), 16,775 (2.8%) had documented non-cirrhotic MASLD. Compared with patients without MASLD, those with MASLD were older (49.5 vs 46.1 years) and had a greater comorbidity burden (mean Elixhauser score 4.01 vs. 2.23; both $p < 0.001$). After multivariable adjustment, MASLD was not associated with inpatient mortality (aOR 0.47, 95% CI 0.19-1.16; $p = 0.10$) but was associated with lower odds of major inpatient complications (aOR 0.72, 95% CI 0.65–0.80; $p < 0.001$), defined as a composite of sepsis, shock, acute kidney injury, respiratory failure, venous thromboembolism, colectomy, and bowel surgery. MASLD was also associated with lower odds of inpatient colectomy (aOR 0.57, 95% CI 0.46-0.70) and non-routine discharge (aOR 0.58, 95% CI 0.50–0.67), as well as shorter length of stay (β -1.08 days, 95% CI -1.35 to -0.82) and lower total hospital charges (β -$9,157, 95% CI -$13,414 to -$4,900) (all $p < 0.001$). Similar findings were observed in analyses stratified by Crohn's disease and ulcerative colitis. **Conclusion:** Despite a higher cardiometabolic burden, documented non-cirrhotic MASLD was not associated with increased short-term inpatient risk and was associated with lower healthcare utilization and complication rates during IBD flare hospitalizations. Further studies are needed to clarify the mechanisms underlying these unexpected findings and to better define the role of the gut–liver axis in acute inflammatory disease states.

Disclosures: Cherechi Nwabueze: Nothing to Disclose, Eunice Omeludike: Nothing to Disclose, chimezirim ezeano: Nothing to Disclose, Yetunde Akande: Nothing to Disclose, Ihunanya Kanu: Nothing to Disclose, Nzubechukwu Okeke: Nothing to Disclose, Ridwan Lawal: Nothing to Disclose, Ifelunwa Osanakpo: Nothing to Disclose.

2616 | PROGNOSTIC BURDEN OF 2023 STEATOTIC LIVER DISEASE SUBTYPES: DIFFERENTIAL IMPACTS ON MORTALITY, CANCER, AND CARDIOVASCULAR OUTCOMES

Parucha Paruchakul[1] Moongmun Anuntasainont[2] Mingkwan Ratanapipop[2] Sakkarin Chirapongsathorn[2], [1]Phramongkutklao Hospital, [2]Department of Medicine, Phramongkutklao Hospital and College of Medicine

Background: The 2023 steatotic liver disease (SLD) classification integrates metabolic dysfunction and alcohol exposure, but its prognostic implications remain uncertain, particularly in Asian populations. We evaluated long-term mortality, cancer, and cardiovascular disease (CVD) outcomes across 2023 SLD subtypes in an Asian cohort. **Methods:** Adults with ultrasonography-defined SLD in 2014 were retrospectively reclassified according to the 2023 SLD criteria and followed for up to 11 years. Outcomes included all-cause and cause-specific mortality, cancer incidence, and CVD incidence. Kaplan–Meier analysis and Cox regression analyses were used for mortality outcomes. Cancer and CVD analyses excluded patients with pre-existing disease and used incidence rate ratios (IRRs) and multivariable Cox models. Advanced fibrosis was defined using the FIB-4 (Fibrosis-4) index (≥ 2.67). **Results:** A total of 1,279 patients were included (median age 57 years; 57% male); advanced fibrosis was present in 11% of 705 evaluated patients. 88% had metabolic dysfunction–associated SLD (MASLD), 3% MASLD with increased alcohol intake (MetALD), 3% alcohol-associated liver disease (ALD), and 6% other SLDs. Over a median follow-up of 10.8 years (67 deaths), ALD had the highest mortality rate (58.6 per 1,000 person-years (PY)) and lowest 10-year survival (58.9%). ALD was independently associated with increased all-cause mortality compared with MASLD (adjusted hazard ratio [aHR] 4.02; 95% CI 1.14–14.15), after adjustment for FIB-4–defined fibrosis and metabolic comorbidities. Older age, diabetes, chronic kidney disease, inflammatory markers, and advanced fibrosis were independent mortality predictors. Mortality was primarily driven by liver- and cancer-related causes, while CVD mortality did not differ across subtypes.Among patients without baseline cancer, 102 cancers occurred over 10,220 PY (997 per 100,000 PY). ALD conferred a significantly increased cancer risk compared with MASLD (IRR 5.08; 95% CI 2.22–11.62; $p < 0.001$), with the highest rates of both hepatocellular and extrahepatic malignancies, particularly lung cancer. In contrast, among those without baseline CVD, 51 events occurred over 10,289 PY (495 per 100,000 PY), with no significant differences in cardiovascular outcomes across subtypes. **Conclusion:** In this long-term Asian cohort reclassified by the 2023 SLD criteria, ALD emerged as a high-risk subtype with markedly increased mortality and cancer burden, whereas cardiovascular risk did not differ significantly across subtypes. These findings suggest that prognostic differentiation in SLD is driven by mortality and malignancy rather than cardiovascular events.

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Table 1. Cancer, cardiovascular disease, and mortality burden across SLD subtypes

The 2023 SLD classification	Cancer events[1]	Cancer Incidence Rate[a,2]	Cancer IRR[b] (95% CI)	CVD events[3]	CVD Incidence Rate[b,3]	Mortality rate[4]	All-cause mortality aHR[c] (95% CI)
MASLD	88	937.6	Reference	46	492.8	4.7	Reference
MetALD	2	891.4	0.74 (0.18–3.00)	2	746.6	3.4	1.18 (0.15 – 9.15)
ALD	6	4,765.4	5.08 (2.22–11.62)	0	0.0	58.6	4.02 (1.14 – 14.15)
Other SLDs	6	1,430.9	1.53 (0.67–3.49)	3	543.6	14.2	1.35 (0.39 – 4.70)

aHR: adjusted hazard ratio; ALD: alcohol-associated liver disease; CI: confidence interval; CVD: cardiovascular disease; IRR: incidence rate ratio; MASLD: metabolic dysfunction-associated SLD; MetALD: MASLD with increased alcohol intake; SLD: steatotic liver disease.

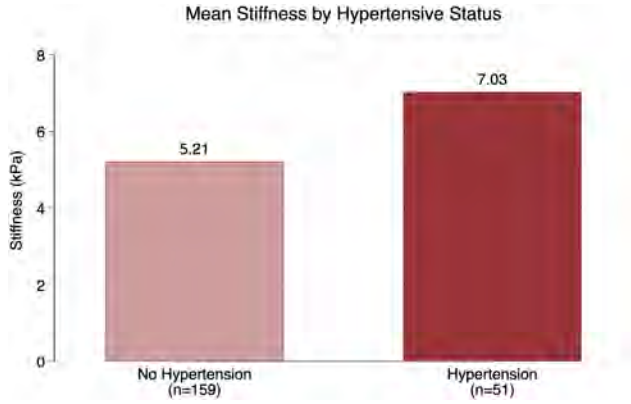
[a]Among patients without baseline cancer.
[b]Incidence rate per 100,000 person-years.
[c]Among patients without baseline CVD.
[d]All-cause mortality rate per 1,000 person-years in the overall cohort.
[e]Adjusted for age, sex, FIB-4-defined fibrosis and metabolic comorbidities in the overall cohort.

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2617 | NOVEL COMMUNITY-BASED LIVER HEALTH AWARENESS INITIATIVE USING NON-INVASIVE TESTING IDENTIFIES UNRECOGNIZED AT-RISK MASLD

Michael Betel[1] Sherri Brown[1] Michael McTighe[2] Lindsay Myles[3] Supriya Joshi[4] Magdy Elkhashab[5] Daniyal Khan[6] Mark Swain[6], [1]Fatty Liver Alliance, [2]Mindray, [3]Simcoe Liver Centre, Fatty Liver Alliance and Mountain Metabolic, [4]Trillium Health Partners (Credit Valley Hospital), [5]Toronto Liver Centre, [6]University of Calgary

Background: Metabolic dysfunction-Associated Steatotic Liver Disease (MASLD) is highly prevalent and often remains undiagnosed until fibrosis has significantly progressed. There is a need for practical, individual-driven, community-based models to improve liver health awareness and support early identification and appropriate action. To address this gap, we developed and implemented a community-based, self-referral, non-invasive testing and education program at the Liver Health Awareness Centre (LHAC) in Toronto, Canada. **Methods:** Individuals ≥18 years of age who self-referred to LHAC were offered a no-cost liver stiffness measurement (LSM) using *Hepatus-5* transient elastography (TE), and provided with a concise NP-led structured liver health overview, including hepatic steatosis, fibrosis, and an interpretation of their LSM results. With consent, individual medical history and demographics were collected, including MASLD metabolic risk factors (dyslipidemia, hypertension, and type 2 diabetes). At-risk (LSM 8-12 kPa) or high-risk (LSM ≥12 kPa) individuals were offered a referral to a hepatologist for further assessment. Group characteristics were compared using chi-square tests for categorical variables, and t-tests and logistic regression for continuous variables. **Results:** A total of 210 individuals were sequentially assessed (128 females (60.9%); mean (SD) age 52.7 years (12.9)). Most individuals learned about LHAC online (65.7%). About half had a known history of liver disease (n = 104, 49.5%), but most had never had a LSM (n = 165, 78.6%, $p < 0.05$). Most individuals (63.8%) had at least one MASLD risk factor, with roughly half (47%) having multiple risk factors. Most common MASLD risk factors were elevated cholesterol (43.3%) and hypertension (24.3%). A total of 79 (37.6%) individuals had liver enzyme tests previously performed, with 43% reporting elevated levels. Individuals with known history of liver disease were more likely to have elevated liver enzymes ($p < 0.05$), higher BMI ($p < 0.05$), presence of a MASLD risk factor ($p < 0.05$), higher steatosis levels ($p < 0.05$), and higher stiffness scores compared to those without ($p < 0.05$). Mean (SD) steatosis scores on TE were 263.2 (42.8) dB/m, with 36.4% having S3 grade steatosis. Mean (SD) LSM measurement was 5.7 (3.1) kPa, with 11.4% assessed as being 'at-risk' or 'high risk' for advanced fibrosis (LSM > 8.0 kPa). Only prior history of hypertension (n = 51, OR: 1.83, $p < 0.05$) was associated with increased odds of at-risk liver stiffness. **Conclusion:** A community-based, no-cost, self-referral Liver Health Awareness Centre program may represent a feasible model for improving public awareness and identifying individuals with at risk MASLD who have been missed by gaps in the current health care processes. These pilot findings may support broader use of this approach as part of MASLD prevention, awareness, and referral pathways.



Disclosures: Michael Betel: Nothing to Disclose, Sherri Brown: Nothing to Disclose, Michael McTighe: Nothing to Disclose, Lindsay Myles: Nothing to Disclose, Supriya Joshi: Nothing to Disclose, Magdy Elkhashab: Madrigal Pharmaceuticals: Independent Contractor, Bio89: Independent Contractor, Akero: Independent Contractor, NovoNordisk: Independent Contractor, Boehringer-Ingelheim: Independent Contractor, Novotech: Independent Contractor, Aligos:

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2618 | DIABETES AND LIVER FIBROSIS AS COMPOUNDING RISK FACTORS FOR CHRONIC KIDNEY DISEASE IN PATIENTS WITH

Seung Up Kim[1] Chan-Young Jung[2], [1]Yonsei University, [2]Asan Medical Center, Seoul, Korea

Background: Diabetes mellitus (DM) and liver fibrosis frequently coexist, yet whether they represent distinct or overlapping pathways for chronic kidney disease (CKD) remains unclear. We investigated whether liver fibrosis independently predicts CKD risk and confers additional risk when coexisting with DM in patients with metabolic dysfunction-associated steatotic liver disease (MASLD). **Methods:** This retrospective cohort included 4,233 adults with MASLD without pre-existing CKD who underwent vibration-controlled transient elastography (VCTE) from 2006 to 2018. Participants were categorized into four groups based on DM and fibrosis status. Liver fibrosis was defined as fibrosis-4 index > 2.67 or liver stiffness ≥ 8 kPa. The primary outcome was incident CKD; secondary outcomes included ≥ 25% eGFR decline and 3- and 5-year CKD risk. **Results:** During a mean follow-up of 2.9 years, 181 (4.3%) participants developed incident CKD. Compared with those without DM or fibrosis, patients with both conditions had the highest adjusted risk of incident CKD (aHR 3.00, 95% CI 1.84–4.89) and 25% eGFR decline (aHR 2.55, 95% CI 1.85–3.51). Neither multiplicative nor additive interaction was significant (all $P > 0.05$), suggesting independent, compounding effects. Mediation analysis showed that liver fibrosis mediated a small but significant proportion of the DM-associated risk of incident CKD (4.8%, $P = 0.028$) and 25% eGFR decline (5.8%, $P = 0.013$). **Conclusion:** In patients with MASLD, DM and liver fibrosis are compounding risk factors for CKD, supporting integrated risk stratification based on both glycemic and hepatic fibrosis status.

Disclosures: Seung Up Kim: Nothing to Disclose, Chan-Young Jung: Nothing to Disclose.

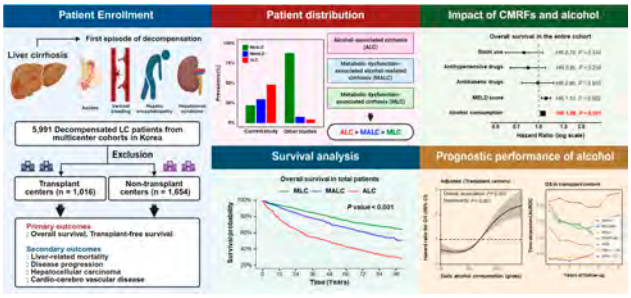
2619 | IMPACT OF CARDIOMETABOLIC RISK FACTORS AND ALCOHOL CONSUMPTION IN DECOMPENSATED LIVER CIRRHOSIS

Keungmo Yang[1] Jaejun Lee[1] Ji Won Han[1] Pil Soo Sung[1] Chang Wook Kim[1] Heechul Nam[1] Ahlim Lee[1] U Im Chang[1] Do Seon Song[1] Haelim Lee[1] Hee Kim[1] Sung Won Lee[1] Jeong Won Jang[1], [1]College of Medicine, The Catholic University of Korea

Background: Cardiometabolic risk factors (CMRFs) and alcohol consumption are recognized determinants of disease progression in metabolic dysfunction–associated steatotic liver disease (MASLD). However, their relative prognostic impacts following the transition to decompensated cirrhosis remain unclear. This study aimed to clarify how CMRFs and alcohol exposure influence clinical outcomes in patients with decompensated cirrhosis. **Methods:** In this multicenter cohort study, 5,991 adults with MASLD-related cirrhosis who experienced their first hepatic decompensation between 2002 and 2024 were screened, and 2,670 were enrolled. Patients were classified into three categories: metabolic dysfunction–associated liver cirrhosis (MLC), metabolic dysfunction–associated alcohol-related liver cirrhosis (MALC), and alcohol–associated liver cirrhosis (ALC). Overall survival (OS) and transplant-free survival (TFS) were analyzed using multivariable Cox models, and discriminative performance was evaluated with the time-dependent area under the receiver operating characteristic curve. **Results:** Survival and liver-related outcomes decreased progressively from MLC to MALC to ALC ($P < 0.001$) **.** The incidences of hepatocellular carcinoma and cardio-cerebrovascular disease did not differ significantly across the subgroups. Daily alcohol consumption was independently associated with mortality in both OS ($P < 0.001$) and TFS ($P < 0.001$). Alcohol intake consistently emerged as a stronger prognostic determinant than CMRFs or related medications. Alcohol consumption showed superior short-term prognostic discrimination and, when incorporated into liver function–based models, significantly improved predictive performance and clinical net benefit, confirming its dominant role in survival. **Conclusion:** In decompensated cirrhosis, alcohol exposure—rather than CMRFs—emerges as the primary determinant of survival, in a dose-dependent manner. These findings underscore the necessity for refined risk stratification in decompensated cirrhosis, where the burden of alcohol consumption is a crucial factor influencing prognosis.

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Disclosures: Keungmo Yang: Nothing to Disclose, Jaejun Lee: Nothing to Disclose, Ji Won Han: Nothing to Disclose, Pil Soo Sung: Nothing to Disclose, Chang Wook Kim: Nothing to Disclose, Heechul Nam: Nothing to Disclose, Ahlim Lee: Nothing to Disclose, U Im Chang: Nothing to Disclose, Do Seon Song: Nothing to Disclose, Haelim Lee: Nothing to Disclose, Hee Kim: Nothing to Disclose, Sung Won Lee: Nothing to Disclose, Jeong Won Jang: Nothing to Disclose.

2620 | PERSISTENT CARE GAPS IN PATIENT-REPORTED STEATOTIC LIVER DISEASE EXPERIENCE ACROSS FIVE NATIONAL SURVEYS (2022-2026), DESPITE THE ARRIVAL OF MASH-SPECIFIC THERAPIES

Tiffany Mensah[1] Neeraj Mistry[1] Jenn Jones[2] Henry Chang[1] Wayne Eskridge[1], [1]Fatty Liver Foundation, [2]Sober Livers

Background: The State of Steatotic Liver Care in America survey serves as a yearly, patient-centered initiative designed to monitor the medical and social journeys of individuals with steatotic liver disease (SLD) across the United States. By examining data collected between 2022 and 2026, this analysis underscores the critical importance of documenting patient-reported experiences to pinpoint deficiencies in care and guide the development of focused policies and clinical interventions. **Methods:** Trends were identified using 2022–2026 data from US adults diagnosed with SLD. The mixed method survey consisted of 49 items across four domains: diagnosis and staging, medical management and physical impact, psycho-social and environmental impact, and current health. Core survey items were held consistent across all five waves to enable inter-year comparison. Items were developed in collaboration with the patient community, Fatty Liver Foundation Medical Advisory Group, and the Survey Analysis Group. Participants were recruited in person at a community clinic and online via email, social media, and patient fora. **Results:** Across all survey years, most respondents identified as living with MASLD or MASH, reflecting the survey's earlier focus on these populations prior to expanded outreach to individuals with ALD, MetALD, DILI, monogenetic or cryptogenic steatotic liver disease beginning in 2024. Diagnoses were most commonly initiated by a primary care provider during routine visits or identified incidentally during evaluation for unrelated issues. Blood-based testing and imaging remain the most common diagnosis methods. Although liver biopsy remains in use, its reported frequency has declined since 2023 relative to non-invasive methods (31.04% in 2023 to 19.09% in 2025). Diet and lifestyle counseling were the most common forms of support received, often paired with co-morbidity management. Few respondents were offered mental health resources, despite reports of anxiety, depression, and irritability; a modest increase in mental health support offered was observed in 2025 (5.83% in 2024 vs. 7.82% in 2025). Respondents identified peer support, condition-specific education, nutritional guidance, and greater physician empathy as their top unmet needs. **Conclusion:** These findings highlight persistent gaps in SLD care across diagnostic, clinical, and psychosocial domains. While non-invasive diagnostic approaches are increasingly favored, mental health support and patient-centered care remain underutilized. The consistency of unmet needs across five survey years underscores an urgent need for systemic improvements in SLD care delivery. Patient-reported data of this nature offer an actionable foundation for policy development, clinical guideline refinement, and the design of targeted support programs. Continued surveillance is essential to monitor progress and evaluate the impact of emerging interventions.
Disclosures: Tiffany Mensah: Madrigal Pharmaceuticals: Consultant, Neeraj Mistry: Nothing to Disclose, Jenn Jones: Nothing to Disclose, Henry Chang: Nothing to Disclose, Wayne Eskridge: Madrigal Pharmaceuticals: Consultant, Regeneron: Consultant, PathAI: Consultant, Novo Nordisk: Consultant.

2621 | MYOSTEATOSIS, RATHER THAN SARCOPENIA, IDENTIFIES PHYSICAL FRAILTY IN COMPENSATED MASH CIRRHOSIS WITH OBESITY

Sobia Laique[1] Awwab Hammad[1] Sameer Gadani[1] Ricardo Rosero-Revelo[1] Nicole Welch[1] Annette Bellar[1] Yael Mauer[1] Paloma Rodriguez Alvarez[1] Shilpa Junna[1] Ali Aminian[1] Srinivasan Dasarathy[1], [1]Cleveland Clinic

Background: Sarcopenia predicts adverse outcomes in decompensated cirrhosis, but muscle quantity alone

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may be an incomplete marker in compensated disease, particularly in patients with obesity. In compensated MASH cirrhosis, preserved skeletal muscle area may obscure impaired muscle quality from myosteatosis. This distinction is increasingly relevant as GLP-1 receptor agonists are widely used in this population and may reduce lean mass during weight loss. We characterized CT-defined body composition phenotypes in adults with compensated MASH cirrhosis and obesity and tested whether skeletal muscle radiodensity (SMD), a measure of muscle quality, was more closely associated with physical function than skeletal muscle index (SMI), a measure of muscle quantity. **Methods:** This cross-sectional study included 31 adults with compensated MASH cirrhosis and BMI ≥ 30 kg/m2 who underwent contrast-enhanced CT with L3-level body composition analysis using a dedicated semi-automated segmentation workstation. Measures included SMI, SMD corrected for portal venous phase contrast enhancement, and visceral and subcutaneous adipose tissue area. Sarcopenia was defined using cirrhosis-specific SMI cutoffs (<50 cm²/m² men, <39 cm²/m² women). Myosteatosis was defined as corrected SMD <33 HU. Liver Frailty Index (LFI) was available in 20 patients. **Results:** Median age was 58 years (IQR 50.7–63.5), 71% were female, median BMI was 39.4 kg/m², median MELD 3.0 was 8, and 58.1% had T2DM. Sarcopenia was present in 12.9% (4/31) vs myosteatosis in 87.1% (27/31; $p<0.001$). Median SMI was 51.1 cm2/m2 (IQR 42.8-56.7), generally above sarcopenia thresholds, while median corrected SMD was 14.4 HU (IQR 1.9-29.6), 18.6 HU below the myosteatosis cutoff. Among 20 patients with concurrent LFI and CT data, 16 (80%) were prefrail and 4 (20%) were robust; none met criteria for frailty. Functional impairment was reflected mainly by reduced grip strength and slower chair stands, while balance was preserved. The effect size for the association between myosteatosis and LFI was larger than that for sarcopenia and LFI (rank-biserial r = 0.89 vs. 0.28). Myosteatosis showed a strong trend toward association with prefrailty (U = 34, p = 0.051), whereas sarcopenia did not (U = 23, p = 0.571). Lower continuous SMI was also associated with prefrailty (U = 10, p = 0.039), but most prefrail patients did not meet binary sarcopenia thresholds. **Conclusion:** In compensated MASH cirrhosis with obesity, myosteatosis was more frequent than sarcopenia and showed strongest separation by frailty status. Conventional SMI-based sarcopenia screening may miss patients with impaired muscle quality and early functional vulnerability. CT-based body composition assessment should incorporate muscle quality metrics, and prospective studies are needed to determine whether myosteatosis predicts decompensation, functional decline, and body composition changes during GLP-1 RA therapy.

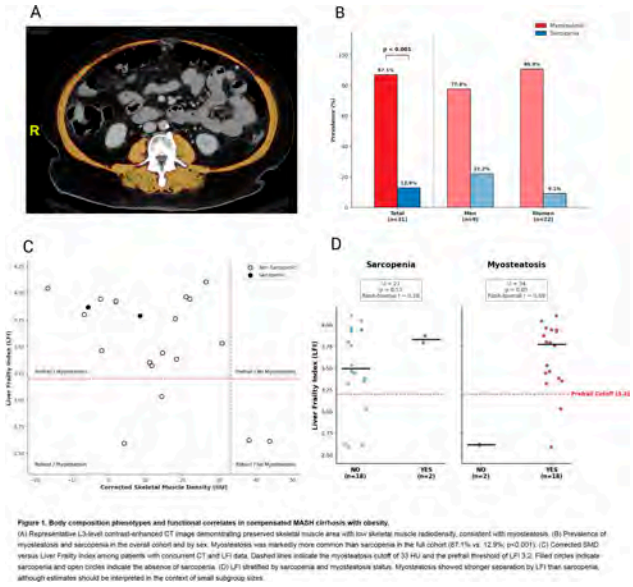


Figure 1. Body composition phenotypes and functional correlates in compensated MASH cirrhosis with obesity.
(A) Representative L3-level contrast-enhanced CT image demonstrating preserved skeletal muscle area with low skeletal muscle radiodensity, consistent with myosteatosis. (B) Prevalence of myosteatosis and sarcopenia in the overall cohort and by sex. Myosteatosis was markedly more common than sarcopenia in the full cohort (87.1% vs. 12.9%; p<0.001). (C) Corrected SMD versus Liver Frailty Index among patients with concurrent CT and LFI data. Dashed lines indicate the myosteatosis cutoff of 33 HU and the prefrail threshold of LFI 3.2. Filled circles indicate sarcopenia and open circles indicate the absence of sarcopenia. (D) LFI stratified by sarcopenia and myosteatosis status. Myosteatosis showed stronger separation by LFI than sarcopenia, although estimates should be interpreted in the context of small subgroup sizes.

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2622 | TRENDS IN DIET QUALITY, SUGAR SWEETENED BEVERAGE CONSUMPTION, AND CALORIE SOURCES AMONG US ADULTS WITH MASLD, 2005-2023

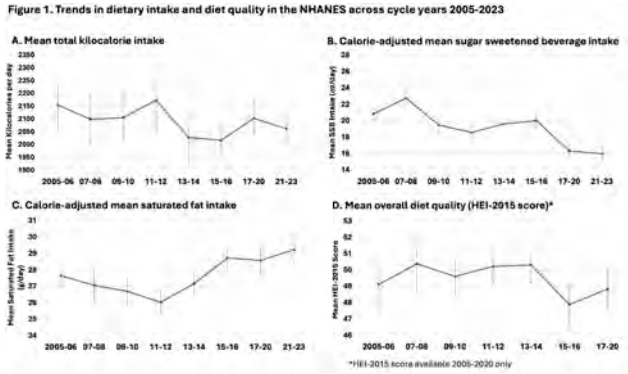
Ani Kardashian[1] Jennifer Dodge[1] Areny Tchalikian[1] Norah Terrault[1], [1]University of Southern California

Background: Poor diet quality (DQ) contributes to metabolic dysfunction-associated steatotic liver disease (MASLD); however contemporary trends in dietary intake and calorie sources are not established. Understanding trends is crucial to inform policies that

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improve DQ and MASLD-related health. **Methods:** We performed a serial cross-sectional analysis using 24-hour dietary recall data from the National Health and Nutrition Examination Survey cycles 2005-2023 in adults ≥20 years with MASLD. MASLD was defined as US Fatty Liver Index >30 and ≥1 cardiometabolic risk factor in the absence of other causes of steatosis or excessive alcohol use (>30 g/day in men, >20 g/day in women). Total caloric intake, sugar-sweetened beverages (SSBs), saturated fats, and calorie sources were assessed across cycle years. Saturated fats and SSBs were calorie-adjusted to minimize measurement error in dietary estimates. DQ was assessed overall by the Healthy Eating Index-2015 (HEI-2015; range 0-100; >74=optimal; available 2005-2020) and by 13 individual components (score range: 0-5 or 0-10 each, higher=better DQ) across cycle years. **Results:** Among 5,872 adults with MASLD, mean age was 53 years, 44% were female, 68% were non-Hispanic White/19% Hispanic, 56% were employed, 40% had public or no insurance, 13% were living in poverty, and 68% had low/32% no alcohol use. From 2005-06 to 2021-23, mean caloric intake decreased from 2,154 to 2,061 kcals (trend $p=0.08$; **Fig 1A**), mean SSBs decreased from 20.8oz to 16.0oz ($p<0.001$; **Fig 1B**), and mean saturated fats increased from 27.6g to 29.2g ($p=0.007$; **Fig 1C**); %kcals from grocery stores decreased (70% to 65%; $p<0.001$) and from fast food increased (11.7% to 13.4%; $p=0.03$). From 2005-06 to 2017-20, mean HEI-2015 was suboptimal and unchanged (49.1 vs 48.8, $p=0.13$; **Fig 1D**). Mean DQ scores worsened for total vegetables (3.3 to 2.9 out of 5, $p=0.001$), total fruits (2.0 to 1.9 out of 5, $p=0.048$), and total dairy (5.2 to 4.8 out of 10, $p=0.04$). There were no changes to whole fruits, whole or refined grains, total or sea/plant protein, fatty acids, sodium, or added sugars. **Conclusion:** From 2005 to 2023, adults with MASLD consumed fewer calories and SSBs. The decline in SSB consumption temporally correlates with the first explicit USDA Dietary Guideline recommendation in 2010 to restrict SSBs, suggesting federal guidance can serve as a powerful public health tool to influence dietary intake. However, overall DQ has remained suboptimal, with increases in saturated fats, decreases in vegetable, total fruit, and dairy intake, no improvement in added sugars, and a shift from grocery to fast food calorie sources. These findings highlight remaining critical gaps between guideline recommendations and real-world dietary behaviors in MASLD, underscoring the need for policy-level strategies to reduce added sugar and saturated fat intake – key MASLD contributors – and for the integration of nutrition interventions into routine hepatology care.



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2623 | LARGE REAL-WORLD GAPS IN NUTRITIONAL MONITORING BEFORE AND AFTER GLP-1 RECEPTOR AGONIST INITIATION IN MASLD/MASH

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Background: Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are increasingly used in patients with metabolic dysfunction-associated steatotic liver disease (MASLD/MASH). Joint advisory of professional societies recommended screening for micronutrient deficiencies, yet real-world surveillance practices remain poorly characterized. We evaluated patterns of nutritional laboratory monitoring before and after GLP-1RA initiation in patients with MASLD/MASH. **Methods:** We conducted a retrospective cohort study using the TriNetX US Collaborative Network (66 healthcare organizations). Adults aged $\geq$18 years with MASLD/MASH initiating GLP-1RA therapy between 2020 and 2026 were included. Patients with prior GLP-1RA exposure, bariatric endoscopy/surgery, Roux-en-Y gastric bypass, colectomy, small bowel resection, other chronic liver diseases, cirrhosis, hepatic decompensation, or alcohol-related disorders were excluded. Nutritional laboratory testing within 120 days before and 180 days after GLP-1RA initiation was assessed for cobalamin, thiamine, calcidiol, iron, ferritin, iron-binding capacity, folate, calcium, magnesium, zinc, albumin, and prealbumin. Analyses were stratified by sex and BMI category. Repeat testing after GLP-1RA initiation was evaluated among patients with baseline deficiencies. **Results:** Among 111,314 patients initiating GLP-1RA therapy (mean age 53.3 ± 13.8 years; 62.0% female), nutritional testing rates were low overall before and after treatment initiation across all sex and BMI subgroups. Calcium and albumin were the most frequently assessed markers (55.7% before vs 55.8% after initiation, and 50.1% before vs 49.2% after initiation), while thiamine, zinc, and prealbumin were rarely tested (<1%), followed by folate (2.6%) and calcidiol (4.2%). Iron-related testing modestly increased after GLP-1RA initiation, including iron (6.8% vs 7.4%), ferritin (6.9% vs 7.5%), and iron-binding capacity (5.9% vs 6.6%). Similar patterns were observed across sex and BMI strata. Among patients with documented baseline deficiencies, less than half had repeat testing for calcidiol (34.4%), iron (36.2%), ferritin (39.6%), iron-binding capacity (38.1%), folate (31.8%), magnesium (47.7%), zinc (27.2%), and prealbumin (32.1%) within 180 days after GLP-1RA initiation. Repeat testing was higher for calcium (76.2%) and albumin (68.8%) deficiencies, and near universal for cobalamin and thiamine deficiencies. **Conclusion:** Nutritional laboratory surveillance was infrequently performed before and after GLP-1RA initiation in patients with MASLD/MASH, regardless of sex or BMI subgroup. Many patients with established deficiencies also lacked follow-up monitoring after treatment initiation. These findings support the need for standardized monitoring strategies in patients receiving GLP-1RA therapy.

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2624 | GLUCAGON-LIKE PEPTIDE-1 (GLP-1) USE IS ASSOCIATED WITH REDUCTION OF HEPATIC STEATOSIS IN ADULTS WITH TYPE 2 DIABETES AND OBESITY

Shivaani Prakash[1] Jamie Dermon[1] Luke Sagers[1] Vincent La[2] Orit Wimpfheimer[3], [1]Dandelion Health, [2]Vincent La Consulting, [3]Nanox Vision

Background: Use of Glucagon-Like Peptide-1 Receptor Agonists (GLP-1s) has increased substantially among patients with type 2 diabetes (T2D) and/or obesity. Whether GLP-1 use affects progression of metabolic dysfunction-associated steatotic liver disease (MASLD) is less established. Changes in liver attenuation on CT, measured in Hounsfield Units (HU), have been shown to correlate with hepatic fat content, with increases indicating reductions in steatosis. We applied an AI-based algorithm to assess liver density in CT scans and evaluate changes in HUs among T2D and/or obese patients taking GLP-1s compared to matched controls, to understand the impact of GLP-1s on hepatic steatosis. **Methods:** The HealthFLD algorithm (Nanox AI) was applied retrospectively to patients within Dandelion Health (a longitudinal, multimodal clinical data platform) who (1) were diagnosed with T2D, obesity, or both; and (2) had at least 2 routine abdominal CT scans as part of clinical care, to quantify liver HUs per scan. Patients who initiated a GLP-1 after the first CT (N = 1,779) were in the treatment cohort, while those with no GLP-1 use at any time were in the control cohort (N = 19,970). Treatment and control patients were matched on baseline characteristics using propensity-score matching to create comparable groups. Difference-in-differences modeling assessed change in HUs pre- vs. post-GLP-1 initiation in the treatment cohort as compared to changes from the first (index) to second CT scan in the matched controls. Survival analyses assessed time to clinically meaningful increases in HUs (10+ units) in the treatment cohort among subgroups with T2D, obesity, or both. Within the treatment cohort, changes in A1C and BMI were assessed. **Results:** Difference-in-differences models showed a statistically significant increase in HUs (+5.5 units, $p < 0.05$) over time in the treatment cohort as compared to control patients, indicating a decrease in steatosis among GLP-1 users. Within the treatment cohort, median time to clinically significant increase in HUs was 746 days; at 1 year post GLP-1 initiation, 35% of the treatment cohort already showed this increase. Of the T2D-only subgroup, 43% achieved HU improvement by 24 months. The obesity-only and both-condition subgroups showed faster improvement, with 50-54% achieving 10+ unit increase in HUs by 24 months. Among GLP-1 users, statistically significant reductions in BMI and A1C were also observed pre vs. post GLP-1 initiation ($p < 0.01$), irrespective of magnitude of increase in HUs. **Conclusion:** T2D and obesity patients taking GLP-1s experienced reversal of MASLD as compared to matched controls. Half of GLP-1 patients achieved clinically meaningful improvement in liver density within 2 years of initiation. This study showcases a novel method

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using an AI-based algorithm to capture physiological outcomes from routine clinical imaging for use in real-world
studies, to assess a previously unquantified impact of GLP-1s.
Disclosures: Shivaani Prakash: Nothing to Disclose, Jamie Dermon: Nothing to Disclose, Luke Sagers: Nothing to Disclose, Vincent La: Nothing to Disclose, Orit Wimpfheimer: Nanox AI: Chief Medical Officer.

2625 | POOR AWARENESS OF FATTY LIVER DISEASE AMONG US PEOPLE WITH MASLD

Mindie Nguyen[1] Vy Nguyen[1] Bui Tam Chi Nguyen[1] Hong Fan[1] Xiaonan Su[1] Thanh Thuy Le[2], [1]Stanford University Medical Center, [2]Osaka Metropolitan University

Background: MASLD is the most common chronic liver disease globally and in the U.S., affecting about one in three Americans. However, prior studies suggested that only a small minority of people with non-alcoholic fatty liver disease, as defined by the U.S. Fatty Liver Index, were aware of having any liver disease. We evaluated the proportion of people who were aware of having a liver disease and more specifically "fatty liver" among a population-based cohort of participants with MASLD as defined by having hepatic steatosis and at least one metabolic dysfunction, with hepatic steatosis identified via Fibroscan. **Methods:** We conducted a cross-sectional analysis with MASLD from the National Health and Nutrition Examination Survey (NHANES) 2017-2023. MASLD was defined as controlled attenuation parameter (CAP) $\geq$263 dB/m, the presence of $\geq$1 cardiometabolic risk, and no significant alcohol use. Awareness was defined with a positive response ("yes") to a survey asking if the participant had ever been told she/he had fatty liver or any liver disease. All analyses were survey-weighted to estimate data representative of the general U.S. population. Multivariable logistic regression was performed adjusting for age, sex, race/ethnicity, birthplace, education, income-to-poverty ratio (IPR), insurance type, alcohol use, diabetes, hypertension, depression, hepatitis B, hepatitis C, liver stiffness, routine place for healthcare, and survey cycle. **Results:** Among 4,739 adults with MASLD with liver disease awareness data, 334 (6.2%) were aware of their diagnosis, including 128 (2.1%) reporting being aware of liver disease and 206 (4.1%) reporting being aware of fatty liver disease, while 4,405 (93.8%) were unaware of having any liver disease. On multivariable analyses, factors associated with lack of disease awareness included non-Hispanic Black race (vs White: aOR 5.53, $p<0.001$), absence of a routine place for healthcare (aOR 2.58, 95% CI 1.18–5.66; $p=0.021$), and higher income-to-poverty ratio (middle-income vs low-income group: aOR 1.70, 95% CI 1.12–2.58, $p=0.017$; high-income vs low-income group: aOR 1.90, 95% CI 1.10–3.28, $p=0.025$), while factors associated with less lack of awareness were liver comorbidities such as hepatitis C (aOR 0.07, 95% CI 0.02–0.18) and B infection (aOR 0.33, 95% CI 0.15–0.73), advanced liver fibrosis (LSM $\geq$12 kPa: aOR 0.32, 95% CI 0.20–0.50), and depression (aOR 0.52, 95% CI 0.32–0.85). **Conclusion:** Overall, 93.8% of the US adults with FibroScan-defined MASLD were unaware of their liver or fatty liver disease, with significant disparities by several demographic, socioeconomic, and clinical factors. Additional efforts are needed to improve screening, diagnosis, and disease awareness of people with MASLD, so appropriate evaluation and treatment can be implemented to prevent and curtail future MASLD-related medical morbidity and mortality.

***Table 1.** Characteristics of US Adults with MASLD by Disease Awareness Status, NHANES 2017–2023*

Characteristic	Overall (N = 4739)[1]	Aware (n = 334)[1]	Unaware (n = 4405)[1]	p-value[2]
Age, years	52.8 (16.3)	56.3 (13.3)	52.6 (16.4)	<0.001
Age group				<0.001
18-29	329 (10.0%)	11 (5.7%)	318 (10.3%)	
30-44	859 (22.3%)	37 (11.6%)	822 (23.0%)	
45-64	1,946 (40.5%)	174 (55.2%)	1,772 (39.6%)	
≥65	1,605 (27.2%)	112 (27.4%)	1,493 (27.1%)	
Sex				0.5
Male	2,419 (55.1%)	164 (52.2%)	2,255 (55.2%)	
Female	2,320 (44.9%)	170 (47.8%)	2,150 (44.8%)	
Race/Ethnicity				0.001
Non-Hispanic White	2,213 (62.1%)	156 (62.6%)	2,057 (62.1%)	
Non-Hispanic Black	789 (9.2%)	22 (2.8%)	767 (9.7%)	
Hispanic	998 (17.1%)	108 (23.3%)	890 (16.7%)	
Non-Hispanic Asian	354 (3.9%)	17 (2.2%)	337 (4.0%)	
Other	385 (7.6%)	31 (9.0%)	354 (7.5%)	
Birthplace				0.8
US-born	3,443 (79.4%)	231 (78.9%)	3,212 (79.5%)	
Foreign-born	1,294 (20.6%)	103 (21.1%)	1,191 (20.5%)	
Marital status				0.7
Married/partnered	2,808 (67.6%)	204 (65.6%)	2,604 (67.7%)	
Widowed/divorced/separated	1,147 (18.8%)	80 (19.2%)	1,067 (18.8%)	
Never married	685 (13.6%)	49 (15.2%)	636 (13.5%)	
Education				<0.001
Less than high school	1,875 (36.7%)	150 (52.3%)	1,725 (37.9%)	
High school graduate	1,536 (31.2%)	112 (29.4%)	1,418 (31.3%)	
Some college or above	1,326 (30.1%)	70 (18.3%)	1,256 (30.9%)	
Income-to-poverty ratio†				0.008
LIG — IPR ≤1	673 (13.0%)	72 (25.6%)	601 (12.1%)	
MIG — IPR 1–5	2,535 (60.2%)	177 (57.1%)	2,358 (60.4%)	
HIG — IPR ≥5	868 (26.9%)	62 (17.3%)	816 (27.5%)	

Disclosures: Mindie Nguyen: Pfizer, Astra Zeneca, Aligos, GSK, Delfi, Innogen, Exact Sci: Grant/Research Support, GSK: Advisor, Vy Nguyen: Nothing to Disclose, Bui Tam Chi Nguyen: Nothing to Disclose, Hong Fan: Nothing to Disclose, Xiaonan Su: Nothing to Disclose, Thanh Thuy Le: Nothing to Disclose.

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2626 | BEYOND STEATOSIS: CONCURRENT LIVER STIFFNESS ELEVATION IDENTIFIES A HIGH-RISK METABOLIC PROFILE

Vishant Vikram Rajkonwar[1] Sakshi Mahesh Taori[1] Vedant Bawa[1] Arjun Jayakumar[1] Kalyanram Naidu Botsa[1], [1]Sri Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu, India

Background: Transient elastography allows for the simultaneous assessment of liver stiffness and steatosis via Controlled Attenuation Parameter (CAP). Despite its growing clinical use, the metabolic correlates of combined hepatic steatosis and fibrosis remain incompletely characterised at the population level. Using a nationally representative U.S. adult population, we sought to identify distinct metabolic risk profiles using multimodal liver assessment. **Methods:** We analyzed NHANES 2017-2020 data in adults with valid liver assessments. We defined 'Elevated liver stiffness' as $\geq$8 kPa with IQR/median ratio $\leq$30% (reliable measurements only). Significant steatosis was defined as CAP $\geq$275 dB/m. We classified the participants into four groups: neither elevated, steatosis only, stiffness only, and both elevated. Survey-weighted prevalence estimates with bootstrapped 95% confidence intervals were calculated. Differences across groups were assessed using one way ANOVA and chi-square tests. Multivariable logistic regression helped us identify independent predictors of elevated liver stiffness. Large language model assistance (Claude, Anthropic) was used to improve readability and language of this abstract. **Results:** Among 8,318 adults, the survey weighted prevalence of elevated liver stiffness was 8.64%. Participants were classified as: neither (62.64%), steatosis only (35.1%), stiffness only (2.8%), and both elevated (7.25%). A stepwise metabolic gradient was observed: survey weighted mean BMI increased from 27.0 kg/m² (95% CI 26.7-27.2) in the neither group to 38.3 kg/m² (95% CI 37.5-39.1) in the both elevated group ($p < 0.0001$). Survey weighted diabetes prevalence followed the same pattern: 6.68% (95% CI 5.8-7.7%) in neither vs. 34.75% (95% CI 29.0-40.2%) in both elevated - a greater than 5 fold difference ($p < 0.0001$). On multivariable logistic regression, male sex (OR 1.93, 95% CI 1.65-2.26), diabetes (OR 2.06, 95% CI 1.73-2.46), and BMI (OR 1.10 per unit, 95% CI 1.09-1.11) were independent predictors of elevated liver stiffness (all $p < 0.0001$). **Conclusion:** Combined elastography based liver assessment identified a clinically distinct subgroup; those with concurrent steatosis and elevated stiffness; marked by substantially higher BMI and diabetes burden. These findings support population level screening strategies that incorporate both parameters to flag patients at greatest risk for progressive liver disease. **Disclosures:** Vishant Vikram Rajkonwar: Nothing to Disclose, Sakshi Mahesh Taori: Nothing to Disclose, Vedant Bawa: Nothing to Disclose, Arjun Jayakumar: Nothing to Disclose, Kalyanram Naidu Botsa: Nothing to Disclose.

2627 | LIVER FAT IN RELATION TO TOXICITIES OF CHEMOTHERAPY AMONG PATIENTS WITH STAGE II-III COLON CANCER

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Background: The liver is involved in metabolism of many chemotherapeutic drugs. Hence, accumulation of liver fat may impact chemotherapy toxicity and efficacy. So far, there are hardly any data on liver fat in relation to chemotherapy-induced toxicities. Here, we evaluated associations between the amount of liver fat at time of diagnosis and toxicity-induced treatment modifications for capecitabine and oxaliplatin among 350 patients with stage II-III colon cancer. **Methods:** We used data from the COLON study, a prospective cohort study conducted among adults newly diagnosed with colorectal cancer (CRC). Liver fat was assessed using contrast-enhanced portal phase CT-scans routinely taken at diagnosis and categorized according to sex-specific tertiles. Data on toxicity-induced treatment modifications (yes/no, and in which cycle) were collected via participants' medical records and included dose reductions, regimen switches, and early discontinuation of treatment. Cox proportional hazards regression analyses adjusted for age, sex, hospital, and starting chemotherapeutic doses, were used to obtain hazard ratios (HRs) and 95% confidence intervals (95%CIs). **Results:** In total, 350 patients who received adjuvant chemotherapy consisting of capecitabine with or without oxaliplatin, were included. Median (Q1-Q3) age of the study population was 64 (60-69) years at diagnosis, 39% (n = 138) were women, and 91% (n = 318) had stage III colon cancer. Most patients received capecitabine combined with oxaliplatin (CAPOX) (n = 301, 86%) whereas 14% (n = 49) received capecitabine monotherapy. Toxicity-induced modifications of treatment were observed in 82% (n = 248) of the patients receiving oxaliplatin, and

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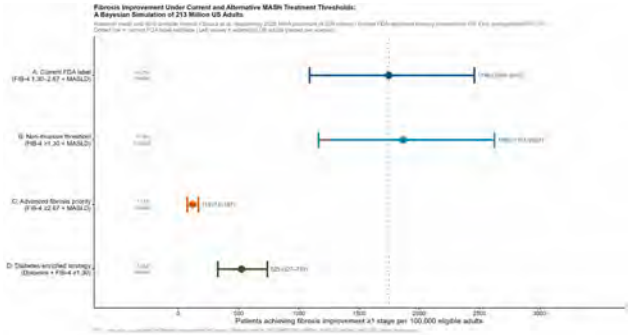
51% (n = 179) of the patients were not able to complete the capecitabine regimen as planned. More liver fat was associated with a lower risk of toxicity-induced treatment modifications for oxaliplatin (HR_{T3vsT1} 0.66, 95%CI 0.44-0.99), whereas the association was not significant for capecitabine (HR_{T3vsT1} 0.73, 95%CI 0.48-1.12). **Conclusion:** Liver fat is associated with a lower risk of oxaliplatin-related toxicities in patients with colon cancer. Further studies are needed to investigate liver fat in relation to oxaliplatin metabolism and exposure.

Disclosures: Deborah Ophoff: Nothing to Disclose, Nienke Zwart: Nothing to Disclose, Daniel Bos: Nothing to Disclose, N. Tjarda van Heek: Nothing to Disclose, Ben Witteman: Nothing to Disclose, Floor Lubberman: Nothing to Disclose, Henk van Halteren: Nothing to Disclose, Harm Westdorp: Nothing to Disclose, Renate Winkels: Nothing to Disclose, Fränzel van Duijnhoven: Nothing to Disclose, Edward Giovannucci: Nothing to Disclose, Ellen Kampman: Nothing to Disclose, Dieuwertje Kok: Nothing to Disclose.

2628 | THE MASH TREATMENT GAP; NATIONAL ESTIMATES OF ELIGIBILITY AND EXPECTED HISTOLOGIC RESPONSE TO FDA-APPROVED THERAPY: A BAYESIAN SIMULATION STUDY

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Background: Resmetirom and semaglutide received FDA approval in 2024 and 2025, respectively, for metabolic dysfunction- associated steatohepatitis (MASH) with moderate-to-advanced fibrosis. The population-level histological benefit of these drugs and the potential incremental gain from expanding diagnostic thresholds or adopting pipeline therapies has not been quantified at a national level. **Methods:** We conducted a Bayesian simulation using NHANES 2017-March 2020 data (n = 7,339 adults aged 18-75 representing ~213M US adults). MASLD was defined by the 2023 Delphi consensus criteria. FIB-4 was calculated from NHANES data. Treatment eligibility was modelled under 4 scenarios: (A) current FDA label (FIB-4 1.30-2.67 + MASLD); (B) non-invasive identification (FIB-4 ≥ 1.30 + MASLD); (C) advanced fibrosis priority (FIB-4 ≥ 2.67); and (D) diabetes-enriched strategy (diabetes + FIB-4 ≥ 1.30). Fibrosis improvement probabilities were derived from the Souza et al. Hepatology 2025 network meta-analysis (29 RCTs, n = 9,324), propagating 4,000 posterior draws of the pooled FDA-approved therapy risk ratio (RR 1.56; pooled resmetirom RR 1.64 and semaglutide RR 1.51 from Figure 3A) through the NHANES population. Survey weights were applied throughout. Drug-specific sensitivity analyses additionally modelled tirzepatide (RR 1.77) and pegozafermin (RR 3.46). **Results:** Approximately 104M US adults are diagnosed with MASLD. Under the current FDA label (Scenario A), an estimated 16.7M adults met treatment eligibility criteria. Applying pooled FDA-approved therapy, 1,746 (95% CI 1,089-2,457) adults per 100,000 eligible were projected to achieve ≥ 1-stage fibrosis improvement per treatment course, equivalent to approximately 291,000 Americans if all eligible patients received therapy. Expanding the diagnostic threshold to FIB-4 ≥ 1.30 (Scenario B) identified 17.8 million eligible adults and yielded 1,865 (1,163-2,624) improvers per 100,000, an additional 119 (74-167) per 100,000 beyond current labelling, with 100% posterior probability of benefit. A diabetes-enriched strategy (Scenario D; 5.0 million eligible) yielded 525 (327-739) improvers per 100,000, representing a more efficient strategy than advanced fibrosis prioritisation alone (Scenario C: 119 [74-167] per 100,000; 1.1 million eligible). Drug-specific sensitivity analyses showed directionally greater projected benefit with tirzepatide (+312/100,000 vs pooled FDA-approved therapy; CrI -639 to +1,515) and pegozafermin (+2,574/100,000; CrI -369 to +6,466), although uncertainty remained substantial. **Conclusion:** Approximately 16.7M US adults meet current FDA eligibility criteria for approved MASH pharmacotherapy, yet real-world treatment rates remain below 1%, representing one of the largest treatment gaps in hepatology. Expanding non-invasive diagnostic thresholds could capture an additional 1.1M eligible patients.



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2629 | IMPACT OF LONGITUDINAL HBA1C CHANGES ON LIVER FIBROSIS PROGRESSION AMONG GENERAL POPULATIONS WITH MASLD

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Background: While diabetes is a known driver of fibrosis in metabolic dysfunction-associated steatotic liver disease (MASLD), the prognostic value of short-term HbA1c dynamics remains unclear. We aimed to characterize the stage-specific longitudinal association between annual HbA1c trajectories and 5-year liver fibrosis progression in a general MASLD population. **Methods:** In this multicenter retrospective cohort study, 1,810 individuals with MASLD from physical examination centers of four Chinese hospitals (2017-2020) were followed for 5 years. Participants were stratified by baseline HbA1c (normoglycemia, prediabetes, and diabetes). Liver fibrosis progression was defined as a $\geq$30% relative increase in FIB-4 index over 5 years, and assessed the association with one-year HbA1c change. Landmark analysis, multivariable Cox regression, restricted cubic spline (RCS) were performed, with subgroup and sensitivity analyses. **Results:** Among 1,810 individuals with MASLD, 484 participants developed fibrosis progression. Baseline HbA1c was not associated with 5-year fibrosis progression in any glycemic stratum. Contrarily, 1-year HbA1c elevation was independently associated with higher risk of fibrosis progression in the prediabetes group (aHR = 1.77, 95% CI: 1.25–2.50, P < 0.01), with no significant association in normoglycemia or diabetes. RCS revealed a striking non-linear risk relationship, with risk sharply increasing beyond a 0.1% annual rise in HbA1c. The association was more pronounced in individuals aged < 65 years, males, and those with normal/overweight BMI in the prediabetes group, and remained robust across sensitivity analyses using stricter fibrosis definitions. **Conclusion:** Short-term HbA1c elevation identifies prediabetic individuals with MASLD at increased risk of accelerated fibrosis progression, highlighting prediabetes as a critical intervention window before irreversible liver injury.

Table 2. Associations Between HbA1c change categories and Subsequent Risk of Fibrosis Progression

HbA1c change	#Incidence(95% CI)	Events(N)	HR(95% CI)	P value	*aHR(95% CI)	P value
Total						
Stable	5.05 (4.41-5.75)	228 (938)	Reference		Reference	
Decrease	4.99 (3.55-6.82)	39 (159)	0.85 (0.61-1.2)	0.35	0.94 (0.67-1.32)	0.72
Increase	6.37 (5.55-7.28)	217 (713)	1.16 (0.97-1.4)	0.11	1.16 (0.96-1.40)	0.13
Normal						
Stable	5.54 (4.49-6.75)	98 (373)	Reference		Reference	
Decrease	5.96 (2.40-12.28)	7 (24)	0.87 (0.40-1.89)	0.73	1.22 (0.56-2.67)	0.62
Increase	5.24 (4.39-6.21)	134 (535)	0.88 (0.68-1.14)	0.33	0.89 (0.69-1.16)	0.40
Prediabetes						
Stable	4.13 (3.28-5.14)	80 (398)	Reference		Reference	
Decrease	3.69 (1.91-6.45)	12 (67)	0.85 (0.46-1.56)	0.60	1.01 (0.55-1.87)	0.97
Increase	7.99 (6.19-10.15)	67 (177)	1.90 (1.37-2.63)	<0.01	1.82 (1.31-2.53)	<0.01
Diabetes						
Stable	7.25 (4.64-10.78)	24 (68)	Reference		Reference	
Decrease	5.83 (3.70-8.75)	23 (79)	0.61 (0.34-1.09)	0.09	0.70 (0.38-1.28)	0.25
Increase	9.00 (6.40-12.30)	39 (89)	1.00 (0.60-1.66)	0.99	1.07 (0.63-1.81)	0.80

*Adjusted for age, gender, BMI, FIB4, hypertension and hyperlipidemia.

#Incidence rates are presented as the crude incidence rate per 100 person-years, with 95% confidence interval (CIs) in parentheses.

Abbreviations: CI, confidence interval; HR, hazard ratio; PY, person year; aHR, adjusted hazard ratio.

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2630 | RISK ALLELES AND THEIR ASSOCIATION WITH FIBROSIS PROGRESSION IN A HIGHLY DIVERSE URBAN POPULATION

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Background: The Mount Sinai Steatotic Liver Disease (SLD) registry and biobank, is a longitudinal study aimed at identifying real-world factors related to fibrosis progression and cardiac clinical outcomes. This study aims to assess demographic and clinical correlates and examine the association between risk allele carriage, fibrosis progression, and cardiac risk factors from baseline in a diverse SLD cohort. **Methods:** Patients with SLD seen for standard of care were enrolled. Demographics, fibrosis, comorbidities, and laboratory values were evaluated. Fibrosis was assessed using Fib-4 or Vibration Controlled Transient Elastography (VCTE) (F2: 8-10kPa; F3: 10-14kPa; F4: >14kPa). Previously enrolled patients from the BioMe® BioBank Program at Mount Sinai Hospital were fully genotyped, and the gene PNPLA3 was analyzed. **Results:** As of April 2026, 1163 patients were enrolled in the SLD registry, only 209 of them were co-enrolled in the BioMe BioBank Program, and only 199 had PNPLA3 gene genotyped. Among 199 participants with PNPLA3 genotyping (Table 1), 64 (32.2%) had no risk alleles (CC) and 135 (67.8%) carried at least one risk allele (CG/GG). The cohort was predominantly female (64.8%) with a mean age of 55.5 years (SD = 14.9), and no significant differences in age or sex between groups. Risk allele carriers were significantly more likely to be Hispanic (69.6% vs 40.6%, p < 0.001), while non-carriers included a higher proportion of non-Hispanic White individuals. Geographic distribution also differed significantly (risk allele more prevalent among South Americans(95%) than Caribbeans(70%) p < 0.001). Lipids and liver enzymes were largely similar, although triglycerides were higher among risk allele carriers (142.8 vs 120.7 mg/dL, p = 0.065). Among patients with longitudinal data (n = 65, cross-sectional models used the full cohort), median follow-up was 25 months. In multivariable logistic regression adjusted for age, sex, diabetes, BMI, and ethnicity, PNPLA3 risk allele was not associated with ALT-defined progression (OR 1.84, 95% CI 0.48–6.91, p = 0.37) or dyslipidemia at enrollment (OR 1.02, 95% CI 0.51–2.03, p = 0.948). When fibrosis progression was analyzed as a continuous variable, multivariable linear regression models adjusted for age, sex, diabetes, BMI, ethnicity, and follow-up duration (kPa models only) showed that PNPLA3 risk allele was not significantly associated

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with change in liver stiffness (β = 0.137, SE = 1.725, p = 0.937). PNPLA3 was also not associated with change in Fib-4 score over time (β = 0.397, SE = 1.854, p = 0.832). **Conclusion:** While PNPLA3 risk allele was significantly associated with demographic variation, no significant differences in fibrosis or metabolic markers were observed. Future work will focus on expanding the genetic scope of this analysis and exploring associations with cardiometabolic markers to better define the clinical impact of genetic risk in MASLD.

Table 1: *PNPLA3* cohort characteristics by risk allele presence and Multivariable Logistic Regression Analysis

PNPLA3 cohort characteristics by risk allele presence

Characteristic	Overall	CC (no risk)	CG/GG (any risk allele)	P-value
N	199	64	135	
Demographics				
Age (years, Mean, SD)	55.5 (14.9) [n=199]	57.7 (14.0) [n=64]	54.5 (15.2) [n=135]	0.160
Sex				0.343
Female	129 (64.8%)	38 (59.4%)	91 (67.4%)	
Male	70 (35.2%)	26 (40.6%)	44 (32.6%)	
Ethnicity				<0.001*
Hispanic or Latino	120 (60.3%)	26 (40.6%)	94 (69.6%)	
Not Hispanic or Latino	79 (39.7%)	38 (59.4%)	41 (30.4%)	
Race				<0.001*
White	53 (26.6%)	25 (39.1%)	28 (20.7%)	
Black or African Descent	19 (9.5%)	14 (21.9%)	5 (3.7%)	
Asian	8 (4.0%)	1 (1.6%)	7 (5.2%)	
American Indian or Alaska Native	2 (1.0%)	1 (1.6%)	1 (0.7%)	
Other	114 (57.3%)	22 (34.4%)	92 (68.1%)	
Unknown	3 (1.5%)	1 (1.6%)	2 (1.5%)	
Diversity Category				<0.001*
Asian alone, non-Hispanic	8 (4.0%)	1 (1.6%)	7 (5.2%)	
Black or African American alone, non-Hispanic	19 (9.5%)	14 (21.9%)	5 (3.7%)	
Hispanic	120 (60.3%)	26 (40.6%)	94 (69.6%)	
Multiracial, non-Hispanic	1 (0.5%)	1 (1.6%)	0 (0.0%)	
Some Other Race alone, non-Hispanic	13 (6.5%)	1 (1.6%)	12 (8.9%)	
White alone, non-Hispanic	38 (19.1%)	21 (32.8%)	17 (12.6%)	
Geographic Area				<0.001*
Caribbean	79 (39.7%)	23 (35.9%)	56 (41.5%)	
Central America	3 (1.5%)	2 (3.1%)	1 (0.7%)	
East Asia	6 (3.0%)	1 (1.6%)	5 (3.7%)	
European	1 (0.5%)	0 (0.0%)	1 (0.7%)	
North American	10 (5.0%)	0 (0.0%)	10 (7.4%)	
South American	20 (10.1%)	1 (1.6%)	19 (14.1%)	
South Asia	2 (1.0%)	0 (0.0%)	2 (1.5%)	
Unknown	78 (39.2%)	37 (57.8%)	41 (30.4%)	
Cohort				
ALD	5 (2.5%)	2 (3.1%)	3 (2.2%)	
MASLD	186 (93.5%)	59 (92.2%)	127 (94.1%)	
MetALD	8 (4.0%)	3 (4.7%)	5 (3.7%)	
Ambulatory Measures at enrollment /VCTE				
CAP (dB/m, Mean, SD)	296.3 (49.6) [n=188]	309.8 (50.2) [n=63]	294.5 (49.0) [n=125]	0.139
Liver Stiffness (kPa, Mean, SD)	9.8 (9.5) [n=188]	8.4 (6.3) [n=63]	10.6 (10.7) [n=125]	0.146
Steatosis (Mean, SD)	2.1 (1.0) [n=188]	2.1 (1.0) [n=63]	2.1 (1.0) [n=125]	0.998
Lipids				
LDL (mg/dL, Mean, SD)	92.9 (36.7) [n=156]	91.6 (29.7) [n=48]	93.4 (39.4) [n=110]	
HDL (mg/dL, Mean, SD)	48.3 (13.6) [n=173]	46.9 (12.6) [n=53]	48.9 (14.0) [n=120]	0.381
Total Cholesterol (mg/dL, Mean, SD)	167.6 (40.7) [n=189]	169.3 (34.8) [n=51]	167.3 (43.2) [n=118]	
Triglycerides (mg/dL, Mean, SD)	136.0 (71.0) [n=189]	129.7 (51.3) [n=52]	142.6 (76.5) [n=117]	0.885
Liver Enzymes & Labs				
AST (U/L, Mean, SD)	34.3 (21.3) [n=195]	33.2 (25.7) [n=62]	34.8 (19.0) [n=133]	0.625
ALT (U/L, Mean, SD)	38.7 (26.3) [n=155]	40.7 (30.6) [n=52]	37.7 (24.0) [n=103]	0.503
Platelets (10³/uL, Mean, SD)	227.3 (83.1) [n=186]	236.9 (68.7) [n=62]	222.5 (89.4) [n=124]	0.267

Linear Regression Analysis of PNPLA3 Risk Alleles and Clinical Outcomes, Including Fibrosis Progression and Dyslipidemia (adjusting for age, sex, diabetes, BMI, ethnicity, and VCTE follow-up duration)

Variable	Beta	SE	P value
PNPLA3 risk allele and fibrosis (kPa) progression rate (VCTE)	0.137	1.725	0.937
PNPLA3 risk allele and Fib 4 progression rate	0.059	1.920	0.976

Logistic Regression Analysis of PNPLA3 Risk Alleles and Clinical Outcomes, Including ALT Progression and Dyslipidemia (adjusting for age, sex, diabetes, BMI, ethnicity)

Variable	OR	95% CI	P value
PNPLA3 risk allele and ALT progression (>20% progression)	1.84	(0-6.6)	0.319
PNPLA3 risk allele and dyslipidemia at enrollment	1.02	(0.51-2.03)	0.948

Disclosures: Alejandra Paredes-Marin: Nothing to Disclose, Julia Napoli: Nothing to Disclose, Xiaotao Zhang: Nothing to Disclose, Meena Bansal: Madrigal: Advisor, Fibronostics: Advisor, NOVO Nordisk: Advisor, GSK: Advisor, Merck: Advisor, Boeheringer-Ingelheim: Advisor, Boston Pharma: Advisor, The Kinetix Group: Advisor, Corcept: Advisor.

2631 | THE ECONOMIC BURDEN OF PATIENTS WITH METABOLIC DYSFUNCTION ASSOCIATED STEATOHEPATITIS STRATIFIED BY BASELINE AND CHANGES IN FIB-4 INDEX

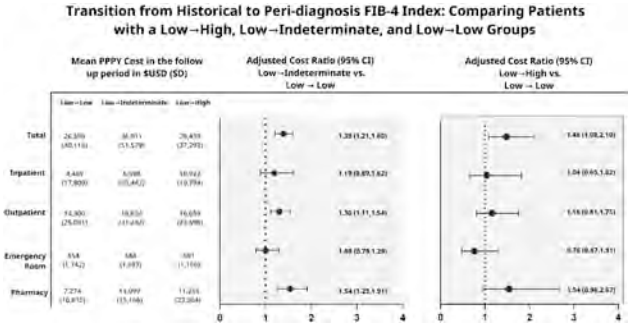
David Shi[1] Abdalla Aly[1] Guanghao Zhang[1] Andres Quintero[1] Husam Albarmawi[1] Hashem El-Serag[2], [1]Novo Nordisk, [2]Baylor College of Medicine

Background: Fibrosis stage is the strongest predictor of long-term liver-related outcomes in patients with metabolic dysfunction-associated steatohepatitis (MASH). This study aimed to assess the impact of baseline and serial changes in Fibrosis-4 (FIB-4) score on subsequent healthcare costs among patients with MASH. **Methods:** This retrospective cohort study used Komodo Healthcare Map™ data from Jan 2017 to Nov 2023. We included patients with MASH diagnosis (ICD-10 code: K75.81; index date) who were ≥35 years old, with ≥12 months of pre- and post-index medical enrollment, and ≥2 calculable FIB-4 results for both: 1) a historical FIB-4 in the 1-2 years prior to diagnosis (hx-FIB-4) and 2) a peri-diagnosis FIB-4 in the ±90-day window from diagnosis (dx-FIB-4). Patients with other liver diseases or decompensation events were excluded. Changes from baseline in all cause per patient per year (PPPY) total costs (i.e., inpatient, outpatient, emergency room, and pharmacy) to follow up were reported by dx-FIB-4 risk categories. Adjusted cost ratios (CRs) were estimated using generalized linear models, using low risk dx-FIB-4 scores (L; <1.3) as a baseline for comparison to indeterminate (I; 1.3-2.67) and high (H; >2.67) risk dx-FIB-4 scores, after adjusting for demographics, comorbidities, liver disease severity, and baseline resource use. Similar analyses compared patients transitioning from L→I and L→H to patients with a consistently low FIB-4 index (L→L). **Results:** The study sample included 4,739 patients (median follow up: 2.8 y, median age: 57 y, male: 60%, mean BMI: 33.2). The most common comorbidities were hyperlipidemia (74%), hypertension (71%), and type 2 diabetes (47%). Changes in PPPY costs from baseline to follow up were largest in the H dx-FIB-4 group (L: $5,535; I: $7,084; H: $9,267). In adjusted models predicting healthcare costs, relative to patients from the L dx-FIB-4 group, those with I and H dx-FIB-4 scores had healthcare costs that were higher by 21% (CR: 1.21; 95% CI (1.10 - 1.34) and 44% (CR: 1.44; 95% CI (1.26 - 1.67), respectively. In patients with a L hx-FIB-4 index (n=3,373), 82% were L→L, 16% were L→I, and 2.5% were L→H. In adjusted models, relative

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to the L→L group, the L→I and L→H groups had significantly higher healthcare costs (Figure). **Conclusion:** The economic burden is highest in patients with a high FIB-4 index at diagnosis. Similarly, compared to patients with a consistently low FIB-4 score, those with increased FIB-4 index had higher economic burden. Early detection is important to reduce advanced disease burden.

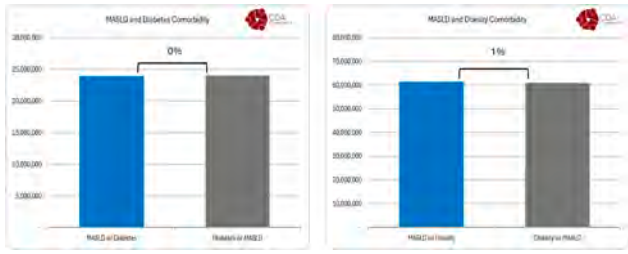


Disclosures: David Shi: Nothing to Disclose, Abdalla Aly: Novo Nordisk Incorporated: Employee, Novo Nordisk Incorporated: Stock - publicly traded company, Guanghao Zhang: Novo Nordisk Inc.: Employee, Andres Quintero: Novo Nordisk: Employee, Pfizer, Inc: Stock - publicly traded company, Viking Therapeutics: Stock - publicly traded company, Eli Lilly: Stock - publicly traded company, Husam Albarmawi: Novo Nordisk Inc.: Employee, Novo Nordisk Inc.: Stock - publicly traded company, Genentech Inc.: Employee, Genentech Inc.: Stock - publicly traded company, Hashem El-Serag: Nothing to Disclose, Nothing to Disclose.

2632 | THE PREVALENCE OF DIABETES AND OBESITY COMORBIDITIES IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) IN THE UNITED STATES IN 2025

Ty Wallace[1] Ivane Gamkrelidze[1] Homie Razavi[1] Carolyn Wallace[1], [1]Center for Disease Analysis Foundation

Background: It is well established that comorbidities, mainly diabetes and obesity, serve as indicators strongly correlated with metabolic dysfunction-associated steatotic liver disease (MASLD) and its outcomes, such as progression to liver cirrhosis, hepatocellular carcinoma, cardiovascular events, liver failure, and a myriad of other life-threatening complications. As MASLD continues to surge worldwide, a pressing need for frequent observation of the disease and its comorbidities has risen to the vanguard. As such, extensive studies have been conducted into the prevalence of both diabetes and obesity in smaller MASLD cohorts; insights for the national population, however, remain more limited. The objective of this analysis was to estimate the prevalence of diabetes and obesity within the MASLD population and compare it to an independent evaluation of the diabetes and obesity populations with MASLD in order to best produce a lucid picture of the current interplay of these comorbidities in the United States in 2025. **Methods:** We conducted a systematic literature review on the prevalence of MASLD, diabetes, and obesity. Large, nationally representative surveys were prioritized and supplemented with robust regional data where necessary. A Markov model was used to estimate the current prevalence of MASLD in the US adult population, and the portion with diabetes and obesity was calculated using empirical data. Separately, populations with diabetes and obesity and comorbid MASLD were calculated using published data. The forecasts were compared to validate the accuracy of the projections. **Results:** Our model estimated the comorbid population in the US in 2025 of MASLD and diabetes as 23,924,000 whereas our analysis of the diabetes population with MASLD yielded 24,031,700. Triangulating the comorbidity resulted in a difference of less than 0.5%. The model estimated the 2025 population of MASLD with obesity as 60,888,300 whereas our analysis of the obesity population with MASLD yielded 61,453,800, resulting in a difference of 1%. **Conclusion:** The use of modeling substantiated by real-world data provides a consensus of the current disease burden of MASLD and diabetes and MASLD and obesity and establishes a framework for public health discussion to facilitate best policies and practices for optimal screening, diagnosis, and management of MASLD. Effective implementation of strategies targeted to these comorbid populations will markedly benefit the growing disease burden and reduce the risks that later stages of MASLD impose, potentially serving as a paradigm for the global population.



Disclosures: Ty Wallace: Nothing to Disclose, Ivane Gamkrelidze: Nothing to Disclose, Homie Razavi: Nothing to Disclose, Carolyn Wallace: Nothing to Disclose.

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2633 | GENDER DISPARITIES IN MASLD SCREENING IN THE RURAL PRIMARY CARE SETTING

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Background: Primary care physicians in rural settings play a key role in early detection of Metabolic-Dysfunction Associated Steatotic Liver Disease (MASLD) through routine screening. The AASLD recommends screening high-risk patients for MASLD with calculation of FIB-4. Persistently elevated liver enzymes (>25U/L in women and >33U/L in men) can also be used as a surrogate marker in identifying MASLD and guiding management. MASLD is affecting patients at younger ages. ALT is particularly useful in patients younger than 35 years old for whom the FIB-4 score is less accurate. Many labs have higher thresholds for abnormal liver enzymes than the values defined by the AASLD. Women progress to cirrhosis sooner than men in established MASLD and MASLD is also the top cause of liver transplant in women. Gender disparities in screening tools and differing thresholds in local lab cutoffs may play a role in the poor identification of women with early MASLD. **Methods:** We conducted a retrospective, cross-sectional study in a single-center internal medicine residency primary care clinic in Western North Carolina to highlight gender disparities in high-risk patients affecting the identification of MASLD. Descriptive statistics were performed on average ALT and FIB-4 scores, and missed ALT separated by gender. Chi-square test was performed to compare differences in missed ALT percentages between men and women. A multivariable logistic regression was performed to evaluate the association between ALT status and gender and ethnicity. **Results:** 3458 individuals met inclusion criteria. 13% (272/2087) of women and 9% (125/1371) of men at high risk for MASLD had abnormal liver enzymes as defined by AASLD but were considered normal by local lab cutoffs. The proportion of missed ALT was significantly high among females compared to males ($\chi^2(1) = 9.99$, $p = 0.0016$). Mean FIB-4 scores were lower for females compared to males across all age groups (18-34: M = 0.53, F = 0.42; 35-64: M = 1.04, F = 0.90; 65+: M = 1.97, F = 1.73). A one-way ANOVA comparing FIB-4 across six age-matched sex groups revealed a statistically significant difference $F(5, 3353) = 235.19$, $p < 0.001$, $R^2 = 0.26$. Black race showed a trend toward lower odds of missed ALT, but this did not reach statistical significance (OR 0.62, 95% CI 0.38-1.01, $p = 0.055$). **Conclusion:** In our rural primary care clinic, we found women across all age groups and ethnicities were more likely than men to have abnormal liver enzymes despite appearing normal by local lab cutoffs. FIB-4 scores were not statistically different between men and women, which is consistent with the validation of FIB-4 cutoffs for both genders. Our study highlights that ALT cutoffs as a screening method can increase the likelihood of missing early MASLD, especially in women <35 years old where the FIB-4 is not as accurate. Our results highlight the importance of future studies focusing on creating and validating accurate screening methods for young patients.

Disclosures: Dana Cornwell: Nothing to Disclose, Jonathan Hong: Nothing to Disclose, Nancy Kubiak: Nothing to Disclose, Adrian Singson: Nothing to Disclose.

2634 | CIRRHOSIS IN FAMILIAL MEDITERRANEAN FEVER IS LINKED TO DISEASE SEVERITY AND METABOLIC RISK RATHER THAN COLCHICINE TOXICITY

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Background: FMF is an autosomal recessive disorder caused by mutations in the MEFV gene, which encodes pyrin, a key regulator of inflammatory pathways, including IL-1β. Although it primarily affects serosal membranes, systemic complications, such as AA amyloidosis, are common and may involve the kidneys, spleen, and liver. The specific causes of liver disease remain unclear. Possible contributors include long-term colchicine use and ongoing inflammation, which could lead to liver damage, including biochemical abnormalities, steatohepatitis, and cirrhosis. Our aim was to examine clinical, metabolic, inflammatory, and treatment-related factors linked to cirrhosis. **Methods:** We conducted a retrospective study of 150 FMF patients at a single center. We compared clinical features, metabolic conditions, inflammatory markers, genetic profiles, medications, and laboratory results between patients with and without cirrhosis. Propensity score matching was used to control for age, FMF severity, FMF mutation, diabetes, hypertension, and metabolic risk factors. The diagnostic performance of FIB-4 for detecting biopsy-confirmed cirrhosis and advanced fibrosis was evaluated using ROC analysis. **Results:** The median age was 58 years, and

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49% were men. Patients with cirrhosis were older (64 vs. 54 years, p < 0.001) and had more metabolic comorbidities, including hypertension (65% vs. 36%, p < 0. 001), diabetes (36.7% vs. 21.3%, p = 0.04), cardiovascular disease (38.3% vs. 21.3%, p = 0.024), renal failure (18.3% vs. 6.7%, p = 0.029), and proteinuria (40.7% vs. 24.7%, p = 0.04). Cirrhosis correlated with FMF severity (r = 0.242, p = 0.003), ESR (r = 0.346, p < 0.001), SAA (r = 0.313, p = 0.017), duration of colchicine therapy (r = 0.252, p = 0.002), and total colchicine dose (r = 0.176, p = 0.035). After propensity matching, only older age and FMF severity score were independently associated with cirrhosis, whereas colchicine exposure and FMF mutation status were not. IL-1 receptor antagonists were prescribed less often to cirrhotic patients (11% vs. 25%, p = 0.034). Those treated had significantly lower transaminase levels after treatment; however, FIB-4 scores did not change during a median follow-up of 4.5 years. Baseline FIB-4 score predicted biopsy-confirmed cirrhosis with an AUC of 0.846 (p < 0.001); a cutoff of 2.07 provided 89.5% sensitivity and 82.4% specificity. **Conclusion:** In FMF patients, cirrhosis is strongly linked to metabolic health issues, inflammation, and disease severity rather than colchicine exposure after adjusting for confounders. The FIB-4 score shows good diagnostic accuracy for detecting advanced liver disease in FMF and could be a useful non-invasive screening tool.

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2635 | PREVALENCE AND SEVERITY OF STEATOSIS AND FIBROSIS IN UNDIAGNOSED VERSUS DIAGNOSED DIABETES: A NATIONALLY REPRESENTATIVE ANALYSIS

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is common in Type 2 Diabetes (T2DM) and metabolic syndrome, increasing the risk of fibrosis and hepatocellular carcinoma. However, individuals with unrecognized insulin resistance or undiagnosed diabetes remain less characterized, even though current screening approaches largely focus on patients with established T2DM. This study used nationally representative data to quantify liver fibrosis burden in undiagnosed diabetes and evaluate FIB-4 performance compared with Vibration Controlled Transient Elastography (VCTE). **Methods:** We analyzed adults ≥18 years from the 2017–2020 NHANES with valid VCTE and complete diabetes status data. Participants were classified by HbA1c and self-reported diagnosis as No Diabetes, Pre-Diabetes, Undiagnosed Diabetes, or Diagnosed Diabetes; Undiagnosed Diabetes was HbA1c ≥ 6.5 without diagnosis.The primary outcome was VCTE-measured liver stiffness (LSM, kPa). Secondary outcomes were CAP score and FIB-4, calculated from age, AST, ALT, and platelets. Analyses used NHANES exam weights for national estimates. Multivariable linear regression assessed diabetes status and liver fibrosis, adjusting for age, sex, race/ethnicity, BMI, and waist circumference. Significance was p < 0.05. **Results:** Adults were stratified by diabetes status. Compared with the No Diabetes group, individuals with Undiagnosed Diabetes had higher BMI and waist circumference (34.3 kg/m² vs 27.8 kg/m²; 111.8 cm vs 94.6 cm; both p < 0.001). In fully adjusted models, liver stiffness was higher in the Undiagnosed group than the No Diabetes group (6.08 vs 5.00 kPa, p < 0.001) and was statistically similar to Diagnosed Diabetes (6.66 kPa, p = 0.07), suggesting comparable fibrosis burden. The Undiagnosed group also had the highest adjusted CAP score (288.7 vs 247.7 dB/m in No Diabetes, p < 0.001). Despite elevated stiffness and steatosis on VCTE, FIB-4 did not detect this risk; mean FIB-4 was not significantly different between the Undiagnosed and No Diabetes groups (1.15 vs 1.07, p = 0.17). **Conclusion:** Individuals with Undiagnosed Diabetes demonstrated a silent burden of liver fibrosis and steatosis, with higher adjusted liver stiffness than those without diabetes (6.08 vs 5.00 kPa, p < 0.001) and levels statistically similar to Diagnosed Diabetes (6.66 kPa, p = 0.07). This group also had the highest adjusted CAP score (288.7 vs 247.7 dB/m, p < 0.001) and the lowest proportion of Non-Hispanic White participants (44.8%), suggesting disproportionate risk among racial and ethnic minorities. Despite elevated VCTE-measured stiffness and steatosis, FIB-4 did not distinguish Undiagnosed Diabetes from No Diabetes (1.15 vs 1.07, p = 0.17), indicating that blood-based screening alone may miss fibrosis risk in this population. These findings

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support earlier VCTE screening among individuals with metabolic risk factors, regardless of formal diabetes diagnosis.

Table I Demographics

	No Diabetes	Pre-Diabetes	Undiagnosed Diabetes	Diagnosed Diabetes	Unknown	P value
Population (Weighted), (%)	175.2 million (54.4%)	52.4 million (16.2%)	5.5 million (1.7%)	28.4 million (8.8%)	60.9 million (18.9%)	—
Age (years)	38.9	54.6	57.1	60.5	12.1	< 0.001
Sex, n (%)						0.015
Male	83.8 million (47.9%)	25 million (47.8%)	2.30 million (41.9%)	15.5 million (55%)	30.9 million (50.7%)	—
Female	91.5 million (52.1%)	27.3 million (53.2%)	3.18 million (58.1%)	12.9 million (45%)	30.0 million (49.3%)	—
Race						<0.001
White	112 million (63.8)	29.6 million (56.5)	1.01 million (41.8)	17.1 million (60.3)	30.5 million (50.1)	—
Black	15.8 million (9.03)	8.86 million (16.9)	1.01 million (18.4)	3.58 million (12.6)	9.31 million (12.3)	—
Mexican	16.9 million (9.66)	4.19 million (8.00)	0.69 million (12.6)	2.66 million (9.36)	8.30 million (13.6)	—
Other Hispanic	14.3 million (9.66)	3.74 million (7.15)	0.63 million (11.4)	1.84 million (6.49)	5.69 million (9.35)	—
Asian	9.00 million (5.14)	3.75 million (7.15)	0.58 million (10.6)	1.68 million (5.92)	3.31 million (5.43)	—
Other	7.23 million (4.13)	2.21 million (4.23)	0.28 million (5.16)	1.52 million (5.35)	3.76 million (6.17)	—
Metabolic Factors						
BMI (kg/m^2)	27.8 (0.18)	31.2 (0.28)	34.4 (0.57)	32.9 (0.35)	—	—
Waist Circumference	93.6 (0.55)	104.7 (0.61)	111.8 (1.18)	111.1 (0.70)	—	—

Table II Primary Outcome – Liver Stiffness

Diabetes Status	Unadjusted Stiffness (kPa)	Adjusted Stiffness (kPa)†	P-Value (vs No Diabetes)
No Diabetes	5.29 (0.10)	5.00 (0.07)	Reference
Pre-Diabetes	6.29 (0.11)	5.43 (0.13)	< 0.001
Undiagnosed	7.40 (0.24)	6.08 (0.21)	< 0.001
Diagnosed	7.90 (0.31)	6.66 (0.25)	< 0.001

† **Adjusted Model:** Least squares mean are adjusted for **age** (continuous), **sex** (male/female), **race/ethnicity** (non-Hispanic White; non-Hispanic Black, Mexican American, Other Hispanic, Asian, Other), **BMI** (continuous), and **waist circumference** (continuous).

Table III Secondary Outcomes

	No Diabetes	Pre-Diabetes	Undiagnosed Diabetes	Diagnosed Diabetes
Liver Fat (CAP)				
Unadjusted	245.2 (1.59)	279.6 (2.27)	319.1 (5.27)	306.4 (3.06)
p – values	Reference	(p < 0.001)	(p < 0.001)	(p < 0.001)
Adjusted†	247.7 (1.26)	265.4 (1.85)	288.7 (3.59)	285.4 (2.36)
p – values	Reference	(p = 0.003)	(p < 0.001)	(p < 0.001)
FIB-4 scores				
Unadjusted‡	1.07 (0.02)	1.18 (0.02)	1.15 (0.05)	1.25 (0.03)
p – values	Reference	(p < 0.001)	(p = 0.17)	(p < 0.001)

Legend: *Values are Mean (Standard Error). P-values compare each group to the "No Diabetes" reference.* † ***Adjusted:*** *Controlled for Age, Sex, Race, BMI, and Waist Circumference.* ‡ ***Unadjusted:*** *FIB-4 is not adjusted for covariates because Age is a component of the score itself.*

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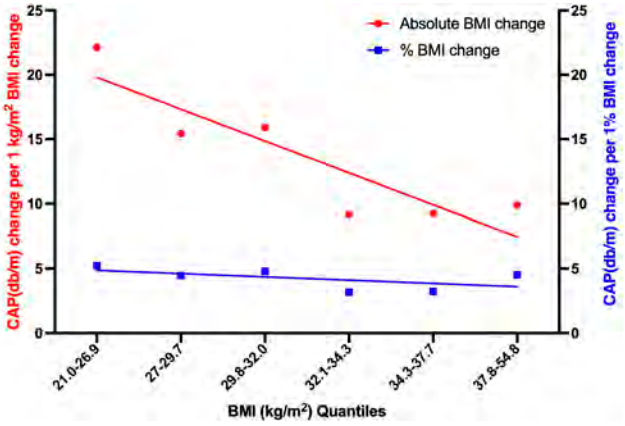
2636 | KILOGRAMS OR PERCENTAGE? WEIGHT LOSS METRICS IN MASLD

Sawsan Fathma[1] Harish Gopalakrishna[2] Natarajan Ravendhran[3] Yaron Rotman[4], [1]National Institutes of Health, [2]UTMB, [3]johns hopkins school of medicine, [4]National Institute of Diabetes and Digestive and Kidney Diseases; National Institutes of Health

Background: Metabolic dysfunction-associated steatotic liver disease is a leading cause of chronic liver disease impacting 30-40% of the general adult population globally. Weight loss is the primary intervention for MASLD and leads to improvement of hepatic steatosis, steatohepatitis and fibrosis. Weight loss recommendations in MASLD are typically geared towards a relative change (e.g. losing 5%) but it is unclear whether this is more relevant than an absolute change, especially at the extreme ends of baseline weight distribution. We aimed to determine whether percent weight change is a superior predictor of improvement in hepatic steatosis compared with absolute body mass index (BMI) reduction in patients with MASLD. **Methods:** We conducted a two-center retrospective cross-sectional study of 284 patients who underwent at least two FibroScan assessments with paired controlled attenuation parameter (CAP) and BMI measurements, with no pharmacological intervention between them. Weight loss was evaluated as both absolute BMI change (DBMI) and percent BMI change (%DBMI). Patients were stratified into six quantiles based on baseline BMI. The primary outcome was change in CAP as a surrogate for change in liver fat content. Linear regression analyses were performed to evaluate the association between weight loss metrics and changes in CAP values within each quantile. **Results:** Among 284 patients with MASLD, the median age was 63 years, 151/284 (53.2%) were female, median BMI was 32.1 kg/m^2 (range 21-54.8) and median CAP 318 dB/m (range 133-400). Median interval between VCTE tests was 287 days and 43.3% had significant fibrosis (TE > 8kPa). DBMI and %DBMI were similarly and linearly associated with improvement in CAP values across the entire cohort ($r = 0.28$ and 0.30, respectively, $p < 0.0001$ for both). To evaluate whether CAP response to changes in DBMI or %DBMI differed according to weight category, participants were stratified into six quantiles of baseline BMI. The effect of absolute BMI change on liver fat varied across BMI quantiles, with a diminishing effect at higher weight ranges. A decrease of 1kg/m^2 led to a 22.1db/m CAP decrease in the lowest BMI quantile but only 9.9dB/m in the highest quantile (p for trend < 0.01). In contrast, the effect of %DBMI on liver fat change remained remarkably consistent across all BMI quantiles, with similar slopes observed across groups (5.3-3.2 dB/m per 1% change, p = ns). **Conclusion:** Our findings suggest that relative weight change is a more physiological driver of liver fat reduction across the spectrum of baseline weights compared to absolute change. These findings support the use of percent weight loss targets when counseling patients with MASLD and monitoring therapeutic response.

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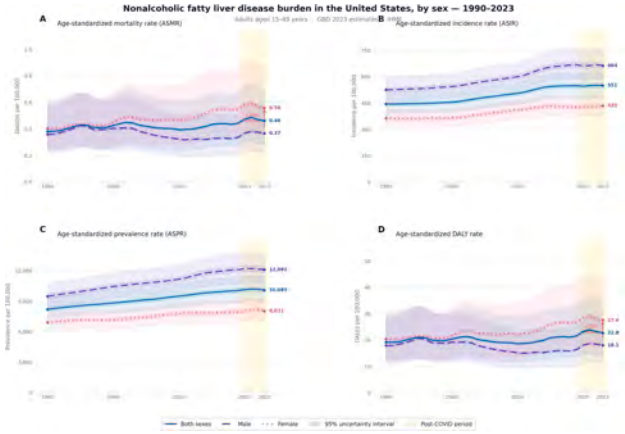


Disclosures: Sawsan Fathma: Nothing to Disclose, Harish Gopalakrishna: Nothing to Disclose, Natarajan Ravendhran: Nothing to Disclose, Yaron Rotman: Nothing to Disclose.

2637 | METABOLIC LIVER DISEASE ON THE RISE: A GBD 2023 ANALYSIS OF MASLD BURDEN BY SEX AMONG US ADULTS AGED 15–49, 1990–2023

Mohammed Y. Youssef[1] Mohamed Eldesouki[2] EzzElDien A. Ibrahim[3] Hazem Abosheaishaa[4] Ahmed Salem[5] Sufiyan kamal[6] Ehab Faheid[1] Sherif Elhanafi[7], [1]Hunt Regional Medical Center, [2]New York Medical College at Saint Michael Medical Center, [3]University of Missouri-Columbia, [4]Brookly Hospital Center, [5]Gastroenterology and Hepatology Department Cleveland Clinic Florida Weston FL, [6]Internal Medicine Department, The University of Texas at Tyler Health Science Center, [7]Gastroenterology Division, The University of Texas at Tyler School of Medicine

Background: Nonalcoholic fatty liver disease (NAFLD), including its advanced manifestation as cirrhosis, is the most rapidly growing cause of chronic liver disease globally. Among working-age adults, NAFLD carries substantial implications for long-term hepatic and metabolic outcomes. This study aims to assess epidemiological trends and burden of NAFLD in the United States from 1990 to 2023 among individuals aged 15–49 years using the Global Burden of Disease (GBD) 2023 dataset. **Methods:** We assessed GBD 2023 estimates for the United States restricted to the 15–49 year age group from 1990–2023. Age-standardized incidence rates (ASIR), age-standardized prevalence rates (ASPR), age-standardized mortality rates (ASMR), and age-standardized disability-adjusted life year (DALY) rates per 100,000 population were analyzed by sex (male, female, both). Corresponding 95% uncertainty intervals (UIs) were obtained directly from the GBD database. **Results:** From 1990 to 2023, the ASMR for NAFLD among adults aged 15–49 years increased from 0.38 (95% UI: 0.24–0.59) to 0.46 (0.29–0.70) per 100,000. Among males, ASMR remained stable from 0.36 (0.22–0.57) to 0.37 (0.23–0.56) per 100,000, whereas in females it rose substantially from 0.40 (0.25–0.62) to 0.56 (0.35–0.88) per 100,000. ASIR increased markedly overall from 445.37 (387.57–508.91) to 550.84 (479.09–628.23) per 100,000, with male incidence rising from 526.17 (461.50–600.27) to 663.77 (583.84–757.48) and female incidence from 364.24 (313.91–416.02) to 434.82 (372.26–497.17) per 100,000. ASPR increased from 8196.58 (7244.61–9323.14) to 10088.60 (8841.63–11493.31) per 100,000 overall, with males rising from 9478.34 (8404.36–10792.29) to 12091.70 (10668.64–13727.69) and females from 6909.69 (6075.07–7831.47) to 8030.63 (6962.58–9177.68) per 100,000. DALY rates increased overall from 19.19 (11.95–29.52) to 22.76 (14.20–34.49) per 100,000, driven predominantly by a rise among females from 20.45 (12.79–30.98) to 27.57 (17.57–42.90) per 100,000, while male DALY rates remained nearly unchanged at 17.94 (11.10–28.35) to 18.07 (11.28–27.70) per 100,000. **Conclusion:** The burden of NAFLD among working-age Americans aged 15–49 years has increased substantially over three decades across all four burden metrics, with incidence and prevalence rising in parallel with the obesity and metabolic syndrome epidemics. Strikingly, the female-specific increases in ASMR and DALY rates, with male mortality essentially flat, suggest a feminizing shift in NAFLD-related disease burden in this age group, possibly reflecting hormonal transitions, reproductive-age metabolic changes, or differential rates of progression to advanced fibrosis. These findings underscore the urgent need for metabolic risk screening, early NAFLD identification, and sex-informed prevention strategies among working-age populations.



Disclosures: Mohammed Y. Youssef: Nothing to Disclose, Mohamed Eldesouki: Nothing to Disclose, EzzElDien A. Ibrahim: Nothing to Disclose, Hazem Abosheaishaa: Nothing to Disclose, Ahmed Salem: Nothing to Disclose, Sufiyan kamal: Nothing to

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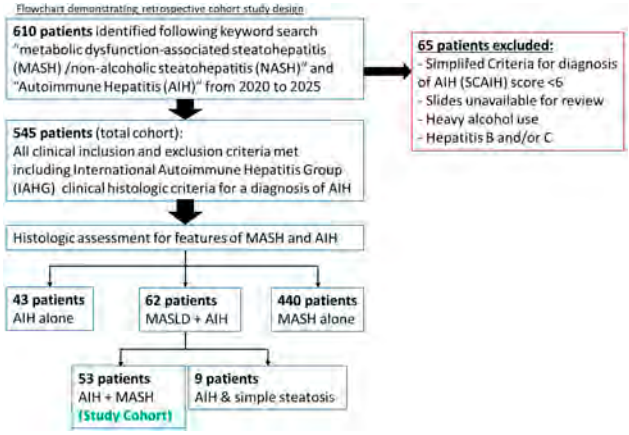
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2638 | LOOKING BEYOND PLASMA CELLS: CLINICAL AND HISTOPATHOLOGIC CHARACTERISTICS OF OVERLAPPING AUTOIMMUNE HEPATITIS (AIH) IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH)

Radhika Sekhri[1] Brent Sterling[1] Krutika Patel[1], [1]Vanderbilt University Medical Center

Background: Metabolic dysfunction-associated steatohepatitis (MASH) is a common cause of chronically elevated liver enzymes. A "biopsy-all" approach is neither appropriate nor applicable due to associated patient morbidity, and costs. MASH and autoimmune hepatitis (AIH) can have similar laboratory and histologic findings. In this clinicopathologic study, we aimed to elucidate the morphologic features of AIH, in patients with MASH. **Methods:** After IRB (Institutional Review Board) approval, we identified MASH and AIH cases in our clinical and pathology laboratory archives from 2020 to 2025. Demographic, serologic, biochemical, and histologic details were recorded. **Results:** We identified 610 patients with keyword search "MASH (or prior diagnosis of Non-alcoholic Steatohepatitis, NASH) and AIH" (Figure 1). 53 patients with concomitant features of MASH and AIH were identified (study cohort). Median age was 55 years with female predominance (85%, $P = 0.03$). Most patients showed increase in serum transaminases. ANA was positive in 79.4% patients. F-Actin was positive in 50% patients. 55% patients have a NAS score ≥ 5 with mild to moderate steatosis, ballooning, Mallory's hyaline, with moderate to severe lobular inflammation. Of the features suggestive of concomitant AIH, most prominent were portal inflammation ($P = 0.025$; mild 53% patients, moderate 38% patients, and severe 9% patients), interface activity ($P = 0.021$, 77% patients), lobular necroinflammatory activity ($P = 0.048$, 55% patients). Equivalent results were observed when accounting for other morphologic features of AIH like clustered plasma cells, acidophil bodies, multinucleation, emperipolesis, and cellular rosettes. Bridging fibrosis or cirrhosis was noted in 63% patients. Most patients responded to corticosteroids or azathioprine therapy. **Conclusion:** The prevalence of overlapping autoimmune hepatitis on index biopsy in patients with metabolic dysfunction-associated steatohepatitis is common. Morphologic features like moderate to severe portal inflammation, interface activity, and lobular necro-inflammatory activity should alert the pathologists to raise a possibility of an overlapping autoimmune hepatitis (AIH) in metabolic dysfunction-associated steatohepatitis (MASH) patients, even in the absence of serologic suspicion or lack of clustered plasma cells on histomorphology.



Disclosures: Radhika Sekhri: Nothing to Disclose, Brent Sterling: Nothing to Disclose, Krutika Patel: Nothing to Disclose.

2639 | ◆ PRECLINICAL EFFICACY OF A PHASE 2-READY ASK1 INHIBITOR, SRT-015, TO TREAT BILIARY ATRESIA

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Background: Biliary atresia (BA) lacks effective pharmacotherapy despite identification of multiple relevant injury pathways and experimental interventions. We investigated signatures of apoptosis signal-regulating kinase 1 (ASK1), an oxidative stress-responsive MAP kinase, in human BA and determined efficacy of SRT-015, a phase 2-ready ASK1 inhibitor, to prevent bile duct atresia and liver pathology in neonatal experimental BA. **Methods:** ASK1-linked pathways were analyzed in RNA-seq and proteomic datasets from normal control (NC) and BA patient liver and serum specimens, patient liver cholangiocyte organoids (NCO/BACO), and murine BA liver RNA-seq. Liver sections from BA patients and murine model were stained for ASK1, p-ASK1, p38, and p-p38 and quantified by mean fluorescence intensity (MFI). Newborn mice received i.p. 0.9% saline or $1.2x10^6$ ffu rhesus rotavirus (RRV) to induce BA, followed by daily vehicle or SRT-015 (10 or 20 mg/kg) treatment. Serum ALT, AST, ALP, total/direct bilirubin, hepatic and organoid qPCR, intrahepatic immune cells by flow cytometry, and H&E/Sirius Red histology were assessed. **Results:** Human BA liver/organoids and experimental BA liver RNA-seq showed increased ASK1-linked

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p38 (*MAPK11/12/13*), JNK (*MAPK9/10*), *CASP1*, *CCL2*, *CXCL3/5/6/8*, *CTGF*, *SPP1*, and *TNF* expression (1.5-15-fold; $P \leq 0.01$). BA livers at diagnosis and experimental BA showed enhanced cholangiocyte and immune-cell MFI for ASK1, p-ASK1, p38, and p-p38 (BA 259 ± 35 vs NC 83 ± 23; $P \leq 0.001$). To test whether ASK1 biology regulates duct atresia, portal inflammation, and biliary fibrosis in vivo, RRV-infected mice were treated daily with SRT-015 or vehicle. SRT-015 treatment reduced jaundice (23% vs 100% in controls) and acholic stools (15% vs 93%) and increased survival (100% vs 12%). Vehicle-treated mice developed segmental extrahepatic duct atresia, cystic malformation, intrahepatic portal inflammation, and biliary fibrosis; SRT-015 prevented duct atresia, maintained luminal continuity and bile flow (100% vs 0%), and attenuated portal inflammation and fibrosis. SRT-015 significantly improved liver biochemistry, decreasing ALT (74 ± 11 vs 164 ± 21), AST (244 ± 88 vs 783 ± 126), ALP (596 ± 159 vs 2170 ± 573), total (1.6 ± 0.6 vs 17 ± 3), and direct bilirubin (3 ± 1 vs 12 ± 2; all $P \leq 0.0001$). SRT-015 also reduced target-engagement transcripts (*Map3k5*, *Map2k3/4/7*, *Mapk13/14*), apoptotic markers (*Casp1/3/4*), and inflammatory markers (*Il1*β, *Tnf*α; $P \leq 0.01$). Flow cytometry showed fewer hepatic $CD45^+$ $COL1A1^+$ fibrocytes, $CD11b^+$ $F4/80^+$ macrophages, plasmacytoid DCs, and activated $TCR\gamma\delta^+$ T cells ($P \leq 0.001$). **Conclusion:** ASK1 is activated in human and experimental BA. SRT-015 improved survival, attenuated MAPK-driven cholestatic injury, inflammation, and apoptosis, while preserving biliary architecture, luminal continuity, and bile flow. These findings support clinical evaluation of ASK1 inhibition as a disease-modifying therapy for BA.

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2640 | ◆ 4-LAYER PARALLEL CIRCUIT AI (HEX + ΔE2000 + LOGISTIC REGRESSION + CNN) WITH HYBRID MEDICAL DECISION ENGINE NAMED LIVERPOOP MOBILE APPLICATION ACHIEVES 100% SENSITIVITY FOR NEONATAL ACHOLIC STOOL WITH GLOBAL OUTREACH: 12-CENTER STARD VALIDATION

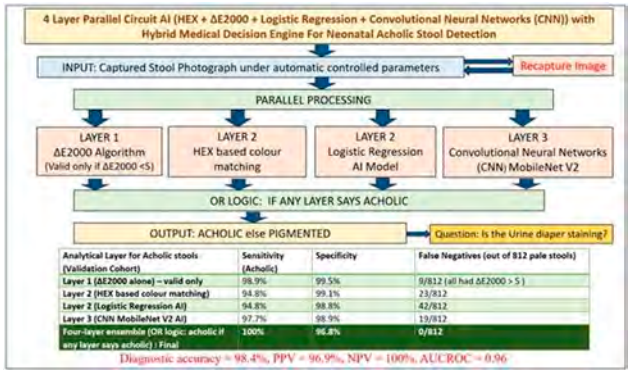
Piyush Upadhyay[1] Ritwik Dixit[1] Manisha Verma[2] Pankaj Kumar[3] Vipul Gautam[4] Aniket Deshmukh[5] Rizwan Ahmar[6] Arya Suchismita[7] Ishaq Maliq[8] Pranab Dey[9] Asritha A[10] Aashay Shah[11] Kalpana Panda[12], [1]Department of pediatrics, Dr RML INSTITUTE OF MEDICAL SCIENCES, [2]Department of Pediatrics, KGMU, Lucknow, [3]Department of Pediatrics, SNMC, Agra, [4]CLBS, Max Hospital, Saket, New Delhi, [5]Grant Medical College, Mumbai and Nanvati Max Hospital, Mumbai, [6]IGIMS, Patna, [7]Jai Prabha Medanta Super Speciality Hospital, Patna, [8]Government Medical College, Srinagar, [9]R.G. Kar Medical College, Kolkata, [10]Aster Hospitals, Bangalore, [11]Prism Pediatric Gastro centre, Ahemdabad, [12]IMS and SUM Hospital, Bhubneshwar

Background: Biliary atresiaBA) is fatal without timely Kasai. Paper stool cards miss up to 24% of cases & require huge logistics. We built a failsafe four-layer parallel Artificial Intelligence(AI) assisted Hybrid Medical Decision Engine(HMDE) using OR logic, with output as ACHOLIC if any layer says ACHOLIC. **Methods:** STARD-compliant, prospective consecutive enrolment of healthy newborns & BA patients across 12 Indian centres. Derivation cohort (used to build the mobile app): 7,247 captured images(6235 images of Pigmented stools and 1012 images of pale stools of biopsy proven cases of BA). Validation Cohort (12centres): 1,936 captured images (1124 images of Pigmented stools and 824 images of pale stools of biopsy proven cases of BA). The backend(python & the Flask web framework) did image preprocessing and normalization to reduce device & environmental variability. Four parallel layers for catching acholic stool colour includes: LAB-ΔE2000(CIEDE2000, valid only if <5), HEX based colour matching, logistic regression AI model, MobileNet V2 Convolutional Neural Networks (CNNs). HMDE integrates: Result is acholic stool if any of the layer detects it as acholic(Parallel circuit). Final step is a question on diaper staining urine an additional feature to also catch neonatal cholestasis disorders where stool is pigmented. **Results:** In the validation cohort, individual layer sensitivities for acholic stool were: Layer 1 (ΔE2000) sensitivity 98.9%, specificity 99.5% (9 false negatives, all $\Delta E2000 \geq 5$). Layer 2 (HEX) sensitivity 97.2%, specificity 99.1%. Layer 3 (logistic regression) sensitivity 94.8%, specificity 98.8% (42 false negatives). Layer 4 (CNN) sensitivity 97.7%, specificity 98.9%. Four-layer HMDE OR logic had a perfect 100% sensitivity (0/812 false negatives) . Final ensemble specificity was 96.8% (95% CI: 95.7–97.7%) , false-positive rate 3.2% , diagnostic accuracy 98.4%, PPV 96.9%, NPV 100%, AUROC 0.96. Critically, all cases with $\Delta E2000 \geq 5$ (borderline colorimetric matches) were successfully rescued by the other analytical layers (Figure 1). **Conclusion:** LiverPoop Mobile application, a 4-layer parallel circuit AI with HMDE achieves unprecedented

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100% sensitivity for acholic stool detection across 12 centres. Zero missed acholic stool cases. The 3.2% false-positive rate is clinically justified to prevent BA. This 40-language (including languages of almost all low and medium income countries-LMIC of the world where implementation of paper based stool chart is near to impossible), cloud-based system with sharable results and already free to download (zero logistics) for usage is ready for global population-wide screening. This mobile application will not only narrow the gap between developed and developing LMIC countries in accessing the heathcare services but also reduce logistics significantlyeven in the developed part of the world, which can be utiliszed for the liver transplant in the diagnosed patients later.



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★ 2641 | LONGITUDINAL URINARY METABOLOMIC PROFILING FOLLOWING KASAI PORTOENTEROSTOMY IN INFANTS WITH BILIARY ATRESIA

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Background: Urinary metabolomic profiling offers a a non-invasive tool to characterise disease-associated metabolic alterations in liver disease and cirrhosis. However its application in biliary atresia (BA) remains poorly defined. We aimed to characterise longitudinal urinary metabolomic changes in infants with BA following Kasai portoenterostomy (KPE) and evaluate clinical and prognostic outcomes including native liver survival at 12 months. **Methods:** Nineteen infants with BA undergoing intraoperative cholangiogram and KPE were prospectively enrolled at a quaternary paediatric liver centre. Urine and blood samples were collected at baseline prior to KPE (n = 11) and at 6 weeks (n = 15) and 6 months (n = 16) post-KPE. Samples from age-matched infants with non-BA cholestasis served as controls (n = 16). Metabolomic profiling was performed using liquid chromatography–mass spectrometry (LC-MS). Clinical and biochemical outcomes were assessed longitudinally. Multivariate modelling was performed using orthogonal partial least squares discriminant analysis (OPLS-DA). **Results:** Median age at KPE was 50 days (range 22–127) and 57% male. By 6 months post-KPE, 36% required liver transplantation (LT). At baseline, no urinary metabolomic signature discriminated BA from non-BA cholestasis, and no baseline metabolomic profile predicted subsequent jaundice clearance or need for LT. However, at 6 weeks post-KPE, a distinct urinary metabolomic signature emerged, characterised by elevated aromatic amino acids, acylcarnitines, and kynurenine, which was associated with subsequent LT ($Q^2 = 0.54$, $p = 0.02$). At this timepoint, Claudin-3 demonstrated a strong negative association with urinary symmetric dimethylarginine (SDMA), an amino acid derivative ($Q^2 = 0.75$, $p = 0.02$). By 6 months, infants requiring LT exhibited a metabolomic profile characterised by increased serotonin, long-chain acylcarnitines, trans-4-hydroxyproline, and persistent dysregulation of amino acid and lipid metabolism ($Q^2 = 0.61$, $p = 0.01$). **Conclusion:** Urinary metabolomic profiling may provide a non-invasive approach for identifying dynamic metabolic alterations in children with BA in the early post-KPE period. Increased urinary kynurenine, aromatic amino acids, and acylcarnitines are associated with poor native liver survival and may represent novel prognostic or mechanistic biomarkers in BA. Claudin-3, a hepatic and intestinal tight junction protein recently linked to poor BA outcomes, was associated with early circulating metabolomic alterations, further supporting its potential as an emerging biomarker. These findings are being validated in a larger cohort.

Disclosures: Elizabeth Wimborne: Nothing to Disclose, Jonathan Swann: Nothing to Disclose, Emma Alexander: Nothing to Disclose, Charlotte Burford:

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Nothing to Disclose, Mark McPhail: Nothing to Disclose, Antonio Riva: Nothing to Disclose, Mark Davenport: Ipsen Ltd: Advisor, Anil Dhawan: Bit Bio: Consultant, Aspect Bio: Consultant, Astellas: Consultant, Univar: Advisor, Orphalan: Advisor, Vandana Jain: Nothing to Disclose.

2642 | POST-NATAL CYP2C70-DEFICIENT MICE DEVELOP TRANSIENT SEVERE CHOLESTATIC LIVER INJURY ASSOCIATED WITH EARLY HEPATIC BILE ACID ACCUMULATION AND UPR ACTIVATION

Ryan Shaw[1] Saul Karpen[2] Paul Dawson[3] Brian LeCuyer[4] Richard Green[1] Alyssa Kriegermeier[4], [1]Northwestern Feinberg School of Medicine, [2]VCU Stravitz-Sanyal Institute for Liver Disease and Metabolic Health, [3]Emory University, [4]Ann and Robert H. Lurie Children's Hospital of Chicago

Background: Cholestatic liver diseases are the leading indication for pediatric liver transplantation and lack therapies addressing disease progression. Toxic bile acid (BA) accumulation drives hepatic injury, ER stress, and the unfolded protein response (UPR). Our prior work showed that impaired hepatic XBP1 and UPR mediator expression contributes to neonatal liver injury, but traditional murine cholestasis models are limited by their hydrophilic BA pool. We used Cyp2c70 knockout (KO) mice, which possess a human-like hydrophobic BA profile, to investigate age-dependent ER stress, injury, and UPR activation in the post-natal period. **Methods:** Female Cyp2c70 KO and heterozygous control mice were assessed at 10 days, 16 days, 18 days, 21 days, and 8 weeks of age. Serum liver chemistries were measured and hepatic BAs quantified by LC-MS. Bulk hepatic RNA-seq was performed, with key ileal targets by qPCR. Data were compared by Welch's t-test or one-way ANOVA; $p < 0.05$ was considered significant. **Results:** At 10 days of age, serum ALT, ALP, and BAs in KO mice were similar to controls. Injury emerged at 16–18 days; ALT peaked at 21 days (4161 ± 1813 vs 37.5 ± 20 U/L) and lessened by 8 weeks (346 ± 157 vs 42 ± 11 U/L). Serum BAs were elevated at 21 days (> 700 vs < 5 µmol/L) and 8 weeks (38 ± 18 vs < 5 µmol/L). Hepatic TCDCA peaked at 21 days and remained elevated through 8 weeks, correlating with ALT. RNA-seq revealed a hepatic stress response at 21 days: induction of PERK/ATF4 (Atf4, Atf3, Ddit3) and IRE1/XBP1 (Xbp1, Hspa5, Dnajc10) arms, downregulation of BA homeostasis networks, and sustained upregulation of acute-phase reactants (Saa1, Saa2) and ductular marker Spp1 through 8 weeks. Ileal Asbt and Ibabp mRNA were nearly undetectable at day 10 and rose by 21 days in both genotypes, indicating normal developmental induction coincident with peak hepatic injury. **Conclusion:** Cyp2c70 KO mice, with a humanized hydrophobic BA pool, develop post-natal hepatic BA accumulation and age-dependent cholestatic liver injury that is most severe at 21 days and improves by 8 weeks. This is accompanied by PERK/ATF4 and IRE1/XBP1 UPR pathway activation and downregulation of BA homeostasis gene networks at 21 days, followed by a sustained acute-phase and ductular-reaction signature through 8 weeks. Notably, peak hepatic injury coincides with normal post-weaning maturation of ileal BA-uptake transporters, suggesting a developmentally timed surge in enterohepatic return of hydrophobic BAs imposes an acute burden on an immature hepatic BA-handling and UPR network. Improvement by 8 weeks parallels maturation of these hepatic defense pathways. Together, these findings define a hepatically driven phenotype of transient post-natal cholestatic injury within a developmentally vulnerable window, with relevance to neonatal- and infantile-onset pediatric cholestatic liver diseases, and identify the immature hepatic UPR and BA homeostasis network as a candidate therapeutic target.
Disclosures: Ryan Shaw: Nothing to Disclose, Saul Karpen: Albireo/Ipsen: Consultant, Mirum: Consultant, Intercept: Consultant, Paul Dawson: Nothing to Disclose, Brian LeCuyer: Nothing to Disclose, Richard Green: Mirum Pharmaceuticals: Advisor, Alyssa Kriegermeier: Mirum Pharmaceuticals: Advisor.

2643 | PARENTERAL NUTRITION AND STARVATION SPECIFIC EFFECTS ON CIRCADIAN TRANSCRIPTION FACTOR EXPRESSION ALONG THE GUT LIVER AXIS

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Background: We have developed a mouse model of Parenteral Nutrition Associated cholestasis (PNAC) in which total PN (TPN) infusion results in biochemical and immunohistochemical liver injury which is associated with discordant expression of circadian transcription factors between the ileum and liver. However, it is not clear if the effect of TPN is because of the lack of nutrition in the GI tract or due to other factors. The aim of this study was to examine the effect of 2-day PN compared to starvation on expression of ileal and hepatic circadian regulatory (CR) genes, Fxr signaling and bile acid homeostasis. **Methods:** WT adult C57/B6 mice were fed Chow alone, NPO except

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for water (Starvation), or continuous soy oil lipid emulsion-based TPN (water was provided ad libitum, no enteral nutrition) through a central venous catheter for 2 days. On d2, mice were sacrificed at 7AM, and serum, ileal and hepatic tissue obtained. **Results:** Administration of 2d PN had no effect on hepatic injury. Compared to Chow fed controls, PN suppressed hepatic mRNA expression of *Cyp7a1, Cyp7b1, Cyp8b1* and *Cyp27a1*, whereas starvation only suppressed *Cyp7a1, Cyp7b1* and *Cyp27a1*. PN had no effect on hepatic mRNA expression of *Nr0b2* (Shp), *Abcc2* (Mrp2) or *Nr1h4* (Fxr) but did significantly increase *Abcb11* (Bsep). Starvation significantly suppressed *Nr0b2, Abcb11* and *Nr1h4* mRNA expression. Examining hepatic circadian transcription factor expression, PN significantly increased *Nr1d1* (Reverba), *Per1, Per2, Dbp, Bhlhe41* (Dec2) and suppressed *Arntl* (Bmal), whereas starvation significantly increased *Nr1d1* and *Per1* but suppressed *Arntl*, *Nr1f1* (Rora), *Nfil3, Bhlhe40* (Dec1) and *Bhlhe41*. In the ileum , PN increased expression of *Nr1d1* and *Nr1f1* but suppressed *Arntl, Cry1, and Bhlhe40*. Starvation significantly increased ileal *Dbp* and *Cry2* and suppressed *Nr1d1, Arntl, Clock, Cry1,* and *Bhlhe41*. PN administration significantly induced increased expression of FXR target genes *Fgf15, Nr0b2, Slc51a* (OSTa) and suppressed of *Slc10a2* (ASBT) whereas starvation had no effect. **Conclusion:** These data indicate that the effect of TPN on ileal and hepatic circadian gene expression is likely not related to the nutritional status of TPN mice. In the liver as well as the ileum, data support specific circadian regulatory genes that are regulated independent of nutritional status. In addition, short term PN is sufficient to activate ileal FXR thereby suppressing hepatic bile acid synthesis in the liver through Fgf15 signaling.

Disclosures: Colin Shearn: Nothing to Disclose, Aimee Anderson: Nothing to Disclose, Michael Devereaux: Nothing to Disclose, Ronald Sokol: Mirum: Advisor, Ipsen/Albireo: Advisor, Malinkrodt: Consultant, Alexion: Consultant, ProQR: Consultant.

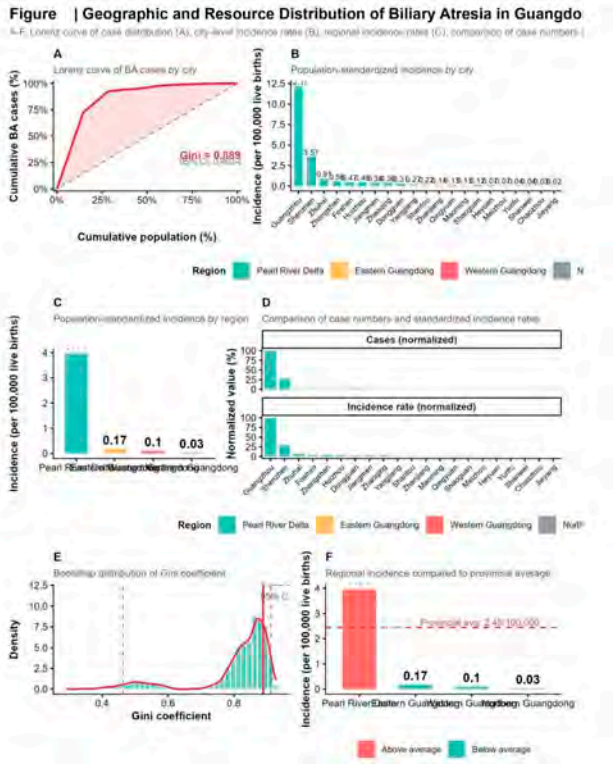
2644 | INEQUALITY IN HEALTHCARE ACCESS AND DISEASE BURDEN OF BILIARY ATRESIA IN SOUTHERN CHINA: A 12-YEAR MULTICENTER RETROSPECTIVE STUDY

Hanshi Zeng[1] Paul KH Tam[1] Yan Chen[1], [1]Macau University of Science and Technology

Background: Biliary atresia (BA) is a rare, progressive fibro-obliterative disease of the extrahepatic bile ducts in infants. Early surgical intervention is central to improving prognosis. Due to the uneven spatial distribution of healthcare resources, the potential role of socioeconomic disparities in the early detection of BA and healthcare utilization remains unclear. Using Guangdong Province (covering a population of 128.59 million) as the study area, this study systematically describes the epidemiological characteristics of BA in southern China and explores disparities in healthcare utilization across populations with different socioeconomic statuses. **Methods:** A multicenter retrospective cohort study of BA infants aged < 1 year was conducted in Guangdong Province from 2012 to 2024. The apparent population-based incidence was calculated. The Gini coefficient was used to assess the inequality of case distribution and healthcare resource allocation. The observed-to-expected (O/E) ratio was calculated to analyze the distribution of cases across regions with different economic levels. Multivariate logistic regression was used to identify factors associated with delayed surgery (> 60 days), and a Gamma regression model was employed to evaluate factors influencing hospitalization costs. **Results:** A total of 3,345 children were enrolled. The apparent incidence of BA was 22.42 per 100,000 live births. Cases showed significant clustering in high-economic-level areas (O/E = 2.02), while the number of cases in medium- and low-economic-level areas was lower than expected (O/E < 1). Both case distribution and healthcare resource allocation were highly unequal, with Gini coefficients of 0.855 and 0.886, respectively. Year of hospital admission was significantly associated with a reduced risk of surgical delay (OR = 0.91, 95% CI: 0.88–0.94), whereas socioeconomic level showed no independent association. Hospitalization costs were closely related to regional socioeconomic level, hospital tier, and length of hospital stay. **Conclusion:** The concentration of BA cases in high-socioeconomic areas more likely reflects disparities in healthcare accessibility and an imbalanced referral system rather than true differences in disease incidence. This study confirms significant inequality in healthcare utilization for BA. There is an urgent need to strengthen early diagnostic capacity for BA and establish a tiered referral system in underdeveloped regions to narrow healthcare disparities.

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Disclosures: Hanshi Zeng: Nothing to Disclose, Paul KH Tam: Nothing to Disclose, Yan Chen: Nothing to Disclose.

2645 | RESULTS OF AN INTERNATIONAL SURVEY DESCRIBING THE HUMANISTIC AND ECONOMIC IMPACT OF BILIARY ATRESIA ON PATIENTS AND THEIR CAREGIVERS

Emmanuelle Kaltenbach[1] Maria Mercadal-Hally[2] Elisa De Carvalho[3] Laure Dorey[4] Jennifer Lau[5] Michelle Wilkins[6] Lorraine Munetsi[7] Bethany Franks[7] Laura Francis[1] Shikha Sundaram[8], [1]Ipsen, London, UK, [2]University Hospital Vall d'Hebron, Barcelona, Spain, [3]Universidade do Distrito Federal, Brasília Childrens' Hospital, Brasília, Brazil, [4]Association Maladies du Foie depuis l'Enfance (AMFE), Paris, France, [5]Biliary Atresia Research & Education (BARE), New York, [6]Liver UK, Winchester, UK, [7]HCD Economics, Worcester, UK, [8]Digestive Health Institute, Department of Pediatrics, University of Colorado School of Medicine, CO,

Background: Complications from progressive liver damage and eventual liver transplant (LT) are devastating and have a profound impact on the lives of patients with biliary atresia (BA) and their caregivers. Published data on the burden of BA are scarce, and further research is needed to capture the disease-specific multidimensional impacts. We conducted an international survey of physicians, patients, and caregivers to describe and quantify the clinical, humanistic, and economic burden of BA; initial results are reported herein. **Methods:** Descriptive, retrospective, cross-sectional, and independent physician, patient, and caregiver surveys were conducted across Australia, Brazil, Canada, Denmark, France, Germany, Italy, Japan, the Netherlands, Poland, South Korea, Spain, Sweden, the UK, and US. Physician surveys collected data on patient symptoms, tests, consultations, medications, comorbidities, and hospitalizations. Patient surveys (≥18 years old) collected data on health-related quality of life (HRQoL; EQ-5D-5L), out-of-pocket costs related to disease management, and impact of disease on employment or education. Caregiver surveys collected data on HRQoL (self, and of the child they care for [proxy]; EQ-5D-5L), out-of-pocket costs related to disease management, and impact of disease (on their employment/education and on their child's education). Data were collected over 12 months for 4 cohorts, depending on disease stage: patients without LT/Kasai HPE in the past 5 years (data collected in the 12 months prior to survey); patients with Kasai HPE in the past 5 years (data collected in the 12 months post-Kasai HPE); and patients with LT in the past 5 years (data collected in the 6 months either pre-LT or post-LT). **Results:** At data cutoff (April 27, 2026), initial results were available from the US and UK. Questionnaires were collected from 47 caregivers (20 US + 27 UK; mean [SD] age, 40.2 [5.8] years]) and 6 UK patients (mean [SD] age, 19.8 [2.1] years). Mean (SD) EQ-5D-5L scores were lower for US/UK caregivers (index: US 0.74 [0.30], UK 0.76 [0.28]; visual analog scale [VAS]: US 73.5 [16.0], UK 67.8 [17.7]) and for UK patients (index: 0.75 [0.11]; VAS: 69.3 [13.3]) than the general population (index: US 0.86, UK 0.90–0.91; VAS: US 78.1–84.9, UK 73.8–86.8). A negative impact of BA on work was reported by caregivers, with 40.6% changing the number of hours they worked regularly. Twenty-two US clinicians and 7 UK clinicians completed 84 questionnaires (60 US + 24 UK) and clinical results are presented (**Table)**. **Conclusion:** Initial survey results from the US and UK indicate that BA adversely affects patient and caregiver QoL, potentially linked to the numerous symptoms and complications experienced by patients independent of their disease stage. BA also has a negative impact on caregiver work. Survey results for the rest of the world, as well as the economic impact of the disease,

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will be presented.

Table. Clinical burden of BA – Combined responses from the US and UK clinicians

	No LT or Kasai HPE in past 5 years (12 months prior to survey) n=60	Kasai HPE in past 5 years (12 months post-Kasai HPE) n=37	LT in past 5 years	
			6 months pre-LT n=17	6 months post-LT n=15
Mean age, years (SD)	12.9 (7.3)	2.8 (1.4)	4.3 (1.9)	4.7 (1.7)
Age at LT (years), n (%)				
0-4	NA		16 (94)	
5-7			1 (6)	
Symptoms experienced in ≥30% of patients in any cohort, n (%)*				
Jaundice	14 (46.7)	13 (35.1)	14 (82.4)	2 (13.3)
Cholestatic pruritus	21 (70.0)	10 (27.0)	6 (35.3)	1 (6.7)
Growth retardation and/or poor weight gain	9 (30.0)	21 (56.8)	11 (64.7)	1 (6.7)
Malnutrition & fat-soluble vitamin deficiencies	11 (36.7)	10 (27.0)	13 (76.5)	8 (53.3)
Abdominal pain	18 (60.0)	9 (24.3)	7 (41.2)	5 (33.3)
Feeding intolerance (vomiting or discomfort after feeds)	3 (10.0)	7 (18.9)	5 (29.4)	5 (33.3)
BA-related complications in ≥30% of patients in any cohort, n (%)*				
None	6 (20.0)	5 (13.5)	0 (0.0)	6 (40.0)
Fat-soluble vitamin deficiencies	13 (43.3)	11 (29.7)	12 (70.6)	5 (33.3)
Cholangitis	12 (40.0)	12 (32.4)	5 (29.4)	1 (6.7)
Hepatomegaly	6 (20.0)	11 (29.7)	12 (70.6)	1 (6.7)
Fibrosis	10 (33.3)	10 (27.0)	3 (17.6)	NA
Portal hypertension	11 (36.7)	1 (2.7)	4 (23.5)	0 (0.0)
Ascites	2 (6.7)	2 (5.4)	9 (52.9)	1 (6.7)
Splenomegaly	10 (33.3)	5 (13.5)	1 (5.9)	1 (6.7)
In-patient time related to BA				
Patients hospitalized, n (%)	15 (50.0)	21 (56.8)	10 (58.8)	0 (0.0)
Length of stay (days), median	1 ()	5 ()	2 ()	0 ()
Reason for hospitalization, n (%)*	N=15	N=21	N=10	N=0
Cholangitis	10 (66.7)	17 (81.0)	6 (60.0)	NA
Other infections	2 (13.3)	7 (33.3)	0 (0.0)	NA
Liver-related complications (excluding cholangitis)	1 (6.7)	0 (0.0)	4 (40.0)	NA
Nutritional/metabolic issues	2 (13.3)	7 (33.3)	2 (20.0)	NA

*Multiple responses permitted.
Abbreviations: BA, biliary atresia; HPE, hepatoportoenterostomy; LT, liver transplant; SD, standard deviation.

Disclosures: EMMANUELLE KALTENBACH: Nothing to Disclose, Maria Mercadal-Hally: IPSEN: Speaking and Teaching, MIRUM: Speaking and Teaching, ALEXION: TRAVEL AND MEETING SUPPORT, Elisa De Carvalho: Nothing to Disclose, Laure Dorey: Mirum Pharmaceuticals and Ipsen: No personal financial relationships. In my role as Director, Jennifer Lau: Nothing to Disclose, Michelle Wilkins: Nothing to Disclose, Lorraine Munetsi: Nothing to Disclose, Bethany Franks: Ipsen: Independent Contractor, LAURA FRANCIS: Nothing to Disclose, Shikha Sundaram: Nothing to Disclose.

2646 | CHANGING SOCIOECONOMIC PATTERNS IN BILIARY ATRESIA (BA): A MULTICENTER RETROSPECTIVE STUDY OF 1082 PATIENTS ACROSS THE COVID-19 PANDEMIC

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Background: Biliary atresia (BA) is a rare, fibro-obliterative disease of the extrahepatic biliary tree that requires timely surgical intervention with a Kasai Portoenterostomy (KP). Despite global disruptions to healthcare access during the COVID-19 pandemic, epidemiological studies of BA have not demonstrated delays in time to KP. We aimed to examine socioeconomic shifts in BA patient demographics that occurred across pre-, peri-, and post-COVID-19 pandemic eras. **Methods:** This is a retrospective analysis of BA patients who underwent KP between 2016–2024 using the Pediatric Health Information System database. Patient-level factors included age at diagnosis, sex, gestational age at birth, race, and ethnicity. Socioeconomic factors included payor type, median household income by census tract (deflated to 2024 dollars and analyzed in quartiles), and child opportunity index. Geographic variables included U.S. census region, urban versus rural residence, and distance to treating hospital. The cohort was stratified into three era-based groups including pre-pandemic era (2016-2019), pandemic (2020-2021), and the post-pandemic era (2022-2024), to examine temporal trends in demographics. **Results:** Amongst 1,082 BA patients who underwent KP, median household income distribution and Child Opportunity Index (COI) demonstrated significant shifts across pandemic eras (p = 0.008 and p < 0.001, respectively). Pre-pandemic (2016–2019), 29.3% (n = 151) of patients were from the lowest income quartile ($0–$58,791). The proportion of patients from this group declined to 18.5% (n = 41) during the pandemic and remained low at 20.3% (n = 58) in the post-pandemic period (2022–2024). In contrast, representation from the highest income quartile ($78,866+) increased from 23.8% (n = 123) pre-pandemic to 28.8% (n = 64) during the pandemic and 31.1% (n = 89) post-pandemic. The COI distribution showed notable shifts across pandemic eras (p < 0.001). Pre-pandemic (2016–2019), 26.3% (n = 135) of the patients came from "Very Low" opportunity neighborhoods. During the pandemic era (2020-2021), this proportion dropped to 18.6% (n = 41) with return to similar proportion in the post-pandemic era with 23.5% (n = 53) from very low COI. Conversely, the "High" and "Very High" COI categories combined increased to 38% (n = 86) during the pandemic era from 34.8% (n = 179) pre- and 35.4% (n = 80) post-pandemic eras. **Conclusion:** The proportion of BA patients from lower median household groups and lower COI decreased during the pandemic and post-pandemic era compared to pre-pandemic era. Vulnerable populations may have been underdiagnosed during the pandemic. Further research should be done on patients with delayed care or missed diagnoses during this time to explore barriers to care.

Select Variables of Biliary Atresia Patients Undergoing Kasai Portoenterostomy during Pre (2016-2019), Peri (2020-2021), and Post (2022-2024) COVID 19 Pandemic Eras

Variables	2016-2019 n = 516	2020-2021 n = 222	2022-2024 n = 344	p-value
Age at first BA diagnosis (days)	55 [37,75]	51 [29,70]	54 [32,72]	0.056
Gestational Age (weeks)	39 [37,40]	38 [37,39]	39 [36,39]	0.22
Race/Ethnicity				0.538
Non-Hispanic White	231 (44.8)	95 (42.8)	158 (45.9)	
Non-Hispanic Black	90 (17.4)	36 (16.2)	55 (16.0)	
Hispanic	101 (19.6)	52 (23.4)	76 (22.1)	
Asian	42 (8.1)	19 (8.6)	16 (4.7)	
Other	52 (10.1)	20 (9.0)	39 (11.3)	
Child Opportunity Index				<0.001
Very Low	135 (26.3)	41 (18.6)	53 (23.5)	
Low	111 (21.6)	51 (23.1)	44 (19.5)	
Moderate	89 (17.3)	43 (19.5)	49 (21.7)	
High	92 (17.9)	42 (19.0)	46 (20.4)	
Very High	87 (16.9)	44 (19.9)	34 (15.0)	
Median Household Income				0.008
$0-$58,791	151 (29.3)	41 (18.5)	58 (20.3)	
$58,792-$45,999	131 (25.4)	57 (25.7)	65 (22.7)	
$46,000-$78,865	111 (21.5)	60 (27)	74 (25.9)	
$76,866+	123 (23.8)	64 (28.8)	89 (31.1)	

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Disclosures: Elise Kang: Nothing to Disclose, Pooja Reddy Spector: Nothing to Disclose, Mercedes Martinez: Mirium: Grant/Research Support, Ipsen: Grant/Research Support, Mirum: Grant/Research Support.

2647 | THIOREDOXIN REDUCTASE 1 REGULATES THE NUCLEOTIDE BINDING OLIGOMERIZATION DOMAIN CONTAINING 2-RECEPTOR INTERACTING SERINE/THREONINE KINASE 2 SIGNALING PATHWAY DURING CHOLESTATIC LIVER INJURY

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Background: The cholestatic liver disease primary sclerosing cholangitis (PSC), is characterized by periportal inflammation with progression to hepatic fibrosis and ultimately cirrhosis. Bacterial PAMPs have been shown to activate the Nucleotide Binding Oligomerization Domain Containing 2- Receptor Interacting Serine/Threonine Kinase 2 (Nod2-Ripk2) intracellular inflammatory signaling pathway in the intestine. Approximately 80% of PSC patients have an additional diagnosis of Crohn's disease, increasing the susceptibility of the liver to exposure of bacterial Pathogen-Associated Molecular Patterns (PAMPs) originating from the intestine. We have recently shown that Thioredoxin Reductase (TrxR1) signaling plays an important role in regulation of inflammation during cholestasis. The objective of this study was to determine if Nod2-Ripk2 signaling is upregulated in PSC and to examine the impact of pharmacological and genetic targeting of TrxR1 on Nod2-Ripk2 signaling in cell culture and a murine model of cholestatic liver injury. **Methods:** Protein and mRNA expression of the Nod2-Ripk2 signaling pathway was examined in liver tissue isolated from patients diagnosed with end stage PSC, Biliary Atresia as well as in murine models of cholestasis (3 day bile duct ligation (BDL) or 3day feeding of 0.1% 3,5-Diethoxycarbonyl-1,4-Dihydrocollidine (DDC)) compared to WT controls. In addition, the effect genetic ablation or pharmacological inhibition of TrxR1 (auranofin 10mg/kg/3d) on Nod2-Ripk2 signaling was analyzed in the bile duct ligation (BDL) model of cholestatic injury. Finally, the effect of pharmacological inhibition of TrxR1 on the Nod2-Ripk2 pathway was examined in cultured macrophages and primary hepatocytes. **Results:** Increased expression of the Nod2-Ripk2 signaling pathway was present in liver tissue isolated from human patients diagnosed with end stage PSC and Biliary Atresia. Similar results were also evident in mice subjected to bile duct ligation or feeding DDC for 3 days. Immunohistochemical analysis of livers from human cholestatic patients, 3d DDC fed and 3d BDL mice revealed increased hepatic Nod2 and Ripk2 staining. Hepatospecific deletion of TrxR1 as well as pharmacological targeting of TrxR1 inhibited BDL-dependent induction of hepatic Nod2-Ripk2 signaling, NFkB activation and proinflammatory cytokine production. In vitro, pharmacological targeting of TrxR1 inhibited Nod2-Ripk2 activation in RAW264.7 macrophages and primary hepatocytes. **Conclusion:** These data demonstrate that the Nod2-Ripk2 inflammatory pathway is activated in murine cholestasis as well as in human cholestasis and implicate TrxR1-signaling as an important regulator of Nod2-Ripk2 activation

Disclosures: Colin Shearn: Nothing to Disclose, Aimee Anderson: Nothing to Disclose, Michael Devereaux: Nothing to Disclose, Edward Schmidt: Nothing to Disclose, Ronald Sokol: Mirum: Advisor, Ipsen/Albireo: Advisor, Malinkrodt: Consultant, Alexion: Consultant, ProQR: Consultant.

2648 | PRURITUS IN CHILDREN WITH BILIARY ATRESIA: AN UNDERRECOGNIZED CLINICAL BURDEN

Natasha Dilwali[1] Shannon Vandriel[2] Nadia Ovchinsky[1] Jennifer Vittorio[1], [1]New York University Grossman School of Medicine, [2]Mirum Pharmaceuticals, Inc.

Background: Biliary atresia (BA) is a progressive, obstructive cholangiopathy and the leading indication for pediatric liver transplant (LT). In contrast to other pediatric cholestatic disorders, such as Progressive Familial Intrahepatic Cholestasis and Alagille Syndrome, pruritus has been less frequently recognized and characterized as a clinical feature of BA. This study aimed to describe the frequency and severity of pruritus in children with BA as reported by their caregivers and health-care providers (HCPs). **Methods:** Cross-sectional survey of caregivers (aged >18 years) and HCPs, including pediatric gastroenterologists, hepatologists, and advanced practice providers, caring for children with BA with native livers (>6 months). Caregivers of children who had undergone LT, had active acute cholangitis, and/or were enrolled in an ileal bile acid transporter (IBAT) inhibitor clinical trial were excluded. Quantitative variables are presented as medians [quartile 1 (Q1), quartile 3 (Q3)] and qualitative variables are reported as frequencies with percentages. **Results:** A total of 57 caregivers (92.3% female) and 67 HCPs participated. The median age of the children was 2 years (Q1, Q3: 0.8, 6), 40% were female and all had undergone a Kasai portoenterostomy (52/52). 19% (11/55) were listed or undergoing evaluation for LT.

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Among caregivers, 41% (22/55) reported that their child had experienced itching related to BA. During the two weeks prior to survey completion, 52% (25/48) reported symptoms suggestive of pruritus in their child, including irritability/fussiness, blood on sheets, sleep difficulties, skin excoriation from scratching, and skin discoloration/hyperpigmentation. Notably, 40% of caregivers reported that their child's HCP had never informed them that itching could be related to BA. Among HCP respondents, the majority were hepatologists (55%; 37/67) and 43% (29/67) reported active involvement in the care of >40 BA patients over the preceding 5 years. Most HCPs (85%; 55/65) reported routinely screening for symptoms of pruritus in children with BA; however, only 15% (10/65) utilized a validated pruritus assessment scale. Despite the high prevalence of pruritus reported by caregivers, HCPs estimated that only 20% (Q1, Q3: 8%, 50%) of children with BA experience itching. 66% (44/67) of HCPs indicated that pruritus negatively impacts both children and caregiver sleep; however, 54% (25/46) of caregivers indicated that their child's HCPs do not routinely inquire about sleep difficulties or trouble falling asleep. Only 37% (25/67) of HCPs routinely measure serum bile acids in patients with BA. **Conclusion:** Collectively, these data indicate that pruritus is an underrecognized feature of BA and underscore the importance of routine screening using standardized assessment methods.

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2649 | OUTCOMES OF KASAI PORTOENTEROSTOMY AFTER INCORPORATION OF PERCUTANEOUS CHOLECYSTOCHOLANGIOGRAPHY FOR DIAGNOSING BILIARY ATRESIA AT AN URBAN PEDIATRIC CENTER

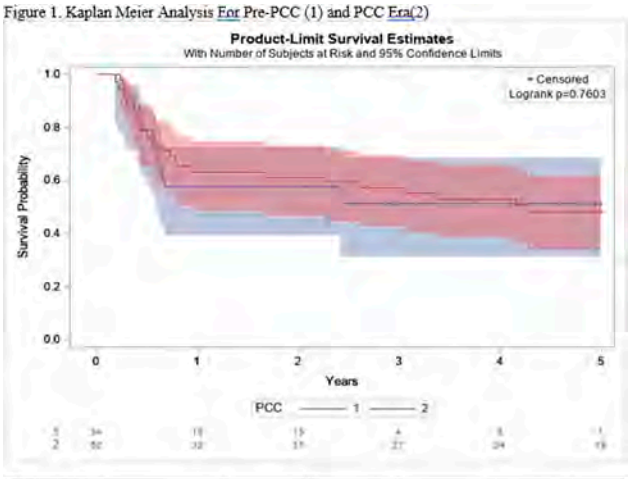
Brooks Melnyk[1] Christopher Nemeh[1] Caitlin Cain-Trivette[1] Paul Park[1] Nicholas Schmoke[1] Chunhui Wang[1] Paul Kurlansky[1] Mercedes Martinez[2] Vincent Duron[1] William Middlesworth[1] Yeu Sanz Wu[3] Steven Stylianos[4] Pooja Reddy Spector[1], [1]Columbia University, [2]NewYork-Presbyterian, [3]University of Rochester, [4]Rutgers University

Background: Percutaneous cholecystocholangiography (PCC) is a minimally invasive tool that can help diagnose biliary atresia (BA). We evaluated the impact of incorporating PCC in the diagnostic algorithm for neonatal cholestasis on outcomes of Kasai Portoenterostomy (KP) before and after PCC was implemented. **Methods:** A single-institution retrospective review was performed for BA patients who underwent KP between January 2010 and July 2023 (n = 86). PCC was implemented in January 2019 and patients who underwent KP after implementation (PCC group) were compared to those who underwent KP in the preceding 9 years (pre-PCC group). Patient demographics, and preoperative and 3-month postoperative laboratory values were obtained as a marker for adequate biliary drainage. Survival with native liver (SNL) at 1 year and sequela of chronic liver disease including portal hypertension (HTN), failure to thrive (FTT) and cholangitis were assessed at one year follow up, in addition to readmission within 30 days. Categorical variables were compared using chi-square tests; continuous variables were reported as median and interquartile range (IQR) and were compared using Mann-Whitney tests, as they were evaluated as non-normal distribution by Shapiro-Wilk tests. Kaplan Meier curves were used to estimate SNL after KP. Univariable cox regression was used to evaluate factors associated with liver transplant or death. Multivariable cox regression model was fitted to assess the effect of PCC on SNL, adjusting for age, time to surgery, gender, prematurity, 3-month lab values, and portal HTN, FTT and cholangitis within 1 year. **Results:** Of the 86 patients included in the study, 46 were male (53.5%). Baseline preoperative laboratory values did not differ significantly between groups. There were 52 patients who underwent Kasai in pre-PCC era. SNL at one year was 63.2% in the pre-PCC era. For the 34 patients who underwent KP in the PCC era, overall SNL was 57.8%. Of these 34 patients, 25 patients (73.5%) underwent PCC and had a SNL of 64%. The median total bilirubin at 3 months post KP in the pre-PCC and PCC groups and the one-year outcomes including cholangitis, portal HTN and FTT had no significant difference between the two groups. Age at KP was significantly less in the PCC group ((51 days [IQR 37,62] vs. 61.5 days [IQR 53.5,72.5], (p = 0.002)). There was no significant difference in time from initial hepatology referral to KP in the Pre-PCC era ((7.5 days, IQR [4, 13.5]) compared to the PCC era (11.5 days [IQR 6,20], (p = 0.10)) **Conclusion:** Biliary drainage as assessed by total bilirubin and time to surgery from initial hepatology referral were not significantly different before and after PCC implementation. Age at KP was significantly lower in the PCC group. This data suggests that incorporating PCC in the diagnostic algorithm for BA is feasible without delaying surgery or affecting SNL.

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Figure 1. Kaplan Meier Analysis For Pre-PCC (1) and PCC Era(2)



Patients at risk	1	2	3	4	5
Pre PCC					
Years	0.94247	1.67945	2.61096	3.37808	4.26849
Survival	0.63	0.61	0.57	0.53	0.48
Survival Standard Error	0.0672	0.0679	0.0692	0.0702	0.0715
PCC Era					
Years	0.67397	0.67397	2.43014	2.43014	2.43014
Survival	0.58	0.58	0.51	0.51	0.51
Survival Standard Error	0.0859	0.0859	0.0974	0.0974	0.0974

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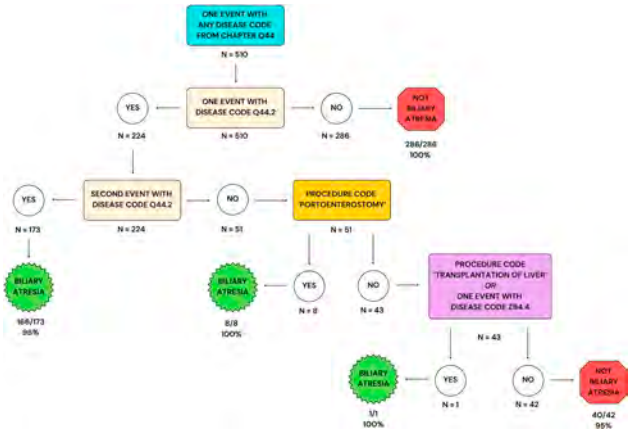
2650 | DESIGN AND VALIDATION OF A CLINICAL CODING ALGORITHM FOR THE NATIONAL IDENTIFICATION OF BILIARY ATRESIA

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Background: Coding systems such as the International Classification of Diseases (ICD) are used to identify research cohorts from health databases when large-scale chart review is impractical. Biliary atresia (BA) studies often utilise diagnosis or procedure codes for case identification, but this process has never been validated and may underrepresent deprived populations. **Methods:** New Zealand (NZ) has universal healthcare, an active ICD-10 coding system since 2000, a high BA incidence, and the centralisation of all BA care to a single national service in 2007. All NZ public and private hospital events from 2000 to 2025 for individuals born 2000 to 2024 with any code from ICD-10 chapter Q44 (congenital hepatobiliary malformations) were extracted from national databases. Operation codes and transplant codes were also extracted. All medical records were reviewed to confirm diagnoses and compared with national service records to obtain a complete list of true BA cases in NZ since 2000, against which to validate the health coding algorithm. Using these data, code combinations were assessed against the true diagnosis of BA to determine the coding accuracy for case identification. Diagnostic performance was assessed by sensitivity and specificity, and receiver operator curves. **Results:** There were 2,336 hospital events over the study years with any Q44 chapter code, comprising 510 individuals. The most used Q44 chapter code was Q44.2 (‘atresia of bile ducts’) for 224 individuals, of whom 177 had true BA and two were known cases of Alagille syndrome misdiagnosed as BA pre-centralisation (1% BA misdiagnosis rate with portoenterostomy). All BA cases were born and/or diagnosed and treated in NZ, with 87% from medium- to high-socioeconomic deprivation domiciles, and 43% indigenous Māori, 25% European, 20% Pacific Islander, and 11% Asian. BA birth incidence was 1 in 8,600 overall, but 1 in 5,000 in indigenous Māori and Pacific Islander, 1 in 11,000 in Asian, and 1 in 15,600 in European. Code Q44.2 identified the complete national series with 100% sensitivity (CI 98, 100), but 86% specificity (CI 82, 89) and 79% PPV (CI 73, 84). Step-wise combination of two hospital events coded by Q44.2, then one Q44.2 event plus operation code ‘portoenterostomy’, then one Q44.2 event plus either operation code ‘transplantation of liver’ or disease code Z94.4 (‘liver transplant status’), created the optimal algorithm for identifying the national series with 99% sensitivity (CI 96, 100), 98% specificity (CI 96, 99), 96% PPV (CI 92, 98), 99% NPV (CI 98, 100), and AUROC of 0.984. **Conclusion:** The ICD-10 code Q44.2, alone without chart review, lacks BA specificity but performs excellently when combined with disease-affiliated codes in an algorithm replicable in other settings. This algorithm was validated against a BA national series with a low misdiagnosis rate and a high burden in indigenous Māori, Pacific Islander and Asian populations from socioeconomically deprived areas.

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Disclosures: Zeba Moin: Nothing to Disclose, Jill Haszard: Nothing to Disclose, Helen Evans: Nothing to Disclose, Cameron Grant: Nothing to Disclose.

2651 | ◆ RESPONSIVENESS OF PATIENTS WITH BILE SALT EXPORT PUMP DEFICIENCY TO THERAPEUTIC INTERRUPTION OF THE ENTEROHEPATIC CIRCULATION ALLOWS FURTHER DETAILING OF GENOTYPE-PHENOTYPE RELATIONSHIPS

Mark Nomden[1] Alise de Groot[1] Elizabeth Bannister[1] Antonia Felzen[2] Pedro Miranda-Afonso[3] Richard Thompson[4] Emmanuel Gonzales[5] Irena Jankowska[6] Etienne Sokal[7] Benjamin Shneider[8] Seema Alam[9] Cigdem Arikan[10] Henrik Arnell[11] Madeleine Aumar[12] Amer Azaz[13] Emna Barkaoui[14] María Belén Pallitto[15] Marisa Beretta[16] Jernej Brecelj[17] Dieter Broering[18] Pier Luigi Calvo[19] Mara Cananzi[20] Huey-Ling Chen[21] Guillermo Costaguta[22] Piotr Czubkowski[23] Lorenzo D'Antiga[24] Elisa Carvalho[25] Dominique Debray[26] Antal Dezsőfi-Gottl[27] Angelo Di Giorgio[28] Ozlem Durmaz[29] Alexandre Fabre[30] Sandra Ferreira[31] Ryan Fischer[32] Björn Fischler[33] Teresa Botelho[31] Tanja Fritz[34] Cristina Gonçalves[35] Enke Grabhorn[36] Tassos Grammatikopoulos[37] Girish Gupte[38] Winita Hardikar[39] Loreto Hierro[40] Giuseppe Indolfi[41] Emmanuel Jacquemin[5] Giulia Jannone[7] Carolina Jimenez-Rivera[42] Marianne Hørby Jørgensen[43] Binita Kamath[44] Wikrom Karnsakul[45] Nanda Kerkar[46] Kyung Mo Kim[47] Jae Sung Ko[48] Denitza Kofinova[49] Nolwenn Laborde[50] Zhongdie Li[51] Patryk Lipinski[52] Rohan Malik[53] Saeed Mohammad[54] Yael Mozer-Glassberg[55] Gema Muñoz Bartolo[40] Gabriella Nebbia[56] Felipe Ordonez-Guerrero[57] Anna Orłowska[6] Arti Pawaria[58] Tudor Pop[59] Jesus Quintero Bernabeu[60] Giusy Ranucci[61] Aathira Ravindranath[62] Nathalie Rock[63] Maria Rogalidou[64] Ioannis Roilidis[65] Mathias Ruiz[66] Thomas Sandahl[67] Srinivas Sankaranarayanan[68] Mohammad Shagrani[18] Eyal Shteyer[69] Pooja Reddy Spector[70] James Squires[71] Ekkehard Sturm[72] Emanuele Nicastro[24] Cristina Targa Ferreira[73] Marise Tofoli[74] Bethany Tucker[37] Christos Tzivinikos[75] Wendy van der Woerd[76] Georg Friedrich Vogel[77] Heng Wang[78] Jian-She Wang[51] Sabina Wiecek[79] Aglaia Zellos[80] Andreanne Zizzo[81] Bettina Hansen[82] Paola Mian[83] Henkjan Verkade[83], [1]University of Groningen, University Medical Center Groningen, [2]Pediatric Gastroenterology and Hepatology, University Medical Center Groningen, [3]Department of Epidemiology and Biostatistics, Erasmus Medical Center, Rotterdam, [4]King's College London, [5]Hopital Bicetre, [6]Children's Memorial Health Institute, Warsaw, [7]Université Catholique de Louvain, Cliniques St Luc, Brussels, [8]Texas Children's Hospital, [9]Institute of Liver and Biliary Sciences, [10]Koc University School of Medicine, Istanbul, [11]Astrid Lindgren Children's Hospital, Karolinska University Hospital & Karolinska Institutet, [12]Lille University Hospital, Lille, [13]Sheikh Khalifa Medical City, Abu Dhabi, [14]Tunis Children Hospital, Tunis, [15]Hospital Italiano, CABA, [16]Wits Donald Gordon Medical Centre, University of the Witwatersrand, [17]University Children's Hospital Ljubljana, [18]King Faisal Specialist Hospital & Research Center, Riyadh, [19]Regina Margherita Children's Hospital, [20]University of Padova, [21]National Taiwan University, [22]CHU de Quebec-Université Laval, Quebec City, [23]The Children's Memorial Health Institute, [24]Hospital Papa Giovanni XXIII, Bergamo, [25]Hospital de Base do Distrito Federal, Hospital da Criança de Brasília, [26]APHP-Necker Enfants Malades University Hospital, Paris, [27]Semmelweis University, Budapest, [28]University of Udine, Udine, [29]Istanbul University Istanbul Medical Faculty, [30]Hôpital de la Timone Enfant,Marseille, [31]Unidade Local de Saúde Coimbra, Coimbra, [32]Children's Mercy Kansas City, [33]Astrid Lindgren Children's Hospital, Karolinska University Hospital, [34]University Children's Hospital Tübingen, Tübingen, [35]Pediatric Gastroenterology/Hepatology Center Lisbon, Lisbon, [36]University Medical Center Hamburg Eppendorf, Hamburg, [37]King's College Hospital, [38]Birmingham Women's and Children's Hospital, Birmingham, [39]Royal Children's Hospital, [40]Children's Hospital La Paz, La Paz University Hospital, Madrid, [41]Meyer

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Background: Patients with bile salt export pump (BSEP, *ABCB11*) deficiency have variable native liver survival (NLS) and serum bile acid (sBA) response to interruption of the enterohepatic circulation (iEHC) via surgical biliary diversion (SBD) or ileal bile acid transporter inhibition (IBATi). The missense variants p.E297G(E)and p.D482G (D) retain residual BSEP transport capacity. Patients who are homozygous or compound heterozygous for these two variants (ED/ED) have longer NLS after iEHC than other patients with BSEP deficiency. Apart from E and D, other missense mutations (MS) have been identified, but their severity and residual BSEP transport capacity remain unclear. Recently, we reported that residual BSEP transport capacity predicts sBA responsiveness to iEHC by IBATi (*Hepatology* 2026; 83: 708-20). We now aimed to grade the severity of different MS variants by assessing sBA responsiveness to surgical or medical iEHC in BSEP deficiency patients, based on their genotype. **Methods:** Patients from the NAPPED registry (NCT03930810) who were homozygous or compound heterozygous for disease-causing variant in *ABCB11* were included. Variants were categorized as ED, MS or truncating (T; variants leading to a truncated protein), and patients were categorized into one of seven genotype categories: ED/ED, ED/MS, ED/T, MS/MS heterozygous (Het), MS/MS homozygous (Hom), MS/T & T/T. sBA response to surgical or medical iEHC was defined as a post-iEHC sBA concentration <102 µmol/L or $\geq 75\%$ decrease of sBA concentration. **Results:** In 99 patients treated by iEHC (SBD: 67; IBATi: 32 [24 odevixibat, 8 maralixibat]), the percentage of sBA response could be calculated. ED/ED patients had the highest sBA response rate (67%; Figure A) and T/T patients the lowest (0%). ED/T patients rarely achieved an sBA response (20%), while 7 MS/T patients (39%) achieved an sBA response. In the MS/T sBA responder group 6 different MS variants were identified, and accordingly, these variants likely have a *higher* residual BA transport capacity than ED (Figure B). MS/MS Hom patients had an sBA response rate of 27%. In the MS/MS Hom sBA responder group, 3 different MS variants were identified, and these variants likely have a residual BA transport capacity *at least similar* to ED. In the MS/MS Hom sBA nonresponder group, 10 different MS variants were identified, and these variants likely have a residual BA transport capacity *lower* than ED (Figure B). **Conclusion:** Assessing the responsiveness of patients with BSEP deficiency to therapeutic interruption of the enterohepatic circulation allows grading of phenotypic severity and the expected residual transport function of specific *ABCB11* variants. This further detailing of genotype-phenotype will improve the predictability

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of responsiveness to iEHC.

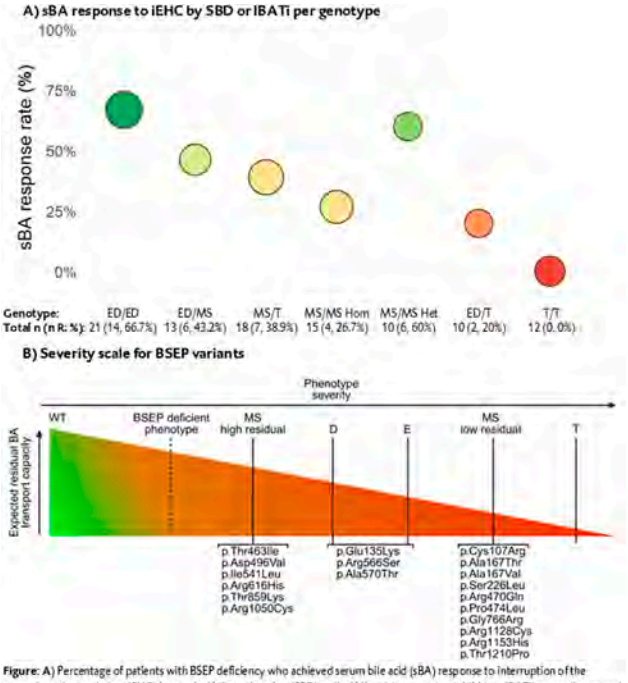


Figure: A) Percentage of patients with BSEP deficiency who achieved serum bile acid (sBA) response to interruption of the enterohepatic circulation (iEHC) by surgical biliary diversion (SBD) or ileal bile acid transporter inhibition (IBATi), according to each genotype group. Dot size represents the number of patients per genotype group. B) Grading of phenotypic severity in relation to expected residual BSEP transport capacity of specific BSEP (*ABCB11*) variants in patients with BSEP deficiency.

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★ 2652 | ◆ THE END OF THE DISCUSSION: SURGICAL BILIARY DIVERSION AND LIVER TRANSPLANTATION INDUCE CATCH-UP GROWTH IN BSEP DEFICIENCY, BUT NOT IN FIC1 DEFICIENCY

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Background: Growth failure is common in severe cholestatic liver diseases of childhood, but growth often improves after liver transplantation (LT). Patients with familial intrahepatic cholestasis 1 (FIC1) deficiency and bile salt export pump (BSEP) deficiency commonly experience growth failure. However, the effects of surgical biliary diversion (SBD) and LT on growth have only been partially characterized. In the largest study of patients with FIC1 and BSEP deficiency to date, integrating data from the global NAPPED and TreatFIC registries, we evaluated the effects of SBD and LT on growth outcomes. **Methods:** We analyzed demographic, growth, and clinical data, including surgical treatments, from patients in the NAPPED and TreatFIC registries with biallelic disease-causing variants in *ATP8B1* (FIC1) or *ABCB11* (BSEP). Height measurements recorded up to 10 years of age were converted into WHO-standardized height-for-age z-scores (HAZ), and analyzed before and after SBD or LT. We defined serum bile acid (sBA) responders to SBD as patients with sBA < 102 µmol/L or > 75% reduction from baseline within 12 months of SBD. We assessed within-patient changes after these events by comparing HAZ 0-12 months prior to surgery and up to 6 years after. LT after SBD was a censoring event. Growth stunting (GS) is defined as HAZ < −2. **Results:** We included 433 patients, 110 with FIC1 deficiency and 323 with BSEP deficiency. Of these patients, 49% with FIC1 and 27% with BSEP deficiency underwent SBD, with median HAZ before SBD of −2.1 (interquartile range [IQR] −3.1 to −1.2) and −1.9 (IQR −2.8 to −0.9), respectively. Patients with BSEP deficiency who had an sBA response to SBD (48%, 24/50 with available sBA) showed significant growth improvement after surgery compared with non-responders, with median HAZ difference of +1.4 ($p < 0.05$; Figure 1A). Patients with FIC1 deficiency had a low sBA response rate to SBD (32%, 7/22 with available sBA) and did not show significant growth improvement after SBD. Among patients who underwent LT, those with FIC1 deficiency had a significantly lower HAZ at LT than those with BSEP deficiency: −2.8 (IQR −3.7 to −1.2) vs. −1.9 (IQR −2.8 to −0.9), respectively ($p < 0.01$). No significant growth recovery was observed in patients with FIC1 deficiency after LT. In contrast, patients with BSEP deficiency showed significant growth improvement from 12 months after LT onwards ($p < 0.01$), which was sustained through 6 years (median HAZ of 0; IQR −1.5 to +1.3; Figure 1B). **Conclusion:** Most patients with FIC1 or BSEP deficiency who undergo SBD or LT are growth restricted at the time of surgery. SBD with sBA responsiveness and LT are associated with improved growth trajectories in children with BSEP deficiency, but not in those with FIC1 deficiency. We speculate that persistent growth failure in FIC1 deficiency is driven by extrahepatic ATP8B1 dysfunction.

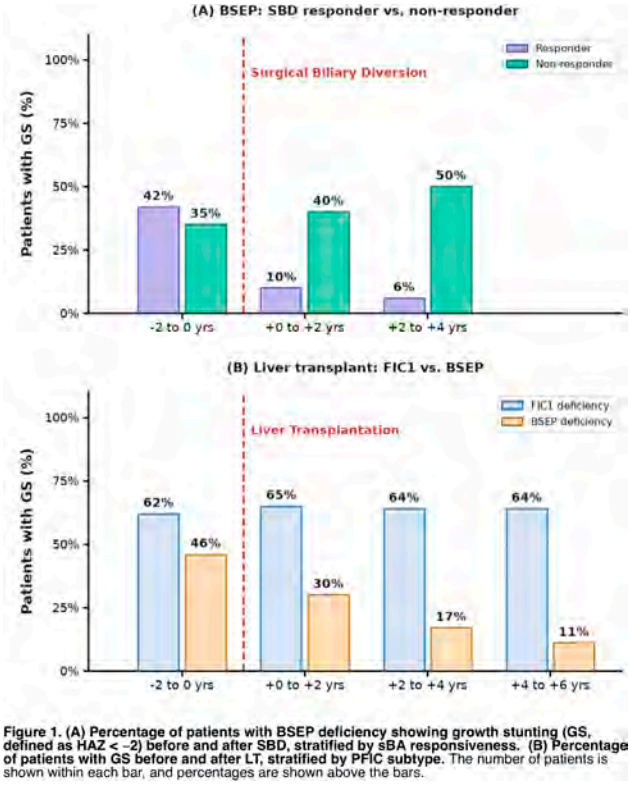


Figure 1. (A) Percentage of patients with BSEP deficiency showing growth stunting (GS, defined as HAZ < -2) before and after SBD, stratified by sBA responsiveness. (B) Percentage of patients with GS before and after LT, stratified by PFIC subtype. The number of patients is shown within each bar, and percentages are shown above the bars.

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2653 | REAL-WORLD EFFICACY OF GLP-1 RECEPTOR AGONISTS IN PEDIATRIC METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD): A COMPARATIVE COHORT STUDY

Chaowapong Jarasvaraparn[1] Laurie Goebel[1] Kathryn Adams[1] Erin Phipps[1] Natalia Plott[1] Kyla Tolliver[2] Sara Naramore[1] Brian DeBosch[3] Jean Molleston[1], [1]Riley

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Background: Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) is rising in the pediatric population alongside obesity rates. While Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have shown efficacy in adults, pediatric data remain limited. This study aims to evaluate the impact of GLP-1RA therapy on anthropometric measures, biochemical markers, and liver stiffness in children with MASLD compared to a matched control group. **Methods:** We conducted a retrospective cohort study of 124 pediatric patients with MASLD, comparing those receiving GLP-1RA therapy due to obesity (n = 62) to those not on GLP-1RA (n = 62). Control group (non-GLP-1RA) was matched for age, sex, race, ethnicity and duration of follow up to GLP-1RA group. Baseline characteristics and treatment outcomes, including anthropometric assessment, liver enzymes, and FibroScan parameters (Controlled Attenuation Parameter; CAP and Liver Stiffness Measurement; LSM), were analyzed. The t -test was used to compare the continuous variables, and the chi-square test was used for categorical variables. **Results:** The average age at presentation was 12.88 years for the non-GLP-1RA group and 13.21 years (p = 0.13) for the GLP-1RA group, with mean follow-up durations of 13.36 and 11.20 months, (p = 0.22) respectively. Compared to the non-GLP-1RA cohort, the GLP-1RA group exhibited a significantly higher prevalence of obstructive sleep apnea (32.26% vs. 1.61%; p = 0.001) and pre-diabetes (24.19% vs. 4.84%; p = 0.001), whereas the prevalence of type 2 diabetes did not significantly differ between groups (8.1% vs. 4.8%; p = 0.26). Patients on GLP-1RA achieved a numeric reduction in mean BMI (43.81 to 41.83, p = 0.26) and BMI z-score (2.68 to 2.61), whereas mean BMI significantly increased in the non-GLP-1 RA group (33.28 to 36.32, p = 0.01). GLP-1RA-treated patients exhibited a significant reduction in ALT (61.98 ± 45.54 to 42.54 ± 33.80 U/L, p = 0.008) and AST (35.77 ± 22.15 to 26.44 ± 13.57 U/L, p = 0.008) at the last follow-up. GLP-1RA-treated patients who achieved 20% ALT reduction had significantly lower baseline BMI (41.02 vs. 46.27, p = 0.03) compared to non-20% ALT reduction. HbA1c, lipid profiles, CAP and LSM at recent follow up were not different in either the two groups. **Conclusion:** GLP-1RA therapy in pediatric MASLD is associated with significant improvements in transaminases and stabilization of BMI compared to traditional management. GLP-1RA therapy for MASLD may be more effective when initiated at an earlier stage of the disease before the development of severe obesity. Future clinical trials should incorporate more robust and sensitive endpoints, such as MRI-PDFF to accurately quantify changes in hepatic steatosis, or liver biopsy to assess histological improvements in inflammation and fibrosis.

Table Comparison of clinical outcomes at baseline and follow-up between pediatric MASLD patients receiving GLP-1 and non-GLP1 therapy.

Outcomes	At presentation	At last follow-up	P value
BMI			
Non-GLP1	33.29 ± 6.58	36.32 ± 6.54	**0.01**
GLP-1	43.81 ± 9.46	41.93 ± 9.31	0.26
BMI z score			
Non-GLP1	2.31 ± 0.38	2.38 ± 0.38	0.32
GLP-1	2.68 ± 0.33	2.61 ± 0.44	0.24
Weight (kg)			
Non-GLP1	86.58 ± 27.39	102.95 ± 27.01	**0.001**
GLP-1	124.96 ± 27.27	121.38 ± 28.32	0.48
Weight z score			
Non-GLP1	2.57 ± 0.74	2.61 ± 0.77	0.77
GLP-1	4.72 ± 12.21	2.83 ± 0.65	0.23
Aspartate Aminotransferase (U/L)			
Non-GLP1	46.16 ± 26.28	44.87 ± 41.10	0.83
GLP-1	35.77 ± 22.15	26.44 ± 13.57	**0.008**
Alanine transaminase (U/L)			
Non-GLP1	77.10 ± 54.42	77.83 ± 87.37	0.96
GLP-1	61.98 ± 45.54	42.54 ± 33.80	**0.008**
Total bilirubin (mg/dL)			
Non-GLP1 (n = 60, 58)	0.46 ± 0.28	0.56 ± 0.31	0.06
GLP-1 (n = 56, 41)	0.49 ± 0.21	0.53 ± 0.21	0.51
Albumin (g/dL)			
Non-GLP1 (n = 61, 57)	4.45 ± 0.62	4.62 ± 0.25	0.06
GLP-1 (n = 56, 41)	4.45 ± 0.33	4.48 ± 0.29	0.72
HbA1C (%)			
Non-GLP1 (n = 48, 53)	5.56 ± 0.51	6.87 ± 1.33	0.33
GLP-1 (n = 57, 46)	5.59 ± 0.39	5.42 ± 0.62	0.12
LDL (mg/dL)			
Non-GLP1 (n = 40, 47)	76.65 ± 4.38	80.72 ± 3.93	0.49
GLP-1 (n = 56, 38)	94.23 ± 27.61	93.21 ± 24.81	0.85
Cholesterol (mg/dL)			
Non-GLP1 (n = 40, 46)	150.47 ± 37.11	148.13 ± 38.90	0.78
GLP-1 (n = 53, 38)	163.72 ± 33.25	159.11 ± 31.17	0.50
Triglyceride (mg/dL)			
Non-GLP1 (n = 40, 46)	176.70 ± 106.31	168.65 ± 113.13	0.74
GLP-1 (n = 53, 38)	146.60 ± 66.22	148.26 ± 107.39	0.93
HDL (mg/dL)			
Non-GLP1 (n = 40, 46)	43.82 ± 7.15	44.96 ± 5.23	0.89
GLP-1 (n = 53, 38)	38.24 ± 6.73	44.61 ± 5.98	0.33
CAP from FibroScan (dB/m)			
Non-GLP1 (n = 23, 23)	309.74 ± 32.78	321.87 ± 41.51	0.28
GLP-1 (n = 32, 19)	338.63 ± 45.24	327.27 ± 59.64	0.48
LSM from FibroScan (kPa)			
Non-GLP1 (n = 23, 23)	7.00 ± 2.59	6.81 ± 2.89	0.81
GLP-1 (n = 32, 19)	7.48 ± 2.69	7.86 ± 3.22	0.66

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2654 | FIBROSIS-ASSOCIATED MICRORNAS AND BIOACTIVITIES OF EXTRACELLULAR VESICLES FROM A LARGE ANIMAL MODEL OF FONTAN-ASSOCIATED LIVER DISEASE

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Background: Fontan palliation is the primary treatment for patients with single ventricle cardiac abnormalities, but it results in high central venous pressure, decreased cardiac output and reduced hepatic oxygenation leading to Fontan-associated liver disease (FALD) which is characterized by liver congestion, fibrosis, and cirrhosis. To improve diagnosis and mechanistic understanding of FALD, we have established models of FALD in sheep from which circulating extracellular vesicles (EVs) are assessed for their molecular cargo components and bioactivities. **Methods:** To create Fontan models in sheep, an extracadiac conduit was used to join the inferior vena cava (IVC) to the main pulmonary artery (MPA) while the superior vena cava (SVC) remained in its normal anatomical position ("Glennless") or was connected to the MPA as part of the surgical procedure on the same day ("single stage") or ~12 months later ("two-stage"). Control animals received either no surgery or a procedure comprising a right thoracotomy through the 4th intercostal space followed by chest closure. EVs were isolated from plasma or serum over the ensuing 12-mo by differential centrifugation and analyzed by Nanosight tracking analysis and protein assay. EV total RNAs were isolated and subjected to small RNA-seq for miRNA and piRNA profiling. iPSC-derived human liver organoids (HLO) were used to assess regulation of fibrosis-related genes by 20ug/ml EVs or expression of candidate miRs. **Results:** As assessed histologically, mild hepatic fibrosis was present at ~6 months and moderate or severe fibrosis was present by 12 mo. Serum or plasma EVs from sham or Fontan sheep ($\leq$12 mo.) shared similar particle size, yield, or protein concentration. Serum and plasma EVs shared similar miRNA profiles but higher piRNA levels were evident in serum EVs compared to plasma EVs. Using regularized feature selection and ordinal logistic regression, 6 miRNAs and 3 piRNAs in serum EVs were identified that, together with time post-surgery, comprised a scoring system predictive of FALD severity. Four of these miRNAs underwent comparable changes in expression in TGF-β-treated HLOs as in serum/plasma EVs during FALD progression supporting a functional role in fibrosis. Plasma EVs collected 1 mo. from either a sham twin or its single stage Fontan twin counterpart suppressed TGF-β-induced fibrotic gene expression in HLOs; at 7mo post-surgery this suppression was maintained in plasma EVs from the sham twin but was lost from plasma EVs of the Fontan twin suggesting that circulating EVs lose anti-fibrotic activity during progression of FALD. **Conclusion:** Circulating EVs from a sheep FALD model exhibit dynamic changes in miRNA/piRNA payloads and fibrosis-related gene modulation. A select miRNA/piRNA panel was predictive of FALD severity and partially implicated in underlying fibrotic mechanisms.

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2655 | LONGITUDINAL PATTERNS OF BILE ACIDS, TOTAL BILIRUBIN, AND PLATELET COUNT PREDICT NATIVE LIVER SURVIVAL IN CHILDREN WITH ALAGILLE SYNDROME

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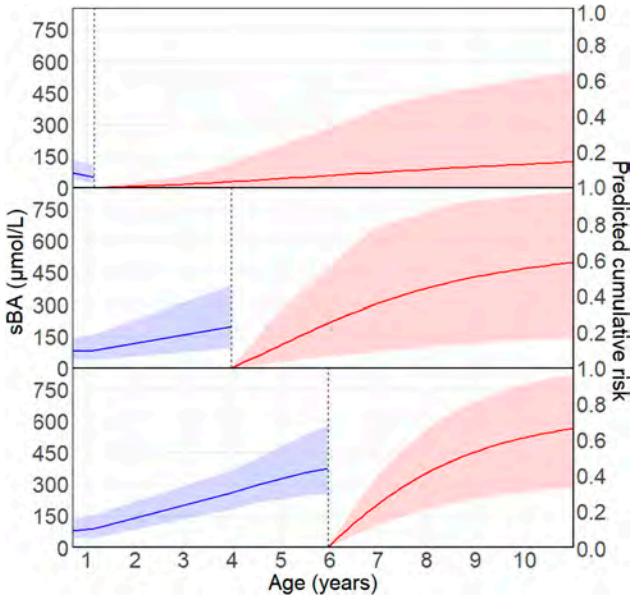
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Background: Accurate individualized prediction of native liver survival (NLS) is needed to support clinical monitoring and decision-making in children with Alagille syndrome (ALGS). Serum bile acids (sBA) and total bilirubin (TB) reflect cholestasis, whereas platelet count (PC) may capture changes in portal hypertension and the progression of liver disease. However, the extent to which longitudinal changes in these routinely collected markers predict NLS in ALGS remains unclear. This study aimed to address this question using a standard-of-care pediatric ALGS cohort. **Methods:** Data on an international cohort of 1562 patients from 81 centers across 34 countries were obtained from the Global Alagille Alliance Study. We included children with confirmed neonatal cholestasis, and we censored follow-up at biliary diversion, hepatocellular carcinoma diagnosis, participation in an IBAT inhibitor trial, or Kasai procedure, the latter in patients who underwent this surgery before ALGS was confirmed. Joint models were fitted to analyze longitudinal sBA, TB, and PC trajectories and the time of death or liver transplantation (LT), while accounting for left truncation due to delayed study entry. Models were compared using the Watanabe–Akaike information criterion, and their discriminative ability was evaluated using the in-sample time-dependent area under the curve (AUC). **Results:** The analysis included 1147 patients (58% male, 95% with *JAG1* mutation), who contributed 12,722 visits over a mean follow-up of 4.2 years. NLS at 18 years old was 34.5% (95% confidence interval [CI] 29.5–40.4). In univariate joint models, higher current values of sBA (per unit increase in log µmol/L: hazard ratio [HR] = 4.30, 95% CI 2.86–6.81) and TB (per unit increase in log mg/dL: HR = 4.59, 95% CI 3.67–5.77) were associated with an increased risk of death and LT. Increasing trajectories of sBA (per unit increase in log µmol/L over 6 months: HR = 1.55, 95% CI 0.93–2.64) and TB (per unit increase in log mg/dL over 1 year: HR = 1.82, 95% CI 1.26–2.66) were also associated with worse NLS. Figure 1 shows the fitted longitudinal sBA trajectories for a specific patient and their associated cumulative risk of death or LT. Conversely, higher PC values (per unit increase in square-root : HR = 0.75, 95% CI 0.72–0.79) and instantaneous increasing PC trajectories (HR = 0.84, 95% CI 0.79–0.91) were associated with improved NLS. At 6 years of age, the univariate time-dependent AUC over a 5-year horizon was 0.72 for sBA, 0.82 for TB, and 0.74 for PC. A multivariate model combining all three biomarkers showed the highest discriminative ability, with an AUC of 0.89. **Conclusion:** Longitudinal trajectories of TB, sBA, and PC, captured through current biomarker values and rates of change, provide information on NLS prognosis in this pediatric ALGS cohort. This model may support personalized risk stratification and inform the evaluation of these biomarkers as potential surrogate endpoints in ALGS.



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2656 | VALIDATION OF FIBROSCAN-BASED NON-INVASIVE SCORES FOR THE DETECTION OF STEATOSIS, ADVANCED FIBROSIS AND FIBROTIC MASH IN CHILDREN WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD)

Abdulmalik Kareem[1] Chao Jarasvaraparn[1], [1]Indiana University School of Medicine

Background: Identifying advanced fibrosis and fibrotic metabolic dysfunction-associated steatotic liver disease (MASH) is critical for pediatric clinical management. While liver stiffness measurement (LSM) is widely used, the performance of multi-parametric scores like AGILE 3 and FAST remains less defined in children. We evaluated the diagnostic accuracy of these scores against blinded histologic assessment in a pediatric cohort. **Methods:** We retrospectively studied 128 children with biopsy-confirmed MASLD who underwent FibroScan within 6 months of liver biopsy. Biopsies were re-read by a blinded pediatric pathologist using the NASH CRN system

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(steatosis 0-3; ballooning 0-2; lobular inflammation 0-3; fibrosis 0-4). We compared the diagnostic performance of APRI, FIB-4, LSM, AGILE 3 and FAST. The FAST (FibroScan-AST) score is designed to identify patients with "at-risk" or fibrotic MASH (NAS $\geq$ 4 and F $\geq$ 2) and is calculated using a proprietary formula incorporating LSM, controlled attenuation parameter (CAP), and AST. The Agile-3 score is a multi-parametric model used to identify advanced fibrosis (Stage $\geq$ F3) by integrating LSM with clinical and laboratory variables, including AST, ALT, platelet count, age, sex, and diabetes status. Advanced fibrosis was defined as Stage 3–4. **Results:** The cohort (mean age 14.2 years; mean BMI 36.5 kg/m2) had an advanced fibrosis prevalence of 14.1%. The CAP was significantly higher in patients with steatosis compared to those without (327.0 ± 43.7 vs. 254.7 ± 47.0 dB/m, p = 0.001). LSM showed the strongest correlation with fibrosis stage (r = 0.57, p < 0.001), followed by AGILE 3 (r = 0.43, p < 0.001); APRI and FIB-4 were significantly weaker (r = 0.31 and 0.20). To detect advanced fibrosis, AGILE 3 $\geq$ 0.059) demonstrated the highest sensitivity (94.4%) and NPV (98.8%; AUC 0.840), while LSM $\geq$ 9.2 kPa) achieved 83.3% sensitivity and 96.3% NPV (AUC 0.771). Mean LSM was significantly higher in advanced fibrosis (15.3 vs. 9.2 kPa, p = 0.001). For fibrotic MASH, a FAST score $\geq$ 0.53 yielded 96.0% sensitivity and 98.0% NPV (p = 0.003). Notably, diagnostic accuracy for advanced fibrosis diminished significantly in patients with BMI $\geq$ 40, with AUCs declining to 0.600–0.646. **Conclusion:** FibroScan-derived scores, particularly AGILE 3 and LSM, provide superior diagnostic accuracy for identifying pediatric advanced fibrosis compared to simple biochemical markers. The high NPV of AGILE 3 and FAST makes them excellent tools to rule out advanced disease, though clinicians should exercise caution in patients with a BMI $\geq$ 40 due to reduced performance.

Table Cut-offs for non-invasive fibrosis scores indicating advanced liver disease on liver biopsy (stage 3-4) in children

	Cut-off	Sensitivity	Specificity	AUC (95% CI)	PPV (%)	NPV (%)	OR (95% CI)	P-value
LSM	≥ 9.2	83.3 (66.1, 100.0)	70.9 (62.4, 79.4)	0.771 (0.673, 0.870)	31.9 (18.6, 45.2)	96.3 (92.2, 100.0)	12.2 (3.30, 44.9)	<0.001
APRI	≥ 0.328358	94.4 (83.9, 100.0)	35.5 (26.5, 44.4)	0.650 (0.579, 0.720)	19.3 (11.1, 27.6)	97.5 (92.7, 100.0)	9.3 (1.20, 72.3)	0.033
FIB-4	≥ 0.253447	77.8 (58.6, 97.0)	50.9 (41.6, 60.3)	0.643 (0.534, 0.753)	20.6 (11.0, 30.2)	93.3 (87.0, 99.7)	3.6 (1.1, 11.7)	0.031
Agile-3	≥ 0.059	94.4 (83.9, 100.0)	73.6 (65.4, 81.9)	0.840 (0.772, 0.909)	37.0 (23.0, 50.9)	98.8 (96.4, 100.0)	47.5 (6.0, 372.8)	<0.001

Table Comparison of Fibroscan Prediction of Fibrosis Stage 3-4 using AUCs

	Overall (n=128)	BMI < 30 (n=29)	BMI 30 – 34.9 (n=32)	BMI 35 – 39.9 (n=27)	BMI 40+ (n=40)
Cut-Points					
LSM ≥ 9.2	0.771 (0.673, 0.870)	0.795 (0.464, 1.000)	0.926 (0.858, 0.994)	0.786 (0.571, 1.000)	0.600 (0.387,0.813)
AGILE 3 ≥ 0.059	0.840 (0.772, 0.909)	0.795 (0.464, 1.000)	0.907 (0.833, 0.982)	0.886 (0.797, 0.976	0.757 (0.673, 0.841)
Continuous Score					
LSM	0.812 (0.711 0.913)	0.885 (0.650, 1.000)	0.941 (0.856, 1.000)	0.932 (0.793, 1.00)	0.606 (0.285, 0.926)

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2657 | LOW SCREENING RATES AND UNEQUAL RISK OF ABNORMAL RESULTS IN PEDIATRIC MASLD

Doris Valenzuela Araujo[1] Jennifer Panganiban[2] Jeremy Michel[1] Katherine Yun[1], [1]Children's Hospital of Philadelphia, [2]The Children's Hospital of Philadelphia

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common pediatric liver disease and disproportionately affects Latino children. Despite this, screening rates remain low and patient-level differences in screening and abnormal results are not well described for Latino children and Spanish-Speaking families. **Methods:** We conducted a retrospective study to evaluate MASLD screening completion and prevalence of abnormal results in children ages 10–17 with BMI $\geq$ 95th percentile seen in primary care at a large academic center in 2023. Completion of screening was defined as having an alanine aminotransferase (ALT) level up to 2 years prior to or 1 year after their qualifying primary care visit, in alignment with American Academy of Pediatrics recommendations. We used logistic regression and adjusted models to evaluate for differences screening and in frequency of ALT value $\geq$ 80 U/L and how this varied by age, sex, ethnicity, language preference, and BMI. **Results:** Our cohort included 16,208 children ages 10-17 with obesity. The mean age was 13.1 years, mean BMI was 31.8 and 46.7% were female. 13.3% of children were Hispanic/Latino and the most prevalent races were White at 43% and Black at 40.1%. Spanish was the preferred language for 4.6%, and 1.5% preferred a non-English, non-Spanish language. Only 7,627 (47%) of children had ALT screening completed with the 17-year-old cohort having the highest screening rate at 54.3%. There were no differences in screening by ethnicity or by language group. An ALT $\geq$ 80 U/L occurred in 149 children (2% of screened), with higher prevalence among Hispanic/Latino (5.3%) and Spanish-speaking children (8.9%). Spanish-preference was associated with higher odds of ALT $\geq$ 80 U/L (aOR 5.58, 95% CI 3.64–8.53 vs English), as was Hispanic/Latino ethnicity (aOR 3.85, 95% CI 0.87–1.05 vs non-Hispanic/Latino). **Conclusion:** We found that less than half of children had screening for MASLD. Among those screened, rates of ALT $\geq$ 80 U/L were significantly higher for Hispanic/Latino children and preferred language of Spanish even after adjusting for confounders. Our findings highlight the need for interventions to

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increase rates of screening particularly among patients with highest risk of abnormal results and poor disease outcomes.



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2658 | MITOCHONDRIAL HEPATOPATHY: GENETIC ETIOLOGY AND CLINICAL SPECTRUM FROM OVER 100 CHILDREN

James Squires[1] Alexander Miethke[2] Kieran Hawthorne[3] Johan Van Hove[4] Simon Horslen[5] Rohit Kohli[6] Akihiro Asai[2] Mark Lovell[7] Estella Alonso[8] Saul Karpen[9] Kathleen Loomes[10] Steve Guthery[11] Jean Molleston[12] Pamela Valentino[13] Benjamin Shneider[14] Kasper Wang[6] Philip Rosenthal[15] John Magee[16] Ronald Sokol[17], [1]Children's Hospital of Pittsburgh, [2]Cincinnati Children's Hospital Medical Center, [3]Arbor Research Collaborative for Health, Ann Arbor, Michigan, United States, [4]Section of Clinical Genetics and Metabolism, Department of Pediatrics, University of Colorado, [5]UPMC Children's Hospital of Pittsburgh, [6]Children's Hospital Los Angeles, [7]Department of Pathology, Children's Hospital Colorado, [8]Ann and Robert H. Lurie Children's Hospital of Chicago, [9]VCU Stravitz-Sanyal Institute for Liver Disease and Metabolic Health, [10]The Children's Hospital of Philadelphia, [11]Primary Children's Hospital, [12]Riley Hospital for Children, Indiana University School of Medicine, [13]University of Washington, [14]Texas Children's Hospital, [15]University of California, San Francisco, [16]University of Michigan Hospitals and Health Centers, [17]University of Colorado School of Medicine

Background: Alterations in mitochondrial structure and function result in a wide range of liver-based pathology termed mitochondrial hepatopathies (MH). Increasingly, MH diagnosis is made by genetic sequencing of both nuclear DNA and mitochondrial DNA (mtDNA). We aim to identify unique clinical features attributable to the underlying molecular etiologies of MH, linking these features with clinical phenotypes and disease course. **Methods:** We interrogated 2 NIDDK/NIH funded prospective studies – the Longitudinal Study of MH (MITOHEP) and the Pediatric Acute Liver Failure Study Group (PALFSG) - to collect and analyze demographic, clinical, laboratory, and outcome data on participants with MH phenotypes. Demographics and baseline characteristics are described using counts and percents or median and range and compared between phenotypic groups using chi-square or Wilcoxon rank sum tests. Time to event analyses were conducted using Kaplan-Meier methods. **Results:** Data from 115 participants (n = 93 MITOHEP, n = 22 PALF) were analyzed. Comprehensive genetic/enzymatic testing was performed in 65% with a final diagnosis in 73% of those tested. Three primary phenotypes were noted - acute liver failure (ALF, n = 43), chronic liver disease (Chronic, n = 62), and post-liver transplant (LT, n = 10). (**TABLE**) Comprehensive testing was performed more often in Chronic than ALF (77% vs 42%); however, etiology was identified more often in ALF (78% vs. 67%) with mtDNA depletion (*POLG*, *DGUOK*, *MPV17*) being most common (ALF: 79% vs Chronic: 41%). Overall, LT-free survival was 47% [95%CI: 36-57%] at 2 years. Those with ALF had worse LT- free survival (ALF15% [95%CI: 5-30%] vs. Chronic 65% [95%CI: 51-76%], $p < 0.001$). LT-free survival was also significantly lower in patients with a known genetic diagnosis (2-year survival 44% [95% CI: 28-58%] vs. 82% [95% CI: 54-94%], $p < 0.01$). Nineteen (17%) underwent LT (*TRMU* n = 5, *DGUOK* n = 3 Complex IV def n = 2, *POLG* n = 2, *TYMP* n = 1, Negative genetic testing n = 2, No genetic testing n = 4). With 99 patient-years of follow-up post-LT, 5 deaths were reported. **Conclusion:** Bi-allelic mutations in genes associated with mtDNA depletion syndromes were the most common identified cause of MH presenting with both ALF and Chronic phenotypes. LT-free survival is poor, with both an ALF phenotype and a known genetic diagnosis portending a poor outcome. In patients who underwent LT, long-term survival is possible highlighting areas for further investigation.

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Table: Genetic Testing

		ALF (N=43)		Chronic (N=82)		Post-transplant (N=10)	
Variable		N	n (%) or median (range)	N	n (%) or median (range)	N	n (%) or median (range)
Genetic/enzymatic testing done		43	18 (41.9%)	82	46 (77.4%)	10	9 (90.0%)
Clinical genetic/enzymatic testing		18	15 (83.3%)	46	46 (55.6%)	9	9 (100.0%)
Targeted gene panel (TGP)		18	7 (38.9%)	46	13 (27.1%)	9	2 (22.2%)
Whole exome sequencing (WES)		18	7 (38.9%)	46	17 (25.0%)	9	
Any genetic/enzymatic diagnosis		18	14 (77.8%)	46	22 (56.7%)	9	9 (100.0%)
Genetic/enzymatic diagnosis	6kb deletion mtDNA	14		32	1 (3.1%)	9	
	CARD				1 (3.1%)		
	Complex I deficiency				2 (6.3%)		
	Complex I, IV, V def				1 (3.1%)		
	Complex IV enzymatic def						1 (11.1%)
	DGUOK		4 (28.6%)		1 (3.1%)		1 (11.1%)
	LCHAD		1 (7.1%)				
	Large mtDNA deletion				1 (3.1%)		
	MPV17		1 (7.1%)		4 (12.5%)		
	MTFS, and BCKDHA				1 (3.1%)		
	MUTYH				1 (3.1%)		
	PDHA1		1 (7.1%)				
	POLG		6 (42.9%)		7 (21.9%)		1 (11.1%)
	POLG2				1 (3.1%)		
	RYR2				1 (3.1%)		
	Possible Complex I and III deficiency				1 (3.1%)		
	TRMU		1 (7.1%)		2 (6.3%)		1 (11.1%)
	TYMP, MNGIE						1 (11.1%)
	mtDNA deletion				2 (6.3%)		
	mtDNA depletion, IV def or combined I + IV deficiency						1 (11.1%)
	mtDNA mutation ATP6				1 (3.1%)		
	single mt DNA deletion				4 (12.5%)		
Genetic grouping	Mitochondrial DNA depletion syndrome	43	11 (25.6%)	82	13 (21.0%)	10	3 (30.0%)
	Mitochondrial RNA translation defect		2 (4.7%)		5 (8.1%)		4 (40.0%)
	Mitochondrial dis by enzymatic testing or FAOxt		1 (2.3%)		4 (6.5%)		2 (20.0%)
	Mt DNA deletion syndrome				9 (14.5%)		
	Negative WES/TGP testing		2 (4.7%)		10 (16.1%)		
	Negative clinical testing, no WES/TGP		2 (4.7%)		6 (9.7%)		
	No genetic testing		25 (58.1%)		14 (22.6%)		1 (10.0%)
	Unknown mechanism				1 (1.6%)		

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2660 | PAIRED EVALUATION OF BIOPSY AND NONINVASIVE TESTS FOR STAGING AND MONITORING ADOLESCENT MASLD ACROSS SLEEVE GASTRECTOMY AND LIFESTYLE INTERVENTION

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Background: Pediatric metabolic dysfunction-associated steatotic liver disease (MASLD), including steatohepatitis (MASH), lacks well-validated noninvasive tests (NITs) for fibrosis staging and treatment monitoring. Pediatric-derived scores and imaging NITs have largely been evaluated cross-sectionally. **Methods:** In a prospective parallel-arm cohort, adolescents aged 12–19 with severe obesity and biopsy-confirmed MASLD underwent vertical sleeve gastrectomy (VSG) or comprehensive lifestyle intervention (CLI), with repeat biopsy at week-52. NITs evaluated were ALT, GGT, Fibro-PeN, pediatric fibrosis-c (pFIB-c), pediatric fibrosis-6 (pFIB-6), MRI proton density fat fraction (MRI-PDFF), and MR elastography (MRE). We assessed baseline and week-52 detection of significant fibrosis (stage ≥ 2), week-52 NIT values for histologic response, and correlation of NIT change with histologic change. Models adjusted for baseline value and treatment arm. **Results:** Of 42 enrolled (VSG = 17; CLI = 25), 27 completed paired biopsies (VSG = 12; CLI = 15). Histologic improvement favored VSG over CLI: NAFLD Activity Score (NAS) improvement 11/12 (92%) vs 3/15 (20%), MASLD resolution 7/12 (58%) vs 0/15 (0%), MASH resolution (among baseline MASH) 8/8 (100%) vs 4/11 (36%), fibrosis improvement (≥ 1 stage) 6/12 (50%) vs 1/15 (7%). At baseline, MRE best discriminated significant fibrosis (AUROC 0.80, 95% CI 0.61–0.94); at week-52, Fibro-PeN (0.85, 0.67–0.97) and GGT (0.85, 0.69–0.97) performed best. In

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unadjusted cross-treatment analyses, the best week-52 NITs were Fibro-PeN for fibrosis improvement (0.90), MRI-PDFF for MASLD resolution (0.88), ALT for NAS improvement (0.86). NIT changes correlated only modestly with histologic change (Fibro-PeN with fibrosis stage, rho = 0.45, P = 0.02; MRI-PDFF with NAS, rho = 0.44, P = 0.03); after adjustment, no NIT-change term independently predicted any histologic outcome. Paired MRE trajectories diverged by arm and baseline stage: in VSG, the 2 with baseline F ≥ 2 (F3→F0, F4→F3) showed expected stiffness decrease, but those with low baseline fibrosis showed post-treatment increase (ΔMRE +0.30 to +0.71 kPa) despite stable or improved histology. Change in MRE was uncorrelated with change in MRI-PDFF in VSG (r = −0.04, P = 0.92), arguing against steatosis loss as explanation. **Conclusion:** Baseline MRE performed best for assessing fibrosis severity. Although week-52 Fibro-PeN, MRI-PDFF, and ALT showed strong unadjusted AUROCs for histologic response, NIT changes did not independently predict response after adjustment, indicating much of the unadjusted discrimination reflects treatment arm rather than biomarker-specific signal. Post-treatment MRE behaved discordantly in low-fibrosis VSG participants, unexplained by hepatic fat loss. Current pediatric NITs may be more useful as point-in-time markers than as change-based monitoring tools across treatments of differing intensity.

Table. Cross-sectional and Post-treatment Discrimination of Noninvasive Tests

Panel A. Cross-sectional discrimination of NITs for biopsy-confirmed significant fibrosis (F≥2)at baseline and week-52 assessment.

Marker	Baseline N	Baseline rho (P)	Baseline AUROC (95% CI)	Week-52 N	Week-52 rho (P)	Week-52 AUROC (95% CI)
ALT	42	0.20 (0.204)	0.54 (0.34–0.72)	27	0.19 (0.331)	0.67 (0.42–0.88)
GGT	42	0.35 (0.024)	0.70 (0.54–0.86)	27	0.42 (0.028)	0.85 (0.69–0.97)
pFIB-c	42	0.03 (0.857)	0.52 (0.35–0.71)	27	0.15 (0.450)	0.72 (0.49–0.91)
pFIB-6	42	-0.16 (0.306)	0.47 (0.29–0.66)	27	0.09 (0.656)	0.66 (0.44–0.85)
Fibro-PeN	42	0.39 (0.046)	0.65 (0.42–0.86)	27	0.38 (0.050)	0.85 (0.67–0.97)
MRI-PDFF	42	-0.06 (0.725)	0.54 (0.36–0.73)	27	0.24 (0.258)	0.69 (0.44–0.90)
MRE	42	0.66 (<0.001)	0.80 (0.61–0.94)	27	-0.07 (0.725)	0.38 (0.17–0.61)

Panel B. Unadjusted, cross-treatment discrimination of histologic response using absolute Week 52 NIT values.

outcome	marker	AUROC
Fibrosis improvement (baseline F≥1)	ALT	0.88 (0.61–1.00)
	GGT	0.80 (0.51–1.00)
	pFIB-c	0.78 (0.47–1.00)
	pFIB-6	0.70 (0.38–0.94)
	Fibro-PeN	0.90 (0.69–1.00)
	MRI-PDFF	0.88 (0.63–1.00)
MASLD resolution	ALT	0.86 (0.72–0.98)
	GGT	0.73 (0.50–0.93)
	pFIB-c	0.70 (0.43–0.92)
	pFIB-6	0.66 (0.38–0.91)
	Fibro-PeN	0.78 (0.54–0.95)
	MRI-PDFF	0.88 (0.61–1.00)
MASH resolution	ALT	0.80 (0.54–0.96)
	GGT	0.85 (0.64–0.98)
	pFIB-c	0.83 (0.60–1.00)
	pFIB-6	0.80 (0.57–0.97)
	Fibro-PeN	0.89 (0.73–1.00)
	MRI-PDFF	0.81 (0.54–0.97)
NAS improvement	ALT	0.86 (0.70–0.98)
	GGT	0.79 (0.61–0.94)
	pFIB-c	0.84 (0.65–0.95)
	pFIB-6	0.79 (0.60–0.93)
	Fibro-PeN	0.80 (0.61–0.95)
	MRI-PDFF	0.84 (0.62–1.00)

Panel B evaluates whether absolute NIT values at Week 52 distinguish participants with versus without histologic improvement or resolution; these AUROCs are not based on NIT change scores.

Abbreviations: AUROC, area under the receiver operating characteristic curve; CI, confidence interval; MASLD, metabolic dysfunction-associated steatotic liver disease; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; NAS, NAFLD Activity Score; pFIB-c, continuous pediatric fibrosis score; pFIB-6, simplified pediatric fibrosis score; pFIB-c, continuous pediatric fibrosis score.

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2661 | REAL-WORLD EXPERIENCE WITH SWITCHING TO ODEVIXIBAT FROM MARALIXIBAT IN PATIENTS WITH ALAGILLE SYNDROME: A RETROSPECTIVE CHART REVIEW

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Background: Two IBAT inhibitors (odevixibat [ODX] and maralixibat [MRX]) are approved for treating cholestatic pruritus in patients (pts) with Alagille syndrome (ALGS). Some pts experience loss of clinical response or gastrointestinal (GI) adverse events (AEs) that require switching to an alternative IBAT inhibitor. Long-term ODX data demonstrate favorable tolerability, sustained improvements in pruritus, and reductions in serum bile acids in the phase III ASSERT/ASSERT-EXT studies (NCT04674761/NCT05035030); limited data are available in pts previously treated with MRX in whom

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switching to ODX may be beneficial. This is particularly important in adolescents requiring transition of care between pediatric and adult hepatologists. In this interim analysis of retrospective chart data, we characterize real-world drivers of switching and post-switch clinical parameters in adolescents with ALGS (age at ODX initiation, 13–18 years). **Methods:** This is a real-world, non-interventional, multicenter, retrospective chart review of pts with ALGS conducted in France and the US. Eligible pts had a genetic diagnosis, ≥4-week treatment with MRX prior to switching, and ≥4-week treatment with ODX after switching. The primary objective was to describe the reasons for discontinuing MRX and reasons for initiating ODX. Secondary objectives included demographics and clinical characteristics prior to switch, and AEs. Data were collected from up to 12 months before the last visit prior to MRX discontinuation, through all visits on MRX and ODX and until the time of data collection or the end of ODX treatment. **Results:** At data cutoff (March 25, 2026), five pts had been recruited, including three adolescents (age at ALGS diagnosis, 5–21 months). MRX was discontinued between 11.5 and 17.1 years of age after median 12.5 weeks of treatment; the observed reasons for MRX discontinuation in these pts were GI AEs (n = 2) or poor adherence to treatment with uncontrolled pruritus (n = 1). Pruritus subsequently improved in all three pts after ODX initiation. The most common GI AEs (Grade 1 & 2) related to MRX included diarrhea (n = 2), vomiting (n = 3), abdominal pain (n = 3), and nausea (n = 1); fewer GI AEs were observed with ODX (diarrhea [n = 2] and abdominal pain [n = 2]), that were transient and resolved by data cutoff without discontinuation. **Conclusion:** In this small cohort of adolescents with ALGS, observed reasons for discontinuing MRX included GI AEs, poor adherence, and uncontrolled pruritus. Switching to ODX from MRX improved pruritus symptoms in all pts, with fewer GI AEs that resolved without discontinuation. These preliminary results suggest that patients with ALGS who experience GI intolerance or inadequate symptom control on MRX could clinically benefit from switching to ODX. This may potentially inform clinical decisions in adolescents with ALGS transitioning to adult hepatology care. Enrollment is ongoing and further analysis will be presented.

Disclosures: Nadia Ovchinsky: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Mathias Ruiz: Nothing to Disclose, Alice Tiret: Nothing to Disclose, Madeleine Aumar: Nothing to Disclose, Henry Lin: Ipsen: Advisor, Mirum: Advisor, Muriel Girard: Nothing to Disclose, Cécile Artaud: Nothing to Disclose, Marie-Cécile Fournier: Nothing to Disclose, Frédérique Thoby: Nothing to Disclose, Etienne Quet: Nothing to Disclose.

2662 | DISCORDANCE BETWEEN METABOLIC BURDEN AND FIBROSIS SEVERITY IN BLACK YOUTH WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD)

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common chronic liver condition in the pediatric population. Although racial and ethnic differences in pediatric MASLD prevalence are recognized, less is known about whether Black youth with MASLD differ in metabolic phenotype, genetic risk, or histologic severity. We compared metabolic and histologic features of Black and White pediatric participants enrolled in the NASH Clinical Research Network. **Methods:** We analyzed baseline characteristics of 1,248 pediatric participants (mean age 12.5 years) enrolled in the NASH CRN. Participants were categorized as non-Hispanic Black (NHB, n = 21), Hispanic Black (HB, n = 20), non-Hispanic White (NHW, n = 306), or Hispanic White/Other (HW/Other, n = 901). Clinical, metabolic, PNPLA3 genotype, and centrally reviewed liver histology data were compared across groups. Logistic regression evaluated the association of race/ethnicity with clinically significant fibrosis, defined as stage 2–4 versus stage 0–1. **Results:** NHB participants had the highest mean weight, BMI z-score, and prevalence of severe obesity; severe obesity was present in 67% of NHB participants compared with 41% of NHW and 25% of HW/Other participants ($p < 0.001$). Metabolic syndrome was significantly more prevalent in NHB and HB cohorts (45% for both) compared to HW (29%; $p < 0.001$). NHB also demonstrated the highest levels of insulin resistance (HOMA-IR median 8.8 vs 5.2 NHW, $p > 0.001$). Triglyceride levels were significantly lower in NHB vs. NHW children (median 116 vs. 140; $p = 0.006$). PNPLA3 risk genotype frequency differed substantially across groups: 36% of NHB participants carried the CG/GG genotype compared with 72% of NHW and 92% of HW/Other participants ($p < 0.001$). On biopsy, NAS and fibrosis scores did not differ between NHB and NHW children. (NAS 4.4 vs 4.2 $p = 0.44$) and fibrosis stage 0.8 vs 1.2, $p = 0.18$). Multivariable logistic regression analysis showed that NHB and HB participants had a lower odds of clinically significant

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fibrosis compared to NHW, adjusted for age, sex, BMI z-score, Type 2 diabetes, hypertension, and triglyceride level (OR = 0.29 [95% CI 0.11, 0.77], p = 0.01), but this association was attenuated when adjusted for PNPLA3 genotype (OR = 0.35 [95% CI 0.11, 1.04), p = 0.06). **Conclusion:** Black youth with MASLD in the NASH CRN had greater obesity, and insulin resistance, but did not have greater histologic severity than White youth. Lower PNPLA3 risk genotype frequency may partly explain the lower adjusted odds of clinically significant fibrosis observed in Black participants. These findings illustrate heterogeneity in pediatric MASLD and support further study of how metabolic, genetic, and social determinants jointly shape disease severity across racial and ethnic groups.

Table Independent association of clinically significant fibrosis (stage 2-4 vs. stage 0-1) with race/ethnicity

	Unadjusted		Adjusted for Demographic and Clinical Covariates*		Adjusted for Demographic, Clinical, and PNPLA3†	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
White, non-Hispanic (ref.)	1.0		1.0		1.0	
Black (combines Hispanic and non-Hispanic)	0.31 (0.12, 0.81)	0.02	0.29 (0.11, 0.77)	0.01	0.35 (0.11, 1.04)	0.06
Hispanic, white/other	0.85 (0.64, 1.13)	0.25	0.90 (0.66, 1.21)	0.47	0.80 (0.57, 1.14)	0.22

Logistic regression analysis with the outcome of fibrosis stage 2-4 vs. fibrosis stage 0-1. N=1,248 for unadjusted models.
* Models adjusted for age, sex, BMI z-score, Type 2 diabetes, hypertension, and triglyceride level; N=1,236 due to missingness in covariates.
† Models adjusted for age, sex, BMI z-score, Type 2 diabetes, hypertension, triglyceride level, and PNPLA3 genotype (CG/GG vs. CC). N=922 due to missingness in covariates, including unavailable genotyping.

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2663 | MODIFIED NEW WILSON INDEX FOR PEDIATRIC HEPATIC WILSON DISEASE WITH LIVER FAILURE: INCORPORATING ENCEPHALOPATHY SEVERITY AND RECALIBRATED INR IMPROVES PROGNOSTICATION

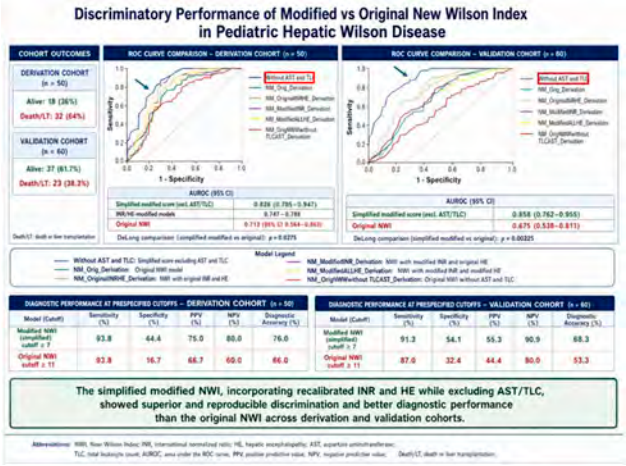
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Background: The New Wilson Index (NWI) is widely used to predict outcomes in severe hepatic Wilson disease (WD), but its performance may vary in modern pediatric cohorts, especially with therapeutic plasma exchange. We assessed whether adjusting admission INR and including hepatic encephalopathy (HE) severity improves prediction of death or liver transplantation (Death/LT). **Methods:** In a single-center observational cohort of **110** children/adolescents with WD presenting with acute-on-chronic liver failure or decompensated chronic liver disease, outcomes were classified as alive versus Death/LT. Patients were split by UHID order into derivation (**n = 50**) and validation (**n = 60**) cohorts. Admission INR was re-categorized into five ordinal bands: $\leq$**2.50, 2.51–3.29, 3.30–3.99, 4.00–5.69,** $\geq$**5.70** . HE was scored as **0** for none, **2** for grade I–II, and **4** for grade III–IV. Candidate modified models were compared with original NWI using AUROC, fixed-cutoff classification, DeLong testing, calibration, reclassification indices, decision-curve analysis, and time-to-event discrimination. **Results:** In the derivation cohort, the simplified modified NWI with inclusion of HE and recalibrated INR cut-offs with exclusion of AST and TLC demonstrated significantly better discrimination than the original NWI, with AUROC improving from 0.713 for original NWI to 0.826 for the modified score (95% CI 0.705-0.947; DeLong p = 0.0275). This improvement was reproducible in the validation cohort, where the simplified modified NWI retained superior discrimination (AUROC 0.858; 95% CI 0.762-0.955) compared with original NWI (AUROC 0.675; 95% CI 0.538-0.811; DeLong p = 0.00225). Using a prespecified high-risk threshold of modified NWI 7, validation cohort sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy were 91.3%, 54.1%, 55.3%, 90.9%, and 68.3%, respectively. In comparison, the conventional original NWI 11 threshold yielded lower performance across all corresponding metrics (87.0%, 32.4%, 44.4%, 80.0%, and 53.3%, respectively), indicating improved classification of Death/LT risk with the modified score. The modified NWI also demonstrated better transported validation calibration, with a lower Brier score than original NWI (0.181 vs 0.253), substantial improvement in risk reclassification (continuous NRI 1.469; IDI 0.202), and higher decision-curve net benefit across clinically relevant threshold probabilities. In time-to-event analysis, the modified NWI showed superior validation discrimination for Death/LT-free survival compared with original NWI (C-index 0.795 vs 0.650), supporting its incremental prognostic value beyond fixed-time binary classification. **Conclusion:** A simplified modified NWI incorporating recalibrated INR and graded HE improves prognostic discrimination, classification, calibration,

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and clinical utility for pediatric hepatic WD with liver failure.



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2664 | GROWTH IN 433 CHILDREN WITH PROGRESSIVE FAMILIAL INTRAHEPATIC CHOLESTASIS (PFIC): THE INFLUENCE OF PFIC SUBTYPE AND SEX

Alise de Groot[1] Elizabeth Bannister[2] Mark Nomden[1] Richard Thompson[3] Benjamin Shneider[4] Emmanuel Gonzales[5] Irena Jankowska[6] Etienne Sokal[7] Seema Alam[8] Cigdem Arikan[9] Henrik Arnell[10] Madeleine Aumar[11] Amer Azaz[12] Emna Barkaoui[13] María Belén Pallitto[14] Marisa Beretta[15] Teresa Botelho[16] Jernej Brecelj[17] Dieter Broering[18] Pier Luigi Calvo[19] Mara Cananzi[20] Huey-Ling Chen[21] Guillermo Costaguta[22] Piotr Czubkowski[23] Lorenzo D'Antiga[24] Elisa Carvalho[25] Dominique Debray[26] Antal Dezs?fi[27] Angelo Di Giorgio[28] Ozlem Durmaz[29] Alexandre Fabre[30] Ryan Fischer[31] Björn Fischler[32] Tanja Fritz[33] Cristina Gonçalves[34] Enke Grabhorn[35] Tassos Grammatikopoulos[36] Girish Gupte[37] Winita Hardikar[2] Loreto Hierro[38] Giuseppe Indolfi[39] Emmanuel Jacquemin[40] Giulia Jannone[7] Carolina Jimenez-Rivera[41] Marianne Hørby Jørgensen[42] Binita Kamath[43] Wikrom Karnsakul[44] Nanda Kerkar[45] Kyung Mo Kim[46] Jae Sung Ko[47] Denitza Kofinova[48] Nolwenn Laborde[49] Zhongdie Li[50] Patryk Lipi?ski[51] Rohan Malik[52] Saeed Mohammad[53] Yael Mozer-Glassberg[54] Gema Muñoz Bartolo[38] Gabriella Nebbia[55] Emanuele Nicastro[24] Felipe Ordoñez Ferrero[56] Anna Orłowska[6] Arti Pawaria[57] Tudor Pop[58] Jesus Quintero Bernabeu[59] Giusy Ranucci[60] Aathira Ravindranath[61] Nathalie Rock[62] Maria Rogalidou[63] Ioannis Roilidis[64] Mathias Ruiz[65] Thomas Sandahl[66] Srinivas Sankaranarayanan[67] Mohammad Shagrani[68] Eyal Shteyer[69] Pooja Reddy Spector[70] James Squires[71] Ekkehard Sturm[72] Cristina Targa Ferreira[73] Marise Tofoli[74] Bethany Tucker[75] Christos Tzivinikos[76] Wendy van der Woerd[77] Georg Friedrich Vogel[78] Heng Wang[79] Jian-She Wang[50] Sabina Wiecek[80] Aglaia Zellos[81] Andreanne Zizzo[82] Pedro Miranda-Afonso[83] Bettina Hansen[83] Paola Mian[1] Henkjan Verkade[1], [1]University of Groningen, University Medical Center Groningen, Groningen, Netherlands, [2]Royal Children's Hospital, [3]King's College London, [4]Texas Children's Hospital, [5]Hopital Bicetre, [6]Children's Memorial Health Institute, Warsaw, Poland, [7]Cliniques St Luc, Brussels, Belgium, [8]Institute of Liver and Biliary Sciences, [9]Koc University School of Medicine, Istanbul, Turkey, [10]Karolinska University Hospital, [11]CHU Lille, Univ. Lille, Lille, France, [12]Sheikh Khalifa Medical City, Abu Dhabi, United Arab Emirates, [13]Tunis Children Hospital, Tunis, Tunisia, [14]Hospital Italiano, CABA, Buenos Aires, Argentina, [15]Wits Donald Gordon Medical Centre, University of the Witwatersrand, Johannesburg, South Africa, [16]Unidade Local de Saúde Coimbra, Coimbra, Portugal, [17]University of Ljubljana, Ljubljana, Slovenia, [18]King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia; Alfaisal, [19]Azienda Ospedaliera Città Della Salute e Della Scienza University Hospital, [20]University of Padova, [21]National Taiwan University, [22]CHU de Quebec-Université Laval, Quebec City, Canada, [23]The Children's Memorial Health Institute, [24]Hospital Papa Giovanni XXIII, Bergamo, Italy, [25]Hospital da Criança de Brasília, Centro Universitário de Brasília, Brasília, Brazil, [26]APHP-Necker Enfants Malades University Hospital, Paris, France, [27]Semmelweis University, Budapest, Hungary, [28]University of Udine, Udine, Italy, [29]Istanbul University Istanbul Medical Faculty, [30]APHM, Hôpital de la Timone Enfant, France, [31]Children's Mercy Kansas City, [32]Karolinska Institutet, Stockholm, Sweden, [33]University Children's Hospital Tübingen, Tübingen, Germany, [34]Pediatric Gastroenterology/Hepatology Center Lisbon, Lisbon, Portugal, [35]University Medical Center Hamburg Eppendorf, Hamburg, Germany, [36]King's College Hospital, [37]Birmingham Women's and Children's Hospital, Birmingham, United Kingdom, [38]Children's Hospital La Paz, La Paz University Hospital, Madrid, Spain, [39]Meyer Children's Hospital, IRCCS, Florence, Italy, [40]Le Kremlin-Bicêtre, and Inserm U1193, Hepatinov, University of Par, Orsay, France, [41]Children's Hospital of Eastern Ontario, University of Ottawa, Ottawa, Canada, [42]Rigshospitalet Copenhagen University Hospital, Copenhagen, Denmark, [43]Children's Hospital of Philadelphia, [44]Johns Hopkins University,

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Background: Growth failure is a frequent complication of pediatric cholestatic liver diseases, including familial intrahepatic cholestasis 1 (FIC1) deficiency and bile salt export pump (BSEP) deficiency. Although the severity of cholestasis is frequently similar in both these conditions, they are genetically distinct, and FIC1 deficiency also has extrahepatic manifestations. Global collaboration within the NAPPED consortium and the prospective TreatFIC registry has created the largest dataset for these rare diseases, enabling for the first time a large-scale, reliable analysis of the growth trajectories in patients with FIC1 and BSEP deficiency. **Methods:** We included demographic and clinical data from patients in the NAPPED and TreatFIC registries with available height measurements and biallelic disease-causing variants in *ATP8B1* (FIC1) or *ABCB11* (BSEP). Height measurements up to the age of 10 years were converted into WHO-standardized height-for-age z-scores (HAZ). Growth stunting (GS) was defined as HAZ < −2. Differences in HAZ over 24-month intervals from 0 to 10 years old between groups were assessed using median regression, adjusting for interruption of the enterohepatic circulation and liver transplantation. **Results:** We included 433 patients, of whom 110 had FIC1 deficiency (male/female 59/41%) and 323 had BSEP deficiency (male/female 52/48%). Median age at first presentation was 0.5 years (interquartile range [IQR] 0.2–1.5) in patients with FIC1 deficiency and 0.8 years (IQR 0.2–1.9) in those with BSEP deficiency. Median follow-up time was 4.8 years (IQR 2.5–7.4) and 5.6 years (IQR 2.5–8.1), respectively. By age 10, 49% of patients with FIC1 deficiency and 27% of those with BSEP deficiency had undergone surgical biliary diversion, 25% vs. 14% had received ileal bile acid transporter inhibitors, and 45% vs. 53% had undergone liver transplantation, respectively. The patients with FIC1 deficiency had a lower median HAZ during the first 10 years of life ($p < 0.05$; Figure 1A), and a higher proportion had GS (FIC1 59% vs. BSEP 42%, $p < 0.01$). In FIC1 deficiency, there were no significant sex differences in HAZ at any time point. In BSEP deficiency, however, growth trajectories differed between boys and girls, with girls aged 4–10 years having a significantly lower HAZ (Figure 1B). The prevalence of GS was 45.8% in girls and 38.1% in boys ($p < 0.05$). **Conclusion:** Children with FIC1 deficiency are shorter and a higher percentage has GS compared with children with BSEP deficiency, which may be related to extrahepatic deficiency of ATP8B1. In BSEP deficiency, girls have more pronounced pre-pubertal growth restriction than boys. Recognition of these disease- and sex-specific growth patterns, together

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with improved understanding of the underlying mechanisms, may target approaches to optimize growth potential.

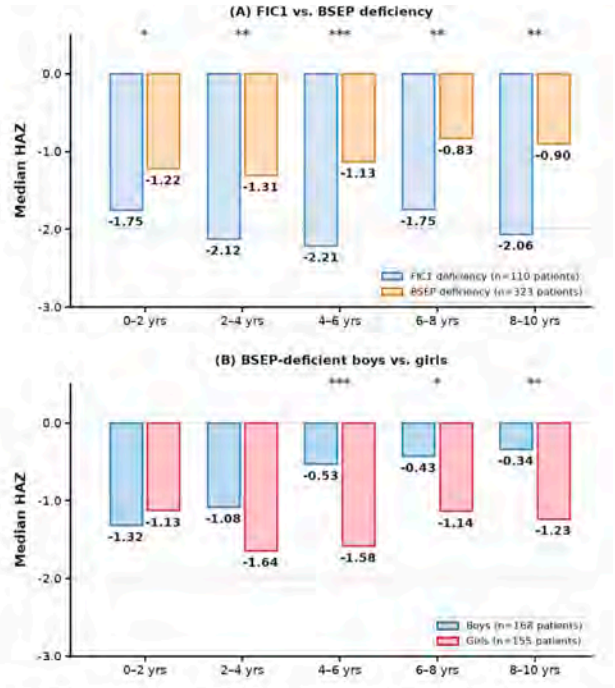


Figure 1. (A) HAZ by absolute age, stratified by PFIC subtype. (B) HAZ by absolute age for BSEP deficiency, stratified by sex. Groups were compared at each 24-month interval using median quantile regression, adjusted for interruption of the enterohepatic circulation (ileal bile acid transporter inhibitor therapy or surgical biliary diversion) and liver transplantation. *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$.

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2665 | ODEVIXIBAT DOES NOT CAUSE FAT-SOLUBLE VITAMIN DEFICIENCY IN PATIENTS WITH PROGRESSIVE FAMILIAL INTRAHEPATIC CHOLESTASIS

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Background: Progressive Familial Intrahepatic Cholestasis (PFIC) is a group of rare cholestatic liver diseases in which impaired bile flow compromises intestinal absorption of fat-soluble vitamins A, D, E and K (FSV). Odevixibat, an ileal bile acid transporter inhibitor (IBATi), has demonstrated efficacy in reducing pruritus and serum bile acid levels in patients with PFIC. By interrupting the enterohepatic circulation, odevixibat may decrease FSV absorption. We evaluated the effect of odevixibat on serum FSV levels in patients with PFIC using the largest global prospective registry with real world data on PFIC, TreatFIC.
Methods: Patient data and serum concentrations of vitamin A, D and E were exported from TreatFIC (NCT06778174, May 2026) and normalized to center-specific lower limits of normal (LLN). For vitamin K deficiency, we used International Normalized Ratio (INR) as surrogate, with 1.2 as upper limit of normal (ULN). A linear mixed-effects model (LMM) was fitted for each FSV separately. Each model was adjusted for supplementation dose, age, sex and northern or southern hemisphere seasonal variation. We compared data from patient visits during odevixibat treatment to those without IBATi-treatment. Visits after liver transplantation were censored. The percentage of FSV deficient visits before and after odevixibat initiation was compared using paired Wilcoxon signed-rank tests. $P < 0.05$ was considered significant.
Results: A total of 132 PFIC patients (FIC1 = 28; BSEP = 56, MDR3 = 31, MYO5B = 6, TJP2 = 5, Other = 6) were included, with 68 patients receiving odevixibat (43 already on treatment upon entering TreatFIC and 25 patients starting treatment during follow-up). Total number of patient visits was 250. Irrespective of odevixibat treatment, 14-29% of all patient visits were below the LLN of vitamins A, D and E, and 15-16% above the ULN for INR (Figure). In line with this, odevixibat use was not significantly associated with decreased serum concentrations of vitamin A, D or E, nor with increased INR. Upon starting odevixibat, the FSV supplementation dosages were not changed in 78% of patients (n = 49 patient-vitamin pairs). Nevertheless, the percentage of visits with FSV deficiency did not change (16% vs. 17%, prior to and after starting odevixibat, resp., NS). Upon starting odevixibat, FSV supplementation dosages were changed in 22% of patients (median

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changes: D, +800 IU/day; E, -77 mg/day; K, +0.8 mg/day; n = 14 patient-vitamin pairs). In these patients, the fraction of FSV deficient visits did not significantly change either (38% vs. 27%, prior to and after starting odevixibat, resp., NS). **Conclusion:** Odevixibat does not cause FSV deficiency in patients with PFIC, despite theoretical concerns related to interruption of the enterohepatic circulation and intestinal bile acid deficiency. Independent of odevixibat use, between 13 and 29% of patients with PFIC have biochemical FSV deficiency.

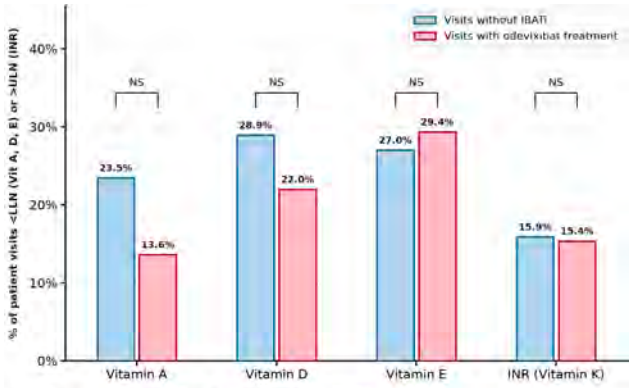


Figure. Percentage of patient visits indicating FSV deficiency

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2666 | SURGICAL BILIARY DIVERSION EFFECTIVELY TREATS CHOLESTATIC PRURITUS IN FIC1 DEFICIENCY PATIENTS NOT RESPONDING TO IBAT INHIBITION

Willem Lexmond[1] Amala Alenchery[2] Alise de Groot[1] Winita Hardikar[3] Anna Orłowska[4] Piotr Czubkowski[4] Pamela Valentino[5] James Squires[2] Henkjan Verkade[1], [1]University Medical Center Groningen, [2]Children's Hospital of Pittsburgh, [3]Royal Children's Hospital, [4]The Children's Memorial Health Institute, [5]Seattle Children's Research Institute

Background: Progressive familial intrahepatic cholestasis (PFIC1) is caused by mutations in *FIC1*. For PFIC1 patients, cholestatic pruritus is usually the most burdensome hepatological symptom that may necessitate liver transplantation even in the absence of end-stage liver disease. The cornerstone of anti-pruritic therapy is interruption of the enterohepatic circulation (iEHC) of bile acids. With the advent of ileal bile acid transporter inhibitors (IBATi), iEHC can now be achieved pharmacologically, with obvious advantages over traditional surgical biliary diversion (SBD). Many PFIC1 patients, however, do not respond to IBATi. IBATi and SBD both interrupt the EHC, but only SBD results in pre-intestinal disposal of bile and conjugated bile acids from the body. In IBATi-treated patients, in contrast, conjugated bile acids remain available for microbial deconjugation and passive re-uptake in the colon. We investigated whether auxiliary treatment with SBD could effectively relieve cholestatic pruritus in IBATi-nonresponsive PFIC1 patients. **Methods:** We retrospectively analyzed data on 10 patients (6 boys) with bi-allelic mutations in *ATP8B1* (*FIC1*) who had undergone SBD while already on IBATi therapy. From these patients, we retrieved data on genetic testing, sex and age of the patients, timing of treatment with IBATi and biochemical and clinical characteristics from clinic visits before and after SBD. **Results:** SBD was performed at a median age of 3.1 years (IQR 1.7 – 5.0) and after a median treatment duration with IBATi of 2.9 years (IQR 1.1 – 3.5). Pruritus was present in all patients before SBD was undertaken. In 8 of 10 patients (80%), itch had resolved within 12 months after diversion. In 2 patients (20%), SBD did not improve pruritus, and one of these is

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currently considered for liver transplantation. Interestingly, the pruritus response appeared to be independent of serum bile acid response. In 4 patients, IBATi therapy has been successfully stopped. The other 6 patients continue to be treated with a combined EHC interruption with both SBD as well as IBATi at a median follow-up time of 1.4 years (IQR 0.8 – 2.8) after SBD. **Conclusion:** Auxiliary SBD can successfully treat cholestatic pruritus in IBATi-nonresponsive PFIC1 patients. Combined surgical and pharmacological interruption of the enterohepatic circulation should be considered before committing PFIC1 patients to liver transplantation for intractable itch.

Disclosures: Willem Lexmond: Mirum Pharmaceuticals: Consultant, Amala Alenchery: Nothing to Disclose, Alise de Groot: Nothing to Disclose, Winita Hardikar: Nothing to Disclose, Anna Orłowska: Nothing to Disclose, Piotr Czubkowski: Nothing to Disclose, Pamela Valentino: Nothing to Disclose, James Squires: Sanofi: Data Safety Committee, Mirum: Advisor, Ipsen: Advisor, Sanofi: Data Safety Committee, Sanofi: Data Safety Committee, Mirum: Advisor, Mirum: Advisor, Ipsen: Advisor, Ipsen: Advisor, Sanofi: Data Safety Committee, Mirum: Advisor, Ipsen: Advisor, Sanofi: Data Safety Committee, Sanofi: Data Safety Committee, Mirum: Advisor, Mirum: Advisor, Ipsen: Advisor, Ipsen: Advisor, Sanofi: Data Safety Committee, Mirum: Advisor, Ipsen: Advisor, Sanofi: Data Safety Committee, Sanofi: Data Safety Committee, Mirum: Advisor, Mirum: Advisor, Ipsen: Advisor, Ipsen: Advisor, Henkjan Verkade: Nothing to Disclose.

2667 | LIGHT AND ELECTRON MICROSCOPY DEMONSTRATE LIMITED DIAGNOSTIC SPECIFICITY IN PEDIATRIC MITOCHONDRIAL HEPATOPATHIES

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Background: Light microscopy (LM) and electron microscopy (EM) are routinely used in evaluating suspected mitochondrial hepatopathy (MH), a heterogeneous group of disorders for which definitive histopathologic correlates and genotype-phenotype relationships remain poorly defined. We assessed LM and EM features relative to genetic diagnoses in a prospectively enrolled pediatric cohort. **Methods:** Liver biopsies from 42 pediatric patients (median age 2.3 years, 73.8% male) clinically enrolled in the prospective MITOHEP mitochondrial hepatopathy study and 2 genetically confirmed cases from PROBE (a prospective database of infants with cholestasis) of the Childhood Liver Disease Research Network were analyzed (LM & EM n = 25; LM only n = 10; EM only n = 7). When available, genetic diagnosis served as the reference standard. Three expert reviewers independently evaluated anonymized LM and EM images blinded to genetic diagnosis, with interobserver discrepancies resolved by group consensus. Features were systematically evaluated using LM and EM and categorized as diagnostic, suspicious, or unlikely for MH, summarized using counts and percentages, and compared across genetic categories using Fisher's exact test. **Results:** Genetic diagnoses varied, most commonly *DGUOK* (n = 5), *POLG* (n = 5), *MPV17* (n = 4), and *TRMU* (n = 4). LM findings were heterogeneous and non-specific, with no significant genotype-phenotype correlations. Microvesicular and macrovesicular steatosis were variably present without significant differences across genetic categories. LM showed minimal inflammatory activity. LM was diagnostic in 5.9%, suspicious in 35.3%, and unlikely in 58.8% of cases. n contrast, EM frequently demonstrated mitochondrial abnormalities but was rarely diagnostic. EM was diagnostic in 3.1%, suspicious in 78.1%, and unlikely in 18.8% of cases. EM abnormalities were heterogeneous and overlapping across genetic groups, without reproducible genotype-specific patterns. LM more frequently classified cases as

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unlikely, whereas EM more frequently classified cases as suspicious. See Table 1. **Conclusion:** LM and EM demonstrate limited utility for mitochondrial hepatopathies and do not reliably distinguish genetic subtypes. LM predominantly reflects nonspecific injury patterns; EM more often identifies mitochondrial abnormalities and increases diagnostic suspicion. These findings highlight the complementary but limited role of histologic and ultrastructural evaluation, with genetic testing remaining essential for definitive diagnosis.

Table 1 (a-d)

a. Histologic and Ultrastructural Features Evaluated

Modality	Features Evaluated
Light microscopy	Hepatocellular steatosis (microvesicular and macrovesicular) and hepatocyte necrosis; oncocytic hepatocytes; portal and lobular inflammation; fibrosis stage
Electron microscopy	Mitochondrial quantity, pleomorphism, cristae morphology, electron density, distribution, and matricial dense granules; hepatocytic lipid

b. Genetic Categories

Genetic Category	Genes	N
mtDNA depletion	*DGUOK, MPV17, POLG, POLG2*	15
RNA translation	*CARS2, MTFMT, TRMU*	6
mtDNA deletion	mtDNA deletion, *ATP6*	4
Enzymatic/FAO	Complex defects	5
Negative genetic testing	*NBAS*/none	9
No genetic testing	N/A	3

Legend: mt, mitochondrial; FAO, mitochondrial fatty acid oxidation defects; WES, whole exome sequencing; TGP, targeted gene panel; NBAS, neuroblastoma amplified sequence (not significant gene in mitochondrial hepatopathy), N/A, not applicable

c. Steatosis by Light Microscopy Across Genetic Categories

Genetic Category (N)	Microvesicular (% of cases)	Macrovesicular (% of cases)
mtDNA depletion (15)	Absent 64%; Present 36% (Rare, 7%; 5-66%, 29%)	Absent 50%; Present 50% (Rare, 21%; Mild, 21%; Moderate, 7%)
RNA translation (6)	Absent 75%; Present 25% (5-66%, 25%)	Absent 50%; Present 50% (Moderate, 25%; Severe, 25%)
mtDNA deletion (4)	Absent 75%; Present 25% (5-66%, 25%)	Absent 25%; Present 75% (Rare, 75%)
Enzymatic/FAO (5)	Absent 50%; Present 50% (Rare, 50%)	Absent 25%; Present 75% (Rare, 50%; Mild, 25%)

Legend: mt, mitochondrial; Absent (0%); Rare (<5%); Present (≥5%); Mild (5-33%); Moderate (>33-66%); Severe (>66%); FAO, mitochondrial fatty acid oxidation defects

d. Electron Microscopy Findings Across Genetic Categories

Genetic Category (N)	Electron Microscopic Findings (% of EM cases)
mtDNA depletion (15)	Increased mitochondria 20%; pleomorphism 30%; abnormal cristae 50%; abnormal electron density 60%; small droplet lipid 70%
RNA translation (6)	Increased mitochondria 40%; pleomorphism 40%; abnormal cristae 20%; abnormal electron density 80%; small droplet lipid 80%
mtDNA deletion (4)	Increased mitochondria 33%; pleomorphism 0%; abnormal cristae 67%; abnormal electron density 33%; small droplet lipid 100%
Enzymatic/FAO (5)	Increased mitochondria 25%; pleomorphism 0%; abnormal cristae 50%; abnormal electron density 25%; small droplet lipid 75%

Legend: mt, mitochondrial; FAO, mitochondrial fatty acid oxidation defects

Disclosures: Mark Lovell: Nothing to Disclose, Eric Wartchow: Nothing to Disclose, M.Cristina Pacheco: Takeda Pharmaceuticals: Part of project. Receive no direct or institutional support, Colleen Kincaid: Nothing to Disclose, Kieran Hawthorne: Nothing to Disclose, Ronald Sokol: Mirum: Advisor, Ipsen/Albireo: Advisor, Malinkrodt: Consultant, Alexion: Consultant, ProQR: Consultant, Estella Alonso: Nothing to Disclose, Steve Guthery: Nothing to Disclose, Simon Horslen: Mirum: Grant/Research Support, Albireo/Ipsen: Consultant, Mallinckrodt Pharma: Consultant, Saul Karpen: Albireo/Ipsen: Consultant, Mirum: Consultant, Intercept: Consultant, Rohit Kohli: Mirum: Consultant, Ipsen: Consultant, Epigen: Grant/Research Support, Sanofi Rare Disease: Consultant, iECURE: Consultant, Solid Biosciences: Consultant, Kathleen Loomes: Nothing to Disclose, John Magee: Nothing to Disclose, Alexander Miethke: Mirum Pharmaceutical Inc: Grant/Research Support, Mirum Pharmaceutical Inc: Consultant, Ipsen: Speaking and Teaching, Perspectum Ltd.: Grant/Research Support, Esperion: Advisor, Jean Molleston: Gillead: Grant/Research Support, Albireo: Grant/Research Support, Abbvie: Grant/Research Support, Mirum/Shire: Grant/Research Support, Phillip Rosenthal: Nothing to Disclose, Benjamin Shneider: Nothing to Disclose, Pamela Valentino: Nothing to Disclose, Kasper Wang: Nothing to Disclose, Grace Kim: Nothing to Disclose, Childhood Liver Disease Research Network (ChiLDRen): Nothing to Disclose.

2668 | PROSPECTIVE LONGITUDINAL CHARACTERIZATION OF A COHORT OF INFANTILE WILSON DISEASE

Rima Fawaz[1] Ayse Coskun[2] Sefa Keserci[1] Hatice Maras[1] Asim Ulcay[1] Pamela Valentino[3] Michael Schilsky[4], [1]Yale University School of Medicine, [2]Creighton University, [3]Seattle Children's Hospital, [4]Yale University Medical Center

Background: Objectives: To characterize the clinical and diagnostic evaluation, treatment and follow up in a cohort of infants with Wilson Disease (WD). **Methods:** Cohort: children with WD age <5 years (N=18, 12 females,12 White, 5 Asian ,1 mixed Asian/white) enrolled in a prospective registry (2018-2026). WD was defined by Leipzig score ≥4. **Results:** All 18 participants were asymptomatic and diagnosed by genetic screening due to parental carrier status, newborn screening or family history. Nine patients had 2 pathogenic(P) *ATP7B* mutations; five had 1P+1 likely pathogenic (LP), two had 2 LP, one had P and a variant of unknown significance. In this last patient, the ceruloplasmin was <3, ALT >3xULN, and they had a sibling with symptomatic WD. Ceruloplasmin was persistently <10 mg/dL in 3, <14 mg/dl in 6 and <20 mg/dl in 11 participants at diagnosis and during follow up. ALT was elevated in 12/16 before treatment (~1.5-2 x ULN). Liver ultrasound was obtained in 13 participants; 9 were normal and 4 had minimal changes reported as increased hepatic echogenicity or coarsened echotexture. One had liver

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biopsy prior to start of therapy at age 5 years; liver copper was 789 mcg/g dry weight. Three did not receive any therapy due to age < 2 years. Zinc monotherapy was started in 15: at 5 months in 1, at 12-23 months in 5, 24-35 months in 7 and 36-50 months in 2. Initial dosages of zinc prescribed were 5 mg daily,12.5 mg bid and 25 mg daily. In one participant initiated on zinc 25 mg bid at 19 months, a year later developed signs of copper deficiency with undetectable serum copper, ceruloplasmin and neutropenia but no anemia. Zinc was stopped for 6 months then restarted as once daily treatment with resolution of neutropenia and slow improvement in serum copper. Liver enzymes continued to be elevated in 9/15 on treatment, but most had an improved trend. All participants on zinc monotherapy with available testing (8/18) had a 24-hour urine copper < 100 mcg. One participant had a liver biopsy at 5 years due to persistently elevated liver enzymes while on zinc monotherapy since age 1 year. Liver copper was 630 mcg/g dry weight. Though they were switched to trientine, liver enzymes were persistently elevated and 24-hour urine copper on therapy was 42 and 70 mcg, suggesting possible overtreatment. **Conclusion:** Genetic/Infantile WD presents a challenging paradigm with lack of clinical and diagnostic hallmarks to inform providers as to the optimal timing of treatment initiation, choice of medication and dosing, and frequency of monitoring. Further access to clinical diagnostic tools and studies to guide uniformity in managing this growing patient population are urgently needed as affordable expanded carrier screening of mothers during pregnancy and newborn screening for WD are becoming a reality.

Characteristics of the study population, with longitudinal laboratory work up with management

Pt	Sex	Age at Dx (m)	Reason for screening	ATP7B mutation (P/LP/VUS)	Age at Tx (m)	Zinc dose	ALT(U/L)	Ceruloplasmin (mg/dL)	Urine Cu (µg/24h)	Liver Biopsy (mcg/g dry weight)/ Ultrasound (age in months)/ Stiffness
1	F	NB	-NB testing	-c.[2207A (P) -c.[2207A(P) *SCID mutation	29	25 mg daily	B: 40, 27 A: 39,41,40,40	B: 19, 18 A: 17, 15		B: (8 m) Cholelithiasis, mild hepatomegaly A: (37 m) mildly enlarged spleen, cholelithiasis
2	M	12	-IVF screening for younger sibling	-c.2503G>A (P) -c.3818C.T (P)	24	12.5 mg bid	B: 40, 45 A: 19	B: 23,20 A: 18		B: (6 m) minimal clustering of liver echodensities A: (29 m) mild heterogeneous hepatic echotexture
3	M	NB	-Carrier status of parents	-c.3904-2A>G (P) -c.3303A>G (LP)	12	25 mg daily Trientine 250 mg BID	B: 167 A: 144, 111 A: 373, 260	B: <3 A: 4	A:42, 70	A: Liver Cu 630
4	F	NB	-Prenatal	-c.331delT>A(LP) and c.589C>A (LP) in trans (c.[=];[331delT>A;589C>A])	26	12.5mg bid	B: 25, 28 A: 29	B: 17, 22 A: 21		B: (11 m) normal
5	F	NB	-Prenatal	-c.2284 C>T (P) -c.3247 C>T (P)			B: 24	B: 18		
6	F	NB	-Carrier status of parents -NB screen*	-c.2800C>T (P) -c.122A>G (LP)	24	12.5 mg bid	B: 29,27, 28 A: 20	B: 13,12, 8 A: 8		B: (8 m) small echogenic mass in liver 0.7cm B: (18 m) normal US
7	M	NB	-Prenatal	-c.2800 C>T (P) -c.2805 G>A (LP)	26	12.5 mg bid	B: 15, 14 A: 19,18,12	B: 15, 16 A: 21, 18,12	A: 9,11	B: (12m) normal US
8	M	NB	-Prenatal	-c.3191 A>C (P) -c.3207 C>A (P)	27	12.5 mg bid	B: 34,56,44 A:57,44, 148,1 10	B: 24,22,26 A: 31,22,18,22	A: 40, 44	B: (4 m) normal A: (31 m) borderline enlarged liver
9	F	NB	-Prenatal -NB screen*	-c.2612del (P) -c.2662 A>T (LP)	5 24	7.5 mg bid 12.5 mg bid	A: 42 , A:18	A: 25, 25 A: 33		
10	F	NB	-Prenatal	-c.3207C>A (P) -c.845delT (P)	19	25mg bid 25 mg daily	B: 25,20 A: 28,29 A:10,26,25,22, 20,17	B: 11,7 A: <3, <3 A: 4,3,6,7,6,8	A: 18,26, 25	
11	F	NB	-Prenatal	-c.2513G>T (P) -c.3207C>A (P)	41	12.5 mg bid	B: 34,37,28 A: 31,47, 70,38	B: 8,11 , A: 9,11,11,11, 11	A: 39, 53	B: (24m) mild heterogenous hepatic parenchymal B: (36m) normal A: (5y) heterogenous parenchyma
12	M	27	-sibling with WD	-c.2968+6T>C (VUS) -c.2133G>A (P)	38	25 mg daily	A: 92	A: 4		B: (22m) normal elasticity 4.3 KPa
13	F	NB	-Prenatal	-c.1543+1G>T (P) -c.2930 C>T (P)	18	25 mg daily	B: 28,27 A: 41	A: 5		B: (6m) normal
14	M	NB	-NB screen	-c.122A>G (LP) -c.2805G>A (LP)			B: 32	B: 25		
15	F	5 year	-Carrier status of parents	-c.[3207A> (P); -c.4122G (LP)	5 years	25 mg bid	B: 22,21,21 A: 21,18,19	B: 17,16 A:15,15,12,14	B: 29 A:33,29, 26	B:LiverCu 789 B:(5y)normal,5.3kPa A:(6y)normal,5.3kPa
16	F	5m	-parental carrier status	-c.3859G>A (LP); -c.3859G>A (LP)			B: 17	B: 13		
17	F	12m	-parental carrier status	-c.3207C>A (P); -c.3207 C>A (P)	12 m	12.5mg/all 25 mg bid 25mg bid	B: 42 A:41,24,47,55, 67,41,77,69,2 9,35, 25	B: 20 A:16,20, 17,24 21,29,19,19,1 5,15,14,17	A:9,25, 67,64,61 59,20,34, 32,22	B: normal A: normal (10y) 4.0kPa
18	F	12 m	-parental carrier status	-c.3207C>A (P); -c.3207 C>A (P)	15 m	12.5mg bid 25 mg bid 25mg bid	A:37,32,39,34 ,53,127,168,23 5,23,65,39	A:18,17,26,27 ,19,19,17,17	A:27, 38, 23,18,73, 23	A: Hepatic stiffness (3y) 3.6kPa

NB= Newborn; Pt=Participant; LP=Likely Pathogenic; VUS= Variant of unknown significance; Dx=Diagnosis; Tx= treatment; SC=Saliva; Ax=Ear; m=months; *SCID= severe combined immune deficiency syndrome; NB screen = Newborn screening through GUARDIAN Study (Genomic Uniform-screening Against Rare Diseases In All Newborns), whole exome sequencing

Disclosures: Rima Fawaz: Mirum: Consultant, Albireo: Data Safety Monitoring Board, Ayse Coskun: Nothing to Disclose, Sefa Keserci: Nothing to Disclose, Hatice Maras: Nothing to Disclose, ASIM ULCAY: Nothing to Disclose, Pamela Valentino: Nothing to Disclose, Michael Schilsky: Vivet Therapeutics: Grant/Research Support, Orphalan: Grant and Advisory, DepYmed: Advisor, Arbomed: Advisor and Consultant, Wilson Disease Association: Grant/Research Support, Prime Medicine: Consultant, Eton Pharma: Consultant, Prime Medicine: Advisor, Prime Medicine: Grant/Research Support.

2669 | EPIDEMIOLOGY AND NATURAL HISTORY OF ALAGILLE SYNDROME: A POPULATION-BASED STUDY USING THE UTAH POPULATION DATABASE

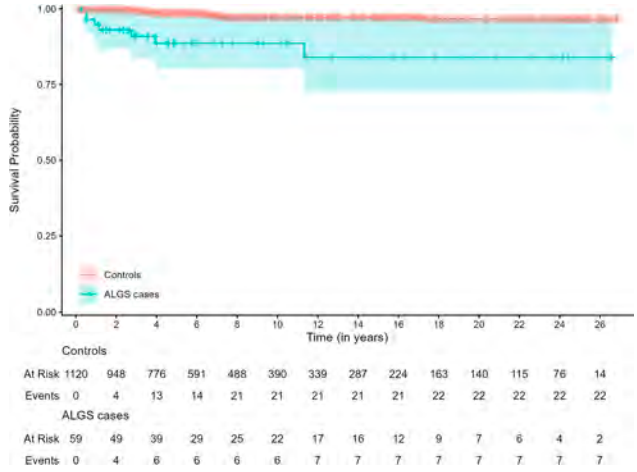
Catalina Jaramillo[1] Brian Avery[2] Michael Madsen[2] Nicola Camp[2] Stephen Guthery[3], [1]University of Utah/ Primary Children's Hospital, [2]University of Utah, [3]University of Utah / Primary Children's Hospital

Background: Alagille Syndrome (ALGS) is an autosomal dominant, life-threatening, multiorgan disease caused by mutations in *JAG1* or *NOTCH2* genes, with variable expression and penetrance within families. Diagnosis is established either by the presence of these variants or by clinical criteria, defined as at least three characteristics, including liver, cardiac, ocular, musculoskeletal, and renal anomalies or typical facial features. To our knowledge, there are no prior studies describing the epidemiology and natural history of ALGS in population-based cohorts. We aimed to characterize the ALGS population in Utah. **Methods:** Patients with an established diagnosis of ALGS followed at our pediatric hepatology and cardiology clinics were identified. Additional cases were identified through an International Classification of Diseases (ICD) code-based search across the enterprise data warehouses of the 2 major health systems, which effectively cover the entire population of Utah. Structured chart reviews were performed to confirm the diagnosis. Individuals with ALGS were sent to the Utah Population Database (UPDB) for probabilistic linking. ALGS cases were compared to population-based controls obtained from the UPDB (1997-2023) and matched on age, sex, and place of birth. Cox proportional hazards regression was used to estimate hazard ratios (HR) with 95% confidence intervals (CI). Survival was assessed using the Kaplan-Meier method from the time of diagnosis to death or last follow-up. **Results:** A total of 69 individuals with ALGS were identified. A molecular diagnosis was available for 50 (47 *JAG1* and 3 *NOTCH2*), and 20 met established clinical criteria. Of the 69 individuals, 59 linked to UPDB and were residents of Utah; 49% were female and predominantly

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white (88%). ALGS disease manifestations included liver involvement in 90% (n = 53), cardiac in 61% (n = 36), renal in 17% (n = 11), cerebrovascular in 15% (n = 9), ophthalmological in 6.8% (n = 4), and musculoskeletal in 6.8% (n = 4). Among those with liver disease, pruritus occurred in 56% (n = 19), and 27% (n = 16) underwent liver transplantation. ALGS had a 6-fold increased hazard of all-cause mortality (HR 6.19, 95% CI 2.64–14.49, p < 0.001). By the end of follow-up (26 years), estimated survival was 85% for cases versus 98% for controls. **(Figure 1)** Point prevalence of ALGS in Utah was estimated at 14.8 per 1 million in 2023 (eligible people were those residing in Utah at the start of 2023). **Conclusion:** We used the UPDB to evaluate the epidemiology and natural history of ALGS in a population-based cohort, showing prevalence estimates similar to those reported in the literature. Overall survival of ALGS cases in the Utah population is significantly lower than matched controls. Future studies using the UPDB may identify kindreds in which ALGS is segregating, may identify family members with subclinical disease, and may serve as a potential resource for future ALGS preventative health studies.



Disclosures: Catalina Jaramillo: Nothing to Disclose, Brian Avery: Nothing to Disclose, Michael Madsen: Nothing to Disclose, Nicola Camp: Nothing to Disclose, Stephen Guthery: Nothing to Disclose.

2670 | IMPROVING IDENTIFICATION OF PATIENTS WITH ALAGILLE SYNDROME USING A MACHINE-LEARNING ALGORITHM APPLIED TO ELECTRONIC HEALTH RECORDS FROM TWO US HEALTH SYSTEMS

Praveen Kumar-M[1] Seema Meloni[2] Jeeva Bharathi[1] Sara Hassan[3], [1]nference, Cambridge, MA, US, [2]Ipsen, Cambridge, MA, US, [3]University of Texas Southwestern, Children's Medical Center, Dallas, TX, US

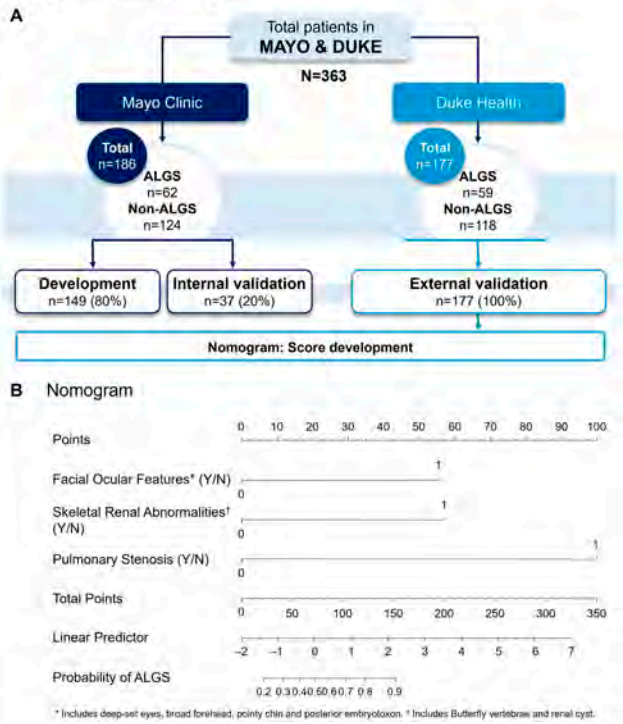
Background: Neonatal and pediatric cholestasis can arise from a wide range of underlying conditions, including Alagille syndrome (ALGS). ALGS is a rare, genetically inherited disease linked to mutations in *JAG1* and *NOTCH2*. Clinical presentation is multifaceted, including characteristic facial features, debilitating pruritus, and life-threatening liver or cardiac disease. An autosomal dominant inheritance pattern and varied penetrance cause phenotypic heterogeneity, which can delay diagnosis. Here, we describe the development of an algorithmic tool to support healthcare practitioner decision-making and facilitate earlier diagnosis of ALGS by differentiating it from other rare cholestatic liver diseases with overlapping features; thereby, enabling earlier intervention. **Methods:** This retrospective, non-interventional study used a previously confirmed ALGS cohort (N = 121) derived from de-identified Mayo Clinic and Duke Health electronic health record data, covering the period from January 1, 2005 to November 15, 2024. The machine-learning algorithm was developed using the Mayo Clinic ALGS cohort and a 1: 2 propensity score–matched cohort of patients < 10 years old with non-ALGS cholestasis. ALGS-discriminating clinical features were evaluated as model inputs, either individually or grouped into clinical feature domains, and assessed for statistical significance using logistic regression. The algorithm was trained on 80% of the Mayo Clinic cohort, internally validated on the remaining 20%, and externally validated on the full Duke Health cohort (**Figure A**). **Results:** The output of the algorithm was a nomogram that scores probability of ALGS based on the presence of key clinical characteristics, including pulmonic stenosis, skeletal/renal abnormalities, and facial/ocular features (**Figure B**). Good discriminatory performance was confirmed in the external cohort with a sensitivity of 0.71 (95% confidence interval [CI]: 0.60 to 0.82) and a specificity of 0.91 (95% CI: 0.86 to 0.96). Precision-recall area under the curve (PR_{AUC}) was reported as 0.81 (95% CI: 0.73 to 0.88), indicating strong performance in identifying positive cases beyond overall classification accuracy. **Conclusion:** To our knowledge, this is the first study to develop and validate an algorithm-based nomogram that can support early identification of patients with a high probability of ALGS. Good discriminatory performance was demonstrated in a matched cholestatic population, with strong specificity, precision, and PR_{AUC} metrics, supporting its potential utility to identify a high-confidence ALGS cohort. This tool may support earlier identification and genetic confirmation of patients with ALGS, particularly for those

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without direct access to pediatric gastroenterology or hepatology care services.

Figure: (A) Model development and validation across Mayo and Duke cohorts. (B) Algorithm-based nomogram



Disclosures: Praveen Kumar-M: Nothing to Disclose, Seema Meloni: Ipsen Biopharmaceuticals: Employee, Jeeva Bharathi: Nothing to Disclose, Sara Hassan: Ipsen: Consultant.

2671 | MANNOSE ATTENUATES HEPATIC STELLATE CELL ACTIVATION AND FIBROGENESIS IN BILIARY ATRESIA

John Hong[1] Poulomi Dey[1] Charles DeRossi[2] Jaime Chu[2], [1]Icahn School of Medicine at Mount Sinai, [2]Icahn School of Medicine at Mount Sinai (ISMMS)

Background: Biliary atresia (BA) is a neonatal cholangiopathy characterized by progressive bile duct injury, inflammation, and fibrosis, with most affected children requiring liver transplantation. Although fibrosis drives disease progression, the role of hepatic stellate cell (HSC) activation (the principal fibrogenic cells of the liver) remains poorly defined in BA. Biliatresone (BT), a plant-derived isoflavone, models BA-related injury and induces glutathione depletion and oxidative stress in zebrafish and murine cholangiocytes. Mannose reduces stellate cell activation in multiple models of liver fibrosis, but its role in BA is unknown. **Methods:** For *in vitro* modeling, human HSCs (LX-2) were treated with BT (0.5 and 1.0 µg/mL) ± mannose (1 and 5 mM). Fibrotic gene expression (*PDGFRB, ACTA2, COL1A1, COL1A2*) was assessed by qPCR and protein levels (αSMA, COL1A2) were assessed by western blot and immunofluorescence. Oxidative stress was measured using CellROX assay. For *ex vivo* modeling, human precision-cut liver slices (hPCLS) from three BA patients were obtained at time of transplant and were treated with mannose (1 and 25 mM) for 24 and 48 hours. Fibrotic markers were quantified by qPCR. **Results:** BT induced dose-dependent increases in ROS generation and fibrogenic activation in HSCs, with significant upregulation at both transcriptional (*PDGFRB, ACTA2*, *COL1A1*) and protein (COL1A2) levels. Mannose treatment significantly attenuated BT-induced ROS accumulation and reduced expression of fibrotic markers in vitro. In *ex vivo* BA hPCLS, mannose consistently reduced *COL1A2* and *ACTA2* expressions across patient samples compared to vehicle-treated controls. **Conclusion:** BT induces oxidative stress and fibrogenic activation in human HSCs, supporting its utility as an in vitro model of BA-associated fibrosis. Mannose attenuates BT-induced oxidative stress and fibrogenic signaling in HSCs and reduces fibrotic marker expression in human BA liver tissue ex vivo. These findings identify mannose as a promising antifibrotic therapeutic candidate for BA with translational relevance.

Disclosures: John Hong: Nothing to Disclose, Poulomi Dey: Nothing to Disclose, Charles DeRossi: Nothing to Disclose, Jaime Chu: Nothing to Disclose.

2672 | CHOLANGIOCYTE-TARGETED AAV-ABCC12 GENE THERAPY PARTIALLY RESTORES MITOCHONDRIAL FUNCTION AND ATTENUATES BILIARY INJURY

Michelle Damen[1] Pervinder Choksi[2] Manavi Singh[1] Tanja Linnerz[1] Bryan Donnelly[1] Ramesh Kudira[1] Annika Yang Vom Hofe[1] Maria Fields (n.e Moreno-Fernandez)[1] Holger Willenbring[3] Alexander Miethke[4] Chunyue Yin[1], [1]Cincinnati Childrens Hospital Medical Center, [2]The University of California, San Francisco, [3]USCF, [4]Cincinnati Children's Hospital Medical Center

Background: We previously identified a homozygous truncating mutation in *ABCC12*, encoding the ABC transporter MRP9, in a child with idiopathic cholestasis and bile duct paucity. In zebrafish, loss of Abcc12 impairs mitochondrial function and predisposes to apoptosis and ferroptosis of cholangiocytes. We evaluated whether an adeno-associated viral (AAV) vector engineered for biliary epithelial cell (BEC)tropism and carrying full-length *ABCC12* restores cholangiocyte function in *Abcc12* knockout

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(KO) mice. **Methods:** CRISPR-Cas9–edited H69 cholangiocytes harboring the deleterious mutation observed in the proband were transduced with AAV-BEC-m*Abcc12*. Transgene expression was assessed by qPCR and immunofluorescence. Mitochondrial function was evaluated using Seahorse assays. *Abcc12* KO and wild-type (WT) mice were evaluated at baseline (8wks old) and following 0.05% DDC diet for 14 days (10wks old). Male *Abcc12* KO mice received AAV-BEC-m*Abcc12* (1.6×10^{10} vg/g) at 4wks old prior to regular diet or 0.05% DDC exposure (14days, 8wks until 10wks old). Hepatobiliary injury was assessed by serum biochemistries, histology, and CK19 immunostaining. Ferroptotic stress was assessed by hyperoxidized PRDX3 staining. **Results:** AAV transduction induced robust *ABCC12* mRNA and protein expression in H69 cells and restored mitochondrial function by Seahorse assay in *ABCC12*-deficient cells. 8-week-old *Abcc12* KO mice exhibited increased serum alkaline phosphatase (ALP) levels, diminished well-formed and increased number of bile duct clusters on examination of CK19-stained liver sections which was accompanied by increased TUNEL staining of BECs compared with WT mice. *mAbcc12*-AAV treatment of *Abcc12* KO mice induced MRP9 expression in BECs (Fig 1A), lowered serum ALP levels (Fig 1B), decreased % area of CK19+ stained cells (Fig 1C) and number of BEC clusters (1D) while increasing number of well-formed bile ducts in portal tracts compared with untreated age-, sex- and genotype matched mice. AAV treatment prior to DDC challenge lowered serum total bilirubin levels (mean ± SEM of 5.97 vs 3.59 mg/dL in Abcc12KO vs *Abcc12* KO + AAV, ***: $p < 0.005$) and reduced cholangiocyte apoptosis in *Abcc12* KO mice by TUNEL staining. DDC induced accumulation of hyperoxidized PRDX3 in hepatocytes and cholangiocytes indicating ferroptotic stress; this effect was ameliorated by AAV-mAbcc12 treatment. **Conclusion:** AAV-mediated *ABCC12* delivery restores mitochondrial function of MRP9-deficient BEC *in vitro*. In *Abcc12* KO mice, it reduces BEC ferroptosis, decreases serum ALP levels, and promotes formation of well-formed bile ducts while preventing BEC cluster formation. Furthermore, it confers partial protection from xenobiotic injury in a model of sclerosing cholangitis. These findings support MRP9 as a regulator of mitochondrial functions and cell death in BEC and establish translational proof-of-concept for gene therapy in inherited cholangiopathies.

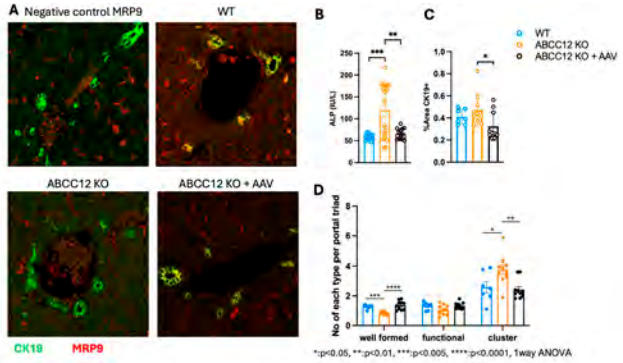


Figure 1. Administration of AAV-BEC-mAbcc12 vector to *Abcc12* KO mice prevents loss of well-formed bile ducts. Representative images of dual-immunofluorescence CK19 (green) and MRP9 (red) on liver sections from WT, Abcc12 KO and Abcc12 KO mice following AAV treatment, Single-plane confocal images 40x (A). Serum ALP was measured at time of harvest at 8 weeks (B). Percent area of CK19+ cells (C) and bile duct profiles classified as well-formed, functional, or clusters were enumerated on liver sections subjected to CK19 IHC (DC).

Disclosures: Michelle Damen: Nothing to Disclose, Pervinder Choksi: Nothing to Disclose, Manavi Singh: Nothing to Disclose, Tanja Linnerz: Nothing to Disclose, Bryan Donnelly: Nothing to Disclose, Ramesh Kudira: Nothing to Disclose, Annika Yang Vom Hofe: Nothing to Disclose, Maria Fields (n.e Moreno-Fernandez): Nothing to Disclose, Holger Willenbring: Nothing to Disclose, Alexander Miethke: Mirum Pharmaceutical Inc: Grant/Research Support, Mirum Pharmaceutical Inc: Consultant, Ipsen: Speaking and Teaching, Perspectum Ltd.: Grant/Research Support, Esperion: Advisor, Chunyue Yin: Nothing to Disclose.

2673 | CONCURRENT CHANGES IN MACROPHAGE AND T CELL SUBSETS OVER TIME IN MURINE OBSTRUCTIVE CHOLESTASIS SUGGEST INTERPLAY BETWEEN MACROPHAGE AND T CELL FUNCTION IN PROMOTION OF HEPATIC INJURY

Lauren Maloney[1] *Ioannis Ziogas*[2] *Matthew Burchill*[3] *Sarah Taylor*[1], [1]*University of Colorado Anschutz*, [2]*University of Colorado*, [3]*University of Colorado - Anschutz*

Background: Macrophages (MΦ) play a key role in disease pathogenesis of both adult and neonatal obstructive cholestasis, however, their role in regulating the T cell response remains poorly defined. Regulatory T cells (Tregs) can protect against lymphocyte activation in immune-mediated bile duct injury, while CD8+ T

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cells have been implicated in driving biliary injury and fibrosis. We aimed to define MΦ-T cell signaling networks over the disease course of obstructive cholestasis. **Methods:** We utilized the bile duct ligation (BDL) model of surgically induced obstructive cholestasis and sham surgical controls in adult Balb/c mice. Single cell RNA-sequencing analysis of hepatic MΦs from BDL and non-diseased controls defined MΦ heterogeneity at post operative day (POD) 7. Multiparameter flow cytometry profiled hepatic immune cell changes over the course of disease after BDL (POD0, 3, and 7). MΦs were characterized by expression of MerTK (receptor important in apoptotic cell engulfment), Ly6c (marker distinguishing recruited pro-inflammatory vs. tissue-repair subsets), and MHCII (indicator of activation and antigen presentation). T cells were identified by flow cytometry using standard sequential gating on singlets/live cells followed by CD45+ leukocytes, CD3+ T cells, and subsequent delineation into CD4+ and CD8+ subsets. Exhausted T-cell populations were defined as CD44+PD1+ cells. **Results:** Transcriptional analysis of BDL versus control MΦs at POD7 showed enrichment for antigen processing and presentation as well as the defense response including increased expression for *Ifitm2* (adjusted p-value = 0, log2FC = 1.9), a gene involved in Treg suppression (**Figure 1A**). Flow cytometry analysis of liver tissue demonstrated a significant increase in total F480+ MΦs in BDL POD 7 compared to BDL POD 3, Sham POD 3 and baseline ($p < 0.05$ for all). Among MΦ subsets, Ly6C+ MΦs had the greatest increase at POD7 from baseline ($p = 0.007$) although MerTK + MΦs and MHC2+ MΦs were also significantly increased (**Figure 1B**). Among T cells, CD8+ T cells were significantly higher in number at BDL POD 3 than in any other condition or timepoint ($p < 0.05$ for all). CD4 T cells were highest in BDL at both POD3 and 7 compared to sham ($p < 0.05$ for both), however, subset analysis demonstrated lower number of Tregs in BDL POD 3 and POD 7 compared to baseline ($p = 0.016$ and $p = 0.018$ respectively). A high proportion of CD4 and CD8 T cells demonstrated the exhausted phenotype at POD7 (**Figure 1C**). **Conclusion:** Our data support an important interplay between MΦs and T cells which may propagate cholestatic injury. We show evidence for increased MHCII+ MΦ antigen presentation, greater CD8 T cell exhaustion, and T regulatory cell inhibition over the disease course of BDL. Future studies defining the mechanism by which MΦs may inhibit T regulatory cells and promote T cell exhaustion in chronic obstructive cholestasis will improve our understanding of disease pathogenesis.

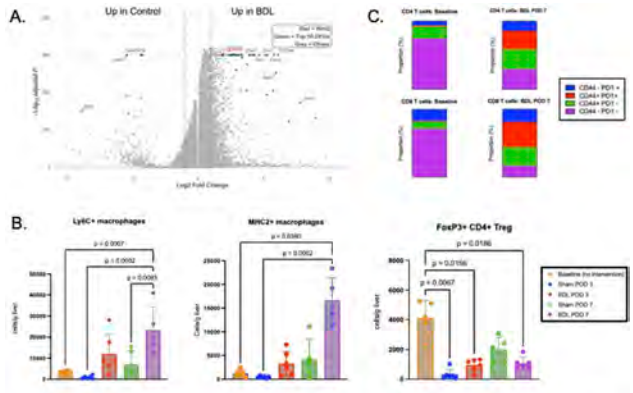


Figure. A. Transcriptional analysis of BDL vs control B. Flow cytometry analysis of liver tissue BDL vs control C. CD4 and CD8 T cell phenotype BDL vs control

Disclosures: Lauren Maloney: Nothing to Disclose, Ioannis Ziogas: Nothing to Disclose, Matthew Burchill: Nothing to Disclose, Sarah Taylor: Ipsen Pharma: Consultant, Mirum Pharma: Consultant, Capsida Biotherapeutics: Consultant.

2674 | SHORT BOWEL SYNDROME ASSOCIATED CHOLESTATIC LIVER INJURY DISRUPTS PANCREATIC ENDOCRINE ARCHITECTURE

Shun Onishi[1] Aakash Nagarapu[1] Takahiro Ohkura[1] Chandrashekhara Manithody[1] Marzena Syn[1] Ajay Jain[1], [1]Saint Louis University

Background: Short bowel syndrome (SBS) causes intestinal failure, dependence on parenteral nutrition, and intestinal failure–associated liver disease (IFALD). Although SBS-associated cholestasis and disrupted enterohepatic signaling are well described, whether this gut–liver injury state affects pancreatic endocrine development is unknown. We hypothesized that neonatal SBS-associated cholestatic liver injury alters pancreatic islet cell cluster (ICC) morphology and endocrine cell composition, and that prebiotic modulation may partially preserve endocrine architecture. **Methods:** Neonatal piglets, 7–10 days old, received enteral milk feeding (EN) or underwent 75% small bowel resection with ileocolonic anastomosis and parenteral nutrition support (SBS). A subgroup of SBS animals received prebiotic supplementation. Cholestatic liver injury and intestinal adaptation were assessed by serum conjugated bilirubin, GGT, and distal gut linear density. Pancreatic sections were stained for insulin, glucagon, and chromogranin A. Five

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representative 20× fields per sample were analyzed using QuPath to quantify ICC size, circularity, cell number, and endocrine cell distribution. **Results:** SBS piglets developed IFALD. Compared with EN controls, SBS animals had markedly elevated conjugated bilirubin, 3.89 ± 0.51 vs 0.036 ± 0.004 mg/dL, increased GGT, 129.97 ± 24.11 vs 19.56 ± 3.12 U/L, and reduced distal gut linear density, 0.11 ± 0.008 vs 0.30 ± 0.02 g/cm. Across groups, ICC frequency declined with increasing cluster size, while ICC circularity did not differ significantly, suggesting that IFALD associated with altered endocrine cellular composition rather than overall cluster shape. In large ICCs measuring 4001–5000 μm², insulin-positive cells were markedly reduced in SBS compared with EN, 6.12 ± 0.00% vs 40.59 ± 9.02%, p = 0.029. Within SBS animals, smaller ICCs, 1001–2000 μm², contained relatively higher insulin-positive and fewer glucagon-positive cells than ICCs measuring 2001–3000 μm², indicating size-dependent endocrine remodeling. Prebiotic supplementation was associated with partial preservation of insulin-positive cell proportions. **Conclusion:** Neonatal SBS-associated cholestatic liver injury is associated with altered pancreatic endocrine architecture, particularly reduced insulin-positive cells in larger ICCs. These findings suggest that IFALD may extend beyond the gut–liver axis to disrupt gut–pancreas endocrine signaling. Partial preservation with prebiotic supplementation supports microbiome modulation as a potential strategy to mitigate adverse effects.

Disclosures: Shun Onishi: Nothing to Disclose, Aakash Nagarapu: Nothing to Disclose, Takahiro Ohkura: Nothing to Disclose, Chandrashekhara Manithody: Nothing to Disclose, Marzena Syn: Nothing to Disclose, Ajay Jain: Nothing to Disclose.

2675 | SINGLE-NUCLEUS MULTIOME PROFILING REVEALS MACROPHAGE SUBTYPE-SPECIFIC CYTOKINE RESPONSES ASSOCIATED WITH FIBROSIS PROGRESSION IN PEDIATRIC AUTOIMMUNE LIVER DISEASE

Zi Yang[1] Ramesh Kudira[1] Annika Yang Vom Hofe[2] Mosab Alquraish[1] Cyd Castro-Rojas[1] Joseph Wayman[1] Pamela Sylvestre[2] Stacey Huppert[2] Anna Peters[2] Matthew Weirauch[1] Lee Denson[1] Leah Kottyan[1] Yunguan Wang[1] Alexander Miethke[2] Emily Miraldi[1], [1]Cincinnati Children's Hospital Medical Center, [2]Cincinnati Children's Hospital Medical Center

Background: Autoimmune liver diseases (AILDs) are a group of chronic immune-mediated disorders that include primary sclerosing cholangitis (PSC), autoimmune hepatitis (AIH), and overlap syndrome autoimmune sclerosing cholangitis (ASC). These rare conditions can lead to progressive liver fibrosis, cirrhosis, and liver failure, and may require liver transplantation at the end-stage. Development of targeted biologic therapies is limited by an incomplete understanding of the cellular programs driving tissue inflammation and fibrosis progression. **Methods:** To identify cellular and molecular drivers of AILD, we generated multiome-seq (tandem single-nuclei (sn)RNA-seq and chromatin accessibility (snATAC)-seq) of frozen explanted liver tissue and biopsy samples. The cohort included patients with PSC (n = 11), AIH (n = 8), ASC(n = 6) spanning multiple fibrosis stages and deceased liver donors serving as healthy controls (HC, n = 5). Cell types were annotated using curated markers and reference-based label transfer, followed by subclustering to resolve macrophage heterogeneity. Compositional changes of macrophage subtype were assessed using centered log-ratio transformation of cell proportions followed by t-test. Fibrosis-associated transcriptional changes were identified using pseudo-bulk differential expression analysis accounting for donor-level variability, tested for enrichment of the ligand-response signatures curated from experimentally derived sc-resolved immune cells dataset *in vivo* (PMID: 38057668). **Results:** Seven major epithelial and immune cell populations were identified across approximately 240,000 nuclei from 30 multiome-seq samples (Fig 1A). Subsequent subclustering of macrophages resolved five distinct subtypes that were reproducibly observed across donors and supported by both transcriptomic and chromatin accessibility profiles (Fig 1B). Composition analysis identified *MHCII*^{high} subtype significantly increased in early/established fibrosis stages compared to controls (Fig 1C). Pseudo-bulk analysis identified 1,350 fibrosis-associated genes that segregated into seven clusters with shared and subtype-specific patterns across diseases and fibrosis stages (Fig 1D). Notably, a fibrosis-associated gene module was selectively expressed in *MHCII*^{high} macrophages and enriched for expression of interferon (IFNG, IFNa1) and IL-1 (IL33, IL36) family response genes, implicating inflammatory cytokine signaling in disease progression (Fig 1E). **Conclusion:** Single-nucleus multiome profiling of pediatric-onset AILD reveals fibrosis stage-dependent changes in macrophage composition, gene expression, and cytokine response programs. These findings highlight a central role for *MHCII*^{high} macrophages in tissue inflammation and identify candidate pathways and therapeutic targets for next-generation biologic

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interventions in AILD.

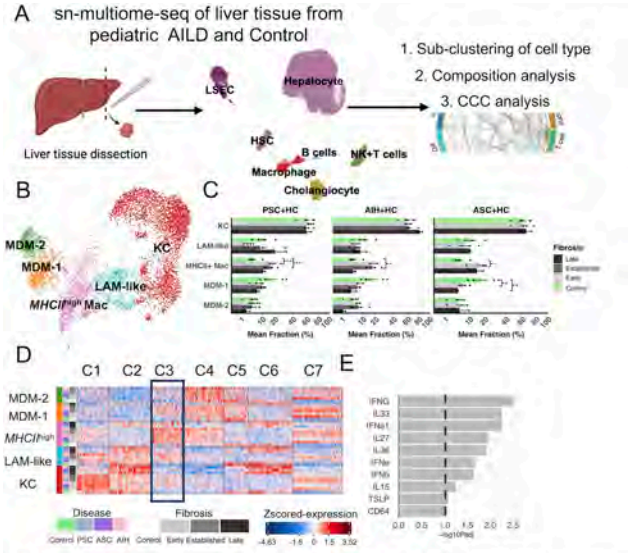


Fig 1. (A) Multiome-seq on cryopreserved tissue samples of explanted livers and clinical biopsies to generate tandem transcriptome and accessible chromatin data powering computational modelling to identify cytokine signals mediating liver inflammation and fibrosis progression in AILD. CCC = Cell-cell communication. (B) Integrated analysis of transcriptome and chromatin accessibility yielded 5 macrophage subtypes. (C) The compositions of macrophage subtypes across disease groups and fibrosis stages (*Padj<0.05, two-sided t-test on centered log-ratio transformed compositions). (E) Fibrosis-dependent differentially expressed genes (FDR ≤ 10%, |fold change| > 1.5) visualized across macrophage subtypes, disease groups, and fibrosis stages. Seven clusters reveal distinct cell type–specific expression patterns. (F) Bar plot of significantly enriched Immune Dictionary cytokine response genes in the MHCIIhigh macrophage–associated genes, which are upregulated in early and established fibrosis stages (cluster C3 of panel D). Pathway significance is shown as −log10(Padj), with multiple testing correction performed using the Benjamini–Hochberg procedure. The dotted line corresponds to Padj<0.1.

Disclosures: Zi Yang: Nothing to Disclose, Ramesh Kudira: Nothing to Disclose, Annika Yang Vom Hofe: Nothing to Disclose, Mosab Alquraish: Nothing to Disclose, Cyd Castro-Rojas: Nothing to Disclose, Joseph Wayman: Nothing to Disclose, Pamela Sylvestre: Nothing to Disclose, Stacey Huppert: Nothing to Disclose, Anna Peters: Nothing to Disclose, Matthew Weirauch: Nothing to Disclose, Lee Denson: Takeda: Grant/Research Support, Leah Kottyan: Nothing to Disclose, Yunguan Wang: Nothing to Disclose, Alexander Miethke: Mirum Pharmaceutical Inc: Grant/Research Support, Mirum Pharmaceutical Inc: Consultant, Ipsen: Speaking and Teaching, Perspectum Ltd.: Grant/Research Support, Esperion: Advisor, Emily Miraldi: Nothing to Disclose.

2676 | IMMUNOLOGICAL CHARACTERISATION OF PAEDIATRIC LIVER DISEASE: MAIT CELL REPROGRAMMING AND FALTERING GROWTH AS MARKERS OF IMMUNE SEVERITY

Eirini Kyrana[1] Tengfei Si[1] Qing Shao[1] Huihong Yu[1] Bethany Tucker[2] Xuan Luo[1] Zao-Hong Carmen Cai[1] Sinead Cunningham[2] Tassos Grammatikopoulos[2] Karishma Manwani[2] Anil Dhawan[2] Yun Ma[1], [1]King's College London, [2]King's College Hospital

Background: Mucosal-associated invariant T (MAIT) cells are innate-like lymphocytes with emerging roles in hepatic immunopathology. Their phenotypic characterisation across disease severity and relationship to clinical markers of nutritional status remains poorly defined in children with liver disease. **Methods:** Ninety-five children were studied: advanced liver disease (ALD, n = 39), stable liver disease (SLD, n = 34), and healthy controls (NLD, n = 22). Peripheral blood immunophenotyping assessed 61 parameters, including MAIT cell frequency and surface markers (CCR4, CD38, CD39, CXCR3). Spearman correlations with clinical predictors (bilirubin, MELD/PELD, weight z-score, platelet count, neutrophil: lymphocyte ratio) were performed with Benjamini-Hochberg false discovery rate correction across 300 tests. Group comparisons used the Mann-Whitney U and Kruskal-Wallis tests with Bonferroni-corrected post hoc analyses. **Results:** MAIT cell frequency was selectively depleted in ALD versus SLD and NLD (median 0.56% vs 1.84% vs 1.46%; $p < 0.001$), whilst phenotypic reprogramming occurred across all liver disease: MAIT %CCR4+, %CD38+, and %CD39+ were each significantly elevated in liver disease versus controls (all $p < 0.001$), and were highest in ALD, significantly exceeding SLD (all adjusted $p < 0.05$). This activation-exhaustion-homing triad was independently predicted by bilirubin ($\rho = +0.479$), MELD/PELD ($\rho = +0.425$), and weight z-score ($\rho = -0.463$; all FDR $q < 0.01$). Weight z-score ≤ -1 identified 27 children (all with liver disease; median age 2.0–6.5 years by severity subgroup), who demonstrated significantly lower peripheral MAIT frequency (0.55% vs 1.37%; $q = 0.011$) and higher sCD163 (1606 vs 544 ng/ml; $q = 0.005$) versus children with weight $z > -1$, with a stepwise gradient of MAIT frequency 1.37% / 0.65% / 0.31% and sCD163 level 544 / 951 / 1947 ng/ml across weight z-score thresholds of > -1 / -1 to -2 / < -2. Bilirubin thresholds of ≥ 17 and ≥ 50 µmol/L correspond to the immunological separation achieved by the weight z-scores of < -1 and < -2, respectively. **Conclusion:** Paediatric liver disease drives progressive MAIT cell depletion and phenotypic reprogramming — activation, exhaustion, and tissue homing — that tracks disease severity across biochemical and nutritional indices. Weight z-score is a sensitive clinical surrogate for immunological burden.

Disclosures: Eirini Kyrana: Nothing to Disclose, Tengfei Si: Nothing to Disclose, Qing Shao: Nothing to Disclose, Huihong Yu: Nothing to Disclose, Bethany Tucker: Nothing to Disclose, XUAN LUO: Nothing to Disclose, Zao-Hong Carmen Cai: Nothing to Disclose, Sinead Cunningham: Nothing to Disclose, Tassos Grammatikopoulos: Nothing to Disclose, Karishma Manwani: Nothing to Disclose, Nothing to Disclose, Anil Dhawan: Bit Bio: Consultant, Aspect Bio:

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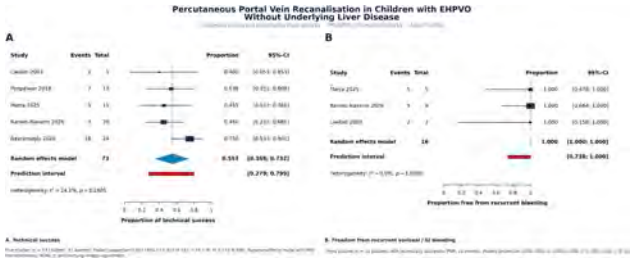
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Consultant, Astellas: Consultant, Univar: Advisor, Orphalan: Advisor, Yun Ma: Nothing to Disclose.

2677 | PERCUTANEOUS PORTAL VEIN RECANALIZATION IN CHILDREN WITH EXTRAHEPATIC PORTAL VEIN OBSTRUCTION WITHOUT UNDERLYING LIVER DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS

Douglas Miotto[1] Alexandra Salazar-Riaño[2] Sabrine Teixeira Ferraz Grunewald[3] Leticia Helena Caldas Lopes[4] Lilian de Carvalho[4] Thaís Silva Martins Shehan[5] Suelen Renoste[6], [1]Universidade Federal de São Paulo, Brazil, [2]Universidad CES de Medellín, Medellín, Colombia, [3]Universidade Federal de Juiz de Fora, [4]Universidade Federal de São Paulo, [5]Universidade Federal Fluminense, [6]Independent Researcher

Background: Extrahepatic portal vein obstruction (EHPVO) is the primary cause of pediatric portal hypertension. The Meso-Rex bypass is the surgical gold standard treatment but requires a patent Rex recessus, which is absent in approximately half of these patients. Percutaneous portal vein recanalization (PVR) restores physiological hepatopetal flow and is cited by Baveno VII and the 2026 European Association for the Study of the Liver (EASL) guidelines, yet no systematic synthesis of pediatric outcomes has been published. We evaluated the technical feasibility, safety profile, and clinical efficacy of PVR in children with EHPVO without underlying liver disease. **Methods:** Systematic review and proportional meta-analysis conducted according to the Cochrane Handbook v6.5 (PROSPERO CRD420261395918) and reported in compliance with the PRISMA 2020 guidelines. PubMed/MEDLINE, Embase, Cochrane and Web of Science were searched from inception to May 2026. Corresponding authors were contacted, yielding unpublished patient-level when necessary. Random-effects models with simple arcsine transformation, restricted maximum likelihood (REML) τ^2 and Hartung–Knapp adjustment yielded pooled proportions with 95% CI and prediction interval (PI). To assess heterogeneity and results robustness, sensitivity leave-one-out were performed for each outcome. Risk of bias was assessed with the Joanna Briggs Institute (JBI) tools. **Results:** Five retrospective single-center cohorts included 73 children undergoing PVR, with a median follow-up of 6–22 months. Pooled technical success reached 55.3% (95% CI 35.9–73.2; I^2 24.1%; PI 27.9–79.9) in the pooled analysis. No procedure-related or all-cause mortality occurred (0/57). Procedure-related hemorrhage was 11.8% (95% CI 4.5–21.9; I^2 0%). Furthermore, heterogeneity was substantially reduced (I^2 from 55% to 0%) after isolating a single outlying cohort sensitivity analysis. The proportion of portal-biliary fistula was 1.3% (95% CI 0–15.1). Among twenty children with technically successful PVR and imaging follow-up, late portal vein patency was achieved in 87.8% (95% CI 34.4–100; PI 15.6–100) of the pooled sample; though 50.8% required at least one endovascular re-intervention with no surgical conversion. The proportion of free-recurrent variceal or gastrointestinal bleeding was 100% (95% CI 100–100; PI 73.8–100) across 16 patients. **Conclusion:** Percutaneous PVR may be feasible in more than half of children with chronic native-vessel EHPVO, demonstrating zero procedure-related mortality and a predictable hemorrhage rate. Given the absence of recurrent variceal bleeding post-recanalization, PVR represents a legitimate first-line alternative to Meso-Rex bypass when Rex anatomy is unfavorable.



Disclosures: Douglas Miotto: Nothing to Disclose, Alexandra Salazar-Riaño: Nothing to Disclose, Sabrine Teixeira Ferraz Grunewald: Nothing to Disclose, Leticia Helena Caldas Lopes: Nothing to Disclose, Lilian de Carvalho: Nothing to Disclose, Thaís Silva Martins Shehan: Nothing to Disclose, Suelen Renoste: Nothing to Disclose.

★ 2678 | LYMPHATIC INTERACTION WITH AND TRAFFICKING OF IMMUNE CELLS IS ALTERED IN CHOLESTATIC LIVER DISEASE

Alyssa Goldberg[1] William Hollenbach[2] Beth Tamburini[2], [1]Children's Hospital Colorado, [2]University of Colorado

Background: The liver lymphatic system supports organ health by draining interstitial fluid and immune cells to the lymph node. Patients with primary sclerosing cholangitis have increased lymphatic vessel density in the liver. These findings are replicated in murine models of cholestasis and are associated with

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increased immune cell infiltrate into the liver. Our study evaluates changes in intrahepatic lymphatic endothelial cells (LECs) in cholestatic liver disease, how lymphatic endothelial cells are affected by bile salts, and how bile salts lead to lymphatic induced changes in T cell activity, viability and changes in immune cell trafficking through the lymphatic vasculature. **Methods:** Using flow cytometry, we evaluate immune cell phenotypes in the liver and in liver draining lymph nodes of mdr2 *(Abcb4)-/-* and 3,5-diethoxycarbonyl-1,4-dihydrocollidine fed (DDC) cholestatic mice. Immune cell phenotypes are combined with histologic findings including liver injury, fibrosis, and spatial information resulting from immune staining and spatial transcriptomics of the liver tissue. *In vitro*, we treat cells with pro-inflammatory cytokine, IFNg, and bile salts to model the cholestatic environment. We evaluate lymphatic endothelial cell expression of immune regulatory markers, chemokines, bile acid signaling, and interferon stimulated genes. Further we co-cultured effector T cells with lymphatic endothelial cells to investigate T cell activation state, chemokinesis, viability, and the impact of immune check-point inhibition. **Results:** Liver lymphatics are expanded in a murine model of cholestasis and expansion is associated with an increase liver-draining lymph node size. T cell accumulation and activation in the liver and liver draining lymph nodes are increased during cholestasis. Spatial and transcriptional analysis of the liver and liver draining lymph nodes during cholestasis demonstrates unique transcriptional changes, particularly in LEC-T cell neighborhoods. In vitro analysis of human LECs with IFNg and bile salts leads to upregulation of the inhibitory molecule, PD-L1, on LECs. Co-culture of the bile treated LECs led to a striking reduction in T cell activation as assessed by decreased T cell activation marker expression and decreased T cell proliferation. Further, T cell adhesion and chemokinesis towards bile salt treated LECs were also affected. **Conclusion:** This study demonstrates LEC-T cell interactions may be an important immune regulatory process in cholestasis. Our *in vitro* data suggests that *in vivo*, intrahepatic LECs directly respond to bile acids and the infiltrating immune cells found within the cholestatic environment. In turn, lymphatic endothelial cells in the liver may drive changes in T cell proliferation and activation. These changes in lymphatics may contribute to the liver inflammation and injury in cholestatic liver disease.

Disclosures: Alyssa Goldberg: Nothing to Disclose, William Hollenbach: Nothing to Disclose, Beth Tamburini: Nothing to Disclose.

2679 | IMPACT OF NON-STANDARD EXCEPTION REQUESTS ON TRANSPLANT ACCESS IN PEDIATRIC LIVER TRANSPLANT CANDIDATES

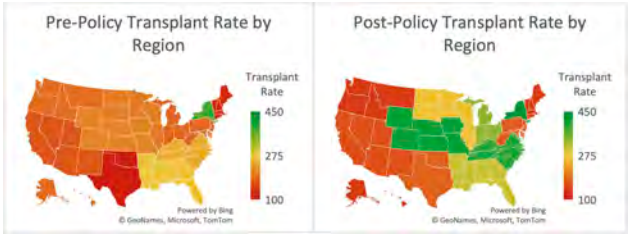
Tess Coker[1] Ruiwen Zhou[2] George Blanco[3] Janis Stoll[4] Adeel Khan[2] Sakil Kulkarni[5], [1]Washington University St. Louis, School of Medicine, [2]Washington University St. Louis, [3]St. Louis University, [4]St. Louis Children's Hospital, [5]Washington University in St. Louis

Background: Non-standard exception requests (NSERs) allow pediatric liver transplant (LT) centers to seek increased allocation priority for candidates in whom priority scores are believed to underestimate true mortality risk, with the goal of facilitating timely LT. National Liver Review Board (NLRB) was established to standardize NSER review in 2019, and the acuity circles (AC) policy was implemented to expand organ sharing in 2020. We aimed to evaluate the impact of NSER use on transplant access among pediatric LT candidates. **Methods:** Using the SRTR database, we identified 1,973 pediatric (0-18 years) candidates listed between 2016 and 2024 for deceased donor LT, who were eligible for NSER, and had one of two outcomes (transplant or death/removal for being too sick). Fine-Gray competing risks models (with death treated as a competing event) were used to evaluate the association of listing with NSER approval with LT. Transplant centers were categorized into three clusters using k-means clustering (Cluster 1: high total and living donor (LD) volume, greater use of deceased-donor technical variant grafts (TVG); Cluster 2: medium-volume centers with lower TVG, lower LD; Cluster 3: low-volume centers with greater use of TVG, minimal LD volume). **Results:** 63.4% of eligible candidates were listed with NSER. Waitlist mortality did not differ between groups ($p = 0.5$). In the adjusted Fine-Gray model, NSER listing was associated with a 26% lower subdistribution hazard (sHR) of transplantation. Amongst other co-variates, higher priority score at outcome (sHR 1.01, $p < 0.001$) and listing in the post-NLRB/AC policy era (2021-24) (sHR 1.21, $p = 0.005$) vs. pre-NLRB/AC era (2016-19) were associated with higher access to LT. Age group 12–17 years (sHR 0.75, $p < 0.001$) and age group 1-5 years vs. infants (sHR 0.86, $p = 0.03$), blood group O (sHR 0.90, $p = 0.01$), LT at cluster 2 (sHR 0.80, $p < 0.001$) or cluster 3 (sHR 0.70, $p < 0.001$) vs. cluster 1 centers were associated with lower access to LT. Candidate sex, race, insurance status and diagnosis were not

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associated with LT. Regional variation in transplant access pre/post NLRB/AC implementation is shown in Figure 1. **Conclusion:** After adjustment for patient-, policy-, and center-level factors, NSER listing was associated with a lower cumulative incidence of transplantation, suggesting that observed differences are influenced by allocation structure and center practices. Notably, regional disparities in transplant access persisted despite NLRB/AC policy.



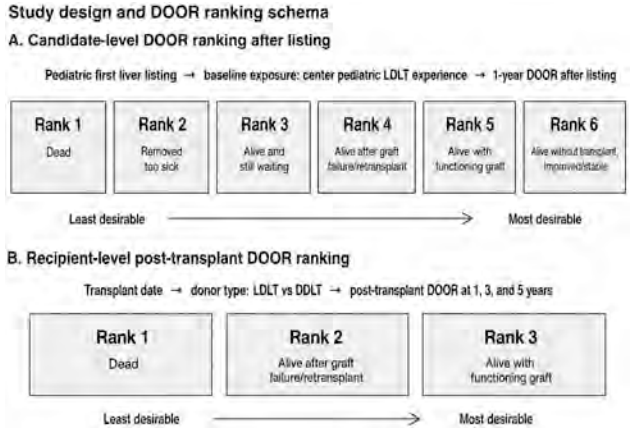
Disclosures: Tess Coker: Nothing to Disclose, Ruiwen Zhou: Nothing to Disclose, George Blanco: Nothing to Disclose, Janis Stoll: Mirum: Medical Advisor, Adeel Khan: Nothing to Disclose, Sakil Kulkarni: Nothing to Disclose.

2680 | DESIRABILITY OF OUTCOME RANKING (DOOR) IN PEDIATRIC LIVER TRANSPLANTATION: LIVING DONOR AND CENTER CAPABILITY

Toshifumi Yodoshi[1] Shuntaro Sato[2] Akihiro Asai[3] Tomohiro Tanaka[4], [1]Cincinnati Children's Hospital Medical Center, [2]Nagasaki University Hospital, [3]Cincinnati Children's Hospital Medical Center, [4]University of Iowa Carver College of Medicine

Background: In pediatric liver transplantation, prior work has compared outcomes between living donor (LDLT) and deceased donor (DDLT) recipients, and has linked higher cumulative center LDLT volume to better outcomes. These analyses share two limitations: recipient-only studies are restricted to children who actually received a transplant, missing those who died or deteriorated while waiting, and any single endpoint captures only one part of the candidate journey; and cumulative historical volume may not reflect a center's current capability for newly listed children. Desirability of Outcome Ranking (DOOR), an ordinal composite endpoint that ranks each patient's outcome from least to most desirable, can integrate competing outcomes into one patient-centered hierarchy. We applied DOOR within a unified framework to evaluate pediatric LDLT both from listing (current active vs historical cumulative center capability) and after transplant (LDLT vs DDLT).

Methods: Using SRTR liver files, we studied children <18 years at first listing and pediatric transplant recipients. Three DOOR comparisons were performed: (1) post-transplant outcomes for LDLT vs DDLT; and, at listing, candidate outcomes by (2) active recent LDLT capability (≥5 pediatric LDLTs at the listing center in the prior 5 years vs none) and (3) cumulative experience (≥20 vs none). Candidate DOOR used six ordered states; recipient DOOR used three (Figure). Results were expressed as DOOR probabilities, the adjusted probability that an LDLT or higher-capability child had a more desirable outcome (0.50 = no difference). Models adjusted for demographic, clinical, severity, exception, era, and center-volume factors with cluster bootstrap 95% CIs. **Results:** We studied 23,150 children at 146 centers and 17,227 recipients (2,019 LDLT) at 131 centers. After transplant, LDLT showed a modest but consistent advantage over DDLT: DOOR 0.512 (95% CI, 0.503-0.520), 0.518 (0.509-0.527), and 0.518 (0.508-0.528) at 1, 3, and 5 years. From listing, current active capability favored candidate DOOR in contemporary cohorts: 2018-or-later, DOOR 0.532 (0.500-0.570) at 1 year and 0.534 (0.505-0.569) at 3 years; 2020-or-later, 1-year 0.549 (0.517-0.586). Cumulative experience alone was not (1-year 0.495 [0.472-0.513]; 3-year 0.495 [0.476-0.512]). High-cumulative centers had more LDLT and less DDLT with similar transplantation and survival, consistent with substitution between donor sources rather than expanded access. **Conclusion:** Within a unified patient-centered framework, DOOR distinguished current programmatic LDLT capability from cumulative experience at listing, and confirmed the post-transplant advantage of LDLT over DDLT. Active recent capability, not cumulative volume, favored listed children. Cumulative volume alone may inadequately proxy current LDLT capability and should not be the sole metric for referral or center assessment.



Disclosures: Toshifumi Yodoshi: Nothing to Disclose, Shuntaro Sato: Nothing to Disclose, Akihiro Asai:

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Nothing to Disclose, Tomohiro Tanaka: Nothing to Disclose.

2681 | MORTALITY AND LIVER TRANSPLANT ACCESS IN CHILDREN WITH BILIARY ATRESIA

Olabade Omole[1] Janet Wojcicki[1] Matthew Pantell[1] Emily Perito[1], [1]University of California San Francisco

Background: Biliary atresia (BA) is the leading cause of pediatric end-stage liver disease and the most common indication for liver transplantation (LT) in children. While outcomes among children with BA who are listed for LT are well described, it is not yet known whether all children with BA and end-stage liver disease are appropriately listed and have access to LT. This analysis aimed to identify children with BA with indication for LT who are not listed and evaluate mortality within this potentially vulnerable population. **Methods:** We performed a retrospective cohort study using the Pediatric Health Information System (PHIS) and Scientific Registry of Transplant Recipients (SRTR) databases. Children < 18 years old with BA between 2010-2020 were identified in PHIS and cross-referenced with SRTR transplant listing data to determine listing status using validated PHIS-SRTR linkage codes. Children were categorized as listed or unlisted for LT, based on PHIS-SRTR merge. Deaths were identified using PHIS mortality data 2010-2020, and listing status among children who died was verified through linkage with SRTR records. **Results:** Among 3,838 children with BA identified in PHIS, 1,171 (30.5%) were listed for liver transplantation in SRTR, while 2,667 (69.5%) were not listed. A total of 152 deaths (4%) occurred within this cohort. 136 deaths (89.5%) occurred among children who were never listed for transplant, whereas 16 deaths (10.5%) occurred among listed children. The 16 identified listed children who died did so during or after LT. Among children with BA who died, median age at death was 6 months (IQR 0–10) in unlisted versus 9.5 months (IQR 7.5–16.5) in listed ($p = 0.002$). Among listed children who died, 62.5% were white compared with 44.9% of unlisted children who died, while 22.1% of unlisted children who died were black compared with 6.2% of listed children who died ($p = 0.025$). Deaths occurred across 35 of 46 PHIS hospitals caring for children with BA. **Conclusion:** In our cohort of children with BA based on PHIS-SRTR merge, deaths occurred among children not listed for LT. Mortality occurred predominantly in infancy, raising concern for a vulnerable subgroup of children who may not be accessing LT evaluation or listing. Children who were not identified as listed for transplant died at younger ages than listed children, further emphasizing the vulnerability of this population. Differences in race distribution between listed and unlisted children who died suggest the possibility of disparities in LT listing process. Mortality was observed across many PHIS centers, suggesting a broadly distributed at-risk population. Further work aims to distinguish children who were not LT candidates from those potentially eligible but never referred or listed, and further characterize mortality outcomes, barriers to listing, and clinical trajectories preceding death.

Disclosures: Olabade Omole: Nothing to Disclose, Janet Wojcicki: Nothing to Disclose, Matthew Pantell: Nothing to Disclose, Emily Perito: Mirum: Consultant, Ultragenyx: Consultant, BridgeBio: Consultant, Amagma: Consultant, Mirum: Grant/Research Support, Albireo: Grant/Research Support, Gilead: Grant/Research Support, Dicerna: Grant/Research Support, Takeda: Grant/Research Support.

2682 | THE 2023 OPTN PEDIATRIC MEDICAL URGENCY UPDATE INITIATED A DURABLE DECLINE IN WAITLIST FAILURE WITHOUT DISRUPTING TRANSPLANT OR EXCEPTION ACCESS: A NATIONAL INTERRUPTED TIME-SERIES EVALUATION

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Background: Legacy pediatric end-stage liver disease (PELD) underestimated short-term waitlist mortality in children younger than 12 years. In July 2023, Organ Procurement and Transplantation Network (OPTN) implemented a pediatric medical urgency update revising PELD, pediatric Status 1A/1B rules, and related National Liver Review Board guidance. National effects on waitlist outcomes and exception access have been understudied. **Methods:** We conducted a national interrupted time-series analysis of OPTN/UNOS STAR liver data linked to the formal exception file for children younger than 12 years listed from January 2019 through December 2024. June and July 2023 were excluded a priori as a transition period; August 2023 onward defined the post-policy era. Adjusted segmented Poisson models, with log person-days offset and two-way clustered standard errors, evaluated waitlist failure (death or removal for clinical deterioration) and transplant rate after adjustment for prespecified demographic and clinical covariates, calendar month, and region. Linked exception analyses used segmented Poisson models for first formal exception request and approval probability, and cause-specific Cox models for post-request outcomes. Supportive recipient analyses used adjusted pre/post models. **Results:** Among 14,639 person-months from 2,791 under-12 registrations, the policy was not associated with an immediate step change in waitlist failure (incidence rate ratio [IRR], 1.25; 95% confidence interval [CI], 0.61-2.57; $P = 0.548$) but was followed by a lower post-policy monthly slope (trend-change IRR, 0.94; 95% CI, 0.88-1.00;

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P = 0.04). No insurance- or race/ethnicity-based differential effect on waitlist failure survived correction. Transplant rates remained stable (step IRR, 1.07; P = 0.54; trend IRR, 1.00; P = 0.81). There was no immediate post-policy change in first formal exception request rate (step IRR, 1.15; 95% CI, 0.84-1.58; P = 0.38), or approval probability among requests (step risk ratio [RR], 1.07; 95% CI, 0.98-1.18; P = 0.13). Post-request waitlist death was unchanged (hazard ratio, 1.00; P = 0.99), whereas post-request transplant hazard was lower (HR, 0.83; P = 0.025). In supportive pre/post recipient analyses, post-policy exception proxy use decreased (RR, 0.91; P = 0.03) and living donor use increased (RR, 1.22; P = 0.04) among recipients younger than 12 years, while 90-day mortality among recipients younger than 18 years did not increase (RR, 0.66; P = 0.18). **Conclusion:** The 2023 OPTN pediatric medical urgency update was associated with a durable decline in waitlist failure among children younger than 12 years without evidence of reduced transplant access or tightened formal exception pathways. Lower exception proxy use among recipients is consistent with improved calibration of urgency to clinical risk.

Figure. Interrupted time-series analysis of waitlist failure and transplant rate among pediatric liver transplant candidates younger than 12 years before and after the 2023 pediatric medical urgency update

Figure 1A. Adjusted monthly waitlist failure rate among candidates younger than 12 years

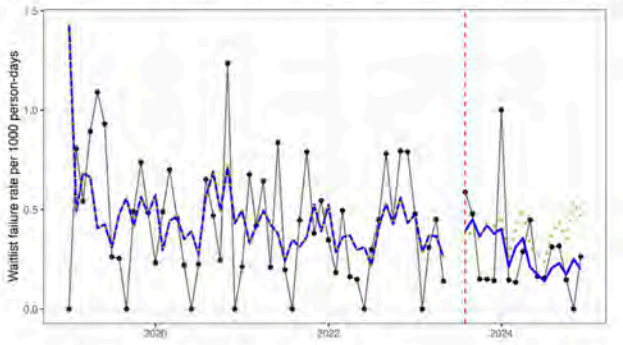
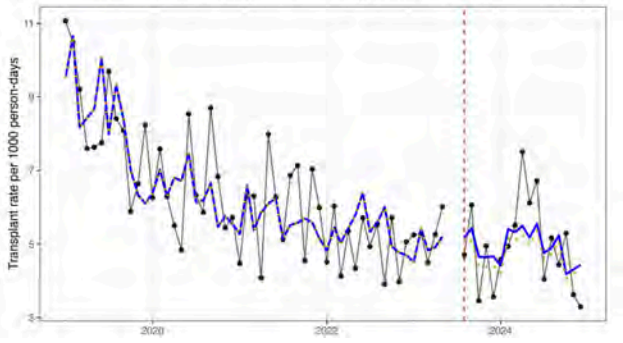


Figure 1B. Adjusted monthly transplant rate among candidates younger than 12 years



Disclosures: Toshifumi Yodoshi: Nothing to Disclose, Akihiro Asai: Nothing to Disclose, Tomohiro Tanaka: Nothing to Disclose.

2683 | NONLINEAR ASSOCIATION OF DONOR AGE WITH GRAFT SURVIVAL AFTER PEDIATRIC LIVER TRANSPLANTATION FOR BILIARY ATRESIA

Ioannis Ziogas[1] Ryan Lavanchy[1] Charalampos Theocharopoulos[1] Dor Yoeli[1] Megan Adams[1] Jonathan Merola[1] Katie Rose Conover[1] Amy Feldman[1] Ronald Sokol[2] Susana Arrigain[1] Deena Brosi[1] Rocio Lopez[1] Jesse Schold[1] Sarah Taylor[1], [1]University of Colorado, [2]University of Colorado School of Medicine

Background: Biliary atresia (BA) is the leading indication for pediatric liver transplantation (LT). Donor age and graft type are important determinants of graft survival; however, their complex and potentially non-linear relationship warrants further investigation in pediatric BA. **Methods:** We performed a retrospective cohort study using the Scientific Registry of Transplant Recipients on children (< 18 years) with BA undergoing first isolated LT (02/2002-09/2025). Graft types included deceased donor whole graft (DDWG), deceased donor technical variant (DDTV), and living donor liver transplantation (LDLT). The primary outcome was graft survival. Multivariable Cox proportional hazards models with restricted cubic splines were used to evaluate the association between donor age and graft survival, stratified by graft type. **Results:** Among 3,910 children with BA, 1,879 received DDWG, 1,220 DDTV, and 811 LDLT. Recipient and donor characteristics differed by graft type: DDWG recipients were older and waited longer, DDTV recipients had the highest burden of growth failure, ascites, ICU status, and dialysis, while LDLT recipients were less critically ill and had shorter cold ischemia time. LDLT was associated with superior unadjusted graft survival (log-rank p < 0.001), with 5-year graft survival of 96.8% vs 92.1% for DDWG and 93.2% for DDTV. Donor age showed non-linear associations with graft loss (**Figure**). In DDWG, donor age < 1 year was associated with increased graft loss compared with age 18 years (adjusted HR 2.36, 95% CI: 1.32–4.23), whereas older donor age was not associated with excess risk. In DDTV, graft loss risk increased progressively with donor age, from HR 1.04 at 19 years (95% CI: 1.02–1.05) to 4.55 at 55 years (95% CI: 2.20–9.40). In LDLT, older donor age was associated with increased graft loss, with HR 3.92 at 64 years (95% CI: 1.00–15.29) and 4.54 at 67 years (95% CI: 1.06–19.48). Additional risk factors for graft loss by graft type included: growth failure, ICU status, and increasing cold ischemia time for DDWG, increasing INR for DDTV, and increasing recipient age, growth failure, and ICU status for LDLT. **Conclusion:** Donor age is a non-linear and graft type–dependent determinant of graft survival in children with BA, with age-related risk emerging later in LDLT than in DDTV.

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These findings support the use of graft-specific, continuous risk assessment to optimize donor selection and improve outcomes. Further studies will assess the generalizability of these associations beyond BA.

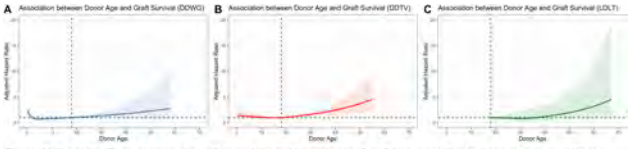


Figure. Multivariable Cox regression by graft type. Adjusted hazard ratio of graft loss according to donor age as a continuous variable using restricted splines with three knots for (A) DDWG, (B) DDTV, and (C) LDLT.

Disclosures: Ioannis Ziogas: Nothing to Disclose, Ryan Lavanchy: Nothing to Disclose, Charalampos Theocharopoulos: Nothing to Disclose, Dor Yoeli: Nothing to Disclose, Megan Adams: Nothing to Disclose, Jonathan Merola: Nothing to Disclose, Katie Rose Conover: Nothing to Disclose, Amy Feldman: Nothing to Disclose, Ronald Sokol: Mirum: Advisor, Ipsen/Albireo: Advisor, Malinkrodt: Consultant, Alexion: Consultant, ProQR: Consultant, Susana Arrigain: Nothing to Disclose, Deena Brosi: Nothing to Disclose, Rocio Lopez: Nothing to Disclose, Jesse Schold: Nothing to Disclose, Sarah Taylor: Ipsen Pharma: Consultant, Mirum Pharma: Consultant, Capsida Biotherapeutics: Consultant.

2684 | INCREASED RISK OF ADENOVIRUS INFECTION IN PATIENTS TREATED WITH BASILIXIMAB-CONTAINING IMMUNOSUPPRESSION FOLLOWING LIVER TRANSPLANTATION

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Background: The optimal immunosuppression (IS) protocol for pediatric liver transplantation (LT) which promotes allograft acceptance while avoiding IS-related end-organ damage and infections remains controversial. Our institution's IS protocol was revised from higher tacrolimus troughs combined with corticosteroids to a basiliximab-containing regimen with lower tacrolimus trough goals in 2022, with aims to improve patient outcomes. **Methods:** This retrospective case-control study aimed to determine the safety and efficacy of the revised IS protocol (RISP) for patients receiving isolated LT between 2022-2024. Historical IS protocol (HISP) were transplanted prior to 2022 and matched 1: 1 to RISP based on transplant age and indication. 1 year outcomes were analyzed with respect to: patient and graft survival; tacrolimus exposure; number, severity, and timing of biopsy-proven acute cellular rejection (BPAR) episodes; post-transplant lymphoproliferative disorder (PTLD), sepsis, viremia, renal function, hypertension, and hospital length of stay and readmissions. **Results:** RISP (n = 39 patients) compared to HISP (n = 35) had similar 1-year patient/graft survival (10% vs. 3%; p = 0.36) and rates of BPAR (46% RISP vs. 49% HISP, p = 0.82). Cystatin C at time of transplant was significantly lower for HISP patients (0.79) vs RISP patients (0.99; p < 0.05), indicating more severe pre-LT renal disease, however, there was no statistical significance in cystatin C values at one year post-LT. As expected, RISP patients had lower mean tacrolimus trough levels at d30 post-LT vs. HISP patients (12.7; p < 0.05). Rates of sepsis (29% HISP vs 21% RISP) and viremia (69% HISP vs 77% RISP) were not statistically different. However, there was a statistically significant increase in adenoviremia of 36% RISP vs. 11% HISP (p = 0.02; n = 4 in RISP treated with cidofovir), yet a decreased use of rituximab for EBV treatment in RISP (3% vs. 17%, p = 0.05). **Conclusion:** Overall, we demonstrate that the basiliximab-containing RISP had similar one-year post-LT outcomes to HISP despite decreased tacrolimus exposure. Surprisingly, there was increased risk of adenovirus infection, yet decreased severity of EBV infections requiring rituximab in RISP. Prospective analysis in a larger cohort with longer follow up is needed to determine whether these trends are durable.

Disclosures: Princess Ogundu: Nothing to Disclose, Julie Bonn: Nothing to Disclose, Teresa Ambrosino: Nothing to Disclose, Jessica Rogers: Nothing to Disclose, Mallory Rosinski: Nothing to Disclose, Kristen Gamm: Nothing to Disclose, Siobhan Cooper: Nothing to Disclose, Anna Peters: Nothing to Disclose.

2685 | TEMPORARY WITHDRAWAL OF IMMUNOSUPPRESSION IS ASSOCIATED WITH IMPROVED SURVIVAL WITHOUT INCREASED REJECTION IN PEDIATRIC PATIENTS WITH PTLD: A REAL-WORLD, PROPENSITY-MATCHED COHORT STUDY OF 1271 LIVER TRANSPLANT RECIPIENTS

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Background: Posttransplantation lymphoproliferative disorder (PTLD) remains a life-threatening complication of pediatric liver transplantation (p-LT), with a high mortality rate even after treatment with the current first-line therapy and a reduction in

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immunosuppression (RIS). The optimal management strategy and effects of immunosuppression (WIS) remain unclear. **Methods:** We analyzed 1271 p-LT recipients from a single center. Management strategies (WIS vs. RIS) were evaluated in children who developed PTLD. To control for confounding by indication, 1: 2 propensity score matching (PSM) was performed between the WIS and RIS groups, and 1: 3 exact match was conducted between the WIS group and a routine follow-up (RF) cohort. Differences in liver function between the WIS and RF groups were evaluated using linear mixed-effects models (LMMs). Long-term liver function, graft survival, and biopsy-proven rejection rates were compared. **Results:** PTLD occurred in 5.98% (76/1271) of patients, with 82.89% being EBV positive. Among these, 49 received WIS (median duration: 93 days; 3 retransplantation patients were excluded) and 24 received RIS. The WIS group had a significantly higher overall survival rate than the RIS group did (95.92% vs. 75.00%, $P = 0.0052$). In the 1: 2 matched cohort, the survival and rejection rates remained comparable between the groups ($P = 0.21$), suggesting that there was no added risk from withdrawal. Furthermore, compared with the RIS group, the WIS group had significantly better liver function (lower DB levels) during follow-up ($P < 0.05$). Longitudinal analysis using linear mixed-effects models demonstrated that compared with the matched RF group, WIS treatment was associated with significantly improved liver function profiles, including lower TB, DB and ALT levels ($P < 0.05$). Crucially, the incidence of acute rejection in the WIS group was not significantly different from that in the RF group (11.76% vs. 10.39%, $P > 0.05$). **Conclusion:** A temporary WIS strategy combined with close clinical monitoring and anti-PTLD therapy was associated with superior patient survival and improved functional recovery without compromising graft safety.

Disclosures: Xu Fang: Nothing to Disclose.

2686 | EMOTIONAL-BEHAVIORAL FUNCTIONING AND QUALITY OF LIFE IN PEDIATRIC BILIARY ATRESIA LIVER TRANSPLANT RECIPIENTS AND THEIR CAREGIVERS: AN ITALIAN SINGLE-CENTER EXPERIENCE

Francesca Boldrini[1] Andrea Pietrobattista[1] Daniela Liccardo[1] Marco Spada[1] Deny Menghini[1], [1]Bambino Gesù Children's Hospital

Background: Biliary atresia (BA) is the leading indication for pediatric liver transplantation. Despite improved survival, BA is associated with complex neuropsychological and psychosocial outcomes. This study evaluates non-verbal cognitive abilities, emotional-behavioral functioning, and quality of life (QoL) in pediatric BA transplant recipients; parental anxiety and depressive symptoms were also considered. **Methods:** During routine post-transplant follow-up, 58 patients (56% F, 44% M; mean age 9.8 ± 3.7 years; mean age at transplant 2.98 ± 4 years; mean time since transplant 6.8 ± 2.8 years) and parents underwent a screening protocol. Patients' non-verbal cognitive abilities were assessed using Raven's Progressive Matrices (2023). Quality of life was measured using the PedsQL Transplant Module (Varni et al., 2000), behavioral difficulties with the SDQ (Goodman, 1997) in self- and parent-report form. Depressive and anxious symptoms were assessed in patients and parents using the PHQ-9 (Kroenke et al., 2001) and the GAD-7 (Spitzer et al., 2006). **Results:** Non-verbal cognitive abilities were homogeneous across the sample. Borderline or clinically significant behavioral problems were reported by 46% of patients and 31% of parents. Both patients and parents identified Physical Appearance and Communication as critical QoL domains. Additionally, patients reported Worry, while parents reported Anxiety, as impaired domains. Correlation analyses showed that higher emotional symptoms were associated with greater behavioral difficulties and poorer QoL. Patient-reported depressive symptoms strongly correlated with SDQ Conduct Problems ($p < 0.002$), Hyperactivity ($p < 0.01$), and Total Difficulties ($p < 0.001$), suggesting an association with broader behavioral dysregulation. Patient anxiety was inversely related to the Total PedsQL Index ($p = 0.03$), indicating lower QoL with higher anxiety. Parental anxiety and depression positively correlated with all SDQ subscales except Prosocial Behavior, suggesting greater perceived child difficulties. Higher parental depressive symptoms were associated with lower QoL scores in Medication Management and Social Relations ($p < 0.01$), Pain Perception ($p < 0.02$), Physical Appearance and Communication ($p < 0.001$). Parental anxiety showed similar correlations, with additional impact on the Anxiety scale ($p < 0.01$). **Conclusion:** Children with BA undergoing liver transplantation exhibit significant emotional-behavioral vulnerabilities despite preserved cognitive abilities. Parental psychological well-being is a relevant factor for child adjustment. Findings support systematic psychological screening and early interventions within multidisciplinary post-transplant care.

Disclosures: FRANCESCA BOLDRINI: Nothing to Disclose, Andrea Pietrobattista: Nothing to Disclose, Daniela Liccardo: Nothing to Disclose, Marco Spada: Nothing to Disclose, Deny Menghini: Nothing to Disclose.

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2687 | ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION IN CHILDREN WITH ADVANCED LIVER FIBROSIS AND CIRRHOSIS: A RETROSPECTIVE COHORT STUDY

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Background: Advanced liver fibrosis and cirrhosis are traditionally considered contraindications to allogeneic hematopoietic cell transplantation (alloHCT) due to concerns for increased transplant-related mortality. Pediatric data in this high-risk population are limited. **Methods:** We conducted a retrospective single-center cohort study of pediatric patients (age 0-21 years) with biopsy-proven stage F3-F4 liver fibrosis or cirrhosis underwent HCT between January 2017 and March 2026 (Table). Clinical characteristics, transplant variables, hepatic outcomes, engraftment, graft versus host disease (GVHD), graft failure, and survival were analyzed. **Results:** Eight patients underwent 11 HCTs for malignant and nonmalignant disorders, including leukemia, transfusion-dependent thalassemia, sickle cell disease, sideroblastic anemia, Wolman's disease, chronic active Epstein–Barr virus infection, and Langerhans cell histiocytosis. Median age at transplantation was 15 years (range, 3–19). Donor sources included matched sibling, matched unrelated and haploidentical family members. Conditioning regimens were myeloablative (n = 8) and reduced intensity (n = 4). Median neutrophil and platelet engraftment occurred at 15 days and 25 days, respectively. At baseline, prior to initiation of conditioning, the median alanine aminotransferase (ALT) was 58 U/L (range, 14–163), and the median total bilirubin was 0.6 mg/dL (range, 0.2–7.2) (Table 1). From the start of conditioning through day +30 post-HCT, median ALT and direct bilirubin increased to 87 U/L (range, 30–248) and 1.6 mg/dL (range, 1.1–17), respectively. Between days +31 and +100, median ALT was 103 U/L (range, 31–596), and direct bilirubin was 1.1 mg/dL (range, 0.4–24) (Table 2). None of the patients received defibrotide for VOD prevention and only one patient was treated with defibrotide for presumed VOD. Acute GVHD occurred in 33% of patients and chronic GVHD in 11%. Two patients experienced graft failure after reduced-intensity conditioning and subsequently achieved durable engraftment following 2nd transplantation. One patient died from Streptococcus mitis sepsis complicated by liver failure. At a median follow-up of 3 years (range, 1–8), 7 of 8 patients were alive and disease-free with native liver. **Conclusion:** Although transient elevations in transaminases and bilirubin were observed after conditioning, most patients experienced only temporary hepatic worsening without progression to irreversible liver failure, suggesting that baseline fibrosis alone may not reliably predict post-HCT hepatic decompensation. Advanced liver fibrosis or cirrhosis should not universally exclude pediatric patients from HCT candidacy. With careful multidisciplinary management and individualized transplant strategies, favorable outcomes may be achievable in selected high-risk patients.

Table: Pre- hematopoietic cell transplant liver functions pathology and ultrasound findings

Patient ID, age & sex	Diagnosis/ year of Tx	Liver Fibrosis	Steatosis	Kupffer cell / parenchymal hemosiderosis	Liver Ultrasound	ALT U/L / total bilirubin mg/dL		
						Pre-transplant	Conditioning-day +30 (peak levels)	day 31-100 (peak levels)
Pt#1, M 15 years	TDT (2017)	Stage 3	Mild	Diffuse/diffuse	Hepatomegaly, homogeneous echogenicity	24/1.0	43/2.8	48/0.9
Pt#2, M HCT#1: 15 years HCT#2: 15 years HCT#3: 18 years	ALL (2018) ALL (2018) AML (2021)	Stage 3	Macrovesicular steatosis involving 90% of the parenchyma	None/none	Diffusely echogenic liver	163/0.6 66/0.9 56/0.4	205/1.5 200/ 1.2 30/1.4	99/0.91 68/0.9 31/0.4
Pt#3, F 4 years	LCH (2020)	Stage 3-4	None	None/none	Coarse echogenicity with lobular contour	157/ 7.2	248/17	125/24
Pt#4, F 3 years	Wolman's (2021) HCT #1 HCT#2	Stage 4	Macrovesicular steatosis, involving approximately 30-40% of the parenchyma	None/none	Coarse, heterogenous liver	32/0.2 82/0.4	174/1.1 42/1.1	127/1.2 89/15
Pt#5, F 10 years	SBA (2022)	Stage 3-4	None	Diffuse / severe	Mildly echogenic liver	60/0.2	240/1.8	536/1.2
Pt#6, F 19 years	CAEBV (2023)	Stage 4	None	None/none	Nodules and ascites	25/0.7	69/2.9	66/1.8
Pt#7, F 19 years	TDT (2025)	Stage 4	None	Diffuse / severe	Coarse, heterogenous liver	17/0.7	37/2.0	147/0.9
Pt#8, M 17 years	ALL (2025)	Stage 3-4	Macrovesicular steatosis involving 40% of the parenchyma	Diffuse/mild	Mildly echogenic liver	95/0.5	105/1.5	109/1.2

HCT: hematopoietic cell transplantation, ALL: acute lymphoblastic leukemia, AML: acute myeloid leukemia, TDT: transfusion dependent thalassemia, LCH: Langerhans cell histiocytosis, SBA: sideroblastic anemia, CAEBV: chronic active Epstein-Barr Virus infection, SCD: sickle cell disease, ALT: alanine transaminases, DFS: disease free survival.

Disclosures: Prakash Satwani: sobi: Consultant, Mercedes Martinez: Mirium: Grant/Research Support, Ipsen: Grant/Research Support, Mirum: Grant/Research Support.

2688 | BASELINE VALUES OF APRI AND FIB-4 DO NOT ALLOW FOR PREDICTING THE DISEASE PROGRESSION IN FONTAN-ASSOCIATED LIVER DISEASE IN CHILDREN

Anna Mania[1] Katarzyna Mazur-Melewska[2] Magdalena Figlerowicz[2], [1]Poznan University of Medical Sciences;, [2]Poznan Univesity of Medical Sciences

Background: The growing need to manage patients with Fontan-associated liver disease (FALD) is being recognised. The Fontan circulation leads to altered hemodynamics, chronic hypoxia, and increased venous pressure, resulting in liver injury and progressive fibrosis. Methods of non-invasive monitoring are required in this group of patients.This study aims to evaluate the clinical utility of non-invasive markers of fibrosis in children with FALD. **Methods:** The study included 31 children (18 girls) who underwent a Fontan procedure (FP) due to inborn heart defects. The median time from FP was 6 years (IQR 3.25-8.00). Children were evaluated every 12 months for the three

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following years in the outpatient hepatology clinic. Physical examination, blood CBC, ALT, AST, ALP, GTP levels, and liver stiffness (LS) by shear-wave elastography were evaluated. FIB-4 and APRI scores were calculated based on the laboratory results. All children received ursodeoxycholic acid at a dose of 15 mg/kg throughout the observation period. **Results:** After 3 years of observation, LS increased in 10 patients, while no progression (constant LS) or improvement (lower LS) was observed in 21 children. There was no difference between the groups in age or time from FP (10 vs 11 years, $p = 0.79$; 6 vs 5 years, $p = 0.95$, respectively). The baseline evaluation did not differ significantly between the groups with LS progression or improvement (7.9 vs 5.9 kPa; $p = 0.374$). Baseline APRI and FIB-4 were higher in children with LS improvement (0.54 vs 0.41; $p = 0.007$; 8.24 vs 5.28, $p = 0.04$). Other baseline parameters did not differ significantly between the groups. **Conclusion:** Liver stiffness monitoring is necessary in the management of children with FALD. Non-invasive markers of fibrosis are not helpful in predicting further outcomes of the diseases.

Disclosures: Anna Mania: Abbvie: Speaking and Teaching, Katarzyna Mazur-Melewska: Nothing to Disclose, Magdalena Figlerowicz: Nothing to Disclose.

2689 | MULTI-CENTER COMPARISON OF "ADJUSTED MEAN ALT" IN THE 5TH YEAR AFTER PEDIATRIC LIVER TRANSPLANTATION (LT)

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Background: Following previous single-center derivation of “adjusted mean ALT” in years 4-5 after LT as a more holistic representation of graft health than a single ALT value[1], we explored this metric and its association with immunosuppression (IS) practices in a multi-center cohort. **Methods:** In this retrospective analysis of children transplanted 2011-17 at 4 geographically diverse pediatric LT centers, all available ALT (IU/L) and tacrolimus trough (mg/dL) levels from each child’s medical record (EMR) were merged with outcomes data from the Society of Pediatric Liver Transplantation registry and the EMR. The mean adjusted ALT and tacrolimus trough levels representative of the 5th year after LT were derived by calculating, for each child, the median for each month of the 5th post-LT year and averaging all the median values.[1] Categorical variables were compared using the Chi-square test of significance, and continuous variables were compared using the Kruskal-Wallis test. **Results:** 321 children were included: 47% male; 33% non-White; median (IQR) age at LT 2 (1, 9) yrs; 40% biliary atresia; 76% deceased donor; race, LT indication, and donor type differed ($p < 0.001$ for all). At 5 yrs after LT, mean adjusted ALT distributions were similar across centers ($p = 0.46$; Fig 1A); means were 29.2, 29.0, 26.0, and 27.1 for sites 1, 2, 3, and 4, respectively. Use of induction and maintenance drugs, both early and late after LT, differed (Table). However, at 5 yrs, centers were similar in their use of monotherapy (62-82%; $p = 0.25$) versus dual therapy (15-31%; $p = 0.41$). **Conclusion:** Mean adjusted ALT distributions for children 5 years post-LT across 4 diverse LT centers were surprisingly similar, despite substantial variability in induction and maintenance IS drug use. Differential IS practices across LT centers appear to yield similar overall allograft health, reflected by a metric derived to holistically represent allograft health over time. Future directions should investigate the long-term outcomes of pediatric patients with the distinct IS regimens reflected in this cohort, as well as perform histological confirmation of allograft health in a similar cohort. [1] PMID: 37458328

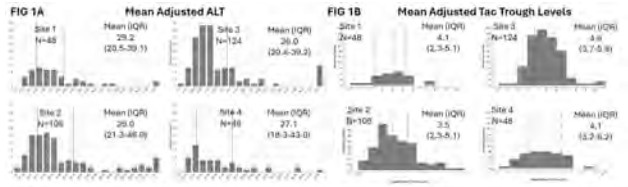


TABLE		Antibody induction		Immunosuppression										
				At Discharge						5th Post-transplant Year				
Site	N	ATG	IL2RAb	Pred	Tac	CYA	MMF	Aza	mTOR	Pred	Tac	MMF	Aza	mTOR
1	48	0	1 (2)	46 (96)	48 (100)	0	8 (17)	3 (6)	0	4 (15)	13 (48)	1 (4)	4 (15)	14 (52)
2	106	0	94 (89)	86 (81)	100 (94)	0	22 (21)	0	1(1)	13 (33)	16 (92)	4 (10)	0	4 (4)
3	120	27 (22)	0	105 (86)	115 (94)	1 (1)	0	0	0	6 (16)	37 (97)	10 (26)	0	1 (1)
4	48	0	0	48 (100)	47 (98)	1 (2)	47 (98)	1 (2)	0	3 (0)	48 (100)	9 (19)	0	1 (2)

BOLD ITALICIZED UNDERLINED variables are statistically significant different ($p<0.05$) among 4 centers

Abbreviations: ATG: antithymocyte globulin; IL2RAb: IL2 receptor antibody; Pred: prednisone; Tac: tacrolimus; CYA: cyclosporine; MMF: mycophenolic acid; Aza: azathioprine; mTOR: mTOR inhibitor

Disclosures: Elizabeth Raby: Nothing to Disclose, Sandy Feng: Nothing to Disclose, Emily Perito: Mirum: Consultant, Ultragenyx: Consultant, BridgeBio: Consultant, Amagma: Consultant, Mirum: Grant/Research Support, Albireo: Grant/Research Support, Gilead: Grant/Research Support, Dicerna: Grant/Research Support, Takeda: Grant/Research Support, SPLIT Society of Pediatric Liver Transplantation: Nothing to Disclose, Elizabeth Rand: Nothing to Disclose, Nitika Gupta: Nothing to Disclose, James Squires: Sanofi: Data Safety Committee, Mirum: Advisor, Ipsen: Advisor, Sanofi: Data Safety Committee, Sanofi: Data Safety Committee, Mirum: Advisor, Mirum: Advisor, Ipsen: Advisor, Ipsen: Advisor, Sanofi: Data Safety Committee, Mirum: Advisor, Ipsen: Advisor, Sanofi: Data Safety Committee, Sanofi: Data Safety Committee, Mirum: Advisor, Mirum: Advisor, Ipsen: Advisor, Ipsen: Advisor, Sanofi: Data Safety Committee, Mirum: Advisor, Ipsen: Advisor, Sanofi: Data Safety Committee, Sanofi:

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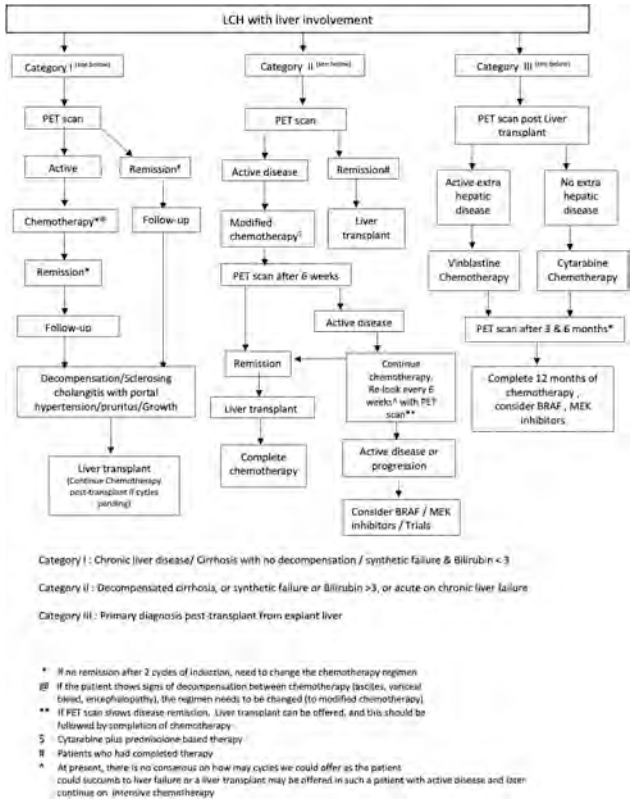
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Data Safety Committee, Mirum: Advisor, Mirum: Advisor, Ipsen: Advisor, Ipsen: Advisor.

2690 | ROLE OF LIVER TRANSPLANTATION IN LANGERHANS CELL HISTIOCYTOSIS IN CHILDREN: LARGEST SINGLE CENTRE EXPERIENCE AND AN ALGORITHM-BASED APPROACH

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Background: Langerhans cell histiocytosis (LCH) is a rare but important cause of end-stage liver disease in children. We describe the largest cohort of patients with LCH who underwent liver transplant (LT) and propose an algorithm to approach them based on our experience. **Methods: Methodology:** All patients aged < 18 years with LCH who underwent a liver transplant (LT) between January 2011 and June 2025 were analysed in this study. Their clinical profile, chemotherapy protocols and outcomes were described, and a therapeutic algorithm was proposed. **Results:** Twenty-three (2.7%) of 835 pediatric liver transplants performed in the aforementioned period were for LCH-related end-stage liver disease, and this included 16 males and 7 females. Diagnosis of LCH was made in the pre-LT period in 17 and post-LT from the explant liver in 6 children, whose pre-LT working diagnosis were Caroli's disease (n = 3) and primary sclerosing cholangitis (PSC) (n = 3). Patients were divided into *Category I* (n = 5), *Category II* (n = 12), and *Category III (n = 6)*. (Ref Figure 1 and notes). Indications for LT included decompensation and/or advanced portal hypertension and intractable pruritus. Median age at transplantation was 48 (11-216) months, and all were liver donor liver transplants (LDLT). Explant was positive for the *V600E BRAF* mutation in 4 patients. Chemotherapy was continued post-LT as per protocol (Figure 1). Trametinib was started for 2 patients, Dabrafenib for 1, and Vemurafenib for 3. There were no surgical complications, and none had rejection or post-transplant lymphoproliferative disorder (PTLD). After a median follow-up of 32 months (10-140 months), 22 (95.6%) patients are alive with normal graft function and in remission. One patient had a recurrence of LCH at the hepaticojejunostomy site post 20 months of LT, and is currently in remission following chemotherapy. **Conclusion:** We propose a therapeutic algorithm for patients with LCH based on our excellent post-LT outcomes. LCH should be strongly considered in patients suspected of Caroli's disease or PSC.



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2691 | TOWARDS PRECISION IMMUNOSUPPRESSION: RISK-STRATIFIED TACROLIMUS WINDOWS IN PAEDIATRIC LIVER TRANSPLANTATION

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Background: Tacrolimus based immunosuppression after paediatric liver transplantation should simultaneously prevent allograft rejection and avoid over-immunosuppresion that drives Epstein-Barr virus

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(EBV)-driven malignancies such as post-transplant lymphoproliferative disorder (PTLD) and EBV-associated smooth muscle tumour (EBV-SMT). Tacrolimus trough targets vary widely between centers, and no risk-stratified, paediatric-specific therapeutic window has been defined. We aim to define individualized tacrolimus trough windows that balance these opposing risks across different clinical recipient groups. **Methods:** We performed a retrospective analysis of paediatric liver transplant recipients in a single quaternary referral center over 10 years (2015 – 2024). The primary endpoint was EBV-related malignancy (both PTLD and EBV-SMT). Secondary endpoints were presence of biopsy-proven acute rejection, the Banff severity grade and the number of rejection episodes. Predictors for each endpoint were first quantified independently as odds ratios (Fisher exact test; Mann-Whitney U and Spearman correlation for continuous variables). The interaction of tacrolimus trough levels with both endpoints was examined to derived safe therapeutic windows for each risk group. **Results:** Between 2015 and 2024, 229 liver-only transplants were performed in 217 recipients. EBV-associated malignancies occurred in 10 patients (4.4%; 9 PTLD and 1 SMT). EBV malignancy was strongly correlated by viral load - peak PCR at or above 10000 copies/mL (OR 12.1, 95% CI 2.4-60.3) and sustained viraemia (OR 17.0, 95% CI 3.4-85.7; 25.8% vs 2.0% malignancy rate). Recipients with PTLD were also correlated with sustained, high-level EBV viraemia ($\geq$1000 copies/mL) over the first 12 months post-transplant, in contrast to transient viraemic episodes in non-PTLD patients. Tacrolimus trough variability was not correlated with rejection (OR 1.3, 95% CI 0.7–2.5) (Table 1). Recipients transplanted for autoimmune indications showed a trend toward higher rejection rates (89%) and moderate / severe rejection episodes (42% vs 15% in the general cohort). Tacrolimus trough windows were then derived for different clinical risk groups: 6-9 ng/mL for general-risk recipients, narrowed to 6-8 ng/mL where EBV-malignancy risk is higher (EBV-seronegative, R-/D+ mismatch, infancy) and raised to 7-10 ng/mL where rejection risk is higher (autoimmune aetiology, prior rejection) (Table 2). **Conclusion:** High-risk EBV mismatch (R −/D+) and sustained EBV viraemia above 1000 copies/mL are clinical indications to reduce tacrolimus trough targets and intensified EBV surveillance. EBV PCR $\log_{10} \geq 3.0$ (1000 copies/mL) should trigger tacrolimus trough review with target de-escalation if rejection risk is acceptable. We propose precision, risk-stratified tacrolimus windows to individualise immunosuppression and support more consistent decision-making across centres.

Table 1. Tacrolimus Trough Bands

Mean Tacrolimus trough POD 1-90 (ng/mL)	N	Rejection		EBV	
		Any rejection	Recurrent rejections	High EBV Viraemia	EBV Malignancy
≤5	6	4 (67%)	0 (0%)	1 (100%)	1 (17%)
5 – 6	14	9 (64%)	4 (29%)	6 (67%)	1 (7%)
6 – 7	43	34 (79%)	16 (37%)	23 (54%)	4 (9%)
7 – 8	80	57 (71%)	27 (34%)	59 (74%)	2 (2%)
8 – 9	56	36 (64%)	23 (41%)	35 (62%)	1 (2%)
9 – 10	19	14 (74%)	9 (47%)	11 (60%)	1 (5%)
10 – 12	9	6 (67%)	4 (44%)	7 (80%)	0 (0%)
>12	1	1 (100%)	0 (0%)	–	0 (0%)

Table 2. Risk-stratified Tacrolimus Therapeutic Windows

Risk group	Safe Therapeutic Window POD 1–90 (ng/mL)	Safe Therapeutic Window >POD 90 (ng/mL)	EBV PCR surveillance
General-risk liver transplant	6 – 9	4 – 7	Monthly EBV PCR × 12 months
EBV-seronegative recipient (R−)	6 – 8	3.5 – 6	Weekly × 3 mo, fortnightly × 3 mo, then monthly
R−/D+ high-risk mismatch	6 – 8	3 – 6	Weekly × 6 mo, then monthly to ≥24 months
Autoimmune aetiology (AIH / PSC)	7 – 10	5 – 8	Monthly EBV PCR × 12 months
Age <1 year at transplant	6 – 9	4 – 7	Weekly × 6 mo, then fortnightly
History of rejection	7 – 10	5 – 8	Monthly EBV PCR × 12 months

Disclosures: Yang Yang Lee: Nothing to Disclose, Jan Sabo: Nothing to Disclose, Alba Bueno: Nothing to Disclose, Hector Vilca-Melendez: Nothing to Disclose, Evelyn Ong: Nothing to Disclose, Khalid Sharif: Nothing to Disclose, Jake Mann: Nothing to Disclose, Girish Gupte: Albireo: Grant/Research Support, Orphalan: Speaking and Teaching.

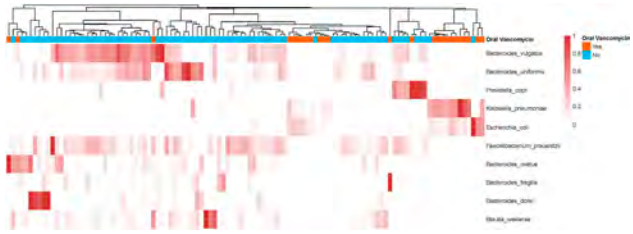
2692 | ◆ THE FECAL MICROBIOME IN PEDIATRIC PRIMARY SCLEROSING CHOLANGITIS – PRELIMINARY FINDINGS OF A MULTICENTER ANALYSIS

Mary Elizabeth Tessier[1] Richard Kellermayer[2] Cara Mack[3] Alexander Miethke[4] Amanda Ricciuto[5] Ronald Sokol[6] Joseph Petrosino[7] Benjamin Shneider[1] ChiLDReN Childhood Liver Disease Research Network[8], [1]Texas Children's Liver Center - Baylor College of Medicine, [2]Baylor College of Medicine/ Texas Children's Hospital, [3]Medical College of Wisconsin, [4]Cincinnati Children's Hospital Medical Center, [5]Hospital for Sick Children, [6]University of Colorado School of Medicine, [7]Baylor College of Medicine, [8]NIH NIDDK

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Background: Pediatric Primary Sclerosing Cholangitis (PSC) associates with inflammatory bowel disease (IBD) and autoimmune hepatitis (AIH) linking the gut-liver axis in pathogenesis. We hypothesized that the microbiome would differ in pediatric PSC between different disease phenotypes, treatments and fibrosis. **Methods:** Stool samples and clinical metadata were prospectively collected from 110 children with PSC through the Childhood Liver Disease Research Network's PSC Observational Study (NCT04181138) from 12 sites in North America. Whole genome shotgun metagenomic sequencing was performed. Statistical modeling was performed in ATIMA (Agile Toolkit for Incisive Microbial Analyses) and R (version 4.5.2), with coding input from Microsoft CoPilot. **Results:** 110 children with PSC (61.8% male) had stool samples sequenced (average age 15.1 years, range 7-25). 81 children had large duct PSC (73.6%) and 29 (26.4%) had small duct PSC. Eighty (72.7%) had IBD and 27 (25%) had PSC-AIH. 25 (23%) were treated with oral vancomycin (OV), and 22 of those had IBD. 59 (69.4%) had liver stiffness (kPa) <7.4, and 11 (12.9%) had kPa ≥ 14.4 as measured by Fibroscan. Children on OV had lower alpha diversity ($p<0.001$) and different overall community structure than those not on OV ($p=0.001$). Increased relative abundance (RA) of *Klebsiella pneumoniae* and *Escherichia coli* and decreased RA of *Bacteriodes vulgatus, B.uniformis* and *Faecalibacterium prausnitzil* were seen with OV use (FDR adj $p<0.001$). MaAsLIn2 analysis revealed 270 metagenomic pathways associated with OV (FDR adj $P<0.05$), including increased propionate synthesis and baiA KEGG ortholog, a bile acid modifier (FDR adj $p<0.001$). No significant differences were seen between large and small-duct PSC nor PSC-AIH vs PSC in alpha or beta diversity. Adjusting for OV, increased *Streptococcus mitis* and decreased *Barnesiella intestine hominis* RA were seen in large-duct PSC (FDR adj $p=0.02, 0.03$). *Veillonella* species had higher RA in PSC-AIH vs PSC, (FDR adj $p=0.03$) aligning with adult studies. Adjusting for OV, *Gemella morbillorum* negatively correlated with GGT level and platelet count (FDR adj $p=0.04, 0.02$). *Clostridium disporicum* and *Turicibacter sanguinis* negatively correlated with fibrosis severity (FDR adj $p=0.01, 0.03$) The methionine degradation pathway (PWY-5464) decreased with increasing fibrosis, suggesting a role in fibrosis-associated methionine disruption. **Conclusion:** OV was the strongest modifier of both the composition and function of the fecal microbiome in pediatric PSC, affecting microbial short chain fatty acid synthesis and bile acid metabolism. Differences across PSC categories and markers of severity were less marked, but linked to microbial mechanisms of hepatic dysfunction; together, these findings warrant further study.



Disclosures: Mary Elizabeth Tessier: Albireo/Ipsen: site PI for a pharmaceutical study, Albireo: Independent Contractor, Mirum: scientific advisory board, Richard Kellermayer: Nothing to Disclose, Cara Mack: Ipsen Pharm: Consultant, Alexander Miethke: Mirum Pharmaceutical Inc: Grant/Research Support, Mirum Pharmaceutical Inc: Consultant, Ipsen: Speaking and Teaching, Perspectum Ltd.: Grant/Research Support, Esperion: Advisor, Amanda Ricciuto: Nothing to Disclose, Ronald Sokol: Mirum: Advisor, Ipsen/Albireo: Advisor, Malinkrodt: Consultant, Alexion: Consultant, ProQR: Consultant, Joseph Petrosino: Nothing to Disclose, Benjamin Shneider: Nothing to Disclose, ChiLDReN Childhood Liver Disease Research Network: Nothing to Disclose.

★ 2693 | ◆ POTENTIAL BIOMARKERS IN ACTIVATED T-CELL PEDIATRIC ACUTE LIVER FAILURE FOR DIAGNOSIS AND RECOVERY: TNFSF11, ITGA11 AND LTA4H

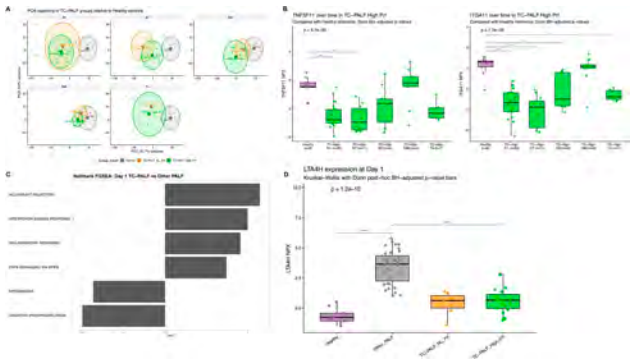
Tamir Diamond[1] Catherine Chapin[2] Alyssa Baccarella[1] Caroline Diorio[1] Portia Kreiger[1] Sarah Henrickson[1] Ezuka Ogbolu[1] Niansheng Chu[1] Anna Banc-Husu[3] Daniel Leung[4] Amrita Narang[5] Beth Carter[6] Scott Elisofon[7] Ryan Fischer[8] Amber Hildreth[9] Mike Leonis[10] Steven Lobritto[11] Saeed Mohammad[12] Anna Peters[13] Norberto Rodriguez-Baez[14] Rene Romero[15] David Rudnick[16] James Squires[17] Shikha Sundaram[18] Kyla Tolliver[19] Pamela Valentino[20] Zemin Su[21] Valerie Durkalski-Mauldin[21] Katie Neighbors[22] Simon Horslen[23] Kathleen Loomes[1] Estella Alonso[2] Edward Behrens[1], [1]The Children's Hospital of Philadelphia, [2]Ann and Robert H. Lurie Children's Hospital of Chicago, [3]Baylor College of Medicine, Texas Children's Hospital, [4]Texas Children's Hospital, [5]Stanford, [6]Children's Hospital Los Angeles, [7]Boston Childrens Hospital, [8]Children's Mercy Kansas City, [9]University of California San Diego, [10]Cleveland Clinic Children's Outpatient Center (R3), [11]NY Presbyterian Hospital - Columbia University, [12]Monroe Carell Jr. Children's Hospital at Vanderbilt, [13]Cincinnati Children's Hospital Medical Center, [14]University of Texas Southwestern Medical Center, [15]Emory University School of Medicine, [16]Washington University Medical Center, [17]Children's Hospital of Pittsburgh, [18]Children's Hospital Colorado, [19]Indiana

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Background: Activated T-cell pediatric acute liver failure (TC-PALF) is the most common cause of liver failure in children in North America. Work from the PALF Immune Response Network (PALF-IRN) described two distinct disease endotypes that differ by their CD8+ T-cell Perforin1 (Prf) expression: TC-PALF High Prf and TC-PALF Normal Prf (TC-PALF NL Prf). We aimed to identify novel non-invasive serum protein biomarkers of disease and recovery that characterize these TC-PALF groups. **Methods:** Serum samples from patients enrolled in the PALF-IRN clinical trial, TReatment for ImmUne Mediated PathopHysiology (TRIUMPH) (NCT04862221), from day 1, 7, 21, 90 and liver transplant were analyzed using a multiprotein assay measuring N = 5400 serum proteins (Olink 5400 HT explore). TRIUMPH patient samples from the TC-PALF High Prf and TC-PALF NL Prf groups were compared to samples of healthy children and other causes of PALF (Oth-PALF) from the PALF-Study Group biorepository (UO1-DK072146). Investigators remain blinded to patient study treatment arm, which included 3 arms- equine anti thymocyte globulin, methylprednisolone or supportive care. Statistical analysis was performed using R studio 4.4.0. **Results:** Healthy (n = 9, 55% male), Oth-PALF (n = 39, 53% male), TC-PALF High Prf (n = 20, 75% male), and TC-PALF NL Prf (n = 8, 50% male) were compared. Principal component analysis (PCA) showed migration of TC-PALF endotype clusters toward healthy over time (figure 1A). The highly expressed proteins driving PC1 included those associated with liver synthetic function: coagulation cascade and complement pathways. PC1 also contained Tumor Necrosis Factor Superfamily Member 11(TNFSF11) and Integrin Subunit Alpha 11 (ITGA11), proteins involved in extracellular matrix production. These markers normalized over time in patients recovering from PALF compared to those undergoing transplantation (figure 1B). Pathways that differentiated TC-PALF from Oth-PALF patients by gene set enrichment analysis (GSEA) involved proteins associated with interferon-ɣ signaling and T-cell cytotoxicity with downregulation of energy metabolism via oxidative phosphorylation (figure 1C). Leukotriene A4 hydrolase (LTA4H), an enzyme involved in activating innate immune responses, was significantly higher in Oth-PALF compared to TC-PALF High Prf patients (figure 1D). **Conclusion:** Patients recovering from TC-PALF have serum biomarkers associated with tissue regeneration, fibrosis and normalization of coagulation and complement pathways. LTA4H is a candidate biomarker for differentiation of etiologies of PALF. These may serve as useful biomarkers for diagnosis or trajectory of illness.



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2694 | THE CHILDHOOD LIVER DISEASE RESEARCH NETWORK PROSPECTIVE CHARACTERIZATION OF PEDIATRIC PRIMARY SCLEROSING CHOLANGITIS

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Background: Primary sclerosing cholangitis (PSC) is a rare biliary fibrosing disease that leads to significant morbidity and the need for liver transplantation. The Childhood Liver Disease Research Network is conducting a prospective, observational longitudinal study to define the natural history of pediatric PSC. The aim of this report is to characterize the clinical phenotypes of the first 175 children enrolled in the PSC study and to determine correlations of specific phenotypes with clinical and laboratory characteristics. **Methods:** Data collected included diagnostic MRCP/ liver histology, history of inflammatory bowel disease (IBD) and/or autoimmune hepatitis (AIH), IBD activity, medications, clinical blood tests, autoantibodies, and fasted liver stiffness measurements (LSM) per protocol. Comparison of phenotypes with/without IBD and/or AIH, and small duct versus large duct PSC was performed. **Results:** 90% of participants had been previously diagnosed with PSC, while 10% were newly diagnosed within 90 days of enrollment. The median age at enrollment was 16.1 years, 60% were male, 78% had large duct PSC and the median duration of PSC was 2.2 years. Frequent medication use at enrollment included ursodeoxycholic acid (51%) and oral vancomycin (27%). The predominant phenotype was PSC/IBD and 96% had quiescent/mild IBD. The majority had evidence of mild liver disease based on biochemistries and LSMs; < 10% had portal hypertension defined as ascites, splenomegaly or thrombocytopenia. Higher LSMs were associated with elevated liver biochemistries. There were no significant characteristics that differentiated the phenotypes, however there was frequent autoantibody positivity in the PSC/IBD cohort at enrollment (56%), despite the fact that the majority of these patients did not have a previous diagnosis of AIH. Furthermore, there was a trend towards a more severe phenotype in the PSC/AIH cohort with higher LSMs, and greater frequency of focal biliary strictures and concentric periductal inflammation based on diagnostic MRCP and histology, respectively. **Conclusion:** This prospective cohort of pediatric PSC revealed mild liver disease in the majority. Laboratory biomarkers of liver injury and fibrosis were associated with LSM elevation, suggesting LSM as a reliable tool to monitor PSC severity. The majority of participants with a positive autoantibody at enrollment were not previously diagnosed with AIH, suggesting that autoantibodies are associated with IBD and not necessarily classical AIH or PSC. This dataset encompasses a well-phenotyped cohort of children with PSC that will be followed prospectively for longitudinal assessment of progression of disease, as well as a model for stratification within future treatment trials.

Disclosures: Cara Mack: Ipsen Pharm: Consultant, Alexander Miethke: Mirum Pharmaceutical Inc: Grant/Research Support, Mirum Pharmaceutical Inc: Consultant, Ipsen: Speaking and Teaching, Perspectum Ltd.: Grant/Research Support, Esperion: Advisor, Kieran Hawthorne: Nothing to Disclose, Lisa Henn: Murata Vios: Consultant, Simon Horslen: Mirum: Grant/Research Support, Albireo/Ipsen: Consultant, Mallinckrodt Pharma: Consultant, Estella Alonso: Nothing to Disclose, Nitika Gupta: Nothing to Disclose, Shikha Sundaram: Nothing to Disclose, Rohit Kohli: Mirum: Consultant, Ipsen: Consultant, Epigen: Grant/Research Support, Sanofi Rare Disease: Consultant, iECURE: Consultant, Solid Biosciences: Consultant, Molly Bozic: Nothing to Disclose, Mark Deneau: Nothing to Disclose, Kathleen Loomes: Nothing to Disclose, Pamela Valentino: Nothing to Disclose, Mary Elizabeth Tessier: Albireo/Ipsen: site PI for a pharmaceutical study,

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Albireo: Independent Contractor, Mirum: scientific advisory board, Benjamin Shneider: Nothing to Disclose, John Magee: Nothing to Disclose, Saul Karpen: Albireo/Ipsen: Consultant, Mirum: Consultant, Intercept: Consultant, Philip Rosenthal: Nothing to Disclose, Kasper Wang: Nothing to Disclose, Amanda Ricciuto: Nothing to Disclose, Ronald Sokol: Mirum: Advisor, Ipsen/Albireo: Advisor, Malinkrodt: Consultant, Alexion: Consultant, ProQR: Consultant, Binita Kamath: Nothing to Disclose, ChiLDReN Childhood Liver Disease Research Network: Nothing to Disclose.

2695 | EARLY BIOCHEMICAL AND CLINICAL PREDICTORS OF OUTCOMES IN PEDIATRIC AUTOIMMUNE HEPATITIS AND AUTOIMMUNE SCLEROSING CHOLANGITIS

Shelley Choudhury[1] Sakil Kulkarni[1] Rebekah Karns[2] Pooja Khonde[1] Adith Boloor[1] Cyd Castro-Rojas[2] Amy Taylor[2] Alexander Miethke[2], [1]Washington University in St. Louis, [2]Cincinnati Children's Hospital Medical Center

Background: In adults with autoimmune hepatitis (AIH), baseline disease characteristics and early biochemical response (EBR) are strong predictors of long-term outcomes. A recent study showed that adult patients who achieve EBR, defined as normalization of ALT, AST, and immunoglobulin G (IgG) levels at 6 months after diagnosis, have significantly improved transplant-free survival. EBR has emerged as a potential surrogate endpoint for clinical trials in adult AIH. However, the prognostic value of baseline disease features and EBR, including optimal definitions, remains unclear in pediatric AIH and autoimmune sclerosing cholangitis (ASC). **Methods:** We performed a retrospective multicenter cohort study of 191 patients aged 2–21 years with AIH (n = 180) or ASC (n = 11) treated at 9 pediatric tertiary centers between 2010–2020. Baseline demographic, clinical and laboratory data were analyzed. EBR at 6 and 12 months was defined using normalization of ALT, AST, IgG and total protein. Outcomes included liver-related events (ascites, encephalopathy, variceal hemorrhage, transplantation), steroid-related complications (obesity, growth impairment, hypertension, diabetes, cataracts), and treatment resistance (steroid dependence or flare within 18 months). **Results:** Among 191 patients with AIH and ASC (median follow-up 3.2 years), liver events occurred in 15.6%, steroid-related complications in 31.1%, and treatment resistance in 56.1%. Liver events were associated with higher baseline INR ($p < 0.001$), bilirubin ($p = 0.005$), APRI ($p = 0.03$), and FIB-4 ($p = 0.003$), and with lower albumin ($p < 0.001$) and platelet count ($p = 0.009$). Steroid-related complications were associated with younger age (median 11 vs 13.5 years, $p < 0.001$), higher alkaline phosphatase ($p = 0.02$), and lower albumin ($p = 0.02$) and creatinine ($p = 0.004$). Treatment resistance was associated with higher baseline IgG ($p = 0.02$) and INR ($p = 0.007$). EBR at 6 months showed limited predictive value (AUC 0.5–0.7). In contrast, EBR at 12 months predicted liver events and treatment resistance, with inclusion of IgG improving discrimination for treatment resistance. **Conclusion:** In pediatric AIH/ASC, early markers of synthetic dysfunction, noninvasive fibrosis indices at baseline, and incomplete biochemical response (abnormal ALT/AST) at 12 months post diagnosis identify patients at higher risk for adverse liver outcomes. Treatment resistance was associated with higher baseline serum IgG and lack of normalization of ALT, AST, and IgG at 12 months post diagnosis.

Parameters used for EBR	ALT and AST threshold for normal	Time after Diagnosis	Liver Event (AUC)	Steroid Complications (AUC)	Treatment resistance (AUC)
ALT and AST	≤ ULN	12 months	0.61	**0.63**	**0.74**
ALT and AST	Boys < 26 U/L Girls < 22 U/L	12 months	0.59	0.60	0.57
ALT, AST and IgG	≤ ULN	12 months	0.63	**0.71**	0.55
ALT, AST and IgG	Boys < 26 U/L Girls < 22 U/L	12 months	0.51	0.52	0.51
ALT, AST and protein	≤ ULN	12 months	0.54	**0.63**	**0.65**
ALT, AST and protein	Boys < 26 U/L Girls < 22 U/L	12 months	0.59	**0.67**	0.57

Table 1: Univariable analyses evaluating the predictive performance of early biochemical response (EBR) markers for clinical outcomes. ALT = alanine aminotransferase; AST = aspartate aminotransferase; U/L = units per liter; AUC = area under the receiver operating characteristic curve. Bolded values indicate statistically significant predictors ($p<0.05$); bolded red values indicate significant predictors with AUC >0.7.

Disclosures: Shelley Choudhury: Nothing to Disclose, Sakil Kulkarni: Nothing to Disclose, Rebekah Karns: Nothing to Disclose, Pooja Khonde: Nothing to Disclose, Adith Boloor: Nothing to Disclose, Cyd Castro-Rojas: Nothing to Disclose, Amy Taylor: Nothing to Disclose, Alexander Miethke: Mirum Pharmaceutical Inc: Grant/Research Support, Mirum Pharmaceutical Inc: Consultant, Ipsen: Speaking and Teaching, Perspectum Ltd.: Grant/Research Support, Esperion: Advisor.

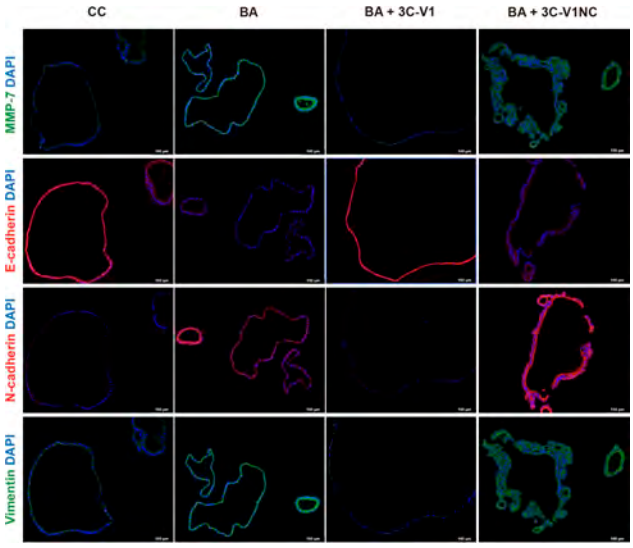
2696 | PROTAC-MEDIATED DEGRADATION OF MMP-7 AS A POTENTIAL THERAPEUTIC STRATEGY FOR BILIARY ATRESIA

Shuiqing Chi[1] Mengxin Zhang[2] Yan Chen[1] Paul Tam[1] Shao-Tao Tang[2], [1]Macau University of Science and Technology, [2]Wuhan Union Hospital

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Background: Matrix metalloproteinase-7 (MMP-7) is not only a diagnostic biomarker for biliary atresia (BA), but also a pathogenic mediator of biliary inflammation and liver fibrosis, making it a critical therapeutic target. Conventional MMP-7 inhibitors mainly suppress extracellular enzymatic activity, whereas they may not effectively reduce the intracellular MMP-7 pool available for continuous secretion by injured cholangiocytes. This study aimed to develop a novel MMP-7-targeting PROTAC, compound 3C-V1, and evaluate whether targeted MMP-7 degradation could provide a protein-level strategy for alleviating BA progression. **Methods:** The MMP-7 degradation efficacy and cytotoxicity of 3C-V1 were first evaluated in vitro. Its functional effects were then assessed in cholangiocyte organoid models derived from rhesus rotavirus (RRV)-induced BA mice, bile duct ligation (BDL) mice, and human BA patients. The in vivo therapeutic efficacy of 3C-V1 was further investigated using the RRV-induced BA mouse model. **Results:** Compound 3C-V1 induced potent MMP-7 degradation in cholangiocyte-derived organoids, with a DC50 of 3 nM and minimal cytotoxicity, as indicated by an IC50 of 16.32 μM. Across RRV, BDL, and human BA organoid models, 3C-V1 consistently reduced intracellular MMP-7 expression, enhanced organoid growth, and attenuated apoptosis. Notably, 3C-V1 decreased MMP-7 secretion in RRV and human BA organoids, suggesting that degradation of the intracellular MMP-7 pool may limit subsequent extracellular release. In contrast, marked MMP-7 secretion was not observed in BDL-derived organoids, indicating that extracellular MMP-7 detection may be influenced by disease-specific epithelial polarity, barrier integrity, and compartmentalized release. In human BA organoids, 3C-V1 reduced the secretion of inflammatory cytokines, including IL-6, IL-8, and IL-17A. In BDL and human BA organoids, 3C-V1 further reversed epithelial-mesenchymal transition-related protein changes, characterized by preservation of epithelial features and reduced cytoplasmic redistribution of β-catenin. In vivo, 3C-V1 delayed the onset of jaundice, reduced the mean jaundice rate by 65%, and improved the 14-day survival rate by 60% in RRV-induced BA mice. These therapeutic effects were accompanied by decreased hepatic MMP-7 expression and reduced inflammatory responses. **Conclusion:** The MMP-7-targeting PROTAC 3C-V1 alleviates BA-associated cholangiocyte injury by degrading intracellular MMP-7, reducing its extracellular availability, and attenuating downstream inflammatory and EMT-associated fibrotic responses. These findings support PROTAC-mediated MMP-7 degradation as a promising strategy to suppress cholangiocyte-derived MMP-7 at the protein level and alleviate BA progression.



Disclosures: Shuiqing Chi: Nothing to Disclose, Mengxin Zhang: Nothing to Disclose, Yan Chen: Nothing to Disclose, Paul Tam: Nothing to Disclose, Shao-Tao Tang: Nothing to Disclose.

2697 | A PROSPECTIVE MULTINATIONAL STUDY OF A FEEDING ULTRASOUND APPROACH TO IDENTIFY BILIARY ATRESIA

Tebyan Rabbani[1] Ashley Upton[2] Ming-Wei Lai[3] Bikrant Lal[4] Pamela Valentino[5] Orith Waisbourd-Zinman[6] Jia-Feng Wu[7] Seema Alam[4] Pazit Bar-Gil[8] Niviann Blondet[5] En-Shuo Chang[3] Mei-Hwei Chang[7] Chieh-Chang Chen[3] Huey-Ling Chen[7] Peace Dike[1] J. Alberto Hernandez[2] Noorie Javer[9] Rajeev Khanna[4] Osnat Konen[8] Nadia Kryvol[1] Amar Mukund[4] Amrita Narang[1] Katelyn Saarela[10] Benjamin Shneider[2] Sanjiv Harpavat[11], [1]Stanford Children's, Stanford University, [2]Texas Children's Hospital, [3]Chang Gung Memorial Hospital, [4]Institute of Liver and Biliary Sciences, [5]Seattle Children's, University of Washington, [6]Schneider Children's Medical Center, [7]National Taiwan University, [8]Schneider Children's Medical Center, [9]Seattle Children's, Washington University, [10]Seattle Children's Hospital, [11]Texas Children's Liver Center - Baylor College of Medicine

Background: We recently reported a single-center experience with a novel feeding ultrasound approach that identifies biliary atresia (BA) based on the absence of a common hepatic duct. This study aimed to assess the approach on a larger scale, by applying it prospectively in a multinational investigation. **Methods:** The feeding ultrasound approach

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was performed prospectively on infants presenting with cholestasis at ≤180 days of life at seven centers across four countries. Each site followed a previously published four-step protocol to visualize a structure consistent with the common hepatic duct, referred to as the "duct at the hilum" or "DaH." Operators at sites were trained through a virtual 30-minute didactic presentation, a 5-minute demonstration video, and, depending on operators' requests, direct instructions during clinical care through live video conferencing. Data for completion of the protocol, as well as demographic information and final diagnoses, were entered into a centralized database by investigators at each site. **Results:** The feeding ultrasound approach was performed on 251 infants between January 2025 and May 2026, including 48 infants eventually diagnosed with BA. The approach's sensitivity, specificity, positive predictive value, and negative predictive value for biliary atresia were 0.96 (95%CI 0.85-0.99), 0.94 (95%CI 0.90-0.97), 0.79 (95%CI 0.66-0.88), and 0.99 (95% CI 0.96-1.00), respectively (Figure 1A). Of the 58 cases in which a DaH was not visualized, 46 infants were eventually diagnosed with BA (true-positives) and 12 infants without BA (false-positives). Eight of the 12 false-positive cases were from a single center at a time before all operators had completed training. In comparison, of the 193 cases in which a DaH was visualized, two infants were eventually diagnosed with BA (false-negatives) and 191 infants without BA (true-negatives). In these infants, the approach was completed in a median of 3.0 minutes (interquartile range 1.0-5.9 minutes). Both false-negative cases had a duct structure labeled as the DaH; however, the structure did not extend into the liver and likely represented the common bile duct instead of the common hepatic duct (Figure 1B). **Conclusion:** This study demonstrates that a novel feeding ultrasound approach can be performed in diverse clinical settings with high diagnostic accuracy, often in <5 minutes. Visualizing the DaH structure both inside and outside the liver could improve the accuracy even more. Taken together, the approach is a simple first-line test with the potential to streamline the evaluation of cholestatic infants by quickly identifying those who may have BA while excluding the majority of infants who have another disorder.

Figure 1

A

	BA +	BA -	
DaH -	46	12	58
DaH +	2	191	193
	48	203	251

Sensitivity	0.96 (95% CI 0.85-0.99)
Specificity	0.94 (95% CI 0.90-0.97)
Positive Predictive Value	0.79 (95% CI 0.66-0.88)
Negative Predictive Value	0.99 (95% CI 0.96-1.00)

B



Disclosures: Tebyan Rabbani: Nothing to Disclose, Ashley Upton: Nothing to Disclose, Ming-Wei Lai: Nothing to Disclose, Bikrant Lal: Nothing to Disclose, Pamela Valentino: Nothing to Disclose, Orith Waisbourd-Zinman: Nothing to Disclose, Jia-Feng Wu: Nothing to Disclose, Seema Alam: Nothing to Disclose, Pazit Bar-Gil: Nothing to Disclose, Niviann Blondet: Nothing to Disclose, En-Shuo Chang: Nothing to Disclose, Mei-Hwei Chang: Nothing to Disclose, Chieh-Chang Chen: Nothing to Disclose, Huey-Ling Chen: Nothing to Disclose, Peace Dike: Nothing to Disclose, J. Alberto Hernandez: Nothing to Disclose, Noorie Javer: Nothing to Disclose, Rajeev Khanna: Nothing to Disclose, Osnat Konen: Nothing to Disclose, Nadia Kryvol: Nothing to Disclose, Amar Mukund: Nothing to Disclose, Amrita Narang: Ipsen: Consultant, Mirum: Consultant, MedaCorp: Consultant, Ipsen: Grant/Research Support, Katelyn Saarela: Nothing to Disclose, Benjamin Shneider: Nothing to Disclose, Sanjiv Harpavat: Syneos Health: I sit on a Data Safety Monitoring Board.

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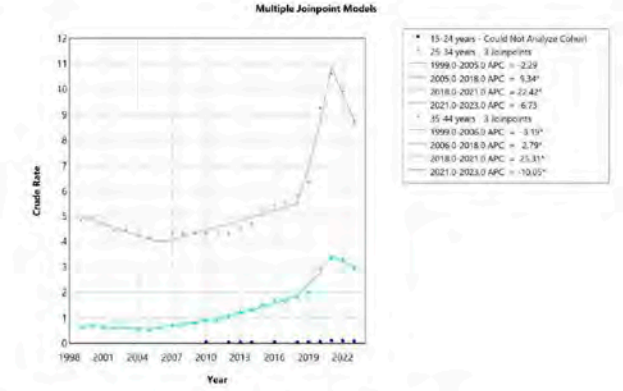
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★ 3001 | ◆ TEMPORAL TRENDS IN MORTALITY BURDEN OF ALCOHOL-ASSOCIATED LIVER DISEASE AND EARLY-ONSET PANCREATIC CARCINOMA IN YOUNG ADULTS (15-44): A CDC WONDER ANALYSIS OF AGE, RACIAL, SEX AND GEOGRAPHIC DISPARITIES 1999-2023

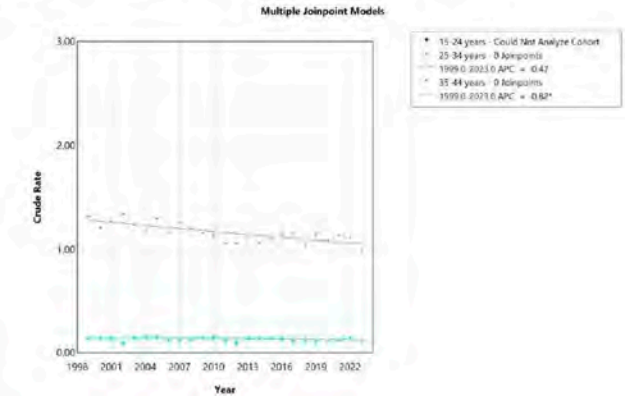
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Background: The rising incidence of early-onset hepatobiliary and gastrointestinal ailments in young adults is a growing public health challenge. However, the intersection of increasing alcohol consumption and mortality in the pre-screening population, particularly following the COVID-19 pandemic, remains under-characterized. **Methods:** We utilized the CDC WONDER Underlying Cause of Death database (1999-2023) to analyze mortality trends for alcohol-associated liver disease (ICD-10 :K70) and early-onset pancreatic carcinoma (ICD-10: C25) in American young adults aged 15-44. Age-adjusted mortality rates (AAMR) per 100,000 were stratified by race/ethnicity, sex, and census region. Annual Percent Change (APC) and 95% Confidence Intervals (CI) were calculated using Joinpoint regression to assess temporal trends. Racial trends were studied separately for 1999-2020 Bridged-race and 2021-2023 Single-race datasets due to incompatible summation of datasets. **Results:** From 1999-2023, a total of 74,298 deaths due to ALD and 13,964 due to EOPC were identified in young American adults. The overall AAMR for ALD decreased from 1999 to 2013 (APC: -1.14%,C.I: -1.72, -0.54; $p < 0.001$) and then dramatically increased from 2013 to 2023 (APC: +4.13; C.I: +2.49, +5.80; $p < 0.001$) with an overall significant AAPC +0.78 (C.I: +0.02, +1.21; $p < 0.05$). In contrast, EOPC mortality exhibited a stable gradual deceleration (AAPC: -0.95, CI: -1.28, -0.614; $p < 0.01$). The 35-44 age group had the highest ALD mortality with significant rise during 2019-2023 (APC: +25.3), while all age groups had a stable decrease in AAMR due to EOPC. Geographically, Western US populations exhibited the highest AAMR due to ALD but the highest rise in AAMR was identified in the Midwest from 2019-2023. Notably, American Indian/Alaska Native adults had the highest AAMR as well as the steepest rise in ALD mortality (APC: +28.48), signaling a hyper-acute mortality crisis. **Conclusion:** Although the decreasing mortality of EOPC is reassuring, the accelerating mortality of ALD in young adults, plausibly exacerbated by pandemic-era behavioral shifts, necessitates urgent public health intervention. The persistence of age, racial, gender and geographic disparities suggest that the current 'one-size-fits-all' screening guidelines fail to capture high-risk minority populations, warranting risk-adapted surveillance strategies.

Age-wise stratification of Mortality due to ALD 1999-2023



Age-wise stratification of EOPC Mortality 1999-2023



Disclosures: adnan Zafar:Nothing to Disclose, Mohammed Misbahuddin:Nothing to Disclose, Afzal Ahmed:Nothing to Disclose, Abdul Rehman:Nothing to Disclose, Abdul Shafi:Nothing to Disclose, Harleen Chela:Nothing to Disclose.

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★ 3002 | ◆ ELEVATED FGF21 IN *TGR5*$^{-/-}$ MICE DIFFERENTIALLY REGULATES ALCOHOL AND SWEET PREFERENCE VIA METABOLIC-REWARD PATHWAYS

Shifat-E Ferdous[1] *Titilayo Olotu*[1] *Elliot Arazi*[1] *Jessica Ferrell*[1], [1]*Northeast Ohio Medical University*

Background: Takeda G-protein coupled receptor 5 (TGR5), a bile acid receptor, regulates metabolism and inflammatory signaling in a tissue-specific manner. We previously reported *TGR5*$^{-/-}$ mice were protected from alcohol-induced liver injury via upregulation of fibroblast growth factor 21 (FGF21), a hepatokine that suppresses alcohol consumption in a negative feedback mechanism via liver, adipose tissue and brain. We also demonstrated that a single ethanol gavage increased hepatic and serum FGF21 2-3-fold in *TGR5*$^{-/-}$ mice compared to wild type-control (WT) mice. When presented with a 2-bottle-choice paradigm, *TGR5*$^{-/-}$ mice showed a reduced preference for ethanol drinking. However, since continuous free access to ethanol rarely induces dependence, we used an intermittent access 2-bottle choice model to better mimic excessive alcohol consumption. As FGF21 is also induced by sugar intake, we tested whether TGR5 deficiency alters FGF21-mediated sugar preference similar to alcohol. **Methods:** 3 different cohorts of chow diet-fed female WT and *TGR5*$^{-/-}$ mice were subjected to 2-bottle choice paradigm with intermittent access to either 10% ethanol (cohort 1, intermittent alcohol choice, IAC), 1% sucrose (cohort 2, intermittent sugar choice, ISC) and 10% ethanol & 1% sucrose combined (cohort 3, intermittent sugar-alcohol choice, ISAC) along with continuous water access for 4 weeks. Upon termination, metabolic, central reward seeking, and inflammatory pathways in the liver and brain were assessed. **Results:** Under IAC, the *TGR5*$^{-/-}$ mice exhibited reduced alcohol consumption and preference compared to WT mice. During ISC, *TGR5*$^{-/-}$ mice initially increased sucrose intake but later declined towards WT drinking levels. In ISAC, the combined ethanol-sucrose consumption was also reduced in *TGR5*$^{-/-}$ mice. Calorie intake from food was reduced in all *TGR5*$^{-/-}$ cohorts with a decreasing trend in the calorie intake from ethanol in IAC. Surprisingly, the calorie intake from sucrose was increased in ISC *TGR5*$^{-/-}$ mice, which showed no change when combined with ethanol (ISAC). Across all cohorts, hepatic *Fgf21* gene expression was significantly increased in *TGR5*$^{-/-}$ mice. Dopamine receptor D1 (*Drd1*), classically associated with positive reinforcement and reward, was decreased in *TGR5*$^{-/-}$ mice of both IAC and ISAC cohorts but not in the ISC group. This may indicate that FGF21-mediated suppression of sugar intake in *TGR5*$^{-/-}$ mice occurs through dopamine-independent pathways. **Conclusion:** Collectively, the persistence of elevated hepatic *Fgf21* with reduced alcohol and sugar preference in *TGR5*$^{-/-}$ mice across all the paradigms TGR5-regulated liver-brain signaling. The molecular mechanism directing TGR5-FGF21 interaction is under investigation which will represent TGR5 as a druggable receptor to induce FGF21-mediated regulation of alcohol use disorder.

Disclosures: SHIFAT-E FERDOUS:Nothing to Disclose, Titilayo Olotu:Nothing to Disclose, Elliot Arazi:Nothing to Disclose, Jessica Ferrell:Nothing to Disclose.

3003 | ◆ LIVERPRO AS A NON-INVASIVE MARKER OF HISTOLOGICAL RESPONSE TRAJECTORIES IN STEATOTIC LIVER DISEASE

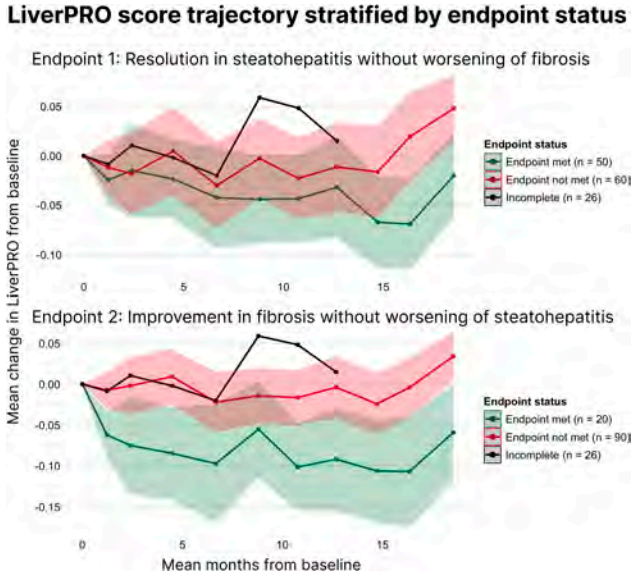
Julie Astono[1] *Nikolaj Torp*[2] *Stine Johansen*[3] *Camilla Hansen*[3] *Sönke Detlefsen*[4] *Peter Andersen*[3] *Johanne Hansen*[3] *Katrine Thorhauge*[3] *Katrine Lindvig*[1] *Morten Karsdal*[5] *Maja Thiele*[1] *Aleksander Krag*[6] *Mads Israelsen*[3], [1]*Evido Health, Copenhagen, Denmark,* [2]*Center for Liver Research, Odense University Hospital, Denmark,* [3]*Liver Research Center, Odense University Hospital, Denmark,* [4]*Department of Pathology, Odense University Hospital, Odense, Denmark,* [5]*Nordic Bioscience Biomarkers and Research, Herlev, Denmark,* [6]*Liver Research Center, Odense University Hospital, Denmark*

Background: Non-invasive tests (NITs) for the assessment of treatment response are essential for clinical trials and treatment of patients with steatotic liver disease (SLD). We evaluated four different NITs as markers of histological endpoints in patients with a current or previous alcohol overuse. **Methods:** We conducted a post-hoc analysis in participants from the phase II GALA-Rif trial randomized (1:1) to 18-months of rifaximin-α or placebo. We pooled all participants and evaluated the regulatory required histological endpoints in MASH trials: 1) resolution in steatohepatitis without worsening of fibrosis, 2) improvement in fibrosis without worsening of steatohepatitis. Associations between histological endpoints and changes in LiverPRO, VCTE, PRO-C3, and FIB-4 from baseline to end-of-study (EOS) were assessed using ANCOVA adjusted for baseline values and treatment assignment. LiverPRO is a flexible blood-based NIT for liver fibrosis risk assessment with scores ranging from 0.0-1.0. **Results:** The study randomized 136 participants of whom 108 completed the study per protocol. 110 had biopsy at EOS and were therefore included. 26 had incomplete

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data to determine endpoint status. 84% were male, median age 60 years (IQR 55-66) and BMI 29.4 kg/m^2 (25.8-32.6). Endpoint 1 was met by 50 patients (45%), 20 (18%) met endpoint 2, and 18 (16%) met both endpoints. Of the 110 patients, LiverPRO was processable in 107, VCTE was available in 107, PRO-C3 in 106, and FIB-4 in 90. Achievement of histological endpoints was associated with lower LiverPRO values at EOS. Participants meeting endpoint 1, endpoint 2, or both endpoints had significantly lower LiverPRO values compared with non-responders (endpoint 1: $\beta = -0.07$; endpoint 2: $\beta = -0.10$; both endpoints: $\beta = -0.10$). The three other NITs likewise showed statistically significant decreases in participants meeting endpoint 1, endpoint 2 and both endpoints compared with non-responders. VCTE) endpoint 1: $\beta = -5.46$; endpoint 2: $\beta = -3.85$; both endpoints: $\beta = -3.78$. PRO-C3) endpoint 1: $\beta = -2.88$; endpoint 2: $\beta = -3.64$; both endpoints: $\beta = -2.50$. FIB-4) endpoint 1: $\beta = -0.62$; endpoint 2: $\beta = -0.57$; both endpoints: $\beta = -0.53$LiverPRO demonstrated distinct trajectories according to endpoint status. Participants meeting endpoints showed a decrease from baseline during the first month, followed by continued decline until ~6 months then stabilisation until an incline at EOS. While non-responders also showed an initial decrease but subsequently a more variable trajectory until increase at EOS. VCTE, PRO-C3, and FIB-4 had only 2-3 repeated measurements, limiting trajectory analysis. **Conclusion:** LiverPRO demonstrated dynamic longitudinal changes associated with histological improvement over time in individuals with SLD and alcohol history. These findings support LiverPRO as a promising non-invasive tool for assessing treatment response and disease progression in alcohol-related liver disease trials.



Disclosures: Julie Astono:Evido Health: Employee, Nikolaj Torp:Nothing to Disclose, Stine Johansen:Nothing to Disclose, Camilla Hansen:Nothing to Disclose, Sönke Detlefsen:Nothing to Disclose, Peter Andersen:Nothing to Disclose, Johanne Hansen:Nothing to Disclose, Katrine Thorhauge:Nothing to Disclose, Katrine Lindvig:Nothing to Disclose, Morten Karsdal:Nothing to Disclose, Maja Thiele: Nothing to Disclose, Aleksander Krag:Nothing to Disclose, Mads Israelsen:Nothing to Disclose.

3004 | ◆ PLASMA CELL-FREE DNA METHYLATION RESOLVES THREE MOLECULAR SUBTYPES OF STEATOTIC LIVER DISEASE AND REVEALS METALD AS BIOLOGICALLY DISTINCT FROM A MASLD-TO-ALD CONTINUUM

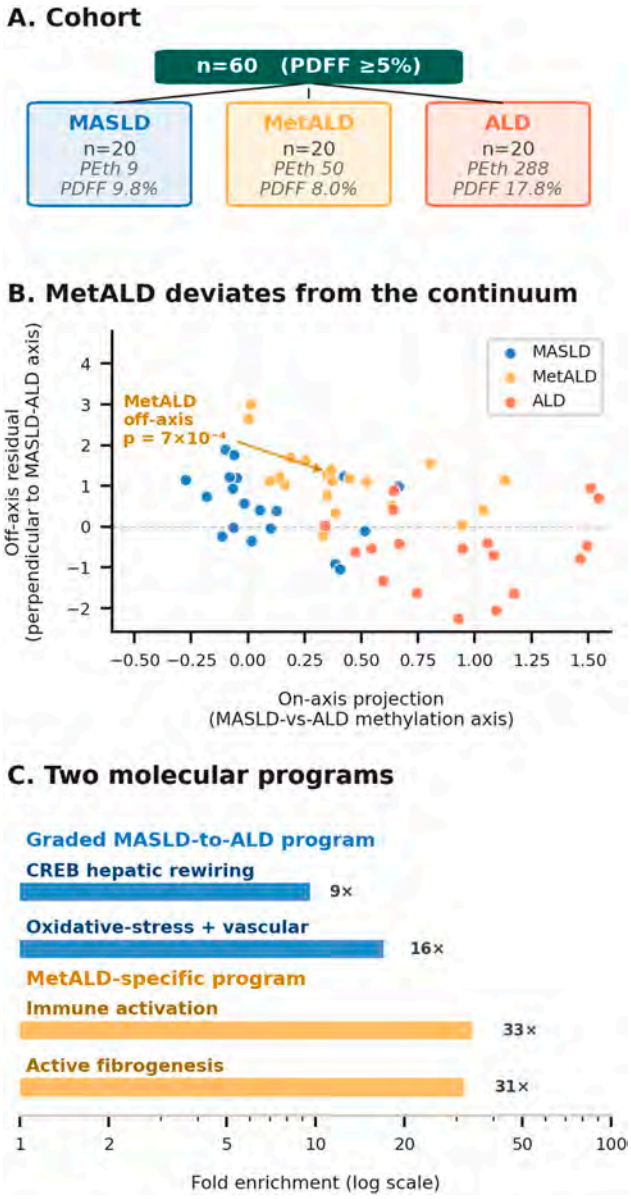
Rohit Loomba[1] Soheil Damangir[2] Egbert Madamba[1] Seema Singh[1] Chong Lu[2] Amin Naghdloo[2] Leila Bazargan[2] Hamed Amini[2], [1]University of California, San Diego, [2]Hepta Bio, Inc.

Background: The 2023 AASLD multi-society nomenclature created MetALD as a mixed metabolic-and-alcohol category of steatotic liver disease (SLD) by alcohol-exposure thresholds, but whether MetALD carries its own molecular biology or only a clinical-history label remains unresolved. Subtype assignment relies on patient-reported alcohol history; no blood test molecularly characterizes these categories. We tested whether plasma cfDNA methylation can resolve this. **Methods:** Sixty patients with hepatic steatosis (MRI-PDFF $\geq$5%) were classified as MASLD (n = 20), MetALD (n = 20), or ALD (n = 20) using phosphatidylethanol (PEth) thresholds aligned with AASLD-2023 categories. Plasma cfDNA whole-methylome sequencing was processed with LiquidTransformer. We tested for an ordinal MASLD-MetALD-ALD methylation gradient with sequential adjustment for age, sex, BMI, and MRI-PDFF. We also tested whether MetALD methylation carries biology distinct from a MASLD-to-ALD continuum using a half-split projection test with permutation calibration. All reported results were significant at $p < 0.01$. **Results:** The population had a mean age 52 ± 12 years; BMI 33 ± 3 kg/m²; 40% female. PEth cleanly separated classes (medians 9, 50, 288 ng/mL); MRI-PDFF was higher in ALD (median 17.8%) than MASLD (9.8%) or MetALD (8.0%).Regions changing across the gradient enriched for hepatic lipid handling (FGF21, ANGPTL4, LIPC), xenobiotic metabolism (ADH4, CES2, BCHE), and hepatocyte tissue identity. After adjusting for level of steatosis, the signal shifted to the canonical alcohol-injury response: CREB-driven rewiring of the hepatic fed/fasted transcriptional program (10 CREB-target genes; CREB Q3 and CREB 02 motifs), oxidative-stress defense (CAT), and sinusoidal vascular destabilization (BDKRB2, ANGPT2), an alcohol-specific signal beyond steatosis severity.The regions best discriminating MASLD from ALD

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define a methylation axis. MetALD samples were significantly deviated from this MASLD to ALD axis. Regions distinguishing MetALD from the MASLD to ALD continuum were enriched for immune activation (CD40, IFNA13, TPO, IL16) and active fibrogenesis (periostin/POSTN). **Conclusion:** Plasma cfDNA methylation distinguishes MASLD, MetALD, and ALD through two molecularly distinct signatures: a graded MASLD-to-ALD signature dominated by hepatic metabolism that resolves to the canonical alcohol-injury response after steatosis adjustment; and a MetALD-specific immune-fibrotic signature absent from this continuum. This is the first molecular characterization of MetALD as biologically distinct from a MASLD-to-ALD continuum, and identifies plasma cfDNA methylation as an objective subtyping tool complementing patient-reported alcohol history, showing the need for a precision approach to SLD management and positioning cell free DNA methylation as noninvasive readout of SLD molecular state.



Disclosures: Rohit Loomba: Eli Lilly and Company: Consultant, 89bio: Consultant, Aardvark Therapeutics: Consultant, Altimmune: Consultant, Alnylam/Regeneron: Consultant, Amgen: Consultant, Arrowhead Pharmaceuticals: Consultant, AstraZeneca: Consultant, Bristol Myers Squibb: Consultant, CohBar: Consultant, Eli Lilly: Consultant, Galmed Pharmaceuticals: Consultant, Gilead: Consultant, Glympse Bio: Consultant, Hightide: Consultant, Inipharma: Consultant, Intercept: Consultant, Inventiva: Consultant, Ionis: Consultant, Janssen, Inc.: Consultant, Madrigal Pharmaceuticals: Consultant, Merck, Metacrine, Inc.: Consultant, NGM Biopharmaceuticals: Consultant, Novartis: Consultant, Novo Nordisk: Consultant, Pfizer: Consultant, Sagimet Biosciences: Consultant, Terns Pharmaceuticals: Consultant, Theratechnologies and Viking Therapeutics: Consultant, 89bio: Stock options, Sagimet Biosciences: Stock options, Arrowhead Pharmaceuticals: Research grant, AstraZeneca: Research grant, Boehringer Ingelheim: Research grant, Bristol Myers Squibb: Research grant, Eli Lilly: Research grant, Galectin Therapeutics: Research grant, Galmed Pharmaceuticals: Research grant, Gilead: Research grant, Hanmi: Research grant, Intercept: Research grant, Inventiva: Research grant, Ionis: Research grant, Janssen, Inc.: Research grant, Madrigal Pharmaceuticals: Research grant, Merck: Research grant, NGM Biopharmaceuticals: Research grant, Novo Nordisk: Research grant, Pfizer: Research grant, Sonic Incytes: Research grant, Terns Pharmaceuticals: Research grant, LipoNexus, Inc.: Co-founder, Cascade Pharmaceuticals: Consultant, Eccogene: Consultant, HeptaBio: Consultant, Metavi: Consultant, Neurobo: Consultant, Novo Nordisk: Consultant, Sourcebio: Consultant, Roche: Consultant, Roche: Consultant, Takeda: Consultant, GSK: Grant/Research Support, Roche: Grant/Research Support, TensorBio: Grant/Research Support, Aarrowhead Pharmaceuticals: Consultant, Boehringer-Ingelheim: Consultant, Altimmune: Grant/Research Support, Eccogene: Grant/Research Support, Heptabio: Grant/Research Support, 89 bio: Grant/Research Support, Takeda: Grant/Research Support, Soheil Damangir:Nothing to Disclose, Egbert Madamba:Nothing to Disclose, Seema Singh:Nothing to Disclose, Chong Lu:Nothing to Disclose, Amin Naghdloo:Hepta Bio: Employee, Leila Bazargan:Nothing to Disclose, Hamed Amini:Nothing to Disclose.

3005 | ◆ AN INPATIENT EMR-BASED INTERVENTION INCREASES MEDICATIONS FOR ALCOHOL USE DISORDER UTILIZATION

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Background: Alcohol use disorder (AUD) is a leading cause of liver-related hospitalization in the United States.[1] Despite strong evidence that medications for AUD (MAUD) reduce hospital readmissions, MAUD remains underutilized.[2-4] Prior electronic medical record (EMR)-based interventions have increased MAUD initiation.[5-6] We evaluated the impact of an EMR-based intervention on MAUD prescribing in hospitalized patients on CIWA protocol. **Methods:** We conducted a retrospective pre-post quality improvement study of hospitalized patients admitted on CIWA protocol from March 2024 to March 2026 at an academic medical center. An EMR-based intervention, proposed by internal medicine and supported by hepatology, launched in March 2025 and consisted of: 1) a modified inpatient CIWA order set with oral naltrexone and acamprosate orders, 2) a best practice advisory for MAUD initiation prior to discharge, and 3) a discharge order set with oral naltrexone and acamprosate prescriptions and specialty referral. Providers were educated on MAUD best practices. Rates of inpatient orders and discharge prescriptions were tracked for one year post-intervention. Demographics, comorbidities, and clinical variables associated with MAUD prescribing were analyzed using chi-square and t-tests. ChatGPT was used solely for language editing and improving conciseness. **Results:** A total of 2,058 CIWA-associated admissions were analyzed. Following implementation, inpatient MAUD initiation increased from 1.7 to 4.4% ($p < 0.001$) and discharge MAUD prescriptions increased from 5.0 to 11.7% ($p < 0.001$). Both increases were primarily driven by naltrexone. Patients aged 40–65 had the highest MAUD prescribing rates (9.7%, $p = 0.018$), with no significant difference by sex ($p = 0.889$). There were no significant differences in AST (65.7 vs 71.0 U/L, $p = 0.689$), ALT (44.7 vs 51.1 U/L, $p = 0.654$), or hospital length of stay (6.31 vs 6.30 days, $p = 0.986$) between patients who did and did not receive MAUD. The increase in prescribing was sustained over the post-intervention year. Importantly, cirrhosis diagnosis and comorbidities were not associated with lower MAUD prescribing rates. **Conclusion:** An EMR-based intervention was associated with a significant increase in MAUD prescribing among hospitalized patients with AUD. Despite improvement, prescribing rates remained low, highlighting persistent barriers to inpatient MAUD initiation. The lack of significant differences in cirrhosis and other comorbidities between the pre- and post-intervention groups suggests the increase was not driven by changes in patient complexity or liver disease severity. Further studies are needed to better understand age-related differences and other barriers to treatment initiation. EMR-based interventions are scalable, low-cost strategies to improve evidence-based care in hospitalized patients with AUD.

Table 1. Impact of EMR-Based Intervention and Characteristics Associated With MAUD Prescribing

Characteristics Associated With MAUD Prescribing				
Variable	Category/Group	No MAUD given n (%) or Mean ± SD	MAUD given n (%) or Mean ±SD	p-value
Age Category	<40 years	502 (90.9%)	50 (9.1%)	0.018
	40-65 years	963 (90.3%)	103 (9.7%)	
	>65 years	417 (94.8%)	23 (5.2%)	
Sex	Male	1338 (91.4%)	126 (8.6%)	0.889
	Female	544 (91.6%)	50 (8.4%)	
AST	Mean ± SD	71.0 ± 162.4	65.7 ± 89.4	0.689
ALT	Mean ± SD	51.1 ± 181.5	44.7 ± 102.0	0.654
Length of Stay (days)	Mean ± SD	6.30 ± 9.62	6.31 ± 6.03	0.986
Comorbidities	Cardiovascular	99 (5.3%)	5 (2.8%)	0.161
	Psychiatric/Neurologic	300 (15.9%)	19 (10.8%)	0.071
	Trauma-related	40 (2.1%)	2 (1.1%)	0.375
	Cirrhosis	53 (2.8%)	6 (3.4%)	0.652
Impact of EMR-Based Intervention				
	Category	**Pre-intervention**	**Post-intervention**	**p-value**
Discharge MAUD	MAUD prescribed	48 (5.0%)	128 (11.7%)	<0.001
Inpatient MAUD	MAUD prescribed	16/962 (1.7%)	48/1096 (4.4%)	<0.001
Sex	Male	32/666 (4.8%)	93/798 (11.7%)	<0.001
	Female	16/296 (5.4%)	35/298 (11.7%)	0.006
Type of MAUD	Naltrexone	34/962 (3.5%)	88/1096 (8.0%)	<0.001
	Acamprosate	13/962 (1.4%)	40/1096 (3.6%)	0.001
Laboratory studies	AST	66.8 ± 124.6 U/L	74.0 ± 182.6 U/L	0.333
	ALT	47.2 ± 104.4	53.6 ± 222.4	0.430
Length of Stay (days)	Mean ± SD	6.78 ± 10.15	6.01 ± 8.55	0.062
Comorbidities	Cardiovascular	52/962 (5.4%)	52/1096 (4.7%)	0.495
	Psychiatric/Neurologic	144/962 (15.0%)	175/1096 (16.0%)	0.532
	Trauma-related	17/962 (1.8%)	25/1096 (2.3%)	0.411
	Cirrhosis	32/962 (3.3%)	27/1096 (2.5%)	0.242

Disclosures: Jazmin Mexía Cabrales:Nothing to Disclose, Christopher Garcia-Wilde:Nothing to Disclose, Claire Garpestad:Nothing to Disclose, Frances Lee: Nothing to Disclose, Linda Wang:Nothing to Disclose.

3006 | ◆ ALCOHOL-DRIVEN MICROBIOME METABOLISM ELEVATES HIPPURATE, TRIGGERING TLR-MEDIATED NEUTROPHIL HYPER-INFLAMMATION AND SEPTIC SHOCK IN ALCOHOL-ASSOCIATED CIRRHOSIS

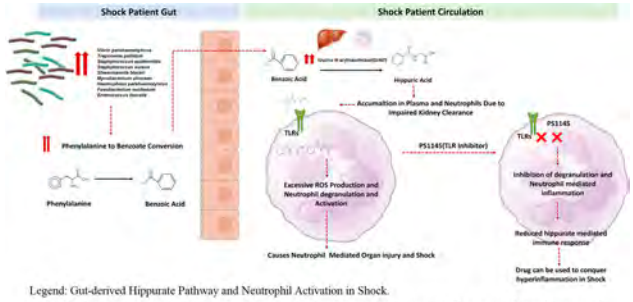
Jaswinder Maras[1] Gaurav Tripathi[2] Vasundhra Bindal[2] Manisha Yadav[2] Vaibhav Tiwari[2] Yash Magar[2] Vipul Sharma[2] Deepanshu Deepanshu[3] Sushmita Pandey[2] Neha Sharma[2] Nupur Sharma[1] Babu Mathew[2] Rimsha Saif[2] Sanju Yadav[4] Rosmy Babu[2] Shimona Ahlawat[2] Jaifrin Daniel[2] Meenu Bajpai[2] Abhishak Gupta[5]

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Background: Patients with alcohol-associated cirrhosis (AAC) are highly vulnerable to infection-triggered sepsis and progression to septic shock. Alcohol-induced gut microbial dysbiosis linked microbial metabolites may contribute to immune dysregulation, exaggerated inflammatory responses, and multi-organ failure. We studied the role of gut-derived microbial metabolites in immune dysregulation in genesis of septic shock. **Methods:** Untargeted metabolomic/metaproteomic of plasma, stool, and neutrophils from healthy (n = 50), non-septic AAC (n = 50), and septic-shock patients (n = 100) identified hippurate as shock-associated microbial metabolite validated in independent AAC cohort (n = 250), benchmarked for outcome stratification. Alcohol-induced gut microbiota–mediated benzoate-to-hippurate metabolism was evaluated in AAC patients and NIAAA mice model. Functional studies for hippurate mediated inflammation with/without PS1145 (TLR-inhibitor) in primary neutrophils, HepG2, HUVECs, and NIAAA mice model was studied, and the efficacy of plasma exchange (plex) in reducing systemic hippurate levels was evaluated in AAC patients. **Results:** Stool metaproteome and plasma metabolome analyses identified > 278 bacterial species and > 293 metabolites specific to septic shock ($p < 0.05$), including Vibrio parahaemolyticus, Staphylococcus aureus and others, converging on a benzoate-hippurate inflammatory axis (FC > 2, $p < 0.05$). Integrated omics cross correlation analysis identified hippurate as the top predictor (FC > 25, $r^2 > 0.89$, $p < 0.05$, AUC > 0.9), validated in an independent cohort (AUC > 0.95; Cox-HR > 3), outperforming SOFA/MELD scores. Plasma hippurate > 415uM segregated Non-survivors (log-rank < 0.02). Alcohol-driven microbiome activity enhanced metabolites and linked enzymes for phenylalanine to benzoate conversion (FC > 1.5, $p < 0.05$) in septic shock patients, further validated in the plasma, stool, intestine and liver of NIAAA mice model. Plasma benzoate/hippurate levels correlated with impaired clearance (AKI > grade2/3). Hippurate at shock-associated concentrations (> 415µM) triggered TLR-mediated neutrophil activation, ROS generation, and degranulation, while promoting hepatic and endothelial inflammatory and oxidative responses ($p < 0.05$); these effects were further amplified in the presence of LPS ($p < 0.05$). TLR inhibition with PS1145 attenuated these responses showing therapeutic validation, while plex significantly reduce circulating hippurate levels, supporting both PS1145 and plex as potential therapeutic strategies for AAC patients. **Conclusion:** Alcohol induced Microbiome drive hippurate accumulation and induces septic shock in AAC via TLR-mediated neutrophil dysfunction and hyper-inflammation. Its diagnostic value and attenuation by PS1145 or plasma exchange highlight a targetable microbiome-neutrophil therapeutic axis.



Legend: Gut-derived Hippurate Pathway and Neutrophil Activation in Shock.

In shock patients, gut dysbiosis promotes the conversion of phenylalanine to benzoic acid. Once in circulation, benzoic acid is metabolized by the liver enzyme GLYAT into hippuric acid. Due to impaired kidney clearance, hippuric acid accumulates and binds to Toll-like Receptors (TLRs) on neutrophils. This triggers excessive ROS production and degranulation, leading to systemic organ injury and shock. The inhibitor PS1145 blocks TLR signaling, reducing this hyper-inflammatory immune response. This pathway represents a potential therapeutic target for mitigating neutrophil-mediated organ damage during shock.

Disclosures: Jaswinder Maras:Nothing to Disclose, Gaurav Tripathi:Nothing to Disclose, Vasundhra Bindal:Nothing to Disclose, Manisha Yadav:Nothing to Disclose, Vaibhav Tiwari:Nothing to Disclose, Yash Magar:Nothing to Disclose, Vipul Sharma:Nothing to Disclose, Deepanshu Deepanshu:Nothing to Disclose, Sushmita Pandey:Nothing to Disclose, Neha Sharma:Nothing to Disclose, Nupur Sharma:Nothing to Disclose, Babu Mathew:Nothing to Disclose, Rimsha Saif:Nothing to Disclose, Sanju Yadav:Nothing to Disclose, Rosmy Babu:Nothing to Disclose, Shimona Ahlawat:Nothing to Disclose, Jaifrin Daniel:Nothing to Disclose, meenu bajpai:Nothing to Disclose, Abhishak Gupta:Nothing to Disclose, Anupma Parasar:Nothing to Disclose, Dinesh Mani Tripathi:Nothing to Disclose, Shvetank Sharma:Nothing to Disclose, Rakhi Maiwall:Nothing to Disclose, Shiv Kumar Sarin:Nothing to Disclose.

3007 | ◆ CHRONIC ETHANOL FEEDING DRIVES GUT MICROBIOME REMODELING AND INFLUENCES CHOLESTATIC LIVER INJURY IN MICE

Jenna Copes[1] Xiao-Ming Yin[1] Shengmin Yan[1], [1]Tulane University School of Medicine

Background: Alcohol-associated liver disease (ALD) is a leading cause of liver-related mortality worldwide and includes a spectrum of disorders ranging from steatosis to cirrhosis and alcohol-associated hepatitis (AH). AH is commonly accompanied by cholestasis, defined by impaired bile flow or bile acid homeostasis. Although accumulating evidence links ALD progression, cholestatic injury, and gut microbiome dysbiosis, the functional role of the gut microbiome in alcohol-associated cholestasis remains unclear. This study investigated the contribution of gut microbiome alterations to ALD

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progression and cholestatic liver injury. **Methods:** Mice were subjected to chronic ethanol (EtOH) feeding or pair feeding for 4 weeks. Fecal samples were collected at 10 days and 4 weeks for shotgun metagenomic sequencing. To evaluate the functional impact of microbiome alterations, cecal contents from male mice after 4 weeks of EtOH or pair feeding were used for fecal microbiota transplantation (FMT). Recipient mice received an antibiotic-containing control diet for 5 days during liquid diet acclimatization, followed by 10 days of EtOH feeding with oral gavage of FMT from EtOH-fed or pair-fed donors every other day. Forty-eight hours before sacrifice, mice were challenged with ANIT at 25 mg/kg to induce cholestatic liver injury. Liver injury, cholestasis, and inflammation were evaluated by biochemical and histological analyses. **Results:** EtOH feeding, but not pair feeding, produced time-dependent changes in the gut microbiome. While ANIT induced only mild cholestatic liver injury in 10-day EtOH-fed female mice in previous experiments, FMT from 4-week pair-fed donors unexpectedly exacerbated liver injury in both male and female EtOH-fed recipient mice. This was evidenced by increased markers of hepatocellular injury, cholestasis, and hepatic inflammation. In contrast, FMT from EtOH-fed donors did not significantly alter liver injury compared with non-FMT controls. **Conclusion:** EtOH exposure is the major factor driving gut microbiome alterations in this model. Moreover, the microbiome established after chronic EtOH feeding may represent an adaptive response that protects against additional cholestatic insults. These findings highlight a complex, context-dependent role of the gut microbiome in alcohol-associated cholestatic liver injury.

Disclosures: Jenna Copes:Nothing to Disclose, Xiao-Ming Yin:Nothing to Disclose, Shengmin Yan:Nothing to Disclose.

3008 | ◆ PHOSPHATIDYLETHANOL POSITIVITY IDENTIFIES UNREPORTED ALCOHOL USE AND IS ASSOCIATED WITH ADVERSE OUTCOMES IN PATIENTS BEING EVALUATED FOR LIVER TRANSPLANTATION

Madeleine Hu[1] Courtney Sherman[1] Aryana Far[1] Jin Ge[1] Jennifer Lai[1] Michael Li[1], [1]University of California, San Francisco

Background: Phosphatidylethanol (PEth) is a highly sensitive and specific biomarker for detection of recent alcohol use. While its use is increasingly widespread in clinical hepatology, there is limited data on the influence of PEth results on outcomes in patients being evaluated for liver transplantation. **Methods:** We extracted all available PEth results from patients enrolled in the FrAILT study, a prospective cohort study of individuals undergoing evaluation for liver transplantation at the University of California San Francisco. Starting in mid-2022, all subjects underwent PEth testing at the outset of transplant evaluation, then received routine testing at pre-specified toxicology screening intervals based on assessment of risk. The primary outcome was the time to first occurrence of an adverse pre-transplant event (death, declined for listing, delisting, or deactivation). The Fine Gray model was used to create a cumulative incidence curve for transplant outcomes. Competing risks regression (with transplant as a competing outcome) was used to adjust for potential confounders. **Results:** Of 1,345 patients who received at least one PEth test, 65 (4.8%) had a positive PEth at their initial pre-transplant evaluation, with a median PEth 16:0/18:1 of 75 ng/dL (SD 210.1). 14 (22%) patients with a positive initial PEth did not have alcohol documented as a contributor to their liver disease. Similarly, 78 (5.8%) patients had a positive PEth on routine testing after initial transplant evaluation; 19 of which (24%) did not have alcohol listed as a liver disease etiology. 81% (n = 93) of patients with a positive PEth at any time prior to transplant experienced an adverse pre-transplant event, as compared to 56% (n = 687) of patients without a positive pre-transplant PEth. The cumulative incidence of adverse pre-transplant events at one year was 59% in those with positive PEths and 28% in those with negative PEths. After adjusting for age and MELD at time of initial transplant evaluation, positive PEth remained significantly associated with adverse pre-transplant outcomes (Figure 1; SHR 2.1, 95% CI 1.6 - 2.8, $p < 0.001$). Rate of being declined for listing was higher in individuals with positive PEths at initial evaluation as opposed to those with subsequent positive PEths (56% vs 44%, RR = 0.92, $p = 0.75$), whereas rate of delisting or listing removal/deactivation for psychosocial reasons was higher in the latter group (19% vs 81%, RR = 3, $p = 0.01$). **Conclusion:** PEth is a highly sensitive marker for alcohol use and can be used to identify unreported alcohol use; over 20% of patients who had positive PEths while being considered for transplant did not have alcohol listed as a contributor to their liver disease. Individuals found to have positive PEth results during the transplant evaluation process were significantly more likely to experience adverse pre-transplant events such as death, being declined for listing, or removal or deactivation from the waitlist.

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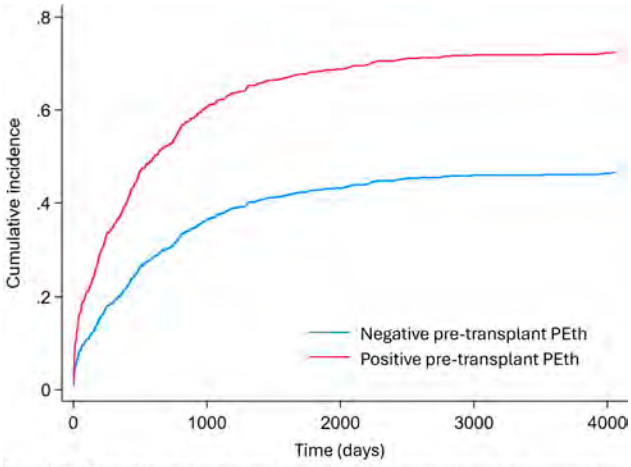


Figure 1: Adjusted cumulative incidence curve showing adverse pre-transplant outcomes in individuals with positive or negative pre-transplant PEth values

Disclosures: Madeleine Hu:Nothing to Disclose, Courtney Sherman:Nothing to Disclose, Aryana Far:Nothing to Disclose, Jin Ge:Merck and Co: Grant/Research Support, Iota Biosciences/Astellas Pharmaceuticals: Consultant, Madrigal Pharamaceuticals: Consultant, Gilead Sciences: Consultant, Jennifer Lai:Nestle Nutrition Institute: Grant/Research Support, Novo Nordisk: Consultant, Genfit: Consultant, Boehringer Ingelheim: Advisor, Lipocine: Site PI, Gilead: Site PI, Insmed: Consultant, Cosmo: Advisor, Michael Li:Nothing to Disclose.

★ 3009 | ◆ AUTOPHAGY REPORTER LC3B MICE ARE PROTECTED FROM ALCOHOL-INDUCED LIVER INJURY THROUGH SUPPRESSION OF ADIPOSE LIPOLYSIS

Ahmed Bakheet[1] Murugadas Anbazhagan[1] Robert Judd[1] Sieun Yoo[1] Paul Thomes[1], [1]Auburn University

Background: Alcohol-associated liver disease (ALD) is driven in part by adipose–liver crosstalk, where alcohol-induced adipose lipolysis elevates circulating free fatty acids (FFAs) and promotes hepatic steatosis and hepatocellular injury. LC3B-based autophagy reporter mice, widely used to monitor autophagic flux, express fluorescent LC3B fusion proteins resulting in LC3B overexpression; however, the physiological impact of LC3B overexpression during chronic alcohol exposure remains unknown. Given the central role of LC3B in autophagy regulation and lipid homeostasis, we investigated whether LC3B reporter mouse models exhibit altered susceptibility to alcohol-induced adipose dysfunction and liver injury. **Methods:** Male and female Wild-type (WT) and two independent LC3B-overexpressing reporter strains, CAG-EGFP-RFP-LC3B (Jackson Laboratory) and GFP-LC3B (RIKEN), were subjected to chronic-binge ethanol feeding. Inguinal white adipose tissue (iWAT) explants were analyzed ex vivo for lipolysis by glycerol release. Hepatic steatosis was assessed by blinded histopathologic scoring of H&E-stained liver sections, and liver injury was evaluated by serum alanine aminotransferase (ALT) levels. Hepatic hormone-sensitive lipase (HSL) activation and adipose/liver PPARα expression were measured by immunoblotting and qPCR. **Results:** Compared with ethanol-fed WT mice, ethanol-fed male CAG-EGFP-RFP-LC3B mice exhibited ~2-fold lower adipose lipolysis, measured by glycerol release from iWAT explants. Ethanol-fed CAG-EGFP-RFP-LC3B mice of both sexes also showed ~2-fold reduced hepatic steatosis and significantly lower serum ALT levels (2.7-fold in males; 1.6-fold in females) relative to ethanol-fed WT mice. In WT female mice, ethanol increased hepatic pHSL/HSL, whereas this response was absent in ethanol-fed CAG-EGFP-RFP-LC3B females. In adipose tissue, ethanol-fed CAG-EGFP-RFP-LC3B mice exhibited ~2-fold higher PPARα mRNA expression compared with ethanol-fed WT mice, while hepatic PPARα expression remained unchanged between genotypes. Similarly, ethanol-fed female GFP-LC3B mice showed a ~1.6-fold reduction in ALT levels compared with ethanol-fed WT mice, with a trend toward significance ($p = 0.08$). **Conclusion:** LC3B-overexpressing autophagy reporter mice are protected against alcohol-induced adipose lipolysis, hepatic steatosis, and liver injury. These findings indicate that LC3B overexpression alters adipose–liver metabolic responses to alcohol and confers protection from liver injury, although the contribution of the reporter construct itself warrants further evaluation.

Disclosures: Ahmed Bakheet:Nothing to Disclose, Murugadas Anbazhagan:Nothing to Disclose, Robert Judd:Nothing to Disclose, Sieun Yoo:Nothing to Disclose, Paul Thomes:Nothing to Disclose.

3010 | ◆ GLP-1 RECEPTOR AGONIST USE AND LIVER-RELATED OUTCOMES IN PATIENTS WITH METABOLIC AND ALCOHOL-RELATED LIVER DISEASE

Karim Besir[1] Don Rockey[1], [1]Medical University of South Carolina (MUSC)

Background: Metabolic and alcohol-related liver disease (MetALD) is increasingly recognized as a major contributor to liver-related morbidity and mortality, with limited therapies available despite the substantial burden of hepatic decompensation and liver-related complications associated with the disease. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have

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demonstrated favorable metabolic effects and have recently shown potential benefit in steatotic liver disease; however, their impact in patients with MetALD is not well understood. **Methods:** We performed a retrospective cohort study using the TriNetX Global Collaborative Network, including adult patients with MetALD between 2010 and 2026. MetALD was defined as alcohol-related liver disease in the presence of at least one metabolic risk factor, including type 2 diabetes mellitus (T2D), obesity, hypertension, or dyslipidemia. Patients receiving GLP-1 RAs were compared with patients not receiving GLP-1 RAs. The index event was defined as the first GLP-1 RA prescription occurring after the diagnosis of MetALD. Outcomes were assessed beginning 90 days after the index event to reduce early event misclassification. Propensity score matching was performed for demographics, comorbidities, medications, and baseline laboratory values. Outcomes included ascites, hepatic encephalopathy (HE), portal hypertension, esophageal variceal bleeding (EVB), hepatorenal syndrome (HRS) and all-cause mortality. **Results:** Before propensity score matching, 11,711 patients receiving GLP-1 RAs and 300,642 patients without GLP-1 RA exposure were identified. After propensity score matching, 6,190 patients remained in each cohort. The matched population had a mean age of 57 years, was predominantly male (66%) and White (71%), and, as expected, had a high prevalence of cardiometabolic risk factors and alcohol-related liver disease. GLP-1 RA use was associated with significantly lower risks of ascites, HE, portal hypertension, EVB, and HRS compared with no GLP-1 RA use **(Table 1):** . GLP-1 RA use was also associated with a significantly lower risk of all-cause mortality compared with no GLP-1 RA use (9% vs 28%: HR 0.41, $p < 0.001$). In addition, patients receiving GLP-1 RAs demonstrated lower rates of positive alcohol-related biomarkers, including ethanol and phosphatidylethanol (PEth), compared with patients not receiving GLP-1 RAs (HR 0.81, $p = 0.043$). **Conclusion:** Among patients with MetALD, GLP-1 RA use was associated with significantly lower risks of hepatic decompensation and mortality. The mechanism of this effect is likely multifactorial, but one possibility is that GLP-1 RA use may be associated with reduced ETOH consumption.

Table 1. Clinical Outcomes After Propensity Matching

Outcome	GLP-1 RA (n, %)	No GLP-1 RA (n, %)	HR	p-value
Ascites	428/4,807 (9)	557/4,033 (14)	0.78	<0.001
Hepatic encephalopathy	327/5,518 (6)	472/5,391 (9)	0.84	<0.001
Esophageal variceal bleeding	95/5,960 (1.6)	125/5,900 (2)	0.93	0.003
Portal hypertension	405/4,491 (9)	597/4,038 (15)	0.70	<0.001
Hepatorenal syndrome	119/6,006 (2)	278/5,803 (5)	0.51	0.001
All-cause mortality	527/6,083 (9)	1567/5,667 (28)	0.41	<0.001

Disclosures: Karim Besir:Nothing to Disclose, Don Rockey:Nothing to Disclose.

3011 | ◆ TARGETING PEPTIDYL-PROLYL CIS-TRANS ISOMERASE NIMA-INTERACTING 1 (PIN1)–METHIONINE ADENOSYLTRANSFERASE α1/α2 INTERACTIONS PROTECTS AGAINST ETHANOL-INDUCED LIVER INJURY

Guo Zhang[1] Sibiao Su[1] Jiaohong Wang[1] Manisha Dagar[1] Lucía Barbier-Torres[1] Ramachandran Murali[1] Jyoti Chhimwal[1] sonal sinha[1] Maria Lauda Tomasi[1] Heping Yang[1] Shelly Lu[1], [1]Cedars-Sinai Medical Center

Background: Alcohol-associated liver disease (ALD) is characterized by mitochondrial dysfunction, oxidative stress, inflammation, and fibrosis. Methionine adenosyltransferase (MAT) catalyzes synthesis of the methyl donor S-adenosylmethionine (SAMe). Normal hepatocytes express MATα1 while nonparenchymal cells express MATα2. We showed MATα1 targets the mitochondria and this pool is depleted in ALD as MATα1-S114 is phosphorylated, which allows PIN1 to bind and block its mitochondrial entry, causing mitochondrial dysfunction. MATα2 is a driver of liver inflammation and fibrosis, shares the PIN1 motif but whether PIN1 interacts and affects its function in ALD is unknown. Here we examined whether pharmacologic disruption of PIN1 interaction with MATα1/MATα2 can protect from ALD. **Methods:** We used the NIAAA chronic-plus-binge ethanol (EtOH) feeding model. Eight compounds were screened for their ability to disrupt endogenous PIN1–MATα1 interaction induced by EtOH using co-immunoprecipitation (co-IP) in human hepatocytes and effects on viability, ATP, reactive oxygen species, release of alanine aminotransferase were measured. PIN1–MATα2 interaction was measured in Kupffer cells (KCs) and hepatic stellate cells (HSCs) by co-IP, immunoblotting, and immunofluorescence. Intracellular SAMe levels and MAT activity were measured using commercial kits. Liver injury, inflammation, fibrosis, and metabolic dysfunction were assessed by histology, immunohistochemistry, and biochemical analyses. **Results:** Among the eight compounds screened, compounds #4 and #7 were equally effective in disrupting PIN1– MATα1 interaction and raising MATα1 level in EtOH-treated human hepatocytes. MATα2 expression, phosphorylation, and interaction with PIN1 were all induced in KCs and HSCs isolated from NIAAA livers. Mechanistically, EtOH activated ERK, phosphorylating MATα2 and promoting PIN1 binding. Compounds #4 and #7 selectively attenuated PIN1-MATα1/α2 interaction without affecting other PIN1 substrates. In vitro EtOH treatment reduced intracellular SAMe levels and MAT activity in hepatocytes, KCs, and HSCs, all of which were attenuated by compounds #4 and #7. EtOH increased MATα2 content in the nuclei and mitochondria of KCs and HSCs, which was attenuated by compound #7 without affecting total MATα2 level. In vivo,

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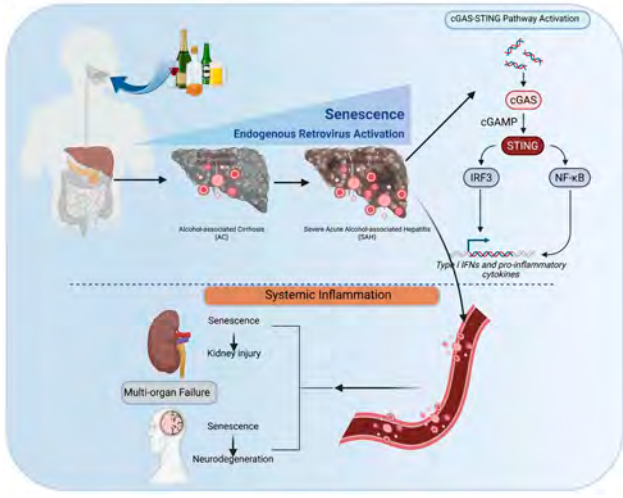
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compound #7 markedly protected against EtOH-induced liver injury, steatosis, oxidative stress, macrophage infiltration, inflammatory cytokine expression, and profibrogenic gene induction, while restoring hepatic ATP and SAMe levels. **Conclusion:** The PIN1–MATα1/MATα2 axis is a major driver of EtOH-induced metabolic dysfunction and liver injury. Pharmacologic disruption of PIN1–MATα1/MATα2 restores hepatic metabolic homeostasis and suppresses inflammation and fibrosis, identifying this as a novel therapeutic approach in ALD.
Disclosures: Guo Zhang:Nothing to Disclose, Sibiao Su:Nothing to Disclose, Jiaohong Wang:Nothing to Disclose, Manisha Dagar:Nothing to Disclose, Lucía Barbier-Torres:Nothing to Disclose, Ramachandran Murali:Nothing to Disclose, Jyoti Chhimwal:Nothing to Disclose, sonal sinha:Nothing to Disclose, Maria Lauda Tomasi:Nothing to Disclose, Heping Yang:Nothing to Disclose, Shelly Lu:Nothing to Disclose.

3012 | ◆ HEPATOCYTE SENESCENCE ACTIVATES ENDOGENOUS RETROVIRUSES TO PROMOTE THE SYSTEMIC INFLAMMATORY RESPONSE SYNDROME AND MULTI-ORGAN FAILURE IN SEVERE ACUTE ALCOHOL-ASSOCIATED HEPATITIS

Anna Mae Diehl[1] Rajesh Dutta[1] Kuo Du[2] Niansheng Ren[1] Seh-Hoon Oh[1] Raquel Maeso-Diaz[1], [1]Duke University, [2]University of Kansas Medical Center

Background: Mortality in severe acute alcohol-associated hepatitis (SAH) results from multi-organ failure (MOF) caused by the systemic inflammatory response syndrome (SIRS). Previously, we showed that accumulation of senescent hepatocytes parallels risk for SAH mortality in humans. Reducing senescent hepatocytes improves alcohol-associated liver disease (ALD) in mice. Thus, the senescence-SIRS axis may be a novel therapeutic target in SAH. Senescent cells often express endogenous retroviruses (ERVs) that are normally repressed in healthy cells. ERVs propagate and sustain inflammation by triggering RIG-I and cGAS-STING signaling that globally up-regulates production of inflammatory cytokines and growth inhibitors. We asked whether senescent hepatocytes activate ERV expression in SAH as ERV expression can be blocked by FDA-approved drugs to provide a novel treatment for SAH. **Methods:** We analyzed bulk RNA-seq and single-nucleus RNA-seq from healthy human livers and explants with alcohol-associated cirrhosis (AC) or SAH to define ERV activation across disease states and liver cell populations. To validate HERVK induction, we assessed expression of HERVK Envelope (Env) protein by Western blotting normal and SAH liver tissues. To determine if inducing senescence activates HERVK in hepatocytes, we treated Huh-7 cells with Palbociclib and performed Western blot analysis of HERVK Env. **Results:** Compared to controls, human liver explants with AC or SAH had increased expression of several endogenous retroviral RNAs, including HERVK, HERVE, HERVL and HERVH. Consistent with this transcriptomic evidence of ERV activation, Western blotting confirmed increased HERVK Env protein expression in SAH liver tissue. Single-nucleus RNA-seq analysis validated expansion of HERVK(+) populations in diseased livers, with the greatest enrichment observed in SAH. Across liver cell populations, hepatocytes showed the highest proportion of HERVK(+) cells. HERVK(+) cells were particularly enriched with TBK1, IRF3, NFKB1 and REL, transcription factors that transduce innate immune signaling by the RIG-I and cGas-STING pathways. HERVK(+) hepatocytes localized to the hepatocyte subpopulation that was most enriched in senescent hepatocyte gene signature (SHGS) positive cells, linking ERV activation to hepatocyte senescence. Treating Huh-7 cells with Palbociclib to induce senescence increased HERVK Env protein expression, confirming that hepatocyte senescence promotes HERVK activation. **Conclusion:** Activation of endogenous retroviral elements (ERVs) in senescent hepatocytes is a feature of life-threatening alcohol-associated liver disease that may propagate and sustain the systemic inflammatory response that leads to progressive multi-organ failure. Targeting the hepatocyte senescence-ERV-SIRS axis may offer a new therapeutic approach for severe alcohol-associated liver disease.



Disclosures: Anna Mae Diehl:Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Rajesh Dutta: Nothing to Disclose, Kuo Du:Nothing to Disclose, Niansheng Ren:Nothing to Disclose, Seh-Hoon Oh:

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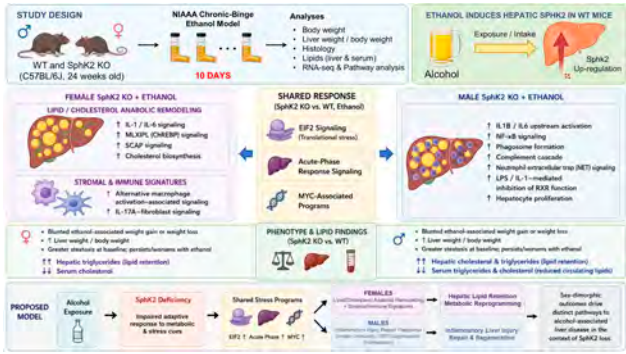
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Nothing to Disclose, Raquel Maeso-Diaz:Nothing to Disclose.

3013 | ◆ SPHK2 DEFICIENCY DRIVES SEX-DIMORPHIC METABOLIC AND INFLAMMATORY REPROGRAMMING IN ALCOHOL-ASSOCIATED LIVER INJURY

Nan Wu[1] Grayson Way[1] Hongkun Lu[1] Derrick Zhao[1] Yun-Ling Tai[1] Chen Chen[1] Meiyi Song[1] Xuan Wang[1] Emily Gurley[1] Phillip Hylemon[1] Huiping Zhou[1], [1]Virginia Commonwealth University

Background: Alcohol-associated liver disease (ALD) exhibits prominent sex dimorphism. Sphingosine kinase 2 (SphK2) regulates sphingolipid metabolism, but its sex-specific role in alcohol-induced liver injury remains unclear. We evaluated how SphK2 deficiency modulates phenotypic, metabolic, and transcriptomic responses to ethanol in both sexes. **Methods:** Male and female WT and SphK2 knockout (KO) C57BL/6J mice (24 weeks old; n = 3-5/group) underwent the NIAAA chronic-binge model (10-day ethanol/control diet plus binge). Phenotypes included body weight and body weight change, liver/body weight (LW/BW) ratio, histology, and liver/serum triglycerides (TG) and cholesterol (Chol). Hepatic transcriptomes were analyzed by RNA-seq and Ingenuity Pathway Analysis (IPA). **Results:** Alcohol upregulated hepatic SphK2 in WT mice, suggesting SphK2 is part of the hepatic adaptive response to ethanol. Under alcohol stress, WT mice gained weight, whereas KO mice showed blunted weight gain or weight loss, increased LW/BW ratio, and worse steatosis. Biochemically, KO males had elevated hepatic Chol/TG with reduced serum Chol/TG, whereas KO females had increased hepatic TG and reduced serum Chol. IPA of ethanol-fed KO versus WT livers revealed shared KO stress signatures: EIF2 signaling (female z = +2.67; male z = +2.50), acute-phase response (female z = +1.61; male z = +1.57), and MYC activation (female z = +4.08; male z = +4.36), consistent with translational stress, inflammatory adaptation, and altered hepatic growth/metabolic programs. Downstream signatures diverged by sex. Females showed IL-1 (z = +2.31) and IL-6 signaling (z = +2.67), with anabolic signaling via MLXIPL/ChREBP (z = +3.70), SCAP (z = +2.94), and cholesterol biosynthesis (z = +2.83), plus macrophage alternative activation (z = +1.80) and fibroblast IL-17A signaling (z = +2.89). Males showed upstream IL1B (z = +2.21) and IL6 (z = +2.42) activation with NF-kB signaling (z = +1.71), phagosome formation (z = +3.35), complement cascade (z = +2.89), NET signaling (z = +2.04), LPS/IL-1-mediated RXR inhibition (z = +1.67), and hepatocyte proliferation (z = +2.14). **Conclusion:** SphK2 deficiency promotes hepatic lipid retention and amplifies ethanol-associated stress responses in a sex-dependent manner. Both sexes share EIF2/acute-phase/MYC activation, but female KO mice preferentially display lipid/cholesterol anabolic and stromal immune signatures, whereas male KO mice exhibit IL1B/IL6-associated inflammatory injury-repair remodeling, innate immune clearance, RXR suppression, and hepatocyte proliferation. These findings identify SphK2 as a sex-dependent regulator of metabolic and inflammatory adaptation in alcohol-associated liver injury.



Disclosures: NAN WU:Nothing to Disclose, Grayson Way:Nothing to Disclose, Hongkun Lu:Nothing to Disclose, Derrick Zhao:Nothing to Disclose, Yun-Ling Tai:Nothing to Disclose, Chen Chen:Nothing to Disclose, Meiyi Song:Nothing to Disclose, Xuan Wang:Nothing to Disclose, Emily Gurley:Nothing to Disclose, Phillip Hylemon:Nothing to Disclose, Huiping Zhou:Nothing to Disclose.

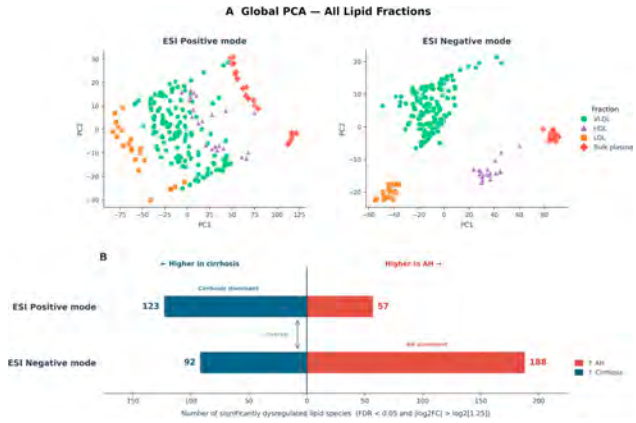
3014 | ◆ A LIVER-SPECIFIC LIPIDOMIC PRISM: PARTICLE-NORMALIZED VLDL SIGNATURES DISTINGUISH ALCOHOL-ASSOCIATED HEPATITIS FROM ALCOHOL-ASSOCIATED CIRRHOSIS

David Guardamino Ojeda[1] Shanshan Su[2] Susmita Bhattarai[3] Zsu-Zsu Chen[3] Gyongyi Szabo[3] Michelle Lai[3] Zachary Fricker[3] Prashanth Thevkar Nagesh[3] Margery Connelly[4] Robert Gerszten[3] Z. Gordon Jiang[3], [1]Jackson Memorial Hospital, University of Miami – Miller School of Medicine, [2]Beth Israel Deaconess Medical Center,Harvard Medical School,The First Affiliated Hospital of Hainan, [3]Beth Israel Deaconess Medical Center, Harvard Medical School, [4]Labcorp

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Background: Alcohol-associated hepatitis (AH) is an acute inflammatory presentation of alcohol-related liver disease (ALD) that often occurs with advanced liver fibrosis or cirrhosis. Because AH and decompensated alcohol-related cirrhosis may overlap clinically, biomarkers capturing acute injury beyond chronic ALD cirrhosis can help the diagnosis of AH and understanding its pathogenesis. As hepatocyte-derived very low-density lipoprotein (VLDL) particles carry lipid cargo only from liver cells, their per-particle composition may capture disease-specific information. We aimed to determine whether untargeted, particle-normalized VLDL lipidomics identifies lipid-class and acyl-chain signatures distinguishing AH from cirrhosis. **Methods:** VLDL plasma fractions from patients with AH (n = 66) and ALD cirrhosis (n = 59) underwent untargeted LC-MS lipidomics. Signal drift was corrected by LOESS, and abundances were normalized to VLDL particle number. Differential abundance of lipids in positive and negative ESI modes was tested using Limma; significant species were defined by FDR < 0.05 and $|Log_2FC| > Log_2(1.25)$. Lipid set enrichment analysis combined Kolmogorov-Smirnov and fgsea algorithms. Structurally aware acyl-chain remodeling was assessed using easyLSEA. **Results:** VLDL carries a distinct lipidome compared to low density lipoprotein (LDL), high density lipoprotein (HDL) or bulk plasma (FIG 1A). Across both ESI modes, 439 unique lipid species met combined significance and effect-size thresholds (FDR < 0.05 and |log2FC| > log2[1.25]), with 21 species independently confirmed in both modes, providing cross-ionization validation. Cirrhosis-enriched species predominated in positive mode (123 vs 57), whereas AH-enriched species predominated in negative mode (188 vs 92), indicating that single-mode profiling substantially underestimates AH-associated lipid dysregulation (FIG 1B). AH was characterized by enrichment of triacylglycerols, ceramides, diacylglycerols, short-chain acylcarnitines (C2:0–C4:0), saturated short-chain phosphatidic acids (C8:0–C13:0), oxylipins ($FDR = 1.3\times10^{-7}$), and conjugated bile acids ($FDR = 2.6\times10^{-7}$), supporting steatotic, mitochondrial, oxidative, and cholestatic lipid stress. In contrast, cirrhosis was characterized by robust SM and PC enrichment across modes, plus PUFA-containing PC, PI, and PE remodeling with unsaturated sn-2 chains including C18:2, C20:4, and C22:6, consistent with chronic membrane lipid remodeling. **Conclusion:** AH and cirrhosis show distinct particle-normalized VLDL lipidomic fingerprints, reflecting acute oxidative/cholestatic lipid stress versus chronic membrane remodeling. AH-enriched oxylipins, conjugated bile acids, and short-chain lipid species, together with cirrhosis-enriched SM/PUFA-glycerophospholipid remodeling, warrant validation as candidate non-invasive biomarkers in severe ALD.



Disclosures: David Guardamino Ojeda:Nothing to Disclose, Shanshan Su:Nothing to Disclose, Susmita Bhattarai:Nothing to Disclose, Zsu-Zsu Chen:Nothing to Disclose, Gyongyi Szabo:CYTA Therapeutics: Consultant, Durect Corporation: Consultant, Pandion Therapeutics: Consultant, Pfizer: Consultant, Surrozen: Advisor, Evive: Advisor, Glympse Bio, Inc (acquired by Sunbird Bio): Advisor, Satellite Biosciences: Advisor, Zomagen Bioscience/Ventyx Biosciences: Consultant, Springer Nature Group: Royalties or patent beneficiary, UpToDate Inc: Royalties or patent beneficiary, Boehringer Ingelheim: Honoraria, Intercept: Contract, NIAAA-NIA: Grant/Research Support, Novo Nordisk: Honoraria, Yale University School of Medicine: Consultant, Resolution Therapeutics: Consultant, US Patent No. 20110293: Intellectual Property, Michelle Lai: Nothing to Disclose, Zachary Fricker:Lipocine, Inc: Grant/Research Support, Pick Research: Consultant, River2Renal Corp: Grant/Research Support, Bausch, Inc.: Grant/Research Support, Guidepoint Global, LLC: Consultant, WL Gore: Speaking and Teaching, Prashanth Thevkar Nagesh:Nothing to Disclose, Margery Connelly:Labcorp: Employee, Robert Gerszten:Nothing to Disclose, Z. Gordon Jiang:Olix Pharmaceutical: Consultant.

3015 | ◆ LARGE LANGUAGE MODEL PIPELINE FOR EXTRACTION OF LONGITUDINAL ALCOHOL USE FROM ELECTRONIC HEALTH RECORDS MATCHES OR EXCEEDS MANUAL CHART REVIEW

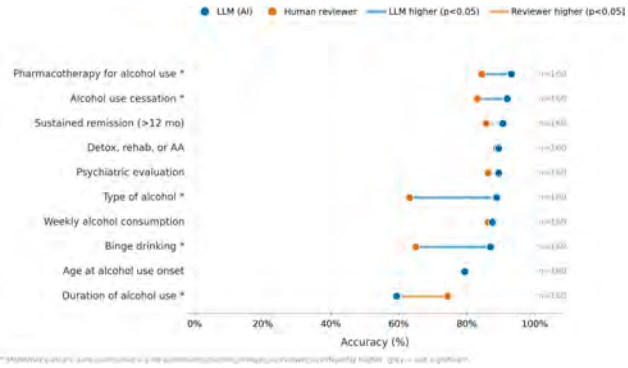
Yigit Yazarkan[1] Alberto Calleri[1] Federico Mastroleo[2] Diego Durmond Westgeest e Sousa[1] Kamalpreet Hara[1] Victoria Kusztos[3] Miguel Gomez[3] Gabriel Prusch Fernandes[4] Mark Waddle[2] Tiffany Wu[1] Patrick Kamath[1] Vijay Shah[1] Douglas Simonetto[1], [1]Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, [2]Department of Radiation Oncology, Mayo

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Background: Longitudinal alcohol use assessment from medical records requires labor-intensive chart review across years of unstructured documentation, limiting registry and observational research in alcohol-associated liver disease (ALD). Conventional NLP has historically struggled with the temporal and narrative complexity of alcohol histories. Thus, we developed and validated a large language model (LLM) pipeline for automated extraction of longitudinal alcohol use phenotypes from EHR notes, benchmarked against trained reviewers. **Methods:** A cohort of 160 patients with ALD was assembled from the Mayo Clinic data lake (BigQuery), sampled to reflect the temporal distribution of ALD diagnoses from 1995–2022. Notes were converted to structured JSON and processed by a prompt-engineered, HIPAA-compliant Gemini 2.5 Flash, developed iteratively on a 40-patient training subset and applied to the full cohort to extract 30 variables per patient (4,800 data points) covering demographics, ALD features, and longitudinal alcohol use (pattern, type, quantity, duration, cessation, treatment). Four reviewers each extracted 40 unique patients, with a shared 20-patient subset to assess inter-rater reliability. LLM–reviewer discrepancies were adjudicated by a blinded second reviewer to establish the reference standard against which both LLM and reviewer accuracy were scored. **Results:** Inter-rater reliability across the 4-reviewer overlap was Fleiss' $\kappa = 0.48$ (objective variables $\kappa = 0.82$; alcohol-quantification variables $\kappa = 0.38$). Overall LLM accuracy was 89.7% (95% CI 88.8–90.5): 93.6% demographics, 88.8% ALD features, 85.6% longitudinal alcohol use. Using a paired analysis with a 5% non-inferiority margin, LLM accuracy was non-inferior or superior to reviewer accuracy for 18 of 30 variables and significantly higher for 5, including type of alcohol (+25.6%; 16.1–35.2), binge drinking (+21.9%; 12.0–31.8), family history of alcohol use (+8.8%; 1.5–16.0), alcohol use pharmacotherapy (+8.8%; 1.3–16.2), and alcohol use cessation (+8.8%; 1.3–16.2). Human reviewer accuracy was significantly higher for 7 variables; the largest difference was alcohol use duration category (−15.0%; −25.4 to −4.6), with the remaining 6 differences $\leq 8.8\%$. Mean extraction time was 2.9 vs 13.8 min/patient (LLM vs manual). **Conclusion:** A prompt-engineered LLM pipeline extracted longitudinal alcohol use and ALD phenotypes with 89.7% accuracy, matching or exceeding trained reviewers on all alcohol history variables except duration, while reducing extraction time ~5-fold. Notably, poor inter-rater agreement on alcohol-quantification ($\kappa = 0.38$) suggests the LLM may add reproducibility, not just efficiency, on tasks where humans themselves disagree. The pipeline supports alcohol use phenotyping at scale.



Disclosures: Yigit Yazarkan:Nothing to Disclose, Alberto Calleri:Nothing to Disclose, Federico Mastroleo:Nothing to Disclose, Diego Durmond Westgeest e Sousa:Nothing to Disclose, Kamalpreet Hara:Nothing to Disclose, Victoria Kusztos:Nothing to Disclose, Miguel Gomez:Nothing to Disclose, Gabriel Prusch Fernandes:Nothing to Disclose, Mark Waddle:Nothing to Disclose, Tiffany Wu:Nothing to Disclose, Patrick Kamath:Sequana: Advisor, NovoNordisk: Advisor, GSK: Advisor, Vijay Shah:Boehringer Ingelheim: Consultant, GSK: Consultant, GENFIT SA: Consultant, Intercept Pharmaceuticals, Inc.: Advisor, Korro Bio, Inc.: Consultant, Novo Nordisk A/S: Consultant, Resolution Therapeutics, Ltd.: Advisor, Seal Rock Therapeutics, Ltd.: Consultant, Surrozen: Advisor, Dexcel Pharma Technologies, Ltd.: Consultant, Dimension Inx.: Advisor, Enveda: Consultant, Ochre Bio: Consultant, Satellite Biosciences, Inc.: Consultant, Douglas Simonetto:Mallinckrodt: Consultant, BioVie: Consultant, Resolution Therapeutics: Consultant, Evive: Consultant, Iota: Consultant, Novo Nordisk: Consultant, Astra Zeneca: Consultant.

3016 | ◆ AN INTEGRATED FIB-4 AND METABOLIC MODEL OPTIMIZES FIBROSIS SCREENING IN SEVERE ALCOHOL USE DISORDER

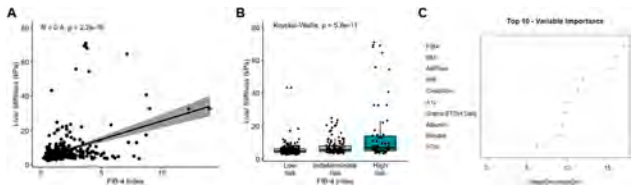
Berenice Ramirez Leal[1] Amelia Orgill[1] Maryam Soltani[2] Heather Patton[3] Cynthia Hsu[3], [1]University of California San Diego, [2]University of California San Diego, & VA San Diego Healthcare System, [3]University of California San Diego & VA San Diego Healthcare System

Background: Screening for early detection of advanced liver disease in severe alcohol use disorder (AUD) is critical, but universal vibration-controlled transient elastography (VCTE/FibroScan) screening is resource-intensive. Fibrosis-4 (FIB-4) index is recommended for risk stratification, but its optimal implementation in AUD remains poorly defined. At the VA San Diego Substance Abuse Residential Rehabilitation Treatment Program (SARRTP), a pilot VCTE initiative

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revealed that 5% of screened individuals had cirrhosis. However, most did not have clinically significant fibrosis (LSM ≥ 8 kPa). Here, we aim to evaluate the performance of FIB-4 index, alone or integrated with metabolic comorbidities and biochemical markers, in identifying patients at risk for elevated LSM. **Methods:** We conducted a retrospective cohort study of 601 patients with severe AUD who underwent VCTE. Random Forest machine learning analysis was utilized to extract features driving advanced fibrosis risk and identify top noninvasive predictors. Optimal thresholds were determined using Youden index optimization. Exploratory multivariable logistic regression models incorporating a FIB-4 threshold of 1.3 alongside metabolic and Random Forest-identified variables were evaluated to optimize the prediction of significant fibrosis. **Results:** In individuals with AUD, though FIB-4 index correlated with LSM by VCTE, substantial diagnostic misclassification persisted (Fig 1a). Among patients with FIB-4 ≥ 1.3, 68% had a false positive result (LSM < 8 kPa) (Fig 1b). FIB-4 cutoff of 1.3 demonstrated poor predictive performance (sensitivity 72%, specificity 62%, accuracy 64%). Random Forest analysis identified alkaline phosphatase (AP), body mass index, INR, creatinine, and hemoglobin A1c, as the top five parameters alongside FIB-4 index differentiating low and high-risk individuals (Fig 1c). Youden index optimization identified an AP threshold of 91 U/L for predicting elevated LSM. A multivariable logistic regression model incorporating a FIB-4 threshold of 1.3 alongside key clinical parameters (obesity, hypertension, diabetes mellitus, and AP) significantly enhanced diagnostic accuracy for predicting LSM ≥ 8 kPa (AUROC 0.81; 95% CI: 0.75-0.87), compared with FIB-4 threshold alone (AUROC 0.67; 95% CI: 0.62-0.73). In this multivariable analysis, elevated AP (OR 3.74, $p < 0.001$), obesity (OR 3.51, $p < 0.001$), FIB-4 ≥ 1.3 (OR 3.42, $p < 0.001$), and hypertension (OR 2.26, $p = 0.027$) were robust independent predictors of elevated liver stiffness, whereas type 2 diabetes mellitus was not significantly associated. **Conclusion:** Standard FIB-4 thresholds alone are insufficient to stratify fibrosis risk in severe AUD. Integrating metabolic comorbidities (obesity, hypertension) and AP significantly improves diagnostic accuracy (AUROC 0.81 vs 0.67), supporting a sequential screening approach to guide VCTE referral.



Disclosures: Berenice Ramirez Leal:Nothing to Disclose, Amelia Orgill:Nothing to Disclose, Maryam Soltani:Nothing to Disclose, Heather Patton:Nothing to Disclose, Cynthia Hsu:Nothing to Disclose.

3017 | ◆ LIVER TRANSPLANTATION FOR ALCOHOL-RELATED HEPATITIS VERSUS ALCOHOL-RELATED CIRRHOSIS IN THE UNITED STATES FROM 2000–2025: DISEASE SEVERITY AND CLINICAL OUTCOMES

Maria Stepanova[1] Giacomo Germani[1] Adrian Gadano[1] Patrizia Burra[1] Rohit Satoskar[2] Linda Henry[1] Zobair Younossi[1], [1]The Global NASH/MASH Council, [2]Georgetown University Hospital

Background: Alcohol-related liver disease (ALD) is the most common cause of cirrhosis in the US. Within the ALD spectrum, severe alcohol-related hepatitis (AH) carries a higher short-term mortality risk compared to ALD cirrhosis (AC). We assessed trends and outcomes of liver transplantations (LT) for AH and AC in the U.S. **Methods:** Adult LT candidates and recipients with primary listing diagnoses of ALD were identified from the U.S. Scientific Registry of Transplant Recipients (SRTR) from 2000-2025. **Results:** Among 274,868 adult LT candidates, 25.4% were listed for AC and 1.7% for AH. LT listings for AC increased from 16.6% (2000) to a peak of 40.7% (2022), followed by a decline to 38.5% (2025). AH listings remained under 100 cases annually until 2018 (< 1%), then increased sharply to 3.7% (2022) and 7.5% (2025). Compared to AC, AH candidates demonstrated higher disease severity with elevated MELD scores (29.4 ± 10.4 vs. 22.7 ± 10.0), and greater life support requirement (9.0% vs. 4.5%) (all $p < 0.01$) but were of younger age (45.9 ± 11.2 vs. 52.7 ± 10.5 years), less commonly male (64.4% vs. 68.3%) with higher private insurance coverage (58.3% vs. 52.9%).Among all ALD candidates, 78.0% of AH vs. 70.2% of AC received LT ($p < 0.0001$). In addition, 4.6% of AH vs. 5.1% of AC candidates died on the list, 2.6% vs. 4.0% were removed due to deterioration, and 4.7% vs. 5.8% improved clinically. In multivariate time-to-event analysis, with LT as a competing risk, AH was independently associated with lower waitlist mortality vs. AC (aHR [95% CI] = 0.77 [0.66–0.88]). Additional independent predictors of waitlist mortality included earlier listing year, advanced age, Medicare/Medicaid coverage, higher MELD scores, life support dependence, encephalopathy, transjugular intrahepatic portosystemic shunt (TIPSS), type 2 diabetes (T2D), and hepatocellular carcinoma (HCC) ($p < 0.01$).Post-transplant survival was comparable between groups: 1-year mortality 5.1% (AH) versus 5.0% (AC), 3-year 9.2%

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versus 10.1%, and 5-year 13.3% versus 15.9% (all $p > 0.05$). Multivariate analysis showed AH was not independently associated with post-LT mortality (aHR [95% CI] = 1.06 [0.93–1.21]). Rather, independent predictors of higher post-LT mortality included earlier transplant era, advanced age, lack of college education, Medicare/Medicaid insurance, T2D, reduced functional status, higher MELD score, HCC, encephalopathy, TIPSS, and re-transplantation ($p < 0.01$). **Conclusion:** Liver transplantations for both alcohol-related cirrhosis and alcohol-related hepatitis have expanded substantially, with particularly marked growth since 2018. Despite presenting higher disease severity at listing, patients with alcohol-related hepatitis achieved superior waitlist outcomes and comparable post-transplant survival to those with cirrhosis, suggesting appropriate patient selection and management strategies.

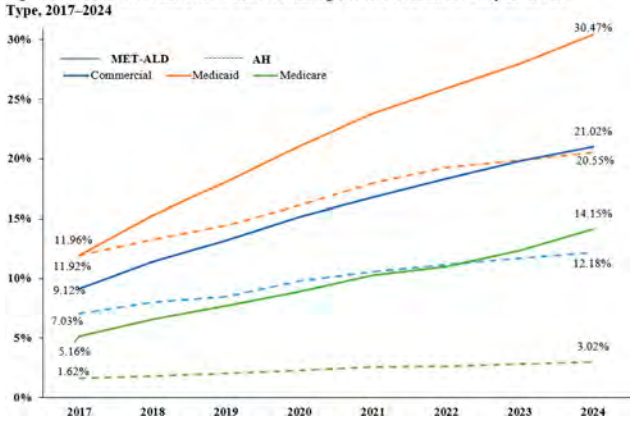
Disclosures: Maria Stepanova:Nothing to Disclose, Giacomo Germani:Nothing to Disclose, Adrian Gadano: Nothing to Disclose, Patrizia Burra:Nothing to Disclose, Rohit Satoskar:Nothing to Disclose, Linda Henry: Nothing to Disclose, Zobair Younossi:Zobair M. Younossi is a consultant or has received research: Consultant, madrigal: Grant/Research Support, Siemens: Research funding, GSK: Consultant, BI: Consultant, Sanofi: Research funding.

3018 | ◆ PREVALENCE OF CIRRHOSIS AND ALCOHOL-RELATED CONDITIONS, INCLUDING MET-ALD AND ALCOHOL-ASSOCIATED HEPATITIS, BY INSURANCE TYPE IN THE UNITED STATES, 2017–2024

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Background: Cirrhosis is an increasing public health burden in the United States, with alcohol-related etiologies contributing substantially. Metabolic dysfunction-associated alcohol-associated liver disease (MET-ALD) reflects the overlap between metabolic and alcohol-related risk factors. Alcohol-associated hepatitis (AH) is a severe manifestation of alcohol-related liver disease. This study assessed recent trends in the prevalence of cirrhosis and alcohol-related conditions among patients with cirrhosis across different insurance populations. **Methods:** This retrospective observational study used administrative claims data from the Komodo Research Database (January 1, 2016–December 31, 2024), including commercially insured, Medicaid, and Medicare Advantage patients. For each calendar year (2017–2024), prevalence of cirrhosis was estimated among patients with continuous enrollment throughout the year, separately by insurance type. Among patients with cirrhosis, the annual prevalence of MET-ALD, defined by the co-occurrence of metabolic dysfunction-associated steatotic liver disease (including fatty liver) and alcohol-associated liver disease, and AH were assessed. **Results:** From 2017 to 2024, the prevalence of cirrhosis increased across all insurance types, rising from 0.21% to 0.35% in Commercial populations, from 0.77% to 1.08% in Medicaid, and from 0.99% to 1.81% in Medicare Advantage. Among patients with cirrhosis, the prevalence of MET-ALD more than doubled across all payer types, increasing from 9.12% to 21.02% in Commercial populations, from 11.96% to 30.47% in Medicaid, and from 5.16% to 14.15% in Medicare Advantage. Similarly, the prevalence of AH increased across all populations, with the highest levels consistently observed in Medicaid (11.92% to 20.55%), compared with Commercial (7.03% to 12.18%) and Medicare Advantage populations (1.62% to 3.02%) **(Figure 1). Conclusion:** Between 2017 and 2024, the prevalence of cirrhosis and alcohol-related etiologies **:** increased substantially across all insurance types in the United States. The increasing burden of alcohol-related conditions, particularly in Medicaid and commercially insured populations, highlights a growing population at risk of severe liver-related outcomes. Given the limited therapeutic options available for certain alcohol-related liver disease manifestations, including AH, these findings underscore an increasing need for improved management strategies in this population.

Figure 1 - Prevalence of MET-ALD and AH Among Patients with Cirrhosis by Insurance Type, 2017–2024



Disclosures: Arun Jesudian:Salix Pharmaceuticals: Consultant, Salix Pharmaceuticals: Speaking and Teaching, Madrigal Pharmaceuticals: Speaking and Teaching, Mallinckrodt Pharmaceuticals: Consultant, Mallinckrodt Pharmaceuticals: Speaking and Teaching, Arthur Voegel:Johnson & johnson: Consultant, Bausch Health: Consultant, Novartis: Consultant, Pfizer: Consultant, BeOne: Consultant, Vertex: Consultant,

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Analysis Group: Employee, Hannah Han:Nothing to Disclose, Fengyi Jiang:Nothing to Disclose, Patrick Gagnon-Sanschagrin:Nothing to Disclose, Annie Guerin:Nothing to Disclose, Olamide Olujohungbe:Bausch Health: Employee, Bausch Health: Stock – privately held company, Aarth Sheth:Nothing to Disclose, Leonardo Passos Chaves:Nothing to Disclose.

3019 | ◆ MECHANISTIC INSIGHTS INTO N-3 PUFA-MEDIATED ATTENUATION OF LIVER INJURY IN EXPERIMENTAL METABOLIC DYSFUNCTION-ASSOCIATED ALCOHOL-RELATED LIVER DISEASE (MET-ALD).

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Background: Metabolic dysfunction-associated alcohol-related liver disease (Met-ALD) is an increasingly recognized condition in which metabolic abnormalities and alcohol consumption may synergistically worsen liver injury. Clinical evidence indicates that nearly 50% of patients with early-stage alcohol-related liver disease (ALD) have a BMI > 25 kg/m2, highlighting the strong association between excess adiposity and alcohol-induced liver damage. n3 polyunsaturated fatty acids (n3 PUFAs) have overall beneficial health effects, including anti-inflammatory, lipid-lowering, and hepatoprotective properties. The current study evaluated the therapeutic potential of endogenous n3 PUFA enrichment in experimental Met-ALD and explored the underlying molecular mechanisms. **Methods:** Male and female C57BL/6J wild-type (WT) and fat-1 transgenic mice, which endogenously produce elevated n3 PUFAs, were exposed to a 12-week high-fat diet (HFD) combined with 10% ethanol supplementation in drinking water to induce metabolic alterations and liver injury Met-ALD phenotype. Metabolic and liver injury markers, inflammatory mediators, and hepatic transcriptomic changes were evaluated. Liver RNA-seq was performed to identify differentially regulated genes, signaling pathways, and immune-cell responses. **Results:** HFD+EtOH induced progressive body weight gain in both WT and fat-1 mice, greater in males. Plasma triglyceride and glucose levels increased significantly in WT but not fat-1 female mice, while both male genotypes showed these metabolic alterations. HFD +EtOH-induced liver injury, as indicated by ALT elevation, was less in fat-1 vs WT females, whereas no genotype-dependent differences were observed in males. However, ALT levels were significantly higher in males overall, indicating sex-dependent differences in liver injury severity. Liver RNAseq analysis revealed that reduced liver injury in fat-1 mice was associated with significant down-regulation of Tnfsf19, a gene implicated in injury-associated inflammatory and stress signaling. Among the 16 up-regulated genes, several were involved in anti-inflammatory responses, tissue repair and resolution of liver injury, including Slpi, Jag2, and Gpc3. In addition, several up-regulated genes were associated with a ductular/progenitor-cell regenerative program, including Krt19. Immune-cell deconvolution analysis revealed increased macrophage infiltration and reduced T-cell signatures, particularly CD8 lymphocytes, in WT male Met-ALD mice compared with controls. **Conclusion:** Endogenous n3 PUFA enrichment in fat-1 mice attenuated liver injury in experimental Met-ALD, with stronger protective effects in females. Transcriptomic findings suggest activation of anti-inflammatory and regenerative pathways, supporting a potential therapeutic role for n3 PUFAs in Met-ALD.
Disclosures: Irina Kirpich:Nothing to Disclose, Dennis Warner:Nothing to Disclose, Yasmeen Abdelfadil:Nothing to Disclose, Craig McClain:Novo Nordisk: Speaking and Teaching, Intercept Pharmaceuticals: Grant/Research Support, Altimmune: Grant/Research Support, Target Pharma Solutions: Grant/Research Support, NIH: Grant/Research Support, VAMC: Grant/Research Support, VAMC: Employee, National Institutes of Health: Grant/Research Support, NovoNordisk: Speaking and Teaching, VAMC: Employee, VAMC: Grant/Research Support, Intercept Pharmaceuticals: Grant/Research Support, Target PharmaSolutions: Grant/Research Support, Jingzhi Wang:Nothing to Disclose.

3020 | ◆ CANNABIS EVER-USE IS INDEPENDENTLY ASSOCIATED WITH LOWER HEPATIC STEATOSIS IN HEAVY ALCOHOL DRINKERS: A CROSS-SECTIONAL ANALYSIS OF NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY (NHANES) DATA

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Background: Alcohol-associated liver disease (ALD) is a major cause of liver-related morbidity and mortality. Cannabis use is common among individuals who drink heavily, yet its hepatic effects in this population remain understudied. Cannabinoid

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receptors CB1 and CB2 are expressed in the liver and are implicated in lipid metabolism and inflammatory regulation, providing a plausible mechanism for cannabis-liver interactions. We evaluated the association between cannabis use and hepatic steatosis, measured by controlled attenuation parameter (CAP), in a nationally representative sample of heavy alcohol drinkers. **Methods:** We analyzed cross-sectional data from the National Health and Nutrition Examination Survey among adults aged 18-79. Heavy drinkers were defined as consuming ≥ 4 drinks/day or drinking ≥ 3 to 4 times/week. The primary exposure was cannabis ever-use. Outcomes were CAP score and severe steatosis, defined as CAP ≥ 280 dB/m. Covariates included age, sex, income, and binge drinking frequency. Income and binge drinking were converted to ordinal numeric scales for adjustment. Analyses included nonparametric testing, logistic regression, and linear regression with interaction modeling. **Results:** Among 951 heavy drinkers, 594 (62.5%) reported cannabis ever-use. Median age was 40.0 years [IQR 29-55], 638 (67%) were male, median income was 7.0 [IQR 5-11] and median binge drinking frequency was 1.0 [IQR 0-4], both on an ordinal scale. Median CAP was 267.0 dB/m [IQR 218-307.5], and 382 participants (40.2%) had severe steatosis. Cannabis users had lower median CAP than non-users (258 vs. 278; $p < 0.0001$). Severe steatosis was less common among cannabis users (36.8% vs. 48.9%; OR = 0.61, 95%CI = 0.47-0.80; $p = 0.0003$). After adjusting for age, sex, and income, cannabis ever-use remained independently associated with a lower CAP score ($\beta = -15.82$, 95%CI = -27.05 to -4.60; $p = 0.006$). Cannabis ever-use remained independently associated with lower odds of severe steatosis (OR = 0.65, 95%CI = 0.45-0.93; $p = 0.019$). After adjusting for binge drinking, the association strengthened (OR = 0.57, 95%CI = 0.40-0.83; $p = 0.003$). A significant cannabis x drinks-per-day interaction was observed ($\beta = -3.01$, 95%CI = -5.95 to -0.07; $p = 0.045$), indicating cannabis use attenuates the positive association between drinks-per-day and CAP. **Conclusion:** Cannabis ever-use is independently associated with lower CAP score and severe steatosis in heavy drinkers, with the association remaining across multiple adjustment strategies. This effect persisted after adjusting for age, sex, and income, and strengthened after accounting for binge drinking frequency. Interaction modeling suggests cannabis may weaken the relationship between daily alcohol consumption and CAP in heavy drinkers. These findings suggest a possible cannabis-liver interaction relevant to hepatic steatosis risk in heavy drinkers.

Predictor / Test	Estimate (β or OR)	SE	95% Confidence Interval	p-value
Model A - Logistic Regression: Severe Steatosis (Adj: age, sex, income; n = 865)				
Cannabis ever-use	OR = 0.721	0.164	0.523–0.995	**0.047***
Age (years)	OR = 1.011	0.005	1.006–1.028	**0.003***
Male sex	OR = 1.439	0.152	1.068–1.941	**0.017***
Income (ordinal 1–12)	OR = 1.017	0.021	0.976–1.061	0.417
Model B - Linear Regression: CAP Score (Adj: age, sex, income, binge freq; n = 666)				
Cannabis ever-use	β = −15.821	5.717	−27.047 to −4.596	**0.006***
Binge Drinking	β = 0.835	0.926	−0.983 to 2.653	0.368
Age (years)	β = 0.859	0.192	0.482 – 1.235	**<0.0001***
Sex (Male)	β = 10.513	5.099	0.501 – 20.526	**0.040***
Income (ordinal 1–12)	β = 1.231	0.736	−0.215 – 2.677	0.095
Model C - Logistic Regression: Severe Steatosis (Adj: age, sex, income, binge freq; n = 666)				
Cannabis ever-use	OR = 0.572	0.188	0.396 – 0.827	**0.003***
Binge Drinking	OR = 0.999	0.031	0.940 – 1.062	0.968
Age (years)	OR = 1.021	0.006	1.008 – 1.034	**0.001***
Sex (Male)	OR = 1.465	0.174	1.042 – 2.060	**0.028***
Income (ordinal 1–12)	OR = 1.028	0.025	0.979 – 1.079	0.268
Model D - Linear Regression with Interaction: CAP Score (Adj: age, sex, income; n = 843)				
Cannabis ever-use	β = −7.821	4.964	−17.565 to 1.923	0.116
Drinks/day *(mean-centered)*	β = 5.325	1.203	2.965 – 7.685	**<0.0001***
Cannabis (ever) × Drinks/day *(interaction)*	β = −3.009	1.496	−5.946 to −0.072	**0.045***
Age (years)	β = 0.942	0.168	0.613 – 1.271	**<0.0001***
Sex (Male)	β = 6.957	4.622	−2.115 – 16.029	0.133
Income (ordinal 1–12)	β = 1.445	0.652	0.166 – 2.724	**0.027***

p < 0.05 (statistically significant); bold p-values indicate significance.

Household Income and Binge Drinking were converted to an ordinal numeric scale (1 = $0–4,999; 12 = $100,000+; 0 = never, 10 = every day) to enable adjustment as a continuous covariable

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3021 | PEGYLATED IFN-α-2B AMELIORATES ALCOHOL-ASSOCIATED LIVER DISEASE BY REMODELING THE GUT MICROBIOTA–BILE ACID–INTESTINAL FXR-FGF15 AXIS

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Background: Alcohol-associated liver disease (ALD) is driven by hepatic lipid accumulation, inflammation, gut dysbiosis, intestinal barrier disruption, and altered bile acid metabolism. Type I interferon has immunomodulatory and metabolic effects, but its role in ALD remains poorly defined. We investigated whether pegylated interferon-α-2b (PEG-IFN-α-2b) protects against alcohol-induced liver injury through modulation of the gut–

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liver axis. **Methods:** A mouse model of alcohol-associated fatty liver disease was established using the NIAAA chronic-plus-binge ethanol feeding protocol. Mice were treated with PEG-IFN-α-2b, followed by assessment of liver injury, serum biochemistry, hepatic lipid metabolism and inflammatory gene expression, intestinal barrier markers, gut microbiota composition by 16S rRNA sequencing, metabolomics, and hepatic transcriptomic analysis. **Results:** PEG-IFN-α-2b markedly attenuated alcohol-induced liver injury, as shown by reduced liver-to-body weight ratio, decreased hepatic triglyceride accumulation, lower serum ALT, AST, and triglyceride levels, and increased HDL-C. PEG-IFN-α-2b also suppressed hepatic inflammatory mediators, including IL-6, TNF-α, and MCP-1, downregulated lipogenic genes such as SREBP-1c and ACC1, and improved intestinal barrier integrity by restoring tight-junction, mucin, and antimicrobial defense markers.16S rRNA sequencing showed that alcohol feeding induced gut dysbiosis, whereas PEG-IFN-α-2b restored microbial homeostasis by reducing potentially pathogenic bacteria and enriching bile salt hydrolase-producing taxa. Bile acid profiling further showed increased unconjugated and secondary bile acids and decreased conjugated bile acids after PEG-IFN-α-2b treatment. Correlation and transcriptomic analyses suggested that these microbiota-derived bile acid changes suppressed intestinal FXR-FGF15 signaling, promoted hepatic bile acid synthesis and secretion, enhanced fecal bile acid excretion, and thereby facilitated cholesterol-to-bile acid conversion and reduced hepatic lipid accumulation. **Conclusion:** PEG-IFN-α-2b protects against alcohol-associated liver injury by restoring intestinal barrier function, reshaping gut microbiota, enriching BSH-producing bacteria, increasing FXR-antagonistic bile acids, and suppressing the intestinal FXR-FGF15 axis. These findings identify a previously unrecognized gut microbiota–bile acid mechanism underlying the therapeutic potential of PEG-IFN-α-2b in ALD.

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3022 | PALLIATIVE CARE IS UNDERUTILIZED IN SEVERE ALCOHOL-ASSOCIATED HEPATITIS: FINDINGS FROM AN INTERNATIONAL SURVEY STUDY

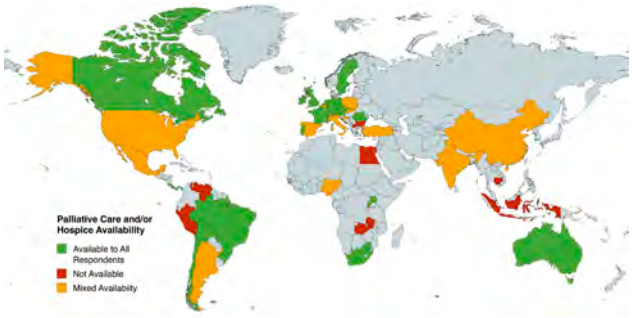
Hanna Blaney[1] Marta Tejedor[2] Jasmohan Bajaj[1] Simone Strasser[3] Svetlana Adamcova Selcanova[4] Lubomir Skladany[5] Marina Berenguer[6] Juan Pablo Arab[1], [1]Virginia Commonwealth University, [2]University of Iowa, [3]New South Wales, [4]Jefferson University Hospital, [5]Roosevelt Univeristy Hospital, [6]University of Valencia

Background: Alcohol-associated hepatitis (AH) has a high short-term mortality. The use of palliative care (PC) or hospice services (HS) in AH is unknown. This study aims to describe current practice patterns and variation in both consultation service use and perceptions of PC and HS in AH. **Methods:** This is an international survey study conducted between January and May 2026. The survey contained four questions on PC and HS in AH. The survey was sent out to 208 hepatologists and surgeons identified through Global AlcHep and International Liver Transplant Society contacts. **Results:** The response rate was 66.8% (139/208) with responses from 46 unique countries. 75.5% of respondents practiced at a liver transplant (LT) center. PC and HS are not universally available: just 63% of respondents have access to PC and HS, while 37% do not, with geographic variability shown in **Figure 1**. Interestingly, 60% of respondents at LT centers had PC or HS services available, compared to 46.9% of those not at an LT center. Consulting habits for PC and HS in AH were variable, with 18.4% regularly consulting regardless of transplant candidacy, 46% regularly consulting only if the patient was not a transplant candidate, 14.9% only consulted at the request of the patient or family, and 17.2% did not consult PC and HS. Perceptions regarding the benefit of PC and HS in AH also varied, with 70.5% of respondents agreeing that all patients with severe AH could benefit from PC and/or HS regardless of whether they were a transplant candidate, and 28.1% felt that only patients with severe AH who were not transplant candidates would benefit. A minority (1.4%) felt that patients with severe AH would not benefit from PC or HS. In LT centers with PC and HS available, 76.2% of participants felt that all patients with severe AH would benefit, compared to 55% at LT centers without these services. When asked about perceived barriers to PC and HS, 45.2% felt that patients or families may not be agreeable to a PC and/or HS consult, 39.3% felt that patients with AH were typically young and may recover, 39.3% felt that PC and HS have a negative connotation, 32.6% cited discomfort with discussing PC and HS, 17.8% believed that patients receiving PC or HS could not receive other treatment, with 5.9% of respondents feeling that PC and HS were the same thing. A minority (11.1%) felt confident in managing end-of-life symptoms in patients with AH and did not need additional help, while 7.4% did not think there was a role for PC or HS care in AH. Additional costs associated with PC and/or HS consultations and care were cited by 14.1% of respondents. **Conclusion:** Availability of and use of PC and/or HS in AH vary globally. Multiple real and perceived barriers exist, including a sizable portion of

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LT centers not having access to these services, discomfort with discussing PC and HS, and several respondents equating PC with HS. This study highlights opportunities to improve complex symptom and end-of-life care in AH.



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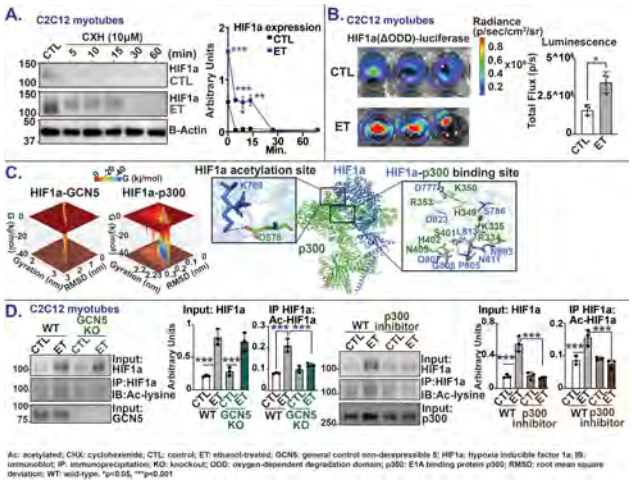
3023 | P300-MEDIATED ACETYLATION STABILIZES HIF1A AND PROMOTES SKELETAL MUSCLE MITOCHONDRIAL DYSFUNCTION IN ALCOHOL ASSOCIATED LIVER DISEASE (ALD)

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Background: Sarcopenia in ALD is severe, persistent, and does not reverse after abstinence or liver transplantation. In ethanol-treated (ET) C2C12 myotubes, human induced pluripotent stem cell-derived myotubes (hiPSCm), mouse ALD (mALD) muscle, and human ALD muscle, HIF1a protein and acetylation increased during normoxia. We tested whether ethanol stabilizes HIF1a through p300-mediated acetylation. **Methods:** C2C12 myotubes and hiPSCm were treated with 100 mM ethanol. 10-wk-old mice received Lieber-DeCarli ethanol or pair-fed (PF) control diet for 10 days, followed by ethanol (5 g/kg) or control gavage on study day. Vastus lateralis muscle was obtained from humans with cirrhosis and heavy drinkers. Myotubes and mALD and human muscle were analyzed for HIF1a protein, target gene mRNA/protein, acetylated (Ac) HIF1a, hydroxylated (OH) HIF1a^{Pro564}, p300. Cycloheximide (CHX) chase and in vivo imaging system HIF1a reporters (GFP-HIF1a-luciferase); GFP-HIF1a-oxygen dependent domain deleted-luciferase) were used to quantify stability. HIF1a acetylation and candidate sites were measured by immunoprecipitation/immunoblotting for Ac-lysine and liquid chromatography-mass spectrometry (LC-MS). p300 inhibitor C646, genetic manipulation, and other acetyltransferases were tested. mTORC1 signaling/protein homeostasis, autophagy, and senescence markers were quantified. **Results:** ET or ALD increased HIF1a stability in all models, with stable HIF1a in myotubes after CHX chase compared with near-complete loss in controls by 30-60 min (**Fig 1a**). HIF1a luciferase activity increased 2-fold in ET myotubes ($p < 0.01$) (**Fig 1b**). HIF1a targets, including PDK1, PDK4, REDD1, and VEGF, increased 1.5- to 2-fold ($p < 0.01$). ET increased Ac-HIF1a 2- to 3-fold in myotubes and mALD muscle ($p < 0.05$ to $p < 0.01$) and reduced OH-HIF1a^{Pro564} by 50% ($p < 0.01$), despite preserved HIF1a degradation components. PHD2 expression did not prevent ethanol-induced HIF1a signaling. p300 protein increased in ET myotubes and mALD and human muscle (6-8-fold, 2-3-fold, and 3-4-fold, respectively; $p < 0.01$ to $p < 0.001$) with no change in GCN5. p300 mRNA increased 1.7-fold after ET ($p < 0.01$). Molecular docking (**Fig 1c**) and LC-MS identified HIF1a$^{K709/K719}$ as a candidate p300-responsive acetylation site. C646 reduced Ac-HIF1a and HIF1a stabilization by 50%, while GCN5 deletion (KO) did not change Ac-HIF1a (**Fig 1d**). In vivo, ALD reduced gastrocnemius weight in HIF1a^{flox} mice from 0.34 g to 0.25 g ($p < 0.01$), while muscle-specific HIF1a KO preserved muscle weight (vs mALD HIF1a^{flox} ,$p < 0.01$). HIF1a KO restored mTORc signaling and reduced autophagy with ET. **Conclusion:** Ethanol stabilizes skeletal muscle HIF1a through p300-mediated acetylation that bypasses canonical degradation. Ac-HIF1a promotes mitochondrial dysfunction, impaired proteostasis, mtROS, and senescence-associated injury, identifying p300-Ac-HIF1a as a targetable pathway in ALD sarcopenia.

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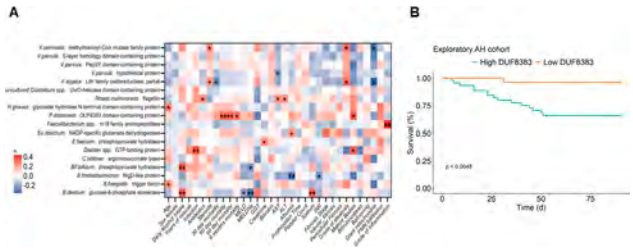


Disclosures: Pugazhendhi Kannan:Nothing to Disclose, Seshu Pothabathula:Nothing to Disclose, Saurabh Mishra:Nothing to Disclose, Annette Bellar:Nothing to Disclose, Inna Serganova:Nothing to Disclose, Abhishek Chakraborty:Nothing to Disclose, Srinivasan Dasarathy:Nothing to Disclose, Nicole Welch:Nothing to Disclose.

3024 | DUF6383-DOMAIN CONTAINING PROTEIN FROM *PARABACTEROIDES DISTASONIS* PREDICTS SURVIVAL IN PATIENTS WITH ALCOHOL-ASSOCIATED HEPATITIS

Henriette Kreimeyer[1] Carlos Gonzalez[2] Marcos Fondevila[3] AlcHepNet Investigators[4] Ali Canbay[5] Peter Stärkel[6] David Gonzalez[2] Bernd Schnabl[7], [1]Universitätsklinikum Knappschaftskliniken Bochum, [2]Department of Pharmacology University of California San Diego, La Jolla, California, USA, [3]Department of Medicine, University of California San Diego, La Jolla, California, USA, [4]IU School of Medicine, Division of Gastroenterology/Hepatology, [5]Universitätsklinikum Knappschaftskrankenhaus Bochum, [6]Department of Hepatology and Gastroenterology, Cliniques Universitaires Saint Luc, Brussels, Belgiu, [7]University of California, San Diego

Background: Alcohol-associated hepatitis is the acute form of alcohol-associated liver disease linked to low short-term survival. Intestinal dysbiosis is a hallmark of alcohol-associated liver disease characterized by a higher abundance of unfavorable species and a reduction of beneficial species. **Methods:** In this study, we aimed to analyze the bacterial proteome of stool samples from patients with alcohol-associated hepatitis (n = 80), alcohol use disorder (n = 20) and controls (n = 19) from an international multicenter cohort using quantitative tandem mass tag (TMT)-based metaproteomic profiling. We validated our results in an independent multicenter cohort of 72 patients with alcohol-associated hepatitis at the genomic level using qPCR. **Results:** Fecal metaproteomic analysis of revealed significantly different bacterial proteomic signatures across all three groups. Fecal samples of patients with alcohol-use disorder and alcohol-associated hepatitis were characterized by a loss of *Firmicutes*-derived proteins and enrichment of proteins from *Bacteroidetes*, *Proteobacteria*, and *Actinobacteria*, accompanied by shifts in specific genera. We identified 18 bacterial proteins that increased with liver disease severity, predominantly produced by Veillonella, Bifidobacterium, and Clostridium-related taxa, including multifunctional "moonlighting" proteins such as enolase and hexokinase (Figure A). The DUF6383 domain-containing protein from *Parabacteroides distasonis* correlated significantly with 90-day mortality and with histological injury and inflammatory cell infiltration (Figure B). Patients with high DUF6383 domain containing protein levels showed significantly worse 90-day survival ($p < 0.05$), independent of the MELD score. This was validated in an independent cohort using qPCR (n = 72, p = 0.045). DUF6383 domain containing protein correlated positively with neutrophil degranulation, autophagy, and mitophagy pathways. We analyzed mortality patterns by taxonomic origin. Proteins from Firmicutes were more closely tied to 30-day outcomes and Proteobacteria proteins dominating 90-day risk. **Conclusion:** Our study reveals that changes in the abundance of specific fecal bacterial proteins are associated with disease severity and progression in alcohol-associated liver disease. Even though, the function of DUF6383 domain containing protein from *P. distasonis* is still unknown, it is a potential prognostic biomarker for short-term mortality in alcohol-associated hepatitis.



Disclosures: Henriette Kreimeyer:Nothing to Disclose, Carlos Gonzalez:Nothing to Disclose, Marcos Fondevila:Nothing to Disclose, AlcHepNet Investigators:Nothing to Disclose, Ali Canbay:Nothing to Disclose, Peter Stärkel:Nothing to Disclose, David Gonzalez:Nothing to Disclose, Bernd Schnabl:Mabwell Therapeutics: Consultant, Ambys Medicines: Consultant, Surrozen: Consultant, Nterica Bio: Stock – privately held company,

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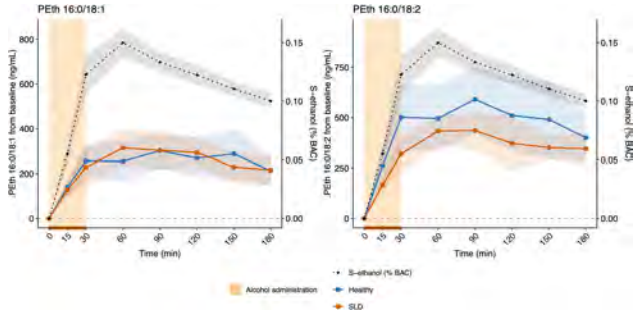
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3025 | PHOSPHATIDYLETHANOL RESPONSE FOLLOWING BINGE DRINKING IN PATIENTS WITH STEATOTIC LIVER DISEASE

Nikolaj Torp[1] Marianne Bergmann[2] Markus Maagaard[1] Ellen Lyngbeck Jensen[1] Stine Johansen[1] Mette lehmann Andersen[3] Peter Andersen[1] Katrine Bech[1] Helle Schnefeld[1] Maria Fogt[1] Ea Kyed[1] Charlotte Gjoel[1] Gunilla Calov[1] Ida Villesen[1] Katrine Thorhauge[1] Johanne Hansen[1] Camilla Dalby Hansen[1] Torben Hansen[4] Mads Israelsen[1] Aleksander Krag[1], [1]Odense University Hospital, [2]Lillebaelt Hospital-University Hospital of Southern Denmark, [3]Herlev Hospital, [4]University of Copenhagen

Background: Phosphatidylethanol (PEth) is a direct alcohol biomarker, where homologues with distinct fatty acid compositions and detection windows can be quantified simultaneously to reflect alcohol consumption patterns. Whether the PEth homologue response to binge drinking differs in patients with steatotic liver disease remains unknown. We therefore aimed to characterize PEth response following controlled binge drinking in patients with SLD compared with healthy controls. **Methods:** We conducted an intervention study of a controlled binge drinking episode in 29 patients with asymptomatic SLD (MASLD: n = 15, MetALD/ALD: n = 14) and 10 healthy individuals serving as controls. Alcohol abstinence was required 48 hours prior to the study visit with confirmation by blood alcohol concentration (%BAC) at baseline. All participants underwent a standardized binge drinking episode consisting of 1 mL ethanol/kg body weight (adjusted for overweight), administered via nasogastric tube over 30 minutes. Two whole-blood PEth homologues with different half-lives (16:0/18:1, $T_{1/2}$ = 8 days and 16:0/18:2, $T_{1/2}$ = 6 days) were quantified by LC-MS/MS and expressed as change from baseline (ΔPEth, ng/mL). Serial systemic venous blood samples were collected at T = 0, 15, 30, 60, 90, 120, 150, and 180 minutes. **Results:** Participants had a median age of 55 years, and 62% were male. Baseline PEth 16:0/18:1 concentrations were median 14 ng/mL (IQR: 6-693 ng/mL) for SLD and median 16 ng/mL (IQR: 8-39 ng/mL) for healthy controls. Prior to binge drinking, PEth 16:0/18:1 had the highest relative abundance in both treatment groups (16:0/18:1 to 16:0/18:2 ratio: 1.33 in SLD and 1.15 healthy controls). Weight-adjusted ethanol dosing to simulate binge drinking ranged from 40 to 98 grams. The resulting serum ethanol peaked after 60 minutes with a mean %BAC of 0.16 (SD: ±0.03) and no difference in %BAC between groups (p = 0.562) (Figure). The PEth 16:0/18:1 response to binge drinking was ≥200 ng/mL in 28 of 29 patients with SLD (97%), while the peak PEth 16:0/18:1 response was comparable between patients with SLD and healthy controls (p = 0.085). Binge drinking induced a selective shift in PEth homologue abundance, where PEth 16:0/18:2 became the dominant homologue (16:0/18:1 to 16:0/18:2 ratio: 0.80 in SLD and 0.55 in healthy controls). Adjusting for peak % BAC, the PEth 16:0/18:1 response was independent of age (p = 0.790), sex (p = 0.547), hemoglobin levels (p = 0.877) and diabetes status (p = 0.581) with similar independencies for the 16:0/18:2 homologue. **Conclusion:** In patients with SLD, a single binge drinking episode leads to substantial PEth elevations with a selective relative shift in homologue abundance. Measuring several PEth homologues with different response and detection windows can provide insights into alcohol consumption beyond quantity alone.



Disclosures: Nikolaj Torp:Nothing to Disclose, Marianne Bergmann:Nothing to Disclose, Markus Maagaard:Nothing to Disclose, Ellen Lyngbeck Jensen: Nothing to Disclose, Stine Johansen:Nothing to Disclose, Mette lehmann Andersen:Nothing to Disclose, Peter Andersen:Nothing to Disclose, Katrine Bech: Nothing to Disclose, Helle Schnefeld:Nothing to Disclose, Maria Fogt:Nothing to Disclose, Ea Kyed:Nothing to Disclose, Charlotte Gjoel:Nothing to Disclose, Gunilla Calov:Nothing to Disclose, Ida Villesen:Nothing to Disclose, Katrine Thorhauge:Nothing to Disclose, Johanne Hansen:Nothing to Disclose, Camilla Dalby Hansen:Novo Nordisk: Speaking and Teaching, Torben Hansen:Nothing to Disclose, Mads Israelsen:Nothing to Disclose, Aleksander Krag:Nothing to Disclose.

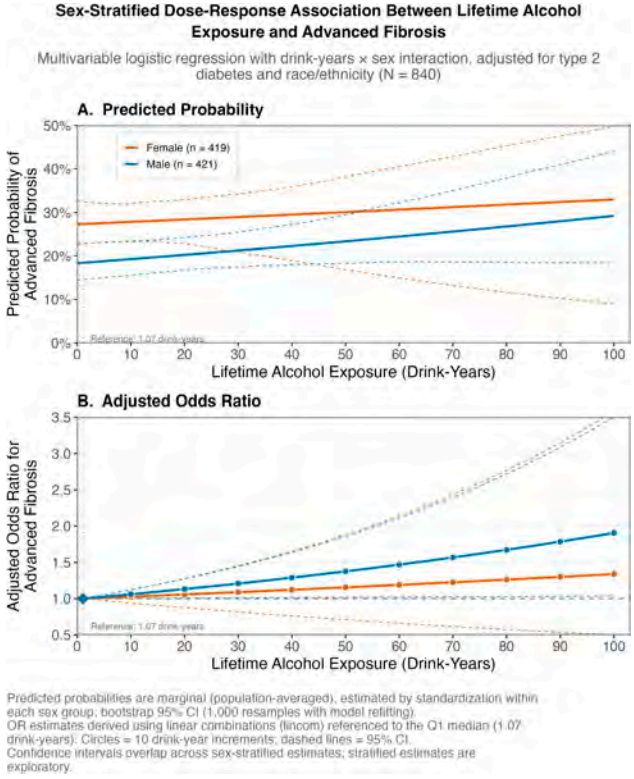
3026 | CUMULATIVE LIFETIME ALCOHOL EXPOSURE AND ADVANCED LIVER FIBROSIS IN BIOPSY-PROVEN MASLD

Alexander Rueda[1] Jennifer Dodge[1] Brian Lee[1], [1]Keck School of Medicine, University of Southern California, Los Angeles, CA

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Background: Current steatotic liver disease (SLD) nomenclature, clinical risk stratification, and MASH trial enrollment criteria rely on alcohol intake assessed over short look-back windows. The contribution of cumulative lifetime alcohol exposure to fibrosis in metabolic dysfunction-associated steatotic liver disease (MASLD) is understudied. We examined the association between cumulative lifetime alcohol exposure and advanced fibrosis in MASLD. **Methods:** We conducted a cross-sectional analysis of adults enrolled in the prospective NASH Clinical Research Network (NASH-CRN) with lifetime alcohol exposure and liver histology. Participants had a diagnosis of MASLD by liver biopsy and average intake of $\leq$14 drinks/week in men or $\leq$7 drinks/week in women at cohort entry. Lifetime alcohol exposure was quantified using the validated Lifetime Drinking History (Skinner). The primary exposure, drink-years (drinks/day × duration, summed across drinking phases), was modeled per 10-unit increase. The primary outcome was advanced liver fibrosis (F3-F4 vs. F0-F2). Multivariable logistic regression adjusted for sex, race/ethnicity, and diabetes. Dose-response and effect modification by sex, age, and beverage type were examined. **Results:** Among 840 participants (mean age = 50.2 years, 50.1% male), 24.3% had advanced fibrosis. Lifetime drinking trajectories revealed that 143 participants (17.0%) had previously crossed MetALD-level drinking threshold ($\geq$140 g/week women; $\geq$210 g/week men) and 65 (7.7%) had crossed ALD-level threshold ($\geq$350 g/week women; $\geq$420 g/week men). In multivariable analysis, each 10 drink-year increase was associated with higher odds of advanced fibrosis (aOR = 1.06, 95% CI: 1.00, 1.11; p = 0.040). A dose-response relationship was observed: compared to the lowest quartile median (1.07 drink-years), aOR was 1.17 (1.01, 1.37) at 30 drink-years and 1.31 (1.01, 1.70) at 50 drink-years. In exploratory sex-stratified analyses, the dose-response trend appeared steeper in males than females, though the sex interaction was not significant (p = 0.55). **Conclusion:** Cumulative lifetime alcohol exposure is associated with higher odds of advanced fibrosis in MASLD, with a dose-response relationship. Nearly one in five had previously exceeded the MetALD drinking threshold, exposing a measurement gap in current SLD nomenclature that relies on recent intake. Routine assessment of lifetime drinking history may improve fibrosis risk stratification, refine SLD subclassification and clinical trial design beyond current consumption alone.



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3027 | ADVERSE CHILDHOOD EXPERIENCE SCORE IS ELEVATED IN ALCOHOL-ASSOCIATED BUT NOT NON-ALCOHOL-ASSOCIATED CIRRHOSIS: EVIDENCE FOR AN ACE&RARR; AUD&RARR;ALD CASCADE FROM A PROSPECTIVE REGISTRY

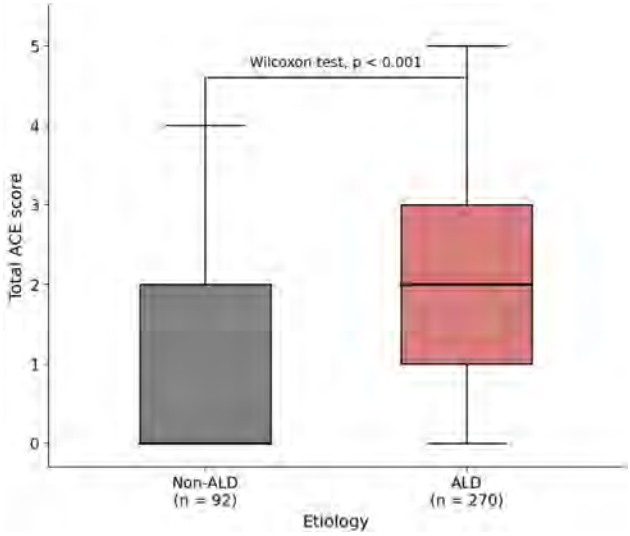
Svetlana Adamcova Selcanova[1] Lubomir Skladany[1] Daniela Zilincanova[1] Karolina Kristina Sulejova[1] Daniel Jan Havaj[2] Ivana Ihnatova[3], [1]F. D. Roosevelt University Hospital, Banská Bystrica, Slovakia, [2]University Hospital of F. D. Roosevelt, [3]Institute of Biology and Ecology, Faculty of Science, Pavol Jozef Safarik University in Kosice

Background: Adverse childhood experience (ACE) score is an established upstream driver of adult alcohol use disorder (AUD). Whether this cascade extends to its end-organ consequence, alcohol-associated liver disease (ALD), at the level of advanced chronic liver disease (ACLD), and whether ACE score tracks ALD phenotypic severity, has not been

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investigated. **Methods:** Single-center analysis within a prospective cirrhosis registry (RH7; NCT04767945). Consecutive ACLD patients (n = 362) received the 10-item ACE questionnaire (ACE-Q) at bedside and were classified as non-ALD (n = 92; including MASLD, autoimmune, viral and metabolic etiologies), ALD without severe alcohol-associated hepatitis (ALD-noSAH; n = 184), and ALD-SAH (n = 86). ACE score was compared by Kruskal-Wallis/Dunn's test with Bonferroni correction and benchmarked against a geographically matched healthy student cohort (n = 3,647; Šulejová et al., 2022) by one-sample Wilcoxon tests. Logistic regression assessed individual ACE items as predictors of ALD etiology. **Results:** ACE score formed a clear stepwise hierarchy across four groups: healthy students (median = 1) and non-ALD patients (median = 0; IQR 0–2) were statistically indistinguishable (p = 0.899), while ALD-noSAH (median = 2; IQR 1–3) and ALD-SAH (median = 2.5; IQR 1–3) both scored significantly above this shared healthy baseline (p < 0.00001 each). Both ALD groups differed markedly from non-ALD (p < 0.00001 each); 51% of non-ALD patients reported zero childhood adversity versus 16% and 15% in ALD groups. The two ALD subgroups did not differ from each other (p = 0.812), indicating ACE score associates with ALD etiology but not with phenotypic severity within ALD. Physical neglect (OR 8.47; 95% CI 1.75–153) and emotional neglect (OR 4.38; 95% CI 2.35–8.80) were the strongest individual predictors of ALD etiology, exceeding all the other abuse-related ACE items. **Conclusion:** Non-ALD cirrhosis patients — including those with MASLD — carry ACE score equivalent to healthy controls, while both ALD phenotypes show a more than twofold elevation. ACE score marks ALD as a category but does not stratify its severity, suggesting childhood adversity is a permissive upstream factor in the ACE→AUD→ALD cascade rather than a modulator of acute disease expression. The predominance of neglect over abuse points to chronic relational deprivation as the key driver. These findings support routine ACE-Q screening in hepatological ALD care.



Disclosures: Svetlana Adamcova Selcanova:Nothing to Disclose, Lubomir Skladany:Worwag: Speaking and Teaching, ProMed: Speaking and Teaching, Abbvie: Speaking and Teaching, Gilead: Speaking and Teaching, RegPharm: Speaking and Teaching, Astellas: Speaking and Teaching, Daniela Zilincanova:Nothing to Disclose, Karolina Kristina Sulejova:Nothing to Disclose, Daniel Jan Havaj:Nothing to Disclose, Ivana Ihnatova:Nothing to Disclose.

3028 | HEPATIC STELLATE CELL-DERIVED FSTL3 DEFINES AN ACTIVIN A-ACTRII AXIS AS A TARGET FOR REPURPOSING CLINICAL-STAGE ANTIBODIES IN ALCOHOL-RELATED LIVER DISEASE

Gloria Alvarez Sola[1] Wei Zhang[1] Jay Luther[1] Esperance Schaefer[2] Russell Goodman[1], [1]Massachusetts General Hospital, [2]Brigham and Women's Hospital

Background: Alcohol-related liver disease (ALD) lacks effective medical therapies. To identify possible new therapeutic targets, we combined a bioinformatics screen of the ethanol-induced hepatic secretome with a human proteomics screen to identify circulating follistatin-like 3 (FSTL3) — a TGF-β superfamily antagonist with no prior role in ALD — as robustly elevate across the spectrum of human disease and in mouse models of ALD. We aimed to define FSTL3's cellular origin, influence on ALD, and therapeutic tractability. **Methods:** We applied cell-type deconvolution of single-cell and spatial transcriptomics to identify the hepatic FSTL3 source, with follow up mechanistic studies employing murine models of ALD, human liver organoids, serum from ALD patients, and bioinformatics analysis of human ALD liver biopsies. **Results:** Spatial and single-cell transcriptomics identified hepatic stellate cells (HSCs) as the dominant source of FSTL3 which was confirmed in HSC cell lines. *in vivo,* FSTL3 overexpression attenuated and knockout exacerbated ALD in mouse models. Mechanistically, FSTL3 exerted its affect via neutralization of hepatocyte-secreted activin A which signals activin type II receptors, with a transcriptional rescue signature highly enriched in human ALD biopsies. We tested three late-stage clinical or FDA approved antibodies targeting different nodes of this pathway: garetsomab, sotatercept, and bimagrumab, all of which phenocopied FSTL3s protective effect in ALD. **Conclusion:** HSC-derived FSTL3 protects against ALD by antagonizing a hepatocyte-autonomous Activin A–ActRII–p21 axis. Three distinct clinical-stage antibodies each recapitulate the protective effects of FSTL3, providing

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preclinical rationale to repurpose an existing pharmacologic pipeline as a novel therapeutic approach for a disease with no effective medical treatments.

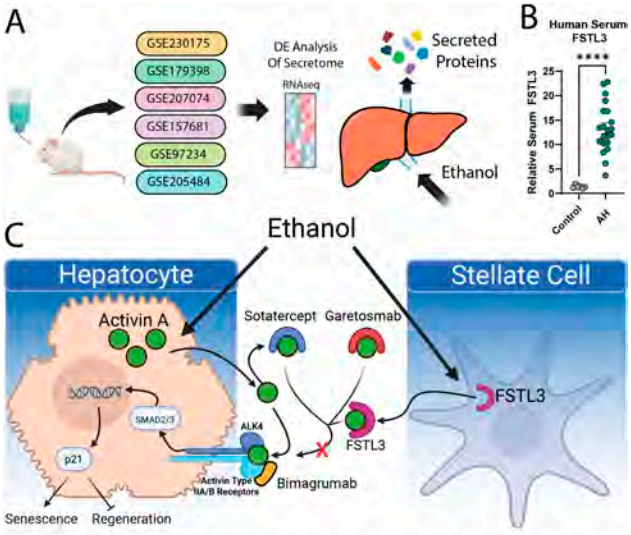


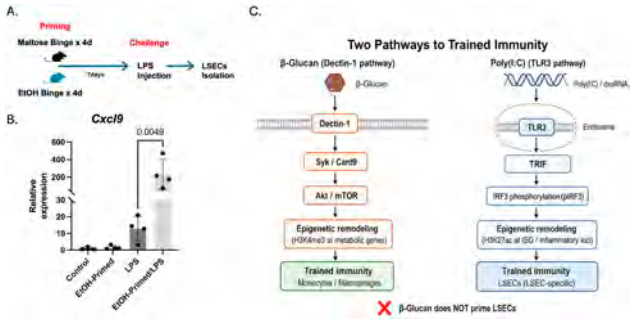
Figure 1. Identification of FSTL3 as a candidate therapeutic target in ALD and its mechanism of action. (A)Analysis of the hepatic secretome across mouse liver RNA-seq datasets identifies ethanol-regulated secreted proteins, converging on FSTL3. (B) Serum FSTL3 is significantly elevated in patients with alcohol-related hepatitis (AH) compared to healthy controls (C) Ethanol drives hepatocyte-autonomous Activin A secretion, which signals through SMAD2/3 to induce p21, impairing regeneration and promoting senescence. Hepatic stellate cell-derived FSTL3 antagonizes this axis. Three clinical-stage antibodies — sotatercept, garetosmab, and bimagrumab — recapitulate FSTL3's protective effect by targeting distinct nodes of the pathway.

Disclosures: Gloria Alvarez Sola:Nothing to Disclose, Wei zhang:Nothing to Disclose, Jay Luther:Nothing to Disclose, Esperance Schaefer:Nothing to Disclose, Russell Goodman:Nothing to Disclose.

3029 | LIVER SINUSOIDAL ENDOTHELIAL CELLS TRAINED IMMUNITY AMPLIFIES INFLAMMATION IN ALCOHOL-ASSOCIATED HEPATITIS

Weizhe Zhong[1] Rafael Ricci de Azevedo[1] Benjamin Swartzwelter[1] Fiona Xhafi[1] Mengfei Liu[1], [1]YALE University

Background: Alcohol-associated hepatitis (AH) is a highly morbid inflammatory liver syndrome with no effective therapy. Liver sinusoidal endothelial cells (LSECs) are angiocrine hubs mediating hepatic immune trafficking and inflammatory amplification. We hypothesize that LSECs undergo trained immunity — a form of innate immune memory in which a primary stimulus induces durable epigenetic and metabolic reprogramming that enhances responses to subsequent challenges, driving a sustained hyperinflammatory state triggered by alcohol-induced endogenous retrovirus reactivation. **Methods:** Bulk RNA-seq deconvolution (BayesPrism) of human AH liver biopsies (GSE136103) quantified LSEC proportions and transcriptional activation. A murine priming–rest–challenge binge alcohol model assessed trained immunity: mice received repeated alcohol binges, 7-day rest, then LPS rechallenge. LSEC Cxcl9 expression, liver injury and inflammation gene expression were measured. CUT&TAG profiled H3K27ac in sorted LSECs from primed versus unprimed mice. PolyI:C or β-glucan were used as defined trained immunity primers followed by LPS rechallenge. ERV reactivation was assessed by qPCR in primary human and mouse LSECs, and phospho-IRF3 by Western blot in ethanol-treated SV40 mouse LSECs. **Results:** Deconvolution of human AH liver revealed marked LSEC inflammatory signaling expansion, with significantly elevated interferon-stimulated and NF-κB-induced signaling, indicating concurrent IRF3 and NF-κB activation in human AH LSECs. In the murine binge model, alcohol-primed LSECs showed greater than 10-fold increase in Cxcl9 upon LPS rechallenge compared to unprimed controls, accompanied by upregulation of liver injury and inflammation gene expression. CUT&TAG demonstrated H3K27ac enrichment at inflammatory gene loci including the Cxcl9 promoter in primed versus unprimed LSECs, confirming priming-induced epigenetic reprogramming. Hepatocytes from the same mice did not exhibit trained responses, establishing LSEC specificity. PolyI:C, but not β-glucan, priming recapitulated alcohol-induced trained immunity with augmented Cxcl9 upon alcohol rechallenge, implicating the TLR3–IRF3 axis. ERV reactivation was confirmed by qPCR in ethanol-treated primary human and mouse LSECs, and phospho-IRF3 was increased by Western blot, identifying ERV-derived nucleic acids as endogenous TLR3 ligands initiating LSEC training. **Conclusion:** LSECs undergo trained immunity in AH, driven by an ERV–TLR3–IRF3 axis that epigenetically programs durable inflammatory hyperresponsiveness across inflammatory gene loci. This represents a previously unrecognized mechanism of sustained hepatic inflammation and a novel therapeutic target in AH.



Disclosures: Weizhe Zhong:Nothing to Disclose, Rafael Ricci de Azevedo:Nothing to Disclose, Benjamin Swartzwelter:Nothing to Disclose, Fiona Xhafi:Nothing to Disclose, Mengfei Liu:Nothing to Disclose.

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3030 | GLP-1 RECEPTOR AGONIST USE AND ALCOHOL-RELATED HOSPITALIZATION AND LIVER OUTCOMES IN ALCOHOL USE DISORDER: A PROPENSITY SCORE–MATCHED COHORT ANALYSIS

Jashanveer Johal[1] Archana Salek[1] Mahmoud Al-Bataineh[1] Brandon Cunha[1] Bianca Patel[1] Abdallah Hussein[1] Yecheskel Schneider[1] Jason Hyman[2] Simona Rossi[1], [1]Virtua Health, [2]Einstein Medical Center, Philadelphia

Background: GLP-1 receptor agonists (GLP-1 RAs) have demonstrated signals of reduced alcohol craving and consumption in preclinical and early clinical studies, yet real-world data on their impact on alcohol-related hospitalizations, liver disease progression, and mortality in patients with alcohol use disorder (AUD) are lacking. **Methods:** We conducted a propensity score–matched retrospective cohort study using the TriNetX Global Collaborative Network (191.9 million patients). Cohort 1 comprised adults with AUD prescribed a GLP-1 RA within one year of diagnosis. Cohort 2 comprised AUD patients with no GLP-1 RA use. Both cohorts excluded prior cirrhosis, HCC, liver transplant, and chronic viral hepatitis. 1:1 PSM yielded 32,572 patients per arm over a 6–60 month follow-up. Outcomes included alcohol-related inpatient admissions, alcoholic cirrhosis, new-onset ascites, incident HCC, need for secondary AUD pharmacotherapy, inpatient encounter burden, and all-cause mortality. **Results:** GLP-1 RA use was associated with dramatically lower rates of alcohol-related admission (4.8% vs. 14.1%; HR 0.38, 95% CI 0.35–0.40; $p < 0.001$) and all-cause mortality (2.8% vs. 9.9%; HR 0.36, 95% CI 0.33–0.39; $p < 0.001$). Alcoholic cirrhosis was significantly lower in the GLP-1 arm (0.5% vs. 1.2%; HR 0.56, 95% CI 0.47–0.68; $p < 0.001$), as was new-onset ascites (0.9% vs. 2.1%; HR 0.55, 95% CI 0.48–0.64; $p < 0.001$). Incident HCC was lower on cumulative risk analysis (RR 0.38; $p = 0.004$) but did not reach significance on KM analysis (HR 0.51; $p = 0.052$), likely reflecting low event counts (11 vs. 29 events). Need for secondary AUD pharmacotherapy was modestly lower by risk ratio (4.8% vs. 5.6%; RR 0.87; $p = 0.0001$) but non-significant on KM analysis (HR 1.06; $p = 0.097$). Inpatient burden was significantly lower in the GLP-1 arm (25.2% vs. 45.9% with any encounter; mean 6.4 vs. 9.2 encounters; $p < 0.001$). **Conclusion:** In this large propensity-matched cohort, GLP-1 RA use within one year of AUD diagnosis was associated with dramatically lower rates of alcohol-related hospitalization, cirrhosis, ascites, and all-cause mortality. While confounding by indication cannot be fully excluded, the breadth and magnitude of these associations support a clinically meaningful role for GLP-1 RAs in reducing alcohol-related harm. These findings complement emerging evidence examining GLP-1 RAs in alcoholic hepatitis, further situating this drug class as a promising intervention across the spectrum of alcohol-related liver disease. Prospective trials are warranted to establish causality and define the populations most likely to benefit.

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3031 | OUTCOMES AND THE LIMITS OF PSYCHOSOCIAL RISK STRATIFICATION IN LIVER TRANSPLANT EVALUATION FOR ALCOHOL-ASSOCIATED LIVER DISEASE

Darine Daher[1] Hassan Azhari[2] Omar Mousa[3] Kymberly Watt[4] William Sanchez[4] Timucin Taner[4] Terry Schneekloth[4] Douglas Simonetto[4], [1]Mayo Clinic, [2]Memorial Sloan Kettering Cancer Center, [3]Mayo Clinic Florida, [4]Mayo Clinic Rochester

Background: Alcohol-associated liver disease (ALD) is a leading indication for liver transplant (LT) evaluation, yet predictors of post-transplant abstinence largely derive from transplanted cohorts. Existing tools, such as the SALT score, are therefore subject to selection bias and cannot characterize patients deferred or denied listing. We evaluated the natural history of patients undergoing LT evaluation for ALD, with particular attention to those deferred or denied. **Methods:** We conducted a multisite observational cohort study of patients evaluated for LT at three Mayo Clinic sites between 1/1/2018 and 1/1/2025. Patients with ALD and alcohol use disorder were included; hepatobiliary or metastatic cancers were excluded. Return to alcohol use was defined as any positive phosphatidylethanol (PEth), ethyl glucuronide, or ethanol test following evaluation. High psychosocial risk was defined by validated instruments (PACT score 0–1, SIPAT score ≥ 40, or SIPAT Section IV score 6–8). **Results:** We identified 2,309 patients (mean age 53.6 years; 63.5% male; 89.1% White); 438 (19.0%) were approved, 1,284 (55.6%) deferred, and 587 (25.4%) denied at initial evaluation. Initial decisions were frequently revised: 434/1,284 (33.8%) deferred and 27/587 (4.6%) denied patients ultimately underwent LT, with 805 (34.9%) transplanted overall. There were 399 deaths (28.3%) among non-transplanted deferred/denied patients ($n = 1,410$) with median follow up time of 433 days.Biochemical return to

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alcohol use was common and similar in observed proportion between non-transplanted denied/deferred (189/786; 24.0%) and transplanted patients (195/765; 25.5%);p = 0.54), despite substantially less frequent testing in the former (56% vs 95% with biomarker data). Of 1,089 patients with available psychosocial evaluation data, 596 (55%) were classified as high risk. High psychosocial risk was associated with greater mortality (HR 1.78, 95% CI 1.40-2.25) and higher rates of return to alcohol use (100/339; 29.4% vs 64/315; 20.3%; p = 0.008), including 41/339 (12.1%) within 90 days of evaluation. Notably, the majority of high-risk patients (239/339; 70.6%) had no detected return to alcohol use. **Conclusion:** Return to alcohol use was common across the evaluation pathway and not confined to transplant recipients, suggesting that listing status alone does not identify relapse risk. While psychosocial risk stratified both mortality and return to alcohol use, the majority of high-risk patients showed no detected alcohol use, suggesting that a high-risk designation has limited individual-level predictive value and, used as a categorical exclusion, may forgo transplant access for many patients who do not return to drinking. These findings support dynamic, biomarker-anchored reassessment, and identify high-risk patients as a group warranting continued surveillance and targeted interventions.m close monitoring or targeted interventions.

Disclosures: Darine Daher:Nothing to Disclose, Hassan Azhari:Nothing to Disclose, Omar Mousa:Nothing to Disclose, Nothing to Disclose, Kymberly Watt: Madrigal: Stock - publicly traded company, Viking: Stock - publicly traded company, Novo Nordisk: Speaking and Teaching, William Sanchez:Nothing to Disclose, Timucin Taner:Nothing to Disclose, Terry Schneekloth:Nothing to Disclose, Douglas Simonetto: Mallinckrodt: Consultant, BioVie: Consultant, Resolution Therapeutics: Consultant, Evive: Consultant, Iota: Consultant, Novo Nordisk: Consultant, Astra Zeneca: Consultant.

3032 | GALECTIN-3 BINDING PROTEIN UPREGULATED IN ALCOHOL-ASSOCIATED CIRRHOSIS PROMOTES BROAD TRANSCRIPTIONAL CHANGES IN HEPATIC STELLATE CELLS, INCLUDING MONOCYTE CHEMOTAXIS AND PROFIBROTIC SIGNALING

Andrea Paola De La Lama Flores[1] Ainsley Baker[2] Rolando Garcia-Milian[3] Yasuko Iwakiri[3] Matthew McConnell[3], [1]Yale University School of Medicine, Section of Digestive Diseases, [2]Yale University School of Medicine, Section of Digestive Diseases (Yale Liver Center), [3]Yale University

Background: Platelets promote metabolic-associated steatotic liver disease (MASH) and other inflammatory liver diseases, but their role in alcohol-associated cirrhosis (AC) remains unclear. We previously showed that platelet-derived microparticles carrying Galectin-3 binding protein (Gal3BP) are significantly upregulated in AC patients, but their pathological role remains unknown. **Methods:** Public liver single-cell RNAseq data from alcohol-associated cirrhosis patients was analyzed for Gal3BP receptor expression and hepatic stellate cell (HSC)-monocyte crosstalk. Primary HSCs were treated with Gal3BP, and their conditioned media was used to treat primary human monocytes. Bulk RNAseq was performed on Gal3BP-treated HSCs and conditioned medium-treated monocytes. THP-1 chemotaxis to Gal3BP-treated HSCs was assessed. qPCR was used to assess key genes in HSCs and monocytes. **Results:** Analysis of publicly available single-cell RNAseq data from AC and control human livers (GSE 136103) revealed that HSCs and myofibroblasts express high levels of the Gal3BP receptors CD248, LGALS3, and LGALS1. To study Gal3BP signaling, HSCs were treated with Gal3BP *in vitro* followed by bulk RNAseq. Ingenuity pathway analysis (IPA) revealed significant upregulation of pathways associated with immune cell chemotaxis, including movement and activation of phagocytes and myeloid cells. qPCR from HSCs confirmed upregulation of chemokines CXCL2 (fold-change 1.8, p < 0.01) and CXCL8 (fold-change 2.2, p < 0.01), along with inflammatory cytokine IL-1β (fold-change 1.6, p < 0.01).To determine whether these transcriptional changes promoted monocyte migration, we performed a transwell migration assay using Gal3BP- or vehicle-treated HSCs in the lower chamber and labeled THP-1 monocytes in the upper chamber. Immunofluorescence showed a significant increase in migrated THP-1 cells over 24 hours in the Gal3BP-treated group compared to control (95.5 cells vs 67.6 cells, p < 0.01), indicating enhanced chemotactic activity induced by Gal3BP.Conditioned medium from Gal3BP-treated HSCs was then used to treat primary human monocytes followed by bulk RNAseq. IPA showed significant upregulation in the monocytes of fibrotic, inflammatory, and immune recruitment pathways, including hepatic fibrosis signaling, collagen trimerization, leukocyte migration, and mononuclear leukocyte activation.To assess *in vivo* relevance, we re-analyzed AC single-cell RNAseq data and found increased HSC expression of CCL2, CXCL2, and IL-1β. We observed increased macrophage abundance along with upregulated mesenchymal-macrophage crosstalk mediated by IL-1β. **Conclusion:** Gal3BP is upregulated in platelet-derived microparticles in AC. Gal3BP signaling to HSCs promotes crosstalk with

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monocytes, promoting chemotaxis and a profibrotic phenotype, and may represent a new therapeutic target in chronic liver disease.

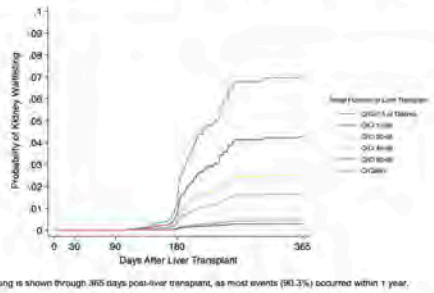
Disclosures: Andrea Paola De La Lama Flores: Nothing to Disclose, Ainsley Baker:Nothing to Disclose, Rolando Garcia-Milian:Nothing to Disclose, Yasuko Iwakiri:Nothing to Disclose, Matthew McConnell:Nothing to Disclose.

3033 | RENAL OUTCOMES AFTER LIVER TRANSPLANTATION FOR ALCOHOL-ASSOCIATED HEPATITIS

Claire Durkin[1] Shari Rogal[1] Ravy Vajravelu[1], [1]University of Pittsburgh

Background: Early liver transplantation (LT) for alcohol-associated hepatitis (AAH) has increased over the past decade, yet long-term renal outcomes and kidney transplant utilization remain poorly characterized in this population. Understanding the impact of current policies, including simultaneous liver-kidney (SLK) transplantation and the kidney-after-liver transplant (KALT) safety net, may inform strategies to optimize renal preservation and organ allocation. **Methods:** This was a retrospective cohort study of the United Network for Organ Sharing (UNOS) database of adults ($\geq$18 years) undergoing first-time LT alone (LTA) or SLK for AAH (1/1/2018-12/31/2024). AAH was identified using primary/secondary diagnosis codes on initial waitlist application. Clinical and demographic characteristics were compared between SLK recipients and LTA recipients who met SLK acute kidney injury (AKI) thresholds (CrCl < 25mL/min or dialysis) at LT. Among patients undergoing LTA, Cox multivariable regression was used to identify predictors of subsequent KALT listing. Follow-up extended from LT to KALT, death, or end of follow-up. Models adjusted for age, sex, race/ethnicity, body mass index, diabetes, Model for End-Stage Liver Disease (MELD) score, ascites, encephalopathy, ventilator use, life support, and LT year, as well as calcineurin inhibitor (CNI) exposure as a binary time-varying covariate. **Results:** Of the 2,528 patients transplanted for AAH, 2,417 (95.6%) underwent LTA and 111 (4.4%) underwent SLK. Renal dysfunction at LT was common with 38.9% of LTA recipients requiring dialysis and over half (51.2%) having CrCl < 30mL/min. Following LT, 298 (12.3%) of LTA recipients were waitlisted for KALT and 165 (6.8%) received a kidney transplant. Nearly all (90.3%) KALT listings occurred within 1 year of LT under the UNOS safety net policy. Compared to SLK recipients, LTA recipients meeting SLK AKI listing thresholds had higher MELD scores (40 vs 34, p < 0.001) and rates of Child Pugh class C (94.6% vs 81.8%, p < 0.001), but were younger (41 vs 45, p < 0.001) and less likely to have diabetes (6.3% vs 14.1%, p = 0.003). Among LTA recipients, predictors of subsequent KALT listing included greater severity of renal dysfunction at LT (**Figure**), CNI exposure (adjusted hazard ratio [aHR] = 7.96, p < 0.001), use of life support (aHR = 1.71, p = 0.019), and class III obesity (aHR = 2.01, p = 0.040). **Conclusion:** Renal dysfunction is highly prevalent among patients undergoing LT for AAH, and approximately one in six ultimately require SLK or KALT. Given the acute presentation of AAH, patients may undergo urgent LT before meeting sustained renal dysfunction criteria for SLK, underscoring the importance of the UNOS safety net in preserving kidney access. Baseline renal dysfunction, post-LT CNI exposure, life support, and severe obesity predict progression to KALT, highlighting opportunities for risk stratification and renal-sparing management following LT.

Figure:
(A) Adjusted probability of waitlisting for kidney-after-liver transplant in alcohol-associated hepatitis by renal function at liver transplant



Note: Kidney waitlisting is shown through 365 days post-liver transplant, as most events (90.3%) occurred within 1 year.

B) Cox multivariable model for waitlisting for kidney-after-liver transplant in alcohol-associated hepatitis

	Adjusted Hazard Ratio	95% Confidence Interval	p-value
Renal function			
CrCl <15 or dialysis	Reference	Reference	Reference
CrCl 15-29	0.59	(0.35-0.99)	0.049
CrCl 30-44	0.19	(0.08-0.45)	<0.001
CrCl 45-59	0.26	(0.11-0.59)	0.001
CrCl 60-89	0.02	(0.00-0.19)	<0.001
CrCl ≥90	0.03	(0.01-0.15)	<0.001
Calcineurin inhibitor exposure	7.96	(4.79-13.23)	<0.001
Age (per decade)	1.11	(0.94-1.30)	0.229
Sex (male)	1.20	(0.84-1.72)	0.320
Race/Ethnicity			
White	Reference	Reference	Reference
Black	0.67	(0.30-1.57)	0.373
Hispanic/Latino	0.58	(0.32-1.03)	0.062
Asian	0.21	(0.03-1.49)	0.117
American Indian/Alaska Native	0.70	(0.17-2.87)	0.615
Multiracial	3.31	(0.79-13.81)	0.101
Body mass index (kg/m²)			
Underweight (<18.5)	1.56	(0.36-6.74)	0.552
Normal (18.5-24.9)	Reference	Reference	Reference
Overweight (25.0-29.9)	1.40	(0.84-2.33)	0.196
Class I obesity (30.0-34.9)	1.18	(0.69-2.02)	0.550
Class II obesity (35.0-39.9)	1.60	(0.88-2.94)	0.125
Class III obesity (≥40)	2.01	(1.03-3.92)	0.040
Diabetes	1.05	(0.56-1.86)	0.875
Transplant year (per year)	0.95	(0.87-1.03)	0.332
Model for End-Stage Liver Disease score (per point)	0.98	(0.95-1.02)	0.332
Ascites			
None	Reference	Reference	Reference
Slight	1.21	(0.62-2.34)	0.573
Moderate	1.00	(0.51-1.94)	0.998
Encephalopathy			
None	Reference	Reference	Reference
Grade 1-2	1.22	(0.77-1.92)	0.396
Grade 3-4	1.27	(0.74-2.16)	0.389
Ventilator use	0.67	(0.32-1.43)	0.305
Life support	1.71	(1.09-2.67)	0.019

Disclosures: Claire Durkin:Nothing to Disclose, Shari Rogal:Nothing to Disclose, Nothing to Disclose, Ravy Vajravelu:Nothing to Disclose.

3034 | NEW SUBMISSION

Muhammad Azhar Nisar[1] Xinjian Li[2] Yaozhong Liu[3] Brandon Peiffer[4] Zhaoli Sun[5] Peng-Sheng Ting[6] Wenke Feng[7] Lixian Chen[7] Xiao-Ming Yin[8] Chiung-Kuei Huang[9], [1]Stonybrook department of Medicine, [2]Department of Medicine, Division of Gastroenterology and Hepatology, Renaissance School of Medicine, [3]Department of Biostatistics and Data Science, Tulane

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University School of Public Health and Tropical, [4]Johns Hopkins University School of Medicine, Baltimore, MD, USA, [5]Johns Hopkins University, [6]Division of Gastroenterology and Hepatology, Tulane University School of Medicine, New Orleans, LA, [7]Department Structural Cellular Biology, Tulane University School of Medicine, New Orleans, LA, USA, [8]Department of Pathology and Medicine, Tulane University School of Medicine, New Orleans, LA, USA, [9]Stony Brook University Renaissance School of Medicine

Background: Alcohol-associated liver disease (ALD) features progressive ductular reaction and cholangiocyte expansion. The origin of these cholangiocytes—whether via hepatocyte transdifferentiation, cholangiocyte proliferation, or stem cell differentiation—remains controversial. Clarifying this origin and its governing mechanisms is essential for developing ALD therapeutic targets. **Methods:** We performed single-nucleus RNA sequencing (snRNA-seq) on liver samples from normal controls, alcoholic hepatitis (AH), and alcoholic cirrhosis (AC) patients. Using Seurat and Slingshot, we conducted cell type, transitional state, and pseudotime trajectory analyses. Transitioning cells were identified via KLF4, KLF6, SOX4, and KRT23. Differential gene expression, pathway enrichment, and marker co-expression were analyzed across disease states. Findings were validated in an independent snRNA-seq cohort (GSE256398). **Results:** We observed significant cholangiocyte expansion in AH and AC with corresponding hepatocyte depletion. Transitioning cell populations also increased in AH and AC. Co-expression analysis revealed normal transitioning cells co-expressed hepatocyte (ALB, APOA1, CYP3A4, HNF4A) and transition markers (KLF4, KLF6), whereas AH and AC transitioning cells showed dramatic loss of hepatocyte markers, suggesting aggressive transdifferentiation. Proliferation markers (MKI67, TOP2A, STMN1) were absent in cholangiocytes, indicating limited contribution from cholangiocyte proliferation. Pseudotime confirmed a continuous hepatocyte-to-cholangiocyte transition, with progressive upregulation of cholangiocyte and downregulation of hepatocyte markers. Mechanistically, transitioning cells showed a transcriptional signature of TGFB2-driven fate switching: TGFB2 was the most upregulated TGF-β ligand across comparisons and datasets, co-occurring with SMAD3 upregulation and loss of inhibitory regulators (SMAD6, SMAD7, SKI, SKIL). This coincided with downregulation of ID1, ID2, and ID3, which normally repress the biliary transcription factor SOX9 in hepatocytes. These findings suggest TGFB2-SMAD3-ID1/2/3 signaling contributes to hepatocyte fate loss and cholangiocyte differentiation in ALD progression. **Conclusion:** ALD cholangiocyte expansion predominantly arises from hepatocyte transdifferentiation, rather than proliferation or stem cell differentiation. This identity loss is an alcohol-induced adaptive response driven by TGFB2-SMAD3-ID1/2/3 signaling, which dismantles hepatocyte identity while de-repressing biliary fate determinants. Targeting this transition and its upstream regulators offers a potential strategy to prevent ALD ductular reactions

Disclosures: Muhammad Azhar Nisar:Nothing to Disclose, Xinjian Li:Nothing to Disclose, Yaozhong Liu:Nothing to Disclose, Brandon Peiffer:Nothing to Disclose, Zhaoli Sun:Nothing to Disclose, Peng-Sheng Ting:Nothing to Disclose, Wenke Feng:Nothing to Disclose, Lixian Chen:Nothing to Disclose, Xiao-Ming Yin:Nothing to Disclose, Chiung-Kuei Huang:Nothing to Disclose.

3035 | BIDIRECTIONAL ASSOCIATION BETWEEN DIABETES MELLITUS AND DISEASE SEVERITY AND LONG-TERM PROGNOSIS IN ALCOHOLIC LIVER DISEASE: A MULTICENTER COHORT STUDY

Yingying Zhao[1], [1]Beijing Ditan Hospital, Capital Medical University

Background: To investigate the bidirectional relationship between diabetes mellitus (DM) and alcoholic liver disease (ALD) in a large cohort of patients with ALD. **Methods:** A total of 2,724 patients with confirmed ALD from five centers were enrolled and divided into two groups based on the presence of diabetes(DM) at baseline. Cross-sectional analysis was performed to compare parameters of liver disease severity (Child-Pugh class, Model for End-Stage Liver Disease(MELD) score, and cirrhosis-related complications) between the two groups. Multivariate logistic regression was used to identify factors associated with severe ALD (e.g., Child-Pugh class B/C), with a specific assessment of the independent contribution of DM. Longitudinal survival data were analyzed using the Kaplan-Meier method and Cox proportional hazards model to evaluate the impact of DM on 1-to 4-year all cause mortality. In the subgroup without DM at baseline, we explored the association between baseline liver disease severity indicators and the risk of incident hyperglycemia or new-onset DM. **Results:** The prevalence of DM among ALD patients was 27.3% (813/2,724). Cross-sectional analysis showed that patients with concomitant DM had significantly higher baseline Child-Pugh scores ($P = 0.037$) and MELD scores ($P = 0.048$), as well as higher rates of complications: ascites (47.4% vs. 16.5%) and hepatic encephalopathy (14.2% vs. 8.6%). The presence of DM was positively correlated with the incidence of hepatic encephalopathy ($r = 0.094$, $P < 0.001$), esophagogastric variceal bleeding ($r = 0.096$, $P < 0.001$), hepatocellular carcinoma ($r = 0.048$, $P = 0.012$), and ascites ($r = 0.117$, $P < 0.001$), but was negatively correlated with the proportion of Child-Pugh class C ($r = -0.040$, $P = 0.039$). Multivariate analysis confirmed that, in addition to age and low serum albumin, DM was an independent risk factor for severe liver disease at baseline (adjusted OR 1.373, 95%

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CI 1.095-1.722). Survival analysis indicated that DM was an independent predictor of long-term mortality in ALD patients (adjusted HR 1.1, 95% CI 0.839–1.445). Alcohol abstinence was negatively correlated with incident DM during follow-up (r = -0.309, P < 0.001). Moreover, more severe liver disease at baseline, as reflected by the ABIC score (r = 0.059, P = 0.03), was associated with worsening glycemic control or an increased risk of new-onset DM during follow-up. **Conclusion:** This study reveals a significant bidirectional adverse relationship between DM and ALD. DM not only serves as a marker and promoter of ALD severity but also as an independent risk factor for poor prognosis. Conversely, severe ALD may exacerbate glucose metabolism disorders. These findings underscore the critical importance of systematic screening and management of DM in ALD care, as well as the assessment of liver status in patients with DM. An integrated management strategy is essential to improve overall patient outcomes.

Table 1. Comparison of Laboratory Parameters Between Different Patient Groups

Parameters	All (n=2724)	Non-DM (n=1911)	DM (n=813)	P valve
ALB(g/l)	31.7(27.1,37.3)	31.7(27.1,37.1)	31.7(27.1,37.4)	0.048
INR	1.3(1.12,1.61)	1.28(1.12,1.55)	1.32(1.11,1.63)	0.052
MDF	13.3(2.92,32.8)	11.94(3.35,29.16)	13.9 (2.73,34.86)	0.111
MELD	6.64(2.73,12.84)	5.94(2.63,11.96)	6.94(2.76,13.32)	0.048
ABIC	7.27(6.5,8.02)	7.31(7.22,8.00)	7.33(6.42,8.01)	0.002
age	55(48,62)	54(39,62)	50(44,57)	<0.001
Gender n(%)				0.172
male	2644(97.1)	1849(67.9)	62(2.3)	
female	80(2.9)	62(2.3)	18(0.7)	
ascite n(%)	622(22.8)	247(9.1)	375(13.8)	<0.001
hepatic encephalopathy n(%)	623(22.9)	235(8.6)	388(14.2)	<0.001
esophageal and gastric variceal rupture bleeding n(%)	445(16.3)	235(8.6)	388(14.2)	<0.001
hepatocellular carcinoma n(%)	91(3.3)	38(1.4)	53(1.9)	0.014

- **Abbreviations**: ALB, albumin; INR, internationalization ratio ;MDF, Maddrey ' s discriminant function; MELD, Model for End-Stage Liver Disease; Age-Bilirubin-INR-Creatinine; ABIC, age–bilirubin–INR–creatinine score

Table 2 Correlation Between Decompensated cirrhosis events and Alcoholic Liver Disease

	diabetes	
	r	P
ascite	0.117	<0.001
hepatic encephalopathy	0.094	<0.001
esophageal and gastric variceal rupture bleeding	0.096	<0.001
hepatocellular carcinoma n(%)	0.048	0.012
Child C grade	0.040	0.039

Table 3 . Binary logistic regression analysis of severe liver disease

	Univariate regression analysis		Multivariate regression analysis	
	OR(95%CI)	P value	OR (95%CI)	P value
age	0.954(0.946,0.962)	<0.001	0.943(0.934,0.952)	<0.001
ALB	0.832(0.816,0.847)	<0.001	0.824(0.808,0.839)	<0.001
DM	1.394(1.148,1.694)	<0.001	1.373(1.095,1.722)	0.006

Disclosures: Yingying Zhao:Nothing to Disclose.

3036 | METALD EXACERBATES HEPATIC STEATOSIS AND RESHAPES THE GUT MICROBIOTA COMPARED WITH MASLD IN MURINE MODELS

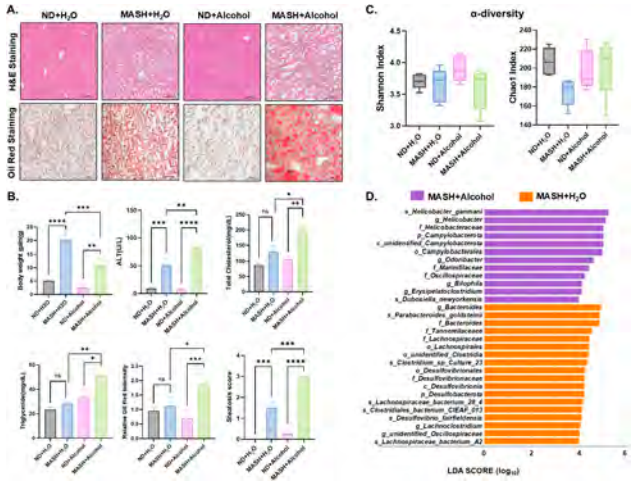
Ning Ma[1] Saisai Zhang[1] Zhe Zhang[1] Fung Yu Huang[1] Man-Fung Yuen[1] Lung-Yi Mak[1] Wai-Kay Seto[1], [1]The University of Hong Kong

Background: Metabolic dysfunction-associated alcohol-related liver disease (MetALD) is defined by the presence of metabolic dysfunction with concurrent alcohol intake. The differences of MetALD with metabolic dysfunction associated steatotic liver disease (MASLD) in hepatic histopathology and gut microbiome profiles remain incompletely understood. This study aimed to characterize these differences using mouse models of MASLD and MetALD. **Methods:** Eight-week-old male C57BL/6J mice were randomly assigned to four groups (n = 4 per group). Mice were initially fed either a high-fat, high-cholesterol, high-sucrose diet (metabolic associated steatohepatitis [MASH] diet) or a standard chow diet and subsequently subdivided into alcohol- or water-treated subgroups for 12 weeks. Mice in the alcohol groups received 10% (v/v) ethanol in drinking water along with weekly oral gavage of ethanol (5g/kg), while control mice received regular water and weekly gavage of water. Mice fed with the MASH diet with alcohol exposure were defined as the MetALD group. Fecal samples were collected for PacBio Full-length 16S rRNA sequencing. **Results:** MetALD mice, when compared with MASLD mice, exhibited significantly lower body weight gain (10.76 ± 2.44 g vs 20.21 ± 2.97 g), but higher serum ALT (82.72 ± 15.37 U/L vs 51.77 ± 11.61 U/L), triglycerides (197.65 ± 26.94 mg/dL vs 132.36 ± 29.56 mg/dL), and total cholesterol (51.67 ± 6.03 mg/dL vs 28.37 ± 1.76 mg/dL) levels (all $p < 0.05$). Histological examination showed MetALD mice having increased steatosis grade (3.00 ± 0.00 vs 1.50 ± 0.50) and Oil Red O-stained area (1.87 ± 0.37 vs 1.13 ± 0.25) (all $p < 0.05$). Gut microbiota analysis based on 16S rRNA sequencing revealed no significant differences in α-diversity between MetALD and MASLD groups. Although principal coordinate analysis (PCoA) indicated that the MASH diet was the dominant factor shaping microbiota variation, with alcohol exposure exerting a comparatively modest effect, permutational multivariate analysis of variance (PERMANOVA) based on Bray-Curtis distance still revealed a significant difference in gut microbial composition between MetALD and MASLD mice (Adonis, R^2 = 0.214, p = 0.036). Linear discriminant analysis effect size (LEfSe) identified enrichment of

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Helicobacter and *Bilophila* at the genus level, as well as *Helicobacter ganmani* at the species level, in the MetALD group. Both *Helicobacter* and *Bilophila* have been reported to promote inflammation, intestinal barrier impairment and bile acid dysmetabolism, exacerbating hepatic steatosis. **Conclusion:** MetALD mice develop more severe hepatic injury, steatosis, and dyslipidemia than MASLD mice. The enrichment of *Helicobacter* and *Bilophila* at the genus level, as well as *Helicobacter ganmani* at the species level, in MetALD mice may contribute to the progression of hepatic steatosis and dyslipidemia. *Supported by the Innovation and Technology Commission, HKSAR Government (ITS/046/22MS).*



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3037 | LONGITUDINAL ALCOHOL CONSUMPTION TRAJECTORIES AND INCIDENT CHRONIC LIVER DISEASE AMONG MIDDLE-AGED AND OLDER CHINESE ADULTS: A NATIONAL COHORT STUDY

Bowen Qin[1] Yue Zhang[1] Ruiyuan Zhang[1] Qiaoman Fei[1] Xiao Liang[1] Qian Wang[1] Huan Deng[1] Qi Shang[1] Yujiao Deng[1] Yi Liu[1] Haidan Shi[1] Yee Hui Yeo[2] Fanpu Ji[1], [1]The Second Affiliated Hospital of Xi'an Jiaotong University, [2]Cedars-Sinai Medical Center

Background: Alcohol consumption is a major modifiable risk factor for chronic liver disease (CLD), but most epidemiologic studies rely on single-time-point drinking assessments. Whether long-term drinking trajectories are associated with incident CLD among aging Chinese adults remains unclear. We examined the incidence of CLD and the associations of drinking history, drinking frequency, longitudinal drinking trajectories, and alcohol dose with incident CLD in a nationally representative cohort. **Methods:** This cohort study used nationally representative data from the China Health and Retirement Longitudinal Study (CHARLS). Middle-aged and older adults without baseline CLD or hepatitis B were followed from 2011 to 2018. Alcohol-related exposures included drinking history, drinking frequency, and longitudinal drinking trajectories across four survey waves, based on the presence or absence of moderate-to-heavy drinking (>210 g/week for men and >140 g/week for women). Incident CLD was defined as self-reported physician-diagnosed CLD identified through structured interviews. Multivariable logistic regression and restricted cubic spline models were used to estimate associations. **Results:** Among 10,384 participants without CLD at baseline, 698 developed CLD during follow-up, yielding a 7-year cumulative incidence of 6.7%. Among 10,384 participants without CLD at baseline, 698 developed CLD during follow-up, yielding a 7-year cumulative incidence of 6.7%. Kaplan–Meier analyses showed significantly higher cumulative incidence among ever drinkers than never drinkers (7.8%

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vs. 6.2%; log-rank P = 0.002), among daily drinkers than less-than-daily drinkers, and among participants with stable or escalating high-level and fluctuating drinking trajectories compared with those with stable low-level trajectories (Figure).After full adjustment, ever drinking (OR, 1.26; 95% CI, 1.04-1.52) and daily drinking (OR, 1.30; 95% CI, 1.02-1.66) were associated with higher odds of incident CLD. Compared with stable low-level drinking trajectories, stable or escalating high-level drinking (OR, 1.39; 95% CI, 1.02-1.90) and fluctuating drinking trajectories (OR, 1.34; 95% CI, 1.04-1.73) had higher odds of incident CLD. Restricted cubic spline analysis indicated a nonlinear dose–response association between alcohol intake and incident CLD (P-overall = 0.023; P-non-linearity = 0.040), with a more evident pattern in men but not women (Figure). Associations were generally consistent in subgroup and sensitivity analyses. **Conclusion:** Among middle-aged and older Chinese adults, the 7-year cumulative incidence of CLD was 6.7%. Drinking history, daily drinking, and unfavorable long-term drinking trajectories were associated with increased CLD risk. These findings support the value of incorporating dynamic alcohol-use patterns into liver disease risk assessment and prevention strategies in aging populations.

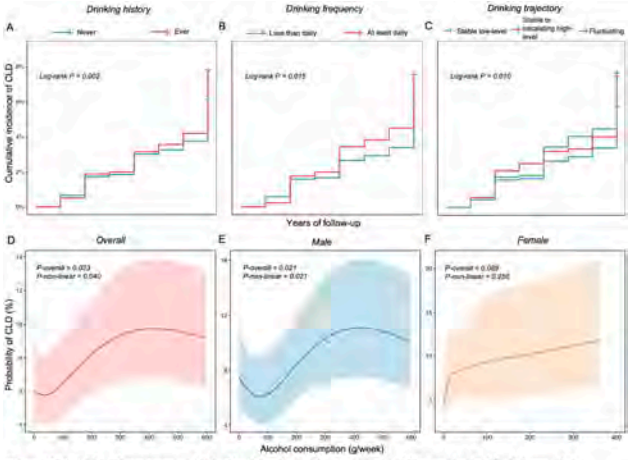


Figure. Alcohol-related exposures and risk of incident chronic liver disease in middle-aged and older Chinese adults.
(A–C) Kaplan–Meier cumulative incidence curves for incident chronic liver disease according to drinking history (A), drinking frequency (B), and drinking trajectory (C) in the overall population. Log-rank P values are shown in each panel. (D–F) Restricted cubic spline curves showing the dose–response association between average weekly alcohol consumption and the predicted probability of incident chronic liver disease in the overall population (D), men (E), and women (F). Shaded areas indicate 95% confidence intervals. Spline models were adjusted for age, sex, body mass index, diabetes, number of chronic conditions, marital status, educational attainment, place of residence, and smoking status. Participants with zero alcohol intake across all four survey waves were excluded from spline analyses.

Disclosures: Bowen Qin:Nothing to Disclose, Yue Zhang:Nothing to Disclose, Ruiyuan Zhang:Nothing to Disclose, Qiaoman Fei:Nothing to Disclose, Xiao Liang: Nothing to Disclose, Qian Wang:Nothing to Disclose, Huan Deng:Nothing to Disclose, Qi Shang:Nothing to Disclose, Yujiao Deng:Nothing to Disclose, Yi Liu: Nothing to Disclose, Haidan Shi:Nothing to Disclose, Yee Hui Yeo:Nothing to Disclose, Fanpu Ji:Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose.

3038 | HEALTHCARE-ASSOCIATED INFECTIONS ARE COMMON AND ASSOCIATED WITH EARLY MORTALITY IN SEVERE ALCOHOL-ASSOCIATED HEPATITIS: A CONTEMPORARY MULTICENTER STUDY

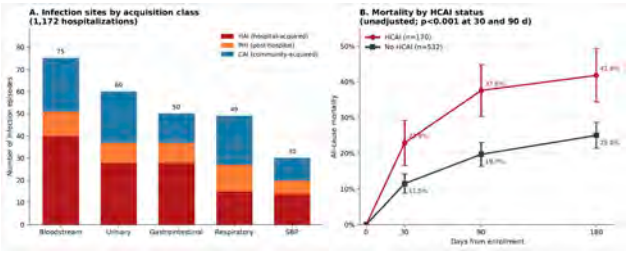
Douglas Simonetto[1] Wanzhu Tu[2] Srinivasan Dasarathy[3] Ashwani Singal[4] Amon Asgharpour[5] Juan Pablo Arab[5] Qing Tang[2] Nicole Welch[3] Vatsalya Vatsalya[4] Jacqueline O'Leary[6] Wanyu Zhang[4] Maiying Kong[4] Patrick Kamath[7] Ramon Bataller[8] Gyongyi Szabo[9] Craig McClain[4] Vijay Shah[1] Naga Chalasani[10] Mack Mitchell[11] Arun Sanyal[5] Samer Gawrieh[2], [1]Mayo Clinic Rochester, [2]Indiana University, [3]Cleveland Clinic, [4]University of Louisville, [5]Virginia Commonwealth University, [6]University of Texas Southwestern, [7]Mayo Clinic, [8]University of Pittsburgh, [9]Beth Israel Deaconess Medical Center, [10]Indiana University Medical Center, [11]University of Texas Southwestern Medical Center

Background: Patients with severe alcohol-associated hepatitis (sAH) are highly susceptible to infection due to immune dysfunction, frequent hospitalization, and exposure to immunomodulatory therapies. However, contemporary multicenter data describing the epidemiology, timing, and clinical risk factors for infection, particularly healthcare–associated infections (HCAI), remain limited. We aimed to characterize the burden and patterns of infection in sAH and identify factors associated with the development of HCAI. **Methods:** We performed a secondary analysis of two NIH-funded multicenter prospective studies (AlcHepNet and TREAT). Adults with sAH (MELD $\geq$ 20) and at least one hospitalization were included. All infections were systematically reviewed and categorized as community-acquired (CAI), hospital-acquired (HAI), or post-hospital (PHI); HCAI was defined as HAI plus PHI. Episode-level infection rates were calculated for all hospitalizations, while patient-level analyses assessed HCAI risk within 90 days. Multivariable logistic regression models evaluated associations between demographic and clinical factors and HCAI risk. **Results:** The cohort consisted of 702 subjects (mean age 45.0 ± 10.3 years; 59.4% male; MELD 27.8 ± 6.6), with 71.7% having ascites and 44.6% receiving corticosteroids, contributing to 1,172 hospitalizations. At the subject level, 35.9% of patients developed at least one infection, and 24.2% had at least one HCAI. Among 170 subjects with HCAI, 128 (75%) had a single episode, and 25% had two or more. Infections were predominantly bacterial (14.5%), followed by fungal (1.5%). Across 1,172 hospitalizations, HAI occurred in 11.1% of hospitalization episodes, CAI in 8.9%, and PHI in 4.6%. The most frequent HCAI sites were

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bloodstream (4.3%), urinary and gastrointestinal (3.2% each), respiratory (2.3%), and spontaneous bacterial peritonitis (1.7%). In multivariable logistic regression analyses, higher MELD score (OR = 1.05 per point, 95% CI: 1.01–1.08), elevated white blood cell count (OR = 1.03, 1.00–1.05), diabetes (OR = 2.88, 1.25–6.65), and higher body mass index (OR = 1.03 per kg/m², 1.00–1.06) were independently associated with increased risk of HCAI, whereas recent alcohol and corticosteroid use were not. In an unadjusted comparison, patients who developed HCAI had substantially higher short-term mortality than those without HCAI: 22.9% vs. 11.5% at 30 days and 37.6% vs. 19.7% at 90 days (both $p < 0.001$). **Conclusion:** In this contemporary multicenter cohort of sAH, infections were common and predominantly bacterial. One in four patients with HCAI experienced recurrent infection, and HCAI was associated with nearly 2-fold higher mortality at 30 and 90 days. Overall, infection risk appeared to be driven primarily by host and disease factors, including MELD, diabetes, and obesity, underscoring the need for better risk-stratified surveillance and prevention strategies.



Disclosures: Douglas Simonetto:Mallinckrodt: Consultant, BioVie: Consultant, Resolution Therapeutics: Consultant, Evive: Consultant, Iota: Consultant, Novo Nordisk: Consultant, Astra Zeneca: Consultant, Wanzhu Tu:Nothing to Disclose, Srinivasan Dasarathy:Nothing to Disclose, Ashwani Singal:Madrigal: Speaking and Teaching, Pleiogenix: Stock – privately held company, Pleiogenix: Consultant, CLD Foundation: Advisor, Medical Speaker's Network: Speaking and Teaching, Up-to-Date: Royalties or patent beneficiary, Medscape: Speaking and Teaching, University of Louisville School of Medicine: Employee, NIAAA: Grant/Research Support, Gastro Endo News: Executive role, Durect: Advisor, University of Louisville Health: Other, Amon Asgharpour:Galectin: Clinical Endpoint Committee, NovoNordisk: Advisor, Madrigal: Advisor, Chronic Liver Disease Foundation: Speaking and Teaching, Intercept: Consultant, Juan Pablo Arab: Nothing to Disclose, Qing Tang:Nothing to Disclose, Nicole Welch:Nothing to Disclose, Vatsalya Vatsalya: Nothing to Disclose, Jacqueline O'Leary:Genfit: Consultant, PharmaIn: Consultant, Mallinckrodt: Consultant, Wanyu Zhang:Nothing to Disclose, Maiying Kong: Nothing to Disclose, Patrick Kamath:Sequana: Advisor, NovoNordisk: Advisor, GSK: Advisor, Ramon Bataller: Nothing to Disclose, Gyongyi Szabo:CYTA Therapeutics: Consultant, Durect Corporation: Consultant, Pandion Therapeutics: Consultant, Pfizer: Consultant, Surrozen: Advisor, Evive: Advisor, Glympse Bio, Inc (acquired by Sunbird Bio): Advisor, Satellite Biosciences: Advisor, Zomagen Bioscience/Ventyx Biosciences: Consultant, Springer Nature Group: Royalties or patent beneficiary, UpToDate Inc: Royalties or patent beneficiary, Boehiringer Ingelheim: Honoraria, Intercept: Contract, NIAAA-NIA: Grant/Research Support, Novo Nordisk: Honoraria, Yale University School of Medicine: Consultant, Resolution Therapeutics: Consultant, US Patent No. 20110293: Intellectual Property, Craig McClain:Novo Nordisk: Speaking and Teaching, Intercept Pharmaceuticals: Grant/Research Support, Altimmune: Grant/Research Support, Target Pharma Solutions: Grant/Research Support, NIH: Grant/Research Support, VAMC: Grant/Research Support, VAMC: Employee, National Institutes of Health: Grant/Research Support, NovoNordisk: Speaking and Teaching, VAMC: Employee, VAMC: Grant/Research Support, Intercept Pharmaceuticals: Grant/Research Support, Target PharmaSolutions: Grant/Research Support, Vijay Shah:Boehringer Ingelheim: Consultant, GSK: Consultant, GENFIT SA: Consultant, Intercept Pharmaceuticals, Inc.: Advisor, Korro Bio, Inc.: Consultant, Novo Nordisk A/S: Consultant, Resolution Therapeutics, Ltd.: Advisor, Seal Rock Therapeutics, Ltd.: Consultant, Surrozen: Advisor, Dexcel Pharma Technologies, Ltd.: Consultant, Dimension Inx.: Advisor, Enveda: Consultant, Ochre Bio: Consultant, Satellite Biosciences, Inc.: Consultant, Naga Chalasani:Madrigal, Eccogene, Insitro, Boston Pharma, Chugai: Consultant, Zydus, GSK, Akero, Plaint, Altimmune: Consultant, Exact Sciences: Grant/Research Support, NIH: Grant/Research Support, Heligenics: Board member, investor, Avant Sante: Board member, investor, Ipsen, Biomea Fusion, Pfizer, Merck: Consultant, Mack Mitchell: Nothing to Disclose, Samer Gawrieh:Transmedics: Consultant, pfizer: Consultant, kowa: Consultant, spruce: Consultant, viking: Grant/Research Support, zydus: Grant/Research Support, dsm: Grant/Research Support, Sonicincytes: Grant/Research Support, Novo Nordisk: Consultant, GSK: Consultant.

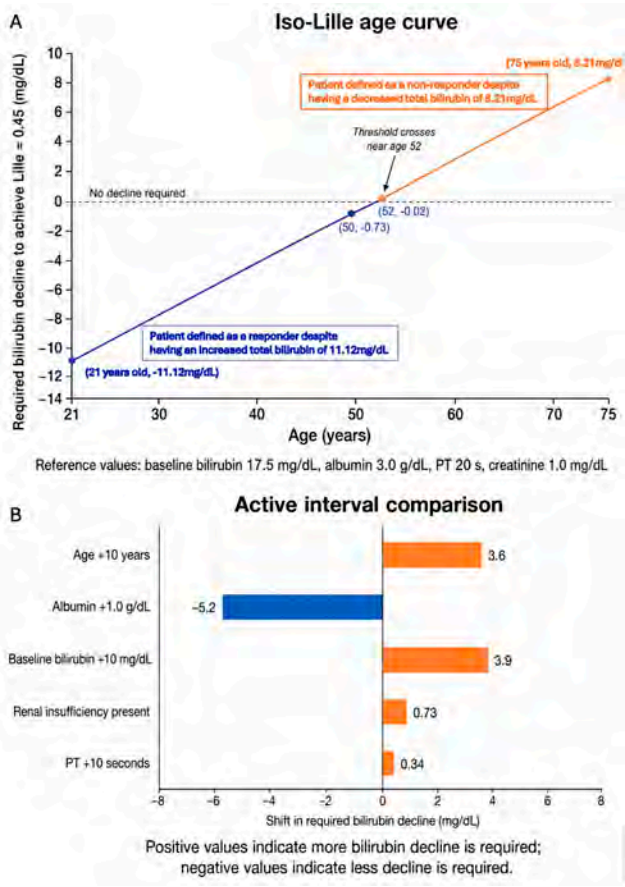
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3039 | REVISITING THE LILLE SCORE: HOW BASELINE CHARACTERISTICS MODIFY THE BILIRUBIN DECLINE REQUIRED TO DEFINE "CORTICOSTEROID RESPONSE"

Yee Hui Yeo[1], [1]Cedars Sinai Medical Center

Background: The Lille score is used to guide corticosteroid management in severe alcohol-associated hepatitis (AH), with the score ≤ 0.45 interpreted as a corticosteroid response. However, the model was originally developed as a mortality prediction tool. We hypothesized that the bilirubin decline required to achieve the conventional Lille threshold varies substantially across baseline characteristics, potentially conflating prognosis with biological treatment response. **Methods:** We performed an algebraic iso-threshold analysis of the 7-day Lille model by inverting the equation to estimate the bilirubin decline required to achieve Lille = 0.45 across values of age, albumin, baseline bilirubin, renal function, and prothrombin time (PT). Analyses used a reference patient with age 50 years, baseline bilirubin 17.5 mg/dL, albumin 3.0 g/dL, PT 20 seconds, creatinine 1.0 mg/dL, and no renal insufficiency. Required bilirubin decline was defined as baseline minus day-7 bilirubin. **Results:** In a reference patient aged 21 years, day-7 bilirubin could increase by up to 11.1 mg/d, and still meet the Lille response threshold, whereas at age 75, bilirubin needed to decrease by 8.2 mg/dL. Each additional year increased the required bilirubin decline by approximately 0.36 mg/dL. Albumin exerted a similarly large effect: each 1 g/dL increase reduced the required bilirubin decline by approximately 5.2 mg/dL. Patients with albumin 3.9 vs. 4.4 g/dL required markedly different bilirubin trajectories despite being within normal range. Renal dysfunction was modelled as a binary variable, producing an abrupt threshold effect with minimal additional penalty for severe renal failure beyond creatinine >1.3 mg/dL. Baseline bilirubin also modified the threshold, with each 10 mg/dL higher baseline bilirubin requiring approximately 3.9 mg/dL greater bilirubin decline. PT had a relatively narrow active interval. **Conclusion:** The bilirubin decline required to achieve Lille ≤0.45 varies substantially according to age, albumin, baseline bilirubin, renal insufficiency, and PT. The Lille score should be interpreted as a dynamic prognostic model rather than a measure of corticosteroid responsiveness. Clinicians should interpret Lille as a prognostic tool incorporating bilirubin or MELD score kinetics. To avoid unnecessary use of corticosteroids and increased risk of infection, shared decision making should be performed in those with a Lille score ≤ 0.45 but presents escalating bilirubin levels.



Disclosures: Yee Hui Yeo:Nothing to Disclose.

3040 | A DEEP-LEARNING MODEL DISTINGUISHES ALCOHOL-ASSOCIATED STEATOHEPATITIS FROM METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS ON ROUTINE H&E LIVER BIOPSY

Chady Meroueh[1] Vijay Shah[2] Samar Ibrahim[2], [1]Mayo Clinic, [2]Mayo Clinic Rochester

Background: Distinguishing alcohol-associated steatohepatitis (ASH) from metabolic dysfunction-associated steatohepatitis (MASH) on liver biopsy is challenging since there are no pathognomonic features. We developed a patch-based ResNet50 convolutional neural network using progressive layer unfreezing and evaluated it on an independent holdout cohort. **Methods:** A transfer learning approach using a ResNet50 model with MoCo v2 contrastive self-supervised learning was fine-tuned on 441 whole slide images (WSI) from H&E stained liver biopsies with steatohepatitis (441 patients, ASH n = 161, MASH n = 280; 40× magnification) using patient-level 5-fold cross-validation. The model was trained in 3 stages:

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Phase 1 updates only the final classification layer, Phase 2 updates layer 4 and classifier, and Phase 3 further updates layer 3, 4, and classifier. Performance was assessed on a separate, never-seen set of 140 WSI (140 patients, ASH n = 43, MASH n = 97). A WSI-level diagnosis was obtained by averaging the model's predictions across all patches, and were compared using DeLong's test (for AUROC) and McNemar's test (for changes in correct classification); effect size was quantified with Cohen's d. **Results:** Phase 1 achieved AUROC 0.587 ± 0.245 and balanced accuracy 0.557 ± 0.129. Phase 2, did not improve metric compared to phase 1. Phase 3 achieved an AUROC 0.863 ± 0.005, balanced accuracy 0.764 ± 0.045, sensitivity 0.651, specificity 0.866, PPV 0.724, and NPV 0.858 (AUROC improvement of +0.277, a large effect size [Cohen's d = 1.14]; DeLong p < 0.0001), outperforming Phase 1 in these metrics. Phase 3 corrected 25 biopsies and introduced 10 errors, a net gain of 15 (McNemar p = 0.018). Performance was strongly stage-dependent: advanced fibrosis (NASH CRN fibrosis stage 3 and 4: AUROC 0.907, balanced accuracy 0.862) outperformed early fibrosis (fibrosis stage < 3: AUROC 0.754, balanced accuracy 0.660), where early-stage ASH was sparse (training n = 54/441; holdout n = 10/140). **Conclusion:** Progressive fine-tuning of a MoCo v2-pretrained ResNet50 achieved an AUROC of 0.86 for ASH versus MASH discrimination on routine H&E at 40× in an independent 140-slide test set, a meaningful level of accuracy for a distinction that lacks pathognomonic features. This model will augment rather than replace a pathologist interpretation. Additional potential application include providing independent adjudication in diagnostically uncertain cases, and supporting patient selection for clinical trial enrollment. Discrimination was strongest in advanced fibrosis where ASH and MASH diverge most architecturally. Key limitations include the single-institution design and the small number of early-stage ASH biopsies. Future work will prioritize enrichment of early-stage ASH cases and multi-site, multi-scanner validation to establish reliability in the low-fibrosis setting and support prospective clinical integration.

Figure 1

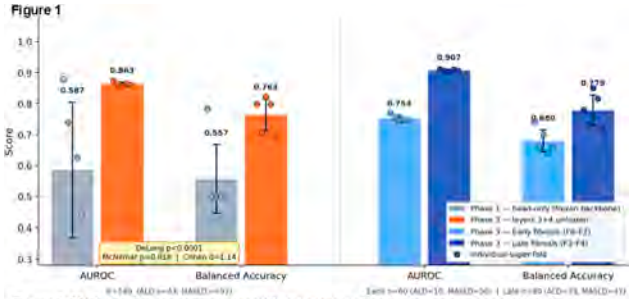


Figure 1. Model performance improves with progressive fine-tuning and varies by fibrosis stage. Compared with Phase 1, which showed variable and often near-chance performance, Phase 3 demonstrated substantially stronger discrimination between ASH and MASH on the separate holdout set of biopsies, with higher AUROC and balanced accuracy. Within Phase 3, performance was better in biopsies with advanced fibrosis than in early fibrosis, particularly for AUROC. This stage-dependent pattern suggests that disease-related histologic differences may be more visually pronounced in advanced fibrosis, whereas early-stage ASH and MASH may overlap more in appearance and fewer early-stage ASH cases were available for the model to learn from. Dots represent individual cross-validation results; bars summarize average performance.

Disclosures: Chady Meroueh:Nothing to Disclose, Vijay Shah:Boehringer Ingelheim: Consultant, GSK: Consultant, GENFIT SA: Consultant, Intercept Pharmaceuticals, Inc.: Advisor, Korro Bio, Inc.: Consultant, Novo Nordisk A/S: Consultant, Resolution Therapeutics, Ltd.: Advisor, Seal Rock Therapeutics, Ltd.: Consultant, Surrozen: Advisor, Dexcel Pharma Technologies, Ltd.: Consultant, Dimension Inx.: Advisor, Enveda: Consultant, Ochre Bio: Consultant, Satellite Biosciences, Inc.: Consultant, Samar Ibrahim: Nothing to Disclose, Nothing to Disclose.

3041 | PNPLA3 RS738409 AND CLINICAL MODIFIERS OF ADVANCED ALCOHOL-ASSOCIATED LIVER DISEASE IN THE ALL OF US RESEARCH PROGRAM

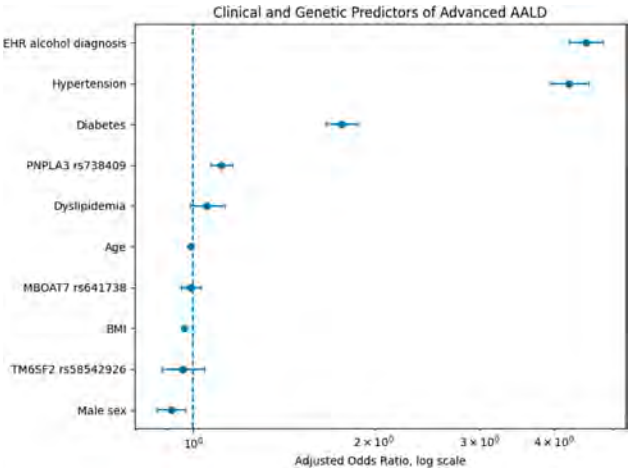
Ihunanya Kanu[1] Sarpong Boateng[2] Chimezirim Ezeano[3] Oladoyin Ogunbayo-Jolaoye[4] Omar Ebrahim Ibrahim[5] Peng-Sheng Ting[6], [1]Baptist Memorial Hospital- Golden Triangle, [2]Yale New Haven Health, Bridgeport Hospital, [3]Advocate Aurora Healthcare, [4]University of illinois College of Medicine, Chicago, IL, [5]Baptist Memorial Hospital - Golden Triangle, [6]Tulane University School of Medicine

Background: Alcohol-associated liver disease (AALD) is a growing cause of cirrhosis-related morbidity and mortality in the United States, yet only a subset of individuals with alcohol exposure progress to advanced disease. This variability suggests that clinical, metabolic, and genetic modifiers influence susceptibility. Variants in PNPLA3 rs738409, TM6SF2 rs58542926, and MBOAT7 rs641738 have been associated with hepatic steatosis, fibrosis, and alcohol-related cirrhosis, with PNPLA3 rs738409 being the most consistently replicated risk locus. However, their independent associations with advanced AALD in large U.S. cohorts with linked EHR, lifestyle survey, and WGS data remain incompletely characterized. We evaluated whether PNPLA3 rs738409 and other candidate variants modify advanced AALD risk in the All of Us Research Program. **Methods:** We conducted a retrospective cohort study using the All of Us Controlled Tier CDR v8. Adults aged ≥ 18 years with EHR data, lifestyle survey responses, and short-read WGS were included. Advanced AALD was defined using EHR diagnosis codes for cirrhosis, alcoholic hepatitis, portal hypertension, ascites, esophageal varices, hepatic encephalopathy, or hepatic failure. Alcohol exposure was assessed using AUDIT-C-derived survey responses and EHR-documented alcohol-related diagnoses. PNPLA3 rs738409, TM6SF2 rs58542926, and MBOAT7 rs641738 were extracted from short-read WGS data using Hail and modeled additively. The primary analytic cohort excluded competing liver disease etiologies. Data extraction used SQL/BigQuery, and analyses were performed in Python using pandas, NumPy, and statsmodels. Multivariable

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logistic regression adjusted for age, sex at birth, race, ethnicity, BMI, diabetes, hypertension, dyslipidemia, and EHR-documented alcohol-related diagnosis. **Results:** The primary analytic cohort included 259,549 adults, with 5,759 advanced AALD cases. EHR-documented alcohol-related diagnosis was strongly associated with advanced AALD (aOR 4.52, 95% CI 4.24–4.83, p < .001). Hypertension (aOR 4.23, 95% CI 3.93–4.56, p < 0.001) and diabetes (aOR 1.77, 95% CI 1.66–1.88, p < 0.001) were independently associated with advanced disease. Among candidate variants, PNPLA3 rs738409 remained independently associated with advanced AALD (per-allele aOR 1.11, 95% CI 1.07–1.16, p < 0.001). In contrast, TM6SF2 rs58542926 was not significantly associated (aOR 0.96, 95% CI 0.89–1.04, p = 0.334), and MBOAT7 rs641738 remained null (aOR 0.99, 95% CI 0.95–1.03, p = 0.608) **Conclusion:** PNPLA3 rs738409 remained independently associated with advanced AALD after excluding competing liver disease etiologies and adjusting for clinical, metabolic, alcohol-related, and sociodemographic factors. EHR-documented alcohol-related diagnosis, hypertension, and diabetes were the strongest clinical predictors, supporting combined clinical-genetic risk stratification for advanced AALD.



Disclosures: Ihunanya Kanu:Nothing to Disclose, Sarpong Boateng:Nothing to Disclose, chimezirim ezeano:Nothing to Disclose, Oladoyin Ogunbayo-Jolaoye:Nothing to Disclose, Omar Ebrahim Ibrahim:Nothing to Disclose, Peng-Sheng Ting:Nothing to Disclose.

3042 | AN ELECTRONIC HEALTH RECORD-BASED HONEST BROKER STRATEGY TO IDENTIFY AND ENGAGE PATIENTS AT RISK FOR ALCOHOL-ASSOCIATED LIVER DISEASE FOR AUD TREATMENT

Allison Kwong[1] John Mendelson[2] Ethan Akama-Garren[1] Amy Chieng[1] Molly Bowdring[1] Judith Prochaska[1], [1]Stanford University, [2]Ria Health

Background: Early identification and linkage to treatment for alcohol use disorder (AUD) can prevent progression to alcohol-associated liver disease (ALD). However, engaging patients with AUD in treatment remains challenging. We describe the novel implementation and yield of an electronic health record (EHR)-based honest broker recruitment strategy to identify and engage patients at risk for ALD for a telehealth AUD treatment trial. **Methods:** From 2024-2025, EHR screening criteria were used to identify adult participants at our institution who within the previous 14-90 days: (a) had at least one elevated ALT, AST, or GGT 1-3x ULN (AST/ALT 45-135 U/L, GGT 100-300 U/L) or (b) had a medical encounter with an associated AUD diagnosis. After initial demonstration of safety and acceptability, the range of abnormal ALT, AST or GGT was expanded to include abnormal values up to 5x ULN. The honest broker, serving as a confidential third party independent of the research team, sent a single study invitation to patients via the Epic MyHealth research portal, indicating their potential eligibility for a study providing telehealth-based AUD treatment (NCT #05747703). Given the sensitive nature of the study, our institutional Research Compliance, Privacy, and Patient Experience offices vetted the recruitment language prior to deployment. Patients who indicated interest were provided a link to complete a screening questionnaire to assess eligibility. Outcomes included the volume of invitations, rate of response, and rate of enrollment based on trial eligibility criteria (i.e. presence of AUD, exclusion of prior AUD treatment, and ability to engage in study procedures). **Results:** Honest Broker study invitations for the AUD treatment study were sent to 60,140 patients (17,739 based on elevated liver tests 1-3x ULN, 38,306 for liver tests 1-5x ULN, and 4,095 for an AUD-related encounter). In total, 471 (0.8%) expressed interest and were provided a link to the screening survey, 335 completed screening, 86 met study eligibility criteria, and 66 ultimately enrolled. Among eligible patients, the median age was 47 years (IQR 37-60), 70% were male, and the median AUDIT-C was 7 (IQR 4-12). Among those who enrolled and completed a MINI interview for alcohol use, 50% had severe AUD, 36% moderate AUD, and 14% mild AUD, with a median baseline PETH of 115 ng/mL (IQR 44-257). **Conclusion:** An EHR-wide honest broker recruitment strategy successfully identified and engaged patients at risk for ALD for participation in a clinical trial. This approach identified several hundred patients interested in AUD treatment and enrolled 66 participants with predominantly moderate-to-severe AUD, without any reported patient complaints. Beyond research recruitment, EHR-based screening using laboratory abnormalities or AUD diagnoses may represent a scalable strategy to improve AUD treatment uptake and reduce the burden of ALD.

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Disclosures: Allison Kwong:Nothing to Disclose, John Mendelson:Nothing to Disclose, Ethan Akama-Garren: Nothing to Disclose, Amy Chieng:Nothing to Disclose, Molly Bowdring:Nothing to Disclose, Judith Prochaska: Nothing to Disclose.

3043 | NEUROPSYCHIATRIC BURDEN ACROSS THE STEATOTIC LIVER DISEASE SPECTRUM: ALCOHOL-ASSOCIATED LIVER DISEASE IS INDEPENDENTLY ASSOCIATED WITH HIGHER DEPRESSIVE SYMPTOM BURDEN

Omar Albhaisi[1] Ayah Albhaisi[2] Lea Assaf[3] Ali Khan[1] Krishan Patel[1] Butros Fakhoury[1] Hannah Blaney[1] Luis Antonio Diaz[4] Juan Pablo Arab[1], [1]Virginia Commonwealth University, [2]Alexandria Faculty of Medicine, [3]American University of Beirut, [4]Pontificia Universidad Católica de Chile

Background: The neuropsychiatric burden across steatotic liver disease (SLD) phenotypes defined by the 2023 Delphi nomenclature remains poorly characterized. Whether depressive symptom burden differs across MASLD, MetALD, and alcohol-associated liver disease (ALD) independent of metabolic comorbidity, fibrosis severity, and binge drinking patterns is unknown. **Methods:** We analyzed 13,066 adults aged 18–80 years with vibration-controlled transient elastography from NHANES 2017–2023. SLD subtypes were classified using 2023 Delphi criteria. Primary outcomes were PHQ-9 total score and moderate-severe depression (PHQ-9 $\geq$10). Secondary outcomes included item-level depressive symptom domains and sleep characteristics. Survey-weighted regression models adjusted for demographics, BMI, diabetes, smoking status, and socioeconomic status. Fibrosis-adjusted models additionally incorporated liver stiffness measurement (LSM). Sensitivity analyses additionally adjusted for annual binge drinking status. **Results:** The analytic cohort included 5,732 MASLD, 286 MetALD, and 154 ALD participants (No SLD reference N = 6,894). Mean PHQ-9 scores progressively increased across No SLD (3.24), MASLD (3.54), MetALD (3.81), and ALD (4.91). After full adjustment, ALD was independently associated with higher depressive symptom burden versus No SLD (β = 1.45, 95% CI 0.50–2.41; p = 0.006), whereas MASLD showed a borderline association (β = 0.21; p = 0.057) and MetALD was not independently associated (β = 0.33; p = 0.386). Adjustment for fibrosis severity did not attenuate the ALD association (β = 1.46; p = 0.006; LSM p = 0.70). Additional adjustment for annual binge drinking status produced minimal attenuation (β = 1.43; p = 0.006), while binge drinking itself was independently associated with higher PHQ-9 score (β = 0.36; p = 0.011). Item-level analyses identified depressed mood (β = 0.32; p = 0.002), sleep disturbance (β = 0.29; p = 0.023), and diminished self-worth (β = 0.29; p = 0.008) as dominant symptom domains. **Conclusions:** Alcohol-associated liver disease is associated with disproportionately greater depressive symptom burden independent of fibrosis severity and binge drinking. These findings suggest neuropsychiatric burden in ALD extends beyond hepatic injury alone and support broader integration of neuropsychiatric assessment into alcohol-associated liver disease care pathways.

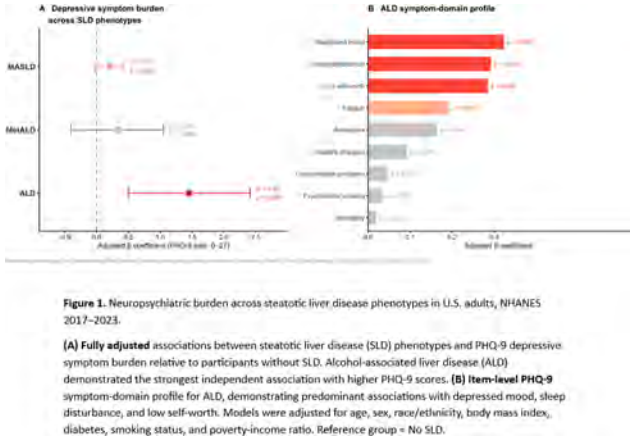


Figure 1. Neuropsychiatric burden across steatotic liver disease phenotypes in U.S. adults, NHANES 2017–2023.

(A) Fully adjusted associations between steatotic liver disease (SLD) phenotypes and PHQ-9 depressive symptom burden relative to participants without SLD. Alcohol-associated liver disease (ALD) demonstrated the strongest independent association with higher PHQ-9 scores. **(B) Item-level PHQ-9** symptom-domain profile for ALD, demonstrating predominant associations with depressed mood, sleep disturbance, and low self-worth. Models were adjusted for age, sex, race/ethnicity, body mass index, diabetes, smoking status, and poverty-income ratio. Reference group = No SLD.

Disclosures: OMAR ALBHAISI:Nothing to Disclose, AYAH ALBHAISI:Nothing to Disclose, Lea Assaf: Nothing to Disclose, Ali Khan:Nothing to Disclose, Krishan Patel:Nothing to Disclose, Butros Fakhoury: Nothing to Disclose, Hannah Blaney:Nothing to Disclose, Luis Antonio Diaz:Novo Nordisk: Consultant, Juan Pablo Arab:Nothing to Disclose.

3044 | THE POST-PANDEMIC "NEW NORMAL" IN U.S. LIVER MORTALITY: INTERRUPTED TIME-SERIES AND YEARS OF POTENTIAL LIFE LOST ANALYSES OF ALCOHOL-ASSOCIATED LIVER DISEASE, MASLD, AND HEPATITIS C, 1999–2024

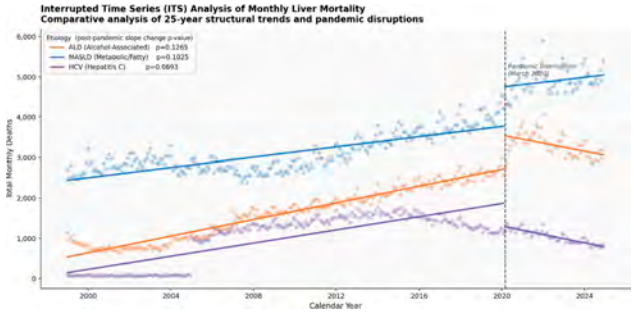
Nafiz Rashid[1] Sumaiyya Syeda[2] Sana Shaik[3] Muhammad Roshaan[4], [1]Dalian Medical University, [2]Gerogia National University, [3]Tbilisi State Medical University, [4]King Edward Medical University, Lahore

Background: Chronic liver disease mortality in the United States significantly changed in the face of COVID-19, but with incomplete definitions of the long-term post-pandemic trajectories of major causes. In this regard, we examined interrupted time-series (ITS)

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trends and years of potential life lost (YPLL) for alcohol-associated liver disease (ALD), metabolic dysfunction-associated steatotic liver disease (MASLD), and hepatitis C virus (HCV) mortality from 1999–2024. **Methods:** Monthly trends in US liver mortality were determined by ITS over 312 months (out of a total of 936 stand alone observations). Changes in structure after the pandemic were evaluated for ALD, MASLD and HCV mortality trajectories. YPLL analyses were also conducted to assess the burden of premature mortality among the different etiologies. **Results:** ITS analysis showed clear structural disruption from 2020, which stabilized mortality trajectories through 2024. Upon the peak mortality observed in 2021, there appeared no substantial downward recovery trend of ALD and MASLD post-pandemic and the overall reductions were plateauing period (ALD: $\chi^2 = 2.33$, $p = 0.1265$; MASLD: $\chi^2 = 2.67$, $p = 0.1025$). HCV mortality likewise could not recover its previous steep decline during the direct-acting antiviral period, an indication that prior enhancement trends had been disrupted ($\chi^2 = 3.30$, $p = 0.0693$). YPLL analyses showed that while MASLD was significant contributor to total number of people dying prematurely compared with ALD by absolute mortality in old age, ALD accounted for the largest proportion of premature mortality burden nationally. ALD accounts for almost half of total relative YPLL burden, indicating the high proportion of deaths among young & middle age populations. **Conclusion:** Post-pandemic liver mortality trends of mortality in the U.S. in the United States have stabilized under stable and consistently altered levels of death caused by major etiologies in the USA post-pandemic. ALD was reported to remain the leading factor for premature mortality burden, while prior improvements in HCV mortality did not fully recover until 2024. Such results could provide insights into future prevention and public health strategies for better liver disease outcomes for the population.



Disclosures: Nafiz Rashid:Nothing to Disclose, Sumaiyya Syeda:Nothing to Disclose, Sana Shaik: Nothing to Disclose, Muhammad Roshaan:Nothing to Disclose, Nothing to Disclose.

3045 | QUANTIFYING CUMULATIVE EXCESS ALCOHOL-ASSOCIATED LIVER DISEASE MORTALITY IN THE UNITED STATES, 2020–2024: A FORMAL INTERRUPTED TIME-SERIES ANALYSIS

Shabi Mohammadi[1] Muhammad Roshaan[2] Sumaiyya Syeda[3] Sana Shaik[4], [1]Shadan Institute of medical sciences, [2]King Edward Medical University, [3]Georgian National University, [4]Tbilisi State Medical University

Background: Mortality among alcohol-associated liver disease (ALD) patients increased in the United States in recent years, with worries that the COVID-19 pandemic may have led to further changes in mortality trajectories. This paper quantified cumulative excess ALD mortality between 2020 and 2024 and assessed trends by using interrupted time series (ITS) analysis to evaluate demographic differences. **Methods:** CDC WONDER mortality data of ALD (ICD-10: K70) were analyzed from 2010–2024. Expected mortality rates for 2020–2024 were estimated using pre-pandemic trends for 2010–2019. Excess mortality was calculated as the difference between observed and expected mortality. ITS regression was used to assess level and slope changes post 2020. Stratified analyses were performed by sex, age group, race/ethnicity. Overall, sex, and race analyses applied age-adjusted rates, and age-group analyses employed crude. **Results:** In the United States, an estimated 14,757 excess ALD deaths occurred between 2020 and 2024, translating to an overall excess mortality of 9.8%. The results of ITS analysis indicated that mortality level increased massively at 2020 (+2.35 per 100,000; $p < 0.001$) followed by gradual attenuation in the years to the next decade. The excess mortality rate peaked in 2021 and went higher than projected through 2023 with rates hovering even until 2023, nearing expected trends by 2024. Females had a proportional excess mortality that was larger than males, reflecting greater females (12.1% compared to 9.0%). Compared to all other age groups, the greatest proportional increase was seen in people aged 15–24 years (41.8%), followed by people aged 35–44 years (27.3%) with a proportionally higher increase, and in people aged 25–34 years (23.3%). American Indian/Alaska Native individuals had the most proportionate excess mortality (24.4%), whereas Asian/Pacific Islander individuals had the lowest positive excess mortality (8.3%) according to race/ethnicity. No sustained excess mortality was observed for adults aged ≥ 85 years. **Conclusion:** ALD mortality in the United States increased significantly above projected pre-pandemic trends during 2020–2024 and greater burden occurred among younger adults, females, and American Indian/Alaska Native populations. These

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results might support the need for targeted public health and preventive policies for high risk populations for ALD-related mortality.

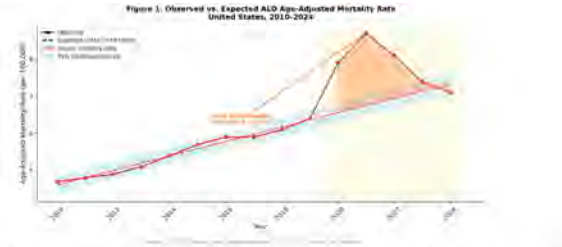


Figure 1. Observed versus expected alcohol-associated liver disease (ALD) age-adjusted mortality rates in the United States, 2010–2024. A solid line denotes observed ALD mortality rates from CDC WONDER data; the dashed line is expected mortality projected from the 2010–2019 pre-pandemic linear trend. The orange shaded area denotes excess mortality from 2020–2024, and the blue shaded band is the 95% prediction interval for expected rates. The total number of excess ALD deaths during this period was estimated at 14,757. Mortality rates were reported per 100,000 population and were age-adjusted to the 2000 U.S. standard population. ALD deaths were identified using ICD-10 code K70.

Disclosures: Shabi Mohammadi:Nothing to Disclose, Muhammad Roshaan:Nothing to Disclose, Nothing to Disclose, Sumaiyya Syeda:Nothing to Disclose, Sana Shaik:Nothing to Disclose.

3046 | HIGHER MEDITERRANEAN DIET ADHERENCE IS ASSOCIATED WITH LOWER LIVER FIBROSIS RISK ACROSS STEATOTIC LIVER DISEASE SUBTYPES

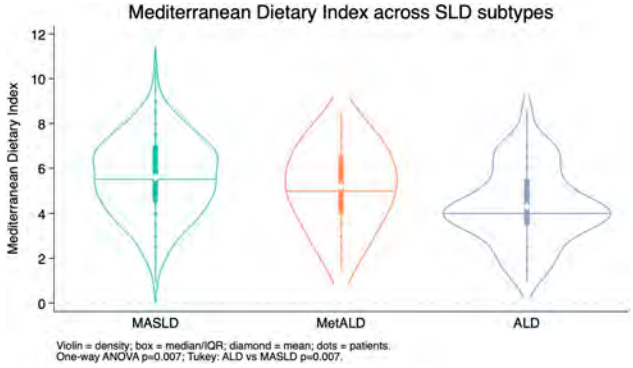
Luis Antonio Diaz[1] Francisco Idalsoaga[1] Mario Pessoa[2] Claudia Oliveira[3] Patricia Ziteli[3] Scherezada Mejia[4] Ezequiel Ridruejo[5] Mirta Peralta[6] César Castro[7] Jorge Garavito[7] Rommel Zambrano-Huailla[7] Gustavo Ayares Campos[1] Nancy Solis López[1] María Paz Orellana[1] Sebastian Marciano[8] Adrián Gadano[8] Jorge Martínez[8] Maria Jose Acosta[8] Martin Tagle[9] Hugo Cedron[9] Ismael Yepes[10] Dalis Perez[10] MaríaFernanda SaavedraChacón[11] Samuel Perez[11] Ignacio Garcia Juarez[12] Orfanel Sebastian Pineda-Arzate[13] Liz Toapanta-Yanchapaxi[13] Aline Sorribas[14] Manuel Mendizabal[14] Lorena Castro Solari[15] Loreto Aguilar Barría[16] Samantha Wu[16] Catalina Roa[16] Fabiana Nina[17] Estefanía Liza Baca[18] Javier Diaz Ferrer[18] Roberto Pérez Ravier[19] María Belen Martinez[19] Natalie Vilcinskas[19] Daniza Alexandra Contreras[20] Daniela Simian[21] Juan Roblero[22] Pamela Gil[21] Arun Sanyal[23] Juan Pablo Arab[23] Marco Arrese[1], [1]Pontificia Universidad Católica de Chile, [2]University of São Paulo, [3]Universidade de São Paulo, [4]Hospital Juárez de México, [5]Centro de Educación Médica e Investigaciones Clínicas Norberto Quirno "CEMIC, [6]Hospital Francisco J Muñiz, [7]Hospital Nacional Arzobispo Loayza, [8]Hospital Italiano de Buenos Aires, [9]Clínica Anglo Americana, [10]Centro Médico Gastropack, [11]Clínica CES, [12]The National Institute of Medical Science and Nutrition, [13]The National Institute of Medical Sciences and Nutrition, [14]Hospital Universitario Austral, [15]Clínica Universidad de los Andes, [16]Universidad de los Andes, [17]Universidad del Alba, [18]Hospital Nacional Edgardo Rebagliati Martins, [19]Hospital Central de Mendoza, [20]National Institute of Diabetes, Nutrition, and Endocrinology (INDEN), [21]Hospital Clínico Universidad de Chile, [22]University of Chile, [23]Virginia Commonwealth University

Background: The Mediterranean diet may play a protective role in steatotic liver disease (SLD), but this relationship remains poorly characterized in Latin America. This multinational study aims to identify the association between Mediterranean diet adherence and the risk of liver fibrosis across the SLD subtypes in Latin America. **Methods:** Cross-sectional analysis of prospectively enrolled adults with SLD (2023 criteria) at 16 tertiary centers in seven countries (Argentina, Brazil, Chile, Colombia, Dominican Republic, Mexico, and Peru). We recorded self-reported alcohol intake and the Chilean Mediterranean Dietary Index (MDI, adapted for regional use). Fibrosis was assessed by liver biopsy and/or vibration-controlled transient elastography (VCTE). Significant fibrosis was defined as $\geq$F2 on biopsy or VCTE $\geq$8 kPa (if biopsy unavailable). Analysis included a binary logistic regression, adjusted for age, sex, ethnicity, body mass index (BMI), type 2 diabetes mellitus (T2DM), MDI, and SLD subtype. **Results:** We included 491 participants (median age 59 [50–60] years; 52.8% women; 78.8% self-reported Hispanic). A total of 81.6% had MASLD, 9.6% MetALD, and 8.8% ALD. Significant fibrosis prevalence was 40.6%. The mean MDI was 5.5 ± 1.8, while by using predefined categories, 35.6% had low adherence, 62.7% had moderate adherence, and only 1.6% had high adherence. Mean MDI differed significantly across SLD subtypes (MASLD: 5.6 ± 1.7, MetALD: 5.2 ± 1.8, and ALD: 4.3 ± 1.7; $p < 0.001$) (**Figure**). In pairwise comparisons, MDI was significantly lower in ALD than in MASLD (mean difference −1.3; Bonferroni-adjusted $p < 0.001$) and MetALD (mean difference −0.9; Bonferroni-adjusted $p = 0.048$). Higher MDI adherence was independently associated with lower odds of significant fibrosis, with each 1-point increase linked to a 17% reduction in odds after adjustment (aOR 0.83; 95% CI 0.74–0.94; $p = 0.003$). **Conclusion:** In this well-characterized multinational Latin American cohort of adults with SLD, Mediterranean diet adherence was suboptimal and differed significantly across SLD subtypes, with the lowest adherence observed in ALD. Higher MDI was independently associated with lower odds of significant fibrosis, supporting the potential role of Mediterranean diet as a modifiable factor across the

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SLD spectrum (FONDECYT 1241450).



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3047 | HEAVY DRINKING PATTERNS AND MULTISYSTEM ALCOHOL-ASSOCIATED DISEASE: A GLOBAL ECOLOGICAL STUDY

Denisse Rubio Cruz[1] Ximena Parraga[2] Kriti Soni[2] Tulio Correa[3] Hyundam (Dami) Gu[2] Rylyn Reyes[2] Adelina Horhat[4] Joshua Chen[2] S. Fisher Rhoads[2] Vinay Jahagirdar[2] Kavin Parmar[2] Krishan Patel[2] Stephen Hoang[2] Luis Díaz[5] Juan Pablo Arab[2], [1]Lahey Hospital; Virginia Commonwealth University, [2]Virginia Commonwealth University, [3]University of Pittsburgh, [4]Department of Hepatology, Henri Mondor University Hospital, [5]Pontificia Universidad Católica de Chile

Background: Alcohol consumption contributes to multisystem cellular injury and has been associated with several malignancies and cardiovascular diseases, including hepatocellular carcinoma (HCC), laryngeal cancer, esophageal cancer (EC), colorectal carcinoma (CRC), and alcohol-associated cardiomyopathy (ACM). Global sex-specific drinking patterns and their relationship with the distribution of these diseases remain incompletely characterized. **Methods:** An ecological analysis including 184 countries across World Health Organization (WHO) regions was conducted for the aforementioned diseases. Heavy episodic drinking (HED), heavy continuous drinking (HCD), and sex-related differences in alcohol exposure patterns were evaluated. Radar plots and correlation heatmaps were used to reveal regional drinking profiles and explore potential relationships between alcohol exposure patterns and disease prevalence. **Results:** HED and HCD stratified by sex demonstrated distinct regional patterns. Male HED represented the most pronounced drinking behavior globally, whereas female HCD had the lowest overall prevalence and the least regional variability. Male HED, female HED, and male HCD were most prevalent within the European Region and the Region of the Americas. Correlation analyses exhibited overall modest relationships, where HCD in both sexes showed relatively stronger correlations with HCC compared with HED. A modest alignment was observed for female HCD with CRC and female HED with ACM. In contrast, EC showed minimal correlation with all the evaluated drinking patterns. Interestingly, geographic concordance between alcohol exposure patterns and disease prevalence was more pronounced among conditions with stronger established epidemiologic associations with alcohol use. **Conclusion:** This study provides an exploratory ecological characterization of sex-related drinking patterns and alcohol-associated disease burden across multiple organ

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systems. Despite subtle correlations, it is a close insight to global patterns integration. More studies are needed to better characterize the mechanisms underlying these relationships.

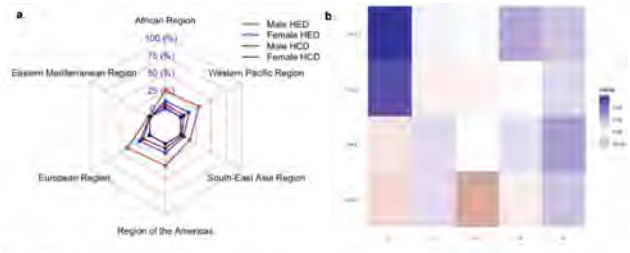


Figure 1a. Regional drinking patterns stratified by sex; each level represents a different percentage of the prevalences per zone. **b.** Correlation between sex-specific patterns and disease burden for different conditions. Drinking patterns include: heavy continuous drinking for females (hcd_f), heavy continuous drinking for males (hcd_m), heavy episodic drinking for females (hed_f), heavy episodic drinking for males (hed_m). Diseases evaluated include: hepatocellular carcinoma (hc), laryngeal cancer (lc), esophageal cancer (ec), colorectal cancer (cc), alcoholic cardiomyopathy (ac); darker colours represent stronger associations between each other.

Disclosures: Denisse Rubio Cruz:Nothing to Disclose, Ximena Parraga:Nothing to Disclose, Kriti Soni:Nothing to Disclose, Tulio Correa:Nothing to Disclose, Hyundam (Dami) Gu:Nothing to Disclose, Rylyn Reyes:Nothing to Disclose, Adelina Horhat:Nothing to Disclose, Joshua Chen:Nothing to Disclose, S. Fisher Rhoads:Nothing to Disclose, Vinay Jahagirdar:Nothing to Disclose, Kavin Parmar:Nothing to Disclose, Krishan Patel:Nothing to Disclose, Stephen Hoang:PS Fertility: Consultant, Remedy Plan Inc. Consultant, Luis Díaz:Nothing to Disclose, Juan Pablo Arab:Nothing to Disclose.

3048 | AI-DRIVEN HISTOPATHOLOGY AND MACHINE LEARNING FOR MORPHOLOGICAL ANALYSIS OF DUCTULAR REACTION AND PREDICTING HEPATIC VENOUS PRESSURE GRADIENT IN ALCOHOL-ASSOCIATED HEPATITIS

Ankita Srivastava[1] Meritxell Cots[2] Ramon Bataller[3] Rajanikanth Vadigepalli[4], [1]Thomas Jefferson University, [2]Vall d'Hebron Institute of Research, Universitat Autònoma de Barcelona, [3]Hospital Clinic of Barcelona, University of Barcelona, Barcelona, Spain, [4]University of New Mexico School of Medicine

Background: Alcoholic Hepatitis (AH) is a clinical syndrome characterized by acute-onset jaundice and liver enzyme abnormalities in the setting of long-term heavy alcohol use with high short-term mortality and limited therapies. AH is a frequent complication of alcohol-associated liver disease (ALD) that accounts for ~40% of liver transplantations. AH is characterized by hepatocellular insufficiency, immune activation, and aberrant proliferation of a biliary phenotype (cholangiocyte-like cells), referred to as the ductular reaction (DR). DR is both a hallmark of AH and a contributor to fibrotic remodeling and portal hypertension. Hepatic venous pressure gradient (HVPG) is the gold-standard measure of portal hypertension and a crucial prognostic indicator in cirrhosis; however, its role in AH is less defined. Since portal hypertension is a key consequence of AH, and DR has a characteristic morphology, we hypothesized that quantifiable morphological features of DR, extracted from histopathology images of the liver needle biopsies, could be used to predict HVPG levels in AH patients. **Methods:** We analyzed Cytokeratin 7 (CK7-DAB) stained whole slide images from 53 AH patients (fibrosis F1-F4) for general CK7+ objects, and 41 AH patients (F3-F4 fibrosis) for specific elongated and circular DR. We developed image analysis workflows, including AI-based U-Net segmentation for refined DR morphologies, to extract numerous shape and size parameters. Feature selection was based on correlation with HVPG. Tabular Prior-data Fitted Network (TabPFN) models, augmented with linear corrections, were used to predict HVPG. Models were evaluated using 80-20 train-test splits over 10 runs and compared to randomized data. **Results:** We identified CK7+ cellular objects with larger than 100 µm2 area and collated data on 43602 CK7+ cellular objects (751.76 ± 509.41; mean ± s.d. per image) across 53 images. For all CK7+ objects, the proportion of CK7-DAB area correlated with HVPG (r = 0.48), with poor prediction performance in model testing. When focusing on elongated and circular DR, the proportion of CK7-DAB area (r = 0.46) and elongated DR count (r = 0.31) also correlated with HVPG. This refined approach significantly improved prediction performance in testing (p-value = 0.0068), outperforming the general CK7+ model. **Conclusion:** Our machine learning approach demonstrates the potential to quantitatively relate the histopathological aspects of AH liver tissue to physiological variables associated with portal hypertension. These findings establish a link between histological remodeling and physiological dysfunction, opening new avenues for risk stratification and therapeutic decision-making in AH.

Disclosures: Ankita Srivastava:Nothing to Disclose, Meritxell Cots:Nothing to Disclose, Ramon Bataller: Nothing to Disclose, Rajanikanth Vadigepalli:Nothing to Disclose.

3049 | C5 COMPLOSOME IN HEPATIC MACROPHAGES IS REQUIRED FOR IMMUNOMETABOLIC SWITCHING REQUIRED FOR PROINFLAMMATORY POLARIZATION IN MODELS OF ALD

Shannon Kirkpatrick[1] James Roede[2] Rebecca McCullough[3], [1]University of Colorado, Anschutz

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Background: Complement activation and hepatic macrophages (HMs), including the resident Kupffer Cells (KCs) and monocyte-derived macrophages (MDMs), play critical roles in alcohol-associated liver disease (ALD) pathogenesis by initiating and maintaining non-resolving hepatic inflammation. During ALD, HMs respond to ethanol (EtOH) and gut-derived microbial-associated molecules [MAP; i.e. lipopolysaccharide (LPS)] by undergoing glycolytic shift required for proinflammatory polarization. The mechanisms underlying how immunometabolic switching initiates and sustains inflammatory HM phenotypes remain unclear. Intracellular complement activation (complosome) has emerged as a mediator of glycolytic switching required for inflammatory macrophage functions. We have shown that the C5 complosome contributes to inflammatory polarization by EtOH and MAP exposure. It is unclear if EtOH-induced C5 complosome activation can impact mitochondrial function following metabolic stress in models of EtOH exposure. **Methods:** C5 complosome components in HMs were assessed by scRNA-seq data from severe alcohol-associated hepatitis (sAH) and healthy control (HC) patients and from EtOH exposed mice. C5/C5aR1 KO immortalized mouse KCs (ImKCs) and C5aR1 antagonists (PMX205, cell-impermeable; JPE1375, cell-permeable) were used to interrogate the C5 complosome in EtOH- and LPS-driven glycolytic shift. Seahorse XF mitochondrial stress testing and Western blotting of glycolytic enzymes assessed metabolic shifts, and MitoSOX was used to quantify mitochondrial superoxide. **Results:** Cell clustering defined by HM lineage markers revealed that sAH macrophages exhibit enhanced expression of C5aR1, with the highest expression in MDMs and neo-KCs when compared to other AH HMs and HC MDMs. HMs from mice exposed to 5% EtOH feeding had increased proportions and mean expression of C5aR1. In human and mouse, C5aR1 expression in HMs were positively associated with proinflammatory and glycolytic gene expression. In WT ImKCs, LPS alone, and with EtOH, suppressed basal, maximal, and ATP-linked respiration but all parameters were restored in EtOH- and LPS-treated C5 KO and C5aR1 KO ImKCs. C5 KO and C5aR1 KO ImKCs were protected against EtOH- and LPS-induced expression of glycolytic enzymes, PFKb3 and TPI. C5aR1 antagonist pretreatment suppressed EtOH- and LPS-induced superoxide production; notably, the JPE1375 achieved greater suppression than the PMX205, implicating intracellular C5aR1 signaling in superoxide generation. **Conclusion:** In summary, human and mouse ALD is defined by enhanced HM C5aR1 expression. Pharmacologic blockage and genetic deficiency indicate a pivotal role for the C5 complosome in glycolytic shift by alcohol. Future directions include profiling how HMs specific expression of the C5 complosome influences downstream effects of mitochondrial dysfunction in models of ALD.
Disclosures: Shannon Kirkpatrick:Nothing to Disclose, James Roede:Nothing to Disclose, Rebecca McCullough:Nothing to Disclose.

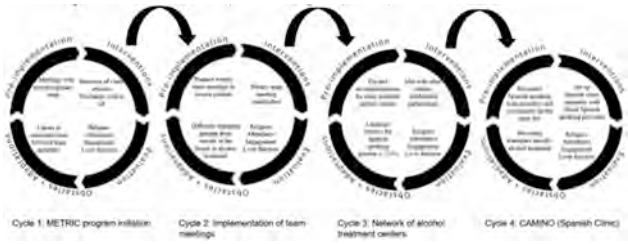
3050 | IMPROVING ENGAGEMENT IN ALCOHOL USE DISORDER TREATMENT THROUGH A MULTIDISCIPLINARY ALD CLINIC

Rebecca Roediger[1] Yael Belinkie[2] Melanie Hundt[2] Katherine Myers[1] Lisa Teh[3] Hamza Sadhra[4] Jessica Jang[5] Alexander Vogel[4] Brett Fortune[6] Kristina Chacko[4], [1]Weill Cornell Medicine, [2]Montefiore Medical Center, [3]Montefiore Einstein Medical Center, [4]Montefiore Einstein, [5]Albert Einstein School of Medicine, [6]Miami Transplant Institute/Jackson Health

Background: Treatment for alcohol-related liver disease (ALD) requires abstinence and therefore addressing alcohol use disorder (AUD). Nationally only 14% of patients with ALD enroll in alcohol treatment and only 10% receive medications for alcohol use disorder (MAUD)[1] . Of ALD patients referred to AUD treatment by a hepatologist, only 35% get connected with care[2] . Multidisciplinary ALD clinics allow patients to receive concurrent ALD and AUD treatment, however time and staffing constraints limit the frequency and extent of targeted interventions. Montefiore Einstein has created the METRIC clinic, which provides multidisciplinary care for ALD within a transplant program while connecting patients to partner AUD treatment programs where they receive more extensive outpatient care. **Methods:** METRIC was implemented to support patients with high-risk alcohol use throughout the liver transplant process. METRIC includes a hepatologist, psychologist, psychiatrist, pharmacist, social workers, dietitian, and certified recovery peer. All METRIC patients are offered MAUD and referred to AUD treatment, which provides counseling, peer support, psychiatry, and psychotherapy services. METRIC has undergone iterative improvements to better serve our patients. We first targeted engagement with our partner outpatient AUD program by implementing weekly meetings to address barriers before missed appointments. Once patients were reliably attending our partner program in the Bronx, we created a network of alcohol treatment centers throughout our catchment area to broaden access. We then sought to address the nearly 25% of our patients whose preferred language is Spanish by creating a variant of METRIC where all providers speak Spanish fluently, allowing the entire visit to be conducted in the patient's preferred

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language. **Results:** METRIC served 82 patients from December 2023 to December 2025. They reflect our diverse community with 65% male, 50% Hispanic, 29% Caucasian and 13% Black. We have a 78% attendance rate and reschedule all missed or cancelled appointments. 69% of our patients have verified attendance at an alcohol treatment program and 76% are taking MAUD. Of METRIC patients referred to our partner AUD program in the Bronx, 82% completed an intake assessment compared to 37% of referrals from non-METRIC sources. After completing an intake, 94% of METRIC referrals enrolled in treatment, and of those 40% have successfully completed their AUD treatment and 43% remain actively engaged.Of patients who attended METRIC pre-transplant, 45% have undergone liver transplant, 21% remain listed for transplant, and 18% became too well for transplant as a result of abstinence. **Conclusion:** We have created a successful multidisciplinary clinic which treats transplant pathway patients with AUD by both integrating alcohol use treatment into the transplant team and bridging patients to outpatient AUD treatment programs.



Disclosures: Rebecca Roediger:Nothing to Disclose, Yael Belinkie:Nothing to Disclose, Melanie Hundt: Nothing to Disclose, Katherine Myers:Nothing to Disclose, Lisa Teh:Nothing to Disclose, Hamza Sadhra:Nothing to Disclose, Jessica Jang:Nothing to Disclose, Alexander Vogel:Nothing to Disclose, Brett Fortune:WL Gore and Associates: Consultant, BD Medical: Consultant, Madrigal Pharm: Consultant, Gilead Sciences: Consultant, Madrigal Pharma: Consultant, WL Gore and Associates: Consultant, BD medical: Consultant, Novo Nordisk: Consultant, Ipsen Pharmaceuticals: Consultant, Kristina Chacko:Nothing to Disclose.

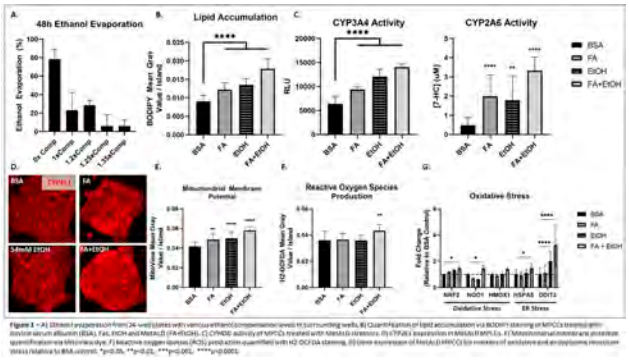
3051 | MODELING HEPATIC DYSFUNCTIONS CAUSED BY METALD USING A HUMAN MICROPHYSIOLOGICAL SYSTEM

Owen Lally[1] Salman Khetani[2], [1]University of Illinois Chicago, [2]University of Illinois at Chicago

Background: Rising rates of obesity combined with prevalent alcohol use have increased the prevalence of metabolic dysfunction-associated steatotic liver disease with increased alcohol intake (MetALD), a disease classification associated with faster disease progression and poor clinical outcomes. However, animal models do not always suffice to investigate the progression of human MetALD, thereby necessitating in vitro human-relevant models. Thus, we utilized micropatterned cocultures (MPCCs) of primary human hepatocytes (PHH) and fibroblasts to investigate the synergistic effects of ethanol (EtOH) and fatty acids (FA) on hepatic function and disease phenotypes. **Methods:** MPCCs were fabricated using established protocols. Briefly, polydimethylsiloxane (PDMS)-based soft lithography was used to pattern collagen I into circular domains (500 µm diameter, 800 µm spacing center-to-center) within multiwell plates. PHHs adhered to the collagen domains and were subsequently surrounded by stromal fibroblasts to stabilize functions for 3+ weeks. MPCCs were exposed to metabolic stressors associated with MASLD, including glucose, insulin, a mixture of saturated and unsaturated fatty acids (FA), and pharmacologically relevant EtOH concentrations for 2 weeks. To reduce EtOH evaporation during daily media exchange, a PDMS sheet was bonded to the plate lid to minimize the air space between the plate bottom and lid; furthermore, EtOH at 1.35X the concentration used for cell treatment was placed in cell-free wells (Fig. 1A). Hepatic CYP450 activity, albumin and urea secretions, steatosis, insulin resistance, and oxidative stress were measured using established assays, while RT-qPCR was used for gene expression analysis. **Results:** While excess glucose induced hepatic steatosis, it did not affect insulin sensitivity or CYP450 activities (not shown). EtOH and FAs, individually, however, did induce steatosis, caused insulin resistance, and altered CYP450 activities. A combination of these triggers (MetALD) produced significantly greater steatosis than either condition alone (Fig. 1B) and resulted in the greatest induction of CYP450 activities and expression (Fig. 1C, D). MetALD also altered EtOH metabolism (not shown), elevated mitochondrial membrane potential (Fig. 1E), increased oxidative stress (Fig. 1E, F), and increased the expression of oxidative stress markers Nrf2 and NQO1 (Fig. 1G). **Conclusion:** MPCCs exposed to physiologically relevant concentrations of FAs and EtOH exhibited additive effects on lipid accumulation and CYP450 induction, as well as synergistic disruption of EtOH metabolism and mitochondrial function, effects not observed with either treatment alone. These findings implicate oxidative stress as a key driver of MetALD-associated hepatocyte dysfunction and position MPCCs as a human-relevant platform for investigating MetALD mechanisms and evaluating therapeutic strategies.

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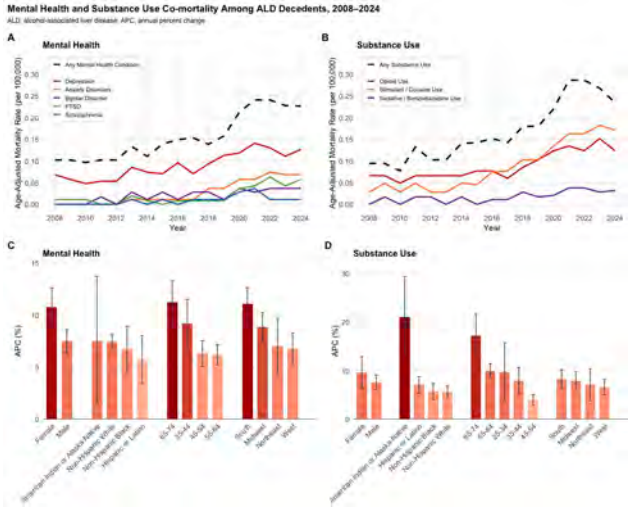


Disclosures: Owen Lally:Nothing to Disclose, Salman Khetani:Nothing to Disclose.

3052 | RISING MENTAL HEALTH AND SUBSTANCE USE COMBINED MORTALITY WITH ALCOHOL-ASSOCIATED LIVER DISEASE IN THE UNITED STATES, 2008–2024

William Oles[1] Jessica Rubin[1] Courtney Sherman[1], [1]University of California, San Francisco (UCSF)

Background: Alcohol-associated liver disease (ALD) is a leading cause of liver-related mortality in the United States. Despite clinical recognition of the psychiatric and substance use comorbidity burden in ALD, contributions to combined mortality have not been characterized nationally. **Methods:** Using the CDC WONDER database (2008–2024) and associated ICD-10 codes, we identified all-cause deaths for which ALD and leading mental health diagnoses (depression, anxiety disorders, bipolar disorder, PTSD, schizophrenia) or substance use (opioid, stimulant, sedative-hypnotic; alcohol excluded) were listed as contributing causes. Annual percent change (APC; 95% CI) in age-adjusted mortality rate (AAMR) was calculated using Joinpoint regression to analyze temporal trends. Analyses were stratified by gender, age, race and ethnicity, and region. **Results:** Co-morbid mental health conditions and substance use accounted for 7,762 and 8,016 ALD deaths between 2008 and 2024, respectively. During this period, the AAMR for mental health mortality increased from 0.10 to 0.23 (APC: 6.5%; 5.2–7.8), while the AAMR for substance use mortality increased from 0.09 to 0.23 (APC: 8.0%; 6.4–9.7). Mortality associated with both mental health and substance use significantly increased in 2019 before plateauing in 2021 (Figure). Depression accounted for 60% of mental health mortality; however, acceleration was greater for anxiety disorders (APC: 15.8%; 13.7–17.9) than depression (APC: 6.3%; 4.4–8.2). Opioid use accounted for 53% of substance use mortality; however, acceleration was greater for stimulant use (APC: 13.7%; 10.5–16.9) than opioid use (APC: 6.1%; 4.2–7.9), with associated AAMR surpassing opioids by 2017. Maximum AAMR for mental health mortality was seen in males, Non-Hispanic Whites, ages 55–64, and those in the West. Maximum AAMR for substance use mortality was similarly distributed, with the exception of Hispanic or Latino and American Indian or Alaska Native (AIAN) populations experiencing greater mortality than Non-Hispanic Whites. The steepest increases across all co-involved mortality occurred in females, ages 65–74, those in the South, and AIAN individuals. **Conclusion:** Mortality from ALD with co-morbid mental health conditions or substance use increased between 2008 and 2024. Temporal analyses suggest that rates rose steadily before increasing rapidly after 2019, likely reflecting COVID-19-era care disruptions. While attention should be paid to historically predominant co-morbidities—such as depression and opioid use—we identified greater acceleration from stimulant use and anxiety disorders, with disproportionate impacts among females, older adults, those in the South, and Hispanic or AIAN individuals. These trends highlight the need for holistic ALD care and targeted interventions, particularly for underserved populations and regions.



Disclosures: William Oles:Nothing to Disclose, Jessica Rubin:Nothing to Disclose, Courtney Sherman: Nothing to Disclose.

3053 | DIAGNOSTIC ACCURACY OF ICD-10 CODES FOR ALCOHOL USE DISORDER IN A REAL-WORLD CIRRHOSIS COHORT: A MANUAL CHART VALIDATION STUDY

Maaz Arif[1] Eric Orman[2] LaKeisha Boyd[1] Yang Li[1] Deborupa Pal[1] Jing Su[1] Wanzhu Tu[1] Naga Chalasani[3] Archita Desai[1] Samer Gawrieh[1], [1]Indiana University

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School of Medicine, [2]Indiana University, [3]Indiana University Medical Center

Background: The accuracy of ICD-based AUD identification in administrative cirrhosis cohorts and real-world data is poorly characterized. We aimed to measure the performance of ICD-10–based AUD identification in the Indiana Cirrhosis Cohort (ICC), a statewide real-world cirrhosis registry derived from a large health information exchange. **Methods:** The total cohort included 10,227 subjects with compensated cirrhosis. ICD code-based AUD diagnosis was compared to manual chart review on a stratified sample from the ICC: 243 adults with an ICD-10 F10.x AUD code and 244 without. Clinical documentation including medication list, medical history, or AUD treatment history when available was reviewed for 18 months before and after the AUD diagnosis date (cases) or index cirrhosis date (non-cases). 200 charts were reviewed by 2 reviewers and the remaining by 1 reviewer. Reviewers were blinded to the AUD code status. A structured form covering 8 keyword categories was used to classify each chart on a 6-point ordinal scale, with "Definitely Yes" or "Probably Yes" treated as AUD-positive. Inter-rater reliability was assessed using weighted Cohen's kappa. A sensitivity analysis restricted AUD classification to 'Definitely Yes' and 'Definitely No' designations only. Subgroup analyses examined ICD performance by sex and race. **Results:** Among 487 patients, ICD-coded patients were younger (53.6 vs 61.9 years), more often male (62% vs 47%), more often had alcoholic etiology (55% vs 13%), and more often had Medicaid (43% vs 27%) with less Medicare (16% vs 35%) coverage than ICD-negative patients (all $p < 0.001$). During chart review, 77 (16%) had insufficient data for determination. Of the remaining 410, 238 (58%) were AUD-positive: 204 of 224 ICD-coded patients (91%) and 34 of 186 ICD-negative patients (18%). Inter-rater reliability on the dually reviewed subset was high (weighted Cohen's kappa 0.90, 95% CI 0.85–0.95). ICD-10 F10.x codes demonstrated an AUROC of 87% (95% CI 84–90%), sensitivity of 85.7% (95% CI 81.3–90.2), specificity of 88.4% (95% CI 83.6–93.2). Performance was preserved across sensitivity analysis that included "Definitely Yes" cases (sensitivity 88.0%, specificity 93.6%) and in males/females (sensitivities 84.8% and 86.9%, specificities 87.5% and 88.8%, respectively); estimates were similar in the Black subgroup (Panel A). AUD ICD-10 F10.x codes showed consistently high (>97%) negative predictive value (NPV) for AUD when applied to the entire ICC (F10.x AUD prevalence 13%) and across subgroups, but moderate positive predictive value (PPV) (48–68%) (Panel B). **Conclusion:** In a real-world cirrhosis cohort, ICD-10 F10.x codes are highly reliable to exclude AUD but when present show only moderate positive predictive value for AUD. Additional methods such as artificial intelligence or large language models may help improve the accuracy of AUD identification in structured administrative data of cirrhosis cohorts.

Table 1. Diagnostic accuracy of ICD-10 F10.x codes for alcohol use disorder identification across sensitivity and subgroup analyses.

Panel A. Sensitivity and specificity from the chart-reviewed sample (n=487)

	Primary	Sensitivity	Subgroup analyses			
Metric	Definitely or Probably Yes n = 410	Definitely Yes only n = 242	Male n = 223	Female n = 187	Black n = 30	Non-Black n = 355
Sensitivity, % (95% CI)	85.7 (81.3–90.2)	88.0 (83.6–92.4)	84.8 (78.6–90.5)	86.9 (79.7–94.1)	90.0 (78.3–100)	84.9 (80.0–89.8)
Specificity, % (95% CI)	88.4 (83.6–93.2)	93.6 (89.2–97.9)	87.5 (79.8–95.1)	88.8 (82.1–95.6)	85.0 (69.4–100)	88.7 (83.6–93.7)

Panel B. PPV and NPV when applied to the Indiana Cirrhosis Cohort, (compensated cirrhosis, n=10,227)

	Primary	Sensitivity	Subgroup analyses			
Metric	Definitely or Probably Yes	Definitely Yes only	Male	Female	Black	Non-Black
PPV, % (95% CI)	53.07 (47.73–63.41)	67.66 (52.95–85.89)	50.99 (35.62–66.81)	54.29 (40.82–68.26)	47.93 (27.75–74.13)	53.86 (47.23–64.69)
NPV, % (95% CI)	97.58 (94.85–98.55)	98.07 (95.55–98.91)	97.40 (95.49–98.89)	97.79 (94.19–98.99)	98.23 (94.13–100)	97.45 (94.63–98.97)

Disclosures: Maaz Arif:Nothing to Disclose, Eric Orman:Sitero: Consultant, Biovie: Advisor, Bausch Health: Consultant, Vertex: Consultant, Zydus: Consultant, Eccogene: Consultant, Zealand: Consultant, LaKeisha Boyd:Nothing to Disclose, Yang Li:Nothing to Disclose, Deborupa Pal:Nothing to Disclose, Jing Su: Nothing to Disclose, Wanzhu Tu:Nothing to Disclose, Naga Chalasani:Madrigal, Eccogene, Insitro, Boston Pharma, Chugai: Consultant, Zydus, GSK, Akero, Plaint, Altimmune: Consultant, Exact Sciences: Grant/Research Support, NIH: Grant/Research Support, Heligenics: Board member, investor, Avant Sante: Board member, investor, Ipsen, Biomea Fusion, Pfizer, Merck: Consultant, Archita Desai:Eli Lily: Consultant, Gilead: Grant/Research Support, Samer Gawrieh: Transmedics: Consultant, pfizer: Consultant, kowa: Consultant, spruce: Consultant, viking: Grant/Research Support, zydus: Grant/Research Support, dsm: Grant/Research Support, Sonicincytes: Grant/Research Support, Novo Nordisk: Consultant, GSK: Consultant.

3054 | TIMING AND TRAJECTORY OF ACUTE KIDNEY INJURY PREDICT MORTALITY IN ALCOHOL-ASSOCIATED HEPATITIS: RESULTS FROM THE GLOBAL ALCHEP CONSORTIUM

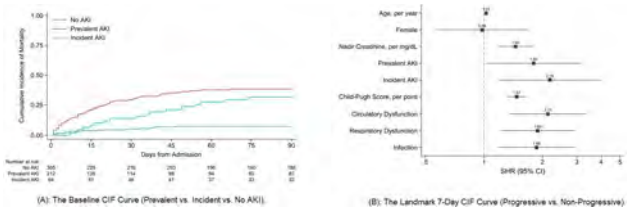
Butros Fakhoury[1] Ali Khan[1] Pojsakorn Danpanichkul[2] Omar Albhaisi[1] Kriti Soni[1] Ximena Parraga[1] Francisco Idalsoaga[3] Arun Valsan[4] Gowripriya Nair[4] Jorge Arnold[5] María Ayala-Valverde[6] Carolina Ramirez-Cadiz[1] Juan Pablo Roblero[7] Daniela Simian[7] José Antonio Velarde-Ruiz Velasco[8] Jacqueline Cordova-Gallardo[9] Manuel Mendizabal[10] Sebastian Marciano[11] Kristina Chacko[12] Lubomir Skladany[13] Michał Kukla[14] Arun Sanyal[1] Vijay Shah[15] Patrick Kamath[6] Marco

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Arrese[5] Winston Dunn[16] Ashwani Singal[17] Ramon Bataller[18] Luis Díaz[5] Juan Pablo Arab[1], [1]Virginia Commonwealth University, [2]Texas Tech University Health Sciences Center, [3]Western University, [4]Amrita Institute of Medical Sciences and Research Centre, [5]Pontificia Universidad Católica de Chile, [6]Pontificia Universidad Católica de Chile, Santiago, [7]Escuela de Medicina Universidad de Chile, [8]Hospital Civil de Guadalajara Fray Antonio Alcalde, [9]Hospital General Manuel Gea González, [10]Hospital Universitario Austral, [11]Hospital Italiano Buenos Aires, [12]Montefiore Medical Center, [13]Slovak Medical University, [14]University Hospital in Kraków, [15]Mayo Clinic, [16]University of Kansas Medical Center, Kansas City, [17]University of Louisville School of Medicine, [18]Hospital Clínic de Barcelona

Background: This prospective, multinational cohort study from the Global AlcHep Database stratified AH patients into three phenotypes: no AKI, prevalent AKI (at admission), and incident AKI (hospital-acquired). 90-day mortality was analyzed via multivariable competing-risks regression (liver transplantation as a competing event). A 7-day landmark analysis among survivors not receiving renal replacement therapy (RRT) evaluated early trajectory. Progression was defined as day 7 creatinine increasing $\geq$50% or $\geq$0.3 mg/dL from admission. **Methods:** This prospective, multinational cohort study from the Global AlcHep Database stratified AH patients into three phenotypes: no AKI, prevalent AKI (at admission), and incident AKI (hospital-acquired). The primary outcome was 90-day mortality, analyzed via multivariable competing-risks regression (treating liver transplantation as a competing event), adjusting for age, nadir creatinine, Child-Pugh score, circulatory/respiratory failure, and infection. A 7-day landmark analysis among 7-day survivors evaluated early renal trajectory. Progression was defined as day 7 creatinine increasing $\geq$50% or $\geq$0.3 mg/dL from admission; patients requiring renal replacement therapy were excluded from the landmark analysis to avoid trajectory confounding. **Results:** Among 581 patients (median age 48; 92% male), 52.5% had no AKI, 36.5% had prevalent AKI, and 11.0% developed incident AKI. Overall 90-day mortality was 18.2%. 42 patients (15.2% of those with AKI) required RRT, with 90-day mortality of 45.2%. Prevalent AKI was predominantly functional (84.4%), while incident AKI had significantly higher rates of structural/acute tubular necrosis (43.8% vs 10.4%, $p < .001$). Despite lower admission disease severity (median MELD 23.5 vs 31.7), incident AKI conferred an independent mortality risk (sHR 2.18, 95% CI 1.19–3.99) comparable to prevalent AKI (sHR 1.80, 95% CI 1.02–3.16). In the 7-day landmark analysis ($N = 457$), patients with prevalent AKI without progression (67.4%) had a mortality hazard statistically similar to those without AKI (sHR 1.27, $p = .52$). Conversely, progressive prevalent AKI carried the worst prognosis (sHR 3.34, 95% CI 1.44–7.77, $p = .005$). Infection and respiratory dysfunction strongly predicted mortality alongside progressive AKI. **Conclusion:** Both prevalent and incident AKI independently drive mortality in AH. Incident AKI confers equivalent risk despite lower baseline severity, enriched for intrinsic renal injury. Early renal trajectory provides essential prognostic discrimination: the absence of progression by Day 7 approximates outcomes of those without AKI, while progressive AKI identifies the highest-risk subgroup. These findings highlight the critical need for dynamic renal monitoring to guide early liver transplant evaluation and RRT considerations.



(A): The Baseline CIF Curve (Prevalent vs. Incident vs. No AKI). (B): The Landmark 7-Day CIF Curve (Progressive vs. Non-Progressive).

Disclosures: Butros Fakhoury:Nothing to Disclose, Ali Khan:Nothing to Disclose, Pojsakorn Danpanichkul: Nothing to Disclose, Omar Albhaisi:Nothing to Disclose, Kriti Soni:Nothing to Disclose, Ximena Parraga:Nothing to Disclose, Francisco Idalsoaga:Nothing to Disclose, Arun Valsan:Nothing to Disclose, Gowripriya Nair: Nothing to Disclose, Jorge Arnold:Nothing to Disclose, María Ayala-Valverde:Nothing to Disclose, Carolina Ramirez-Cadiz:Nothing to Disclose, Juan Pablo Roblero:Nothing to Disclose, Daniela Simian:Nothing to Disclose, José Antonio Velarde-Ruiz Velasco:Nothing to Disclose, Jacqueline Cordova-Gallardo:Nothing to Disclose, Manuel Mendizabal:Nothing to Disclose, Sebastian Marciano:Nothing to Disclose, Kristina Chacko:Nothing to Disclose, Lubomir Skladany:Worwag: Speaking and Teaching, ProMed: Speaking and Teaching, Abbvie: Speaking and Teaching, Gilead: Speaking and Teaching, RegPharm: Speaking and Teaching, Astellas: Speaking and Teaching, Michał Kukla: Nothing to Disclose, Arun Sanyal: Nothing to Disclose, Vijay Shah:Boehringer Ingelheim: Consultant, GSK: Consultant, GENFIT SA: Consultant, Intercept Pharmaceuticals, Inc. Advisor, Korro Bio, Inc. Consultant, Novo Nordisk A/S: Consultant, Resolution Therapeutics, Ltd. Advisor, Seal Rock Therapeutics, Ltd. Consultant, Surrozen: Advisor, Dexcel Pharma Technologies, Ltd. Consultant, Dimension Inx. Advisor, Enveda: Consultant, Ochre Bio: Consultant, Satellite Biosciences, Inc. Consultant, Patrick Kamath:Nothing to Disclose, Marco Arrese:Nothing to Disclose, Nothing to Disclose, Winston Dunn:Nothing to Disclose, Ashwani Singal:Madrigal: Speaking and Teaching, Pleiogenix: Stock – privately held company, Pleiogenix: Consultant, CLD Foundation: Advisor, Medical Speaker's Network: Speaking and Teaching, Up-to-Date:

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Royalties or patent beneficiary, Medscape: Speaking and Teaching, University of Louisville School of Medicine: Employee, NIAAA: Grant/Research Support, Gastro Endo News: Executive role, Durect: Advisor, University of Louisville Health: Other, Ramon Bataller: Nothing to Disclose, Luis Díaz:Nothing to Disclose, Juan Pablo Arab:Nothing to Disclose.

3055 | HEPATOCYTE-INTRINSIC FKBP5 DRIVES ALCOHOL-ASSOCIATED HEPATIC STEATOSIS THROUGH HSD17B7 STABILIZATION AND LIPID DROPLET BIOGENESIS

Hui Gao[1] Ge Zeng[2] Themis Thoudam[1] Yanchao Jiang[1] Nazmul Huda[1] Zhihong Yang[1] Jing Ma[1] Suthat Liangpunsakul[1], [1]Indiana University, [2]Indiana University; Southern Medical University

Background: Alcohol-associated liver disease (ALD) is a leading cause of liver-related morbidity and mortality worldwide. FK506-binding protein 5 (FKBP5) is a stress-responsive co-chaperone and scaffolding protein that modulates glucocorticoid receptor signaling, protein stability, and metabolic homeostasis. Notably, FKBP5 is robustly induced by both alcohol and cellular stress, and has emerging roles in lipid metabolism, insulin signaling, and the regulation of protein turnover via chaperone-assisted degradation pathways. We previously identified FKBP5 as a pathological driver of alcohol-induced liver injury; however, its hepatocyte-intrinsic mechanisms remain undefined. **Methods:** Hepatocyte-specific *Fkbp5* knockout (*Fkbp5*$^{\Delta Hep}$) mice and wild-type (WT) littermates underwent the chronic-plus-binge ethanol feeding model. Liver, blood, and and other relevant tissues were harvested 9 hours post-gavage for histological, biochemical, and transcriptomic analyses. FKBP5-interacting proteins were identified by co-immunoprecipitation coupled with mass spectrometry. Mechanistic studies employed overexpression and siRNA knockdown in AML12 hepatocytes, and in vivo rescue via AAV8-mediated hepatic Hsd17b7 reconstitution in *Fkbp5*$^{\Delta Hep}$ mice. **Results:** *Fkbp5*$^{\Delta Hep}$ mice were markedly protected from ethanol-induced hepatic steatosis, exhibiting significantly reduced liver triglyceride content and lipid deposition alongside suppression of the lipogenic program (ACC, FASN, CD36, cleaved SREBP1) at both mRNA and protein levels. Proteomic screening identified hydroxysteroid 17-beta dehydrogenase 7 (HSD17B7) as a novel FKBP5 partner: FKBP5 directly binds and stabilizes HSD17B7 by inhibiting ubiquitin-proteasome-mediated degradation. In AML12 cells, HSD17B7 overexpression exacerbated, while knockdown attenuated, ethanol-induced lipid accumulation in parallel with lipogenic gene expression. AAV8-mediated hepatic HSD17B7 restoration in *Fkbp5*$^{\Delta Hep}$ mice fully reversed the reductions in triglycerides and lipogenic proteins, abolishing the protective phenotype. Interestingly, confocal microscopy and lipid droplet (LD) fractionation revealed that HSD17B7 redistributes to and localizes to the LD surface under metabolic stress, an association that was markedly diminished in *Fkbp5*$^{\Delta Hep}$ livers and restored upon HSD17B7 reconstitution, implicating HSD17B7 as a FKBP5-dependent participant in LD membrane biogenesis (**Fig 1**). **Conclusion:** These findings establish a hepatocyte-intrinsic FKBP5–HSD17B7 signaling axis that coordinately drives lipogenesis and lipid droplet biogenesis in ALD. Targeting this pathway represents a novel therapeutic strategy for alcohol-associated hepatic steatosis.

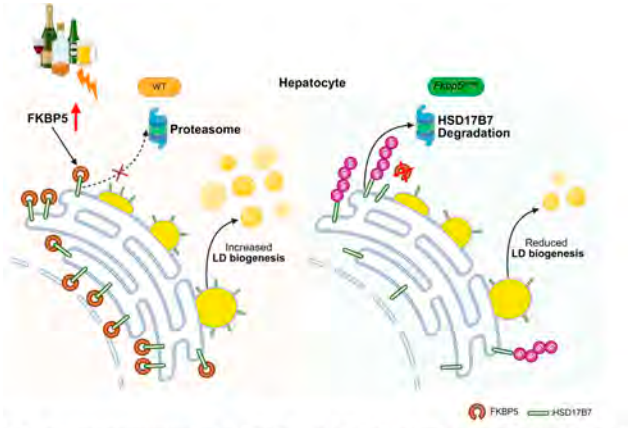


Fig 1. Mechanism of hepatocyte-intrinsic FKBP5–HSD17B7 axis in alcohol-associated hepatic steatosis. Alcohol consumption robustly induces FKBP5 expression, which directly interacts with and stabilizes HSD17B7 by inhibiting its ubiquitin-proteasome-mediated degradation. The stabilized HSD17B7 subsequently localizes to and enriches within lipid droplets (LD), driving LD biogenesis. Conversely, hepatocyte-specific deficiency of FKBP5 (*Fkbp5*$^{\Delta Hep}$) disrupts this interaction, compromising HSD17B7 stability and its enrichment on LDs, which ultimately attenuates lipid accumulation and protects against ethanol-induced steatosis.

Disclosures: Hui Gao:Nothing to Disclose, Ge Zeng: Nothing to Disclose, THEMIS THOUDAM:Nothing to Disclose, Yanchao Jiang:Nothing to Disclose, Nazmul Huda:Nothing to Disclose, Zhihong Yang:Nothing to Disclose, Jing Ma:Nothing to Disclose, Suthat Liangpunsakul:Durect Corporation: Consultant, Surrozen: Consultant, Korro Bio: Consultant, Durect Corporation: Consultant, Dimension Bio: Consultant.

3056 | FAS-ASSOCIATED FACTOR FAMILY MEMBER 2 AMELIORATES ALCOHOL-ASSOCIATED LIVER DISEASE VIA PROMOTION OF THE STEROID BIOSYNTHESIS PATHWAY

Norihiro Imai[1] Jingjing Zhang[2] Akiko Sugiyama[3] Dongming Liu[4] Hanna Kawecka[5] Michitaka Suzuki[6] Yuki Ohsaki[7] Shinya Yokoyama[2] Kenta Yamamoto[2] Takanori Ito[2] Yoji Ishizu[2] Takashi Honda[2] Michał Woźniak[5] David Cohen[8] Hiroki Kawashima[2], [1]Nagoya University Graduate School of Medicine, [2]Nagoya University, [3]Cedars Sinai Medical Center, [4]Tianjin

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Medical University Cancer Institute & Hospital, [5]Medical University of Gdańsk, [6]Fukushima Medical University, [7]Sapporo Medical University, [8]Cedars-Sinai Medical Center

Background: Genetic polymorphisms in Fas-associated factor family member 2 (FAF2) have been reported as protective factors that reduce the risk of liver cirrhosis in heavy drinkers. This study aimed to clarify the pathophysiological role of FAF2 in alcohol-associated liver disease (ALD). **Methods:** (1) RNA-sequencing data from liver tissues of patients with ALD were obtained from the NCBI Gene Expression Omnibus (GEO) database. Hepatic *FAF2* mRNA expression levels were compared between control and ALD groups. The datasets were integrated and stratified into high and low *FAF2* expression groups to identify gene expression profiles associated with differences in *FAF2* expression.(2) To further investigate the role of FAF2 in ALD pathogenesis, hepatocyte-specific FAF2 knockout mice (FAF2-LKO) generated using the LoxP-Cre system and their littermate controls were subjected to a chronic ethanol feeding plus binge administration model (NIAAA model). Both male and female mice were analyzed at 12 weeks of age. To evaluate the impact of aging-related metabolic changes, the same analyses were also performed in 12-month-old mice. **Results:** (1) Across all GEO datasets analyzed (GSE142530, GSE143318, GSE155907), hepatic *FAF2* mRNA expression was significantly higher in the ALD group than in controls. Integrated dataset analysis indicated that elevated *FAF2* mRNA expression was most strongly associated with modulation of the steroid biosynthesis pathway in the liver of patients with ALD. **:** (2) In the mouse model, FAF2-LKO mice exhibited a significantly increased liver-to-body weight ratio compared with control mice, along with elevated serum levels of free fatty acids and free cholesterol. Histopathological analysis revealed significantly exacerbated steatosis, predominantly in zone 2, in both male and female FAF2-LKO mice (male 4% vs. 16%; female 2% vs. 13%; both $P < 0.05$%), whereas no significant differences in liver fibrosis were observed. Similar findings were obtained in 12-month-old mice, in which steatosis was significantly more severe in FAF2-LKO mice (male 5% vs. 22%; female 4% vs. 24%; both $P < 0.05$), with no significant differences in fibrosis. RNA-sequencing of liver tissues demonstrated significant downregulation of *Stard4* (cholesterol transport-related) and *Hsd11b* and *Hsd17b* (steroid metabolism-related), along with suppression of the steroid biosynthesis pathway in FAF2-LKO mice. Metabolomic analysis further revealed alterations in lipid metabolism accompanied by broader reprogramming of amino acid metabolism, particularly involving aromatic amino acid pathways. **Conclusion:** These findings suggest that FAF2 promotes the steroid biosynthesis pathway, thereby suppressing lipid accumulation in hepatocytes during ALD progression. FAF2 may represent a novel therapeutic target for ALD through its role in regulating steroid metabolism.

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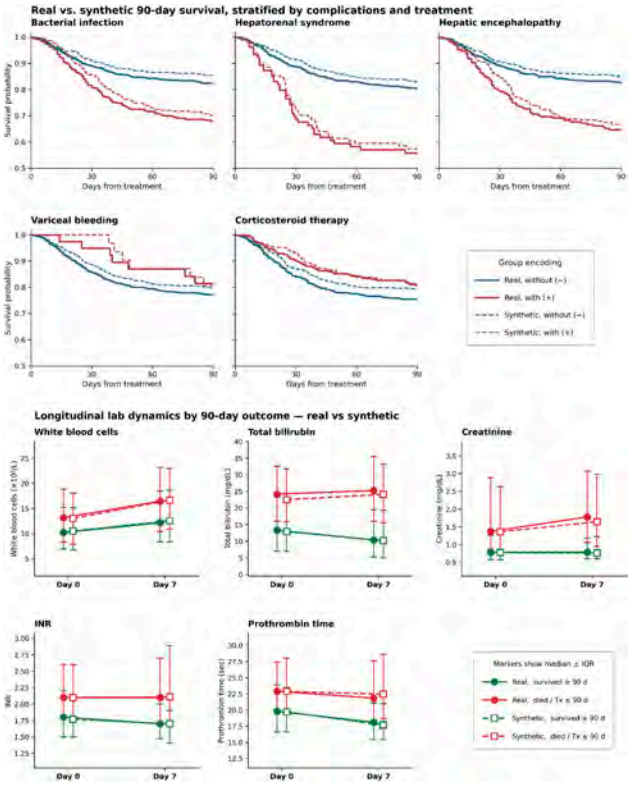
3057 | ALCHEPNET DIGITAL TWINS ENABLE HIGH-FIDELITY SYNTHETIC CONTROL ARMS FOR IN-SILICO TRIALS IN ALCOHOL-ASSOCIATED HEPATITIS

Joseph Ahn[1] Mingzhao Hu[1] Sonam Palmo[1] Soheil Rasoolzadegan[1] Sori Lundin[1] Xinyue Hu[1] Avanti Bhandarkar[1] AlcHepNet Investigators[2] Douglas Simonetto[3] Patrick Kamath[1] Wanzhu Tu[4] Cui Tao[1] Vijay Shah[3], [1]Mayo Clinic, [2]AlcHepNet Consortium, [3]Mayo Clinic Rochester, [4]Indiana University

Background: Clinical trials in alcohol-associated hepatitis (AH) are hampered by slow recruitment, attrition, and ethical barriers to placebo or standard-care control arms. Synthetic data can provide virtual replicas, or digital twins, of individual patients that preserve the statistical patterns and clinical relationships of the original cohort. Digital twins are a promising approach increasingly relevant to FDA/EMA interest in externally controlled and model-informed trial designs and may reduce reliance on placebo. We developed and validated a generative model for AH digital twins and tested whether an in-silico corticosteroid trial could reproduce treatment-effect estimates from the source cohort. **Methods:** A tabular denoising diffusion probabilistic model (TabDDPM) was trained on multisite AlcHepNet consortium trial data from 788 patients with AH, spanning demographics, day-0/day-7 labs, baseline and in-hospital complications, and 90-day death-or-transplant. Fidelity was assessed via marginal distributions, joint relationships, derived severity scores, and stratified survival patterns. A two-stage diffusion model then generated baseline cohorts and simulated 90-day outcomes under randomized corticosteroid assignment across 50 Monte Carlo trials of 2,000 patients. The in-silico hazard ratio (HR) was compared with unadjusted Cox, propensity-score matching, inverse-probability weighting (IPW), and augmented IPW in the real

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cohort. **Results:** Synthetic patients closely matched the real cohort: numerical features differed by < 2% using normalized Wasserstein distance, categorical proportions by < 4%, with complete real/synthetic overlap on visual clustering. Derived MELD/Maddrey DF/ABIC scores, though not modeled directly, were reproduced with fidelity comparable to measured inputs. Survival curves preserved complication risk gradients: 90-day survival was 83% without HRS vs 58% with HRS, with similar gradients for HE and infection. Day-0 to day-7 lab trajectories reproduced the classic AH prognostic divergence: 90-day survivors showed falling bilirubin and stable renal function, while decedents showed rising bilirubin and creatinine with persistent coagulopathy. The in-silico RCT estimated a 90-day mortality HR of 0.78 (95% CI 0.69–0.90; 67.7% vs 61.8% survival, 5.9-point absolute benefit, NNT ~17), directionally consistent with real-cohort methods (HR 0.71–0.86). **Conclusion:** A diffusion-based generative model produced high-fidelity AH digital twins that preserved clinical phenotypes, severity scores, complications, survival trajectories, longitudinal lab dynamics, and corticosteroid treatment-effect patterns. With further validation in prospective trials, synthetic control arms may help address ethical and practical barriers in AH trials by reducing recruitment burden and limiting reliance on placebo or standard-care arms in a high-mortality population.



Disclosures: Joseph Ahn:Nothing to Disclose, Mingzhao Hu:Nothing to Disclose, Sonam Palmo:Nothing to Disclose, Soheil Rasoolzadegan:Nothing to Disclose, Sori Lundin:Nothing to Disclose, Xinyue Hu: Nothing to Disclose, Avanti Bhandarkar:Nothing to Disclose, AlcHepNet Investigators:Nothing to Disclose, Douglas Simonetto:Mallinckrodt: Consultant, BioVie: Consultant, Resolution Therapeutics: Consultant, Evive: Consultant, Iota: Consultant, Novo Nordisk: Consultant, Astra Zeneca: Consultant, Patrick Kamath:Sequana: Advisor, NovoNordisk: Advisor, GSK: Advisor, Wanzhu Tu:Nothing to Disclose, Cui Tao:Nothing to Disclose, Vijay Shah:Boehringer Ingelheim: Consultant, GSK: Consultant, GENFIT SA: Consultant, Intercept Pharmaceuticals, Inc. Advisor, Korro Bio, Inc. Consultant, Novo Nordisk A/S: Consultant, Resolution Therapeutics, Ltd. Advisor, Seal Rock Therapeutics, Ltd. Consultant, Surrozen: Advisor, Dexcel Pharma Technologies, Ltd. Consultant, Dimension Inx. Advisor, Enveda: Consultant, Ochre Bio: Consultant, Satellite Biosciences, Inc. Consultant.

3058 | MARIJUANA USE AND ALCOHOL CO-USE AMONG ADULTS WITH CIRRHOSIS: A REPEATED CROSS-SECTIONAL STUDY

Stephanie Mrowczynski[1] Alexander Siebert[2] Brigham Walker[2] Lixian Chen[1] Meghana Vankina[1] Peng-Sheng Ting[1] Allison Ju-Chen Hu[2], [1]Tulane University School of Medicine, [2]Tulane University

Background: Marijuana use is becoming more prevalent as its legalization expands. Individuals with alcohol-associated liver disease (ALD) who are interested in alcohol cessation may perceive marijuana as a safer, less addictive alternative. One recent study suggests alcohol craving acutely decreased following cannabis consumption. However, the landscape of marijuana use, including its combination with alcohol use among patients with cirrhosis, remains understudied. We examine the prevalence and patient characteristics associated with marijuana use and co-use of marijuana and alcohol among this patient population. **Methods:** This study uses a repeated cross-sectional, nationally representative, sample from the 2021-2024 National Survey on Drug Use and Health (NSDUH), which includes 519 adults with cirrhosis. The survey includes questions that assess whether the patient used, at any point within the prior 12 months: (1) marijuana, (2) alcohol, and (3) both marijuana and alcohol. We use logistic regression to examine the association between patient characteristics and each outcome. All estimates are adjusted for complex survey design and sampling weights. **Results:** Among patients with cirrhosis, 25.2% used marijuana, 43.7% used alcohol, and 15.1% used both substances in the past year. Females were less likely than males to use marijuana (OR [odds ratio] = 0.38, 95% CI = 0.18-

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0.80, p = 0.012). Compared to patients aged 18-34, those aged 35-49 years were more likely to use marijuana (OR = 5.8, 95% CI = 1.36-24.69, p = 0.018) but less likely to use alcohol (OR = 0.08, 95% CI = 0.02-0.3, p < 0.001). Compared to Non-Hispanic White patients, Non-Hispanic Black (OR = 3.21, 95% CI = 1.33-7.22, p = 0.01) and Hispanic patients (OR = 11.64, 95% CI = 2.05-66.03, p = 0.006) were more likely to use both marijuana and alcohol. Patients with past-year alcohol use disorder were more likely to use both marijuana and alcohol in comparison to those without alcohol use disorder (OR = 7.93, 95% CI = 3.34-18.80, p < 0.001). **Conclusion:** Using a nationally representative sample of cirrhotic individuals, we find that male patients and those aged 35-49 were more likely to use marijuana. Hispanic and Black patients, as well as patients with alcohol use disorder, were more likely to use both alcohol and marijuana. These results demonstrate marijuana use has disparate prevalence among individuals with cirrhosis. This may help guide further public health screening and interventions for patients with cirrhosis, particularly in the context of liver transplant evaluation.

Table 1. Regression results, NSDUH 2021-2024

	Past-year marijuana use			Past-year alcohol use			Past-year alcohol and marijuana use		
	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
Female	0.38	0.18–0.80	0.012	0.59	0.27–1.28	0.178	0.43	0.17–1.09	0.062
Age (ref=18-34)									
35–49	5.8	1.36–24.69	0.018	0.08	0.02–0.30	<0.001	2.85	0.67–12.26	0.207
50–64	2.38	0.58–9.76	0.225	0.09	0.02–0.29	<0.001	1.41	0.34–5.94	0.629
65+	0.97	0.21–4.42	0.965	0.09	0.02–0.42	0.003	0.87	0.12–6.16	0.888
Race and ethnicity (ref= Non-Hispanic White)									
Non-Hispanic Black	1.09	0.40–2.93	0.863	1.49	0.55–4.06	0.425	3.21	1.33–7.72	0.01
Non-Hispanic Asian/PI or >1 race	0.08	0.01–0.52	0.016	0.02	0.00–0.16	<0.001	0.48	0.02–2.08	0.164
Hispanic	3.04	0.87–10.18	0.187	1.76	0.24–12.63	0.567	11.64	2.05–66.03	0.006
Education (ref=less than high school)									
High school	0.77	0.28–2.64	0.662	1.43	0.40–5.12	0.572	1.04	0.16–6.64	0.966
Some college, associate degree	1.16	0.48–4.19	0.36	1.69	0.46–6.27	0.424	1.23	0.19–7.93	0.826
College graduate	0.85	0.16–1.91	0.34	5.52	1.65–17.65	0.007	0.68	0.10–3.24	0.623
Mental Health									
Past year major depressive episode (MDE)	1.38	0.49–3.85	0.531	0.85	0.28–2.49	0.758	0.75	0.27–2.09	0.574
Past year serious psychological distress (SPD)	1.86	0.76–5.48	0.194	0.63	0.28–1.43	0.265	1.09	0.45–2.84	0.851
Past-year alcohol use disorder	1.43	0.57–3.58	0.437	1	1.00–1.00	-	7.93	3.34–18.80	<0.001
Self-reported chronic conditions									
Heart condition	1.4	0.63–3.07	0.401	1.58	0.70–3.58	0.263	2.47	1.21–5.02	0.014
Diabetes	0.41	0.15–1.12	0.081	1.0	0.52–2.91	0.603	0.49	0.17–1.36	0.166
Hepatitis B or C	2.4	1.19–4.84	0.016	0.84	0.32–2.20	0.72	2.69	1.15–6.83	0.058
High blood pressure	0.49	0.25–0.97	0.041	0.64	0.29–1.42	0.266	0.48	0.18–1.20	0.078

Disclosures: Stephanie Mrowczynski:Nothing to Disclose, Alexander Siebert:Nothing to Disclose, Brigham Walker:Nothing to Disclose, Lixian Chen:Nothing to Disclose, Meghana Vankina:Nothing to Disclose, Peng-Sheng Ting:Nothing to Disclose, Allison Ju-Chen Hu: Nothing to Disclose.

3059 | ASPIRIN ATTENUATES HEPATIC STEATOSIS AND SUPPRESSES INFLAMMATORY TRANSCRIPTIONAL PROGRAMS IN AN ALCOHOL-ASSOCIATED HEPATITIS MODEL

Nima Fattahi[1] Fallyn Kirlin[2] Yasuko Iwakiri[1] Matthew McConnell[1], [1]Yale University, [2]Internal medicine department, yale school of medicine

Background: Alcohol-associated liver disease (ALD) is a leading cause of liver-related morbidity and mortality worldwide. Platelet-mediated inflammatory signaling has emerged as an important contributor to hepatic injury and liver disease progression. Aspirin (ASA), an irreversible cyclooxygenase inhibitor with anti-inflammatory and antiplatelet properties, has demonstrated hepatoprotective effects in chronic liver disease; however, its role in alcohol-associated liver injury remains incompletely understood. We investigated the effects of ASA treatment on hepatic histologic and transcriptional responses in a murine model of alcohol-associated hepatitis (AH). **Methods:** Female mice aged 10–13 weeks underwent the 10-day NIAAA chronic-plus-binge ethanol feeding protocol consisting of a 5% Lieber-DeCarli ethanol diet followed by a single 31.5% ethanol binge gavage on the final day. Mice received either daily ASA treatment (1 mg/mL aspirin in PBS, 100 µL by gavage) or PBS vehicle control throughout the experiment. Liver tissues were collected for hematoxylin and eosin (H&E) staining and bulk liver RNA sequencing analysis (n = 7-8/group). Differential gene expression and pathway enrichment analyses were performed using an FDR threshold of < 0.05. **Results:** ASA-treated mice demonstrated significantly reduced hepatic steatosis on H&E staining compared with vehicle-treated controls (log2 steatotic area 15.79 vs 14.98, p < 0.05). Bulk liver RNA-seq analysis revealed distinct transcriptional alterations associated with ASA treatment, including modulation of inflammatory and metabolic pathways. Differential expression analysis identified significant upregulation of metabolic-associated genes including Aldob, Acly, Slc2a4, Gpi1, and Espn in ASA-treated livers, suggesting altered glucose and lipid metabolic regulation. In contrast, inflammatory-associated genes including Ikbke and Jam2 were significantly downregulated following ASA treatment. Hallmark pathway enrichment analysis demonstrated suppression of multiple inflammatory and stress-response pathways in ASA-treated mice, including TNFα signaling via NF-κB, inflammatory response, IL6-JAK-STAT3 signaling, apoptosis, epithelial-mesenchymal transition, and KRAS signaling pathways. Gene ontology analyses additionally demonstrated downregulation of immune-related pathways associated with T-cell activation and differentiation. **Conclusion:** ASA treatment reduces hepatic steatosis and suppresses inflammatory transcriptional signaling in a AH model. These findings support a potential hepatoprotective role for ASA in alcohol-associated liver injury and suggest that modulation of inflammatory and platelet-associated pathways may represent a therapeutic strategy in ALD.

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Disclosures: Nima Fattahi:Nothing to Disclose, Fallyn Kirlin:Nothing to Disclose, Yasuko Iwakiri:Nothing to Disclose, Matthew McConnell:Nothing to Disclose.

3060 | GLP-1 RECEPTOR AGONISTS AND ALCOHOL-RELATED HEALTHCARE UTILIZATION IN ADULTS WITH AUD: REAL-WORLD EVIDENCE FROM A MATCHED COHORT

Suthat Liangpunsakul[1] Chi Mai Nguyen[2] Yi Zhao[2] Yining Li[2] Shihui Jiang[2] Jing Su[2] Samer Gawrieh[1] Wanzhu Tu[2], [1]Division of Gastroenterology and Hepatology, Indiana University School of Medicine, Indianapolis, IN, [2]Department of Biostatistics and Health Data Science, Indiana University School of Medicine, Indiana.

Background: GLP-1 receptor agonists (GLP-1RAs) are widely prescribed for type 2 diabetes (T2DM) and obesity. Preclinical and clinical evidence suggests GLP-1 signaling modulates reward pathways and may reduce alcohol intake. A substantial proportion of patients initiating GLP-1RAs carry a concurrent alcohol use disorder (AUD) diagnosis, yet real-world associations between GLP-1RA exposure and alcohol-related healthcare utilization remain uncharacterized. the objective of this study is to estimate the association between GLP-1RA initiation and alcohol-coded healthcare utilization and direct medical costs over 12 months in adults with comorbid AUD and metabolic disease. **Methods:** We conducted a matched cohort study using IBM MarketScan Commercial databases (2016–2024). Eligible adults (ages 21–64) had AUD with coexisting T2DM, obesity, or both, and continuous enrollment ≥6 months pre- and ≥12 months post-index. The exposed cohort comprised new GLP-1RA initiators (dulaglutide, exenatide, liraglutide, semaglutide, or tirzepatide) with ≥4 weeks dispensed. Controls received no GLP-1RA or AUD pharmacotherapy. Patients were matched 1:1 via logit propensity score with exact matching on clinical strata. Alcohol-coded outpatient, ED, and inpatient encounters and direct medical costs (2024 USD) were assessed over 12 months. Matched-pair differences were evaluated using Wilcoxon signed-rank tests. **Results:** The analytic sample comprised 1,203 matched pairs. Exposed patients had a median age of 51 years (IQR 44–56), and 68.8% were male. Metabolic comorbidities included T2DM alone (44.4%), obesity alone (28.9%), and both conditions (26.7%); 22.9% had baseline liver disease, and 96.1% initiated therapy in the outpatient setting.Over 12 months, GLP-1RA initiators had significantly fewer alcohol-coded encounters than controls, including outpatient visits (mean 1.5 vs. 3.0), ED visits (0.03 vs. 0.06), and inpatient admissions (0.04 vs. 0.11; all $p < 0.01$). Despite lower encounter counts, mean direct costs were higher in the GLP-1RA arm across all settings: outpatient ($2,037 vs. $1,820), ED ($359 vs. $119), and inpatient ($7,120 vs. $5,298; all $p < 0.001$), reflecting greater per-encounter spending. Mean GLP-1RA pharmacy expenditure was $7,699 over the same period. **Conclusion:** Among adults with AUD and coexisting metabolic disease, GLP-1RA initiation was associated with fewer alcohol-coded healthcare encounters over 12 months; however, per-encounter and pharmacy costs were higher, and the net economic implications remain uncertain. These claims-based findings are hypothesis-generating, as confounding by indication, differential coding of alcohol-related care, and unmeasured AUD severity cannot be excluded. Prospective studies evaluating the effects of GLP-1RA on alcohol consumption and downstream healthcare utilization are warranted.

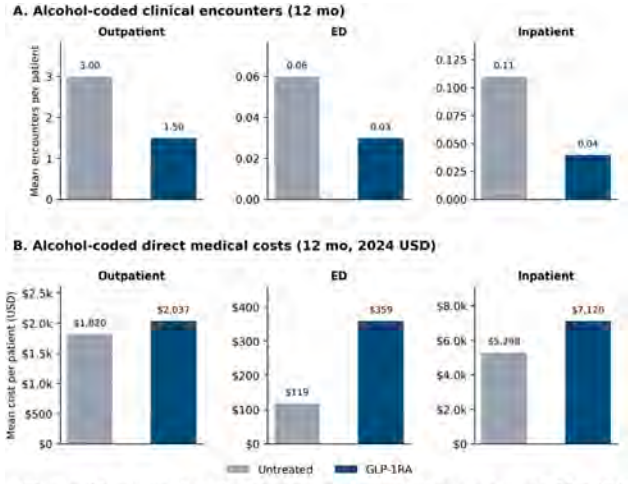


Figure. Alcohol-related utilization and medical costs among GLP-1RA users and non-users. All comparisons are significant with p<0.001.

Disclosures: Suthat Liangpunsakul:Durect Corporation: Consultant, Surrozen: Consultant, Korro Bio: Consultant, Durect Corporation: Consultant, Dimension Bio: Consultant, Chi Mai Nguyen:Nothing to Disclose, Yi Zhao:Nothing to Disclose, Yining Li:Nothing to Disclose, Shihui Jiang:Nothing to Disclose, Jing Su:Nothing to Disclose, Samer Gawrieh: Transmedics: Consultant, pfizer: Consultant, kowa: Consultant, spruce: Consultant, viking: Grant/Research Support, zydus: Grant/Research Support, dsm: Grant/Research Support, Sonicincytes: Grant/Research Support, Novo Nordisk: Consultant, GSK: Consultant, Wanzhu Tu:Nothing to Disclose.

3061 | SOCIAL DETERMINANTS OF HEALTH DIFFERENTIALLY ASSOCIATED WITH MASLD, METALD, AND ALD: A NATIONAL REAL-WORLD ANALYSIS

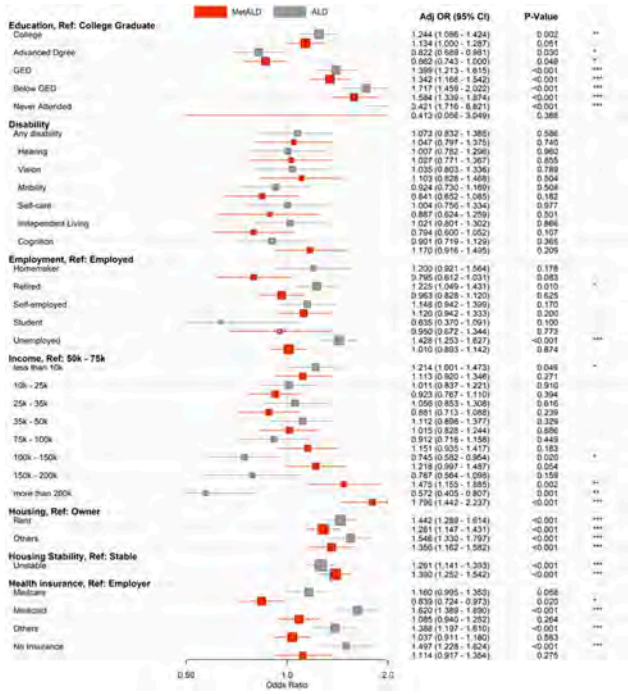
Chenxi Xiong[1] Wanzhu Tu[2] Baijian Yang[3] Suthat Liangpunsakul[4] Jing Su[5], [1]Department of Biostatistics and Health Data Science, Indiana University School of Medicine, Indiana, [2]Department of Biostatistics and Health Data Science, Indiana University School of

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Medicine, Indiana,, [3]School of Applied and Creative Computing, Purdue University, Indiana, USA, [4]Division of Gastroenterology and Hepatology, Indiana University School of Medicine, [5]Department of Biostatistics and Health Data Science, Indiana University School of Medicine

Background: Social determinants of health (SDoHs) play a critical role in the development, progression, and management of steatotic liver disease across the metabolic and alcohol-related spectrum, yet their associations with the newly defined metabolic dysfunction–associated alcohol-related liver disease (MetALD) remain poorly characterized in real-world populations. The NIH-sponsored All of Us (AoU) Research Program, with its deliberate inclusion of historically underrepresented groups, offers a unique national platform to examine these relationships. We aimed to identify SDoHs differentially associated with MetALD compared with metabolic dysfunction–associated steatotic liver disease (MASLD) and alcohol-related liver disease (ALD). **Methods:** This cross-sectional study leveraged AoU Research Program data (data release: April 18, 2023; N = 413,376). Eligible participants had liver disease per the Charlson Comorbidity Index with available AUDIT-C survey responses and longitudinal electronic medical record (EMR) data. MetALD was defined as meeting cardiometabolic criteria with alcohol consumption (AUDIT-C ≥ 5 in men, ≥ 4 in women); MASLD as meeting the same cardiometabolic criteria below the alcohol threshold; and ALD by ICD codes 571.0–.3/K70 without cardiometabolic criteria. Covariates included demographics, cardiometabolic variables (physical measurements, laboratory values, drug exposures, diagnoses, and procedures), and SDoHs (insurance type, housing stability, educational attainment, income, disability status, and employment). Multivariable logistic regression assessed differential SDoH associations across disease groups, with MASLD as the reference. **Results:** A total of 30,407 participants were included (median age 59 years; 57% female; 40% from racial/ethnic minority groups, including 19% Hispanic), comprising 2,776 MetALD, 24,655 MASLD, and 2,976 ALD cases. Compared with MASLD, both MetALD and ALD were independently associated with rental housing versus homeownership (aOR: 1.28–1.44), housing instability (aOR: 1.26–1.39), and lower educational attainment including GED certification (aOR: 1.34–3.42). Income showed a divergent pattern: higher annual income (>$100,000) was more prevalent in the MetALD group (aOR: 1.21–1.80) but less prevalent in ALD (aOR: 0.57–0.79) relative to MASLD. Non–employer-provided insurance was significantly associated with ALD (aOR: 1.16–1.62) but not MetALD (aOR: 0.84–1.11), indicating distinct socioeconomic patterning between these two alcohol-associated phenotypes (**Figure 1**). **Conclusion:** In this real-world cohort, MetALD and ALD had greater housing instability and lower education than MASLD, but differed in income and insurance. MetALD emerged as a distinct phenotype in employed, insured, higher-income patients, supporting tailored screening for steatotic liver disease.



Disclosures: Chenxi Xiong:Nothing to Disclose, Wanzhu Tu:Nothing to Disclose, Baijian Yang:Nothing to Disclose, Suthat Liangpunsakul:Durect Corporation: Consultant, Surrozen: Consultant, Korro Bio: Consultant, Durect Corporation: Consultant, Dimension Bio: Consultant, Jing Su:Nothing to Disclose.

3062 | ALIGNMENT BETWEEN PHOSPHATIDYLETHANOL (PETH) AND ALCOHOL-ASSOCIATED LIVER DISEASE (ALD) ICD CODING IN A US-BASED STEATOTIC LIVER DISEASE COHORT

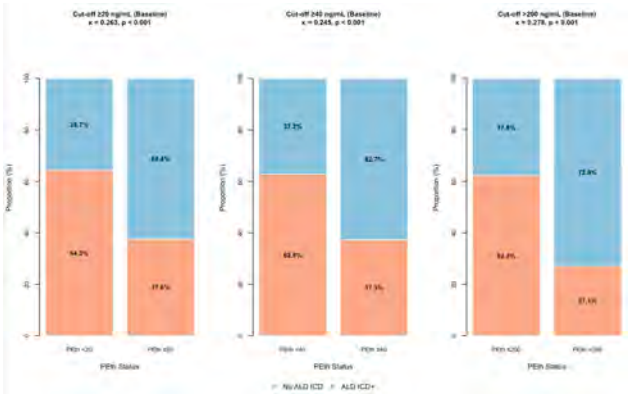
Hyundam (Dami) Gu[1] Samuel Rhoads[1] Stephen Hoang[1] Ronnie Li[1] Butros Fakhoury[1] Krishan Patel[1] Juan Pablo Arab[1], [1]Virginia Commonwealth University

Background: Phosphatidylethanol (PEth) is a sensitive and specific biomarker of alcohol consumption, yet its administration and utilization in clinical settings are limited. Currently in SLD, it is believed that using Peth testing can play in favor of correctly placing individuals in each disease category, overcoming existing reporting issues including recall and social desirability bias. In this study, we evaluated the matching rate between PEth levels and ALD ICD coding at baseline across multiple clinically relevant thresholds, and to

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identify patient factors associated with discordance. **Methods:** Among 415 patients in a US-based SLD registry who have MASLD-related or ALD-related ICD codes with available PEth measurements, agreement between PEth positivity and ALD ICD coding was assessed at three thresholds ($\geq$20, $\geq$40, and >200 ng/mL) using Cohen's kappa. ALD ICD positivity was defined as the presence of any of the following diagnoses in the electronic medical record: 'alcohol-induced mental disorders', 'acute alcohol intoxication', 'alcohol dependence', 'alcohol abuse', 'personal history of alcoholism', 'alcoholic fatty liver', 'acute alcoholic hepatitis', 'alcoholic cirrhosis', 'alcoholic liver damage', or 'alcoholic liver disease'. MASLD was defined by the presence of 'chronic nonalcoholic liver disease', 'unspecified chronic liver disease', 'hepatic steatosis', or 'nonalcoholic steatohepatitis (NASH)' (ICD-9/10). Logistic regression was performed to identify predictors of discordance (PEth-positive but ICD-negative, or vice versa), adjusting for age, sex, and race. **Results:** The cohort included patients with codes of MASLD (386, 93%) and ALD (195, 47%). The mean value of Peth was 184ng/mL. Agreement between PEth and ALD ICD coding was fair but statistically significant across all thresholds (κ = 0.263, 0.245, and 0.278 for $\geq$20, $\geq$40, and >200 ng/mL cutoffs respectively, all p < 0.001). Of those who had PEth $\geq$ 20 ng/mL, 37.6% were not coded properly. When the $\geq$ 40 ng/mL cut-off was applied, similar results of 37.3% were observed. Using the >200 ng/mL threshold, 72.9% of heavy drinkers had an ALD ICD code, yet 27.1% lacked ALD documentation despite biochemical evidence of heavy alcohol use. Overall, 34.7% of patients (n = 144) showed discordance between PEth and ALD ICD coding. In logistic regression, older age was the only significant predictor of discordance (OR = 1.06 per year [1.00–1.12], p < 0.05), while sex and race were not independently associated. **Conclusion:** A significant portion of MASLD patients have records of significant alcohol consumption. Moreover, the overall discordance rate was up to 38%, demonstrating that PEth utilization can be used to set more accurate diagnosis, as well as raising awareness that the temporality of biomarkers should be taken account when establishing a proper SLD diagnosis.



Disclosures: Hyundam (Dami) Gu:Nothing to Disclose, Samuel Rhoads:Nothing to Disclose, Stephen Hoang:PS Fertility: Consultant, Remedy Plan Inc. Consultant, Ronnie Li:Nothing to Disclose, Butros Fakhoury:Nothing to Disclose, Krishan Patel:Nothing to Disclose, Juan Pablo Arab:Nothing to Disclose.

3063 | ASSOCIATION OF AUTOMATED LIVER AND SPLEEN MEASUREMENTS WITH TRANSPLANT-FREE SURVIVAL IN ALCOHOL-ASSOCIATED HEPATITIS

Previn Ganesan[1] Richie Manikat[1] Ethan Akama-Garren[1] Ashley Jowell[2] Weiyu Wu[1] Paul Kwo[3] Nishita Kothary[1] Akshay Chaudhari[1] Robert Boutin[1] Vivek Charu[1] Allison Kwong[3], [1]Stanford University School of Medicine, [2]Duke University Medical Center, [3]Stanford University Medical Center

Background: Alcohol-associated liver disease (ALD) is a leading indication for liver transplantation. Yet, spontaneous hepatic recovery has been observed in 10-35% of patients with alcohol-associated hepatitis (AH). Liver transplantation poses unique risks and requires significant resource allocation. It is imperative to identify those who will spontaneously recover from those who are unlikely to survive without transplantation. We aim to assess whether (1) an automated deep-learning algorithm can reliably measure liver/spleen volume and (2) these radiographic parameters are associated with survival without transplant in AH. **Methods:** We identified patients hospitalized with AH [AK1] at our center between 2018 and 2023 that underwent abdominal computed tomography (CT) during admission. Demographic and anthropometric data were collected. Liver/spleen volumes were measured manually and with an automated deep learning algorithm for body composition analysis (*Comp2-Comp*). Liver and spleen size were normalized to body surface area; hepatomegaly was defined by established nomograms. Attenuation (in Hounsfield units, HU) was estimated by the algorithm; steatosis was defined as mean liver attenuation <40 HU on non-contrast CT or difference in liver-spleen attenuation >10 HU. Correlation between manual and automated measurements was assessed using intraclass correlation (ICC) and Bland-Altman analysis. One-year survival was assessed using Fine-Gray competing risk analysis, with liver transplant considered as a competing risk. **Results:** A total of 196 patients were included with a median age of 43 years (IQR 38-52) and MELD of 32 (IQR 25-38). Median liver volumes by manual and automated measurement were 2177 cm^3 (IQR 1473-3124) and 2087 cm^3 (IQR 1416-3006), respectively (ICC coefficient 0.95, p < 0.01). Median spleen volumes by manual and automated measurement were 565 cm^3 (IQR 383-853) and 543 cm^3 (IQR 360-808),

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respectively (ICC 0.94, p < 0.01). Bland-Altman analysis confirmed agreement between measurements. Automated measurement of liver and spleen volumes was lower than manual measurement (mean percent difference of 4.9% and 5.7%, respectively). Increased liver volume was associated with improved survival, independent of age, sex, MELD, and steatosis (sHR 0.45, 95% CI 0.26-0.79, p < 0.01). The presence of hepatic steatosis was associated with increased mortality (sHR 1.91, 95% CI 1.10-3.32, p = 0.02), whereas the liver/spleen ratio and spleen volume were not independently associated with survival (p > 0.05). **Conclusion:** This study validates the use of a deep-learning algorithm — which may be applied at scale — to measure radiographic parameters that may predict outcomes in liver disease. In patients with AH, greater liver volume and the absence of radiographic steatosis is associated with higher transplant-free survival and may help identify those who are more likely to spontaneously recover.

Table – Competing risk analysis (fine-gray) for 1-year survival.

	Univariable (sHR, 95% CI)	Multivariable (sHR, 95% CI)*
Liver volume †	0.56 (0.34-0.92)	0.45 (0.26-0.79)
Spleen volume†	0.10 (0.02-0.67)	0.29 (0.03-2.42)
Liver/spleen ratio†	1.01 (0.94-1.08)	1.00 (0.93-1.08)
MELD‡	1.03 (1.00-1.06)	1.05 (1.02-1.08)
Liver steatosis§	1.29 (0.79-2.11)	1.91 (1.10-3.32)

*Adjusted for age, sex, MELD
† Normalized to body surface area, sHRs correspond to per-point increase in each measure
§ Corresponds to categorical/binary variable of steatosis

Disclosures: Previn Ganesan:Nothing to Disclose, Richie Manikat:Nothing to Disclose, Ethan Akama-Garren:Nothing to Disclose, Ashley Jowell:Nothing to Disclose, Weiyu Wu:Nothing to Disclose, Paul Kwo: Arbutus: Advisor, Aligos: Advisor, Ausper Bio: Grant/Research Support, Altimmune: Grant/Research Support, Amgen: Advisor, Eiger: Consultant, Eiger: Grant/Research Support, Inventiva: Consultant, Novo Nordisk: Consultant, Novo Nordisk: Grant/Research Support, Takeda: Grant/Research Support, Madrigal: Grant/Research Support, Gilead: Consultant, Gilead: Grant/Research Support, Salix: Advisor, Ultragenyx: Grant/Research Support, Hepquant: Consultant, Target Registries: Grant/Research Support, Abbvie: Consultant, Mallinckrodt: Advisor, Takeda: Grant/Research Support, Genentech: Consultant, Glaxo Smith Kline: Consultant, Akero: Grant/Research Support, 89Bio: Grant/Research Support, Vir Bio: Grant/Research Support, Precision BioSciences: Consultant, Tune Therapeutics: Consultant, Mirum: Consultant, Target Registries: Advisor, Takeda: Advisor, Lygenesis: Advisor, Ausper Bio: Advisor, Nishita Kothary:Nothing to Disclose, Akshay Chaudhari:Nothing to Disclose, Robert Boutin:GE Healthcare: Grant/Research Support, Vivek Charu:Nothing to Disclose, Allison Kwong:Nothing to Disclose.

3064 | STIMULATING SURVIVAL: G-CSF AS A LAST RESORT IN ALCOHOL-ASSOCIATED HEPATITIS

Madeline Hathoot[1] Alicia Clum[1] Maiying Kong[1] Wanyu Zhang[1] Luis Marsano-Obando[1] Ashwani Singal[1], [1]University of Louisville

Background: Alcohol-associated hepatitis (AH) has a potential for mortality of up to 50% within a month in a severe episode (sAH), MELD score ≥ 20. Corticosteroids, the only available treatment is limited by ineligibility in 40-50%, non-response in 50-60% in eligible patients, survival benefit limited to a short-term period of 28 days in responders (day 4-7 Lille score ≤ 0.45), and infection risk in non-responders. Granulocyte colony-stimulating factor (G-CSF) is studied as an alternative therapy for steroid nonresponders or those with contraindications. Data on the survival benefit of G-CSF are conflicting. **Methods:** We conducted a retrospective study (07/2023-07/2025) at a tertiary center in sAH patients aged 18-65 yrs. Each patient receiving G-CSF (cases) s/c at 5 mcg/kg twice daily (300-480 mcg/dose) were matched with two patients not receiving G-CSF (controls) on baseline MELD score. Kaplan-Meier analysis with stratified long-rank testing and Cox regression were used to evaluate overall survival and liver transplant (LT)-free survival during hospitalization, and at 90 and 365 days. **Results:** Of 185 patients with sAH, 18 (10%) were treated with G-CSF (9 each for ineligibility and for non-response to steroids). Patients with vs. without G-CSF differed in disease severity, with a higher baseline MELD score and its variables (Table). Of 36 controls, 13 received steroids during hospitalization (5 responders), with a mean Lille score of 0.38 on day 4 and 0.32 on day 7. Baseline characteristics were similar between cases and controls (Table). A total of 28 patients died (11 cases) within a year, 25 within 90-d (11 cases), and 23 during hospitalization (11 cases). One of the controls underwent a liver transplant during the hospitalization. Patients receiving G-CSF had a 1.46-fold hazard of death vs. controls, which was not statistically significant (95% CI 0.485-4.395). Of the 11 deaths in cases, all had acute kidney injuries (AKI) due to hepatorenal syndrome (HRS), and 6 had a concomitant bacterial infection. Of 12 deaths in the control group during hospitalization, 11 had AKI (7 HRS), and 8 had a concomitant bacterial infection. **Conclusion:** In this limited retrospective study, G-CSF

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did not demonstrate a survival benefit in sAH. Multicenter randomized studies with a uniform population and the regimen are needed in the Western world to investigate the benefit of G-CSF in patients with sAH.

Table. Baseline characteristics in patients with severe alcohol-associated hepatitis: G-CSF vs no G-CSF treatment

	Unmatched patients			Propensity score matched for MELD score		
	No G-CSF (n=167)	G-CSF (n=18)	P-value	No G-CSF (n=36)	G-CSF (n=18)	P-value
Mean Age, SD	45.5 (±11.2)	49.0 (±9.1)	0.16	47.7 (±9.9)	49.0 (±9.1)	0.71
% Males	65.9%	66.7%	1.00	66.7%	66.7%	1.0
% White	78.4%	94.4%	0.12	86.1%	94.4%	0.53
% Cirrhosis	49.7%	50.0%	1.00	61.1%	50.0%	0.63
% Decomp.	54.5%	55.6%	1.00	63.9%	55.6%	0.77
% Steroids	36.9%	50.0%	0.32	38.1%	50.0%	0.43
WBC	11.8 (±7.8)	14.2(±8.4)	0.17	14.6 (±6.4)	14.2 (±8.4)	0.55
Platelets	137.5 (±97.2)	138.4 (±79.0)	0.88	105.3 (±57.9)	138.4 (±79.0)	0.32
MELD score (mean, SD)	24.8(±9.4)	34.4(±7.1)	<0.0001	34.4 (±7.1)	34.4 (±7.1)	0.96
S. bilirubin (mean, SD)	14.6 (±11.8)	25.0 (±9.9)	0.0002	21.9 (±12.1)	25.0 (±9.9)	0.23
INR (mean, SD)	2.0 (±0.7)	2.5 (±1.1)	0.002	2.5 (±0.7)	2.5 (±1.1)	0.56
S. creatinine (mean, SD)	1.6 (±1.6)	2.1 (±1.6)	0.078	2.9 (±2.1)	2.1 (±1.6)	0.17

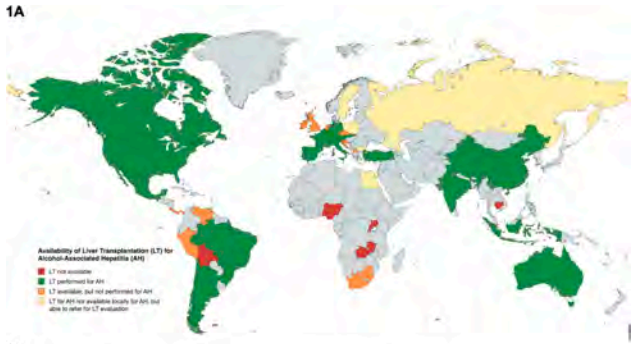
Disclosures: Madeline Hathoot:Nothing to Disclose, Alicia Clum:Nothing to Disclose, Maiying Kong:Nothing to Disclose, Wanyu Zhang:Nothing to Disclose, Luis Marsano-Obando:Nothing to Disclose, Ashwani Singal: Madrigal Pharmaceuticals: Speaking and Teaching, Pleiogenix Pharmaceuticals: Stock – privately held company, Bausch Pharmaceuticals: Advisor, NIAAA: Grant/Research Support, Up-to-Date: Royalties or patent beneficiary, Practice Point: Speaking and Teaching, Gastro Endo News: Executive role.

3065 | VARIABILITY IN ACCESS TO EARLY LIVER TRANSPLANTATION FOR ALCOHOL-ASSOCIATED HEPATITIS: A GLOBAL SURVEY STUDY

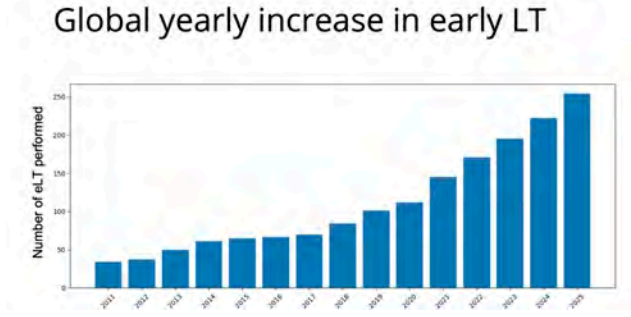
Hanna Blaney[1] Marta Tejedor[2] Rym Yousfi[3] Simone Strasser[4] Svetlana Adamcova Selcanova[5] Lubomir Skladany[6] Marina Berenguer[7] Juan Pablo Arab[1], [1]Virginia Commonwealth University, [2]University of Iowa, [3]Virginia Common Wealth University, [4]New South Wales, [5]Roosevelt Teaching Hospital, [6]Roosevelt Univ. Hospital, [7]University of Valencia

Background: Alcohol-associated hepatitis (AH) is a severe form of liver disease with limited medical management and a high short-term mortality. Early liver transplant (LT) without a prescribed period of sobriety is increasingly performed, with excellent survival benefit. However, early LT is not universally available. This study aims to understand global access and barriers to early LT for AH. **Methods:** This is an international survey study conducted between January and May 2026. The survey was sent to 208 hepatologists and surgeons identified through Global AlcHep and International Liver Transplant Society contacts. **Results:** The response rate was 66.8% with responses from 46 unique countries, and 75.5% of respondents practiced at a transplant center. LT was offered in 94.9% of respondent countries; however, only 71.4% of respondents at transplant centers offered early LT for AH (Figure 1a). 46.7% of respondents at LT centers not offering early LT cited local or national policies prohibiting early LT as the reason that early LT was not offered. Living donation LT (LDLT) was performed at centers of 40.3% of respondents, with just 22.3% respondents offering LDLT for AH. Early LT for AH has become increasingly available, with most programs started in 2022 (Figure 1b). The median MELD at transplant for AH was 28. A majority of 96.4% of respondents agreed that selected patients with severe AH should be offered early LT. Frequency of perceived barriers to early LT included 77% concerned about return to drinking post-LT, 45.3% concerned over the impact on other patients waiting for LT, 38.8% concerned over the potential for poor post-LT outcomes, 36% concerned about the recovery and survival without LT, 23% concerned about lay perception and effect on organ donation,16.5% had uncertainty about the need for LT, and 7.9% felt that patients with severe AH did not deserve LT. Return to alcohol use was tracked by 89.9% of respondents. However, phosphatidylethanol was only available to 32.4% of respondents. The estimated return to any alcohol use at 1 year was 16.5%, with return to heavy use at 1-year of 5.6%. Estimated mean survival was 88.75% (SD 14.4), with a 5-year mean survival of 77% (SD 13.6). **Conclusion:** There is marked geographic variation in access to early LT. While a majority of hepatologists agree that early LT should be considered in AH, multiple barriers to early LT for AH exist, including local and national policy as well as overwhelming concern regarding return to alcohol use.

1A



1B



Disclosures: Hanna Blaney:Nothing to Disclose, Marta Tejedor:Nothing to Disclose, Rym Yousfi:Nothing to Disclose, Simone Strasser:Nothing to Disclose,

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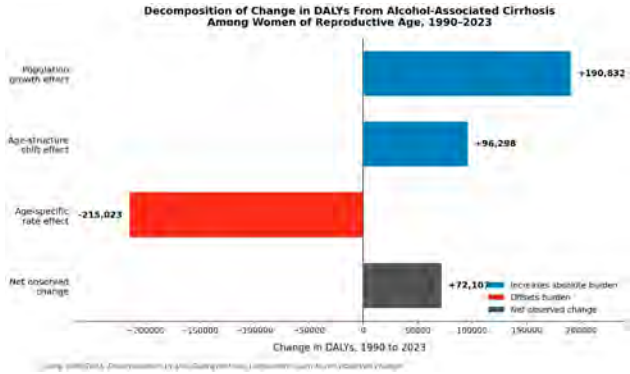
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Svetlana Adamcova Selcanova:Nothing to Disclose, Lubomir Skladany:Nothing to Disclose, Marina Berenguer:Orphalan: Consultant, Gilead: Grant/Research Support, Chiesi: Speaking and Teaching, astellas: Consultant, Ipsen: Consultant, Mirum: Consultant, Grifols: Consultant, Juan Pablo Arab:Nothing to Disclose.

3066 | BURDEN AND DRIVERS OF ALCOHOL-ASSOCIATED CIRRHOSIS AMONG WOMEN OF REPRODUCTIVE AGE, 1990–2023: IMPLICATIONS FOR REPRODUCTIVE HEALTH- A GLOBAL BURDEN OF DISEASE 2023 ANALYSIS

Yeshika Thapa[1] Carson Creamer[2] Tony Brar[1] Yaseen Perbtani[1], [1]UCF/HCA Florida North Florida, [2]University of Central Florida, HCA Healthcare GME

Background: Alcohol-associated cirrhosis among women of reproductive age has implications for liver-related morbidity, pregnancy outcomes, and fetal alcohol spectrum disorder prevention. We evaluated global trends and drivers of burden among women aged 15–49 years using GBD 2023 estimates. **Methods:** We performed a secondary analysis of GBD 2023 estimates for females aged 15–49 years with alcohol-associated cirrhosis from 1990–2023. Outcomes included DALYs and deaths with 95% uncertainty interval (UI), and corresponding crude rates. Trends were assessed by estimated annual percentage change (EAPC). Absolute burden changes were partitioned into population growth, age structure, and age specific rate contributions using Das Gupta decomposition. Geographic Variation in 2023 was assessed by SDI, GBD region, and country. **Results:** Among women aged 15–49 years, global DALYs rose from 444,951 (95% UI 289,880–656,333) to 517,058 (95% UI 348,080–739,910) (+16.2%) and deaths from 8,857 (95% UI, 5,833–12,930) to 10,451 (95% UI, 7,078–14,857) (+18.0%). In contrast, the DALY rate declined from 33.22 to 26.21 per 100,000 (−21.1%), and the death rate declined from 0.66 to 0.53 (−19.9%). EAPC showed significant annual declines in DALY rate (−0.84%/year, 95% CI −1.05 to −0.63, $p < 0.001$) and death rate(−0.80%/year, 95% CI −1.01 to −0.58, $p < 0.001$). Decomposition showed that rising DALYs were driven by population growth (+190,832) and age-structure shift toward older reproductive ages (+96,298), partially offset by declining age-specific rates (−215,023); deaths showed the same pattern. In 2023, the highest reproductive-age DALY rate was in High SDI settings (36.36 per 100,000), inverting the all-age GBD pattern, followed by Eastern Europe (202.06 per 100,000) and the Republic of Moldova (231.91 per 100,000), likely reflecting high alcohol exposure in several high-income and post-Soviet settings. **Conclusion:** Despite declining reproductive-age rates, absolute burden of alcohol-associated cirrhosis in women aged 15–49 rose from 1990 to 2023. This rise was largely demographically driven rather than worsening underlying risk, supporting earlier alcohol-use screening and integration of hepatology, addiction, and reproductive-health services for this population.



Disclosures: Yeshika Thapa:Nothing to Disclose, Carson Creamer:Nothing to Disclose, Tony Brar:Nothing to Disclose, Yaseen Perbtani:Nothing to Disclose.

3067 | GREATER SEX-ADJUSTED SKELETAL MUSCLE DEFICIT IS ASSOCIATED WITH INCREASED MORTALITY IN ACUTE ALCOHOL-ASSOCIATED HEPATITIS

Beatriz Sordi Chara[1] Anahita Rabiee[2] Gabrielle Pakravan[2] Praveena Narayanan[3] Pramod Mistry[2] Guadalupe Garcia-Tsao[2], [1]Yale New Haven Hospital/ Yale School of Medicine, [2]Yale University, [3]UW-Madison

Background: Sarcopenia is recognized as a marker of frailty and poor outcomes in advanced liver disease, but its prognostic significance in alcohol-associated hepatitis (AAH) remains incompletely characterized. Given the catabolic and inflammatory

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milieu of AAH, we hypothesized that lower skeletal muscle mass would be associated with increased mortality. We evaluated the association between sex-adjusted skeletal muscle deficit and mortality in patients with confirmed AAH and advanced fibrosis/cirrhosis. **Methods:** We performed a retrospective cohort study of patients with biopsy-confirmed AAH and bridging fibrosis/cirrhosis with decompensation (ascites, variceal bleeding, or hepatic encephalopathy) at a tertiary care hospital between 2013–2022. Patients without baseline CT imaging were excluded. Skeletal muscle index (SMI) was measured on baseline CT imaging. We derived a continuous sex-adjusted SMI deficit variable relative to cirrhosis-specific sarcopenia thresholds: < 50 cm²/m² in men and < 39 cm²/m² in women. The primary outcome was mortality, with liver transplantation treated as censoring. Multivariable Cox proportional hazards models adjusted for age, MELD-Na, and fibrosis stage used restricted cubic splines to evaluate nonlinear associations between sex-adjusted SMI deficit and mortality. **Results:** Among 107 patients, median age was 47 years (IQR 36–55), median MELD-Na was 27 (IQR 22–32), 60% were male, and median follow-up was 1.6 years (IQR 0.2–3.1). During follow-up, 49 (46%) deaths and 5 transplants occurred. Sixty-four patients (60%) met criteria for sex-specific sarcopenia. Most patients (85%) had cirrhosis (F4), while 15% had bridging fibrosis (F3). In multivariable Cox models adjusted for MELD-Na, age, and fibrosis stage, restricted cubic spline analysis demonstrated a nonlinear association between greater sex-adjusted SMI deficit and increased mortality risk, approaching significance ($p = 0.054$). Mortality risk appeared to rise disproportionately at greater muscle deficits. In secondary analyses using a binary sarcopenia definition, sarcopenia was associated with higher mortality risk, although this did not reach significance (HR 1.49, 95% CI 0.82–2.72, $p = 0.19$). Older age (HR 1.03/year, 95% CI 1.00–1.06, $p = 0.028$), higher MELD-Na (HR 1.05/point, 95% CI 1.01–1.09, $p = 0.010$), and F4 fibrosis (HR 4.39, 95% CI 1.35–14.34, $p = 0.014$) were independently associated with mortality. Model concordance was 0.714. **Conclusion:** Spline modeling suggested a nonlinear association between lower sex-adjusted skeletal muscle reserve and mortality risk in AAH after adjustment for MELD-Na, age, and fibrosis stage. Risk appeared to rise disproportionately at greater SMI deficits, suggesting CT-derived muscle depletion may capture physiologic vulnerability not reflected by liver disease severity alone. These findings support further evaluation of skeletal muscle metrics as prognostic biomarkers in AAH.

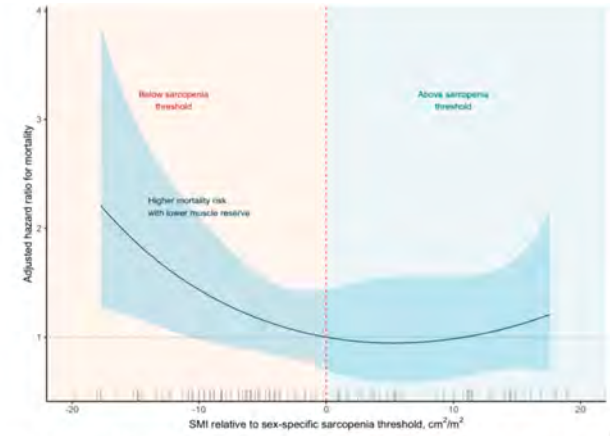


Figure 1: Adjusted association between sex-adjusted skeletal muscle deficit and mortality risk in acute alcohol-associated hepatitis. Restricted cubic spline modeling demonstrates higher predicted mortality risk at greater skeletal muscle deficits after adjustment for MELD-Na, age, and fibrosis stage.

Disclosures: Beatriz Sordi Chara:Nothing to Disclose, Anahita Rabiee:Grifols: Investigator-initiated studies (IIS), Grifols: Investigator-initiated studies (IIS), Grifols: Investigator-initiated studies (IIS), Grifols: Investigator-initiated studies (IIS), Gabrielle Pakravan:Nothing to Disclose, Praveena Narayanan:Nothing to Disclose, Pramod Mistry:Sanofi: Grant/Research Support, Guadalupe Garcia-Tsao:Nothing to Disclose.

3068 | MYCOPHENOLATE MOFETIL IS SAFER AND EQUALLY EFFICACIOUS AS STEROIDS IN IMPROVING 90-DAY SURVIVAL IN SEVERE ALCOHOLIC HEPATITIS – A PILOT RCT

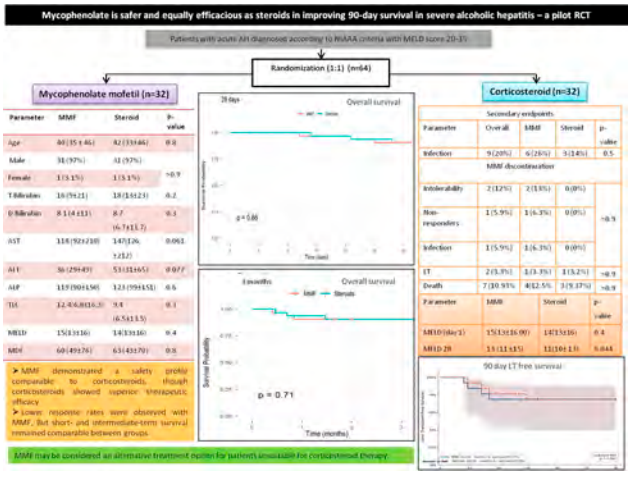
Ananthu Narayan[1] Saggere Muralikrishna Shasthry[1] Satender Pal Singh[1] Vinod Arora[1] Sanda Kavitha[1] Shiv Kumar Sarin[1], [1]Institute of Liver and Biliary Sciences, Delhi

Background: Corticosteroids continue to be the primary treatment for severe alcoholic hepatitis (SAH), despite controversial efficacy and an increased risk of infections. Additionally, many patients are either non-responsive or unsuitable for steroid therapy, highlighting the need for alternative treatments. Mycophenolate mofetil (MMF), an immunomodulatory agent with established safety in liver diseases, has shown safety in steroid non-responsive AH patients in an initial trial. However, comparative evidence on their efficacy and safety in AH remains limited. **Methods:** Patients with SAH was identified based on national institute on alcohol abuse and alcoholism criteria and a MELD score of 20-35 were randomized to receive either MMF or corticosteroid. MMF group received 750 mg twice daily, while steroid

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group received prednisolone 40 mg/day. Patients were followed for 90 days with assessments on days 4, 7 and 28. Steroids were discontinued in non-responders based on Lille score on days 7. Primary end point was survival at 28 days. Clinical outcomes, including hospitalization, liver related events, and survival at 90 days have been evaluated. **Results:** A total of 64 patients with SAH were randomized equally to receive MMF (n = 32) or steroids (n = 32). Baseline MELD (15 vs 14, p = 0.4) and MDF (60 vs 63, p = 0.8), were comparable between groups. The 28-day transplant-free survival was 90.3% in the MMF group and 93.5% in the steroid group, while the 90-day transplant-free survival was 90.3% in both groups. Kaplan–Meier analysis showed no significant difference in survival between MMF and steroid groups at 28 days (p = 0.66) or 90 days (p = 0.71).Overall incidence of infection was 20%, with no significant difference between MMF and steroid groups (26% vs 14%, p = 0.5). Among patients receiving MMF, 76% completed therapy without interruption; treatment discontinuation occurred due to intolerance (12%), clinical non-response (5.9%), and infection (5.9%).Steroid-treated patients also had lower day-28 INR (1.51 vs 1.82, p = 0.031) and MELD scores (11 vs 13, p = 0.044). Death occurred in 7 patients (4 vs 3), while liver transplantation was done in 2 patients (1 patient each). **Conclusion:** MMF demonstrated an acceptable safety profile comparable to corticosteroids with respect to survival and liver related events. Short- and intermediate-term survival were comparable between groups, suggesting that MMF may be considered as an alternative treatment option in patients with alcoholic hepatitis.



Disclosures: Ananthu Narayan:Nothing to Disclose, Saggere Muralikrishna Shasthry:Nothing to Disclose, Satender Pal Singh:Nothing to Disclose, Vinod Arora: Nothing to Disclose, Sanda Kavitha:Nothing to Disclose, Shiv Kumar Sarin:Nothing to Disclose.

3069 | RISING DISCORDANCE BETWEEN ADMINISTRATIVE CODING AND CLINICAL PHENOTYPE OF ALCOHOLIC HEPATITIS AMONG LIVER TRANSPLANT RECIPIENTS AFTER 2020: A UNOS MACHINE LEARNING ANALYSIS

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Background: Alcohol-associated liver disease (ALD) has emerged as an increasingly common indication for liver transplantation in the United States, particularly following 2019. However, it remains unclear whether these changes were driven disproportionately by alcoholic hepatitis (AH) compared with chronic alcohol-associated liver disease, and whether the clinical phenotype and severity of affected transplant recipients have evolved over time. Administrative diagnosis codes are frequently used to identify AH in large transplant datasets, although coding practices and diagnostic classification may change over time. We therefore aimed to evaluate temporal changes in alcohol-related liver transplantation patterns before and after 2019 within the UNOS registry, assess changes in AH-like clinical phenotype and disease severity, and determine the extent of discordance between administrative diagnosis coding and phenotype-defined disease in the post-2020 era. **Methods:** Adult liver transplant recipients in the UNOS database with a primary diagnosis of alcohol-associated liver disease (ALD) or AH were identified, while recipients with multiple etiologies were excluded. A logistic classification model was trained using the pre-2020 cohort, with AH diagnosis code as the outcome variable. Clinical and demographic predictors included MELD score, bilirubin, INR, creatinine, sodium, albumin, age, BMI, sex, ethnicity, diabetes, and obesity. The trained model was subsequently applied to the post-2020 cohort to identify an AH-like clinical phenotype. Model discrimination was evaluated using area under the receiver operating characteristic curve (AUC). A prevalence-calibrated probability threshold derived from the pre-2020 AH prevalence was used to classify AH-like phenotype. Discordance was defined as mismatch between administrative diagnosis coding

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and model-predicted phenotype. **Results:** The classifier demonstrated good discrimination in the post-2020 test cohort (AUC 0.836). Patients coded with AH exhibited a clinically distinct phenotype characterized by higher MELD score (OR 1.32, p = 0.017), bilirubin (OR 2.15, p < 0.001), creatinine (OR 1.24, p < 0.001), and sodium (OR 1.21, p = 0.012), alongside lower albumin (OR 0.82, p = 0.003), younger age (OR 0.52, p < 0.001), and lower prevalence of diabetes mellitus (OR 0.48, p = 0.014). Male sex (OR 0.65, p = 0.004) and Hispanic ethnicity (OR 0.53, p = 0.007) were associated with lower odds of AH coding. From the pre-2020 to post-2020 era, the proportion of transplant recipients demonstrating an AH-like clinical phenotype increased from 4.7% to 7.1%. Concurrently, discordance between administrative diagnosis coding and phenotype-defined disease increased from 6.0% to 9.9%. In multivariable analysis, the post-2020 era was independently associated with greater discordance between coded diagnosis and clinical phenotype (OR 1.71). **Conclusion:** Alcohol-related liver transplant recipients demonstrated an increasingly AH-like clinical phenotype following 2020, suggesting that post-2019 increases in alcohol-related transplantation may have been driven disproportionately by more acute and severe alcohol-associated liver disease. However, this was accompanied by substantially greater discordance between administrative diagnosis coding and phenotype-based classification. These findings suggest evolving diagnostic classification and/or shifts in disease presentation in the post-2020 era, with important implications for epidemiologic and transplant outcomes studies relying on administrative definitions of alcoholic hepatitis.

Regression Analysis Table

Variable	OR (95% CI), p-value
MELD score	1.32 (1.05–1.66), p=0.017
Bilirubin	2.15 (1.87–2.46), p<0.001
INR	0.74 (0.60–0.92), p=0.008
Creatinine	1.24 (1.11–1.39), p<0.001
Sodium	1.21 (1.04–1.40), p=0.012
Albumin	0.82 (0.72–0.94), p=0.003
Age	0.52 (0.44–0.60), p<0.001
BMI	0.88 (0.71–1.08), p=0.232
Gender	
Female	1.00 (reference)
Male	0.65 (0.49–0.87), p=0.004
Ethnicity	
Caucasian	1.00 (reference)
African-American	0.89 (0.43–1.86), p=0.762
Hispanics	0.53 (0.33–0.84), p=0.007
Asians	1.55 (0.75–3.18), p=0.234
Others	0.89 (0.39–2.01), p=0.779
Diabetes	
No	1.00 (reference)
Yes	0.48 (0.26–0.86), p=0.014
Obesity	
No	1.00 (reference)
Yes	1.17 (0.73–1.86), p=0.509

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3070 | GLP-1 RECEPTOR AGONISTS AND LIVER OUTCOMES IN METABOLIC DYSFUNCTION-ASSOCIATED ALCOHOL-RELATED LIVER DISEASE: A PROPENSITY SCORE-MATCHED COHORT STUDY

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Background: Metabolic dysfunction-associated alcohol-related liver disease (MetALD) represents a growing clinical challenge. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) show promise in managing metabolic dysregulation and addictive behaviors, but their impact on clinical outcomes in patients with MetALD remains poorly defined. We evaluated the impact of GLP-1 RA exposure on hepatic decompensation and alcohol-related outcomes in this population. **Methods:** We conducted a retrospective 1:1 propensity score-matched cohort study using the TriNetX Research Network (106 healthcare organizations; N = 117,955,548). MetALD was defined by ICD-10 codes for alcoholic liver disease (K70) and hepatic steatosis (K76.0) with BMI $\geq$ 27 kg/m^2 or diabetes. Patients with hepatocellular carcinoma, type 1 diabetes, prior liver transplantation, or pregnancy were excluded. The GLP-1 cohort required documented use of semaglutide, tirzepatide, dulaglutide, exenatide, liraglutide, or lixisenatide. Matching variables included demographics, liver disease severity, metabolic comorbidities, cardiovascular disease, chronic kidney disease, psychiatric disease, medication exposure, and laboratory values. Outcomes were assessed from 90 days to 5 years post-index. **Results:** Of 5,018 GLP-1 RA-exposed and 69,567 non-exposed MetALD patients initially identified, 3,525 and 56,670 remained after exclusions, respectively. Following 1:1 propensity score matching on 40+ covariates (all post-match SMDs < 0.06), 2,703 patients were included per cohort. Compared to non-GLP-1 patients, GLP-1 RA use was associated with lower rates of: listing for liver transplant (1.0% vs 1.8%; HR 0.56, 95% CI 0.35–0.90; p = 0.015), all-cause hepatic decompensation (3.1% vs 8.4%; HR 0.36, 95% CI 0.28–0.47; p < 0.001), alcohol-associated hepatitis (4.1% vs 9.5%; HR 0.41, 95% CI 0.33–0.52; p < 0.001), cirrhosis progression (3.4% vs 7.6%; HR 0.46, 95% CI 0.35–0.61; p < 0.001), alcohol withdrawal (3.0% vs 7.9%; HR 0.36, 95% CI 0.28–0.47; p < 0.001), alcohol intoxication (1.8% vs 6.4%; HR 0.28, 95% CI 0.20–0.39; p < 0.001), and all-cause hospitalization (1.5% vs 4.9%; HR 0.30, 95% CI 0.21–0.43; p < 0.001). GLP-1 RA users also had lower rates of alcohol use remission coding (11.4% vs 13.6%; HR

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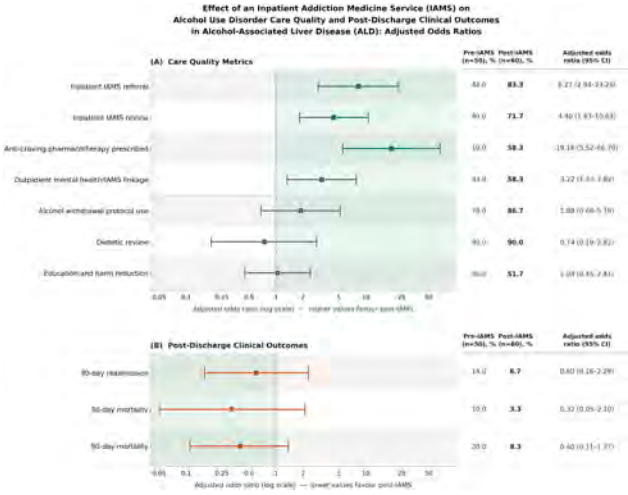
0.83, 95% CI 0.71–0.97; p = 0.018), potentially reflecting reduced severity of active alcohol use in this group. **Conclusion:** In a large, propensity-matched real-world cohort of patients with MetALD, GLP-1 RA therapy was associated with a profound reduction in all-cause hepatic decompensation, liver disease progression, hospitalizations, and severe alcohol-related clinical events. These findings suggest that GLP-1 RAs may serve as a powerful therapeutic strategy to modify the clinical trajectory of MetALD.

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3071 | INPATIENT ADDICTION MEDICINE SERVICE IMPROVES ANTI-CRAVING PHARMACOTHERAPY AND MULTIDISCIPLINARY CARE IN ALCOHOL-ASSOCIATED LIVER DISEASE: AN AUSTRALIAN COHORT STUDY

James Chen[1] Kavindya Perera[1] Damien Foo[2] Kavita Seth[1] Ashleigh Kapnoullas[1] Simon Hazeldine[1], [1]Fiona Stanley Hospital, [2]Curtin University

Background: Anti-craving pharmacotherapy and integrated multidisciplinary care for alcohol use disorder (AUD) are markedly underutilised in inpatients with alcohol-associated liver disease (ALD), despite consistent evidence of benefit. The clinical impact of a the introduction of a hosptial inpatient addiction medicine service (IAMS) on hepatology patients is poorly understood. We evaluated whether IAMS implementation improved adherence to British Association for the Study of the Liver (BASL)/British Society of Gastroenterology (BSG) alcohol-related liver disease (ArLD) quality standards and short-term clinical outcomes. **Methods:** Single-centre retrospective pre–post cohort study at a Western Australian tertiary referral centre. Consecutive adult inpatients admitted under hepatology with ALD and active alcohol use (or < 60 days' abstinence) were identified across two 6-month study periods: pre-IAMS (2021; n = 50) and post-IAMS (2024; n = 60). Seven BASL/BSG quality domains and clinical outcomes were assessed. Comparisons used logistic regression and log-binomial generalised linear models, adjusted *a priori* for age, sex, Model for End-Stage Liver Disease (MELD) score and Charlson Comorbidity Index (CCI). **Results:** Cohorts were balanced for age (51.3 ± 10.4 years), MELD (22.7 ± 8.0), CCI (4.0 ± 1.7) and length of stay (7.9 days); 11.8% identified as Aboriginal and/or Torres Strait Islander. Post-IAMS, adjusted process metrics improved markedly: AUDIT-C screening 0% to 56.7%; inpatient alcohol and other drug (AOD) referral 44% to 83.3% (aOR 8.27, 95% CI 2.94–23.26) and review 40% to 71.7% (aOR 4.40, 1.83–10.63); and any anti-craving pharmacotherapy 10% to 58.3% (aOR 19.18, 5.52–66.70). Addiction medicine initiated 38.3% of post-IAMS prescriptions versus 2% pre-IAMS, directly implicating the service model. Outpatient mental health/AOD linkage rose 34% to 58.3% (aOR 3.22, 1.33–7.82). Pre-existing care domains — withdrawal protocol use (78% to 86.7%), dietetic review (90% to 90%) and education/harm reduction (56% to 51.7%) — showed no significant change. Favourable but underpowered trends were observed for post-discharge 30-day readmission (14% to 6.7%), 30-day mortality (10% to 3.3%) and 90-day mortality (20% to 8.3%). **Conclusion:** Introduction of a dedicated inpatient addiction medicine service for hepatology produced a near 20-fold adjusted increase in anti-craving pharmacotherapy and substantial gains in screening, multidisciplinary engagement and outpatient linkage for ALD inpatients, without disrupting existing care domains. This study demonstrates that integrated addiction–hepatology pathways can rapidly close a longstanding evidence–practice gap in AUD pharmacotherapy, with clinical outcomes trending favourably and warranting powered prospective evaluation.



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3072 | NALTREXONE VERSUS ACAMPROSATE IN COMPENSATED ALCOHOL-ASSOCIATED CIRRHOSIS: A PROPENSITY-MATCHED ANALYSIS OF MORTALITY AND LIVER-RELATED OUTCOMES

Davis Kuruvilla[1] Elan Adhami[1] Amanda Julia-Rios[1] Paul Alvarez[1] John Nahas[1] Aya Akhras[1] Waseem Wahood[2] Samer Wahood[3] Bernardo Reyes[1], [1]HCA Aventura Florida, [2]University of Miami, [3]Warren Alpert Medical School

Background: Alcohol use disorder (AUD) drives progression of alcohol-associated liver disease (ALD), yet pharmacotherapy remains underutilized in cirrhosis. The 2019 AASLD Practice Guidance suggests acamprosate or baclofen in ALD but does not endorse naltrexone due to historical hepatotoxicity concerns, despite the FDA removing its black box warning in 2013. The 2024 ACG guideline conditionally suggests both agents in compensated ALD. No study has directly compared liver-specific outcomes between naltrexone and acamprosate in compensated alcohol-associated cirrhosis. This study compared hepatic decompensation, all-cause mortality, and hospitalizations between these agents in this population. **Methods:** We conducted a retrospective cohort study using the TriNetX US Collaborative Network, identifying adults ≥18 years with compensated alcoholic cirrhosis and concurrent AUD. Patients with decompensation, viral hepatitis coinfection, hepatocellular carcinoma, or prior liver transplant were excluded. Cohorts were defined by receipt of naltrexone or acamprosate after cirrhosis diagnosis; cross-over patients were excluded. Propensity score matching (1:1) balanced demographics, comorbidities, and laboratory values. Outcomes over 5 years included hepatic decompensation, all-cause mortality, alcohol-related hospitalizations, and liver-related hospitalizations. Kaplan-Meier survival analysis and Cox proportional hazards models were used. $P < 0.05$ was significant. **Results:** After matching, 801 patients were included per cohort. Mean age (51.3 ± 12.0 vs 51.6 ± 11.8 years; p = 0.536) and sex (71.2% male both) were comparable. Baseline comorbidities and labs were well-balanced (all standardized differences < 0.05). Mean follow-up was 700 ± 619 vs 657 ± 621 days. Hepatic decompensation rates were similar (5.6% vs 5.4%; OR 1.02, 95%CI 0.65-1.62, p = 0.922; HR 0.95, 95%CI 0.61-1.49, p = 0.836). Naltrexone was associated with lower all-cause mortality (9.5% vs 13.1%; RR 0.72, 95%CI 0.55-0.96, p = 0.022; HR 0.68, 95%CI 0.50–0.91, log-rank p = 0.009). Alcohol-related hospitalizations did not differ (79.3% vs 76.3%; OR 1.19, 95%CI 0.94-1.51, p = 0.149). Liver-related hospitalizations were comparable (64.7% vs 65.3%; OR 0.97, 95%CI 0.79-1.20, p = 0.793), though survival analysis trended toward naltrexone (HR 0.89, 95% CI 0.78-1.00, p = 0.050). **Conclusion:** In this propensity score-matched cohort with compensated alcohol-associated cirrhosis, naltrexone was associated with a 28% relative reduction in all-cause mortality compared to acamprosate, with similar rates of hepatic decompensation and hospitalizations. These findings challenge historical reluctance to prescribe naltrexone in cirrhosis and support its consideration as first-line AUD pharmacotherapy in compensated ALD. Prospective trials are warranted.

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3073 | MAPPING GLOBAL VARIATION IN STANDARD DRINK DEFINITIONS AND THEIR RELATIONSHIP WITH ALCOHOL-RELATED OUTCOMES

Kriti Soni[1] Rylyn Reyes[1] Ximena Parraga[1] Denisse Rubio Cruz[2] Joshua Chen[3] Adelina Horhat[4] Hyundam (Dami) Gu[1] S. Fisher Rhoads[1] Vinay Jahagirdar[1] Kavin Parmar[1] Krishan Patel[1] Stephen Hoang[1] Luis Díaz[5] Juan Pablo Arab[1], [1]Virginia Commonwealth University, [2]Lahey Hospital; Virginia Commonwealth University, [3]Virginia Commonwelath University, [4]Department of Hepatology, Henri Mondor University Hospital, [5]Pontificia Universidad Católica de Chile

Background: Alcohol-related risk assessment, surveillance, and public health guidance rely on standardized definitions of alcohol exposure; however, national "standard drink" definitions vary substantially across countries. Because drinking behaviors, heavy drinking thresholds, and risk communication are frequently reported in units of drinks rather than grams of ethanol, inconsistent definitions may limit cross-country comparisons and distort the interpretation of alcohol-related risk. Despite the World Health Organization (WHO) recommendation of a 10-g ethanol benchmark, the global distribution of standard drink definitions and their relationship with alcohol-related outcomes remain poorly characterized. **Methods:** A cross-sectional ecological analysis was conducted using data from the 2024 WHO Global Status Report on Alcohol and Health, the WHO Global Information System on Alcohol and Health, the World Bank, national guidelines, and published literature across 185 countries. The exposure of interest was the national standard drink definition (grams of ethanol). Primary outcomes included heavy episodic drinking (HED), alcohol use disorder (AUD), and cirrhosis mortality rates (per 100,000). Alcohol per capita (APC) was assessed as a potential confounder.

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Bivariate relationships were evaluated using Spearman's rank correlation. **Results:** Among 185 countries, 64 (34.6%) had available standard drink definitions (M = 11.8g, SD = 2.9), ranging from 4-25 g. Missing formal definitions were non-random and concentrated in African and Eastern Mediterranean regions. The analytic sample was dominated by the Americas (63.6%) with a median of 14 g and Europe (53%) with a median of 10 g. HED prevalence ranged from 0.2-48.5% (M = 20.2%), AUD prevalence averaged 2.3%, and cirrhosis mortality averaged 7.4 per 100,000. APC was strongly correlated with HED (ρ = 0.78). Standard drink size displayed weak-to-modest associations with HED (ρ = 0.02), AUD (ρ = 0.07, and cirrhosis mortality (ρ = 0.16). Regional clustering was identified as a primary source of confounding, limiting the interpretability of bivariate associations. **Conclusion:** Wide variation in standard drink definitions globally limits the comparability of alcohol surveillance and risk communication. The observed regional clustering and weak bivariate associations highlight the need for more robust analytical approaches to clarify their public health implications.

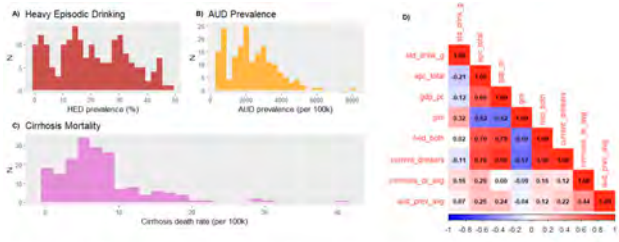


Figure 1. A. HED prevalence distribution; **B.** AUD prevalence distribution; **C.** Cirrhosis mortality distribution; **D.** Spearman correlation matrix among key variables.

Disclosures: Kriti Soni:Nothing to Disclose, Rylyn Reyes:Nothing to Disclose, Ximena Parraga:Nothing to Disclose, Denisse Rubio Cruz:Nothing to Disclose, Joshua Chen:Nothing to Disclose, Adelina Horhat: Nothing to Disclose, Hyundam (Dami) Gu:Nothing to Disclose, S. Fisher Rhoads:Nothing to Disclose, Vinay Jahagirdar:Nothing to Disclose, Kavin Parmar:Nothing to Disclose, Krishan Patel:Nothing to Disclose, Stephen Hoang:PS Fertility: Consultant, Remedy Plan Inc. Consultant, Luis Díaz:Nothing to Disclose, Juan Pablo Arab:Nothing to Disclose.

3074 | SMALL ACTIVATING RNA RESTORES HNF4α DYSREGULATION IN ALCOHOL ASSOCIATED HEPATITIS

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Background: Alcohol-associated hepatitis (AH) represents a severe form of alcohol-associated liver disease (ALD) with high mortality and limited effective medical therapies. Hepatocyte Nuclear Factor 4 Alpha (HNF4α), a master hepatocyte transcription factor, maintains liver function, metabolic homeostasis, hepatocyte differentiation and maturation. Driven by distinct promotors, HNF4α has two major isoforms: HNF4α -P1 (P1) found in normal adult liver maintaining mature liver function and HNF4α –P2 (P2) predominantly in fetal, supporting proliferation and regeneration. Oxidative stress and inflammation in AH lead to dysregulation of HNF4a isoforms, loss of P1 dominance and liver function. Long noncoding antisense RNA: HNF4α-AS1 may contribute to P1 and P2 balance. We hypothesize: restoring P1 expression in AH will enhance hepatocyte maturation and function. Thus, we aim to develop a novel therapeutic strategy that can modulate P1 expression using small activating RNA (saRNA) targeting HNF4α-AS1. **Methods:** P1 and P2 isoforms were analyzed in liver tissues from AH and control patients using RT-PCR and *in situ* hybridization (ISH). Screenings in Huh7 cells were performed to identify saRNA that upregulate P1 expression. Transforming growth factor-beta 1(TGFβ1) was used to treat Huh7 cells and induce HNF4α dysregulation as seen in AH patients. RNA sequencing was performed to define transcriptomic changes. GalNAc conjugated saRNA was validated in precision cut liver slices (PCLS) derived from ALD patients. **Results:** P1 and HNF4a-AS1 levels were significantly reduced in AH livers compared to control human livers, shown by both mRNA and isoform-specific ISH via Basescope. TGFβ1 induced P1 down-regulation and P2 upregulation in Huh7 cells *in vitro* in both RNA and protein analyses. Large-scale screening identified multiple saRNAs that significantly upregulate P1 expression. Efficacy of HNF4α-saRNA was validated by enhanced P1 (Fig.1), HNF4α-AS1 expressions, significantly upregulated downstream genes (OTC, CYP3A4, CYP27A1, CYP7A1 and HNF1a). RNAseq showed elevated epithelial cell proliferation pathways upon saRNA treatment. *ex vivo* PCLS from ALD patients, showed robust GalNAc-HNF4α saRNA uptake by hepatocytes and upregulation of P1 along with downstream genes, similar to findings *in vitro*. **Conclusion:** Dysregulation of HNF4α isoforms represents a key pathogenic factor in AH leading to the loss of hepatocellular maturity and liver function. saRNA targeting HNF4α-AS1 induces P1 expression, restoring P1-specific transcriptome linked to normal liver function in both *in vitro* and *ex vivo* human models. GalNAc-HNF4α-saRNA may represent a novel therapeutic strategy for the treatment of AH.

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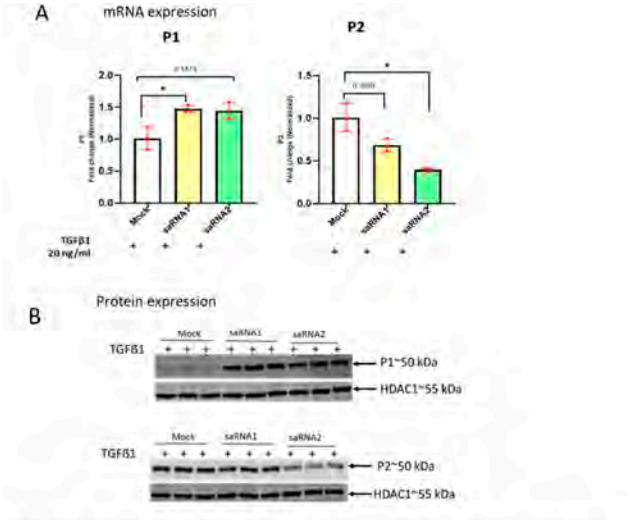


Figure 1. Huh7 cells treated with two saRNA (saRNA1 and saRNA2) following 8 hours of TGFβ1 treatment. **A** and **B**: mRNA and protein expression of HNFα4-P1 and HNFα4-P2 in saRNA treated cells.

Disclosures: Susmita Bhattarai:Nothing to Disclose, Sehrish Naz:Nothing to Disclose, Shanshan Su:Nothing to Disclose, Hua Xu:Nothing to Disclose, Nezam Afdal:Nothing to Disclose, Pooja Dua:Nothing to Disclose, Zhenghui Jiang:Nothing to Disclose.

3075 | NATIONAL TRENDS, INPATIENT OUTCOMES, AND RESOURCE UTILIZATION AMONG ALCOHOL-ASSOCIATED HEPATITIS, ALCOHOL-ASSOCIATED CIRRHOSIS, AND NON-ALCOHOL CIRRHOSIS IN THE UNITED STATES, 2016–2023

Talal Bhatti[1] Wanyu Zhang[2] Mangesh Padala[3] Jamil Abdo[2] David Maundu[4] Suthat Liangpunsakul[5] Maiying Kong[2] Ashwani Singal[2] Fatima Elmustafa[6], [1]Northwell Health, [2]University of Louisville, [3]Liver Institute -Methodist Dallas Medical Center, [4]KUMC Wichita,, [5]Indiana University, [6]Henry Ford Warren

Background: Cirrhosis, including alcohol-associated liver disease, remains a major cause of liver-related hospitalization in the United States, yet contemporary national data comparing alcohol-associated hepatitis (AH), alcohol-associated cirrhosis (AC), and non-alcohol cirrhosis (NAC) are limited. We evaluated temporal trends, inpatient outcomes, and resource utilization across these phenotypes. **Methods:** Weighted hospitalizations from the National Inpatient Sample (2016–2023) were analyzed using ICD-10 codes to identify patients with AH, AC, and NAC. Trends were examined between 2016 and 2023. Healthcare resource utilization was compared for 2023 using survey-weighted statistical tests with Bonferroni-adjusted pairwise analyses **Results:** From 2016 to 2023, hospitalizations increased across all cohorts, with AH admissions increasing from 116,880 to 163,220 (+39.6%), AC from 291,240 to 392,490 (+34.8%), and NAC from 403,870 to 546,925 (+35.4%). Mean hospitalization charges also increased from $53,527.58 to $84,712 in AH, from $66,662.65 to $101,585 in AC, and from $65,001 to $98,394 in NAC. In 2023, compared with AC and NAC, hospitalizations with AH had higher rates of intensive care for mechanical ventilation (2.9%), management of shock (0.9%), and continuous renal replacement therapy, or CRRT (1.3%). Inpatient mortality was 6.2% in AC vs. 5.6% in NAC and 4.5% in AH. AC also had the longest average hospitalization (6.62 days) with the total charges ($100,049). Disposition among survivors of hospitalization, AH had the highest rates of discharge to home and leaving against medical advice in 69% and 6.2%, respectively. In contrast, AC and NAC were more likely to be transferred to another hospital or use home health care. During the hospital stay, NAC had the highest rates of dialysis at 7.0%, whereas AC had the highest rates of paracentesis (27.9%) and of liver transplant (1.1%). Palliative care was used most often in AC and NAC at 9.0 and 9.3%, respectively (**Table**). **Conclusion:** Inpatient burden of advanced liver disease of cirrhosis and AH is increasing in the US. The healthcare and resource utilization in 2023 varied, with the highest a) inpatient mortality and resource utilization in AC, b) palliative care, dialysis, and transfer to another facility and home health care in NAC, and c) ICU care, discharge to home, and leaving against medical advice in AH. These differences in healthcare and resource use are relevant in building strategies to optimize inpatient care and transition to outpatient management, with the long-term goal of improving morbidity and mortality in hospitalized patients with advanced liver disease.

Table. Healthcare Burden and Resource Utilization in 2023: Alcohol-Associated Hepatitis vs. Alcohol-Associated Cirrhosis vs. Non-Alcohol-Associated Cirrhosis

	Alcohol-Associated Hepatitis n=163,220	Alcohol-Associated Cirrhosis n=332,500	Non-Alcohol Cirrhosis n=536,545	P value
Survival				
Inpatient mortality	7,265 (4.5)[a]	20,570 (6.2)[a]	30,150 (5.6)[a]	<0.001
Liver Care Procedures / Resources				
Paracentesis	25,700 (15.7)[a]	92,685 (27.9)[a]	93,795 (17.5)[a]	<0.001
Liver transplant	750 (0.5)[a]	3,760 (1.1)[a]	3,985 (0.7)[a]	<0.001
Dialysis	3,225 (2.0)[a]	13,100 (3.9)[a]	37,725 (7.0)[a]	<0.001
Palliative care consultation	8,810 (5.3)[a]	30,100 (9.0)[a]	50,025 (9.3)[a]	<0.001
Intensive Care Unit Management				
Mechanical ventilation	4,680 (2.9)[a]	9,250 (2.5)[a]	8,765 (1.6)[a]	<0.001
Shock	1,405 (0.9)[a]	2,740 (0.8)[a]	3,570 (0.7)[a]	0.0001
CRRT	2,050 (1.3)[a]	3,570 (1.1)[a]	4,520 (0.8)[a]	<0.001
Resource Utilization				
Length of stay in days (mean, SE)	6.34 (0.06)[a]	6.62 (0.06)[a]	6.46 (0.05)[a]	<0.001
Total charges in $ (mean, SE)	84,711.98 (1,911.24)[a]	100,048.80 (2,063.34)[a]	98,355.53 (1,616.56)[a]	<0.001
Disposition of Survivors				<0.001
Routine discharge to home	112,425 (69.0)	186,560 (56.2)	267,945 (50.0)	
Transfer to a short-term hospital	4,285 (2.6)	10,070 (3.0)	15,160 (2.8)	
Transfer to another facility	17,215 (10.6)	54,386 (16.4)	102,955 (19.2)	
Home health care	11,755 (7.2)	47,575 (14.3)	107,375 (20.0)	
Against medical advice	10,055 (6.2)	13,020 (3.9)	12,625 (2.4)	

For categorical variables, weighted counts and percentages are shown. For continuous variables, weighted means and standard errors are shown

[a] Significant difference between alcohol-associated hepatitis and alcohol-associated cirrhosis, excluding alcohol-associated hepatitis.

[b] Significant difference between alcohol-associated hepatitis and non-alcohol-associated cirrhosis.

[c] Significant difference between alcohol-associated cirrhosis excluding alcoholic hepatitis and non-alcohol-associated cirrhosis.

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3076 | THE DESIGNER CYTOKINE IC7FC ATTENUATES ALCOHOL-ASSOCIATED LIVER DISEASE THROUGH IL-22–STAT3–DRIVEN LIVER REGENERATION

Fernanda Raya Tonetti[1] Phillipp Hartmann[2] Hui Han[1] Noemi Cabre[1] Marcos Fondevila[1] Alvaro Eguileor[1] Abraham Meijnikman[1] Yuxuan Jiang[1] Peter Starkel[3] Michael Karin[1] Mark Febbraio[4] Bernd Schnabl[2] Cristina Llorente[2], [1]University of California San Diego, [2]University of California, San Diego, [3]Cliniques Universitaires Saint-Luc, Brussels, Belgium, [4]Monash Institute of Pharmaceutical Sciences, Monash University, Melbourne, Victoria, Australia

Background: Alcohol-associated liver disease (ALD) is a leading cause of chronic liver disease worldwide and is characterized by hepatocyte injury, inflammation, steatosis, and impaired regenerative responses. Although activation of IL-22–STAT3 signaling promotes hepatocyte survival and tissue repair, therapeutic approaches targeting this pathway remain limited. IC7Fc is a designer gp130 agonist engineered to selectively activate regenerative signaling while avoiding the pro-inflammatory effects associated with IL-6 trans-signaling. However, its therapeutic potential in ALD has not been explored. **Methods:** Here, we investigated whether IC7Fc protects against ethanol-induced liver injury through hepatocyte-intrinsic IL-22–STAT3 signaling. Alcohol-associated liver disease was induced using the chronic-plus-binge NIAAA ethanol feeding model in wild-type (WT), hepatocyte-specific Stat3-deficient (*Stat3*$^{\Delta hep}$), and hepatocyte-specific Il22ra1-deficient (*Il22ra1*$^{\Delta hep}$) mice. During the final 7 days of ethanol feeding, mice received daily intraperitoneal injections of IC7Fc (1 mg/kg/day) or vehicle control. **Results:** IC7Fc markedly attenuated ethanol-induced liver injury in WT mice, as demonstrated by reduced plasma alanine aminotransferase levels, decreased hepatic steatosis, and attenuation of hepatic inflammation and fibrosis. Mechanistically, IC7Fc increased hepatic STAT3 phosphorylation and elevated hepatic IL-22 protein expression, accompanied by induction of hepatoprotective genes including Mcl1 and Bcl-xL and increased hepatic PCNA protein expression. Bulk liver RNA sequencing further revealed enrichment of regenerative and STAT3-associated transcriptional programs in IC7Fc-treated mice. In contrast, the protective effects of IC7Fc were completely abolished in *Stat3*$^{\Delta hep}$ and *Il22ra1*$^{\Delta hep}$ mice, demonstrating that IC7Fc promotes a hepatocyte IL-22–STAT3 regenerative program required for protection against ALD. Analysis of publicly available human liver RNA-seq datasets from patients with alcohol-associated hepatitis confirmed dysregulation of regenerative and STAT3-related pathways in human disease. **Conclusion:** Together, these findings identify IC7Fc as a potent therapeutic activator of hepatocyte IL-22–STAT3 signaling that promotes liver regeneration and protects against alcohol-associated liver disease. Our study establishes selective gp130 pathway activation as a promising regenerative strategy for ALD while avoiding the inflammatory liabilities associated with conventional IL-6 signaling.

Disclosures: Fernanda Raya Tonetti:Nothing to Disclose, Phillipp Hartmann:Nothing to Disclose, Hui Han: Nothing to Disclose, Noemi Cabre:Nothing to Disclose, Marcos Fondevila:Nothing to Disclose, Alvaro Eguileor: Nothing to Disclose, Abraham Meijnikman:Nothing to Disclose, Yuxuan Jiang:Nothing to Disclose, Peter Starkel:Nothing to Disclose, Michael Karin:Nothing to Disclose, Mark Febbraio:Nothing to Disclose, Bernd Schnabl:Mabwell Therapeutics: Consultant, Ambys Medicines: Consultant, Surrozen: Consultant, Nterica Bio: Stock – privately held company, Axial Biotherapeutics: Grant/Research Support, Prodigy Biotech: Grant/Research Support, CymaBay Therapeutics: Grant/Research Support, Intercept Pharmaceuticals: Grant/Research Support, ChromoLogic: Grant/Research Support, Apollo Biotherapeutics: Grant/Research Support, Boehringer Ingelheim Pharma: Consultant, Cristina Llorente:Nothing to Disclose.

3077 | INTEGRATED SPATIAL LIPIDOMICS AND PROTEOMICS REVEAL REGION-SPECIFIC LIPID COMPARTMENTALIZATION AND DISTINCT LIPID METABOLIC REPROGRAMMING IN ALCOHOL-ASSOCIATED CIRRHOSIS AND HEPATITIS

Le Day[1]; [1]Pacific Northwest National Laboratory

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Background: Alcohol-associated liver disease (ALD) encompasses a spectrum of progressive injuries, including alcohol-associated hepatitis (AH) and alcohol-associated cirrhosis (AC). Despite the significant morbidity and mortality associated with ALD, the molecular mechanisms underlying the progression of these conditions remain poorly understood and spatial molecular heterogeneity is increasingly recognized as a driver of disease progression. **Methods:** We applied matrix-assisted laser desorption/ionization mass spectrometry imaging (MALDI-MSI) at 20 μm resolution to generate high-plex spatial lipidomics maps of human liver explants from healthy controls (HC) and patients with AC and AH. The spatially resolved lipid signatures were subsequently used to guide laser capture microdissection (LCM) for precise sampling of three distinct micro-environments: lipid-rich/fibrotic regions, the border of lipid-rich and lipid-depleted regions, and the center of lipid-depleted/non-fibrotic areas. Captured material underwent microscale proteomics sample preparation (microPOTS) followed by data-independent acquisition (DIA) analysis on the Orbitrap Astral mass spectrometer. **Results:** In AC, unsupervised clustering and region-of-interest analysis identified discrete lipid species selectively enriched within fibrotic septa versus non-fibrotic parenchyma. In contrast, the lipids that distinguish fibrosis and non-fibrosis regions in AC exhibited markedly more dispersed, non-specific distributions across AH tissue, losing clear spatial segregation. The spatial lipidomics informed spatial proteomics analysis yielded deep proteome coverage (>6,000 proteins) from ~100 cells. Quantitative proteomics demonstrated distinct lipid metabolism between AH and AC. AC samples showed coordinated upregulation of lipid mediators and extracellular matrix-remodeling enzymes within lipid-rich/fibrotic and border regions, whereas AH tissue exhibited broader dysregulation of mitochondrial β-oxidation, peroxisomal lipid catabolism, and phospholipid remodeling enzymes across the regions. Pathway enrichment further highlighted AH-specific enrichment of pro-inflammatory signaling that was absent in AC. **Conclusion:** Taken together, MALDI-MSI-guided spatial proteomics demonstrates that lipid compartmentalization is preserved in AC but disrupted in AH, corresponding to distinct proteomic reprogramming of lipid metabolic networks. This integrated spatial multi-omic approach provides mechanistic insight into ALD progression and identifies spatially restricted therapeutic targets linked to lipid dysregulation in ALD.
Disclosures: Le Day:Nothing to Disclose.

3078 | SIPAT SUBSTANCE DOMAIN, NOT OVERALL SIPAT SCORE, IS PREDICTIVE OF SUSTAINED ALCOHOL RECIDIVISM AT 1-YEAR POST-LIVER TRANSPLANT AMONG PATIENTS WITH ALCOHOL ASSOCIATED CIRRHOSIS

Chung-Heng Liu[1] Manida Wungjiranirun[2] Dekey Lhewa[1] Arnab Mitra[2], [1]Oregon Health & Science University, [2]Oregon Health And Science University

Background: The Stanford Integrated Psychosocial Assessment for Transplantation (SIPAT) offers a standardized method for psychosocial evaluation for liver transplant. Current data suggest SIPAT is predictive of mortality and medication adherence post- liver transplant. However, data on SIPAT in predicting return to alcohol use, using objective markers, among those with alcohol-related cirrhosis is limited. The primary aim of this study is to evaluate whether overall SIPAT score or individual SIPAT domains are predictive of alcohol recidivism, measured by an objective method like phosphatidylethanol (PEth). **Methods:** This was a retrospective analysis of liver transplant performed at a large transplant center from 2015-2024. All patients with alcohol-associated cirrhosis (AC) who underwent pre-transplant evaluation and transplant with PEth within 1-year post-liver transplant were included. Primary outcome was PEth positivity, defined as more than 20ng/mL from 2 or more consecutive follow-ups, within 1-year after liver transplant. Individual domain within the SIPAT (readiness, social support, psychological, and substance use), total SIPAT score, and SIPAT $\geq$ 21 (suggestive of high psychosocial risk) were evaluated as predictors of PEth positivity. Logistic regression was used to assess the associations between SIPAT score and PEth positivity. Kaplan-Meier was performed to evaluate time to first PEth positivity stratified by SIPAT $\geq$ 21. **Results:** A total of 187 patients with alcohol-associated cirrhosis who underwent liver transplant were included. 62% were male, 72% white and 12% Latinx, median age 52 (IQR 45-59), median MELD 29 (IQR 25-34), and 15% had positive PEth within 1 year of liver transplant. Among SIPAT domains, higher substance use scores were significantly associated with increased odds of alcohol recidivism (OR 1.13, p= 0.016). After adjusting for gender, age at transplant, MELD, race/ethnicity, insurance type, each 1-point increase in the SIPAT substance use domain score was associated with a

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13% increase in odds of 1-year PEth positivity (p = 0.042) (Figure 1). In addition, there was no significant difference in time to PEth positivity between patients with total SIPAT < 21 and those SIPAT ≥ 21 (p = 0.266) (Figure 2). **Conclusion:** Less than a quarter of patients with alcohol-related cirrhosis had sustained alcohol relapse. Total SIPAT score and individual SIPAT domains of readiness, social support, and psychological were not independently associated with alcohol use post liver transplant. Substance use domain is a predictor of recidivism of alcohol within 1 year of transplant among patients with alcohol-associated cirrhosis. These findings suggest the substance use domain may provider greater utility than total SIPAT score in predicting post-transplant alcohol use. Further studies are needed to further validate psychosocial assessments in predicting recidivism.

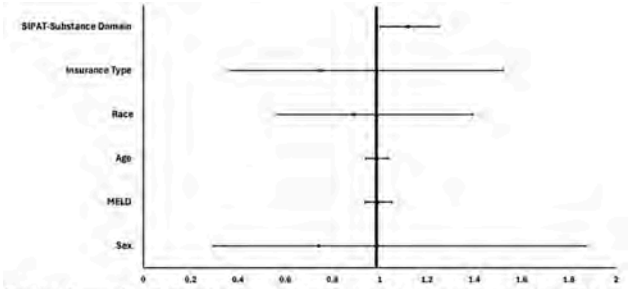


Figure 1. Forrest plot of adjusted odds ratio for predictors of 1-year post liver transplant PEth positivity

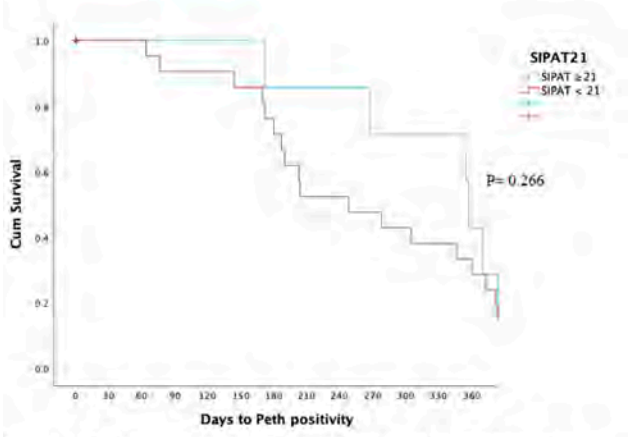


Figure 2. Time to PEth positivity after liver transplantation by SIPAT risk category: high risk (total SIPAT ≥21) and low risk (total SIPAT < 21).

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3079 | TRENDS AND DISPARITIES IN ALCOHOLIC CIRRHOSIS MORTALITY IN THE UNITED STATES, 1999–2024: A 25-YEAR CDC WONDER ANALYSIS INCLUDING THE POST-COVID ERA

Faraz Waheed[1], [1]Benefis Health System

Background: Alcoholic cirrhosis is a leading cause of liver-related mortality in the United States, with rates rising over the past two decades. Prior analyses have ended at 2022, leaving the post-pandemic recovery period uncharacterized. We examined alcoholic cirrhosis mortality trends from 1999 through 2024, with particular attention to the COVID-19 era and subsequent recovery, and stratified findings by sex, race and ethnicity, age group, and US census region **Methods:** We conducted a retrospective cross-sectional analysis using the CDC WONDER Multiple Cause of Death databases. Decedents aged 25 years and older with alcoholic cirrhosis (ICD-10 K70.3) listed as the underlying cause of death were identified using the Bridged-Race database (1999–2020) and the Single-Race expanded database (2018–2024). Age-adjusted mortality rates (AAMRs) were calculated per 100,000 population using the year 2000 US standard population. Joinpoint regression was used to identify inflection points and to compute annual percent change (APC) and average annual percent change (AAPC) with 95% confidence intervals. **Results:** Between 1999 and 2024, 351,453 alcoholic cirrhosis deaths were recorded. The AAMR for alcoholic cirrhosis more than doubled from 4.1 to 8.7 per 100,000 (AAPC +3.2%). Joinpoint analysis identified three inflection points (2009, 2018, 2021) with the steepest acceleration during 2018–2021 (APC +11.88%, 95% CI 7.49–13.82, p < 0.001). After peaking at 10.1 per 100,000 in 2021, mortality declined through 2024 (APC −4.40%, p = 0.006) but remained 19% above the 2019 baseline. Disproportionate increases were observed among adults aged 25–34 years (COVID-era APC +25.53%) and 35–44 years (+23.39%); among American Indian and Alaska Native individuals (2021 AAMR 39.9, nearly four times the national rate); and among women, whose male-to-female AAMR ratio narrowed from 3.5:1 in 1999 to 2.2:1 in 2021. Geographic acceleration was greatest in the Midwest (+14.89%) and Northeast (+12.79%) during 2018–2021. **Conclusion:** Alcoholic cirrhosis mortality

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surged dramatically during COVID-19 and remains elevated through 2024, with no major subgroup recovering to pre-pandemic levels. The disproportionate burden in young adults, women, and AIAN populations represents an evolving public health crisis requiring targeted prevention, expanded access to alcohol use disorder treatment, integration of liver disease screening into primary care, and culturally tailored interventions in high-risk communities.



Disclosures: Faraz Waheed:Nothing to Disclose.

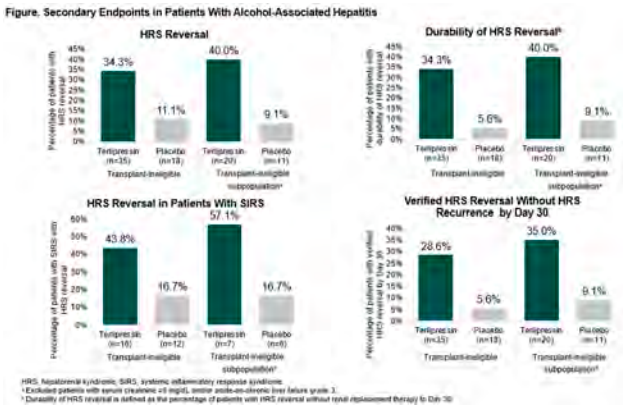
3080 | EFFICACY AND SAFETY OF TERLIPRESSIN IN PATIENTS INELIGIBLE FOR LIVER TRANSPLANT WITH HEPATORENAL SYNDROME-ACUTE KIDNEY INJURY AND ALCOHOL-ASSOCIATED HEPATITIS: AN EXPLORATORY ANALYSIS OF THE CONFIRM TRIAL

Todd Frederick[1] Nancy Reau[2] Laurie Larson[3] HoChong Gilles[4] Nneka Ufere[5] Kevin Regner[6] Anooj Shah[7] Richard Wu[8] Christopher White[8] Kavish Patidar[9], [1]California Pacific Medical Center, San Francisco, CA, [2]Rush University Medical Center, Chicago, IL, [3]University of Minnesota Physicians, Minneapolis, MN, [4]Central Virginia VA Health Care System, Richmond, VA, [5]Massachusetts General Hospital, Boston, MA, [6]Medical College of Wisconsin, Milwaukee, WI, [7]formerly affiliated with Mallinckrodt Hospital Products, Inc (A Keenova Therapeutics Company), [8]Mallinckrodt Hospital Products, Inc (A Keenova Therapeutics Company), Bridgewater, NJ, [9]Houston Methodist Hospital, Houston, TX

Background: Hepatorenal syndrome-acute kidney injury (HRS-AKI) is a functional renal failure caused by hemodynamic changes in patients (pts) with ascites and portal hypertension. The standard of care for treatment of HRS-AKI is vasoconstrictor therapy, preferably terlipressin, which is FDA-approved for use in adults with HRS with rapid reduction in kidney function. Liver transplant (LT) is a curative treatment, but pts with HRS-AKI and alcohol-associated hepatitis (AH) are often ineligible for LT and have a poor prognosis, particularly if HRS-AKI remains untreated. In the phase 3 CONFIRM trial (NCT02770716), alcohol/substance use was the most common reason for LT ineligibility (terlipressin, 53.5%; placebo [PBO], 59.5%). Here, we performed an exploratory analysis using CONFIRM data to understand the benefits of terlipressin use in pts with HRS-AKI and AH who were LT-ineligible. **Methods:** In CONFIRM, pts with HRS-AKI were randomized 2:1 to terlipressin or PBO, and concomitant albumin was strongly recommended if clinically appropriate. This exploratory analysis evaluated efficacy and safety of terlipressin in the overall LT-ineligible population with AH and an LT-ineligible subpopulation with AH excluding pts with serum creatinine $\geq$5 mg/dL and/or acute-on-chronic liver failure grade 3. Primary and secondary endpoints from CONFIRM, safety, and incidence of renal replacement therapy (RRT) in pts alive from Day 14 to 90 were analyzed. **Results:** There were 120 pts in CONFIRM with HRS-AKI and AH (n = 81 terlipressin, n = 39 PBO), 53 of whom were LT-ineligible (n = 35 terlipressin, n = 18 PBO). Among pts with AH who were LT-ineligible, 31 pts were also in the subpopulation (n = 20 terlipressin, n = 11 PBO). The percentage of pts with AH with verified HRS reversal was higher for terlipressin vs PBO in both the LT-ineligible population (28.2% vs 5.6%) and subpopulation (35.0% vs 9.1%). Pts with AH who received terlipressin vs PBO also demonstrated better response for all secondary endpoints (Figure). Incidence of RRT in pts with AH who were alive through Day 90 was lower with terlipressin vs PBO (LT-ineligible, 14.3% vs 40.0%; subpopulation, 12.5% vs 25.0%). The percentage of pts with AH experiencing adverse events in the LT-ineligible population receiving terlipressin (88.6%) was similar to the subpopulation (85.0%) and consistent with the overall CONFIRM population (88.0%). Abdominal pain, dyspnea, and respiratory failure were reported in $\geq$10% of pts treated with terlipressin. **Conclusion:** For pts with HRS-AKI and AH in the LT-ineligible population and subpopulation in CONFIRM, terlipressin was more effective than PBO for improving outcomes, including reducing incidence of RRT. The safety profile in these populations was also consistent with the overall CONFIRM population. These results suggest that pts with HRS-AKI and AH who are LT-ineligible may benefit from terlipressin treatment.

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3081 | IGA-TARGETED DYSBIOSIS AND COMPARTMENTALIZED IGA RESPONSES ARE ASSOCIATED WITH DISEASE SEVERITY IN ALCOHOL-ASSOCIATED LIVER DISEASE

David Schöler[1] Cynthia Hsu[2] Takao Miwa[1] Linton Freund[1] Sonja Lang[3] Derrick Fouts[4] Peter Starkel[5] AlcHepNet Investigators[6] Bernd Schnabl[2], [1]Medicine, University of California, San Diego, CA, USA, [2]Medicine, University of California and VA San Diego Healthcare System, San Diego, CA, USA, [3]Gastroenterology and Hepatology, Faculty of Medicine and University Hospital, Cologne, Germany, [4]Human Genomic Medicine, J. Craig Venter Institute, Rockville, MD, USA, [5]Hepatology and Gastroenterology, St. Luc Univ. Hosp., UCLouvain, Brussels, Belgium, [6]Alcoholic Hepatitis Network Investigators

Background: Alcohol-associated liver disease (ALD) is characterized by intestinal dysbiosis, impaired gut barrier function, and microbial translocation that contribute to hepatic inflammation. Immunoglobulin A (IgA), the dominant mucosal antibody, plays a central role in intestinal homeostasis by coating luminal bacteria. We aimed to define fecal and serum IgA responses and characterize IgA-bound bacterial communities across the spectrum of ALD. **Methods:** We included 617 individuals (healthy controls (HC) n = 107, patients with alcohol use disorder (AUD) n = 150, patients with alcohol associated hepatitis (AH) n = 360). Stool IgA was measured in 199 individuals and IgA-bound microbiota in a subset, while serum IgA was measured in 522 individuals. Paired samples from a subset of patients with AUD was available following abstinence. IgA-bound bacteria were isolated using magnetic activated cell sorting (MACS) and analyzed by 16S rRNA gene sequencing. **Results:** Fecal IgA increased with disease severity (AH > AUD > HC) and were associated with distinct microbial compositions. IgA-bound microbial diversity was reduced in AH and partially recovered after abstinence. Beta diversity analyses demonstrated clear separation of IgA-bound bacterial communities by disease state, with enrichment of pathobiontic genera (e.g., *Streptococcus*, *Enterococcus*, *Escherichia/Shigella*) and depletion of beneficial and short chain fatty acid producing families including *Lachnospiraceae* and *Ruminococcaceae*. IgA-bound taxa were associated with disease severity, with commensal bacteria inversely and *Campylobacteraceae* positively correlated with MELD-Na scores. Serum IgA levels were markedly elevated in AH, decreased after abstinence, and were not correlated with fecal IgA, indicating compartmentalized regulation. While fecal IgA was not associated with survival, higher serum IgA was independently associated with reduced 6-month survival in patients with AH. **Conclusion:** ALD is associated with altered mucosal IgA responses and IgA-targeted dysbiosis, characterized by reduced diversity and enrichment of IgA-bound pathobionts. Distinct regulation of

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fecal and serum IgA highlights compartmentalized immune responses in ALD. Serum IgA is linked to disease severity and clinical outcomes, identifying it as a potential prognostic biomarker in ALD.

Disclosures: David Schöler:Nothing to Disclose, Cynthia Hsu:Nothing to Disclose, Takao Miwa:Nothing to Disclose, Linton Freund:Nothing to Disclose, Sonja Lang:Nothing to Disclose, Derrick Fouts:Nothing to Disclose, Peter Starkel: Nothing to Disclose, AlcHepNet Investigators:Nothing to Disclose, Bernd Schnabl:Nothing to Disclose.

3082 | ATRIAL FIBRILLATION AS A PREDICTOR OF ADVERSE HOSPITAL OUTCOMES IN CIRRHOSIS: FINDINGS FROM A NATIONWIDE DATABASE

Frank Lin[1] Brett Cohen[1] Nishanth Eluri[1] Kimberly Chaput[1] Noel Martins[1], [1]St. Luke's University Health Network

Background: Atrial fibrillation (AF) is a common arrhythmia associated with increased mortality, particularly in patients with liver cirrhosis, which exacerbates cardiovascular risks through inflammation and coagulopathy. Alcohol-associated cirrhosis and metabolic-dysfunction associated steatohepatitis (MASH)-related cirrhosis represent distinct etiologies, yet their impact with AF outcomes remains understudied. We aimed to evaluate in-hospital mortality and other outcomes in AF patients with alcohol-associated, MASH, or metabolic-dysfunction and alcohol associated liver disease (MetALD) using a large national database. **Methods:** We analyzed the 2018–2022 National Inpatient Sample (NIS), representing 20% of U.S. hospitalizations. Adult AF patients were stratified by cirrhosis type: alcohol-associated, MASH, and MetALD. Primary outcome was in-hospital mortality. Multivariable logistic regression adjusted for age, sex, race, income, Charlson comorbidity index, hospital characteristics, and comorbidities. ORs with 95% CIs were reported. Analyses used Stata 17. **Results:** Among 22.9 million weighted AF hospitalizations, 190,395 (0.8%) had alcohol-associated cirrhosis, 505,645 (2.2%) had MASH cirrhosis, and 691,820 (3.0%) had MetALD cirrhosis (Table 1). Patients with alcohol-associated cirrhosis were younger (mean age 64.9 years) than those with MASH (71.1 years) or no cirrhosis (75.1 years), with higher male predominance (80.3% vs. ~58% in no cirrhosis). Comorbidity burdens were elevated in cirrhosis groups, with Charlson index ≥ 3 in 82.8% (alcohol-associated), 87.2% (MASH), and 86.0% (MetALD) vs. 56.4% in no cirrhosis. In-hospital mortality was higher in alcohol-associated cirrhosis (9.2%, 17,485 deaths) and MASH (7.9%, 39,860 deaths) compared to no cirrhosis (5.4%, 1.2 million deaths) (Figure 1). OR for mortality was 1.76 (95% CI 1.69-1.82) for alcohol-associated cirrhosis vs. no cirrhosis, 1.26 (95% CI 1.23-1.29) for MASH, and 1.37 (95% CI 1.35-1.40) for MetALD. After full adjustment including comorbidities, ORs attenuated to 1.53 (95% CI 1.47-1.59) for alcohol-associated, 1.23 (95% CI 1.20-1.26) for MASH and 1.23 (95% CI 1.20-1.26) for MetALD. Mean LOS and charges were higher in cirrhosis groups (7.1-7.5 days, $89k-$95k) vs. no cirrhosis (6.1 days, $81k) (Figure 2). **Conclusion:** Cirrhosis significantly elevates in-hospital mortality in AF patients with alcohol-associated etiology conferring the highest risk. Attenuated post-adjustment ORs suggest comorbidities such as malnutrition and ESRD mediate much of the excess risk, highlighting opportunities for targeted interventions including nutritional support and renal management. MASH's rising prevalence underscores its growing public health burden. Limitations include administrative data biases and lack of longitudinal follow-up. Future studies should explore outpatient outcomes and strategies to mitigate cirrhosis-AF interactions.



Figure 1

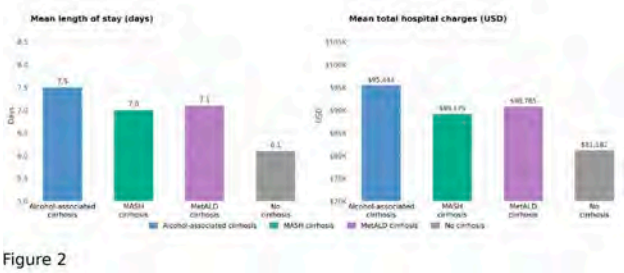


Figure 2

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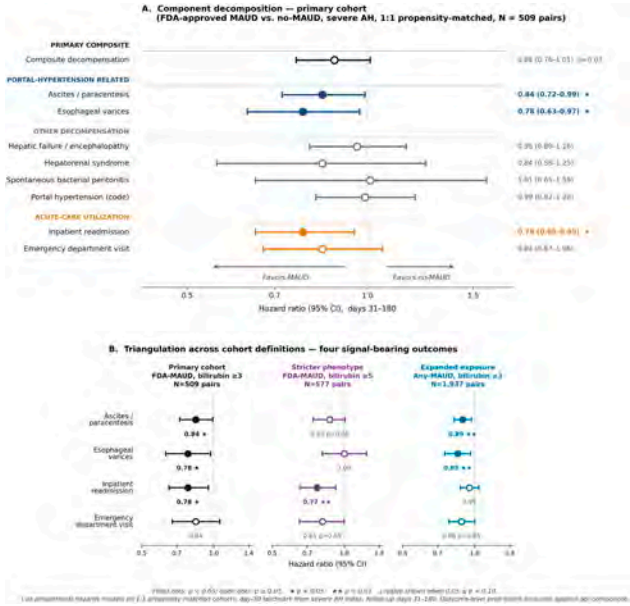
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Disclosures: Frank Lin:Nothing to Disclose, Brett Cohen:Nothing to Disclose, Nishanth Eluri:Nothing to Disclose, Kimberly Chaput:Nothing to Disclose, Noel Martins:Nothing to Disclose.

3083 | EARLY MEDICATION FOR ALCOHOL USE DISORDER AFTER SEVERE ALCOHOL-ASSOCIATED HEPATITIS: PORTAL HYPERTENSION-RELATED EVENTS AND ACUTE-CARE UTILIZATION IN A PROPENSITY-MATCHED TRINETX COHORT

Nourhan Saleh[1] EzzElDien A. Ibrahim[1] Bjorn Rodriguez[1] Mahmoud Majed Mansour[1] Darian Fard[1] Khulood Ahmed[1], [1]University of Missouri

Background: Severe alcohol-associated hepatitis (AH) carries high short-term mortality, readmission, and downstream decompensation. Fewer than 6% of post-AH patients receive FDA-approved medication for alcohol use disorder (MAUD) at discharge despite guideline endorsement. Whether early post-discharge MAUD changes 6-month liver-event trajectories in real-world data remains unsettled while ITAALD recruits. **Methods:** TriNetX US Collaborative Network. Adults ≥18 with severe AH (AH diagnosis plus AST 50–<400 U/L, total bilirubin ≥3 mg/dL, and INR ≥1.5 within ±7 days of index) required a day-30 observability landmark and 365-day MAUD washout. Cohort A initiated FDA-approved MAUD (naltrexone, acamprosate, or disulfiram) in days 0–30 post-AH; Cohort B initiated none. Exclusions: prior transplant, viral/competing liver disease, ESRD, pregnancy, warfarin. 1:1 propensity matching at caliper 0.10 SD logit balanced demographics, binned severity labs, baseline decompensation, acute AH treatment, psychiatric and substance-use comorbidity, healthcare engagement, and concomitant medications (estimable post-match SMDs <0.10). Primary outcome: hepatic decompensation burden/progression composite over days 31–180. Secondary: acute-care utilization and recurrent AH code reappearance. Sensitivities: stricter severe-AH (bilirubin ≥5) and any-MAUD (adding baclofen, gabapentin, topiramate). Cox models estimated HRs. **Results:** 509 FDA-MAUD initiators matched to 509 no-MAUD comparators. Early MAUD was associated with directionally lower 180-day decompensation burden (composite HR 0.88, 95% CI 0.76–1.01, p = 0.07), driven by lower ascites/paracentesis (HR 0.84, 0.72–0.99, p = 0.03) and esophageal varices (HR 0.78, 0.63–0.97, p = 0.03); hepatic failure/encephalopathy, hepatorenal syndrome, and SBP were null. MAUD was associated with lower 180-day inpatient readmission (HR 0.78, 0.65–0.95, p = 0.01), consistent across segments (HR 0.69 days 31–60; 0.71 days 61–120; 0.74 days 121–180). The bilirubin ≥5 cohort showed favorable ascites and hospitalization estimates (N = 577 pairs: ascites HR 0.87, p = 0.06; hospitalization HR 0.77, p = 0.004). The any-MAUD cohort also favored MAUD (N = 1,937 pairs: ascites HR 0.89, p = 0.008; varices HR 0.85, p = 0.008; ED visit HR 0.88, p = 0.05). Recurrent AH code reappearance was null across cohorts, arguing against coding persistence as the main explanation. Mortality and negative-control outcomes were uninterpretable due to event suppression. **Conclusion:** Early FDA-approved MAUD within 30 days after severe AH was associated with lower portal hypertension-related decompensation burden and inpatient utilization within 6 months, with directionally consistent sensitivity analyses. Findings support real-world post-AH MAUD pathways while awaiting ITAALD efficacy data.



Disclosures: Nourhan Saleh:Nothing to Disclose, EzzElDien A. Ibrahim:Nothing to Disclose, Bjorn Rodriguez:Nothing to Disclose, Mahmoud Majed Mansour: Nothing to Disclose, Darian Fard:Nothing to Disclose, Khulood Ahmed:Nothing to Disclose.

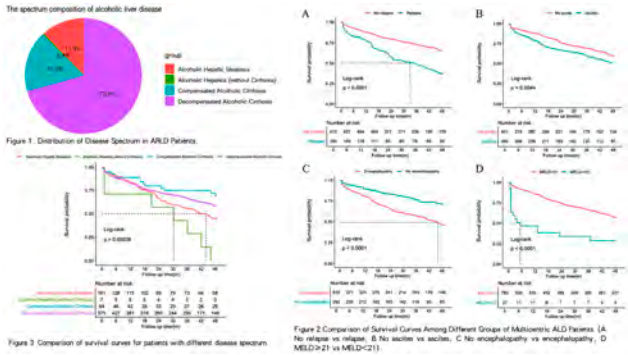
3084 | ANALYSIS OF BASELINE TRAITS, DISEASE SPECTRUM, AND SEVERITY DETERMINANTS IN A MULTICENTER COHORT WITH ALCOHOL-RELATED LIVER DISEASE

Fangfang Duan[1]; [1]Department of Hepatology, Capital Medical University Affilia

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Background: The disease burden of alcohol-related liver disease (ALD) is increasing, and its disease spectrum and clinical outcomes are highly heterogeneous. Currently, there is a lack of systematic characterization of clinical features in large-scale Chinese ALD populations. This study aimed to: (1) describe the baseline characteristics and disease spectrum distribution in a multicenter Chinese ALD cohort; (2) identify independent factors influencing disease severity; (3) explore predictors associated with 4-year survival. **Methods:** This was a multicenter observational study, enrolling a total of 2724 diagnosed ALD patients from five medical centers. Baseline clinical, laboratory, and imaging data were collected, and 4-year survival follow-up was conducted. Disease severity was assessed using a Model for End-Stage Liver Disease (MELD) score ≥ 21 (defined as severe ALD). Logistic regression analysis was used to identify factors influencing disease severity, and Cox proportional hazards models were used to analyze factors influencing survival. **Results:** The cohort was predominantly male (97.1%), with a mean age of 54.51 ± 10.65 years. Disease spectrum distribution showed that decompensated alcoholic cirrhosis was the most prevalent (70.8%). Multivariate logistic regression analysis indicated that ascites (OR = 1.672, p = 0.009), decreased hemoglobin (OR = 0.992, p = 0.002), thrombocytopenia (OR = 0.991, p < 0.001), AST/ALT ratio > 1.5 (OR = 1.068, p = 0.007), and elevated GGT (OR = 1.000, p = 0.003) were independent factors influencing disease severity. Among 807 patients with complete follow-up data, the cumulative 4-year survival rate was 55.2%. Multivariate Cox analysis revealed that failure to abstain from alcohol at baseline (HR = 2.129, p < 0.001),presence of ascites (HR = 1.314, p = 0.047), hepatic encephalopathy (HR = 0.387, p < 0.001), elevated white blood cell count (HR = 1.034, p = 0.001), decreased hemoglobin (HR = 0.96, p = 0.044), AST/ALT ratio > 1.5 (HR = 1.055, p < 0.001), MELD score ≥ 21 (HR = 3.088, p < 0.001), and comorbid diabetes (HR = 0.405, p < 0.001) were independent predictors of 4-year survival. **Conclusion:** This study delineates a disease spectrum in Chinese ALD patients that is predominantly decompensated cirrhosis. It identifies key clinical determinants of disease severity and long-term prognosis, highlighting the prognostic significance of baseline inflammatory markers and continued alcohol use. These findings provide a basis for risk stratification and individualized patient management.



Disclosures: fangfang Duan:Nothing to Disclose.

3085 | MEAN ARTERIAL PRESSURE IS INDEPENDENTLY ASSOCIATIED WITH 90-DAY MORTALITY IN

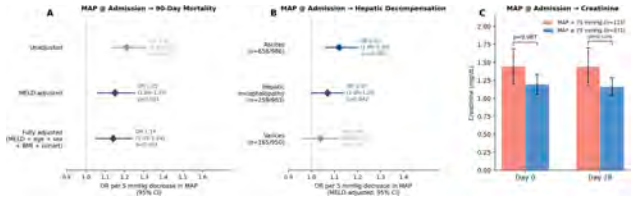
Samer Gawrieh[1] Wanzhu Tu[2] Qing Tang[2] Merixtell Ventura Cots[3] Srinivasan Dasarathy[4] Mack Mitchell[5] Vijay Shah[6] Arun Sanyal[7] Craig McClain[8] Gyongyi Szabo[9] Juan Pablo Arab[7] Ashwani Singal[8] Suthat Liangpunsakul[2] Ramon Bataller[10] Naga Chalasani[11] AlcHepNet Investigators[12], [1]Indiana University School of Medicine, [2]Indiana University, [3]Barcelona Clinic, [4]Cleveland Clinic, [5]University of Texas Southwestern Medical Center, [6]Mayo Clinic Rochester, [7]Virginia Commonwealth University, [8]University of Louisville, [9]Beth Israel Deaconess Medical Center, [10]University of Pittsburgh, [11]Indiana University Medical Center, [12]AlcHepNet

Background: The existing prognostic scores for alcohol-associated hepatitis (AH), such as MELD, are derived from biochemical markers of hepatic and renal failure and do not capture hemodynamic status. Mean arterial pressure (MAP) is a proxy for circulatory dysfunction and reflects effective arterial underfilling, a central feature of AH pathophysiology. Whether MAP carries independent prognostic value beyond the biochemistry markers in AH remains poorly studied. **Methods:** We analyzed data from two prospective cohorts: the Alcoholic Hepatitis Network Observational Study cohort (AHNOBS; N = 706) and the TREAT cohort (N = 271). The primary outcome was 90-day all-cause mortality. The association between MAP at admission and mortality was examined in three sequential logistic regression models: MELD alone, MELD + MAP, and a fully adjusted model (MELD + MAP + age + sex + BMI + cohort). MAP's association with baseline decompensation symptoms and its influence on renal function were examined as secondary analyses. **Results:** The analytic sample included 943 patients (184 deaths, 19.5%). Non-survivors had lower MAP than survivors (80.0 ± 12.1 vs. 84.7 ± 11.2 mmHg). Each 5 mmHg decrease in MAP was associated with

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increased 90-day mortality after adjusting for MELD (OR 1.15, 95% CI 1.06–1.24, p = 0.001) and after full covariate adjustment (OR 1.13, 95% CI 1.04–1.23, p = 0.003). MAP added significant prognostic value beyond MELD (likelihood ratio test p = 0.001). The cohort indicator was not significant (p = 0.74). Lower MAP was associated with ascites (OR 1.13 per 5 mmHg decrease, p < 0.001) and hepatic encephalopathy (OR 1.08, p = 0.027) but not varices (p = 0.22). The prognostic effect of MAP was amplified in patients with concurrent renal impairment (creatinine ≥ 1.2 mg/dL; OR 1.23, p = 0.001) compared with those with preserved renal function (OR 1.06, p = 0.35), **:** suggesting an interaction between hemodynamic compromise and renal dysfunction. In AHNOBS, the low-MAP group (MAP < 75 mmHg) had persistently higher creatinine through day 28 (1.44 vs. 1.16 mg/dL, p = 0.058). **Conclusion:** MAP at admission is independently associated with 90-day mortality in patients with AH. MAP effects are amplified in patients with concurrent renal impairment.



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3086 | IMPACT OF RENAL DYSFUNCTION ON CLINICAL OUTCOMES IN PATIENTS HOSPITALIZED WITH ALCOHOL-ASSOCIATED HEPATITIS

Ahmed Ibrahim[1] Don Rockey[2], [1]San Joquin General Hospital, [2]Medical University of South Carolina

Background: Alcohol-associated hepatitis (AH) is associated with high morbidity and mortality, particularly in patients with renal dysfunction. While acute kidney injury (AKI) and hepatorenal syndrome (HRS) are recognized complications, their impact on clinical outcomes in AH remains incompletely defined. We aimed to evaluate the association of AKI and HRS at presentation with liver-related outcomes and mortality in patients hospitalized with AH. **Methods:** We conducted a cohort study using the TriNetX multicenter database (n = 114,456,231 patients in total), including adult patients hospitalized with AH between 2010 and 2025. Patients were stratified into three groups: AH with AKI (AKI-AH), AH with AKI caused by HRS (HRS-AH), and AH without AKI (control). Baseline characteristics were assessed prior to propensity score matching. The primary outcome was all-cause mortality.

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Secondary outcomes included hepatic decompensation events (ascites, hepatic encephalopathy, variceal hemorrhage). Outcomes were analyzed using Kaplan–Meier survival analysis, and Cox proportional hazards models were reported as hazard ratios (HR) with 95% confidence intervals (CI). **Results:** A total of 2,324 patients with AKI-AH, 1,447 patients with HRS-AH, and 22,567 control patients were included (**Table 1A**). At baseline, patients had similar demographic features, and the majority of patients were White males. Patients with HRS more frequently had ascites (38%) and hepatic encephalopathy (HE) (34%) compared to other groups. HRS patients also had more abnormal laboratory parameters, including higher bilirubin, INR, and creatinine levels. After propensity matching, at 90 days post-admission, mortality was significantly higher in patients with AKI-AH than controls, and patients with HRS-AH had the highest mortality, **Table 1B**). Additionally, hepatic decompensation, including ascites and HE occurred more frequently in patients with AKI-AH as compared to controls, with the highest rates of decompensation occurring in those with AKI caused by HRS). HE was the most common decompensation event followed by ascites. Interestingly, variceal hemorrhage occurred in less than 5% of patients and rates were not significantly different between groups. Finally, KM analysis showed that survival rates at 90 days were the lowest in those with AKI caused by HRS as compared to AKI-AH and controls. **Conclusion:** AKI at presentation identifies a high-risk phenotype in patients hospitalized with AH and is associated with an increased risk of hepatic decompensation and mortality. HRS confers the highest risk of adverse outcome, suggesting a distinct and more severe disease phenotype.

Table 1A. Demographics and baseline characteristics before propensity score matching

Variable	AKI-AH (N=2,324)	HRS-AH (N=1,447)	No AKI-HRS-AH (N=22,567)
Age (yrs, mean ± SD)	46 ± 11	46 ± 11	47 ± 11
Female, n (%)	832 (36%)	540 (37%)	7,772 (34%)
White, n (%)	1,716 (74%)	1,072 (74%)	16,998 (75%)
Black, n (%)	195 (8%)	95 (7%)	1,987 (9%)
Hispanic, n (%)	253 (11%)	167 (12%)	2,492 (11%)
Cirrhosis, n (%)	887 (38%)	653 (45%)	7,838 (35%)
Ascites, n (%)	732 (32%)	545 (38%)	5,933 (26%)
HE, n (%)	533 (23%)	488 (34%)	3,240 (14%)
Platelets	150 ± 93	133 ± 89	152 ± 90
Albumin (g/dL)	2.6 ± 0.7	2.5 ± 0.6	2.9 ± 0.7
T bilirubin (mg/dL)	16 ± 10	22 ± 11	10 ± 7
INR	1.9 ± 0.8	2.2 ± 0.8	1.7 ± 0.7
Creatinine	1.7 ± 1.5	2.4 ± 4.3	1.0 ± 1.7

Table 1B. Clinical outcomes at 90 days.

Outcome	AKI-AH (n/N (%))	No AKI-AH (n/N (%))	HR (95% CI)	p
Ascites	382/1,326 (29%)	253/1,243 (20%)	1.475 (1.258–1.729)	<0.001
HE	598/1,166 (51%)	383/1,129 (34%)	1.735 (1.526–1.973)	<0.001
Death	469/2,289 (21%)	307/2,284 (13%)	1.545 (1.338–1.784)	<0.001
	HRS-AH (n/N (%))	**No HRS-AH (n/N (%))**	**HR (95% CI)**	**p**
Ascites	238/630(38%)	149/677 (22%)	1.959 (1.595–2.406)	<0.001
HE	375/477(79%)	201/539 (37%)	3.274 (2.750–3.897)	<0.001
Death	445/1,319 (34%)	218/1,367 (16%)	2.401 (2.041–2.824)	<0.001

Disclosures: Ahmed Ibrahim:Nothing to Disclose, Don Rockey: Nothing to Disclose.

3087 | INTEGRATION OF CLINICAL PARAMETERS AND CYTOKINE PROFILES TO PREDICT 90-DAY OUTCOMES IN ADULTS WITH ALCOHOL-ASSOCIATED HEPATITIS

Stephen Samuel[1] Prashanth Thevkar Nagesh[1] Yun-Cheng Hsieh[1] - AlcHepNet Clinical Centers investigators[2] Yunpeng Yu[3] Wanzhu Tu[3] Gyongyi Szabo[1], [1]Beth Israel Deaconess Medical Center, Harvard Medical School, [2]-, [3]Indiana University

Background: Alcohol-associated hepatitis (AH) has high short-term mortality. Conventional clinical scores incompletely capture systemic inflammation, a major contributor to pathogenesis and outcomes, prompting integration of cytokines with clinical variables to improve 90-day mortality prediction. **Methods:** Retrospective analysis of the AlcHepNet multicenter study (NCT03850899). Adults ≥21 years with AH (NIAAA) treated with prednisone (40 mg/d; n = 71) or anakinra (100 mg s.c./d) plus zinc (220 mg/d; n = 72) were included. Cytokines were measured using a 48-plex Luminex assay (8-time points: days 0, 3, 7, 14, 28, 60, 90, 180). The primary endpoint was 90-day mortality. Predictors were assessed by univariable analysis, Cox-LASSO with bootstrapping, and multivariable Cox regression adjusting for treatment arm. Model performance was evaluated via the C-index and internally validated using bootstrap resamples. A weighted scorecard was derived from Cox model beta-coefficients. **Results:** Among 144 patients, 90-day mortality was 18%. Mortality was higher with anakinra+zinc vs. prednisone (72% vs. 28%, P < 0.001). Non-survivors had higher MELD (27 vs. 24, P = 0.005) and lower hemoglobin (8.65 vs. 9.85 g/dL, P = 0.014), platelets (124 vs. 151×10³/μL, P = 0.031), and alkaline phosphatase (121 vs. 177 U/L, P = 0.012) when compared to survivors. No baseline cytokines differed; however, day-7 log changes in eotaxin, IL-13, IL-17A, IL-17F, and VEGF-α were greater in non-survivors when compared to survivors. In the anakinra + zinc group, non-survivors had lower baseline IL-1RA (P = 0.04) and IL-2 (P = 0.01). Univariable predictors in 90-day non-survivors included MELD, hemoglobin, INR, BUN, bilirubin, alkaline phosphatase, IL-3, IL-6, M-CSF and prednisone when compared to anakinra+zinc. LASSO regression model identified IL-1RA, IL-3, and IL-6. After adjusting for treatment arm, we identified independent predictors of 90-day mortality: INR (HR 2.44; 95% CI, 1.29 to 4.61; P = 0.006), BUN (HR 1.04; 95% CI, 1.01 to 1.07; P = 0.019), total bilirubin (HR 1.07; 95% CI, 1.02 to 1.11; P = 0.004), and $\log_{10}$ IL-6 (HR 2.33; 95% CI, 1.14 to 4.76; P = 0.021). No significant interaction was observed between treatment arm

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and IL-6 (P > 0.05). A 4-variable score card (bilirubin, BUN, INR, IL-6) had numerically higher AUC vs. MELD (73.3% vs. 68%, P = 0.24), with sensitivity 84.6%, specificity 56.3%, and NPV 93.9%. It also demonstrated an apparent C-index of 0.779 and an optimism-corrected C-index of 0.746; outperforming MELD score, which yielded an optimism-corrected C-index of 0.679 in this cohort. Calibration analysis showed high agreement between predicted and observed survival (mean absolute error of 0.11). **Conclusion:** Cytokine dysregulation is associated with mortality in AH; IL-6 found to be an independent predictor of 90-day mortality. A combined clinical–cytokine model may show promise in improving risk stratification.

Disclosures: Stephen Samuel:Nothing to Disclose, Prashanth Thevkar Nagesh:Nothing to Disclose, Yun-Cheng Hsieh:Nothing to Disclose, - AlcHepNet Clinical Centers investigators:Nothing to Disclose, Yunpeng Yu:Nothing to Disclose, Wanzhu Tu:Nothing to Disclose, Gyongyi Szabo:CYTA Therapeutics: Consultant, Durect Corporation: Consultant, Pandion Therapeutics: Consultant, Pfizer: Consultant, Surrozen: Advisor, Evive: Advisor, Glympse Bio, Inc (acquired by Sunbird Bio): Advisor, Satellite Biosciences: Advisor, Zomagen Bioscience/Ventyx Biosciences: Consultant, Springer Nature Group: Royalties or patent beneficiary, UpTo-Date Inc: Royalties or patent beneficiary, Boehiringer Ingelheim: Honoraria, Intercept: Contract, NIAAA-NIA: Grant/Research Support, Novo Nordisk: Honoraria, Yale University School of Medicine: Consultant, Resolution Therapeutics: Consultant, US Patent No. 20110293: Intellectual Property.

3088 | DYNAMIC LIVER STIFFNESS MEASUREMENT CHANGES PREDICT LIVER-RELATED EVENTS ACROSS FIBROSIS STRATA IN STEATOTIC LIVER DISEASE

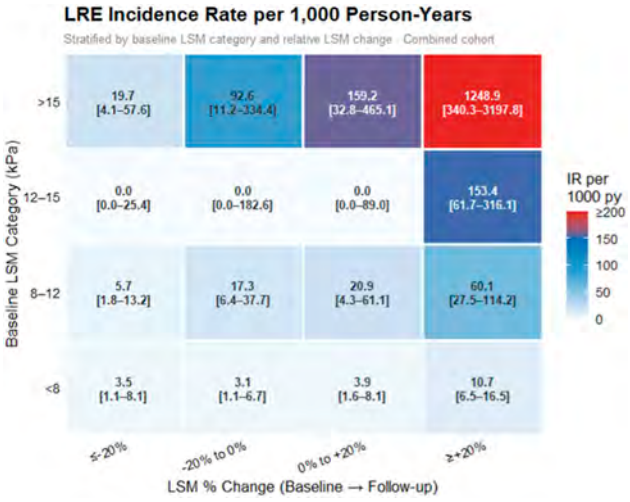
Hyundam (Dami) Gu[1] Luis Díaz[2] Natalia Baeza[2] Francisco Idalsoaga[3] Cristiane Villela-Nogueira[4] Natalia Balassiano Wajsbrot[4] Ana Carolina Cardoso[4] Nathalie Leite[4] Gil Salles[4] Claudia Cardoso[4] Anand Kulkarni[5] Ramagundam Ramyasri[6] William Alazawi[7] Wenhao Li[7] Laura Temperley[7] Maria Poca[8] Berta Cuyas[8] Terry Cheuk-Fung Yip[9] Vincent Wai-Sun Wong[9] Grace Wong[9] Jimmy Che-To Lai[9] Jose Velarde Ruiz Velasco[10] Juan Roblero[11] Daniela Simian[12] Pamela Gil Galleguillos[12] Mohamed El-Kassas[13] Claudia Couto[14] Guilherme Grossi Cancado[15] Sebastian Marciano[16] Jorge Martínez[16] Maria Jose Acosta[16] Adrián Gadano[16] Ismael Yepes[17] Luis Molina Barrios[17] Argemiro Lara[17] MaríaFernanda SaavedraChacón[18] Eira Cerda Reyes[19] Stefanny Cornejo Henández[19] Graciela Castro-Narro[20] Sheel Patel[21] Ashwani Singal[21] Katrina Pekarska[22] Richard Parker[22] Mohamad Ali Ibrahim[23] Prasun Jalal[23] Mazen Noureddin[24] Naim Alkhouri[25] Winston Dunn[26] Patrick Kamath[27] Arun Sanyal[1] Richard Sterling[1] Maraco Arrese[2] Ramon Bataller[28] Juan Pablo Arab[1], [1]Virginia Commonwealth University, [2]Pontificia Universidad Católica de Chile, [3]Pontificia Universidad Católica de Chile; Western University, [4]Universidade Federal do Rio de Janeiro, [5]Asian Institute of Gastroenterology, [6]AIG Hospitals, [7]Blizard Institute, Queen Mary University of London, [8]Institut de Recerca Hospital de Sant Pau-IIB Sant Pau, Universitat Autònoma de Barcelona, [9]The Chinese University of Hong Kong, [10]Hospital Civil de Guadalajara, [11]University of Chile, [12]Universidad de Chile, [13]Capital University, [14]Federal University of Minas Gerais, [15]Universidade Federal de Minas Gerais, [16]Hospital Italiano de Buenos Aires, [17]Universidad de Cartagena, [18]Clínica CES, [19]Central Military Hospital, [20]Hospital Médica Sur, Ciudad de México. Instituto Nacional de Ciencias Médicas y Nutrición, [21]University of Louisville, [22]Leeds Teaching Hospitals NHS Trust, [23]Baylor College of Medicine, [24]Houston Methodist Hospital, [25]Summit Clinical Research, [26]University of Kansas Medical Center, [27]Mayo Clinic, [28]University of Pittsburgh

Background: Serial vibration-controlled transient elastography (VCTE) offers a practical, non-invasive approach for longitudinal monitoring of hepatic fibrosis in patients with steatotic liver disease (SLD); however, the prognostic significance of interval liver stiffness measurement (LSM) changes across baseline fibrosis strata remains incompletely defined. We aimed to evaluate whether the magnitude of LSM percentage change between serial measurements predicts liver-related events (LREs) across baseline fibrosis strata in a large combined international cohort. **Methods:** We analyzed 2,978 patients with MASLD or MetALD/ALD from an international cohort (n = 2,320) and US-based SLD registry (n = 658) with ≥ 2 VCTE measurements. LSM change was categorized as ≤ -20%, -20–0%, 0–+20%, and ≥ +20%. The composite LRE endpoint included incident cirrhosis, hepatic decompensation, hepatocellular carcinoma (HCC), and liver transplantation, whichever occurred first. LRE incidence rates (per 1,000 person-years) were stratified by baseline LSM category (< 8, 8–12, 12–15, and > 15 kPa) and LSM change category. Pairwise rate ratios were estimated using Poisson regression with Holm correction for multiple comparisons. **Results:** The cohort included patients with MASLD (2815, 94.2%), MetALD/ALD (172, 5.8%). [HG1] Median age and baseline LSM were 54 years and 6.3 kPa, respectively. Median time between VCTEs were 2.2 and 3.5 years in the SLD and International cohorts, respectively. 94 LREs occurred during follow-up. Across all baseline LSM categories, ≥ +20% worsening was associated with the highest LRE incidence. ≥ 20% improvement conferred an 11-fold lower LRE incidence compared with ≥ 20% worsening (RR = 0.09 [95% CI:

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0.03–0.28], p < 0.001) in the 8–12 kPa group. In the > 15 kPa group, ≥ 20% improvement showed similar signal of lower LRE incidence (RR = 0.02 [95% CI: 0.00–0.07], p < 0.001). In subgroup analysis of more improvement groups, substantial LSM reduction of ≥ 30% was associated with 88% lower LRE incidence compared to stable LSM in baseline advanced fibrosis (LSM > 15 kPa, both p < 0.05). **Conclusion:** Serial LSM improvement of ≥ 20% was associated with substantially lower LRE risk across different baseline fibrosis strata. These findings support the prognostic value of LSM dynamics and reinforce the utility of serial VCTE monitoring to identify patients who may benefit from continued or escalated therapeutic intervention in SLD.



Disclosures: Hyundam (Dami) Gu:Nothing to Disclose, Luis Díaz:Nothing to Disclose, Natalia Baeza:Nothing to Disclose, Francisco Idalsoaga:Nothing to Disclose, Cristiane Villela-Nogueira:Nothing to Disclose, Natalia Balassiano Wajsbrot:Nothing to Disclose, Ana Carolina Cardoso:Nothing to Disclose, Nathalie Leite:Nothing to Disclose, Gil Salles:Nothing to Disclose, Claudia Cardoso:Nothing to Disclose, Anand Kulkarni:Nothing to Disclose, Ramagundam Ramyasri:Nothing to Disclose, William Alazawi:Nothing to Disclose, Wenhao Li:Nothing to Disclose, Laura Temperley:Nothing to Disclose, Maria Poca:Nothing to Disclose, Berta Cuyas:Nothing to Disclose, Terry Cheuk-Fung Yip:Gilead Sciences: Consultant, Gilead Sciences: Speaking and Teaching, Gilead Sciences: Grant/Research Support, Altimmune: Advisor, GSK: Advisor, Vincent Wai-Sun Wong:Nothing to Disclose, Grace Wong:Advisory committee member: AstraZeneca, Barinthus Bio: Consultant, Abbott, AbbVie, Bristol-Myers Squibb, Echosens, Ferring: Speaking and Teaching, Gilead Sciences, GlaxoSmithKline, Janssen, Otsuka, Roche and Virion: Speaking and Teaching, AstraZeneca, Barinthus Biotherapeutics, Gilead Gilead Sciences, GlaxoSmithKline, Janssen and Virion: Consultant, Gilead Sciences: Grant/Research Support, Jimmy Che-To Lai: Nothing to Disclose, JOSE VELARDE RUIZ VELASCO: Nothing to Disclose, Juan Roblero:Nothing to Disclose, Daniela Simian:Nothing to Disclose, Pamela Gil Galleguillos:Nothing to Disclose, Mohamed El-Kassas:Nothing to Disclose, Claudia Couto:Nothing to Disclose, Guilherme Grossi Cancado:Nothing to Disclose, Sebastian Marciano: Nothing to Disclose, Jorge Martínez:Nothing to Disclose, Maria Jose Acosta:Nothing to Disclose, Adrián Gadano: Nothing to Disclose, Ismael Yepes:Nothing to Disclose, Luis Molina Barrios:Nothing to Disclose, Argemiro Lara: Nothing to Disclose, MaríaFernanda SaavedraChacón: Nothing to Disclose, Eira Cerda Reyes:Nothing to Disclose, Stefanny Cornejo Henández:Nothing to Disclose, Graciela Castro-Narro:Novonordisk: Speaker honoraria and advisory board, Gilead: Speaker honoraria, Grünanthalñ: Speaker honoraria, Boehringer Ingelheim: Speaker honoraria, Sheel Patel:Nothing to Disclose, Ashwani Singal:Madrigal: Speaking and Teaching, Pleiogenix: Stock – privately held company, Pleiogenix: Consultant, CLD Foundation: Advisor, Medical Speaker's Network: Speaking and Teaching, Up-to-Date: Royalties or patent beneficiary, Medscape: Speaking and Teaching, University of Louisville School of Medicine: Employee, NIAAA: Grant/Research Support, Gastro Endo News: Executive role, Durect: Advisor, University of Louisville Health: Other, Katrina Pekarska:Nothing to Disclose, Richard Parker: Nothing to Disclose, Mohamad Ali Ibrahim:Nothing to Disclose, Prasun Jalal:Madrigal, GSK, Mirum, Ipsen, Gilead, Genentech, Zydus: Grant/Research Support, Intercept, Genfit: Grant/Research Support, Mazen Noureddin:Nothing to Disclose, Naim Alkhouri:Madrigal: Speaking and Teaching, Novo Nordisk: Consulting, Novo Nordisk: Grant/Research Support, Corcept: Grant/Research Support, Echosens: Speaking and Teaching, Perspectum: Consultant, Cima: Consultant, Fibronostics: Consultant, 89Bio: Grant/Research Support, Inventiva: Grant/Research Support, Merck: Grant/Research Support, Pfizer: Grant/Research Support, Ipsen: Speaking and Teaching, Intercept: Speaking and Teaching, Madrigal: Consulting, Research Funding, Novo Nordisk: Consulting, Research Funding, Inventiva: Research Funding, Boehringer Ingelheim: Consulting, Research Funding, Corcept: Research Funding, Ipsen: Consulting, Research Funding, Gliead: Consulting, Research Funding, Speaking, Perspectum: Consulting, Research Funding, Cima: Advisor, 89Bio: Consulting, Research Funding, Arbutus: Grant/Research Support, GSK: Grant/Research Support, Regeneron: Grant/Research Support, AstraZeneka: Grant/Research Support, Madrigal: Grant/Research Support, Akero: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Eli Lilly: Grant/Research Support, Gilead: Grant/Research Support, Galectin: Grant/Research Support, Boston Pharma: Grant/Research Support, Winston Dunn:Nothing to Disclose, Patrick Kamath:Sequana: Advisor, NovoNordisk: Advisor, GSK: Advisor, Arun Sanyal: Nothing to Disclose, Richard Sterling:ABIM: GI Specialty Board, Abbott: Grant/Research Support, GSK: Grant/Research Support, HCV Vax: Grant/Research Support, Gilead: Grant/Research Support,

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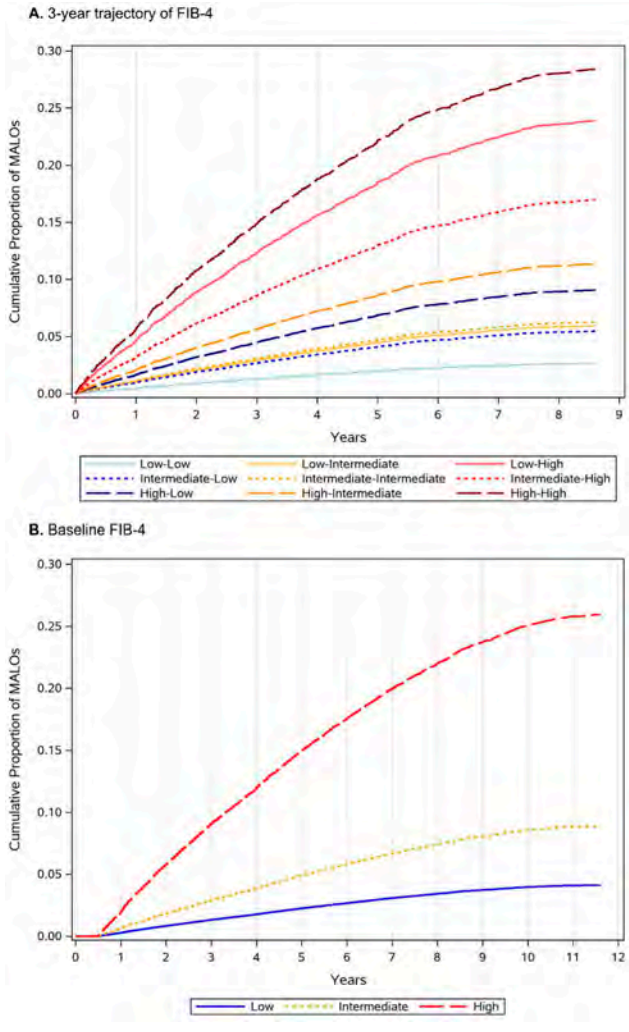
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3089 | BASELINE AND LONGITUDINAL CHANGES IN SERUM BASED NON-INVASIVE TESTS (NITS) FOR PREDICTING MAJOR ADVERSE LIVER OUTCOMES IN PATIENTS WITH METABOLIC AND ALCOHOL ASSOCIATED STEATOTIC LIVER DISEASE (METALD)

Binu John[1] Dustin Bastaich[2] Bassam Dahman[2], [1]University of Miami and Miami VA, [2]Virginia Commonwealth University

Background: Metabolic and alcohol-associated steatotic liver disease (MetALD) represents a distinct and emerging entity within the steatotic liver disease spectrum, yet optimal fibrosis risk stratification strategies for this population remain poorly defined. We evaluated the prognostic performance of serum based non-invasive tests (NITs) (FIB-4, APRI, NAFLD fibrosis score, and SAFE score), using standard MASLD risk categories, for predicting major adverse liver outcomes (MALO: hepatocellular carcinoma (HCC), decompensation, liver transplantation, or liver-related death) in patients with MetALD. **Methods:** This retrospective cohort study utilized data from the Veterans Health Administration Corporate Data Warehouse (January 2013-June 2025). MetALD was identified using a validated algorithm combining natural language processing of abdominal imaging reports with cardiometabolic risk factor and alcohol use data ($\kappa = 0.87$). Patients were excluded for alternative etiologies of liver disease, < 6 months of follow-up, death within 12 months of steatosis, or with MALO within 6 months of steatosis identification. NITs were classified as low, intermediate, or high based on established thresholds. NIT risk categories were included in univariable Cox proportional hazard models predicting MALO. The C-statistics (c) of these models were evaluated for predictive performance, and p-values for differences in Uno's concordance statistics were used to test for significant differences in predictive performance. We also examined the performance of the 3-year trajectory of NITs for predicting following MALOs compared to using risk groups at the 3-year landmark alone. **Results:** There were 114,833 participants with MetALD in the analytic sample after exclusions (median age 62 years (IQR 18), 92.3% male). Among baseline NITs, FIB-4 demonstrated superior discrimination for MALO (C-statistic 0.70; 95% CI 0.69–0.72) compared to APRI (0.65; $p < 0.0001$), NFS (0.66; $p = 0.0006$), and SAFE score (0.66; $p < 0.0001$). Relative to low FIB-4 (< 1.3), intermediate (1.3–2.67) and high-risk (> 2.67) categories conferred markedly elevated MALO risk (HR 2.21 [95% CI 2.06–2.38] and HR 7.13 [6.64–7.66], respectively; $p < 0.0001$). Three-year FIB-4 trajectory significantly outperformed baseline classification (C-statistic 0.72 [0.70–0.73]; $p < 0.0001$). Patients with persistently elevated FIB-4 carried the highest MALO risk (HR 12.48 [10.68–14.59]), followed by those progressing from low-to-high (HR 10.20 [7.50–13.88]) and intermediate-to-high (HR 6.95 [5.76–8.37]). (**Figure 1**). **Conclusion:** In this large national MetALD cohort, FIB-4 was the most accurate serum-based NIT for MALO prediction. Serial FIB-4 monitoring with trajectory-based risk stratification substantially improved prognostic accuracy over single-time-point measurement, supporting its integration into longitudinal surveillance strategies for patients with MetALD.



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3090 | ETHANOL ACTIVATES YAP SIGNALING AND DRIVES PRO-INFLAMMATORY MACROPHAGE POLARIZATION UNDER METABOLIC STRESS IN METALD

Swastika Tripathi[1] Zeinab Heidariyan[1] Wenyu Lin[1] Yongtao Wang[1] Raymond Chung[1] Shadi Salloum[1], [1]Massachusetts General Hospital

Background: Hepatic macrophages are key amplifiers of liver injury, capable of shifting between pro-inflammatory and pro-fibrotic polarization states central to the progression from steatosis to cirrhosis. In Metabolic dysfunction and alcohol-associated liver disease (MetALD), alcohol superimposed on metabolic stress accelerates fibrosis and increases liver-related mortality. Critically, ethanol and free fatty acids, the dual stressors defining MetALD, are established inducers of Hippo pathway dysregulation; whether these signals converge on YAP activation to reprogram macrophage polarization and amplify fibrogenic signaling remains unexplored. Here, we interrogated YAP-associated transcriptional programs across complementary human macrophage platforms, including our novel iPSC-derived macrophages (MACs), to define how ethanol and lipid stress shape macrophage-driven fibrogenic crosstalk. **Methods:** To simulate the dual metabolic-alcoholic stress of MetALD, primary monocyte-derived macrophages (MDMs), U937 cells, and MACs were exposed to ethanol (0–2%) ± free fatty acid cocktail for 5 days. YAP activation, pro-inflammatory, and pro-fibrotic polarization were assessed by qRT-PCR and Western blot. Conditioned media from ethanol-treated macrophages were applied to iPSC-derived hepatic organoids to investigate paracrine fibrogenic capacity. **Results:** Across all three platforms, ethanol consistently activated YAP signaling in a dose-dependent manner, establishing it as a downstream effector of ethanol stress in human macrophages. When the ethanol treatment was paired with free fatty acid treatment to model the dual-stressor environment of MetALD, YAP target gene induction was attenuated under combined exposure. In parallel, ethanol treatment preferentially induces macrophages toward a pro-inflammatory polarization state, rather than a more pro-fibrotic state, across all cell lines, identifying inflammation as the dominant macrophage response to ethanol stress. Most compellingly, conditioned media from ethanol-stimulated macrophages induced fibrogenic gene expression in hepatic organoids at levels comparable to TGF-β, demonstrating that an inflammatory macrophage state retains full paracrine fibrogenic capacity. **Conclusion:** These findings reveal that fibrosis in MetALD may not require macrophages to adopt a classical pro-fibrotic identity. Combined alcohol and metabolic stress may instead sustain an inflammatory state capable of driving fibrogenesis via paracrine crosstalk. This work positions macrophage YAP signaling as a mechanistic bridge between metabolic injury, alcohol exposure, and fibrosis amplification thereby highlighting a tractable therapeutic axis for progressive MetALD.

Disclosures: Swastika Tripathi:Nothing to Disclose, Zeinab Heidariyan:Nothing to Disclose, Wenyu Lin:Nothing to Disclose, Yongtao Wang:Nothing to Disclose, Raymond Chung:Nothing to Disclose, Shadi Salloum:Nothing to Disclose.

3091 | LIVER VOLUME IS ASSOCIATED WITH MORTALITY IN ALCOHOL ASSOCIATED HEPATITIS

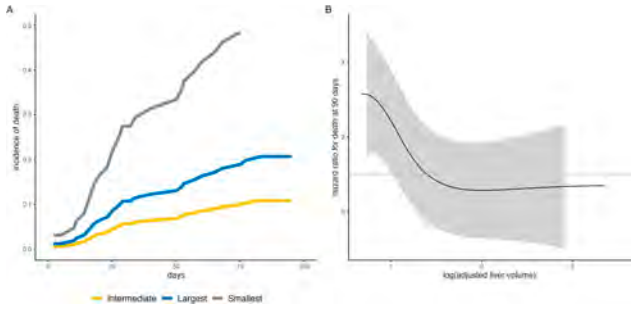
Francisco Idalsoaga[1] Amy Hicks[2] Nawaz Safdar[3] Darwish Khizindar[4] Vincent Haghnejad[4] Joaquin Hevia-Morel[5] Ashwani Singal[6] Juan Pablo Arab[7] Richard Parker[8], [1]Western University, Canada, [2]Leeds Liver Unit, St James's University Hospital, Leeds, UK., [3]School of Medicine, Faculty of Medicine and Health, University of Leeds, Leeds, UK, [4]Department of Hepatology and Gastroenterology, University Hospital of Nancy, Nancy, France., [5]Departamento de Radiología, Escuela de Medicina, Pontificia Universidad Católica de Chile, Santiago,, [6]University of Louisville, [7]Virginia Commonwealth University School of Medicine, Richmond, VA, USA., [8]Leeds Teaching Hospitals NHS Trust

Background: Alcohol-associated hepatitis (AH) is associated with high short-term mortality, but prognostic assessment relies mainly on clinical and laboratory variables. Imaging-based markers may provide additional risk stratification. We evaluated whether computed tomography (CT)-derived liver volume and steatosis were associated with clinically relevant outcomes in patients hospitalized with AH. **Methods:** We conducted a multicenter retrospective cohort study of patients hospitalized with AH between 2009 and 2023 who underwent abdominal CT within 5 days of admission. Liver volume was measured by CT volumetry and compared with the predicted liver volume based on body surface area. Hepatic steatosis was assessed using the liver-to-spleen attenuation ratio. The primary outcome was 90-day mortality. Secondary

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outcomes were 30-day mortality, corticosteroid response, and infection. Associations were assessed using Cox regression and logistic regression models. **Results:** We included 122 patients with AH. Median age was 46 [41-53] years, 40 (33%) were women, and median MELD score was 22 [19-26]. Median liver volume was 2,535 [1,908-3,304] cm^3, and the median observed-to-predicted liver volume ratio was 1.61 [1.17-2.11]. Ninety-day mortality occurred in 28 patients (23%). Body surface area-adjusted liver volume was inversely associated with 90-day mortality (HR 0.32, 95% CI 0.12-0.83, p = 0.019), and this association remained significant after adjustment for age, sex, and MELD (HR 0.24, 95% CI 0.07-0.87, p = 0.029). Compared with the smallest tertile, patients in the intermediate and largest liver volume tertiles had significantly lower 90-day mortality. Liver volume was also associated with 30-day mortality in univariable analysis (HR 0.20, 95% CI 0.06-0.89, p = 0.034), but was not associated with corticosteroid response or infection. Hepatic steatosis was not associated with mortality, infection, or corticosteroid response. Liver volume showed moderate discrimination for 90-day mortality (AUROC 0.70). **Conclusion:** In this multicenter cohort of patients hospitalized with AH, a smaller CT-derived liver volume was independently associated with higher 90-day mortality, whereas CT-assessed steatosis was not associated with outcomes. CT-derived liver volume may provide additional prognostic information in AH and warrants validation in larger prospective cohorts.



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3092 | PREVALENCE AND RISK FACTORS OF RENAL IMPAIRMENT IN PATIENTS WITH ALCOHOLIC LIVER DISEASE: A MULTICENTER STUDY IN CHINA

Wei Li[1]; [1]Beijing Ditan Hospital, Capital Medical University

Background: Alcoholic liver disease (ALD) has become a common chronic liver disease in China. Current research on ALD, both domestically and internationally, has largely focused on liver pathology, whereas studies on renal impairment in ALD patients remain insufficient, lacking large-sample, multicenter epidemiological data. The prevalence of renal impairment in Chinese ALD patients, its independent risk factors, and its impact on patient survival are still unclear. **Methods:** This study is a cross-sectional analysis combined with retrospective follow-up. A total of 2,724 ALD patients from four medical centers were enrolled. Renal impairment was defined as an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 (calculated using the CKD-EPI equation based on serum creatinine). Baseline demographic data, alcohol consumption history, laboratory parameters (liver and kidney function, blood count, coagulation profile), and complications were collected. Baseline characteristics were compared between the renal impairment group and the non-renal impairment group. Multivariable logistic regression analysis was performed to identify independent risk factors for renal impairment. The Kaplan-Meier curve was used to preliminarily assess the effect of renal impairment on 1-year survival. **Results:** The prevalence of renal impairment (eGFR < 60) in this cohort was 7% (101/1,442). Multivariable logistic regression identified age, abstinence from alcohol, aspartate aminotransferase, total bilirubin, and white blood cell count as independent risk factors for renal impairment in ALD patients (Table1). Univariate analysis showed that factors such as presence of cirrhosis, cirrhotic complications (ascites, hepatic encephalopathy, portal hypertensionrelated gastrointestinal bleeding), diabetes mellitus, hypoalbuminemia, Maddrey discriminant function, MELD score, and ChildPugh score were associated with renal impairment (P < 0.05); however, these independent associations disappeared after adjusting for confounders (P > 0.05). Patients with baseline renal

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impairment had a significantly lower estimated 12-month survival rate than those with normal renal function (P < 0.001)(Figure1). **Conclusion:** Renal impairment is not uncommon in ALD patients and represents an important component of systemic damage in this disease. Its occurrence is driven by multiple factors. Early identification of high-risk patients and intervention on modifiable factors may be of great significance for improving the overall prognosis of ALD patients.

Table 1. Multivariable logistic regression analysis of factors associated with renal impairment in ALD patients.

Step 1[a]	Variable	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I. for Exp(B)	
								Lower	Upper
Step 1[a]	age	.061	.011	33.224	1	<.001	1.063	1.041	1.086
	cirrhosis	.235	.525	.200	1	.655	1.265	.452	3.535
	ascite	.061	.296	.043	1	.836	1.063	.595	1.899
	encephalopathy	.357	.241	2.206	1	.137	1.430	.892	2.291
	variesbleeding	.536	.277	3.737	1	.053	1.709	.993	2.942
	diabetes	.022	.151	.022	1	.883	1.023	.761	1.374
	abstinence	.582	.276	4.432	1	.035	1.790	1.041	3.076
	AST	.001	.000	12.276	1	<.001	1.001	1.000	1.002
	TBIL	.002	.001	6.667	1	.010	1.002	1.001	1.004
	ALB	−.035	.020	2.860	1	.091	.966	.928	1.006
	WBC	.081	.017	23.288	1	<.001	1.084	1.049	1.120
	HB	−.001	.004	.017	1	.898	.999	.991	1.008
	MDF score	−.001	.007	.007	1	.934	.999	.986	1.013
	MELD	.054	.030	3.126	1	.077	1.055	.994	1.120
	CTP	−.069	.078	.775	1	.379	.933	.800	1.088
	Constant	−6.885	1.284	28.738	1	<.001	.001		

[a] Dependent variable: renal impairment. Independent variables entered: age, abstinence from alcohol, aspartate aminotransferase, total bilirubin, and white blood cell count.

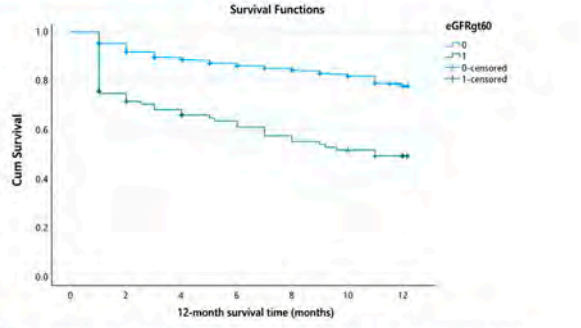


Figure 1. Kaplan–Meier analysis of 12-month survival in ALD patients stratified by baseline renal function (eGFR > 60 vs. ≤ 60 mL/min/1.73 m²). Patients with baseline renal impairment had a significantly lower estimated 12-month survival rate than those with normal renal function ($P < 0.001$, log-rank test).

Disclosures: Wei Li:Nothing to Disclose.

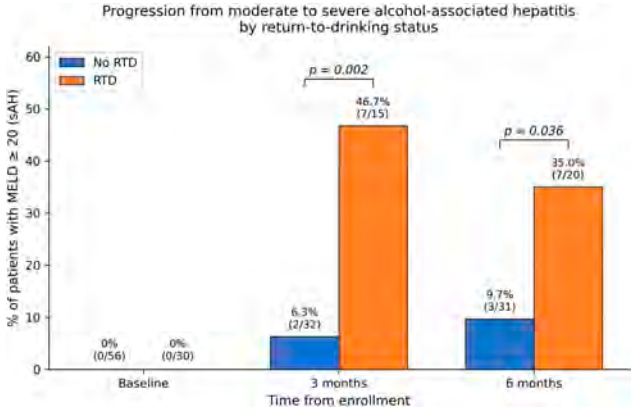
3093 | PROGRESSION TO SEVERE ALCOHOL-ASSOCIATED HEPATITIS (AH) IS COMMON IN PATIENTS WITH MODERATE AH AND IS ASSOCIATED WITH A HIGHER RISK OF MAJOR ADVERSE LIVER OUTCOMES

Ashwani Singal[1] Wanzhu Tu[2] Yunpeng Yu[2] Vatsalya Vatsalya[1] Nicole Welch[3] Douglas Simonetto[4] Juan Pablo Arab[5] Jacqueline O'Leary[6] Srinivasan Dasarathy[3] Suthat Liangpunsakul[2] Mack Mitchell[7] Arun Sanyal[5] Naga Chalasani[8] Gyongyi Szabo[9] Ramon Bataller[10] Craig McClain[1] Samer Gawrieh[8], [1]University of Louisville, [2]Indiana University, [3]Cleveland Clinic, [4]Mayo Clinic Rochester, [5]Virginia Commonwealth University, [6]UTSW, [7]University of Texas Southwestern Medical Center, [8]Indiana University Medical Center, [9]Beth Israel Deaconess Medical Center, [10]University of Pittsburgh

Background: Data on the natural history of moderate alcohol-associated hepatitis (mAH, MELD score < 20) and its progression to severe AH (sAH) are limited **Methods:** In a prospective multicenter AlcHepNet (AHN) observational study, participants with mAH were enrolled and followed for 6 months. The primary outcome was progression to sAH (MELD ≥ 20) within 6 months, stratified by return to drinking (RTD). The effect of RTD on outcomes was estimated using Cox proportional hazards models with RTD as a time-varying covariate. Progression to sAH by RTD status was compared cross-sectionally using Fisher's exact test. **Results:** Of 712 participants with AH (2020-2024), 148 (20.8%) had mAH at enrollment (mean age 45.0 ± 11.5 years, 44.6% females, 82% white, mean MELD 16.7 ± 2.1). Among those with available follow-up data on MELD and RTD, the overall rate of progression to sAH was 22.1% (19/86). Cross-sectional progression rates were 14.3% (10/70), 19.1% (9/47), and 19.6% (10/51) at 1, 3, and 6 months, respectively. Progressors vs. non-progressors had a higher baseline MELD (17.7 ± 1.6 vs. 16.6 ± 2.1, p = 0.033), with no differences in demographics, comorbidities, and alcohol use. Participants with RTD (n = 30, 34.9%) had a higher frequency of progression to sAH than those without RTD: 46.7% vs 6.3% at 3 months (p = 0.002) and 35.0% vs 9.7% at 6 months (p = 0.036) (**Figure**). MELD score comparing progressors vs. non-progressors was 21.2 ± 5.3 vs. 10.9 ± 3.5 at 3 months (p < 0.001) and 20.3 ± 6.1 vs. 10.6 ± 5.2 at 6 months (p < 0.001). Major adverse liver outcome (MALO) at 6 months (decompensation, mortality, liver-related hospital admission, or liver transplantation) was more frequent in progressors (68.4% vs. 28.4%, p = 0.001). Of 6 deaths, 3 each occurred in progressors and non-progressors, 15.8% vs. 4.5%, p = 0.119. In time-varying Cox models adjusted for age, sex, race, body mass index, MELD, albumin, WBC, and mean arterial pressure, RTD was associated with a 4.4-fold (95% CI 1.6–12.3; p = 0.005), 2.2-fold (1.0-4.5, p = 0.04), and 9.4-fold (1.2-73.3, p = 0.032) hazard of progression to sAH, MALO, and mortality at 6 months. **Conclusion:** About 22% of participants with mAH are at risk of progression to sAH within 6 months. This progression is associated with RTD and increased risk of MALO. These findings support a close follow-up, integrated management of liver disease and of alcohol-use disorder, and highlight an unmet need for drug development in patients with mAH.

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3094 | ALCOHOL-INDUCED METABOLIC STRESS ACTIVATES AN ACETATE–ACSS2 EPIGENETIC AXIS IN LIVER SINUSOIDAL ENDOTHELIAL CELLS

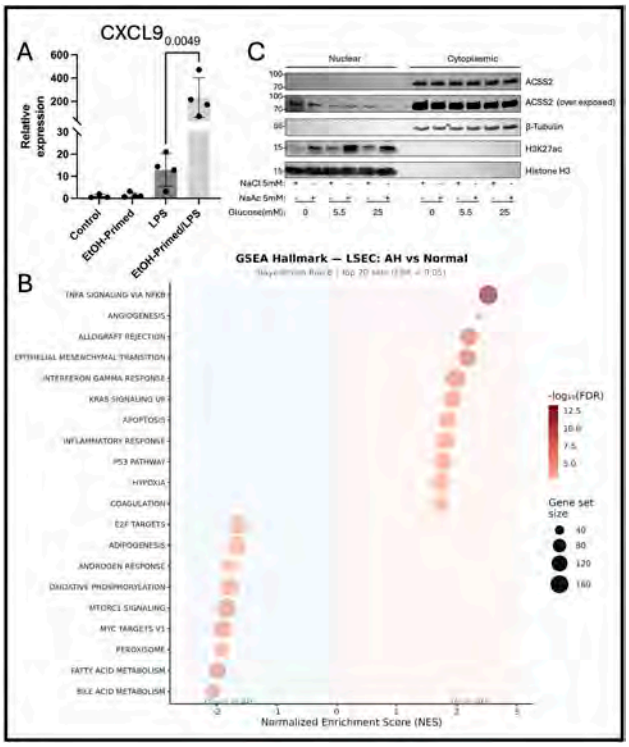
Rafael Ricci de Azevedo[1] Weizhe Zhong[1] Mengfei Liu[1],
[1]Yale

Background: Alcohol-associated hepatitis (AH) features metabolic reprogramming and sustained hepatic inflammation with no effective therapy. Alcohol metabolism generates millimolar circulating acetate while impairing glucose utilization. In innate immune cells, nuclear acetyl-CoA drives histone acetylation underlying trained immunity — durable epigenetic reprogramming that amplifies inflammatory responses upon rechallenge. Liver sinusoidal endothelial cells (LSECs) are angiocrine gatekeepers of hepatic immune trafficking, but whether acetate-derived acetyl-CoA via ACSS2 contributes to epigenetic reprogramming in LSECs under the metabolic conditions of AH is unknown. **Methods:** A murine priming–rest–challenge binge alcohol model assessed LSEC trained immunity: mice received 4-day alcohol binges, 7-day rest, then LPS rechallenge, with Cxcl9 as the inflammatory recall readout. Bulk RNA-seq deconvolution (BayesPrism) of human AH liver biopsies quantified LSEC transcriptional programs. Primary human LSECs were subjected to glucose deprivation and 5 mM acetate treatment to model alcohol-induced metabolic stress. ACSS2 subcellular localization and global H3K27ac were assessed by Western blot of nuclear and cytoplasmic fractions. **Results:** Alcohol-primed LSECs showed greater than 10-fold increase in Cxcl9 upon LPS rechallenge compared to unprimed controls, demonstrating robust trained immunity in LSECs in vivo. Deconvolution of human AH liver revealed upregulated TNF and interferon signaling alongside suppressed mTOR, oxidative phosphorylation, pyruvate metabolism, and fatty acid oxidation in LSECs, indicating inflammatory activation

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concurrent with broad metabolic stress. In primary human LSECs, glucose deprivation increased ACSS2 nuclear translocation, and acetate treatment increased global H3K27ac, demonstrating that the metabolic conditions of AH are sufficient to activate the ACSS2-dependent histone acetylation axis in LSECs. **Conclusion:** LSECs in AH exhibit a trained-immunity phenotype accompanied by broad metabolic suppression. Glucose deprivation drives ACSS2 nuclear translocation and acetate increases histone acetylation in primary human LSECs, implicating the acetate–ACSS2 axis as a metabolic mechanism supporting epigenetic inflammatory reprogramming in LSECs during AH.



Disclosures: Rafael Ricci de Azevedo:Nothing to Disclose, Weizhe Zhong:Nothing to Disclose, Mengfei Liu:Nothing to Disclose.

3095 | PYRUVATE DEHYDROGENASE KINASE 4 LINKS ALCOHOL METABOLISM TO MONOCYTE/MACROPHAGE-MEDIATED INFLAMMATION IN ALCOHOL-ASSOCIATED LIVER DISEASE

Jianguo Wu[1] Zhiwei Guo[1], [1]Northeast Ohio Medical University

Background: Mitochondria harbor key alcohol-metabolizing enzymes and serve as active mediators of alcohol-induced toxicity. Canonically regulating glycolysis and exhibiting higher activity than its paralogues, pyruvate dehydrogenase kinase 4 (PDK4) plays a pivotal role in metabolic reprogramming and tissue homeostasis. Hepatic PDK4 is overexpressed in murine models of alcohol-associated liver disease (ALD) and in patients with alcohol-associated hepatitis (AH), implicating it in disease progression. However, its precise role in the pathogenesis of ALD remains incompletely understood. Here, we investigate the potential role of PDK4 in hepatic alcohol metabolism and monocyte/macrophage-mediated inflammatory responses in ALD. **Methods:** PDK4-interacting proteins in PDK4-overexpressing cells were identified by immunoaffinity purification followed by LC-MS/MS. Acetaldehyde-induced oxidative stress, with or without the PDK4 inhibitor diisopropylamine dichloroacetate (DADA), was assessed by measuring reactive oxygen species (ROS) production using a DCF-DA assay. Inflammatory gene expression in murine models of acute and chronic liver injury was quantified by qPCR and ELISA. Expression of signal transducers and activators of transcription (STATs), known regulators of PDK4 expression, was analyzed in monocyte subclusters from peripheral blood mononuclear cells (PBMCs) of patients with AH using a single-cell RNA-seq dataset. **Results:** Immunoaffinity purification revealed that ALDH2, a key enzyme in the oxidative pathway of alcohol metabolism, co-immunopurified with PDK4 in PDK4-overexpressing cells. Pharmacological inhibition of PDK4 by DADA increased ROS levels following acetaldehyde exposure in hepatocytes, suggesting a role for PDK4 in hepatic alcohol detoxification. PDK4 deficiency in mice altered inflammatory gene expression in both acute and chronic liver injury models. Analysis of scRNA-seq data demonstrated increased STAT expression in monocytes from patients with AH. Specifically, STAT2, STAT3, and STAT6 were upregulated across monocyte subclusters, while STAT1 was increased in most clusters except CD16^{+} monocytes, suggesting a possible role of the downstream PDK4 in response to STATs to regulate monocyte/macrophage-driven inflammatory responses in ALD. **Conclusion:** PDK4 may coordinate alcohol metabolism and monocyte/macrophage-mediated inflammatory activation in the pathogenesis of ALD. These findings provide insight into regulators linking alcohol metabolism, mitochondrial function, and innate immune activation in ALD.

Disclosures: Jianguo Wu:Nothing to Disclose, Zhiwei Guo:Nothing to Disclose.

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3096 | MATRIX-BOUND NANOVESICLES AS MODULATORS IN ALCOHOL-RELATED LIVER DISEASE

Yekaterina Krutsenko[1] Bashar Al Matour[1] Jiang Li[1] Jia-Jun Liu[1] Lorien Walker[1] Michael Merchant[2] Silvia Liu[1] George Hussey[1] Melanie Scott[1] Gavin Arteel[1], [1]University of Pittsburgh, [2]University of Louisville

Background: Alcohol-related liver disease (ALD) lacks effective therapies, and understanding extracellular matrix (ECM) remodeling during disease progression may reveal novel therapeutic targets. Matrix-bound nanovesicles (MBVs) are ECM-embedded vesicles enriched in bioactive proteins and microRNAs that regulate cell-matrix signaling and tissue repair in multiple injury settings. However, the contribution of MBVs to ALD pathogenesis has not been yet examined. In the present study, we not only characterized how alcohol alters hepatic MBV composition, but also evaluated therapeutic effects of exogenous healthy MBVs in alcohol-induced liver injury. **Methods:** Using the NIAAA chronic-plus-binge ethanol model, we first isolated hepatic MBVs and performed LC-MS/MS proteomic analysis with pathway enrichment to define alcohol-induced cargo alterations. We then administered MBVs from healthy porcine urinary bladder matrix to ethanol-exposed mice and assessed therapeutic effects through histopathological evaluation and bulk RNA sequencing. **Results:** Chronic ethanol exposure induced marked remodeling of hepatic MBV cargo, with enrichment of proteins associated with metabolic stress responses and detoxification pathways. Administration of healthy MBVs attenuated ethanol-induced steatosis, and lipid peroxidation, while partially normalizing transcriptional programs related to oxidative stress, inflammation, and metabolic regulation. Transcriptomic analyses further demonstrated that MBV administration partially reversed ethanol-induced pathways associated with oxidative stress, inflammatory signaling, cytokine responses, and metabolic dysfunction. Interestingly, MBV treatment improved hepatocellular injury despite persistent neutrophil-associated inflammatory responses, suggesting selective immunomodulation rather than broad immunosuppression. **Conclusion:** These findings identify hepatic MBVs as dynamic components of the ECM microenvironment in ALD. MBVs appear to modulate hepatic homeostasis in a context-dependent manner rather than acting as direct immunosuppressive agents, supporting their potential utility as both biomarkers of ECM remodeling and therapeutic modulators in alcohol-related liver disease.

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3097 | CONTEXT-DEPENDENT FEATURES OF SENESCENT HEPATIC STELLATE CELLS IN LIVER DISEASE

Daniel Lin[1] Hye Yeon Choi[2] Yixin Bai[2] Yoann Daniel[2] Stephanie Pan[2] Qihong Yang[2] Hyun Young Kim[3] Sadatsugu Sakane[3] Meng Li[2] Linda Sher[2] Satoshi Haneda[4] Zhaoli Sun[5] Tatiana Kisseleva[3] Hidekatzu Tsukamoto[2], [1]University of Southern Callifornia, [2]University of Southern California, [3]University of California, San Diego, [4]Sekisui Chemical Co. Ltd., [5]Johns Hopkins University

Background: Hepatic stellate cells (HSCs) undergo senescence to contribute to liver inflammation, regeneration and HCC development. However, single cell transcriptomic profiling of senescent HSCs in liver disease of different etiology, is yet to be assessed. Further, the relationship of HSC senescence with cell activation state, vitamin A content, and ECM scaffold, are elusive. This study aimed to address these knowledge gaps. **Methods:** *Col1a1-GFP* mice underwent alcohol associated-hepatitis (AH); liver fibrosis by bile duct ligation or CCl4; or HCC induced by DEN and alcohol western diet. HSCs were FACS-sorted into VitA+GFP- quiescent HSCs, VitA+GFP+ and VitA-GFP+ activated HSCs (aHSCs). Senescence was assessed by *Glb1+Cdkn2a+* expression via scRNA-seq and SA-β-gal staining in culture. AH or HCC patient livers analyzed by snRNA-seq and/or Visium spatial analysis. ALD patient-derived HSCs and etoposide-induced senescent LX2 cells were cultured on wells coated with chemically defined scaffold Ceglu™ vs. plastic wells to assess its effects. **Results:** scRNA-seq of *Glb1+Cdkn2a+* HSCs across the 4 disease models identifies a common set of induced core senescence markers including *Cdkn1a*, *Serpine1*, and *Atm*. Concurrently, AH senescent HSCs uniquely over-express inflammatory (*Cxcl2*, *Cxcl5*, *Spp1*, *Saa3, C3, Cd5l*) and lipid metabolism (*Ptgs2*, *Pla2g4a*, *Vps13c*, *Apoc1)* genes while HCC senescent HSCs distinctly upregulate immunosuppressive (*Fcgr2b, Dnase1l3*) and tumor-promoting (*Col6a5*,*Stab1, Sox18*) genes. Cross-species conservation is supported by upregulation of *VPS13C*, *APOC1*, *C3*, and *CXCL2* in senescent HSCs in patient AH. Spatial analysis reveals enrichment of senescent HSCs within *AFP+* regenerative nodules in AH patient liver and within patient HCC nodules with *AFP+* cancer cells and *CD4+FOXP3+* Tregs. The senescence rate assessed by *Glb1+Cdkn2a+* is low in control mouse HSCs including VitA+GFP- quiescent HSCs. However, VitA+GFP- cells from AH have a higher senescence rate (3.22%) than VitA+GFP+ (2.30%) or VitA-GFP+ (1.04%) *Lrat+* aHSCs. This surprising result is confirmed by SA-β-gal staining showing 10.67% positivity in the former vs. 2.41%

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and 2.55% in the latter two. *Glb1+Cdkn2+* vs. *Glb1-Cdkn2-* VitA+GFP- HSCs have higher expression of genes previously shown to be associated with inactivated HSCs (*Csf1r, Csf2rb, Il7r, Ly86, Aft3*). VitA+GFP + senescent aHSCs have higher expression of inflammatory genes vs. VitA-GFP+ senescent aHSCs that express immunosuppressive genes. Ceglu™ coated vs. plastic wells reduces etoposide-induced LX2 senescence and partially rescues the senescence of ALD patient HSCs. **Conclusion:** These results suggest HSC senescence is context-dependent and shaped by disease etiology, activation state, vitamin A content, and ECM microenvironment. VitA+GFP- senescent HSCs identified in AH mice, may constitute inactivated HSCs which were once activated.

Disclosures: Daniel Lin:Nothing to Disclose, Hye Yeon Choi:Nothing to Disclose, Yixin Bai:Nothing to Disclose, Yoann Daniel:Nothing to Disclose, Stephanie Pan: Nothing to Disclose, Qihong Yang:Nothing to Disclose, Hyun Young Kim:Nothing to Disclose, Sadatsugu Sakane:Nothing to Disclose, Meng Li:Nothing to Disclose, Linda Sher:Nothing to Disclose, Satoshi Haneda: Nothing to Disclose, Zhaoli Sun:Nothing to Disclose, Tatiana Kisseleva:Nothing to Disclose, Hidekatzu Tsukamoto:Nothing to Disclose.

3098 | CONTINGENCY MANAGEMENT FOR PATIENTS WITH ALCOHOL-ASSOCIATED LIVER DISEASE FOLLOWING LIVER TRANSPLANTATION: A PILOT STUDY

Vanessa Ryan[1] Nicole Prause[1] Akshay Shetty[1] Jasleen Singh[1] Trent Ford[2] Natalie Cohen[2] Steven Shoptaw[1] Arpan Patel[1], [1]University of California, Los Angeles, [2]RELIVE

Background: Alcohol-associated liver disease (ALD) is a leading indication for liver transplantation, yet 20-40% of recipients return to alcohol use after transplant, with harmful drinking linked to graft injury, morbidity and mortality. Contingency Management (CM), an evidence-based behavioral intervention that uses escalating rewards to reinforce abstinence, is effective in many substance use disorders but has not been well-studied among post-liver transplant patients with ALD. This pilot study evaluated the feasibility and acceptability of CM among post-liver transplant patients with ALD and explored preliminary effects on alcohol use and quality of life. **Methods:** This pilot randomized clinical trial aimed to enroll 30 post-liver transplant patients with ALD; only 10 participants were enrolled and randomized to either 10 weeks of CM or treatment as usual (TAU). Eight participants completed all study procedures (CM = 4, TAU = 4), including weekly visits assessing alcohol use with blood and urine biomarkers. Both groups were compensated for study visits; CM participants received escalating incentives (from $5 to up to $70 per week) for negative alcohol biomarkers. CM participants also completed weekly Client Satisfaction Questionnaire (CSQ-8) and semi-structured interviews at Week 2, 5, and 10. All participants completed the PROMIS-29+2 Profile (PROPr) at baseline and study completion. **Results:** Retention among enrolled participants was high (80%). CM participants reported that CM was very acceptable to them (CSQ-8 mean = 30.9 ± 0.6, out of 32). Two participants (one in each arm) reported alcohol use during the study. Although underpowered for efficacy analyses, improvements were observed across 7 of 8 PROPr domains (except physical function). Themes that emerged during interviews included improved accountability, trust, and self-motivation. Reported barriers included laboratory testing burden and limited incentive variety. Participants recommended peer involvement, extended follow-up, and incentive options for future CM programs **(Table):** . **Conclusion:** CM was feasible and highly acceptable among enrolled post-live transplant patients with ALD, though recruitment proved challenging. Exploratory findings suggest potential benefits for patient engagement, increasing abstinence, and improving health-related quality of life. Future studies should focus on optimizing recruitment strategies and reducing participation burden while evaluating CM effectiveness across larger post-liver transplant populations.

Table: Interview Themes and Representative Quotes

	Theme	Quote
CM Acceptability	Trust	"I think as far as making it a **no judgement and a safe space, that was huge, and I really feel like it is a safe space**. So, I think the way that was approached was really important. Because being a transplant recipient, there is a lot of judgement that comes with it once they hear liver."
	Accountability	"For me it is **accountability**, knowing I am part of this study, and it is a good motivator too."
	Internal Motivation And Self Awareness	"I haven't had to give up anything for the program. It's **just a way of life**. I know what I have to do for me and the program is just a reminder of what I need to do to keep me right." "This program has **kept me focused** on what's ahead of me. Not trying to recall what was behind me…" "Overall, the program has opened my eyes to lot of things **Making myself aware of certain things** even as far as what I eat because there are meals where they use cooking wine and sherry and stuff like that…"
	External Support	"Believe in yourself and have a **great support system**. "You can go through a lot of pressure and not give in if you want to live…"
CM Program Suggestions	Contributions from those who completed CM	"Finding out from people who already did it. **I think maybe if you have people like that, who have done it and experienced it**, and have people reach out to those people and ask them what they think… Sometimes, people take it more personally from a person rather than staff, a doctor, a nurse, or an administrator."
	Flexibility in incentives	"But what if **some people don't go to Target**, and maybe some people go to Walmart? Maybe some people shop at other grocery stores or other clothing stores. Maybe it's an option maybe to mix up with the Target gift cards, because some things at Target is more expensive than other places." "Maybe instead of something where they have to go to a certain store, **$25.00 cash might can have them to go to buy something that they might need medically.**"
	Lab Draws	"I wish there was **some way that we could have a home test** afterward so that I could check myself periodically, even though I know what I am doing, just to check myself periodically."
	Create longer follow up	"No. Like I said, **the program is awesome**. It is excellent. I am open to if you guys want to call me in **30, 60, 90 days just** for a **checkup**. That is how good the program was to me, and for me to open up myself to say at your will, come check me, I think that says a whole lot because you guys did a whole lot for me."

Disclosures: Vanessa Ryan:Nothing to Disclose, Nicole Prause:Nothing to Disclose, Akshay Shetty: Nothing to Disclose, Jasleen Singh:Madrigal: Speaking and Teaching, Madrigal: Speaking and Teaching, Trent

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Ford:Nothing to Disclose, Natalie Cohen:Nothing to Disclose, Steven Shoptaw:Clear Scientific: Research Consultation, Gilead Sciences: Clinical Supplies for Research, Braeburn: Clinical Supplies for Research, Arpan Patel:Nothing to Disclose, Nothing to Disclose.

3099 | ADMISSION NEUTROPHIL-TO-LYMPHOCYTE RATIO IS ASSOCIATED WITH 90-DAY MORTALITY IN ALCOHOL-ASSOCIATED HEPATITIS: AN INTERNATIONAL MULTICENTER COHORT STUDY

Gabriel Prusch Fernandes[1] Hamza Sadhra[1] Kristina Chacko[1] Ronnie Li[2] Stephen Hoang[2] S. Fisher Rhoads[2] Mark Thursz[3] Winston Dunn[4] Ashwani Singal[5] Yanhang Gao[6] Roberta Araújo[7] Fatima Higuera-de la Tijera[8] Rakhi Maiwall[9] Ramon Bataller[10] Lubomir Skladany[11] Luis Antonio Diaz[12] Juan Pablo Arab[2], [1]Montefiore Einstein, [2]Virginia Commonwealth University, [3]Imperial College London, [4]University of Kansas Medical Center, [5]University of Louisville, [6]The First Hospital of Jilin University, [7]Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto, [8]General Hospital of Mexico, [9]Institute of Liver and Biliary Sciences, [10]Hospital Clínic de Barcelona, [11]F.D. Roosevelt University Hospital, [12]Pontificia Universidad Católica de Chile

Background: The neutrophil-to-lymphocyte ratio (NLR) is an inexpensive marker of systemic inflammation derived from routine complete blood counts. NLR reflects the balance between innate (neutrophil-driven) and adaptive (lymphocyte) immune responses and rises during the prominent neutrophilic inflammation and systemic inflammatory response characteristic of alcohol-associated hepatitis (AH). Its prognostic role at hospital admission has not been well evaluated in large international cohorts. We evaluated the association between admission NLR and 90-day mortality in hospitalized patients with AH. **Methods:** We conducted a retrospective multicenter cohort study of 1,433 patients hospitalized with AH from 14 centers in 8 countries within the GlobalAlcHep collaboration. Admission NLR was categorized as low (<3), moderate (3 to <6), or high (≥ 6). Missing data were handled with multiple imputation across 30 datasets. Kaplan-Meier survival curves and multivariable Cox proportional hazards regression were used to assess 90-day all-cause mortality. **Results:** Median age was 46 years (IQR 38–54); 70.8% were male. Median admission NLR was 6.6 (IQR 3.8–11.1), and 90-day mortality was 28.6% (410/1,433). Kaplan-Meier analysis demonstrated significantly worse 90-day survival across rising NLR categories (log-rank $p<0.001$). In multivariable analysis, high admission NLR was independently associated with 90-day mortality compared with low NLR (HR 1.55, 95% CI 1.09–2.21; $p=0.02$); moderate NLR did not differ from low (HR 1.13, 95% CI 0.77–1.66; $p=0.54$). Admission MELD was also independently associated with 90-day mortality (HR 1.50 per 5-point increase, 95% CI 1.41–1.61; $p<0.001$). **Conclusion:** In a large international multicenter AH cohort, high admission NLR was independently associated with increased 90-day mortality. As a simple day-0 biomarker derived from the complete blood count, admission NLR may provide additional risk stratification at the time of presentation but should be considered an adjunct rather than a replacement for established prognostic tools.

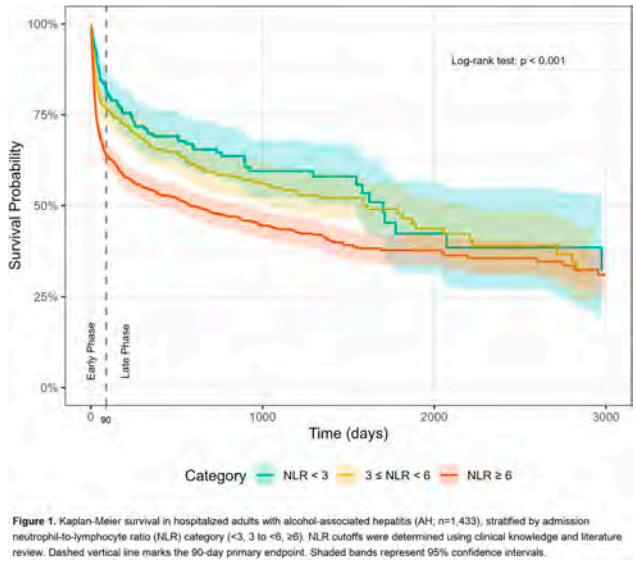


Figure 1. Kaplan-Meier survival in hospitalized adults with alcohol-associated hepatitis (AH; n=1,433), stratified by admission neutrophil-to-lymphocyte ratio (NLR) category (<3, 3 to <6, ≥6). NLR cutoffs were determined using clinical knowledge and literature review. Dashed vertical line marks the 90-day primary endpoint. Shaded bands represent 95% confidence intervals.

Disclosures: Gabriel Prusch Fernandes:Nothing to Disclose, Hamza Sadhra:Nothing to Disclose, Kristina Chacko:Nothing to Disclose, Ronnie Li:Nothing to Disclose, Stephen Hoang:PS Fertility: Consultant, Remedy Plan Inc. Consultant, S. Fisher Rhoads: Nothing to Disclose, Mark Thursz:GSK: Consultant, Resolution Tx: Consultant, Intercept: Consultant, Galecto: Consultant, Durect: Consultant, Winston Dunn:Nothing to Disclose, Ashwani Singal:Madrigal: Speaking and Teaching, Pleiogenix: Stock – privately held company, Pleiogenix: Consultant, CLD Foundation: Advisor, Medical Speaker's Network: Speaking and Teaching, Up-to-Date: Royalties or patent beneficiary, Medscape: Speaking and Teaching, University of Louisville School of Medicine: Employee, NIAAA: Grant/Research Support, Gastro Endo News: Executive role, Durect: Advisor, University of Louisville Health: Other, Yanhang Gao:Nothing to Disclose, Roberta Araújo:Nothing to Disclose, Fatima Higuera-de la Tijera:Nothing to Disclose, Rakhi Maiwall:Nothing to Disclose, Ramon Bataller:Nothing to Disclose, Lubomir Skladany:Nothing to Disclose, Luis Antonio

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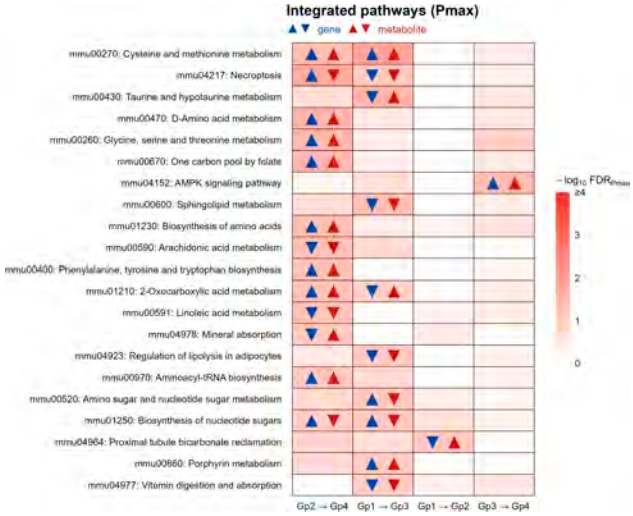
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Diaz:Novo Nordisk: Consultant, Juan Pablo Arab: Nothing to Disclose.

3100 | METABOLIC AND MOLECULAR PERTURBATIONS UNDERLYING METABO-INFLAMMATORY-NECROTIC ACTIVITY INDUCED BY ALCOHOL EXPOSURE IN THE PRESENCE OF OBESITY WITH METABOLIC DYSFUNCTION AND PNPLA3^{I148M} MUTATION

Isabel Veloso Alves Pereira[1] Gamze Bulut[2] Faridoddin Mirshahi[2] Mulugeta Seneshaw[3] Shailaja Lakshmana Reddy[3] Stephen Hoang[3] Thomas Andl[3] Ekaterina Smirnova[2] Arun Sanyal[2], [1]Universidade de São Paulo, [2]Virginia Commonwealth University, [3]Stravitz-Sanyal Institute for Liver Disease and Metabolic Health

Background: Alcohol-associated liver disease (ALD) and obesity with metabolic dysfunction often co-exist. The PNPLA3^{I148M} variant increases the risk of cirrhosis in both ALD and MASLD. The metabolic-molecular perturbations when all three co-exist are not known. **Aim:** To define the impact of (1) alcohol consumption on metabo-inflammatory pathways when obesity and PNPLA3^{I148M} are already present, and (2) PNPLA3^{I148M} on background of obesity and alcohol use. **Methods:** The following interventions were performed on 8wk old male DIAMOND mice: (Group (Gp) 1) high fat diet (HFD), (Gp 2) HFD + AAV-PNPLA3^{I148M} for liver-specific overexpression, (Gp 3) HFD + 20% alcohol (v/v) in drinking water, and (Gp 4) HFD + AAV-PNPLA3^{I148M} + 20% alcohol. Histological, laboratory, tissue SnRNAseq and metabolomic analyses were performed after 16 weeks of treatment. Pseudo-bulked snRNAseq datasets were batch-corrected and integrated with metabolomics data. Gene expression across cell types in the entire liver was constructed using Stouffer weighting with cell-type proportions. For joint pathway analysis, the maximum p value was used to combine metabolites with genes using gene or metabolite set enrichment analysis (ssGSEA GenePattern Module), and a similar enrichment analysis was performed using the KEGG database and custom functions in R Studio. Significance was set to alpha = 0.05 and FDR to 0.1. **Results: Results:** ***A: Effect of alcohol on background of obesity + PNPLA3^{I148M} (Gp 4 vs 2)*****:** Group 4 had the highest histological and molecular metabo-inflammatory activity. 13 pathways were concordantly (gene + metabolite) significantly upregulated (Fig. 1 below) including cysteine-methionine metabolism (FDR 0.05), glycine, serine and threonine (FDR 0.03), one-carbon folate (FDR 0.03). Arachidonic acid (FDR 0.48) and linoleic acid metabolism (0.58) were down-regulated driven by suppression of Cyp4a10 and Cyp2e1 (CT-weighted logFC = -2.78 and -0.8 respectively). Necroptosis was activated by alcohol in this but not in mice without PNPLA3^{I148M} (gp 3). ***B: Effect of PNPLA3^{I148M} on background of obesity + alcohol*****:** A signature of altered AMPK signaling was noted as the only concordant (transcription/metabolite) change (FDR 0.04). **Conclusion:** Alcohol alters amino acid metabolism and transcriptionally activates necroptotic pathways in the background of obesity + PNPLA3^{I148M} . In the presence of obesity and alcohol use, PNPLA3^{I148M} increases AMPK signaling.



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3101 | BIOMARKER-BASED CLASSIFICATION IDENTIFIES POTENTIAL UNDER-RECOGNITION OF ALCOHOL-ASSOCIATED STEATOTIC LIVER DISEASE IN A NATIONALLY REPRESENTATIVE U.S. COHORT

Katharine Tippins[1] Adnan Said[2], [1]University of Wisconsin Hospitals and Clinics, [2]University of Wisconsin School of Medicine and Public Health

Background: Classification of steatotic liver disease (SLD) relies on self-reported alcohol intake to distinguish metabolic dysfunction-associated steatotic liver disease (MASLD) from alcohol-associated phenotypes.

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However, self-report may underestimate alcohol exposure. The MetALD-ALD Prediction Index (MAPI), incorporating routinely available laboratory parameters, was developed to identify alcohol-associated SLD using objective biomarkers. We applied this framework to a nationally representative U.S. cohort to evaluate potential misclassification of alcohol-associated disease. **Methods:** We conducted a cross-sectional, survey-weighted analysis of adults ≥20 years in NHANES 2017–2020 with vibration-controlled transient elastography and complete MAPI components (sex, mean corpuscular volume, GGT, HDL cholesterol, hemoglobin A1c) and alcohol quantity-frequency questionnaires. SLD was defined by controlled attenuation parameter (CAP) ≥280 dB/m and categorized using AASLD-aligned alcohol intake thresholds. Participants were stratified by MAPI risk categories (rule-out ≤0.09, indeterminate 0.09-0.33, rule-in ≥0.33). Primary outcomes were distribution of MAPI risk across self-reported alcohol phenotypes and discordance between self-reported classification and biomarker-based risk. Survey weights were applied to generate nationally representative estimates. **Results:** Among 2,883 adults with SLD, metabolic dysfunction, and complete MAPI variables, 32.5% were classified as MAPI rule-out, 48.7% as indeterminate, and 18.7% as rule-in for alcohol-associated disease. Among participants with MASLD-range self-reported alcohol intake, 18.8% met MAPI rule-in criteria for MetALD-ALD and 68.7% were classified as indeterminate or high-risk for alcohol-associated disease, indicating discordance between self-report and biomarker-based risk. MAPI classification demonstrated a graded increase across self-reported alcohol categories, with rule-in prevalence rising from 18.8% in MASLD-range intake to 51.2% in MetALD-range and 75.7% in ALD-range intake, supporting biological plausibility. Weighted to the U.S. population, these findings correspond to approximately 10.1 million adults with MASLD-range self-reported alcohol intake who meet MAPI rule-in criteria for alcohol-related disease, with 37.0 million classified as indeterminate or high-risk for alcohol-related disease. **Conclusion:** In a nationally representative U.S. cohort, biomarker-based classification using MAPI identifies a substantial subset of individuals with SLD who may have under-recognized alcohol-associated disease despite low self-reported intake. These findings highlight potential limitations of reliance on self-reported alcohol exposure in current SLD classification frameworks and support further evaluation of objective, biomarker-based approaches in population-based liver disease research.

Disclosures: Katharine Tippins:Nothing to Disclose, Adnan Said:Mallinckrodt: Speaking and Teaching, Madrigal Pharmaceuticals: Speaking and Teaching, Novo Nordisk: Speaking and Teaching, GIlead: Speaking and Teaching, Delcath: Consultant.

3102 | SARCOPENIA AND MALNUTRITION ARE ASSOCIATED WITH HEPATIC DECOMPENSATION AND MORTALITY IN HOSPITALIZED PATIENTS WITH ALCOHOL-ASSOCIATED HEPATITIS: A MULTICENTER PROPENSITY-MATCHED ANALYSIS

Ahmed Ibrahim[1] Eisha Mohsin[2] David Maundu[3] Sajid Jalil[4] Ashwani Singal[5], [1]San Joquin General Hospital, [2]Agha Khan Univeristy, [3]University of Kansas School of Medicine–Wichita, [4]Stanford University, [5]University of Louisville

Background: Alcohol-associated hepatitis (AH) is associated with substantial morbidity and mortality. Sarcopenia and malnutrition reflect diminished physiologic reserve and impaired ability to recover from acute illness, yet their impact on outcomes in hospitalized AH is not well described. We aimed to evaluate the association between sarcopenia/malnutrition and hepatic decompensation, as well as mortality among patients hospitalized with AH. **Methods:** We conducted a retrospective cohort study using the TriNetX Research Network to identify adults hospitalized with AH between 2010 and 2025. Adult patients hospitalized with AH and coexisting sarcopenia/malnutrition were identified using validated ICD diagnosis codes. Patients with AH and sarcopenia and/or malnutrition were propensity matched (1:1) with those without sarcopenia/malnutrition. Variables for matching were demographics, comorbidities, and laboratory values. The primary outcome was all-cause mortality. Secondary outcomes included new onset hepatic decompensation [ascites, hepatic encephalopathy (HE), variceal hemorrhage (VH)]. Hazard ratios (HR) with 95% confidence intervals (CI) were calculated using Cox regression models to measure outcomes at 90 days post-admission. **Results:** Among 27,649 patients hospitalized with AH, 6,099 (22%) had sarcopenia/malnutrition. After 1:1 propensity score matching, 5,987 patients remained in each cohort. Matched cohorts were well balanced with respect to age (48.0 ± 11.6 vs 48.3 ± 11.4 years), sex (female: 37.6% vs 38.4%), race, chronic kidney disease, INR, and platelet count (**Table 1**). Sarcopenia/malnutrition was associated with increased risk of hepatic decompensation and adverse outcomes. Compared with patients without sarcopenia/malnutrition, affected patients had significantly had higher risk of ascites (28.9% vs 21.0%; HR 1.436, 95%CI 1.287–1.602; $p < 0.001$), HE (19.7% vs 8.9%; HR 1.333, 95%CI 1.299–1.579; $p < 0.001$), VH (4.2% vs 3.1%; HR 1.370, 95%CI 1.119–1.678; $p = 0.002$), and all-cause mortality (26.9% vs 20.0%; HR 1.349, 95%CI 1.251–1.453; $p = 0.001$) (**Table 2**). **Conclusion:** Sarcopenia/malnutrition is associated with increased hepatic

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decompensation and mortality among patients hospitalized with AH. Early recognition of sarcopenia/malnutrition may improve risk stratification and identify patients who could benefit from targeted nutritional, physical rehabilitation, and multidisciplinary interventions.

Table 1. Demographic and clinical features

Variable	Before matching		Std. Diff	P-value	After matching		Std. Diff	P-value
	AH with sarcopenia or malnutrition (N=6,099)	AH without sarcopenia or malnutrition (N=21,550)			AH with sarcopenia or malnutrition (N=5,987)	AH without sarcopenia or malnutrition (N=5,987)		
Age, mean ± SD	48.0 ± 11.6	47.7 ± 11.3	0.023	0.106	48.0 ± 11.6	48.3 ± 11.4	0.026	0.162
Female, n (%)	2,308 (37.8)	7,128 (33.1)	0.100	<0.001	2,252 (37.6)	2,297 (38.4)	0.015	0.397
White race, n (%)	4,429 (72.6)	15,864 (73.6)	0.022	0.120	4,350 (72.7)	4,356 (72.8)	0.002	0.902
CKD, n (%)	641 (10.5)	1,077 (5.0)	0.207	<0.001	567 (9.5)	581 (9.7)	0.008	0.664
BMI, mean ± SD	26.8 ± 6.6	28.6 ± 6.7	0.260	<0.001	26.7 ± 6.5	28.9 ± 6.9	0.321	<0.001
Albumin, mean ± SD	2.8 ± 0.7	3.0 ± 0.8	0.308	<0.001	2.8 ± 0.7	2.8 ± 0.7	0.093	<0.001
Total bilirubin, mean ± SD	10.4 ± 9.4	6.9 ± 7.5	0.403	<0.001	10.3 ± 9.3	8.7 ± 8.4	0.175	<0.001
INR, mean ± SD	1.9 ± 0.9	1.7 ± 0.7	0.268	<0.001	1.9 ± 0.9	1.9 ± 0.8	0.038	0.125
Platelets (×10³/μL), mean ± SD	124.3 ± 87.7	130.6 ± 88.3	0.072	<0.001	125.2 ± 88.3	122.4 ± 83.2	0.032	0.170

Table 2. Clinical outcomes at 90 days

Outcome	AH with sarcopenia or malnutrition n (%)	AH without sarcopenia or malnutrition n (%)	Hazard Ratio (95% CI)	P-value
Ascites, n (%)	664/2,295 (28.9%)	616/2,940 (21.0%)	1.436 (1.287–1.602)	<0.001
Hepatic encephalopathy, n (%)	464/2,353 (19.7%)	250/2,789 (8.9%)	1.333 (1.299–1.579)	<0.001
Variceal hemorrhage, n (%)	221/5,292 (4.2%)	162/5,302 (3.1%)	1.370 (1.119–1.678)	0.002
All-cause mortality, n (%)	1,609/5,987 (26.9%)	1,199/5,987 (20.0%)	1.349 (1.251–1.453)	0.001

Disclosures: Ahmed Ibrahim:Nothing to Disclose, Eisha Mohsin:Nothing to Disclose, David Maundu: Nothing to Disclose, Sajid Jalil:Nothing to Disclose, Ashwani Singal:Madrigal: Speaking and Teaching, Pleiogenix: Stock – privately held company, Pleiogenix: Consultant, CLD Foundation: Advisor, Medical Speaker's Network: Speaking and Teaching, Up-to-Date: Royalties or patent beneficiary, Medscape: Speaking and Teaching, University of Louisville School of Medicine: Employee, NIAAA: Grant/Research Support, Gastro Endo News: Executive role, Durect: Advisor, University of Louisville Health: Other.

3103 | PEPTIDYL-PROLYL CIS-TRANS ISOMERASE NIMA-INTERACTING 1 (PIN1) REGULATES C/EBPβ-MEDIATED TRANSCRIPTIONAL RESPONSES IN ALCOHOLIC LIVER DISEASE

Manisha Dagar[1] *Manisha Dagar*[1] *Jyoti Chhimwal*[1] *Jiaohong Wang*[1] *Maria Lauda Tomasi*[1] *Shelly Lu*[1], [1]*Cedars-Sinai Medical Center*

Background: Alcohol-associated liver disease (ALD) from excessive alcohol intake can lead to steatosis, inflammation, cirrhosis, and hepatocellular carcinoma. PIN1 binds to target proteins phosphorylated at consensus binding motifs (p-S/T-P) that can affect the proteins' stability, subcellular targeting, interactome, and activity. We reported nuclear PIN1 content is higher in ALD, and this contributed to induction of FOXM1. Here, we analyzed PIN1 nuclear interactome in ALD to better understand how an increase in nuclear PIN1 affects ALD. **Methods:** We used the NIAAA protocol for murine ALD model and human hepatocyte spheroids treated with 100mM ethanol (EtOH) for 24 hours to confirm human relevance. Total liver protein lysates from NIAAA-fed and pair-fed control mice (n = 3 per group) were subjected to co-immunoprecipitation (co-IP) with an anti-PIN1 antibody, followed by mass spectrometry to identify PIN1-interacting proteins. Proteins annotated as nuclear were selected for Network analysis using Cytoscape with ReactomeFIViz. *In silico* analysis using NetPhos and ClusPro identified potential PIN1-binding motifs. RT-qPCR and western blotting measured gene and protein expression, respectively. Functional regulation of C/EBPβ was measured using a stable C/EBPβ GFP reporter cell line via lentiviral transduction of AML12 mouse hepatocytes, with or without PIN1 silencing by siRNA and 100mM EtOH treatment for 24 hours. **Results:** Mass spectrometry identified 84 PIN1-interacting nuclear proteins enriched in NIAAA livers (fold change > 2), with C/EBPβ being one of the top 10 proteins. Network analysis suggested shared clustering of C/EBPβ and PIN1 in a transcriptional regulation module, and in silico docking predicted PIN1 binding to phosphorylated serine/threonine-proline motifs on C/EBPβ (S231/P232, T235/P236, S237/P238), which are known to be phosphorylated by MAPKs and GSK3β. C/EBPβ protein expression was increased 2.6-fold ($p = 0.04$) in NIAAA livers, and in primary human hepatocyte spheroids treated with EtOH (1.6-fold increase). RNA expression of C/EBPβ target genes showed significant elevation in NIAAA livers: *Il6* (2.93-fold, $p = 0.002$), *Il1β* (2.85-fold, $p = 0.04$), and *Pparg* (6.14-fold, $p = 0.02$). C/EBPβ transcriptional activity as measured by the GFP reporter was significantly higher following EtOH treatment, which was mitigated by prior PIN1 silencing (49.8 versus 23.3 RFU, $p = 0.002$), suggesting involvement of PIN1 in the regulation of C/EBPβ transcriptional activity. **Conclusion:** Our findings suggest that in ALD there is increased nuclear PIN1 interaction with C/EBPβ and this activates C/EBPβ's transcriptional activity. C/EBPβ has been implicated in dysregulated inflammatory and fibrotic responses. Our findings suggest a novel role of PIN1 in regulating C/EBPβ transcriptional responses in ALD, which warrants further investigation as a potential therapeutic target.

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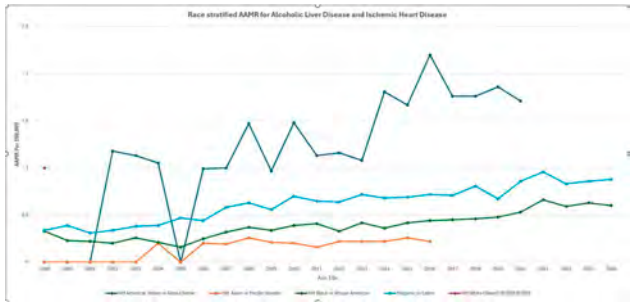
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3104 | CHANGING MORTALITY PATTERNS IN ALCOHOL-ASSOCIATED LIVER DISEASE WITH CONCURRENT ISCHEMIC HEART DISEASE IN THE UNITED STATES: CDC WONDER ANALYSIS FROM 1999 TO 2024

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Background: Alcohol associated liver disease(ALD) and Ischemic Heart disease(IHD) are major causes of morbidity and mortality in the United States. Long-term alcohol use and its effect on hypertension, cardiomyopathy, and atherosclerosis can affect both liver and cardiac conditions at the same time. With a change in population and changing drinking patterns, the burden of concurrent IHD and ALD needs to be explored. This study focuses on trends and demographic disparities in age-adjusted mortality (AAMR) for adults (25-85+) with comorbid ALD and IHD from 1999 to 2024. **Methods:** We performed a retrospective national level mortality analysis with the help of CDC WONDER cause of Death Database from 1999-2024 among patients aged 25-85 and above for Alcoholic liver disease (ICD-10 code: K70) and Cardiovascular disease (ICD code: I20-I25). Data were stratified by Race (Non-Hispanic [NH] American Indian or Alaska Native, NH Asian or Pacific Islander, NH Black or African American, NH White, Hispanic or Latino), sex and age groups. We calculated age-adjusted mortality rates per 100,000 population based on the 2000 US standard population. Temporal trends were assessed using Joinpoint regression to calculate annual percent change (APC), with statistical significance defined by $p < 0.05$. **Results:** From 1999 to 2024, total 37496 deaths were observed and ALD associated IHD mortality showed a statistically significant increase with a steeper recent slope. AAMRs for males exhibited a biphasic statistically significant increase (APC = 5.2%, $p < 0.05$) with upward shifts noted after 2017. Females showed a similar pattern in mortality, but acceleration was observed earlier than males in 2015 and persisted through 2021 (APC = 8.8%, $p < 0.05$) before reaching stabilization. According to racial analysis, AAMRs for NH White population was consistently increasing with statistical significance (APC = 4.9%, $p < 0.05$) while a significant inflection point was observed for the NH Black or African American population in 2012 (APC = 6.2%, $p < 0.05$) after which mortality rates increased significantly. Among Hispanic or Latino populations, mortality rate increased significantly after 2010 (APC = 5.8%, $p < 0.05$). These findings suggest that the coexistence of ALD and IHD represents a widespread and worsening public healthconcern across all demographic groups, without significant long-term improvement throughout the study period. **Conclusion:** Mortality associated with coexisting ALD and IHD has significantly increased since 1999, becoming more prominent over the last decade. The lack of any clear stabilization or decline in mortality trends, especially in recent years, suggests that current screening and management approaches are still falling short of addressing the true burden of these coexisting diseases in the population.



Disclosures: Neha Singh:Nothing to Disclose, MANISH KC:Nothing to Disclose.

3105 | REPRODUCTIVE HEALTH CARE UTILIZATION AMONG REPRODUCTIVE-AGED WOMEN WITH ALCOHOL-ASSOCIATED VERSUS NON–ALCOHOL-ASSOCIATED CIRRHOSIS

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Background: The burden of cirrhosis among reproductive-aged women is rising, driven in part by alcohol-associated liver disease (ALD). Although reproductive counseling and preventive care are essential in this population, little is known about whether reproductive health care utilization differs between women with ALD and non–alcohol-associated liver disease. **Methods:** We identified females diagnosed with cirrhosis between the ages of 18-45 from 2020–2023 with ≥ 1 healthcare

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visit in the year before and after diagnosis using TriNetX. Patients were categorized by etiology: ALD or non-ALD. The index date was the first qualifying cirrhosis/decompensation event. Outcomes were assessed from 1 day through 1095 days after index. Propensity score matching was performed on age, race, ethnicity, menopausal/perimenopausal disorders, and hysterectomy history The primary outcomes were routine women's health related care, including cervical cancer screening, mammography, sexually transmitted infection/HIV screening, and well-woman examination/ referral to a gynecologist. Secondary outcomes included pregnancy, emergency contraception use, and sterilization procedures. Comparisons were made using logistic regression within the matched cohorts. **Results:** A total of 2,978 matched patient pairs, mean age 36 years, were analyzed. Compared with women with non-ALD cirrhosis, women with ALD had lower documented pregnancy (6.0% vs 7.6%; OR 0.78, 95% CI 0.64-0.95; p = 0.016), mammography (12.5% vs 14.9%; OR 0.81, 95% CI 0.70-0.94; p = 0.005), and well-woman/OB-GYN care (10.9% vs 12.8%; OR 0.84, 95% CI 0.72-0.98; p = 0.028). Cervical cancer screening was higher among women with ALD (18.6% vs 15.6%; OR 1.24, 95% CI 1.08–1.42; p = 0.002) as was screening for sexually transmitted infections (STI) (8.2% vs 6.9%; OR 1.21, 95% CI 1.00–1.47; p = 0.05). Emergency contraception (4.2% vs 4.9%; OR 0.86, 95% CI 0.67-1.09; p = 0.214), and sterilization (3.3% vs 3.9%; OR 0.84, 95% CI 0.64-1.10; p = 0.210) did not differ significantly. Interestingly, liver/abdominal cross-sectional imaging was more common in ALD (30.7% vs 26.2%; OR 1.24, 95% CI 1.11-1.39; p < 0.001). **Conclusion:** In a large multi-institutional cohort of reproductive-aged women with cirrhosis, women with ALD demonstrated a selective preventive care pattern. Higher rates of cervical cancer and STI screening may reflect greater attention to infection-related screening in ALD, while routine women's preventive health services remain comparatively underused. These findings highlight an opportunity to broaden ALD care beyond liver monitoring and targeted infectious-risk screening to include routine gynecologic, breast cancer screening, and contraceptive care.

Outcome	ALD, N (%)	Non-ALD, N (%)	OR (95% CI)	p-value
Well-woman/OB-GYN care	326 (10.9)	381 (12.8)	0.84 (0.72–0.98)	0.028
Cervical cancer screening	553 (18.6)	464 (15.6)	1.24 (1.08–1.42)	0.002
Mammography	371 (12.5)	445 (14.9)	0.81 (0.70–0.94)	0.005
STI/HIV screening	245 (8.2)	205 (6.9)	1.21 (1.00–1.47)	0.05
Pregnancy	179 (6.0)	226 (7.6)	0.78 (0.64–0.95)	0.016
IUD or implant	130 (4.4)	141 (4.7)	0.92 (0.72–1.17)	0.494
Emergency contraception	126 (4.2)	146 (4.9)	0.86 (0.67–1.09)	0.214
Sterilization	98 (3.3)	116 (3.9)	0.84 (0.64–1.10)	0.210
Liver imaging	913 (30.7)	781 (26.2)	1.24 (1.11–1.39)	<0.001

Disclosures: Katherine Cooper:Nothing to Disclose, Ami Patel:Nothing to Disclose, Rachael Mahle:Nothing to Disclose, Jordan Tralins:Nothing to Disclose, Jay Luther:Nothing to Disclose, Deepika Devuni:Nothing to Disclose.

3106 | COMPARING HEPATIC OUTCOMES FOLLOWING TIPS IN ALCOHOL-ASSOCIATED VERSUS NON-ALCOHOL-ASSOCIATED CIRRHOSIS: A RETROSPECTIVE COHORT STUDY

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Background: Given the divergent natural histories of cirrhosis etiologies and the potential reversibility of alcohol-associated liver injury with abstinence, post-transjugular intrahepatic portosystemic shunt (TIPS) outcomes may differ by underlying etiology, yet comparative data remain limited. We compared one-year post-TIPS hepatic outcomes between patients with alcohol-associated cirrhosis (ALD-cirrhosis) and non-alcohol-associated cirrhosis, with prespecified subgroup analyses against metabolic dysfunction-associated steatotic liver disease (MASLD)-related and viral hepatitis-related cirrhosis. **Methods:** Using the TriNetX US Collaborative Network, we identified adults with cirrhosis who underwent TIPS placement between 2015 and 2025. Cirrhosis etiology was defined using ICD-10 diagnostic codes. The index date was the date of TIPS placement. Patients with ALD-cirrhosis were compared with patients with non-alcohol-associated cirrhosis using 1:1 propensity score matching on demographics, prior hepatic decompensation, and MELD components (bilirubin, INR, and creatinine), with parallel matched comparisons against MASLD- and viral hepatitis-related subgroups. The primary endpoint was a one-year composite of hepatic decompensation, comprising ascites, spontaneous bacterial peritonitis (SBP), hepatorenal syndrome, variceal hemorrhage, or hepatic encephalopathy. Hazard ratios (HR) with 95% confidence intervals (CI) were estimated using Cox proportional hazards models, with patients censored at loss to follow-up or one year. **Results:** In the primary matched analysis (n = 2,148 pairs), ALD-cirrhosis was associated with a lower one-year risk of composite hepatic decompensation versus non-alcohol-associated cirrhosis (58.2% vs. 65.2%; HR 0.85, 95% CI 0.78–0.91; p < 0.001), driven by lower risks of ascites (43.8% vs. 55.7%; HR 0.72, 95% CI 0.66–0.79), SBP (HR 0.72, 95% CI 0.56–0.93), and variceal hemorrhage (HR 0.77, 95% CI 0.64–0.93; all p < 0.01). Conversely, ALD-cirrhosis was associated with a higher risk of

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hepatic encephalopathy (HR 1.23, 95% CI 1.08–1.39; p = 0.002). In prespecified subgroup analyses, ALD-cirrhosis remained associated with lower one-year hepatic decompensation versus MASLD-related cirrhosis (HR 0.87, 95% CI 0.78–0.96; p = 0.006) and viral hepatitis-related cirrhosis (HR 0.84, 95% CI 0.73–0.96; p = 0.008). **Conclusion:** In this large multicenter cohort, ALD-cirrhosis was associated with lower one-year rates of post-TIPS hepatic decompensation but a higher risk of hepatic encephalopathy compared with non-alcohol-associated cirrhosis, including MASLD- and viral hepatitis-related subgroups. These findings suggest cirrhosis etiology may modify post-TIPS outcomes and may reflect, in part, the potential reversibility of alcohol-associated liver injury with abstinence, warranting prospective investigation with granular data on post-TIPS alcohol use.

Disclosures: Laith Alomari:Nothing to Disclose, Zaid Al-Fakhouri:Nothing to Disclose, Daniel Simadibrata: Nothing to Disclose, Ghideon Ezaz:Nothing to Disclose.

3107 | SOCIODEMOGRAPHIC AND PSYCHOSOCIAL PREDICTORS OF RECOMPENSATION IN PATIENTS WITH DECOMPENSATED STEATOTIC LIVER DISEASE REFERRED FOR LIVER TRANSPLANT EVALUATION

Mohamad Ali Ibrahim[1] Nagham Ramadan[1] Allan Zhang[1] Hannah Wani[1] That Hein[1] Fareen Dhuka[1] Prachi Kaur[1] Mazen Elsheikh[1] Sherry Fares[1] Karim Adhem[1] Humberto Nieves-Jiménez[1] Youseph Karouni[1] Ximena Ramirez Morales[1] Megha Bhongade[1] Prasun Jalal[1], [1]Baylor College of Medicine

Background: Recompensation is increasingly recognized as a clinically meaningful outcome in patients with decompensated steatotic liver disease (SLD). However, the impact of sociodemographic and psychosocial factors on recompensation after liver transplant (LT) evaluation remains poorly defined. We aimed to identify predictors of recompensation among patients with decompensated SLD referred for LT evaluation. **Methods:** We conducted a retrospective cohort study of 175 patients with decompensated SLD, including alcohol-associated liver disease (ALD) and MetALD, referred for LT evaluation at a single U.S. transplant center. Sociodemographic predictors included age, sex, race, ethnicity, education, insurance, income, social support, and Area Deprivation Index (ADI). Psychosocial and substance-use predictors included psychiatric comorbidity, tobacco use, history of drug use, active alcohol use, and prior alcohol use disorder treatment. Recompensation was defined according to the BAVENO VII expanded definition (Tonon et al.). Cox regression analysis was performed to assess the predictors of recompensation. **Results:** Among 175 patients, the median age was 51 years, 61.7% were male, 87.4% were White, 31.0% were Hispanic, the median ADI was 57, and the median MELD 3.0 was 28. Overall, 23/171 patients (13.5%) achieved recompensation, 72/175 (41.1%) underwent LT, and 69/174 (39.7%) died. On univariable analysis, higher ADI was associated with lower recompensation (HR 0.979, p = 0.021), White race was associated with lower recompensation hazard (HR 0.301, p = 0.012), and some college or higher education was associated with higher recompensation hazard (HR 2.823, p = 0.029). On multivariable analysis, lower MELD 3.0 (aHR 0.891, p = 0.002), non-white race (aHR 0.085, p < 0.001), and lower ADI (aHR 0.975, p = 0.013) were independently associated with increased recompensation hazard. **Conclusion:** In patients with decompensated SLD referred for LT evaluation, lower deprivation index, lower MELD 3.0, and non-white race were associated with higher rates of recompensation. These findings suggest that both disease severity and social determinants of health may significantly influence recovery trajectories following LT evaluation and may help identify patients with a greater likelihood of recompensation.

Disclosures: Mohamad Ali Ibrahim:Nothing to Disclose, Nagham Ramadan:Nothing to Disclose, Allan Zhang: Nothing to Disclose, Hannah Wani:Nothing to Disclose, That Hein:Nothing to Disclose, Fareen Dhuka:Nothing to Disclose, Prachi Kaur:Nothing to Disclose, Mazen Elsheikh:Nothing to Disclose, Sherry Fares:Nothing to Disclose, Karim Adhem:Nothing to Disclose, Humberto Nieves-Jiménez:Nothing to Disclose, Youseph Karouni: Nothing to Disclose, Ximena Ramirez Morales:Nothing to Disclose, Megha Bhongade:Nothing to Disclose, Prasun Jalal:Mallinckrodt Pharmaceuticals: Advisor, Madrigal: Grant/Research Support, Ipsen: Grant/Research Support, mirum: Advisor.

3108 | TRANSCRIPTOMIC FINGERPRINTING REVEALS DISTINCT IMMUNE, SECRETORY, AND METABOLIC SIGNATURES IN ALCOHOL-ASSOCIATED HEPATITIS

Brandon Peiffer[1] Zhe Deng[1] Ali Reza Ahmadi[2] Yongchun Wang[1] Yukun Guan[3] Heng Zhu[1] Russell Wesson[1] Jiang Qian[1] Andrew Cameron[1] Bin Gao[3] Zhaoli Sun[1], [1]The Johns Hopkins University School of Medicine, [2]MedRegen LLC, [3]NIH/NIAAA

Background: Alcohol-associated hepatitis (AH) is a severe inflammatory liver disease characterized by immune dysregulation and impaired hepatic function. However, the molecular pathways distinguishing AH from other chronic liver diseases remain incompletely understood. We performed comprehensive transcriptomic

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profiling to identify disease-specific cellular, inflammatory, and metabolic signatures associated with AH. **Methods:** Bulk RNA sequencing data from liver tissues of patients with AH and comparator liver diseases, including alcohol-associated cirrhosis (AC), metabolic dysfunction-associated steatohepatitis (MASH), hepatitis B virus (HBV), hepatitis C virus (HCV), primary biliary cholangitis (PBC), and autoimmune hepatitis (AIH), were analyzed using differential gene expression, cellular deconvolution, pathway enrichment, and secretome-focused analyses. Chemokine/cytokine signaling pathways, receptor expression, growth factor networks, and liver-derived secreted proteins were systematically evaluated. **Results:** Transcriptomic fingerprinting identified molecular features that distinguished AH from other liver diseases. Cellular deconvolution demonstrated increased proportions of adipocytes, common lymphoid precursors, pericytes, and eosinophils in AH livers, whereas plasma cells and megakaryocyte–erythroid precursors were reduced. Chemokine and cytokine analyses revealed upregulation of CCL11, CCL28, CXCL6, IL33, FLT1, and multiple TNF superfamily members. Several immune-related receptors, including CXCR4, CXCR7, CCR3, IL6R, IL10RB, IFNAR2, and IFNGR2, were also increased, indicating enhanced inflammatory signaling in AH. Secretome analysis demonstrated reductions in proteins involved in hepatic synthetic function, including ALB, HPX, APOB, and APOF, as well as coagulation-related proteins (SERPINC1, FGA, FGG, PLG, F2, F7, F11, and F12) and complement components (C2, C6, C8A, C8B, and C9). Growth factor profiling showed increased TGFB1, BMP1, FGF7, FGF12, and FGF13, whereas HDGF and BMP10 were decreased. Pathway enrichment analysis revealed activation of cytoskeletal remodeling, extracellular matrix interactions, infection-related pathways, and immune cell functional programs, while pathways associated with peroxisome activity, metabolic processes, and responses to chemically induced DNA adducts were suppressed. **Conclusion:** Compared with other liver diseases, AH exhibits a distinct transcriptomic signature characterized by altered cellular composition, enhanced inflammatory and chemokine signaling, impaired hepatic synthetic and complement functions, and profound metabolic dysregulation. These findings provide new insights into the molecular pathogenesis of AH and identify potential biomarkers and therapeutic targets for disease progression and treatment.

Disclosures: Brandon Peiffer:Nothing to Disclose, Zhe Deng:Nothing to Disclose, Ali Reza Ahmadi:Nothing to Disclose, Yongchun Wang:Nothing to Disclose, Yukun Guan:Nothing to Disclose, Heng Zhu:Nothing to Disclose, Russell Wesson:Nothing to Disclose, Jiang Qian:Nothing to Disclose, Andrew Cameron:Nothing to Disclose, Bin Gao:Nothing to Disclose, Zhaoli Sun:Nothing to Disclose.

3109 | PROTEOSTASIS CHAPERONES AND PERIPHERAL IMMUNE CELL ALTERATIONS IN PATIENTS WITH ALCOHOL ABUSE AND ALCOHOL-ASSOCIATED HEPATITIS

Abhishek Mandal[1] Jeevitha Thanikasalam[1] Alessandro Colletta[1] Deepika Devuni[1] Rachel Gerstein[1] Pranoti Mandrekar[1], [1]University of Massachusetts Chan Medical School, Worcester, MA, USA

Background: Chronic alcohol consumption induces systemic physiological stress and compromises host immune function. Elucidating immune cell frequencies, and stress mediated proteostasis chaperones in patients with alcohol-associated hepatitis (AH) and alcohol abuse (AA) without any liver disease is critical to unraveling mechanisms related to immune function and liver disease. **Methods:** Peripheral blood mononuclear cells (PBMC) were isolated from healthy volunteers (n = 17), AA (n = 7) and AH (n = 21) patients. Immunophenotyping was performed via flow cytometry. The expression of proteostasis chaperones and cytokines was analyzed by RT-PCR. PBMCs were treated in-vitro with Hsp90 inhibitor (17-DMAG) and immune cell frequencies and pro-inflammatory cytokines were measured. **Results:** Proteostasis chaperones Hsp90AA1, Hsp90AB1, Hsp90B1/GP96, Hsp70, BiP/GRP78, but not HSP90L/TRAP1, are induced in PBMC of AH but not AA patients compared to healthy. Immunophenotyping exhibits increased intermediate monocytes ($p < 0.05$) and decreased non-classical monocytes ($p < 0.05$) without any change in classical monocytes in AH patients but not in AA patients compared to healthy. CD206+ intermediate monocytes are increased in AH patients compared to healthy or AA patients, whereas antigen-presentation markers, HLA-DR and CD86 on non-classical monocytes are reduced in AH compared to healthy and AA patients. Frequency of CCR2+ classical monocytes and CCR5+ intermediate monocytes remain unchanged between healthy, AH and AA patients. Interestingly, in-vitro 17-DMAG treatment reduced the intermediate monocytes ($p < 0.05$) in AH, suggesting decreased inflammatory phenotype. CD3+ CD4+ T cells ($p < 0.001$) and CD4+CD45RO+ memory T cells ($p < 0.05$) were increased whereas CD8+T cells ($p < 0.005$) and Treg cells ($p < 0.05$) decreased in AA and AH patients compared to healthy. However, no significant change in the frequency of T cells was observed after treatment with 17-DMAG. Notably, percentage of intermediate monocytes positively correlated with CD3+CD4+ T cells in AH patients. While baseline mRNA expression of pro-inflammatory TNFα, CCL2, IL-1β and IL-6 was not altered in PBMCs of AA and AH patients, LPS induced IL-1β was higher whereas LPS induced TNFα was

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lower in AH PBMC compared to healthy controls. Further, 17-DMAG significantly reduced ($p < 0.05$) LPS-induced TNFα and IL-1β in AH patients compared to healthy controls. **Conclusion:** Our data show that stress mediated proteostasis chaperones are increased in AH patients but not AA. Further, increased intermediate monocytes and CD4+T cells indicate pro-inflammatory responses in AH whereas reduced CD86 and HLA-DR in non-classical monocytes suggest immunosuppressive phenotypes. Finally, inhibition of Hsp90 in-vitro reduced intermediate monocytes and pro-inflammatory cytokines in AH, suggesting a role for Hsp90 in pro-inflammatory responses in AH.
Disclosures: Abhishek Mandal:Nothing to Disclose, Jeevitha Thanikasalam:Nothing to Disclose, Alessandro Colletta:Nothing to Disclose, Deepika Devuni: Nothing to Disclose, Rachel Gerstein:Nothing to Disclose, Pranoti Mandrekar:Nothing to Disclose.

3110 | BUILDING A PATIENT-INFORMED FRAMEWORK FOR ALD THERAPEUTIC DEVELOPMENT THROUGH THE EXTERNALLY LED PATIENT-FOCUSED DRUG DEVELOPMENT (EL-PFDD) PROCESS

Neeraj Mistry[1] Jenn Jones[2] Lindsey Moore[2], [1]Fatty Liver Foundation, [2]Sober Livers

Background: Despite growing research interest in ALD, there remains a significant unmet need in patient-centered outcomes research and approved therapies, especially as recent therapeutic advances across the Steatotic Liver Disease (SLD) spectrum create a timely opportunity to ensure ALD patient perspectives are included in the evolving drug development landscape. The EL-PFDD is a specialized forum where patient advocacy organizations and disease communities engage directly with the US FDA, pharmaceutical developers and researchers, to share lived experiences, challenges, and treatment priorities. The EL-PFDD process is intended to help the FDA and other stakeholders better understand patient experiences, treatment priorities, and risk tolerance relevant to drug development. **Methods:** Under the leadership and coordination of Sober Livers, an initiative housed at the Steatotic Liver Foundation, an EL-PFDD meeting letter of intent (LOI) was submitted and accepted in 2025, for hosting late 2026/early 2027. The preparation in advance of the EL-PFDD forum is a representative and participatory process to ensure that patient perspectives on ALD are represented equitably, commensurate with the burden of disease and etiology, and reflect the heterogeneous social conditions of people living with ALD. The process will highlight qualitative issues surrounding the patient experience, which will then be assessed and stratified by the Expert Steering Committee, for further qualitative research on patient perspectives and priorities. **Results:** The preparation for the EL-PFDD process has commenced, and various tools are being employed to engage patients, including: a discussion framework to capture their day-to-day experiences, current and future concerns, and wishes; multi-media platforms such as blogs, videos, and surveys; leveraging various patient support and advocacy networks; and a lean planning committee and multistakeholder steering committee. The intended outputs of these processes are: 1. A participatory and representative voice of the ALD patient in the drug development process at the EL-PFDD forum 2. A concise and workable document capturing patient perspectives for consideration in the FDA approval process and to inform the bio-life-science research and development sector. **Conclusion:** As therapeutic innovation in SLD accelerates, there is a growing need to better understand ALD-specific patient priorities, treatment goals, and acceptable benefit-risk tradeoffs to support development of safe, effective, and patient-centered therapies. ALD stakeholders have a timely and important opportunity to capture patient priorities and concerns for drug development in a clearly defined space. Given the overlap in lifestyle risks and liver pathology, it is hoped that patient perspectives on research into and approval of ALD therapies can inform and accelerate access to safe and effective treatment options.
Disclosures: Neeraj Mistry:Nothing to Disclose, Jenn Jones:Nothing to Disclose, Lindsey Moore:Nothing to Disclose.

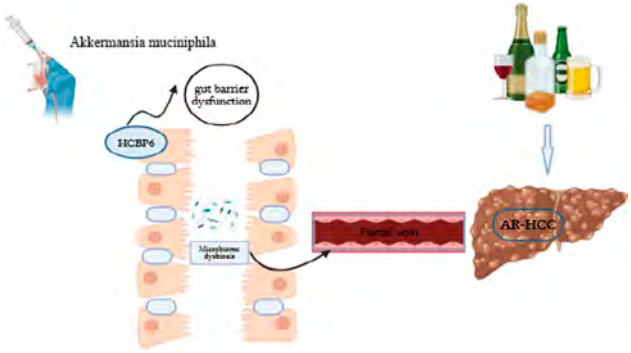
3111 | MECHANISM STUDY ON THE ROLE OF GUT HCBP6 IN ALCOHOL-RELATED HEPATOCELLULAR CARCINOMA PROGRESSION VIA THE GUT-LIVER AXIS

Xuanxuan Niu[1] Huichun Xing[1] Xiaoxue Yuan[1], [1]Beijing Ditan Hospital, Capital Medical University

Background: The occurrence and development of alcohol related hepatocellular carcinoma (AR-HCC) are closely associated with gut-liver axis dysfunction and gut microbiota dysbiosis. However, the role and regulatory mechanism of gut HCBP6 in this process are not yet clear. **Methods:** Six-week-old SPF mice were divided into CCl4 and ETOH+CCl4 groups to establish an AR-HCC model. MRI, HE staining, TEM, FITC-dextran assays, Alcian blue staining, and Western blot were used to evaluate liver injury, intestinal barrier function, and HCBP6/Occludin expression. Fecal metagenomic sequencing and AKK gavage were

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further performed to assess microbiota-mediated effects on tumor progression. **Results:** MRI results demonstrated obvious tumor-like nodules in the livers of mice in the ETOH+CCl4 group. HE staining revealed marked dysplasia and tumor-like lesions in liver tissues, accompanied by destruction of intestinal villi, disorganized villus arrangement, and inflammatory cell infiltration.TEM analysis showed that intestinal microvilli in the CCl4 group were relatively intact with clear tight junction structures, whereas the ETOH+CCl4 group exhibited disorganized microvilli and widened intercellular junctions. FITC-dextran assays demonstrated significantly increased intestinal permeability in the ETOH+CCl4 group. Alcian blue staining further revealed damage to the intestinal mucus layer.Western blot analysis showed that the expression levels of HCBP6 and Occludin were significantly downregulated in intestinal tissues from the ETOH+CCl4 group.Fecal metagenomic sequencing demonstrated a significant reduction in the abundance of Akkermansia muciniphila in the ETOH+CCl4 group. Following AKK intervention, liver tumor burden was reduced, intestinal inflammation was alleviated, and villus architecture was partially restored. TEM analysis demonstrated improved microvillus integrity, while FITC-dextran assays indicated reduced intestinal permeability. Metagenomic analysis further showed that AKK treatment remodeled the gut microbiota composition. Meanwhile, the expression levels of HCBP6 and Occludin were upregulated in the ETOH+AKK group compared with the ETOH+PBS group. **Conclusion:** HCBP6 may be involved in the regulation of intestinal barrier function during alcohol-related liver cancer, and together with changes in gut microbiota, participate in disease progression through the gut liver axis. AKK intervention can partially improve intestinal barrier damage and reduce tumor burden, suggesting that intestinal HCBP6 and related microbiota may become potential targets for alcohol-related liver cancer intervention.



Disclosures: Xuanxuan Niu:Nothing to Disclose, HUICHUN XING:Nothing to Disclose, Xiaoxue Yuan:Nothing to Disclose.

3112 | A REFINED SLD CLASSIFICATION IMPROVES FIBROSIS RISK STRATIFICATION IN METALD

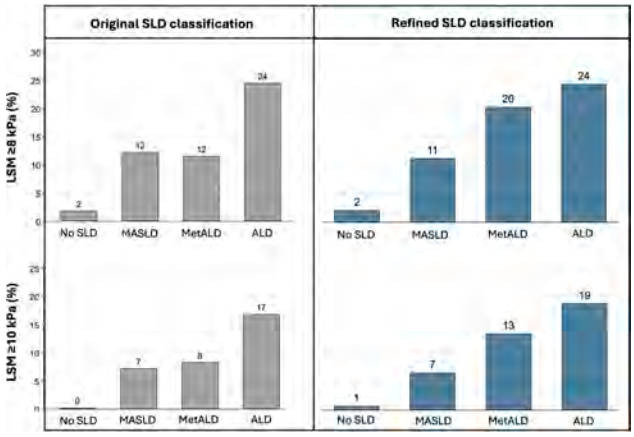
Camilla Dalby Hansen[1] Charlotte Mary Bastida Gjøl[1] Helle Lindholm Schnefeld[1] Katrine Tholstrup Bech[1] Ellen Lyngbeck Jensen[1] Nikolaj Torp[1] Stine Johansen[1] Peter Andersen[1] Ida Falk Villesen[1] Katrine Thorhauge[1] Johanne Hansen[2] Mads Israelsen[1] Aleksander Krag[3], [1]Centre for Liver Research, Department of Gastroenterology and Hepatology, Odense University Hospital, [2]Odense University Hospital, [3]University of Southern Denmark

Background: Current evidence suggests that the Steatotic Liver Disease (SLD) subgroup metabolic- and alcohol related steatotic liver disease (MetALD) do not provide additional risk stratification for liver fibrosis beyond MASLD, as fibrosis prevalence appears similar between the two groups in several population-based cohorts. We therefore evaluated a refined exposure-based SLD classification incorporating both current and historical high-risk alcohol consumption to assess its association with liver fibrosis across SLD. **Methods:** Cross-sectional analysis from a large community-based cohort with metabolic and/or alcohol-related risk factors. Hepatic fibrosis was assessed using transient elastography. Participants were classified according to the current SLD nomenclature and according to a refined exposure-based classification incorporating current and historical high-risk alcohol exposure. Historical high-risk alcohol exposure was defined as alcohol consumption >50 g/day in women or >60 g/day in men for more than five years. Beyond the prevalence of hepatic steatosis, ALD was refined as having both a current and a historical high-risk alcohol exposure, MetALD as either current or a historical high-risk alcohol exposure in the presence of cardiometabolic risk factors (CMR), and MASLD as the absence of both current and historical high-risk alcohol exposure in the presence of CMR. **Results:** We included 3,123 participants, age of 56,5 years (SD, 9.6), 50.1% males, BMI of 31 kg/m^2 (IQR, 27-35). The refined classification of SLD resulted in a marginal reduction in the overall prevalence of diagnosed SLD (n = 2,197 (70.3%) vs. n = 2,181 (69.8%)), a higher prevalence of MASLD (n = 1,603 (51.3%) vs. n = 1,766 (56.6%)), and a corresponding lower prevalence of both MetALD (n = 398 (12.7%) vs. n = 306 (9.8%)) and ALD (n = 196 (6.3%) vs. n = 109 (3.5%)). Interestingly, the refined classification substantially altered the distribution of fibrosis across SLD subgroups, resulting in a markedly higher fibrosis burden within the MetALD phenotype (LSM ≥8 kPa: 11.6% to 20.3%), whereas the fibrosis burden remained largely unchanged in both MASLD (LSM ≥8 kPa: 12.2% to 11.3%) and ALD (LSM ≥8 kPa: 24.5% vs. 24.3%). The observed redistribution of

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fibrosis burden remained consistent when applying LSM ≥10 kPa. In a multivariable model adjusted for CMR, age and sex the reclassification resulted in adjusted odds of significant fibrosis in the MetALD subgroup from OR 5.6 ((95%CI; 3.13-10.18), p < 0.001) to OR 8.8 (95%CI; 5.1-15.1, p < 0.001) while fibrosis risk estimates for MASLD and ALD changed only modestly. **Conclusion:** Incorporating historical alcohol consumption appeared to enrich the MetALD phenotype for individuals with clinically relevant fibrosis risk, suggesting that this might better capture the cumulative hepatic injury than the current classification.



Disclosures: Camilla Dalby Hansen:Novo Nordisk: Speaking and Teaching, Charlotte Mary Bastida Gjøl: Nothing to Disclose, Helle Lindholm Schnefeld:Nothing to Disclose, Katrine Tholstrup Bech:Nothing to Disclose, Ellen Lyngbeck Jensen:Nothing to Disclose, Nikolaj Torp:Nothing to Disclose, Stine Johansen: Nothing to Disclose, Peter Andersen:Nothing to Disclose, Ida Falk Villesen:Nothing to Disclose, Katrine Thorhauge:Nothing to Disclose, Johanne Hansen: Nothing to Disclose, Mads Israelsen:Nothing to Disclose, Aleksander Krag:Nothing to Disclose.

3113 | UBC9 TRANSCRIPTIONAL REGULATION REWIRES NF-κB SIGNALING IN ALCOHOL-ASSOCIATED LIVER DISEASE

Swati Chandla[1] Youngyi Lim[2] Manisha Dagar[2] Joshua Martinez[2] Komal Ramani[3] Maria Lauda Tomasi[2],
[1]Cedars Sinai Medical Center, [2]Cedars Sinai Medical Center, Los Angeles, [3]Cedars-Sinai Medical Center

Background: Alcohol abuse promotes alcoholic-associated liver disease (ALD) by increasing gut-derived endotoxin translocation, which activates Kupffer cells (KCs) and NF-κB–dependent inflammatory signaling. UBC9, the sole E2 enzyme for SUMOylation, regulates transcriptional responses by modulating nuclear factor activity. We previously showed that alcohol induces SRC-mediated phosphorylation of UBC9 at Y68 in KCs, thereby promoting hepatocyte lipogenic gene expression. Here, we investigated how UBC9 phosphorylation remodels its interactome and inflammatory signaling in ALD. **Methods:** RAW 264.7 and THP-1 cells were used for in vitro studies, with validation by CRISPR/Cas9-CD68–mediated UBC9 Y68 editing in the NIAAA mouse model. UBC9-interacting proteins were identified in KCs lysates from ethanol-fed and pair-fed mice by anti-UBC9 antibody via co-immunoprecipitation (co-IP) and mass spectrometry (MS), followed by Omics Playground network analysis. Additional assays included RT-qPCR, UBC9 promoter reporter, chromatin immunoprecipitation (ChIP), CHX chase, and proteasome inhibition. **Results:** LPS stimulation of RAW 264.7 and THP-1 cells reduced UBC9 promoter activity and mRNA expression, resulting in lower total UBC9 protein levels. Despite this reduction, LPS induced phosphorylation of the remaining UBC9 pool, with phosphorylated UBC9 accounting for approximately 95% of detectable UBC9 protein. ChIP analysis revealed LPS-mediated binding of HIF-1 to the UBC9 promoter, which is known to be a negative regulator of UBC9 when hypermethylated. CHX chase assays showed that UBC9 has a half-life of approximately 9 hours without enriching phosphorylated UBC9. This indicates that phosphorylation is not a simple passive consequence of UBC9 loss but rather requires active, translation-dependent processes. We also found that MG132 prevented LPS-induced reduction of UBC9, indicating proteasome-dependent degradation. MS interactome analysis revealed that phosphorylated UBC9 preferentially associated with NF-κB family members, including p65, p52, and p50, as validated by co-IP. Mechanistically, we found that NF-κB family members were SUMOylated in a paralog-specific manner: p65 and p52 were modified by SUMO1, whereas p50 was modified by SUMO2/3. These findings identify NF-κB subunits as plausible SUMO-sensitive transcriptional mediators linking phosphorylated UBC9 to cytokine secretion in activated macrophages. **Conclusion:** These findings identify UBC9 as a regulatory switch in ALD, whereby reduced UBC9 mRNA level and SRC-mediated Y68 phosphorylation reprogram SUMOylation-related signaling toward NF-κB activation in KCs. Targeting upstream pathways that link UBC9 mRNA loss to UBC9 phosphorylation may provide novel therapeutic strategies for ALD.

Disclosures: Swati Chandla:Nothing to Disclose, Youngyi Lim:Nothing to Disclose, Manisha Dagar: Nothing to Disclose, Joshua Martinez:Nothing to Disclose, Komal Ramani:Nothing to Disclose, Maria Lauda Tomasi:Nothing to Disclose.

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3114 | ALCOHOL EXPOSURE IDENTIFIES INDIVIDUALS AT HIGH-RISK OF INCREASED LIVER STIFFNESS MISSED BY FIB-4 IN ALCOHOL USE DISORDER

Omar Albhaisi[1] Monica Melmer[1] Anna Peyton[1] Hannah Kissel-Smith[1] Brandon Wills[1] Matthew Way[1] Megan Lemay[1] Andy Pinson[1] Crystal Watts[1] Chareece Williams[1] Tara Kilman[1] Brian Singh[1] James White[1] Gerry Moeller[1] Juan Pablo Arab[1], [1]Virginia Commonwealth University

Background: Background & Aims: FIB-4 is commonly used to screen individuals for liver fibrosis, but its role as a gatekeeper for vibration-controlled transient elastography (VCTE) in alcohol use disorder (AUD) is uncertain. We evaluated whether a high-FIB-4-only strategy would miss clinically meaningful increased liver stiffness in an integrated AUD clinic cohort. **Methods:** We analyzed patients with AUD who underwent VCTE with paired FIB-4 at the MOTIVATE Clinic, an integrated addiction program at Virginia Commonwealth University. LSM was categorized as <8 (low-risk/rule-out range), 8–11 kPa (indeterminate/elevated stiffness), and ≥ 12 kPa (high-risk stiffness suggestive of advanced fibrosis) per AASLD 2025 NIT guidelines. FIB-4 was grouped as <1.30 (low), 1.30–2.67 (intermediate), and ≥ 2.67 (high). Patients with FIB-4 <2.67 but LSM ≥ 12 kPa were classified as potentially missed by high-FIB-4-only gating. Drinking pattern, PEth, liver biochemistries, and platelets were compared between missed and non-missed patients using Mann-Whitney U and Fisher's exact tests. **Results:** We included 94 patients with AUD and paired VCTE/FIB-4 data; mean age was 50 years; 60% were male; 72% met DSM-5 criteria for severe AUD. Median LSM increased across FIB-4 categories: 5.9 kPa for FIB-4 <1.30, 6.9 kPa for FIB-4 1.30–2.67, and 32.7 kPa for FIB-4 ≥ 2.67. Among 71 patients with FIB-4 <2.67, 12 (16.9%) had LSM ≥ 12 kPa and would have been missed by a high-FIB-4-only strategy. Most missed cases were in the intermediate FIB-4 subgroup: 10/36 (27.8%) with FIB-4 1.30–2.67 had LSM ≥ 12 kPa. Compared with non-missed patients ($n=59$), missed patients had higher AUDIT-C (median 12 vs 8, $p<0.001$), more often had the maximum AUDIT-C score of 12 (83% vs 22%, $p<0.001$), higher alcohol use (11 vs 3 standard drinks/day, $p=0.013$), and more frequent ≥ 10 drinks/day (75% vs 29%, $p=0.006$). Missed patients also had higher AST (45 vs 29 U/L, $p=0.008$), higher ALT (48 vs 22 U/L, $p=0.008$), and lower platelets (176 vs 261 $\times 10^9$/L, $p<0.001$). PEth >200 ng/mL and beverage type did not significantly differ between groups. **Conclusion:** In AUD patients, high-risk FIB-4 alone may miss a clinically important subgroup with LSM ≥ 12 kPa. Intermediate FIB-4 combined with higher questionnaire-defined alcohol exposure and platelet/aminotransferase abnormalities may identify patients who should proceed directly to VCTE rather than being excluded by FIB-4 gating alone.

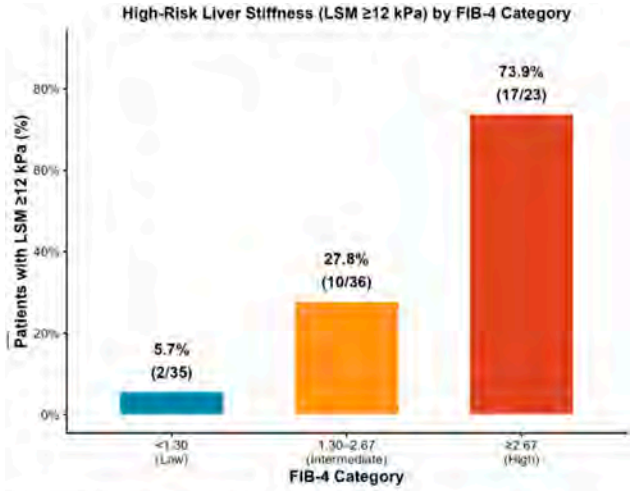


Figure 1. High-risk liver stiffness by FIB-4 category.

Proportion of patients with alcohol use disorder who had high-risk liver stiffness, defined as liver stiffness measurement (LSM) ≥12 kPa, across FIB-4 risk categories. High-risk LSM was present in 5.7% of patients with FIB-4 <1.30, 27.8% with FIB-4 1.30–2.67, and 73.9% with FIB-4 ≥2.67.

Disclosures: OMAR ALBHAISI:Nothing to Disclose, Monica Melmer:Nothing to Disclose, Anna Peyton:Nothing to Disclose, Hannah Kissel-Smith:Nothing to Disclose, Brandon Wills:Nothing to Disclose, Matthew Way:Nothing to Disclose, Megan Lemay:Nothing to Disclose, Andy Pinson:Nothing to Disclose, Crystal Watts:Nothing to Disclose, Chareece Williams:Nothing to Disclose, Tara Kilman:Nothing to Disclose, Brian Singh:Nothing to Disclose, James White:Nothing to Disclose, Gerry Moeller:Nothing to Disclose, Juan Pablo Arab:Nothing to Disclose.

3115 | FRONTLINE PROVIDER ATTITUDES, PRACTICES, AND BARRIERS TO ALCOHOL USE DISORDER PHARMACOTHERAPY IN PATIENTS WITH ALCOHOL-ASSOCIATED LIVER DISEASE: A MULTISPECIALTY SURVEY

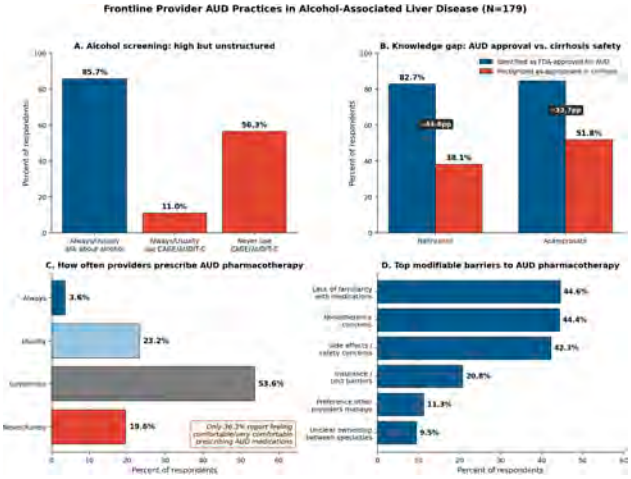
James Vu[1] Lindsey Immers[2] Jordan Holliday[2] Robert Pecha[2] Vikrant Rachakonda[2], [1]UC Davis Medical Center, [2]University of California Davis Medical Center

Background: Alcohol use disorder (AUD) drives mortality in alcohol-associated liver disease (ALD), yet AUD pharmacotherapy remain underutilized in this

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population. Prior AASLD ALD Special Interest Group (SIG) survey data showed the majority of GI/Hepatology providers had never prescribed AUD pharmacotherapy due to low comfort. Because most ALD patients first present outside hepatology, we examined frontline provider attitudes, practices, and modifiable barriers to AUD pharmacotherapy. **Methods:** A 34-item survey adapted from the AASLD ALD SIG instrument was distributed across frontline specialties at a tertiary academic center to assess respondent demographics, AUD pharmacotherapy prescribing patterns, knowledge of FDA-approved AUD medications and their safety in liver disease and cirrhosis, and perceived barriers to screening and pharmacotherapy. Responses were summarized with descriptive statistics; open-ended responses were reviewed qualitatively for recurring themes. **Results:** 179 providers responded across internal medicine (62.0%), emergency medicine (22.9%), family medicine (7.3%), psychiatry/addiction medicine (7.3%), and GI/hepatology (5.0%); 53.1% were trainees and 44.1% attendings with 86.6% stating they encountered ALD patients at least monthly. Only 36.3% felt comfortable/very comfortable prescribing AUD pharmacotherapy, and only 26.8% reported being regular prescribers. 66.1% incorrectly believed there is a safe level of alcohol use in liver disease. While most recognized FDA approved AUD medications (naltrexone 82.7%, acamprosate 84.5%), recognition of their utility in cirrhosis dropped to 38.1% and 51.8% respectively. 35.7% agreed/strongly agreed that the risks of AUD pharmacotherapy outweigh the benefits in ALD cirrhosis. Top reasons therapy was not initiated by providers included: patient refusal (77.6%), outpatient deferral (55.8%), and AUD not addressed during hospitalization (45.8%). Top medication specific barriers included lack of familiarity (44.6%) and concern about side effects/safety (42.3%). The majority of providers (47.1%) felt ownership of AUD pharmacotherapy should fall to the primary internal medicine team during hospitalizations, versus being deferred to primary care (17.2%) or addiction medicine (16.7%). **Conclusion:** Despite frequent contact with ALD patients, frontline providers harbor misconceptions about safe alcohol use and AUD pharmacotherapy in ALD cirrhosis, and rarely initiate AUD pharmacotherapy. Primary inpatient teams, while identified as primarily responsible for inpatient AUD treatment, reported the greatest knowledge deficits. Modifiable barriers include gaps in knowledge and lack of treatment pathways and protocols. These findings extend the AASLD SIG findings beyond the GI/Hepatology specialty, and targeted educational and systematic interventions are warranted to improve the quality of care of AUD in the ALD population.



Disclosures: James Vu:Nothing to Disclose, Lindsey Immers:Nothing to Disclose, Jordan Holliday:Nothing to Disclose, Robert Pecha:Nothing to Disclose, Vikrant Rachakonda:Nothing to Disclose.

3116 | PSYCHOTHERAPY AUGMENTATION OF MEDICAL ALCOHOL DETERRENT THERAPY AND 90-DAY OUTCOMES IN ALCOHOLIC HEPATITIS AND ALCOHOL USE DISORDER: A PROPENSITY SCORE–MATCHED COHORT ANALYSIS

Bianca Patel[1] Jashanveer Johal[1] Archana Salek[1] Mahmoud Al-Bataineh[1] Brandon Cunha[1] Abdallah Hussein[1] Jason Hyman[2] Yecheskel Schneider[1], [1]Virtua Health, [2]Einstein Medical Center

Background: Pharmacologic relapse-prevention therapy (naltrexone, acamprosate, or disulfiram) is standard in alcohol use disorder (AUD), yet recidivism remains common. The impact of adding structured psychotherapy on clinical and hepatic outcomes in alcoholic hepatitis is unclear. **Methods:** We conducted a propensity score–matched retrospective cohort study using the TriNetX Global Collaborative Network (191.9 million patients). Cohort 1 comprised patients with alcoholic hepatitis (K70.1), alcohol abuse (F10.1), or alcohol dependence (F10.2) who received pharmacologic alcohol deterrent therapy (naltrexone, acamprosate, or disulfiram) within one month of diagnosis and had structured psychotherapy (CPT codes 99408, 99409, G0442, G0443, 90832, 90834, or 90853) documented concurrently. Cohort 2 comprised patients receiving deterrent pharmacotherapy alone without any structured psychotherapy. Both cohorts excluded prior CKD stage 5 or ESRD, liver transplant status, and

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hepatocellular carcinoma. Cohorts were balanced via 1:1 PSM, yielding 16,477 patients per arm. Pre-specified 90-day outcomes included repeat alcoholic hepatitis or acute hepatic failure, progression to cirrhosis, alcohol withdrawal, ICU admission, inpatient encounters, and all-cause mortality. **Results:** Recurrent alcoholic hepatitis/hepatic failure (3.6% vs. 3.6%; HR 0.95, p = 0.41) and cirrhosis progression (0.6% vs. 0.7%; HR 0.84, p = 0.21) were similar between groups. Alcohol withdrawal was more frequent with psychotherapy (11.3% vs. 9.6%; HR 1.12, p = 0.0006), as were inpatient encounters (4.5 vs. 3.0 mean encounters; p < 0.001). ICU admissions were absent in both groups. All-cause mortality was significantly lower with psychotherapy (0.58% vs. 0.85%; HR 0.63, p = 0.0005). **Conclusion:** In this propensity-matched real-world cohort, combining structured psychotherapy with pharmacologic alcohol deterrent therapy was not associated with lower rates of repeat alcoholic hepatitis, hepatic failure, or cirrhosis over 90 days, but was associated with significantly lower all-cause mortality. The paradoxical increase in withdrawal events and inpatient encounters in the psychotherapy arm most likely reflects greater healthcare engagement and detection bias rather than clinical worsening. These findings support psychotherapy integration as a mortality-reducing complement to pharmacologic AUD therapy and highlight the need for prospective studies with longer follow-up.

Disclosures: Bianca Patel:Nothing to Disclose, Jashanveer Johal:Nothing to Disclose, Archana Salek:Nothing to Disclose, Mahmoud Al-Bataineh:Nothing to Disclose, Brandon Cunha:Nothing to Disclose, Abdallah Hussein:Nothing to Disclose, Jason Hyman:Nothing to Disclose, Yecheskel Schneider:Nothing to Disclose.

3117 | PREDICTING ALCOHOL RELAPSE AFTER LIVER TRANSPLANTATION FOR ALCOHOL-ASSOCIATED LIVER DISEASE: TWO-YEAR OUTCOMES OF THE SALT AND HALT SCORES AT A SINGLE ACADEMIC CENTER

Alex Chang[1] Anwesha Satapathy[2] Nishi Joshi[2] James Park[2] Sanjaya Satapathy[3], [1]Brown University, [2]Northwell Health, [3]Northshore University Hospital/Northwell Health

Background: Accurate prediction of post-transplant alcohol relapse is critical for patient selection, organ stewardship, and implementation of targeted harm-reduction strategies. Although the Sustained Alcohol Use Post-Liver Transplant (SALT) and Harmful Alcohol Use Post-Liver Transplant (HALT) scores have been proposed as relapse prediction tools, external validation data remain limited. We evaluated the performance of SALT and HALT scores in predicting post-transplant alcohol relapse in a single-center cohort of patients transplanted for alcohol-associated liver disease (ALD). **Methods:** We conducted a retrospective study of adults who underwent liver transplantation for ALD between December 2019 and August 2023, with minimum follow-up of 2 years. Clinical and psychosocial variables were obtained through chart review, and SALT and HALT scores were retrospectively calculated. Alcohol relapse wasFig defined by self-reported alcohol use or positive phosphatidylethanol (pETH) testing. Relapse was categorized as either any relapse (including slips) or harmful relapse, defined as alcohol consumption exceeding 3 drinks per week post-transplant or alcohol use resulting in hospital readmission. Receiver operating characteristic (ROC) analyses were performed using SAS 9.4. **Results:** A total of 82 patients were included, incuding 51 patients with < 6 months of abstinence. In the overall cohort, the HALT score demonstrated moderate performance for predicting harmful relapse (AUC 0.70, 95% CI 0.56–0.83), whereas the SALT score showed limited discrimination (AUC 0.57, 95% CI 0.43–0.72). Among patients transplanted with < 6 months of abstinence, predictive performance improved substantially for both scores, with HALT achieving an AUC of 0.78 (95% CI 0.60–0.96) and SALT an AUC of 0.71 (95% CI 0.54–0.89) for harmful relapse within 1 year post-transplant.Both scores performed poorly in predicting any relapse, including slips (HALT AUC 0.53; SALT AUC 0.53). However, among patients with < 6 months of abstinence, HALT demonstrated improved discrimination for any relapse (AUC 0.72, 95% CI 0.56–0.88). Using established thresholds, HALT $\leq$ 0.30 demonstrated better negative predictive value than SALT $\leq$ 5, particularly among patients transplanted with shorter abstinence periods. **Conclusion:** Both HALT and SALT scores demonstrated improved predictive performance among patients transplanted with < 6 months of abstinence and for identifying harmful relapse within the first year after transplantation. HALT appeared to have stronger predictive ability in identifying clinically significant relapse when including patients with > 6 months of abstinence. However, neither score reliably predicted isolated slips, limiting their utility as standalone selection tools. These findings support the

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use of relapse risk stratification models as adjunctive tools to guide post-transplant monitoring and targeted behavioral interventions.

Table 1

	PPV	NPV	Sensitivity	Specificity
All Patients (n = 82)				
SALT ≥ 5	25%	79%	21%	87%
HALT ≥ 0.30	54%	83%	37%	90%
<6 months of abstinence (n =51)				
SALT ≥ 5	50%	84%	30%	93%
HALT ≥ 0.30	55%	90%	60%	88%

Figure 1A Harmful Relapse **1B Harmful Relapse, Abstinence < 6 mo**

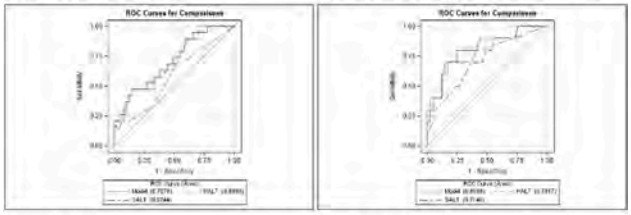
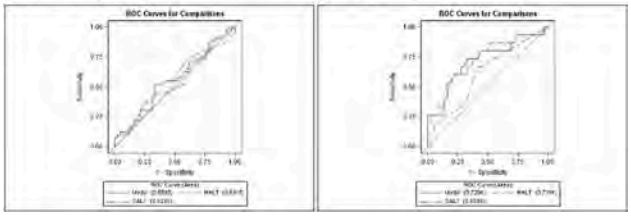


Figure 2A Any Relapse **2B Any Relapse, Abstinence < 6 mo**



Disclosures: Alex Chang:Nothing to Disclose, Anwesha Satapathy:Nothing to Disclose, Nishi Joshi:Nothing to Disclose, James Park:Nothing to Disclose, Sanjaya Satapathy:Gilead Sciences: Grant/Research Support, Durect Pharma: Grant/Research Support, Fibronostics: Grant/Research Support, Novartis: Grant/Research Support, Zydus Pharma: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Intercept Pharma: Grant/Research Support, AKERO: Grant/Research Support, Altimmune: Grant/Research Support, IPSEN: Grant/Research Support, Madrigal: Grant/Research Support.

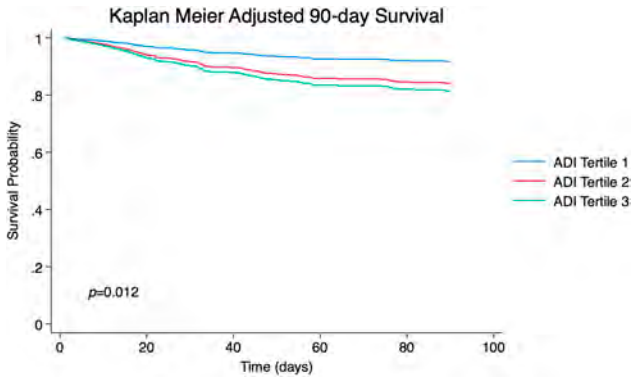
3118 | HIGH AREA DEPRIVATION INDEX IS ASSOCIATED WITH INCREASED NINETY-DAY MORTALITY IN ALCOHOL-ASSOCIATED HEPATITIS: A RETROSPECTIVE COHORT STUDY

Lindsey Immers[1] James Vu[1] Robert Pecha[1] Jordan Holliday[1] Vikrant Rachakonda[1], [1]University of California Davis Medical Center

Background: Alcohol associated hepatitis (AH) is a severe form of alcohol-related liver disease (ALD) associated with disparate outcomes based on socioeconomic factors. The Area Deprivation Index (ADI) is a validated composite measure of neighborhood-level socioeconomic disadvantage. This study evaluated the association between ADI and clinical outcomes in patients hospitalized with alcohol associated hepatitis. **Methods:** This was a single-center retrospective cohort study of 572 patients admitted with AH (October 2017–July 2024), defined by NIAAA criteria. National ADI scores were obtained using the University of Wisconsin Neighborhood Atlas based on patient addresses and divided into tertiles (low [1, N = 218], intermediate [2, N = 166] and high [3, N = 188] risk), with tertile 3 being the most disadvantaged population; unhoused patients (N = 29) were assigned national ADI score of 99 and placed in the third tertile. Baseline demographic, clinical, and socioeconomic characteristics were compared across ADI tertiles. The primary outcome was 90-day survival, and secondary analyses examined predictors of survival. **Results:** While there were no differences in age between ADI tertiles, fewer female (34.0% vs. 46.3% in low-risk, $p = 0.038$), white (40.4% vs. 59.6%, $p < 0.001$), and non-English speaking (87.2% vs. 98.6%, $p < 0.001$) patients were observed in tertile 3. There were no significant differences across ADI tertiles in MELD 3.0, ascites, gastrointestinal bleeding (GIB), acute kidney injury, or hepatic encephalopathy. Patients in tertile 3 had higher rates of Medicaid insurance (75.5% vs. 45.9%, $p < 0.001$) and lower rates of private insurance (6.9% vs. 21.1%, $p < 0.001$). Alcohol use disorder (AUD) medications were less frequently prescribed to tertile 3 (16.0% vs. 26.6%, $p = 0.004$), with no differences in substance use navigator utilization. Kaplan Meier analysis demonstrated significantly lower 90-day mean survival in tertile 3 compared to tertiles 1 and 2 [tertile 3: 73 (95% CI 69 – 77) vs tertile 2: 76 (72 – 80) vs tertile 1: 81 (78 – 84) days, $p = 0.012$]. Multivariate Cox proportional hazards models showed that ADI tertiles 2 [aHR 2.007 (95% CI 1.204 – 3.346), $p = 0.008$] and 3 [aHR 2.371 (95% CI 1.465 – 2.837), $p < 0.001$] were associated with increased 90-day mortality independent of MELD 3.0, ascites, GIB, age, and ICU admission. **Conclusion:** This study demonstrated that higher neighborhood-level socioeconomic disadvantage, as measured by ADI, is independently associated with lower 90-day survival in patients hospitalized with AH. As a freely available and easily ascertained metric, ADI may serve as a practical tool to identify high-risk populations and complement existing prognostic models. Future prospective studies should evaluate whether ADI-guided early interventions targeting modifiable social determinants can improve outcomes in this vulnerable population.

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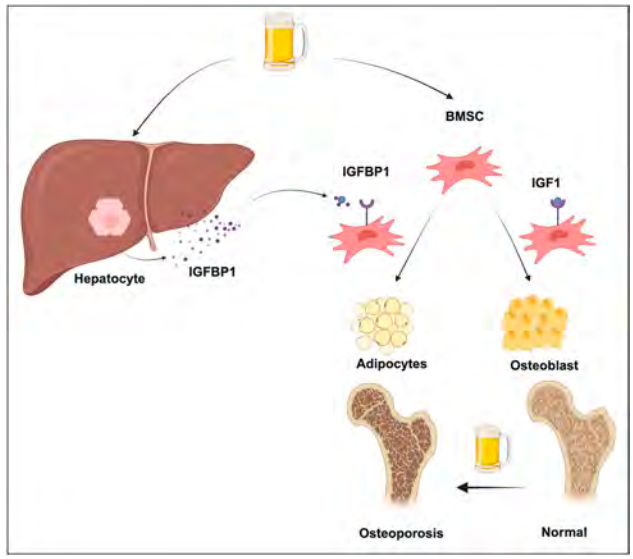


Disclosures: Lindsey Immers:Nothing to Disclose, James Vu:Nothing to Disclose, Robert Pecha:Nothing to Disclose, Jordan Holliday:Nothing to Disclose, Vikrant Rachakonda:Nothing to Disclose.

3119 | LIVER-DERIVED IGFBP1 DRIVES ALCOHOL-ASSOCIATED OSTEOPENIA BY INHIBITING OSTEOBLAST DIFFERENTIATION

Guangyu Liu[1], [1]National Institutes of Healthy

Background: Alcohol-associated bone loss is traditionally attributed to the direct toxic effects of ethanol on bone. However, whether liver-derived endocrine signaling contributes to alcohol-induced osteopenia remains largely unknown. In this study, we investigated the liver-bone crosstalk in alcohol-associated bone loss and explored the contribution of acetaldehyde to this process. **Methods:** We used a chronic-plus-binge ethanol feeding model in mice to assess the effects of alcohol exposure on bone mass and osteoblast function, and combined micro-CT, histology, serum analysis, transcriptomics, in vitro osteoblast assays, and trans-genetic mice model to identify and validate liver-derived mediators of bone injury. **Results:** Alcohol induced significant osteopenia in wild-type mice, as demonstrated by reduced bone mineral density and decreased newly formed trabecular bone. This phenotype was associated with impaired osteoblast differentiation. To determine whether ethanol or acetaldehyde aggravate skeletal injury, we utilized ALDH2 knock-in (KI) mice which have slower ALDH2 enzyme activity and therefore accumulate more acetaldehyde. Compared with wild-type controls, ALDH2 KI mice developed more severe bone loss. Transcriptomic analysis of liver tissue from ethanol-fed wild-type and ALDH2 KI mice identified insulin-like growth factor binding protein 1 (IGFBP1) as a prominently upregulated liver-derived factor. Consistently, circulating IGFBP1 levels increased after ethanol exposure, with a greater increase in ALDH2 KI mice. Functional studies demonstrated that recombinant IGFBP1 directly suppressed osteoblast differentiation in vitro. Importantly, deletion of IGFBP1 significantly attenuated alcohol-induced bone loss, including in the ALDH2 KI background, establishing a causal role for IGFBP1 in mediating skeletal deterioration. **Conclusion:** Alcohol-associated osteopenia is driven not only by the direct toxic effects of alcohol, but also by a liver-derived endocrine mechanism. Alcohol, particularly in the setting of impaired acetaldehyde metabolism, induces hepatic IGFBP1, which acts through a liver-bone endocrine axis to suppress osteoblast differentiation and promote bone loss. These findings identify IGFBP1 as a key mediator of alcohol-induced liver-bone crosstalk and suggest that targeting IGFBP1 may represent a promising therapeutic strategy for preventing skeletal complications associated with alcohol exposure.



Disclosures: Guangyu Liu:Nothing to Disclose.

3120 | CLINICAL IMPACT OF ACUTE KIDNEY INJURY IN ALCOHOL-ASSOCIATED HEPATITIS: A SYSTEMIC REVIEW AND META-ANALYSIS

Frhaan Zahrawi[1] Mohamed Alharami[2] Omar Alwan[3] Fawzy Naga[4] Khaled Zahrawi[5] Omar Khattab[6] Sarpong Boateng[7] Farooq Khan[1] Basile Njei[8] Wajahat Mehal[8] Bubu Banini[8], [1]Prime health Olympia Fields, [2]Henry Ford Warren, [3]Hamilton Medical Center, [4]Alexandria

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University, [5]South Texas Health System, [6]University Of California, Riverside, [7]Yale New Haven Health, Bridgeport Hospital, [8]Yale University

Background: Acute kidney injury (AKI) is one of the most common and devastating extrahepatic complications of acute **:** alcohol associated hepatitis (AH), a potentially severe subtype of alcohol associated liver disease. We aimed to quantify the pooled impact of AKI on 28-day and 90-day all-cause mortality, severity risks and clinical markers in patients with AH. **Methods:** A systemic search utilizing PubMed, Embase, Web of Science, and Scopus database were used to search for articles. Data from five studies (n = 2306) were pooled. The primary outcomes were mortality at 28 days and 90 days. Secondary outcomes included hepatic encephalopathy, Systemic Inflammatory Response Syndrome (SIRS), infection, and upper GI bleed. Additional analysis assessed laboratory data including total bilirubin, creatinine, albumin, INR, Maddrey's discriminant function (MDF), and ABIC score and study demographic (Age, Sex). Mean difference (MD) was calculated for continuous variables for individuals with versus without AKI. OR and MD were calculated using common-effect and random-effect models. We reported the random-effect model analysis. Heterogeneity was assessed using Cochran's Q, I^2, and τ^2 statistics. A leave one out meta-analysis was conducted to assess the influence of each individual study on the pooled estimate and to explore potential contribution to heterogeneity. **Results:** Five studies with 2306 total population were included in the analysis. Serum creatinine was significantly higher in the AKI vs non-AKI group (MD of 0.51, $p < 0.0001$; $I^2 = 2.3\%$). AKI was significantly associated with increased short-term mortality at day 28 (OR 2.37, $p < 0.0001$; $I^2 = 1\%$) and day 90 (OR = 2.39, $p < 0.0001$; $I^2 = 62.7\%$). AKI was also significantly associated with higher rate of hepatic encephalopathy (OR = 2.78, $p < 0.0001$; $I^2 = 80\%$), SIRS (OR = 2.39, $p < 0.004$; $I^2 = 62.7\%$), and infection (OR = 1.81, $p < 0.0001$; $I^2 = 61\%$); no significant association was observed with upper GI bleeding (OR = 1.02, $p = 0.8$; $I^2 = 27.8\%$). Patients with AKI demonstrated significantly higher levels of total bilirubin (MD = 6.80, $p < 0.0001$; $I^2 = 13.2\%$), MDF score (MD = 16.67, $p < 0.0001$; $I^2 = 51\%$), MELD score (MD = 5.85; $I^2 = 94.4\%$), and INR (MD = 0.24, $p < 0.0001$; $I^2 = 18\%$). **Conclusion:** AKI is associated with significantly increased 28- and 90-day mortality in patients with AH. AKI is also associated with higher rates of hepatic encephalopathy, SIRS, infection, higher INR, total bilirubin, and MDF. Our findings highlight the critical prognostic impact of AKI and emphasize the need for early detection and targeted management strategies to improve patient outcomes.

Disclosures: Frhaan Zahrawi:Nothing to Disclose, Mohamed Alharami:Nothing to Disclose, Omar Alwan: Nothing to Disclose, Fawzy Naga:Nothing to Disclose, Khaled Zahrawi:Nothing to Disclose, Omar Khattab: Nothing to Disclose, Sarpong Boateng:Nothing to Disclose, Farooq Khan:Nothing to Disclose, Basile Njei:Nothing to Disclose, Wajahat Mehal:Nothing to Disclose, Bubu Banini:Nothing to Disclose.

3121 | MULTIDISCIPLINARY HEPATOLOGY AND ADDICTION PSYCHIATRY CARE FOR ALCOHOL-ASSOCIATED LIVER DISEASE (ALD) AND ALCOHOL USE DISORDER (AUD): A DESCRIPTIVE ANALYSIS

Danielle Morelli[1] Stephanie Rutledge[1] Gilbert Vasquez[1] Mashal Khan[1] Danielle Brandman[2] Rebecca Roediger[2], [1]Weill Cornell Medical Center-New York Presbyterian, [2]Weill Cornell Medicine

Background: ALD affects 3.5% of the general population and 55% among those with AUD. AUD is increasing in young adults, women, racial/ethnic minorities, yet longitudinal care engagement for ALD-AUD remains low. Nationally, behavioral therapy engagement is 10% and medication for alcohol use disorder (MAUD) use is < 1.5%. Meta-analysis data show integration of hepatology and addiction care improves outcomes. Barriers include resource limitations, care sustainability, lack of provider awareness, and engagement. We describe the successful implementation of the Center for Alcohol & Liver Medicine (CALM), an integrated hepatology and addiction psychiatry clinic that delivers patient-centered care, tailored to disease stage and motivational readiness in a diverse urban environment. **Methods:** CALM operates one half-day weekly, enrolling patients across the spectrum of ALD-AUD. The care team includes a Hepatologist, Addiction Psychiatrist, and Credentialed Alcoholism and Substance Abuse Counselor. Care is grounded in motivational interviewing and patient-driven goals, with same-day individualized care plans for liver disease management, MAUD use, mental health treatment, and linkage to alcohol treatment programs. **Results:** Intake engagement rate after referral was 78% (n = 80/102). Intake cohort demographics: average age 52 (SD 12.2); 37% female, 63% male; 52% publicly insured. A large proportion had cirrhosis: n = 45/80, of which 35% were decompensated. MAUD use in CALM was 69% (n = 55/80). Mean intake PETH was 492 (SD 527.8). Intake PETH was significantly higher among patients who initiated MAUD vs those who did not (median 455 vs 13.5 ng/mL, U = 754.0, $p = 0.004$). Intake PETH level ≥ 200

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is strongly associated with abstinence outcome at follow up: Fisher Exact, OR = 0.07, $p < 0.001$. Clinic follow-up rate (defined as at least one follow-up visit) was 71%, with a lower rate in the compensated cirrhosis subgroup of 53%. Referral rates to alcohol treatment programs were high at 79% (n = 63/80) with a 60% (n = 38/63) engagement rate. No statistically significant associations were identified between patient sex, age, ALD severity, insurance type for follow-up rate, MAUD use, or enrolling in treatment programs (all $p > 0.05$). **Conclusion:** We have demonstrated that patients with ALD had high levels of engagement in an integrated clinic, with similar rates of engagement across liver disease severity and insurance types, including 52% of the cohort with public insurance suggesting equitable program reach. The observed follow-up rate and MAUD use were similar regardless of sex, age, liver disease severity, and insurance type, suggesting that CALM's care model may reduce barriers to engagement that typically disadvantage higher-risk or publicly insured patients. Future research will focus on the impact of CALM on liver-, AUD- and patient-related outcomes, with attention on program methodology to optimize outcomes.



Disclosures: Danielle Morelli:Nothing to Disclose, Stephanie Rutledge:Nothing to Disclose, Gilbert Vasquez: Nothing to Disclose, Mashal Khan:Nothing to Disclose, Danielle Brandman:Novo Nordisk: Consultant, Madrigal: Consultant, Rebecca Roediger:Nothing to Disclose.

3122 | ALCOHOL EXPOSURE IMPAIRS KUPFFER CELL–MEDIATED ANTIBACTERIAL DEFENSE THROUGH ZONAL REMODELING RATHER THAN SUPPRESSION OF ANTIMICROBIAL GENE PROGRAM

Tiantian Yao[1]; [1]Peking University First Hospital

Background: Alcohol use is a major risk factor for severe bacterial infections in humans, yet the cellular and molecular mechanisms underlying alcohol-induced susceptibility remain incompletely understood. Hepatocytes, neutrophils and Kupffer cells (KC) play essential roles in hepatic antibacterial defense, but how alcohol reshapes these responses during infection remains unclear. **Methods:** We established a mouse model of alcohol acceleration of bacterial infection by using alcohol-plus-binge and *K. pneumoniae* (*K. P.*) infection. We performed survival studies, bacterial burden analysis, histology, immunostaining, bulk and single-cell RNA sequencing, acetaldehyde-accumulation experiments (Aldh2*1/*2 KI), and zonal quantification of KC distribution. Neutrophil-specific antimicrobial pathways were interrogated using *Ncf1*–KO, *Mrp8*–KO, *Cxcl1*–KO, and IL-8 transgenic mice. **Results:** Alcohol exposure markedly reduced survival following *K. P.* infection, despite comparable bacterial loads and hepatic injury markers between pair-fed and ethanol-fed mice. Single cell RNA-seq demonstrated that a large number of hepatocyte-derived acute phase protein (APP) genes were upregulated during infection; however, chronic-plus-binge ethanol did not affect hepatic expression of these APP genes. Alcohol exposure did not alter the induction of neutrophil-associated antimicrobial genes, nor did it affect hepatic neutrophil recruitment. Functionally, *Ncf1* deficiency impaired survival in control-fed mice but not in ethanol-fed mice, whereas *Mrp8*–KO, *Cxcl1*–KO, and IL-8 transgenic mice showed no differences from WT controls under either dietary condition, indicating that alcohol overrides individual neutrophil effector pathways. Alcohol exposure remodels Kupffer cell morphology and impairs phagocytic function. Alcohol feeding also profoundly disrupted the zonal organization of hepatic KC, reflected by a marked loss of zone 1 KC and an aberrant accumulation of KC in zone 3. *Aldh2*1/2 KI* mice showed survival rates comparable to *WT* mice, indicating that acetaldehyde accumulation is not the primary driver of alcohol-induced mortality. **Conclusion:** Alcohol exposure increases susceptibility to bacterial infection not by suppressing APP expression or neutrophil antimicrobial gene programs, but by inducing zone-specific remodeling and altering the morphology of KC. These findings identify a previously unrecognized mechanism by which alcohol disrupts

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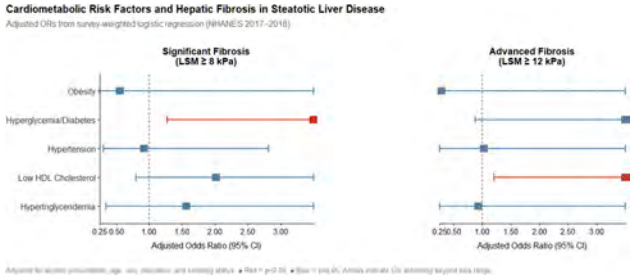
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hepatic innate immune architecture, resulting in compromised antibacterial defense.
Disclosures: TIANTIAN Yao:Nothing to Disclose.

3123 | CARDIOMETABOLIC RISK FACTOR SPECIFICITY AND ALCOHOL INTERACTION IN LIVER FIBROSIS ACROSS SLD SUBTYPES: A POPULATION-BASED ANALYSIS

Rylyn Reyes[1] Hyundam Gu[2] Samuel Rhoads[3] Juan Pablo Arab[4], [1]Virginia Commonwealth University, [2]VCU Stravitz-Sanyal Institute for Liver Disease and Metabolic Health, [3]Stravitz Sanyal Institute for Liver Disease and Metabolic Health, [4]Stravitz-Sanyal Institute for Liver Disease and Metabolic Health

Background: SLD has emerged as a leading cause of chronic liver disease globally, with liver fibrosis representing a critical determinant of liver-related morbidity and mortality. However, prior studies have focused predominantly on aggregate cardiometabolic risk factor count rather than the independent effect of the contribution of individual risk factors, and have largely been restricted to MASLD populations. This study examined the associations between individual cardiometabolic risk factors and alcohol consumption with significant and advanced liver fibrosis in MASLD and MetALD/ALD populations. **Methods:** This cross-sectional study used 2017-2018 NHANES data. Significant and advanced fibrosis were defined as LSM $\geq$ 8 kPa and LSM $\geq$ 12 kPa, respectively, measured by VCTE; hepatic steatosis was defined as a CAP $\geq$280 dB/m. Alcohol consumption was expressed in grams of ethanol per week (14g per standard drink) and modeled continuously and categorically using sex-specific thresholds. Multivariable logistic regression evaluated associations between individual cardiometabolic risk factors and liver fibrosis outcomes, adjusting for covariates. All analyses accounted for NHANES complex survey design. **Results:** A total of 1,955 adults with SLD were included: 1,864 (95.3%) with MASLD and 91 (4.65%) with MetALD/ALD across very low, low, moderate, and increased alcohol consumption groups. Significant fibrosis prevalence was 20.9% in MASLD and 16.5% in MetALD/ALD; advanced fibrosis prevalence was 11.7% in MASLD and 9.89% in MetALD/ALD, respectively. In adjusted models, elevated fasting glucose was independently associated with significant fibrosis (aOR: 5.52, 95% CI: 1.28-23.9, p = 0.030). Dyslipidemia was independently associated with advanced fibrosis (aOR: 3.94, 95% CI: 1.20-12.9, p = 0.031), as well as in unadjusted models (OR: 4.01, 95% CI: 1.98-8.10, p < 0.001). A significant interaction was identified between obesity and alcohol consumption of significant fibrosis (OR: 0.86 95% CI: 0.84-0.88, p < 0.001), suggesting the association between obesity and significant fibrosis attenuates with increasing alcohol consumption. **Conclusion:** Among U.S. adults with SLD, elevated fasting glucose and dyslipidemia emerged as the primary cardiometabolic drivers of significant and advanced fibrosis, respectively, independent of alcohol consumption level. However, a significant interaction between obesity and alcohol consumption for significant fibrosis indicates that increasing alcohol consumption may attenuate the effect of obesity on fibrosis risk, warranting further investigation into the relationship between metabolic and alcohol-related pathways across the SLD spectrum in larger data or prospective study.



Disclosures: Rylyn Reyes:Nothing to Disclose, Hyundam Gu:Nothing to Disclose, Samuel Rhoads:Nothing to Disclose, Juan Pablo Arab:Nothing to Disclose.

3124 | DIFFERENTIAL RISK OF ADVANCED LIVER DISEASE FOLLOWING ALCOHOL-ASSOCIATED PANCREATITIS VS ALCOHOL WITHDRAWAL SYNDROME

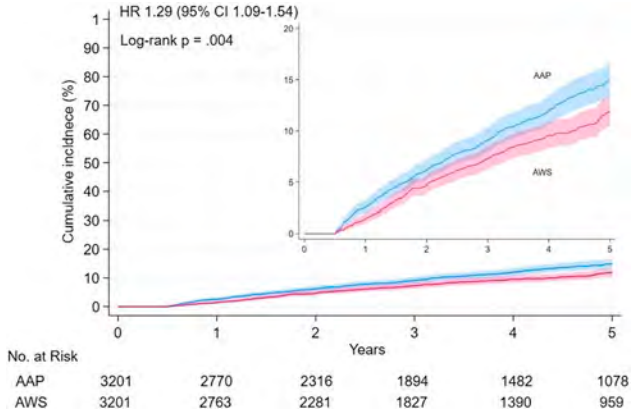
Butros Fakhoury[1] Leandro Sierra[2] Krishan Patel[1] Hyundam Gu[1] Luis Díaz[3] Juan Pablo Arab[1], [1]Virginia Commonwealth University, [2]Cleveland Clinic Foundation, [3]Pontificia Universidad Católica de Chile

Background: Unhealthy alcohol use is a leading cause of preventable mortality, with alcohol-associated liver disease (ALD) frequently presenting late as decompensated cirrhosis. Extrahepatic presentations requiring acute care, such as alcohol-associated pancreatitis (AAP) and alcohol withdrawal syndrome (AWS), indicate significant alcohol exposure but reflect fundamentally different pathophysiologic processes. We hypothesized that AAP, representing direct alcohol-mediated tissue toxicity, differentially predicts progression to advanced chronic liver disease (ACLD) compared to AWS, identifying a high-risk phenotype for targeted intervention. **Methods:** This retrospective cohort study utilized the federated TriNetX US Collaborative Network. We identified adults with a first diagnosis of AAP or AWS (2016-2023) without pre-existing liver disease.

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To ensure clinical severity, AWS cases required benzodiazepines or phenobarbital within 2 days of index. To isolate incident disease, patients with baseline or 6-month post-index diagnoses of any liver disease, fibrosis, or decompensation were excluded. Analysis was restricted to complete cases with available baseline laboratories within 6 months of index. Propensity score matching (1:1) balanced cohorts across demographics, metabolic comorbidities, social determinants of health, and baseline laboratories. The primary outcome was incident ACLD (composite of hepatic fibrosis, cirrhosis, or decompensation). Secondary outcomes included all-cause mortality and prescriptions for medications for alcohol use disorder (MAUD). **Results:** After matching, 3,201 patients per cohort were analyzed (median age 50-51 years). Over a median follow-up of 3.5-3.7 years, patients with AAP demonstrated a significantly higher cumulative incidence of ACLD compared to AWS (9.3% vs 7.0%; HR 1.29; 95% CI 1.09-1.54; $p = 0.004$). This was primarily driven by a higher rate of hepatic decompensation in the AAP cohort (7.0% vs 4.6%; HR 1.50; 95% CI 1.22-1.85; $p < 0.001$). Conversely, patients with AWS experienced higher all-cause mortality (12.7% vs 9.5%; HR 0.72; $p < 0.001$) and were nearly twice as likely to receive MAUD prescriptions during follow-up (15.1% vs 7.7%; HR 0.47; 95% CI 0.40-0.54; $p < 0.001$). Sensitivity analyses restricting AWS to severe phenobarbital-treated cases (HR 1.45; $p = 0.002$) and negative control exposure (appendicitis) and control outcome (osteoarthritis) confirmed the specificity of these findings. **Conclusion:** Among heavy drinkers without pre-existing liver disease, AAP is associated with a 29% higher risk of developing ACLD compared to AWS, yet these patients receive significantly less pharmacological addiction treatment. AAP represents a critical sentinel event and a distinct hepatotoxic phenotype that warrants prioritized systematic liver surveillance and aggressive linkage to AUD care to prevent decompensated ALD.



Disclosures: Butros Fakhoury:Nothing to Disclose, Leandro Sierra:Nothing to Disclose, Krishan Patel: Nothing to Disclose, Hyundam Gu:Nothing to Disclose, Luis Díaz:Nothing to Disclose, Juan Pablo Arab: Nothing to Disclose.

3125 | GLP-1 RECEPTOR AGONISTS MAY REDUCE RISK OF ALCOHOL-ASSOCIATED HEPATITIS

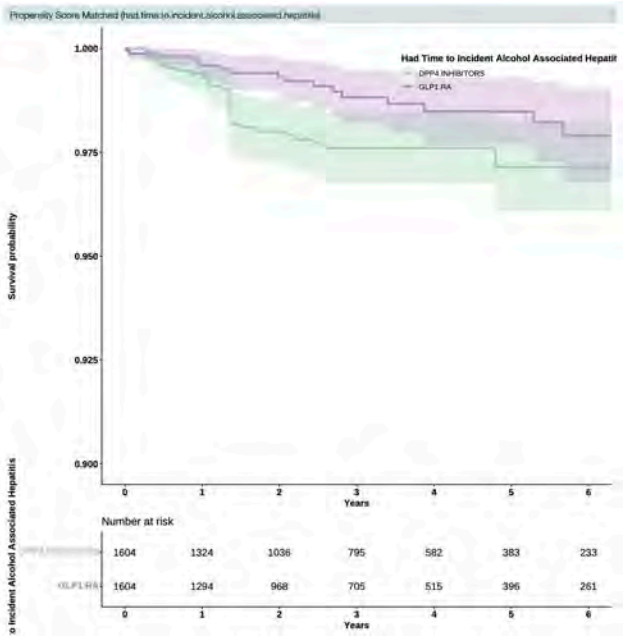
Judah Kupferman[1] Aparna Goel[1] Amir Hossein Gougol[1] Sajid Jalil[1] Allison Kwong[1] Ashwani Singal[2] Natalie Torok[1] Saurabh Gombar[3] Paul Kwo[1], [1]Stanford University Medical Center, [2]University of Louisville, [3]Atropos Health

Background: Glucagon-like peptide-1 receptor agonists (GLP-1 RA) and dipeptidyl peptidase-4 inhibitors (DPP-4i) are established treatments for glycemic control for patients with type 2 diabetes mellitus (T2DM). GLP-1 RAs also demonstrate effectiveness in reducing alcohol craving and consumption among people with alcohol use disorder (AUD). Whether GLP-1 RAs can reduce the risk of complications from AUD, such as alcohol-associated hepatitis (AH), remains uncertain. We aimed to assess the effect of GLP-1 RA in patients with T2DM and AUD. **Methods:** Using data from the Apollo Atropos Evidence Network, we performed a retrospective cohort study to evaluate whether GLP-1 RA therapy is associated with reduced incidence of AH in adults with T2DM and AUD. Subjects were 18 years or older with both T2DM and AUD and newly treated with either GLP-1 RAs (lixisenatide, albiglutide, dulaglutide, semaglutide, tirzepatide, liraglutide, exenatide) (exposure) or DPP-4i (linagliptin, alogliptin, sitagliptin, vildagliptin, saxagliptin) (controls) from 2015 to 2025. T2DM and AUD were defined by ICD-9/10 codes within 1 year prior to medication initiation. AH was defined by ICD-9/10 codes or laboratory-confirmed criteria. Patients with cirrhosis or chronic liver disease, hepatocellular carcinoma, liver transplant, prior AH, or those undergoing treatment for AUD were excluded. Continuous medication use for at least 90 days was required for inclusion. Propensity score matching was performed to balance baseline characteristics. **Results:** 5147 GLP-1 RA users and 2173 DPP-4i users (30.6% vs 22.5% female) were compared. Ages ranged from 18 to 89 years (mean 57.5 +/- 11.9 y vs 60.1 +/- 12.0 y). GLP-1 RA users had greater rates of emergency room visits (20.7% vs 10.3%), obesity (76.1% vs 52.1%), mean BMI (35.9 vs 31.7), and outpatient visits (42.4% vs 19.1%), compared to the DPP-4i group. After propensity score matching, GLP-1 RA exposure was associated with reduced incidence of AH (HR 0.55, 95% CI 0.30-0.99; $p = 0.046$) (Figure 1). **Conclusion:** In patients with T2DM and AUD, GLP-1 RA use was associated with reduced risk of AH compared to DPP-4i use. These real-world data

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suggest the potential benefit of repurposing GLP-1RA in patients with T2DM to control AUD and subsequent complications and warrant further investigation.



Disclosures: Judah Kupferman:Nothing to Disclose, Aparna Goel:Gilead Sciences: Grant/Research Support, Kezar Life Sciences: Consultant, Ipsen Pharmaceuticals: Advisor, Mirum Pharmaceuticals: Advisor, Amgen: Consultant, RegCell: Consultant, DrenBio: Consultant, Amir Hossein Gougol:Nothing to Disclose, Sajid Jalil:Nothing to Disclose, Allison Kwong:Nothing to Disclose, Ashwani Singal:Madrigal: Speaking and Teaching, Pleiogenix: Stock – privately held company, Pleiogenix: Consultant, CLD Foundation: Advisor, Medical Speaker's Network: Speaking and Teaching, Up-to-Date: Royalties or patent beneficiary, Medscape: Speaking and Teaching, University of Louisville School of Medicine: Employee, NIAAA: Grant/Research Support, Gastro Endo News: Executive role, Durect: Advisor, University of Louisville Health: Other, Natalie Torok:Nothing to Disclose, Saurabh Gombar:Nothing to Disclose, Paul Kwo:Arbutus: Advisor, Aligos: Advisor, Ausper Bio: Grant/Research Support, Altimmune: Grant/Research Support, Amgen: Advisor, Eiger: Consultant, Eiger: Grant/Research Support, Inventiva: Consultant, Novo Nordisk: Consultant, Novo Nordisk: Grant/Research Support, Takeda: Grant/Research Support, Madrigal: Grant/Research Support, Gilead: Consultant, Gilead: Grant/Research Support, Salix: Advisor, Ultragenyx: Grant/Research Support, Hepquant: Consultant, Target Registries: Grant/Research Support, Abbvie: Consultant, Mallinckrodt: Advisor, Takeda: Grant/Research Support, Genentech: Consultant, Glaxo Smith Kline: Consultant, Akero: Grant/Research Support, 89Bio: Grant/Research Support, Vir Bio: Grant/Research Support, Precision BioSciences: Consultant, Tune Therapeutics: Consultant, Mirum: Consultant, Target Registries: Advisor, Takeda: Advisor, Lygenesis: Advisor, Ausper Bio: Advisor.

3126 | ALCOHOL CESSATION AFTER DEVELOPMENT OF ALD INDUCES RAPID EMERGENCE OF NEW MONOCYTE DERIVED KUPFFER CELLS WITHIN HEPATIC CROWN-LIKE STRUCTURES

Isabel Aranzazu Pulido Ruiz[1] Kyle Yuquimpo[2] Sheetalnath Rooge[2] Ayobami Dare[1] Irina Tikhanovich[2] Steven Weinman[2], [1]The University of Kansas Medical Center, [2]University of Kansas Medical Center

Background: Resolution of alcohol-associated liver disease (ALD) is often slow and incomplete, even after alcohol cessation. Hepatic macrophages are central regulators of ALD recovery through their roles in lipid handling and tissue remodeling. However, the mechanisms and spatial niches that support effective resolution remain poorly understood. Preliminary data suggest that alcohol cessation promotes the emergence of specific macrophage populations with defined spatial organization, which may promote disease recovery. We investigated the identity and spatial localization of macrophage populations emerging during ALD resolution. **Methods:** C57BL/6J and Cx3cr1-Cre×ROSA-CAG-LSL-TdTomato mice were fed a high-fat Western diet with ad libitum 10–20% alcohol in drinking water (WDA) for 16 weeks, then transitioned to chow and water for 3, 7 or 28 days. Liver tissue was analyzed by immunofluorescence (IF), flow cytometry, and qPCR. Cx3cr1 lineage TdTomato positive cells (TdT+) identified infiltrating monocyte derived macrophages (moMac) at the time of stopping WDA. **Results:** Cessation of high fat and alcohol consumption resulted in a progressive loss of liver fat and inflammation over the course of 28 days. Alcohol cessation induced a loss of Kupffer cell (KC) gene expression and an increase in moMac gene expression within 3 days of stopping WDA. By 7 days, KC gene expression was restored. Crown-like structures (CLS) were present in the liver, and these consisted largely of macrophages expressing both KC and lipid associated macrophages (LAM) markers. We performed lineage tracing using a tamoxifen pulse to label monocytes and moMac with TdT. In mice that remained on the WDA diet, there was minimal TdT incorporation into KCs by 7 days. In mice that stopped alcohol after the tamoxifen pulse, both flow cytometry and IF showed that TdT abundantly labeled a subset of VSIG4+ KCs that were found exclusively in CLS. Ki67 staining demonstrated that these newly formed TdT labeled KCs were proliferating

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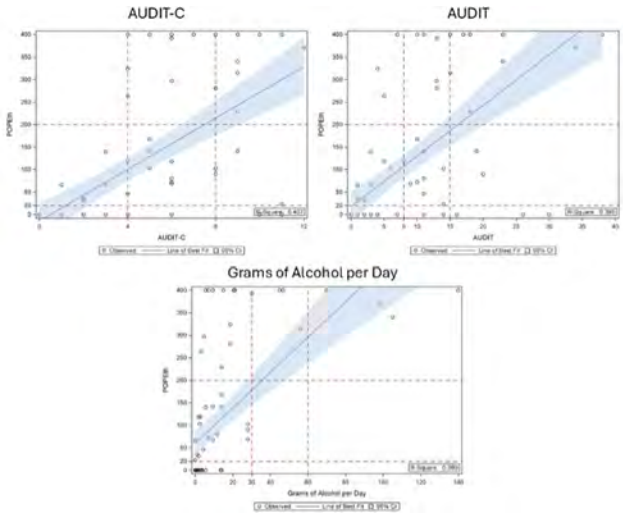
within the CLS. By 28 days after WDA stopped, CLS became more abundant but were primarily composed of LAMs expressing GPNMB and CD11c. The TdT+ VSIG4+ newly formed KCs were no longer restricted to CLS and were observed in the sinusoids throughout the liver parenchyma. **Conclusion:** These findings demonstrate that sudden cessation of high fat diet and alcohol induces a rapid change in hepatic macrophage populations. Existing KCs are lost, and new monocyte-derived KCs rapidly form and proliferate. Early during disease resolution, the CLS are the sites of new KC formation. These cells eventually distribute throughout the liver parenchyma. We speculate that the unique lipid rich environment of the CLS supplies the extrinsic signals necessary to imprint developing KC with the phenotype necessary to optimally dispose of excess lipid and promote disease resolution.

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3127 | AUDIT-C OUTPERFORMS SELF-REPORTED ALCOHOL CONSUMPTION FOR STEATOTIC LIVER DISEASE CLASSIFICATION: VALIDATION AGAINST PHOSPHATIDYL ETHANOLAMINE (PETH)

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Background: Steatotic liver disease (SLD), including metabolic-associated steatotic liver disease (MASLD), metabolic and alcohol-related liver disease (MetALD), and alcohol-related liver disease (ALD), is classified based on self-reported alcohol use, which is susceptible to recall bias, potentially leading to misclassification. Phosphatidylethanol (PEth), while objective, is limited by costs (> $100/test) while AUDIT and AUDIT-C are validated, structured inexpensive screening tools. We examined whether AUDIT and AUDIT-C more accurately classify SLD compared to self-reported alcohol use, using PEth as the objective reference. **Methods:** This prospective study recruited consecutive U. S Veterans whose self-reported alcohol consumption corresponded to a diagnosis of MASLD, MetALD, or ALD. All participants provided IRB approved written informed consent, completed a questionnaire capturing self-reported grams of alcohol per day, AUDIT, and AUDIT-C, and underwent PEth measurement during a single visit. PEth was categorized as low (< 20), intermediate (20–200), or high (> 200 ng/mL), while AUDIT-C cut-offs were Male (M) < 4/Female (F) < 3 (MASLD), M4–8/F3–6 (MetALD), and M > 8/F > 6 (ALD) as previously validated. AUDIT cut-offs defined low (0–7), moderate (8–15), and heavy (> 15) use. Alcohol use thresholds followed the Delphi consensus (M < 30/F < 20, M30–60/F20–50, M > 60/F > 50). Agreement with PEth was assessed via weighted kappa and classification accuracy; continuous associations were evaluated using R^2 from linear regression. **Results:** Of 93 recruited participants, 87 were retained after excluding those with a failed PEth assay due to drug interference. AUDIT-C demonstrated moderate agreement with PEth ($\kappa = 0.58$, 95% CI 0.44–0.71) with 69.0% classification accuracy. AUDIT performed similarly ($\kappa = 0.56$, 95% CI 0.41–0.71; 71.3% accuracy). Among AUDIT-C discordant cases, 16 participants under-reported and 11 over-reported; notably, no participant with a high PEth category had a low AUDIT-C. Self-reported alcohol use showed weak agreement ($\kappa = 0.25$, 95% CI 0.10–0.40) and lower (60.5%) accuracy, with all discordant cases reflecting under-reporting. In continuous analyses, AUDIT-C modestly outperformed AUDIT and self-reported alcohol use in predicting PEth ($R^2 = 0.41$ vs. 0.40 vs. 0.39). **Conclusion:** AUDIT and AUDIT-C outperformed self-reported alcohol consumption in classifying SLD etiology against the objective standard of PEth. Self-reported alcohol use consistently underestimated consumption, likely reflecting recall and social desirability bias, while AUDIT and AUDIT-C demonstrated more balanced over- and under-reporting. These findings support adopting AUDIT-C to categorize SLD with cut-offs of < 4/ < 3 for MASLD, 4–8/3–6 for MetALD, > 8/ > 6 for ALD in males and females respectively, given the superior accuracy over self-reported alcohol use, ease of administration, and cost-effectiveness relative to PEth



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3128 | PROGNOSTICATION OF OUTCOMES IN ALCOHOL-RELATED LIVER DISEASE (ALD) USING ELECSYS® PRO-C3, A NON-INVASIVE TEST MEASURED ON A FULLY AUTOMATED IN VITRO DIAGNOSTIC ANALYZER

Andressa de Zawadzki[1] Maja Thiele[2] Stine Johansen[3] Ida Villesen[3] Peter Andersen[3] Morten Karsdal[1] Aleksander Krag[4] Diana Leeming[5], [1]Nordic Bioscience, [2]Evido.health, [3]Odense University Hospital, [4]University of Southern Denmark, [5]Nordic Bioscience A/S

Background: Diagnosis of alcohol-related liver disease (ALD) is often made when liver fibrosis becomes irreversible. Therefore, prognostication in patients using high-throughput non-invasive tests (NITs) has become increasingly important. The prognostic performance of PRO-C3 using ELISA technology has been widely demonstrated in chronic liver diseases. The current study aimed to investigate the prognostic utility of Roche Elecsys® PRO-C3 for ALD risk stratification. **Methods:** Elecsys® PRO-C3 (N-terminal pro-peptide of type III collagen) was measured on the fully automated CE marked Roche COBAS® e801 in vitro diagnostic (IVD) analyzer in serum of 450 biopsy-proven F0-F4 ALD patients from the GALAXY consortium derived "GALA-ALD" cross-sectional cohort having 5 years of follow-up. PRO-C3 was also measured in the same samples using a fully validated enzyme-linked immunosorbent assay (ELISA). Risks of hepatic decompensation were estimated using Fine–Gray competing-risk models, while Kaplan–Meier and Cox regression analyses were used for mortality. Patients were stratified into tertiles (T) or quartiles (Q) according to baseline PRO-C3 levels, and a cut-off value was defined based on the category with the highest hazard ratio (HR). Prognostic performance of Elecsys® PRO-C3 was compared to PRO-C3 ELISA Generation 2. **Results:** Elecsys® PRO-C3 demonstrated good prognostic utility to stratify ALD patients at risk of all-cause mortality (hazard ratio for mortality (HRM) of 3.75 [95% CI 2.53-5.54], $p < 0.001$) and decompensation (hazard ratio for decompensation (HRD) of 10.5 [95% CI 5.86-18.8], $p < 0.001$) using a cut-off of 63 ng/mL which was defined as the upper quartile (Q4) of Elecsys® PRO-C3 concentrations, showing similar prognostic performance in comparison to PRO-C3 ELISA (HRM of 5.10 [95% CI 2.60-10.0], $p < 0.001$; HRD of 13.2 [95% CI 4.79-36.2], $p < 0.001$ using a predefined cut-off of 12.6 ng/mL. **Conclusion:** Roche Elecsys® PRO-C3 within the ADAPT score has previously demonstrated diagnostic utility in steatotic liver diseases (SLD) and PRO-C3 as a single marker has been incorporated in clinical trials for evaluation of therapeutic efficacy on fibrogenesis. The present study suggests Roche Elecsys® PRO-C3 as an efficient NIT for risk stratification in ALD, offering patient prognostication in a high-throughput CE marker IVD platform intended for use in routine clinical laboratories in the future.

Disclosures: Andressa de Zawadzki:Nothing to Disclose, Maja Thiele: Nothing to Disclose, Stine Johansen:Nothing to Disclose, Ida Villesen:Nothing to Disclose, Peter Andersen:Nothing to Disclose, Morten Karsdal:Nothing to Disclose, Aleksander Krag:Nothing to Disclose, Diana Leeming:Nordic Bioscience: Employee.

★ 3129 | DNASE I PROTECTS AGAINST ALCOHOL-INDUCED INTESTINAL BARRIER FAILURE AND ENDOTOXEMIA

Scott Minchenberg[1] Marti Ortega-Ribera[1] Alejandro Hionides Gutierrez[1] Siddharth Ghosh Roy[1] Aditi Ashish Datta[1] Viliam Brezani[1] Bruna Santos[1] Prashanth Thevkar Nagesh[1] Gyongyi Szabo[1], [1]BIDMC - Harvard Medical School

Background: Alcohol binges inflict significant damage to the proximal small intestine (PSI), driving epithelial dysfunction, increased intestinal permeability, and systemic exposure to gut-derived microbial products, key events that drive alcohol-associated inflammation. In the context of alcohol associated liver disease (ALD), binge drinking disrupts the gut barrier and may contribute to infections from gut-derived pathogens. Despite the central role of early intestinal mucosal disruption in alcohol-related pathology, effective therapeutic strategies remain limited. Emerging evidence suggests that extracellular DNA released from alcohol-induced tissue injury amplifies inflammation after alcohol exposure. DNase I is an extracellular DNA–degrading enzyme with established clinical use in other disease states. We hypothesize that DNase I treatment mitigates PSI injury and prevents downstream endotoxemia due to alcohol binges. **Methods:** Eight to twelve week female C57BL/6J mice ($n = 4$-8 per group) received daily oral alcohol gavages (3.5 g/kg) for 3 days. DNase I (5 mg/kg) was administered I.P. 1 h before each binge. The intestines were collected 3 h after the final binge to evaluate for histologic injury, neutrophil recruitment, cytokine expression, and innate immune signaling. Serum was also collected for quantification of endotoxin. **Results:** Alcohol binges induce a PSI enteropathy with a 3-fold

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reduction in villous height:crypt depth ($p < 0.001$), a 100-fold increase in Ly6G$^+$ neutrophil infiltration ($p < 0.01$), and a 2.5-fold increase in citrullinated histone H3 ($p < 0.001$) consistent with neutrophil extracellular trap (NET) formation. These changes were accompanied by a 2-fold elevation in serum endotoxin levels ($p < 0.01$) 3 hours after the third binge. DNase I pre-treatment conferred mucosal protection with a 2-fold increase in villous height:crypt depth ($p < 0.05$) while reducing Ly6G$^+$ neutrophil infiltration by 3.5-fold ($p < 0.05$) and NET formation by 2-fold ($p < 0.01$) compared to vehicle-treated alcohol binged mice. DNase I pre-treatment also reduced serum endotoxin levels by 2-fold ($p < 0.05$), consistent with improved intestinal barrier integrity. **Conclusion:** DNase I pre-treatment confers robust protection against alcohol-induced PSI enteropathy and microbial translocation, reflected by decreased serum LPS and preserved villous height–crypt depth ratios. These findings propose DNase I as a novel therapeutic strategy to disrupt early gut-derived inflammatory pathways that contribute to alcohol-associated liver disease.

Disclosures: Scott Minchenberg:Nothing to Disclose, Marti Ortega-Ribera:Nothing to Disclose, Alejandro Hionides Gutierrez:Nothing to Disclose, Siddharth Ghosh Roy:Nothing to Disclose, Aditi Ashish Datta: Nothing to Disclose, Viliam Brezani:Nothing to Disclose, Bruna Santos:Nothing to Disclose, Prashanth Thevkar Nagesh:Nothing to Disclose, Gyongyi Szabo:CYTA Therapeutics: Consultant, Durect Corporation: Consultant, Pandion Therapeutics: Consultant, Pfizer: Consultant, Surrozen: Advisor, Evive: Advisor, Glympse Bio, Inc (acquired by Sunbird Bio): Advisor, Satellite Biosciences: Advisor, Zomagen Bioscience/Ventyx Biosciences: Consultant, Springer Nature Group: Royalties or patent beneficiary, UpToDate Inc: Royalties or patent beneficiary, Boehiringer Ingelheim: Honoraria, Intercept: Contract, NIAAA-NIA: Grant/Research Support, Novo Nordisk: Honoraria, Yale University School of Medicine: Consultant, Resolution Therapeutics: Consultant, US Patent No. 20110293: Intellectual Property.

3130 | DEFINING CLINICALLY MEANINGFUL CHANGES IN TRANSIENT ELASTOGRAPHY FOR ENDPOINT DESIGN IN METALD AND ALD TRIALS

Ellen Lyngbeck Jensen[1] Stine Johansen[2] Nikolaj Torp[2] Katrine Tholstrup Bech[2] Helle Schnefeld[2] Katrine Thorhauge[2] Ida Villesen[2] Mette Lehmann Andersen[2] Markus Maagaard[2] Peter Andersen[2] Johanne Kragh Hansen[2] Camilla Dalby Hansen[2] Aleksander Krag[2] Mads Israelsen[2], [1]Centre for Liver Research, Odense University Hospital, [2]Centre For Liver Research, Department of Gastroenterology and Hepatology, Odense University Hospital

Background: Vibration-Controlled transient elastography (VCTE) is increasingly used for monitoring and may serve as surrogate endpoint in clinical trials in patients with MetALD and ALD. The thresholds for changes in VCTE best reflecting risk of a liver-related outcome are debated, but it remains uncertain whether higher thresholds provide better prognostic value. Furthermore, therapeutic efficacy in steatotic liver disease trials has traditionally been defined by inducing fibrosis regression, while the clinical relevance of preventing progression remains less well established. We evaluated the association between changes in VCTE and subsequent hepatic decompensation, comparing different VCTE response thresholds. **Methods:** We performed a prospective longitudinal cohort study including individuals with MetALD and ALD who underwent two valid VCTE measurements at least 6 months apart and were subsequently followed for hepatic decompensation.The study evaluated candidate decrease/increase thresholds of $\geq 20\%$, $\geq 25\%$, $\geq 30\%$, $\geq 35\%$ and $\geq 40\%$ in VCTE. For decrease thresholds, hazard ratios were inverted to reflect the risk associated with not achieving the decrease threshold. Cox regression analyses adjusted for age, sex, BMI, type 2 diabetes and baseline VCTE were used to evaluate correlation between changes in VCTE and hepatic decompensation (defined by Baveno VII criteria). Subgroup analyses were performed according to baseline VCTE (< 10 and ≥ 10 kPa) and active alcohol intake status. **Results:** This study included 539 patients with baseline VCTE of 6.2 [IQR 4.7-10.6] and 34 developed hepatic decompensation during a median follow-up of 2.3 years [IQR 1.8-2.9]. The multiple candidate thresholds (20-40%) for increases in VCTE were consistently associated with subsequent hepatic decompensation with adjusted HRs ranging from 5.4-6.7 and higher response thresholds did not substantially improve prognostic discrimination. A $\geq 20\%$ increase in VCTE resulted in HR of 6.7 (95% CI: 2.6-17.5) whereas the $\geq 40\%$ threshold showed similar prognostic performance (HR 5.4, 95% CI 2.1-14.1). Similarly, across the same candidate thresholds, failure to achieve VCTE decrease thresholds was associated with increased risk of hepatic decompensation across candidate thresholds (HRs 2.3-6.3) and event rates were consistently higher in individuals with VCTE progression compared with those without progression. Associations were strongest among individuals with baseline VCTE ≥ 10 kPa and similar trends were observed among individuals with active alcohol intake.

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Conclusion: Changes in VCTE reflected the risk of subsequent hepatic decompensation across multiple candidate response thresholds. More stringent response thresholds did not improve prognostic discrimination. These findings support paired VCTE measurements as clinically meaningful monitoring tools and may help inform potential surrogate endpoint definitions in MetALD and ALD trials.

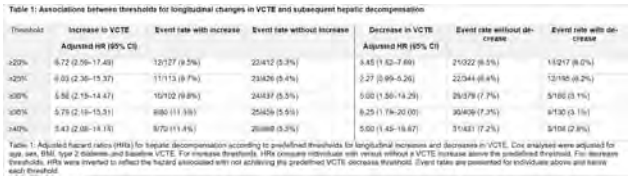


Table 1: Associations between thresholds for longitudinal changes in VCTE and subsequent hepatic decompensation

Threshold	Increase in VCTE Adjusted HR (95% CI)	Event rate with increase	Event rate without increase	Decrease in VCTE Adjusted HR (95% CI)	Event rate without decrease	Event rate with decrease
≥20%	6.72 (2.59–17.49)	12/127 (9.5%)	22/412 (5.3%)	3.45 (1.62–7.69)	21/322 (6.5%)	13/217 (6.0%)
≥25%	8.03 (2.36–15.37)	11/113 (9.7%)	23/426 (5.4%)	3.27 (0.99–6.26)	22/344 (6.4%)	12/195 (6.2%)
≥30%	5.56 (2.15–14.47)	10/102 (9.8%)	24/437 (5.5%)	5.00 (1.56–14.29)	29/379 (7.7%)	5/160 (3.1%)
≥35%	5.79 (2.16–15.51)	8/80 (11.3%)	25/459 (5.5%)	8.25 (1.79–20.00)	30/409 (7.3%)	4/130 (3.1%)
≥40%	5.43 (2.08–14.18)	8/70 (11.4%)	25/469 (5.3%)	5.00 (1.45–19.67)	31/431 (7.2%)	3/108 (2.8%)

Table 1: Adjusted hazard ratios (HRs) for hepatic decompensation according to predefined thresholds for longitudinal increases and decreases in VCTE. Cox analyses were adjusted for age, sex, BMI, type 2 diabetes, and baseline VCTE. For increase thresholds, HRs compare individuals with versus without a VCTE increase above the predefined threshold. For decrease thresholds, HRs were inverted to reflect the hazard associated with not achieving the predefined VCTE decrease threshold. Event rates are presented for individuals above and below each threshold.

Disclosures: Ellen Lyngbeck Jensen:Nothing to Disclose, Stine Johansen:Nothing to Disclose, Nikolaj Torp:Nothing to Disclose, Katrine Tholstrup Bech: Nothing to Disclose, Helle Schnefeld:Nothing to Disclose, Katrine Thorhauge:Nothing to Disclose, Ida Villesen:Nothing to Disclose, Mette Lehmann Andersen:Nothing to Disclose, Markus Maagaard:Nothing to Disclose, Peter Andersen:Nothing to Disclose, Johanne Kragh Hansen:Nothing to Disclose, Camilla Dalby Hansen:Novo Nordisk: Speaking and Teaching, Aleksander Krag:Nothing to Disclose, Mads Israelsen: Nothing to Disclose.

3131 | MAUD SAFETY AND TOLERABILITY IN DECOMPENSATED ALCOHOL-ASSOCIATED CIRRHOSIS AND ALCOHOL-ASSOCIATED HEPATITIS – A MULTICENTER, REAL-WORLD ANALYSIS

Frances Lee[1] Jeffrey Singer[2] Anagha Ashokan[2] Hassan Sinan[1] Elina Stoffel[3] Preethy Abraham[2] Alex Chang[4] Sanjaya Satapathy[5] Jay Luther[6] Manhal Izzy[7] Gene Im[8], [1]Icahn School of Medicine, [2]Vanderbilt University, [3]New York Presbyterian - Columbia University, [4]Northwell Hospital, [5]Northshore University Hospital/Northwell Health, [6]Massachusetts General Hospital, [7]Vanderbilt University Medical Center, [8]Center for Liver Disease and Transplantation, Division of Digestive and Liver Diseases Columbia Univ

Background: The safety, tolerability, and efficacy of medications for alcohol use disorder (MAUD) in patients with alcohol-associated cirrhosis (AC) and -hepatitis (AH) in real-world settings are largely unknown. **Methods:** This was a retrospective cohort analysis of AC and AH patients newly initiated on MAUD with a minimum of 6-month follow-up from ALD-CORE, a multicenter collaborative of five centers in New York, Tennessee, and Massachusetts from 2020-2025. The outcomes were MAUD-related adverse events, DILI, discontinuation rates, change in alcohol use, and liver decompensation events. Regression analysis was completed after adjusting for medication type, history of rehabilitation, age, sex, and decompensation. **Results:** 271 patients with AC (60%), AH (15%), AC+AH (24%) were included, with a mean age of 50 years, mostly male (64%) and White (78%), and high baseline rates prior decompensation (69%). 56% of patients were on acamprosate, followed by oral naltrexone (24%), gabapentin (9%), and baclofen (3%). Most MAUD (76%) was initiated while patient was hospitalized. The overall adverse event rate from MAUD was 16%, most commonly nausea/vomiting (7.4%), without statistical difference across all MAUD or AC/AH designation. There were no significant changes in liver tests during MAUD treatment consistent with DILI. 40% of patients discontinued MAUD at six months due to self-discontinuation (39%), adverse events (27%), other MAUD therapy (20%), and lack of efficacy (11%); there was no association between reason for discontinuation and medication type, provider specialty, inpatient/outpatient setting, or duration of therapy. Per patient report, 35% patients had total abstinence and 65% had ongoing alcohol intake. AH and prior decompensation may increase likelihood of total abstinence on multivariate analysis (OR 2.71 (0.93 -7.93), p = 0.07; OR 2.3 (0.98-5.43), p = 0.06). 19.4% of patients experienced new/worsening ascites, 15.8% with new/worsening hepatic encephalopathy, and 5.2% with portal hypertensive bleeding. Though MAUD subtype and MELD were not associated with decompensation events on multivariate analysis, AH and higher albumin levels were associated with reduced decompensation rates (OR 0.1 (0.02-0.48)) while abstinence was associated with hepatic decompensation (OR 3.21 (1.07-9.61)). **Conclusion:** In this multicenter, real-world analysis, MAUD appears to be safe and reasonably tolerated in AC and AH patients, though with high rates of discontinuation. History of decompensation and AH diagnosis may increase likelihood of total abstinence by 6 months. While AH or higher albumin levels decrease decompensating events, we observed a paradoxical increase in hepatic decompensation with abstinence, which may be explained by discontinued alcohol intake with clinical decline. Future studies should investigate efficacy of MAUD with a matched cohort of AH and AC patients not on MAUD with the additional of PETH results.

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Variable		Overall (N=271)	AC (N=164)	AH (N=40)	AC+AH (N=66)	p-value (AC vs AH)
Age (years)		50.61 (11.58)	53.52 (10.79)	44.85 (11.59)	46.58 (10.92)	0.0001
Sex						
	Male	172 (63.5%)	107 (65.2%)	29 (72.5%)	35 (53%)	
	Female	98 (36.2%)	56 (34.1%)	11 (27.5%)	31 (47%)	0.429
	Other	1 (0.4%)	1 (0.6%)	0 (0%)	0 (0%)	
Race						
	White	206 (77.7%)	121 (75.6%)	28 (77.8%)	57 (87.7%)	
	Black	23 (8.7%)	14 (8.8%)	6 (16.7%)	3 (4.6%)	
	Hispanic	20 (7.5%)	13 (8.1%)	3 (7.7%)	3 (4.6%)	0.2774
	Asian	6 (2.3%)	5 (3.1%)	0 (0%)	1 (1.5%)	
	Other	10 (3.8%)	7 (4.4%)	2 (5.1%)	1 (1.5%)	
Prior Decompensation		180 (66.7%)	115 (70.8%)	15 (45.5%)	50 (75.8%)	0.0099
	Baseline Ascites	153 (81.3%)	99 (81.8%)	6 (40%)	48 (94.1%)	0.0009
	Baseline Hepatic Encephalopathy	85 (45.5%)	61 (50.4%)	5 (33.3%)	19 (37.3%)	0.3268
	Prior History of Variceal Bleeding	55 (29.4%)	44 (36.4%)	5 (33.3%)	6 (11.8%)	1
Pretreatment labs						
	Platelets	137.9 (69.77)	129.59 (60.37)	169.41 (124.26)	138.73 (63.4)	0.0629
	AST	116.42 (87.08)	97.54 (74.99)	173.13 (129.45)	128.67 (66.3)	0.001
	ALT	50.32 (40.83)	43.7 (31.42)	65.21 (60.95)	57.73 (55.95)	0.0035
	ALP	175.95 (111.85)	181.88 (104.75)	216.62 (171.63)	166.36 (68.77)	0.0619
	Total Bilirubin	7.05 (8.68)	3.76 (4.79)	9.33 (9.63)	13.8 (10.96)	0.0013
	INR	1.64 (1.14)	1.66 (1.45)	1.39 (0.44)	1.76 (0.45)	0.0724
	Creatinine	0.87 (0.53)	0.97 (0.64)	0.79 (0.23)	0.6 (0.28)	0.0585
	Albumin	3.07 (0.7)	3.2 (0.71)	3.09 (0.76)	2.75 (0.54)	0.0046
	MELD	25.21 (11.24)	19 (9.45)	24.74 (11.71)	31.46 (9.79)	0.0115
Concurrent mental health disorder						
	Depression	126 (46.5%)	76 (46.2%)	17 (42.5%)	30 (45.5%)	0.8401
	Anxiety	87 (32.1%)	49 (29.8%)	16 (40%)	22 (33.3%)	0.2971
	Bipolar Disorder	22 (8.1%)	14 (8.5%)	1 (2.5%)	7 (10.6%)	0.3302
	Schizoaffective Disorder	2 (0.7%)	1 (0.6%)	0 (0%)	1 (1.5%)	1
	PTSD	37 (13.7%)	28 (17.1%)	4 (10%)	5 (7.6%)	0.3890
Concomit substance use disorder						
	Tobacco Use	124 (47.7%)	78 (48.4%)	13 (35.1%)	33 (50.8%)	0.1679
	Cannabis Use	37 (14.2%)	18 (11.4%)	7 (18.9%)	12 (18.5%)	0.3373
	Opioid Use	32 (12.3%)	22 (13.9%)	4 (10.8%)	6 (9.2%)	0.8159
	Cocaine Use	20 (7.7%)	17 (10.8%)	3 (8.1%)	0 (0%)	0.0591
	Amphetamine Use	6 (2.3%)	3 (1.9%)	2 (5.4%)	1 (1.5%)	0.3241
Concomitant liver disease						
	HBV	6 (6.2%)	5 (7.1%)	1 (7.7%)	0 (0%)	1
	HCV	23 (23.7%)	18 (25.7%)	3 (23.1%)	2 (14.3%)	1
	NASH/BMI>30	58 (59.8%)	39 (55.7%)	9 (69.2%)	10 (71.4%)	0.5482
	HCC	3 (3.1%)	3 (4.3%)	0 (0%)	0 (0%)	1
Employment						
	Employed	89 (35.9%)	44 (29.8%)	15 (41.7%)	30 (49.2%)	0.013
	Unemployed	99 (39.4%)	59 (39.8%)	18 (50%)	22 (36.1%)	
	Disabled	63 (25.1%)	50 (32.7%)	3 (8.3%)	9 (14.8%)	
Medication type						
	Acamprosate	151 (55.7%)	81 (49.4%)	24 (60%)	45 (68.2%)	
	Baclofen	10 (3.7%)	8 (4.9%)	1 (2.5%)	1 (1.5%)	
	Gabapentin	25 (9.2%)	13 (7.9%)	5 (12.5%)	7 (10.6%)	
	Naltrexone	65 (24%)	50 (30.5%)	5 (12.5%)	10 (15.2%)	
	Vivitrol	7 (2.6%)	6 (3.7%)	1 (2.5%)	0 (0%)	0.122
	Topiramate	4 (1.5%)	4 (2.4%)	0 (0%)	0 (0%)	
	Acamprosate+Naltrexone	1 (0.4%)	0 (0%)	1 (2.5%)	0 (0%)	
	Acamprosate+Gabapentin	4 (1.5%)	0 (0%)	2 (5%)	2 (3%)	
	Gabapentin+Naltrexone	4 (1.5%)	2 (1.2%)	1 (2.5%)	1 (1.5%)	
Prescriber specialty						
	Inpt Hepatology MD/DO	8 (3.1%)	6 (3.8%)	1 (2.5%)	1 (1.6%)	
	Inpt IM/Fam MD/DO	30 (11.5%)	16 (10%)	9 (22.5%)	5 (8.1%)	
	Outpt IM/Fam MD/DO	8 (3.1%)	7 (4.4%)	0 (0%)	1 (1.6%)	
	Outpt IM/Fam APP	3 (1.1%)	3 (1.9%)	0 (0%)	0 (0%)	0.2773
	Outpt Hepatology MD/DO	15 (5.7%)	12 (7.5%)	2 (5%)	1 (1.6%)	
	Outpt Hepatology APP	16 (6.1%)	13 (8.1%)	2 (5%)	1 (1.6%)	
	Addiction Professional	177 (67.6%)	98 (61.3%)	26 (65%)	53 (85.5%)	
	Other	5 (1.9%)	5 (3.1%)	0 (0%)	0 (0%)	
Setting						
	Inpatient	201 (75.8%)	108 (67.1%)	35 (87.5%)	58 (90.6%)	0.0185
	Outpatient	64 (24.2%)	53 (32.9%)	5 (12.5%)	6 (9.4%)	
Duration (months)		6.38 (9.45)	6.65 (9.58)	7.34 (13.01)	4.77 (6.17)	
Any Dose Change		38 (14.7%)	25 (15.3%)	8 (20.5%)	5 (8.1%)	0.6553

Table 1. Baseline demographic information. Data presented as mean (SD) for continuous variables and n (%) for categorical variables. p-value column compares AC vs AH only (Both AC/AH excluded from p-value calculation) Bold p-values = p<0.05

Disclosures: Frances Lee:Nothing to Disclose, Jeffrey Singer:Nothing to Disclose, Anagha Ashokan:Nothing to Disclose, Hassan Sinan:Nothing to Disclose, Elina Stoffel:Nothing to Disclose, Preethy Abraham:Nothing to Disclose, Alex Chang:Nothing to Disclose, Sanjaya Satapathy:Gilead Sciences: Grant/Research Support, Durect Pharma: Grant/Research Support, Fibronostics: Grant/Research Support, Novartis: Grant/Research Support, Zydus Pharma: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Intercept Pharma: Grant/Research Support, AKERO: Grant/Research Support, Altimmune: Grant/Research Support, IPSEN: Grant/Research Support, Madrigal: Grant/Research Support, Jay Luther:Nothing to Disclose, Manhal Izzy:Mallinckrodt: Speaking and Teaching, Madrigal: Advisor, Natera: Advisor, Mirum: Advisor, Gene Im:KorroBio: Consultant, Echosens: Device support for research, Novo Nordisk: Advisor, Alimentiv: Consultant, GSK: Consultant, Altimmune: Consultant, Bayer: Consultant.

3132 | HEPATOCYTE SOD1 DEFICIENCY ACCELERATES ALCOHOL-ASSOCIATED LIVER DISEASE VIA OXIDATIVE STRESS AND NEUTROPHIL ACTIVATION

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Background: Liver is a primary organ involved in ethanol metabolism and is highly susceptible to ethanol-induced organ injury. Evidence suggests that superoxide dismutase 1 (SOD1) plays a crucial role in protecting against alcohol-associated liver disease (ALD). Although a link exists between SOD1 and ALD, the role and mechanisms by which hepatocyte SOD1 alters liver injury upon ethanol exposure is yet to be determined. We hypothesize that deletion of SOD1 specifically in hepatocytes aggravates alcohol-induced hepatocyte oxidative stress which, in turn, enhances the progression of ALD. **Methods:** We developed conditional knock-out mice lacking SOD1 specifically in hepatocytes (Hepato-SOD$^{-/-}$ hereafter referred to as KO mice) by breeding SOD1$^{flox/flox}$ with Albumin^{Cre} mice. The littermate wild type mice (Hepato-SOD$^{+/+}$ hereafter referred to as WT mice) were used as controls. Mice were fed a Lieber-DeCarli control diet or ethanol (EtOH) diet for 1, 4 or 6 wk. **Results:** We observed an increase in plasma markers of liver injury in KO mice compared to WT mice as early as 1 week of EtOH exposure, and this increase was sustained through 6 weeks. We also noted a profound increase in the mRNA levels of inflammatory genes in the KO:EtOH mice, compared to WT:EtOH group. Moreover, Sirius red staining of liver sections revealed a pronounced increase in fibrotic lesions in KO:EtOH mice, compared to all groups, indicating that deletion of SOD1 only in hepatocytes leads to an aggravated liver injury upon EtOH exposure. The proteomics analysis in the liver samples shows that the top canonical pathways altered in KO:EtOH mice include neutrophil degranulation and NRF2-mediated oxidative stress response. The significantly altered proteins in KO:EtOH mice represent various diseases and disorders including cancer, gastrointestinal disease, and hepatic system disease. Regarding hepatotoxicity, we noted that proteins regulating hepatocellular carcinoma, liver hyperplasia/hyperproliferation, and liver steatosis are altered significantly between groups. NRF2-mediated oxidative stress response was identified as the top toxicity response in KO:EtOH mice, compared to WT:EtOH mice. **Conclusion:** Taken together, our data suggest that hepatocyte SOD1 plays an indispensable role in protecting the liver against ALD by regulating ethanol-induced oxidative stress and neutrophil

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activation. Therefore, targeting SOD1 may represent a promising strategy to attenuate ALD

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3133 | A CIRCULATING PROTEOMIC SIGNATURE PREDICTS DISEASE PROGRESSION IN ALCOHOL-ASSOCIATED LIVER DISEASE

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Background: Alcohol-associated liver disease (ALD) encompasses a broad spectrum of clinical phenotypes from mild steatosis to decompensated cirrhosis. While emerging data suggest that a combination of metabolic and genetic factors may help assess risk of advanced ALD, there remains significant uncertainty in identifying those with at-risk drinking who will progress. We have previously identified a proteomic signature correlating with disease severity in ALD. In this study, we sought to determine whether circulating markers predict progression of liver disease during follow-up. **Methods:** From our cohort of 93 patients with at-risk drinking, we identified those who did not have decompensated liver disease at baseline (defined as decompensated cirrhosis and severe alcohol-associated hepatitis [AH]); we excluded those without follow-up. This discovery cohort included 46 patients (compensated cirrhosis n = 11, mild or moderate AH n = 19, and alcohol use disorder without clinically evident liver disease n = 16), with mean follow-up of 3.8 years. Disease progression was defined as decompensation of known cirrhosis, or new diagnosis of cirrhosis or severe AH. Our previously published proteins associated with ALD were quantified using the SomaScan proteomics aptamer-based platform. Analysis was performed using logistic regression and Wilcoxon Rank Sum testing. **Results:** In the discovery cohort of 46 patients, there were a total of 10 progressors identified during follow-up. Six proteins, assayed at baseline, were found to be significantly associated with disease progression: TIMP1 (OR 1.78, 1.12-2.82, p = 0.014), LTBP4 (OR 1.51, 1.05-2.16, p = 0.025), THBS2 (OR 1.07, 1.01-1.13, p = 0.029), NTN4 (OR 2.34 1.06-5.17, p = 0.036), FSTL3 (OR 1.37, 1.02 – 1.84, p = 0.037), and CXCL6 (OR 1.43, 1.01-2.01, p = 0.044). In a subgroup analysis based on index disease severity, CXCL6 was a significant predictor of development of incident cirrhosis or severe AH in patients with alcohol use disorder (OR 21.42, 1.10-418.19, p = 0.043). **Conclusion:** Circulating proteins may lend an important and clinically viable tool for risk assessment of disease progression in ALD. Importantly, these proteins also lend critical insights into the biological underpinnings of disease severity. In particular, several of these proteins (TIMP1, CXCL6, LTBP4, THBS2) have been associated with hepatic stellate cell activation, and thus represent promising candidates to non-invasively determine risk of advancing fibrosis and guide early intervention.

Protein	B1	OR (95% CI)	p value
TIMP1	0.5762	1.78 (1.12 - 2.82)	0.014
LTBP4	0.4118	1.51 (1.05 - 2.16)	0.025
THBS2	0.0653	1.07 (1.01 - 1.13)	0.029
NTN4	0.8507	2.34 (1.06 - 5.17)	0.036
FSTL3	0.3138	1.37 (1.02 - 1.84)	0.037
CXCL6	0.3544	1.43 (1.01 - 2.01)	0.044
PIGR	0.1325	1.14 (0.96 - 1.36)	0.133
FLRT3	0.291	1.34 (0.88 - 2.03)	0.169
COLEC11	0.0697	1.07 (0.97 - 1.19)	0.180
MRC1	0.2664	1.31 (0.88 - 1.93)	0.181
TNFRSF1B	0.3067	1.36 (0.83 - 2.21)	0.217
GDF15	0.0525	1.05 (0.95 - 1.17)	0.334
TFF1	0.1304	1.14 (0.86 - 1.50)	0.358
CD300C	0.2728	1.31 (0.62 - 2.80)	0.480
IL1RL1	0.0101	1.01 (0.96 - 1.06)	0.673
CD163	0.0133	1.01 (0.71 - 1.45)	0.942

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3134 | FK506 DECREASES MITOCHONDRIAL INJURY AND RELEASE OF MITOCHONDRIAL DAMAGE-ASSOCIATED MOLECULAR PATTERNS (MTDAMPS) AFTER CHRONIC-BINGE ETHANOL (CBE) TREATMENT IN MICE

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Background: A pattern of chronic plus binge drinking is observed in many alcohol-associated hepatitis patients. Our previous study showed that chronic-binge ethanol treatment (CBE) leads to mitochondrial depolarization (mtDepo), dysregulation of mitophagic processing, and release of mtDAMPs. In this study we examined whether FK506 (tacrolimus), a drug that decreases mitochondrial dysfunction after acute ethanol treatment, protects the liver during CBE. **Methods:** Mice were fed a liquid diet containing 5% ethanol for 10 days and then gavaged once with ethanol (5 g/kg)

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on day 11. FK506 (1mg/kg, i.g.) was given once daily during CBE treatment. **Results:** CBE increased serum ALT from a basal level of 40 U/L to 310 U/L at the end of treatment and caused moderate hepatic steatosis, scattered necrotic cell death, and leukocyte infiltration histologically. FK506 decreased serum ALT by ~75% and also decreased steatosis, cell death, and leukocyte infiltration. After CBE, mtDepo occurred in ~80% hepatocytes. Moreover, many microvesicular and some macro-vesicular fat droplets appeared in hepatocytes. More and larger fat droplets developed in hepatocytes with mtDepo. FK506 decreased mtDepo and fat droplets after CBE. mtDepo drives Type 2 mitophagy. After CBE, mitophagic burden was high as indicated by increased PINK1 and LC3. Lysosomal degradation is needed to remove damaged mitochondria after CBE. However, TFEB, the master regulator of lysosomal enzyme expression, and LAMP2, a marker of lysosomes, decreased, suggesting suppressed lysosomal processing of mitophagosomes after CBE, which may result in release of cytotoxic, pro-inflammatory, and/or profibrotic mtDAMPs. As evidence of mtDAMP release after CBE, serum mtDNA/nuclear DNA ratios increased ~940%, and serum cytochrome *c* increased from 1.0 to 3.3ng/ml. FK506 increased TFEB and LAMP2 expression. Moreover, with FK506 treatment, serum mtDNA/nDNA ratios only increased 140%, and cytochrome *c* only increased to 1.2ng/ml. Associated with increased mtDAMP release after CBE, expression of NLRP3 (inflammasome activation) in the liver increased by ~250%, and hepatic myeloperoxidase (MPO, neutrophil marker) increased by ~370% after CBE. FK506 blunted these inflammatory reactions. **Conclusion:** Taking together, these data demonstrated that FK506 decreases liver injury and inflammation after CBE, at least in part, by suppressing mtDepo and inhibiting mtDAMP release.

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3135 | ALCOHOL POTENTIATES PANOPTOSIS IN HIV-INFECTED HEPATOCYTES THROUGH ZBP1-ASSOCIATED SIGNALING PATHWAYS

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Background: Alcohol use disorder accelerates liver disease progression in people living with HIV (PLWH), yet the mechanisms driving hepatocyte injury remain poorly understood. PANoptosis pathways, including apoptosis, necroptosis, and pyroptosis, contribute to inflammatory liver injury. Z-DNA-binding protein 1 (ZBP1), an innate immune sensor involved in inflammatory and lytic cell death signaling, may regulate these pathways during HIV-alcohol hepatotoxic stress. This study investigated activation of oxidative stress and programmed cell death signaling in alcohol-pretreated HIV-infected hepatocytes and evaluated the role of ZBP1. **Methods:** Huh7.5-CYP2E1 were pretreated with acetaldehyde-generating system (AGS) and infected with HIV-1 $_{ADA}$ at a multiplicity of infection (MOI) of 0.1. Cells were harvested at days 1, 3, and 5 post-infection to assess hepatocyte injury and regulated cell death signaling. Cell viability, cytotoxicity, and reactive oxygen species (ROS) assays were evaluated using MTT, lactate dehydrogenase (LDH) release, DCFDA-based assays respectively. Expression of cleaved caspase-3, cleaved PARP, RIPK3, pMLKL, NLRP3, caspase-1, gasdermin D, IL-1β, and IL-18 was analyzed by immunoblotting and molecular assays. Based on timed profiling, days 1 and 3 were selected for mechanistic studies using caspase-1, caspase-3, necrostatin-1 inhibitors and ZBP1 gene silencing. **Results:** AGS pretreatment increased HIV infected hepatocyte injury compared with HIV infection alone. MTT assays reduced viability, while LDH release assays showed increased cytotoxicity at day 3 post-infection. DCFDA analysis revealed significantly elevated ROS production in AGS-pretreated HIV-infected hepatocytes. Analysis demonstrated peak activation of PANoptosis pathways at day 3 by increased cleaved caspase-3 and cleaved PARP expression. Necroptotic activation was confirmed by elevated RIPK3 and pMLKL expression, while pyroptotic activation was associated with increased NLRP3 signaling, caspase-1 activation, gasdermin D cleavage, and elevated IL-1β and IL-18 expression. Caspase-3 inhibition attenuated apoptotic activation, caspase-1 inhibition reduced pyroptotic responses, and necrostatin-1 decreased necroptotic signaling. Importantly, ZBP1 silencing significantly attenuated oxidative stress, inflammatory signaling, and PANoptosis activation **Conclusion:** These findings demonstrate that alcohol-associated stress potentiates HIV-induced hepatocyte injury through coordinated activation of oxidative stress and multiple regulated cell death pathways. Peak hepatotoxic signaling at day 3 post-infection suggests a critical temporal window for inflammatory liver injury progression. ZBP1 silencing identifies ZBP1 as a key upstream mediator of HIV/alcohol-associated hepatocyte injury and a potential therapeutic target for reducing liver disease progression in PLWH with alcohol use disorder.

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3136 | EXPLORING THE ROLE OF RECEPTOR-INTERACTING PROTEIN KINASE 1 UBIQUITINATION IN INFLAMMASOME ACTIVATION IN ALCOHOL-ASSOCIATED LIVER DISEASE

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Background: Alcohol-associated liver disease (ALD) is driven by inflammation and regulated cell death, but effective therapies remain limited. Receptor-interacting protein kinase 1 (RIP1) regulates inflammatory signaling and cell fate through scaffold and kinase functions controlled by post-translational modifications, including ubiquitination, and operates in coordination with RIP3 in necroptotic signaling pathways. Although RIP1 is classically activated through TNF-α/TNFR1 and non-canonically through TLR4, the role of RIP1 ubiquitination in inflammasome activation in ALD remains unclear. We investigated RIP1 ubiquitination and its regulatory mechanisms in ALD, focusing on immune cells and inflammasome signaling. **Methods:** Murine ALD models and liver samples from patients with alcohol-associated hepatitis (AH) were analyzed using tandem ubiquitin-binding entity (TUBE) pull-down assays to assess RIP1 ubiquitination. Bulk and single-cell RNA sequencing datasets were used to define E3 ligases and deubiquitinases regulating RIP1 signaling in liver and peripheral blood mononuclear cells (PBMCs). Mechanistic studies were performed in THP-1 monocytes stimulated with TNF-α ± ethanol. Inflammasome activation was assessed by ASC speck formation in THP1-ASC-GFP cells and IL-1β ELISA in THP-1 cells. siRNA knockdown and pharmacologic inhibition were used to define the downstream functional outcomes. **Results:** RIP1 ubiquitination was reduced in murine ALD and AH patient livers compared with healthy controls. Transcriptomic analysis revealed dysregulation of RIP1-associated ubiquitin enzymes in liver and PBMCs, identifying TNFAIP3/A20 as a potential candidate. In THP-1 cells, A20 knockdown decreased TNF-α–induced RIP1 ubiquitination and enhanced inflammasome activation, with increased ASC speck formation and IL-1β release, further amplified by ethanol. RIP1 knockdown or RIP1 kinase inhibition with necrostatin-1 suppressed inflammasome activation, whereas RIP3 kinase inhibition had no effect, indicating a RIP3-independent role for RIP1. **Conclusion:** RIP1 ubiquitination is disrupted in ALD and regulates inflammasome activation in immune cells via a RIP3-independent mechanism. These findings identify ubiquitination-dependent RIP1 signaling as a potential therapeutic target in alcohol-associated liver inflammation.

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3137 | HOW PATIENTS WITH ALCOHOL-RELATED LIVER DISEASE FEEL AND FUNCTION: TOWARD A LITERATURE-INFORMED PATIENT-REPORTED OUTCOME

Yekaterina Poloz[1] Farrah Pompilus[1] Helen Smith[1] Samantha Linton[2] Nina Galipeau[2] Benjamin Banderas[2] Daniella Olonilua[2] Nikhil Vergis[1] Dharmraj Sauriyal[1], [1]GSK, [2]Adelphi Values

Background: Patients with alcohol-related liver disease (ALD) experience numerous signs, symptoms, and health-related quality of life (HRQoL) impacts, such as physical function decline. However, a validated patient-reported outcome (PRO) in ALD does not exist. We aimed to characterize the patient experience of ALD via a literature-based conceptual model to inform development of a novel PRO. **Methods:** A targeted, concept-focused literature review was conducted in OvidSP (supplement searches: Google, Google Scholar, PubMed) to identify and synthesize evidence on ALD-relevant concepts and PROs. Eligible publications describing ALD-related signs, symptoms, and HRQoL impacts underwent full-text review. Identified concepts were mapped to existing PROs and used to create a conceptual model, which informed initial development of a novel PRO for ALD. **Results:** The OvidSP search identified 251 abstracts (n = 6, full-text review); supplemental searches identified 16 publications (n = 3, full-text review). Across 9 publications, 38 signs and symptoms were identified; 18 were deemed suitable for PRO report. Most frequently reported were: fatigue and jaundice (n = 6/9 publications each, 66.7%), ascites (n = 5/9, 55.5%), and encephalopathy (n = 4/9, 44.4%). Among 41 identified HRQoL impacts, the most frequently reported were: depression (n = 4, 44.4%), feeling stigmatized, and cognitive impairment (n = 3 each, 33.3%). The search yielded 46 PROs: 36 from the targeted OvidSP instrument-identification search (172 screened abstracts) and 10 from the supplemental search. Five underwent concept mapping: Chronic Liver Disease Questionnaire (CLDQ; 29 items), PRO Measurement Information System version 29 (PROMIS-29), Liver Disease Symptom Index version 2.0 (LDSI 2.0), Liver Cirrhosis Patient-Reported Outcome Measure (LC-PROM; 55 items), and Sickness Impact Profile 68 (SIP-68; 68 items). LC-PROM provided the most conceptual coverage of signs and symptoms (n = 10/18 concepts, 55.6%), followed by CLDQ (n = 7/18, 39.4%).

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SIP-68 provided the most conceptual coverage of HRQoL impacts (n = 14/41 concepts, 34.2%), followed by LC-PROM (n = 12/41, 29.3%), and PROMIS-29 (n = 10/41, 24.4%). Of the identified concepts, 33 (18 signs and symptoms, 15 HRQoL impacts) were included in a draft novel PRO. **Conclusion:** Existing PROs do not adequately capture the identified ALD-related signs, symptoms, and HRQoL impacts. Qualitative research is underway to further understand the patient experience of ALD and evaluate the novel PRO.

Disclosures: Yekaterina Poloz:GSK: Employee, GSK: Stock - publicly traded company, Farrah Pompilus: Nothing to Disclose, Helen Smith:Nothing to Disclose, Samantha Linton:Nothing to Disclose, Nina Galipeau: Nothing to Disclose, Benjamin Banderas:Nothing to Disclose, Daniella Olonilua:Nothing to Disclose, Nikhil Vergis:Nothing to Disclose, Dharmraj Sauriyal:Nothing to Disclose.

3138 | SASP PROFILING REVEALS SHARED AND ETIOLOGY-SPECIFIC SENESCENCE SIGNATURES IN ALD AND MASLD BEFORE AND AFTER LIVER TRANSPLANTATION

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Background: Cellular senescence and its proinflammatory secretome, the senescence-associated secretory phenotype (SASP) contribute to chronic liver diseases pathogenesis across etiologies. Whether circulating SASP profiles attenuate after restoration of hepatic function, and whether they differ by underlying etiology remains unexplored. Thus, we characterized the SASP before and after liver transplantation in patients with alcohol-associated liver disease (ALD) and metabolic dysfunction-associated steatotic liver disease (MASLD). **Methods:** Plasma samples from patients with ALD (n = 24) and MASLD (n = 21) pre-transplant and one-year post-transplant were profiled using the Luminex Discovery Assay to assess a panel of 31 SASP proteins. Pre-and post-transplant protein levels were analyzed by paired analysis with Benjamini-Hochberg FDR-adjusted p-values to account for multiple hypothesis testing. **Results:** Baseline characteristics were similar between the ALD and MASLD groups with a median age of 56 years, 73% male sex, and a median MELD score of 21. Compared with paired pre-transplant baseline, 9 proteins were differentially expressed post-transplant in the plasma of patients with MASLD and 13 proteins in patients with ALD. Both groups showed down regulation of CCL20, GDF-15, HGF, IL-6, MMP-2, MMP-8, and MMP-10 (median fold change 0.41 to 1.54) with increased detection of IGFBP-3 (fold change 1.85). IL-8 was also downregulated in patients with MASLD (fold change 1.14). In ALD, MMP-9 and TRAIL were additionally downregulated while PDGF-AA, PDGF-AB/BB, and TRAIL were upregulated (fold change 0.26 to 3.54). **Conclusion:** Attenuation pro-inflammatory (IL-6, CCL20), matrix remodeling (MMP-2, MMP-8, MMP-10) and hepatocyte injury-associated (HGF, GDF-15) SASP factors after transplantation suggest a core senescence signature of advanced liver disease. Etiology-specific findings, particularly persistent upregulation of pro-fibrogenic PDGF isoforms in ALD, implicate distinct, residual senescence biology that endures beyond removal of the diseased liver. SASP profiling helps define etiology-targeted senolytics or senomorphic strategies in cirrhosis.

Disclosures: Kianna Nguyen:Nothing to Disclose, Douglas Simonetto:Mallinckrodt: Consultant, BioVie: Consultant, Resolution Therapeutics: Consultant, Evive: Consultant, Iota: Consultant, Novo Nordisk: Consultant, Astra Zeneca: Consultant, Timucin Taner: Nothing to Disclose, Ethan Leitschuh:Nothing to Disclose, Marissa Schafer:Nothing to Disclose.

3139 | IMPACT OF BARIATRIC SURGERY TYPE ON LIVER OUTCOMES IN ALCOHOL USE DISORDER

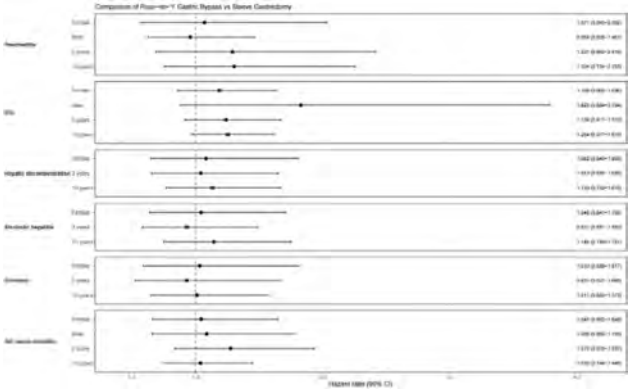
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Background: The benefits of bariatric surgery (Roux-en-Y gastric bypass [RYGB] and sleeve gastrectomy [SG]) are well-known, including substantial weight loss and improvements in complications related to obesity. However, physiological and anatomical changes that result from this surgery affect alcohol absorption and metabolism, leading to adverse effects in patients with alcohol use disorder (AUD). There is little known regarding whether the impact of these changes varies based on the type of bariatric surgery. This study aims to compare liver-related outcomes among patients with AUD who underwent RYGB versus SG. **Methods:** This retrospective cohort study was performed using TriNetX. The study population consisted of adult patients

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with a diagnosis of AUD according to ICD 10 codes identified on or before December 31, 2020. Patients with underlying chronic liver disease according to ICD 10 codes before the index events were excluded. Demographic characteristics, comorbidities, medications, and laboratory variables were included for balancing both groups using propensity score matching. Primary outcomes were mortality, incidence of cirrhosis, and alcohol-associated hepatitis. Secondary outcomes were hepatic decompensation, critical care admission, and acute alcohol-associated pancreatitis. Cox proportional hazards models were used for all analyses. **Results:** Initial search yielded a total of 2,452 patients with AUD, of whom 965 patients had a history of RYGB and 1,487 had a history of SG. At 5-year follow-up, there were no statistically significant differences in mortality (HR 0.970; 95% CI, 0.682—1.378), cirrhosis (HR 0.934; 95% CI, 0.588—1.484), and alcohol-associated hepatitis (HR 1.045; 95% CI, 0.670—1.630). Secondary outcomes did not demonstrate statistically significant differences. Subsequent sensitivity analyses were consistent with the primary findings. **Conclusion:** Patients with AUD who underwent RYBG and SG had similar rates of mortality and liver-related complications. These findings suggest that procedure type alone may not independently determine risk of adverse liver-related outcomes in this population. Further research measuring patterns of alcohol consumption via self-report and direct alcohol biomarkers is needed to further characterize the association between bariatric surgery type and liver-related outcomes among patients with AUD.



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3140 | DECOMPOSING THE POST-PANDEMIC RISE IN LIVER FIBROSIS BURDEN IN THE UNITED STATES: STRUCTURAL RATHER THAN POPULATION COMPOSITION EFFECTS

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Background: Liver fibrosis burden increased in the United States following the COVID-19 pandemic; however, the relative contributions of alcohol exposure, metabolic dysfunction, demographic composition, and changing fibrosis-risk relationships remain unclear. We quantified contributors to rising fibrosis burden using formal decomposition methods in a nationally representative cohort. **Methods:** We analyzed adults aged 18–80 years undergoing vibration-controlled transient elastography (VCTE) in NHANES 2017–2023. Significant fibrosis was defined as liver stiffness measurement (LSM) $\geq$8 kPa and advanced fibrosis as LSM $\geq$12 kPa. Steatotic liver disease phenotypes were classified according to 2023 multi-society nomenclature criteria (No SLD, MASLD, MetALD, ALD). Survey-weighted analyses assessed trends in metabolic burden, alcohol exposure, and fibrosis prevalence. Three-component Oaxaca-Blinder decomposition quantified fibrosis changes attributable to shifts in population risk-factor distribution versus changes in fibrosis-risk associations. The analytic cohort included 13,167 adults; decomposition analyses were restricted to 11,127 participants with complete covariate data. **Results:** Significant fibrosis increased from 9.0% pre-pandemic to 11.4% post-pandemic (+2.43 percentage points [pp]), while advanced fibrosis increased from 3.4% to 4.4% (+1.06 pp). Alcohol exposure increased substantially across periods, including annual binge drinking and severe episodic drinking, whereas overall metabolic burden remained stable. For significant fibrosis, population composition changes did not explain the observed increase (composition effect: −0.36 pp, 95% CI −0.95 to 0.23; p = 0.23), whereas amplified associations between established risk factors and fibrosis accounted for the entirety of the increase (structure effect: +2.84 pp, 95% CI 1.24 to 4.45; p = 0.0005). Structural effects explained 117.0% of the observed fibrosis increase, while compositional shifts contributed −14.9%. Similar patterns were observed for advanced fibrosis (composition: −0.05 pp [−5.2%]; structure: +1.23 pp [116.0%]). Sensitivity analyses

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incorporating binge drinking demonstrated consistent findings. **Conclusion:** Rising liver fibrosis burden in the United States was not primarily explained by changes in population composition, alcohol exposure distribution, or metabolic burden. Instead, strengthened associations between established risk factors and fibrosis accounted for most of the observed increase. These findings suggest that post-pandemic fibrosis trends may reflect evolving susceptibility to established risk factors — potentially including synergistic alcohol-metabolic interactions — and highlight the need to identify emerging determinants of fibrosis progression.

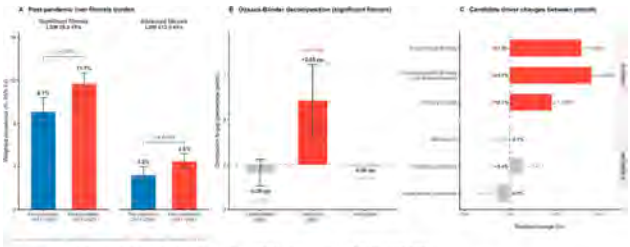


Figure 1. Post-pandemic liver fibrosis burden and Oaxaca-Blinder decomposition — NHANES 2017–2023.
(A) Weighted prevalence of significant fibrosis (LSM ≥8.0 kPa) and advanced fibrosis (LSM ≥12.0 kPa) in pre-pandemic (2017–2020) and post-pandemic (2021–2023) NHANES cycles (N = 13,167). Error bars represent 95% confidence intervals. **(B)** Three-component Oaxaca-Blinder decomposition of the observed significant fibrosis increase (+2.43 percentage points) into composition effects (changes in population risk factor distribution), structural effects (changes in associations between risk factors and fibrosis), and interaction. Decomposition N = 11,127 complete cases; bootstrap standard errors (R = 300). Error bars represent 95% confidence intervals for composition and structural effects. **(C)** Relative percent change in candidate drivers between periods. Red bars indicate statistically significant increases (p < 0.05); gray bars indicate non-significant changes.
LSM = liver stiffness measurement; **SLD** = steatotic liver disease; **pp** = percentage points.

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3141 | PROTON PUMP INHIBITORS USE IN HOSPITALIZED PATIENTS WITH ALCOHOL-ASSOCIATED HEPATITIS IS ASSOCIATED WITH HIGHER RATES OF LIVER DECOMPENSATION, MORTALITY, AND INFECTIOUS COMPLICATIONS COMPARED TO H2-RECEPTOR ANTAGONISTS: A PROPENSITY SCORE-MATCHED ANALYSIS

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Background: Proton Pump Inhibitors (PPIs) are frequently prescribed during inpatient hospitalizations, often initiated empirically for stress ulcer prophylaxis. In patients hospitalized with Alcohol-associated Hepatitis (AH), the choice of acid suppression carries particular significance given the compromised hepatic reserve, systemic inflammation, and susceptibility to infectious complications. Despite the prevalence of PPI prescribing in this setting, comparative effectiveness data against H2-receptor antagonists (H2RAs) in AH remain limited. **Methods:** Using TriNetX (111 healthcare organizations), we identified adult patients hospitalized with AH (ICD-10 K70.1) between January 2015 and January 2026 receiving either a PPI (n = 6,008) or H2RA (n = 677) within 7 days of admission. Patients with prior GI bleeding, peptic ulcer disease, or prior use of the comparator agent were excluded. Propensity score matching on 33 characteristics—including demographics, sepsis, liver fibrosis/cirrhosis, disease severity markers (bilirubin, INR, creatinine, sodium), and baseline medications—yielded matched cohorts of 673 patients each with standardized mean difference (SMD) < 0.1. Outcomes including composite hepatic decompensation, ascites, hepatic encephalopathy (HE), mortality, pneumonia, and renal impairment were assessed at 90 days, 6 months, and 1 year. **Results:** PPI-treated patients demonstrated significantly worse outcomes across all time points. At 90 days, PPI use was associated with higher risks of ascites (RR 2.74, p < 0.001) and mortality (RR 1.57, p = 0.001). At 6 months, PPI patients had higher rates of composite decompensation (RR 1.87, p = 0.039), ascites (RR 2.86, p < 0.001), HE (RR 3.22, p < 0.001), mortality (RR 1.46, p = 0.002), pneumonia (RR 3.00, p = 0.001), and renal impairment (RR 3.72, p < 0.001). At 1 year, all differences remained significant, with notably elevated risks of renal impairment (RR 4.03), HE (RR 3.30), and pneumonia (RR 2.40). Kaplan-Meier analysis confirmed lower event-free survival in the PPI cohort across all outcomes (log-rank p < 0.05). **Conclusion:** In a large propensity-matched cohort of hospitalized AH patients, PPI use was associated with substantially worse hepatic, infectious, and renal outcomes compared to H2RAs at all follow-up intervals. These findings suggest H2RAs may represent a safer alternative for acid suppression in this population and challenge the routine empiric use of PPIs during AH hospitalizations.

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3142 | RISK OF DEVELOPING ALCOHOL-ASSOCIATED LIVER DISEASE IN PATIENTS WITH ALCOHOL USE DISORDER IN THE UNITED STATES

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Background: Patients with alcohol use disorder (AUD) are at elevated risk for alcohol-associated liver disease (ALD), but real-world estimates of ALD incidence and determinants are limited. We estimated risk of developing ALD among patients with AUD and identified factors associated with incident ALD. **Methods:** We used the Oracle Health Real World Data, a nationally representative database comprising over 100 million U.S. adults, to identify adults with hospital or outpatient encounters for alcohol use disorder (AUD) and/or alcohol-associated liver disease (ALD) between January 2015 and April 2025. For incidence analyses, adults with AUD were identified using ICD-9/10 codes, and AUD index dates were defined as the first qualifying encounter. Adults with prior ALD and those with AUD or ALD evidence during a 12-month baseline period before the index date were excluded. Non-AUD controls were matched 3:1 to AUD patients by age, sex, U.S. region, and race/ethnicity. Incident ALD was assessed after the AUD index date. Annual age-adjusted prevalence estimates of ALD and cardiometabolic risk factors were calculated. Cumulative incidence, incidence rates per 100 person-years, and Fine-Gray subdistribution hazard ratios (sHRs) were estimated, with death and liver transplantation treated as competing events. **Results:** The matched cohort included 1,106,101 AUD patients and 3,318,303 non-AUD controls. Among AUD patients, ALD developed in 231,987 (20.9%) compared with 175,966 (5.3%) controls. The crude ALD incidence rate was 1.69 per 100 person-years (95% CI, 1.67–1.70). Compared with AUD patients who did not develop ALD, those who developed ALD were more frequently male (67.6% vs 55.0%), aged 40–64 years (58.7% vs 47.3%), and had higher prevalences of chronic hepatitis C (12.4% vs 4.8%), diabetes (19.8% vs 14.9%), and hypertension (43.7% vs 37.9%).In multivariable analyses among patients with AUD (Table 1), the strongest predictors of developing ALD were chronic hepatitis C (aHR 2.45, 95% CI 2.31–2.59), age 40–54 years (aHR 1.78, 95% CI 1.74–1.82), American Indian race/ethnicity (aHR 1.68, 95% CI 1.62–1.74), chronic hepatitis B (aHR 1.41, 95% CI 1.13–1.76), and heart failure (aHR 1.31, 95% CI 1.26–1.37). Diabetes and hypertension were also associated with increased risk. Conversely, GLP-1–based therapies (aHR 0.50, 95% CI 0.45–0.56) and statin use (aHR 0.58, 95% CI 0.57–0.60) were associated with lower ALD risk. **Conclusion:** In a nationally representative US real-world cohort, more than 7% of patients with AUD developed ALD within 5 years. Chronic viral hepatitis and cardiometabolic comorbidities were major risk factors, whereas GLP-1–based therapies and statin use were associated with substantially lower ALD risk. These findings identify potentially modifiable factors that may help guide risk stratification and prevention efforts and warrant prospective evaluation of metabolic therapies for ALD risk

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reduction.

Table 1. Predictors for developing ALD among AUD patients

	Unadjusted sHR (95% CI)	Adjusted sHR (95% CI)
Age, categorical (reference, under 40)		
40-54	1.78(1.74-1.82)	1.78(1.74-1.82)
55-64	1.66(1.62-1.70)	1.65(1.61-1.69)
65 and older	0.78(0.76-0.80)	0.76(0.74-0.79)
Gender (reference, male)		
Female	0.68(0.67-0.69)	0.72(0.71-0.74)
Race/ethnicity (reference, Non-Hispanic White)		
Hispanic	1.25(1.22-1.28)	1.09(1.06-1.12)
Black	0.78(0.76-0.81)	0.71(0.69-0.74)
Asian	1.03(0.92-1.14)	0.88(0.79-0.98)
American Indian	2.01(1.94-2.08)	1.68(1.62-1.74)
U.S. Census Region (reference, Midwest)		
Northeast	0.82(0.80-0.85)	0.85(0.83-0.88)
South	1.15(1.12-1.18)	1.16(1.13-1.19)
West	1.29(1.27-1.32)	1.23(1.20-1.26)
Other Liver Disease		
Chronic Hepatitis B	1.92(1.55-2.39)	1.41(1.13-1.76)
Chronic Hepatitis C	2.32(2.19-2.45)	2.45(2.31-2.59)
Comorbidities		
Diabetes mellitus	1.08(1.06-1.11)	1.11(1.07-1.15)
Hypertension	1.01(1.00-1.03)	1.14(1.12-1.16)
Obesity	0.94(0.92-0.95)	0.88(0.86-0.90)
Cardiovascular Disease	0.80(0.79-0.82)	0.84(0.82-0.86)
Heart Failure	1.04(1.00-1.08)	1.31(1.26-1.37)
Chronic Kidney Disease	0.85(0.82-0.89)	0.96(0.92-1.01)
Hypothyroidism	0.73(0.71-0.76)	0.91(0.88-0.94)
Other medications		
Any AUD medical treatment	1.03(1.01-1.06)	1.14(1.12-1.17)
Metformin	0.95(0.91-0.98)	0.96(0.92-1.01)
Insulin	1.19(1.16-1.22)	1.23(1.19-1.27)
Any GLP-1-based therapies	0.49(0.44-0.55)	0.50(0.45-0.56)
Any statin use	0.60(0.59-0.62)	0.58(0.57-0.60)
Follow-up time	0.95(0.95-0.95)	0.93(0.93-0.94)
Psychiatric Category		
Major Depression	0.64(0.62-0.65)	0.76(0.74-0.78)
Bipolar Disorder	0.48(0.45-0.50)	0.59(0.56-0.62)
Anxiety Disorder	0.71(0.70-0.73)	0.89(0.87-0.91)
Substance use Disorder / Drug Use (other than AUD)	0.59(0.58-0.61)	0.58(0.57-0.60)

Disclosures: George Cholankeril:Nothing to Disclose, Robert Taylor:Nothing to Disclose, Ramzi Argoubi: Nothing to Disclose, Fasiha Kanwal:Nothing to Disclose, Aaron Thrift:Nothing to Disclose, Hashem El-Serag:Nothing to Disclose, Nothing to Disclose.

3143 | GRAPHENE OXIDE NANOPARTICLES MITIGATE ETHANOL-INDUCED LIVER INJURY BY MODULATING MIR 21, MIR-122 AND MIR-214–ASSOCIATED AUTOPHAGY PATHWAYS

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Background: Alcohol-associated liver disease (ALD) is characterized by hepatic lipid accumulation, inflammation, and impaired autophagy, leading to progressive liver injury. Dysregulation of microRNAs (miRNAs), including miR-21, miR-122, and miR-214, plays a key role in regulating lipid metabolism and inflammatory responses during ethanol-induced liver damage. Graphene oxide nanoparticles (GNPs) have emerged as biologically active nanomaterials with the potential to modulate cellular stress responses. This study aimed to evaluate whether GNPs mitigate ethanol-induced liver injury by restoring autophagy through miRNA modulation. **Methods:** In vitro studies were performed using HepG2 hepatocyte cells exposed to ethanol, followed by GNP treatment. The protective effects of GNPs were assessed using Oil Red O staining and analysis of autophagy and inflammation-associated mRNA expression. To assess in vivo relevance, male Wistar rats were fed a liquid diet containing 5% ethanol for 28 days. During the ethanol-feeding period, rats received oral administration of GNPs (10 mg/kg, water suspended) at 5-day intervals. Hepatic injury was evaluated using serum biochemical parameters, histopathological assessment, and lipid staining. Hepatic mRNA expression of autophagy- and inflammation-related genes, along with miRNA expression profiling (miR-21, miR-122, and miR-214), was performed at the end of the study. **Results:** Ethanol exposure induced significant lipid accumulation and suppression of autophagy associated mRNA expression in HepG2 cells, accompanied by increased inflammatory gene expression. GNP treatment markedly reduced intracellular lipid accumulation and restored autophagy-related mRNA expression. In vivo, chronic ethanol feeding resulted in hepatic steatosis, elevated serum biochemical markers of liver injury, and histological evidence of liver damage. GNP administration significantly attenuated these effects, reducing hepatic lipid accumulation and improving liver histology. Ethanol-induced dysregulation of hepatic miRNAs, characterized by decreased miR-122 and increased miR-21 and miR-214 expression, was normalized following GNP treatment. These changes were associated with restoration of autophagy-related mRNA expression and attenuation of inflammatory signalling. **Conclusion:** Graphene oxide nanoparticles mitigate ethanol-induced liver injury by modulating miR-21, miR-122, and miR-214–associated autophagy pathways. These findings support GNPs as a protective nanoplatform for limiting disease progression in alcohol-associated liver disease.

Disclosures: Hiral Aghara:Nothing to Disclose, Palash Mandal:Nothing to Disclose.

3144 | TRENDS AND CLINICAL CORRELATES OF PHOSPHATIDYLETHANOL TESTING DURING LIVER TRANSPLANT EVALUATION

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Background: Phosphatidylethanol (PEth) is a highly sensitive direct biomarker of recent alcohol use and is increasingly used during liver transplant evaluation. However, patterns of PEth testing and associations with transplant evaluation outcomes remain incompletely described. We evaluated PEth testing practices, patient-level predictors of testing, and associations between PEth results and waitlisting/transplantation among adults undergoing liver transplant evaluation at a large academic transplant center. **Methods:** We performed a retrospective cohort study of adults undergoing initial liver transplant evaluation from 2016-2026. PEth testing was defined as any PEth assay obtained within ±90 days of evaluation. PEth results were categorized as no PEth, negative/<20 ng/mL, 20-199 ng/mL, and ≥200 ng/mL. Patient demographics, metabolic comorbidities, liver disease etiology, evaluation setting, waitlisting, and transplantation outcomes were extracted from institutional transplant and EHR data. Multivariable logistic regression assessed predictors of PEth testing and associations between PEth category and transplant outcomes. **Results:** Among 3,028 liver transplant evaluation patients, 874 (28.9%) underwent PEth testing within ±90 days. Among tested patients, 719 (82.3%) were negative/<20 ng/mL, 97 (11.1%) had PEth 20-199 ng/mL, and 55 (6.3%) had PEth ≥200 ng/mL; 3 results were uninterpretable. PEth testing was more common among patients with ALD or MetALD and among those evaluated in inpatient/recent inpatient settings. In multivariable analysis, compared with HCV, PEth testing was more likely among patients with MASLD, ALD, MetALD, and other/unknown liver disease, and less likely among outpatient evaluations. Listing decreased stepwise with increasing PEth category: 26.6% of patients with negative/<20 PEth were listed compared with 15.5% with PEth 20-199 ng/mL and 1.8% with PEth ≥200 ng/mL (**Table 1**). Transplantation similarly declined across PEth categories: 12.1%, 6.2%, and 0%, respectively. After adjustment, PEth ≥20 ng/mL was associated with lower odds of listing (OR 0.28, 95% CI 0.15-0.52) and transplantation (OR 0.20, 95% CI 0.07-0.56) among tested patients. **Conclusion:** In this single-center cohort of adults undergoing liver transplant evaluation, PEth testing was performed in approximately one-third of patients and was strongly associated with alcohol-related liver disease phenotypes and evaluation setting. Positive PEth results were associated with markedly lower likelihood of waitlisting and transplantation. These findings highlight the growing role of PEth in transplant evaluation and support further study of how biomarker-based alcohol assessment influences candidate selection, equity, and transplant outcomes.

Table - PEth Testing Results and Transplant Outcomes Among Adults Undergoing Liver Transplant Evaluation

Key measure	Result
Total liver transplant evaluations	3,028
PEth checked within ±90 days	874 / 3,028 (28.9%)
No PEth checked	2,154 / 3,028 (71.1%)
Negative / <20 ng/mL among tested	719 / 874 (82.3%)
PEth 20–199 ng/mL among tested	97 / 874 (11.1%)
PEth ≥200 ng/mL among tested	55 / 874 (6.3%)
Listed: negative / <20	26.6%
Listed: PEth 20-199	15.5%
Listed: PEth ≥200	1.8%
Transplanted: negative / <20	12.1%
Transplanted: PEth 20-199	6.2%
Transplanted: PEth ≥200	0.0%
Adjusted OR for listing, PEth ≥20 vs <20	0.28 (95% CI 0.15-0.52)
Adjusted OR for transplant, PEth ≥20 vs <20	0.20 (95% CI 0.07-0.56)

Disclosures: Natalia Salinas Parra:Nothing to Disclose, Marina Serper:Transplant Genomics: Grant/Research Support, Grifols: Grant/Research Support, Nadim Mahmud:Nothing to Disclose.

3145 | DOES STANDARD DRINK SIZE INFLUENCE HEAVY EPISODIC DRINKING? A CROSS-NATIONAL MULTIVARIABLE ECOLOGICAL ANALYSIS

Kriti Soni[1] Rylyn Reyes[1] Ximena Parraga[1] Denisse Rubio Cruz[2] S. Fisher Rhoads[1] Adelina Horhat[3] Hyundam (Dami) Gu[1] Joshua Chen[1] Vinay Jahagirdar[1] Kavin Parmar[1] Krishan Patel[1] Stephen Hoang[1] Luis Díaz[4] Juan Pablo Arab[1], [1]Virginia Commonwealth University, [2]Lahey Hospital; Virginia Commonwealth University, [3]Department of Hepatology, Henri Mondor University Hospital, [4]Pontificia Universidad Católica de Chile

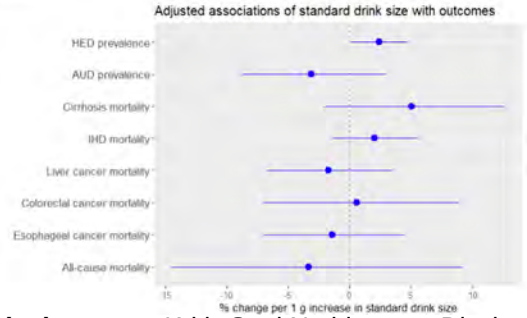
Background: Standard drink definitions are central to quantifying alcohol exposure in epidemiologic surveillance, clinical guidance, and alcohol control policies, yet they vary widely across countries. Because thresholds for heavy drinking and self-reported alcohol intake are commonly framed in “drinks,” larger national drink definitions may alter population-level estimates of alcohol exposure and drinking behavior. Whether variation in standard drink size is associated with heavy episodic drinking and alcohol-related outcomes has not been systematically evaluated. **Methods:** Data were obtained from the 2024 WHO Global Status Report on Alcohol and Health,the WHO Global Information System on Alcohol and Health, the World Bank, and

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national guidelines. Disease prevalence and mortality data were obtained from the Global Health Data Exchange from the years 2017-2023, excluding 2020 and 2021. Unadjusted and multivariable linear regression models were used to assess the relationship between national standard drink size (in grams of ethanol) and the following outcomes across 64 countries: heavy episodic drinking (HED) prevalence, alcohol use disorder (AUD) prevalence, cirrhosis mortality, and other alcohol-attributable outcomes. Multivariable models adjusted for alcohol per capita consumption (APC), GDP per capita (log-transformed), GINI coefficient, and WHO region. Robust standard errors were used to address heteroskedasticity in the regression. Within-region analyses were conducted to evaluate whether associations were driven by between-region variation. **Results:** In the unadjusted models, standard drink size was not significantly associated with any outcome. After multivariable adjustment, standard drink size was positively associated with HED prevalence (?? = 0.651, robust p = 0.048). The HED estimate was minimally impacted by APC adjustment (?? = 0.702 without vs. ?? = 0.651 with APC included), suggesting independence from total consumption volume. The cirrhosis mortality association was positive in the conventional model (?? = 0.049, p = 0.039) but attenuated to non-significance with robust standard errors (robust p = 0.178). No significant associations were observed for AUD prevalence, IHD, liver cancer, colorectal cancer, esophageal cancer, or all-cause mortality. Within-region analyses indicated no significant association between standard drink size and HED in any WHO region, indicating overall association was driven by between-region variation. **Conclusion:** Our findings show that a 1g increase in a country's standard drink definition is associated with an increase in HED prevalence by 0.65%. There is an association between a country's standard drink size and cirrhosis mortality.

Figure 1. Forest plot for adjusted association of standard drink definition (per 1 g increase) with each outcome.



Disclosures: Kriti Soni:Nothing to Disclose, Rylyn Reyes:Nothing to Disclose, Ximena Parraga:Nothing to Disclose, Denisse Rubio Cruz:Nothing to Disclose, S. Fisher Rhoads:Nothing to Disclose, Adelina Horhat: Nothing to Disclose, Hyundam (Dami) Gu:Nothing to Disclose, Joshua Chen:Nothing to Disclose, Vinay Jahagirdar:Nothing to Disclose, Kavin Parmar:Nothing to Disclose, Krishan Patel:Nothing to Disclose, Stephen Hoang:PS Fertility: Consultant, Remedy Plan Inc. Consultant, Luis Díaz:Nothing to Disclose, Juan Pablo Arab:Nothing to Disclose.

3146 | DETECTING ALCOHOL-RELATED LIVER DISEASE IN INDIVIDUALS WITH ALCOHOL USE DISORDER: A SYSTEMATIC REVIEW AND META-ANALYSIS

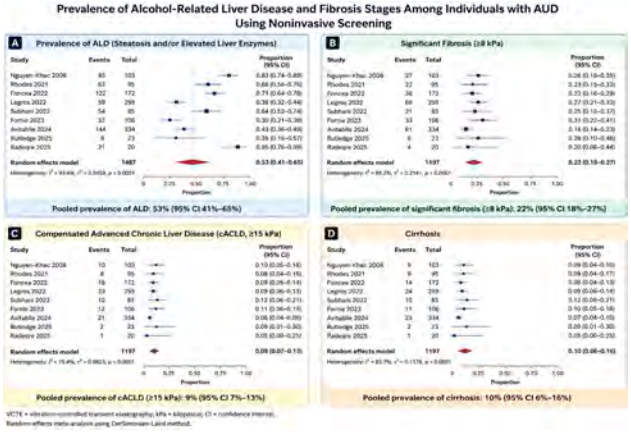
David Maundu[1] Mohamed Omar[2] Manisha Verma[3] Aleksander Krag[4] Zobair Younossi[5] Mary Rinella[6] Winston Dunn[7] Ashwani Singal[8], [1]University of Kansas School of Medicine–Wichita,, [2]University of Kansas School of Medicine–Wichita, [3]SKMC, Thomas Jefferson University, [4]University of Southern Denmark, [5]The Global NASH/MASH Council, [6]The University of Chicago, [7]University of Kansas Medical Center, [8]University of Louisville

Background: Alcohol-associated liver disease (ALD) in individuals with alcohol use disorder (AUD) frequently presents at an advanced stage with cirrhosis and /or complications. Detecting ALD at an early stage and controlling AUD prevents the development of cirrhosis. This systematic review and meta-analysis aims to determine the prevalence and stage of inapparent ALD through noninvasive screening in individuals with AUD **Methods:** A literature search using Embase and PubMed through April 2026 was performed for studies on adults with AUD receiving noninvasive fibrosis assessment (kilopascals, kPa), primarily by vibration-controlled transient elastography (VCTE), were included. Data were pooled for a) prevalence of ALD defined by steatosis and/or elevated liver enzymes, b) ALD fibrosis stage [significant fibrosis, ≥8 kPa; compensated advanced chronic liver disease or cACLD, ≥15 kPa; and cirrhosis], c) follow-up in a liver clinic, d) abstinence, and e) mortality. Random-effects meta-analysis was performed using Der Simonian–Laird models. Heterogeneity was evaluated using the I^2 statistic. **Results:** 24 studies (12 abstracts) on 53,156 individuals with AUD were included. The pooled prevalence of ALD was 53% (95% CI 41%–65%). Fibrosis stage, assessed with VCTE, was 22% (18–27%) for significant fibrosis, 9% (7–13%) for cACLD, and 10% (6–16%) for cirrhosis. The detection yield was higher in inpatient settings compared to addiction services (48% versus 35%). All analyses showed heterogeneity (I^2 > 50%), which was

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reduced after excluding outliers, and when comparing abstracts vs. full-text publications, with the estimates remaining similar. Further, screening for ALD was associated with liver clinic follow-up in 68% (49–82%) of cases and abstinence at follow-up in 38% (31–45%) of cases. In three studies, a repeat VCTE after abstinence showed a mean reduction of 0.62 (0.34-0.91) kPa. The mortality rate, based on two studies with a median follow-up period of 10.5 months, was 40 per 1000 person-years. Screening was consistently associated with reductions in alcohol consumption; however, heterogeneity among studies prevented pooled quantitative estimates (Figure 1). **Conclusion:** Noninvasive fibrosis screening among individuals with AUD offers benefits beyond detection by facilitating linkage to care and encouraging behavioral change. These results support an approach to enable earlier disease detection and potentially modify disease progression.



Disclosures: David Maundu:Nothing to Disclose, Mohamed Omar:Nothing to Disclose, Manisha Verma: Nothing to Disclose, Aleksander Krag:Nothing to Disclose, Zobair Younossi:Zobair M. Younossi is a consultant or has received research: Consultant, madrigal: Grant/Research Support, Siemens: Research funding, GSK: Consultant, BI: Consultant, Sanofi: Research funding, Mary Rinella:akero: Consultant, akero: Consultant, 89Bio: Consultant, 89Bio: Consultant, Boehringer Ingelheim: Consultant, Boehringer Ingelheim: Consultant, Cytodyn: Consultant, Cytodyn: Consultant, Echosens: Consultant, Echosens: Consultant, Histoindex: Consultant, Histoindex: Consultant, Intercept: Consultant, Intercept: Consultant, Madrigal: Consultant, Madrigal: Consultant, GSK: Consultant, GSK: Consultant, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Eli Lilly: Consultant, Eli Lilly: Consultant, Takeda: Consultant, Takeda: Consultant, Sagimet: Consultant, Sagimet: Consultant, Sonic Incytes: Consultant, Sonic Incytes: Consultant, NGM Bio: Consultant, NGM Bio: Consultant, Regeneron: Consultant, Boston Pharma: Consultant, Eccogene: Consultant, Inventiva: Consultant, Sagimet: Consultant, Madrigal: Consultant, akero: Consultant, akero: Consultant, 89Bio: Consultant, 89Bio: Consultant, Boehringer Ingelheim: Consultant, Boehringer Ingelheim: Consultant, Cytodyn: Consultant, Cytodyn: Consultant, Echosens: Consultant, Echosens: Consultant, Histoindex: Consultant, Histoindex: Consultant, Intercept: Consultant, Intercept: Consultant, Madrigal: Consultant, Madrigal: Consultant, GSK: Consultant, GSK: Consultant, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Eli Lilly: Consultant, Eli Lilly: Consultant, Takeda: Consultant, Takeda: Consultant, Sagimet: Consultant, Sagimet: Consultant, Sonic Incytes: Consultant, Sonic Incytes: Consultant, NGM Bio: Consultant, NGM Bio: Consultant, Regeneron: Consultant, Boston Pharma: Consultant, Eccogene: Consultant, Inventiva: Consultant, Sagimet: Consultant, Madrigal: Consultant, Winston Dunn:Nothing to Disclose, Ashwani Singal:Madrigal: Speaking and Teaching, Pleiogenix: Stock – privately held company, Pleiogenix: Consultant, CLD Foundation: Advisor, Medical Speaker's Network: Speaking and Teaching, Up-to-Date: Royalties or patent beneficiary, Medscape: Speaking and Teaching, University of Louisville School of Medicine: Employee, NIAAA: Grant/Research Support, Gastro Endo News: Executive role, Durect: Advisor, University of Louisville Health: Other.

3147 | PREDICTORS OF ABSTINENCE AT ONE-YEAR FOLLOW UP IN A MULTIDISCIPLINARY ALCOHOL-ASSOCIATED LIVER DISEASE CLINIC

Andrew Turunen[1] Patrick Kittredge[1] Bikrum Chahal[1] Fauzia Hollnagel[1] Jessica Musto[1] Margarita German[1], [1]University of Wisconsin

Background: Alcohol-associated liver disease (ALD) is a leading cause of liver-related mortality in the US. Alcohol abstinence is the strongest predictor of survival in ALD. Multidisciplinary care models integrating hepatology and addiction medicine improve outcomes; however, predictors of sustained abstinence remain poorly defined. We aimed to compare baseline and treatment-related factors among patients who achieved abstinence at one-year follow up versus those that had ongoing alcohol use in a multidisciplinary ALD clinic. **Methods:** We performed a retrospective cohort study of patients evaluated at a single-center multidisciplinary ALD clinic. Baseline demographic, psychiatric, substance use, liver disease severity, and treatment-related variables were compared between patients who were abstinent versus those who had ongoing alcohol use at 1 year follow up (+/-45 days). Patients meeting criteria for early or sustained remission from AUD

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were categorized as achieving abstinence. Continuous and categorical variables were compared using chi-squared or Fisher's exact testing. Univariable logistic regression identified variables associated with abstinence and were incorporated into multivariable regression modeling. **Results:** Forty-eight patients met inclusion criteria, 27 (56.3%) were abstinent at follow-up and 21 (43.7%) continued drinking. Abstinent patients had significantly higher baseline MELD-Na scores compared to patients who continued drinking (15.2 ± 4.9 vs. 11.9 ± 4.4, p = 0.02). Emergency department (ED) visits were significantly lower among abstinent patients (2.3 ± 3.3 vs. 5.4 ± 6.5, p = 0.04). In univariable logistic regression, higher MELD-Na score was associated with increased odds of abstinence (OR 1.17, 95% CI 1.02–1.33, p = 0.026). Positive phosphatidylethanol (PEth) testing at follow-up was more common among patients who continued drinking as expected, however, 2 patients who reported abstinence had a positive PEth (12 (70.6%) vs. 2 (11.1%), p < 0.001). Sex, race, marital status, use of medication-assisted therapy for AUD, among other variables were not independent predictors of abstinence. **Conclusion:** In this multidisciplinary ALD clinic cohort, 56% of patients achieved alcohol abstinence at one year follow up. Abstinent patients demonstrated higher baseline MELD-Na scores and lower ED utilization, suggesting sustained abstinence may improve disease stability and reduce healthcare utilization. Although higher MELD-Na scores were associated with abstinence in univariable analyses, this relationship was attenuated after adjustment for behavioral and substance use-related variables. These findings support integrated hepatology-addiction medicine care models for management of patients with ALD.

Table 1. Univariable logistic regression predicting abstinence at follow-up

Variable	OR (95% CI)	*p*-value
DEMOGRAPHICS		
Age	0.98 (0.92–1.05)	0.575
Body mass index (BMI)	1.02 (0.91–1.14)	0.756
Male sex	0.44 (0.14–1.41)	0.169
PSYCHIATRIC COMORBIDITIES		
Anxiety	0.84 (0.27–2.64)	0.771
Depression	1.07 (0.34–3.37)	0.912
Trauma	0.23 (0.02–2.40)	0.220
Tobacco use disorder	0.39 (0.11–1.30)	0.123
LIVER DISEASE SEVERITY		
Ascites	3.14 (0.93–10.58)	0.065
Variceal bleed	2.10 (0.47–9.36)	0.331
Hepatic encephalopathy	1.30 (0.41–4.16)	0.658
MELD-Na score	1.17 (1.02–1.33)	0.026*
AUD TREATMENT HISTORY		
Past behavioral AUD treatment	0.53 (0.15–1.90)	0.330
Past use of MAT	1.38 (0.42–4.51)	0.599
Current MAT use at initial evaluation	0.73 (0.23–2.28)	0.585
VALIDATED SCALES		
PHQ-8	0.96 (0.87–1.06)	0.431
DAST-10	0.83 (0.57–1.21)	0.336
GAD-7	0.99 (0.90–1.08)	0.838
HEALTHCARE UTILIZATION		
Emergency room admissions	0.87 (0.76–1.01)	0.062

* Statistically significant ($p < 0.05$)
Abbreviations: AUD, alcohol use disorder; DAST-10, Drug Abuse Screening Test; GAD-7, Generalized Anxiety Disorder 7-item scale; MAT, medication-assisted treatment; MELD-Na, Model for End-Stage Liver Disease–Sodium; OR, odds ratio; PHQ-8, Patient Health Questionnaire 8-item scale.

Disclosures: Andrew Turunen:Nothing to Disclose, Patrick Kittredge:Nothing to Disclose, Bikrum Chahal: Nothing to Disclose, Fauzia Hollnagel:Nothing to Disclose, Jessica Musto:Nothing to Disclose, Margarita German:Nothing to Disclose.

3148 | PROJECTED TRENDS IN ALCOHOL CONSUMPTION AND ALCOHOL USE DISORDER AMONG U.S. ADULTS THROUGH 2050: A MICROSIMULATION ANALYSIS

Ha Tran[1] Michael Rothberg[2] Katharine Bradley[3] Daniel Jonas[4] Olajide Adekunle[2] Phuc Le[2] Srinivasan Dasarathy[2], [1]Cleveland Clinic Foundation, [2]Cleveland Clinic, [3]Kaiser Permanente Washington, [4]The Ohio State University Wexner Medical Center

Background: Alcohol Use Disorder (AUD) affects 29.5 million U.S. adults and contributes substantially to preventable morbidity and mortality. However, long-term national projections of alcohol consumption patterns and AUD burden across demographic subgroups are limited. This study projected alcohol consumption and AUD prevalence among U.S. adults through 2050 to identify subgroups likely to bear a disproportionate future burden. **Methods:** We developed an individual-level state-transition microsimulation model with annual cycles to follow the US adult population through 2050. The model incorporated population turnover using US Census Bureau projections, transitions across drinking states defined by WHO drinking risk levels (abstinence, low, moderate, high, very high), and transitions across AUD severity states (mild, moderate, severe). Transition probabilities were derived from 7 waves of the Population Assessment of Tobacco and Health and waves 1-2 of the National Epidemiologic Survey on Alcohol and Related Conditions. The model was also calibrated to 2002-2009 National Survey on Drug Use and Health and validated against 2010-2023 NSDUH. COVID-19 disruptions were incorporated using year-specific adjustments to 2020-2021 drinking transitions. **Results:** Model projections showed good agreement with observed 2010-2023 NSDUH estimates for drinking levels and AUD prevalence. The model projected that the number of adult drinkers would increase from 111.3 million in 2024 to 125.6 million in 2050, driven by growth in low-risk drinking which accounted for 90% of net new drinkers. At the same time, the number of adults with AUD was projected to reach 33.1 million (11.3%) by 2050, increasing from 28.2 million (10.8%) in 2024. Severe AUD increased by 60.8% from 4.5 million to 7.2 million. AUD prevalence was projected to decrease among adults aged 18-25 years, from 22.3% to 14.1%, but to more than double among those ≥ 50 years, from 4.2% to 10.4%. AUD prevalence also increased faster among males than females, widening the sex gap from 2.6 to 6.8 percentage points. By 2050, males accounted for 64.7% of the total AUD burden. **Conclusion:** AUD burden is projected to rise through 2050, driven by a growth in severe AUD and a shift toward adults aged ≥ 50 years.

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Future alcohol-related prevention, screening, and treatment efforts should focus on severe AUD, males, and middle-aged and older adults.

Disclosures: Ha Tran:Nothing to Disclose, Michael Rothberg:Moderna: Stock - publicly traded company, Katharine Bradley:Nothing to Disclose, Daniel Jonas: Nothing to Disclose, Olajide Adekunle:Nothing to Disclose, Phuc Le:Nothing to Disclose, Srinivasan Dasarathy:Nothing to Disclose.

3149 | PETH-DEFINED HEAVY ALCOHOL USE AND OBESITY: A DUAL-HIT STEATOTIC PHENOTYPE IN ALCOHOL USE DISORDER

Omar Albhaisi[1] Monica Melmer[1] Anna Peyton[1] Hannah Kissel-Smith[1] Brandon Wills[1] Matthew Way[1] Megan Lemay[1] Andy Pinson[1] Crystal Watts[1] Chareece Williams[1] Tara Kilman[1] Brian Singh[1] James White[1] Gerry Moeller[1] Juan Pablo Arab[1], [1]Virginia Commonwealth University

Background: Alcohol-associated liver disease (ALD) frequently overlaps with metabolic risk, but the combined relationship of objective alcohol exposure and adiposity with VCTE CAP-defined steatosis is not well defined. We evaluated whether PEth-defined heavy alcohol use and obesity identify a high-steatosis phenotype in patients with alcohol use disorder (AUD). **Methods:** We analyzed patients enrolled in the MOTIVATE Clinic, an outpatient substance use treatment program providing addiction medicine, behavioral health, peer recovery, and care coordination services. All patients underwent VCTE with CAP measurement and BMI assessment. PEth was categorized per local laboratory reference ranges as <20 ng/mL, 20–200 ng/mL, and >200 ng/mL, with >200 indicating heavy or chronic alcohol use. Obesity was defined as BMI ≥ 30 kg/m². The primary steatosis threshold was CAP ≥ 248 dB/m; CAP ≥ 263 and ≥ 275 dB/m were evaluated as sensitivity thresholds. **Results:** We included 94 patients with AUD and available VCTE CAP and BMI; PEth was available in 89 patients. Among patients with PEth, 37 had PEth <20, 17 had PEth 20–200, and 35 had PEth >200 ng/mL. CAP-defined steatosis (≥ 248 dB/m) increased stepwise across PEth categories: 21.6%, 23.5%, and 62.9%, respectively; median CAP also differed across PEth categories (Kruskal-Wallis $p = 0.002$). A stepwise gradient was also observed across combined PEth-obesity phenotypes: 18.4% (PEth ≤ 200 + BMI <30, $n = 38$), 31.2% (PEth ≤ 200 + BMI ≥ 30, $n = 16$), 52.4% (PEth >200 + BMI <30, $n = 21$), and 78.6% (PEth >200 + BMI ≥ 30, $n = 14$). The dual-hit group had the highest median CAP compared with the reference group (285 vs 202 dB/m). Findings were directionally consistent at CAP ≥ 263 and ≥ 275 dB/m. **Conclusion:** In patients with AUD, PEth-defined heavy alcohol use and obesity identify a dual-hit steatotic phenotype with markedly higher CAP-defined steatosis burden. These findings support systematic combined PEth and BMI assessment for steatosis risk stratification in integrated hepatology-addiction care.

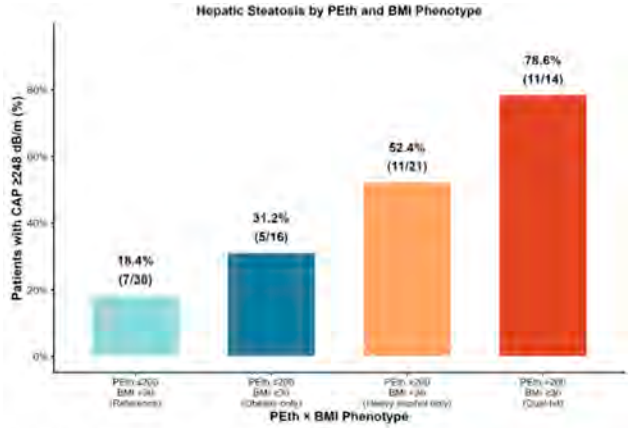


Figure 2. CAP-defined steatosis by PEth and BMI phenotype.
Proportion of patients with hepatic steatosis, defined as CAP ≥248 dB/m, across combined PEth and BMI phenotypes. CAP-defined steatosis increased stepwise from PEth ≤200/BMI <30 to PEth >200/BMI ≥30, reaching 78.6% in the dual-hit group.

Disclosures: OMAR ALBHAISI:Nothing to Disclose, Monica Melmer:Nothing to Disclose, Anna Peyton: Nothing to Disclose, Hannah Kissel-Smith:Nothing to Disclose, Brandon Wills:Nothing to Disclose, Matthew Way:Nothing to Disclose, Megan Lemay:Nothing to Disclose, Andy Pinson:Nothing to Disclose, Crystal Watts:Nothing to Disclose, Chareece Williams:Nothing to Disclose, Tara Kilman:Nothing to Disclose, Brian Singh:Nothing to Disclose, James White:Nothing to Disclose, Gerry Moeller:Nothing to Disclose, Juan Pablo Arab:Nothing to Disclose.

3150 | PHOSPHATIDYLETHANOL-BASED VALIDATION OF SELF-REPORTED ALCOHOL MEASURES AND CHARACTERIZATION OF UNDERREPORTING IN EARLY ALCOHOL-ASSOCIATED LIVER DISEASE

Elias Rady[1] Thomas Cotter[1] Ahmad Anouti[1] Thomas Kerr[1] Samer Gawrieh[2] Amit Singal[1] Mack Mitchell[1], [1]University of Texas Southwestern Medical Center, [2]Indiana University School of Medicine

Background: Underreporting of alcohol intake is common in steatotic liver disease (SLD) and contributes to misclassification of SLD subtypes. Phosphatidylethanol (PEth), a biomarker of recent alcohol use,

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has emerged as an objective tool to complement self-report, but the clinicodemographic and psychosocial factors associated with underreporting remain poorly characterized. **Methods:** We performed a cross-sectional analysis of the Dallas Dionysus Study, a prospective early ALD/MetALD cohort at UT Southwestern Medical Center and Parkland Health. Eligible participants had hepatic steatosis, ALT > 33 U/L in men or > 25 U/L in women, and alcohol intake > 210 g/week in men or > 140 g/week in women within the prior 2 years; those with hepatic decompensation were excluded. At the research visit, participants completed standardized alcohol-use questionnaires, including AUDIT-C, Timeline Followback (TLFB), beverage-specific quantity-frequency (BSQF), and Lifetime Drinking History (LDH), and underwent same-day PEth testing. Alcohol use disorder (AUD) severity was assessed via SCID-5. Psychosocial questionaires included B-IPQ (illness perception), PHQ-8 (depression), GAD-7 (anxiety), ISI (insomnia), UCLA Loneliness Scale, and GBMMS (medical mistrust). Underreporting was defined as a TLFB drinking category (no/light < 2, moderate 2–< 4, heavy ≥ 4 drinks/day) below the corresponding PEth category (< 20, 20–199, ≥ 200 ng/mL). Clinicodemographic correlates of underreporting were identified using multivariable logistic regression. Correlation between PEth and each self-report measure were assessed by Spearman correlation. Psychosocial scores were compared between underreporters and accurate reporters using Mann-Whitney U. **Results:** Among 93 participants, 82.8% were men, median age was 46 years (IQR 36–57). PEth correlated moderately with AUDIT-C ($\rho = 0.66$), BSQF ($\rho = 0.62$), and TLFB ($\rho = 0.60$), and weakly with physician-documented intake ($\rho = 0.54$) and LDH ($\rho = 0.44$). AUDIT-C had the highest accuracy for detecting PEth ≥ 20 ng/mL at a cutoff ≥ 3 (sensitivity 92%, specificity 83%) and PEth ≥ 200 ng/mL at a cutoff ≥ 8 (sensitivity 76%, specificity 83%). Concordance between PEth and TLFB was 63.4%; 31 participants (33.3%) underreported, whereas overreporting was uncommon (3.2%). PEth reclassified 17 participants with MASLD and 6 with MetALD as ALD. Underreporting was associated with female sex (aOR 5.78 CI 1.61–20.72) and inversely associated with severe AUD (aOR 0.30 CI 0.09–0.95) (Table 1). Underreporters had lower perceived illness threat (B-IPQ; $p < 0.01$), depression (PHQ-8; $p = 0.05$), and insomnia (ISI; $p = 0.04$) scores than accurate reporters. **Conclusion:** Underreporting is prevalent in early ALD and MetALD, particularly among patients with less severe AUD, lower illness awareness, and lower psychosocial burden. Identifying this profile can facilitate targeted alcohol assessment and timely engagement with AUD-directed care.

Table 1. Factors Associated with Underreported Alcohol Use

	Univariable		Multivariable	
Variable	**OR (95% CI)**	**p**	**aOR (95% CI)**	**p**
Demographics				
Age, per year	1.05 (1.01–1.08)	**0.005**	1.01 (0.96–1.06)	0.795
Female sex	3.21 (1.07–9.70)	**0.043**	5.78 (1.61–20.72)	**0.008**
Hispanic	0.47 (0.17–1.32)	0.225	—	—
White	1.07 (0.45–2.54)	1.000	—	—
Black	1.79 (0.50–6.42)	0.497	—	—
Medicare insurance	5.90 (1.94–17.88)	**0.002**	4.01 (0.86–18.65)	0.076
Family history of AUD	0.73 (0.30–1.79)	0.508	—	—
College education or higher	1.22 (0.42–3.48)	0.787	—	—
Annual income ≥$50,000	1.82 (0.75–4.42)	0.269	—	—
Unemployed or disabled	0.68 (0.26–1.78)	0.484	—	—
Clinical Characteristics				
BMI ≥30 kg/m²	0.63 (0.24–1.65)	0.481	—	—
Severe AUD (DSM-V)	0.24 (0.10–0.61)	**0.003**	0.30 (0.09–0.95)	**0.041**
Advanced fibrosis	0.93 (0.36–2.38)	1.000	—	—
Hypertension	1.79 (0.75–4.29)	0.197	—	—
Type 2 diabetes	0.47 (0.09–2.34)	0.487	—	—
Dyslipidemia	1.73 (0.71–4.19)	0.258	—	—

P values are calculated using multivariable logistic regression. Variables associated with underreporting at $p < 0.05$ in univariable analysis were entered into the multivariable logistic regression model. Bold values denote statistical significance at $p < 0.05$.

Abbreviations: aOR, adjusted odds ratio; AUD, alcohol use disorder; AUC, area under the receiver operating characteristic curve; BMI, body mass index; CI, confidence interval; OR, odds ratio; SCID-5, Structured Clinical Interview for DSM-5.

Disclosures: Elias Rady:Nothing to Disclose, Thomas Cotter:Nothing to Disclose, Ahmad Anouti:Nothing to Disclose, Thomas Kerr:Madrigal: Consultant, GSK: Grant/Research Support, Alnylam: Consultant, Salix: Consultant, Alexion: Grant/Research Support, Samer Gawrieh:Transmedics: Consultant, pfizer: Consultant, kowa: Consultant, spruce: Consultant, viking: Grant/Research Support, zydus: Grant/Research Support, dsm: Grant/Research Support, Sonicincytes: Grant/Research Support, Novo Nordisk: Consultant, GSK: Consultant, Amit Singal:Genentech: Consultant, AstraZeneca: Consultant, Bayer: Consultant, Eisai: Consultant, Exelixis: Consultant, Merck: Consultant, Elevar: Consultant, FujiFilm Medical Sciences: Consultant, Exact Sciences: Consultant, Glycotest: Consultant, Boston Scientific: Consultant, Sirtex: Consultant, HelioGenomics: Consultant, ImCare: Consultant, DELFI: Consultant, Curve Biosciences: Consultant, Catalym: Consultant, Verve: Consultant, Mack Mitchell: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose.

3151 | RECEIPT OF MEDICATIONS FOR ALCOHOL USE DISORDER IS INDEPENDENTLY ASSOCIATED WITH REDUCED 30 AND 90-DAY READMISSIONS FOR ALCOHOL-ASSOCIATED HEPATITIS

Krishan Patel[1] Vinay Jahagirdar[2] Omar Albhaisi[2] Husam Mikati[3] Shaanit Sen[4] Butros Fakhoury[1] Na Bo[5] Hannah Kissel-Smith[2] Juan Pablo Arab[1], [1]Virginia Commonwealth University, [2]VCU Medical Center,

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Background: Alcohol-associated hepatitis (AH) is a severe manifestation of alcohol related liver disease that is growing in incidence and associated with a high readmission rate and mortality. Growing evidence demonstrates that medications for alcohol use disorder (MAUD) may mitigate future alcohol related liver injury and decompensation. Thus the goal of this study was to assess the impact of receipt of MAUD on short term readmissions after index AH hospitalization. **Methods:** We performed a retrospective chart review at a single transplant center for patients ≥ 18 years with index admission for AH between March 2023 and March 2025. Clinical and demographic characteristics, substance use, psychiatric diagnoses, receipt of MAUD (naltrexone, acamprosate, gabapentin, baclofen, disulfiram) at discharge, addiction medicine consultation, readmission date and reason, phosphatidylethanol (PEth) (ng/ml), drinks per day, receipt of liver transplant were abstracted. Patients who died or received liver transplant during index were excluded. Primary outcomes were 30 and 90-day unplanned readmission. Multivariate logistic regression was performed. **Results:** A total of 230 patients with AH were included for analysis. Mean age was 44.7 ± 11.3 years, 40.4% were female, 75% white, and median MELD 3.0 score 25 (IQR 22-29). In total, 79 patients (34%) received MAUD, of which were primarily acamprosate (68%) and/or gabapentin (45%) or naltrexone (7.5%). Addiction medicine was consulted in 68% of cases, which was similar for those who were and were not readmitted (p = 0.775). Overall readmission rates at 30 and 90 days were 32% and 43%, respectively. Overall reasons for first readmission were ascites/volume overload (29%), infection (27%), and alcohol-related (15%). In multivariate models, patients with receipt of any MAUD had a lower risk of readmission at both 30 days (aOR 0.30, 95% CI 0.12-0.71) and 90 days (aOR 0.44, 95% CI 0.20-0.93). Additional predictors of 30-day readmission included male sex, presence of HE, receipt of antibiotics, and higher MELD 3.0 score, and receipt of antibiotics and higher MELD 3.0 score for 90-day readmission (Table 1). **Conclusion:** In patients hospitalized for index AH, the receipt of MAUD at discharge was independently associated with reduced odds of 30 and 90-day unplanned readmissions. Other predictors included receipt of antibiotics, higher discharge MELD 3.0, and presence of HE. Notably, ascites and infection were leading causes of readmission, with a lesser contribution from alcohol-related conditions, supporting the idea that MAUD may be hepatoprotective by mitigating harmful alcohol use. Systems level efforts to optimize MAUD prescriptions are necessary to improve outcomes in AH and ALD.

Table 1. Multivariate logistic regression model for predictors of unplanned 30 and 90-day readmission in patients with index alcohol-associated hepatitis hospitalization

	30-day Readmission		90-day Readmission	
Variable	aOR (95% CI)	P value	aOR (95% CI)	P value
Age (per year)	1.01 (0.98-1.05)	0.513	1.00 (0.97-1.03)	0.905
Sex				
Male	0.42 (0.18-0.94)	**0.036**	0.74 (0.35-1.54)	0.423
Race				
Asian/Other/Unknown	Ref		Ref	
Black	0.33 (0.05-2.14)	0.234	0.81 (0.16-4.18)	0.794
Hispanic	0.22 (0.02-2.09)	0.197	0.46 (0.06-3.24)	0.431
White	0.31 (0.07-1.57)	0.139	0.52 (0.13-2.15)	0.350
Discharge MELD 3.0 (per point)	1.13 (1.05-1.23)	**0.001**	1.15 (1.07-1.24)	**<0.001**
MAUD at discharge	0.30 (0.12-0.71)	**0.008**	0.44 (0.20-0.93)	**0.035**
Average drinks per day (per drink)	1.07 (1.00-1.14)	0.058*	1.02 (0.95-1.08)	0.587
PETH >200 ng/ml	0.65 (0.30-1.41)	0.273	0.84 (0.41-1.74)	0.636
Outside hospital transfer	0.83 (0.35-1.92)	0.659	0.50 (0.23-1.07)	0.079*
Antibiotics used	2.57 (1.17-5.75)	**0.020**	2.83 (1.38-5.95)	**0.005**
Hepatic encephalopathy at index	2.45 (1.09-5.61)	**0.032**	1.93 (0.91-4.16)	0.086*
Ascites at index	1.36 (0.59-3.28)	0.480	1.16 (0.56-2.45)	0.687
GI bleeding at index	1.45 (0.50-4.13)	0.483	1.36 (0.53-3.55)	0.520

PETH: phosphatidylethanol, GI: gastrointestinal, MAUD: medications for alcohol use disorder, MELD: model for end stage liver disease. P values in bold are statistically significant, and * indicates trend toward significance

Disclosures: Krishan Patel:Nothing to Disclose, Vinay Jahagirdar:Nothing to Disclose, OMAR ALBHAISI: Nothing to Disclose, Husam Mikati:Nothing to Disclose, Shaanit Sen:Nothing to Disclose, Butros Fakhoury: Nothing to Disclose, Na Bo:Nothing to Disclose, Hannah Kissel-Smith:Nothing to Disclose, Juan Pablo Arab:Nothing to Disclose.

3152 | ETHANOL RESHAPES FFC-DRIVEN STEATOHEPATITIS THROUGH TIME-DEPENDENT FIBROSIS AND LIPID-DROPLET REMODELING

Jasmin Weninger[1] Amani Lee[2] George Marek[3] Naomi Lange[4] Amy Mauer[3] Gyanendra Puri[5] Vijay Shah[3] Harmeet Malhi[3], [1]Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, 55905, [2]University of Minnesota Medical School, Minneapolis, MN, 55455, [3]Mayo Clinic Rochester, [4]Department of Visceral Surgery and Medicine, Inselspital, Bern University Hospital, Switzerland, [5]Department of Medicine, St. Francis Medical Center, Monroe, LA, 71201

Background: Metabolic dysfunction and alcohol exposure commonly coexist in steatotic liver disease, yet whether alcohol uniformly worsens MASH or selectively modifies disease biology remains unclear. We developed an iterative murine model to define how chronic ethanol alters high-fat, high-fructose, high-cholesterol (FFC)-driven liver injury and to identify MetALD-relevant features beyond routine injury markers. **Methods:** A pilot study in male and female C57BL/6J mice compared chow diet (CD), FFC, CD+ethanol (E), and FFC+E on a high-sugar-water background, with sacrifice at 6, 16, or 24 weeks. A subsequent redesigned study used lower sugar exposure, modified ethanol acclimation and five male cohorts: CD, CD+sugar-

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water (SW), FFC+SW, CD+SW+E, and FFC+SW+E, analyzed at 16 and 24 weeks (n = 4/group/timepoint). Outcomes included body/liver mass, ALT/AST, H&E histology, Sirius Red fibrosis, BODIPY lipid-droplet morphometry, qPCR, *aSMA* immunohistochemistry, and NanoString immune profiling. Statistical analysis was performed in R, GraphPad Prism and NanoString nSolver. **Results:** In the pilot study, FFC induced hepatomegaly, aminotransferase elevation, steatosis, chemokine induction, and fibrosis, but ethanol did not additively increase ALT/AST, or fibrosis, indicating a dominant effect of FFC/high-sugar. Female cohorts showed greater variability and no reproducible ethanol-dependent separation, supporting the redesign in male mice. In the redesigned model, FFC remained the dominant driver of weight gain, hepatomegaly, steatosis, aminotransferase elevation, and *Ccl2/Timp1*-associated fibroinflammatory remodeling. However, ethanol selectively modulated this phenotype. At 16 weeks, FFC+SW+E mice had greater Sirius Red-positive area than FFC+SW despite lower body/liver mass and no broad additive aminotransferase response. BODIPY morphometry showed enlarged lipid droplets in both FFC groups, but combined FFC/ethanol reduced lipid-positive area and the lipid droplet-to-nucleus ratio compared with FFC alone, indicating altered lipid-storage architecture rather than greater steatosis. *Cxcl1* emerged as an ethanol-responsive signal in chow-fed mice but was not uniformly amplified by ethanol on the FFC background. By 24 weeks fibrosis, qPCR markers, *aSMA* staining, and NanoString immune profiles largely converged between FFC+SW and FFC+SW+E. **Conclusion:** In a mouse model of MetALD chronic ethanol does not uniformly intensify FFC-induced liver injury. Instead, it modifies selected aspects of disease progression to early fibrosis, altered lipid-droplet architecture, and context dependent *Cxcl1*-skewed inflammatory signaling, while FFC drives dominant *Ccl2/Timp1*-associated remodeling and later convergence. This refined model supports MetALD as a timing- and pathway-dependent modification of metabolic steatohepatitis.

Disclosures: Jasmin Weninger:Nothing to Disclose, Amani Lee:Nothing to Disclose, George Marek:Nothing to Disclose, Naomi Lange:Nothing to Disclose, Amy Mauer:Nothing to Disclose, Gyanendra Puri:Nothing to Disclose, Vijay Shah:Boehringer Ingelheim: Consultant, GSK: Consultant, GENFIT SA: Consultant, Intercept Pharmaceuticals, Inc. Advisor, Korro Bio, Inc. Consultant, Novo Nordisk A/S: Consultant, Resolution Therapeutics, Ltd. Advisor, Seal Rock Therapeutics, Ltd. Consultant, Surrozen: Advisor, Dexcel Pharma Technologies, Ltd. Consultant, Dimension Inx. Advisor, Enveda: Consultant, Ochre Bio: Consultant, Satellite Biosciences, Inc. Consultant, Harmeet Malhi:MERCK: Consultant, Takeda: Consultant.

3153 | ADDICTION MEDICINE CONSULTATION SIGNIFICANTLY IMPROVES PRESCRIPTION OF MEDICATIONS FOR ALCOHOL USE DISORDER IN PATIENTS HOSPITALIZED WITH ALCOHOL-ASSOCIATED HEPATITIS

Krishan Patel[1] Vinay Jahagirdar[2] Omar Albhaisi[2] Husam Mikati[3] Shaanit Sen[4] Na Bo[5] Butros Fakhoury[1] Hannah Kissel-Smith[2] Juan Pablo Arab[1], [1]Virginia Commonwealth University, [2]VCU Medical Center, [3]Virginia Commonwealth University Health System, [4]VCU School of Medicine, [5]VCU

Background: Alcohol-associated hepatitis (AH) is a severe inflammatory manifestation of alcohol induced liver injury associated with high mortality, and increasing alcohol consumption has led to a growing incidence of AH. Continued alcohol intake is a key driver of hepatic decompensation after AH, and alcohol cessation remains a mainstay of treatment. Despite growing evidence supporting the use of MAUD in patients with alcohol related liver disease (ALD), multiple barriers exist that lead to suboptimal prescriptions for MAUD in practice. Therefore, the aim of this study was to examine factors associated with MAUD presciprtions at discharge in patients with AH. **Methods:** We performed a retrospective chart review in a single transplant center for patients ≥ 18 years with first known admission for AH from March 2023 to March 2025. Clinical characteristics, substance use, psychiatric diagnoses, receipt of MAUD (naltrexone, acamprosate, gabapentin, baclofen, disulfiram) at discharge, hepatology and addiction medicine consultation, phosphatidylethanol (PEth) (ng/ml), drinks per day, and receipt of liver transplant were abstracted. Primary outcome was receipt of prescription for any MAUD at discharge. Multivariate Cox regression was performed. Patients who died, were discharged to hospice, or received liver transplant during admission were excluded. **Results:** A total of 230 patients with AH were included for analysis. The mean age was 44.7 ± 11.3 years, with 40% female, 72% white, and median MELD 3.0 score of 25 (IQR 21-29). In total, 79 patients (34%) received MAUD, with nearly all receiving either acamprosate (68%) and/or gabapentin (45%). Addiction medicine was consulted for 68% of patients, and was higher in those with vs without MAUD at discharge (91% vs 56%, $p < 0.001$). Furthermore, those with MAUD had higher mean PEth (663 vs 464, $p = 0.19$) and daily drinks (10.1 vs 7.4, $p = 0.009$). In multivariate models, receipt of MAUD prescription at discharge was independently associated with addiction medicine consult (aOR 7.44, 2.77-24.3), increasing daily drinks (aOR 1.07,1.01-1.15), PEth >200 ng/ml (aOR 2.70,1.22-6.29), ICU admission (aOR 3.18, 1.11-

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9.66), and younger age (aOR 0.96, 0.93-0.99) (Table 1). **Conclusion:** Addiction medicine consultation was a strong independent predictor of receipt of MAUD at discharge in patients with AH. Interestingly, patients with PEth >200 ng/ml, greater drinks per day, and ICU stay were more likely to receive MAUD, suggesting that those with more severe drinking or illness may be more willing to receive, or were more likely offered, these medications from inpatient teams. Future studies should focus on strategies to improve MAUD prescription, such as integrating electronic decision support to facilitate addiction medicine consultation, increasing addiction education, and empowering both patients and primary teams to engage in conversations regarding MAUD and overall health.

Table 4: Multivariate regression model for predictors of receipt of MAUD prescription at discharge for patients at index alcohol-associated hepatitis hospitalization

Variable	aOR (95% CI)	P value
Age (per year)	0.96 (0.93-0.99)	**0.039**
Male	0.57 (0.26-1.21)	0.147
Race		
Asian/Other/Unknown	Ref	
Black	1.25 (0.24-6.44)	0.790
Hispanic	1.04 (0.15-7.18)	0.966
White	0.53 (0.14-2.05)	0.351
PEth >200 ng/mL	2.70 (1.22-6.29)	**0.017**
Average drinks per day (per drink)	1.07 (1.01-1.15)	**0.040**
Addiction medicine consult	7.44 (2.77-24.3)	**<0.001**
Substance use	1.14 (0.48-2.69)	0.761
Steroids started	1.83 (0.86-4.00)	0.123
ICU admission	3.18 (1.11-9.66)	**0.034**
HE at index	1.08 (0.49-2.37)	0.840

PEth: phosphatidylethanol, ICU: intensive care unit, HE: hepatic encephalopathy

Disclosures: Krishan Patel:Nothing to Disclose, Vinay Jahagirdar:Nothing to Disclose, OMAR ALBHAISI: Nothing to Disclose, Husam Mikati:Nothing to Disclose, Shaanit Sen:Nothing to Disclose, Na Bo:Nothing to Disclose, Butros Fakhoury:Nothing to Disclose, Hannah Kissel-Smith:Nothing to Disclose, Juan Pablo Arab: Nothing to Disclose.

3154 | CLINICAL BURDEN AND OUTCOMES IN A LARGE REAL-WORLD COHORT OF PATIENTS HOSPITALIZED WITH SEVERE ALCOHOL-ASSOCIATED HEPATITIS

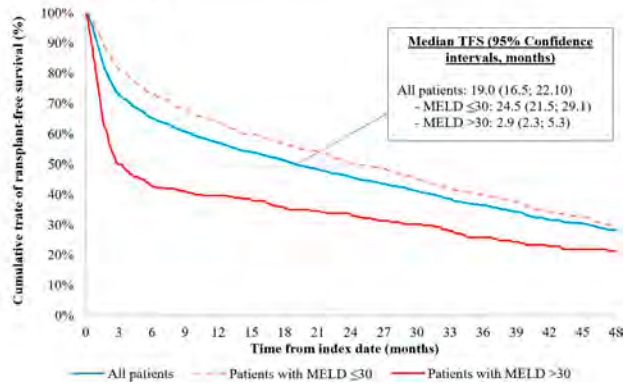
Arun Jesudian[1] Arthur Voegel[2] Patrick Gagnon-Sanschagrin[2] Debbie Goldschmidt[2] Kana Yokoji[2] Annie Guerin[2] Olamide Olujohungbe[3] Aarth Sheth[3] Leonardo Passos Chaves[3], [1]Weill Cornell Medicine, [2]Analysis Group, [3]Bausch Health

Background: Alcohol-associated hepatitis (AH) is characterized by high short-term mortality and limited treatment options. Real-world evidence on outcomes is limited, particularly in severe disease. This study evaluated a large real-world US cohort of patients hospitalized with severe AH. **Methods:** This retrospective study used insurance claims and laboratory data from the Komodo Research Database (01/01/2016–07/31/2025). Adults (≥18 years) with an AH-related hospitalization and a Model for End-Stage Liver Disease score (MELD) >20 or Maddrey's discriminant function ≥32 during hospitalization were included. The index date was the admission date of the first qualifying hospitalization. Prior to index, patients had ≥6 months of continuous insurance enrollment and no history of liver transplant. Clinical characteristics were assessed during the 6-month baseline period and index hospitalization. Overall survival (OS), transplant-free survival (TFS), and time to liver transplant were assessed from index date, and time to all-cause rehospitalization from discharge date, using Kaplan-Meier methods. Analyses were conducted overall and stratified by maximum MELD (≤30 vs >30) during the index hospitalization. **Results:** 1,630 patients with severe AH were included (mean age 48.7 years; 56.5% male; 62.9% White). Common baseline liver-related complications included cirrhosis (82.3%), ascites (81.4%), and hepatic encephalopathy (59.0%). Maximum MELD during the index hospitalization was 27.2 on average (median 26.0), and median index hospitalization duration was 11.0 days (IQR: 6.0-23.0). At 3 and 12 months, OS was 76.6% and 62.0%, and TFS was 72.9% and 57.0% (**Figure 1**), respectively. Liver transplant rates were 5.0% and 8.5% and rehospitalization rates were 48.1% and 69.1%.Among 1,303 patients with available MELD, 934 had MELD ≤30 and 369 had MELD >30. At 3 months, OS was 83.3% for MELD ≤30 and 57.5% for MELD >30, and TFS was 81.2% and 49.9%, respectively. At 12 months, OS was 67.5% and 48.0%, TFS was 63.7% and 39.7%, and transplant rates were 6.4% and 17.0% for the MELD ≤30 and >30 subgroups, respectively. Rehospitalization rates were similar across groups. **Conclusion:** In this large real-world cohort of patients hospitalized with severe AH, mortality was high and rehospitalization was frequent. While outcomes were worse among patients with higher MELD, the clinical burden remained substantial across both subgroups, highlighting a pressing unmet therapeutic need.

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Figure 1 – Kaplan-Meier estimates of transplant-free survival among patients hospitalized with severe alcohol-associated hepatitis, overall and by maximum MELD score during the index hospitalization (≤30 vs >30)



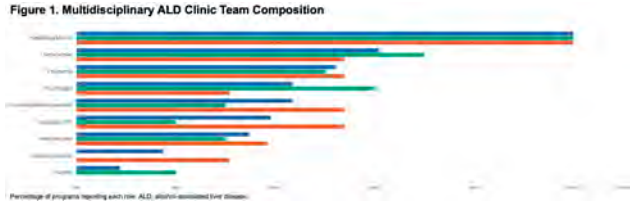
Disclosures: Arun Jesudian:Salix Pharmaceuticals: Consultant, Salix Pharmaceuticals: Speaking and Teaching, Madrigal Pharmaceuticals: Speaking and Teaching, Mallinckrodt Pharmaceuticals: Consultant, Mallinckrodt Pharmaceuticals: Speaking and Teaching, Arthur Voegel:Johnson & johnson: Consultant, Bausch Health: Consultant, Novartis: Consultant, Pfizer: Consultant, BeOne: Consultant, Vertex: Consultant, Analysis Group: Employee, Patrick Gagnon-Sanschagrin: Nothing to Disclose, Debbie Goldschmidt:Bausch Health: I am an employee of Analysis Group, a consulting firm, Kana Yokoji:Nothing to Disclose, Annie Guerin:Nothing to Disclose, Olamide Olujohungbe: Bausch Health: Employee, Bausch Health: Stock – privately held company, Aarth Sheth:Nothing to Disclose, Leonardo Passos Chaves:Nothing to Disclose.

3155 | PRACTICE PATTERNS ACROSS MULTIDISCIPLINARY ALCOHOL-ASSOCIATED LIVER DISEASE CLINICS IN THE UNITED STATES: A NATIONAL SURVEY

Sasha Deutsch-Link[1] Rebecca Roediger[2] Robin Casey[3] Nader Dbouk[3] Ryan Ford[3] Lamia Haque[4] Kandi Schmidt[5] Isabelle Byers[6] Hersh Shroff[1], [1]UNC Chapel Hill, [2]Weill Cornell Medicine, [3]Emory University School of Medicine, [4]Yale School of Medicine, [5]Loyola University School of Medicine, [6]Univeristy of North Carolina School of Medicine

Background: Optimal management of alcohol-associated liver disease (ALD) involves coordinated ALD and alcohol use disorder (AUD) care. Multidisciplinary clinics (MDCs) integrating ALD and AUD treatment have emerged across the U.S., however clinic prevalence, structure, and practice patterns remain poorly characterized. We conducted a national survey to evaluate structure and practice patterns across MDCs. **Methods:** 119 active U.S. liver transplant centers were contacted between October 2025 and March 2026. Responses were received from 86 institutions (72.3%). Of all contacted centers, 30 (25.2%) confirmed an active MDC and 56 (47.1%) reported no MDC. Among centers with confirmed MDCs, 23 (76.7%) completed the survey. Survey domains assessed clinic structure, staffing, patient population, biomarker use, and provision of AUD medications (MAUD) and behavioral interventions. Data were summarized descriptively and stratified by clinic type (transplant versus general hepatology). **Results:** Among the 23 MDCs that completed the survey, 10 (43.5%) were transplant clinics and 13 (56.5%) were general hepatology clinics, with the majority of clinics established within the past two years (median 26.8 months, IQR 13.9-43.4). Staffing included hepatologists (100%), psychiatrists (52.5%), psychologists (43.5%), social workers (60.9%), and licensed addiction counselors (43.5%). (Figure 1) Most clinics had co-located multidisciplinary services at initial (87.0%) and return visits (72.7%). 17.6% included patients with early stages of ALD and 60.9% required alcohol use within the past 12 months. Nearly all clinics prescribed MAUD (95.7%), most commonly naltrexone (63.6%) or acamprosate (22.7%) as first-line agents. Only 42.9% prescribed oral naltrexone regardless of liver disease severity. All clinics used phosphatidylethanol for biomarker testing. Behavioral therapy was offered in 73.9% of clinics, delivered primarily by psychologists (47.1%) or master's-level therapists (41.2%). **Conclusion:** This national survey demonstrated that MDCs are present in at least one quarter of U.S. transplant centers and are relatively new. While some elements such as hepatologist involvement and biomarker use are nearly universal, significant heterogeneity exists across staffing, patient inclusion criteria, and MAUD prescribing. Overall, survey results indicate a need for evidence-based frameworks to guide multidisciplinary ALD clinic development and implementation.

Figure 1. Multidisciplinary ALD Clinic Team Composition



Disclosures: Sasha Deutsch-Link:Nothing to Disclose, Rebecca Roediger:Nothing to Disclose, Robin Casey: Nothing to Disclose, Nader Dbouk:Nothing to Disclose, Ryan Ford:Nothing to Disclose, Lamia Haque:Nothing to Disclose, Kandi Schmidt:Nothing to Disclose,

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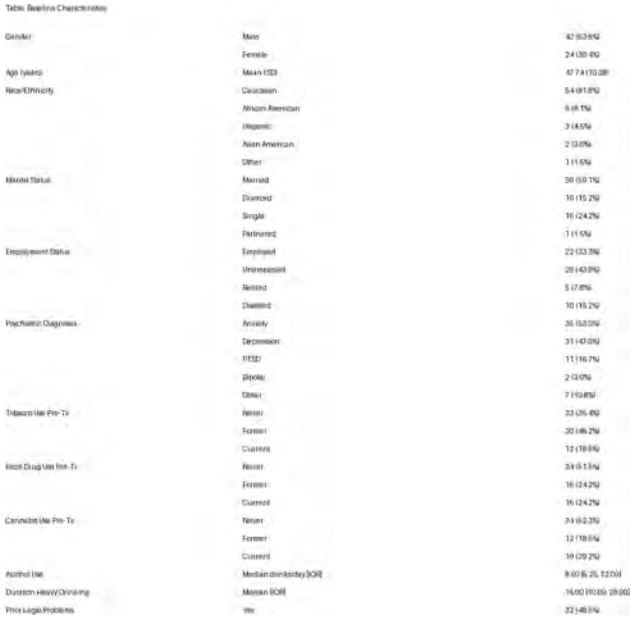
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Isabelle Byers:Nothing to Disclose, Hersh Shroff:Glaxo-Smith-Kline: Grant/Research Support.

3156 | EARLY OUTCOMES OF A MULTIDISCIPLINARY ALD CLINIC FOR HIGH-RISK LIVER TRANSPLANT RECIPIENTS

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Background: Alcohol-associated liver disease (ALD) is the leading indication for liver transplantation (LT), with a growing burden among young patients and women. Recidivism is a key concern, with at least 10-20% of high-risk patients returning to harmful drinking post LT. Multidisciplinary care models may improve outcomes, but supporting data is limited. We aimed to evaluate the impact of a dedicated multidisciplinary ALD clinic on outcomes in high-risk LT recipients. **Methods:** We conducted a mixed retrospective-prospective study of LT recipients (n = 66) with ALD considered high risk for recidivism (based on SALT and ARRA scores), who were enrolled in a multidisciplinary ALD clinic at Emory University between 11/2024 and 3/2026. The clinic integrates hepatology, transplant behavioral health, and addiction psychology to provide longitudinal care for patients with ALD. Outcomes included alcohol recidivism, follow-up adherence, and patient and graft survival. ChatGPT (OpenAI) was used solely to assist with language refinement and improve readability of the abstract. **Results:** Key baseline characteristics are summarized in Table 1. Follow-up compliance was 81.8%. Fourteen patients (21.2%) experienced post-LT alcohol use and 9 (13.6%) met criteria for sustained or harmful drinking. Pre-transplant participation in mutual support groups was associated with recidivism (OR 5.75, p = 0.012) and sustained drinking (OR 4.90, P = 0.039), likely reflecting greater underlying alcohol use disorder (AUD) severity. Higher pre-transplant PEth levels were associated with increased recidivism. PTSD was a significant predictor of sustained harmful drinking (OR 5.71, p = 0.026). Illicit drug and cannabis use showed non-significant trends toward increased recidivism, while tobacco use demonstrated a non-significant association with sustained drinking. A diagnosis of depression was significantly associated with better follow-up compliance (OR 5.80, p = 0.032). Longer duration of pre-transplant sobriety was also associated with higher follow-up compliance (median 193 days for compliant vs. 72.5 days for non-compliant patients; p = 0.044) as was longer duration from last positive PEth to LT (median 118 days for compliant vs 23 days for non-compliant patients; p = 0.038). Two patients who relapsed experienced graft rejection, but there were no graft losses or patient deaths during follow-up. **Conclusion:** High-risk LT recipients in a multidisciplinary ALD clinic demonstrated excellent follow-up compliance and survival rates. Compliance was particularly high among patients with depression, reflecting greater engagement with integrated mental health services. Recidivism rates were comparable to published data. Pre-transplant group therapy, illicit drug or cannabis use, and tobacco use were associated with higher rates of recidivism and sustained drinking.



Disclosures: Nishita Sunkara:Nothing to Disclose, Jarah Whitehead:Nothing to Disclose, Dominique Mosley:Nothing to Disclose, Tabitha Casey:Nothing to Disclose, Ryan Ford:Nothing to Disclose, Kandi Schmidt:Nothing to Disclose, Nader Dbouk:Nothing to Disclose.

3157 | BILIRUBIN-DRIVEN PHENOTYPE IDENTIFIES HIGHER MORTALITY RISK IN SEVERE ALCOHOL-ASSOCIATED HEPATITIS

Tewodros Ayele[1] Tomohiro Tanaka[1], [1]University of Iowa

Background: Among patients with severe alcohol-associated hepatitis (AH), the prognostic relevance of

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the dominant component of Maddrey's Discriminant Function (MDF) is unclear. **Methods:** We conducted a retrospective cohort study of adults with AH treated with corticosteroids at a US academic center (January 2016 - December 2024). Using K-means clustering of the bilirubin and prothrombin time (PT) components of MDF, patients were classified into "PT-driven" vs. "bilirubin-driven" phenotypes. The primary outcome was 90-day all-cause mortality. Inverse probability of treatment weighting (IPTW)-weighted Cox proportional hazards (PH) models were performed under an intention-to-treat framework, in which patients were not censored at liver transplantation (LT). Secondary analyses used Fine-Gray competing risk models with LT as a competing event. **Results:** Among 212 patients, 56 (26.4%) died within 90 days. Despite similar Model for End-Stage Liver Disease (MELD), the bilirubin-driven group (n = 100) had significantly lower MDF scores, and less hepatic encephalopathy compared to the PT-driven group (n = 112). Nevertheless, in IPTW-weighted Cox PH model, the bilirubin-driven phenotype was associated with higher 90-day mortality (HR 2.06; 95% CI, 1.05-4.04). Findings were consistent in the Fine-Gray competing risks model (sHR 2.11; 95% CI, 1.03-4.35). **Conclusion:** A bilirubin-dominant phenotype in severe alcohol-associated hepatitis was associated with significantly higher 90-day mortality, highlighting disease heterogeneity and suggesting potential value for risk stratification and for guiding future research on individualized care and optimal timing of liver transplant evaluation.

Disclosures: Tewodros Ayele:Nothing to Disclose, Tomohiro Tanaka:Nothing to Disclose.

3158 | ALCOHOL SUPPRESSES KC MATURATION IN A MODEL OF STEATOTIC LIVER DISEASE

Kyle Yuquimpo[1] Sheetalnath Rooge[1] Isabel Aranzazu Pulido Ruiz[2] Lucas Tian[1] Ann Wozniak[1] Steven Weinman[1], [1]University of Kansas Medical Center, [2]The University of Kansas Medical Center

Background: Alcohol consumption is a strong determinant of the severity of liver disease in patients with Met-ALD. The exact mechanisms for how alcohol accelerates disease progression are not well understood. We have previously shown that chronic depletion of mature Kupffer Cells (KCs) in a model of ALD leads to a liver failure phenotype with similar characteristics as alcohol-associated hepatitis, highlighting a critical role of macrophages in maintaining liver function. The replacement of embryonic-derived KCs by monocyte-derived KCs (moKCs) is known to occur in all forms of SLD but whether alcohol alters this process is unknown. The aim of this study was to determine whether the presence of alcohol in SLD alters KC replacement and maturation thus contributing to a more severe disease phenotype. **Methods:** Adult male mice were fed a high fat western diet (WD), or western diet with alcohol (WDA) for 16 weeks. Ms4a3-TdT mice were used to distinguish moKCs expressing TdT from embryonic KCs (emKCs). Clec4f-DTR mice were used to ablate KCs. They were injected with a single dose of DT at the end of feeding and followed 1-2 weeks after ablation to assess the rate of macrophage replacement. Livers were processed for histology and whole tissue analyses or underwent perfusion for isolation of non-parenchymal cells for analytical flow cytometry or separation by FACS. mRNA from FACS-sorted cells was analyzed by qPCR. **Results:** During steady state conditions, BM-derived sinusoidal KCs were present in both WDA and WD mice, but CD163+ TdT+ moKCs were more abundant in WD compared with WDA mice. Using the ClecDTR model to ablate mature KCs, we were able to determine the kinetics of new KC formation from monocyte precursors. After KC ablation, infiltrating macrophages were readily able to take on the mature VSIG4+ moKC phenotype in WD fed mice but this was diminished in the WDA-fed animals. In WDA, recovery from KC ablation led to a paucity of VSIG4+ moKCs and a marked accumulation of macrophages representing intermediate forms along the maturation pathway toward KCs. These represented LAMs and LAM-like KCs. These intermediate forms accumulated in crown-like structures (CLS) which, after KC ablation, were greatly expanded in WDA compared to WD. We isolated mRNA from 2-wk replacement macrophages to assess differences in transcription factor expression between WD and WDA. Egr2, an M2-identify forming macrophage transcription factor, was markedly elevated in the WD but not the WDA condition. **Conclusion:** The addition of alcohol to high fat diet suppresses the maturation of KCs from monocyte precursors. This results in the accumulation of KC intermediate forms, and a paucity of mature KCs. Transcription factors related to macrophage differentiation are suppressed by alcohol and may account for the effects. Impaired KC replacement may contribute to accelerated pathogenesis caused by alcohol consumption in steatotic liver disease.

Disclosures: Kyle Yuquimpo:Nothing to Disclose, Sheetalnath Rooge:Nothing to Disclose, Isabel Aranzazu Pulido Ruiz:Nothing to Disclose, Lucas Tian: Nothing to Disclose, Ann Wozniak:Nothing to Disclose, Steven Weinman:Nothing to Disclose.

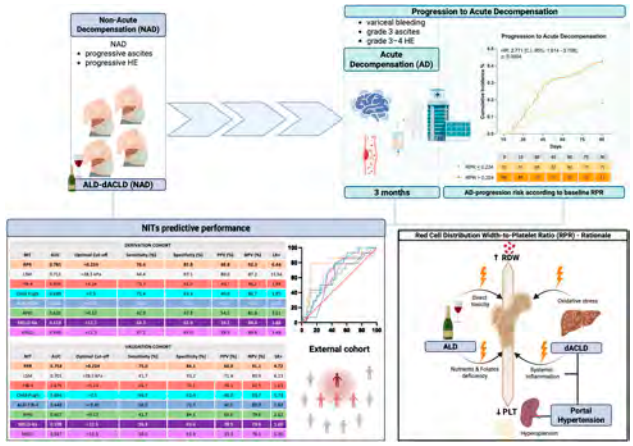
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3159 | RED CELL DISTRIBUTION WIDTH-TO-PLATELET RATIO PREDICTS SHORT-TERM ACUTE DECOMPENSATION IN PATIENTS WITH ALCOHOL-RELATED DECOMPENSATED ADVANCED CHRONIC LIVER DISEASE AND ONGOING NON-ACUTE DECOMPENSATION: A MULTICENTER STUDY WITH EXTERNAL VALIDATION

Mario Romeo[1] Viktor Domislovic[2] Marcello Dallio[1] Fiammetta Di Nardo[1] Carmine Napolitano[1] Paolo Vaia[1] Claudio Basile[1] Luigi Maria Vitale[1] Borna Curtic[2] Anna Mrzljak[2] Alessandro Federico[1], [1]University Hospital Luigi Vanvitelli, Piazza Miraglia 2, 80138, Naples, Italy, [2]University Hospital Centre Zagreb, Zagreb 10000, Croatia

Background: Alcohol-related decompensated advanced chronic liver disease (ALD-dACLD) evolves through non-acute decompensation (NAD) or acute decompensation (AD) (**Figure**). Nearly 30% of patients with ongoing NAD develop AD within 3 months, yet tools for short-term risk stratification remain limited.The red cell distribution width (RDW)-to-platelet (PLT) ratio (RPR) is an index derived from routine hematological parameters. Elevated RDW reflects systemic inflammation, oxidative stress, impaired erythropoiesis, and nutritional deficiencies. In ALD, chronic alcohol exposure further contributes to anisocytosis through bone marrow toxicity and folate deficiency, leading to increased RDW values. Reduced PLT reflects portal hypertension and is exacerbated by alcohol-induced bone marrow suppression (**Figure**). By integrating these mechanisms, RPR is a promising noninvasive tool (NIT) for adverse liver outcomes, particularly in ALD-dACLD.We evaluated the performance of RPR and its consistency across established NITs for predicting 3-month AD in patients with ALD-dACLD and ongoing NAD. **Methods:** Patients with ALD-dACLD and ongoing NAD (n: 122) were enrolled at the University Hospital “Vanvitelli”, Naples, Italy. An independent external validation cohort included 57 patients from another tertiary European center (Hepatology, University Hospital, Zagreb, Croatia). At baseline, clinical and biochemical data were collected, and NITs [RPR, APRI, FIB-4, ALBI-FIB-4, Child-Pugh, MELD, MELD-Na, and liver stiffness measurement (LSM)] were determined. Patients were prospectively followed for 3 months for AD occurrence. Predictive accuracy was assessed by ROC and multivariate analysis; the optimal cut-off was identified using the Youden index and externally validated. **Results:** Baseline RPR was significantly higher in patients who developed AD (n = 53) (0.23 ± 0.07 vs 0.13 ± 0.05, p < 0.0001). In the derivation cohort, RPR had the highest AUC (0.785), followed by LSM (0.713), FIB-4 (0.699), and Child-Pugh (0.689). The optimal cut-off was >0.224 (78.6% sensitivity, 87.8% specificity, 68.8% PPV, 92.3% NPV, and LR+ 6.44). Patients with RPR >0.224 had a higher 3-month cumulative incidence of AD (HR 2.77, 95%CI 1.61–3.76; p = 0.0004). In multivariate analysis, RPR remained independently associated with the outcome after proper adjustment. In the external validation cohort, RPR maintained good performance (AUC 0.758; using the predefined cut-off, sensitivity: 75.0%, specificity: 84.1%, PPV: 60.0%, NPV:91.1%, and LR+ 4.72), confirming reproducibility across independent cohorts. **Conclusion:** RPR is a practical bedside tool for short-term risk stratification in ALD-dACLD with ongoing NAD, enabling personalized monitoring and timely intervention. To our knowledge, this is the first prospective multicenter study demonstrating the ability of RPR to predict 3-month AD in this setting.



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3160 | SEX DISPARITY IN CLINICAL OUTCOMES IN ALCOHOL-ASSOCIATED LIVER DISEASE WITH CARDIOMETABOLIC RISK FACTORS

Pojsakorn Danpanichkul[1] Matheus Henrique Gonçalves de Souza[2] Thanida Auttapracha[3] Ahmad Anouti[4] Nkengeh Tazinkeng[5] Thanathip Suenghataiphorn[6] Karn Wijarnpreecha[7] Donghee Kim[8] Suthat Liangpunsakul[9], [1]Texas Tech University Health Sciences Center, [2]Department of Internal Medicine,

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Background: Sex disparities in steatotic liver disease (SLD) are well recognized, yet sex-specific differences in clinical outcomes among patients with alcohol-associated liver disease (ALD) and concurrent cardiometabolic risk factors (CMRF) remain poorly characterized. **Methods:** We conducted a population-based retrospective cohort study using the TriNetX platform, a federated research network aggregating de-identified electronic health record data from healthcare organizations across the United States. Adults with ALD and CMRF were identified using the updated fatty liver disease nomenclature and stratified by biological sex. Female and male cohorts were balanced using 1:1 propensity score matching, and outcomes were assessed over a 5-year follow-up period using Cox proportional hazards models. **Results:** After propensity score matching, female and male patients with ALD and CMRF had comparable all-cause mortality [hazard ratio (HR) 0.96, 95% confidence interval (CI) 0.91–1.01]. Female patients had higher risks of major adverse liver outcomes [HR 1.13, 95% CI 1.09–1.18] and alcohol-associated hepatitis [HR 1.11, 95% CI 1.05–1.18], but lower risks of major adverse cardiovascular events [HR 0.86, 95% CI 0.81–0.90], arrhythmia [HR 0.87, 95% CI 0.83–0.91], and heart failure [HR 0.81, 95% CI 0.76–0.88]. Female patients also had a substantially higher risk of urinary tract infection [HR 2.66, 95% CI 2.46–2.88] and modestly higher sepsis risk [HR 1.08, 95% CI 1.01–1.17], while pneumonia risk was similar between sexes [HR 0.99, 95% CI 0.91–1.07]. **Conclusion:** In this large, propensity score-matched cohort, female sex was associated with a distinct clinical risk profile among patients with ALD and CMRF, higher liver-related and infection-related morbidity, but lower cardiovascular risk, despite equivalent all-cause mortality. These findings reveal that aggregate mortality metrics can obscure clinically meaningful sex-based differences in organ-specific morbidity, underscoring the need for sex-specific risk stratification and tailored surveillance in this high-risk population.

Table 1: Clinical outcomes post-propensity score matching

Outcome	Female with ALD with CMRF Events N (%)	Male ALD with CMRF Events N (%)	Hazard Ratio (95% CI)	p-value
Death	2,429 (16.6%)	2,492 (17.0%)	0.96 (0.91 - 1.01)	0.137
Liver Outcomes				
Major adverse liver outcome	4,539 (28.5%)	4,052 (25.4%)	1.13 (1.09 - 1.18)	<0.001
Alcohol-associated hepatitis	2,177 (13.7%)	1,954 (12.3%)	1.11 (1.05 - 1.18)	0.001
Cardiovascular Outcomes				
Major Adverse Cardiovascular Events	2,420 (15.2%)	2,736 (17.2%)	0.86 (0.81 - 0.90)	<0.001
Arrhythmia	3,150 (19.8%)	3,494 (21.9%)	0.87 (0.83 - 0.91)	<0.001
Heart failure	1,291 (8.1%)	1,544 (9.7%)	0.81 (0.76 - 0.88)	<0.001
Infection Outcomes				
Urinary tract infection	2,217 (13.9%)	872 (5.5%)	2.66 (2.46 - 2.88)	<0.001
Sepsis	1,544 (9.7%)	1,408 (8.8%)	1.08 (1.01 - 1.17)	0.029
Pneumonia	1,254 (7.9%)	1,249 (7.8%)	0.99 (0.91 - 1.07)	0.741

Abbreviation: ALD: alcohol-associated liver disease; CI: confidence interval ;CMRF: cardiometabolic risk factors

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3161 | EXPLORATORY ANALYSIS OF THRESHOLD OF SIPAT LIFESTYLE AND SUBSTANCE USE DOMAIN FOR PREDICTION OF ALCOHOL RELAPSE AFTER LIVER TRANSPLANTATION AMONG PATIENTS WITH ALCOHOL ASSOCIATED CIRRHOSIS

Chung-Heng Liu[1] Manida Wungjiranirun[2] Dekey Lhewa[1] Arnab Mitra[2], [1]Oregon Health & Science University, [2]Oregon Health And Science University

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Background: The Stanford Integrated Psychosocial Assessment for Transplantation (SIPAT) offers a standardized method for psychosocial evaluation for liver transplant. Our group found SIPAT lifestyle & substance use domain, and not overall SIPAT score, is independently associated with phosphatidylethanol (PEth) positivity, an objective marker of alcohol use, at 1-year after liver transplant. The aim of this study is to evaluate whether there is a threshold of SIPAT lifestyle and substance use domain score that predicts PEth positivity within 1-year post liver transplant amongst patients with alcohol-associated cirrhosis (AC). **Methods:** This was a retrospective analysis of liver transplant performed at a large transplant center from 2015-2024. All patients with alcohol-associated cirrhosis (AC) who underwent pre-transplant evaluation and transplant with PEth within 1-year post-liver transplant were included. PEth positivity is defined as more than 20ng/mL from 2 or more consecutive follow-ups, within 1-year after liver transplant. Receiver operating characteristic (ROC) analysis was performed to evaluate discriminatory performance of the SIPAT lifestyle and substance use domain for predicting 1-year post-transplant PEth positivity. Youden index optimization was then used to identify a cutoff value. Chi-square and logistic regression were subsequently performed to evaluate associations between SIPAT substance use domain score and post-transplant 1-year PEth positivity. **Results:** A total of 187 patients with alcohol-associated cirrhosis who underwent liver transplant were included. 62% were male, 72% white and 12% Latinx, median age 52 (IQR 45-59), median MELD 29 (IQR 25-34), and 15% had positive PEth within 1 year of liver transplant. ROC analysis demonstrated modest discriminatory performance of the SIPAT substance use domain for predicting 1-year PEth positivity (AUC 0.64), compared to that of the total SIPAT score (AUC 0.58). Exploratory threshold analysis demonstrated cutoff of SIPAT substance use domain of $\geq$ 10. Patients with substance use domain score $\geq$ 10 demonstrated significantly higher post-transplant PETH positivity ($p = 0.029$), and it is independently associated with PEth positivity (OR 3.31, $p = 0.034$). **Conclusion:** SIPAT lifestyle and substance domain may outperform the total SIPAT score. In addition, among patients with alcohol related cirrhosis, SIPAT substance use domain score $\geq$ 10 was associated with increased odds of PEth positivity at 1-year post-liver transplant. These findings suggest SIPAT substance domain threshold may be better at identifying alcohol relapses. External validation in large multicenter studies is needed.

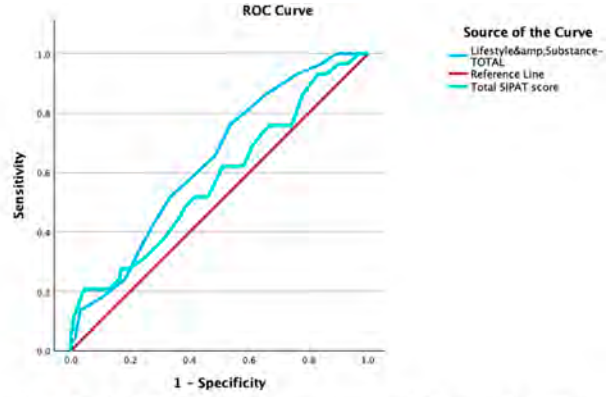


Figure 1: SIPAT lifestyle & substance domain demonstrates modestly improved discriminatory performance for 1-year post-transplant PEth positivity compared to total SIPAT score (AUC 0.64 vs 0.58).

Disclosures: Chung-Heng Liu:Nothing to Disclose, Manida Wungjiranirun:Nothing to Disclose, Dekey Lhewa:Nothing to Disclose, Arnab Mitra:Nothing to Disclose.

3162 | EVIDENCE FROM AN XGBOOST FEATURE IMPORTANCE ANALYSIS: HOW ARE RISK FACTORS OF POST-TRANSPLANT ALCOHOL RELAPSE APPLIED IN PRACTICE?

Sue Hyon Kim[1] Ethan Weinberg[1] Jonathan Nahas[1] Renee Maggiaro[1] Kimberley Johnson[1] Emily Patrick[1] Christina Cerra[1] Robert Weinrieb[1] Arpita Goswami Banerjee[1] Marina Serper[2], [1]University of Pennsylvania, [2]University of Pennsylvania Health System

Background: Alcohol consumption is reported in over 30% of liver transplant (LT) recipients with alcohol-associated liver disease (ALD) and may compromise post-transplant outcomes. Despite growing evidence on risk factors of alcohol relapse, how they translate into practice is unknown, especially because key factors are not readily captured within structured EHR data. **Methods:** This retrospective cohort study included patients with ALD who underwent LT evaluation at our transplant center. Based on a review of existing literature, we outlined risk factors of post-LT alcohol relapse. We then identified these risk factors from 3373 clinical notes for 829 patients using large language models hosted on Microsoft Azure Databricks, a secure HIPAA-compliant environment. Notes documented by physicians, nurses, social workers, and psychiatrists during the evaluation period up to the selection

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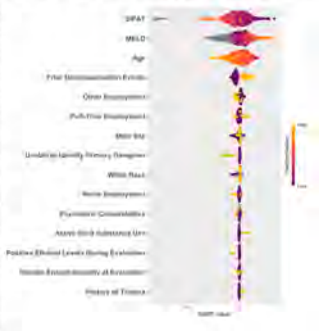
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committee's decision were included. Multivariable logistic regression was used to evaluate associations between the risk factors and waitlist outcome (listed vs. denied). Variables with high multicollinearity were excluded. We additionally employed XGBoost, a machine learning algorithm robust to missing data and multicollinearity, to validate logistic regression findings and to incorporate 184 patients who had been excluded due to missing data. A subsequent multivariable logistic regression was performed to examine alcohol relapse (reported PEth values >10ng/mL) among 237 LT recipients, using the same variables as the primary model. **Results:** Our sample was predominantly White (80%) and male (67%), with a mean age of 55 ± 10 years. Nearly a quarter were employed full-time (23%) and 21% were retired. Mean MELD score was 19 ± 7 and mean SIPAT score was 23 ± 11. 56% of patients were denied listing and alcohol relapse occurred in 11% of LT recipients.Of the outlined risk factors, logistic regression found prior decompensation events and a positive ethanol lab result during evaluation to be associated with waitlist outcomes (Figure 1A). The XGBoost model achieved good discrimination (AUC = 0.765, accuracy 70.7%), with composite scores and sociodemographic variables emerging as the strongest contributors (Figure 1B). Consistent with logistic regression findings, higher SIPAT scores were associated with reduced odds of listing and higher MELD scores were associated with greater odds of listing. Of the outlined risk factors, prior decompensation events were the most influential feature for predicting waitlist outcomes. In the post-LT logistic regression model, continued drinking after liver disease diagnosis was the only significant factor associated with alcohol relapse (OR = 5.404). **Conclusion:** Differences between the logistic regression and XGBoost models imply nonlinear relationships between sociodemographic characteristics and established risk factors of alcohol relapse, suggesting gaps in risk assessment and management.

A. Multivariable Logistic Regression for Waitlist Outcome

Predictors	OR (95% CI)	p-value
Age	0.991 (0.971 – 1.011)	0.385
Sex (Male)	1.250 (0.864 – 1.812)	0.237
Race (White)	1.166 (0.745 – 1.823)	0.498
Employment (full-time)	0.919 (0.505 – 1.686)	0.781
Employment (retired)	0.631 (0.338 – 1.175)	0.147
Employment (other)	0.637 (0.367 – 1.094)	0.102
MELD	1.055 (1.028 – 1.084)	<0.001***
SIPAT	0.951 (0.934 – 0.968)	<0.001***
Prior decompensation events	1.934 (1.228 – 3.072)	0.004**
Hepatic encephalopathy at evaluation	1.247 (0.704 – 2.236)	0.451
Lack insight into alcohol use disorder	0.711 (0.242 – 2.068)	0.529
Unable to identify primary caregiver	0.625 (0.278 – 1.439)	0.265
Active illicit substance use	1.957 (0.840 – 4.753)	0.121
Psychiatric comorbidities	1.190 (0.674 – 2.112)	0.549
Legal consequences due to alcohol	0.565 (0.174 – 1.906)	0.348
Alcohol-related hospital admissions	1.029 (0.394 – 2.856)	0.954
Positive ethanol levels during evaluation	0.235 (0.070 – 0.693)	0.008**
Drinking after liver disease diagnosis	0.958 (0.468 – 2.003)	0.902
History of trauma	1.015 (0.431 – 2.434)	0.973

B. XGBoost Feature Contributions to Waitlist Outcome Prediction



Disclosures: Sue Hyon Kim:Nothing to Disclose, Ethan Weinberg:Nothing to Disclose, Jonathan Nahas:Nothing to Disclose, Renee Maggiaro:Nothing to Disclose, Kimberley Johnson:Nothing to Disclose, Emily Patrick:Nothing to Disclose, Christina Cerra: Nothing to Disclose, Robert Weinrieb:Nothing to Disclose, Nothing to Disclose, Arpita Goswami Banerjee: Nothing to Disclose, Marina Serper:Transplant Genomics: Grant/Research Support, Grifols: Grant/Research Support.

3163 | WAITLIST OUTCOMES AND POST-TRANSPLANT SURVIVAL AMONG CANDIDATES WITH ALCOHOL-ASSOCIATED LIVER DISEASE WITH AND WITHOUT METABOLIC DYSFUNCTION: A UNOS/OPTN ANALYSIS (2012–2024)

Jobin Chandi[1] Tiffany Sahadeo[1] James Park[1] Nabil Dagher[1] Lau Lawrence[1] Nishi Joshi[2] Sanjaya Satapathy[1], [1]Northshore University Hospital/Northwell Health, [2]Northshore University Hospital/Northwell

Background: Alcohol-associated liver disease (ALD) has become the leading indication for liver transplantation in the United States. The increasing prevalence of metabolic dysfunction among liver transplant candidates with ALD has led to the emergence of metabolic–alcohol-associated liver disease (MetALD), but its impact on waitlist and post-transplant outcomes remains unclear. **Methods:** We retrospectively analyzed first-time liver transplant candidates with alcohol-associated liver disease listed in the UNOS/OPTN database from 2012 to 2024. Candidates were classified as ALD-only or MetALD based on the presence of obesity (body mass index ≥ 30 kg/m²) and/or diabetes mellitus. Waitlist outcomes were evaluated using cumulative incidence functions and Fine–Gray competing risks regression. Post-transplant patient and graft survival were assessed using Kaplan–Meier methods and multivariable Cox proportional hazards models. Temporal trends in listing proportions were examined using logistic regression. **Results:** Among 51,325 eligible candidates, 27,953 (54.5%) were classified as ALD-only and 23,372 (45.5%) as MetALD. MetALD candidates were older and had greater metabolic comorbidity burden (all $p < 0.001$). While on the waitlist, MetALD candidates experienced a higher cumulative incidence of transplantation and a lower incidence of death or clinical deterioration compared with ALD-only candidates (Gray's test $p < 0.001$). Median waitlist time was shorter for MetALD candidates (72 vs. 81 days, $p < 0.001$). Among transplanted recipients (ALD: n = 15,796; MetALD: n = 14,159), unadjusted patient survival differed between groups (log-rank $p < 0.001$), but MetALD was not independently associated with post-transplant mortality after multivariable adjustment (adjusted hazard ratio 1.07, 95% CI 0.97–1.18;

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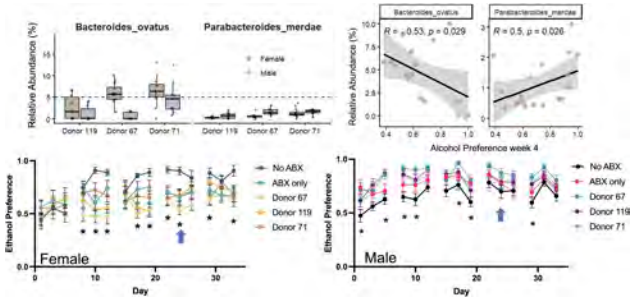
p = 0.16). Graft survival did not differ between groups (log-rank p = 0.13). The proportion of MetALD listings remained relatively stable from 2012 to 2024, with a small but statistically significant downward trend over time (p for trend = 0.0001). **Conclusion:** Metabolic dysfunction is common among liver transplant candidates with alcohol-associated liver disease and is associated with distinct waitlist outcomes; specifically, higher transplant rates and lower waitlist mortality. However, MetALD is not independently associated with worse post-transplant patient or graft survival. These findings underscore the importance of incorporating metabolic risk factors into the evaluation of transplant candidates with ALD.

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3164 | SEX-SPECIFIC REDUCTIONS IN ETHANOL CONSUMPTION FOLLOWING HUMAN FECAL MICROBIOTA TRANSPLANT CORRELATE WITH MICROBIOME CHANGES IN MICE

Jennifer Wolstenholme[1] Jasmohan Bajaj[1] Lauren May[1] Alexander Khoruts[2] Andrew Sommer[2], [1]Virginia Commonwealth University, [2]University of Minnesota

Background: Alcohol use disorder (AUD) remains a significant burden of health worldwide, but treatment options continue to remain limited. Chronic alcohol use leads to changes in the gastrointestinal tract, including changes in the diversity and function of the gut microbiome which can result in the depletion of beneficial taxa and the expansion of potentially harmful taxa. These changes have far-reaching effects, therefore, manipulating the gut microbiome is a potential therapeutic approach for treating AUD. Previous work has shown that a fecal microbiota transplant (FMT) can alter AUD-related behaviors in patients and can improve short-chain fatty acid (SCFA) levels, which were correlated with reduced craving for alcohol and a reported improved quality of life. However, the mechanisms behind why FMT is able to induce these changes is not well understood. Therefore, the goal of this study is to use stools from healthy human donors in a mouse model of alcohol consumption to determine what donor stool characteristics lead to reductions in alcohol consumption. **Methods:** Male and female C57BL/6J mice were treated with a course of antibiotics prior to FMT administration to remove the endogenous mouse microbiome and encourage cross-species engraftment. Three donor stools from healthy donors were used. Following FMT administration, mice began five weeks of drinking in an intermittent two-bottle choice paradigm with intermittent stool collection for metagenomic sequencing. **Results:** In female mice, receiving a FMT significantly decreased ethanol intake and preference with two of the three donor samples. In male mice, the opposite effect was observed: receiving a FMT resulted in an increase in ethanol intake and preference. Alpha and beta diversity changes were greater in female mice than males and female biomes clustered closer to the donor samples suggesting more successful engraftment in female mice. Species-specific changes were also found where *Bacteroides ovatus, a* commensal bacterium with anti-inflammatory properties which produces *GABA,* was significantly increased after donor 67 FMT and remained elevated and negatively correlated to alcohol preference during the 4 week course of drinking. In contrast, *Parabacteroides merdae,* associated with gut dysbiosis, was positively correlated to alcohol preference and higher in males. **Conclusion:** Together, these data show that a cross-species in FMT results in sex-specific changes in ethanol consumption and preference. These changes are further correlated with sex-specific differences in engraftment and in the abundance of specific taxa.



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3165 | EFFECT OF DIET, EXERCISE, AND ALCOHOL ABSTINENCE IN A PRE-CLINICAL MODEL OF METALD

Josiah Hardesty[1] Anjali kumari[1] Rui Treves[1] Craig McClain[1] Banrida Wahlang[1] Oluwanifemi Bolatimi[1] Yuan Hua[1] Nicolli Butzke-Souza[1], [1]University of Louisville

Background: Metabolic dysfunction- and alcohol-associated liver disease (MetALD) is a growing health concern due to rising rates of poor metabolic health and over-consumption of alcohol. Diet, exercise, and alcohol abstinence are the most effective and clinician recommended options to improve health outcomes for MetALD patients. However, we know very little about what these lifestyle intervention strategies do in the context of regressing MetALD pathology. This study aimed to identify signatures that are impacted by these lifestyle interventions in a mouse model of MetALD. **Methods:** Male (n = 10 per group) and female (n = 10 per group) mice were fed a high fat diet (HFD, 60% kcal from fat) and given 10% ethanol (EtOH) for 12 weeks (MetALD group) or for 6 weeks followed by the respective intervention including diet (HFD replaced with chow diet), exercise (3 days a week of 30 minute treadmill exercise), alcohol abstinence (10% EtOH replaced with water) or all interventions together. In addition, there was a control group that received all interventions for 12 weeks. Liver and plasma proteins were measured via ELISA and hepatic RNASeq was performed. Data were statistically compared via a one-way ANOVA with a Tukey's multiple comparison test and $p < 0.05$ was considered statistically significant. **Results:** MetALD induction with high-fat diet and EtOH resulted in marked hepatic steatosis, elevated AST/ALT, hyperglycemia, hyperinsulinemia, and increased inflammatory cytokines compared to controls. Lifestyle interventions produced differential improvements. Dietary intervention significantly reduced steatosis and blood transaminases, whereas exercise and alcohol abstinence yielded more modest effects. In contrast, combined intervention produced the most robust recovery, with significant reductions in steatosis and AST/ALT activity, approaching control levels. Glucose and insulin levels were also decreased across intervention groups, with the greatest normalization observed in the combined group. Inflammatory markers, including TNF-α and KC/GRO were elevated in MetALD and attenuated following intervention, most prominently with combined treatment. Exercise induced the greatest change in hepatic differentially expressed genes (DEGs) (3,116 DEGs) followed by dietary intervention (2,682 DEGs), all interventions (2,593 DEGs) and alcohol abstinence (1,857 DEGs). Overall, integrated lifestyle intervention produced the most consistent improvement across hepatic, metabolic, inflammatory, and hepatic gene expression endpoints. **Conclusion:** Integrated lifestyle modification is associated with consistent improvement in hepatic, metabolic, and inflammatory features of MetALD, supporting a multi-component approach for disease reversal.

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3166 | ANTI-INFLAMMATORY ACTION OF 18:2 CARDIOLIPIN TREATMENT IN AN *EX VIVO* MODEL OF ALCOHOL-ASSOCIATED LIVER DISEASE

Josiah Hardesty[1] Nicolli Butzke-Souza[1] Rui Treves[1], [1]University of Louisville

Background: Alcohol-associated liver disease (ALD) is characterized by unresolved chronic inflammation that drives chronic liver injury. Previous studies have demonstrated that unsaturated cardiolipin (CL) species can inhibit lipopolysaccharide (LPS)-mediated TLR4 activation, thereby limiting inflammatory signaling. However, this has not been evaluated in models of ALD where both ethanol (EtOH) and LPS are present. We hypothesized that 18:2 CL reduces inflammatory responses in mouse and human whole blood *ex vivo* models. **Methods:** Whole blood was extracted from naïve male (n = 10) and female (n = 9) C57Bl6/J mice (8-12 weeks) and stimulated for 2 hours with vehicle control, EtOH (40 mM), LPS (1 ng/mL), and 18:2 CL (1 -1000 nM). Whole blood from male (n = 10) and female (n = 10) human donors were treated in the same

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experimental paradigm. Cell supernatants were collected and cytokines were measured via a multiplex ELISA (MSD). Data were statistically compared by Kruskal-Wallis test followed by Dunn's post hoc analysis, and $p < 0.05$ was considered statistically significant. **Results:** In mouse samples, 18:2 CL reduced IL-2, IL-6, IL-10, and TNFα across all concentrations. IL-2 showed modest reductions (-1.46 -fold). IL-6 was markedly reduced by CL (-12.63-fold). IL-10 levels were also decreased following CL treatment (-2.79-fold). TNFα showed the most pronounced reductions with CL (-139.32-fold). In human samples, the same overall pattern was observed. 18:2 CL reduced IL-2, IL-6, IL-10, and TNFα across all concentrations. IL-2 showed modest reductions (-3.10-fold). Surprisingly, IL-6 showed the strongest response, with great reductions induced by CL (-48.27-fold). IL-10 was decreased following native CL treatment (-2.01-fold). TNFα was markedly reduced with CL (-26.30-fold). **Conclusion:** 18:2 CL attenuated inflammatory cytokine responses under combined EtOH and LPS exposure. This effect was consistent across both mouse and human *ex vivo* whole blood models. These findings suggest that cardiolipin composition influences inflammatory signaling, potentially through modulation of TLR4-dependent pathways and downstream cytokine production. Collectively, our results support 18:2 CL as a potential regulator of inflammation in ALD and highlight lipid peroxidation as a key determinant of its immunoregulatory function.

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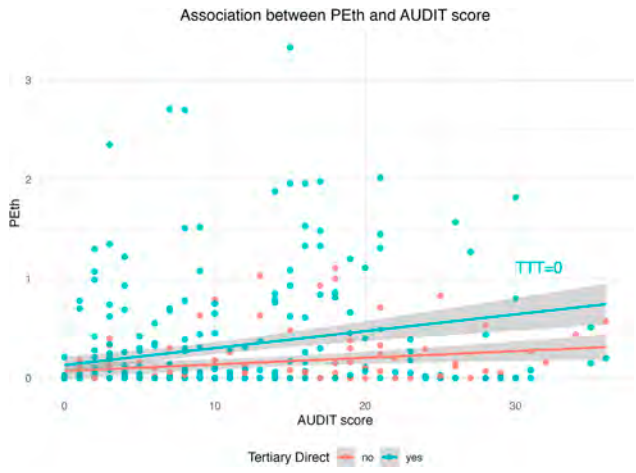
3167 | IMPACT OF TIME-TO-TERTIARY CARE ON PHOSPHATIDYLETHANOL LEVELS IN HOSPITALIZED PATIENTS WITH ADVANCED CHRONIC LIVER DISEASE: INSIGHTS FROM THE PROSPECTIVE RH7 REGISTRY

Svetlana Adamcova Selcanova[1] Daniela Zilincanova[2] Lubomir Skladany[3] Jana Ciefova[2] Daniel Jan Havaj[4] Karolina Kristina Sulejova[5] Martin Janicko[6] Lukas Laffers[7] Luis Díaz[8] Juan Pablo Arab[9], [1]Div.Hepatology, Gastroenterology, Liver Transplantation, [2]Div. Hepatology, Gastroenterology and Liver transplantation, [3]Faculty Hospital FD Roosevelt, [4]University Hospital of F. D. Roosevelt, [5]Dic. Hepatology, Gastroenterology and Liver Transplantation, [6]2nd Department of Internal Medicine, Medical school of PJS University, Kosice, [7]Department of Mathematics, Faculty of Natural Sciences, Matej Bel University, Banska Bystrica, [8]Division of Gastroenterology, Hepatology, and Nutrition, Department of Internal Medicine, Virginia, [9]Virginia Commonwealth University

Background: In hospitalized patients with advanced chronic liver disease (ACLD), objective assessment of alcohol consumption is essential. Phosphatidylethanol (PEth) is a promising biomarker for evaluating recent alcohol intake; however, its interpretation may be influenced by clinical factors, including hospitalization prior to tertiary admission. We aimed to evaluate the impact of time-to-tertiary care (TTT) on PEth concentrations and to examine whether TTT modifies the association between PEth and self-reported alcohol use estimated by the Alcohol Use Disorders Identification Test (AUDIT). **Methods:** This prospective cohort study included consecutive patients hospitalized with ACLD enrolled in the RH7 cirrhosis registry (NCT04767945). AUDIT and PEth have been included in RH7 since 2019 and 2020, respectively. TTT was treated as a binary variable (TTT = 0: direct admission; TTT > 0: prior secondary-care stay). The PEth–AUDIT association was examined separately in each TTT group using linear regression. **Results:** Of 387 patients, 287 (74%) were admitted directly to our tertiary liver and transplant unit (TTT = 0) and 100 (26%) were transferred from secondary hospitals (TTT > 0). Mean PEth did not differ significantly between groups (0.28 ± 0.53 vs. 0.16 ± 0.26 µmol/L; p = 0.91). However, when PEth was interpreted relative to AUDIT scores, a clinically meaningful discrepancy emerged: transferred patients reported significantly higher alcohol use by AUDIT (13.1 ± 9.9 vs. 8.6 ± 8.4; p < 0.001), had higher MELD scores (p < 0.001) and greater SAH prevalence (51% vs. 29%; p < 0.001), yet their PEth was numerically lower. This pattern — high self-reported alcohol exposure alongside attenuated PEth — is consistent with time-dependent biomarker washout during enforced abstinence prior to tertiary referral. The PEth–AUDIT association differed significantly between groups (Figure), identifying TTT as a relevant temporal confounder of PEth interpretation in hospitalized ACLD patients. **Conclusion:** TTT significantly influences PEth interpretation in hospitalized patients with ACLD. By attenuating PEth during enforced pre-referral abstinence, TTT may lead to underestimation of recent alcohol exposure despite high AUDIT scores.

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3168 | LIVER-SPECIFIC BHMT DEFICIENCY RECAPITULATES ALCOHOL-ASSOCIATED LIVER DISEASE PROGRESSION AND HEPATOCARCINOGENESIS DURING AGING

Ramachandran Rajamanickam[1] Sathish kumar Perumal[1] Karuna Rasineni[1] Kurt Fisher[1] Kusum Kharbanda[2]; [1]University of Nebraska Medical Center, [2]Omaha VA Medical Center and University of Nebraska Medical Center

Background: Betaine-homocysteine methyltransferase (BHMT) maintains hepatic methylation potential by regulating intracellular SAH levels and sustaining the SAM:SAH ratio. Chronic alcohol exposure disrupts this pathway, driving steatosis, inflammation, fibrosis, and hepatocellular carcinoma (HCC). To determine whether BHMT loss alone is sufficient to drive a similar disease trajectory, we evaluated aging-associated liver injury in liver-specific BHMT knockout (BHMT LKO) mice maintained on standard chow. **Methods:** BHMT floxed and BHMT LKO mice were aged to 6 months, 1 year, and 2 years. Endpoints included biochemical indices of liver injury, histopathology, fibrosis, lipid peroxidation, inflammation, and expression of canonical HCC markers and oncogenic signaling mediators. **Results:** BHMT LKO mice exhibited progressive, age-dependent liver injury mirroring alcohol-associated liver disease. By 2 years, LKO livers demonstrated marked steatosis, inflammation and fibrosis. Histological evaluation of hematoxylin-eosin and reticulin stained slides demonstrated markedly expanded hepatocyte plates, nuclear atypia, necrotic foci, central tumors, and architectural collapse, collectively consistent with malignant transformation and HCC development.Molecular profiling revealed a pronounced increase in HCC-associated markers, including the cellular myelocytomatosis oncogene (c-myc), golgi phosphoprotein 73, neutrophil gelatinase-associated lipocalin, glypican 3, and cyclin D2. This upregulation was accompanied by activation of multiple oncogenic and stress-responsive signaling pathways involving protein kinase B, nuclear factor kappa-light-chain enhancer of activated B cells, c-jun N-terminal kinase, extracellular signal-regulated kinase, p38 mitogen-activated protein kinase, and signal transducer and activator of transcription 3. Collectively, these molecular alterations mirror those typically induced by chronic alcohol exposure, underscoring that disrupted BHMT-dependent methylation control is a powerful driver of tumor-prone hepatic remodeling during aging. **Conclusion:** These findings establish that hepatic BHMT deficiency alone, even under basal nutritional conditions, is sufficient to trigger a progressive liver disease continuum culminating in HCC. The results highlight the BHMT-betaine metabolic axis as a critical endogenous defense against age-related hepatic injury and tumorigenesis and underscore the potential clinical relevance of BHMT loss-of-function variants in human liver disease risk.

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3169 | ENDOCRINE–METABOLIC REPROGRAMMING DRIVES A DISTINCT ONCOGENIC TRANSITION IN METALD

Sundararajan Mahalingam[1] Ramesh Bellamkonda[1] Ojeshvi Ethiraj[1] Carol Casey[1] Kusum Kharbanda[1] Karuna Rasineni[1]; [1]University of Nebraska Medical Center

Background: Steatotic liver disease (SLD) affects over 35% of the global population and is driven by metabolic dysfunction, alcohol use, or their combination. While metabolic dysfunction-associated steatotic liver disease (MASLD) and alcohol-associated liver disease (ALD) are well characterized, metabolic dysfunction and alcohol-associated liver disease (MetALD) has

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emerged as a highly aggressive and clinically distinct entity with increased risk of cirrhosis and mortality. The molecular mechanisms underlying this synergistic pathology remain poorly understood. **Methods:** We established experimental mouse models for MetALD (Western diet (ResearchDiets D12079B) + 15% alcohol in drinking water), ALD (chow diet + 15% alcohol in drinking water), and MASLD (Western diet + regular water). This feeding regimen was maintained for 18 weeks. **Results:** MetALD showed greater insulin resistance, hepatic steatosis, apoptosis, inflammation and fibrosis than either MASLD or ALD. Despite severe metabolic dysfunction, GLP-1 levels were paradoxically elevated alongside hyperghrelinemia that suppressed GLP-1 function through direct GHSR-GLP-1R interaction. This hormonal dysregulation was accompanied by amplified pro-fibrotic serotonin signaling, increased peripheral serotonin, and markedly reduced thyroid hormone receptor-β (THRB) signaling, exceeding the suppression observed in MASLD.These endocrine disruptions induce massive lipid accumulation and exacerbate a pathological nuclear lipid shunt via marked upregulation of fatty acid binding protein 5. Consequently, MetALD undergoes a unique and aggressive "metabolic oncogenic transition," linking metabolic dysfunction to early oncogenic reprogramming and accelerated fibrosis. Central to this transition is activation of the hepatocyte nuclear factor 4α (HNF4A), wherein it shifts from a homeostatic regulator to a co-activator of pro-proliferative forkhead box M1 and oncogenic MYC signaling, thereby promoting proliferation and fibrogenesis. **Conclusion:** MetALD is not merely an additive phenotype of MASLD and ALD, but a distinct endocrine-metabolic disorder driven by the ghrelin–serotonin-THRB axis. This axis precipitates metabolic dysfunction and reprograms hepatic signaling toward an oncogenic state. Targeting these converging pathways may provide novel therapeutic strategies to halt disease progression and prevent malignancy in MetALD.

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3170 | LONG-TERM BENEFITS OF ALCOHOL REHABILITATION IN PATIENTS WITH ALCOHOL-ASSOCIATED LIVER DISEASE: A CALL FOR ACTION

Ahmed Ibrahim[1] Mohamed Eldesouki[2] Eisha Saadat[3] Sajid Jalil[4] Ashwani Singal[5], [1]San Joquin General Hospital, [2]New York Medical College at Saint Michael Medical Center, [3]Agha Khan University, [4]Stanford University, [5]University of Louisville

Background: Alcohol-associated liver disease (ALD) is associated with a high morbidity and mortality. Currently, there are no liver-directed therapies for ALD, with control of alcohol use disorder (AUD) as the sole determinant to improve long-term outcomes. Data on the impact of alcohol rehabilitation on long-term outcomes is limited. **Methods:** We used the TriNetX Research Network (2010-2023), to examine adult patients with alcohol use disorder (AUD) and ALD. The study cohort was extracted using ICD codes. The cohort was stratified based on alcohol rehabilitation within 90 days, defined as ≥ 1 of: (1) enrollment in alcohol/substance use counseling, or (2) initiation of FDA-approved medications for AUD (acamprosate or naltrexone). The primary outcome was all-cause mortality at 3, 6, 12, and 36 months. Secondary outcomes included hospital readmission and liver-related decompensation (ascites, hepatic encephalopathy, variceal bleeding) at the same time. Propensity score matching (PSM) was used to balance baseline characteristics. **Results:** A total of 19,572 patients with AUD and ALD were identified; 1,035 (5.3%) engaged in alcohol rehabilitation within 90 days of discharge from the hospital. After PSM, 1,026 well-balanced pairs were analyzed. Alcohol rehabilitation was associated with lower all-cause mortality at 3 months (HR 0.55; 95%CI 0.50–0.58; $p = 0.02$), 6 months (HR 0.51; 95%CI 0.32–0.82; $p = 0.004$), 12 months (HR 0.67; 95%CI 0.49–0.92; $p = 0.01$), and 36 months (HR 0.63; 95%CI0.56–0.80; $p = 0.004$). Similarly, hospital readmission was consistently lower among patients receiving alcohol rehabilitation at 3 months (HR 0.87; 95%CI 0.76–0.98; $p = 0.02$), 6 months (HR 0.89; 95%CI 0.78–0.97; $p = 0.04$), 12 months (HR 0.93; 95%CI 0.82–0.99; $p = 0.04$), and 36 months (HR 0.80; 95% CI 0.70–0.95; $p = 0.03$). In addition, alcohol rehabilitation was associated with lower rates of liver-related decompensation, including ascites, hepatic encephalopathy, and variceal hemorrhage at 3, 6, 12, and 36 months (Table). **Conclusion:** In this real-world study, engagement with alcohol treatment was low. Alcohol rehabilitation appeared to improve patient survival, with reduced odds for readmission and decompensation. These findings underscore the clinical unmet need to adapt an integrated model with a focus on liver-targeted management combined with treatment for alcohol use, as a basis for providing comprehensive, holistic care to patients with ALD.

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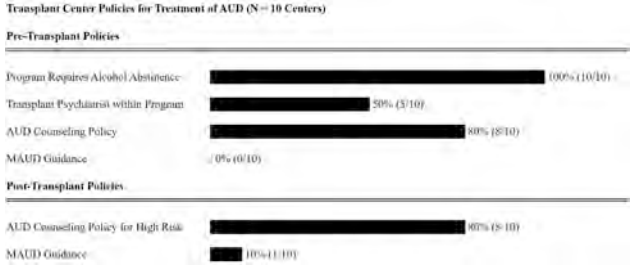
Outcomes	Alcohol rehab	No rehab	HR (95% CI), P	Alcohol rehab	No rehab	HR (95% CI), P
	3 months			6 months		
Ascites, n (%)	209 (20.4%)	276 (26.9%)	0.72 (0.60-0.88), <0.001	243 (23.6%)	306 (29.8%)	0.75 (0.63-0.86), <0.001
Hepatic encephalopathy, n (%)	374 (36.5%)	459 (44.7%)	0.76 (0.67-0.88), <0.001	402 (39.2%)	487 (47.5%)	0.77 (0.68-0.88), <0.001
Variceal bleeding, n (%)	48 (4.4%)	70 (6.8%)	0.63 (0.43-0.92), 0.01	63 (6.1%)	84 (8.2%)	0.73 (0.53-0.88), 0.04
Readmission, n (%)	423 (41.2%)	475 (46.3%)	0.87 (0.76-0.98), 0.02	451 (43.9%)	494 (48.1%)	0.89 (0.78-0.97), 0.04
All-cause mortality, n (%)	17 (1.7%)	34 (3.3%)	0.55 (0.50-0.58), 0.02	26 (2.5%)	50 (4.9%)	0.51 (0.32-0.82), 0.004
	12 months			36 months		
Ascites, n (%)	270 (26.3%)	329 (32.1%)	0.78 (0.66-0.91), 0.002	330 (32.2%)	388 (37.8%)	0.82 (0.71-0.95), 0.01
Hepatic encephalopathy, n (%)	445 (43.4%)	521 (50.8%)	0.79 (0.70-0.91), <0.001	518 (50.5%)	582 (56.7%)	0.85 (0.75-0.96), 0.007
Variceal bleeding, n (%)	80 (7.8%)	100 (9.7%)	0.78 (0.58-0.91), 0.01	110 (11.1%)	129 (12.6%)	0.76 (0.62-0.88), 0.03
Readmission, n (%)	490 (47.8%)	517 (50.4%)	0.93 (0.82-0.99), 0.04	559 (52.5%)	582 (56.7%)	0.80 (0.70-0.95), 0.03
All-cause mortality, n (%)	50 (4.9%)	94 (6.2%)	0.67 (0.49-0.92), 0.01	147 (14.3%)	184 (17.9%)	0.63 (0.56-0.80), 0.004

Disclosures: Ahmed Ibrahim:Nothing to Disclose, Mohamed Eldesouki:Nothing to Disclose, Eisha Saadat:Nothing to Disclose, Sajid Jalil:Nothing to Disclose, Ashwani Singal:Madrigal: Speaking and Teaching, Pleiogenix: Stock – privately held company, Pleiogenix: Consultant, CLD Foundation: Advisor, Medical Speaker's Network: Speaking and Teaching, Up-to-Date: Royalties or patent beneficiary, Medscape: Speaking and Teaching, University of Louisville School of Medicine: Employee, NIAAA: Grant/Research Support, Gastro Endo News: Executive role, Durect: Advisor, University of Louisville Health: Other.

3171 | TREATMENT OF AUD IN LIVER TRANSPLANT PATIENTS: A SURVEY OF TRANSPLANT CENTER POLICIES

Sheila Eswaran[1] Megan Saucke[2] Brian Fisher[2] Esra Alagoz[2] Sue Hyon Kim[3] Brian Lee[4] Marina Serper[5] Ethan Weinberg[3] Keren Ladin[6] John Rice[2] George Therapondos[7] Mohamed Shoreibah[8] R. Mark Ghobrial[9] Neha Jakhete[10] Kirti Shetty[11] Christine Hsu[12] Amol Rangnekar[13] Norah Terrault[14] Michael Lucey[2], [1]Northwestern Medicine, [2]University of Wisconsin, [3]University of Pennsylvania, [4]Keck School of Medicine, [5]University of Pennsylvania Health System, [6]Tufts Medical Center, [7]Ochsner Medical Center, [8]University of Alabama at Birmingham, [9]Houston Methodist JC Walter Transplant Center, [10]University of Maryland, [11]University of Maryland, Baltimore, [12]National Institute of Diabetes, Digestive, [13]Georgetown University Hospital, [14]University of Southern California

Background: Alcohol-associated liver disease (ALD) is the leading indication for liver transplantation (LT) in the United States, and while strategies to support long-term abstinence are endorsed by experts, relevant components of management of alcohol use disorder (AUD) in the pre- or post-LT setting are not established. This study characterizes institutional policies related to AUD management across 10 centers with dedicated focus of LT for ALD to gain insights into agreement and variation in practice. **Methods:** ACCELERATE consortium LT centers (geographically distributed across US) provided internal program policies related to AUD treatment before and after LT. All protocols were developed or revised between 2019 and 2025. We conducted a comparative analysis of internal institutional protocols based on the principles of qualitative document analysis using inductive thematic analysis. Documents were independently reviewed systematically and themes were developed inductively to capture emergent patterns. For higher level analysis, we constructed data matrices to facilitate comparison of policies across institutions. **Results:** All centers required patients to remain abstinent from alcohol before and after LT (10/10, 100%). Eight centers outlined an AUD treatment policy in both pre- and post-LT periods (8/10, 80%). Five centers explicitly stated that a transplant psychiatrist was available within the program to assess pre-LT AUD (5/10, 50%). Eight centers recommended post-LT AUD treatment for patients at high risk for return to drinking, as determined by pre-LT characteristics such as early LT (ie recent drinking) or being too ill to engage in pre-LT AUD treatment (8/10, 80%). Only one center specified treatment for patients with documented post-LT return to drinking, in addition to those at high risk (1/10, 10%). None of the policies specified whether AUD treatment was delivered by the LT program, the broader LT center, or external providers (0/10, 0%). No centers had a policy for MAUD pre-LT (0/10, 0%), and one center had a policy for MAUD post-LT (1/10, 10%). **Conclusion:** There is substantial center-level heterogeneity in specialist resources and in pre- and post-LT approaches to AUD treatment, including MAUD. Treatment policies tended to be vague about where and by whom treatment should be delivered. Typically, policies recommending MAUD were absent. Treatment of AUD in the post-LT period represents a key opportunity to intervene before returning to drinking becomes clinically harmful. Centers should strengthen internal resources, standardize their approach to AUD, and integrate MAUD to promote consistent, patient-centered care.



Disclosures: Sheila Eswaran:Nothing to Disclose, Megan Saucke:Nothing to Disclose, Brian Fisher:

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Nothing to Disclose, Esra Alagoz:Nothing to Disclose, Sue Hyon Kim:Nothing to Disclose, Brian Lee:NIAAA: Grant/Research Support, Novo Nordisk: Advisor, GSK: Advisor, HepaTx: Advisor, Siemens Healthineers: Grant/Research Support, AltImmune: Advisor, Assertio: Consultant, Marina Serper:Transplant Genomics: Grant/Research Support, Grifols: Grant/Research Support, Ethan Weinberg:Nothing to Disclose, Keren Ladin: Nothing to Disclose, John Rice:Nothing to Disclose, Nothing to Disclose, George Therapondos:Novo Nordisk: Consultant, Intercept: Speaking and Teaching, Madrigal: Speaking and Teaching, Ipsen: Speaking and Teaching, Gilead: Speaking and Teaching, Mohamed Shoreibah:Nothing to Disclose, R. Mark Ghobrial: Nothing to Disclose, Neha Jakhete:Gilead: Advisor, Ipsen: Advisor, Kirti Shetty:Nothing to Disclose, Christine Hsu:Nothing to Disclose, Amol Rangnekar:Nothing to Disclose, Norah Terrault:Elseiver: Royalties or patent beneficiary, GSK: Grant/Research Support, Elseiver: Royalties or patent beneficiary, Elseiver: Royalties or patent beneficiary, Eiger Pharmaceuticals: Grant/Research Support, GSK: Grant/Research Support, GSK: Grant/Research Support, Helio Health: Grant/Research Support, Eiger Pharmaceuticals: Grant/Research Support, Eiger Pharmaceuticals: Grant/Research Support, Durect Corp: Grant/Research Support, Helio Health: Grant/Research Support, ImmunoCore: Grant/Research Support, Helio Health: Grant/Research Support, Durect Corp: Grant/Research Support, HBV Foundation: Board member, Durect Corp: Grant/Research Support, AASLD: Executive role, ImmunoCore: Grant/Research Support, ImmunoCore: Grant/Research Support, Genentech-Roche: Grant/Research Support, HBV Foundation: Board member, HBV Foundation: Board member, Hepatitis B Foundation: Executive role, AASLD: Executive role, AASLD: Executive role, Genentech-Roche: Grant/Research Support, Genentech-Roche: Grant/Research Support, Hepatitis B Foundation: Executive role, Hepatitis B Foundation: Executive role, Elseiver: Royalties or patent beneficiary, Elseiver: Royalties or patent beneficiary, Elseiver: Royalties or patent beneficiary, Eiger Pharmaceuticals: Grant/Research Support, GSK: Grant/Research Support, GSK: Grant/Research Support, Helio Health: Grant/Research Support, Eiger Pharmaceuticals: Grant/Research Support, Eiger Pharmaceuticals: Grant/Research Support, Durect Corp: Grant/Research Support, Helio Health: Grant/Research Support, ImmunoCore: Grant/Research Support, Helio Health: Grant/Research Support, Durect Corp: Grant/Research Support, HBV Foundation: Board member, Durect Corp: Grant/Research Support, AASLD: Executive role, ImmunoCore: Grant/Research Support, ImmunoCore: Grant/Research Support, Genentech-Roche: Grant/Research Support, HBV Foundation: Board member, HBV Foundation: Board member, Hepatitis B Foundation: Executive role, AASLD: Executive role, AASLD: Executive role, Genentech-Roche: Grant/Research Support, Genentech-Roche: Grant/Research Support, Hepatitis B Foundation: Executive role, Hepatitis B Foundation: Executive role, Elseiver: Royalties or patent beneficiary, GSK: Grant/Research Support, Elseiver: Royalties or patent beneficiary, Elseiver: Royalties or patent beneficiary, Eiger Pharmaceuticals: Grant/Research Support, GSK: Grant/Research Support, GSK: Grant/Research Support, Helio Health: Grant/Research Support, Eiger Pharmaceuticals: Grant/Research Support, Eiger Pharmaceuticals: Grant/Research Support, Durect Corp: Grant/Research Support, Helio Health: Grant/Research Support, ImmunoCore: Grant/Research Support, Helio Health: Grant/Research Support, Durect Corp: Grant/Research Support, HBV Foundation: Board member, Durect Corp: Grant/Research Support, AASLD: Executive role, ImmunoCore: Grant/Research Support, ImmunoCore: Grant/Research Support, Genentech-Roche: Grant/Research Support, HBV Foundation: Board member, HBV Foundation: Board member, Hepatitis B Foundation: Executive role, AASLD: Executive role, AASLD: Executive role, Genentech-Roche: Grant/Research Support, Genentech-Roche: Grant/Research Support, Hepatitis B Foundation: Executive role, Hepatitis B Foundation: Executive role, Michael Lucey:Nothing to Disclose.

3172 | OUTCOMES FOLLOWING INDEX PRESENTATION WITH DECOMPENSATED ALCOHOL RELATED LIVER DISEASE PRE AND POST COVID: A RETROSPECTIVE COHORT STUDY

Sofia Baldelli[1] Yazan Haddadin[1] Sumita Verma[2], [1]University Hospitals Sussex, [2]Brighton and Sussex Medical School

Background: Liver deaths in England have increased by more than 60% in the past 20 years, largely due to increased prevalence of alcohol-related liver disease (ARLD). National surveys have shown a change in the pattern of alcohol consumption amongst high-risk drinkers following the COVID-19 lockdowns. The aim of this study was to assess the impact of the pandemic on the severity of local hospital admissions with ARLD.
Methods: A retrospective cohort study was conducted in a large teaching hospital in England across two three-year periods: pre-COVID19 (PrC19) and post-COVID19 (PoC19), 1st Jan 2017-31st Dec 2019 and 1st Jan 2021-31st Dec 2023 respectively. Patients who had an unplanned index admission with a decompensation event secondary to ARLD were screened. Eligibility criteria were a coded diagnosis of

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ARLD and a Child-Pugh Score (CPS) ≥8 and/or MELD ≥ 15. Demographic, socialand clinical data relating to the admission were collected from electronic hospital records. Outcomes included alcohol drinking patterns, prevalence of liver related complications, length of stay (LoS), and inpatient mortality. **Results:** A total of 210 patients met our eligibility criteria, 99 in the PrC19 period and 111 in the PoC19 period. Across our cohort mean age was 53 years and 66.2% were male. There were no differences in baseline demographics between the two groups. Alcohol consumption was significantly higher in the PoC19 cohort compared to the PrC19 group (200 vs 130 units/week, p = 0.004). During their index admission, the PrC19 cohort had significantly higher MELD (26 vs 22, p = 0.008),and UKELD scores (62.2 vs 59.7, p = 0.03), higher rates of admission to ITU (23.4% vs 11.1%, p = 0.019) and longer LoS (18 vs 12 days, p < 0.001) compared to the PoC19 cohort. Inpatient mortality rates were higher in PrC19 but did not reach statistical significance (25.2% vs 16.1%, p = 107). There were no differences in the prevalence of spontaneous bacterial peritonitis, ascites, hepatic encephalopathy, sepsis or variceal bleeding between the two groups. On multivariate analysis predictors of inpatient mortality were an admission to ITU (OR 12.7 [95%CI 3.0-54.1], p < 0.001), a higher UKELD score on admission (OR 1.15 [95%CI 1.05-1.26], p = 0.003) and older age (OR 1.08 [95%CI 1.02-1.14], p-0.013). **Conclusion:** This study highlights a concerning trend in the alcohol drinking habits of high-risk users in the years following the COVID-19 pandemic. This was associated with increasing severity of hospital admissions as well as resource utilisation. Our results are consistent with reported national trends and highlight the need for continued support in the community for patients with alcohol use disorder who might have been impacted by the social restrictions relating to the pandemic.

Disclosures: Sofia Baldelli:Nothing to Disclose, Yazan Haddadin:Nothing to Disclose, Sumita Verma:Beckton Dickinson: Grant/Research Support, Rocket Medical: Grant/Research Support, Gilead Sciences: Grant/Research Support.

3173 | PATTERNS AND OUTCOMES OF INPATIENT NUTRITION CONSULTATION IN HOSPITALIZED PATIENTS WITH CIRRHOSIS

Jazmin Mexia Cabrales[1] Hassan Sinan[1] Marcin Drzal[1] Joy Kim[1] Frances Lee[2], [1]Department of Medicine, NYC Health + Hospitals/Elmhurst, Icahn School of Medicine At Mt. Sinai, [2]Division of Liver Diseases, Icahn School of Medicine At Mount Sinai, New York, NY

Background: Malnutrition is highly prevalent in patients with cirrhosis and is independently associated with increased morbidity and mortality.[1,2] Both EASL and AASLD guidelines recommend nutrition consultation for hospitalized patients with cirrhosis, with AASLD suggesting evaluation within 24 hours of admission.[3,4] However, data evaluating the association between inpatient nutrition consultation and short-term clinical outcomes in this population remain limited. We aimed to evaluate the association between inpatient nutrition consultation and clinical outcomes in this high-risk population. **Methods:** We conducted a single-center retrospective cohort study of adult patients hospitalized with cirrhosis. Patients were stratified by receipt of inpatient nutrition consultation. Baseline demographics, comorbidities, laboratory values, MELD-Na score, and markers of hepatic decompensation were collected. The primary outcome was 90-day all-cause mortality. Secondary outcomes included ICU admission and 30-day readmission. Baseline characteristics and outcomes were compared between groups using chi-square and Mann–Whitney U tests, as appropriate. Multivariable logistic regression identified independent predictors of nutrition consultation and 90-day mortality. **Results:** Among 1151 patients, 198 (17.2%) received an inpatient nutrition consult. Patients receiving a consult were more frequently male, and demonstrated significantly greater liver disease severity, including lower BMI and albumin levels, higher MELD-Na, and greater prevalence of ascites. 30-day readmission did not differ between groups (26.5% vs 29.3%, p = 0.481). However, patients receiving a consult had higher ICU admission rates (7.1% vs 11.6%, p = 0.047) and 90-day mortality (7.1% vs 15.2%, p < 0.001). On multivariable regression, lower BMI, lower albumin, higher bilirubin, and higher creatinine were independently associated with receiving a consult. Although consultation was associated with higher 90-day mortality in unadjusted analysis, this was no longer significant after adjustment (OR 1.37, 95% CI 0.87–2.13, p = 0.166). Independent predictors of 90-day mortality included higher MELD-Na (OR 1.12, 95% CI 1.09-1.15) and lower albumin levels (OR 0.57, 95% CI 0.41-0.79). **Conclusion:** Despite guideline recommendations for nutrition assessment in all hospitalized patients with cirrhosis, a nutrition consult was obtained in fewer than one in five patients. Consults were directed toward patients with advanced liver disease, reflecting selective rather than systematic utilization. The association between nutrition consult and higher 90-day mortality was explained by disease severity rather than the consults themselves. These findings underscore the need for standardized nutrition screening protocols and prospective studies evaluating whether early, routine nutrition intervention improves outcomes in this population.

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Table A. Characteristics and Outcomes by Nutritio Consult Status

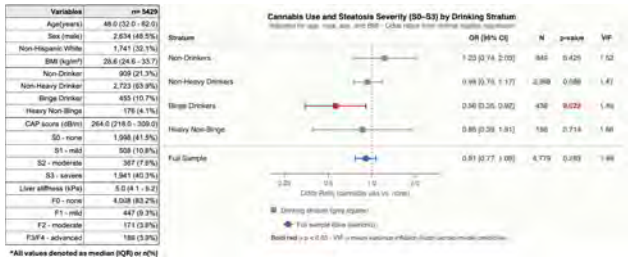
Variable	No Consult (N=953)	Nutrition Consult (N=198)	p-value
Demographics			
Age, median (IQR)	54.76 (43.97–67.34)	54.99 (44.53–68.88)	0.675
Male sex, n (%)	717 (75.2%)	157 (79.3%)	**0.037**
BMI, median (IQR)	27 (23.7–30.9)	26 (23.3–29.1)	**0.017**
Comorbidities			
Diabetes, n (%)	185 (19.4%)	37 (18.7%)	0.891
HCC, n (%)	18 (1.8%)	2 (1.0%)	0.398
Liver disease characteristics			
ALD cirrhosis, n (%)	878 (92.2%)	184 (92.9%)	0.735
Decompensated cirrhosis, n (%)	274 (28.8%)	88 (44.4%)	**<0.001**
Laboratory values			
Albumin, median (IQR)	3.5 (3–3.9)	2.9 (2.6–3.5)	**<0.001**
WBC, median (IQR)	6.96 (4.91–10.29)	8.5 (5.81–11.48)	**<0.001**
Sodium, median (IQR)	137 (134–140)	136 (131–140)	**0.034**
Creatinine, median (IQR)	0.82 (0.64–1.22)	0.89 (0.65–1.48)	0.086
INR, median (IQR)	1.3 (1.1–1.6)	1.4 (1.2–1.7)	**0.003**
Total Bilirubin, median (IQR)	1.3 (0.7–2.6)	2 (0.78–5.15)	**<0.001**
Severity scores			
MELD-Na, median (IQR)	12 (8–20)	18 (12–24)	**<0.001**
MELD 3.0, median (IQR)	14 (10–21)	19 (13–25)	**<0.001**
Decompensation events			
Ascites, n (%)	220 (23.1%)	79 (39.9%)	**<0.001**
Esophageal Variceal Bleeding, n (%)	67 (7%)	15 (7.6%)	0.904
Hepatic Encephalopathy, n (%)	50 (5.2%)	10 (5.1%)	1.000
SBP, n (%)	15 (1.6%)	3 (1.5%)	1.000
Clinical outcomes			
30-day Readmission, n (%)	253 (26.5%)	58 (29.3%)	0.481
ICU Admission, n (%)	68 (7.1%)	23 (11.6%)	**0.047**
90-day Mortality, n (%)	68 (7.1%)	30 (15.2%)	**<0.001**

Disclosures: Jazmin Mexia Cabrales:Nothing to Disclose, Hassan Sinan:Nothing to Disclose, Marcin Drzal: Nothing to Disclose, Joy Kim:Nothing to Disclose, Frances Lee:Nothing to Disclose.

3174 | CANNABIS USE IS ASSOCIATED WITH LOWER STEATOSIS SEVERITY AMONG BINGE DRINKERS: A NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY (NHANES) TRANSIENT ELASTOGRAPHY ANALYSIS

Calvin Tan[1] Rachan Narala[2] Brian Lee[3], [1]University of Southern California, [2]Stanford University, [3]Keck School of Medicine

Background: Alcohol-associated liver disease (ALD) causes liver-related morbidity and mortality. Prior studies suggest an inverse association between cannabis use and liver disease severity, particularly with heavy alcohol exposure, potentially mediated by cannabinoid receptor anti-inflammatory and anti-fibrogenic signaling. Whether this varies by alcohol-use pattern remains unclear. Binge drinking may provoke inflammatory cascades amenable to cannabinoid modulation. We assessed whether cannabis use is associated with steatosis severity across mutually exclusive drinking groups in a nationally representative cohort. **Methods:** We performed a cross-sectional analysis of National Health and Nutrition Examination Survey participants with transient elastography, a cohort with clinically suspected liver disease. Steatosis was assessed by controlled attenuation parameter (CAP) and staged S0-S3; fibrosis was assessed by liver stiffness measurement (LSM) and staged F0-F4. Participants were categorized as non-drinkers, non-heavy drinkers, binge drinkers, or heavy non-binge drinkers. Cannabis exposure was ever-use. Ordinal logistic regression was used for severity stages; linear regression was used for CAP and LSM. All models adjusted for age, race, sex, and BMI; variance inflation factors assessed multicollinearity. **Results:** Among 5,429 participants, median age was 48.0 years [IQR 32.0-62.0], 48.5% were male, 32.1% were non-Hispanic White, and median BMI was 28.6 kg/m² [IQR 24.6-33.7]. Most were non-heavy drinkers (63.9%), followed by non-drinkers (21.3%), binge drinkers (10.7%), and heavy non-binge drinkers (4.1%). Median CAP was 264.0 dB/m [IQR 218.0-309.0] and median LSM was 5.0 kPa [IQR 4.1-6.2]; severe steatosis and advanced fibrosis were present in 40.3% and 3.9% of participants, respectively. Among binge drinkers (N = 438), cannabis use was associated with 44% lower odds of more severe steatosis after covariate adjustment (OR = 0.56, 95%CI = 0.35-0.92; p = 0.022). A consistent but non-significant association was observed for CAP (β = -7.4 dB/m, 95%CI = -18.0 to 3.2; p = 0.17). Cannabis use was not associated with steatosis severity among non-drinkers (OR = 1.23; p = 0.43), non-heavy drinkers (OR = 0.94; p = 0.59), or heavy non-binge drinkers (OR = 0.86; p = 0.71). In the full sample (N = 4,779), cannabis use was not associated with steatosis severity after adjustment (OR = 0.91; p = 0.29). No associations were identified for fibrosis outcomes. **Conclusion:** Cannabis use was associated with lower hepatic steatosis severity exclusively among binge drinkers, who are most exposed to episodic alcohol-mediated inflammatory injury. The absence of a similar signal in other drinking groups or the pooled sample suggests the association may depend on alcohol-use behavior or exposure intensity. The biologic and behavioral mechanisms underlying this finding remain to be defined and should be explored in future studies.



Disclosures: Calvin Tan:Nothing to Disclose, Rachan Narala:Nothing to Disclose, Brian Lee:NIAAA: Grant/ Research Support, Novo Nordisk: Advisor, GSK: Advisor, HepaTx: Advisor, Siemens Healthineers:

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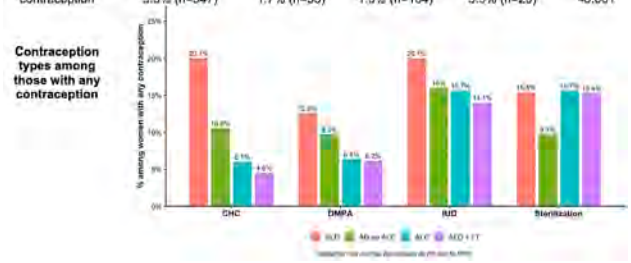
Grant/Research Support, AltImmune: Advisor, Assertio: Consultant.

3175 | CONTRACEPTIVE CARE ACROSS THE SPECTRUM OF LIVER DISEASE SEVERITY IN WOMEN WITH ALCOHOL-RELATED LIVER DISEASE

Rachael Mahle[1] Katherine Cooper[1] Haemi Lee[2] Jay Luther[1] Deepika Devuni[3], [1]Massachusetts General Hospital, [2]Ascension Columbia St Mary's, [3]UMass Memorial Health

Background: As alcohol-related liver disease (ALD) increasingly affects younger women, reproductive counseling and contraceptive care have growing importance. For the last decade, CDC guidance has supported broad contraceptive eligibility for women with liver disease, with no liver-specific contraindications in the absence of overt hepatic decompensation. However, real-world contraception use in reproductive-aged women with ALD remains poorly characterized. We aimed to evaluate contraceptive utilization across the spectrum of ALD severity. **Methods:** We performed a retrospective cohort study using the TriNetX US Collaborative Network of women aged <55 years (2019-2023) diagnosed with ALD or who underwent liver transplant (LT) for ALD. Patients were categorized as ALD without advanced liver disease, alcohol-related hepatitis (AH) without cirrhosis (K70.1 and bilirubin >3mg/dL), alcohol-related cirrhosis (ALC), or post-liver transplant (post-LT). Cohorts were mutually exclusive. The primary outcome was documented contraception use within 2 years of ALD diagnosis; the secondary outcome was incident pregnancy. Exploratory analyses evaluated contraception types, including intrauterine devices (IUD), combined hormonal contraceptives (CHCs), depot medroxyprogesterone acetate (DMPA), and sterilization. Group comparisons were performed using chi-square testing for overall contraception and for pairwise comparisons of contraception subtypes. **Results:** Among 32,176 women identified, 15,637 had ALD without documented ALC/AH, 3,092 had AH without ALC, 12,572 had ALC with or without AH, and 875 had ALD after LT. Documented contraception use differed significantly across ALD phenotypes, with the lowest rates observed among women with AH (11.3%) and ALC (11.6%) compared with women with ALD without ALC/AH (17.6%). Contraception was significantly higher in the post-LT cohort (27.5%) than in all three non-transplant ALD groups. Among women with any documented contraception, method of contraception differed across ALD phenotypes. CHC represented 20.1% of contraception use in ALD without AH/ALC, compared with 10.6% in AH without ALC and 6.1% in ALC. IUD utilization was similar in ALC and AH without ALC, while sterilization was more common in ALC than AH without ALC. Incident pregnancy was most common in women with ALD without AH or ALC. **Conclusion:** Contraception utilization declined with increasing ALD severity, with a marked increase in use after liver transplant. Notably, women with AH but no cirrhosis had contraception rates similar to women with ALC, though this did not apply to CHC. These results suggest that AH represents a clinical "gray zone" that may be approached cautiously due to diagnostic uncertainty or lack of clear management guidance. Future research is needed to understand contraception use in women with AH and to inform recommendations in this high-risk cohort.

	ALD (n=15,637)	AH no ALC (n=3,092)	ALC (n=12,572)	ALD + LT (n=875)	p-value
Age, median (IQR)	38 (13)	37 (11)	41 (10)	41 (7)	—
Any contraception	17.4% (n=2,721)	11.3% (n=349)	11.6% (n=1,452)	27.5% (n=241)	<0.001
CHC (pills, patch)	3.5% (n=547)	1.2% (n=37)	0.7% (n=88)	1.3% (n=11)	<0.001
DMPA shot	2.2% (n=344)	1.1% (n=34)	0.7% (n=93)	1.7% (n=15)	<0.001
Intrauterine device	3.5% (n=547)	1.8% (n=56)	1.8% (n=228)	3.9% (n=34)	<0.001
Pregnancy	6.7% (n=1,048)	2.5% (n=77)	2.3% (n=288)	2.3% (n=20)	<0.001
Sterilization	2.7% (n=422)	1.1% (n=34)	1.8% (n=228)	4.2% (n=37)	<0.001
Emergency contraception	3.5% (n=547)	1.7% (n=53)	1.5% (n=184)	3.3% (n=29)	<0.001



Disclosures: Rachael Mahle:Nothing to Disclose, Katherine Cooper:Nothing to Disclose, Haemi Lee: Nothing to Disclose, Jay Luther:Nothing to Disclose, Deepika Devuni:Nothing to Disclose.

3176 | ENVIRONMENTAL FOREVER CHEMICAL EXPOSURES ALTER SEVERITY AND METABOLIC SIGNATURES OF ALCOHOL-ASSOCIATED STEATOHEPATITIS VIA PPARA

Frederick Ekuban[1] Adrian Centers[1] Matthew Smith[2] Vatsalya Vatsalya[1] Kushal Biswas[3] Dhimiter Bello[3] Jennifer Schlezinger[4] Hao Zheng[1] Wanyu Zhang[1] Jasey McNabb[1] Addison Wiggam[1] Maiying Kong[1] Dean Jones[5] Craig McClain[1] Matthew Cave[1], [1]University of Louisville, [2]Emory University, Atlanta, [3]University of Massachusetts Lowell, [4]Boston University, [5]Emory University, Children's Healthcare of Atlanta

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Background: Although alcohol use is widespread, only a subset develop advanced liver injury, implicating modifiers beyond ethanol. Per- and polyfluoroalkyl substances (PFAS) are persistent chemicals linked to MASLD and recently detected in US beers above EPA limits (PMID: 40272161), creating exposure pathways for drinkers. Their role in alcohol-associated steatohepatitis (ASH) warrants investigation. We hypothesized that perfluorooctanoic acid (PFOA) disrupts hepatic metabolism and modifies ASH severity via PPARα-dependent mechanisms. **Methods:** Exposomics and metabolomics (LC-MS² & GC-MS²) were performed in archived plasmas from subjects with ASH (severe = 96, moderate = 28) and non-drinking controls (n = 11). Associations between biomarkers of PFOA exposure, ASH severity, and metabolome were determined using linear regression models. Male C57BL/6J mice on chronic-binge ethanol (EtOH) feeding were co-exposed to PFOA (2 mg/kg) or vehicle for 10 days, followed by a 5 g/kg EtOH binge. Liver disease phenotyping, including plasma/hepatic biochemistry, histology, qPCR, and Western blotting were performed. **Results:** Plasma PFOA was elevated in ASH versus controls ($P = 0.02$; 100% detection). MWAS vs PFOA identified 3,318 metabolic features ($P < 0.05$) enriching 32 pathways (fatty acid β-oxidation, glycerophospholipid, alanine/aspartate, urea cycle, glutathione, CYP450); 19 overlapped with the ASH disease-group MWAS, suggesting PFOA contributes to the ASH metabolomic signature. In mice, PFOA worsened EtOH-induced steatosis, hepatic triglycerides, and lipid peroxidation, and activated PPARα targets (*Cyp4a10, Acox1, Cpt1a, Cpt2, Fabp4, Scd2*) and CYP4A10 protein in both pair-fed and EtOH-fed mice, with upregulation of *Pxr, Cyp3a11, Cyp2b10, Pparγ, Cd36*. Interestingly, plasma ALT and AST were paradoxically reduced in EtOH+PFOA despite intensified tissue injury induction of *CHOP* (~50-fold), *Hmox1, Nqo1, Sod1/2; Tnf-α, Il-1β, Il-6*). Notably, this dissociation occurred alongside PFOA-driven induction of ethanol-metabolizing enzymes (*Adh1, Adh5, Aldh1a1, Aldh2, catalase*), CYP2E1 and ALDH1A1 protein, and markedly lowered blood alcohol ($P < 0.0001$). Cross-species pathway overlap spanned fatty acid β-oxidation, glycerophospholipid, transaminase substrates, glutathione, and CYP450. **Conclusion:** PFOA is elevated in ASH and broadly disrupts the plasma metabolome. In mice, PFOA exacerbates ALD severity through PPARα-driven hepatic lipid reprogramming and accelerated ethanol metabolism, producing a complex dissociation between reduced plasma injury biomarkers and intensified tissue injury. These findings identify PFOA as a candidate disease-modifying environmental factor in ASH and have implications for biomarker interpretation in environmentally exposed alcohol consumers. More data are required to establish clarity on the complex interactions between PFAS and alcohol and their role in liver disease.

Disclosures: Frederick Ekuban:Nothing to Disclose, Adrian Centers:Nothing to Disclose, Matthew Smith: Nothing to Disclose, Vatsalya Vatsalya:Nothing to Disclose, Kushal Biswas:Nothing to Disclose, Dhimiter Bello:Nothing to Disclose, Jennifer Schlezinger:Nothing to Disclose, Hao Zheng:Nothing to Disclose, Wanyu Zhang:Nothing to Disclose, Jasey McNabb:Nothing to Disclose, Addison Wiggam:Nothing to Disclose, Maiying Kong:Nothing to Disclose, Dean Jones:Nothing to Disclose, Craig McClain:Novo Nordisk: Speaking and Teaching, Intercept Pharmaceuticals: Grant/Research Support, Altimmune: Grant/Research Support, Target Pharma Solutions: Grant/Research Support, NIH: Grant/Research Support, VAMC: Grant/Research Support, VAMC: Employee, National Institutes of Health: Grant/Research Support, NovoNordisk: Speaking and Teaching, VAMC: Employee, VAMC: Grant/Research Support, Intercept Pharmaceuticals: Grant/Research Support, Target PharmaSolutions: Grant/Research Support, Matthew Cave:Nothing to Disclose.

3177 | GLOBAL PATTERNS OF ALCOHOL-RELATED CARDIOMYOPATHY AND ALCOHOL CONSUMPTION: AN ECOLOGICAL STUDY FROM 2017–2023

Denisse Rubio Cruz[1] Ximena Parraga[1] Kriti Soni[1] Tulio Correa[2] Rylyn Reyes[1] Hyundam (Dami) Gu[1] Joshua Chen[1] Adelina Horhat[1] Vinay Jahagirdar[1] Kavin Parmar[1] Krishan Patel[1] S. Fisher Rhoads[1] Stephen Hoang[1] Luis Antonio Diaz[1] Juan Pablo Arab[1], [1]Virginia Commonwealth University, [2]University of Pittsburgh

Background: Alcohol-related cardiomyopathy (ACM) is a severe complication of chronic alcohol exposure. Emerging evidence suggests that ACM may represent a more complex disease process than the sole consequence of end-organ ethanol toxicity. Nonetheless, ecological studies characterizing the global burden and geographic heterogeneity of ACM remain limited. **Methods:** We conducted a global ecological analysis including 184 countries across World Health Organization (WHO) regions. Country-level ACM prevalence and alcohol exposure metrics from 2017–2023 were analyzed to characterize geographic and temporal patterns of disease burden. Additionally, a multivariable linear regression was performed to illustrate the association between ACM prevalence and average daily alcohol intake (grams/day), adjusting for gross domestic product (GDP) per capita. To explore distributional differences, sex-specific analyses of alcohol exposure were also included. **Results:** An evident regional heterogeneity in ACM prevalence was

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observed, with the highest burden in the region of the Americas, and a relative stability throughout the available years. Higher daily alcohol intake by nations demonstrated a modest positive association with ACM, with slightly stronger effects on men compared to women; however, none of these models reached statistical significance ($p = 0.16$). The substantial disparities across regions may align with prior observations that cardiac susceptibility to alcohol is highly variable and potentially influenced by other determinants. Given the relatively short study period, delayed clinical manifestations of ACM might not be totally captured. **Conclusion:** Global ACM exhibits a wide geographic dispersion, where country-level alcohol consumption alone may not fully explain the observed trend. These findings may support the multifactorial nature of the ethanol-associated myocardial injury and highlight the need for further studies exploring environmental, socioeconomic, and biologic factors.

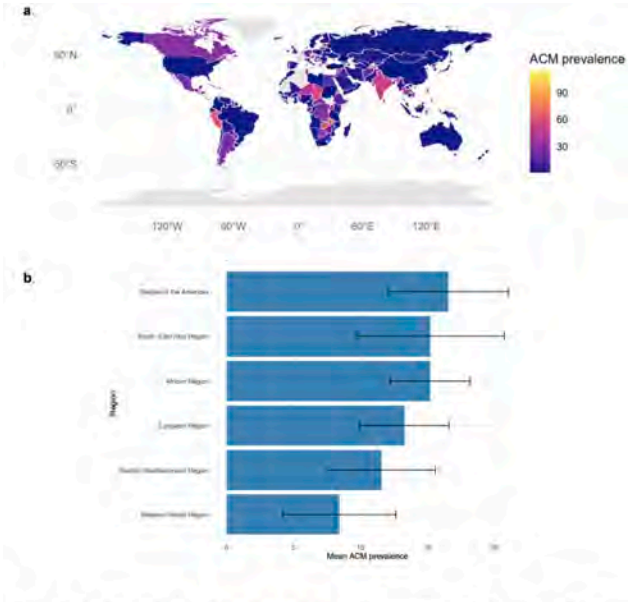


Figure 1a. Global prevalence of Alcoholic Cardiomyopathy by countries. **b.** Regional distribution according to the definitions of the World Health Organization (WHO); variability between nations is shown as standard error bars.

Disclosures: Denisse Rubio Cruz:Nothing to Disclose, Ximena Parraga:Nothing to Disclose, Kriti Soni:Nothing to Disclose, Tulio Correa:Nothing to Disclose, Rylyn Reyes:Nothing to Disclose, Hyundam (Dami) Gu: Nothing to Disclose, Joshua Chen:Nothing to Disclose, Adelina Horhat:Nothing to Disclose, Vinay Jahagirdar: Nothing to Disclose, Kavin Parmar:Nothing to Disclose, Krishan Patel:Nothing to Disclose, S. Fisher Rhoads: Nothing to Disclose, Stephen Hoang:PS Fertility: Consultant, Remedy Plan Inc. Consultant, Luis Antonio Diaz:Nothing to Disclose, Juan Pablo Arab:Nothing to Disclose.

3178 | TRENDS IN EXTRAHEPATIC ORGAN FAILURE CONTRIBUTING TO ALCOHOL-ASSOCIATED LIVER DISEASE MORTALITY IN THE UNITED STATES, 1999-2024: A NATIONAL DEATH CERTIFICATE ANALYSIS

Gabriel Lupu[1] A. Sidney Barritt[1] Isabelle Byers[1] Oren Fix[1] Andrew Moon[1] Anne Peery[1] Neil Shah[1] Hersh Shroff[1] Sasha Deutsch-Link[1], [1]University of North Carolina, Chapel Hill

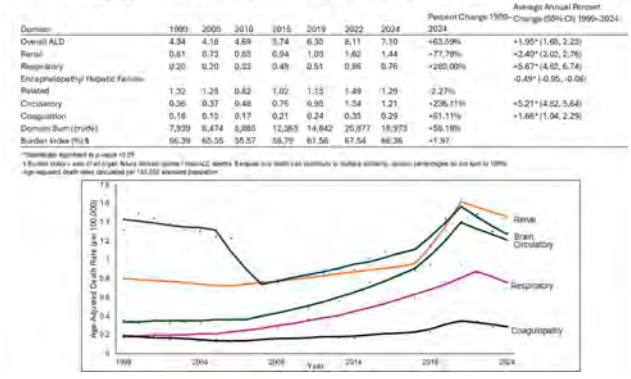
Background: Alcohol-associated liver disease (ALD) mortality has nearly doubled from 1999 to 2024, a trend further accelerated by increased alcohol consumption during the COVID-19 pandemic. Alcohol contributed to half of all cases of hepatic decompensation globally. In the US, ALD-related hospitalizations were rising among younger populations prior to the pandemic. Hospitalization in ALD is often complicated by acute-on-chronic liver failure (ACLF), a multiorgan failure syndrome triggered by hepatic injury in chronic liver disease and is associated with poor prognosis. We aimed to characterize temporal trends in extrahepatic organ failure domains contributing to ALD mortality across the United States. **Methods:** Data were extracted from the CDC WONDER Multiple Cause of Death (MCOD) publicly available database from 1999-2024 using ICD-10 codes to identify relevant cases. ALD (K70) was selected as the underlying cause of death. Contributing causes were grouped into organ dysfunction domains: renal (N17.0, N17.9, N19, K76.7), respiratory (J96.0, J96.9), circulatory (R57.1, R57.8, R57.9, A41.8, A41.9), encephalopathy/hepatic failure-related (G93.4, K72.0, K72.1, K72.9), and coagulopathy (D65, D68.4, D68.9). We calculated age-adjusted mortality rates and performed a Joinpoint regression to estimate annual percent change (APC) and overall average annual percentage change (AAPC) from 1999 to 2024. A yearly composite organ dysfunction burden index was also constructed. **Results:** Age-adjusted ALD-associated mortality nearly doubled from 1999 (4.34) to 2024 (7.10), with an AAPC of 1.95 (95% CI: 1.65, 2.25). Four of five organ failure domains contributing to ALD mortality increased: respiratory (AAPC: 5.67; 95% CI: 4.62, 6.74), circulatory (AAPC: 5.21; 95% CI: 4.82, 5.64), renal (AAPC: 2.40; 95% CI: 2.02, 2.76), and coagulopathy (AAPC: 2.40; 95% CI: 2.02, 2.76). The encephalopathy/hepatic failure-related domain slightly declined (-0.49; 95% CI: -0.95, -0.06). After 2021, ALD mortality and all organ domain trends declined. The composite organ dysfunction burden index increased from 66.4% to 68.4%. **Conclusion:** ALD mortality has increased substantially in the

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United States since 1999, with parallel increases of contributing extrahepatic organ dysfunction domains. We observed a parallel rise in multiorgan system failures among ALD deaths, most pronounced within circulatory and respiratory domains, and an increase in the composite organ dysfunction index. The absolute burden of systemic critical illness accompanying ALD mortality increased markedly, highlighting significant and persistent contribution of extrahepatic organ dysfunction to ALD mortality in the United States. The burden of ALD-associated mortality is accompanied by a greater severity of illness indicating a growing need for critical care interventions including circulatory and respiratory support.

Age-Adjusted Death Rates and Joinpoint Regression Analysis of Alcohol-Associated Liver Disease (ALD) with Contributing Organ Failure Domains, Selected Years 1999–2024



Disclosures: Gabriel Lupu:Nothing to Disclose, A. Sidney Barritt:Nothing to Disclose, Isabelle Byers: Nothing to Disclose, Oren Fix:Nothing to Disclose, Andrew Moon:TARGET RWE: Consultant, DCN Diagnostics: Grant/Research Support, Intercept Pharmaceuticals: DSMB, IDEOlogy: Consultant, Eisai: Consultant, AstraZeneca: Consultant, Sirtex: Consultant, Madrigal: Grant/Research Support, Anne Peery:Nothing to Disclose, Neil Shah:GSK: Consultant, GSK: Consultant, Ipsen: Consultant, Ipsen: Consultant, GSK: Consultant, GSK: Consultant, Ipsen: Consultant, Ipsen: Consultant, Hersh Shroff:Glaxo-Smith-Kline: Grant/Research Support, Sasha Deutsch-Link:Nothing to Disclose.

3179 | BEYOND MELD: ORGAN FAILURE MARKERS IMPROVE PREDICTION OF TRANSPLANT-FREE SURVIVAL IN SEVERE ALCOHOL-ASSOCIATED HEPATITIS

Elina Stoffel[1] Jacky Choi[2] Olivia Blocker[2] Himel Mallick[2] Gene Im[3] Elizabeth Verna[1] Stephanie Rutledge[2], [1]Columbia University Medical Center, [2]Weill Cornell Medicine, [3]Center for Liver Disease and Transplantation, Division of Digestive and Liver Diseases Columbia Univ

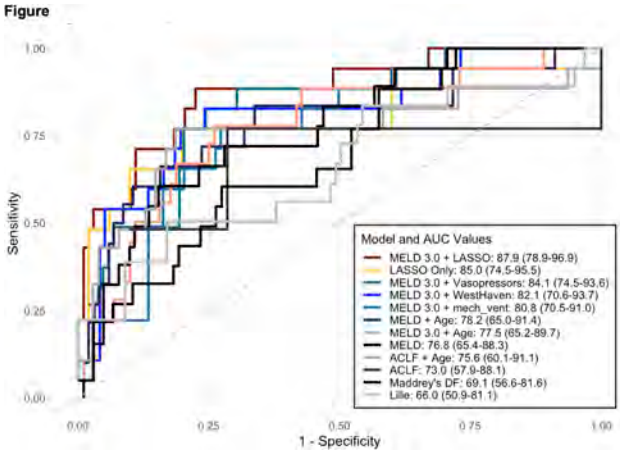
Background: Severe alcohol-associated hepatitis (sAH) carries high short-term mortality, particularly in the setting of acute-on-chronic liver failure (ACLF). Early liver transplantation (eLT) is lifesaving for selected patients, yet existing prognostic scores have limited discriminative ability in this population. We aimed to develop a prognostic model for transplant-free survival in patients with sAH undergoing eLT evaluation. **Methods:** This retrospective cohort study included adults hospitalized with sAH (NIAAA criteria; MELD >20) evaluated for eLT at two transplant centers (2012–2025). The primary outcome was death without LT at 90 days, with LT treated as a competing risk. LASSO stability selection (100 iterations, 80% subsamples) identified predictors beyond MELD 3.0 components. Four cause-specific Cox regression models were compared: (1) LASSO-selected variables only; (2) MELD 3.0 alone; (3) MELD 3.0 + all LASSO-selected variables; and (4) MELD 3.0 + individual LASSO variables. Discriminative performance was assessed using time-dependent AUC at 30, 90, and 180 days and benchmarked against established scores (Lille, Maddrey, ACLF grade, MELD-Age, MELD 3.0-Age, ACLF-Age). Optimal binary cutoffs were derived via stability-based subsampling. **Results:** Among 135 patients (median age 43; 62% male; 71% with ACLF), 21/135 (16%) died without LT, 67/135 (50%) underwent LT, and 47/135 (35%) survived without transplant. LASSO stability selection identified vasopressor use (100%), West -Haven encephalopathy grade (96%), and mechanical ventilation (53%) as stable predictors. The combined MELD 3.0 + LASSO model achieved the highest 90-day AUC (87.9%, 95% CI 78.9–96.9), substantially outperforming MELD 3.0 alone (76.8%, 95% CI 65.4–88.3) and all established scores, including Lille (66.0%), Maddrey (69.1%), and ACLF-Age (75.1%). Among individual additions to MELD 3.0, vasopressor use provided the greatest incremental improvement (AUC 84.1%). Optimal binary thresholds of MELD 3.0 ≥35 and West Haven grade ≥2 preserved discriminative performance (AUC 73.8%) There was no statistically significant difference in MELD 3.0 or ACLF grade between transplant-accepted and transplant-declined candidates. Results were consistent at 30 and 180 days. **Conclusion:** Incorporating markers of multiorgan dysfunction including vasopressor use, hepatic encephalopathy grade, and mechanical ventilation with MELD 3.0 substantially improves prediction of transplant-free mortality in patients with sAH undergoing eLT evaluation, demonstrating its clinical utility and practical applicability as a mortality risk tool for this population. Given the scarcity of donor organs and the potential for spontaneous recovery in a subset of patients with sAH, accurate risk

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stratification is essential to guide timely and equitable transplant decision-making.

Figure



Disclosures: Elina Stoffel:Nothing to Disclose, Jacky Choi:Nothing to Disclose, Olivia Blocker:Nothing to Disclose, Himel Mallick:Nothing to Disclose, Gene Im: KorroBio: Consultant, Echosens: Device support for research, Novo Nordisk: Advisor, Alimentiv: Consultant, GSK: Consultant, Altimmune: Consultant, Bayer: Consultant, Elizabeth Verna:Nothing to Disclose, Stephanie Rutledge: Nothing to Disclose.

3180 | FGF21 ORCHESTRATES HEPATIC PHOSPHOLIPID REMODELING TO MITIGATE ALCOHOL-INDUCED LIVER INJURY IN AGED MICE

Fangfang Zeng[1] Alday Alejandro[1] Qinggong Ping[1] Mengwei Zang[1], [1]University of Texas Health Science Center at San Antonio

Background: Alcohol-associated liver disease (ALD) is a leading cause of liver-related morbidity and mortality worldwide, yet targeted clinical interventions are absent. Although aged individuals exhibit susceptibility to severe liver injury and mortality, the underlying molecular mechanisms remain largely elusive. Our previous studies established fibroblast growth factor 21 (FGF21) as a critical metabolic hepatokine, which has recently emerged as a novel longevity factor. Here, we investigated how aging shapes the hepatic lipidome and phospholipid landscape to influence ALD pathogenesis. **Methods:** Young and aged mice were subjected to the NIAAA chronic-plus-binge ethanol feeding model. FGF21 knockout mice were utilized, and pharmacological recombinant FGF21 (1 mg/kg/day) was administered. **Results:** Lipidomic analysis revealed age-associated remodeling of the hepatic phospholipid landscape. Specifically, phosphatidylethanolamine (PE), a critical structural phospholipid required for membrane integrity, exhibited a selective depletion and a reduction of docosahexaenoic acid (DHA)-containing PE species in aged livers, suggesting disrupted membrane lipid homeostasis. Coinciding with this PE depletion, aged livers displayed a significant decrease in PCYT2, the rate-limiting enzyme in the Kennedy pathway for PE biosynthesis. Following chronic-binge ethanol feeding, aged mice displayed impaired PCYT2 signaling and developed severe ALD, suggesting that aged mice exhibited amplified hepatocellular phospholipid remodeling. Furthermore, ethanol consumption resulted in an accumulation of senescent hepatocytes and a robust pro-inflammatory SASP signature in aged mice, which accelerates alcohol-induced liver fibrosis. Interestingly, genetic FGF21 deficiency further aggravated ALD in aged mice, which was accompanied by downregulation of PCYT2 and activation of SASP signaling. Therapeutically, pharmacological administration of FGF21, which is currently in clinical trials, protected against age-related ALD by restoring PCYT2 expression and repressing hepatocyte senescence. **Conclusion:** The aging liver undergoes selective PE depletion and distinct phospholipid remodeling that promotes hepatocyte senescence and shapes a pro-inflammatory microenvironment. FGF21 functions as a previously unrecognized upstream regulator of the PCYT2-driven Kennedy pathway to control ALD progression, offering a potential therapeutic avenue specifically for ALD in the aged population.

Disclosures: Fangfang Zeng:Nothing to Disclose, Alday Alejandro:Nothing to Disclose, Qinggong Ping: Nothing to Disclose, Mengwei Zang:Nothing to Disclose.

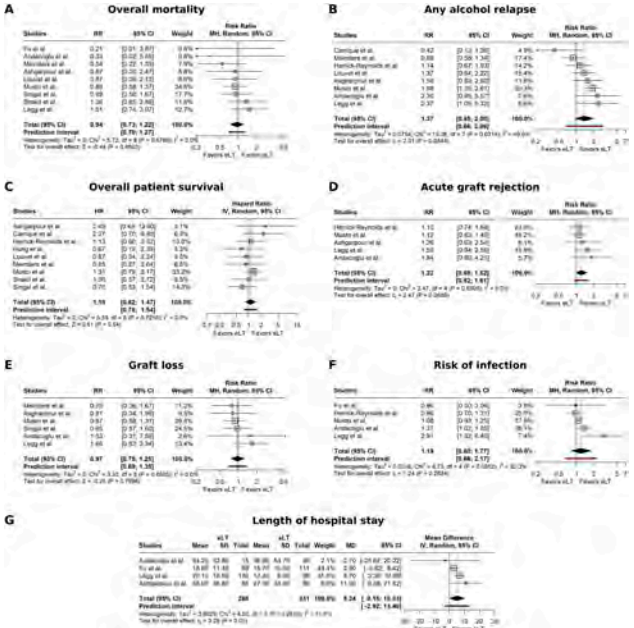
3181 | TRANSPLANT TIMING IN ALCOHOL-RELATED LIVER DISEASE: A META-ANALYSIS OF EARLY VERSUS STANDARD LIVER TRANSPLANTATION

Solonas Symeou[1] Eitan Dines[2] Ricardo Andre Rios Esparza[3] Georgios Tsoulfas[4], [1]University of Ioannina, [2]Carmel Medical Center, [3]Universidad Autonoma De Ciudad Juarez, [4]Aristotle University of Thessaloniki

Background: The 6-month abstinence period before listing patients with alcohol-associated liver disease (ARLD) for liver transplantation (LT) is the current standard practice, followed by most transplant centers worldwide. However, its prognostic validity is still debated for two main reasons: (a) it has not been prospectively validated; (b) patients with ARLD may not survive long enough to make it onto the waitlist. **Methods:** A systematic literature search across three

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databases (Medline, Scopus, Cochrane Library) was conducted to identify relevant studies comparing early LT (eLT; <6 months of alcohol abstinence) and standard LT (sLT; >6 months of alcohol abstinence). The primary outcomes were overall mortality and any alcohol relapse. Secondary outcomes were risk of graft loss, acute graft rejection, post-operative infection rate, and length of hospital stay. A random-effects model was used for all statistical inferences. **Results:** Twelve studies comparing eLT and sLT for ARLD were included in the quantitative synthesis. Although the trend for overall mortality (RR = 0.94, 95% CI: 0.73–1.22) and any alcohol relapse (RR = 1.37, 95% CI: 0.95–2.00) favored the sLT group, neither was statistically significant. Interestingly, even though the risk of acute graft rejection was higher for eLT patients (RR = 1.22, 95% CI: 0.98–1.52), the risk of graft loss was lower in the same group (RR = 0.97, 95% CI: 0.75–1.25), but none statistically significant. Post-operative infection was higher for eLT patients (RR = 1.19, 95% CI: 0.80–1.77) and, although not significant, it might be associated with the significantly higher length of hospitalization (MD = 5.24 days, 95% CI: 0.15–10.33). **Conclusion:** In appropriately selected ARLD patients, eLT appears to be a comparable approach to sLT. Although length of hospitalization may be higher with eLT, the available data do not suggest it is inferior to sLT. Therefore, eLT should be encouraged as an alternative treatment for ARLD when medical therapy fails.



Disclosures: SOLONAS SYMEOU:Nothing to Disclose, EITAN DINES:Nothing to Disclose, RICARDO ANDRE RIOS ESPARZA:Nothing to Disclose, GEORGIOS TSOULFAS:Nothing to Disclose.

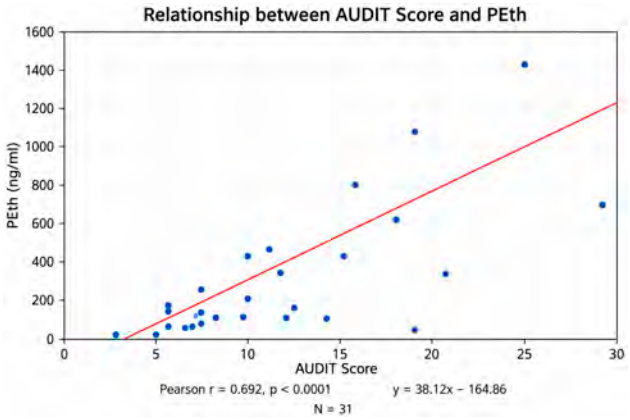
3182 | CLINICAL APPLICATION OF PHOSPHATIDYLETHANOL IN ALCOHOL-ASSOCIATED LIVER DISEASE IN TAIWAN

Chun-Ming Hong[1] Ching-Hua Lee[2] Ching-Hua Kuo[1] Tung-Hung Su[1] Shih-Jer Hsu[1] Tai-Chung Tseng[1] Hung-Chih Yang[1] Shang-Chin Huang[3] Jia-Horng Kao[1] Chun Jen Liu[1] Pei-Jer Chen[1], [1]National Taiwan University Hospital, [2]School of Pharmacy, College of Medicine, National Taiwan University, [3]National Taiwan University Hospital Bei-Hu Branch

Background: Alcohol-associated liver disease (ALD) has become a serious issue worldwide in recent years and the most common cause of advanced liver disease and leading indication for liver transplantation. It is essential to recognize ALD patients. Acquiring the information of alcohol intake is essential though challenging. Under-reporting may happen and some patients may not be able to report the accurate amount of alcohol intake or cannot be interviewed due to encephalopathy or alcohol intoxication. Therefore, a biomarker with the ability to detect recent alcohol intake is helpful. Phosphatidylethanol (PEth), an ethanol metabolite, can be used as a biomarker for alcohol use in recent 1-4 weeks. There is a consensus that a cut-off value for PEth (16:0/18:1) over 20ng/mL indicates excessive alcohol use. However, usage of PEth is limited in most countries. Our study tried to investigate clinical application of PEth in ALD patients in Taiwan. **Methods:** We conducted a prospective study in National Taiwan University Hospital from May 2025 to March 2026. Upon recruitment, clinical information, AUDIT (Alcohol Use Disorders Identification Test) questionnaire, laboratory tests, and blood were obtained. PEth (16:0/18:1) was measured by liquid chromatography-tandem mass spectrometry from whole blood samples. Testing for PEth was conducted with an Agilent (Santa Clara, USA) 1290 UHPLC system coupled with an Agilent 6460 triple quadrupole LC/MS system. **Results:** Forty-one patients were recruited. Thirty-seven (90.2%) were male. Average age was 58 years old. 22 patients (53.7%) had HBV infection and one had positive anti-HCV Ab. Nine patients (22%) were cirrhotic. Average total bilirubin was 1.2 mg/dL, average AST was 41.5 U/L, average ALT was 36 U/L, and average GGT was 184.9 U/L. 21 patients (51.2%) had AUDIT scores more than 8 points. Average PEth (16:0/18:1) was 256.6 ng/mL. Pearson correlation coefficient between AUDIT score and PEth (16:0/18:1) concentration was 0.692. **Conclusion:** PEth proves to be a reliable biomarker for recent alcohol exposure and its levels correlate with AUDIT scores. Despite its cost and limited accessibility, measurement of PEth should be implemented in the workup of ALD in Taiwan.

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3183 | THERMONEUTRAL HOUSING ALTERS ETHANOL METABOLISM AND EXACERBATES GUT PERMEABILITY IN A MOUSE MODEL OF ALCOHOL-ASSOCIATED LIVER DISEASE

Monica Barrios López[1] Laura Fàbrega[1] Susana Nuñez[1] Nayra Rico[2] Carmen Garcia-Ruiz[1] Jose Fernandez-Checa[1], [1]Institute of Biomedical Research of Barcelona (IIBB-CSIC), [2]Biochemistry and Molecular Genetics Department-CDB, Hospital Clínic de Barcelona, 08036 Spain

Background: Current mouse models of alcohol-associated liver disease (ALD) are typically housed at 22°C, which imposes chronic cold stress on rodents whose thermoneutral zone is 30–32°C. This variable may alter disease severity and the mechanisms under study. This study investigates the impact of thermoneutral housing on ALD development, hypothesizing that it elicits distinct metabolic and pathological responses compared to standard housing conditions **Methods:** Male C57BL/6J 8 wks old mice were housed at 22°C or 30°C and subjected to the NIAAA acute-on-chronic ethanol feeding model. Histological and biochemical analysis were assessed in serum and liver tissue. Intestinal barrier integrity was also evaluated. **Results:** Thermoneutral housing attenuated ethanol-induced weight loss and developed exacerbated hepatomegaly with more pronounced histological tissue disorganization, inflammatory infiltration, and ballooning compared to 22°C counterparts. Besides blood ethanol levels were lower in mice housed at 30°C, hepatic acetaldehyde concentration was higher under thermoneutral conditions, what was accompanied by a significant increase in CYP2E1 activity in mice under thermoneutral conditions, suggesting a dissociation between ethanol clearance and toxic metabolite accumulation. Interestingly, serum ALT and AST were elevated by ethanol exposure but not significantly differences were observed between the ethanol-fed groups. Moreover, occludin expression in the gut was lower in mice housed at 30ºC than 22ºC, indicating a temperature-dependent effect on gut barrier homeostasis. These observations paralleled the levels of NO, which were elevated under thermoneutral conditions and further exacerbated by alcohol consumption. **Conclusion:** These data demonstrate that thermoneutral housing elicits distinct metabolic and pathological changes in response to ethanol compared to standard housing, primarily through altered ethanol metabolite dynamics and disrupted gut barrier function. This refined model allows for the study of ALD complexities, potentially offering a more comprehensive understanding of the disease and the influence of environmental factors on its progression and severity.
Disclosures: Monica Barrios López:Nothing to Disclose, Laura Fàbrega:Nothing to Disclose, Susana Nuñez:Nothing to Disclose, Nayra Rico:Nothing to Disclose, Carmen Garcia-Ruiz:Nothing to Disclose, Jose Fernandez-Checa:Nothing to Disclose.

3184 | ASSESSING ALCOHOL RELAPSE AFTER ADOPTION OF EARLY LIVER TRANSPLANTATION IN ALCOHOL-ASSOCIATED LIVER DISEASE

Amani Allen[1] Karen Young[1] Stephanie Garbarino[1], [1]Duke University

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Background: Alcohol-associated liver disease (ALD) is now the leading indication for liver transplantation (LT) in the United States. Many transplant centers have shifted away from the traditional 6-month abstinence requirement and toward individualized psychosocial risk assessment to allow expedited liver transplant (ELT) for eligible patients. Although intended to expand transplant access, the impact of this policy on alcohol relapse and post-transplant outcomes remains poorly understood relative to pre-policy outcomes at the same center. **:** This study compares outcomes of patients transplanted for ALD after implementation of an early access policy with historical controls under stricter criteria at the same institution. **Methods:** This single-center, retrospective cohort study evaluated adult LT recipients transplanted for ALD. Patients transplanted after implementation of an early access policy without a 6-month abstinence period ("post-policy cohort": 01/01/2023 – 08/31/2024) were compared with a historical cohort transplanted under the 6-month abstinence requirement ("pre-policy cohort": 01/01/2018 – 12/31/2020). Outcomes were collected through May 2026 (minimum 9 months of follow up) in the post-policy cohort, and at least 6 months in the pre-policy cohort. Demographic, clinical, and post-transplant outcomes were extracted from the electronic medical record. Categorical variables were compared using $\chi 2$ and continuous variables using t tests. Median values were compared. **Results:** 141 patients underwent LT during the study period, including 69 patients in the pre-policy cohort and 72 patients in the post-policy cohort. Baseline demographic characteristics were similar between groups. Patients in the post-policy cohort had significantly fewer relapses prior to LT (50.1% vs 25.0%, $p = 0.002$). The post-policy cohort also demonstrated higher median MELD 3.0 scores (21 vs 26, $p = 0.0198$) at the time of LT. Overall relapse rates were similar between groups (26.1% vs 15.3%, $p = 0.112$), with no significant differences in time to relapse, graft dysfunction, or post-transplant mortality. Among patients who relapsed, heavy alcohol use was lower in the post-policy cohort (13.0% vs 0%, $p = 0.005$). **Conclusion:** Despite shorter pre-LT abstinence and greater illness severity, relapse and graft dysfunction rates were similar in patients undergoing LT at the same transplant center with a less strict transplant policy. These findings support expanding transplant access with individualized, evidence-based relapse risk assessment while preserving favorable long-term outcomes.

Table 1. Patient characteristics and relapse outcomes

Characteristic	Pre-policy (N = 69)	Post-policy (N = 72)	Total (N = 141)	p-value
Age, median (IQR)	54 (47-61)	51 (41-59)	53 (43-60)	0.19
Gender (male)	51 (73.9%)	44 (61%)	95 (67.4%)	0.11
Race				
White	62 (89.9%)	60 (83.3%)	122 (86.5%)	
Black	3 (4.3%)	6 (8.3%)	9 (6.4%)	
Asian	2 (2.9%)	0 (0%)	2 (1.4%)	0.43
Hispanic	1 (1.4%)	3 (4.2%)	4 (2.8%)	
Other	1 (1.4%)	3 (4.2%)	4 (2.8%)	
Medicaid-primary	7 (10.1%)	8 (11.1%)	15 (10.6%)	0.75
Listing days, median (IQR)	106 (35-181)	107.5 (31-182.5)	107 (33-181)	0.649
History of prior relapse	35 (50.1%)	18 (25%)	53 (37.6%)	0.002
10+ drinks per day pre-LT	26 (37.7%)	30 (41.7%)	56 (39.7%)	0.629
Legal history related to alcohol	20 (30.0%)	16 (22.2%)	36 (25.5%)	0.357
Drinking after cirrhosis	33 (47.8%)	29 (40.3%)	62 (44.0%)	0.367
Significant psychiatric comorbidities	20 (30.0%)	28 (38.9%)	48 (34.0%)	0.215
Time from last drink, (mos) median (IQR)	12 (7-19)	9.5 (9.5-20.5)	11 (6-19)	0.15
<6-month sobriety	7 (11.3%)	19 (35.8%)	26 (18.4%)	0.013
MELD 3.0, median (IQR)	21 (17-30)	26 (20-32)	24 (19-31)	0.0198
MELD Na, median (IQR)	22 (17-29)	26 (19.5-31.5)	24 (18-30)	0.022
Overall relapse	18 (26.1%)	11(15.3%)	29 (20.1%)	0.11
PEth score, median (IQR)*	338 (159-511)	53 (25-115)	153.5 (47-362.5)	0.0013
Time to relapse after LT, (mos) median (IQR)	20 (15-29)	15 (12-19)	19 (12-24)	0.144
Relapse detected	18 (26.1%)	11 (15.3%)	29 (20.6%)	0.112
Heavy alcohol use based on first reported PEth†	9/18 (50.0%)	0/11 (0.0%)	9/29 (31.0%)	0.005
Graft dysfunction	7 (10.1%)	2 (2.8%)	9 (6.4%)	0.074
Mortality	7 (10.1%)	3 (4.2%)	10 (7.1%)	0.167

*First positive post-transplant PEth score.
†Heavy alcohol use was defined as a PEth score >200.

Disclosures: Amani Allen:Nothing to Disclose, Karen Young:Nothing to Disclose, Stephanie Garbarino:Nothing to Disclose.

3185 | BRIDGING GAPS IN ALCOHOL-ASSOCIATED LIVER DISEASE SCREENING WITHIN ADDICTION MEDICINE

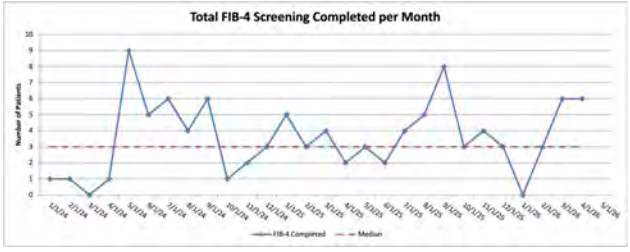
Michael Carducci[1] Natalie Buslach[2] Vilajet Kovaci[1] Talia Ostrow[1] Jeremy Ziring[1] Sharon Rikin[1] Laila Khalid[1] Rebecca Roediger[3] Alexander Vogel[4] Clara Tow[1], [1]Montefiore Medical Center, [2]Montefiore Medical Center, [3]Weill Cornell Medicine, [4]Montefiore Einstein

Background: The global burden of excessive alcohol consumption constitutes over 3 million deaths, including 25% of global cirrhosis deaths. Early diagnosis of alcohol-associated liver disease is complicated by a long asymptomatic latency period. Identifying high risk patients can provide opportunity to intervene prior to developing cirrhosis. Many at-risk patients are seen outside of specialized hepatology clinics, necessitating screening pathways adapted for primary care and addiction medicine clinics. We aim to (1) identify gaps in screening for alcohol-associated liver disease within

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an addiction medicine clinic and (2) introduce a standardized pathway to increase screening rates for alcohol related liver disease. **Methods:** We created a screening pathway with addiction and hepatology faculty, adapted from metabolic liver disease guidelines, to risk stratify patients with alcohol use disorder (AUD) at an addiction medicine clinic in a large, urban, academic medical center. It was formatted into an electronic medical record smart phrase and distributed to all providers. An education session was held during grand rounds prior to implementation. New patients with AUD were classified as low, indeterminant, or high-risk with the FIB-4 using labs within 3 months of initial visit. Low-risk patients required no evaluation. Indeterminant-risk patients (FIB-4 1.31-2.67) were referred for vibration-controlled transient elastography (VCTE), while high-risk patients (FIB-4 >2.68) were referred to hepatology. A baseline review of new patients between 1/2024 and 12/2025 was conducted. The intervention was implemented 2/3/2026. **Results:** Baseline review identified 148 patients. Of these, 82 had an initial FIB-4; 43 were low-risk, 19 were indeterminate-risk and 20 were high-risk. Among indeterminate-risk patients, VCTE was ordered for four (two completed) and three were referred to hepatology (two completed visit). Among high-risk patients, one VCTE was ordered (not completed). Five were referred to hepatology (four completed visit). After the implementation of the workflow, there were 24 new patients between 2/3/2026-5/1/2026. FIB-4 was completed for 15 patients. In total, 6 were indeterminant-risk, two of whom were referred for VCTE. Two were high-risk, and both were referred to hepatology. The remainder did not have FIB-4 screening. Two patients who were not high risk were referred to hepatology. **Conclusion:** In our clinic, screening for alcohol-associated liver disease is underutilized in patients with AUD. Referral to hepatology is similarly underutilized, though appointment attendance rates were high. Following the introduction of a screening algorithm implemented through a smart phrase, limited initial data trend towards increased FIB-4 screening and appropriate referral to hepatology, though fibroscan was still underutilized. Though preliminary, this is a promising intervention to improve screening rates.



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3186 | VISIUM HD ANALYSIS IDENTIFIES HEPATIC CELL TYPE TRANSCRIPTOME CHANGES DUE TO HEPATOCYTE *PTPMT1*$^{-/-}$ IN ALCOHOL-ASSOCIATED LIVER DISEASE

Josiah Hardesty[1] Rui Treves[1] Nicolli Butzke de Souza[1] Anjali Kumari[1], [1]University of Louisville

Background: Alcohol-associated liver disease (ALD) impacts multiple cell types within the liver contributing to disease pathogenesis. Our group has identified hepatocyte cardiolipin (CL) deficiency as a contributing factor to ALD pathogenesis using a protein tyrosine phosphatase mitochondrial 1 (Ptpmt1, rate limiting enzyme for CL synthesis) hepatocyte specific KO model. In this study we performed Visium HD analysis on liver tissues for WT and *Ptpmt1*$^{-/-}$ mice at 9 and 48 h post ethanol+galactosamine (EtOH-GalN) exposure. Our goal for this study was to identify cell types affected by hepatocyte specific *Ptpmt1* KO in an experimental animal model of ALD. **Methods:** Visium HD analysis was performed on 4 individual liver sections per experimental group. Space ranger was performed to generate count data followed by bin2cell analysis and data visualization in SpatialX software. A two-way ANOVA with a Tukey multiple-comparison test was performed for the transcriptome of each hepatic cell type identified. **Results:** There were 433 differentially expressed genes (DEGs), 243 of which were downregulated with *Ptpmt1*$^{-/-}$. Genes involved in cell cycle progression (*Ccna1*) and mitochondria coded genes (*mt-Co1*) were downregulated in hepatocytes with *Ptpmt1*$^{-/-}$. In the Kupffer cell (KC) population there were 149 DEGs. Among the downregulated KC DEGs in the KO vs WT was *Mki67* which may be indicative of reduced KC repopulation after injury. *Csf3r* was upregulated in KCs which may indicate a novel KC subtype in ALD. In the hepatic neutrophil population there only 16 DEGs when comparing KO vs WT. *Pgm2* was upregulated in neutrophils of KO vs WT mice which can suggest metabolic changes promoting infiltration. *Axl* was reduced in neutrophils in KO vs WT mice which could be a novel neutrophil subtype in ALD. **Conclusion:** A spatial transcriptomic approach and data analysis method was performed to identify hepatic cell type transcriptomic changes in an experimental model of ALD. Future studies are needed to validate novel cell

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subtype and identify how they are changing due to hepatocyte specific *Ptpmt1*$^{-/-}$ in ALD.
Disclosures: Josiah Hardesty:Nothing to Disclose, Rui Treves:Nothing to Disclose, Nicolli Butzke de Souza: Nothing to Disclose, Anjali kumari:Nothing to Disclose.

3187 | CXCL12–CXCR4 AXIS IS ASSOCIATED WITH ENRICHMENT OF CXCR4$^+$ CD8$^+$ T CELLS IN ALCOHOL-ASSOCIATED LIVER DISEASE

Gil Won Lee[1] Pil Soo Sung[2] Ji Won Han[2] Hee Sun Cho[2] Kwon Yong Tak[2], [1]Liver Research Center, [2]Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea

Background: Chemokine-mediated immune cell trafficking contributes to alcohol-associated liver disease (ALD), but mechanisms linking stromal remodeling to CD8$^+$ T-cell recruitment remain unclear. This study aimed to characterize CXCR4$^+$ CD8$^+$ T cells and evaluate the role of the CXCL12–CXCR4 axis in ALD. **Methods:** Peripheral blood mononuclear cells from patients with ALD and healthy controls were analyzed by single-cell RNA sequencing and flow cytometry. Public liver single-cell datasets were integrated to identify CXCR4- and CXCL12-expressing populations. Chemotaxis was assessed using transwell assays, and liver tissues were analyzed by immunohistochemistry. **Results:** Single-cell analysis identified an exhausted/activated CD8$^+$ T-cell subset characterized by PDCD1 (PD-1) and TOX expression, with enriched CXCR4 expression and activation/cytotoxic gene signatures. In peripheral blood, CXCR4$^+$ CD8$^+$ T cells showed increased activation (CD38$^+$HLA-DR$^+$) and cytotoxicity (GrB$^+$Perforin$^+$), associated with disease severity. These cells were detected in both blood and liver, with enrichment in the liver. CXCL12 induced dose-dependent migration of CD8$^+$ T cells, with enrichment of CXCR4$^+$ CD8$^+$ T cells in migrated populations. Liver single-cell analysis identified mesenchymal stromal populations, including stellate-like and perivascular cells, as major sources of CXCL12, with CXCL12–CXCR4 signaling identified as a potential interaction pathway. **Conclusion:** CXCR4$^+$ CD8$^+$ T cells represent a functionally distinct subset with enhanced activation and cytotoxic features in ALD. These findings support a model in which mesenchymal cell–derived CXCL12 contributes to the enrichment and spatial positioning of CXCR4$^+$ CD8$^+$ T cells within fibrotic niches in ALD.
Disclosures: Gil Won Lee:Nothing to Disclose, Pil Soo Sung:Nothing to Disclose, Ji Won Han:Nothing to Disclose, Hee Sun Cho:Nothing to Disclose, Kwon Yong Tak:Nothing to Disclose.

3188 | RELATIONSHIP OF PRESCRIPTION FOR MEDICATIONS FOR ALCOHOL USE DISORDER AND RETURN TO DRINKING AFTER ADMISSION FOR ALCOHOL-ASSOCIATED HEPATITIS

Krishan Patel[1] Vinay Jahagirdar[2] Omar Albhaisi[2] Husam Mikati[3] Shaanit Sen[4] Butros Fakhoury[1] Na Bo[5] Hannah Kissel-Smith[2] Juan Pablo Arab[1], [1]Virginia Commonwealth University, [2]VCU Medical Center, [3]Virginia Commonwealth University Health System, [4]VCU School of Medicine, [5]VCU

Background: Alcohol-associated hepatitis (AH) is a severe inflammatory manifestation of alcohol induced liver injury associated with high mortality, and increasing alcohol consumption has led to a growing incidence of AH. Continued alcohol intake is a primary driver of poor outcomes after AH, and alcohol cessation remains a mainstay of treatment. Unfortunately, patients with AH are known to be at an increased risk of return to drinking. Growing evidence demonstrates that medical therapy for alcohol use disorder (MAUD) may mitigate this risk in patients with alcohol related liver disease (ALD) and may improve clinical outcomes. The aim of this study was to assess the impact of receipt of MAUD on 30 and 90-day return to drinking after AH hospitalization. **Methods:** We performed a retrospective single center chart review for patients age $\geq$ 18 years with index admission for AH from March 2023 to March 2025. Patient characteristics, receipt of MAUD (naltrexone, acamprosate, gabapentin, baclofen, disulfiram) at discharge, addiction medicine consult, readmission date and reason, phosphatidylethanol (PEth) (ng/ml), drinks per day, receipt of liver transplant, and date and reason for first unplanned readmission were abstracted. Primary outcomes were return to any drinking within 30 and 90 days as noted in subsequent clinic or inpatient documentation. Multivariate regression was performed. Patients who died, were readmitted due to non-alcohol related reasons, or had liver transplant during admission were excluded. **Results:** A total of 230 patients with AH were included. Mean age was 44.7 ± 11.3 years, with 40% female, 72% white, and median MELD 3.0 of 25 (IQR 21-29). Addiction medicine was consulted for 68% of patients. In total 79 patients (34%) received MAUD, of which were primarily acamprosate (68%) and/or gabapentin (45%). Mean PEth was 575ng/ml. Return to drinking occured in 23% and 34% of patients at 30 and 90 days, respectively. In multivariate models, patients who received MAUD trended toward higher odds of return to drinking at 30 days (aOR 3.05, 95% CI 0.97-10.8) but no difference at 90 days (aOR 1.35, 0.50-3.84) (Table 1). Predictors of return to drinking at 30 days were outside hospital transfer (aOR 4.78, 1.46-17.9) and age (aOR

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1.07,1.01-1.14) and at 90 days were ascites (2.87,1.08-7.91), higher MELD (aOR 1.10,1.02-1.20), and less likely PEth >200ng/ml (aOR 0.30, 0.09-0.87). **Conclusion:** In patients hospitalized for AH, the receipt of MAUD at discharge did not mitigate return to drinking at 30 and 90 days; however, the retrospective nature of this analysis limits standardized alcohol reporting in patients who did not have interval clinic follow up or hospitalization. Prospective studies are needed to assess differences in time-to-drinking and impact of MAUD on return to harmful drinking specifically, impact of comorbid psychiatric conditions, and differential efficacy of certain MAUD agents over others.

Table 1. Multivariate regression model for predictors of return to any drinking at 30 and 90-days in patients with index alcohol-associated hepatitis hospitalization

	30 day return to drinking		90 day return to drinking	
Variable	aOR (95% CI)	P value	aOR (95% CI)	P value
Race				
Asian/Other/Unknown	Ref		Ref	
Black	0.33 (0.01-3.79)	0.413	0.27 (0.02-2.28)	0.254
Hispanic	0.56 (0.01-22.9)	0.740	0.05 (0.00-0.75)	0.042
White	0.58 (0.02-4.88)	0.657	0.75 (0.07-5.15)	0.787
Male	0.70 (0.20-2.22)	0.549	1.02 (0.35-2.93)	0.964
PEth >200 ng/ml	0.37 (0.10-1.17)	0.108	0.30 (0.09-0.87)	**0.036**
Housing status				
Stable	Ref		Ref	
Unstable/homeless	1.51 (0.23-14.5)	0.688	0.88 (0.15-5.60)	0.890
Employment status				
Disability/Retired	Ref		Ref	
Employed	4.96 (1.10-24.1)	0.039	2.45 (0.60-10.5)	0.216
Unemployed	5.06 (0.97-30.7)	0.063	2.82 (0.63-13.4)	0.179
Substance use	0.91 (0.25-3.70)	0.895	0.61 (0.19-1.98)	0.407
Psychiatric diagnosis	0.35 (0.10-1.11)	0.086*	0.35 (0.11-1.00)	0.056*
Outside hospital transfer	4.78 (1.46-17.9)	**0.013**	1.95 (0.68-5.68)	0.221
HE at index	0.99 (0.30-3.24)	0.987	0.68 (0.24-1.85)	0.448
Ascites at index	2.85 (0.91-9.14)	0.071*	2.87 (1.08-7.91)	**0.036**
GI bleeding at index	1.52 (0.32-11.5)	0.634	1.18 (0.32-5.06)	0.812
Receipt of MAUD	3.05 (0.97-10.8)	0.068	1.35 (0.50-3.84)	0.558
Age (per year)	1.07 (1.01-1.14)	**0.039**	1.03 (0.98-1.09)	0.230
Discharge MELD 3.0 (per point)	1.03 (0.94-1.12)	0.524	1.10 (1.02-1.20)	**0.019**
Drinks per day (per drink)	1.00 (0.91-1.09)	0.914	1.03 (0.96-1.12)	0.466

PEth: phosphatidylethanol HE: hepatic encephalopathy, GI: gastrointestinal, MAUD: medication for alcohol use, MELD: model for end stage liver disease. P values in bold= statistically significant, and * denotes trend toward significance

Disclosures: Krishan Patel:Nothing to Disclose, Vinay Jahagirdar:Nothing to Disclose, OMAR ALBHAISI: Nothing to Disclose, Husam Mikati:Nothing to Disclose, Shaanit Sen:Nothing to Disclose, Butros Fakhoury: Nothing to Disclose, Na Bo:Nothing to Disclose, Hannah Kissel-Smith:Nothing to Disclose, Juan Pablo Arab:Nothing to Disclose.

3189 | SEASONAL PATTERNS IN ALCOHOL-ASSOCIATED LIVER DISEASE MORTALITY IN THE UNITED STATES: A NATIONWIDE ANALYSIS FROM 1999-2024

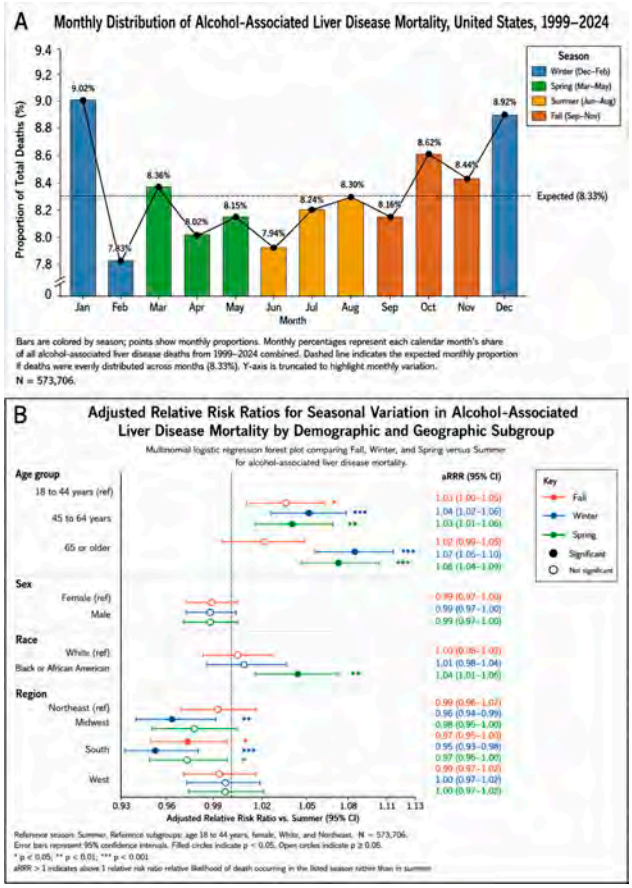
EzzElDien A. Ibrahim[1] Mohammad Alkhateeb[1] Akram Alnounou[2] Nourhan Saleh[1] Mahmoud Majed Mansour[1] Islam Mohamed[1] Jeremy Louissaint[3] Juan Pablo Arab[4] Karn Wijarnpreecha[5] Nikki Duong[6], [1]University of Missouri, Columbia, MO, USA, [2]Western Michigan University Homer Stryker M.D. School of Medicine, USA, [3]University of Texas Southwestern, Dallas, TX, USA, [4]Virginia Commonwealth University School of Medicine, Richmond, VA,USA, [5]Mayo Clinic, Jacksonville, FL, USA, [6]Stanford University, Palo Alto, CA, USA

Background: Alcohol-associated liver disease (ALD) is the leading cause of liver-related mortality in the United States (U.S.). However, seasonal variation in ALD-related mortality and its interaction with demographic and geographic factors remain poorly characterized. We aimed to evaluate potential patterns in seasonal variation in ALD mortality. **Methods:** This is a retrospective cross-sectional analysis of U.S. death certificate data from the CDC WONDER multiple cause of death database from 1999 to 2024. Adults aged ≥18 years with ALD-related mortality were identified using the ICD-10 code K70. Deaths were categorized by meteorological season (Winter: December–February; Spring: March–May; Summer: June–August; Fall: September–November), age group (18–44, 45–64, ≥65 years), sex, race (White, Black), and U.S. Census region. Multinomial logistic regression with summer as the reference season was used to estimate adjusted relative risk ratios (aRRR) with 95% confidence intervals (CIs), adjusting for age, sex, race, and region. **Results:** Among 573,706 ALD-related deaths, the seasonal distribution was winter 25.8%, fall 25.2%, spring 24.5%, and summer 24.5%. January (9.02%) and December (8.92%) accounted for the greatest monthly proportions of deaths, while February had the lowest (7.83%). Compared with summer, adults aged ≥65 had significantly higher relative risk of death during winter (aRRR 1.07, 95% CI 1.05–1.10, p < 0.001) and spring (aRRR 1.06, 95% CI 1.04–1.09, p < 0.001). Adults aged 45–64 years demonstrated increased winter (aRRR 1.04, 95% CI 1.02–1.06, p < 0.001) and spring (aRRR 1.03, 95% CI 1.01–1.06, p = 0.004) mortality, whereas adults aged 18–44 (reference) showed a relative summer excess. Compared with White individuals, Black individuals demonstrated increased mortality in spring (aRRR 1.04, 95% CI 1.01–1.06, p = 0.006). Compared with the Northeast, the South had significantly lower relative risk of mortality in fall (aRRR 0.97, 95% CI 0.95–1.00, p = 0.031) and winter (aRRR 0.95, 95% CI 0.93–0.98, p < 0.001), while the Midwest had lower mortality in winter (aRRR 0.96, 95% CI 0.94–0.99, p = 0.005). **Conclusion:** ALD mortality in the United States demonstrates significant seasonal variation, with differential patterns across age, race, and geographic regions. Older adults (≥45 years) showed increased winter–spring mortality, while younger adults (18–44) showed a relative summer excess. Though effect sizes were modest, the consistency of these findings across a large national cohort suggests that seasonally targeted hepatology outreach and alcohol cessation programs

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during higher-risk periods may help reduce ALD mortality in vulnerable populations.



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3190 | PREDICTORS OF ALCOHOL RELAPSE AFTER LIVER TRANSPLANTATION FOR ALCOHOL-RELATED LIVER DISEASE: A RETROSPECTIVE COHORT ANALYSIS

Christina Leyson[1] Bipneet Singh[1] Mustafa Alzubaidi[1] Fady Salama[1] Venkata Rajesh Konjeti[1] Nimish Thakral[1], [1]University of Kentucky

Background: Alcohol relapse after liver transplantation (LT) for alcohol-related liver disease (ALD) threatens graft survival. Identifying modifiable predictors including pharmacotherapy type, timing, transplant indication, and pre-LT abstinence is critical. **Methods:** Retrospective analysis of patients transplanted for ALD at a single center. AUD-specific pharmacotherapy included naltrexone, acamprosate, disulfiram, and topiramate. Gabapentin (neuropathy), baclofen (cramps), and varenicline (smoking) were analyzed separately. Early initiation was defined as prescription at first post-LT visit. Relapse was classified as slip or sustained relapse. **Results:** Sixty-eight patients were included (75% male; mean age 50 ± 11; mean BMI 30 ± 7). Most were transplanted for alcoholic cirrhosis (AC, 84%) versus alcoholic hepatitis (AH, 10%). At median 4-year follow-up, 19 patients (28%) relapsed: 7 slips, 12 sustained relapses. Relapse rates were similar between AH (29%) and AC (26%). Mean pre-LT abstinence was shorter among relapsers (5 vs. 10 months). Only 22 patients (32%) received AUD-specific pharmacotherapy; 9 (41%) relapsed, versus 22% of untreated patients — likely reflecting reactive prescribing after relapse. Early AUD pharmacotherapy (n = 6, 9%) was associated with 17% relapse versus 50% with late initiation. Gabapentin users had lower relapse (23%, 10/43) than non-users (36%, 9/25). Baclofen (27%, 3/11) and varenicline (17%, 1/6) showed similar trends. Two patients on GLP-1 RAs had no relapse. Non-pharmacological interventions were used in only 12%. **Conclusion:** In this cohort of patients transplanted for ALD, the overall alcohol relapse rate was 28%, with no significant difference between AH and AC indications. Shorter pre-LT abstinence was associated with higher relapse risk. AUD-specific pharmacotherapy was prescribed in only one-third of patients and was predominantly initiated late, likely as a reactive measure after relapse. Early proactive AUD pharmacotherapy at the first post-LT visit was rare (9%) but was associated with a numerically lower relapse rate (17% vs. 50% for late initiation. Gabapentin, though prescribed for neuropathy/pain, was associated with a lower relapse rate (23%) compared to non-users (36%), hinting that known anti-craving properties may confer incidental benefit even when prescribed for other indications. Both AUD-specific pharmacotherapy and non-pharmacological interventions were markedly underutilized, suggesting a need to shift focus from reactive to proactive AUD management.

Disclosures: Christina Leyson:Nothing to Disclose, Bipneet Singh:Nothing to Disclose, Mustafa Alzubaidi:

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Nothing to Disclose, Fady Salama:Nothing to Disclose, Venkata Rajesh Konjeti:Nothing to Disclose, Nimish Thakral:Nothing to Disclose.

3191 | INTEGRATING AI-DRIVEN HISTOPATHOLOGY AND SPATIAL TRANSCRIPTOMICS IDENTIFIES CELLULAR FUNCTIONAL STATES OF DUCTULAR REACTION IN ALCOHOL ASSOCIATED LIVER FAILURE

Ankita Srivastava[1] Madison Shoraka[2] Rajanikanth Vadigepalli[2], [1]Thomas Jefferson University, [2]University of New Mexico School of Medicine

Background: Alcohol-associated Hepatitis (AH) is a severe inflammatory manifestation of ALD characterized by acute-onset jaundice and liver enzyme abnormalities in the setting of long-term heavy alcohol use with high short-term mortality and limited therapies. AH is a frequent complication of alcohol-associated liver disease (ALD) that accounts for ~40% of liver transplantations. AH is characterized by hepatocellular dysfunction, immune activation, and aberrant proliferation of biliary phenotypic cells, referred to as the ductular reaction (DR). We hypothesize that morphological and molecular features within the liver tissue microenvironment can identify cellular functional states associated with the metabolic dysfunction in AH. **Methods:** High-resolution spatial transcriptomics (Visium HD) and histopathology data were obtained from human liver FFPE tissue from non-ALD (n = 1), AH (n = 6), and alcohol associated cirrhosis (n = 1). The spatial molecular data was analyzed at 16um resolution to identify hepatocyte- and cholangiocyte-like cell subtypes and their functional states. These molecularly defined cell states were positioned along a transcriptional continuum spanning fully hepatocyte-like to fully cholangiocyte-like gene expression profiles. We used AI-driven histopathology to segment the morphology associated with transitioning cells and progressive DR, and mapped the associated spatial molecular profiles with the DR morphologies. **Results:** We found multiple cholangiocyte-like cell states associated with proliferation, inflammation, progenitor cells, secretory cells, and ductular reaction in AH. The distribution of cells partitioned along the transcriptional continuum from fully hepatocyte-like to fully cholangiocyte-like gene expression profiles revealed transitioning states that correlated with the cholangiocyte subgroups. The differential gene expression analysis along the continuum identified metabolic processes with altered expression based on the proportion of hepatocyte versus cholangiocyte archetype. **Conclusion:** Our results point to a spectrum of metabolic, inflammatory, and proliferative cellular states across hepatocytes and cholangiocytes as underlying the progressive ductular reaction in AH.

Disclosures: Ankita Srivastava:Nothing to Disclose, Madison Shoraka:Nothing to Disclose, Rajanikanth Vadigepalli:Nothing to Disclose.

3192 | UNRAVELING THE PROGRESSIVE REMODELING AND FUNCTIONAL EXHAUSTION OF PERIPHERAL NK CELLS IN ALCOHOL-ASSOCIATED LIVER DISEASE PROGRESSION

Young-Sun Lee[1] Ji Hoon Kim[2] Yang Jae Yoo[2] Jong eun Yeon[2] Eunho Choi[2] Yeon Seok Seo[3] Hyung Joon Yim[3] Young Kul Jung[3] Seong Hee Kang[4] Taehyung Kim[3] Sungjun Jang[2], [1]Korea University College of Medicine, [2]Korea university Guro Hospital, [3]Korea university, [4]4 Seasons Granwell Corp.

Background: Alcohol-associated liver disease (ALD) remains a leading cause of liver-related mortality worldwide, yet the immunological mechanisms driving its progression from steatosis to cirrhosis remain incompletely defined. Although natural killer (NK) cells are central mediators of anti-fibrotic surveillance, their progressive functional impairment is a hallmark of chronic liver injury. We aimed to delineate the high-resolution transcriptomic and functional landscape of peripheral $CD56^{dim}$ NK cells—the principal cytotoxic subset—across the clinical spectrum of ALD. **Methods:** We integrated single-cell RNA sequencing (scRNA-seq) with flow cytometry to profile peripheral blood mononuclear cells (PBMCs) from healthy controls (n = 4), patients with alcoholic fatty liver (AFL, n = 6), and patients with alcoholic cirrhosis (n = 3). A dedicated computational pipeline was applied to resolve subset heterogeneity, functional states, and molecular programs within the $CD56^{dim}$ NK compartment. **Results:** Analysis of 7,354 high-quality $CD56^{dim}$ NK cells revealed four transcriptionally distinct subsets, including a terminally exhausted population that expanded markedly with disease progression and dominated the cirrhotic compartment. Functional trajectory analysis uncovered a biphasic course: transient hyperactivation at the AFL stage was followed by collapse into terminal dysfunction in cirrhosis. Mechanistically, exhausted NK cells in cirrhosis exhibited a fixed molecular program defined by co-upregulation of canonical checkpoints (*TIGIT*, *LAG3*) together with previously unappreciated regulators, including the post-transcriptional repressor *ZFP36* and the GPCR-desensitizing β-arrestin *ARRB2*. **Conclusion:** ALD progression is driven by the systematic expansion and molecular "lockdown" of exhausted peripheral $CD56^{dim}$ NK cells, reflecting a stepwise failure of anti-fibrotic immune surveillance. This

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biphasic exhaustion trajectory nominates *ZFP36* and *ARRB2* as candidate therapeutic targets and provides a blood-based molecular signature with potential utility for non-invasive staging of ALD.

Disclosures: Young-Sun Lee:Nothing to Disclose, Ji Hoon Kim:Nothing to Disclose, Yang Jae Yoo:Nothing to Disclose, Jong eun Yeon:Nothing to Disclose, Eunho Choi:Nothing to Disclose, Yeon Seok Seo:Nothing to Disclose, Hyung Joon Yim:Nothing to Disclose, Young Kul Jung:Nothing to Disclose, Seong Hee Kang: Nothing to Disclose, Taehyung Kim:Nothing to Disclose, Sungjun Jang:Nothing to Disclose.

3193 | HEPATIC SIRT7 MODULATES BILE ACID HOMEOSTASIS PROMOTES PMN-MDSC DIFFERENTIATION AND AGGRAVATES ALCOHOL-ASSOCIATED LIVER INJURY

Yicheng Teng[1] Gaoshuang Liang[1] Qin Jiang[2] Qikun Fan[1] Zhuan Li[1], [1]Hunan Normal University, [2]the Second Xiangya Hospital of Central South University

Background: Polymorphonuclear myeloid-derived suppressor cells (PMN-MDSCs), a pathologically activated subset of neutrophils, implicated in the progression of alcohol-associated liver disease (ALD). However, the mechanisms by which injured hepatocytes shape the hepatic immune microenvironment and influence PMN-MDSC differentiation remain unveil. **Methods:** Hepatocyte-specific *SIRT7*-deficient mice (*Alb-Cre SIRT7*$^{-/-}$) and wild-type littermates were subjected to a Lieber-DeCarli ethanol diet to model ALD. Hepatic immune cell populations were characterized using flow cytometry and single-cell transcriptomic analysis. Targeted metabolomic analyses were performed to assess alterations in bile acid composition. PMN-MDSC differentiation was comprehensively tracked using a panel of canonical markers, including *CD300ld*, *Arg1*, and *S100A8/A9 both in vivo* and *in vitro*. **Results:** Analysis of clinical samples and experimental ALD models indicated an enrichment of *CD300ld*$^{+}$ PMN-MDSCs in the diseased liver. Hepatocyte-specific deletion of *SIRT7* was associated with attenuated alcohol-induced liver injury and a reduction in hepatic PMN-MDSC accumulation. Mechanistic investigations revealed that the loss of hepatocyte *SIRT7* resulted in a profoundly altered bile acid spectrum, identifying deoxycholic acid (DCA). *In vitro* studies demonstrated that DCA acts as a potent metabolic signal to drive the differentiation of induced neutrophils toward a PMN-MDSC-like phenotype in a strictly dose- and time-dependent manner, an effect precisely mediated through the activation of *TGR5* receptors on neutrophils. **Conclusion:** Our findings unveil previously unrecognized involvement of hepatocyte SIRT7 orchestrates ALD progression by modulating bile acid homeostasis which in turn promotes PMN-MDSC differentiation. Elucidating this novel *SIRT7-DCA-TGR5* axis provides mechanistic framework for decoding hepatocyte-immune cell crosstalk and uncovers promising therapeutic targets for ALD intervention.

Disclosures: Yicheng Teng:Nothing to Disclose, Gaoshuang Liang:Nothing to Disclose, Qin Jiang: Nothing to Disclose, Qikun Fan:Nothing to Disclose, ZHUAN LI:Nothing to Disclose.

3194 | A NOVEL PERSPECTIVE ON THE ROLE OF CHOLINERGIC ANTI-INFLAMMATION IN ALCOHOLIC STEATOHEPATITIS: THE SPLEEN–LIVER AXIS

Nan Zhang[1] Lin Jia[1], [1]UT Dallas

Background: Alcohol-associated liver disease (ALD) is a leading cause of chronic liver disease worldwide. Alcoholic steatohepatitis, a severe form of ALD, is characterized by hepatic steatosis and inflammation, partially driven by macrophage-mediated immune responses. The α7 nicotinic acetylcholine receptor (α7-nAChR), encoded by the *Chrna7* gene, plays an important role in the cholinergic anti-inflammatory pathway. ALD progression is closely associated with activation of hepatic resident Kupffer cells and infiltrating macrophages. However, the contributions of these two Chrna7-expressing macrophage populations to alcoholic steatohepatitis remain unclear. The spleen is recognized as a reservoir of macrophages that infiltrate target organs and contribute to various inflammatory diseases. However, the potential role of spleen-liver immune crosstalk in ALD remains unknown. **Methods:** Myeloid cell-specific and Kupffer cell–specific Chrna7 knockout mice were generated and subjected to acute-on-chronic (NIAAA) alcohol feeding model. To determine the contribution of spleen-derived macrophages to ALD, splenectomy was performed in C57BL/6J mice prior to alcohol exposure. In addition, *in vivo* splenic macrophage tracking was also used to explore alcohol-induced remodeling of hepatic macrophage populations and spleen-liver immune interactions. **Results:** Myeloid-specific deletion of *Chrna7* exacerbated alcoholic steatohepatitis, with increased plasma ALT, hepatic triglyceride accumulation, and elevated inflammatory cytokines, such as TNF-α and IL-1β. In contrast, Kupffer cell–specific *Chrna7* deletion unexpectedly attenuated liver injury, showing reduced ALT and a modest reduction in pro-inflammatory gene expression. Splenectomized mice displayed significantly reduced ALT and hepatic IL-1β after alcohol feeding. Excessive alcohol intake significantly increased the recruitment of spleen-derived macrophages into the liver in mice. **Conclusion:** Our findings demonstrate that myeloid cell α7-nAChR exerts anti-inflammatory and hepatoprotective effects, whereas its deletion in Kupffer cells

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attenuates ALD, suggesting that macrophage heterogeneity differentially regulates ALD progression. This paradoxical effect may be related to altered spleen-derived macrophage recruitment, indicating spleen-liver immune crosstalk as an underappreciated mechanism in ALD.

Disclosures: Nan Zhang:Nothing to Disclose, Lin Jia: Nothing to Disclose.

3195 | ◆ ENTRY INHIBITOR HEPALATIDE AT 4.2 MG ACHIEVED SUBSTANTIAL HDV RNA UNDETECTABILITY AT WEEK 48: FINAL RESULTS FROM A PHASE IIB MULTICENTER RANDOMIZED CONTROLLED TRIAL IN HYPERENDEMIC MONGOLIAN PATIENTS WITH CHRONIC HEPATITIS D

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Background: Chronic hepatitis Delta (CHD) is the most aggressive form of viral hepatitis. The recent FDA approval of bulevirtide has further validated HBV/HDV entry inhibitor monotherapy in CHD treatment; however, post-treatment relapse remains a central challenge. Achievement of undetectable HDV RNA is considered a prerequisite for discontinuing entry inhibitors with a low risk of relapse. Yet in MYR301, Week 48 HDV RNA undetectability with bulevirtide at an 8.5 mg/day delivered dose remained limited (20%). Here, we report the Week 48 results from a phase IIb trial of the entry inhibitor hepalatide in Mongolian patients with CHD, in which hepalatide 4.2 mg achieved a substantial rate of HDV RNA undetectability. **Methods:** This multicenter, randomized, open-label, delayed-treatment–controlled trial enrolled adults aged 18–65 years with compensated CHD and quantifiable HDV RNA in Mongolia (NCT06505928). Participants were randomized 1:1:1 to once-daily subcutaneous hepalatide 2.1 mg, hepalatide 4.2 mg, or delayed treatment for 48 weeks, followed by a 96-week extension with hepalatide. Virological response was defined as undetectable HDV RNA (10 decline from baseline, biochemical response as ALT normalization, and combined response as both. Combined response and safety were assessed at Week 48. **Results:** Ninety participants were randomized to hepalatide 2.1 mg, hepalatide 4.2 mg, or delayed treatment (n = 31, 29, and 30), and 87 completed Week 48. Hepalatide was generally well tolerated, with no grade ≥ 3 treatment-related adverse events. At Week 48, virological response was achieved in 52%, 79%, and 0% of subjects in the 2.1 mg, 4.2 mg, and delayed-treatment groups; mean HDV RNA changes from baseline were −2.2, −3.4, and +0.2 $\log_{10}$ IU/mL. Biochemical response occurred in 65%, 76%, and 7%, and combined response in 45%, 59%, and 0%. Both hepalatide groups showed significantly higher virological, biochemical, and combined response rates than delayed treatment ($P < 0.001$ for each comparison). HDV RNA was undetectable in 16% (5/31) of subjects in the 2.1 mg group and 41% (12/29) in the 4.2 mg group, compared with none in delayed treatment. The 4.2 mg dose yielded a higher virological response rate than 2.1 mg ($P = 0.03$) and more than doubled the HDV RNA undetectability rate ($P = 0.04$). **Conclusion:** Hepalatide demonstrated significant virological, biochemical, and combined responses with good tolerability through Week 48 in Mongolian patients with CHD. Building on MYR301 data showing broadly comparable responses across bulevirtide dose groups, the higher response and HDV RNA undetectability rates observed with hepalatide 4.2 mg versus 2.1 mg add a dose-related signal to the clinical evidence for HBV/HDV entry inhibition. These findings suggest the potential for sustainable post-treatment virological suppression with entry inhibitors in this highly endemic Mongolian population.



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★ 3196 | ◆ CIRRHOSIS DOES NOT IMPACT BULEVIRTIDE RESPONSE OR VIROLOGICAL AND BIOCHEMICAL BREAKTHROUGHS IN CHRONIC HEPATITIS DELTA: DATA FROM THE PROSPECTIVE MULTICENTER D-SHIELD STUDY

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Background: Bulevirtide (BLV) was licensed in Italy in May 2023 for patients with chronic hepatitis delta (CHD), but no real-life studies have addressed differences in responses rates among patients with and without cirrhosis. **Methods:** CHD patients starting BLV 2 mg/day monotherapy were included in a multicenter prospective real-life Italian study (D-SHIELD). Patients' features and treatment responses were assessed at baseline and trimonthly afterwards. Virological response (VR) ($\geq$2 LogIU/mL HDV-RNA decline *vs.* baseline or HDV RNA undetectable), biochemical and combined responses (BR and CR), incidence of virological breakthroughs (VBK; >1 Log HDV RNA increase *vs.* previous timepoint), biochemical breakthroughs (BKK, >x1.5 ALT increase >1.5× from nadir in patients without BR, or loss of BR with ALT >1.5×ULN in patients previously achieving BR), and

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safety were assessed comparing patients with and without cirrhosis. **Results:** 501 patients treated with BLV monotherapy up to 96 weeks from 46 centers were enrolled, 358 (72%) with cirrhosis and 142 without cirrhosis. Patients without cirrhosis were younger (54 *vs.* 49, $p < 0.001$), were less commonly treated with NA (98% *vs.* 91%, $p < 0.001$), had lower LSM values (15.8 *vs.* 8.2 kPa, $p < 0.001$) and higher HDV RNA levels (5.2 *vs.* 5.3 Log IU/L $p = 0.02$), PLTs (99 *vs.* 189 $\times 10^9$/L $p < 0.001$), and HBsAg (3.71 *vs.* 3.85 Log IU/mL, $p = 0.03$). ALT did not significantly differ at baseline (75 *vs.* 71 U/L, $p = 0.25$). VR, BR and CR rates increased progressively throughout treatment and did not significantly differ between patients with and without cirrhosis at any timepoint. At week 96, BR rates were 70% *vs.* 69% ($p = 1.00$), VR 75% *vs.* 83% ($p = 0.72$), and CR 61% *vs.* 58% ($p = 0.85$), respectively. Only HDV RNA undetectability rates (HDV RNA vs. 12% $p = 0.005$, p = ns for other timepoints). Overall, 46 patients (9.2%) experienced VBK,[1] most commonly between weeks 48 and 72 (37, 80%). VBK incidence did not differ between patients with and without cirrhosis (9.2% vs. 9.1%, $p = 1.00$). Among patients with available data, VBK was persistent up to week 96 in 44% of cases. 14 patients (2.8%) experienced BKK, [2] [3] again without differences according to cirrhosis status (3.5% vs. 2.5%, $p = 0.55$). Most BKK events (75%) occurred between weeks 48 and 72. Among patients with available data, BKK was persistent up to week 96 in 25% of cases. 8 patients both had a VBK and a BKK. No significant differences were observed in the incidence of adverse events among patients with and without cirrhosis, (15% *vs.* 15%, $p = 1.00$), with mild and transient pruritus and injection site reaction being the most common. Patients with cirrhosis showed higher baseline and on-therapy bile acids levels ($p < 0.001$ at all time-points). **Conclusion:** The effectiveness and safety profile of BLV monotherapy did not differ in patients with or without compensated cirrhosis in this large prospective multicenter Italian study.

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3197 | ◆ ORAL NTCP INHIBITOR ABI-6250 ELEVATES BILE ACIDS IN A RANDOMIZED, BLINDED, PHASE 1A STUDY IN HEALTHY SUBJECTS

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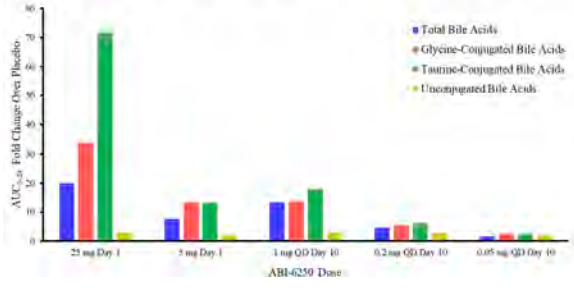
Background: ABI-6250 (6250) is an orally bioavailable, small molecule inhibitor of the sodium taurocholate cotransporting polypeptide (NTCP), a bile acid (BA) transporter that both the hepatitis B and D viruses utilize as an entry receptor into hepatocytes. ABI-6250-101 (NCT06740474) was a randomized, blinded study assessing the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of 6250 in healthy

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participants. PD was assessed by evaluating total BA (tBA) and fractional BA (fBA) levels. **Methods:** Two single-dose (SD) cohorts of 5mg and 25mg, and 3 multiple-dose cohorts of 0.05mg, 0.2mg and 1mg 6250 once-daily (QD) for 10 days were evaluated. In each cohort, 8 participants were randomized 3:1 to 6250 or placebo (PBO). Plasma tBA levels were measured by enzymatic colorimetric assay. Plasma fBAs including unconjugated (UCBA), Glycine-Conjugated (GCBA), and Taurine-Conjugated (TCBA) were measured by Liquid Chromatography Mass Spectrometry (LCMS). Area under plasma concentration curve over 24 hours (AUC_{0-24}) values for each BA were calculated using non-compartmental methods. **Results:** The AUC_{0-24} values for tBA increased by approximately 20-fold, 8-fold, 13-fold, 5-fold, and 2-fold for the 25 mg SD, 5 mg SD, 1 mg QD, 0.2 mg QD, and 0.05 mg QD doses compared with PBO (Figure 1). UCBA levels did not increase significantly after 6250 administrations, and AUC_{0-24} values were generally $\leq$3-fold higher across all doses compared with PBO. GCBA and TCBA levels increased in a dose dependent manner. At the 25 mg SD dose, AUC_{0-24} values increased by approximately 34-fold for GCBA and 72-fold for TCBA compared with PBO. On Day 10 at the 1 mg QD dose, AUC_{0-24} values increased by approximately 14-fold for GCBA and 18-fold for TCBA compared with PBO. **Conclusion:** Elevations in tBAs and fBAs observed with 6250 are consistent with those reported for bulevirtide, a specific inhibitor of NTCP, and indicate potent target engagement of 6250. fBA analysis showed GCBA and TCBA levels, considered measures of on-target NTCP engagement, increased in a dose-dependent and reversible manner, whereas there were no considerable increases in UCBA levels.

Figure 1. Comparative Analysis of tBA, GCBA, TCBA, and UCBA AUCs Relative to Placebo Across ABI-6250 Dose Levels in Study ABI-6250-101



Disclosures: Edward Gane:Nothing to Disclose, Christian Schwabe:Nothing to Disclose, Katie Zomorodi: Nothing to Disclose, Jinghu Carl Li:Nothing to Disclose, Sam Kim:Assembly Biosciences, Inc. Employee, Gilead Sciences, Inc. Employee, Assembly Biosciences, Inc. Stock - publicly traded company, Gilead Sciences, Inc. Stock - publicly traded company, Lewyn Li:Assembly Biosciences: Employee, Grace Wang:Nothing to Disclose, Anuj Gaggar:Nothing to Disclose, Mathias Haag:Assembly Biosciences: Independent Contractor, Assembly Biosciences: Grant/Research Support, Matthias Schwab:Robert Bosch GmbH: Grant/Research Support, HepaRegenix GmbH: Grant/Research Support, Boehringer International GmbH: Grant/Research Support, Agena Bioscience GmbH: Grant/Research Support, Assembly Biosciences: Grant/Research Support, Worldwide Clinial Trials: Consultant.

3198 | ◆ BULEVIRTIDE MONOTHERAPY FOR UP TO 4 YEARS IN CHD PATIENTS WITH CIRRHOSIS: CLINICAL AND VIROLOGICAL OUTCOMES IN LARGE MULTICENTER STUDY (SAVE-D)

Elisabetta Degasperi[1] Maria Paola Anolli[1] Dana Sambarino[1] Marta Borghi[1] Riccardo Perbellini[1] Liana Gheorghe[2] Mirela Chitul[3] Christoph Schramm[4] Hartmut Schmidt[4] Mathias Jachs[5] Thomas Reiberger[5] Ivana Carey[6] Kosh Agarwal[6] Maria Buti[7] Adriana Palom[8] Gianpiero Doffizi[9] Francesco De Maria[9] Caroline Zöllner[10] Frank Tacke[10] Christopher Dietz Fricke[11] Heiner Wedemeyer[11] Margarita Papatheodoridi[12] George Papatheodoridis[12] Florian van Bömmel[13] Sabela Lens[14] Maurizia Brunetto[15] Alessandro Federico[16] Elena Rosselli del Turco[17] Magdalena Meszaros[18] Alessia Ciancio[19] Álvaro Giráldez-Gallego[20] Filipe Calinas[21] Fabien Zoulim[22] Soo Aleman[23] Nasser Semmo[24] Sophie Metivier[25] Carla Coffin[26] Sébastien Poulin[27] Alessandra Mangia[28] Marie-Noëlle Hilleret[29] Uta Merle[30] Mariana Cardoso[31] Alexandra Martins[32] Catarina Gouveia[33] Karen Doucette[34] Sergio Borgia[35] Alessandro Loglio[36] Teresa Santantonio[37] Nicola Coppola[38] Adriano Pellicelli[39] Juliette Foucher[40] Bruno Roche[41] Xavier Causse[42] Louis D'Alteroche[43] Jerome Dumortier[44] Nathalie Ganne Carrie[45] Frédéric Heluwaert[46] Isabelle Ollivier-Hourmand[47] Dominique Roulot[48] Isabelle Rosa[49] Ines Costa Santos[50] Ana Margarida Vieira[51] Francesca Pileri[52] Monia Maracci[53] Matteo Tonnini[54] Jean Pierre Arpurt[55] Karl Barange[56] Eric Billaud[57] Lucia Parlati[58] Anne Gervais[59] Anne Minello[60] Massimo Puoti[61] Ana Horta[62] Mariana Machado[63] Dália Fernandes[64] Joaquim Oliveira[65] João Vaz Alves[66], [1]Division of Gastroenterology and Hepatology, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlini, [2]Center for Digestive Diseases and Liver Transplantation, Fundeni Clinical Institute, Bucharest, [3]Center for Digestive Diseases and Liver Transplantation, Fundeni Clinical Institute, Bucharest, [4]Department of Gastroenterology, Hepatology and Transplant Medicine, University of Duisburg-Essen, [5]Medical University of Vienna, [6]Institute of Liver Studies, King's College Hospital, London, UK, [7]Hospital Valle Hebron, [8]Hospital Vall d'Hebron, [9]Division of Infectious Diseases - Hepatology, Ist. Naz. Malattie Infettive "L. Spallanzani" IRCCS, [10]Department of Hepatology and Gastroenterology,

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Background: Bulevirtide (BLV) is approved by EMA for treatment of chronic hepatitis Delta (CHD), however data about long-term outcomes in patients with cirrhosis are limited. **Methods:** CHD patients with cirrhosis treated with BLV 2 mg/day in the SAVE-D study (51 centers) were included. Virological (HDV RNA undetectable or ≥ 2 Log_{10} decline *vs.* baseline), biochemical (ALT < 40 U/L), combined response, viral breakthroughs (VBK: 1 Log_{10} HDV RNA increase *vs.* previous timepoint) and liver-related events (LREs) were assessed. Clinically significant portal hypertension (CSPH) was defined according to Baveno VII criteria. **Results:** 424 patients treated with BLV up to 192 weeks (W) were included: age 50 (IQR 40-58) years, 61% men, ALT 78 (51-128) U/L, liver stiffness measurement (LSM) 16.5 (12.6-25.3) kPa, platelets 101 (68-149) x10^9 /L, 96% CPT score A, 51% with varices, 9% with previous decompensation, 90% on NUC. Baseline HDV-RNA was 5.4 (4.2-6.3) Log_{10}IU/mL and qHBsAg 3.7 (3.2-4.1) Log_{10}IU/mL. After W144 of BLV, 73%, 69%, 54% and 35% of patients achieved virological, biochemical, combined response, and HDV RNA undetectability, respectively. In 59 patients with available W192 data, the corresponding figures were 79%, 71%, 59% and 41%. Patients with < 1 Log_{10} HDV RNA decline *vs.* baseline decreased from 20% (W48) to 14% (W144). VBK occurred in 7% between W48-W96 (77% normal ALT) and 9% between W96-W144 (70% normal ALT). Clinically significant portal hypertension according to Baveno VII non-invasive definitions improved in up to 40% of patients. 29 patients developed a LRE, 9 decompensation and 20 HCC: the 3-year cumulative incidences were 2.3% (95% CI 1-4%) and 6.8% (95% CI 3-9%), respectively. Lower baseline albumin independently predicted decompensation, whereas age, BMI and albumin predicted HCC occurrence. 29 patients underwent LT (22 HCC, 7 decompensation) and 14 patients died, 9 of LREs. Persistence on-treatment was maintained by 93%

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of patients, 30 discontinued BLV monotherapy (7 add-on IFN, 2 skin allergy, 2 decompensation, 3 undetectable HDV RNA, 3 non-compliance, 2 non-response, 2 clinical trial entry, 1 HBsAg loss), 8 were lost to follow-up. **Conclusion:** In CHD patients with cirrhosis, BLV monotherapy 2 mg/day up to 192 weeks was safe and effective. Virological and clinical responses increased over-time. Rates of de-novo liver-related events remained low, especially liver decompensation.

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Background: Chronic hepatitis delta (CHD) carries the highest risk of cirrhosis progression and hepatocellular carcinoma (HCC) among viral hepatitis. However, disease-specific models to guide HCC risk stratification and surveillance in CHD remain undefined. **Methods:** CHD patients with cirrhosis from the retrospective multicenter real-world European SAVE-D study were included. PAGE-B and AMAP scores were calculated at BLV start as previously described. PAGE-B was defined as low (<10) *vs.* intermediate (10-17) *vs.* high (≥ 18) risk profile. AMAP was defined as low (<50) vs. medium (50–59) vs. high (≥ 60) risk profile. HCC incidence rates in the different PAGE-B and AMAP groups during Bulevirtide (BLV) monotherapy were assessed. Patients with previous HCC were excluded. **Results:** 391 patients with cirrhosis treated with BLV monotherapy up to 240 weeks were included: age 49 (IQR 40-57) years, 60% men, median platelet (PLT) count 102 (69-148) x 10^9 /L. At BLV start, 117 (30%) patients had low risk PAGE B score, 255 intermediate risk (65%), and 19 (5%) had high-risk PAGE B score. Median PLT count in the PAGE B high risk score was 75 (60-90), median age 64 (62-67). AMAP score could be calculated in 387 patients: 10 patients (3%) had low risk AMAP score (3%), 84 (22%) intermediate, and 293 (76%) high risk AMAP score. During 240 weeks of BLV monotherapy, 17 de-novo HCC occurred. When analyzing incidence of de novo HCC according to HCC risk scores, 2 (12%) HCC developed in the PAGE-B low-risk group, 11 (65%) in the intermediate-risk group, and 4 (24%) in the high-risk group. The corresponding 240-week cumulative incidence in the 3 groups was 2.2%, 5.7%, and 30.9%, respectively. Concerning AMAP score, no HCC developed in the low-risk group, 1 (6%) in the intermediate risk score, and the remaining 16 (94%) in the high-risk score. No HCC occurred in the 4 patients for whom AMAP could not be calculated due to missing data. The corresponding 240-week cumulative incidence of HCC in the 3 AMAP groups was: 0%, 1.3% and 7.7%, respectively. Median time to HCC was 11 (10-25) months. At baseline lower albumin levels (HR 0.22, 95% CI 0.09-0.56, $p=0.001$), higher bilirubin (HR 2.02; 95% CI 1.12-3.65, $p<0.001$), and higher LSM (HR 1.05; 95% CI 1.02-1.08, $p=0.003$) independently predicted HCC development. **Conclusion:** PAGE-B and AMAP scores retained clinical utility for HCC risk stratification in CHD patients receiving long-term BLV monotherapy, although HDV-specific risk models are still needed for an HDV-tailored HCC surveillance strategy.

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3200 | ◆ CHARACTERISTICS AND OUTCOMES OF ON-TREATMENT ALT FLARES IN PATIENTS WITH HEPATITIS DELTA VIRUS RECEIVING BULEVIRTIDE AND PEGYLATED INTERFERON

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Background: Bulevirtide (BLV) monotherapy is approved to treat chronic hepatitis delta virus (HDV) in the US, Europe, and other regions, and has demonstrated virologic response (VR) and alanine aminotransferase (ALT) normalization in clinical trials alone and with pegylated interferon alfa-2a (PegIFN). ALT flares can occur during PegIFN therapy and may be beneficial in inducing a VR. This study evaluated on-treatment (on-tx) ALT flares occurring with BLV +PegIFN vs PegIFN monotherapy. **Methods:** A pooled analysis evaluated characteristics and outcomes of on-tx ALT flares in the phase 2 MYR203 (NCT02888106) and MYR204 (NCT03852433) studies in participants (pts) who received PegIFN alone or with BLV 2, 5, or 10 mg, for 48 weeks (wks). On-tx ALT flares were defined as ALT > 10× upper limit of normal (ULN) and > 1× baseline (BL); ALT > 2.5× BL; or ALT > 2.5× previous on-tx nadir and > 2.5× ULN. Beneficial flares were defined as HDV RNA newly undetectable or decline of > 1 $\log_{10}$ IU/mL; or hepatitis B surface antigen (HBsAg) loss or decline of > 0.5 $\log_{10}$ IU/mL; simultaneously or within 8 wks of flare onset. **Results:** Of 184 pts, 56 (30%) had an on-tx ALT flare by Week (W) 48: 28% (40/145) BLV+PegIFN; 41% (16/39) PegIFN (**Table**). Median flare onset for BLV+PegIFN was 8 wks and 78% (31/40) resolved by W48, vs 14 wks and 69% (11/16), respectively, for PegIFN. BLV+PegIFN and PegIFN groups had the same rate (13%) of bilirubin elevation > 2 mg/dL (5/40 and 2/16, respectively); no pts had an international normalized ratio > 1.5. In the BLV+PegIFN group with on-tx ALT flares, 10% (4/40) had a PegIFN dose reduction; 8% (3/40) discontinued PegIFN due to hepatic adverse events (AEs) associated with the flares; 48% (19/40) had on-tx hepatic AEs,

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with 1 on-tx liver-related event of hepatic cirrhosis with no decompensation events. Overall, similar safety outcomes of on-tx ALT flares were observed for PegIFN (**Table**). For the 40 pts receiving BLV+PegIFN with on-tx ALT flares, mean change (SD) from pre-flare in HDV RNA was –2.1 (1.1) log_{10} IU/mL and HBsAg was –0.5 (0.8) log_{10} IU/mL within 8 wks of flare onset; 85% (34/40) had a beneficial flare, with all 34 having undetectable or a decline in HDV RNA and 38% (13/34) having a loss or decline in HBsAg within 8 wks of flare onset. Only 38% (6/16) of pts receiving PegIFN with on-tx ALT flares had beneficial flares. HDV RNA undetectability and HBsAg loss rates at W48 were higher in pts receiving BLV+PegIFN with on-tx ALT flares (n = 40; 73% and 10%) vs pts without flares (n = 105, 54% and 4%). **Conclusion:** Rates of on-tx ALT flares were lower with BLV+PegIFN than PegIFN alone (28% vs 41%), but a higher proportion (85% vs 38%) were beneficial and accompanied by declines in viral markers. As safety outcomes observed with the flares were similar between groups this suggests BLV may have positively mediated ALT flares caused by PegIFN. ALT flares during BLV+PegIFN treatment generally self-resolved before end of treatment and were accompanied by a positive treatment response.

Table. Characteristics of On-treatment ALT Flares by Week 48 with Bulevirtide and Pegylated Interferon alfa-2a

n (%), unless otherwise specified	Participants with on-tx ALT flare by Week 48	
	BLV (2 mg, 5 mg, or 10 mg) + PegIFN (n=40)	PegIFN (n=16)
ALT >10× ULN and >1× baseline	9 (23)	5 (31)
ALT >2.5× baseline	25 (63)	11 (69)
ALT >2.5× nadir and >2.5× ULN[c]	29 (73)	12 (75)
Time to flare onset, median (Q1, Q3), weeks	8 (4, 18)	14 (8, 20)
Flare resolved on-tx by Week 48	31 (78)	11 (69)
PegIFN dose reduction due to hepatic AEs[a]	4 (10)	2 (13)
Hepatic AEs leading to PegIFN discontinuation[a,d]	3 (8)	1 (6)
Bilirubin elevation >2 mg/dL[e]	5 (13)	2 (13)
International normalized ratio >1.5[e]	0	0
Hepatic AEs[a,d]	19 (48)	9 (56)
Liver-related events[d,f]	1 (3)	0
Beneficial flare[f]	34 (85)	6 (38)
Decline >1 log_{10} IU/mL or undetectability of HDV RNA[g]	34 (85)	5 (31)
Undetectability of HDV RNA at Week 48	29 (73)	2 (13)
Loss or decline >0.5 log_{10} IU/mL in HBsAg[g]	13 (33)	2 (13)
HBsAg loss at Week 48	4 (10)	0

On-treatment period ends at PegIFN last dose +7 days for BLV+PegIFN and PegIFN groups.
[c]Nadir is the lowest on-treatment ALT value previously. [d]Defined as AEs suggestive of hepatitis flares. [a]Also includes discontinuation due to drug-induced liver injury. [e]Safety outcomes are from on-treatment ALT flare onset up to Week 48 in the on-treatment period. [d]Defined as liver-related clinical events such as cirrhosis development; liver decompensation including development or worsening jaundice, coagulopathy, ascites, hepatic encephalopathy, bleeding from varices, and liver failure; HCC development; liver transplantation and liver related death. [f]Beneficial flares were defined as an HDV RNA newly undetectable or decline of >1 log_{10} IU/mL or HBsAg loss or decline of >0.5 log_{10} IU/mL simultaneously or within subsequent 8 weeks of flare onset in the on-treatment period by Week 48. [g]HDV RNA decline of >1 log_{10} IU/mL or newly undetectable simultaneously or within subsequent 8 weeks of flare onset in the on-treatment period by Week 48. [h]HBsAg loss or decline of >0.5 log_{10} IU/mL simultaneously or within 8 weeks following flare onset in the on-treatment period by Week 48.
AEs, adverse events; ALT, alanine aminotransferase; BLV, bulevirtide; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; HDV, hepatitis delta virus; on-tx, on-treatment; PegIFN, pegylated interferon alfa-2a; ULN, upper limit of normal.

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3201 | COMPARATIVE EFFICACY AND SAFETY OF TREATMENTS FOR HEPATITIS DELTA VIRUS INFECTION: A BAYESIAN DOSE-POOLED NETWORK META-ANALYSIS

Rahul Falodia[1] Ehsanullah Alokozay[2] Muhammad Junaid Azhar[3] Taha Alam[4] Hamza Sajid[5] Farhan Murtaza[6] Muhammad Zawar Asif[7] Ali Chand[8] Syed Asjad Tauheed Zaidi[8] Miriam Michael[8] Delilah Easom[9] Anand Deonarine[8], [1]All India Institute of Medical Sciences, Jodhpur, [2]Faculty of Medicine, Kandahar University, Kandahar, Afghanistan, [3]Howard University Hospital, Washington DC, [4]Dow University of Health Sciences, Karachi Pakistan, [5]Allama Iqbal Medical College, Lahore, Pakistan, [6]HCA Houston Healthcare/ University of Houston Program, [7]Mercy Hospital Fort Smith, Arkansas/ Arkansas College of Osteopathic Medicine, [8]Howard University Hospital, [9]Mercy Hospital Fort Smith Arkansas College of Ostepathic Medicine

Background: Chronic hepatitis delta virus (HDV) infection is the most severe form of viral hepatitis, frequently leading to liver cirrhosis and hepatocellular carcinoma. Recently, several pharmacological interventions, including entry inhibitors and prenylation inhibitors, have emerged as potential therapeutic options. We conducted a comprehensive Bayesian dose-pooled network meta-analysis (NMA) to evaluate the relative efficacy and safety of current pharmacological treatments for chronic HDV infection. **Methods:** Pubmed, Cochrane, Embase and Scopus were systematically searched for relevant RCTs. Efficacy outcomes included virological response (VR; $\geq$2 log10 HDV RNA decline or undetectable), undetectable HDV RNA (UR), ALT normalization (ALT-N), and a combined response (CR). Safety outcome included Grade $\geq$3 adverse events (AEs). A Bayesian random-effects model was implemented using the gemtc package in R, and odds ratios (OR) with 95% credible intervals (CrIs) was calculated. Treatments were ranked using the Surface Under the Cumulative Ranking curve (SUCRA). **Results:** Thirteen direct comparison edges across eight treatment nodes were analyzed. Bulevirtide plus peginterferon (BLV + Peg-IFN) demonstrated the highest efficacy across all virological and biochemical outcomes, ranking first for VR (OR 393.49; SUCRA 99%), UR (SUCRA 99%), ALT-N (SUCRA 85%), and CR (SUCRA 96%). Bulevirtide monotherapy was consistently identified as the second most effective treatment, showing significant superiority over control for VR (OR 35.88; SUCRA 72%) and CR (SUCRA 76%). Peginterferon-based regimens and Lonafarnib plus ritonavir showed intermediate efficacy while adefovir monotherapy was ineffective (SUCRA 1%). Safety analysis revealed that peginterferon plus adefovir was the safest treatment regarding Grade $\geq$3 AEs (OR 2.26; SUCRA 79%), followed by peginterferon monotherapy (OR 2.11; SUCRA 60%). BLV + Peg-IFN showed a higher AE burden (OR 7.63; SUCRA 29%), likely reflecting the additive toxicity of the interferon component. Disconnected evidence from one study indicated that tobevibart plus elebsiran had a numerically higher VR rate than tobevibart alone (OR 5.94), though this didn't reach statistical significance. **Conclusion:** Bulevirtide in combination with peginterferon is the most effective therapeutic strategy though it carries a higher risk of adverse events. Bulevirtide monotherapy presents as an effective alternative with better-tolerated long-term maintenance strategy While peginterferon-based regimens offer intermediate efficacy with a favorable safety profile, adefovir monotherapy lacks clinical benefit. These findings establish a comprehensive hierarchy of treatments, while transitioning HDV management toward optimized, patient-specific strategies that balance treatment intensity with long-term safety.

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3202 | A SYSTEMATIC LITERATURE REVIEW AND META-ANALYSIS EVALUATING POST-TREATMENT HDV RNA–BASED SURROGATE ENDPOINTS FOR PREDICTING LONG-TERM CLINICAL OUTCOMES IN HEPATITIS DELTA VIRUS INFECTION

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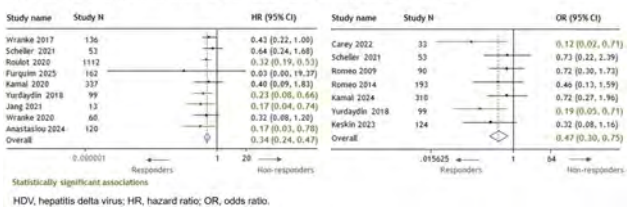
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Background: Hepatitis delta virus (HDV) infection is associated with substantial liver-related morbidity and mortality. Evaluation of treatment response through reliable surrogate endpoints is critical for timely treatment decisions. This systematic literature review (SLR) and meta-analysis aim to evaluate the association between post-treatment HDV RNA–based surrogate endpoints and long-term clinical outcomes in adults with HDV infection. **Methods:** Embase, PubMed, and Cochrane were searched from inception to August 2025 for studies evaluating associations between HDV RNA–based surrogate endpoints and any clinical outcomes. The review followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Reported hazard ratios (HRs) and odds ratios (ORs) were extracted directly, where available. In some cases, ORs were calculated from categorical data, and HRs were derived from digitized Kaplan–Meier (KM) curves. Meta-analysis was performed in Stata 19 using the DerSimonian-Laird random-effects model. A separate pooled KM curve analysis was also conducted using metaSurvival package. **Results:** Seventeen studies (15 full-text studies; 2 abstracts) evaluated the association between post-treatment HDV RNA undetectability and any liver-related event, including hepatic decompensation, hepatocellular carcinoma, liver transplantation, and liver-related death. Most studies were retrospective (n = 14) and conducted in Europe (n = 10). In most studies (n = 16), patients were treated with interferon ± nucleotide analogues (IFN ± NAs) while 1 study used NAs only. The HR-based meta-analysis showed that post-treatment undetectable HDV RNA, most often defined as off-treatment sustained response, was significantly associated with a reduced risk of any liver-related event compared to patients with detectable HDV RNA (HR: 0.34; 95% CI: 0.24–0.47, **Figure**). Findings were consistent in the OR-based analysis (OR, 0.47; 95% CI, 0.30–0.75, **Figure**). Overall, the meta-analysis findings were concordant with results reported across individual studies included in the SLR. Pooled KM curve analysis further supported these findings, demonstrating the robustness and reliability of the observed associations; (HR: 0.10; 95% CI: 0.05-0.18). **Conclusion:** Achieving undetectable HDV RNA, most often as off-treatment sustained response after IFN ± NAs therapy, was strongly associated with a reduced risk of liver disease progression and complications. HDV RNA undetectability should be interpreted by treatment context: off-treatment sustained undetectability reflects durable disease control, while the effects of on-treatment suppression depend on mechanism of action. These findings highlight the importance of improved HDV screening among HBV infected patients to support earlier diagnosis and timely treatment.

Figure: Association of post-treatment HDV undetectability with any liver-related events



HDV, hepatitis delta virus; HR, hazard ratio; OR, odds ratio.

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3203 | INTEGRATED EFFICACY ANALYSIS OF BULEVIRTIDE 10 MG MONOTHERAPY IN PATIENTS WITH CHRONIC HEPATITIS DELTA

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Background: Based on its efficacy and safety profile in multiple clinical trials, bulevirtide (BLV), a first-in-class entry inhibitor, is approved in the US, the European Economic Area, and other regions **:** for the treatment of patients (pts) with chronic hepatitis delta. To further evaluate the efficacy of BLV 10 mg, an integrated analysis was conducted up to week (W) 96. **Methods:** Data from pts receiving BLV 10 mg/day (d) or 48W of delayed treatment (control group) in the Phase 3 MYR301 (NCT03852719) and Phase 2 MYR204 (NCT03852433) studies were analyzed. Analyses at W48 and W96 included efficacy assessments of virologic response (VR; undetectable hepatitis delta virus [HDV] RNA or ≥ 2 $\log_{10}$ IU/mL decline from baseline), alanine aminotransferase (ALT) normalization, combined response (CR; VR + ALT normalization), and liver stiffness (LS). Partial VR (PR) was defined as ≥ 1 to < 2 $\log_{10}$ IU/mL decline in HDV RNA from baseline, and nonresponse (NR) was defined as < 1 $\log_{10}$ IU/mL decline from baseline; pts with undetectable HDV RNA were not considered to have PR or NR. Subgroup analyses by ALT normalization and suboptimal VR responses at week 96 included pts with observed data at this time point. **Results:** Overall, 150 pts receiving BLV 10 mg and 51 control pts were included. Baseline mean (SD) age in the BLV 10 mg group was 41 (8.2) years; 63% of patients were male, 84% were White, 43% had compensated cirrhosis, and 55% received nucleos(t)ide analogues; and mean (SD) ALT, HDV RNA, and LS were 108 (85) U/L, 5.2 (1.4) $\log_{10}$ IU/mL, and 14.5 (9.5) kPa. Baseline characteristics were similar for pts in the control group. Most pts completed treatment through the end of treatment (EOT; BLV 10 mg: n = 143, 95%; controls, n = 50, 98%). A higher proportion of pts had undetectable HDV RNA and higher mean decreases in HDV RNA at W48 with BLV 10 mg vs control (18% vs 0%; −3.3 vs −0.1 $\log_{10}$ IU/mL; **Table**). CR, VR, and ALT normalization rates and mean (SD) change from baseline in LS at W48 and W96 among pts treated with BLV 10 mg were higher than those of pts in the control group (**Table**). Pts receiving BLV 10 mg with and without a VR at W96 (NR, n = 6 [4%]; PR, n = 11 [7%]; VR, n = 124 [83%]; no data, n = 9 [6%]) had improvements in mean (SD) change from baseline to W96 for ALT and LS (ALT, U/L: VR, −64 [63]; PR, −80 [84]; NR, −168 [280]; and LS, kPa: VR, −4.5 [5.6]; PR, −3.3 [6.0]; NR, −1.2 [4.6]). Pts without ALT normalization at W96 also had improvements in ALT and LS at W96 (ALT normalized [n = 91, 61%]: ALT, −74 [89]; LS, −4.5 [5.9]; ALT not normalized [n = 50, 33%]: ALT, −61 [78]; LS, −4.0 [4.9]; no data, n = 9 [6%]). Of pts without ALT normalization, 30/50 (60%) had ALT ≤ 1.5 × the upper limit of normal (ULN) at W96, and only 1 pt had ALT > 3 × ULN. **Conclusion:** Long-term treatment with BLV 10 mg monotherapy was associated with greater HDV RNA decline and improvements in ALT levels and LS vs the control group at W48, which improved through W96. Reductions in ALT levels and LS were observed in pts both with and without VR and/ or ALT normalization.

Table. Efficacy Outcomes for Integrated Analysis of Bulevirtide Treatment Groups at Weeks 48 and 96

	Control Group (n = 51)	Bulevirtide 10 mg (n = 150)	
	Week 48	Week 48	Week 96
Combined response, n (%)	1 (2)	69 (46)	80 (53)
Virologic response, n (%)	2 (4)	122 (81)	124 (83)
Undetectable HDV RNA, n (%)[a]	0	27 (18)	55 (37)
Change from baseline in HDV RNA, $\log_{10}$ IU/mL, mean (SD)	−0.1 (1.0)	−3.3 (1.4)	−3.8 (1.5)
ALT normalization, n (%)	6 (12)	81 (54)	91 (61)
Change from baseline in liver stiffness, kPa, mean (SD)	0.7 (7.4)	−3.4 (4.6)	−4.3 (5.6)

[a]Defined as <LLOQ (50 IU/mL), target not detected.
For combined response, virologic response, undetectable HDV RNA, and ALT normalization, the missing-equals-failure approach was used; for change from baseline in HDV RNA and liver stiffness, the missing values remained missing.
ALT, alanine aminotransferase; HDV, hepatitis delta virus; LLOQ, lower limit of quantitation.

Disclosures: Pietro Lampertico:ROCHE PHARMA/ DIAGNOSTICS, GILEAD SCIENCES, GSK, ABBVIE, JANS: Advisor, Soo Aleman:Nothing to Disclose, Tarik Asselah:Nothing to Disclose, Pavel Bogomolov:Nothing to Disclose, Maurizia Brunetto:Nothing to Disclose, Vladimir Chulanov:Nothing to Disclose, George Gherlan:Nothing to Disclose, Stefan Lazar:Nothing to

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Disclose, Morozov Viacheslav:Nothing to Disclose, Olga Sagalova:Nothing to Disclose, Tatiana Stepanova:Nothing to Disclose, Adrian Streinu-Cercel:Nothing to Disclose, Fabien Zoulim:Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Amos Lichtman:Nothing to Disclose, Mingyang Li:Nothing to Disclose, Dmitry Manuilov:Nothing to Disclose, Heiner Wedemeyer:Gilead Sciences GmbH & Gilead Sciences Ltd. Grant/Research Support, Madrigal Pharmaceuticals, Inc. Grant/Research Support, Biotest AG: Grant/Research Support, Gilead Sciences GmbH & Gilead Sciences Ltd. Clinical Trials / Investigator, Madrigal Pharmaceuticals, Inc. Clinical Trials / Investigator, Dr. Falk Pharma GmbH: Clinical Trials / Investigator, IPSEN Pharma S.A.S. Clinical Trials / Investigator, AstraZeneca GmbH: Clinical Trials / Investigator, Bluejay Therapeutics: Clinical Trials / Investigator, GlaxoSmithKline Services Unlimted: Clinical Trials / Investigator, Lilly Deutschland GmbH: Clinical Trials / Investigator, Mirum Pharmaceuticals Germany GmbH: Clinical Trials / Investigator, Takeda Pharma Vertrieb GmbH & Co. KG: Clinical Trials / Investigator, BioMarin Pharmaceuticals Inc. Clinical Trials / Investigator, Vir Biotechnology: Clinical Trials / Investigator, Gilead Sciences GmbH & Gilead Sciences Ltd. Consultant, Madrigal Pharmaceuticals, Inc. Consultant, Dr. Falk Pharma GmbH: Consultant, IPSEN Pharma S.A.S. Consultant, AstraZeneca GmbH: Consultant, Bluejay Therapeutics: Consultant, Bluejay Therapeutics: Consultant, GlaxoSmithKline Services Unlimited: Consultant, Lilly Deutschland GmbH: Consultant, Mirum Pharmaceuticals Germany GmbH: Consultant, Takeda Pharma Vertrieb GmbH & Co. KG: Consultant, Vir Biotechnology, Inc. Consultant, MSD Sharp & Dohme GmbH: Consultant, Novo Nordisk Pharma GmbH: Consultant, Abbott Laboratories & Abbott Molecular Inc. Consultant, Alfasigma GmbH: Consultant, Aligos Therapeutics, Inc. Consultant, Atea Pharmaceuticals, Inc. Consultant, Bristol-Myers-Squibb: Consultant, EIT Pharma, Inc. Consultant, F. Hoffmann-La Roche Ltd. Consultant, IntergerBio, Inc. Consultant, Orphalan GmbH: Consultant, Pfizer Pharma GmbH: Consultant, Primmune Therapeutics, Inc. Consultant, Ribocure Pharmaceuticals AB: Consultant, Gilead Sciences GmbH & Gilead Sciences Ltd. Speaking and Teaching, Dr. Falk Pharma GmbH: Speaking and Teaching, IPSEN Pharma S.A.S. Speaking and Teaching, MSD Sharp & Dohme GmbH: Speaking and Teaching, Novo Nordisk Pharma GmbH: Speaking and Teaching, BioMarin Pharmaceuticals Inc. Speaking and Teaching, Biotest AG: Speaking and Teaching, CSL Behring: Speaking and Teaching, SANOFI Aventis Deutschland GmbH: Speaking and Teaching, Verein Falk Foundation e.V. Speaking and Teaching.

3204 | THE SAFETY AND TOLERABILITY OF ABI-6250, AN ORALLY ADMINISTERED NTCP INHIBITOR IN HEALTHY PARTICIPANTS

Edward Gane[1] Christian Schwabe[2] Grace Wang[3] Jieming Liu[3] Nuruddin Unchwaniwala[3] Lewyn Li[3] Steven Knox[3] Anuj Gaggar[3] Katie Zomorodi[3], [1]University of Auckland, [2]New Zealand Clinical Research, [3]Assembly Biosciences, Inc.

Background: Chronic hepatitis D virus (HDV) infection (cHDV), the most severe form of viral hepatitis, is estimated to affect 12-72 million patients worldwide. Patients with cHDV are at high risk of developing advanced liver disease and treatment options are limited. HDV utilizes the sodium taurocholate cotransporting polypeptide (NTCP), a transmembrane bile acid transporter on hepatocytes, as an entry receptor into the liver. Bulevirtide (BLV), an NTCP inhibitor administered once-daily (QD) by subcutaneous injection, reduces HDV RNA and ALT and leads to dose-dependent and reversible elevations in total bile acids in patients with cHDV. Orally administered HDV entry inhibitors may provide improved dosing convenience compared to daily subcutaneous BLV injections. ABI-6250-101 (NCT06740474) was a randomized, blinded Phase 1a study assessing the safety and tolerability of a potentially first in class, oral NTCP inhibitor ABI-6250 (6250) in healthy participants. **Methods:** Two single-dose cohorts of 5mg and 25mg, and 3 multiple-dose cohorts of 0.05mg, 0.2mg and 1mg 6250 QD for 10 days were evaluated. In each cohort, 8 subjects were randomized in a 3:1 ratio to receive 6250 or placebo (PBO). Safety was assessed by physical examination, adverse events (AEs), and lab parameters. Genomic DNA from participant peripheral whole blood underwent whole exome sequencing (WES) to characterize variants associated with potential safety observations. **Results:** Overall, treatment-emergent (TE)AEs were reported in 67% (20/30) and 40% (4/10) of 6250 and PBO recipients respectively; all were Grade 1 or 2. No serious AEs were reported. Lab abnormalities were observed in 60% (18/30) and 70% (7/10) of 6250 and PBO recipients respectively; all were Grade 1 or 2 except for a Grade 4 unrelated, self-limited creatine kinase increase in a 5mg recipient. Self-limited, asymptomatic ALT elevations were observed at all dose levels including PBO, with the exception of the 0.05mg dose level; 5 Grade 1, 1 Grade 2. Grade 1 ALT elevations were observed in similar proportions across the multiple-dose groups; 16.7% (1/6) at 1mg, 0.2mg, and PBO, and 0% at 0.05mg. One subject in the 1mg dose group discontinued 6250 due to a treatment-related, Grade 1 ALT elevation (64 U/L); resolved post discontinuation. Dose dependent and reversible

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increases in total bile acids, a marker of NTCP engagement, were observed without any associated pruritus. WES revealed no association between observed ALT elevations and polymorphisms in NTCP, CYP enzymes, HLA alleles, UGT enzymes, or other bile acid transporter genes. Safety and tolerability will be further described by subgroup analyses. **Conclusion:** Overall, 6250 was well tolerated when administered as single doses up to 25 mg, and up to 1mg QD for 10 days. Total bile acids increased in a dose-dependent and reversible manner without any associated pruritus. Phase 2 studies in participants with chronic HDV infection are planned to start by year end.

	Single-Dose Cohorts			Multiple-Dose Cohorts			
n (%) of Participants	5 mg 6250 (n=8)	25 mg 6250 (n=6)	All Cohorts PBO (n=4)	0.05 mg QD 6250 (n=6)	0.2 mg QD 6250 (n=8)	1.0 mg QD 6250 (n=6)	All Cohorts PBO QD (n=6)
TEAEs	4 (66.7)	2 (33.3)	0	6 (100.0)	4 (66.7)	4 (66.7)	4 (66.7)
Grade 1	4 (66.7)	2 (33.3)	0	6 (100.0)	3 (50.0)	4 (66.7)	4 (66.7)
Grade 2	0	0	0	0	2 (33.3)[a]	0	0
Grade ≥3	0	0	0	0	0	0	0
TEAEs leading to 6250/PBO DC	0	0	0	0	0	1 (16.7)[b]	0
TE SAEs	0	0	0	0	0	0	0
TE gradied laboratory abnormalities[c]	4 (66.7)	3 (50.0)	2 (50.0)	3 (50.0)	5 (83.3)	3 (50.0)	5 (83.3)
Grade 1	4 (66.7)	2 (33.3)	2 (50.0)	2 (33.3)	5 (83.3)	3 (50.0)	4 (66.7)
Grade 2	0	1 (16.7)	0	1 (16.7)	1 (16.7)	0	3 (50.0)
Grade 3	0	0	0	0	0	0	0
Grade 4	1 (16.7)[d]	0	0	0	0	0	0

[a]gout and headache (different participants). [b]Grade 1 ALT increase. [c]Any postbaseline abnormality of Grade 1 or higher. [d]Grade 4 creatine kinase increase.
6250, ABI-6250; DC, discontinuation; PBO, placebo; QD, once daily; SAE, serious adverse event;
TE, treatment-emergent; TEAE, treatment-emergent adverse event.

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3205 | PROTECTIVE ISGYLATION OF HIV PROTEINS IN HEPATOCYTES IS COMPROMISED BY ETHANOL EXPOSURE: CONTRIBUTION TO LIVER FIBROSIS DEVELOPMENT

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Background: Liver fibrosis is diagnosed in 33.9% People Living with HIV (PLWH), making liver disease one of the leading comorbidities. Alcohol consumption for more than 50g/day increases fibrosis risk, and the mechanisms behind this are multifactorial. Ethanol-induced accumulation of HIV proteins in hepatocytes causes hepatotoxicity and is associated with extracellular vesicle (EV) release. Post-translational modification of these proteins makes them more susceptible to degradation. Ubiquitin-like modifier, ISG15, covalently attaches to metabolically active viral proteins, and ISGylated proteins become a preferable substrate for the lysosome, which regulates EV release. Protein ISGylation is interferon (IFN)-type 1- activated process and is also controlled by de-ISGylase, USP18. We hypothesize that ethanol metabolism increases the release of non-IGylated HIV proteins with hepatocyte-derived EVs, and that engulfment of these EVs by Hepatic Stellate Cells (HSCs) promotes their activation, thereby initiating liver fibrosis. **Methods:** The study was performed on Huh7.5-CYP cells treated with an acetaldehyde-generating system (AGS, for ethanol non- or weak metabolizers) and HIV_{ADA}. Cells differentially overexpressing Nef, Tat, and p24 have also been used. The results were confirmed on primary human hepatocytes (PHH) treated with HIV_{ADA} and 50 mM ethanol. ISG15, USP18, and protein ISGylation were induced by IFNα exposure and visualized by Western Blot and immunoprecipitation (IP). mRNAs were quantified by RT-PCR. **Results:** Ethanol or AGS exposure to cells suppressed protein ISGylation and enhanced EV release. Mechanistically, this happened due to suppression of IFNα signaling at the level of STAT1 phosphorylation, diminishing IFNα-triggered ISG15 induction. Conjugation of HIV proteins with ISG15 was also impaired at the level of the E3 ISGylation enzyme, HERC5, whereas the E1 and E2 enzymes were minimally affected. Additionally, upregulation of USP18 by ethanol metabolites and ROS led to protein de-ISGylation and the accumulation of free, unconjugated ISG15. Finally, non-ISGylated HIV proteins were selected for EVs. Treatment of HSC (LX2) with Nef, Tat, and P24 in hepatocyte EVs induced the expression of Col1A1, SMA, and TIMP1 genes in these cells. **Conclusion:** Ethanol metabolism-induced suppression of HIV protein ISGylation in HIV-accumulating hepatocytes promotes the sorting of non-ISGylated proteins into EV to activate HSC and liver fibrosis.

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3206 | TRENDS IN INCIDENCE, INTERVENTIONS, AND OUTCOMES OF PYOGENIC LIVER ABSCESS IN THE UNITED STATES, 1993–2020

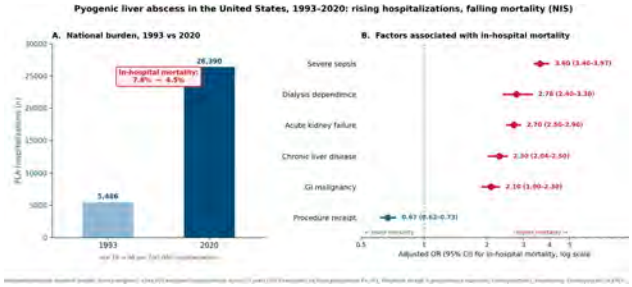
Akram Alnounou[1] Brian Nohomovich[2] Mohammad Alabbas[3] Eric Sieloff[1] Thomas Melgar[1], [1]Western Michigan University Homer Stryker MD SOM, [2]Henry

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Ford Health System, Providence, [3]Cleveland Clinic Foundation

Background: Pyogenic liver abscess (PLA) causes substantial inpatient morbidity, and contemporary U.S. national trends after 2010 are limited. We evaluated PLA hospitalization burden, procedure utilization, and factors associated with in-hospital mortality. **Methods:** Adult hospitalizations with a PLA diagnosis were identified in the Nationwide/National Inpatient Sample, 1993–2020, excluding 2015, using ICD-9-CM 572.0 or ICD-10-CM K75.0. Amebic abscess and candidiasis were excluded. Survey-weighted analyses accounted for the NIS sampling design. Temporal trends were assessed with the Cochran-Armitage test, and survey-weighted logistic regression estimated odds ratios (ORs) for factors associated with inpatient mortality. **Results:** Weighted analyses identified approximately 344,000 adult PLA hospitalizations across 27 study years. PLA hospitalizations rose from 5,486 (1993) to 26,390 (2020), and the rate increased from 19 to 98 per 100,000 hospitalizations. In-hospital mortality declined from 7.8% to 4.5%. A total of 132,557 procedures were performed: percutaneous aspiration (92,381; 70%), cholecystectomy (16,366; 12%), hepatotomy (14,622; 11%), other cholangiogram (8,343; 6.3%), and ERCP (845; 0.6%). Procedure receipt was associated with lower odds of inpatient mortality (OR, 0.67; 95% CI, 0.62–0.73; $P < .001$). Higher mortality was associated with severe sepsis (OR, 3.6; 95% CI, 3.4–3.97), dialysis dependence (OR, 2.78; 95% CI, 2.4–3.3), acute kidney failure (OR, 2.7; 95% CI, 2.5–2.9), chronic liver disease (OR, 2.3; 95% CI, 2.04–2.5), and gastrointestinal malignancy (OR, 2.1; 95% CI, 1.9–2.3; all $P < .001$). **Conclusion:** PLA hospitalizations and hospitalization rate increased from 1993 to 2020 while in-hospital mortality declined. Procedure receipt was associated with lower inpatient mortality, and severe sepsis, dialysis dependence, acute kidney failure, chronic liver disease, and gastrointestinal malignancy were associated with higher mortality.



Disclosures: Akram Alnounou:Nothing to Disclose, Brian Nohomovich:Nothing to Disclose, Mohammad Alabbas:Nothing to Disclose, Eric Sieloff:Nothing to Disclose, Thomas Melgar:Nothing to Disclose.

3207 | CANNABIS USE IN ALCOHOL ASSOCIATED HEPATITIS ADMISSIONS: A TWENTY-THREE-YEAR REVIEW OF PREVALENCE, DEMOGRAPHICS, AND HOSPITAL CHARGES

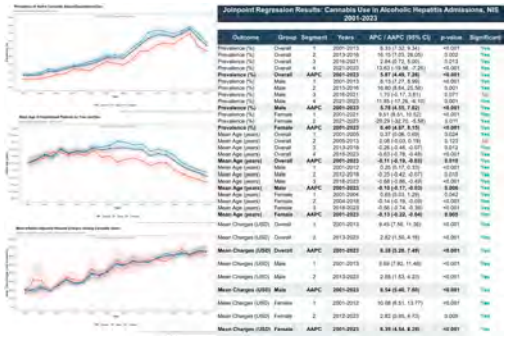
Renuka Verma[1] Ezzeldien Ibrahim[2] Maria Ortega Abad[3] Kamleshun Ramphul[4] Karn Wijarnpreecha[5] Nikki Duong[6], [1]Kirk Kerkorian School of Medicine at the University of Nevad, [2]University of Missouri – Columbia, [3]Cleveland clinic, [4]Independent researcher, [5]University of Arizona College of Medicine-Phoenix, [6]Stanford University

Background: The burden of alcohol associated hepatitis (AAH) in the United States has risen markedly over the past two decades, with recent studies estimating nearly a doubling in admissions between 2009 and 2019. Cannabis use has also increased substantially, with expanding state-level legalization since 2012. At present, there are no national analyses investigating active cannabis use among patients admitted with AAH. We sought to evaluate these trends from 2001 to 2023. **Methods:** Data were collected from the National Inpatient Sample (2001–2023) for admissions for AAH. The mean ages of these patients using cannabis were also explored, along with inflation-adjusted hospital charges. The trends were also stratified for males and females. Appropriate adjustments were made to the database to ensure proper national estimation, as per HCUP's guidelines. Joinpoint regression was used to estimate Annual Percent Changes (APCs) and Average Annual Percent Changes (AAPCs). **Results:** The prevalence of active cannabis use among AAH admissions rose from 1.52% in 2002 to a peak of 7.49% in 2021, before declining to 5.37% in 2023 (AAPC 5.87%; 95% CI 4.49–7.28), driven by a rise of 8.33%/year through 2013, 16.15%/year between 2013–2016, 2.84%/year between 2016–2021, and a sharp reversal of −13.63%/year thereafter. Both males (lowest 1.70% in 2002, peak 7.78% in 2021; AAPC 5.78%) and females (lowest 1.03% in 2002, peak 6.89% in 2021; AAPC 6.40%) showed similar reversals beginning in 2021 (males −11.85%/year, females −20.29%/year). The mean age of cannabis-using AAH patients was highest in 2009 (48.56 years) and lowest in 2023 (46.58 years), with an overall AAPC of −0.11% (95% CI −0.19 to −0.03); the decline accelerated after 2018 (APC −0.63%/year, compared to −0.26%/year from 2013–2018). Inflation-adjusted mean hospital charges rose more than three-fold, from $19,234 in 2004 to $65,828 in 2022 (AAPC 6.38%; 5.28–7.49), with the steepest rise before 2013 (APC 9.45%/year) and slower growth thereafter (APC 2.82%/year). All trends were statistically significant. **Conclusion:** Active cannabis use among AAH

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admissions in the United States rose substantially from 2001 to 2021 in both sexes before declining in the final two years. These patients have become progressively younger and incur markedly higher inflation-adjusted hospital charges. These findings highlight an evolving demographic and economic burden of cannabis use among AAH hospitalizations and warrant further investigation into its clinical implications.



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3208 | BULEVIRTIDE IMPROVES QUALITY OF LIFE AND MAINTAINS HIGH TREATMENT ADHERENCE AT 12 MONTHS IN CHRONIC HDV INFECTION: DATA FROM THE ENHANCE COHORT

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Background: Bulevirtide (BLV) is the first approved entry inhibitor for chronic HDV infection. Its impact on treatment adherence and quality of life (QoL) across specific domains, and their relationship with virological response and baseline viremia, remain poorly characterized. **Aim:** To evaluate treatment adherence (MMAS-8) and QoL (HQLQ) at 12 months of BLV therapy and to identify associations with virological response category and baseline HDV viremia. **Methods:** Treatment adherence was assessed using MMAS-8 (score 0–10; high ≥ 8, medium 6–7, low < 6) and QoL using the HQLQ (12 subscales, 0–100) at baseline and W48 (12 months) in a prospective cohort of 124 HDV/HBV patients initiated on BLV 2 mg/day s.c. Virological response at W48: complete (CVR, $> 2\log_{10}$ HDV RNA reduction), partial (PVR, 1–$2\log_{10}$), no response (NR, $< 1\log_{10}$). Wilcoxon signed-rank, Kruskal–Wallis tests and Spearman correlations were applied. **Results:** Virological evaluation at W48 revealed: CVR 64%, PVR 18.6%, NR 17.4%; ALT normalisation at 12 months was present in 76% of patients. ***Treatment adherence:*** Mean MMAS-8 score was 7.48 ± 1.05 (median 8). High adherence (score = 8) was present in 62.3% of patients, medium adherence (6–7) in 32.1%, and low adherence (< 6) in only 5.7%. Adherence remained stable from 6 to 12 months (7.67 vs 7.53, $p = 0.403$). MMAS scores did not differ across virological response groups (CVR: 7.46 ± 1.08; PVR: 7.34 ± 1.28; NR: 7.75 ± 0.46; $p = 0.736$) and did not correlate with baseline HDV RNA ($r = 0.02$, $p = 0.89$). ***Quality of life*****:** Of 12 HQLQ subscales, Hepatitis-specific Distress improved significantly from baseline to 12 months (+14.5 points, $p = 0.012$), with a trend in Daily Activities/Well-being (+6.3 points, $p = 0.074$). No subscale differed significantly across virological response groups (CVR vs PVR vs NR; all $p > 0.60$), indicating that QoL benefit is independent of viral suppression depth. Higher baseline HDV RNA correlated with better Physical Functioning ($r = +0.28$, $p = 0.049$) and fewer Hepatitis-related Physical Limitations ($r = +0.29$, $p = 0.037$) at 12 months; improvement in Bodily Pain also correlated positively with baseline viremia ($r = +0.37$, $p = 0.042$). **Conclusion:** BLV treatment sustains high adherence at 12 months, independent of virological outcome. Hepatitis-specific QoL improves significantly at 12 months, particularly Hepatitis Distress, regardless of virological response category. Higher baseline viremia predicts better functional QoL outcomes at one year. These findings support a broad QoL benefit of BLV therapy that is dissociated from the degree of viral suppression.

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3209 | BRELOVITUG DEMONSTRATES BIOCHEMICAL AND VIROLOGICAL IMPROVEMENTS IN PATIENTS WITH CHRONIC HEPATITIS D AND CIRRHOSIS: RESULTS FROM A PHASE 2 EXTENSION STUDY

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Background: Chronic hepatitis D (CHD) represents the most aggressive type of viral hepatitis with increased complications of cirrhosis such as hepatocellular carcinoma and death. Brelovitug (BJT-778) is a fully human monoclonal antibody targeting HBsAg, a protein required for viral entry into hepatocytes, and is being evaluated for the treatment of CHD including patients with cirrhosis. Here we describe the response for up to 84 weeks of brelovitug in cirrhotic patients with CHD from BJT-778-001. **Methods:** In BJT-778-001, a phase 1/2, international, open-label, adaptive trial, adults with CHD received 1 of 3 regimens of brelovitug for 48 weeks. After 48 weeks of treatment, participants with cirrhosis (n = 15) defined as a liver stiffness ≥ 12 kPa at any time during the study, were offered up to an additional 3 years of treatment with brelovitug 900 mg Q4W. Key endpoints included virologic response (HDV RNA ≥ 2 $\log_{10}$ IU/mL reduction from baseline or < LLOQ, target not detected [TND]), ALT normalization, combined virologic and ALT response, and safety/tolerability. Analyses were descriptive. **Results:** All 15 participants have reached at least 24 weeks in the extension period. At Baseline, participants had a median (min, max) age of 47 (37, 68) years, HDV RNA 5.66 (1.34, 7.36) $\log_{10}$ IU/ml and ALT 67 (15, 202) IU/ml; Baseline transient elastography (TE) was 14.2 (9.5, 46.4) kPa. and max TE was 15.3 (12.0, 46.4) kPa. During initial treatment phase, brelovitug dosing included 5 (33%) who received 300 mg once weekly, 1 (7%) who received 600 mg QW from Baseline to Week 12 and then every 2 weeks, and 9 (60%) who received 900 mg every 4 weeks with a loading dose at Week 2. At the end of the first 48 weeks of treatment, all 15 (100%) participants had a virologic response including 10 (67%) who achieved < LLOQ (< 10 IU/ml HDV RNA) and 4 (27%) who achieved TND; ALT normalization and a combined response occurred in 10 (67%) participants. Eight participants had a dose interruption between Week 48 and start of the extension ranging from 44 to 284 days. Data on additional treatment were available for all 15 participants at 24 Weeks (72 weeks total) and for 13 participants at 36 Weeks (86 weeks total). At last follow-up, all 15 (100%) participants had a virologic response, including 11 (73%) who achieved < LLOQ including 9 (60%) who achieved TND; ALT normalization and combined response occurred in 14 (93%). There were no serious AEs, AEs ≥ Grade 3, or AEs that led to study or treatment discontinuation, and the most common treatment-related AEs were mild/moderate injection site reactions and flu-like symptoms, both occurring in 2 (13%) individuals. **Conclusion:** Brelovitug continued to demonstrate efficacy and was well-tolerated in patients with CHD and cirrhosis with up to 86 weeks of treatment. The response was durable; HDV RNA suppression generally deepened, and frequency of ALT normalization increased with longer treatment. Phase 3 registrational trials of brelovitug for CHD are ongoing.

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3210 | AVOIDING SCREENING ENDOSCOPY FOR HIGH-RISK VARICES IN HDV CIRRHOSIS: PERFORMANCE OF BAVENO AND AASLD 2024 CRITERIA AND DEVELOPMENT OF THE BAVENO-HDV MODEL

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Background: Patients with cirrhosis and high-risk varices (HRV) are at substantial risk of variceal bleeding, a major cause of liver-related morbidity and mortality. The Baveno consensus and AASLD 2024 guidance endorse non-invasive tests (NITs) to identify patients who may safely avoid screening endoscopy for HRV, but data in chronic hepatitis delta (CHD) are lacking. We evaluated the performance of Baveno and AASLD 2024 criteria in untreated patients with HDV-related cirrhosis and derived disease-specific criteria (Baveno-HDV). **Methods:** Untreated patients with HDV-related compensated cirrhosis and available liver stiffness measurement (LSM) and esophagogastroduodenoscopy (EGD) enrolled in the multicenter SAVE-D and D-SHIELD studies were included. Baveno VI and AASLD criteria were applied to identify patients in whom screening endoscopy could have been avoided (LSM <20 kPa + platelets [PLT] count $>150x10^9$ /L). Disease-specific LSM and PLT cut-offs for an "avoid endoscopy" rule applicable to CHD patients was identified. Internal validation of our findings was performed using nonparametric bootstrap resampling. **Results:** 347 patients were included in this analysis (median age 54, 56% males, median LSM 16.7 (11.8-25.2) kPa, PLT 95 (65-147) $x10^9$ /L; spleen size 14 (12-17) cm). 156 (45%) patients showed gastroesophageal varices, of whom 93 (27%) HRV. Avoiding screening endoscopy by Baveno VI/AASLD 2024 criteria resulted in 4 (6.2%) missed HRV (Sn 95.7%, NPV 93.8%). Bootstrap internal validation showed substantial uncertainty around the estimated false negative rate, with a bias-corrected 95% confidence interval (BC-CI) of 1.15%-13.88%. Since only 2 patients had PLT count exactly equal to 150 $x10^9$ /L PLT, and both had LSM 20kPa, no patient was differently classified according to AASLD 2024 criteria. Therefore, the Baveno VI and AASLD criteria were equivalent in our cohort. New cut-offs, "Baveno-HDV", defined by grid search derived combination of LSM ≤ 19 kPa and PLT $\geq 110 \times 10^9$/L, showed improved performances with only 3.6% missed HRV (Sn 95.7% NPV 96.4%) and an increased number of patients avoiding endoscopy (32% *vs.* 19%). Bootstrap validation demonstrated narrower variability estimates, with a 95% BC-CI for the false negative rate of 0.87%-7.76% **Conclusion:** In untreated patients with HDV-related cirrhosis, the Baveno and AASLD 2024 "avoid endoscopy" criteria showed suboptimal performance, with misclassification of patients harboring HRV

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and at risk of variceal bleeding. The newly developed disease-specific Baveno-HDV criteria significantly reduced missed HRV while increasing the number of safely spared screening endoscopies.

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3211 | LOW BURDEN OF CARDIOMETABOLIC RISK FACTORS IN HDV-RELATED LIVER DISEASE: A EUROPEAN POOLED ANALYSIS OF THE SAVE-D AND D-SHIELD COHORTS

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Background: Chronic hepatitis Delta is the most severe form of viral hepatitis, with accelerated progression to cirrhosis and increased hepatocellular carcinoma (HCC) risk. While cardiometabolic risk factors influence outcomes in other chronic liver diseases, their prevalence and clinical relevance in CHD remain poorly defined. **Methods:** CHD patients included in the retrospective multicenter real-world European SAVE-D study and in the prospective multicenter Italian D-SHIELD study were included. The prevalence of cardiometabolic risk factors (arterial hypertension, type 2 diabetes, overweight/obesity) were evaluated at BLV start. **Results:** 828 patients treated with BLV 2 mg/day subcutaneous monotherapy up to 144 weeks were included in this analysis: age 52 (IQR 42-60) years, 57% men, 698 (84%) with cirrhosis, median BMI was 24.8 (22.7-27.4). 39 (5%) patients had type 2 diabetes (T2DM), and 126 (15%) patients had arterial hypertension (AHTN), 85 (10%) patients had obesity (defined as BMI $\geq$30), of whom 13 (15%) grade II obesity (BMI 35-39) and 2 (2%) grade III obesity (BMI $\geq$40). Controlled Attenuation Parameter (CAP) on Fibroscan ®**:** was available in 484 (59%) patients: median CAP values were 209 (181-238) dB/m. 50 (5%) patients showed hepatic steatosis (by CAP >275 dB/m): median BMI in these patients was 28.4, 6 (12%) patients had T2DM, 11 (22%) AHTN. Overall, median alanine aminotransferase (ALT) levels were 79 (50-129) U/L and 62 (47-94) in patients without and with T2DM, respectively (p=0.04). Median gamma glutamyl transferase (gGT) were 58 (35-97) and 44 (27-74) U/L in patients without and with T2DM, respectively (p=0.03). When analyzing the impact of cardiometabolic risk factors (AHTN, T2DM), BMI and CAP values on responses rates to BLV, only CAP values predicted the achievement of a biochemical response at on-treatment week 48 (OR 1.01 95% CI 1.00-1.02, p=0.02). Conversely, none of the baseline features predicted the achievement of a virological response, combined response, and of HDV RNA undetectability at week 48 of BLV monotherapy. **Conclusion:** European patients with CHD exhibited an unexpectedly low prevalence of cardiometabolic risk factors (MetHDV), compared to other viral hepatitis, with no measurable effect on BLV treatment responses during the first year of therapy.

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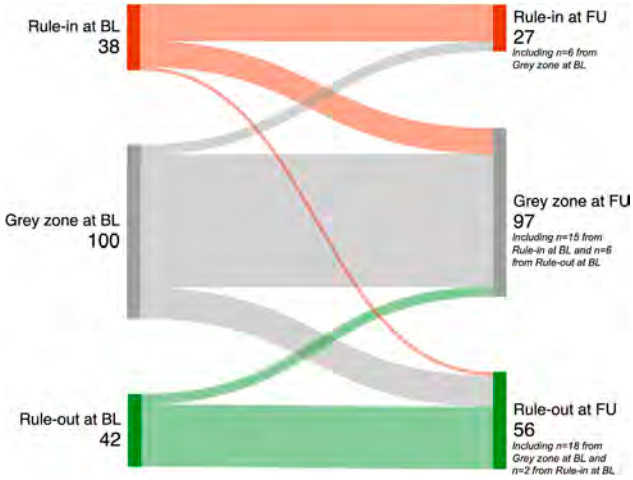
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3213 | BULEVIRTIDE MONOTHERAPY IMPROVES VALIDATED CSPH CRITERIA (BAVENO AND ANTICIPATE) IN HDV PATIENTS WITH ACLD

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Background: Patients with chronic hepatitis delta (CHD) are at high risk of clinically significant portal hypertension (CSPH) and liver-related complications. Treatment with bulevirtide (BLV) is approved for CHD and is accompanied by a reduction in hepatic venous pressure gradient. In clinical practice, however, liver stiffness (LSM) and platelet count (PLT) are used for non-invasive CSPH assessment. The primary endpoint was to assess improvement of CSPH risk using validated non-invasive CSPH criteria. **Methods:** CHD patients receiving BLV monotherapy at 2mg/day for ≥48 weeks at 7 European centres were included. LSM and PLT data at baseline (BL) and week (W) 48 were recorded. CSPH risk was assessed by Baveno-VII criteria: rule-out (LSM ≤15kPa plus normal PLT ≥150G/L), rule-in LSM >25kPa. Within the grey zone (GZ), we identified probable CSPH [probCSPH] by either LSM >20kPa plus PLT <150G/L or LSM >15 plus PLT <110G/L. The ANTICIPATE model reflecting CSPH risk [%] was calculated, with ≥75% and <60% indicating high and low risk of CSPH, respectively. Improvement was defined as a reduction in estimated CSPH risk and/or regression to a lower CSPH category. **Results:** In total, 188 patients were included: 54.8% male; median for age: 50 years, BMI: 25kg/m2, LSM: 16kPa, PLT: 117G/L and ALT: 79IU/L. At BL, Baveno-VII CSPH criteria classified n=44 (23.4%) as rule-in, n=43 (22.9%) as rule-out, and n=101 as GZ, including n=37 (19.7%) with probCSPH. The ANTICIPATE model at BL yielded a median CSPH risk of 49.1% - identifying n=68 (36.2%) and n=109 (58.0%) as high and low CSPH risk patients, respectively. N=180 (95.7%) had longitudinal data on LSM/PLT at W48 available: 66.6%, 68.9% and 51.1% achieved virologic response (VR), ALT normalization, and complete response (CR) respectively. At W48, median LSM significantly decreased (16.0 vs. 12.6kPa; p<0.001) and PLT significantly increased (117 vs. 132G/L; p<0.001) compared to BL. Baveno-VII CSPH criteria re-classified n=27 (15.0%) as rule-in, n=56 (31.1%) as rule-out, and n=97 as GZ, including 13.9% with probCSPH (Figure-1). The ANTICIPATE CSPH risk decreased to 27.0% at W48 - identifying n=46 (25.6%) and n=119 (66.1%) as high and low CSPH risk patients; respectively. The median relative change in ANTICIPATE CSPH risk was similar for patients with vs. without VR (-21.1% vs. -24.1%, p=0.899) and CR (-21.1% vs. -24.1%, p=0.549), respectively.Overall, improvements in Baveno-VII at W48 (rule-in to GZ/rule-out or GZ to rule-out) and ANTICIPATE CSPH risk categories (negative relative change) were found in 19.4% and 75.0% of CHD patients, respectively. **Conclusion:** After one year of BLV monotherapy, many CHD patients showed improvements in validated non-invasive CSPH tests, i.e. the Baveno-VII criteria and the ANTICIPATE models. While the lack of an untreated control group needs to be acknowledged, the positive signals suggest beneficial effects of BLV monotherapy on the risk of CSPH-driven clinical events.



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3214 | SEPSIS-RELATED MORTALITY IS RISING DISPROPORTIONATELY IN CIRRHOSIS COMPARED WITH OTHER CHRONIC DISEASE POPULATIONS: A US-BASED POPULATION STUDY, 1999-2020

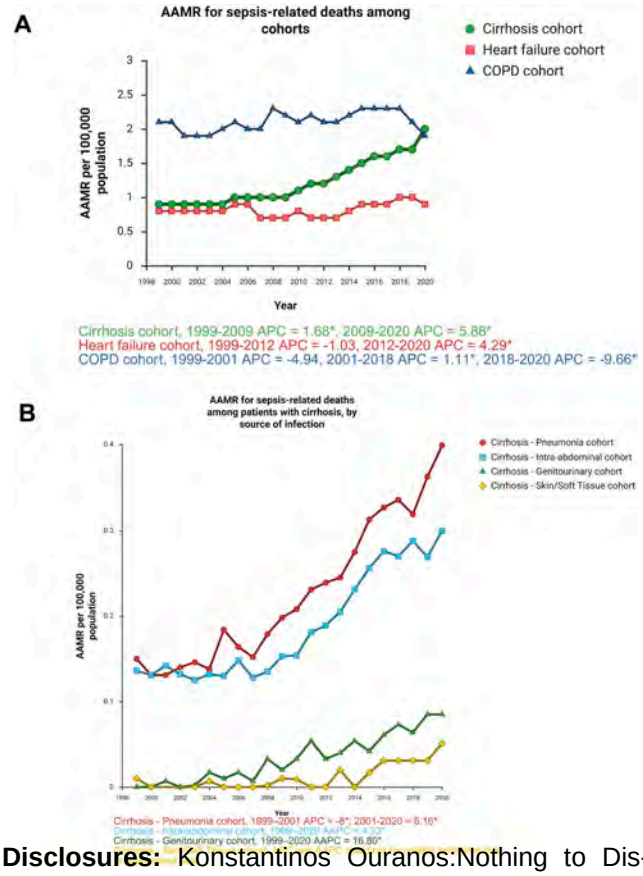
Konstantinos Ouranos[1] Chanyanuch Nakapakorn[2] Mark Michael[1] Sudha Kodali[1] David Victor[1] Mazen Noureddin[1] Douglas Simonetto[3] Jody Olson[4] Sumeet Arsani[2] Constance Mobley[1] Mark Ghobrial[1] Eleftherios Mylonakis[5] Kavish Patidar[1], [1]Houston Methodist Hospital, [2]Baylor University Medical Center, Dallas, TX, USA, [3]Mayo Clinic Rochester, [4]Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, USA, [5]Houston Methodist

Background: Patients with cirrhosis are highly susceptible to sepsis due to immune dysregulation and bacterial translocation, but temporal trends in sepsis-related mortality compared with other chronic diseases remain unclear. We evaluated national

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trends in sepsis-related mortality among patients with cirrhosis versus congestive heart failure (CHF) and chronic obstructive pulmonary disease (COPD), and characterized the major infection types associated with sepsis in cirrhosis. **Methods:** We performed a cross-sectional analysis of the CDC WONDER Multiple Cause of Death database (1999–2020). Adults with cirrhosis, CHF, and COPD were identified from death certificates using mutually exclusive cohorts. Sepsis-related mortality was determined from listed causes of death. Age-adjusted mortality rates were calculated, and Joinpoint regression was used to estimate annual percent change (APC) and average annual percent change (AAPC). Prespecified subgroup analyses were conducted by sex, age, race, and ethnicity. **Results:** From 1999 to 2020, sepsis-related mortality increased substantially among patients with cirrhosis, with significantly greater rise compared to CHF and COPD. Patients with cirrhosis demonstrated an AAPC of 3.86%, compared to 0.96% among patients with CHF and –0.56% among patients with COPD (**Figure 1A**). Among patients with cirrhosis, rate of increase of annual sepsis-related mortality was highest for genitourinary infections (AAPC 16.8%), followed by pneumonia (AAPC 4.73%) and intra-abdominal infections (AAPC 4.33%) (**Figure 1B**) **.** Across demographic subgroups, cirrhosis consistently demonstrated the steepest increases in sepsis-related mortality. Among adults ≥65 years, sepsis-related mortality increased in cirrhosis (AAPC 3.74%) but declined in CHF and COPD (both AAPC –0.19%). Similarly, among adults <65 years, mortality increased in cirrhosis (AAPC 3.7%) and CHF (AAPC 3.93%), and to a lower extent in COPD (AAPC 0.93%). Hispanic patients with cirrhosis experienced particularly marked increases in sepsis-related mortality (AAPC 2.21%) than those with CHF (–0.77%) or COPD (–2.14%), with similar patterns in non-Hispanic individuals. Female patients with cirrhosis also experienced greater increases in sepsis-related mortality (AAPC 4.4%) compared to males (AAPC 3.45%), while CHF and COPD showed only modest sex-specific changes. **Conclusion:** Sepsis-related mortality has increased among patients with cirrhosis and has outpaced trends in CHF and COPD over past two decades. Genitourinary infections, pneumonia, and intra-abdominal infections represent contributors to sepsis-related mortality in cirrhosis. These findings identify cirrhosis as a uniquely vulnerable population and support development of cirrhosis-specific strategies focused on infection prevention, early sepsis recognition, vaccination, antimicrobial stewardship, and optimized management of high-risk infections.



Disclosures: Konstantinos Ouranos:Nothing to Disclose, Chanyanuch Nakapakorn:Nothing to Disclose, Mark Michael:Nothing to Disclose, Sudha Kodali: Nothing to Disclose, David Victor:Intercept: Speaker, and Advisor, Gilead: Speaking and Teaching, Madrigal: Speaker, BMS: Stock - publicly traded company, Pfizer: Stock - publicly traded company, Mazen Noureddin: Akero: Advisor, Alligos: Advisor, Altimmune: Advisor, AstraZeneca: Advisor, Boehringer Ingelheim: Advisor, Boston Pharma: Advisor, Cytodyn: Advisor, GSK: Advisor, Lilly: Advisor, Madrigal: Advisor, Merck: Advisor, Novo Nordisk: Advisor, Sagimet: Advisor, Terns: Advisor, Takeda: Advisor, Akero: Principal Investigator, Allergan: Principal Investigator, Altimmune: Principal Investigator, Boehringer Ingelheim: Principal Investigator, Bristol Myers Squibb: Principal Investigator, Boston Pharma: Principal Investigator, Conatus: Principal Investigator, Corcept: Principal Investigator, Galectin: Principal Investigator, Genfit: Principal Investigator, GSK: Principal Investigator, Kowa: Principal Investigator, Enanta: Principal Investigator, Madrigal: Principal Investigator, Lilly: Principal Investigator, Merck: Principal Investigator, Novartis: Principal Investigator, Novo Nordisk: Principal Investigator, Rivus: Principal Investigator, Shire: Principal

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3215 | ON-TREATMENT AND POSTTREATMENT PATTERNS OF NON-INVASIVE TESTS OF FIBROSIS WITH LONG-TERM BULEVIRTIDE TREATMENT FOR CHRONIC HEPATITIS DELTA: AN INTEGRATED ANALYSIS

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Background: Bulevirtide (BLV) is approved to treat chronic hepatitis delta (CHD) in the United States, European Economic Area, and other regions. Long-term therapy with BLV has demonstrated improvements in liver disease burden test results, including in patients with suboptimal virologic response. To further evaluate responses with BLV monotherapy, an integrated analysis was conducted. **Methods:** Data from patients receiving BLV 10 mg or 2 mg in the Phase 3 MYR301 (NCT03852719) and Phase 2 MYR204 (NCT03852433) studies were pooled and analyzed on treatment up to 96 weeks and posttreatment (PT) through 48 weeks of follow-up (FU48). Alanine aminotransferase (ALT) levels and non-invasive tests (NITs) including the aspartate aminotransferase to platelet ratio index (APRI), Fibrosis-4 Index (FIB-4), and liver stiffness (LS) were evaluated. Subgroups based on end-of-treatment (EOT) outcomes included virological responders (VR) excluding undetectable hepatitis delta virus (HDV) RNA (VRnU; ≥ 2 $\log_{10}$ IU/mL decline in HDV RNA from baseline [BL]), partial VR (PR, ≥ 1 to < 2 $\log_{10}$ IU/mL decline), and nonresponders (NR, < 1 $\log_{10}$ IU/mL decline). Patients with undetectable HDV RNA at EOT were divided based on PT viral status into the following categories: sustained PT undetectable (Und-S), low viremic relapse (Und-LV; detectable PT HDV RNA < 50 IU/mL), and high viremic relapse (Und-HV; PT HDV RNA ≥ 50 IU/mL). **Results:** Overall, 183 patients were included, of whom 76 had undetectable HDV RNA at EOT; 81 were VRnU; 13, PR; and 13, NR. Of patients with undetectable HDV RNA at EOT, during FU, 26 were Und-S; 10, Und-LV; and 39, Und-HV; 1 had no FU data. Improvements in NITs from BL to week 96 were seen in all virologic response subgroups (**Table**), with median LS decreases of −3.1, −3.9, −3.7, −3.6, −1.3, and −2.5 kPa in the Und-S, Und-LV, Und-HV, VRnU, PR, and NR groups, respectively. In the PT period, only patients with Und-S sustained improvements in median LS and ALT and patients with Und-LV sustained median ALT improvements from BL through FU48. Results were not as consistent for FIB-4 and APRI, possibly due to low subgroup sample sizes. **Conclusion:** Long-term therapy with BLV over 96 weeks improved NITs regardless of virologic response; however, these improvements decreased after treatment cessation through FU48 in all patients except the subsets with sustained undetectability or only low-level PT viremia. Most patients with CHD benefit from ongoing long-term BLV treatment, and treatment discontinuation should be considered only in those with a low likelihood of relapse.

Table. On-Treatment and Posttreatment Burden of Liver Disease Tests Stratified by Virologic Response and Relapse Status

	Bulevirtide Monotherapy (N=183)											
	Liver Stiffness, kPa Median (Q1, Q3)			ALT, U/L Median (Q1, Q3)			APRI Median (Q1, Q3)			FIB-4 Median (Q1, Q3)		
	BL	W96	FU48	BL	W96	FU48	BL	W96	FU48	BL	W96	FU48
Und-S (n=26)	13.6 (9.7, 19.1)	8.9 (6.4, 17.2)	8.6 (6.8, 12.9)	93 (64, 117)	35 (26, 62)	30 (22, 48)	1.1 (0.8, 1.5)	0.5 (0.3, 1.1)	0.5 (0.3, 0.7)	1.9 (1.3, 2.4)	1.6 (1.1, 2.8)	1.8 (1.4, 2.7)
Und-LV (n=10)	11.6 (8.9, 20.3)	7.7 (5.7, 9.6)	9.0 (6.9, 9.4)	103 (50, 166)	37 (32, 58)	30 (22, 47)	0.8 (0.7, 1.4)	0.5 (0.3, 1.0)	0.6 (0.4, 0.6)	1.6 (1.2, 2.8)	1.8 (0.8, 2.8)	2.1 (1.1, 3.3)
Und-HV (n=39)	11.4 (8.8, 16.7)	7.7 (6.1, 11.7)	8.9 (6.5, 12.8)	73 (57, 104)	31 (21, 44)	48 (38, 75)	0.8 (0.7, 1.4)	0.4 (0.3, 0.7)	0.7 (0.4, 1.0)	1.7 (1.3, 2.1)	1.3 (1.0, 1.8)	1.5 (1.1, 2.2)
VRnU (n=81)	11.9 (8.8, 17.3)	8.2 (5.8, 12.0)	11.7 (7.6, 16.5)	80 (57, 127)	34 (28, 43)	92 (48, 163)	1.0 (0.6, 1.6)	0.5 (0.4, 0.7)	1.2 (0.5, 2.1)	1.8 (1.1, 2.8)	1.4 (1.0, 2.0)	2.0 (1.1, 3.0)
PR (n=13)	8.5 (7.8, 13.8)	7.6 (6.7, 10.7)	7.5 (6.6, 10.4)	96 (80, 145)	38 (33, 48)	68 (48, 108)	1.1 (0.7, 1.2)	0.5 (0.3, 0.6)	0.7 (0.7, 0.8)	1.3 (1.1, 1.4)	1.0 (0.8, 1.8)	1.4 (1.1, 1.8)
NR (n=13)	12.0 (9.9, 14.8)	8.2 (7.8, 12.3)	10.7 (8.0, 11.7)	138 (105, 189)	64 (23, 76)	95 (76, 121)	1.3 (0.8, 2.2)	0.8 (0.3, 0.8)	0.8 (0.7, 1.1)	2.0 (1.3, 2.5)	1.2 (0.8, 1.6)	1.3 (1.1, 2.0)

Undetectable HDV RNA was defined as HDV RNA less than the lower limit of quantification, target not detected; patients with undetectable HDV RNA were excluded from NR and PR.
ALT, alanine aminotransferase; APRI, aspartate aminotransferase to platelet ratio index; BL, baseline; EOT, end of treatment; FIB-4, Fibrosis-4 Index; FU48, follow-up at 48 weeks posttreatment; HDV, hepatitis delta virus; NR, nonresponders (defined as having <1 $\log_{10}$ IU/mL decline in HDV RNA from BL at EOT); PR, partial responders (defined as having ≥1 to <2 $\log_{10}$ IU/mL decline in HDV RNA from BL at EOT); Q, quartile; Und-HV, high viremic relapse (defined as posttreatment HDV RNA ≥50 IU/mL) after undetectable HDV RNA at EOT; Und-LV, low viremic relapse (defined as detectable posttreatment HDV RNA <50 IU/mL) after undetectable HDV RNA at EOT; Und-S, sustained posttreatment undetectable HDV RNA after undetectable HDV RNA at EOT; VRnU, virological responders excluding undetectable HDV RNA (and defined as ≥2 $\log_{10}$ IU/mL decline in HDV RNA from BL at EOT); W, week.

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3216 | DISEASE PROGRESSION AMONG A NATIONALLY REPRESENTATIVE COHORT OF COMMERCIALLY INSURED PATIENTS WITH HEPATITIS DELTA VIRUS IN THE UNITED STATES

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Background: Coinfection with hepatitis delta virus (HDV) and hepatitis B virus (HBV) is associated with significantly greater risks of progression to cirrhosis, hepatocellular carcinoma (HCC), liver transplant (LT), and liver-related mortality compared with HBV monoinfection. However, it is unclear how the magnitude of increased risk of disease progression varies by baseline liver disease severity. We evaluated the risk of liver disease complications and how this risk varies by severity of baseline liver disease state among adults with HDV infection. **Methods:** A retrospective cohort study using the PharMetrics database searched from 1/1/2006 to 8/31/2022 identified commercially insured adults aged ≥18 years with an HDV diagnosis using *ICD-9/10-CM* codes. Patients were required to have ≥12 months of continuous enrollment pre-index (ie, diagnosis date) and 1 day post-index. Disease progression from baseline to the next disease state was assessed using Kaplan-Meier curves and multivariable Cox proportional-hazards regression models adjusting for patient characteristics. Disease states included noncirrhotic disease (NCD), compensated cirrhosis (CC), decompensated cirrhosis (DC), HCC, and LT. **Results:** Of the 272,148,753 patients identified within the database, 2,317 with HDV met the enrollment criteria, and 2,268 were analyzed after exclusion of patients with LT at baseline. Overall, patients had a mean (SD) age of 48 (11.4) years, and 59% were male. At baseline, liver disease severity was NCD in 70% (1,577/2,268) of patients, CC in 6% (125/2,268), DC in 19% (441/2,268), and HCC in 6% (125/2,268). Patients with more severe disease at baseline had significantly greater risks of further disease progression. Compared to patients with NCD at baseline, those with baseline CC demonstrated a higher rate of progression to DC (log rank $P < .0001$), HCC (log rank $P = .029$), and LT (log rank $P = .003$); those with baseline DC demonstrated a higher rate of progression to HCC and LT (log rank $P < .0001$ for both); and those with baseline HCC demonstrated a higher rate of progression to LT (log rank $P < .0001$). Mean (SD) months to the next disease state were as follows: NCD to CC, 46 (37.2); CC to DC, 37 (32.4); DC to HCC, 37 (40.7); and HCC to LT, 35 (35.7). Using a multivariable Cox regression model, compared to patients with baseline NCD, those with baseline CC had a significantly higher risk of transitioning to DC (hazard ratio, 2.43; 95% CI, 1.70–3.48; $P < .001$). Similar findings were observed for those with baseline DC or HCC (**Figure**). **Conclusion:** Among a large, nationally representative cohort of US adults, more advanced baseline liver disease severity at the time of HDV diagnosis was associated with significantly greater risks of further disease progression. These results highlight the importance of early HDV identification and subsequent linkage to care to prevent further disease progression and reduce the overall burden of disease.

Figure. Risk of Transitioning to More Severe Liver Disease States



Bold values indicate statistical significance. Results were estimated using Cox proportional-hazards regression models.

CC, compensated cirrhosis; DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; HR, hazard ratio; LT, liver transplantation; NCD, noncirrhotic disease.

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3217 | CLOSING THE CLINICAL GAP IN HEPATITIS E IN EUROPE: ONWARD, A PAN-EUROPEAN ONE HEALTH NETWORK ADDRESSING THE RISING BURDEN OF ACUTE AND CHRONIC HEV INFECTION

Imran Hasanoglu[1] Adriana Anita[2] Florence Abravanel[3] Gábor Reuter[4] Susanne Dudman[5] Nassim Kamar[6] Lorena Jemeršić[7] Ilaria Di Bartolo[8] Nigel Cook[9] Simona Ruta[10] Inne Nauwelaers[11] Lazar Milojević[12] Elena Todorovska[13] Sandra Mojsova[14] Arjana Zerja[15] Ana Avellon[16] Renate Hakze[17] Branko Velebit[12] Reimar Johne[18] João Mesquita[19] Antonio Rivero-Juarez[20], [1]Ankara Yildirim Beyazit University Bilkent City Hospital, [2]University of Life Sciences Ion Ionescu de la Brad, [3]Toulouse University Hospital, [4]Pecsi Tudomanyegyetem - University Of Pecs, [5]University of Oslo, [6]Centre Hospitalier Universitaire De Toulouse, [7]Hrvatski Veterinarski Institut, [8]Istituto Superiore Di Sanita, [9]Jorvik Food and Environmental Virology Ltd., [10]Universitatea De Medicina Si Farmacie Carol Davila Din Bucuresti, [11]Sciensano Belgium, [12]Institute of Meat Hygiene and Technology, [13]Agrobioinstitute Bulgaria, [14]Ss. Cyril and Methodius University in Skopje, [15]University of Medicine Tirana, [16]Instituto De Salud Carlos III, [17]Wageningen University, [18]German Federal Institute for Risk Assessment, [19]Universidade Do Porto, [20]Instituto Maimonides de Investigación Biomédica de Córdoba (IMIBIC)

Background: Hepatitis E virus (HEV) causes an estimated 20 million infections worldwide each year and is now the leading cause of acute viral hepatitis in Europe, yet most clinicians have rarely diagnosed a case. Chronic HEV has emerged as a serious complication in a rapidly expanding population of immunocompromised hosts: solid-organ transplant recipients, patients on biologic or cytotoxic therapy, and those with hematological malignancies. Extrahepatic and neurological manifestations are increasingly recognized. Yet across European centers, testing remains inconsistent, no antiviral or vaccine is licensed, ribavirin remains off-label, and immunosuppression reduction is not standardized. The emergence of *Rocahepevirus ratti* (ratHEV) as a cause of acute and chronic hepatitis further complicates routine diagnostics. Europe has lacked a coordinated clinical response. **Methods:** ONWARD (One Health Zoonotic Hepevirus Network; COST Action CA24140; 2025–2029) is the first dedicated pan-European platform for zoonotic hepeviruses. It unites 34 countries and more than 160 experts across hepatology, transplant medicine, virology, microbiology, veterinary science, food safety and public health. Five integrated Working Groups cover diagnostics and surveillance, clinical management and therapeutics, prevention and control, dissemination, and policy synergies. ONWARD engages European scientific societies, regulatory bodies and public health organizations to turn scientific consensus into harmonized clinical practice. **Results:** ONWARD's clinical focus translates into a concrete delivery agenda for hepatologists. Within its first year, the network has built an operational structure aligned with the SAPEA criteria for One Health Governance in the European Union, to develop harmonized diagnostic protocols for HEV and rat HEV; a shared framework for clinical trial design, outcome measures and biomarkers in chronic HEV; consensus on antiviral candidates and treatment strategies for immunocompromised hosts; targeted training for early-career hepatology and infectious disease clinicians; and active engagement to position HEV within the European hepatitis elimination agenda. Short-Term Scientific Missions, conference grants and the network's communication platform (hev-onward.eu) are already accelerating cross-border clinical collaboration. **Conclusion:** ONWARD delivers the first

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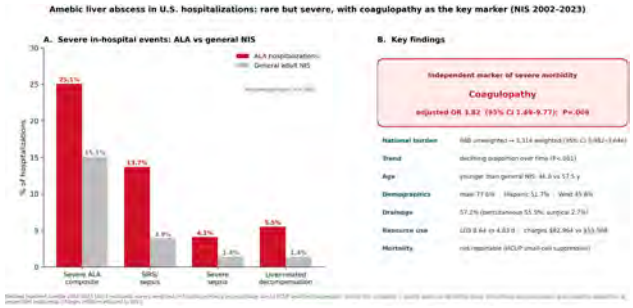
coordinated European response to the rising clinical burden of HEV and rat HEV, directly relevant to hepatologists managing acute hepatitis of unknown origin and chronic infection in immunocompromised patients. Its outputs will support harmonized diagnostic and treatment pathways, inform future ECDC and EFSA guidance, and strengthen preparedness for emerging hepeviruses across Europe and beyond.

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3218 | COAGULOPATHY AND SEVERE MORBIDITY IN U.S. HOSPITALIZATIONS FOR AMEBIC LIVER ABSCESS, 2002-2023

Akram Alnounou[1] Brian Nohomovich[2] Mohammad Alabbas[3] Eric Sieloff[1] Syed-Mohammed Jafri[4] Serge Sorser[2] Thomas Melgar[1], [1]Western Michigan University Homer Stryker MD SOM, [2]Henry Ford Health System, Providence, [3]Cleveland Clinic Foundation, [4]Henry Ford Health System

Background: U.S. population-based data on amebic liver abscess (ALA) are limited in the ICD-10 era. We evaluated national trends, inpatient outcomes, and markers of severe morbidity among adult ALA hospitalizations. **Methods:** Adult hospitalizations in the 2002–2023 National Inpatient Sample (NIS), excluding 2015, were analyzed. ALA was identified by ICD-9-CM 006.3 or ICD-10-CM A06.4. The primary outcome was a severe ALA composite (severe sepsis, acute kidney injury, liver-related decompensation, gram-negative septicemia, or unspecified septicemia). Analyses incorporated discharge weights, strata, and clustering. Markers of the composite were assessed with survey-weighted multivariable logistic regression, using general adult NIS hospitalizations as a benchmark. **Results:** We identified 688 ALA hospitalizations, representing 3,314 weighted national hospitalizations (95% CI, 2,982–3,646). The annual proportion of ALA hospitalizations declined (Cochran-Armitage P < .001). ALA hospitalizations were younger than general adult hospitalizations (mean age, 46.8 vs 57.5 years), predominantly male (77.6%), and frequently Hispanic (51.7%) or in the West (45.6%). Drainage was performed in 57.2% (percutaneous, 55.5%; surgical, 2.7%). The severe ALA composite occurred in 25.1% vs 15.1% of general hospitalizations (P < .001); SIRS/sepsis (13.7% vs 3.9%), severe sepsis (4.1% vs 1.4%), and liver-related decompensation (5.5% vs 1.4%) were also more frequent (all P < .001). In-hospital mortality was not reportable (HCUP small-cell suppression). Mean length of stay was longer (8.64 vs 4.83 days) and mean 2023-adjusted charges higher ($82,964 vs $55,508; both P < .001). Within ALA hospitalizations, coagulopathy was the only independent marker of the severe composite (adjusted OR, 3.82; 95% CI, 1.49–9.77; P = .006). **Conclusion:** ALA is rare in U.S. inpatient practice but is associated with severe morbidity, frequent drainage, longer stays, and higher charges. Coded coagulopathy identifies ALA hospitalizations with higher odds of severe in-hospital events, while administrative data remain insufficient for individual-level risk stratification.



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3219 | HDV STRAIN-SPECIFIC FITNESS AND HBSAG PAIRING REFINE THE GENOTYPE-BASED PARADIGM OF HDV PATHOBIOLOGY

Takeshi Saito[1] Daniel Pinski[2] Masashi Okawa[2] Shiuan-Chi Wang[2] Meng Li[1] Garnik Arustamyan[2], [1]University of Southern California, [2]Keck School of Medicine, University of Southern California

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Background: Hepatitis delta virus (HDV) accelerates HBV-associated liver disease and exhibits marked genetic diversity across eight genotypes. Certain HDV genotypes have been clinically linked to aggressive necroinflammation, fibrosis progression, and hepatocellular carcinoma; however, these associations are confounded by strain diversity, co-infecting HBV, host genetics, and regional comorbidities. Building on our prior cross-genotype HDV platform, this study tested whether clinically recognized genotype differences reflect intrinsic HDV genotype properties, strain-specific hepatocyte fitness, or functional compatibility between HDV genomes and HBV surface antigen (HBsAg). **Methods:** We analyzed 25 full-length HDV strains spanning all eight genotypes, including strains from genotypes clinically associated with aggressive disease. Using our established cross-genotype HDV-HBsAg platform, each HDV construct was evaluated with HBsAg expression systems representing distinct HBV envelope backgrounds. Producer-cell readouts included intracellular HDV RNA replication, S-HDAg/L-HDAg production, extracellular HDV RNA release, and particle-associated HDV output. The resulting HDV preparations were then assessed in optimized PHH cultures under HDV-alone and HBV-HDV coinfection conditions. PHH-based analyses quantified HDV entry/propagation, intracellular and extracellular HDV RNA, HBV-HDV interactions, and HBV-envelope–supported HDV particle production. **Results:** Across 25 HDV strains, we observed marked strain-to-strain variability in intracellular HDV RNA replication and S-HDAg/L-HDAg production. These phenotypes were not consistently predicted by HDV genotype as strains within the same genotype differed in replication efficiency and antigen production. HBsAg pairing further modified HDV propagation in a bidirectional and combination-specific manner. For a given HDV strain, selected HBsAg backgrounds enhanced intracellular HDV RNA replication and increased extracellular virion production, whereas others suppressed both intracellular and extracellular HDV readouts. Conversely, the same HBsAg background supported different levels of intracellular replication and virion production depending on the paired HDV strain. In most combinations, intracellular HDV replication and virion output changed in parallel, although select pairings showed partial dissociation between genome replication and envelope-supported particle production. **Conclusion:** This cross-sectional analysis of HDV strains and HBsAg pairings refines the genotype-based view of HDV pathobiology. HDV replication, HDAg production, and virion formation were determined by strain-specific fitness and HBsAg compatibility rather than genotype alone, suggesting that aggressive disease may reflect high-fitness HDV-HBsAg pairings.

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3220 | HBCRAG LEVELS IN PATIENTS WITH HDV-RELATED CIRRHOSIS TREATED WITH BULEVIRTIDE MONOTHERAPY FOR 3 YEARS: A SINGLE-CENTER REAL-WORLD STUDY

Elisabetta Degasperi[1] Floriana Facchetti[1] Dana Sambarino[1] Caroline Scholtes[2] Barbara Testoni[3] Sara Uceda Renteria[4] Maria Paola Anolli[1] Caroline Charre[5] Marie-Laure Plissonnier[6] Riccardo Perbellini[1] Annapaola Callegaro[4] Massimo Levrero[7] Fabien Zoulim[8], [1]Division of Gastroenterology Hepatology, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, [2]Virology Department, Hospices Civils de Lyon (HCL) and Université Claude Bernard Lyon 1, Lyon, [3]CRCL - INSERM U1052, [4]Microbiology and Virology Unit, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, [5]INSERM U1016, CNRS, UMR8104, Paris, [6]INSERM U1052, CNRS UMR-5286, Cancer Research Center of Lyon (CRCL), Lyon, [7]University Claude Bernard Lyon 1 - INSERM U1350, [8]Lyon 1 University

Background: Serum HBcrAg is a useful biomarker in the management of HBV patients, however its role in patients with chronic hepatitis Delta (CHD) under treatment with Bulevirtide (BLV) is currently unknown. Aim of the study was to investigate HBcrAg levels in CHD patients treated with BLV monotherapy. **Methods:** CHD patients treated with BLV 2 mg/day monotherapy in a single Center from the multicenter retrospective SAVE-D study were enrolled. Serum HBcrAg levels were quantified by LUMIPULSE® G HBcrAg assay (Fujirebio Europe, LLOQ 3 Log_{10} U/mL). Virological (HDV-RNA undetectable or ≥ 2 Log_{10} decline *vs.* baseline), biochemical (ALT < 40 U/L) and combined response (biochemical+virological) were assessed. **Results:** 405 serum samples were collected from 79 patients treated with BLV up to W144. At BLV start, median age was 55 (IQR 37-43) years, 53% males, 100% with cirrhosis (CPT-A score A in 87%), 100% NUC-treated, median ALT 97 (52-151) U/L, HBsAg 3.7 (3.4-3.9) Log_{10}IU/mL, 92% HBeAg-negative, 90% HBV DNA undetectable, median HDV RNA 5.5 (4.2-6.2) Log_{10}IU/mL. HBcrAg tested positive in 63 (80%) patients [4.0 (3.5-4.8) Log_{10} U/mL]. HBcrAg

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levels positively correlated with HBsAg ($r = 0.37$, $p = 0.002$) and HDV RNA levels ($r = 0.30$, $p = 0.01$), but not with ALT or HBV DNA. After 144 weeks of BLV monotherapy, rates of virological, biochemical, combined response and HDV RNA undetectability were 70%, 64%, 52% and 33%, respectively. HBcrAg levels significantly declined during therapy: -0.31 Log_{10} at week 48 ($p = 0.02$), -0.63 Log_{10} at week 96 ($p = 0.003$), and -0.62 Log_{10} at week 144 ($p = 0.01$). During treatment, HBcrAg levels did not correlate with HDV RNA levels at single on-treatment timepoints but maintained a positive correlation with HBsAg levels over-time at all on-treatment timepoints (W48: $r = 0.35$, $p = 0.007$; W96: $r = 0.45$, $p = 0.006$; W144: $r = 0.50$, $p = 0.01$). Neither baseline nor on-treatment HBcrAg levels were associated with virological response or HDV RNA undetectability rates. Overall, HBcrAg levels became negative in 10 patients (week 48 in $n = 5$, week 96 in $n = 3$; week 144 in $n = 2$): at the time of HBcrAg negativity, 7 had achieved a virological response (HDV RNA undetectable in 3), while 3 patients were suboptimal responders (< 2 Log_{10} HDV RNA decline). Conversely, HBcrAg levels became positive during treatment in 5 patients who tested negative at baseline (< 3.5 Log_{10} U/mL in all cases; $n = 4$ at week 48, $n = 1$ at week 144): at the time of HBcrAg positivity, 3 had achieved a virological response (HDV RNA undetectable in $n = 2$), while 2 patients were suboptimal responders. During BLV monotherapy, no significant changes of HBsAg levels were observed. **Conclusion:** In CHD patients with cirrhosis treated with BLV monotherapy up to W144, HBcrAg levels were detectable in most patients at baseline and correlated with HBsAg and HDV RNA levels. During BLV, HBcrAg declined and correlated with HBsAg levels, but not with HDV virological responses.

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3221 | NATIONAL TRENDS AND OUTCOMES OF HERPES SIMPLEX VIRUS HEPATITIS IN THE UNITED STATES

Lindsey Martens[1] Spencer Goble[1] Thomas Leventhal[1], [1]University of Minnesota

Background: Herpes simplex virus (HSV) is a rare cause of viral hepatitis. Severe cases of HSV hepatitis including acute liver failure have been reported, but large-scale analysis of HSV hepatitis hospitalizations and outcomes is lacking. We aimed to describe cases of HSV hepatitis using a generalizable, national database. **Methods:** Adult hospitalizations for HSV hepatitis, defined by the ICD-10 code B00.81, were assessed using the National Inpatient Sample from 2016-2023. Outcomes assessed included: the rate of HSV hepatitis hospitalizations in the US, in-hospital mortality, and index admission liver transplantation. Annual and overall hospitalization and inpatient mortality rates were calculated. Logistic regression was used to assess factors associated with the composite outcome of liver transplantation or inpatient death. An immunocompromised state was defined using ICD-10 codes for primary immunodeficiency disorders, neutropenia, aplastic anemia, chronic corticosteroid use, antineoplastic immunotherapy, and other immunosuppressive drug therapy. **Results:** A total of 995 hospitalizations for HSV hepatitis were identified. The median age was 39 years (IQR 27-57 years). Most patients were female (n = 605, 60.8%), and 125 (20.7%) of the included females were pregnant at the time of admission. An immunocompromised state was documented in 36.2% (n = 360). The overall rate of HSV hepatitis hospitalizations was 3.78 per 10,000,000 and peaked in 2017 at 5.24 (Figure 1). Overall mortality was 10.6% (n = 105), and 20 patients underwent liver transplantation (2.0%). Age (OR per 10 years = 1.40, 95% CI: 1.15-1.71, p = 0.001) and immunocompromised state (OR = 4.25, 95% CI: 1.71-10.55, p = 0.002) were associated with the composite outcome of liver transplantation or death. No deaths or liver transplantations were reported in pregnant patients. **Conclusion:** In the largest to date assessment of HSV hepatitis, we found largely stable rates of HSV hepatitis hospitalizations from 2016-2023. Mortality was high in the cohort, particularly in patients with an immunocompromised state, underscoring the importance of prompt recognition and antiviral therapy.

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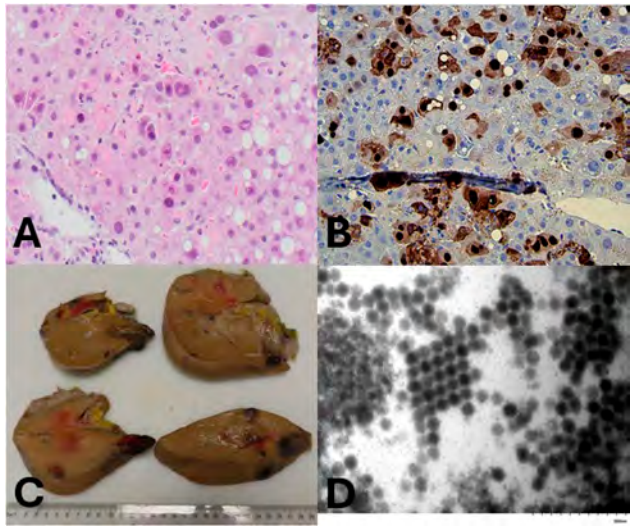


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3222 | "LIVER" MORTIS: A CASE OF ACUTE ADENOVIRUS HEPATITIS, FROM ANTEMORTEM BIOPSY TO POSTMORTEM EXAMINATION

David Jumes[1] Jamie Kallan[1] Adnan Said[1] Megan Campbell[1] Jefree Schulte[1] Anna Fox[2] Heidi Stingley[2] Carla Zuniga[2] Charles Rohrer[1], [1]University of Wisconsin School of Medicine and Public Health, [2]William S. Middleton Memorial Veterans Hospital and Clinics

Background: Human Adenovirus is a common non-enveloped, double-stranded DNA virus that infects the upper respiratory, ocular, or gastrointestinal systems, and often has a mild, self-limited course in immunocompetent patients. Immunosuppressed patients experience more severe infections including pneumonia, enterocolitis, hepatitis, meningoencephalitis, hemorrhagic cystitis, and disseminated disease. Adenovirus viremia is detectable via polymerase chain reaction (PCR). Adenovirus hepatitis has no proven effective treatment and often results in liver failure and death. Histopathologic diagnosis of acute adenovirus hepatitis is made nearly as frequently during liver biopsy (49%) as it is during autopsy (51%). Our report illustrates this aggressive disease in a fatal case that was initially seen on antemortem liver biopsy and more thoroughly documented during autopsy. **Methods:** A 62-year-old woman with multiple myeloma status-post autologous stem cell transplant and CAR-T therapy was seen as an outpatient for presumed sinusitis and treated with azithromycin; a respiratory viral panel at the time was positive for Adenovirus. Two days later she presented to the hospital with several days of fever (100-101°F) and malaise. She was found to have an acute liver injury (AST 7,423 U/L; ALT 4,072 U/L; ALKP 258 U/L; total bilirubin 2.5 mg/dL, normal INR). Labs were also remarkable for pancytopenia, low fibrinogen (137 mg/dL), elevated triglycerides (287 mg/dL), and markedly elevated ferritin (182,289 ng/mL). Hepatology was consulted. There was concern for hemophagocytic lymphohistiocytosis (HLH) with a differential diagnosis including viral infection, autoimmune hepatitis, and drug induced liver injury. An ultrasound guided percutaneous liver biopsy was obtained. Later that day she was found pulseless and died despite resuscitative efforts. Shortly after her death, quantitative Adenovirus PCR resulted with >2 million copies/mL. An autopsy was requested by the patient's family. **Results:** Antemortem liver biopsy showed acute hepatitis with lobular disarray, numerous hepatocytes with viral cytopathic effect and degenerative changes with frequent apoptosis and relatively scant inflammatory infiltrate (Figure 1A). Features of HLH were not observed. Adenovirus immunohistochemistry (IHC) stain showed strong nuclear and cytoplasmic positivity (Figure 1B). Autopsy showed 1,350 mL of hemoperitoneum and widespread hepatic necrosis (Figure 1C). Electron microscopy confirmed virion ultrastructure (Figure 1D). **Conclusion:** Adenovirus hepatitis is often fatal in immunocompromised patients and presents with distinct pathologic findings as demonstrated in this case. Due to the patient's strong adenovirus IHC staining, over 600 blocks of liver tissue from autopsy were retained at our institution to develop new IHC control slides, now used by our laboratory and distributed to other laboratories.



Disclosures: David Jumes:Nothing to Disclose, Jamie Kallan:Nothing to Disclose, Adnan Said:Mallinckrodt: Speaking and Teaching, Madrigal Pharmaceuticals:

Symbols: ♦, Poster of Distinction; ★, Foundation Award Recipient

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Speaking and Teaching, Novo Nordisk: Speaking and Teaching, GIlead: Speaking and Teaching, Delcath: Consultant, Megan Campbell:Nothing to Disclose, Jefree Schulte:Nothing to Disclose, Anna Fox:Nothing to Disclose, Heidi Stingley:Nothing to Disclose, Carla Zuniga:Nothing to Disclose, Charles Rohrer:Nothing to Disclose.

3223 | REGIONAL DISPARITIES IN HEPATITIS D SCREENING AND PREVALENCE ACROSS TURKEY:A MULTICENTER COHORT STUDY

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Background: Hepatitis D virus (HDV) continues to be underdiagnosed worldwide. In this study, we aimed to describe (1) the referral patterns between HDV screening practices and hospital departments and regions of Turkey, and (2) the clinical characteristics associated with HDV positivity in patients under specialist follow-up. **Methods:** This multicenter cohort study, consisting of two parts, evaluated 31,657 HBsAg-positive patients covering a total of 20 hospitals within 6 participating centers: four single-hospital academic centers in Istanbul, one single-hospital academic center in Diyarbakir (endemic Southeast Turkey [SET]), and one 15-hospital private health network in Western Turkey [WT]. During the pre-COVID (2016-18) and post-COVID (2022-24) periods, independent predictors of anti-HDV status and HDV positivity were identified by multivariable logistic regression in a total of 11,515 patients followed by Gastroenterology (GE) and Infectious Diseases (ID) departments in three centers. **Results:** Of 31,657 HBsAg-positive patients, only **39.8%** of those diagnosed outside specialist departments were referred to GE/ID; **60.2% never reached specialist care**. Post-COVID anti-HDV testing reached **68.9%** in specialist versus only **15.3%** in non-specialist settings (4.5-fold difference, $p < 0.001$), with marked regional disparity (SET 37.2% vs WT 9.5%, $p < 0.001$). Anti-HDV testing declined post-COVID in GE (84.1→67.6%) and non-specialist departments (24.5→15.3%, $p < 0.001$). **HDV prevalence was higher in SET than WT (7.0% vs 4.9%, $p = 0.001$).** In the GE/ID cohort, independent predictors of anti-HDV testing included younger age (aOR 0.98), post-COVID period (aOR 2.20), GE setting (aOR 1.17), and higher ALT (aOR 1.07). Among tested patients, the strongest predictor of HDV positivity was **lower platelet count** (aOR 0.26 per log unit, 95% CI 0.19–0.35), followed by post-COVID period (aOR 5.45), **female sex** (aOR 1.92), and GE setting (aOR 1.91). **Lifetime cirrhosis was 8-fold more common in HDV-positive patients** (36.7% vs 6.7%, OR 8.06, 95% CI 6.54–9.95). **Conclusion:** Significant gaps in HDV screening remain: 60% of HBsAg-positive patients detected in non-specific departments never reach GE/ID and their screening rates remain extremely low. Clinicians make ALT-based selection, but HDV-positive patients are best differentiated by thrombocytopenia; this mismatch supports a reflex universal screening approach rather than symptom-triggered testing.

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3224 | POTENT INHIBITION OF HEPATITIS DELTA VIRUS REPLICATION BY THE ANTISENSE OLIGONUCLEOTIDE ALG-215007

Yannick Debing[1] Caroline Pons[2] Jin Hong[3] Lars Degrauwe[1] Isabel Heremans[1] Kellan Passow[3] Lawrence Blatt[3] Julian Symons[4] Vivek Rajwanshi[3] David Smith[3] Eloi Verrier[2] David Durantel[5] Julie Lucifora[2], [1]Aligos Belgium BV, [2]Centre International de Recherche en Infectiologie (CIRI), INSERM, U1111, CNRS, UMR-5308, Univ. Lyon, [3]Aligos Therapeutics, Inc., [4]Aligos Therapeutics, [5]INSERM U1052

Background: Chronic hepatitis delta virus (HDV) infection is a severe form of viral hepatitis and often accelerates the progression to liver cirrhosis and hepatocellular carcinoma. Currently approved treatments rarely cure patients. Direct inhibition of viral replication has been underexplored as a therapeutic strategy. Since HDV replicates its RNA genome in the nucleus via rolling-circle amplification, it may efficiently be targeted by antisense oligonucleotides (ASOs). In addition, unconjugated ASOs such as the HBV-directed

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bepirovirsen could distribute significantly to Kupffer cells and potentially stimulate Toll-like receptor 8 (TLR8) and contribute to the antiviral effects. From our initial screening, we identified ALG-215007 as a lead candidate for further exploration. Here, we describe its in vitro antiviral activity. **Methods:** Antiviral activity was assessed in HDV mono-infected HepG2-NTCP and differentiated Huh7-NTCP cells by RT-qPCR, hepatitis delta antigen immunofluorescent staining and Western blotting. Time-resolved effects on HDV genome, antigenome and mRNA levels were investigated through an RNA species-specific droplet digital PCR protocol. Induction of TLR activity was assessed in HEK-Blue hTLR3, 7, 8 and 9 cells. The HBV-directed ASO bepirovirsen was used as a non-targeting ASO control. **Results:** ALG-215007 showed potent inhibition of HDV replication in multiple cellular systems and all read-outs with calculated EC_{50} values around or below 1 nM. This is considerably more potent than other ASOs, which typically require higher concentrations to reach a similar level of efficacy. As expected, it was less efficacious when combined with ASOs carrying a complementary sequence. In an in vitro system that supports bona fide HDV spread under cell culture conditions, ALG-215007 demonstrated strong impairment of HDV propagation, slightly faster than a presS1 peptide equivalent to bulevirtide. Finally, ALG-215007 also stimulated hTLR8 activation, but not hTLR3, hTLR7 and hTLR9, with a profile similar to bepirovirsen. **Conclusion:** ALG-215007 is a highly potent ASO directly targeting HDV replication in the hepatocyte and possibly also inducing antiviral cytokines, making it a promising candidate for further explorations.

Disclosures: Yannick Debing:Aligos Therapeutics, Inc. Employee, Aligos Therapeutics, Inc. Stock - publicly traded company, Caroline Pons:Nothing to Disclose, Jin Hong:Nothing to Disclose, Lars Degrauwe:Nothing to Disclose, Isabel Heremans:Nothing to Disclose, Kellan Passow:Nothing to Disclose, Lawrence Blatt: Nothing to Disclose, Julian Symons:Aligos Therapeutics Inc. Employee, Vivek Rajwanshi:Nothing to Disclose, David Smith:Nothing to Disclose, Eloi Verrier:Nothing to Disclose, David Durantel:Nothing to Disclose, Julie Lucifora:Nothing to Disclose.

3225 | LIVER STIFFNESS MEASUREMENT WITH MAGNETIC RESONANCE ELASTOGRAPHY ACROSS THE SPECTRUM OF CHRONIC HEPATITIS DELTA: FROM NON-CIRRHOTIC TO DECOMPENSATED CIRRHOSIS

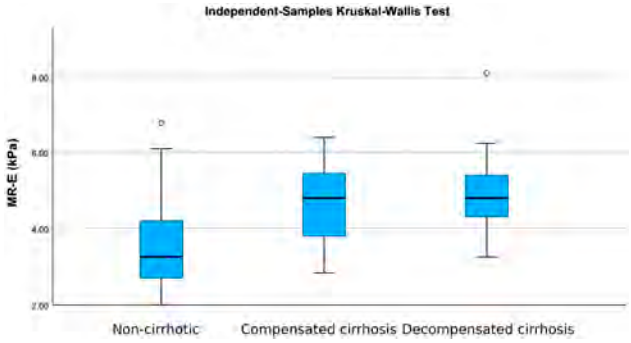
Özge Koç[1] Diğdem Kuru Öz[1] Emin Bodakci[2] Fatih Karakaya[3] Zeynep Ellik[1] Volkan Yilmaz[1] Mesut Gumussoy[4] Ramazan Erdem Er[1] Atilla Halil Elhan[1] Hale Gokcan[1] Gul Ayse Erden[1] Ramazan Idilman[1],

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Background: Non-invasive assessment of liver stiffness has good diagnostic accuracy for advanced fibrosis. Magnetic resonance elastography (MRE) is a non-invasive technique used to detect and stage hepatic fibrosis in patients with chronic liver disease. However, there are no data on the application of MRE in patients with chronic hepatitis delta (CHD). This study aimed to evaluate the diagnostic accuracy of MRE for assessing liver fibrosis in patients diagnosed with CHD. **Methods:** A total of 59 patients with CHD were included in the study. Magnetic resonance imaging was performed using a 1.5-T MR system (Magnetom Aera, Siemens Healthcare), including magnetic resonance elastography (MRE) for liver stiffness measurement (LSM). FIB-4 and APRI scores were calculated using laboratory parameters obtained on the day of the MRE examination. As demonstrated in previous studies, the MEFIB index, defined by the combination of MRE-LSM $\geq$ 3.3 kPa and FIB-4 $\geq$ 1.6, can identify patients with stage $\geq$2 fibrosis and has a high positive predictive value; therefore, it was also evaluated in the present study. **Results:** All 59 patients were Caucasian (male/female ratio: 26/33), with a median age of 56 years (interquartile range [IQR]: 14 years). Twenty-five patients were non-cirrhotic, whereas 25 had compensated cirrhosis and nine had decompensated cirrhosis. The median MELD score was 8.0. The mean FIB-4 and APRI scores were 3.78 ± 3.52 (median: 2.97, IQR: 3.07) and 1.15 ± 1.13 (median: 0.74, IQR: 1.08), respectively. Overall, the mean MRE-LSM was 4.30 ± 1.27 kPa (median: 4.30 kPa, IQR: 2.14 kPa).The mean MRE-LSM values in non-cirrhotic patients, patients with compensated cirrhosis, and patients with decompensated cirrhosis were 3.58 ± 1.22 kPa (median: 3.26 kPa, IQR: 1.62 kPa), 4.71 ± 0.96 kPa (median: 4.80 kPa, IQR: 1.75 kPa), and 5.02 ± 1.17 kPa (median: 4.80 kPa, IQR: 1.13 kPa), respectively ($p < 0.001$) (Figure 1). MRE demonstrated good diagnostic performance for detecting cirrhosis, with an area under the receiver operating characteristic curve (AUROC) of 0.809 ± 0.065 (95% CI: 0.681–0.937) and a cutoff value of 4.2 kPa (sensitivity: 72%; specificity: 72.3%). Logistic regression analysis revealed that MRE-LSM was a significant predictor of cirrhosis (odds ratio [OR]: 5.789; 95% CI: 1.452–23.087; $p = 0.013$).The MEFIB index was positive in 36.4% of non-cirrhotic patients, 71.4% of patients with compensated cirrhosis, and 76.9% of patients with decompensated cirrhosis ($p = 0.018$). **Conclusion:** MRE demonstrated good diagnostic performance for detecting cirrhosis and decompensated cirrhosis in patients with CHD, with a cutoff value of 4.2 kPa and acceptable sensitivity and specificity. In addition, combining MRE-LSM with other non-invasive fibrosis markers may improve diagnostic accuracy in patients with CHD.

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3226 | EXTREMELY LOW PREVALENCE OF ANTI-HDV IN PATIENTS WITH HBV-RELATED FIBROSIS: A LARGE NATIONAL MULTICENTER COHORT STUDY IN MAINLAND CHINA

Xiaoning Wu[1] Bingqiong Wang[1] Jialing Zhou[1] Tongtong Meng[1] Shuyan Chen[1] Yameng Sun[1] Luqi Tang[1] Qiushuang Guan[1] Tongtong Wang[1] Shuai Xia[1] Zhiying He[2] Wentao Tan[1] Xiaojuan Ou[1] Jidong Jia[2] Hong You[2], [1]Beijing Friendship Hospital , Capital Medical University, [2]Beijing Friendship Hospital, Capital Medical University

Background: China is the world's largest potential reservoir for HDV infection. However, the overall prevalence of anti-HDV among patients with HBV-related liver fibrosis remains unknown. **Methods:** We retrospectively enrolled patients with HBV-related liver fibrosis from five national cohorts. Serum samples were tested for anti-HDV, with reflex testing for HDV RNA in anti-HDV-positive cases. Clinical data were collected at enrollment and every six months thereafter until October 2025. **Results:** A total of 2,661 patients from 55 centers across mainland China were screened and 2,085 were enrolled. Of these, 74.4% were male, with a median age of 46.0 years. There were 751 patients had biopsy-proven liver fibrosis, and 1,334 (64.8%) had cirrhosis diagnosed by biopsy or clinically. Samples from 1,709 patients were collected before antiviral treatment, and 376 samples were from patients on treatment. Anti-HDV was positive in 23 patients (1.10%; 95% CI 0.73%–1.65%). Only one patient was HDV RNA positive (4.3% in anti-HDV-positive patients; 0.05% in all patients). Among patients with ALT $\leq$40 U/L, the anti-HDV positive rate was higher in cirrhosis group than non-cirrhosis group (1.89% vs 0.43%; P = 0.034). In patients with histological activity index $\geq$9, the positive rate was higher in treated group than in un-treated group (10.0% vs 0, P = 0.042). No significant differences were observed in virological response, biochemical response, liver stiffness, or HBsAg change between anti-HDV-positive or not. During 4 to 10 years of follow-up, 264 patients developed liver-related events, including two who were anti-HDV positive (P = 0.929). **Conclusion:** The overall seroprevalence of anti-HDV in patients with HBV-induced fibrosis/cirrhosis was extremely low at 1.10% in mainland China.

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3227 | DISCORDANCE BETWEEN TWO HDV RNA ASSAYS IS LIMITED TO LOW-LEVEL VIREMIA IN CHRONIC HEPATITIS D

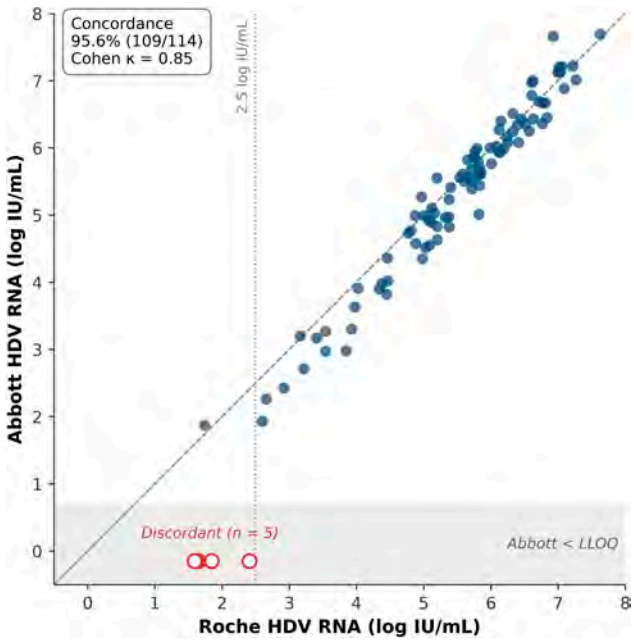
Wesam Aleyadeh[1] Jenny Oh[2] Gian Rodriguez Franco[3] Lezlie Kelzenberg[4] Laura Spina[5] Tiffany Fortney[6] Christian Voitenleitner[7] Mark Anderson[6] Gavin Cloherty[8] Ashli Rode[4] Marc Ghany[9], [1]National Institute of Diabetes and Digestive and Kidney Diseases; National Institutes of Health, [2]NIDDK, NIH, [3]Texas Tech University Health Science Center El Paso, [4]Diasorin Inc, [5]Diasorin SPA, [6]Abbott Diagnostics, [7]Roche Diagnostics International AG, [8]Abbott, [9]NIH/NIDDK

Background: Anti-HDV indicates exposure, whereas active infection requires HDV RNA confirmation. Several non-FDA-authorized HDV RNA assays are available in the U.S., but comparative performance data are limited. We compared 2 quantitative HDV RNA assays and 5 anti-HDV serologic assays in patients with presumed chronic hepatitis D (CHD). **Methods:** Among 896 HBsAg-positive persons evaluated at a tertiary liver clinic, anti-HDV testing was performed using the FDA-authorized LIAISON XL MUREX (DiaSorin), 3 laboratory-developed tests (Quest, Eurofins Viracor, Mayo Clinic Laboratories), and a research-use-only (RUO) Abbott assay. CHD was classified as confirmed (delta antigen staining on liver biopsy) or probable (compatible risk factors, elevated ALT, and low HBV DNA). Equivocal anti-HDV results were considered positive.

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Samples with sufficient volume underwent quantitative HDV RNA testing using Roche and Abbott RUO assays; the Abbott assay was performed at 1:10 dilution. Results below the lower limit of quantification were considered negative. **Results:** Of 896 HBsAg-positive persons, 146 (16%) were anti-HDV positive by at least one assay (63 confirmed, 83 probable). The cohort was 62% male, 42% Asian, 30% White, 24% Black, and 70% foreign-born. Of 146 anti-HDV-positive persons, 114 had evaluable results from both HDV RNA assays (51 biopsy-proven, 63 probable). Anti-HDV positivity was 100% by LIAISON XL and Abbott (114/114), 93.9% (107/114) by LDT1, 99.1% (113/114) by LDT2, and 98.1% (104/106) by LDT3. HDV RNA was detected in 97/114 (85.1%) by Roche and 92/114 (80.7%) by Abbott, with median viral loads of 5.66 and 5.58 log10 IU/mL, respectively. Seventeen samples (15%) were negative by both HDV RNA assays. Among these, anti-HDV was positive by all 5 assays in 4 cases, 4 assays in 10 cases, and 3 assays in 3 cases. Concordance between assays was 95.6% (109/114; 95% CI, 90.1–98.1%; $\kappa = 0.85$). All 5 discordant samples were positive only by Roche at low viral loads (1.6–2.4 log10 IU/mL) and likely reflect sample dilution in the Abbott assay; no discordance occurred above 2.5 log10 IU/mL. The 5 discordant cases comprised 1 confirmed and 4 probable and occurred in both sexes and across all races. **Conclusion:** Approximately 15% of CHD cases likely represented resolved HDV infection. Agreement between HDV RNA assays was excellent overall (96%); however, differences at low-level viremia may affect treatment eligibility, highlighting the need for standardized HDV RNA testing.



Disclosures: Wesam Aleyadeh:Nothing to Disclose, Jenny Oh:Nothing to Disclose, Gian Rodriguez Franco: Nothing to Disclose, Lezlie Kelzenberg:Nothing to Disclose, Laura Spina:Nothing to Disclose, Tiffany Fortney:Nothing to Disclose, Christian Voitenleitner: Roche International Diagnostics AG: Employee, Mark Anderson:Nothing to Disclose, Gavin Cloherty:Nothing to Disclose, Ashli Rode:Nothing to Disclose, Marc Ghany:Vir Bio: Grant is to NIDDK, NIH not to Investigator.

3228 | CLINICAL OUTCOMES IN UNTREATED AND BULEVIRTIDE-TREATED PATIENTS WITH CHRONIC HEPATITIS DELTA COULD BE PREDICTED BY ARTIFICIAL INTELLEGENCE (AI) ASSISTED SYNTHETIC DATA GENERATION

Saverio D'Amico[1] Elisabetta Degasperi[2] Stella De Nicola[3] Nicola Pugliese[3] Maria Paola Anolli[2] Marta Borghi[2] Sara Baccino[1] Ivan Ferrari[1] Dominique Roulot[4] Matteo Della Porta[1] Alessio Aghemo[3], [1]IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy, [2]Division Gastroenterology and Hepatology, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, [3]Division of Internal Medicine and Hepatology, IRCCS Humanitas Research Hospital, [4]Liver Unit, Avicenne Hospital, AP-HP, Sorbonne Paris Nord University, Bobigny, France

Background: Bulevirtide (BLV) monotherapy induces virological and biochemical responses in patients with CHD, but the possibility to evaluate its impact on clinical outcomes is currently limited by unavailability of comparable untreated controls. Synthetic data (SD) mimic real-patient statistical and clinical properties, potentially overcoming limitations. We aimed to generate and validate high-fidelity SD evaluating disease outcomes in BLV-treated versus untreated CHD patients with cirrhosis. **Methods:** Clinical data from 344 CHD patients with cirrhosis treated with BLV in the SAVE-D study and two historical BLV-untreated cohorts from Italy and France (n = 298) were used to train models. Two settings were defined: A) 1:1 generation of both cohorts assessing clinical fidelity and privacy standards; B) generation of balanced, augmented cohorts (n = 3000/group), reproducing clinical endpoints and addressing matching challenges. SD were evaluated using SAFE framework (PMID: 41197110) against a real data pool excluded from the training phase. Fidelity and privacy were evaluated by Clinical Synthetic Fidelity (CSF) score (average of statistical metrics) and Nearest Neighbour Distance Ration (NNDR) (optimal 0.65-0.85).

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Propensity score matching (logistic regression) aligned clinical and demographic covariates (SMD < 0.1). Primary endpoint compared three-year incidences of liver-related events (hepatocellular carcinoma [HCC] and decompensation). **Results:** In setting A, synthetic cohorts of BLV-treated and untreated patients showed high fidelity and privacy (CSF 90%/94%, NNDR 0.71/0.85). In setting B, propensity score matching identified 624 pairs from 3,000 SD samples per group with consistent SAFE metrics. 3-year cumulative incidences of decompensation and HCC were similar across real *vs.* synthetic BLV-treated and untreated patients: decompensation 2.7% *vs.* 4.2% (BLV-treated) and 11.3% *vs.* 10.0% (untreated), HCC 6.6% *vs.* 8.5% (BLV-treated) and 3.6% *vs.* 4.8% (untreated), respectively. Compared to real patients, the synthetic cohort significantly improved statistical robustness, due to the larger pool of matched individuals with perfectly comparable characteristics (real: $p = 0.054$ and $p = 0.378$ *vs.* synthetic: $p = 0.039$ and $p = 0.546$). **Conclusion:** High-fidelity synthetic patient-level data accurately reproduce clinical outcomes in untreated and BLV-treated CHD patients with cirrhosis. This strategy may overcome some of the challenges in rare diseases.

Disclosures: Saverio D'Amico:Nothing to Disclose, Elisabetta Degasperi:Gilead: Speaking and Teaching, Roche: Advisor, Abbvie: Speaking and Teaching, IPSEN: Speaking and Teaching, MIRUM: Advisory Board, Stella De Nicola:Nothing to Disclose, Nicola Pugliese:Nothing to Disclose, Maria Paola Anolli: Nothing to Disclose, Marta Borghi:Nothing to Disclose, Sara Baccino:Nothing to Disclose, Ivan Ferrari:Nothing to Disclose, Dominique Roulot:Gilead: Consultant, Matteo Della Porta:Nothing to Disclose, Alessio Aghemo:Nothing to Disclose.

3229 | REAL-WORLD EPIDEMIOLOGY, DISEASE BURDEN, AND BULEVIRTIDE TREATMENT EXPERIENCE IN A MULTICENTRE COHORT WITH HEPATITIS DELTA VIRUS INFECTION IN CANADA

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Background: Hepatitis D virus (HDV) infection is the most severe form of chronic viral hepatitis, characterized by accelerated fibrosis progression, cirrhosis, and increased liver-related mortality. Despite its clinical burden, treatment options remain limited, and real-world data in emerging therapies such as bulevirtide (BLV) are scarce. We aimed to characterize the epidemiology, clinical burden, and treatment outcomes of HDV infection within a Canadian cohort. **Methods:** We conducted a retrospective multicentre cohort study of HBsAg+/anti-HDV+ patients enrolled in the Canadian Hepatitis B Network registry, followed from 2004-2026 (8.7yrs [3.6-11.1] since initial visit). Demographic characteristics, genotypes, antiviral treatment, and clinical outcomes were summarized. A secondary analysis compared BLV-treated patients with untreated HDV RNA+ patients using the most recent available clinical data. Median (IQR) values were reported and continuous variables were compared using the Wilcoxon rank-sum test. **Results:** The most common countries of birth ($N = 225$) were Canada (8.9%; $n = 20$), Mongolia (8.4%; $n = 19$), Cameroon (8%; $n = 18$), and Sudan (6.7%; $n = 15$). 28 (12.4%) had HIV or HCV and 5 had triple HDV/HIV/HCV infection. Of patients with HBV genotype data ($n = 44/225$), 26 (59%) were HBV-D, 11 (25%) HBV-E and 4 (9%) HBV-A. Of those with HDV genotype data ($n = 107/225$), HDV genotype 1 was most prevalent ($n = 86$, 80%), followed by genotype 5 ($n = 14$, 13%). 160/225 patients received anti-HBV nucleos(t)ide analog and/or interferon-based therapy. During follow-up, 22 patients (9.8%) underwent liver transplant or died. Over follow-up of 4.9yrs (2.4-7.5), 27/51 (52.9%) HDV RNA+, non-BLV-treated patients had increased median liver stiffness measurements (LSM) from 7.4 to 11.3kPa, with a median patient-level increase of 2.7kPa. At baseline, 12/51 (23.5%) had evidence of cirrhosis. At follow-up, this had increased to 24/51 (47.1%), including 12/39 (30.8%) who had developed new cirrhosis evidence during follow-up based on LSM and/or clinical criteria. Compared to untreated HDV RNA+ ($n = 127$), BLV-treated patients ($n = 17$) had lower ALT levels (Table 1, $p = 0.003$) and lower HDV RNA levels (Table 1, $p = 0.024$). HDV RNA became undetectable in 31.3% (5/16) of BLV-treated patients, with no decompensating events occurring in this cohort. **Conclusion:** In this Canadian HDV cohort, HDV genotype 1 and HBV genotype D predominated. A

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significant proportion of patients were HDV RNA+ and had advanced liver disease at initial presentation. A subset of BLV-treated patients showed improved biochemical and virological response. HDV RNA+ patients not on BLV showed progressive liver disease during follow-up. These findings highlight the aggressive natural history of HDV infection and support the urgent need for expanded access to effective antiviral therapies and longitudinal monitoring strategies.

Table 1. *Comparison of Clinical, Biochemical, and Fibrosis Parameters Between Bulevirtide-Treated and Bulevirtide-Untreated HDV RNA-Positive Patients at last available follow-up*

Parameter	BLV-Treated (n=17*)	HDV RNA-Positive, No BLV (n=128*)
Treatment Duration		
Weeks since BLV initiation, median (IQR) or since initial assessment	139.1 (90.3–139.3)	463.7 (193.0–710.8)
Virology		
HDV RNA detected, n/N (%)	11/16 (68.8%)	128/128 (100.0%)
HDV RNA, IU/mL — median (IQR)†	325 (159–1,770)	90,100 (2,750–1,390,000)
qHBsAg, IU/mL — median (IQR)	6,429 (3,777–10,061)	4,057 (1,461–11,450)
Liver Biochemistry		
ALT, U/L — median (IQR)	29 (23–40)	50 (30–109.5)
ALT above ULN, %	47.1%	70.9%
AFP, ng/mL — median (IQR)	3.5 (2.5–5.0)	3.5 (2.9–5.4)
Fibrosis Assessment		
Liver stiffness, kPa — median (IQR)	12.3 (7.8–17.6)	9.0 (6.4–14.1)
FIB-4 — median (IQR)	2.61 (2.01–4.07)	1.77 (1.24–3.15)

All continuous variables expressed as median (IQR). BLV = bulevirtide; ULN = upper limit of normal; qHBsAg = quantitative hepatitis B surface antigen; IQR = interquartile range; AFP = alpha-fetoprotein.

** Sample sizes vary by parameter: time since initial assessment n=17 (BLV, n=127 (no BLV); liver stiffness n=10 (BLV), n=104 (no BLV); FIB-4 n=17 (BLV), n=123 (no BLV); AFP n=13 (BLV), n=84 (no BLV); qHBsAg n=11 (BLV), n=56 (no BLV); HDV RNA n=9 (BLV, detected only), n=58 (no BLV); ALT n=17 (BLV), n=127 (no BLV).*

† HDV RNA reported among patients with detectable viral load only.

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3230 | PREVALENCE OF HEPATITIS D VIRUS INFECTION AMONG IN CHINESE INDIVIDUALS AGED 1–69 YEARS

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Background: Nationwide data on hepatitis D virus (HDV) prevalence in China are scarce. This study aimed to determine the seroprevalence and correlates of HDV infection among HBsAg-positive individuals in a national, population-based cohort. **Methods:** A

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stratified, three-stage cluster study was conducted within the 2020 national HBV sero-survey (91,896 participants aged 1–69 years). Among 4,321 HBsAg-positive participants, anti-HDV antibodies were screened using chemiluminescent immunoassay. HDV RNA was quantified and genotyped in positive samples. Demographic, virological, and clinical correlates were analyzed. **Results:** The overall anti-HDV seroprevalence among HBsAg-positive individuals was 1.32% (95%CI: 1.09–1.55%), implying approximately 990,000 HDV-infected individuals among China's estimated 75 million CHB carriers. Age-specific analysis revealed parallel epidemiological curves for HBsAg and anti-HDV prevalence, with both peaking in middle-aged and older adults (40–69 years). Prevalence was significantly higher in males (1.90% vs. 0.78%; OR = 2.48, 95%CI: 1.41–4.36) and in Tibetans (2.71% vs. 1.11% in Han). Virologically, anti-HDV positivity was associated with HBeAg seropositivity (OR = 2.07), higher HBV viral load (≥ 1,000 IU/mL), and HBV genotype CD. Clinically, it was linked to active liver disease (elevated ALT: OR = 3.19; chronic hepatitis diagnosis: OR = 3.20). The HDV RNA positivity rate among anti-HDV-positive individuals was 1.89% (1/53). **Conclusion:** The nationwide survey reveals a lower HDV seroprevalence in China (1.32%) than clinic-based estimates, but indicates a substantial absolute burden. The epidemiology is characterized by specific demographic and virological correlates. The extremely low HDV RNA detection rate highlights challenges in population-level assessment of active infection.
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3231 | SUPPRESSION OF FIBROGENESIS DURING BULEVIRTIDE THERAPY IN HEPATITIS D: A LONGITUDINAL ANALYSIS USING PRO-C3 DYNAMICS

Giuseppe Rusignuolo[1] Philipp Mathe[2] Thomas Wiggers Møller[3] Morten Karsdal[3] Diana Leeming[4] Christoph Neumann-Haefelin[5] Robert Thimme[6] Tobias Boettler[6], [1]Department of Medicine II, University Hospital Freiburg, Ge, [2]University Hospital Freiburg, Germany, [3]Nordic Bioscience, [4]Nordic Bioscience A/S, [5]University Hospital Freiburg, [6]University of Freiburg

Background: Chronic hepatitis D virus (HDV) infection is associated with rapid fibrosis progression and poor clinical outcomes. While bulevirtide effectively suppresses viral replication, its impact on fibrogenesis is insufficiently characterized. We aimed to assess dynamic changes in fibrogenesis using PRO-C3 and to define temporal patterns and determinants of treatment response using a proportional log-ratio framework. **Methods:** In this longitudinal monocentric cohort study, 13 patients with chronic HDV infection undergoing bulevirtide therapy were analyzed (45 observations). Serial measurements of HDV RNA, PRO-C3, PRO-C6, and ALT were collected. Liver stiffness measurement at baseline was used for stratification. The primary endpoint was proportional change in PRO-C3 from baseline to furthest follow-up, expressed as log(follow-up/baseline). Linear regression models adjusted for follow-up duration were used. Secondary analyses included associations with viral-load log-ratio, temporal modeling, baseline fibrosis burden, and relationships with ALT. **Results:** Virological response was independently associated with a greater proportional reduction in PRO-C3 ($\beta = -0.60$, $p = 0.008$). Responders showed a mean PRO-C3 reduction of −30.9% compared to no meaningful change in non-responders. Continuous viral decline, expressed as viralload log-ratio, was associated with PRO-C3 reduction ($\beta = 0.071$, $p = 0.040$; Spearman $\rho = 0.63$, $p = 0.021$), whereas no significant associations were observed for PRO-C6. Longitudinal analysis revealed a marked latency effect, with no early change (0–3 months: $p = 0.93$) but significant PROC3 reduction emerging after 6–12 months ($p = 0.0077$) and persisting beyond 12 months ($p = 0.0034$). Baseline liver stiffness was associated with treatment response, with higher baseline values predicting attenuated PRO-C3 decline ($\beta = 0.021$, $p = 0.032$). Additionally, proportional changes in ALT were significantly associated with PRO-C3 dynamics ($\beta = 0.31$, $p = 0.012$; Spearman $\rho = 0.58$, $p = 0.037$), indicating that biochemical activity closely reflects fibrogenesis suppression. **Conclusion:** Bulevirtide therapy is associated with delayed but significant suppression of fibrogenesis in virological responders. The observed latency suggests that extracellular matrix remodeling requires sustained viral suppression. The association with baseline fibrosis burden supports early treatment initiation before advanced structural damage occurs
Disclosures: Giuseppe Rusignuolo:IPSEN Pharma: Consultant, Falk Pharma: Speaking and Teaching, Philipp Mathe:Nothing to Disclose, Thomas Wiggers Møller:Nothing to Disclose, Morten Karsdal:Nothing to Disclose, Diana Leeming:Nordic Bioscience: Employee, Christoph Neumann-Haefelin:Nothing to

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Disclose, Robert Thimme:Nothing to Disclose, Tobias Boettler:Nothing to Disclose.

3232 | PREVALENCE AND INCIDENCE OF HEPATITIS D VIRUS INFECTION AMONG PATIENTS WITH HEPATITIS B: A REAL-WORLD ANALYSIS OF 4,966,701 PATIENTS FROM THE TRINETX GLOBAL NETWORK

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Background: Hepatitis D virus (HDV) is the most severe form of viral hepatitis. It infects individuals with concurrent or prior hepatitis B virus (HBV) infection, as it requires the HBV surface antigen (HBsAg) for virion assembly. HDV co-infection with HBV is associated with accelerated progression to cirrhosis, hepatic decompensation, and hepatocellular carcinoma compared to HBV mono-infection. Despite this significance, HDV testing remains underperformed in routine practice, and the prevalence of HDV among HBV-infected patients in the United States—stratified by demographic characteristics—has not been well characterized using large-scale electronic health record data. **Methods:** We conducted an incidence and prevalence analysis using the TriNetX Global Collaborative Network, involving 173 healthcare organizations. Our study cohort included all patients with documented hepatitis B, identified through ICD-10 codes (B18.1, B19.10, B16.1, Z22.51), serologic tests (LOINC 55275-2), HBV-related medications (RxNorm: 1427211, 26744), and SNOMED procedure codes. We analyzed data from 4,966,701 patients from May 2000 to May 2026, focusing on HDV-related events defined by relevant diagnosis codes (ICD-10: B17.0, B17.8, B16.1, B18.0), serologic tests, and HDV RNA quantification. Results were stratified by age, sex, race, and ethnicity. **Results:** Among 4,966,701 patients with documented HBV infection, the documented prevalence of HDV co-infection was **0.86%** (incidence proportion 0.86%; incidence rate 2.45 × 10^{-6} cases/person-day). HDV prevalence increased with age from childhood, peaking in the **25–29 year age group (1.26%)**, followed by a progressive decline in older adults, reflecting the predominance of HDV acquisition through parenteral and sexual routes in young adulthood.Marked racial and ethnic differences in HDV prevalence were observed. **Native Hawaiian or Pacific Islander patients had the highest HDV prevalence (4.39%)**, followed by Asian patients (3.05%) — both substantially exceeding the overall rate. Black or African American patients had a prevalence of 1.12%, while White patients had the lowest documented rate (0.52%). Male patients had nearly 1.5-fold higher prevalence than female patients (**1.04% vs. 0.70%**). By ethnicity, non-Hispanic or Latino patients had higher HDV prevalence than Hispanic or Latino patients (**1.09% vs. 0.55%**), likely reflecting the demographic composition of HBV-endemic immigrant populations. **Conclusion:** Disparities were noted among racial groups, with Asian and Native Hawaiian or Pacific Islander patients most affected, reflecting global HDV trends. These results underscore the need for universal HDV testing in all HBV-positive patients, highlighting a critical gap in clinical practice for minority and immigrant populations.

KEY STATISTICS

Stratum	Group	Prevalence (%)	Incidence Rate (/person-day)
Overall	All HBV patients	0.86%	2.45×10^{-6}
Age (peak)	25–29 years	1.26%	3.49×10^{-6}
Age (lowest)	75–79 years	0.23%	9.02×10^{-7}
Sex	Male	1.04%	3.16×10^{-6}
Sex	Female	0.70%	1.87×10^{-6}
Race (highest)	Native Hawaiian/Pacific Islander	4.39%	1.02×10^{-5}
Race (highest)	Asian	3.05%	8.39×10^{-6}
Race	Black/African American	1.12%	2.49×10^{-6}
Race (lowest)	White	0.52%	1.20×10^{-6}
Ethnicity	Not Hispanic or Latino	1.09%	2.45×10^{-6}
Ethnicity	Hispanic or Latino	0.55%	1.39×10^{-6}

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3233 | EVALUATION OF HIV-REPROGRAMMED LIVER MACROPHAGES USING A NOVEL *EX VIVO* HUMAN LIVER MODEL

Yongtao Wang[1] Xia Xiao[1] Tanvi Patel[1] Shadi Salloum[1] Zeinab Heidariyan[1] Wenyu Lin[1] Ibrahim Eissa[1] Ben Leaker[1] Thien Nguyen[1] Olivia Mezzetti[1] Swastika Tripathi[1] Zhu Zhang[1] Nadia Alatrakchi[1] Kenneth Tanabe[1] Raymond Chung[1], [1]Massachusetts General Hospital and Harvard Medical School

Background: Current animal models, including non-human primates, fail to effectively recapitulate the complex interplay of human HIV infection and associated hepatic pathology. Consequently, physiologically relevant and tractable models for HIV-related liver

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research are urgently required. The *ex vivo* precision-cut liver slice (PCLS) platform preserves the native, three-dimensional architecture of the human liver, allowing for the precise modeling of cell-to-cell signaling pathways. This includes the responses of resident tissue macrophages, which drive hepatic damage through localized cytokine production. **Methods:** Bioinformatic profiles of *in vitro* Kupffer cells (resident liver macrophages) exposed to HIV were analyzed. Concurrently, human PCLS were prepared, infected with HIV *ex vivo*, and subjected to further molecular and phenotypic assessments. **Results:** Bioinformatic analysis revealed that HIV infection drives a robust immune activation program in cultured Kupffer cells, characterized by the marked upregulation of TNFA signaling, IL-6 signaling, and interferon responsive genes. Notably, gene sets responding to interferon-gamma, the prototypical driver of classical macrophage activation, were significantly positively enriched. Signatures of interferon gamma-stimulated macrophage were also positively enriched, indicating that Kupffer cells undergo functional reprogramming upon HIV exposure. In the *ex vivo* human PCLS model, viral entry and active transcription were confirmed via detectable mRNA expression of the HIV *Gag* gene alongside the host co-receptors *CCR5* and *CXCR4*. Flow cytometric analysis revealed an expansion of $CD45^+$ intrahepatic leukocytes in HIV-infected slices, indicating elevated immune activation within the tissue microenvironment. Furthermore, HIV infection prompted a distinct reprogramming of resident macrophage phenotypes toward a hybrid activation state. Specifically, the expression of pro-inflammatory M1-associated gene (e.g., *TNFA*) increased significantly, and pro-fibrotic M2-associated markers (including *ARG1*, *LY75*/CD205, and *TGFB*) were concurrently elevated. Driven by this macrophage reprogramming, downstream hepatic inflammatory and profibrogenic gene expression were significantly upregulated in the infected PCLS tissue. **Conclusion:** These findings demonstrate that human PCLS represents a robust *ex vivo* platform to investigate HIV-mediated macrophage reprogramming. This tractable human-tissue model offers a powerful alternative to accelerate the study of HIV-associated liver disease and therapeutic intervention.

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3234 | CLINICAL CORRELATES OF BULEVIRTIDE PLASMA LEVELS IN PATIENTS WITH CHRONIC HEPATITIS DELTA DURING THERAPEUTIC DRUG MONITORING: A CROSS-SECTIONAL ANALYSIS

Elisabetta Degasperi[1] Amedeo De Nicolo[2] Dana Sambarino[1] Alice Palermiti[2] Alessandra Manca[2] Maria Paola Anolli[1] Marta Borghi[1] Riccardo Perbellini[1] Roberta Soffredini[1] Sara Monico[1] Floriana Facchetti[1] Antonio D'Avolio[2], [1]Division of Gastroenterology Hepatology, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, [2]Laboratory of Clinical Pharmacology and Pharmacogenetics, University of Turin

Background: Bulevirtide (BLV) monotherapy achieves efficient responses in patients with chronic hepatitis Delta (CHD), however little is known about plasma drug concentrations. Aim of the study was to evaluate BLV levels in CHD patients treated in a real-world setting. **Methods:** Consecutive CHD patients treated with BLV in an Italian center underwent single timepoint plasma sampling for BLV quantification between November 2024 and April 2025. BLV plasma levels were assessed through a validated ultra-high performance liquid chromatography coupled with tandem-mass spectrometry method (UHPLC-MS/MS). **Results:** 72 CHD patients were enrolled: at sampling, median age was 56 (IQR 43-61) years, 53% males, BMI 25 (23-27), 81% with cirrhosis (100% CPT-A; CPT A6 in 28%), ALT 32 (26-43) U/L, bile acids 20 (9-36) µmol/L, vitamin D 16 (11-20) ng/mL, HBsAg 3.7 (3.1-3.9) Log_{10}IU/mL, HDV RNA 2.3 (0.7-3.3) Log_{10}IU/mL. Patients had been under BLV treatment for a median of 84 (72-138) weeks; 78% had achieved virological response, 24% target not detected. At sampling, 70/72 (97%) of the patients had detectable BLV plasma levels, overall median values were 1.8 (0.6-7.8) ng/mL. BLV levels did not correlate with age ($p = 0.17$), sex ($p = 0.78$), BMI ($p = 0.22$), and presence of cirrhosis ($p = 0.44$). Among the 56 patients with cirrhosis, BLV levels were similar across CPT subclasses [A5 vs A6: 1.5 (0.6-7.2) ng/mL *vs.* 4.5 (1.1-9.5) ng/mL, $p = 0.27$]. When analyzing biochemical and virological features at sampling, BLV levels did not correlate with ALT ($p = 0.44$), bile acids ($p = 0.67$), vitamin D ($p = 0.20$), and HDV RNA ($p = 0.74$), while there was a trend towards an inverse correlation with HBsAg levels ($r = 0.23$; $p = 0.06$). BLV levels did not differ according to time interval between BLV injection and sampling (≤ 12 *vs.* > 12 hours, $p = 0.13$), and duration of BLV treatment: concentrations were 1.5 (0.8-2.9) ng/mL in patients treated with BLV for ≤ 48 weeks *vs.* 2.9 (1.5-8.6) ng/mL for 49-96 weeks *vs.* 1.7 (0.6-9.3) ng/mL for 97-144 weeks *vs.* 0.6 (0.4-2.5) ng/mL for > 144 weeks, respectively ($p = 0.13$). BLV levels were also independent of virological response ($p = 0.67$). **Conclusion:** In a preliminary cross-sectional therapeutic drug monitoring of BLV performed in a single-center cohort of CHD patients,

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BLV levels was quantifiable in 97% of patients 12-24 hours after the last administration but did not significantly correlate with patient features and/or virological outcomes.
Disclosures: Elisabetta Degasperi:Gilead: Speaking and Teaching, Roche: Advisor, Abbvie: Speaking and Teaching, IPSEN: Speaking and Teaching, MIRUM: Advisory Board, Amedeo De Nicolo:Nothing to Disclose, Dana Sambarino:Nothing to Disclose, Alice Palermiti:Nothing to Disclose, Alessandra Manca:Nothing to Disclose, Maria Paola Anolli:Nothing to Disclose, Marta Borghi:Nothing to Disclose, Riccardo Perbellini: Nothing to Disclose, Roberta Soffredini:Nothing to Disclose, Sara Monico:Nothing to Disclose, Floriana Facchetti:Nothing to Disclose, Antonio D'Avolio:Nothing to Disclose.

3235 | REAL-WORLD ADHERENCE TO BULEVIRTIDE IN CHRONIC HEPATITIS D: A MULTICENTER PROSPECTIVE STUDY USING TWO VALIDATED INSTRUMENTS

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Background: Chronic hepatitis D virus (HDV) infection is the most severe form of viral hepatitis, with rapid progression to cirrhosis and limited therapeutic options. Bulevirtide (BLV) has recently changed the treatment landscape, but real-world data on adherence remain scarce. We aimed to assess adherence to BLV in routine clinical practice and identify associated factors. **Methods:** Prospective multicenter study including patients with chronic HDV infection receiving BLV at three tertiary hospitals. Adherence was evaluated using the Morisky–Green Test and the Simplified Medication Adherence Questionnaire (SMAQ). Demographic and clinical variables were analyzed. **Results:** Thirty patients were included (40% male, mean age 46.6 years, 33% born in Spain, 43% with cirrhosis, and mean time since diagnosis was 17.3 years). Most patients (83%) had been on BLV for >6 months. According to the Morisky–Green scale, 57% showed high adherence, 20% intermediate, and 23% low adherence. SMAQ classified 67% as adherent. Both tools showed good overall agreement in adherence classification. No differences in adherence were observed by sex, origin, treatment duration, or fibrosis stage. Longer time since diagnosis was significantly associated with higher adherence ($p = 0.005$). Patients with high adherence had longer disease duration than those with intermediate adherence (22.06 vs. 5.67 years). **Conclusion:** In this real-world cohort, adherence to BLV was remarkably high despite its daily injectable administration, particularly among patients with a long disease duration. Both validated tools provided consistent adherence classifications. Given that a shorter time since diagnosis significantly correlates with lower adherence, early clinical support and targeted education strategies are crucial for newly diagnosed patients initiating BLV therapy.
Disclosures: Amanda Beatriz Cohn Vaya:Nothing to Disclose, Elena Vargas Accarino:Nothing to Disclose, Carles Aracil Blanch:Nothing to Disclose, Adrià Rodríguez Castellano:Nothing to Disclose, Patricia Huelin Alvarez:Nothing to Disclose, Judit Romero:Nothing to Disclose, Adriana Palom:Nothing to Disclose, Juan Carlos Ruiz Cobo:Nothing to Disclose, Maria Buti Ferret:Nothing to Disclose.

3236 | DIAGNOSTIC PERFORMANCE OF NONINVASIVE TESTS FOR HEPATIC FIBROSIS IN PATIENTS WITH CHRONIC HEPATITIS DELTA RECEIVING BULEVIRTIDE

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Background: Liver stiffness measurement (LSM) by transient elastography has shown good diagnostic performance as an indirect noninvasive test (NIT) for hepatic fibrosis, but limited data are available in patients (pts) with chronic hepatitis delta (CHD). Integrated clinical trial data on bulevirtide (BLV) evaluated the relationship of LSM and other NITs with necroinflammation and fibrosis by biopsy. **Methods:** Pts with CHD, with or without compensated cirrhosis, with baseline (BL) biopsy data were included from the MYR202, MYR203, MYR204, and MYR301 trials. On/post-treatment (Tx) biopsy data from pts receiving BLV +/− pegylated interferon alfa-2a (PegIFN) at weeks 24 and 48, and post-Tx week 24 were analyzed. Only on-Tx biopsies (1/pt) were selected from pts with both on- and post-Tx samples. Biopsies were scored with METAVIR for fibrosis stage (F0–F4) and necroinflammation grade (Histological Activity Index [HAI]/A0–A3). NITs included LSM, aspartate aminotransferase to platelet ratio index (APRI), and Fibrosis-4 (FIB-4). Diagnostic accuracy for advanced fibrosis ($\geq$F3) and cirrhosis (F4) was assessed using area under the receiver operating characteristic curves (AUROC). **Results:** Of 308 pts with BL biopsies, 263 had LSM, 279 had FIB-4, and 279 had APRI within 3 months of biopsy. BL fibrosis stages were 43% F0–F1, 34% F2, 17% F3, and 6% F4; HAI scores were 7% A0, 37% A1, 30% A2, and 25% A3. Of this cohort, 73 (24%) with BL classification by investigator assessment had cirrhosis; 56% (10/18) F4 vs 22% (63/290) $\leq$F3 (30 pts missing status). At BL, LSM had good diagnostic accuracy (AUROC) for detecting cirrhosis (F4; 0.82 [95% CI 0.69–0.94]), similar to FIB-4 and higher vs APRI (**Table**); for advanced fibrosis ($\geq$F3), LSM, FIB-4, and APRI AUROCs were 0.72, 0.67, and 0.63, respectively. For diagnosing cirrhosis at BL, an LSM cutoff of $\geq$15.2 kPa had 56% sensitivity and 84% specificity (positive predictive value [PPV] 18%, negative PV [NPV] 97%). For excluding advanced fibrosis at BL, a <10.2 kPa LSM cutoff had 57% sensitivity and 72% specificity (PPV 86%, NPV 35%). In the on/post-Tx group, fibrosis stages (n=166) were 52% F0–F1, 34% F2, 13% F3, and 1% F4; HAI scores (n=167) were 23% A0, 46% A1, 21% A2, and 10% A3. The LSM AUROC of 0.74 for advanced fibrosis was similar to BL but had a wide CI. A <10.2 kPa LSM cutoff had similar specificity for excluding advanced fibrosis in the on/post-Tx group (LSM cirrhosis cutoff not evaluated due to limited pts). **Conclusion:** In pts with CHD, LSM identified advanced fibrosis and cirrhosis at BL and on/post BLV Tx with good diagnostic specificity. A limitation is that a mixed on/post-BLV cohort was used for Tx status and type (with or without PegIFN). Interestingly, the LSM cutoff to exclude advanced fibrosis on/post-Tx had similar specificity to that seen at BL, despite the reduction in necroinflammation seen with BLV.

Table. Diagnostic Performance of LSM, FIB-4, and APRI for Advanced Fibrosis and Cirrhosis at Baseline, on BLV Treatment, and Post BLV Treatment

Liver Fibrosis Stage	Time Point	NIT	Events, n/N (%)	AUROC (95% CI)	LSM Cutoff, kPa	Sensitivity, %	Specificity, %	PPV, %	NPV, %
Advanced fibrosis (≥F3)	Baseline	LSM	64/263 (24)	0.72 (0.64–0.79)	<10.2	57	72	66	35
		FIB-4	65/279 (23)	0.67 (0.59–0.75)	—	—	—	—	—
		APRI	65/279 (23)	0.63 (0.55–0.71)	—	—	—	—	—
	On/post BLV treatment	LSM	18/143 (13)	0.74 (0.61–0.87)	<10.2	72	72	95	27
		FIB-4	23/165 (14)	0.73 (0.60–0.85)	—	—	—	—	—
		APRI	23/165 (14)	0.65 (0.53–0.77)	—	—	—	—	—
Cirrhosis (F4)	Baseline	LSM	10/283 (6)	0.82 (0.69–0.94)	≥15.2	56	84	18	97
		FIB-4	15/279 (5)	0.82 (0.70–0.95)	—	—	—	—	—
		APRI	15/279 (5)	0.76 (0.62–0.90)	—	—	—	—	—

The AUROC was estimated using a logistic regression model of METAVIR stages of liver fibrosis (evaluated at thresholds of ≥F3 and F4) by LSM, FIB-4, and APRI. Patients with LSM/laboratory data and biopsy dates more than 90 days apart were excluded from analysis. An LSM cutoff of <10.2 kPa was used to exclude advanced fibrosis (≥F3). An LSM cutoff of ≥15.2 kPa was used for diagnosis of cirrhosis (F4).
APRI, aspartate aminotransferase to platelet ratio index; AUROC, area under the receiver operating characteristic curve; BLV, bulevirtide; FIB-4, Fibrosis-4; LSM, liver stiffness measurement; NIT, noninvasive test; NPV, negative predictive value; PPV, positive predictive value.

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3237 | LOW ADHERENCE TO GUIDELINE-RECOMMENDED HDV-RNA RETESTING IN ANTI-HDV POSITIVE INDIVIDUALS: A MULTICENTER REAL-WORLD STUDY FROM CATALONIA

Ariadna Rando-Segura[1] Adriana Palom[1] Laura Calatayud-Samper[2] Gema Fernández-Rivas[3] Alicia Sellés-Sanchez[4] Saray Mormeneo-Bayo[5] Dúnia Pérez del Campo[6] Eva del Corral[7] Tomàs Balari Balari[2] Rosa Maria Morillas[3] Adrià Rodríguez-Castellano[4] Patricia Huelin[5] Carmen López[6] Darly Salazar[7] Joana Villaverde[8] Indiana Abdo[9] José Castellote[2] Joan Carles Quer[4] Carlos Aracil Blanch[6] Andrés Marco[9] Maria Buti[1], [1]Hospital Universitari Vall d'Hebron, [2]Hospital Universitari De Bellvitge, [3]Hospital Universitari Germans Trias I Pujol, [4]Hospital Universitari Joan XXIII De Tarragona, [5]Hospital Universitari Arnau De Vilanova, [6]Hospital Universitari Doctor Josep Trueta, [7]Hospital Universitari Verge De La Cinta, [8]Hospital de Viladecans, [9]Penitentiary Health Program, Catalan Institute of Health

Background: Hepatitis D virus (HDV) infection is associated with accelerated liver disease progression. Current EASL guidelines recommend repeat HDV-RNA testing in anti-HDV positive individuals with initially undetectable viremia because viral replication may fluctuate over time. However, real-world data on implementation and yield of this strategy remain limited. We aimed to evaluate the rate of HDV-RNA positivity upon repeat testing in anti-HDV positive individuals with initially undetectable HDV-RNA. **Methods:** OPTI-HEP-D is a prospective intervention study implementing universal anti-HDV reflex testing in all HBsAg-positive individuals across seven hospital centers covering > 95% of the adult population in Catalonia, Spain. Anti-HDV positive individuals with initially undetectable HDV-RNA who underwent repeat testing during follow-up were included in this analysis. Timing of repeat testing was not protocolised and performed opportunistically at the discretion of treating physicians or triggered by laboratory follow-up processes cohort. **Results:** Among 107 newly identified anti-HDV positive individuals with initially undetectable HDV-RNA, 28 (26.2%) underwent repeat HDV-RNA testing during follow-up. Median time to retesting was 5.3 months (range, 0.2–15.7 months). One patient (3.6%) had detectable HDV-RNA upon retesting, identifying an active infection that would have been missed on initial assessment. **Conclusion:** Although EASL guidelines recommend repeat HDV-RNA testing at 3–6 month intervals, implementation in real-world clinical practice remains limited, with only one quarter of eligible patients undergoing repeat testing and heterogeneous follow-up timing. These findings highlight gaps in the cascade of care beyond initial reflex screening. Despite these limitations, repeat testing identified one additional case of active HDV infection that would have been missed on initial assessment.

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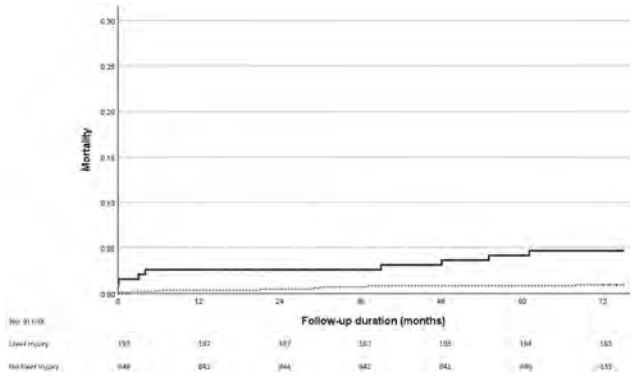
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Disclose, Andrés Marco:Nothing to Disclose, Maria Buti:Gilead: Advisor, AbbVie: Advisor, Janssen: Advisor, gsk: Advisor, mIRIUM: Consultant, Aligos: Advisor.

3238 | LIVER INJURY IS ASSOCIATED WITH LONG-TERM MORTALITY IN PATIENTS WITH COVID-19 – A 6-YEAR ANALYSIS

Grace Wong[1] Vincent Wong[1] Jimmy Che-To Lai[1] Grace Lui[1] Terry Cheuk-Fung Yip[1], [1]The Chinese University of Hong Kong

Background: We previously demonstrated the impact of liver injury on short-term adverse clinical outcomes, including intensive care unit (ICU) admission, use of invasive mechanical ventilation and/or death, in patients with COVID-19. We aimed to evaluate the 6-year outcome of patients with liver injury during COVID-19. **Methods:** This was a real-world cohort study with data retrospectively collected in May 2020, followed by long-term prospective follow-up from May 2020 to May 2026 of patients with COVID-19 recruited in 2020 during the early days of the pandemic. Liver injury was defined as elevation of plasma alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) to $\geq 2 \times$ upper limit of normal (i.e., 80 U/L). The primary endpoint was all-cause mortality. **Results:** Among the 1,040 patients with COVID-19 (mean age 38 years, 54% men, 4.1% chronic hepatitis B, 0.3% chronic hepatitis C), liver injury occurred in 192 (18.5%) patients, which was comparable in patients with and without chronic hepatitis B or C. Seventeen patients died during a median (interquartile range) follow-up of 74.2 (73.7-74.6) months. Four patients died during the acute episode of COVID-19, another four patients died within the first six months, and the remaining nine patients died from 21 to 68 months after COVID-19. The 6-year mortality rate was higher in patients with liver injury during COVID-19 (4.7% vs. 0.9%, $p < 0.001$ by log-rank test; Figure 1). Liver injury remained the independent risk factor of all cause-mortality after adjusted for older age, presence of diabetes mellitus, low platelet and albumin, and high creatinine. **Conclusion:** Liver injury is associated with higher risk of all-cause mortality in patients with COVID-19; the excess risk concentrated in the early post-COVID period within the first six months. Whereas the absolute long-term mortality remains low. The impact of liver injury is the greatest in short term. Further evaluation to understand the factors contributing to these deaths would provide important information to mitigate the mortality in the post-COVID-19 era.



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3239 | OCULAR HSV-1 INFECTION DRIVES HEPATIC SYMPATHETIC NEUROPATHY RESULTING IN THE DISRUPTION OF ENERGY METABOLISM HOMEOSTASIS IN THE LIVER

Jonathan Toriumi[1] Hemant Borase[1] Ipsita Volety[1] Chandrashekhar Patil[1] Deepak Shukla[1], [1]University of Illinois Chicago

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Background: Herpes Simplex Virus Type 1 (HSV-1) is a DNA virus in the human Herpesviridae family. As of 2025, 3.8 billion individuals under age 50 are seropositive worldwide. Mucosal tissues like the cornea are common infection sites and can result in Herpes simplex keratitis (HSK). As a neurotropic virus, its role in the central nervous system (CNS) has been widely studied in the context of herpes simplex encephalitis, but its impact on the sympathetic nervous system is less defined. Metabolic stress drives sympathetic dysregulation in the liver, and ocular HSV-1 infection significantly alters host metabolism. We hypothesized that ocular infection disrupts catecholaminergic signaling and alters hepatic homeostasis. **Methods:** Wildtype (WT) C57/BL6 Mice were ocularly infected with the neurovirulent McKrae HSV-1 strain with a titer of 10^6 PFU via corneal scarification. Mice were then sacrificed at 4, 8 and 18 days post infection (dpi) and the livers were collected. Eye washes were collected on 1, 2, and 4dpi to quantify HSV-1 replication using plaque assays and animal body weights are measured throughout the duration of infection. Protein expression and transcript levels were measured through western blot and RT-qPCR respectively. Liver pathology was scored blindly using immunohistochemistry. Data was analyzed by one-way ANOVA and t-test. **Results:** We found that key sympathetic markers like Tyrosine Hydroxylase (TH), Dopa decarboxylase (DDC), and Dopamine B-hydroxylase (DBH) showed significant reduction in protein expression at 4, 8, and 18dpi. To measure hepatic neuropathy, we measured PGP9.5 levels and found a significant loss of expression at 18dpi. To understand the downstream effects of the loss of sympathetic nerve markers, we measured the expression of key glycogen homeostasis markers; Glycogen synthase 2 (GYS2) and Liver glycogen phosphorylase (PYGL) and found that both were significantly reduced at all three 3 timepoints. With glycogen input and output both being halted, we wanted to see if there was an energy switch towards fatty acid oxidation. We measured Carnitine palmitoyltransferase 1a (CPT1a), the rate limiting enzyme for fatty acid oxidation and found that expression levels at 4 and 8dpi were downregulated. With both glycogen homeostasis and fatty acid oxidation being significantly inhibited, we wanted to measure PGC-1a, which is the master regulator of energy metabolism and beta-oxidation and lies downstream of this pathway. We found that PGC-1a is significantly reduced at 4, 8 and 18dpi. **Conclusion:** Overall, our findings show that ocular HSV-1 infection is able to induce sympathetic neuropathy in the liver at 18dpi which may be due to acute metabolic stress. This leads to the inhibition of catecholaminergic signaling, resulting in the disruption of glycogen and fatty acid oxidation homeostasis due to the loss of PGC-1a expression.

Disclosures: Jonathan Toriumi:Nothing to Disclose, Hemant Borase:Nothing to Disclose, Ipsita Volety: Nothing to Disclose, Chandrashekhar Patil:Nothing to Disclose, Deepak Shukla:Nothing to Disclose.

3240 | TEMPORAL TRENDS & DEMOGRAPHIC DISPARITIES IN LIVER DISEASE & ISCHEMIC HEART DISEASE MORTALITY AMONG OLDER ADULTS IN THE UNITED STATES, 1999–2024

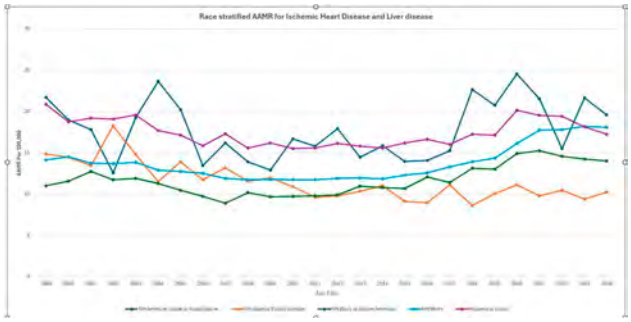
Manish KC[1] Sujata Lamichhane[1] Sae-Jong Oum[1] Anam Farrukh[1] Neha Singh[1], [1]North Alabama Medical Center

Background: This study analyzes the temporal trends in sex & race-stratified age-adjusted mortality rates (AAMR) for concurrent liver disease & IHD among the aging population in the US over the period of 25 years (1999-2024). **Methods:** We performed a retrospective national level mortality analysis with the help of CDC WONDER cause of Death Database from 1999-2024 among patients aged 65-85 & above for IHD (I20–I25) & Liver Disease (B15–B19, C22, K70–K76). Data were stratified by Race, sex & age groups. We calculated AAMR per 100,000 population based on the 2000 US standard population. Temporal trends were assessed using Joinpoint regression to calculate annual percent change (APC), with statistical significance defined by $p < 0.05$. **Results:** AAMR with liver & IHD showed marked temporal fluctuation in all groups (1999-2024). In females AAMR decreased from 1999-2013 (APC = -2.45%, $p < 0.05$), showed non-significant increase in 2013-2018 (APC = 2.23%), rapid rise in 2018-2021 (APC = 9.93%, $p < 0.05$) & plateau in 2021-2024 (APC = -0.39%). In males, AAMRs decreased during 1999-2008 (APC = -2.59%, $p < 0.05$), remained stable in 2008-2016 (APC = 0.95%) & increased during 2016-2021(APC = 6.65%, $p < 0.05$) & plateau thereafter (APC = 0.79%).By race, Non-Hispanic [NH] whites decreased during 1999-2009 (APC = -2.17%, $p < 0.05$), increased during 2014-2018 (APC = 3.36%, $p < 0.05$) & 2018-2021 (APC = 9.05%, $p < 0.05$), and ultimately reached stabilization from 2021-2024 (APC = 1.06%). AAMRs for NH Blacks decreased from 2001-2007 (APC = -5.02%, $p < 0.05$), increased from 2015-2021 (APC = 5.75%, $p < 0.05$) with a subsequent plateau from 2021-2024 (APC = -2.91%). Hispanics decreased during 1999-2009 (APC = -2.61%, $p < 0.05$) increased from 2017-2021 (APC = 5.56%, $p < 0.05$) & decreased in 2021 to 2024 (APC = -4.92%, $p < 0.05$). NH American Indian/Alaska Native populations showed a non-significant decline from 1999-2009 (APC = -3.31%) followed by increase during 2009-2024 (APC = 2.56%, $p < 0.05$). Asian/Pacific Islanders

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decreased till 2020 (APC = -2.18%, p < 0.05) & later stabilized from 2021-2024 (APC = 0.34%). **Conclusion:** After ten years of improving death rate, deaths from comorbid liver disease and ischemic heart disease among older US individuals have been on the rise over the last decade, with a prominent rise during 2018-2021 across all demographic groups. For Hispanic populations, mortality rates have stabilised or are trending downward, while NH American Indian or Alaskan Native populations face an ongoing rise in mortality from 2009-2024. These findings present a concerning setback in health progress and highlight growing disparities between different populations.



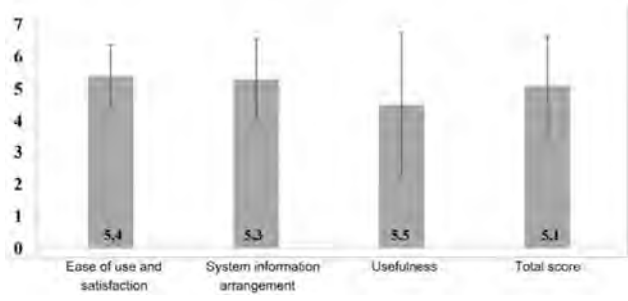
Disclosures: Manish KC:Nothing to Disclose, Sujata Lamichhane:Nothing to Disclose, Sae-Jong Oum:Nothing to Disclose, Anam Farrukh:Nothing to Disclose, Neha Singh:Nothing to Disclose.

3241 | FROM USABILITY TO UPTAKE: REAL-WORLD EXPERIENCE WITH A DIGITAL HEALTH TOOL IN CHRONIC HEPATITIS D

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Background: Hepatitis D virus (HDV) is the most severe form of chronic viral hepatitis and is associated with rapid progression to cirrhosis and increased risk of hepatocellular carcinoma. Digital health tools may support long-term follow-up and patient engagement in this complex condition. We aimed to evaluate the usability, user experience, and perceived usefulness of the NORA mobile application in patients with chronic HDV infection, and to identify barriers to non-use. **Methods:** We conducted a cross-sectional observational study in patients with chronic hepatitis D. Participants were classified as users and non-users of the NORA app (1). The application provided a secure chat for communication with healthcare staff, quality of life and knowledge questionnaires, and medication reminders. Usability and user experience were assessed using the Mobile App Usability Questionnaire (MAUQ). Sociodemographic, clinical, and app-related variables were collected.(1) Romero-Vico J, Feliu A, Vargas-Accarino E, Sánchez-Gavilán E, Ribó M, Palom A, Ruiz-Cobo JC, Riveiro M, Fabrellas N, Buti M. Enhancing Chronic Hepatitis B and D Management Through a Tailored Mobile Health Application: Real-World Outcomes From the Adaptation of the NORA App. J Viral Hepat. 2026 Apr;33(4):e70160. **Results:** Fifty-two patients were included: 19 users and 33 non-users (22 newly enrolled). Overall usability was high (MAUQ 5.07 ± 1.43). Quality-of-life monitoring and educational modules were the most used features, while biometric tracking showed low engagement. Patients prioritized expanded educational content (57.9%), improved data visualization (31.6%), and better communication with clinicians (21.1%). Lack of motivation was the leading barrier to adoption among non-users (72.7%). Perceived usefulness exceeded actual use across most functions, indicating a clear engagement gap. App uptake was higher in patients with detectable HDV RNA and recent diagnosis, suggesting greater engagement in those perceiving higher disease burden. **Conclusion:** NORA was well accepted among patients with chronic hepatitis D and may represent a useful tool for patient monitoring.. Engagement was driven by perceived need; motivation was the main barrier. These findings highlight that successful digital health implementation in HDV requires not only technical design but also behavioural and educational strategies. Tailoring content, strengthening clinician–patient communication, and aligning app functions with patient-perceived need may substantially improve engagement and long-term utility in real-world care.

Figure. Mobile App Usability Questionnaire (MAUQ) dimension scores



Disclosures: Judit Romero:Nothing to Disclose, Belen Duarte:Nothing to Disclose, Elena Vargas-Accarino: Nothing to Disclose, Adriana Palom:Nothing to

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3242 | INCONSISTENT HDV-1 SUBGENOTYPE CLASSIFICATION LIMITS EPIDEMIOLOGICAL COMPARABILITY

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Background: Hepatitis delta virus (HDV) genotype assignment is well established; however, HDV-1 subgenotype classification remains inconsistent across phylogenetic frameworks. Different reference sequence sets and clustering criteria generate non-equivalent subtype definitions, limiting comparability between studies and potentially affecting epidemiological interpretation and genotype–phenotype analyses. We therefore evaluated the level of agreement between two published HDV-1 subgenotype classification systems and assessed how reference selection influences subgenotype assignment in clinical isolates. **Methods:** A comparative phylogenetic analysis was performed using 357 near full-length HDV genome sequences obtained from individuals with detectable HDV-RNA. Sequences were aligned using MAFFT v7 and phylogenetic trees were generated in MEGA v6 using the Neighbor-Joining method under the Tamura 92 + gamma model with 1,000 bootstrap replicates. Subgenotype assignment was independently performed according to the reference frameworks proposed by Le Gal et al. (HDV-1a–1d) and Karimzadeh et al. (HDV-1a–1e). Potential recombination events were screened using sliding-window similarity analysis and will be further validated using RDP. **Results:** Genotype-level classification showed complete concordance across both systems. HDV genotype 1 predominated (329/357, 92.2%), followed by genotype 5 (23/357, 6.4%), while genotypes 3, 6 and 7 were infrequent. Among genotype 5 isolates, subgenotypes 5a (n = 7) and 5b (n = 16) were identified. Thirty potential HDV-1 recombinant strains were initially detected.After excluding putative recombinant sequences, 299 genotype 1 isolates were retained for subtype comparison. Marked discrepancies were observed between classification systems. Only 10/299 sequences (3.3%) showed concordant subtype assignment using both frameworks. Using the Le Gal classification, subgenotype 1d predominated (245/299, 81.9%), whereas 1a, 1b and 1c accounted for smaller proportions (8%, 6.4% and 3.7%, respectively). When the Karimzadeh references were applied, the distribution shifted markedly: subgenotype 1e became predominant (172/299, 57.5%), followed by 1c (90/299, 30.1%), while 1a, 1b and 1d were infrequent (5.7%, 6.4% and 0.3%, respectively). **Conclusion:** HDV genotype determination appears robust across classification systems; however, HDV-1 subgenotype assignment is highly dependent on the selected phylogenetic references. These findings highlight the need for a harmonized consensus-based classification framework to improve epidemiological comparability and support future clinical and translational HDV research.

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3243 | CLINICALLY SIGNIFICANT PORTAL HYPERTENSION MAY IMPROVE IN SOME PATIENTS WITH CHRONIC HEPATITIS DELTA AFTER 48 WEEKS OF BULEVIRTIDE TREATMENT – A POOLED ANALYSIS OF PHASE II/III CLINICAL TRIALS

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Background: Patients (pts) with chronic hepatitis delta (CHD) often show rapid fibrosis progression and may develop clinically significant portal hypertension (CSPH), which increases the risk of liver-related events. Models based on liver stiffness measurement (LSM) and platelet count (PLT) enable noninvasive CSPH assessment in pts with CHD. Bulevirtide (BLV) is approved in the US, EU, and other countries for CHD. This analysis evaluated CSPH prevalence and impact of BLV monotherapy on noninvasive CSPH criteria in pts with CHD. **Methods:** LSM and PLT data at BL and week (W) 48 of pts with CHD treated with BLV 10 or 2 mg monotherapy in the MYR301 (NCT03852719), MYR204 (NCT03852433) and MYR203 (NCT02888106) studies were analyzed. Outcomes were compared to pts with delayed treatment (control) for 48W in MYR301. CSPH risk was assessed using Baveno-VII (LSM/PLT) criteria: rule-out (LSM $\leq$15 kPa + PLT $\geq$150 109/L), rule-in (LSM >25kPa), and gray zone (GZ; all other pts, including probable CSPH [probCSPH]: LSM >20 to $\leq$25 kPa + PLT <150 109/L or LSM >15 to $\leq$20 kPa + PLT <110 109/L). The ANTICIPATE model (reflecting CSPH risk [%]) was calculated based on LSM and PLT, with $\geq$75% and <60% indicating high and low CSPH risk, respectively. **Results:** At BL, of 206 BLV pts, 51.5% (n=106) and 10.7% (22) met Baveno-VII CSPH rule-out and rule-in criteria, respectively, while 37.9% (78) were in GZ (including 7.3% [15] with probCSPH) (Table). By ANTICIPATE, 13.6% (28/206) were $\geq$75%, 3.9% (8/206) were $\geq$60% to <75%, and 82.5% (170/206) were <60% CSPH risk at BL. Distribution was similar for control pts (n=45). At W48, 59.1% (13/22) of BLV pts with Baveno-VII rule-in criteria improved to GZ or rule-out vs 25.0% (1/4) of control pts. Of the 13 improving BLV pts, 69.2% (n=9) had virologic response (VR; $\geq$2 log10 IU/mL decline in HDV RNA or undetectable), 46.2% (6) had alanine aminotransferase (ALT) normalization and 30.8% (4) had a combined response (CR; VR+ALT normalization) at W48. Of 28 BLV pts with BL ANTICIPATE $\geq$75%, 18 (64.3%) improved to <75% at W48; of these 18 pts, 66.7% (n=12) had VR, 44.4% (8) had ALT normalization, and 33.3% (6) had CR at W48. Of 8 BLV pts with BL ANTICIPATE $\geq$60% to <75%, 75.0% (6) improved to <60% at W48.Overall, for BLV pts, 41.0% (41/100) without rule-out CSPH at BL improved in CSPH category by Baveno-VII vs 23.1% (6/26) of control pts; 66.7% (24/36) of BLV pts without <60% ANTICIPATE risk at BL had improvement in ANTICIPATE vs 45.5% (5/11) of control pts. Worsening of CSPH category in pts without rule-in CSPH or $\geq$75% ANTICIPATE risk at BL occurred in 8.2% (15/184) and 2.8% (5/178) for BLV pts vs 14.6% (6/41) and 7.9% (3/38) for control pts. **Conclusion:** BLV may improve or prevent progression of CSPH in select pts with CHD, even in those without VR or ALT normalization; pts receiving BLV were over twice as likely to improve from rule-in CSPH at BL to GZ or rule-out by Baveno-VII criteria by W48 vs control. Results were consistent across CSPH diagnostic models.

Table. Changes in Clinically Significant Portal Hypertension Risk Characteristics With Bulevirtide Treatment

	Control		Bulevirtide 2 mg and 10 mg	
n (%)	Baseline (N=45)	Week 48 (N=45)	Baseline (N=206)	Week 48 (N=206)
Baveno-VII criteria[a]				
Rule-in CSPH	4 (9)	5 (11)	22 (11)	9 (4)
Gray zone	22 (49)	22 (49)	78 (38)	77 (37)
Gray zone – probable CSPH	7 (16)	4 (9)	15 (7)	18 (9)
Rule-out CSPH	19 (42)	18 (40)	106 (51)	120 (58)
ANTICIPATE CSPH (%) ≥75%[b]	7 (16)	6 (13)	28 (14)	13 (6)
ANTICIPATE CSPH (%) ≥60 to <75%[b]	4 (9)	2 (4)	8 (4)	11 (5)
ANTICIPATE CSPH (%) <60%[b]	34 (76)	37 (82)	170 (83)	182 (88)

Patients with detectable baseline HDV RNA, and LS and PLT values at baseline and week 48 were included in the analysis.

[a] Baveno-VII (LSM/PLT) criteria: rule-out (LSM ≤15kPa plus PLT ≥150 10^9/L), rule-in (LSM >25kPa), gray zone (all other pts) with probable CSPH (LSM >20 to ≤25 kPa + PLT <150 10^9/L *or* LSM >15 to ≤20 kPa + PLT <110 10^9/L).

[b] ANTICIPATE model (Abraldes JG, et al, 2016): Logit = −6.3320165 + 3.1001014 × ln(LSM) − 0.0204815 45 × PLT (PLT >150 set to 150). ANTICIPATE-predicted CSPH probability (%) = 1 / (1 + exp(−Logit)) × 100. LSM units: kPa. PLT units: 10^9/L. ANTICIPATE ≥75% indicates high-risk of CSPH, ≥60% to <75% is intermediate risk of CSPH, and <60% indicates low risk of CSPH.

CSPH, clinically significant portal hypertension; HDV, hepatitis delta virus; LSM, liver stiffness measurement; PLT, platelets.

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3244 | HEPATITIS D VIRUS SCREENING AND TESTING AT A COMMUNITY HEALTH CENTER IN THE SAN FRANCISCO BAY AREA

Morgan Manter[1] Zinnia Dong[1] Amy Tang[1], [1]North East Medical Services

Background: Hepatitis D virus (HDV) infection causes severe liver disease and occurs in 1-5% of individuals with hepatitis B virus (HBV) infection. Federally-funded community health centers (CHCs) provide care for many vulnerable patients with chronic HBV infection, yet HBV and HDV care in these settings remains understudied. North East Medical Services (NEMS) is a CHC in the San Francisco Bay Area serving a large Asian immigrant population and uses an electronic health record (EHR)-based HBV registry with a universal HDV screening prompt for all patients with chronic HBV. We aimed to describe the demographic and clinical care characteristics of patients receiving primary care-based HDV screening at NEMS. **Methods:** We conducted a retrospective analysis of HBV registry patients with at least one primary care medical visit at NEMS between 10/3/2023 and 4/14/2026 and their HDV testing status. Demographic and clinical data were extracted from NEMS' EHR-based HBV registry report, including HDV antibody total (HDV Ab) and HDV RNA testing. **Results:** Of the 3,544 HBV registry patients who met study criteria, 59% (2,086/3,544) were screened for HDV Ab, with 1.6% (34/2,086) HDV Ab test positivity. Of the 34 HDV Ab+ patients, 76% (26/34) had follow-up HDV RNA testing, with 19% (5/26) HDV RNA detected. Of the 5 total patients diagnosed with active HDV co-infection based on detectable HDV RNA, all were male with a median age of 49 (range: 40-61) and were born in China (60%, 3/5) or Mongolia (40%, 2/5), 80% (4/5) were on antiviral treatment, and 60% (3/5) had a cirrhosis diagnosis. **Conclusion:** At this large CHC, we found HDV testing was completed in over 2,000 patients with chronic HBV. This finding suggests that implementation of universal HDV screening prompt in the EHR for patients with chronic HBV patients can improve HBV and HDV care delivery in the primary care setting. Further expansion of HDV testing among patients with HBV would allow for more timely diagnosis and treatment of liver complications associated with HBV-HDV coinfection.

Table 1. Demographics of NEMS HBV Registry Patients with HDV Screening

Characteristic	HDV Ab Negative N = 2,052 n (column%)	HDV Ab Positive and HDV RNA Negative or Unknown N = 29 n (column%)	HDV Ab Positive and HDV RNA Positive N = 5 n (column%)	Total N=2,086
Age, median (SD)	58 (13)	56 (13)	49 (7)	
Gender				
Female	1,025 (50%)	15 (52%)	0 (0%)	1040
Male	1,027 (50%)	14 (48%)	5 (100%)	1046
Place of Birth[1]				
China	1,619 (79%)	23 (82%)	3 (60%)	1,645
Vietnam	150 (7%)	1 (4%)	0 (0%)	151
Myanmar	36 (2%)	1 (4%)	0 (0%)	37
Hong Kong	34 (2%)	1 (4%)	0 (0%)	35
Mongolia	3 (0%)	1 (4%)	2 (40%)	6
Hepatocellular Carcinoma Diagnosis	30 (2%)	1 (3%)	0 (0%)	31
Cirrhosis Diagnosis	68 (3%)	3 (10%)	3 (60%)	74
Smoking Status				
Current & Former Smoker	576 (95%)	7 (78%)	3 (75%)	586
HBV Antiviral Prescription	769 (37%)	8 (28%)	4 (80%)	781

[1] Only top 5 results included for HDV Ab positive, 2 HDV Ab positive with unknown place of birth

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3245 | ACUTE LIVER FAILURE FROM DISSEMINATED HSV-2 IN AN IMMUNOCOMPETENT PATIENT: THE DIAGNOSTIC VALUE OF MUCOCUTANEOUS LESIONS

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Background: Herpes simplex virus (HSV) hepatitis is an exceedingly rare but often fatal cause of acute liver failure (ALF), representing less than 1% of ALF cases. Mortality remains as high as nearly 90 % due to delayed recognition, as presentation is frequently anicteric with disproportionate aminotransferase elevation. Although classically associated with pregnancy and immunosuppression, disseminated HSV infection can occur in immunocompetent patients and should not be excluded based on immune status alone. Early diagnosis is essential, as prompt antiviral therapy can be life-saving. **Methods:** A 43-year-old immunocompetent man with type 2 diabetes and recent thoracolumbar surgery for an epidural abscess presented with fever, chills, and right upper-quadrant pain. Initial labs revealed severe hepatocellular injury with AST and ALT exceeding 5,000 IU/L, while total bilirubin and INR were near normal, consistent with anicteric ALF. Mental status progressively declined. He denied alcohol, illicit drugs, high-risk sexual behavior, and hepatotoxic exposures. Serologies for hepatitis A, B, C, and E were negative. Autoimmune markers were unremarkable. Abdominal ultrasound demonstrated diffuse hepatic hypoechogenicity with patent vasculature consistent with acute hepatic injury.As encephalopathy worsened with ammonia >100 µmol/L and MELD-Na of 26, N-acetylcysteine and lactulose were initiated and transplant referral was pursued. Careful examination revealed painful oral ulcerations involving the lips, buccal mucosa, and tongue, and healed vesicular lesions on the right index finger consistent with herpetic whitlow. Mucocutaneous swabs and serum HSV PCR both returned positive for HSV-2 DNA, confirming disseminated infection. Intravenous acyclovir was started promptly. Liver enzymes declined dramatically within 48 hours. On hospital day four, stage 3 acute kidney injury developed (creatinine rising from 1.19 to 3.30 mg/dL), attributed to acyclovir crystal nephropathy compounded by vancomycin tubular toxicity. Vancomycin was replaced with daptomycin, and aggressive hydration was administered. Renal function recovered, encephalopathy resolved, and liver enzymes normalized prior to discharge. **Results:** Covered in methods section. **Conclusion:** Disseminated HSV must be considered in any patient with severe anicteric acute liver failure, regardless of immune status. A meticulous skin and mucosal examination may reveal subtle but decisive diagnostic clues, allowing early diagnosis without invasive liver biopsy. Serum HSV PCR is a rapid test that confirms viremia and supports the diagnosis of disseminated disease. Early empiric acyclovir with renal monitoring can ensure recovery of both hepatic and renal function.

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3246 | RISK FACTORS FOR LIVER FAILURE IN PATIENTS WITH HEPATITIS E VIRUS INFECTION: A SYSTEMATIC REVIEW AND NARRATIVE SYNTHESIS

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Background: Hepatitis E virus (HEV) infection is an important etiology of liver failure, but risk factors for liver failure among patients with acute hepatitis E remain inconsistently reported. This study aimed to identify candidate risk factors and assess whether quantitative synthesis was appropriate. **Methods:** PubMed, Web of Science, Embase, the Cochrane Library, CNKI, and WanFang databases were systematically searched from database inception to May 17, 2026. Studies were eligible if they included HEV-infected patients, reported liver failure or severe hepatitis, and compared patients with and without liver failure. Study characteristics, definitions of liver failure, adjusted effect estimates, candidate risk factors, and study quality assessed using the Newcastle-Ottawa Scale were extracted. Variables overlapping with liver failure definitions, including bilirubin, INR, hepatic encephalopathy, and ascites, were not considered antecedent risk factors. Meta-analysis was considered only when comparable adjusted estimates were reported for the same factor and outcome. **Results:** Out of 5206 records identified, 12 studies met inclusion criteria and were included in the review. Six evaluated liver failure, ALF, or ACLF; three evaluated severe hepatitis; and three focused on biomarker or prediction profiles. Most studies were retrospective and hospital-based, with substantial variation in outcome definitions, exposure cutoffs, covariate adjustment, and effect measures. In studies with stricter liver failure definitions, older age (adjusted odds ratios [aORs] 2.08-2.50), HBV-related status including HBsAg positive or HBV coinfection (aORs 3.70-5.62), and cirrhosis (aORs 2.10-6.05) were repeatedly reported as independent risk factors. Thrombocytopenia was associated with liver failure in one large cohort (aOR 5.90). Other predictors included respiratory infection, hydrothorax, neutrophil-to-lymphocyte-related indices, lipid profiles, and fibrosis markers. However, these were generally single-study findings or prediction-marker studies and were not suitable for primary pooling. Because no factor was supported by at least three directly comparable adjusted estimates, a formal primary meta-analysis was not performed. **Conclusion:** Older age, HBV-related

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infection status, and cirrhosis were repeatedly reported as candidate risk factors, while thrombocytopenia was identified in one large cohort. Heterogeneity in liver failure definitions, exposure definitions, and adjustment strategies limits quantitative synthesis. Standardized prospective studies are needed to clarify independent risk factors of HEV-related liver failure.

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3247 | SERIAL ORAL CHOLATE CHALLENGE (HEPQUANT DUO®) TESTING ENHANCES PREDICTION OF CLINICAL OUTCOME IN COMPENSATED CHRONIC LIVER DISEASE

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Background: Identifying patients with compensated advanced chronic liver disease at risk for decompensation remains a central clinical goal. In the HALT-C quantitative liver function ancillary study (hepatitis C), 215 subjects with advanced fibrosis (n = 124) or compensated cirrhosis (n = 91) had serial Disease Severity Index (DSI) assessments by the oral cholate challenge test (OCCT) and were followed for up to 7.9 years (Everson et al. 2012). We evaluated whether repeated DSI measurements added prognostic value beyond baseline assessment alone. **Methods:** The OCCT was performed at baseline and approximately 2 years and 4 years. The composite outcome included liver-related death, Child-Pugh progression, variceal hemorrhage, ascites, and/or encephalopathy. Subject-level 5-fold cross-validated landmark Cox models with a fixed 2-year prediction horizon were fit for each visit (baseline, 2-year, and 4-year) using DSI as the only predictor. At each visit, three models were compared: (1) baseline DSI, (2) most recent DSI, and (3) serial DSI (DSI values from current visit and the previous visit). Model performance was assessed by cross-validated AUROC, Brier score, and calibration intercept and slope. A fixed 4-year prediction horizon was additionally evaluated and compared to the 2-year prediction results. **Results:** The cohort had mean age 50 ± 7 years, 75% were male, and 50 of 215 subjects experienced a clinical progression event during overall follow-up. At baseline, 215 subjects were available with 23 events observed within the subsequent 2 years. The baseline model had an AUC of 0.79, Brier score of 0.08, calibration intercept of -0.17, and calibration slope of 0.90. At 2 years, 160 subjects were available with 11 events observed within the subsequent 2 years. The updated model improved discrimination compared with the baseline-only model (AUC 0.91 vs 0.84), reduced prediction error (Brier 0.05 vs 0.06), and improved calibration (intercept -0.11 vs -0.59; slope 0.93 vs 0.73). At 4 years, 108 subjects were available with 10 events observed within the subsequent 2 years. The updated model again outperformed the baseline-only model (AUC 0.81 vs 0.61; Brier score 0.095 vs 0.102; calibration intercept -0.54 vs -1.50; slope 0.72 vs 0.30). When the period of follow-up was extended to 4 years, although more outcomes were encompassed, the prognostic performance decreased (AUC range 0.82-0.91 for 2-year horizon versus 0.79-0.82 for 4-year horizon). **Conclusion:** Repeated DSI measurements provided incremental prognostic value beyond baseline assessment, with the largest gain in discrimination observed at later follow-up. These findings support dynamic risk updating with serial liver function testing rather than reliance on a single baseline measurement alone. Based on the comparison of prognosing outcomes over 2 years vs 4 years, the recommended time interval for repeat testing is 2 years.

Comparison of models for predicting 2-year clinical outcomes

	Baseline DSI	Most recent DSI	Serial DSI
AUROC (95% CI)			
t=0 (baseline) [a]	0.795 (0.672-0.897)	-	-
t=2 years [b]	0.842 (0.742-0.942)	0.908 (0.827-0.978)	0.913 (0.833-0.977)
t=4 years [c]	0.657 (0.465-0.829)	0.790 (0.632-0.911)	0.816 (0.666-0.926)
Brier score			
t=0 (baseline) [a]	0.084 (0.057-0.116)	-	-
t=2 years [b]	0.062 (0.031-0.098)	0.051 (0.026-0.081)	0.048 (0.023-0.077)
t=4 years [c]	0.106 (0.061-0.158)	0.106 (0.065-0.156)	0.115 (0.068-0.166)
Calibration Intercept			
t=0 (baseline) [a]	-0.170	-	-
t=2 years [b]	-0.712	-0.138	-0.157
t=4 years [c]	-1.531	-1.029	-1.334
Calibration Slope			
t=0 (baseline) [a]	0.928	-	-
t=2 years [b]	0.773	0.989	0.988
t=4 years [c]	0.46	0.678	0.538

[a] Beginning at the baseline visit, there were 23 events within the subsequent 2 years in 215 subjects with follow-up
[b] Beginning at the 2-year visit, there were 11 events within the subsequent 2 years in 160 subjects with follow-up
[c] Beginning at the 4-year visit, there were 10 events within the subsequent 2 years in 108 subjects with follow-up

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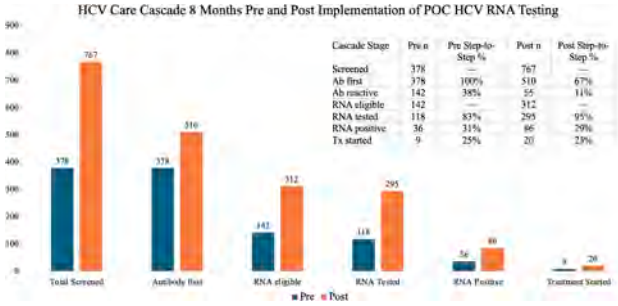
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3248 | HCV CARE CASCADE AFTER IMPLEMENTATION OF POC RNA TESTING IN AN URBAN MOBILE HCV CARE UNIT

Bharathi Selvan[1] Katie Burk[2] Sara Duran[2] Shelley Facente[2] Cecilia Rivas Alfaro[1] May Myat Mon[1] Srilakshmi Seetharaman[1] Yesenia Laguardia[1] Pauli Gray[1] Rosaura Camberos[1] Jennifer Price[1], [1]University of California San Francisco, [2]Facente Consulting

Background: Traditional hepatitis C virus (HCV) testing paradigms are insufficient to overcome the barriers faced by marginalized communities. Point-of-care (POC) RNA testing may improve HCV diagnosis and care linkage by removing need for venipuncture and providing same-day confirmation of viremia. We aimed to evaluate the initial impact of using POC RNA testing on an urban mobile HCV testing and treatment van. **Methods:** The UCSF DeLIVER van is a mobile liver care unit with two outreach shifts per week, offering free HCV screening and on-site treatment via telehealth. Prior to July 2025, all screening was performed using POC HCV antibody tests, followed by on-site venipuncture for laboratory-based confirmatory RNA testing. Starting in July 2025, we offered the Cepheid Xpert HCV POC RNA testing on the mobile van in place of laboratory-based confirmatory testing. Individuals who reported a history of hepatitis C or recent high-risk exposure underwent viral-first RNA testing rather than HCV antibody testing. We compared HCV care cascade data from 8 months pre-(11/2024-6/2025) and post-(7/2025-2/2026) POC RNA implementation. We also interviewed 8 patients using a semi-structured guide to elicit their experience with the POC RNA test. **Results:** HCV testing on the van increased from 378 people pre-implementation to 767 people post-implementation (Figure). Pre-implementation, 142 (38%) had reactive HCV antibody and thus were eligible for RNA testing. Post-implementation, 510 (67%) underwent antibody-first testing and 55 (11%) had reactive HCV antibody. Combined with those triaged to RNA-first testing, 312 individuals were eligible for RNA testing, and 295 RNA tests were completed (96% with Xpert, per patient preference over traditional venipuncture). Pre-implementation, 36 cases of active HCV were identified, and 9 (25%) started treatment. Post-implementation, 86 cases of active HCV were identified, and 20 (23%) started treatment. All interviewees endorsed positive experiences with the POC RNA test, sharing that it felt comfortable, painless, and quick. Participants stated feeling ready to start treatment, even same day, if offered. **Conclusion:** After offering HCV POC RNA on a mobile HCV van, overall screening volume doubled, identification of individuals with HCV viremia increased 2.4-fold, and treatment initiation increased 2.2-fold. However, despite diagnosing more people and using a testing modality preferred over venipuncture, only one-quarter started treatment, similar to pre-implementation. Our findings underscore that improving HCV diagnosis is necessary, but not sufficient, to achieve HCV elimination and that focused efforts are needed to support patients in starting treatment after RNA positivity. Same-day treatment initiation may help overcome barriers and is an acceptable option to patients but will require further investment and resources.



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3249 | IMPLEMENTATION OF A TEST AND TREAT MODEL FOR HCV CARE UTILIZING POINT OF CARE HCV RNA TESTING IN LA BODEGA

Anthony Martinez[1] Scott Springer[2] Alexander Zhu[3] Sean Owen[4], [1]University at Buffalo, [2]Erie County

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Background: The World Health Organization (WHO) aims to eliminate hepatitis C virus (HCV) by 2030; however, the United States (US) is unlikely to meet this target. Screening, linkage to care, and treatment initiation rates remain suboptimal, hindering progress toward elimination targets. HCV point-of-care testing has been shown to shorten the time from diagnosis to treatment initiation and increase treatment uptake. The recent FDA approval of the Point-of-Care (POC) HCV RNA test (Xpert® HCV) enables viral-first testing, potentially shortening time to diagnosis and overall treatment uptake, particularly in priority settings such as addiction medicine clinics, incarceration settings, and among unhoused individuals. **Methods:** La Bodega, a co-localized hepatology and addiction medicine program in Buffalo, New York (NY), specializes in HCV management among active People Who Use Drugs (PWUD). HCV medications are kept on the shelf in an on-site pharmacy, facilitating same-day treatment initiation. Between January and December 2025, POC HCV RNA testing was utilized on-site among PWUD being seen for evaluation of substance use disorder. Patients with a positive HCV RNA were initiated on HCV therapy at the time of the initial visit. POC HCV RNA testing was also used in conjunction with lab-based RNA testing on serum to evaluate SVR4 when indicated. **Results:** 100 people were screened with POC HCV RNA testing, of whom 66 had a prior HCV antibody test. 38 had previously received treatment.19 individuals were found to be HCV RNA positive, all of whom were linked to care. Among RNA-positive individuals, 1 was linked to their primary care clinic based on the patient's preference, and 18 initiated therapy and received the full 8- or 12-week course, depending on the chosen regimen. 12 individuals achieved SVR, one of whom was pregnant and treated with sofosbuvir/velpatasvir, and 6 were lost to follow-up. Of the 12 individuals achieving SVR, all had both undetectable serum HCV RNA and negative POC HCV RNA results. There were 11 invalid tests, 7 due to insufficient sample, 2 due to air bubbles, and 2 due to loss of electrical power. **Conclusion:** POC HCV RNA testing is advantageous in shortening the HCV care cascade, resulting in rapid identification and initiation of therapy. POC HCV RNA testing enables a true test-and-treat model of care for HCV, particularly in decentralized settings such as addiction medicine clinics. Data regarding the use of Xpert HCV for SVR assessment is encouraging, and further evaluation is warranted.

Disclosures: Anthony Martinez:Gilead: Consultant, Gilead: Speaking and Teaching, Abbvie: Consultant, Abbvie: Speaking and Teaching, Arbutus: Consultant, Braeburn: Speaking and Teaching, Sirtex: Consultant, Roche: Consultant, Syneos/VBI: Consultant, Madrigal: Speaking and Teaching, Altimune: Consultant, Madrigal: Consultant, Ipsen: Consultant, novo: Speaking and Teaching, atea: Consultant, cepheid: Consultant, Scott Springer:AbbVie: Advisory board, Speaker bureau, GIlead Sciences: Advisory board, Speaker bureau, Salix: Advisor, Ipsen: Advisor, Alexander Zhu:Nothing to Disclose, Sean Owen:Nothing to Disclose.

3250 | CHARACTERIZATION OF THE CIRCULATING SMALL NON-CODING RNA PROFILE IN PATIENTS WITH CHRONIC HEPATITIS C VIRUS INFECTION BEFORE AND AFTER SUSTAINED VIROLOGICAL RESPONSE TO DIRECT ACTING ANTIVIRAL AGENTS

Samantha Muccilli[1] Jordan Pardoe[1] Amanda Henning[1] Marc Ghany[2] Valeria De Giorgi[1], [1]NIH Clinical Center, [2]NIDDK

Background: Chronic hepatitis C virus (HCV) infection is known to modulate the expression of small non-coding RNAs (sRNAs). These sRNAs are promising noninvasive biomarkers of disease severity and progression. Since the discovery of direct acting antivirals (DAAs), over 12 million people have been cured of HCV. While some studies have examined the expression of miRNAs following DAA treatment, very little is known about how the full sRNA repertoire changes following sustained virological response (SVR). We sought to characterize the sRNA profiles of patients before and longitudinally after DAA treatment to gain new insights into how viral clearance modulates the sRNA repertoire following HCV cure. **Methods:** As part of a large, ongoing prospective clinical study (18DK0091), serum samples were collected from 105 chronic HCV-infected patients prior to DAA treatment, immediately following SVR, and every 48 weeks for up to ten years post-treatment. In this pilot study, we analyzed the longitudinal changes to the sRNA profiles of 34 HCV patients at 8 timepoints (pretreatment, 12-, 36-, 84-, 132-, 180-, 228-, and 276-weeks post-treatment) and compared them to 15 healthy donors using next generation sequencing. **Results:** We characterized the distribution of sRNA species present in each sample. The most highly expressed sRNA class in both HCV patients and healthy donors was miRNAs (60%) followed by piRNAs (7%), miscRNAs (5%), and snoRNAs (4%). Following DAA treatment, the distribution pattern did not significantly change. While the overall expression pattern did not change, initial analyses indicate that some sRNAs were uniquely differentially expressed at each timepoint while others were common among post-treatment timepoints. Indeed, 5 differentially expressed miRNAs were common between 12- and 276-weeks post-treatment and four of those genes (miR-122, miR-205, miR-885, and miR-4662a) have known functions in either HCV

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infection or immune modulation. Further, there were no differentially expressed snoRNAs at 12-weeks post-treatment but there were 5 differentially expressed snoRNAs at 276-weeks post-treatment. Interestingly, two of the snoRNAs that were downregulated at 276-weeks post-treatment (SNORD15B and SNORD3A) were also downregulated in healthy donors indicating that snoRNA regulation may take longer to equilibrate following SVR. **Conclusion:** In all, our early results indicate that while the overall distribution of sRNAs does not change over time, individual sRNA species can be tracked longitudinally and are differentially regulated at different timepoints post cure. In the future, we hope to correlate these sRNA profiles to the clinical characteristics of our unique cohort to identify biomarkers of complications following SVR and reveal novel insights into the role sRNAs play in recovery from chronic HCV infection.

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3251 | REFINING BIDIRECTIONAL DISCORDANCE BETWEEN FIB-4 AND ELASTOGRAPHY USING LIVER FUNCTION BIOMARKERS IN HCV PATIENTS RECEIVING OPIOID SUBSTITUTION THERAPY

Nikolaos Papadopoulos[1] Eleni Myrto Trifylli[2] Charikleia Kranidioti[3] Nikolaos Tsiaberas[3] Dimitrios Papanikolaou[3] Pinelopi Antonakaki[1] Thalia Lehmann[1] Melanie Deutsch[3] Spilios Manolakopoulos[3], [1]National Organization for the Prevention and Treatment of Addictions (EOPAE), Athens, Greece, [2]GI-Liver Unit, 2d Academic Dpt Internal Medicine, NKUA,, [3]GI-Liver Unit, 2nd Department of Internal Medicine, General Hospital of Athens "Hippocratio", Nation

Background: Discordance between serum fibrosis scores and transient elastography is frequently encountered in chronic hepatitis C (HCV). We aimed to evaluate bidirectional discordance between FIB-4 and Baveno VII–defined compensated advanced chronic liver disease (cACLD) in compensated HCV patients receiving opioid substitution therapy (OST), and to assess whether liver function biomarkers could refine discordant phenotypes. **Methods:** We retrospectively analyzed baseline pre-treatment data from compensated HCV-infected patients receiving OST. Liver stiffness measurement (LSM) was assessed by vibration-controlled transient elastography (VCTE). According to Baveno VII–informed thresholds, LSM <10 kPa was considered cACLD unlikely, 10–14.9 kPa possible cACLD, and ≥ 15 kPa highly suggestive cACLD. Low FIB-4 was defined as <1.45 and high FIB-4 as >3.25. Bidirectional discordance was defined as either low FIB-4 despite LSM ≥ 10 kPa or high FIB-4 despite LSM <10 kPa. ROC analyses and exploratory multivariable models were used to evaluate the contribution of liver function biomarkers. **Results:** A total of 459 were included, 52/459 (11.3%) had LSM 10–14.9 kPa, and 48/459 (10.5%) had LSM ≥ 15 kPa. Among patients with low FIB-4 (<1.45), 28/267 (10.5%) had LSM ≥ 10 kPa. Conversely, among patients with high FIB-4 (>3.25), 16/49 (32.7%) had LSM <10 kPa. Compared with concordant low-risk patients, the low FIB-4 + high LSM phenotype demonstrated significantly higher AST (median 78 vs 42 U/L), ALT (96 vs 51 U/L), bilirubin (1.1 vs 0.7 mg/dL), and GGT levels (132 vs 48 U/L). Exploratory ROC analysis identified albumin ≤ 4.2 g/dL and bilirubin ≥ 0.61 mg/dL as optimal phenotype-associated thresholds. Adding albumin and bilirubin to FIB-4 improved discrimination for LSM ≥ 10 kPa (AUC 0.787 vs 0.733 for FIB-4 alone). Compared with concordant high-risk patients, the high FIB-4 + low LSM phenotype demonstrated higher AST (112 vs 74 U/L) but lower bilirubin levels (0.8 vs 1.4 mg/dL). In exploratory ROC analysis within the high FIB-4 subgroup, albumin ≥ 4.3 g/dL and bilirubin ≤ 0.41 mg/dL were associated with the discordant low-LSM phenotype. **Conclusion:** Distinct discordance phenotypes between FIB-4 and elastography demonstrate different biochemical profiles, while routine liver function biomarkers may improve phenotype characterization beyond isolated interpretation of FIB-4 or elastography alone.

Disclosures: Nikolaos Papadopoulos:Nothing to Disclose, Eleni Myrto Trifylli:Nothing to Disclose, CHARIKLEIA KRANIDIOTI:Nothing to Disclose, Nikolaos Tsiaberas:Nothing to Disclose, Dimitrios Papanikolaou: Nothing to Disclose, Pinelopi Antonakaki:Nothing to Disclose, Thalia Lehmann:Nothing to Disclose, Melanie Deutsch:Gilead: Speaking and Teaching, Roche: Speaking and Teaching, Integris: Speaker, ASTRA: Speaking and Teaching, Ipsen: Speaking and Teaching, Spilios Manolakopoulos:Nothing to Disclose.

3252 | DE NOVO MASLD AND METABOLIC OUTCOMES FOLLOWING DAA-MEDIATED HCV ERADICATION: A PROPENSITY SCORE–MATCHED COHORT ANALYSIS

Jashanveer Johal[1] Bianca Patel[1] Mahmoud Al-Bataineh[1] Archana Salek[1] Brandon Cunha[1] Abdallah Hussein[1] Yecheskel Schneider[1] Jason Hyman[2], [1]Virtua Health, [2]Einstein Medical Center, Philadelphia

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Background: Patients achieving sustained virologic response (SVR) following direct-acting antiviral (DAA) therapy for hepatitis C represent a growing post-cure cohort at theorized risk for de novo metabolic dysfunction–associated steatotic liver disease (MASLD). Viral clearance removes HCV's suppressive effect on hepatic lipid metabolism, potentially unmasking underlying metabolic dysfunction. Whether SVR12 is associated with incident MASLD or paradoxically confers protection through reduced hepatic inflammation remains poorly characterized. **Methods:** We conducted a propensity score–matched retrospective cohort study using the TriNetX Global Collaborative Network (191.9 million patients). Cohort 1 comprised adults with HCV who received DAA therapy and achieved SVR12 (HCV RNA $\leq$10 IU/mL within 12 months). Cohort 2 comprised DAA-treated patients with persistent viremia (HCV RNA $\geq$10,000 IU/mL), representing treatment non-responders. Both cohorts excluded prior MASLD, cirrhosis, HCC, and liver transplant. 1:1 PSM yielded 3,133 patients per arm over a 6–60 month follow-up. Outcomes included incident MASLD, new cirrhosis, incident HCC, new-onset T2DM, incident hyperlipidemia, AST/ALT normalization, all-cause mortality, and inpatient encounters. **Results:** Post-PSM cohorts were well-balanced. Contrary to the pre-specified hypothesis, incident MASLD was equivalent between arms (5.1% vs. 5.4%; HR 0.99, 95% CI 0.78–1.25; p = 0.92). SVR12 was associated with lower rates of new cirrhosis on MOA analysis (4.2% vs. 5.5%; RR 0.78; p = 0.049), though KM analysis trended non-significant (HR 0.80; p = 0.084). Incident T2DM was significantly lower in the SVR arm (4.2% vs. 5.6%; HR 0.78, 95% CI 0.60–1.00; p = 0.050). Incident HCC trended lower with SVR (1.3% vs. 1.8%; RR 0.72; p = 0.108). All-cause mortality was lower on MOA analysis (6.6% vs. 8.2%; RR 0.80; p = 0.014) and trended lower on KM analysis (HR 0.83; p = 0.052). Inpatient burden trended lower with SVR (28.5% vs. 33.2%; mean 8.4 vs. 10.0 encounters; p = 0.10). **Conclusion:** DAA-mediated SVR12 was not associated with increased de novo MASLD incidence, arguing against the "metabolic unmasking" hypothesis in the short-to-medium term. SVR was associated with lower incident T2DM, a trend toward reduced cirrhosis and all-cause mortality, and numerically lower HCC incidence. These findings support viral eradication as metabolically protective and suggest post-SVR MASLD surveillance should be guided by underlying cardiometabolic risk burden rather than SVR status alone.

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3253 | DETECTION OF ADVANCED FIBROSIS USING GLAS IN HCV PATIENTS IN TAIWAN

Jenna Bedrava[1] Claire Chen[1] Susan Gawel[1] Randal Schneider[1] Chen-Hua Liu[2], [1]Abbott Laboratories, [2]National Taiwan University Hospital

Background: The Asia-Pacific region bears a disproportional burden of liver disease mortality. This burden is largely attributable to complications of cirrhosis and hepatocellular carcinoma (HCC), both of which are highly associated with Hepatitis C infection (HCV), underscoring the necessity of liver disease surveillance in HCV populations. Biomarker-based classification models such as GLAS (GP73, LG2m, age, and sex) have become an area of increased interest, as they potentiate earlier identification of advanced liver fibrosis and a reduction in the risk of progression to malignancy. In this study, we evaluate the performance of GLAS in the detection of advanced fibrosis in a cohort of HCV positive patients in Taiwan. **Methods:** We retrospectively enrolled 960 patients with HCV, for whom samples collected both prior to direct-acting antiviral (DAA) treatment and after achieving sustained virological response (SVR) were available. Fibrosis stages were diagnosed pre-DAA using vibration-controlled transient elastography (VCTE) with cutoff values of $\leq$ 7.0, 7.1-9.4, 9.5-12.4, and $\geq$ 12.5 kPa corresponding to F0-F1, F2, F3, and F4. Serum GP73 and LG2m levels were measured on both samples using Abbott Alinity assays. The diagnostic performance of the GLAS model in pre-DAA samples in the discrimination of early-stage fibrosis (defined as F0-F2) and advanced fibrosis (defined as F3-F4) was compared to that of other models, including FIB-4, APRI, and NFS using receiver operating (ROC) curves and area under the curve (AUC) values. Optimal cutoffs for each model were determined by Youden's Index. **Results:** Our sample was comprised of 56.6% males with a median age of 57 years. Of the 960 patients, 284 (29.6%) were determined to have advanced fibrosis. GLAS had the highest AUC value in the discrimination of early and advanced fibrosis compared to FIB-4, APRI, and NFS. GLAS yielded an AUC of 0.89 (95% CI: 0.87, 0.91), significantly higher than that of APRI (p-value < 0.001) and NFS (p-value = 0.003). At the validated cutoff of 0.50, GLAS had a sensitivity of 100.0%, but a specificity of 10.9%. The optimal GLAS cutoff for this discrimination was determined to be 0.98. Changes in GLAS scores from pre-DAA to post-SVR were significant (p-value < 0.001). On average, patients with early-stage fibrosis saw a decrease of 0.064 in GLAS score from pre-DAA to post-SVR, a significantly larger decrease than those with advanced fibrosis

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(p-value < 0.001). **Conclusion:** GLAS had the highest AUC in the discrimination of early and advanced fibrosis compared to other risk models in pre-DAA HCV patients. The suboptimal specificity observed with the validated cutoff of 0.50 and the high optimal cutoff of 0.98 prompts the need for future evaluations to determine a more optimal cutoff. The significant decrease in GLAS scores from pre-DAA to post-SVR underscores the importance of early HCV diagnosis and treatment and early fibrosis detection.

Disclosures: Jenna Bedrava:Abbott: Employee, Claire Chen:Abbott Laboratories: Employee, Susan Gawel: Abbott: Employee, Randal Schneider:Nothing to Disclose, Chen-Hua Liu:Nothing to Disclose.

3254 | EMERGENCY DEPARTMENT–BASED OPT-OUT VIRAL HEPATITIS SCREENING WITHIN AN INTEGRATED SYNDEMIC CARE MODEL

Sarah Merchant[1] James d'Etienne[1] Nanda Reamy[2] Sally Spann[1] Suzana Limones[2], [1]Integrative Emergency Services, JPS Health Network, [2]JPS Health Network

Background: Emergency departments (EDs) are critical access points for identifying viral hepatitis among underserved populations with limited engagement in longitudinal care. JPS Health Network, the safety-net health system for Tarrant County, Texas, expanded an existing opt-out HIV screening program into an integrated ED-based syndemic screening initiative incorporating hepatitis C virus (HCV), hepatitis B virus (HBV), syphilis, and HIV testing within routine workflows. The program aimed to normalize blood-borne virus screening, improve equitable access to testing, and strengthen linkage to hepatology and prevention services. **Methods:** A systems-based screening and linkage model was implemented using automated electronic medical record eligibility triggers, reflex laboratory testing, and closed-loop referral pathways. Opt-out age-based screening protocols reduced reliance on disclosure of sexual behaviors or substance use histories. Integrated workflows aligned ED screening with outpatient hepatology, infectious disease, and prevention services. Patients with negative screening results were evaluated using EMR-supported prevention eligibility logic incorporating historical laboratory data and syndemic vulnerability indicators. Eligible individuals received culturally responsive prevention navigation, behavioral risk-reduction education, vaccination support, and referrals for biomedical prevention services. ED clinicians and nursing staff received standardized training on trauma-informed communication, stigma-free screening, and coordinated linkage strategies. **Results:** From June 2025 through February 2026, 3,688 HCV antibody tests identified 259 positive results (7.0%). Among these, 74 individuals were HCV RNA-positive and referred for treatment coordination. HBV screening included 2,378 HBsAg tests identifying 19 positive results (0.8%). Integrated screening additionally identified 312 HIV-positive results among 34,288 tests and 408 positive syphilis results among 4,098 tests. Implementation demonstrated the feasibility of embedding high-volume viral hepatitis screening and coordinated linkage pathways into routine ED practice using automated EMR decision support and reflex testing protocols. The opt-out framework facilitated identification of new diagnoses, late diagnoses, and previously diagnosed individuals out of care who may not have engaged in traditional risk-based screening models. **Conclusion:** ED-based opt-out viral hepatitis screening integrated within syndemic prevention workflows is feasible and may improve identification of HBV and HCV infection among underserved populations disproportionately impacted by liver disease. Automated EMR decision support, prevention navigation, and coordinated referral systems can strengthen linkage to hepatology care while reducing barriers associated with stigma and risk-based screening approaches.

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3255 | ◆ ROADMAP TO ACHIEVE HEPATITIS C ELIMINATION AMONG LOW-RISK POPULATION IN INDIA: A MODELLING STUDY USING 67 MILLION BLOOD DONOR DATA COLLECTED OVER A DECADE

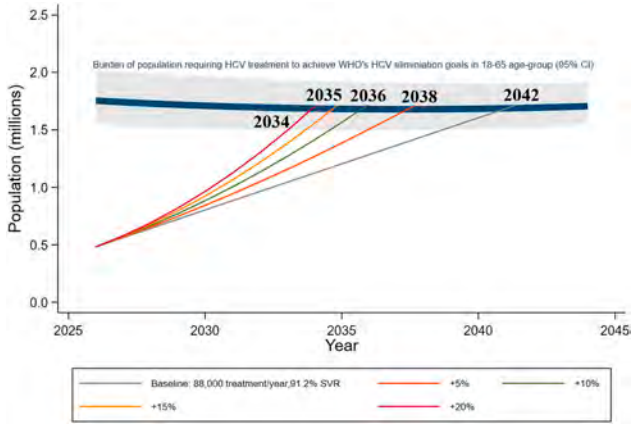
Amit Goel[1] Ashish Awasthi[2] Manisha Dubey[1] Ajay Kumar Mishra[1] Surender Singh[1] Radha Dhiman[3], [1]Sanjay Gandhi Postgraduate Institute of Medical Sciences (SGPGI), [2]CSIR-Central Drug Research Institute, Lucknow, India, [3]Sanjay Gandhi Postgraduate Institute of Medical Sciences

Background: Hepatitis C virus (HCV) claims ~240,000 lives globally and target is to eliminate HCV by 2030. Countries need a well-articulated and realistic roadmap to achieve the elimination. We modelled the HCV elimination framework for India based on granular seroprevalence data and estimated the HCV burden, mortality, and elimination trajectories through 2050. **Methods:** Administratively, India is divided into state followed by districts. District level blood-donors HCV screening data, gathered from blood-units donated

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between 2011-2020, were used to estimate the district level anti-HCV seroprevalence, treatment eligible HCV population, and HCV-related deaths. Weighted pooled estimates were generated for the states and the country. Age- and fibrosis-stage specific transition probabilities were applied to estimate progression, mortality, and hepatocellular carcinoma. We applied standard demographic methods, on country's census 2011 data, to project 18-65 years population from 2012 to 2050. Data on annual HCV treatment capacity and treatment success were collected from published reports. Developed a compartment model at base year 2025, assuming 88,000 being treated annually with 0.44 million already treatment so far since the inception of the national program, 91.2% treatment response rate, no-reinfection, and 110 new infections per million of population at risk. The Rogan–Gladen estimator was used for prevalence correction. Probabilistic sensitivity analysis and 95% confidence interval (CI), was performed using 10,000 Monte Carlo simulations. **Results:** Anti-HCV seroprevalence (95% CI) in 666,875,796 blood-units, donated between 2011-2020 in 609/640 districts, was 0.32% (0.28-0.36). At base-year 2025, estimated anti-HCV reactive burden among 18-65 year at base-year 2025 was 2.72 million (95%CI 2.39-3.14). Of them, 1.77 million (95%CI 1.55-2.04) require treatment to achieve HCV elimination goal (90% of anti-HCV reactive identified, 80% are viremic, and 80% of viremic are started on treatment). Estimated annual HCV-related deaths were 36,945 (95%CI 32,460-42-622). With current efforts, India can achieve HCV elimination among low-risk population aged 18-65 by the year 2042. By enhancing the existing treatment capacity by 5%, 10%, 15%, and 20%, HCV elimination goal could be achieved by the year 2038, 2036, 2035, and 2034 respectively (Figure 1). **Conclusion:** At the current pace of treatment, India is unlikely to achieve HCV elimination target by the year 2030. Scaling-up the existing treatment capacity by 20% could help to achieve the elimination by 2034.



Disclosures: Amit Goel:Nothing to Disclose, Ashish Awasthi:Nothing to Disclose, Manisha Dubey:Nothing to Disclose, Ajay Kumar Mishra:Nothing to Disclose, Surender Singh:Nothing to Disclose, Radha Dhiman: Nothing to Disclose.

3256 | ◆ SCALING UP HEPATITIS C SCREENING IN LOW-ENDEMIC AREA: EXPLORATION OF STRATEGIES INTEGRATING BIG DATA RISK CONCENTRATION AND LOW-COST ONE-SAMPLE SCREENING IN CHINA

Qiran Zhang[1] Feng Sun[2] Hongrang Zhou[3] Zhe Zhou[3] Yiqi Yu[2] Guifu Li[3] Sen Wang[2] Wenhong Zhang[2], [1]Huashan Hospital, Fidan University, [2]Huashan Hospital, Fudan University, [3]Center for Disease Control and Prevention of Qingpu District

Background: Low-endemic areas face a critical dilemma in hepatitis C elimination, where universal screening is costly,while screening only high-risk groups misses a substantial number of infections. One-sample testing and big data-driven risk concentration may be useful to address this dilemma, yet real-world public health practice is lacking to confirm their feasibility and benefits. **Methods:** This study employed a real-world evidence-driven modeling approach. In phase I, we took real-world public health practice to investigate the feasibility of low-cost one-sample testing and big data-driven risk concentration in large-scale HCV screening, and derived empirical parameters. In this phase, firstly a universal screening was conducted in the general population across four provinces in China,implementing low-cost POCT antibody screening, and diagnosis with one-sample reflex HCV RNA testing or two-step process. Secondly, A big data risk concentration model was developed and field-validated inShanghai for HCV screening. In phase II, we conducted health economic modeling to compare HCV screening strategies. All empirically derived parameters were input into a Marko model to compare the cost-effectiveness of eight strategies (defined by screening pools and testing methods). **Results:** In phase I, 21598 individuals were screened and the anti-HCV prevalence in the general population was0.088%. Linkage rate between screening and diagnostic was 100% in one-sample reflex testing and 46%in two-step process. Then in Shanghai, 4349 individuals from concentrated pool were screened, and the anti-HCV positivity rate was 1.17% in this group. In phase II, screening big data-concentrated population using low-cost one-sample testing achieved the most favorable

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cost-effectiveness profile. Universal screening with one-sample testing was also cost-effective over the long term, and threshold analysis showed that when the test cost falls below 6.9 RMB, universal screening becomes cost-effective within a10-year horizon. To achieve WHO's target of a 65% reduction in mortality, either the rate of confirmatory testing completion or the linkage-to-care must be increased from the current site-measured rate of 80%to above 87.4%. **Conclusion:** The strategy using low-cost one-sample testing with big data risk concentration is the optimal pathway for large-scale HCV screening in low-endemic areas. In conditions where big-data are not available,universal screening using low-cost one-sample testing is also cost-effective in long term.

Disclosures: Qiran Zhang:Nothing to Disclose, Feng Sun:Nothing to Disclose, Hongrang Zhou:Nothing to Disclose, Zhe Zhou:Nothing to Disclose, Yiqi Yu: Nothing to Disclose, Guifu Li:Nothing to Disclose, Sen Wang:Nothing to Disclose, Wenhong Zhang:Nothing to Disclose.

3257 | ◆ NATIONAL TRENDS AND HEALTHCARE UTILIZATION OF CHRONIC HEPATITIS C AMONG HOMELESS HOSPITALIZATIONS: A NATIONWIDE ANALYSIS, 2016–2023

Renuka Verma[1] Maria Ortega Abad[2] Ezzeldien n Ibrahim[3] Kamleshun Ramphul[4] Karn Wijarnpreecha[5] Nikki Duong[6], [1]Kirk Kerkorian School of Medicine at the University of Nevad, [2]Cleveland clinic, [3]University of Missouri – Columbia, [4]Independent reseacher, [5]University of Arizona College of Medicine-Phoenix, [6]Stanford University

Background: An estimated 2.7 to 3.9 million Americans live with chronic hepatitis C (HCV), with approximately 17,000 new cases reported each year. Homeless populations bear a high burden of HCV due to higher rates of intravenous drug use and systemic barriers to healthcare. We aim to explore the prevalence and predictors of HCV among homeless hospitalizations in the United States, along with its healthcare burden. **Methods:** The National Inpatient Sample (NIS), the largest inpatient database in the United States, was queried for hospitalizations of homeless patients between 2016 and 2023. The prevalence of HCV was examined over the study period. Baseline demographics, comorbidities, and independent predictors of HCV were analyzed, along with mean length of stay (LOS) and inflation-adjusted hospital charges. **Results:** A total of 3,334,534 weighted hospitalizations among homeless patients were analyzed, of whom 4.4% had HCV, with the prevalence declining significantly from 4.71% in 2016 to 3.40% in 2023 (p- trend <0.001). Affected patients were predominantly male (75.66%; aOR 1.10, 95% CI 1.07 to 1.14, $p<0.001$), older (49.4 vs. 46.6 years), and carried a greater comorbidity burden (Charlson index 2.61 vs. 1.22). Most were admitted to urban teaching hospitals (83.65%; aOR 1.46, 95% CI 1.32 to 1.61, $p<0.001$), and both Medicaid (63.09%; aOR 1.53, 95% CI 1.47 to 1.59, $p<0.001$) and uninsured status (9.76%; aOR 1.09, 95% CI 1.02 to 1.17, $p=0.017$) were independently associated with higher odds compared to Medicare. Compared to those without HCV, affected patients had a higher prevalence of drug abuse (72.91%; aOR 3.08, 95% CI 2.98 to 3.17, $p<0.001$), alcohol use disorder (37.64%; aOR 1.22, 95% CI 1.18 to 1.25, $p<0.001$), HIV/AIDS (7.66%; aOR 2.40, 95% CI 2.26 to 2.56, $p<0.001$), and cachexia (2.64%; aOR 1.74, 95% CI 1.61 to 1.89, $p<0.001$). Weekend admission was independently associated with higher odds of HCV (aOR 1.06, 95% CI 1.04–1.09, $p<0.001$).. Mean LOS increased significantly from 8.12 to 8.43 days (p-trend = 0.009), peaking at 8.92 days in 2022, while inflation-adjusted total charges showed no significant differences (p-trend = 0.241), ranging from $72,371 to $79,529. **Conclusion:** Despite a significant decline in HCV prevalence among homeless hospitalizations over time, affected patients continue to experience a disproportionately high burden of comorbid illness and healthcare utilization. Substance use, HIV/AIDS, and inadequate insurance coverage remained strong independent predictors, reflecting persistent structural barriers to HCV care. Expanded harm reduction strategies, improved linkage to treatment, and integrated care models are needed to reduce ongoing disparities in this vulnerable population.

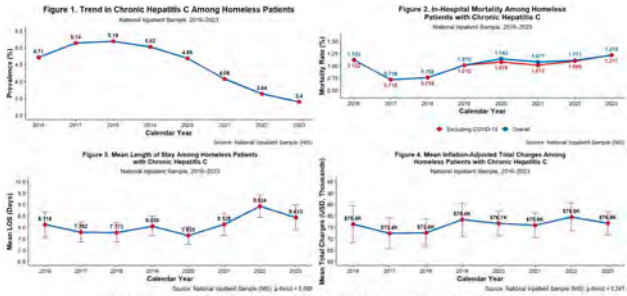


Table. Temporal Trends in Chronic Hepatitis C Among Homeless Patients National Inpatient Sample, 2016–2023

Year	Prevalence (Figure 1)	Mortality - Overall (Figure 2)	Mortality - No COVID (Figure 2)	Mean LOS, days (Figure 3)	Mean Total Charges (Figure 4)
2016	4.712%	1.122%	1.122%	8.118	$76,391.74
2017	5.142%	0.718%	0.718%	7.792	$72,371.12
2018	5.187%	0.758%	0.758%	7.773	$72,633.40
2019	5.025%	1.010%	1.010%	8.055	$78,401.31
2020	4.688%	1.143%	1.078%	7.635	$76,722.05
2021	4.076%	1.077%	1.013%	8.128	$75,862.53
2022	3.640%	1.111%	1.099%	8.924	$79,529.18
2023	3.398%	1.218%	1.217%	8.433	$76,786.92
p-trend	<0.001	0.293	0.355	0.009	0.241

Disclosures: Renuka Verma:Nothing to Disclose, Maria Ortega Abad:Nothing to Disclose, Ezzeldien n Ibrahim:Nothing to Disclose, Kamleshun Ramphul:

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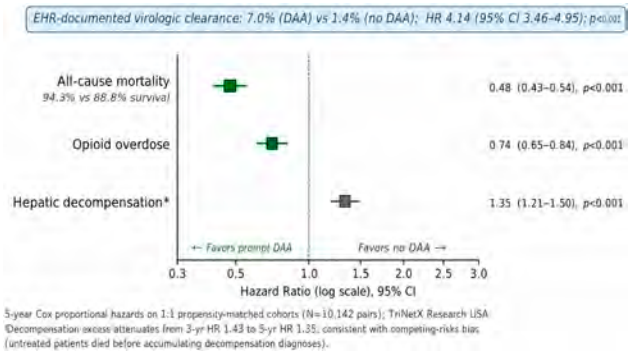
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Nothing to Disclose, Karn Wijarnpreecha:Nothing to Disclose, Nikki Duong:Nothing to Disclose.

3258 | ◆ FIVE-YEAR MORTALITY, OVERDOSE, AND HEPATIC OUTCOMES ASSOCIATED WITH PROMPT DIRECT-ACTING ANTIVIRAL THERAPY IN ADULTS WITH OPIOID USE DISORDER AND CHRONIC HEPATITIS C: A PROPENSITY-MATCHED COHORT STUDY

EzzElDien A. Ibrahim[1] Mahmoud Majed Mansour[1] Nourhan Saleh[1] Mohamed Omar[1] Mostafa Adel T. Mahmoud[2] Akram Alnounou[3] Nour Aldin T. Ahmed[4] Youssef Hafez[5] Mohammad Alabbas[6] Nathan Tofteland[7], [1]University of Missouri, Columbia, MO, USA, [2]Beni Suef university, Beni Suef, Egypt, [3]Western Michigan University Homer Stryker M.D. School of Medicine, [4]Beni-Suef university, Beni-Suef, Egypt, [5]St. Louis University School of Medicine, [6]Cleveland Clinic Foundation, Cleveland, Ohio, USA, [7]University of Kansas Medical Center

Background: Adults with opioid use disorder (OUD) carry the largest pool of new and prevalent hepatitis C virus (HCV) infection in the United States, yet have the lowest direct-acting antiviral (DAA) treatment uptake. Guidelines endorse universal DAA therapy regardless of substance use, but the recommendation rests largely on viral cure as a surrogate. Real-world long-term clinical outcomes after prompt DAA initiation in OUD populations remain limited. **Methods:** Retrospective propensity-matched cohort study on TriNetX Research USA (147M patients, 113 HCOs). Adults ≥18 with chronic HCV (B18.2, B19.2, B17.1, Z22.52, or HCV RNA ≥15 IU/mL) and OUD identified by the Wakeman 2020 composite definition (inpatient F11.x, repeated outpatient F11.x, or F11.x with overdose, injection-drug-use-related infection, or methadone/buprenorphine prescription) were included; pre-index HCC, liver transplant, HIV, or chronic HBV excluded. The index date was the first qualifying HCV anchor. A 180-day landmark required survival and observability through day 180. Cohort 1 had ≥1 DAA RxNorm fill in days 0–180; Cohort 2 had none. 1:1 propensity matching used 25+ covariates (demographics, era, prior methadone/buprenorphine, prior overdose, IDU-proxy infections, psychiatric comorbidity, baseline labs, liver-disease context; all post-match SMDs <0.05). Primary outcomes (days 181–1825, 5 years): all-cause mortality, opioid overdose, hepatic decompensation, and confirmed virologic clearance. Cox proportional hazards models estimated hazard ratios (HR). **Results:** 10,142 matched pairs were analyzed. Over 5 years, prompt DAA initiation was associated with lower all-cause mortality (5-year survival 94.3% vs 88.8%; HR 0.48, 95% CI 0.43–0.54; p<0.001), lower opioid overdose (HR 0.74, 95% CI 0.65–0.84; p<0.001), and higher confirmed virologic clearance (HR 4.14, 95% CI 3.46–4.95). Coded hepatic decompensation was higher among DAA-treated patients (HR 1.35, 95% CI 1.21–1.50) but attenuated from the 3-year HR of 1.43 — a pattern more consistent with competing-risks bias than with treatment harm, as untreated patients died before accumulating decompensation diagnoses. Findings were similar at 3-year follow-up (mortality HR 0.42; overdose HR 0.76; decompensation HR 1.43). Absolute 5-year differences in the DAA arm: 5.5 percentage-point lower mortality and 2.3 percentage-point higher coded decompensation, for a net 3.2 fewer adverse events per 100 patients. **Conclusion:** In adults with OUD and chronic HCV, prompt DAA initiation within 180 days was associated with lower 5-year mortality and overdose, and higher virologic clearance. The decompensation excess attenuated with longer follow-up, a pattern more consistent with competing-risks bias than with treatment harm. Findings are consistent with the case for universal, prompt DAA delivery in OUD populations regardless of perceived cascade barriers.



Disclosures: EzzElDien A. Ibrahim:Nothing to Disclose, Mahmoud Majed Mansour:Nothing to Disclose, Nourhan Saleh:Nothing to Disclose, Mohamed Omar: Nothing to Disclose, Mostafa Adel T. Mahmoud:Nothing to Disclose, Akram Alnounou:Nothing to Disclose, Nour Aldin T. Ahmed:Nothing to Disclose, Youssef Hafez: Nothing to Disclose, Mohammad Alabbas:Nothing to Disclose, Nathan Tofteland:Nothing to Disclose.

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3259 | ◆ URGEN-C: EARLY OUTCOMES FROM A NOVEL TELEHEALTH HCV TREATMENT PROGRAM FOR GEORGIANS WITH SUBSTANCE USE DISORDERS

Jake MacDonald[1] Kirsten Dodson[1] Marie Sutton[2] Patrick Reilly[2] Lesley Miller[1], [1]Emory University School of Medicine, [2]Imagine Hope, Inc.

Background: Hepatitis C virus (HCV) disproportionately affects people with substance use disorders (SUD), yet access to curative direct-acting antiviral (DAA) therapy remains limited, even for those with health insurance. Multiple telehealth models have demonstrated high sustained virologic response (SVR) rates in vulnerable populations, but few have targeted patients identified through publicly-funded substance use disorder (SUD) treatment programs. Urgen-C partners Imagine Hope, Inc. (IH) with the Grady Memorial Hospital Liver Clinic (GLC), using publicly-funded SUD treatment sites as HCV screening access points. We report early outcomes. **Methods:** Retrospective chart review of all patients referred to GLC from IH through May 2026. Primary outcome: per-protocol SVR12 (undetectable HCV RNA $\geq$12 weeks post-DAA). Secondary outcomes included care cascade metrics. **Results:** Of 78 patients referred (June 2025–May 2026), 80.8% were White, with a mean age of 45.4 years, and 51.3% were male. Most had a history of intravenous drug use (IVDU) (78.2%), 91.0% were insured, 9.0% were experiencing homelessness, and 24.4% had mental health comorbidities; no patients had HIV co-infection. Of the 78 referred, 76 (97.4%) attended an initial telehealth appointment and 61 (78.2%) started DAAs (86.4% sofosbuvir/velpatasvir). Median time from referral to treatment start was 54 days (IQR 36–82). HCV genotype 1a was most common (n = 30, 38.5%), followed by genotype 2 (n = 11, 14.1%) and genotype 3 (n = 10, 12.8%), with genotype unknown or not reported in 24 patients (30.8%). Fibrosis staging by FIB-4, APRI, and/or previous imaging was available in 74 patients (94.9%), the majority of whom had early-stage disease (F0–F1, 67.6%), while advanced fibrosis or cirrhosis (F3–F4) was present in only 2 patients (2.8%), and imaging evidence of portal hypertension was identified in 5 patients (6.4%). Forty-one patients (52.6%) completed treatment, 10 (12.8%) were lost to follow-up during treatment, and 10 (12.8%) remain on treatment as of May 2026. Among the 51 patients who had completed treatment at the time of analysis (excluding 10 currently on treatment), 41 (80.4%) completed a full course of DAA therapy; confirmed SVR was achieved in 17 patients (33.3%), while 24 patients (47.1%) completed treatment but did not have confirmatory SVR labs drawn. Of 41 completers with SVR testing, all achieved undetectable HCV RNA (per-protocol SVR 100%; 17/17). **Conclusion:** Urgen-C achieved high appointment attendance and treatment initiation rates comparable to prior telehealth HCV interventions, with a 100% per-protocol cure rate among those with confirmatory testing. SVR12 follow-up failure (58.5% of completers) was the primary gap, underscoring the need for community-based testing strategies. Urgen-C is a scalable model for advancing HCV elimination among people with SUD.

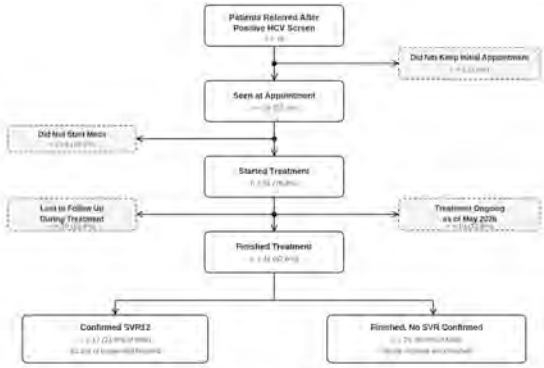


Figure 1. Care cascade of patients referred to Urgen-C.

HCV=hepatitis C virus; SVR12=sustained virologic response at 12 weeks; Finished, No SVR Confirmed = patients who completed medication course, but no confirmatory lab result was obtained.

Disclosures: Jake MacDonald:Nothing to Disclose, Kirsten Dodson:Nothing to Disclose, Marie Sutton: Nothing to Disclose, Patrick Reilly:Nothing to Disclose, Lesley Miller:Gilead Sciences: Grant/Research Support, Cepheid: Grant/Research Support, AbbVie: Advisor.

3260 | PROGRESS TOWARD WHO 2030 TARGETS: 46-MONTH RESULTS OF THE NATIONAL HEPATITIS C SCREENING AND ELIMINATION PROGRAM IN LITHUANIA

Limas Kupcinskas[1] Janina Petkeviciene[1] Artur Kozlov[2] Jurate Sabaliene[2] Alexis Voeller[3] Devin Razavi-Shearer[3] John Ward[4] Juozas Kupcinskas[5], [1]Lithuanian University of Health Sciences, Kaunas, Lithuania, [2]National Health Insurance Fund under the Ministry of Health, Vilnius, Lithuania, [3]Center for Disease Analysis Foundation, Lafayette, United States, [4]Coalition for Global Hepatitis Elimination, Decatur, United States, [5]Lithuanian University of Health Sciences, Kaunas, Lithuania

Background: The Lithuanian National HCV screening and elimination program was launched in May 2022. General practitioners (GPs) received special promoting fee for serological HCV antibody testing: (1) a one-time test for individuals born between 1945 and 1994, and (2) annual testing for people who inject drugs (PWID) and people with HIV. This initiative is the first of its kind in Central and Eastern Europe. The aim of this study

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was to assess the results of the first 46 months of the program and the different scenarios for achieving the WHO 2030 targets. **Methods:** GPs invited people to perform a serum blood test for HCV antibodies. Anti-HCV+ patients were referred to a specialist (gastroenterologist or infectologist) for HCV RNA testing, and if result was positive, direct-acting antiviral (DAA) therapy was prescribed. Information about patients was obtained from the National Health Insurance Fund. The Markov disease progression model elaborated by the CDA Foundation was used to assess HCV elimination progress. The data from the 2022-2023 screening were used as inputs. Three scenarios were developed: the 'Base' scenario - return to pre-screening level and 2 scenarios with different extents of treatment. **Results:** At the beginning of 2022, about 1.8 million people born in 1945-1994 lived in Lithuania. Between May 5, 2022, and Feb 28, 2026, from this population 1494093 people (83.7%) were tested for HCV antibodies. Positive test results were found in 1.32% of cases. In the risk group, 13019 PWID and/or HIV+ people were screened, of whom 28.2 % were seropositive. Specialists consulted 62% anti-HCV+ persons, but only 29% from risk group ($p < 0.001$). Viremia was detected in 51.2 %. During the 46-month of the program (May 2022- Feb 2026) 2.4 times more HCV patients were treated by specialists with DAA in comparison to the same period before starting of the program (9256 vs 3890). The Markov disease progression model to assess HCV elimination progress showed the following scenarios: Scenario 1: if the same number of patients are treated as before the screening, the WHO targets will not be reached. Scenario 2: treating 70% of infected patients will meet most but not all WHO targets. Scenario 3: by treating all infected patients by 2030, the WHO target will be met by saving 150 lives and preventing 90 new cases of decompensated cirrhosis and 120 cases of hepatocellular carcinoma. **Conclusion:** Our data show that promotion fee effectively motivated family physicians to perform anti-HCV antibodies screening and more than 83 % (approximately 1.5 million) of the target population was tested. However, 38% of people with positive HCV antibodies in the general population and 71% in high-risk groups still need to be examined by specialists. Therefore, additional measures to increase GP's motivation for rapid referral of anti-HCV+ persons to specialists and enhance compliance of risk group participants to program logistic are necessary to achieve WHO 2030 targets in Lithuania.

Disclosures: Limas Kupcinskas:Abbvie: Honorarium for lecture, Janina Petkeviciene:Nothing to Disclose, Artur Kozlov:Nothing to Disclose, Jurate Sabaliene:Nothing to Disclose, Alexis Voeller:Nothing to Disclose, Devin Razavi-Shearer:Nothing to Disclose, John Ward:Nothing to Disclose, Juozas Kupcinskas:Nothing to Disclose.

3261 | INFECTION CONTROL APPROACH TO HEPATITIS C VIRUS SCREENING AT A TERTIARY CARE CANCER CENTER IN THE UNITED STATES

Harrys Torres[1] Khalis Mustafayev[1] Bruno Granwehr[1] Adina Feldman[1] Amy Spallone[1] Eduardo Yepez Guevara[1], [1]The University of Texas MD Anderson Cancer Center

Background: Universal hepatitis C virus (HCV) screening is recommended nationwide. Acute HCV is a reportable condition in the United States. In many healthcare centers, infection prevention and control (IPC) teams collect reactive HCV antibody (anti-HCV) test results for public health reporting purposes, while also obtaining additional information to differentiate between acute and chronic HCV infections. Herein, we describe the 14-year experience leveraging HCV as a reportable infection to optimize screening and linkage to care at a tertiary care cancer center in the United States. **Methods:** All patients screened at MD Anderson Cancer Center for HCV from May 2012 to May 2026 were analyzed retrospectively. During that period, Infection Preventionists sent weekly reports of reactive anti-HCV results to a physician screening champion. Afterward, the champion contacted ordering providers and educated them about the need for confirmatory testing to reduce HCV-associated morbidity and mortality. Reflex HCV RNA testing was excluded from the testing sequence to prevent gaps in the discussion of anti-HCV results with patients. Descriptive statistics were used to state the prevalence of reactive anti-HCV and the patient's progression through the HCV care cascade. **Results:** Of 133,222 patients screened, 4,889 (3.7%) had reactive anti-HCV results. After excluding 1,107 patients initially referred to HCV specialists, ordering providers were contacted for 2,063 patients (Figure 1). Only five patients had acute HCV, and their cases were reported to the local health department. When providers were contacted, 876/2,063 (42.5%) of patients were linked to care. Most of the patients not linked to care came to our institution for a second opinion about cancer treatment and were asked to address their HCV locally. Of the patients linked to HCV care at our center, 556 (63.5%) had proven HCV (detectable HCV RNA or history of treated HCV). The majority of patients with proven HCV (341/556 [61.3%]) received direct-acting antivirals and had sustained virologic responses (SVRs; 340/341 [99.7%]) (Figure 1). **Conclusion:** HCV screening can be successfully performed in cancer hospitals using existing IPC platforms combined with HCV screening champions. This approach enabled high-volume screening, systemic reporting to health departments, provider education, care coordination, and excellent SVR. These results underscore that although treatment

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is highly effective, enhanced outreach and navigation strategies are needed to close care cascade gaps and achieve HCV elimination targets.

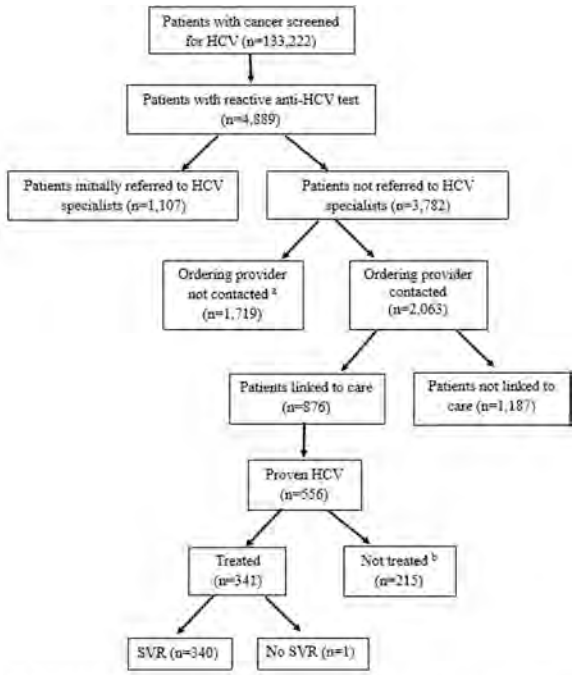


Figure 1. Study flow diagram.
[a] The main reasons for not contacting providers were: 1) HCV management was addressed by the oncology team (n=745) and 2) HCV treatment was contraindicated (n=583).
[b] Of the 215 patients not treated, 85 were lost to follow-up, 62 had advanced cancer, 38 died, 16 did not receive treatment due to potential drug-drug interactions with cancer treatment, 10 had decompensated cirrhosis, 2 had no insurance, and 2 refused treatment.

Disclosures: Harrys Torres:Gilead: Principal Investigator, Merck: Principal Investigator, Khalis Mustafayev: Nothing to Disclose, Bruno Granwehr:Nothing to Disclose, Adina Feldman:Nothing to Disclose, Amy Spallone:Nothing to Disclose, Eduardo Yepez Guevara:Nothing to Disclose.

3262 | GUT MICROBIOME–ASSOCIATED PERSISTENCE OF PORTAL VEIN SUCCINATE ACCUMULATION AFTER HEPATITIS C VIRUS ERADICATION

Nivedha Vaidy[1] Mary Winnicki[1] Moumita Chakraborty[1] Kareen Akiva[2] Grace Zhang[3] Gabriella Quinn[1] Elizabeth Townsend[4] Lisa Scheuing[1] Elliott Levy[5] David Kleiner[6] Christopher Koh[1] Ohad Etzion[1] Anjali Rai[7] Rownock Afruza[1] Rabab Ali[8] Theo Heller[7], [1]NIDDK, [2]University of Maryland Medical System, [3]University of California, San Francisco, [4]NewYork-Presbyterian/ Columbia University Irving Medical Center, [5]NIH, [6]National Cancer Institute, Bethesda, [7]NIH/NIDDK, [8]McGaw Medical Center at Northwestern University

Background: Despite effective direct-acting antiviral therapy for Hepatitis C Virus (HCV), many patients remain cirrhotic and at risk for hepatocellular carcinoma after sustained virologic response (SVR), suggesting persistent disease mechanisms after viral clearance. Cirrhosis is characterized by dysregulation of the gut–liver axis, in which microbiome-derived metabolites are delivered via the portal circulation to regulate hepatic inflammatory and fibrotic signaling. Among these, succinate is a gut-derived metabolite that can bind and activate SUCNR1 signaling in the liver, promoting inflammation and fibrosis. However, whether portal succinate is an upstream driver of this pathway in cirrhosis remains unclear. Thus, we investigated portal succinate dynamics during and after HCV eradication and their association with gut microbial and hepatic transcriptional changes. **Methods:** We studied paired samples from patients (n = 22) during active HCV infection (HCVi) and 6 months post-SVR. We analyzed liver biopsy, portal and peripheral blood, and stool samples using liver transcriptomics, metabolomics, and 16S rRNA sequencing. Patients were classified as non-cirrhotic (n = 14) or cirrhotic (n = 8). **Results:** In non-cirrhotic patients, portal succinate significantly decreased following SVR, consistent with metabolic recovery after viral clearance. In contrast, cirrhotic patients exhibited persistent elevation of portal succinate post-SVR, indicating sustained gut–liver axis dysregulation despite viral clearance. In cirrhotic patients, succinate showed state-dependent microbial associations, including a strong negative correlation with the succinate-consuming *Dialister pneumosintes* during HCVi (r = −0.86) and a strong positive correlation with the succinate-producing *Odoribacter splanchnicus* after SVR (r = 0.83). During active infection, portal succinate correlated with hepatic inflammatory and fibrotic gene programs, but these associations were lost after SVR. **Conclusion:** Collectively, these findings suggest that in cirrhosis, portal succinate remains elevated after HCV eradication and reflects persistent gut metabolic input, but decouples from hepatic transcriptional programs. This work highlights succinate as a candidate biomarker of persistent metabolic dysfunction after HCV clearance that may play a role in persistent metabolic dysregulation in cirrhosis and warrants further mechanistic investigation.

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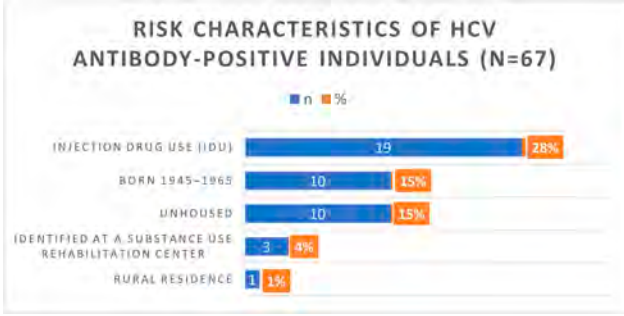
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3263 | TARGETED HEPATITIS C PREVENTION, TESTING, AND LINKAGE TO CARE THROUGH CLINIC AND MOBILE OUTREACH IN SOUTHERN NEVADA

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Background: Hepatitis C virus (HCV) disproportionately affects underserved populations, including people who inject drugs, unhoused individuals, rural communities, and adults born between 1945–1965. In 2025, The LGBTQ+ Center of Southern Nevada expanded HCV prevention, testing, and linkage-to-care services through fixed-site and mobile outreach programs emphasizing culturally competent care and wraparound services. **Methods:** The Center operates a Sexually Transmitted Infection (STI) Clinic, Primary Care Clinic, and Mobile Health Clinic. All patients were offered free HIV and HCV testing and received biomedical and behavioral prevention interventions with individualized assessments. Care delivery was guided by culturally competent, trauma-informed approaches and integrated wraparound services, including syringe services, substance use recovery linkage, peer navigation, bilingual support, housing and social service referrals, and prevention supplies. Community-based HCV education and testing were conducted across substance use treatment facilities, Native American Reservations, libraries, shelters, and outreach events throughout Southern Nevada. Patients with reactive HCV antibody (HCV Ab) tests were referred for confirmatory HCV RNA testing and linkage to treatment coordinated by a dedicated Hepatitis C Manager. Pharmacy services at both clinic locations provide medication delivery to support timely initiation and adherence to HCV therapy. **Results:** In 2025, 2,062 individuals were tested for HCV Ab; 67 (3.2%) tested positive. Of those, 63 (94%) completed confirmatory HCV RNA testing. 31 of 63 (49.2%) had detectable HCV RNA indicating active infection. All 31 initiated treatment and achieved subsequent HCV RNA negativity following therapy. Four patients pending confirmatory testing remain engaged in follow-up care coordination.Among the 67 HCV Ab-positive individuals, 10 (15%) were unhoused, 1 (1.5%) resided in a rural community, 3 (5%) were identified through a substance use rehabilitation center (Crossroads), 19 (28%) reported injection drug use, and 10 (15%) were born between 1945–1965.The Mobile Health Clinic, launched in 2025, tested 71 individuals, identifying 3 (4.2%) HCV Ab-positive cases; all 3 were linked to care and initiated treatment (100%). Mobile outreach expanded testing access among rural and high-risk populations, including individuals with substance use disorder and housing instability. **Conclusion:** Integrated clinic and mobile outreach achieved high rates of HCV confirmatory testing, linkage to care, treatment initiation, and cure among underserved populations in Southern Nevada. A model combining culturally competent care, wraparound services, and mobile delivery reduced structural barriers to HCV care and supported progress toward HCV elimination in high-risk communities.



Disclosures: Darya Fridman:Nothing to Disclose.

3264 | GENDER DIFFERENCES IN STAGES OF LINKAGE-TO-CARE AMONG PERSONS WITH UNTREATED OR INCOMPLETELY DIAGNOSED HEPATITIS C VIRUS INFECTION IN SAN FRANCISCO

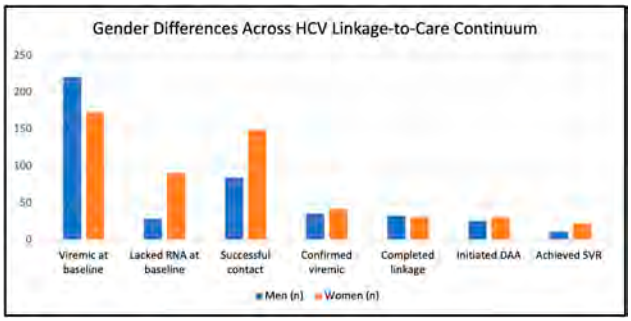
Rena Fox[1] Matthew Caliz[1] Jennifer Price[2] Mai Sedki[3] Jeffrey McKinney[3] Katrina Alcantara[3] Tasha Toliver[3] Michael Helle[3], [1]Division of General Internal Medicine, UCSF, [2]Division of Gastroenterology and Hepatology, UCSF, [3]University of California, San Francisco

Background: Prior studies of the hepatitis C virus (HCV) care cascade have reported gender differences, but findings vary across settings and treatment eras. Women spontaneously clear HCV more often but face access barriers related to caregiver responsibilities and had lower treatment uptake during the interferon era, while men engage with healthcare less regularly. We evaluated gender differences at each stage of the cascade in a large HCV outreach program in the direct-acting antiviral (DAA) era in San Francisco. **Methods:** Using the electronic medical record (EMR), we identified adults seen in an urban healthcare system from 2020–2024 who either had 1) detectable or quantified HCV RNA at most recent testing or 2) HCV antibody reactive without RNA testing. Manual review then incorporated unstructured external laboratory data. Two patient navigators attempted a minimum of three outreach calls per patient and offered laboratory testing at the site of the patient's choice and linkage visits by telephone, video, mobile van, or in person. No incentives were provided. **Results:** EMR query followed by manual review identified 514 living patients

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with current HCV viremia or incomplete diagnostic testing. Men had higher rates of viremia (88% vs. 65%), while more women (34% vs. 12%) lacked RNA testing. Navigators reached 234 patients, with higher success rates among women (56% vs 34%). Of these, 159 agreed to confirmatory RNA testing and linkage visits. At confirmatory testing, 45 were undetected, of whom 36 completed linkage visits, and 78 were viremic. Among the viremic, more than half were women. Overall, 82% of viremic patients completed linkage visits and 89% initiated DAA (100% of women vs 79% of men). To date, 67% achieved documented sustained virologic response (SVR) (73% of women vs 58% of men). Overall linkage was achieved in 100/159 patients (63%). **Conclusion:** Important gender differences persist in the HCV care cascade in the DAA era. We found at baseline, substantially more women lacked confirmatory RNA testing while more men had untreated viremia. However, once they were reached and completed testing, women had equivalent rates of viremia, linkage, and DAA initiation, and ultimately higher rates of documented SVR. These data suggest that upstream differences in the cascade, such as completed diagnosis and entry into care, are the key barriers for women. This pattern raises the possibility that gender disparities in HCV care may be driven in part by missed opportunities for early diagnosis rather than unwillingness to participate in care, and that navigator-based outreach programs that offer flexible testing and multiple care modalities may be particularly effective in achieving HCV elimination for women.



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3265 | EVOLVING EPIDEMIOLOGY AND DISEASE BURDEN OF HEPATITIS C AMONG US ADULTS AGED 15–49 YEARS, 1990–2023

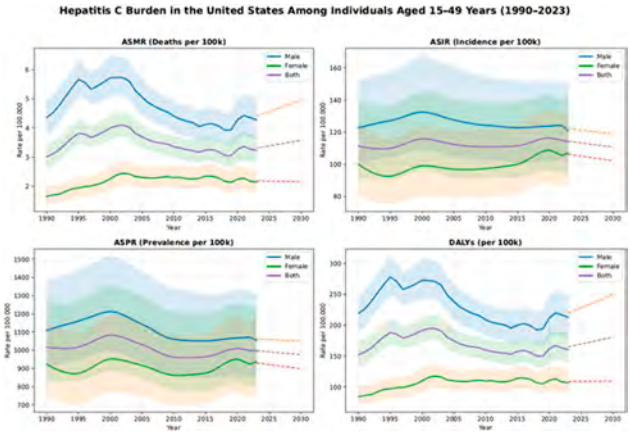
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Background: Hepatitis C virus (HCV) infection remains a significant contributor to chronic liver disease, cirrhosis, and hepatocellular carcinoma in the United States. This study aimed to evaluate epidemiologic trends and disease burden of HCV among individuals aged 15–49 years in the United States from 1990 to 2023 using Global Burden of Disease (GBD) data. **Methods:** In this retrospective epidemiologic analysis, we assessed GBD 2023 estimates for the United States from 1990–2023. Age-standardized mortality rates (ASMR), age-standardized incidence rates (ASIR), prevalence rates (ASPR), and disability-adjusted life year (DALY) rates per 100,000 population were analyzed by sex. Corresponding 95% uncertainty intervals (UIs) were obtained directly from the GBD database. **Results:** From 1990 to 2023, the ASMR for HCV among individuals aged 15–49 years increased from 3.01 per 100,000 population (95% UI, 2.60–3.44) to 3.23 per 100,000 (2.78–3.71). In males, ASMR remained relatively stable, changing from 4.36 (3.75–4.99) to 4.28 (3.63–5.04) per 100,000, whereas in females it increased from 1.65 (1.39–2.00) to 2.15 (1.78–2.59) per 100,000. ASIR rose slightly overall from 111.38 (91.35–138.03) to 114.02 (94.12–142.46) per 100,000 population. Male incidence rates decreased modestly from 122.74 (99.97–152.09) to 120.90 (100.69–150.45), while female incidence rates increased from 99.97 (82.23–125.49) to 106.96 (87.39–133.54) per 100,000. ASPR remained relatively stable overall, decreasing slightly from 1017.31 (830.51–1270.07) to 996.67 (805.57–1249.52) per 100,000 population. DALY rates increased from 151.98 (131.87–174.10) to 160.58 (138.14–185.09) per 100,000 population overall. Among females, DALY rates rose substantially from 84.34 (71.33–101.46) to 106.87 (88.33–128.39), whereas rates in males remained relatively unchanged. **Conclusion:** Despite major therapeutic advances in HCV management, the burden of hepatitis C among Americans aged 15–49 years has remained substantial over the past three decades. Mortality and DALY rates increased modestly overall, with particularly notable increases among females. Stable prevalence and incidence rates

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may reflect ongoing transmission alongside improved survival due to effective antiviral therapies. These findings highlight the continued need for expanded screening, prevention initiatives, linkage to care, and equitable access to curative treatment in younger populations at risk for HCV infection.



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3266 | DERIVATION AND EXTERNAL VALIDATION OF THE BILIRUBIN-ALBUMIN-DIABETES-SCORE FOR PREDICTION OF TRANSPLANT-FREE SURVIVAL AFTER SVR IN PATIENTS WITH DECOMPENSATED HCV CIRRHOSIS

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Background: High rates of sustained virological response (SVR) can be achieved with direct acting antivirals (DAAs) in patients with decompensated hepatitis C virus (HCV) cirrhosis. However, despite SVR, these patients remain at risk for liver-related events (LREs). We aimed to derive and externally validate a risk score that predicts transplant-free survival in patients with decompensated HCV cirrhosis who have achieved SVR. **Methods:** We included patients with decompensated HCV cirrhosis (Child-Turcotte-Pugh (CTP) ≥ 7 and/or history of decompensating events) who achieved SVR after DDA therapy from 16 centers in Europe, and Canada (derivation cohort) and 9 centers in Spain (validation cohort). Predictive factors for transplant-free survival, were assessed in the derivation cohort using multivariable Cox regression, and a risk score was constructed based on the obtained hazard ratios. The performance of the score was subsequently assessed in the external validation cohort. **Results:** A total of 561 patients were included in the derivation cohort. Median age was 54.3 (IQR 48.7-59.1) years, 70% was male, 23% had DM, and the median MELD score at the time of SVR was 11.2 (IQR 9.2-13). Median follow-up time after SVR was 24 (IQR 9-33) months. In the derivation cohort, the 1-, and 3-year transplant-free survival was 86% and 62%. Presence of DM (aHR: 1.5, $p = 0.026$), lower albumin (aHR 28-35g/L: 2.2, aHR $<$ 28g/L: 3.8, $p < 0.001$), and higher bilirubin (aHR 34.2-51.3 umol/L: 1.7, aHR $>$ 51.3 umol/L: 2.2, $p < 0.001$) were associated with an increased risk of LT and death. Patients were

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allocated to a low risk (no risk factors [31%]), intermediate risk (1-3 risk points [53%]) and high risk group (≥ 4 risk points [16%]). Amongst patients with no risk factors, the 1-year and 3-year transplant-free survival was 93% and 82%, compared to 87% and 58% in the intermediate group, and 71% and 41% in the high risk group ($p < 0.001$) (Figure 1A). Similar findings were observed when HCC, orfurther decompensation were added as outcomes. In the validation cohort, 131 patients were included; median age was 55 (IQR 49-65) years, 68% was male, 28% had DM, and the median MELD score at the time of SVR was 10 (IQR 9-13). Median follow-up time after SVR was 54 (IQR 26-87) months. In the validation cohort, 47% of patients were at low predicted risk, 45% at intermediate risk and 8.4% at high risk. Amongst patients at low predicted risk, the 3-year transplant-free survival was 81%, compared to 68% in the intermediate group and 54% in the high risk group ($p = 0.027$) (Figure 1B). **Conclusion:** Patients with decompensated HCV cirrhosis remain at high risk of LREs despite SVR. The externally validated bilirubin-albumin-DM (BAD) score, effectively predicts transplant-free survival and can be used to guide management.

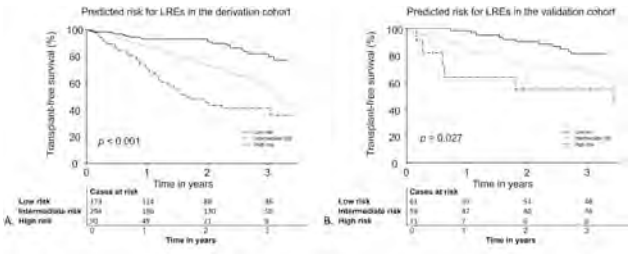


Figure 1. Transplant-free survival after SVR in patients with decompensated HCV cirrhosis stratified for a predicted high, intermediate and low risk in A) the derivation cohort, and B) the external validation cohort.

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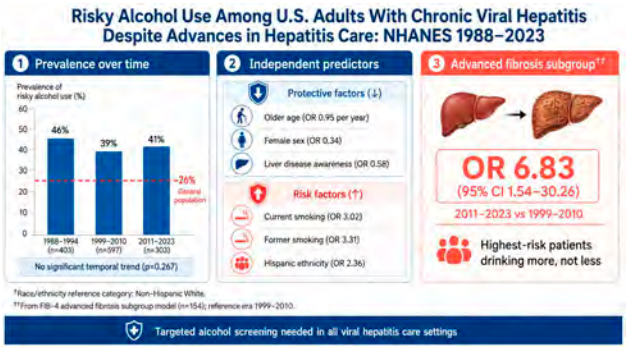
3267 | PERSISTENT RISKY ALCOHOL USE AMONG U.S. ADULTS WITH CHRONIC VIRAL HEPATITIS DESPITE ADVANCES IN HEPATITIS CARE: NHANES 1988-2023 NEW SUBMISSION

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Background: Risky alcohol use accelerates fibrosis progression and hepatocellular carcinoma risk in chronic viral hepatitis. Despite advances in antiviral therapy, screening, and public awareness, nationally representative data on temporal trends in alcohol use among HBV- and HCV-infected adults remain limited. We evaluated the prevalence, temporal trends, and predictors of risky alcohol use among U.S. adults with viral hepatitis using NHANES 1988-2023. **Methods:** We identified 1,303 adults with serologically confirmed HBV or HCV infection from NHANES 1988–2023. Risky alcohol use was defined as binge drinking (≥ 5 drinks/occasion for men, ≥ 4 for women) or heavy weekly consumption (>14 drinks/week for men, >7 for women). Survey-weighted logistic regression examined predictors of risky alcohol use across three eras (1988-1994, 1999-2010, 2011-2023), adjusting for sociodemographic characteristics, smoking, and fibrosis severity (FIB-4). **Results:** The weighted prevalence of risky alcohol use was 46.0% (95% CI 36.8-55.3), 39.4% (33.1-45.6), and 41.3% (31.7-50.9) across the three eras, with no significant decline over more than three decades ($p=0.267$). Older age (OR 0.95 95% CI 0.92–0.98 per year) and female sex (OR 0.34 95% CI 0.19–0.59) were independently associated with lower odds of risky drinking, whereas current (OR 3.02 95% CI 1.52–5.98) and former smoking (OR 3.31 95% CI 1.49–7.34) were associated with higher odds. Compared with Hispanic participants, non-Hispanic Black (OR 0.43 95% CI 0.21–0.88) and non-Hispanic White participants (OR 0.42 95% CI 0.20–0.91) had lower odds of risky use. Self-reported awareness of underlying liver disease was associated with lower odds of risky drinking (OR 0.58, 95% CI 0.36-0.94, $p=0.028$). In advanced fibrosis (FIB-4 >2.67), odds of risky drinking were higher in 2011-2023 versus 1999-2010 (OR 6.83, 95% CI 1.54-30.26, $p=0.017$), though subgroup size was limited. Hepatitis type was not associated with risky drinking (HCV vs HBV: OR 0.88, $p=0.740$). **Conclusion:** Risky alcohol use remained persistently high (39-46%) among US adults with chronic viral hepatitis over more than three decades, with no significant decline despite advances in antiviral therapy and hepatitis screening. Liver disease awareness was modestly protective, yet individuals with advanced fibrosis continued to show signals of risky alcohol use. These findings highlight persistent gaps in alcohol-related risk reduction, support routine alcohol screening and behavioral intervention in viral hepatitis care.

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3268 | IMPACT OF CHRONIC HEPATITIS C VIRUS INFECTION AND ANTIVIRAL TREATMENT ON COMPOSITE CARDIOVASCULAR DISEASE RISK: A NATIONWIDE COHORT STUDY

Min Kyung Park[1] Hwa Young Choi[2] Hyung Jun An[1] Chang Wook Park[1] Gwang Hyun Choi[1] Eun Sun Jang[1] Moran Ki[2] Kyung-Ah Kim[3] Sook-Hyang Jeong[1], [1]Department of Internal Medicine, Seoul National University Bundang Hospital, [2]Department of Cancer Control and Policy, National Cancer Center, [3]Department of Internal Medicine, Inje University Ilsan Paik Hospital

Background: Chronic hepatitis C virus (HCV) infection triggers systemic inflammation, potentially elevating cardiovascular risk. We evaluated the independent association between HCV infection and composite cardiovascular disease (CVD) risk, alongside the impact of antiviral treatment completion on this risk. **Methods:** Utilizing the South Korean National Health Insurance Service (NHIS) database, we analyzed 40,724 HCV patients and 610,860 age- and sex-matched controls (1:10 ratio). Individuals with prior liver transplantation, decompensated cirrhosis, or pre-existing CVD were excluded. The composite CVD outcome comprised ischemic heart disease, stroke, or peripheral artery disease. Multivariable Cox models and competing risk regressions adjusted for socio-economic status, lifestyle factors, and comorbidities. **Results:** The mean age was 46.0 ± 12.8 years in both groups. During follow-up, 30,348 patients developed composite CVD outcomes (incidence rate: 4.7 per 1,000 person-years). At baseline, the HCV group exhibited a higher prevalence of diabetes (17.6% vs. 13.1%, P < 0.001) and hypertension (24.2% vs. 20.1%, P < 0.001) than the control group. Despite these unfavorable baseline profiles, HCV infection remained an independent predictor of CVD. After adjusting for all covariates and accounting for competing risks of death, the HCV group showed a significantly higher composite CVD risk (adjusted hazard ratio [aHR], 1.17; 95% confidence interval [CI], 1.12–1.22). Within the HCV cohort (treatment completion rate: 33.4%), the risk was markedly lower among those who completed therapy; the untreated group carried a substantially higher CVD risk compared to the treated group (aHR, 1.67; 95% CI, 1.51–1.85). **Conclusion:** Chronic HCV infection is an independent risk factor for composite CVD in this nationwide cohort. Crucially, successful antiviral therapy significantly mitigates this risk, underscoring that HCV eradication confers systemic benefits extending well beyond hepatic outcomes and serving as a vital strategy for cardiovascular prevention.

Disclosures: Min Kyung Park:Nothing to Disclose, Hwa Young Choi:Nothing to Disclose, Hyung Jun An: Nothing to Disclose, Chang Wook Park:Nothing to Disclose, Gwang Hyun Choi:Nothing to Disclose, Eun Sun Jang:Nothing to Disclose, Moran Ki:Nothing to Disclose, Kyung-Ah Kim:Nothing to Disclose, Sook-Hyang Jeong:Nothing to Disclose.

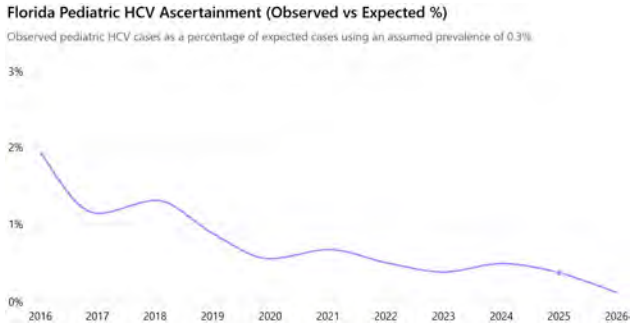
3269 | CASE ASCERTAINMENT RATES FOR CHILDREN INFECTED WITH HEPATITIS C IN FLORIDA: EPIDEMIOLOGIC EVIDENCE OVER ONE DECADE

Madison Machado[1] Palack Agrawal[2] Aymin Delgado-Borrego[3], [1]Kidz Medical Research Trainee from the University of Central Florida, [2]Ssm Cardinal Glennon Children's Hospital/ St. Louis University, [3]KIDZ Medical Multispecialty Group

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Background: Hepatitis C virus (HCV) infection remains the most common chronic bloodborne infection in the U.S. and a major cause of liver-related morbidity and mortality worldwide (*JAMA.* 2020;323:970-975). Despite effective curative therapies, HCV incidence in the U.S. increased 106% between 2015 and 2021 (*JAMA.* 2023;330:2200-2208). A prior epidemiologic survey demonstrated that only 12% of expected pediatric HCV cases in Florida and 4.9% nationwide were identified between 2000 - 2009 (*J Pediatr.* 2012;161:915-21). The objective of this study was to evaluate the current rate of pediatric HCV case ascertainment relative to the estimated number of actual cases. **Methods:** All HCV antibody-positive cases reported to the FL Department of Health among individuals aged 0–19 years between May 10, 2016 and May 9, 2026 were analyzed using the statewide MERLIN surveillance database which excludes duplicate reports. Pediatric cases were analyzed by year of diagnosis and age group. Florida population estimates per age group were obtained (Florida EDR and U.S. Census). Expected pediatric HCV cases were calculated using estimated pediatric prevalences of 0.3% based on published literature (*J Pediatr.* 2012;161:915–921; *Am J Gastroenterol.* 2021;116:2068–2078). The primary outcome was the percentage of expected cases identified within the surveillance system. (identified cases ÷ expected cases) × 100. **Results:** Between 2016 and 2026, a total of 1,198 pediatric chronic HCV cases were identified in Florida. Adolescents aged 15–19 years accounted for 949 cases (79.2%) of the entire pediatric cohort. In comparison, only 118 cases (9.8%) were identified among children aged 0–4 years, 70 cases (5.8%) among children aged 5–9 years, and 61 cases (5.1%) among children aged 10–14 years. Annual reported pediatric HCV cases declined from 267 in 2016 to 58 in 2025. Adolescents aged 15-19 years represented the largest age group, with cases decreasing from 222 to 35 over the same timeframe. Using an expected pediatric chronic HCV prevalence estimate of 0.3%, observed-to-expected (O/E) ratios remained low throughout the study period. Overall O/E ratios declined from 0.0192 (1.92%) in 2016 to 0.0038 (0.38%) in 2025. **Conclusion:** Pediatric HCV case identification in Florida, despite one of the nation's strongest surveillance systems, has declined precipitously which likely reflects a national trend. Pediatric case ascertainment in Florida decreased from 12% of expected cases in 2000–2009 to 1.92%–0.38% in 2016–2026 despite curative therapies and universal screening recommendations, highlighting an urgent public health gap.Urgent strategies are needed for the implemenation of effective surveilance and linkage to care among pediatric patients at risk of HCV infection.



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3270 | RISK FACTORS FOR LIVER-RELATED OUTCOMES AFTER HEPATITIS C VIRUS TREATMENT WITH SUSTAINED VIROLOGICAL RESPONSE IN THE DIRECT-ACTING ANTIVIRAL ERA

Mai Sedki[1] Jennifer Price[1] Matthew Caliz[1] Rena Fox[1],
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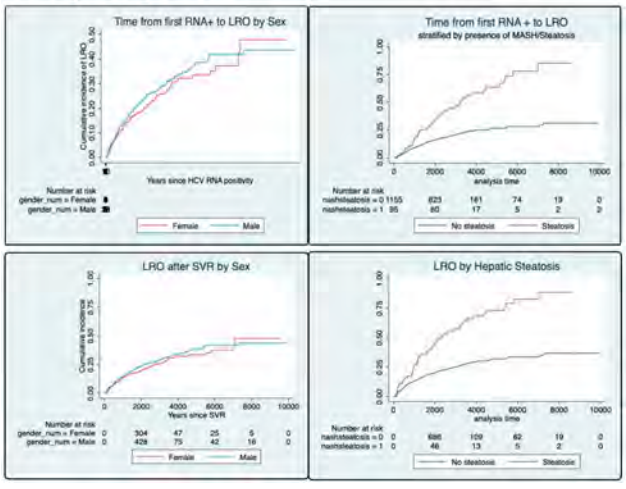
Background: Sustained virological response (SVR) after chronic hepatitis C virus (HCV) treatment reduces, but does not eliminate, the risk of liver-related outcomes (LRO), including hepatocellular carcinoma (HCC). As time into the direct-acting antiviral (DAA) era lengthens, predictors of post-SVR outcomes may be evolving. Although prior studies have identified independent risk factors for LRO after SVR, few have evaluated interactions among these factors in time-to-event analyses. **Methods:** We conducted a retrospective cohort study using electronic medical record data from a large urban medical center from 2016–2024. Adults with detectable HCV RNA at any time were included. SVR was defined as detectable HCV RNA followed by undetectable HCV RNA. LRO was defined by ICD codes for cirrhosis, HCC, or liver transplantation. The primary analysis evaluated time from first detectable HCV RNA to first LRO using Cox proportional hazards models. A secondary analysis evaluated time from SVR to LRO among patients achieving SVR. Models included sex, HbA1c, BMI, hepatic steatosis, and alcohol use disorder (AUD) with time-updated metabolic covariates. Interaction terms assessed effect modification by sex. Robust standard errors accounted for clustering. **Results:** Among 4,916 patients with detectable HCV RNA, 2,146 LRO events occurred over a median follow-up

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of 7.43 years. In the primary analysis, higher HbA1c was independently associated with increased LRO risk (hazard ratio [HR] 1.15 per 1% increase, 95% confidence interval [CI] 1.03–1.28, p = 0.01). Hepatic steatosis was also associated with increased risk (HR 1.72, p≈0.001). Sex, BMI, and AUD were not independently associated with LRO. No significant sex interactions were observed for HbA1c or BMI. Interactions between sex and hepatic steatosis (p = 0.06) and sex and alcohol abuse (p = 0.05) approached significance, although confidence intervals were wide. In the SVR-restricted analysis, higher HbA1c remained independently associated with increased LRO risk, whereas sex, BMI, and AUD were not associated with outcomes. No major violations of proportional hazards assumptions were identified. **Conclusion:** Metabolic health remains a major determinant of liver-related outcomes in patients with HCV, including after SVR. The persistent association between elevated HbA1c and LRO, together with the effect of hepatic steatosis, underscores the importance of routine metabolic risk assessment and management in patients with HCV both before and after cure. As many patients achieving SVR are transitioned out of specialty care, greater attention to long-term metabolic monitoring in primary care settings may be critical to reducing ongoing liver-related risk. Although definitive sex-based differences were not identified, potential interactions involving hepatic steatosis and alcohol use warrant further investigation.

Figure 1. Time-to-Liver-Related Outcomes from initial HCV RNA detection and from SVR, stratified by sex and hepatic steatosis



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3271 | IMPACT OF DEFAULT REFLEX HCV RNA TESTING ON TIMELY DIAGNOSTIC COMPLETION AND DOWNSTREAM CARE

Jacqueline Henson[1] Andrew Muir[1], [1]Duke University

Background: Incomplete confirmatory RNA testing after a positive hepatitis C virus (HCV) antibody test remains a critical gap in the HCV care cascade and a barrier to elimination efforts. We evaluated the impact of implementing default reflex HCV RNA testing on timely diagnostic completion and downstream care. **Methods:** We conducted a quasi-experimental pre-post study of patients with positive HCV antibody tests from January 2023 to December 2025 across a large academic health system. Default reflex RNA testing for positive antibody results was implemented in July 2024. The primary outcome was the proportion of patients with positive antibody testing without RNA testing within 90 days. Secondary analyses evaluated outcomes by care setting (emergency department [ED], inpatient, outpatient). Among patients with detectable HCV RNA and ≥6 months of follow-up, we assessed hepatology or infectious disease clinic visits and HCV treatment initiation within 6 months of positive antibody test. **Results:** Among 3,599 patients with positive antibody tests, the proportion without RNA testing within 90 days decreased from 14.9% pre-intervention (254/1,699) to 2.2% post-intervention (41/1,900) (p < 0.001). This corresponded to a reduction in the median number of patients per quarter without RNA testing from 42 (IQR 39-47) to 6 (IQR 4-11), with sustained improvement over 12 months (**Figure**). Reductions were observed across care settings and were most pronounced in the ED (61.9% vs 9.1%), followed by inpatient (14.6% vs 2.4%) and outpatient settings (13.4% vs. 1.7%). Among patients with detectable HCV RNA and ≥6 months follow-up (n = 872; 444 pre, 428 post), the proportion with a hepatology or infectious diseases clinic visit (27.3% vs. 27.6%) or treatment initiation within 6 months (29.0% vs. 30.7%) was similar pre- and post-intervention. **Conclusion:** Default reflex HCV RNA testing was associated with a large, sustained improvement in timely diagnostic completion across care settings, particularly in the ED. However, improved diagnostic completion did not translate into improved specialty linkage or treatment initiation, highlighting persistent downstream barriers in the HCV care cascade.

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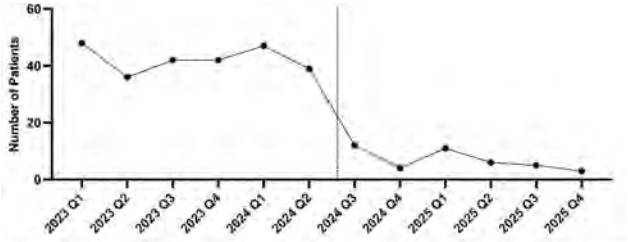


Figure. Number of patients per quarter with positive HCV antibody tests without subsequent RNA testing within 90 days. Default reflex testing was implemented in July 2024 (dashed line).

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3272 | UNIVERSAL INTEGRATED HBV AND HCV SCREENING IN PRIMARY CARE REVEALS A SUBSTANTIAL HIDDEN BURDEN AND ACHIEVES EXCELLENT LINKAGE TO CARE: A WHO-ALIGNED DECENTRALIZED MODEL

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Background: Risk-based screening for hepatitis B virus (HBV) and hepatitis C virus (HCV) misses many infected individuals, particularly those without recognized risk factors or elevated liver enzymes. Decentralized screening integrated into primary care may improve diagnosis and linkage to treatment. We evaluated the feasibility and effectiveness of a universal HBV/HCV screening program embedded in routine primary care and linked to hepatology referral pathways. **Methods:** We conducted a prospective interventional study including adults attending a primary care center for routine blood testing between February 2023 and February 2025. Universal screening for HBsAg and anti-HCV was incorporated into standard laboratory panels. Positive serologies automatically triggered reflex HBV-DNA and HCV-RNA testing. Liver fibrosis was assessed using non-invasive markers (FIB-4 and APRI), and participants completed a structured risk factor questionnaire. Positive cases were referred directly to hepatology through an integrated electronic pathway designed to facilitate rapid linkage to care. **Results:** A total of 3,103 individuals were screened; 41% were male, mean age was 51 years, 69% were Caucasian, and 64% were born in Spain.Anti-HCV prevalence was 2%, while active HCV infection (HCV-RNA positive) was identified in 0.35% of participants. Among viremic individuals, 82% were successfully linked to hepatology care and initiated antiviral therapy. HBsAg prevalence was 0.8%, and 92% of newly identified or previously unlinked HBV-positive individuals were connected to specialist care. Among patients evaluated by hepatologists, 25% initiated HBV treatment. Non-invasive fibrosis assessment identified advanced fibrosis in two anti-HCV-positive patients (FIB-4 >3.25 and APRI >1.5), highlighting the potential clinical impact of missed diagnoses.In multivariable analysis, recognized risk factors (OR 2.52, $p<0.001$) and elevated ALT levels (OR 1.007, $p=0.002$) were independently associated with anti-HCV positivity. Elevated ALT was also associated with detectable HCV-RNA (OR 1.007, $p=0.015$). No significant predictors were identified for HBsAg positivity.Importantly, 45% of individuals with active HCV infection and 44% of HBsAg-positive patients had neither recognized risk factors nor elevated ALT levels and therefore would likely have remained undiagnosed under current risk-based screening approaches. **Conclusion:** Universal HBV/HCV screening integrated into primary care identified a substantial hidden burden of viral hepatitis missed by conventional risk-based approaches. Reflex testing and automated referral pathways achieved high linkage-to-care and treatment rates, supporting universal primary care-based screening as a pragmatic strategy to advance viral hepatitis elimination goals.

Disclosures: Imma Valls figueras:Nothing to Disclose, Maria Santos:Nothing to Disclose, Montse Mullol: Nothing to Disclose, ARIADNA RANDO-SEGURA: Nothing to Disclose, Elena Vargas-Accarino:Nothing to Disclose, Maria Buti:Roche Pharma/Diagnostics: Consultant, Gilead Sciences: Consultant, GSK: Consultant, Abbvie: Consultant, Janssen: Consultant, Roche Pharma/Diagnostics: Speaking and Teaching, Gilead Sciences: Speaking and Teaching, GSK: Speaking and Teaching, Abbvie: Speaking and Teaching, Janssen: Speaking and Teaching, Bepirovirsen – GSK: Referral to unlabelled/unapproved products.

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3273 | IMPACT OF CARDIOMETABOLIC RISK ON RESIDUAL HCC RISK AFTER HCV CURE DIFFERS BY HEPATIC STEATOSIS STATUS: A REAL-C STUDY

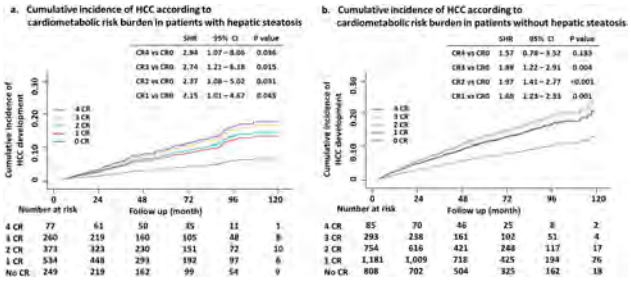
Haruki Uojima[1] Hidenori Toyoda[2] Rui Huang[3] Takanori Suzuki[4] Chung-Feng Huang[5] Eiichi Ogawa[6] Dae Won Jun[7] Akito Nozaki[8] Manabu Morimoto[8] Treta Purohit[9] Huy Trinh[10] Takashi Honda[11] Cheng-Hao Tseng[12] Yao-Chun Hsu[13] Masanori Atsukawa[14] Tsunamasa Watanabe[15] Hiroshi Abe[16] Fanpu Ji[17] Carmen Preda[18] Masaru Enomoto[19] Philip Vutien[20] Toru Ishikawa[21] Carla Lam[22] Koichi i Takaguch[23] Hiroaki Haga[24] Norio Itokawa[14] Motoyuki Kohjima[25] Hideyuki Nomura[26] Eiji Kajiwara[27] Koichi Azuma[28] Kazufumi Dohmen[29] Akira Kawano[30] Toshimasa Koyanagi[31] Aritsune Ooho[32] Takeaki Satoh[33] Kazuhiro Takahashi[34] Eileen Yoon[35] Sang Bong Ahn[36] Do Seon Song[37] Hyun Jin Cho[38] Jang Han Jeong[39] Seung Ha Bak[40] Satoshi Yasuda[41] Yunyu Zhao[17] Yishan Liu[17] Ritsuzo Kozuka[42] Mayumi Maeda[43] Yoshiyuki Ueno[24] Wan Long Chuang[44] Jee-Fu Huang[44] Chia-Yen Dai[44] Ramsey Cheung[45] Ming-Lun Yeh[46] Pei-Chien Tsai[44] Man-Fung Yuen[47] Norihiro Furusyo[48] Chao Wu[49] Jun Hayashi[50] Ming-Lung Yu[51] Yasuhito Tanaka[1] Mindie Nguyen[43], [1]Kumamoto University, [2]Department of Gastroenterology, Ogaki Municipal Hospital, Gifu, Japan, [3]Nanjing Drum Tower Hospital, [4]Nagoya City University Graduate School of Medical Sciences, [5]Kaohsiung Medical University Hospital, [6]Kyushu University Hospital, [7]Hanyang University, [8]Yokohama City University Medical Center, [9]San Jose Gastroenterology, [10]Gastroenterology & Hepatology, [11]Nagoya University Graduate School of Medicine, [12]E-Da Cancer Hospital/I-Shou University, [13]E-Da Hospital/I-Shou University, [14]Division of Gastroenterology and Hepatology, Nippon Medical School, [15]Division of Gastroenterology and Hepatology, St. Marianna University School of Medicine, [16]Division of Gastroenterology and Hepatology, Shinmatsudo Central General Hospital, [17]The Second Affiliated Hospital of Xi'an Jiaotong University, [18]Gastroenterology&Hepatology Department, Clinic Fundeni Institute, [19]Osaka Metropolitan University, [20]Division of Gastroenterology and Hepatology, University of Washington, [21]Department of Gastroenterology, Saiseikai Niigata Hospital, [22]Department of Medicine, The University of Hong Kong, [23]Department of Hepatology, Kagawa Prefectural Central Hospital, [24]Department of Gastroenterology, Yamagata University of Medicine, [25]Department of Gastroenterology, NHO Kyushu Medical Center, [26]Department of Internal Medicine, Haradoi Hospital, [27]Kajiwara Clinic, [28]Department of Hepatology, Kyushu Central Hospital, [29]Department of Internal Medicine, Chihaya Hospital, [30]Department of Hepatology, Kitakyushu Municipal Medical Center, [31]Department of Hepatology, Fukuoka City Hospital, [32]Department of Hepatology, Steel Memorial Yawata Hospital, [33]Center for Liver Disease, NHO Kokura Medical Center, [34]Department of Internal Medicine, Hamanomachi Hospital, [35]Department of Internal Medicine, Hanyang University, College of Medicine, [36]Department of Internal Medicine, Eulji University Seoul hospital, [37]The Catholic University of Korea, [38]Departments of Internal Medicine, Gyeongsang National University Hospital, [39]Departments of Internal Medicine, Hallym University Dongtan Scared Heart Medical center, [40]Departments of Internal Medicine, Inje University Haeundae Paik Hospital, [41]Ogaki Municipal Hospital, [42]Graduate School of Medicine Department of Clinical Medical Science, Osaka Metropolitan Universit, [43]Stanford University Medical Center, [44]Kaohsiung Medical University Hospital, Kaohsiung Medical University, [45]Division of Gastroenterology and Hepatology, Veterans Affairs Palo Alto Health Care System, [46]Kaohsiung Medical University, [47]The University of Hong Kong, [48]Taihaku Avenue Clinic, [49]Affiliated Hospital of Medical School, Nanjing Universit, [50]Kyushu University, [51]Kaohsiung Medical University/ Kaohsiung Medical University Hospital

Background: Cardiometabolic risk (CMR) is increasingly recognized as a contributor to hepatocarcinogenesis after HCV cure. However, hepatic steatosis may diminish with aging and fibrosis progression, potentially modifying the association between cardiometabolic risk and HCC risk after HCV cure. We aimed to evaluate the impact of CMR on residual HCC risk according to HS status after HCV cure. **Methods:** We conducted a multinational retrospective cohort study using data from the REAL-C consortium, including 4,614 patients with HCV infection who achieved HCV cure (sustained virologic response, SVR) following direct-acting antiviral therapy across 23 centers in six countries/regions. Patients were stratified according to the presence or absence of hepatic steatosis at baseline. CMR burden was defined according to the number of CMR factors, including obesity, diabetes mellitus, dyslipidemia, and hypertension. The primary endpoint was incident HCC after SVR, evaluated according to CMR burden stratified by the presence of hepatic steatosis. Fine–Gray competing-risk regression models were applied, with non-HCC death treated as a competing event. **Results:** This study evaluated 4,614 patients with HCV cure, including 1,493 patients with hepatic steatosis and 3,121 patients without hepatic steatosis. Patients with hepatic steatosis were younger and exhibited lower fibrosis burden. During follow-up, HCC occurred in 108 patients with hepatic steatosis and 326 patients without hepatic steatosis

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(P < 0.001). In patients with hepatic steatosis, cumulative HCC incidence demonstrated a graded increase according to increasing CMR burden, with progressively higher subdistribution hazard ratios across risk categories (Figure 1a). In contrast, among patients without hepatic steatosis, although CMR burden was also associated with HCC risk, the incremental increase in cumulative HCC incidence across categories appeared less distinct (Figure 1b). In multivariable analysis, increasing CMR burden remained independently associated with HCC development in patients with hepatic steatosis (adjusted SHR 2.42, 95% CI 1.03–5.67, P = 0.038), together with cirrhosis (adjusted SHR 3.61, 95% CI 2.18–5.98, P < 0.001). In contrast, among patients without hepatic steatosis, the association between CMR burden and HCC risk was attenuated after adjustment (adjusted SHR 1.37, 95% CI 0.97–1.94, P = 0.073), whereas cirrhosis remained the predominant determinant of HCC development (adjusted SHR 3.93, 95% CI 2.91–5.31, P < 0.001). **Conclusion:** The impact of CMR on residual HCC risk after HCV cure differed according to hepatic steatosis status. A graded increase in HCC risk with increasing CMR burden was observed in patients with hepatic steatosis, but not among those without hepatic steatosis.



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BioSciences: consultancy, Ausperbio: consultancy, IntergerBio: consultancy, Tune Therapeutics: consultancy, Clear B Therapeutics, GSK, Immuncore, Janssen, Vir Biotechnology: Speaking and Teaching, Norihiro Furusyo:Nothing to Disclose, Chao Wu:Nothing to Disclose, Jun Hayashi:Nothing to Disclose, Ming-Lung Yu:Abbvie, Gilead and Roche diagnostics. Grant/Research Support, Abbott, Abbvie, Gilead, Roche and Roche diagnostics: Consultant, Abbvie, BMS, Gilead, Roche and Roche diagnostics: Speaking and Teaching, Yasuhito Tanaka:Nothing to Disclose, Mindie Nguyen: Pfizer, Astra Zeneca, Aligos, GSK, Delfi, Innogen, Exact Sci: Grant/Research Support, GSK: Advisor.

3274 | A CASE SERIES ON OUTCOMES OF HEPATITIS C INFECTED PATIENTS WHO RECEIVED FULL COURSE OF 84 TABLETS OF SOFOSBUVIR/ VELPATASVIR AT THE BEGINNING OF THERAPY

Farrah Black[1] Stacey Scherbakovsky[1] Amy Seale[2], [1]Gilead Sciences, [2]Gastro Group

Background: There are limited data around prescribing and dispensing 84 tablets of SOF/VEL at the onset of treatment. A phase 4, open-label, single-arm trial (MINMON) was published evaluating the safety and efficacy of prescribing and dispensing all 84 tablets at the onset of treatment with no scheduled in person follow-up visits. The study included 399 patients and resulted in an overall 95% sustained virologic response rate (SVR) with no treatment related serious adverse events and no treatment discontinuations.(1) Despite these findings, the standard of care continues to rely on monthly prescription refills and frequent in-person follow-up visits. This approach is not patient-centered and poses significant barriers to access, particularly for individuals in rural settings. This case series addresses this by providing data on dispensing all 84 tablets at once with minimal monitoring during therapy. **Methods:** This case series includes patients from a single center in rural Louisiana. A retrospective chart review was conducted from January 1, 2022, through March 1, 2025. Patients with an HCV viral load (VL) who were then prescribed 84 tablets of SOF/VEL were included. Data collected included: age, sex, genotype, HBV and/or HIV co-infection, housing stability, history of and/or active IV drug use, specific medications, follow-up contact at treatment completion week 12 and 12 weeks post treatment, reported adverse events, self-reported adherence and SVR (drawn between 4-24 weeks post treatment). **Results:** 55 patients were included in the analysis. The mean age was 49.5 years (range 25-78), and 42% were female. The SVR12 per-protocol analysis was 100%, and the intention to treat analysis was 78.8%. 43 patients achieved SVR and 12 patients were lost to follow up and did not have SVR labs drawn. 41 patients had a history of IV drug use and 3 were actively using. 14 patients were on Medication Assisted Treatment: 11 buprenorphine, 1 methadone and 2 naltrexone. There were no reported treatment discontinuations. **Conclusion:** This case series of 55 patients in the real world support the implementation of the updated simplified treatment algorithm recommended by AASLD and demonstrates patients can be safely and effectively treated and cured with 84 tablets dispensation and minimal monitoring.

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3275 | TRACKING OF HCV VIREMIA RATES IN VANCOUVER, CANADA'S INNER-CITY REVEALS CONSISTENT AND SUSTAINED DECREASES OVER TIME

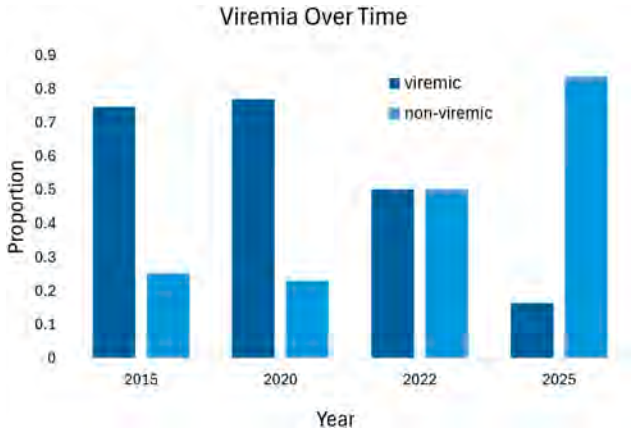
Christina Wiesmann[1] Shana Yi[2] David Truong[2] Brian Conway[2], [1]Simon Fraser University, [2]Vancouver Infectious Diseases Centre

Background: Vancouver, Canada's downtown east side (DTES) neighbourhood is known for high rates of poverty, drug use, and Hepatitis C (HCV) infection, with up to 40% of individuals having HCV exposure. The Vancouver Infectious Diseases (VIDC) has been providing accessible point-of-care HCV testing and treatment (as allowed by treatment restrictions), to individuals living in this neighborhood for more than 10 years. **Methods:** VIDC has provided and continues to provide regular point-of-care antibody testing, follow-up confirmation of viremia, and HCV treatment to individuals encountered at various inner-city locations including community centers, shelters, and single room occupancy buildings for more than 10 years. In addition, the physicians at the clinic receive a large number of referrals for providing HCV treatment to individuals who are part of Vancouver's inner-city population. **Results:** The proportion of individuals tested who are positive for HCV antibodies each year from 2015 to 2025 revealed no clear differences or trends, with similar rates of antibody positivity across all 10 years. In 2015, more than 70% of individuals we encountered at our

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community pop-up clinics were viremic for HCV. In 2020, the proportion of viremic individuals encountered was similar (~70%); however, in 2022 the proportion was reduced to around 50% and in 2025 the proportion was less than 20% (Figure 1). From 2015 until 2018 (inclusive), VIDC treated an average of 20-40 individuals actively using drugs per year. From 2019 until 2024, this number increased to around 100 individuals or more per year, and in 2025 was around 40 individuals. **Conclusion:** Through universal access to highly effective curative DAA treatments and high rates of treatment, we are well on our way to achieving HCV elimination in Vancouver's DTES neighbourhood. Follow-up work will determine if the rates of antibody positivity and viremia continue to decrease in the population over time. This work will ultimately help to inform and provide evidence-based support for micro-elimination efforts in similar communities around the world.



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3276 | AN INNOVATIVE MULTICENTER COLLABORATIVE RE-LINK MODEL SIGNIFICANTLY IMPROVES RE-ENGAGEMENT AND TREATMENT IN DIAGNOSED BUT UNTREATED CHRONIC HEPATITIS C PATIENTS

Aiqi Lu[1] Jinfeng Liu[2] Guangda Tang[3] Yuqian Du[1] Shuxin Mo[1] Zhijiao Xiong[4] Mingya Xiao[5] Wenli Li[5] Long Xu[6] Runqi Luo[6] Hong Li[7] Lingjie Wu[7] Fengdi Chen[8] Xi He[8] Simin Lai[9] Xiaocong Wu[10] Zeng Pang[10] Jianping Li[1] Yinjiao Cai[3] Honglian Bai[2] Yujuan Guan[11], [1]Guangzhou Eighth People's Hospital , Guangzhou Medical University, [2]The First People's Hospital of Foshan, [3]Luoding People's Hospital, [4]Guangdong North Second People's Hospital, [5]Guangdong Second Provincial General Hospital, [6]The Second Affiliated Hospital of Guangzhou Medical University, [7]Shantou Central Hospital, [8]Qingyuan People's Hospital, [9]The Fourth Affiliated Hospital of Guangzhou Medical University, [10]Central People's Hospital of Zhanjiang, [11]Guangzhou Eighth People's Hospital, Guangzhou Medical Univ.

Background: Chronic hepatitis C patients who are diagnosed but untreated (DBU) frequently fail to re-engage in care, representing a major barrier to hepatitis C virus (HCV) elimination. We developed a multicenter, cross-regional re-link (re-engagement to care) model led by a specialized hospital and evaluated its effectiveness and determinants of successful re-link. **Methods:** We conducted a prospective multicenter interventional study in Guangdong Province, China. From 2022 to 2023, 24,664 HCV RNA–positive patients without records of direct-acting antiviral (DAA) therapy were identified through the Center for Disease Control and Prevention surveillance system in Guangdong. Adult DBU patients ($\geq$18 years) were eligible; exclusions included invalid contact information or death prior to outreach. Dedicated hepatitis C re-link teams across 10 hospitals in 7 cities implemented standardized telephone outreach. The teams are responsible for the hepatitis C patient re-link program in partial areas of Guangdong Province.The primary outcome was the re-link rate, defined as the proportion of successfully contacted patients who returned to hospital for follow-up. Secondary outcomes included DAA treatment initiation among re-linked patients and independent predictors of re-link success, assessed by multivariable logistic regression. HCV knowledge was measured using a structured questionnaire (score 0–8; $\geq$6 defined as high knowledge). **Results:** Among 5,254 eligible patients, 3,343 (63.6%) were successfully contacted. Of those contacted, 2,052 returned for follow-up, yielding a re-link rate of 61.4%, substantially higher than the historical baseline (<20%). Among re-linked patients, 2,027 completed questionnaires (98.8%). The mean age was 51.6 ± 12.4 years; 27.0% were $\geq$60 years, 62.8% were male, 20.8% had at least a college education, 44.7% had urban employee medical insurance, and 60.2% demonstrated high HCV knowledge. Higher education, urban employee insurance, and high HCV knowledge were independently associated with successful re-link (all $P < 0.001$), whereas age $\geq$60 years, perceived absence of symptoms or treatment need, and concerns about treatment cost were associated with unsuccessful re-link (all $P < 0.01$). Among re-linked patients, 1,691 initiated DAA therapy (treatment initiation rate 82.4%). Re-link and treatment rates were comparable across different city tiers (table 1). **Conclusion:** This multicenter collaborative re-link model substantially improved re-engagement of DBU hepatitis C patients, achieving a 61.4% re-link rate and high treatment rate (>80%) across diverse hospital settings. The establishment of a dedicated, well-trained re-link team operating under a clear and standardized process was central to its

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success. This scalable model provides a practical strategy to strengthen linkage to care and supports progress toward HCV elimination.

Table 1. City Tier–Stratified Analysis of Re-link Outcomes Among DBU Hepatitis C Patients

Distribution of Medical Institutions by City Tier	Number of centers	Patients eligible for re-link	Patients successfully contacted by phone	Patients who returned for follow-up	Re-link rate (%)	Difference from overall mean (%)	Patients initiating treatment	Treatment rate (%)	Difference from overall mean (%)
First-tier / New first-tier cities	5	3058	1832	1155	63.0	+1.6	923	79.9	-2.5
Third-tier / Fourth-tier cities	4	1676	1120	629	56.2	-5.2	539	85.7	+3.3
County-level cities	1	520	391	268	68.5	+7.1	229	85.4	+3.0
Total	10	5254	3343	2052	61.4	NA	1691	82.4	NA

Note: City tiers were defined according to the "2023 City Business Attractiveness Ranking" by the Yicai (First Financial) New First-tier Cities Research Institute. First-tier/New first-tier city centers include Guangzhou Eighth People's Hospital Guangzhou Medical University, The Fourth Affiliated Hospital of Guangzhou Medical University, The Second Affiliated Hospital of Guangzhou Medical University, Guangdong Second Provincial General Hospital, and The First People's Hospital of Foshan; third-/fourth-tier city centers include Shaoxing Central Hospital, Central People's Hospital of Zhanjiang, Guangdong North Second People's Hospital, and Qingyuan People's Hospital; the county-level city center is Laoding People's Hospital.

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3277 | EVALUATING EHR-BASED PATIENT IDENTIFICATION STRATEGIES FOR HEPATITIS C LINKAGE TO CARE IN NORTH CAROLINA

Lauryn Ursery[1] Corinne Spencer[2], [1]Gillings School of Global Public Health, University of North Carolina, Chapel Hill, USA, [2]School of Medicine, University of North Carolina, Chapel Hill, USA

Background: Hepatitis C (HCV) remains a leading contributor to liver cancer and liver disease in the United States. Creating accurate registries of diagnosed but untreated (DBU) patients is vital for hepatitis elimination, but methods used to generate registries vary in effectiveness, cost, and time. To evaluate the effectiveness of new tools, we compared three methods to generate registries of DBU HCV-positive individuals. **Methods:** We utilized three patient extraction methods to generate registries of DBU HCV-positive individuals living in North Carolina between May 1, 2024 and May 7, 2025. First, we used EPIC's SlicerDicer, a self-service reporting tool, to identify HCV-positive individuals. We excluded individuals with visits to infectious diseases (ID) or gastroenterology (GI) specialists, with this criterion intended to serve as a proxy for excluding those who were likely to have already received HCV care. The second approach involved partnering with a programmer from UNC's Perinatal Research Service Center (PRSC), who queried patient data to identify HCV-positive individuals and include indicators for whether patients had already seen a specialist or been prescribed HCV medications. Finally, we used SideKick, an AI tool embedded into EPIC, to identify HCV-positive individuals while excluding those who had seen a specialist or were prescribed HCV medication. All data were collected in REDCap and aggregate statistics were computed in R. **Results:** The SlicerDicer registry identified 724 HCV-positive individuals. After screening out patients who were deceased (n = 61), did not live in North Carolina (n = 19), or did not have true HCV RNA+ test results (n = 24), 624 individuals remained. The majority (63.9%, n = 399) of these individuals were confirmed to be DBU via chart review, while 36.1% (n = 225) were found to have already been linked to care (Table 1). Approximately 66.7% of those previously linked received hepatitis care via a GI or ID specialist, while one quarter (25.1%) received care via a generalist. The PRSC registry identified 1,236 HCV-positive individuals, almost half (51.1%, n = 632) of whom also appeared in the SlicerDicer registry. Among the 605 individuals captured by both registries and eligible for chart review, 64.0% (n = 389) were confirmed to be DBU (Table 1). The EPIC SideKick AI tool identified 508 DBU HCV patients, 71.1% (n = 361) of whom were also captured in the SlicerDicer registry. Among the 336 individuals appearing in both registries and eligible for chart review, 65.8% (n = 221) were confirmed to be DBU (Table 1). **Conclusion:** Each patient registry method showed flaws in identifying DBU individuals. Using visits with specialists as a proxy for HCV care failed to capture the growing number of patients receiving treatment through generalists. New AI-based tools show promise, but refining search criteria to reflect how HCV care is delivered is essential to building accurate DBU registries.

Table 1. Comparison of Search Criteria and Effectiveness Across Three Generation Methods for HCV Patient Registries.

Search Criteria	Slicer Dicer	Programmer-Defined Query	SideKick
HCV RNA Positivity	√	√	√
Excluded Patients with ID/GI Visits	√	√	√
Excluded Patients with HCV Treatment Prescription	–	√	√
Effectiveness	*N* (%)	*N* (%)	*N* (%)
Total Identified	724	1,236	508
Overlap with Slicer Dicer	–	632 (51.1)	361 (71.1)
Number eligible for chart review[a]	624 (86.2)	608 (49.2)	336 (66.1)
Confirmed DBU by chart review[b]	399 (63.9)	389 (64.0)	221 (65.8)
Chart review showed ID visit[c]	50 (8.01)	49 (8.10)	27 (8.04)
Chart review showed GI visit[c]	100 (16.0)	93 (16.1)	48 (14.2)
Chart review showed generalist visit[c]	57 (9.13)	56 (9.21)	31 (9.22)

[a] Eligibility for chart review was defined as individuals who were alive, resided in North Carolina, had a positive HCV RNA test result.
[b] Confirmed DBU by chart review was defined as patients who had not already received HCV treatment per manual review of their electronic health records.
[c] Chart review showed ID/GI/generalist visit was defined as individuals who were found to have already been connected to HCV care via an ID or GI specialist or generalist, respectively, via manual review of their electronic health records.

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3278 | INCENTIVIZING ADHERENCE TO IMPROVE OUTCOMES IN A HEPATITIS C VIRUS (HCV) TREATMENT TRIAL: RESULTS FROM THE KENTUCKY VIRAL HEPATITIS TREATMENT (KEY TREAT) STUDY

Jennifer Havens[1] Takako Schaninger[2] Michelle Lofwall[1] Sharon Walsh[1], [1]University of Kentucky College of Medicine, [2]University of Kentucky

Background: As we march towards worldwide elimination of the hepatitis C virus (HCV), critical gaps still exist in treatment access for those at greatest risk for HCV transmission; namely those who use and inject drugs. The purpose of this analysis is to examine the role of incentives to improve adherence to direct acting antiviral (DAA) treatment and HCV cure among rural HCV+ individuals with a history of drug use. **Methods:** KeY Treat was conducted between 2019-2025 in Appalachian Kentucky, enrolling 380 rural residents. Point-of-care (POC) RNA testing was conducted with most RNA-positive participants initiating same day treatment with sofosbuvir/velpatasvir (sof/vel). Incentivized daily medication reminders (tailored to the individuals' chosen time) were provided via text or Facebook (for those without a phone/stable phone number). A response to daily reminders (any acknowledgement was considered a response – text, emojis, pictures) earned participants $1, and they could earn up to $84 for responding to each daily reminder during the treatment regimen. Sustained virologic response was established using POC RNA testing at least 12-weeks after treatment completion (SVR-12). Generalized linear modeling was used to estimate the impact of medication reminders on SVR-12. **Results:** Most participants preferred SMS reminders (53.9%), followed by Facebook (33.7%). The median proportion of response to reminders, calculated as the total number of responses divided by 84 days, was 74.4% (interquartile range: 42.3%, 92.8%). Response rates were significantly lower among people who continued to inject drugs (54.3% vs. 71.7%, $p < 0.001$), men, and those reporting unstable housing. Intent-to-treat analyses revealed that for each additional percentage point increase in incentive response rate, the odds of SVR-12 increased by 1.22 (95% confidence interval [CI]: 1.02, 1.48). **Conclusion:** Incentivizing adherence to DAAs using medication reminders shows promise in improving cure rates. Compared to the significant costs associated with not treating and/or not achieving SVR due to suboptimal adherence, incentivizing at $1/day is likely highly cost-effective, with or without insurance reimbursement. Limitations of the study include greater likelihood that response to reminders was a proxy for greater overall stability and that response was not a guarantee that participants took the medication. Even with these potential limitations, results from this study indicate that minimal investment via incentivized medication reminders may improve treatment outcomes.

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3279 | INCIDENCE AND PREVALENCE OF DECOMPENSATED CIRRHOSIS AMONG PATIENTS WITH HEPATITIS C VIRUS INFECTION: POOLED ESTIMATES ACROSS US CLAIMS DATABASES, 2011 TO 2023

Patrick Horne[1] Kevin Leyden[2] Joseph Guilfoyle[3] Julie Zhao[3] Lisa Johnson[3] Anthony Martinez[4], [1]University of Florida, [2]NJCRI (North Jersey Community Research Initiative), [3]AbbVie Inc, [4]University at Buffalo Jacobs School of Medicine

Background: Decompensated cirrhosis is a serious complication in adults with chronic hepatitis C virus (HCV) infection, leading to increased morbidity and health care utilization. There is limited data on incidence and prevalence of HCV-related decompensated cirrhosis in the United States. This study aimed to estimate annual incidence and prevalence of HCV-associated decompensated cirrhosis in insured US populations with HCV, but without other chronic liver disease. **Methods:** MarketScan commercial, Medicare, and Medicaid claim databases were analyzed for adults aged 18 years or older with at least one claims diagnosis of chronic HCV (ICD-9: 070.44, 070.54, V02.62; ICD-10: B18.2) from 2011 to 2023. Individuals with hepatitis B, metabolic dysfunction-associated steatotic liver disease (MASLD), metabolic dysfunction-associated steatohepatitis (MASH), alcohol-associated liver disease, autoimmune or drug-induced hepatitis, hepatocellular carcinoma, or liver transplantation were excluded. Decompensated cirrhosis was identified using validated diagnosis algorithms based on clinical complications such as variceal bleeding,

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hepatic encephalopathy, ascites, or jaundice.[1] Annual incidence rates were calculated for 2011–2023 in patients with ≥1 year continuous prior enrollment. Prevalence was calculated for 2020–2023, accruing cases from 2018 onward. All rates were age- and sex-standardized to the 2020 US census population. **Results:** Overall, 616,137 patients with HCV and without other diseases were included, of whom 19,125 had decompensated cirrhosis and >1 year enrollment prior to index. Annual incidence rates of HCV-associated decompensated cirrhosis in adults ranged from 0.7% to 1.3% during 2011–2023. Incidence has decreased by 44% from its peak in 2016 to 2023. Annual prevalence of HCV-related decompensated cirrhosis ranged from 2.5% to 2.9% for 2020–2023. Stratified analyses showed higher incidence and prevalence among older age groups (over 4% for age 75 and older) and among males compared to females. Prevalence was elevated in Medicare and Medicaid populations versus commercial insurance ranging from 1.3-2.8%, 1.7-3.0%, and 0.9-2.1% respectively. **Conclusion:** HCV-related decompensated cirrhosis prevalence among insured US adults has remained stable over eight years. These findings highlight the ongoing need for targeted interventions, particularly for at-risk populations such as older adults, males, and those covered by Medicare or Medicaid, as well as the necessity for further research into uninsured groups to fully understand the national impact.Reference: 1. Lapointe-Shaw L, et al. *PLoS ONE* 2018; 13 (8): e0201120. Published 2018 Aug 22.

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3280 | EVALUATING DETECTION AND OUTCOMES BEFORE AND AFTER UNIVERSAL HEPATITIS C SCREENING IN PREGNANCY RECOMMENDATION

Priyanka Gaur[1] Daniel Chang[2] Suzy Newton[2] Keira Hall[2] Talia Pindyck[2] Lindsey Sizemore[2] Kate Woodworth[2] Jason Hsi[2] Lorraine Yeung[2] Moeun Son[1] Van Tong[2], [1]Weill Cornell Medicine, [2]Centers for Disease Control and Prevention

Background: To evaluate detection and outcomes among women with preconception and prenatal hepatitis C virus (HCV) infection before and after universal HCV screening recommendation in 2020, using the U.S. Centers for Disease Control and Prevention (CDC) Surveillance for Emerging Threats to Mothers and Babies Network (SET-NET). **Methods:** Pregnancies among women with a laboratory-confirmed HCV infection during or up to 1 year prior to pregnancy ("in pregnancy") with a singleton, live birth between 2018-2023 were reported from Massachusetts, New York City, New York State, Los Angeles County, Pennsylvania, Tennessee, and Washington. We calculated rates of HCV detection in pregnancy per 100,000 live births and examined outcomes pre- (January 2018-December 2019) and post-implementation (July 2020-December 2023) of the universal screening recommendation. January-June 2020 was a washout period for the COVID-19 pandemic peak and guideline dissemination. HCV rates and obstetric outcomes were compared using t-tests or chi-square tests. **Results:** 3,694 pregnancies were included: 1,446 pre-implementation, 1,896 post-implementation, and 352 in the washout period. HCV detection increased from 172.6 to 210.0 cases per 100,000 live births post-implementation (i.e., approximately 37 additionally detected HCV-affected pregnancies per 100,000 births) ($p < 0.001$). Post-implementation, there was a shift toward earlier detection of HCV in the first trimester ($p = 0.001$, Table 1). There were similar proportions of cesarean and breastfeeding. Only 4.3% and 5.8% of women had a prior history of HCV treatment pre- and post-implementation, respectively ($p = 0.16$). **Conclusion:** These preliminary findings suggest a modest increase in the HCV detection rate and earlier detection of HCV in pregnancy after the universal screening recommendation. Aligned with no contraindications to vaginal delivery or breastfeeding related to HCV, there are no observed changes in cesarean or breastfeeding frequency. There are opportunities for antiviral treatment to attain HCV elimination goals, particularly for women who do not breastfeed and may be considered for expedited antiviral treatment.

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Table 1. Characteristics and outcomes in pregnancies among pregnancies with HCV identified prior to or in pregnancy pre- and post-implementation of universal HCV screening recommendation in 2020, SET-NET

	Pre-recommendation Jan 2018-Dec 2019 N = 1446 (%)	Post-recommendation July 2020-Dec 2023 N = 1896 (%)	P-value †
Characteristics			
Maternal age, mean (SD)	28.5 (4.9)	29.8 (5.1)	**< 0.001**
Any substance use during pregnancy	**N=1174**	**N=1718**	
Yes	954 (81.3)	1414 (82.5)	0.4
No	220 (18.7)	300 (17.5)	
Missing	*272*	*182*	
Polysubstance	**N=973**	**N=1412**	0.8
Yes	656 (67.4)	945 (66.9)	
No	317 (32.6)	467 (33.1)	
Missing	*473*	*484*	
Prescription opioids	**N=1172**	**N=1710**	0.144
Yes	80 (6.8)	125 (7.3)	
Illicit opioids	**N=1172**	**N=1705**	
Yes	464 (39.6)	628 (36.8)	0.67
Alcohol	**N=977**	**N=1560**	
Yes	97 (9.9)	147 (9.4)	0.74
Medication for opioid use disorder	**N=1174**	**N=1715**	**0.01**
Yes	641 (45.4)	854 (50.2)	
No	533 (54.6)	861 (49.8)	
Missing	*272*	*187*	
Trimester of prenatal care initiation	**N=933**	**N=1488**	**< 0.001**
Trimester 1 (< 14 weeks)	544 (58.3)	734 (49.3)	
Trimester 2 (14-28 weeks)	240 (25.7)	444 (29.8)	
Trimester 3 (>28 weeks)	92 (9.9)	170 (11.4)	
No care reported	57 (6.1)	140 (9.4)	
Missing/Not reported	*513*	*408*	
Timing of 1st detection of HCV RNA	**N=1429**	**N=1857**	**< 0.001**
Preconception	324 (22.7)	405 (21.8)	
First trimester	351 (24.6)	523 (28.2)	
Second trimester	381 (26.7)	462 (24.9)	
Third trimester	373 (26.1)	465 (25.0)	
Missing	*17*	*39*	
Outcomes			
Breastfeeding	**N=1230**	**N=1795**	**0.60**
Initiated at birth	659 (53.6)	943 (52.5)	
Not initiated at birth	571 (46.4)	852 (47.5)	
Not reported/missing	*216*	*101*	
Mode of delivery	**N=1431**	**N=1891**	0.84
Vaginal delivery	929 (64.9)	1220 (64.5)	
Cesarean section	502 (35.1)	671 (35.5)	
Not reported/missing	*15*	*5*	
Gestational diabetes	**N=1326**	**N=1838**	0.44
Yes	81 (6.1)	126 (6.9)	
No	1245 (93.9)	1712 (93.1)	

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3281 | DYNAMIC EVOLUTION OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE, STEATOTIC LIVER DISEASE, AND CARDIOMETABOLIC RISK FACTORS AFTER DIRECT-ACTING ANTIVIRAL-INDUCED HEPATITIS C CURE

Chen-Hua Liu[1] Yun-Chu Chen[1] Yu-Ping Chang[2] Pin-Nan Cheng[3] Yu-Jen Fang[4] Chi-Yi Chen[5] Wei-Yu Kao[6] Chih-Lin Lin[7] Sheng-Shun Yang[8] Yu-Lueng Shih[9] Cheng Yuan Peng[10] Fu-Jen Lee[11] Ming-Chang Tsai[12] Chih-Horng Wu[13] Shang-Chin Huang[14] Tung-Hung Su[1] Tai-Chung Tseng[1] Chun Jen Liu[1] Pei-Jer Chen[1] Jia-Horng Kao[1], [1]National Taiwan University Hospital, [2]National Taiwan University Biomedical Park Hospital, [3]National Cheng Kung University Hospital, [4]National Taiwan University Hospital, Yun-Lin Branch, [5]Chia-Yi Christian Hospital, [6]Taipei Medical University Hospital, [7]Taipei City Hospital, Ren-Ai Branch, [8]Kuan Tien General Hospital, [9]Tri-Service General Hospital, [10]China Medical University Hospital, [11]Fu Jen Catholic University Hospital, [12]Chung Shan Medical University Hospital, [13]Shuang Ho Hospital, [14]National Taiwan University

Background: Data on dynamic changes in determinants of metabolic dysfunction–associated steatotic liver disease (MASLD) following direct-acting antiviral (DAA)-induced hepatitis C virus (HCV) cure remain limited. **Methods:** We enrolled 1,661 patients achieving sustained virologic response after DAAs. MASLD was defined as presence of steatotic liver disease (SLD), identified by controlled attenuation parameter (CAP) $\geq$248 dB/m, along with $\geq$1 cardiometabolic risk factor (CMRF). Distributions of MASLD, SLD, and CMRFs before and after viral cure were compared. Akaike information criterion (AIC)-based multivariable regression models were used to identify factors associated with MASLD, SLD, and CMRF changes. **Results:** The prevalence of MASLD (44.2% vs. 35.8%, $p<0.001$), SLD (44.5% vs. 35.9%, $p<0.001$), and CMRF burden ($p=0.047$) decreased after HCV cure. Glycemic (45.2% vs. 42.5%, $p=0.012$) and triglyceride (15.3% vs. 23.9%, $p<0.001$) criteria changed significantly. Age >50 years (aOR: 1.60, 95% CI: 1.07–2.43), absence of glycemic criterion (aOR: 1.37, 95% CI: 1.04–1.97), and absence of high-density lipoprotein-cholesterol (HDL-C) criterion (aOR: 1.58, 95% CI: 1.10–2.27) predicted SLD regression. Age $\leq$50 years (aOR: 1.73, 95% CI: 1.18–2.52), absence of SLD (aOR: 1.45, 95% CI: 1.01–2.07), and absence of hypertension (aOR 1.72, 95% CI 1.15–2.60) predicted glycemic criterion regression. Age $\leq$50 years (aOR: 1.48, 95% CI: 1.07–2.04), absence of SLD (aOR: 1.41, 95% CI: 1.07–1.93), and absence of HDL-C criterion (aOR: 2.31, 95% CI: 1.68–3.19) predicted triglyceride criterion emergence. **Conclusion:** Following HCV cure, MASLD, SLD, and glycemic abnormalities decreased, whereas triglyceride abnormalities increased, indicating heterogeneous metabolic trajectories after viral eradication.

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3282 | HCV TREATMENT TIMING AND HEPATOCELLULAR CARCINOMA RISK AMONG PEOPLE WHO INJECT DRUGS IN TAIWAN AFTER NATIONWIDE HCV ELIMINATION

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Background: People who inject drugs (PWID) are at high risk for chronic hepatitis C virus (HCV) infection and hepatocellular carcinoma (HCC). Taiwan launched a nationwide HCV elimination program in 2018, but its impact on high-risk populations remains unclear. We evaluated the association between HCV treatment timing, cirrhosis, and HCC risk among PWID with incarceration history in Taiwan. **Methods:** We conducted a retrospective cohort study using linked incarceration and National Health Insurance databases in Taiwan. Chronic HCV infection was identified using repeated HCV diagnoses, HCV RNA testing, or antiviral treatment records. Participants were followed until HCC diagnosis, death, or December 31, 2022. HCC incidence rates were calculated across three periods: 2008–2012, 2013–2017, and 2018–2022.In the primary analysis, HCV treatment was modeled as a time-varying exposure in multivariable Cox proportional hazards models adjusting for age, sex, HBV, HIV, and cirrhosis. Secondary analyses classified participants into three groups: untreated, treated without pre-existing cirrhosis, and treated with pre-existing cirrhosis. Untreated individuals were not further stratified by cirrhosis because untreated cirrhosis accounted for only 1.5% of the cohort. **Results:** A total of 29,189 PWID with chronic HCV infection were included; 67.9% received HCV treatment. Overall, 87.5% were male, 16.7% had HBV coinfection, 17.3% had HIV infection, and 12.1% had cirrhosis.HCC incidence increased from 1.28 per 1,000 person-years in 2008–2012 to 2.15 in 2013–2017 and 2.91 in 2018–2022. The relative increase was 67.7% before 2018 and 35.3% after implementation of the nationwide HCV elimination program.In the primary time-varying Cox model, HCV treatment was independently associated with reduced HCC risk (adjusted hazard ratio [aHR] 0.81, 95% confidence interval [CI]: 0.66–0.99, p = 0.045). Male sex, older age, HBV coinfection, and cirrhosis were independently associated with increased HCC risk. Cirrhosis was the strongest predictor of HCC (aHR 23.65, 95% CI: 18.44–30.33, p < 0.001).In secondary analyses, individuals treated without pre-existing cirrhosis had substantially lower HCC risk than untreated individuals (aHR 0.25, 95% CI: 0.20–0.32, p < 0.001). In contrast, individuals treated with pre-existing cirrhosis had higher HCC risk than untreated individuals (aHR 2.37, 95% CI: 1.91–2.94, p < 0.001) and markedly higher risk than treated individuals without pre-existing cirrhosis (aHR 9.41, 95% CI: 7.25–12.22, p < 0.001). **Conclusion:** HCC incidence remained high among PWID despite nationwide HCV elimination efforts in Taiwan. HCV treatment was associated with reduced HCC risk, particularly when initiated before cirrhosis development. Cirrhosis remained the dominant predictor of HCC, highlighting the importance of early HCV diagnosis and timely antiviral treatment in marginalized populations.



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3283 | ENHANCING HEPATITIS C SCREENING AND MANAGEMENT THROUGH A HOSPITAL-COMMUNITY BIDIRECTIONAL-DRIVEN HCV CARE INTEGRATION MODEL

Panpan Zhai[1] Xueting Ou[1] Liyang Zhou[1] Jiayi Chen[2] Shiyun Wu[1] Yinxing Lin[3] Yi Gao[4] Jing Hu[1] Xing-Fei Pan[1], [1]The Third Affiliated Hospital, Guangzhou Medical University, [2]The Third Affiliated Hospital, [3]he Third Affiliated Hospital, Guangzhou Medical University, [4]Department of Infectious Diseases

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Background: There are about 50 million people who globally have chronic hepatitis C virus infection. Direct-acting antivirals (DAAs) can cure over 95% of people with HCV infection. However, insufficient screening remains the major barrier to HCV elimination. We developed a hospital-community bidirectional-driven HCV care integration model. This model can enhance hepatitis C screening and management to meet and exceed the WHO's expectations. **Methods:** We developed the in-hospital and community bidirectional-driven HCV care integration model. Hospital management mainly included Department of Infectious Disease, Department of Hospital Infection Control, Laboratory Department, Information Department. Community management included public education, community-wide screening, accurate identification high-risk groups, peer education, targeted referrals, and following-up. We calculated the change of HCV RNA testing volumes, the number of treated and cured patients, and community outreach events. We designed a questionnaire to understand the view of hospital physicians/community physicians, and a random sampling telephone survey questionnaire for patients to understand the impact of community peer education. **Results:** During the implementation period from 2021 to 2024, HCV RNA testing volumes were strategically increased for four consecutive years. The annual HCV RNA testing volume raised from 169 tests in 2020 to 2,201 tests in 2024. The cumulative growth rate of HCV RNA testing volume ranged from 13% to 362%. Since the initiation of the program, 3,219 individuals were diagnosed as HCV infection, and were timely treated with antiviral drugs. During the four-year implementation period, 1,995 individuals had received antiviral treatment, 1,895 achieved sustained HCV cure (Table 1a). 86.6% (13/15) of hospital-based physicians and 90% (72/80) of community physicians indicated that the model had strengthened the hospital-community collaboration. 93.3% (14/15) of hospital physicians and 62.5% (50/80) of community physicians indicated that the model substantially made a progress towards elimination of HCV(Table 1b,c). 35.8% (114/318) and 25.8% (82/318)were referred to our hospital by Community referrals and HCV-cured relatives or friends, respectively(Table 1d). The total number of community outreach events had increased by 3.2-fold (from 5 in 2021 to 16 in 2022), with sustained engagement thereafter (n = 20 in 2023 and 2024). Collectively, these 61 outreach activities doubled the number of communities participating in this activity (from 5 to 10), reaching over 1800 attendees, and 920 patients who sought treatment(Table 1e). **Conclusion:** The volumes of viral testing, diagnosis, treatment, cure for HCV patients were substantially improved following implementation of the hospital-community bidirectional-drive HCV care integration model.

Table 1a. Annual patient numbers across the HCV care cascade, 2020–2024*

Year	HCV RNA testing (n)	HCV RNA positive (n)	Treatment (n)	Cure (n)	Cure (%)
2020 (pre implementation period)	169	39	33	33	93.94%
2021	781	115	118	112	94.92%
2022	1650	722	688	654	95.06%
2023	1860	1046	515	489	95.00%
2024	2201	1336	674	640	95.00%
2021-2024 (during implementation period)	6492	3219	1995	1895	94.99%

*This project was implemented across four components: screening, diagnosis, treatment, and cure. (follow-up) . At each stage, there was a dynamic bidirectional flow of patients—some were referred to our hospital after being screened or diagnosed at external institutions, while others were screened or diagnosed at our hospital and sought care elsewhere. This reflects the dynamic nature of patient movement across institutions. The year-on-year increase in the number of diagnosed and treated patients suggests the effectiveness of the project.

Table 1b. Community physicians' perceptions of barriers and benefits of the HCV elimination program (n=80)

Items / Options	Major barrier	Some barrier	No impact	Some benefit	Major benefit	Not sure / Not familiar with this program
Yourself	0(0%)	2(2.5%)	6(7.5%)	28(35.0%)	41(51.3%)	3(3.8%)
Your patients	0(0%)	2(2.5%)	4(5%)	25(31.25%)	45(56.25%)	4(5%)
Progress of hepatitis C elimination efforts	0(0%)	1(1.25%)	3(3.75%)	22(27.5%)	50(62.5%)	4(5%)
Healthcare network relationships (e.g., collaboration between hospitals and community clinics)	0(0%)	0(0%)	4(5%)	26(32.5%)	46(57.5%)	4(5%)

Table 1c. Hospital physicians' perceptions of barriers and benefits of the HCV elimination program (n=15)

Items / Options	Major barrier	Some barrier	No impact	Some benefit	Major benefit	Not sure / Not familiar with this program
Yourself	0(0%)	0(0%)	0(0%)	1(6.7%)	13(86.7%)	1(6.7%)
Your patients	0(0%)	0(0%)	0(0%)	4(26.7%)	11(73.3%)	0(0%)
Progress of hepatitis C elimination efforts	0(0%)	0(0%)	0(0%)	1(6.7%)	14 (93.3%)	0(0%)
Healthcare network relationships (e.g., collaboration between hospitals and community clinics)	0(0%)	0(0%)	0(0%)	2 (13.3%)	11(73.3%)	2 (13.3%)

Table 1d. Telephone survey results: patient contact outcomes, drivers of re-engagement, and willingness to refer (2021–2024)*

Year	Sampled patients (n)	Successfully contacted patients (n)	Drivers of re-engagement with hospital care				Willingness to refer family/friends with hepatitis C for treatment
			Community referrals	Family/friends referrals	Self-initiated visit after HCV antibody-positive screening	Symptom-driven visit	
2021	21	19	6	7	4	2	11
2022	124	109	41	24	33	11	30
2023	93	83	24	24	30	5	46
2024	122	107	43	27	33	4	80
2021-2024	360	318	114	82	100	22	147

*A total of 360 patients treated between 2021 and 2024 were randomly selected via telephone sampling; 318 were successfully contacted, while 42 did not respond. Among contacted patients, care-seeking was driven by community referral, recommendations from relatives or friends, positive anti-HCV screening results, or physical discomfort. Notably, 147 patients expressed willingness to recommend our hospital to relatives or friends diagnosed with hepatitis C.

Table 1e. Community-based health education activities and patient participation (2021–2024)

	Covered Communities (n)	Education sessions (n)	Education participants (n)	Treated patients who participated in community education (n)
2021	5	5	163	37
2022	8	16	600	299
2023	10	20	496	223
2024	10	20	602	361
Total	10	61	1861	920

Disclosures: Eric Tatara:Nothing to Disclose, Louis Shekhtman:Nothing to Disclose, Scott Cotler:Nothing to Disclose, Marian Major:Nothing to Disclose, Basmattee

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Boodram:Nothing to Disclose, Jonathan Ozik:Nothing to Disclose, Harel Dahari:VIR: Advisor.

3284 | INTEGRATING SOCIAL DETERMINANTS OF HEALTH INTO MACHINE LEARNING MODELS TO PREDICT HEPATITIS C TREATMENT INITIATION AMONG MEDICAID BENEFICIARIES

Suk-Chan Jang[1] Wei-Hsuan Lo-Ciganic[2] Chanakan Jenjai[1] Pilar Hernandez-Con[1] Khoa Nguyen[1] Robert Cook[1] Christine Gage[1] David Nelson[1] Haesuk Park[1], [1]University of Florida, [2]University of Pittsburgh

Background: Despite high cure rates with direct acting antivirals, treatment initiation remains suboptimal among Medicaid beneficiaries with HCV, a population disproportionately affected by adverse social determinants of health (SDoH). We developed and validated machine learning prediction models to identify Medicaid beneficiaries with HCV who were unlikely to initiate treatment and compared model performance with and without regional-level SDoH predictors. **Methods:** We conducted a prognostic modeling using the 2016–2023 OneFlorida+ database for Florida Medicaid beneficiaries aged 18–79 years with laboratory-confirmed HCV infection. Least Absolute Shrinkage and Selection Operator (LASSO) regression models were used to predict treatment initiation. Model 1 included 42 individual-level predictors, encompassing sociodemographic characteristics and clinical characteristics (e.g., cirrhosis, substance use disorders, HIV) during the 6 months prior to the HCV diagnosis date. Model 2 extended Model 1 by adding 57 regional-level predictors based on beneficiaries' residential zip codes, including measures from the Agency for Healthcare Research and Quality SDoH data, Area Deprivation Index, Social Vulnerability Index, and Rural-Urban Commuting Area codes. Model performances were assessed using C-statistics (based on the DeLong test), sensitivity, and specificity. **Results:** Among 4,032 Medicaid beneficiaries with HCV, 8.73% initiated treatment within one year. Training (75%) and validation (25%) samples had similar characteristics (age [SD], 46 [15] years; 52% female; 33% Black). Model 2 achieved a C-statistic of 0.793 (95% CI 0.754–0.833), significantly outperforming Model 1 (0.754 [95% CI 0.715–0.795]; p=0.027). Using the Youden index, Model 2 achieved 66% sensitivity and 80% specificity, with a number needed to screen of 4. Key risk predictors for remaining untreated included HIV infection, opioid injection drug use, pregnancy, and homelessness at the individual level, and residence in areas with higher proportions of Hispanic residents, higher uninsured rates or poverty, and greater area deprivation at the regional level. **Conclusion:** Incorporating regional-level SDoH predictors in addition to individual-level predictors significantly improved the prediction of HCV treatment initiation. These findings underscore the importance of contextual SDoH barriers among Medicaid beneficiaries at risk of remaining untreated or delayed treatment initiation.

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3285 | RELINKING PATIENTS WITH HEPATITIS C WHO ARE DIAGNOSED BUT UNTREATED TO CARE IN THE BRONX, NY

Jared Coe[1] Hannah Manley[2] Nicolette Fitzgibbons[3] Matthew Akiyama[1], [1]Albert Einstein College of Medicine/Montefiore Medical Center, [2]Albert Einstein College of Medicine, [3]Montefiore Medical Center

Background: In New York City (NYC), an estimated 59,400 people have chronic hepatitis C virus infection (HCV), with the Bronx having a higher proportion of newly diagnosed cases compared to the citywide average. While the number of people with chronic infections has been declining, many individuals remain eligible for treatment but have been lost to follow-up. This project evaluated a program to link diagnosed but untreated (DBU) patients to care. **Methods:** We created a retrospective cohort of patients with positive HCV antibody and detectable viral load results between 1/1996 and 10/2023 from inpatient, emergency department, or outpatient encounters at Montefiore Medical Center's 3 hospitals and 31 clinics in the Bronx and Westchester County. We began reviewing Epic patient charts in 12/2024 to determine who remained DBU. We also searched the Bronx Regional Health Information (RHIO) database for records at outside facilities as well as city, state, and federal incarceration databases in case patients were in jail/prison over the course of the outreach period. We attempted to contact patients by telephone and/or mail. We also outreached to emergency contacts if the patient could not be reached. Lastly, we sent patient names to the NYC Department of Health (DoH) to request test results that were not available via Epic and RHIO chart review as well as the Department of Homeless Services (DHS) to identify those currently in an NYC shelter. **Results:** In total, 1798 patient charts were reviewed and addressed as of 5/21/2026 with further outreach ongoing. Of the 1046

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patients who were cured, 968 (92.5%) cases were closed based on chart review and 48 (4.6%) based on updated test records from DoH. Outreach to DHS did not lead to any linkages or updates to contact information as DHS could only provide information on people who were currently residing in a shelter at the time of our outreach. Most mail outreach did not yield any response, although 164 letters were returned and 13 did prompt the patient to call the navigator. 432/1798 (24%) of patients were eligible for relinkage and 15/432 patients were successfully relinked to care yielding a relinkage rate of 3.5% with an additional 8 patients with upcoming appointments. **Conclusion:** HCV elimination will require improvements in information sharing across health record systems and robust outreach to people who are difficult to reach by traditional means. Direct outreach to patients through phone calls and mail, plus searches of public health databases may help link DBU individuals to care; however, additional outreach methods, including home and shelter visits, are needed to increase relinkage rates.

Table 1 Demographic Data (n=2331)	
% Female	829 (35.5%)
% Male	1502 (64.4%)
Median Age (IQR)	67 (15)
Race	
White	431 (18.4%)
African American	804 (34.4%)
Asian/Pacific Islander	22 (1.0%)
Native American	2 (0.1%)
2 or More Races/Other	115 (4.9%)
Declined to Answer	120 (5.1%)
Unknown	843 (34.7%)
Ethnicity	
Hispanic	956 (40.9%)
Non-Hispanic	1137 (48.6%)
Unknown	242 (10.4%)
Charts Reviewed and Closed (n=1798)	
Outcome:	
Cured (Data Source):	1046 (58.2%)
Chart Review	968 (92.5%)
DoH	48 (4.6%)
Patient contact	30 (2.9%)
Deceased	320 (17.8%)
Eligible for Relinkage	432
Unreachable	179 (41.4%)
Not Eligible	54 (12.5%)
Relocated	51 (11.8%)
Declined Care	50 (11.6%)
No Record of HCV	41 (9.5%)
Incarcerated	15 (3.5%)
Relinked	15 (3.5%)
Discharged	10 (2.3%)
Do Not Call	9 (2.1%)
Upcoming Appointment	8 (1.9%)

Disclosures: Jared Coe:Gilead: Independent Contractor, Hannah Manley:Nothing to Disclose, Nicolette Fitzgibbons:Nothing to Disclose, Matthew Akiyama: Nothing to Disclose.

3287 | IS THERE A DIFFERENCE IN THE PREVALENCE OF NS5A RESISTANT-ASSOCIATED SUBSTITUTIONS BY EXPOSURE TO DIFFERENT NS5A-CONTAINING REGIMENS?

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Background: NS5A resistance-associated substitutions (RAS) may persist after prior exposure to NS5A-containing direct-acting antiviral regimens and can complicate retreatment decisions in individuals with hepatitis C virus infection (HCV). The two most commonly used regimens for treatment-naive individuals with HCV are sofosbuvir/velpatasvir (S/V) and glecaprevir/pibrentasvir (G/P), In this study, we are interested in the prevalence of RAS to NS5A comparing a prior exposure to each of those agents. **Methods:** We conducted a retrospective review of prospectively collected data from our telehealth-based HCV treatment model in New Jersey among individuals who underwent NS5A resistance testing. Individuals were classified as treatment-naive (TN) to NS5A-containing regimen or treatment-experienced (TE) using documented treatment history. Among treatment-experienced individuals, prior regimen exposure was categorized as S/V, G/P, or other regimens. The primary outcome was the presence of NS5A RAS. Resistance prevalence was compared between TN and TE and across prior regimen exposure groups using Fisher's exact testing. **Results:** A total of 96 individuals underwent NS5A resistance testing, including 41 TN and 55 TE. Overall, NS5A RAS was detected in 14 individuals (14.6%) (Table 1). Resistance was more frequent among TE compared with TN, although the difference did not reach statistical significance (11/55 [20.0%] vs 3/41 [7.3%]; Fisher's exact p = 0.142).Among TE, prior regimen exposure included S/V in 27 individuals, G/P in 20 individuals, and other regimens in 8 individuals. NS5A RAS was detected in 6/27 individuals (22.2%) previously exposed to S/V, 4/20 (20.0%) previously exposed to G/P, and 1/8 (12.5%) in the other-regimen group. There was no significant difference in resistance prevalence across prior regimen exposure groups (exact p = 1.000).Compared with TN, NS5A resistance was numerically higher among individuals previously exposed to S/V (22.2% vs 7.3%; Fisher's exact p = 0.140) and G/P (20.0% vs 7.3%; Fisher's exact p = 0.203), although neither comparison reached statistical significance. **Conclusion:** In this real-

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world cohort, NS5A RAS was detected in approximately 15% of individuals tested and was numerically more common among TE than TN. Among TE, NS5A RAS rates were similar after prior exposure to S/V and G/P, with no statistically significant difference by prior regimen. These findings support the need for larger real-world studies to better define the burden of NS5A RAS and its implications for retreatment strategies.

Table 1: NS5A RAS detected among individuals

Mutation Group	n (%)
Y93 substitutions (Y93H/Y93C/Y93Y-H/Y93Y-C-N)	7 (50.0%)
M28 substitutions (M28T/M28E/M28M-T/M28M-V)	4 (28.6%)
Q30 substitutions (Q30Q-H/Q30R)	2 (14.3%)
L31 substitutions (L31L-M/L31L-V)	2 (14.3%)
Combination/complex RASs	4 (28.6%)

Disclosures: Murad Qirem:Nothing to Disclose, jihad slim:gilead: Speaking and Teaching, abbvie: Speaking and Teaching, Lina AlQirem:Nothing to Disclose, Shahd Yaghi:Nothing to Disclose, Ahmad AlQirem: Nothing to Disclose, Corey Rosmarin-DeStefano:Nothing to Disclose, Kevin Leyden:Gilead Sciences: Speaking and Teaching, Abbvie, Inc.: Advisor.

3288 | RE-ENGAGING DIAGNOSED BUT UNTREATED INDIVIDUALS THROUGH A HEPATITIS TREATMENT RELINKAGE PROGRAM

Leigh Brooks[1], [1]Bluestone Health Association Inc

Background: Despite highly effective antiviral therapies, many people diagnosed with viral hepatitis remain untreated because of loss to follow-up, fragmented records, and barriers to navigating care. Closing this gap is essential to hepatitis elimination. This relinkage initiative was implemented within a primary care program that also provides substance use disorder services, enabling hepatitis evaluation and treatment to be delivered in the same clinical setting. **Methods:** A centralized relinkage registry was created by integrating data from the electronic health record (EHR), laboratory reporting, public health/ surveillance line lists, and referral logs. Records were deduplicated and treatment status was verified. Outreach staff conducted structured re-engagement using phone calls, text messages, mailed letters, and coordination with care teams and community partners. Patients who were reached were navigated to appointments, laboratory workup, and clinical evaluation within primary care, with care coordinated alongside substance use disorder visits when applicable to facilitate treatment initiation. **Results:** A total of 697 individuals with diagnosed viral hepatitis and no documented treatment initiation were identified. Outreach was initiated for all 697 individuals; 697 (100.0%) were successfully contacted and 680 (97.6%) were linked to hepatitis care with a documented linkage date indicating successful connection to treatment services (e.g., referral or appointment coordination completed). Embedding hepatitis care within primary care that manages substance use disorder improved care navigation and strengthened documentation of treatment status across systems. **Conclusion:** A structured, data-driven relinkage model embedded in primary care with substance use disorder services can rapidly reconnect diagnosed but untreated individuals to hepatitis care. Combining robust data reconciliation with multimodal outreach and coordinated navigation supports closing treatment gaps and advancing hepatitis elimination efforts in rural, high-burden settings.
Disclosures: Leigh Brooks:Gilead: Speaker Bureau, AbbVie: Speaking and Teaching.

3289 | HEPATITIS C ELIMINATION IN HIGH-RISK PSYCHIATRIC AND ADDICTION POPULATIONS: PREVALENCE AND TREATMENT OUTCOMES

Cristina del Rio Cubilledo[1] Luis Enrique Morano Amado[2] Denise Montserrat Arroyo Jarrin[3] Miriam Soriano Garcia[3] Catalina Fernandez Mendez[3] Maria Jose Alvarez Alonso[4] Francisco Otero Lamas[4] Jesus Cancelo[5] Sandra Cortizo Vidal[3] Isabel Coejo[6] Begoña Chapela Broullon[7] Laura Labajo Leal[8] Antonio Ocampo Hermida[8] Antonio Ocampo Hermida[8] Jose Manuel Olivares Diez[9] Aitana Morano Vazquez[10], [1]University of La Rioja, La Rioja, Spain, [2]Universitiy Hospital Alvaro Cunqueiro, Vigo, Spain, [3]University Hospital Alvaro Cunqueiro, Vigo, Spain, [4]Addictions Unit CEDRO, Vigo, Spain, [5]Addictions Unit Alborada, Vigo, Spain, [6]Addictions Unit Alborada Vigo. Spain., [7]Addictions Unit Cangas. Spain. [8]University Hospital Alvaro Cunqueiro. Vigo. Spain., [9]Hospital Alvaro Cunqueiro. Vigo. Spain., [10]University Hospital Gregorio Marañon. Madrid. Spain.

Background: Hepatitis C virus (HCV) affects an estimated 50 million people chronically worldwide (2022). In Spain, HCV antibody prevalence is 0.85%, with active infection in 0.14–0.22%. Prevalence is higher among people with substance use disorders (SUD), severe mental illness (SMI), and dual disorder (DD). Despite efficacy of direct-acting antivirals (DAA), individuals with SUD and DD remain under-prioritized for screening. We analysed HCV prevalence in SMI and DD patients attending a Psychiatry Unit and SUD patients attending four Substance Abuse Units (SAU) in Vigo, Spain. **Methods:** Retrospective study (January 2019 – December 2025) including 2,693 SAU users and 2,026 Psychiatry Unit patients (339 DD). Users were classified as anti-HCV status (positive, negative,

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unknown). Covariates: Age, sex, and type of user or patient. **Results:** In the Psychiatry Unit (2,206; mean age 48), 1,494 (67.7%) were tested and 134 (9.0%) were anti-HCV positive. 131 were tested for RNA, of these 122 (93.2%) had undetectable RNA: 88 (72.1%) achieved sustained virological response (SVR) after treatment and the rest spontaneous clearance (SVC). Schizophrenia (24.6%) and other psychotic disorders (19.4%) were most frequent. Positives were older than negatives (51.7 ± 8.4 vs. 47.0 ± 16.6 years; $p < 0.001$). Prevalence was higher in men (13.2% vs. 4.7%; OR 3.09; $p < 0.001$). In DD patients (339; mean age 42.3), 289 (85.2%) were tested and 71 (24.6%) were anti-HCV positive. Of these 100% were tested for RNA, 68 (95.7%) had undetectable RNA: 52 (76.5%) SVR and 16 SVC. Substance use was multiple in 63%, single in 30%, and alcohol in 7%. Higher prevalence occurred in psychotic disorders (22.5%), schizophrenia (19.7%), and personality disorders (18.3%). Positives were older (50.3 ± 7.7 vs. 39.6 ± 12.7; $p < 0.001$). Male prevalence was higher but not significant (27.8% vs. 18.1%; OR 1.75; $p = 0.098$). In SAU users (2,693; mean age 46), 22.3% had alcohol use disorder, 44.7% single drug use, and 33% multiple drug use. Testing coverage was 81.3%, with 52.2% anti-HCV positive. Of these 1057 were tested for RNA, 86.2% had undetectable RNA (77.2% SVR, 22.8% SVC). Prevalence was higher in men (52.9% vs. 47.9%; OR 1.22; $p = 0.063$). Positives were older (50.1 vs. 43.4 years; $p < 0.001$). **Conclusion:** HCV prevalence was 52.3-fold higher in SAU, 10.5-fold in SMI, and 28.9-fold in DD patients. SVR after DAA was comparable to the general population. Systematic test-and-treat strategies in psychiatric units and SAU are essential to improve care and support WHO 2030 elimination goals.

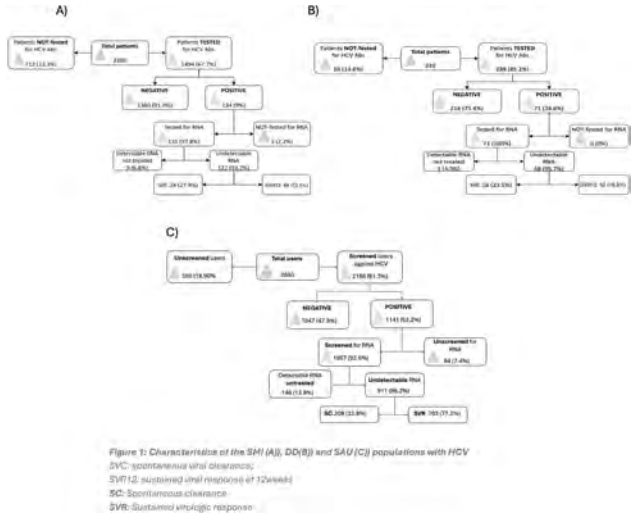


Figure 1: Characteristics of the SMI (A)), DD(B)) and SAU (C)) populations with HCV
SVC: spontaneous viral clearance;
SVR12: sustained viral response at 12weeks
SC: Spontaneous clearance
SVR: Sustained virologic response

Disclosures: Cristina del Rio Cubilledo:Nothing to Disclose, Luis Enrique Morano Amado:Nothing to Disclose, Denise Montserrat Arroyo Jarrin:Nothing to Disclose, Miriam Soriano Garcia:Nothing to Disclose, Catalina Fernandez Mendez:Nothing to Disclose, Maria Jose Alvarez Alonso:Nothing to Disclose, Francisco Otero Lamas:Nothing to Disclose, Jesus Cancelo: Nothing to Disclose, Sandra Cortizo Vidal:Nothing to Disclose, Isabel Coejo:Nothing to Disclose, Begoña Chapela Broullon:Nothing to Disclose, Laura Labajo Leal:Nothing to Disclose, Antonio Ocampo Hermida: Nothing to Disclose, Nothing to Disclose, Antonio Ocampo Hermida:Nothing to Disclose, Nothing to Disclose, Jose Manuel Olivares Diez:Nothing to Disclose, Aitana Morano Vazquez:Nothing to Disclose.

3290 | LIVER DISEASE SEVERITY, COMORBIDITY BURDEN, AND SUSTAINED VIROLOGIC RESPONSE AMONG ADULTS WITH HCV VIREMIA

Hannah Fry[1] Leah Harvey[2] Mark Rosenberg[1] Filipe Monteiro[2], [1]Warren Alpert Medical School of Brown University, [2]Brown University Health

Background: Hepatitis C (HCV) remains a significant public health challenge due to persistent gaps along the care cascade. Understanding predictors of failure to achieve sustained virologic response (SVR) is essential for targeting interventions to medically complex populations. This study evaluated (1) the proportion of adults with active HCV viremia who achieved SVR within a large regional health system and (2) clinical factors associated with incomplete progression through the care cascade. **Methods:** We conducted a retrospective cohort study of 1,039 patients diagnosed with HCV viremia within an academic medical center in New England between 1/1/2018 - 12/31/2018. Treatment completion and SVR were measured by repeat HCV RNA testing within 40 weeks of treatment initiation, accounting for real-world delays. Demographic, clinical, and social variables, including liver disease severity (MELD and cirrhosis status) and comorbidity burden (Charlson Comorbidity Index [CCI]) were extracted from the electronic health record. Group differences were assessed using chi-square, Fisher's exact, and t-tests. Logistic regression models generated adjusted odds ratios (aOR) for SVR and clinical severity predictors. **Results:** Among 1,039 adults with HCV viremia, the mean age was 49.4 ± 12.8 years, 61.6% were male, 72.1% White, and 15.4% Hispanic. Mild liver disease (MELD 6-10) was present in 56.9% of the cohort, while 5.1% had severe liver disease. Most patients had low comorbidity burden (CCI 0–1 in 54.6%). Overall, 771 patients (74.2%) achieved SVR and 268 (25.8%) did not. Higher MELD scores were predictive of not achieving SVR: MELD 20–29 (aOR 4.01, 95% CI 1.77–9.08) and MELD >39 (unadjusted OR 7.31, 1.41–37.9). Fibrosis severity was not independently associated with SVR when controlling for other variables. Higher CCI scores significantly

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increased the likelihood of severe liver disease (aORs 3.91–10.71), and CCI remained an independent predictor of not achieving SVR even after adjusting for demographic and social factors. **Conclusion** Clinical complexity, described by MELD score, fibrosis markers, and comorbidity burden, is associated with decreased likelihood of achieving SVR. These findings highlight the need for multidisciplinary coordination and closer monitoring for medically complex patients with HCV. Integrating social supports, early cirrhosis evaluation, and comorbidity-focused care pathways may improve treatment completion and optimize cure rates in high-risk clinical subgroups.

Variables	Total (n=1039)	Sustained Virologic Response[a]		SMD	Univariate OR [95% CI]	P-Value
		Achieve[b] (n=771, 74.2%)	Did not achieve[d] (n=268, 25.8%)			
MELD Score[c], mean±SD	3 [11±14.05]	2.66±13.67	3.84±15.11	-0.0684	0.995 [0.98-1.008]	0.44
<10	499 (48.05)	371 (48.04)	124 (46.27)	0.0475	0.93 [0.67-1.293]	0.50
10-19	78 (7.51)	56 (7.26)	22 (8.21)	-0.0354	1.14 [0.68-1.913]	0.61
20-29	38 [3.66]	32 [4.15]	6 [2.24]	**0.1087**	0.53 [0.22-1.258]	0.16
30-39	12 [1.15]	7 [0.91]	5 [1.87]	-0.0820	2.08 [0.65-6.665]	0.22
>39	7 [0.67]	2 [0.26]	5 [1.87]	**-0.1572**	7.31 [1.41-37.883]	**0.02**
Labs[c], mean (SD)						
Creatinine (mg/dL)	1.34±2.14	1.42±1.81	1.07±1.88	**-0.1547**	0.91 [0.83-0.999]	**0.05**
Bilirubin (mg/dL)	1.65±3.82	1.34±2.93	1.98±5.12	**-0.1005**	0.97 [0.93-1.023]	0.19
INR	1.35±0.65	1.24±0.64	1.28±0.73	-0.0630	0.91 [0.73-1.137]	0.46
NA (mEq/L)	140.88±4.11	140.7±4.25	141.3±3.65	**-0.1343**	0.97 [0.93-1.013]	0.16
Glucose (mg/dL)	308.70±150.46	314.86±156.9	294.3±135.8	**0.1587**	1.00 [0.998-1.003]	0.47
APRI[c], mean (SD)	0.48±0.46	0.48±0.41	0.46±0.47	0.0147	1.01 [0.74-1.453]	0.64
< 0.7, n(%)	814 (87.66)	621 (87.34)	213 (89.50)	0.0267	1.24 [0.77-1.983]	0.38
0.7 to <1	70 (7.88)	56 (7.88)	14 (5.88)	0.0644	0.73 [0.40-1.344]	0.31
1 to <2	37 (3.90)	30 (4.22)	7 (2.94)	0.0722	0.69 [0.30-1.599]	0.38
2	8 (0.84)	4 (0.56)	4 [1.68]	-0.0977	3.00 [0.75-12.183]	0.12
CCI[c], mean±SD	3.11±3.39	3.02±3.45	2.84±3.22	**0.1083**	1.03 [0.99-1.081]	0.13
No comorbidity, n (%)	187 (18.00)	138 (17.90)	59 (22.01)	**-0.1031**	1.30 [0.93-1.821]	0.14
1 comorbidity	240 (23.10)	169 (21.92)	71 (26.49)	**-0.1069**	1.28 [0.93-1.77]	0.13
2 comorbidities	172 (16.55)	138 (17.90)	34 (12.69)	**0.1452**	0.67 [0.43-0.999]	**0.049**
3 or more comorbidities	430 (41.39)	326 (42.28)	104 (38.81)	0.0709	0.87 [0.65-1.151]	0.32
Mild Liver Disease	583 (56.88)	446 (57.85)	143 (54.10)	0.0756	0.86 [0.63-1.14]	0.27
Severe Liver Disease	34 (3.20)	41 (5.32)	13 (4.85)	0.0213	0.91 [0.48-1.72]	0.77
HIV/AIDS	79 (7.6)	65 (8.43)	14 (5.22)	**0.1274**	0.60 [0.33-1.091]	0.09

Disclosures: Hannah Fry:Nothing to Disclose, Leah Harvey:Nothing to Disclose, Mark Rosenberg:Nothing to Disclose, Filipe Monteiro:Nothing to Disclose.

3291 | CHARACTERISTICS OF INDIVIDUALS WITH HIV EXPOSURE: INSIGHTS FROM 10 YEARS OF HEPATITIS C TESTING IN VANCOUVER, CANADA'S INNER-CITY

Christina Wiesmann[1] Shana Yi[2] David Truong[2] Brian Conway[2], [1]Simon Fraser University, [2]Vancouver Infectious Diseases Centre

Background: Vancouver, Canada's inner-city, or downtown east side (DTES) neighborhood is known for high rates of poverty and drug use. The Vancouver Infectious Diseases Centre (VIDC) has been carrying out point-of-care testing at DTES community locations, and providing HCV treatment to viremic individuals for more than 10 years. We chose to evaluate both characteristics associated with HCV exposure, and proportions of HCV exposure and viremia over time. **Methods:** VIDC provides regular point-of-care antibody testing in various inner-city locations including community centers, shelters, and single room occupancy buildings. We collect data about HCV antibody and viremia status, as well as a range of other demographic and social variables. We used odds ratios to determine characteristics significantly associated with HCV exposure from 2015 until September of 2025. **Results:** A range of characteristics were found to be significantly associated with individuals with HCV exposure (Table 1). The most strongly associated characteristic was having a history of injection drug use. Smoking, poorer health status, being unemployed, having no post-secondary education, and having an HIV infection were also significantly associated with having been exposed to HCV.We saw that in 2025, individuals testing positive for HCV exposure were significantly older than individuals with no exposure (44.5 YO vs. 48.6 YO; p = 3.16E-07).We saw no clear trend in the proportion of individuals testing positive for HCV antibodies over time, but saw that a much lower proportion of individuals were viremic in 2025 (~15%) compared to 2015 (~70%). **Conclusion** We identified many factors associated with HCV exposure, most of which are consistent with variables previously identified by other research groups. The observation that individuals without HCV exposure were significantly younger in 2025 is a novel finding that may indicate that sustained treatment of HCV in this population is reducing the risk of HCV acquisition by individuals new to drug use. Follow-up analyses will further investigate this intriguing finding. This work will ultimately help to inform and provide evidence-based support for micro-elimination efforts in Vancouver's inner-city community, as well as similar communities around the world.

Characteristic		Unadjusted OR (95% CI); HCV+ vs. HCV-
Gender	Male vs. Not Male	1.06 (0.78 - 1.44)
HIV result	HIV+ vs. HIV-	**3.74** (1.37 - 10.18)
Ethnicity	Indigenous vs. Non-Indigenous	1.31 (0.90 - 1.90)
Relationship Status	Single vs. Married/Common Law	1.39 (0.89 - 2.18)
Education Level	<= High school vs. > High School	**1.78** (1.23 - 2.60)
Employment Status	Not Working vs. Working/Studying	**1.77** (1.12 - 2.79)
Incarceration History	Yes vs. No	0.93 (0.65 - 1.33)
Health Status	Poor/Fair vs. Good/VG/Excellent	**1.71** (1.18 - 2.47)
Alcohol Consumption	>1 drink/day vs <1 drink/day	0.83 (0.50 - 1.40)
Smoking	Yes vs. No	**2.23** (1.33 - 1.74)
Injection Drug Use History	Yes vs. No	**13.98** (8.62 - 13.98)

Disclosures: Christina Wiesmann:Nothing to Disclose, Shana Yi:Nothing to Disclose, David Truong:Nothing to Disclose, Brian Conway:Nothing to Disclose.

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3292 | EVALUATING POSTPARTUM LINKAGE TO HEPATITIS C CARE: RESULTS OF A PATIENT OUTREACH STUDY

Megan Betancourt[1] Jasmine Gamez[2] Jennifer Price[1] Annie Leutkemeyer[1] Dominika Seidman[1] Monika Sarkar[2], [1]University of California San Francisco, [2]University of California, San Francisco

Background: Recommendations to universally screen for hepatitis C virus (HCV) during pregnancy have increased HCV diagnosis in this population. However, peripartum linkage to care remains a major challenge. In our prior retrospective study, most pregnant patients with HCV viremia were lost to follow-up. Our current study investigates patient-reported barriers and facilitators to postpartum linkage of care. **Methods:** We identified patients with HCV viremia in pregnancy who delivered at an urban tertiary academic center and affiliated county hospital from 1/1/2014 – 12/31/2024. We designed a structured telephone survey to determine whether patients and their offspring received follow-up HCV care and to solicit barriers and facilitators to access. Initial patient contact was conducted by phone call and text. **Results:** Between 2014-2024 we identified 110 qualifying pregnancies. Of these, 11 patients (10%) could be reached at a median of 9 years after pregnancy (IQR 6.5 – 10.5), 10 of whom responded to text outreach but not to initial phone. All respondents consented to and completed the telephone survey. Regarding psychosocial stressors, 9 patients (82%) experienced housing instability, and 10 (91%) reported substance use prior to pregnancy (opiates 70%, methamphetamine 30%) with all 10 having prior injecting drug use. Two respondents noted active substance use during pregnancy, and all 7 with opiate use reported being managed with methadone intrapartum. Notably, 6 (55%) reported no healthcare provider discussed their HCV during their pregnancy and therefore did not think postpartum HCV follow-up was needed. 5 (45%) reported a clear follow-up plan after delivery. Despite this, 9 patients (82%) received antiviral therapy initiated ~6-8 months postpartum with one receiving treatment 3 years postpartum. Six of these 9 (67%) received HCV treatment at their methadone clinic, even if lost to follow-up through their hospital system. Most (82%) felt comfortable discussing HCV with providers and only 1 reported feeling judged or stigmatized due to HCV. Regarding infant follow-up, 10 of the 11 respondents (91%) reported their infant received HCV testing. One patient reported her infant was diagnosed with HCV at 48 months and received antiviral therapy. **Conclusion:** Postpartum follow-up after HCV diagnosis in pregnancy remains challenging with low successful outreach, underscoring the need for routine and structured models of postpartum linkage to care. Integration of addiction medicine and HCV treatment programs, patient outreach through text messaging, and enhanced counseling regarding HCV treatment in pregnancy may be additional strategies to optimize peripartum HCV management.

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3293 | RELINK ANGH, FINDING PATIENTS WITH LOST-TO-FOLLOW-UP VIRAL HEPATITIS: A NATIONAL MULTICENTRE STUDY IN NON-UNIVERSITY HOSPITALS

Andre Jean Remy[1] Edoardo Poli[2], [1]Centre Hospitalier De Perpignan, [2]Centre Hospitalier Nord Essonne

Background: The recall of patients diagnosed with HCV+ but lost to follow-up or untreated has been shown to be effective in some countries, including France. The first Relink-C program was set up at the Annecy hospital and successfully replicated in 3 other general hospitals (Perpignan, Créteil and Avignon). Systematic screening for all pregnant women is mandatory for HBV and strongly recommended for HCV in France. No recent data are available on the rates of screening for these two viruses in pregnant women. In the patients who were screened, HBsAg was globally positive in 0.8%, but this rate ranged from 0.3% in women born in France to 6.7% in those born in Africa. The French Describe study finds a HDV screening rate in pregnant women with positive Ag HBS of less than 10%. No data on the care pathway and access to treatment is available. **Methods:** For RELINK generalist to find untreated and lost-to-follow-up HCV (+/- HDV) patients diagnosed with HCV and for RELINK pregnant women to find lost-to-follow-up HCV (+/- HDV) patients whose diagnosis has been made or confirmed during pregnancy monitoring. Each center used its internal, virological or hepatological databases. For HBV patients found, a HDV serology was systematically performed. **Results:** As of May 12, 2026, 197 patients (23% women) had been included in the general RELINK observatory and 38 patients in the pregnant RELINK observatory. Sixteen centers included at least one patient. The average response rate

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was 79%. The table below details the main characteristics of the two groups: **Conclusion** All patients diagnosed with chronic viral hepatitis B and C who have been lost to follow-up may return to a care pathway after being contacted again. Direct contact is the preferred way to find these patients, followed by referral to a general practitioner or midwife. The diagnosis was known for 8 to 7 years on average. HBV is predominant in women followed in obstetrics. In the random access patients, there was equality between HBV and HCV and 23% had an F3F4 fibrosis.

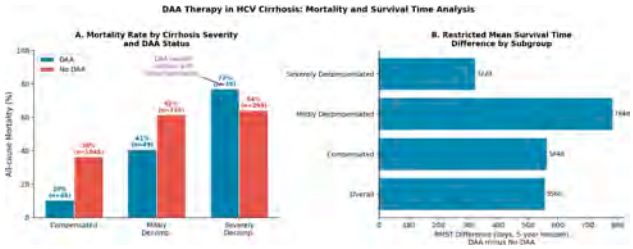
RELINK	number	average age	HCV	HBV	HDV	diagnotic	contact method	F0-F1	F3-F4	HCV treatment	HBV treatment	HDV treatment
General	194	45	49,0%	50,5%	0,5%	8 years	61% direct 26% GP	56,7	43,2%	91,5	36%	33%
Pregnant women	38	35	5,3%	92,1%	2,6%	7 years	68% direct 25% midwife	97,30%	0%	100%	12%	0%

Disclosures: ANDRE JEAN REMY:GILEAD: Royalties or patent beneficiary, GSK: Consultant, MADRIGAL: Grant/Research Support, NOVONORDOSK: CONGRESS, EDOARDO POLI:Nothing to Disclose.

3294 | ABSOLUTE SURVIVAL BENEFIT OF DAA THERAPY IN HOSPITALIZED PATIENTS WITH HCV-RELATED CIRRHOSIS: A RESTRICTED MEAN SURVIVAL TIME ANALYSIS

Innocent Lutaya[1] Brian Xu[1] Vicki Oladoyin[1] Shanelle Brodeur[1] Christopher Fay[1] Shahena Polynice[1] Chioma Nwabuoku[1] Tsering Shola[1] Chima Amadi[1] Shaikhoon Mohammed[1] Nicolas Bakinde[1], [1]Morehouse School of Medicine

Background: Direct-acting antiviral (DAA) therapy achieves sustained virologic response (SVR) >95% in hepatitis C (HCV), but data regarding absolute survival benefit in hospitalized patients with advanced cirrhosis remains unquantified. Most studies report hazard ratios, which quantify relative risk reduction, but do not convey the absolute survival gain, which is most meaningful to patients and clinicians. We used restricted mean survival time (RMST) to address this gap, by providing a direct estimate of life-months gained with DAA therapy. **Methods:** We conducted a retrospective cohort study of 2,205 adults hospitalized with HCV-related cirrhosis at a major academic medical center (Beth Israel Deaconess Medical Center, 2008–2019). Rather than reporting relative risk alone, our primary outcome was survival benefit measured in life-months gained; specifically, the restricted mean survival time (RMST) difference at 12 and 36 months between DAA-treated and untreated patients. Secondary outcomes included Kaplan-Meier survival curves to visually compare how patients did based on whether they had liver cancer (HCC) and how advanced their cirrhosis was, with multivariable Cox regression confirming that DAA treatment independently predicted better survival after accounting for differences between groups. **Results:** Of 2,205 patients (mean age 56.3 years, 29.3% female), 136 (6.2%) received DAA therapy. At 36 months, DAA was associated with 10.3 additional life-months (RMST 32.4 vs 22.1 months; 95% CI 8.5-12.0). Benefit was greatest in mildly decompensated cirrhosis (+13.9 months) and patients with HCC (+11.9 months). In severely decompensated patients, RMST gain was +6.3 months (95% CI 2.9-9.5; p=0.275). DAA therapy independently reduced mortality based on our adjusted hazard ratio after accounting for other factors that could influence survival, like cirrhosis severity (aHR 0.45, 95% CI 0.34-0.59; p<0.001). **Conclusion** DAA therapy added nearly 10 months of life at 3 years, even in hospitalized patients with advanced cirrhosis. The survival benefit was largest in those with liver cancer (+11.9 months) and mild decompensation (+13.9 months), while gains in severely decompensated patients were smaller and did not reach statistical significance. Our data is meant to highlight a window of opportunity where treatment makes the greatest difference.



Disclosures: Innocent Lutaya:Nothing to Disclose, Brian Xu:Nothing to Disclose, Vicki Oladoyin:Nothing to Disclose, Shanelle Brodeur:Nothing to Disclose, Christopher Fay:Nothing to Disclose, Shahena Polynice:Nothing to Disclose, Chioma Nwabuoku:Nothing to Disclose, Tsering Shola:Nothing to Disclose, Chima Amadi:Nothing to Disclose, Shaikhoon Mohammed:Nothing to Disclose, Nicolas Bakinde:Nothing to Disclose.

3295 | MODELING PREDICTS 12 VERSUS 8 WEEKS OF DAA TREATMENT IS MORE COST EFFECTIVE FOR HCV MICRO-ELIMINATION AMONG PERSONS WHO INJECT DRUGS IN METROPOLITAN CHICAGO

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Background: Persons who inject drugs (PWID) are at high risk for acquiring and transmitting hepatitis C virus (HCV). Direct-acting antiviral (DAA) therapy can not only cure HCV but can also protect PWID from repeat infections by suppressing viral replication while on treatment. Currently approved DAA regimens have an 8 or 12 week treatment duration and similar efficacy. We aimed to study the effect and cost of DAA treatment duration for PWID in the context of efforts to achieve HCV micro-elimination in metropolitan Chicago, IL, USA. **Methods:** We used our advanced Hepatitis C Elimination in PWID (HepCEP) agent-based model [10.1093/ofid/ofag297] in which HCV transmission probability is determined using a mathematical model that includes HCV RNA titers among needle/syringe-sharing donors [Sci Transl Med 2018; 10(449): eaao4496], to identify and optimize DAA therapy scale-up and treatment strategies. DAA treatment adherence was fixed at 90% and assumed a conservative estimate for cure rates of 90%. DAA treatment enrollment is modelled as (unbiased) random sampling of infected PWID using an annual target enrollment rate of 7.5% of the total PWID population in Chicago and surrounding area (32,000 individuals). Access to DAAs was simulated for 10 years. We compared the mean frequencies (using stochastic model replicates) of repeat infections, and number of unique treatment courses for DAA treatment duration lengths of 8 and 12 weeks. **Results:** The model predicts that during a 10-year period, a 12-week treatment duration results in fewer total infections (4,567, 95%CI: 4,376-4,758) compared to an 8-week treatment duration (5,214, 95%CI: 5,023-5404), many of which consist of repeat infections (12-week: 2,042, 95%CI: 1,917-2,166; 8-week: 2,581, 95%CI: 2,448-2,715). The need for DAA re-treatments for re-infected individuals and the total number of treatments was smaller in the 12-week group compared to the 8-week group. Specifically, use of a 12-week regimen (17,437 treatments) was projected to result in the need for 715 fewer treatments compared to an 8-week regimen (18,152 treatments) (Table 1). The total DAA cost to reach elimination for 8-week and 12-week treatment duration were estimated at ~$200 and ~192 million, respectively. **Conclusion** Our modeling results indicate that a 12-week DAA treatment would result in a smaller number of repeat infections and an estimated mean DAA cost reduction of about $8 million compared to 8-week DAA treatment over a 10-year effort to reach HCV micro-elimination in metropolitan Chicago due to a longer period of protection from infections during the DAA treatment window.

	8-week DAA Treatment Duration				12-week DAA Treatment Duration				Diff vs 12wk total treatment counts/cost difference
Times Treated	Number of PWID Treated (95% CI)		Total Treatments Received (95% CI)		Number of PWID Treated (95% CI)		Total Treatments Received (95% CI)		
1	6,434	(6,398-6,470)	6,434	(6,398-6,470)	6,514	(6,475-6,553)	6,514	(6,475-6,553)	-80
2	1,933	(1,912-1,964)	3,675	(3,824-3,928)	1,981	(1,961-2,001)	3,962	(3,921-4,002)	-88
3	866	(848-884)	2,598	(2,544-2,652)	883	(862-903)	2,648	(2,586-2,710)	-50
4	469	(458-481)	1,878	(1,832-1,924)	452	(433-471)	1,808	(1,731-1,882)	72
5	271	(258-283)	1,354	(1,290-1,415)	230	(215-245)	1,152	(1,077-1,227)	202
6	145	(134-156)	869	(804-936)	111	(102-119)	665	(615-715)	204
7+	140	(119-153)	1,143	(912-1,187)	79	(59-99)	699	(389-727)	453
Total Treatments			**18,152**	**(17,625-18,636)**			**17,437**	**(16,797-17,811)**	**715**
Total cost ($M)			**200**	**(194-204)**			**192**	**(185-196)**	**8**

Table 1. Mean PWID treatment enrollment frequency for treatment durations of 8 and 12 weeks. We used the lowest reported 8-week and 12-week DAA costs per treatment course in the US (after discounts) at $11,000 (https://stallardhepc.org)

Disclosures: Eric Tatara:Nothing to Disclose, Louis Shekhtman:Nothing to Disclose, Scott Cotler:Nothing to Disclose, Marian Major:Nothing to Disclose, Basmattee Boodram:Nothing to Disclose, Jonathan Ozik:Nothing to Disclose, Harel Dahari:VIR: Advisor.

3296 | HEPATITIS C RETREATMENT DURING THE DIRECT-ACTING ANTIVIRAL ERA, UNITED STATES, 2014-2025

Eyasu Teshale[1] Yuna Zhong[1] Brooke Hoots[1] Hasan Symum[1] Julian Grass[1], [1]Center for Disease Control and Prevention

Background: Despite the effectiveness of direct-acting antiviral (DAA) drugs for hepatitis C treatment, a subset of persons require retreatment for various reasons. Because DAA regimens are costly, retreatment adds substantial burden to patients and health care systems. In this large population of DAA-treated persons, we aimed to quantify retreatment and describe characteristics associated with retreatment. **Methods:** Using IQVIA's Longitudinal Prescription Claims data, we identified persons who received more than one DAA treatment course during 2014—2025. Retreatment was defined as initiation of a new DAA treatment $\geq$6 months after the last date of the prior treatment. We described persons who were retreated and compared demographics, payer type, and prescriber specialty corresponding to the first retreatment with the characteristics of those who were treated only once. We used logistic regression to determine factors associated with retreatment. **Results:** 1,119,896 persons were treated with DAAs, of whom 36,089 (3.2%) were retreated. Most (93.7%) had only one retreatment. Among those retreated, 66.2% were male and 55.8% were aged $\geq$ 60 years; 35.9% had private insurance, 31.0% had Medicaid, and 27.6% had Medicare. Over half (52.5%) received prescriptions from specialists. Retreatment was higher during 2014–2016 (4.4%), at the start of the DAA era compared to 2023–2025 (1.6%), and among persons initially treated with earlier generation DAAs (8.4%) than with pangenotypic drugs (2.5%). Younger age, male sex, treatment with earlier generation DAAs, and non-

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private insurance were significantly associated with retreatment compared to being treated once. Those who were prescribed treatment by nurse practitioners or primary care physicians were more likely to be retreated than those prescribed treatment by specialists. **Conclusion:** During 2014–2025, 3.2% of persons treated with DAAs underwent retreatment. Better understanding of factors associated with retreatment—including age, sex, insurance type, and prescriber characteristics—is essential for optimizing clinical management and reducing the long-term health and economic impacts of hepatitis C.

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3297 | LEAVING MONEY ON THE TABLE: THE COST OF MISSED HEPATITIS C TREATMENT OPPORTUNITIES AMONG PREGNANT AND POSTPARTUM WOMEN

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Background: With the injection drug use (IDU) epidemic, hepatitis C virus (HCV) has emerged as a public health threat to pregnant women and their infants, increasing the risk of adverse pregnancy outcomes including perinatal HCV transmission. Despite availability of curative treatment (direct-acting antivirals [DAA]), poor treatment uptake is a prevalent issue depreciating the value of universal HCV screening mandate from 2019. 340B funding offers a path to recover administrative costs associated with DAA prescription, but perceived low numbers of eligible (privately insured) patients in this population disincentivizes institutional investment. We examined the HCV care utilization and cost of untreated maternal HCV in a large academic health system in Alabama, a non-Medicaid expansion state. **Methods:** We abstracted electronic medical records using the International Classification of Diseases (10th Revision) clinical and procedural codes, clinic notes, pharmacy records, and laboratory results to elucidate the care cascade of pregnant women with HCV who delivered at our institution's health system between 2018-2024. We derived the rates of healthcare utilization of these women and private insurance coverage rates. Accounting for the 35% discount rate and the local staffing model and care therapies, we estimated the financial advantage (2026 USD) of treating all pregnant women with HCV and capturing all who were eligible to generate 340B savings in comparison to status quo. Sensitivity analyses were conducted to explore the robustness of the result. **Results:** There were 28,616 pregnancies among 23,268 women aged 18-51 years old. HCV screening was performed in 21,502 women and 492 (1.7%) pregnancies had positive HCV antibody. Positive HCV RNA was detected in 316 (1.4%) of pregnant women - averaging to 45 women per year. Of the 316 HCV RNA positive women, only 52 (16.3%) were prescribed DAA during pregnancy or within 12 months of delivery. Pregnant women with HCV viremia were less likely to be enrolled in private insurance (7% vs 40%) than pregnant women without HCV. Despite this cohort of pregnant women with HCV only including 22 women (7%) who were eligible to generate 340B cost-savings, had all been treated, the financial gain still would have been $215,000 in comparison to status quo. **Conclusion:** Despite universal HCV screening at our institution since 2017, DAA uptake among pregnant and postpartum women remains unacceptably low. **:** Our data demonstrates potential direct and immediate financial gain to investing in improved DAA uptake among pregnant and postpartum women with HCV, despite the small percentage eligible to generate 340B cost savings.

Table 1. Staffing model to provide Hepatitis C treatment in Status quo vs. Treat All

Staff	Percentage of FTE* for 52 patients** (Status quo)	Percentage of FTE* for 316 patients** (Treat All)
Pharmacist	4.16%	25.28%
Pharmacy technician	4.16%	25.28%
Case manager	2.60%	15.80%
Clinical research nurse practitioner	1.25%	7.58%
Gastroenterologist	1.25%	7.58%
Infectious disease physician	1.25%	7.58%
Radiologist	0.22%	1.36%
Ultrasound technician	1.08%	6.59%
Fibroscan technician	0.57%	3.45%

*FTE, one year of full time equivalent; **each patient is treated only once

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3298 | HEPATOCELLULAR CARCINOMA RISK AFTER DIRECT-ACTING ANTIVIRAL-INDUCED SUSTAINED VIROLOGIC RESPONSE ACCORDING TO BIOPSY-PROVEN FIBROSIS STAGE AND CLINICAL RISK FACTORS IN CHRONIC HEPATITIS C

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Background: Although direct-acting antiviral (DAA) therapy markedly reduces the risk of hepatocellular carcinoma (HCC) in patients with chronic hepatitis C, HCC continues to occur after sustained virologic response (SVR). Current surveillance strategies differ across regions, particularly for patients without cirrhosis. We aimed to clarify HCC incidence after SVR according to biopsy-proven fibrosis stage and to identify risk factors for HCC among patients with non-advanced fibrosis. **Methods:** We analyzed patients with chronic hepatitis C who initiated DAA therapy between September 2014 and July 2022 and achieved SVR. Patients with prior HCC, coinfection with HBV or HIV, autoimmune liver disease, primary biliary cholangitis, prior liver transplantation, or unavailable post-SVR HCC assessment were excluded. SVR was defined as serum HCV-RNA negativity at 24 weeks after the end of therapy. Among 3,369 SVR patients without prior HCC, 1,096 who underwent liver biopsy within 1 year before DAA initiation and had adequate histological assessment were included. Fibrosis stage was assessed using the METAVIR score and categorized as F0–2, F3, or F4. Follow-up started at SVR24. The cumulative incidence of HCC was evaluated using a competing-risk model, and risk factors were analyzed using Fine–Gray hazard regression. **Results:** The study cohort included 904 patients with F0–2, 103 with F3, and 89 with F4 fibrosis. During a median follow-up of 58.8 months from SVR24, 53 patients developed de novo HCC. The 5-year cumulative incidence of HCC increased with fibrosis stage: 3.6% in F0–2, 6.8% in F3, and 11.3% in F4. Annual HCC incidence remained below 1.5%, a commonly cited threshold for cost-effective for HCC surveillance, throughout follow-up in F0–2 patients, whereas it exceeded or approached this threshold in several post-SVR periods among patients with F3 or F4 fibrosis. Among F0–2 patients, multivariable Fine–Gray analysis identified age $\geq$75 years, diabetes mellitus, AST levels $\geq$30 U/L at SVR24, albumin levels $<$4.0 g/dL at SVR24, and AFP levels $\geq$5.0 ng/mL at SVR24 as independent risk factors for HCC. **Conclusion:** In patients with chronic hepatitis C who achieved DAA-induced SVR, biopsy-proven advanced fibrosis, particularly F4 fibrosis, was associated with a higher cumulative incidence of HCC, supporting continued long-term surveillance. Although most patients with F0–2 fibrosis had low annual HCC incidence, older age, diabetes, higher AST, lower albumin, and higher AFP levels were associated with HCC occurrence. These findings may help refine post-SVR HCC surveillance strategies beyond fibrosis stage alone.

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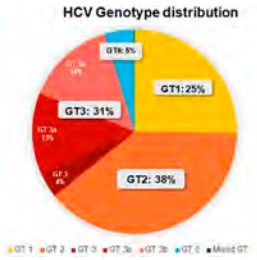
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3299 | A SIMPLIFIED APPROACH TO CURE CONFIRMATION USING SVR4 TO REPLACE SVR12 FOR PATIENTS WITH HCV WITH LEDIPASVIR/SOFOSBUVIR OR SOFOSBUVIR/VELPATASVIR WITH OR WITHOUT RIBAVIRIN TREATMENT (LEAP STUDY)

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Background: In western China, hepatitis C virus (HCV) exhibits substantial genotype diversity. Although sustained virologic response at post-treatment week 12 (SVR12) remains the standard endpoint for cure confirmation, loss to follow-up can be frequent in routine practice, limiting the feasibility of SVR12-based monitoring. In line with WHO-recommended simplified care models for HCV care, we evaluated whether sustained virologic response at post-treatment week 4 (SVR4) can reliably replace SVR12 after Ledipasvir/Sofosbuvir (LDV/SOF) or Sofosbuvir/Velpatasvir (SOF/VEL) with or without ribavirin (RBV) treatment. **Methods:** We performed a multicenter retrospective study across 10 hospitals (May 2018–February 2026). We assessed the concordance between SVR4 and SVR12 among patients with available results at both time points. **Results:** A total of 3676 patients with both SVR4 and SVR12 were included. Of these, 2029 were males, with a median age of 51 years (range 12-98). The HCV genotype was undetected for 1628 patients. Among the remaining 2048 patients, the proportions of genotype 1/2/3/6 and mixed genotypes were 25.39%, 38.38%, 31.15%, 4.98% and 0.10%, respectively. In the entire population, 97.77% (3594/3676) achieved SVR4 and 97.42% (3581/3676) achieved SVR12. Among SVR4 achievers, 13 failed to maintain SVR12, while all patients (82/82) who did not achieve SVR4 also failed SVR12. The positive predictive value (PPV) and negative predictive value (NPV) of SVR4 to predict SVR12 were 99.64% (95% confidence interval: 99.44-99.84) and 100%. **Conclusion:** Post-treatment week 4 HCV RNA testing provides excellent replacement of SVR12 and may serve as an earlier endpoint for cure confirmation in patients treated with LDV/SOF or SOF/VEL ± RBV. Shifting SVR assessment from week 12 to week 4 post-treatment may simplify cure confirmation and reduce loss to follow-up, particularly in regions with complex genotype distributions.



Concordance between SVR4 and SVR12

	Achieved SVR12	Failed SVR12	Total
Achieved SVR4	99.64% (3581/3594)	0.36% (13/3594)	3594
Failed SVR4	0	100% (82/82)	82
Total	3581	95	3676

Disclosures: Li Liu:Nothing to Disclose, Xiaobo Lu: Nothing to Disclose, Zhu Chen:Nothing to Disclose, Junmin Huang:Nothing to Disclose, Xiaoyun Peng: Nothing to Disclose, Caixia Yang:Nothing to Disclose, Chunfang You:Nothing to Disclose, Jie Wang:Nothing to Disclose, Cunliang Deng:Nothing to Disclose, Peng Hu:Nothing to Disclose.

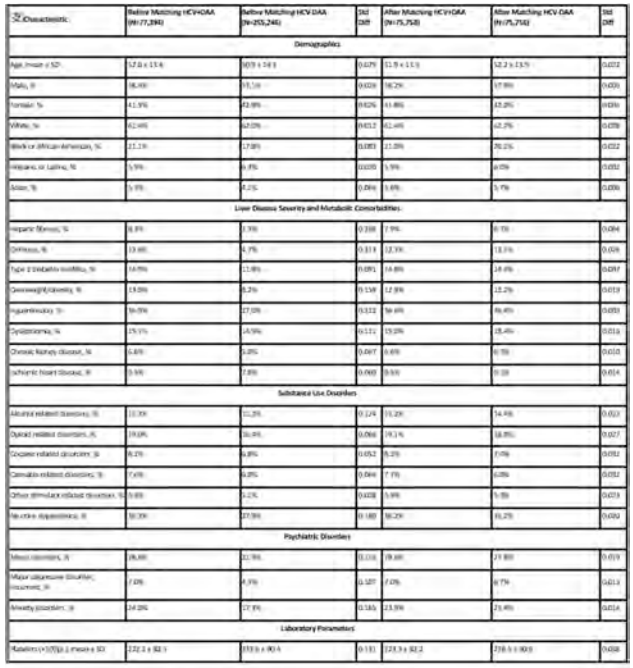
3300 | DIRECT-ACTING ANTIVIRAL THERAPY IS ASSOCIATED WITH REDUCED CARDIOVASCULAR, PSYCHIATRIC, AND MORTALITY OUTCOMES IN CHRONIC HEPATITIS C: A PROPENSITY SCORE-MATCHED ANALYSIS

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Background: Chronic HCV infection drives extrahepatic morbidity across cardiovascular, metabolic, and psychiatric systems. DAA therapy achieves SVR in >95% of patients, yet US treatment uptake remains ~30%. Quantifying the full spectrum of extrahepatic benefits is critical to reframing DAAs as a multisystem intervention and strengthening the case for universal treatment. **Methods:** This retrospective propensity score-matched cohort study utilized the TriNetX federated network (111 healthcare organizations). Adults (≥18 years) with chronic HCV (ICD-10: B18.2) diagnosed ≥2014 were stratified by DAA exposure. Patients with HIV, hepatitis B, liver transplant, HCC, chronic hepatic failure, variceal bleeding, or ascites were excluded. 1:1 propensity score matching balanced demographics, comorbidities (fibrosis, cirrhosis, diabetes, obesity, hypertension, dyslipidemia, CKD, ischemic heart disease, substance use disorders, mood/anxiety disorders, nicotine dependence), and platelet count. Primary outcomes were assessed 180–1,825 days post-index; a sensitivity analysis used unlimited follow-up. Kaplan-Meier analyses with hazard ratios (HR) were calculated. **Results:** After matching, 75,758 patients per cohort were analyzed (mean age ~52; ~58% male; ~61% White; ~21% Black; all standardized differences <0.1). DAA treatment was associated with significantly lower risk of MACE (HR 0.730, 95% CI 0.700–0.761), heart failure (HR 0.838, 0.791–0.888), type 2 diabetes (HR 0.830, 0.787–0.875), major depressive disorder (HR 0.859, 0.824–0.895), anxiety disorders (HR 0.876, 0.843–0.911), and all-cause mortality (HR 0.576, 0.547–0.606; all $p < 0.001$). Atrial fibrillation trended toward benefit (HR 0.909, $p = 0.009$). CKD, PAD, and liver cancer were not significant. Sensitivity analysis with unlimited follow-up confirmed all significant associations. **Conclusion:** DAA therapy was associated with significant reductions in MACE (27%), heart failure (16%), diabetes (17%), depression (14%), anxiety (12%), and mortality (42%) across >150,000 chronic HCV patients. These benefits demonstrate that DAAs function as a multisystem intervention beyond viral eradication. Current cost-effectiveness models focusing on liver outcomes likely underestimate treatment value. These findings support prioritizing DAA uptake toward HCV elimination.



Characteristic	Before Matching HCV+DAA (N=77,894)	Before Matching HCV DAA (N=255,246)	Std Diff	After Matching HCV+DAA (N=75,758)	After Matching HCV DAA (N=75,758)	Std Diff
Demographics						
Age [mean ± SD]	52.8 ± 13.4	50.9 ± 14.3	0.139	51.9 ± 13.3	52.2 ± 13.5	0.022
Male, %	58.4%	55.1%	0.066	58.2%	57.8%	0.008
Female, %	41.9%	43.9%	0.042	41.8%	42.2%	0.008
White, %	61.4%	62.0%	0.013	61.4%	62.2%	0.016
Black or African American, %	22.1%	17.8%	0.103	21.8%	20.1%	0.042
Hispanic or Latino, %	5.9%	6.4%	0.020	5.9%	6.0%	0.002
Asian, %	5.9%	4.2%	0.084	5.6%	5.7%	0.006
Liver Disease Severity and Metabolic Comorbidities						
Hepatic fibrosis, %	6.8%	1.5%	0.288	7.9%	6.7%	0.044
Cirrhosis, %	13.6%	4.7%	0.313	12.5%	13.1%	0.018
Type 2 diabetes mellitus, %	16.9%	13.8%	0.091	16.8%	16.4%	0.011
Overweight/obesity, %	13.8%	8.2%	0.178	12.8%	13.2%	0.013
Hypertension, %	36.9%	27.0%	0.212	36.6%	36.4%	0.003
Dyslipidemia, %	15.1%	10.5%	0.131	15.0%	15.4%	0.011
Chronic kidney disease, %	5.6%	3.8%	0.087	6.6%	6.7%	0.004
Ischemic heart disease, %	5.9%	3.8%	0.090	5.6%	5.7%	0.004
Substance Use Disorders						
Alcohol-related disorders, %	13.3%	11.2%	0.124	13.2%	14.4%	0.033
Opioid-related disorders, %	19.0%	10.4%	0.266	19.1%	18.9%	0.007
Cocaine-related disorders, %	8.2%	4.8%	0.152	8.2%	7.9%	0.012
Cannabis-related disorders, %	7.6%	6.8%	0.034	7.7%	6.9%	0.032
Other stimulant-related disorders, %	5.6%	3.2%	0.118	5.6%	5.3%	0.013
Nicotine dependence, %	30.3%	27.9%	0.160	30.2%	31.2%	0.022
Psychiatric Disorders						
Mood disorders, %	26.8%	21.9%	0.116	26.6%	27.8%	0.019
Major depressive disorder, recurrent, %	7.0%	4.3%	0.107	7.0%	6.7%	0.013
Anxiety disorders, %	24.0%	17.9%	0.165	23.9%	25.4%	0.014
Laboratory Parameters						
Platelets [×10⁹/µL; mean ± SD]	222.1 ± 82.1	233.6 ± 90.4	0.131	224.3 ± 82.2	218.1 ± 80.0	0.038

Table 1. Baseline Characteristics of the Study Cohorts Before and After 1:1 Propensity Score Matching

Disclosures: Muhammad Hassaan Arif Maan:Nothing to Disclose, Anand Shah:Nothing to Disclose, Rohan Karkra:Nothing to Disclose, Muhammad Mursaleen Ahmad:Nothing to Disclose, Sunnia Khan:Nothing to Disclose, Ethan Shamsian:Nothing to Disclose, Kaveh Hajifathalian:Nothing to Disclose, Ahmed Al-Khazraji: Nothing to Disclose.

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3301 | PREGNANCY OUTCOMES FOLLOWING GLECAPREVIR/PIBRENTASVIR EXPOSURE IN PREGNANT WOMEN WITH HEPATITIS C: A PHARMACOVIGILANCE ANALYSIS

Tatyana Kushner[1] Barbra Cave[2] John Marcinak[2] Catherine Chappell[3] Laura Marks[4] Madeline McCrary[4] Ahizechuwu Eke[5] Alexandru Iacob[2] Josephine Kwong[2] Rinal Patel[2] Ravi Jhaveri[6], [1]Weill Cornell Medicine, [2]AbbVie Inc, [3]University of Pittsburgh Medical Center, [4]Washington University School of Medicine, St. Louis, [5]Johns Hopkins University, [6]Northwestern University Feinberg School of Medicine

Background: Despite highly effective direct-acting antivirals (DAAs) for hepatitis C virus (HCV), safety data during pregnancy remain limited. As HCV rates increase among women of childbearing age, clinicians increasingly encounter inadvertent early pregnancy exposure to DAAs or would like to offer antenatal treatment, including the pangenotypic regimen glecaprevir/pibrentasvir (GLE/PIB). There is a lack of treatment recommendation for HCV during pregnancy, but AASLD/IDSA guidance states treatment can be considered during pregnancy on an individual basis after patient-physician discussion about the potential risks and benefits. **Methods:** We conducted a cumulative and descriptive analysis of pregnancy cases reported to AbbVie's global pharmacovigilance database (July 2017 to March 2026) from clinical trials, spontaneous reports, solicited sources and literature. Pregnancy cases with reported exposure were identified, and duplicate reports were reconciled. Maternal and fetal safety data, together with pregnancy outcomes, evidence of vertical transmission, and sustained virologic response at post-treatment week 12 (SVR12) following GLE/PIB exposure, were reviewed and analyzed. **Results:** A total of 328 pregnancies with reported GLE/PIB exposure were identified (**Table 1**); data were reported for 4 mother–neonate pairs. Most cases were spontaneous reports (N = 202); others were from solicited sources (N = 109), clinical trials (N = 10), and literature (N = 7). Of the 87 cases (26.5%) with documented pregnancy outcomes, 45 (51.7%) were live births, 17 (19.5%) were elective abortions, and 25 (28.7%) were spontaneous abortions. Among live births, 3 (6.7%) were preterm and 2 had reported congenital anomalies, including one case of patent ductus arteriosus/ventricular septal defect (PDA/VSD) after second-trimester exposure in a mother with comorbid substance use, and one case of early infantile epileptic encephalopathy with unknown timing of exposure. Treatment status was available for 223 cases: 58 ongoing at the time of reporting, 19 completed and 146 discontinued. No cases of vertical transmission were reported. 17 cases contained information consistent with achieving SVR. **Conclusion:** In this pharmacovigilance database analysis, reporting rates of spontaneous abortion and preterm birth in pregnancies with known outcomes were lower than rates reported in pregnant people with HCV without DAA exposure. Congenital anomalies were rarely reported, limiting detection of a pattern or trend. Interpretation is limited by missing outcome data and potential reporting bias inherent in real-world sources. The high rate of discontinuation may reflect a lack of shared decision making between patients and providers. These findings add to the collection of evidence of GLE/PIB in pregnancy and underscore the need for prospective studies to better define the safety of GLE/PIB exposure in pregnancy.

Table. Maternal characteristics of mothers with reported GLE/PIB exposure

Characteristic	Value
Region (n, %)	
United States	194 (59.1)
Germany	20 (6.1)
Japan	17 (5.2)
United Kingdom	13 (4.0)
Others	84 (25.6)
Ethnicity (n, %)	
Unknown	303 (92.4)
Caucasian	21 (6.4)
Asian	2 (0.6)
African American	1 (0.3)
Hispanic	1 (0.3)
Median age (years, IQR; n=147)	31 (26–35)
Age range (years)	17-52
Timing of GLE/PIB exposure (n, %)	
Unknown	190 (57.9)
Preconception	52 (15.9)
1st trimester	70 (21.3)
2nd trimester	11 (3.4)
3rd trimester	5 (1.5)

Note: Due to the nature of data collection in the pharmacovigilance database, some cases were reported as preconception exposures without clarifying if the exposure carried into the 1st trimester. In cases where continuation of treatment into the 1st trimester were clearly reported, they were counted as 1st trimester exposures.

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Consultant, Sanofi: Consultant, Seqirus: Consultant, Gilead: Advisor, GSK: Grant/Research Support, UptoDate: Royalties or patent beneficiary.

3302 | PERSISTENT NS5A RESISTANCE AFTER DIRECT-ACTING ANTIVIRAL FAILURE IN GENOTYPE 3 HEPATITIS C: IMPLICATIONS FOR RETREATMENT IN RESOURCE-LIMITED ELIMINATION PROGRAMS

Saima Mushtaq[1] Amjad Khan[1] Aaron Lim[2] Yu Fang[3] Tayyab Saeed Akhter[4], [1]The First Affiliated Hospital of Xi'an Jiaotong University, [2]University Of Bristol, [3]Xi'an Jiaotong University, [4]Center for Liver and Digestive Diseases, Holy Family Hospital, Rawalpindi Medical University, Pak

Background: Hepatitis C virus genotype 3 (HCV GT3) remains difficult to cure in patients with cirrhosis and prior direct-acting antiviral (DAA) exposure, particularly in low- and middle-income countries where access to high-barrier salvage regimens is limited. Pakistan has one of the world's largest HCV burdens, with GT3 predominance, yet real-world data on post-failure NS5A resistance and its persistence are scarce. We evaluated treatment failure, NS5A resistance-associated substitutions (RASs), and RAS persistence in a multicenter GT3 cohort from Pakistan. **Methods:** Adults with chronic HCV GT3 receiving DAA therapy through tertiary centers linked to hepatitis control programs in Pakistan were enrolled and followed for SVR12. Treatment-naïve patients received sofosbuvir/daclatasvir, while treatment-experienced patients received sofosbuvir/velpatasvir; patients with compensated cirrhosis received extended therapy with ribavirin according to local practice. Among patients with virological failure, NS5A RASs were assessed by Sanger sequencing. Longitudinal post-failure samples were evaluated up to 24 months to assess RAS persistence. Outcomes were stratified by prior treatment status and compensated cirrhosis. **Results:** Of 2,000 enrolled patients, 1,390 had evaluable SVR12 outcomes, including 972 treatment-naïve and 418 treatment-experienced patients. Overall SVR12 was 93.3% but was substantially lower in treatment-experienced than treatment-naïve patients. Treatment failure occurred in 93 patients and was strongly concentrated among those with compensated cirrhosis: 64 of 127 cirrhotic patients failed treatment compared with 29 of 1,263 non-cirrhotic patients. The risk of failure was approximately 22-fold higher in patients with cirrhosis than in those without cirrhosis. Among treatment failures, NS5A RASs were common, with Y93H detected more frequently in treatment-experienced than treatment-naïve patients. Multi-site RAS patterns were especially enriched in treatment-experienced patients with cirrhosis, suggesting accumulation of resistance after sequential NS5A-containing regimens. In the longitudinal subset, NS5A RASs persisted for up to 24 months, with the slowest clearance observed in treatment-experienced patients with compensated cirrhosis and faster decline among treatment-naïve non-cirrhotic patients. **Conclusion:** In this real-world HCV GT3 cohort from Pakistan, virological failure was concentrated in patients with compensated cirrhosis and prior DAA exposure, who also showed frequent and persistent NS5A resistance. These findings support risk-stratified retreatment pathways, avoidance of regimen recycling after NS5A failure, and prioritization of resistance-informed salvage strategies in resource-limited HCV elimination programs.

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3303 | COMPARATIVE EFFICACY AND SAFETY OF GLECAPREVIR/PIBRENTASVIR VERSUS SOFOSBUVIR/VELPATASVIR IN PATIENTS WITH HEPATITIS C: A MULTICENTER PROSPECTIVE STUDY

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Background: Direct-acting antivirals, including glecaprevir/pibrentasvir (GLE/PIB) and sofosbuvir/velpatasvir (SOF/VEL), have revolutionized hepatitis C virus (HCV) treatment. However, comparative data regarding their clinical outcomes and long-term risk of hepatocellular carcinoma (HCC) after sustained virologic response at 12 weeks (SVR12) remain limited. This study aimed to compare the clinical outcomes of these two regimens and identify predictors of post-SVR12 HCC development. **Methods:** A total of 478 patients with chronic HCV infection treated with GLE/PIB or SOF/VEL were prospectively enrolled in a multicenter cohort between January 2016 and June 2025. Changes in liver enzymes, renal function, hepatic function, and fibrosis markers, including fibrosis-4 (FIB-4) index and aspartate aminotransferase-to-platelet ratio index (APRI), were assessed from baseline to end of treatment (EOT) and SVR12. Logistic regression analysis was performed to identify independent predictors of post-SVR12 HCC. **Results:** The mean age was 60.5 ± 11.8 years, 46.8% were male, and the mean follow-up duration was 26.5 ± 19.9 months. Overall, 474 patients (99.2%) achieved SVR12, while the 4 patients who failed to achieve SVR12 had all received GLE/PIB

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therapy. Both regimens significantly improved liver enzymes and fibrosis markers from baseline to EOT and SVR12 (all $P < 0.001$). At EOT, alanine aminotransferase reduction was greater in the GLE/PIB group than in the SOF/VEL group (-45.9 ± 63.6 vs. -21.4 ± 41.9, $P < 0.001$). Estimated glomerular filtration rate (eGFR) significantly decreased in the SOF/VEL group, but not in the GLE/PIB group, with a significant between-group difference ($P = 0.009$). At SVR12, eGFR decreased in both groups, with a greater decline in the SOF/VEL group (P-between = 0.02). During follow-up after SVR12, 9 patients developed de novo HCC. Multivariable analysis identified EOT ALBI > -2.6 (adjusted odds ratio [aOR] 5.98, 95% confidence interval [CI] 1.06–33.68), FIB-4 > 3.25 (aOR 6.74, 95% CI 0.97–46.95), and APRI > 1.0 (aOR 15.26, 95% CI 2.18–106.55), as well as SVR12 APRI > 1.0 (aOR 16.36, 95% CI 2.38–112.51), as predictors of HCC development. **Conclusion:** Both GLE/PIB and SOF/VEL achieved excellent antiviral efficacy and improved hepatic inflammation and fibrosis markers. GLE/PIB showed greater improvement in liver enzymes, whereas SOF/VEL was associated with greater renal function decline. Residual fibrosis and liver dysfunction after SVR12 remained associated with de novo HCC development.

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3304 | SHORTER, FASTER: PATIENT CHARACTERISTICS ASSOCIATED WITH 12- VERSUS 8-WEEK SOFOSBUVIR/VELPATASVIR IN AN INCARCERATED HCV COHORT

Christine Wong[1] Victoria Galustian[1] Juneho Jang[1] Grace Ruhnke[1] Mahesh Patel[2] Scott Borgetti[2] Juliana Chan[3], [1]University of Illinois Chicago Retzky College of Pharmacy, [2]University of Illinois Chicago, [3]University of Illinois at Chicago

Background: Chronic hepatitis C virus (HCV) infection is disproportionately prevalent in incarcerated populations. Sofosbuvir/velpatasvir (SOF/VEL) is an effective, well-tolerated therapy with a standard 12-week duration. Available data suggest that an 8-week course may achieve comparable sustained virologic response (SVR) in treatment-naïve, non-cirrhotic patients. Shorter regimens may offer logistical advantages in correctional settings, where treatment continuity is challenged by transfers and variable release dates. Real-world data describing patient characteristics by SOF/VEL treatment duration in carceral systems remain limited. This study compared patient characteristics by treatment duration and evaluated SVR outcomes. **Methods:** We conducted an IRB-approved retrospective chart review of incarcerated adults treated with SOF/VEL in the Illinois Department of Corrections from 1/29/2016 to 11/25/2025. Patients without documented fibrosis stage or HCV genotype were excluded. Variables included age, race/ethnicity, HCV genotype, and fibrosis stage (F0-F1, F2, F3, F4). Patient characteristics were compared by treatment duration (12 versus 8 weeks). Mean age differences were assessed using Welch's t-test and chi-square tests were used for categorical variables. SVR was defined as undetectable HCV RNA ≥ 12 weeks post-treatment. Ribavirin use was evaluated descriptively. **Results:** Among 1065 incarcerated adults, 873 (81.9%) received 12-weeks and 192 (18%) received 8-week therapy. SVR was similar between regimens (12-week: 96.4%; 8-week: 95.8%). Mean age differed by treatment duration, with older patients receiving 12-week versus 8-week (48.2 ± 12.9 versus 36.5 ± 8.9 years; $p < 0.0001$). Fibrosis stage differed by duration ($p < 0.001$): 26.7% of F0-F1, 11.5% of F2, 8.8% of F3, and 1.4% of F4 patients received 8-week therapy. HCV genotype distribution differed by duration in unadjusted analysis ($p = 0.001$). Race/ethnicity differed by duration ($p < 0.001$): 23% White, 4.6% Black, and 7.5% Hispanic patients received 8-week therapy. Ribavirin use differed between regimens, with greater use in the 8-week group (53.6% versus 43.8%; $p = 0.014$). **Conclusion:** In this incarcerated cohort, age, fibrosis stage, genotype, and race/ethnicity differed between patients receiving 12- versus 8-week SOF/VEL in unadjusted analyses, while SVR remained high across all treatment groups. These findings support real-world treatment selection practices and suggest that individualized use of shortened SOF/VEL therapy may improve treatment efficiency and offer potential cost savings in correctional health systems.

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3305 | ANTIVIRAL CHOICE AT THE METABOLIC CROSSROADS: TENOFOVIR VERSUS ENTECAVIR AND RISK OF CIRRHOSIS AND HEPATIC DECOMPENSATION IN CHRONIC HEPATITIS B WITH METABOLIC DYSFUNCTION

Chimezirim Ezeano[1] Ifelunwa Osanakpo[2] Ihunanya Kanu[3] Sarpong Boateng[4] Guy Loic Nguefang Tchoukeu[5] Cherechi Nwabueze[6] Emeka Stanley Obi[7] Goodness Joseph[8] Onyinyechukwu Ozumba[0] Samuel Ayedun[10] David Narvaez-De los Rios[11] Madu

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Background: Metabolic dysfunction may worsen liver disease progression in chronic hepatitis B (CHB), yet whether antiviral choice is associated with differential hepatic outcomes in patients with concurrent type 2 diabetes mellitus (T2DM) and MASLD/MASH remains unclear. We compared incident cirrhosis and hepatic decompensation among adults with CHB, T2DM, and MASLD/MASH treated with tenofovir versus entecavir. **Methods:** We performed a retrospective propensity score–matched cohort study using a federated electronic health record network. Adults with CHB, T2DM, and MASLD/MASH were grouped by tenofovir-based therapy or entecavir. Patients with chronic hepatitis C, alcohol-associated liver disease, autoimmune liver disease, cholestatic liver disease, or inherited liver disease were excluded. Outcomes were assessed from 1 day after index through available follow-up. The primary outcome was incident cirrhosis; the secondary outcome was hepatic decompensation, defined by ascites, hepatic encephalopathy, variceal bleeding, hepatorenal syndrome, hepatic failure, or spontaneous bacterial peritonitis. Patients with the outcome before the time window were excluded. Matching yielded 255 patients per cohort **Results:** After matching, median follow-up was 1,233 days in the tenofovir cohort and 1,195 days in the entecavir cohort. For incident cirrhosis, 89 tenofovir-treated and 94 entecavir-treated patients were excluded for prior cirrhosis, leaving 166 and 161 patients, respectively. Incident cirrhosis occurred in 25 tenofovir-treated patients versus 24 entecavir-treated patients, with similar risk between groups (15.1% vs 14.9%; risk difference [RD] 0.002, 95% CI -0.076 to 0.079, p = 0.969; risk ratio [RR] 1.010, 95% CI 0.603–1.693). Kaplan-Meier analysis showed no significant difference in time-to-cirrhosis (HR 0.816, 95% CI 0.460–1.446; log-rank p = 0.484). For hepatic decompensation, 47 tenofovir-treated and 61 entecavir-treated patients were excluded for prior decompensation, leaving 208 and 194 patients, respectively. Decompensation occurred in 17 tenofovir-treated patients versus 18 entecavir-treated patients (8.2% vs 9.3%; RD -0.011, 95% CI -0.066 to 0.044, p = 0.694; RR 0.881, 95% CI 0.468–1.659). Time-to-decompensation was not significantly different between groups (HR 0.739, 95% CI 0.377–1.448; log-rank p = 0.377). **Conclusion:** In this propensity-matched real-world cohort of adults with CHB, T2DM, and MASLD/MASH, tenofovir-based therapy and entecavir were associated with similar risks of incident cirrhosis and hepatic decompensation. These findings suggest comparable hepatic effectiveness between antiviral strategies in a metabolically high-risk CHB population, although residual confounding, coding-based ascertainment, and lack of granular liver disease severity measures limit causal interpretation.

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3306 | REDEFINING THRESHOLDS FOR APRI AND FIB-4 SCORES IN DIAGNOSING CIRRHOSIS: EVIDENCE FROM A HIGH-PREVALENCE DISTRICT IN KARACHI, PAKISTAN

Ursala Adil[1], [1]Rutgers Health Trinitas Regional Medical Center

Background: Chronic infection with hepatitis C virus (HCV) is a major public health problem. Simplified and cost-effective diagnostic algorithms and decentralized care can improve access to treatment and reduce delays between testing and treatment initiation. APRI and FIB-4 scores are widely used scoring systems for liver fibrosis and have been validated against transient elastography. A cut-off of 1.5 and 3.25 for APRI and FIB-4 respectively is highly specific but not sensitive enough for diagnosing cirrhosis. **Methods:** This study was conducted in rural communities of district Malir of Karachi which is a high burden area for Hepatitis C. As part of micro elimination efforts in this area from Oct 2019 to June 2022, door-to-door screening was performed using RDTs, those with a positive HCV Ab result were reflex tested for HCV RNA, CBC, and liver enzymes (AST and ALT). Patients with APRI $\geq$ 1.5 and/or FIB-4 $\geq$ 3.25 were categorized as having cirrhosis and prescribed a 24-week DAA regimen of Sofosbuvir and Daclatasvir. Those with APRI < 1.5 and FIB-4 < 3.25 were considered to be non-cirrhotics and received a 12-week treatment. SVR 12 testing was done to assess treatment outcomes, and ROC curves were used to determine APRI and FIB-4 cutoffs based on SVR 12 results. Chi-square test was applied to determine any significant association between

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treatment outcome (SVR 12 result) and duration of treatment using the new threshold for APRI and FIB-4. **Results:** The study included 1,424 individuals with chronic HCV (average age: 47), with 64% females and 36% males who completed treatment with DAAs and SVR 12 testing. Of these, 87% received a 12-week treatment, and 13% received a 24-week treatment. The overall SVR 12 rate was 88%. Based on the ROC analysis, we determined a cutoff value of 0.639 as the predicted threshold for APRI and 1.351 as the predicted threshold for FIB-4 requiring a 24-week treatment duration.With the existing cut-off for APRI, 11.3% of individuals who received 12 weeks of treatment did not achieve SVR 12. However, upon categorizing using a new threshold ($\leq$0.639), there was a reduction in treatment failures in those who received 12 weeks of treatment to 9.7%. Similarly, applying the established FIB-4 cutoff of 3.25 showed 11.4% treatment failures in individuals on a 12-week treatment, however categorizing with a new threshold ($\leq$1.351) reduced treatment failures to 9.4%. **Conclusion:** Lowering the threshold for APRI to 0.639 and FIB-4 to 1.35 for determining cirrhosis in patients with chronic HCV can improve SVR 12 results after treatment with Sofosbuvir and Daclatasvir.

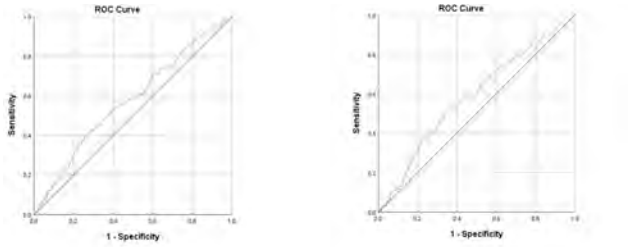


Figure: Receiver-operating characteristic (ROC) curve for APRI (left) and FIB-4 (right) scores in predicting optimal cirrhosis cutoff threshold to determine appropriate treatment duration to achieve SVR12

Disclosures: Ursala Adil:Nothing to Disclose.

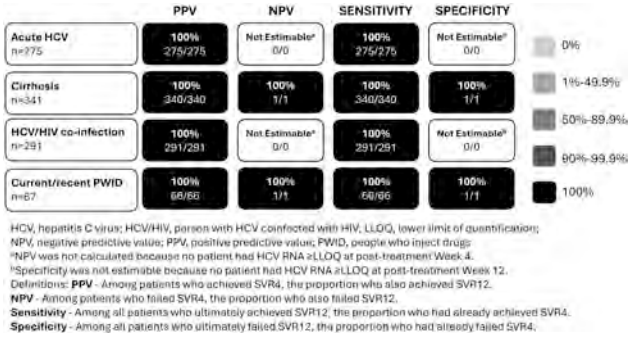
3307 | PREDICTIVE VALUE OF SVR4 WITH GLECAPREVIR/PIBRENTASVIR IN PATIENTS WITH CIRRHOSIS, HCV/HIV COINFECTION, RECENT INJECTION DRUG USE, OR ACUTE INFECTION

Mark Sulkowski[1] Marina Klein[2] Chris Fraser[3] Barbra Cave[4] Rinal Patel[5] Yanna Song[4] Dimitri Semizarov[4] Karine Lacombe[6] Julio Gutierrez[7], [1]Johns Hopkins Medicine, [2]McGill University Health Centre, Montreal, QC, Canada, [3]Cool Aid Community Health Centre, Victoria, BC, Canada, [4]AbbVie Inc, [5]rinal.patel@abbvie.com, [6]Sorbonne Université, Paris, France, [7]Scripps Center for Organ and Cell Transplantation, La Jolla, CA

Background: Capturing sustained virologic response at post-treatment week 12 (SVR12) can be challenging in real-world clinical practice. Concordance between SVR4 and SVR12 is well established in chronic HCV, and guidelines have introduced SVR4 as a potential endpoint for some populations. However, the predictive value of SVR4 is incompletely understood in acute HCV cases and in special populations, such as those with compensated cirrhosis, HIV coinfection (HCV/HIV), or people who inject drugs (PWID). **Methods:** SVR data were pooled from 14 Phase 2/3 studies of patients with chronic or acute HCV treated for 8 weeks with glecaprevir/pibrentasvir (G/P). To determine the concordance of SVR4 with SVR12, we measured positive predictive value (PPV), negative predictive value (NPV), sensitivity, and specificity of SVR4 in 4 cohorts: cirrhosis, HCV/HIV, current/recent (within the last 12 m) PWID, and acute HCV infection. Missing HCV RNA values in the SVR window were imputed backward, where possible, first using the nearest post-window central lab HCV RNA result and then using a local lab HCV RNA result (if central lab results were unavailable). In the primary analysis, patients with missing HCV RNA data within the SVR4 and/or SVR12 window after imputations were excluded; also excluded were those with adjudicated reinfection (new infection) at SVR12. In the sensitivity analysis, patients with missing SVR4 and/or SVR12 after backward imputation were deemed as failures. **Results:** Among 2824 patients with HCV, 12.3% (n = 348) had cirrhosis, 10.5% (n = 296) had HCV/HIV, 2.7% (n = 75) were current/recent PWID, and 10.1% (n = 286) had acute HCV infection. In the primary analysis, PPV of SVR4 was 100% across all cohorts; NPV and specificity were 100% for the cirrhosis and PWID cohorts; they were not estimable for HCV/HIV or acute infection. Sensitivity was 100% across all cohorts. The small sample sizes in the nonresponder categories limited the assessment of specificity and NPV in some cohorts. In the sensitivity analysis, when missing values after imputation, relapses, and reinfections were treated as failures, PPV was 100% in cirrhosis (340/340), 99.3% in HCV/HIV (291/293), 97.1% in PWID (66/68), 97.9% in acute HCV (275/281); NPV and sensitivity were 100% throughout. Specificity was 100% in cirrhosis, 60.0% in HCV/HIV, 77.8% in PWID, and 45.5% in acute HCV. **Conclusion:** In patients with cirrhosis, HCV/HIV coinfection, current/recent illicit drug use or acute HCV, treated with 8-week G/P for HCV in clinical trials, SVR4 and SVR12 were concordant, with high PPV and NPV. These data support SVR4 as a potential surrogate for HCV cure in clinical practice when SVR12 may later be unavailable. Although the clinical trial results may not be fully generalizable to real-world patient behavior and visit adherence, confirmation of SVR12 remains important for patients with HCV who may be at risk for early reinfection or relapse.

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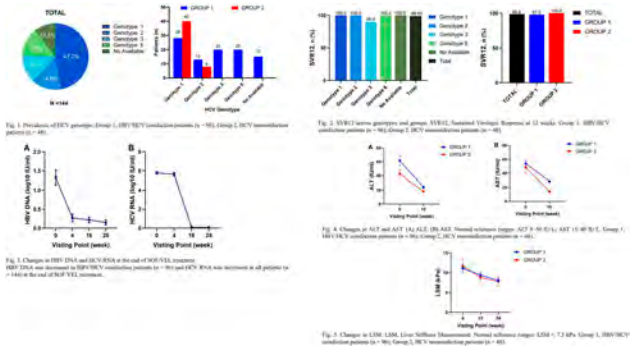


Disclosures: Mark Sulkowski:AbbVie: Advisor, Arbutus: Advisor, Aligos: Advisor, Gilead: DSMB member, Precision Biosciences: Advisor, Vir: Advisor, Vir: Grant/Research Support, GSK: Advisor, GSK: Grant/Research Support, Virion: Advisor, ImmunoCore: DSMB member, Pfizer: Advisor, Marina Klein:Nothing to Disclose, Chris Fraser:Abbvie: Grant/Research Support, Gilead Sciences: Grant/Research Support, ViiV Healthcare: Grant/Research Support, Indivior: Speaking and Teaching, Barbra Cave:Nothing to Disclose, Rinal Patel:Abbvie Pharmaceuticals: Employee, Yanna Song:Nothing to Disclose, Dimitri Semizarov:Nothing to Disclose, Karine Lacombe:Nothing to Disclose, Julio Gutierrez:Nothing to Disclose.

3308 | COMPARISON OF EFFICACY BETWEEN 12-WEEK SOFOSBUVIR/VELPATASVIR (SOF/VEL) REGIMEN COMBINED WITH PRE-USE TENOFOVIR ALAFENAMIDE (TAF) FOR HCV/HBV COINFECTION AND SOF/VEL ALONE FOR HCV MONOINFECTION

Ning Lin[1] Yifan Han[1] Qingya Wang[1] Haiyang Zhou[2] Ying Liu[2] Mengqi Li[3] Yanyan Yu[1] Xiaoyuan Xu[1], [1]Peking University First Hospital, [2]Beijing iGandan Foundation, [3]Beijing Ditan Hospital, Capital Medical University

Background: Compare and evaluate the efficacy and safety of the 12-week sofosbuvir/velpatasvir (SOF/VEL) regimen combined with pre-use tenofovir alafenamide (TAF) for 4 weeks in the treatment of hepatitis C virus (HCV)/hepatitis B virus (HBV) coinfection, and SOF/VEL alone for 12 weeks in the treatment of HCV monoinfection, in treatment-naive adult patients with genotype 1–6 HCV, with or without compensated cirrhosis in China. **Methods:** This was a multi-center, prospective, single-arm, open-label clinical trial (ChiCTR2000033390). Eligible treatment-naive adult patients were enrolled and divided into the HCV/HBV coinfection group and the HCV monoinfection group according to the infection type. The coinfection group was treated with the 12-week SOF/VEL regimen combined with pre-use TAF for 4 weeks, while the monoinfection group was treated with the 12-week SOF/VEL regimen alone. The primary endpoint was the sustained virological response (SVR12) for HCV at 12 weeks after the discontinuation of SOF/VEL treatment. The secondary endpoints included HBV virological response in the coinfection group, changes in ALT, AST and liver stiffness in both groups, incidence of adverse reactions, and comparisons of the above indicators between the two groups. **Results:** A total of 144 eligible patients were enrolled, including 96 patients in the HCV/HBV coinfection group (Group 1) and 48 patients in the HCV monoinfection group (Group 2). There were no statistically significant differences in baseline data (age, gender, distribution of HCV genotypes, proportion of cirrhosis, etc.) between the two groups ($P > 0.05$). After treatment, the overall SVR12 rates were 97.9% in the coinfection group and 100% in the monoinfection group, with no significant difference ($P > 0.05$). HCV RNA levels were dramatically decreased in all patients. In the co-infection group, the HBV DNA level was significantly decreased compared with the baseline, and one patient experienced HBV reactivation. Liver stiffness measurements (LSM), ALT, and AST were all significantly improved in both groups, with no between-group differences ($P > 0.05$). During the entire treatment process, the incidence of adverse reactions in both groups was low (5.2% vs 4.1%), most of which were mild to moderate (such as fatigue and nausea), and there were no serious adverse reactions or treatment-related withdrawal events. **Conclusion:** The 12-week SOF/VEL regimen combined with pre-use TAF for 4 weeks for HCV/HBV coinfection and SOF/VEL alone for HCV monoinfection both achieve excellent efficacy and favorable safety, with no significant difference between regimens. Pre-use TAF effectively prevents HBV reactivation in patients with coinfection, providing a reliable basis for the individualized treatment of patients with different HCV-related infection types in clinical practice.



Disclosures: Ning Lin:Nothing to Disclose, Yifan Han: Nothing to Disclose, Qingya Wang:Nothing to Disclose, Haiyang Zhou:Nothing to Disclose, Ying Liu:Nothing to Disclose, Mengqi Li:Nothing to Disclose, yanyan yu: Nothing to Disclose, Xiaoyuan Xu:Nothing to Disclose.

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3309 | REAL-WORLD IMPACT OF DRUG-DRUG INTERACTIONS (DDI): WHY COMPLEX HCV PATIENTS ARE PREFERENTIALLY TREATED WITH SOFOSBUVIR/VELPATASVIR (SOF/VEL) OVER GLECAPREVIR/PIBRENTASVIR (GLE/PIB)

Juan Macias[1] Francisco Tellez[2] Angela Camacho[3] Pilar Rincon[4] Antonio Rivero[3] Dolores Arenga-Barrios[2] Juan Pineda[5], [1]Departamento de Medicina. Universidad e Sevilla, [2]Hospital Universitario Puerto Real, Cadiz, Spain, [3]Hospital Universitario Reina Sofía, Cordoba, Spain, [4]Hospital Universitario Virgen de Valme, Seville, Spain, [5]Departamento de Medicina. Universidad de Sevilla, Spain

Background: Direct-acting antivirals (DAAs) share pharmacokinetic pathways with comedications, posing a risk for DDIs. Despite this, there is limited information on whether these DDIs translate into changes in toxicity or efficacy in clinical practice. We aimed to compare the impact of DDIs on safety and efficacy of GLE/PIB vs SOF/VEL, as well as the clinical actions (comedication switches, withdrawals, or dose reductions) required to address DDIs with either regimen in real-world conditions of use. **Methods:** This multicenter, retrospective, observational study included HCV treatment-naive patients from the GEHEP 001/HEPAVIR cohort taking ≥ 1 comedication or recreational drug. Data from patients treated with SOF/VEL or GLE/PIB in clinical practice between January 2018 and December 2023 were analyzed. **Results:** 542 patients were evaluated (SOF/VEL: 354; GLE/PIB: 188). Baseline patient characteristics for SOF/VEL vs GLE/PIB were: Age, 53.7 vs 51 ($p = 0.002$); HIV, 151 (42.7%) vs 50 (26.6%), ($p < 0.001$); cirrhosis 107 (31.0%) vs 15 (8.2%), ($p < 0.001$); comorbidities, 303 (86%) vs 128 (68%), $p < 0.001$. Before treatment, clinical actions were observed in 101 (31%) SOF/VEL and 44 (23%) GLE/PIB patients ($p = 0.199$). GLE/PIB required more drug discontinuations [35 (80%) vs 44 (44%); $p < 0.001$]. More dose/schedule changes were recorded for SOF/VEL [38 (35%) vs 7 (16%); $p = 0.009$]. During treatment, there were 54 (15.3%) clinical actions in SOF/VEL and 30 (16.0%) in GLE/PIB groups ($p = 0.830$). Discontinuations were more frequent with GLE/PIB [14 (46.7%) vs 4 (7.4%); $p < 0.001$]. Adverse events (AE) were recorded in 93 (26%) SOF/VEL and 36 (19%) GLE/PIB patients ($p = 0.064$). Out of those AE, 20 (22%) SOF/VEL vs 17 (47%) GLE/PIB patients suffered AE attributable to comedication ($p = 0.007$). AE's related with DDIs were identified in 3 (8.3%) patients on GLE/PIB vs none on SOF/VEL ($p = 0.021$). Virological response to SOF/VEL and GLE/PIB was similar. **Conclusion:** In clinical practice, because of the different DDI profile, SOF/VEL may be suitable in a broader spectrum of patients than GLE/PIB, including those with more comorbidities and comedications. Permanent comedication discontinuations are more frequent with GLE/PIB, before and during treatment. Conversely, SOF/VEL was associated with more dose/schedule modifications pre-treatment. Patients on GLE/PIB show a higher frequency of adverse effects related to comedications and with DDIs, but no differences in the rate of SVR.

Disclosures: JUAN MACIAS:Gilead: Speaking and Teaching, FRANCISCO TELLEZ:Nothing to Disclose, ANGELA CAMACHO:Nothing to Disclose, PILAR RINCON:Nothing to Disclose, ANTONIO RIVERO:Nothing to Disclose, DOLORES ARENGA-BARRIOS:Nothing to Disclose, JUAN PINEDA:Nothing to Disclose.

3310 | DOES THE PRESENCE OF NS5A RESISTANCE-ASSOCIATED SUBSTITUTION SIGNIFICANTLY AFFECT THE SVR RATE?

Murad Qirem[1] Jihad Slim[1] Lina AlQirem[2] Shahd Yaghi[1] Ahmad AlQirem[3] Kevin Leyden[4] Corey Rosmarin-DeStefano[5], [1]New York Medical College, [2]UAMS, [3]Jordan University Of Science and Technology, [4]NJCRI (North Jersey Community Research Initiative), [5]North Jersey Community Research Initiative

Background: NS5A resistance-associated substitutions (RAS) may be an important predictor of treatment response among individuals infected with chronic hepatitis C virus (HCV), particularly among genotype 1a and genotype 3. However, real-world data evaluating sustained virologic response (SVR) in individuals harbouring clinically significant NS5A mutations remain limited. **Methods:** We conducted a retrospective review of prospectively collected data through our telehealth model of HCV treatment in New Jersey among individuals with HCV infection who underwent NS5A resistance testing. Individuals with genotype 1a and genotype 3 infection harbouring significant NS5A RAS were included. Demographic, laboratory, fibrosis, treatment, and virologic outcome data were collected. The primary outcome was achievement of SVR following direct-acting antiviral therapy. **Results:** A total of 14 HCV-infected individuals with significant NS5A RAS were identified. The mean age was 49.3 ± 12.3 years, and 78.6% were males. Race included 42.9% African American, 35.7% White, and 14.3% Hispanic or Latin American. Genotype 1a was present in 57.1% of individuals, while 42.9% had genotype 3 infection. Mean baseline HCV viral load was 2.52 ± 2.73 million IU/mL. Fibrosis staging demonstrated predominantly minimal fibrosis, with 57.1% of patients classified as F0/F1 fibrosis (Table 1).Treatment regimens included sofosbuvir/velpatasvir (S/V) (n = 6), glecaprevir/

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pibrentasvir (G/P) (n = 4), and sofosbuvir/velpatasvir/voxilaprevir (S/V/V) (n = 4). Overall, SVR was achieved in 11 out of 14 (78.6%). Individuals treated with S/V/V achieved the highest SVR rate at 100% (4/4), followed by S/V at 83.3% (5/6). Patients treated with G/P demonstrated a lower SVR rate of 50% (2/4). Three patients failed to achieve SVR, including two treated with G/P and one treated with S/V. **Conclusion:** In this real-world cohort of HCV patients with clinically significant NS5A RAS mutations, high SVR rates remained achievable with direct-acting antiviral therapy, particularly with salvage therapy using S/V/V. Lower response rates observed with G/P may highlight the importance of resistance profiling when selecting antiviral regimens. Larger studies are needed to further define optimal treatment strategies for patients with NS5A RAS.

Table 1. Baseline Characteristics of Patients With Significant NS5A Mutations (n=14)

Characteristic	Value
Age, mean ± SD (years)	49.3 ± 12.3
Sex, n (%)	Male: 11 (78.6%); Female: 3 (21.4%)
Race, n (%)	White: 5 (35.7%)
	Black or African American: 6 (50%)
	Hispanic or Latin American: 2 (14.3%)
Genotype, n (%)	Genotype 1a: 8 (57.1%)
	Genotype 3: 6 (42.9%)
Baseline HCV Viral Load, mean ± SD (IU/mL)	2,519,704 ± 2,726,167
Fibrosis Stage, n (%)	F0/F1: 8 (57.1%)
	F2/F3: 4 (28.6%)
	F4: 2 (14.3%)

Disclosures: Murad Qirem:Nothing to Disclose, jihad slim:gilead: Speaking and Teaching, abbvie: Speaking and Teaching, Lina AlQirem:Nothing to Disclose, Shahd Yaghi:Nothing to Disclose, Ahmad AlQirem: Nothing to Disclose, Kevin Leyden:Gilead Sciences: Speaking and Teaching, Abbvie, Inc.: Advisor, Corey Rosmarin-DeStefano:Nothing to Disclose.

3311 | ◆ PRE-TREATMENT HCV VIRAL LOAD IS ASSOCIATED WITH BLUNTED ISG RESPONSES IN POST-CURE PBMCS

Olivia Mezzetti[1] Jasneet Aneja[1] Min Xu[1] Thien Trang Nguyen[1] Yongtao Wang[1] Shadi Salloum[1] Swastika Tripathi[1] Zeinab Heidariyan[1] Raymond Chung[1] Wenyu Lin[1], [1]Massachusetts General Hospital, Harvard Medical School

Background: Despite successful cure with direct-acting antiviral (DAA) therapy, chronic Hepatitis C virus (HCV) infection may induce persistent alterations in innate immune function. Previous transcriptomic analyses demonstrated lower post-cure interferon-stimulated gene (ISG) expression in patients with high pre-treatment viral load (VL) compared to those with low VL. Because type I interferons play a central role in antiviral immunity through induction of ISGs, we investigated whether immune cell responsiveness to exogenous type I IFN remains altered after cure and whether the magnitude of these responses is associated with pre-treatment viral load. **Methods:** Preliminary tests of uninfected PBMCs treated with 2, 10, and 30 IU/mL IFN-α for 4, 6, 8, 12, and 24 hours were used to determine optimal IFN dosage and time course for ISG responses. Patients cured of HCV within the past 4 years, defined by sustained virologic response 12 weeks after treatment completion (SVR12), were then identified from our extensive repository. All patients were treatment naïve. Pre-treatment and post-SVR PBMC samples were obtained from 15 patients who harbored high VL (>500K) and 15 patients who harbored low VL (<500K) prior to treatment. PBMC samples were also obtained from 15 uninfected control patients. PBMCs from each time point (pre-treatment or post-cure) were treated with 10 IU IFN-α for 4 hours, and expression of a panel of 20 ISGs was assessed by qPCR. Post-cure ISG expression at baseline and in response to IFN stimulation was compared between VL groups and as a continuous function of pre-treatment VL. **Results:** Preliminary findings in healthy PBMCs showed that 10 IU/mL IFN-α treatment for 4 hours showed the most significant increase in expression of 15 of the 20 target ISGs. Prior to IFN stimulation, baseline ISG expression in post-cure PBMC samples was found to be lower in patients who had a high VL prior to DAA therapy compared to those who had a low VL, supporting previous findings. In response to IFN stimulation, post-cure PBMCs from the high VL group exhibited a lower fold change in ISG expression than the low VL group on average. Further, pre-treatment VL exhibited a significant negative linear correlation with IFN-stimulated ISG fold change. All post-cure PBMCs, regardless of viral load, exhibited a lower fold change in expression compared to the healthy controls. **Conclusion:** Post-cure PBMC interferon responsiveness was altered in a viral load–dependent manner. Specifically, individuals with higher pre-treatment viral load exhibited persistently reduced baseline ISG expression and diminished ISG induction in response to exogenous type I IFN compared to low viral load individuals and healthy controls, suggesting that chronic infection persistently impairs innate immune signaling pathways and may durably alter host immune responses even after cure. These findings have potential implications for immune function in cured HCV patients.

Disclosures: Olivia Mezzetti:Nothing to Disclose, Jasneet Aneja:Nothing to Disclose, Min Xu:Nothing to Disclose, Thien Trang Nguyen:Nothing to Disclose, Yongtao Wang:Nothing to Disclose, Shadi Salloum: Nothing to Disclose, Swastika Tripathi:Nothing to Disclose, Zeinab Heidariyan:Nothing to Disclose,

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Raymond Chung:Nothing to Disclose, Wenyu Lin: Nothing to Disclose.

3312 | ◆ MULTISTEP AND DE NOVO-LIKE HEPATOCARCINOGENESIS AFTER SUSTAINED VIROLOGIC RESPONSE FOR CHRONIC HEPATITIS C: AN EOB-MRI-BASED ANALYSIS

Tomoko Tanaka[1] Takuto Nosaka[1] Shouichi Namikawa[1] Arisa Saito[1] Yosuke Murata[1] Yu Akazawa[1] Kazuto Takahashi[1] Tatsushi Naito[1] Yasunari Nakamoto[2], [1]University of Fukui, [2]University of Fukui

Background: Although sustained virologic response (SVR) after antiviral therapy reduces hepatocellular carcinoma (HCC) incidence in chronic hepatitis C virus (HCV) patients, hepatocarcinogenesis can still occur post-SVR. Hepatobiliary phase (HBP)-hypointense nodules on Gd-EOB-DTPA-enhanced magnetic resonance imaging (EOB-MRI) are considered precursors of multistep hepatocarcinogenesis; however, hypervascular HCC may also develop without detectable antecedent lesions. This study aimed to characterize imaging progression patterns of HCC post-SVR and investigate their associated clinicobiological features. **Methods:** We retrospectively analyzed 134 patients with chronic HCV infection who achieved SVR and underwent serial follow-up EOB-MRI examinations between January 2015 and December 2022. Newly developed hypervascular HCCs were classified into a multistep group, showing progression from preceding HBP-hypointense nodules, or a de novo-like group, developing without detectable precursor lesions. Clinical characteristics, metabolic factors, and serum cytokine profiles were compared between the two groups. **Results:** A total of 50 hypervascular HCC nodules were identified in 33 patients and classified into multistep (25 nodules in 17 patients) or de novo-like groups (25 nodules in 16 patients). Serial EOB-MRI demonstrated stepwise hypervascular transformation from HBP-hypointense nodules in the multistep group, whereas hypervascular HCC newly appeared without antecedent lesions in the de novo-like group. Compared with the multistep group, the de novo-like group showed significantly larger tumor sizes. An increase in HbA1c from SVR to HCC diagnosis was observed more frequently in the de novo-like group, suggesting the involvement of metabolic abnormalities after SVR. Serum cytokine analysis revealed significantly higher TNF-α levels and lower MIG levels in the de novo-like group, suggesting distinct inflammatory and metabolic backgrounds associated with imaging progression patterns. **Conclusion:** HCC developing after HCV-related SVR may exhibit heterogeneous imaging progression patterns, including multistep hepatocarcinogenesis and de novo-like tumor development. These radiologic patterns may reflect different inflammatory and metabolic backgrounds associated with hepatocarcinogenesis after SVR. Longitudinal EOB-MRI assessment may provide clinically relevant insight into the heterogeneity of post-SVR hepatocarcinogenesis.
Disclosures: Tomoko Tanaka:Nothing to Disclose, Takuto Nosaka:Nothing to Disclose, Shouichi Namikawa:Nothing to Disclose, Arisa Saito:Nothing to Disclose, Yosuke Murata:Nothing to Disclose, Yu Akazawa:Nothing to Disclose, Kazuto Takahashi:Nothing to Disclose, Tatsushi Naito:Nothing to Disclose, Yasunari Nakamoto:Nothing to Disclose.

3313 | LEVERAGING HUMANIZED LIVER CHIMERIC MOUSE MODELS TO CHARACTERIZE HCV INFECTIVITY AND STANDARDIZE CHALLENGE INOCULA FOR CONTROLLED HUMAN INFECTION MODELS (CHIM)

Seung Bum Park[1] Justin Shields[2] Laura Collignon[3] Kenn Holmbeck[3] Atif Zahoor[4] Lorne Tyrrell[2] Jens Bukh[3] Jordan Feld[4] T. Jake Liang[1], [1]National Institutes of Health, [2]University of Alberta, [3]University of Copenhagen, [4]University of Toronto

Background: A major obstacle in hepatitis C virus (HCV) vaccine development is the lack of standardized, high-titer challenge inocula suitable for Controlled Human Infection Models (CHIM). Humanized liver chimeric mouse models, including Fah−/−/Rag2 −/−/Il2rg−/− (FRG) and urokinase-type plasminogen activator–severe combined immunodeficiency (uPA-SCID) mice, support robust HCV infection and provide a potential platform for evaluating clinically relevant infectious materials. However, their utility in characterizing qualitative and quantitative determinants of HCV infectivity in human-derived serum remains incompletely defined. **Methods:** Primary human hepatocytes were engrafted into FRG and uPA-SCID mice, followed by infection with HCV derived from human serum or lipid nanoparticle (LNP)-encapsulated full-length HCV RNA. Viral replication kinetics and infectivity were evaluated across multiple HCV genotypes. Human donor sera were further analyzed to determine the relationship between antibody-free HCV RNA fractions and *in vivo* infectivity. In selected experiments, infected

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mice were treated with direct-acting antiviral (DAA) regimens to assess virologic response. **Results:** Humanized liver chimeric mice supported sustained HCV viremia reaching up to 10^8 copies/mL across multiple genotypes. Analysis of human donor serum demonstrated that higher proportions of antibody-free HCV RNA correlated with increased *in vivo* infectivity, identifying a potential metric for selecting optimal donor serum for CHIM applications. In addition, LNP-mediated delivery of full-length HCV RNA established productive infection in chimeric mice with infection kinetics comparable to serum-derived HCV infection, supporting the feasibility of RNA-based generation of infectious challenge inocula. Infected mice also responded to DAA treatment with sustained virologic response. **Conclusion:** Humanized liver chimeric mouse models provide a robust platform not only for antiviral studies but also for characterization and quality control of clinically relevant HCV infectious materials. These findings support the use of chimeric mouse systems to evaluate donor serum infectivity and develop standardized challenge inocula for future HCV controlled human infection models.

Disclosures: Seung Bum Park:Nothing to Disclose, Justin Shields:Nothing to Disclose, Laura Collignon: Nothing to Disclose, Kenn Holmbeck:Nothing to Disclose, Atif Zahoor:Nothing to Disclose, Lorne Tyrrell: Nothing to Disclose, Jens Bukh:Nothing to Disclose, Jordan Feld:AbbVie: Advisor, Bluejay: Advisor, Gilead: Advisor, GlaxoSmithKline: Advisor, Precision Biosciences: Advisor, Arbutus: Advisor, Astra Zeneca: Advisor, Roche: Advisor, Vir: Advisor, Orphalan: Advisor, Pfizer: Advisor, Abbvie: Grant/Research Support, Gilead: Grant/Research Support, GlaxoSmithKline: Grant/Research Support, Atea: Advisor, Atea: Grant/Research Support, Roche: Grant/Research Support, Vir: Grant/Research Support, Mirum: Grant/Research Support, Mirum: Advisor, AusperBio: Advisor, T. Jake Liang:Nothing to Disclose.

3314 | EFFECT OF DIRECT-ACTING ANTIVIRALS (DAA'S) ON HEPATIC STEATOSIS AND INSULIN RESISTANCE IN TREATMENT-NAIVE HEPATITIS C PATIENTS IN INDIA

Mayank Agarwal[1] Sumit Rungta[2] Kothalkar Srikanth[3], [1]King George Medical University, Lucknow, India, [2]KGMU, [3]KGMU, Lucknow, India

Background: Chronic Hepatitis C virus (HCV) infection is closely associated with insulin resistance (IR) and hepatic steatosis, both of which contribute to accelerated fibrosis progression, cirrhosis, and hepatocellular carcinoma. Genotype 3, the predominant genotype in India, is particularly associated with severe metabolic derangements. Although direct-acting antivirals (DAAs) achieve high sustained virologic response (SVR) rates, their impact on insulin resistance and hepatic steatosis in treatment-naïve non-diabetic Indian patients remains inadequately studied. The present study was conducted to evaluate the effect of DAA therapy on insulin resistance, insulin sensitivity, and hepatic steatosis in chronic HCV-infected non-diabetic patients. **Methods:** This prospective analytical study was conducted at the Department of Medical Gastroenterology, King George's Medical University, Lucknow, among 200 treatment-naïve non-diabetic chronic HCV-infected patients. Baseline demographic, clinical, biochemical, and radiological parameters were recorded. Insulin resistance and insulin sensitivity were assessed using Homeostasis Model Assessment for Insulin Resistance (HOMA-IR) and Quantitative Insulin Sensitivity Check Index (QUICKI), respectively. Hepatic steatosis and liver stiffness were evaluated using FibroScan-controlled attenuation parameter (CAP) and liver stiffness measurement (LSM). Patients received DAA therapy according to national guidelines and were reassessed 12 weeks after completion of treatment (SVR12). Statistical analysis was performed using SPSS version 25.0. **Results:** The mean age of participants was 42.49 ± 13.05 years, and 43.5% were males. Before treatment, insulin resistance was present in 58.5% patients by HOMA-IR and in 77% by QUICKI criteria. Mean HOMA-IR significantly decreased from 3.09 ± 2.11 to 1.65 ± 1.17, while QUICKI significantly increased from 0.336 ± 0.037 to 0.367 ± 0.035 following DAA therapy ($p < 0.001$). The proportion of insulin-resistant patients declined markedly after treatment. Mean CAP values significantly decreased from 265.03 ± 35.32 dB/m to 225.44 ± 34.28 dB/m, indicating substantial improvement in hepatic steatosis. Severe steatosis decreased from 21.5% to 2.0%. Liver stiffness also improved significantly. All patients achieved SVR. Hepatic steatosis emerged as an independent predictor of insulin resistance. **Conclusion:** DAA therapy significantly improves insulin resistance, insulin sensitivity, hepatic steatosis, and liver stiffness in treatment-naïve non-diabetic chronic HCV patients. Viral eradication not only achieves virological cure but also favorably modifies important metabolic abnormalities associated with HCV infection. These findings support early diagnosis and prompt DAA treatment to reduce long-term hepatic and metabolic complications in chronic HCV infection.

Disclosures: Mayank Agarwal:Nothing to Disclose, SUMIT RUNGTA:Nothing to Disclose, Kothalkar Srikanth:Nothing to Disclose.

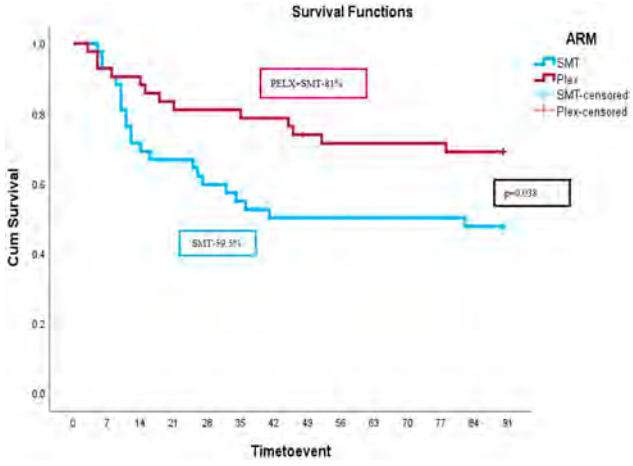
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3315 | ◆ EFFICACY OF PLASMAPHERESIS VERSUS STANDARD MEDICAL THERAPY IN PATIENTS WITH SEVERE DRUG-INDUCED LIVER INJURY (DILI) AND UNDERLYING CHRONIC LIVER DISEASE: INTERIM ANALYSIS OF AN OPEN-LABEL RANDOMISED CONTROLLED TRIAL

Khushboo Yadav[1] Shiv Kumar Sarin[2] Saggere Muralikrishna Shasthry[2] Ankur Jindal[2] Rajan Vijayaraghavan[2] Satender Pal Singh[1] Harsh Tevethia[3] Vinod Arora[4] Manoj Sharma[2] Ashok Kumar Choudhury[5], [1]institute of liver and biliary science, [2]Institute of Liver and Biliary Sciences, [3]Institute Of Liver And Biliary Sciences(ILBS), New Delhi, [4]institiute of liver and biliary sciences, [5]institute of liver and bilary sciences

Background: Drug-induced liver injury (DILI) superimposed on chronic liver disease (CLD) poses a distinct and under recognised clinical challenge. In this setting, DILI presents with greater severity, and carries a higher mortality risk. Therapeutic plasma exchange (PLEX) can remove albumin-bound toxins, damage-associated molecular patterns (DAMPs), bile acids, cytokines, and inflammatory mediators, and may offer benefit through immunomodulatory and haemodynamic mechanisms. We undertook a randomised controlled trial to evaluate SMT with SMT plus PLEX therapy in CLD patients with DILI **Methods:** This prospective, randomised, active-controlled, open-label trial (NCT06797011) conducted at ILBS, New Delhi, enrolled adults (18–75 years) with CLD and severe DILI (bilirubin >12 mg/dL or INR >2, confirmed by RECAM score), excluding those with active infection, PLEX contraindications, creatinine >2 mg/dL, or HCC. Patients were randomised 1:1 to PLEX (≥3 alternate-day sessions) plus SMT (Gr. A) or SMT alone (Gr. B), with transplant-free survival at 30 days as the primary endpoint. **Results:** Of 151 patients assessed for eligibility, 96 were randomised (48 per arm). The two groups were well-matched at baseline: mean age 47.2 vs 44.7 years, male sex 79.2% vs 85.4%, mean MELD score 26.9 vs 26.8, and CTP score 11.4 vs 11.0 (all p>0.05). ACLF with DILI was present in 64.6% of the SMT group and 66.7% of the PLEX group (p=ns). The predominant aetiology of CLD was metabolic (MASLD/MASH: 45.8% vs 52.1%), followed by alcohol-related liver disease. The most frequent implicating agent was complementary and alternative medicine (CAM/Ayurvedic preparations: 52.6%), followed by anti-tubercular therapy (9.5%).The primary endpoint of 30-day transplant-free survival was significantly higher in the PLEX+SMT group compared with SMT alone (81.0% vs 59.5%; p=0.038). This survival advantage was sustained at 90 days (69.0% vs 47.6%; p=0.076). The most common PLEX-related adverse events were shivering (25.3%), dyselectrolytaemia (13.7%), tingling (13.7%), fever (11.6%), and post-PLEX sepsis (10.5%). Among patients who died, sepsis/septic shock was the leading cause in both arms (27.3% SMT vs 61.5% PLEX; p=0.075). Of 96 patients, all 96 completed 1-month follow-up and 80 have completed 3-month follow-up **Conclusion:** This interim analysis from an ongoing RCT demonstrates that the addition of PLEX to SMT improves 30-day transplant-free survival in patients with severe DILI presenting as ACLF and acute decompensation PLEX is feasible and tolerable, though post-procedure complications and sepsis require vigilant monitoring.



Disclosures: Khushboo Yadav:Nothing to Disclose, Shiv Kumar Sarin:Nothing to Disclose, Saggere Muralikrishna Shasthry:Nothing to Disclose, Ankur Jindal: Nothing to Disclose, Rajan Vijayaraghavan:Nothing to Disclose, Satender Pal Singh:Nothing to Disclose, Harsh Tevethia:Nothing to Disclose, Vinod Arora: Nothing to Disclose, Manoj Sharma:Nothing to Disclose, Ashok Kumar Choudhury:Nothing to Disclose.

3316 | ◆ STATIN HEPATOTOXICITY PATIENTS WITH PROLONGED LATENCY (> 1 YEAR) HAVE MORE AUTOIMMUNE FEATURES AND GREATER RATE OF CHRONIC LIVER INJURY: RESULTS FROM THE US DRUG INDUCED LIVER INJURY NETWORK (DILIN)

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Symbols: ◆, Poster of Distinction; ★, Foundation Award Recipient

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Background: Statins are widely used with an estimated 100 million prescriptions per year in the US. However, rare instances of clinically significant statin hepatoxicity have been reported. The aim of this study was to describe the presenting laboratory and histological features and 6-month outcomes amongst 88 high confidence cases enrolled in the Drug Induced Liver Injury Network (DILIN) prospective registry study. **Methods:** Adjudicated cases of statin-DILI with a causality score of definite/highly likely/probable DILI enrolled between Sept 2004 and Jan 2026 were included. Analyses were stratified by drug latency: standard (< 365 days) vs prolonged (> 365 days). 28 of the 42 patients had their liver biopsies centrally reviewed by an experienced hepatopathologist (DEK) and 14 others were retrieved from local records. Simplified autoimmune hepatitis (AIH) scores were calculated to identify cases with probable/definite AIH (score >/=6). Chronic DILI was defined as laboratory evidence of ongoing injury at 6 months after DILI onset. **Results:** 88 cases of definite (5), high-likely (49), or probable (34) statin-DILI are included. Atorvastatin (67%) was most frequently implicated followed by rosuvastatin (11.4%). 7 (8%) developed DILI after a dose increase and another 7 (8%) after switching statins. Median age was 64 years, 74% female, 75% White. The liver injury was hepatitic in 48 (55%) and mixed-cholestatic in 40 (45%). Median drug latency was 132 (67.5, 367.5) days with 66 (75%) having standard latency (365 days). Prolonged latency cases were less likely White (55% vs 82%), but more likely had hepatocellular injury (63.6% vs 51.5%), ANA positivity (62% vs 38%), and were more likely to develop chronic DILI (36.8% vs 14.3%). Of 42 liver biopsies, 10 were typical for and 12 were compatible with AIH. 20 (23%) cases were scored as probable/definite AIH based on simplified AIH score (>/=6) and this was more common in the prolonged latency group (40.9% vs 16.7%). Regarding severity, 33 (37.4%) were hospitalized, 2 (2.3%) underwent liver transplant, and 4 (5%) died with 2 (2.6%) liver-related deaths. The prolonged latency group were more likely to develop chronic DILI (37 vs 14%) but use of corticosteroids was similar. **Conclusion:** Statin-DILI most commonly develops within 12 months after drug initiation, but 25% had prolonged drug latency exceeding 12 months. Over 20% of statin-DILI patients met clinical criteria for autoimmune hepatitis. The prolonged latency patients were more likely to have autoimmune- features and evolve into chronic DILI. HLA data will be presented at the meeting.

Table 1: Clinical Characteristics of 88 statin-DILI patients stratified by drug latency (drug start to DILI onset).

Clinical features	Latency </=365 days (n=66)	Latency >365 days (n=22)	p-value
Age (years)	64 (53, 70)	68 (59, 74)	0.11
Female	48 (73%)	17 (77%)	0.67
White	53 (82%)	12 (55%)	**0.006**
BMI (kg/m^2)	27 (23, 34)	26 (25, 31)	0.66
Statin			0.70
Atorvastatin	43 (65.1%)	16 (72.7%)	
Rosuvastatin	7 (10.6%)	3 (13.6%)	
Simvastatin	9 (13.6%)	0	
Pravastatin	4 (6.1%)	1 (4.5%)	
Lovastatin	2 (3%)	1 (4.5%)	
Fluvastatin	1 (1.5%)	1 (4.5%)	
Statin dose changes	10 (15.2%)	4 (18.2%)	
Latency (days)	94.5 (51, 155)	955 (728, 2238)	**<0.001**
Hepatocellular/ Mix-chol (%)	34 (51.5%)/ 32 (48.5%)	14 (63.6%)/ 8 (36.4%)	0.07
Initial ALT (U/L)	525 (307, 1119)	842 (371, 1181)	0.23
Initial ALk P (U/L)	299 (194, 575)	253 (145, 425)	0.21
Initial INR	1.2 (1, 1.9)	1.2 (1, 1.2)	0.41
Initial bilirubin (mg/dL)	2.7 (1, 6.7)	1.2 (0.8, 2.8)	0.21
R-value	5.1 (1.5, 12.2)	8.6 (3.5, 15.5)	0.09
Peak bilirubin (mg/dL)	4 (1.2, 11.8)	1.7 (0.9, 10.4)	0.24
Peak INR	1.1 (1, 1.4)	1.1 (1, 1.3)	0.66
ANA (1:40)	24 (38%)	13 (62%)	0.06
ASMA (1:40)	26 (42%)	12 (57%)	0.23
IgG (mg/dL)	1150 (861, 1410)	1565 (1155, 1967)	0.06
Liver biopsy performed	28 (42.4%)	14 (63.6%)	0.09
Simplified AIH score >/=6	11 (16.7%)	9 (40.9%)	**0.02**
Treated with corticosteroids	13 (19.7%)	5 (22.7%)	0.77
DILIN Severity score			0.27
Mild (1+)	25 (37.9%)	14 (63.6%)	
Moderate (2+)	14 (21.2%)	2 (9.1%)	
Moderate Hospitalized (3+)	15 (22.7%)	5 (22.7%)	
Severe (4+)	8 (12.1%)	1 (4.5%)	
Fatal (5+)	4 (6.1%)	0	
Chronic liver injury	8 (14.3%)	7 (36.8%)	**0.048**
Liver transplant	2 (3%)	0	>0.99
Death	3 (5.2%)	1 (5%)	>0.99

Disclosures: Alisa Likhitsup:Meridian Bioscience: Grant/Research Support, Naga Chalasani:Madrigal, Eccogene, Insitro, Boston Pharma, Chugai: Consultant, Zydus, GSK, Akero, Plaint, Altimmune: Consultant, Exact Sciences: Grant/Research Support, NIH: Grant/Research Support, Heligenics: Board member, investor, Avant Sante: Board member, investor, Ipsen, Biomea Fusion, Pfizer, Merck: Consultant, Ronald Kamusiime:Nothing to Disclose, Huiman Barnhart: Nothing to Disclose, David Kleiner:Nothing to Disclose, Robert Fontana:kezar pharmaceuticals: Grant/Research Support, Takeda Pharmaceuticals: Grant/Research Support, moderna: Consultant, MasterSwitch Bio: Stock ownership, Fractyl: Grant/Research Support, MiroMatrix: Grant/Research Support, Roche: Consultant, roche: Consultant, egenesis: Advisor, intellius: Consultant.

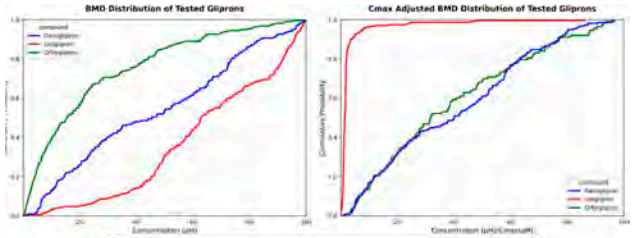
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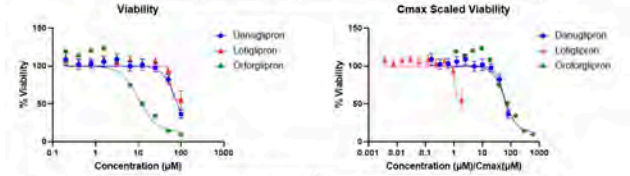
3317 | ◆ COMPARATIVE EVALUATION OF SMALL MOLECULE GLP-1RA-INDUCED HEPATOTOXICITY IN IPSC-DERIVED HUMAN LIVER ORGANOIDS

Samantha Boisvert[1] Max Garcia[1] Jonathan Sexton[2] Jacob Calka[1] Joel Yates[1] Robert Fontana[3], [1]University of Michigan, [2]University of Michigan Medical Center, [3]University of Michigan Hospitals and Health Centers

Background: Orforglipron, the first FDA-approved, orally bioavailable small molecule glucagon-like peptide-1 receptor agonist (GLP-1RA), has rapidly emerged as an important treatment for obesity/metabolic disease. Adverse events were observed in clinical studies for lotiglipron and danuglipron that ultimately halted their development, including drug-induced liver injury (DILI) and adverse gastrointestinal effects. The mechanisms underlying the divergent outcomes for the gliprons remain poorly understood. Here, we evaluated the effects of three gliprons in human liver organoid (HLO) models to investigate early signatures associated with hepatotoxicity risk. **Methods:** iPSC-derived HLOs were treated with orforglipron, danuglipron, and lotiglipron for 24 or 72 hours. High-content imaging was performed using a multiplexed dye panel to assess effects on viability, cellular perturbations, lipid accumulation, and mitochondrial stress. Segmentation and feature extraction was performed with CellPose/CellProfiler, and per-cell features were aggregated to the well level for morphological analysis. Mahalanobis distance scores were tabulated relative to DMSO controls and unsupervised dimensionality reduction and clustering analyses were performed. BMDExpress3 was used to assess the concentration of the phenotypic "point-of-departure" (PoD) to estimate the toxicity threshold for each compound. Bulk RNA sequencing was done with paired samples for transcriptomic analysis to inform the mechanism of toxicity. **Results:** Preliminary analyses demonstrate compound and concentration-dependent phenotypic perturbations across gliprons. Unsupervised analyses supported the sensitivity of the HLO phenotypic platform in detecting differential responses at clinically meaningful concentrations. Orforglipron exhibited the most potent in vitro toxicity with a phenotypic PoD of 15 uM, followed by danuglipron (45 uM) and lotiglipron (62 uM). To contextualize these thresholds against clinical exposure, both peak (Cmax) and time-averaged steady-state (Css,avg = AUC24/24 h) plasma concentrations were derived from published Phase 1 PK studies. The computed safety margins (PoD/Css,avg): orforglipron 139x, danuglipron 52x, and lotiglipron 1.8x, exhibit a wide safety margin for orforglipron, and indicate a narrow safety margin for lotiglipron, consistent with its observed transaminase elevations. **Conclusion:** These findings demonstrate the utility of phenotypic profiling in HLOs for detecting cytotoxicity and hepatocellular perturbations induced by gliprons and demonstrate orforglipron has the largest safety margin. Ongoing transcriptomic and image-based analyses aim to identify pathways and cellular phenotypes associated with differential hepatotoxic liability among the compounds.



Compound	Raw BMD50	Cmax Adjusted BMD50	Css avg Adjusted BMD50
Danuglipron	45.5616	40.0084	40.23908046
Lotiglipron	62.8544	1.464736842	2.162776389
Orforglipron	15.53645	31.76270588	39.98436364



Compound	Raw IC50	Cmax Adjusted IC50	Css avg Adjusted IC50
Danuglipron	82	65.6	94.26
Orforglipron	10.32	60.7	93.81
Lotiglipron	56.62	1.064	1.573

Disclosures: Samantha Boisvert:Nothing to Disclose, Max Garcia:Nothing to Disclose, Jonathan Sexton: Nothing to Disclose, Jacob Calka:Nothing to Disclose, Joel Yates:Nothing to Disclose, Robert Fontana:kezar pharmaceuticals: Grant/Research Support, Takeda Pharmaceuticals: Grant/Research Support, moderna: Consultant, MasterSwitch Bio: Stock ownership, Fractyl: Grant/Research Support, MiroMatrix: Grant/Research Support, Roche: Consultant, roche: Consultant, egenesis: Advisor, intellius: Consultant.

3318 | OVER 50% OF HIGH CONFIDENCE STATIN- DILI PATIENTS UNDERGOING LIVER BIOPSY MEET HISTOLOGICAL CRITERIA FOR AUTOIMMUNE HEPATITIS

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Background: Statins can rarely cause drug-induced liver injury (DILI) but the histopathological features of

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patients with statin DILI are not well described. In this study, we report the histological features in 28 patients with statin hepatotoxicity enrolled in the US Drug Induced Liver Injury Network (DILIN) whose biopsies were centrally reviewed. **Methods:** Adjudicated high causality cases of statin-DILI with an evaluable liver biopsy enrolled between September 2004 to January 2026 were included. Liver biopsies were interpreted using a standardized scoring system and scored as unlikely, compatible with, or typical of autoimmune hepatitis (AIH) by an expert hepatopathologist (DEK). **Results:** 28 statin-DILI cases adjudicated as definite (2), highly-likely (16), or probable (10) were included. The suspect drugs were atorvastatin (68%), simvastatin (14%), rosuvastatin (7%) and others (11%). Median age was 65 years, 64% female, 89% White, and the median latency to DILI onset was 125 (range 11 - 3572) days. The median time from DILI onset to liver biopsy was 11 (range 1 to 46) days, and 6 (21.4%) were receiving corticosteroids at the time of biopsy. Histological pattern of liver injury was hepatitic in 15 (54%) and mixed/cholestatic in 13 (46%). With respect to features of AIH, 8 (29%) were typical, 7(25%) were compatible, and 13 (46%) were unlikely AIH. Simplified AIH scores were higher among typical/possible vs unlikely (5 vs 3.2, $p = 0.007$. When compared with unlikely AIH, histologically compatible/typical for AIH had higher onset ALT levels [1383 vs 338 U/L, $p < 0.001$], higher R-values [14 vs 1.8, $p < 0.001$], and a trend towards higher IgG levels [1230 vs 1070, $p = 0.12$]. Although ANA/ASMA positivity were similar, the compatible/typical AIH patients were more likely to receive corticosteroids. Histologically compatible/typical of AIH demonstrated more severe interface hepatitis (73 vs 15%), lobular hepatitis (87% vs 46%), and portal inflammation (27% vs 0), increased plasma cells (67% vs 0), coagulative necrosis (37.5% vs 0), bridging necrosis (47% vs 0), central vein endophlebitis (21% vs 0), and hemorrhage (38% vs 0), compared to unlikely AIH (**Table 1**) Ductal paucity and advanced fibrosis were more prevalent among the unlikely AIH cases. Overall, 50% were hospitalized, 2 (7.1%) underwent liver transplantation, and 2 deaths occurred amongst the unlikely AIH while 6 (22%) developed chronic DILI. **Conclusion:** Over 50% of high confidence causality statin DILI cases showed histological findings which were compatible with or typical of sporadic AIH. Clinically, these patients have markedly higher serum aminotransferase levels at presentation, a higher simplified AIH score, and are more likely to receive corticosteroids. These findings raise the possibility that statins may be a precipitant of an autoimmune-like hepatitis in susceptible white patients.

Table 1: Clinical and Histologic Findings of selected statin-DILI cases enrolled in the Drug Induced Liver Injury Network (DILIN)

Histological findings of AIH	Typical/compatible (n=15)	Unlikely (n=13)	p-value
Age (years)	65 (59, 74)	64 (55, 73)	0.70
Female (n, %)	10 (67)	8 (62)	>0.99
White (n, %)	14 (100)	10 (77)	0.10
Drug latency to DILI onset (days)	134 (99, 828)	129 (77, 398)	0.80
Duration from DILI to liver biopsy (days)	9 (7, 17)	13 (6, 28)	0.91
Initial ALT (U/L)	1383 (587, 2399)	338 (212, 595)	**<0.001**
Initial ALP (U/L)	211 (176, 676)	472 (161, 811)	0.49
Initial Total bilirubin (mg/dL)	2.7 (1.2, 10.4)	2.5 (1.2, 7.7)	0.61
Initial INR	1.2 (1, 1.4)	1.1 (1, 1.2)	0.36
R-value	14 (7.6, 23.8)	1.8 (1.2, 4.1)	**<0.001**
Peak Total bilirubin (mg/dL)	3.2 (1.7, 18.8)	8.3 (1.3, 11.8)	0.71
Peak INR	1.2 (1.1, 1.5)	1.3 (1.2, 1.9)	0.34
ANA (1:40)	4 (26.7)	5 (38.5)	0.70
ASMA (1:40)	7 (46.7)	8 (61.5)	0.55
IgG (mg/dL)	1230 (1191, 1770)	1070 (883, 1403)	0.12
Simplified AIH score (mean)	5 (2.04)	3.2 (1.07)	**0.007**
Histological features			
Total portal areas	17 (12, 23)	14 (10, 16)	0.91
Interface hepatitis ≥ 3	11 (73.3)	2 (15.4)	**0.03**
Lobular inflammation ≥ 3	13 (86.7)	6 (46.2)	**0.01**
Portal inflammation ≥ 3	4 (26.7)	0	**0.007**
Confluent necrosis ≥ 4	7 (46.7)	1 (7.7)	0.13
Plasma cells increased	10 (66.7)	0	**<0.001**
Steatosis present	10 (66.7)	11 (84.6)	0.56
Hepatocyte rosettes present	3 (37.5)	2 (15.4)	0.54
Coagulative necrosis present	3(37.5)	0	**0.02**
Bridging necrosis present	7 (46.7)	0	**0.01**
Central vein endophlebitis	3 (21.4)	0	0.22
Hemorrhage	3 (37.5)	0	**0.004**
Ductular reaction	5 (62.5)	3 (23.1)	0.23
Ductal paucity present	0	1 (7.7)	0.48
Chronic DILI (%)	3 (21.4)	3(23.1)	>0.99
Treated with corticosteroids	6 (40)	0	**0.02**
Liver transplant (%)	1 (6.7)	1(7.7)	0.73
Death (%)	0	2 (15.4)	0.21

Disclosures: Alisa Likhitsup:Meridian Bioscience: Grant/Research Support, Naga Chalasani:Madrigal, Eccogene, Insitro, Boston Pharma, Chugai: Consultant, Zydus, GSK, Akero, Plaint, Altimmune: Consultant, Exact Sciences: Grant/Research Support, NIH: Grant/Research Support, Heligenics: Board member, investor, Avant Sante: Board member, investor, Ipsen, Biomea Fusion, Pfizer, Merck: Consultant, Ronald Kamusiime:Nothing to Disclose, Huiman Barnhart: Nothing to Disclose, David Kleiner:Nothing to Disclose, Robert Fontana:kezar pharmaceuticals: Grant/Research Support, Takeda Pharmaceuticals: Grant/Research Support, moderna: Consultant, MasterSwitch Bio: Stock ownership, Fractyl: Grant/Research Support, MiroMatrix: Grant/Research Support, Roche: Consultant, roche: Consultant, egenesis: Advisor, intellius: Consultant.

3319 | CHARACTERIZATION OF IBUPROFEN-INDUCED LIVER INJURY: A GLOBAL MULTI-REGISTRY STUDY

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Background: Idiosyncratic drug-induced liver injury (DILI) due to non-steroidal anti-inflammatory agents is responsible for 3 to 10% of cases in different registries. Ibuprofen use is widespread both by prescription and over the counter. While generally safe, ibuprofen can rarely cause severe liver injury but has not been frequently implicated in many registries. We aimed to describe the frequency and clinical features of ibuprofen DILI using globally diverse registries. **Methods:** We reviewed 50 high confidence (probable, highly likely and definite) cases of ibuprofen DILI from multiple prospective and globally diverse registries including; European [Spanish (n = 23), iDILIC (n = 5), Eudragene (n = 4) and ProEuroDILI (n = 1)], Latin American [LatinDILI (n = 13)], North American [US DILIN (n = 3)], and Indian [Bangalore (n = 1)]. Demographics, clinical characteristics, and outcomes were analyzed. **Results:** The majority (72%) of patients with high confidence ibuprofen DILI were reported from Spain and Latin America, 20% from Northern Europe, and only 8% from North America and India. The median age was 46 (range 18 to 83) years and 52% were women. Ibuprofen was used for analgesia in 84%. The injury pattern was hepatocellular in 56%, mixed in 27% and cholestatic in 17% of patients, with similar proportions in the Spanish and LatinDILI vs other registries. Demographic and clinical variables in 38 patients with complete data are described in **Table 1** . The median daily dose of ibuprofen was 1,200 (range 400 to 3600) mg, median duration of use 15 (range 1 to 980) days. 3 patients developed severe skin reactions (DRESS in 2 and Steven-Johnson Syndrome in 1). Among 9 patients undergoing liver biopsy, all featured hepatitis, 2 had cholestasis, and 1 had bile duct loss at 3 weeks after onset. Overall, 3 patients died from liver failure, and 8 patients had abnormal liver chemistries at 6 months or more after onset. There were no sex-based differences in baseline characteristics, liver injury phenotype, or outcome. Ibuprofen treatment continued for 4 days or more (median 11, range 4 to 95 days) after onset in 9 (24%) patients including 2 of the 3 fatal cases. **Conclusion:** Global reporting rates of ibuprofen DILI vary significantly, suggesting an impact of biological or genetic risk factors. However, phenotypic similarities of DILI in Spanish/Latin vs. other registries suggest that this variability may be related to non-biological factors as well, such as prescription policies and dose regimen. Ibuprofen DILI can present with variable patterns of injury, and a low threshold of suspicion to implicate it is needed to avoid misdiagnosis. Delays in withdrawal of ibuprofen suggest lack of recognition of its potential to cause liver injury or overlooking an ibuprofen history due to its over-the-counter use and perceived safety.

Table 1: Selected Characteristics of Ibuprofen DILI Among 38 Cases With Detailed Data

Variable	Number (percentage) or median (range)
Age (yr)	45 (18-83)
Female sex	19 (50%)
Race	
White	36 (95%)
Black	1 (2.6%)
South Asian	1 (2.6%)
BMI (kg/m^2)	26 (21-36)
Region and DILI registry	
Europe-Spanish DILI registry	21 (55%)
Latin America (LatinDILI)	12 (32%)
North America (DILIN)	3 (8%)
India, Bangalore registry	1 (2.6%)
Europe-Switzerland (ProEuroDILI)	1 (2.6%)
Latency	
≤ 1 week	11(29%)
1 week to 1 month	16 (42%)
1 to 4 months	10 (26%)
>4 months	1 (2.6%)
R-value	6.3 (0.8-40.8)
Positive ANA or SMA titer	10 (29%)
Rash	7 (18%)
Absolute eosinophil count ≥500/μL	2 (5%)
Values at onset	
Bilirubin (mg/dL)	3.9 (0.4-31.0)
Alanine Aminotransferase (U/L)	483 (39-2356)
Alkaline Phosphatase (U/L)	285 (86-1176)
Peak Values	
Bilirubin (mg/dL)	4.3 (0.5-46.2)
Alanine Aminotransferase (U/L)	509 (39-2691)
Alkaline Phosphatase (U/L)	298 (126-3110)
DILIN severity score	
Mild (*Elevated liver enzymes but no jaundice. Total bilirubin <2.5 mg/dL*).	15 (39%)
Moderate (*Total bilirubin ≥2.5 mg/dL or INR> 1.5*)	3 (8%)
Moderate to severe (*Total bilirubin ≥2.5 mg/dL or INR> 1.5 and hospitalization or prolongation of hospitalization*).	16 (42%)
Severe (*Jaundice and hepatic failure, ascites or hepatic encephalopathy*).	1 (2.6%)
Fatal (*Death related to liver failure or liver transplantation*)	3 (8%)

Abbreviations: ANA, antinuclear antibody; SMA, smooth muscle antibody; DILI, drug-induced liver injury; DILIN, Drug-Induced Liver Injury Network.

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3320 | FREQUENCY, CAUSES, AND CONSEQUENCES OF LIVER INJURY IN PATIENTS WITH DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS (DRESS)

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Background: Drug reaction with eosinophilia and systemic symptoms (DRESS) is a severe adverse drug reaction to a medication. Liver injury can occur in DRESS, but its characteristics remain unclear. We describe the frequency, causative agents, and outcomes of liver injury in a large cohort of patients with DRESS. **Methods:** We manually examined the records of patients with DRESS at a tertiary care dermatology practice from 2014–2024. Cases meeting Registry of Severe Cutaneous Adverse Reactions criteria ≥ 3 were included. Liver injury was defined as AST or ALT > 3 x ULN or AP > 2 x ULN, or total bilirubin > 2 X ULN during the DRESS episode. Cases with and without liver injury were compared according to clinical data and drug exposures. Beta lactams, sulfa compounds, and antiepileptics were considered as one class for analysis. Finally, multiple agents were considered as "antibiotics of different classes" and "unrelated drugs". **Results:** Liver injury was present in 105 DRESS cases (62.1%). Demographics were not different between DRESS cases with and without liver injury. However, DRESS cases with liver injury had higher rates of fever, peak creatinine, peak AST, peak ALT, peak Alkaline Phosphatase, and peak total bilirubin compared to cases without liver injury (p-value < 0.05 for all, Table1). The most frequent drugs associated with DRESS cases were mixed classes of antibiotics (17%), beta-lactam antibiotics (15%), glycopeptide antibiotics (12%), sulfa compounds (12%) and anti-epileptics (10%). In terms of frequency of liver injury in DRESS, vancomycin-DRESS and lamotrigine-DRESS had highest frequency of liver injury (90% and 89%, respectively) for single agents, followed by trimethoprim sulfamethoxazole (62%), piperacillin/tazobacam (60%), and allopurinol (50%). Among the 105 cases of liver injury, 61% were considered cholestatic, 25% were hepatocellular, 14% were mixed. Patients with DRESS and liver injury had significantly higher 6-month mortality than DRESS patients without liver injury (26.7%, vs 10.9%, OR: 2.96 95% 95% CI: 1.2- 7.3). Among 28 deaths in DRESS cases with liver injury, 2 were directly related to liver injury, while in 3, liver injury was considered contributory. All liver related deaths had underlying liver disease. **Conclusion:** Liver injury was observed in ~ 60% of patients with DRESS and vancomycin and lamotrigine demonstrated high rates of liver injury. Liver injury was associated with significantly higher 6-month mortality in patients with DRESS.

Table 1: Comparison of selected characteristics of patients with DRESS with and without liver injury

Characteristic	Liver injury n=105	No liver injury n=64	P-value
Age (years)	45.92 ± 22.06	49.09 ± 25.07	0.41
Weight (kg)	80.32 ± 33.24	82.07 ± 37.78	0.76
Female sex	53 (50.5%)	39 (60.9%)	0.24
White	88 (83.8%)	55 (85.9%)	0.88
Latency (days)	19.92 ± 12.62	17.89 ± 14.94	0.40
Glycopeptide Antibiotics	18 (17%)	2(3%)	0.01
Antiepileptics	13(12%)	4(%)	0.20
Mixed Antibiotic Classes**	18(%)	7(6%)	0.37
Beta-Lactams	13(12%)	12(19%)	1.0
Sulfa Compounds***	11(10%)	9(14%)	0.48
Fever	71 (67.6%)	32 (50.0%)	0.03
Lymphadenopathy	27 (25.7%)	9 (14.1%)	0.11
Edema	63 (60.0%)	36 (56.2%)	0.75
Pre-existing Cirrhosis	9 (8.6%)	7 (10.9%)	0.81
Peak Absolute Eosinophil Count (k/mm³)	1.70 ± 2.19	1.49 ± 2.54	0.61
Peak Eosinophil Percentage	12.52 ± 11.56	10.29 ± 11.57	0.25
Peak AST (units/L)	312.51 ± 591.51	40.56 ± 22.38	<0.01
Peak ALT (units/L)	338.30 ± 657.13	38.40 ± 25.70	<0.01
Peak AP (units/L)	318.27 ± 242.92	109.29 ± 53.72	<0.01
Peak Total Bilirubin (mg/dL)	3.44 ± 5.86	0.73 ± 0.47	<0.01
Peak Creatinine (mg/dL)	1.95 ± 1.60	1.31 ± 0.87	0.01
Death within 6 months	28 (26.7%)	7 (10.9%)	0.02

*AST-Aspartate Aminotransferase, ALT-Alanine Aminotransferase, AP-Alkaline Phosphatase

**Mixed antibiotic classes: defined as more than one antibiotic of different classes that could be causative

***sulfa class/compounds: trimethoprim/sulfamethoxazole, dapsone, sulfasalazine

Disclosures: Divya Minnaganti:Nothing to Disclose, Craig Lammert:Eli Lilly: Consultant, Kezar Life Sciences: Consultant, Amgen: Consultant, Autoimmune Hepatitis Association: Consultant, RegCell: Consultant, Regeneron: Consultant, Marwan Ghabril:BioCryst: Consultant, Akero: Consultant, ABIM: Advisor, CymaBay: Consultant, Gilead: Consultant, MoonLake Therapeutics: Consultant, Salix/Bausch: Grant/Research Support, Zydus: Consultant, PPD: Consultant, ACTC-DSMB: Consultant, Cook: Consultant, Elizabeth Phillips:Nothing to Disclose, Naga Chalasani:Madrigal, Eccogene, Insitro, Boston Pharma, Chugai: Consultant, Zydus, GSK, Akero, Plaint, Altimmune: Consultant, Exact Sciences: Grant/Research Support, NIH: Grant/Research Support, Heligenics: Board member, investor, Avant Sante: Board member, investor, Ipsen, Biomea Fusion, Pfizer, Merck: Consultant, Sahand Rahnama-Moghadam:Nothing to Disclose.

3321 | CLINICAL PHENOTYPE AND AUTOIMMUNE MIMICRY IN TINOSPORA CORDIFOLIA HEPATOTOXICITY-A SYSTEMATIC REVIEW AND META-ANALYSIS

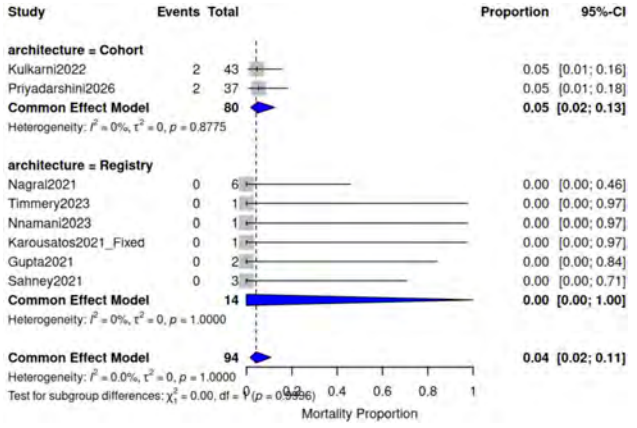
Keeranmayee Mishra[1] Chirag Doshi[2] Abeer Abukamil[3] Rakshana Ravichandran[1] Apurba Mishra[4] Mrudulla Alla[1] Deekshita Alla[5] Ramy Mansour[1], [1]Trinity Health Oakland/Wayne State University, [2]Banas Medical

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Background: Tinospora cordifolia (Giloy) is an increasingly recognized cause ofherb-induced liver injury that can closely resemble autoimmune hepatitis, creating a majordiagnostic challenge. Prior systematic evaluations have been limited by inadvertent poolingof look-alike species, particularly T. crispa, and by small-sample rare-event bias. To ourknowledge, this is the first species-restricted meta-analysis of T. cordifolia-induced liverinjury focused on phenotype, autoimmune serology, and outcomes. **Methods:** We systematically identified clinical studies of T. cordifolia-induced liver injury.Reports involving alternative species, unverified polyherbal exposures, or absent botanicalvalidation were excluded. Rare-event outcomes were pooled using generalized linear mixedmodels with random-intercept logistic regression; higher-heterogeneity endpoints wereanalyzed with inverse-variance random-effects models using Paule-Mandel au^2 estimation. **Results:** Eight studies comprising 94 species-verified patients met inclusion criteria. Pooledmortality was 4.26% (95% CI, 1.62–10.79%; $I^2 = 0.0\%$), representing 4 deaths across theliterature. The pooled transplantation rate was 3.19% (95% CI, 1.03–9.43%). Among 92evaluable cases, a hepatocellular phenotype predominated in 80.43% (95% CI, 71.07–87.31%). ANA positivity was present in 44.20% of tested patients and SMA positivity in14.60%. Corticosteroids were administered in 33.33% of cases with available therapeutic data(n = 78). Complete recovery occurred in 73.10% of the cohort. **Conclusion:** Tinospora cordifolia hepatotoxicity is an important and underrecognized cause of herb-induced liver injury that often mimics autoimmune hepatitis. In this species-restricted synthesis, the injury pattern was predominantly hepatocellular, and autoimmune serologies were frequently positive, especially ANA, supporting the clinical challenge of distinguishing toxic injury from true autoimmune disease. The observed corticosteroid use likely reflects diagnostic uncertainty rather than evidence that steroids are routinely needed. Most patients recovered after exposure cessation, reinforcing that the mainstay of management is prompt withdrawal of the offending herb and supportive care. Rare outcomes such as liver transplantation and death highlight that this entity is not always benign. Clinicians should specifically ask about herbal supplements, particularly T. cordifolia, before diagnosing autoimmune hepatitis or starting immunosuppression.Figure legend- Pooled All-Cause Mortality in Species-Restricted Tinospora cordifolia-Induced-Liver Injury. The common effect model indicates an estimated pooled mortality of 4.26% (95% CI: 1.62%–10.79%)



Disclosures: Keeranmayee Mishra:Nothing to Disclose, Chirag Doshi:Nothing to Disclose, Abeer Abukamil:Nothing to Disclose, Rakshana Ravichandran:Nothing to Disclose, Apurba Mishra:Nothing to Disclose, Mrudulla Alla:Nothing to Disclose, Deekshita Alla: Nothing to Disclose, Ramy Mansour:Nothing to Disclose.

3322 | COMPARATIVE EVALUATION OF ROENIGK, METAVIR, AND SAF SCORING SYSTEMS IN METHOTREXATE-INDUCED LIVER INJURY: CLINICAL IMPLICATIONS FOR FIBROSIS ASSESSMENT

Melina Almeida Dias Torres[1] Maria Chiara Chindamo[1] Cristiane Villela-Nogueira[1] Renata Perez[1] Vera Lucia Nunes Pannain[1], [1]Federal University of Rio de Janeiro

Background: Long-term methotrexate (MTX) therapy has historically been associated with concerns regarding liver fibrosis, leading to the development of the Roenigk classification for histological monitoring. As liver biopsy has become less frequent with the widespread adoption of non-invasive fibrosis assessment, familiarity with MTX-specific histological classifications has declined. We aimed to evaluate the agreement between the Roenigk classification and contemporary fibrosis staging systems (METAVIR and SAF) and to assess the reproducibility of Roenigk scoring among pathologists with different levels of expertise. **Methods:** We performed a retrospective cross-sectional study of 61 liver biopsies obtained from 43 patients receiving chronic MTX therapy between 2000 and 2019. Biopsies originally evaluated by general pathologists were independently re-reviewed by an experienced hepatopathologist using the Roenigk, METAVIR, and SAF classifications. Agreement for significant fibrosis (Roenigk $\geq$ IIIa, METAVIR $\geq$ F2, and SAF $\geq$ F2) was

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assessed using Cohen's kappa coefficient (κ). **Results:** Agreement for significant fibrosis was substantial between Roenigk and METAVIR (κ = 0.681, p < 0.0001) and moderate between Roenigk and SAF (κ = 0.496, p < 0.0001). The prevalence of significant fibrosis varied according to the scoring system, ranging from 8.2% with Roenigk to 14.7% with METAVIR and 21.3% with SAF. No cases of cirrhosis were identified. Interobserver agreement for Roenigk classification was low between general pathologists and a hepatopathologist (κ = 0.299), but substantial between hepatopathologists (κ = 0.690), highlighting the influence of subspecialty expertise on score interpretation. **Conclusion:** The Roenigk classification demonstrated substantial agreement with METAVIR for identifying clinically significant fibrosis in MTX-treated patients. However, its limited reproducibility among non-specialist pathologists may restrict its applicability in contemporary practice. These findings support the use of more widely adopted fibrosis staging systems, such as METAVIR, and underscore the importance of standardized histological assessment in the evaluation of MTX-associated liver injury.

Disclosures: Melina Almeida Dias Torres:Nothing to Disclose, Maria Chiara Chindamo:Nothing to Disclose, Cristiane Villela-Nogueira:Nothing to Disclose, Renata Perez:Nothing to Disclose, Vera Lucia Nunes Pannain: Nothing to Disclose.

3323 | USE OF POTENTIALLY HEPATOXIC BOTANICAL PRODUCTS HAS SIGNIFICANTLY INCREASED AMONG US ADULTS; NHANES 2003-2023

Alisa Likhitsup[1] Vincent Chen[1] Robert Fontana[2], [1]University of Michigan, [2]University of Michigan Hospitals and Health Centers

Background: Millions of US adults consume Dietary Supplement (DS) for a variety of perceived health benefits. With an increased number of dietary supplements available online, consumers have shifted from traditional multivitamin/mineral formulations to multi-ingredient botanical and synthetic mixtures products. Some botanicals such as those containing Green tea extract, turmeric, *Garcinia cambogia*, and ashwanganda have been associated with hepatotoxicity. Our study explored trends over time of DS and potentially hepatotoxic botanical products use among US adults. **Methods:** DS use within the past 30 days from 2003-2023 NHANES biannual survey of adults (>/= 18 years) were analyzed. Botanical ingredients were identified using detailed ingredients database. Average biennial percentage change (ABPC) and biennial percentage change (BPC) were reported. Joinpoint regression analysis was performed for trends of DS and potentially hepatotoxic botanical use over time. Data from NHANES Population Totals were used for population size estimates. **Results:** Amongst 59,753 adults surveyed between 2003 to 2023, 28,467 (53.2%) consumed at least one DS and 7,096 (17.2%) consumed botanical products. The most commonly reported potential hepatotoxic botanicals consumed were GTE (1.9%), turmeric (1.7%), ashwagandha (0.26%), and *Garcinia cambogia* (0.16%). Since 2003, DS use increased in all age groups; ABPC 2.63(95%CI 0.33, 4.89) for age 18-39 years, ABPC 1.54(95%CI 0.5, 2.86) for age 40-59 years, and ABPC 2.50(95%CI.98, 3.75) for age >/= 60 years (P < 0.05). Botanical products use also increased since 2010 (BPC 6.22 [95% CI, 5.00 -8.36], p = 0.001), but non-botanical products use remained stable. Botanical use particularly increased since 2003 among females >/= 60 years old (BPC 2.81(95% CI, 1.53- 4.10), p = 0.001) and since 2010 among females age 40-59 years old (BPC 4.10 (95% CI, 1.82- 6.42), p = 0.005), and since 2012 among men 40-59 years old (BPC 10.59(95%CI, 1.95- 19.98), p = 0.03). Since 2003, there was a significant increase in turmeric; ABPC 9.62(95% CI 5.88, 15.83) and ashwagandha use; ABPC 28.9(95% CI 20, 45.7) over time (p < 0.0001), but GTE and *Garcinia cambogia* use remained stable. In 2021-2023, an estimated 155.4 million Americans consumed a DS, an estimated 62.3 million Americans consumed a botanical products and an estimated 30.9 million American adults consumed at least one potentially hepatotoxic botanical. Population-based estimate exposures include 14.3 million turmeric, 8 million ashwagandha, 6.8 million GTE, and 1.8 million *Garcinia cambogia*. **Conclusion:** The prevalence of DS use among US adults has increased over time and primarily driven by a disproportionate increase in a multitude of multi-ingredient botanical products used some of which are potentially hepatotoxic. The trends of botanical products use significantly increased particularly among middle-aged men and women (40-59), and in women >/= 60 years old.

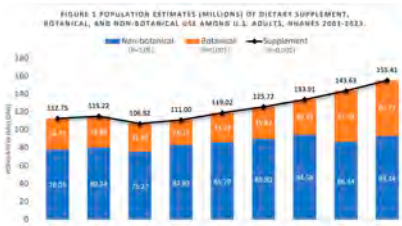


Table 1. Top 15 botanical products used by US adults, NHANES 2017-2023

Products	n	LiverTox likelihood
Turmeric	373	A
Bioflavonoid complex	194	nc
Cranberry	118	E
Ginger	111	E
Green tea	107	A
Ginkgo	99	E
Garlic	90	nc
Saw palmetto	89	D
Cinnamon	73	nc
Echinacea	71	D
Horsetail	71	C
Quercetin	66	E
Ashwagandha	62	B
Apple cider vinegar	58	nc
Resveratrol	57	F

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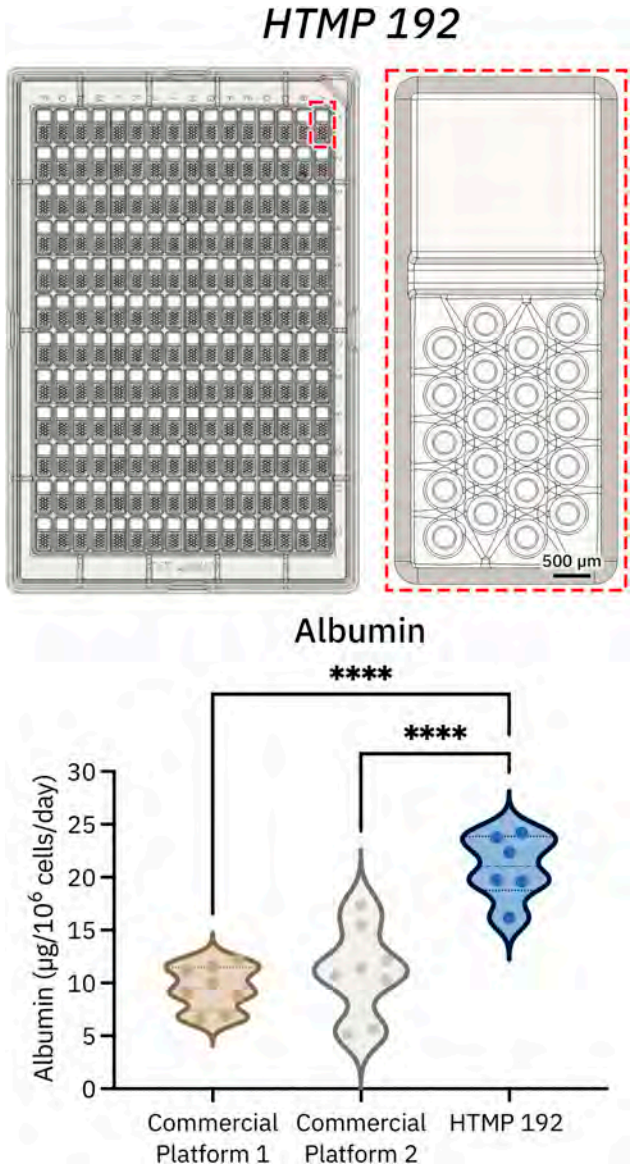
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GSK: Site PI for clinical trial, CSL: Site PI for clinical trial, Robert Fontana:kezar pharmaceuticals: Grant/Research Support, Takeda Pharmaceuticals: Grant/Research Support, moderna: Consultant, MasterSwitch Bio: Stock ownership, Fractyl: Grant/Research Support, MiroMatrix: Grant/Research Support, Roche: Consultant, roche: Consultant, egenesis: Advisor, intellius: Consultant.

3324 | HTMP 192: AN IMPROVED HIGH-THROUGHPUT MICROWELL PLATFORM FOR LONGITUDINAL 3D HEPATIC CELL CULTURE AND HEPATOTOXICITY SCREENING

Dominick Hellen[1] Saul Karpen[2], [1]HTMP Inc., [2]VCU Stravitz-Sanyal Institute for Liver Disease and Metabolic Health

Background: Multicellular 3D culture represents an expanding framework of methodologies for physiologically relevant in vitro drug discovery, screening, and disease modeling. Microwell platforms have garnered interest in hepatobiliary research for the development and maintenance of in-suspension size-controlled spheroids and organoids with enhanced transcriptomic and morphologic maturity. These microwell platforms, however, remain constrained in high-throughput settings by longitudinal cell-loss, inter-well variability, and difficult handling, ultimately limiting their broader adoption. **Methods:** To address these limitations, the spacing of a 384-well pitch was modified to engineer a patent pending 192-well High-Throughput Microphysiological Platform (HTMP 192), with each well incorporating a microwell field, an adjacent pipette-access region, and flow-reducing partition wall (Figure). 300 cell spheroids comprised of human hepatocellular carcinoma (HepG2; 95%) and immortalized stellate (LX-2; 5%) cells were seeded in the HTMP 192 and two commercially available high throughput microwell plates. Over 7 days in culture, cells in the 3 platforms were compared for numerous endpoints (spheroid retention, viability [WST-8], albumin [immunofluorescence and ELISA], uniformity, total media exchange) and hepatotoxicity assays following concentration-dependent exposures to diclofenac, tamoxifen, troglitazone, and acetylsalicylic acid. **Results:** Repeated media exchange in the two commercial microwell platforms results in non-circular spheroid formation and significant longitudinal spheroid displacement / loss of 35.4% & 57.8% over 7 days, respectively. In contrast, the HTMP 192 platform maintained longitudinal spheroid and organoid stability (< 5% loss) while enabling > 85% media exchange per well, compared with 50-75% in the commercial platforms. Enabled by this improved retention and media exchange profile, albumin secretion was significantly higher in the HTMP 192 platform compared with both commercial platforms (Figure). Hepatotoxicity screening yielded reproducible dose-response curves in the HTMP 192 platform, supporting compatibility with downstream drug-response assays. **Conclusion:** The HTMP 192 platform provides a longitudinally stable, high-throughput, physiologically relevant microwell culture system with replicability and operational simplicity. These results support consideration of the HTMP 192 platform as an improved infrastructure for reproducible 3D hepatobiliary culture, drug screening, and new approach methodological development. Ongoing studies are extending the platform to additional cell types, molecular exposures, and translational disease models.



Disclosures: Dominick Hellen:Nothing to Disclose, Saul Karpen:Albireo/Ipsen: Consultant, Mirum: Consultant, Intercept: Consultant.

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3325 | MULTICELLULAR 3D BIOPRINTED LIVER MODELS FOR LIVER TISSUE MODELING, DRUG SCREENING, AND CANCER IMMUNO-ONCOLOGY

Ting-Yu Lu[1], [1]UCSD

Background: Advanced in vitro liver models are needed to improve human-relevant drug screening, toxicology assessment, disease modeling, and NAM-compatible testing. Liver biology is regulated by hepatocytes, endothelial cells, stellate cells, immune cells, extracellular matrix, and tissue architecture. These interactions influence xenobiotic metabolism, inflammation, fibrosis signaling, injury response, and tumor-immune crosstalk. Conventional 2D cultures and many 3D systems do not capture this complexity or allow control of tissue composition, matrix context, geometry, spatial organization, and reproducibility. We developed a 3D bioprinted liver platform for tissue modeling and oncology applications. **Methods:** Printable hydrogel bioinks generated 3D liver constructs with defined cell composition, matrix context, geometry, and spatial organization. For tissue modeling and toxicology studies, constructs incorporated hepatocytes or iPSC-derived hepatocyte-like cells to assess hepatic function, metabolism, and drug-induced injury. For oncology modeling, the hepatic compartment was replaced with hepatocellular carcinoma cells to evaluate tumor behavior and therapeutic response. Both configurations included endothelial, stellate, and immune cells. In the immuno-oncology model, liver cancer cells were combined with myeloid cells under stromal, vascular, and fibrosis-associated cues. **Results:** Our current assay framework focuses on two key performance areas: drug response and CYP-mediated hepatic function. Printed constructs will be evaluated for viability, morphology, albumin secretion, urea production, and CYP450 activity, with emphasis on drug-metabolizing enzymes such as CYP3A4. Drug testing will use benchmark hepatotoxic or metabolism-related compounds to assess dose-dependent changes in viability, ATP activity, LDH release, hepatic function, CYP activity, and inflammatory cytokine secretion. In the multicellular liver cancer model, tumor viability, immune activation, cytokine response, and CYP-related metabolic changes will be assessed to determine how stromal, endothelial, and immune components influence therapeutic response. **Conclusion:** This project positions 3D bioprinting as an engineering-driven approach for modeling liver biology in a controllable, scalable format. By integrating hepatic or liver cancer cells with immune, endothelial, and stellate components, the platform moves beyond simple cultures toward a human-relevant model of liver function, inflammation, fibrosis signaling, and tumor-immune interaction. Its combination of engineering precision, multicellular biology, drug response testing, and CYP readouts supports hepatotoxicity screening, liver cancer modeling, therapeutic development, and NAM-compatible drug testing.

Disclosures: Ting-Yu Lu:Nothing to Disclose.

3327 | EX VIVO HUMAN LIVER PLATFORM FOR PHARMACOLOGY AND TOXICOLOGY RESEARCH

Carly Strelez[1] Yumeng (Angela) Sun[1] Virginia Orozco[1] Dan Fower[2] Clare Swift[2] Chris Morris[2] Rachel Perez[1] Cara Sake[1] Desirea Mecenas[1] Brianna Simental[1] Denisse Sibrian[1] Arely Gil[1] Yuyuan Zhou[1] Kruttika Dabke[1] Charlie Ambrose[1] Lily Dara[3] Pratik Mehta[4] Sergei Tatishchev[3] Jonathan Katz[1] Andy Self[2] Shannon Mumenthaler[1], [1]Ellison Medical Institute, [2]OrganOx Ltd, [3]University of Southern California, [4]Procure On-Demand

Background: Preclinical models poorly predict human hepatotoxicity, contributing to drug attrition and safety failures. Advances in ex vivo organ perfusion systems, such as normothermic machine perfusion (NMP), have extended viability for organs prior to transplantation and offer a compelling platform for testing drug metabolism and toxicity. These systems maintain donor organs at physiological body temperature while circulating oxygenated, nutrient-rich blood solutions through the organ. **Methods:** We utilized a modified NMP system (Organox *metra* platform) to perform long-term perfusion on whole, human livers that are unsuitable for transplantation and would otherwise have been discarded. We used APAP as proof of concept to perform toxicological studies. A total of 6 livers were used (n = 3 APAP-dosed, n = 3 controls) in our cohort. During perfusion, viability and function were assessed by lactate clearance, liver enzymes levels, pH maintenance, bile production, and cytokine secretion. Histological assessment of the degree of fibrosis, steatosis, inflammation, injury, and necrosis was performed on pre- and post-perfusion biopsies. Phase I and II metabolites were detected by mass spectrometry. Markers of hepatocellular injury in the perfusate, including GSTα and HMGB1 were measured. **Results:** We demonstrate, in an experimental setting, that successful NMP sustained liver viability for 96-hour in 5/6 donor livers, demonstrating stable performance even in marginal livers, including those with up to 30hrs of cold ischemia times and steatosis levels as high as 40%. Based on H&E, Mason's trichrome, periodic acid-Schiff (PAS), and glutamine synthetase (GS) staining, we showed that the baseline fibrosis and steatosis grade influenced long-term perfusion outcomes. As a case study, three livers were administered

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acetaminophen (APAP), and metabolism and excretion were monitored in a time- and dose-dependent manner. APAP-treated human livers displayed elevated GSTα and HMGB1 levels, compared with controls in a dose-dependent manner. Histological analysis of pre- and post- perfusion biopsies demonstrated centrilobular necrosis, sinusoidal injury, inflammation, and loss of GS staining in an APAP dose-dependent manner. **Conclusion:** Long-term human liver NMP provides a robust, physiologically relevant platform for real-time assessment of drug metabolism and toxicity, with broad applications in preclinical development, precision therapeutics, and organ-focused research.

Disclosures: Carly Strelez:Nothing to Disclose, Yumeng (Angela) Sun:Nothing to Disclose, Virginia Orozco:Nothing to Disclose, Dan Fower:OrganOx Ltd: Employee, Clare Swift:Nothing to Disclose, Chris Morris:Nothing to Disclose, Rachel Perez:Nothing to Disclose, Cara Sake:Nothing to Disclose, Desirea Mecenas:Nothing to Disclose, Brianna Simental:Nothing to Disclose, Denisse Sibrian:Nothing to Disclose, Arely Gil:Nothing to Disclose, Yuyuan Zhou:Nothing to Disclose, Kruttika Dabke:Nothing to Disclose, Charlie Ambrose:Nothing to Disclose, Lily Dara:Intercept Pharmaceuticals: Consultant, Intercept Pharmaceuticals: Grant/Research Support, Kezar Pharmaceuticals: Consultant, Agios: Consultant, Amgen: Consultant, OPKO: Consultant, Mirum: Consultant, Ipsen: Consultant, Pratik Mehta:Nothing to Disclose, Sergei Tatishchev: Nothing to Disclose, Jonathan Katz:Nothing to Disclose, Andy Self:OrganOx Limited: Employee, Shannon Mumenthaler:Nothing to Disclose.

3328 | EVALUATING LIVER TOXICOLOGY OF MEDICAL COUNTERMEASURES AGAINST HIGH CONTAINMENT PATHOGENS USING PRIMARY HEPATOCYTES GROWN ON THE PHYSIOMIMIX LC12 MICROPHYSIOLOGICAL SYSTEM

Jennifer Chua[1] Marjorie Torres[1] Jade Spencer[1] Bobby Curry[1] James Meinig[1], [1]US Army Medical Research Institute of Infectious Diseases

Background: The use of animal testing to evaluate pharmacokinetics, pharmacodynamics, and toxicokinetics of therapeutics may be limited in its translatability to humans. Therapeutics developed for pathogens of biodefense concern requiring high biological containment are uniquely exposed to this risk due to reliance on the FDA “Animal Rule” pathway for development. Interspecies differences in liver response and drug induced liver injury (DILI) remain major concerns. New approach methodologies (NAM) such as microphysiological systems (MPS) using human hepatocytes to mimic the structure, function, zonality and compartmentalization of the liver show greater promise in predicting responses to drugs and potential DILI. **Methods:** Here, we have established a NAM to investigate candidates against biodefense pathogens using the perfusable PhysioMimix LC12 microphysiological system. To directly compare risk between human and relevant animal models, primary hepatocytes from four species (human, rat, dog, non-human primate) were cultured and compared for interspecies differences in cell health (LDH, urea, albumin), metabolic activity (CYP3A4), toxicity (AST, ALT) and 3D structural organization (microscopy) in response to rifampin, a test case antibiotic and second-line agent against *Bacillus anthracis*. **Results:** Minimal effects with rifampicin treatment have been shown, which is supported by rifampicin being a low risk of idiosyncratic DILI. Results continue to support study designs and power analysis for future novel therapeutics within the biodefense pipeline. **Conclusion:** Future work will examine the inclusion of feeder cells for supporting hepatocyte health and longevity and Kupffer cells to assess immune responses. Together this work supports transitioning of the NAM system into high biological containment to support mixed toxicological evaluations during infection studies.The views expressed in this abstract are those of the authors and do not necessarily reflect the official policy or position of the Defense Health Agency, Department of War, nor the U.S. Government.

Disclosures: Jennifer Chua:Nothing to Disclose, Marjorie Torres:Nothing to Disclose, Jade Spencer:Nothing to Disclose, Bobby Curry:Nothing to Disclose, James Meinig:Nothing to Disclose.

3329 | DELAMANID-ASSOCIATED METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE RISK: A PHARMACOVIGILANCE ANALYSIS COMBINING FAERS AND JADER DATABASES WITH NETWORK TOXICOLOGY STUDY

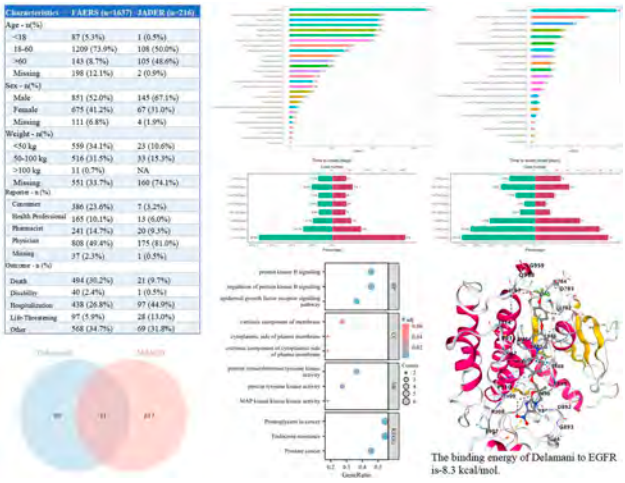
Ke Mi[1] Wei Tang[1] Zhidan Zuo[2] Qianjun Zhao[3] Sha Lin[1] Zhixiong Fang[1], [1]Xiangtan Central Hospital, Hunan University, [2]Hunan University, [3]Nanhua University

Background: Delamanid is a novel anti-tuberculosis drug used for multidrug-resistant tuberculosis. Previous studies have suggested its potential for metabolic adverse reactions such as hyperlipidemias, but systematic safety studies are lacking. This study aims to systematically evaluate the risk signals and potential mechanisms of delamanid-associated MASLD by jointly analyzing the FDA Adverse Event Reporting System (FAERS) and Japanese Adverse Drug Event

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Report (JADER) pharmacovigilance databases, combintegrated with network toxicology methodanalysis. **Methods:** Based on FAERS (2014-2025) and JADER (2014-2025) data, reports identified as primary suspect were screened. Four disproportionality analysis methods and Bayesian analysis were applied, and resuignalts pdetected consistivently across all methods were considered associated with delamanid. Network toxicology was used to screen delamanib targets, explore key gproteines involved in inducing MASLD, and perform pathway enrichment analysis. **Results:** A total of 1,637 adverse event reports from FAERS and 216 from JADER were analyzed. Metabolic and nutritional disorders showed significant adverse signals associated with delamanid in both databases (FAERS ROR: 3.63 (3.18-4.14); JADER ROR: 1.88 (1.24-2.86)). Subgroup analysis from FAERS indicated that male sex may be negatively associated with delamanid-related metabolic disorders (ROR = 0.72 (0.55-0.95)). The median time to adverse event occurrence was 56 days (IQR: 15-148) in FAERS and 65 days (IQR: 28.5-155.75), respectivelyn JADER. Network toxicology revealed that delamanid may promote MASLD through regulation of protein kinase B signaling pathway, modulation of protein tyrosine kinase activity, and induction of insulin resistance. Molecular docking suggested stable interactions between delamanid and key gproteines such as EGFR, PTK2, and IGF1R. **Conclusion:** Delamanid may increase the risk of MASLD, particularly in female patients. Clinical monitoring of liver function and metabolism should be strengthened in patients receiving delamanid for antituberculosis treatment. Future prospective cohort studies and animal experiments are needed to validate its toxicological mechanisms.



Disclosures: Ke Mi:Nothing to Disclose, Wei Tang: Nothing to Disclose, Zhidan Zuo:Nothing to Disclose, Qianjun Zhao:Nothing to Disclose, Sha Lin:Nothing to Disclose, Zhixiong Fang:Nothing to Disclose.

3330 | LLM-AUGMENTED EHR PHENOTYPING IDENTIFIES UNDERRECOGNIZED SEVERE DRUG-RELATED LIVER INJURY IN HOSPITALIZED ADULTS

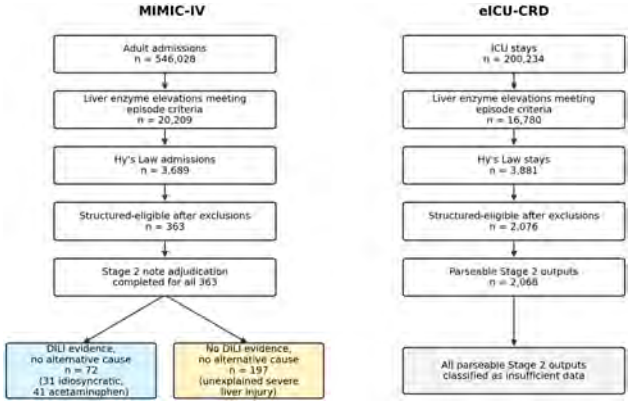
Thanathip Suenghataiphorn[1] Kochakorn Buasri[2] Narathorn Kulthamrongsri[3] Pojsakorn Danpanichkul[4], [1]Yale/Griffin Hospital, [2]Cincinnati Children's Hospital Medical Center, [3]University of Hawaii, [4]Texas Tech University Health Sciences Center

Background: Drug-induced liver injury (DILI) is diagnostically challenging and may be underrecognized during hospitalization because relevant evidence is often distributed across laboratory data, imaging, medication exposures, and narrative documentation. We developed a two-stage electronic health record phenotyping pipeline combining structured data filters with large language model-assisted chart review to identify severe, potentially underrecognized drug-related liver injury. **Methods:** We performed a retrospective cross-sectional study using the MIMIC-IV and eICU-CRD datasets. Adult admissions were screened for biochemical Hy's Law laboratory thresholds, followed by structured exclusions for common competing etiologies using diagnosis codes and baseline laboratory filters. In MIMIC-IV, an open-source large language model analyzed discharge summaries and radiology reports for evidence of DILI, culprit medications, and alternative explanations. Robustness was assessed using two auxiliary LLMs. A selected subset of adjudicated cases underwent independent dual-reviewer manual validation. **Results:** In MIMIC-IV, 3,689 admissions met biochemical Hy's Law thresholds, of which 363 remained after structured exclusions. LLM-assisted adjudication identified 72 admissions with evidence of drug-related liver injury and no clear alternative explanation, including 31 probable idiosyncratic cases. An additional 197 admissions had severe hepatocellular injury without documented DILI recognition or another clear cause, representing a clinically enriched pool of potentially missed cases requiring focused manual review. Auxiliary LLMs matched the primary model's final binary classification in 88.7% and 89.5% of cases. In the manual validation subset, reviewers agreed on 93 of 100 charts, with substantial interrater agreement (κ = 0.86). Compared with independent reviewer adjudication, the primary model achieved 78.0% and 83.0% accuracy against reviewers A and B, respectively, with higher precision than the auxiliary models. **Conclusion:** A two-stage structured EHR and LLM-assisted phenotyping strategy identified a clinically enriched subgroup of severe, potentially underrecognized drug-related liver injury among hospitalized adults. The pipeline also identified a larger group with severe unexplained hepatocellular

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injury who may benefit from focused manual review. LLM-augmented EHR phenotyping may support scalable surveillance for severe DILI, but prospective validation and expert adjudication remain necessary before clinical deployment.

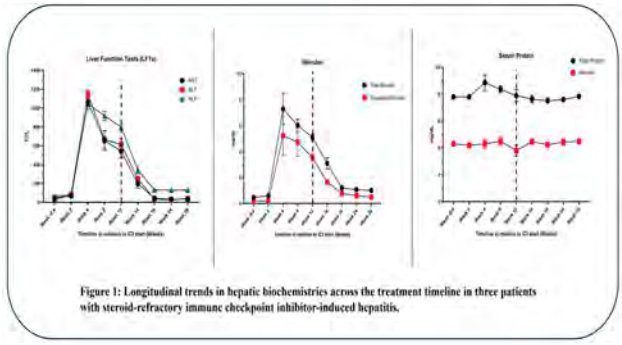


Disclosures: Thanathip Suenghataiphorn:Nothing to Disclose, Kochakorn Buasri:Nothing to Disclose, Narathorn Kulthamrongsri:Nothing to Disclose, Pojsakorn Danpanichkul:Nothing to Disclose.

3331 | A NOVEL ADJUNCTIVE APPROACH WITH N-ACETYLCYSTEINE AND URSODIOL IN IMMUNOSUPPRESSIVE THERAPY-REFRACTORY IMMUNE CHECKPOINT INHIBITOR-INDUCED HEPATITIS&MDASH;CASE SERIES

Yao (Michelle) Lan[1] Beshoy Yanny[2] Kirellos Mikhail[3] Parsia Vazirnia[2] Trinity Michael[2], [1]UCI Health, [2]University of California, Irvine, [3]University of California, Los Angeles

Background: Immune checkpoint inhibitor (ICI)-induced hepatitis occurs in up to 25% of patients ICIs. Immunosuppressive therapy (IST) is considered first line treatment. When patients have contraindication or fail IST, it becomes a necessity to explore adjunctive therapies. N-acetylcysteine (NAC) and Ursodeoxycholic acid (UDCA) have promising roles in other forms of liver injury but lack data when used together in ICI-induced hepatitis. In this case series, we aim to evaluate the addition of NAC and UDCA in patients with immune suppressive therapy-refractory (ISTR) ICI-induced hepatitis and assess efficacy, safety, and monitoring strategies. **Methods:** Retrospective case series of three patients diagnosed with ISTR-ICI-induced hepatitis who received NAC and UCDA as adjunctive therapy. Diagnosis was via liver biopsy. Liver chemistries were obtained at presentation and monthly. Patients with persistent elevated liver chemistries at week 4 of IST were classified as refractory and received adjunctive ursodiol (12.5 mg/kg/day) and NAC (500 mg PO TID). Percentage change from baseline was calculated for each parameter post-NAC/ursodiol. Data were expressed as mean percentage change ± standard error of the mean (SEM). Paired t-tests were used to compare biochemical responses between the two timepoints, with each patient serving as their own control. A two-tailed p-value of 0.05 was considered significant. We also studied the adverse drug reactions with NAC and ursodiol therapy using the FDA Adverse Event Reporting System (FAERS). **Results:** Addition of NAC and ursodiol, significantly improved AST (Mean decrease from 543 to 44 IU/L) with percent change p-value = 0.016, ALP (Mean decrease from 797 to 130 IU/L) with percent change p-value = 0.008, total bilirubin (Mean decrease from 5.1 to 1.2 mg/dL) with percent change p-value = 0.027, and conjugated bilirubin (Mean decrease from 3.5 to 0.77 mg/dL) with percent change p-value = 0.008. ALT showed a trend toward greater reduction (Mean decrease from 614 to 33 IU/L) with percent change p-value = 0.066. Total protein (p-value for percent change = 0.926) and albumin (p-value for percent change = 0.660) remained stable. No adverse events were reported. IS therapy was fully tapered off by week 28. Adverse drug reactions with NAC and ursodiol therapy using the FDA Adverse Event Reporting System (FAERS) and significant low odds ratio further support the safety profile for these drugs and potential therapeutic benefit in treatment of ICI-induced hepatitis. (ROR 0.136, 95% CI 0.019–0.97; p = 0.0465). **Conclusion:** NAC and UDCA combined use in ISTR-ICI-induced hepatitis was effective, safe and associated with statistically significant improvement in hepatocellular and cholestatic markers beyond what was achieved with corticosteroids and MMF alone. Larger prospective studies are needed to evaluate the efficacy and generalization of this approach.


Figure 1: Longitudinal trends in hepatic biochemistries across the treatment timeline in three patients with steroid-refractory immune checkpoint inhibitor-induced hepatitis.

Disclosures: Yao (Michelle) Lan:Nothing to Disclose, Beshoy Yanny:IPSEN Pharmaceuticals: Speaker, IPSEN Pharmaceuticals: Speaker, Madrigal Pharmaceutical: Speaker, Kirellos Mikhail:Nothing to Disclose, Parsia Vazirnia:Nothing to Disclose, Trinity Michael: Nothing to Disclose.

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3332 | STUDY DESIGN AND BASELINE CHARACTERISTICS OF APOLLO: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED CONFIRMATORY TRIAL OF BITOPERTIN IN ADULTS AND ADOLESCENTS WITH ERYTHROPOIETIC PROTOPORPHYRIA OR X-LINKED PROTOPORPHYRIA

Amy Yeung[1] Gayle Ross[2] Mark Amster[3] Karl Anderson[0] Manisha Balwani[5] Herbert Bonkovsky[6] Edward Cordasco[7] Manucher Darani[8] Laurent Gouya[9] Sioban Keel[10] Janneke Langendonk[11] Cynthia Levy[12] Tasneem Mohammad[13] Bruce Wang[14] Will Savage[15], [1]Harvard Medical School and Massachusetts General Hospital, Boston, MA, USA, [2]Royal Melbourne Hospital, Melbourne, Australia, [3]MetroBoston Clinical Partners, Boston, MA, [0]University of Texas Medical Branch, Galveston, TX , [5]Icahn School of Medicine at Mount Sinai, [6]Wake Forest University School of Medicine and Atrium Health Wake Forest Baptist, Winston-Salem, NC, [7]Remington-Davis Clinical Research, Columbus, OH, [8]Marvel Clinical Research, Huntington Beach, CA, [9]University of Paris Diderot, Paris, France, [10]University of Washington/Fred Hutch Cancer Institute, Seattle, WA, [11]Erasmus MC, University Medical Center Rotterdam, Rotterdam, Netherlands, [12]University of Miami, [13]Henry Ford Health System, Detroit, MI, [14]University of California San Francisco Porphyria Center, San Francisco, CA, [15]Disc Medicine

Background: Erythropoietic protoporphyria (EPP) and X-linked protoporphyria (XLP) are characterized by the accumulation of photoreactive protoporphyrin IX (PPIX), causing debilitating cutaneous phototoxic reactions and, in some cases, protoporphyric hepatopathy. Glycine transporter 1 (GlyT1) supplies extracellular glycine for erythroid heme biosynthesis. Bitopertin is an investigational oral GlyT1 inhibitor shown in Phase 2 studies (AURORA [NCT05883748], BEACON [ACTRN12622000799752]) to significantly reduce PPIX and improve light tolerance and quality of life. APOLLO (NCT06910358) was designed to confirm safety, tolerability, and efficacy of bitopertin in adults and adolescents with EPP or XLP. **Methods:** APOLLO is a global randomized, double-blind, placebo-controlled Phase 3 study evaluating once-daily oral bitopertin 60 mg versus placebo over 24 weeks. Eligible participants were $\geq$12 years of age with confirmed EPP or XLP by biochemical and/or genetic testing. Co-primary endpoints are 1) percent change in whole blood metal-free PPIX and 2) average monthly total time in sunlight without pain from a phototoxic reaction between 10:00 and 18:00 after 24 weeks of treatment. Secondary endpoints include occurrence of phototoxic reactions, cumulative sunlight exposure without pain, and change from baseline in time to first prodromal symptoms. Other assessments will evaluate patient-reported quality-of-life measures. Participants completing treatment may continue into the HELIOS open-label extension study. **Results:** Between April 2025 and March 2026, 199 patients were screened at 28 study sites in the US, Canada, Europe, United Kingdom, and Australia; 183 participants were randomized. Mean (SD) age was 37.1 ± 17.1 years; 59% were female and 91% were White. Most participants (93%) had EPP, while 7% had XLP. Diagnostic confirmation was supported by biochemical testing in 52% and genetic testing in 48% of participants. Overall, 60% had not received prior treatment for EPP; 28% and 18% previously received afamelanotide or dersimelagon, respectively. Baseline light tolerance was balanced between participants with $<$30 versus $\geq$30 minutes of tolerance. Adolescents (12 to $<$18 years) represented 19% of enrolled participants, and most adolescents (85%) had not previously received afamelanotide or dersimelagon. Other baseline characteristics were generally similar across adolescent and adult subpopulations. **Conclusion:** APOLLO is designed to evaluate bitopertin as a potential disease-modifying treatment for EPP and XLP. Baseline demographic and disease characteristics were generally consistent with prior EPP/XLP studies and reflective of the broader patient population, supporting the relevance and generalizability of the study results.

Disclosures: Amy Yeung:Nothing to Disclose, Gayle Ross:Sanofi: Honoraria for speaking, Medison: Paid focus group, Abbvie: Medical Advisor, Mark Amster: Nothing to Disclose, Karl Anderson:Nothing to Disclose, Manisha Balwani:Alnylam Pharmaceuticals: Consulting/Advisory Board/Speaker's Bureau, Mitsubishi Tanabe: Grant/Research Support, Disc Medicine: Grant support/ Advisory board fees, Genzyme/Sanofi: Advisor, CRISPR Therapeutics: Advisor, Herbert Bonkovsky:Nothing to Disclose, Edward Cordasco:Nothing to Disclose, Manucher Darani:Nothing to Disclose, Laurent Gouya:Alnylam Pharmaceuticals.: received travel support from Alnylam Pharmaceuticals., Sioban Keel:Nothing to Disclose, Janneke Langendonk:Nothing to Disclose, Cynthia Levy:Gilead: Grant/Research Support, Ipsen: Grant/Research Support, GSK: Grant/Research Support, Intercept: Grant/Research Support, Calliditas: Grant/Research Support, Zydus: Grant/Research Support, LisCure: Grant/Research Support, TARGET RWE: Grant/Research Support, Pliant: Grant/Research Support, NGM: Grant/Research Support, Mitsubishi Tanabe: Grant/Research Support, DISC: Grant/Research Support, Takeda: Grant/Research Support, Kowa: Grant/Research Support, Mirum: Grant/Research Support, Tasneem Mohammad:

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Nothing to Disclose, Bruce Wang:Nothing to Disclose, Will Savage:Disc Medicine: Employee.

★ 3333 | PPARA-MEDIATED SPECIES-SPECIFIC HEPATIC RESPONSES TO PFOS EXPOSURE IN HUMANIZED AND KNOCKOUT MOUSE MODELS OF ALCOHOL-ASSOCIATED LIVER DISEASE

Frederick Ekuban[1] Paxton Ames[1] Abigail Ekuban[1] Oluwanifemi Esther[1] Adrian Centers[1] Yuan Hua[1] Jianzhu Luo[1] Josiah Hardesty[1] Jasey McNabb[1] Addison Wiggam[1] Walter Watson[1] Banrida Wahlang[1] Dhimiter Bello[2] Jennifer Schlezinger[3] Craig McClain[1] Matthew Cave[1], [1]University of Louisville, [2]University of Massachusetts Lowell, [3]Boston University

Background: Perfluorooctane sulfonate (PFOS) is increasingly linked to metabolic dysfunction-associated steatotic liver disease (PMID: 35475652), yet its role in alcohol-associated liver disease (ALD) is understudied. Our prior studies showed that PFOS exacerbates ALD via PPARα (PMID: 40347464), but its mechanistic role and species specificity remain unclear. As PFOS is a strong mouse but weak human PPARα agonist, the human relevance of murine models is uncertain. We investigated species-specific hepatic responses using humanized PPARα (hPPARα) and PPARα-knockout (KO) mice. **Methods:** Male hPPARα and PPARα-KO mice (C57BL/6J) received Lieber-DeCarli diet with 5% ethanol (EtOH) or isocaloric control, with concurrent gavage of 1 mg/kg PFOS or vehicle for 10 days, then a 5 g/kg EtOH binge and euthanasia 5-6h later. Assessments included biochemistry, histology (H&E), gene expression, and high-content imaging of primary hepatocytes. **Results:** PFOS exposure increased EtOH-induced hypertriglyceridemia and elevated VLDL in both genotypes. PFOS decreased EtOH-induced ALT/AST in both genotypes, contrasting prior wild-type findings (PMID:40347464). Blood alcohol levels decreased significantly in KO and trended lower in hPPARα mice with PFOS. Histology revealed genotype-dependent differences: hPPARα mice showed progressive steatosis (mild PFOS, moderate EtOH, severe PFOS +EtOH), whereas KO mice exhibited baseline steatosis with persistent severity across treatments. PFOS+EtOH upregulated *PXR/Cyp3a11* in both genotypes; *CAR/Cyp2b10* remained stable in KO but declined in hPPARα. Lipogenic genes (*PPARγ, Cd36, Fasn*) were upregulated in KO but trended downward in hPPARα. High-content imaging showed enhanced mitochondrial function (4-fold) in hPPARα hepatocytes, versus increased lipid peroxidation (5-fold) in KO. PFOS altered mitochondrial dynamics in a genotype-dependent manner by enhancing ethanol-induced gene expression of *Pink1*, *Park2*, *Drp1*, and *Mfn2* in hPPARα mice while driving a robust, diet-independent upregulation that reflects exaggerated mitochondrial stress in PPARα-KO mice. **Conclusion:** These findings reveal species-specific, PPARα-mediated responses and underscore its central role in modulating hepatic outcomes during PFOS–ethanol co-exposure. Mechanistically, PPARα exhibits dual and context-dependent functions: it preserves lipid homeostasis yet exacerbates hepatocellular injury under combined PFOS and ethanol exposure. Humanized PPARα mice display intermediate phenotypes, underscoring translational differences in receptor activation. Compensatory activation of PXR and CAR pathways in the absence of PPARα suggests cross-regulatory crosstalk. This work provides mechanistic and translational insight into pollutant–alcohol liver interactions and underscores the need for human-relevant models in risk assessment.

Disclosures: Frederick Ekuban:Nothing to Disclose, Paxton Ames:Nothing to Disclose, Abigail Ekuban:Nothing to Disclose, Oluwanifemi Esther:Nothing to Disclose, Adrian Centers:Nothing to Disclose, Yuan Hua:Nothing to Disclose, Jianzhu Luo:Nothing to Disclose, Josiah Hardesty:Nothing to Disclose, Jasey McNabb:Nothing to Disclose, Addison Wiggam:Nothing to Disclose, Walter Watson:Nothing to Disclose, Banrida Wahlang:Nothing to Disclose, Dhimiter Bello:Nothing to Disclose, Jennifer Schlezinger:Nothing to Disclose, Craig McClain:Novo Nordisk: Speaking and Teaching, Intercept Pharmaceuticals: Grant/Research Support, Altimmune: Grant/Research Support, Target Pharma Solutions: Grant/Research Support, NIH: Grant/Research Support, VAMC: Grant/Research Support, VAMC: Employee, National Institutes of Health: Grant/Research Support, NovoNordisk: Speaking and Teaching, VAMC: Employee, VAMC: Grant/Research Support, Intercept Pharmaceuticals: Grant/Research Support, Target PharmaSolutions: Grant/Research Support, Matthew Cave:Nothing to Disclose.

3334 | HEPATIC ADAPTATION TO EXPERIMENTAL DRUGS IN CLINICAL TRIALS: RESULTS OF THE IQ DILI INITIATIVE SURVEY OF MULTI-STAKEHOLDER EXPERTS: IMPACT ON DRUG DEVELOPMENT AND IMPLICATIONS FOR DILI DETECTION AND EVALUATION

Melissa Palmer[1] John Caminis[2] Eric Cohen[3] Daniel Seekins[4] Lucy Walker[5] James Philip Esteban[5] James Lewis[6] Don Rockey[7] Nefeteria Coffee[8], [1]CEO Liver Consulting LLC, [2]Gilead, [3]Abbvie, [4]Bristol-Myers Squibb, [5]GSK, [6]Georgetown University Hospital, [7]MUSC, [8]Sanofi

Background: The liver typically adapts after exposure to experimental drugs by modulating cellular and

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metabolic processes, resulting in transient increases in liver tests that return to normal or baseline despite continued dosing. This phenomenon, known as hepatic adaptation, is often observed in clinical trials, but is likely underestimated due to conservative and unnecessary stopping criteria (ALT or AST ≥3×ULN), often leading to premature subject withdrawal, study pause or termination, or discontinuation of drug development altogether. In addtiion the definition of hepatic adaptation has never been clearly and universally defined. To assess how key stakeholders define and manage adaptation, two workstreams of investigation were implemented **Methods:** First, a comprehensive literature search (PubMed, MEDLINE, EMBASE) was conducted using key words "hepatic" and "liver" adaptation or tolerance, alone or combined with: drug-induced liver injury (DILI), hepatotoxicity, liver enzyme elevations, liver adverse events, and liver toxicity. Second, a 14-question survey was administered to DILI academic and regulatory experts and representatives from IQ DILI Industry partners, to assess the current state of practice and its potential impact on drug development and implications for DILI detection/assessment. **Results:** Except for INH-based regimens, the literature review was limited, especially on the topics addressed in the survey. Among 43 respondents (25 industry, 14 academic, 3 regulatory, 1 other), opinions sometimes varied. For example: 68% defined adaptation as liver enzyme elevations returning to baseline or normal despite continued dosing, 22% reported that symptoms were a component of adaptation, 30% reported that a negative rechallenge qualified as adaptation and 11% reported that elevations of liver tests that plateaued defined adaptation. All respondents associated ALT with adaptation, 50% and 42% included ALP and TBIL respectively. To qualify as adaptation, 81% expected liver test elevations to normalize or return to baseline, 30% required them to decrease to <3xULN, 22% felt liver tests can reach a plateau (not elevte further) and 14% proposed liver tests decrease by 50%. Latency was most commonly considered to occur between 1-3 months of exposure (58%), although 20% and 22% of respondents stated that it could occur within the first 72 hours and > 6 months of drug exposure, respectively, to be defined as adaptation. **Conclusion:** There is limited literature on the details of hepatic adaptation and key aspects remain poorly understood. Practices and perspectives among key stakeholders sometimes varied. Improved understanding will impact decision-making in drug development and have implications on identification and evaluation of potential DILI cases. These survey results will be used to develop a multi-stakeholder expert consensus opinion, recommendations, best practices and research priorities.

Disclosures: Melissa Palmer:Nothing to Disclose, John Caminis:Nothing to Disclose, Eric Cohen:Nothing to Disclose, Daniel Seekins:Bristol-Myers Squibb: Employee, Lucy Walker:Nothing to Disclose, James Philip Esteban:GSK: Employee, James Lewis:Boehringer Ingelheim: Consultant, Biogen: Consultant, Astra Zeneca: Consultant, Astellas: Consultant, Bayer: Consultant, Bausch: Consultant, Madrigal: Consultant, Pfizer: Consultant, Takeda: Consultant, Intercept: Consultant, Tenaya: Consultant, Sanofi: Consultant, Abbvie: Consultant, Ipsen: Consultant, Akero: Consultant, Genentech: Consultant, GSK: Consultant, F2G: Consultant, Vertex: Consultant, Zydus Tech Observer: Consultant, Don Rockey:Nothing to Disclose, nefeteria coffee:Nothing to Disclose.

3335 | GENETIC ARCHITECTURE OF PRURITUS IN IDIOSYNCRATIC DRUG-INDUCED LIVER INJURY (DILI): HLA AND GENE-LEVEL BURDEN TESTING USING WHOLE-EXOME SEQUENCING IN A DEEPLY PHENOTYPED DISCOVERY COHORT

Stuart Astbury[1] Jessica Wong Sun Wai[1] Jane Grove[1] Liou Wei Lun[1] Paola Nicoletti[2] Guruprasad Aithal[1], [1]University of Nottingham, [2]Icahn School of Medicine at Mount Sinai

Background: About 40% of patients with DILI present with itching which reduces quality of life substantially. Despite major advances in the understanding of the genetic susceptibility to DILI, correlations between genotypes and phenotypes are sparse. We investigated genetic factors underlying itching in patients with DILI. **Methods:** In a prospective cohort of 135 patients with DILI evaluated systematically to exclude alternative etiologies and adjudicated following formal causality assessment, genomic DNA of 59 patients with and 76 without itching was sequenced using a whole exome capture panel (Twist Bioscience). STAARpipeline was used to perform both single-variant and gene-based analyses in a model weighted by functional annotation scores (FAVORannotate). Analyses were restricted to the Genomics England Cholestasis v3 panel of 58 candidate genes. In addition, HLA types were imputed using HLA-LA. All analyses were adjusted for population structure and injury pattern (hepatocellular n = 67, cholestatic/mixed n = 64 and unknown n = 4). **Results:** The T allele of ABCC2 rs3740066 (c.3972C > T) was associated with lack of itching (AF 0.23 cases vs 0.42

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controls; gnomAD NFE 0.37; OR 0.37 (0.20 – 0.67), P = 6.0×10^{-4}). Gene-level STAAR-O analysis indicated that pruritic cases were significantly enriched for missense variants in SMPD1 (4 variants carried by 13% of cases, p = 0.039), NPC1 (3 variants, 4% cases, p = 0.044), and LRP5 (7 variants, 16% cases, p = 0.040). We imputed 66 HLA alleles across 8 loci, and observed a significant association between itching and HLA-C*06:02 (OR 2.93, p = 0.007). **Conclusion:** We present several potential genetic links with pruritus in DILI in a deeply phenotyped cohort. Itching in DILI was associated with genetic factors increasing the level of lysophosphatidylcholine (LPC), its conversion through the autotaxin-lysophosphatidic acid (LPA) axis and subsequent activation of skin C-fibres as well as HLA alleles involved in drug-specific immune reactions. Variants in LRP5, NPC1 and ABCC2 have been linked to pruritus through an upregulation in autotaxin expression observed in cholestasis. Variants in NPC1 and SMPD1 will both alter the amount of substrate available for autotaxin and may also influence pruritus directly through LPC levels.

Gene/Locus	OR (95% CI)	P	AF DILI	AF DILI + pruritus
Single variant				
DBT (rs12021720)	5.83 (1.95 – 17.40)	4.9×10^{-4}	0.03	0.14
ABCC2 (rs3740066)	0.37 (0.20 – 0.67)	6.0×10^{-4}	0.43	0.24
ALG9 (rs10502151)	2.79 (1.50 – 5.19)	6.9×10^{-4}	0.23	0.39
NLRP4 (rs421810)	0.50 (0.30 – 0.83)	9.9×10^{-3}	0.49	0.35
Gene-level				
SMPD1 (4 variants)	–	0.029	–	–
DCDC2 (2 variants)	–	0.030	–	–
LRP5 (7 variants)	–	0.040	–	–
NPC1 (3 variants)	–	0.044	–	–
HLA association				
HLA-C*06:02	2.93 (1.35 – 6.58)	0.0076	0.10	0.21
HLA-A*02:01	2.39 (1.19 – 4.86)	0.015	0.22	0.37
HLA-DRB1*07:01	2.40 (1.13 – 5.22)	0.025	0.10	0.20
HLA-DQB1*03:01	0.40 (0.17 – 0.87)	0.026	0.21	0.10
HLA-B*57:01	2.45 (1.04 – 5.97)	0.043	0.07	0.15

Disclosures: Stuart Astbury:Nothing to Disclose, Jessica Wong Sun Wai:Nothing to Disclose, Jane Grove: Nothing to Disclose, Liou Wei Lun:Nothing to Disclose, Paola Nicoletti:Nothing to Disclose, Guruprasad Aithal: Nothing to Disclose.

3336 | ENVIRONMENTAL CO-EXPOSURE TO PFAS AND HEAVY METALS CREATES A CLINICALLY RELEVANT PRO-TUMORIGENIC TRANSCRIPTOMIC SIGNATURE IN A NON-TUMOR MASLD MOUSE MODEL

Haley Arbore[1] Hamda Siddiqui[1] Shannon Heinig[1] Pooja Muddasani[1] Charis-Marie Vanderpuye[1] Jiang Li[1] Natalie Price[1] Zachary Zimmerman[1] Shuai Yuan[1] Sudrishti Chaudhary[1] Noriko Kitano[1] Tyler Yasaka[1] Jia-Jun Liu[1] Silvia Liu[1] Gavin Arteel[1] Junyan Tao[1] Satdarshan (Paul) Monga[1] Alison Sanders[1] Juliane Beier[1], [1]University of Pittsburgh

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the fastest-growing etiology of hepatocellular carcinoma (HCC), yet environmental factors that accelerate MASH-to-HCC progression remain poorly understood. "Rust to Resilience" (R2R) chemical mixtures containing heavy metals (lead, cadmium, arsenic) and PFAS represent environmentally relevant co-exposures common to industrialized regions worldwide. This study investigates the capacity of R2R mixture exposure to promote a pro-tumorigenic hepatic transcriptomic environment in the absence of frank tumor formation, in the context of diet-induced MASLD. **Methods:** C57Bl/6J mice were fed a western diet (WD) or control diet (CD) for 12 weeks with concurrent exposure to vehicle or 1X R2R mixture in drinking water. Bulk RNA-sequencing was performed on liver tissue with DESeq2, KEGG enrichment, and upstream regulatory analysis (IPA/StringDB). Mouse transcriptomic data were cross-referenced against TCGA-LIHC to identify concordantly dysregulated genes, from which a 7-gene prognostic signature was derived via elastic net Cox regression and validated for overall survival and etiology-specific prognostic impact (n = 366). **Results:** R2R exposure worsened WD-induced liver injury. Importantly, none of the animals developed hepatic tumors. Upstream regulatory network analysis revealed dysregulation of HCC-associated upstream regulators including PPARA, FOXO1, CREBBP/EP300, KRAS, MAPK1, and IGF1R, suggesting coordinated suppression of metabolic homeostasis together with oncogenic and epigenetic reprogramming. These findings were further supported by Wnt/β-catenin oncogenic signaling, HCC pathway enrichment (FDR = 5.13×10^{-7}), and suppression of cytotoxic T lymphocyte checkpoints (CTLA4/PD-1). Cross-referencing with TCGA-LIHC identified 90 concordantly dysregulated genes. Elastic net Cox regression derived a 7-gene signature (GAS2L3, SNHG4, CCNB1, ME1, RAPGEF3, SLC22A7, GNA14) predicting worse overall survival (HR = 2.54, 95% CI:1.77-3.65, p < 0.0001), with markedly amplified prognostic impact in MASLD-enriched HCC patients

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(HR = 3.17, 95% CI:1.70-5.90, p < 0.0001; median OS 20.6 vs. 70.0 months). **Conclusion:** In the absence of frank tumor formation, R2R co-exposure induced a pro-tumorigenic transcriptomic program in MASLD mice, that maps onto human HCC and carries the greatest prognostic impact in metabolic-etiology disease. These data position environmental chemical mixtures as modifiable contributors to MASH-to-HCC progression and underscore the need to account for industrial toxicant co-exposure in at-risk populations globally. Importantly, preliminary evidence of R2R-associated tumorigenesis has been observed in a hepatic tumor induction model, with full histopathological characterization pending.

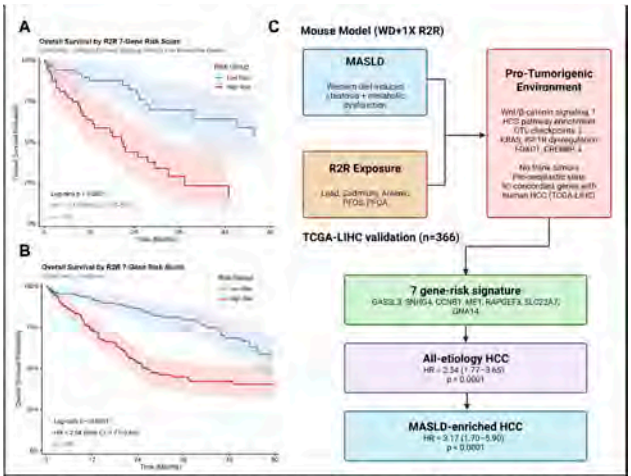


Figure 1. R2R chemical mixture exposure promotes a pro-tumorigenic hepatic transcriptomic environment in MASLD that is clinically validated in human HCC. (A) Kaplan-Meier overall survival in the TCGA-LIHC MASLD-enriched subgroup (n=103), stratified by a 7-gene R2R-derived elastic net risk score (HR=3.17, 95% CI: 1.70–5.90; log-rank p<0.0001). **(B)** Kaplan-Meier overall survival in the full TCGA-LIHC cohort (n=366) stratified by the same signature (HR=2.54, 95% CI: 1.77–3.65; log-rank p<0.0001). Shaded regions represent 95% confidence intervals. **(C)** In a WD+1X R2R mouse model, exposure to R2R chemical mixtures combined with WD-induced MASLD, generating a pro-tumorigenic hepatic environment characterized by Wnt/β-catenin signaling, HCC pathway enrichment, CTL checkpoint suppression, and dysregulation of HCC-associated upstream regulators in the absence of frank tumor formation. Cross-referencing with TCGA-LIHC identified 90 concordantly dysregulated genes, from which a 7-gene prognostic signature was derived and validated in human HCC with greatest prognostic impact in MASLD-enriched patients.

Disclosures: Haley Arbore:Nothing to Disclose, hamda siddiqui:Nothing to Disclose, Shannon Heinig: Nothing to Disclose, Pooja Muddasani:Nothing to Disclose, Charis-Marie Vanderpuye:Nothing to Disclose, Jiang Li:Nothing to Disclose, Natalie Price: Nothing to Disclose, Zachary Zimmerman:Nothing to Disclose, Shuai Yuan:Nothing to Disclose, Sudrishti Chaudhary:Nothing to Disclose, Noriko Kitano:Nothing to Disclose, Tyler Yasaka:Nothing to Disclose, Jia-Jun Liu:Nothing to Disclose, Silvia Liu:Nothing to Disclose, Gavin Arteel:Nothing to Disclose, Junyan Tao:Nothing to Disclose, Satdarshan (Paul) Monga:Vicero Inc.: Advisor, Alnylam: Grant/Research Support, Alnylam: Consultant, Vicero: Advisor, UbiquiTx: Consultant, Alnylam: Grant/Research Support, Alnylam: Consultant, UbiquiTx: Consultant, Revolution Medicines: Grant/Research Support, Antlera: Advisor, Vicero Inc.: Advisor, Alnylam: Grant/Research Support, Alnylam: Consultant, Vicero: Advisor, UbiquiTx: Consultant, Alnylam: Grant/Research Support, Alnylam: Consultant, UbiquiTx: Consultant, Revolution Medicines: Grant/Research Support, Antlera: Advisor, Alison Sanders:Nothing to Disclose, Juliane Beier:Nothing to Disclose.

3337 | INVESTIGATING SIRTUIN DEACETYLASE INHIBITION AS A MECHANISM OF PFAS-INDUCED METABOLIC STRESS AND STEATOSIS

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Background: Per- and polyfluoroalkyl substances (PFAS) are persistent environmental contaminants detected in > 99% of the global population. Their widespread use and resistance to biodegradation contribute to bioaccumulation in the liver. Exposure to the legacy PFAS perfluorooctane sulfonic acid (PFOS) has been associated with an increased risk of metabolic-associated fatty liver disease (MAFLD), but the steatotic potential of next-generation PFAS remains less established. Because sirtuins (SIRTs) regulate hepatocyte lipid metabolism and PFOS has been reported to target sirtuin 1 (SIRT1), we hypothesized that both legacy and next-generation PFAS promote fatty liver via inhibition of SIRTs 1-3. **Methods:** Potential PFAS-SIRT interactions were evaluated using in silico molecular docking (Autodock Vina v1.2; Schrodinger). Predicted binding affinities and interaction profiles were analyzed for SIRT1-3. PFAS-mediated effects on SIRT deacetyl activity were assessed in vitro using a deacetylation-based recombinant protein assay with Superoxide Dismutase 3 (SOD3) and NAD(P)H quinone oxidoreductase 1 (NQO1) as the acetyl targets. To evaluate SIRT inhibition and lipid accumulation in cells, differentiated human hepatocyte-like HepaRG cells were exposed for 72 hrs to 25 µM PFOS or next-generation PFAS: perfluorobutane sulfonic acid (PFBS), perfluorohexane sulfonic acid (PFHxS), perfluorobutane sulfonamide (FBSA), perfluorohexane sulfonamide (FHxSA), or 1,1,2,2 perfluorohexane sulfonic acid (4:2 FTS). Total protein acetylation was quantified via Western Blot, and neutral lipid accumulation was quantified by Nile Red staining. SIRT-selective inhibitors served as positive controls (SIRT1 = EX-527, SIRT2 = AGK2, SIRT3 = 3-TYP), along with the pan-SIRT inhibitor (FK866 and

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nicotinamide [NAM]). **Results:** Across compounds, PFAS preferentially docked within the NAD+ cofactor site of SIRTs and adopted consistent orientations within the pocket. Docking suggested hydrogen-bond and VDW interactions with residues key for SIRT activation, substrate/partner interactions, and catalytic deacetylation. Predicted binding affinity positively correlated with PFAS backbone length, but not with PFAS subclass. In vitro, PFAS inhibition across SIRT isoforms was SIRT3 > SIRT1 > SIRT2. In HepaRG cells, all PFAS increased total protein acetylation and neutral lipid load, consistent with diminished SIRT-mediated deacetylation and altered hepatocyte metabolic regulation. **Conclusion:** These findings support a model where PFAS interact with SIRTs, disrupting SIRT-mediated deacetylation, providing a plausible mechanistic link to PFAS-driven hepatic steatosis and MAFLD. Future work will define PFAS-associated changes in the hepatic acetylome to identify the most affected SIRT-regulated metabolic pathways. This work was supported in part by NIH/NIEHS grants R21ES032529 to JL/RM and T32ES029074 (JB/JW).

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3338 | POST-TREATMENT SYMPTOMS AND HEALTHCARE UTILIZATION ARE COMMON AFTER EXTERNAL BEAM RADIOTHERAPY FOR HEPATOCELLULAR CARCINOMA BUT DO NOT PREDICT LIVER DECOMPENSATION

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Background: External beam radiation therapy (EBRT) has been incorporated into treatment guidelines for hepatocellular carcinoma (HCC). Although EBRT is associated with low rates of severe toxicity, the relationship between early toxicity and subsequent hepatic decompensation remains incompletely characterized. We sought to evaluate the incidence of acute symptom burden and healthcare utilization during EBRT and assess whether these factors predict clinically significant deterioration in liver function. **Methods:** We performed a retrospective cohort study of 192 patients with HCC treated with liver-directed EBRT at a single tertiary center. Acute toxicities were recorded, including the rate of new or worsening symptoms during treatment requiring new prescription medication. Healthcare utilization included emergency department visits or hospitalizations within 90 days of treatment completion. The primary outcome was a $\geq$2-point increase in Child-Pugh (CP) score at 6 months. Univariable logistic regression was performed, followed by a prespecified multivariable model adjusting for baseline liver function, age, acute toxicity, and liver dose. **Results:** Fifty-eight percent of patients reported at least one acute symptom during EBRT, and 20% required new prescription medications. Acute healthcare utilization occurred in 12.5% of patients. At 6 months, 14.7% experienced a $\geq$2-point increase in CP score. Acute toxicity measures, including nausea/vomiting requiring medication (OR 1.01, $p = 0.98$) and acute care utilization (OR 1.51, $p = 0.55$), were not associated with CP worsening on univariable analysis. In contrast, higher baseline Albumin-Bilirubin (ALBI) score (OR 3.16 per SD, $p < 0.001$) and liver V15 (OR 1.28 per 100 cc, $p = 0.015$) were associated with increased odds of hepatic decompensation. In mulivariable analysis, ALBI score remained strongly associated with 6-month CP worsening (OR 3.94 per standard deviation increase, $p < 0.001$). Liver V15 was also independently associated with CP worsening (OR 1.54 per 100 cc increase, $p = 0.001$) **Conclusion:** In patients treated with EBRT for HCC, post-treatment hepatic decompensation was associated with baseline liver function and the volume of liver receiving at least 15 Gy, but not acute symptom burden and post-treatment healthcare utilization. These findings inform predictions of post-EBRT hepatic decompensation and suggest that patient-reported acute toxicity may not reflect underlying hepatic reserve.

Disclosures: Patrick Hazelrigg:Nothing to Disclose, Elizaveta Lavrova:Nothing to Disclose, Vir Kalaria:Nothing to Disclose, Panayiotis Mavroidis:Nothing to Disclose, Allison Jones:Nothing to Disclose, Chidi Iloabachie:Nothing to Disclose, Merete Lund:Nothing to Disclose, Arjun Juneja:Nothing to Disclose, Parsa Pazooki:Nothing to Disclose, Sydney Power:Nothing to Disclose, Gabriel Lupu:Nothing to Disclose, Joyce Badal:Nothing to Disclose, Lawrence Marks:Nothing to Disclose, Shiva Das:Nothing to Disclose, Theodore Yanagihara:Nothing to Disclose, Andrew Moon:TARGET RWE: Consultant, DCN Diagnostics: Grant/Research Support, Intercept Pharmaceuticals: DSMB, IDEOlogy: Consultant, Eisai: Consultant, AstraZeneca: Consultant, Sirtex: Consultant, Madrigal: Grant/Research Support.

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3339 | CLINDAMYCIN-INDUCED LIVER INJURY: PHENOTYPE, OUTCOMES, AND HLA RISK ALLELES

Wesam Aleyadeh[1] Yi-Ju Li[2] Samuel Broderick[3] Huiman Barnhart[3] Jay Hoofnagle[4], [1]National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, [2]Duke University School of Medicine, [3]Duke Clinical Research Institute, Duke University, Durham, NC, [4]NIH, NIDDK

Background: Clindamycin is a widely used lincosamide antibiotic but is infrequently reported as a cause of drug-induced liver injury (DILI). HLA associations have been identified for DILI caused by several antibiotics but have not been evaluated for clindamycin. We describe the clinical phenotype, outcomes, and HLA associations of clindamycin DILI in the DILIN prospective registry. **Methods:** We identified DILIN-enrolled cases in which clindamycin was listed as a primary or secondary suspected cause. Causality was adjudicated by expert opinion as definite (1), highly likely (2), probable (3), possible (4) or unlikely (5). Cases were reviewed for latency, R ratio at onset, peak liver biochemistries, drug allergies, comorbidities, and outcomes. HLA class I and II typing was performed on available samples and compared with population controls and with other DILIN cohorts (non-antibiotic drug associated cases). **Results:** Clindamycin was a suspected agent in 33 cases: 6 high-confidence (causality 1 to 3), 22 possible, and 5 unlikely. Twenty-seven cases had complete HLA data. The 6 high-confidence cases comprised 4 scored as highly likely and 2 as probable, with clindamycin the sole implicated drug in 5. In this cohort, median age was 51 years (range 29-73) and 3 (50%) were women. Median latency to symptom onset was 17 days (range 3-36) after a median 10-day course. Injury pattern was predominantly mixed (median R 2.4), with one strongly hepatocellular outlier (R 61, ALT 5625 U/L). Median peak ALT was 886 U/L, alkaline phosphatase 272 U/L, and bilirubin 3.1 mg/dL. A history of beta-lactam allergy was reported in 4 of 6 cases. All 6 cases recovered without evidence of chronic injury. The HLA allele DQA1*03:01 combined with either DQB1*03:01, *03:02, or both) was present in 4 of 5 high-confidence cases with HLA data (carrier frequency 80%) and 9 of 18 possible cases (50%). The single high-confidence case lacking this allele combination was the hepatocellular outlier. Allele frequency was 0.31 across all clindamycin cases versus 0.11 in a DILI control population. **Conclusion:** Clindamycin DILI is typically mild, mixed and self-limited, which makes it more likely to be missed or misattributed. It is strongly associated with an uncommon combination of HLA class II alelles, DQA1*03:01 together with DQB1*03:01 and/or DQB1*03:02, that is shared by DILI from several structurally unrelated antibiotics. This overlap points to a mechanism driven by shared antibacterial activity rather than chemical structure. HLA testing offers insight into the pathogenesis of antibiotic DILI and may inform causality assessment and future approaches to its prevention and treatment.

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3340 | HISTOLOGICAL ASSOCIATIONS WITH HLA RISK ALLELES IN LIVER INJURY DUE TO AMOXICILLIN-CLAVULANATE

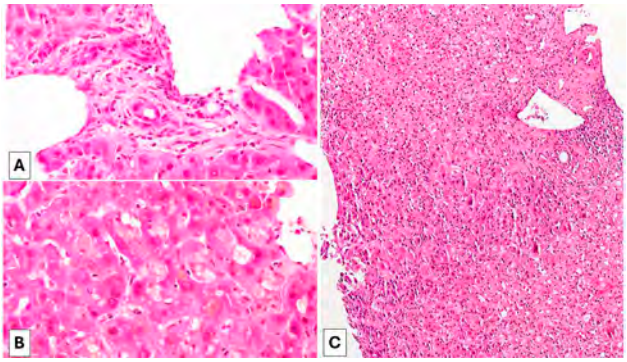
David Kleiner[1] Yi-Ju Li[2] Paola Nicoletti[3] Naga Chalasani[4], [1]National Cancer Institute, Bethesda, [2]Duke University, [3]Icahn School of Medicine at Mount Sinai, [4]Indiana University Medical Center

Background: Drug-induced liver injury (DILI) is a rare but potentially serious adverse event. Genetic factors, especially HLA alleles, have been associated with liver injury in many drugs. In amoxicillin-clavulanate (AC) injury, the HLA alleles A*02:01 and DRB1*15:01 have been identified as risk factors. We hypothesized that the presence of HLA risk alleles may be associated with varied histological injury patterns in AC DILI. **Methods:** Among high causality cases of AC DILI evaluated in the Drug-Induced Liver Injury Network, cases with adequate biopsy material and known HLA haplotypes were identified. Biopsies were evaluated by previously published criteria (PMID: 24037963). Histological features and the overall pattern of injury were analyzed with respect to the presence or absence of the A*02:01 and DRB1*15:01 alleles as well as the total number of risk alleles and the combination of risk alleles. Chi-square and Kruskal-Wallis tests were used to identify possible associations. **Results:** 52 subjects met the inclusion criteria for analysis. At DILI onset, mean age was 60 years (range 13-87) and 18 were female. 23 subjects had only A*02:01 alleles, 6 had only DRB1*15:01 alleles, 16 subjects had at least one allele of each and 7 subjects had neither risk allele. Biopsies in subjects with risk alleles showed more duct injury ($p = 0.03$) (Figure Panel A) and more cholestasis ($p = 0.009$) (Panel B), while cases without risk alleles showed more confluent necrosis ($p = 0.046$) (Panel

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C). Increased eosinophils were seen more often in subjects with HLA-A*02:01 risk alleles. **Conclusion:** We are unaware of any systematic histological comparisons of single agent DILI stratified by HLA genotype. Although the number of subjects with biopsy material is low, the data suggests that there could be histological differences between subjects with risk alleles and those without. The immunological injury mechanism may therefore be different when mediated by specific HLA alleles.



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3341 | ACUTE EXPOSURE TO AN ENVIRONMENTALLY RELEVANT DIOXIN MIXTURE INDUCES SEX-SPECIFIC HEPATIC METABOLIC DYSREGULATION IN A HUMANIZED AHR MOUSE MODEL

Oluwanifemi Esther Bolatimi[1] Yuan Hua[1] Shikshita Singh[2] Marissa Johns[1] Abigail Ekuban[1] Gavin Philips[1] Frederick Ekuban[1] Banrida Wahlang[1], [1]University of Louisville, [2]Rocky Vista University College of Osteopathic Medicine

Background: Exposure to persistent organic pollutants like ‘dioxins’ has shown causal and correlation effects in metabolic dysfunction-associated steatotic liver disease (MASLD). Dioxins are potent aryl hydrocarbon receptor (AHR) activators and have been reported to induce hepatoxicity via this pathway. However, majority of mechanistic studies utilize murine models expressing murine AHR (mAHR) which has significantly higher ligand affinity and responsiveness than the human AHR for xenobiotics. Thus, this study investigates the translational relevance of acute exposure to an environmentally relevant dioxin mixture in the context of underlying sex differences, using a humanized AHR (hAHR) mouse model. **Methods:** Male and female hAHR-C57BL/6 mice (6-8-week-old) fed a low-fat diet were administered a weekly oral dose of a dioxin mixture: 2,3,7,8-Tetrachlorodibenzo-p-dioxin (10ng/kg) + 2,3,4,7,8 Pentachlorodibenzofuran (80ng/kg) + Polychlorinated biphenyl 126 (140ng/kg) or vehicle control for 2 weeks. At euthanasia, plasma and tissues were collected for downstream analyses. Parallel *in vitro* dioxin exposures were conducted using primary mAHR and hAHR hepatocytes. **Results:** Dioxin exposure induced striking sex-specific metabolic phenotypes. Females exhibited higher hepatic triglyceride and cholesterol levels than males. Plasma glucose and glucose uptake levels were increased in exposed males but decreased in females. Dioxin exposure also reduced insulin resistance and pancreatic insulin production in males, while exposed females displayed increased levels of these measurements. Notably, the dioxin mixture did not significantly activate hepatic hAHR *in vivo* as canonical target genes (*Cyp1a1* and *Cyp1a2*) were not induced in either sex. However, hepatic gene expression of xenobiotic (*Car* and *Pxr*) and nuclear receptors (*Lxr* and *Pparα*) were selectively decreased in exposed females. *In vitro*, exposure of primary hAHR-C57BL/6 hepatocytes to higher concentrations of individual components of the dioxin mixture led to induction of *Cyp1a1* and *Cyp1a2*, with the magnitude of induction differing by sex and chemical. Importantly, induction in males was more robust in wildtype C57BL6 mouse hepatocytes expressing mAHR versus hAHR-C57BL/6 hepatocytes. **Conclusion:** Acute exposure to the dioxin mixture resulted in sex-specific disruptions in glucose and lipid metabolism as well as in hepatic transcriptional machinery independent of canonical hepatic hAHR activation *in vivo*, suggesting off-target effects and mechanisms. The contrast in hepatocyte responsiveness between mAHR and hAHR highlights the necessity of humanized models. Comprehensive evaluation of non-canonical AHR mechanisms, extrahepatic responses, and chronic outcomes in this human-relevant model is critical to accurately assess how current environmental dioxin levels drive sex-specific liver and metabolic toxicity in humans.

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3342 | INNATE LYMPHOID CELL 1 IS ASSOCIATED WITH DISEASE SEVERITY AND PROTECTS AGAINST DRUG INDUCED LIVER INJURY

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Background: Drug nduced liver injury (DILI) is a major cause of acute liver injury, yet the immune mechanisms that govern tissue damage and recovery remain poorly defined. Innate lymphoid cell 1 (ILC1), a liver-enriched innate immune subset, has been implicated in hepatic immune surveillance, but its clinical significance and functional role in DILI are unknown. **Methods:** Peripheral blood ILC subsets were quantified by flow cytometryin patients with DILI and healthy controls, and their associations with biochemical markers of liver injury were assessed. Acetaminophen (APAP)-induced liver injury was established in mice to characterize the dynamic changes of circulating and hepatic ILC1. Functional relevance was tested by Anti-AsGM1-mediated depletion and adoptive transfer of purified hepatic ILC1. Liver injury and repair were assessed by serum aminotransferases, histological necrosis, hepatocyte proliferation, and regeneration-associated signaling proteins. **Results:** Circulating ILC1 frequencies were significantly decreased in patients with DILI, declined with increasing disease severity, and were negatively correlated with total bilirubin levels ($r = -0.4614$, $p = 0.0001$). In APAP-treated mice, circulating ILC1 showed an early decline at 6 h after injury and reached the lowest level at 12 h. In contrast, hepatic ILC1 rapidly accumulated and peaked at 12 h. Anti-AsGM1-mediated depletion aggravated APAP-induced liver injury at 24 h and 48 h, as shown by increased serum ALT and AST levels and enlarged hepatic necrotic areas. ILC1-depleted also impaired reflected reparative responses, with fewer Ki67-positive hepatocytes and reduced expression of PCNA, Cyclin D1, and phosphorylated STAT3. In contrast, adoptive transfer of hepatic ILC1 attenuated liver injury, reduced necrosis, and restored regeneration-associated protein expression. **Conclusion:** Circulating ILC1 are closely associated with DILI severity, while hepatic ILC1 rapidly expand in response to APAP-induced liver injury. In vivo depletion and adoptive transfer experiments identify ILC1 as a previously underappreciated hepatoprotective population that limits liver injury and promotes liver regeneration in DILI.

Disclosures: Rongtao Lai:Nothing to Disclose, Jingjing Jiang:Nothing to Disclose, Weiwei Lou:Nothing to Disclose, Mei Huang:Nothing to Disclose, Qing Li:Nothing to Disclose, Ziqiang Li:Nothing to Disclose, QING XIE:Nothing to Disclose.

3343 | TARGETING MITOCHONDRIA TO AMELIORATE MICROCYSTIN-LR-INDUCED LIVER TOXICITY

Neeraja Purandare[1] Apurva Lad[1] Steven Haller[1] David Kennedy[1] Andrew Fribley[1], [1]University of Toledo

Background: Cyanotoxins generated by harmful algal-blooms are increasingly being recognized as important modulators of human disease. One of the most commonly identified toxins in contaminated water is microcystin-LR (MC-LR) which is a potent hepatotoxin. Animal studies have revealed that MC-LR exacerbates liver diseases such as non-alcoholic steatohepatitis. At the intracellular level, MC-LR induces liver damage by activating pro-inflammatory signaling via NF-kappaB, but the upstream signal for this pathway is not well-defined. RNA-sequencing analysis from mouse livers of mice who ingested MC-LR revealed that mitochondrial beta-oxidation (breakdown of fatty acids) is down-regulated with a concomitant upregulation of pro-inflammatory pathways. Mitochondria are important organelles that generate energy by utilizing various substrates such as glucose, glutamine and fatty acids. We hypothesized that MC-LR induces mitochondrial dysfunction activates pro-inflammatory NF-kappaB signaling and induce liver inflammation. **Methods:** This work utilized high-throughput RNA-seq and metabolomic analyses and mitochondria-specific assays (Seahorse bioanalyzer for oxygen consumption, MitoSOX red for reactive oxygen species), NF-kappaB-luciferase reporter assays, luminescence-based ELISAs (cytokines) and qPCR for mitochondrial DNA (mtDNA) measurements. **Results:** We first tested the effect of MC-LR in an in vitro model of human liver cells (Hep3B) and found that MC-LR induces mitochondrial dysfunction by reducing mitochondrial oxygen consumption and increasing ROS. It also reduced mtDNA and protein levels. Mitochondria-specific metabolite and lipid analysis identifed several significantly differentially regulated factors. Of these, carnitine an important precursor involved in mitochondrial beta-oxidation and the fatty acid palmitate were accumulated in liver cells, suppporting the in vivo findings that MC-LR impairs beta-oxidation. To assess the effects on inflammatory signaling, we measured the levels of NF-kappaB phosphorylation, and the levels of TNF-alpha and IFN-gamma, two important pro-inflammatory cytokines which were increased in MC-LR treated hepatocytes. To block these pathogenic effects, we also used an FDA-approved drug nitazoxanide that was identified on a screen of compounds that could activate mitochondria. Nitazoxanide rescued the MC-LR induced oxygen consumption deficit and blocked activation of NF-kappaB. **Conclusion:** Taken together, these findings suggest that mitochondria play a key role in MC-LR-

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induced liver damage and therefore, serve as an important mechanistic target to reduce inflammation. This work is particularly significant in the context of preventing effects of this environmental toxin in the pathogenesis and exacerbation of pre-existing liver conditions such as non-alcoholic steatohepatitis and metabolic dysfunction-associated steatotic liver disease.

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3344 | RIBOCICLIB INDUCED HEPATOTOXICITY: INSIGHTS INTO THE MECHANISM OF LIVER INJURY, CLINICAL COURSE, AND MANAGEMENT

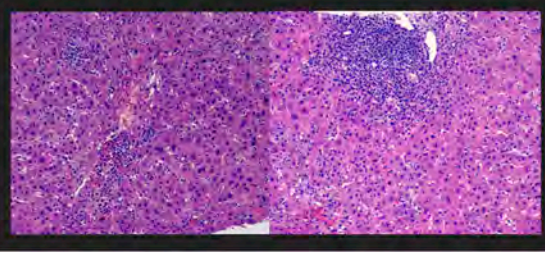
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Background: Ribociclib, a selective cyclin dependent kinase 4 and 6 (CDK 4/6) inhibitor, has been increasingly used for the treatment of hormone receptor-positive (HR+), human epidermal growth factor receptor-2 negative (HER2-) breast cancer. Ribociclib has been shown to cause acute liver injury. The exact mechanism of hepatotoxicity with ribociclib is unclear. **Methods:** We present a case series of five consecutive patients with ribociclib induced hepatotoxicity. Clinical course, laboratory trends, histopathology, and response to therapy were assessed, and a mechanism of liver injury from ribociclib is discussed. **Results:** Five consecutive patients with ribociclib induced liver injury were studied. Median age was 58 years. The onset of liver injury from the time of initiation of ribociclib ranged from 5 to 12 weeks. All 5 patients developed hepatocellular pattern of injury. Peak alanine aminotransferase (ALT) ranged from 271 to 1125 IU/ml (Table 1). Thorough work up for viral hepatitis (A, B, C, E), EBV, CMV, HSV viral loads, autoimmune markers, ferritin, ceruloplasmin, contrast enhanced imaging were negative in all patients. No alternate medication for drug induced liver injury was noted and no patient had significant alcohol use. All patients had persistent elevation in liver enzymes despite discontinuation of ribociclib. Patients A and B developed grade 4 liver injury while patients C, D, and E had grade 3 liver injury. Patient A developed hyperbilirubinemia. Liver biopsy in patient A revealed acute severe hepatitis with centrilobular hepatocyte dropout, marked lobular and portal lymphocytic inflammation without interface hepatitis, parenchymal collapse and Kupffer cell hyperplasia. Systemic corticosteroid therapy resulted in rapid biochemical improvement and normalization. She was then started on palbociclib, another selective CDK 4/6 inhibitor, resulting in an elevation in AST/ALT, suggesting a class effect of hepatotoxicity. Palbociclib was held and liver enzymes normalized. Prednisone was started in all our patients resulting in rapid improvement and normalization of liver enzymes. Based on our experience with patients A, B, and C, corticosteroid therapy was started early in patients D and E resulting in faster resolution of liver injury and enabling early initiation of alternative breast cancer therapy. **Conclusion:** We believe that ribociclib causes indirect hepatotoxicity, mechanistically like immunotherapy induced hepatitis (ICH) as seen with immune check point inhibitors. Hepatotoxicity from ribociclib, like ICH, is dose-independent with variable latency period. Liver biopsy showed features commonly seen in ICH. While it is possible that liver enzymes may improve eventually without corticosteroid therapy, we recommend considering early initiation of corticosteroids in patients with liver injury grades 3 or 4, to allow for faster resolution and minimize delays in further oncologic treatment.

Table 1: Demographic and Clinical Data of patients with Ribociclib induced hepatotoxicity.

Patient	Age (years)	Onset of liver injury from start of Ribociclib (days)	Peak bilirubin (mg/dl)	Peak ALP (U/L)	Peak AST (U/L)	Peak ALT (U/L)	Start of Prednisone from onset of DILI (days)	Time to normalize liver enzymes from start of prednisone (days)
A	46	55	5.3	230	873	1125	57	78
B	56	83	0.8	67	583	815	61	84
C	68	41	1.3	103	238	417	48	8
D	69	47	0.5	82	215	511	14	27
E	50	41	0.7	97	99	271	21	18

Figure 1. Liver biopsy showing marked lobular and portal inflammation with lymphocytes, plasma cells, neutrophils and eosinophils, along with centrilobular hepatocyte drop out, parenchymal collapse, and Kupffer cell hyperplasia.



Disclosures: Shelbie Manna:Nothing to Disclose, Shaun Li:Nothing to Disclose, Arvind Murali:Madrigal Pharmaceuticals: Speaking and Teaching.

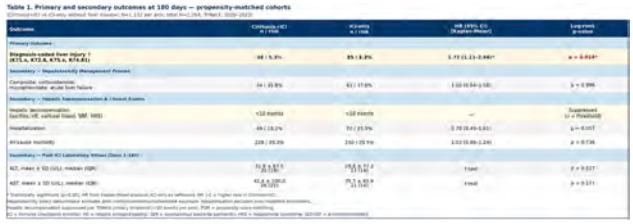
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3345 | ◆ IMMUNE CHECKPOINT INHIBITOR THERAPY FOR NON-HEPATIC CANCERS IS ASSOCIATED WITH INCREASED RISK OF LIVER INJURY AMONG PATIENTS WITH COMPENSATED CIRRHOSIS: A MULTICENTER PROPENSITY-MATCHED COHORT STUDY

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Background: Immune checkpoint inhibitors (ICIs) are increasingly used in patients with chronic liver disease, yet individuals with cirrhosis have been underrepresented in pivotal ICI trials. The hepatic safety of ICIs in compensated cirrhosis for non-hepatic malignancies remains poorly defined. We evaluated this in a multicenter real-world cohort. **Methods:** We performed a propensity score–matched cohort study using the TriNetX Global Collaborative Network of 172 U.S. healthcare organizations (2020–2025). Adults with compensated cirrhosis receiving ICI therapy for non-hepatic cancers were matched 1:1 to ICI-treated adults without liver disease. Patients with prior hepatic decompensation, hepatocellular carcinoma, viral hepatitis, autoimmune hepatitis, or cholestatic liver disease were excluded. Cohorts were matched on demographics, comorbidities, cancer treatment, hepatotoxic medications, and baseline liver-related laboratory values. Primary outcome: diagnosis-coded liver injury within 180 days. Secondary outcomes: hepatotoxicity management proxies, hospitalization, all-cause mortality, hepatic decompensation, and post-ICI transaminases. Hazard ratios were estimated using Kaplan-Meier analysis with log-rank testing. **Results:** Before matching, 1,132 patients with compensated cirrhosis and 118,534 ICI-treated patients without liver disease were identified. After 1:1 propensity matching, 1,132 patients per arm (total N = 2,264). Compensated cirrhosis was associated with significantly higher 180-day liver injury after ICI initiation (5.3% vs 3.3%; HR 1.72, 95% CI 1.11–2.66; p = 0.014). Hepatotoxicity management proxies were similar (35.8% vs 37.6%; HR 1.00, 95% CI 0.64–1.58; p = 0.986). All-cause mortality was similar (20.3% vs 20.5%; HR 1.03, 95% CI 0.86–1.24; p = 0.736). Hospitalization was not significantly increased in cirrhosis patients (18.1% vs 25.9%; HR 0.70, 95% CI 0.49–1.01; p = 0.057). Hepatic decompensation events were uncommon and suppressed due to privacy thresholds. Post-ICI ALT and AST did not significantly differ between cohorts. **Conclusion:** Among ICI-treated patients with non-hepatic cancers, compensated cirrhosis was associated with a higher 180-day hazard of clinically recognized liver injury, without higher mortality or hospitalization. These findings support cirrhosis-specific hepatic risk stratification, closer biochemical monitoring after ICI initiation, and prospective studies to define predictors and management of ICI hepatotoxicity in cirrhosis.



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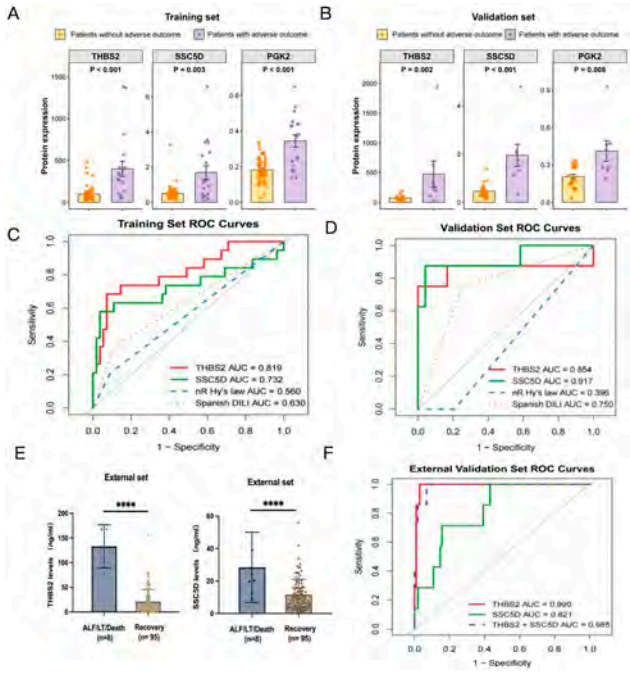
3346 | SERUM PROTEOMICS IDENTIFIES THBS2 AS A NON-INVASIVE BIOMARKER FOR PREDICTING ADVERSE OUTCOMES IN IDIOSYNCRATIC DRUG-INDUCED LIVER INJURY

You Deng[1] Mengmeng Zhang[1] Yu Wang[1] Yan Wang[1] Jianping Li[2] Zikun Ma[1] Yun Zhu[3] Liwei Liu[4] Liuyi Chang[5] Chunxia Zhang[6] Qiuju Tian[7] Lixia Qiu[8] Fangcheng Zhao[9] Juan Li[10] Shirui Lian[11] Jikang Yang[11] Yao Meng[1] Tiantian Guo[1] Jinxin Gu[1] Cen Zhang[1] Mengyu Zhao[1] Runjie Wei[1] Meng He[1] Min Li[1] Zhengsheng Zou[3] Yu Chen[4] Jing Zhang[4] Rongkuan Li[9] Pingying Li[10] Liang Wang[6] Jidong Jia[1] Xinyan Zhao[1], [1]Liver Research Center, Beijing Friendship Hospital, Capital Medical University, [2]Department of Rare Liver Diseases, Guangzhou Eighth People's Hospital, Guangzhou Medical University, [3]Senior Department of Hepatology, The Fifth Medical Center of PLA General Hospital, [4]Fourth Department of Liver Disease (Difficult & Complicated Liver Diseases and Artificial Liver Cent, [5]Gastroenterology Department, Yuncheng Central Hospital, Shanxi Medical University, [6]Infectious Diseases Department, The Second Hospital & Clinical Medical School, Lanzhou University, [7]Division of Hepatology, Liver Disease Center, The Affiliated Hospital of Qingdao University, [8]Department of Hepatology, Beijing You'an Hospital, Capital Medical University, [9]Infectious Disease Department, The Second Affiliated Hospital of Dalian Medical University, [10]Department of Gastroenterology, Qinghai Provincial People's Hospital, Qinghai Provincial Clinical Me, [11]Department of Infectious Diseases, Jiaozuo People's Hospital Affiliated Xinxiang Medical University

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Background: Idiosyncratic drug-induced liver injury (DILI) follows a highly variable clinical course, ranging from spontaneous recovery to liver failure, liver transplantation, or death. Reliable serum biomarkers for early risk stratification remain lacking. We aimed to identify and validate serum proteomic biomarkers associated with adverse outcomes in DILI. **Methods:** Patients with idiosyncratic DILI were prospectively enrolled from 11 Chinese hospitals. In the discovery phase, serum samples from 106 patients enrolled between June 2022 and August 2025 underwent 4D-DIA proteomics and were randomly split into a training set (n = 74) and an internal validation set (n = 32). Adverse outcomes were defined as liver failure, liver transplantation, or death. Machine-learning algorithms were used to identify prognostic biomarkers, whose performance was assessed by ROC analysis and compared with established prognostic scores. Selected biomarkers were validated by ELISA in an independent temporal cohort of 109 patients enrolled between September and December 2025. Functional enrichment, single-cell transcriptomic, and immunohistochemical analyses were performed for biological validation. **Results:** Proteomic profiling and machine-learning screening identified THBS2, SSC5D, and PGK2 as candidate biomarkers associated with adverse outcomes, all of which were significantly elevated in patients with adverse outcomes in both the training and internal validation sets (Figure 1A, B). Because PGK2 has limited established biological relevance to DILI pathobiology, subsequent validation focused on THBS2 and SSC5D. THBS2 and SSC5D showed higher discriminatory performance than nR Hy's law and the Spanish DILI score in both the training set (AUCs: 0.819, 0.732, 0.560, and 0.630, respectively) and internal validation set (AUCs: 0.854, 0.917, 0.396, and 0.750, respectively) (Figure 1C, D). In the independent validation cohort, ELISA confirmed higher serum THBS2 and SSC5D levels in patients with adverse outcomes, with THBS2 showing superior discriminatory performance (Figure 1E, F). THBS2 and SSC5D were correlated with ALB, INR, PLT, and TBIL. Single-cell analysis localized THBS2 upregulation to hepatocytes and mesenchymal cells in DILI-related liver failure, whereas SSC5D upregulation was mainly observed in mesenchymal cells. Immunohistochemistry further confirmed marked hepatic THBS2 upregulation. **Conclusion:** This multicenter proteomic study identified a three-protein serum signature associated with adverse outcomes in idiosyncratic DILI. THBS2 showed robust external validation performance and consistent cellular and tissue-level evidence, supporting its potential as a non-invasive serum biomarker for early risk stratification in DILI.



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3347 | A NEW AND IMPROVED REVISED ELECTRONIC CAUSALITY ASSESSMENT METHOD (RECAM) FOR DIAGNOSIS OF HERBAL AND DIETARY SUPPLEMENT INDUCED LIVER INJURY: THE HDS RECAM

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Background: The Revised Electronic Causality Assessment Method (RECAM) is a computerized causality assessment instrument that was validated against expert opinion for the diagnosis of drug-induced liver injury (DILI) due to a single medication. However, the use of Drug RECAM in assessing the likelihood of liver injury due to herbal and dietary supplements (HDS) indicates a lower level of agreement with expert opinion. Our study aimed to develop a new and improved HDS RECAM for HDS-induced liver injury (HILI) by using clinical data from participants enrolled in the Drug Induced Liver Injury Network (DILIN) Registry study. **Methods:** Data from DILIN patients with suspected single-agent HILI enrolled between 2014-24 were reviewed. Cases attributed to anabolic steroids or those with missing data were excluded. Drug RECAM Domains 1a and 3 were modified to arrive at the new HDS-RECAM to improve agreement in the overall score with expert opinion scores. New domain 1a includes point values of 4, 2 and 0 for HILI latency intervals of 0- 6 months, 6-10 months, and > 10 months, respectively. New domain 3 has point values 3, 1 and 0 based on LiverTox likelihood classification of HDS agent: A /B, C/ D/ E or unknown/not listed, respectively. The resulting HDS-RECAM instrument has values ranging from -6 to 14. **Results:** Amongst the 64 cases of single agent HILI, 54 were definite/high likely/ probable cases and 16 possible/unlikely cases. Median age was 50.9 years, 59.4% female, 70.3% were hepatocellular and 77% required hospitalization. The most commonly implicated HDS were products containing Turmeric (n = 13), Green Tea Extract (n = 8), and Kratom (n = 7). Classification tree analysis found diagnostic cutoffs for overall HDS RECAM scores to be -6 to -2 for 'Unlikely', -1 to 2 for 'Possible', 3 to 5 for 'Probable', and $\geq$ 6 for 'Definite/Highly Likely'. The HDS RECAM outperformed Roussel Uclaf Causality Assessment Method (RUCAM) in identifying at least probable HILI with AUCs of 0.84 vs. 0.59, respectively (p = 0.003). Additionally, the HDS RECAM categories had better overall agreement with expert opinion as compared to RUCAM categories (54.7% vs. 31.3%, p = 0.01) and Drug RECAM categories (54.7% vs. 39.1%, p = 0.052) **(Table 1)** . The HDS RECAM also had better sensitivity than both RUCAM and Drug RECAM to categorize definite/highly likely /probable cases versus possible/ unlikely cases. **Conclusion:** The HDS RECAM is a newly developed causality assessment tool to help adjudicate HILI cases attributed to a single implicated HDS product. It has superior sensitivity and accuracy compared to the RUCAM and Drug-RECAM in high causality HILI cases. HDS RECAM's increased objectivity and ease of use compared to the RUCAM may help improve precision, reliability, and standardization of HILI diagnosis, but additional refinement and validation in other cohorts is needed.

Table 1: Diagnostic Performance of HDS RECAM vs RUCAM and the Drug RECAM in 64 Single HDS Agent Cases Adjudicated By Expert Opinion

Performance Statistic	Causality Score Category	HDS-RECAM	RUCAM	Drug RECAM*	P-value*	P-value**
Percent Agreement with Expert Opinion (95% CI)		54.7 (42.5, 66.9)	31.3 (19.9, 42.6)	39.1 (27.1, 51)	0.01	0.052
AUC (95% CI)	Definite/ Highly likely/Probable	0.84 (0.74, 0.95)	0.59 (0.43, 0.76)	0.82 (0.70, 0.94)	0.003	0.40
Sensitivity (%) (95% CI)	Definite/ Highly likely/Probable	91.5 (83.5, 99.5)	78.7 (67.0, 90.4)	76.6 (64.5, 88.7)	0.048	0.004
Specificity (%) (95% CI)	Definite/ Highly likely/ Probable	58.8 (35.4, 82.2)	35.3 (12.6, 58.0)	76.5 (56.3, 96.6)	0.08	0.056

*P-value comparing HDS-RECAM to RUCAM
**P-value comparing HDS-RECAM to Drug RECAM

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3348 | DO CASES OF HERB AND DIETARY SUPPLEMENTS-INDUCED ACUTE LIVER FAILURE HAVE A WORSE PROGNOSIS THAN CONVENTIONAL DILI?

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Background: Acute liver failure (ALF) is an uncommon but fatal outcome of drug-induced liver injury (DILI). Limited data are available comparing the clinical phenotype and outcomes of ALF according to liver injury pattern and causative agent, particularly herbal and dietary supplements (HDS) versus conventional medications. We aimed to characterize the ALF cases from the Spanish DILI Registry and the Latin American DILI Network (LATINDILI) according to liver injury pattern and to compare the clinical characteristics and outcome between HDS- and conventional drug-induced ALF. **Methods:** We performed a retrospective analysis of adjudicated ALF cases identified from the Spanish DILI Registry and LATINDILI Network. Demographic, clinical, biochemical, and outcome variables were analyzed according to liver injury pattern (hepatocellular, cholestatic, or mixed) and causative agent (HDS vs conventional drugs). **Results:** Among 1,546 DILI/HDS cases, 59 (3.8%) ALF cases were identified and analyzed. Hepatocellular injury predominated (90%), whereas cholestatic and mixed patterns each accounted for 5% of cases. Mean age was 51 ± 17 years, and 73% of patients were female. Antituberculosis agents were the most frequently implicated drugs, followed by HDS [*Chelidonium majus*, *Peumus boldus*, *Senecio brasilensis*, *Garcinia cambogia*, *Lipodex and Herbalife Products (reported in 2012)],* amoxicillin-clavulanate, nimesulide, and flutamide.Hepatocellular cases showed significantly higher AST and ALT levels and lower ALP values compared with mixed and cholestatic injury ($p = 0.032$, $p = 0.011$, and $p = 0.002$, respectively). Classical Hy's law and nR-based Hy's criteria were met in 91% of hepatocellular clinical pattern. Fifty-nine of cases died (liver-related death), while 41% underwent liver transplantation. Strikingly, no cases of spontaneous resolution were observed in the present cohort.HDS accounted for 10% (n = 6) of ALF cases and tended to occur in younger individuals (40 ± 13 vs 52 ± 17 years) and more frequently in women (83% vs 72%). Notably, most ALF cases due to conventional drugs were hospitalized (96%) compared with 67% of HDS-induced ALF ($p = 0.048$). Importantly, no significant differences were observed between HDS- and conventional drug-induced ALF regarding liver-related mortality (50% vs 60%, respectively) or liver transplantation rates (50% vs 40%, respectively) (Table). **Conclusion:** In this cohort, ALF developed in 3.8% of DILI/HDS cases and was associated with high liver-related mortality and transplantation rates. HDS accounted for 10% of ALF cases and predominantly affected younger women. Outcomes of HDS-related ALF were comparable to those of conventional drug-induced ALF.

Table. Comparison of demographics, clinical characteristics, and outcome according to causative agent in DILI cases in the Spanish DILI registry and the Latin American DILI (LATINDILI) Network.

	Total registry n=59	HDS induced ALF n=6	Conventional drug-induced ALF n=53	p value
Age (y), mean±SD	51±17	40±13	52±17	0.109
Female sex, n (%)	43 (73)	5 (83)	38 (72)	1.000
Underlying hepatic disease, n (%)	8 (14)	1 (17)	7 (13)	1.000
Type of liver injury, n (%)				0.490
Hepatocellular	53 (90)	5 (83)	48 (91)	
Cholestatic	3 (5.1)	1 (17)	2 (3.8)	
Mixed	3 (5.1)	0 (0)	3 (5.7)	
DILI episode characteristics				
Jaundice, n (%)	57 (97)	6 (100)	51 (96)	1.000
Hospitalization, n (%)	55 (93)	4 (67)	51 (96)	0.048
Hypersensitivity features, n (%)	23 (39)	2 (33)	21 (40)	1.000
Rash, n (%)	5 (8.5)	0 (0)	5 (9.4)	1.000
Total daily dose (mg), median (IQR)	500 (200-1.800)	300 (300-300)	520 (200-1.800)	0.681
Duration of therapy (d), median (IQR)	33 (14-69)	34 (21-61)	33 (12-70)	0.831
Time to onset (d), median (IQR)	33 (11-67)	36 (11-76)	33 (12-67)	0.890
Eosinophilia, n (%)	8 (14)	2 (33)	6 (11)	0.183
Lymphopenia, n (%)	13 (22)	0 (0)	13 (25)	0.322
Positive autoantibody titers, n (%)	10 (17)	0 (0)	10 (19)	0.577
Outcome				
Liver-related death, n (%)	35 (59)	3 (50)	32 (60)	0.679
Liver transplantation, n (%)	24 (41)	3 (50)	21 (40)	0.679

ALF, acute liver failure; d, days; HDS, herbal and dietary supplements; IQR, interquartile range (25%-75%); SD, standard deviation; ULN, upper limit of normal; y, years.

Disclosures: Fernando Bessone:Nothing to Disclose, Nelia Hernandez:Nothing to Disclose, Ismael Alvarez-Alvarez:Nothing to Disclose, Inmaculada Medina-Caliz: Nothing to Disclose, Hao Niu:Nothing to Disclose, Maria Isabel Schinoni:Nothing to Disclose, Daniela Chiodi:Nothing to Disclose, Pedro Montes:Nothing to Disclose, Nothing to Disclose, Hugo Tanno:Nothing to Disclose, Maria Virginia Reggiardo:Nothing to Disclose, Nothing to Disclose, Federico Tanno:Nothing to Disclose, Ezequiel Ridruejo:Nothing to Disclose, Manuel Mendizabal:Gilead: Speaking and Teaching, Biosidus: Speaking and Teaching, Gador: Speaking and Teaching, Knight: Speaking and Teaching, Novo Nordisk: Advisor, Raymundo Paraná:Nothing to Disclose, Eduardo Fassio:Nothing to Disclose, Mercedes Robles-Díaz:Nothing to Disclose, Ana Marrero-Capitán:Nothing to Disclose, Elvira Bonilla-Toyos:Nothing to Disclose, José Pinazo-Bandera:Nothing to Disclose, Miren Garcia-Cortez:Nothing to Disclose, Juan Pedro Toro-Ortiz:Nothing to Disclose, Maria Isabel Lucena: Nothing to Disclose, Raul Andrade:Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose.

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3349 | MASLD AND DRUG-INDUCED LIVER INJURY AFTER AMOXICILLIN-CLAVULANATE EXPOSURE: A LARGE REAL-WORLD COHORT STUDY

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Background: Amoxicillin-clavulanate is a leading cause of drug-induced liver injury (DILI), but whether metabolic dysfunction-associated steatotic liver disease (MASLD) modifies DILI risk or biochemical severity is unclear. We evaluated outcomes after amoxicillin-clavulanate exposure among patients with and without MASLD. **Methods:** We performed a retrospective cohort study using the TriNetX US Collaborative Network. Adults aged ≥18 years who received amoxicillin-clavulanate between 2010 and 2025 were included. MASLD was defined by ICD-10 codes for fatty liver disease or non-alcoholic steatohepatitis, within 3 years of antibiotic exposure. Patients with underlying chronic liver diseases were excluded. The primary comparison evaluated MASLD vs. no liver disease after propensity score matching for demographics, tobacco use, alcohol-related disorders, and BMI. Outcomes from 1 day to 365 days after exposure included new abnormal liver function tests (R94.5) and toxic liver disease/DILI using (K71). Kaplan-Meier analysis was used to estimate hazards. Among patients with DILI, serial ALT, AST, alkaline phosphatase (ALP), and total bilirubin were compared at baseline, 1 week, 1 month, and 1 year. **Results:** Among approximately 6.15 million adults who received amoxicillin-clavulanate, 164 patients with MASLD and 1,236 patients without MASLD had DILI. After matching, 155,478 patients were included in each cohort (Figure). Compared with matched patients without liver disease, MASLD patients had higher 1-year hazards of new diagnoses of abnormal liver function test (HR 3.25, 95% CI 2.90-3.65) and toxic liver disease/DILI (HR 1.86, 1.25 -2.78) after antibiotic exposure. Among patients with DILI, baseline aminotransferases were modestly higher in MASLD versus non-MASLD patients: ALT 38 vs 33 U/L and AST 34 vs 29 U/L. Liver tests peaked within 1 week in both groups, with ALT 96 vs 84 U/L, AST 59 vs 52 U/L, ALP (153 vs 159 U/L, and total bilirubin 0.8 vs 0.6 mg/dL. Values declined by 1 month and approached baseline by 1 year. **Conclusion:** MASLD was associated with higher DILI within 1 year after amoxicillin-clavulanate exposure. However, absolute event rates were low, and MASLD was not clearly associated with greater biochemical severity among patients with DILI. Further studies using peak labs, R-ratio, INR, latency, competing hepatotoxic exposures, and adjudicated DILI definitions are needed.

Figure. Baseline characteristics, 1-year liver-related outcomes, and serial liver biochemistries after amoxicillin-clavulanate exposure stratified by MASLD status. After propensity score matching, baseline demographic, alcohol/tobacco use, and BMI distributions were well balanced between patients with MASLD and those without liver disease. MASLD was associated with higher 1-year hazards of abnormal liver function test diagnosis and ICD-10-coded toxic liver disease/DILI. Among patients with coded DILI, liver tests peaked within 1 week after exposure and declined over time, with broadly similar biochemical trajectories in patients with and without MASLD.

Characteristic after PSM	MASLD + Amoxicillin-clavulanate (n=155,478)	No liver disease + Amoxicillin-clavulanate (n=155,478)
White race	77.9%	78.0%
Female sex	58.0%	58.0%
Male sex	42.0%	42.0%
Not Hispanic or Latino	73.8%	73.9%
Hispanic or Latino	9.9%	9.9%
Black or African American	9.6%	9.5%
Asian	3.3%	3.3%
Tobacco use	4.6%	4.6%
Alcohol-related disorders	4.6%	4.5%
BMI 20–30 kg/m²	29.7%	29.6%
BMI 30–40 kg/m²	44.8%	44.9%
BMI ≥40 kg/m²	21.0%	21.0%

Outcomes in 1 year	Risk % MASLD + Amoxicillin-clavulanate	Risk % No liver disease + Amoxicillin-clavulanate	Hazard ratio (95% CI)	Log-rank p value
Abnormal LFT diagnosis (R94.5)	0.84%	0.25%	3.25 (2.90–3.65)	<0.001
Toxic liver disease / DILI (K71)	0.05%	0.02%	1.86 (1.25–2.78)	0.002

Lab Median (IQR)	Baseline		1 week		1 month		1 year	
Cohort	DILI with MASLD	DILI without MASLD	DILI with MASLD	DILI without MASLD	DILI with MASLD	DILI without MASLD	DILI with MASLD	DILI without MASLD
ALT (U/L)	38 (70)	33 (78)	96 (158)	84 (162)	47 (73)	40 (67)	29 (37)	23 (32)
AST (U/L)	34 (48)	29 (55)	59 (80)	52 (88)	36 (45)	31 (37)	28 (28)	24 (22)
ALP (U/L)	110 (122)	106 (110)	153 (247)	159 (234)	131 (144)	130 (164)	109 (94)	100 (80)
Total bilirubin (mg/dL)	0.5 (0.6)	0.5 (0.5)	0.8 (1.1)	0.6 (1.2)	0.6 (0.8)	0.6 (0.7)	0.6 (0.5)	0.5 (0.5)

Disclosures: Skylar Hargrove:Nothing to Disclose, Vinay Jahagirdar:Nothing to Disclose, Butros Fakhoury:Nothing to Disclose, Vaishali Patel:Nothing to Disclose, Amon Asgharpour:Galectin: Clinical Endpoint Committee, NovoNordisk: Advisor, Madrigal: Advisor, Chronic Liver Disease Foundation: Speaking and Teaching, Intercept: Consultant, Richard Sterling: ABIM: GI Specialty Board, Abbott: Grant/Research Support, GSK: Grant/Research Support, HCV Vax: Grant/Research Support, Gilead: Grant/Research Support, Zydus: Grant/Research Support, Vertex: Consultant, Madrigal: Advisor, Gigagen: Grant/Research Support, Atea: Grant/Research Support, Cima Science: Consultant, Celaris: Consultant, GSK: Advisor.

3350 | VALIDATION OF A MODIFIED VERSION OF RECAM IN A COMMUNITY-BASED COHORT OF NORTH AMERICAN PATIENTS WITH SUSPECTED IDIOSYNCRATIC DRUG-INDUCED LIVER INJURY

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Background: The Revised Electronic Causality Assessment Method (RECAM) is an updated, electronic version of the Roussel Uclaf Causality Assessment Method (RUCAM) to diagnose drug-induced liver injury (DILI). A modification of RECAM (RECAM-V3) significantly improved agreement between RECAM and DILIN expert opinion in a retrospective cohort (Am J Gastroenterol 2024;120:1325). However, RECAM-V3 requires validation and refinement. This study compared RECAM-V3 vs. RECAM and RUCAM for patients with suspected idiosyncratic DILI in a community-based cohort. **Methods:** Patient encounters from 10/1/2015 to 9/30/2023, at TriHealth, a large community-based health system, were searched for suspected DILI using ICD-10 K71 codes for toxic liver disease. DILIN expert opinion scores were assigned to each case (1/2/3 = probable-DILI, 4/5 = non-DILI). RECAM-V3 modified scoring of domain 4 of the original RECAM with HCV RNA and anti-HEV testing being optional and a dynamic range of – 6 to +20 points like the original RECAM. RECAM-V3, RECAM, and RUCAM scores were compared with DILIN expert opinion scores. **Results:** After excluding 30 cases of acetaminophen hepatotoxicity, 135 patients with suspected idiosyncratic DILI were analyzed. The average age was 56.9 ± 15.4, 47.4% female, 82.9% Caucasian, and 53.3% hepatocellular injury. Sixty-eight (50.4%) of the 135 cases were adjudicated as probable-DILI, and 67 cases (49.6%) as non-DILI using DILIN expert opinion. The most frequent suspect drugs for probable-DILI were antimicrobial (32.4%), anti-neoplastic (16.2%), statin (13.2%), and herbal supplement (7.4%). The most frequent alternative diagnoses for non-DILI were viral hepatitis (26.9%), decompensated cirrhosis (19.4%), ischemic hepatitis (14.9%), and biliary obstruction (14.9%). RUCAM classified 57 cases (42.2%) as probable-DILI, RECAM classified 28 cases (20.7%) as probable-DILI, while RECAM-V3 classified 59 cases (43.7%) as probable-DILI. RECAM-V3 had better overall agreement with DILIN expert opinion for probable-DILI vs. RUCAM (77.9% vs. 63.2%, $p = 0.09$) or RECAM (77.9% vs. 38.2%, $p < 0.0001$). The overall sensitivity of RECAM-V3 was significantly better than the original RECAM (77.9 % vs 38.2%, $p < 0.0001$) while both instruments had high specificity (Table 1). **Conclusion:** Among 135 suspected idiosyncratic DILI cases, RECAM-V3 had better overall agreement with DILIN expert opinion compared to RECAM or RUCAM. With HCV RNA and anti-HEV IgM testing optional, RECAM-V3 had better sensitivity than the RECAM and RUCAM instruments, suggesting that the proposed modifications improve DILI diagnosis without compromising specificity in this independent validation cohort.

Table 1: Comparison of RECAM-V3, Original RECAM and RUCAM to DILIN Expert Opinion amongst 135 patients with suspected DILI*

Metric	RECAM-V3 Estimate (95% CI)	Original RECAM Estimate (95% CI)	RUCAM Estimate (95% CI)
Sensitivity	77.9 (66.2 – 87.1)	38.2 (26.7 – 50.8)	63.2 (50.7 – 74.6)
Specificity	82.1 (70.8 – 90.4)	97.0 (89.6 – 99.6)	79.1 (67.4 – 88.1)
Positive predictive value	81.6 (72.3 – 88.2)	92.9 (76.3 – 98.1)	75.4 (65.1 – 83.5)
Negative predictive value	78.6 (69.8 – 85.3)	60.7 (56.1 – 65.2)	67.9 (60.3 – 74.8)
Accuracy	80.0 (72.3 – 86.4)	67.4 (58.8 – 75.2)	71.1 (62.7 – 78.6)

*Reference = DILIN expert opinion causality assessment method

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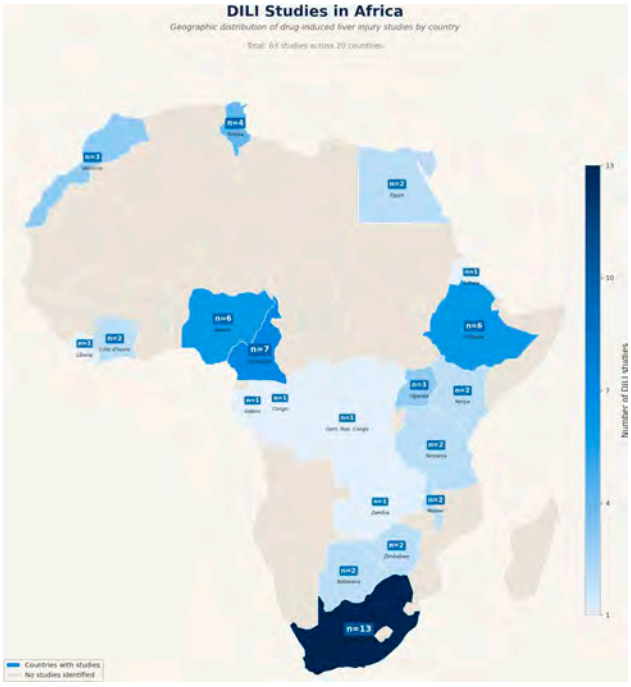
3351 | ETIOLOGY, AND RISK FACTORS OF DRUG-INDUCED LIVER INJURY IN AFRICA: A SYSTEMATIC REVIEW

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Background: Drug-induced liver injury (DILI) is a major contributor to acute liver failure worldwide. However, little is known about the population-level epidemiology, causative drug spectrum, and risk factor profile of DILI in Africa, where the use of potentially hepatotoxic antimicrobial therapies and traditional medicine is common. We conducted a systematic review to address these gaps. **Methods:** We performed a systematic search of PubMed, EMBASE, and African Journals Online from inception to February 16, 2026, to identify studies reporting the epidemiology, causative agents, and risk factors of DILI in Africa. We extracted data on study design, population denominators, incidence and prevalence estimates, implicated drug classes, and risk

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factors including host, demographic, pharmacogenomic, and comorbidity variables. **Results:** After screening for eligibility, we included 63 studies published between 1975 and 2025 across 20 African countries. Geographically, the majority of studies came from South Africa (n = 13 studies), Cameroon (n = 7), Ethiopia (n = 6), and Nigeria (n = 6). All included studies were hospital-based. There were no national DILI registries used in our included studies. Population-level incidence data were largely absent; most studies reported proportions of hepatotoxicity among drug-exposed cohorts rather than true incidence rates, thus preventing reliable continent-wide estimates. Antituberculosis medications (ATT), particularly isoniazid, rifampicin, and pyrazinamide, were the most common implicated causes of DILI, followed by nevirapine- and efavirenz-based antiretroviral therapy (ART). Beyond antimicrobials, NSAIDs (such as diclofenac), acetaminophen overdose, carbamazepine, antineoplastic agents, and herbal or traditional medicines (including Senecio-type plants and khat) were identified as causes of DILI. The most commonly reported risk factors of DILI were concurrent HIV and TB treatment, malnutrition and low BMI, alcohol use, and polypharmacy. **Conclusion:** This study reveals that DILI in Africa is predominantly driven by ATT and ART. The true population-level incidence of DILI remains unknown due to the absence of national registries and reliance on hospital-based cohort designs. Establishing continent-wide pharmacovigilance infrastructure and expanding DILI surveillance beyond tertiary hospital settings are urgent priorities for health systems within Africa.



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3352 | ETIOLOGICAL SPECTRUM, HISTOPATHOLOGICAL FEATURES, AND PREDICTORS OF OUTCOME IN SEVERE DRUG-INDUCED LIVER INJURY: A TERTIARY-CENTER EXPERIENCE FROM INDIA

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Background: Drug-induced liver injury (DILI) is an important cause of acute liver dysfunction and liver-related mortality. Data regarding the etiological spectrum, histopathological characteristics, treatment practices, and outcomes of severe DILI from India remain limited. We evaluated the clinical profile, histopathological features, management strategies, and outcomes of patients with DILI at a tertiary liver center. **Methods:** Consecutive patients with DILI managed at a tertiary liver center were evaluated. Demographic, clinical, biochemical, histopathological, treatment, and outcome data were collected. Severity was assessed using Drug-Induced Liver Injury Network (DILIN) severity grading. Factors associated with mortality were evaluated using logistic and Cox regression analyses. Multivariable models adjusting for MELD score and lactate were used to account for baseline disease severity. **Results:** A total of 136 patients were included. Complementary and alternative medicines (CAM) were the commonest cause of DILI (52.2%), followed by over-the-counter medications (13.2%), miscellaneous agents (12.5%), anti-tubercular therapy (ATT) (8.8%), antimetabolites (8.8%), and antibiotics (4.4%). Underlying liver disease was present in 45.6% of patients. Most patients had severe liver injury, with DILIN grade 4 observed in 92.6% of cases. Overall mortality was 11.8% (16/136).Histopathological findings included cholestasis (49.3%), necrosis (29.4%), fibrosis (26.5%), steatosis (22.1%), eosinophilic infiltrates (16.2%), granulomas (13.2%), and interface hepatitis (11.0%). Neither DILIN severity grade nor histological features, including necrosis and fibrosis, were associated with mortality.ATT-related DILI was associated with higher crude mortality than non-ATT DILI (33.3% vs 9.7%; OR 4.59, p = 0.036). However, this association was attenuated after adjustment for MELD score and lactate (adjusted OR 2.10, 95% CI 0.18–19.29). Patients receiving combined steroid and plasma exchange (PLEX) therapy had substantially greater baseline disease severity (median MELD 26 vs 15 among untreated patients) but demonstrated

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comparable mortality (7.5% vs 6.9%). In adjusted logistic and Cox regression analyses incorporating MELD score and lactate, neither steroid therapy nor plasma exchange independently predicted mortality. **Conclusion:** CAM predominated in severe DILI, whereas ATT-related DILI showed the highest crude mortality. Histological features were not prognostic. Larger multicenter cohorts are needed to identify robust outcome predictors and guide therapeutic interventions in severe DILI.

Table 1. Baseline Disease Severity and Mortality According to Treatment Strategy

Treatment Group	n	Median MELD	Mortality (%)
Neither	29	15	6.9
Steroid	54	22	13.0
Steroid + PLEX	40	26	7.5
PLEX	13	27	30.8

Table 2. Adjusted Predictors of Mortality in Patients with Drug-Induced Liver Injury

Variable	HR	95% CI	p
Steroid only vs Both*	1.83	0.46–7.26	0.388
PLEX only vs Both*	2.51	0.28–22.87	0.414
Neither vs Both*	1.08	0.12–9.70	0.948
MELD	1.05	0.94–1.18	0.385
Lactate	1.33	0.72–2.48	0.364

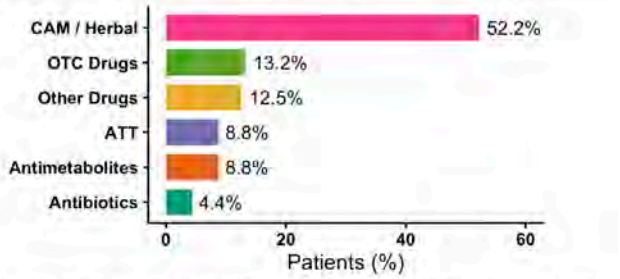


Figure 1. Complementary and Alternative Medicines Account for More Than Half of Drug-Induced Liver Injury Cases

Disclosures: Babu Lal Meena:Nothing to Disclose, SUNIL TANEJA:Nothing to Disclose, Ajay Duseja:Nothing to Disclose, Arka De:Nothing to Disclose, Suvradeep Mitra: Nothing to Disclose, Bijaylaxmi Behera:Nothing to Disclose, Nipun Verma:Nothing to Disclose.

3353 | ESTABLISHMENT OF BASELINE ALT LEVELS IN CLINICAL TRIALS OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH): RESULTS OF >5200 PATIENTS FROM THE IQ DILI INITIATIVE DATA SHARING PROJECT: IMPLICATIONS FOR DILI DETECTION AND EVALUATION

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Background: Patients with MASH exhibit spontaneous fluctuations in serum ALT levels over time which can complicate identification and evaluation of DILI during clinical trials. This variability has led some experts to recommend obtaining as many as 3 screening ALT measurements to establish a more accurate and reliable baseline level to use for comparison if treatment-emergent ALT elevations occur during the trial. However, this approach has never been evaluated in a systematic manner and is the focus of this data analysis of MASH patients from 12 combined clinical trials. **Methods:** MASH trials listed on clinicaltrials.gov prior to 06/06/22 were identified using search terms: NASH, steatohepatitis and cirrhosis. Included studies were required to have been: completed and unblinded; with or without compensated cirrhosis; placebo-controlled; histologically confirmed; MASH; an IQ DILI member industry company; and have informed consent. By pooling data from numerous clinical trials, we aimed to define the expected range of ALT variability in MASH patients with and without compensated cirrhosis during the pre-treatment period. Differences between screening and baseline ALT values of patients ultimately randomized to either the placebo or active arm were evaluated to determine the degree of variance between screening and baseline ALT values, and establish the adequate number of measurements needed to determine baseline values. Comparisons were also made between patients with and without cirrhosis. **Results:** 12 clinical trials were identified (4 in compensated cirrhosis) that met inclusion criteria and were enrolled. A total of 4860 (93.4%) subjects had 1, 325 (6.3%) had 2 and 16 (0.3%) had $\geq$3 screening ALT assessments. The mean interval between successive screening ALT assessments was 65 days for 1, 24 days for 2, and 16 days for 3 of more assessments. Overall, ALT values did not significantly differ between screening (mean 59 U/L (SD 39); median 48 U/L) and baseline (mean 56 U/L (SD 38); median 46 U/L), independent of the number of screening values obtained. Most subjects (68%) did not have a clinically relevant change (+/- 25%) in ALT from screening to baseline visit, and only 7.5% had a $\geq$50% increase or decrease ALT value difference between screening and baseline visit. A total of 12.6% exhibited $\geq$30% within subject ALT variability. Less variability in ALT was observed in cirrhotic than in noncirrhotic patients. **Conclusion:** Analysis of 12 MASH clinical trials which included 4 trials in cirrhotics, involving 5201 patients revealed that

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< 7% had > 1 screening ALT value performed. Most patients had minimal variation in ALT levels between screening and baseline visits. Fluctuations in ALT levels were less for cirrhotic than non-cirrhotic patients. These data demonstrate that more than one screening ALT value is uncommonly measured and may not be necessary in MASH clinical trials to establish an accurate and reliable baseline level.

Comparison of ALT Values at Screening and Baseline Between Patients With and Without Cirrhosis *

	Overall		With Cirrhosis		Without Cirrhosis	
Characteristic	N = 5,559	N = 5,098	N = 1,807	N = 1,651	N = 3,752	N = 3,447
ALT (U/L)	Screening	Baseline	Screening	Baseline	Screening	Baseline
N	5,543	5,085	1,807	1,651	3,736	3,434
Mean (SD)	58.7 (38.7)	56.1 (38.0)	50.4 (31.0)	48.0 (28.3)	62.7 (41.3)	59.9 (41.3)
Median	48.0	46.0	42.0	41.0	52.0	49.0
Min	6.0	3.0	6.0	7.0	6.0	3.0
Max	469	506	286	286	469	506

*N= number of assessments. N's at screening are larger compared to the unique subjects' N's due to multiple screening values as below:

Number of Screening Assessments	Number of total patients = 5201
1	4,860 (93.4%)
2	325 (6.3%)
≥3	16 (0.3%)

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3354 | ◆ HEPATIC STELLATE CELL–SPECIFIC MFAP-4 ENHANCES LIVER FIBROSIS BY STABILIZING THE EXTRACELLULAR MATRIX AND ACTIVATING INTRACELLULAR RHO-ROCK SIGNALING

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Background: Microfibril-associated protein 4 (MFAP-4) is a member of the fibrinogen-related protein superfamily and a key component of the extracellular matrix (ECM). However, its role in the pathogenesis of liver fibrosis remains poorly defined. **Methods:** Liver biopsy samples from cirrhotic patients of different etiologies and several mouse models of liver fibrosis were used to examine MFAP-4 expression and cellular localization. To explore its role in hepatic stellate cells (HSCs) in vivo, HSC-specific deletion of *Mfap4* was induced in *Mfap4*$^{fl/fl}$ mice using AAV6-*Lrat-Cre* in the CCl_4 fibrosis model. In vitro, LX-2 cells with MFAP-4 overexpression or knockdown were used to assess HSC activation, while 3D ECM culture, collagen gel contraction, and immunofluorescence were performed to evaluate its functional effects. Potential MFAP-4 interacting proteins and related pathways were identified by IP-MS and further verified using pathway inhibitors. The antifibrotic potential of MFAP-4 inhibition was tested using AAV6-mediated Mfap4 shRNA delivery in CCl_4 and BDL models, together with a small-molecule MFAP-4 inhibitor identified through virtual screening. **Results:** MFAP-4 was predominantly enriched in activated HSCs and significantly upregulated in advanced liver fibrosis in both humans and mice. HSC-specific suppression of *Mfap4* in *Mfap4*$^{\triangle HSC}$ mice markedly attenuated fibrosis and intrahepatic inflammation after CCl_4 treatment. Mechanistically, MFAP-4 promoted Collagen I and Elastin deposition, as well as gel contraction, thereby enhancing ECM stiffness-mediated HSC activation. IP-MS analysis showed that MFAP-4 interacts with multiple

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components of the Rho-ROCK pathway; inhibition of this pathway reversed MFAP-4-induced HSCs activation and gel contraction in the 3D ECM. Notably, selective knockdown of *Mfap4* by either AAV6-GFAP-sh*Mfap4* or AAV6-U6-sh*Mfap4* significantly retarded liver fibrosis in CCl_4 and BDL models. BJFSH102, a selective small-molecule MFAP-4 inhibitor, ameliorated liver fibrosis by disrupting MFAP-4 interactions with Elastin and Collagen I in CCl_4 models. **Conclusion:** Our findings indicate that HSC-derived MFAP-4 drives liver fibrogenesis by promoting Elastin and Collagen I deposition and reinforcing ECM stiffness-mediated HSC activation. Selective inhibition of HSC-derived MFAP-4 effectively attenuates fibrosis, representing a promising therapeutic strategy for liver fibrosis.

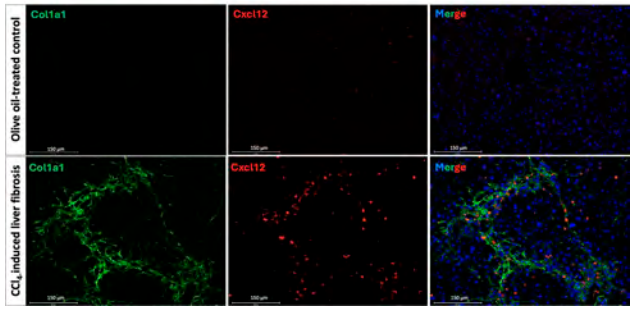
Disclosures: Wenyue Wu:Nothing to Disclose, Wen Zhang:Nothing to Disclose, Hong Li:Nothing to Disclose, Haodong Ma:Nothing to Disclose, Ziyan Pan:Nothing to Disclose, Caihong Wang:Nothing to Disclose, Yameng Sun:Nothing to Disclose, Ning Zhang:Nothing to Disclose, Xuzhen Yan:Nothing to Disclose, Aiting Yang:Nothing to Disclose, Wei Chen:Nothing to Disclose, Hong You:Nothing to Disclose.

3355 | ◆ HEPATIC STELLATE CELL–DERIVED CXCL12 PROMOTES LIVER FIBROSIS BY SUPPRESSING T CELL–INDUCED HSC APOPTOSIS

Maria Hernandez Tejero[1] Sofia Jerez[1] Shawna Cooper[1] Usman Yaqoob[1] Soo Mi Kim[1] Luke Doskey[1] Dawood Al Dawood[2] Colin Chen[1] Mobin Ibne Mokbul[1] Kun Cao[1] Zeba Firdaus[1] Le Z Day[3] Papawee Sutthirat[1] Kevin Pavelko[1] Jon Jacobs[3] Moira Hilscher[4] Nidhi Jalan-Sakrikar[1] Sheng Cao[1] Vijay Shah[1], [1]Mayo Clinic Rochester, [2]Mayo Clinic, [3]Pacific Northwest National Laboratory, Richland, WA, [4]Penn Medicine

Background: Liver fibrosis is driven by persistent activation of hepatic stellate cells (HSCs) and their interactions with the immune microenvironment. However, the molecular mechanisms by which HSCs sustain immune-mediated pro-fibrotic circuits remain poorly defined. We investigated whether HSC-derived signals establish a pro-fibrotic immune loop. **Methods:** Spatial proteomics of human cirrhotic liver tissue was performed using laser capture microdissection coupled with nanoPOTS-based sample preparation and liquid chromatography–tandem mass spectrometry (LC–MS/MS) to identify proteins enriched in collagen-rich fibrotic niches. Findings were validated in murine carbon tetrachloride (CCl_4)-induced fibrosis using spatial transcriptomics, RNA in situ hybridization, and single-cell RNA sequencing (scRNA-seq). HSC-specific Cxcl12 knockout mice (Cre^+, CXCL12-deficient) were compared with CXCL12-expressing controls (Cre^-). Fibrosis, immune infiltration, DNA damage, and T-cell phenotypes were evaluated using histology, immunofluorescence, TUNEL assay, and Cytometry by Time-Of-Flight (CyTOF). In vitro assays assessed the effects of CXCL12 on $CD8^+$ T-cell function and CXCR4 signaling. **Results:** Spatial proteomics demonstrated marked enrichment of CXCL12 within collagen-rich fibrotic niches in human cirrhotic liver compared to non-fibrotic regions ($p < 0.0001$). Spatial transcriptomics and RNA in situ hybridization confirmed these findings in murine CCl_4-induced fibrosis **(Fig. 1)** . scRNA-seq identified activated collagen-producing HSCs as the predominant source of Cxcl12, with increased expression during fibrosis. Control mice expressing HSC-derived CXCL12 (Cre^-) developed significantly greater CCl_4-induced fibrosis and intrahepatic immune cell infiltration compared to HSC-specific Cxcl12 knockout mice (Cre^+) ($p < 0.0001$ and $p < 0.05$, respectively). CyTOF revealed expansion of a distinct $CD8^+CXCR6^+$ T-cell population expressing inhibitory receptors including PD-1, TIM3, and TIGIT in Cre^- versus Cre^+ mice (all $p < 0.001$). In vitro, CXCL12 suppressed $CD8^+$ T-cell IFNγ production, an effect reversible with CXCR4 inhibition. TUNEL staining showed increased DNA fragmentation in fibrotic livers from Cre^- mice compared to Cre^+ mice, supporting a role for CXCL12 in regulating immune-mediated HSC apoptosis. **Conclusion:** HSC-derived CXCL12 promotes a pro-fibrotic immune circuit by inducing a hypofunctional, inhibitory receptor–expressing $CD8^+$ T-cell phenotype within the fibrotic niche, thereby limiting immune-mediated HSC apoptosis. The CXCL12–CXCR4 axis represents a key regulator of HSC–immune crosstalk and a potential therapeutic target.

Figure 1. Spatial redistribution of Cxcl12 along fibrotic septa in a CCl_4-induced mouse model of liver fibrosis



Disclosures: Maria Hernandez Tejero:Nothing to Disclose, Sofia Jerez:Nothing to Disclose, Shawna Cooper:Nothing to Disclose, Usman Yaqoob:Nothing to Disclose, Soo Mi Kim:Nothing to Disclose, Luke Doskey:Nothing to Disclose, Dawood Al Dawood:Nothing to Disclose, Colin Chen:Nothing to Disclose, Mobin Ibne Mokbul:Nothing to Disclose, Kun Cao:Nothing to Disclose, Zeba Firdaus:Nothing to Disclose,

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3357 | ◆ HEPATIC STELLATE CELL-SPECIFIC *NTRK3* DELETION ATTENUATES LIVER FIBROGENESIS IN MICE

Bruno Cogliati[1] Aina Anton[1] Dipankar Bhattacharya[1] Li Chen[2] Shuang Wang[1] Scott Friedman[3], [1]Icahn School of Medicine at Mount Sinai, [2]PharmaNest, [3]Icahn School of Medicine at Mount Sinai (ISMMS)

Background: Neurotrophic receptor tyrosine kinase 3 (NTRK3) has been discovered as a component of an autocrine signaling network among activated hepatic stellate cells (HSC) in advanced liver fibrosis, implicating NTRK3-dependent pathways in its pathogenesis (DOI: 10.1126/scitranslmed.add3949). To definitely establish NTRK3 as a driver of hepatic fibrosis, we investigated whether inducible, HSC-specific deletion of *Ntrk3* modulates liver fibrogenesis or its resolution in mice. **Methods:** A novel Colec11-Cre^{ERT2} mouse line whose expression is highly restricted to HSCs was crossed with *Ntrk3* floxed mice (Ntrk3$^{fl/fl}$) to generate tamoxifen (TAM)-inducible HSC-specific *Ntrk3* knockout (Ntrk3$^{\Delta HSC}$) and heterozygous deletion (Ntrk3$^{\Delta/+}$) mice. Cre-negative littermates served as controls. To assess fibrosis progression, mice received TAM (75 mg/kg/day, i.p.) for 5 consecutive days, followed by 20% CCl_4 (i.p., 3x per week) for 6 weeks before euthanasia. For fibrosis regression analysis, mice received 20% CCl_4 for 4 weeks, followed by TAM treatment and continued CCl_4 to complete 6 weeks of injury, and then recovered for 2 weeks before euthanasia. Fibrosis and stromal/immune remodeling were assessed by AI-assisted digital pathology, flow cytometry, RT-qPCR, and western blotting. In parallel, primary Ntrk3$^{fl/fl}$ HSCs were transduced with adenoviral Cre to assess the cell-autonomous effects of *Ntrk3* loss *in vitro.* **Results:** In CCl_4-treated male mice, both Ntrk3$^{\Delta HSC}$ and Ntrk3$^{\Delta/+}$ livers developed less fibrosis during disease progression compared with controls. This was associated with lower expression of canonical markers of HSC activation and extracellular matrix remodeling, including *Acta2*, *Col1a1*, *Col1a2*, *Mmp2*, and *Pdgfr*β. Western blot documented reduced protein expression of α-SMA, COL1A1, and COL1A2 in *Ntrk3*-deficient livers. By flow cytometric profiling *Ntrk3* deletion also reshaped the non-parenchymal cell compartment, characterized by decreased natural killer and endothelial cell populations and increased macrophage abundance. In contrast, HSC-specific *Ntrk3* deletion had no effect on fibrosis regression. These findings suggest that *Ntrk3* contributes more to active fibrogenesis than to spontaneous fibrosis resolution. *In vitro*, adenoviral Cre-mediated *Ntrk3* depletion in primary Ntrk3$^{fl/fl}$ HSCs attenuated profibrogenic gene expression, supporting an HSC-intrinsic role for NTRK3 signaling in fibrogenic activation. **Conclusion:** 1) Our newly developed, highly specific, regulable Cre mouse line is a powerful new tool for *in vivo* studies of HSC biology; 2) HSC-specific *Ntrk3* ablation attenuates CCl_4-induced liver fibrogenesis *in vivo*, identifying Ntrk3 as an autocrine regulator of fibrosis progression and a potential antifibrotic target; 3) Mediators of fibrosis resolution likely engage different mediators and signaling loops than those driving progression.

Disclosures: Bruno Cogliati:Nothing to Disclose, Aina Anton:Nothing to Disclose, Dipankar Bhattacharya: Nothing to Disclose, Li Chen:Nothing to Disclose, Shuang Wang:Nothing to Disclose, Scott Friedman:89 Bio: Consultant, Boehringer Ingelheim: Consultant, Boston Pharmaceutical: Consultant, Bristol Myers Squibb: Consultant, Merck: Consultant, Glycotest: Consultant, Morphic Therapeutics: Consultant, HepGene: Consultant, North Sea Therapeutics: Consultant, Pfizer Pharmaceuticals: Consultant, Sagimet: Consultant, Scholar Rock: Consultant, Prosciento: Consultant, Seal Rock: Consultant, Surrozen: Consultant, Takeda Pharmaceuticals: Consultant, Junevity: Consultant, Therasid Bio: Consultant, Ochre Bio: Consultant, Gordian Biotechnology: Consultant, Abalone Bio: Grant/Research Support, Prosciento: Consultant, Abbvie: Consultant, Curie Bio: Consultant, Forth Therapeutics: Advisor, Mediar Therapeutics: Consultant, Hepta BIo: Consultant, In sitro: Consultant, Kerna Ventures: Consultant, Resolution Therapeutics: Consultant, Takeda: Consultant, Variant Bio: Consultant.

3358 | MYELOID RBFOX2 CONTROLS USF2 SPLICING TO PREVENT MACROPHAGE–HEPATIC STELLATE CELL CROSSTALK AND LIVER FIBROSIS

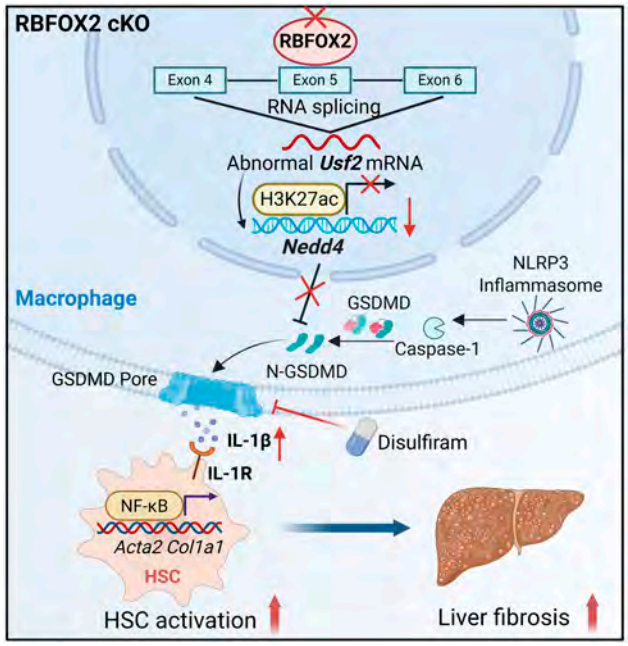
Xuewen Duan[1], [1]Shanghai Jiao Tong University School of Medicine

Background: Macrophage pyroptosis is a key driver of inflammation and fibrogenesis in liver injury. Increasing evidence implicates alternative splicing in the regulation

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of inflammatory signaling, yet whether it modulates macrophage pyroptosis remains unclear. Here, we investigated the role of RBFOX2 in macrophage pyroptosis and macrophage–hepatic stellate cell (HSC) crosstalk during liver fibrosis and explored the therapeutic potential of targeting RBFOX2 for fibrosis resolution. **Methods:** Circulating monocytes and liver tissues from healthy controls and patients with liver fibrosis of diverse etiologies were examined for RBFOX2 expression and its clinical relevance. Myeloid-specific Rbfox2 knockout (Rbfox2 cKO) mice were subjected to carbon tetrachloride-, bile duct ligation-, and high-fat high-cholesterol diet-induced fibrosis models to define RBFOX2 function. RNA sequencing, histological analyses, and phenotypic characterization assessed macrophage pyroptosis, HSC activation, and fibrosis progression. Single-cell RNA sequencing profiled immune remodeling. CLIP-seq and epigenetic analyses defined mechanisms regulating inflammasome activation. Rbfox2 cKO; Il1r1$^{-/-}$ mice and disulfiram-mediated GSDMD inhibition tested whether blockade of IL-1R or pyroptosis signaling attenuated fibrosis caused by Rbfox2 deficiency. AAV8-mediated Rbfox2 restoration was evaluated in fibrotic wild-type mice. **Results:** RBFOX2 expression was increased in circulating monocytes and liver tissues from patients with liver fibrosis and was associated with fibrosis severity. Myeloid-specific Rbfox2 knockout mice exhibited exacerbated liver injury and fibrosis, accompanied by increased macrophage pyroptosis, inflammatory cytokine release, and HSC activation. Mechanistically, loss of Rbfox2 promoted *Usf2* exon 5 skipping, impairing USF2 transcriptional activity and reducing H3K27ac enrichment at the NEDD4 promoter, thereby relieving repression of inflammasome activation and enhancing NLRP3 inflammasome-dependent macrophage pyroptosis. In macrophage–HSC co-culture systems and fibrosis models, Rbfox2-deficient macrophages exhibited increased IL-1β secretion, activating IL-1R/NF-κB signaling in HSCs to promote profibrotic gene expression and HSC activation. Genetic deletion of Il1r1 or pharmacological inhibition of GSDMD with disulfiram reversed macrophage pyroptosis and fibrosis induced by Rbfox2 deficiency. AAV8-mediated Rbfox2 restoration alleviated liver fibrosis in wild-type mice, highlighting RBFOX2 as a potential therapeutic target. **Conclusion:** Our findings identify RBFOX2 as a critical suppressor of inflammasome activation and macrophage pyroptosis in liver fibrosis. Loss of RBFOX2 amplifies macrophage–HSC crosstalk, driving HSC activation and fibrosis progression. Targeting the RBFOX2-regulated pyroptosis pathway may provide a therapeutic strategy for liver fibrosis.



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3359 | HETEROZYGOUS LOXL1 MUTATION IMPAIRS FIBROSIS REVERSAL AND PRIMES A PRO-TUMORIGENIC NICHE VIA ENHANCED ECM CROSS-LINKING

Wen Zhang[1] Wenyue Wu[1] Hong Li[1] Ning Zhang[1] Ziyan Pan[1] Haodong Ma[1] Caihong Wang[1] Ruoyu Gao[1] Qiushuang Ji[1] Zhi Chen[1] Xuzhen Yan[1] Aiting Yang[1] Wei Chen[1] Hong You[2], [1]Beijing Friendship Hospital, Capital Medical University, [2]Capital Medical University

Background: Lysyl oxidase-like 1 (LOXL1) is a copper-dependent enzyme that plays a critical role in extracellular matrix (ECM) cross-linking, contributing to tissue remodeling and fibrotic processes. Although LOXL1 mutations are known to enhance ECM cross-linking in glaucoma, their involvement in liver fibrosis remains poorly understood. **Methods:** LOXL1 single nucleotide polymorphisms (SNPs) were analyzed in genomic DNA from 168 patients with chronic hepatitis B (CHB)-related liver fibrosis, and their associations with fibrosis progression and regression were examined. Functional validation was performed using heterozygous Loxl1G153D mutant mice in a carbon tetrachrachloride (CCl_4)-induced liver fibrosis model with spontaneous regression. Integrated proteomic, transcriptomic, and metabolomic analyses of decellularized livers were conducted to characterize mutation-associated biological changes. In vitro assays were performed to assess

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LOXL1 cleavage, enzymatic activity, and ECM crosslinking capacity. **Results:** Patients harboring the heterozygous LOXL1G153D mutation exhibited a significantly lower rate of fibrosis reversal after 78 weeks of antiviral therapy compared with non mutant patients (26.3% vs. 52.4%, P = 0.025), along with higher post treatment levels of alanine aminotransferase (ALT), gamma glutamyl tansferase (GGT), liver stiffness measurement (LSM), and Ishak fibrosis scores. The G153D mutation resides adjacent to the putative bone morphogenetic protein 1 (BMP1)-binding region of LOXL1, and functional assays demonstrated that it enhances BMP1 mediated LOXL1 cleavage, increases the activity of mature LOXL1, and augments ECM crosslinking capacity. In CCl_4 induced fibrosis models, Loxl1 G153D mice displayed exacerbated perisinusoidal fibrosis, increased ECM deposition, lipid accumulation, and delayed fibrosis regression. Decellularized liver proteomics confirmed enhanced ECM stabilization and crosslinking, and in vivo tumorigenesis experiments showed that the mutation increases susceptibility to hepatocellular carcinoma (HCC) development. Integrated transcriptomic and metabolomic analyses further revealed a hepatic microenvironment characterized by immunosuppression and metabolic activation, supporting the formation of a protumorigenic niche. These findings suggest that LOXL1G153D promotes fibrosis persistence by enhancing LOXL1 cleavage and ECM remodeling, while also shaping a protumorigenic microenvironment. **Conclusion:** The heterozygous LOXL1G153D mutation impairs fibrosis regression by enhancing LOXL1 cleavage, enzymatic activation, and ECM crosslinking, while promoting a metabolically active and immunosuppressive microenvironment that may favor HCC development.

Disclosures: Wen Zhang:Nothing to Disclose, Wenyue Wu:Nothing to Disclose, Hong Li:Nothing to Disclose, Ning Zhang:Nothing to Disclose, Ziyan Pan:Nothing to Disclose, Haodong Ma:Nothing to Disclose, Caihong Wang:Nothing to Disclose, Ruoyu Gao:Nothing to Disclose, Qiushuang Ji:Nothing to Disclose, Zhi Chen:Nothing to Disclose, Xuzhen Yan:Nothing to Disclose, Aiting Yang:Nothing to Disclose, Wei Chen:Nothing to Disclose, Hong You:Nothing to Disclose.

3360 | THE FGF21 ANALOG EFX REGULATES INTERCELLULAR FIBROGENIC SIGNALING BY DISRUPTING HEPATOCYTE TO STELLATE CELL TRANSFER OF DYSFUNCTIONAL MITOCHONDRIA.

Suyavaran Arumguam[1] Xinshou Ouyang[1] Timothy Rolph[2] Erik Tillman[2] Wajahat Mehal[1], [1]Yale School of Medicine, Yale University, [2]Akero Therapeutics, a Novo Nordisk Company, Boston, United States

Background: Mitochondrial dysfunction in steatotic hepatocytes drives MASLD progression, but how organelle-level injury is communicated to hepatic stellate cells (HSCs) to initiate fibrosis remains unresolved. Horizontal mitochondrial transfer is an emerging pathophysiological regulator. We previously showed self-mtDNA leakage activates STING in HSCs under TGF-β stimulation (Arumugam et al., Hepatology 2023), implicating mitochondrial signals as fibrogenic effectors. Efruxifermin (EFX), a long-acting FGF21 analog, has diverse effects on hepatocytes and has demonstrated anti-fibrotic effects in clinical trials. **Aim:** To determine whether lipotoxic hepatocytes transfer mitochondria to HSCs and whether EFX disrupts this fibrogenic axis. **Methods:** Primary human hepatocytes (PHH) and primary human HSCs were co-cultured under palmitate-induced steatosis ± EFX (6hrs pre/16hrs post-EFX exposure to palmitate), and HSC activation was assessed by α-SMA immunofluorescence with intensity quantification. To track mitochondrial transfer, HepG2 (Mito-RFP/TOM20-mPLUM, red) and LX-2 (Mito-GFP, green) reporter co-cultures were imaged by high-resolution confocal microscopy (Leica SP5, 40×; Leica Stellaris 8 DIVE, 100×). MitoSOX (mitochondrial ROS), TMRE (mitochondrial membrane potential [MMP]), MitoPQ (ROS inducer), and MitoTEMPO (antioxidant) dissected ROS causality. **Results:** Palmitate stressed PHH induced robust α-SMA expression in HSCs ($P < 0.0001$ vs control), which was significantly attenuated by EFX treatment ($P < 0.01$ vs PA). In HepG2-LX-2 co-cultures, palmitate increased mitochondrial oxidative stress and impaired MMP in HepG2 cells, (while triggering horizontal transfer of HepG2-derived damaged mitochondria into LX-2 cells. Mitochondrial fragments delivered to LX-2 were selectively enriched for high mitoROS ($P < 0.05$) and low MMP ($P < 0.01$), indicating lipotoxicity-induced active export of ROS-enriched and damaged organelles. MitoPQ was sufficient to drive mito transfer ($P < 0.01$), while the anti-oxidant MitoTEMPO reduced mtROS but failed to abrogate palmitate-induced mitochondrial transfer, establishing mitoROS as sufficient but not necessary to drive hepatocyte-to-HSC mito transfer. EFX abrogated this fibrogenic signal by suppressing MitoROS ($P < 0.05$), preserving MMP ($P < 0.01$), and abrogating hepatocyte-to-HSC mitochondrial transfer ($P < 0.01$). **Conclusion:** Lipotoxicity in hepatocytes selectively segregate and transfer ROS-enriched, depolarized mitochondria to HSCs, driving their activation. EFX restores hepatocyte mitochondrial quality and interrupts this intercellular, organelle-transfer driven profibrogenic signaling, identifying a novel therapeutic node in MASLD and MASH-associated fibrosis.

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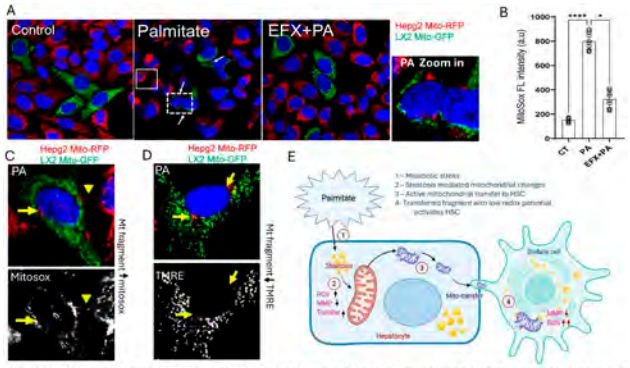


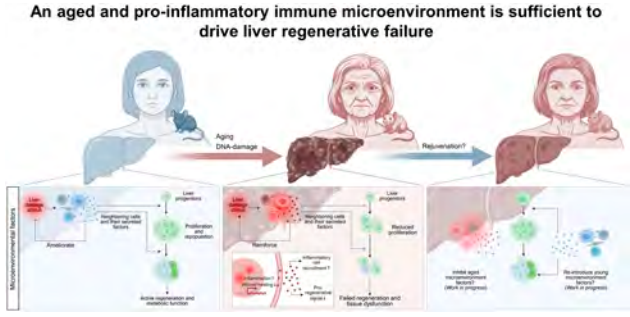
Figure 1. **(A)** Confocal imaging of HepG2 Mito-RFP (red) / LX-2 Mito-GFP (green) / DAPI co-cultures shows palmitate (PA)-induced horizontal transfer of HepG2 mitochondria into LX-2 cells (arrows, inset), which is abolished by EFX. **(B)** EFX suppresses PA-induced hepatocyte MitoROS (MitoSOX FL; ****P<0.0001 PA vs Control, *P<0.05 EFX+PA vs PA). **(C–D)** Transferred mitochondrial fragments in LX-2 cells (arrows) are selectively enriched for high MitoSOX **(C)** and low TMRE/MMP **(D)**. **(E)** Working model: lipotoxic hepatocytes segregate and export ROS-high, depolarized mitochondria to HSCs to drive their activation, an organelle-level fibrogenic axis interrupted by EFX.

Disclosures: Suyavaran Arumguam:Nothing to Disclose, Xinshou Ouyang:Nothing to Disclose, Timothy Rolph:Akero Therapeutics: Employee, Bioage Labs: Stock - publicly traded company, SourceBio: Stock – privately held company, Erik Tillman:Novo Nordisk: Employee, Novo Nordisk: Stock - publicly traded company, Akero Therapeutics: Employee, Akero Therapeutics: Stock - publicly traded company, Wajahat Mehal:Nothing to Disclose.

3361 | AN AGED IMMUNE MICROENVIRONMENT IS SUFFICIENT TO PROMOTE REGENERATIVE FAILURE AND LIVER FIBROSIS

Rahagir Salekeen[1] Elizabeth Schmidt[1] Samuel Peters[1] Laura Niedernhofer[1], [1]University of Minnesota – Twin Cities

Background: Chronic liver disease is projected to impose a global economic burden exceeding $2.8 trillion by 2050. Aging is the strongest risk factor for chronic disease and regenerative failure, with liver-related mortality tripling in patients over 65. While immune cells are essential mediators of liver homeostasis and repair, how age-associated immune dysfunction affects regenerative decline remains unexplored. Using human clinical samples and novel transgenic mouse models, we investigated the impact of immune aging on liver regeneration and fibrotic resolution. **Methods:** Human liver single-cell RNA-seq and spatial transcriptomics datasets were analyzed to define conserved regenerative and immune aging states. To model immune-driven aging, we used Cre-loxP mouse models subjected to chemical liver injury and assessed using histochemistry, RNA-seq and 3D spheroid cultures. **Results:** Human single-cell RNA-seq and spatial transcriptomic profiling across aging and pathological grades revealed progressive disruption of regenerative immune–epithelial coordination, accompanied by expansion of inflammatory states and near complete loss of spatially organized periportal progenitor niches. Cell–cell communication analyses of hepatic niches further implicated aberrant interactions with both infiltrating and resident macrophage compartments as key contributors to age-associated transcriptional remodeling.These signatures were functionally modeled using Vav1-Cre and Cx3cr1-Cre conditional systems, where we selectively accelerated DNA damage and aging signatures in hematopoietic stem and monocyte compartments respectively. Following chemical liver injury, both models exhibited impaired regenerative recovery relative to controls, with significant increases in bridging fibrotic lesions and non-parenchymal infiltration, and prolonged persistence of injury-associated states. Spatial analyses revealed disruption of organized regenerative microenvironments, characterized by sustained pro-inflammatory signaling, skewing toward inflammatory macrophage polarization states, and aberrant recruitment of B-cell populations. Mechanistically, co-culture and conditioned media experiments using hepatic spheroids identified immune-derived signals that suppress mitogenic responses, hepatic identities and organization. **Conclusion:** Aging drives maladaptive immune–epithelial interactions in the liver that disrupts regenerative niche organization and coordinated repair. Immune aging is a previously underappreciated driver of fibrotic progression, revealing a targetable non-autonomous mechanism of liver disease etiology. These insights have immense implications in translational frameworks aiming to improve outcomes in aged patients – including enhancing graft recovery, optimizing transplant resilience, and informing immune-targeted therapies in chronic disease management.



Disclosures: Rahagir Salekeen:Nothing to Disclose, Elizabeth Schmidt:Nothing to Disclose, Samuel Peters: Nothing to Disclose, Laura Niedernhofer:Nothing to Disclose.

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3362 | ISOGENIC HIPSC DERIVED LIVER-ON-CHIP SYSTEM: A VALUABLE TOOL FOR MODELLING FIBROSIS

Kehinde Oluwasegun Aina[1], [1]Friedrich Schiller University Jena

Background: Background and aimsModeling the human liver in vitro is a challenging task. Yet information from such models about the architecture of the liver is important for the development of drugs and the study of different liver diseases. The functional characterization of these components remains difficult owing in part to a scarcity of human model systems. To improve the predictive power of in-vitro models, (HLA-matched) hiPSCs from a healthy and diseased donor were used in this study to generate parenchyma and non- parenchyma liver-like cells, through tissue engineering approaches interfaced with organ- on-chip technology. **Methods:** This system was designed to allow for long-term investigation of tissue-tissue crosstalk without any bias and recapitulation of micro-environmental cues in a 3D culture format.The platform is intended for the culture and co-culture of isogenic cells (hepatocytes, stellate cells, endothelial cells (EC), and macrophages) and its application in the context of disease modeling. Firstly, HLA-matched hiPSC-derived liver cells were generated, functionally characterized, and bio banked. To investigate vascular-immune cellular crosstalk, hiPSC-derived endothelial cells were co- cultured with polarized macrophages, on chip under static and dynamic flow conditions. **Results:** Fibrosis phenotype was validated based on endothelial cell dysfunction, stellate cell activation, and deposition of extracellular matrix. This phenotype was more pronounced in LoC models treated with TGFβ compared to untreated controls. The TGFβ treated models were characterized by the extracellular deposition of collagen, upregulation of fibrosis markers (Alpha- smooth muscle actin, Fibronectin, Glial fibrillary acidic protein, Col1ά1, PDGRFβ), and activation of stellate cells as indicative markers related to fibrosis development. Thus, the data suggest that the dynamic interactions between diMerent liver cell types via soluble mediators and cytokines play an important role in the progression of fibrosis. **Conclusion:** ConclusionThis lays the groundwork for its use in preclinical studies and the investigation of the of new molecules such as short-chain fatty acids and bile acids on disease progression or therapeutics for disease intervention. Therefore, these LoC systems oMer the advantage of the combination of different liver cells with matched donors with individualized study of monogenic diseases.

Disclosures: Kehinde Oluwasegun Aina:Nothing to Disclose.

3363 | HIV COINFECTION EXACERBATES HBV-INDUCED LIVER FIBROGENESIS THROUGH AN EXOSOMAL MIR-103A-3P DEPENDENT PATHWAY

Min Xu[1] Olivia Mezzetti[1] Thien Nguyen[1] Sreya Biswas[2] Cecilie Back-Nielsen[1] Charlotte Warner[1] Xiaoqiong Duan[3] Shasha Li[4] Yongtao Wang[1] Volney Spalding[1] Zeinab Heidariyan[1] Shadi Salloum[1] Chuanlong Zhu[5] Xu Yu[6] Benjamin Burwitz[2] Raymond Chung[1] Wenyu Lin[7], [1]Massachusetts General Hospital, Harvard Medical School, [2]Oregon National Primate Research Center, Oregon Health and Science University, [3]Chinese Academy of Medical Sciences and Peking Union Medical College, [4]The Second People's Hospital of Fuyang City, [5]The First Affiliated Hospital of Nanjing Medical University, [6]The Ragon Institute of Massachusetts General Hospital, MIT, and Harvard University, [7]Massachusetts General Hospital

Background: Approximately 4 million people worldwide are co-infected with HBV and HIV, yet the mechanisms by which HIV accelerates HBV-induced liver fibrosis remain unclear. Pantothenate kinase 2 (PANK2) and PANK3 encode rate-limiting enzymes in coenzyme A synthesis, and each hosts an intronic miRNA (MIR103A2 and MIR103A1, respectively) that produces miR-103a, a potential regulator of fibrotic and metabolic pathways. Here we integrate transcriptomics and functional experiments to explore how HIV-induced dysregulation of the PANK2–MIR103A2 and PANK3–MIR103A1 loci contributes to fibrogenesis. **Methods:** RNA-seq (GSE76246) of PBMCs from HBV mono-infected individuals and rhesus macaques (HBV mono-infection vs. SHIV/HBV co-infection) were examined. Infectious HBV viral particles (HBVvp) were purified from the supernatant (HBVsup) of HepAD38 cells. HIV NL4-3 strain viral particles (HIVvp) and exosomes were isolated from the supernatants of HIV-infected (HIVexo) and uninfected (U937exo) U937 macrophages. NTCP-HepG2 cells, LX-2 cells, primary human hepatocytes, and primary human hepatic stellate cells, as well as 3D co-culture models and precision-cut liver slice (PCLS) models, were directly exposed to HIVsup, HIVvp, HIVexo, or U937exo in both mono- and co-culture settings. These cells and culture systems were also treated with synthetic miR-103a-3p mimics or inhibitors with or without siRNA-mediated knockdown of inhibitor of DNA-binding protein 2 (ID2), which was identified as a potential target of miR-103a-3p by bioinformatic analysis. **Results:** Compared to uninfected PBMCs, HIV infection was associated with upregulated PANK2, PANK3, and miR-103a-3p in human PBMCs and in HBV/SHIV-infected macaque livers, along with profibrotic genes (TGFB1, TIMP1, ACTA2, COL1A1) and collagen deposition. These

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changes were only partially reversed by ART. HIV-positive exosomes enhanced HBV-induced fibrogenic responses in our cell culture models. Mechanistically, miR-103a-3p directly suppressed ID2 and was associated with increasing HIF1α and TGF-β1 consequently accelerated HBV-induced liver fibrogenesis. A miR-103a-3p inhibitor attenuated the pro-fibrotic effects in 3D co-culture models with HIV and HBV coinfection, while treatment with ID2 siRNA partially reversed these effects. Notably, because *MIR103A2* and *MIR103-A1*are embedded within PANK2 and PANK3 respectively, coordinated regulation of these loci by HIV infection links metabolic reprogramming to fibrogenesis. **Conclusion:** HIV co-infection exacerbates HBV-induced liver fibrogenesis via upregulation of miR-103a-3p, which suppresses ID2 and hyperactivates HIF1α/TGF-β1 signaling. The embedded location of miR-103a-3p within PANK2/3 suggests a conserved regulatory axis. These results highlight miR-103a-3p as a potential diagnostic and therapeutic target for liver fibrosis in individuals living with HBV and HIV co-infection.

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3364 | MATRIX STIFFNESS INDUCES CXCL12 IN HUMAN HEPATIC STELLATE CELLS AND HI-C REVEALS A PRECONFIGURED CHROMATIN DOMAIN AT THE CXCL12 LOCUS

Dawood Al Dawood[1] Luke Doskey[2] Usman Yaqoob[2] Shawna Cooper[2] Sofia Jerez[2] Maria Hernandez Tejero[2] Soo Mi Kim[2] Sheng Cao[2] Vijay Shah[2], [1]Mayo Clinic, [2]Mayo Clinic Rochester

Background: Liver fibrosis is driven by hepatic stellate cell (HSC) activation, extracellular matrix deposition, and progressive tissue stiffening. CXCL12 is highly expressed by HSCs during fibrosis and mediate fibrotic stromal signaling. However, whether stiffness induces CXCL12 in human HSCs, and whether the CXCL12 locus is organized within a defined 3D chromatin regulatory neighborhood, remain unclear. **Methods:** Primary human HSCs were cultured on soft (0.5 kPa) or stiff (32 kPa) matrices, and CXCL12 was quantified by qPCR. Genome-wide 3D chromatin organization was evaluated by Hi-C from vehicle- and TGF-β-treated human HSC cell line LX-2 cultured on stiff plastic. Results were visualized with the Juicebox web app and analyzed in IGV using genome assembly GRCh38/hg38 and *CXCL12* transcript NM_199168.4 ($n = 3$ each). CRISPRi was used for functional testing with sgRNA designed using the UCSC Genome Browser to target the mouse *Cxcl12* promoter on chromosome 6. Transfection was done on primary fibroblasts expressing dCas9-KRAB and *Cxcl12* expression was measured by qPCR. Candidate *Cxcl12* mechanoenhancer regions centered at chr6:117,300,000 and chr6:117,325,000 were identified by comparing H3K27ac ChIP-seq in activated/quiescent HSCs (GSM4176113) with snATAC-seq peaks from a CCl_4-induced fibrosis model HSCs. sgRNA were designed to target the mechanoenhancer region. **Results:** A stiff matrix increased CXCL12 in primary human HSCs compared to a soft matrix ($FC = 6$, $p < 0.05$). In stiff-cultured LX-2 cells, Hi-C maps revealed a reproducible local interaction domain encompassing the CXCL12 locus on chromosome 10. IGV tracks showed recurrent upstream-to-CXCL12 contacts, consistent with a pre-established regulatory neighborhood, with no major changes following TGF-β treatment. In mouse CRISPRi experiments, promoter-targeting sgRNAs achieved >80% knockdown of *Cxcl12*; the top-performing guide is being packaged for lipid nanoparticle delivery. Mechanoenhancer-targeting sgRNAs are being tested in parallel. **Conclusion:** Fibrotic-like stiffness induces CXCL12 in primary human HSCs. Hi-C/IGV analysis support the presence of a preconfigured CXCL12 chromatin neighborhood in stiff-cultured LX-2 cells, and CRISPRi identifies promoter and candidate mechanoenhancer elements for future in vivo validation.

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3365 | PRO-FERROPTOTIC AND ANTI-FIBROTIC FUNCTIONS OF MIR-122-ENRICHED HEPATOCYTE EXTRACELLULAR VESICLES

Xinlei Li[1] Sherri Kemper[1] David Brigstock[1], [1]Nationwide Children's Hospital

Background: Hepatocyte extracellular vesicles (EVs) are anti-fibrotic in toxin- or fatty acid-induced liver fibrosis. While the underlying mechanisms are elusive, we have explored the involvement of miRNAs which efficiently regulate post-transcriptional gene expression by targeting a mRNA 3'UTR. Here we investigate the role of miR-122, which is abundant in hepatocytes and their EVs, in driving ferroptosis in activated hepatic stellate cells (HSC), a novel mechanism which likely contributes to the anti-fibrotic actions of hepatocyte EVs. **Methods:** Mouse hepatocyte AML-12 EVs were purified from 48-hr conditioned medium of cell cultures, and their constituent miRNAs were profiled by small RNA-seq. Human LX2 HSC were incubated with AML-12 EVs for 48 h and with erastin for the last 24 h prior to measuring ferroptosis. Scramble control (LX2-miR-NC) or miR-122 stably expressing LX2 cells (LX2-miR-122) were generated by lentiviral transduction. The cells were treated with erastin, RSL-3, FIN56, or in cystine-depleted medium along with inhibitors of apoptosis, necroptosis, or pyroptosis. Intracellular ferrous levels in cells under normal or serum-free culture condition were measured by FerroOrange. Wildtype or mutant NRF1 3'UTR reporters were used for miR-122 target assays. GPX4, NRF1 knockdown or overexpression was achieved by lentiviral transduction. iPSCs were differentiated into multicellular human liver organoids (HLO) which were treated with 20ng/ml TGFβ for 72 h to induce fibrogenesis. miR-122-enriched lentiviruses or EVs were added 24 h post TGFβ treatment in HLOs. **Results:** MiR-122 was the most abundant of 156 miRs in AML-12 EVs, which exacerbated erastin-induced LX2 cell death. Transient or stable expression of miR-122 in LX2 cells led to drastic ferroptosis induced by erastin, RSL-3, FIN56, or cystine depletion. miR-122-induced cell death was reversed by inhibitors of ferroptosis but not of apoptosis, necroptosis, or pyroptosis. Serum-starved quiescent HSCs but not activated HSC were resistant to miR-122-induced ferroptosis. In HSC, miR-122 enhanced cellular ferrous levels, reduced expression of NRF1 and GPX4, and targeted the NRF1 3'UTR. Knockdown of GPX4 or NRF1 led to enhanced ferroptosis in LX2 cells. NRF1 overexpression partially reversed miR-122-induced ferroptosis. Multicellular HLOs comprising hepatocytes, HSCs, macrophages, endothelial cells, and cholangiocytes demonstrated fibrosis-related changes at protein and transcript levels in response to TGF-β, but this was significantly ameliorated by delivery of miR-122. **Conclusion:** Hepatocyte EVs potentiate ferroptosis in activated HSC by delivering miR-122, which leads to elevated cellular ferrous iron level and reduction of GPX4 expression by directly repressing NRF1 expression. HLOs are a promising platform for investigating miR-122-mediated fibrosis therapy.

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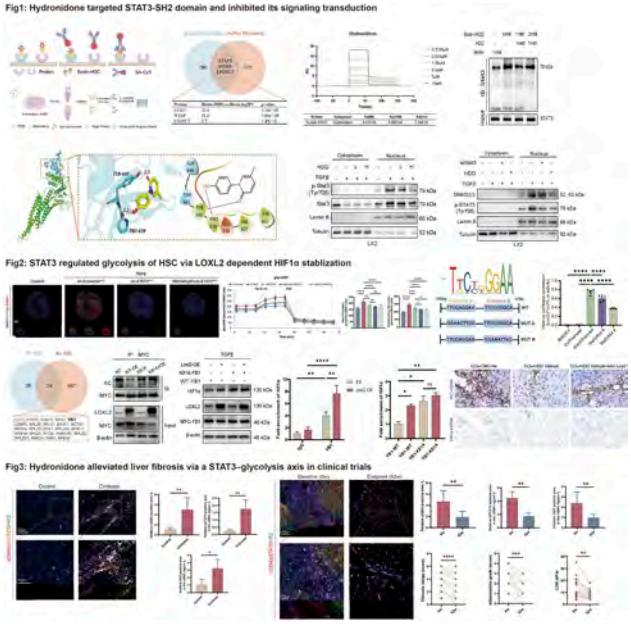
3366 | HYDRONIDONE REVERSES GLYCOLYTIC REPROGRAMMING AND LIVER FIBROSIS BY TARGETING THE STAT3/LOXL2-MEDIATED STABILIZATION OF HIF1α IN HEPATIC STELLATE CELL

Qichao Ge[1] Zhangdi Hangjing[1] Yufei Yang[1] Ling Zhang[2] Ying Luo[2] Lungen Lu[1], [1]Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, [2]Continent Pharmaceuticals Co. ,Ltd., Beijing, China

Background: Hepatic stellate cell (HSC) activation is central to liver fibrosis. Hydronidone (HDD) is a clinically advanced anti-fibrotic candidate, but its direct target and mechanism of action remain incompletely defined. We sought to identify the molecular target of HDD and determine how it modulates HSC activation. **Methods:** Fibrotic multilineage human liver organoids (hLOs), murine and human HSC models, multi-omics profiling, target deconvolution, and mouse fibrosis models were combined with HSC-specific genetic manipulation. Human relevance was assessed in HBV-related cirrhosis and paired biopsies from a phase II HDD trial. **Results:** Target discovery and orthogonal validation identified STAT3 as a direct HDD-binding protein. HDD engaged the STAT3 SH2 domain through Pro639/Tyr640, inhibiting STAT3 signal transduction and STAT3–SMAD2/3 crosstalk. Functionally, HDD preferentially blunted glycolysis-associated remodeling during HSC activation and LOXL2 was identified as a direct STAT3 target and a key HDD-reversible effector. Mechanistically, intracellular LOXL2 bound YB1 and promoted YB1 Lys81 deacetylation, enhancing YB1 binding to *Hif1a* mRNA and increasing HIF1α synthesis, thereby driving glycolysis reprogramming. In paired phase II biopsies, HDD reduced αSMA, pSTAT3, and HK2 in fibrotic regions, accompanied by improved fibrosis/inflammation scores, liver stiffness, and transaminases. **Conclusion:** HDD exerts anti-fibrotic activity by directly targeting STAT3 and suppressing a LOXL2-YB1-HIF1α axis that links HSC activation to glycolysis-associated metabolic reprogramming.

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3367 | INTEGRIN αVβ3/αVβ5 INHIBITION AMELIORATES LIVER FIBROSIS AND PORTAL HYPERTENSION IN CONGESTIVE HEPATOPATHY

Hayato Hikita[1] Seiya Kato[1] Yasuharu Kawamoto[1] Kenji Fukumoto[1] Yuta Myojin[1] Yuki Makino[1] Yoshinobu Saito[1] Takahiro Kodama[1], [1]The University of Osaka, Graduate School of Medicine

Background: Congestive hepatopathy induces liver fibrosis and portal hypertension despite minimal hepatic inflammation and without marked AST/ALT elevation. Recently, we demonstrated that activation of the integrin αV-YAP-CTGF pathway in liver sinusoidal endothelial cells (LSECs) promotes liver fibrosis, portal hypertension, and hepatocarcinogenesis in congestive hepatopathy. In this study, we investigated the therapeutic potential of integrin inhibitors for congestive hepatopathy. **Methods:** Congestive hepatopathy was induced in mice by partial inferior vena cava ligation (pIVCL). Two weeks after pIVCL, mice were subcutaneously treated with either the pan-integrin αV inhibitor CWHM-12 (100 mg/kg/day) or the integrin αVβ3/αVβ5 inhibitor cilengitide (10 mg/kg/day). Mice were analyzed after 4 weeks of treatment. Liver samples from patients with Fontan-associated liver disease (FALD) were analyzed as clinical specimens of congestive hepatopathy. **Results:** pIVCL induced liver fibrosis and portal hypertension accompanied by YAP pathway activation and CTGF overexpression in LSECs. Administration of the pan-integrin αV inhibitor significantly reduced Sirius Red-positive fibrotic areas and portal pressure. Single-cell RNA-seq (scRNA-seq) analysis of pIVCL livers revealed reduced expression of YAP/TAZ target genes, including CTGF, in LSEC clusters after treatment, indicating suppression of the integrin αV-YAP-CTGF pathway in LSECs. Since integrin αV forms heterodimers with multiple β subunits, we further investigated the involved β subunits to improve therapeutic specificity. In pIVCL livers, expression of *Itgb3* and *Itgb5*, encoding integrin β3 and β5, respectively, was significantly increased. Moreover, scRNA-seq analysis demonstrated increased expression of Itgb3 in the LSEC fraction. Based on these observations, mice were treated with cilengitide, a selective inhibitor of integrin αVβ3 and αVβ5. Cilengitide significantly attenuated liver fibrosis and reduced portal pressure in pIVCL mice, similar to the effects of the pan-integrin αV inhibitor. Furthermore, scRNA-seq analysis of FALD livers revealed expression of ITGAV, ITGB3, and ITGB5 within LSEC clusters, supporting the relevance of integrin αVβ3/αVβ5 signaling in human congestive hepatopathy. **Conclusion:** Integrin αVβ3/αVβ5 signaling contributes to the progression of congestive hepatopathy through activation of the YAP-CTGF pathway and may represent a novel therapeutic target for congestive hepatopathy, including FALD.

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Teaching, GSK: Speaking and Teaching, Roche: Speaking and Teaching, Kowa: Speaking and Teaching, Kowa: Speaking and Teaching, Shinogi: Independent Contractor, Astrazeneca: Independent Contractor.

3368 | PRIMARY CILIA IN HEPATIC STELLATE CELLS PROMOTE LIVER FIBROSIS

Yang Xiao[1] Zeba Firdaus[1] Alexander Washington[1] Emily Rogers[1] Kai He[1] Jinghua Hu[1] Enis Kostallari[2], [1]Mayo Clinic, [2]Mayo Clinic Rochester

Background: Hepatic stellate cell (HSC) activation via profibrotic factors, such as platelet-derived growth factor B (PDGF), leads to liver fibrosis. PDGF receptors (PDGFRs) are the first to be identified on primary cilia. However, the role of primary cilia in HSCs remains unclear and is the aim of this study. **Methods:** Primary human HSCs were activated by PDGF treatment. Primary mouse HSCs were activated by culturing them for 5 days on plastic culture dishes. Primary cilia were characterized by public single-cell RNAseq (scRNA-seq) datasets and immunofluorescence. Primary cilia formation was inhibited by intraflagellar transport 88 (*IFT88*) siRNA transfection. HSC proliferation was assessed by 5-Ethynyl-2'-deoxyuridine (EdU) incorporation. *In vivo*, *Ift88* deletion in HSCs was achieved by breeding *Lrat-Cre* mice to *Ift88-flox* mice. Liver fibrosis was induced by intraperitoneal injection of carbon tetrachloride (CCl_4) for 6 weeks and analyzed by immunofluorescence (IF), Sirius Red staining, and Western blot (WB). **Results:** To know whether HSCs can develop primary cilia, we first analyzed several public scRNAseq datasets, where HSCs expressed several primary cilia genes, including *IFT88*, suggesting that HSCs might develop primary cilia. Activated primary mouse HSCs cultured for 5 days developed primary cilia compared to mouse HSCs cultured for 2 days, as assessed by ARL13B and glutaminated tubulin immunofluorescence. Primary human HSCs treated with PDGF increased the development of primary cilia *in vitro* by 1.6-fold ($n = 3$, $p < 0.05$). Primary cilia on HSCs expressed PDGFRs, which are important for HSC proliferation. Thus, we next examined the role of primary cilia on HSC proliferation *in vitro* and found that PDGF increased 5.5-fold EdU incorporation ($p < 0.001$), which was significantly reduced 1.8-fold when *IFT88* was knocked down by siRNA ($n = 3$, $p < 0.05$). Finally, CCl_4 administration increased liver fibrosis 5-fold in *Ift88*-flox control mice (WB, $p < 0.001$), which was significantly reduced 2.8-fold when *Ift88* was selectively deleted in HSCs ($p < 0.05$, $n = 6$-7 mice/group). Altogether, these results suggest that activated HSCs develop primary cilia, leading to HSC proliferation and liver fibrosis in vivo. **Conclusion:** The development of primary cilia in HSCs can be a therapeutic target against the progression of liver fibrosis.

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3369 | SINGLE-CELL TRANSCRIPTOMICS IDENTIFIES CCDC80 AS A CONSERVED BIOMARKER OF HEPATIC STELLATE CELL ACTIVATION AND FIBROSIS SEVERITY IN MASLD

Le Thuy[1] Hoang Hai[2] Tuan Anh Pham[2] Duc Pham Minh[2] Bui Tam Chi Nguyen[2] Thi Ha Nguyen[2], [1]Osaka Metropolitan University, [2]Graduate School of Medicine, Osaka Metropolitan University

Background: Liver fibrosis is a complex pathological process driven by the activation of hepatic stellate cells (HSCs), which transition from a quiescent (qHSC) to an activated, myofibroblastic phenotype (aHSC). Identifying specific markers that define these transitions and offer therapeutic targets remains a critical unmet need. In this study, we employed single-cell RNA sequencing (scRNA-seq) to explore HSC heterogeneity and identify novel regulatory factors involved in fibrosis progression and regression. **Methods:** Liver fibrosis was induced in eight-week-old mice by intraperitoneal injection of CCl_4 for 6 weeks, with or without a spontaneous recovery period. Non-parenchymal cells (NPCs) were isolated for scRNA-seq. Bioinformatic analyses included subclustering, trajectory analysis (pseudotime), and Gene Ontology (GO) enrichment. Findings were validated across multiple mouse models (CCl_4, TAA, CDAA) and human MASLD (F1–F4) samples. Mechanistic studies were conducted in vitro using human hepatic stellate cells (HHSteCs). **Results:** scRNA-seq identified three distinct HSC clusters: qHSCs, aHSCs, and inactivated HSCs (iHSCs). Coiled-coil domain-containing protein 80 (CCDC80) emerged as one of the most significantly upregulated genes in aHSCs, with a strong positive correlation with Col1a1 expression (Pearson $R = 0.65$ in human liver data). Trajectory analysis confirmed that CCDC80 expression increases progressively along the HSC activation path. In vivo, CCDC80 protein levels were elevated with advancing fibrosis stage in both mouse and human HSCs across CCl_4, TAA, and CDAA diet-induced models. Notably, CCDC80 expression correlated with fibrosis severity in human MASLD (F3–F4 vs. F1–F2). Mechanistically, silencing CCDC80 in HHSteCs significantly attenuated expression of fibrogenic markers (α-SMA, COL1A1) by inhibiting

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phosphorylation of the JAK2/STAT3 signaling pathway. **Conclusion:** This study identifies CCDC80 as a novel, evolutionarily conserved marker of activated HSCs. Its dynamic expression across both mouse models and human MASLD highlights its potential as a biomarker for fibrosis severity. Furthermore, our findings demonstrate that CCDC80 promotes fibrogenesis via the JAK2/STAT3 pathway, positioning it as a promising therapeutic target for liver fibrosis.

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3370 | QFIBROSIS-BASED COLLAGEN MICROARCHITECTURE PROFILING IDENTIFIES RECURRENCE-ASSOCIATED FIBROTIC SIGNATURES IN HCC BIOPSIES

Kutbuddin Akbary[1] Vlad Ratziu[2] Chia-Jui Yen[3] Chih-Chieh Yen[4] I-Ting Liu[4] Yayun Ren[5] Dean Tai[6], [1]HistoIndex Pte Ltd, [2]Sorbonne Université, Institute for Cardiometabolism and Nutrition, Hospital Pitié-Salpêtrière, Paris, [3]National Cheng Kung University Hospital, College of Medicine, National Cheng, [4]National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, [5]HistoIndex Pte Ltd, Singapore, [6]HistoIndex

Background: Hepatocellular carcinoma (HCC) develops within a complex fibrotic & stromal microenvironment that influences tumor progression, treatment response and recurrence risk. Conventional fibrosis staging systems provide limited spatial and quantitative characterization of collagen remodelling within HCC-associated liver tissue. qFibrosis, an AI-based second harmonic generation/two-photon excitation-based quantitative histopathology platform, enables detailed assessment of collagen features and microarchitectural profiling across anatomically distinct tissue zones within the lobule. This study evaluated whether region-specific qFibrosis parameters are associated with the timing of recurrence post-surgical resection in HCC. **Methods:** Peri-tumoral liver samples from 85 HCC patients surgically resected (National Cheng Kung University Hospital, Taiwan) were analysed for qFibrosis-based collagen morphometry. Patients had either cirrhotic [n = 40; (HBV = n26, HCV = n14)] or non-cirrhotic [n = 45; (HBV = n40, HCV = n5)] backgrounds. Early recurrence was defined as disease-free survival (DFS) < 1 year (n30), and late recurrence as DFS ≥ 1 year (n55). Quantitative fibrosis parameters were assessed and compared across multiple hepatic lobule regions (overall liver tissue, portal tract, peri-portal, zone 2, peri-central, central vein, chicken-wire fibrosis). **Results:** In early recurrence, distinct collagen morphology was seen in patients with vs. without cirrhosis. In the peritumoral region non-cirrhotic biopsies, displayed higher qFibrosis parameters ($p < 0.05$-$p < 0.01$) in zone 2 and chicken-wire fibrosis regions, suggesting localized sinusoidal/pericellular collagen remodelling in absence of cirrhosis (Fig.1). Cirrhotic biopsies with early recurrence had distinct pattern of high pericentral qFibrosis parameters ($p < 0.05$-$p < 0.01$). These findings show recurrence-associated collagen remodelling patterns could differ by underlying cirrhosis status and may be localized to distinct hepatic regions. Comparisons in cirrhotic and non-cirrhotic biopsies within early and late recurrence groups (Fig.1) demonstrated significantly higher qFibrosis parameters across multiple regions in cirrhotic biopsies (portal, peri-portal, zone 2, and chicken-wire fibrosis). **Conclusion:** qFibrosis-based collagen morphometry identifies distinct spatial fibrosis patterns associated with early HCC recurrence in cirrhotic and non-cirrhotic liver backgrounds. These findings suggest that region-specific ECM alterations may reflect biologically distinct tumor-stroma interactions and recurrence mechanisms across different HCC backgrounds. Quantitative spatial fibrosis profiling using qFibrosis may provide clinically relevant prognostic information beyond conventional fibrosis staging and support biomarker-driven patient stratification in HCC clinical trials.

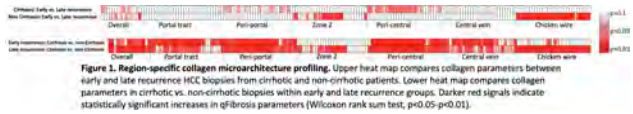


Figure 1. Region-specific collagen microarchitecture profiling. Upper heat map compares collagen parameters between early and late recurrence HCC biopsies from cirrhotic and non-cirrhotic patients. Lower heat map compares collagen parameters in cirrhotic vs. non-cirrhotic biopsies within early and late recurrence groups. Darker red signals indicate statistically significant increases in qFibrosis parameters (Wilcoxon rank sum test, p<0.05-p<0.01).

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3371 | HEPATIC ORGANOIDS AS A TOOL TO STUDY THE IMPACT OF NEUTROPHIL EXTRACELLULAR TRAPS ON STELLATE CELL AND PORTAL FIBROBLAST ACTIVATION

Lisa Fraser[1] Samantha Atkinson[2] Megan Larson[2] Cara Mack[2], [1]Medical College of Wisconsin, Department of Pediatrics, [2]Medical College of Wisconsin

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Background: Biliary atresia (BA) is an inflammatory fibrosing disease of the biliary tree that is the most common cause of pediatric liver transplant. Previous work demonstrated a correlation between neutrophil extracellular trap (NETs) and worse clinical outcomes; however, the mechanisms remain unclear. Portal fibroblasts (PFs) and hepatic stellate cells (HSCs) are the primary precursors of myofibroblasts in the liver and activation of these cells leads to fibrosis. Hepatic organoids (HOs) present an ex vivo model to study the role of NETs in the pathogenesis of BA. The aim of this study was to develop a HO model that could be used to study the role of NETs in PF and HSC activation. **Methods:** HOs were derived from induced human pluripotent stem cells (iPSC) using a series of media changes containing various growth factors and small molecules. HOs were characterized using RT-qPCR and immunohistochemistry (IHC). HOs were treated with NETs purified from PMA-activated neutrophils or vehicle only (control) and analyzed by single cell RNA sequencing (scRNA seq). **Results:** HO characterization: H&E, IHC and RT-qPCR demonstrated that HOs develop complex structures, including vasculature (CD31+), bile ducts (CD19+), hepatocytes (HNF4a+) and HSC (smooth muscle actin+). scRNA seq confirmed the presence of these major cell types in HOs. HOs exposed to NETs: scRNA seq revealed that NET exposure altered HO gene expression. Differential expression analysis of the PFs cluster identified 1,269 genes whose expression was significantly altered in response to NETs ($p < 0.05$). When Bonferroni correction was applied for multiple comparisons, insulin-like growth factor 2 (*IGF2)*, was found to be significantly increased in PFs in response to NET treatment ($q < 0.05$). Differential expression analysis of HSCs predicted 4,115 quiescent and 2,836 myofibroblast genes whose expression was significantly altered in response to NET treatment. Bonferroni correction revealed 245 quiescent and 42 myofibroblast genes whose expression was significantly altered in response to NETs ($q < 0.05$), including quiescent HSC genes (*NFATC2*, *HSPH1*, *PDLIM5*, *EGR3*) and myofibroblast genes (*HSPA1A*, *MRTFA*, *HSPA1B* and *IGF2)* that were previously shown to be enriched in fibrotic livers. **Conclusion:** iPSC-derived HOs are a functional model of the human liver, containing complex structures, all major liver cell types, and the ability to respond to profibrotic factors such as NETs. HOs exposed to NETs resulted in upregulation of many pro-fibrogenic genes within HSCs and PFs, suggesting that NETs play a role in liver fibrogenesis. Future HO co-culture studies will involve NETs isolated from BA or other liver disease control neutrophils, to determine the role of NETs in BA fibrogenesis.

Disclosures: Lisa Fraser:Nothing to Disclose, Samantha Atkinson:Nothing to Disclose, Megan Larson: Nothing to Disclose, Cara Mack:Ipsen Pharm: Consultant.

3372 | CTX-343, A SELECTIVE, POTENT, PERIPHERALLY RESTRICTED LPA RECEPTOR 1 (LPAR1) ANTAGONIST FOR TREATING MASH AND OTHER FIBROTIC LIVER DISEASES

Didier Bagnol[1] James Swaney[1] Dan Lorrain[1] Kym Lorrain[1] Alex Broadhead[1] Chris Baccei[1] Lisa Eide[1] Bryanna Paulson[1] Geraldine Edu[1] John Atkins[1] Karin Stebbins[1] Michael Poon[1] Austin Chen[1], [1]Contineum Therapeutics

Background: Repeated liver injury results in progressive hepatocellular damage and hepatic stellate cell (HSC) differentiation into myfibroblasts, ultimately leading to tissue fibrosis and cirrhosis. The underlying mechanism involves aberrant upregulation of LPA and increased LPAR1 expression on activated HSCs. LPAR1 stimulation is believed to be a key fibrotic driver in liver disease. In support of this, LPAR1 antagonists inhibit HSC proliferation and activation, and reduce liver fibrosis in preclinical models of Metabolic Dysfunction-Associated Steatohepatitis (MASH). Here, we characterized the potency, selectivity, PK/PD profile and efficacy of CTX-343, a peripherally restricted LPAR1 antagonist as a potential treatment for liver fibrosis/MASH. **Methods:** CTX-343 binding kinetics and functional activity were evaluated in B103 cells stably expressing human LPAR1. CTX-343 selectivity for human LPAR1-6 was evaluated using transiently transfected HEK293T cells. CTX-343 inhibition of primary human HSC activation was evaluated by immunocytochemistry. C57Bl6/N female mice (8-10 weeks old) were dosed intraperitoneally twice a week for 6 weeks with 1 mL/kg of CCl_4 dissolved in corn oil to induced liver injury. Cholestatic liver injury was induced in C57Bl6/N male mice (8-10 weeks old) by performing a double ligation of the common bile duct for 11 days. Wistar male rats (7-8 weeks old) were dosed intraperitoneally weekly with 50 mg/Kg of diethylnitrosamine (DEN) dissolved in PBS for 18 weeks to induce severe liver fibrosis and cirrhosis. CTX-343 with doses ranging from 0.003 to 3 mg/kg was formulated as a suspension in vehicle (1%HPMC/0.1%TWEEN80) and administered orally once a day in all models. **Results:** In human LPAR1 overexpressing B103 cells, CTX-343 inhibited LPA-stimulated Ca^{+2} mobilization with an IC_{50} of 44.1 nM. In HEK293T cells overexpressing human LPAR1-6, CTX-343 was >17-fold selective for LPAR1 versus LPAR2, and >82 fold selective for LPAR3-6. CTX-343 exhibited slow binding kinetics in a human LPAR1 membrane binding assay (3 h, K_i = 5.6 nM)

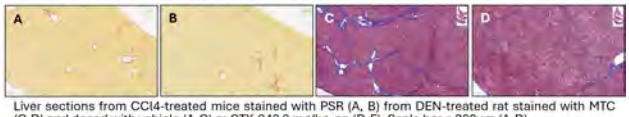
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with steady state reached at 12 h, a residence time (1/K_{off}) of 46 h, and a dissociation constant (K_d) of 1.2 nM. *In vitro,* CTX-343 inhibited LPA-induced human HSC activation (IC_{50} = 40 nM). In mice, single oral administration of CTX-343 blocked LPA induced histamine release (3 h, EC_{50} = 110 nM; 24 h EC_{50} = 4.6 nM). In adult male rats, CTX-343 exhibited good overall PK properties and distributed preferentially to the liver. In models of liver fibrosis (mouse CCl_4 and rat DEN), CTX-343 reduced liver total soluble collagen, fibrotic gene expression, proportional fibrosis (up to 50%), and protected against hepatic necrosis in the mouse cholestasis model. **Conclusion:** These data indicate that CTX-343 is a potent and selective LPAR1 antagonist that may serve as a novel treatment for MASH and other fibrotic liver diseases.

Species	Model	CTX-343 dose (mg/kg, po)	Soluble collagen	% reduction in fibrosis (histology)
Mouse	CCl4	0.03	29	11
		0.3	51*	40***
		3	74**	36**
Rat	DEN	0.3	42.9**	50.4*
		3	36*	52**

* p < 0.05; **, p < 0.01; p< 0.001. ANOVA with Dunnett's multiple comparisons test to vehicle group.



Liver sections from CCl4-treated mice stained with PSR (A, B) from DEN-treated rat stained with MTC (C,D) and dosed with vehicle (A-C) or CTX-343 3 mg/kg, po (D-F). Scale bar = 200um (A-D)

Disclosures: Didier Bagnol:Contineum Therapeutics: Employee, James Swaney:Nothing to Disclose, Dan Lorrain:Nothing to Disclose, Kym Lorrain:Nothing to Disclose, Alex Broadhead:Nothing to Disclose, Chris Baccei:Nothing to Disclose, Lisa Eide:Nothing to Disclose, Bryanna Paulson:Nothing to Disclose, Geraldine Edu:Nothing to Disclose, John Atkins:Nothing to Disclose, Karin Stebbins:Contineum Therapeutics: Employee and share holder, Michael Poon:Nothing to Disclose, Austin Chen:Contineum Therapeutics: Employee.

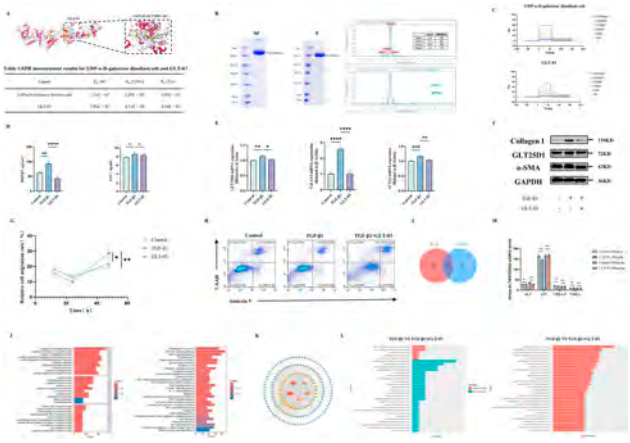
3373 | A NOVEL SMALL-MOLECULE GLT25D1 INHIBITOR SUPPRESSES HEPATIC STELLATE CELL ACTIVATION AND FIBROGENESIS

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Background: Hepatic fibrosis is characterized by excessive extracellular matrix (ECM) deposition and may progress to cirrhosis and hepatocellular carcinoma (HCC). GLT25D1, a key enzyme involved in collagen glycosylation and maturation, has recently emerged as a potential regulator of hepatic fibrogenesis, although its therapeutic targeting remains largely unexplored. We identified a novel GLT25D1 inhibitor, GLT-03, through AlphaFold2-guided virtual screening and investigated its antifibrotic effects and underlying mechanisms in hepatic stellate cells (HSCs). **Methods:** MOE-based virtual screening using an AlphaFold2-predicted GLT25D1 structure identified GLT-03. GLT25D1–GLT-03 interactions were evaluated by CB-Dock2 and surface plasmon resonance (SPR). TGF-β1-activated LX-2 cells were treated with GLT-03 (1 μM). PIIINP and CIV levels were measured by sandwich immunoassay, while GLT25D1, COL1A1, and α-SMA expression was assessed by qPCR and western blotting. Cell migration and apoptosis were evaluated by scratch assay and flow cytometry, respectively. Network pharmacology, GO/KEGG enrichment, PPI-Cytoscape analysis, and RNA-seq were performed to explore the underlying molecular mechanisms. Acute toxicity was evaluated in male C57BL/6 mice after oral GLT-03 administration (50 or 100 mg/kg). **Results:** GLT-03 showed favorable binding to GLT25D1 (MOE S-score: −11.75; CB-Dock2 Vina: −8.5; Fig. 1A). Purified GLT25D1 was >97% pure by SEC-HPLC and predominantly monomeric (Fig. 1B). SPR demonstrated a KD comparable to UDP-α-D-galactose but with slower dissociation, indicating greater binding stability. (Table 1, Fig. 1C). In TGF-β1-activated LX-2 cells, GLT-03 reduced PIIINP secretion without affecting CIV levels, decreased GLT25D1, COL1A1, and α-SMA expression, inhibited migration, and promoted apoptosis (Fig. 1D–H). Network pharmacology identified 246 overlapping targets associated with hepatic fibrosis (Fig. 1I). GO/KEGG analyses revealed enrichment in leukocyte migration, insulin signaling, and MAPK/PI3K-Akt pathways (Fig. 1J). PPI-Cytoscape identified five hub targets: TP53, SRC, EGFR, HSP90AA1, and AKT1 (Fig. 1K). RNA-seq identified 359 DEGs in GLT-03-treated activated LX-2 cells; GO analysis further confirmed enrichment in MAPK/ERK regulation, FGFR binding, and negative regulation of collagen metabolism, consistent with network pharmacology predictions (Fig. 1L). Acute toxicity studies showed no significant changes in ALT, AST, CREA-S, or UREA levels compared with controls (Fig. 1M). **Conclusion:** GLT-03 attenuated HSC activation and fibrogenesis while exhibiting a favorable preliminary safety profile, potentially through modulation of MAPK/ERK and PI3K-Akt signaling pathways. These findings identify GLT25D1-mediated collagen glycosylation as a promising therapeutic target and suggest a novel antifibrotic strategy for hepatic fibrosis.

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Disclosures: Mengqi Li:Nothing to Disclose, Xiaoyuan Xu:Nothing to Disclose, Hongshan Wei:Nothing to Disclose.

3374 | BRD4 CONDENSATES REGULATE COL1A1 EXPRESSION IN ACTIVATED HEPATIC STELLATE CELLS

Luke Doskey[1] Dawood Al Dawood[1] Usman Yaqoob[1] Maria Hernandez Tejero[2] Sofia Jerez[1] Sheng Cao[2] Vijay Shah[2], [1]Mayo Clinic, [2]Mayo Clinic Rochester

Background: Liver fibrosis is characterized by excessive extracellular matrix (ECM) deposition by activated Hepatic Stellate Cells (HSCs). The main component of fibrotic ECM is collagen 1 (COL), encoded by *COL1A1*. Transcriptional condensates are molecular phase-separated assemblies of transcriptional machinery known to regulate the expression of key cell identity genes. They also bind clusters of positive co-regulatory elements known as Super Enhancers (SEs) and influence chromatin interactions. Previously, we showed that BRD4 condensate formation is induced by TGFβ in HSCs in vitro and in a CCl_4-induced fibrosis mouse model in vivo, also, that BRD4 and histone acetylation inhibition, reduces COL expression. However, the epigenetic mechanisms linking TGFβ signaling, super enhancer (SE) formation, and chromatin organization to COL1A1 expression in HSCs remain unclear. **Methods:** To assess BRD4 and H3K27ac occupancy chromatin immunoprecipitation sequencing (ChIP-Seq) was performed on an HSC cell line (LX-2) after TGFβ stimulation, with or without the BRD4 inhibitor I-BET151. H3K27ac signals were analyzed using the LILY algorithm to rank order SEs and identify genes regulated by SEs. Treatment with the condensate inhibitor 1,6-Hexanediol was used to determine the effect of condensate disruption *on COL1A1* expression, measured by qPCR. Finally, the chromatin conformation capture method Hi-C was performed to study the effect of TGFβ on chromatin organization using LX-2 cells. **Results:** ChIP-Seq revealed a regulatory region 10 kb upstream of *COL1A1* locus enriched with H3K27ac and BRD4 following TGFβ stimulation, consistent with the presence of a SE. Ranking of SEs by LILY identified 807 SEs under basal conditions. The putative *COL1A1* SE ranking shifted from 55 to 17 with TGFβ stimulation, and BRD4 inhibition reduced the ranking to 44. Pharmacologic disruption of condensates with 1,6-hexanediol reduced TGFβ-induced *COL1A1* expression by 50%, supporting a role for condensate formation in regulating *COL1A1* expression. Finally, Hi-C demonstrated the presence of contact points between the *COL1A1* promoter and the *TMEM92* promoter, which also interacts with the *PDK2* and *SGCA* loci, suggesting a coordinated co-regulatory gene network in HSCs. **Conclusion:** These findings support a novel model for the regulation of collagen expression, whereby TGFβ induces the formation of BRD4 condensates at the *COL1A1* SE region to regulate the expression of COL1A1 and a coordinated gene network in HSCs. Targeting transcriptional condensates may offer a novel therapeutic approach for the treatment of liver fibrosis.

Disclosures: Luke Doskey:Nothing to Disclose, Dawood Al Dawood:Nothing to Disclose, Usman Yaqoob:Nothing to Disclose, Maria Hernandez Tejero: Nothing to Disclose, Sofia Jerez:Nothing to Disclose, Sheng Cao:Nothing to Disclose, Vijay Shah:Boehringer Ingelheim: Consultant, GSK: Consultant, GENFIT SA: Consultant, Intercept Pharmaceuticals, Inc.: Advisor, Korro Bio, Inc.: Consultant, Novo Nordisk A/S: Consultant, Resolution Therapeutics, Ltd.: Advisor, Seal Rock Therapeutics, Ltd.: Consultant, Surrozen: Advisor, Dexcel Pharma Technologies, Ltd.: Consultant, Dimension Inx.: Advisor, Enveda: Consultant, Ochre Bio: Consultant, Satellite Biosciences, Inc.: Consultant.

3375 | C3 COMPLOSOME-DEPENDENT METABOLIC REPROGRAMMING REGULATES HEPATIC STELLATE CELL ACTIVATION AND FIBROGENESIS IN METALD

Lauren N. Rutt[1], Kris Fritz, Rebecca L. Mccullough[2], [1]University of Colorado, Anschutz Medical Campus, [2]University of Colorado - Anschutz

Background: Metabolic alcohol-associated liver disease (MetALD) is a leading cause of liver-related morbidity and mortality, with fibrosis serving as the

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strongest predictor of clinical outcomes. Despite this burden, therapies targeting fibrogenic mechanisms remain limited, leaving liver transplantation the only viable option for end-stage liver disease. Hepatic stellate cells (HSCs), the primary fibroblast of the liver, transdifferentiate into activated myofibroblasts and undergo metabolic adaptations to support excessive extracellular matrix production in response to injury. Although HSC metabolic reprogramming is a key driver of fibrogenesis, the upstream mechanisms coordinating these adaptations remain poorly understood. Intrinsic Complement C3 is increased in activated fibroblasts in other fibrotic diseases and linked to profibrotic metabolic programs; however, its role in HSC biology remains undefined. Emerging evidence suggests intracellular complement signaling through mitochondrial C3a receptor (C3aR1) regulates mitochondrial function and oxidative stress, identifying the C3 complosome as a potential mediator of metabolic reprogramming during fibrogenesis. We hypothesize that activation of the alternative complement pathway enhances mitochondrial C3aR1 signaling in HSCs, driving metabolic reprogramming that promote HSC activation and fibrogenesis in MetALD. **Methods:** Alcohol-associated hepatitis (AH) explanted and healthy donor liver tissue from the R24 resource at Johns Hopkins University underwent multispectral imaging of C3, C3aR1, VDAC, and aSMA. To determine if the C3 complosome is associated with HSC activation and fibrosis, a murine model of MetALD , eight-week-old male mice were fed a GAN diet (high fat/cholesterol/sugar) for 12 weeks and received weekly oral ethanol gavages thrice weekly on weeks 8-12, and primary human and mouse HSCs were used to evaluate complement activation and glycolytic remodeling during HSC activation. **Results:** C3aR1 expression and colocalization with alpha smooth muscle actin (a-sma)-positive cells was increased in AH liver compared to healthy donor tissue. RNA-sequencing of liver tissue revealed enrichment of genes associated with acute phase/injury response, extracellular matrix reorganization and fibrosis, myofibroblast activation, complement, and glycolysis, which were further increased in GAN+Ethanol treated mice. *In vitro*, ethanol increased colocalization of C3aR1 with the mitochondrial marker Tom20 in primary hHSCs, which was attenuated by pretreatment with the mitochondrial-targeted antioxidant MitoTEMPO. **Conclusion:** These studies identify intrinsic C3 complement as a potential regulator of HSC metabolic reprogramming and fibrogenesis in MetALD. Targeting complement-dependent metabolic dysfunction may represent a novel therapeutic strategy to limit HSC activation and fibrosis progression during liver disease.

Disclosures: Lauren Rutt:Nothing to Disclose, Rebecca McCullough:Nothing to Disclose.

3376 | CXCR4 PROMOTES HEPATIC STELLATE CELL ACTIVATION AND LIVER FIBROSIS THROUGH THE PI3K/AKT SIGNALING PATHWAY

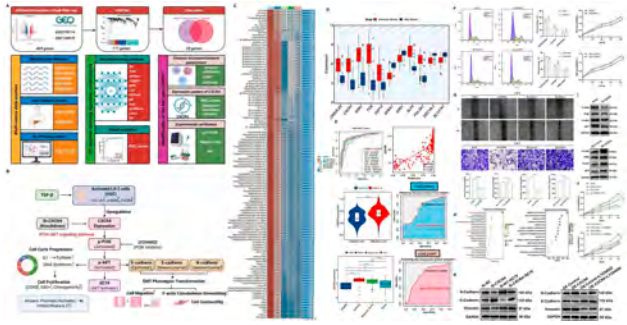
Huiru Liu[1] Yuexi Yu[1] Fengmei Wang[1], [1]Tianjin First Central Hospital

Background: Liver fibrosis is a progressive wound-healing response to chronic liver injury characterized by excessive extracellular matrix deposition and activation of hepatic stellate cells (HSCs). Persistent fibrosis can progress to cirrhosis and hepatocellular carcinoma, yet effective antifibrotic therapies remain limited. The chemokine receptor CXCR4 and its ligand CXCL12 have been implicated in fibrotic diseases in multiple organs. However, the role of CXCR4 in liver fibrosis and its regulatory mechanisms in HSC activation remain incompletely understood. This study aimed to investigate the function and molecular mechanisms of CXCR4 in liver fibrosis. **Methods:** Public liver fibrosis transcriptomic datasets from the Gene Expression Omnibus (GEO) were analyzed to identify fibrosis-related genes using differential expression analysis and weighted gene co-expression network analysis (WGCNA). A diagnostic model was constructed using 127 machine-learning algorithm combinations and evaluated using receiver operating characteristic analysis. Immune cell infiltration was assessed using CIBERSORT and single-sample gene set enrichment analysis (ssGSEA). Single-cell RNA sequencing data were analyzed to construct a cirrhotic liver atlas and evaluate cellular hypoxia using a LightGBM-based cell hypoxia prediction framework. CXCR4 expression was validated in human liver tissues using qRT-PCR, Western blotting, and immunohistochemistry. Functional experiments were performed in TGF-β–stimulated LX-2 cells with CXCR4 knockdown or overexpression. Cell proliferation, migration, epithelial–mesenchymal transition (EMT), and cytoskeletal remodeling were assessed using CCK-8, colony formation, EdU, wound-healing, Transwell, phalloidin staining, and cell cycle analysis. Transcriptomic sequencing and pathway analyses were used to identify downstream signaling pathways. **Results:** Integrated analyses identified 23 fibrosis-associated core genes and established an 11-gene diagnostic model with strong predictive performance. CXCR4 demonstrated the highest diagnostic value and was significantly correlated with fibrosis risk scores. Immune analyses revealed enhanced immune activation in advanced fibrosis. CXCR4 expression was significantly elevated in cirrhotic liver tissues and positively correlated with fibrosis markers COL1A1 and α-SMA. In vitro, CXCR4 knockdown suppressed LX-2 cell proliferation, migration, EMT, and cytoskeletal remodeling,

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whereas CXCR4 overexpression promoted these phenotypes. Mechanistically, CXCR4 regulated HSC activation primarily through activation of the PI3K/AKT signaling pathway. **Conclusion:** CXCR4 plays a critical role in liver fibrosis progression by promoting HSC activation and profibrotic phenotypes via the PI3K/AKT pathway. Targeting CXCR4 may represent a potential therapeutic strategy for liver fibrosis.



Disclosures: Huiru Liu:Nothing to Disclose, Yuexi Yu:Nothing to Disclose, Fengmei Wang:Nothing to Disclose.

3377 | A NOVEL FGFR INHIBITOR IN COMBINATION WITH A PDE4B INHIBITOR SYNERGISTICALLY ATTENUATES LIVER FIBROSIS IN LX-2 CELLS

Dongke Yu[1] Yating Li[2] Liang Qi[3] Hongqiong Yuan[4] Lin Cheng[5] Jianyou Shi[6], [1]Sichuan Provincial People's Hosptial, [2]Chengdu University of Traditional Chinese Medicine, [3]University of Electronic Science and Technology of China, [4]Xihua University, [5]Southwest Jiaotong University, [6]Sichuan Provincial People's Hospital

Background: FGFR is a potential target for liver fibrosis therapy, and PDE4 mediates immunomodulatory and anti-inflammatory effects. This study investigated the therapeutic effects and mechanisms of a novel FGFR inhibitor B102 combined with the PDE4B inhibitor BI1015550 in TGF-β1 induced LX-2 cells, an in vitro model of liver fibrosis. **Methods:** The in vitro kinase inhibitory activity of B102 was determined by Eurofins KinaseProfiler™. CCK-8 assay was used to evaluate B102 toxicity on LX-2 cells, and acute toxicity experiments in mice assessed its safety. An in vitro fibrosis model was established using TGF-β1 induced LX-2 cells. RT-qPCR measured treatment effects on mRNA expression, and the combination index (CI) was calculated via CompuSyn software. **Results:** B102 exhibited potent inhibitory activity against FGFR1, FGFR2, and FGFR3, with IC50 values of 3 nM, 2 nM, and 3 nM, respectively, while showing slightly weaker activity against FGFR4 (IC50 = 33 nM). Additionally, B102 strongly inhibited Fms (CSF1R) with an IC50 of 9 nM, moderately inhibited Flt1, KDR, and Flt4 (IC50 = 42, 51, and 112 nM, respectively), and only weakly suppressed Ret and ALK (IC50 = 295 and 497 nM). To evaluate the in vivo safety of B102, mice received a single dose of 2000 mg/kg. No significant differences in body weight change, organ indices (heart, liver, spleen, lung, and kidney), or plasma biochemical parameters (ALT, ALP, TBIL, BUN, CREA, and CK) were observed between the vehicle and treatment groups ($p > 0.05$), and all biochemical values fell within normal reference ranges. Furthermore, the CCK-8 assay showed that B102 was safe for LX-2 cells at 5 μmol/L within 24 hours. In TGF-β1 induced LX-2 cells, the combination of B102 and the PDE4B inhibitor BI1015550 significantly downregulated the mRNA levels of TGF-β1, COL1A1, and TIMP1. CI was less than 1, indicating a synergistic effect of the two drugs in inhibiting the expression of liver fibrosis-related genes. Western blot analysis revealed that the phosphorylation levels of FGFR1, FGFR2, and FGFR3 were significantly increased in TGF-β1 induced LX-2 cells. Combination treatment markedly suppressed the phosphorylation of these FGFR proteins, showing superior effects compared to either monotherapy. Moreover, the combination treatment also significantly inhibited the phosphorylation of the key FGFR substrates PLCγ1 and FRS2α. STAT3, a downstream target of FGFR, promotes the expression of fibrosis-related genes upon activation; combination treatment significantly downregulated STAT3 phosphorylation. **Conclusion:** B102, a potent and selective FGFR inhibitor with nanomolar activity and a favorable in vivo safety profile, synergistically downregulates fibrosis markers, suppresses FGFR signaling, and reduces inflammation-related proteins when combined with the PDE4B inhibitor BI1015555 in TGF-β1 induced LX-2 cells, providing an in vitro basis for liver fibrosis treatment.

Disclosures: Dongke Yu:Nothing to Disclose, Yating Li:Nothing to Disclose, Liang Qi:Nothing to Disclose, Hongqiong Yuan:Nothing to Disclose, Lin Cheng:Nothing to Disclose, Jianyou Shi:Nothing to Disclose.

3378 | HEPCIDIN TO FERRITIN RATIO DRIVEN ENHANCED LIVER FIBROSIS INDEX AND FIBROSIS-4 SCORES FOR HEPATIC FIBROGENESIS RISK IN β-THALASSEMIA PATIENTS

Narayan Gautam[1] Mukesh Sharma Paudel[2] Bipin Adhikari[3] Prabodh Risal[4], [1]Universal College of Medical Sciences (UCMS), Bhairahawa and KUSMS, Dhulikhel, Nepal (PhD scholar), [2]National Academy of Medical Sciences (NAMS), Kathmandu, Nepal, [3]Mahidol-Oxford Tropical Medicine Research Unit,

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Background: β-thalassemia is characterized by ineffective erythropoiesis, chronic anemia, and dysregulated iron homeostasis. Beyond transfusion-related iron overload, suppression of the hepcidin axis promotes increased intestinal iron absorption and macrophage iron release, potentially contributing to hepatic injury and fibrogenesis. This study investigated iron regulatory biomarkers, fibrogenic signaling, and non-invasive fibrosis indices in β-thalassemia and non-β-thalassemia microcytic hypochromic anemia (N-βT McHc) participants and assessed independent risk factors. **Methods:** A cross-sectional study was conducted among the study population (n = 768) for the screening of β-thalassemia by multistage random sampling in four districts of Lumbini Province, Nepal. Suspected β-thalassemia (n = 117) identified through hemogram, peripheral blood smear examination, and high-performance liquid chromatography (HPLC) confirmed 39 β-thalassemia and 78 N-βT McHc cases. Liver fibrosis risk was evaluated using the Enhanced Liver Fibrosis (ELF) score and Fibrosis-4 (FIB-4) index. Iron homeostasis was assessed using serum ferritin and hepcidin concentrations, while fibrogenic activity was evaluated using transforming growth factor-beta 1 (TGF-β1), hyaluronic acid (HA), procollagen III N-terminal peptide (PIII-NP), and tissue inhibitor of matrix metalloproteinase-1 (TIMP-1). Multivariable logistic regression analyses were performed to identify factors associated with advanced fibrosis. **Results:** Although serum hepcidin concentrations were significantly higher in β-thalassemia participants than in N-βT McHc participants (86.51 vs. 58.35 ng/mL), the hepcidin-to-ferritin ratio was substantially lower (0.65 versus 1.41), indicating relative hepcidin insufficiency in relation to iron burden. β-thalassemia participants demonstrated significantly higher ELF scores and circulating TGF-β1 levels, consistent with enhanced fibrogenic activity. In multivariable analysis, increasing age (aOR: 1.15, 95% CI: 1.09–1.22; $p < 0.001$), rural residence (aOR: 4.516, 95% CI: 1.31–14.34; $p = 0.016$), and lower odds of β-thalassemia category (aOR: 0.17, 95% CI: 0.04–0.76; $p = 0.020$) were independently associated with the advanced fibrosis FIB-4 model. In contrast, TGF-β1 was the only independent predictor with higher odds of ELF for the probability of cirrhosis risk (aOR: 1.003, 95% CI: 1.001–1.006; $p = 0.008$). **Conclusion:** β-thalassemia was characterized by evidence of disrupted iron regulation, reflected by a reduced hepcidin-to-ferritin ratio, and increased fibrogenic signaling, reflected by elevated TGF-β1 levels. The independent association between TGF-β1 and ELF score supports a potential link between profibrotic pathways and extracellular matrix remodeling in β-thalassemia in resource-limited settings.

Disclosures: Narayan Gautam:Nothing to Disclose, Mukesh Sharma Paudel:Nothing to Disclose, Bipin Adhikari:Nothing to Disclose, Prabodh Risal:Nothing to Disclose.

3379 | HISTOPATHOLOGICAL COMPARISON OF ENDOSCOPIC ULTRASOUND-GUIDED FINE-NEEDLE BIOPSY AND PERCUTANEOUS LIVER BIOPSY

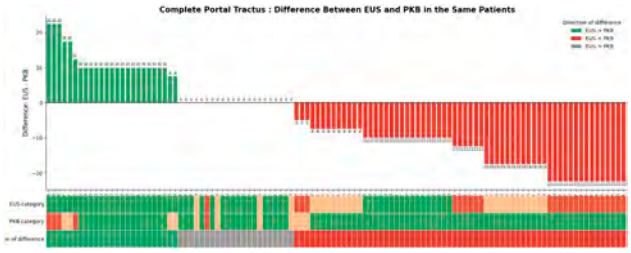
Hayri Kagan Goren[1] Burcu Saka[1] Ayse Armutlu[1] Hale Kirimlioglu[2] Genco Gencdal[3] Sidar Copur[1] Murat Akyildiz[4], [1]Koc University, [2]Acibadem University, [3]Liv Hospital, [4]University Of South Caroline, School of Medicine-Greenville, DEPARTMENT OF GASTROENTEROLOGY&HEPATOLO

Background: Liver biopsy is a gold standart procedure for the diagnosis, treatment response and follow up of liver disease. In recent years, endoscopic ultrasound-guided liver biopsy has also gained attention and there have been developed some conflicts about especially adequate sample size and histopathological evaluation perspectives between EUS FNB vs percutaneous liver biopsy.In this study, we aimed to compare the histolopathologic adequacy and interpretation of percutaneous liver biopsy vs endoscopic ultrasound-guided liver biopsy samples from the same patients by two independent, blinded hepatopathologist. **Methods:** A total of 60 different liver biopsy specimens were evaluated in this study. Of these, 30 were obtained by the percutaneous method and 30 by endoscopic ultrasound guidance. After anonymization, all specimens were evaluated in a blinded manner by two different hepatopathologists, with the aim of reducing observer-related bias and assessment bias.The adequacy of the biopsy materials was primarily evaluated based on the number of portal tracts/islands. Portal areas were classified as complete and incomplete portal islands, and the number of complete portal islands was accepted as the primary adequacy criterion. In addition, the evaluability of key histopathological parameters such as fibrosis staging, degree of steatosis, ballooning degeneration, bile duct atrophy, and cholestasis was assessed as secondary adequacy criteria. **Results:** All the biopsy samples had at least 10 portal areas and there were no inadequate sample for the evaluation.The number of complete portal areas, was significantly higher in the percutaneous biopsy group compared with the EUS-guided biopsy group [percutan vs EUS , 20 vs 15, $p < 0.001$]. A significant difference was observed between the two groups in terms of the number of fragments containing more than three portal areas ($p = 0.0006$). In contrast, no significant difference was found in the number of incomplete

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portal areas (p = 0.7072). When secondary histopathological parameters were evaluated, no statistically significant difference was detected between the two methods in terms of major findings such as fibrosis, steatosis, ballooning degeneration, bile duct atrophy, and cholestasis, except for cholangiolar proliferation (p = 0.0129) and lobular inflammation (p = 0.0347). **Conclusion:** In light of these findings, there was no significant difference between EUS vs percutaneous liver biopsy in terms of adequate sampling and diagnostic criteria and histopathogic evaluation. In conclusion, EUS-guided liver biopsy may be considered a good alternative to percutaneous liver biopsy.



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3380 | ◆ PERFORMANCE OF NON-INVASIVE LIVER DISEASE ASSESSMENT (NILDA) MEASURES AND CLINICAL PREDICTORS OF THRESHOLD ATTAINMENT IN COMPENSATED CIRRHOSIS (CC): EXPERIENCE FROM THE LIVER CIRRHOSIS NETWORK (LCN)

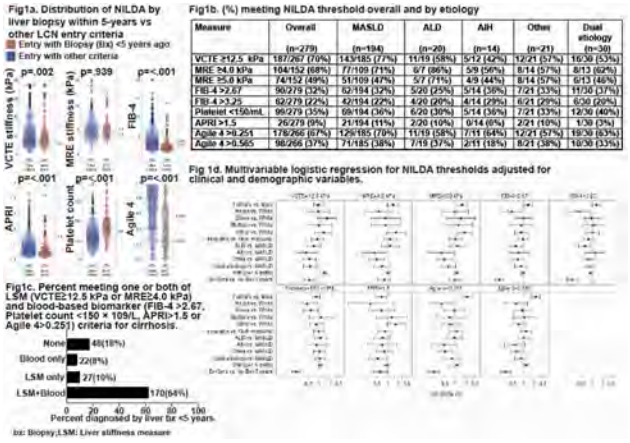
Nicole Welch[1] Abigail Smith[2] Bilal Hameed[3] Monica Tincopa[4] Manal Abdelmalek[5] Jasmohan Bajaj[6] Giuseppe Cullaro[7] Amreen Dinani[8] David Goldberg[9] Patricia Jones[10] Ani Kardashian[11] Mandana Khalili[12] Rohit Loomba[4] Neehar Parikh[13] Douglas Simonetto[5] Elliot Tapper[13] Elizabeth Verna[14] Kara Wegermann[15] Norah Terrault[11] Srinivasan Dasarathy[1] Richard Sterling[6], [1]Cleveland Clinic, [2]Northwestern University, [3]University of San Francisco, [4]University of California, San Diego, [5]Mayo Clinic Rochester, [6]Virginia Commonwealth University, [7]Columbia University, [8]Duke University School of Medicine, [9]University of Miami, [10]University of North Carolina at Chapel Hill, [11]University of Southern California, [12]University of California, San Francisco, [13]University of Michigan Medical Center, [14]Columbia University Medical Center, [15]Duke University

Background: NILDA are increasingly used to diagnose cirrhosis, but their performance across etiologies in CC has not been well characterized. We aimed to determine how often NILDA thresholds were met in biopsy-confirmed CC and whether baseline characteristics were associated with meeting thresholds. **Methods:** The LCN Cohort Study is a prospective observational study at 10 US centers. Adults met LCN cirrhosis criteria by liver biopsy < 5 yrs or by > 2 other criteria: biopsy > 5 yrs ago, vibration-controlled transient elastography (VCTE) ≥ 12.5 kPa, magnetic resonance elastography (MRE) ≥ 5.0 kPa, nodular liver and splenomegaly/recanalized umbilical vein < 1 yr on imaging, esophageal varices < 3 yrs, FIB-4 > 2.67, or platelets < 150,000 < 6 months. In this cross-sectional baseline analysis, we summarized VCTE, MRE, FIB-4, platelets, APRI, and Agile 4 in biopsy-confirmed cirrhosis and fit multivariable logistic regression models for meeting NILDA thresholds adjusted for entry criteria, sex, race, ethnicity, etiology, and BMI. **Results:** Among 1199 subjects, 279 entered via biopsy < 5 yrs and 920 by other criteria. In the biopsy < 5 yrs group, median (IQR) NILDA were VCTE 16.6 (11.4, 24.7) kPa, MRE 4.8 (3.7, 6.0) kPa, FIB-4 1.99 (1.48, 2.98), platelets 171 (131, 213) x 10^9 /L, APRI 0.542 (0.359, 0.874), and Agile 4 0.408 (0.163, 0.703). VCTE, FIB-4, APRI, and Agile 4 were higher and platelets lower in the other criteria group, whereas MRE distributions were similar (**Fig 1a**). Despite biopsy-confirmed cirrhosis, only 70% met VCTE ≥ 12.5 kPa, 68% and 49% met MRE ≥ 4.0 and ≥ 5.0 kPa, 32% and 22% met FIB-4 > 2.67 and > 3.25, 35% had platelets < 150 x 10^9 /L, 9% met APRI > 1.5, and 67% and 37% met Agile 4 > 0.251 and > 0.565. Threshold attainment differed by etiology: highest with VCTE in MASLD and MRE in ALD (**Fig 1b**). Combination of VCTE ≥ 12.5 kPa, Agile 4 > 0.251, and platelets < 150 x 10^9 /L increased identification of biopsy-confirmed cirrhosis from 70% (VCTE alone) to 79%, with minimal gain from FIB-4 > 2.67 (80%); 18% met no NILDA criteria (**Fig 1c**). In compensated cirrhosis, each 1-unit increase in BMI was associated with higher odds of meeting VCTE ≥ 12.5 kPa (OR 1.13, 95% CI 1.07-1.20), MRE ≥ 4.0 kPa (OR 1.08, 1.01-1.16), and MRE ≥ 5.0 kPa (OR 1.06, 1.00-1.13). Compared with MASLD, ALD was associated with lower odds of meeting FIB-4 thresholds, while other and dual etiologies were associated with lower odds of meeting VCTE/MRE thresholds (**Fig 1d**). **Conclusion:** Commonly used, non-etiology specific NILDA thresholds were not met uniformly in CC, including biopsy-confirmed disease, suggesting that individual NILDA criteria may lack sensitivity as stand-alone tests in compensated disease. A combined VCTE, Agile 4, and platelet-based strategy improved

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identification of cirrhosis beyond VCTE alone. These findings support a combined NILDA panel, rather than any single threshold, to identify suspected CC and future evaluation of lower thresholds in combination.



Measure	Overall (n=279)	MASLD (n=194)	ALD (n=20)	AIH (n=14)	Other (n=21)	Dual etiology (n=30)
VCTE ≥12.5 kPa	187/267 (70%)	143/185 (77%)	11/19 (58%)	5/12 (42%)	12/21 (57%)	16/30 (53%)
MRE ≥4.0 kPa	104/152 (68%)	77/109 (71%)	6/7 (86%)	5/9 (56%)	8/14 (57%)	8/13 (62%)
MRE ≥5.0 kPa	74/152 (49%)	51/109 (47%)	5/7 (71%)	4/9 (44%)	8/14 (57%)	6/13 (46%)
FIB-4 >2.67	90/279 (32%)	62/194 (32%)	5/20 (25%)	5/14 (36%)	7/21 (33%)	11/30 (37%)
FIB-4 >3.25	62/279 (22%)	42/194 (22%)	4/20 (20%)	4/14 (29%)	6/21 (29%)	6/30 (20%)
Platelet <150/mL	99/279 (35%)	69/194 (36%)	6/20 (30%)	5/14 (36%)	7/21 (33%)	12/30 (40%)
APRI >1.5	26/279 (9%)	21/194 (11%)	2/20 (10%)	0/14 (0%)	2/21 (10%)	1/30 (3%)
Agile 4 >0.251	178/266 (67%)	125/185 (70%)	11/19 (58%)	7/11 (64%)	12/21 (57%)	19/30 (63%)
Agile 4 >0.565	98/266 (37%)	71/185 (38%)	7/19 (37%)	2/11 (18%)	8/21 (38%)	10/30 (33%)

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3381 | PERFORMANCE EVALUATION OF A LARGE LANGUAGE MODEL FOR AUTOMATED FIBROSIS STAGING FROM LIVER BIOPSY REPORTS: A MULTISITE VALIDATION STUDY

Marwan Qasem[1] Kamalpreet Hara[1] Alberto Calleri[1] Hugo Vargas[2] Andrew Keaveny[3] Daniel Penrice[4] Patrick Kamath[1] Vijay Shah[1] Douglas Simonetto[1], [1]Mayo Clinic Rochester, [2]Mayo Clinic Arizona, [3]Mayo Clinic Florida, [4]Mayo Clinic Health System - Eau Claire

Background: Accurate fibrosis staging from liver biopsy reports is essential for cohort construction, real-world evidence generation, and clinical trial recruitment in liver research. Manual review of large pathology datasets is labor-intensive and subject to inter-reviewer variability, representing an unmet need for scalable automated solutions. We assessed whether a locally deployed, HIPAA-compliant large language model (LLM) based on Gemini 2.5 Flash

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could accurately stage hepatic fibrosis from unstructured liver biopsy reports. **Methods:** This retrospective multisite validation included adult liver biopsy reports (2004–2026) from 3 Mayo Clinic sites (MN, AZ, FL) and Mayo Clinic Health System. Of 67,454 liver biopsy reports, 21,262 (31.5%) parenchymal adult liver biopsy reports were identified via structured-field and free-text filters. An LLM prompt was iteratively refined against a held-out set (n = 100). It was then applied to the full cohort to assign an F0-F4 stage by concordance mapping from established staging systems or by characteristic histological features and to flag reports it deemed unstageable. Two site-stratified samples were drawn: 500 stageable reports (125 per site; 100 per LLM-assigned stage) and 100 unstageable reports. Two blinded hepatology research MD fellows independently staged each report, with discordance resolved by a blinded transplant hepatologist, yielding a composite reference standard. LLM performance was evaluated at the stage level and at significant (≥F2) and advanced (≥F3) fibrosis thresholds. **Results:** Among 500 LLM-staged reports, 492 were judged stageable and 8 (1.6%) uninterpretable by the reference standard. Exact agreement was 91.6% overall and 93.1% in the 492 stageable reports, with 100% within-one-stage agreement and a quadratic-weighted κ of 0.983 (95% CI 0.977–0.989). Per-stage sensitivity ranged from 86.4% (F2) to 98.8% (F1) and specificity from 96.6% (F1) to 99.7% (F0) across all stages. The LLM achieved 97.6% accuracy for ≥F2 (95% CI 95.8–98.6; sensitivity 96.1%, specificity 100%, PPV 100%, NPV 93.9%) and 97.4% accuracy for ≥F3 (95% CI 95.5–98.4; sensitivity 94.6%, specificity 99.3%, PPV 99.0%, NPV 96.3%). On the 492 stageable pairs, exact inter-reviewer agreement was 93.9% with weighted κ 0.973 (95% CI 0.960–0.987). Adjudication for disagreements was needed in 37 reports (7.4%). Inter-reviewer agreement was comparable to LLM and reference agreement. Of 100 unstageable reports, 12 (12.0%) were judged stageable on manual review. Performance was consistent across all sites, time, age, sex, and race. **Conclusion:** This LLM-enabled approach accurately identified and staged liver fibrosis from unstructured biopsy reports, with strong agreement compared to expert staging, including high accuracy at both significant and advanced fibrosis thresholds. Findings support LLM use for scalable identification and characterization of liver fibrosis in research.

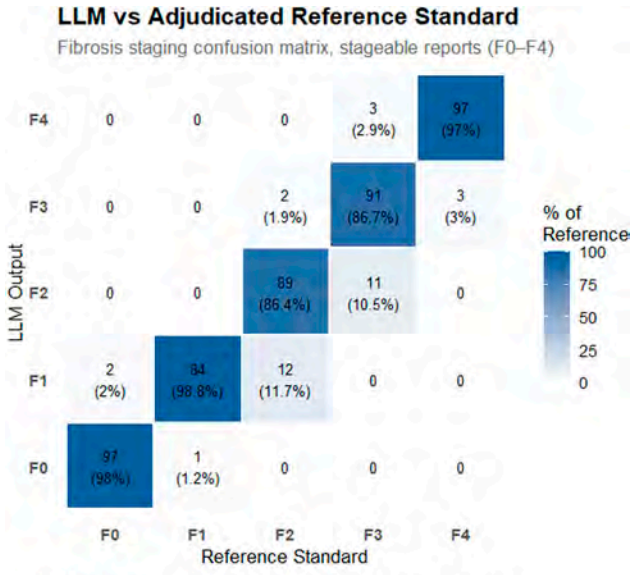


Figure 1. Confusion matrix of LLM-assigned fibrosis stage versus the adjudicated reference standard among 492 stageable reports (F0–F4). Cell values show counts with column percentages (% of each reference standard category). Diagonal cells represent exact agreement; off-diagonal cells represent misclassifications. Colour intensity reflects column percentage.

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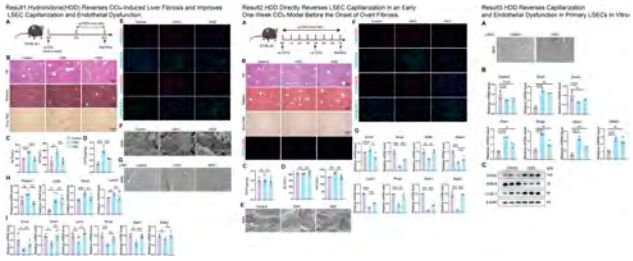
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3382 | HYDRONIDONE ATTENUATES LIVER FIBROSIS PROGRESSION BY AMELIORATING LSEC ENDOTHELIAL DYSFUNCTION

Zhuqiong Lu[1] Guangwen Chen[1] Hanjing Zhangdi[1] Qichao Ge[1] Yufei Yang[1] Jianxiang Wang[1] Yuchen Ding[1] Yuecheng Guo[1] Jie Jian[1] Ying Luo[2] Ling Zhang[2] Hui Dong[1] Lungen Lu[1] Xiaobo Cai[1], [1]Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, [2]Continent Pharmaceuticals Co. ,Ltd., Beijing, China

Background: LSEC capillarization and endothelial dysfunction are early events in liver fibrogenesis and may precede overt fibrosis. Hydronidone (HDD), a novel pirfenidone-related antifibrotic compound, has shown antifibrotic activity in preclinical studies and clinical benefit in chronic hepatitis B-related liver fibrosis. Previous mechanistic studies have suggested that HDD exerts antifibrotic effects mainly by inhibiting hepatic stellate cell activation through modulation of TGF-β/Smad signaling. However, whether HDD directly protects sinusoidal endothelial cells, rather than improving endothelial injury secondarily through fibrosis regression, remains unclear. This study therefore investigated the direct effect of HDD on LSEC capillarization and endothelial dysfunction. **Methods:** A classical CCl_4-induced fibrosis model was used to evaluate the anti-fibrotic and endothelial-protective effects of HDD in vivo.An early one-week CCl_4 model was established to assess whether HDD could reverse LSEC capillarization before overt fibrosis developed. Primary LSECs were isolated for in vitro experiments to determine the direct effect of HDD on capillarization and endothelial dysfunction.Endothelial- and capillarization-related markers were analyzed by qPCR and Western blotting following HDD treatment.LSEC fenestrae were examined by scanning electron microscopy (SEM) to evaluate the effect of HDD on fenestrae. **Results:** In the classical CCl_4-induced fibrosis model, HDD markedly alleviated liver fibrosis and was accompanied by significant improvement in LSEC capillarization and endothelial dysfunction.In the early one-week CCl_4 model, HDD improved capillarization-related changes before obvious fibrosis developed, suggesting a direct protective effect on LSECs.In primary LSECs, HDD directly improved capillarization- and endothelial dysfunction-related phenotypes in vitro.qPCR and Western blot analyses showed restoration of endothelial-associated markers and reduction of capillarization-related markers after HDD treatment.SEM further demonstrated that HDD preserved LSEC fenestrae and attenuated fenestrae loss **Conclusion:** HDD alleviates liver fibrosis by directly improving LSEC capillarization and endothelial dysfunction, suggesting that protection of sinusoidal endothelial homeostasis is an important component of its anti-fibrotic action. Further studies will focus on the underlying eNOS-related mechanisms.



Disclosures: Zhuqiong Lu:Nothing to Disclose, Guangwen Chen:Nothing to Disclose, Hanjing Zhangdi:Nothing to Disclose, Qichao Ge:Nothing to Disclose, Yufei Yang:Nothing to Disclose, Jianxiang Wang:Nothing to Disclose, Yuchen Ding:Nothing to Disclose, Yuecheng Guo:Nothing to Disclose, Jie Jian: Nothing to Disclose, Ying Luo:Nothing to Disclose, Ling Zhang:Nothing to Disclose, Hui Dong:Nothing to Disclose, Lungen Lu:Nothing to Disclose, Xiaobo Cai: Nothing to Disclose.

3383 | ASSOCIATION OF DIABETIC NEPHROPATHY WITH LIVER FIBROSIS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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Symbols: ♦, Poster of Distinction; ★, Foundation Award Recipient

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Background: To investigate the association between diabetic nephropathy (DN) and liver fibrosis in patients with type 2 diabetes mellitus (T2DM), and to further evaluate whether metabolic associated fatty liver disease (MAFLD) status influences this relationship. **Methods:** Data were obtained from the National Health and Nutrition Examination Survey (NHANES) 2017–2020 cycle. Participants with T2DM who underwent vibration-controlled transient elastography were included. DN was defined based on estimated glomerular filtration rate and urinary albumin-to-creatinine ratio (UACR). Liver fibrosis was defined as liver stiffness measurement ≥ 6 kPa. Multivariable logistic regression models were applied to assess the association between DN and liver fibrosis. Dose–response relationships were examined according to UACR categories. Stratified analyses by MAFLD status and interaction tests were performed. Inverse probability of treatment weighting (IPTW) was used to evaluate the robustness of the findings. **Results:** A total of 1,104 participants with T2DM were included,of whom 449 (40.67%)had DN.DN was independently associated with an increased risk of liver fibrosis(adjusted odds ratio[aOR]1.46, 95% confidence interval [CI] 1.11–1.93, P = 0.006). A dose–response relationship was observed across UACR categories: compared with UACR < 30 mg/g, the risks of liver fibrosis were higher in the 30–300 mg/g and ≥ 300 mg/g groups (aOR 1.47 and 1.70, respectively; both P < 0.05). Stratified analyses showed consistent directions of association across MAFLD subgroups, and no statistically significant interaction was observed (P for interaction = 0.742). IPTW-weighted analyses yielded similar results (aOR 1.44, 95%CI 1.20–1.73, P < 0.001). **Conclusion:** DN is significantly associated with an increased risk of liver fibrosis in patients with T2DM, and this association remains consistent across MAFLD status. Higher UACR levels are positively associated with liver fibrosis risk, suggesting that markers of renal injury may help identify individuals at high risk of liver fibrosis. These findings highlight the importance of considering kidney–liver interactions in the management of T2DM.

Figure 1. Flow Chart

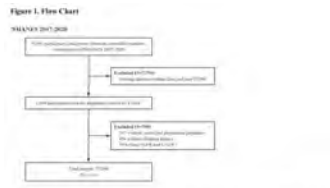


Table 1.Demographics and clinical characteristics of the patients with T2DM according to diabetic nephropathy (DN) in NHANES 2017-2020.

	Overall T2DM	Non-diabetic epheropathy	Diabetic nephropathy	P value
	N=1,104	N=655	N=449	
Age, years	61.0 (53.0, 70.0)	59.0 (48.0, 67.0)	65.0 (56.0, 74.0)	<0.001
Male, %	389 (52.35)	326 (49.77)	263 (58.57)	0.005
PIR	2.10 (1.33, 4.07)	2.19 (1.36, 4.31)	2.00 (1.09, 3.94)	0.217
Race, %				0.022
Mexican American 154 (13.95)		97 (14.81)	57 (12.69)	
Other Hispanic 117 (10.60)		81 (12.37)	36 (8.02)	
Non-Hispanic white 507 (27.81)		177 (27.02)	330 (28.93)	
Non-Hispanic Black 326 (29.53)		180 (27.48)	146 (32.52)	
Non-Hispanic Asian 140 (12.68)		91 (13.89)	49 (10.91)	
Other Race 60 (5.43)		29 (4.43)	31 (6.90)	
Drink status, %	848 (76.81)	519 (79.24)	329 (73.27)	0.020
Hypertension, %	520 (50.91)	280 (42.76)	240 (62.91)	<0.001
BMI (kg/m2)	31.25 (27.20, 36.10)	31.20 (27.30, 36.80)	31.30 (26.80, 35.40)	0.231
Waist circumference	107.20 (97.50, 118.50)	106.60 (97.20, 118.60)	108.30 (98.50, 118.40)	0.076
SBP (mmHg)	128.17 (116.67, 141.73)	124.67 (114.67, 136.17)	133.67 (120.67, 191.33)	<0.001
DBP (mmHg)	74.33 (65.67, 83.00)	74.67 (68.33, 82.33)	74.33 (66.33, 84.00)	0.201
PLT (10^9/L)	238.00 (195.75, 278.25)	236.00 (200.00, 283.50)	230.00 (189.00, 229.00)	0.013
FBG (mmol/L)	7.44 (6.62, 9.00)	7.38 (6.61, 9.10)	7.77 (6.68, 10.30)	0.011
HbA1c, %	7.29 (6.67, 8.13)	7.09 (6.54, 7.88)	7.60 (6.89, 8.66)	<0.001
ALT (U/L)	19 (14, 28)	20 (15, 28)	18 (13, 28)	0.018
AST (U/L)	19 (15, 24)	19 (15, 24)	19 (15, 25)	0.578
ALP (U/L)	80 (65, 98)	80 (65, 97)	81 (66, 100)	0.155
GGT (U/L)	26 (18, 42)	26 (18, 42)	23 (17, 44)	0.748
TC (mmol/L)	4.55 (3.83, 5.33)	4.68 (3.93, 5.33)	4.37 (3.72, 5.34)	0.088
TG (mmol/L)	1.26 (0.90, 1.77)	1.23 (0.89, 1.76)	1.28 (0.93, 1.77)	0.712
HDL-C (mmol/L)	1.19 (1.01, 1.43)	1.19 (1.03, 1.43)	1.16 (1.01, 1.40)	0.140
UA (mmol/L)	327.3 (267.7, 398.5)	321.2 (267.7, 386.7)	336.9 (279.6, 416.6)	<0.001
Scr (mg/dL)	0.83 (0.70, 1.06)	0.79 (0.67, 0.92)	1.01 (0.79, 1.30)	<0.001
UACR (mg/g)	13.33 (7.14, 66.48)	8.86 (5.58, 13.52)	66.13 (32.86, 184.47)	<0.001
eGFR (mL/min/1.73 m2)	87.23 (67.38, 105.63)	92.76 (79.57, 103.09)	67.89 (40.48, 88.16)	<0.001
Insulin usage status, %	109 (18.01)	73 (11.80)	123 (27.84)	<0.001
Fibrosis stages, %				0.218
F0 (LSM<8)(663 (54.62)		377 (57.56)	226 (50.31)	
F1 (8≤LSM<9)(245 (22.19)		135 (20.61)	110 (24.50)	
F2 (9≤LSM<11)(97 (8.79)		54 (8.24)	43 (9.58)	
F3 (10≤LSM<13)(66 (5.98)		38 (5.80)	28 (6.24)	
F4 (LSM≥13)(93 (8.42)		51 (7.79)	42 (9.35)	
MASLD, %	810 (74.18)	513 (78.63)	304 (67.71)	<0.001

Note: Continuous values are presented as median (interquartile range) and categorical variables as count (percentage). Liver fibrosis stages were evaluated by vibration-controlled transient elastography. T2DM, type 2 diabetes mellitus; PIR, poverty income ratio; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; PLT, platelet; FBG, fasting blood glucose; ALT, alanine transaminase; AST, aspartate transaminase; ALP, alkaline phosphatase; GGT, gamma-glutamyltransferase; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; UA, uric acid; Scr, serum creatinine; eGFR, estimated glomerular filtration rate; UACR, urinary albumin/creatinine ratio; MASLD, metabolic dysfunction-associated steatotic liver disease.

Table 2. Univariate and multivariate logistic regression analysis for the association between diabetic nephropathy and liver fibrosis (LSM≥8 kPa) in NHANES 2017-2020.

	Univariate analysis		Model 1		Model 2		Model 3	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Diabetic nephropathy	**1.34 (1.05-1.70)**	**0.0 18**	**1.40 (1.09-1.81)**	**0.0 09**	**1.46 (1.11-1.93)**	**0.0 06**	**1.41 (1.07-1.87)**	**0.01 5**
UACR								
UACR<30mg/g	Reference		Reference		Reference		Reference	
30≤UACR<300 (mg/g	1.32 (0.96-1.80)	0.0 86	1.29 (0.93-1.84)	0.0 84	**1.47 (1.08-2.00)**	**0.0 15**	**1.41 (1.03-1.94)**	**0.03 1**
UACR≥300mg/g	1.62 (0.98-2.69)	0.0 61	**1.73 (1.08-2.77)**	**0.0 23**	**1.70 (1.01-2.84)**	**0.0 44**	1.63 (0.96-2.76)	0.06 8

Model 1: adjusted by diabetic nephropathy,UACR, and demographic data (age, sex, PIR, and race); Model 2: model 1+ metabolic risk factors (BMI, FC, waist circumference and hypertension); Model 3: model 2+ insulin usage status and HbA1c.

Disclosures: Sisi Zhou:Nothing to Disclose, Xinyu Hu: Nothing to Disclose, Qianqian Chen:Nothing to

Symbols: ♦, Poster of Distinction; ★, Foundation Award Recipient

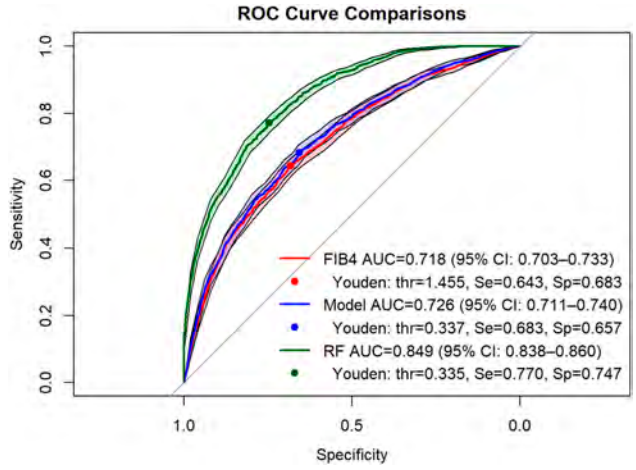
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Disclose, Fajuan Rui:Nothing to Disclose, Jie Li: Nothing to Disclose.

3384 | MACHINE LEARNING ALGORITHMS USING ELECTRONIC HEALTH RECORD DATA OUTPERFORM FIB-4 INDEX IN DETECTION OF CLINICALLY SIGNIFICANT FIBROSIS

Ashley Spann[1] Natalie Vellutini[1] Dameia Brewster[1] Qingxia Chen[1] Jackson Resser[1] Manhal Izzy[1], [1]Vanderbilt University Medical Center

Background: Clinically significant fibrosis (F2+) is a major determinant of liver-related morbidity and mortality, and accurate predictive models of fibrosis staging would have substantial clinical significance in facilitating earlier disease detection and therapeutic opportunities. The FIB-4 index represents a common tool for detecting advanced fibrosis stages (stage F3-F4) and is routinely used in clinical practice for screening for liver disease. However, FIB-4 performs poorly for detection of earlier stages of fibrosis (stage F2), which is a pharmacotherapeutic target/threshold for initiation of anti-fibrotic therapies. Machine learning methodologies that leverage readily available electronic health record data may improve upon the accuracy of earlier detection of moderate fibrosis. We aimed to develop a predictive model to improve the predictive accuracy of detecting clinically significant fibrosis. **Methods:** This single center retrospective cohort study of patients undergoing either transient (TE) or MRI elastography (MRE) study between 01/01/2018 – 12/31/2025 included those with pre-assessment FIB-4 data and excluded liver transplant recipients and those with poor quality elastography studies (IQR >30 or unsatisfactory MRE). Fibrosis was evaluated using normalcy cutoffs for FIB-4 (1.3 for those age < 65; 2.0 for those age ≥ 65), and current society guidelines for TE & MRE cutoffs for F0-F1 versus F2+. Prediction models included logistic regression and random forest (RF) with covariates including FIB-4, sex, BMI, race/ethnicity, diabetes, hypertension, hyperlipidemia, and interaction between FIB-4 and diabetic status. Missing data underwent multiple imputation with the bootstrap method. Performance metrics were calculated for all algorithms, including AUROC, accuracy, precision, recall, and F1-score. SHAP score was constructed to assess RF model feature importance. Delong's test was performed to assess differences in ROC curves between models. **Results:** Of 5045 total patients, 1750 (34.7%) had F2+ fibrosis. The FIB-4 AUC was 0.718 [CI 0.703-0.733], which was not significantly different from the logistic regression model AUC of 0.726 [CI 0.711-0.74, p = 0.147] whereas the RF model AUC was significantly different than the FIB-4 performance with an AUC of 0.849 [CI 0.838-0.86, p < 0.001]. Additionally, the RF model performed the best overall with respect to accuracy (0.759 [0.724, 0.778]), precision (0.633 [0.572, 0.690]), recall (0.727 [0.643, 0.820]), and F1 score (0.674 [0.660, 0.686]). The most important features contributing to the RF model's performance was an interaction term between FIB4 value & diabetes status, followed by hypertension & patient sex. **Conclusion:** In this large cohort of patients with fibrosis data, a machine learning algorithm remarkably outperformed FIB-4 in the detection of patients with clinically significant fibrosis (F2+) using available electronic health record data.



Disclosures: Ashley Spann:Bristol Myers Squibb Foundation: Grant/Research Support, Novo Nordisk: Consultant, Madrigal Pharmaceuticals: Consultant, Natalie Vellutini:Nothing to Disclose, Dameia Brewster:Nothing to Disclose, Qingxia Chen:Nothing to Disclose, Jackson Resser:Nothing to Disclose, Manhal Izzy:Mallinckrodt: Speaking and Teaching, Madrigal: Advisor, Natera: Advisor, Mirum: Advisor.

3385 | PERFORMANCE OF METABOLOMICS-BASED LIPID SIGNATURES FOR FIBROSIS RISK STRATIFICATION IN MASLD PATIENTS WITH INDETERMINATE FIB-4 VALUES

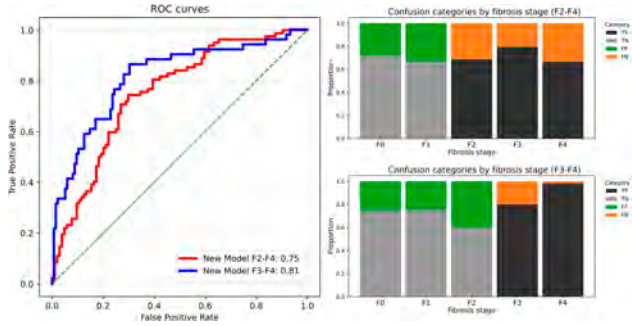
Cristina Alonso[1] Andres Duarte-Rojo[2] Mazen Noureddin[3] Jesús María Bañales Asurmendi[4] Marco Arrese[5] Ibon Martínez-Arranz[6] Manuel Romero-Gómez[7] Paula Iruzubieta[8] rocio aller[9] Javier Ampuero[10] Richard Sterling[11] Jose Luis Calleja[12] Luis Ibáñez Samaniego[13] Javier Crespo[8] Arun Sanyal[14], [1]Rubio Metabolomics, S.L.U., [2]Northwestern Medicine, [3]Houston Methodist Hospital, [4]Biogipuzkoa Health Research Institute, San Sebastian, Spain CIBERehd,

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Background: FIB-4 is widely used as a first-line non-invasive liver disease assessment (NILDA) test for fibrosis in metabolic dysfunction-associated steatotic liver disease (MASLD). However, patients with indeterminate FIB-4 results require additional evaluation. We evaluated the diagnostic performance of two metabolomics-based models for detecting at least significant fibrosis (F2–F4) or advanced fibrosis (F3–F4) in patients with MASLD and indeterminate FIB-4 values. **Methods:** We included 218 patients with biopsy-confirmed MASLD and indeterminate FIB-4 values, defined as FIB-4 1.30–2.67 in patients $\leq$65 years and FIB-4 2.0–2.67 in those >65 years. The cohort included 94 women (43%), with a mean BMI of 33 ± 7 kg/m², ALT 67 ± 46 U/L, and AST 50 ± 31 U/L. Fibrosis stages were: F0 18.8%, F1 38.8%, F2 18.2%, F3 21.6%, and F4 2.6%. Significant and advanced fibrosis were assessed using two models based on 19 and 13 circulating lipids, respectively. Diagnostic performance was evaluated across probability cutoffs using sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy; optimal cutoffs were selected with the Youden index. **Results:** The 19-lipid model demonstrated good diagnostic performance for detecting significant fibrosis achieving an AUROC of 0.75. The optimal probability cutoff identified by the Youden index was 0.519. At this threshold, the model achieved balanced diagnostic performance, with S 72%, Sp 74%, PPV 66%, NPV 74%, and accuracy 70%. The 13-lipid model demonstrated good discrimination for advanced fibrosis with an AUROC of 0.81. The optimal cutoff identified by the Youden index provided balanced diagnostic performance, with S 82%, Sp 72%, PPV 53%, NPV 92%, and accuracy 75%. Unsurprisingly, the two models showed progressive improvement in Sp and PPV with increasing probability thresholds at the expense of sensitivity, supporting its utility for identifying patients at higher risk of advanced fibrosis within the FIB-4 grey zone. A sensitivity analysis considering OWLiver as the first-line test resulted in 4.6-fold and 5.6-fold increases in the number of participants correctly classified as F2–F4 and F3–F4, respectively, compared with FIB-4. **Conclusion:** Metabolomics-based signatures demonstrated clinically relevant diagnostic performance for detecting both significant fibrosis and advanced fibrosis in MASLD patients with indeterminate FIB-4 values. These findings suggest that metabolomics-based risk stratification may serve as a valuable second-line NILDA to refine fibrosis assessment and improve clinical decision-making in patients within the FIB-4 indeterminate range.



Disclosures: Cristina Alonso:Rubió Metabolomics, S.L.U.: Employee, Andres Duarte-Rojo:Echosens: Grant/Research Support, Echosens: Grant/Research Support, CIMA Sciences: Consultant, HepQuant: Advisor, Merz: Advisor, CIMA Sciences: Grant/Research Support, Merz Therapeutics: Advisor, Mazen Noureddin:Akero: Advisor, Alligos: Advisor, Altimmune: Advisor, AstraZeneca: Advisor, Boehringer Ingelheim: Advisor, Boston Pharma: Advisor, Cytodyn: Advisor, GSK: Advisor, Lilly: Advisor, Madrigal: Advisor, Merck: Advisor, Novo Nordisk: Advisor, Sagimet: Advisor, Terns: Advisor, Takeda: Advisor, Akero: Principal Investigator, Allergan: Principal Investigator, Altimmune: Principal Investigator, Boehringer Ingelheim: Principal Investigator, Bristol Myers Squibb: Principal Investigator, Boston Pharma: Principal Investigator, Conatus: Principal Investigator, Corcept: Principal Investigator, Galectin: Principal Investigator, Genfit: Principal Investigator, GSK: Principal Investigator, Kowa: Principal Investigator, Enanta: Principal Investigator, Madrigal: Principal Investigator, Lilly: Principal Investigator, Merck: Principal Investigator, Novartis: Principal Investigator, Novo Nordisk: Principal Investigator, Rivus: Principal Investigator, Shire: Principal Investigator, Takeda: Principal Investigator, Terns: Principal Investigator, Viking: Principal Investigator, Zydus: Principal Investigator, Rivus: Stock – privately held company, Cytodyn: Stock - publicly traded company, ChronWell: Stock – privately held company, Madrigal: Speakers bureau, Gilead Sciences: Principal Investigator, Akero: Consultant, Altimmune: Consultant, Alligos: Consultant, AstraZeneca: Consultant, BI: Consultant, Boston Pharma: Consultant, Curve bioscience: Consultant, Cytodyn: Consultant, GSK: Consultant, Histoindex: Consultant, Lilly: Consultant, Madrigal: Consultant, Merck: Consultant, Novo Nordisk: Consultant, Sagimet: Consultant, Terns: Consultant, Allergan: Grant/Research Support, Altimmune: Grant/Research

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3386 | A METABOLOMICS-BASED EXTENSION OF THE OWLIVER TEST IMPROVES FIBROSIS STAGING IN STEATOTIC LIVER DESEASE

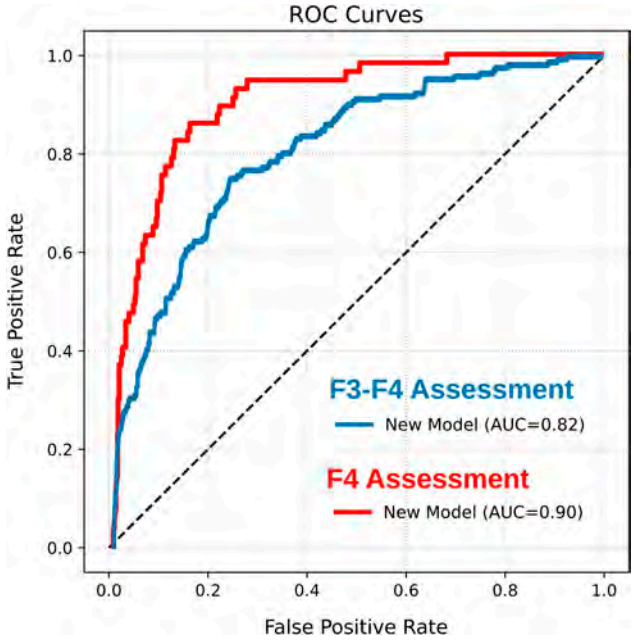
Andres Duarte-Rojo[1] Mazen Noureddin[2] Jesús María Bañales Asurmendi[3] Marco Arrese[4] Ibon Martínez-Arranz[5] Manuel Romero-Gómez[6] Paula Iruzubieta[7] Rocio Aller[8] Richard Sterling[9] Javier Ampuero[10] Jose Luis Calleja[11] Cristina Alonso[12] Luis Ibáñez Samaniego[13] Javier Crespo[7] Arun Sanyal[14], [1]Northwestern Medicine, [2]Houston Methodist Hospital, [3]Biogipuzkoa Health Research Institute, San Sebastian, Spain CIBERehd, Instituto de Salud Carlos III, [4]Pontificia Universidad Católica de Chile, Santiago de Chile, Chile, [5]Rubió Metabolomics, S.L.U., [6]Virgen del Rocio University Hospital, [7]Marqués de Valdecilla University Hospital, Cantabria University, IDIVAL, Santander, Spain, [8]Clinic University Hospital, University of Valladolid, Valladolid, Spain, [9]VCU Medical Center, [10]Virgen del Rocío University Hospital, Sevilla, Spain, [11]Puerta del Hierro University Hospital, Madrid, Spain, [12]Rubio Metabolomics, S.L.U., [13]Gregorio Marañón University Hospital, Madrid, Spain, [14]Virginia Commonwealth University

Background: The OWLiver test is a robust serum lipidomics-based non-invasive liver disease assessment (NILDA) algorithm developed for steatosis and steatohepatitis (including at-risk MASH). Since OWLiver was not specifically designed for fibrosis assessment, we expanded the algorithm framework into a broader metabolomic space and developed complementary models optimized for detecting at least advanced fibrosis (F3–F4) and cirrhosis (F4), irrespective of MASH features **Methods:** A total of 849 biopsy-confirmed patients across fibrosis stages F0–F4 were included (F0: 25.9%; F1: 37.9%; F2: 18.1%; F3: 12.1%; F4: 6.0%). Metabolomic profiling comprised 245 circulating lipid and other metabolite species. Model development followed a standardized machine learning workflow including feature selection and logistic regression, with cross-validation and an independent validation-cohort to ensure robust performance assessment. Two binary classification models were trained for the detection of F3–F4 and F4, using liver biopsy as reference standard. Model's performance was assessed by AUROC, sensitivity, specificity, and Youden index-derived cut-offs. **Results:** Metabolomics-enhanced models showed improved discrimination with increasing fibrosis severity. The model for advanced fibrosis (F3–F4) achieved an AUROC of 0.82, with 75% sensitivity and 77% specificity. The cirrhosis (F4) model showed the highest diagnostic performance, reaching an AUROC of 0.90, with 86% sensitivity and 85% specificity. These findings indicate that broader metabolomic signatures improve classification of clinically relevant fibrosis stages beyond the performance of our previously reported lipid-based OWLiver test. **Conclusion:** Our upgraded OWLiver test, which was specifically designed as a fibrosis NILDA, showed excellent to outstanding diagnostic accuracy for advanced fibrosis and cirrhosis. We achieved this goal by extending the original algorithm

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framework into a broader metabolomic space, through dedicated fibrosis models that were agnostic to MASH features. The improved discrimination capacity in subpopulations with advanced fibrosis and cirrhosis may enhance patient stratification and clinical decision-making in steatotic liver disease.



Disclosures: Andres Duarte-Rojo:Echosens: Grant/Research Support, Echosens: Grant/Research Support, CIMA Sciences: Consultant, HepQuant: Advisor, Merz: Advisor, CIMA Sciences: Grant/Research Support, Merz Therapeutics: Advisor, Mazen Noureddin: Akero: Advisor, Alligos: Advisor, Altimmune: Advisor, AstraZeneca: Advisor, Boehringer Ingelheim: Advisor, Boston Pharma: Advisor, Cytodyn: Advisor, GSK: Advisor, Lilly: Advisor, Madrigal: Advisor, Merck: Advisor, Novo Nordisk: Advisor, Sagimet: Advisor, Terns: Advisor, Takeda: Advisor, Akero: Principal Investigator, Allergan: Principal Investigator, Altimmune: Principal Investigator, Boehringer Ingelheim: Principal Investigator, Bristol Myers Squibb: Principal Investigator, Boston Pharma: Principal Investigator, Conatus: Principal Investigator, Corcept: Principal Investigator, Galectin: Principal Investigator, Genfit: Principal Investigator, GSK: Principal Investigator, Kowa: Principal Investigator, Enanta: Principal Investigator, Madrigal: Principal Investigator, Lilly: Principal Investigator, Merck: Principal Investigator, Novartis: Principal Investigator, Novo Nordisk: Principal Investigator, Rivus: Principal Investigator, Shire: Principal Investigator, Takeda: Principal Investigator, Terns: Principal Investigator, Viking: Principal Investigator, Zydus: Principal Investigator, Rivus: Stock – privately held company, Cytodyn: Stock - publicly traded company, ChronWell: Stock – privately held company, Madrigal: Speakers bureau, Gilead Sciences: Principal Investigator, Akero: Consultant, Altimmune: Consultant, Alligos: Consultant, AstraZeneca: Consultant, BI: Consultant, Boston Pharma: Consultant, Curve bioscience: Consultant, Cytodyn: Consultant, GSK: Consultant, Histoindex: Consultant, Lilly: Consultant, Madrigal: Consultant, Merck: Consultant, Novo Nordisk: Consultant, Sagimet: Consultant, Terns: Consultant, Allergan: Grant/Research Support, Altimmune: Grant/Research Support, Akero: Grant/Research Support, BI: Grant/Research Support, BMS: Grant/Research Support, Boston Pharma: Grant/Research Support, Conatus: Grant/Research Support, Corcept: Grant/Research Support, Gilead: Grant/Research Support, Galectin: Grant/Research Support, Genfit: Grant/Research Support, GSK: Grant/Research Support, Kowa: Grant/Research Support, Enanta: Grant/Research Support, Madrigal: Grant/Research Support, Lilly: Grant/Research Support, Merck: Grant/Research Support, Novartis: Grant/Research Support, Novo Nordisk: Grant/Research Support, Rivus: Grant/Research Support, Shire: Grant/Research Support, Takeda: Grant/Research Support, Terns: Grant/Research Support, Viking: Grant/Research Support, Akero: Stock - publicly traded company, Zydus: Grant/Research Support, Takeda: Consultant, Madrigal: Speaking and Teaching, Novo Nordisk: Speaking and Teaching, HepaNova: Consultant, Daiichi Sankyo: Advisor, Daiichi Sankyo: Consultant, Curve Bioscience: Advisor, Curve Bioscience: Consultant, HepaNova: Advisor, HepaTx: Advisor, HepaTx: Consultant, HepaTx: Stock - publicly traded company, HepaTx: Stock - publicly traded company, HepaNova: Stock - publicly traded company, Histoindex: Advisor, Histoindex: Consultant, Kryia: Advisor, Kryia: Consultant, Kryia: Stock - publicly traded company, Neuraly: Advisor, Neuraly: Consultant, Novo Nordisk,: Consultant, OPKO: Advisor, OPKO: Consultant, OPKO: Stock - publicly traded company, OPKO: Stock - publicly traded company, OPKO: Stock - publicly traded company, Rivus: Advisor, Rivus: Consultant, Rivus: Stock - publicly traded company, Jesús María Bañales Asurmendi: Nothing to Disclose, Marco Arrese:Nothing to Disclose, Ibon Martínez-Arranz:Nothing to Disclose, Manuel Romero-Gómez:Nothing to Disclose, Paula Iruzubieta: Nothing to Disclose, rocio aller:Nothing to Disclose, Richard Sterling:ABIM: GI Specialty Board, Abbott: Grant/Research Support, GSK: Grant/Research Support, HCV Vax: Grant/Research Support, Gilead: Grant/Research Support, Zydus: Grant/Research Support, Vertex: Consultant, Madrigal: Advisor, Gigagen: Grant/Research Support, Atea: Grant/Research Support, Cima Science: Consultant, Celaris: Consultant, GSK: Advisor, Javier Ampuero:Nothing to Disclose, Jose Luis Calleja:Nothing to Disclose, Cristina Alonso:Rubió Metabolomics, S.L.U.: Employee, Luis Ibáñez

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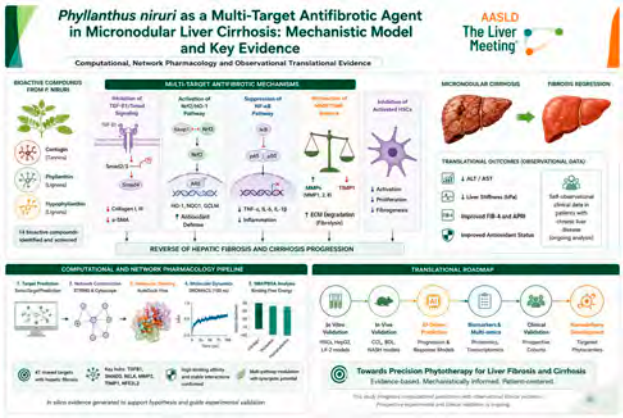
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3387 | IN SILICO MULTI-TARGET EVALUATION OF PHYLLANTHUS NIRURI BIOACTIVE COMPOUNDS AGAINST HEPATIC FIBROSIS PATHWAYS: MOLECULAR DOCKING, 300-NS MOLECULAR DYNAMICS, AND MM-GBSA BINDING FREE ENERGY ANALYSIS

Fabian Rodolfo Jimenez Patino[1] William Lituma[1] Alexandra Nataly Culqui Medina[2] Tanishque Verma[3] Hugo Chancay[1], [1]NF Innovations, [2]Universidad Técnica del Norte, [3]Sidda Vetha Multiversity

Background: Micronodular liver cirrhosis remains a major cause of hepatic morbidity with limited antifibrotic therapies. Phyllanthus niruri has demonstrated hepatoprotective, antioxidant, and anti-inflammatory activity in preclinical and clinical studies; however, its molecular antifibrotic mechanisms remain incompletely characterized. This study integrates network pharmacology, molecular docking, molecular dynamics simulation, and clinical biomarker analysis to investigate the antifibrotic potential of key P. niruri bioactive compounds targeting TGF-beta/Smad, Nrf2/HO-1, and NF-kB pathways in hepatic fibrosis.Multi-target phytochemical strategies may offer mechanistic advantages over single-pathway antifibrotic approaches. **Methods:** An integrative computational-clinical approach was applied. Network pharmacology identified fibrosis-related targets of 14 P. niruri bioactive compounds using SwissTargetPrediction, GeneCards, and OMIM. Molecular docking evaluated corilagin, phyllanthin, and hypophyllanthin interactions with TGF-beta1 and SMAD2/3 using AutoDock Vina. GROMACS molecular dynamics simulations and MM/PBSA calculations assessed ligand-protein stability. Clinical fibrosis biomarkers (ALT/AST, Fib-4, APRI, elastography), inflammatory cytokines, and oxidative stress markers were analyzed. HPLC and LC-MS/MS were used for phytochemical standardization.Protein-protein interaction networks were constructed using STRING and Cytoscape to identify hub genes associated with hepatic fibrogenesis. **Results:** Network pharmacology identified 47 shared fibrosis-related targets associated with P. niruri bioactive compounds. Corilagin, phyllanthin, and hypophyllanthin demonstrated high connectivity within TGF-beta/Smad and Nrf2/ARE pathways. Molecular docking showed strong binding affinity of corilagin to TGF-beta1 (-8.3 kcal/mol). Molecular dynamics and MM/PBSA analyses confirmed stability of corilagin-TGF-beta1 and phyllanthin-SMAD3 complexes. Predicted mechanisms included suppression of TGF-beta/Smad signaling, reduction of collagen deposition, modulation of MMP2/TIMP1 imbalance, activation of Nrf2/ARE antioxidant pathways, and inhibition of NF-kB-mediated inflammation. Clinical biomarker analysis correlated reduced inflammatory markers with improved fibrosis indices.KEGG enrichment analysis demonstrated significant association with TGF-β, NF-κB, and oxidative stress-related signaling pathways involved in hepatic fibrosis progression, **Conclusion:** P. niruri bioactive compounds demonstrated a multi-target antifibrotic profile in micronodular cirrhosis through modulation of TGF-beta/Smad, oxidative stress, and inflammatory pathways. Integrative computational-clinical analysis supports P. niruri as a promising candidate for translational antifibrotic therapy development.



Disclosures: FABIAN RODOLFO JIMENEZ PATINO: Nothing to Disclose, William Lituma:Nothing to Disclose, Alexandra Nataly Culqui Medina:Nothing to Disclose, Tanishque Verma:Nothing to Disclose, Hugo Chancay:Nothing to Disclose.

3388 | IMPAIRED ENDOGENOUS DNASE I ACTIVITY AND ALTERED EXTRACELLULAR MTDNA PROFILE IN SERUM OF CIRRHOSIS PATIENTS

Zaur Abilov[1] Yoshiko Nanki[1] Arvo Justice[1] Pinzhu Huang[1] Chandra S Shankar[1] Victor Turkowski[1] Gloria Horta[1] Michelle Lai[1] Yury Popov[1], [1]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, United States

Background: Mitochondrial DNA (mtDNA) is a pro-inflammatory and pro-fibrogenic damage-associated molecular pattern (DAMP) with a pathogenic role in chronic liver diseases. However, little is known about the circulating mtDNA pathogenic role and its turnover in end-stage liver disease. In this pilot study, we measured extracellular levels of mtDNA and two major endogenous nucleases potentially responsible its breakdown in cirrhosis. **Methods:** DNase I enzymatic activity was measured in serum

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from the pilot cirrhosis cohort due to various etiology (n = 47) and age- and sex-matched healthy controls (n = 10) using fluorometric activity assay. DNase I and DNase1L3 protein levels were measured by ELISA. Absolute quantification of circulating mitochondrial DNA in plasma was performed by novel in-house duplex digital droplet PCR assay. Group comparisons were performed using Mann–Whitney tests, and associations with clinical laboratory parameters, MELD, and Child-Pugh scores analyzed using Spearman correlation. **Results:** In cirrhotic serum, average DNase I activity was decreased over 5-fold, compared with healthy controls (0.51 ± 0.07 μU/mL vs 2.71 ± 0.83 μU/mL, p = 0.0006). DNase I protein levels did not differ significantly between patients with cirrhosis and healthy controls (p = 0.620), whereas DNase1L3 protein levels were near or below detection level. DNase I protein concentration did not correlate with DNase I activity in cirrhosis samples (Spearman r = -0.067, p = 0.746), suggesting a discordance between protein abundance and corresponding enzymatic activity in cirrhosis. Average plasma cell-free mtDNA levels were 5-fold lower in cirrhotics compared to healthy controls (3.39 ± 0.45 copies/ul vs 15.59 ± 5.35, p < 0.0001). In cirrhotic cohort, serum DNase I activity was negatively correlated with ALP (Spearman r = -0.3408, p = 0.0486) and GGT (Spearman r = -0.7110, p = 0.0120) levels. **Conclusion:** Patients with cirrhosis demonstrate markedly suppressed DNase I enzymatic activity despite preserved circulating DNase I protein levels, suggesting the presence of endogenous DNAse I inhibitor(s). Reduced nuclease activity suggests extracellular mtDNA degradation is markedly impaired in cirrhosis, and support further investigation into functional significance of endogenous nuclease inhibitors in cirrhosis. **Disclosures:** Zaur Abilov:Nothing to Disclose, Yoshiko Nanki:Nothing to Disclose, Arvo Justice:Nothing to Disclose, Pinzhu Huang:Nothing to Disclose, Chandra S Shankar:Nothing to Disclose, Victor Turkowski: Nothing to Disclose, Gloria Horta:Nothing to Disclose, Michelle Lai:Nothing to Disclose, Yury Popov:Nothing to Disclose.

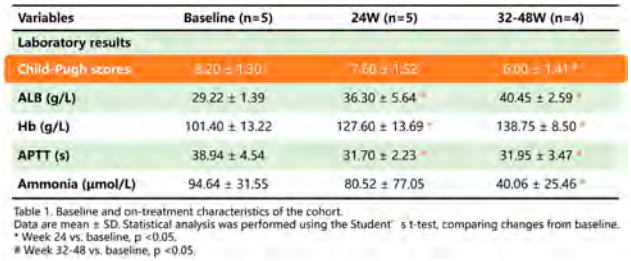
3389 | ALLOGENEIC HEPATOCYTE-DERIVED LIVER PROGENITOR-LIKE CELLS ARE ASSOCIATED WITH LIVER FUNCTION IMPROVEMENT AND RECOMPENSATION IN DECOMPENSATED CIRRHOSIS: A POOLED ANALYSIS OF TWO INVESTIGATOR-INITIATED TRIALS

Hexin Yan[1] Weijian Huang[2] Hanyong Sun[1] Xiaosong Chen[1] Meng Li[1] Chenpeng Zhong[1] Xiaoyan Jin[1] Yonghong Yin[2] Weifeng Yu[1] Qiang Xia[1], [1]Renji Hospital Shanghai Jiaotong University School of Medicine, [2]Shanghai Celliver Biotechnology Inc

Background: Allogeneic hepatocyte-derived liver progenitor-like cells (HepLPCs) represent a potential cell-based therapy for cirrhosis. A first-in-human 3+3 investigator-initiated trial (IIT; NCT04806581) demonstrated the safety and tolerability of HepLPCs across three dose levels. A second IIT (NCT06306781) was subsequently initiated to further evaluate preliminary efficacy and dose selection in patients with decompensated cirrhosis. This pooled analysis focused on the medium-dose cohort to assess liver function recovery and recompensation signals. **Methods:** In the second IIT, six patients were enrolled between February and June 2024, including three receiving low-dose HepLPCs (1.0×10^6 cells/kg) and three receiving medium-dose HepLPCs (2.0×10^6 cells/kg). Because follow-up completion was limited in the low-dose cohort, efficacy analyses were performed by pooling medium-dose recipients from both IITs who completed at least 24 weeks of follow-up. Five patients were included: three with HBV-related cirrhosis and two with alcohol-related cirrhosis. Liver function was assessed by Child-Pugh score, albumin, prealbumin, hemoglobin, coagulation parameters, total bilirubin, and blood ammonia at baseline, Week 24, and Weeks 32–48. Recompensation was assessed according to Baveno VII criteria. **Results:** No dose-limiting toxicities were observed in the medium-dose cohort. Among the five evaluable patients, mean Child-Pugh score improved from 8.20 ± 1.30 at baseline to 6.00 ± 1.41 at Weeks 32–48 after treatment (p < 0.05). Two patients, both with HBV-related cirrhosis, achieved hepatic recompensation according to Baveno VII criteria. At Weeks 32–48, albumin and hemoglobin increased, while APTT and blood ammonia decreased significantly from baseline (all p < 0.05). Albumin, hemoglobin, and APTT had already improved significantly by Week 24, suggesting their potential utility as early indicators of treatment response. Prealbumin, PT, and INR showed favorable trends, whereas total bilirubin remained stable during follow-up. **Conclusion:** Medium-dose allogeneic HepLPC therapy was safe and associated with sustained improvement in liver function and clinically meaningful recompensation signals in patients with decompensated cirrhosis. Albumin, hemoglobin, and APTT may serve as early response indicators. Ongoing studies incorporating HVPG assessment and liver histology will further define the therapeutic effects of HepLPCs in decompensated cirrhosis.

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Variables	Baseline (n=5)	24W (n=5)	32-48W (n=4)
Laboratory results			
Child-Pugh scores	8.20 ± 1.30	7.60 ± 1.52	6.00 ± 1.41 *
ALB (g/L)	29.22 ± 1.39	36.30 ± 5.64 *	40.45 ± 2.59 *
Hb (g/L)	101.40 ± 13.22	127.60 ± 13.69 *	138.75 ± 8.50 *
APTT (s)	38.94 ± 4.54	31.70 ± 2.23 *	31.95 ± 3.47 *
Ammonia (μmol/L)	94.64 ± 31.55	80.52 ± 77.05	40.06 ± 25.46 *

Table 1. Baseline and on-treatment characteristics of the cohort.
Data are mean ± SD. Statistical analysis was performed using the Student' s t-test, comparing changes from baseline.
* Week 24 vs. baseline, p <0.05.
Week 32-48 vs. baseline, p <0.05.

Disclosures: HEXIN YAN:Nothing to Disclose, WEI-JIAN HUANG:Nothing to Disclose, HANYONG SUN: Nothing to Disclose, XIAOSONG CHEN:Nothing to Disclose, MENG LI:Nothing to Disclose, CHENPENG ZHONG:Nothing to Disclose, XIAOYAN JIN:Nothing to Disclose, YONGHONG YIN:Nothing to Disclose, WEI-FENG YU:Nothing to Disclose, QIANG XIA:Nothing to Disclose.

3390 | DEVELOPMENT AND EVALUATION OF A PLATELET-INDEPENDENT MODIFIED FIB-4-LIKE SCORE FOR LIVER DISEASE ASSESSMENT: UTILITY IN SETTINGS WITH CONFOUNDED PLATELET COUNTS

Kiandokht Bashiri[1], [1]MedStar Washington Hospital Center

Background: The Fibrosis-4 (FIB-4) index is widely used for noninvasive liver disease assessment; however, its reliance on platelet count limits applicability in patients with thrombocytopenia due to hematologic disorders, chemotherapy, bone marrow suppression, or other non-hepatic etiologies. We aimed to develop and evaluate a platelet-independent modified FIB-4-like score incorporating markers of hepatic synthetic and cholestatic dysfunction. **Methods:** Using the publicly available UCI Indian Liver Patient Dataset (n = 583; 416 with liver disease), we calculated a modified FIB-4-like score as (Age × AST) / (Albumin × $\sqrt{}$ALT), substituting albumin as a marker of synthetic function. Spearman rank correlations were assessed between this score and markers not incorporated in its formula (total bilirubin, direct bilirubin, alkaline phosphatase, A/G ratio, total protein, and gender). Machine learning models (Random Forest, XGBoost) were evaluated with 5-fold stratified cross-validation for liver disease classification. **Results:** The modified FIB-4-like score showed a moderate-to-strong correlations with direct bilirubin (Spearman ρ = 0.483, $p < 0.0001$), total bilirubin (ρ = 0.476, $p < 0.0001$), alkaline phosphatase (ρ = 0.274, $p < 0.0001$), and strong inverse correlations with A/G ratio (ρ = -0.486, $p < 0.0001$) and total protein (ρ = -0.389, $p < 0.0001$). Random Forest achieved accuracy 0.696 and AUC-ROC 0.749; XGBoost showed accuracy 0.691 and AUC-ROC 0.730 in predicting liver disease. **Conclusion:** This platelet-independent modified FIB-4-like score correlates with both cholestatic and synthetic dysfunction markers and may provide a useful alternative to standard FIB-4 in patients whose platelet counts are affected by non-hepatic conditions such as bone marrow disorders or HIT. While performance remains moderate, this proof-of-concept supports further development of accessible, platelet-independent tools for liver disease risk stratification in complex, comorbid populations. Prospective validation in targeted cohorts is warranted.

Disclosures: Kiandokht Bashiri:Nothing to Disclose.

3391 | PERFORMANCE OF A SALIVA-BASED DIAGNOSTIC TEST FOR LIVER FIBROSIS

Namratha Reddy[1] Abolfazl Jangholi[2] Kim Bridle[3] Hasaranga KLJ[2] Lucas Trevisan Franca de Lima[2] Randi DeArmitt[4] Melyssa Bratton[4] Chamindie Punyadeera[2] George Therapondos[4] Darrell Crawford[5], [1]Greenslopes Private Hospital, [2]Griffith University, [3]The University of Queensland, [4]Ochsner Health, [5]Gallipoli Medical Research

Background: Chronic liver disease (CLD) is a major global health problem which impacts more than one-third of the world's population. Since the risk of adverse liver outcomes increases incrementally with the degree of liver fibrosis, the assessment of liver fibrosis is an essential element of the evaluation of affected patients. Current methods for assessing liver fibrosis are not easily accessed, expensive and/or invasive, resulting in many affected patients either not being identified early or presenting with advanced liver disease when treatment options are limited. To mitigate these barriers, we have developed a saliva test to diagnose liver fibrosis. **Methods:** We measured three fibrosis-related proteins in saliva - hyaluronic acid (HA), tissue-inhibitor of metalloproteinases 1 (TIMP-1), and alpha-2-macroglobulin (A2M) - in patients with liver disease and varying degrees of hepatic fibrosis from two specialist referral centers (Queensland Gastroenterology, Australia and Ochsner Health, USA). Transient elastography (n = 205, Queensland Gastroenterology cohort) and liver biopsy (n = 44, Ochsner Health cohort) were used as comparators. By regression analysis on a discovery cohort, we developed a score (SALF) based on the measurement of these proteins to predict severity of hepatic fibrosis. **Results:** Table 1 shows test performance for detecting liver stiffness measurement (LSM) ±12, LSM ± 8 and fibrosis stage ± F2.

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Median SALF for LSM < 8 was 0.011 vs 0.921 for LSM > 8 (P < 0.05) and median SALF for LSM < 12 was 0.012 vs 0.992 for LSM > 12 (P < 0.05). Median SALF for fibrosis < F2 was 0.39 vs 0.67 for fibrosis ≥ F2 (P < 0.05). **Conclusion:** In these two cohorts, the measurement of salivary fibrosis-related proteins provided a reliable guide to the risk of significant hepatic fibrosis. Saliva is a readily accessible and acceptable bio-medium and is ideal for a community and/or point of care-based program to evaluate the possibility of liver fibrosis and the need for further assessment in those with risk factors for liver disease. A community-based test for liver fibrosis will dramatically increase community access to testing and overcome obstacles inherent in current testing strategies.

Table 1: Performance of SALF Score in Validation Cohort

LSM	Marker (Threshold)	AUC	Sensitivity	Specificity
LSM≥8	HA (240 μg/L)	0.73	80%	45%
	TIMP-1 (181 μg/L)	0.67	80%	35%
	A2M (1835 μg/L)	0.74	80%	53%
	SALF (0.11)	***0.83***	***80%***	***76%***
LSM≥12	HA (386 μg/L)	0.74	72%	71%
	TIMP-1 (412 μg/L)	0.78	56%	92%
	A2M (3216 μg/L)	0.84	75%	79%
	SALF (0.20)	***0.88***	***89%***	***78%***
Fibrosis Stage≥F2	HA (83 μg/L)	0.7	63%	73%
	TIMP-1 (102 μg/L)	0.76	78%	67%
	A2M (789 μg/L)	0.64	78%	53%
	SALF (0.51)	***0.81***	***81%***	***73%***

Disclosures: Namratha Reddy:Nothing to Disclose, Abolfazl Jangholi:Nothing to Disclose, Kim Bridle: Nothing to Disclose, Hasaranga KLJ:Nothing to Disclose, Lucas Trevisan Franca de Lima:Nothing to Disclose, Randi DeArmitt:Nothing to Disclose, Melyssa Bratton:Nothing to Disclose, Chamindie Punyadeera: Nothing to Disclose, George Therapondos:Novo Nordisk: Consultant, Intercept: Speaking and Teaching, Madrigal: Speaking and Teaching, Ipsen: Speaking and Teaching, Gilead: Speaking and Teaching, Darrell Crawford:Nothing to Disclose.

3392 | DIAGNOSTIC ACCURACY OF TWO-DIMENSIONAL SHEAR-WAVE ELASTOGRAPHY (2D-SWE) VERSUS VIBRATION-CONTROLLED TRANSIENT ELASTOGRAPHY (VCTE) FOR LIVER FIBROSIS STAGING IN A REAL-WORLD COHORT

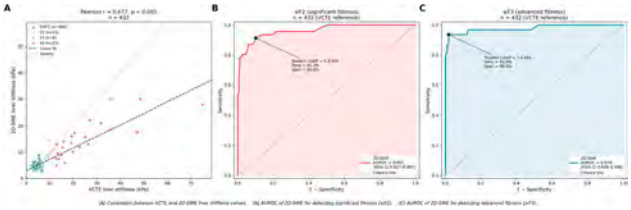
Joao Marcello de Araujo-Neto[1] Flavia Fernandes[2] Priscila Flores[3] Melina Torres[1] Mauren Machado[1] Larissa Oliveira Miranda[1] Ida Arzolla[1] Marcio Miguez[1] Priscilla Calvet Nelson-Smith[1] Adriana Souza e Silva[1] Christina Bahia[1] Juliana Piedade[2] Vania Cristina de Sant`Anna Rocha-Nunnes[1] Celia Rotstein[1] Claudia Oliveira[4], [1]Federal University of Rio de Janeiro, [2]Hospital Federal de Bonsucesso, [3]Federal Fluminense University, [4]University of Sao Paulo School of Medicine

Background: Vibration-controlled transient elastography (VCTE) has been widely validated over the past two decades and is currently the reference non-invasive method for liver fibrosis staging in clinical practice. Newer ultrasound-based techniques such as two-dimensional shear-wave elastography (2D-SWE), integrated into conventional ultrasound platforms, have recently emerged but still require broader validation. We aimed to evaluate the diagnostic accuracy of 2D-SWE for liver fibrosis staging in a real-world cohort, using VCTE as the reference standard. **Methods:** In this single-center cross-sectional study, 432 consecutive adults with chronic liver disease of mixed etiologies referred for liver evaluation were prospectively assessed on the same day with VCTE (FibroScan, Echosens, Paris, France) and 2D-SWE (Samsung RS85, Samsung Medison, Seoul, South Korea); the controlled attenuation parameter (CAP) was also obtained for steatosis assessment. Both examinations were performed after a minimum 4-hour fasting period, and reliability criteria for VCTE included ≥10 valid measurements with an IQR/median ratio ≤30%. VCTE was used as the reference standard for liver fibrosis staging, applying the thresholds F0/F1 <7.0 kPa, F2 7.0–9.4 kPa, F3 9.5–12.4 kPa, and F4 ≥12.5 kPa. **Results:** In the 432 paired measurements, 2D-SWE showed excellent diagnostic accuracy for the detection of significant fibrosis (≥F2: AUROC 0.961, 95% CI 0.927–0.987, cutoff 5.9 kPa, sensitivity 91.3%, specificity 89.6%), advanced fibrosis (≥F3: AUROC 0.976, 0.938–0.998, cutoff 7.4 kPa, sensitivity 93.5%, specificity 98.0%), and cirrhosis (≥F4: AUROC 0.967, 0.921–0.996, cutoff 7.4 kPa, sensitivity 92.0%, specificity 96.6%). Negative predictive values were 98.9%, 99.5%, and 99.5% for ≥F2, ≥F3, and ≥F4, respectively. Bland–Altman analysis showed a minimal mean bias (+0.7 kPa) but wide 95% limits of agreement (−8.2 to +9.6 kPa). 2D-SWE correlated strong with transient elastography (Pearson r = 0.677; both p < 0.001), with a stepwise increase in median 2D-SWE values across VCTE stages (F0/F1: 4.8 kPa, F2: 6.4 kPa, F3: 9.9 kPa, F4: 13.4 kPa; Kruskal-Wallis p < 0.001). Linear regression of the Fib–SWE bias on CAP revealed no significant association (slope = 0.004 kPa per dB/m, p = 0.31), indicating that hepatic steatosis did not introduce a systematic bias between the two elastography techniques. **Conclusion:** 2D-SWE demonstrated excellent diagnostic accuracy across all fibrosis stages and consistently high NPV for ruling out significant and advanced fibrosis. Its performance was not influenced by the degree of hepatic steatosis. These findings support

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2D-SWE as a reliable, B-mode integrated alternative for non-invasive liver fibrosis assessment.

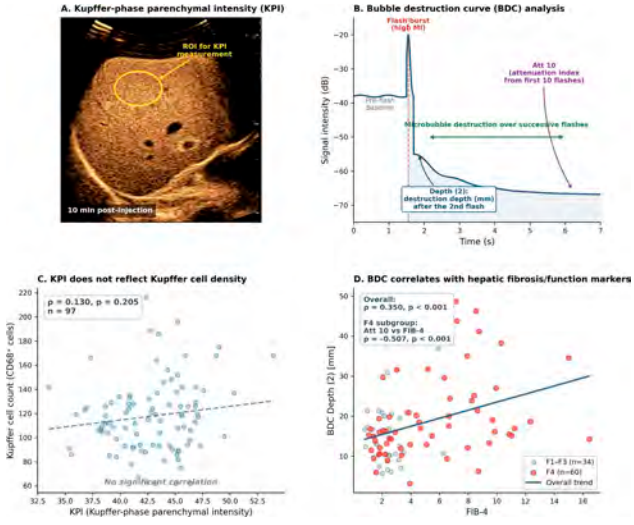


Disclosures: Joao Marcello de Araujo-Neto:Nothing to Disclose, Flavia Fernandes:Nothing to Disclose, Priscila Flores:Nothing to Disclose, Melina Torres:Nothing to Disclose, Mauren Machado:Nothing to Disclose, Larissa Oliveira Miranda:Nothing to Disclose, Ida Arzolla:Nothing to Disclose, Marcio Miguez:Nothing to Disclose, Priscilla Calvet Nelson-Smith:Nothing to Disclose, Adriana Souza e Silva:Nothing to Disclose, Christina Bahia:Nothing to Disclose, Juliana Piedade: Nothing to Disclose, Vania Cristina de Sant`Anna Rocha-Nunnes:Nothing to Disclose, Celia Rotstein: Nothing to Disclose, Claudia Oliveira:Nothing to Disclose, Nothing to Disclose.

3393 | BUBBLE DESTRUCTION CURVE PARAMETERS ON SONAZOID-ENHANCED ULTRASONOGRAPHY REFLECT HEPATIC FUNCTION AND FIBROSIS BEYOND KUPFFER CELL DENSITY: A PROSPECTIVE COMPARISON WITH GADOXETIC ACID–ENHANCED MRI AND PATHOLOGY

Jae Seok Bae[1], [1]Seoul National University Hospital

Background: Kupffer-phase parenchymal brightness on Sonazoid-enhanced contrast-enhanced ultrasonography (Sz-CEUS) is commonly assumed to reflect Kupffer cell (KC) density, but lacks pathological validation. Bubble destruction curve (BDC) analysis—a quantitative parameter from microbubble destruction kinetics in the Kupffer phase—has unclear biological correlates. We evaluated whether Kupffer-phase parenchymal intensity (KPI) and BDC parameters correlate with pathological KC density, hepatobiliary-phase (HBP) enhancement on gadoxetic acid–enhanced MRI (GA-MRI), and noninvasive markers of hepatic function and fibrosis. **Methods:** Ninety-seven patients scheduled for hepatectomy or liver transplantation (68 [70%] HBV; 63 [65%] METAVIR F4) prospectively underwent Sz-CEUS, GA-MRI, and pathology. KPI was measured as median Kupffer-phase parenchymal intensity in a standardized ROI. BDC parameters—attenuation at 10 seconds (Att 10) and Depth (2)—were derived from microbubble destruction time-intensity curves. RSE was measured on HBP MRI; KC density (KCC) by CD68 immunohistochemistry. Spearman and partial correlations adjusted for fibrosis stage were used, with post-hoc F4 subgroup analyses. An AI language model (Claude, Anthropic) was used for language editing; all analyses and conclusions are the authors' responsibility. **Results:** KPI did not correlate with KCC ($\rho = 0.130$, $p = 0.205$) or any reference parameter (RSE, FIB-4, APRI, albumin, total bilirubin; all $p > 0.20$). In contrast, BDC parameters showed consistent associations: Depth (2) correlated with FIB-4 ($\rho = 0.350$), APRI ($\rho = 0.312$), and RSE ($\rho = –0.282$; all $p < 0.01$); similar patterns occurred for Att 10. These BDC associations persisted after fibrosis adjustment (partial ρ 0.275–0.348), indicating information beyond fibrosis stage. RSE itself correlated strongly with FIB-4 ($\rho = –0.565$) and APRI ($\rho = –0.596$; both $p < 0.001$), and KCC was lower in cirrhotic vs non-cirrhotic livers (mean 108 vs 135 CD68+ cells, $p < 0.001$). The BDC–KCC association did not survive fibrosis adjustment. In the F4 subgroup with evaluable BDC (n = 60), BDC–reference associations strengthened (Att 10 vs FIB-4: $\rho = –0.507$, $p < 0.001$; Att 10 vs RSE: $\rho = 0.395$, $p = 0.002$), suggesting BDC may differentiate functional heterogeneity within cirrhotic livers. **Conclusion:** KPI on Sz-CEUS does not reflect pathological Kupffer cell density, challenging a common interpretive assumption. In contrast, BDC parameters from the same examination consistently correlate with noninvasive fibrosis indices, hepatic function markers, and HBP MRI enhancement, with associations preserved after fibrosis adjustment. These findings raise the possibility that BDC reflects properties of the sinusoidal microenvironment (e.g., sinusoidal capillarization) rather than KC number per se, supporting BDC as a candidate noninvasive imaging biomarker of liver function and fibrosis in chronic liver disease.



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3394 | SUBCLINICAL BUT PROGRESSIVE: LONGITUDINAL VCTE AND NONINVASIVE LIVER ASSESSMENT IN TELOMERE BIOLOGY DISORDERS

Sana Pirzada[1] Sawsan Fathma[1] Wesam Aleyadeh[1] Tania Machado[2] Bhavisha Patel[2] Emma Groarke[2] Theo Heller[1], [1]Translational Hepatology Section, Liver Diseases Branch, NIDDK, NIH, Bethesda, MD, USA, [2]Hematology Branch, NHLBI, NIH, Bethesda, MD, USA

Background: Telomere biology disorders (TBD) are rare inherited disorders of telomere maintenance genes. Hepatic involvement occurs in 40–72% of patients and can progress to porto-sinusoidal vascular disease (PSVD) or cirrhosis, yet is often subclinical and missed by routine liver biochemistries. Liver biopsy is often impractical due to thrombocytopenia from bone marrow failure. We aimed to define the burden and longitudinal trajectory of noninvasive hepatic abnormalities, including vibration-controlled transient elastography (VCTE), in a large single-center TBD cohort. **Methods:** We retrospectively identified patients with TBD, defined by a pathogenic germline variant or lymphocyte telomere length <10th percentile by flow-FISH with a compatible phenotype, who underwent at least 1 reliable VCTE (IQR/median $\leq 30\%$). Liver stiffness measurement (LSM) and controlled attenuation parameter (CAP) were collected. LSM ≥ 7.0 kPa was considered suggestive of increased likelihood of fibrosis. A composite liver abnormality was defined as ≥ 1 of the following: LSM ≥ 7.0 kPa, alanine aminotransferase (ALT) >110 U/L, gamma-glutamyl transferase (GGT) >36 U/L, or abnormal liver ultrasound (nodular surface, coarse echotexture, splenomegaly ≥ 13 cm, portal vein >13 mm, collaterals, ascites, or regenerative nodules). Aspartate aminotransferase, alkaline phosphatase, bilirubin, and platelet count were excluded because of frequent extrahepatic confounding. Annualized change in LSM was calculated in patients with serial VCTE. **Results:** 50 patients were included. Median age was 40 years (21.8–63.3), 56% were male, and 85.4% were White. Baseline median LSM was 4.7 kPa (4.0–6.9), and 20% (10/50) had LSM ≥ 7.0 kPa. Median CAP was 224.0 dB/m (198.5–273.5). 2% (1/50) and 30% (15/50) of patients showed abnormal ALT and GGT respectively. 78% (39/50) had at least 1 composite liver abnormality, including enlarged portal vein in 10% and splenomegaly in 14%. Among patients with liver abnormalities, the most common genes were TERT (13/39, 33.3%), TERC (9/39, 23.1%), and RTEL1 (7/39, 17.9%).32 patients underwent serial VCTE over a median follow-up of 2.9 years (1.0–4.0). Of these, 43.8% (14/32) had a positive annualized change in LSM, with a median increase of 0.55 kPa/year (0.21–1.09); LSM ranged from 4.0 to 13.7 kPa, and 34.4% (11/32) had a $\geq 20\%$ increase from baseline. Annualized change in LSM correlated with change in portal vein diameter and spleen size ($r=0.93$, $p<0.0001$; $r=0.65$, $p=0.013$). During follow-up, 90.6% (29/32) had at least 1 composite liver abnormality. **Conclusion:** Liver disease in TBD is often underrecognized early in its course. The association between rising liver stiffness and evolving portal hypertensive features suggests that VCTE and imaging may identify clinically meaningful liver disease before overt presentation, particularly in patients with PSVD. These data support routine noninvasive liver surveillance in TBD.

Disclosures: Sana Pirzada:Nothing to Disclose, Sawsan Fathma:Nothing to Disclose, Wesam Aleyadeh:Nothing to Disclose, Tania Machado:Nothing to Disclose, Bhavisha Patel:Nothing to Disclose, Emma Groarke:Nothing to Disclose, Theo Heller:Nothing to Disclose.

3395 | IMPACT OF GLP1-RECEPTOR ANTAGONISTS ON TIME TO PLATEAUING OF LIVER STIFFNESS MEASUREMENTS

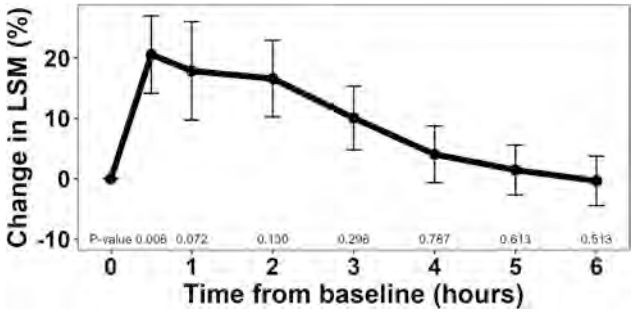
Sunny Sandhu[1] Maria Romero[2] Victoria Fuentes[2] Ruth Canovas[2] Cindy Delgado[2] Sara Patino[3] Farah Alkilani[3], [1]Stanford University School of Medicine, [2]University of Miami Miller School of Medicine, [3]Jackson Memorial Hospital

Background: Patients who receive a liver stiffness measurement (LSM) examination by vibration controlled transient elastography (VCTE) are instructed to fast for at least three hours to ensure accurate results because a meal can increase blood flow to the liver, and therefore, the LSM. GLP1-receptor agonists (GLP-1 RAs) delay gastric emptying, which could lead to a longer period of blood flow to the liver, potentially requiring longer fasting prior to having an VCTE. Our aim was to determine whether GLP1-RAs delay the time to plateauing of LSM following ingestion of a standardized meal. **Methods:** We recruited adults from the hepatology clinic on any GLP1-RA for at least two months, from 9/1/2024-4/30/2026. Participants were instructed to fast for at least 8 hours prior to their visit.

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After obtaining informed consent, participants underwent a baseline LSM by VCTE (FibroScan, Echosnes), followed by intake of a standardized liquid meal (Ensure Plus Drink, Abbot). Subsequently participants had LSM examinations after 30 minutes, 1, 2, 3, 4, 5, and 6 hours. All examinations were reviewed and only included if they met reliability criteria established by Echosens (i.e., at least 10 measurements and an IQR/LSM ratio of <30%). We fit a linear mixed effect model to analyze the effect of a meal on liver stiffness, in which time was the covariate and LSM was the outcome, with participant included as a random effect. **Results:** During the study period, 25 participants consented, but only 23 completed the 6-hour exam and were included. Of the 23 included participants, the median age was 61 years, 16 (69.6%) were female, median BMI was 29.5 (IQR: 26.6-40.2), 21 (91.3%) were White race, 17 (73.9%) were Hispanic, and 17 (73.9%) had MASLD. The median baseline fasting LSM was 13.7kPa (IQR: 13.7-21.3kPa). At 30 minutes after ingesting a standardized meal, the mean percent increase in LSM was 20.6% (± 6.4%), and was relatively stable compared to baseline at the 1-hour (17.8% ± 8.1%) and 2-hour (16.5% ± 6.3%) post-meal ingestion timepoints. By 3 hours, the mean percent increase in LSM was 10.1% ± 5.3%, with near normalization to baseline by four hours (Figure). **Conclusion:** In this study of patients on GLP1 RAs, the mean percent change in LSM after ingesting a standardized meal was 10% at 3 hours, similar to established values for patients not on GLP1 RAs. These data suggest that despite alterations in gastric emptying, patients on GLP1 RAs do not require an extended period of fasting prior to having a Fibroscan.



Disclosures: Sunny Sandhu:Nothing to Disclose, Maria Romero:Nothing to Disclose, Victoria Fuentes: Nothing to Disclose, Ruth Canovas:Nothing to Disclose, Cindy Delgado:Nothing to Disclose, Sara Patino: Nothing to Disclose, Farah Alkilani:Nothing to Disclose.

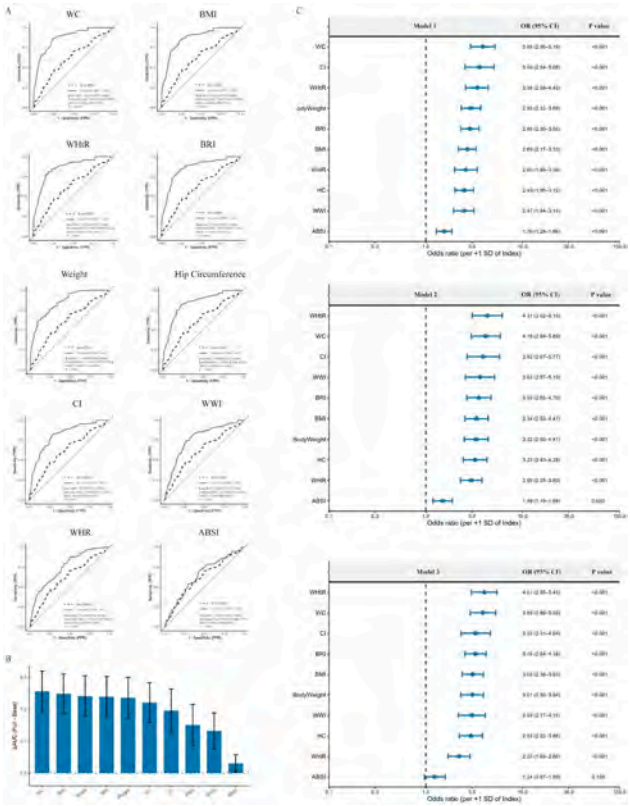
3396 | INTEGRATION OF WAIST CIRCUMFERENCE INTO FIB-4 IMPROVES SCREENING FOR ADVANCED LIVER FIBROSIS IN POPULATION-BASED COHORTS: INSIGHTS FROM NHANES TO A CHINA CLINICAL COHORT

Qiuhong Liu[1] Jie Wang[2] Qi Xia[2] Qing Zhao[2] Wei Wu[2], [1]The First Affiliated Hospital of Zhejiang University School, [2]The First Affiliated Hospital of Zhejiang University School of Medicine

Background: FIB-4 is the standard first-line triage for liver fibrosis screening but frequently underestimates advanced fibrosis in metabolically at-risk individuals. We aimed to evaluate whether anthropometric indices could refine risk stratification within a FIB-4-based framework. **Methods:** We analyzed 5,311 adults from NHANES 2017-2020 (derivation) and 465 patients from a Chinese outpatient cohort (external validation). Advanced fibrosis was defined as liver stiffness measurement (LSM) ≥12 kPa. 10 anthropometric indices were systematically evaluated through multivariable logistic regression (odds ratios [OR]), area under the receiver operating characteristic curve (AUC) and decision curve analysis (DCA). **Results:** Among 5,311 participants, the non-high-risk stratum (FIB-4 <2.67, n =5,175) harbored 138 cases of advanced fibrosis (weighted prevalence 2.9%), accounting for 87.0% of the total advanced fibrosis, while the high-risk stratum (FIB-4 ≥2.67, n =136) identified 30 cases (weighted prevalence 25.6%). While all strata were assessed, significant diagnostic gains from anthropometry were concentrated in the non-high-risk population. Waist circumference (WC) yielded the largest incremental gain compared with only-FIB-4 (AUC 0.874, ΔAUC 0.256; P <0.001) and remained a potent independent predictor (adjusted OR 3.89; P <0.001). A pragmatic WC threshold of 110 cm also effectively enriched risk (AUC 0.807; ΔAUC 0.189; P <0.001). The result was consistent among the FIB-4 <1.3 and 1.3 <FIB-4 <2.67 strata and most subgroups. External Asian validation confirmed a significant improvement in discrimination (AUC 0.756, P =0.017). **Conclusion:** A substantial disease burden overlooked by traditional biochemical triage reside within the FIB-4 non-high-risk population. Incorporating WC as a pragmatic adjunctive tool may offers a simple, scalable strategy to refine risk stratification and prioritize confirmatory assessment.

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Disclosures: QIUHONG LIU:Nothing to Disclose, Jie Wang:Nothing to Disclose, QI XIA:Nothing to Disclose, QING ZHAO:Nothing to Disclose, WEI WU:Nothing to Disclose.

3397 | THE COMPOUNDING BURDEN OF FRAILTY IN CIRRHOSIS: MORTALITY, DECOMPENSATION, AND BEYOND

Chibuzor Nwachukwu[1] Abdulkarim Ben Yezza[2] Rawan Elkomi[2] Suzan Jamal[3] Somtochukwu Abazu[1] Miriam Michael[4], [1]Howard University Hospital, [2]Howard University Hospital Department of Medicine, [3]Howard University Hospital Deoartment of Medicine, [4]Howard University Hospital; University of Maryland Department of Medicine

Background: Cirrhosis carries significant morbidity and mortality, yet risk stratification beyond MELD remains limited. Frailty, cachexia, malnutrition, and sarcopenia are increasingly recognized as prognostically relevant in chronic liver disease, but large-scale real-world evidence is lacking. To this end, we evaluated whether frailty-proxy burden is independently associated with 1-year mortality in adults with cirrhosis using a large federated health network. **Methods:** We conducted a retrospective cohort study using the TriNetX EMEA Collaborative Network (31,983,306 patients; 32 healthcare organizations). Adults aged 18 or older with cirrhosis (ICD-10: K74.60, K74.69, K70.3, K70.30, K70.31), without hepatocellular carcinoma or prior liver transplant, were stratified by presence or absence of frailty-proxy diagnoses (R54 age-related debility, R64 cachexia, E43/E44/E46 malnutrition, M62.84 sarcopenia). The unmatched cohorts included 2,348 patients with frailty-proxy burden and 19,952 without. Propensity score matching in a 1:1 ratio based on age, sex, and race yielded 2,348 patients per group. The primary outcome was all-cause mortality at 1 year. Analyses included risk comparisons and Kaplan Meier survival evaluation. **Results:** After matching, patients with frailty-proxy burden had significantly higher 1-year mortality than matched controls (25.4% vs 21.5%; risk difference 3.9%, 95% CI 1.5–6.3%; risk ratio 1.18, 95% CI 1.07–1.31; p = 0.0015). Kaplan Meier analysis showed lower survival probability at end of follow-up in the frailty-proxy group (69.6% vs 72.4%; log-rank p = 0.106; HR 1.10, 95% CI 0.98–1.24). Median follow-up was 365 days in Cohort A and 363 days in Cohort B. **Conclusion:** In a large real-world cohort of adults with cirrhosis, frailty-proxy burden identified through routine ICD coding was associated with significantly higher 1-year mortality. These findings suggest frailty screening may offer clinical utility for risk stratification in cirrhosis and support further prospective evaluation of frailty-directed interventions in this population.

Disclosures: Chibuzor Nwachukwu:Nothing to Disclose, Abdulkarim Ben Yezza:Nothing to Disclose, Rawan Elkomi:Nothing to Disclose, Suzan Jamal:Nothing to Disclose, Somtochukwu Abazu:Nothing to Disclose, Miriam Michael:Nothing to Disclose.

3398 | MULTIPARAMETRIC HYPERPOLARIZED-^{13}C-MRI FOR SENSITIVE ASSESSMENT OF EARLY-STAGE LIVER DISEASE

Bukola Adebesin[1] Alexander Zavriyev[1] Lena Hsia[1] Jiangsheng Yu[1] Gabor Mizsei[1] Molly Sheehan[1] Rebecca Wells[1] Kelley Weinfurtner[1] Emma Furth[1] Stephen Kadlecek[1] Terence Gade[1], [1]University of Pennsylvania

Background: Optimal locoregional therapy for hepatocellular carcinoma (HCC) requires maximizing oncologic efficacy while mitigating liver injury. Existing clinical staging systems primarily capture late-stage structural damage and hepatic decompensation, with limited sensitivity to early functional decline. Hyperpolarized (HP)-^{13}C-MRI is a powerful technology capable of non-invasively interrogating real-time cellular metabolism and tissue perfusion. We hypothesize that HP-^{13}C-MRI identifies the metabolic and perfusion remodeling that precede structural and functional decline, providing a more sensitive assessment of hepatic

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reserve that is required to inform the selection of locoregional therapy. **Methods:** Chronic liver disease was induced in male Wistar rats via ad-libitum oral administration of diethylnitrosamine (DEN) in drinking water. Rats were randomized into three cohorts (control, 6 weeks, and 12 weeks of DEN exposure) to capture progressive stages of hepatic fibrosis. Simultaneous HP-MRI of 1-^{13} C pyruvate and ^{13} C urea was performed at 7T using an EPSI sequence. Liver tissue was collected for histopathology and immunohistochemistry (H&E, Sirius red, CD45, and Ki-67). **Results:** At 6 weeks of DEN exposure, HP imaging detected an early significant decline in oxidative metabolism (HP Bicarbonate, $p < 0.01$) alongside a sharp increase in HP lactate production ($p < 0.001$), despite a median METAVIR stage of F0. This early metabolic shift coincided with peak inflammation (CD45+, $p < 0.05$) and elevated cellular proliferation (Ki-67+, $p = 0.07$). By 12 weeks, while bicarbonate levels, inflammation, and proliferation stabilized at 6-week levels, HP pyruvate conversion to lactate and alanine, as well as urea perfusion all significantly declined ($p < 0.01$). Underscoring these shifts, HP alanine, lactate, and urea significantly correlated with fibrosis severity on histology ($p < 0.05$) (Fig. 1A-D). **Conclusion:** Our findings demonstrate that HP-^{13} C-MRI non-invasively detects metabolic and perfusion alterations prior to structural fibrotic remodeling, providing a highly sensitive readout of functional liver reserve.At 6 weeks, HP detected early metabolic shifts within a structurally preserved liver landscape. By 12 weeks, metabolic and perfusion signals declined steeply, reflecting the replacement of functional parenchyma with collagen and microvascular impairment due to sinusoidal capillarization. Critically, HP imaging metrics correlated significantly with histological fibrosis severity, establishing a quantitative structural-functional link that underscores the molecular basis of concurrent architectural and physiological liver decline.In conclusion, this technology offers promise as a powerful non-invasive platform for assessing liver function, providing the precise assessment of hepatic reserve necessary to guide locoregional therapy selection and minimize treatment-induced injury.

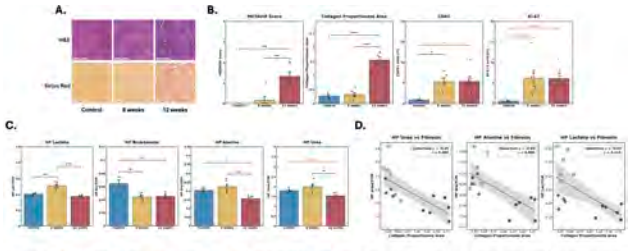


Figure 1: (A) H&E and Sirius red images of the liver from a rat within each of the cohorts. **(B)** Histopathological metrics of fibrosis severity, inflammation, and proliferation for the 3 rat cohorts. The METAVIR score represents the median score of the 3 liver specimens collected per rat. The Collagen Proportionate Area, CD45, and Ki-67 represent the mean of the 3 liver specimens collected per rat. **(C)** HP imaging metrics of cellular metabolism and perfusion for the 3 rat cohorts. TCM = total carbon metabolites (sum of HP pyruvate, lactate, alanine, and bicarbonate). **(D)** Correlation between HP imaging metrics and fibrosis severity on histology for the 3 rat cohorts.

Disclosures: Bukola Adebesin:Nothing to Disclose, Alexander Zavriyev:Nothing to Disclose, Lena Hsia:Nothing to Disclose, Jiangsheng Yu:Nothing to Disclose, Gabor Mizsei:Nothing to Disclose, Molly Sheehan:Nothing to Disclose, Rebecca Wells:Nothing to Disclose, Kelley Weinfurtner:Nothing to Disclose, Emma Furth:Nothing to Disclose, Stephen Kadlecek:Nothing to Disclose, Terence Gade:Nothing to Disclose.

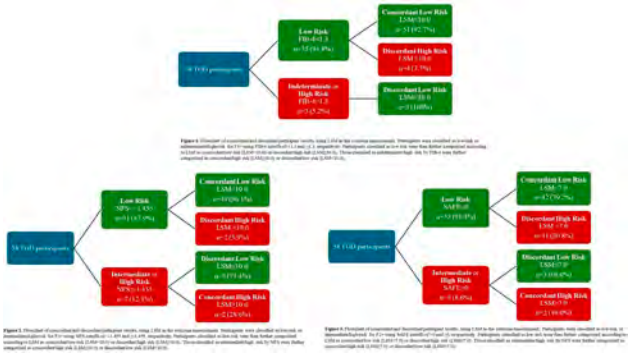
3399 | VARIABLE CONCORDANCE BETWEEN SERUM-BASED FIBROSIS SCORES AND VIBRATION-CONTROLLED TRANSIENT ELASTOGRAPHY IN A GENDER-DIVERSE SAMPLE IN NEWARK, NJ

Tess Olsson[1] Corey DeSteafno[1] Paul Buensuceso[2] Diana Finkel[3], [1]North Jersey Community Research Initiative (NJCRI), [2]Gilead Sciences, [3]Rutgers New Jersey Medical School

Background: Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) has emerged as a leading cause of liver disease in the United States. Non-invasive serum-based tests (NIT), such as the FIB-4, NAFLD Fibrosis Score (NFS), and SAFE score, are used to identify patients at risk for hepatic fibrosis and reduce the need for liver biopsy. However, the relationship between these indices and vibration-controlled transient elastography (VCTE)-defined fibrosis remains poorly characterized, particularly in transgender and gender diverse (TGD) populations. **Methods:** TGD participants (N = 58) were recruited via convenience sampling from a community-based TGD health clinic (March 2025–February 2026) as part of a longitudinal study. Participants completed a survey, venipuncture, and VCTE. NIT (i.e., FIB-4, SAFE, and NFS) were calculated. VCTE fibrosis staging followed manufacturer cutoffs for the liver stiffness measurement (LSM): F0–F1 (< 7.0 kPa), F2 (7–9.9 kPa), and F3–F4 (≥ 10 kPa). Concordance was defined using clinically aligned thresholds for each score relative to VCTE (≥ 10 kPa for FIB-4 and NFS; ≥ 7 kPa for SAFE). **Results:** Concordance between NIT and VCTE varied and was driven primarily by agreement in low-risk classifications. Discordance most commonly reflected misclassification of participants with elevated LSM as low risk. SAFE had the highest discordance relative to VCTE with 19.0% misclassified as low risk, 5.2% misclassified as high risk, 3.5% concordant high risk, and 75.9% concordant low risk. FIB-4 misclassified 6.9% as low risk and 5.2% as high risk, while 87.9% were concordant low risk. NFS demonstrated 84.5% concordant low risk and 3.5% concordant high risk, with 8.6% misclassified as high risk, and 3.4% misclassified as low risk. The majority (91.8%) of the sample had ever taken hormones for gender affirmation, of which the majority (65.6%) were taking estradiol. There were

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no associations between hormone use and discordant results. Discordant SAFE classification was associated with higher CAP scores (p = 0.020), BMI (p = 0.042), and systolic blood pressure (bp) (p = 0.013). FIB-4 discordance was associated with older age (p = 0.011) and higher systolic bp (p = 0.013). NAFLD Fibrosis Score discordance demonstrated the strongest association with age (p = 0.001) and was associated with higher systolic (p = 0.015) and diastolic bp (p = 0.003). **Conclusion:** NIT demonstrated distinct patterns of discordance with VCTE in a TGD population. SAFE discordance was more strongly associated with steatosis-related measures, whereas FIB-4 and NFS discordance were more strongly associated with age and blood pressure. These findings suggest that commonly used fibrosis scores may capture different underlying risk domains and may differentially misclassify fibrosis risk in gender-diverse populations. Further studies with larger sample sizes should continue to explore this topic.

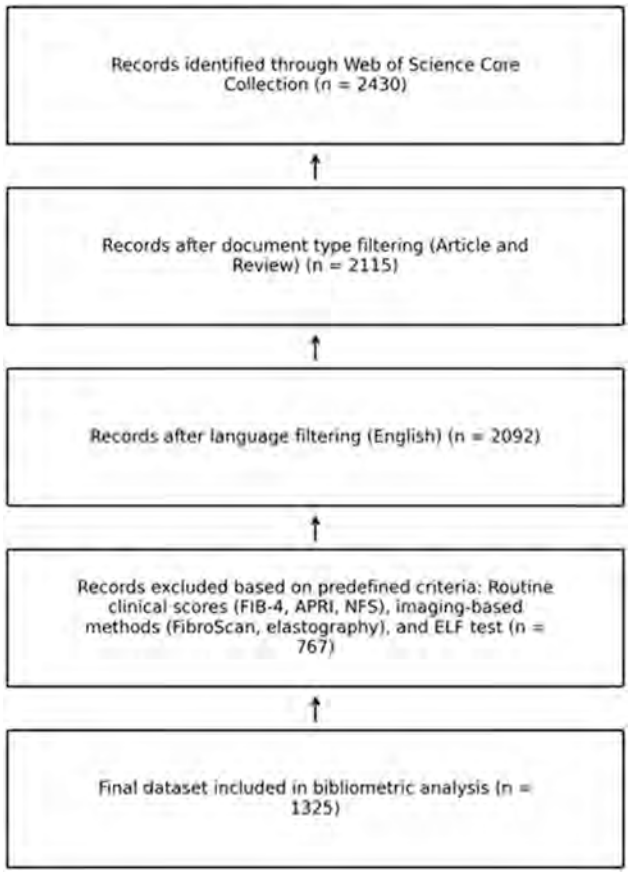


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3400 | EMERGING SERUM BIOMARKERS IN LIVER FIBROSIS: GLOBAL RESEARCH TRENDS FROM A BIBLIOMETRIC ANALYSIS (2010–2025)

Dogan Can Gavcar[1] Nilay Danis[2], [1]Izmir Atatürk Education and Research Hospital, [2]Dokuz Eylül University

Background: Liver fibrosis critically determines the prognosis of chronic liver diseases, making early detection clinically essential. Despite the growing body of publications on serum/plasma biomarkers, the overall trends and thematic structure of this literature remain incompletely characterized. This study aimed to map research trends and the intellectual structure of publications investigating novel experimental serum/plasma biomarkers in liver fibrosis between 2010 and 2025. **Methods:** Publications indexed in the Web of Science Core Collection (SCI-Expanded) from January 2010 to January 2025 were retrieved using a structured search strategy. Studies focused on established non-invasive tests (FIB-4, APRI, NAFLD Fibrosis Score, elastography, ELF) were excluded. A total of 1,325 publications were analyzed. Keyword co-occurrence, co-citation, journal co-citation, and country collaboration networks were constructed using VOSviewer. **Results:** Publication output increased markedly after 2015. Thematic focus shifted from classical extracellular matrix markers toward hepatic stellate cell activation, molecular regulators, and omics-based approaches. Co-citation analysis demonstrated a continuum from fundamental fibrogenesis mechanisms to clinical assessment frameworks. Country collaboration analysis revealed a globally distributed, multi-center research network. **Conclusion:** Future research should prioritize multi-biomarker panels and composite scoring systems over single-marker approaches, alongside analytical standardization and prospective clinical validation.



Disclosures: Dogan Can Gavcar:Nothing to Disclose, Nilay Danis:Nothing to Disclose.

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3401 | THE IMPORTANCE OF ELABELA IN THE DIAGNOSIS OF ADVANCED LIVER FIBROSIS AND CARCINOGENESIS

Monika Pazgan-Simon[1] Grzegorz Popek[2] Ewa Jarowicz[3] Monika Mazur[4] Joanna Górka-Dynysiewcz[5], [1]Department of Infectious Dieases and Hepatology, Wroclaw Medical Inivercity,, [2]Faculty of Computer Science and Telecommunications, Wrocław University of Science and Technology, [3]Regional Specialist Hospital Jerzy Gromkowski, [4]Diagnostyka S.A, Wroclaw, Poland, [5]Department of Pharmaceutical Biochemistry, Faculty of Pharmacy, Wroclaw Medical University

Background: Diagnosing advanced liver disease is a key task for hepatologists today. Traditional biopsy assessment is time-consuming and anxiety-inducing for patients. Liver MRI is a difficult-to-access and expensive procedure. Therefore, we are searching for non-invasive methods for diagnosing advanced fibrosis. Elabela is a hormonal peptide encoded by the APELA gene. It acts via the APLNR receptor. It is produced in embryonic cells, but also in heart, kidney, and endothelial cells, and circulates in serum. Elabela already has an established role in the diagnosis of heart disease, preeclampsia, and acute liver injury.The aim of the project was to evaluate the measurement of Elabela in the diagnosis of advanced fibrosis and hepatic oncogenesis, regardless of the etiology of liver disease. **Methods:** The study included 124 patients with a mean age of 55 years and a mean BMI of 25, including 51 women and 73 men: The study included 125 patients: 32 with no significant fibrosis, 54 with significant fibrosis, 29 with diagnosed hepatocellular carcinoma, and 10 control subjects.Serum elabela levels were measured using an enzyme-linked immunosorbent assay (ELISA) kit (ELK Biotechnology, Denver, USA).Intergroup comparisons were presented as median (interquartile range, IQR) and evaluated using the Levene's test for evaluation of the homogeneity of variance, the Mann-Whitney U-Test for comparison in presence of homoscedasticity, and the non-parametric Brunner-Munzel test for comparison in presence of heteroscedasticity. **Results:** The study demonstrated that serum elabela levels were significantly higher in patients with hepatocellular carcinoma [12.60 (8.12–15.48) ng/mL] compared to no significant fibrosis [11.47 (9.76–12.66) ng/mL, p = 0.00076] and significant fibrosis [6.93 (4.16–11.91) ng/mL, p = 0.0132]. A statistically significant positive correlation was also observed between elabela concentration and disease severity, as assessed by the CTP and MELD scores. **Conclusion:** 1.Elabela appears to be a good marker of advanced fibrosis in patients with liver disease.2. Elabela may serve as a useful biomarker for distinguishing hepatocellular carcinoma from no significant and significant of liver fibrosis.

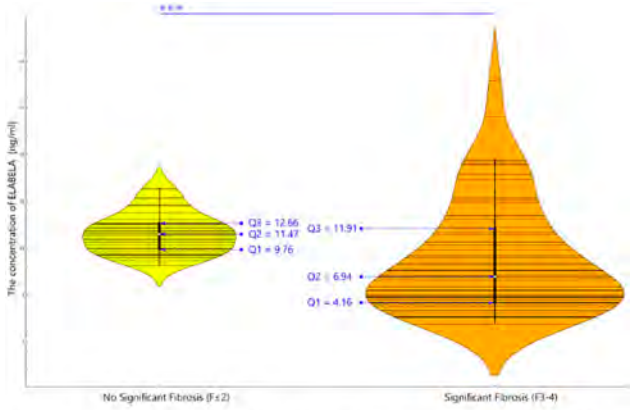


Figure 2. A comparison of the concentration of ELABELA [ng/ml] in patients with No Significant Fibrosis (F≤2) vs patients with Significant Fibrosis (F3-4). A statistically significant difference between the groups was evaluated as *** in Brunner-Munzel Test (used due to heteroscedasticity), p= 0.00030.

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3402 | RETINOIC ACID RECEPTOR SIGNALING PROMOTES LIVER NICHE REMODELING AND FIBROSIS RESOLUTION AFTER ALCOHOL CESSATION VIA MACROPHAGE FIBROLYTIC PHENOTYPE SHIFT

Samson Mah[1] Michael Schonfeld[1] Miki Hodel[1] Kruti Nataraj[1] Isabel Aranzazu Pulido Ruiz[1] Steven Weinman[2] Irina Tikhanovich[2], [1]The University of Kansas Medical Center, [2]University of Kansas Medical Center

Background: Abstinence is beneficial for patients with alcohol-associated liver disease (ALD), but disease resolution after alcohol cessation occurs slowly and only in a subset of patients. Mechanisms of fibrosis resolution in ALD are not yet fully understood. Previous work highlights the importance of liver niche remodeling, a process which occurs around areas of fibrosis and involves protein and metabolite mediated cell-cell crosstalk between hepatocytes and non-parenchymal cells. In this work we aimed to study the role of retinol metabolism in ALD resolution. **Methods:** Mice were fed western diet and 20% alcohol in the drinking water (WDA model of ALD) followed by 4 weeks of disease resolution. We used spatial metabolomics and spatial transcriptomics to assess spatially distinct changes during ALD resolution. Mice were treated with bexarotene (50mg/kg), AC-261066 (10 mg/kg), or AM580

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(5mg/kg) to activate RAR/RXR, or with BMS493 (5mg/kg) to inhibit RAR/RXR. **Results:** We found that retinoic acid metabolism strongly associated with improved fibrosis resolution. Additionally, retinol metabolites were enriched in liver niches characterized by improved ALD resolution in a mouse model. In agreement with these findings, mice treated with RAR agonist AM580 after alcohol cessation showed improved fibrosis resolution. Spatial transcriptomics analysis of agonist treated mice and controls suggested that RAR activation dramatically altered liver niches such as the progenitor-enriched niche, fibrogenic niche, and inflammation-associated niche, in part through macrophage phenotype shift. We confirmed that RAR activation in macrophages resulted in an accumulation of *Marco* high/*Cd163* high/*Vsig4* high macrophages that showed increased fibrolytic activity *in vitro* and *in vivo*.Previously, we identified Serum Amyloid A (SAA), a known retinol transporter, as an important player in fibrolytic niches. We found that SAA promoted fibrosis resolution in part through RAR signaling. RAR inhibition prevented SAA-mediated macrophage phenotype shift and fibrosis resolution in mice, suggesting that the SAA-RAR axis controls macrophage-mediated niche remodeling required for fibrosis resolution in ALD. **Conclusion:** Retinoic acid signaling is necessary and sufficient for improved fibrosis resolution after alcohol cessation. Targeting RAR may be beneficial for disease resolution in patients with ALD.

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3403 | KUPFFER CELL-MEDIATED CLEARANCE OF DENGUE VIRUS FROM THE BLOOD CIRCULATION IS IMPAIRED DURING METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

Erin Fish[1] Kathryn Carpentier[1] Megan Stumpf[1] David Orlicky[1] Sofia Christensen[1] Bennett Davenport[1] Matthew Burchill[1] Thomas Morrison[1], [1]University of Colorado - Anschutz

Background: Dengue virus (DENV) is the most prevalent mosquito-transmitted virus, causing ~500 million infections and 40,000 deaths annually. Efficient DENV transmission depends on the magnitude and duration of viremia in the blood circulation; and high viremia is associated more severe disease. Patient-specific factors also increase morbidity and mortality during infection, including underlying metabolic dysfunction-associated steatotic liver disease (MASLD). Given the liver's important role in surveilling pathogens in the blood, we hypothesized that the liver's ability to control DENV viremia is fundamentally impaired during MASLD, thus resulting in more severe disease. **Methods:** To investigate mechanisms controlling DENV viremia, we developed a murine model of vascular clearance in which we inoculate mice intravenously (IV) with DENV to mimic high viremia and collect serum 15 – 180 minutes post-inoculation (mpi) to assess viral clearance from the blood circulation by RTqPCR. We evaluated clearance in mice fed standard versus MASLD-inducing diets (high-fat high-cholesterol, high-fat, and methionine-choline-deficient); as well as following Kupffer cell (KC) depletion (clodronate-liposomes or *Clec4f-DTR* mice) and scavenger receptor (SR) blockade (IV poly(I) or dextran sulfate). Immune cell populations of interest were further characterized by flow cytometry and bulk RNA sequencing. **Results:** C57BL/6 mice efficiently cleared DENV from the blood by 30 mpi, but clearance was impaired in mice with MASLD, coinciding with a loss of liver KCs. We then specifically depleted KCs, which also resulted in impaired clearance. Upon KC loss, bone marrow-derived macrophages (BMDMs) repopulate KCs within days. However, one week after KC depletion and repopulation, DENV clearance remained impaired, suggesting that functional differences between tissue-resident KCs and BMDMs contribute to delayed clearance. KCs express several SRs that function in pathogen surveillance of the blood. When mice were injected with SR blocking reagents before DENV inoculation, clearance was impaired. These data suggest a KC-expressed SR mediates clearance. We then performed bulk RNA sequencing on isolated mouse KCs and BMDMs and identified several SRs that are more highly expressed by KCs than BMDMs that may contribute to KCs' ability to efficiently clear DENV. **Conclusion:** Our studies defined key host factors involved in DENV clearance from the blood circulation, including liver KCs and a SR, suggesting that alterations to these cells or molecules may promote high viremia in individuals and populations. Moreover, we found that MASLD-induced loss of KCs impairs clearance of DENV, and that repopulation by BMDMs is not sufficient to restore clearance, suggesting a mechanism for more severe disease in patients with MASLD. Collectively, this work improves our understanding of the role of liver KCs in pathogen defense in both healthy and liver disease states.

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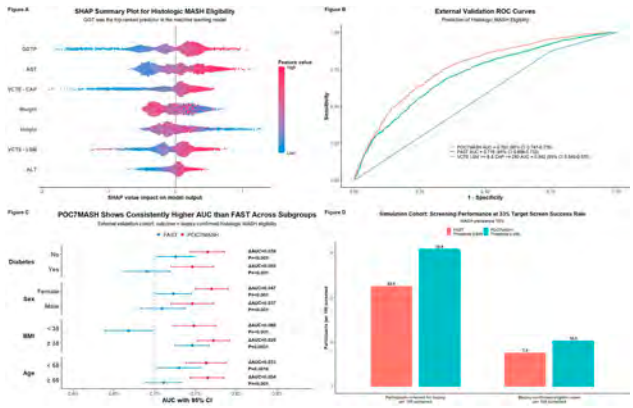
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3404 | ◆ NONINVASIVE POINT-OF-CARE PRESCREENING STRATEGIES FOR NON-CIRRHOTIC MASH CLINICAL TRIALS USING MACHINE LEARNING

Winston Dunn[1] Mazen Noureddin[2] Elizabeth Brombosz[3] Gražina Binkauskiene[3] Rashmee Patil[4] Rohit Puskoor[5] David Huang[6] Nirupama Esther Jerome[5] John Poulos[7] Alaa Abousaif[8] Aasim Sheikh[9] Alma Laura Ladrón de Guevara[10] Marcelo Kugelmas[11] Mousab Tabbaa[12] Sam Moussa[13] Vlad Ratziu[14] Meena Bansal[15] Jörn Schattenberg[16] Naim Alkhouri[17],
[1]University of Kansas Medical Center, [2]Houston Methodist Hospital, Houston Research Institute, Summit Clinical Research Solutions, [3]Summit Clinical Research Solutions, [4]Pinnacle at San Antonio, Summit Clinical Research Solutions, [5]Pinnacle at Austin, Summit Clinical Research Solutions, [6]Houston Research Institute – Main, [7]Coastal Research Institute, [8]Providence St. Joseph Hospital-Orange, [9]GI Specialists of Georgia, [10]CENTRO DE INVESTIGACION Y GASTROENTEROLOGIA, [11]South Denver Gastroenterology, [12]Clinical Research Institute of Ohio, [13]Adobe Clinical Research, [14]Service D' Hepatogastroenterologie (FR), [15]Icahn School of Medicine at Mount Sinai (ISMMS), [16]Saarland University Medical Center, [17]Summit Clinical Research

Background: Non-cirrhotic MASH clinical trials have high liver biopsy screen-failure rates, largely driven by failure to meet histologic eligibility criteria. Point-of-care (POC) prescreening algorithms using VCTE, including FAST and CAP ≥280 dB/m with LSM ≥8 kPa, have been proposed. We evaluated a machine learning (ML)–based prescreening strategy using point-of-care Piccolo Xpress® Chemistry Analyzer and VCTE variables compared with FAST and a standard VCTE-based strategy. **Methods:** A total of 3,511 patients were included in the derivation cohort, of whom 1,159 had biopsy-confirmed MASH meeting histologic eligibility criteria. Clinical, VCTE, and Piccolo variables underwent SHAP-based feature selection and ML optimization exclusively within the derivation cohort to avoid data leakage. External validation was independently performed in an independent cohort of 3,618 patients, including 1,392 biopsy-confirmed eligible cases. A simulation cohort with 15% prevalence was generated to model community screening and evaluate a 33% liver biopsy screen-success rate. **Results:** The top seven SHAP-ranked variables in descending order were GGT, AST, CAP, weight, height, and LSM. SHAP analysis demonstrated that GGT was the highest-ranking predictor (Figure A). In external validation, the ML-derived POC6MASH score demonstrated significantly superior discrimination compared with FAST and the standard VCTE-based strategy (CAP ≥280 dB/m and LSM ≥8 kPa), achieving an AUC of 0.763 (95% CI 0.747–0.779) versus 0.716 (95% CI 0.699–0.733) and 0.595 (95% CI 0.576–0.614), respectively (all $p < 0.0001$) (Figure B). The superiority of POC6MASH over FAST was consistently observed across all major clinical subgroups, including diabetes status, sex, BMI, and age categories (Figure C). In the simulation cohort targeting a 33% liver biopsy screen-success rate, POC6MASH identified 10.3 biopsy-confirmed eligible cases per 100 screened participants, compared with 7.6 cases for FAST, representing a 35.5% increase in biopsy-confirmed eligible case identification (Figure D). **Conclusion:** A web- and ML–based POC prescreening strategy significantly improved identification of patients meeting histologic eligibility criteria for non-cirrhotic MASH clinical trials compared with conventional prescreening. Notably, GGT emerged as the single most important predictor of histologic eligibility yet is not incorporated into current prescreening algorithms. https://aihepatology.shinyapps.io/POC7MASH/



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3405 | ◆ FASTING HYPERINSULINEMIA IS MORE TIGHTLY ASSOCIATED WITH PROGRESSIVE LIVER DISEASE IN MASLD THAN POSTPRANDIAL INSULIN LEVELS

Fernando Bril[1] Michael McPhaul[2] Kenneth Cusi[3], [1]University of Alabama at Birmingham, [2]UT Southwestern, [3]University of Florida

Background: The development of MASLD, and its progression to MASH and clinically significant fibrosis are closely linked to insulin resistance and hyperinsulinemia. However, insulin levels may be quite different in the fasting versus postprandial state, representing different pathophysiologic processes. While fasting hyperinsulinemia may reflect hepatic insulin resistance, postprandial hyperinsulinemia also accounts for skeletal muscle insulin resistance. Little is known as to whether fasting or postprandial hyperinsulinemia preferentially drives liver disease in patients with MASLD. **Methods:** We included in this study patients with available liver histology, as well as an oral glucose tolerance test with insulin levels available at 0, 30, 60, 90, and 120 minutes (n = 222). Patients on insulin therapy were excluded (only metformin and sulfonylureas were allowed). Based on median fasting insulin levels (< 11.5 vs. ≥ 11.5 μU/mL) as well as median incremental insulin levels[MM1] during the OGTT (< 6405 vs. ≥ 6405 μU/mL · min), patients were divided in 4 groups: low fasting and postprandial levels ('both LOW'), high fasting and low postprandial levels ('HIGH fasting only'), low fasting and high postprandial levels ('HIGH postprandial only'), and high fasting and postprandial levels ('both HIGH'). A subset of patients (n = 122) underwent a hyperinsulinemia euglycemic clamp to measure insulin sensitivity. **Results:** A total of 222 patients were included (53 ± 11 years, 77% male, 34.1 ± 4.4 kg/m^2, 65% with diabetes, A1c 6.4 ± 0.9%). **Table 1** summarizes the characteristics of the 4 groups and overall results. As can be observed, all groups had similar liver fat accumulation (p = 0.24), and except for the 'both LOW' group, they also had similar BMI. Patients in the 'HIGH postprandial only' group had the second worst whole-body insulin sensitivity based on Matsuda Index and insulin-stimulated glucose uptake. Despite this, this group had lower liver fibrosis (mean stage 0.3 ± 0.6, p < 0.001 against other groups) and lower overall activity score (NAS: 3.2 ± 1.6, p = 0.006). Only 4.3% of this group had clinically significant fibrosis, as compared to 26.7% and 18.8% in the 'HIGH fasting only' and 'both HIGH' groups, respectively (p = 0.004). Of note, the group with 'HIGH postprandial only' had a similar prevalence of clinically significant fibrosis as the 'both LOW' group. **Conclusion:** Our results suggest that fasting insulin, rather than postprandial insulin levels, may play a more central role in liver disease progression in MASLD. These findings raise the possibility that chronic basal hyperinsulinemia may be more relevant to hepatic inflammation and fibrogenesis than exaggerated meal-stimulated insulin responses. Further studies are needed to determine whether interventions specifically aimed at reducing fasting hyperinsulinemia may alter the natural history of MASLD and fibrosis progression.

	Both LOW (n=66)	HIGH fasting (insulin) only (n=45)	HIGH postprandial (insulin) only (n=47)	Both HIGH (n=64)	p value
Age (years)	55 ± 10	57 ± 10	48 ± 12	52 ± 11	<0.001
Sex (M/F %)	77/23	84/16	64/36	81/19	0.083
BMI (kg/m^2)	32.4 ± 4.4	35.8 ± 4.4	34.1 ± 3.9	34.7 ± 4.2	<0.001
Prevalence of prediabetes or diabetes (%)	92%	100%	94%	94%	0.26
A1c (%)	6.6 ± 0.9	7.3 ± 0.9	5.8 ± 0.5	6.1 ± 0.7	<0.001
Liver fat by ^{1}H-MRS (%)	13 ± 8	15 ± 8	14 ± 10	17 ± 10	0.24
Inflammation grade	1.5 ± 0.7	1.7 ± 0.5	1.3 ± 0.6	1.7 ± 0.5	0.001
Ballooning grade	0.5 ± 0.6	0.5 ± 0.5	0.5 ± 0.5	0.6 ± 0.5	0.65
NAS	3.6 ± 1.5	3.9 ± 1.6	3.2 ± 1.6	4.2 ± 1.4	0.006
Fibrosis stage	0.6 ± 0.8	1.2 ± 1.2	0.3 ± 0.6	1.0 ± 1.0	<0.001
Prevalence of F2-F4 (%)	7.6%	26.7%	4.3%	18.8%	0.004
HOMA-IR	2.1 ± 1.1	7.7 ± 5.0	2.0 ± 0.8	6.8 ± 3.6	<0.001
Whole body insulin sensitivity (Matsuda Index)	5.1 ± 1.9	2.0 ± 0.6	3.5 ± 1.1	1.39 ± 0.5	<0.001
Insulin-stimulated glucose uptake (mg/kg/min)	5.1 ± 2.1	3.3 ± 1.1	4.9 ± 1.8	3.4 ± 1.4	<0.001
Fasting insulin (μU/mL)	6.5 ± 2.5	19.7 ± 10.2	7.4 ± 2.4	23.0 ± 11.8	<0.001
Incremental insulin AUC during OGTT (μU/mL · min)	3272 ± 1717	3436 ± 1581	8708 ± 2964	13978 ± 6782	<0.001

Disclosures: Fernando Bril:NovoNordisk: Consultant, NovoNordisk: Speaking and Teaching, Boehringer Ingelheim: Consultant, Madrigal: Consultant, Boehringer-Ingelheim: Speaking and Teaching, Michael McPhaul:Nothing to Disclose, Kenneth Cusi:Amgen, Boehringer, Echosens, LabCorp, Lilly, Perspectum: Grant/Research Support, Boehringer, BMS, Echosens, Lilly, Novo, GSK, Zealand: Consultant.

3406 | ◆ CIRCULATING PROTEOMIC SIGNATURES OF FIBROSIS REGRESSION IN MASLD PATIENTS UNDERGOING LIFESTYLE INTERVENTION

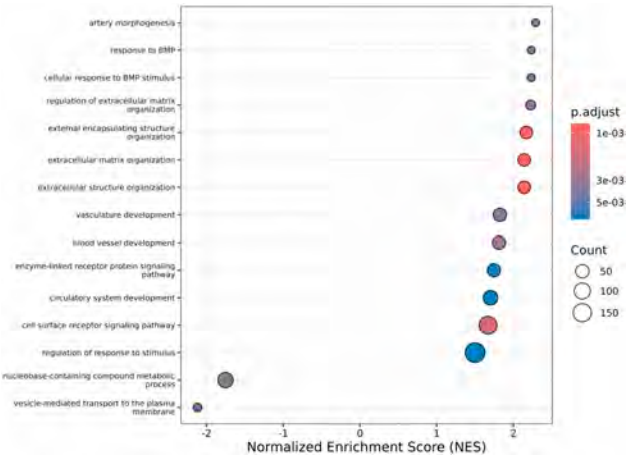
Rocío Muñoz Hernández[1] Carmen Lara Romero[2] Rocio Aller[3] Sheila Gato-Zambrano[2] Antonio Gil-Gómez[2] Maria De Los Angeles Rojas[1] Vanessa Garcia-Fernandez[4] Javier Perez-Florido[5] Miguel Fernández -Gómez[6] Maria Calero[2] Carola Zurita[2] Paloma Carrillo-Fernández[2] Blanca Escudero[2] Genoveva Berná[7] Raquel Millán Domínguez[2] Isabel Fernandez[2] Franz Martin[7] Javier Castell-Monsalve[8] Manuel Romero-Gómez[9], [1]Instituto de Biomedicina de Sevilla, [2]Seliver Group. Institute of Biomedicine of Seville (IBiS)University of Seville, Seville, Spain, [3]Digestive Diseases Unit, University Hospital of Valladolid, Valladolid, Spain, [4]Instituto de Biomedicina de Sevilla (IBiS), [5]Platform of Computational Medicine, Andalusian Public Foundation Progress and Health-FPS, 41013 Sevi, [6]Sports and Health Activities Service

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Background: MASLD is a major cause of chronic liver disease, for which lifestyle interventions are the first-line therapy and improve steatosis and fibrosis; however, the molecular mechanisms underlying fibrosis regression remain poorly understood. We aimed to characterize longitudinal proteomic changes and identify differential signatures between fibrosis responders and non-responders. **Methods:** A prospective longitudinal study included 96 MASLD patients undergoing a combined dietary and supervised exercise intervention. Clinical and imaging assessments were performed at baseline, 3, and 6 months. Fibrosis regression was defined as a >19% reduction in liver stiffness by magnetic resonance elastography. Circulating proteomic profiling using HPLC–mass spectrometry was conducted at all time points in 46 patients, who were stratified as fibrosis responders (n = 13) and non-responders (n = 28). **Results:** Differential proteomic expression analysis comparing baseline and 6 months post-intervention identified changes in 75 proteins with a raw p-value <0.05 and log2 fold change (log2FC) >1. However, after adjustment for multiple comparisons, only two proteins remained statistically significant. Both proteins, PSMA4 (log2FC = −1.91; p = 0.025) and PCBP1 (log2FC = −1.91; p = 0.042), were significantly downregulated in patients who exhibited fibrosis improvement, suggesting their potential association with a favorable response to the lifestyle intervention and a shift towards improved cellular homeostasis, with reduced proteostasis- and oxidative stress-related signaling. Functional enrichment analysis identified 34 significantly altered biological processes, of which the 15 most relevant are shown in Fig.1. Thirteen of these pathways displayed a positive normalized enrichment score (NES), indicating increased activity in patients who exhibited fibrosis improvement. Among the most prominent processes were extracellular matrix organization, extracellular structure organization, and vasculature development. The enrichment of these pathways in fibrosis responders likely reflects active tissue remodeling and repair processes, rather than ongoing fibrogenesis, supporting a dynamic model of fibrosis regression. **Conclusion:** Fibrosis regression following lifestyle intervention in MASLD patients is associated with a coordinated shift in the circulating proteome, characterized by the downregulation of stress-related proteins, including PSMA4 and PCBP1, together with the activation of biological pathways involved in extracellular matrix remodeling and tissue repair. These findings support a model in which fibrosis improvement reflects an active process of hepatic reprogramming, marked by resolution of cellular stress and dynamic tissue remodeling, highlighting potential proteomic signatures of therapeutic response.



Disclosures: Rocío Muñoz Hernández:Nothing to Disclose, Carmen Lara Romero:Nothing to Disclose, rocio aller:Nothing to Disclose, Sheila Gato-Zambrano:Nothing to Disclose, Antonio Gil-Gómez:Nothing to Disclose, Maria De Los Angeles Rojas:Nothing to Disclose, Vanessa Garcia-Fernandez:Nothing to Disclose, Javier Perez-Florido:Nothing to Disclose, Miguel Fernández -Gómez: Nothing to Disclose, Maria Calero:Nothing to Disclose, Carola Zurita:Nothing to Disclose, Paloma Carrillo-Fernández:Nothing to Disclose, Blanca Escudero:Nothing to Disclose, Genoveva Berná:Nothing to Disclose, RAQUEL MILLÁN DOMÍNGUEZ:Nothing to Disclose, Isabel Fernandez:Nothing to Disclose, Franz Martin:Nothing to Disclose, JAVIER CASTELL-MONSALVE:Nothing to Disclose, Manuel Romero-Gómez:Nothing to Disclose.

3407 | ◆ LINKING LIVER TO BRAIN: THE MEDIATING ROLE OF LIVER STIFFNESS IN MASLD-ASSOCIATED NEUROVASCULAR DYSFUNCTION

Zhuoru Jiang[1] Qian Chen[1] Jun Chen[2] Jie Li[3], [1]Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University, [2]Mayo Clinic Rochester, [3]Nanjing Drum Tower Hospital

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is increasingly linked to cognitive decline, yet the specific hepatic drivers of neurovascular coupling (NVC) dysfunction remain poorly understood. This study aimed to investigate the independent contributions of liver stiffness and steatosis to NVC alterations and to elucidate the mechanistic pathways within the liver-brain axis. **Methods:** A total of 130 participants (98 MASLD patients and 32 age- and education-matched healthy controls) underwent comprehensive clinical assessment,

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neuropsychological testing, and multi-modal MRI. Liver stiffness and fat content were quantified using MR elastography (MRE) and MRI-proton density fat fraction (PDFF). NVC was indexed by the ratio of CBF to regional homogeneity (ReHo). Multivariable regression and mediation analyses were employed to identify independent predictors and mechanistic pathways. **Results:** Compared to healthy controls and patients with low liver stiffness (MASLD_low), patients with high liver stiffness (MASLD_high) exhibited significantly reduced NVC values, primarily localized to the bilateral superior temporal gyrus (TPOsup). Multivariable regression revealed that liver stiffness, rather than steatosis or liver enzymes, was the sole independent predictor of NVC deficits (P < 0.001). Furthermore, mediation analysis demonstrated that the impact of hepatocellular injury on neurovascular function was fully mediated by elevated liver stiffness (indirect effect 95% CI: 0.054–0.285). **Conclusion:** These findings suggest that MRE-defined liver stiffness is associated with altered resting-state perfusion-functional coupling in MASLD and may serve as a promising imaging marker of early neurological involvement.

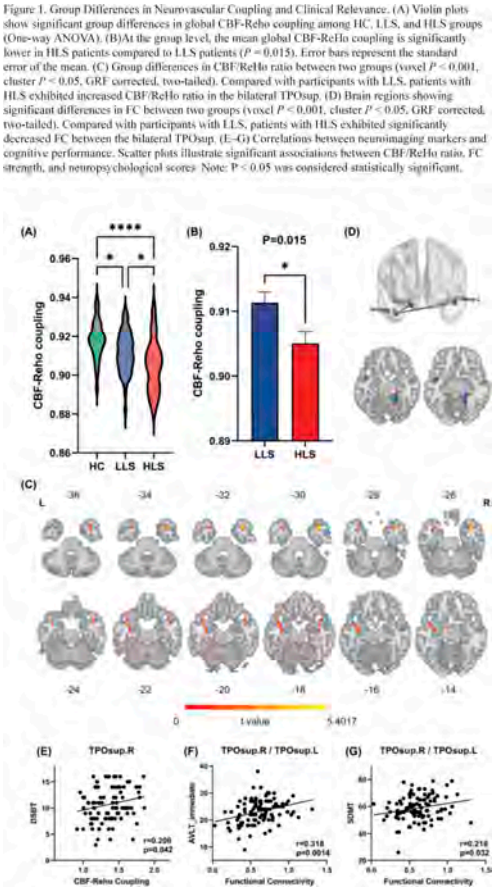


Figure 1. Group Differences in Neurovascular Coupling and Clinical Relevance. (A) Violin plots show significant group differences in global CBF-Reho coupling among HC, LLS, and HLS groups (One-way ANOVA). (B)At the group level, the mean global CBF-ReHo coupling is significantly lower in HLS patients compared to LLS patients (P = 0.015). Error bars represent the standard error of the mean. (C) Group differences in CBF/ReHo ratio between two groups (voxel P < 0.001, cluster P < 0.05, GRF corrected, two-tailed). Compared with participants with LLS, patients with HLS exhibited increased CBF/ReHo ratio in the bilateral TPOsup. (D) Brain regions showing significant differences in FC between two groups (voxel P < 0.001, cluster P < 0.05, GRF corrected, two-tailed). Compared with participants with LLS, patients with HLS exhibited significantly decreased FC between the bilateral TPOsup. (E–G) Correlations between neuroimaging markers and cognitive performance. Scatter plots illustrate significant associations between CBF/ReHo ratio, FC strength, and neuropsychological scores. Note: P < 0.05 was considered statistically significant.

Disclosures: Zhuoru Jiang:Nothing to Disclose, Qian Chen:Nothing to Disclose, Jun Chen:Nothing to Disclose, Jie Li:Nothing to Disclose.

★ 3408 | ◆ 4-HYDROXY-2-NONENAL DIRECTLY INDUCES MITOCHONDRIAL ULTRASTRUCTURAL INJURY IN MASLD

Hidenori Kido[1] Takuya Seike[1] Masahiro Yanagi[1] Andon Mladenov[1] Eishiro Mizukoshi[2] Tetsumori Yamashima[1] Taro Yamashita[1], [1]Kanazawa University, [2]Kanazawa Medical University

Background: Oxidative stress and mitochondrial dysfunction are key features of MASLD progression, but mechanisms linking lipid peroxidation to hepatocellular organelle injury remain unclear. 4-Hydroxy-2-nonenal (4-HNE), a reactive aldehyde derived from omega-6 polyunsaturated fatty acids, accumulates in MASLD and modifies proteins and membranes through covalent adduct formation. We investigated whether HNE directly induces mitochondrial ultrastructural injury in hepatocytes. **Methods:** We analyzed liver tissues from 28 patients (MASLD, n = 25; non-MASLD, n = 3) and HNE-treated models. HepG2 cells were treated with 100 μM HNE. Male C57BL/6 mice received saline, 5 mg/kg HNE, or 10 mg/kg HNE three times weekly (n = 15/group), with livers collected at 4 and 8 weeks. Female Japanese macaques received saline (n = 2) or intramuscular HNE at 5 mg/week for 24 weeks (n = 3), with serial blood tests, ultrasonography, and liver biopsy. Cell mitochondria were assessed by Mito-Tracker time-lapse imaging and TEM. In liver tissues, HNE accumulation was evaluated by Western blotting and immunohistochemistry. Mitochondrial ultrastructure was scored by TEM and quantified using ImageJ for electron density, cross-sectional area, and aspect ratio. Statistical comparisons were performed using the Mann–Whitney U test, and correlations were assessed using Spearman's rank correlation coefficient. **Results:** MASLD patients showed greater hepatic HNE accumulation than non-MASLD controls (p = 0.008) and higher mitochondrial TEM injury scores (p = 0.039). Mitochondrial TEM scores correlated with hepatic HNE accumulation (r = 0.502, p = 0.01) and NAFLD activity score (r = 0.750, p < 0.0001). In HepG2 cells, time-lapse imaging and TEM revealed disruption of individual mitochondrial membranes and reduced mitochondrial number after HNE treatment. In HNE-treated mice and macaques, hepatic HNE deposition was accompanied by spherical mitochondrial deformation and disrupted cristae. Quantitative analysis of > 500 mitochondria/group showed increased electron density, enlarged cross-sectional area, and aspect ratios closer to 1 in HNE-treated groups, indicating mitochondrial swelling and spherical remodeling (all p < 0.0001). **Conclusion:** HNE accumulation is associated with disease activity and mitochondrial ultrastructural injury in MASLD liver. Across cell, mouse, and

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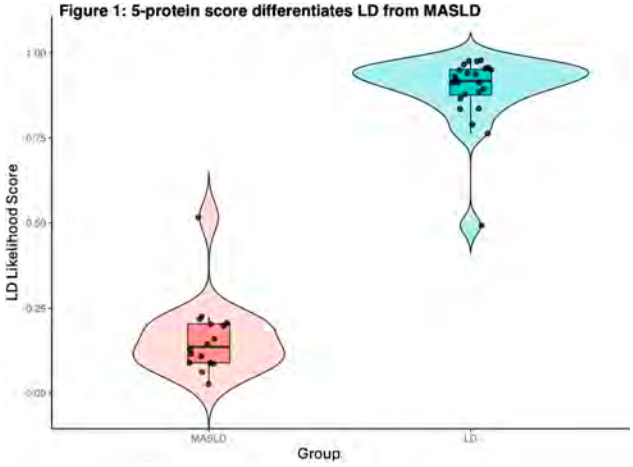
nonhuman primate models, HNE directly induced mitochondrial membrane disruption, cristae disorganization, swelling, and spherical remodeling. HNE may be a pathogenic mediator linking lipid peroxidation to mitochondrial injury in MASLD and a potential therapeutic target.

Disclosures: Hidenori Kido:Nothing to Disclose, Takuya Seike:Nothing to Disclose, Masahiro Yanagi: Nothing to Disclose, Andon Mladenov:Nothing to Disclose, Eishiro Mizukoshi:Nothing to Disclose, Tetsumori Yamashima:Nothing to Disclose, Taro Yamashita:Nothing to Disclose.

3409 | DOES LIPODYSTROPHY CONTRIBUTE TO LEAN MASLD? A PLASMA PROTEOMIC STUDY

Wesam Aleyadeh[1] Maria Mironova[2] Carolin Victoria Schneider[3] Rebecca Brown[4] Yaron Rotman[1], [1]National Institute of Diabetes and Digestive and Kidney Diseases; National Institutes of Health, [2]UCSD, [3]RWTH Aachen, [4]NIDDK, NIH

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is defined by hepatic steatosis in the presence of metabolic risk factors. A subset of people with MASLD are lean, yet it is unclear if these represent a distinct entity or are similar to adiposity-associated MASLD. In lipodystrophy (LD), a rare disorder of adipose tissue deficiency characterized by severe insulin resistance, hepatic steatosis and steatohepatitis can occur in the absence of obesity. Genetic LD-like features may contribute to MASLD pathogenesis. We hypothesized that some people with lean MASLD share pathophysiologic features with LD and developed a plasma proteomic score to identify LD-like features in MASLD. **Methods:** Plasma proteins were measured using SomaScan 7K in patients aged ≥ 12 years with LD (n = 24) or MASLD (n = 16). Analytes were filtered for cross-platform compatibility between SomaScan and the UK Biobank (UKB) Olink proteomic assay to enable external validation. Differentially expressed proteins (FDR q < 0.05) were used for unsupervised hierarchical clustering. A parsimonious score was derived by elastic net logistic regression with nested cross-validation (10 folds, 10 repeats). The score was applied to UK Biobank (UKB) participants with available proteomics (n = 22,287) to seek individuals with LD-like phenotype. **Results:** LD and MASLD patients in the derivation group had marked insulin resistance (median HOMA-IR 11.6 [IQR 6.6–29.5] in LD vs 6.5 [5.8–9.5] in MASLD), with similar rates of steatohepatitis and cirrhosis among those biopsied. Of 7,481 measured proteins, 1,816 passed cross-platform filtering and 116 were differentially expressed. Unsupervised hierarchical clustering and principal component analysis showed complete separation of LD from MASLD. A 5-protein (SFRP1, GBA, F9, TIMP4, FCN1) LD-likelihood score > 0.65 differentiated the groups with no overlap ($p < 0.001$), with a cross-validated AUC of 0.961 (95% CI 0.893–1.000) and Brier score of 0.083. There were 7320 UKB participants with BMI < 25, of whom 31 (0.4%) had high (> 0.65) LD-likelihood. 1127 individuals had potential lean steatotic liver disease (SLD) (ALT > 40 and/or GGT > 40), of whom only < 5 (< 0.4%) had high LD-likelihood. Using unsupervised clustering based on all 116 differentially expressed proteins, subjects with potential lean SLD and high LD scores did not cluster with patients with LD. In a subset of 763 UKB participants with MR-PDFF-defined steatosis, no lean individual had high LD-likelihood. The score was not correlated with hepatic fat fraction, and body composition measures were similar across score categories. **Conclusion:** A 5-protein plasma proteomic score distinguishes LD from MASLD. Most individuals with lean SLD have proteomic features consistent with "regular" MASLD. Our findings do not support a contribution of LD to lean MASLD.



Disclosures: Wesam Aleyadeh:Nothing to Disclose, Maria Mironova:Nothing to Disclose, Carolin Victoria Schneider:Nothing to Disclose, Rebecca Brown:Pfizer: Grant/Research Support, Marea: Grant/Research Support, Regeneron: Grant/Research Support, Chiesi: Grant/Research Support, Yaron Rotman:Nothing to Disclose.

3410 | A HERITABLE TRANSFERRIN-RECEPTOR AXIS TRACKS HEPATIC IRON IN MASLD: A TWIN STUDY

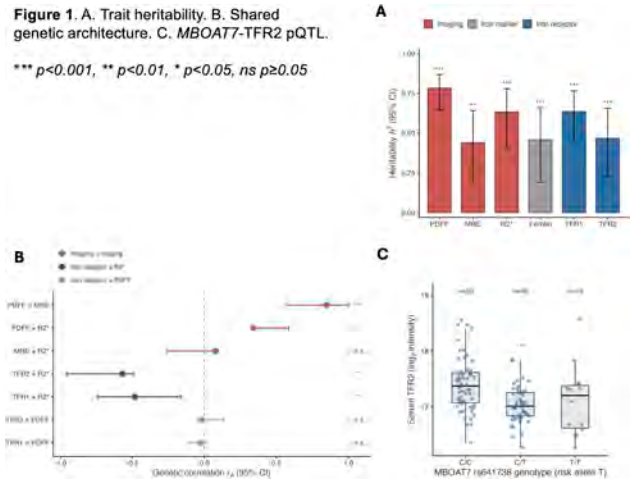
Maria Mironova[1] Igor Wierzbicki[1] Chi-Hua Chen[1] Veeral Ajmera[2] Kaleb Tesfai[1] Seema Singh[1] Egbert Madamba[1] Mary Dalupang[1] Samir Gupta[1] Shailja

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Shah[1] Tatiana Kisseleva[2] Amit Majithia[1] Claude Sirlin[1] David Gonzalez[1] Rohit Loomba[2], [1]UCSD, [2]University of California, San Diego

Background: MASLD is present in up to 30% of adults globally. Iron overload may affect approximately 30% of people with MASLD and is prognostic for fibrosis progression. The aim of this study was to examine whether hepatic iron in MASLD reflects an independently heritable axis or is genetically co-inherited with steatosis and fibrosis in a unique well-characterized twin cohort. **Methods:** From a prospectively enrolled twin cohort we identified an analytic cohort of 118 subjects – 42 monozygotic and 17 dizygotic pairs with available clinical laboratory data, MRI-PDFF, MRE and R2* on both co-twins and plasma proteomics (approximately 850 proteins measured with Orbitrap-Astral MS), and six MASLD-GWAS SNPs (*PNPLA3, MBOAT7, TM6SF2, GCKR, HSD17B13, MARC1*). Univariate and bivariate AE models, which partition phenotypic variance into additive genetic (A) and unique environmental (E) components, were used to estimate heritability (h^2) and genetic correlation (rA), with age, sex, and race as covariates. Protein-level associated SNPs were estimated using mixed-effects model with family as random intercept. **Results:** This twin-study (N = 118) included 24 participants with MASLD (MRI-PDFF > = 5%) and 94 participants without MASLD (MRI-PDFF < 5%). MASLD twins had higher median BMI (32.3 vs 23.5 kg/m^2), triglycerides (156 vs 72 mg/dL), ALT (22 vs 17 U/L), PDFF (9.0 vs 2.1%), liver stiffness by MRE (2.6 vs 2.2 kPa), and R2* (53.5 vs 45.3 s^{-1}), lower HDL (45 vs 64 mg/dL) – all $p < 0.001$. The traits measured by imaging, including steatosis, fibrosis and hepatic iron content, were heritable, $h^2(PDFF) = 0.78$, $h^2(MRE) = 0.44$, $h^2(R2^*) = 0.64$, as well as serum ferritin ($h^2 = 0.46$, $p = 0.002$).(Fig. 1A) Hepatic iron shared modest heritable architecture with steatosis (rA = 0.34, p = 0.03) but not fibrosis (rA = 0.08, NS). This iron-specific signal converged at transferrin receptors: serum TFR2 ($h^2 = 0.47$) and TFR1 ($h^2 = 0.63$) were strongly inversely genetically correlated with hepatic iron (rA = −0.57 and rA = −0.48, both p = 0.006) but did not correlate with steatosis (rA = −0.02 and −0.03, NS).(Fig. 1B) Furthermore, *MBOAT7* T risk allele significantly lowered serum TFR2 (pQTL $\beta = -0.58$, $p < 0.001$).(Fig. 1C) **Conclusion:** Hepatic iron content in MASLD is heritable, phenotypically distinct from yet partially co-inherited with steatosis. The heritable transferrin-receptor axis tracks hepatic iron through distinct mechanisms. TFR1 follows classical iron-deficiency feedback and increases when iron stores are low. The inverse relationship TFR2-iron is unexpected, since it is normally stabilized by transferrin and increases with iron. The opposite pattern fits inherited low TFR2 acting upstream to raise hepatic iron, like in hemochromatosis type 3, assuming circulating TFR2 reflects hepatic signaling. Transferrin receptor axis along with *MBOAT7* genotype should be further explored as driver of MASLD pathophysiology and disease biomarker.



Disclosures: Maria Mironova:Nothing to Disclose, Igor Wierzbicki:Nothing to Disclose, Chi-Hua Chen:Nothing to Disclose, Veeral Ajmera:Nothing to Disclose, Kaleb Tesfai:Nothing to Disclose, Seema Singh:Nothing to Disclose, Egbert Madamba:Nothing to Disclose, Mary Dalupang:Nothing to Disclose, Samir Gupta:Nothing to Disclose, Shailja Shah:Nothing to Disclose, Tatiana Kisseleva:Nothing to Disclose, Amit Majithia:Nothing to Disclose, Claude Sirlin:Bayer: Grant/Research Support, GE Healthcare: Grant/Research Support, Pfizer: Grant/Research Support, Siemens: Grant/Research Support, Butterfly: Grant/Research Support, AMRA: Grant/Research Support, Perspectum: Grant/Research Support, OrsoBio: Independent Contractor, Prosciento: Independent Contractor, Velocity: Independent Contractor, Bayer: Consultant, Boehringer-Ingelheim: Consultant, Ascelia: Consultant, Livivos: Advisor, Livivos: Executive role, Wolters Kluwer: Royalties or patent beneficiary, HealthPro Match: Speaking and Teaching, Foundation for Care Management: Speaking and Teaching, David Gonzalez:Nothing to Disclose, Rohit Loomba:Eli Lilly and Company: Consultant, 89bio: Consultant, Aardvark Therapeutics: Consultant, Altimmune: Consultant, Alnylam/Regeneron: Consultant, Amgen: Consultant, Arrowhead Pharmaceuticals: Consultant, AstraZeneca: Consultant, Bristol Myers Squibb: Consultant, CohBar: Consultant, Eli Lilly: Consultant, Galmed Pharmaceuticals: Consultant, Gilead: Consultant, Glympse Bio: Consultant, Hightide: Consultant, Inipharma: Consultant, Intercept: Consultant, Inventiva: Consultant, Ionis: Consultant, Janssen, Inc.: Consultant, Madrigal Pharmaceuticals: Consultant, Merck, Metacrine, Inc.: Consultant, NGM Biopharmaceuticals: Consultant, Novartis: Consultant, Novo Nordisk: Consultant, Pfizer: Consultant, Sagimet Biosciences:

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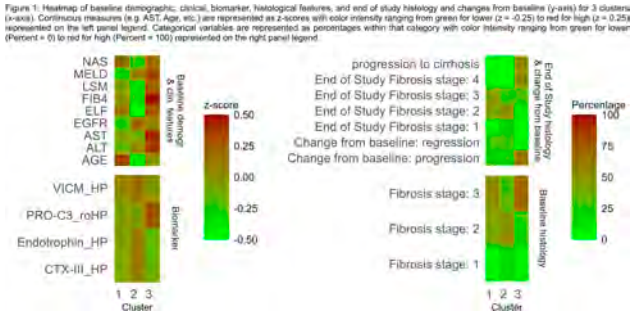
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3411 | A "HOT" INJURY-FIBROGENIC ENDOTYPE IDENTIFIES PATIENTS WITH METABOLIC DYSFUNCTION AND STAGE 2 OR 3 FIBROSIS WHO WILL PROGRESS TO CIRRHOSIS WITHIN FOUR YEARS

Ekaterina Smirnova[1] Mary Erickson[2] Vlad Ratziu[3] Mary Rinella[4] Rina Levya[5] Diana Leeming[6] Andressa de Zawadzki[6] Morten Karsdal[6] Jennifer Sayne[1] Arun Sanyal[1], [1]Virginia Commonwealth University, [2]Alfasigma, [3]Service D' Hepatogastroenterologie (FR), [4]The University of Chicago, [5]Alpfasigma, [6]Nordic Bioscience

Background: Fibrosis can progress or regress in those with pre-cirrhotic MASH and only a 10-20% develop cirrhosis. There is an unmet need to identify those most likely to progress and develop cirrhosis. **Hypothesis:** Distinct fibrogenic endotypes exist within populations with histologically similar MASH and endotypes reflecting injury-inflammation (hot) fibrogenic endotype are more likely to progress. **Methods:** A retrospective analysis of the placebo arm of the REGENERATE trial (NCT02548351) was performed. Four serum biomarkers were evaluated at baseline: VCIM (inflammation), ProC3, Endotrophin (fibrogenesis) and CTXIII (fibrolytic). K-medoid clustering was performed using baseline clinical, laboratory, histological data and outcomes over 48 months. The distribution of these parameters and biomarkers was evaluated across clusters. Regression analyses were used to model profiles at risk of progression to cirrhosis. **Results:** A total of 307 individuals with biopsy-confirmed MASH (stage 1: n = 31, stage 2: n = 124 and stage 3: n = 152) with complete data were analyzed. 1-stage (n = 82) and 2-stage progression (n = 8) with 41 cases of progression to cirrhosis (n = 34 from stage 3, n = 7 from stage 2) occurred by month 48. Fibrosis regression occurred in 69 cases. Three subpopulations were identified via clustering analyses. Cluster 3 was characterized by higher (vs clusters 1 and 2) baseline PROC3, AST, ALT, GGT, FIB4, ELF and liver stiffness measurement (LSM). 36/67 (54%) in cluster 3 progressed to cirrhosis compared to 4/136 (3%) in cluster 1 and 1/104 (1%) in cluster 2 ($p < 0.001$ for both). Those in cluster 3 also experienced greater rates of 1- (n = 36/67, 54%) and 2-stage fibrosis progression (n = 6/67, 9%) compared to cluster 1 (1-stage: n = 27 (20%) and 2-stage (n = 1 (0.7%)) and cluster 2 (1-stage: n = 19, 18%, and 2-stage: n = 1, 1%) $p < 0.001$ for all. Cluster 3 also had lower rates of regression ($p < 0.001$ vs other clusters). Although progression and regression rates were similar for clusters 1 and 2, cluster 2 had significantly lower steatosis, inflammation, ballooning, AST, ALT, GGT, A1C, FIB-4, ELF and LSM. Regression models allowed identification of those at risk of progression to cirrhosis (cluster 3) with an AUROC 0.78. **Conclusion:s:** A "hot" injury-fibrogenesis predominant endotype identifies individuals who will progress to cirrhosis. This is likely to inform future therapeutic targeting, trial-design and precision medicine approaches.



Disclosures: Ekaterina Smirnova:Nothing to Disclose, Mary Erickson:Nothing to Disclose, Vlad Ratziu:Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Mary Rinella:akero: Consultant, akero: Consultant, 89Bio: Consultant, 89Bio: Consultant, Boehringer Ingelheim: Consultant, Boehringer

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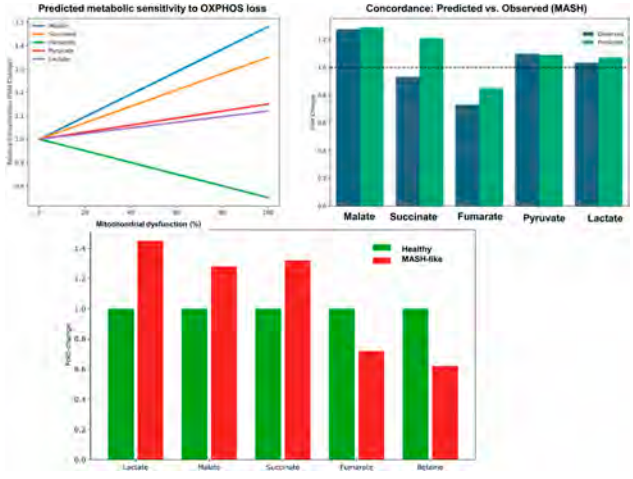
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3412 | KINETIC MODELING OF HEPATIC METABOLISM MAPS MITOCHONDRIAL HETEROPLASMY THRESHOLDS DRIVING CIRCULATING METABOLITE SIGNATURES IN MASH

Carlos Pirola[1] Silvia Sookoian[2], [1]CENITRES, UMAI-CONICET, [2]CONICET-UMAI

Background: Mitochondrial DNA (mtDNA) variants in OXPHOS-encoding genes correlate with histological severity in MASH. However, the quantitative link between specific heteroplasmy burdens and systemic metabolic alterations remains poorly defined. We developed a physiology-based kinetic model to dynamically explore the impact of mtDNA-encoded respiratory chain impairment on perturbations in the TCA cycle and one-carbon metabolism in the liver. **Methods:** We constructed a kinetic model of human hepatocyte metabolism by extending the HEPATOKIN1 framework, comprising 209 reactions across the cytosol, mitochondria, endoplasmic reticulum, and extracellular space. All enzymatic and transport processes were modeled using reversible Michaelis-Menten kinetics with explicit thermodynamic displacement. For respiratory chain complexes I, III, and IV, the rate laws were modified to incorporate the electrochemical driving force of the mitochondrial membrane potential. To simulate disease progression, we mapped mtDNA heteroplasmy burden (0–1) to effective enzymatic capacity (Vmax) using a cooperative Hill function with a phenotypic threshold (K50) at 60% heteroplasmy. Steady-state fold-changes were validated against patient-derived serum metabolomics and liver proteomics. **Results:** Simulations demonstrated that a 65% loss in Complex I capacity—consistent with observed heteroplasmy burdens—precisely recapitulated systemic shifts in TCA cycle intermediates and redox state. Specifically, the model predicted malate accumulation (+28% vs +27–31% observed) and succinate (+32% vs +29.5% observed), with corresponding fumarate depletion (−28% vs −24% observed). While predicted lactate levels (+45%) exceeded observed serum levels (+10%), they correctly captured the direction and order of magnitude of the hepatic redox shift. Furthermore, the model linked betaine insufficiency to a 38% reduction in flux through the mitochondrial dimethylglycine dehydrogenase (DMGDH) reaction, identifying a critical bottleneck in one-carbon metabolism. **Conclusion:** This work provides a mechanistic bridge between mitochondrial genetics and the metabolic landscape of MASH. By identifying a 60% heteroplasmy threshold as a trigger for TCA cycle disruption and betaine depletion, these findings suggest that personalized assessment of mitochondrial functional reserve could improve patient stratification and identify the metabolic thresholds that drive disease progression.



Disclosures: Carlos Pirola:Nothing to Disclose, Silvia Sookoian:Nothing to Disclose.

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★ 3413 | FADS2 RS174583 TT GENOTYPE IDENTIFIES PNPLA3 GG CARRIERS WITH AT-RISK MASH AND A PRO-FIBROGENIC LIPID SIGNATURE

Shunsuke Ikejima[1] Kazuyoshi Kon[1] Hyeon-Cheol Lee[2] Kumiko Arai[1] Kyoko Fukuhara[1] Reiko Yaginuma[1] Kei Ishizuka[1] Hiroo Fukada[1] Akira Uchiyama[1] Shunhei Yamashina[1] Takehiko Yokomizo[2] Kenichi Ikejima[1], [1]Juntendo University Graduate School of Medicine, [2]Juntendo University School of Medicine

Background: At-risk MASH represents a high-risk subgroup of metabolic dysfunction-associated steatotic liver disease (MASLD) with increased risk of cardiovascular events and progression to cirrhosis and hepatocellular carcinoma. In animal models, we have previously shown that reduced expression of fatty acid desaturases (FADS) promotes steatohepatitis. This study investigated the impact of single nucleotide polymorphisms (SNPs) in FADS genes on hepatic lipid profiles and susceptibility to at-risk MASH. **Methods:** We enrolled 51 patients with biopsy-proven MASLD diagnosed between 2021 and 2025 who provided informed consent for SNP analysis. At-risk MASH was defined as NAFLD activity score ≥ 4 and fibrosis stage ≥ 2. Genomic DNA was extracted from peripheral blood, and SNPs were genotyped using TaqMan PCR. In a subset of patients, hepatic lipidomics was performed by LC–MS, and lipid species with $p < 0.05$ and a fold change (FC) ≥ 1.5 between FADS2 rs174583 TT and non-TT genotypes were identified. Cardiovascular burden, including clinical cardiovascular disease and CT-detected atherosclerotic findings, was assessed from medical records. **Results:** Among the 51 MASLD patients, 20 satisfied the criteria for at-risk MASH. While none of the PNPLA3 (rs738409) GG, MBOAT7 (rs641738) CC, TM6SF2 (rs58542926) CT, FADS1 (rs174556) TT, or FADS2 (rs174583) TT genotypes were individually associated with at-risk MASH, a logistic regression model including two SNPs and their interaction term revealed a significant PNPLA3 GG × FADS2 TT interaction for at-risk MASH (interaction OR 29.7, $p = 0.010$). Among 26 carriers of PNPLA3 GG, 10 had at-risk MASH. In this subgroup, univariate analysis identified age, BMI, TM6SF2 CT, FADS1 TT, and FADS2 TT as associated factors, whereas multivariate analysis demonstrated FADS2 TT as the only independent risk factor for at-risk MASH ($p = 0.047$). Notably, cardiovascular burden was observed in 80% of patients with the FADS2 TT genotype, compared with 13% of those with the CC or CT genotypes ($p = 0.002$). Of 13 hepatic lipid species significantly associated with FADS2 TT, α-hydroxyceramides (ahCer d18:1/22:0, d18:1/h24:1, d18:1/h24:0), hydroxy-hexosylceramide (hHexCer d18:1/h24:0), phosphatidylcholine (PC 16:0/20:1), phosphatidylethanolamine (PE 22:6/16:1), and phosphatidylinositol (PI 18:1/20:4) showed strong positive correlations with fibrosis stage ($r \geq 0.7$), whereas cholesterol ester (CE 18:3n-6) and phosphatidylcholine (PC 18:0/18:3n-3) showed strong negative correlations. **Conclusion:** In PNPLA3 GG carriers, the FADS2 rs174583 TT genotype identifies a distinct subgroup characterized by at-risk MASH, frequent cardiovascular burden, sphingolipid accumulation, and depletion of PUFA-containing cholesterol esters and phosphatidylcholines. These findings highlight FADS2-related lipid remodeling as a key modifier linking genetic susceptibility to hepatic fibrosis and cardiometabolic risk.

Disclosures: Shunsuke Ikejima:Nothing to Disclose, Kazuyoshi Kon:Nothing to Disclose, Hyeon-Cheol Lee:Nothing to Disclose, Kumiko Arai:Nothing to Disclose, Kyoko Fukuhara:Nothing to Disclose, Reiko Yaginuma:Nothing to Disclose, Kei Ishizuka:Nothing to Disclose, Hiroo Fukada:Nothing to Disclose, Akira Uchiyama:Nothing to Disclose, SHUNHEI YAMASHINA:Nothing to Disclose, Takehiko Yokomizo:Nothing to Disclose, Kenichi Ikejima:Nothing to Disclose.

3414 | SODIUM-GLUCOSE COTRANSPORTER-2 INHIBITOR MITIGATES KIDNEY INJURIES BY OXIDATIVE STRESS REDUCTION AND ACTIVATION OF AMPK–ADIPONECTIN SIGNALING IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS

Jee-Fu Huang[1] Hugo Y-H Lin[1] Yu-Min Ko[2] Ming-Lun Yeh[1] Wan Long Chuang[3] Ming-Lung Yu[1], [1]Kaohsiung Medical University Hospital, [2]Tajen University, [3]Kaohsiung Medical University

Background: Metabolic dysfunction associated steatotic liver disease (MASLD) contributes to chronic kidney disease (CKD) development. The protective efficacy of sodium-glucose cotransporter-2 inhibitor (SGLT2i), a cardiometabolic drug, in alleviating renal injury in MASLD remains elusive. We constructed a MASLD mouse model aiming to investigate the potential mitigation of renal tubular injury by SGLT2i. **Methods:** Metabolic dysfunction-associated steatohepatitis (MASH) were induced in 8-week-old C57BL/6 male mice using a high-fat diet (HFD) with 5% fructose for 24 weeks. Mice were divided into two groups: dapagliflozin (DPG) group (1 mg/kg/day) and the vehicle group. Metabolic parameters and renal function were assessed through biochemical assays and transmission electron microscopy for mitochondrial ultrastructure analysis. **Results:** DPG-treated mice did not

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exhibit significant weight loss compared to the vehicle group ($p = 0.11$). However, DPG group significantly improved glucose handling ($p = 0.03$ for fasting glucose levels; $p = 0.02$ for glucose tolerance) and the insulin resistance was alleviated ($p < 0.0001$ for HOMA-IR). Furthermore, DPG group mitigated renal function deterioration, as evidenced by lower serum creatinine ($p = 0.01$) and proteinuria ($p = 0.01$). *In vitro*, dapagliflozin directly protected palmitic acid-treated HK-2 cells against lipotoxicity by significantly reducing tubular reactive oxygen species (ROS) levels ($p = 0.03$). DPG group elicited a dose-dependent increase in AMPK phosphorylation at 0.5 and 1μM ($p = 0.001$ and $p < 0.0001$, respectively). This activation was successfully abrogated by the co-administration of the AMPK inhibitor dorsomorphin ($p < 0.0001$). **Conclusion:** The study demonstrated the renoprotective effects of DPG in MASLD. The engaged mechanisms included oxidative stress reduction and activation of AMPK–adiponectin signaling.

Disclosures: Jee-Fu Huang:Roche: Consultant, Gilead: Consultant, Sysmex: Consultant, Aligos: Consultant, Abbvie: Speaking and Teaching, Gilead: Speaking and Teaching, Sysmex: Speaking and Teaching, Novo Nordisk: Consultant, Berlinger-Ingelheim: Consultant, Hugo Y-H Lin:Nothing to Disclose, Yu-Min Ko:Nothing to Disclose, Ming-Lun Yeh:Nothing to Disclose, Wan Long Chuang:Gilead: Speaking and Teaching, AbbVie: Speaking and Teaching, BMS: Speaking and Teaching, Vaccitech: Consultant, PharmaEssentia: Consultant, GSK: Consultant, Ming-Lung Yu:Abbvie, Gilead and Roche diagnostics.: Grant/Research Support, Abbott, Abbvie, Gilead, Roche and Roche diagnostics: Consultant, Abbvie, BMS, Gilead, Roche and Roche diagnostics: Speaking and Teaching.

★ 3415 | METABOLIC–ALCOHOL SPECTRUM OF STEATOTIC LIVER DISEASE AND RISK OF INCIDENT GOUT: A MULTI-NATIONAL COHORT STUDY IN KOREA, JAPAN, AND THE UNITED KINGDOM

Yeowool Kang Sang Yi Moon[1] Min kook Son[2] Joon Yong Park[1], [1]Department of Internal Medicine, Dong-A University College of Medicine, [2]Department of Physiology, Dong-A University College of Medicine

Background: Metabolic dysfunction–associated steatotic liver disease (MASLD) is closely linked to insulin resistance and cardiometabolic dysfunction, both of which may contribute to hyperuricemia and gout. Insulin resistance and fructose metabolism increase hepatic uric acid production, whereas alcohol consumption impairs renal uric acid excretion, suggesting mechanistic links between steatotic liver disease (SLD) and gout. However, large-scale multinational evidence regarding the metabolic–alcohol spectrum of SLD and incident gout remains limited. We investigated the association between SLD subtypes and gout risk using three population-based cohorts from Korea, Japan, and the United Kingdom. **Methods:** We performed a retrospective cohort study using the Korean National Health Insurance Service–Health Screening Cohort, the Japanese Medical Data Center database, and the UK Biobank. Participants were classified as no SLD without cardiometabolic risk factors, no SLD with risk factors, MASLD without alcohol consumption, MASLD with alcohol consumption, metabolic dysfunction–associated alcohol-related liver disease (MetALD), or alcohol-related liver disease (ALD). Incident gout was identified using diagnostic codes, and hyperuricemia was additionally assessed in the Japanese cohort. Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using multivariable Cox proportional hazards models controlling for demographic factors, metabolic comorbidities, kidney function, smoking, and physical activity. **Results:** Across all cohorts, gout risk increased progressively along the metabolic–alcohol spectrum of SLD. In the Korean cohort, compared with individuals without SLD and without cardiometabolic risk factors, adjusted HRs for gout were 2.33 (95% CI, 2.09–2.59) for MASLD without alcohol consumption, 2.62 (95% CI, 2.35–2.93) for MASLD with alcohol consumption, 3.02 (95% CI, 2.67–3.42) for MetALD, and 3.11 (95% CI, 2.66–3.64) for ALD. Similar graded associations were consistently observed in the Japanese and UK cohorts. In Japan, associations were stronger when hyperuricemia was included as an outcome. A significant interaction between MASLD and alcohol consumption was observed (P for interaction < 0.001), suggesting synergistic effects on gout risk. **Conclusion:** Across three large cohorts from Asia and Europe, SLD across the metabolic–alcohol spectrum was independently associated with increased gout risk. These findings support the combined contribution of metabolic dysfunction and alcohol exposure to gout development and highlight the importance of integrated metabolic and lifestyle risk assessment in patients with SLD.

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Figure 1. The flow of study population (Korea & Japan & UK)

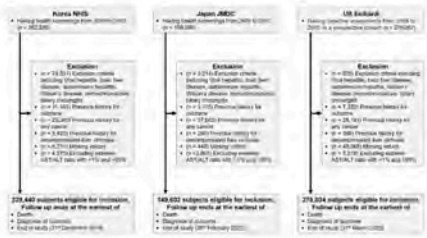


Figure 2. Kaplan–Meier curve for the association between steatotic liver disease and gout

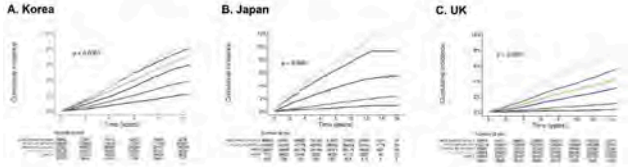
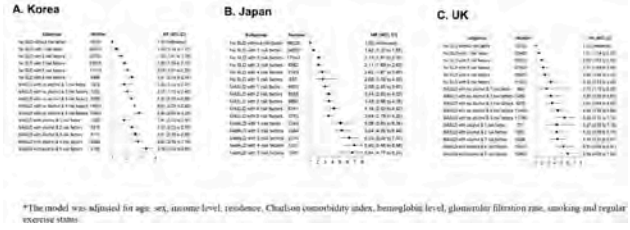


Figure 3. Subgroup analysis according to steatotic liver disease, cardiometabolic risk factors, and alcohol consumption (Korea).



*The model was adjusted for age, sex, income level, residence, Charlson comorbidity index, hemoglobin level, glomerular filtration rate, smoking and regular exercise status.

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3416 | WHY DO MASH AND MASH CIRRHOSIS TRIALS FAIL TO ENROLL? INSIGHTS FROM OVER 5,000 SCREEN FAILURES IN PHASE 3 STUDIES

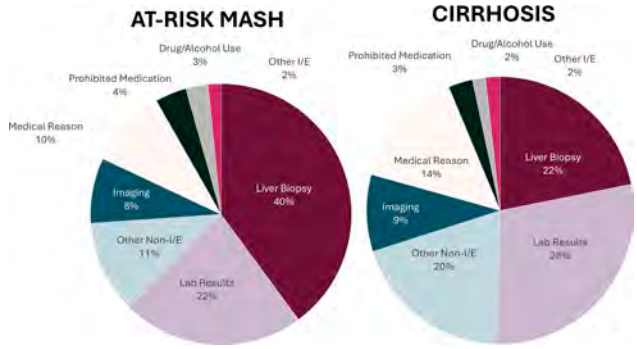
Mazen Noureddin[1] Winston Dunn[2] Elizabeth Brombosz[3] Gražina Binkauskiene[3] Rashmee Patil[2] Rohit Puskoor[4] David Huang[5] Nirupama Esther Jerome[4] John Poulos[6] Alaa Abousaif[7] Aasim Sheikh[8] Alma Laura Ladrón de Guevara[9] Marcelo Kugelmas[10] Mousab Tabbaa[11] Sam Moussa[12] Sudha Kodali[13] Vlad Ratziu[14] Meena Bansal[15] Jörn Schattenberg[16] Naim Alkhouri[17], [1]Houston Methodist Hospital, Houston Research Institute, Summit Clinical Research Solutions, [2]Pinnacle at San Antonio, Summit Clinical Research Solutions, [3]Summit Clinical Research Solutions, [4]Pinnacle at Austin, Summit Clinical Research Solutions, [5]Houston Research Institute – Main, [6]Coastal Research Institute, [7]Providence St. Joseph Hospital-Orange, [8]GI Specialists of Georgia, [9]CENTRO DE INVESTIGACION Y GASTROENTEROLOGIA, [10]South Denver Gastroenterology, [11]Clinical Research Institute of Ohio, [12]Adobe Clinical Research, [13]JC Walter Jr Transplant Center, Houston Methodist Hospital, [14]Service D' Hepatogastroenterologie (FR), [15]Icahn School of Medicine at Mount Sinai (ISMMS), [16]Saarland University Medical Center, [17]Summit Clinical Research

Background: High screen failure rates continue to be a major barrier to the development of pharmacotherapies for MASH. As more therapies progress to phase 3 trials, there is a growing need to understand the barriers to recruitment for these studies. The purpose of this study is to identify the major reasons for screen failure for phase 3 clinical trials in a large multicenter cohort of potential clinical trial participants. **Methods:** Potential participants in phase 3 trials were identified from a multicenter database of patients screened for inclusion in MASH and MASH cirrhosis clinical trials. The primary reason for screen failure was captured systematically by medical science representatives on the clinical trial team. Separate descriptive analyses were performed for trials targeting MASH vs MASH cirrhosis. **Results:** In phase 3 studies of patients with at-risk MASH (n = 3397 of 8636 screen fails), the most common reason for screen failure was liver biopsy (51.5% F0/F1; 13.1% F4; 79.7% did not have hepatocyte ballooning; Figure 1), followed by laboratory results, most frequently low AST/ALT (6.8% of those screened for phase 3 MASH trials), AST results alone (4.8%), HbA1c (2.9%), and bilirubin (2.0%; Figure 1). Common reasons for screen failure not related to inclusion/exclusion (I/E) criteria were concerns about study compliance (3.1%) and withdrawal of consent (2.1%). In phase 3 studies of MASH cirrhosis (n = 1766 of 5135 screen fails), laboratory results were the primary cause of screen failure, most frequently bilirubin (7.4%), albumin (3.5%), HbA1c (3.1%), ELF score (2.5%), and INR (2.1%). Of the patients who screen failed on biopsy, 22.7% were F0/F1, 67.5% were F2/F3, and 77.4% had NAS < 4. The most common non-I/E reasons for screen failure were concerns about study compliance (4.6%) and subject withdrawal (4.9%). **Conclusion:** In this large analysis for screening failure for MASH phase 3 studies we found that biopsy and laboratory results are major hurdles to enrollment in phase 3 trials for MASH and MASH cirrhosis. These trials may benefit from enhanced pre-screening algorithms to identify potential

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participants most likely to qualify for enrollment. The role of ballooning assessment in at-risk MASH trials, along with NAS requirements for biopsy-confirmed MASH cirrhosis studies, warrants reconsideration by the hepatology community.



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3417 | ENVIRONMENTAL POLLUTANT EXPOSURES ARE ASSOCIATED WITH FIBROSIS SEVERITY IN METABOLIC DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE (MASLD)

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Background: Environmental pollutants are disease modifying factors that may impact the severity of metabolic dysfunction associated steatotic liver disease (MASLD). A pilot exposomics study of 140 subjects with MASLD demonstrated that fluorene exposures were associated with the severity of hepatic steatosis and fibrosis. Here, a larger validation study is performed on fibrosis. **Methods:** Exposomics (GC-MS^2) was performed in 366 serum samples from IU MASLD prospective observational study. MASLD was diagnosed based on the AASLD guidelines. Fibrosis severity was determined by liver stiffness measurement (LSM) using vibration controlled transient elastography (VCTE). Exposome-wide association studies (EWAS) were performed using quantile normalized and log2 transformed linear exposure and LSM using ANOVA models in R. Statistical significance was set at FDR < 0.20. **Results:** Subjects were 42% female, 96% White with mean age of 53.3 years and mean BMI of 35.7 kg/m^2 . Type 2 diabetes (DM2) was present 49%, dyslipidemia in 51% and hypertension in 59%. Of the 146 unique pollutants detected with annotations confirmed by authentic standards, 11 were associated with hepatic fibrosis, of which 5 were associated with worse fibrosis. Dichloro diphenyl ethylene (DDE) a metabolite of the insecticide DDT, was the most statistically significant ($p = 0.00001$, FDR = 0.002). Benzoic acid, a food preservative commonly found in sugar-sweetened beverages, was detected in 100% of these serum samples ($p = 0.001$, FDR = 0.08). Fluoranthene, a polycyclic aromatic hydrocarbon similar to fluorene, ($p = 0.01$, FDR = 0.19), tis(2-butoxyethyl) phosphate (TBEP), an organophosphate flame retardant ($p = 0.007$, FDR = 0.16) and 2-amino-4-nitrotoluene, used in dye/pigment manufacturing was also associated with fibrosis severity. Six pollutants, bensulfuronmethyl, ethylheptanotate, 25-hydroxycholesterol, dimethoxy benzidine, ethyl myristate and tris(tribromoneopentyl) phosphate (TBNP) were negatively associated with fibrosis severity. **Conclusion:** Environmental pollutants- DDE (insecticide), benzoic acid (food additive), TBEP (flame retardant), 2-amino-4-nitrotoluene (pigments/dyes), and fluoranthene (dyes/incomplete combustion) were associated with worse fibrosis in individuals with MASLD. Reverse causality cannot be excluded and future research on these pollutants is warranted.

Table 1: Environmental Exposures Associated with Fibrosis Severity in the MASLD Cohort (N=366)

Chemical Name	Chemical Classification	P value	FDR	Directionality
DDE	Insecticide metabolite	0.00001	0.002	Positive
Benzoic Acid	Food additive (preservative)	0.001	0.08	Positive
Tris(2-butoxyethyl) phosphate (TBEP)	Flame Retardant	0.007	0.16	Positive
2-amino-4-nitrotoluene	Dyes and Pigments	0.010	0.19	Positive
Fluoranthene	Polycyclic aromatic hydrocarbon	0.010	0.18	Positive
Bensulfuronmethyl	Herbicide	0.002	0.08	Negative
Ethylheptanoate	Food additive (flavoring)	0.002	0.08	Negative
25-hydroxycholesterol	Endogenous oxysterol	0.002	0.08	Negative
Dimethoxy benzidine	Dyes and Pigments	0.002	0.08	Negative
Ethyl myristate	Food additive (flavoring), personal care products	0.003	0.09	Negative
Tris(tribromoneopentyl) phosphate (TBNP)	Flame Retardant	0.004	0.11	Negative

Disclosures: Matt Cave:Nothing to Disclose, Matthew Smith:Nothing to Disclose, Jianzhu Luo:Nothing to

Symbols: ♦, Poster of Distinction; ★, Foundation Award Recipient

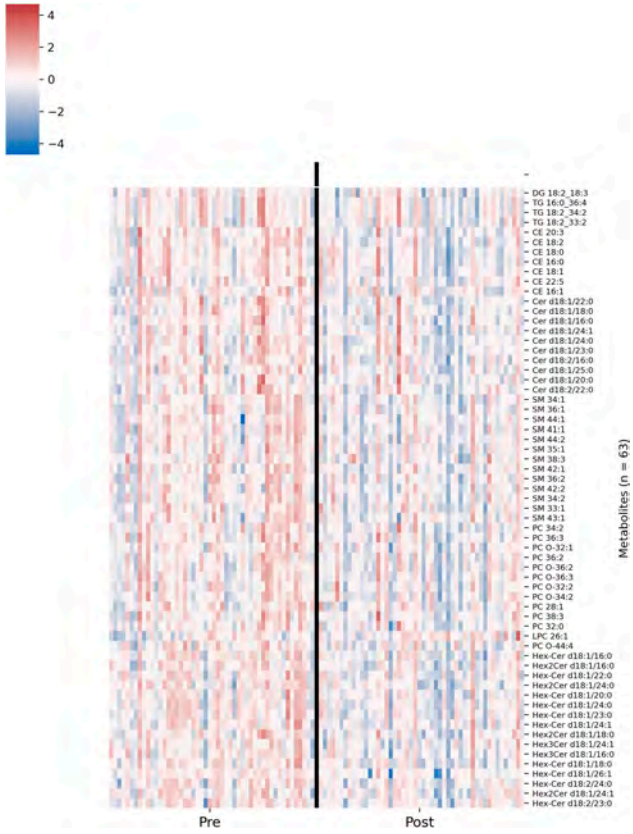
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Disclose, Young-Mi Go:Nothing to Disclose, Christina Pinkston:Nothing to Disclose, Shesh Rai:Nothing to Disclose, Dean Jones:Nothing to Disclose, Naga Chalasani:Madrigal, Eccogene, Insitro, Boston Pharma, Chugai: Consultant, Zydus, GSK, Akero, Plaint, Altimmune: Consultant, Exact Sciences: Grant/Research Support, NIH: Grant/Research Support, Heligenics: Board member, investor, Avant Sante: Board member, investor, Ipsen, Biomea Fusion, Pfizer, Merck: Consultant, Niharika Samala:Novo Nordisk: Consultant, Madrigal: Advisor, Petauri Kinect: Grant/Research Support, Eli Lilly: Grant/Research Support, Regeneron: Grant/Research Support, GSK: Grant/Research Support.

3418 | STATIN INITIATION MODIFIES THE LIPID METABOLOMIC PROFILE IN PEOPLE WITH HIV AND MASLD

Kara Wegermann[1] Xiaoyue Yan[2] Joseph Lucas[2] Rebecca Mangus[3] Zhong Li[3] Amreen Dinani[1] Cynthia Moylan[3] Susanna Naggie[4], [1]Duke University School of Medicine, [2]Vital Statistics LLC, [3]Duke University, [4]Duke Clinical Research Institute

Background: MASLD affects up to 40% of people with HIV (PWH), but prevention and treatment strategies are limited. Although statins are associated with lower MASLD prevalence and progression in the general population, data in PWH are sparse. The aim of this study was to characterize plasma lipidomic alterations associated with statin initiation in PWH with MASLD. **Methods:** We examined 50 PWH with MASLD from the Duke HIV Research Database and Repository before and after starting moderate or high intensity statins. MASLD was defined by hepatic steatosis index > = 36. We analyzed the Biocrates Q500 assay and a separate oxylipin panel on blood samples 6 months prior, and approximately 1 year after, statin initiation. One-sample paired t-tests were used to compare metabolites pre- and post-statin initiation, with statistical significance defined as $p < 0.05$ and FDR < 0.10. **Results:** Of 50 PWH included, 33 (66%) were assigned male sex at birth and 33 (66%) reported Black race. The median age was 53 years [IQR 48-57]. Median BMI was 33.6 kg/m2 and 9 (18%) had diabetes. Median HSI was 42.7 [IQR 40.2-49.9] and FIB-4 was 1.2 [0.9-1.5]. Untargeted metabolomic profiling identified 63 metabolites that differed significantly post-statin versus pre-statin; all were lipids and all were reduced following statin initiation (Figure). The most common classes were hexosylceramides (N = 16), sphingomyelins (N = 13), phosphatidylcholines (N = 12), ceramides (N = 10), cholesterol esters (N = 7) and triglycerides (N = 3). Gene set enrichment analysis revealed 6 pathways associated with metabolites that differed after statin initiation: amino acids related ($p < 0.001$, FDR < 0.001), sphingolipids ($p < 0.001$, FDR < 0.001), glycosylceramides ($p < 0.001$, FDR < 0.001), ceramides ($p = 0.0005$, FDR = 0.0006), cholesterol esters ($p = 0.0005$, FDR = 0.001), and carboxylic acids ($p = 0.03$, FDR = 0.09). **Conclusion:** Changes in plasma metabolite levels following statin initiation were largely restricted to lipid species and pathways previously found to be relevant to steatotic liver disease risk and progression. Our prior work demonstrating elevated ceramides, triglycerides, and select amino acids in PWH with MASLD suggests that statins act on steatotic liver disease-associated lipid perturbations. Whether these metabolomic changes translate into improvements in MASLD progression warrants further study.Figure Legend: Cluster diagram showing plasma metabolites before (left side of figure) and after (right side of figure) statin initiation. Blue indicates lower relative metabolite level, while red indicates higher relative metabolite level, when pre- and post-statin levels were compared. Metabolites are grouped by class.



Disclosures: Kara Wegermann:Mirum Pharmaceuticals: Study investigator (research funds to institution), Madrigal Pharmaceuticals: Study investigator (research funds to institution), FocusMed CME: Speaking and Teaching, Xiaoyue Yan:Nothing to Disclose, Joseph Lucas:Nothing to Disclose, Rebecca Mangus:Nothing

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to Disclose, Zhong Li:Nothing to Disclose, Amreen Dinani:Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Cynthia Moylan: GSK: Grant/Research Support, GSK: Grant/Research Support, Madrigal Pharmaceuticals: Grant/Research Support, Madrigal Pharmaceuticals: Grant/Research Support, Exact Sciences: Grant/Research Support, Exact Sciences: Grant/Research Support, Sirtex: Advisor, Sirtex: Advisor, NovoNordisk: Consultant, NovoNordisk: Consultant, GSK: Grant/Research Support, GSK: Grant/Research Support, Madrigal Pharmaceuticals: Grant/Research Support, Madrigal Pharmaceuticals: Grant/Research Support, Exact Sciences: Grant/Research Support, Exact Sciences: Grant/Research Support, Sirtex: Advisor, Sirtex: Advisor, NovoNordisk: Consultant, NovoNordisk: Consultant, Susanna Naggie:BMS/PRA: Event Adjudication Committee, Vir Biotechnology: Stock – privately held company, Astra Zeneca: Advisor.

3419 | UNDERUTILIZATION OF THE FIB-4 INDEX TO IDENTIFY LIVER DISEASE IN PATIENTS WITH METABOLIC DYSFUNCTION IN PRIMARY CARE

Mirjana Grocic[1] Husam Mikati[1] Richard Sterling[1] Alex Krist[1] Tamas Gal[2] Amanda Robinson[2] Roy Sabo[3], [1]Virginia Commonwealth University Hospital Systems, [2]Virginia Commonwealth University, [3]Viriginia Commonwealth University

Background: MASLD affects ~30% of adults and is associated with type 2 diabetes (T2DM), hypertension (HTN), dyslipidemia (DL), and obesity. ADA, AGA, and AASLD guidelines recommend the FIB-4 index to identify patients (pts) who may have liver fibrosis. FIB-4 is not routinely used by primary care providers (PCPs). With therapies, i.e. thyroid hormone receptor beta and glucagon-like peptide-1 (GLP-1) receptor agonists (RA), identifying pts at risk may prove beneficial. We hypothesize that underuse of FIB-4 results in underdiagnosis of MASLD and low referral rates to GI/Hepatology. **Methods:** Data were extracted from the Epic Systems electronic health record (EHR) at VCU Health System under approved IRB protocol. The analytical data set included pts aged 18—70 with ≥ 1 ambulatory visit 12/4/2021 to 11/30/2025. Extracted variables included demographics, BMI, encounter data including history of GI/Hepatology visits, lab values necessary for FIB-4 index calculation (AST/ALT/platelets), low-density lipoprotein (LDL), high-density lipoprotein (HDL), total cholesterol, triglycerides, HBV surface antigen, hepatitis C antibody, and GLP-1 RA use. Diagnostic indicators were derived from EHR data to identify liver diseases (MASLD/HBV/HCV), T2DM, and HTN. Pts seen in the ED or hospitalized were excluded and data were analyzed across all FIB-4 groups (<1.3, 1.3—2.7, >2.7). **Results:** The final cohort comprised 359,994 unique pts (mean age 45.8, 57% Female, 50% White, 15% T2DM, 35% HTN, 39% obesity, and liver disease [6% MASLD, 11.2% other]). Only 45% (163,991) had lab data to calculate FIB-4 (median 1.03: 64.4% <1.3, 27.8% 1.3—2.7, 7.7% >2.7). Pts without FIB-4 had missing AST (93.6%), ALT (96.7%), platelets (77.7%), and low liver disease prevalence (5.2%). Pts with FIB-4 <1.3 were younger ($p < .001$) and had lower metabolic and liver disease rates compared to pts with higher FIB-4 ($p < .001$). GI/Hepatology referral was 13.6% with FIB-4 <1.3, 19.7% with FIB-4 1.3—2.7, and 27.8% with FIB-4 >2.7. GLP-1 use was lowest with FIB-4 >2.7 (9.6%) compared to FIB-4 <2.7 (13%; $p < .001$). (Table 1) **Conclusion:** Despite the ease of calculation, FIB-4 is underutilized by PCPs, with most pts missing ≥ 1 component. Most pts with FIB-4 >1.3 are not referred to GI/Hepatology, suggesting a disconnect between FIB-4 calculations and proposed workup and consultation. More evidence is needed on the value of FIB-4 calculations in PCP routine care and integration criteria/parameters.

Variable	FIB-4 <1.3 N =105577	FIB-4 1.3-2.7 N =45608	FIB-4 >2.7 N =12706	Missing FIB-4 N =196003	Overall N =359994
FIB-4 (mean, SD)	0.768 (0.283)	1.78 (0.365)	13.8 (72.8)	n/a	2.06 (20.6)
Female (%)	(61.5%)	(50.1%)	(41.1%)	(57.5%)	(57.2%)
Age (yrs) (mean, SD)	41.7 (14.2)	59.3 (10.2)	59.7 (10.4)	44.1 (16)	45.8 (15.9)
Race: Black or African American	(35.9%)	(39.1%)	(38.4%)	(31.9 %)	(34.2%)
Race: White	(49.7%)	(52.1%)	(51.5%)	(50.5%)	(50.5%)
Race: Other	(14.4%)	(5.2%)	(6.7%)	(10.4%)	(8.8%)
Ethnicity: Hispanic or Latino	(6.4%)	(2.7%)	(2.8%)	(6%)	(5.6%)
Ethnicity: Non-Hispanic or Latino	(89%)	(93.1%)	(90.8%)	(85.6%)	(87.7%)
Ethnicity: Unknown/other	(4.7%)	(4.1%)	(6.3%)	(8.4%)	(6.7%)
BMI (mean, SD)	30.9 (22.9)	30.5 (128)	28.8 (7.92)	31.3 (387)	31 (281)
Obesity (BMI ≥ 30 kg/m²) (Yes)	(45.5%)	(40.6%)	(35.7%)	(36.2%)	(39.5%)
T2DM (Yes)	(16.4%)	(28.4%)	(33.7%)	(10.9%)	(15.5%)
Hypertension (Yes)	(35.9%)	(62.8%)	(65.1%)	(26%)	(35%)
MASLD (Yes)	(8.8%)	(13%)	(22.1%)	(1.8%)	(6%)
Other liver disease (Yes)	(15%)	(24.4%)	(52.5%)	(3.4%)	(11.2%)
GI/Hepatology visit (Yes)	(13.6%)	(19.7%)	(27.8%)	(2.9%)	(9%)
GLP-1 RA use (Yes)	(13.4%)	(13.7%)	(9.6%)	(6.1%)	(9.3%)
AST U/L (mean, SD)	26.3 (13.8)	34.5 (25.9)	223 (1250)	30.8 (324)	42.9 (351)
AST Missing	n/a	n/a	n/a	(93.6%)	(50.9%)
ALT U/L Mean (SD)	28.4 (37)	29.9 (42.9)	97.9 (452)	31.9 (184)	34.1 (134)
ALT Missing	n/a	n/a	n/a	(96.7%)	(52.6%)
Platelets x10³ (mean, SD)	294 (84)	221 (57.1)	144 (72)	262 (87.6)	262 (89.2)
Platelets Missing	n/a	n/a	n/a	77.7%	42.3%
HDL ≤ 50 mg/dL	22.8%	24.3%	22.6%	2.6%	12%
TG ≥ 150 mg/dL	10.5%	11.6%	11.9%	1.2%	5.6%

Disclosures: Mirjana Grocic:Nothing to Disclose, Husam Mikati:Nothing to Disclose, Richard Sterling: ABIM: GI Specialty Board, Abbott: Grant/Research Support, GSK: Grant/Research Support, HCV Vax: Grant/Research Support, Gilead: Grant/Research Support, Zydus: Grant/Research Support, Vertex: Consultant, Madrigal: Advisor, Gigagen: Grant/Research

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Support, Atea: Grant/Research Support, Cima Science: Consultant, Celaris: Consultant, GSK: Advisor, Alex Krist:Nothing to Disclose, Tamas Gal:Nothing to Disclose, Amanda Robinson:Nothing to Disclose, Roy Sabo:Nothing to Disclose.

3420 | DOSE-DEPENDENT IMPROVEMENTS IN HEPATIC AND CARDIOMETABOLIC BIOMARKERS WITH ELECOGLIPRON IN ADULTS WITH MASLD

Jonathan Stine[1] Melanie Davies[2] Sue Pedersen[3] Roy Rasalam[4] Stephen Rush[5] Peter Johansson[5] Erika Morizzo[6] Sonali Singh[7] Jennie Lin[7] Ehsan Parvaresh Rizi[5] C David Sjöström[5], [1]Penn State College of Medicine, [2]Diabetes Research Centre, University of Leicester, Leicester, UK, [3]C-ENDO Diabetes & Endocrinology Clinic Calgary, Calgary, AB, Canada, [4]Alfred Health (Endocrinology and Diabetes), University of Melbourne, Melbourne, Australia, [5]AstraZeneca, Gothenburg, Sweden, [6]AstraZeneca, Cambridge, UK, [7]AstraZeneca, Boston, MA, USA

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is closely linked to obesity and cardiometabolic risk. Weight loss pharmacotherapies have been shown to improve hepatic biomarkers. We performed a post hoc analysis of the VISTA phase 2b trial to evaluate the effects of elecoglipron 50 mg and 75 mg on hepatic and cardiometabolic markers in adults living with obesity or overweight without type 2 diabetes. **Methods:** This analysis included adults with MASLD at baseline, defined by Fatty Liver Index (FLI) $\geq$60. The primary endpoint was proportion of participants achieving MASLD resolution, defined as FLI <30, with FLI <60 indicating values below the steatosis rule-in threshold. Changes from baseline to week 36 were assessed for alanine aminotransferase (ALT), body weight (BW), waist circumference (WC) and other metabolic parameters. Binary responder endpoints included clinically meaningful reduction in WC (>5 cm or >5%), and ALT (>17 IU/L). Furthermore, outcomes by achieved percent BW reduction at pre-specified thresholds (>5%, >7%, >10%) were explored. Mixed-effects models for repeated measures and logistic regression were used with prespecified covariate adjustment. Confidence intervals were not adjusted for multiplicity. **Results:** The analysis included 194 participants with FLI $\geq$60 (n=125 elecoglipron, n=69 placebo). Elecoglipron demonstrated improvements in hepatic and cardiometabolic biomarkers at week 36 across both 50 mg and 75 mg doses, with larger effects observed with 75 mg. 18.4% of participants receiving elecoglipron 75 mg achieved definitive MASLD resolution versus 2.3% with placebo (OR 5.8, 95% CI 0.9-38.3) and 11.4% receiving elecoglipron 50 mg (OR 2.0, 95% CI 0.3-15.4). Reduction in FLI below the steatosis threshold (<60) was observed in 40.8% elecoglipron 75 mg group vs. 7.0% placebo (OR 10.8, 95% CI 2.5-46.8) and 31.4% elecoglipron 50 mg group (OR 4.2, 95% CI 0.9-19.5). MASLD resolution was observed alongside a greater mean reduction in ALT (-9.2 IU/L for 75mg, -8.8 IU/L for 50 mg versus -0.8 IU/L for placebo) with 28.0% and 17.1% achieving ALT responder thresholds with 75 mg and 50 mg respectively, versus 9.1% with placebo. Clinically meaningful WC reduction occurred in 73.1% of 75 mg elecoglipron participants versus 21.4% of placebo participants (OR 8.9, 95% CI 3.5-22.8) and 69.4% of 50 mg elecoglipron participants (OR 6.9, 5% CI 2.5-18.8). Higher rates of MASLD resolution were observed with both doses of elecoglipron versus placebo across multiple thresholds of BW loss. **Conclusion:** Elecoglipron was associated with greater rates of MASLD resolution than placebo with dose-dependent improvements in noninvasive hepatic, metabolic, and cardiometabolic biomarkers in participants with MASLD and overweight/obesity.

Disclosures: Jonathan Stine:Novo Nordisk: Consultant, Galectin: Grant/Research Support, Novo Nordisk: Grant/Research Support, Astra Zeneca: Grant/Research Support, Noom: Grant/Research Support, Zydus: Grant/Research Support, Kowa: Grant/Research Support, Regeneron: Grant/Research Support, Madrigal: Advisor, Astra Zeneca: Employee, Astra Zeneca: Stock - publicly traded company, Melanie Davies:Nothing to Disclose, Sue Pedersen:astra zeneca: Consultant, astra zeneca: Independent Contractor, boehringer: Consultant, boehringer: Independent Contractor, novo nordisk: Consultant, novo nordisk: Independent Contractor, lilly: Advisor, lilly: Consultant, lilly: Independent Contractor, amgen: Consultant, regeneron: Consultant, roche: Consultant, roche: Independent Contractor, abbvie: Consultant, bayer: Consultant, bausch: Consultant, Roy Rasalam:Nothing to Disclose, Stephen Rush:AstraZeneca: Employee, Peter Johansson:Nothing to Disclose, Erika Morizzo:Nothing to Disclose, Sonali Singh:Nothing to Disclose, Jennie Lin: AstraZeneca: Employee, Ehsan Parvaresh Rizi:Nothing to Disclose, C David Sjöström:AstraZeneca: Employee, AstraZeneca: Stock – privately held company.

3421 | TEMPORAL TRENDS IN PREVALENCE OF DEPRESSION AND MENTAL HEALTH SERVICE UTILIZATION AMONG INDIVIDUALS WITH AND WITHOUT METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) IN THE UNITED STATES FROM 2005 TO 2023

Catherine Garcia[1] Vy Nguyen[2] Hong Fan[2] Michael Le[3] Mindie Nguyen[2] Ramsey Cheung[2], [1]Mountain View

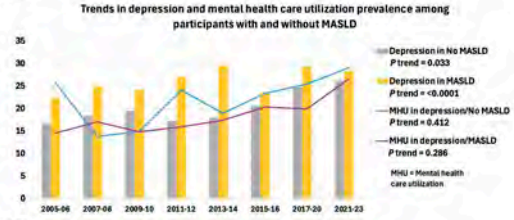
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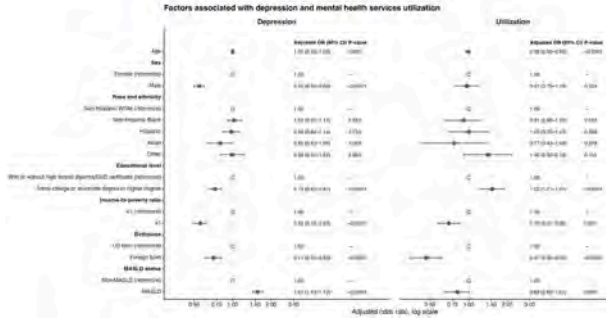
High School, [2]Stanford University Medical Center, [3]UCLA

Background: Depression is increasingly recognized as an important comorbidity of MASLD. However, national data on changes in its prevalence and access to mental health care use (MHU) over the years is limited. We aimed to characterize the temporal trends and predictors of depression and MHU among those with depression. **Methods:** We analyzed U.S. adults (≥18 years) from the National Health and Nutrition Examination Survey (NHANES) 2005 – 2023 using NHANES survey weights to ensure representativeness of the US population. MASLD was defined by hepatic steatosis (US Fatty Liver Index ≥ 30 or controlled attenuation parameter ≥ 302 dB/m), ≥1 cardiometabolic risk and without significant alcohol use. Depression was defined by the presence of depressive symptoms through the Patient Health Questionnaire-9 score ≥ 5. Among those with depression, MHU was assessed via survey querying a history of seeing mental health professional(s) in the past year. **Results:** We analyzed 19,576 adults: 6,448 (32.9%) with MASLD and 13,128 (67.1%) without. Those with MASLD were more likely to have depression (26.3% vs 20.3%, $p<0.0001$) and depressed adults with MASLD were less likely to utilize mental health service than depressed adults without MASLD (18.5% vs 22.56%, $p=0.011$). Among those with MASLD, depression was more common in females (vs. males: 34.5% vs 20.4%), with low income (income-to-poverty ratio <1 vs. ≥1: 39.0% vs. 24.7%) and most prevalent among non-Hispanic (NH) Black followed by NH White, Hispanic, Other and Asian adults (30.3%, 26.8%, 24.4%, 23.4% and 16.9%, respectively), all $P<0.0001$. In depressed adults with MASLD, MHU decreased with older age (>20%, 15-18%, and 10.8% in <50, 50-69 and >70 years), lower education, lower income, and lowest in Asian adults (7.1% vs 18-38% for other groups), all $P<0.0001$. Between 2005 and 2023 (**Figure 1A**), depression became more prevalent in both the MASLD (22.4% to 28.4%, P_{trend}=0.033) and non-MASLD groups (16.7% to 26.2% ($P_{trend}<0.0001$); however, there was no significant changes in MHU in either group (P_{trend} =0.282 and 0.412). In multivariable adjusted models (**Figure 1B**), MASLD was associated with higher odds of depression (adjusted odds ratio [aOR]: 1.57, 95% CI: 1.43 – 1.72, $p<0.0001$), with older age, male sex, Asian race, having higher education or income, and being foreign-born associated with lower odds of having depression (all $P<0.05$); while factors associated with lower odds of MHU were also older age, lower education or income, and being foreign born, with MASLD also trending towards a lower odds of MHU (aOR: 0.82, 95% CI: 0.66 – 1.01, $p=0.067$). **Conclusion:** US adults with MASLD were more likely to suffer from depression but less likely to seek mental health care. The prevalence of depression also increased over time but without corresponding increase in MHU. These findings support integrating mental health screening and care in MASLD management, especially for higher risk subgroups.

1A



1B



Disclosures: Catherine Garcia:Nothing to Disclose, Vy Nguyen:Nothing to Disclose, Hong Fan:Nothing to Disclose, Michael Le:Nothing to Disclose, Mindie Nguyen:Pfizer, Astra Zeneca, Aligos, GSK, Delfi, Innogen, Exact Sci: Grant/Research Support, GSK: Advisor, Ramsey Cheung:Nothing to Disclose.

3422 | BOTH NUTRITIONAL INTERVENTION AND LOW-DOSE ORAL SEMAGLUTIDE DECREASE HEPATIC FAT IN ADOLESCENTS WITH POLYENDOCRINE METABOLIC OVARY SYNDROME AND HEPATIC STEATOSIS

Gabriel Medrano[1] Nazeen Morelli[1] Jaclyn Lo[1] Grayson Carey[1] Meredith Ware[1] Yesenia Garcia-Reyes[1] Carly Faulkner[2] Allison Shapiro[1] Melanie Cree[1], [1]Children's Hospital Colorado, University of Colorado Anschutz Medical Campus, [2]Children's Hospital Colorado

Background: Polyendocrine metabolic ovary syndrome (**PMOS**), formerly known as PCOS, is a hyperandrogenic condition affecting up to 20% of females with obesity and is associated with increased risk of metabolic dysfunction-associated steatotic liver disease (**MASLD**). Despite the high prevalence of MASLD in adolescent-onset PMOS, there are

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currently no approved pharmacologic therapies. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) improve hepatic steatosis and fibrosis in adults, yet effects in youth remain unclear. We investigated if low-dose oral semaglutide treatment reduces hepatic fat in adolescents with obesity, hepatic steatosis (**HS**), and PMOS compared with dietary intervention. **Methods:** Adolescents with PMOS and obesity were enrolled in a 16 week partially randomized trial (n = 54, 12-21 years, BMI ≥ 90th percentile for age and sex; NCT03919929). Girls received either 16 weeks of oral semaglutide (**SEMA**, Rybelsus©) or intensive nutritional counseling (**DIET**). The dose of SEMA was 3 mg/day for 4 weeks followed by 7 mg/day for 12 weeks. Participants completed pre and post intervention visits with hepatic fat fraction quantified via MRI, and anthropometric measurements and fasting labs were obtained. Data from a subset of participants with HS (liver fat of ≥ 5.5%) are in this analysis (SEMA n = 24, DIET n = 9). Separate linear mixed effect models were used to examine change in hepatic fat (%), weight (kg), aspartate aminotransferase (AST, IU/L), alanine aminotransferase (ALT, IU/L), fasting glucose (mg/dL), HbA1c (%) from baseline to END.Data are shown as mean [SE], statistical significance was defined as $p < 0.1$. **Results:** After 16 weeks, both SEMA (-4.6 [0.84]) and DIET (-2.5 [0.6]) lost weight, with more in SEMA vs DIET ($p = 0.04$). Hepatic fat decreased in both (DIET: pre = 10.6 [2.0], post = 7.8 [1.9]; SEMA: pre = 13.1 [1.2], post = 9.8 [1.2]), with no difference in change between groups ($p = 0.75$). The relationship between change in hepatic fat and change in weight was not different between groups ($p = 0.97$). ALT and AST decreased in SEMA (ALT = -6.8 [2.9];AST = -2.0 [2.2]) compared to no change in DIET (ALT = 0.0 [3.1]; AST = 3.4 [4.4]), yet change between groups was not different ($p = 0.14$ and $p = 0.29$, respectively). Fasting glycerol, a marker of lipolysis, decreased more with SEMA ($p < 0.01$). Change in fasting glucose was similar for SEMA and DIET, but HbA1c decreased more in SEMA ($p = 0.09$). **Conclusion:** Sixteen weeks of dietary intervention or low-dose oral semaglutide both decreased hepatic fat in adolescents with PMOS, HS, and obesity. These data confirm the rapidity of decreases in hepatic fat in the setting of minimal weight loss. Future work with a larger cohort and longer duration of treatment with a stronger GLP1-RA are needed.

Disclosures: Gabriel Medrano:Nothing to Disclose, Nazeen Morelli:Nothing to Disclose, Jaclyn Lo:Nothing to Disclose, Grayson Carey:Nothing to Disclose, Meredith Ware:Nothing to Disclose, Yesenia Garcia-Reyes:Nothing to Disclose, Carly Faulkner:Nothing to Disclose, Allison Shapiro:Nothing to Disclose, Melanie Cree:Nothing to Disclose.

3423 | PERIPHERAL IMMUNE PROFILES DURING INTERFERON THERAPY IN CHRONIC HEPATITIS B PATIENTS WITH AND WITHOUT MASLD

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Background: Chronic hepatitis B (CHB) frequently occurs with metabolic dysfunction-associated steatotic liver disease (MASLD), but whether MASLD modifies peripheral immune-cell changes during interferon (IFN) therapy remains unclear. We assessed peripheral blood mononuclear cells (PBMCs) and clinical responses during IFN therapy in CHB patients with and without MASLD. **Methods:** We enrolled HBeAg-negative CHB patients receiving IFN-based therapy. A total of 41 patients were included, comprising 22 with CHB alone and 19 with CHB and concomitant MASLD. Clinical data and PBMCs were collected at weeks 0, 12, 24, and 48. NK, T, and NKT cells, B-cell subsets, and monocyte/myeloid subsets were quantified by flow cytometry. Treatment response was defined as a reduction in log10 HBsAg of ≥ 1 from baseline. On-treatment changes were analyzed using linear mixed-effects models (LMMs), and associations between immune-cell changes and log10 HBsAg decline were assessed using Spearman correlation analysis. **Results:** At baseline, CHB+MASLD patients had higher GGT, triglyceride levels, and platelet counts and lower HDL-C, consistent with a metabolic phenotype. During IFN therapy, log10 HBsAg declined significantly over time in both groups (LMM time effect, $P < 0.001$). However, neither the overall difference between CHB and CHB+MASLD nor the group-by-time interaction was significant. Treatment response rates were similar between groups [CHB: 8(36.4%); CHB +MASLD: 7(36.8%)]. However, aminotransferase trajectories differed: ALT and AST increased transiently at week 12 and then declined in CHB alone, whereas both enzymes peaked at week 24 in CHB+MASLD, suggesting delayed aminotransferase elevation during IFN therapy. Flow cytometry showed significant on-treatment changes in multiple peripheral immune-cell subsets. Response-stratified LMMs identified response-by-time interactions for CD27+ NK cells, transitional B cells, plasma cells, and CD14-CD16- myeloid/monocyte-like cells. PCA indicated treatment-related shifts in the overall immune-cell profile, with different patterns between CHB and CHB+MASLD patients. HBsAg decline was associated with changes in CD57+ NKT cells, CD57+ T cells, NKG2A+ NK cells,

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mDCs, and CD14-CD16- myeloid/monocyte-like cells. Stratified analyses suggested different immune correlates of HBsAg decline: M1-like monocytes and CD57+ NKT cells in CHB, and CD14-CD16- myeloid/monocyte-like cells and B cells percentage in CHB+MASLD. **Conclusion:** IFN therapy was associated with marked changes in peripheral immune-cell subsets. Concomitant MASLD did not affect short-term response, but was linked to distinct biochemical trajectories and immune-cell response patterns. Larger studies are needed to validate these findings and define the immune mechanisms of IFN response in CHB with MASLD.

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3425 | SPLEEN STIFFNESS AND SEVERITY OF MUSCLE FAT QUANTITY ARE INDEPENDENT DETERMINANTS OF NEUROCOGNITIVE FUNCTION IN COMPENSATED CIRRHOSIS DUE TO METABOLIC DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE (MASLD)

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Background: Sarcopenia and myosteatosis are associated with overt hepatic encephalopathy. However, in compensated cirrhosis due to MASLD, the effects of muscle volume versus fat quantity in specific compartments on neurocognitive function are unknown especially after correcting for confounders (visceral adipose tissue (VAT) volume, liver function, fibrosis-burden and portal hypertension). **Aims:** To define (1)alternations in specific muscle compartments (2) the relationship of muscle volume vs fat in limb vs central muscles on neuro-cognitive function in MASH cirrhosis. **Methods:** A prospective study of compensated MASH. Muscle fat was quantified as the muscle fat infiltration (MFI); MFI, muscle and adipose tissue volumes (total, abdominal subcutaneous, and visceral) were quantified by highly reproducible MRI methods. Liver- and spleen-stiffness measurements (LSM, SSM) served as surrogates for fibrosis burden and portal hypertension respectively. Neuro-cognitive function was assessed from the Stroop test off-time (psychomotor function), on-time (cognitive flexibility) and difference in on- and off-times (higher time = worse cognition). Concordance was determined from Pearson correlation. Multiple regression was used to determine determinants Stroop off and ontime. **Results:** 127 individuals with compensated MASH cirrhosis were evaluated. The cohort was predominantly white (90%) and female (69%). Mean LSM was 23 kPa and CAP was 287 db/m while SSM was 46 kPa. Laboratory showed (mean): bilirubin 0.85 mg/dl, AST 44 IU/l, ALT 44 IU/l, albumin 4.2 gm/dl, INR 1.1, creatinine 0.85 mg/dl. Mean off-time was 79 sec and on-time was 95 sec with 5.5 (off time) and 5.8 (on-time) runs needed. There was strong concordance between ASAT and VAT as well as between spinal erector and thigh muscle volume and MFI ($p < 0.01$ for all). There was strong concordance between right and left side and between anterior vs posterior thigh for muscle parameters ($p < 0.001$ for all). Regression analyses (univariate followed multivariate) identified SSM, MFI (either spinal or thigh) and VAT to be independent predictors of off-time, on-time and their difference. LSM, CAP, BMI, total adipose tissue and ASAT, muscle volumes, liver enzymes and function were not significantly associated. **Conclusion:s:** SSM and MFI rather than sarcopenia or liver stiffness are key determinants of psychomotor and cognitive flexibility outcomes of neuro-cognitive functions in compensated MASH cirrhosis.

	Coefficients	p	$r_{partial}$
Spleen stiffness	0.65	<0.0001	0.75
Spinal MFI	1.8	0.008	0.44
Spinal Muscle volume	28	n.s.	0.18
VAT	-2.6	n.s.	-0.3
LSM	-0.1	n.s.	-0.22
Bilirubin	-0.9	n.s.	-0.045

F-ratio 8.35, p< 0.0001, n.s. = not significant

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3426 | THE LEAN MASLD PARADOX: WORSE LIVER BIOMARKERS WITH LOWER ADVANCED LIVER DISEASE BURDEN

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Background: Metabolic dysfunction–associated steatotic liver disease (MASLD) is a leading cause of chronic liver disease and is associated with obesity and metabolic syndrome. Lean MASLD has emerged as a distinct phenotype that may still carry significant fibrosis risk despite lower metabolic burden. Our aim is to compare fibrosis burden and liver disease severity between lean and non-lean MASLD patients, with a focused subgroup analysis in Hispanic patients. **Methods:** We conducted a cross-sectional study on inpatient adults with MASLD between January 2025 and January 2026 at a large urban safety-net hospital in a major metropolitan area. Lean was defined as BMI < 25 kg/m^2 (< 23 for Asian patients). Patients with other chronic liver diseases such as hepatitis B, hepatitis C, alcohol-related liver disease, autoimmune hepatitis, primary biliary cholangitis, and primary sclerosing cholangitis, were excluded. Noninvasive testing for fibrosis was assessed using FIB-4 and SAFE scores. Multivariable logistic regression evaluated lean status as a predictor of advanced fibrosis , defined as FIB-4 > 2.6 , and cirrhosis, based on imaging, adjusting for demographics, metabolic comorbidities, and liver biochemistries. A pre-specified subgroup analysis was performed in Hispanic patients. **Results:** A total of 1,545 patients with MASLD were included. 471 (30.5%) were classified as lean and 1,074 (69.5%) as non-lean. Lean patients were significantly older than non-lean patients (56.0 vs 52.8 years, $p = 0.001$), had lower triglyceride levels (148.0 vs 257.1, $p = 0.001$) and mean lower systolic blood pressure (129.2 vs 133.1 mmHg, $p = 0.004$). Lean patients had significantly higher AST: ALT ratios (1.83 vs. 1.60, $p < 0.001$) and higher FIB-4 score (6.27 vs 5.32, $p = 0.05$) with the FIB-4 stage distribution differing between groups ($p = 0.016$) with lean patients more frequently classified within the F4–F6 fibrosis category (56.8% vs 52.5%). However, lean patients had lower mean SAFE score (194.3 vs 218.6, $p = 0.019$) and lower rates of cirrhosis (6.8% vs. 11.2%, $p = 0.010$). On multivariate analysis, lean status was independently associated with lower odds of cirrhosis (adjusted OR 0.46, 95% CI 0.29–0.69, $p < 0.001$). In a subgroup analysis, compared to their non-lean Hispanic counterparts, lean Hispanic patients had higher AST:ALT ratios (1.84 vs. 1.65, $p = 0.02$), but had lower odds of cirrhosis (adjusted OR 0.47, 95% CI 0.27–0.80, $p = 0.006$) and lower odds of advanced fibrosis (adjusted OR 0.59, 95% CI 0.37–0.93, $p = 0.02$). **Conclusion:** Lean MASLD patients demonstrated a distinct clinical and biochemical profile compared to non-lean MASLD patients. Despite exhibiting higher AST:ALT ratios and elevated FIB-4 scores, lean patients had lower rates of cirrhosis and lower odds of advanced liver disease. These findings highlight the heterogeneity of MASLD and reinforce the importance of individualized fibrosis risk stratification.

	Overall (N=1545)	Lean (N=471)	Non-Lean(N=1074)	p-value
Baseline demographics and clinical comorbidities				
Age [years]: Mean (SD)	53.76 (16.85)	56.01 (18.14)	52.77 (16.15)	0.0058*
Sex at birth : Male	1029 (66.6%)	313 (66.5%)	716 (66.7%)	0.98
Race				
White	186 (12%)	79 (16.8%)	107 (10%)	
Black	80 (5.2%)	35 (7.4%)	45 (4.2%)	
Asian	268 (17.3%)	74 (15.7%)	194 (18.1%)	
Other	996 (64.6%)	279 (59.2%)	719 (66.9%)	0.0001*
Ethnicity				
Hispanic	950 (61.5%)	266 (56.5%)	684 (63.7%)	
Non-Hispanic	595 (38.5%)	205 (43.5%)	390 (36.3%)	0.008*
Current Smoker : Yes	211 (13.7%)	75 (15.9%)	136 (12.7%)	0.07
Ever Smoker : Yes	402 (26%)	133 (28.2%)	269 (25%)	0.16
BMI : Mean (range)	27.92 (6.36)	21.83 (2.34)	30.59 (5.69)	<0.0001
Diabetes Mellitus: Yes	671 (43.4%)	195 (41.4%)	476 (44.3%)	0.31
Hypertension :Yes	825 (40.5%)	193 (41%)	432 (40.2%)	0.82
Hyperlipidemia : Yes	453 (29.3%)	136 (28.9%)	317 (29.5%)	0.85
Coronary artery disease :Yes	116 (7.5%)	39 (8.3%)	77 (7.2%)	0.51
Congestive Heart Disease :Yes	210 (13.6%)	64 (13.6%)	146 (13.6%)	1
Chronic Kidney Disease :Yes	101 (6.5%)	41 (8.7%)	60 (5.6%)	0.03*
Laboratory values and fibrosis scores on presentation				
SBP, mean (SD)	131.89 (24.16)	129.21 (23.64)	133.06 (24.3)	0.003*
A1C, mean (SD)	6.76 (2.14)	6.58 (2.24)	6.83 (2.1)	0.18
Triglycerides, mean (SD)	224.62 (481.61)	147.96 (191.13)	257.1 (558.1)	0.0005*
HDL, mean (SD)	46.01 (28.4)	48.77 (27.74)	44.85 (28.63)	0.12
LDL, mean (SD)	83.45 (45)	81.15 (45.31)	84.47 (44.88)	0.42
Fasting Glucose, mean (SD)	148.52 (99.26)	144.26 (103.75)	150.4 (97.21)	0.27
AST, mean (SD)	149.84 (269.02)	149.32 (271.97)	150.07 (267.86)	0.96
ALT, mean (SD)	110.93 (251.48)	93.48 (171.33)	118.58 (279.2)	0.03*
ALP, mean (SD)	161.2 (162.22)	180.25 (202.29)	152.91 (140.57)	0.009*
GGT, mean (SD)	533.62 (658.98)	548.98 (633.04)	524.93 (676.23)	0.62
Platelets, mean (SD)	206.21 (110.73)	209.44 (126.81)	204.79 (102.92)	0.48
FIB4 Score, mean (SD)	5.61 (8.7)	6.27 (8.83)	5.32 (8.62)	0.05
APRI Score, mean (SD)	2.86 (5.5)	3.12 (6.06)	2.75 (5.23)	0.26
SAFE Score, mean (SD)	211.20 (182.67)	194.30 (181.08)	218.61 (182.96)	0.019*
AST:ALT Ratio, mean (SD)	1.67 (1.09)	1.83 (1.09)	1.6 (1.08)	0.0001*
FIB4 Category				
Low <1.3	344 (23.6)	87 (19.6)	257 (25.4)	
Moderate (>=1.3 and <=2.6)	329 (22.6)	105 (23.6)	224 (22.1)	
Hight (>2.6)	783 (53.8)	252 (56.8)	531 (52.5)	0.05*
SAFE score risk				
Low <0	191 (13.2)	65 (14.6)	126 (12.5)	
Intermediate <100	251 (17.2)	86 (19.4)	165 (16.3)	
High >=100	1014 (69.6)	293 (66.0)	721 (71.2)	0.13
Cirrhosis	152 (9.8%)	32 (6.8%)	120 (11.2%)	0.01*

Table : Baseline characteristics, clinical comorbidities, laboratory values and fibrosis score on presentation stratified by lean vs non-lean

Disclosures: Hassan Sinan:Nothing to Disclose, Jazmin Mexia Cabrales:Nothing to Disclose, Fatima Shafiq:Nothing to Disclose, Madonna Johnson:Nothing

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to Disclose, Philip Juliano:Nothing to Disclose, Frances Lee:Nothing to Disclose.

3427 | PERFORMANCE OF THE METABOLIC DYSFUNCTION-ASSOCIATED FIBROSIS 5 (MAF-5) SCORE, FIBROSIS-4 (FIB-4) INDEX, AND ASPARTATE AMINOTRANSFERASE-TO-PLATELET RATIO INDEX (APRI) FOR IDENTIFYING SIGNIFICANT LIVER FIBROSIS IN A SAUDI COHORT: THE GENESIS STUDY

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Background: Non-invasive scores are recommended to triage patients at risk of significant liver fibrosis. The Metabolic Dysfunction-Associated Fibrosis 5 (MAF-5) score was recently derived and externally validated in European and Latin American populations. Performance in Middle Eastern cohorts is limited. We evaluated MAF-5, the Fibrosis-4 (FIB-4) Index, and the Aspartate Aminotransferase-to-Platelet Ratio Index (APRI) against vibration-controlled transient elastography (VCTE)-defined significant fibrosis in the Saudi GENESIS cohort. **Methods:** We analyzed 2,979 adults with valid VCTE and laboratory data enrolled in GENESIS. The reference outcome for fibrosis was liver stiffness measurement (LSM) ≥8 kPa by VCTE, indicating significant fibrosis. We calculated FIB-4, APRI, and MAF-5 using published formulas. APRI used a constant aspartate aminotransferase (AST) upper limit of normal of 40 U/L. We assessed discrimination using the area under the receiver operating characteristic curve (AUC). We reported sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy at prespecified high-risk cutoffs with Wilson 95% confidence intervals (CIs). **Results:** LSM ≥8 kPa was present in 57 of 2,979 participants (1.9%) in the GENESIS cohort. MAF-5 achieved the highest discrimination (AUC 0.868, 95% CI 0.821–0.916) and demonstrated higher discrimination than APRI (AUC 0.665, 95% CI 0.583–0.747) and FIB-4 (AUC 0.651, 95% CI 0.580–0.721). At the high-risk cutoff, MAF-5 (>1) detected 75.9% (95% CI 63.1–85.4) of cases with 84.3% specificity (95% CI 82.9–85.7). FIB-4 (>2.67) and APRI (>1.50) detected 1.8% (95% CI 0.3–9.4) and 0.0% (95% CI 0.0–6.4) of cases, respectively. PPV was low across all scores (MAF-5 9.1%, FIB-4 5.9%, APRI 0.0%), reflecting the low prevalence of significant fibrosis in this cohort. Overall accuracy was 84.2% for MAF-5, 97.4% for FIB-4, and 97.8% for APRI; the apparently higher accuracy of FIB-4 and APRI reflects their near-universal classification of participants as low-risk in a low-prevalence cohort rather than true diagnostic performance. **Conclusion:** MAF-5 showed better discrimination and substantially higher sensitivity for VCTE-defined significant fibrosis than FIB-4 and APRI in this Saudi cohort. FIB-4 and APRI at standard high cutoffs missed the majority of cases with LSM ≥8 kPa. These findings, limited by the small number of fibrosis cases, support further evaluation of MAF-5 in regional fibrosis screening pathways.

Table 1. Diagnostic performance of MAF-5, FIB-4, and APRI for liver stiffness measurement ≥8 kPa in the GENESIS cohort (n = 2,979).

Score	AUC (95% CI)	High-risk cutoff	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	Accuracy, % (95% CI)
MAF-5	0.868 (0.821–0.916)	>1	75.9 (63.1–85.4)	84.3 (82.9–85.7)	9.1 (6.7–12.0)	99.4 (99.0–99.7)	84.2 (82.7–85.5)
FIB-4	0.651 (0.580–0.721)	>2.67	1.8 (0.3–9.4)	99.4 (99.0–99.6)	5.9 (1.0–27.0)	97.9 (97.3–98.4)	97.4 (96.7–97.9)
APRI	0.665 (0.583–0.747)	>1.50	0.0 (0.0–6.4)	99.9 (99.7–100.0)	0.0 (0.0–56.1)	97.9 (97.3–98.4)	97.8 (97.2–98.3)

Abbreviations: APRI, Aspartate Aminotransferase-to-Platelet Ratio Index; AUC, area under the receiver operating characteristic curve; CI, confidence interval; FIB-4, Fibrosis-4 Index; MAF-5, Metabolic Dysfunction-Associated Fibrosis 5; NPV, negative predictive value; PPV, positive predictive value.

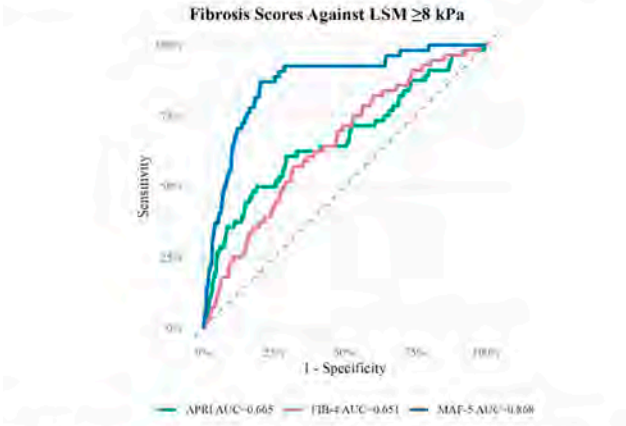


Figure 1. Receiver operating characteristic curves for the Metabolic Dysfunction-Associated Fibrosis 5 (MAF-5) score, the Fibrosis-4 (FIB-4) Index, and the Aspartate Aminotransferase-to-Platelet Ratio Index (APRI) against liver stiffness measurement (LSM) ≥8 kPa in the GENESIS cohort. The diagonal dashed line represents non-informative discrimination.

Abbreviations: APRI, Aspartate Aminotransferase-to-Platelet Ratio Index; AUC, area under the receiver operating characteristic curve; FIB-4, Fibrosis-4 Index; LSM, liver stiffness measurement; MAF-5, Metabolic Dysfunction-Associated Fibrosis 5.

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Alwaleed Almojel:Nothing to Disclose, Dieter Broering: Nothing to Disclose, Faisal Sanai:Nothing to Disclose, Waleed Alhazzani:Nothing to Disclose.

3428 | MASLD AS A PREDICTOR OF HEPATOTOXICITY AND CLINICAL OUTCOMES IN LUNG CANCER PATIENTS RECEIVING IMMUNE CHECKPOINT INHIBITORS: A PROPENSITY-MATCHED STUDY

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Background: Metabolic dysfunction–associated steatotic liver disease (MASLD) is increasingly recognized as a systemic metabolic disorder that may influence cancer outcomes, immune response, and susceptibility to liver injury. Although immune checkpoint inhibitors (ICIs) have significantly improved outcomes in lung cancer, hepatotoxicity remains an important immune-related adverse event. Data evaluating the impact of MASLD on ICI-related hepatotoxicity and other clinical outcomes in lung cancer are limited. We aimed to assess the association between MASLD and hepatotoxicity-related and systemic outcomes among lung cancer patients treated with ICIs. **Methods:** We performed a retrospective cohort study using the TriNetX Research Network. Adult lung cancer patients receiving immune checkpoint inhibitors (ICIs) were stratified by the presence or absence of MASLD. After propensity score matching for baseline demographic and clinical characteristics, 17,589 patients remained in each cohort. Post-matching outcomes included acute liver injury, acute liver failure, hyponatremia, ICU admission, hemolytic anemia, acute kidney injury (AKI), sepsis, gastrointestinal immune-related adverse events, and all-cause mortality. Associations were reported as odds ratios (ORs) with 95% confidence intervals (CIs). **Results:** After propensity matching, baseline characteristics were well balanced between cohorts. MASLD was associated with higher odds of acute liver injury (OR 2.38, 95% CI 1.88–3.02) and acute liver failure (OR 3.17, 95% CI 2.43–4.13). Increased odds of AKI, sepsis, hyponatremia, and GI immune-related adverse events were also observed (Table 1). Despite this, MASLD was associated with lower all-cause mortality (OR 0.78, 95% CI 0.73–0.84) and reduced ICU admission (OR 0.35, 95% CI 0.21–0.60). Kaplan-Meier analysis similarly demonstrated lower mortality in the MASLD cohort (HR 0.78, 95% CI 0.73–0.83; log-rank $P < 0.001$). **Conclusion:** In this large propensity-matched analysis, MASLD was associated with significantly increased odds of liver-related toxicity and systemic complications, including AKI, sepsis, hyponatremia, and GI immune-related adverse events. To our knowledge, this represents one of the largest real-world studies evaluating MASLD as a predictor of ICI-related hepatotoxicity in lung cancer. Although lower mortality was observed in the MASLD cohort, this finding should be interpreted cautiously given the potential for residual confounding and selection bias. These findings suggest MASLD may identify a high-risk subgroup warranting closer hepatic and systemic toxicity surveillance during ICI therapy.

Table 1. Propensity-Matched Analysis of Hepatic and Systemic Outcomes by MASLD Status in Lung Cancer Patients Receiving ICIs

Outcome	MASLD events / N	MASLD risk	No MASLD events / N	No MASLD risk	Risk difference (95% CI)	Risk ratio (95% CI)	Odds ratio (95% CI)	P value
Acute liver injury	234 / 17,589	1.33%	99 / 17,589	0.56%	0.77% (0.57 to 0.97)	2.36 (1.87-2.99)	2.38 (1.88-3.02)	<0.001
Acute liver failure	226 / 17,589	1.28%	72 / 17,589	0.41%	0.88% (0.68 to 1.07)	3.14 (2.41-4.09)	3.17 (2.43-4.13)	<0.001
Hyponatremia	1,907 / 17,589	10.84%	1,644 / 17,589	9.35%	1.50% (0.87 to 2.12)	1.16 (1.09-1.23)	1.16 (1.10-1.26)	<0.001
ICU admission	18 / 17,589	0.10%	51 / 17,589	0.29%	-0.19% (-0.28 to -0.10)	0.35 (0.21-0.60)	0.35 (0.21-0.60)	<0.001
Mortality	1,710 / 17,589	9.72%	2,124 / 17,589	12.08%	-2.35% (-3.00 to -1.70)	0.81 (0.76-0.85)	0.78 (0.73-0.84)	<0.001
Hemolytic anemia	52 / 17,361	0.30%	34 / 17,411	0.20%	0.10% (-0.00 to 0.21)	1.53 (1.00-2.36)	1.54 (1.00-2.37)	0.050
AKI	1,621 / 17,589	9.22%	1,428 / 17,589	8.12%	1.10% (0.51 to 1.69)	1.14 (1.06-1.22)	1.15 (1.07-1.24)	<0.001
Sepsis	1,326 / 17,589	7.54%	1,164 / 17,589	6.62%	0.92% (0.39 to 1.46)	1.14 (1.06-1.23)	1.15 (1.06-1.25)	<0.001
GI irAEs (Gastritis and colitis)	633 / 14,375	4.40%	525 / 15,287	3.43%	0.97% (0.53 to 1.41)	1.28 (1.14-1.44)	1.30 (1.15-1.46)	<0.001

Disclosures: Adham Obeidat:Nothing to Disclose, Muralidhar Idamakanti:Nothing to Disclose, Ahmad Alqam:Nothing to Disclose, Christopher Chang:Nothing to Disclose.

3429 | HETEROGENEOUS BRAIN INVOLVEMENT IN MASLD: INSIGHTS FROM CONTINUOUS AND PHENOTYPE-BASED ANALYSES

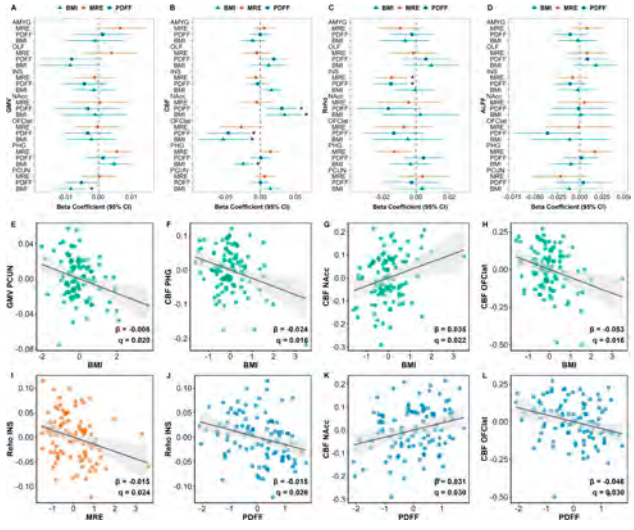
Zhuoru Jiang[1] Qian Chen[1] Jun Chen[2] Jie Li[3], [1]Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University, [2]Mayo Clinic Rochester, [3]Nanjing Drum Tower Hospital

Background: Previous studies have shown that liver fibrosis is associated with changes in brain imaging. However, the relationship between other dimensions of MASLD and brain imaging remains unclear. This study

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aims to determine which brain regions are associated with different parameters of MASLD, and then to observe the brain changes of MASLD subtypes according to these parameters. **Methods:** This study included 34 healthy controls and 101 MASLD patients. Regression models were used to examine associations of body mass index (BMI), hepatic fat content, and liver stiffness with brain structure, function and perfusion of pre-defined regions across the continuous disease spectrum. K-means clustering based on systemic metabolic and hepatic indices was applied to identify distinct clinical phenotypes and compare their neuroimaging profiles. **Results:** Higher BMI was associated with lower gray matter volume in the precuneus, increased cerebral blood flow in the nucleus accumbens, and reduced cerebral blood flow in the lateral orbitofrontal and parahippocampal regions. Higher hepatic fat content showed a similar perfusion pattern, whereas liver stiffness demonstrated a more limited association pattern and was linked mainly to reduced regional homogeneity in the insula. The subgroup characterized by severe obesity and steatosis exhibited the most pronounced brain abnormalities, whereas the liver stiffness-dominant phenotype showed less extensive alterations. **Conclusion:** The neurological involvement of MASLD is better characterized using complementary continuous and phenotype-based frameworks than by viewing the disease as a uniform entity. The findings suggest that obesity-related burden and hepatic steatosis are more strongly associated with multimodal brain abnormalities than liver stiffness in this cohort., highlighting the importance of moving beyond liver-centered evaluation in MASLD.



Disclosures: Zhuoru Jiang:Nothing to Disclose, Qian Chen:Nothing to Disclose, Jun Chen:Nothing to Disclose, Jie Li:Nothing to Disclose.

3430 | HIGH-DIMENSIONAL MASS CYTOMETRY PROFILING OF CIRCULATING IMMUNE ALTERATIONS IN MASLD AND DRUG-INDUCED STEATOSIS

Raúl J. Andrade[1] Daniel Di Zeo-Sánchez[2] Marina Villanueva[3] Vanesa Garrido-Rodríguez[4] Irene Díaz Alberola[3] Ángela Remesal Doblado[3] Gonzalo Matilla Cabello[2] Antonio Segovia-Zafra[3] José Pinazo Bandera[5] Miren Garcia Cortes[5] Francisco Ruiz Cabello[6] Mercedes Robles-Díaz[2] Eduardo García Fuentes[7] Camilla Stephens[2] M Lucena[2],
[1]IBIMA-Plataforma Bionand / Universidad de Málaga / CIBERehd, [2]IBIMA-Plataforma Bionand, UMA, CIBERehd, [3]IBIMA-Plataforma Bionand, UMA, [4]IBIMA Plataforma Bionand, UMA, [5]IBIMA-Plataforma Bionand, HUVV, [6]IBS, Hospital Universitario Virgen de las Nieves, [7]IBIMA-Plataforma Bionand, CIBERehd

Background: Immune mechanisms contributing to MASLD progression and drug-induced steatosis (DIS) remain incompletely characterized. We applied high-dimensional single-cell mass cytometry (CyTOF) to define circulating immune alterations across MASLD fibrosis stages and compare MASLD with DIS. **Methods:** Peripheral blood was obtained from 32 healthy controls (HC), 17 patients exposed to steatogenic drugs with normal liver tests (CON), 13 DIS patients, 16 MASLD patients with F0-F1 fibrosis, and 15 MASLD patients with F2-F4 fibrosis. Whole blood was analyzed by CyTOF using a 30-marker panel. PBMC and granulocyte populations were identified by unsupervised FlowSOM and PhenoGraph clustering, respectively. Cell frequencies and median marker intensities were compared using Kruskal-Wallis/Dunn tests with Benjamini-Hochberg correction. **Results:** 38 PBMC metaclusters and 17 granulocyte clusters were identified. Compared with HC, MASLD F0-F1 and F2-F4 patients showed 29 and 28 significantly altered immune parameters, respectively. Regardless of fibrosis stage, MASLD patients exhibited higher frequency of an activated γδ T-cell-enriched metacluster, reduced CD127 expression in CD4+ T-cell subsets with mixed Th phenotypes and in MAIT/NKT-like cells. MASLD with F2-F4 showed additional loss of MAIT/NKT-like cells and lower frequency of activated plasmacytoid dendritic cells than HC. Differences between MASLD fibrosis stages were limited to the granulocyte compartment, where F2-F4 patients showed lower CD45RA expression than F0-F1 patients in several neutrophil clusters. DIS showed no significant differences compared with CON or MASLD F0-F1, but displayed higher activated pDC frequency than MASLD F2-F4.

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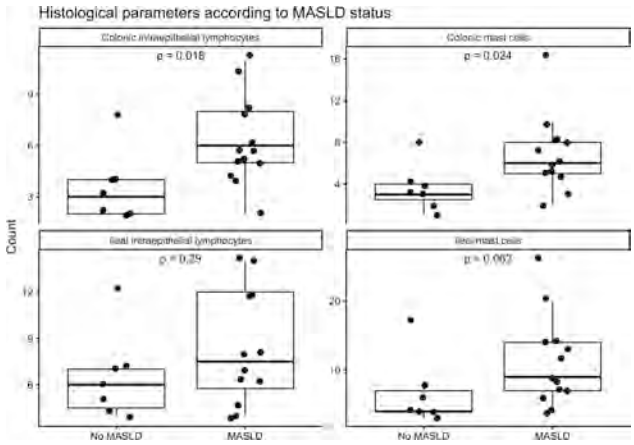
Conclusion: MASLD was associated with a circulating immune profile consistent with chronic immune activation and altered immune regulation, involving γδ T cells, reduced CD127 expression in T-cell subsets, and granulocyte remodeling. The additional reduction of MAIT/NKT-like cells in MASLD F2-F4 may reflect overactivation or exhaustion of innate-like T cells, potentially contributing to advanced disease by limiting their regulatory functions. These findings highlight the potential of immune profiling for patient risk stratification and monitoring in steatotic liver disease, paving the way for more personalized patient management. Funding: CIBERehd-ISCIII-FEDER, PI19/00883, PI21/01248, PID2022-140169OB-C21, PI24/0125, DGP_PIDI_2024_002644, HORIZON-HLTH-2022-STAYHLTH-02.

Disclosures: Raúl J. Andrade:Nothing to Disclose, Daniel Di Zeo-Sánchez:Nothing to Disclose, Marina Villanueva:Nothing to Disclose, Vanesa Garrido-Rodríguez:Nothing to Disclose, Irene Díaz Alberola:Nothing to Disclose, Ángela Remesal Doblado:Nothing to Disclose, Gonzalo Matilla Cabello:Nothing to Disclose, Antonio Segovia-Zafra:Nothing to Disclose, José Pinazo Bandera:Nothing to Disclose, MIREN GARCIA CORTES:Gilead: Speaking and Teaching, ORPHALAN: Speaking and Teaching, IPSEN: Advisor, EISAI: Speaking and Teaching, Francisco Ruiz Cabello: Nothing to Disclose, Mercedes Robles-Díaz:Nothing to Disclose, Eduardo García Fuentes:Nothing to Disclose, Camilla Stephens:Nothing to Disclose, M Lucena:Nothing to Disclose.

3431 | INTESTINAL MUCOSAL AND IMMUNE ALTERATIONS IN MASLD: A PILOT STUDY

Nicolás Ortiz-López[1] Tamara Alarcón[1] María Jesús Vera[2] Camila Farías[2] Rodrigo Valenzuela[2] Jaime Poniachik[1], [1]Hospital Clínico Universidad de Chile, Santiago, Chile, [2]Universidad de Chile, Santiago, Chile

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) has been increasingly associated with alterations in the gut–liver axis. However, intestinal histological findings in MASLD remain poorly characterized in humans. We aim to characterize histological alterations in the intestinal mucosa in patients with MASLD. **Methods:** In this prospective cross-sectional pilot study, consecutive adults undergoing screening colonoscopy were recruited. Participants with known inflammatory bowel disease, functional gastrointestinal disorders, or other chronic liver diseases were excluded. Ileal and colonic biopsies were obtained, and all participants subsequently underwent FibroScan®. MASLD was defined by the presence of hepatic steatosis and at least one cardiometabolic risk factor. Histological evaluation was performed by a blinded gastrointestinal pathologist using hematoxylin-eosin, alcian blue, and Giemsa stains. **Results:** Twenty patients were included (13 with MASLD and 7 without MASLD). Median age was 60 (47–65) years in the MASLD group and 62 (55–65) years in the non-MASLD group. Patients with MASLD had significantly higher body mass index. Colonic intraepithelial lymphocyte counts per 100 enterocytes were significantly higher in MASLD patients compared with controls (6 [2–11] vs 3 [2–8], p = 0.018). Colonic mast cell density per high-power field was also increased in MASLD (6 [2–16] vs 3 [1–8], p = 0.024). Ileal mast cell counts showed a similar trend in MASLD patients (9 [4–26] vs 4 [3–17], p = 0.062). Colonic immune alterations were more pronounced than ileal changes (Figure). Additional histological findings, including epithelial erosions, architectural alterations, mucin depletion, and cytoplasmic vacuolization, were observed without significant between-group differences. Correlation analyses demonstrated a positive correlation between colonic mast cell density and liver stiffness measurements (rho = 0.49, p = 0.048), while colonic intraepithelial lymphocyte counts showed a similar non-significant trend (rho = 0.46, p = 0.061). **Conclusion:** MASLD was associated with increased colonic immune cell infiltration, particularly intraepithelial lymphocytes and mast cells. The observed correlations between colonic immune cell density and liver stiffness measurements suggest a potential link between intestinal immune activation and liver disease severity in MASLD. These findings support a potential role of intestinal immune activation in MASLD pathophysiology and further reinforce the relevance of the intestine within the gut–liver axis.



Disclosures: Nicolás Ortiz-López:Nothing to Disclose, Tamara Alarcón:Nothing to Disclose, María Jesús Vera:Nothing to Disclose, Camila Farías:Nothing to Disclose, Rodrigo Valenzuela:Nothing to Disclose, Jaime Poniachik:Nothing to Disclose.

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3432 | LISINOPRIL FOR FIBROSIS AND HEPATOCELLULAR CARCINOMA RISK MODULATION IN MASLD WITH ADVANCED FIBROSIS: RESULTS FROM A PHASE IIA MULTICENTER CLINICAL TRIAL

Ju Dong Yang[1] Manal Abdelmalek[2] Cynthia Moylan[3] Augusto Villanueva[4] Douglas Dieterich[5] Masha Kocherginsky[6] Latifa Bazzi[6] Tia Schering[7] Kelly Benante[7] Yujin Hoshida[8] Courtney Katz[8] Osama Khattab[1] Ashley Kim[1] Manaf Alsudaney[1] Mai Abdusamad[1] Ekihiro Seki[1] Jieun Kim[1] Luz Maria Rodriguez[9] Asad Umar[9] Gary DellaZanna[9] Mazen Noureddin[10] Seema Khan[11], [1]Karsh Division of Gastroenterology and Hepatology, Cedars-Sinai Medical Center, Los Angeles, CA, USA, [2]Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, USA, [3]Division of Gastroenterology, Duke University Health System, Durham, NC, USA, [4]NYU Langone Health, [5]Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA, [6]Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL,, [7]Robert H. Lurie Comprehensive Cancer Center, Northwestern Memorial Hospital, Chicago, IL, USA, [8]Division of Digestive and Liver Diseases, University of Texas Southwestern Medical Center, Dallas, T, [9]Division of Cancer Prevention, NCI, Bethesda, MD, USA, [10]Lynda K. and David M. Underwood Center for Digestive Disorders Sherrie & Alan Conover Center for Liv, [11]Department of Surgery, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Background: Metabolic dysfunction–associated steatotic liver disease (MASLD) is an emerging leading cause of hepatocellular carcinoma (HCC). The renin–angiotensin system contributes to hepatic fibrogenesis and carcinogenesis. Lisinopril, an angiotensin-converting enzyme inhibitor, has demonstrated anti-fibrotic and anti-inflammatory effects in preclinical models and may reduce HCC risk. This phase IIa study evaluated the effect of lisinopril on fibrosis and HCC-related biomarkers in patients with MASLD and advanced fibrosis. **Methods:** Multicenter, single-arm phase IIa clinical trial enrolled adults with MASLD and advanced fibrosis based on liver histology or screening transient elastography (TE) between12-25kPa with a target enrollment goal of 45. Participants received lisinopril 10 mg daily for 24 weeks. The primary endpoint was the change in PRO-C3. Secondary endpoints included changes in PRO-6, hepatic steatosis (CAP by TE), liver stiffness by magnetic resonance elastography [MRE] and TE, FIB-4, NFS, and inflammatory cytokines. Exploratory endpoints included changes in PLSec, liver enzymes, hepatic steatosis (MRI PDFF) and blood pressure. We hypothesized that treatment of MASLD with advanced fibrosis using lisinopril will lead to improvement in PRO-C3 values, which will correlate with decrease in measurements of MASLD disease activity. **Results:** A total of 35 patients (median age 63, female 43%, Hispanic 31%) were enrolled and started the intervention. Participants had a median liver stiffness of 15.7 kPa and CAP of 309 dB/m at baseline. The primary endpoint, change in PRO-C3, did not demonstrate a significant difference after 24 weeks of lisinopril therapy (**Table**). Despite this, significant improvements were observed in several key secondary endpoints. Hepatic steatosis decreased as measured by CAP (mean 320 to 307 dB/m; $p = 0.04$), and liver stiffness measured by MRE improved (mean 4.78 to 4.48 kPa; $p = 0.04$). Exploratory analyses demonstrated additional favorable changes. Systolic blood pressure significantly decreased (133 to 127 mmHg; $p < 0.01$). Alkaline phosphatase also declined (102 to 94 U/L; $p = 0.03$), suggesting potential improvement in cholestatic or inflammatory pathways. The prognostic liver secretome signature (PLSec), a novel biomarker associated with HCC risk, showed a trend toward reduction (3.26 to 2.81; $p = 0.09$). Lisinopril was generally well-tolerated. Grade ≥ 3 adverse events were infrequent ($n = 4$) and included infection and gastrointestinal events, not related to intervention. **Conclusion:** Lisinopril did not significantly improve PRO-C3 but demonstrated favorable changes in steatosis (CAP) and liver stiffness (MRE), with promising signals in PLSec, an exploratory HCC surrogate biomarker. The treatment was safe and supports further investigation in larger trials.

Table

Parameter	Baseline	Post-Treatment	P-value
PRO-C3 (ng/mL)	48	49	0.7
PRO-C6 (ng/mL)	14.1	13.6	0.6
CAP (dB/m)	320	307	0.04
MRE stiffness (kPa)	4.78	4.48	0.04
TE stiffness (kPa)	16.1	16.7	0.8
FIB-4 score	2.10	2.17	0.2
NFS	0.02	-0.01	0.9
Systolic BP (mmHg)	133	127	<0.01
MRI PDFF (%)	9	8	0.6
AST(U/L)	46	43	0.6
ALT(U/L)	55	51	0.2
Bilirubin (mg/dL)	0.75	0.76	0.7
ALP (U/L)	102	94	0.03
PLSec	3.26	2.81	0.09

Disclosures: Ju Dong Yang:Exact Sciences: Consultant, Exact Sciences: Consultant, AstraZeneca: Consultant, AstraZeneca: Consultant, Eisai: Consultant, Eisai: Consultant, Fujifilm Medical Sciences: Consultant, Fujifilm Medical Sciences: Consultant, Exact Sciences: Consultant, Exact Sciences: Consultant, AstraZeneca: Consultant, AstraZeneca: Consultant, Eisai: Consultant, Eisai: Consultant, Fujifilm Medical Sciences: Consultant, Fujifilm Medical Sciences: Consultant, Manal Abdelmalek:89Bio, Akero, Madrigal, Inventiva, Novo Nordisk, , Intercept, Merck,: Advisor, Hanmi, Novo Nordisk: Consultant, Madrigal,

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3433 | SEX-STRATIFIED DIETARY CORRELATES OF MASLD IN SAUDI ADULTS: LOWER CAFFEINE INTAKE AMONG WOMEN IN THE GENESIS COHORT

Saleh Alqahtani[1] Tagreed Mazi[2] Shadan AlMuhaidib[3] Samar Alqussayer[3] Habeeb Razack[2] Basmah Khoja[4] Layan Alsubki[5] Saleh Alessy[5] Jehan Mahdi[6] Sara Khalil[6] Mona Ismail[7] Khalid AlNaamani[8] Waleed Alhazzani[3], [1]King Faisal Specialist Hospital & Research Center, [2]King Saud University, Riyadh, Saudi Arabia, [3]Research and Innovation Institute, Ministry of Defense Health Services, Riyadh, Saudi Arabia, [4]King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia, [5]King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia, [6]King Fahad Armed Forces Hospital, Jeddah, Saudi Arabia, [7]Imam Abdulrahman Bin Faisal University, [8]The Medical City for Military and Security Services, Muscat, Oman

Background: Metabolic dysfunction–associated steatotic liver disease (MASLD) is the most common chronic liver disease worldwide, yet sex-stratified dietary correlates remain poorly characterized in Middle Eastern populations. We aimed to characterize sex-stratified dietary intake patterns associated with MASLD in Saudi adults enrolled in the prospective GENESIS cohort. **Methods:** We conducted a cross-sectional analysis within the prospective, population-based GENESIS study across seven primary care centers in Saudi Arabia between March 2024 and June 2025. Eligible adults underwent clinical assessment, laboratory testing, standardized vibration-controlled transient elastography (VCTE)-based hepatic phenotyping, and structured dietary assessment using a food frequency questionnaire (FFQ). MASLD was defined as controlled attenuation parameter (CAP) ≥ 268 dB/m with ≥ 1 cardiometabolic risk factor. We compared FFQ-derived intake of energy, macronutrients, fatty acids, and micronutrients between participants with and without MASLD, stratified by sex, using non-parametric tests. **Results:** Of 2,979 participants in the GENESIS cohort (mean age 41.9 years), 1,486 were men (49.9%) and 1,493 were women (50.1%). MASLD was present in 649 men (43.7%) and 462 women (30.9%). Participants with MASLD reported higher total daily energy intake than those without MASLD (2,729 versus 2,616 kcal/day, $P = 0.04$), and similar patterns were observed for several micronutrients, carotenoids, and saturated fatty acids across both sexes. Caffeine intake showed a sex-stratified pattern. Women with MASLD reported lower caffeine intake than those without MASLD (77.4 versus 104.3 mg/day; interquartile ranges [IQRs] 57.9–135.9 and 63.4–165.1, respectively; $P < 0.001$), representing a 25.8% relative difference. In men, caffeine intake did not differ between groups (143.2 versus 143.6 mg/day, $P = 0.86$). **Conclusion:** In this cross-sectional analysis within a prospective Saudi cohort, MASLD was associated with higher reported overall dietary intake, while lower caffeine intake was observed as an exploratory sex-stratified correlate among women with MASLD. This inverse association was observed despite higher total energy intake in the MASLD group, distinguishing caffeine from the broader dietary pattern and warranting further evaluation in energy-adjusted and metabolic-adjusted analyses. These findings support

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prospective evaluation of caffeine intake as a sex-stratified dietary correlate of MASLD risk.

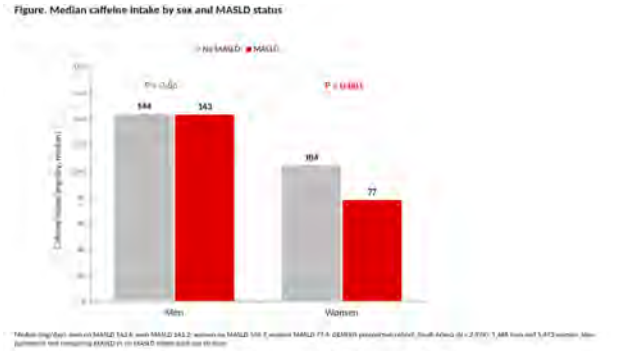


Figure 1. Sex-specific differences in caffeine intake by MASLD status.
GENESIS prospective cohort, Saudi Arabia (N = 2,979); 1,486 men (649 with MASLD) and 1,493 women (462 with MASLD). Median caffeine intake (mg/day): men without MASLD 143.6 versus men with MASLD 143.2 (P=0.86); women without MASLD 104.3 versus women with MASLD 77.4 (P<0.001). Group differences within each sex stratum assessed using non-parametric tests.

Disclosures: Saleh Alqahtani:Nothing to Disclose, Tagreed Mazi:Nothing to Disclose, Shadan AlMuhaidib:Nothing to Disclose, Samar Alqussayer:Nothing to Disclose, Habeeb Razack:Nothing to Disclose, Basmah Khoja:Nothing to Disclose, Layan Alsubki:Nothing to Disclose, Saleh Alessy:Nothing to Disclose, Jehan Mahdi:Nothing to Disclose, Sara Khalil:Nothing to Disclose, Mona Ismail:Nothing to Disclose, Khalid AlNaamani:Nothing to Disclose, Waleed Alhazzani: Nothing to Disclose.

3434 | DOACS IN MASLD: ARE WE TARGETING FIBROSIS BY ACCIDENT?

Candy Lin[1] Mark Thursz[1] Shahid Khan[1] Fernando Lorra[1] Michael Yee[2] Pinelopi Manousou[1], [1]Imperial College London, [2]Imperial College Healthcare Trust

Background: Fibrosis stage is the main determinant of liver-related and all-cause mortality in metabolic dysfunction-associated steatotic liver disease (MASLD), yet effective antifibrotic therapies remain limited. Thrombin and Factor Xa promote fibrogenesis via protease-activated receptor (PAR) signalling in hepatic stellate cells. Direct oral anticoagulants (DOACs) inhibit these proteases and are commonly prescribed in patients with MASLD. We therefore hypothesised that DOAC exposure would be associated with reduced fibrosis progression in MASLD. **Methods:** We conducted a retrospective cohort study of adults with MASLD at Imperial College Healthcare NHS Trust (2017-2026), assessing fibrosis longitudinally using Fibrosis-4 (FIB-4) and transient elastography (TE) in a subset of patients. Exposure was defined as an active DOAC prescription at baseline. Consecutive patients receiving DOACs were compared with BMI and T2DM-matched MASLD control patients not receiving DOAC therapy. ANCOVA was used to compare follow-up FIB-4 between the DOAC-exposed group and the controls, adjusting for baseline FIB-4, age, sex, BMI, T2DM and hypertension. **Results:** Among 455 patients, 117 (25.7%) were DOAC-exposed. DOAC-exposed patients were older (median 65 vs 63 years, $p = .023$) and had higher baseline FIB-4 (2.16 vs 1.55, $p < .001$). Unadjusted FIB-4 change did not differ between groups (median ΔFIB-4: 0.03 vs 0.04, $p = .844$). In adjusted analyses, DOAC exposure was not associated with follow-up FIB-4 (β = -0.35, 95% CI -1.18-0.48; p = .405). Baseline FIB-4 was the strongest predictor of follow-up FIB-4 (β = 1.20, 95% CI 0.68-1.72; $p < .001$). TE-based analyses were consistent (ΔLSM: -0.9 vs -0.5kPa; p = .849). **Conclusion:** DOAC exposure was not associated with fibrosis progression in this cohort. Competing fibrogenic drivers (including lipotoxicity, inflammation and compensatory profibrotic pathways not targeted by anticoagulation) limit clinical translation of experimental antifibrotic effects. Prospective studies, including randomised controlled trials, evaluating histological or imaging-based endpoints, longer follow-up and detailed exposure stratification in people with MASLD are warranted.

Disclosures: Candy Lin:Nothing to Disclose, Mark Thursz:GSK: Consultant, Resolution Tx: Consultant, Intercept: Consultant, Galecto: Consultant, Durect: Consultant, Shahid Khan:Nothing to Disclose, Fernando Iorra:Nothing to Disclose, Michael Yee:Nothing to Disclose, Pinelopi Manousou:Nothing to Disclose.

3435 | A NON-INVASIVE DIAGNOSTIC PREDICTION MODEL FOR LEAN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE PATIENTS

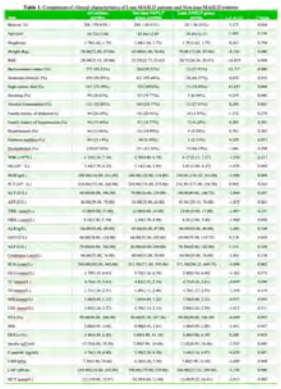
Weihua Cao[1] Yao Xie[1] Minghui Li[1], [1]Beijing Ditan Hospital, Capital Medical University

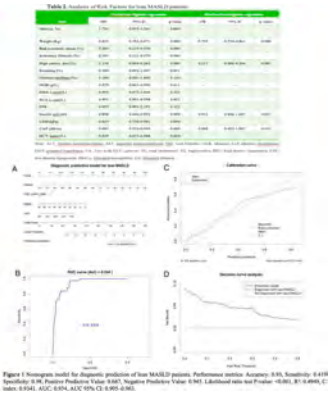
Background: Lean metabolic dysfunction-associated steatotic liver disease (Lean MASLD) is increasingly recognized, yet distinguishing it from non-lean MASLD remains a clinical challenge due to overlapping features. This study aimed to develop and validate a non-invasive diagnostic prediction model specifically for identifying Lean MASLD patients. **Methods:** This retrospective study included patients who underwent liver biopsy were diagnosed with MASLD at Beijing Ditan Hospital. Patients were categorized into Lean MASLD (BMI < 24 kg/m², n = 43) and Non-lean MASLD (BMI ≥ 24 kg/m², n = 440) groups. Clinical, laboratory, and transient elastography data were compared. Univariate and multivariate logistic regression analyses

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were performed to identify independent predictors of Lean MASLD, which were then used to construct a nomogram. **Results:** A total of 483 biopsy-proven MASLD patients were retrospectively enrolled. Compared to the Non-lean group, the Lean MASLD group had significantly lower weight (median 65.00 vs. 79.00 kg, P < 0.001), BMI (23.29 vs. 28.71, P < 0.001), insulin (7.80 vs. 13.82 μU/ml, P < 0.001), liver stiffness measurement (LSM, 6.20 vs. 7.40 kPa, P < 0.001), and controlled attenuation parameter (CAP, 198.00 vs. 268.00 dB/m, P < 0.001), and a lower prevalence of high-caloric diet (34.88% vs. 80.00%, P < 0.001),in Table 1. Multivariate analysis confirmed lower weight (OR = 0.793, P < 0.001), lower insulin (OR = 0.915, P = 0.021), lower CAP (OR = 0.988, P = 0.011), and absence of a high-caloric diet (OR = 0.217, P = 0.001) as independent negative predictors for Lean MASLD in Table 2. The resulting nomogram demonstrated excellent discrimination, with an AUC of 0.934 (95% CI: 0.905-0.963), specificity of 0.98, and a significant likelihood ratio test (P < 0.001) in Figure 1. **Conclusion:** A highly specific nomogram based on readily available clinical parameters can effectively discriminate Lean MASLD from Non-lean MASLD. This tool may assist clinicians in the non-invasive identification of Lean MASLD, facilitating targeted management.





Disclosures: Weihua Cao:Nothing to Disclose, Yao Xie:Nothing to Disclose, Minghui Li:Nothing to Disclose.

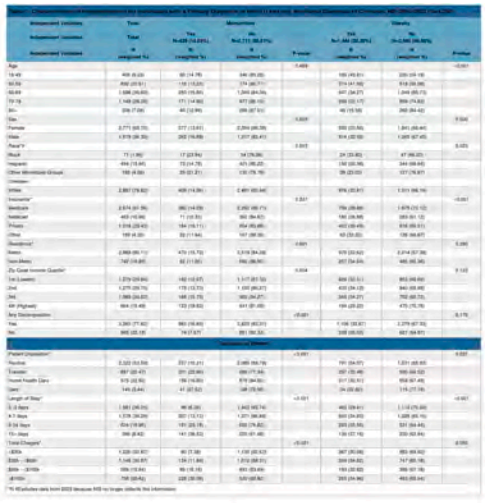
3436 | MALNUTRITION AND OBESITY ARE INDEPENDENTLY ASSOCIATED WITH NON-ROUTINE DISCHARGE AMONG HOSPITALIZED PATIENTS WITH MASLD CIRRHOSIS

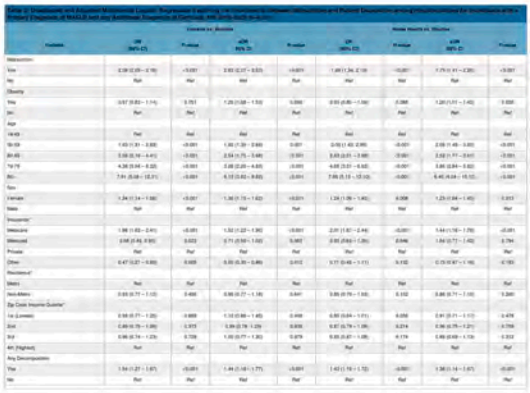
McKenna Andrews[1] Paul Scott[2] Melissa White-Archer[2] Chakradhar Reddy[3], [1]East Tennessee State University Department of Internal Medicine, [2]East Tennessee State University, [3]East Tennessee State University Division of Gastroenterology

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a leading cause of cirrhosis and liver-related hospitalization in the United States. We evaluated the association of malnutrition and obesity with inpatient outcomes among hospitalizations involving MASLD cirrhosis. **Methods:** Hospitalizations with a primary diagnosis of MASLD/NAFLD/ MASH (ICD-10: K76.0, K75.81) were selected from the Nationwide Inpatient Sample (2016-2023), Healthcare Cost and Utilization Project, Agency for Healthcare Research and Quality. Alcohol-related liver disease or viral hepatitis were excluded. Malnutrition was defined using ICD-10 codes E40–E46 or R64, and obesity using E66.x codes excluding E66.3. The primary outcome was discharge disposition; secondary outcomes included length of stay and total hospital charges. Weighted descriptive statistics and chi-square analyses were performed. Multinomial logistic regression models evaluated relationships between malnutrition, obesity, and discharge disposition before and after adjustment for demographic and clinical covariates, including decompensation events. An interaction term assessed whether obesity modified the effect of malnutrition on patient disposition. **Results:** Among 4,350 hospitalizations, most patients were older than 59 years (70.2%), female (63.7%), White (79.8%), and insured by Medicare (61.6%). Malnutrition was present in 14.7% and obesity in 33.2% of hospitalizations. Malnutrition was significantly associated with discharge disposition, length of stay, and total hospital charges (all p < 0.001). After excluding in-hospital deaths (N = 149), 4,201 hospitalizations were included in regression analyses. In adjusted models, malnutrition (aOR 2.83, 95% CI 2.27–3.53; p < 0.001) and obesity (aOR 1.28, 95% CI 1.08–1.53; p = 0.006) were associated with increased odds of transfer to another facility and discharge with home health services (malnutrition: aOR 1.79, 95% CI 1.41–2.26; p < 0.001; obesity: (aOR 1.20, 95% CI 1.01–1.42; p = 0.035) compared to routine discharge. No significant interaction was observed between malnutrition and obesity before (p = 0.655) or after adjustment (p = 0.790). Stratified analyses showed malnutrition remained associated with higher odds of transfer among both obese (aOR 2.59, 95% CI 1.65–4.06; p < 0.001) and non-obese patients (aOR 2.91, 95% CI 2.26–3.75; p < 0.001). Malnutrition was associated with home health discharge only among non-obese patients (aOR 1.86, 95% CI 1.42–2.43; p < 0.001). **Conclusion:** Among hospitalizations involving MASLD cirrhosis, both malnutrition and obesity were independently associated with increased odds of non-routine discharge. Malnutrition demonstrated the strongest association with adverse disposition outcomes regardless of obesity status. These findings support nutritional screening in hospitalized patients with MASLD cirrhosis.

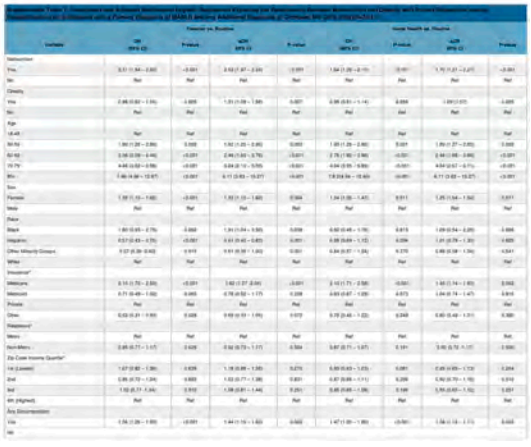
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Disclosures: McKenna Andrews:Nothing to Disclose, Paul Scott:Nothing to Disclose, Melissa White-Archer: Nothing to Disclose, Chakradhar Reddy:Gilead Sciences: Speaking and Teaching, Madrigal Pharma: Speaking and Teaching, Abbvie Pharma: Speaking and Teaching, Ipsen: Advisory Board.

3437 | PHYSICIANS' KNOWLEDGE, ATTITUDES, AND PRACTICES REGARDING PHYSICAL ACTIVITY IN MASLD MANAGEMENT: A CROSS-SECTIONAL SURVEY FROM SAUDI ARABIA

Salvatore Petta[1] Faisal Abaalkhail[2] Saad Alghamdi[3] Mohammed Alghamdi[4] Reem AlAhmed[2] Amwaj Alanazi[2] Sadeem Aldarwesh[2] Alanoud AlAdel[5] Ciro Celsa[1] Grazia Pennisi[1] Gabriele Di Maria[1] Saleh Alqahtani[2], [1]University of Palermo, Palermo, Italy, [2]King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia, [3]King Faisal Specialist Hospital and Research Center, [4]King Fahad Military Medical Complex, Dhahran, Saudi Arabia, [5]King Saud University, Riyadh, Saudi Arabia

Background: Physical activity is a cornerstone intervention for metabolic dysfunction-associated steatotic liver disease (MASLD), yet its implementation in clinical practice remains suboptimal. In Saudi Arabia, local data on physician-level implementation gaps remain limited. We assessed physicians' knowledge, attitudes, and practices regarding physical activity in the management of MASLD across Saudi Arabia. **Methods:** This cross-sectional survey (December 2025–January 2026) included hepatologists and other physicians managing patients with MASLD across Saudi Arabia. A 30-item questionnaire, developed by expert hepatologists and assessed for face and content validity, measured physical-activity knowledge, attitudes, clinical practices including counseling and referral, guideline use, and perceived barriers. Responses were compared by specialty (hepatologists vs. non-hepatologists) and experience (<10 vs. ≥ 10 years) using chi-square or Fisher's exact tests, with p-values adjusted using the Benjamini-Hochberg false discovery rate correction. **Results:** Among 171 physicians (63.7% hepatologists), 87.7% rated physical activity as "very important" in MASLD management. Knowledge gaps were substantial: only 58.5% correctly identified MASLD prevalence in Saudi Arabia, and only 23.4% correctly identified advanced fibrosis prevalence in the general population, with no significant difference by specialty or experience for either item. Guideline adherence differed markedly: 33.9% of non-hepatologists followed no clinical guidelines vs. 5.5% of hepatologists ($p<0.001$). Although 52.0% counseled at every visit, 76.6% spent <3 minutes doing so, with low use of written materials (8.2%) or specialist referrals (11.1%). Primary barriers were time constraints (62.6%), lack of resources (52.0%),

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and limited referral options (50.3%). Interest in additional training was high (70.8%), particularly among non-hepatologists. **Conclusion:** Despite broadly positive attitudes, Saudi physicians reported significant knowledge gaps and implementation barriers for physical activity counseling in MASLD. The low rate of guideline use among non-hepatologists represents a critical quality-of-care gap. Targeted educational interventions, enhanced guideline dissemination to non-specialists, and improved access to exercise specialists may help translate evidence into routine clinical practice.

Disclosures: Salvatore Petta:Madrigal: Consultant, Novonordisk: Consultant, Boehringer: Consultant, Faisal Abaalkhail:Nothing to Disclose, Saad Alghamdi: Nothing to Disclose, Mohammed Alghamdi:Nothing to Disclose, Reem AlAhmed:Nothing to Disclose, Amwaj Alanazi:Nothing to Disclose, Sadeem Aldarwesh:Nothing to Disclose, Alanoud AlAdel:Nothing to Disclose, Ciro Celsa:Nothing to Disclose, Grazia Pennisi:Nothing to Disclose, Gabriele Di Maria:Nothing to Disclose, Saleh Alqahtani:Nothing to Disclose.

3439 | PREVALENCE OF CHYLOMICRONEMIA SYNDROME AND SEVERE HYPERTRIGLYCERIDEMIA AMONG PATIENTS WITH HEPATIC STEATOSIS IN THE UNITED STATES

Lana Bridi[1] Ricki Bettencourt[2] Egbert Madamba[2] Matthew Tsai[2] Denise Kalmaz[2] Nedret Copur-Dahi[2] Rohit Loomba[2], [1]University of California San Diego, [2]University of California, San Diego

Background: Dysregulated lipid metabolism is closely linked to steatotic liver disease and impacts management. There is limited data on the prevalence of triglyceride (TG) abnormalities, including chylomicronemia syndrome and severe hypertriglyceridemia (HTG) among individuals with steatosis. The objective is to determine the prevalence of TG disorders among patients who are overweight or obese with MRI-determined hepatic steatosis. **Methods:** This study is a cross-sectional analysis of a prospective cohort study of patients with overweight or obesity and hepatic steatosis, defined by MRI-PDFF $\geq$5%, residing in the Greater San Diego Area. Participants were recruited from primary care clinics and using community-based strategies. They underwent standardized research visits with imaging (MRI-PDFF, MRE, or VCTE with CAP). HTG was defined as $\geq$150 mg/dL, severe HTG as $\geq$500 mg/dL, and chylomicronemia as $\geq$880 mg/dL. Multivariable logistic regression evaluated associations of TG levels with steatosis and fibrosis. **Results:** The study included 855 participants. The mean age was 51.2 ($\pm$13) years, with 52.9% female and 38.2% Hispanic. Type 2 diabetes was present in 24.4%, and 61.0% had obesity. HTG was present in 33.3%, while severe HTG or chylomicronemia were rare (0.7%, n = 6). Participants with HTG had significantly higher prevalence of metabolic syndrome (81.7% vs 28.2%, $p < 0.0001$) and type 2 diabetes (30.5% vs 21.3%, $p = 0.001$); there was no significant difference in obesity rates (62.5% vs 60.1% $p = 0.764$) or FIB-4 score (0.9 vs 0.9, $p = 0.058$). Mean MRI-PDFF differed significantly, measuring 14.3% in severe HTG or chylomicronemia, 14.6% in HTG, and 7.5% in those without HTG ($p < 0.0001$). Mean MRE was significantly higher among those with HTG compared to those without (2.3 kPa vs 2.2 kPa, $p = 0.036$). TGs had a graded association with hepatic steatosis (adjusted OR per 100 mg/dL increase 2.10, 95% CI 1.63–2.72; $p < 0.0001$). Steatosis prevalence rose from 45.7% (Q1) to 79.8% (Q4) (adjusted OR 4.46, 95% CI 2.89–6.89; $p < 0.0001$). TG levels correlated with MRI-PDFF ($\rho = 0.348$), insulin resistance (HOMA-IR $\rho = 0.315$), and inversely with HDL ($\rho = -0.398$) ($p < 0.001$). No significant association was observed between TG level quartiles and advanced fibrosis (p-trend = 0.917). **Conclusion:** While severe HTG and chylomicronemia are rare, HTG is common and shows a strong dose-dependent association with steatosis but not fibrosis. These findings, in conjunction with what is known regarding TG dysregulation in hepatic steatosis pathogenesis, support further investigation into whether TG-lowering interventions could improve liver-related outcomes. The lack of association with fibrosis may reflect the cross-sectional design limitation and insufficient time for HTG exposure to translate into fibrotic change. Future studies should explore if HTG contributes to progression from steatosis to fibrosis longitudinally.

Disclosures: Lana Bridi:Nothing to Disclose, Ricki Bettencourt:Nothing to Disclose, Egbert Madamba: Nothing to Disclose, Matthew Tsai:Nothing to Disclose, Denise Kalmaz:Nothing to Disclose, Nedret Copur-Dahi:Nothing to Disclose, Rohit Loomba:Eli Lilly and Company: Consultant, 89bio: Consultant, Aardvark Therapeutics: Consultant, Altimmune: Consultant, Alnylam/Regeneron: Consultant, Amgen: Consultant, Arrowhead Pharmaceuticals: Consultant, AstraZeneca: Consultant, Bristol Myers Squibb: Consultant, CohBar: Consultant, Eli Lilly: Consultant, Galmed Pharmaceuticals: Consultant, Gilead: Consultant, Glympse Bio: Consultant, Hightide: Consultant, Inipharma: Consultant, Intercept: Consultant, Inventiva: Consultant, Ionis: Consultant, Janssen, Inc.: Consultant, Madrigal Pharmaceuticals: Consultant, Merck, Metacrine, Inc.: Consultant, NGM Biopharmaceuticals: Consultant, Novartis: Consultant, Novo Nordisk: Consultant, Pfizer: Consultant, Sagimet Biosciences: Consultant, Terns Pharmaceuticals: Consultant, Theratechnologies and Viking Therapeutics: Consultant, 89bio: Stock options,

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3440 | SAUDI NORM-BASED HEALTH-RELATED QUALITY OF LIFE PROFILES IN INDIVIDUALS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE: A LATENT PROFILE ANALYSIS FROM THE GENESIS PROSPECTIVE COHORT

Saleh Alqahtani[1] Shadan AlMuhaidib[2] Faisal Sanai[3] Feras Altunisi[2] Haifa Alotaibi[2] Basmah Khoja[4] Layan Alsubki[4] Alwaleed Almojel[5] Eman Alanazi[6] Nouf Al-Turki[7] Alanood Aladel[8] Waleed Alomaim[4] Amr Arafat[9] Waleed Alhazzani[2], [1]King Faisal Specialist Hospital & Research Center, [2]Research and Innovation Institute, Ministry of Defense Health Services, Riyadh, Saudi Arabia, [3]King Abdulaziz Medical City, King Abdullah International Medical Research Center, Jeddah, KSA, [4]King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia, [5]King Fahad Military Medical Complex, Dhahran, Saudi Arabia, [6]Prince Sultan Military Medical City, Riyadh, Saudi Arabia, [7]King Abdulaziz University, Jeddah, Saudi Arabia, [8]King Saud University, Riyadh, Saudi Arabia, [9]Prince Sultan Cardiac Center, Riyadh, Saudi Arabia

Background: Health-related quality of life (HRQoL) in metabolic dysfunction-associated steatotic liver disease (MASLD) remains poorly characterized in Saudi populations, and prior analyses rarely apply local population norms. We aimed to identify Saudi norm-based HRQoL profiles in adults with MASLD in the GENESIS prospective cohort and characterize clinical and demographic differences across profiles. **Methods:** We conducted a cross-sectional analysis of 1,110 adults with MASLD and complete SF-36 data enrolled in the GENESIS prospective cohort across seven primary care centers in three regions of Saudi Arabia between March 2024 and June 2025. MASLD was defined as a controlled attenuation parameter $\geq$268 dB/m on vibration-controlled transient elastography with at least one cardiometabolic risk factor. We assessed HRQoL using the 36-Item Short Form Health Survey (SF-36) and converted crude domain scores to Saudi norm-based T-scores using published Saudi SF-36v2 reference means and SDs (T-score 50 = Saudi mean; 10 points = one SD). We assessed high risk for obstructive sleep apnea (OSA) using the Berlin Questionnaire ($\geq$2 positive categories). We fit latent profile analysis (LPA) models on the 8 SF-36 domain T-scores from 1 to 6 profiles and selected the optimal solution using Bayesian Information Criterion (BIC), sample-size adjusted BIC (SABIC), entropy, posterior probability, and class size. We compared variables across profiles using Kruskal-Wallis and chi-square tests. **Results:** The 4-profile solution provided the best fit (BIC 77,045.2; SABIC 76,908.6; entropy 0.922; average posterior probability 0.958). We identified four profiles: High Saudi norm-based HRQoL (n = 684, 61.6%), Mixed low-vitality/emotional HRQoL (n = 178, 16.0%), Physical-functioning limitation (n = 158, 14.2%), and Severe role/vitality-emotional limitation (n = 90, 8.1%). The Severe profile had the highest prevalence of high risk for OSA (64.4% vs 28.8% in the High HRQoL profile) and the highest hypertension prevalence (38.9% vs 18.0%). The Physical-functioning limitation profile was the oldest (median age 58.0 years) and had the highest dyslipidemia prevalence (62.0%). The High HRQoL profile was younger (median age 44.0 years), predominantly male (68.0%), and showed the lowest cardiometabolic burden. Profiles differed significantly in age, sex, BMI, high-OSA-risk classification, cardiometabolic risk factor count, diabetes, hypertension, dyslipidemia, and thyroid disease (all $p < 0.001$). **Conclusion:** Four clinically meaningful HRQoL profiles characterize Saudi adults with MASLD, with high OSA risk, age, and cardiometabolic burden distinguishing the profiles. The Severe role/vitality-emotional limitation profile identifies a small high-burden subgroup that warrants targeted clinical

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attention. These findings support population-specific HRQoL assessment in MASLD care and inform stratified interventions in Saudi Arabia.

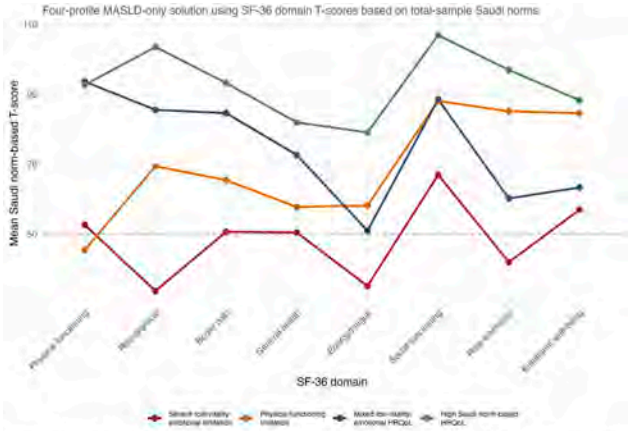


Figure 1. Saudi norm-based SF-36 mean T-score profiles in adults with MASLD from the GENESIS prospective cohort (n=1,110). Lines show mean T-scores for each of the four latent profiles across all eight SF-36 domains: physical functioning, role-physical, bodily pain, general health, energy/fatigue, social functioning, role-emotional, and emotional well-being. The dashed line at T=50 represents the published Saudi SF-36v2 reference means, with 10 points equal to one reference SD. T-scores are not constrained to the 0–100 raw scale range; values above 100 reflect raw scores more than five standard deviations above the Saudi reference mean, consistent with standard SF-36v2 norm-based scoring conventions. Profile sizes: Severe role/vitality-emotional limitation (n=90, 8.1%); Physical-functioning limitation (n=158, 14.2%); Mixed low-vitality/emotional HRQoL (n=178, 16.0%); High Saudi norm-based HRQoL (n=684, 61.6%).

Disclosures: Saleh Alqahtani:Nothing to Disclose, Shadan AlMuhaidib:Nothing to Disclose, Faisal Sanai: Nothing to Disclose, Feras Altunisi:Nothing to Disclose, Haifa Alotaibi:Nothing to Disclose, Basmah Khoja: Nothing to Disclose, Layan Alsubki:Nothing to Disclose, Alwaleed Almojel:Nothing to Disclose, Eman Alanazi: Nothing to Disclose, Nouf Al-Turki:Nothing to Disclose, Alanood Aladel:Nothing to Disclose, Waleed Alomaim: Nothing to Disclose, Amr Arafat:Nothing to Disclose, Waleed Alhazzani:Nothing to Disclose.

3441 | ROLE OF GLUCAGON- LIKE PEPTIDE- 1 RECEPTOR AGONISTS COMBINED WITH PIOGLITAZONE FOR TREATMENT OF METABOLIC DYSFUNCTION- ASSOCIATED STEATOHEPATITIS

Katherine Ripley[1] Jawairia Memon[2], [1]Univerity of New Mexico Hospital, [2]University of New Mexico

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly nonalcoholic fatty liver disease, affects nearly 40% of U.S. adults and is strongly associated with obesity, insulin resistance, metabolic syndrome, and type 2 diabetes mellitus (T2DM). Current pharmacologic therapies include glucagon-like peptide-1 receptor agonists (GLP-1 RAs), pioglitazone, resmetirom, and sodium-glucose cotransporter-2 inhibitors. GLP-1 RAs improve weight loss and glycemic control, while pioglitazone has demonstrated histologic liver improvement but is limited by weight gain and fluid retention. Given their complementary mechanisms, combination therapy may provide synergistic metabolic and hepatic benefit in MASLD. The aim of this study is to evaluate whether combined GLP-1 RA and pioglitazone therapy improves hepatic and metabolic outcomes compared with GLP-1 RA monotherapy in patients with MASLD. **Methods:** This retrospective cohort study utilized the TriNetX U.S. Collaborative Network, a federated electronic health record database. Adults aged 18–75 years with hepatic steatosis (K76.0) or nonalcoholic steatohepatitis (K75.81) between January 1, 2020, and December 31, 2025, were identified. Patients were grouped based on exposure to GLP-1 RAs with or without concomitant pioglitazone. Patients with alternative chronic liver diseases, including alcoholic liver disease, viral hepatitis, autoimmune hepatitis, and hemochromatosis, were excluded. Propensity score matching balanced demographics, metabolic comorbidities, liver disease severity, and diabetes-related medication use. Outcomes from 1 day to 5 years after index exposure included hepatic fibrosis/cirrhosis, portal hypertension, ascites, esophageal varices, hepatocellular carcinoma, liver enzymes, HbA1c, BMI, and LDL. **Results:** After propensity score matching, 9,634 patients remained in each cohort. Compared with combination therapy, GLP-1 RA monotherapy was associated with lower risk of hepatic fibrosis/cirrhosis (8.71% vs 12.23%; RR 0.71, $p < 0.0001$), nonalcoholic steatohepatitis (11.59% vs 15.16%; RR 0.77, $p < 0.0001$), portal hypertension (2.14% vs 3.24%; RR 0.66, $p < 0.0001$), ascites (2.09% vs 2.72%; RR 0.77, $p < 0.0001$), esophageal varices (1.52% vs 2.32%; RR 0.66, $p < 0.0001$), and hepatocellular carcinoma (0.52% vs 0.76%; RR 0.69, $p = 0.0019$). AST and ALT levels were similar between cohorts. Combination therapy was associated with lower BMI and LDL but higher HbA1c values. **Conclusion:** Combination therapy with GLP-1 RAs and pioglitazone was not associated with improved hepatic outcomes compared with GLP-1 RA monotherapy in patients with MASLD. GLP-1 RA monotherapy demonstrated lower rates of fibrosis, portal hypertension, hepatic decompensation, and hepatocellular carcinoma. Prospective studies are needed to further define the role of combination therapy in MASLD management.

Disclosures: Katherine Ripley:Nothing to Disclose, Jawairia Memon:Nothing to Disclose.

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3442 | BREAKFAST SKIPPING AND IRREGULAR MEAL TIMING IN SAUDI ADULTS WITH MASLD: INTERIM FINDINGS FROM A CASE-CONTROL CHRONONUTRITION STUDY

Thuraya Alaidarous[1] Mahmoud M. Abulmeaty[1] Khalid Alswat[2] Faisal Abaalkhail[3] Waleed Alhamoudi[3] Bandar Al-Judaibi[3] Saleh Alessy[3] Saad Alghamdi[3] Lama Amer[3] Saleh Alqahtani[3] Maha Alhussain[1], [1]King Saud University, Riyadh, Saudi Arabia, [2]King Saud University/KKUH, [3]King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia

Background: Chrononutrition is a growing field that examines how eating patterns, including meal timing, frequency, and regularity, interact with endogenous circadian rhythms to influence human health. Emerging evidence suggests that disruptions in chrononutrition may adversely affect metabolic homeostasis and hepatic fat accumulation. We aimed to explore differences in chrononutrition patterns between individuals with metabolic dysfunction–associated steatotic liver disease (MASLD) and controls. **Methods:** This interim analysis included 40 participants enrolled to date in an ongoing case–control study, comprising 20 patients with MASLD [SAA1] and 20 controls aged 18–65 years. They were recruited from two tertiary centers in Riyadh, Saudi Arabia. Anthropometric measurements were collected. Chrononutrition patterns were assessed using the Chrononutrition Profile Questionnaire (CP-Q) (Veronda et al 2020). Group differences were assessed using independent-samples t tests for continuous variables and Fisher's exact or chi-square tests for categorical variables, as appropriate. **Results:** In this interim analysis, distinct differences in breakfast-related chrononutrition patterns were observed between groups. Participants with MASLD were significantly more likely to exhibit irregular meal timing compared with controls (80.0% vs. 20.0%; P < 0.001). Breakfast consumption between 6:00 and 9:00 AM was more common among controls (73.7% vs. 26.3%), whereas delayed breakfast intake was more frequently reported among participants with MASLD (70.0% vs. 30.0%; P = 0.027). Weekly breakfast skipping frequency was significantly higher in the MASLD group (3.25 ± 2.53 vs. 1.65 ± 2.23; P = 0.041). Participants with MASLD also had higher body weight and body mass index than controls (87.70 ± 13.16 vs. 65.78 ± 12.11 kg and 32.34 ± 3.98 vs. 23.88 ± 3.55 kg/m², respectively; both P < 0.001) **Conclusion:** Altered breakfast timing, frequent breakfast skipping, and irregular eating patterns were associated with MASLD and higher adiposity/body-composition measures. These interim findings suggest that optimizing meal-timing regularity may represent a modifiable behavioral strategy warranting further evaluation for metabolic health and supporting MASLD management, although confirmation in the full study cohort is needed.

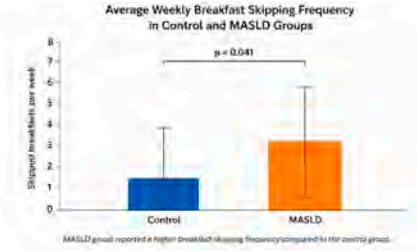


Figure: Comparison of Weekly Breakfast Skipping Frequency between Control and MASLD

Table: Anthropometric Characteristics and Chrononutrition Behaviors of Study Participants by Group

Variable	Control	MASLD	p-value
Age (years)	39.20 ± 7.96	41.65 ± 9.95	0.395
Weight (kg)	65.78 ± 12.11	87.70 ± 13.16	<0.001*
BMI (kg/m²)	23.88 ± 3.55	32.34 ± 3.98	<0.001*
Weekly Breakfast Skipping Frequency	1.65 ± 2.23	3.25 ± 2.53	0.041*
Post-dinner snack frequency	1.75 ± 1.48	2.10 ± 2.02	0.536
Night waking to eat frequency	0.40 ± 0.82	0.10 ± 0.31	0.139
Largest meal			
Breakfast	3 (15.0%)	3 (15.0%)	0.900
Lunch	11 (55.0%)	13 (65.0%)	
Dinner	6 (30.0%)	4 (20.0%)	

An independent samples t-test was used for continuous variables, and a Chi-square test was used for categorical variables(*Fisher's Exact Test was used for categorical variables due to small expected cell counts. Statistical significance was considered at p < 0.05.*

Disclosures: Thuraya Alaidarous:Nothing to Disclose, Mahmoud M. Abulmeaty:Nothing to Disclose, Khalid Alswat:Nothing to Disclose, Faisal Abaalkhail:Nothing to Disclose, Waleed Alhamoudi:Nothing to Disclose, Bandar Al-Judaibi:Nothing to Disclose, Saleh Alessy: Nothing to Disclose, Saad Alghamdi:Nothing to Disclose, Lama Amer:Nothing to Disclose, Saleh Alqahtani:Nothing to Disclose, Maha Alhussain:Nothing to Disclose.

3443 | ◆ TWELVE-MONTH CHANGES IN LABORATORY- AND IMAGING-BASED BIOMARKERS FOLLOWING RESMETIROM INITIATION: A REAL-WORLD ANALYSIS ACROSS CARDIOMETABOLIC AND CONCOMITANT MEDICATION SUBGROUPS

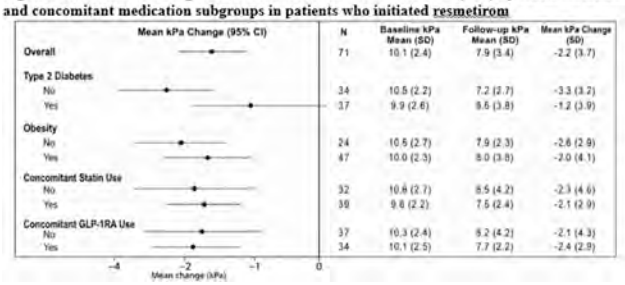
Anthony Martinez[1] Susan Thapa[2] Christina Parrinello[2] Yestle Kim[2] John O'Donnell[2], [1]University at Buffalo, [2]Madrigal Pharmaceuticals, Inc

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Background: Resmetirom is a thyroid hormone receptor β–selective agonist conditionally approved in the United States (US) for adults with noncirrhotic metabolic dysfunction-associated steatohepatitis (MASH) with moderate-to-advanced fibrosis. MASH frequently coexists with obesity, type 2 diabetes (T2D), and use of GLP-1 receptor agonists (GLP-1 RA) and statins. Real-world studies describing biomarker changes across these subgroups are limited. **Methods:** An electronic health record-based retrospective cohort study was conducted using Truveta de-identified data from US health systems linked to third-party dispensing data. Adults ≥18 years with a resmetirom fill on or after March 14, 2024 (index date = first fill) were followed through April 6, 2026. Eligible patients had ≥1 healthcare interaction during the pre-index year, no other or advanced liver disease, and ≥1 year of follow-up. Outcomes included vibration-controlled transient elastography (VCTE)-derived liver stiffness measurement (LSM) and controlled attenuation parameter (CAP) extracted from clinical notes using large language models, liver enzymes (alanine transaminase [ALT] and aspartate aminotransferase [AST]), lipids (low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], and triglycerides [TGs]), and derived scores (FibroScan-AST [FAST] and Steatosis-Associated Fibrosis Estimator [SAFE]). Baseline and follow-up (12 ± 3 months) means, and standard deviations (SD) were estimated. Mean changes were compared using paired t-tests and evaluated across subgroups (obesity, T2D, and concomitant use of GLP-1 RA and statins). **Results:** Among 1,405 patients with ≥1 year of follow-up (median 15.8 months), mean age was 58 years, 63% female, 78% White, 57% T2D, 61% obesity, 50% used GLP-1 RA and 55% used statins. In those with paired measurements, mean LSM decreased at 12 months (-2.2 kPa [3.7], $p < 0.001$). Directionally similar reductions in LSM were observed across subgroups, with overlapping confidence intervals suggesting no clear heterogeneity (**Figure**). Improvements were also observed across all subgroups in CAP, ALT, AST, LDL-c, HDL-c, TG, SAFE, and FAST (all statistically significant except HDL-c). Across subgroups, 28–43% of patients had ≥40 dB/m CAP reduction, 40–59% ≥20% ALT reduction, 38–51% ≥20% AST reduction, and 39–59% ≥0.22 FAST reduction. **Conclusion:** Among patients initiating resmetirom, improvements in imaging- and blood-based biomarkers at 12 months were observed across clinically relevant cardiometabolic and concomitant medication subgroups. Subgroup sample sizes were limited, particularly for imaging measures, and the study was not designed to formally compare treatment response between subgroups. Future analyses with larger samples and longer follow-up will further characterize biomarker changes across clinically relevant subgroups.

Figure. Twelve-month changes in VCTE liver stiffness measurement (kPa) by cardiometabolic and concomitant medication subgroups in patients who initiated resmetirom



Disclosures: Anthony Martinez:Gilead: Consultant, Gilead: Speaking and Teaching, Abbvie: Consultant, Abbvie: Speaking and Teaching, Arbutus: Consultant, Braeburn: Speaking and Teaching, Sirtex: Consultant, Roche: Consultant, Syneos/VBI: Consultant, Madrigal: Speaking and Teaching, Altimune: Consultant, Madrigal: Consultant, Ipsen: Consultant, novo: Speaking and Teaching, atea: Consultant, cepheid: Consultant, Susan Thapa:Nothing to Disclose, Christina Parrinello:Madrigal Pharmaceuticals: Employee, Madrigal Pharmaceuticals: Stock - publicly traded company, Yestle Kim:Nothing to Disclose, John O'Donnell:Madrigal Pharmaceuticals: Share Holder.

3444 | ◆ GLP-1 RECEPTOR AGONIST IS ASSOCIATED WITH LOWER MORTALITY, CARDIOVASCULAR EVENTS, AND ACUTE KIDNEY INJURY IN COMPENSATED CIRRHOSIS: AN ACTIVE-COMPARATOR, NEW-USER STUDY OF 11,972 PATIENTS

Saad Nadeem[1] David Victor[2] Sudha Kodali[2] Tamneet Basra[2] Michelle Jones-Pauley[2] Mazen Noureddin[2] Kavish Patidar[2], [1]Texas A&M College of Medicine, [2]Houston Methodist Hospital

Background: GLP-1 receptor agonists (GLP-1RAs) improve metabolic and liver-related outcomes in metabolic dysfunction-associated steatotic liver disease (MASLD), but evidence in cirrhosis—particularly outside MASLD—is limited and lacks active-comparator data. Whether GLP-1RAs confer extrahepatic benefits beyond those of sodium-glucose cotransporter-2 inhibitors (SGLT2i) remains unknown. **Methods:** We conducted a retrospective active-comparator new-user cohort study within the TriNetX Research Collaborative Network (113 healthcare organizations). Adults with compensated cirrhosis initiating a new GLP-1 RAs (semaglutide or tirzepatide) or SGLT-2i (empagliflozin, dapagliflozin, canagliflozin, or ertugliflozin) within 12 months of cirrhosis diagnosis were 1:1 propensity

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score matched (PSM). Covariates matched for included demographics, comorbidities, medications, and labs. Outcomes were assessed over 2 years from the index date. Subgroup analyses by MASLD, alcohol-associated (ALD), and viral cirrhosis. Hazard ratios (HR) were estimated using Cox proportional hazards models. **Results:** After 1:1 PSM, 5,986 GLP-1 RA initiators were matched to 5,986 SGLT2i initiators, with balance achieved for nearly all covariates (SMD < 0.1), except for albumin (SMD 0.17). Compared with SGLT2i initiation, GLP-1 RA initiation was associated with lower 2-year all-cause mortality (4.3% vs 6.8%; HR 0.65; 95% CI, 0.56–0.76; p < 0.001), major adverse cardiovascular events (7.2% vs 10.2%; HR 0.73; 95%CI, 0.63–0.85; p < 0.001), and acute kidney injury (7.4% vs 9.2%; HR 0.83; 95%CI, 0.72–0.96; p = 0.011) (Table 1). No differences in hepatic decompensation, HCC, or transplant between groups. In etiology-stratified analysis, the AKI benefit was concentrated in viral cirrhosis (HR 0.56, 0.33–0.98, p = 0.033), with no significant difference in MASLD cirrhosis (HR 0.88, 95% CI 0.65–1.20, p = 0.42) or ALD cirrhosis. **Conclusion:** In this active-comparator, new-user analysis of adults with recently diagnosed compensated cirrhosis, GLP-1 RA initiation was associated with lower 2-year mortality, MACE, and AKI compared with SGLT2i initiation, without significant differences in hepatic decompensation, HCC, or liver transplantation. Prospective studies are needed to confirm these findings and define the role of GLP-1 RAs in cardiometabolic and renal risk modification among patients with compensated cirrhosis.

Table 1. Primary and secondary outcomes — overall cohort (5,986 matched pairs, 2-year follow-up).

Outcome	GLP-1 RA events / N (risk)	SGLT-2i events / N (risk)	Hazard ratio	95% CI	p-value
PRIMARY OUTCOMES					
All-cause mortality	262 / 6,089 (4.30%)	413 / 6,090 (6.78%)	0.649	0.556–0.758	<0.0001
MACE	301 / 4,167 (7.22%)	401 / 3,930 (10.20%)	0.734	0.632–0.853	<0.0001
SECONDARY OUTCOMES					
Acute kidney injury	349 / 4,708 (7.41%)	423 / 4,618 (9.16%)	0.832	0.722–0.958	0.011
Decompensation (composite)	355 / 5,665 (6.27%)	373 / 5,678 (6.57%)	0.980	0.847–1.133	0.51
Decompensation only	301 / 5,724 (5.26%)	332 / 5,729 (5.80%)	0.931	0.796–1.088	0.21
Hepatocellular carcinoma	91 / 6,046 (1.51%)	88 / 6,054 (1.45%)	1.035	0.774–1.385	0.81
Liver transplant	33 / 6,075 (0.54%)	31 / 6,094 (0.51%)	1.068	0.655–1.741	0.79

Disclosures: Saad Nadeem:Nothing to Disclose, David Victor:Intercept: Speaker, and Advisor, Gilead: Speaking and Teaching, Madrigal: Speaker, BMS: Stock - publicly traded company, Pfizer: Stock - publicly traded company, Sudha Kodali:Nothing to Disclose, Tamneet Basra:Nothing to Disclose, Michelle Jones-Pauley:Nothing to Disclose, Mazen Noureddin:Akero: Advisor, Alligos: Advisor, Altimmune: Advisor, AstraZeneca: Advisor, Boehringer Ingelheim: Advisor, Boston Pharma: Advisor, Cytodyn: Advisor, GSK: Advisor, Lilly: Advisor, Madrigal: Advisor, Merck: Advisor, Novo Nordisk: Advisor, Sagimet: Advisor, Terns: Advisor, Takeda: Advisor, Akero: Principal Investigator, Allergan: Principal Investigator, Altimmune: Principal Investigator, Boehringer Ingelheim: Principal Investigator, Bristol Myers Squibb: Principal Investigator, Boston Pharma: Principal Investigator, Conatus: Principal Investigator, Corcept: Principal Investigator, Galectin: Principal Investigator, Genfit: Principal Investigator, GSK: Principal Investigator, Kowa: Principal Investigator, Enanta: Principal Investigator, Madrigal: Principal Investigator, Lilly: Principal Investigator, Merck: Principal Investigator, Novartis: Principal Investigator, Novo Nordisk: Principal Investigator, Rivus: Principal Investigator, Shire: Principal Investigator, Takeda: Principal Investigator, Terns: Principal Investigator, Viking: Principal Investigator, Zydus: Principal Investigator, Rivus: Stock – privately held company, Cytodyn: Stock - publicly traded company, ChronWell: Stock – privately held company, Madrigal: Speakers bureau, Gilead Sciences: Principal Investigator, Akero: Consultant, Altimmune: Consultant, Alligos: Consultant, AstraZeneca: Consultant, BI: Consultant, Boston Pharma: Consultant, Curve bioscience: Consultant, Cytodyn: Consultant, GSK: Consultant, Histoindex: Consultant, Lilly: Consultant, Madrigal: Consultant, Merck: Consultant, Novo Nordisk: Consultant, Sagimet: Consultant, Terns: Consultant, Allergan: Grant/Research Support, Altimmune: Grant/Research Support, Akero: Grant/Research Support, BI: Grant/Research Support, BMS: Grant/Research Support, Boston Pharma: Grant/Research Support, Conatus: Grant/Research Support, Corcept: Grant/Research Support, Gilead: Grant/Research Support, Galectin: Grant/Research Support, Genfit: Grant/Research Support, GSK: Grant/Research Support, Kowa: Grant/Research Support, Enanta: Grant/Research Support, Madrigal: Grant/Research Support, Lilly: Grant/Research Support, Merck: Grant/Research Support, Novartis: Grant/Research Support, Novo Nordisk: Grant/Research Support, Rivus: Grant/Research Support, Shire: Grant/Research Support, Takeda: Grant/Research Support, Terns: Grant/Research Support, Viking: Grant/Research Support, Akero: Stock - publicly traded company, Zydus: Grant/Research Support, Takeda: Consultant, Madrigal: Speaking and Teaching, Novo Nordisk: Speaking and Teaching, HepaNova: Consultant, Daiichi Sankyo: Advisor, Daiichi Sankyo: Consultant, Curve Bioscience: Advisor, Curve Bioscience: Consultant, HepaNova: Advisor, HepaTx: Advisor, HepaTx: Consultant,

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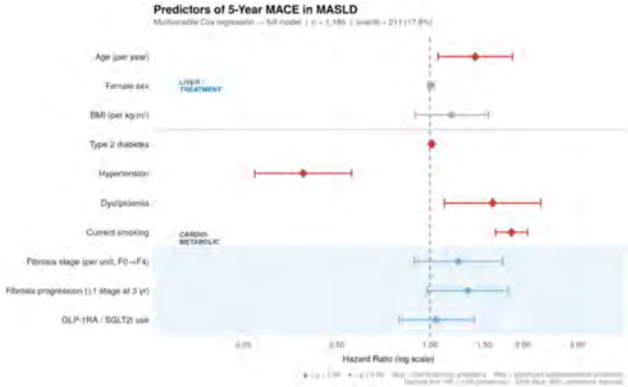
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3445 | ◆ FIBROSIS PROGRESSION AND CARDIOVASCULAR OUTCOMES IN MASLD WITH GLP1/SGLT2I USE: A PROSPECTIVE LONGITUDINAL STUDY

Rahul Falodia[1] Maryum Shah[2] Ubaid Ahmed[3], [1]All India Institute of Medical Sciences Jodhpur, [2]UAB SOM Montgomery Internal Medicine Residency Program, [3]Dow university of health Sciences

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is now recognized as an independent cardiovascular risk factor, yet fibrosis staging is rarely incorporated into cardiometabolic risk models. Whether histological fibrosis progression confers MACE risk beyond established cardiometabolic predictors or GLP-1 receptor agonist or SGLT2 inhibitor use modifies this risk remains unknown. **Methods:** 1,186 adults with biopsy-confirmed MASLD enrolled in a prospective longitudinal registry (mean age 53.9 years, 41.3% female, 52.6% type 2 diabetes, mean BMI 33.4 kg/m²). Baseline fibrosis was staged F0–F4. Fibrosis progression was defined as $\geq$1-stage worsening on repeat liver biopsy or validated transient elastography at 3 years. GLP-1RA or SGLT2i use was recorded at enrollment (31% of cohort). The primary endpoint was 5-year MACE (composite of non-fatal MI, non-fatal stroke, and cardiovascular death). Three sequential Cox proportional hazards models were constructed: Model 1 (fibrosis stage alone), Model 2 (fibrosis stage + standard cardiometabolic covariates: age, sex, BMI, diabetes, hypertension, dyslipidemia, smoking), and Model 3 (full model adding fibrosis progression and GLP-1RA/SGLT2i use). Discrimination was assessed by Harrell's C-statistic. **Results:** Over 5 years, 211 patients (17.8%) experienced MACE. Fibrosis stage showed a steep gradient of MACE risk: 4.4% (F0), 11.9% (F1), 13.6% (F2), 25.7% (F3), and 41.2% (F4). 3-year fibrosis progression occurred in 17.1% of patients and was significantly more common in patients not receiving GLP-1RA/SGLT2i (19.4% vs. 12.1%, $p < 0.001$). On adjusted Cox regression (Model 2), each unit increase in baseline fibrosis stage independently predicted MACE risk after full cardiometabolic adjustment (HR 1.75, 95% CI 1.56–1.96, $p < 0.001$), demonstrating that fibrosis severity carries prognostic information orthogonal to traditional risk factors. In the full model (Model 3), fibrosis stage remained the dominant predictor (HR 1.84, 95% CI 1.63–2.07, $p < 0.001$); 3-year progression conferred additional independent MACE risk (HR 1.59, 95% CI 1.11–2.28, $p = 0.011$); and GLP-1RA/SGLT2i use was associated with a 61% relative reduction in MACE risk (HR 0.39, 95% CI 0.27–0.56, $p < 0.001$), independent of fibrosis stage and cardiometabolic covariates. **Conclusion:** In MASLD cohort, baseline fibrosis stage and 3-year histological progression are independent determinants of 5-year MACE, with a risk signal that is not captured by conventional cardiometabolic risk factors alone. GLP-1RA and SGLT2i use was associated with both attenuated fibrosis progression and substantially lower MACE risk. These findings support routine fibrosis staging as a cardiovascular risk stratification tool in MASLD and provide mechanistic rationale for prioritizing these agents in patients with advanced fibrosis.



Disclosures: Rahul Falodia:Nothing to Disclose, Maryum Shah:Nothing to Disclose, Ubaid Ahmed:Nothing to Disclose.

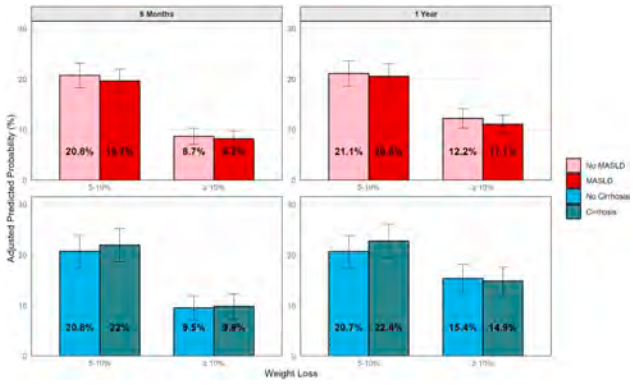
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3446 | ◆ MASLD ATTENUATES SEMAGLUTIDE-INDUCED WEIGHT LOSS WHILE CIRRHOSIS PARADOXICALLY ENHANCES IT: A REAL-WORLD ANALYSIS OF 30,767 VETERANS

Binu John[1] Samuel Soon[2] Dustin Bastaich[2] Ashwani Singal[3] Bassam Dahman[2], [1]University of Miami and Miami VA, [2]Virginia Commonwealth University, [3]University of Louisville

Background: Semaglutide promotes significant weight loss in clinical trials, yet its real-world efficacy in patients with metabolic dysfunction-associated steatotic liver disease (MASLD), remains poorly defined. Whether concurrent cirrhosis further modifies weight loss response is unknown. **Methods:** This retrospective cohort study used the Veterans Health Administration (VHA) national database to identify adults who were new users of subcutaneous semaglutide with at least 12 months of follow-up. Patients with active malignancy, hepatic decompensation, hazardous alcohol use, or prior bariatric surgery were excluded. MASLD was identified from imaging reports using validated natural language processing ($\kappa = 0.87$ vs. manual chart review). The primary outcome was percentage weight loss at 6 and 12 months, categorized as $< 5\%$, 5–10%, and $\geq 10\%$. Multivariable logistic and multinomial regression models adjusted for age, sex, race, BMI, diabetes, cirrhosis, and achieved semaglutide dose. **Results:** Among 30,767 new semaglutide users, 17,565 (57.1%) had MASLD and 13,202 had no hepatic steatosis on imaging. The cohort had a median age of 67.5 years and was predominantly male (87.5%). Participants with and without MASLD had similar prevalence of diabetes (91%) with no difference in median HgbA1C (7.7%). Among the 17,565 patients with MASLD, 1193 had cirrhosis. Weight loss demonstrated a dose-dependent pattern across semaglutide doses (0.25–2.4 mg).Compared to controls, MASLD was associated with modestly but significantly lower adjusted odds of achieving $\geq 5\%$ weight loss at both 6 months (aOR 0.92 [5–10%] and 0.95 [$> 10\%$]; both $p \leq 0.033$) and 12 months (aOR 0.92 [5–10%] and 0.90 [$> 10\%$]; both $p < 0.0001$). Conversely, among patients with MASLD, concurrent cirrhosis was paradoxically associated with *higher* adjusted odds of achieving $\geq 5\%$ weight loss at 6 months (aOR 1.08; 95% CI 1.03–1.13; $p = 0.0009$) and 12 months (aOR 1.07; 95% CI 1.02–1.12; $p = 0.003$). **Conclusion:** In this large real-world cohort of veterans, MASLD was independently associated with attenuated semaglutide-induced weight loss at 6 and 12 months, potentially driven by insulin resistance impairing GLP-1 receptor signaling. Paradoxically, among patients with MASLD, cirrhosis was associated with greater weight loss, a finding that may reflect sarcopenia-related loss of lean mass rather than true adipose reduction, underscoring the limitations of weight-based endpoints in this population. These findings have direct implications for patient counseling, dose optimization, and the selection of body composition–based endpoints in future MASLD trials involving GLP-1 receptor agonists.



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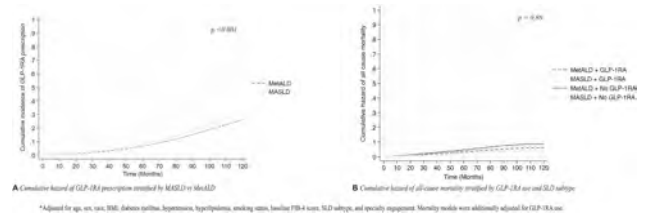
3447 | ◆ SURVIVAL IMPACT OF GLP-1RA TREATMENT IN MASLD VS METALD: EQUAL BENEFIT, UNEQUAL ACCESS

Dilara Hatipoglu[1] Nadim Mahmud[2], [1]University of Pennsylvania, [2]Hospital of the University of Pennsylvania

Background: Obesity is a major driver of fibrosis progression in steatotic liver disease (SLD). Glucagon-

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like peptide-1 receptor agonists (GLP-1RAs) promote weight loss and improve hepatic steatosis, but it remains unclear whether pharmacologic obesity management differs by SLD subtype. **Methods:** We performed a retrospective cohort study using VOCAL, a national Veterans Health Administration registry of patients with chronic liver disease. Adults with BMI ≥ 35 and imaging-confirmed non-cirrhotic SLD were classified as metabolic dysfunction-associated steatotic liver disease (MASLD) or metabolic dysfunction and alcohol-related liver disease (MetALD) using metabolic criteria and AUDIT-C data. We included patients who were obesity treatment-naïve at baseline, including no prior lifestyle program referral (MOVE!), bariatric surgery, or anti-obesity medication use. Follow-up began at date of first imaging-confirmed steatosis and continued until death, maximum follow-up, or 10 years. The first model utilized adjusted Cox proportional hazards regression with time to obesity intervention as the primary outcome. A second time-updated Cox model assessed the association between GLP-1RA exposure and all-cause mortality, including an interaction term between GLP-1RA use and SLD subtype. **Results:** Among 23,332 patients, 19,628 had MASLD and 3,704 had MetALD. Most patients were men (90.1% MASLD, 92.4% MetALD). Compared with MetALD, MASLD patients had higher median BMI (38.2 vs 37.7), diabetes prevalence (33.6% vs 22.9%), and hyperlipidemia (50.1% vs 46.4%). In adjusted analyses, MetALD patients were less likely to receive GLP-1RA therapy (HR 0.83, 95% CI 0.74-0.94, $p = 0.002$; **Figure 1A**) than those with MASLD. Rates of referral to MOVE!, non-GLP-1RA medications, bariatric surgery, and nutrition services were similar. In time-updated intention-to-treat analyses, GLP-1RA use was associated with lower all-cause mortality (HR 0.55, 95% CI 0.44-0.68, $p < 0.001$), while MetALD was associated with higher mortality (HR 1.21, 95% CI 1.08-1.37, $p = 0.002$). The interaction between GLP-1RA use and SLD subtype was not significant ($p = 0.86$), suggesting similar survival benefit across subtypes. Cumulative hazard curves are displayed in **Figure 1B. Conclusion:** Among patients with non-cirrhotic SLD and obesity, MetALD patients were less likely to receive GLP-1RA therapy despite comparable survival benefit to MASLD patients. These findings suggest GLP-1RAs may improve outcomes regardless of SLD subtype and may be underutilized in MetALD.



Disclosures: Dilara Hatipoglu:Nothing to Disclose, Nadim Mahmud:Nothing to Disclose.

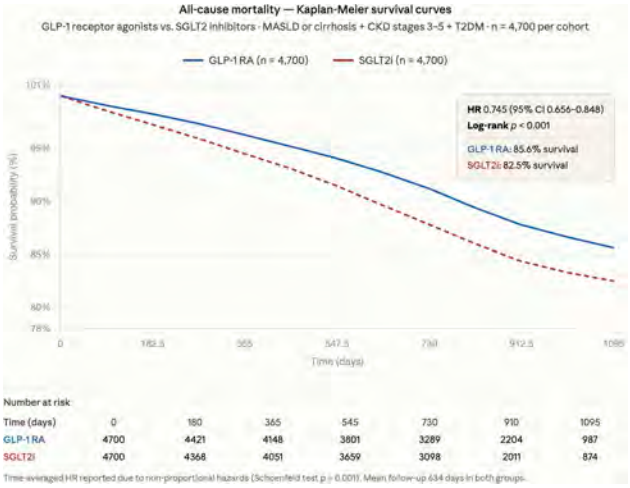
3448 | ◆ SURVIVAL ADVANTAGE OF GLP-1 RECEPTOR AGONISTS OVER SGLT2 INHIBITORS IN PATIENTS WITH MASLD OR CIRRHOSIS AND CHRONIC KIDNEY DISEASE

Urveesh Sharma[1] Yash Shah[2] Ragesh Thandassery[3], [1]University of Arkansas for Medical Sciences, [2]UAMS, LR, [3]CAVHS, Little Rock

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) and cirrhosis frequently coexist with chronic kidney disease (CKD) and type 2 diabetes (T2DM), creating a high-risk population. Both GLP-1 receptor agonists (GLP-1 RAs) and SGLT2 inhibitors (SGLT2is) are widely used in this patient population, and are known to improve cardiometabolic outcomes, but their relative effect on survival when CKD and MASLD/cirrhosis overlap has not been studied well. **Methods:** We conducted a retrospective cohort study using the TrinetX database where adults (≥ 18 years) with pre-existing MASLD or cirrhosis, CKD stages 3-5, and T2DM were divided into two cohorts based on whether they were newly started on a GLP-1 RA or a SGLT2i. We excluded patients with cross-drug class exposure, alcoholic liver disease, viral hepatitis, prior liver transplant, HCC, ESRD, or dialysis. 1:1 propensity score matching (PSM) on demographics, comorbidities, medications, and laboratory values was done. The primary outcome was all-cause mortality at 3 years and was assessed by Kaplan-Meier analysis with log-rank testing. **Results:** After 1:1 PSM, 4,700 patients remained per cohort with well-balanced baseline characteristics. Mean age was 67.9 years; 57.2% were female, 73.7% were White, and 18.7% carried a cirrhosis diagnosis. Mean follow-up was 634 days in both groups. GLP-1 RA users had significantly lower all-cause mortality at 3 years vs SGLT2i users (8.7% vs. 11.6%; RR 0.753, 95% CI 0.666–0.850; $p < 0.001$). On Kaplan-Meier analysis, 3-year survival probability was 85.6% with GLP-1 RAs versus 82.5% with SGLT2is (log-rank $p < 0.001$). Since the proportionality test was significant ($p = 0.001$), a time-averaged Cox HR is reported: HR 0.745 (95% CI 0.656–0.848). This reflects a mortality benefit that widened progressively over the observation period. **Conclusion:** Among patients with coexisting MASLD/cirrhosis, CKD stages 3-5, and T2DM, GLP-1 RA use was associated with roughly 25% lower all-cause mortality compared to SGLT2i use over 3 years, with the benefit appearing to grow over time.

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3449 | ASSOCIATIONS OF RENIN–ANGIOTENSIN SYSTEM INHIBITORS AND CALCIUM CHANNEL BLOCKERS WITH LIVER STIFFNESS DYNAMICS AND LONG-TERM LIVER-RELATED EVENTS IN MASLD

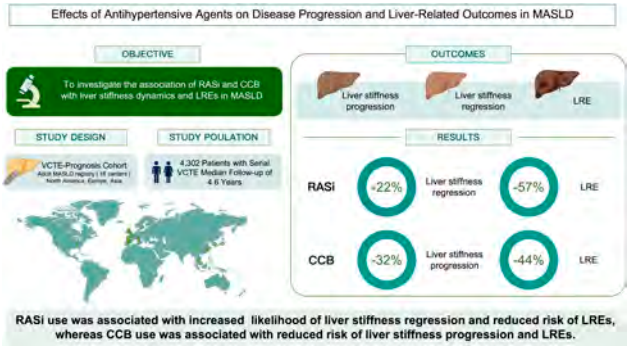
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Background: Hypertension is common in metabolic dysfunction-associated steatotic liver disease (MASLD), but the effects of specific antihypertensive drug classes on liver fibrosis and liver-related events (LREs) remain unclear. We evaluated the associations of renin–angiotensin system inhibitors (RASi) and calcium channel blockers (CCB) with liver stiffness changes and long-term LRE risk. **Methods:** We analyzed data from the VCTE-Prognosis cohort, a multicenter prospective study with serial liver stiffness measurements. Outcomes included advanced liver fibrosis (LSM $\geq$ 10 kPa), liver stiffness progression ($\geq$ 20% increase and Baveno category upshift), liver stiffness regression ($\geq$ 20% decrease and Baveno category downshift), and incident LREs. Associations between baseline antihypertensive therapy and

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outcomes were assessed using Cox proportional hazards models with inverse probability of treatment weighting, comparing RASi users versus non-users, CCB users versus non-users. **Results:** 4,302 individuals with MASLD and hypertension were followed for a median of 4.6 years, with 41.2% receiving RASi and 32.0% receiving CCB. RASi use was associated with a higher chance of liver stiffness regression (adjusted HR = 1.220, 95%CI 1.010–1.474; P = 0.039) and a lower risk of long-term LREs (adjusted HR = 0.431, 95%CI 0.261–0.714; P = 0.001), with no significant effect on liver stiffness progression. In contrast, CCB use was associated with lower risks of liver stiffness progression (adjusted HR = 0.681, 95%CI 0.521–0.89; P = 0.005) and LREs (adjusted HR = 0.559, 95%CI 0.326–0.958; P = 0.034), but not liver stiffness regression. Findings were consistent across subgroup and sensitivity analyses. **Conclusion:** Both RASi and CCB were associated with beneficial liver-related outcomes, although with different patterns: RASi was more strongly associated with fibrosis regression, whereas CCB was more strongly associated with reduced fibrosis progression.



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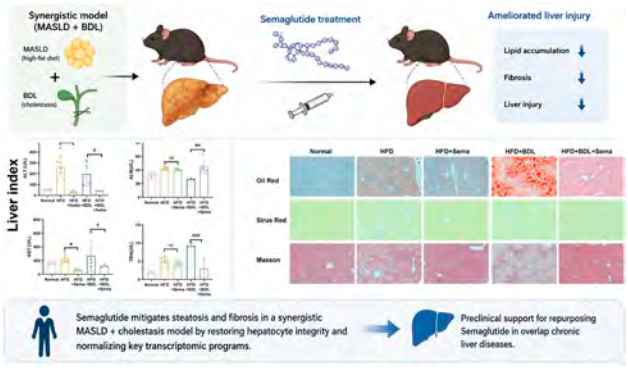
3450 | SEMAGLUTIDE AMELIORATES HEPATIC FIBROSIS AND LIPOTOXICITY IN A SYNERGISTIC MURINE MODEL OF CHOLESTASIS AND STEATOSIS

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Background: The global surge in metabolic syndrome, and the clinical convergence of metabolic dysfunction-associated steatotic liver disease (MASLD) and chronic cholestatic insults present an escalating challenge. Up to 45% of patients with chronic cholestasis present with concurrent MASLD, which nearly triples the risk of advanced fibrosis and significantly accelerates hepatic decompensation. However, therapeutic options targeting this synergistic "double-hit" pathology remain elusive. This study evaluates the therapeutic efficacy of Semaglutide, a GLP-1 receptor agonist, in mitigating hepatic fibrosis and lipotoxicity utilizing

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a synergistic murine model of MASLD and bile duct ligation (BDL) designed to recapitulate the complex, multi-factorial disease progression and the high fibro-inflammatory burden observed in clinical overlap syndromes. **Methods:** A comprehensive array of in vivo models was employed, specifically focusing on the synergistic MASLD+BDL composite murine model to simulate clinical cholestatic steatohepatitis. Hepatic functions were evaluated via serum biochemistry. Histopathological architecture was assessed using Oil Red O staining for lipid deposition, alongside Sirius Red and Masson staining to visualize collagen fibril organization. The cellular impact of Semaglutide was evaluated utilizing advanced hepatocyte organoid culture systems coupled with bulk RNA sequencing to profile global transcriptomic alterations. **Results:** Semaglutide administration notably ameliorated the pathological landscape in the synergistic model. Histological examination demonstrated that treatment effectively attenuated hepatic lipid accumulation and significantly abrogated fibrotic remodeling, preserving liver tissue architecture despite the combined metabolic and biliary insult. Ex vivo hepatocyte organoid assays corroborated these findings, demonstrating a direct protective effect of Semaglutide on hepatocyte integrity and survival under co-exposure to lipotoxic and cholestatic stress. Bulk RNA sequencing revealed that Semaglutide treatment leads to a profound restoration of the hepatic transcriptomic profile, modulating key networks involved in lipid homeostasis and extracellular matrix regulation. **Conclusion:** Collectively, these findings indicate that Semaglutide exerts potent anti-steatotic and anti-fibrotic effects in the context of combined metabolic and cholestatic liver injury. By addressing the synergy between MASLD and cholestasis—a clinical scenario characterized by a 3-fold higher risk of advanced fibrosis and high morbidity—this study provides a strong preclinical rationale for repurposing Semaglutide as a targeted therapeutic strategy for patients facing the severe intersection of multi-etiological chronic liver diseases.



Disclosures: Bao Xiaowen:Nothing to Disclose, Yan Chen:Nothing to Disclose, Paul KH Tam:Nothing to Disclose.

3451 | TREATMENT WITH RESMETIROM IMPROVES SYMPTOM BURDEN IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS

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Background: Metabolic dysfunction-associated steatohepatitis (MASH) is characterized by substantial health-related quality of life (HRQL) impairment and symptom burden. We evaluated the effect of resmetirom on MASH-specific symptoms using the CLDQ-MASH Symptom Questionnaire (CLDQ-MASH-SQ). **Methods:** In this post-hoc analysis of the MAESTRO-NAFLD-1 and MAESTRO-NASH studies, patients with MASH were stratified as early MASH, MASH with F2-F3 fibrosis, and MASH with compensated cirrhosis. Changes in CLDQ-MASH-SQ domain and item scores (8 domains, 36 items; scores range 1-7, higher scores indicate better HRQL, lower symptom burden) from baseline to week 52 treatment with resmetirom or placebo were evaluated. **Results:** A total of 2066 MASH patients were included; baseline symptom burden increased with disease severity across multiple domains ($p < 0.01$). At week 52, patients with early MASH treated with resmetirom demonstrated improvements in Abdominal symptoms and Health distress domains that were not observed with placebo; among MRI-PDFF responders, these mean (95% CI) improvements were +0.16 (0.06, 0.26) and +0.17 (0.08, 0.25), respectively, and were accompanied by greater improvements in anxiety (mean change +0.17 vs. -0.05 in non-responders, $p = 0.045$) and feeling unhappy (+0.14 vs. -0.06, respectively, $p = 0.036$) item scores. In patients with MASH F2-F3, Health distress domain scores improved significantly from baseline across treatment groups. Among patients with MASH cirrhosis, improvement in Health distress domain scores were observed in those with higher baseline liver stiffness, and VCTE responders demonstrated improvements in selected peripheral symptoms. **Conclusion:** Across all stage of MASH, treatment with resmetirom is associated with improvement in multiple aspects of disease-specific symptom burden.

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3452 | EARLY EXPERIENCE WITH RESMETIROM IN ADOLESCENTS AND YOUNG ADULTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS: A CASE SERIES

Andrea Tou[1] Brandon Perumpail[1] Jennifer Panganiban[2], [1]Children's Hospital of Philadelphia, [2]The Children's Hospital of Philadelphia

Background: Pediatric metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH) lack approved pharmacologic therapies. Resmetirom, a thyroid hormone receptor-β agonist, is approved for adults with noncirrhotic MASH and moderate-to-severe fibrosis. Pediatric data are lacking. We report early use of resmetirom in adolescents/young adults with MASH. **Methods:** This single-center case series included 4 patients ≤21 years old with MASH treated with resmetirom. Dosing followed adult labeling (80mg if ≤100kg, 100mg if ≥100kg). Two received monotherapy, with two on concurrent tirzepatide. Serial alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), lipid panel, Magnetic Resonance Imaging-Proton Density Fat Fraction (MRI-PDFF) fat fraction and Magnetic Resonance Elastography liver stiffness measurement (LSM), and FibroScan controlled attenuation parameter (CAP) and LSM data were collected at variable follow-up intervals during clinical care. Clinically meaningful changes are described without inferential statistics. **Results:** Patients were 75% male, median age 19 years (range 18–20). Follow-up ranged from 3–9 months. Case 1 (18 M, monotherapy, at 9 months): ALT 232 to 58 U/L, AST 119 to 38 U/L, MRI-PDFF 25.8 to 10.0% (61% relative reduction), MRE LSM 2.45 to 2.16 kPa, FibroScan LSM 9.4 to 5.3 kPa, triglycerides 285 to 159 mg/dL, and BMI 32.9 to 30.8 kg/m^2 . Case 2 (20 F, concurrent tirzepatide, at 6 months): ALT 69 to 28 U/L, AST 101 to 31 U/L, GGT 286 to 71 U/L, LDL 122 to 92 mg/dL, cholesterol 203 to 169 mg/dL, MRI-PDFF 15.0 to 11.0%, MRE LSM 4.66 to 4.20 kPa, FibroScan CAP 320 to 247 dB/m, FibroScan LSM 16.3 to 10.4 kPa, and BMI 30.7 to 26.8 kg/m^2 (−12% weight loss). Case 3 (20 M, monotherapy, up to 9 months): ALT 101 to 54 U/L, LDL 128 to 58 mg/dL, cholesterol 192 to 116 mg/dL, triglycerides 180 to 137 mg/dL, FibroScan LSM 11.0 to 5.9 kPa (despite persistent CAP elevation), and BMI 29.2 to 29.0 kg/m^2 . Case 4 (19 M, concurrent tirzepatide, at 3 months): ALT 51 to 40 U/L, AST 43 to 29 U/L, and triglycerides 149 to 116 mg/dL. Resmetirom was well tolerated without adverse events. **Conclusion:** This is the first reported use of resmetirom in adolescents with MASH. Resmetirom was well-tolerated and associated with improvements in liver enzymes, steatosis, and liver stiffness. ALT decreased in all patients from baseline, with peak reductions of 61–75% in three patients. Monotherapy was associated with hepatic improvements despite minimal BMI change, consistent with resmetirom's weight-independent mechanism of action. One patient achieved a >30% relative reduction in MRI-PDFF, a threshold linked to histologic improvement. Combination therapy was associated with concurrent weight loss, consistent with complementary incretin effects. Larger prospective studies are needed to establish the safety and efficacy of resmetirom in youth with MASH.

Longitudinal Hepatic, Metabolic, and Imaging Outcomes

Variable	Timepoint	Case 1	Case 2	Case 3	Case 4
Indication for resmetirom		MASH with F2 fibrosis	MASH with F3 fibrosis	MASH with F3 fibrosis	MASH with F2 fibrosis
Concurrent therapy		—	Transitioned from dulaglutide to tirzepatide 2-months into resmetirom for T2DM treatment	—	Initiated on tirzepatide 9-months prior to resmetirom for T2DM treatment
ALT (U/L)	Baseline	232	69	101	51
	3–6 mo	65	28	54	40
	9 mo	58	—	79	—
AST (U/L)	Baseline	119	101	71	43
	3–6 mo	33	31	47	29
	9 mo	38	—	73	—
GGT (U/L)	Baseline	43	286	32	66
	3–6 mo	27	71	17	74
	9 mo	30	—	18	—
Total cholesterol (mg/dL)	Baseline	133	203	192	161
	3–6 mo	123	169	—	181
	9 mo	123	—	116	—
Triglycerides (mg/dL)	Baseline	285	167	180	149
	3–6 mo	196	188	—	116
	9 mo	159	—	137	—
HDL (mg/dL)	Baseline	32	52	32	40
	3–6 mo	31	45	—	57
	9 mo	31	—	31	—
LDL (mg/dL)	Baseline	64	122	128	91
	3–6 mo	53	92	—	121
	9 mo	60	—	58	—
HbA1c (%)	Baseline	5.7	8.4	4.7	5.5
	3–6 mo	5.5	8.4	4.8	4.9
	9 mo	5.4	—	4.9	—
BMI (kg/m^2)	Baseline	32.9	30.7	29.2	21.4
	3–6 mo	30.9	26.8	29.4	21.4
	9 mo	30.8	—	29.0	—
Weight (kg)	Baseline	103.8	81.6	101.6	59.1
	3–6 mo	96.5	71.8	101.9	58.9
	9 mo	96.5	—	100.3	—
MRI-PDFF (%)	Baseline	25.8	15.0	—	11.3
	6-9mo	10.0	11.0	—	—
MRE LSM (kPa)	Baseline	2.45	4.66	—	3.66
	6-9mo	2.16	4.20	—	—
FibroScan CAP (dB/m)	Baseline	196	320	349	—
	3–6 mo	247	247	352	—
	9 mo	199	—	375	—
FibroScan LSM (kPa)	Baseline	9.4	16.3	11.0	—
	3–6 mo	6.9	10.4	11.0	—
	9 mo	5.3	—	5.9	—

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CAP, controlled attenuation parameter; GGT, gamma-glutamyl transferase; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LSM, liver stiffness measurement; MASH, metabolic dysfunction-associated steatohepatitis; MRI-PDFF, magnetic resonance imaging proton density fat fraction; mo, months; MRE, magnetic resonance elastography; T2DM, type 2 diabetes mellitus.

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3453 | COMPARATIVE SAFETY OF GLP-1 RECEPTOR AGONISTS VERSUS SGLT2 INHIBITORS IN PATIENTS WITH MASLD OR CIRRHOSIS AND CHRONIC KIDNEY DISEASE: RISK OF PANCREATITIS AND ACUTE KIDNEY INJURY

Urveesh Sharma[1] Yash Shah[2] Manesh Gangwani[2], [1]University of Arkansas for Medical Sciences, [2]UAMS, LR

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Background: Both GLP-1 RAs and SGLT2is are increasingly prescribed in patients with MASLD or cirrhosis and CKD, yet their safety profiles in this population have never been directly compared. In a population with already compromised liver and kidney function, even modest drug-related toxicity can translate into serious harm. **Methods:** We conducted a retrospective cohort study using the TrinetX database where adults (≥18 years) with pre-existing MASLD or cirrhosis, CKD stages 3-5, and T2DM were divided into two cohorts based on whether they were newly started on a GLP-1 RA or a SGLT2i. We excluded patients with cross-drug class exposure, alcoholic liver disease, viral hepatitis, prior liver transplant, HCC, ESRD, or dialysis. 1:1 propensity score matching (PSM) on demographics, comorbidities, medications, and laboratory values was done. Primary outcomes were incident acute pancreatitis and incident AKI within 3 years of starting the GLP-1 RA or SGLT2i. Kaplan-Meier analysis with log-rank testing and Cox regression were performed and the proportional hazards assumption was met for both pancreatitis (p = 0.749) and AKI (p = 0.333). **Results:** 1:1 PSM yielded 4,700 patients per cohort. Acute pancreatitis rates were low and statistically comparable between both groups (0.7% vs. 1.0%; HR 0.721, 95% CI 0.455–1.143; log-rank p = 0.162), with no evidence of excess risk with GLP-1 RAs. For AKI, GLP-1 RA users had numerically lower event rates (13.5% vs. 15.6%; RR 0.867, 95% CI 0.754–0.996; p = 0.043), and the time-to-event analysis showed a trend favoring GLP-1 RAs but it did not reach statistical significance (HR 0.869, 95% CI 0.748–1.011; log-rank p = 0.068). **Conclusion:** In patients with MASLD or cirrhosis, CKD, and T2DM, GLP-1 RA use was not associated with increased pancreatitis risk compared to SGLT2is. AKI rates trended lower with GLP-1 RAs, though this did not reach significance on time-to-event analysis. These findings offer reassurance about GLP-1 RA safety in a population with baseline hepatic and renal vulnerability.

Table 1. Safety outcomes at 3 years — GLP-1 receptor agonists vs. SGLT2 inhibitors

Outcome	GLP-1 RA (%)	SGLT2i (%)	HR (95% CI)	RR (95% CI)	p value (log-rank)
Acute pancreatitis	0.7	1.0	0.721 (0.455–1.143)	—	0.162
Acute kidney injury	13.5	15.6	0.869 (0.748–1.011)	0.867 (0.754–0.996)	0.068

HR = hazard ratio; RR = risk ratio; CI = confidence interval; AKI = acute kidney injury. RR not reported for pancreatitis due to low event rates. AKI risk ratio analysis significant at p = 0.043; time-to-event analysis p = 0.068 (non-significant).

Disclosures: Urveesh Sharma:Nothing to Disclose, Yash Shah:Nothing to Disclose, Manesh Gangwani: Nothing to Disclose.

3454 | NUTRITIONAL STRATEGIES FOR MUSCLE PRESERVATION DURING SEMAGLUTIDE THERAPY IN MASLD: A STRUCTURED NARRATIVE REVIEW WITH DEVELOPMENT OF LIVER-SPECIFIC CLINICAL TOOLS

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Background: Semaglutide is FDA-approved for MASH with F2–F3 fibrosis, yet 25–40% of weight loss occurs as fat-free mass. In the STEP 1 DEXA subgroup (n = 140), lean mass loss was 6.92 kg (~39% of total). Patients with MASLD face compounded sarcopenia risk (~23% prevalence overall; 30–70% in advanced liver disease) from GLP-1RA-induced lean mass loss superimposed on hepatic catabolic dysfunction. Existing nutritional frameworks (JAMA MEAL mnemonic, ACLM/ASN/OMA/TOS Joint Advisory) were developed for general obesity populations and do not incorporate liver-specific considerations such as overnight catabolism prevention or hepatic monitoring endpoints. We aim to identify the evidence gap at the intersection of GLP-1RA therapy, liver disease, and muscle preservation, and develop paired clinical tools adapting general obesity nutritional guidance for MASLD. **Methods:** A structured narrative review across four evidence streams (GLP-1RA body composition, liver disease sarcopenia/nutrition, GLP-1RA dietary/exercise guidance, and their intersection) was conducted. A patient infographic and clinician companion card were developed with liver-specific adaptations **Results:** Only 5 included studies examined muscle outcomes during GLP-1RA therapy in liver disease, reflecting a critical evidence gap. Preliminary data are mixed: SLIM LIVER (n = 46, PWH with MASLD) showed 9.3% psoas volume decline despite preserved physical function; Kakegawa et al. (n = 21, T2DM/MASLD) reported preserved skeletal muscle area with reduced muscle steatosis. Six liver-specific adaptations were identified: (1) protein 1.2–1.5 g/kg/day per AASLD/ACG; (2) structured late-evening snack with complex carbohydrates and protein to prevent overnight catabolism; (3) complete alcohol abstinence; (4) liver-specific monitoring (VCTE, FIB-4) alongside body composition; (5) zinc supplementation; (6) dose adjustment triggers incorporating sarcopenia red flags and hepatic response. These were operationalized into paired tools: a 10-panel patient infographic and an 8-section clinician card featuring dual-track liver/

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muscle monitoring aligned with semaglutide dose titration. **Conclusion:** General obesity GLP-1RA nutritional frameworks require meaningful adaptation for MASLD. These paired tools—the first bridging general guidance to liver-specific practice—provide an actionable framework for clinicians prescribing semaglutide for MASH. Prospective validation is warranted.



Disclosures: Keeranmayee Mishra:Nothing to Disclose, Bireera Muzaffar:Nothing to Disclose, Hanna Bowers:Nothing to Disclose, Ramy Mansour:Nothing to Disclose.

3455 | GLP-1 RECEPTOR AGONISTS USE IS ASSOCIATED WITH REDUCED NEURODEGENERATIVE AND CEREBROVASCULAR RISK IN MASLD: A PROPENSITY SCORE-MATCHED ANALYSIS

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Background: MASLD is increasingly recognized as a risk factor for neurocognitive impairment and cerebrovascular disease through systemic inflammation, neurodegeneration, and liver-brain axis dysregulation. While GLP-1 receptor agonists (GLP-1 RAs) have demonstrated benefits in improving MASLD disease activity, their comparative effect on neurological outcomes versus DPP-4 inhibitors in this population remains unknown. **Methods:** Using the TriNetX federated electronic health record network, we identified adults with MASLD initiating either a GLP-1 RA (n = 226,194) or a DPP-4 inhibitor (n = 54,351). Cohorts were balanced via 1:1 propensity score matching (PSM) on demographics, metabolic comorbidities, cardiovascular risk factors, laboratory parameters, medication use, and psychiatric disease burden. Primary outcomes including incident dementia, Alzheimer disease, vascular dementia, Parkinson disease, cerebral infarction, mild cognitive impairment, and falls, were assessed at 1 and 5 years following treatment initiation using Kaplan-Meier analysis and Cox proportional hazards modeling. A BMI-stratified sensitivity analysis was performed given residual BMI imbalance after PSM. **Results:** Following PSM, 48,833 patients were included per cohort. GLP-1 RA therapy in patients with MASLD was associated with significantly lower risk of all-cause dementia compared with DPP-4 inhibitor use at both 1 year (HR 0.60, 95% CI 0.47–0.76; $p < 0.001$) and 5 years (HR 0.64, 95% CI 0.57–0.72; $p < 0.001$), as well as reduced risk of cerebral infarction at 1 year (HR 0.67, 95% CI 0.56–0.80; $p < 0.001$) and 5 years (HR 0.72, 95% CI 0.65–0.78; $p < 0.001$). At 5 years, GLP-1 RA use was further associated with lower risks of vascular dementia (HR 0.70, 95% CI 0.55–0.89; $p = 0.003$) and Alzheimer disease (HR 0.70, 95% CI 0.54–0.89; $p = 0.004$). No significant differences were observed for Parkinson disease, mild cognitive impairment, or falls. BMI-stratified sensitivity analyses confirmed the persistence of the dementia association with improved covariate balance, supporting the robustness of these findings. **Conclusion:** Among patients with MASLD, GLP-1 RA therapy was associated with significantly lower risks of dementia, Alzheimer disease, vascular dementia, and cerebral infarction compared with DPP-4 inhibitors, with effects sustained at 5 years. These findings suggest GLP-1 RAs may reduce neurological risk in MASLD through pathways beyond shared glycemic and metabolic improvement. Prospective studies are warranted to clarify underlying mechanisms, including the potential role of liver-brain axis modulation, and to establish causality.

Disclosures: Maya Mahmoud:Nothing to Disclose, Muhammad Haris Latif:Nothing to Disclose, Lina

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Okar:Nothing to Disclose, Mohamed Awali:Nothing to Disclose, Kamran Qureshi:Nothing to Disclose.

3456 | FGF21-BASED THERAPIES AND DUAL INCRETIN AGONISTS LEAD HISTOLOGIC RESPONSE IN MASH: A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS

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Background: Metabolic dysfunction–associated steatohepatitis (MASH) is a common liver disease with no universally accepted first-line pharmacotherapy. Multiple drug classes, including FXR agonists, PPAR agonists, GLP-1 receptor agonists, FGF21-based therapies, thyroid hormone receptor-β agonists, and combination regimens, have been evaluated, but their comparative efficacy and safety remain unclear. We performed a systematic review and network meta-analysis (NMA) to evaluate and rank major therapeutic classes based on histologic and non-invasive endpoints in MASH. **Methods:** A comprehensive search of PubMed, CENTRAL, and Scopus was conducted through September 2025. We included RCTs enrolling adults with biopsy-proven MASH. Primary outcomes were MASH resolution without worsening of fibrosis and ≥1-stage fibrosis improvement without worsening of MASH. A Bayesian network meta-analysis using random-effects models was performed. **Results:** Out of 1,924 screened records, 20 RCTs met inclusion criteria. For MASH resolution without worsening of fibrosis, pegozafermin showed the highest efficacy (RR 13.86–21.79). Dual incretin agonists were also ranked among the strongest therapies, with tirzepatide (RR 4.29–6.00) and survodutide (RR 3.20–4.63) showing strong and consistent benefits. Semaglutide demonstrated moderate, dose-dependent efficacy (RR 2.15–3.45), while resmetirom showed similar mid-range effects (RR 2.02–2.65). Vitamin E showed no benefit over placebo.For ≥1-stage fibrosis improvement without worsening of MASH, pegozafermin showed strong antifibrotic efficacy (RR up to 15.59, 95% CrI 1.87–129.93). Tirzepatide 15 mg (RR 4.19) and survodutide 6 mg (RR 1.56) also showed significant benefit, reflecting dual incretin activity. Resmetirom (80–100 mg) showed moderate benefit (RR 1.68–1.79), while semaglutide showed modest antifibrotic activity (RR 1.13–1.40).For the composite endpoint, FGF21-based therapies showed the greatest efficacy, with pegozafermin (RR 4.19, 3.93, 3.27 across doses) and efruxifermin (RR 3.33, 3.08, 2.77) showing the strongest effects. Dual incretin agonists showed moderate benefit (tirzepatide RR 1.75–1.90; survodutide RR 1.77), while dapagliflozin showed a weaker signal (RR 2.27). Semaglutide showed minimal benefit (RR 0.90–1.04), and vitamin E showed modest, low-precision effect (RR 1.71). **Conclusion:** Across both key histologic outcomes—MASH resolution and ≥1-stage fibrosis improvement—FGF21-based therapies and dual incretin agonists demonstrated the strongest efficacy, outperforming other drug classes. Resmetirom showed moderate, consistent antifibrotic benefit, while semaglutide produced modest improvements. Traditional agents had minimal effect. Overall, FGF21-based therapies and dual incretin agonists appear to be the most promising disease-modifying treatments for MASH.



Disclosures: Maheen Afzal:Nothing to Disclose, Ubaid Ahmed:Nothing to Disclose, Rahul Falodia:Nothing to Disclose.

3457 | SEMAGLUTIDE IS ASSOCIATED WITH MASH RESOLUTION AND REDUCED HEPATIC STEATOSIS IN CHILDREN WITH MASLD IN A MULTICENTER RETROSPECTIVE STUDY

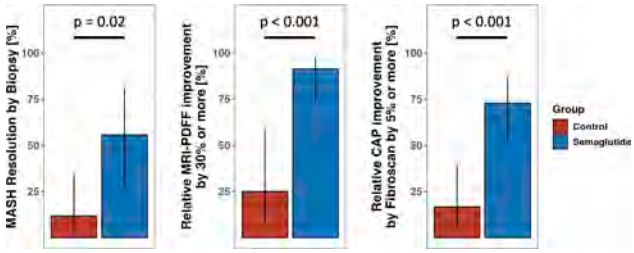
Phillipp Hartmann[1] Andrea Tou[2] Dieudonne Nonga[3] Xinlian Zhang[1] Brandon Perumpail[4] Rachel Herdes[5] Shilpa Sood[6] Erin Mauney[7] Sara Hassan[8] Rahiya Rehman[9] Joanna Yeh[10] Nikhil Pai[4] Marwa Abu El Haija[5] Sara Karjoo[11] Mohit Kehar[12] Jennifer Panganiban[13], [1]University of California San Diego, [2]Children's Hospital of Philadelphia, [3]Nationwide Children's Hospital, [4]Children's Hospital of Philadelphia, [5]Stanford University, [6]Boston Children's

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD), with its severe form metabolic dysfunction-associated steatohepatitis (MASH), affects up to 10% of children globally and causes significant morbidity and mortality. It has no FDA-approved therapy. Semaglutide is effective in adult MASLD/MASH and conditionally approved for adults with non-cirrhotic MASH, but pediatric effectiveness is unclear. We assessed semaglutide in a multicenter cohort of children with MASLD using histology, MRI, and FibroScan. **Methods:** We retrospectively included 102 children with biopsy- or imaging-confirmed MASLD from 2020-2026 (44 on semaglutide and 58 contemporary controls). Outcomes were NAFLD activity score (NAS), MASH resolution (NAS < 4, lobular inflammation = 0-1, ballooning = 0, no worsening of fibrosis), fibrosis stage, MR elastography (MRE), MRI-proton density fat fraction (PDFF), and FibroScan liver stiffness measurement (LSM) and controlled attenuation parameter (CAP). Analyses used t-tests/chi-squared tests. **Results:** Semaglutide-treated children were older (14.8 vs 12.6 years), with higher BMI (37.8 vs 31.7) and BMI z-score (2.84 vs 2.42), but with similar sex distribution, NAS (4.72 vs 4.33), and fibrosis stage (1.56 vs 1.56). Most subjects reached 2.4 mg weekly as maintenance (70.5%); mean treatment was 53.4 weeks.In 38 children with paired biopsies (14 semaglutide, 24 controls; mean 24.0-month interval), NAS improved by -2.14 vs 0 ($p = 0.002$), and fibrosis stage changed by -0.43 vs +0.17 ($p = 0.06$). Among patients with MASH, semaglutide resolved MASH in 55.6% vs 11.8% ($p = 0.02$; Figure) and improved NAS by > = 3 points in 66.7% vs 5.9% ($p < 0.001$). Notably, semaglutide prevented further worsening of fibrosis in all patients with fibrosis (n = 12).In 32 children with paired MRIs (23 semaglutide, 9 controls; 16.4-month interval), MRE changes did not differ. MRI-PDFF improved more with semaglutide (absolute -16.3% vs -1.7%, $p = 0.003$; relative -70.5% vs +1.3%, $p = 0.006$). Relative MRI-PDFF improvement > = 30% occurred in 91.3% vs 25% ($p < 0.001$; Figure), and > = 60% in 69.6% vs 0% ($p < 0.001$).At 6 months, paired FibroScan was available in 40 children (22 semaglutide, 18 controls). FibroScan LSM change did not differ, but CAP improved (absolute -29.6 dB vs +15.8 dB; relative -8.8% vs +5.7%; both $p < 0.001$). CAP improved by > = 5% in 72.7% vs 16.7% ($p < 0.001$; Figure) and by > = 10% in 59.1% vs 11.1% ($p = 0.002$). At 12 months (n = 24; 12/group), LSM remained nonsignificant, while CAP improved by -47.7 vs +25.0 dB and -13.8% vs +9.5% (both $p < 0.001$); CAP improved by > = 5% in 66.7% vs 16.7% ($p = 0.01$) and by > = 10% in 58.3% vs 8.3% ($p = 0.009$). **Conclusion:** In this first retrospective multicenter pediatric MASLD cohort, semaglutide was associated with histologic MASH resolution and improved MRI-PDFF, and FibroScan CAP, while MRE/Fibroscan LSM changes were not significant. These findings suggest pediatric efficacy and warrant confirmation in RCTs.



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3458 | EFFECTS OF GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS ON SKELETAL MUSCLE MASS, WEIGHT LOSS, AND LIVER ENZYMES IN MASLD: A SYSTEMATIC REVIEW AND META-ANALYSIS

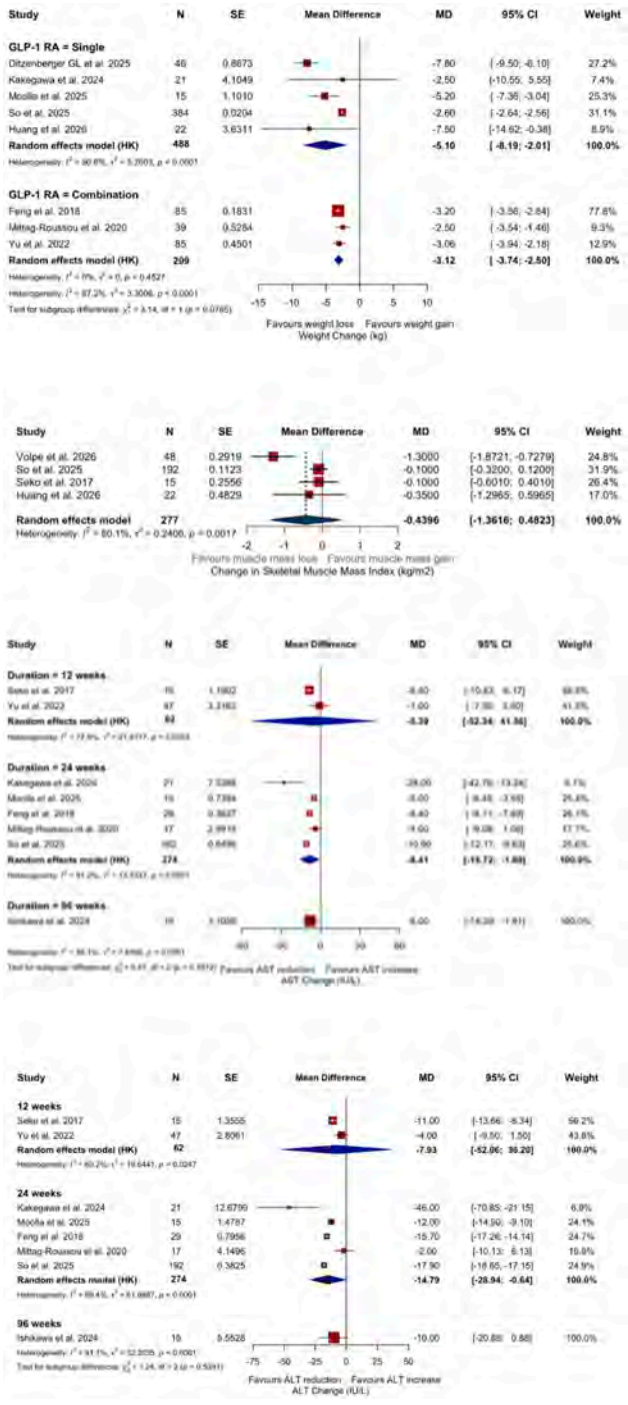
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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is closely associated with

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obesity and insulin resistance, making weight reduction a key therapeutic target. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) improve weight loss, glycemic control, and hepatic inflammation in MASLD. However, reductions in lean body mass raise concerns regarding sarcopenia. We performed a systematic review and meta-analysis evaluating the effects of GLP-1RAs on skeletal muscle mass, weight, body mass index (BMI), and liver enzymes in MASLD. **Methods:** This review followed PRISMA guidelines. Embase, PubMed, and ScienceDirect were systematically searched for studies evaluating GLP-1RAs in MASLD. Parameters including BMI, AST, ALT, and skeletal muscle indices assessed by bioelectrical impedance analysis were analyzed. Subgroup analyses were performed by treatment duration and regimen, with monotherapy compared against GLP-1RAs combined with oral hypoglycemic agents (combination). Statistical analysis was conducted in RStudio using random-effects models to calculate mean differences (MD), with heterogeneity assessed using the I^2 statistic. **Results:** Ten studies involving 846 patients were included. GLP-1RA therapy demonstrated a trend toward reduction in skeletal muscle index (MD −0.44 kg/m², 95% CI −1.36 to 0.48, p = 0.0017). Significant reductions were observed in body weight (MD −4.60 kg, 95% CI −6.27 to −2.93, p < 0.0001), AST (MD −7.64 IU/L, 95% CI −11.40 to −3.89, p < 0.0001), and ALT (MD −14.79 IU/L, 95% CI −28.94 to −0.64, p < 0.0001). Subgroup analysis demonstrated greater weight reduction with single-agent GLP-1RA therapy (MD −5.10 kg, 95% CI −8.19 to −2.01, p < 0.0001) compared with combination regimens (MD −3.12 kg, 95% CI −3.74 to −2.50, p = 0.4527). Duration-based subgroup analysis showed progressive weight reduction over time, with the greatest reduction observed at 48 weeks (MD −7.80 kg, 95% CI −9.50 to −6.10), compared with 24 weeks (MD −2.93 kg, 95% CI −3.78 to −2.08, p = 0.0028) and 12 weeks (MD −3.06 kg, 95% CI −3.94 to −2.18). For liver enzymes, single-agent GLP-1RA therapy demonstrated greater AST reduction (MD −9.99 IU/L, 95% CI −21.43 to 1.45, p < 0.0001) compared with combination therapy (MD −6.14 IU/L, 95% CI −11.41 to −0.88, p = 0.0540). Similarly, ALT reduction was greater with single-agent therapy (MD −15.00 IU/L, 95% CI −27.70 to −2.30, p < 0.0001) compared with combination regimens (MD −8.41 IU/L, 95% CI −18.83 to 2.01, p < 0.0001). Duration-based subgroup analysis demonstrated the greatest AST and ALT reductions at 24 weeks (AST: MD −8.41 IU/L, 95% CI −15.72 to −1.09, p < 0.0001; ALT: MD −14.79 IU/L, 95% CI −28.94 to −0.64, p < 0.0001). **Conclusion:** GLP-1RAs in MASLD were associated with significant reductions in weight and liver enzymes, while demonstrating a trend toward lower skeletal muscle index. Larger studies are needed to define the long-term impact of GLP-1RAs on sarcopenia risk in MASLD.



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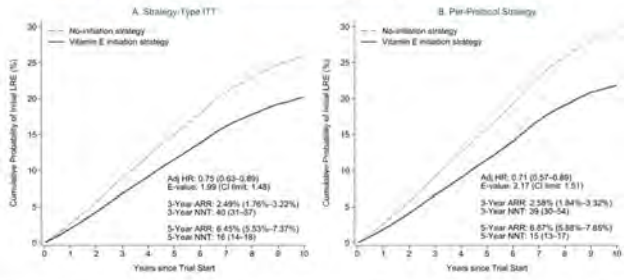
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3459 | VITAMIN E INITIATION IS ASSOCIATED WITH FEWER LIVER-RELATED EVENTS IN ADVANCED MASH: A SEQUENTIAL TARGET TRIAL EMULATION IN THE NASH CRN

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Background: Vitamin E improves histologic MASH in randomized trials, but its effect on major liver-related events (LREs) in advanced fibrosis remains uncertain. Because conventional observational analyses may be biased by delayed treatment initiation and time-varying confounding, we emulated a sequential target trial in NASH CRN prospective studies to estimate the association between vitamin E initiation and LREs. **Methods:** We used NASH CRN prospective data from 2005–2021, including Database 2 and post-trial follow-up from placebo arms of PIVENS and FLINT. The cohort included 476 adults with biopsy-proven MASH and advanced fibrosis: 328 with bridging fibrosis and 148 with compensated cirrhosis. Prevalent vitamin E users were excluded, consistent with an incident-user design. Vitamin E use was systematically obtained from structured medication inventories at regular visits and defined as the first recorded therapeutic use $\geq$200 IU/day after time zero. Eligibility and covariates were updated at sequential trial starts every 60 days during the first 5 years. We compared initiation within 365 days versus no initiation within 365 days using clone-censor-weight methods and weighted Cox models; covariates were well balanced after weighting. The primary endpoint was first centrally adjudicated LRE: hepatic decompensation, hepatocellular carcinoma, liver transplantation, or liver-related death. **Results:** Ninety-nine patients initiated vitamin E, with a median recorded use of 5.8 years, and 60 patients experienced a first LRE. The strategy-type ITT analysis accrued 54,657 weighted clone-person-years in the pooled sequential trial pseudo-population. In the strategy-type ITT analysis, vitamin E initiation was associated with lower LRE risk (HR, 0.75; 95% CI, 0.63–0.89), with 5-year absolute risk reduction (ARR) of 6.45%, number needed to treat (NNT) of 16, and 0.90-year gain in 10-year restricted mean event-free survival. Per-protocol analysis showed a stronger association (HR, 0.71; 95% CI, 0.57–0.89), with a 5-year ARR of 6.87%, NNT of 15, and 1.03-year event-free survival gain. Vitamin E initiation was not associated with non-liver mortality in strategy-type ITT (HR, 1.00; 95% CI, 0.61–1.64) or per-protocol analyses (HR, 0.87; 95% CI, 0.52–1.47). **Conclusion:** In adults with MASH and advanced fibrosis, vitamin E initiation was associated with fewer incident LREs in a sequential target trial emulation. These findings support individualized consideration of vitamin E in selected high-risk patients and further evaluation of vitamin E as a potential strategy to reduce liver-related complications.

Figure. Cumulative Probability of an Initial Liver-Related Event by Vitamin E Initiation Strategy



Abbreviations: ARR, absolute risk reduction; CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; NNT, number needed to treat; PP, per-protocol.
Legend. Cox-specific weighted models were used for the first liver-related event, defined as hepatic decompensation, hepatocellular carcinoma, liver transplantation, or liver-related death, comparing vitamin E initiation (≥200 IU/day) versus no initiation in adults with MASH and advanced fibrosis. Panels display inverse probability–weighted cumulative probability curves from Cox models.
Panel A (left) shows the strategy-type intention-to-treat analysis, in which patients remain in their assigned strategy after the 365-day grace period regardless of subsequent treatment initiation.
Panel B (right) shows the per-protocol analysis, in which patients are censored at the time of deviation from their assigned strategy.
Hazard ratios with 95% confidence intervals, E-values, absolute risk reductions, and numbers needed to treat are reported inside each panel.

Disclosures: Eduardo Vilar-Gomez:Nothing to Disclose, Wanzhu Tu:Nothing to Disclose, Yi Zhao:Nothing to Disclose, Jeanne Clark:Boehringer Ingelheim: Advisor, Novo Nordisk: Advisor, Brent Neuschwander-Tetri: Nothing to Disclose, Rohit Loomba:Eli Lilly and Company: Consultant, 89bio: Consultant, Aardvark Therapeutics: Consultant, Altimmune: Consultant, Alnylam/Regeneron: Consultant, Amgen: Consultant, Arrowhead Pharmaceuticals: Consultant, AstraZeneca: Consultant, Bristol Myers Squibb: Consultant, CohBar: Consultant, Eli Lilly: Consultant, Galmed Pharmaceuticals: Consultant, Gilead: Consultant, Glympse Bio: Consultant, Hightide: Consultant, Inipharma: Consultant, Intercept: Consultant, Inventiva: Consultant, Ionis: Consultant, Janssen, Inc.: Consultant, Madrigal Pharmaceuticals: Consultant, Merck, Metacrine, Inc.: Consultant, NGM Biopharmaceuticals: Consultant, Novartis: Consultant, Novo Nordisk: Consultant, Pfizer: Consultant, Sagimet Biosciences: Consultant, Terns Pharmaceuticals: Consultant, Theratechnologies and Viking Therapeutics: Consultant, 89bio: Stock options, Sagimet Biosciences: Stock options, Arrowhead Pharmaceuticals: Research grant, AstraZeneca: Research

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3460 | POST-12-MONTH CARDIOVASCULAR AND MORTALITY OUTCOMES IN MASLD

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is closely linked to cardiovascular risk. While bariatric surgery, GLP-1 receptor agonists (GLP-1 RA), and SGLT2 inhibitors (SGLT2i) are established treatments for obesity and metabolic disease, direct comparative data on major adverse cardiovascular events (MACE) and mortality across these interventions in MASLD patients remain limited. **Methods:** This retrospective multicenter cohort study utilized data from the Banner Health System. MASLD patients were identified using ICD codes for non-alcoholic fatty liver disease plus at least one of five metabolic criteria. Patients were categorized into four intervention groups: bariatric surgery, GLP-1 RA, SGLT2i, or combination therapy. Multinomial propensity score-based inverse probability of treatment weighting (IPTW) was applied to reduce baseline selection bias, adjusting for age, sex, BMI, race, tobacco use, hypertension, hyperlipidemia, and diabetes mellitus. A post 12-month landmark analysis was employed to mitigate immortal-time bias. Propensity score-matched survival analyses were performed. The primary outcome was MACE after 12 months post-intervention; secondary outcome was all-cause mortality following the landmark period. **Results:** The cohort included 8,619 patients: 5.8% underwent bariatric surgery, 39.3% received GLP-1 RA, 23.4% received SGLT2i, and 31.5% received combination therapy. After IPTW adjustment, compared to bariatric surgery, the post-12-month MACE risk was significantly higher in the GLP-1 RA group (HR 2.22, 95% CI 1.40–3.55, $p = 0.001$), SGLT2i group (HR 2.15, 95% CI 1.32–3.50, $p = 0.002$), and combination therapy group (HR 1.84, 95% CI 1.15–2.93, $p = 0.010$). No statistically significant differences in 12-month mortality were observed across pharmacologic groups (GLP-1 RA: HR 1.97, 95% CI 0.60–6.46, $p = 0.262$; SGLT2i: HR 1.88, 95% CI 0.54–6.52, $p = 0.323$; combination: HR 0.71, 95% CI 0.20–2.45, $p = 0.584$) **.** Propensity score-matched survival curves for post-12-month MACE and all-cause mortality are displayed in Figure 1. **Conclusion:** Bariatric surgery demonstrated a more favorable post 12-month landmark MACE risk compared with pharmacologic interventions. Propensity score-matched survival analysis suggested a significant survival benefit with bariatric surgery; however, this was not confirmed in IPTW- adjusted mortality models, warranting cautious interpretation. These findings underscore the need for prospective trials examining cardiovascular and survival outcomes across metabolic interventions in MASLD.

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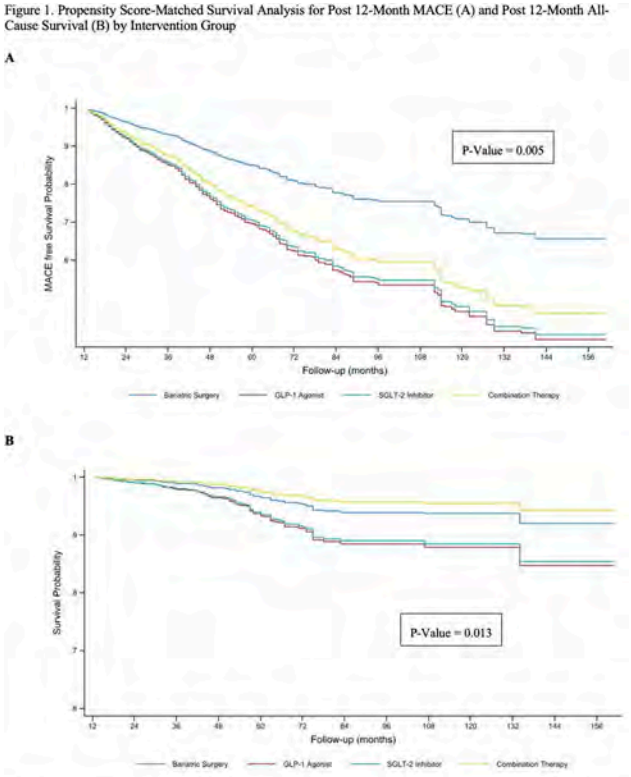


Figure 1. Propensity Score-Matched Survival Analysis for Post 12-Month MACE (A) and Post 12-Month All-Cause Survival (B) by Intervention Group

Figure 1. Propensity Score-Matched Survival Analysis for Post-12 Month MACE (A) and Post 12-Month All-Cause Mortality (B) by Intervention Group.

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★ 3461 | REAL-WORLD EFFECTIVENESS AND SAFETY OF RESMETIROM IN PATIENTS WITH MASH: A DESCRIPTIVE COHORT STUDY

Michelle Maguire[1] Anthony Michaels[1] James Hanje[1] Ruchi Bhatia[1] Pranav Penninti[1] Kathy Foreman[1] Gretchen Calhoun[1] Charlie McGuire[1] Shireen Saa[1], [1]Ohio Gastroenterology Group

Background: Resmetirom received accelerated FDA approval in March 2024 for noncirrhotic MASH with moderate-to-advanced fibrosis (F2–F3). Real-world data on outcomes, persistence, and interdisciplinary care models remain limited. We describe clinical characteristics, noninvasive test (NIT) outcomes, and treatment persistence of patients prescribed resmetirom in a hepatology practice with integrated clinical pharmacist and nurse practitioner (NP) MASH clinic support. **Methods:** This single-center, retrospective study included adults who started resmetirom between March 14, 2024 and March 31, 2026. Baseline demographics, fibrosis stage, ALT, and BMI were collected. Follow-up included ALT at 3, 6, and 12 months and fibrosis reassessment (primarily vibration-controlled transient elastography [VCTE]) at 6 and 12 months. Fibrosis stage changes were examined by GLP-1 receptor agonist (GLP-1 RA) use and $\geq$5% body weight loss. **Results:** Of 244 patients prescribed resmetirom, 226 initiated therapy (mean age 58.5 years; 39.3% $\geq$65 years; 57.2% female; 70.8% with diabetes/prediabetes; 75% with obesity; 38% on baseline GLP-1 RA, 19% added GLP-1 RA during treatment). Baseline fibrosis was F2 in 45.1%, F3 in 46.9%, and F3-4 in 7.96%. Staging was by elastography in 92.5% (VCTE 84.5%) and biopsy in 7.5%. Mean baseline VCTE was 10.67 kPa; mean ALT 53.16 U/L. At 3 months (n = 164), mean ALT decreased 9.8%; 37.2% achieved ALT < 30 U/L. At 6 months (n = 145), mean ALT decreased 9.5%; 49.7% achieved ALT < 30 U/L and 44.1% achieved $\geq$30% ALT reduction. Among 127 patients with paired VCTE at 6 months, mean stiffness decreased 1.43 kPa; 75% improved (mean 3.65 kPa reduction) and 41.4% achieved $\geq$25% kPa reduction. Mean CAP decreased 50.1 (14.8%). At 12 months (n = 68 paired VCTE), mean kPa decreased 2.84 (25.3%, p = 0.009); 81% improved (mean 4.30 kPa reduction) and 66.2% achieved $\geq$25% kPa reduction. Mean CAP decreased 53.3 (16%, p = 0.58). Fibrosis at 12 months (n = 85): F0-1 57.6%, F2 18.8%, F3 21.2%, F4 2.4%. At 6 months, 35.7% (80/224) lost $\geq$5% body weight with higher F0-1 rates (45% vs 36.9%). At 12 months, 21.9% (49/224) lost $\geq$5%, with F0-1 rates of 63% vs 50%. GLP-1 RA use showed a similar trend (F0-1: 46.6% vs 37% at 6 months; 60% vs 54% at 12 months). Persistence was 87.6% (28/226 discontinued); adverse events accounted for 13 discontinuations. 93.4% were seen by MASH clinic pharmacist and/or NP. **Conclusion:** In this large real-world cohort, resmetirom demonstrated significant improvement in liver stiffness (p = 0.009) and progressive ALT improvements through 12 months. Fibrosis regression to F0-1 occurred in over half of patients at 12 months. CAP reduction was not statistically significant. Weight loss and GLP-1 RA use appeared to provide incremental benefit. Persistence was high, supported by an integrated pharmacist and nurse practitioner care model. These findings complement trial data and support resmetirom effectiveness in routine practice.

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3462 | CORRELATION ANALYSIS BETWEEN RNA SEQUENCING OF MASH ANIMAL MODELS AND HUMAN DATA

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Background: Affecting 5-8% of the global population, Metabolic Dysfunction-Associated Steatohepatitis (MASH) is a growing public health concern that demands novel therapeutic strategies. Its complex and multifactorial pathogenesis suggests a need for multifaceted treatment modalities but selecting appropriate animal models that accurately reflect human disease is crucial for translational success. Through a human transcriptomic-guided analysis, we aim to identify the strengths of different MASH models, thereby refining the selection process for drug evaluation and enhancing predictability of preclinical studies. **Methods:** Well-recognized rodent MASH models were generated using the GAN diet (Gubra Amylin NASH diet), CDAHFD (Choline-Deficient, L-amino acid-defined, High-Fat Diet), LIDPAD (Liver Disease Progression Aggravation Diet), and HFD (High-Fat Diet) plus CCl4 (Carbon Tetrachloride). Corresponding healthy control groups were established for each model. Liver samples were collected for transcriptional profiling. A human transcriptomic-guided analysis was performed, comparing the transcriptional profiles of rodent MASH models and human MASH patients. **Results:** All murine MASH models exhibited an increase in NAS and liver fibrosis scores compared to healthy controls. The CDAHFD and HFD+CCl4 models showed more severe liver fibrosis, while the LIDPAD and GAN diet models exhibited significant insulin resistance and metabolic abnormalities. Transcriptomic analysis revealed substantial perturbations in lipid metabolism, xenobiotic metabolism, inflammation, and extracellular matrix regulation across these models, collectively capturing distinct pathological stages and mechanistic facets of human MASH progression. The CDAHFD and HFD plus CCl4 models replicated fibrogenesis, as evidenced by enrichment of TGF-β signaling and disrupted choline metabolism. The GAN diet and LIDPAD model captured the progressive transition from steatosis to inflammatory and fibrotic remodeling, enabling rapid progression of MASH while preserving key metabolic features of disease evolution. **Conclusion:** Collectively, these findings demonstrate that transcriptomic profiling extends model evaluation beyond conventional histological assessment by providing a mechanistic and quantitative framework to resolve how individual models engage disease-driving pathways relevant to human MASH. This approach reveals that distinct murine models preferentially capture different pathological stages and biological programs, thereby refining interpretation of model-specific strengths and limitations. By integrating histological and transcriptional alignment with human disease, the study establishes a more objective and translationally relevant strategy for selecting preclinical models and improving prediction of therapeutic responses prior to clinical testing.

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3463 | METABOLIC DYSFUNCTION IS ASSOCIATED WITH FURTHER HEPATIC DECOMPENSATION DESPITE CARVEDILOL IN DECOMPENSATED ADVANCED CHRONIC LIVER DISEASE

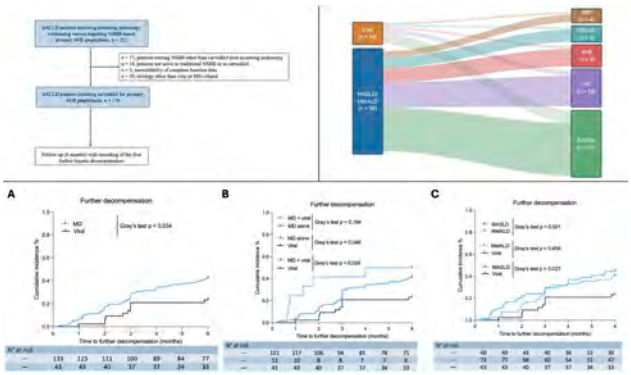
Mario Romeo[1] Viktor Domislovic[2] Fiammetta Di Nardo[1] Carmine Napolitano[1] Paolo Vaia[1] Claudio Basile[1] Giuseppe De Girolamo[3] Moris Sangineto[3] Borna Cutic[2] Anna Mrzljak[2] Alessandro Federico[1] Marcello Dallio[1], [1]Hepatogastroenterology Division, University Hospital Luigi Vanvitelli, 80138 Naples, Italy, [2]Liver Transplant Center, University Hospital Center Zagreb, 10000 Zagreb, Croatia, [3]C.U.R.E. (University Center for Liver Disease Research), Liver Unit), Foggia, 71121, Italy

Background: Metabolic dysfunction (MD) is increasingly recognized as a major determinant of cirrhosis progression and may attenuate the response to non-selective beta-blockers (NSBB). Whether MD influences the risk of further hepatic decompensation in patients with decompensated advanced chronic liver disease (dACLD) receiving carvedilol-based primary prophylaxis remains unknown. **Methods:** In this multicenter cohort study, consecutive adults with dACLD and esophageal varices requiring primary

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prophylaxis were enrolled at three European tertiary centers. All patients started carvedilol and were prospectively followed for 6 months. Patients were classified according to the presence of MD, including metabolic dysfunction-associated steatotic liver disease (MASLD), metabolic dysfunction-associated alcohol-related liver disease (MetALD), and mixed MD plus viral etiologies, and compared with patients with viral-related cirrhosis without MD. The primary endpoint was first further hepatic decompensation, defined as new or recurrent ascites, overt hepatic encephalopathy, acute variceal bleeding, spontaneous bacterial peritonitis, or hepatorenal syndrome-acute kidney injury. Death and liver transplantation were treated as competing events. **Results:** Among 176 included patients, 133 (75.6%) had MD and 43 (24.4%) had viral-related cirrhosis without MD. Baseline liver function, Child-Pugh class, MELD score, and variceal characteristics were comparable between groups. During follow-up, 66 patients (37.5%) developed further hepatic decompensation. The 6-month cumulative incidence was significantly higher (42.1% vs 23.3%) in patients with MD than in those without MD [SHR: 2.06, 95% CI 1.19-3.52; $p = 0.009$]. After adjustment for serum albumin, diabetes, body mass index, mean arterial pressure, and recruiting center, MD remained independently associated with the outcome [adjusted SHR 1.98, 95% CI 1.15-3.45; $p = 0.015$]. Lower serum albumin was also independently associated with further decompensation. Excess risk was driven predominantly by non-bleeding events, particularly ascites. Carvedilol exposure, target dose achievement, hemodynamic changes, and treatment discontinuation rates were similar across etiological groups. No significant differences were observed between MASLD and MetALD patients. **Conclusion:** MD is independently associated with a nearly twofold higher risk of further hepatic decompensation despite guideline-directed carvedilol therapy in dACLD. These findings support the concept of a distinct metabolic phenotype of portal hypertension and suggest that patients with MD may require closer monitoring and personalized management strategies beyond standard therapeutic approaches.



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3464 | SGLT-2 INHIBITOR USE AND LIVER-RELATED OUTCOMES IN T2DM-ASSOCIATED MASLD: A PROPENSITY-SCORE MATCHED ANALYSIS

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Background: SGLT-2 inhibitors reduce hepatic steatosis, intrahepatic inflammation, and fibrogenic signaling through insulin-sensitizing and weight-independent mechanisms, making them a biologically compelling candidate in MASLD. Despite accumulating preclinical and trial data, real-world evidence quantifying their impact on hard liver-related outcomes — cirrhosis progression, hepatic decompensation, and transplantation — in patients with comorbid T2DM and MASLD remains limited. **Methods:** We performed a propensity score–matched retrospective cohort study using the TriNetX Global Collaborative Network (~192 million patients). Adults with concurrent T2DM and MASLD/NASH initiating an SGLT-2 inhibitor (without GLP-1 RA use) were matched 1:1 to T2DM/MASLD patients receiving neither drug class. Both cohorts excluded pre-existing cirrhosis, HCC, or viral hepatitis. Outcomes included cirrhosis progression, hepatic decompensation, liver transplantation, HCC incidence, inpatient admission burden, all-cause mortality, and new CKD $\geq$ stage 3. **Results:** After 1:1 PSM, 38,033 patients per arm were analyzed. SGLT-2 inhibitor use was associated with significantly lower rates of cirrhosis progression (0.23% vs. 0.68%; RR 0.34; HR 0.42, 95% CI 0.33–0.53), hepatic decompensation (1.77% vs. 4.28%; RR 0.41; HR 0.49, 95% CI 0.45–0.54), and liver transplantation (0.05% vs. 0.20%; RR 0.25; HR 0.31, 95% CI 0.19–0.51). HCC events were absent in both cohorts, consistent with the protracted natural history of hepatocarcinogenesis. Among hospitalized patients, SGLT-2 users had fewer inpatient encounters (mean 7.5 vs. 9.4; $p < 0.001$). All-cause mortality was markedly lower in the SGLT-2 arm (6.79% vs. 14.84%; RR 0.46). New CKD incidence was similar on point-in-time

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analysis, though time-to-event modeling suggested early divergence likely reflecting the transient hemodynamic GFR effect prior to long-term renoprotection. **Conclusion:** In this large propensity-matched cohort of patients with T2DM and MASLD, SGLT-2 inhibitor use was associated with substantial reductions in cirrhosis progression, hepatic decompensation, liver transplant need, and all-cause mortality. Reductions of 59–75% across hard hepatic endpoints suggest disease-modifying potential well beyond glycemic control, supporting earlier, more deliberate use of SGLT-2 inhibitors as a hepatoprotective strategy in this high-risk population.
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3465 | INTENSIVE LDL REDUCTION AND HEPATIC DISEASE PROGRESSION IN MASLD WITHOUT PRIOR ACS: A PROPENSITY SCORE–MATCHED THREE-WAY COHORT ANALYSIS

Jashanveer Johal[1] Brandon Cunha[1] Mahmoud Al-Bataineh[1] Archana Salek[1] Bianca Patel[1] Abdallah Hussein[1] Yecheskel Schneider[1] Jason Hyman[2], [1]Virtua Health, [2]Einstein Medical Center, Philadelphia

Background: Statins are increasingly recognized as potentially hepatoprotective in MASLD, with preclinical evidence suggesting anti-inflammatory and antifibrotic effects. Whether achieving more intensive LDL targets confers incremental hepatic benefit in real-world populations remains uncharacterized. **Methods:** We conducted three parallel propensity score–matched retrospective cohort analyses using the TriNetX Global Collaborative Network (191.9 million patients). All patients carried a diagnosis of MASLD, were on statin therapy, and had most recent on-treatment LDL within pre-defined thresholds. Patients with prior ACS were excluded. Three pairwise comparisons were performed: LDL <55 vs. <100 mg/dL ($n \asymp 15{,}475$/arm), LDL <70 vs. <100 mg/dL ($n \asymp 36{,}133$/arm), and LDL <55 vs. <70 mg/dL ($n \asymp 19{,}507$/arm), balanced via 1:1 PSM over a 6–120 month follow-up. Outcomes included cirrhosis, hepatic fibrosis, HCC, portal hypertension, hepatic decompensation, serologic hepatic dysfunction, HRS/ARF, and liver transplantation. **Results:** Across all three comparisons, lower achieved LDL targets were paradoxically associated with a dose-dependent gradient of higher hepatic event rates on KM analysis. In the <55 vs. <100 comparison, LDL <55 was associated with significantly higher hazard of cirrhosis (HR 1.18; $p = 0.005$), hepatic fibrosis (HR 1.18; $p = 0.019$), portal hypertension (HR 1.18; $p = 0.049$), serologic hepatic dysfunction (HR 1.11; $p = 0.018$), and HRS/ARF (HR 1.14; $p = 0.001$). In the <70 vs. <100 comparison, LDL <70 was associated with higher hazard of cirrhosis (HR 1.10; $p = 0.020$), hepatic fibrosis (HR 1.19; $p = 0.0002$), portal hypertension (HR 1.14; $p = 0.022$), hepatic decompensation (HR 1.11; $p = 0.009$), serologic hepatic dysfunction (HR 1.06; $p = 0.032$), and HRS/ARF (HR 1.07; $p = 0.011$). In the <55 vs. <70 comparison, LDL <55 demonstrated higher hazard of cirrhosis (HR 1.12; $p = 0.037$), serologic hepatic dysfunction (HR 1.08; $p = 0.039$), and HRS/ARF (HR 1.08; $p = 0.030$). HCC and liver transplant were not significantly different across any comparison. **Conclusion:** Lower achieved LDL targets in statin-treated MASLD patients without prior ACS were associated with a consistent, dose-dependent gradient of worse hepatic outcomes. These findings most likely reflect reverse causation — impaired hepatic cholesterol synthesis in advanced liver disease driving lower observed LDL — rather than statin toxicity. These data do not support restricting statin use in MASLD, but underscore the need for fibrosis stage–stratified analyses and prospective studies evaluating lipid targets in this population.
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3466 | RESMETIROM IN MASLD: 12-MONTH REAL-WORLD CLINICAL OUTCOMES

Lauren Rivera[1] Sameera Shuaibi[1] Ian Tobal[1] Ricardo David Espinosa[1] James Gore[1] Ruona Ebiai[1] Amanda Mooney[1] Taylor Shano[1] Jill Rovira[1] Erin Biggs[1] Claire Ozoral[1] George Therapondos[1], [1]Ochsner Health

Background: Resmetirom became the first FDA-approved therapy for non-cirrhotic MASLD with moderate to advanced fibrosis. Real-world outcomes data on resmetirom use remain limited. This study evaluates early outcomes and adverse events associated with resmetirom use at 12 months. **Methods:** This retrospective observational study at Ochsner Health (April–September 2024) included adults $\geq$ 18 years with confirmed fibrosis who received resmetirom for at least three months with follow-up data. The primary endpoint was clinical response at 12 months based on ALT/AST changes or $\geq$1-stage fibrosis change by VCTE, MRE, or biopsy. ALT/AST were measured at baseline and 12 months, with median changes assessed by

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Wilcoxon signed-rank test. Secondary endpoints included GLP 1- use, access barriers, and time to approval and fill, adverse events, treatment discontinuation, hospitalizations, mortality, hepatotoxicity, and BMI/weight changes. **Results:** Resmetirom was prescribed for 136 patients, with 130 (95.6%) receiving insurance approval. Among 76 patients with at least 3 months of treatment and 12-month fibrosis assessment, 75% showed at least 1 fibrosis stage improvement, 19.7% remained unchanged, and 5.3% experienced worsening. Financial assistance was required for 86 patients, and 31 required appeals. Mean time to insurance approval and fill was 12 and 13 days, respectively. Among patients with at least 3 months of treatment, 38.9% were current GLP-1 users, 16.8% had previous use, and 44.3% never used GLP-1s. Serum ALT levels decreased from a median of 44.0 U/L at baseline to 36.0 U/L at 12 months (median change -3.0 U/L; p = 0.001), whereas AST levels showed no significant change over the same period, with medians of 35.0 U/L at baseline and 32.0 U/L at 12 months (median change 0.0 U/L; p = 0.555). Resmetirom was well tolerated, with low discontinuation rates and no significant differences in hospitalization, mortality, hepatotoxicity, or BMI/weight. **Conclusion:** Twelve-month outcomes in the real-world show that resmetirom treatment is associated with fibrosis improvement in F2/3 MASLD. With good tolerability and few safety concerns, resmetirom appears at least as effective in the real world as in clinical trials. Resmetirom demonstrated high access with specialty pharmacy support, highlighting the importance of healthcare access and coordinated care. In addition, we observed exposure to GLP-1 medications in approx. 50% of our cohort which may have treatment implications in the future given the approval of semaglutide for F2/3 MASLD.

Fibrosis Stage	Baseline	12 months
F0	0 (0.0%)	13 (11.5%)
F1	0 (0.0%)	31 (27.4%)
F2	48 (42.5%)	21 (18.6%)
F3	61 (54.0%)	10 (8.9%)
F4	4 (3.5%)	1 (0.9%)
Fibrosis Stage Trend	**Frequency**	**Percent**
Improved	57	75.00%
Unchanged	15	19.74%
Worsened	4	5.26%

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3467 | GLP-1 RECEPTOR AGONISTS ARE ASSOCIATED WITH REDUCED RISK OF MORTALITY, CARDIOVASCULAR EVENTS, AND HEPATIC DECOMPENSATION IN PATIENTS WITH MASLD-RELATED CIRRHOSIS: A PROPENSITY SCORE-MATCHED ANALYSIS

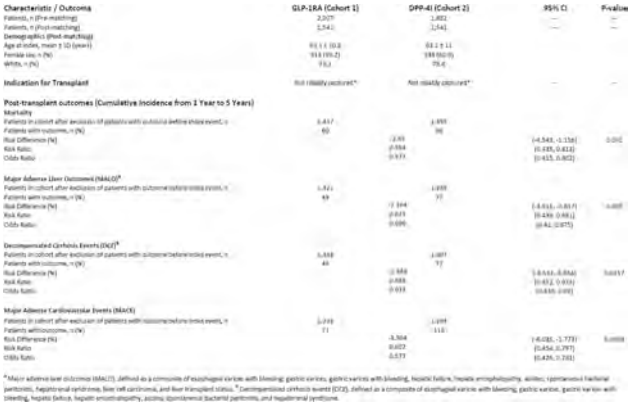
Allan Zhang[1] Mohamad Ali Ibrahim[2] Kimberly Taing[1] Prasun Jalal[2], [1]University of Texas Southwestern Medical Center, [2]Baylor College of Medicine

Background: GLP-1 receptor agonists (GLP-1RAs) have demonstrated hepatic and cardiovascular benefits in patients with metabolic dysfunction-associated steatotic liver disease (MASLD), though their impact on clinical outcomes in patients with established cirrhosis remains incompletely characterized. This study evaluated long-term hepatic and cardiovascular outcomes among patients with T2DM and MASLD cirrhosis treated with GLP-1RAs compared with dipeptidyl peptidase-4 inhibitors (DPP-4is). **Methods:** Using the TriNetX Research Network, adult patients with T2DM and established MASLD cirrhosis were identified and stratified in cohorts by new exposure to GLP-1RAs (semaglutide, liraglutide, or tirzepatide) or DPP-4is (sitagliptin, saxagliptin, linagliptin, or alogliptin). Patients with hepatocellular carcinoma (HCC), autoimmune or cholestatic liver disease, viral hepatitis, alcohol-associated liver disease, decompensated cirrhosis, or other chronic liver diseases prior to index event (date of medication initiation) were excluded. Outcomes included mortality, major adverse liver outcomes (MALO), decompensated cirrhosis events (DCE), and major adverse cardiovascular events (MACE) assessed by cumulative incidence between 1 and 5 years after index. Cohorts were propensity score matched (PSM) 1:1 for demographics, metabolic comorbidities, cardiovascular risk factors, medication exposure, and laboratory metrics. **Results:** Among 3,859 eligible patients, 2,007 patients receiving GLP-1RAs and 1,852 patients receiving DPP-4is were identified, with 1,541 patients remaining in each cohort after PSM. GLP-1RA therapy was associated with significantly reduced risk of mortality (RR 0.594, 95% CI 0.435-0.813, P = 0.001), MALO (RR 0.621, 95% CI 0.438-0.881, P = 0.007), DCE (RR 0.646, 95% CI 0.452-0.924, P = 0.0157), and MACE (RR 0.602, 95% CI 0.454-0.797, P = 0.0003) compared with DPP-4i treatment over 5 years of follow-up. **Conclusion:** In patients with T2DM

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and MASLD cirrhosis, GLP-1RA therapy was associated with decreased long-term hepatic and cardiovascular complications compared with DPP-4i therapy. These findings support the potential role of GLP-1RAs in treatment of MASLD cirrhosis and warrant prospective studies to further determine their influence on hepatic outcomes and disease progression. Limitations include retrospective design and reliance on accuracy of administrative data.

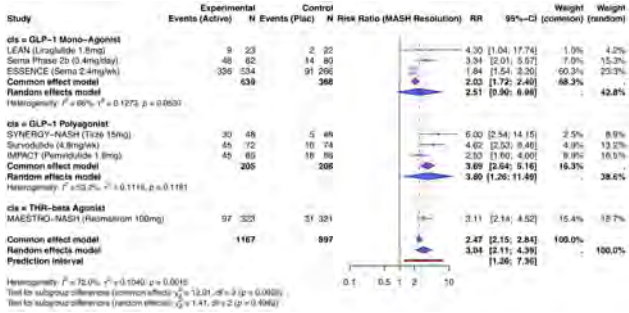


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3468 | COMPARATIVE EFFICACY OF INCRETIN-BASED AGONISTS AND THR-BETA AGONISTS FOR MASH RESOLUTION AND FIBROSIS IMPROVEMENT: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: GLP-1 receptor mono-agonists (liraglutide, semaglutide), GLP-1-based polyagonists (tirzepatide, survodutide, pemvidutide), and thyroid hormone receptor-beta (THR-beta) agonists (resmetirom) have each demonstrated histological efficacy for metabolic dysfunction-associated steatohepatitis (MASH) in randomized controlled trials. Whether weight loss mediates MASH resolution across drug classes, and whether weight-independent hepatic mechanisms achieve comparable histological improvement, has not been systematically examined. **Methods:** A systematic review following PRISMA 2020 guidelines searched through April 2025 for randomized, placebo-controlled trials evaluating pharmacological agents for biopsy-confirmed MASH with histological endpoints. For multi-dose trials, the highest dose arm was selected for analysis (semaglutide 0.4 mg/day, survodutide 4.8 mg/wk, pemvidutide 1.8 mg/wk). The primary outcome was MASH resolution without worsening of fibrosis (risk ratio). The secondary outcome was fibrosis improvement by at least one stage without worsening of MASH. Subgroup analyses were performed by drug class. To understand if greater weight loss leads to higher rates of MASH resolution,we performed an exploratory analysis to compare these two factors across the included studies.An AI-assisted tool and R software were used to assist with literature review, data verification, and manuscript editing; final was verified by the authors, who assume full responsibility for the accuracy and integrity of this work. **Results:** Seven trials (N = 2,064; 1,167 active, 897 placebo) were included. The pooled risk ratio for MASH resolution was 3.04 (95% CI 2.11-4.39; I-squared = 72%; GRADE: moderate). The pooled risk difference was 0.38 (95% CI 0.28-0.49; NNT = 3). By class, GLP-1 mono-agonists achieved a risk ratio of 2.51 (95% CI 0.90-6.98), polyagonists 3.80 (95% CI 1.26-11.49), and resmetirom 3.11 (95% CI 2.14-4.52). Subgroup differences were not significant under random-effects assumptions (p = 0.49). For fibrosis improvement (5 trials; N = 1,375), the pooled risk ratio was 1.52 (95% CI 1.30-1.79; I-squared = 0%; GRADE: high). Exploratory meta-regression showed a positive association between weight loss and MASH resolution among incretin-based agents, while resmetirom achieved comparable benefit with minimal weight change. This analysis is exploratory (k = 7) and underpowered. **Conclusion:** All three pharmacological classes significantly improve MASH resolution versus placebo (NNT approximately 3). Fibrosis improvement is consistent across incretin classes (high GRADE certainty). While weight loss contributes to MASH resolution among incretin-based agents, resmetirom achieves comparable histological improvement through weight-independent hepatic mechanisms, supporting mechanistically complementary therapeutic strategies and potential combination approaches.



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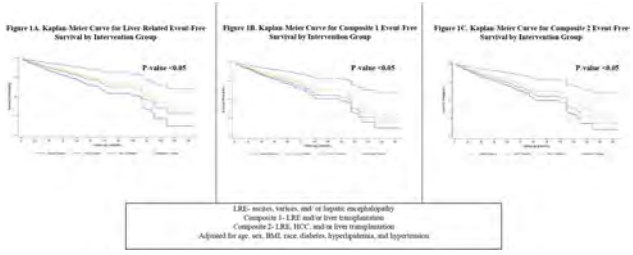
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Ravi Patel:Nothing to Disclose, Aditya Kohli:Nothing to Disclose, Ramy Mansour:Nothing to Disclose.

3470 | COMPARATIVE EFFECTIVENESS OF BARIATRIC SURGERY, GLP-1 A, AND SGLT2I ON COMPOSITE LIVER OUTCOMES IN PATIENTS WITH MASLD: A MULTICENTER IPTW AND PROPENSITY SCORE-MATCHED SURVIVAL ANALYSIS

Diwanshu Soni[1] Leith Ghani[2] Majd Aboona[2] Pooja Rangan[3] Chih Hua Chung[4] Yu Cin Chang[4] Mark Wong[4] Karn Wijarnpreecha[2] Rohit Nathan[4] Moises Nevah Rubin[4] Michael Fallon[4] Farah Husain[3] Ma Ai Thanda Han[4], [1]University of Arizona College of Medicine- Phoenix, [2]University of Arizona College of Medicine-Phoenix, [3]University of Arizona College of Medicine – Phoenix, [4]University of Arizona College of Medicine - Phoenix

Background: Metabolic dysfunction-associated steatoic liver disease (MASLD) is the leading cause of chronic liver disease globally and a major contributor to cirrhosis-related complications, including ascites, varices, hepatic encephalopathy, hepatocellular carcinoma (HCC), and liver transplantation. Bariatric surgery, glucagon-like peptide-1 receptor agonists (GLP-1 RA), and sodium-glucose cotransporter-2 inhibitors (SGLT2i) have each been associated with improved outcomes; however, comparative data evaluating composite liver outcomes remain limited. We aim to compare the effects of these interventions on incident liver-related events in patients with MASLD. **Methods:** We conducted a multicenter, retrospective cohort study across the Banner Health System, including adults with MASLD receiving bariatric surgery, GLP-1 RA, SGLT2i, or combination therapy between July 2012 and December 2023. Patients with other etiologies of liver disease, BMI < 30 kg/m^2, or a < 12 months of follow-up were excluded. The primary outcome was liver-related events (LRE) – ascites, varices, and/or hepatic encephalopathy. The secondary outcomes included composite liver events consisting of LRE, HCC, and/or liver transplantation. A 1-year landmark analysis was performed. Propensity scores for the four treatment groups were estimated using multinomial logistic regression and applied as inverse probability of treatment weights (IPTW) in Cox proportional-hazards models, with bariatric surgery as the reference group. Propensity score-matched Kaplan-Meier (KM) curves were used to compare event-free survival across groups. **Results:** After multinomial IPTW adjustment, bariatric surgery was associated with the lowest risk of LRE and composite liver outcomes. Compared with bariatric surgery, GLP-1 RA therapy was associated with increased risk of LRE (aHR 2.55, 95% CI 1.38-4.69; p = 0.003), Composite 1 (aHR 2.43, 95% CI 1.36-4.33; p = 0.003), and Composite 2 (aHR 2.52, 95% CI 1.42-4.46; p = 0.002). SGLT2i therapy was also associated with increased risk of LRE (aHR 2.00, 95% CI 1.04-3.86; p = 0.038), Composite 1 (aHR 2.18, 95% CI 1.18-4.03; p = 0.013), and Composite 2 (aHR 2.18, 95% CI 1.18-4.01; p = 0.012). Combination therapy showed a non-significant trend toward higher LRE risk (aHR 1.78, 95% CI 0.96-3.28; p = 0.064), but higher risk of Composite 1 (aHR 1.81, 95% CI 1.01-3.24; p = 0.045) and Composite 2 (aHR 1.81, 95% CI 1.02-3.23; p = 0.044). Propensity score-matched KM analysis demonstrated superior liver event-free survival with bariatric surgery across all outcomes (Figure 1). **Conclusion:** In MASLD patients, bariatric surgery demonstrated superior liver-related and composite outcomes compared with GLP-1 RA and SGLT2i therapies after 1-year landmark, multinomial IPTW-adjusted, and propensity score-matched KM analyses. Future studies should stratify these outcomes based on fibrosis stage.



Disclosures: Diwanshu Soni:Nothing to Disclose, Leith Ghani:Nothing to Disclose, Majd Aboona:Nothing to Disclose, Pooja Rangan:Nothing to Disclose, Chih Hua Chung:Nothing to Disclose, Yu Cin Chang:Nothing to Disclose, Mark Wong:Nothing to Disclose, Karn Wijarnpreecha:Nothing to Disclose, Rohit Nathan:Nothing to Disclose, Moises Nevah Rubin:Nothing to Disclose, Michael Fallon:Nothing to Disclose, Farah Husain: Johnson & Johnson (Ethicon): Speaking and Teaching, W.L. Gore: Speaking and Teaching, Ma Ai Thanda Han:Nothing to Disclose.

3471 | GLP-1 THERAPY PROVIDES SUPERIOR LIVER STIFFNESS CHANGE OVER LIFESTYLE-MEDIATED WEIGHT LOSS IN SUSPECTED MODERATE TO SEVERE METABOLIC DYSFUNCTION ASSOCIATED STEATOHEPATITIS AND SUSPECTED CIRRHOSIS

Nicholas Kruzdlo[1] Joseph Scaravalle[1] Stephanie Oliveros-Diaz[1] Kirsten Hobson[1] Elisabeth Verwest[1] Lily Lu[1] Raymond Bell[1] Yovanni Rosario[1] Cameron Rolph[1]

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Isabelle Crotsley[1] Guy Neff[1], [1]Covenant Metabolic Specialists

Background: Weight loss is central to managing Metabolic Dysfunction Associated Steatotic Liver Disease (MASLD) and Metabolic Dysfunction Associated Steatohepatitis (MASH), and metabolic dysfunction-associated cirrhosis. GLP-1 receptor agonists now offer a pharmacologic pathway to weight loss alongside lifestyle modifications. It is currently unclear if GLP-1-mediated weight loss produces additional hepatic fibrosis reduction benefits compared to lifestyle-mediated weight loss. This study evaluated whether GLP-1 associated weight loss produces greater liver stiffness change (% kPa) compared to lifestyle modification, and whether this relationship differs by fibrosis severity across minimal, mild-moderate, and moderate-severe strata. **Methods:** A retrospective analysis was performed on 200 patients who completed baseline and follow-up visits within 11–36 months with FibroScan, weight, medication, and clinical data recorded at both time points. After excluding patients who experienced weight gain between visits, linear regression modeled % kPa change, chosen to normalize outcomes across strata with substantially different baseline ranges, against GLP-1 use, change in weight, age, sex, baseline kPa, and follow-up duration. This was applied across the full cohort (3–38.6 kPa, n = 130) and three baseline kPa strata: minimal (3–6 kPa, n = 52), mild-moderate (6.1–9.9 kPa, n = 55), and moderate-severe (10–38.6 kPa, n = 23). Weight loss was comparable between subgroups within each stratum, and weight change was included as a covariate to isolate the independent effect of GLP-1 on kPa reduction. **Results:** GLP-1 use produced a significant decrease in % kPa across the full cohort ($\beta = -16.58$, $p = 0.006$). Stratified analysis revealed no significant difference between modalities in minimal or mild-moderate fibrosis strata. In moderate-severe fibrosis, GLP-1 use was associated with a greater reduction in fibrosis compared to lifestyle-mediated weight loss ($\beta = -31.33$, $p = 0.013$). Age was inversely associated with fibrosis reduction across the full cohort ($p < 0.001$), and longer follow-up duration predicted greater improvement in the moderate-severe fibrosis cohort ($p = 0.031$). **Conclusion:** In patients with moderate-to-severe fibrosis, GLP-1 therapy was associated with 31.3% greater liver stiffness reduction compared with lifestyle-mediated weight loss despite comparable weight loss between modalities, suggesting a weight loss independent antifibrotic effect. In contrast, no significant difference was observed between modalities at lower fibrosis stages (kPa 3–9.9), supporting lifestyle modification as equally effective at lower fibrosis stages. At kPa ≥ 10, GLP-1 therapy may provide additional antifibrotic benefits and may warrant preferential consideration. Older age independently predicted attenuated fibrosis response ($p < 0.001$), underscoring the need for age and stage-stratified treatment in MASLD/MASH.

Table 1. Multivariable Linear Regression — Predictors of % kPa Change by Fibrosis Stratum

Negative coefficients indicate reduction in liver stiffness. % kPa change used to normalize outcomes across strata with substantially different baseline ranges. N = 130

Variable	GLP-1 (n)	Lifestyle (n)	Total (n)	Coefficient (% kPa)	95% CI	p-value
GLP-1 Use by Fibrosis Stratum						
Minimal fibrosis (3–6 kPa)	20	32	52	−3.80	−23.1, 15.5	0.694
Mild-moderate fibrosis (6.1–9.9 kPa)	18	37	55	−5.24	−18.8, 8.3	0.441
Moderate-severe fibrosis (10–38.6 kPa)	17	6	23	**−31.33**	−55.1, −7.5	**0.013**
Full Cohort (3–38.6 kPa)						
GLP-1 Use (all fibrosis strata combined)	55	75	130	**−16.58**	−28.2, −4.9	**0.006**
Significant Covariates						
Age (all fibrosis strata combined)	55	75	130	**+0.90**	0.38, 1.42	**< 0.001**
Follow-up duration (moderate-severe cohort)	17	6	23	**−1.85**	−3.5, −0.19	**0.031**

1.) GLP-1 receptor agonist use defined as documented use for ≥3 months within the follow-up visit window.
2.) Weight loss was comparable between GLP-1 and lifestyle subgroups; change in weight was included as a covariate to isolate the independent effect of GLP-1 use.
3.) Age coefficient is positive (+0.90), indicating older age is associated with less fibrosis reduction across the full cohort.

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3472 | REAL-WORLD CHANGES IN NON-INVASIVE LIVER FIBROSIS STAGE AND BIOMARKERS AFTER RESMETIROM FOR METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS

Emilee Hall[1] Dauris Rosario[1] Nancy Reau[1], [1]Rush University Medical Center

Background: Resmetirom is approved for metabolic dysfunction-associated steatohepatitis (MASH) with fibrosis. We evaluated real-world changes in non-invasive fibrosis stage and metabolic markers after resmetirom initiation in a tertiary hepatology clinic. **Methods:** We performed a retrospective cohort study of adults initiated on resmetirom between June 2024 and May 2025 (data cut-off 1 December 2025). Fibrosis stage was derived from liver stiffness measurement (LSM) by transient elastography (TE; FibroScan) or magnetic resonance elastography (MRE) at baseline and at most recent follow-up when available. Paired LSM-derived stage and laboratory values were compared pretreatment vs most recent follow-up using Wilcoxon signed-rank or paired t tests, as appropriate. Alanine aminotransferase (ALT) response was defined as at least a 30% reduction. Associations of statin use and glucagon-like peptide 1 receptor agonist (GLP-1 RA) use with LSM stage improvement (any decrease in stage) were explored using multivariable logistic regression. **Results:** Thirty-four patients were included (mean age 55.3 years; 58.8% female; mean body mass index 35.8 kg/m2). Mean time on resmetirom was 14 months. Twenty-five had paired LSM (TE or MRE)

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over a median of 9.2 months (interquartile range [IQR] 7.1 to 11.5). Fibrosis stage improved in 21 of 25 (84.0%), was unchanged in 2 (8.0%), and worsened in 2 (8.0%) (Z = -4.04, p < 0.001). Median ALT decreased from 42.5 (IQR 28.3 to 76.3) to 36.5 (IQR 25.8 to 48.3) IU/L (Z = -2.06, p = 0.040), and median aspartate aminotransferase (AST) decreased from 47.0 (IQR 23.3 to 68.5) to 31.5 (IQR 23.0 to 38.8) IU/L (Z = -2.82, p = 0.005). ALT response occurred in 13 of 34 (38.2%). Low-density lipoprotein (LDL) cholesterol decreased from a mean of 101.6 to 76.7 mg/dL (mean change -24.9 mg/dL, p = 0.001), while glycated hemoglobin (HbA1c) showed no significant change (p = 0.236). In multivariable logistic regression, neither statin use nor GLP-1 RA use was associated with likelihood of LSM stage improvement (likelihood ratio p = 0.37; statin p = 0.22; GLP-1 RA p = 0.76). **Conclusion:** In this real-world cohort, resmetirom therapy was associated with significant improvement in non-invasive fibrosis stage assessed by TE or MRE, reductions in aminotransferases, and lower LDL cholesterol over approximately 9 months. Larger studies with longer follow-up are needed to confirm durability and identify predictors of response.

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3473 | SEMAGLUTIDE IN MASLD REDUCES LIVER FAT AND ENERGY INTAKE, BUT DOES NOT IMPROVE DIET QUALITY

Sana Pirzada[1] Sara Turner[2] Shanna Yang[2] Kayla Airaghi[2] Natalie Vallone[2] Harish Gopalakrishna[1] Elenita Rivera[1] Yaron Rotman[1], [1]Translational Hepatology Section, Liver Diseases Branch, NIDDK, NIH, Bethesda, MD, USA, [2]Nutrition Department, Clinical Center, NIH, Bethesda, MD, USA

Background: Obesity and unhealthy diets are linked to incidence and severity of metabolic dysfunction-associated steatotic liver disease (MASLD). GLP-1 receptor agonists decrease energy intake and improve obesity and MASLD. We aimed to assess how longitudinal changes in energy intake, macronutrients, diet quality, and food choices during semaglutide treatment affect liver fat content in adults with MASLD. **Methods:** In a prospective mechanistic trial (NCT03884075), adults with biopsy-proven MASLD were treated for 30 weeks with semaglutide (1.0 mg/wk). Three-day food records were collected at baseline and weeks 2, 12, and 30. Diet quality was assessed using the Healthy Eating Index (HEI; range 0-100). Objective energy intake and food choice were assessed by ad libitum food array, weighed pre- and post-consumption at baseline and week 30. Liver fat content was measured by MR spectroscopy and body composition by DEXA at baseline and week 30. **Results:** Twenty-nine participants were included (age 44.7 ± 10.6 years, 59% female, BMI 35.1 ± 5.8 kg/m2). At week 30, participants lost 8.1 ± 6.6% body weight, 14.0 ± 10.6% fat mass, 2.8 ± 3.6% lean mass, and 8.7 ± 4.9% liver fat. Reductions in BMI and body fat correlated with reduction in liver fat ($r = 0.45$, $p = 0.012$ and $r = 0.38$, $p = 0.048$, respectively). Energy intake (baseline 1590 ± 137 kcal/d) decreased significantly by week 2, reached nadir at week 12 (1235 ± 79 kcal, $p < 0.001$) and remained lower through week 30. Macronutrient distribution (baseline 46.5% carbohydrate, 33.6% fat, 17.5% protein) remained similar at all time points. Total HEI decreased modestly from 65.8 ± 2.3 at baseline to 56.2 ± 2.3 at week 30 (p for trend = 0.04) with HEI component scores for seafood and plant proteins and unsaturated:saturated fat ratio significantly decreasing by weeks 12 and 30 (all $p < 0.05$). Similarly, total energy intake on ad libitum food array decreased at week 30 (940.7 ± 545.0 kcal) versus baseline (1129.6 ± 57.7 kcal, $p < 0.010$), without change in macronutrient composition. Reduction in energy intake correlated with decrease in total body fat ($r = 0.46$, $p = 0.017$) and BMI ($r = 0.44$, $p = 0.018$), and was non-significantly associated with liver fat reduction. Changes in total HEI scores were not associated with changes in weight, body composition, or liver fat, and did not modulate the effects of weight change on liver fat content. **Conclusion:** In adults with MASLD, semaglutide decreases energy intake on self-reported and objective measures of food intake, but does not lead to changes in macronutrient composition or improved diet quality. Changes in energy balance (and resultant decreased adiposity) but not in food quality drive liver fat reduction. To improve diet quality as well, semaglutide treatment alone does not suffice in the absence of additional dietary counseling.

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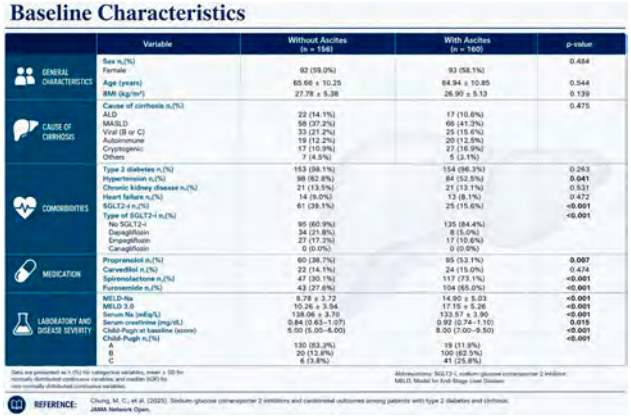
Disclosures: Sana Pirzada:Nothing to Disclose, Sara Turner:Nothing to Disclose, Shanna Yang:Nothing to Disclose, Kayla Airaghi:Nothing to Disclose, Natalie Vallone:Nothing to Disclose, Harish Gopalakrishna: Nothing to Disclose, Elenita Rivera:Nothing to Disclose, Yaron Rotman:Nothing to Disclose.

3474 | SGLT2 INHIBITOR USE IS ASSOCIATED WITH LOWER ODDS OF ASCITES IN PATIENTS WITH CIRRHOSIS AND TYPE 2 DIABETES: A CROSS-SECTIONAL STUDY

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Background: Sodium-glucose cotransporter-2 inhibitors (SGLT2-i) have shown favorable cardiorenal and metabolic effects, and emerging evidence suggests a potential role in portal hypertension and fluid retention in cirrhosis. However, data regarding the association between SGLT2-i use and ascites in patients with cirrhosis remain limited. **Methods:** We conducted a cross-sectional study including adults with cirrhosis and T2DM evaluated at a tertiary referral center. Demographic, clinical, and biochemical variables were collected. Ascites was categorized as absent, grade 1, or grade 2–3. Logistic regression analysis was performed to evaluate the association between SGLT2-i use and the presence of ascites.Objective: To evaluate whether iSGLT2 use is associated with lower presence and severity of ascites in patients with cirrhosis and type 2 diabetes mellitus, as well as its relationship with liver disease severity parameters, including Child-Pugh, MELD-Na, MELD 3.0, serum sodium, and serum creatinine. **Results:** A total of 316 patients were included. Overall, 58.5% were women, with a mean age of 65.3 ± 10.6 years and a mean BMI of 27.3 ± 5.3 kg/m2. MASLD was the most common etiology of cirrhosis (39.2%). Moreover, 27.2% of patients received SGLT2-i therapy, including dapagliflozin (13.3%) and empagliflozin (13.9%). Ascites was present in 50.6% of patients, with grade 1 in 34.8% and grade 2–3 in 15.8%. Patients with ascites had significantly lower SGLT2-i use compared with those without ascites (15.6% vs 39.1%, $p < 0.001$). Patients with ascites also had higher MELD-Na scores, higher MELD 3.0 scores, lower serum sodium levels, and more advanced Child-Pugh stage (all $p < 0.001$). In multivariable logistic regression analysis, SGLT2-i use was independently associated with lower odds of ascites (OR 0.288, 95% CI 0.169–0.492; $p < 0.001$). **Conclusion:** In this cross-sectional study of patients with cirrhosis and type 2 diabetes, SGLT2-i use was independently associated with lower odds of ascites. These findings support the potential role of SGLT2-i in fluid-related complications of cirrhosis and warrant prospective studies to further evaluate their therapeutic impact.

Baseline Characteristics



	Variable	Without Ascites (n = 156)	With Ascites (n = 160)	p-value
GENERAL CHARACTERISTICS	Sex n,(%)			0.484
	Female	92 (59.0%)	93 (58.1%)	
	Age (years)	65.66 ± 10.25	64.94 ± 10.85	0.544
	BMI (kg/m²)	27.78 ± 5.38	26.90 ± 5.13	0.139
CAUSE OF CIRRHOSIS	Cause of cirrhosis n,(%)			0.475
	ALD	22 (14.1%)	17 (10.6%)	
	MASLD	58 (37.2%)	66 (41.3%)	
	Viral (B or C)	33 (21.2%)	25 (15.6%)	
	Autoimmune	19 (12.2%)	20 (12.5%)	
	Cryptogenic	17 (10.9%)	27 (16.9%)	
	Others	7 (4.5%)	5 (3.1%)	
COMORBIDITIES	Type 2 diabetes n,(%)	153 (98.1%)	154 (96.3%)	0.263
	Hypertension n,(%)	98 (62.8%)	84 (52.5%)	0.041
	Chronic kidney disease n,(%)	21 (13.5%)	21 (13.1%)	0.531
	Heart failure n,(%)	14 (9.0%)	13 (8.1%)	0.472
	SGLT2-i n,(%)	61 (39.1%)	25 (15.6%)	<0.001
	Type of SGLT2-i n,(%)			<0.001
	No SGLT2-i	95 (60.9%)	135 (84.4%)	
	Dapagliflozin	34 (21.8%)	8 (5.0%)	
	Empagliflozin	27 (17.3%)	17 (10.6%)	
	Canagliflozin	0 (0.0%)	0 (0.0%)	
MEDICATION	Propranolol n,(%)	60 (38.7%)	85 (53.1%)	0.007
	Carvedilol n,(%)	22 (14.1%)	24 (15.0%)	0.474
	Spironolactone n,(%)	47 (30.1%)	117 (73.1%)	<0.001
	Furosemide n,(%)	43 (27.6%)	104 (65.0%)	<0.001
LABORATORY AND DISEASE SEVERITY	MELD-Na	9.78 ± 3.72	14.90 ± 5.03	<0.001
	MELD 3.0	10.26 ± 3.94	17.15 ± 5.26	<0.001
	Serum Na (mEq/L)	138.06 ± 3.70	133.57 ± 3.90	<0.001
	Serum creatinine (mg/dL)	0.84 (0.63–1.07)	0.92 (0.74–1.10)	0.015
	Child-Pugh at baseline (score)	5.00 (5.00–6.00)	8.00 (7.00–9.50)	<0.001
	Child-Pugh n,(%)			<0.001
	A	130 (83.3%)	19 (11.9%)	
	B	20 (12.8%)	100 (62.5%)	
	C	6 (3.8%)	41 (25.6%)	

Data are presented as n (%) for categorical variables, mean ± SD for normally distributed continuous variables, and median (IQR) for non-normally distributed continuous variables.

Abbreviations: SGLT2-i, sodium-glucose cotransporter 2 inhibitor; MELD, Model for End-Stage Liver Disease.

REFERENCE: Chung, M. C., et al. (2025). Sodium-glucose cotransporter 2 inhibitors and cardiorenal outcomes among patients with type 2 diabetes and cirrhosis. JAMA Network Open.

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3475 | COMPARATIVE EFFECTIVENESS OF BARIATRIC SURGERY, GLP-1 RA, AND SGLT2I ON LIVER OUTCOMES IN NON-CIRRHOTIC MASLD: A MULTICENTER IPTW AND PROPENSITY SCORE-MATCHED SURVIVAL ANALYSIS

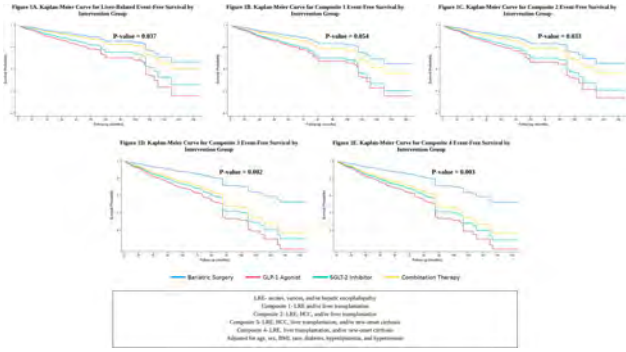
Leith Ghani[1] Diwanshu Soni[2] Majd Aboona[3] Pooja Rangan[4] Chih Hua Chung[5] Yu Cin Chang[5] Mark Wong[5] Karn Wijarnpreecha[2] Rohit Nathan[5] Moises Nevah Rubin[6] Mike Fallon[7] Farah Husain[8] Ma Ai Thanda Han[1], [1]University of Arizona College of Medicine Phoenix, [2]University of Arizona College of Medicine-Phoenix, [3]University of Arizona College of Medicine - Phoenix, [4]Banner University Medical Center- Phoenix, [5]Banner University Medical Center-P, [6]Banner University Medical Center, [7]University of Arizona, [8]Oregon Health & Science University

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common cause of chronic liver disease worldwide and is associated with progressive hepatic fibrosis and

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liver-related morbidity, including cirrhosis. Early intervention in non-cirrhotic disease may reduce progression. While bariatric surgery, glucagon-like peptide-1 receptor agonists (GLP-1 RA), and sodium-glucose cotransporter-2 inhibitors (SGLT2i) have each demonstrated benefit in MASLD, comparative data on liver outcomes in non-cirrhotic patients remain limited. We compared these interventions on liver-related outcomes in non-cirrhotic MASLD. **Methods:** This multicenter retrospective cohort study across the Banner Health System included adults with non-cirrhotic MASLD treated with bariatric surgery, GLP-1 RA, SGLT2i, or combination therapy between July 2012 and December 2023. Patients with other etiologies of liver disease, BMI < 30 kg/m², or < 12 months of follow-up were excluded. The primary outcome was liver-related events (LRE) - ascites, varices, and/or hepatic encephalopathy; secondary outcomes were four progressively inclusive composites (Composites 1-4). A 1-year landmark analysis was performed. Propensity scores for the four groups were estimated by multinomial logistic regression and applied as inverse probability of treatment weights (IPTW) in Cox proportional-hazards models, with bariatric surgery as reference. Propensity score-matched survival curves compared event-free survival across groups. **Results:** After multinomial IPTW adjustment, bariatric surgery was associated with the lowest risk of liver-related and composite outcomes. Compared with bariatric surgery, GLP-1 RA was associated with increased risk of LRE (aHR 2.11, 95% CI 1.10-4.07; p = 0.026), Composite 1 (aHR 2.02, 1.09-3.73; p = 0.024), and Composite 2 (aHR 2.10, 1.14-3.86; p = 0.017); risks for SGLT2i and combination therapy trended higher but were non-significant. When new-onset cirrhosis was incorporated (Composites 3 and 4), all three therapies carried significantly increased risk versus bariatric surgery: for Composite 3, GLP-1 RA (aHR 2.63, 1.59-4.36; p < 0.001), SGLT2i (aHR 2.22, 1.28-3.85; p = 0.005), and combination therapy (aHR 1.98, 1.19-3.29; p = 0.009), with comparable findings for Composite 4. Propensity score-matached survival analysis showed superior liver event-free survival with bariatric surgery across all outcomes (Figure 1). **Conclusion:** In non-cirrhotic MASLD, bariatric surgery was associated with superior liver-related and composite outcomes compared with GLP-1 RA, SGLT2i, and combination therapy after 1-year landmark and multinomial IPTW-adjusted analyses. Differences were most pronounced for composites incorporating new-onset cirrhosis, suggesting progression to cirrhosis is the predominant early liver event in this population. Future studies should stratify by fibrosis stage.



Disclosures: Leith Ghani:Nothing to Disclose, Diwanshu Soni:Nothing to Disclose, Majd Aboona:Nothing to Disclose, Pooja Rangan:Nothing to Disclose, Chih Hua Chung:Nothing to Disclose, Yu Cin Chang:Nothing to Disclose, Mark Wong:Nothing to Disclose, Karn Wijarnpreecha:Nothing to Disclose, Rohit Nathan:Nothing to Disclose, Moises Nevah Rubin:Nothing to Disclose, Mike Fallon:Nothing to Disclose, Farah Husain:Johnson & Johnson (Ethicon): Speaking and Teaching, W.L. Gore: Speaking and Teaching, Ma Ai Thanda Han:Nothing to Disclose.

3476 | POTENTIAL INFLUENCE OF PNPLA3 GENOTYPE ON SEMAGLUTIDE RESPONSE IN METABOLIC DYSFUNCTION–ASSOCIATED STEATOTIC LIVER DISEASE: REAL-WORLD DATA IN KOREAN COHORT

Hee Sun Cho[1] Pil Soo Sung[1] Jaejun Lee[1] Jung Hoon Cha[2], [1]The Catholic University of Korea, [2]The Catholic University Liver Research Center

Background: Semaglutide is widely used for obesity and metabolic-associated steatotic liver disease (MASLD), but real-world data in Korean populations remain limited. Genetic variants in PNPLA3 are known to be associated with MASLD progression. We aimed to evaluate the real-world clinical outcomes of semaglutide and to determine whether the PNPLA3 genotype affects therapeutic response in Korean patients. **Methods:** We retrospectively enrolled 137 patients who received once-weekly semaglutide at 2 tertiary hospitals (Seoul St. Mary's Hospital and Eunpyeong St. Mary's Hospital) in Korea between March and December 2025. Clinical outcomes, including weight loss and changes in liver fibrosis and steatosis markers, were assessed. To evaluate the impact of the PNPLA3 genotype on treatment response, outcomes were compared according to genotype, and the association between PNPLA3 variants and therapeutic response was analyzed. **Results:** At 3 and 6 months, 99

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(72.3%) and 73 (53.3%) patients achieved weight reduction, with mean losses of 5.15 kg (6.13%) and 7.55 kg (9.50%), respectively; at 6 months, 57 (78.1%), 33 (45.2%), and 10 (13.7%) achieved ≥5%, ≥10%, and ≥15% weight loss. Among patients with paired FibroScan data (n = 38), mean liver stiffness decreased from 7.65 to 5.74 kPa (P < 0.001), and mean CAP decreased from 315 to 271 dB/m (P < 0.001). APRI, AST, and ALT also showed significant reductions at 6 months (all p < 0.001). The PNPLA3 variant homozygous genotype (GG) showed a tendency toward an attenuated therapeutic response to semaglutide compared with the GC/CC genotype, with fewer responders observed for ALT at 6 months, CAP, and TE. Responder analyses revealed fewer responders among GG carriers, with the 6-month ALT response approaching statistical significance (p = 0.082). **Conclusion:** In this multicenter real-world Korean cohort, once-weekly semaglutide was associated with significant weight loss and improvements in hepatic steatosis and fibrosis-related markers. The PNPLA3 genotype may be served as a potential biomarker for predicting therapeutic response to semaglutide.

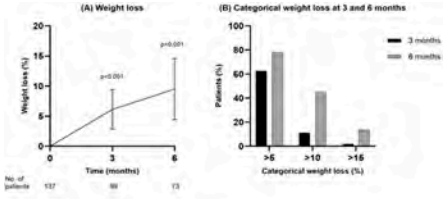


Figure 1.

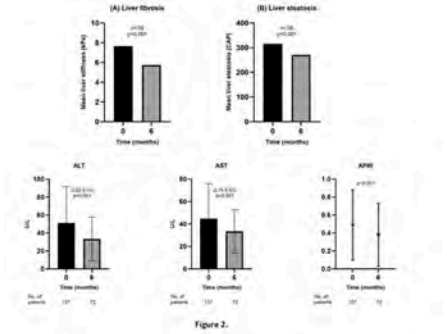
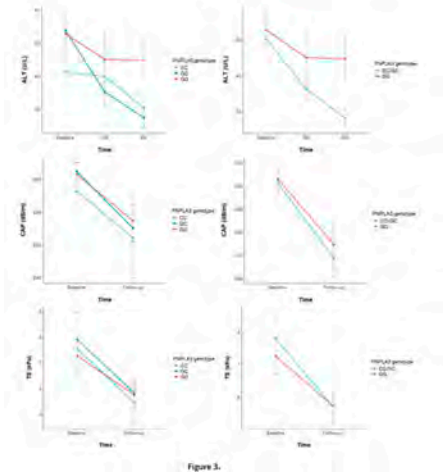


Figure 2.


Figure 3.

Disclosures: Hee Sun Cho:Nothing to Disclose, Pil Soo Sung:Nothing to Disclose, Jaejun Lee:Nothing to Disclose, Jung Hoon Cha:Nothing to Disclose.

3477 | TWELVE-MONTH CHANGES IN LABORATORY AND IMAGING-BASED BIOMARKERS IN PATIENTS WHO HAVE INITIATED RESMETIROM: A REAL-WORLD RETROSPECTIVE COHORT ANALYSIS USING ELECTRONIC HEALTH RECORDS

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Background: Resmetirom is a thyroid hormone receptor β-selective agonist, conditionally approved in the United States (US) for adults with noncirrhotic metabolic dysfunction-associated steatohepatitis with moderate-to-advanced fibrosis. Emerging real-world data have shown improvements in blood- and imaging-based biomarkers, but follow-up durations and sample sizes remain limited. This study evaluated characteristics and 12-month changes in biomarkers in patients who initiated resmetirom. **Methods:** This retrospective cohort study used Truveta deidentified electronic health record (EHR) data from US health systems linked to third-party medication dispensing data. Patients aged ≥ 18 years were indexed at first resmetirom fill on or after March 14, 2024 and followed through April 6, 2026. During the 1-year pre-index baseline period, patients were required to have ≥1 documented healthcare interaction (visit, prescription or treatment, lab test, procedure, diagnosis) and no evidence of other causes of liver disease (e.g., alcohol use, hepatitis) or advanced liver disease (e.g., cirrhosis). Analyses were restricted to patients with ≥1 year of observed follow-up. Biomarkers included alanine transaminase (ALT), aspartate aminotransferase (AST), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TGs), FibroScan-AST (FAST) score, Steatosis-Associated Fibrosis Estimator (SAFE) score, and liver stiffness measurement (LSM) and controlled attenuation parameter (CAP) from vibration-controlled transient elastography (VCTE) (LSM and CAP extracted from unstructured EHR clinical notes using large language models). Means and standard deviations (SDs) were calculated at baseline (closest value within 1 year prior to index) and follow-up (value closest to 12 months ± 3 months), as well as mean changes and p-values from paired t-tests. **Results:** There were 1,405 patients with ≥1 year of observed follow-up (median 15.8 months) after resmetirom initiation, with a mean age of 58 years, 63% female, 78% White, 40% from the South, 61% hypertension, 74% dyslipidemia, 57% type 2 diabetes, 61% obesity, 50% concomitant GLP-1 use and 55% concomitant statin use. Among patients with both baseline and follow-up measurements, all evaluated biomarkers showed statistically

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significant improvements 12 months after resmetirom initiation (**Table**). Improvements were also observed across key thresholds: 54% and 49% with ≥25% and ≥30% decrease in LSM kPa, respectively; 37% with ≥40 dB/M decrease in CAP; 37% with ≥17 U/L and 48% with ≥20% decrease in ALT; and 48% with ≥0.22 decrease in FAST. **Conclusion:** In this descriptive analysis, 12-month improvements in blood- and imaging-based biomarkers were observed in patients who initiated resmetirom. Changes in VCTE LSM were, on average, consistent with a shift into a lower fibrosis risk category.

Table. Twelve-month changes in blood- and imaging-based biomarkers in patients who initiated resmetirom

Biomarker	N with baseline and follow-up	Baseline Mean (SD)	Follow-up Mean (SD)	Change Mean (SD)	P-value	Days from Baseline to Follow-up Value Mean (SD)
ALT, U/L	661	57.3 (45.7)	39.5 (26.9)	-16.8 (42.8)	<0.001	360.2 (42.7)
AST, U/L	660	43.2 (32.3)	33.0 (19.2)	-10.2 (30.9)	<0.001	360.2 (42.7)
LDL-c, mg/dL	367	92.9 (38.8)	78.1 (33.3)	-14.8 (34.0)	<0.001	360.8 (47.9)
HDL-c, mg/dL	370	43.4 (14.8)	44.6 (14.8)	1.1 (9.8)	0.02	360.9 (47.6)
TG, mg/dL	378	170.1 (113.7)	127.2 (75.5)	-42.9 (93.4)	<0.001	361.6 (47.2)
SAFE score	370	116.6 (98.7)	92.9 (103.8)	-23.7 (80.5)	<0.001	345.9 (35.6)
VCTE LSM, kPa	71	10.1 (2.4)	7.9 (3.4)	-2.2 (3.7)	<0.001	351.1 (46.2)
VCTE CAP, dB/m	60	309.6 (51.2)	275.3 (53.1)	-34.3 (65.2)	<0.001	351.1 (46.2)
FAST score	50	0.45 (0.21)	0.26 (0.16)	-0.19 (0.19)	<0.001	351.3 (34.3)

P-values were calculated from paired t-tests.
Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; CAP, controlled attenuation parameter; FAST, FibroScan-AST; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; LSM, liver stiffness measurement; SAFE, Steatosis-Associated Fibrosis Estimator; TG, triglycerides; VCTE, vibration-controlled transient elastography.

Disclosures: Susan Thapa:Nothing to Disclose, Christina Parrinello:Madrigal Pharmaceuticals: Employee, Madrigal Pharmaceuticals: Stock - publicly traded company, Yestle Kim:Nothing to Disclose, John O'Donnell:Madrigal Pharmaceuticals: Share Holder, Anthony Martinez:Gilead: Consultant, Gilead: Speaking and Teaching, Abbvie: Consultant, Abbvie: Speaking and Teaching, Arbutus: Consultant, Braeburn: Speaking and Teaching, Sirtex: Consultant, Roche: Consultant, Syneos/VBI: Consultant, Madrigal: Speaking and Teaching, Altimune: Consultant, Madrigal: Consultant, Ipsen: Consultant, novo: Speaking and Teaching, atea: Consultant, cepheid: Consultant.

3478 | RED BLOOD CELL OMEGA-3 INDEX IS INVERSELY ASSOCIATED WITH THE PREVALENCE OF MASLD AND MASLD-ASSOCIATED SIGNIFICANT FIBROSIS: A CROSS-SECTIONAL MEDIATION ANALYSIS OF NHANES 2021–2023

Siyu Jiang[1] Jiwei Wang[1] Yicheng Zhu[2] Yunxing Huang[3] Qing Xie[1] Zhujun Cao[1], [1]Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, [2]Faculty of Biochemistry, University of British Columbia, [3]Shenzhen college of international education

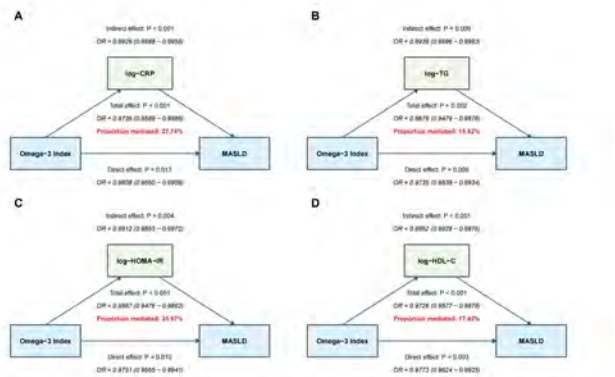
Background: An imbalance characterized by excessive omega-6 intake or a skewed omega-3/omega-6 ratio can exacerbate liver injury and promote the transition to steatohepatitis. The red blood cell (RBC) omega-3 index provides a stable, integrated reflection of habitual fatty acid status during the prior 2-4 month. We evaluated its association with metabolic dysfunction-associated steatotic liver disease (MASLD) and significant fibrosis in a nationally representative population under the updated diagnostic criteria. **Methods:** We analyzed 4,735 adults from the NHANES 2021-2023 cycle. MASLD was defined by a controlled attenuation parameter (CAP) > = 274 dB/m plus cardiometabolic criteria. Notably, significant fibrosis (liver stiffness measurement [LSM] > 8.0 kPa) was evaluated exclusively conditional on the MASLD population. Given the high outcome prevalences (>10%), we utilized survey-weighted Poisson regression as the primary framework to generate conservative adjusted prevalence ratios (aPRs), rigorously preventing the effect size overestimation (inflated ORs) inherent in logistic regression. Mediation analyses explored the roles of systemic inflammation (hs-CRP), insulin resistance (HOMA-IR), and lipid metabolism (triglycerides [TG], HDL-C). Missing data were handled via multiple imputation. **Results:** The weighted prevalence of MASLD was 40.1%, and significant fibrosis within the MASLD cohort was 22.2%. In fully adjusted conservative Poisson models, each 1% absolute increase in the RBC Omega-3 Index was independently associated with a 5% lower prevalence of MASLD (aPR: 0.95, 95% CI: 0.92-0.99, P = 0.017) and an 11% lower prevalence of significant fibrosis (aPR: 0.89, 95% CI: 0.81-0.99, P = 0.038). Mediation analysis indicated that the protective association between the RBC Omega-3 Index and MASLD was largely accounted for by concurrent metabolic and inflammatory pathways. Systemic inflammation (hs-CRP) and insulin resistance (HOMA-IR) were the potential mediators, accounting for 27.74% (P < 0.001) and 25.97% (P = 0.004) of the effect, respectively, followed by TG (18.52%, P = 0.006) and HDL-C (17.42%, P < 0.001). Conversely, the inverse association of significant fibrosis was specifically and significantly mediated by the inflammatory pathway (hs-CRP: 13.30%, P = 0.014). **Conclusion:** A higher RBC Omega-3 index is associated with a lower prevalence of MASLD and significant fibrosis. Using conservative Poisson models, we establish that the benefits against MASLD are overwhelmingly (nearly 90%) mediated by quantifiable improvements in insulin sensitivity, inflammation, and lipid profiles, whereas fibro-protection is predominantly anti-inflammatory. Maintaining optimal

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habitual omega-3 status is a viable, multifaceted preventive strategy for metabolic liver health.

Figure 1. Mediation analysis of the association between the RBC Omega-3 Index and MASLD.



Combined multi-pathway diagram illustrating statistical mediation via inflammatory and metabolic markers. All values are derived from pooled multiple imputation datasets. CI, confidence interval; log-CRP, log-transformed high-sensitivity C-reactive protein; log-HDL-C, log-transformed high-density lipoprotein cholesterol; log-HOMA-IR, log-transformed homeostasis model assessment of insulin resistance; log-TG, log-transformed triglycerides; OR, odds ratio.

Disclosures: Siyu Jiang:Nothing to Disclose, Jiwei Wang:Nothing to Disclose, Yicheng Zhu:Nothing to Disclose, Yunxing Huang:Nothing to Disclose, Qing Xie:Nothing to Disclose, Zhujun Cao:Nothing to Disclose.

3479 | COMPARATIVE REAL-WORLD EFFECTIVENESS OF RESMETIROM, INJECTABLE SEMAGLUTIDE, AND COMBINATION THERAPY IN PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS

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Background: Metabolic dysfunction-associated steatohepatitis (MASH) is characterized by hepatic inflammation, steatosis, and progressive fibrosis. Resmetirom and glucagon-like peptide-1 receptor agonists (GLP-1RAs) have independently demonstrated efficacy in MASH; however, comparative real-world effectiveness data and outcomes with combination therapy remain limited. **Methods:** We performed a retrospective cohort study of adults with MASH treated between April 2023 and April 2025 at a single tertiary liver center. Patients received resmetirom monotherapy, injectable semaglutide monotherapy, or combination therapy consisting of resmetirom with semaglutide or tirzepatide. Baseline demographics, fibrosis stage, steatosis measurements, liver biochemistries, and cardiometabolic parameters were collected. The primary outcome was improvement in fibrosis and steatosis by transient elastography at 6 and 12 months. Secondary outcomes included alanine aminotransferase (ALT) normalization and changes in weight, hemoglobin A1c, and lipid parameters. **Results:** A total of 108 patients were included. Mean age was 55.6 years, 51.9% were female, and mean body mass index was 32.1 kg/m². Type 2 diabetes mellitus and dyslipidemia were present in 33.0% and 52.7% of patients, respectively. Fibrosis stages ranged from F0–F4, including 11.1% with advanced fibrosis (F4). Treatment distribution included 45 patients (41.7%) receiving resmetirom monotherapy, 30 (27.8%) semaglutide monotherapy, and 33 (30.6%) combination therapy.At 12 months, fibrosis improvement occurred in 20.0% of patients on resmetirom monotherapy, 16.7% on semaglutide monotherapy, and 48.5% on combination therapy ($p = 0.0216$). No significant differences were observed between groups in fibrosis improvement at 6 months or in steatosis improvement at either 6 or 12 months. ALT normalization at 6 months occurred more frequently in the combination therapy group (44%) compared with resmetirom monotherapy (37%) and semaglutide monotherapy (19%) ($p = 0.008$), although this difference was not sustained at 12 months. Within the combination cohort, initiation of resmetirom prior to incretin-based therapy demonstrated numerically greater improvements in fibrosis and steatosis at 12 months. No significant intergroup differences were observed in cardiometabolic outcomes. **Conclusion:** In this real-world cohort of patients with MASH, combination therapy with resmetirom and an incretin mimetic was associated with greater fibrosis improvement at 12 months. Although steatosis outcomes were similar across groups, combination therapy demonstrated early biochemical improvement and favorable liver stiffness outcomes. Sequential initiation with resmetirom prior to incretin-based therapy may provide additional benefit. These findings support the potential role of combination therapy strategies and highlight the need for prospective validation studies.

Table 1. Primary Outcome

Primary Outcome	Resmetirom Monotherapy (n=45)	Semaglutide Monotherapy (n=30)	Combination Therapy* (n=33)	P-value
Fibrosis improvement at 6 months, n (%)	11 (24.4)	2 (6.7)	8 (24.2)	0.105
Fibrosis improvement at 12 months, n (%)	9 (20.0)	5 (16.7)	16 (48.5)	**0.022**
Steatosis improvement at 6 months, n (%)	10 (22.2)	2 (6.7)	8 (24.2)	0.127
Steatosis improvement at 12 months, n (%)	7 (15.6)	6 (20.0)	11 (33.3)	0.181

*Combination therapy included resmetirom with semaglutide or tirzepatide.

Disclosures: Ngan Nguyen:Gilead Pharmaceuticals: Advisor, Giavanna Carr:Nothing to Disclose, Sanjaya Satapathy:Gilead Sciences: Grant/Research Support, Durect Pharma: Grant/Research Support, Fibronostics: Grant/Research Support, Novartis: Grant/Research Support, Zydus Pharma: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support,

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3480 | IMPACT OF GLP-1 RECEPTOR AGONISTS ON LIVER ENZYMES AND NONINVASIVE FIBROSIS MARKERS IN PATIENTS WITH ULCERATIVE COLITIS AND OBESITY: A MATCHED COHORT STUDY

Budoor Alqinai[1] Swapna Gayam[1], [1]West Virginia University

Background: Patients with moderate ulcerative colitis (UC) and obesity are at increased risk for metabolic dysfunction-associated steatotic liver disease (MASLD) and hepatic fibrosis. The impact of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) on liver enzymes and noninvasive fibrosis markers in this population is not well established. **Methods:** We performed a retrospective matched cohort study using electronic health records from a single tertiary academic center (2022–2024). Adults with moderate UC and obesity (BMI $\geq$30 kg/m²) who initiated liraglutide or semaglutide for metabolic indications and remained on therapy for $\geq$12 weeks were included. A 1:1 matched control cohort of patients with moderate UC and obesity not receiving GLP-1 RAs was constructed, matched on age, sex, BMI, baseline partial Mayo score, and concomitant UC therapy. The primary outcome was change in alanine aminotransferase (ALT) at 12 weeks. Secondary outcomes included changes in aspartate aminotransferase (AST), FIB-4, and APRI scores. Multivariable linear regression adjusted for age, sex, baseline liver enzymes, BMI, and weight loss. **Results:** 85 GLP-1 RA-treated patients were matched to 85 controls with well-balanced baseline characteristics. At 12 weeks, GLP-1 RA therapy was associated with significantly greater reductions in ALT (-24.8 ± 16.9 U/L vs -5.6 ± 11.2 U/L, $p < 0.001$) and AST (-16.7 ± 12.8 U/L vs -3.9 ± 8.8 U/L, $p < 0.001$). Noninvasive fibrosis markers also improved more in the GLP-1 RA group, with greater reductions in FIB-4 score (-0.31 ± 0.24 vs -0.06 ± 0.19, $p < 0.001$) and APRI (-0.18 ± 0.15 vs -0.04 ± 0.12, $p < 0.001$). GLP-1 RA therapy was well tolerated, with no serious hepatic complications and adverse event rates comparable to controls. In multivariable analysis, GLP-1 RA use remained independently associated with ALT reduction after adjustment for weight loss and other baseline factors (adjusted β = -18.6, 95% CI -23.4 to -13.8, $p < 0.001$). **Conclusion:** In patients with moderate ulcerative colitis and obesity, GLP-1 RA therapy was associated with significant improvements in liver enzymes and noninvasive fibrosis markers compared with matched controls, along with a favorable safety profile. These findings suggest a potential hepatoprotective benefit of GLP-1 RAs in this high-risk population. Prospective studies are warranted to confirm these findings and evaluate long-term hepatic outcomes.

Disclosures: Budoor Alqinai:Nothing to Disclose, Swapna Gayam:Nothing to Disclose.

3481 | REAL-WORLD CHARACTERISTICS AND CLINICAL EFFECTIVENESS OUTCOMES AMONG MASH PATIENTS INITIATING RESMETIROM

Jeevin Sandhu[1] Gene Felber[2] Tara McKinley[2] Christina Parrinello[2] Samantha Clark[3] Francis Lobo[2] Parvez Mantry[1], [1]Methodist Dallas Medical Center, [2]Madrigal Pharmaceuticals, [3]Medicus Economics

Background: The FDA approved resmetirom for adults with noncirrhotic metabolic dysfunction-associated steatohepatitis (MASH) with moderate-to-advanced fibrosis on March 14, 2024, based on the results of the MAESTRO-NASH trial. Real-world evidence (RWE) for the effectiveness of resmetirom remains limited. This study aimed to describe patient characteristics and treatment effectiveness among US patients initiating resmetirom in a cohort of patients diagnosed with MASH. **Methods:** Data from the Methodist Dallas Medical Center EMR systems were used for this study. The cohort included adults with $\geq$1 resmetirom prescription between March 14, 2024, and January 21, 2026, with the first observed prescription designated = index date. Patients were required to have continuous healthcare engagement during the 12-month baseline period ($\geq$1 encounter, observation, or medication request in each 6-month interval). Patients with advanced liver disease or liver disease due to other causes during the 12-month baseline period were excluded. Follow-up was from index to last encounter. Effectiveness outcomes included changes in biomarkers (from structured data) and noninvasive liver measures (VCTE extracted using NLP from progress notes) at 6 and 12 months ± 90 days. Wilcoxon signed-rank tests were used to assess changes, with statistical significance defined as $p < 0.05$. All variables were summarized using descriptive statistics. VCTE data will be reported in the full presentation. **Results:** A total of 443 patients met the study criteria (mean age, 60.03 years; 58.7% female; 46.0% White and 33.4% Hispanic/Latino). Baseline key comorbidities included type 2 diabetes (62.5%), obesity (61.2%), hyperlipidemia (72.5%), and hypertension (74.7%). Concurrent

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use of GLP-1 receptor agonists was observed in 37.2% of patients. After resmetirom initiation, clinically meaningful improvements were observed in key liver enzymes. At 6 and 12 months, among patients with available data, the following changes in biomarkers versus baseline were observed: 1) AST change (median): -1.00 U/L and -3.00* U/L ($p < 0.05$ at 12 months); 2) AST median percentage change: -3.78% and -9.38%; 3) ALT change (median): -4.00* U/L and -6.50* U/L ($p < 0.05$ at 12 months); 4) ALT median percentage change: -10.26% and -17.80%; 5) $\geq$17 U/L reduction in ALT: achieved by 31.4% and 27.9% of patients, respectively; and 6) $\geq$20% decrease in ALT: achieved by 41.5% and 47.7% of patients, respectively (see Table 1).*The Wilcoxon signed-rank test showed a statistically significant difference between paired measurements ($p < 0.05$). **Conclusion:** In this retrospective real-world analysis, clinically meaningful 6- and 12-month improvements in liver-specific biomarkers were observed in patients prescribed resmetirom. Further study with longer follow-up is needed to assess long-term effectiveness.

Table 1: Changes in Liver Enzymes at 6 and 12-months in MASH patients initiating resmetirom

Measurement	Timepoint	N	Baseline Median (IQR)	Median at Timepoint (IQR)	Median Change (IQR)	Median % Change (IQR)
ALT (U/L)	6 Months	159	37 (26, 57.5)	34 (24, 45)	-4* (-20, 7)	-10.26 (-42.37, 30.91)
	12 Months	86	38.5 (26.25, 54.75)	31.5 (24.25, 42.75)	-6.50* (-19.75, 5.75)	-17.8 (-42.19, 14.27)
AST (U/L)	6 Months	160	33 (24, 47)	31 (24, 42)	-1 (-13, 7.25)	-3.78 (-29.16, 27.17)
	12 Months	86	33 (25, 46.25)	29 (23, 41.75)	-3.00* (-13, 4.75)	-9.38 (-34.59, 15.41)

Disclosures: Jeevin Sandhu:Nothing to Disclose, Gene Felber:Nothing to Disclose, Tara McKinley: Madrigal Pharmaceuticals: Employee, Christina Parrinello:Madrigal Pharmaceuticals: Employee, Madrigal Pharmaceuticals: Stock - publicly traded company, Samantha Clark:Nothing to Disclose, Francis Lobo: Nothing to Disclose, Parvez Mantry:Nothing to Disclose.

3482 | RESMETIROM IN MASH AND HIV: A SINGLE-CENTER DESCRIPTIVE COHORT

Alexander Zhu[1] Inioluwa Dada[1] Anthony Martinez[1],
[1]University at Buffalo

Background: Resmetirom is the first FDA-approved therapy for metabolic dysfunction-associated steatohepatitis (MASH) with significant fibrosis. People living with HIV (PLWH) carry a substantial burden of MASH and progressive fibrosis, driven by chronic immune activation, antiretroviral therapy (ART)-associated metabolic effects, and ectopic fat deposition at lower BMI than in the general population. Yet PLWH are commonly excluded from MASH trials due to concerns of drug-drug interactions, and to our knowledge, no real-world data on resmetirom in this population have been reported. We describe our single-center experience with resmetirom in PLWH with MASH. **Methods:** We retrospectively reviewed all adults prescribed resmetirom for MASH with significant fibrosis at our center between April 2024 and December 2025. Patients with HIV and confirmed resmetirom exposure (notes and/or pharmacy fill records) were included; those with unclear initiation or compliance were excluded. Baseline demographics, comorbidities, ART regimen, dosing, duration, adverse events (AEs), and serial vibration-controlled transient elastography (VCTE) and ALT values were extracted from the medical record. Response was defined a priori as $\geq$25% reduction in liver stiffness (kPa) at approximately 12 months. **Results:** Six PLWH (5.3% of 114 resmetirom-treated patients) were identified. Median age was 58 years (37–70); 4 were male; race/ethnicity was evenly split among African American, Hispanic, and White. Median BMI was 34 kg/m^2 (25–46). Comorbidities included hypertension (n = 5), dyslipidemia (n = 4), and type 2 diabetes (n = 2). All were on integrase inhibitor- or NNRTI-based regimens without pharmacologic boosters: bictegravir/emtricitabine/tenofovir alafenamide (n = 4), dolutegravir/lamivudine (n = 1), and emtricitabine/rilpivirine/tenofovir alafenamide (n = 1). Median ALT was 44 U/L. Median FIB-4 was 1.5. Four received 100 mg and two 80 mg daily. Median duration was 12.5 months (10.8–24.5). One patient discontinued due to diarrhea; one had a 4-month patient-initiated interruption with reinitiation; no other AE-related events occurred. Paired baseline and 12-month VCTE were available for only 2 patients; both met responder criteria (liver stiffness 8.1 to 5.6 and 11.1 to 6.4 kPa) with fibrosis-stage regression. ALT was available for 5 patients: among 4 with follow-up near 12 months, ALT decreased in 3; the fourth had a normal baseline ALT that remained within normal limits; a fifth had an early decrease (27 to 21 U/L at 3 mo) but no later follow-up. **Conclusion:** In this first real-world cohort of resmetirom in PLWH, the drug was tolerated on contemporary unboosted ART regimens, with one discontinuation for diarrhea, a known resmetirom effect. Liver stiffness and ALT improved in most evaluable patients. These data support the feasibility of resmetirom in PLWH and merit further study of resmetirom in this population.

Disclosures: Alexander Zhu:Nothing to Disclose, Inioluwa Dada:Nothing to Disclose, Anthony Martinez: Gilead: Consultant, Gilead: Speaking and Teaching, Abbvie: Consultant, Abbvie: Speaking and Teaching, Arbutus: Consultant, Braeburn: Speaking and Teaching, Sirtex: Consultant, Roche: Consultant, Syneos/VBI: Consultant, Madrigal: Speaking and Teaching, Altimune: Consultant, Madrigal: Consultant, Ipsen:

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Consultant, novo: Speaking and Teaching, atea: Consultant, cepheid: Consultant.

3483 | EFFECT OF RESMETIROM ON LIVER STIFFNESS IN MASH: A REAL-WORLD LONGITUDINAL ANALYSIS

Alexander Zhu[1] Inioluwa Dada[1] Anthony Martinez[1],
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Background: Resmetirom is the first FDA-approved therapy for non-cirrhotic MASH with moderate to advanced fibrosis. AASLD guidance recommends assessment at 12 months, with ≥25% reduction in vibration-controlled transient elastography (VCTE) liver stiffness as the response threshold. Real-world reports to date have largely described single-timepoint changes at 3–6 months, and longitudinal data characterizing how liver stiffness evolves throughout the first year of therapy remain limited. Our aim was to characterize the trajectory of liver stiffness during treatment and to evaluate 12-month outcomes in a real-world cohort. **Methods:** We conducted a single-center retrospective cohort study of 114 adults with MASH initiated on resmetirom. The trajectory cohort had a baseline VCTE within 12 months before or 1 month after initiation and ≥1 on-treatment VCTE (n = 57, 129 scans). The effectiveness cohort was a subset with paired 12-month VCTE (n = 32). Liver stiffness trajectory was modeled by a log-linear mixed-effects regression with random patient intercepts; paired changes were compared by Wilcoxon signed-rank test. Effectiveness outcomes assessed at 12 months were median change in kPa, ≥25% reduction in kPa, and regression or progression of VCTE-derived fibrosis stage. Safety outcomes were treatment discontinuation due to adverse effects and treatment interruption. **Results:** Baseline characteristics: median age 57 years, 51% female, 45% with type 2 diabetes; effectiveness cohort baseline VCTE stage was 44% F2, 47% F3, 9% F4, with median liver stiffness 11.0 kPa (IQR 9.0–12.5). Of 3 patients staged F4 by baseline VCTE, all had clinical or histologic evidence of VCTE overestimation (BMI-related confounding [n = 1]; biopsy-proven F2 or F3 within 24 months [n = 2]). Liver stiffness declined during therapy at −24.1% per year (95% CI −30.2% to −17.4%, p < 0.001). Model-predicted decline in kPa was approximately 13% at 6 months, 19% at 9 months, and 24% at 12 months. Among 32 patients with paired 12-month VCTE, median kPa decreased from 11.0 to 7.3 (median change −39.4%, p < 0.001), and 20/32 (62.5%) met the ≥25% threshold. VCTE-derived stage regressed in 22/32 (68.8%, p < 0.001) and progressed in 4/32 (12.5%); among baseline F3 patients (n = 15), 12 (80%) regressed and none progressed. 9/114 (7.9%) discontinued due to adverse effects, most commonly abdominal pain or diarrhea; 4/114 (3.5%) temporarily interrupted treatment and resumed. **Conclusion:** In this real-world cohort, liver stiffness declined continuously from the start of resmetirom therapy, with model-predicted decline of approximately 13% by 6 months and 24% by 12 months. These findings suggest that interval VCTE may provide an earlier objective signal of treatment response, complementing the AASLD-recommended 12-month reassessment and offering potential utility for shared decision-making and patient counseling during the first year of therapy.

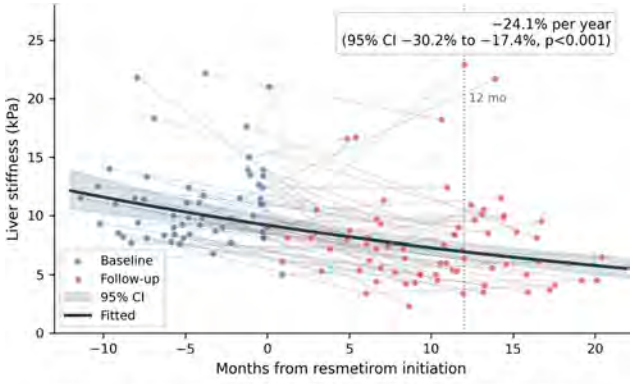


Figure 1. Liver stiffness trajectory during resmetirom therapy. Baseline (blue) and follow-up (red) liver stiffness measurements (kPa) by VCTE, with gray lines connecting serial scans for each patient. The bold dark line shows the mixed-model fitted mean with shaded 95% CI; liver stiffness declined an estimated 24.1% per year (95% CI −30.2% to −17.4%, p<0.001). n = 57 patients, 129 scans.

Disclosures: Alexander Zhu:Nothing to Disclose, Inioluwa Dada:Nothing to Disclose, Anthony Martinez: Gilead: Consultant, Gilead: Speaking and Teaching, Abbvie: Consultant, Abbvie: Speaking and Teaching, Arbutus: Consultant, Braeburn: Speaking and Teaching, Sirtex: Consultant, Roche: Consultant, Syneos/VBI: Consultant, Madrigal: Speaking and Teaching, Altimune: Consultant, Madrigal: Consultant, Ipsen: Consultant, novo: Speaking and Teaching, atea: Consultant, cepheid: Consultant.

3484 | PHARMACIST-DIRECTED GLP-1 AGONIST THERAPIES FOR STEATOTIC LIVER DISEASE: A REAL-WORLD COHORT STUDY

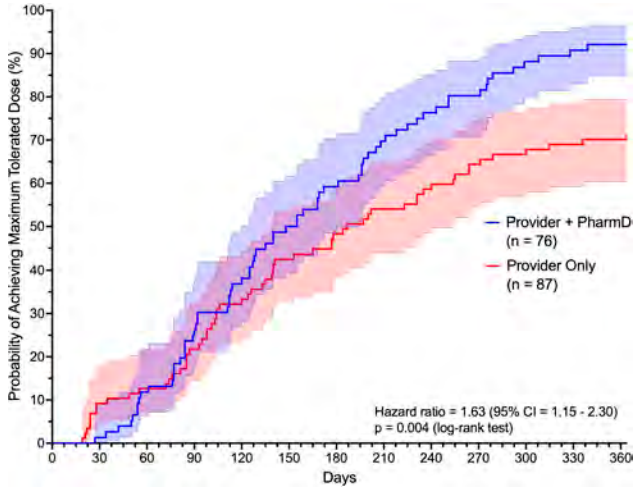
James Vu[1] Maria Golovkina[2] Tina Ho[2] Khang Nguyen[2] Jazmin Valencia Chavez[2] Jeremiah Duby[2] Albert Do[2],

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Background: Incretin-based therapies (GLP-1 agonists) have clinical benefits for multiple metabolic diseases, including metabolic dysfunction-associated steatotic liver disease (MASLD). Clinical pharmacists support incretin-based therapy provision through therapy initiation, patient education, dose titration, adherence support, and adverse effect management. Despite routine reliance on pharmacist-directed patient care, there are limited data for steatotic liver disease with metabolic contributor to disease. We aim to study whether pharmacist management of GLP-1 agonists affects process- and clinical outcomes in patients with MASLD and metALD in a large tertiary health care system. **Methods:** This was a historical cohort study of adults aged ≥18 years with MASLD and metALD initiating GLP-1 therapies from January 1, 2023, to November 1, 2025. Patients were stratified as (1) pharmacist-directed cohort with therapy monitoring and adjustment by a clinical pharmacist, or (2) no pharmacist involvement. Clinical outcomes were defined as time to maximum tolerated dose and time to first titration. We compared clinical characteristics between groups and performed comparisons between time-to-event outcomes using log-rank test and Cox proportional hazard regression. **Results:** The analysis cohort included 183 patients, with 81 receiving pharmacist-led therapy and 102 without pharmacist management. The mean age (58.9 vs. 58.0 years, p = 0.32) proportion of female patients (63.0% vs. 59.8%, p = 0.66) did not differ between groups at baseline The pharmacy group was more likely to be prescribed tirzepatide (50.6% vs 34.3%, p = 0.03) and more likely to have MASLD as the prescription indication (28.4% vs 5.9%, p = 0.001). Pharmacy involvement was associated with a significantly higher likelihood of increasing beyond the initial titration dose (HR 1.48, 95% CI 1.02-2.13, p = 0.04). Pharmacy involvement was also associated with significantly earlier achievement of maximum tolerated doses (HR 1.63, 95% CI 1.15-2.30, p = 0.004). Pharmacist co-management was associated with significantly greater weight loss at 26 weeks (–6.9% vs. –4.6%, p = 0.032) but not at 52 weeks (–8.1% vs. –7.3%, p = 0.655). **Conclusion:** Pharmacy involvement improved timeliness of GLP-1 therapy optimization for patients with steatotic liver disease, and was associated with faster therapy titration. We find that such involvement may accelerate early weight loss through support with titration, adherence, and side-effect management, which may enable decisions for next therapies if needed. Further characterization of pharmacist-led interventions my refine patient-centered treatment approaches, and scaling efforts would enable cost justification to larger populations.



Disclosures: James Vu:Nothing to Disclose, Maria Golovkina:Nothing to Disclose, Tina Ho:Nothing to Disclose, Khang Nguyen:Nothing to Disclose, Jazmin Valencia Chavez:Nothing to Disclose, Jeremiah Duby: Nothing to Disclose, Albert Do:Madrigal Pharmaceuticals: Speaking and Teaching, Ipsen: Consultant.

3485 | PLASMA CELL-FREE DNA METHYLATION RECOVERS SEMAGLUTIDE PHARMACOLOGY IN MASH TRIALS DESPITE AN UNINFORMATIVE MRI-PDFF ENDPOINT

Rohit Loomba[1] Soheil Damangir[2] Egbert Madamba[1] Seema Singh[1] Chong Lu[2] Leila Bazargan[2] Hamed Amini[2], [1]University of California, San Diego, [2]Hepta Bio, Inc.

Background: Phase 2 trials can miss their endpoints because of small samples and heterogeneous response, even for drugs that would succeed at Phase 3. Semaglutide is a clear example: Newsome 2021 missed biopsy fibrosis improvement and Flint 2021 missed MRE liver stiffness, yet Phase 3 ESSENCE confirmed fibrosis improvement in a larger and longer trial. We asked whether plasma cfDNA methylation can read drug-engaged biology directly at the molecular and pathway level, distinguishing real drug action from statistical artefact when endpoints are uninformative. **Methods:** SAMARA randomized 35 patients with at-risk MASH (defined by FAST) to semaglutide or placebo for 52 weeks. Paired plasma cfDNA whole-methylome sequencing at baseline and end-of-treatment was processed with a custom-built AI platform, LiquidTransformer. MRI-PDFF responders were defined as PDFF percent change > 15% and absolute

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change > 5%. Methylation changes defining the drug effect and the baseline responder state were tested for cell-type, transcription-factor, ligand-perturbation and pathway enrichment against the measured methylome background. **Results:** Responders were similarly distributed across arms, leaving the PDFF endpoint uninformative for treatment effect. Yet treatment-arm methylation read canonical semaglutide pharmacology across organs. In the liver, hepatocyte programs were activated while five bile-duct subtypes were coherently suppressed, the cellular signature of reduced ductular reaction and mechanistically upstream of the fibrosis improvement that ESSENCE later confirmed at biopsy. Drug-affected gene sets matched the methylation fingerprints of three relevant ligand stimulations: FGF21 (8.1-fold), galanin (6.1-fold) and leptin (17-fold, all $p < 0.001$), engaging the canonical MASH and feeding-regulation drug axes. Drug-activated genes were enriched for hepatic nuclear-receptor regulons including NR1I2 (PXR) and RARA; drug-suppressed regulons were dominated by GFI1, FOXQ1, GATA3 and YY1 cell-state TFs. Genes distinguishing MASH responders at baseline overlapped drug-effect genes 4.6- and 7.5-fold in the opposite direction (hypergeometric $p < 0.001$); same-direction overlap was not significant. These findings suggest that MASH is biologically heterogeneous, and that responders are the patients whose pre-treatment state is the specific dysregulation semaglutide can reverse. **Conclusion:** Plasma cfDNA methylation recovered organ-resolved semaglutide pharmacology, FGF21- and leptin-class ligand fingerprints, and the mechanistic link between baseline responder state and drug action in a trial where the MRI-based response stratification did not separate arms. ESSENCE has since validated semaglutide's fibrosis efficacy at scale, confirming the biology detected here from blood. Plasma cfDNA methylation thus provides a mechanism-resolved readout of MASH drug engagement that extends beyond clinical endpoints.

Disclosures: Rohit Loomba:Eli Lilly and Company: Consultant, 89bio: Consultant, Aardvark Therapeutics: Consultant, Altimmune: Consultant, Alnylam/Regeneron: Consultant, Amgen: Consultant, Arrowhead Pharmaceuticals: Consultant, AstraZeneca: Consultant, Bristol Myers Squibb: Consultant, CohBar: Consultant, Eli Lilly: Consultant, Galmed Pharmaceuticals: Consultant, Gilead: Consultant, Glympse Bio: Consultant, Hightide: Consultant, Inipharma: Consultant, Intercept: Consultant, Inventiva: Consultant, Ionis: Consultant, Janssen, Inc.: Consultant, Madrigal Pharmaceuticals: Consultant, Merck, Metacrine, Inc.: Consultant, NGM Biopharmaceuticals: Consultant, Novartis: Consultant, Novo Nordisk: Consultant, Pfizer: Consultant, Sagimet Biosciences: Consultant, Terns Pharmaceuticals: Consultant, Theratechnologies and Viking Therapeutics: Consultant, 89bio: Stock options, Sagimet Biosciences: Stock options, Arrowhead Pharmaceuticals: Research grant, AstraZeneca: Research grant, Boehringer Ingelheim: Research grant, Bristol Myers Squibb: Research grant, Eli Lilly: Research grant, Galectin Therapeutics: Research grant, Galmed Pharmaceuticals: Research grant, Gilead: Research grant, Hanmi: Research grant, Intercept: Research grant, Inventiva: Research grant, Ionis: Research grant, Janssen, Inc.: Research grant, Madrigal Pharmaceuticals: Research grant, Merck: Research grant, NGM Biopharmaceuticals: Research grant, Novo Nordisk: Research grant, Pfizer: Research grant, Sonic Incytes: Research grant, Terns Pharmaceuticals: Research grant, LipoNexus, Inc.: Co-founder, Cascade Pharmaceuticals: Consultant, Eccogene: Consultant, HeptaBio: Consultant, Metavi: Consultant, Neurobo: Consultant, Novo Nordisk: Consultant, Sourcebio: Consultant, Roche: Consultant, Roche: Consultant, Takeda: Consultant, GSK: Grant/Research Support, Roche: Grant/Research Support, TensorBio: Grant/Research Support, Aarrowhead Pharmaceuticals: Consultant, Boehringer-Ingelheim: Consultant, Altimmune: Grant/Research Support, Eccogene: Grant/Research Support, Heptabio: Grant/Research Support, 89 bio: Grant/Research Support, Takeda: Grant/Research Support, Soheil Damangir:Nothing to Disclose, Egbert Madamba:Nothing to Disclose, Seema Singh:Nothing to Disclose, Chong Lu:Nothing to Disclose, Leila Bazargan:Nothing to Disclose, Hamed Amini:Nothing to Disclose.

3486 | RISK OF HEPATIC DECOMPENSATION WITH GLP-1 RECEPTOR AGONISTS VERSUS SGLT2 INHIBITORS IN PATIENTS WITH MASLD OR CIRRHOSIS AND CHRONIC KIDNEY DISEASE

Urveesh Sharma[1], [1]University of Arkansas for Medical Sciences

Background: Hepatic decompensation is a major driver of morbidity in metabolic dysfunction-associated steatotic liver disease (MASLD) and cirrhosis, and the risk increases when chronic kidney disease (CKD) coexists. Both GLP-1 receptor agonists (GLP-1 RAs) and SGLT2 inhibitors (SGLT2is) have shown hepatic benefits in early-phase studies, but the evidence regarding one class performing better than the other at preventing hard liver endpoints in patients with

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concurrent CKD remains limited. **Methods:** We conducted a retrospective cohort study using the TrinetX database where adults (≥18 years) with pre-existing MASLD or cirrhosis, CKD stages 3-5, and T2DM were divided into two cohorts based on whether they were newly started on a GLP-1 RA or a SGLT2i. We excluded patients with cross-drug class exposure, alcoholic liver disease, viral hepatitis, prior liver transplant, HCC, ESRD, or dialysis. 1:1 propensity score matching (PSM) on demographics, comorbidities, medications, and laboratory values was done. The primary outcome was a hepatic decompensation composite: ascites, variceal bleeding, hepatic encephalopathy, hepatic failure, HCC, or liver transplant, within 3 years. Kaplan-Meier analysis with log-rank testing and Cox regression were performed. The proportional hazards assumption was met (p = 0.968). **Results:** After matching, 4,700 patients per group were analyzed. Mean age was 67.9 years, 57.2% were female, 18.7% had cirrhosis, 97.4% had CKD stage 3, and mean BMI was 35.3 kg/m2. The hepatic decompensation composite occurred at similar rates in both groups (GLP-1 RA: 134/4,318 [3.1%] vs SGLT2i: 126/4,219 [3.0%]; HR 1.049, 95% CI 0.823-1.338; log-rank p = 0.698). Three-year event-free survival was 94.8% and 95.0%, respectively. **Conclusion:** In patients with MASLD or cirrhosis, CKD, and T2DM, GLP-1 RA and SGLT2i use were associated with comparable rates of hepatic decompensation over 3 years, and both drug classes appear similarly effective at preventing liver-specific complications in this population. This suggests that the choice between them may be guided by other factors, like their differing effects on cardiovascular and mortality endpoints rather than liver-specific outcomes.

Table 1. Hepatic decompensation outcomes at 3 years — GLP-1 receptor agonists vs. SGLT2 inhibitors

Outcome	GLP-1 RA n/N (%)	SGLT2i n/N (%)	HR (95% CI)	3-yr event-free survival	p value (log-rank)
Hepatic decompensation composite†	134/4,318 (3.1)	126/4,219 (3.0)	1.049 (0.823–1.338)	94.8% vs. 95.0%	0.698

† Composite of ascites, variceal bleeding, hepatic encephalopathy, hepatic failure, HCC, or liver transplant. HR = hazard ratio; CI = confidence interval; HCC = hepatocellular carcinoma.

Disclosures: Urveesh Sharma:Nothing to Disclose.

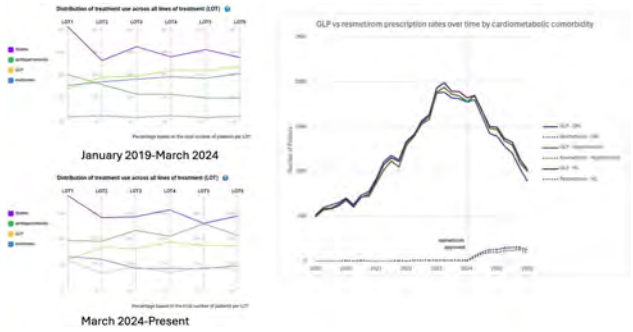
3487 | REAL WORLD PRESCRIBING PATTERNS OF PROVIDERS IN PATIENTS WITH MASH FIBROSIS AND CARDIOMETABOLIC DISEASE

Clara McNatt[1] Allysa Saggese[1] Tatyana Kushner[1] Sonal Kumar[1], [1]Weill Cornell Medicine

Background: Metabolic-dysfunction associated steatohepatitis (MASH) is the liver manifestation of the metabolic syndrome (MS). Prior to March 2024, management relied on lifestyle modifications and therapies for cardiometabolic comorbidities. We aimed to characterize real-world prescribing patterns of providers treating patients with MASH fibrosis and cardiometabolic disease before and after the approvals of resmetirom and semaglutide. **Methods:** We conducted a retrospective cohort study using the TriNetX research network. Patients with MASH fibrosis were identified using the diagnosis codes for steatohepatitis/steatosis (K75.81 or K76.0) and liver fibrosis (K74.0). Cardiometabolic comorbidities included type 2 diabetes (T2D), thyroid disorders, lipid disorders and hypertension. Medications evaluated included statins, GLP-1 receptor agonists (GLP-1 RAs), anti-hypertensives and metformin. Prescribing frequency and sequence were compared pre- and post-March 2024 using line of treatment (LOT) analyses. **Results:** Patients were 53% female, 71% white, 11-15% Hispanic or Latino, 7-11% Black or African American, and 7-9% Asian. Prior to March 2024, statins were the most common first-line cardiometabolic therapy (>40%). GLP-1 RAs were least frequently used prescribed first (13%) (Figure 1). After March 2024, statins and antihypertensives remained the most common first-line therapy, with GLP-1RAs, resmetirom and metformin prescribed in less than 15% of patients (Figure 1). Patients were more likely to be prescribed a GLP-1 RA if they were female (p < 0.0001), white (p < 0.0001), or Black (p = 0.0180), or if they had a diagnosis of T2D, hypertension, hyperlipidemia, or thyroid disease (all p < 0.0001). Asian patients were less likely to be prescribed a GLP-1 RA (p < 0.0001). GLP-1 RA prescriptions increased steadily between 2019 and 2023, declined after March 2024 and increased again after August 2025 (Figure 1). Resmetirom was steadily prescribed first in 10% of patients with MASH fibrosis since March 2024 (Figure 1). Statins remain the most frequent first prescription; however, overall number of prescriptions have declined. GLP-1 RAs and antihypertensive prescriptions have remained consistent, while metformin prescriptions have declined since March 2024. **Conclusion:** In patients with MASH fibrosis and cardiometabolic disease, statins remain the most commonly prescribed medication. Use of MASH-directed therapies remains relatively limited in routine clinical practice. The modest uptake of newly approved MASH therapies highlights potential gaps in implementation and warrants further investigation into provider, patient and system level factors that may influence treatment. Limitations of this study include the reliance on ICD10 coding in a larger research network and the aggregation of all GLP-1 RAs into a single treatment category.

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3488 | DOES GLP-1RA THERAPY HAVE AN IMPACT ON MUSCLE FUNCTION IN PATIENTS WITH MASLD?

Jasmin Ravindra[1] Fernando Iorra[1], [1]Imperial College London

Background: Glucagon like peptide-1 receptor agonists (GLP-1RAs) are increasingly prescribed in patients with metabolic-dysfunction associated steatotic liver disease (MASLD). However, MASLD patients have an increased susceptibility to sarcopenia. Despite this, the impact of GLP-1RA-induced weight loss on muscle function and mass in this population remains poorly characterised. This study aimed to evaluate the effect of GLP-1RA therapy on muscle function, body composition, and quality of life in patients with MASLD. **Methods:** This prospective cohort study, conducted at a specialist metabolic liver centre in Northwest London from November 2015 to April 2026, enrolled consecutive adult patients with MASLD. Patients receiving GLP-1RA therapy (n = 54) were matched by age and gender to those not receiving GLP-1RA therapy (n = 76). Muscle function, body composition, quality of life and physical activity were measured using the hand grip and five times sit-to-stand-test (FTSST), bioelectrical impedance analysis, the Short Form 36 (SF-36) and the International Physical Activity Questionnaire respectively. **Results:** Hand grip remained stable over time in both cohorts (GLP-1RA: 27.3kg-29.6 kg, p = 0.3654; no-GLP-1RA: 27.6kg-28.3 kg, p = 0.9656), with no significant between-group difference at end of follow-up (p = 0.687). FTSST also remained consistent in both groups (GLP-1RA: 11.00s-10.78s, p = 0.7582; no-GLP-1RA: 10.82s-10.39s, p = 0.0827) and not significant between groups (p = 0.397). Muscle mass decreased numerically in both cohorts (GLP-1RA: 55.7kg-52.6kg, p = 0.3832; no-GLP-1RA: 51.8kg-49.9kg, p = 0.6019) without a significant intergroup difference (p = 0.795). No SF-36 domain changed significantly in the GLP-1RA cohort though bodily pain worsened significantly in no-GLP-1RA cohort by the end of the study period (p = 0.034). **Conclusion:** GLP-1RA therapy was not associated with an impairment of muscle function or mass in MASLD patients, a reassuring preliminary finding given the high risk of sarcopenia in this group. Multi-centre randomised trials incorporating standardised functional assessments and imaging-based body composition are needed to definitively characterise GLP-1RA effects on the MASLD-skeletal muscle axis.
Disclosures: Jasmin Ravindra:Nothing to Disclose, Fernando Iorra:Nothing to Disclose.

3489 | A CME VIRTUAL PATIENT CASE SIMULATION IMPROVED CLINICIAN PERFORMANCE IN MANAGING MASH

Shari Dermer[1] Julie Schrand[1] Roderick Smith[1] Sonal Kumar[2] Anita Kohli[3], [1]Medscape Education, [2]Weill Cornell, [3]Arizona Liver Health

Background: As there are now treatment options available for metabolic dysfunction-associated steatohepatitis (MASH) identification of candidates for these treatments is increasingly important in the care pathway. This study evaluated the effect of online virtual patient simulation (VPS)-based CME in improving the assessment and management of MASH, including risk-stratification, evaluation of liver fibrosis, and treatment initiation. **Methods:** An online VPS platform allowed learners to order tests, and select treatments supported by an extensive database matching the scope and depth of actual practice. Learners received immediate feedback in a short-form clinical guidance (CG) based on current evidence. Learners were permitted to modify their decisions post-CG. Pre- to post-CG decisions were compared using a McNemar's test with $P < .05$ as significant. The intervention launched on September 12, 2025, and data were collected through January 12, 2026. **Results:** We report on data from n = 38 to 51 gastroenterologists/ hepatologists (GI/heps) and n = 112 to 135 NP/PAs who participated in the virtual cases. Significant performance-based improvements were made in patient cases following CG (%pre vs % post; *P*-value). **Selecting noninvasive modalities for risk-stratification** : Performance improved by 8% (86% vs 94%; $P < .01$) and 18% (53% vs 71%; $P < .001$) for GI/heps and NP/PAs, respectively in case 1.

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For case 2, GI/heps had 10% (82% vs 92%; $P < .01$) and NP/PAs had 16% (63% vs 79%; $P < .001$) improvement in performance. **Staging of liver fibrosis:** Performance improved by 14% (47% vs 61%; $P < .001$) and 19% (24% vs 43%; $P < .001$) for GI/heps and NP/PAs, respectively in case 1. For case 2, GI/heps had 26% (42% vs 68%; $P < .001$) and NP/PAs had 31% (14% vs 45%; $P < .001$) improvement in performance. **Choosing evidence-based therapies:** Performance improved by 45% (22% vs 67%; $P < .001$) and 29% (6% vs 35%; $P < .001$) for GI/heps and NP/PAs, respectively in case 1. For case 2, GI/heps had 26% (24% vs 50%; $P < .001$) and NP/PAs had 30% (17% vs 47%; $P < .001$) improvement in performance. **Conclusion: Discussion:** Although there was increased performance in clinical decision-making with CG, most initial decisions indicate gaps in diagnosing F2/F3 MASH and in selecting appropriate evidence-based treatments.Reference:Kumar S., Kohli A. Are You a Master at Managing MASH? A Case Simulation Challenge.September 12, 2025. https://www.medscape.org/viewarticle/are-you-master-managing-mash-case-simulation-challenge-2025a1000nc9?page=2

Disclosures: Shari Dermer:Nothing to Disclose, Julie Schrand:Nothing to Disclose, Roderick Smith:Nothing to Disclose, Sonal Kumar:Nothing to Disclose, Anita Kohli:Nothing to Disclose.

3490 | LEVOTHYROXINE DOES NOT PROTECT AGAINST MAJOR ADVERSE LIVER OUTCOMES IN PATIENTS WITH MASLD AND HYPOTHYROIDISM: A PROPENSITY SCORE-MATCHED ANALYSIS

Rowan Bandaranaike[1] Travis Rutland[2] Samuel Tarwater[2] Tyler Black[2] George Nelson[3], [1]Southeast Health Hospital, [2]Digestive Health Specialists, [3]University of Alabama at Birmingham

Background: Hypothyroidism is associated with metabolic dysfunction-associated steatotic liver disease (MASLD) progression through shared metabolic pathways. Resmetirom, the first FDA-approved treatment for MASH, acts via liver-selective thyroid hormone receptor-β (THR-β) agonism. Whether systemic levothyroxine replacement affects hard clinical liver outcomes: cirrhosis, HCC, and liver failure in patients with established MASLD has not been evaluated in large real-world cohorts. **Methods:** We conducted a retrospective cohort study using the TriNetX Global Collaborative Network (44 U.S. health systems). Adults ($\geq$18 years) with MASLD (K76.0, K75.81) and hypothyroidism (E03.9, E03.8, E89.0, E02) were stratified by levothyroxine use; competing liver etiologies were excluded. One-to-one PSM balanced cohorts on age, sex, race, ethnicity, obesity, diabetes, dyslipidemia, and hypertension. The primary composite outcome, major adverse liver outcomes (MALO), comprised incident cirrhosis, hepatocellular carcinoma, liver transplant, ascites, and hepatic failure, assessed over 10 years via Kaplan-Meier analysis and Cox regression. Sensitivity analyses included E-value calculation for unmeasured confounding and a negative control outcome (appendicitis) to assess outcome specificity. **Results:** Among 365,579 eligible adults, 1:1 PSM yielded 142,869 patients per cohort with excellent covariate balance (all SMD < 0.02). Levothyroxine users had significantly higher MALO risk (5.1% vs 4.1%; RR 1.249, 95% CI 1.207-1.293; $p < 0.001$) and lower 10-year event-free survival (89.69% vs 91.63%; log-rank $p < 0.001$). Cox regression confirmed a 23% higher hazard (HR 1.230, 95% CI 1.187–1.274; $p < 0.001$; proportional hazards assumption confirmed, $p = 0.719$). The E-value was 1.76 (lower CI bound 1.66), indicating an unmeasured confounder would require $\geq$1.76-fold independent associations with both exposure and outcome to explain the result. Appendicitis incidence did not differ between cohorts (RR 1.02, 95% CI 0.99-1.08; $p = 0.07$), confirming absence of systematic detection or healthcare utilization bias. **Conclusion:** In 285,738 total propensity score-matched patients, levothyroxine use was associated with 23% higher MALO risk in MASLD with hypothyroidism over 10 years. These findings suggest systemic thyroid hormone replacement may not confer the hepatoprotective effects observed with liver-selective THR-β agonists. Residual confounding from hypothyroidism severity, including TSH levels unavailable in administrative data, cannot be excluded and likely contributes to the observed association. Studies examining TSH optimization targets and levothyroxine dose adequacy on liver outcomes are needed to guide treatment decisions in the growing population of patients with concurrent MASLD and hypothyroidism.

Disclosures: Rowan Bandaranaike:Nothing to Disclose, Travis Rutland:Nothing to Disclose, Samuel Tarwater:Nothing to Disclose, Tyler Black:Nothing to Disclose, George Nelson:Nothing to Disclose.

3491 | WHO GETS WEIGHT LOSS THERAPY? ANTI-OBESITY MEDICATION USE IN MASLD AND METALD

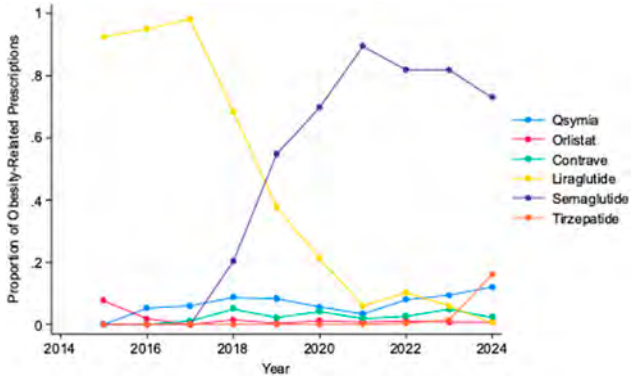
Dilara Hatipoglu[1] Nadim Mahmud[2], [1]University of Pennsylvania, [2]Hospital of the University of Pennsylvania

Background: Obesity is a major driver of fibrosis progression in steatotic liver disease (SLD). Lifestyle modification alone is often insufficient, making anti-obesity medications (AOMs) an important therapeutic option. We compared AOM utilization and predictors of prescription in patients with metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic

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dysfunction-associated alcohol-related liver disease (MetALD) **Methods:** This retrospective cohort study utilized VOCAL, a national Veterans Health Administration registry of patients with chronic liver disease. Adults (≥18 years) with non-cirrhotic steatotic liver disease on imaging, BMI ≥35 kg/m² , and no prior obesity treatment were included. MASLD and MetALD were classified using metabolic criteria and AUDIT-C data according to a validated algorithm. Multivariable logistic regression identified predictors of receiving any AOM. Trends in individual AOM use over time were assessed with linear regression. A post hoc subgroup analysis was performed by diabetes status. **Results:** Among 23,333 veterans in the cohort, 19,629 (84.1%) had MASLD and 3,704 (15.9%) had MetALD. Overall, 5,971 (25.6%) received at least one AOM. GLP-1 receptor agonists (GLP-1RAs) were the most prescribed class. Compared with MASLD, patients with MetALD were less likely to receive GLP-1RAs overall (18.5% vs 25.1%, $p<0.001$), including semaglutide (16.6% vs 23.1%, $p<0.001$) and liraglutide (2.1% vs 3.4%, $p<0.001$), while use of other AOMs was similar. Over time, liraglutide use declined (β = −0.11, 95% CI −0.139 to −0.084; p < 0.001), while semaglutide (β = 0.085, 95% CI 0.046 to 0.125; p = 0.001) and tirzepatide (β = 0.019, 95% CI 0.003 to 0.036; p = 0.025) use increased significantly (Figure 1).In adjusted analysis, diabetes mellitus was the strongest predictor of receiving any AOM (OR 3.53, 95% CI 3.26-3.83), while female sex (OR 1.52, 95% CI 1.37-1.70) and higher BMI (OR 1.06 per kg/m², 95% CI 1.05-1.07) were also independently associated with treatment. MetALD was independently associated with lower odds of AOM receipt compared with MASLD (OR 0.80, 95% CI 0.73-0.89), including in non-diabetics (OR 0.83, 95% CI 0.74-0.94). **Conclusion:** AOMs remain underutilized in patients with SLD. Patients with MetALD were less likely to receive AOMs, particularly GLP-1RAs, independent of diabetes status, suggesting disparities in obesity pharmacotherapy utilization and opportunities to improve fibrosis risk mitigation.



Disclosures: Dilara Hatipoglu:Nothing to Disclose, Nadim Mahmud:Nothing to Disclose.

3492 | COMPARATIVE ANALYSIS OF THE EFFICACY OF GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS VERSUS BARIATRIC SURGERY IN PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE IN A LARGE, INTEGRATED HEALTHCARE SYSTEM IN NORTHERN CALIFORNIA

Molly Chou[1] Miguel Nunez[2] Mehrnaz Siavoshi[3] Varun Saxena[2] Sreepriya Balasubramanian[4] Brock Macdonald[5] Suk Seo[6] Krisna Chai[7] Jeffrey Lee[1] Neil Mehta[2] Nizar Mukhtar[1], [1]Kaiser Permanente San Francisco Medical Center, [2]University of California, San Francisco, [3]Kaiser Permanente, [4]Kaiser Permanente Roseville Medical Center, [5]Kaiser Permanente, San Rafael, [6]Kaiser Permanente Antioch Medical Center, [7]Kaiser Permanente Santa Clara

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common chronic liver disease globally and is strongly linked to obesity. Both bariatric surgery and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) improve steatosis, fibrosis, weight, and cardiometabolic outcomes. However, no large-scale studies have directly compared these interventions in MASLD. This study aims to compare the effectiveness of GLP-1 RAs to bariatric surgery for patients with MASLD in a large community practice setting—the Kaiser Permanente Northern California (KPNC) healthcare system—to inform best practices in management. **Methods:** This retrospective cohort study included adults (≥18 years) with MASLD diagnosed between 1/1/2014 and 12/31/2022 within KPNC who underwent bariatric surgery (Roux-en-Y gastric bypass, sleeve gastrectomy, or gastric banding; N = 5,258) or received a GLP-1 RA for at least 6 months over a 12-month period (N = 26,976). Analyses used propensity score-adjusted Cox proportional hazards models starting from the date of bariatric surgery or GLP-1 RA initiation. The primary outcomes were: 1) progression to cirrhosis among patients without baseline cirrhosis, 2) occurrence of a composite outcome that includes hepatic decompensation, hepatocellular carcinoma, liver transplantation, and death among patients with baseline cirrhosis, and 3) occurrence of major adverse cardiovascular events (MACE) among patients with baseline cirrhosis. **Results:** Among the 32,234 patients, mean age was 50.6 years; 64% were female, 44% White, 23% Hispanic, 13% Asian, and 7% Black. Treatment was initiated a mean of 4.8 years after MASLD diagnosis. On the date of treatment initiation, 2.3% of patients had cirrhosis; over 50% had diabetes, hypertension, or hyperlipidemia; and 9% had chronic kidney

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disease. Compared to patients who underwent bariatric surgery, patients who received GLP-1 RAs were more likely to be older (mean, age 51 vs. 47 years; $p < 0.001$), male (39% vs. 23%; $p < 0.001$), and non-White (57% vs. 51%; $p < 0.001$); to take longer to initiate treatment (5.3 vs. 2.1 years; $p < 0.001$), have a lower BMI (mean, 37.8 vs. 40.7; $p < 0.001$), and a lower rate of baseline cirrhosis (2.1% vs. 3.1%; $p < 0.001$); and to have higher rates of diabetes (64% vs. 24%; $p < 0.001$), hypertension (61% vs. 43%; $p < 0.001$), hyperlipidemia (57% vs. 36%; $p < 0.001$), and chronic kidney disease (10% vs. 5%; $p < 0.001$) (Table 1). Analyses are ongoing and preliminary results for primary outcomes will be provided. **Conclusion:** Patients who received GLP-1 RAs differed from those who underwent bariatric surgery in age, gender, race, BMI, baseline cirrhosis rate, and presence of co-morbidities, including those pre-disposing to MASLD. Data regarding progression to cirrhosis, rates of hepatic complications, and MACE will be discussed.

Table 1. Baseline Demographics

Characteristic	Overall N = 32,234[1]	Exposure Group		p-value[2]
		Bariatric surgery N = 5,258[1]	GLP-1 RA N = 26,976[1]	
Sex				<0.001
Female	20,574 (64%)	4,024 (77%)	16,550 (61%)	
Male	11,639 (36%)	1,232 (23%)	10,407 (39%)	
Other	2 (<0.1%)	0 (0%)	2 (<0.1%)	
Unknown	19 (<0.1%)	2 (<0.1%)	17 (<0.1%)	
Race				<0.001
White	14,103 (44%)	2,582 (49%)	11,521 (43%)	
Hispanic	7,464 (23%)	1,282 (24%)	6,182 (23%)	
Asian	4,238 (13%)	342 (6.5%)	3,896 (14%)	
Black	2,370 (7.4%)	363 (6.9%)	2,007 (7.4%)	
Other (Hawaiian/Pacific Islander, American Indian/Alaska Native, Multiple)	3,883 (12%)	676 (13%)	3,207 (12%)	
Unknown	176 (0.5%)	13 (0.2%)	163 (0.6%)	
Age at MASLD diagnosis, years	50.6 (12.4)	47.0 (13.7)	51.3 (11.9)	<0.001
Years from diagnosis to treatment	4.8 (2.9)	2.1 (2.4)	5.3 (2.7)	<0.001
BMI, kg/m²	38.3 (7.7)	40.7 (8.6)	37.8 (7.4)	<0.001
BMI category				<0.001
Underweight	21 (<0.1%)	19 (0.4%)	2 (<0.1%)	
Normal	427 (1.3%)	178 (3.4%)	249 (0.9%)	
Overweight	3,572 (11%)	365 (7.0%)	3,207 (12%)	
Obese I	7,339 (23%)	501 (9.6%)	6,838 (26%)	
Obese II	8,500 (27%)	1,178 (23%)	7,322 (27%)	
Obese III	12,074 (38%)	2,992 (57%)	9,082 (34%)	
Baseline cirrhosis	735 (2.3%)	164 (3.1%)	571 (2.1%)	<0.001
Diabetes mellitus	18,425 (57%)	1,280 (24%)	17,145 (64%)	<0.001
Hypertension	18,637 (58%)	2,283 (43%)	16,354 (61%)	<0.001
Hyperlipidemia	17,337 (54%)	1,906 (36%)	15,431 (57%)	<0.001
Chronic kidney disease	3,054 (9.5%)	276 (5.2%)	2,778 (10%)	<0.001

[1] Mean (SD); n (%); Median (IQR)
[2] Welch Two Sample t-test; Pearson's Chi-squared test
[3] Total 301 patients with unknown BMI removed from counts (25 patients in bariatric surgery group and 276 patients in GLP-1 RA group)

Disclosures: Molly Chou:Nothing to Disclose, Miguel Nunez:Nothing to Disclose, Mehrnaz Siavoshi:Nothing to Disclose, Varun Saxena:Nothing to Disclose, Sreepriya Balasubramanian:Nothing to Disclose, Brock Macdonald:Nothing to Disclose, Suk Seo: Nothing to Disclose, Krisna Chai:Nothing to Disclose, Jeffrey Lee:Nothing to Disclose, Neil Mehta:Merck: Consultant, FujiFilm WAKO: Consultant, Merck: Consultant, FujiFilm WAKO: Consultant, Boston Scientific: Consultant, FujiFilm: Grant/Research Support, FujiFilm: Consultant, Merck: Consultant, FujiFilm WAKO: Consultant, Merck: Consultant, FujiFilm WAKO: Consultant, Boston Scientific: Consultant, FujiFilm: Grant/Research Support, FujiFilm: Consultant, Nizar Mukhtar: Nothing to Disclose.

3493 | WHO GETS GLP-1RA THERAPY? SPECIALTY CARE STRONGLY PREDICTS TREATMENT IN MASLD AND METALD

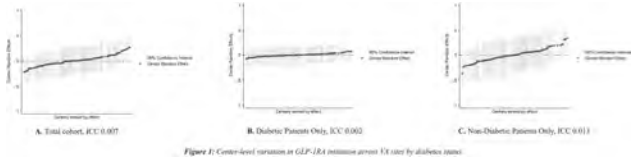
Dilara Hatipoglu[1] Nadim Mahmud[2], [1]University of Pennsylvania, [2]Hospital of the University of Pennsylvania

Background: GLP-1 receptor agonists (GLP-1RAs) are increasingly used for obesity management and may improve liver-related outcomes in steatotic liver disease (SLD). However, provider- and center-level determinants of GLP-1RA initiation remain unclear. We evaluated patient, specialty care, and site-level predictors of GLP-1RA use in veterans with MASLD and MetALD. **Methods:** This was a retrospective cohort study using VOCAL, a national Veterans Health Administration registry of chronic liver disease representing 128 centers. Adults ($\geq$18 years) with non-cirrhotic SLD on imaging, BMI $\geq$35 kg/m², and no prior obesity treatment were included. MASLD and MetALD were classified using metabolic criteria and AUDIT-C data. The outcome was GLP-1RA initiation after steatosis diagnosis. Exposures included post-diagnosis healthcare utilization, specialty follow-up, and number of specialties seen. Multivariable logistic regression identified predictors of GLP-1RA initiation. Mixed-effects models with VA site as a random intercept evaluated center-level variation. Prespecified subgroup analyses were performed by diabetes status. **Results:** Among 23,333 veterans, 51.2% established care with at least one new specialty after steatosis diagnosis. Greater specialty exposure was associated with GLP-1RA initiation (OR 1.52, 95% CI 1.46-1.57, $p < 0.001$). Endocrinology had the highest odds (OR 2.53, 95% CI 2.35-2.73, $p < 0.001$), followed by hepatology (OR 1.33, 95% CI 1.19-1.48, $p < 0.001$) and gastroenterology (OR 1.30, 95% CI 1.21-1.39, $p < 0.001$), while primary care was not associated with GLP-1RA prescribing. Diabetes was strongly associated with increased use (OR 3.45, 95% CI 3.22–3.70, $p < 0.001$), while MetALD (OR 0.83, 95% CI 0.75-0.91, $p < 0.001$) and higher FIB-4 category (OR 0.85, 95% CI 0.80–0.87, $p < 0.001$) were associated with lower use. In non-diabetic patients, primary care showed modest association, while specialty care remained a strong predictor. Center-

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level variation was minimal overall (ICC 0.007) but higher in non-diabetic patients (ICC 0.013), demonstrated in **Figure 1. Conclusion:** GLP-1RA prescribing in SLD is strongly associated with specialty care, particularly endocrinology. Patients with MetALD and higher fibrosis risk were less likely to receive therapy, indicating gaps in treatment among higher-risk groups. Center-level variation was minimal overall but greater among non-diabetics, suggesting more heterogeneous obesity driven prescribing pathways in this subgroup.

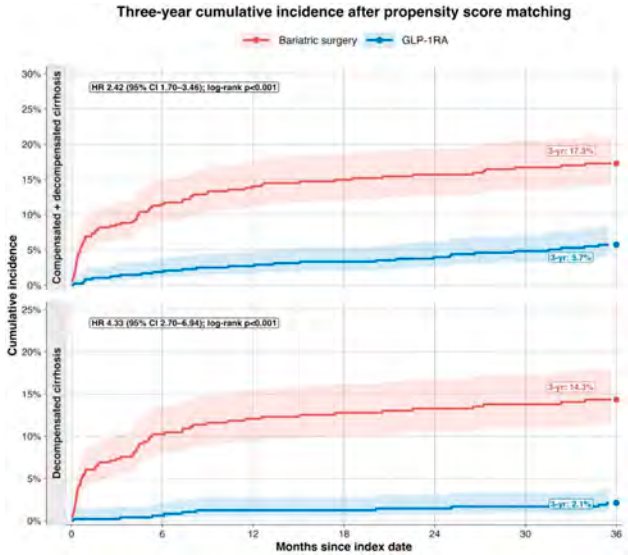


Disclosures: Dilara Hatipoglu:Nothing to Disclose, Nadim Mahmud:Nothing to Disclose.

3494 | HIGHER RISK OF CIRRHOSIS WITH BARIATRIC SURGERY COMPARED WITH GLP-1RA THERAPY IN ALD PATIENTS WITH OBESITY

Sheng-Yin Chen[1] Hanyou Loh[2] lingyu bao[3], [1]Massachusetts General Hospital, [2]Canton Medical Education Foundation, [3]Children's Hospital at Montefiore

Background: Alcohol-associated liver disease (ALD) and class I obesity confer an increased risk of advanced liver disease. While both bariatric surgery and glucagon-like peptide-1 receptor agonist (GLP-1RA) are recommended treatment for this population, alcohol use may pose harm in those who undergo bariatric surgery. We aimed to compare the effectiveness of bariatric surgery versus GLP-1RA-based therapies in preventing cirrhosis among patients with ALD and class I obesity. **Methods:** We conducted a retrospective cohort study using the TriNetX US Collaborative Network (66 healthcare organizations). Adults aged ≥18 years with ALD and obesity who underwent bariatric surgery or initiated GLP-1RA therapy between 1/1/2010 and 5/31/2023 were included. The body mass index (BMI) group of 30–35 kg/m² was chosen to ensure the comparability of both arms. Patients with pre-existing liver cirrhosis, prior bariatric surgery, or GLP-1RA exposure were excluded. The index date was defined as the date of bariatric surgery or first GLP-1RA prescription. Follow-up continued until 5/25/2026 or until the incident cirrhosis. Propensity score matching (PSM) adjusted for demographics, BMI, metabolic and psychiatric comorbidities, laboratory test, medication use, and healthcare utilization. Cox proportional hazards analysis was used to compare risk between groups. **Results:** A total of 5,355 patients met the inclusion criteria, including 669 patients undergoing bariatric surgery and 4,686 receiving GLP-1RA therapy. After 1:1 PSM, 489 patients remained in each group with balanced baseline characteristics. Mean age after matching was 54.1 ± 13.4 years in the bariatric surgery group and 54.3 ± 11.2 years in the GLP-1RA group. Mean BMI was 32.4 ± 5.0 versus 33.9 ± 4.1 kg/m², respectively. Patients in the bariatric surgery group demonstrated a significantly higher cumulative incidence of liver cirrhosis compared with the GLP-1RA cohort during follow-up. Bariatric surgery was associated with a higher risk of cirrhosis (HR 2.42, 95% CI 1.70-3.46) compared to GLP-1RA therapy. When categorized by sex, the risk of cirrhosis is similar between males (HR 2.87, 95% CI 1.70-4.85) and females (HR 2.37, 95% CI 1.36). Sensitivity analysis demonstrated a significantly higher risk for decompensated cirrhosis (HR 4.33, 95% CI 2.70-6.94). **Conclusion:** In this propensity score-matched cohort, GLP-1RA therapy was associated with a lower observed risk of incident cirrhosis and decompensated cirrhosis than bariatric surgery in patients with ALD and class I obesity. Prospective studies are warranted to validate the findings and to determine the role of alcohol cessation in patients who receive bariatric surgery.



Disclosures: Sheng-Yin Chen:Nothing to Disclose, Hanyou Loh:Nothing to Disclose, lingyu bao:Nothing to Disclose.

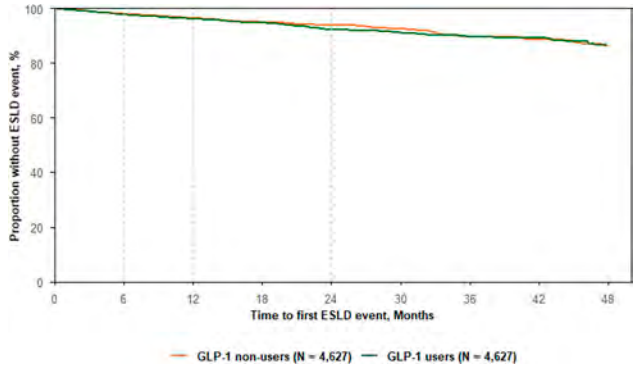
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3495 | ASSOCIATION OF GLP-1 USE AND END-STAGE LIVER DISEASE EVENTS IN US ADULTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS

Dominic Nunag[1] Christina Parrinello[2] Nipun Atreja[2] Arushi Chadha[1] Samantha Clark[1] Matthew Davis[1] Blake Thomas[2] Francis Lobo[2] John O'Donnell[2] Anthony Martinez[3], [1]Medicus Economics LLC, [2]Madrigal Pharmaceuticals Inc, [3]University at Buffalo

Background: Metabolic dysfunction-associated steatohepatitis (MASH) is an inflammatory and progressive form of metabolic dysfunction-associated steatotic liver disease and is associated with end-stage liver disease (ESLD) complications. Because obesity and type 2 diabetes (T2D) are key metabolic drivers of MASH, many patients are eligible for GLP-1 receptor-targeting therapies. Assessments of ESLD outcomes in GLP-1 trials are limited by short follow-up duration and small sample sizes. We evaluated the relationship between GLP-1 use and risk of progression to ESLD among patients with MASH using real-world data. **Methods:** This retrospective cohort study used Optum Market Clarity data from December 5, 2015, through December 31, 2024. Adults with a MASH diagnosis code, evidence of obesity and/or T2D, and $\geq$24 months of continuous enrollment were eligible for study entry. Patients with other causes of liver disease or severe MASH-related complications during the 24-month pre-index period were excluded. Following the pre-index period, GLP-1 initiators (semaglutide or tirzepatide [any dose]; first fill defined as the index date) were 1:1 propensity score matched to controls of the same age, sex, and indication (obesity and/or T2D) who met the inclusion criteria as of the index date but did not have prior GLP-1 use (i.e. risk-set sampling). Outcomes included compensated and decompensated cirrhosis, hepatocellular carcinoma, liver transplant, or death. Time to first ESLD event was estimated overall and by indication using Kaplan-Meier analyses and marginal Cox models, with censoring at disenrollment or end of data availability. **Results:** The matched sample included 4,627 patients each in the GLP-1 user and non-user cohorts. Overall, 59.9% of patients were female, mean (SD) age was 51.6 (11.6) years, and 85.7%, 78.8%, and 64.6% had obesity, T2D, and both conditions, respectively. Mean (median) follow-up was 17.5 (14.7) and 18.0 (14.9) months in the GLP-1 user and non-user cohorts, respectively. In survival analyses, the cumulative incidence of ESLD events at 6, 12, and 24 months was 2%, 4%, and 8% among GLP-1 users and 2%, 4%, and 6% among GLP-1 non-users, respectively (HR = 1.05; p = 0.56). Event rates were not significantly different between cohorts in subgroup analyses of patients with obesity, T2D, and both conditions (all p > 0.05). **Conclusion:** In this real-world matched cohort of adults with MASH, no statistically significant difference in ESLD risk was observed between GLP-1 users and non-users. Comparable ESLD event rates suggest that longer-term studies are needed to better understand the potential impact of GLP-1 therapies on MASH progression.



Disclosures: Dominic Nunag:Madrigal Pharmaceuticals Inc: Consultant, Christina Parrinello:Madrigal Pharmaceuticals: Employee, Madrigal Pharmaceuticals: Stock - publicly traded company, Nipun Atreja: madrigal pharmaceuticals: Employee, Arushi Chadha: Nothing to Disclose, Samantha Clark:Nothing to Disclose, Matthew Davis:Medicus Economics, LLC: Employee, Blake Thomas:Madrigal Pharmaceuticals: Employee, Francis Lobo:Nothing to Disclose, John O'Donnell:Nothing to Disclose, Anthony Martinez:Gilead: Consultant, Gilead: Speaking and Teaching, Abbvie: Consultant, Abbvie: Speaking and Teaching, Arbutus: Consultant, Braeburn: Speaking and Teaching, Sirtex: Consultant, Roche: Consultant, Syneos/VBI: Consultant, Madrigal: Speaking and Teaching, Altimune: Consultant, Madrigal: Consultant, Ipsen: Consultant, novo: Speaking and Teaching, atea: Consultant, cepheid: Consultant.

3496 | COMPARATIVE EFFECTIVENESS OF TIRZEPATIDE VERSUS GLP-1 RECEPTOR AGONISTS ON MORTALITY, CARDIOVASCULAR, AND HEPATIC OUTCOMES IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE: A PROPENSITY-MATCHED ANALYSIS

Yetunde Akande[1] Cherechi Nwabueze[2] Eunice Omeludike[3] Nzubechukwu Okeke[4] Ihunanya Kanu[5], [1]John H Stroger Jr. Hospital of Cook County, [2]John H. Stroger Jr. Hospital of Cook County, [3]Piedmont Athens Regional Medical Center, [4]Zucker school of medicine at

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is strongly associated with obesity, type 2 diabetes mellitus, and increased cardiovascular morbidity. Tirzepatide has demonstrated significant metabolic benefits; however, comparative real-world data evaluating its effectiveness against other GLP-1 receptor agonists in MASLD remain limited. We compared mortality, cardiovascular, and hepatic outcomes among MASLD patients treated with tirzepatide versus GLP-1 receptor agonists. **Methods:** We performed a retrospective cohort study using the TriNetX US Collaborative Network. Adult patients with MASLD receiving tirzepatide or GLP-1 receptor agonists were identified. Propensity score matching (1:1) was performed to balance demographics and comorbidities between cohorts. Outcomes were assessed over a 1-year follow-up period and included all-cause mortality, major adverse cardiovascular events (MACE), stroke, myocardial infarction (MI), cirrhosis, and hepatocellular carcinoma (HCC). **Results:** Before matching, 65,454 patients receiving tirzepatide were compared with 153,060 patients receiving GLP-1 receptor agonists. After propensity matching, 65,452 patients remained in each cohort. Tirzepatide use was associated with significantly lower all-cause mortality compared with GLP-1 receptor agonists (0.5% vs 0.9%; RR 0.52, 95% CI 0.46–0.60; HR 0.63, $p < 0.001$). Patients treated with tirzepatide also had lower risk of MACE (2.5% vs 3.3%; RR 0.78, $p < 0.001$), stroke (1.4% vs 1.6%; RR 0.85, $p < 0.001$), myocardial infarction (1.2% vs 1.5%; RR 0.75, $p < 0.001$), and hepatocellular carcinoma (0.5% vs 0.6%; RR 0.76, $p < 0.001$). There was no significant difference in progression to cirrhosis between groups (4.0% vs 3.9%; RR 1.02, $p = 0.56$). Kaplan-Meier analysis demonstrated improved overall survival and lower cardiovascular event rates in the tirzepatide cohort. **Conclusion:** In this large multicenter propensity-matched analysis, patients on tirzepatide demonstrated reduced mortality, cardiovascular events, and HCC risk compared with GLP-1 receptor agonists among patients with MASLD. These findings suggest tirzepatide may provide additional cardiometabolic and hepatic benefits in MASLD management. Prospective randomized studies are warranted to further define its long-term impact on hepatic disease progression and clinical outcomes.

Disclosures: Yetunde Akande:Nothing to Disclose, Cherechi Nwabueze:Nothing to Disclose, Eunice Omeludike:Nothing to Disclose, Nzubechukwu Okeke:Nothing to Disclose, Ihunanya Kanu:Nothing to Disclose.

3497 | CARDIOVASCULAR OUTCOMES WITH GLP-1 RECEPTOR AGONISTS VERSUS SGLT2 INHIBITORS IN PATIENTS WITH MASLD OR CIRRHOSIS AND CHRONIC KIDNEY DISEASE

Urveesh Sharma[1] Yash Shah[2] Manesh Gangwani[2] Ragesh Thandassery[3], [1]University of Arkansas for Medical Sciences, [2]UAMS, LR, [3]CAVHS, Little Rock

Background: Patients with metabolic dysfunction-associated steatotic liver disease (MASLD) or cirrhosis and chronic kidney disease (CKD) face a disproportionately high cardiovascular burden. While both GLP-1 receptor agonists (GLP-1 RAs) and SGLT2 inhibitors (SGLT2is) have shown cardiovascular benefits in diabetic populations, no study has directly compared them in patients with both MASLD or cirrhosis and CKD. **Methods:** We conducted a retrospective cohort study using the TrinetX database where adults ($\geq$18 years) with pre-existing MASLD or cirrhosis, CKD stages 3-5, and T2DM were divided into two cohorts based on whether they were newly started on a GLP-1 RA or a SGLT2i. We excluded patients with cross-drug class exposure, alcoholic liver disease, viral hepatitis, prior liver transplant, HCC, ESRD, or dialysis. 1:1 propensity score matching (PSM) on demographics, comorbidities, medications, and laboratory values was done. The primary outcome was 3-year major adverse cardiovascular event (MACE), a composite of acute myocardial infarction (MI), cerebral infarction and intracerebral hemorrhage. Secondary outcomes included the individual MACE components. Kaplan-Meier analysis with log-rank testing and Cox regression were used. The proportional hazards assumption was satisfied for the MACE composite ($p = 0.250$) and for MI ($p = 0.704$). For cerebral infarction, the proportionality test was significant ($p = 0.029$), so the HR is reported as a time-averaged estimate. **Results:** GLP-1 RA use was associated with significantly lower MACE (6.3% vs 8.5%; HR 0.721, 95% CI 0.606-0.857; log-rank $p < 0.001$). Three-year MACE-free survival was 89.8% versus 86.9%. For individual components, GLP-1 RA use was associated with lower acute MI risk (3.8% vs 5.6%; HR 0.668, 95% CI 0.544-0.821; log-rank $p < 0.001$) and lower cerebral infarction risk (2.9% vs 3.9%; time-averaged HR 0.747, 95% CI 0.589-0.948; log-rank $p = 0.016$). **Conclusion:** In patients with concurrent MASLD or cirrhosis, CKD, and T2DM, GLP-1 RAs were associated with a 28% relative reduction in MACE compared to SGLT2is, with lower rates of both MI and stroke contributing to this difference. These findings point to a meaningful cardiovascular advantage for GLP-1 RAs in this high-

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risk population.

Table 1. Cardiovascular outcomes at 3 years — GLP-1 receptor agonists vs. SGLT2 inhibitors

Outcome	GLP-1 RA (%)	SGLT2i (%)	HR (95% CI)	3-yr event-free survival	p value
MACE composite	6.3	8.5	0.721 (0.606–0.857)	89.8% vs. 86.9%	<0.001
Acute myocardial infarction	3.8	5.6	0.668 (0.544–0.821)	—	<0.001
Cerebral infarction*	2.9	3.9	0.747 (0.589–0.948)*	—	0.016

* Time-averaged HR (Schoenfeld p = 0.029). HR = hazard ratio; CI = confidence interval; MACE = acute MI + cerebral infarction + intracerebral hemorrhage.

Disclosures: Urveesh Sharma:Nothing to Disclose, Yash Shah:Nothing to Disclose, Manesh Gangwani: Nothing to Disclose, Ragesh Thandassery:Nothing to Disclose.

3498 | MORTALITY, HEPATIC, AND CARDIOVASCULAR OUTCOMES ASSOCIATED WITH ATYPICAL ANTIPSYCHOTIC EXPOSURE IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE: A PROPENSITY-MATCHED REAL-WORLD STUDY

Yetunde Akande[1] Cherechi Nwabueze[2] Gedion Amdetsion[1] Philip Sarpong-Mensah[1] Emmanuel Ansah[1] Ayokunle Abegunde[3], [1]John H Stroger Jr. Hospital of Cook County, [2]John H. Stroger Jr. Hospital of Cook County, [3]Division of Gastroenterology and Hepatology. John H Stroger Jr. Hospital of Cook County

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) affects approximately 30% of adults globally and confers substantial hepatic and cardiovascular risk. Antipsychotic medications promote weight gain, dyslipidemia, and insulin resistance, which are core drivers of MASLD progression. However, their independent impact on discrete clinical outcomes in this population remains poorly characterized. **Methods:** We conducted a retrospective cohort study using the TriNetX Network. Adults (≥18 years) with a diagnosis of MASLD were identified and stratified based on exposure to atypical antipsychotics. Propensity score matching (1:1) was performed on demographics, comorbidities, and clinical covariates. Outcome included mortality, MACE, stroke, MI, cirrhosis, and HCC, which were assessed over a 3-year follow-up window. Risk analysis and Kaplan-Meier survival analyses with log-rank testing were performed; risk ratios (RR), and hazard ratios (HR) with 95% confidence intervals (CI) are reported. **Results:** After propensity score matching (PSM), each cohort comprised 112,178 patients. Antipsychotic use was associated with significantly higher rates of mortality (16.4% vs. 9.6%), MACE (15.0% vs. 10.9%), stroke (5.9% vs. 4.1%), and MI (6.1% vs. 5.2%), all $p < 0.001$. Conversely, antipsychotic-exposed patients had lower rates of cirrhosis (3.6% vs. 5.2%) and HCC (1.3% vs. 1.8%), both $p < 0.001$. **Conclusion:** In this large propensity score-matched analysis, antipsychotic use among patients with MASLD was independently associated with significantly increased risks of all-cause mortality and adverse cardiovascular outcomes, including MACE, stroke, and MI. Paradoxically, antipsychotic exposure was associated with lower rates of cirrhosis and HCC. These findings highlight the importance of close cardiovascular risk assessment and monitoring in MASLD patients receiving antipsychotic therapy and warrant further investigation into the mechanisms underlying the observed reduction in hepatic complications.



Disclosures: Yetunde Akande:Nothing to Disclose, Cherechi Nwabueze:Nothing to Disclose, Gedion Amdetsion:Nothing to Disclose, Philip Sarpong-Mensah:Nothing to Disclose, Emmanuel Ansah:Nothing to Disclose, Ayokunle Abegunde:Nothing to Disclose.

3499 | PEG-IFN&ALPHA;-2B AMELIORATES METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS THROUGH THE GUT-LIVER AXIS

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Background: Metabolic dysfunction-associated steatohepatitis (MASH) is driven by hepatic steatosis, inflammation, fibrosis, and gut-liver axis dysfunction. Type I interferons regulate lipid metabolism and immunity, but whether PEG-IFNα-2b protects against MASH through gut microbiota and bile acid remodeling remains unclear **Methods:** Diet-induced MASH mice were treated with PEG-IFNα-2b. Liver injury, steatosis, inflammation, fibrosis, intestinal barrier integrity, gut microbiota, bile acid profiles, and hepatic transcriptomic

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changes were evaluated by biochemistry, histology, qPCR, immunofluorescence, 16S rRNA sequencing, bile acid metabolomics, and RNA sequencing. **Results:** PEG-IFNα-2b improved liver injury in MASH mice, reducing liver-to-body weight ratio and serum ALT, AST, LDL, total bilirubin, and triglycerides, while increasing HDL. Histology showed reduced lipid droplets, ballooning, and collagen deposition. PEG-IFNα-2b suppressed lipogenic genes (ACC1, ACC2, Srebp1c, FASN), increased PPARα and FGF21 expression, and enriched fatty acid oxidation pathways. Treatment also decreased hepatic and intestinal IL-6, IL-1β, TNF-α, and F4/80, while increasing IL-10. In the intestine, PEG-IFNα-2b restored villus architecture, increased goblet cells, upregulated Claudin-1 and Occludin, enhanced Reg3b, Reg3g, IL-22, and mucin-related genes, and reduced circulating lipopolysaccharide.16S rRNA sequencing showed that PEG-IFNα-2b reduced potentially harmful taxa, including Erysipelatoclostridium and Enterobacteriaceae, and enriched Lactobacillus, Akkermansia muciniphila, and Clostridium. Bile acid profiling revealed decreased primary/conjugated bile acids (TCA, GCA, GCDCA, TUDCA) and increased secondary bile acids, including UDCA and LCA. UDCA negatively correlated with intestinal FXR-FGF15 signaling and positively correlated with hepatic Cyp7a1 and Cyp8b1. Consistently, PEG-IFNα-2b decreased intestinal FXR and FGF15 expression, increased hepatic Cyp7a1 and Cyp8b1, reduced serum total bile acids, and promoted fecal bile acid excretion. **Conclusion:** PEG-IFNα-2b alleviates experimental MASH by activating hepatic PPARα-FGF21 signaling, restoring intestinal barrier integrity, reshaping gut microbiota, increasing secondary bile acids, suppressing intestinal FXR-FGF15 signaling, and promoting bile acid synthesis and fecal excretion. These findings support PEG-IFNα-2b as a potential microbiota-bile acid–targeted therapy for MASH.
Disclosures: TUO SHAO:Nothing to Disclose, Enfei Qiang:Nothing to Disclose, Qian Zhu:Nothing to Disclose, Weifeng Zhao:Nothing to Disclose, Raymond Chung:Nothing to Disclose.

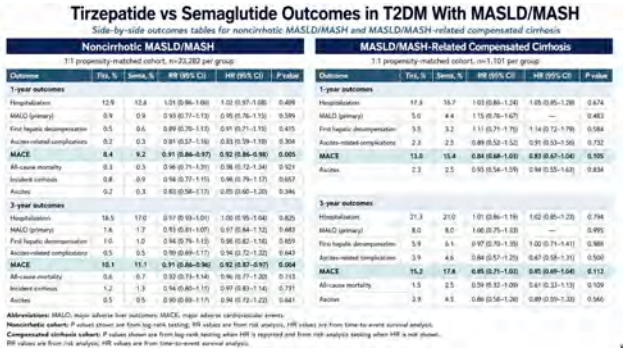
3500 | CARDIOMETABOLIC ADVANTAGE WITHOUT HEPATIC TRADEOFF: TIRZEPATIDE VERSUS SEMAGLUTIDE ACROSS THE MASLD/MASH SPECTRUM IN TYPE 2 DIABETES (T2DM)

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Background: Tirzepatide and semaglutide are increasingly used in T2DM with MASLD/MASH, but comparative real-world outcomes across liver-disease stage are limited. We compared hepatic, cardiovascular, hospitalization, mortality, and cirrhosis-related outcomes after tirzepatide versus semaglutide initiation in adults with noncirrhotic MASLD/MASH and MASLD/MASH-related compensated cirrhosis. **Methods:** Using TriNetX Research Network data from 110 healthcare organizations, we identified adults with T2DM and MASLD/MASH initiating tirzepatide or semaglutide. Patients were stratified as noncirrhotic or compensated cirrhosis; compensated cirrhosis required cirrhosis codes without prior decompensation. Exclusions included prior hepatic decompensation, malignancy, competing liver disease, transplant, end-stage renal disease/dialysis, HIV, or prior comparator exposure. Tirzepatide and semaglutide users were 1:1 propensity-score matched on demographics, comorbidities, medications, and laboratory values. Outcomes were assessed from day 1 after index through 1 and 3 years. The primary outcome was major adverse liver outcomes (MALO: decompensation-related events, hepatocellular carcinoma, liver transplantation, or death); secondary outcomes included hospitalization, first hepatic decompensation, ascites-related complications, major adverse cardiac event (MACE), mortality, incident cirrhosis, and ascites. **Results:** In the noncirrhotic cohort, 23,282 tirzepatide users were matched to 23,282 semaglutide users. At 1 year, hospitalization (12.9% vs 12.8%; HR 1.02, 95% CI 0.97–1.08; p = 0.409) and MALO (0.9% vs 0.9%; HR 0.95, 0.78–1.15; p = 0.599) did not differ, while MACE was lower with tirzepatide (8.4% vs 9.2%; HR 0.92, 0.86–0.98; p = 0.005). At 3 years, MALO (1.6% vs 1.7%; p = 0.683), first decompensation (1.0% vs 1.0%; p = 0.859), mortality (0.6% vs 0.7%; p = 0.713), and incident cirrhosis (1.2% vs 1.3%; p = 0.731) were similar; MACE remained lower with tirzepatide (10.1% vs 11.1%; HR 0.92, 0.87–0.97; p = 0.004). In compensated cirrhosis, 1,101 patients were matched per group. At 1 year, MALO (5.0% vs 4.4%; p = 0.483), first decompensation (3.5% vs 3.2%; p = 0.584), and MACE (13.0% vs 15.4%; RR 0.84, 0.68–1.03; p = 0.105) did not differ. At 3 years, MALO (8.0% vs 8.0%; p = 0.995), first decompensation (5.9% vs 6.1%; p = 0.988), mortality (1.5% vs 2.5%; p = 0.109), ascites (3.9% vs 4.5%; p = 0.566), and MACE (15.2% vs 17.8%; RR 0.85, 0.71–1.03; p = 0.112) were similar. **Conclusion:** Tirzepatide and semaglutide showed similar hepatic, hospitalization, mortality, and cirrhosis/decompensation-related outcomes through 3 years across noncirrhotic MASLD/MASH and compensated cirrhosis. Tirzepatide was associated with lower MACE in noncirrhotic MASLD/MASH, with a nonsignificant directional reduction in compensated cirrhosis. Prospective head-to-head studies are warranted.

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3501 | CHARACTERIZATION AND THERAPEUTIC RESPONSE OF PATIENTS WITH METABOLIC-DYSFUNCTION ASSOCIATED STEATOHEPATITIS (MASH) AFTER 12 MONTHS OF TREATMENT WITH RESMETIROM

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Background: Resmetirom has been conditionally approved to treat individuals with metabolic dysfunction-associated steatohepatitis (MASH) and significant fibrosis (≥ F2 fibrosis) since March 2024. The ongoing phase 3 trial relied on biopsy-proven data, yet treatment response in practice based on non-invasive liver disease assessments (NILDAs) remains unknown. This study aims to describe the characteristics of individuals who are prescribed resmetirom, assess 12-month response, and characterize the efficacy and tolerability at a single tertiary care center. **Methods:** This is a retrospective cohort study of adults with MASH and ≥ F2 fibrosis who were prescribed resmetirom from 3/15/2024 to 5/1/2025 at Duke University Healthcare System. Baseline characteristics were described for all prescribed resmetirom. For those who started resmetirom, outcomes are summarized at baseline and after 12 months of treatment. The primary endpoint is change in liver stiffness measurement (LSM) via transient elastography (TE) from baseline to 12 months. The secondary endpoints include change in ALT, hemoglobin A1c, lipid profiles, and body-mass index (BMI), as well as additional NILDAs such as enhanced liver fibrosis score (ELF), MR elastography (MRE), calculated FAST score, and controlled attenuation parameter (CAP) via TE. Changes were assessed using paired tests. **Results:** Of the 91 prescribed resmetirom, 70 (77%) started treatment. Among those who started, 44% were female, 84% were White, 56% had private insurance, with a mean (SD) age of 57 years (13.7) and BMI of 33.6kg/m^2 (6.4). Statins were the most common concurrent medication (64%), followed by GLP-1 receptor agonists (39%). Most (89%) had TE performed at baseline, while 26% had MRE. By 12 months, 50/70 were still on resmetirom. The primary reason for discontinuation was gastrointestinal side effects, usually within 6 months. Unadjusted analyses of primary and secondary outcomes are shown in Table 1. After 12 months of treatment, patients had a significant decrease in LSM ($p = 0.02$) and ALT ($p < 0.01$) as well as CAP, FAST score, triglycerides, LDL, and BMI. **Conclusion:** In this real-world cohort of patients with fibrotic MASH with comprehensive NILDA assessment, resmetirom was prescribed predominantly to middle-aged adults with a high burden of metabolic comorbidities. It demonstrated good tolerability with strong treatment retention. At 12 months, treatment was associated with early improvements in noninvasive markers of liver disease severity and metabolic health. This is consistent with the results of the published phase 3 trial. Planned multivariable analyses adjusting for age, sex, GLP-1 receptor agonist use, diabetes status, and baseline fibrosis stage will further clarify predictors and the magnitude of treatment response.

Table 1: Treatment response outcomes

Median (Q1, Q3)	T1: Baseline (N=70)	T2: 12 months (N=50)	Diff (Δ)	p-value
LSM (KPa)	9.5 (8.3, 11.2)	7.2 (6.1, 8.8)	**-1.3** (-2.3, -0.5)	0.014
N	62	27	26	
ALT (U/L)	47.5 (30.0, 71.0)	37.0 (23.0, 49.0)	**-6.0** (-21.0, 4.0)	0.004
N	70	43	43	
ELF	9.6 (9.2, 10.1)	9.1 (8.8, 9.8)	0.0 (-0.1, 0.2)	0.688
N	31	8	6	
FAST score	0.5 (0.4, 0.6)	0.3 (0.2, 0.4)	**-0.2** (-0.3, 0.0)	0.009
N	56	25	20	
CAP (dB/m^2)	313.0 (274.5, 345.5)	268.0 (239.0, 326.0)	**-34.5** (-82.0, 13.0)	0.015
N	56	27	22	
FIB-4	1.6 (1.1, 2.3)	1.5 (1.1, 2.2)	-0.1 (-0.3, 0.2)	0.18
N	69	41	41	
MRE (kPa)	3.5 (3.1, 4.1)	3.7 (2.5, 4.2)	0.1 (-0.3, 0.3)	1.00
N	18	11	8	
HbA1C (%)	6.0 (5.4, 6.6)	6.1 (5.4, 6.9)	-0.1 (-0.4, 0.2)	0.423
N	64	23	23	
Triglycerides (mg/dL)	158.0 (114.0, 217.0)	84.0 (52.0, 147.5)	**-40.5** (-68.9, -6.5)	0.003
N	61	24	24	
LDL (mg/dL)	74.0 (55.0, 106.0)	55.0 (43.5, 74.0)	**-12.0** (-33.0, -6.0)	<0.001
N	59	24	24	
HDL (mg/dL)	45.0 (37.0, 55.0)	46.0 (40.3, 53.5)	0.0 (-4.5, 6.0)	0.813
N	61	24	24	
BMI (kg/m^2)	33.7 (29.7, 37.1)	30.9 (26.7, 34.4)	**-0.9** (-2.8, 0.3)	0.002
N	70	46	46	

LSM = Liver Stiffness Measurement, ELF = Enhanced Liver Fibrosis, CAP = Controlled Attenuation Parameter, MRE = Magnetic Resonance Elastography HbA1c = Hemoglobin A1c, LDL = Low Density Lipoprotein, HDL = High Density Lipoprotein, BMI = Body Mass Index

Table 1: Unadjusted paired treatment response outcomes to resmetirom at 12 months. P-values calculated by the Wilcoxon signed rank test. P-value significance is defined by <0.05.

Disclosures: Larissa Lushniak:Nothing to Disclose, Chukwuemeka Oko:Nothing to Disclose, Alice Parish:Nothing to Disclose, Donna Niedzwiecki:Toray

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3502 | BASELINE DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF PATIENTS RECEIVING RESMETIROM, GLP-1 AGONIST, AND COMBINATION THERAPY FOR MASH: A REAL-WORLD U.S. CLAIMS ANALYSIS

Anthony Yu[1] Zulkarnain Pulungan[1] Gabrielle Miller[1], [1]Inovalon

Background: Following approval of resmetirom (Rezdiffra), limited evidence exists describing real-world utilization patterns among patients with metabolic dysfunction-associated steatohepatitis (MASH). This study evaluated demographic and clinical characteristics of patients initiating Rezdiffra, glucagon-like peptide-1 receptor agonists (GLP-1 RAs), including semaglutide (Wegovy), and combination therapy in a large U.S. claims database. **Methods:** This retrospective study utilized de-identified claims data from the Inovalon MORE² Registry from March 1, 2023 to March 31, 2026. Patients with a MASH diagnosis code receiving Rezdiffra and/or GLP-1 therapy and ≥12 months continuous enrollment prior to first treatment claim were included. Patients were grouped into three mutually exclusive cohorts: Rezdiffra monotherapy, Rezdiffra with concomitant GLP-1 therapy, and GLP-1 monotherapy. Wegovy users were evaluated as subgroups within GLP-1-containing cohorts. Baseline demographics, comorbidities, and liver-specific diagnostic procedures were assessed descriptively. **Results:** Among 6,504 eligible Rezdiffra-treated patients, 3,541 (54.4%) received Rezdiffra monotherapy and 2,963 (45.6%) received concomitant GLP-1 therapy. Of all Rezdiffra-treated patients, 364 (5.6%) received concomitant Wegovy. Among 260,943 eligible GLP-1 monotherapy users, 37,643 (14.4%) received Wegovy.Rezdiffra monotherapy patients were older than GLP-1 monotherapy patients (mean age: 53.6 vs 51.4 years). Females predominated across cohorts, highest among dual-therapy users (69.0%). Dual-therapy patients demonstrated higher comorbidity burden than monotherapy cohorts. Obesity prevalence was 77% in the dual-therapy cohort versus 60% in the Rezdiffra monotherapy cohort and 71% in the GLP-1 monotherapy cohort. T2DM prevalence was 82%, 35%, and 75%, respectively.Baseline liver disease assessment was substantially more common in Rezdiffra-containing cohorts than GLP-1 monotherapy cohorts. Liver elastography was performed in 69.0% of Rezdiffra monotherapy patients and 69.7% of dual-therapy patients versus 7.2% of GLP-1 monotherapy patients. Liver biopsy was observed in 11.4%, 10.5%, and 0.8% of patients, respectively. ELF testing and magnetic resonance elastography followed similar patterns. **Conclusion:** Adoption of FDA-approved combination therapy with Rezdiffra and Wegovy remains limited, with only 5.6% of Rezdiffra-treated patients receiving concomitant Wegovy. Combination therapy use appears concentrated among patients with substantial cardiometabolic comorbidity burden. Rezdiffra-treated patients demonstrated substantially greater utilization of liver-specific diagnostic procedures than GLP-1-treated patients, highlighting potential differences in care pathways and the need for broader implementation of non-invasive liver disease assessment strategies in routine clinical practice.

Disclosures: Anthony Yu:Nothing to Disclose, Zulkarnain Pulungan:Nothing to Disclose, Gabrielle Miller: Nothing to Disclose.

3503 | GLP-1 RECEPTOR AGONIST USE AND HISTOLOGIC MASH SEVERITY DISCORDANT FROM NON-INVASIVE TESTING: A SINGLE-CENTER OBSERVATIONAL COHORT

Joseph Scaravalle[1] Nicholas Kruzdlo[2] Elisabeth Verwest[2] Stephanie Oliveros Diaz[2] Lily Lu[2] Kirsten Hobson[2] Cameron Rolph[2] Isabelle Crotsley[2] Yovanni Rosario[2] Raymond Bell[2] Guy Neff[2], [1]Covenant Metabolic Specialists LLC, [2]Covenant Metabolic Specialists, LLC

Background: Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have demonstrated therapeutic potential in metabolic dysfunction-associated steatohepatitis (MASH), though real-world histologic data remains limited when controlling for noninvasive testing. We evaluated whether GLP-1 RA use was independently associated with lower odds of biopsy-confirmed MASH with significant fibrosis after adjustment for FibroScan, demographic, and metabolic covariates. **Methods:** We retrospectively analyzed patients screened for a MASH clinical trial who completed FibroScan and liver biopsy within 90 days. Study eligibility was defined as biopsy-confirmed MASH with a NAFLD Activity Score (NAS) ≥4 and fibrosis stage F2–F3. Patients with cirrhosis (F4 fibrosis) were excluded. Covariates included age, sex, body mass index (BMI), FibroScan controlled attenuation parameter (CAP), liver stiffness measurement (LSM), and type 2 diabetes mellitus (T2D). GLP-1 RA exposure was

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defined as continuous use for at least 6 months prior to the index visit with ongoing therapy at biopsy. The outcome of interest was biopsy-confirmed MASH meeting trial criteria (NAS $\geq$4, F2-3). **Results:** After excluding 18 patients with F4 fibrosis, 83 patients met inclusion criteria, including 11 receiving GLP-1 RA therapy. Baseline FibroScan parameters were comparable between groups (avg CAP 322.1 vs 329.6, p = 0.54; avg LSM 12.2 vs 12.3 kPa, p = 0.95), as were age and BMI; T2D prevalence differed significantly (100% vs 51%, p < 0.001). After adjustment for CAP, LSM, BMI, T2D, age, and sex, GLP-1 RA use was independently associated with lower odds of meeting biopsy criteria (OR 0.07, 95% CI 0.007–0.67, p = 0.021). Male sex was also associated with lower odds (OR 0.36, 95% CI 0.13–0.95, p = 0.040). Age, T2D status, CAP, LSM, and BMI were not significantly associated with the outcome. **Conclusion:** In this single-center retrospective cohort, GLP-1 RA use was associated with lower odds of biopsy-confirmed MASH with significant fibrosis, even among patients with comparable FibroScan CAP and LSM (OR 0.07, 95% CI 0.007–0.67). Given the small exposure group (n = 11) and unmeasured confounders including A1c and weight-loss trajectory, these findings are hypothesis-generating. If confirmed, they suggest non-invasive parameters may underestimate histologic response to GLP-1 therapy and support prospective investigation.

Multivariable Logistic Regression Results

Chi Square= 16.5935, df= 7, p-value= 0.0202

Variable	Coefficient	Standard Error	p-value	Odds Ratio	95% Confidence Interval
Sex	-1.0351	0.503	**0.0396**	0.3552	(0.1325, 0.9520)
Age	0.0007	0.0228	0.9769	1.0007	(0.9569, 1.0465)
T2D	0.2542	0.5535	0.646	1.2894	(0.4358, 3.8153)
CAP	0.0092	0.0071	0.1987	1.0092	(0.9952, 1.0234)
LSM (kPa)	0.0777	0.0536	0.1471	1.0808	(0.9730, 1.2005)
BMI	0.0072	0.0455	0.8747	1.0072	(0.9213, 1.1011)
GLP1	-2.679	1.1642	**0.0214**	0.0686	(0.0070, 0.6722)
Constant	-3.9217	2.8017	0.1616		

Baseline Table

Variable	GLP-1 (n=11)	Non-GLP-1 (n=72)	p-value
Avg Age	58.818	55.778	0.166
%Male	36.4%	47.2%	0.517
Avg CAP	322.091	329.556	0.542
Avg LSM (kPa)	12.200	12.296	0.951
% T2D	100%	51.4%	**7.264E-12**
Avg BMI	38.638	38.669	0.987

Disclosures: Joseph Scaravalle:Nothing to Disclose, Nicholas Kruzdlo:Nothing to Disclose, Elisabeth Verwest:Nothing to Disclose, Stephanie Oliveros Diaz: Nothing to Disclose, Lily Lu:Nothing to Disclose, Kirsten Hobson:Nothing to Disclose, Cameron Rolph: Nothing to Disclose, Isabelle Crotsley:Nothing to Disclose, Yovanni Rosario:Nothing to Disclose, Raymond Bell:Nothing to Disclose, Guy Neff:Nothing to Disclose.

3504 | PUTTING MASH ON PRIMARY CARE'S RADAR: FINDINGS FROM AN EDUCATIONAL ACTIVITY ON SCREENING AND MANAGEMENT

Jaime Symowicz[1] Amy Corum[1] Jay Shubrook[2] Naim Alkhouri[3], [1]Med-IQ, [2]Touro University California College of Osteopathic Medicine, [3]Clinical Research Institute of Ohio

Background: More than 95% of patients with or at high risk of developing metabolic dysfunction–associated steatohepatitis (MASH) are seen in primary care settings. Although many primary care professionals (PCPs) recognize that MASH incidence is increasing, they do not have a clear understanding of their role. To address these gaps, we designed an online educational activity that allowed clinicians to work through recommended risk stratification pathways for screening and management. **Methods:** This educational activity comprised 2 modules; the first focused on applying screening pathways for primary and secondary fibrosis risk stratification in patients with MASH risk factors, and the second addressed selecting MASH management strategies based on patients' fibrosis risk stratification and comorbidities. Rich media assets were integrated to improve the learner experience and were combined with data tracking to reveal insights about knowledge gaps and practice behaviors. Faculty experts then presented guidance and supporting evidence. **Results:** To date, 1,050 learners participated in the activity, with 602 claiming CE credit. Learners more frequently recognized patients who were candidates for MASH screening (87%; n = 1,015) than those who were not (51%; n = 1,174). They also spent less time in the case scenario for a patient who was a candidate for MASH screening (31 vs 50 seconds). During the education, 40% and 27% of learners correctly identified an ELF blood test and VCTE, respectively, as appropriate follow-up testing for a patient with a high-risk FIB-4 (n = 958 nonunique responses). Notably, 86% of learners correctly identified a high-risk patient as needing referral to gastroenterology/hepatology (n = 964). When asked about their practice settings, only 28% had access to an EHR system that prompted them to calculate FIB-4 scores and order additional testing for secondary risk stratification; only 30% had access to transient elastography (n = 599). Learners took ~56 seconds to select a care plan for a patient with stage F3 fibrosis, hypertension, obesity, and dyslipidemia. They recommended pioglitazone, resmetirom, and semaglutide at similar frequency prior to the FDA approval of semaglutide for MASH. Following the FDA approval, they recommended resmetirom and semaglutide at greater frequency than pioglitazone. Postactivity competence gains were observed in recognizing

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appropriate initial fibrosis risk stratification, follow-up testing, and management strategies. Lastly, 29% of learners (n = 609) planned to make changes; the top 3 were increasing screening, increasing use of FIB-4 tool, and starting treatment. **Conclusion:** This educational activity used an engaging format to increase PCPs' knowledge and competence related to risk stratification pathways for screening and managing MASH, while also uncovering additional educational needs and practice barriers.

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3505 | HEPATIC STEATOSIS REDUCTION WITH GLP-1 AND LIFESTYLE-MEDIATED WEIGHT LOSS IN MASLD/MASH: A RETROSPECTIVE CONTROLLED ATTENUATION PARAMETER (CAP) SCORE ANALYSIS

Nicholas Kruzdlo[1] Joseph Scaravalle[1] Stephanie Oliveros-Diaz[1] Elisabeth Verwest[1] Kirsten Hobson[1] Isabelle Crotsley[1] Lily Lu[1] Raymond Bell[1] Cameron Rolph[1] Yovanni Rosario[1] Guy Neff[1], [1]Covenant Metabolic Specialists

Background: Weight loss is a fundamental intervention for the management of Metabolic Dysfunction Associated Steatotic Liver Disease (MASLD) and Metabolic Dysfunction Associated Steatohepatitis (MASH). GLP-1 receptor agonists offer an effective pharmacologic pathway to weight loss alongside traditional lifestyle modifications. Prior studies have demonstrated hepatic fat reduction with GLP-1 use, but none have directly compared equivalent weight loss achieved pharmacologically versus through lifestyle modification alone. The independent contribution of the GLP-1 mechanism to hepatic steatosis reduction remains unclear. The minimum % body weight loss threshold required for statistically significant hepatic steatosis reduction in a real-word MASLD/MASH population also remains undefined. We sought to identify this threshold and determine if steatosis outcomes differ between GLP-1 and lifestyle mediated weight loss using CAP score. **Methods:** A retrospective cohort of 200 patients with baseline and follow-up FibroScan, body weight, demographic, and medication data collected 11–36 months apart (mean 19.6 months, comparable across cohorts) was identified, excluding patients who underwent bariatric surgery, or received investigational MASH therapies. 70 additional patients were then excluded due to weight gain, resulting in a final analytic cohort of 130 patients with 0–24.2% body weight loss. Patients were stratified into five weight loss strata: 0–2.49% (reference), 2.5–4.99%, 5–8.99%, 9–12.49%, and ≥12.5%. GLP-1 use was defined as documented use for ≥ 3 months. Multivariable linear regression modeled CAP changes against weight loss category, GLP-1 use, age, sex, baseline CAP, and follow-up duration. Interaction terms were included to evaluate modality effects on CAP reduction. **Results:** Significant CAP reductions occurred at 9–12.49% and ≥12.5% weight loss versus the reference group. Weight loss below 9% did not produce significant CAP reduction. Baseline CAP independently predicted degree of change. Both GLP-1-treated (n = 55) and lifestyle-only (n = 75) subgroups demonstrated significant reductions at ≥9% weight loss. GLP-1 interaction terms were non-significant across all strata (all $p > 0.05$), indicating no significant difference in CAP reduction between modalities. **Conclusion:** Weight loss exceeding 9% was associated with a significant predicted CAP reduction of ~60 dB/m, consistent with a clinically meaningful one-grade histologic steatosis improvement based on biopsy-validated CAP thresholds. Hepatic steatosis reduction appeared comparable between modalities, suggesting weight loss magnitude, rather than modality, may be the primary determinant of hepatic steatosis improvement. These findings support targeting ≥9% body weight loss in MASLD/MASH patients, with similar steatosis benefits anticipated whether achieved pharmacologically or through lifestyle intervention alone.

Table 1. Multivariable Linear Regression — Predictors of Change in CAP Score (dB/m)

Negative coefficients indicate reduction in hepatic steatosis (improvement). N = 130.

Weight Loss Cohort (reference: 0 – 2.49% body weight loss)

Variable	Cohort (n)	Coefficient	95% CI	p-value
0 – 2.49% Weight Loss (reference group)	47	—	—	—
2.50 – 4.99% Weight Loss	21	+2.51	−23.2, 28.3	0.847
5.00 – 8.99% Weight Loss	22	−10.57	−40.0, 12.9	0.373
9.00 – 12.50% Weight Loss	17	**−77.24**	−110.6, −43.9	**< 0.001**
> 12.51% Weight Loss	23	**−58.17**	−88.6, −27.5	**< 0.001**
Significant Covariate				
Baseline CAP score	130	**−0.45**	−0.63, −0.28	**< 0.001**

1.) Reference group: patients with 0 – 2.49% body weight loss were the omitted comparator category.

2.) Model adjusted for: baseline CAP, age, sex, months between initial visit and follow up, and GLP-1 agonist use (yes/no).

3.) Interaction terms (WL category × GLP-1 use) were tested for all four WL cohorts and were non-significant across all groups (all p > 0.05).

4.) CAP = controlled attenuation parameter. A negative coefficient indicates reduction in hepatic steatosis.

Table 2. Cohort Breakdown by GLP-1 Agonist Use and Lifestyle Intervention

Cohort	Total Population (n)	GLP-1 Use (n)	Lifestyle (n)
0 – 2.49% Weight Loss (reference group)	47	11	36
2.50 – 4.99% Weight Loss	21	10	11
5.00 – 8.99% Weight Loss	22	8	14
9.00 – 12.50% Weight Loss	17	11	6
> 12.51% Weight Loss	23	15	8
Total	130	55	75

GLP-1 = glucagon-like peptide-1 agonist. Lifestyle mediated population reflects patients who achieved weight loss through diet and lifestyle modification without GLP-1 pharmacotherapy.

Disclosures: Nicholas Kruzdlo:Nothing to Disclose, Joseph Scaravalle:Nothing to Disclose, Stephanie Oliveros-Diaz:Nothing to Disclose, Elisabeth Verwest: Nothing to Disclose, Kirsten Hobson:Nothing to Disclose, Isabelle Crotsley:Nothing to Disclose, Lily Lu: Nothing to Disclose, Raymond Bell:Nothing to Disclose, Cameron Rolph:Nothing to Disclose, Yovanni Rosario: Nothing to Disclose, Guy Neff:Nothing to Disclose.

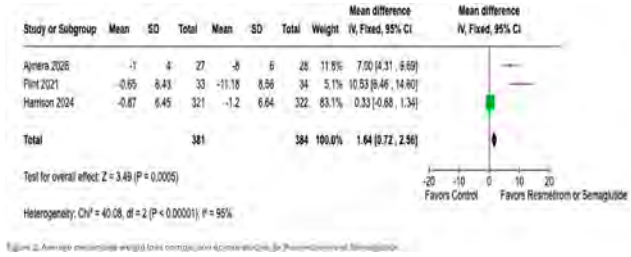
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3506 | METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS SYSTEMATIC REVIEW: FROM DIAGNOSIS TO NEWEST AVAILABLE MEDICATIONS AND OUTCOMES, TWO AGENTS ARE BETTER THAN ONE

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Background: Metabolic dysfunction–associated steatotic liver disease (MASLD) is a growing public health and economic challenge. A subset of patients can progress to metabolic dysfunction–associated steatohepatitis (MASH), a more advanced inflammatory phenotype associated with progressive fibrosis and hepatocellular injury. In this study, we aim to evaluate the efficacy of Resmetirom and glucagon-like peptide-1 (GLP-1) medications in the treatment of MASH. **Methods:** A literature review was conducted across PubMed and ClinicalTrials.gov through April 2026. Randomized controlled trials in phase 3 or higher, case reports, and retrospective studies were included. The primary outcomes investigated were improvement of transaminase levels, improvement in lipid levels, weight loss, side effects, improvement in fibrosis achieved by kilopascal (Kpa), and improvement in steatosis based on Controlled Attenuation Parameter (CAP) score. **Results:** Seven studies with 1766 total patients [GU1] were included. The percentage change in median for aminotransferase levels ranged from –23.07% to –58.5% in treatment groups and –9% to –16.51% in control groups. The percentage change in median for low density lipoprotein ranged from –3.41% to –33.7% in treatment groups and –13% to –16.47% in control groups. The percentage change in median for triglycerides ranged from –13% to –21.83% in treatment groups and –9% to –14.17% in control groups. The treatment groups showed significant improvements in weight loss ($p = 0.0005$). Treatment groups showed statistically significant increased rates of nausea and vomiting ($p < 0.05$). [GU2] The percentage change in median Kpa ranged from –9.86% to –22.64% in treatment groups and –7.86% to –22.4% in control groups. The percentage change in median CAP score ranged from –6% to –17.75% in treatment groups and –10.85% in a control group. **Conclusion:** Dual therapy with Resmetirom and GLP-1 agonist showed better improvement in metabolic risk factors, including improvement in cholesterol level, triglyceride level, and weight loss, which were statistically significant when compared to single agent.



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3507 | REAL WORLD PRACTICE AND ATTITUDES TOWARDS TREATING ELIGIBLE AT-RISK MASH PATIENTS WITH RESMETIROM IN AN URBAN SETTING

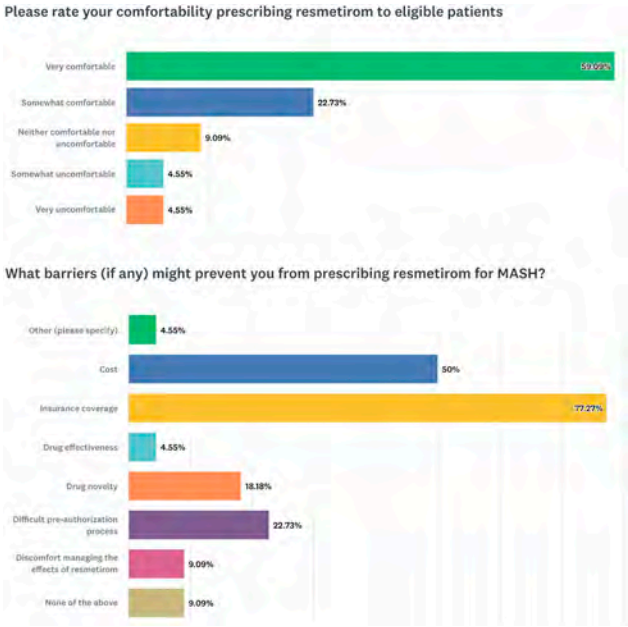
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Background: Metabolic dysfunction associated steatohepatitis (MASH) is a growing public health concern. Curbing its impact requires early identification, risk stratification, and prompt treatment. In 2024, the FDA approved resmetirom for treatment of at-risk MASH patients identified through non-invasive testing (NIT). In this study, we examined the practice and attitudes towards resmetirom prescription for at-risk patients identified through ultrasound elastography in an urban U.S. city. **Methods:** Patient data, including NIT, was collected across community-based centers in North Carolina's Research Triangle Area between March 2025 and March 2026. Ultrasound elastography was used to identify at-risk patients who were eligible for resmetirom. Electronic health records were cross-referenced to determine whether at-risk patients were prescribed resmetirom.To understand physician attitudes towards resmetirom prescription, an eight-question survey was designed and distributed. Responses were received from twenty-three practicing physicians across the community-based centers. The survey asked how physicians treat MASH patients, their comfortability prescribing resmetirom, and their likelihood of

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prescribing resmetirom in the future. **Results:** A total of 489 ultrasound elastography exams were conducted over the 12 months described above. Of those scans, 145 patients were found to have a fibrosis stage of F2 or F3. Of those eligible MASH patients, 38 (26%) were prescribed resmetirom.Seven in ten (70%) physicians report prescribing resmetirom for MASH patients in the past year, and half of those somewhat or strongly agree that the quality of life of those patients has improved. The most frequently cited attractive attributes of resmetirom as a prescribing physician were the lack of side effects and tolerability of the treatment (35%), its ability to reverse fibrosis (30%), and its ease of use as a once-daily pill (26%).The majority (59%) of responding physicians report being very comfortable prescribing resmetirom to eligible patients. The most commonly cited barriers to resmetirom prescription were insurance coverage (77%), cost (50%), the difficult preauthorization process (23%), and drug novelty (18%). Four in five (77%) physicians reported being very likely to prescribe resmetirom for MASH over the next year. **Conclusion:** Roughly three-quarters (74%) of eligible patients were not prescribed resmetirom. Despite physician comfort and reported likelihood of prescribing resmetirom, various administrative and structural factors, including insurance coverage, cost, and the required preauthorization process, may serve as barriers to the medication's prescription.Increased prescriber education and improved authorization services are essential to ensure that all eligible patients receive treatment.Future studies should examine the effectiveness of interventions on resmetirom prescription patterns.



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3508 | REAL-WORLD CHARACTERISTICS, TREATMENT PATTERNS, AND CLINICAL OUTCOMES AMONG PATIENTS WITH MASH INITIATING RESMETIROM

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Background: Resmetirom is the first FDA-approved therapy for adults with noncirrhotic metabolic dysfunction-associated steatohepatitis (MASH) and moderate-to-advanced fibrosis. Although MAESTRO-NASH demonstrated histologic benefit, real-world data remain limited. This study characterized patients initiating resmetirom in US clinical practice and evaluated 6- and 12-month changes in biochemical and noninvasive liver measures. **Methods:** This retrospective cohort study used deidentified Trio Health EMR data covering over 75 million lives across the United States, 2 out of 3 data sources are represented here. Adults with at least one resmetirom prescription from March 14, 2024 to January 21, 2026 were included; the first prescription served as the index date. Continuous healthcare engagement during the 12-month baseline period was required, defined as at least one encounter, observation, or medication request in each 6-month interval. Patients with advanced liver disease or other causes of chronic liver disease during baseline were excluded. Effectiveness outcomes included changes in structured biomarkers and noninvasive liver measures; VCTE-derived measures were extracted from progress notes using natural language processing. Paired changes from baseline to 6 and 12 months (+/- 90 days) were assessed using Wilcoxon signed-rank tests, with $p < 0.05$ considered statistically significant. **Results:** Overall, 4,886 patients met study criteria (mean age 59.1 years; 60.3% female; 67.6% White). Common baseline comorbidities included type 2 diabetes (45%), obesity (53.9%), dyslipidemia (61.5%), and hypertension (61.8%). GLP-1 receptor agonist use was observed in 28.4% of patients at baseline and 27.4% during follow-up. Among patients with available paired data, resmetirom initiation was associated with clinically meaningful improvements in liver enzymes, lipids, and noninvasive fibrosis/steatosis measures (Table). At 6 and 12-months, respectively, 40.6% and 45.8%

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achieved at least a 20% ALT decrease. FAST decreased by at least 0.22 units in 36.2% and 43.6% of patients, and CAP decreased by at least 40 dB/m in 43.4% and 54%. LSM decreased by at least 25% in 36.5% and 45.5% of patients and by at least 30% in 29.8% and 38.6%. Among patients with F-scores recorded at baseline and 12 months after resmetirom initiation (n = 128 for F-score), at least 1-stage improvement was observed in 36.7%, and at least 2-stage improvement was observed in 23.4%. **Conclusion:** In this large US real-world cohort, resmetirom-treated patients demonstrated early 6- and 12-month improvements in biomarkers and noninvasive measures of fibrosis and steatosis. These findings support the emerging real-world effectiveness of resmetirom, although longer follow-up and analyses accounting for missing paired assessments are needed to confirm durability and clinical impact.

Measurement	Timepoint	N	Baseline Median (IQR)	Median at Timepoint (IQR)	Median Change (IQR)	Median % Change (IQR)
ALT (U/L)	6 Months	1228	45 (29, 69)	37 (25, 56)	-4 (-20, 7)*	-10.3 (-35.6, 21.2)
	12 Months	475	48 (29, 69)	36 (25, 51.5)	-6 (-23, 5)*	-15.35 (-42.1, 15)
AST (U/L)	6 Months	1013	35 (25, 52)	31 (24, 43)	-2 (-12, 5)*	-5.3 (-30, 20.7)
	12 Months	394	36 (25, 53)	32 (23, 42)	-3 (-14, 4)*	-9.1 (-35.9, 16.7)
Triglycerides (mg/dL)	6 Months	643	154 (108, 210)	119 (87, 167)	-26 (-67.5, 7.5)*	-19.3 (-39.3, 7.2)
	12 Months	250	147.5 (105, 201)	107 (81.5, 164.5)	-26.5 (-99.8, -0.3)*	-22.5 (-39.5, -0.2)
Cholesterol (mg/dL)	6 Months	650	161.5 (136, 193)	142 (117, 172.8)	-18 (-37, 3)*	-11.5 (-22.6, 1.7)
	12 Months	251	164 (139, 191)	144.5 (117.8, 173)	-17 (-38.5, 1)*	-9.5 (-22.5, 0.9)
LDL (mg/dL)	6 Months	434	88 (64, 115)	74 (51.5, 98)	-11 (-29, 4)*	-14.2 (-30.2, 6.4)
	12 Months	158	91 (67.3, 113)	72.5 (52, 90)	-14 (-30.5, 3.8)*	-14.55 (-32.8, 6.3)
HDL (mg/dL)	6 Months	497	42 (35, 50)	42.9 (36, 51)	0 (-4, 3)	0 (-9.4, 11.8)
	12 Months	185	43 (37, 51)	44 (37, 53)	1 (-3, 5)	2.8 (-8.3, 13.3)
Platelet count	6 Months	984	238.5 (196, 283)	234 (195, 282)	-2 (-24, 17)*	-1 (-10, 7.6)
	12 Months	403	239 (198, 285.5)	235 (195.5, 286.5)	-2 (-25, 20.5)	-0.8 (-11.3, 9.3)
FIB-4	6 Months	607	1.3 (0.9, 1.9)	1.3 (0.9, 1.8)	0 (-0.2, 0.2)	-0.3 (-16.8, 18.2)
	12 Months	295	1.3 (0.9, 1.9)	1.3 (0.9, 1.8)	0 (-0.3, 0.2)	-0.2 (-20.8, 19.8)
FAST	6 Months	47	0.5 (0.4, 0.7)	0.3 (0.1, 0.5)	-0.2 (-0.3, 0)*	-30.5 (-54.2, -5.2)
	12 Months	39	0.5 (0.3, 0.6)	0.3 (0.1, 0.5)	-0.1 (-0.3, 0)*	-41.2 (-72.8, -0.7)
LSM (kPa)	6 Months	104	9.6 (7.7, 11.5)	7.3 (5.4, 10.1)	-1.4 (-3.7, 0)*	-12.7 (-37.5, 0)
	12 Months	88	9.9 (8.1, 13.9)	7.3 (5.3, 10.4)	-1.7 (-4, 0.1)*	-22.6 (-44.1, 1.9)
CAP (dB/m)	6 Months	76	317 (295.3, 348)	279 (234.3, 316.3)	-33 (-63.3, 0)*	-10.6 (-19.4, 0)
	12 Months	63	314 (285.5, 356)	262.5 (228, 305.3)	-49 (-85, -21.5)*	-15.3 (-25.5, -6.7)

Table. Changes at 6 and 12 months followup compared to baseline among patients with available data who were prescribed resmetirom
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CAP, controlled attenuation parameter; FIB-4, Fibrosis-4 index for liver fibrosis; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LSM, liver stiffness measurement.
*The Wilcoxon signed-rank test showed a statistically significant difference between paired measurements ($p < 0.05$).

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3509 | THE IMPACT OF MASLD PHARMACOTHERAPY ON ESTIMATED CARDIOVASCULAR RISK: A PREVENT SCORE ANALYSIS OF RESMETIROM AND GLP-1–BASED THERAPY

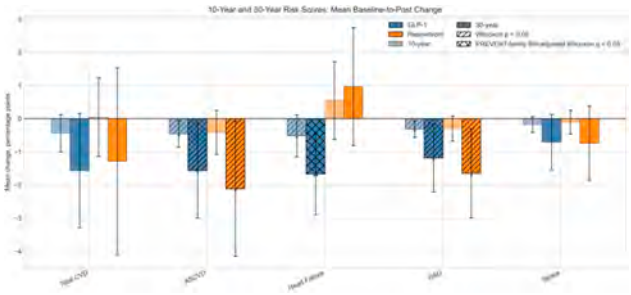
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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is associated with a 1.5-fold increased cardiovascular disease risk. Resmetirom and semaglutide are approved for F2-F3 MASH. These therapies have been evaluated using selected cardiometabolic risk factors, but impact on integrated estimated cardiovascular risk has not been standardized. We applied the 2023 AHA PREVENT equations, recently developed race-free tools estimating 10- and 30-year overall cardiovascular, ASCVD, and heart failure risk, to evaluate risk changes among patients with MASLD treated with resmetirom or GLP-1 therapy. **Methods:** We conducted a retrospective multicenter cohort study of patients with MASLD treated with approved therapy. Patients were included if they received resmetirom for $\geq$12 months or semaglutide 2.4 mg weekly for $\geq$3 months. Liver, cardiometabolic, and PREVENT risk data were collected at baseline and post-therapy follow-up. Paired changes were assessed using Wilcoxon signed-rank and paired t-tests; between-group differences used Mann-Whitney and Welch t-tests. Benjamini-Hochberg correction was applied, with a heart-failure-specific sensitivity correction. **Results:** We identified 25 resmetirom-treated and 73 GLP-1–treated patients. Paired PREVENT data were available for 16 and 38 patients, respectively, with median post-therapy follow-up of 409 and 106 days. As shown in Figure 1, GLP-1 therapy was associated with reductions across multiple PREVENT estimates, with the strongest signal for 30-year heart failure risk, which remained significant after correction. Resmetirom was associated with unadjusted reductions in long-term ASCVD and CAD risk and significant lipid reductions. Direct comparisons showed no significant differences in total CVD, ASCVD, CAD, or stroke risk change. GLP-1 therapy showed greater improvement in estimated heart failure risk than resmetirom in unadjusted analyses, persisting after sensitivity correction. Results are summarized in Figure 1 **Conclusion:** Using AHA PREVENT as a standardized cardiovascular risk framework, GLP-1–based therapy demonstrated the strongest improvement in estimated heart failure risk, while resmetirom showed greater reductions in estimated ASCVD and CAD risk. These

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findings suggest comorbidity profiles may help guide MASLD pharmacotherapy selection, including adjunctive or combination approaches when cardiovascular risk modification is a priority. Larger cohort studies are needed to confirm these preliminary findings.



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3510 | HUMANIZING DYSLIPIDEMIA IN MASH: A PCSK9-DRIVEN DYSLIPIDEMIA GAN DIO MASH MODEL

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Background: Dyslipidemia, characterized by hypercholesterolemia and hypertriglyceridemia, is a central component of metabolic dysfunction-associated steatohepatitis (MASH) pathogenesis. While being highly instrumental in drug development, preclinical models of MASH often fail to recapitulate a human-like lipoprotein profile. To enhance translational relevance, the present study aimed to establish a humanized dyslipidemia profile in the GAN diet-induced obese (DIO) mouse model of MASH through AAV-mediated PCSK9 overexpression. **Methods:** Male C57BL/6 mice were fed the GAN diet (high fat, fructose, and cholesterol) for 39 weeks prior to study start. Only mice with biopsy-confirmed MASH (NAFLD Activity Score (NAS) ≥ 5) and fibrosis (stage F2-F3) were included and stratified into treatment groups (n = 18 pr. group). One week after single AAV-PCSK9 injection, GAN DIO-MASH mice were administered (SC) vehicle, semaglutide (GLP-1 receptor agonist, 30 nmol/kg, once daily), efruxifermin (FGF21 analogue. (EFX, 1 mg/kg, biweekly), or alirocumab (PCSK9 inhibitor, 10mg/kg) for 8 weeks. Endpoints included plasma lipid biochemistry. **Results:** AAV-PCSK9 GAN DIO-MASH mice exhibited markedly elevated circulating levels of LDL-cholesterol, total cholesterol, and triglycerides compared with chow-fed mice and AAV-CAG GAN DIO-MASH controls. MASH severity remained stable throughout the study period in AAV-PCSK9 GAN DIO-MASH mice. Semaglutide, EFX, and alirocumab all significantly improved LDL hypercholesterolemia and hypertriglyceridemia. Semaglutide and EFX additionally reduced HDL-cholesterol levels, whereas alirocumab increased HDL-cholesterol levels. **Conclusion:** AAV-mediated PCSK9 overexpression in the GAN DIO-MASH mouse model induces a robust, human-relevant dyslipidemic phenotype characterized by LDL hypercholesterolemia and hypertriglyceridemia. Pharmacological intervention with semaglutide, EFX, and alirocumab differentially improved the dyslipidemic profile. These findings highlight the utility of the AAV-PCSK9 GAN DIO-MASH mouse model for evaluating lipid-modulating therapies in MASH and support its translational relevance for therapeutic development.

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3511 | A MULTIMODAL NONINVASIVE APPROACH TO INITIATION AND MONITORING OF RESMETIROM THERAPY IN MASH - UPDATE

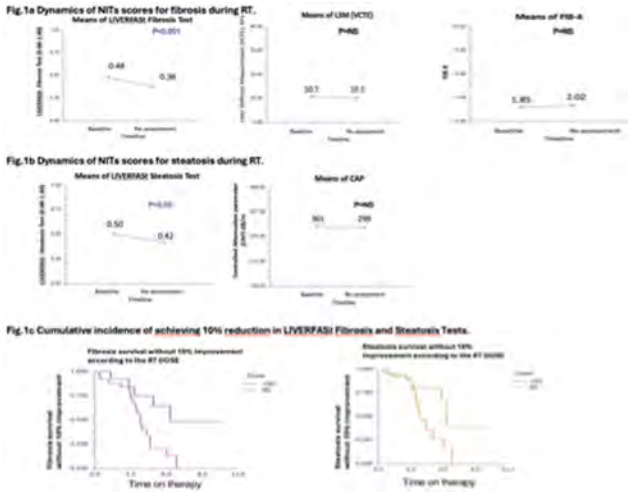
Mona Munteanu[1] Jeevin Sandhu[2] Shaheen Mehrara[3] Akash Pagadala[4] Ashwini Mehta[5] John Lee[6] Obinna Okolo[3] Parker Woods[3] Parvez Mantry[3], [1]Fibronostics US Inc., [2]Methodist Dallas Medical Center, [3]Methodist Dallas Medical Center, Liver Institute, Dallas, US, [4]University of Southern California, Los Angeles, US;, [5]Methodist Dallas Medical Center, Division of Hepatology, Dallas, Texas, US, [6]Fibronostics U.S., Inc, New Orleans, US

Background: LIVERFAST (Fibronostics US, Inc.) is a new blood-based NIT that assesses quantitatively fibrosis, activity, and steatosis. Aims: To assess the dynamics of LIVERFAST, FIB-4 and VCTE and CAP in monitoring patients on Resmetirom therapy (on-RT) [fibrosis/steatosis $\geq$ 10% regression rate (10%RR) from baseline to repeated NIT]. **Methods:** On-RT patients with baseline (t0) and repeated (t1) NITs have been included retrospectively. Statistics included Kaplan Meier non-parametric censored at 10% RR from t0, Tukey-Kramer Multiple-Comparison Test and subgroup analysis for dose/GLP-1 receptor agonists (GLP-1RA)

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analysis. **Results:** N = 147 Eligible patients without RT discontinuation, 62% 80mg-dose, 39%-male, 55%-T2D, 46% GLP-1RA, mean(se) age 62.4(1.3), BMI 33.7(0.7), ALT 44(4), FIB4 1.79(0.14). T0-prevalence of F2F3 were 61%(LFAST) and 44%(VCTE). Median (max) delays(mths) t0-to-t1 were 3.4(LFAST), 7.6 (VCTE) and 6.7(FIB4). 67pts. with t0-FIB4 had no change at t1, (1.85vs2.02), or AST (44vs36), platelets count (230vs224*10^9), all p = ns, and ALT (53vs40, p < 0.05). 30 pts had repeated VCTE (median t0-10.7 vs t1-10.1Kpa) and CAP (t0-301 vs t1-299dB/m), all p = ns regardless the dose or the association with GLP-1RA. 44pts achieved t1-LFAST with median scores (t0vst1): fibrosis (0.48vs0.38,p < 0.001), steatosis (0.50vs0.42, p < 0.05), activity (0.45vs0.42,p = ns), mainly in the 80mg group (n = 27) and in either groups of RT-alone or in combination to GLP-1RA for fibrosis (p < 0.05). LFAST-fibrosis 10%RR from t0 has been achieved more within 80mg-RT group than within 100mg-RT at 3 and 6mths, respectively: 23.8%vs20.7% and 79.2% vs37.5%, overall logrank p < 0.05). LFAST-steatosis 10%RR from t0 has been achieved more within 80mg-RT group (overall logrank p < 0.05). The significant decrease t0-to-t1 in the total cholesterol has neither impacted the ApolipoproteinA1 [131 vs 146mg/dl] or LFAST-fibrosis score. **Conclusion:** RT-Initiation based on NITs is efficient and allows further non-invasive monitoring. LIVERFASt is an efficient monitoring test that reflects histology remodeling and provides earlier insights into disease progression and RT response. A significant improvement (≥ 10%) in LIVERFASt fibrosis and steatosis scores have been observed after the 3rd month of RT mainly in the 80mg group. FIB-4 and VCTE/CAP scores showed limited change at reassessment.



Disclosures: Mona Munteanu:Fibronostics: Employee, Jeevin Sandhu:Nothing to Disclose, Shaheen Mehrara: Nothing to Disclose, Akash Pagadala:Nothing to Disclose, Ashwini Mehta:Nothing to Disclose, John Lee:Nothing to Disclose, Obinna Okolo:Nothing to Disclose, Parker Woods:Nothing to Disclose, Parvez Mantry:Nothing to Disclose.

3512 | TRANSLATIONAL EFFICACY VERSUS REAL-WORLD EFFECTIVENESS OF CHIGLITAZAR IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE: A SYSTEMATIC REVIEW AND NARRATIVE SYNTHESIS

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Background: Chiglitazar is a novel pan-peroxisome proliferator-activated receptor (PPAR) agonist that activates PPAR-α, -γ, and -δ to improve metabolic homeostasis and reduce hepatic lipid accumulation. Evaluating how controlled trial efficacy translates into heterogeneous real-world populations is essential to defining its therapeutic utility. **Objective:** To compare the clinical efficacy and real-world effectiveness of chiglitazar for hepatic steatosis and fibrosis in metabolic dysfunction-associated steatotic liver disease (MASLD). **Methods:** A systematic literature search identified prospective human studies evaluating chiglitazar in MASLD or metabolic dysfunction-associated steatohepatitis (MASH). Owing to heterogeneity in study designs and comparator strategies, findings were synthesised qualitatively using a narrative efficacy-effectiveness framework. **Results:** Two prospective studies met inclusion criteria: a Phase II randomized controlled trial (RCT) and a real-world observational cohort study.In the efficacy setting, 104 patients with MASLD, hypertriglyceridemia, and insulin resistance received chiglitazar 48 mg (n = 42), 64 mg (n = 41), or placebo (n = 21) for 18 weeks. MRI-PDFF showed marked dose-dependent reductions in liver fat content of -28.1% and -39.5% versus -3.2% with placebo (p < 0.05 and p < 0.001). Alanine aminotransferase decreased by -38.0 U/L and -51.5 U/L compared with -17.2 U/L in placebo-treated patients. Controlled attenuation parameter (CAP) values decreased by -13.7 dB/m and -20.5 dB/m versus +7.7 dB/m with placebo. However, liver stiffness measurements (LSM) did not significantly differ between groups.In the effectiveness setting, 235 patients with type 2 diabetes and MASLD received flexible-dose chiglitazar alongside background antidiabetic therapy. After 1:1 propensity score matching, 31 comparable patient pairs were analysed over 24 weeks. Chiglitazar produced greater

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CAP reduction than other glucose-lowering therapies (-28.38 vs. -16.74 dB/m; between-group difference -11.64 dB/m; P = 0.038). Benefits remained consistent across age, sex, BMI, and concomitant SGLT-2 inhibitor or GLP-1 receptor agonist use. Similar to the RCT, LSM changes did not significantly differ between treatment groups (P = 0.813). Safety profiles were favourable across both studies. **Conclusion:** Chiglitazar demonstrates a highly successful clinical translation from experimental efficacy to real-world effectiveness, successfully engineering substantial reductions in hepatic steatosis across both rigidly structured clinical trial cohorts and unselected, multi-morbid type 2 diabetes populations. Its therapeutic impact on the non-invasive regression of liver fibrosis is limited in the short term, indicating that longer follow-up windows are methodologically mandatory to confirm its true long-term antifibrotic potential.

Disclosures: Choudhary Ahmed Maqbool:Nothing to Disclose, Ubaid Ahmed:Nothing to Disclose, Rahul Falodia:Nothing to Disclose.

3513 | REAL-WORLD EFFECTIVENESS OF 1 YEAR OF RESMETIROM MONOTHERAPY IN AT-RISK METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS PATIENTS IN A COMMUNITY BASED HEPATOLOGY PRACTICE

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Background: Resmetirom, a selective thyroid hormone receptor-β agonist, has demonstrated histologic efficacy in the treatment of metabolic dysfunction–associated steatohepatitis (MASH). However, real-world data evaluating treatment response is limited. We aimed to assess hepatic and metabolic responses to resmetirom in a real-world MASH population treated for a minimum of one year using changes in NITs. **Methods:** We conducted a retrospective real-world study of adults with presumptive F2 or F3 MASH (at-risk MASH) treated with resmetirom in an outpatient hepatology practice. Patients who had completed at least one year of resmetirom therapy were included (n = 361). Patients on GLP-1 or GIP analog therapies were excluded from analysis. Liver disease activity and fibrosis were assessed at baseline and follow-up using NITs including serum aminotransferases, fibrosis scores (e.g., FIB-4, FAST), and vibration-controlled transient elastography (VCTE). Treatment response was defined as improvement in liver enzymes and percent changes in hepatic steatosis and fibrosis NITs. Secondary outcomes included changes in lipid parameters and resmiterom tolerability. **Results:** 361 patients who completed atleast 52 weeks of resmiterom were included (mean age 58 years; 47% male; mean BMI 39.7 kg/m²). 51.5% of patients had T2DM, 36.8% dyslipidemia, and 58.4% hypertension. After 52 weeks of treatment, 57.9% of patients had a one stage or greater reduction in liver fibrosis by VTCE. Mean reduction in VCTE kpa was 37.2%. Mean reduction in hepatic steatosis as measured by VCTE CAP was 29.1%. Decrease in hepatic inflammation at 52 weeks seen with mean reduction of AST and ALT 11.5 IU/L and 25.44 IU/L respectively. Total cholesterol reduced by a mean of 22.16 mg/dL, LDL cholesterol by 27.19 mg/dL, triglycerides by 71.6 mg/dL, and HDL increased by a 6.5 mg/dL after 52 weeks. Approximately 10% of patients discontinued therapy due to adverse events. **Conclusion:** In a real-world clinical setting, 52 weeks of resmetirom treatment was associated with significant improvements in hepatic fibrosis and steatosis, as well as multiple biochemical and cardiometabolic parameters in patients with at-risk MASH. Therapy was safe and well tolerated across a diverse patient population with multiple comorbidities. These findings support the efficacy of resmetirom in a real world patient population where NITs are routinely used to intiate and guide therapy.

Disclosures: Rida Nadeem:Boehringer Ingelheim: other, Anita Kohli:Nothing to Disclose, Richard Manch:Gilead: Speaking and Teaching, AbbVie: Speaking and Teaching, Intercept: Speaking and Teaching, Madrigal: Speaking and Teaching, Justin Reynolds:Madrigal: Speaking and Teaching, Novo Nordisk: Speaking and Teaching, Gilead: Speaking and Teaching, Ipsen: Speaking and Teaching, Ann Moore:Abbvie: Speaking and Teaching, Gilead: Speaking and Teaching, Ipsen: Speaking and Teaching, madrigal: Speaking and Teaching, Siemans: Consultant, GSK: Advisor, Tessa Janovsky:Nothing to Disclose, Jessica Omana Castaneda:Nothing to Disclose, Himanshi Kapoor:Nothing to Disclose, Abderrahman Benmaghnia:Nothing to Disclose, Saba Asadipour: Nothing to Disclose, Cody Chen:Nothing to Disclose, Noor Virk:Nothing to Disclose.

3514 | TREATMENT CONTINUITY WITH RESMETIROM: A REAL-WORLD STUDY OF ADHERENCE AND PERSISTENCE IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH)

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Background: MASH, a serious form of fatty liver disease linked to metabolic health problems (e.g., obesity, diabetes), is a leading cause of liver-related mortality and an increasing burden on healthcare systems globally. The United States (US) Food and Drug Administration (FDA) approved resmetirom (Rezdiffra®) in conjunction with diet/exercise for adults with MASH on 3/14/2024. Meaningful resmetirom clinical benefit is dependent on sustained persistence/adherence for ≥52 weeks. This study quantified the real-world persistence/adherence of resmetirom in a large, geographically representative administrative claims database. **Methods:** A retrospective cohort analysis was conducted using the McKesson Compile™ Multi-Payer Closed Claims ReadyData (captures 80 US payers [commercial, Medicare, Medicaid]). Adults ≥18 years who newly initiated resmetirom between 3/14/24-2/28/25 were identified (first paid prescription with non-zero days supply = index date). New users were required to have continuous enrollment in both the 12-month pre- and post-index periods. Exclusion criteria included ICD-10 codes indicative of liver cirrhosis or alternative causes of liver disease (or related complications/conditions) during the 12-month pre-index period or missing demographic data. Persistence was calculated as time from resmetirom initiation to discontinuation (≥60-day gap following expected end date of last resmetirom prescription fill) or end of the 12-month post-index period (whichever came first). Adherence was measured among persistent patients using proportion of days covered (PDC), with the number of days of resmetirom on hand divided by the number of days the patient was considered persistent (6 or 12 months). Days supplied from overlapping prescription fills were adjusted to avoid overcounting (only one day of drug supply was credited/calendar day). **Results:** Total of 373 patients with ≥2 resmetirom fills over the 12-month post-index period were included. Mean (SD) age was 55.9 (13.4) with the majority in the 45-64 age group (53.9%) (27.1% ≥65, 11.8% 35-44, 7.2% 18-34). Over half of the sample were female (60.3%). For the first 6 months of the 12-month post-index period, 82.3% of patients were considered persistent. Persistent patients exhibited high adherence, with a mean (SD) PDC of .897 (.114). The overwhelming majority (83.7%) of the sample exhibited high adherence (≥80% PDC). Over the 12-month post-index period, 60.9% of the sample were considered persistent, with mean (SD) persistent days of 299.5 (96.6). Mean (SD) PDC was .901 (.075), with 89.4% of the persistent patients being considered as having high adherence. **Conclusion:** High adherence/persistence to resmetirom observed in this real-world cohort underscore its acceptability and tolerability in routine clinical practice, supporting its long-term use for MASH management.

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3515 | IMPLICATIONS OF THE 2026 ACC/AHA DYSLIPIDEMIA GUIDELINE FOR PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

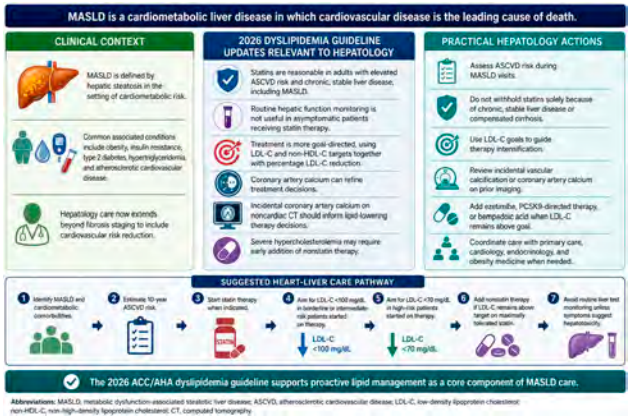
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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a multisystem metabolic disorder in which cardiovascular disease remains the leading cause of death. The 2026 ACC/AHA/AACVPR/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Dyslipidemia replaces the 2018 cholesterol guideline and introduces clinically important updates in lipid thresholds, subclinical atherosclerosis imaging, combination therapy and safety monitoring. These changes are highly relevant to hepatologists, who increasingly co-manage metabolic risk in patients with MASLD. **Methods:** We performed a narrative review of the 2026 multisociety dyslipidemia guideline with focused extraction of recommendations applicable to chronic stable liver disease, MASLD, compensated cirrhosis, diabetes and hypertriglyceridemia. Recommendations were contextualized within contemporary MASLD guidance emphasizing multidisciplinary cardiometabolic care. **Results:** The 2026 guideline formally states that in adults at elevated ASCVD risk with stable liver disease, including MASLD, statin therapy is reasonable, directly countering persistent underuse of statins in hepatology practice. The guideline also states that routine hepatic function monitoring is not useful in asymptomatic statin-treated patients. In primary prevention, treatment is now more explicitly goal-directed with stricter targets and recommendations for serial LDL-C monitoring. In severe hypercholesterolemia, maximally tolerated statin therapy with early addition of ezetimibe, PCSK9 inhibitors, bempedoic acid and in selected cases inclisiran, is recommended to achieve target LDL-C thresholds. For hepatologists, one of the most practice-changing updates is the stronger integration of coronary artery calcium (CAC). CAC greater than 0 supports lipid-lowering therapy, and incidental CAC on noncardiac CT

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should inform statin initiation or intensification. This is particularly relevant because patients with MASLD frequently undergo abdominal and thoracic imaging where subclinical atherosclerosis may be identified. Additional relevant updates include stronger treatment targets in diabetes, incorporation of non-HDL-C and apoB in selected patients with elevated triglycerides, and structured triglyceride management, all of which align with the common dyslipidemic phenotype seen in MASLD. **Conclusion:** The 2026 ACC/AHA dyslipidemia guideline reframes lipid management as a core component of hepatology care. Its explicit endorsement of statin safety in stable liver disease, use of LDL-C goal-based intensification and incorporation of incidental CAC provide a practical framework for hepatologists to reduce cardiovascular mortality in MASLD. These updates support a more proactive heart-liver model of care and should be incorporated into hepatology clinic workflows and multidisciplinary MASLD management pathways.



Disclosures: Pranav Ramamurthy:Nothing to Disclose.

3516 | A 12-MONTH REAL-WORLD ASSESSMENT OF CLINICAL CHARACTERISTICS AND BIOMARKER CHANGES FOLLOWING RESMETIROM INITIATION IN PATIENTS WITH MASH: A DESCRIPTIVE COHORT STUDY USING ELECTRONIC MEDICAL RECORDS IN THE UNITED STATES

Yestle Kim[1] John O'Donnell[1] Romina Fakhraei[2] Christina Parrinello[1] Karissa Johnston[2] Yael Silberberg[3] Andrew Kennedy[2] Emily Mercer[2] Robert Eisdorfer[3] Karin Keren[3] Rajagopal Chadalavada[4] Naim Alkhouri[5] Pradeep Bekal[4], [1]Madrigal Pharmaceuticals, [2]Broadstreet HEOR, [3]Latica, [4]Gastro Health, [5]Summit Clinical Research

Background: Resmetirom (Rezdiffra™), a THR-β agonist, is conditionally FDA-approved for adults with noncirrhotic MASH and moderate-to-advanced fibrosis. We descriptively assessed real-world clinical characteristics and early mean changes in liver and metabolic biomarkers among patients with ≥12 months of follow-up after resmetirom initiation. **Methods:** This descriptive, retrospective cohort study used the Latica real-world repository from the Gastro Health integrated delivery system and included adults with ≥1 resmetirom prescription between April 2024 and April 2025 (index date: first prescription) and ≥12 months of follow-up; those with end-stage liver disease during the 2-year pre-index were excluded. Baseline (12 months pre-index) demographics, comorbidities, concomitant medications, and laboratory measurements (AST, ALT, platelets, lipid markers FibroScan AST [FAST] score, vibration-controlled transient elastography liver stiffness measurement [VCTE LSM]) were captured and, when available, reassessed during follow-up. Responder endpoints were defined as a FAST score reduction of ≥0.22, ALT reduction of ≥17 U/L or 20%, and LSM reductions of ≥25% or ≥30% from baseline. **Results:** Of 2,147 patients who initiated resmetirom, 658 (31%) met inclusion. Mean age was 58.6 years (SD: 12.9). The cohort was predominantly female (56%), White (37%), and commercially insured (71%). At baseline, median BMI was 33.1 kg/m^2 with 68% classified as obese and 25% as overweight. The most common comorbidities were hypertension (76%), dyslipidemia (71%), obesity (70%), and type 2 diabetes (61%); 88% had two or more of these cardiometabolic conditions. At baseline, 128 patients (20%) were using a GLP-1RA, of whom 13 (2% of overall cohort) switched to resmetirom at index. Overall, 235 patients (36%) had concomitant GLP-1RA use during follow-up, including 120 patients (18% of overall cohort) who initiated a GLP-1RA post-index. Among patients with both baseline and follow-up values, statistically significant median reductions were observed in ALT (n = 410; -6.5 U/L), AST (n = 409; -4.0 U/L), BMI (n = 525; -0.6 kg/m²), body weight (n = 526; -1.8 kg), VCTE LSM (n = 112; -2.2 kPa), CAP (n = 112; -30.0 dB/m), and FAST scores (n = 85; -0.1); all p ≤ 0.001. Statistically significant reductions were also observed in total cholesterol (n = 24; -12.1 mg/dL; p = 0.049) and triglycerides (n = 24; -43.2 mg/dL; p = 0.009). Overall, 50% of patients achieved a ≥17 U/L reduction in ALT, 47% a ≥25% LSM response, 38% a ≥30% LSM response, and 35% a ≥0.22 reduction in FAST scores. **Conclusion:** In this real-world cohort, patients initiating resmetirom showed improvements in liver and blood-based biomarkers over the first 12 months, supporting

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early real-world effectiveness of resmetirom in routine clinical practice.

Table 1. Changes in Laboratory, Liver, and Metabolic Assessments from Baseline to Follow-Up

Biomarker (unit)	Time to FU measurement in months, mean (SD)	n	Median BL value (Q1, Q3)	Median FU value (Q1, Q3)	Median difference (Q1, Q3)
LDL (mg/dL)	10.0 (4.5)	14	97.5 (52.0, 111.8)	75.5 (48.5, 102.8)	-6.0 (-23.0, 0.8)
HDL (mg/dL)	9.6 (4.5)	15	45.0 (41.5, 55.0)	46.0 (39.5, 61.5)	2.0 (-6.0, 5.0)
Cholesterol (mg/dL)	11.7 (5.0)	24	168.5 (124.0, 198.8)	144.0 (120.8, 186.2)	-7.5 (-32.8, 3.2)*
Triglycerides (mg/dL)	11.7 (5.0)	24	138.0 (114.8, 195.2)	131.5 (75.8, 173.2)	-28.0 (-77.2, -5.2)*
Platelets (10^3/µl)	11.7 (5.9)	302	229.0 (180.0, 273.8)	224.0 (183.2, 267.0)	0.0 (-25.8, 18.0)
ALT (U/L)	11.9 (5.4)	410	42.5 (25.2, 70.0)	31.0 (23.0, 47.8)	-6.5 (-28.0, 4.8)†
AST (U/L)	11.9 (5.5)	409	34.0 (23.0, 51.0)	28.0 (20.0, 39.0)	-4.0 (-18.0, 4.0)†
VCTE (kPa)	13.3 (4.4)	112	9.7 (8.6, 11.0)	8.0 (6.0, 9.3)	-2.2 (-3.8, -0.2)†
CAP (dB/m)	13.3 (4.4)	112	329.0 (283.0, 352.2)	287.0 (245.8, 331.8)	-30.0 (-79.8, 20.5)†
FAST score	NA‡	85	0.4 (0.2, 0.6)	0.2 (0.1, 0.5)	-0.1 (-0.3, 0.0)†
BMI (kg/m^2)	11.8 (5.1)	525	33.1 (29.0, 38.1)	31.9 (28.0, 36.7)	-0.6 (-2.0, 0.4)†
Body weight (kg)	11.8 (5.1)	526	94.3 (79.4, 109.8)	91.6 (77.6, 107.1)	-1.8 (-5.4, 1.2)†

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BL, baseline; BMI, body mass index; CAP, controlled attenuation parameter; FibroScan AST, FAST; FU, follow up; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NA, not applicable; SD, standard deviation; VCTE, vibration-controlled transient elastography. **Notes:** Sample sizes (n) reported reflect patients with BL and FU measurements of each corresponding biomarker; p-values were determined by paired Wilcoxon signed-rank test to circumvent potential issues with small sample sizes and high variability in the data; *p≤0.05, †p<0.001; ‡FAST scores are derived from multiple biomarker measurements that may occur at different FU intervals

Disclosures: Yestle Kim:Nothing to Disclose, John O'Donnell:Madrigal Pharmaceuticals: Share Holder, Romina Fakhraei:Madrigal Pharmaceuticals: Consultant, Christina Parrinello:Madrigal Pharmaceuticals: Employee, Madrigal Pharmaceuticals: Stock - publicly traded company, Karissa Johnston:Nothing to Disclose, Yael Silberberg:Nothing to Disclose, Andrew Kennedy: Madrigal Pharmaceuticals Inc.: Independent Contractor, Emily Mercer:Madrigal Pharmaceuticals: Consultant, Robert Eisdorfer:Nothing to Disclose, Karin Keren: Nothing to Disclose, Rajagopal Chadalavada:Nothing to Disclose, Naim Alkhouri:Madrigal: Speaking and Teaching, Novo Nordisk: Consulting, Novo Nordisk: Grant/Research Support, Corcept: Grant/Research Support, Echosens: Speaking and Teaching, Perspectum: Consultant, Cima: Consultant, Fibronostics: Consultant, 89Bio: Grant/Research Support, Inventiva: Grant/Research Support, Merck: Grant/Research Support, Pfizer: Grant/Research Support, Ipsen: Speaking and Teaching, Intercept: Speaking and Teaching, Madrigal: Consulting, Research Funding, Novo Nordisk: Consulting, Research Funding, Inventiva: Research Funding, Boehringer Ingelheim: Consulting, Research Funding, Corcept: Research Funding, Ipsen: Consulting, Research Funding, Gliead: Consulting, Research Funding, Speaking, Perspectum: Consulting, Research Funding, Cima: Advisor, 89Bio: Consulting, Research Funding, Arbutus: Grant/Research Support, GSK: Grant/Research Support, Regeneron: Grant/Research Support, AstraZeneka: Grant/Research Support, Madrigal: Grant/Research Support, Akero: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Eli Lilly: Grant/Research Support, Gilead: Grant/Research Support, Galectin: Grant/Research Support, Boston Pharma: Grant/Research Support, Pradeep Bekal:Nothing to Disclose.

3517 | CASE-BASED ONLINE CME IMPROVES ASSESSMENT AND IDENTIFICATION OF PATIENTS WHO ARE CANDIDATES FOR MASH PHARMACOTHERAPY

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Background: Management of metabolic dysfunction-associated steatohepatitis (MASH) requires assessing patients for liver fibrosis using noninvasive modalities and identifying patients who are candidates for pharmacologic therapy. **Methods:** This study evaluated the effect of online certified continuing healthcare professional education on the assessment and management of MASH, including the identification of patients who are candidates for pharmacologic therapy for MASH. Learners participated in an online educational activity on MASH that featured video with synchronized slides. A repeated pairs pre-/post-assessment study design study including a 4-item, multiple choice competence questionnaire and a confidence assessment question was used and McNemar's test ($P < .05$) assessed educational effect. The activity launched December 5, 2025 and data were collected through May 7, 2026. **Results:** We report on data from gastroenterologists/hepatologists (GI/heps, n = 163) and NP/PAs (n = 333) who participated in the activity. Data are presented as absolute % change pre- to post-education. Overall, competence increased by 31% for GI/heps and by 55% for NP/PAs. after education. **Evidence-based risk stratification** : There was an 8% increase (58% pre/66% post; $P < .01$) for GI/heps and a 13% increase (43% pre/56% post; $P < .001$) in competence related to interpretation of FIB-4 and ELF scores. **Identifying candidates for liver-directed pharmacotherapy:** There was an 11% increase (55% pre/66% post; $P < .01$) for GI/heps and an 18% increase (36% pre/54% post; $P < .001$) for NP/PAs in interpreting results from VCTE to determine if patients meet guideline-based criteria for treatment with pharmacotherapy. **Managing cardiometabolic comorbidities:** GI/heps had a 56% shift and NP/PAs had a 69% shift in confidence in their ability to manage cardiometabolic comorbidities associated with MASH. **Conclusion:** Online case-based certified education improved competence in risk stratification and identification of patients who are candidates for MASH therapy. However, results prior to

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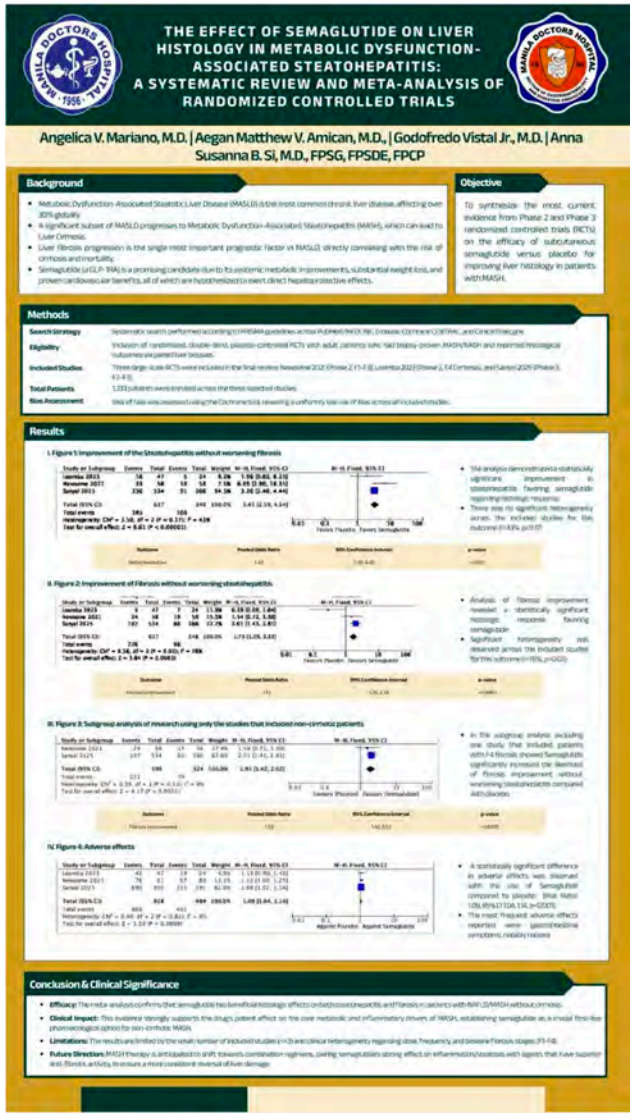
participation education reveal that there are gaps remaining in appropriate care pathways for MASH management.Reference:Rajpal A, Kumar S. Cases and Care Pathways in MASH. December 5, 2025. https://www.medscape.org/viewarticle/cases-and-care-pathways-mash-2025a1000xpc?page = 1

Disclosures: Shari Dermer:Nothing to Disclose, Julie Schrand:Nothing to Disclose, Aman Rajpal:Madrigal: Advisor, Madrigal: Speaking and Teaching, Ionis: Advisor, Novo Nordisk: Advisor, Boehringer Ingelheim: Advisor, Sonal Kumar:Nothing to Disclose, Roderick Smith:Nothing to Disclose.

★ 3518 | THE EFFECT OF SEMAGLUTIDE ON LIVER HISTOLOGY IN METABOLIC DYSFUNCTION ASSOCIATED STEATOHEPATITIS: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

Angelica Mariano[1] Aegan Matthew Amican[1] Godofredo Vistal[1], [1]Manila Doctors Hospital

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common chronic liver disease, affecting over 30% globally. Defined by hepatic fat accumulation within the context of metabolic syndrome, it poses a major public health challenge and is a leading cause of liver-related illness and death. A significant subset of MASLD progresses to metabolic dysfunction-associated steatohepatitis (MASH) and the worst outcome is Liver Cirrhosis. Histologically, MASH involves hepatocyte injury and lobular inflammation, which primarily drives hepatic fibrogenesis. Liver fibrosis progression is the single most important prognostic factor in MASLD, directly correlating with the risk of cirrhosis, hepatic failure, hepatocellular carcinoma, the need for liver transplantation, and all-cause mortality. **Methods:** The study conducted in accordance with PRISMA guidelines. We performed a systematic search of PubMed/MEDLINE, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov for RCTs published in the last 20 years. Meta-analysis was performed using RevMan 5.4 tool. **Results:** The search identified three large-scale RCTs that met the strict inclusion criteria, enrolling a total of 1,233 patients between the selected studies. The pooled analysis of all three trials found statistical significance in histological improvement in steatohepatitis without worsening fibrosis odds ratio of 3.43 (95% CI 2.59-4.53, $p < 0.001$) and improvement in fibrosis without worsening steatohepatitis odds ratio 1.73 (95% CI 1.29, 2.33, $p < 0.0003$). **Conclusion:** In conclusion, the meta-analysis demonstrates that semaglutide has beneficial histologic effects: both in Steatohepatitis and Fibrosis in patients with MAFLD with F2-F3 Fibrosis, with a well-tolerated safety profile. However, the results are limited by the small number of included studies and clinical heterogeneity, which restricts the generalizability of these findings across the spectrum of MAFLD.



Disclosures: Angelica Mariano:Nothing to Disclose, Aegan Matthew Amican:Nothing to Disclose, Godofredo Vistal:Nothing to Disclose.

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3519 | COMPARISON OF EFFECTIVENESS BETWEEN PHENTERMINE/TOPIRAMATE AND LIRAGLUTIDE IN OBESE PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

Young Eun Chon[1] Yeonjung Ha[1] Kwan Sik Lee[1] Sung Jun Park[1], [1]CHa University

Background: Anti-obesity drugs improve hepatic inflammation in patients with metabolic dysfunction–associated steatotic liver disease (MASLD). We aimed to compare the effects of phentermine/topiramate and liraglutide in obese MASLD patients. **Methods:** This retrospective study included 438 obese MASLD patients who received phentermine/topiramate (n = 320) or liraglutide (n = 118) for more than 12 months. Steatosis was assessed using the hepatic steatosis index (HSI) and controlled attenuation parameter (CAP). Fibrosis was assessed using the fibrosis index based on four factors (FIB-4) and liver stiffness (LS). Changes in steatosis and fibrosis were compared at 12 months after treatment. **Results:** After propensity score (PS) matching, 108 patients were equally assigned to the two treatment groups. After 12 months of treatment, HSI (40.584→36.556 in phentermine/topiramate; 40.284→ 39.347 in liraglutide) and CAP (321→299 dB/m in phentermine/topiramate; 306→288 dB/m in liraglutide) decreased significantly in both groups (all $p < 0.05$). However, FIB-4 (0.838→0.717; $p = 0.025$) and LS (6.0→4.9 kPa; $p = 0.011$) decreased significantly only in the liraglutide group. The phentermine/topiramate group showed a significantly greater reduction in steatosis from baseline to 12 months, as assessed by HSI (−9.32% vs. −1.87%; $p < 0.001$) and CAP (−10.15% vs. −5.22%; $p < 0.001$), compared with the liraglutide group. In contrast, the percent changes from baseline to 12 months in FIB-4 (1.58% vs. −3.83%; $p = 0.297$) and LS (−7.37% vs. −12.50%; $p = 0.144$) were not significantly different between the two groups. **Conclusion:** In obese patients with MASLD, phentermine/topiramate resulted in greater improvement in hepatic steatosis; however, fibrosis regression was comparable between the treatment groups.

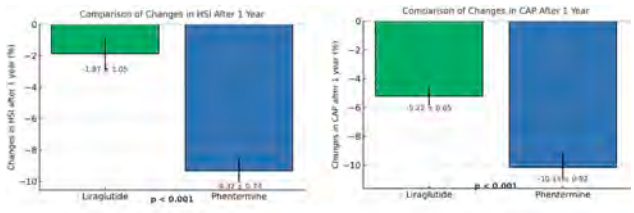


Figure 1. Comparison of steatosis improvement in obese MASLD patients treated with liraglutide and phentermine/topiramate (A) HIS (B) CAP

Disclosures: Young Eun Chon:Nothing to Disclose, Yeonjung Ha:Nothing to Disclose, Kwan Sik Lee: Nothing to Disclose, Sung Jun Park:Nothing to Disclose.

3520 | REAL-WORLD OUTCOMES AMONGST MASLD PATIENTS TREATED WITH RESMETIROM PLUS SEMAGLUTIDE VERSUS TIRZEPATIDE: A SINGLE-CENTER OBSERVATIONAL ANALYSIS

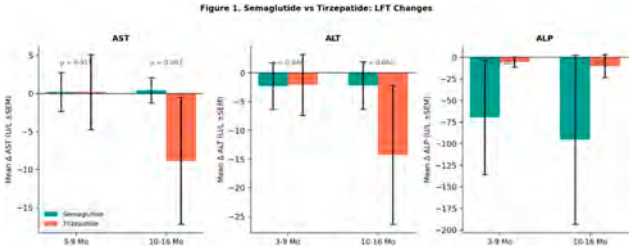
Rukmoni Balasubramanian[1] Anjali Rajagopal[1] Christian Tallo[1] Megan Carugati[1] Parvir Aujla[1] Roopjeet Bath[1], [1]University of Connecticut

Background: Resmetirom, a liver-targeted thyroid hormone receptor-β agonist, is the first FDA-approved pharmacotherapy for metabolic dysfunction-associated steatotic liver disease (MASLD) with moderate-to advanced fibrosis. GLP-1 receptor agonists (GLP-1RAs) are frequently co-prescribed given overlapping cardiometabolic comorbidities. Real-world data on hepatic outcomes by incretin agent is limited. We compare fibrosis regression and hepatic biochemistry between resmetirom plus semaglutide versus tirzepatide in a single-center cohort. **Methods:** We performed a retrospective subgroup analysis of 29 MASLD patients receiving resmetirom (80 or 100 mg daily) with a specified incretin agent: semaglutide (n = 16) versus tirzepatide (n = 13). Liver biochemistry (AST, ALT, and ALP) was asssessed at 3-9 and 10-16 months. Fibrosis response was assessed using serial imaging-based fibrosis stage from fibroscan, ultrasound elastography or MR elastography reports at 3-9 months, 10-16 months, with modalities reported as fibrosis stage. Patients with shorter treatment durations lacked repeat imaging. Baseline variables were compared by t-tests; outcome changes by Mann-Whitney U tests. **Results:** Baseline fibrosis stage was similar between semaglutide and tirzepatide groups (2.73 ± 0.56 vs. 2.77 ± 0.60; p = 0.871). Baseline AST and ALP were not significantly different, while baseline ALT was numerically higher in the tirzepatide group (44.3 ± 21.8 vs. 31.2 ± 12.9 U/L; p = 0.054). No statistically significant between-group differences were observed in AST, ALT, or ALP at either follow-up window (Figure 1). At 10-16 months, AST changed by +0.4 ± 5.3 vs. -8.9 ± 22.1 U/L (p = 0.883), ALT by -2.2 ± 13.0 vs. -14.3 ± 31.9 U/L (p = 0.660), and ALP by -95.5 ± 309.7 vs. -10.0 ± 35.2 U/L (p = 1.000). There was no statistically significant imaging-based fibrosis change by incretin agent. Best available fibrosis stage change was -0.83 ± 0.52 in semaglutide (n = 6) versus -1.08 ± 1.69 in tirzepatide (n = 6; p = 0.935). Descriptively, when both incretin groups were pooled, paired imaging showed significant fibrosis regression from 2.96 ± 0.62 to 2.00 ± 1.11 (mean change -0.96 stages; Wilcoxon p = 0.023). **Conclusion:** No statistically significant differences were detected in AST, ALT, ALP, or fibrosis stage change between resmetirom plus semaglutide versus tirzepatide; these comparisons were

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underpowered and should be interpreted as hypothesis-generating. Descriptively, when pooled as a resmetirom plus incretin cohort, patients with paired imaging demonstrated significant fibrosis regression, consistent with a potential additive hepatic benefit of combination therapy. Larger prospective studies are needed to confirm these preliminary findings.

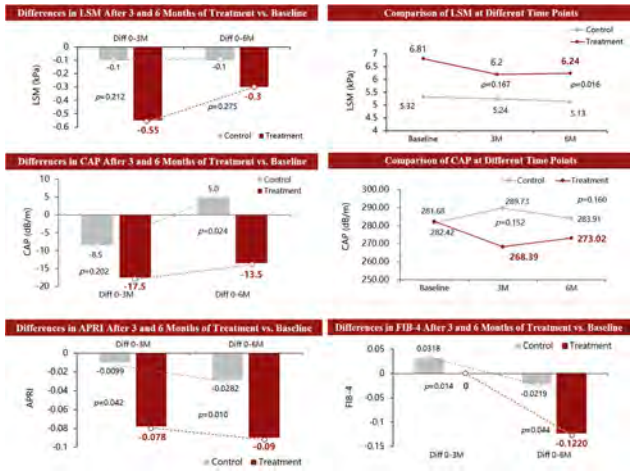


Disclosures: Rukmoni Balasubramanian:Nothing to Disclose, Anjali Rajagopal:Nothing to Disclose, Christian Tallo:Nothing to Disclose, Megan Carugati:Nothing to Disclose, Parvir Aujla:Nothing to Disclose, Roopjeet Bath:Nothing to Disclose.

3521 | EFFICACY OF SILYBIN PHOSPHOLIPID COMPLEX IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

Qianli Zhao[1] Manman Xu[1] Pengfei Yu[1] Junfeng Li[2] Ming Kong[1] Yu Chen[1], [1]Fourth Department of Liver Disease, Beijing You'an Hospital Affiliated to Capital Medical University, [2]The First Hospital of Lanzhou University

Background: Silybin-phospholipid complex is a commonly used hepatoprotective agent. In vitro studies have demonstrated its effects in reducing hepatic steatosis and liver fibrosis. The aim of this study was to evaluate the clinical efficacy of silybin-phospholipid complex in improving liver fat content and fibrosis in patients with metabolic dysfunction-associated steatotic liver disease (MASLD). **Methods:** MASLD patients admitted to Beijing You'an Hospital and the First Hospital of Lanzhou University between January 1, 2020 and December 31, 2025 were retrospectively included. Patients were assigned to a treatment group receiving silybin-phospholipid complex monotherapy or to a control group without treatment. Changes in liver fat content, fibrosis indices, and liver function parameters were analyzed. The primary endpoints were reductions in liver fat content and fibrosis indices, and secondary endpoints were improvements in liver function tests. **Results:** A total of 231 patients were included (177 in the treatment group, 54 in the control group). After 3 and 6 months of continuous therapy, the treatment group showed greater decreases in ALT (Diff 0–3M: −15 vs −5; Diff 0–6M: −16 vs −1) and AST (Diff 0–3M: −8 vs −2.5; Diff 0–6M: −7 vs −0.5) compared with the control group. Controlled attenuation parameter (CAP) values were lower in the treatment group (3M: 258.47 ± 61.78 vs 289.73 ± 61.82; 6M: 272.81 ± 43.16 vs 283.91 ± 47.27), with a significant reduction at 6 months (Diff 0–6M: −13 vs 5, p = 0.024). In a subset of patients with regular follow-up, multivariable GEE analysis confirmed a significant CAP reduction in the treatment group (β = −16.31, p = 0.0138). For liver fibrosis, both groups showed decreased LSM, but the treatment group had a greater reduction (Diff 0–3M: −0.55 vs −0.1; Diff 0–6M: −0.3 vs −0.1). FIB-4 decreased more in the treatment group compared with control at 3 months (0.0 vs 0.0318, p = 0.014) and 6 months (−0.122 vs −0.0219, p = 0.044). Similarly, APRI declined more in the treatment group at 3 months (−0.078 vs −0.0099, p = 0.042) and 6 months (−0.09 vs −0.0282, p = 0.010). **Conclusion:** Silybin-phospholipid complex appears to reduce liver fat content and attenuate fibrosis in patients with MASLD, representing a potential therapeutic option for clinical management of this condition.



Disclosures: Qianli Zhao:Nothing to Disclose, manman xu:Nothing to Disclose, Pengfei Yu:Nothing to Disclose, Junfeng Li:Nothing to Disclose, Ming Kong: Nothing to Disclose, yu chen:Nothing to Disclose.

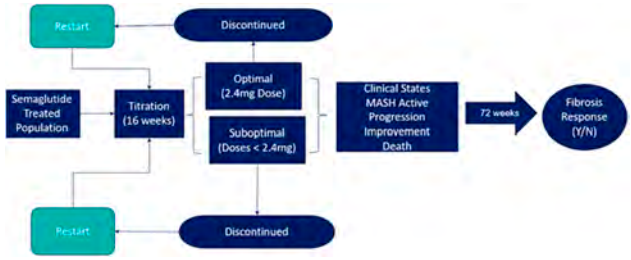
3522 | ESTIMATING REAL WORLD CLINICAL AND ECONOMIC IMPLICATIONS OF GLP-1 PERSISTENCE AND DOSING IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH)

Florencio Calderon[1] Lester Lachuk[1] Nipun Atreja[2] Francis Lobo[2], [1]Sapere Health Solutions [2]Madrigal Pharmaceuticals

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Background: Background: Recent studies estimate that metabolic dysfunction-associated steatohepatitis (MASH) cases in the United States are expected to increase 82.6% by 2039. MASH has significant ramifications in liver-related sequelae (cirrhosis, cancer, decompensation) and cost burden[1] . Real-world disparities in GLP-1 semaglutide's therapeutic dose exposure and premature discontinuation[2-5] limits overall efficacy and effectiveness for MASH. Wastage modeling based on real-world data can identify disparities within estimated clinical outcomes and the consequential economic impact of MASH treatment. **Aim:** To elucidate the estimated clinical effects of Wegovy (semaglutide) dependent on real-world dose exposure, persistence, and consequential economic wastage. **Methods:** We developed a wastage model that leverages a Markov state-transition structure to estimate the number of clinical responders and progressors, discontinuations, and economic wastage from the use of Wegovy (semaglutide) in a MASH population. Optimal dose responders were defined as maintaining persistence on the 2.4mg dose by 72 weeks as in the ESSENCE trial and yielding the clinical response of fibrosis improvement without steatosis worsening. Economic wastage was defined by the excess medical and pharmacy costs experienced by a commercial health plan for all MASH patients treated with Wegovy who did not reach fibrosis improvement with FDA approved therapeutic dose by the end of time horizon. To inform the real-world 72-week persistence and dose states, an Optum Market Clarity Dataset cohort of 1,013 patients initiating SC semaglutide with a target dosage of 2.4 mg/week for weight management (Wegovy) was used. Probabilistic and deterministic sensitivity analyses were completed for parameters of uncertainty inclusive of fibrosis mix and non lean mix. **Results:** In a modeled commercial population of 80,000 members, an estimated 100 patients will be diagnosed and eligible (F2/F3) for MASH treatment with Wegovy (semaglutide). Of the 100 patients, 24 remain persistent at 72 weeks of which 3.25 patients will be optimal dose responders. Additionally, 29 patients will experience fibrosis progression (20 new F4 and 9 new F3). It is estimated that a commercial health plan would experience a wastage of $1.3M total cost (pharmacy and medical) to yield one optimal dose responder. **Conclusion:** Our wastage model demonstrates that the low persistence of MASH patients on an optimal dose of semaglutide (2.4mg) in the real-world environment, compared to the clinical trial, results in a higher number of progressors, a lower number of responders, and significant economic wastage to be experienced by commercial health plans.Witkowski M et al. *Pharmacoeco.* 2022;40:751-776Do D et al. *JAMA Netw.* 2024;7:e2413172Gleason PP et al. *JM Care Spec Pharm.* 2024;30:860-867Polonsky WH et al. *Diabetes.* 2025;74:786-PAlvarez G et al. *Obesities.* 2025;5:90



Disclosures: Lester Lachuk:Nothing to Disclose, Florencio Calderon:Nothing to Disclose.

3523 | ◆ SODIUM-GLUCOSE COTRANSPORTER-2 INHIBITORS (SGLT2I) VERSUS DPP-4 INHIBITORS (DDP-4I) INITIATION IN TYPE 2 DIABETES MELLITUS (T2DM) WITH MASLD/MASH-RELATED COMPENSATED CIRRHOSIS: A TARGET-TRIAL EMULATION OF MAJOR ADVERSE LIVER OUTCOMES (MALO) AND MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE)

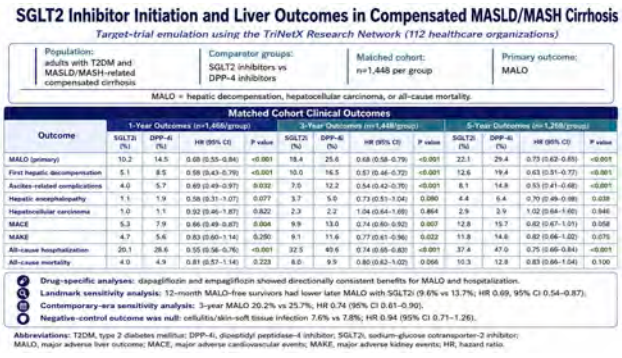
Mohammad Alabbas[1] Akram Alnounou[2] Ahmad Alhusen[3] Kenan Abou Chaer[4] EzzElDien A. Ibrahim[5] Omar Sims[1] Richard Sterling[6], [1]Cleveland Clinic Foundation, [2]Department of Internal Medicine, Western Michigan University Homer Stryker M.D. School of Medicine,, [3]Department of Internal Medicine, Advocate Illinois Masonic Medical Center, Chicago, IL, USA, [4]Department of Internal Medicine, Detroit Medical Center/Wayne State University, Detroit, MI, USA, [5]Department of Medicine, University of Missouri-Columbia 1 Hospital Dr, Columbia, Missouri, USA 65212, [6]Virginia Commonwealth University

Background: Adults with T2DM and MASLD/MASH-related compensated cirrhosis face high risks of hepatic decompensation, hospitalization, cardiovascular and kidney events, and death. Whether SGLT2i reduce hard liver outcomes in this population is uncertain. We emulated a target trial comparing SGLT2i versus DPP-4i initiation. **Methods:** Using the TriNetX Research Network (112 healthcare organizations), we identified adults with T2DM and MASLD/MASH-related compensated cirrhosis initiating an SGLT2i or DPP-4 inhibitor. Time zero was the first qualifying prescription. Patients with prior exposure to

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either class, hepatic decompensation, MALO components, hepatocellular carcinoma, transplant, competing liver diseases, ESRD/dialysis, HIV, or malignancy were excluded. SGLT2i and DPP-4i initiators were 1:1 propensity-score matched on demographics, comorbidities, medications, and laboratory values. The primary outcome was MALO: hepatic decompensation, hepatocellular carcinoma, or death. Secondary outcomes included first decompensation, ascites-related complications, hepatic encephalopathy, MACE, MAKE, hospitalization, and mortality. Outcomes were assessed at 1, 3, and 5 years with Kaplan-Meier methods. **Results:** Before matching, 4,446 SGLT2i and 2,130 DPP-4i initiators were eligible; 1,448 pairs formed the main 3-year cohort with all post-match SMD < 0.10. At 3 years, SGLT2i initiation was associated with lower MALO (18.4% vs 25.6%; HR 0.68, 95% CI 0.58–0.79), first decompensation (10.0% vs 16.5%; HR 0.57, 95% CI 0.46–0.72), ascites-related complications (7.0% vs 12.2%; HR 0.54, 95% CI 0.42–0.70), MACE (9.9% vs 13.0%; HR 0.74, 95% CI 0.60–0.92), MAKE (9.1% vs 11.6%; HR 0.77, 95% CI 0.61–0.96), and hospitalization (32.5% vs 40.6%; HR 0.74, 95% CI 0.65–0.83; all $p \leq 0.022$). Hepatic encephalopathy, hepatocellular carcinoma, and mortality did not significantly differ. MALO reductions were consistent at 1 year (10.2% vs 14.5%; HR 0.68, 95% CI 0.55–0.84) and 5 years (22.1% vs 29.4%; HR 0.73, 95% CI 0.62–0.85). Dapagliflozin and empagliflozin analyses, stratified analyses across albumin, BMI, eGFR, HbA1c, and age, 12-month landmark sensitivity analysis, contemporary-era analysis, E-values, and a null negative-control outcome supported robustness. **Conclusion:** In adults with T2DM and MASLD/MASH-related compensated cirrhosis, SGLT2i initiation was associated with lower MALO, hepatic decompensation, ascites-related complications, cardiovascular and kidney events, and hospitalization versus DPP-4i initiation, without excess hepatic encephalopathy, hepatocellular carcinoma, or mortality. These data support prospective trials of SGLT2i as a liver-relevant metabolic strategy in compensated MASLD/MASH cirrhosis.



Disclosures: Mohammad Alabbas:Nothing to Disclose, Akram Alnounou:Nothing to Disclose, Ahmad Alhusen:Nothing to Disclose, Kenan Abou Chaer: Nothing to Disclose, EzzElDien A. Ibrahim:Nothing to Disclose, Omar Sims:Nothing to Disclose, Richard Sterling:ABIM: GI Specialty Board, Abbott: Grant/Research Support, GSK: Grant/Research Support, HCV Vax: Grant/Research Support, Gilead: Grant/Research Support, Zydus: Grant/Research Support, Vertex: Consultant, Madrigal: Advisor, Gigagen: Grant/Research Support, Atea: Grant/Research Support, Cima Science: Consultant, Celaris: Consultant, GSK: Advisor.

3524 | ◆ BASELINE BAVENO PORTAL HYPERTENSION AND ELF RISK STRATIFICATION PREDICT VARICEAL DEVELOPMENT IN COMPENSATED MASH CIRRHOSIS: FINDINGS FROM THE NAVIGATE TRIAL

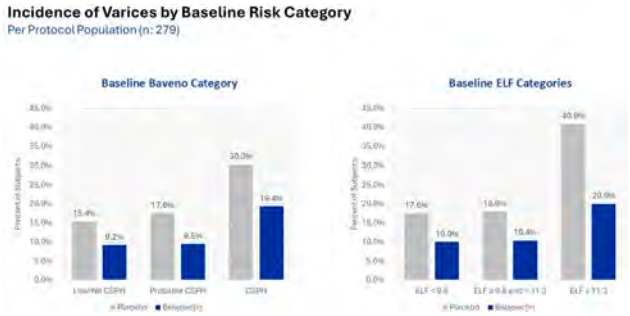
Naim Alkhouri[1] Raj Vuppalanchi[2] Eric Lawitz[3] Khurram Jamil[4] Seth Zuckerman[4] Naga Chalasani[5], [1]Summit Clinical Research, [2]Indiana University School of Medicine, [3]The Texas Liver Institute, University of Texas San Antonio, [4]Galectin Therapeutics, [5]Indiana University Medical Center

Background: Development of esophageal varices (EV) in compensated cirrhosis reflects worsening portal hypertension and increased risk of decompensation. - Baveno VI criteria and Enhanced Liver Fibrosis (ELF) score, enable risk stratification for clinically significant portal hypertension (CSPH) and risk of decompensation, respectively. NAVIGATE is a global, randomized, placebo-controlled trial that evaluated belapectin, a galectin-3 inhibitor, in patients with compensated MASH cirrhosis without baseline varices. Belapectin demonstrated a lower incidence of new varices at 18 months versus placebo. Here, we assessed the relationship between baseline Baveno VI and ELF risk categories and incidence of varices, we also evaluated treatment effects across risk strata. **Methods:** Subjects underwent upper endoscopy at baseline and 18 months with central blinded review. Incidence of new EV was assessed across Baveno portal hypertension categories (low/no risk, probable CSPH, definite CSPH) and predefined ELF categories (< 9.8, ≥ 9.8–< 11.3, ≥ 11.3). Analyses were conducted in subjects with evaluable endoscopy at both timepoints. For this analysis, both belapectin dose groups (2 mg/kg and 4 mg/kg) were combined and compared with placebo. Comparisons were performed using the chi-square test. **Results:** Baveno stratification (n = 115 low/no CSPH, 59 probable CSPH, 100 definite CSPH) demonstrated increasing incidence of varices with greater portal hypertension severity

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(11.3%, 11.9%, and 23.0%, respectively; p = 0.08 and p = 0.02 across category comparisons vs CSPH). Within each Baveno category, incidence of varices remained lower with belapectin versus placebo (9.2% vs 15.4%, 9.5% vs 17.6%, and 19.4% vs 30.3%, respectively).Similarly, incidence of new varices increased stepwise with higher baseline ELF category (n = 57, 156, 67), with rates of 12.3%, 12.8%, and 26.9%, respectively. The highest ELF category ($\geq$ 11.3) had a significantly greater incidence compared with lower categories (p = 0.04 and p = 0.01). Within each ELF stratum, belapectin-treated subjects had consistently lower incidence of varices compared with placebo (10.0% vs 17.6%, 10.4% vs 18.0%, and 20.0% vs 40.9%, respectively). **Conclusion:** In NAVIGATE, baseline Baveno and ELF risk categories demonstrated increased risk, with Baveno CSPH category and ELF $\geq$ 11.3 associated with significantly greater incidence of varices at 18 months. Belapectin treatment was associated with lower variceal incidence compared with placebo. These findings support baseline risk stratification as a strategy for enrichment and treatment effect detection in future Phase 3 variceal prevention trials in MASH cirrhosis.



Disclosures: Naim Alkhouri:Madrigal: Speaking and Teaching, Novo Nordisk: Consulting, Novo Nordisk: Grant/Research Support, Corcept: Grant/Research Support, Echosens: Speaking and Teaching, Perspectum: Consultant, Cima: Consultant, Fibronostics: Consultant, 89Bio: Grant/Research Support, Inventiva: Grant/Research Support, Merck: Grant/Research Support, Pfizer: Grant/Research Support, Ipsen: Speaking and Teaching, Intercept: Speaking and Teaching, Madrigal: Consulting, Research Funding, Novo Nordisk: Consulting, Research Funding, Inventiva: Research Funding, Boehringer Ingelheim: Consulting, Research Funding, Corcept: Research Funding, Ipsen: Consulting, Research Funding, Gliead: Consulting, Research Funding, Speaking, Perspectum: Consulting, Research Funding, Cima: Advisor, 89Bio: Consulting, Research Funding, Arbutus: Grant/Research Support, GSK: Grant/Research Support, Regeneron: Grant/Research Support, AstraZeneka: Grant/Research Support, Madrigal: Grant/Research Support, Akero: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Eli Lilly: Grant/Research Support, Gilead: Grant/Research Support, Galectin: Grant/Research Support, Boston Pharma: Grant/Research Support, Raj Vuppalanchi:Eli LIlly: Grant/Research Support, GSK: Consultant, Madrigal: Consultant, Zydus Therapeutics: Grant/Research Support, Galectin Therapeutics: Grant/Research Support, Kowa: Grant/Research Support, Takeda: Grant/Research Support, UBC: Consultant, Gilead: Grant/Research Support, GSK: Grant/Research Support, 89 Bio: Consultant, Eric Lawitz:89Bio: Grant/Research Support, Akero Therapeutics: Grant/Research Support, Astrazeneca: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Bristol-Myers Squibb: Grant/Research Support, Cour Pharmaceuticals: Grant/Research Support, Cymabay Therapeutics: Grant/Research Support, Eli Lilly and Company: Grant/Research Support, Galectin Therapeutics: Grant/Research Support, Gilead Sciences: Grant/Research Support, GlaxoSmithKline: Grant/Research Support, Hanmi Pharmaceuticals: Grant/Research Support, Hightide Biopharma: Grant/Research Support, Intercept Pharmaceuticals: Grant/Research Support, Inventiva: Grant/Research Support, Ipsen: Grant/Research Support, Madrigal Pharmaceuticals: Grant/Research Support, Merck & Co: Grant/Research Support, NGM Biopharmaceuticals: Grant/Research Support, Novartis: Grant/Research Support, Novo Nordisk Inc: Grant/Research Support, Regeneron: Grant/Research Support, Sagimet Biosciences: Grant/Research Support, Takeda: Grant/Research Support, Terns Pharmaceuticals: Grant/Research Support, Viking Therapeutics: Grant/Research Support, Zydus Pharmaceuticals: Grant/Research Support, Gilead Sciences: Speaking and Teaching, Abbvie: Speaking and Teaching, Intercept: Speaking and Teaching, Madrigal Pharmaceuticals: Speaking and Teaching, 89Bio: Consultant, Boehringer Ingelheim: Consultant, Merck & Co: Consultant, Novo Nordisk Inc: Consultant, Organovo: Consultant, Regeneron: Grant/Research Support, Sagimet Biosciences: Consultant, Corcept Therapeutics: Consultant, Corcept Therapeutics: Grant/Research Support, Astrazeneca: Consultant, inventiva: Consultant, Khurram Jamil:Mallinckrodt Pharmaceuticals: Employee, Galectin Therapeutics: Stock - publicly traded company, Galectin Therapeutics: Employee, Seth Zuckerman:Nothing to Disclose, Naga Chalasani:Madrigal, Eccogene, Insitro, Boston Pharma, Chugai: Consultant, Zydus, GSK, Akero, Plaint, Altimmune: Consultant, Exact Sciences: Grant/Research Support, NIH: Grant/Research Support, Heligenics: Board member, investor, Avant Sante: Board member, investor, Ipsen, Biomea Fusion, Pfizer, Merck: Consultant.

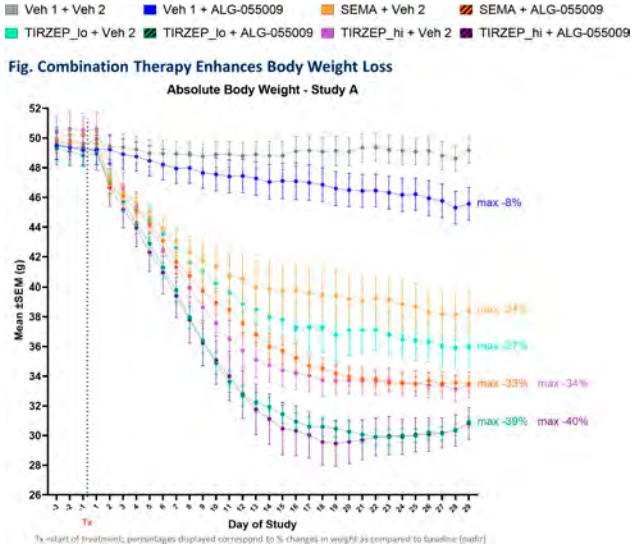
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3525 | ◆ CO-ADMINISTRATION OF THYROID HORMONE RECEPTOR B AGONIST ALG-055009 AND INCRETIN RECEPTOR AGONISTS LEADS TO SYNERGISTIC FAT MASS LOSS AND MODULATION OF KEY MOLECULAR PATHWAYS IN THE LIVER AND ADIPOSE TISSUE OF DIET-INDUCED OBESE MICE

Peter Althoff[1] Jieun Song[1] Kusum Gupta[1] Lillian Adame[1] Dinah Misner[1] Tse-I Lin[2] Lawrence Blatt[1] Julian Symons[3] Sushmita Chanda[1] Xuan Luong[1], [1]Aligos Therapeutics, Inc., [2]Aligos Belgium BV, [3]Aligos Therapeutics

Background: ALG-055009 is a potent, selective thyroid hormone receptor β (THR-β) agonist that has demonstrated significant reductions in liver fat (placebo-adjusted median relative reductions up to 46.2%) and atherogenic lipids in clinical subjects with presumed metabolic dysfunction-associated steatohepatitis (MASH) and stage 1-3 liver fibrosis. Thyroid hormone is crucial in regulating metabolism, and THR activation has been shown to enhance energy expenditure and promote weight loss. Here, the ability of ALG-055009 to augment the weight loss effects of approved incretin receptor agonists (RAs) was assessed in diet-induced obese (DIO) mice. **Methods:** Mice were fed a high-fat diet for 23-25 weeks to induce obesity. In Part I, mice were treated once daily with vehicle, oral 1 mg/kg ALG-055009, subcutaneous incretin RAs, 10.0 nmol/kg semaglutide (SEMA), 3.0 nmol/kg tirzepatide (TIRZEP_lo), 10.0 nmol/kg tirzepatide (TIRZEP_hi), or combinations of ALG-055009 with incretin RAs for 4-5 weeks. In Part II, SEMA treatment was discontinued in the SEMA monotherapy and SEMA + ALG-055009 groups, and animals were continued on either vehicle treatment or ALG-055009 maintenance therapy and monitored for 4 more weeks. Assessments included body weight (BW), body composition, and tissue-specific gene expression via RT-qPCR. **Results:** ALG-055009 in combination with incretin RAs resulted in profound, synergistic weight loss in DIO mice, with up to 39-40% decreases in body weight within 4-5 weeks. Notably, the additional weight loss conferred by ALG-055009 was from reduction of fat mass without changes to lean mass or food intake. Administration of ALG-055009 to animals already receiving SEMA still produced meaningful effects, with significantly greater reductions in body weight and fat tissue mass compared to animals on SEMA monotherapy. Following SEMA withdrawal, animals regained nearly all lost weight, while those maintained on ALG-055009 preserved 48–57% of weight loss and 47–57% of fat mass reduction. Gene expression analysis showed that combination therapy synergistically modulated several key genes in the liver to restore hepatic heath, while ALG-055009 uniquely shifted the liver towards a less fibrotic and more metabolically functional state. **Conclusion:** In DIO mice, ALG-055009 drove synergistic, fat-selective weight loss when combined with incretin RAs, likely via browning of white adipose and increased energy expenditure. Combination therapy also synergistically modulated hepatic gene expression, promoting a less fibrotic, more metabolically functional liver. Beyond its clinical efficacy in MASH, THR-β agonism is potentially a powerful, complementary strategy to combat obesity by enhancing the magnitude and durability of incretin RA-mediated weight loss.



Disclosures: Peter Althoff:Aligos Therapeutics: Employee, Jieun Song:Aligos Therapeutics: Employee, Kusum Gupta:Nothing to Disclose, Lillian Adame: Nothing to Disclose, Dinah Misner:Nothing to Disclose, Tse-I Lin:Nothing to Disclose, Lawrence Blatt:Nothing to Disclose, Julian Symons:Aligos Therapeutics Inc.: Employee, Sushmita Chanda:Nothing to Disclose, Xuan Luong:Aligos Therapeutics: Employee.

3526 | ◆ ADENOVIRUS-ASSOCIATED VECTOR 1 FGF21 GENE THERAPY REVERTS THE MASH LIVER TRANSCRIPTOME PROFILE TOWARD HEALTHY STATE

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Background: Metabolic dysfunction-associated steatohepatitis (MASH) affects ~40 million people in the U.S. and E.U. and can progress to cirrhosis, hepatocellular carcinoma, and death. Fibroblast growth factor 21 (FGF21) is a pleiotropic regulator of metabolic function and fibrosis, making it a promising therapeutic target for MASH. Several engineered FGF21 analogs, administered chronically as subcutaneous injections, have reached approval or are in clinical development for patients with MASH and MASH-related cirrhosis. KRIYA-497, a one-time adenovirus associated vector 1 FGF21 (AAV1.FGF21) intramuscular (IM) gene therapy, drives sustained skeletal muscle expression of native human FGF21. Previous studies showed AAV1.mFGF21 reverses steatohepatitis and fibrosis in animal models of MASH. Here, we evaluate whether AAV1.FGF21 administration normalizes the hepatic transcriptional state toward that of healthy livers in a preclinical model of MASH, providing rationale for RESTORE, a Phase 1/2 first-in-human trial of KRIYA-497. **Methods:** Liver tissue was obtained from 70-week-old C57BL/6J mice treated with low- or high-dose AAV1.mFGF21, alongside untreated high-fat diet (HFD) and chow controls, as previously described (Jimenez et al., *Mol Ther*, 2024). Bulk RNA-seq was performed; HFD-responsive genes were classified as fully or partially rescued (significant return toward chow), unchanged, or otherwise altered. Mouse profiles were then compared with human liver transcriptome data (Govaere et al., *Sci Transl Med*, 2020) from the European NAFLD registry comprising histologically characterized MASH samples from 206 patients across the liver fibrosis spectrum. **Results:** HFD altered ~20% of the liver transcriptome versus chow. Low-dose AAV1.mFGF21 fully or partially rescued 47% of HFD-responsive genes; high-dose AAV1.mFGF21 fully or partially rescued 74%, including normalization of transcripts associated with fibrosis, inflammation, and lipid metabolism. In cross-species principal component analysis, HFD livers co-localized with human F3/F4 MASH, while high-dose AAV1.mFGF21 livers shifted toward chow controls and human NAFL/F0-F1, consistent with reversion toward a healthy hepatic state. **Conclusion:** One-time IM AAV1.FGF21 reverts the MASH liver transcriptome toward a healthy phenotype in a mouse model of MASH, establishing the anti-fibrotic and anti-inflammatory potential of KRIYA-497. These data support the translation of KRIYA-497 to the first clinical trial of an AAV gene therapy for MASH (Phase 1/2 RESTORE study), to evaluate safety, tolerability, and metabolic and hepatic outcomes in adults with MASH and clinically significant (> F2) fibrosis.

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3527 | ◆ ER-300M (AAV-OSK) IMPROVES LIVER INJURY AND STEATOSIS ENDPOINTS IN THE GAN DIET-INDUCED OBESE AND BIOPSY-CONFIRMED MOUSE MODEL OF MASH

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Background: Metabolic dysfunction–associated steatohepatitis (MASH) is a progressive liver disease associated with fibrosis and altered DNA methylation. In optic neuropathies, epigenetic restoration via expression of OCT4, SOX2, and KLF4 (OSK) has been linked to improved cellular function and regenerative capacity while maintaining cellular identity without de-differentiation. ER-300m is an adeno-associated virus (AAV) vector delivering OSK for hepatic expression. We evaluated ER-300m in the GAN diet-induced obese (DIO) and biopsy-confirmed mouse model of MASH. **Methods:** Male C57BL/6JRj mice were fed the GAN diet, which is high in saturated fat, fructose, and cholesterol, for 36–38 weeks and underwent liver biopsy to confirm MASH pathology (steatosis score 3, inflammation score ≥ 2, fibrosis stage F2–F3). Mice were randomized based on fibrosis staining. GAN DIO-MASH mice received vehicle or ER-300m (IV) and were evaluated after ~10 weeks using plasma biochemistry, liver weight, quantitative histology, ELISA, immunohistochemistry (IHC), and whole genome bisulfite sequencing. **Results:** ER-300m improved multiple clinically relevant liver injury and metabolic endpoints relative to vehicle. ER-300m significantly reduced plasma ALT and AST and lowered plasma total bile acids and total cholesterol compared with vehicle. ER-300m also reduced liver weight and decreased the percent of hepatocytes containing lipid droplets, indicating improvement in steatosis-associated pathology.

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Histologic score outcomes showed an increased proportion of animals achieving ≥1-point improvements in NAFLD activity score and steatosis score versus vehicle. IHC confirmed hepatic transduction and transgene expression, with 13% SOX2-positive cells detected in the liver. Consistent with IHC findings, ELISA analysis demonstrated robust transgene protein expression: SOX2 levels were 9.16 ± 1.1 ng/mg (mean ± SEM) with no endogenous SOX2 detected in vehicle-treated animals, while KLF4 levels were 1.43 ± 0.13 ng/mg versus 0.06 ± 0.03 ng/mg in vehicle controls. Whole genome bisulfite sequencing showed that ER-300m treatment restored DNA methylation profiles toward lean controls. **Conclusion:** ER-300m improved liver injury, steatosis and DNA methylation in a biopsy-confirmed MASH model, with clear evidence of hepatic SOX2 and KLF4 expression. Given the role of epigenetic dysregulation in MASH, these findings support continued evaluation of epigenetic restoration as a therapeutic strategy for metabolic liver disease. These data demonstrate that OSK-induced epigenetic restoration transcends organs and provides evidence of the transformational ability of OSK to reverse or prevent diseases of aging.

Disclosures: Kasia Broniowska:Life Biosciences: Employee, Lisa Stanek:Nothing to Disclose, Sadie Crocker:Life Biosciences: Employee, Richard Davis: Life Biosciences: Employee, Xiaohong Cao:Nothing to Disclose, Michel Wathier:life Biosciences: Employee, Michael Feigh:Nothing to Disclose, Sharon Rosenzweig-Lipson:Nothing to Disclose.

3528 | ◆ IMPROVEMENT IN NON-INVASIVE BIOMARKERS AFTER ONCE-WEEKLY UTREGLUTIDE (GL0034) TREATMENT FOR 24 WEEKS IN SUBJECTS WITH AT-RISK MASH: A PHASE 2A STUDY

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Background: Utreglutide (UTG, GL0034), a novel, once-weekly glucagon-like peptide-1 (GLP-1) receptor agonist, demonstrated safety in phase 1 study in individuals with overweight and obesity. In phase 1b/2a study, improvements in MASH biomarkers were evident in subjects with MASLD. Herein, interim data from phase 2a study in at-risk MASH subjects with 24 week once-weekly UTG dosing schedule is presented. **Methods:** In this randomized, double-blind, placebo-controlled, parallel group, multicenter study 60 participants, both male and female, aged 18 to 75 years with a BMI ≥30 kg/m^2 and ≤ 50 kg/m^2 or BMI ≥ 27.0 kg/m^2 along with at least one of the comorbidities (current or new diagnosis of T2DM with HbA_{1c} < 10% or hypertension or dyslipidemia); MRE liver stiffness ≥ 2.7 kPa and < 5.0 kPa and liver fat content ≥ 8.5% as assessed by MRI-PDFF were randomized (2:1) to subcutaneous UTG doses with dose escalation schedule (4×0.35, 4×0.75, 4×1.5, 4×3.0, 4×4.5 mg) of 20 weeks and final dose period (4.5 mg-cohort 1 and 6.0 mg-cohort 2) of 4 weeks or placebo once-weekly for 24 weeks.Safety, tolerability, and key efficacy along with exploratory biomarkers were assessed at baseline (BL) and week 24. In this interim analysis a pooled data of treatment and placebo group with N = 29 has been provided. The efficacy markers presented include BMI, body weight (BW), waist circumference (WC), liver fat content by MRI-PDFF, liver stiffness by magnetic resonance elastography (MRE), controlled attenuated parameter (CAP) mean as assessed by FibroScan@, alanine aminotransferase (ALT) and HbA_{1c}. **Results:** Utreglutide was well-tolerated and related adverse effects were mainly gastrointestinal including nausea, vomiting, and diarrhea which were mild to moderate. Pooled data of N = 19 for UTG treatment and pooled placebo N = 10 is presented. The mean BW reduction at week 24 from BL was 11.3 kg (9.7%, $p < 0.0001$), accompanied by 7.9 cm reduction in WC ($p = 0.0006$) and the decrease in BMI was -3.9 kg/m^2 ($p < 0.0001$). The mean percent change in relative liver fat content as assessed by MRI-PDFF from BL to week 24 was -35.1% ($p < 0.0001$) and half of the study participants achieved ≥30% relative liver fat reduction. Interestingly, in a short duration of 24 weeks dosing MRE liver stiffness reduction was significant ($p = 0.0123$). The CAP mean reduced by 40.4 dB/m. In addition, the subjects with ≥17 U/L ALT reduction were 40% and the mean change in ALT was -10.8 U/L. A meaningful reduction in HbA_{1c} of 0.58% ($p < 0.0001$) was observed. The placebo group showed little or no change at week 24 from baseline for all the parameters, except for CAP mean (see Table). **Conclusion:** Once-weekly utreglutide dosing for 24 weeks in subjects with at-risk MASH was well tolerated and produced improvements in body weight, hepatic steatosis, MRE liver stiffness, ALT and HbA_{1c} levels. The magnitude and pattern of response are clinically relevant, demonstrating utreglutide's potential as a GLP-1–based therapy for MASH.

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Table: Effect of once-weekly UTG treatment for 24 weeks on biomarkers in at-risk MASH subjects

Sr. No.	Parameters	Week	Pooled UTG (N=19)	Pooled PBO (N=10)
1	BMI (kg/m²)	BL	**41.1±5.16**	**42.3±4.13**
		W24	37.3±6.24 (-3.9/-9.7%) ***	41.4±3.79 (-0.86/-1.9%)
2	BW (kg)	BL	**115.3±24.11**	**120.1±17.97**
		W24	104.2±22.64 (-11.3/-9.7%) ***	117.6±16.13 (-2.6/-1.9%)
3	WC (cm)	BL	**121.7±12.42**	**125.4±8.49**
		W24	114.9±13.71 (-7.9) ***	126.1±11.02 (0.6)
4	MRI-PDFF (%)	BL	**16.8±5.83**	**21.1±7.63**
		W24	11.4±4.96(-6.3/-35.1%) ***	22.0±7.19 (0.9/7.2%)
5	Proportion of participants with ≥30% relative reduction in MRI-PDFF	W24	**8/16 (50.0%)**	**0/10 (0.0%)**
6	MRE Liver Stiffness (kPa)	BL	**3.0±0.45**	**2.9± 0.24**
		W24	2.8±0.60 (-0.24) *	2.9±0.27 (0.01)
7	CAP Mean (dB/m)	BL	**328.6±43.06**	**320.3±39.17**
		W24	297.9±58.38 (-40.4)	299.5±16.92 (-20.8)
8	ALT (U/L)	BL	**37.7±19.71**	**46.4±19.00**
		W24	27.3±14.38 (-10.8)	45.2±21.88 (-1.2)
9	Proportion of participants with ≥17 U/L reduction in ALT	W24	**6/15 (40.0%)**	**0/10 (0.0%)**
10	HbA1c (%)	BL	**5.75±0.57**	**5.72±0.46**
		W24	5.25±0.42 (-0.58) ***	5.69±0.40 (-0.03)

Disclosures: Rajamannar Thennati:Sun Pharmaceutical Industries Limited: Employee, Vinod Burade:Nothing to Disclose, Richard Pratley:Nothing to Disclose, Rohit Loomba:Eli Lilly and Company: Consultant, 89bio: Consultant, Aardvark Therapeutics: Consultant, Altimmune: Consultant, Alnylam/Regeneron: Consultant, Amgen: Consultant, Arrowhead Pharmaceuticals: Consultant, AstraZeneca: Consultant, Bristol Myers Squibb: Consultant, CohBar: Consultant, Eli Lilly: Consultant, Galmed Pharmaceuticals: Consultant, Gilead: Consultant, Glympse Bio: Consultant, Hightide: Consultant, Inipharma: Consultant, Intercept: Consultant, Inventiva: Consultant, Ionis: Consultant, Janssen, Inc.: Consultant, Madrigal Pharmaceuticals: Consultant, Merck, Metacrine, Inc.: Consultant, NGM Biopharmaceuticals: Consultant, Novartis: Consultant, Novo Nordisk: Consultant, Pfizer: Consultant, Sagimet Biosciences: Consultant, Terns Pharmaceuticals: Consultant, Theratechnologies and Viking Therapeutics: Consultant, 89bio: Stock options, Sagimet Biosciences: Stock options, Arrowhead Pharmaceuticals: Research grant, AstraZeneca: Research grant, Boehringer Ingelheim: Research grant, Bristol Myers Squibb: Research grant, Eli Lilly: Research grant, Galectin Therapeutics: Research grant, Galmed Pharmaceuticals: Research grant, Gilead: Research grant, Hanmi: Research grant, Intercept: Research grant, Inventiva: Research grant, Ionis: Research grant, Janssen, Inc.: Research grant, Madrigal Pharmaceuticals: Research grant, Merck: Research grant, NGM Biopharmaceuticals: Research grant, Novo Nordisk: Research grant, Pfizer: Research grant, Sonic Incytes: Research grant, Terns Pharmaceuticals: Research grant, LipoNexus, Inc.: Co-founder, Cascade Pharmaceuticals: Consultant, Eccogene: Consultant, HeptaBio: Consultant, Metavi: Consultant, Neurobo: Consultant, Novo Nordisk: Consultant, Sourcebio: Consultant, Roche: Consultant, Roche: Consultant, Takeda: Consultant, GSK: Grant/Research Support, Roche: Grant/Research Support, TensorBio: Grant/Research Support, Aarrowhead Pharmaceuticals: Consultant, Boehringer-Ingelheim: Consultant, Altimmune: Grant/Research Support, Eccogene: Grant/Research Support, Heptabio: Grant/Research Support, 89 bio: Grant/Research Support, Takeda: Grant/Research Support.

3529 | EFFICACY OF EFRUXIFERMIN ON LIVER INJURY BIOMARKERS ACROSS THE MASLD/MASH SPECTRUM: A META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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Background: Efruxifermin, an Fc-FGF21(Fc-fused fibroblast growth factor 21) analogue, has shown promising results, with histologic outcome data generally trending toward benefit in randomized trials of precirrhotic MASH(Metabolic dysfunction-associated steatohepatitis) and compensated cirrhosis caused by MASH. Here, we conducted a meta-analysis to synthesize the effects of Efruxifermin on circulating fibrosis and liver injury biomarkers across the spectrum of disease severity. **Methods:** We conducted a random-effects meta-analysis of placebo-controlled randomized trials of Efruxifermin in MASLD/MASH, evaluating changes in ELF (Enhanced Liver Fibrosis score) score, Pro-C3(N-terminal propeptide of type III collagen), ALT(Alanine aminotransferase), AST(Aspartate aminotransferase), GGT(Gamma-glutamyl transferase), ALP(Alkaline phosphatase), and urate. Mean differences were used for all biomarkers except Pro-C3, which was analyzed using standardized mean differences. In trials with multiple Efruxifermin dose arms, the shared placebo group was split across comparisons to avoid double-counting participants. **Results:** Across 4 randomized trials, Efruxifermin favored improvement

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in all pooled biomarker outcomes. In all-stage analyses, pooled effects were: ELF score, MD -0.718 (95% CI, -0.861 to -0.574); Pro-C3, SMD -4.510 (-5.065 to -3.954); ALT, MD -15.692 U/L (-23.392 to -7.992); AST, MD -12.448 U/L (-18.125 to -6.771); GGT, MD -24.672 U/L (-34.427 to -14.918); ALP, MD -8.269 U/L (-12.365 to -4.174); and urate, MD -0.609 mg/dL (-0.769 to -0.448). Heterogeneity was low for ELF, GGT, ALP, and urate, moderate for AST and Pro-C3, and highest for ALT, consistent with biologic differences across fibrosis stages. Stage-stratified analyses supported benefit in both F1-F3 and F4 populations. **Conclusion:** Efruxifermin was associated with broad improvement in fibrosis, liver injury, and metabolic stress biomarkers across the MASLD/MASH spectrum, including compensated cirrhosis caused by MASH. These findings support biomarker responsiveness across disease stages and reinforce the potential disease-modifying activity of Efruxifermin.

Table 1. Random-effects pooled biomarker estimates

Updated layout with exploratory removed from subgroup labels and study count column removed

Biomarker	Effect measure	Subgroup	Pooled effect (95% CI)	I² (%)	Tau²	P overall	P heterogeneity
ELF Score	MD	F1-F3 stratum	-0.769 [-0.911, -0.626]	0.0	0.0	<0.001	0.990
ELF Score	MD	F4 stratum	-0.661 [-0.826, -0.495]	0.0	0.0	<0.001	0.711
ELF Score	MD	All trials pooled	-0.718 [-0.862, -0.574]	0.0	0.0	<0.001	0.906
Pro-C3	SMD	F1-F3 stratum	-4.847 [-5.540, -4.155]	0.0	0.0	<0.001	0.737
Pro-C3	SMD	F4 stratum	-4.053 [-4.942, -3.163]	45.7	0.1867	<0.001	0.054
Pro-C3	SMD	All trials pooled	-4.510 [-5.065, -3.954]	46.6	0.2813	<0.001	0.049
ALT	MD	F1-F3 stratum	-19.481 [-30.819, -8.143]	0.0	0.0	<0.001	0.980
ALT	MD	F4 stratum	-7.171 [-12.584, -1.758]	0.0	0.0	0.009	0.489
ALT	MD	All trials pooled	-15.692 [-23.392, -7.992]	57.9	60.1896	<0.001	0.02
AST	MD	F1-F3 stratum	-18.942 [-26.797, -11.177]	0.0	0.0	<0.001	0.599
AST	MD	F4 stratum	-6.181 [-10.824, -1.538]	0.0	0.0	0.009	0.789
AST	MD	All trials pooled	-12.448 [-18.125, -6.771]	38.6	23.7412	<0.001	0.133
GGT	MD	F1-F3 stratum	-28.009 [-42.536, -13.482]	0.0	0.0	<0.001	0.992
GGT	MD	F4 stratum	-18.216 [-30.051, -6.381]	0.0	0.0	0.016	0.295
GGT	MD	All trials pooled	-24.672 [-34.427, -14.918]	0.0	0.0	<0.001	0.796
ALP	MD	F1-F3 stratum	-9.477 [-14.718, -4.236]	0.0	0.0	<0.001	0.991
ALP	MD	F4 stratum	-6.876 [-12.996, -0.756]	0.0	0.0	0.057	0.936
ALP	MD	All trials pooled	-8.269 [-12.365, -4.174]	0.0	0.0	<0.001	0.906
Urate	MD	F1-F3 stratum	-0.642 [-0.837, -0.448]	0.0	0.0	<0.001	0.681
Urate	MD	F4 stratum	-0.571 [-0.810, -0.332]	0.0	0.0	<0.001	0.913
Urate	MD	All trials pooled	-0.609 [-0.769, -0.448]	0.0	0.0	<0.001	0.916

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★ 3530 | STEATOHEPATITIS AND FIBROSIS-RELATED OUTCOMES FOR RESMETIROM AND CO-PRESCRIPTIONS WITH GLP1 RECEPTOR AGONISTS, VITAMIN E, AND STATINS

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Background: Resmetirom is the first FDA-approved therapy for at-risk MASH, granted accelerated approval based on the MAESTRO NASH Study. As a thyroid hormone receptor beta agonist, resmetirom increases hepatic fatty acid oxidation and suppresses lipogenesis, with demonstrated LDL reduction. Expert panel recommendations in 2024 advised against concomitant use of GLP-1 receptor agonists and resmetirom. We aimed to characterize prescribing patterns of clinicians treating patients with resmetirom at a large US referral center. **Methods:** Using TriNetX, we identified all patients prescribed resmetirom at our health system and performed chart review of patients treated for at-risk MASH from March 2024–December 2025. Comparative statistical analysis was performed using two-sided t-test and chi-squared analysis. **Results:** 119 eligible patients were treated. 68 (51%) were female, mean age 57.2 years, 92% Caucasian, mean BMI 35.3 kg/m², and mean weight 116 kg. 71 (59.7%) had co-prescriptions for a GLP-1, 70 (58.8%) a statin, and 10 (8.4%) vitamin E. Of GLP-1 co-prescribed patients, 38 were on a GLP-1, on average of 15 months before resmetirom, while 31 started a GLP-1 an average of 9.4 months after. Patients prescribed a GLP-1 after resmetirom had higher GI side effects (16/38) compared to those already on a GLP-1 (1/31). GLP-1-naive patients at resmetirom initiation had mean LSM and CAP of 11.6 kPa and 312, improving to 8.4 kPa and 264 at 12 months. Patients already on a GLP-1 had mean LSM and CAP of 10.8 kPa and 325 at initiation, and 13.7 kPa and 271 at 12 months. Fibrosis regression was similar with and without vitamin E. No increased hepatic adverse events or rhabdomyolysis occurred with concomitant statin use, and LDL reduction was preserved with or without statins. **Conclusion:** This real-world study demonstrates that concomitant resmetirom and GLP-1 use is common, with nearly 60% of patients having treatment overlap. GLP-1-naive patients on resmetirom had greater LSM reduction compared to those on existing GLP-1, representing a population with advanced fibrosis despite GLP-1 therapy necessitating resmetirom. Patients on stable GLP-1 who then started resmetirom had fewer GI side effects; clinicians should be aware of potential GI intolerance when adding a GLP-1 after resmetirom. Vitamin E was seldomly used and had no significant impact on 12-month liver stiffness. No increase in adverse events was observed with statin co-prescription, and LDL reduction was preserved. In clinical practice, resmetirom demonstrates good efficacy for MASH with moderate fibrosis despite GLP-1 therapy.

Disclosures: Resham Ramkissoon:Nothing to Disclose, Alekhya Mannava:Nothing to Disclose, Japhet

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Amoah:Nothing to Disclose, Samir Barazi:Nothing to Disclose, Akash Chavan:Nothing to Disclose, Adily Elmi:Nothing to Disclose, Julie Gartland:Nothing to Disclose, Jaime Abraham Perez:Nothing to Disclose, Naemat Sandhu:Ultragenyx Pharmaceutical Inc.: Grant/Research Support, Stanley Cohen:Nothing to Disclose, Seth Sclair:Nothing to Disclose.

3531 | ◆ PNPLA3, TM6SF2 AND HSD17B13 GENOTYPES DO NOT IMPACT HISTOLOGIC TREATMENT RESPONSE TO SURVODUTIDE IN A MASH PHASE II STUDY

Arun Sanyal[1] Daniel Mazo[2] Malgorzata Borowska[2] Julian Schwab[2] Panagiotis Papavasileiou[2] Corinna Schoelch[2] Raphael Hesse[2], [1]Virginia Commonwealth University, [2]Boehringer Ingelheim

Background: Genetic variation, particularly in *PNPLA3*, *TM6SF2* and *HSD17B13*, is a major determinant of susceptibility and progression in metabolic dysfunction–associated steatohepatitis (MASH). Survodutide, a glucagon receptor/ glucagon-like peptide-1 (GLP-1) receptor dual agonist, is being developed for MASH and obesity. This pharmacogenomic analysis from the MASH phase II study evaluated whether *PNPLA3*, *TM6SF2* and *HSD17B13* genotypes influences two predefined histological endpoints. **Methods:** Participants underwent baseline genotyping for *PNPLA3* variant rs738409 (I148M), *TM6SF2* variant rs58542926 and *HSD17B13* variant rs72613567. In addition, an unweighted polygenic risk score (PRS) was calculated from these three variants. Associations between genotypes/PRS and (1) histological resolution of MASH without worsening of fibrosis, and (2) fibrosis improvement without worsening of MASH were assessed. Their effect modifications were evaluated by fitting a multivariable logistic regression model, including a treatment-by-genotype interaction term. Within each single nucleotide polymorphism (SNP)/ PRS genotype stratum, response rates between active treatment and placebo were compared using Fisher's exact test. The p-values were adjusted for multiple hypothesis testing using False discovery rate. **Results:** *PNPLA3*, *TM6SF2* and *HSD17B13* genotypes as well as a PRS calculated from these 3 variants did not impact histological treatment response to survodutide. Rates of MASH resolution without fibrosis worsening, and fibrosis improvement without worsening of MASH were comparable across genotypes ($p = 0.782$ and $p = 0.984$, respectively) and PRS groups ($p = 0.816$ and $p = 0.694$, respectively). Survodutide demonstrated consistent efficacy independent of *PNPLA3*, *TM6SF2* and *HSD17B13* variant status, including the risk alleles. No evidence of effect modification by genotype was detected. **Conclusion:** In this phase II trial in participants with MASH, *PNPLA3*, *TM6SF2* and *HSD17B13* genotypes did not influence response to survodutide with respect to two histological endpoints. These findings suggest that the efficacy of survodutide treatment is independent of *PNPLA3*, *TM6SF2* and *HSD17B13* genetic variation, supporting its therapeutic potential across genetically diverse patient populations. **Disclosures:** Arun Sanyal: Nothing to Disclose, Daniel Mazo:Boehringer Ingelheim International GmbH: Employee, Malgorzata Borowska:Nothing to Disclose, Julian Schwab:Boehringer Ingelheim Pharma GmbH&Co.KG: Employee, Panagiotis Papavasileiou: Nothing to Disclose, Corinna Schoelch:Nothing to Disclose, Raphael Hesse:Boehringer Ingelheim: Employee.

3532 | RESEARCH ON THE PATHOLOGICAL MECHANISM OF DRAK2 IN MEDIATING MASH PROGRESSION AND NOVEL DRUG DISCOVERY

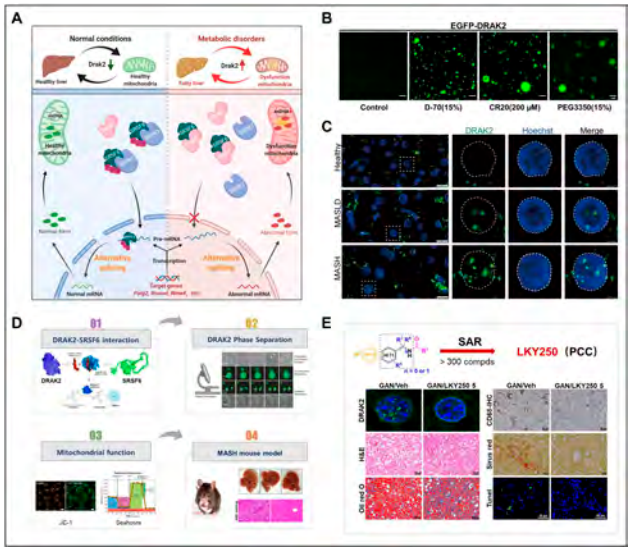
Yufeng Li[1] Yidan Huang[2], [1]Shanghai Institute of Materia Medica, CAS, [2]Shanghai Institute of Materia Medica, Chinese Academy of Sciences

Background: Metabolic dysfunction-associated steatohepatitis (MASH) is a progressive liver disease driven by lipotoxicity, yet how lipid overload is transduced into inflammation and fibrosis remains incompletely understood. Dysregulated RNA splicing contributes to MASH pathogenesis. DRAK2 (STK17B) is a DAPK family kinase linked to cell survival and proliferation. DRAK2 is upregulated in MASLD/MASH. Our previous work showed DRAK2 binds SRSF6, regulates alternative splicing of mitochondrial genes (e.g., *Polg2*), and drives mitochondrial dysfunction (Cell Metabolism, 2021). Here, we further investigate the underlying mechanism and identify a small-molecule inhibitor targeting DRAK2-SRSF6 interaction and DRAK2 phase separation. **Methods:** Human liver biopsies, GAN-diet fed mice, primary hepatocytes, and purified proteins were used. Multi-omics, Co-IP, RNA-seq, and alternative splicing analysis were performed. Phase separation was assessed by turbidity, FRAP, and mutagenesis. A NANOBIT-based screen was conducted to discover inhibitors of DRAK2-SRSF6 interaction. LKY250 was validated in vitro and in a therapeutic MASH model. **Results:** DRAK2 was markedly upregulated in MASLD/ MASH patients and model mice. Hepatic DRAK2 deletion suppressed steatosis-to-MASH progression. DRAK2 directly bound SRSF6, inhibited its phosphorylation by SRPK1, and regulated alternative splicing of mitochondrial function-related genes, including pathological splicing of *Polg2* which reduced mtDNA

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replication efficiency and impaired mitochondrial homeostasis. In further studies, we found that DRAK2 underwent aberrant liquid-to-solid phase transition under lipotoxic stress, forming condensates that sequestered SRSF6 and spliceosomal components, leading to spliceosome solidification and widespread splicing errors. Through screening, we identified LKY250, a first-in-class inhibitor that disrupts DRAK2-SRSF6 interaction and DRAK2 condensation. LKY250 restored splicing fidelity, preserved mitochondrial integrity, and attenuated inflammation and fibrosis in MASH mice. **Conclusion:** DRAK2 drives MASH by both SRSF6-mediated splicing regulation and phase separation-induced spliceosome dysfunction. Targeting DRAK2-SRSF6 interaction or DRAK2 condensation with LKY250 offers a promising therapeutic strategy for the inflammatory-fibrotic axis of advanced MASH.



Disclosures: Yufeng Li:Nothing to Disclose, Yidan Huang:Nothing to Disclose.

3533 | SAFETY AND EFFICACY OF J2H-1702, A NOVEL 11β-HSD1 INHIBITOR, IN MASLD: A PHASE 2A RANDOMIZED CONTROLLED TRIAL

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Background: Intrahepatic glucocorticoid excess, mediated by 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1), is a validated mechanism driving hepatic steatosis and metabolic dysfunction. J2H-1702, a novel selective 11β-HSD1 inhibitor, demonstrated favorable metabolic and antifibrotic effects in preclinical models. We evaluated the efficacy and safety of J2H-1702 in patients with metabolic dysfunction-associated steatotic liver disease (MASLD). **Methods:** In this multicenter, randomized, double-blind, and placebo-controlled trial, 87 patients with MASLD were randomly assigned to oral administration of J2H-1702 50 mg, 100 mg, 200 mg, or placebo once daily for 12 weeks in a 1:1:1:1 ratio. MASLD was defined as magnetic resonance imaging-proton density fat fraction (MRI-PDFF) $\geq$8% and magnetic resonance elastography (MRE) $\geq$2.5 kPa. Co-primary endpoints were percent change in hepatic fat by MRI-PDFF and hepatic stiffness by MRE at week 12. **Results:** All 87 patients were included in the full analysis set (50 mg, n = 22; 100 mg, n = 22; 200 mg, n = 22; placebo, n = 21). At week 12, J2H-1702, especially 200 mg, produced a significant reduction in hepatic fat by MRI-PDFF (−18.7% vs. +3.1%; LS mean difference, −22.3%; p = 0.011), alongside improvements in liver enzymes, body weight, and low-density lipoprotein cholesterol. No significant change in hepatic stiffness by MRE was observed. Treatment-emergent adverse events were mild and comparable across groups. Increases in adrenocorticotropic hormone and dehydroepiandrosterone, consistent with on-target 11β-HSD1 inhibition, were transient and resolved after treatment discontinuation. **Conclusion:** In this exploratory phase 2a study, J2H-1702 showed a reduction in hepatic steatosis, liver enzymes, and cardiometabolic parameters with a favorable safety profile in patients with MASLD over 12 weeks, supporting further clinical development.

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3534 | DISCOVRY OF A NOVEL ACLY INHIBITOR FOR MASH TREATMENT AND CLINICAL TRANSLATION

Zhifu Xie[1] Jingya Li[2] Fajun Nan[2], [1]Shanghai Institute of Materia Medica, [2]Shanghai Institute of Materia Medica, Chinese Academy of Sciences

Background: Metabolic dysfunction-associated steatohepatitis (MASH) is a progressive liver disease characterized by excessive lipid accumulation, inflammation, and hepatocyte injury, which can develop into cirrhosis and hepatocellular carcinoma. Hepatic de novo lipogenesis (DNL) is significantly elevated in MASH patients, and ATP-citrate lyase (ACLY) is a key enzyme promoting DNL. Peroxisome proliferator-activated receptor α (PPARα) activation enhances fatty acid oxidation but has limited efficacy in treating hepatic steatosis. The enedioic acid analog 326E, an ACLY inhibitor with proven efficacy in atherosclerosis and hypercholesterolemia (***Acta Pharm***

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Sin B . 2023), has not been investigated for its therapeutic potential in MASH. **Methods:** RNA sequencing and immunohistochemistry were used to analyze ACLY expression in liver samples from MASH patients and mice. Primary mouse hepatocytes and Acly-knockout (Acly-KO) hepatocytes were employed to evaluate 326E's effect on DNL. Multiple MASH models were established, including high-fructose diet (HFrD)-induced, Gan diet-induced ob/ob, and choline-deficient L-amino acid-defined high-fat diet (CDAA-HFD) mouse models, as well as cynomolgus monkey models, to assess 326E's in vivo efficacy. Lipid-targeted metabolomics, BODIPY staining, and biochemical analyses were used to detect lipid accumulation and liver function indices. A phase 1b/2a clinical trial (NCT06491576) was conducted to evaluate 326E's safety and efficacy in MASH patients. **Results:** ACLY expression was significantly upregulated in MASH patients and positively correlated with NAS score, ALT, and AST. 326E selectively inhibited ACLY to reduce DNL in a dose-dependent manner, and this effect was abolished in Acly-KO hepatocytes. In various MASH mouse models, 326E reduced hepatic lipid accumulation, improved steatosis, alleviated inflammation and fibrosis, and regulated lipid metabolism. It dual-targeted ACLY and PPARα (as an allosteric modulator) to enhance fatty acid oxidation and mitochondrial function, which was PPARα-dependent. 326E effectively alleviated MASH symptoms in cynomolgus monkeys and showed good tolerability and oral bioavailability in clinical trials, reducing circulating γ-glutamyl transferase (γ-GGT) levels in MASH (Clinical trial: NCT06491576; ***Cell Metab.***, 2025). **Conclusion:** 326E exerts therapeutic effects on MASH by dual targeting ACLY and PPARα, inhibiting DNL and enhancing fatty acid oxidation. Its favorable preclinical and clinical performance supports its potential as a promising candidate for MASH treatment, warranting further clinical evaluation.

Disclosures: ZHIFU XIE:Nothing to Disclose, Jingya Li:Nothing to Disclose, Fajun Nan:Nothing to Disclose.

3535 | FIRST-IN-CLASS ORAL IKKK/α INHIBITOR HPN-01 DEMONSTRATES DISEASE-MODIFYING ACTIVITIES THROUGH SUPPRESSION OF HEPATIC FIBROGENESIS AND INFLAMMATION ASSOCIATED WITH MASH

Belle Wang[1] Yongmei Li[1] Min Zhang[1] Amy Pan[1] T Jake Liang[2] Qisheng Li[1], [1]Hepanova, Inc., [2]National Institute of Diabetes, Digestive

Background: Metabolic dysfunction-associated steatohepatitis (MASH) with fibrosis is a leading cause of cirrhosis and hepatocellular carcinoma (HCC). Current therapies primarily target hepatic steatosis but incompletely address inflammation and fibrogenesis, key drivers of disease progression. Hepatic stellate cell (HSC) activation plays a central role in fibrosis development and remains an important unmet therapeutic target. HPN-01 is a first-in-class, orally administered, highly selective long-acting dual IKKα/β inhibitor designed to simultaneously modulate steatosis, inflammation, and fibrosis. We evaluated the mechanistic and comparative efficacy profile of HPN-01, with emphasis on its anti-fibrotic and anti-inflammatory activities. **Methods:** Mechanistic studies investigated IKKα-regulated pathways involved in hepatic inflammation, lipogenesis and fibrogenesis using transcriptomic analyses by RNA-Seq. Anti-fibrotic activity was evaluated in diet-induced MASH animal models through histopathology, collagen deposition, fibrosis scoring, and molecular analyses of key inflammatory and fibrogenic mediators. Comparative efficacy studies were performed against resmetirom. Clinical safety and pharmacokinetic (PK) characteristics were assessed in a randomized, placebo-controlled Phase 1 study in healthy volunteers (25–150 mg; n = 8/cohort). **Results:** HPN-01 directly suppresses multiple IKKα-regulated pathways involved in hepatic inflammation, fibrogenesis and HSC activation. Treatment significantly reduced expression of fibrosis- and inflammation-associated mediators including MCP-1, LOX, TGF-β, and ITGA2, accompanied by reductions in α-SMA expression, collagen-I deposition, and fibrosis scores. Concurrent improvements in steatosis and inflammatory activities resulted in reduced NAS scores in MASH models. Compared with resmetirom, HPN-01 demonstrated greater suppression of key fibrogenic pathways, stronger attenuation of liver inflammation, and improved protection against liver injury without ALT/AST elevation. While resmetirom primarily improved lipid parameters, HPN-01 exhibited disease-modifying activities centered on inflammation and fibrosis pathway regulation. HPN-01 additionally suppressed HCC progression and tumor burden in preclinical models. In a Phase 1 study, HPN-01 was well tolerated without dose-limiting toxicities and demonstrated an extended half-life, supporting infrequent oral dosing. **Conclusion:** HPN-01 is a mechanistically novel first-in-class IKKα/β inhibitor that directly suppresses MASH-related liver injury including inflammation, fibrogenesis and steatosis in preclinical models. Its unique anti-fibrotic/inflammatory activities, favorable safety profile, and long-acting PK support further clinical development as

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a potential disease-modifying therapy for advanced MASH and prevention of progression to HCC.
Disclosures: Belle Wang:Nothing to Disclose, Yongmei Li:Nothing to Disclose, Min Zhang:Hepanova, Inc.: Employee, Amy Pan:Nothing to Disclose, T Jake Liang: Nothing to Disclose, Qisheng Li:Nothing to Disclose.

3536 | AN ORAL INHIBITOR OF CBP/β-CATENIN SIGNALING IMPROVES HEPATIC STEATOSIS, FIBROSIS,

Kenzaburo Yamaji[1] Risa Kono[1] Ryusei Furusawa[1] Tadashi Imafuku[2] Sadahiro Iwabuchi[2] Shinichi Hashimoto[2] kiminori Kimura[3] Takeshi Okanoue[4] Kyoko Tsukiyama-Kohara[5] Michinori Kohara[1], [1]Tokyo Metropolitan Institute of Medical Science, [2]Wakayama Medical University, [3]Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, [4]Saiseikai Suita Hispital, [5]Kagoshima University

Background: Metabolic dysfunction associated steatohepatitis (MASH) is a progressive liver disease. However, an effective treatment strategy has yet to be established. We have previously reported on the efficacy of PRI-724, a second-generation, selective CBP/β-catenin antagonist. PRI-724 recovered from liver fibrosis and inflammation induced by choline-deficient, L-amino acid-defined, high-fat diet (CDAHFD) in mice. However, PRI-724 must be administered intravenously. It is a prodrug that is rapidly hydrolyzed *in vivo* to form its active metabolite, C-82. In this study, we investigated the efficacy of oral C-82 administration in an MASH animal model and elucidated its mechanism of action. **Methods:** To establish an obese mouse model of MASH, we used two mouse models, C57/BL6J mice fed GAN (Gubra-Amylin NASH) diet for 46 weeks or 7 weeks of age db/db mice. C-82 was administered orally in GAN diet-fed mice once daily for 12 weeks or in db/db mice once daily for 10 weeks. The efficacy of C-82 was evaluated based on the resolution of fatty liver disease, improvements in liver function, and reductions in liver fibrosis. Furthermore, glucose tolerance tests and analyses of changes in skeletal muscle strength and mass were conducted to assess hepatocyte function. **Results:** GAN diet-fed mice exhibited obesity, hypercholesterolemia, and liver fibrosis characterized by steatosis, lobular inflammation, hepatocyte damage, and collagen deposition. Prothrombin time (PT) activity (%) decreased significantly by week 46. Administering C-82 to GAN diet-fed mice significantly reduced body weight and serum total cholesterol levels. PT (%) improved from 38.8 ± 11.2% to 63.3 ± 31.6%. Additionally, hepatic lipid droplets and hepatic type I and III collagen expression levels (markers of liver fibrosis) were significantly reduced. Serum ALT levels, which were elevated in MASH model mice, decreased significantly, indicating an anti-inflammatory effect. Furthermore, glucose AUC values were significantly reduced, indicating improved glucose tolerance. Although muscle mass in db/db mice was lower than that in age-matched C57BL/6J mice, it was significantly higher in db/db mice treated with C-82 (C57BL/6J = 502.6 ± 47.8 mg/100 g BW, db/db vehicle = 159.6 ± 20.9 mg/100 g BW, db/db C-82 = 250.6 ± 58.5 mg/100 g BW). Furthermore, grip strength in C-82-treated db/db mice was significantly higher than in the untreated group. **Conclusion:** Oral administration of C-82 improves MASH-like liver damage (steatosis, dysfunction, and inflammation) and liver fibrosis. Furthermore, improvements in glucose tolerance and increases in muscle strength and mass were observed. C-82, an oral inhibitor of the CBP/β-catenin signaling pathway, demonstrates potent therapeutic effects on MASH-associated liver fibrosis, steatosis, glucose tolerance, and muscle loss.
Disclosures: Kenzaburo Yamaji:Nothing to Disclose, Risa Kono:Nothing to Disclose, Ryusei Furusawa: Nothing to Disclose, Tadashi Imafuku:Nothing to Disclose, Sadahiro Iwabuchi:Nothing to Disclose, Shinichi Hashimoto:Nothing to Disclose, kiminori Kimura: Nothing to Disclose, Takeshi Okanoue:Nothing to Disclose, Kyoko Tsukiyama-Kohara:Nothing to Disclose, Michinori Kohara:Nothing to Disclose.

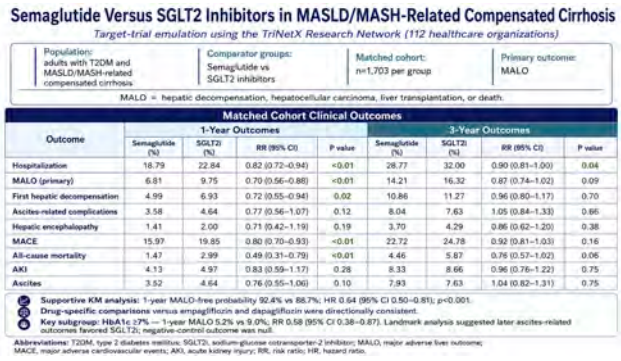
3537 | SEMAGLUTIDE VERSUS SGLT2 INHIBITORS IN MASLD/MASH-RELATED COMPENSATED CIRRHOSIS: A TARGET-TRIAL EMULATION OF MAJOR ADVERSE LIVER OUTCOMES (MALO) AND MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE)

Mohammad Alabbas[1] Akram Alnounou[2] Ahmad Alhusen[3] Riddhi Machchhar[4] Omar Sims[1] Richard Sterling[5], [1]Cleveland Clinic Foundation, [2]Department of Internal Medicine, Western Michigan University Homer Stryker M.D. School of Medicine,, [3]Department of Internal Medicine, Advocate Illinois Masonic Medical Center, Chicago, IL, USA, [4]Department of Internal Medicine, Hackensack Meridian Health Ocean University Medical Center, Brick,, [5]Virginia Commonwealth University

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Background: Adults with type 2 diabetes mellitus (T2DM) and MASLD/MASH-related compensated cirrhosis have high risks of decompensation, cardiovascular events, hospitalization, and death. Semaglutide and SGLT2 inhibitors (SGLT2i) are metabolic therapies, but comparative data on hard cirrhosis outcomes are limited. **Methods:** We emulated a target trial in the TriNetX Research Network (112 healthcare organizations). Adults with T2DM, MASLD/MASH, and compensated cirrhosis initiating semaglutide or an SGLT2i on or after January 1, 2018, were included. Patients with prior exposure to either class, hepatic decompensation/MALO components, HCC, transplant, ESRD/dialysis, HIV, malignancy, or other liver diseases were excluded. New users were 1:1 propensity-score matched on demographics, comorbidities, medications, and laboratory values. The primary outcome was major adverse liver outcome (MALO: decompensation, HCC, liver transplantation, or death). Secondary outcomes included hospitalization, first decompensation, MACE, mortality, acute kidney injury (AKI), encephalopathy, ascites, and ascites-related complications. Supportive analyses included Kaplan–Meier, drug-specific, subgroup, 12-month MALO-free landmark, E-value, and negative-control analyses. **Results:** After matching, 1,703 semaglutide and 1,703 SGLT2i initiators were well balanced (all SMD < 0.10). At 1 year, semaglutide was associated with lower MALO (6.8% vs 9.7%; RR 0.70, 95% CI 0.56–0.88; $p < 0.01$), hospitalization (18.8% vs 22.8%; RR 0.82, 95% CI 0.72–0.94), first decompensation (5.0% vs 6.9%; RR 0.72, 95% CI 0.55–0.94), MACE (16.0% vs 19.9%; RR 0.80, 95% CI 0.70–0.93), and mortality (1.5% vs 3.0%; RR 0.49, 95% CI 0.31–0.79; all secondary $p \leq 0.02$). MALO-free probability was 92.4% versus 88.7% (HR 0.64, 95% CI 0.50–0.81; $p < 0.001$). AKI, encephalopathy, ascites, and ascites-related complications did not differ. At 3 years, hospitalization remained lower (28.8% vs 32.0%; RR 0.90, 95% CI 0.81–1.00; $p = 0.04$), whereas MALO, MACE, mortality, decompensation, AKI, and ascites-related outcomes were not significantly different. Drug-specific comparisons versus empagliflozin and dapagliflozin were directionally consistent; the strongest MALO signal occurred with HbA1c $\geq 7\%$ (5.2% vs 9.0%; RR 0.58, 95% CI 0.38–0.87). In landmark analysis, late ascites-related outcomes favored SGLT2i; the negative-control outcome was null. **Conclusion:** In T2DM with MASLD/MASH-related compensated cirrhosis, semaglutide initiation was associated with early reductions in liver and cardiometabolic events versus SGLT2i, without excess AKI or ascites-related events. Benefit attenuated over time except for hospitalization, while landmark findings suggest a potential later SGLT2i advantage for fluid/ascites phenotypes, supporting prospective phenotype-guided trials of GLP-1 receptor agonist, SGLT2i, and combination strategies.



Disclosures: Mohammad Alabbas:Nothing to Disclose, Akram Alnounou:Nothing to Disclose, Ahmad Alhusen:Nothing to Disclose, Riddhi Machchhar:Nothing to Disclose, Omar Sims:Nothing to Disclose, Richard Sterling:ABIM: GI Specialty Board, Abbott: Grant/Research Support, GSK: Grant/Research Support, HCV Vax: Grant/Research Support, Gilead: Grant/Research Support, Zydus: Grant/Research Support, Vertex: Consultant, Madrigal: Advisor, Gigagen: Grant/Research Support, Atea: Grant/Research Support, Cima Science: Consultant, Celaris: Consultant, GSK: Advisor.

3538 | NOVEL ANTISENSE OLIGONUCLEOTIDES ENHANCE ENDOGENOUS FGF21 EXPRESSION AND AMELIORATE DYSLIPIDEMIA AND HEPATIC STEATOSIS IN PRECLINICAL METABOLIC DISEASE MODELS

Lingdi Zhang[1] Lansha Peng[1] Jian Li[1] Surendra Jain[1] Rich Thai[1] Xing Xian Yu[1] Yanfeng Wang[1] Xuehai Liang[1], [1]Arnatar Therapeutics INC

Background: Fibroblast growth factor 21 (FGF21) is a liver-derived metabolic hormone that regulates lipid metabolism, fatty acid oxidation, and inflammation. Pharmacologic FGF21 analogs have demonstrated clinical activity. However, increasing endogenous FGF21 may offer advantages by preserving physiologic regulation and tissue-specific responses. We developed ART7, a proprietary dual-functional antisense oligonucleotide (ASO) that increases endogenous FGF21 expression by simultaneously stabilizing FGF21 mRNA and enhancing translation. This study evaluated the pharmacologic activity and efficacy of the lead ASO candidate ART7 and active compounds in preclinical models of metabolic disease. **Methods:** FGF21-upregulating ASOs were evaluated in human, nonhuman primate, mouse, and rat cell lines. FGF21

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expression was assessed by qRT-PCR, Western blotting, and ELISA. In vivo pharmacodynamic and efficacy studies were conducted in normal mice and rats, with proof-of-concept studies performed in diet-induced obese (DIO) mice and LDL receptor knockout (LDLR−/−) mice. Plasma lipids, liver histology, FGF21 protein expression, and downstream metabolic pathway markers were analyzed. **Results:** ART7 increased FGF21 mRNA expression by approximately 50–100% and elevated FGF21 protein levels by approximately 50–200% across multiple species and cell types in vitro. In vivo, subcutaneous administration induced sustained plasma FGF21 upregulation lasting 4–5 weeks after dosing. In DIO mice, ART7 treatment reduced liver weight, hepatic fat accumulation, AST, and cholesterol levels, while increasing markers associated with fatty acid oxidation and suppression of inflammatory signaling pathways. In LDLR−/− mice, ART7 reduced triglycerides by up to 56%, LDL-C by >35%, and non-HDL cholesterol by >35%, without lowering HDL-C. Significant reductions in hepatic steatosis (~60–75%), liver fat content, and plasma nonesterified fatty acids (NEFA) were also observed. Additional active ASOs demonstrated comparable or improved lipid-lowering efficacy, achieving triglyceride reductions of up to 70%. In head-to-head studies, FGF21-targeting ASOs achieved triglyceride lowering comparable to or greater than that achieved with FGF21 analogs. **Conclusion:** ART7 FGF21-upregulating ASOs represent a novel therapeutic strategy that enhances endogenous FGF21 expression and produces durable improvements in plasma lipid profiles and hepatic steatosis across multiple preclinical models. These findings support further development of FGF21-targeting ASOs as long-acting therapies for severe hypertriglyceridemia (SHTG) and metabolic liver disease.

Disclosures: Lingdi Zhang:Nothing to Disclose, Lansha Peng:Nothing to Disclose, Jian Li:Nothing to Disclose, Surendra Jain:Nothing to Disclose, Rich Thai:Nothing to Disclose, Xing Xian Yu:Nothing to Disclose, Yanfeng Wang:Nothing to Disclose, Xuehai Liang:Nothing to Disclose.

3539 | EFFICACY AND SAFETY OF LIVPHCD™ CAPSULES VERSUS PLACEBO IN METABOLIC DYSFUNCTION-ASSOCIATED FATTY LIVER DISEASE: A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL

Chun-Jen Liu[1] Cheng Tiong[2] Yi-Hsiang Huang[3] Tung-Hung Su[1] Wei-Yu Kao[2] Chun-Chao Chang[2] Hsing-Jung Yeh[2] Wen-Chao Chen[2] Ya-Chun Wang[4] Wen Chuan Huang[4], [1]National Taiwan University Hospital, [2]Taipei Medical University Hospital, [3]Taipei Veterans General Hospital, [4]TCM Biotech International Corp.

Background: Metabolic dysfunction-associated fatty liver disease (MASLD) is the most common liver disease around the world. LivPhcD™ Capsule have shown hepatoprotective effects in both animal and human data. The aim of this clinical study (LivPhcD-001) is to assess LivPhcD™ Capsules's efficacy and safety in patients with MASLD. **Methods:** This clinical trial, LivPhcD-001, is a multicenter, randomized, double-blind, placebo-controlled, 36-week study that was initiated at 3 medical centers in Taiwan. Adults with FibroScan™ confirmed MASLD, defined as having a hepatic steatosis level with a controlled attenuated parameter (CAP) score of 238 dB/m or higher, with stage F0 to F3 fibrosis, were randomly assigned (1:1:1:1) to receive placebo or LivPhcD™ Capsules, low dose: 2 capsules, intermediate dose: 4 capsules, or high dose: 6 capsules per day. The primary endpoint was the proportion of patients with improvement in hepatic steatosis of at least 10% of CAP, based on analyses of baseline, week 24, and week 36 by FibroScan™. Prespecified secondary and exploratory efficacy and safety endpoints were also evaluated. **Results:** Totally, 125 patients with MASLD were screened, and 110 were randomized to receive either 2, 4, or 6 capsules of LivPhcD™ Capsule (n = 27, 28, 27) or placebo (n = 28). By Week 36, the treatment groups showed improvements in hepatic steatosis and biochemistry. Low and high dose groups showed a statistically significant reduction in CAP. MRI-PDFF in the high dose group decreased by 2.348% while the placebo group increased by 2.158%. A significant ALT improvement was also observed as early as week 24 in the intermediate and high dose groups ($P < 0.05$). At week 36, serum ALT level was significantly reduced in the low (-4.9 U/L), intermediate (-5.4 U/L), and high (-3.0 U/L) dose groups, whereas increased in the placebo group (6.5 U/L). Furthermore, the high dose group demonstrated lipid-lowering effects, with placebo-adjusted reductions of 19 mg/dL in total cholesterol and 19.5 mg/dL in LDL-C ($P < 0.05$). **Conclusion:** Patients with MASLD, treated with LivPhcD™ Capsule over 36 weeks demonstrated clinical benefits in reducing hepatic fat content, as evidenced by the consistent improvements in CAP and MRI-PDFF, alongside the stabilization of liver biochemistry. Notably, the significant reductions of LDL-C and total cholesterol showed that LivPhcD™ Capsule may offer additional cardiometabolic protection beyond its hepatic effects. These findings indicate the therapeutic potential of LivPhcD™ Capsule in addressing both liver steatosis and the associated cardiovascular metabolic risks in the MASLD population, and also support its continuing clinical development.(ClinicalTrials.gov,

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NCT05930093)

Parameters		Week	Placebo (N=28)	Low Dose (N=27)	Mid Dose (N=28)	High Dose (N=27)
CAP Mean (dB/m)		BL	304.1 ± 30.5	311.4 ± 44.5	308.6 ± 36.8	305.9 ± 34.1
	CFB	W24	5.3 ± 37.5	-19.1± 38.5*	-14.6 ± 41.0	-13.4 ± 29.6*
	Diff	W24		-24.4	-19.9	-18.7
	CFB	W36	-5.3 ± 42.9	-28.4 ±47.6	-18.1 ±40.3	-22.8 ±38.0
	Diff	W36		-23.1	-12.8	-17.5
MRI-PDFF(%)$		BL	12.705 ± 7.976			14.276 ± 10.278
	CFB	W36	2.158 ±8.098			-2.348 ±4.235
	Diff	W36				-4.506
ALT (U/L)		BL	36.5 ± 22.9	41.6 ± 26.6	36.0 ± 18.3	31.5 ± 22.0
	CFB	W24	6.3 ±14.0	-2.0 ± 29.7	-3.5 ± 18.7*	-0.9 ± 10.6*
	Diff	W24		-8.3	-9.8	-7.2
	CFB	W36	6.5 ±14.3	-4.9 ±24.9*	-5.4 ±17.1*	-3.0 ±16.0*
	Diff	W36		-11.4	-11.9	-9.5
AST (U/L)		BL	25.9 ± 11.4	30.4 ± 14.9	26.3 ± 12.1	23.7 ± 11.4
	CFB	W24	2.0 ±10.9	-2.5 ± 15.4	-3.1 ± 13.6	-1.6 ± 6.5
	Diff	W24		-4.5	-5.1	-3.6
	CFB	W36	3.3 ±13.3	-4.0 ±13.6*	-3.9 ±12.0*	-2.3 ±9.9
	Diff	W36		-7.3	-7.2	-5.6
TC (mg/dL)		BL	194.1 ± 49.0	182.6 ± 39.2	191.9 ± 39.0	193.0 ± 38.2
	CFB	W36	8.7 ±27.7	-5.9 ±27.7	-5.5 ±29.9	-10.3 ± 28.8*
	Diff	W36		-14.6	-14.2	-19.0
LDL-C (mg/dL)		BL	126.1± 43.7	108.2 ± 33.6	124.7 ± 32.9	127.0 ± 36.1
	CFB	W36	8.4 ± 25.3	-6.0 ± 23.1*	-3.3 ± 25.4	-11.1 ± 26.0*
	Diff	W36		-14.4	-11.7	-19.5

All values are mean ± SD;
*$P<0.05$, pairwise comparisons between each dose group and placebo are based on independent-sample t test.
AST, aspartate aminotransferase; ALT, alanine aminotransferase; BL, baseline, performed at screening; CAP, controlled attenuated parameters as determined by FibroScan™; CBL: change from baseline; Diff: mean difference vs placebo; LDL-C, low-density lipoprotein cholesterol; TC, cholesterol, W24, Week 24; W36, Week 36.
$, for MRI-PDFF in placebo group N=6 and High Dose group N=17.

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3540 | SYNERGY OF SOAT2-INHIBITOR PRD001 WITH RESMETIROM IN REDUCING MASH AND FIBROSIS IN OBESE LDLR-/-.LEIDEN MICE

Eveline Gart[1], [1]TNO

Background: Metabolic-dysfunction associated steatohepatitis (MASH) is characterized by hepatic lipid accumulation and inflammation. Sterol *O*-acyltransferase 2 (SOAT2), formerly known as ACAT2, plays a key role in intestinal cholesterol absorption and hepatic secretion. Pharmacological inhibition of SOAT2 reduces cholesterol uptake, thereby limiting hepatic lipid accumulation and secretion. Combining a SOAT2-inhibitor with resmetirom, a thyroid hormone receptor-β (THR-β) agonist that promotes lipid oxidation, could provide complementary reductions in fat and plasma lipids. This study aimed to assess the effects of PRD001, a SOAT2-inhibitor, combined with resmetirom on MASH and liver fibrosis. **Methods:** 20-week high-fat diet (HFD) without cholesterol supplementation fed Ldlr-/-.Leiden mice received vehicle, resmetirom (3 mg/kg), or resmetirom + PRD001 (30 mg/kg) for 12 weeks. **Results:** Resmetirom and the combination treatment reduced body weight and fat mass, while increasing lean body mass as % of body weight. Fecal neutral sterol excretion, mainly driven by cholesterol excretion, was significantly increased with resmetirom and tended to be further enhanced when combined with PRD001. Resmetirom decreased plasma lipids and apoB with a significant further decrease for both when combined with PRD001. Lipoprotein profiles confirmed that this additional decrease was primarily due to a further decrease in VLDL- and LDL-cholesterol. Hepatic triglycerides and cholesterol esters were significantly decreased as well with resmetirom and combination with PRD001 led to a significant further decrease in hepatic cholesterol ester content. Hepatic macrovesicular steatosis, microvesicular steatosis, inflammation and fibrosis were all significantly reduced upon resmetirom treatment with a further decease in macro- and microvesicular steatosis when combined with PRD001. Hepatic gene expression confirmed involvement of (lipid)metabolism, inflammation pathways and mitochondrial pathways with more significant genes when resmetirom was combined with PRD001. **Conclusion:** Using an advanced translational MASH model, we demonstrate resmetirom improved MASH and hepatic fibrosis. Adding PRD001 provided additional benefits on cholesterol excretion, plasma lipids, lipoproteins and steatosis highlighting the complementary mechanisms of PRD001 and resmetirom. Given the CVD risk in MASH patients, the observed lowering of atherogenic lipoproteins underscore substantial clinical advantages for the combination treatment.
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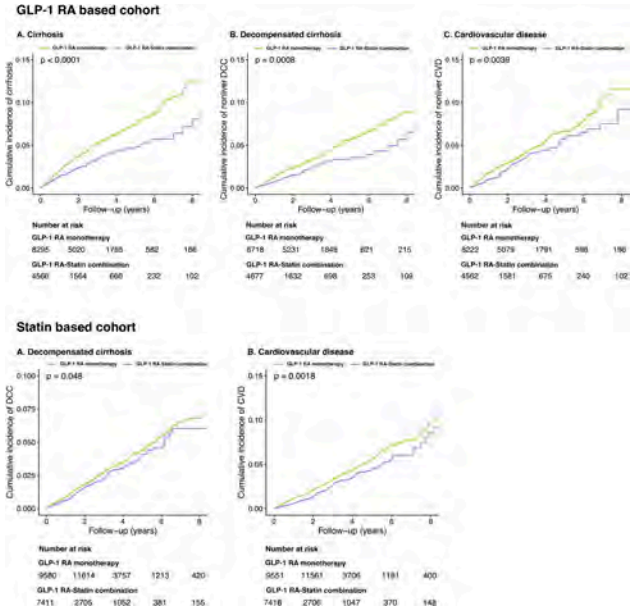
3541 | | CLINICAL OUTCOMES ASSOCIATED WITH GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONIST-STATIN COMBINATION VS MONOTHERAPY IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE - A TARGET TRIAL EMULATION STUDY

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Background: Metabolic dysfunction–associated steatotic liver disease (MASLD) is a multisystem condition characterized by intertwined metabolic, hepatic, and cardiometabolic risks. Although glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and statins have been associated with improved hepatic and cardiometabolic outcomes, evidence on the real-world effectiveness of their combined use across different background treatment contexts remains limited. Our goal was to examine the associations of GLP-1 RA-statin combination therapy with hepatic and extrahepatic outcomes among patients with MASLD according to background treatment context. **Methods:** We conducted a large real-world cohort study emulating a target trial using a nationally representative claims database (Merative™ MarketScan®). Using an active-comparator new-user design with time-conditional propensity score matching, we compared add-on statin therapy versus continuation of GLP-1 RA monotherapy among GLP-1 RA initiators, and add-on GLP-1 RA therapy versus continuation of statin monotherapy among statin initiators, and evaluated the associated risks of cirrhosis, decompensated cirrhosis (DCC), hepatocellular carcinoma (HCC), cardiovascular disease (CVD), chronic kidney disease (CKD), and non-liver cancers among patients with MASLD. **Results:** Among GLP-1 RA initiators, add-on statin use was associated with lower risks of cirrhosis (hazard ratio [HR], 0.65; 95% CI, 0.53–0.80), DCC (HR, 0.65; 95% CI, 0.50–0.84), and non-liver cancers (HR, 0.73; 95% CI, 0.59–0.90) compared with GLP-1 RA monotherapy. Conversely, among statin initiators, add-on GLP-1 RA use was associated with a lower risk of CVD in the overall population (HR, 0.74; 95% CI, 0.61–0.89) and with lower risks of cirrhosis and DCC in metabolically high-risk subgroups (e.g., higher CCI, diabetes). Protective associations were more pronounced in metabolically high-risk subgroups in both sequential add-on cohorts. No significant associations were observed for other outcomes, and findings were consistent across sensitivity analyses. **Conclusion:** In this real-world MASLD population, GLP-1 RA-statin combination therapy was associated with significant clinical benefits compared with either monotherapy, with patterns of benefit varying by background treatment context that likely reflect differences in dominant clinical risk pathways. Findings support individualized and complementary treatment strategies in MASLD, in which GLP-1 RAs and statins may be used to target residual hepatic, metabolic, and cardiovascular risk according to patients' dominant disease pathways and background treatment context.



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3542 | ANTISENSE-MEDIATED UPREGULATION OF HNF4α IMPROVES LIVER FIBROSIS IN PRECLINICAL MODELS OF MASH AND TOXIN-INDUCED LIVER INJURY

Lingdi Zhang[1] Terry Lin[1] Surendra Jain[1] Jian Li[1] Rich Thai[1] Lansha Peng[1] Xing Xian Yu[1] Yanfeng Wang[1] Xuehai Liang[1], [1]ARNATAR THERAPEUTICS INC

Background: HNF4α is a master transcription factor essential for hepatic differentiation, metabolic homeostasis, and liver function. Reduced hepatic HNF4α expression is associated with metabolic dysfunction-associated steatohepatitis (MASH), liver fibrosis, cirrhosis, and hepatocellular carcinoma. Although restoration of HNF4α expression has demonstrated therapeutic benefit in preclinical models, safe and clinically feasible strategies to precisely enhance endogenous HNF4α expression remain limited. Here, we developed antisense oligonucleotides (ASOs) using Arnatar's ACT-UP1™ upregulation platform to specifically enhance endogenous HNF4α protein translation and evaluated their therapeutic potential in preclinical liver fibrosis models. **Methods:** GalNAc-conjugated ACT-UP1 ASOs targeting the HNF4α 3′UTR were screened in cells across multiple species, followed by *in vivo* pharmacodynamic evaluation after subcutaneous administration.

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The lead candidate, ART10, was evaluated in choline-deficient, L-amino acid-defined high-fat diet (CDAHFD)-induced MASH/fibrosis and carbon tetrachloride (CCl4)-induced liver fibrosis mouse models. Hepatic HNF4α expression and fibrosis markers, including αSMA and Collagen I, were quantified by Western blot. Downstream mRNA markers were analyzed by qRT-PCR. Fibrosis and steatosis were assessed by picrosirius red staining and histopathology. Plasma ALT and AST were measured as indicators of liver injury. **Results:** ACT-UP1 ASOs increased HNF4α protein expression by approximately 50–150% across *in vitro* systems and elevated hepatic HNF4α protein up to two-fold *in vivo*, with activity sustained for more than 3 weeks following dosing. In the CDAHFD-induced model, ART10 restored hepatic HNF4α expression, improved hepatic steatosis, and, importantly, reduced liver fibrosis, as demonstrated by decreased picrosirius red staining and reduced αSMA expression. In the CCl4-induced fibrosis model, ART10 also increased hepatic HNF4α protein, reduced fibrosis-associated markers, improved liver histopathology, and lowered plasma ALT and AST levels. ART10 treatment increased expression of downstream HNF4α target genes, including Albumin, F7, and Otc, while reducing expression of fibrosis and inflammatory markers, such as Col1a1, Acta2, and TNFα. ART10 was well tolerated in mice and no significant abnormalities were observed at doses up to 200 mg/kg. **Conclusion:** ASO-mediated translational upregulation of HNF4α using the ACT-UP1 platform restored hepatic HNF4α expression and reduced liver fibrosis, steatosis, and liver injury in multiple preclinical disease models, supporting ASO-mediated HNF4α upregulation as a promising disease-modifying therapeutic strategy for liver fibrosis.

Disclosures: Lingdi Zhang:Nothing to Disclose, Terry Lin:Arnatar Therapeutics: Employee, Surendra Jain: Nothing to Disclose, Jian Li:Nothing to Disclose, Rich Thai:Nothing to Disclose, Lansha Peng:Nothing to Disclose, Xing Xian Yu:Nothing to Disclose, Yanfeng Wang:Nothing to Disclose, Xuehai Liang:Nothing to Disclose.

3543 | SPIRONOLACTONE IS ASSOCIATED WITH ALT REDUCTIONS IN REPRODUCTIVE-AGED WOMEN WITH MASH: RESULTS OF A PILOT RANDOMIZED CONTROLLED TRIAL

Amanda Laguna[1] Ala Koreitem[1] Marcelle Cedars[1] Michael Ohliger[1] Helen Oberweis-Manion[1] Norah Terrault[2] Monika Sarkar[1], [1]University of California, San Francisco, [2]Keck Medical Center of USC

Background: Rates of metabolic dysfunction-associated steatohepatitis (MASH) have risen significantly over the past three decades, particularly in young adults. While higher androgen levels increase risk for presence and severity of MASH, the potential role of androgen receptor blockade on MASH-related outcomes has not been studied. **Methods:** This was a double-blind, pilot randomized controlled trial conducted at our center from 2017-2022 in reproductive-aged women with biopsy-confirmed MASH (n = 17). Participants were randomized 2:1 to spironolactone 100mg daily (n = 11) or placebo (n = 6). Study duration was 6 months with optional extension to 12 months, with end of study measures including metabolic labs, liver tests, magnetic resonance elastography (MRE), and proton-density fat fraction (PDFF). Between-group differences were evaluated using a Hodges-Lehmann estimate. Adjusting for baseline ALT, a linear mixed model was used to compare ALT levels at 6 months and 12 months. **Results:** Median ages in the spironolactone and the placebo groups were 35 and 27 years old, respectively (p = 0.48), with a lower percentage in the spironolactone group reporting Hispanic ethnicity (36% vs 83%, p = 0.13). Presence of polyendocrine metabolic ovarian syndrome (PMOS), formerly known as polycystic ovary syndrome, was more common in the spironolactone group (55% vs 33%, p = 0.62). Most of the participants had baseline biopsy-proven stage 1 (47%) or stage 2 (47%) fibrosis, and a smaller proportion had baseline stage 3 fibrosis (6%). Baseline ALT levels (71 U/L vs 59 U/L), body mass index (40 kg/m^2 vs 35 kg/m^2), presence of dyslipidemia (36% vs 33%), median HOMA-IR (5.4 vs 6.3), PDFF (19.6 vs 23.9%), and liver stiffness by MRE (2.5 kPa vs 2.2 kPa) were not significantly different between the spironolactone and placebo groups. On average, the ALT levels in the spironolactone group after 6 months of treatment were 77.0 units lower compared to those in the placebo group (95% CI, –201.0 to –10.0; p = 0.011; Figure 1A). Eleven patients (n = 8 spironolactone and n = 3 placebo) continued treatment to 12 months; both median free testosterone (95% CI, -52.5 to -0.60; p = 0.02) and total testosterone (95% CI -0.41 to -0.009; p = 0.032; Figure 1B) showed greater decline in the spironolactone vs the placebo group. There were no significant changes in BMI, lipid level, HOMA-IR, PDFF or MRE at 6 or 12 months. ALT levels were significantly lower in the spironolactone group at 12 months after adjusting for baseline ALT; the between-group difference in ALT levels was 131 U/L in the spironolactone vs placebo group (95% CI 33.5 to 229, p = 0.011). **Conclusion:** Spironolactone was associated with ALT reductions in reproductive-aged women with MASH. These data support the need to explore hormonal modulation as a potential mechanism for MASH treatment in the rising population of young female adults

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with MASLD.

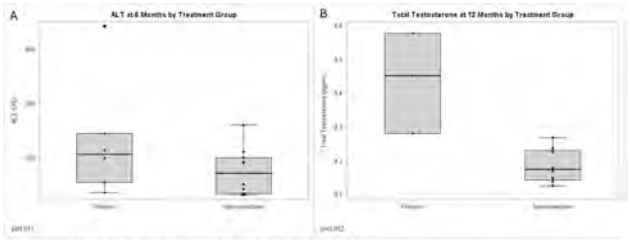


Figure 1: Change in ALT and Total Testosterone After Treatment with Spironolactone
(A) After 6 months, participants who received spironolactone had significantly lower ALT levels compared with those who received the placebo (p=0.011).
(B) After 12 months, participants who received spironolactone had significantly lower total testosterone levels compared with those who received the placebo (p=0.032).

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3544 | MULTI-OMIC DISSECTION OF THE DIRECT MECHANISM OF ACTION OF EFRUXIFERMIN-MEDIATED REVERSAL OF LIPOTOXICITY IN PRIMARY HUMAN HEPATOCYTE

Michail Kokkorakis[1] Suyavaran Arumugam[2] Wajahat Mehal[2] Tim Rolph[3] Erik Tillman[3], [1]Yale School of Medicine, [2]Yale University, [3]Akero Therapeutics, a Novo Nordisk Company, Boston, United States

Background: Efruxifermin (EFX), a long-acting FGF21 analog, is in phase 3 development for MASH, yet the extent to which its therapeutic benefit derives from direct hepatocyte-autonomous action versus extrahepatic systemic effects remains unclear. We characterized the direct hepatocyte response to EFX using bulk RNA-sequencing and quantitative 4D-DIA proteomics in palmitate (PA) stressed primary human hepatocytes (PHH). **Methods:** PHH (single donor) were exposed to vehicle (Ctrl), PA (200 µM), or PA + EFX (10 nM) co-administered. Transcriptome (trans) was profiled at 4, 12, and 20h; proteome (prot) at 8, 16, and 24h. Differential expression analysis used DESeq2 (RNA) and limma (protein) with significance adjusted at $P < 0.05$ and $|\log2FC| > 0.5$. Pathway-level mean log2FC was computed across curated gene sets (MitoCarta, OXPHOS, fatty acid oxidation [FAO], TCA cycle, glycolysis/gluconeogenesis, ER stress, unfolded protein response (UPR), reactive oxygen species (ROS), translation). A rescue index was defined as the fraction of PA-dysregulated features whose direction of change was reversed by EFX co-treatment. Cross-omic discordance was assessed by matching RNA and protein significance status at corresponding timepoint pairs. **Results:** PA significnatly and extensively remodeled the trans (n = 7,581) and prot (n = 2,970 proteins), with induction of transcripts for UPR (mean log2FC +1.43 at 12 h, +1.68 at 20 h), ER stress (+1.04 at 20 h), suppression of OXPHOS (−1.02 at 12 h) and translation-machinery proteins (−0.63 at 24 h). EFX co-administration broadly reversed this signature: rescue index 81% (RNA, 20 h) and 97% (protein, 24 h). All 26 of 26 PA-perturbed FAO proteins were direction-reversed by EFX (24 of 26 with statistical significance), further rescue of gluconeogenesis (+1.70), glycolysis (+1.15), TCA (+0.56), and translation machinery (+0.44). GLYAT (log2FC +8.3) and ALDH1L1 (log2FC +4.6) were highly induced. 60–70% of EFX-modulated proteomic changes lacked a corresponding trans change at matched RNA timepoints (1,459 of 2,080 at 16 h; 1,261 of 2,095 at 24 h), implicating a substantial post-transcriptional component in the EFX response. PA expanded the mitochondrial proteome (+1.07 at 8 h), and EFX reversed it toward Ctrl by 24 h (−0.34). **Conclusion:** In primary human hepatocytes, PA induces extensive transcriptomi and proteomic reprogramming consistent with lipotoxicity, characterized by upregulation of the UPR and ER stress response, and downregulation of key metabolic pathways (FAO, glycolysis/gluconeogenesis, TCA cycle, protein translation). EFX reverses the lipotoxic transcriptional and proteomic signature induced by PA. A substantial post-transcriptional component implicates translational regulation and protein-stability control as a previously underappreciated layer of FGF21 signaling in human hepatocytes, consistent with the regulation of UPR and ER stress response pathways.

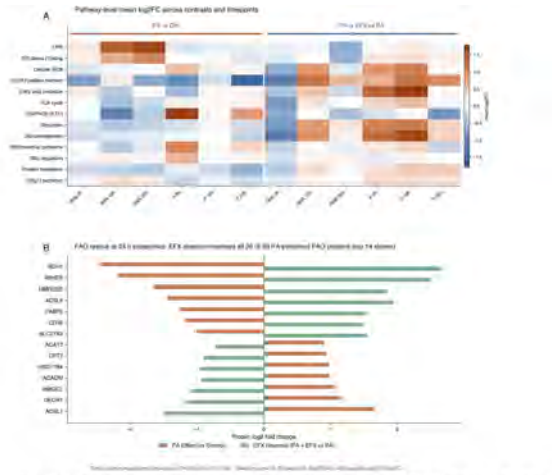


Figure. (A) Pathway-level mean log2FC across PA vs Ctrl and PA + EFX vs PA at all RNA-seq (4, 12, 20 h) and proteomics (8, 16, 24 h) timepoints. (B) Fatty acid oxidation proteins rescued by EFX co-administration at 24 h proteomics (top 14 shown of 26 PA-perturbed FAO proteins; EFX direction-reversed all 26, with 24 of 26 reaching statistical significance). Selection: significant in PA vs Ctrl (padj<0.05, |log2FC|>0.5) and showing opposite-direction log2FC in PA + EFX vs PA. Red bars = PA effect (vs Ctrl); green bars = EFX reversal (PA + EFX vs PA).

Disclosures: Michail Kokkorakis:Nothing to Disclose, Suyavaran Arumugam:Nothing to Disclose, Wajahat Mehal:Nothing to Disclose, Tim Rolph:Nothing to Disclose, Erik Tillman:Novo Nordisk: Employee, Novo

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3545 | REAL-WORLD POST-MARKETING SAFETY PROFILE OF RESMETIROM COMPARED WITH PHASE 3 CLINICAL TRIAL: A FAERS PHARMACOVIGILANCE STUDY

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Background: Resmetirom is a newly approved therapy for metabolic dysfunction-associated steatohepatitis (MASH) and real-world safety data is limited. We aimed to characterize post-marketing adverse events and evaluate disproportionality signals for resmetirom. **Methods:** We analyzed data from the FDA Adverse Event Reporting System (FAERS) from 2024-2025. Case reports identifying resmetirom as the primary suspect were isolated and deduplicated. Adverse events (AE) were categorized using MedDRA preferred terms. Disproportionality analyses were conducted using reporting odds ratios (RORs) with 95% confidence intervals (CIs) comparing resmetirom-associated reports with all other drugs in FAERS database. Stratified sub-analyses evaluated safety outcomes across age, sex, polypharmacy (≥ 5 concurrent medications), and concomitant statin use. **Results:** A total of 1,279 unique resmetirom-associated FAERS reports were identified. Among reports with available demographic data, 66% were female, mean age was 56.7 ± 13.0 years (94% aged ≥ 65 years), with polypharmacy (31%) and concurrent statin use (16%). Gastrointestinal AEs predominated, including diarrhea (242), nausea (228), vomiting (76), constipation (60), and abdominal pain (58), while pruritus was reported in 207 cases. Hepatic AEs included alanine aminotransferase elevation (113), aspartate aminotransferase elevation (110), bilirubin elevation (53), 6 reports of drug-induced liver injury and rare cases of acute-on-chronic liver failure. Gallbladder-related AEs included cholelithiasis (9), cholecystitis (7), and cholangitis (3). Among reports with serious outcomes (370), hospitalization occurred in 24%, death in 13%, life-threatening events in 2.2%, and disability in 1.6%. Strong disproportionality signals were identified across all domains, with hepatic AEs showing the highest signal (ROR 12.17; 95% CI 10.43-14.21). Significant signals were also seen for GI events (ROR 3.94; 95% CI 3.53–4.39), driven by diarrhea (ROR 5.03), nausea (ROR 4.50), and vomiting (ROR 2.46), as well as gallbladder-related events (ROR 3.62). Hepatic AEs were absent in patients < 45 years but occurred in 14.8% of those 45–64 years and 14.7% of those ≥ 65-years. Polypharmacy was associated with higher hepatic (22.2% vs 11.1%) and GI event reporting rates (41.9% vs 31.5%). Concurrent statin use was associated with increased hepatic (29.3% vs. 11.8%), GI (39.9% vs 33.8%), and gallbladder-related events (3.5% vs. 1.4%). GI and hepatic reporting frequencies were comparable between sexes. **Conclusion:** Post-marketing resmetirom safety data align with Phase 3 trial findings for GI adverse events but demonstrate stronger hepatobiliary signals, particularly in older adults, those with polypharmacy, and concomitant statin users. While causality cannot be established, these findings support ongoing surveillance and targeted clinical monitoring as real-world resmetirom use expands.

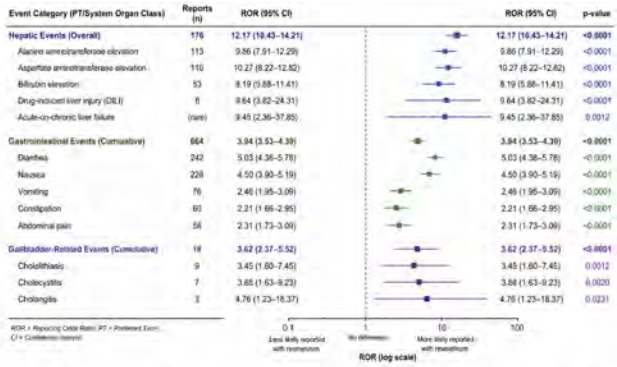


Figure. Frequency and Forest Plot of Disproportionality Signals for Resmetirom-Associated Adverse Events (FAERS)

Disclosures: Cherechi Nwabueze:Nothing to Disclose, Yetunde Akande:Nothing to Disclose, chimezirim ezeano:Nothing to Disclose, Eunice Omeludike:Nothing to Disclose, Ridwan Lawal:Nothing to Disclose, Ihunanya Kanu:Nothing to Disclose, Nzubechukwu Okeke:Nothing to Disclose, Ifekunwa Osanakpo:Nothing to Disclose, Ayokunle Abegunde:Nothing to Disclose.

3546 | HEPATIC IRON DEPOSITION MODIFIES RESPONSE TO VITAMIN E AMONG PATIENTS WITH MASH: A POOLED ANALYSIS OF NASH CRN TRIALS

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Symbols: ♦, Poster of Distinction; ★, Foundation Award Recipient

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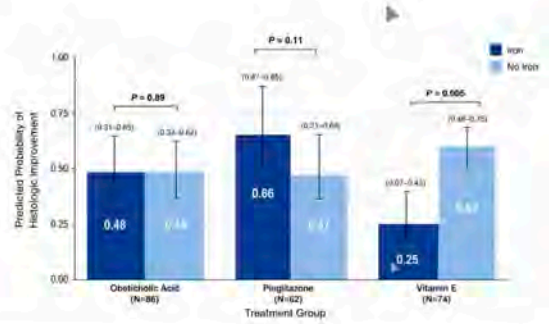
Background: Metabolic dysfunction-associated Steatotic liver disease (MASLD) affects ~ 30% of the global population with a subset progressing to MASH, which is associated with increased risk of cirrhosis and liver-related morbidity. Hepatic iron deposition is observed in 35-48% of patients with MASLD and has been implicated in hepatocellular injury and fibrogenesis through oxidative stress-mediated mechanisms. Prior studies have reported associations between hepatic iron deposition patterns and advanced histologic disease severity. However, the impact of hepatic iron on response to pharmacologic therapy in MASH has not been evaluated. We aimed to determine whether baseline hepatic iron deposition influences treatment response in patients enrolled in NASH CRN trials. **Methods:** We conducted a pooled secondary analysis of adults with biopsy-proven MASH enrolled in the NASH Clinical Research Network. 374 patients (201 from PIVENS and 173 from FLINT) with baseline and end of treatment liver biopsies with iron staining data were included. Participants randomized to obeticholic acid (n = 87), pioglitazone (n = 62), vitamin E (n = 76) or placebo (n = 149) were included. The primary outcome was histologic improvement, defined as ≥ 2-point reduction in NAFLD Activity Score (NAS) without worsening of fibrosis. Multivariable logistic regression was used to evaluate the association between iron deposition and histologic improvement, including interaction terms between iron deposition and treatment group. Models were adjusted for age, sex, Hispanic ethnicity, BMI, and diabetes. Adjusted predicted probabilities of histologic improvement were estimated for each combination of iron deposition and treatment group using marginal effects from the fitted model. Additional analyses stratified by treatment group were performed. **Results:** Mean age was 49 yrs, 63% were female, 13% Hispanic, and mean BMI was 34.3 ± 6.6. Hepatic iron deposition was present in 38% of baseline biopsies. The mean NAS score was comparable between patients with and without iron deposition (5.1 vs 5.2, p = 0.46). Response to Vitamin E was significantly influenced by iron deposition (P for interaction = 0.001), while no significant effect modification was observed for obeticholic acid or pioglitazone. In treatment-stratified analyses, Vitamin E treated patients with iron deposition had lower odds of histologic improvement compared to those without iron deposition (aOR-0.16 (95% CI 0.04-0.57), p = 0.005) (T1).The predicted histologic improvement among Vitamin- E treated with iron deposition was 0.25 (0.07-0.43), compared with 0.62 (0.48-0.75) among those without iron deposition (F1) **Conclusion:** Presence of stainable hepatic iron is associated with the attenuation of histological response to Vitamin E. We hypothesize that increased oxidative stress generated by hepatic iron deposition limits the efficacy of Vitamin E among patients with MASH

Table 1. Stratified analysis – logistic regression analysis of iron deposition on histologic improvement by treatment group*

	Odds Ratio (95% PI) for Histologic Improvement	P
Any iron vs. no iron – Obeticholic acid group (N=86)	1.07 (0.43 – 2.66)	0.89
Any iron vs. no iron – Pioglitazone group (N=62)	3.03 (0.79 – 11.67)	0.11
Any iron vs. no iron – Vitamin E group (N=74)	0.16 (0.04 – 0.57)	0.005

*Individual logistic regression models for each treatment group; outcome was histologic improvement, and primary covariate was any iron deposition vs. no iron deposition. Models were adjusted for age, sex, Hispanic ethnicity, and BMI. Obeticholic acid model N=86 and vitamin E model N=74 due to missing BMI in 3 participants.

Figure 1- Predicted probability of histologic improvement by iron deposition and treatment group*



* Adjusted predicted probabilities from logistic regression model with interaction terms for iron deposition and treatment group; models adjusted for age, sex, Hispanic ethnicity, BMI, and diabetes status.

Disclosures: Sheena Bhushan:Nothing to Disclose, Aalam Sohal:Nothing to Disclose, Laura Wilson:Nothing to Disclose, David Kleiner:Nothing to Disclose, Rohit Loomba:Eli Lilly and Company: Consultant, 89bio: Consultant, Aardvark Therapeutics: Consultant, Altimmune: Consultant, Alnylam/Regeneron: Consultant, Amgen: Consultant, Arrowhead Pharmaceuticals: Consultant, AstraZeneca: Consultant, Bristol Myers Squibb: Consultant, CohBar: Consultant, Eli Lilly: Consultant, Galmed Pharmaceuticals: Consultant, Gilead: Consultant, Glympse Bio: Consultant, Hightide: Consultant, Inipharma: Consultant, Intercept: Consultant, Inventiva: Consultant, Ionis: Consultant, Janssen, Inc.: Consultant, Madrigal Pharmaceuticals: Consultant, Merck, Metacrine, Inc.: Consultant, NGM Biopharmaceuticals: Consultant, Novartis: Consultant,

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3547 | COMPARATIVE EFFICACY OF MONO- AND DUAL-INCRETIN AGONISTS FOR HISTOLOGIC OUTCOMES IN MASH: A SYSTEMATIC REVIEW AND META-ANALYSIS WITH NARRATIVE SYNTHESIS OF EMERGING TRIPLE INCRETIN AGONIST DATA

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Background: Metabolically-dysfunction-associated steatohepatitis (MASH) is a progressive liver disease and the leading indication of liver transplantation, with semaglutide representing the first approved pharmacotherapy as of 2025. Mono- and dual-incretin-based therapies targeting glucagon-like-peptide-1(GLP-1), glucose-dependent insulinotropic polypeptide, and glucagon receptor pathways have demonstrated reductions in hepatic steatosis, inflammation, and fibrosis, whereas evidence for triple agonists remains limited to radiologic outcomes. We performed a PRISMA-compliant systematic review and meta-analysis of incretin-based therapies with a narrative synthesis of triple agonist data. **Methods:** Randomized controlled trials published through April 2026 were included. Six biopsy-confirmed trials (n = 1,371) evaluating mono GLP-1 receptor agonists (semaglutide, liraglutide) and dual incretin agonists (tirzepatide, survodutide, pemvidutide) assessed MASH resolution without worsening fibrosis as the primary outcome. A parallel radiologic subanalysis included six trials (n = 556) reporting $\geq$30% reduction in MRI-PDFF. Pooled risk ratios were estimated using Mantel-Haenszel random-effects models with REML. Heterogeneity was assessed using I^2 and Cochran's Q, with robustness evaluated through leave-one-out sensitivity analyses. Small-study effects were explored using contour-enhanced funnel plots, and risk of bias was assessed using Cochrane Risk of Bias 2.0. **Results:** Incretin-based therapies significantly increased MASH resolution without worsening fibrosis compared with placebo (RR 3.19, 95% CI 2.15–4.75; $p < 0.001$). Between-study heterogeneity was substantial ($I^2 = 74.4\%$; $\tau^2 = 0.147$), but pooled estimates remained consistent; the test for subgroup differences between mono- and dual-incretin agonists was not significant ($\chi^2 = 3.15$, $p = 0.207$)Radiologically, incretin therapy was associated with a greater likelihood of $\geq$30% MRI-PDFF (RR 5.54, 95% CI 4.03–7.61; $p < 0.001$) without heterogeneity ($I^2 = 0\%$, Q $p = 0.53$). Leave-one-out analyses confirmed robustness (biopsy RR range 2.86–3.72; MRI-PDFF RR range 5.27–6.54). Funnel plots showed no asymmetry, though interpretation was limited by a small trial count (k = 6). The retatrutide phase 2a substudy demonstrated substantial reductions in liver fat (up to 86% at 48 weeks) and cardiometabolic improvements, but lacked biopsy-confirmed endpoints, precluding quantitative analysis. **Conclusion:** Mono- and dual-incretin agonists significantly improve histologic and radiologic outcomes in MASH with consistent effects across drug classes. No definitive class differences can be established without head-to-head trials. Evidence for triple agonists remains limited to early radiologic outcomes, and phase 3 biopsy-confirmed data for retatrutide are needed to

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define its histologic efficacy and clinical role.

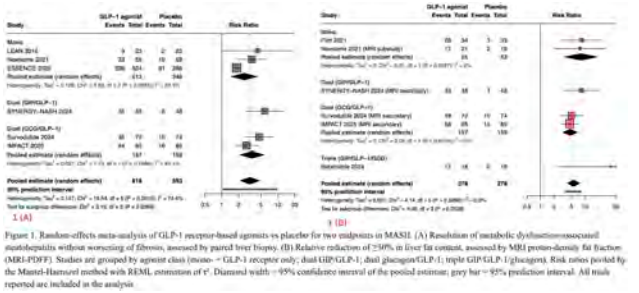


Figure 1. Random-effects meta-analysis of GLP-1 receptor-based agonists vs placebo for two endpoints in MASH. (A) Resolution of metabolic dysfunction-associated steatohepatitis without worsening of fibrosis, assessed by paired liver biopsy. (B) Relative reduction of ≥30% in liver fat content, assessed by MRI proton-density fat fraction (MRI-PDFF). Studies are grouped by agonist class (mono- = GLP-1 receptor only; dual GIP/GLP-1; dual glucagon/GLP-1; triple GIP/GLP-1/glucagon). Risk ratios pooled by the Mantel-Haenszel method with REML estimation of τ^2. Diamond width = 95% confidence interval of the pooled estimate; grey bar = 95% prediction interval. All trials reported are included in the analysis.

Disclosures: Gunjan Malhotra:Nothing to Disclose, Gurkirat S. Brar:Nothing to Disclose, Simrat Kaur Parmar:Nothing to Disclose, Ankuriti Singla:Nothing to Disclose, Hargun Malhotra:Nothing to Disclose, Christine Bruno:Nothing to Disclose, Anish Chopra:Nothing to Disclose.

3548 | EFRUXIFERMIN IMPROVED FIBROSIS IN PARTICIPANTS WITH MASH CIRRHOSIS AND MULTIPLE CARDIOMETABOLIC COMORBIDITIES: A POST HOC ANALYSIS OF THE SYMMETRY PHASE 2B TRIAL

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Background: Individuals with MASH and multiple cardiometabolic (CM) comorbidities are at higher risk for adverse outcomes. Efruxifermin improved fibrosis and CM parameters in phase 2b trials in participants with MASH. We evaluated the efficacy of efruxifermin in subgroups of participants with MASH and compensated cirrhosis (F4c) based on the number of CM comorbidities at baseline. **Methods:** This post hoc analysis included participants with MASH and biopsy-defined F4c from the SYMMETRY randomized placebo-controlled trial (NCT05039450). Participants were grouped by the number of baseline CM comorbidities: T2D, obesity, hyperlipidemia, and hypertension. We evaluated the change from baseline at Week 96 in fibrosis improvement and additional efficacy measures. **Results:** Most participants had ≥2 CM comorbidities at baseline (1 comorbidity n = 5, 2 n = 35, 3 n = 62, 4 n = 79). Baseline characteristics were generally more severe for participants with 3 or 4 comorbidities (mean ± SD LSM 25.1 ± 13.7 kPa, ELF 10.5 ± 0.8, TG 156 ± 74 mg/dL, HOMA-IR 13.0 ± 11.6, HbA1c 6.8 ± 1.1%) than the group with ≤2 comorbidities (mean ± SD LSM 22.2 ± 11.8 kPa, ELF 10.5 ± 0.9, TG 132 ± 54 mg/dL, HOMA-IR 7.1 ± 5.9%, HbA1c 6.2 ± 0.9). Regardless of the number of comorbidities at baseline, 96 weeks of treatment with efruxifermin vs placebo resulted in improvements in fibrosis and CM parameters (Table). Efruxifermin was generally well tolerated. Mild to moderate gastrointestinal events were more common with efruxifermin than placebo. **Conclusion:** Participants with MASH and compensated cirrhosis and more CM comorbidities had worse measures of disease severity, indicating higher risk of clinical outcomes. In these participants, efruxifermin improved fibrosis and other efficacy measures at Week 96. Phase 3 trials of efruxifermin in MASH with moderate to severe (F2/F3) fibrosis or cirrhosis are ongoing.

Table. Summary of Week 96 efficacy measures in participants with F4c MASH by number of baseline cardiometabolic comorbidities.

	≤2 comorbidities			3-4 comorbidities		
	Placebo	Efruxifermin 28 mg	Efruxifermin 50 mg	Placebo	Efruxifermin 28 mg	Efruxifermin 50 mg
Fibrosis improvement	1/6 (17%)	3/10 (30%)	7/15 (47%)	6/41 (15%)	9/31 (29%)	11/31 (35%)*
ELF test score	0.1±0.2	-0.4±0.2	-0.7±0.2*	0.2±0.1	-0.4±0.2*	-0.5±0.1*
LSM, kPa	-0.3±2.3	-2.7±2.0	-8.6±1.9*	-7.8±1.3	-9.8±1.5	-8.6±1.5
ALT, U/L	-9.1±4.7	-7.9±4.2	-15.9±3.5	-8.0±2.6	-11.9±3.0	-12.1±2.9
AST, U/L	-6.7±3.8	-9.2±3.5	-14.7±2.9	-1.4±1.9	-9.2±2.2*	-11.1±2.2*
Triglycerides, mg/dL	23.3±14.6	-10.3±13.0	-32.7±10.8*	-10.7±8.6	-35.6±10.0*	-40.2±9.7*
HDL-cholesterol, mg/dL	1.0±3.6	5.2±3.5	5.1±2.9	-2.2±1.8	5.6±2.0*	11.4±2.0*
LDL-cholesterol, mg/dL	-15.2±6.8	-12.5±6.1	-12.9±5.1	-9.1±3.5	-13.5±4.2	-14.4±4.1
C-peptide, ng/mL	1.0±0.5	0.3±0.5	-1.2±0.4*	-0.4±0.3	-1.3±0.3*	-0.9±0.3
Adiponectin, % change	7±24%	31±23%	62±20%	7±13%	33±14%	72±14%*
HOMA-IR	18.5±4.5	2.6±4.4*	-1.3±3.6*	-1.4±1.3	-5.0±1.4*	-4.7±1.4
HbA1C, %	0.4±0.2	0.7±0.2	0.2±0.2	0.2±0.2	-0.3±0.2*	-0.1±0.2

Fibrosis improvement is defined as the proportion of participants with ≥1-stage fibrosis decrease without MASH worsening from baseline at Week 96. Other data are LSmean (SE) absolute or percent change from baseline at Week 96. *p<0.05 vs placebo.

Disclosures: Mary Rinella:akero: Consultant, akero: Consultant, 89Bio: Consultant, 89Bio: Consultant, Boehringer Ingelheim: Consultant, Boehringer Ingelheim: Consultant, Cytodyn: Consultant, Cytodyn: Consultant, Echosens: Consultant, Echosens: Consultant, Histoindex: Consultant, Histoindex: Consultant, Intercept: Consultant, Intercept: Consultant, Madrigal: Consultant, Madrigal: Consultant, GSK: Consultant, GSK: Consultant, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Eli Lilly: Consultant, Eli Lilly: Consultant, Takeda: Consultant, Takeda: Consultant, Sagimet: Consultant, Sagimet: Consultant, Sonic Incytes: Consultant, Sonic Incytes: Consultant, NGM Bio: Consultant, NGM Bio: Consultant, Regeneron: Consultant, Boston Pharma: Consultant, Eccogene: Consultant, Inventiva: Consultant, Sagimet: Consultant, Madrigal: Consultant, akero: Consultant, akero: Consultant, 89Bio: Consultant, 89Bio: Consultant, Boehringer Ingelheim: Consultant, Boehringer Ingelheim: Consultant, Cytodyn: Consultant, Cytodyn: Consultant, Echosens: Consultant, Echosens: Consultant, Histoindex: Consultant, Histoindex: Consultant, Intercept: Consultant, Intercept: Consultant, Madrigal: Consultant, Madrigal: Consultant, GSK: Consultant, GSK: Consultant, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Eli Lilly: Consultant, Eli Lilly: Consultant, Takeda:

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3549 | TIRZEPATIDE VS. CAGRISEMA IN TREATING OBESE PATIENTS WITH TYPE 2 DIABETES MELLITUS AND METABOLIC DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE

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Background: Recent research has been focused on the development of more effective anti-obesity drugs like the dual glucogen like peptide (GLP)-1 / gastric inhibitory polypeptide (GIP) agonist, tirzepatide, and the combination of GLP-1 semaglutide with the amylin analogue cagrilintide, named CagriSema. Aim of this study was to compare the efficacy of these two pharmacological agents in a small cohort of obese patients with type 2 diabetes mellitus (T2DM) and metabolic dysfunction associated steatotic liver disease (MASLD). **Methods:** Data was recorded retrospectively from consecutive patients who were treated with subcutaneous weekly injections of either tirzepatide 15mg (=group 1) or CagriSema 2.4mg (=group 2) for a six-month period following gradual drug titration as indicated per study protocols. Apart from recordings of glycated haemoglobulin (HbA1c), body weight and lipidemic profile, liver biochemistry as well as non-invasive scores of fibrosis (FIB-4 and Liver Risk score) were calculated. Statistical comparison between groups was performed with chi-square and Mann-Whitney U test, while Wilcoxon signed rank test for paired samples was used in order to investigate drug efficacy. **Results:** A total of 30 patients with obesity, T2DM and MASLD were included, with their baseline characteristics shown in Table 1. Group 1 patients were almost 1 decade younger and had higher baseline ALT. Both groups included mostly MASLD patients with low risk for advanced fibrosis (FIB-4 < 1.30) and minimal to

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low risk for liver-related outcomes (Liver Risk score < 10).Treatment led the total of participants to lose weight (median -8,46kg, range -1.6 to 20.2kg, Δ = -9.4% from baseline), to improve glycemic control (median HbA1c -1.75%, range -0.8 to 2.4%), to reduce total cholesterol (median drop -20.4mg/dL) and to improve ALT by median 20U/L (IQR -9 to -31) (Wilcoxon signed rank test, p < 0.01). When comparing two groups, CagriSema led to higher weight loss (-16.4% vs.-5.9%, p < 0.001), even though there was no benefit regarding all other parameters investigated. **Conclusion:** The results of this small, short-term, intervention study showed that both tirzepatide and CagriSema were effective in improving body weight, glycemic control, lipids and hepatic biochemisty when administered to patients with obesity, T2DM and MASLD.

	Group 1 (tirzepatide, n=15)	Group 2 (CagriSema, n=15)	p values
Gender (M/F)	6/9	9/6	NS
Age (years)	54.8 ± 11.1	66.6 ± 9.8	0.004
BMI (kg/m^2)	37.0 ± 5.8	34.3 ± 6.1	NS
HbA1c (%)	8.3 (IQR 7.7-9.6)	8.0 (IQR 7.7-8.2)	NS
Total cholesterol (mg/dL)	173.8 ± 51.6	175.0 ± 40.0	NS
AST (U/L)	26 (IQR 25-34)	24 (IQR 23-27)	NS
ALT (U/L)	44 (39-47)	20 (IQR 14-40)	0.001
PLT (x 10^9/L)	325 (IQR 266-340)	359 (IQR 312-418)	NS
FIB-4	0.74 (IQR 0.73-0.91)	0.90 (IQR 0.75-1.09)	NS
Liver Risk score	5.61 (IQR 5.50-6.18)	4.97 (IQR 4.89-5.53)	NS

Disclosures: Savvoula Savvidou:Nothing to Disclose, Aikaterini Damianakou:Nothing to Disclose, Elektra Augousti-Varela:Nothing to Disclose, Miltiadis Chalkias: Nothing to Disclose, Ioannis Stergiou:Nothing to Disclose.

3550 | IMEGLIMIN MITIGATES LIVER INJURY IN A NONDIABETIC MASH MODEL THROUGH IMPROVEMENT OF MITOCHONDRIAL FUNCTION

Kosuke Kaji[1] Norihisa Nishimura[1] Shinya Sato[1] Masafumi Oyama[1] Tatsuya Nakatani[1] Tadashi Namisaki[2] Hitoshi Yoshiji[1], [1]Department of Gastroenterology, Nara Medical University, [2]Nara medical university

Background: Metabolic dysfunction–associated steatohepatitis (MASH) may develop and progress to fibrosis even in individuals without diabetes. Impaired mitochondrial function is considered a key driver of disease progression by reducing fatty acid oxidation, increasing oxidative stress, and promoting hepatocellular injury and fibrogenesis. Imeglimin is an antidiabetic drug known to improve mitochondrial bioenergetics, but its potential hepatoprotective effects independent of glucose metabolism remain poorly characterized. This study investigated whether imeglimin ameliorates liver injury and fibrosis in a nondiabetic model of MASH by restoring mitochondrial function. **Methods:** Male C57BL/6J mice were fed a choline-deficient, L-amino acid-defined, high-fat diet (CDAHFD) for 8 weeks to establish a nondiabetic MASH model. Mice received oral imeglimin (100 or 200 mg/kg, twice daily) or vehicle. Hepatic steatosis, inflammation, apoptosis, and fibrosis were evaluated using histological and biochemical analyses. Mitochondrial function was assessed by examining oxidative stress, mitochondrial biogenesis, and fatty acid oxidation–related pathways. In vitro experiments were performed using palmitic acid (PA)-treated human hepatocytes to assess the effects of imeglimin on lipid accumulation, inflammatory responses, apoptosis, mitochondrial membrane potential, respiratory chain activity, and oxygen consumption. **Results:** CDAHFD-fed mice developed steatohepatitis and liver fibrosis without evidence of hyperglycemia. Treatment with imeglimin markedly improved hepatic steatosis, inflammatory activity, and hepatocyte ballooning. These improvements were associated with recovery of genes involved in fatty acid oxidation and a substantial reduction in hepatic reactive oxygen species levels. Imeglimin also promoted mitochondrial biogenesis, as indicated by increased expression of PGC-1α and TFAM, while reducing hepatocyte apoptosis and macrophage-driven inflammatory responses. As a result, hepatic fibrotic changes were significantly attenuated. In cultured hepatocytes, imeglimin reduced PA-induced lipid accumulation, inflammatory cytokine expression, and apoptotic cell death. Furthermore, imeglimin restored mitochondrial membrane potential, enhanced respiratory chain complex activity, increased oxygen consumption, and stimulated mitochondrial biogenesis. **Conclusion:** Imeglimin alleviates liver injury and fibrosis in a nondiabetic MASH model by improving mitochondrial function, promoting fatty acid oxidation, and limiting oxidative stress–induced hepatocyte damage. These glucose-independent hepatoprotective actions suggest that imeglimin could be a promising therapeutic strategy targeting mitochondrial dysfunction in MASH.

Disclosures: KOSUKE KAJI:Nothing to Disclose, NORIHISA NISHIMURA:Nothing to Disclose, Shinya Sato:Nothing to Disclose, Masafumi Oyama:Nothing to Disclose, Tatsuya Nakatani:Nothing to Disclose, Tadashi Namisaki:Nothing to Disclose, Hitoshi Yoshiji: Nothing to Disclose.

3551 | TARGETED DEGRADATION OF STING (STIMULATOR OF INTERFERON GENES) BY SP2H REDUCES NAFLD ACTIVITY SCORE AND LIVER FIBROSIS IN A MOUSE MODEL OF MASH

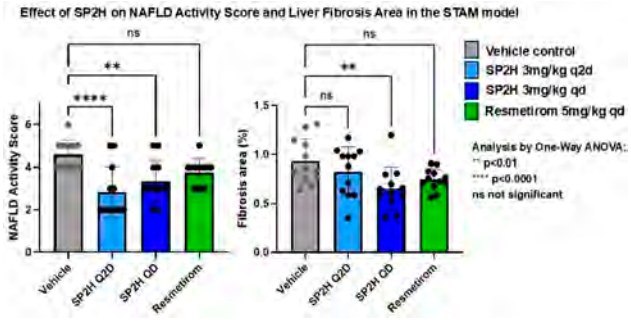
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Background: As well as inducing inflammation, STING has been reported to regulate metabolic pathways and induce fibrosis, and its genetic depletion in mice protects against the development of MASLD and MASH. SP2H is a potent and highly selective targeted STING degrader that causes deep depletion of STING in the liver and other peripheral organs in mice. To date, drug-target Mendelian Randomization (MR), a genetic epidemiology approach that uses inherited genetic variants as "natural" experiments to assess the causal effects of altering drug target expression on disease outcome, has not been applied to STING and MASLD. **Methods:** The effect of genetic variants on STING expression was assessed using expression quantitative trait locus data from the GTEx consortium. The effects of these variants on MASLD risk and on expression biomarkers were assessed using inverse-variance weighted MR, weighted median MR and MR-Egger regression methods to account for correlated variants. The effect of SP2H in the STAM model of MASH was assessed in male C57BL6 mice (n = 12/group). Mice received a low dose of streptozotocin at age two days and were then fed a high fat diet starting at four weeks of age. Mice were treated with vehicle, or one of two SP2H regimens (3mg/kg sc qd or 3mg/kg sc q2d), or resmetirom (5mg/kg po qd) for three weeks, starting at age five weeks. At week eight the liver fibrosis area, assessed by Sirius Red staining, and NAFLD Activity Scores (NAS) in fixed liver tissue samples were quantified by pathologists blinded to group assignment. **Results:** A significant positive correlation between STING expression and MASLD risk was found using data from the GWAS metaanalysis of the eMERGE, Estonian Biobank, UK Biobank and Finngen cohorts. This result was supported by significant correlations between STING expression and biomarkers that have been shown to be correlated with the risk of MASLD from individual GWAS cohorts. The effect estimates in all the MR studies were positive.Both SP2H dose regimens led to numerical reductions in all three components of NAS in STAM mice, leading to > 1.0 reductions in the NAS compared to the vehicle control group ($p < 0.0001$ for SP2H q2d, $p < 0.01$ for SP2H qd, 1-way ANOVA). The higher dose of SP2H also significantly reduced liver fibrosis area compared to the control group ($p < 0.01$, 1-way ANOVA). While resmetirom treatment resulted in numerical reductions in NAS and liver fibrosis, these effects did not reach statistical significance. SP2H was well tolerated, with no clinical signs, in both dose groups. **Conclusion:** The MR analysis provides robust evidence that STING expression is positively correlated with the risk of developing MASLD in large population cohorts. In the STAM model, both SP2H treatment regimens resulted in significant reductions in NAS, and the higher dose also had a significant antifibrotic effect. These translational data provide strong support for the clinical development of SP2H as a treatment for MASLD and MASH.



Disclosures: Magnus Strandh:Nothing to Disclose, Hannes Baukmann:Nothing to Disclose, Roman Fudim:Nothing to Disclose, Martin Jakobsen:Sulis Therapeutics: Stock – privately held company, Claus Olesen:Nothing to Disclose, Marco Schmidt:Nothing to Disclose, Richard Bethell:GSK plc: Stock - publicly traded company, Sulis Therapeutics ApS: Stock – privately held company, Sulis Therapeutics ApS: Executive role, Medivir AB: Stock - publicly traded company.

3552 | LANIFIBRANOR IMPROVES LIVER SINUSOIDAL ENDOTHELIAL CELL DYSFUNCTION AND VASCULAR ALTERATIONS ACROSS ALL STAGES FROM MASH TO CIRRHOSIS

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Background: Metabolic dysfunction-associated steatohepatitis (MASH) is traditionally characterized by steatosis, inflammation and fibrosis. However, growing evidence indicates that vascular dysfunction is an additional and crucial hallmark of disease pathogenesis. Liver sinusoidal endothelial cell (LSEC) capillarisation, increased intrahepatic vascular

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resistance and portal hypertension have been shown to develop early in the disease course, already at the stage of isolated steatosis, and to contribute to disease progression to steatohepatitis and progressive fibrosis through impaired hepatic microcirculation, inflammation and fibrogenesis. We assessed the effects of the pan-PPAR agonist lanifibranor on LSEC phenotype and on vascular abnormalities across the spectrum from isolated steatosis over MASH to cirrhosis. **Methods:** Human liver biopsies from patients with MASLD/MASH enrolled in the NATIVE Phase2b study were examined by CD34 staining. Also, preclinical models of early MASLD, MASH and cirrhosis, were analyzed. In the latter, LSEC capillarisation was also evaluated using CD34 staining and additionally by ultrastructural analyses using Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM). Furthermore, LSEC phenotypes, portal pressure, intrahepatic vascular resistance and the determinants hereof were extensively studied in experimental models. **Results:** In human MASLD liver biopsies, we demonstrated a progressive pattern of sinusoidal remodelling across inflammation grades and fibrosis stages, ranging from preserved fenestrae in isolated steatosis to pronounced capillarisation in advanced fibrotic and cirrhotic MASH. In preclinical models, LSEC capillarisation was detected at the earliest stages of MASLD, including isolated steatosis, and progressively worsened with increasing inflammation and fibrosis. Increased CD34 staining, impaired endothelial function and elevated intrahepatic vascular resistance were consistently observed before the development of advanced fibrosis. In these models, lanifibranor improved LSEC fenestrae frequency and porosity observed by TEM and SEM. These changes were associated with reduced portal pressure and, in the models of cirrhosis, reduced features of decompensation (*e.g.*, ascites). In patients treated with lanifibranor, CD34 staining patterns significantly decreased compared to placebo, demonstrating an improvement of liver endothelial alterations. **Conclusion:** Vascular dysfunction represents an early and central feature of MASH pathophysiology. LSEC alterations occur early in the disease course, contribute to early-onset portal hypertension and to disease progression and ultimate severity. Lanifibranor improves LSEC alterations and associated intrahepatic vascular abnormalities across multiple stages of disease, supporting the development of lanifibranor in MASH patients, including those suffering from advanced disease/cirrhosis.

Disclosures: Guillaume Wettstein:Inventiva: Employee, Pierre-Emmanuel Rautou:Genfit: Consultant, Jazz: Speaking and Teaching, Cook: Consultant, AstraZeneca: Consultant, Shivani Chotkoe:Nothing to Disclose, Wilhelmus Kwanten:Nothing to Disclose, Valerie PAradis:Nothing to Disclose, Jordi Gracia-Sancho:Nothing to Disclose, Manal Abdelmalek:89Bio, Akero, Madrigal, Inventiva, Novo Nordisk, , Intercept, Merck,: Advisor, Hanmi, Novo Nordisk: Consultant, Madrigal, Gilead, Inventiva, 89Bio, Akero, Hanmi: Grant/Research Support, Medscape; Clinical Care Options; Fishawack Inc, LLC; CLDF: Speaking and Teaching, Up-to-Date: Royalties or patent beneficiary, Prometheus: Advisor, Novo Nordisk: Consultant, Boehringer-Ingelheim: Grant/Research Support, Sven Francque:Nothing to Disclose.

3553 | EVALUATION OF TAURINE AS TREATMENT IN DIET-INDUCED METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS

Yongtao Wang[1] Jonathan Williams[2] Tanvi Patel[1] Wenyu Lin[1] Kenneth Tanabe[1] Snehal Chaudhari[2] Raymond Chung[1], [1]Massachusetts General Hospital and Harvard Medical School, [2]University of Wisconsin-Madison

Background: Taurine is a naturally occurring amino sulfonic acid vital for cardiovascular, neurological, and muscular function, playing crucial roles in nerve growth, cellular hydration, and antioxidant defense. While we have observed a depletion of taurine across several metabolic dysfunction-associated steatohepatitis (MASH) models, its therapeutic potential remains unclear. Here, we hypothesize that taurine supplementation can prevent and alleviate liver injury and fibrosis. **Methods:** Eight-week-old male Wistar rats were fed a choline-deficient, L-amino acid-defined, high-fat diet (CDAHFD) for 6 weeks to induce MASH. After the initial 2 weeks of diet induction, rats were treated with either taurine (1 g/kg body weight) *ad libitum* in drinking water or a water control for the remaining 4 weeks (n = 8 per group). Molecular, biochemical, and histological assessments were subsequently performed. **Results:** In prior work, hepatic taurine deficiency and the down-regulation of its key regulatory gene, cysteine dioxygenase 1 (*Cdo1*), were observed in both CDAHFD and Gubra Amylin NASH (GAN) diet-induced MASH models. Bioinformatics analysis confirmed decreased *Cdo1* expression in GAN-induced MASH livers, which negatively correlated with inflammatory and profibrogenic markers. This decreased hepatic taurine content was also observed in human MASH. In the CDAHFD model, taurine supplementation successfully restored hepatic taurine content and rescued the suppressed *Cdo1* expression. Consequently, taurine treatment led to an increase in body weight, improved serum liver chemistry indices (total bilirubin and albumin), and attenuated hepatic lipid accumulation. Histological analysis via the NAFLD Activity Score (NAS) revealed that taurine supplementation significantly reduced hepatocyte ballooning. Furthermore, taurine intervention ameliorated liver fibrosis, as evidenced by reduced collagen deposition, improved fibrosis scores,

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and the downregulation of inflammatory and profibrogenic genes. **Conclusion:** Taurine supplementation mitigates hepatic taurine deficiency and alleviates liver damage and fibrosis in a CDAHFD-induced MASH model via a *Cdo1*-dependent pathway. These findings suggest that taurine supplementation holds therapeutic promise for the treatment of MASH and related progressive liver diseases.
Disclosures: Yongtao Wang:Nothing to Disclose, Jonathan Williams:Nothing to Disclose, Tanvi Patel:Nothing to Disclose, Wenyu Lin:Nothing to Disclose, Kenneth Tanabe:Nothing to Disclose, Snehal Chaudhari:Nothing to Disclose, Raymond Chung:Nothing to Disclose.

3554 | METABOLIC AND IMMUNOREGULATORY EFFECTS OF CBG IN MASLD AND MASH *IN VITRO* AND *IN VIVO*

Fariha Tasnim[1] Kira Villarreal[1] Cayla Jackson[1] Dexter Chiong[1] Nicholas Pullen[1] Yuyan Han[1], [1]University of Northern Colorado

Background: Emerging evidence suggests activation of different immune cell populations is involved in the progression of MASLD to its advanced stage, MASH. Thus, along with lipogenic, oxidative, and fibrotic markers, exploring immune cell activation and recruitment can enhance the understanding of MASLD pathogenesis and identify therapeutic targets. Previous studies have showed that, CBG, a non-psychotropic cannabinoid, reduces low grade chronic inflammation in MCD diet-induced MASH in mice. However, its role on macrophage polarization as well its effects on HFD diet induced MASLD mice models that better recapitulate metabolic dysfunction remain unexplored. **Considering this, the study explores the efficacy of CBG in MASLD and MASH-associated metabolic dysfunction, inflammation, and the underlying molecular mechanism. Methods:** To find the potential of CBG in reducing the metabolic syndrome, serum insulin and adiponectin (insulin-sensitizing hormone) levels were evaluated by ELISA. Additionally, A combination of free fatty acids (palmitic and oleic acid) followed by CBG treatment was applied to evaluate lipid accumulation in an immortalized hepatocyte cell line (FL83B). To test CBG's effect in MASLD and MASH-associated inflammation, the general leukocyte population (CD45+), ductal proliferation (CK19), and liver resident macrophages (F4/80) were assessed by IHC. To evaluate the effect of CBG on macrophage polarization, infiltrating monocyte-derived macrophages— pro-inflammatory M1 (CD86) and anti-inflammatory M2 (CD206) were assessed by flow cytometry in hepatic non-parenchymal cells (NPC) and in bone marrow derived macrophages (BMDMs). The inflammatory cytokines, IL-6, and IFN-γ in BMDM supernatants were assessed by ELISA. Finally, to understand the mechanisms of disease pathogenesis, nuclear receptor (PPARγ, a CBG agonist), the fatty acid transporter (CD36), de novo lipogenesis (DNL) enzyme (ACC1), transcription factor (SREBP-1c), and a mitochondrial beta oxidation biomarker (PPARα) were evaluated using the Western blot. **Results:** CBG treatment significantly increased serum adiponectin levels in male mice and showed a trend of decrease in insulin levels in female mice. In vitro, CBG treatment significantly reduced intracellular lipid accumulation in the FL83B cell line. Regarding inflammation, CBG reduced leukocyte and Kupffer cell population, ductular proliferation and secretion of proinflammatory cytokines—IL-6 and IFN-γ. CBG also reduced M1 macrophage populations in both NPCs and in BMDMs. Additionally, CBG showed an increased trend for both PPARα and PPARγ level, with no change in CD36 and ACC1 level. **Conclusion:** Our findings highlight the promising therapeutic potential of CBG in MASLD and MASH and support further investigation of CBG in mitigating disease progression by targeting hepatic inflammation and metabolic dysregulation.
Disclosures: Fariha Tasnim:Nothing to Disclose, Kira Villarreal:Nothing to Disclose, Cayla Jackson:Nothing to Disclose, Dexter Chiong:Nothing to Disclose, Nicholas Pullen:Nothing to Disclose, Yuyan Han:Nothing to Disclose.

3555 | HYDRONIDONE ALLEVIATING MASLD-ASSOCIATED LIVER FIBROSIS BY TARGETING THRSP

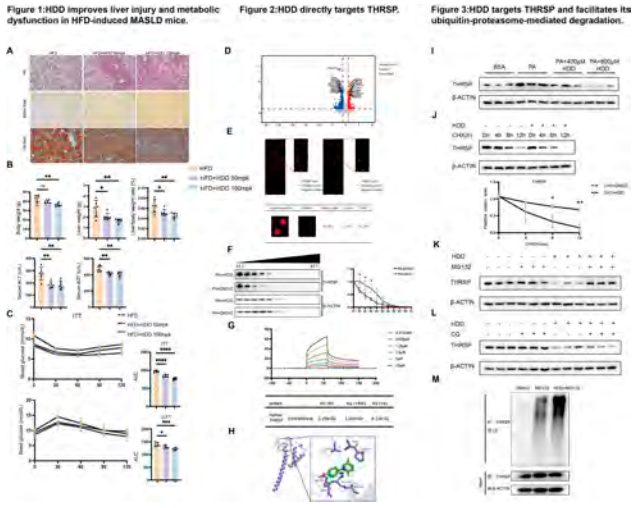
Yufei Yang[1] Qichao Ge[1] Yuecheng Guo[1] Junjun Wang[1] Hanjing Zhangdi[1] Zhuqiong Lu[1] Jie Jian[1] Guangwen Chen[1] Ying Luo[2] Ling Zhang[2] Hui Dong[1] Lungen Lu[1], [1]Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, [2]Continent Pharmaceuticals Co. ,Ltd., Beijing, China

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a chronic liver disease characterized by hepatic steatosis, inflammation, hepatocellular injury, and liver fibrosis, yet effective therapeutic targets remain limited.Hydronidone(HDD) has demonstrated favorable therapeutic efficacy against liver fibrosis in patients with hepatitis B in both Phase II and Phase III clinical trials. In this study, we investigated the therapeutic effects of HDD on MASLD and explored the underlying molecular mechanism. **Methods:** Male mice aged 6–8 weeks were fed a high-fat diet (HFD) and administered HDD by oral gavage at doses of 50 mpk and 100 mpk. A protein microarray was employed to identify the therapeutic targets of HDD, which were further validated by **cellular thermal shift assay (CETSA), surface plasmon resonance (SPR),** and **molecular docking analyses**. Protein expression levels were determined by Western blotting (WB). **Results:** HDD significantly improved hepatic steatosis and fibrosis in HFD mouse models. HDD reduced THRSP expression in liver tissues

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and hepatocytes.Protein microarray, SPR, CETSA, and molecular docking confirmed that HDD directly binds THRSP.MG132 treatment restored HDD-induced THRSP reduction, whereas chloroquine failed to rescue THRSP expression, suggesting that HDD promotes THRSP degradation through the ubiquitin–proteasome pathway rather than the lysosomal pathway.Ubiquitination assays demonstrated that HDD enhanced THRSP ubiquitination. **Conclusion:** HDD alleviated hepatic steatosis and fibrosis in MASLD models.Mechanistically, HDD directly targeted THRSP and promoted its ubiquitin–proteasome-dependent degradation, thereby improving lipid metabolic disorders and liver injury.



Disclosures: Yufei Yang:Nothing to Disclose, Qichao Ge:Nothing to Disclose, Yuecheng Guo:Nothing to Disclose, Junjun Wang:Nothing to Disclose, Hanjing Zhangdi:Nothing to Disclose, Zhuqiong Lu:Nothing to Disclose, Jie Jian:Nothing to Disclose, Guangwen Chen:Nothing to Disclose, Ying Luo:Nothing to Disclose, Ling Zhang:Nothing to Disclose, Hui Dong:Nothing to Disclose, Lungen Lu:Nothing to Disclose.

3556 | SEMAGLUTIDE, TIRZEPATIDE AND RETATRUTIDE PROMOTE METABOLIC BENEFITS AND SHOW DIFFERENT EFFECTS ON LIVER FAT REDUCTION IN OBESE HAMSTERS

Francois Briand[1] Estelle Grasset[1] Natalia Breyner[1] Claire Bigot[1] Thierry Sulpice[1], [1]Physiogenex

Background: Semaglutide (SEMA), a GLP-1 receptor, Tirzepatide (TIRZE), a GIP/GLP-1 receptors dual agonist, and retatrutide (RETA), a GIP/GLP-1/glucagon receptors triple agonist, have all demonstrated significant body weight loss and liver fat reduction in patients with obesity. Here our aim was to compare the metabolic effects of these drugs in the free choice diet-induced obese and dyslipidemic hamster, a preclinical model with a human-like lipoprotein metabolism used to assess new therapies targeting obesity and MASH. **Methods:** Obesity and MASH were induced with a 20-week free choice diet, which presents hamsters with a choice between control chow diet or high fat/high cholesterol (HF/HC) diet, and normal water or 10% fructose water. Obese hamsters were then treated subcutaneously Q3D for 5 weeks with vehicle, SEMA 15nmol/kg, TIRZE 15nmol/kg or RETA 15nmol/kg. **Results:** SEMA, TIRZE and RETA significantly reduced body weight and altered food preference with greater chow diet intake and lower HF/HC diet and 10% fructose water intake. The weight lowering effect was associated with significant reduction in fat and lean mass. However, the lean mass was not different after 5 weeks of treatment for both TIRZE and RETA. SEMA, TIRZE and RETA significantly reduced glycemia and insulinemia, leading to lower HOMA-IR index of insulin resistance: -67%, -68% and -83%, respectively (all $p < 0.001$ vs. vehicle). The three drugs significantly reduced plasma free fatty acids and triglycerides, lower VLDL- and LDL-cholesterol but unchanged HDL-cholesterol levels. Although histopathological scoring was not improved, there was a 58% and 44% reduction in hepatic triglycerides content with TIRZE ($p < 0.01$) and RETA ($p < 0.05$), respectively, while semaglutide showed a weaker effect (-23%, not significant). While SEMA and TIRZE had no effect, RETA significantly reduced the hepatic expression of genes involved in inflammation and fibrosis. **Conclusion:** SEMA, TIRZE and RETA demonstrate multiple metabolic benefits in obese hamsters. Our preclinical setting will help to assess the efficacy of novel obesity and MASH therapies versus those drugs.

Disclosures: Francois Briand:Physiogenex: Employee, Physiogenex: Stock – privately held company, Estelle Grasset:Nothing to Disclose, Natalia Breyner:Nothing to Disclose, Claire Bigot:Nothing to Disclose, Thierry Sulpice:Nothing to Disclose.

3557 | SURVODUTIDE, A GLUCAGON RECEPTOR/GLP-1 RECEPTOR DUAL AGONIST, IN PEOPLE WITH COMPENSATED METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH) CIRRHOSIS: RATIONALE AND DESIGN OF AN EVENT-DRIVEN, MULTINATIONAL, RANDOMIZED, PLACEBO-CONTROLLED, PHASE 3 TRIAL (LIVERAGE™- CIRRHOSIS)

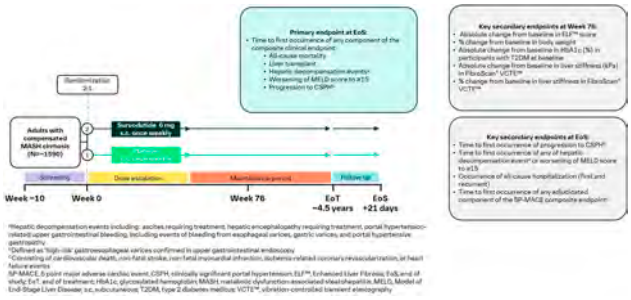
Mazen Noureddin[1] Daniel Mazo[2] Jörn Schattenberg[3] Naim Alkhouri[4] Luiza Borowska[2] Martina Brueckmann[2] Mandy Fraessdorf[5] Samina Ajaz Hussain[2] Ramy Younes[2] Arun Sanyal[6], [1]Houston Research Institute,

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Background: Survodutide is a glucagon receptor and glucagon-like peptide-1 (GLP-1) receptor dual agonist under investigation for treatment of metabolic dysfunction-associated steatohepatitis (MASH). Treatment with survodutide showed improvement in steatohepatitis and liver fibrosis in a 48-week phase 2 trial in people with MASH and fibrosis stages F1–F3. We describe the design of an ongoing phase 3 trial of survodutide for treatment of compensated MASH cirrhosis (LIVERAGE™ - Cirrhosis), an area of urgent unmet need. **Methods:** In this trial in ~1590 participants in 36 countries (NCT06632457), the main eligibility criteria include age ≥18 years, BMI ≥27 kg/m^2 (≥25 kg/m^2 for Asian participants), compensated MASH cirrhosis diagnosed by current or historical liver biopsy or determined by definitions based on histology, metabolic comorbidities and/or liver fibrosis non-invasive tests, adapted from the Liver Forum criteria; and magnetic resonance imaging-proton density fat fraction (MRI-PDFF) ≥5% or FibroScan® with controlled attenuation parameter (CAP™) ≥288 dB/m. Key exclusion criteria include current or previous significant alcohol consumption, other chronic liver disease, or hepatic decompensation event, Model for End-stage Liver Disease (MELD) score >12, albumin <3.5 g/dL, international normalised ratio of prothrombin time >1.3, total bilirubin >1.2x upper limit of normal [ULN], platelets <100,000/µL, aspartate and/or alanine aminotransferase ≥5x ULN. Participants are randomized 2:1 to double-blind, once-weekly, subcutaneous injections of either survodutide up-titrated to 6.0 mg or placebo. The study period of this event-driven trial is estimated to be ~4.5 years. The primary endpoint at End of Study (EoS) is time to first occurrence of a composite endpoint: all-cause mortality, liver transplant, hepatic decompensation, worsening of MELD score to ≥15, or progression to clinically significant portal hypertension (CSPH) defined as 'high-risk' gastroesophageal varices (GOVs). Key secondary endpoints at Week 76 are shown in the figure. At EoS, key secondary endpoints are occurrence of all-cause hospitalization, time to first occurrences of progression to CSPH, any of the hepatic decompensation events listed in the figure or worsening of MELD score to ≥15, or any adjudication confirmed components of the composite endpoint: cardiovascular death, non-fatal stroke, non-fatal myocardial infarction, ischemia-related coronary revascularization, or heart failure events. Safety evaluation is based on treatment-emergent adverse events and laboratory tests. **Results:** Recruitment of participants began in November 2024. Follow-up is estimated to end in 2029. **Conclusion:** The phase 3 LIVERAGE™ - Cirrhosis trial will investigate the effects of survodutide on liver-related outcomes, and all-cause mortality in people with compensated MASH cirrhosis, as well as its tolerability and safety.



Disclosures: Mazen Noureddin:Nothing to Disclose, Daniel Mazo:Boehringer Ingelheim International GmbH: Employee, Jörn Schattenberg:Akero: Consultant, 89Bio: Consultant, Boehringer Ingelheim: Consultant, Ipsen: Consultant, Inventiva Pharma: Consultant, Madrigal: Consultant, Northsea Therapeutics: Consultant, Novo Nordisk: Consultant, Roche: Consultant, Siemens Healthineers: Consultant, Boehringer Ingelheim: Advisor, AGED diagnostics: Stock – privately held company, Hepta Bio: Stock – privately held company, Novo Nordisk: Speaking and Teaching, Madrigal: Stock - publicly traded company, MedPublico GmbH: Speaking and Teaching, Eli Lilly: Advisor, Altimmune: Consultant, Astra Zeneca: Consultant, Gilead Science: Consultant, Merck: Consultant, MSD Sharp & Dohme GmbH: Consultant, AbbVie: Advisor, Naim Alkhouri:Madrigal: Speaking and Teaching, Novo Nordisk: Consulting, Novo Nordisk: Grant/Research Support, Corcept: Grant/Research Support, Echosens: Speaking and Teaching, Perspectum: Consultant, Cima: Consultant, Fibronostics: Consultant, 89Bio: Grant/Research Support, Inventiva: Grant/Research Support, Merck: Grant/Research Support, Pfizer: Grant/Research Support, Ipsen: Speaking and Teaching, Intercept: Speaking and Teaching, Madrigal: Consulting, Research Funding, Novo Nordisk: Consulting, Research Funding, Inventiva: Research Funding, Boehringer Ingelheim: Consulting, Research Funding, Corcept: Research Funding, Ipsen: Consulting, Research Funding, Gliead: Consulting, Research Funding, Speaking, Perspectum: Consulting, Research Funding, Cima: Advisor, 89Bio: Consulting, Research Funding, Arbutus: Grant/Research Support, GSK: Grant/Research Support, Regeneron: Grant/Research Support, AstraZeneka: Grant/Research Support, Madrigal: Grant/Research Support, Akero: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Eli Lilly: Grant/Research Support, Gilead: Grant/Research Support, Galectin: Grant/Research Support, Boston Pharma: Grant/Research Support, Luiza

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3558 | NEBULA-1 AND NEBULA-2: PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIALS IN PROGRESS OF EFIMOSFERMIN ALFA IN PARTICIPANTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH) AND COMPENSATED CIRRHOSIS

Mazen Noureddin[1] Naga Chalasani[2] Meena Bansal[3] Laurent Castera[4] Rohit Loomba[5] Arun Sanyal[6] Margaret James Koziel[7] Stuart Kendrick[8] Beth Ann Reedy[9] Theresa Peterson[9] Andrea Ribeiro[10] Patricia Mendez[9] Jörn Schattenberg[11], [1]Houston Methodist Hospital and Houston Research Institute, Houston, TX, USA, [2]Indiana University School of Medicine, Indianapolis, IN, USA, [3]Icahn School of Medicine at Mount Sinai, New York, NY, USA, [4]Service d'Hépato-gastroentérologie, Hôpital Haut-Lévêque, CHU de Bordeaux, Pessac, France, [5]MASLD Research Center, University of California at San Diego, La Jolla, CA, USA, [6]Stravitz-Sanyal Institute for Liver Disease and Metabolic Health, Richmond, VA, USA, [7]Boston Pharmaceuticals, Cambridge, MA, USA, [8]GSK, Stevenage, UK, [9]GSK, Collegeville, PA, USA, [10]GSK, Madrid, Spain, [11]Saarland University Medical Center, Homburg and Saarland University, Saarbrücken, Germany

Background: MASH with compensated cirrhosis (F4) is becoming a leading cause of liver transplantation, death, and development of hepatocellular carcinoma, with high unmet medical need and no approved therapies. Efimosfermin alfa, a long-acting fibroblast growth factor 21 analog, demonstrated statistically significant improvements in steatohepatitis, fibrosis, non-invasive tests, and liver/metabolic biomarkers in a Phase 2 study (NCT04880031) in participants with MASH F2/F3, and is being investigated in an ongoing Phase 2 trial in participants with MASH with cirrhosis (NCT06920043), supporting further evaluation in advanced disease. **Methods:** NEBULA-1 and NEBULA-2 are randomized, double-blind, placebo-controlled, multicenter phase 3 studies to evaluate the safety and efficacy of efimosfermin alfa in adults aged 18–75 years with compensated cirrhosis due to MASH, identified either noninvasively (NEBULA-1) or confirmed by historical or fresh biopsy (NEBULA-2). In NEBULA-1, participants will receive efimosfermin alfa or placebo. In NEBULA-2, participants will receive efimosfermin alfa or placebo with an optional open-label extension. Eligibility includes, but is not limited to, compensated cirrhosis, absence of prior liver decompensation, and stable dosing of antidiabetic or antilipid medications. **Results:** The primary endpoint of NEBULA-1 is time to composite clinical outcome (all-cause mortality, liver transplantation, hepatic decompensation events, and an increase in Model for End-Stage Liver Disease score) compared with placebo. In NEBULA-2, the primary endpoint is fibrosis improvement of ≥ 1 stage without worsening of MASH. Secondary endpoints include reduction from baseline in liver stiffness (assessed by vibration-controlled transient elastography [VCTE-LSM]) and in Enhanced Liver Fibrosis (ELF) score, as well as safety, tolerability, and health-related quality of life (HRQoL). **Conclusion:** NEBULA-1 and NEBULA-2 will evaluate the safety and efficacy of efimosfermin alfa in MASH with cirrhosis, using accepted regulatory primary endpoints with meaningful secondary and exploratory endpoints spanning noninvasive liver, metabolic, and measures of HRQoL. The data will inform whether efimosfermin alfa can modify disease progression and improve clinical outcomes in this high-risk population with a significant unmet need.

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3559 | TREATMENT PERSISTENCE AMONG PATIENTS PRESCRIBED RESMETIROM IN A US CLAIMS-BASED COHORT

Ruth Dixon[1] Zi Wang[1] Chia-Chen Teng[1] John Barron[1] Blake Thomas[2] Karen Phillips[2] Yestle Kim[2] Francis Lobo[2], [1]Carelon Research, [2]Madrigal Pharmaceuticals

Background: Resmetirom is the first FDA conditionally approved therapy for MASH with moderate-to-advanced liver fibrosis (F2–F3). Understanding the real-world treatment journey, especially long-term resmetirom persistence is essential for optimizing clinical integration. **Methods:** Patients were identified from Carelon Research Healthcare Integrated Research Dataset (HIRD). This US-based study was a non-interventional, retrospective cohort study of patients aged ≥18 years with ≥1 claim for resmetirom fill between 01 April 2024 and 31 October 2025 (intake period). The index date was the earliest resmetirom fill during the intake period. Patients were required to have ≥1-year continuous enrollment before index date. The study defined the lookback period as the day before the index date back to October 1, 2015. Liver biopsy status within three years of index date was used to create patient subgroups.We report resmetirom persistence (therapy without a gap of ≥60 days between prescription fills) at 6 and 12 months post-index. Proportion of Days Covered (PDC) is a patient level adherence measure. **Results:** Of 1,592 patients, PDC and persistence were assessed for patients eligible at 6 months (n = 880) and 12 months (n = 392) post-index. At 6 months post-index, median PDC was 93.0% (IQR 78.0% – 98.0%) while persistence was 81.0% with similar rates between biopsy and non-biopsy groups. At 12 months post-index, median adherence (PDC) was 87.0% (IQR 65.0% – 95.0%); and 89.0% [71.0%–96.0%] with biopsy vs 87.0% [61.0% – 94.0%] without biopsy, p-value = 0.367. Persistence was 68.4% overall (75.0% with biopsy; 66.0% without biopsy), p-value = 0.116. See table attached (Table 1) **Conclusion:** In this real-world study among MASH patients being treated with resmetirom, high PDC's at 6 and 12 months, together with high persistence, suggest that many patients can maintain long-term, continuous resmetirom therapy in routine practice, supporting its feasibility as a chronic treatment option.

Table 1: Resmetirom persistence at 6 and 12-months

	Overall	With Biopsy[1]	Without Biopsy[2]	P-value
Number of patients, N	**1,592**	**339**	**1,253**	
6-month post index				
Patients with 6-month eligibility post-index, n (%)	880 (55.3%)	213 (62.8%)	667 (53.2%)	0.002
Rezdiffra Treated Days				0.489
Mean (SD)	148.8 (47.3)	150.7 (45.6)	148.2 (47.9)	
Median (IQR)	170.0 (142.8-180.0)	171.0 (145.0-181.0)	170.0 (142.0-180.0)	
Adherence - Proportion of Days Covered (PDC), mean (SD)	81.0% (26.0%)	82.0% (25.0%)	81.0% (26.0%)	0.489
Adherence - Proportion of Days Covered (PDC), Median (IQR)	93.0% (78.0%-98.0%)	93.0% (79.0%-99.0%)	93.0% (77.0%-98.0%)	
Adherence (PDC≥80%), n (%)	634 (72.1%)	157 (73.7%)	477 (71.5%)	0.594
Persistence[3], n (%)	713 (81.0%)	173 (81.2%)	540 (81.0%)	NR
12-month post index				
Patients with 12-month eligibility post-index, n (%)	392 (24.6%)	104 (30.7%)	288 (23.0%)	0.004
Rezdiffra Treated Days				0.367
Mean (SD)	270.6 (106.8)	278.7 (106.2)	267.7 (107.1)	
Median (IQR)	320.0 (236.8-348.0)	324.5 (261.0-351.5)	320.0 (224.8-345.0)	
Adherence - Proportion of Days Covered (PDC), mean (SD)	74.0% (29.0%)	76.0% (29.0%)	73.0% (29.0%)	0.367
Adherence - Proportion of Days Covered (PDC), Median (IQR)	87.0% (65.0%-95.0%)	89.0% (71.0%-96.0%)	87.0% (61.0%-94.0%)	
Adherence (PDC≥80%), n (%)	242 (61.7%)	71 (68.3%)	171 (59.4%)	0.138
Persistence, n (%)	268 (68.4%)	78 (75.0%)	190 (66.0%)	0.116

Disclosures: Ruth Dixon:Nothing to Disclose, Zi Wang:Nothing to Disclose, Chia-Chen Teng:Nothing to Disclose, John Barron:Nothing to Disclose, Blake Thomas:Madrigal Pharmaceuticals: Employee, Karen

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Phillips:Nothing to Disclose, Yestle Kim:Nothing to Disclose, Francis Lobo:Nothing to Disclose.

3560 | CANNABIS USE AND HEPATIC DISEASE PROGRESSION IN MASLD: A PROPENSITY SCORE–MATCHED COHORT ANALYSIS

Jashanveer Johal[1] Archana Salek[1] Mahmoud Al-Bataineh[1] Brandon Cunha[1] Bianca Patel[1] Abdallah Hussein[1] Jason Hyman[2] Yecheskel Schneider[1], [1]Virtua Health, [2]Einstein Medical Center, Philadelphia

Background: Cannabinoid receptor signaling exerts biologically opposing effects on the liver — CB1 activation promotes hepatic lipogenesis and stellate cell activation, while CB2 activation is anti-inflammatory and antifibrotic. Whether cannabis use modifies MASLD disease trajectory remains unresolved and increasingly clinically relevant given rising use prevalence. **Methods:** We conducted a propensity score–matched retrospective cohort study using the TriNetX Global Collaborative Network (191.9 million patients). Cohort 1 comprised adults with MASLD and documented cannabis use disorder. Cohort 2 comprised MASLD patients without cannabis use. Both cohorts excluded alcoholic fatty liver, alcohol dependence, opioid dependence, and chronic viral hepatitis. 1:1 PSM yielded 53,311 patients per arm over a 6–120 month follow-up. Outcomes included incident cirrhosis, ascites, HCC, hepatic encephalopathy (HE), esophageal varices, SBP, all-cause mortality, and inpatient encounters. **Results:** Cannabis use was associated with lower rates across all hepatic progression endpoints. Incident cirrhosis was lower on both cumulative risk (2.6% vs. 4.1%; RR 0.64; $p < 0.001$) and KM analysis (HR 0.82, 95% CI 0.76–0.88; $p < 0.001$). Incident ascites was lower on cumulative risk (3.6% vs. 4.8%; RR 0.76; $p < 0.001$), though KM analysis was borderline (HR 0.95; $p = 0.076$). Incident HCC showed the most striking reduction (0.24% vs. 0.71%; RR 0.34; HR 0.44, 95% CI 0.36–0.54; $p < 0.001$). Incident HE was significantly lower (1.6% vs. 2.6%; HR 0.75; $p < 0.001$), as were esophageal varices (0.80% vs. 1.83%; HR 0.53; $p < 0.001$) and SBP (0.49% vs. 0.71%; HR 0.81; $p = 0.011$). All-cause mortality was significantly lower with cannabis use (7.1% vs. 11.2%; HR 0.80; $p < 0.001$). Inpatient encounter rates were paradoxically higher in the cannabis arm (44.8% vs. 42.0%; HR 1.32; $p < 0.001$), with shorter median time to first encounter (1,002 vs. 1,712 days). **Conclusion:** In this large propensity-matched cohort, cannabis use in MASLD was associated with significantly lower rates of cirrhosis, HCC, HE, esophageal varices, SBP, and all-cause mortality. These findings are directionally consistent with CB2-mediated hepatoprotective mechanisms and challenge the assumption that cannabis use accelerates MASLD progression. Residual confounding cannot be fully excluded, and higher inpatient utilization warrants further investigation. Prospective studies with controlled cannabis exposure characterization are needed to establish causality and inform clinical counseling.

Disclosures: Jashanveer Johal:Nothing to Disclose, Archana Salek:Nothing to Disclose, Mahmoud Al-Bataineh:Nothing to Disclose, Brandon Cunha:Nothing to Disclose, Bianca Patel:Nothing to Disclose, Abdallah Hussein:Nothing to Disclose, Jason Hyman:Nothing to Disclose, Yecheskel Schneider:Nothing to Disclose.

3561 | NLT-101 PROTECTS AGAINST LIPOTOXIC HEPATOCELLULAR INJURY DEPENDENT ON NUCLEAR ENVELOPE LAMIN B1

Michael Cooreman[1] Stefan Hoenow[2] Thomas Ryan[3] Daniel Bakowski[3] Christopher Shepard[1], [1]Nula Therapeutics, [2]Apollo VC, [3]Sygnature discovery

Background: Lipotoxicity is critical for the pathogenesis of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) as a stressor of the endoplasmic reticulum (ER) and by reducing nuclear envelope lamin B1 (LMNB1), which regulates expression of lipid metabolism related genes. We have previously shown that NLT-101, a selective partial estrogen receptor alpha (ERa) agonist which mediates insulin-sensitizing effects, prevents the palmitate-induced decrease of LMNB1. We further investigated the effects of NLT-101 and 17a-estradiol (17aE2) on the Unfolded Protein Response (UPR), aimed at restoring ER homeostasis and cell survival following lipotoxic stress. **Methods:** 100 uM palmitate, a saturated fatty acid (FA) that induces cellular lipotoxicity, or oleate, an unsaturated FA that protects from lipotoxicity, was added to HepG2 cell cultures for 6 hours. Treatment with NLT-101, 17aE2 and 17bE2, with concentrations ranging from 0.1 to 10 uM, was applied starting 30 min before beginning of lipotoxic stress. The ratio of spliced to unspliced

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XBP1 (sXBP1/uXBP1) was measured by qRT-PCR as a representation of the Unfolded Protein Response (UPR) to endoplasmic reticulum stress. Dependency of XBP1 splicing on the presence of ERa and NE LMNB1 was evaluated using the selective ERa degrading PROTAC ARV-471 and an LMNB1 knock-out (LMNB1-/-) cell line, respectively. Viable cells as percentage of BSA control were assessed with the CellTiter-Glo luminicent Cell Viability Assay. **Results:** The ratio of sXBP1/uXBP1 in palmitate 100 uM stressed HepG2 cells increased significantly with both 17aE2 and NLT-101, but not with 17bE2 exposure, while no effect of either NLT-101 or 17aE2 was seen in LMNB1 -/- cells or in cells treated with ARV-471. In the absence of palmitate lipotoxic stress, no increase in XBP1 spicing occurred with NLT-101 or 17aE2 exposure. No increase in XBP1 splicing was seen in oleate treated cells. Dose-dependent cell death was observed with palmitate, with 100 uM palmitate reducing cell viability to 65% after 18 hours. Oleate had no comparable effect on cell viability. Both NLT-101 and 17aE2, but not 17bE2, increased cell viability of cells under palmitate stress in a dose-dependent way, with 10uM NLT achieving 100% rescue; this effect was entirely absent in LMNB1 -/- cells. Cell viability rescue aligned with XBP-1 splicing for NLT-101 and 17aE2 ligands. **Conclusion:** NLT-101 and 17aE2 protect a hepatocellular cell line against lipotoxicity-induced cell death through a similar pathway involving the UPR, which is dependent on ERa and nuclear envelope lamin B1. These data support the evaluation of the therapeutic potential of NLT-101 for MASLD.

Disclosures: Michael Cooreman:Inventiva: Independent Contractor, Stefan Hoenow:Nothing to Disclose, Thomas Ryan:Nothing to Disclose, Daniel Bakowski: Nothing to Disclose, Christopher Shepard:Nothing to Disclose.

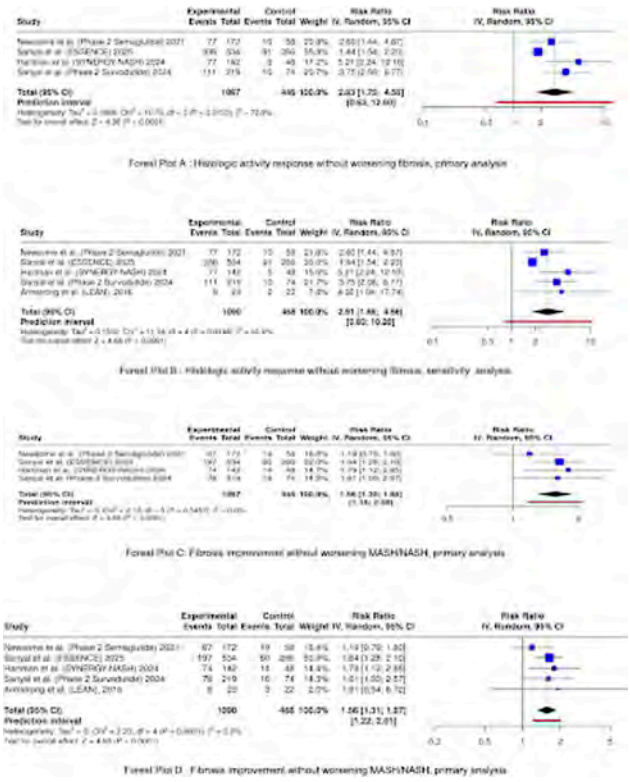
3562 | INCRETIN-BASED THERAPIES FOR BIOPSY-CONFIRMED NON-CIRRHOTIC MASH: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED PLACEBO-CONTROLLED TRIALS

Hima Varsha Voruganti[1] Rohit Sekandlapuram[2] Ravi Patel[3] Shravya Ginnaram[4] Aashay Dharia[5] Pratiksha Moliya[6] Hasan Al-Obaidi[7] Yagnesh Nandikanti[8] Roshitha Bheemaneni[9] Manasa Ginjupalli[5], [1]North Alabama Medial Center, [2]Montefiore Medical Center, Bronx, [3]Trinity Health Okland, [4]HCA Florida Citrus Hospital/USH Morsani College of Medicine, [5]Brooklyn Hospital Center, [6]University of Nebraska Medical center, [7]University of Toledo, [8]Siddhartha Medical College, [9]Gandhi Medical College

Background: Metabolic dysfunction-associated steatohepatitis (MASH) has limited disease-modifying treatment options. Incretin-based therapies have shown promising histologic effects, but differences in fibrosis-stage eligibility and endpoint definitions have complicated cross-trial interpretation. **Methods:** We searched PubMed, Embase, and the Cochrane Library for randomized controlled trials of incretin-based therapies in adults with biopsy-confirmed non-cirrhotic NASH/MASH. Eligible studies required a placebo or standard-care comparator, treatment duration ideally $\geq$48 weeks, and reporting of at least 1 histologic endpoint: NASH/MASH resolution or improvement without worsening fibrosis, or $\geq$1-stage fibrosis improvement without worsening NASH/MASH. Studies were excluded from the primary non-cirrhotic analysis if they included cirrhosis/F4, were imaging-only, biomarker-only, non-randomized, or used combination therapy with unequal background treatment. Active-dose arms were pooled within study, and random-effects risk ratios were used for meta-analysis. Armstrong et al., 2016 (LEAN) was excluded from the primary model and retained only for sensitivity analysis because the study included compensated cirrhosis/F4 participants. **Results:** Four trials met criteria for the primary analysis: Newsome et al., 2021 (Phase 2 Semaglutide), Sanyal et al., 2025 (ESSENCE), Hartman et al., 2024 (SYNERGY-NASH), and Sanyal et al., 2024 (Phase 2 Survodutide). Incretin-based therapies significantly improved histologic activity response without worsening fibrosis versus placebo (RR 2.83, 95% CI 1.75-4.56; I^2 = 72.0%). They also improved fibrosis without worsening MASH/NASH (RR 1.56, 95% CI 1.30-1.86; I^2 = 0%). Sensitivity analysis including Armstrong et al., 2016 (LEAN) yielded similar results for histologic activity response (RR 2.91, 95% CI 1.86-4.56; I^2 = 65.9%) and did not materially change the fibrosis estimate (RR 1.56, 95% CI 1.31-1.87; I^2 = 0%). **Conclusion:** In placebo-controlled biopsy-based trials, incretin-based therapies showed a compelling histologic signal in non-cirrhotic MASH, combining a strong likelihood of steatohepatitis improvement with a consistent fibrosis benefit. These findings support incretin-based agents as leading disease-modifying candidates for biopsy-confirmed non-cirrhotic MASH and justify continued class-specific, longer-term evaluation.

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3563 | ASSOCIATION BETWEEN GLP-1 RECEPTOR AGONISTS AND FRACTURE RISK IN POSTMENOPAUSAL WOMEN WITH MASLD: A RETROSPECTIVE COHORT STUDY USING TRINETX

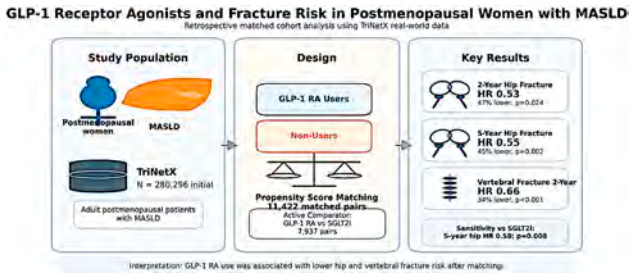
Ridwan Lawal[1] Guy Loic Nguefang Tchoukeu[2] Bright Nwatamole[3] Cherechi Nwabueze[4] Oladoyin Ogunbayo-Jolaoye[5] Sarpong Boateng[6] Basile Njei[7], [1]University of Texas Rio Grande Valley, [2]Texas Tech University Health Science Center, Permian Basin, [3]Zucker School of Medicine at Hofstra/Northwell at Vassar Brothers Medical Center, Poughkeepsie, [4]John H. Stroger Jr. Hospital of Cook County, [5]University of Illinois Chicago Peoria, [6]Yale New Haven Health, Bridgeport Hospital, [7]Yale University

Background: Postmenopausal women with metabolic dysfunction-associated steatotic liver disease (MASLD) face elevated fracture risk driven by the intersection of estrogen deficiency, chronic inflammation, and metabolic dysregulation. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) demonstrate pleiotropic benefits in glycemic control, weight reduction, cardiovascular protection, and MASH resolution, but their effects on skeletal outcomes in this population remain undefined. This study evaluated the association between GLP-1 RA use and fracture risk among postmenopausal women with MASLD over a 5-year follow-up period. **Methods:** We conducted a retrospective study using the TriNetX federated research network. Postmenopausal women ≥ 50 years with MASLD were divided into GLP-1 RA users and non-users. Propensity score matching (PSM) on 38 baseline covariates, demographics, comorbidities, medications, and laboratory values produced 11,422 patients per arm. The primary outcome was pathologic (fragility) fracture; secondary outcomes included site-specific fractures at the hip, vertebra, wrist, and humerus. An active-comparator sensitivity analysis compared GLP-1 RA users (n = 7,937) against sodium-glucose cotransporter-2 (SGLT2) inhibitor users (n = 7,937) after separate PSM. Hazard ratios (HR) were estimated using Cox proportional hazards regression with Kaplan-Meier survival analysis. Outcomes were assessed at 2-, 3-, and 5-year windows. **Results:** In the primary analysis, GLP-1 RA use was associated with a statistically significant 47.2% reduction in hip fracture risk at 2 years (HR 0.528, 95% CI 0.301–0.927; $p = 0.024$) and a 34.3% reduction in vertebral fracture risk (HR 0.657, 95% CI 0.521–0.828; $p < 0.001$). At 5 years, hip fracture reduction persisted at 45.2% (HR 0.548, 95% CI 0.370–0.812; $p = 0.002$). The pathologic fracture primary outcome did not reach significance at any time point. In the SGLT2 inhibitor active-comparator analysis, GLP-1 RA use was associated with a significant 42.9% reduction in humerus fracture at 2 years (HR 0.571, 95% CI 0.376–0.867; $p = 0.008$) and a 42.5% reduction in hip fracture at 5 years (HR 0.575, 95% CI 0.380–0.870; $p = 0.008$). **Conclusion:** GLP-1 RA use in postmenopausal women with MASLD was associated with consistent and clinically meaningful reductions in site-specific fractures, particularly at the hip and vertebra, across multiple follow-up intervals. These findings, reinforced by sensitivity analyses against an active comparator, suggest that GLP-1

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RAs may confer skeletal protection beyond their established metabolic benefits in this high-risk population.



Disclosures: Ridwan Lawal:Nothing to Disclose, GUY LOIC NGUEFANG TCHOUKEU:Nothing to Disclose, Bright Nwatamole:Nothing to Disclose, Cherechi Nwabueze:Nothing to Disclose, Oladoyin Ogunbayo-Jolaoye:Nothing to Disclose, Sarpong Boateng:Nothing to Disclose, Basile Njei:Nothing to Disclose.

3564 | NEW THERAPY, OLD EQUITY QUESTIONS: RACIAL DISPARITIES IN RESMETIROM USE FOR MASLD

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Background: Resmetirom use is expanding for metabolic dysfunction-associated steatohepatitis, but early adoption may not reach all patient groups equally. We compared patients with metabolic dysfunction-associated steatotic liver disease (MASLD) with and without resmetirom exposure to describe early race and ethnicity signals in real-world use. **Methods:** We performed a retrospective real-world baseline comparison of MASLD patients with resmetirom exposure versus MASLD patients without resmetirom exposure. Demographic, race/ethnicity, laboratory, diagnosis, and medication characteristics were compared using P values and standardized mean differences (SMD). Insurance coverage, income, and education level data were limited. **Results:** The resmetirom cohort included 747 patients and the comparator cohort included 169,839 patients. Patients receiving resmetirom were slightly older (57.6 ± 13.0 vs 56.1 ± 15.7 years; P = 0.0086; SMD 0.1046). Hispanic ethnicity was equally represented (12% vs 12%; P = 0.7018; SMD 0.0142). Race composition showed the most notable equity-relevant differences. Black or African American patients represented 5% of the resmetirom cohort versus 9% of comparators (P = 0.0008; SMD 0.1367), while unknown race represented 20% versus 16% (P = 0.0002; SMD 0.1288). White race was similar (64% vs 65%; P = 0.5074; SMD 0.0242). Patients receiving resmetirom had higher body mass index (33.8 ± 6.92 vs 32.8 ± 7.61; P = 0.0008; SMD 0.1338), lower total cholesterol (157 ± 44.1 vs 172 ± 51.9; P < 0.0001; SMD 0.2977), lower low-density lipoprotein cholesterol (83.2 ± 35.7 vs 98.1 ± 38.3; P < 0.0001; SMD 0.4013), and similar hemoglobin A1c (6.11 ± 1.0 vs 6.08 ± 1.27; P = 0.6841; SMD 0.0192). Antilipemic medication exposure was higher (62% vs 48%; P < 0.0001; SMD 0.2929), as was glucagon-like peptide-1 receptor agonist exposure (39% vs 20%; P < 0.0001; SMD 0.4331). **Conclusion:** In this early real-world MASLD comparison, resmetirom-treated patients differed from untreated comparators by race composition, lipid profile, body mass index, and cardiometabolic medication exposure. The lower representation of Black or African American patients should be interpreted as a modest access signal, not proof of independent prescribing inequity, especially given higher unknown race documentation and limited socioeconomic data. As resmetirom use grows, adjusted studies should evaluate fibrosis stage, payer status, specialty access, geography, and treatment eligibility to ensure that MASH-directed therapy does not widen existing liver-disease disparities.

Disclosures: chimezirim ezeano:Nothing to Disclose, Ihunanya Kanu:Nothing to Disclose, Sarpong Boateng:Nothing to Disclose, GUY LOIC NGUEFANG TCHOUKEU:Nothing to Disclose, Emeka Stanley Obi:Nothing to Disclose, Cherechi Nwabueze:Nothing to Disclose, IFELUNWA OSANAKPO:Nothing to Disclose, Goodness Joseph:Nothing to Disclose, David Narvaez-De los Rios:Nothing to Disclose, Onyinyechukwu Ozumba:Nothing to Disclose, Chimezie Madu:Nothing to Disclose, Angel Umahi:Nothing to Disclose.

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3565 | BEYOND OBESITY: GLP-1RAS VS AMYLIN ANALOGS IN A PRECLINICAL RAT MODEL OF MASH

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Background: Metabolic dysfunction-associated steatohepatitis (MASH) is a progressive form of NAFLD associated with obesity, insulin resistance, and type 2 diabetes. GLP-1 receptor agonists (GLP-1RAs) and amylin analogs both induce weight loss and improve metabolic parameters, and have shown promise for reducing hepatic steatosis and inflammation. Direct, controlled comparisons of these drug classes in standardized preclinical MASH models are limited. We therefore compared semaglutide (GLP-1RA) and cagrilintide (amylin analog) with the approved thyroid hormone receptor-β agonist resmetirom in a high-fat diet + CCl4 rat model of MASH to evaluate metabolic and histologic effects. **Methods:** MASH was induced by high-fat diet combined with carbon tetrachloride (CCl_4). Study groups included healthy controls and MASH cohorts treated with vehicle, resmetirom, semaglutide, or cagrilintide. Dosing and schedules were optimized for each compound. Animals were monitored for clinical condition and metabolic parameters throughout 6 weeks of treatment. Endpoints assessed in collected liver tissue included steatosis, inflammation, and fibrosis by conventional histology, digital image analysis, and molecular assays. **Results:** All active treatments produced significant improvements versus vehicle-treated MASH controls. Semaglutide and cagrilintide produced greater and more sustained body-weight reductions than resmetirom. All therapies lowered NAS by approximately 2–4 points and reduced fibrosis area to varying extents. Cagrilintide showed a pronounced anti-fibrotic effect in addition to reducing steatosis and inflammation. Digital histology revealed that cagrilintide more clearly reduced fibrosis in both portal and septal regions compared with semaglutide, consistent with reduced liver injury and structural recovery. Overall, GLP-1RA and amylin analog therapies effectively mitigated key pathological features of MASH in this model. **Conclusion:** In this preclinical MASH model, semaglutide effectively reversed steatosis and inflammation, while resmetirom and cagrilintide had stronger anti-fibrotic effects. The fibrosis reduction observed with the amylin analog suggests that targeting amylin pathways may offer a complementary approach to current treatments and merits further clinical investigation.

Disclosures: Sitong Zhang:Nothing to Disclose, Yan Zhou:Nothing to Disclose, Miao Yuan:Nothing to Disclose, Renjie Ding:Nothing to Disclose, Jiliang Zhang:Nothing to Disclose, Wenjie Gao:Nothing to Disclose, Letian Kuai:Nothing to Disclose.

3566 | EDL6D, A BIOACTIVE PEPTIDE PHENOCOPYING SHBG-ASSOCIATED METABOLIC EFFECTS: A NEW PRECLINICAL LEAD COMPOUND FOR TREATING THE METABOLIC DYSFUNCTION-ASSOCIATED FATTY LIVER DISEASE

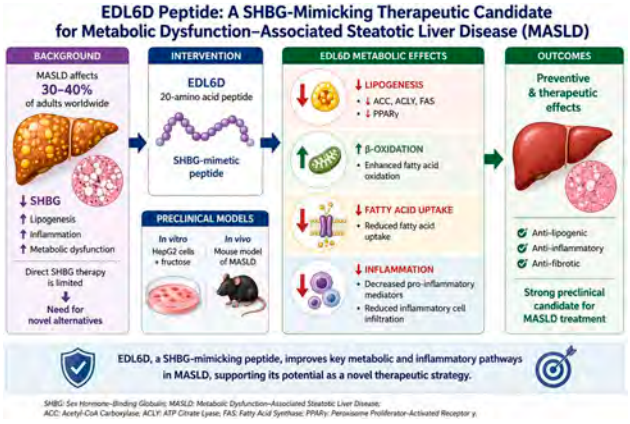
David Martinez Selva[1] Anna Alvarez-Guaita[1] Julia Cabrera-Serra[1] Beatriz Perez-Gonzalez[2] María Teresa Salcedo[3] Lidia Fuertes-Rioja[1] Lorena Ramos-Perez[1] Cristina Hernandez[4] Rafael Simo[5], [1]Vall d'Hebron Research Institute, UAB, [2]Endolipid Therapeutics S.L,, [3]Vall d'Hebron University Hospital, [4]Vall Hebron Institut de Recerca, UAB, [5]rafael.simo@vhir.org

Background: Metabolic dysfunction-associated fatty liver disease (MASLD) is linked to low plasma levels of sex hormone-binding globulin (SHBG). Previous studies showed that SHBG overexpression reduces liver fat accumulation by inhibiting lipogenesis. In the present work, we have developed an SHBG mimetic peptide (EDL6D) that could be used as a new treatment to prevent and treat MASLD development and arrest its progression to MASH. **Methods:** We have first tested the EDL6D effects in in vitro experiments using HepG2 cells treated daily with 30 mM fructose. We next have studied the preventive and therapeutic effects of EDL6D using wild-type mice developing MASLD induced by high fat diet and 30% fructose in the drinking water over 8 and 20 weeks respectively **Results:** Our results clearly showed that the treatment with EDL6D was able to reduce liver fat accumulation and regress MASLD by reducing the mRNA expression and protein levels of key lipogenic enzymes (ACLY, ACC and FAS) as well as PPARγ. Moreover, EDL6D was able to prevent the development of mild fibrosis, which can be attributed to its capacity to downregulates the intrahepatic production of collagen 1A1 (Col1A1) and transforming growth factor beta 1 (TGF-β1). **Conclusion:** In summary, we have shown that EDL6D, an SHBG mimetic peptide reduces de novo and exerts an important anti-inflammatory effect preventing fibrosis development in MASLD mouse models. These results suggested that EDL6D could be used as a new treatment to prevent and treat MASLD development and arrest its

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progression to MASH



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3567 | GLP-1 RECEPTOR AGONISTS AND INCIDENCE OF HEPATOCELLULAR CARCINOMA IN PATIENTS WITH METABOLIC STEATOTIC LIVER DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Hepatocellular carcinoma (HCC) is an increasingly important complication of metabolic liver disease. GLP-1 receptor agonists (GLP-1RAs) may reduce liver-related risk through effects on weight, glycemic control, insulin resistance, and hepatic inflammation; however, their association with HCC risk in MASLD/MASH populations remains uncertain. **Methods:** We performed a systematic review and meta-analysis of observational cohort studies reporting HCC outcomes among adults with MASLD, MASH, or legacy NAFLD/NASH exposed to GLP-1RAs. The primary comparative analysis pooled adjusted hazard ratios (HRs) for incident HCC using random-effects models with Hartung-Knapp adjustment. Single-arm random-effects meta-analyses estimated the cumulative incidence of HCC among GLP-1RA-exposed participants. **Results:** Sixteen studies were identified, of which 14 adjusted HR estimates were included in the primary comparative meta-analysis. GLP-1RA exposure was associated with lower adjusted hazard of incident HCC compared with comparator groups (HR 0.68, 95% CI 0.50–0.91; p = 0.014). Findings were directionally similar in cirrhosis cohorts (HR 0.72, 95% CI 0.48–1.09) and non-cirrhotic cohorts (HR 0.59, 95% CI 0.24–1.45), with no significant subgroup difference (p = 0.578). In single-arm analyses, 16 GLP-1RA-exposed arms included 380,852 participants and 1,212 HCC events. The pooled cumulative HCC incidence among GLP-1RA users was 0.32% (95% CI 0.13–0.77), with higher incidence in cirrhosis than non-cirrhotic cohorts (0.67% vs 0.14%; p = 0.018). **Conclusion:** Among patients with MASLD/MASH populations, GLP-1RA exposure was associated with a lower adjusted hazard of incident HCC. HCC incidence among GLP-1RA-treated patients was low overall but higher in cirrhosis cohorts. These findings are hypothesis-generating and limited by observational designs, heterogeneity, variable liver disease definitions, and incomplete fibrosis staging. Prospective studies and target-trial emulations are needed to clarify whether GLP-1RAs causally reduce HCC risk.

Disclosures: Gurjit Mander:Nothing to Disclose, Yashasavi Sachar:Nothing to Disclose, Sanewal Singh:Nothing to Disclose, Mayur Brahmania:Nothing to Disclose.

3568 | DEMOGRAPHIC, CLINICAL, AND MEDICATION USE PROFILES OF PATIENTS PRESCRIBED RESMETIROM : A US CLAIMS-BASED ANALYSIS

Ruth Dixon[1] Zi Wang[1] Chia-Chen Teng[1] John Barron[1] Blake Thomas[2] Karen Phillips[2] Yestle Kim[2] Francis Lobo[2], [1]Carelon Research, [2]Madrigal Pharmaceuticals

Background: Resmetirom received FDA conditional approval in March 2024 as the first pharmacotherapy for metabolic dysfunction-associated steatohepatitis (MASH) with moderate-to-advanced fibrosis. Real-world data describing patients prescribed resmetirom remain limited. **Methods:** This US retrospective cohort study used Carelon Research Healthcare Integrated Research Dataset (HIRD). Adults aged ≥ 18 years with ≥ 1 resmetirom claim between 1 April 2024 and 31 October 2025 and ≥ 1 year of continuous enrollment before the first fill (index date) were included. Baseline demographics, social drivers of health, comorbidities, laboratory values, non-invasive testing (NIT), medication use, and statin intensity were assessed during the year before index. Findings were compared between patients with liver biopsy (LB) and no liver biopsy (NLB) within 3 years before resmetirom initiation. **Results:** Among 2,042 patients with ≥ 1 resmetirom claim, 1,592 met inclusion criteria; 339 (21.3%) had prior LB and 1,253 (78.7%) did not. Higher rates of biopsy were seen in Midwest (26.7%) and among Asian patients (31.3%); lower biopsy utilization

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rates were noted in patients with rural residency (15.3%), the bottom 25% Socioeconomic Status Index category (14.9%) and Black race (9.5%). Mean age was 55.4 years; LB patients were younger than NLB patients (53.4 vs 56.0 years). Overall, 54.5% were female and 80.4% commercially insured. Mean ALT and AST were 51.1 U/L and 41.2 U/L, respectively, and were higher in LB patients. Common comorbidities included dyslipidemia (73.0%), hypertension (69.2%), type 2 diabetes (50.1%), and obesity/overweight (58.0%), with higher prevalence among NLB patients. Mean Quan Charlson Comorbidity Index was 2.9. Among patients with available FIB-4 scores, 53.1% were low risk (< 1.3), 38.6% intermediate risk (1.3–2.67), and 8.3% high risk (> 2.67). LB patients were more likely to have intermediate/high-risk scores than NLB patients (54.3% vs 43.0%).All patients underwent ≥ 1 prior NIT; ultrasound (80.0%) and vibration-controlled transient elastography (75.8%) were most common. Median time from last NIT to resmetirom initiation was 69 days (IQR, 29–173), longer in LB versus NLB patients (107 vs 61 days).During the pre-index year, 40.2% used GLP-1 receptor agonists, 35.2% metformin, and 16.1% SGLT2 inhibitors. Statins were used by 49.4% of patients: 17.6% high-intensity, 29.6% moderate-intensity, and 2.2% low-intensity. Statin and GLP-1 receptor agonist use were lower in LB versus NLB patients. **Conclusion:** Most patients initiated resmetirom without prior liver biopsy though differences in baseline characteristics were observed by biopsy status. Patients demonstrated substantial cardiometabolic comorbidity burden and frequent use of multiple metabolic therapies, highlighting the complexity of MASH management.

Table 1: Non-Invasive Testing for Patients Receiving Rezdiffra

	Overall	With Biopsy[1]	Without Biopsy[1]	P-value
Number of patients, N	**1,592**	**339**	**1,253**	
Number of Biopsies before Rezdiffra Initiation (dating back to the beginning of the study period on October 1, 2015).				
Mean (SD)	–	2.6 (3.4)	–	–
Median (IQR)	–	2.0 (2.0-2.0)	–	–
Number of days between the last 2 biopsies				
Patients with at least 2 biopsies, n (%)		280 (82.6%)		
Mean (SD)	–	1,047.8 (999.5)	–	–
Median (IQR)	–	893.5 (116.25-1,528.8)	–	–
Time in days from biopsy (closest to the index) to Rezdiffra initiation date				
Mean (SD)	–	243.6 (280.9)	–	–
Median (IQR)	–	100.0 (41.0-384.0)	–	–
Non-Invasive Tests (NITs), n (%)				
Ultrasounds (abdominal, liver)	1,273 (80.0%)	279 (82.3%)	994 (79.3%)	0.256
Elastography or VCTE Fibroscan	1,207 (75.8%)	238 (70.2%)	969 (77.3%)	0.008
Magnetic Resonance Imaging (MRI)	356 (22.4%)	88 (26.0%)	268 (21.4%)	0.086
Enhanced Liver Fibrosis (ELF)	118 (7.4%)	28 (8.3%)	90 (7.2%)	0.579
Magnetic Resonance Elastography (MRE)	100 (6.3%)	21 (6.2%)	79 (6.3%)	NR
Other blood-based tests (Fibrosure and FibroTest)	12 (0.8%)	0.0 (0.0%)	12 (1.0%)	–
Time in days from the most recent NITs to index Rezdiffra initiation date				
Patients with any Non-Invasive Tests, n (%)	1,592 (100%)	339 (100%)	1,253 (100%)	0.002
Mean (SD)	160.6 (287.4)	207.0 (300.6)	148.1 (282.5)	
Median (IQR)	69.0 (29.0-173.0)	107.0(48.5-244.5)	61.0 (25.0-148.0)	

Disclosures: Ruth Dixon:Nothing to Disclose, Zi Wang:Nothing to Disclose, Chia-Chen Teng:Nothing to Disclose, John Barron:Nothing to Disclose, Blake Thomas:Madrigal Pharmaceuticals: Employee, Karen Phillips:Nothing to Disclose, Yestle Kim:Nothing to Disclose, Francis Lobo:Nothing to Disclose.

3569 | CARDIOMETABOLIC OUTCOMES OF RESMETIROM IN PATIENTS WITH MASLD: A PROPENSITY-MATCHED COHORT STUDY

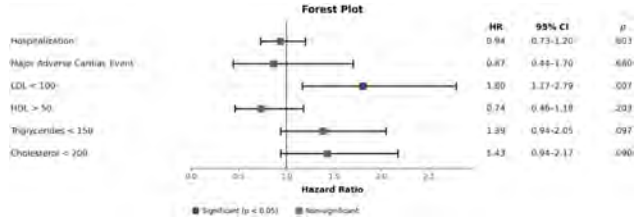
Amber Hussain[1] Yusef Saeed[1], [1]University Hospitals Cleveland Medical Center

Background: Resmetirom is a liver-directed, thyroid hormone receptor β-selective agonist approved in March 2024 for adults with metabolic dysfunction-associated steatotic liver disease (MASLD) and moderate to advanced hepatic fibrosis. By targeting disease earlier, it may reduce progression to cirrhosis and need for transplantation. However, its broader cardiometabolic effects remain unclear. This study evaluated clinical and metabolic outcomes associated with Resmetirom use in patients with MASLD compared with matched controls. **Methods:** Using the TriNetX US Collaborative Network, adults (≥ 18 years) between January 31, 2020 and January 31, 2025 were identified. From 1,642,840 patients with cirrhosis, two cohorts were defined: MASLD patients prescribed Resmetirom (n = 854) and MASLD patients not prescribed Resmetirom (n = 3,102,308). The MASLD control cohort was required to have a diagnostic test for liver disease (i.e. FibroScan, MRI, or biopsy) to increase diagnostic certainty. After applying inclusion and exclusion criteria, 1:1 propensity score matching yielded 852 matched pairs. Outcomes at 12 months included hospitalization, major adverse cardiovascular events (MACE, as defined by myocardial infarction, stroke, or all cause mortality), and metabolic endpoints (LDL < 100 mg/dL, HDL > 50 mg/dL, triglycerides < 150 mg/dL, total cholesterol < 200 mg/dL). Kaplan-Meier analysis was used. Event rates were derived as 1 minus survival probability. Hazard ratios (HR) with 95% CI and log-rank p-values were reported. Artificial intelligence tools were used to improve abstract readability, enhance word flow, and optimize figure formatting for presentation purposes. **Results:** Cardiac, metabolic, hepatic, and substance use related comorbidities were matched for. After matching, baseline characteristics were largely balanced. Outcomes are shown in Figure 1 (Forest Plot). No significant difference was observed in hospitalization (15.43% vs 16.09%; HR 0.94, 95% CI 0.73 - 1.20; p = 0.603) or MACE (1.99% vs 2.37%; HR 0.87, 95% CI 0.44 - 1.70; p = 0.680). Resmetirom was associated with improved LDL target attainment (11.75% vs 6.91%; HR 1.80, 95% CI 1.17 - 2.79; p = 0.007). No significant differences were observed for HDL > 50 mg/dL (5.21% vs 7.33%; HR 0.74; p = 0.203),

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triglycerides < 150 mg/dL (13.25% vs 9.76%; HR 1.39; p = 0.097), or total cholesterol < 200 mg/dL (13.07% vs 9.55%; HR 1.43; p = 0.090). **Conclusion:** Resmetirom was not associated with reduced short-term clinical events but improved LDL target attainment. Although Resmetirom did not significantly affect the other lipid markers (HDL, triglycerides, cholesterol), it was associated with a trend toward improved values. Longer-term studies are needed to determine whether metabolic benefits translate into improved cardiovascular or hepatic outcomes.



Disclosures: Amber Hussain:Nothing to Disclose, Yusef Saeed:Nothing to Disclose.

3570 | LANIFIBRANOR TARGETS MULTIPLE HEPATIC CELL POPULATIONS TO REDUCE FIBROSIS THROUGH BALANCED PAN-PPAR ACTIVATION

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Background: Fibrosis is the strongest predictor of liver-related morbidity and mortality in metabolic dysfunction-associated steatohepatitis (MASH). Fibrogenesis results from complex interactions between multiple hepatic cell populations including hepatocytes, Kupffer cells, liver sinusoidal endothelial cells (LSECs) and hepatic stellate cells (HSCs). Peroxisome proliferator-activated receptors (PPARs) are key regulators of metabolism, inflammation and fibrogenesis, with distinct but complementary functions across liver cell types. We aimed to highlight how balanced pan-PPAR activation by lanifibranor simultaneously targets multiple cellular drivers of fibrosis in MASH and advanced chronic liver disease (ACLD). **Methods:** The effects of lanifibranor were evaluated across several preclinical models in rodents reproducing key features of MASH and fibrosis, including diet-induced steatohepatitis, CCl_4-induced fibrosis, and ACLD models such as Thioacetamide and bile duct ligation. Liver histology, inflammatory and fibrotic pathways, macrophage phenotype, HSC activation and LSEC dysfunction were assessed using molecular, histological and functional analyses. Human hepatic cells and liver biopsies were also evaluated to characterize the translational relevance of pan-PPAR activation. **Results:** Lanifibranor improved all major histological components of MASH and fibrosis across independent experimental models and in NATIVE clinical trial phase 2b. At the hepatocyte level, PPARα activation promoted fatty acid β-oxidation, reduced lipotoxicity and improved metabolic homeostasis. In macrophages, PPARδ activation shifted inflammatory polarization toward a less pro-inflammatory phenotype, reduced monocyte infiltration and decreased cytokine expression including TNF-α, IL-6 and CCL2. In HSCs, PPARγ activation maintained a quiescent phenotype and directly inhibited fibrogenic activation, reducing expression of α-SMA, TGF-β and collagen genes leading to inhibition of fibrogenesis. Finally, lanifibranor restored LSEC phenotype and improved hepatic microvascular dysfunction through the activation of the three isoforms. By doing so lanifibranor interrupts the pathological crosstalk between injured LSECs, activated HSCs and inflammatory macrophages that promote fibrosis progression. **Conclusion:** Lanifibranor addresses liver fibrosis through coordinated actions on multiple hepatic cell populations involved in MASH pathogenesis. Balanced activation of PPARα, PPARδ and PPARγ simultaneously improves hepatocyte metabolism, dampens macrophage-driven inflammation, restores LSEC function and maintains HSC quiescence. This pleiotropic multicellular mechanism distinguishes pan-PPAR agonism from selective PPAR approaches and supports lanifibranor as a promising antifibrotic therapy for MASH and ACLD.

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3571 | 7-METHYLXANTHINE DEMONSTRATES RESMETIROM-COMPARABLE EFFICACY IN A RAT MODEL OF MASH WITH SUPPORTING ANTIFIBROTIC AND ANTI-INFLAMMATORY MECHANISMS

Dinesh Tripathi[1] Arpita Malhan[2] Mridul Guleria[2] Saketh Dinavahi[3] Sundeep Aurora[3] Subheet Jain[2], [1]Institute of Liver and Biliary Sciences, [2]Guru Nanak Dev University, [3]Anari Therapeutics

Background: Metabolic dysfunction-associated steatohepatitis (MASH) is a progressive inflammatory and fibrotic liver disease with high cardiometabolic risk and limited pharmacotherapies. Resmetirom, a selective thyroid hormone receptor-β agonist, has recently been approved, but additional, mechanistically distinct agents are needed. 7-Methylxanthine, a xanthine derivative, was evaluated in a diet-induced rat model of MASH with resmetirom as an active comparator to benchmark efficacy. **Methods:** Male Wistar rats (n = 24) received a high-fat diet (60% kcal fat) plus fructose in drinking water for 13 weeks; controls received standard chow. MASH induction was confirmed by body weight, serum biochemistry, ultrasonography, relative organ weight, and NAS/MAS scoring. MASH-positive animals were randomised (n = 6/group) to diseased control (HFD only), 7-methylxanthine (1200 mg/kg BID, oral), or resmetirom (2.5 mg/kg QD, oral) while maintained on HFD. From weeks 14–27, body weight, serum lipids, liver function tests, glucose, bilirubin and liver ultrasonography were assessed; post-treatment histology, MAS/NAS, inflammatory biomarkers and IND-enabling toxicology are ongoing. **Results:** Induction produced obesity, severe dyslipidaemia, elevated transaminases, ALP and bilirubin, Grade III steatosis, increased liver weight and a NAS of 7 vs 1 in controls, confirming severe MASH. During treatment, diseased controls showed continued weight gain and biochemical deterioration, whereas 7-methylxanthine and resmetirom attenuated further weight gain and reduced body weight versus diseased controls despite ongoing HFD. Both treatments lowered total cholesterol, triglycerides, LDL, glucose, transaminases, ALP and bilirubin and restored HDL toward normal; across metabolic and hepatic endpoints, 7-methylxanthine effects were broadly comparable to resmetirom. Ultrasonography showed persistent Grade III steatosis in diseased controls but near-normal echotexture and vascular definition in both active groups, indicating substantial and comparable reversal of fatty infiltration. In parallel, 7-methylxanthine dose-dependently reduced TGF-β1-driven myofibroblast and extracellular matrix markers (α-SMA, fibronectin, vimentin, FSP1) and modulated MMP9, and dampened cytokine/LPS-induced epithelial responses, supporting an antifibrotic and anti-inflammatory mechanism. **Conclusion:** 7-Methylxanthine produced marked improvements in metabolic, biochemical and imaging endpoints in HFD+fructose-induced MASH that were broadly comparable to resmetirom, supporting competitive efficacy versus an approved THR-β agonist in a clinically relevant, diet-driven model. Together with complementary antifibrotic and anti-inflammatory activity and ongoing IND-enabling toxicology, these data support the translational potential of 7-methylxanthine as a hepatoprotective and anti-steatotic candidate for MASH.

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3572 | MACADAMIA NUT SUPPLEMENTATION PROTECTS AGAINST MASLD-INDUCED ALTERATIONS IN LIPID AND BILE ACID METABOLISM IN A MOUSE MODEL

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Background: Metabolic Associated Steatotic Liver Disease (MASLD) is a significant global health concern, linked to high-fat diets that promote obesity, insulin resistance, hepatic lipid accumulation, liver inflammation, and disruptions in lipid and bile acid metabolism. MASLD significantly affecting 47% of the U.S. population, while Metabolic Associated Steatohepatitis (MASH) affects approximately 2-7% of Americans. The molecular mechanisms underlying MASLD pathogenesis and diet-based nutritional interventions are still under investigation. Macadamia nuts (MN), rich in monounsaturated fatty acids, have been shown to prevent lipopolysaccharide (LPS)- induced proinflammatory responses and exhibit established anti-inflammatory properties. We hypothesize that dietary supplementation of macadamia nuts restores lipid and bile acid dysregulation in high-fat, fructose, and cholesterol-containing diets (FFC)-induced MASLD in the rodent model. **Methods:** Eight-week-old C57BL/6J mice were divided into four groups: Control, FFC, FFC + 5% MN, and FFC + 10% MN, containing the diet for either 16 or 24 weeks. Glucose tolerance tests (GTT) and insulin tolerance tests (ITT) were measured to evaluate metabolic function. Fecal samples were

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collected for microbial analysis. After 16 and 24 weeks, blood and tissue samples were collected. Serum bile acid levels were measured using targeted LC-MS/MS. Liver tissues were examined for pathological MASH scoring. Hepatic and intestinal gene and protein expression were assessed by qPCR and immunoblot analyses. **Results:** FFC diets with 5% or 10% of Macadamia nuts showed improved GTT and ITT, ce at 24 weeks compared to MN-FFC diet-fed mice. Liver histopathology revealed an improvement in the NASH score, with a significant decrease in hepatic steatosis scores in both MN-FFC diet-fed groups after 16 weeks of the study. Serum bile acid analysis showed a non-significant change at 16 weeks; however, at 24 weeks, a significant decrease in cholic acid and its conjugated bile acids, taurocholic acid and taurodeoxycholic acid, was observed, indicating improved bile acid metabolism in MN-diet groups. We also observed a significant decrease in sterol regulatory binding proteins SREBP1 and SREBP2 at 16 and 24 weeks. The pro-inflammatory cytokine TNF-α showed a significant decrease at 16 weeks, indicating improved lipid metabolism and cholesterol biosynthesis with MN-FFC diet-fed groups compared to FFC alone. Additionally, the intestinal mRNA expression profile showed a significant decrease in Mucin 2 and TNF-α at both 16 and 24 weeks in MN-FCC, denoting dramatic improvements from MASLD-induced intestinal barrier dysfunction. **Conclusion:** Together, these data indicate that a diet containing macadamia nuts, rich in MUFA, improves liver injury by restoring the MASLD pathophysiology, suggesting its potential as a nutritional intervention for preventing MASLD-related complications.

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3573 | REAL-WORLD USE OF RESMETIROM FOR METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS IN A COMMUNITY-BASED OUTPATIENT HEPATOLOGY CLINIC

Giselle Ellis[1] Emily Ellis[2] Anthony Michaels[3] Adam James Hanje[3], [1]OhioHealth Riverside Methodist Hospital, [2]Riverside Methodist Hospital, [3]Ohio Gastroenterology Group

Background: Resmetirom, a liver-directed thyroid hormone receptor beta-selective agonist, received FDA approval in March 2024 for adults with MASH and F2-F3 fibrosis. In MAESTRO-NASH, resmetirom demonstrated MASH resolution in up to 29.9% of patients and fibrosis improvement by ≥ 1 stage in up to 25.9% at 52 weeks ($P < 0.001$ for both). Real-world data on prescribing patterns, response, tolerability, and access remain limited. This study evaluated resmetirom use in an interprofessional outpatient hepatology clinic within a large community-based hospital system. **Methods:** Investigators performed retrospective chart review of all patients prescribed resmetirom at a single hepatology clinic staffed by physicians, nurse practitioners, and a clinical pharmacist between March 2024 and March 2026. Patients who never filled the prescription were excluded. Baseline demographics, fibrosis stage, diagnostic modality, insurance type, and GLP-1 receptor agonist (GLP-1RA) use were collected. Outcomes included changes in liver stiffness (kPa), controlled attenuation parameter (CAP), and transaminases at 6 and 12 months. Adverse events and discontinuation rates were recorded. **Results:** Of 161 patients prescribed resmetirom, 22 never filled and were excluded; 2 additional patients were excluded due to insufficient data. At baseline, 84.7% were staged via elastography; whereas, 13.9% of patients had biopsy-confirmed diagnosis. Patients' average age was 55 years-old; 57% were female, and the 80% were Caucasian. The insurance breakdown was: 50.4% commercial, 18.3% Medicaid, 24.8% Medicare, 8.8% charitable. 90.5% had obesity (BMI > 30), 14.6% prediabetes, 61.3% diabetes; 46.7% were on a GLP-1RA at baseline, increasing to 55.5% during therapy. At 6 months ($n = 58$), liver stiffness (9.8 ± 2.1 to 8.6 ± 3.8 kPa, $p = 0.01$) and CAP (289 ± 88 to 255 ± 82, $p = 0.01$) improved significantly compared to baseline, with trends for improvement in AST (36.7 to 33.8, $p = 0.08$) and ALT (46.2 to 40.3, $p = 0.065$). At 12 months ($n = 30$), kPa (10.6 ± 1.7 to 9.6 ± 6.4, $p = 0.169$) and CAP (314 ± 45 to 285 ± 45, $p = 0.219$) trended toward improvement compared to baseline; AST (42.7 to 35.7, $p = 0.022$) and ALT (56.7 to 36.2, $p = 0.002$) improved significantly. 11 patients (8%) of those included were lost to follow-up, which contributed to the limited numbers for repeat imaging. Diarrhea occurred in 17.5%, nausea 12.4%, and 5% reported vomiting, constipation, pruritus, or other GI effects . Discontinuation due to adverse effects was 16.8%. **Conclusion:** Resmetirom is prescribed across a broad range of fibrosis stages and payer types in community practice, with noninvasive testing as the predominant diagnostic modality. Early treatment response was observed at 6-12 months. While GI side effect rates were lower than MAESTRO-NASH, the discontinuation rate was notably higher, suggesting real-world tolerability and patient support strategies warrant further study.

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privately held company, Adam James Hanje:Nothing to Disclose.

3574 | ADVANCING GLP-1 RA USE IN OBESITY-RELATED MASH: IMPACT OF A MULTIDISCIPLINARY CME PROGRAM

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Background: Due to the growing prevalence of MASH driven by the obesity epidemic, the significant impact of advanced fibrosis on long-term patient outcomes, and the emergence of glucagon-like peptide-1 (GLP-1) receptor agonist (RA)-based options targeting this condition, it is imperative for clinicians to stay informed about the latest advancements in therapeutic strategies to optimize outcomes for obesity-related liver disease. To assess whether digital, short-form, continuing medical education (CME) can enhance clinicians' knowledge and competence related to the impact of obesity on MASH and the role of GLP-1 RA-based therapies in managing MASH. **Methods:** Endocrinologists, gastroenterologists, and hepatologists from a global audience participated in a 15-minute on-demand e-learning module titled "Bridging Disciplines to Advance Care in MASH: Exploring GLP-1 RAs for Obesity-Related Liver Disease", presented by an endocrinologist and a hepatologist. This activity launched on September 19, 2025. Pre- and post-activity assessments were used to collect information regarding learners' baseline scores as well as the impact of the education on knowledge and competence. Assessments were analyzed in aggregate and at the individual level. **Results:** As of March 12, 2026, 7,718 learners participated in the program, with the leading specialties being endocrinologists (42%) and gastroenterologists (46%) (data collection is ongoing). A subset of responses (n = 1,800) were collected from pre- and post-test assessments. Endocrinologists showed greater gains (73% baseline, +11%) than hepatologists (80%, +7%). Post-education, learners demonstrated an improvement in knowledge/competence related to the impact of obesity on MASH progression (13%), the role of current/emerging GLP-1 RAs for managing MASH (9%), and strategies to optimize obesity-related MASH outcomes (12%). Using learners' self-reported number of patients seen per week (6-14), this program potentially impacted 63,512 patient interactions. More than 80% of learners intended to change practice based on this education, and more than 50% expressed interest in receiving further education. **Conclusion:** Digital, short-form, CME, including multidisciplinary perspectives, improved clinicians' knowledge and competence related to the impact of obesity on MASH progression and the role of GLP-1 RAs in managing MASH. This program also identified persisting educational needs and interests among learners.

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3575 | GASTROINTESTINAL TOLERABILITY OF PEMVIDUTIDE WITHOUT DOSE TITRATION IN PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS FROM THE PHASE 2B IMPACT TRIAL

Mazen Noureddin[1] Silvia Urbina[2] Shaheen Tomah[3] John Suschak[4] Scot Roberts[2] Rachel Garner[2] Christophe Arbet-Engels[2], [1]Houston Methodist Hospital, [2]Altimmune, Inc., [3]Altimmune, [4]Altimmune, Inc

Background: Pemvidutide is a balanced 1:1 glucagon/GLP-1 dual receptor agonist that contains the EuPort side chain, which provides for weekly dosing and slows entry into the circulation, possibly contributing to improved tolerability. In IMPACT, a 48-week, phase 2b, randomized, placebo-controlled, double-blind trial in patients with biopsy-confirmed F2/F3 MASH (NCT05989711), we assessed the incidence, severity, and clinical impact of commonly reported gastrointestinal (GI) adverse events (AEs). **Methods:** 212 patients were randomized 1:2:2 to receive once-weekly subcutaneous pemvidutide (1.2 mg or 1.8 mg) administered without dose titration, or placebo for 48 weeks. Safety was monitored throughout the trial and data regarding the incidence of GI AEs of interest were analyzed. **Results:** The mean age was 53 years, mean BMI was 39 kg/m^2, 58% were female, and 43% had type 2 diabetes. Pemvidutide was generally well tolerated in this MASH population. Most patients completed study treatment as planned, with treatment completion rates of 85.4%, 84.7%, and 76.7% in the pemvidutide 1.2 mg, pemvidutide 1.8 mg, and placebo groups, respectively. Treatment discontinuations due to AEs were rare, occurring in 0.0% and 1.2%, in the 1.2 mg and 1.8 mg groups, compared to 3.5% in the placebo group. GI TEAEs were reported in 41.5%, 64.7%, and 41.9% of patients in 1.2 mg, 1.8 mg, and

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placebo groups, respectively. Nausea, diarrhea, constipation, and vomiting were the most common GI AEs (reported by ≥5% of patients overall) and followed a dose-dependent pattern, with GI AEs at the 1.2 mg dose roughly equivalent to placebo. Two patients (2.3%) discontinued the study due to GI AEs in the placebo group and one patient (1.2%) in the 1.8 mg group. No GI serious AEs related to drug study and no severe GI TEAEs were reported. All GI AEs were mild to moderate, with the majority of GI AEs occurring within the first 4-8 weeks of treatment followed by marked diminution regardless of the cohort analyzed. **Conclusion:** In patients with MASH, pemvidutide was generally well tolerated with fewer AE discontinuations than placebo. GI AEs were mild to moderate and followed a dose-dependent pattern. The pharmacokinetic profile of pemvidutide, conferred by the EuPort side chain, may contribute to its observed tolerability. These findings support simple 1 or 2 step titration regimens to exploit the inherent tolerability of the 1.2 mg dose while providing escalation to 1.8 mg and higher for improved tolerability over the non-titrated dose.

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3576 | ZENITH-1 AND ZENITH-2: PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIALS IN PROGRESS OF EFIMOSFERMIN ALFA IN PARTICIPANTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH) AND F2/F3 FIBROSIS

Mazen Noureddin[1] Naga Chalasani[2] Meena Bansal[3] Jörn Schattenberg[4] Rohit Loomba[5] Arun Sanyal[6] Margaret James Koziel[7] Stuart Kendrick[8] Beth Ann Reedy[9] Patricia Mendez[9] Grace Dolman[8] Paul Lochhead[10] Laurent Castera[11], [1]Houston Methodist Hospital and Houston Research Institute, Houston, TX, USA, [2]Indiana University School of Medicine, Indianapolis, IN, USA, [3]Icahn School of Medicine at

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Background: MASH with stages F2/F3 fibrosis is associated with increased liver-related morbidity and mortality but there are limited approved treatment options available. Treatment with efimosfermin alfa, a long-acting fibroblast growth factor 21 analog given every 4 weeks, demonstrated MASH resolution and improvements in fibrosis, hepatic fat, and both fibrosis-related and metabolic biomarkers compared with placebo, along with an acceptable safety and tolerability profile in a Phase 2 Part B trial (NCT04880031). **Methods:** ZENITH-1 (NCT07221227) and ZENITH-2 (NCT07221188) are randomized, double-blind, placebo-controlled, multicenter Phase 3 trials enrolling approximately 1200 and 1250 participants, respectively. Participants are adults aged 18–75 years with biopsy-confirmed (ZENITH-1) or known/suspected MASH (ZENITH-2) and F2/F3 fibrosis. In ZENITH-1, participants are randomized to one of two doses of efimosfermin alfa or placebo given subcutaneously every 4 weeks. In ZENITH-2, participants are randomized to receive the same dosages as ZENITH-1, but treatment duration differs. Independent data monitoring and clinical event adjudication committees are established for both trials. Both trials are ongoing with enrollment underway; completion is planned for December 2031 for ZENITH-1 and March 2028 for ZENITH-2. **Results:** Primary endpoints in ZENITH-1 include histologic outcomes ($\geq$1-stage fibrosis improvement without worsening of MASH or MASH resolution without fibrosis worsening) at 52 weeks, with an additional analysis at Month 48 of a composite of liver-related clinical outcome events; safety and tolerability are assessed throughout. Primary endpoints in ZENITH-2 include incidence and severity of adverse events and incidence of Grade 3 or 4 laboratory abnormalities over 52 weeks. Secondary endpoints include changes in noninvasive fibrosis measures (Enhanced Liver Fibrosis score), measurements of liver stiffness and steatosis, as well as metabolic biomarkers in both trials. Assessments of bone health, including imaging and biomarkers, are evaluated in ZENITH-1. Adverse events of special interest in both trials include gastrointestinal events of Grade $\geq$3, hepatic decompensation or other liver events requiring increased monitoring or discontinuation from the study, hypersensitivity reactions, injection site reactions, and changes to the menstrual cycle. **Conclusion:** The findings of the Phase 3 ZENITH-1 and ZENITH-2 trials will provide critical insights into the clinical efficacy, durability of response, and safety profile of efimosfermin alfa for the treatment of MASH with F2/F3 fibrosis. These trials will help inform future treatment strategies in MASH.

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3577 | PATIENT CHARACTERISTICS, TREATMENT PATTERNS, AND CHANGES IN LIVER FUNCTION LABORATORY TESTS AMONG RESMETIROM TREATED PATIENTS IN A REAL-WORLD MASH POPULATION

Earl Burrell[1] Nipun Atreja[2] Meena Bansal[3] Cynthia Gutierrez[1] Aaron Crowley[1] Damon Van Voorhis[1] Joanna MacEwan[1] Blake Thomas[2] Francis Lobo[2] John O'donnell[2], [1]Genesis Research Group, [2]Madrigal Pharmaceuticals, [3]Icahn School of Medicine at Mount Sinai (ISMMS)

Background: Metabolic dysfunction-associated steatohepatitis (MASH) involves fat buildup leading to inflammation and liver scarring. Resmetirom was the first therapy approved by the United States (US) Food & Drug Administration in March 2024 for treatment of MASH with moderate or advanced fibrosis. Due to the recent approval of resmetirom, there remains a need for real-world evidence. This study aimed to capture treatment patterns and lab changes among MASH patients (pts) using resmetirom in a real-world US setting. **Methods:** This was a descriptive and retrospective study of adult pts with ≥ 1 paid claim for resmetirom on or after 3/14/2024 (study period: 3/14/2023-12/31/2025) in the Optum de-identified Market Clarity database. Pts with record of ≥1 diagnosis for non-MASH liver conditions, cirrhosis-related complications, or heavy-metal exposures in the 12-month pre-index period were excluded. Baseline demographics, clinical characteristics, and treatment patterns were summarized. Changes in liver function tests (LFTs) and relevant labs (alkaline phosphatase [ALP], alanine aminotransferase [ALT], aspartate aminotransferase [AST], total bilirubin, albumin, high-density lipoproteins [HDLs], low-density lipoproteins [LDLs], and triglycerides) between baseline and 9 months of follow-up were evaluated using paired T-tests among pts with labs at both baseline and 270 days post-index (± 45 days). **Results:** A total of 2,429 pts met the inclusion criteria. Mean (standard deviation [SD]) age was 61.3 yrs (12.8 yrs) and 61.7% of pts were female. Among pts with body mass index (BMI) information, mean (SD) BMI was 34.0 (6.3). Over half of pts were obese (59.3%) or had type 2 diabetes (T2D) (52.3%). At baseline, 34.8% of pts were prescribed glucagon-like peptide 1 receptor agonists (GLP-1 RAs). Follow-up results are shown in **Table** . Overall mean (SD) proportion of days covered (PDC) was 0.73 (0.33). Among these, 42.9% of pts had ≥9 months of follow-up with a mean (SD) 9-month PDC of 0.66 (0.34) and 48.9% reached PDC≥80%. At 9 months of follow-up, pts with available labs had a significant decrease in ALT (n=98; -12.6 U/L; 95% confidence interval [CI], -18.4, -6.8; $P<0.001$), AST (n=98; -8.8 U/L; 95% CI, -14.0, -3.6; $P=0.001$), and triglycerides (n=32; -27.2 mg/dL; 95% CI, -44.4, -9.9; $P=0.003$). **Conclusion:** This study provides an extended look at the early uptake of resmetirom in a real-world setting. At baseline, ≥50% of pts were obese and had T2D, with many pts having already initiated a GLP-1 RA. After 9 months of follow up, nearly half of pts were considered adherent (PDC≥80%). Pts also had significant decreases in several LFTs and triglycerides at 9 months. Further follow-up studies are needed to continue observing this trend.

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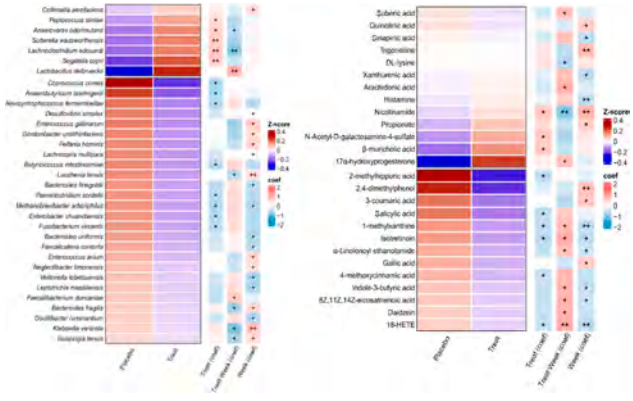
Treatment Patterns During Follow-up	Resmetirom Cohort (N = 2,429)	
Duration of follow-up		
≥9 months, n (%)	1,042 (42.9%)	
PDC		
Overall, Mean (SD)	0.73 (0.33)	
9 months, Mean (SD)	0.66 (0.34)	
PDC≥80%, n (%)		
9 months, n (%)	510 (48.9%)	
Lab Values		
Measurement	**9 months**	**p-value**
ALP (U/L)		
N	94	
Baseline (mean [SD])	92.4 (35.2)	
9 months (mean [SD])	89.5 (29.9)	
Within person change (mean [95% CI])	-2.9 (-8.0, 2.2)	0.257
Within person % change (mean [95% CI])	1.2 (-5.1, 7.5)	
ALT (U/L)		
N	98	
Baseline (mean [SD])	48.0 (32.4)	
9 months (mean [SD])	35.3 (20.1)	
Within person change (mean [95% CI])	-12.6 (-18.4, -6.8)	<0.001
Within person % change (mean [95% CI])	-8.7 (-22.3, 4.8)	
AST (U/L)		
N	98	
Baseline (mean [SD])	42.6 (26.4)	
9 months (mean [SD])	33.8 (19.3)	
Within person change (mean [95% CI])	-8.8 (-14.0, -3.6)	0.001
Within person % change (mean [95% CI])	-3.2 (-19.1, 12.8)	
Total bilirubin (mg/dL)		
N	95	
Baseline (mean [SD])	0.54 (0.24)	
9 months (mean [SD])	0.57 (0.26)	
Within person change (mean [95% CI])	0.03 (-0.02, 0.08)	0.258
Within person % change (mean [95% CI])	12.6 (3.1, 22.2)	
Albumin (g/dL)		
N	92	
Baseline (mean [SD])	4.28 (0.32)	
9 months (mean [SD])	4.25 (0.33)	
Within person change (mean [95% CI])	-0.03 (-0.10, 0.04)	0.402
Within person % change (mean [95% CI])	-0.4 (-2.1, 1.3)	
HDLs (mg/dL)		
N	31	
Baseline (mean [SD])	47.9 (9.9)	
9 months (mean [SD])	50.9 (12.0)	
Within person change (mean [95% CI])	3.0 (-0.2, 6.2)	0.061
Within person % change (mean [95% CI])	7.3 (0.0, 14.6)	
LDLs (mg/dL)		
N	31	
Baseline (mean [SD])	90.6 (35.8)	
9 months (mean [SD])	86.9 (38.3)	
Within person change (mean [95% CI])	-3.8 (-13.6, 6.1)	0.440
Within person % change (mean [95% CI])	-0.5 (-12.1, 11.1)	
Triglycerides (mg/dL)		

Disclosures: Earl Burrell:Nothing to Disclose, Nipun Atreja:madrigal pharmaceuticals: Employee, Meena Bansal:Madrigal: Advisor, Fibronostics: Advisor, NOVO Nordisk: Advisor, GSK: Advisor, Merck: Advisor, Boeheringer-Ingelheim: Advisor, Boston Pharma: Advisor, The Kinetix Group: Advisor, Corcept: Advisor, Cynthia Gutierrez:Nothing to Disclose, Aaron Crowley:Nothing to Disclose, Damon Van Voorhis:Nothing to Disclose, Joanna MacEwan:Nothing to Disclose, Blake Thomas: Madrigal Pharmaceuticals: Employee, Francis Lobo: Nothing to Disclose, John O'donnell:Nothing to Disclose.

3578 | SAFETY AND EFFICACY OF LACTOBACILLUS DELBRUECKII SUBSP. LACTIS CKDB001 IN PATIENTS WITH METABOLIC-ASSOCIATED STEATOTIC LIVER DISEASE: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE II CLINICAL TRIAL

Jung Hee Kim[1] Ki Tae Suk[1], [1]Hallym university College of medicine

Background: Lactobacillus delbrueckii subsp. lactis CKDB001 is a probiotic derived from raw milk fermentation with hepatoprotective and metabolic effects mediated through bile acid metabolism, lipid handling, and gut–liver axis signaling. This study evaluated its safety, clinical efficacy, and gut microbiome–metabolome modulation in patients with metabolic dysfunction–associated steatotic liver disease (MASLD). **Methods:** In this randomized, double-blind, placebo-controlled trial, patients with MASLD received CKDB001 (5.0 ×109 CFU/day, one capsule twice daily; n = 46) or placebo (n = 43) for 12 weeks. Primary outcomes were changes in serum AST and ALT. Secondary outcomes included liver function markers, lipid and glucose metabolism parameters, and fatigue. Exploratory outcomes assessed anthropometry, hepatic steatosis and stiffness by transient elastography, and gut microbiome and metabolome profiles using anintegrative multi-omics. **Results:** Eighty-nine participants (mean age 44.7 years; mean BMI 29.9 kg/m2) were included, with comparable baseline characteristics between groups and no withdrawals. CKDB001 was well tolerated, with no differences in adverse events or aminotransferase levels compared with placebo. Favorable trends were observed in insulin resistance and hepatic steatosis. Significant reductions in waist and hip circumference were observed exclusively in the intervention group (all $p < 0.005$). Multi-omics analyses revealed stable microbial diversity but intervention-specific shifts in microbial taxa and metabolites at Week 12. Treatment-by-time interactions were identified for 8 taxa and 12 metabolites, including increases in L.delbrueckii and the butyrate-producing Faecalibacterium duncaniae (all $p < 0.001$). Lipid-related and bioactive metabolites involved in inflammation and host signaling were significantly altered. Correlation analyses linked L. delbrueckii with indole-3-butyric acid and 17α-hydroxyprogesterone, andF. duncaniae with arachidonic acid–related metabolites, indicating coordinated microbe–metabolite modulation. **Conclusion:** CKDB001 supplementation modulated key metabolites and lipid mediators associated with gut–liver axis signaling in patients with MASLD. These findings suggest a mechanistic basis for its metabolic benefits and support further large-scale studies to evaluate its potential as a therapeutic target for MASLD.



Disclosures: Jung Hee Kim:Nothing to Disclose, Ki Tae Suk:Nothing to Disclose.

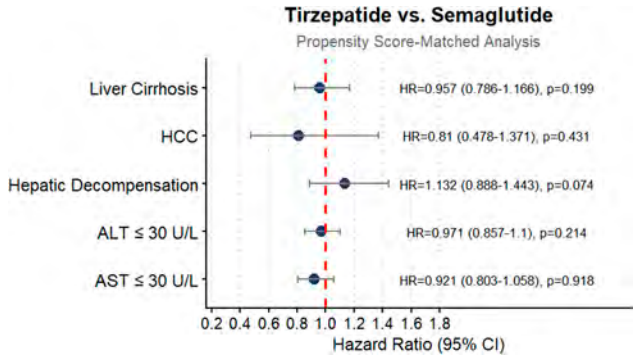
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3579 | COMPARATIVE HEPATIC OUTCOMES OF TIRZEPATIDE AND SEMAGLUTIDE IN PATIENTS WITH MASLD/MASH, OBESITY, AND TYPE 2 DIABETES MELLITUS: A MATCHED COHORT STUDY

Moataz Aboeldahb[1] Ahmed Ibrahim[2] EzzElDien Ibrahim[3] Sherif Elhanafi[4], [1]Department of Medicine, Division of Hospital Medicine, University of Colorado School of Medicine, An, [2]San Joquin General Hospital, [3]Department of Medicine, University of Missouri-Columbia 1 Hospital Dr, Columbia, Missouri, USA 65212, [4]Division of Gastroenterology, University of Texas at Tyler School of Medicine, Tyler, Texas, USA

Background: Diabetic and obese patients commonly have metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic-associated steatohepatitis (MASH). Both tirzepatide and semaglutide have demonstrated cardiometabolic benefits including weight reduction, improved glycemia, and cardiovascular outcomes. The aim of this study is to assess the effect of tirzepatide compared to semaglutide on hepatic outcomes in patients with MASLD/MASH in a large real-world US population. **Methods:** We performed a retrospective cohort study using the TriNetX U.S. Collaborative Research Network (2010–2024). Adult patients ($\geq$18 years) with MASLD/MASH, BMI $\geq$30 kg/m², and type 2 diabetes were identified using validated ICD-10 codes. The exposure group consisted of patients receiving tirzepatide, while the comparison group included patients receiving semaglutide. Propensity score matching (1:1) was performed based on demographics, comorbidities (hypertension, heart failure, chronic kidney disease, hyperlipidemia, alcohol use, and smoking), and liver-related laboratory parameters (ALT, AST, GGT, bilirubin, albumin, INR, creatinine, sodium, and platelet count). The primary outcomes were the incidence of liver cirrhosis, hepatocellular carcinoma (HCC), and hepatic decompensation. The secondary outcome was liver enzyme normalization (ALT $\leq$30 U/L, AST $\leq$30 U/L) over a 2-year follow-up period. **Results:** Before matching, 8,382 patients on tirzepatide and 55,592 patients on semaglutide were identified. After matching, 8,382 patients remained in each cohort. All clinical variables had standardized differences $<$0.1, consistent with well-matched covariates, including baseline AST (38.2 ± 20.1 vs 39.1 ± 23.6 U/L) and ALT (45.5 ± 29.7 vs 46.6 ± 31.2 U/L). In the matched analysis, progression to liver cirrhosis (2.4% vs 2.6%; HR: 0.957, 95% CI: 0.786–1.166, p = 0.199), HCC (0.3% vs 0.4%; HR: 0.810, 95% CI: 0.478–1.371, p = 0.431), and hepatic decompensation (1.7% vs 1.5%; HR: 1.132, 95% CI: 0.888–1.443, p = 0.074) were observed in the tirzepatide vs semaglutide groups, respectively. Liver enzyme normalization rates for ALT (56.2% vs 57.5%; HR: 0.971, 95% CI: 0.857–1.100, p = 0.214) and AST (84. vs 9%85.7%; HR: 0.921, 95% CI: 0.803–1.058, p = 0.918) were similar between groups. **Conclusion:** In this large real-world cohort, tirzepatide demonstrated comparable hepatic outcomes to semaglutide in patients with MASLD/MASH, obesity, and type 2 diabetes, supporting its potential role in the management of MASLD/MASH.Further prospective randomized studies are needed to further validate these observations and assess long-term liver-related outcomes.



Disclosures: Moataz Aboeldahb:Nothing to Disclose, Ahmed Ibrahim:Nothing to Disclose, EzzElDien Ibrahim:Nothing to Disclose, Sherif Elhanafi:Nothing to Disclose.

3580 | ◆ PROSPECTIVE VALIDATION OF RISK OF LIVER FIBROSIS PROGRESSION ASSOCIATED WITH ADDED SUGAR INTAKE IN PATIENTS WITH MASLD USING OBJECTIVE BLOOD BIOMARKERS AND MICROPHYSIOLOGICAL SYSTEM

Jaideep Behari[1] Olivia Popovich[1] Renwei Wang[1] Mark Miedel[1] Mahboubeh Varmazyad[1] Dillon Gavlock[1] D. Lansing Taylor[1] Jian-Min Yuan[1], [1]University of Pittsburgh

Background: Poor nutritional quality is associated with development of metabolic dysfunction-associated

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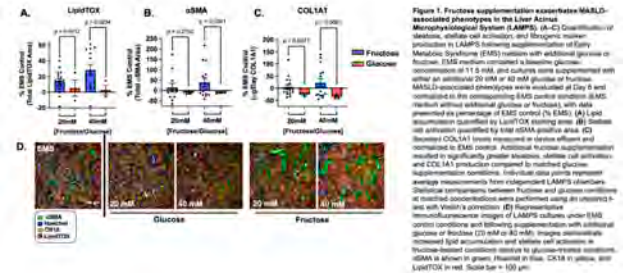
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steatotic liver disease (MASLD). This study aimed to determine the most important MASLD-associated dietary factors potentially targetable for dietary intervention. **Methods:** We prospectively enrolled 150 healthy controls and 779 patients with MASLD from the Midwestern US. Clinical history, body composition by body impedance analyzer, liver stiffness measurement (LSM) by Transient Elastography (TE), dietary history using validated ASA24 and DHQ3 questionnaires were obtained at enrollment. Carbon isotope ratio (CIR, $^{13}C/^{12}C$), a biomarker of dietary added sugar intake, and nitrogen isotope ratio (NIR, $^{15}N/^{14}N$), a biomarker of animal protein intake, expressed as delta values in permil (‰, parts per thousand) relative abundance of heavy isotope, were measured in plasma samples from 360 subjects with an elemental analyzer and continuous-flow isotope ratio mass spectrometry. Impact of fructose supplementation on MASLD development was studied *in vitro* in a liver acinus microphysiological system (LAMPS) platform following supplementation of medium with glucose or fructose. **Results:** Among patients with MASLD, 429 had F0/F1 (mild), 212 F2/3 (moderate), and 138 F4 fibrosis (cirrhosis). The trends of male gender ($p = .0023$), age, type 2 diabetes, body mass index, waist circumference, use of GLP1 receptor agonist medications (all $p < .0001$) progressively increased from healthy controls to cirrhosis. Self-reported total energy, carbohydrate, whole grain, refined grain, and fiber intake were not significantly different amongst the groups. However, self-reported added sugar ($p = .047$) progressively increased and added sugar/fiber ratio ($p = .0005$) progressively decreased from healthy controls to cirrhosis. Plasma CIR ratios were strongly correlated with disease stage (healthy controls -20.20, mild -19.75, moderate -19.63, advanced -19.43, with less negative numbers representing higher added sugar intake; $p < .0001$). NIR ratios were similar in healthy controls and early and moderate MASLD groups, but lower in advanced MASLD (8.18, 8.19, 8.17, and 7.97, respectively, $p = .01$). Compared to the first tertile of CIR, the odds ratio (95% confidence interval) of fibrosis progression over one year was 2.6 (0.58, 11.71) for the second tertile, and 4.97 (1.17, 21.08; $p_{trend} = .0183$) for the third tertile. There was no difference in fibrosis progression risk between NIR tertiles. In the in vitro LAMPS model, additional fructose supplementation resulted in significantly greater steatosis, stellate cell activation, and Collagen Type 1 Alpha 1 production compared to matched glucose supplementation conditions. **Conclusion:** Higher dietary added sugar intake is associated with higher MASLD risk in both patients and in a LAMPS model *in vitro*. Strategies specifically targeting dietary added sugar may be critical for MASLD management.

Table 1. Plasma Carbon Isotope Ratios (CIR) And Nitrogen Isotope Ratios (NIR) By Fibrosis Stage.

Fibrosis Stage	No. of subjects	CIR, Mean (95% CI)*‡	NIR, Mean (95% CI)†‡
Healthy controls	86	-20.20 (-20.48, -19.92)	8.18 (8.01, 8.34)
MASLD F0-F1	98	-19.75 (-19.99, -19.50)	8.19 (8.05, 8.35)
MASLD F2-F3	105	-19.63 (-19.88, -19.37)	8.17 (8.02, 8.31)
MASLD F4	71	-19.43 (-19.71, -19.15)	7.97 (7.80, 8.13)
P value		<0.0001	0.0099

* Expressed as $\Delta^{13}C = \frac{(R_{sample} - R_{reference})}{R_{reference}} \times 1000$, R_{sample} is the $^{13}C/^{12}C$ ratio of the test sample, $R_{reference}$ = 0.001124, an internationally recognized standard calibrated to Vienna Pee Dee Belmnite.
† Expressed as $\Delta^{15}N = \frac{(R_{sample} - R_{reference})}{R_{reference}} \times 1000$, R_{sample} is the $^{15}N/^{14}N$ ratio of the test sample, $R_{reference}$ = 0.003677, an internationally recognized standard calibrated to atmospheric nitrogen.
‡The means and 95% CIs were derived from Analysis of Covariance (ANCOVA) with baseline age, sex, race, and smoking status as covariates.



Disclosures: Jaideep Behari:Pfizer: Grant/Research Support, AstraZeneca: Grant/Research Support, Gilead: Grant/Research Support, Pfizer: Institutional research contract, Intercept: Institutional research contract, Madrigal: Institutional research contract, Inventiva: Institutional research contract, Rhythm: Institutional research contract, Galectin: Institutional research contract, Akero: Institutional research contract, Madrigal: Grant/Research Support, Olivia Popovich:Nothing to Disclose, Renwei Wang:Nothing to Disclose, Mark Miedel:Nothing to Disclose, Mahboubeh Varmazyad:Nothing to Disclose, Dillon Gavlock: Nothing to Disclose, D. Lansing Taylor:Nothing to Disclose, Jian-Min Yuan:Nothing to Disclose.

3581 | ◆ THE VISCERAL FAT–MUSCLE TRADE-OFF IN OBESE CHRONIC LIVER DISEASE: INSIGHTS FROM SMA-LEVEL PERIPORTAL VAT

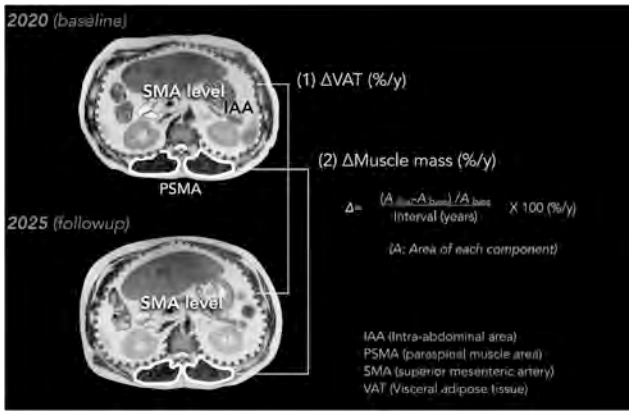
Atsushi Nakamura[1], [1]Nippon kokan hospital

Background: Periportal visceral adipose tissue, including omental and mesenteric VAT, contributes to MASLD progression through the portal vein theory [*Item & Konrad, 2012*], whereby free fatty acids and inflammatory mediators from VAT drain directly into the liver. Although weight reduction is the cornerstone of MASLD treatment and current guidelines recommend at least 5% weight loss, skeletal muscle is closely linked to MASLD pathophysiology and liver-related prognosis. However, the muscular cost of guideline-recommended weight reduction remains unclear in obese CLD. In this synchronized multimodal MRI study, we simultaneously quantified pVAT, skeletal muscle mass, hepatic steatosis, and fibrosis at the SMA level to investigate the hepatic benefits and muscular risks associated with

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weight loss. **Methods:** In 286 non-cirrhotic obese CLD patients (age, 60 ± 15 years; 62% male; approximately 60% MASLD), intra-abdominal area (IAA) at the SMA level—capturing periportal adipose tissue—and paraspinal muscle area were quantified by MRI. Longitudinal changes in IAA (ΔpVAT), muscle mass, proton density fat fraction (PDFF), ALT, and liver stiffness (LS) were calculated as annualized rates. Cross-sectional associations were evaluated in the overall cohort (n = 286); longitudinal relationships were assessed in patients with serial MRI examinations under clinical management (n = 141, median follow-up: 36 months). **Results:** In the overall cohort, higher IAA was independently associated with higher LS beyond FIB-4, higher body weight, and lower muscle mass (all $P < 0.01$). In the longitudinal cohort, ALT significantly decreased and serum albumin significantly increased, despite a significant decline in muscle mass. In multivariable analysis of annualized changes, pVAT reduction was independently associated with improvements in PDFF and LS, while greater pVAT reduction showed a nonlinear association with accelerated muscle loss ($R^2 = 0.336$, $P < 0.001$). In MASLD (n = 78), ≥ 4% IAA reduction—corresponding to 5% body weight loss—was achieved in 28% and was more frequent early. This threshold was associated with significant improvements in PDFF, ALT, and LS, but was accompanied by muscle loss (−3.9%/year). Although serum albumin was independently associated with ΔpVAT in the longitudinal multivariable model, albumin did not decrease at this threshold ($P = 0.968$). **Conclusion:** Assessment of VAT at the SMA level allowed IAA to capture hepatic, nutritional, and muscular consequences of visceral fat change beyond body weight alone. VAT reduction conferred hepatic benefit but accelerated muscle loss, while coupled changes in IAA, albumin, and muscle suggested skeletal muscle mobilization to support hepatic protein synthesis. Thus, weight loss remains necessary in obese CLD, particularly MASLD, but protein intake during weight reduction should not be overlooked to limit skeletal muscle catabolism while preserving hepatic benefits.



Disclosures: ATSUSHI NAKAMURA:Nothing to Disclose.

3582 | ◆ BRAZZEIN-SWEETENED ICE CREAM REDUCES POSTPRANDIAL GLYCEMIC EXPOSURE IN MASLD: A RANDOMIZED DOUBLE-BLIND CROSSOVER TRIAL

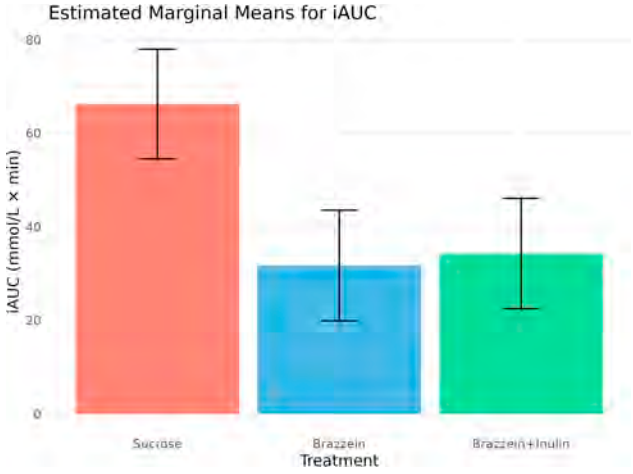
Vasily Isakov[1] Alexei Goncharov[1] Vladimir Pilipenko[1] Armida Sasunova[1], [1]Federal research Center of Nutrition, Biotechnology & Food Safety

Background: Dietary sugar reduction is a central recommendation in metabolic dysfunction-associated steatotic liver disease (MASLD), but clinical data on natural sweet proteins as sugar substitutes are limited. Brazzein is a heat-stable sweet protein 500–2000 times sweeter than sucrose. We evaluated whether brazzein-sweetened ice cream reduces acute postprandial glycemic exposure versus sucrose-sweetened ice cream in adults with MASLD. **Methods:** In a double-blind, randomized, three-period crossover trial (ClinicalTrials.gov NCT06724913), 101 adults with MASLD consumed 100 g of vanilla ice cream sweetened with sucrose (14 g), brazzein (0.014%), or brazzein plus inulin (0.014% + 4 g) on separate study days under standardized feeding conditions. MASLD was confirmed by ultrasound and vibration-controlled transient elastography. Factory-calibrated continuous glucose monitoring (FreeStyle Libre 2, Abbott Diabetes Care, Witney, UK) assessed glucose at baseline and every 15 min for 150 min after product consumption. The primary endpoint was incremental area under the glucose curve (iAUC0–150). Linear mixed-effects models adjusted for baseline glucose, period, sequence, and diabetes status, with participant as a random effect. **Results:** Participants had mean age 54.6 years, 76% were female, 97% had obesity, and 44% had type 2 diabetes. All participants completed all three periods and consumed the full product portion; no adverse events or tolerability issues were reported. Postprandial glucose trajectories differed significantly by treatment (treatment × time, $P < 0.001$). Compared with sucrose, brazzein reduced tissue glucose from 30 to 135 min, with a maximum difference at 75 min (−0.86 mmol/L; $P < 0.001$); brazzein plus inulin reduced glucose from 45 to 135 min, with a maximum difference at 75 min (−0.64 mmol/L; $P < 0.001$). Model-adjusted iAUC0–150 was 66.3 mmol/L×min (95% CI, 54.5–78.0) for sucrose, 31.7 (19.9–43.6) for brazzein, and 34.3 (22.5–46.1) for brazzein plus inulin, corresponding to 52% and 48% reductions versus sucrose, respectively (both $P < 0.001$). The two brazzein formulations did not differ ($P = 0.94$). Treatment effects on glucose trajectories were more pronounced in participants with diabetes (interaction $P = 0.042$). No period, sequence, or carry-over effects were detected. **Figure:** Model-adjusted iAUC0–150 by treatment. **Conclusion:** In adults with

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MASLD, replacing sucrose with brazzein in a real dessert matrix substantially reduced acute CGM-derived postprandial glycemic exposure, with or without added inulin. Brazzein-based sugar replacement may be a practical nutritional strategy to reduce postprandial glycemic burden in MASLD, particularly among patients with concomitant type 2 diabetes.



Disclosures: Vasily Isakov:Nothing to Disclose, Alexei Goncharov:Nothing to Disclose, Vladimir Pilipenko: Nothing to Disclose, Armida Sasunova:Nothing to Disclose.

3583 | EFFECTS OF INTERMITTENT VERSUS CONTINUOUS CALORIE RESTRICTION ON HEPATIC OUTCOMES, BODY COMPOSITION, AND GLYCOMETABOLIC PARAMETERS: A SYSTEMATIC REVIEW AND META-ANALYSIS

Kelsey Wright[1] Margarita Pipinos[1] Cindy Schmidt[1] Yeongjin Gwon[1] Hwi Young Kim[1], [1]University of Nebraska Medical Center

Background: Intermittent fasting (IF) has gained interest as a possible dietary approach for MASLD management. While these lifestyle modification strategies offer benefits such as improvements in cardiometabolic parameters in addition to weight loss-related MASLD improvement, their comparative efficacy on hepatic outcomes, body composition, and glycometabolic parameters have not been fully elucidated compared to continuous calorie restriction (CCR). **Methods:** A systematic review and network meta-analysis (PROSPERO: CRD420251164973) was conducted by searching EMBASE, MEDLINE, CINAHL, Cochrane Library, and Scopus through October 2025. Fifteen randomized trials (N = 710) and one prospective observation study (N = 34) comparing IF to CCR or control in adults with MASLD were included. Primary outcomes were liver fat content and fibrosis; secondary outcomes included body composition, glycemic parameters, and lipid profiles. A random-effects network meta-analysis was performed using the netmeta package in R. **Results:** IF ranked as the highest-ranked intervention by P-score across every hepatic outcome and most body composition and metabolic outcomes. Hepatic Outcomes: IF produced significant reductions in liver fat content (MD = −3.36; 95% CI: −5.34 to −1.39), ALT (MD = −11.50; 95% CI: −20.63 to −2.37), and GGT (MD = −18.46; 95% CI: −33.86 to −3.06) versus control. CCR (MD = −0.38, 95% CI: −0.72 to −0.04) also demonstrated significant reduction in LFC compared with control. No intervention achieved significant fibrosis reduction or reduction in AST. Meta-regression analysis demonstrated that weight change was a significant moderator of treatment effects on LFC (β = −3.10, 95% CI: −5.18 to −1.02) and fibrosis (β = −0.55, 95% CI: −1.02 to −0.07). Body Composition Outcomes: All interventions produced statistically significant weight reductions and BMI reductions as compared with control. IF (MD = −4.06 cm, 95% CI: −5.49 to −2.62) and TRF (MD = −3.21 cm, 95% CI: −4.49 to −1.93) reduced waist circumference as compared to control. No intervention significantly affected lean mass or fat mass versus control. Metabolic Outcomes: IF was the only intervention to significantly reduce fasting glucose (MD = −4.69; 95% CI: −9.24 to −0.14), HOMA-IR (MD = −0.84; 95% CI: −1.69 to −0.005), and triglycerides (MD = −29.93; 95% CI: −54.71 to −5.16) as compared to control. No intervention significantly affected HbA1c, fasting insulin, total cholesterol, LDL, or HDL. **Conclusion:** This network meta-analysis demonstrates that IF is the most consistently effective dietary strategy for adults with MASLD, ranking highest across hepatic, and most anthropometric and metabolic outcomes. Importantly, the hepatic benefits of IF appear to extend beyond weight loss alone, as reductions in liver fat content and fibrosis persisted after controlling for weight change on meta-regression analysis.

Disclosures: Kelsey Wright:Nothing to Disclose, Margarita Pipinos:Nothing to Disclose, Cindy Schmidt: Nothing to Disclose, Yeongjin Gwon:Nothing to Disclose, Hwi Young Kim:Nothing to Disclose.

3584 | SEARCHING HOW THE EXTRACT REBAUDIOSIDE OCCLUDES EXCESS STEATOSIS (SUPER HEROES): A PROSPECTIVE INTERVENTIONAL PILOT STUDY FOR PEDIATRIC MASLD

Blake Rosenthal[1] Paula Mrowczynski-Hernandez[1] Michael Goran[1] Jashdeep Bhattacharjee[1] Rohit Kohli[1] Tania Mitsinikos[1], [1]Children's Hospital Los Angeles

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Background: The prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD) continues to rise in the pediatric population. Murine models indicate that stevia-derived sweeteners, particularly rabaudioside A, may improve hepatic steatosis and inflammation through modulation of adipogenesis and insulin resistance. These pre-clinical findings prompted us to test commercially available stevia-sweetened beverages as a practical dietary intervention for pediatric patients with MASLD. **Methods:** This pilot study evaluated the effects of daily consumption of a commercially available stevia-sweetened beverage in children and adolescents with biopsy proven metabolic dysfunction-associated steatohepatitis (MASH) over an 8-week intervention period. Eligible participants were 10-18 years old with ALT >45 IU/L, BMI >85th percentile, and fat >5% and kPa >2.0 on liver MR elastography. Participants were randomized into three groups: stevia-sweetened beverage consumption, water consumption, or standard of care nutrition counseling (RD). Our primary outcome measure was change in ALT after 8 weeks with secondary outcomes being liver fat and fibrosis measured by MR elastography, anthropomorphic measurements, and additional laboratory markers. Participants tracked beverage intake using sticker charts with weekly phone follow-up to assess adherence, which was defined as completion of at least 80% of the target intervention dose. **Results:** We prospectively randomized 20 patients (8 to the stevia group, 5 to the water group, and 7 to RD counseling). Due to adherence issues, patient drop-out, and missing data, the final data set included 6 participants from the stevia group, 4 from the water group, and 6 from the RD group. Paired t-test analysis demonstrated significant improvement in ALT levels pre- and post-intervention in the water group (–36.5 U/L; $p = 0.044$) but not in the stevia group (3.2 U/L; $p = 0.955$) or RD group (–35U/L; $p = 0.207$). Notably, weight and BMI showed an increase in the stevia group that trended towards significance (weight +1.2kg; $p = 0.051$; BMI +0.4 kg/m2; $p = 0.058$). **Conclusion:** Our findings from this small pilot study are consistent with prior research suggesting that nutrition counseling and water consumption may support improvements in hepatic enzyme levels in pediatric MASLD/MASH. Given the small sample size, larger adequately powered studies are needed to better define the role of stevia-sweetened beverages in MASLD management.

Disclosures: Blake Rosenthal:Nothing to Disclose, Paula Mrowczynski-Hernandez:Nothing to Disclose, Michael Goran:Nothing to Disclose, Jashdeep Bhattacharjee:Nothing to Disclose, Rohit Kohli:Mirum: Consultant, Ipsen: Consultant, Epigen: Grant/Research Support, Sanofi Rare Disease: Consultant, iECURE: Consultant, Solid Biosciences: Consultant, Tania Mitsinikos:Nothing to Disclose.

3585 | CONTINUOUS GLUCOSE MONITORING (CGM)-DERIVED GLYCAEMIC VARIABILITY METRICS ARE STRONGLY ASSOCIATED WITH HEPATIC STEATOSIS AND FIBROSIS IN MASLD- AN EVIDENCE REVIEW

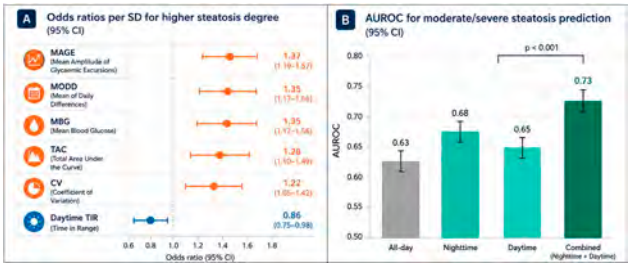
Ashok Kumar Choudhury[1] Adhithya Mullath Ullas[2] Mirza Khalid Baig[3] Manoj Kumar Sharma[1] Shiv Kumar Sarin[2] Bishnupriya Sahoo[4] Sanghamitra Pati[5], [1]Institute of Liver and Biliary Sciences, [2]Institute of Liver and Billiary Sciences, [3]National Instiute of Technology, Rourkela, [4]SGT University Gurugram Haryana India, [5]ICMR Delhi

Background: MASLD affects nearly one-third of the global population. Glycaemic dysregulation is central to MASLD pathogenesis, yet hepatology practice relies primarily on static parameters i.e. HbA1c and fasting glucose. Continuous Glucose Monitoring (CGM) becoming the standard of diabetes care and may provide a non-invasive metabolic phenotyping tool to complement existing liver risk stratification like FIB-4 and VCTE. We aimed to synthesise current evidence evaluating associations between CGM-derived glycaemic metrics and hepatic steatosis and fibrosis. **Methods:** A structured emerging-evidence review was conducted of original studies reporting CGM-derived glycaemic metrics alongside validated hepatic endpoints including liver biopsy, MRI-PDFF, VCTE/FibroScan, ultrasound, and FIB-4. Eight eligible studies encompassing over 5,000 participants from type 2 DM and non-diabetic populations with CGM were identified. Liver disease assessment methods included liver biopsy (3 studies, including 2 using Brunt's histological classification), MRI-PDFF (1), VCTE/FibroScan (2), abdominal ultrasound (2), and FIB-4 index (1). Only studies with validated liver endpoints and original CGM or glucose-profiling data were included. **Results:** Across all eight studies, CGM-derived glycaemic variability metrics demonstrated consistent and independent associations with hepatic steatosis and fibrosis. The strongest evidence emerged from MRI-PDFF cohort ($n = 1,180$), where all-day mean amplitude of glycaemic excursions (MAGE) (OR 1.37, 95% CI 1.19–1.57), mean of daily differences (MODD) (OR 1.35, 95% CI 1.17–1.56), and mean blood glucose (OR 1.35, 95% CI 1.17–1.56) were independently associated with hepatic steatosis. Time-stratified analyses identified nighttime MODD as the strongest predictor of steatosis, while a combined nighttime and daytime CGM model achieved superior discrimination (AUROC 0.73) compared with all-day metrics alone (AUROC 0.63; $p < 0.001$). In biopsy-proven MASLD, 24-hour glucose level associated with 2.3-fold higher number of cases with advanced fibrosis ($p = 0.002$), while CGM-derived hyperglycaemia correlated with fibrosis severity

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(r = 0.65, p < 0.05) and identified three-fold more glucose intolerance than conventional testing. CGM uniquely detected postprandial reactive hypoglycaemia in 70% of MASLD patients. Across all studies, conventional glycaemic markers were insufficient to capture the dynamic glycaemic phenotypes most strongly associated with liver disease severity. **Conclusion:** Emerging evidence suggests that CGM-derived glycaemic variability metrics are closely associated with hepatic steatosis and fibrosis severity across MASLD populations. Prospective longitudinal studies are required to determine whether CGM metrics predict disease progression and treatment response in MASLD.



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3586 | HEALTH-RELATED QUALITY OF LIFE IN MASLD/MASH TREATED WITH ESSENTIAL PHOSPHOLIPIDS SHOWS IMPROVEMENT IN FATIGUE AND ACTIVITY: CLDQ-MASH RESULTS FROM THE EXCEL RANDOMIZED TRIAL

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Background: MASLD/MASH is associated with substantial impairment in health-related quality of life (HRQoL) and other patient-reported outcomes (PROs). Essential phospholipids (EPL) are widely used as adjunctive therapy in chronic liver diseases; however, their impact on MASH-specific PROs remain unestablished. This study evaluated the effect of adding EPLs to standard of care (SoC) on changes in CLDQ-MASH scores. **Methods:** EXCEL was a Phase 4, multicenter, double-blind, randomized, placebo-controlled study conducted in Germany and Poland (2022-2024). Adults with MASLD and metabolic comorbidities (type 2 diabetes, hyperlipidemia and/or obesity) were randomized 1:1 to EPL + SOC or placebo + SOC for 6 months. PROs were assessed using CLDQ-MASH (total score and 7 domains) at baseline, 3, 6, and 9 months (with 9-month assessment conducted after treatment discontinuation). In CLDQ-MASH, 4 of 7 domains retained a structure similar to CLDQ-NAFLD/NASH, 2 were reorganized and renamed, and 1 new domain (sleep) was added. The digestive symptoms and diet domain highlights MASH-specific burden, while the shared domain structure enables consistent HRQoL assessment and meaningful cross-disease comparisons. Change from baseline scores were analysed by the treatment arm and clinical subgroups. Proportions of HRQoL responders at 6 months (improvement of 0.3 or more on CLDQ-MASH domains) were calculated. **Results:** The modified intention-to-treat population included 165 patients (EPL: n = 82; placebo: n = 83) with comparable baseline characteristics. Across all post-baseline visits, both treatment arms demonstrated statistically significant within-group improvements across most CLDQ-MASH domains (p < 0.05). At 6 months, EPL showed greater improvement vs placebo in the CLDQ-MASH total score (+0.40 vs +0.26; LSMD: 0.14, SE: 0.09; p = 0.097) and the Fatigue domain (+0.55 vs +0.28; LSMD: 0.27, SE: 0.13; p = 0.046). At 9 months, activity scores also improved significantly in EPL group vs placebo (+0.45 vs +0.19; LSMD: 0.26, SE: 0.12; p = 0.038). Other CLDQ-MASH domains remained numerically greater with EPL at 6- and 9-month assessments. The proportion of fatigue responders was higher with EPL (59.8% vs. 44.6%, p = 0.051). Treatment effects were consistent across subgroups (CAP, triglycerides, sex, BMI). EPL treated patients with baseline CAP of at least 288 dB/m showed greater improvement in worry at 6 months vs placebo (LSMD: 0.32 (SE: 0.16), p = 0.049), and among male patients, EPL treatment was associated with greater improvement in fatigue (LSMD: 0.36 (SE: 0.18), p = 0.048). **Conclusion:** EPL added to SoC was associated with consistent, sustained improvements in HRQoL in MASLD/MASH patients, with greater improvements in fatigue and activity domains, suggesting additional benefits beyond SoC.

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3587 | CLINICAL EVALUATION OF A ONCE-DAILY POLYHERBAL NUTRACEUTICAL ON LIVER FUNCTION IN HEALTHY ADULTS: A RANDOMIZED, PLACEBO-CONTROLLED STUDY

Benjamin Tillisch[1] Saumin Shah[2] Ghanashyam Patel[3], [1]Dose Daily, [2]Unity Trauma Center, [3]Eetho Brands (DBA: Dose Daily)

Background: Recent data suggest there may be a subclinical drift toward metabolic dysfunction of the liver, even among healthy individuals. This clinical study evaluated the efficacy and safety of a nutraceutical containing organic extracts of turmeric, dandelion, milk thistle, and ginger on liver function parameters in healthy participants. **Methods:** This was a randomized, placebo-controlled study. Healthy adults aged 18-60 years with liver function test values within upper normal limits were randomized 1:1 to receive the nutraceutical or placebo (60 mL) once daily for 90 days. Primary endpoint was change in liver function tests (alanine aminotransaminase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], gamma-glutamyl transferase [GGT], bilirubin) from baseline to end of treatment (EOT). Safety was also evaluated. Intergroup and intragroup comparisons were analyzed using paired t-tests and analysis of covariance, respectively. **Results:** 108 participants enrolled; 54 randomized to each group. From baseline to EOT, mean levels of ALT, AST, ALP, GGT, and total bilirubin (primary endpoints) were significantly decreased with the nutraceutical ($p < 0.05$ for all) and significantly increased with placebo ($p < 0.05$). Mean improvements from baseline to EOT in each of these parameters was significantly greater with the nutraceutical than placebo ($p < 0.01$ for all). No adverse events were reported. **Conclusion:** Daily single-dose (60 mL) supplementation of this nutraceutical was safe and demonstrated significant improvements in liver function tests in healthy participants. These results suggest that the nutraceutical product may provide meaningful improvements in attenuating the progress of early signs of metabolic liver dysfunction in healthy individuals.

Disclosures: Benjamin Tillisch:Eetho Brands (DBA: Dose Daily): Employee, Saumin Shah:Nothing to Disclose, Ghanashyam Patel:Nothing to Disclose.

3588 | SINGLE CENTER RETROSPECTIVE EXPERIENCE EVALUATING THE EFFECTS OF BARIATRIC SURGERY ON METABOLIC ASSOCIATED STEATOHEPATITIS WITH FIBROSIS.

Teresa Del Rio Montesinos[1] Asma Siddique[1] Blaire Burman[2], [1]Virginia Mason Medical Center, [2]University of Washington

Background: Hepatic steatosis is now the leading cause of cirrhosis in the United States. The prevalence of metabolic-associated steatoliver disease (MASLD) and metabolic-associated steatohepatitis (MASH) is estimated to affect 25-30% of the population and is expected to double by 2030. Prevalence varies by race, ethnicity, and clinical setting, and due to its asymptomatic nature, MASLD is often underdiagnosed. Complications include fibrosis, cirrhosis, and hepatocellular carcinoma. Lifestyle changes are currently the only established means to prevent or regress the disease, though pharmacological and surgical interventions are available for treating MASH. This study aimed to evaluate the impact of bariatric surgery (gastric bypass and sleeve gastrectomy) on patients with MASH and fibrosis (stage 1 or higher, with stage 4 indicating cirrhosis). Our objectives were to assess the reduction in fibrosis stage or resolution of hepatic fibrosis post-surgery and to emphasize the role of sustained weight loss in decreasing steatohepatitis and fibrosis. **Methods:** Patients(100) were selected based on history of bariatric surgery (sleeve gastrectomy or RYGB), aged 18-65 and documentation of MASH with fibrosis at Virginia Mason Franciscan Health hospital in Seattle, WA. Reviewed MR elastography, liver biopsy and transient elastography prior to surgery with a documentation of fibrosis stage I or above. Patients identified with fibrosis, after the bariatric surgery a repeat MR elastography or transient elastography was done to assess the fibrosis score. Fibrosis score improved at least one stage or resolved completely. **Results:** Results showed 34 patients had MASH cirrhosis at different fibrosis stages all above F1. Out of the 34 patients, 52.9 % (18 patients) of patients had an improvement in fibrosis. Our findings show that bariatric surgery significantly improved hepatic fibrosis. On average, patients needed to lose 78 lbs within the first 9-12 months to observe a decrease in fibrosis stage. Notably, patients with compensated cirrhosis (stage 4 fibrosis) showed regression, with some reducing by two stages to no fibrosis. **Conclusion:** Even though bariatric surgery has proven to be one of the only therapies available to effectively reduce the fibrosis stage and even lead to complete resolution of liver fibrosis for patients suffering from fibrosis secondary to MASH, it does have significant complications and

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is considered an invasive procedure. Weight loss is not always maintained and, in many cases, patients regain the weight they had lost prior to surgery. Again, lifestyle changes; diet, exercise, and education of healthy habits the continued treatment even after surgery. While the primary treatment and prevention option is still lifestyle changes, bariatric surgery is a good resource to help improve fibrosis due to MASH.

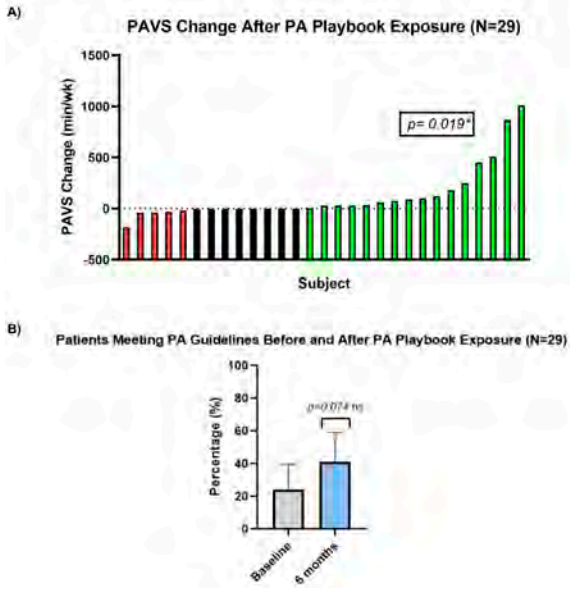
Disclosures: Teresa Del Rio Montesinos:Nothing to Disclose, Asma Siddique:Nothing to Disclose, Blaire Burman:Nothing to Disclose.

3589 | INTEGRATING A PHYSICAL ACTIVITY PLAYBOOK INTO MULTIDISCIPLINARY MASLD CARE INCREASES PHYSICAL ACTIVITY OVER 6 MONTHS

Hannah Mohr[1] Breianna Hummer-Bair[2] Kofi Clarke[3] Britney Fitzgerald[3] Samantha Garcia[3] Karen Krok[4] Heather Tressler[3] Nataliya Smith[5] Kyra VanKirk[6] Jonathan Stine[1], [1]Penn State College of Medicine, [2]Pennsylvania State University, [3]Division of Gastroenterology & Hepatology, Penn State Health Milton S. Hershey Medical Center, [4]Penn State Milton S. Hershey Medical Center, [5]Pennsylvania State University, College of Medicine, [6]College of Medicine, Penn State Health Milton S. Hershey Medical Center, Hershey PA, USA

Background: Lifestyle intervention in metabolic dysfunction-associated steatotic liver disease (MASLD) requires scalable physical activity (PA) assessment and behavior support. However, clinics often lack standardized workflows. We aimed to determine if implementation of a standardized workflow that embeds screening, brief intervention and referral to treatment can help adults with at-risk MASH increase weekly moderate-to-vigorous PA. **Methods:** Using the Screening, Brief Intervention, and Referral (SBIRT) framework, we developed and implemented the MASLD Physical Activity Playbook in a multidisciplinary MASLD clinic. The playbook includes three questionnaires (American College of Sports Medicine (ACSM) Physical Activity Vital Sign, MASLD Barriers to Exercise Survey, Duke Activity Status Index) to assess current PA level, PA barriers and facilitators and functional capacity followed by education with the ACSM MASLD PA handout. In some cases, the Playbook was coupled with a personalized exercise prescription. Change in moderate-to-vigorous PA was measured six months after implementation. **Results:** A total of n = 29 adults with at-risk MASH were included (mean age 58 years, 55% female, mean BMI 34.8 kg/m$^{2)}$. At baseline, 56% of patients had a fibrosis level of F2 or greater as measured by Vibration Controlled Elastography (FibroScan). At baseline, mean PAVS was 101.6 min/week (± 124 min/week) of moderate-to-vigorous PA. At 6-month follow-up, mean PAVS increased to 223 min/wk (mean change +122.1 min/wk, p = 0.011). The proportion of patients meeting ACSM PA guidelines increased from 24.1% to 41.3%, though this did not reach statistical significance (p = 0.07). Exercise barriers decreased and functional capacity (DASI) increased after intervention, though neither reached statistical significance. Exploratory outcomes including weight, aspartate aminotransferase (AST), alanine aminotransferase (ALT), hemoglobin A1c (HbA1c), and Fibrosis-4 scores (FIB-4) show decreasing trends but did not reach statistical significance at this sample size. **Conclusion:** A brief, standardized PA Playbook integrating screening, education, and individualized exercise prescription, where necessary, can be feasibly implemented into routine MASLD care and is associated with a significant increase in moderate-to-vigorous PA at 6 months. These findings support further implementation and evaluation of the PA playbook within MASLD care settings to confirm efficacy and assess impact on hepatic outcomes.

Figure 1: Exposure to PA Playbook leads to a meaningful increase in physical activity in those with MASLD/MASH



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Advisor, Pfizer: Consultant, Britney Fitzgerald:Nothing to Disclose, Samantha Garcia:Nothing to Disclose, Karen Krok:Abbvie: Advisor, Intercept: Advisor, Gilead: Consultant, Ipsen: Consultant, Gilead: Consultant, Heather Tressler:Nothing to Disclose, Nataliya Smith: Nothing to Disclose, Kyra VanKirk:Nothing to Disclose, Jonathan Stine:Novo Nordisk: Consultant, Galectin: Grant/Research Support, Novo Nordisk: Grant/Research Support, Astra Zeneca: Grant/Research Support, Noom: Grant/Research Support, Zydus: Grant/Research Support, Kowa: Grant/Research Support, Regeneron: Grant/Research Support, Madrigal: Advisor, Astra Zeneca: Employee, Astra Zeneca: Stock - publicly traded company.

3590 | MANAGING MASH AND CARDIOMETABOLIC COMORBIDITIES: THE IMPLICATIONS OF SPECIALTY-NUANCED TREATMENT DECISIONS

Lizy Gill[1] Ramya Logendra[1] Ayse Levent[1] Rhoda Schmuecking[1], [1]Ipsos

Background: Metabolic dysfunction-associated steatohepatitis (MASH) and associated cardiometabolic conditions are major causes of morbidity and mortality. The care pathway for MASH patients involves a multidisciplinary approach that often results in referrals and complex diagnostic and treatment processes, driven by comorbidities. **Methods:** Data are from the Ipsos Syndicated MASH Therapy Monitor, an online medical chart review and physician perceptual study including 646 physicians in the US (212), Germany (170), Japan (114) and China (150) treating MASH patients, collected between Feb-Apr 2026. Participants consisted of primary care physicians (PCPs), diabetologists/endocrinologists and gastroenterologists/hepatologists and were screened for caseload. Physicians reported on 2450 MASH patients in the US (727), Germany (551), Japan (422) and China (750) seen in the last 3 months. **Results:** When aggregating regional data, cardiometabolic conditions have a strong influence on MASH treatment decisions for hepatologists, endocrinologists and PCPs. Across these specialties, over 81% of MASH treatment decisions are reported to be strongly influenced by Type 2 Diabetes (T2D), >61% by hypertension, and >71% by dyslipidemia/hyperlipidemia/hypercholesterolemia. In contrast, gastroenterologists specialising in both liver and non-liver conditions report lower influence rates; T2D 67%, hypertension 39%, dyslipidemia 45%.This divergence extends beyond comorbidity influence on MASH treatment management, to physicians' prioritisation of conditions treated. While most gastroenterologists do manage MASH and cardiometabolic conditions concurrently, a subset prioritise managing MASH *over* the cardiometabolic conditions. Specifically, 16% of gastroenterologists prioritise managing MASH over T2D, compared to only 5-6% among other specialties. For hypertension, 22% prioritise MASH management over hypertension, versus ≤10% in other specialties. **Conclusion:** This specialty-based fragmentation suggests there's a divergence in MASH patient care; that gastroenterologists appear to be taking a more liver-specific approach while hepatologists, endocrinologists and PCPs are treating more holistically along with MASH. By prioritising MASH over cardiometabolic conditions, this liver-centric approach taken by gastroenterologists may potentially limit the benefits of addressing comorbidities on disease progression. Ultimately, this specialty-based fragmentation may compromise optimal patient outcomes and suggests the need for standardised, multidisciplinary approaches to MASH care that balance hepatic and metabolic therapeutic targets.

Disclosures: Lizy Gill:Nothing to Disclose, Ramya Logendra:Nothing to Disclose, Ayse Levent:Nothing to Disclose, Rhoda Schmuecking:Nothing to Disclose.

3591 | MULTIDISCIPLINARY CARE SIGNIFICANTLY IMPROVES WEIGHT LOSS OUTCOMES IN MASLD COMPARED TO STANDARD HEPATOLOGY CARE: A REAL-WORLD COHORT STUDY

Tolga Gidener[1] Saumya Srivastava[2] Lisa Yanek[3] Tyrus Vong[4] Victor Arahirwa[5] Alexandra Strauss[1] Arunkumar Krishnan[6] Selvi Rajagopal[7] Yuval Pinto[7] James Hamilton[8] Tinsay Woreta[9], [1]Division of Gastroenterology and Hepatology, Johns Hopkins University School of Medicine, Baltimore, [2]Section of Digestive Diseases, Yale School of Medicine, New Haven, CT, USA, [3]Division of General Internal Medicine, Department of Medicine, Johns Hopkins University School of Me, [4]Division of Gastroenterology and Hepatology, Johns Hopkins University School of Medicine, Baltimore., [5]Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA, [6]Department of Medicine, Wake Forest University School of Medicine, Charlotte, North Carolina, USA, [7]Division of General Internal Medicine, Johns Hopkins University School of Medicine, [8]Johns Hopkins University, [9]Johns Hopkins University School of Medicine

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Background: The 2023 AASLD Practice Guidance recommends a multidisciplinary approach for the management of MASLD. However, data comparing outcomes between multidisciplinary and standard hepatology care remains limited. In June 2020, our institution established the Healthful Eating, Activity and Weight Program (HEAWP), a multidisciplinary clinic staffed by obesity medicine physicians, hepatologists, an endocrinologist, and bariatric surgeons, with psychology and nutrition collaboration. Patients undergo evaluation with an obesity medicine physician assessing nutrition, sleep, mood, medications, and physical activity in addition to Hepatology evaluation. Individualized goals are established, with frequent follow-up for support with behavior change and treatment. We aimed to evaluate the impact of this multidisciplinary clinic on clinical outcomes in patients with MASLD. **Methods:** Adults with MASLD seen in the HEAWP vs. standard hepatology clinics between 2020-2025 were identified using our liver disease Precision Medicine Analytics Platform. Baseline characteristics were compared between groups using Chi-squared or Fisher's exact tests and student's t-tests or Wilcoxon tests. Changes in weight, ALT, and liver stiffness measurement (LSM) by transient elastography (TE) were assessed using paired Wilcoxon tests. Multivariable regression models assessed changes in weight adjusted for GLP-1 receptor agonist use. **Results:** 103 patients with MASLD were identified in the HEAWP clinic cohort, and 1,050 patients in the standard hepatology cohort. Compared to the hepatology cohort, patients in the HEAWP cohort were more likely to be prescribed semaglutide (43% vs 25%) and tirzepatide (31% vs 17%). At 12 months, patients in the HEAWP cohort had substantially greater weight loss compared to those receiving standard hepatology care (-5.61 kg vs. -0.6 kg; $p = 0.02$). The mean percent body weight reduction in the HEAWP cohort reached –6.1% at 12 months, compared to only -0.7% in the standard hepatology cohort. After adjustment for usage of GLP-1 medications, the difference in weight loss at 12 months (-4.5 kg [95% CI -7.98, -1.04]) remained statistically significant between the two cohorts. Change in ALT and LSM by TE did not significantly differ between cohorts, likely due to small sample sizes. **Conclusion:** In this real-world comparison of multidisciplinary versus standard hepatology care for MASLD, patients managed in a multidisciplinary clinic achieved substantially greater weight loss, even after adjustment for GLP-1 receptor agonist use. Our findings highlight the promise of multidisciplinary care models for achieving clinically meaningful weight loss in patients with MASLD. In our model, hepatologists collaborating with obesity medicine physicians who provided comprehensive, individualized care led to significant weight loss benefits beyond pharmacotherapy alone.

Disclosures: Tolga Gidener:Nothing to Disclose, Saumya Srivastava:Nothing to Disclose, Lisa Yanek: Nothing to Disclose, Tyrus Vong:Nothing to Disclose, Victor Arahirwa:Nothing to Disclose, Alexandra Strauss:Nothing to Disclose, Arunkumar Krishnan: Nothing to Disclose, Selvi Rajagopal:Nothing to Disclose, Yuval Pinto:Nothing to Disclose, James Hamilton:orphalan pharmaceuticals: Advisor, mirum pharmacueticals: Advisor, Tinsay Woreta:Nothing to Disclose.

3592 | BRAZZEIN-SWEETENED ICE CREAM SHOWS HIGH ACCEPTANCE IN MASLD PATIENTS ACROSS LIVER FIBROSIS SEVERITY

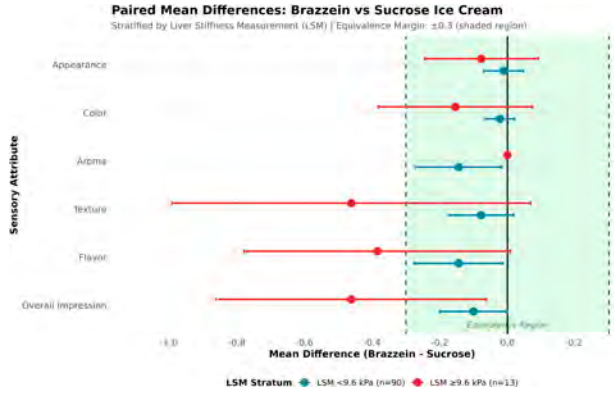
Vasily Isakov[1] Alexei Goncharov[2] Armida Sasunova[2], [1]Federal Research Center of Nutrition and Biotechnology, [2]Federal Research Center of Nutrition, Biotechnology & Food Safety

Background: Sugar reduction is a key dietary target in metabolic dysfunction-associated steatotic liver disease (MASLD), but acceptable sugar-reduced foods are needed to support adherence. Brazzein is an intensely sweet natural protein with potential for sugar replacement, but sensory data in clinically characterized MASLD patients, including those with significant liver fibrosis, are limited. **Methods:** In a double-blind, randomized, two-period crossover sensory study, 103 adults with MASLD evaluated iso-sweet vanilla ice cream sweetened with brazzein or sucrose. Overall impression and sensory attributes, including appearance, color, aroma, taste, and texture, were rated on 5-point hedonic scales. Consumption of each 100 g portion was measured. Liver fibrosis was assessed by vibration-controlled transient elastography. Exploratory analyses compared sensory responses by liver stiffness measurement (LSM), with LSM ≥ 9.6 kPa used to define advanced fibrosis. **Results:** Fourteen participants had F3/F4 fibrosis. Overall acceptance was very high for both products: 96.1% for brazzein and 98.1% for sucrose. Mean portion consumption was also high and did not differ significantly between formulations: 98.01% for brazzein vs 99.61% for sucrose; mean difference −1.60% (95% CI −3.64 to 0.44; $p = 0.122$). Liver stiffness was the only significant predictor of consumption, with each 1 kPa increase in LSM associated with a 0.81% lower intake ($\beta = -0.812$; 95% CI −1.432 to −0.193; $p = 0.012$). In exploratory interaction analysis, the effect of sweetener on overall

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impression varied by LSM category (LR $\chi^2 = 12.26$; $p = 0.002$). In participants with LSM < 9.6 kPa, paired mean differences for all sensory attributes remained within the prespecified ±0.3 practical-equivalence margin. In contrast, among participants with LSM ≥ 9.6 kPa, confidence intervals were wider and several attributes extended beyond this margin, including texture, taste, and overall impression, with mean differences numerically favoring sucrose. Nevertheless, acceptance remained >95% across LSM strata. **Conclusion:** Brazzein-sweetened ice cream showed very high short-term acceptability and near-complete consumption in MASLD patients. Patients with higher liver stiffness consumed slightly less ice cream overall and showed greater uncertainty in sensory equivalence, but acceptance remained high. These findings support further evaluation of brazzein-containing sugar-reduced foods in MASLD, including adequately powered studies in patients with advanced fibrosis.



Disclosures: Vasily Isakov:Nothing to Disclose, Alexei Goncharov:Nothing to Disclose, Armida Sasunova: Nothing to Disclose.

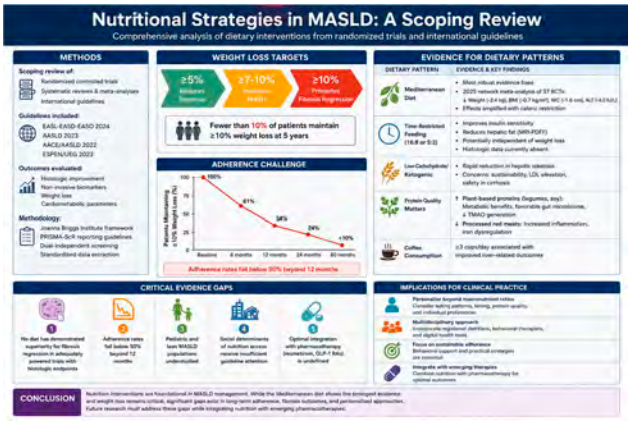
3593 | NUTRITIONAL STRATEGIES IN MASLD: A SCOPING REVIEW

Pranav Ramamurthy[1] Tejashree Rajhans[2], [1]University of Massachusetts Chan Medical School, [2]N/A

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) affects over 30% of adults globally and is now the leading indication for liver transplantation. Nutrition remains foundational to management, even in the wake of pharmacologic advances such as resmetirom and incretin-based therapies. However, substantial heterogeneity exists in guideline recommendations and real-world effectiveness remains limited by poor adherence and lack of standardized protocols. **Methods:** We conducted a comprehensive review of randomized controlled trials, systematic reviews, and international guidelines (EASL-EASD-EASO 2024, AASLD 2023, AACE/AASLD 2022) to evaluate dietary interventions for MASLD. Outcomes included histologic improvement, non-invasive biomarker changes, weight loss and cardiometabolic parameters. **Results:** Weight loss targets are consistent across guidelines: ≥5% reduces steatosis, ≥7%-10% improves MASH, and ≥10% promotes fibrosis regression. However, fewer than 10% of patients maintain ≥10% loss at five years.Among dietary patterns, the Mediterranean diet demonstrates the most robust evidence. A 2025 network meta-analysis of 37 RCTs confirmed significant reductions in body weight (-2.4 kg), BMI (-0.7 kg/m²), waist circumference (-1.6 cm), and ALT (-4.0 IU/L) versus control, with effects amplifying with caloric restriction. Time-restricted feeding (16:8 or 5:2 protocols) shows promise for insulin sensitivity and hepatic fat reduction, potentially independent of weight loss, though histologic data are absent. Low-carbohydrate and ketogenic diets achieve rapid steatosis reduction but raise concerns regarding sustainability, LDL elevation and safety in cirrhosis.Plant-based proteins confer metabolic advantages through favorable gut microbiome effects and reduced trimethylamine N-oxide generation, while processed red meats exacerbate inflammation and iron dysregulation. Coffee consumption (≥3 cups/day) is associated with improved liver-related outcomes.Critical evidence gaps include: (1) no dietary approach has demonstrated superiority for fibrosis regression in adequately powered trials with histologic endpoints; (2) adherence rates fall below 50% beyond 12 months; (3) pediatric and lean MASLD populations remain understudied; (4) social determinants of nutrition access receive insufficient guideline attention; (5) optimal integration with pharmacotherapy (resmetirom, GLP-1 RAs) is undefined. **Conclusion:** Nutrition interventions for MASLD require personalization beyond macronutrient ratios to incorporate eating patterns, timing, protein quality and behavioral support. Future research must prioritize durable adherence strategies and integration with emerging pharmacotherapy. Multidisciplinary delivery incorporating registered dietitians, behavioral therapists and digital health tools represents the optimal implementation framework.

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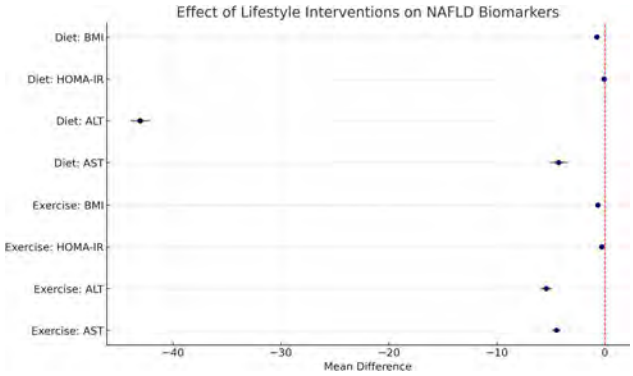


Disclosures: Pranav Ramamurthy:Nothing to Disclose, Tejashree Rajhans:Nothing to Disclose.

3594 | LIFESTYLE MODIFICATION IN EARLY NON-ALCOHOLIC FATTY LIVER DISEASE: A META-ANALYSIS AND SUBGROUP COMPARISON OF EXERCISE AND DIET INTERVENTIONS

Chanpreet SIngh[1] Prince Shah-Riar[2] Nimish Thakral[3] Asif Zamir[4] Theodore Pettle[1] Valeska Balderas[1] Bipneet Singh[5], [1]South Texas Health System-Universal Health Services, [2]DHR Health, [3]University of Kentucky Medical Center, [4]DHR Hospital, [5]Univeristy of Ketuncky

Background: Non-alcoholic fatty liver disease (NAFLD) is the most prevalent chronic liver disease globally and a growing public health burden. In the absence of approved pharmacologic therapies, structured lifestyle interventions are the cornerstone of management. This meta-analysis evaluates the effectiveness of physical exercise and dietary modification in reversing key clinical and biochemical markers of early-stage NAFLD, with a subgroup analysis comparing their differential impacts. **Methods:** A systematic search of PubMed, ScienceDirect, Cochrane Library, ClinicalTrials.gov, Google Scholar, and PLOS ONE was conducted. Fourteen randomized controlled trials (RCTs) involving adult patients with NAFLD were included. Interventions consisted of either structured physical exercise or a controlled diet, compared to usual care. Primary outcomes included liver enzymes [AST, ALT], insulin resistance (HOMA-IR), and body mass index (BMI). Results were pooled using mean differences (MD) with 95% confidence intervals (CI). Subgroup analysis was performed to evaluate biomarker-specific effects by intervention type. **Results: Exercise Subgroup:** Significantly reduced AST (MD: -4.48; CI: -4.82 to -4.14), ALT (MD: -5.43; CI: -5.91 to -4.94), HOMA-IR (MD: -0.29; CI: -0.35 to -0.23), and BMI (MD: -0.66; CI: -0.74 to -0.58). **Diet Subgroup:** Reduced AST (MD: -4.28; CI: -5.09 to -3.48), ALT (MD: -5.04; CI: -5.91 to -4.16), and BMI (MD: -0.76; CI: -0.81 to -0.70), but did not significantly affect HOMA-IR (MD: -0.08; CI: -0.17 to 0.01). Both interventions improved overall quality of life and physical fitness. **SubgroupAnalysis:** As illustrated in Figure 1 and Figure 2, exercise uniquely improved insulin resistance, while both interventions demonstrated comparable benefits in liver enzymes and BMI. These findings suggest distinct metabolic advantages of exercise in NAFLD reversal. **Conclusion:** Structured exercise and dietary interventions significantly improve metabolic and hepatic outcomes in early NAFLD. Exercise appears to offer broader benefits, particularly in insulin sensitivity, supporting its prioritization in personalized lifestyle protocols. These findings may inform updated NAFLD guidelines and support integration of structured exercise into first-line management.



Disclosures: Chanpreet SIngh:Nothing to Disclose, Prince Shah-Riar:Nothing to Disclose, Nimish Thakral:Nothing to Disclose, Asif Zamir:Nothing to Disclose, Theodore Pettle:Nothing to Disclose, Valeska Balderas:Nothing to Disclose, Bipneet Singh:Nothing to Disclose.

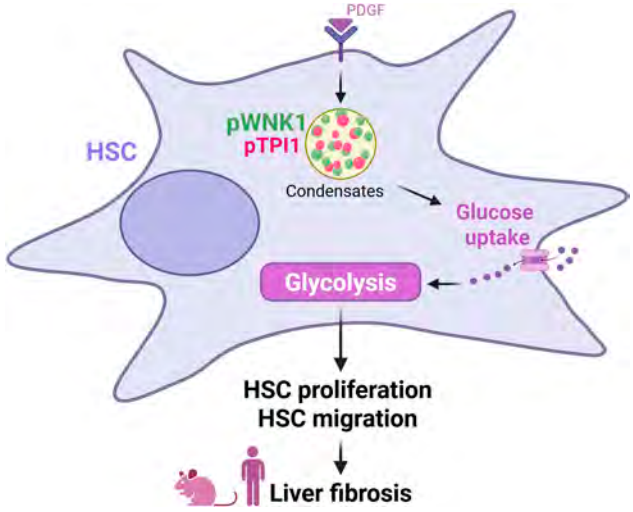
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3595 | WITH NO LYSINE KINASE 1 (WNK1) FORMS CONDENSATES WITH GLYCOLYTIC TRIOSEPHOSPHATE ISOMERASE 1 (TPI1) IN HEPATIC STELLATE CELLS TO PROMOTE MOUSE AND HUMAN LIVER FIBROSIS

Zeba Firdaus[1] Alexander Washington[1] Jasper Solverson[1] Luke Doskey[1] Vijay Shah[2] Patrick Starlinger[1] Gina Razidlo[1] Matthew Schellenberg[1] Enis Kostallari[2], [1]Mayo Clinic, [2]Mayo Clinic Rochester

Background: Platelet-derived growth factor B (PDGF)-mediated hepatic stellate cell (HSC) activation is a hallmark of liver fibrosis. HSC activation is accompanied by increased glycolysis to meet high energy demands. However, the signaling leading to this metabolic shift, subsequent HSC activation, and liver fibrosis remains unclear and is the focus of this study. **Methods:** Primary human HSCs and mouse liver tissues were analyzed by chemical genetics, western blot, or immunofluorescence. Liver fibrosis was induced by carbon tetrachloride (CCl_4) or high-fat, choline-deficient, amino acid-defined (HF-CDAA) diet. Human precision-cut liver slices (PCLS) were obtained from patient liver resections. **Results:** We identified with no lysine kinase 1 (WNK1) as a new kinase promoting HSC proliferation and migration (TLM 2025). Chemical genetics, a method we described to identify direct substrates of kinases (TLM 2025), detected triose phosphate isomerase 1 (TPI1), a glycolytic enzyme, as a novel WNK1 substrate. PDGF increased the formation of WNK1 condensates (3-fold, $n = 3$, $p < 0.05$), a liquid-liquid phase separation entity. PDGF also enhanced the TPI1-WNK1 co-localization in these condensates (4-fold, $n = 3$, $p < 0.05$). Functionally, TPI1 knockdown reduced PDGF-mediated glucose consumption (4-fold, $n = 4$, $p < 0.05$), HSC proliferation (EdU incorporation, 3-fold, $n = 3$, $p < 0.05$) and migration (transwell assay, 2.3-fold, $n = 3$, $p < 0.05$). Condensate inhibition using 1,6-hexanediol reduced HSC proliferation (3-fold, $n = 3$, $p < 0.05$) and migration (2.3-fold, $n = 3$, $p < 0.05$). These results suggest that WNK1-TPI1 interaction in condensates contributes to HSC activation. *In vivo*, HSC-specific WNK1 deletion in *Wnk1*$^{\Delta HSC}$ mice reduced liver fibrosis compared to *Wnk1*$^{fl/fl}$ controls as evidenced by Sirius-red staining, collagen 1 (COL1), COL3, and α-smooth muscle actin protein levels, both in CCl_4 (4-fold, 2.8-fold, 3-fold, and 5-fold, respectively, $n = 5$ mice/group, $p < 0.05$) and HF-CDAA diet (4-fold, 3-fold, 4-fold, and 2-fold, respectively, $n = 3$-5 mice/group, $p < 0.05$) models. Finally, activated phospho-WNK1 increased 5-fold in human cirrhotic liver tissues compared to healthy controls ($n = 3$, $p < 0.05$) and WNK1 pharmacological inhibition reduced COL1 expression (3-fold, $n = 3$, $p < 0.05$) in human cirrhotic PCLS. **Conclusion:** Together, these results identify WNK1-TPI1 axis as a novel mechanism promoting liver fibrosis in mouse and human liver tissues, that can be pharmacologically targeted.



Disclosures: Zeba Firdaus:Nothing to Disclose, Alexander Washington:Nothing to Disclose, Jasper Solverson:Nothing to Disclose, Luke Doskey:Nothing to Disclose, Vijay Shah:Boehringer Ingelheim: Consultant, GSK: Consultant, GENFIT SA: Consultant, Intercept Pharmaceuticals, Inc.: Advisor, Korro Bio, Inc.: Consultant, Novo Nordisk A/S: Consultant, Resolution Therapeutics, Ltd.: Advisor, Seal Rock Therapeutics, Ltd.: Consultant, Surrozen: Advisor, Dexcel Pharma Technologies, Ltd.: Consultant, Dimension Inx.: Advisor, Enveda: Consultant, Ochre Bio: Consultant, Satellite Biosciences, Inc.: Consultant, Patrick Starlinger:Nothing to Disclose, Gina Razidlo:Nothing to Disclose, Matthew Schellenberg:Nothing to Disclose, Enis Kostallari:Nothing to Disclose.

3596 | ALCOHOL-ASSOCIATED LIVER DISEASE MORTALITY RATES PEAKED IN 2021 AND ARE NOW DECLINING

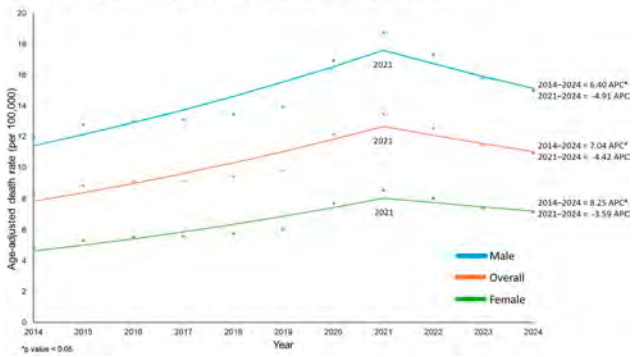
Cassie Almond[1] Gabriel Lupu[1] Andrew Moon[2] Anne Peery[1] Hersh Shroff[3] Sasha Deutsch-Link[3], [1]University of North Carolina School of Medicine, [2]University of North Carolina, [3]UNC Chapel Hill

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Background: Over the past 2 decades, alcohol consumption in the United States has increased considerably. Previous work demonstrated that alcohol-associated liver disease (ALD) mortality increased from 2017 to 2020 and accelerated during the COVID-19 pandemic. However, it is unclear how these trends have evolved following the pandemic. We aimed to examine ALD-related mortality in the United States from 2014 to 2024. **Methods:** Using national data from the Centers for Disease Control and Prevention, we examined ALD-related mortality rates from 2014 to 2024. ALD-related deaths were defined as the presence of an ICD-10 code for ALD (K70) listed as the underlying cause of death. We determined the annual age-adjusted mortality rates stratified by sex and race/ethnicity and crude age-cohort mortality rates stratified by sex. We performed a Joinpoint analysis to examine annual percent change (APC) and average annual percent change (AAPC) in ALD mortality, stratified by sex. **Results:** ALD mortality rates increased from 2014-2024 with an AAPC of 3.46 (1.72-5.68; $p < 0.01$) and a significant change-point identified in 2021. From 2014 to 2021, ALD mortality increased nearly every year across age, sex, and race/ethnicity. Mortality was highest among American Indian, Hispanic, and White individuals and ages 55 to 64 years. From 2014-2021, the overall APC was 7.04 (5.02-14.2; $p < 0.01$). By sex, the 2014-2021 APC was 6.40 (4.36-14.36; $p < 0.01$) among males and 8.25 (6.24-12.86; $p = 0$) among females. ALD mortality peaked in 2021 with age-adjusted rates of 18.70 per 100,000 (95% CI 18.45-18.95) among males and 8.55 per 100,000 (95% CI 8.39-8.73) among females. While there was no significant trend in AAPC or APC following 2021, there was a relative decrease in ALD mortality rates observed among both sexes. The overall AAPC 2020-2024 was -1.68 (1.98-0.34; $p = 0.34$); -2.2 (-6.82-1.58; $p = 0.22$) among males and -0.76 (-4.13-2.43; $p = 0.66$) among females. The overall APC 2021-2024 was -4.42 (-14.16-1.83; $p = 0.16$); -4.91 (-15.81-1.48; $p = 0.12$) among males and -3.59 (-12.2-2.04; $p = 0.23$) among females. Furthermore, from 2021 to 2024, ALD mortality decreased nearly every year across age and race/ethnicity. **Conclusion:** ALD mortality steadily rose from 2014-2019 and experienced a significant acceleration during the COVID-19 pandemic. However, one year following the onset of the pandemic, ALD mortality peaked. From 2021, a non-significant trend towards a decline in ALD mortality was observed across sexes and nearly all ages and races/ethnicities.

Figure 1: Joinpoint analysis of age-adjusted ALD-related mortality (2014-2024)



Disclosures: Cassie Almond:Nothing to Disclose, Gabriel Lupu:Nothing to Disclose, Andrew Moon: TARGET RWE: Consultant, DCN Diagnostics: Grant/Research Support, Intercept Pharmaceuticals: DSMB, IDEOlogy: Consultant, Eisai: Consultant, AstraZeneca: Consultant, Sirtex: Consultant, Madrigal: Grant/Research Support, Anne Peery:Nothing to Disclose, Hersh Shroff:Glaxo-Smith-Kline: Grant/Research Support, Sasha Deutsch-Link:Nothing to Disclose.

3597 | EFFICACY AND SAFETY OF NALTREXONE IMPLANT IN PATIENTS WITH MILD ALCOHOL-ASSOCIATED LIVER DISEASE: A POST HOC SUBGROUP ANALYSIS OF A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE II TRIAL

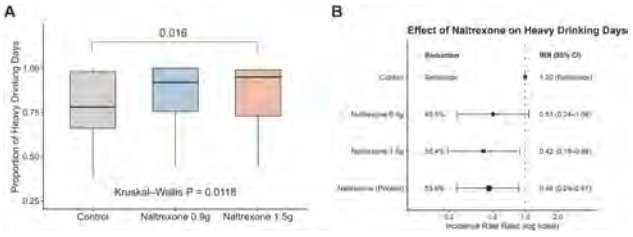
Yi-Zhou Jiang[1], [1]China-Japan Friendship Hospital

Background: Naltrexone is an established pharmacological therapy for alcohol use disorder (AUD); however, evidence in patients with alcohol-associated liver disease (ALD), particularly those with early-stage disease, remains limited. Long-acting formulations may improve adherence and treatment outcomes, but data on implantable naltrexone in this population are lacking. We aimed to evaluate the efficacy and safety of naltrexone implant in patients with mild ALD. **Methods:** This study represents a post hoc subgroup analysis of a multicenter, randomized, double-blind, placebo-controlled phase II trial (ClinicalTrials.gov identifier: NCT07014644). Adult patients with AUD who met predefined criteria for mild ALD at baseline were included. Participants were randomized to receive

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naltrexone implant (0.9 g or 1.5 g) or placebo and followed for 24 weeks. The primary endpoint was the proportion of heavy drinking days (PHDD). Secondary endpoints included abstinence-related outcomes and breath alcohol concentration. Safety was assessed by treatment-emergent adverse events. **Results:** Among 149 participants with mild ALD, naltrexone implant was associated with a significant reduction in PHDD at week 24, with the greatest effect observed in the 1.5 g group. In regression analyses, naltrexone treatment was associated with a clinically meaningful reduction in the incidence rate of heavy drinking days compared with placebo. Secondary outcomes showed consistent trends favoring naltrexone but did not reach statistical significance. Breath alcohol concentration analyses suggested that the treatment effect was more pronounced early after implantation and attenuated over time. Naltrexone implant was generally well tolerated, with no increase in serious adverse events or evidence of hepatotoxicity. **Conclusion:** In this post hoc subgroup analysis, naltrexone implant was associated with reduced heavy drinking and demonstrated an acceptable safety profile in patients with mild ALD. These findings support the potential role of implantable naltrexone as a novel adherence-optimizing strategy in early-stage ALD and warrant confirmation in prospective, adequately powered studies.



Disclosures: Yi-Zhou Jiang:Nothing to Disclose.

3598 | INOSITOL HEXAPHOSPHATE PROTECTS AGAINST METABOLIC ASSOCIATED STEATOHEPATITIS IN MICE VIA THE PI3K/AKT/PLA2G2A SIGNALING PATHWAY

Zhao Chen[1] Huiying Rao[1], [1]Peking University Hepatology Institute

Background: Recently, inositol hexakisphosphate (Phytic acid, IP6), primarily extracted from plants, possess anti-oxidative and anti-tumor effects. However, whether it can alleviate MASH remains unclear. This study aimed to explore the preventive and therapeutic effects and mechanisms of IP6 on MASH phenotypes and the alteration of metabolomics and transcriptomic profiles in MASH mice. **Methods:** A western diet combined with low doses of CCl4 (WD/CCl4) was used to induce MASH in mice and evaluate the protective effects of IP6. Additionally, the effects of IP6 and in vitro using free fatty acid (FFA)-treated HepG2 cells and activated hepatic stellate cells were investigated. Assessments of transcriptomics, metabolomics, and lipidomics analyses were conducted to explore potential molecular mechanisms. Furthermore, the involvement of the PI3K/Akt/PLA2G2A signaling pathway was examined through in vivo and in vitro experiments, including molecular docking, PLA2G2A overexpression assays, and measurements of key fibrotic markers (α-SMA and COL-1) and lipid accumulation. **Results:** The results showed that pretreatment with IP6 significantly reduced obesity, fibrosis and lipid accumulation, alleviated insulin resistance, and prevented hyperglycemia in MASH mice. IP6 also alleviated free fatty acid (FFA)-induced lipid accumulation in HepG2 cells. Transcriptomics analysis of the liver revealed that IP6 reversed MASH-related transcriptomic changes, suppressing the expression of pro-fibrotic, pro-inflammatory, and lipid-metabolic genes. Integrated metabolomics and lipidomics revealed that the preventive effect of IP6 against MASH was mediated through the rectification of disordered glycerophospholipid metabolism. Mechanistically, both in vivo and in vitro experiments showed that IP6 inhibited MASH-induced elevation of PI3K and Akt phosphorylation. Molecular docking suggested a strong binding affinity between AKT and PLA2G2A. Importantly, in vitro overexpression of PLA2G2A completely abolished IP6-mediated inhibition of lipid accumulation and the expression of key fibrotic markers (α-SMA and COL-1). Collectively, these findings indicate that IP6 modulates glycerophospholipid metabolism through the PI3K/Akt/PLA2G2A signaling pathway in MASH. **Conclusion:** Our findings demonstrate that IP6 protects against MASH by inhibiting the PI3K/Akt signaling pathway, thereby downregulating PLA2G2A expression and improving glycerophospholipid homeostasis in hepatocytes, which provides novel insights into MASH treatment.

Disclosures: Zhao Chen:Nothing to Disclose, Huiying Rao:Nothing to Disclose.

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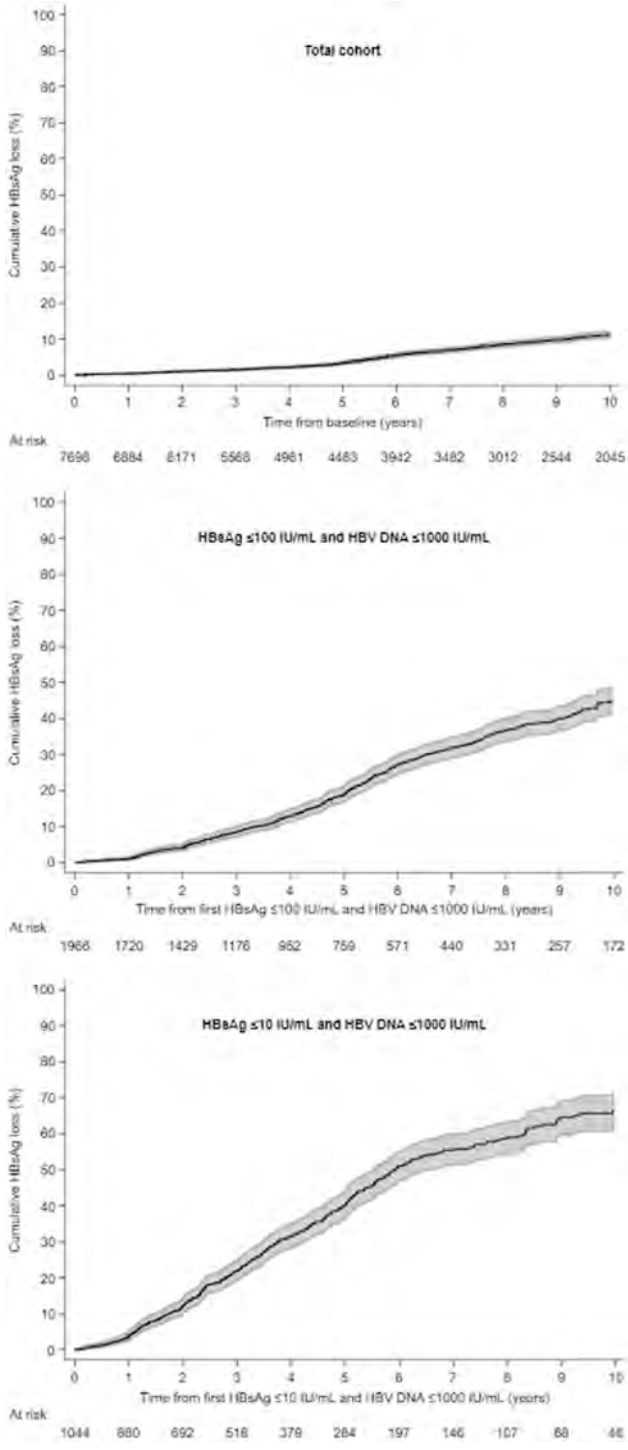
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4001 | ◆ PREDICTORS OF FUNCTIONAL CURE AMONG PATIENTS WITH LOW HBSAG LEVELS: RESULTS OF THE SIGNAL STUDY

Sanam Tabataba Vakili[1] Grishma Hirode[2] Andrew Mendlowitz[2] Leila Amiri[1] Aaron Vanderhoff[2] Saima Naim[1] Adam Gehring[3] Scott Fung[3] Jordan Feld[4], [1]Toronto Centre for Liver Disease, University Health Network, Canada, [2]Toronto Centre for Liver Disease, University Health Network, Canada;Viral Hepatitis Care Network,UHN, [3]University Health Network, [4]Toronto General Hospital

Background: Lower hepatitis B surface antigen (HBsAg) levels are a well-established predictor of higher rates of functional cure, defined as HBsAg loss. However, whether there are additional predictors among chronic hepatitis B (CHB) patients with already low HBsAg levels remains unknown. We aimed to examine factors associated with HBsAg loss among patients with low HBsAg levels and HBV DNA below treatment thresholds. **Methods:** Cohort study of CHB patients with ≥1 qHBsAg measurement ≥0.05 IU/mL between 2010-2022. We compared characteristics of patients with and without HBsAg loss in the total cohort at the first qHBsAg measurement (baseline), and in subgroups who had ≥1 instance of HBsAg ≤10 and ≤100 IU/mL with HBV DNA ≤1000 IU/mL at first occurrence, regardless of duration in that state, treatment or phase of infection. Cumulative incidence and factors associated with HBsAg loss were analyzed using survival analysis methods. **Results:** Among the total cohort of 8239 patients (mean age 48 years, HBsAg 2.6 $\log_{10}$ IU/mL, HBV DNA 3.4 $\log_{10}$ IU/mL, median ALT 29 U/L, 56% male, 81% Asian, 76% HBeAg-neg, 7% cirrhosis), 558 had HBsAg loss with a 5-year cumulative probability of 3.3% over a mean follow-up of 6.1 years. Among the subgroup of 2230 patients with HBsAg ≤100 IU/mL and HBV DNA ≤1000 IU/mL (mean age 54 years, HBsAg 1.1 $\log_{10}$ IU/mL, HBV DNA 1.5 $\log_{10}$ IU/mL, median ALT 24 U/L, 64% male, 83% Asian, 90% HBeAg-neg, 13% cirrhosis), 522 had HBsAg loss with a 5-year cumulative probability of 19% over a mean follow-up of 7.4 years. Asian race (aHR 0.7) and presence of cirrhosis (aHR 0.7) were associated with lower rates of HBsAg loss ($p < 0.05$). Among the subgroup of 1288 patients with HBsAg ≤10 IU/mL and HBV DNA ≤1000 IU/mL (mean age 54 years, HBsAg 0.1 $\log_{10}$ IU/mL, HBV DNA 1.5 $\log_{10}$ IU/mL, median ALT 23 U/L, 63% male, 81% Asian, 92% HBeAg-neg, 11% cirrhosis), 516 had HBsAg loss with a 5-year cumulative probability of 40% over a mean follow-up of 7.3 years. After achieving this state, no factors remained significant on adjusted regression. **Conclusion:** Our results highlight that in addition to HBsAg levels, race and cirrhosis status are important predictors of HBsAg loss among patients who achieve HBsAg ≤100 IU/mL and HBV DNA ≤1000 IU/mL even once. Once HBsAg levels fall below 10 IU/mL, the probability of HBsAg loss is high enough that no clinical factors further predict clearance. These factors can help prioritize patients for curative treatment regimens.

Keywords: hepatitis B, HBsAg loss, HBV DNA, predictors, functional cure, cirrhosis



Disclosures: Sanam Tabataba Vakili:Nothing to Disclose, Grishma Hirode:Nothing to Disclose, Andrew

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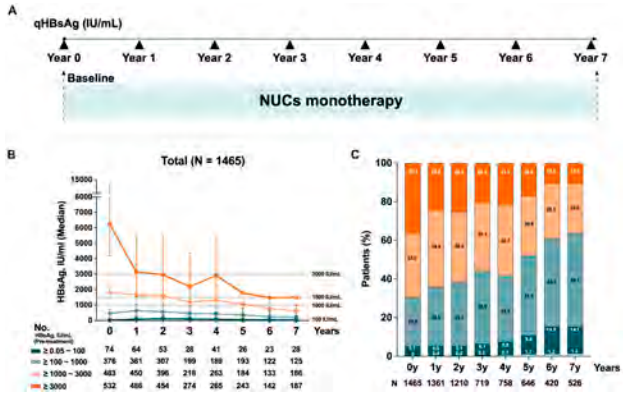
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4002 | SUSTAINED DECLINE OF SERUM QHBSAG DURING LONG-TERM NUCLEOS(T)IDE ANALOGS THERAPY IN CHRONIC HEPATITIS B: A 7-YEAR TRAJECTORY ANALYSIS

Shuyan Chen[1] Siru Zhao[2] Tongtong Meng[1] Xinyu Zhao[1] Xiaoqian Xu[1] Xiaoning Wu[1] Jialing Zhou[1] Xinyan Zhao[1] Xiaojuan Ou[1] Jidong Jia[1] Zhizhen Hu[3] Yameng Sun[1] Rong Fan[2] Hong You[1], [1]Beijing Friendship Hospital, Capital Medical University, [2]Department of Infectious Diseases, Nanfang Hospital, Southern Medical University, [3]Hansoh Pharmaceutical Group Co, Ltd, Shanghai, China

Background: Quantitative hepatitis B surface antigen (qHBsAg) is the critical predictor of functional cure in chronic hepatitis B (CHB). However, the long-term dynamics of qHBsAg during nucleos(t)ide analogues (NUCs) therapy, particularly in treatment-naïve patients, remain unclear. This study aimed to elucidate the longitudinal trajectory of serum qHBsAg in treatment-naïve CHB patients undergoing 7 years of NUCs monotherapy. **Methods:** Treatment-naïve CHB patients who initiated NUCs monotherapy treatment were enrolled from three different cohorts. Baseline and serial on-treatment qHBsAg levels were prospectively collected over 7 years of continuous antiviral therapy. **Results:** A total of 1465 CHB patients with longitudinal qHBsAg data over 7 years of antiviral therapy were included. The cohort was predominantly male (75%), with a mean age of 42 years. At baseline, 53.0% (n = 777) were HBeAg-positive, 48.1% (n = 705) had cirrhosis, and the median qHBsAg level was 1993.0 IU/mL at baseline. In patients with baseline qHBsAg > 3000 IU/mL (n = 532, 36.3%), the median qHBsAg level declined from 6233.6 IU/mL to 3154.9 IU/mL during the first year, followed by a further decrease from 2971.1 IU/mL to 1509.5 IU/mL over the subsequent 6 years. The probability of achieving qHBsAg ≤ 3000 IU/mL was 22.7% at year 1, rising gradually to 64.2% by year 7. In patients with baseline qHBsAg ≥ 1000 ~ 3000 IU/mL (n = 483, 33.0%) and ≥ 100 ~ 1000 IU/mL (n = 376, 25.6%), median levels decreased from 1828.6 IU/mL (baseline) to 639.10 IU/mL (year 7), and from 468.9 IU/mL (baseline) to 229.0 IU/mL (year 7), respectively. These longitudinal qHBsAg trajectories were consistent regardless of HBeAg status or cirrhosis. In patients with baseline HBsAg > 3000 IU/mL, multivariable analysis identified detectable HBV DNA at year 2 as an independent factor associated with reduced likelihood of achieving qHBsAg ≤ 3000 IU/mL (HR, 0.611; 95% CI, 0.403-0.925; P = 0.020). **Conclusion:** During 7 years of NUCs monotherapy, serum qHBsAg levels declined progressively in treatment-naïve CHB patients. Notably, those with baseline qHBsAg > 3000 IU/mL exhibited a rapid decline in the first year, followed by a slow but overall declining trend over the next 6 years.



Disclosures: Shuyan Chen:Nothing to Disclose, Siru Zhao:Nothing to Disclose, Tongtong Meng:Nothing to Disclose, Xinyu Zhao:Nothing to Disclose, Xiaoqian Xu:Nothing to Disclose, Xiaoning Wu:Nothing to Disclose, Jialing Zhou:Nothing to Disclose, Xinyan Zhao:Nothing to Disclose, Xiaojuan Ou:Nothing to Disclose, Jidong Jia:Nothing to Disclose, Zhizhen Hu:Nothing to Disclose, Yameng Sun:Nothing to Disclose, Rong Fan:Nothing to Disclose, Hong You:Nothing to Disclose.

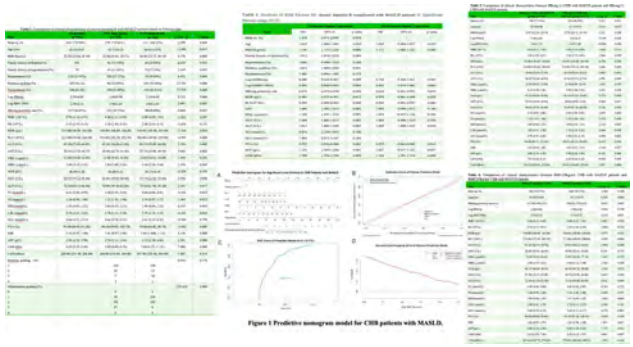
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4003 | IMPACT OF METABOLIC AND VIRAL FACTORS ON SIGNIFICANT LIVER FIBROSIS IN TREATMENT-NAÏVE PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE AND CHRONIC HEPATITIS B: A CROSS-SECTIONAL STUDY OF 562 LIVER BIOPSIES

Weihua Cao[1] Yao Xie[1] Minghui Li[1], [1]Beijing Ditan Hospital, Capital Medical University

Background: The coexistence of metabolic dysfunction-associated steatotic liver disease (MASLD) and chronic hepatitis B (CHB) is increasingly recognized, but the independent drivers of significant liver fibrosis in this dual-aetiology population remain unclear, especially in treatment-naïve patients. This study aimed to identify independent metabolic and viral risk factors for significant fibrosis (F ≥ 2) using liver biopsy as the gold standard. **Methods:** A cross-sectional study was conducted on 562 treatment-naïve patients with concurrent MASLD and CHB confirmed by liver biopsy. All patients underwent clinical, laboratory, and transient elastography assessments. Liver fibrosis was staged according to the Metavir system (F0–F4). Significant fibrosis was defined as Metavir F ≥ 2. Univariate and multivariable logistic regression analyses were performed to identify independent risk factors for significant fibrosis. Subgroup analyses were performed by stratifying patients according to HBeAg status (for metabolic factors) and BMI < 25 vs. ≥ 25 kg/m² (for viral factors). Interaction was formally tested using product terms. **Results:** Among the 562 treatment-naïve patients with concurrent MASLD and CHB (mean age 42.53 ± 9.87 years, 72.95% male), 192 (34.2%) had significant liver fibrosis (Metavir F ≥ 2). Compared with patients at F0-1, those with significant fibrosis had significantly higher BMI, higher prevalence of diabetes mellitus and dyslipidemia, lower platelet count, higher LSM value, and a lower proportion of HBeAg positivity (all P < 0.05) in Table 1. Multivariable logistic regression identified that higher BMI (OR = 1.173, 95% CI: 1.082–1.525, P < 0.001), HBeAg negative status (OR for HBeAg positivity = 0.624, 95% CI: 0.421–0.925, P = 0.019), lower platelet count (OR = 0.994, 95% CI: 0.991–0.997, P < 0.001), lower prothrombin time activity (PTA) (OR = 0.979, 95% CI: 0.962–0.996, P = 0.014), and higher liver stiffness measurement (LSM) (OR = 1.344, 95% CI: 1.191–1.516, P < 0.001) were independent risk factors for significant fibrosis, while conventional metabolic and viral parameters such as diabetes, dyslipidemia, HBV DNA, and HBsAg lost their independent significance after adjustment in Table 2. Subgroup analyses showed that the effect of BMI on fibrosis was significant only in HBeAg (-) patients (P for interaction = 0.009) in Table 3, and the effect of HBeAg negative status on fibrosis in Table 4 was significant only in patients with BMI < 25 kg/m² (P for interaction = 0.02), indicating effect modification by HBeAg status and BMI, respectively. **Conclusion:** In treatment-naïve CHB-MASLD patients, high BMI, HBeAg negativity, low PLT, low PTA, and elevated LSM are independent risk factors for significant fibrosis, with metabolic factors and HBeAg negativity driving progression, supporting early risk stratification based on metabolic and virological parameters.



Disclosures: Weihua Cao:Nothing to Disclose, Yao Xie:Nothing to Disclose, Minghui Li:Nothing to Disclose.

4004 | DEVELOPMENT OF A SIMPLE METHOD FOR MEASURING HBVCCCDNA USING CHIP-BASED DIGITAL PCR

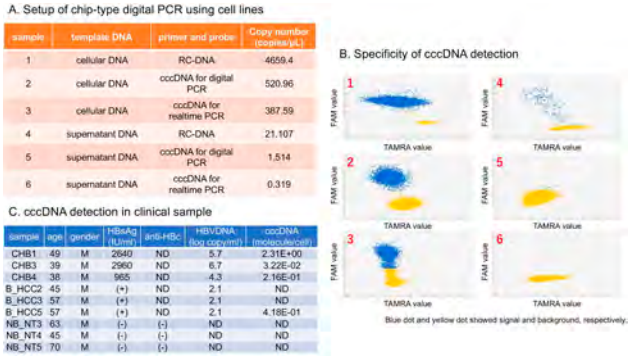
Yoshiki Murakami[1] Takahide Niijima[2] Yoshihiko Yano[3] Takashi Honda[4] Tomohiro Umezu[2] Masahiko Kuroda[2], [1]Tokyo Medical Univesity/Asahi University, [2]Tokyo Medical University, [3]Kobe University, [4]Nagoya University Graduate School of Medicine

Background: A major technical challenge in hepatitis B virus (HBV) research is the selective detection of covalently closed circular DNA (cccDNA) from the more abundant relaxed circular DNA (rcDNA). Because these DNA species share overlapping HBV genomic sequences, conventional PCR can amplify both, limiting cccDNA-specific quantification without laborious pretreatment. We developed a chip-based digital PCR method for simple detection and quantification of HBV cccDNA without enzymatic digestion pretreatment. **Methods:** QuantStudio chip-based digital PCR was used. Primers were designed to flank the HBV direct repeat region, and a probe was designed to recognise the PCR product. Genomic DNA from Hep38.7-tet cells, which contain one cccDNA molecule per cell, was used as the template. RNase P, present as two copies per cell, served as an internal control to calculate cccDNA copies per cell. We also analyzed liver biopsy tissue from 4 cases of chronic hepatitis B (CHB) treated at Kobe University Hospital, 7 cases of HBV-positive

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hepatocellular carcinoma (BHCC), 3 cases of non-cancerous tissue (NBNT) derived from HCC without HBV infection. **Results:** HBV cccDNA was quantified directly from cell-derived genomic DNA without digestion of single-stranded or gapped DNA. No cccDNA signal was detected in cell culture supernatant DNA, which lacks cccDNA, indicating selective discrimination from rcDNA-dominant samples. In cell-derived DNA, both cccDNA and rcDNA were detected, allowing evaluation of intracellular HBV DNA species. This assay detected the number of cccDNA copies per cell in liver biopsy tissue and resected material after RNase P treatment. As a result, the cccDNA copy number was measured in 3 out of 4 cases of chronic hepatitis B (CHB), 1 out of 7 cases of hepatocellular carcinoma (BHCC), and 0 out of 3 cases of non-B hepatitis (NBNT). **Conclusion:** This chip-based digital PCR method enables simple quantification of HBV cccDNA distinct from rcDNA. Unlike droplet-based digital PCR, which requires enzymatic removal of non-cccDNA species, this method omits this step, simplifying workflow and reducing cost and DNA loss. RNaseP-based cell number correction enables absolute quantification of cccDNA copies per cell, supporting applications in HBV reactivation risk assessment, treatment monitoring and drug development endpoints.



sample	template DNA	primer and probe	Copy number (copies/μL)
1	cellular DNA	RC-DNA	4659.4
2	cellular DNA	cccDNA for digital PCR	520.96
3	cellular DNA	cccDNA for realtime PCR	387.59
4	supernatant DNA	RC-DNA	21,107
5	supernatant DNA	cccDNA for digital PCR	1,514
6	supernatant DNA	cccDNA for realtime PCR	0.319

sample	age	gender	HBsAg (IU/ml)	anti-HBc	HBVDNA (log copy/ml)	cccDNA (molecule/cell)
CHB1	49	M	2640	ND	5.7	2.31E+00
CHB3	39	M	2960	ND	6.7	3.22E-02
CHB4	38	M	965	ND	4.3	2.16E-01
B_HCC2	45	M	(+)	ND	2.1	ND
B_HCC3	57	M	(+)	ND	2.1	ND
B_HCC5	57	M	(+)	ND	2.1	4.18E-01
NB_NT3	63	M	(-)	(-)	ND	ND
NB_NT4	45	M	(-)	(-)	ND	ND
NB_NT5	70	M	(-)	(-)	ND	ND

Disclosures: Yoshiki Murakami:Nothing to Disclose, Takahide Niijima:Nothing to Disclose, Yoshihiko Yano:Nothing to Disclose, Takashi Honda:Nothing to Disclose, Tomohiro Umezu:Nothing to Disclose, Masahiko Kuroda:Nothing to Disclose.

4005 | DYNAMIC CHANGES IN HBSAG OUTPERFORM HBV RNA IN PREDICTING RESPONSE TO PEGIFN-α ADD-ON THERAPY IN NUCLEOS(T)IDE ANALOGUE-EXPERIENCED PATIENTS WITH CHRONIC HEPATITIS B

Ziyu Zhang[1] Minghui Li[2], [1]Beijing Ditan Hospital affiliated Capital Medical University, [2]Capital Medical University Affiliated Beijing Ditan Hospital

Background: HBV RNA has been considered a surrogate marker of HBV covalently closed circular DNA (cccDNA) transcriptional activity; however, its predictive value for treatment response during PegIFN-α add-on therapy in nucleos(t)ide analogue (NA)-experienced patients with chronic hepatitis B (CHB) remains unclear. This study aimed to compare the predictive performance of HBV RNA and dynamic HBsAg changes for treatment response. **Methods:** A total of 295 NA-experienced patients with CHB who received PegIFN-α add-on therapy on the basis of ongoing NA treatment were retrospectively enrolled. The primary endpoint was an HBsAg decline $\geq$1 log IU/mL at week 48. Correlations between HBV RNA and virological markers were analyzed. Receiver operating characteristic (ROC) curve analysis and logistic regression analysis were performed to evaluate the predictive value of HBV RNA and dynamic HBsAg changes for treatment response. **Results:** At baseline, HBV RNA was positively correlated with HBsAg ($r = 0.597$, $P < 0.001$), HBV DNA ($r = 0.590$, $P < 0.001$), and HBeAg ($r = 0.792$, $P < 0.001$). At week 48, 28.52% (73/256) of patients achieved an HBsAg decline $\geq$1 log IU/mL. The magnitude of HBsAg decline at weeks 12 and 24 was significantly greater in responders than in non-responders (both $P < 0.001$), whereas HBV RNA clearance and HBV DNA clearance showed no significant predictive value (both $P > 0.05$).ROC analysis demonstrated that the area under the curve (AUC) of HBsAg decline at week 12 for predicting week-48 response was 0.815, which further increased to 0.879 at week 24. Multivariate logistic regression analysis identified an HBsAg decline $\geq$1 log at week 24 as an independent predictor of week-48 response (OR = 491.509, $P < 0.001$). **Conclusion:** HBV RNA may reflect HBV transcriptional activity but has limited value in predicting treatment response to PegIFN-α add-on therapy. In contrast, early on-treatment dynamic changes in HBsAg demonstrated superior predictive performance and may serve as an important marker for individualized treatment strategies in NA-experienced patients with CHB.

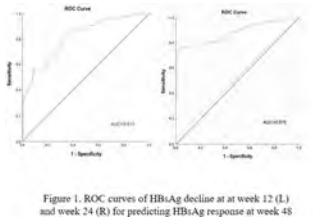


Figure 1. ROC curves of HBsAg decline at at week 12 (L) and week 24 (R) for predicting HBsAg response at week 48

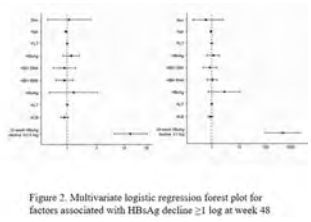


Figure 2. Multivariate logistic regression forest plot for factors associated with HBsAg decline ≥1 log at week 48

Disclosures: Ziyu Zhang:Nothing to Disclose, Minghui Li:Nothing to Disclose.

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4006 | MIDKINE GENE EXPRESSION IS ASSOCIATED WITH FIBROTIC PROGRESSION IN CHRONIC HEPATITIS B PATIENTS

Shasha Li[1] Meng Yi[2] Olivia Mezzetti[3] Thien Nguyen[3] Min Xu[3] Shuhan Li[2] Ning Jiang[4] Jing Xu[4] Yufeng Gao[5] Shilin Li[2] Raymond Chung[3] Limin Chen[2] Jiabin Li[5] Xiaoqiong Duan[2] Wenyu Lin[3], [1]The Second People's Hospital of Fuyang City, China, [2]Chinese Academy of Medical Sciences and Peking Union Medical College, [3]Massachusetts General Hospital, Harvard Medical School, [4]The Second People's Hospital of Fuyang City, [5]The First Affiliated Hospital of Anhui Medical University

Background: Chronic hepatitis B (CHB) is a leading cause of liver cirrhosis and hepatocellular carcinoma (HCC). Blood-based biomarkers have been proposed as an alternative to liver biopsy for noninvasive liver disease assessment. We sought to identify the genes significantly associated with the occurrence of hepatic fibrosis in CHB patient peripheral blood mononuclear cells (PBMCs) and preliminarily explore their regulatory mechanisms. **Methods:** We recruited 104 patients with confirmed chronic HBV infection, 79 patients in the inactive carrier stage of chronic HBV (CHBV-I) and 25 patients with advanced fibrotic CHB (CHB-F), from The Second People's Hospital of Fuyang City. We also recruited 33 healthy subjects (HC) with no history of HBV infection. We selected 16 genes that are associated with liver fibrosis-related pathways and examined the transcriptional profiling of these genes in PBMCs from CHB patients. Midkine (MDK) expression was assessed in HepAD38 cells with or without tetracycline (to inhibit HBV replication), uninfected and HBV-infected NTCP-HepG2 cells, pAAV-HBV1.2 carrier mice, and HBV transgenic (HBV-Tg) mice. MDK siRNA and recombinant MDK supplementation was used to determine its role in pro-fibrotic gene expression. **Results:** We identified 14 regulated genes in PBMCs from CHB patients. Six of these genes (MDK, AFP, VCAM1, AEBP1, LOXL2 and IGFBP7) were significantly upregulated in PBMCs from CHBV-I and CHBV-F patients compared to the HC group. The expression of MDK and AFP were also significantly increased in CHBV-F patients compared to CHBV-I patients. We observed a significant moderate positive correlation between the expression of MDK, VCAM1, AFP, LOXL2 and the progression of CHB-I and CHB-F, while CREB1 and FBN1 were negatively correlated with CHB-I and CHB-F progression. We also found that HBV infection significantly increased MDK expression in HBV-infected NTCP-HepG2 cells, precision-cut liver slices (PCLS) and mouse models. Knockdown of MDK significantly suppressed the induction of pro-fibrotic gene expression by TGF-β1, while MDK recombinant protein increased pro-fibrotic gene expression. **Conclusion:** We found that advanced chronic hepatitis B is associated with increased MDK in PBMCs. MDK is a multifunctional secreted protein which can be induced by TGF-β1 and promotes fibrosis. These findings suggest that MDK could be used as a biomarker in PBMCs for CHB-induced liver fibrosis and as a possible target for therapeutic intervention.

Disclosures: Shasha Li:Nothing to Disclose, Meng Yi:Nothing to Disclose, Olivia Mezzetti:Nothing to Disclose, Thien Nguyen:Nothing to Disclose, Min Xu:Nothing to Disclose, Shuhan Li:Nothing to Disclose, Ning Jiang:Nothing to Disclose, Jing Xu:Nothing to Disclose, Yufeng Gao:Nothing to Disclose, Shilin Li:Nothing to Disclose, Raymond Chung:Nothing to Disclose, Limin Chen:Nothing to Disclose, Jiabin Li:Nothing to Disclose, Xiaoqiong Duan:Nothing to Disclose.

4008 | LIMITED CLINICAL UTILITY OF BASELINE HBV DNA TESTING IN PATIENTS UNDERGOING AUTOLOGOUS STEM CELL TRANSPLANTATION

Sanam Tabataba Vakili[1] Leila Amiri[1] Lauren Finlay[2] Christine Chen[2] Michael Crump[2] Scott Fung[3] Jordan Feld[4], [1]Toronto Centre for Liver Disease, Toronto General Hospital, University Health Network, Toronto, Can, [2]Princess Margaret Cancer Centre, University Health Network, Toronto, Canada, [3]University Health Network, [4]Toronto General Hospital

Background: Hepatitis B virus (HBV) reactivation is a recognized complication of autologous stem cell transplantation (auto-SCT), particularly after prior HBV exposure. International guidelines recommend serologic screening before transplantation, but the role of baseline HBV DNA testing, particularly in HBsAg-negative patients, remains unclear. We evaluated the clinical utility of baseline HBV DNA testing in auto-SCT candidates. **Methods:** We conducted a retrospective study of adults undergoing autologous stem cell transplantation at the University Health Network, Toronto, from 2017-2022. Baseline HBV serology (HBsAg, anti-HBc, anti-HBs) and HBV DNA testing results were reviewed. HBV DNA testing was performed in HBsAg-positive and anti-HBc-positive patients, and selectively in isolated anti-HBs-positive patients with unclear vaccination history. Antiviral prophylaxis was routinely used in HBsAg-positive and anti-HBc-positive patients, but not in isolated anti-HBs-positive patients. Patients were categorized as HBsAg-positive, HBsAg-negative/anti-HBc-positive, isolated anti-HBs-positive, or triple-negative. HBV DNA results, antiviral prophylaxis, liver biochemistry, and HBV-related outcomes were assessed. **Results:** Among

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1,600 patients (60% male, median age 60.5 years [IQR 53.2–66.2]), most undergoing auto-SCT for multiple myeloma and lymphoma, baseline serologic profiles were HBsAg-positive in 18 patients, HBsAg-negative/anti-HBc-positive in 134, isolated anti-HBs-positive in 393, and triple-negative in 1,055 (Table 1). HBV DNA testing was performed in 298 patients (18.6%). Among tested patients, HBV DNA was detectable in 10/18 (55.6%) HBsAg-positive patients, 15/131 (11.5%) anti-HBc-positive patients, and 4/142 (2.8%) isolated anti-HBs-positive patients, while no triple-negative patients had detectable HBV DNA. Three additional HBV DNA–positive patients could not be classified because of missing baseline serology. In anti-HBc-positive patients, detectable HBV DNA was low level or intermittent and did not alter antiviral management, as all received prophylaxis based on serologic status alone. Among isolated anti-HBs-positive patients, HBV DNA levels were very low (< 10–50 IU/mL), and none developed HBV-related hepatitis or transplant-related hepatic complications. **Conclusion:** Routine baseline HBV DNA testing demonstrated limited clinical utility in auto-SCT candidates beyond standard HBV serologic screening. HBV DNA results did not alter management in anti-HBc-positive patients and had very low diagnostic yield in isolated anti-HBs-positive and triple-negative individuals. These findings support limiting routine HBV DNA testing to HBsAg-positive patients. In immunosuppressed patients with unexplained ALT elevation, repeat HBsAg testing remains important, particularly in those with humoral immune dysfunction. **HBV DNA testing; auto-SCT; HBV reactivation**

Table 1. Baseline HBV DNA positivity by serologic group in auto-SCT candidates (2017–2022)

HBV serologic group	Total patients, n	Underwent HBV DNA testing, n (%)	HBV DNA positive, n (%) among those tested	HBV DNA negative, n
HBsAg-positive	18	18 (100.0%)	10 (55.6%)	8
HBsAg-negative/anti-HBc-positive	134	131 (97.8%)	15 (11.5%)	116
Isolated anti-HBs-positive	393	142 (36.1%)	4 (2.8%)	138
Triple-negative	1,055	7 (0.7%)	0 (0.0%)	7
Total	1,600	298 (18.6%)	29 (9.7%)	269

Footnote: Percent HBV DNA positivity is calculated among patients who underwent HBV DNA testing within each serologic group. Overall, 32 patients had at least one detectable HBV DNA result; 3 could not be assigned to a serologic group because of missing baseline serology and are therefore not included in the group-specific patient counts.

Disclosures: Sanam Tabataba Vakili:Nothing to Disclose, Leila Amiri:Nothing to Disclose, Lauren Finlay: Nothing to Disclose, Christine Chen:Nothing to Disclose, Michael Crump:Nothing to Disclose, Scott Fung:Gilead Sciences: Advisor, Gilead Sciences: Speaking and Teaching, Abbvie: Speaking and Teaching, Abbvie: Advisor, Novo Nordisk: Speaking and Teaching, Novo Nordisk: Advisor, Novo Nordisk: Grant/Research Support, GSK: Advisor, GSK: Speaking and Teaching, Lupin: Speaking and Teaching, AstraZeneca: Speaking and Teaching, AstraZeneca: Advisor, Jordan Feld:AbbVie: Advisor, Bluejay: Advisor, Gilead: Advisor, GlaxoSmithKline: Advisor, Precision Biosciences: Advisor, Arbutus: Advisor, Astra Zeneca: Advisor, Roche: Advisor, Vir: Advisor, Orphalan: Advisor, Pfizer: Advisor, Abbvie: Grant/Research Support, Gilead: Grant/Research Support, GlaxoSmithKline: Grant/Research Support, Atea: Advisor, Atea: Grant/Research Support, Roche: Grant/Research Support, Vir: Grant/Research Support, Mirum: Grant/Research Support, Mirum: Advisor, AusperBio: Advisor.

4009 | LONGITUDINAL QHBSAG TRAJECTORIES PREDICT FUNCTIONAL CURE IN CHRONIC HEPATITIS B: A LARGE REAL-WORLD STUDY

Leila Amiri[1] Sanam Tabataba Vakili[2] Aaron Vanderhoff[3] Andrew Mendlowitz[4] Grishma Hirode[4] Saima Naim[2] Adam Gehring[5] Scott Fung[5] Jordan Feld[5], [1]University Health Network, [2]Clinical Research Coordinator, [3]Community Outreach Coordinators, [4]Research Fellow, [5]Clinical Research Staff – Hepatology

Background: Chronic hepatitis B remains a major cause of cirrhosis and hepatocellular carcinoma worldwide. Functional cure, defined as hepatitis B surface antigen (HBsAg) loss, is rare but associated with favorable long-term outcomes. While quantitative HBsAg (qHBsAg) is a promising biomarker, the value of longitudinal qHBsAg trajectories compared with single measurements and other routine biomarkers has not been well defined. We aimed to identify longitudinal biomarkers predictive of HBsAg loss. **Methods:** We conducted a cohort study of patients with chronic hepatitis B followed at the Toronto Centre for Liver Disease between 2010 and 2022 with ≥ 2 visits and ≥ 6 months follow-up. Longitudinal qHBsAg trajectories were modeled using the longitudinal discriminant analysis (LoDA) framework proposed by Fan et al. (GOLDEN Rule, 2024). Separate mixed-effects models were fitted for patients with and without HBsAg loss. We evaluated whether HBV DNA and ALT improved prediction beyond qHBsAg alone. **Results:** Among 7338 patients with chronic hepatitis B (median age 48.1 years, 56.2% male, 82.2% Asian, median follow-up 84.1 months), 552 (7.5%) achieved HBsAg

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loss. The LoDA-based longitudinal qHBsAg-only model demonstrated excellent predictive performance for HBsAg loss (AUC 0.965, 95% CI 0.953–0.975; sensitivity 94.2%; specificity 96.4%) and identified patients a mean of 21.2 months before HBsAg loss. Addition of HBV DNA and ALT did not meaningfully improve predictive performance, as no model improved the AUC by more than 0.0004 beyond longitudinal qHBsAg alone.Compared with a single baseline qHBsAg measurement, the longitudinal model showed significantly greater discrimination for HBsAg loss (AUC 0.965 vs 0.830; DeLong $p < 0.001$), with the greatest improvement observed among patients with baseline qHBsAg > 10000 IU/mL (AUC 0.985 vs 0.420). Using the optimal LoDA threshold defined by the Youden index, 768 (10.5%) patients were classified into the predicted HBsAg loss group and 6570 (89.5%) into the predicted non-loss group, with 5-year cumulative HBsAg loss rates of 27.6% versus 0.4%, respectively.Among 1044 patients with baseline qHBsAg >10000 IU/mL, the predicted likelihood of HBsAg loss increased from 0.4% in patients with minimal qHBsAg decline (< 1 $\log_{10}$; $n = 751$) to 8.8% with moderate decline (1–2 $\log_{10}$; $n = 194$) and 61.6% among those with large decline (≥ 2 $\log_{10}$; $n = 99$). **Conclusion:** Longitudinal qHBsAg trajectories accurately predicted functional cure nearly two years before HBsAg loss and substantially outperformed single baseline qHBsAg measurements, particularly among patients with high baseline qHBsAg levels. Addition of HBV DNA and ALT provided minimal incremental predictive value beyond longitudinal qHBsAg alone. These findings support serial qHBsAg monitoring as a clinically applicable approach for early functional cure prediction and patient stratification in chronic hepatitis B.

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4010 | QUANTITATIVE HBSAG LEVELS AND POTENTIAL ELIGIBILITY FOR FUTURE FUNCTIONAL CURE THERAPIES AMONG NUCLEOS(T)IDE ANALOGUE–TREATED AND UNTREATED INDIVIDUALS WITH CHRONIC HEPATITIS B IN ALBERTA, CANADA

Carla Coffin[1] Stephen Congly[1] Brendan Lethebe[1] Mayur Brahmania[1] Laura Stinton[1] Matthew Sadler[1] Karen Doucette[2] Conar O'Neil[2] Vanessa Meier-Stephenson[2] Robert Bailey[3] Mang Ma[2] Carlos Moctezuma-Velazquez[2] Jordyn Vienneau[1] Pam Crotty[1] Carmen Charlton[4], [1]University of Calgary, [2]University of Alberta, [3]Bailey Health Clinic, [4]Provincial Laboratory for Public Health

Background: Quantitative hepatitis B surface antigen (qHBsAg) is an important biomarker for refining chronic hepatitis B management and identifying individuals who may be eligible for future finite functional cure therapies. We used linked laboratory and administrative health data to evaluate qHBsAg levels and longitudinal trends among untreated and nucleos(t)ide analogue (NA)-treated individuals with chronic hepatitis B in Alberta. **Methods:** Linked administrative health data were used to identify individuals with hepatitis B who underwent qHBsAg testing using the Abbott ARCHITECT assay between 2015 and 2023. Laboratory results were linked with clinical encounter and medication dispensing records to compare baseline and follow-up qHBsAg levels among NA-treated and untreated individuals. **Results:** A total of 6,507 unique individuals with qHBsAg testing were identified. Median age was 46.3 years, and 44.2% were female. At baseline, defined as the index qHBsAg measurement, 1,404 (21.6%) individuals were receiving NA therapy, of whom 210 (39.7%) were HBeAg positive. Among NA-treated individuals, median HBV DNA was 10 IU/mL (IQR 10–18), and median qHBsAg was 1,463 IU/mL (IQR 361–4,508). In comparison, among 5,103 untreated individuals, 294 were HBeAg positive (11.5%; $p < 0.001$), median HBV DNA was significantly higher at 176 IU/mL (IQR 5.2–2,608; $p < 0.001$), and median qHBsAg was 2,264 IU/mL (IQR 30-4,851; $p = 0.279$).Follow-up qHBsAg data were available for 4,058 individuals, including 1,094 NA-treated and 2,964 untreated individuals. Median follow-up qHBsAg was 772 IU/mL overall, 832 IU/mL in the NA-treated group, and 660 IU/mL in the untreated group. The most recent follow-up was a median of 5.4 years after index HBsAg

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test for NA-treated individuals (n = 2003) and 3.8 years for untreated individuals (n = 2055). In the NA treatment group, qHBsAg levels were < 100 IU/mL in 481 (24.0%), ≥ 100–1000 IU/mL in 591 (29.5%), ≥ 1000–3000 IU/mL in 388 (19.4%), and ≥ 3000 IU/mL in 543 (27.1%). Among untreated individuals, corresponding values were 810 (39.4%), 299 (14.5%), 283 (13.8%), and 663 (32.3%), respectively. **Conclusion:** In this large cohort of individuals with chronic hepatitis B in Alberta, more than half of those with follow-up qHBsAg testing had levels < 1,000 IU/mL, including 53.5% of NA-treated individuals and 53.9% of untreated individuals. An additional 16.5% overall had qHBsAg levels between 1,000 and 3,000 IU/mL when last tested. These findings suggest that a significant proportion of people living with hepatitis B in Alberta are potentially eligible for future functional cure therapies.

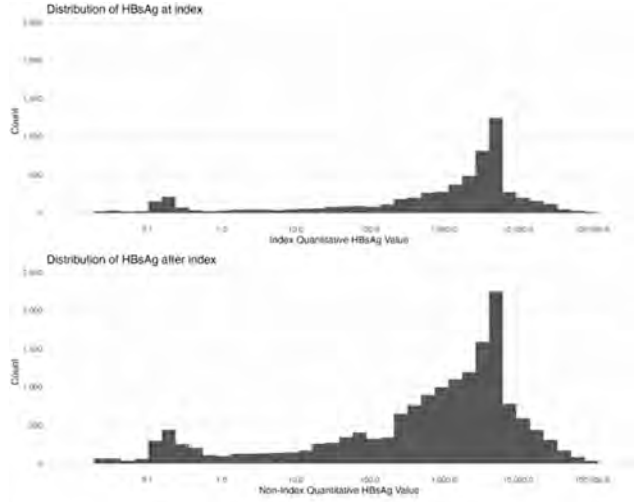


Figure 1. Distribution of quantitative hepatitis B surface antigen (qHBsAg) levels at index (top panel; n=6,507) and most recent follow-up (bottom panel; n=4,058) among individuals with chronic hepatitis B in Alberta. qHBsAg values (IU/mL) are displayed on a logarithmic scale.

Disclosures: Carla Coffin:Gilead: Grant/Research Support, GSK: Grant/Research Support, Janssen: Grant/Research Support, Gilead (paid to the University of Calgary): Consultant, Roche (paid to the University of Calgary): Consultant, GSK: Consultant, Gilead (paid to the University of Calgary): Speaking and Teaching, GSK (paid to the University of Calgary): Speaking and Teaching, Ausperbio: Funds Paid to the University of Calgary, Vir Pharmaceuticals: Funds Paid to the University of Calgary, Stephen Congly:Nothing to Disclose, Brendan Lethebe:Nothing to Disclose, Mayur Brahmania:Nothing to Disclose, Laura Stinton:Nothing to Disclose, Matthew Sadler:Nothing to Disclose, Karen Doucette:Roche: Grant/Research Support, GSK: Grant/Research Support, Altimmune: Grant/Research Support, Aligos: Grant/Research Support, Mirum: Grant/Research Support, Conar O'Neil:Nothing to Disclose, Vanessa Meier-Stephenson:AVIGAS Ltd: Stock – privately held company, Quadrumix Ltd: Royalties or patent beneficiary, Robert Bailey:Nothing to Disclose, Mang Ma:Nothing to Disclose, Carlos Moctezuma-Velazquez:Nothing to Disclose, Jordyn Vienneau:Nothing to Disclose, Pam Crotty:Nothing to Disclose, Carmen Charlton:Merck: Investigator initiated grant, Roche: Provided reagents and kits for research, GSK: Consultant.

4011 | HIGH FREQUENCY OF SERUM HEPATITIS B SURFACE ANTIGEN (HBSAG) < 3000 IU/ML AND THE ASSOCIATED FACTORS IN US PATIENTS WITH CHRONIC HEPATITIS B VIRUS (HBV) INFECTION

Ke-Qin Hu[1] Kim Huynh[2] Tung Huynh[3], [1]University of California, Irvine, [2]Fairmont Preparatory Academy, [3]University of California Irvine Medical Center

Background: Studies demonstrated a low serum HBsAg level is associated with spontaneous HBsAg clearance and treatment-induced HBV functional cure. However, the actual frequency of low HBsAg level is unknown in US patients with chronic HBV infection. The present study assessed the distribution of serum HBsAg level, the frequency of HBsAg < 3000 IU/mL and the associated factors in US patients with chronic HBV infection. **Methods:** A single center retrospective study on 74 cases with chronic HBV infection, regular follow-up (f/u) in our liver clinic, UCI Health, and HBsAg quantitative tests (Immunometric Immunoassay with cut off value of 0.05 IU/mL, sensitivity > 99.9%, and specificity of 99.4%, QUEST) every 6 months for a total 36 months. The data were collected by chart review; Chi square test and likelihood ratio test were used for statistical analysis. **Results:** In 74 cases, the mean age was 55 year old; 63 (85.1%), > 40 years; 36 (48.6%), males; 68 (91.9%), Asian; 47 (63.5%), on HBV treatment; 31 (41.9%) had history of perinatal transmission; 7 (9.5%), stage 3-4 liver fibrosis by shear wave elastography; 8 (11.8%), HBeAg+; 27 (62.8%), pre-core mutation (PCM); 21 (56.8%), basal core promotor (BCP) mutation. HBV genotype distribution was A = 3 (6.4%); B = 32 (68%); C = 9 (19.1%); D = 2 (4.3%); and H = 1 (2.1%); 29 (46%), baseline HBV DNA < 2000 IU/mL. The baseline distribution of HBsAg level was > 10000 = 5 (6.8%), 5000-10000 = 4 (5.4%); 3000-5000 = 1 (1.4 %), 1000-3000 = 17 (23%), 500-1000 = 11 (14.9%), 100- 500 = 19 (25%); < 100 IU/mL = 17 (23%). Baseline HBsAg < 3000 was seen in 64 (85.5%); < 500 IU/mL, 36 (48.6%). During follow-up, 4 (12.9%) had rising; 21 (67.7%) stable; and 6 (19.4%), down trending HBsAg level. The Chi Square test showed that baseline HBsAg < 3000 was significantly associated with Asian ethnicity (89.7% vs. 50%, P = 0.006), HBeAg- (50% vs. 10%, P = 0.003), PCM+ (100% vs. 62.5%, P = 0.001), end of f/u HBsAg < 1000 (98 % vs. 55.6%, P = 0.0006), and < 500 IU/mL (100% vs. 73.5%, P = 0.002), but not associated with gender (P = 0.927), age (P = 0.624),

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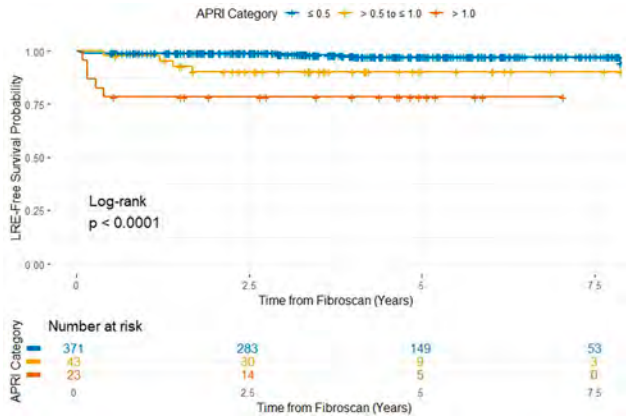
transmission mode (P = 0.896), BMI ≥ 25 (P = 0.655), liver fibrosis (P = 0.272), BCP mutation (P = 0.416), and HBV treatment history (P = 0.452). Multivariable analysis by Likelihood Ratio Test showed baseline HBsAg < 3000 IU/mL was associated with PCM+ (P = 0.005) and end of f/u HBsAg < 1000 IU/mL (P = 0.017), independent of HBeAg- (P = 0.436) and HBV treatment history (p = 0.721). **Conclusion:** This study revealed that in our single center cohort of 74 US patients with chronic HBV infection, as high as 85.5% have serum HBsAg level < 3000 IU/mL, that is associated with HBV PCM+ and end of f/u HBsAg level < 1000 IU/mL, independent of HBeAg status and HBV treatment history during 3-years follow-up. Our data support the clinical utility and value of HBsAg quant test in identifying the patients who may need only definitive course of HBV treatment and could be benefited by upcoming innovative treatment, such as bepirovirsen for HBV functional cure.

Disclosures: Ke-Qin Hu:Medrigal: honomarium, Kim Huynh:Nothing to Disclose, Tung Huynh:Nothing to Disclose.

4012 | PREDICTING LIVER-RELATED OUTCOMES USING WHO-RECOMMENDED APRI CUTOFFS: A MULTICENTER COHORT STUDY OF THAI CHB PATIENTS

Pimsiri Sripongpun[1] Chitchai Rattananukrom[2] Huttakan Navadurong[3] Kessarin Thanapirom[4] Kanokwan Pinyopornpanish[5] Supot Nimanong[6] Apichat Kaewdech[1] Sakkarin Chirapongsathorn[7] Chalermrat Bunchorntavakul[8] Chanunta Hongthanakorn[9] Sith Siramolpiwat[10] Abhasnee Sobhonslidsuk[11] Sarita Ratana-Amornpin[11] Watcharasak Chotiyaputta[6] Sombat Treeprasertsuk[4] Teerha Piratvisuth[1], [1]Prince of Songkla University, [2]Khon Kaen University, [3]Navamindradhiraj University, [4]Chulalongkorn University, [5]Chiang Mai University, [6]Siriraj Hospital, [7]Phramongkutklao Hospital and College of Medicine, [8]Rajavithi Hospital, [9]Bhumibol Adulyadej Hospital, [10]Thammasart University, [11]Ramathibodi Hospital

Background: The World Health Organization (WHO) guidelines expand chronic hepatitis B (CHB) treatment criteria, recommending the AST-to-Platelet Ratio Index (APRI) as a primary noninvasive test in resource-limited settings where vibration-controlled transient elastography (VCTE) is unavailable. While APRI is validated to cross-sectionally identify significant fibrosis (SF; ≥ F2), data remains limited regarding the prognostic value of WHO-recommended cutoffs (< 0.5 for excluding SF, ≥ 0.5 for diagnosing SF, and > 1.0 for diagnosing cirrhosis; corresponding to VCTE thresholds of 7 and 12.5 kPa). We aimed to evaluate the long-term prognostic performance for liver-related events (LREs) of these WHO-recommended APRI cutoffs in CHB patients. **Methods:** This multicenter retrospective cohort study utilized data from the Gastroenterological Association of Thailand (GAT) Fibroscan registry, including CHB patients who underwent VCTE between 2014 and 2026 across six tertiary centers. Patients with incomplete data for APRI calculation, or follow-up < 6 months were excluded. Patients were stratified by baseline APRI: < 0.5, 0.5–1.0, and > 1.0. The primary outcome was LREs, defined as a composite of hepatocellular carcinoma and/or hepatic decompensation (ascites, variceal bleeding, encephalopathy). Long-term outcomes were analyzed using Kaplan-Meier curves, log-rank tests, and multivariable Cox regression adjusted for age and sex. **Results:** Of 437 eligible patients (mean age 52.6 ± 11.8 years; 50.8% female), 371 (84.9%)/ 43 (9.8%)/ 23 (5.3%) were categorized into APRI ≤ 0.5, > 0.5–1.0, and > 1.0, respectively. Median VCTE-measured liver stiffness in each stratum was 5.6 (IQR 4.5–7.4), 12.0 (IQR 8.1–16.4), and 17.9 (IQR 9.2–25.6) kPa, respectively. The WHO APRI categories significantly discriminated LRE development as shown in Figure (p < 0.001). The 5-year LRE-free survivals were 97.2%, 90.3%, and 78.3% for the APRI < 0.5, 0.5–1.0, and > 1.0 groups, respectively. In a multivariable analysis, the WHO-recommended APRI strata were independently associated with LRE risk, with an adjusted hazard ratio (aHR) of 3.21 (95%CI 0.98-10.51, p = 0.05) for the 0.5–1.0 group, and aHR 11.93 (95%CI 3.90-36.51, p < 0.001) for the > 1.0 group. **Conclusion:** The WHO-recommended APRI cutoffs effectively stratify the long-term risk of LREs in CHB patients, demonstrating strong prognostic utility. These baseline thresholds offer critical clinical value for risk-stratification and intensive surveillance or treatment initiation in resource-limited settings. While lacking granular data on serial HBV DNA, HBeAg status, or specific antiviral therapy due to the nature of a retrospective registry, our findings provide a crucial, real-world body of evidence validating the long-term prognostic sustainability of this simplified, WHO-endorsed public health strategy.



Disclosures: Pimsiri Sripongpun:Novo Nordisk: Speaking and Teaching, Takeda: Speaking and Teaching, Nestle: Speaking and Teaching, Zuellig Pharma: Speaking and Teaching, Thai Meiji: Speaking and Teaching, Thai Otsuka: Speaking and Teaching,

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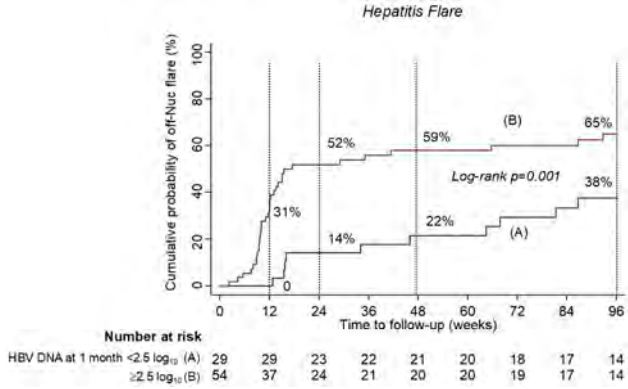
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4013 | MONTH-1 POST-CESSATION HBV DNA OUTPERFORMS END-OF-TREATMENT HBSAG IN PREDICTING HEPATITIS FLARE AFTER TDF/TAF CESSATION IN HBEAG-NEGATIVE CHRONIC HEPATITIS B

Yen-Chun Liu[1] Rachel Wen-Juei Jeng[1] Rong-Nan Chien[1], [1]Chang Gung Memorial Hospital, Linkou medical center

Background: Hepatitis flares after discontinuation of tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF) may occur rapidly, predominantly within the first 6 months after treatment cessation. Early identification of patients at risk for imminent flare is critical for safe off-therapy monitoring. We evaluated whether HBV DNA measured at 1 and 3 months after TDF/TAF cessation predicts subsequent hepatitis flare in HBeAg-negative chronic hepatitis B (CHB). **Methods:** HBeAg-negative CHB patients who discontinued TDF or TAF after sustained virological suppression, defined as consecutive undetectable HBV DNA measurements at least 6 months apart, were included. After treatment cessation, patients underwent monthly monitoring during the first 3 months and every 3 months thereafter during the first year. Off-therapy hepatitis flare was defined as ALT $\geq$5×ULN with HBV DNA $\geq$2000 IU/mL. Predictive performance of month 1 and month 3 HBV DNA after cessation and end-of-treatment (EOT) HBsAg, was assessed using AUROC analysis. Kaplan-Meier analysis compared cumulative flare incidence by Youden index-derived HBV DNA cutoffs. **Results:** Among 83 HBeAg-negative CHB patients who discontinued TDF or TAF, median age was 55 years, 84% were male, and 78% had genotype B. Median pretreatment HBV DNA and EOT HBsAg levels were 6.6 and 2.4 $\log_{10}$ IU/mL, respectively. During a median follow-up of 5.0 years, 48 patients (56%) developed off-therapy hepatitis flare, with a median time to flare of 14 weeks. Flares clustered early after cessation: 17, 32, 38 patients flared within 3, 6, 12 months, respectively, and 84% of the first-year flares occurred within the first 6 months. Month-1 HBV DNA outperformed EOT HBsAg in predicting 3-month flare, with AUROCs of 0.825 versus 0.474, respectively; p = 0.007. Month-1 HBV DNA also predicted 6-month flare, with an AUROC of 0.716, compared with 0.460 for EOT HBsAg. Using 2.5 $\log_{10}$ IU/mL as the optimal month-1 HBV DNA cutoff, cumulative flare incidence was higher in patients with HBV DNA $\geq$2.5 versus <2.5 $\log_{10}$ IU/mL at 3 months and 6 months: 31% versus 0% and 52% versus 14%, respectively; log-rank p < 0.01. For predicting 3-month flare, this cutoff identified all flare cases, yielding a sensitivity and NPV of 100%, with a specificity of 43.9% and PPV of 31.5%. Month-3 HBV DNA further improved prediction of 6- and 12-month flare, with AUROCs of 0.888 and 0.876, respectively. **Conclusion:** In HBeAg-negative CHB patients after TDF/TAF cessation, month-1 HBV DNA outperformed EOT HBsAg in predicting early off-therapy hepatitis flare. A month-1 HBV DNA level <2.5 $\log_{10}$ IU/mL identified patients at low risk for imminent 3-month flare, while levels $\geq$2.5 $\log_{10}$ IU/mL may warrant closer early monitoring. Month-3 HBV DNA further refined prediction of 6- and 12-month flare, supporting individualized post-cessation surveillance.



Disclosures: Yen-Chun Liu:Nothing to Disclose, Rachel Wen-Juei Jeng:GSK: Advisor, Gilead: Advisor, BMS: Speaking and Teaching, Roche: Advisor, Rong-Nan Chien:Nothing to Disclose.

4014 | ON-TREATMENT CK18-M30 AND CK18-M65 DYNAMICS REFLECT HEPATOCYTE DEATH PATTERNS ASSOCIATED WITH END-OF-TREATMENT HBSAG SEROCLEARANCE IN CHRONIC HEPATITIS B

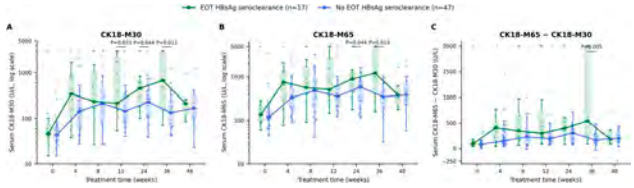
Xinyue Meng[1] Jing Zhao[1] Jianxia Dong[1] Pengxuan Wu[1] Shan Ren[1] Xinyue Chen[1] Sujun Zheng[1], [1]First Department of Hepatology, Beijing YouAn Hospital, Capital Medical University, Beijing, China

Background: Peg-IFN α-based therapy can induce HBsAg seroclearance in selected patients with chronic hepatitis B (CHB), but the treatment-phase biological

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events associated with HBsAg loss remain incompletely defined. CK18-M30 reflects caspase-cleaved CK18 and is commonly considered an apoptosis-related marker, whereas CK18-M65 reflects total CK18 release. We aimed to investigate whether on-treatment CK18 dynamics were associated with end-of-treatment HBsAg seroclearance. **Methods:** We analyzed 64 CHB patients who received 48 weeks of peg-IFN α-based therapy. The primary endpoint was HBsAg seroclearance at week 48. Serum CK18-M30 and CK18-M65 were measured longitudinally at baseline and during treatment. CK18-M65 − CK18-M30 was calculated as an exploratory indicator of non-M30 CK18 release. CK18 trajectories were compared between patients with and without end-of-treatment HBsAg seroclearance using Mann–Whitney U tests at each time point and repeated-measures models. **Results:** Seventeen patients achieved HBsAg seroclearance at week 48, whereas 47 did not. Baseline CK18-M30 and CK18-M65 levels did not differ significantly between the two groups. During therapy, patients who achieved end-of-treatment HBsAg seroclearance showed more pronounced increases in CK18 markers, with separation mainly emerging between weeks 12 and 36. At week 36, CK18-M30 was higher in the seroclearance group than in the non-seroclearance group (670.8 vs. 133.5 U/L, $P = 0.011$), as was CK18-M65 (1209.0 vs. 349.2 U/L, $P = 0.013$). The most pronounced difference was observed for CK18-M65 − CK18-M30(538.2 vs. 167.4 U/L, $P = 0.005$). Repeated-measures analysis further supported distinct on-treatment CK18 trajectories between the two groups. After accounting for ALT and AST, CK18-M65 and CK18-M65 − CK18-M30 remained informative, suggesting that CK18 dynamics were not fully captured by aminotransferase changes alone. **Conclusion:** In CHB patients receiving peg-IFN α-based therapy, end-of-treatment HBsAg seroclearance was associated with distinct on-treatment CK18 dynamics, particularly increased CK18-M65 and CK18-M65 − CK18-M30 during the mid-treatment phase. These findings suggest that CK18-based markers may provide complementary information on hepatocyte death patterns associated with peg-IFN α-induced HBsAg seroclearance.



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4015 | ASSAY-DEPENDENT CATEGORICAL DIVERGENCE OF LOW-LEVEL HBSAG REACTIVITY IN CHRONIC HEPATITIS B POST-CLEARANCE SURVEILLANCE

Haishi Wu[1] Zhiliang Gao[1] Na Gao[1], [1]Sun Yat-sen University Third Affiliated Hospital

Background: As more chronic hepatitis B patients approach or achieve HBsAg seroclearance, very low-level HBsAg reactivity is increasingly encountered across surveillance. Whether commercial HBsAg platforms remain categorically concordant near their lower analytical range, and how often residual low-level reactivity remains observable in samples already classified as clinically cleared, are not well characterized in real-world surveillance. **Methods:** We retrospectively analyzed 885 samples from 329 chronic hepatitis B patients at a tertiary center across two surveillance-relevant settings: (1) 145 low-titer samples for comparison of four commercial HBsAg assays (Abbott, Roche, Mindray, Autobio; hereafter Assays 1–4, respectively); and (2) 740 archived follow-up samples from 275 patients with documented HBsAg seroclearance (defined a priori by Assay 2 HBsAg < 0.05 IU/mL in routine care), retrospectively re-tested with the four conventional assays and an ultrasensitive qualitative HBsAg assay. Sample stratification by HBsAg concentration used quantitative values from one of the four conventional assays as a within-cohort scale. No assay was treated as a reference standard; sensitivity, specificity, PPV, and NPV were not calculated. **Results:** Among 145 low-titer samples, Assays 1 and 2 were reactive in all 145, Assay 3 in 141 (97.2%), and Assay 4 in 124 (85.5%). Categorical agreement across the four platforms ranged from 85.5% to 100%, with the lowest agreement in comparisons involving Assay 4. Divergence was concentration-dependent and most pronounced at the lower analytical range: among samples within the lowest HBsAg stratum (< 0.1 IU/mL, n = 7), Assay 4 was reactive in 1 and Assay 3 in 6, despite categorical reactivity by Assays 1 and 2 in all 7; within the 0.1-0.5 IU/mL stratum (n = 77), reactivity by the four assays ranged from 62 to 77. Pairwise Spearman correlation across platforms remained high (rho 0.92-0.95), confirming that strong quantitative correlation coexisted with categorical divergence near the lower analytical range. Among the 740 clinically cleared samples, low-level conventional HBsAg reactivity was uncommon (range 0–3.6% across the four platforms; Assay 2, the cohort-defining assay, was reactive in 0/740 as expected). The ultrasensitive HBsAg assay was reactive in 138/740 samples (18.6%), including 108/740 samples (14.6%) with no reactivity by any conventional platform. **Conclusion:** Conventional HBsAg platforms diverge categorically

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near the lower analytical range despite strong quantitative correlation, and a measurable subset of clinically cleared samples retains low-level reactivity visible only under extended-range testing. Across surveillance of chronic hepatitis B patients approaching or after HBsAg seroclearance, platform choice materially shapes the observable analytical window.

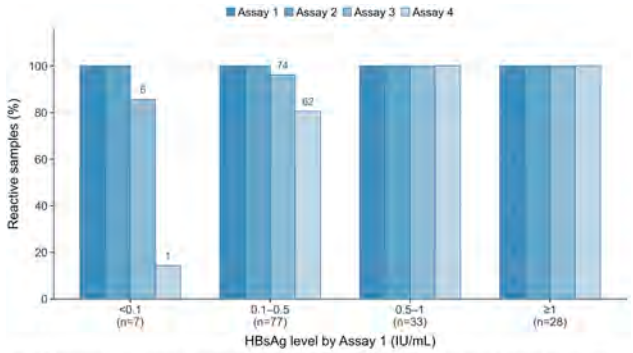


Figure 1. Categorical reactivity of four conventional HBsAg assays (Assay 1, Abbott; Assay 2, Roche; Assay 3, Minilray; Assay 4, Autobio) across low-titer concentration strata (n=145). Reactivity was assessed at each platform's routine clinical cutoff. Samples were stratified by quantitative HBsAg values from one of the conventional assays, used solely as a within-cohort scale rather than as a reference standard. Numbers above non-100% bars indicate the count of reactive samples in that stratum.

Disclosures: Haishi Wu:Nothing to Disclose, Zhiliang Gao:Nothing to Disclose, Na Gao:Nothing to Disclose.

4016 | HIV COINFECTION ALTERS THE RELATIONSHIP BETWEEN QHBSAG AND PLASMA HBV PGRNA IN HBEAG-POSITIVE CHRONIC HEPATITIS B

Tetiana Pozniak[1] Alip Ghosh[2] Gaayathri Krishnan[2] Shyam Kottilil[2] Lydia Tang[3], [1]Institute of Human Virology University of Maryland, [2]Institute of Human Virology, University of Maryland School of Medicine, [3]University of Maryland, Baltimore

Background: Globally, chronic hepatitis B (CHB) is a leading cause of cirrhosis and hepatocellular cancer. Eliminating or silencing covalently closed circular DNA (cccDNA), the transcriptional template responsible for persistent hepatitis B virus (HBV) infection, is a goal of CHB cure. Direct measurement of intrahepatic cccDNA requires liver biopsy, highlighting the need for non-invasive biomarkers of cccDNA activity to guide CHB cure strategies. Currently, reduction in quantitative hepatitis B surface antigen (qHBsAg) is a key endpoint in CHB cure studies; however, circulating HBsAg may derive from both cccDNA and integrated HBV DNA. In contrast, pregenomic RNA (pgRNA) is transcribed exclusively from cccDNA and therefore represents a promising biomarker of cccDNA activity. HIV coinfection with CHB may alter HBV transcriptional activity and potentially affect interpretation of biomarkers used in CHB cure studies. We therefore developed a pgRNA assay and evaluated the effect of HIV coinfection on the relationship between qHBsAg and pgRNA in people with HBeAg positive CHB. **Methods:** Plasma samples from adults with HBeAg-positive CHB with and without HIV coinfection were analyzed. All participants were HBV virally suppressed on nucleos(t)ide analogue (NUC) antivirals. Participants with HIV coinfection were also HIV RNA suppressed on antiretroviral therapy containing two NUCs active against HBV. A quantitative qPCR assay for plasma HBV pgRNA quantification was developed and standardized using an in-house HBV plasmid clone generated from HepG2.2.15-derived HBV DNA. qHBsAg was quantified from serum by Chemiluminescent Immunoassay (Ig Biotechnology, CA). **Results:** Plasma samples from 13 patients with HIV/CHB and 12 with CHB monoinfection were analyzed. pgRNA was quantifiable in all samples (mean ± SD, 2.50 ± 1.06 log U/μL). HBV pgRNA levels were positively correlated with qHBsAg (mean ± SD, 3.5 ± 1.07 log U/mL) in all HBeAg-positive patients with HIV/CHB coinfection receiving NUC ($P = 0.0189$). No significant correlation was observed among patients with CHB monoinfection. **Conclusion:** Using a newly developed quantitative plasma pgRNA assay, we demonstrate persistent cccDNA transcriptional activity despite HBV suppression and further show that HIV coinfection influences relationships between qHBsAg and pgRNA. Detectable pgRNA in all participants supports ongoing cccDNA activity as a major barrier to CHB cure with NUC therapy alone. HIV coinfection altered the relationship between quantitative HBsAg and pgRNA, reflecting differing contributions of cccDNA and integrated HBV DNA-derived HBsAg production. In people with HIV/CHB, qHBsAg may remain a useful biomarker of active cccDNA transcription for monitoring responses in CHB-cure studies.

Disclosures: Tetiana Pozniak:Nothing to Disclose, Alip Ghosh:Nothing to Disclose, Gaayathri Krishnan:Nothing to Disclose, Shyam Kottilil:Red Queen Therapeutics: Consultant, Orsobio: Stock – privately held company, Lydia Tang:Arbutus: Grant/Research Support, Gilead Sciences: Grant/Research Support, Moderna: Grant/Research Support, Ausperbio: Grant/Research Support.

4017 | SERUM HBV RNA KINETICS AND TREATMENT RESPONSE IN PATIENTS WITH CHRONIC HEPATITIS B RECEIVING NUCLEOS (T)IDE ANALOGUE THERAPY

Jian Wang[1] Ye Xiong[2] Shaoqiu Zhang[1] Hongpan Xu[1] Juan Xia[1] Xiaomin Yan[1] Yuxin Chen[1] Rui Huang[1] Chao Wu[1], [1]Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University, [2]Nanjing Drum Tower Hospital Clinical College of Nanjing University of Chinese Medicine

Background: Serum HBV RNA reflects intrahepatic cccDNA transcriptional activity in chronic hepatitis B (CHB). We explored the serum HBV RNA kinetics and treatment response in patients with CHB receiving

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nucleos(t)ide analogue (NA) therapy. **Methods:** This retrospective study included treatment-naïve CHB patients initiating NA therapy. Serum HBV RNA was detected at baseline and during NA treatment, which was quantified using the Cobas HBV RNA real-time PCR assay on the Cobas 6800 Systems (Roche Diagnostics), with a lower limit of quantification of 10 copies/mL. We explored the association of HBV RNA with virologic (VR, HBV DNA undetectable), and serologic (SR, HBeAg clearance) and combination (CR, HBeAg clearance and HBsAg < 3000 IU/ml) response. **Results:** A total of 654 patients were included, of whom 51.8% were HBeAg-positive. HBeAg-positive patients (vs. HBeAg-negative) had higher baseline HBV RNA levels (6.3 vs. 2.3 $\log_{10}$ copies/mL, $P < 0.001$). Baseline HBV RNA (aOR: 0.505, 95%CI: 0.355-0.719, $P < 0.001$) and HBeAg-positive status (aOR: 0.346, 95%CI: 0.138-0.869, $P = 0.024$) were significantly associated with undetectable HBV RNA at week 48 of treatment. The 5-year cumulative incidence of VR, SR and CR were significantly higher in patients who had a greater HBV RNA decline (> 1 $\log_{10}$ copies/mL) at weeks 12, 24, and 48 of treatment in HBeAg-positive patients. On-treatment HBV RNA decline at weeks 12, 24, and 48 were independently associated higher chance of achieving VR, SR, and CR in such patients. **Conclusion:** Higher baseline HBV RNA and HBeAg-positive status were significantly associated with lower chance of undetectable HBV RNA in CHB with NA treatment. Early on-treatment decline (> 1 $\log_{10}$ copies/mL) in serum HBV RNA is associated with VR, SR and CR in HBeAg-positive CHB patients receiving NA therapy. Serum HBV RNA may help guide individualized treatment strategies for patients with CHB.

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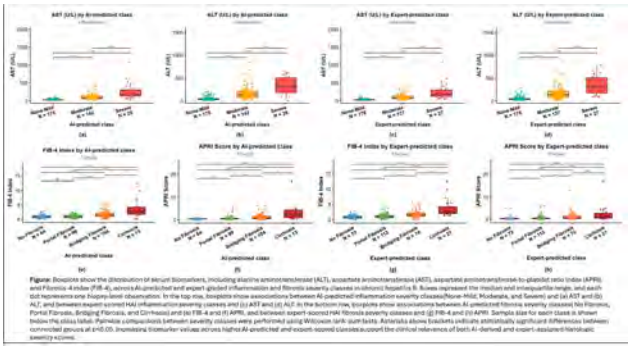
4018 | ASSOCIATIONS OF AI-BASED HISTOLOGIC ASSESSMENT WITH SURROGATE MARKERS OF LIVER DISEASE SEVERITY AMONG PERSONS WITH CHRONIC HEPATITIS

Fahmida Haque[1] Veronica Locker[2] Haoyue Zhang[1] Sushant Patkar[1] Zahra Sarrafan-Chaharsoughi[2] Stephen Hewitt[1] Barbara Rehermann[2] Peter Choyke[1] Stephanie Harmon[3] Devid Kleiner[1] Baris Turkbey[1] Marc Ghany[4], [1]NCI, NIH, [2]NIDDK, NIH, [3]NCI,NIH, [4]NIH/NIDDK

Background: Liver biopsy remains the gold standard for histologic assessment in chronic hepatitis B (CHB), but Histologic Activity Index (HAI) scoring is subjective and prone to inter-observer variability. We evaluated the performance of two previously developed artificial intelligence (AI)-based classification models for assessing hepatic inflammation and fibrosis by comparing AI-derived scores with pathologist-assigned HAI scores and established clinical markers of disease severity, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), aspartate aminotransferase-to-platelet ratio index (APRI), and Fibrosis-4 index (FIB-4). **Methods:** Liver biopsies of CHB patients with pathologist-assigned Knodell scores were categorized for inflammation as none/mild (0–6), moderate (7–12), and severe (13–18), and for fibrosis as none (F0), portal fibrosis (F1), bridging fibrosis (F3), and cirrhosis (F4). H&E-stained and Masson's trichrome-stained slides were used to train AI models that rely on pathology foundation model features and slide-level weakly supervised classification techniques to predict inflammation and fibrosis severity, respectively. Agreement between AI and pathologist scores was assessed using weighted Cohen's kappa (κ) with bootstrapped 95% confidence intervals (CI). Spearman correlation coefficients (ρ) were used to evaluate associations between histologic scores and clinical markers. Differences across severity classes were assessed using Wilcoxon rank-sum tests, with statistical significance defined as $p < 0.05$. **Results:** A total of 342 biopsies from 205 patients and 282 biopsies from 147 patients were used for assessment of inflammation and fibrosis, respectively. AI and pathologist's assessments showed substantial agreement for inflammation ($\kappa = 0.73$, 95% CI: 0.68–0.78) and fibrosis ($\kappa = 0.60$, 95% CI: 0.55–0.65). AI-predicted inflammation severity correlated strongly with ALT ($\rho = 0.69$, 95% CI: 0.62–0.74) and AST ($\rho = 0.72$, 95% CI: 0.66–0.77), and was comparable to correlations between pathologist's scores with ALT ($\rho = 0.71$, 95% CI: 0.64–0.76) and AST ($\rho = 0.72$, 95% CI: 0.66–0.76). For fibrosis, AI-predicted severity correlated significantly with APRI ($\rho = 0.44$, 95% CI: 0.33–0.53) and FIB-4 ($\rho = 0.34$, 95% CI: 0.22–0.45). In contrast, pathologist-assessed fibrosis correlated more strongly with FIB-4 ($\rho = 0.46$, 95% CI: 0.35–0.55), while the association with APRI ($\rho = 0.37$, 95% CI: 0.27–0.47) was lower. Significant differences across AI- and pathology-assessed inflammation and fibrosis severity classes were observed for all clinical markers ($p < 0.05$). **Conclusion:** AI-derived histologic scoring demonstrated clinically meaningful associations with established surrogates of liver disease severity, supporting its potential role as an objective complement to pathological and clinical evaluation.

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4019 | STUDY ON THE DYNAMIC CHANGES OF HBV RNA AND ITS PREDICTIVE VALUE FOR EARLY EFFICACY IN TREATMENT-NAÏVE PATIENTS WITH CHRONIC HEPATITIS B RECEIVING PEGIFNα-2B COMBINED WITH NAS

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Background: To investigate the dynamic changes of serum hepatitis B virus ribonucleic acid (HBV RNA) and its predictive value for early treatment response in treatment-naïve patients with chronic hepatitis B (CHB) receiving pegylated interferon α-2b (PegIFNα-2b) combined with nucleos(t)ide analogues (NAs). **Methods:** A total of 132 treatment-naïve CHB patients with positive HBV RNA who visited Beijing Ditan Hospital from December 2023 to December 2024 were enrolled. All patients received PegIFNα-2b combined with NAs for 48 weeks. Serum samples were collected at baseline and at weeks 12,24, 36, and 48 of treatment to detect HBV RNA, HBV DNA, hepatitis B surface antigen (HBsAg), and alanine aminotransferase (ALT). Spearman correlation analysis, Logistic regression, receiver operating characteristic (ROC) curve, and Kaplan-Meier survival analysis were employed to evaluate the correlation between HBV RNA and various indicators, as well as its predictive value for 48-week treatment outcomes. **Results:** At week 48 of treatment, the rates of HBV RNA undetectability, significant HBsAg decline (>1 $\log_{10}$ IU/mL), and HBeAg seroconversion were 59.85%,42.42%, and 4.92%, respectively. HBV RNA showed significant positive correlations with HBV DNA at all time points (r = 0.18–0.63, all P < 0.05), with the strongest correlation with HBsAg at week 24 (r = 0.563, P < 0.01), and with ALT only at baseline and week 12. Baseline, week 12, and week 24 HBV RNA levels were significantly negatively associated with HBV RNA undetectability at week 48(OR = 0.543–0.658, all P < 0.01), but showed no significant predictive value for significant HBsAg decline. The median time to HBV RNA undetectability was 36 weeks in the rapid decline group, compared to 48 weeks in the slow decline and plateau groups; however, the differences among the three groups were not statistically significant (P > 0.05). **Conclusion:** HBV RNA declined continuously during combination therapy and correlated with HBV DNA and HBsAg dynamics, although more slowly than HBV DNA. Baseline, week 12, and week 24 HBV RNA levels independently predicted week 48 HBV RNA undetectability, while week 12 HBV RNA also predicted HBeAg seroconversion. Patients with rapid HBV RNA decline at week 24 achieved earlier RNA clearance than slow-decline groups. High viral load HBeAg-positive patients showed lower HBV RNA and HBV DNA clearance rates, but no significant differences in HBeAg seroconversion, HBsAg decline, or functional cure.



Disclosures: Xinxin Li:Nothing to Disclose.

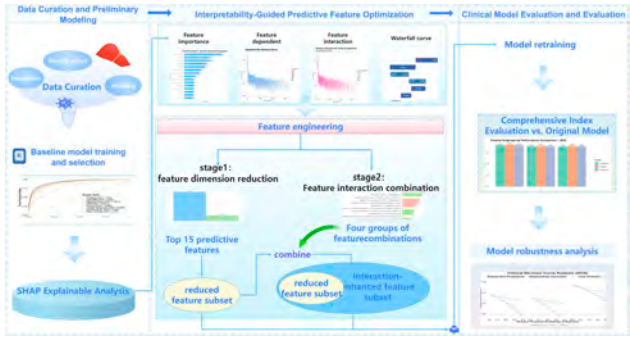
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4020 | INTERPRETABILITY-GUIDED FEATURE ENGINEERING FOR COMPACT, ACCURATE MULTI-OUTCOME PROGRESSION RISK STRATIFICATION IN CHRONIC HEPATITIS B

Shu Su[1] Huiyi Zhang[2] Qingxian Song[2] Jun Yuan[3], [1]Second Affiliated Hospital of Chongqing Medical University, [2]The Second Affiliated Hospital of Chongqing Medical University, [3]Chongqing Medical University

Background: Clinical artificial intelligence (AI) often encounters a trade-off between predictive performance and interpretability. Most existing predictive tools prioritize statistical performance over clinical transparency, relying on post-hoc explanations that fail to guide targeted feature optimization. This study aims to develop an interpretability-driven framework for accurate and interpretable prediction of hepatitis B progression. **Methods:** A total of 36,024 hospitalized CHB patient records were enrolled in this retrospective observational study. We constructed an interpretable machine learning framework integrating SHAP-based main effect quantification and pairwise interaction analysis, and adopted a two-stage modeling strategy of feature dimensionality reduction and clinical interaction augmentation. Different from traditional post-model interpretation, this study embedded interpretability analysis into the feature engineering process to screen core clinical indicators and synergistic feature combinations, finally developing simplified and interaction-enhanced multi-outcome predictive models for CHB non-progression, liver cirrhosis, and hepatocellular carcinoma (HCC). **Results:** The proposed modeling framework achieved strong discriminatory performance, with AUCs of 0.930, 0.900, and 0.905 for predicting disease non-progression, liver cirrhosis, and hepatocellular carcinoma (HCC) at the patient level, respectively. SHAP analyses identified distinct stage-specific biomarker contributions and synergistic interaction patterns across three CHB progression endpoints. AFP predominantly predicted HCC risk, while platelet-related indicators served as core predictors for cirrhosis progression, demonstrating clear outcome-specific feature heterogeneity. Our interpretability-guided feature engineering yielded a compact 15-feature simplified model, which retained promising predictive performance with only a small average AUC reduction of 0.014 compared with the original 78-feature baseline model. Further embedding validated feature interactions effectively elevated HCC predictive sensitivity to 0.700 without compromising specificity. **Conclusion:** This study proposed an interpretability-guided feature optimization paradigm for CHB progression prediction. Embedding interpretability analysis into the early modeling stage avoids the limitations of passive post-hoc interpretation, enabling the construction of compact, high-performance, and clinically transparent multi-outcome models. This framework provides a practical, scalable strategy for individualized risk stratification and clinical decision-making for CHB patients.



Disclosures: Shu Su:Nothing to Disclose, Huiyi Zhang: Nothing to Disclose, Qingxian Song:Nothing to Disclose, Jun Yuan:Nothing to Disclose.

4021 | DYNAMICS IN CONTROLLED ATTENUATION PARAMETER (CAP) PROVIDE INCREMENTAL PREDICTIVE VALUE FOR PROGNOSIS IN ON-TREATMENT CHB PATIENTS WITH SIGNIFICANT FIBROSIS AND CIRRHOSIS

Xiaowei Ai[1] Mengyang Zhang[1] Shuyan Chen[1] Xinyu Zhao[1] Jialing Zhou[1] Tongtong Meng[1] Bingqiong Wang[1] Chenglin Sun[1] Xiao Han[1] Yankun Gao[1] Xiaoning Wu[1] Yameng Sun[1] Hong You[2], [1]Liver Research Center, Beijing Friendship Hospital, Capital Medical University, [2]Capital Medical University

Background: The coexistence of hepatic steatosis and CHB is increasingly common in clinical practice, leading to a growing focus on the prognosis of this dual-burden population. Although the controlled attenuation parameter (CAP) has been widely used to quantify hepatic steatosis in CHB patients, the prognostic value of longitudinal changes in CAP remains unknown. This study aimed to evaluate whether dynamic changes in CAP are associated with liver-related events (LREs) in on-treatment CHB patients with significant fibrosis and cirrhosis. **Methods:** CHB patients with significant fibrosis or cirrhosis before antiviral treatment were included in this prospective cohort. CAP was used to assess hepatic steatosis. LREs were defined as hepatic decompensations, hepatocellular carcinoma (HCC), liver transplantation, or liver-related death. Joint models were employed to analyze associations between CAP trajectory and risk of LREs. **Results:** A total of 573 CHB patients were followed for a median of 6.9 years, during which 51 LREs occurred, including 26 cases of hepatic decompensations and 33 cases of HCC. We evaluated 5,967 individual VCTE

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assessments. CAP-dynamics independently predicted LREs (per 10 dB/m increase aHR: 0.86, 95% CI: 0.78 - 0.96, P = 0.006). After adjusting for LSM-dynamics, CAP-dynamics remained an independent protective factor for LREs (per 10 dB/m increase aHR: 0.85, 95% CI: 0.77 - 0.95, P = 0.005), hepatic decompensations (per 10 dB/m increase aHR: 0.79, 95% CI: 0.68 - 0.91, P = 0.001), and HCC (per 10 dB/m increase aHR: 0.85, 95% CI: 0.75 - 0.96, P = 0.011).Among 355 patients with clinically diagnosed cirrhosis before treatment, with 3350 individual measurements, CAP-dynamics remained independently associated with LREs (per 10 dB/m increase aHR: 0.87, 95% CI: 0.78 - 0.97, P = 0.015).Multivariate joint model integrating CAP and LSM dynamics, improved predictive performance compared to LSM alone, with the 7-year AUROC increasing from 0.70 to 0.75. A CAP being greater than 236 dB/m over time was associated with a reduced risk of LREs (aHR: 0.69, 95% CI: 0.55-0.85, P < 0.001) **Conclusion:** Among on-treatment CHB patients with significant fibrosis or cirrhosis, a longitudinal decline in CAP was associated with a higher risk of LREs. Regular monitoring of CAP can improve prognostic value beyond LSM alone.

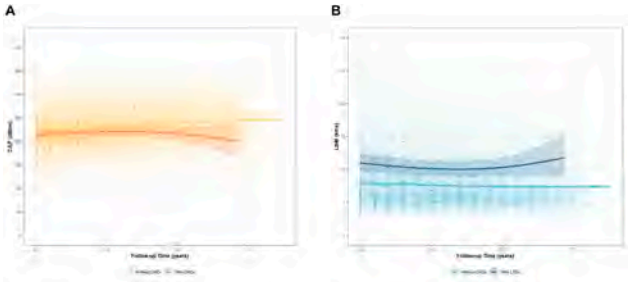


Fig.1 VCTE trajectories in patients with and without LREs. Individual VCTE measurements over time (dots), individual VCTE trajectories (shaded lines), and the population average VCTE trajectory (solid lines) before the development of LREs. Trajectories are color-coded by LREs status (light orange and light blue: without LREs; dark orange and dark blue: with LREs). (A) CAP; (B) LSM. Abbreviations: LSM, liver stiffness measurements; CAP, controlled attenuation parameter; LREs, liver-related events.

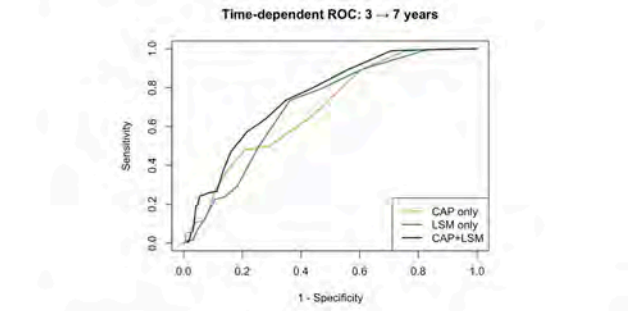


Fig.2 Time-dependent ROC curves for joint models using VCTE collected up to year 3 to predict LREs at year 7. CAP only: Joint model analysis for CAP-dynamics; LSM only: Joint model analysis for LSM-dynamics; CAP+LSM: multivariable Joint model analysis for both CAP-dynamics and LSM-dynamics. Abbreviations: LSM, liver stiffness measurements; CAP, controlled attenuation parameter; LREs, liver-related events.

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4022 | COMPARATIVE ACCURACY OF BLOOD-BASED BIOMARKERS: FIB-4, APRI, AND SAFE SCORE FOR IDENTIFYING SIGNIFICANT FIBROSIS IN PATIENTS WITH CHRONIC HEPATITIS B

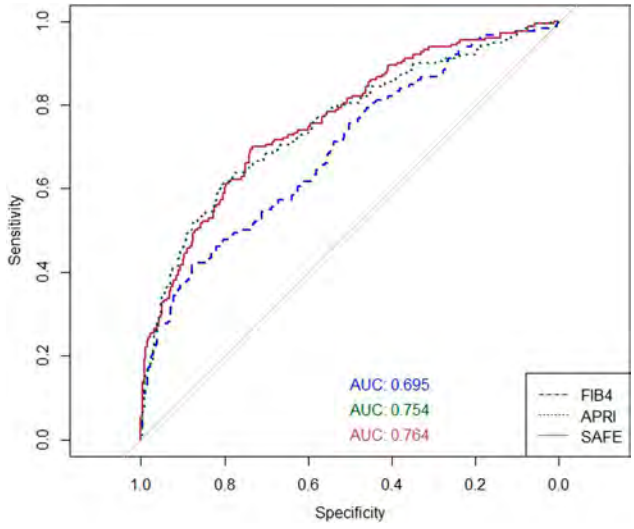
Pimsiri Sripongpun[1] Chitchai Rattananukrom[2] Huttakan Navadurong[3] Kessarin Thanapirom[4] Kanokwan Pinyopornpanish[5] Supot Nimanong[6] Apichat Kaewdech[1] Sakkarin Chirapongsathorn[7] Chalermrat Bunchorntavakul[8] Chanunta Hongthanakorn[9] Sith Siramolpiwat[10] Abhasnee Sobhonslidsuk[11] Sarita Ratana-Amornpin[11] Watcharasak Chotiyaputta[6] Sombat Treeprasertsuk[4] Teerha Piratvisuth[1], [1]Prince of Songkla University, [2]Khon Kaen University, [3]Navamindradhiraj University, [4]Chulalongkorn University, [5]Chiang Mai University, [6]Siriraj Hospital, [7]Phramongkutklao Hospital and College of Medicine, [8]Rajavithi Hospital, [9]Bhumibol Adulyadej Hospital, [10]Thammasart University, [11]Ramathibodi Hospital

Background: International hepatology society guidelines recommend antiviral therapy for viremic chronic hepatitis B (CHB) patients with significant liver fibrosis (SF; ≥F2). Although liver stiffness measurement via vibration-controlled transient elastography (VCTE) is widely accepted as the standard noninvasive test for treatment decisions, its accessibility remains limited in many CHB-endemic regions. We aimed to validate the diagnostic performance of blood-based biomarkers, specifically FIB-4, APRI, and SAFE score, in identifying SF among patients with CHB. **Methods:** As part of the Gastroenterological Association of Thailand (GAT) Fibroscan registry, this multicenter retrospective study included patients with CHB who underwent VCTE between 2014 and 2026 across six centers in Thailand. Patients with unreliable VCTE results or incomplete data for FIB-4, APRI, or SAFE score calculations were excluded. Laboratory results obtained within 3 months of the index VCTE were analyzed. The reference standard for SF diagnosis was defined as a VCTE-measured liver stiffness ≥7 kPa. Diagnostic performance was evaluated using the area under the receiver operating characteristic curve (AUROC), with the DeLong test used for comparisons. Specificities at established cutoffs were also calculated. **Results:** A total of 459 CHB patients were eligible for analysis. The median age of the cohort was 53 years (IQR 44–61), and 51.2% were male. Patients with SF were

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significantly older, had higher BMIs, higher prevalence of diabetes, and higher values of FIB-4, APRI, and SAFE than those without SF. The SAFE score yielded the highest AUROC at 0.764 (95% CI 0.719–0.809), which was non-significantly higher than APRI (AUROC 0.754, 95% CI 0.708–0.801, p = 0.626) but significantly superior to FIB-4 (AUROC 0.695, 95% CI 0.646–0.744, p < 0.001) as shown in Figure. At recommended cutoffs, the specificities of SAFE ≥100, APRI >0.5, and FIB-4 >1.3 for diagnosing SF were 92.5%, 94.3%, and 65.6%, respectively. **Conclusion:** Both APRI and SAFE outperform FIB-4 in diagnosing SF among Thai CHB patients, offering high specificity to rule in treatment candidates. However, APRI offers distinct practical advantages due to fewer required variables. Additionally, our study validates the WHO guidelines, demonstrating that its simplified APRI-based strategy is acceptably reliable for expanding CHB care in resource-limited settings.



Disclosures: Pimsiri Sripongpun:Novo Nordisk: Speaking and Teaching, Takeda: Speaking and Teaching, Nestle: Speaking and Teaching, Zuellig Pharma: Speaking and Teaching, Thai Meiji: Speaking and Teaching, Thai Otsuka: Speaking and Teaching, Chitchai Rattananukrom:Nothing to Disclose, Huttakan Navadurong:Nothing to Disclose, Kessarin Thanapirom:Nothing to Disclose, Kanokwan Pinyopornpanish:Nothing to Disclose, Supot Nimanong:Nothing to Disclose, Apichat Kaewdech:Nothing to Disclose, Sakkarin Chirapongsathorn:Nothing to Disclose, Chalermrat Bunchorntavakul:Nothing to Disclose, Chanunta Hongthanakorn:Nothing to Disclose, Sith Siramolpiwat:Nothing to Disclose, Abhasnee Sobhonslidsuk: Nothing to Disclose, Sarita Ratana-Amornpin:Nothing to Disclose, Watcharasak Chotiyaputta:Nothing to Disclose, Sombat Treeprasertsuk:Nothing to Disclose, Teerha Piratvisuth:Nothing to Disclose.

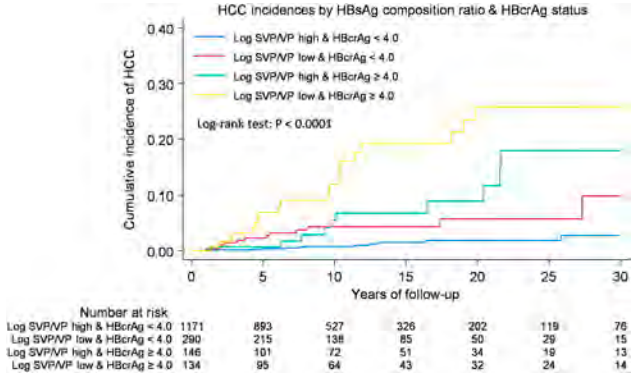
4023 | THE ASSOCIATION BETWEEN THE COMPOSITION RATIO OF HBSAG (SUBVIRAL PARTICLES/VIRAL PARTICLES) AND HCC DEVELOPMENT IN HBEAG-NEGATIVE CHB

Tetsuya Hosaka[1] Fumitaka Suzuki[1] Yasue Takeuchi[1] Hitomi Sezaki[1] Satoshi Saitoh[1] Shunya Goto[1] Shigeki Yamamoto[1] Yasuka Eriksson[1] Yoshiyuki Suzuki[1] Norio Akuta[1] Hiromitsu Kumada[1], [1]Toranomon Hospital

Background: HBsAg is translated not only from cccDNA but also from integrated HBV and released into the bloodstream. Furthermore, HBsAg in the blood includes both viral particle (VP)-derived forms and subviral particles (SVP), with SVP constituting the majority. In this study, we evaluated the association between VP and SVP equivalents in HBsAg levels and HCC development. **Methods:** We enrolled 1,741 HBeAg-negative and non-cirrhotic patients without antiviral therapy who were followed for at least one year. For VP and SVP equivalents in HBsAg, values derived from VP were converted to HBV DNA in copies/mL. SVP values were converted using the formula 1 IU of HBsAg = 8×10^8 SVP (Luckenbaugh K, et al. JVH 2014). We evaluated HCC development based on baseline HBsAg composition ratio (log SVP/VP). **Results:** (1) The median log SVP/VP was 8.1. By disease stage, it was 8.8 in the inactive phase, 7.6 in the indeterminate, and 6.0 in the active phase, showing a tendency for Log SVP/VP to decrease with progression of disease stage (P-trend < 0.001). Furthermore, patients with genotype B had significantly lower Log SVP/VP compared to other genotypes (7.1 vs 8.5, P < 0.001).(2) When the Log SVP/VP cutoff was set at 7.0, annual HCC incidence rates were 6.6 per 1,000 P-Y in the low Log SVP/VP group and 1.4 per 1,000 P-Y in the high group, showing a significantly higher incidence in the low group (P < 0.001). Multivariable Cox regression showed the low log SVP/VP was associated with HCC development, adjusted for age, sex, ALT, platelet counts, genotype, HBcrAg, and HBV DNA. Conversely, raw HBsAg level itself was not associated with HCC. Furthermore, we stratified the cohort into four groups by log SVP/VP and HBcrAg status as shown in Figure. Patients with low log SVP/VP and HBcrAg levels ≥ 4 log U/mL had the highest incidence rate of HCC (Figure). **Conclusion:** The composition ratio of HBsAg levels between SVP and VP was associated with HCC development in HBeAg-negative and non-cirrhotic patients without antiviral therapy. This suggests that, together with HBcrAg, it may reflect the transcriptional activity of cccDNA in the liver.

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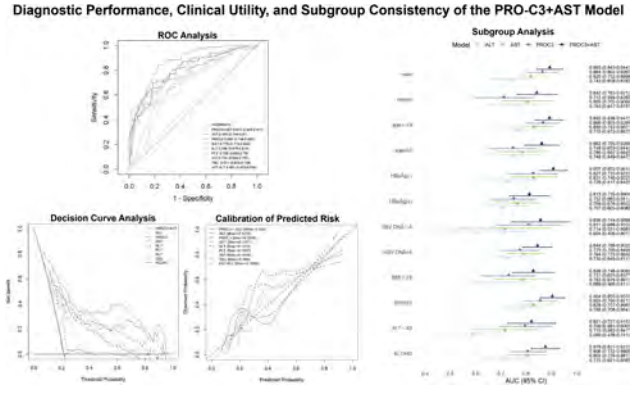


Disclosures: Tetsuya Hosaka:Gilead Sciences: Speaking and Teaching, Eisai: Speaking and Teaching, Fujirebio Inc.: Speaking and Teaching, Fumitaka Suzuki:Nothing to Disclose, Yasue Takeuchi:Nothing to Disclose, Hitomi Sezaki:Nothing to Disclose, Satoshi Saitoh:Nothing to Disclose, Shunya Goto:Nothing to Disclose, Shigeki Yamamoto:Nothing to Disclose, Yasuka Eriksson:Nothing to Disclose, Yoshiyuki Suzuki:Nothing to Disclose, Norio Akuta:Nothing to Disclose, Hiromitsu Kumada:Nothing to Disclose.

4024 | A PROCOLLAGEN TYPE III N-TERMINAL PROPEPTIDE BASED NONINVASIVE MODEL FOR ASSESSING HEPATIC INFLAMMATION IN CHRONIC HEPATITIS B

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Background: Accurate identification of significant liver inflammation is essential for risk stratification and treatment decision-making in patients with chronic hepatitis B (CHB). Serum PRO-C3, a marker of type III collagen formation and active fibrogenesis, may reflect ongoing hepatic injury. This study aimed to evaluate the diagnostic value of PRO-C3 for identifying significant liver inflammation in patients with CHB. **Methods:** A total of 324 patients with CHB who underwent liver biopsy between October 2017 and December 2021 were retrospectively enrolled. Liver inflammation was graded using the Scheuer scoring system, with significant inflammation defined as grade ≥ 3. Baseline clinical, virological, biochemical, and noninvasive fibrosis-related parameters were compared between groups. Independent predictors were identified by multivariable logistic regression. Diagnostic performance was assessed using receiver operating characteristic, calibration, decision curve, and subgroup analyses. **Results:** Among 324 patients with CHB, 70 (21.6%) had significant liver inflammation (G3–4). Compared with patients with G0–2 inflammation, those with G3–4 inflammation had significantly higher levels of ALT, AST, GGT, HBV DNA, PRO-C3, APRI, FIB-4, and liver stiffness, but lower platelet counts. Median PRO-C3 was markedly higher in the G3–4 group than in the G0–2 group (51.84 vs. 20.86 ng/mL, $P < 0.001$). In multivariable analysis, PRO-C3 remained independently associated with significant inflammation (adjusted OR 1.114, 95% CI 1.036–1.241, $P = 0.014$), along with AST and total bilirubin. PRO-C3 alone showed good diagnostic performance, with an AUC of 0.806 (95% CI 0.748–0.865). At the optimal cutoff of 42.72 ng/mL, PRO-C3 achieved 70.0% sensitivity, 81.5% specificity, and 90.8% negative predictive value. Combining PRO-C3 with AST improved discrimination, yielding an AUC of 0.873 (95% CI 0.829–0.917), with 84.3% sensitivity, 77.2% specificity, and 94.7% negative predictive value. Decision curve and calibration analyses further supported its clinical utility, showing the highest net benefit and lowest Brier score (0.105). Subgroup analyses confirmed stable diagnostic performance across age, sex, BMI, HBeAg status, HBV DNA, and ALT strata. **Conclusion:** Serum PRO-C3 is an independent and clinically useful noninvasive biomarker for identifying significant liver inflammation in patients with chronic hepatitis B. A simple model combining PRO-C3 with AST provides superior diagnostic accuracy, improved calibration, and greater clinical net benefit compared with conventional biochemical markers. These findings support the potential role of PRO-C3-based assessment as a practical tool for noninvasive inflammatory risk stratification in CHB, including patients with normal ALT levels.



Disclosures: Xinyu Hu:Nothing to Disclose, Qianqian Chen:Nothing to Disclose, Fajuan Rui:Nothing to Disclose, Jie Li:Nothing to Disclose.

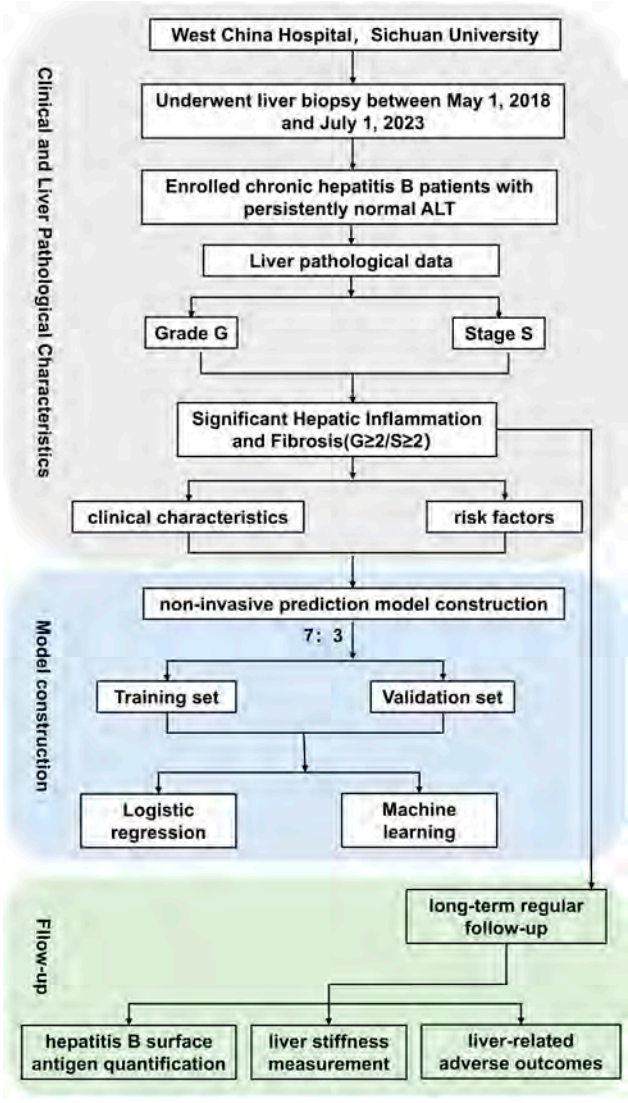
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4025 | NON-INVASIVE PREDICTION MODEL CONSTRUCTION AND FOLLOW-UP OF SIGNIFICANT HEPATIC INFLAMMATION AND FIBROSIS IN CHRONIC HEPATITIS B PATIENTS WITH NORMAL ALT

Xiong Pei[1] Dongbo Wu[2] Hong Tang[3], [1]Sichuan University West China Hospital, [2]West China hospital, Sichuan University, [3]West China hospital, Sichuan University

Background: Many chronic hepatitis B (CHB) patients with persistently normal alanine transaminase (ALT) have hidden liver inflammation and fibrosis, but they are often neglected in clinical practice. Reliable non-invasive tools for risk stratification are lacking. This study aimed to investigate the clinical and liver pathological characteristics of treatment-naive CHB patients with normal ALT; to establish and validate non-invasive models for significant hepatic inflammation and fibrosis, and to explore long-term outcomes after antiviral therapy. **Methods:** A retrospective study enrolled 235 patients who underwent liver biopsy between May 2018 and July 2023 at West China Hospital. Demographic, laboratory, liver stiffness measurement (LSM), and pathological data ($G \geq 2$ for significant inflammation, $S \geq 2$ for significant fibrosis) were collected. Patients were randomly divided into training and validation sets at a 7:3 ratio. Logistic regression and machine learning models were constructed. Independent predictors were screened, and model performance was evaluated by AUC, calibration, and DCA. Long-term follow-up was performed in 168 patients who received antiviral therapy, with liver-related adverse events recorded. **Results:** Among 235 patients, significant inflammation was found in 56 (23.83%) and significant fibrosis ($S \geq 2$) in 44 (18.72%). Age > 40 years, BMI ≥ 24 kg/m², HBeAg negativity, and moderate HBV DNA (10^4–10^7 IU/mL) were associated with higher histological risks. For significant inflammation, we established the BLA (BMI-Liver stiffness-Albumin) model. The AUC were 0.81 (95%CI: 0.73–0.90) and 0.80 (95%CI: 0.67–0.93) for the training and validation set, seperately. SHAP analysis revealed albumin contributed most to model prediction. We further compared the performance of seven machine learning models, and the naive Bayes model achieved the highest AUC (0.8015) .For significant liver fibrosis, we constructed the H-BA2LF (History-BMI-Age/ALP-LSM-Fibrinogen) model. The training set AUC reached 0.88 (95%CI: 0.81–0.95), and the validation set AUC was 0.82 (95%CI: 0.70–0.94). SHAP analysis demonstrated fibrinogen was the most important predictor. Among all machine learning models, logistic regression showed the highest AUC (0.8185) .During up to 7 year follow-up of 168 treated patients, 32 developed liver nodules , 20 developed cirrhosis, and 2 developed HCC. Multivariate analysis confirmed that baseline ALT and LSM were independent risk factors for adverse outcomes. Moreover, HBsAg decreased continuously from 6 months onward, and LSM improved early and remained stable. **Conclusion:** ALT-normal CHB patients carry substantial risks of hidden significant inflammation and fibrosis. Our BLA and H-BA2LF show good predictive performance. Albumin and fibrinogen are the most important features in each model. Long-term antiviral therapy improves liver status, but close monitoring remains necessary.



Disclosures: Xiong Pei:Nothing to Disclose, Dongbo Wu:Nothing to Disclose, Hong Tang:Nothing to Disclose.

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4026 | PERFORMANCE OF PAGE-B AND MODIFIED PAGE-B SCORES FOR HEPATOCELLULAR CARCINOMA IN A MULTI-NATIONAL LATIN AMERICAN HEPATITIS B COHORT

Erin Mann[1] Enrique Carrera Estupiñan[2] Javier Diaz Ferrer[3] Jhon Prieto Ortiz[4] Domingo Balderramo[5] Marco Arrese[6] Andre Boonstra[7] Angelo Mattos[8] Jose Debes[1], [1]University of Minnesota, [2]Universidad San Francisco de Quito, [3]Universidad de San Martin de Pores, [4]CEHYD (Centro de Enfermedades Hepáticas y Digestivas), [5]Instituto Universitario de Ciencias Biomédicas de Córdoba, [6]Pontificia Universidad Católica de Chile, [7]Erasmus University Medical Center, [8]Federal University of Health Sciences of Porto Alegre

Background: The PAGE-B score predicts hepatocellular carcinoma (HCC) risk in patients with chronic hepatitis B virus (HBV) infection and is used to guide surveillance decisions. Performance of PAGE-B in Latin American populations has not been well characterized, with the available data coming only from Brazil. We evaluated PAGE-B and modified PAGE-B (mPAGE-B) in a multi-national Latin American HBV cohort. **Methods:** We analyzed HBV patients from cross-sectional and prospective cohorts at sites in Argentina, Brazil, Chile, Colombia, Ecuador, and Peru. The analytic cohort was restricted to patients with complete data for the PAGE-B components (age, gender, platelets). PAGE-B was calculated for all patients; mPAGE-B, which adds serum albumin, was calculated for the subset with albumin data and compared with PAGE-B in the same patients. Analyses were performed in the full cohort and in the subgroup of patients with documented HBV treatment. In the prospective cohort, incident HCC over 12 months from first visit was identified. Negative predictive value (NPV) and positive predictive value (PPV) were calculated for each score at its low-risk cutoff. NPV and PPV were compared between scores using a paired test for predictive values. **Results:** The cross-sectional cohort included 258 patients (mean age 57.5 years, SD 13.8; 58.1% male), of whom 91 (35.3%) had HCC. Patients were from Argentina (n = 14), Brazil (n = 92), Chile (n = 3), Colombia (n = 4), Ecuador (n = 48), and Peru (n = 97). In the full cohort, PAGE-B had an NPV of 73.3% and PPV of 37.9%. Among patients with available albumin (n = 201), of whom 49 had HCC (24.4%), mPAGE-B performed slightly better than PAGE-B (NPV 94.4% vs. 93.2%, p = 0.61; PPV 28.5% vs. 29.3%, p = 0.40), though differences were not statistically significant. In the treated subgroup (n = 103), PAGE-B had an NPV of 88.5% and PPV of 13.0%; among treated patients with albumin values (n = 93), of whom 11 had HCC (11.8%), mPAGE-B again outperformed PAGE-B (NPV 90.5% vs. 87.5%, p = 0.49; PPV 12.5% vs. 11.6%, p = 0.51), though differences were not statistically significant. Only one patient developed incident HCC in the prospective cohort, limiting evaluation of the scores' prognostic performance. **Conclusion:** In this first multi-country Latin American evaluation, both PAGE-B and mPAGE-B demonstrated high NPV for HCC, with mPAGE-B performing slightly better. These findings support the utility of PAGE-B and mPAGE-B in guiding HCC surveillance decisions in Latin American patients with HBV.

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4027 | EARLY QHBSAG NON-DECLINE IS NOT TREATMENT FAILURE: WEEK-24 REASSESSMENT IDENTIFIES DELAYED RESPONDERS TO PEG-IFNα

Haishi Wu[1] Zhiliang Gao[2] Na Gao[1], [1]Sun Yat-sen University Third Affiliated Hospital., [2]Sun Yat-sen University Third Affiliated Hospital

Background: During 48-week Peg-IFNα therapy for chronic hepatitis B (CHB), week-12 qHBsAg non-decline can create uncertainty but may not indicate uniform non-response. We tested whether week-12 and week-24 qHBsAg reassessment stratifies seroclearance probability and whether aminotransferase activation marks favorable dynamics. **Methods:** From the Everest Project, a real-world multicenter study in China, we analyzed 15,897 NA-suppressed, HBeAg-negative CHB patients with low HBsAg treated with 48-week Peg-IFNα. HBsAg seroclearance was defined as the first documented HBsAg < 0.05 IU/mL within 0-370 days. Week-12 non-decline was defined as no seroclearance by week 12 and a < 0.5-log10 qHBsAg decline from baseline. A favorable week-24 trajectory was defined as seroclearance by week 24 or an additional ≥ 0.5-log10 qHBsAg decline between weeks 12 and 24. Wilson CIs and logistic regression adjusted for baseline/week-12 qHBsAg were used. **Results:** Overall, 3,972/15,897 patients (25.0%; 95% CI 24.3%-25.7%) achieved HBsAg seroclearance. Among week-12 evaluable patients, a favorable week-12 trajectory

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(seroclearance by week 12 or a ≥0.5-log10 qHBsAg decline) identified higher seroclearance probability (2,506/4,658; 53.8%), whereas week-12 non-decliners had lower probability (581/6,356; 9.1%; 95% CI 8.5%-9.9%). Among week-24 evaluable non-decliners, 1,352/4,105 (32.9%) showed a favorable week-24 trajectory. This trajectory was associated with substantially higher seroclearance probability than persistent plateau, weak decline, or rise (408/1,352 [30.2%; 95% CI 27.8%-32.7%] vs 43/2,753 [1.6%; 95% CI 1.2%-2.1%]; adjusted OR 30.8, 95% CI 21.7-43.8; P < 0.001). Week-24 reassessment thus separated this subgroup into ~30% versus near-zero seroclearance probabilities. ALT elevation ≥2-fold baseline was associated with delayed qHBsAg decline among week-12 non-decliners after adjustment for baseline/week-12 qHBsAg (OR 1.42, 95% CI 1.24-1.63; P < 0.001). **Conclusion:** Week-12 qHBsAg non-decline should not be interpreted as treatment failure during Peg-IFNα therapy. Week-24 reassessment identifies non-decliners who remain likely to achieve HBsAg seroclearance, while ALT elevation ≥2-fold baseline may signal delayed qHBsAg decline despite an unfavorable week-12 trajectory. These findings support patient counseling and post-treatment planning during a 48-week course.

Disclosures: Haishi Wu:Nothing to Disclose, Zhiliang Gao:Nothing to Disclose, Na Gao:Nothing to Disclose.

4028 | ENHANCED HBCAG IMMUNOASSAY ENABLES DETECTION OF CLINICALLY RELEVANT LOW-LEVEL HBV VIREMIA FOR TREATMENT ELIGIBILITY

Rene Geissler[1] Megha Patel[1] Anika Koehler[1] Joerg Herzogenrath[1] Eddie Almaraz[1] Justin Blumenthal[1] Amit Kumar[1] Todd Solbrig[1] Cyrille Kouligueul Diedhiou[2] Moustapha Mbow[2] Noel Manga[3] Souleymane Mboup[2] Ambroise Ahouidi[2] Michael Berg[1] Gavin Cloherty[1], [1]Abbott, [2]IRESSEF, [3]Hôpital Universitaire de la Paix

Background: Accurate staging of chronic hepatitis B is essential for guiding treatment decisions and predicting clinical outcomes. Current treatment guidelines rely on HBV DNA quantification, with therapeutic thresholds set at ≥2,000 IU/mL or ≥20,000 IU/mL depending on liver enzyme levels, HBeAg status, and evidence of fibrosis or cirrhosis. Despite these guidelines, access to molecular diagnostics for HBV DNA measurement remains limited in many low- and middle-income countries (LMICs) where most infections (~80%) occur, creating barriers to timely and effective care. Importantly, non-phosphorylated HBcAg, located in HBV DNA-containing particles, has emerged as surrogate biomarker for HBV DNA. However, more sensitive HBcAg immunoassays could offer additional clinical utility by enabling HBV detection at clinically relevant thresholds. **Methods:** We modified a first-generation (v1) HBcAg-specific assay by incorporating a new formulation and monoclonal antibodies. Additionally, this updated assay format was implemented on a digital platform (v2), improving clinical sensitivity on average 225-fold. **Results:** The enhanced version (v2) achieved a limit of quantification of 30 fg/mL, corresponding to approximately 1,000 HBV DNA IU/mL. Comparative analysis of v1 and modified v2 assays demonstrated a reduction in the detection threshold from $4.9x10^5$ to 1,000 HBV DNA IU/mL, which aligns with treatment eligibility criteria. Longitudinal blood draws from acute HBV patients and single timepoint specimens from treatment-naïve blood donors showed significantly improved detection and quantification using the v2 HBcAg assay. **Conclusion:** The HBcAg v2 assay enables increased detection of low viral titers consistent with treatment guidelines and corresponds directly to HBV DNA levels. Its ability to specifically detect low-abundance HBcAg enhances disease staging and may support therapeutic management, particularly in resource limiting settings, where affordable and deployable diagnostic tools are urgently needed.

Disclosures: Rene Geissler:Abbott: Employee, Abbott: Stock – privately held company, Megha Patel:Nothing to Disclose, Anika Koehler:Nothing to Disclose, Joerg Herzogenrath:Nothing to Disclose, Eddie Almaraz: Nothing to Disclose, Justin Blumenthal:Abbott Laboratories: Employee, Amit Kumar:Abbott Laboratories: Employee, Todd Solbrig:Nothing to Disclose, Cyrille Kouligueul Diedhiou:Nothing to Disclose, Moustapha Mbow:Nothing to Disclose, Noel Manga:Nothing to Disclose, Souleymane Mboup:Nothing to Disclose, Ambroise Ahouidi:Nothing to Disclose, Michael Berg: Nothing to Disclose, Gavin Cloherty:Nothing to Disclose.

4029 | HBCRAG AS A BIOMARKER FOR PREDICTING RELAPSE FOLLOWING NUCLEOS(T)IDE ANALOGUE DISCONTINUATION IN CHRONIC HEPATITIS B: A PROSPECTIVE PILOT STUDY

Premashis Kar[1] Pravinkumar Rejliwal[2] Pabitra Sahu[3], [1]Maulana Azad Medical College, [2]Max Superspeciality HOPSITAL, [3]Max Superspeciality Hospital

Background: Discontinuation of nucleos(t)ide analogue (NA) therapy in selected patients with chronic hepatitis B (CHB) may achieve functional cure but

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carries a risk of virological and biochemical relapse. Hepatitis B core-related antigen (HBcrAg), a surrogate marker of intrahepatic covalently closed circular DNA (cccDNA) activity, may help identify patients suitable for treatment cessation. We evaluated the utility of HBcrAg in combination with HBV DNA for predicting relapse after NA discontinuation. **Methods:** In this prospective pilot study, 59 consecutive non-cirrhotic, HBeAg-positive CHB patients aged 18–80 years who had received ≥ 12 months of NA therapy and achieved undetectable HBV DNA and HBcrAg were enrolled. Antiviral therapy was discontinued, and patients were followed for 6 months with serial HBV DNA and HBcrAg measurements. Relapse was defined as HBV DNA > 2000 IU/mL and/or alanine aminotransferase (ALT) > 2× the upper limit of normal. **Results:** During the 6-month follow-up period, a proportion of patients experienced virological and/or biochemical relapse despite undetectable HBV DNA at treatment cessation. Patients who maintained HBcrAg negativity after discontinuation were more likely to remain in sustained remission. Persistent HBcrAg negativity demonstrated potential utility as an adjunctive marker for identifying patients at lower risk of relapse following NA withdrawal. **Conclusion:** HBcrAg may complement HBV DNA in monitoring treatment response and predicting relapse after NA discontinuation in CHB. Sustained HBcrAg negativity was associated with a lower likelihood of relapse and may aid in selecting candidates for treatment cessation. Larger studies with longer follow-up are needed to validate the role of HBcrAg in guiding NA discontinuation strategies.

Disclosures: Premashis Kar:Nothing to Disclose, PRAVINKUMAR REJLIWAL:Nothing to Disclose, PABITRA SAHU:Nothing to Disclose.

4030 | MACHINE LEARNING–BASED MODEL FOR PREDICTING SIGNIFICANT FIBROSIS IN CHRONIC HEPATITIS B PATIENTS IN THE INDETERMINATE PHASE

Shaoqiu Zhang[1] Li Zhu[2] Haiqin Pu[3] Jian Wang[1] Tao Fan[4] Ye Xiong[4] Chao Jiang[5] Juan Xia[1] Yuanwang Qiu[6] Xingxiang Liu[3] Chuanwu Zhu[2] Rui Huang[1] Qun Zhang[7] Chao Wu[1], [1]Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University, [2]The Affiliated Infectious Diseases Hospital of Soochow University, [3]Huai'an No. 4 People's Hospital, [4]Nanjing Drum Tower Hospital Clinical College of Nanjing University of Chinese Medicine, [5]Nanjing Drum Tower Hospital Clinical College of Jiangsu University, [6]The Fifth People's Hospital of Wuxi, [7]Zhongda Hospital, School of Medicine, Southeast University

Background: Although the shared decision-making approach is recommended for the management of chronic hepatitis B (CHB) patients with indeterminate phase according to the AASLD 2025 hepatitis B guidelines, the presence of significant fibrosis is an important factor informing antiviral treatment decisions. Using machine learning approaches, we developed and validated a noninvasive model to accurately predict significant fibrosis in CHB patients in the indeterminate phase. **Methods:** A total of 751 patients with CHB who fulfilled the 2025 AASLD criteria for the indeterminate phase and underwent liver biopsy were retrospectively included from 5 medical centers in China. Significant fibrosis was defined as liver fibrosis of stage ≥ S2 according to Scheuer's classification. Patients were randomly divided into a training cohort and a validation cohort at a ratio of 7:3. Candidate variables were selected by LASSO logistic regression and Boruta algorithm in the training cohort. Clinically relevant feature sets were compared using gradient boosting machine (GBM) with 10-fold cross-validation, and multiple machine learning algorithms were trained using the final feature set, including logistic regression, random forest, extreme gradient boosting (XGBoost), GBM, support vector machine (SVM), and decision tree. The final model was compared with aspartate aminotransferase (AST) to platelet ratio index (APRI) and fibrosis index based on 4 factors (FIB-4) in the validation cohort by the area under the receiver operating characteristic curve (AUROC), calibration, and decision curve analysis. **Results:** The training and validation cohorts included 522 and 229 patients, respectively, with significant fibrosis observed in 301 (57.7%) and 132 (57.6%) patients. The final model was constructed using GBM and incorporated five variables (HBV DNA, platelet count, prothrombin time, albumin, and AST). In the validation cohort, the GBM model achieved an AUROC of 0.755 (95% confidence interval [CI]: 0.693-0.816), which was significantly higher than APRI (AUROC: 0.681, 95% CI: 0.611-0.750, P = 0.015) and FIB-4 (AUROC: 0.669, 95% CI: 0.599-0.738, P = 0.012). It also showed reliable calibration function (Brier score of 0.199 and Hosmer-Lemeshow test of P > 0.05) and had higher net benefit in decision curve analysis. **Conclusion:** This novel machine learning model, which includes five routinely available variables, outperformed APRI and FIB-4 and provided reliable risk prediction for significant liver fibrosis in CHB patients with indeterminate phase. This model may serve as a practical tool for treatment decision-making in such population.

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Nothing to Disclose, Chuanwu Zhu:Nothing to Disclose, Rui Huang:Nothing to Disclose, Qun Zhang:Nothing to Disclose, Chao Wu:Nothing to Disclose.

4031 | CLINICAL AND LIPID-RELATED METABOLIC BIOMARKERS ASSOCIATED WITH LIVER FIBROSIS IN PATIENTS WITH CHRONIC HEPATITIS B AND MASLD: A SYSTEMATIC REVIEW AND META-ANALYSIS

Zhenghaoyu Huang[1] Jinyang Gong[1] Han Lin[1] Mengmeng Liu[2] Xu Li[2] Yonghong Guo[2], [1]University of Shanghai for Science and Technology, [2]Gongli Hospital of Shanghai Pudong New Area

Background: Chronic hepatitis B (CHB) and metabolic dysfunction-associated steatotic liver disease (MASLD) frequently coexist and may jointly contribute to liver fibrosis progression. Metabolic dysregulation, including lipid-related abnormalities and liver injury markers, may reflect fibrogenic activity in this dual-etiology population. We aimed to systematically evaluate clinical and lipid-related metabolic biomarkers associated with significant liver fibrosis in patients with CHB and MASLD. **Methods:** We systematically searched PubMed, Embase, Cochrane Library, Web of Science, CBM, CNKI, Wanfang, and VIP from inception to May 6, 2026, following PRISMA 2020 guidance. Eligible studies included adults with CHB and concomitant MASLD who reported serum metabolic or clinical biomarkers according to liver fibrosis status. Significant fibrosis was defined as fibrosis stage $\geq$F2, assessed by liver biopsy or validated non-invasive methods including liver stiffness measurement, FIB-4, or NFS. Pooled mean differences (MDs) with 95% confidence intervals (CIs) were calculated using fixed- or random-effects models according to heterogeneity. Study quality was assessed using the Newcastle–Ottawa Scale. **Results:** A total of 11 studies involving 3,431 patients with CHB and MASLD were included, of whom 1,143 had significant fibrosis and 2,288 had non-significant fibrosis. Compared with patients without significant fibrosis, those with significant fibrosis had higher levels of gamma-glutamyl transferase (GGT; MD = 14.51, 95% CI 9.68–19.34; I^2 = 72%; P < 0.001) and alanine aminotransferase (ALT; MD = 8.59, 95% CI 6.14–11.04; I^2 = 0%; P < 0.001). Platelet count was significantly lower in patients with significant fibrosis (MD = -33.81, 95% CI -51.38 to -16.23; I^2 = 85%; P < 0.001). HDL-C was also lower in the significant fibrosis group (MD = -0.05, 95% CI -0.08 to -0.02; I^2 = 80%; P = 0.001). No significant differences were observed for total cholesterol (MD = 0.01, 95% CI -0.10 to 0.12; I^2 = 14%; P = 0.86), triglycerides (MD = -0.04, 95% CI -0.17 to 0.09; I^2 = 62%; P = 0.53), or LDL-C (MD = 0.21, 95% CI -0.11 to 0.54; I^2 = 82%; P = 0.20). **Conclusion:** In patients with CHB and concomitant MASLD, significant liver fibrosis was associated with higher GGT and ALT levels and lower platelet count and HDL-C levels. In contrast, total cholesterol, triglycerides, and LDL-C were not significantly associated with fibrosis status. These findings highlight the close relationship between liver biochemical abnormalities and fibrosis in this dual-etiology population, supporting closer monitoring and optimized management to improve liver biochemical profiles. These readily available biomarkers may help support non-invasive liver fibrosis risk stratification in patients with coexisting CHB and MASLD.

Disclosures: Zhenghaoyu Huang:Nothing to Disclose, Jinyang Gong:Nothing to Disclose, Han Lin:Nothing to Disclose, Mengmeng Liu:Nothing to Disclose, Xu Li:Nothing to Disclose, Yonghong Guo:Nothing to Disclose.

4032 | INTEGRATION OF MICROBIAL SIGNATURES INTO MACHINE LEARNING MODELS SIGNIFICANTLY IMPROVES PREDICTION OF ADVERSE OUTCOMES IN PATIENTS WITH HEPATITIS B-RELATED CIRRHOTIC ASCITES

Jiaran Sun[1] Ruifeng Yang[1], [1]Department of Clinical Laboratory, Peking University Shougan

Background: Traditional clinical assessment methods have limitations in early identification of poor prognosis in hepatitis B-related cirrhotic ascites. This study aimed to evaluate the value of a novel machine learning model that integrates microbial signatures with conventional clinical features for predicting 90-day end-stage liver disease (ESLD) events in patients with hepatitis B-related cirrhotic ascites. **Methods:** A total of 306 patients with cirrhotic ascites who underwent ascitic fluid culture between 2019 and 2024 were retrospectively enrolled. Among them, 206 patients from 2019–2022 were assigned as the training set, and 100 patients from 2022–2024 served as an independent test set. The primary outcome was ESLD events occurring within 90 days after ascitic fluid sampling, including liver failure-related death, liver transplantation, hepatorenal syndrome, or grade III–IV hepatic

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encephalopathy. Clinical and microbial features were analyzed. Three models were constructed: a baseline MELD-Na model, a logistic regression model, and an eXtreme Gradient Boosting (XGBoost) model integrating all features. Model performance was evaluated on the independent test set. For the XGBoost model, SHapley Additive exPlanations (SHAP) values were used to rank feature importance. **Results:** The overall 90-day endpoint event rate was 35%. Compared to the non-ESLD group, patients with ESLD exhibited significantly worse microbial profiles (higher rates of positive ascitic fluid culture, polymicrobial infection, carbapenem resistance, and availability of fewer than two effective antibiotics) and clinical parameters (MELD-Na score, ascitic fluid polymorphonuclear leukocyte count, procalcitonin, and serum creatinine). The XGBoost model demonstrated significantly superior predictive performance, with an AUC of 0.85 on the test set, outperforming both the MELD-Na model (AUC = 0.72) and the logistic regression model (AUC = 0.78) ($P < 0.05$). SHAP analysis further confirmed that carbapenem resistance was the most influential microbial predictor, while MELD-Na score, procalcitonin, and availability of fewer than two effective antibiotics were also important features. **Conclusion:** Integrating microbial signatures, with a focus on antimicrobial resistance, substantially improves the prediction of short-term adverse outcomes in patients with cirrhotic ascites. This model may facilitate early identification of high-risk patients and guide precise clinical intervention.
Disclosures: Jiaran Sun:Nothing to Disclose, Ruifeng Yang:Nothing to Disclose.

4033 | CLINICAL APPLICATION OF SERUM ALBUMIN BINDING FUNCTION DETECTION METHOD BASED ON ELECTRON PARAMAGNETIC RESONANCE

Wen Xie[1] Ge Yidi[1], [1]Beijing Ditan Hospital

Background: As an important protein that reflects the synthetic function of the liver, the structural integrity and binding function of albumin are often damaged during the progression of liver disease, and the traditional total albumin concentration detection is difficult to accurately reflect the true functional state of albumin. This research aims to establish and verify a serum albumin binding function detection method based on Electron paramagnetic resonance (EPR) technology, and verify its application in different evolutionary stages of hepatitis B-related liver disease. **Methods:** This study uses EPR technology as the detection method, and uses 16-bit nitrogen oxide free radical labeling stearic acid as a spin probe. Based on the principles of age, gender and underlying disease matching, the study included a total of 180 cases in six groups, including chronic hepatitis B, hepatitis B cirrhosis, hepatocellular carcinoma and healthy control groups. Analyze the EPR spectrum through the spectrum fitting methods. The experimental spectrum of the complex formed after the combination of HSA and 16-DSA is mainly composed of three different components, namely the strong-binding component, the weak-binding component and the free component. Among them, the strong binding component corresponds to the probe part that binds to the albumin molecule with high intensity; the weak binding component reflects the medium-strength binding state between the probe and the albumin; the free component represents the free probe molecule that is not bound to albumin. Under the condition that the molar ratio of the probe and albumin remains constant, the higher the proportion of free components in the total spectrum, indicating that the comprehensive binding ability of albumin to foreign molecules is weaker, that is, the binding performance is poor.This research was approved by the Ethics Committee of Ditan Hospital. (AF/SS-21/05.2) **Results:** Based on the system optimization of EPR detection conditions, this study has established a set of serum albumin binding function detection methods with high accuracy and excellent detection efficiency. On the basis of this study, this study further carried out testing and verification. This study results showed that the albumin binding function gradually decreased with the severity of liver disease. **Conclusion:** Based on EPR technology to detect serum albumin binding function technology, this study further optimizes the detection conditions to establish a more efficient detection process. Through verification in different stages of liver disease, it was found that albumin binding function gradually decreased with the aggravation of the severity of hepatitis B-related liver disease.

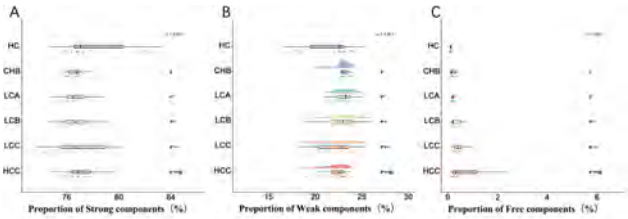


Figure. Comparison of the proportion of different components after spectrum fitting in the healthy control and hepatitis B-related liver disease group
A. Comparison of the proportion of free components; B. Comparison of the proportion of strong binding components; C. Comparison of the proportion of weakly combined components.The p value in the figure represents the overall comparison result between the four groups. Each group made a two-by-two comparison, # indicating that compared with the healthy control group. The difference is statistically significant ($p< 0.05$), * indicates that the difference with the chronic hepatitis B group is statistically significant ($p< 0.05$). + indicates that the difference with hepatitis B cirrhosis Child-pugh A-level group is statistically significant ($p< 0.05$), ÷ indicates that the difference with hepatitis B cirrhosis Child-pugh A-level group is statistically significant ($p< 0.05$), ※ indicates that it is compared with hepatitis B cirrhosis Child-pugh B-level group The difference is statistically significant ($p< 0.05$). If it is not marked, the difference is not statistically significant.
CHB: Chronic hepatitis B; HCC: Hepatocellular carcinoma; HC: Healthy control; LCA: Child-Pugh class A liver cirrhosis; LCB: Child-Pugh class B liver cirrhosis; LCC: Child-Pugh class C liver cirrhosis; LC: Liver cirrhosis.

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Disclosures: wen Xie:Nothing to Disclose, ge yidi: Nothing to Disclose.

4034 | ◆ FORTY YEARS AFTER UNIVERSAL HEPATITIS B VACCINATION IN TAIWAN: CURRENT SEROEPIDEMIOLOGY AND REMAINING GAPS TOWARD ELIMINATION

Kai-Chi Chang[1] Mei-Hwei Chang[1] Huey-Ling Chen[1] Yen-Hsuan Ni[1], [1]National Taiwan University Hospital

Background: Universal infant hepatitis B virus (HBV) vaccination programs have substantially reduced the prevalence of HBV infection worldwide. We aimed to evaluate the long-term efficacy of universal HBV vaccination after 40 years of implementation in Taiwan and to identify the remaining barriers toward HBV elimination. **Methods:** A total of 2,378 individuals aged 0–60 years were recruited in 2025 from four administrative regions in Taiwan according to population distribution. Serum levels of hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), and hepatitis B core antibody (anti-HBc) were assessed. **Results:** After 40 years of universal vaccination, the overall seropositivity rates for HBsAg and anti-HBc in Taiwan were 3.36% and 18.8%, respectively. Compared with the pre-vaccination cohort, the post-vaccination cohort demonstrated markedly lower seropositivity rates for both HBsAg (0.82% vs. 7.5%, $p < 0.001$) and anti-HBc (2.85% vs. 44.7%, $p < 0.0001$). Among breakthrough HBsAg-positive cases in the vaccinated cohort, mother-to-child transmission remained the predominant route of HBV infection.Among participants without evidence of HBV infection (HBsAg-negative/anti-HBc-negative), detectable protective anti-HBs levels (> 10 mIU/mL) were observed in 49.5% (708/1429) of the vaccinated cohort. Anti-HBs seropositivity varied across age groups within the vaccinated cohort, reaching the lowest level in adolescents aged 10–19 years (35.7%), compared with 63.3% in children aged < 10 years, 56.5% in individuals aged 20–29 years, and 60.2% in those aged 30–39 years. **Conclusion:** A profound reduction in HBV infection has been achieved after 40 years of universal HBV vaccination in Taiwan. However, despite the persistently low prevalence of HBsAg positivity, complete eradication of HBV infection has not yet been achieved. Vaccine-induced anti-HBs antibodies waned over time while still maintaining effective protection against chronic HBV infection. Mother-to-child transmission remains a critical barrier to HBV elimination, highlighting the importance of optimizing perinatal screening and antiviral intervention strategies.

Disclosures: Kai-Chi Chang:Nothing to Disclose, Mei-Hwei Chang:Nothing to Disclose, Huey-Ling Chen: Nothing to Disclose, Yen-Hsuan Ni:Nothing to Disclose.

4035 | ◆ THE HIDDEN BURDEN OF CHRONIC HEPATITIS B: MORTALITY AND DISABILITY PERSIST DESPITE DECLINING INCIDENCE: A GLOBAL BURDEN OF DISEASE ANALYSIS, 1990–2023

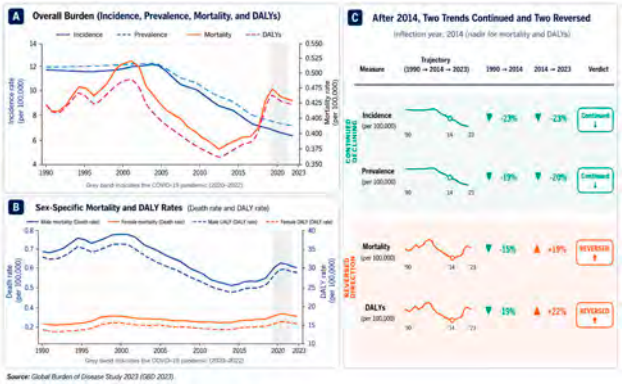
Mohamed Eldesouki[1] Mohammed Youssef[2] Ahmed Ibrahim[3] Omar Alkasabrah[4] Mohammad Nabil Rayad[5] Abdelfattah Taha[6] Theodore Dacosta[5] Yatinder Bains[1], [1]New York Medical College at Saint Michael Medical Center, [2]Hunt Regional Medical Center, [3]San Joquin General Hospital, [4]Landmark Medical Center, [5]New York Medical College at Saint Michael's Medical Center, [6]LSCFT Trust

Background: Chronic hepatitis B (HBV) is a leading driver of liver-related morbidity and mortality in the United States. However, contemporary U.S. trends among young and middle-aged individuals are incompletely characterized. We examined three decades of chronic HBV incidence, prevalence, mortality, and disability-adjusted life year (DALY) trends to characterize the contemporary burden in this middle-aged population. **Methods:** We analyzed Global Burden of Disease Study 2023 estimates from the IHME for chronic hepatitis B among U.S. adults aged 15–49 years from 1990–2023. Annual age-standardized rates per 100,000 were extracted for incidence, prevalence, mortality, and DALYs, overall and by sex. Temporal trends were characterized by cumulative percent change from 1990 to 2023. We also compared two analytic epochs (1990→2014 and 2014→2023) and identified inflection points. Sex disparities were assessed using annual male-to-female rate ratios. Estimates are reported with 95% uncertainty intervals. **Results:** Among U.S. adults aged 15–49 years, chronic HBV incidence declined by 40.6% from 1990 to 2023, decreasing from 11.66 to 6.92 per 100,000, while prevalence declined by 35.0%, from 475.3 to 309.0, reflecting vaccination and screening gains. In contrast, mortality increased by 0.6% from 0.452 to 0.455, while DALYs decreased by only 0.9%, from 22.66 to 22.45 per 100,000 (Figure 1A).Sex-based disparities were pronounced in 2023: men had approximately 2-fold higher mortality than women (0.60 vs 0.30 per 100,000) and 2-fold higher DALY rates (29.77 vs 14.92 per 100,000). The male-to-female gap was smaller for prevalence (350.96 vs 265.92 per 100,000) and incidence (8.16 vs 5.65 per 100,000), corresponding to ratios of 1.32–1.44 (Figure 1B).Period-specific analysis showed a clear divergence after 2014. From

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1990 to 2014, all four measures declined, including incidence (−23%), prevalence (−19%), mortality (−15%), and DALYs (−19%). From 2014 to 2023, incidence and prevalence continued to decline by 23% and 20%, respectively. In contrast, mortality and DALYs shifted from prior decline to large increases, rising by 19% and 22%, respectively. Mortality and DALYs reached their lowest levels around 2014–2015, followed by a sustained increase through 2023, with both measures peaking in 2021 during the COVID-19 pandemic period. (Figure 1C) **Conclusion:** Despite substantial declines in chronic HBV incidence and prevalence among U.S. young adults, mortality and DALYs rates did not decline over three decades and increased sharply after 2014, with further increases during the COVID-19 pandemic period. This divergence reflects the ongoing burden of established chronic HBV infection and gaps in diagnosis, linkage to care, and antiviral treatment. Intensified HBV screening, treatment initiation, and longitudinal liver disease prevention are needed to convert gains in HBV prevention into reductions in mortality and disability.

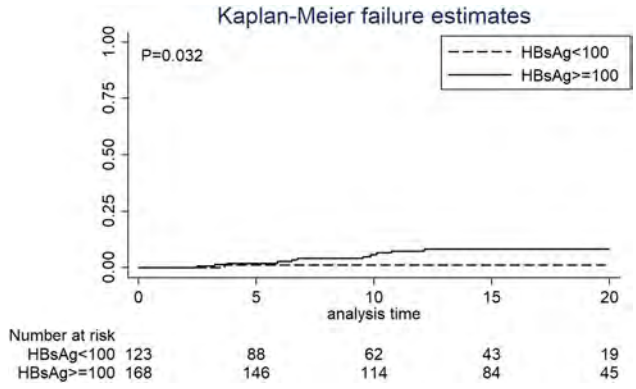


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4036 | ◆ BASELINE HEPATITIS B SURFACE ANTIGEN LEVEL PREDICTS IMMUNE-ACTIVE PHASE TRANSITION IN INACTIVE CHRONIC HEPATITIS B

Tai-Chung Tseng[1] Shang-Chin Huang[2] Pei-Yu Yang[1] Tung-Hung Su[1] Hung-Chih Yang[2] Chen-Hua Liu[1] Jia-Horng Kao[1], [1]National Taiwan University Hospital, [2]National Taiwan University

Background: Chronic hepatitis B (CHB) remains a major global health concern, primarily because of the development of hepatocellular carcinoma (HCC). Previous studies have shown that inactive CHB patients with hepatitis B surface antigen (HBsAg) levels < 100 IU/mL have a negligible risk of HCC. Since transition to the immune-active (IA) phase is a key driver of HCC development and a major indication for antiviral treatment initiation, this study aimed to explore whether a baseline HBsAg level < 100 IU/mL is associated with a lower risk of IA phase transition in inactive CHB patients. **Methods:** A total of 291 inactive CHB patients (non-cirrhotic, HBeAg-negative, normal ALT levels, and HBV DNA < 2,000 IU/mL) were retrospectively enrolled from National Taiwan University Hospital between 2000 and 2010. Patients underwent regular follow-up at least twice yearly. The primary endpoint was IA phase transition, defined as ALT > 2× the AASLD-defined upper limit of normal together with HBV DNA > 2,000 IU/mL. HBV DNA and HBsAg levels were measured using stored serum samples. **Results:** Over a median follow-up of 12.4 years, 15 inactive CHB patients developed IA phase transition, corresponding to an annual incidence of 0.35%. Among the cohort, 124 (42.0%) patients had HBsAg levels < 100 IU/mL. Patients with HBsAg < 100 IU/mL (vs. ≥ 100 IU/mL) had lower risk of IA phase transition, with a crude hazard ratio (HR) of 0.11 (95% CI: 0.01-0.89). This association remained significant after adjustment for age and sex. Notably, only one inacitve CHB patients with HBsAg < 100 IU/mL developed IA phase transition during the follow-up. **Conclusion:** Serum HBsAg levels < 100 IU/mL effectively identify inactive CHB patients with a minimal risk of IA phase transition. Since an HBsAg level < 100 IU/mL has been shown to identify inactive CHB patients with an HCC risk below the HCC surveillance threshold, our data suggest that excluding these patients from regular follow-up carries a minimal risk of missing the opportunity for antiviral treatment initiation, which is a key component in defining partial HBV cure.



Disclosures: Tai-Chung Tseng:Nothing to Disclose, Shang-Chin Huang:Gilead Sciences: Speaking and

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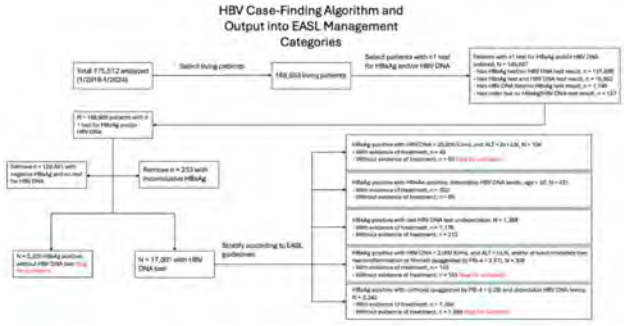
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Teaching, Pei-Yu Yang:Nothing to Disclose, Tung-Hung Su:Gilead Sciences: Consultant, AbbVie: Speaking and Teaching, Bristol-Myers Squibb: Speaking and Teaching, Gilead Sciences: Speaking and Teaching, Merck Sharp and Dohme: Speaking and Teaching, Roche: Speaking and Teaching, Sysmex: Speaking and Teaching, Eisai: Speaking and Teaching, Abbott: Speaking and Teaching, Hung-Chih Yang:Nothing to Disclose, Chen-Hua Liu:Nothing to Disclose, Jia-Horng Kao:Nothing to Disclose.

4037 | ◆ AN OPEN-SOURCE PHENOTYPING ALGORITHM TO SUPPORT HEPATITIS B CASE-FINDING AND LINKAGE TO CARE

Nathaniel Ash[1] Brandon Mui[2] Brooke Wyatt[3] Anna Mageras[1] Jihae Jeon[1] Alyson Harty[3] Lauren Alpert[1] Mark Miller[1] Tatyana Kushner[4] Douglas Dieterich[1] Andrea Branch[3], [1]Icahn School of Medicine at Mount Sinai, [2]Renaissance School of Medicine at Stony Brook University, [3]Icahn School of Medicine at Mount Sinai (ISMMS), [4]Weill-Cornell Medical College

Background: Chronic hepatitis B virus (HBV) infection affects 296 million people globally and remains a major public health threat. Antiviral therapy remains underutilized even among treatment-eligible patients. Proactive case-finding tools have previously been shown to close care gaps in other chronic liver diseases and are needed to improve the HBV care pipeline. We aimed to develop an open-source phenotyping algorithm to facilitate HBV case-finding and linkage to care. **Methods:** An HBV case-finding algorithm was developed using structured query language coding to collect and analyze data from EPIC electronic medical records, incorporating 145 laboratory test values, five antiviral medications, patient age, and last date of data entry or death. Algorithm performance was validated against manual review of 200 randomly selected patient charts. The validated algorithm was then applied to records of 4,095,070 individuals in the Mount Sinai Data Warehouse (2003–2024). Treatment eligibility was assessed per EASL guidelines using HBsAg, HBV DNA, ALT, and FIB-4 scores. Patients eligible for treatment without a recorded prescription were flagged for outreach. **Results:** The algorithm achieved 99.0% accuracy, with 90.9% sensitivity, 99.5% specificity, 90.9% PPV, and 99.5% NPV. Among 4,095,070 individuals, 149,037 had HBsAg and/or HBV DNA testing and 17,001 had HBV DNA data available for treatment eligibility assessment. Significant treatment gaps were identified across all eligibility categories. Notably, 54.6% of patients with HBV DNA > 20,000 IU/mL and ALT > 2x ULN lacked a prescription; 52.9% of those with HBV DNA > 2,000 IU/mL, ALT > ULN, and/or FIB-4 > 2.67 lacked a prescription; and 58.2% of patients with FIB-4 > 3.25, indicating likely cirrhosis, had no recorded HBV prescription. Additionally, 2,205 HBsAg-positive patients lacked HBV DNA testing, including 83 with ALT > 2x ULN, precluding treatment eligibility assessment. **Conclusion:** We developed a high-performance, portable HBV case-finding algorithm. It revealed substantial treatment gaps across a large, diverse health system. Over half of treatment-eligible patients with advanced fibrosis or cirrhosis lacked antiviral prescriptions, highlighting a critical need for proactive outreach and longitudinal care management. The algorithm is freely available on GitHub with a user manual and is adaptable to both EPIC and non-EPIC systems, enabling scalable implementation to improve HBV care delivery.



Disclosures: Nathaniel Ash:Nothing to Disclose, Brandon Mui:Nothing to Disclose, Brooke Wyatt:Nothing to Disclose, Anna Mageras:The Kinetix Group: Advisor, Novo Nordisk: Advisor, Gilead Sciences: Grant/Research Support, Gilead Sciences: Advisor, Jihae Jeon:Nothing to Disclose, Alyson Harty:Nothing to Disclose, Lauren Alpert:Nothing to Disclose, Mark Miller:Nothing to Disclose, Tatyana Kushner:Gilead: Grant/Research Support, Gilead: Advisor, GSK: Advisor, Eiger: Advisor, GSK: Consultant, Madrigal: Advisor, Ipsen: Advisor, Mirum: Advisor, Mirum: Grant/Research Support, Ipsen: Grant/Research Support, Douglas Dieterich:Nothing to Disclose, Andrea Branch:Nothing to Disclose.

4038 | ◆ LONG-TERM RISK OF LIVER-RELATED EVENTS IN PATIENTS WITH RESOLVED HDV INFECTION COMPARED WITH HBV MONOINFECTION: A PROPENSITY SCORE-MATCHED ANALYSIS

Habiba Kamal Khodir[1] Karin Lindahl[2] Katarina Århem[2] Caroline Gahrton[2] Heiner Wedemeyer[3] Soo Aleman[2], [1]Karolinska Institutet, [2]1Dept of Infectious Diseases, Karolinska University Hospital/ Karolinska Institutet, Stockholm, Swede, [3]3D-SOLVE: EU-funded Network on individualized management of hepatitis D, 4Department of Gastroentero

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Background: Patients with resolved HDV replication have a more favorable prognosis compared to those with persistent HDV replication. However, the long-term risk of liver-related events compared with HBV-monoinfection remains unclear. We aimed to compare liver disease progression between patients with resolved HDV infection and HBV monoinfection. **Methods:** We conducted a retrospective cohort study including all adults with resolved HDV infection, defined as anti-HDV positivity with at least two negative HDV RNA tests, and patients with chronic HBV monoinfection attending the Department of Infectious Diseases at Karolinska University Hospital, Stockholm, Sweden between 1990-2024. Data were retrieved from InfCare Hepatitis registry. Patients with resolved HDV infection were propensity score-matched up to 1:5 with HBV-monoinfected controls by birth, sex, date of initial visit, HBeAg status, and region of origin. Patients with prior liver transplantation, HCC at baseline, or < one year follow-up were excluded. The incidence rates and cumulative risks of liver-related events (decompensation, HCC, liver-related death, or liver transplantation) were assessed using Kaplan-Meier analysis and compared with Cox regression. **Results:** In total, 110 patients with resolved HDV infection were matched to 522 patients with HBV monoinfection. Median age at diagnosis was 34.5 years in both groups. The resolved HDV group included more males (79.1% vs. 56.3%, $p < 0.001$), Caucasians (31.1% vs 18.8%), anti-HCV positive patients (56.4% vs 0.4%), and patients with alcohol overconsumption (52.7% vs. 5.9%). Baseline ALT, AST, bilirubin, albumin, INR, and liver stiffness values were comparable, but cirrhosis was more frequent in the resolved HDV group (21.8% vs 9.6%). During a median follow-up of 9.5 (IQR 5.1-16.8) years, liver-related events occurred in 20 (18.2%) of resolved group versus 30 (5.2%) of HBV-monoinfection group. This corresponds to annual incidence rates of 1.7%, and 0.5%, respectively, and 10-, 15- and 20-year cumulative risks of 15.8%, 19.9% and 23.3% in the resolved group vs, 4.8%, 7.5% and 8.3% in the HBV monoinfection group (all $p < 0.05$). Independent predictors of liver events were older age (aHR = 1.1), diabetes (aHR = 2.30), alcohol overconsumption (aHR = 2.3), anti-HDV+ (aHR = 2.44) and baseline cirrhosis (aHR = 2.67). **Conclusion:** Patients with resolved HDV infection showed a higher long-term risk of liver events than those with HBV-monoinfection. This excess risk was driven by previous HDV infection as well as comorbid factors and baseline liver cirrhosis. Closer monitoring and multidisciplinary management should be considered in this population.

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4039 | ◆ THE MISSING CASES: A NATIONWIDE SURVEY OF HEPATITIS B KNOWLEDGE AND PRACTICE AMONG 1,107 TURKISH PRIMARY CARE PHYSICIANS

Imran Hasanoglu[1] Rahmet Guner[1], [1]Ankara Yildirim Beyazit University Bilkent City Hospital

Background: Primary care physicians (PCPs) are the frontline workforce for hepatitis B virus (HBV) screening, vaccination, and long-term monitoring; their performance

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directly shapes a country's capacity to reach the WHO 2030 elimination targets. Despite national elimination targets, real-world knowledge and practice patterns among PCPs remain poorly characterized. **Methods:** A cross-sectional, face-to-face survey was conducted across all 81 provinces of Türkiye between December 2024 and November 2025. With the logistical support and dedication of the Humanis team, a 105-member field team surveyed 1,107 PCPs at 634 primary care centers. The 11-question survey assessed HBV prevalence, risk-group recognition, screening test selection, natural history, management of HBsAg-positive mothers and patients, treatment principles, and doctors' perception of HBV caseload on their own patient lists. **Results:** A total of 1,107 PCPs completed the survey. Correct-answer rates ranged from 33% to 89% across the eleven questions. Recognition of routine preventive concepts was high: 89% correctly interpreted isolated anti-HBs positivity as prior vaccination and 86% the combined approach to HBsAg-positive mothers and newborns. In contrast, only 33% correctly identified Türkiye's HBsAg prevalence as ~4%, and only 40% recognized that perinatally acquired HBV becomes chronic in ~90% of cases. Half (50%) misclassified HBcAb as a routine screening test, and 58% answered the chronic HBV treatment question incorrectly. Risk-group recognition was uneven: dialysis patients (96%) and injection drug users (95%) were widely recognized, whereas household contacts (74%) and travelers to endemic regions (75%) were least recognized. When asked whether the HBV cases on their patient list matched the caseload expected under Türkiye's ~4% prevalence, 65% (725/1,107) answered "no"; of these, 76% (671/888) also reported patients of unknown HBV serology. **Conclusion:** This nationwide study, the largest HBV knowledge assessment ever conducted among PCPs in Türkiye, demonstrates substantial gaps in fundamental HBV management. These deficiencies may delay diagnosis, contribute to missed chronic infections, and undermine elimination strategies. Targeted educational interventions and simplified primary-care algorithms may strengthen the role of PCPs in HBV elimination.

Disclosures: Imran Hasanoglu:Pfizer: Speaking and Teaching, Biotest: Grant/Research Support, RAHMET GUNER:Nothing to Disclose.

4040 | ◆ PRACTICE PATTERNS AND DETERMINANTS OF HEPATOCELLULAR CARCINOMA (HCC) SURVEILLANCE IN PATIENTS WITH CHRONIC HEPATITIS B VIRUS (HBV) INFECTION: RESULTS FROM A WORLDWIDE SURVEY OF CLINICAL PRACTICE

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Background: Despite declining HBV-related HCC incidence due to vaccination and antiviral therapy, HBV remains a leading etiology of HCC in many regions. Appropriate HCC surveillance enables earlier diagnosis and improves curative treatment outcomes. We assessed global HCC surveillance practice patterns among clinicians managing chronic HBV patients and factors affecting these patterns. **Methods:** An international group of experts from the Global Liver Council developed and conducted a global online survey on HBV/HDV clinical practice patterns from June-September 2025. Based on HCC screening responses, participants were classified as screening: a) all HBsAg-positive patients (universal), b) only those with cirrhosis or HCC risk factors (risk-based), or c) none. Multivariable analysis identified factors independently associated with screening practices ($P < 0.05$). Variables evaluated included: provider demographics (sex, age, medical degree, years in practice), specialty, practice setting, HBV patient caseload, HBV knowledge, comfort treating HBV, patient encounter and treatment frequencies, guidelines followed, and geographic region. **Results:** There were 611 survey responses [hepatologists/gastroenterologists (68%), infectious disease (11.5%), and other specialties (20.5%)] from 7 global regions [Southeast (SE) Asia 25%, Europe 24%, Middle East & North Africa (MENA) 21%, South Asia 11%, USA 9%, Latin America 8%, Africa 3%]. EASL guidelines were most frequently followed (46%), then AASLD (21%), WHO (12.6%), APASL (10.1%) or other guidelines (10%). Of 561 participants responding to HCC screening practices, 4 (0.7%) reported no screening for HBsAg-positive patients and were excluded. Among the remaining 557 participants, 48.8% screened all HBsAg-positive patients (universal), while 51.2% screened only those with cirrhosis or HCC risk factors (risk-based). Associated factors by screening pattern are shown in Table. Universal screening was independently associated with practicing outside USA or Europe: Middle East/North Africa [OR = 1.91 (95% CI: 1.18–3.10), $P = 0.008$], Southeast Asia [OR = 1.97 (1.30–2.97), $P = 0.001$], and Africa [OR = 2.87 (1.03–8.02), $P = 0.044$]; and with infectious disease specialty [OR = 1.98 (1.08–3.62), $P = 0.028$]. **Conclusion:** HCC surveillance practice patterns in chronic HBV patients are independently affected by geographic region and medical specialty. Risk-based screening, recommended by most guidelines, is more frequently adopted in USA/Europe and by hepatologists/gastroenterologists, while universal screening of all HBsAg-positive patients is more common in Asia/Africa and among infectious disease specialists. Standardized, evidence-based HCC screening approaches are needed globally to improve outcomes in HBsAg-positive patients.

Table. Factors affecting current practice patterns of HCC surveillance in chronic HBV patients (patients)

		All HBsAg+ N=272	Risk based N=285	P value
Sex	Male	161 (59.6%)	163 (57.6%)	0.63
	Female	109 (40.4%)	120 (42.4%)	0.63
Age	18-34 years	59 (21.7%)	65 (22.8%)	0.75
	35-54 years	150 (55.1%)	158 (55.4%)	0.94
	≥55 years	63 (23.2%)	62 (21.8%)	0.69
Medical degree	Medical Doctor	253 (93.0%)	262 (92.6%)	0.84
	Advanced Practice Provider /Trainee	15 (5.5%)	21 (7.4%)	0.36
Years of practice after training	≤10 years	110 (40.4%)	125 (43.9%)	0.41
	>10 years	162 (59.6%)	160 (56.1%)	0.41
Specialty	Hepatology	92 (33.9%)	114 (40.0%)	0.13
	Gastroenterology	102 (37.5%)	96 (33.7%)	0.35
	Infectious Disease	42 (15.4%)	21 (7.4%)	0.003
	Other	36 (13.2%)	54 (18.9%)	0.07
Practice setting	Academic health institution	176 (64.7%)	187 (65.6%)	0.82
	Private Practice	31 (11.4%)	38 (13.3%)	0.49
	Other	65 (23.9%)	60 (21.1%)	0.42
Area of practice setting	Rural setting	26 (9.6%)	33 (11.6%)	0.44
	Urban setting	246 (90.4%)	252 (88.4%)	0.44
% practice with chronic HBV	≤50%	244 (89.7%)	253 (88.8%)	0.72
	>50%	28 (10.3%)	32 (11.2%)	0.72
Level of knowledge on HBV	None/Basic	25 (9.2%)	39 (13.7%)	0.10
	Adequate/Superior	246 (90.8%)	246 (86.3%)	0.10
Comfort treating HBV patients	No/Somewhat comfortable	41 (15.1%)	60 (21.1%)	0.07
	(Very) Comfortable	230 (84.9%)	225 (78.9%)	0.07
# HBsAg+ patients seen in 1 month	≤50	212 (78.2%)	237 (84.3%)	0.07
	>50	59 (21.8%)	44 (15.7%)	0.07
# HBsAg+ patients ever seen	≤100	58 (21.4%)	84 (29.7%)	0026
	>100	213 (78.6%)	199 (70.3%)	0.026
# HBsAg+ patients treated in 1 month	≤10	160 (59.3%)	178 (64.3%)	0.23
	>10	110 (40.7%)	99 (35.7%)	0.23
# HBsAg+ patients ever treated	≤50	68 (25.2%)	71 (25.4%)	0.96
	>50	202 (74.8%)	209 (74.6%)	0.96
Guidelines for HBV treatment	AASLD	58 (21.4%)	59 (20.8%)	0.87
	EASL	125 (46.1%)	134 (47.3%)	0.77
	APASL	35 (12.9%)	22 (7.8%)	0.046
	Others	53 (19.6%)	68 (24.0%)	0.20
Region of practice	USA	14 (5.1%)	32 (11.2%)	0.009
	Europe	53 (19.5%)	80 (28.1%)	0.017
	Latin America	18 (6.6%)	24 (8.4%)	0.42
	MENA	68 (25.0%)	45 (15.8%)	0.007
	South Asia	23 (8.5%)	31 (10.9%)	0.33
	SE Asia	84 (30.9%)	67 (23.5%)	0.05
	Africa	12 (4.4%)	6 (2.1%)	0.12

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4041 | ◆ ACCELERATED HEPATITIS B VACCINATION YIELDS HIGH SEROPROTECTION INDEPENDENT OF IFNL3 POLYMORPHISMS IN HAITIAN MIGRANTS

Javier Perez-Valenzuela[1] Patricio Astudillo[1] Javier Uribe[1] José Ignacio Vargas[1] Carlos Benitez[1] Marcelo López-Lastra[1] Ruth Nuñez[1] Valentina Ross[1] Jacinta Soza[1] Karla Pino[1] Francisco Fuster[2] Alejandro Soza Ried[1], [1]Pontificia Universidad Católica de Chile, [2]Hospital Gustavo Fricke

Background: Hepatitis B virus (HBV) infects over 240 million people worldwide, increasing the risk of cirrhosis and hepatocellular carcinoma. While Chile has a low chronic HBV prevalence (0.15%), recent migration trends may alter this figure. Previous research demonstrated a significantly higher prevalence of HBV infection among Haitian migrants in Chile versus the local population. Achieving World Health Organization's (WHO) 2030 elimination goals requires innovative strategies targeting high-risk populations. Vaccination is the most effective preventive strategy, and an accelerated schedule could improve adherence. Genetic polymorphisms are associated with vaccine responses; in particular, favorable IFNL3 polymorphisms may be linked to an enhanced immune response. We evaluated the immune response to an accelerated HBV schedule in Haitian migrants in Chile and identified clinical, demographic, and genetic factors. **Methods:** This open-label prospective study enrolled adult Haitian migrants given an accelerated HBV vaccination schedule (0, 1, and 2 months). Immune response (anti-HBs $\geq$10 mIU/mL) was assessed 4-8 weeks post-vaccination. Additionally, IFNL3 SNPs rs12979860 and rs8099917 were genotyped; their distribution was tested for Hardy-Weinberg equilibrium (HWE). Clinical, demographic, and genetic associations were analyzed using Fisher's exact test and the Mann-Whitney U test ($p<0.05$ considered significant). **Results:** Eighty-two participants completed the full vaccination schedule (median age 37 years, 54.9% female). Seroprotection rate was 91.5% (95% CI: 85.3-97.6%); anti-HBs geometric mean titer (GMT) among responders was 529.7 mIU/mL (95% CI 362.4-774.2), with 88% (66/75) achieving high response ($\geq$100 mIU/mL). No immediate adverse effects occurred. Genotype analysis was performed in a subset. For rs12979860 (n = 67), distribution was TT: 64.2% (n = 43), CT: 28.4% (n = 19), and CC: 7.5% (n = 5). For rs8099917 (n = 70), distribution was TT: 88.6% (n = 62) and TG: 11.4% (n = 8). Both SNPs were in HWE. No significant

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differences were found between responders and non-responders regarding age, sex, body mass index, obesity, diabetes, hypertension, smoking status, or IFNL3 genotype distribution. **Conclusion:** The accelerated HBV vaccination schedule elicited a high immune response comparable to standard approaches and was independent of IFNL3 genetic polymorphisms. High GMT and proportion of responders suggest robust and potentially durable protection. This is epidemiologically vital for key migrant populations, as high seroprotection reduces HBV susceptibility, limits transmission, and reinforces national control strategies. The data suggest that accelerated HBV vaccination could be a cornerstone of public health policy for migrants, offering an effective solution to adherence challenges and helping achieve WHO HBV elimination targets in high-prevalence groups.

Characteristic	Vaccinated (n=82)	Non-responders (n=7)	Responders (n=75)	p-value
Female sex, n (%)	45/82 (54.9)	4/7 (57.1)	41/75 (54.7)	> 0.9
Age, years (median, IQR)	37 (12)	39 (15)	36 (13)	0.6
Body Mass Index, kg/m² (median, IQR)	26.9 (6.9)	28.7 (7.6)	26.7 (6.0)	0.11
Obesity, n (%)	20/73 (27.4)	2/5 (40.0)	18/68 (26.5)	0.6
Hypertension, n (%)	23/76 (30.3)	4/6 (66.7)	19/70 (27.1)	0.064
Diabetes Mellitus, n (%)	5/82 (6.1)	0/7 (0)	5/75 (6.7)	> 0.9
Waist circumference, cm (median, IQR)	88.5 (17.0)	91.0 (15.0)	88 (13.5)	0.156
Smoking, n (%)	1/82 (1.2)	0/7 (0)	1/75 (1.3)	> 0.9
SNP *rs12979860*, n (%)				0.2
CC	5/67 (7.5)	1/3 (33.3)	4/64 (6.2)	
CT/TT	62/67 (92.5)	2/3 (66.7)	60/64 (93.8)	
SNP *rs8099917*, n (%)				> 0.9
TT	62/70 (88.6)	4/4 (100)	58/66 (87.9)	
TG/GG	8/70 (11.4)	0/4 (0)	8/66 (12.1)	
Anti-HBs response category, n (%)				NA
Non-responder (10 mIU/mL)	7/82 (8.5)	7/7 (100)	0/75 (0)	
Low response (10-99 mIU/mL)	9/82 (11.0)	0/7 (0)	9/75 (12.0)	
High response (100 mIU/mL)	66/82 (80.5)	0/7 (0)	66/75 (88.0)	
GMT in responders, mIU/mL (95% CI)	NA	529 (362-774)	NA	NA

Table 1. Characteristics of Vaccinated Participants, Non-Responders, and Responders

Disclosures: Javier Perez-Valenzuela:Nothing to Disclose, Patricio Astudillo:Nothing to Disclose, Javier Uribe:Nothing to Disclose, José Ignacio Vargas:Nothing to Disclose, Carlos Benitez:Nothing to Disclose, Marcelo López-Lastra:Nothing to Disclose, Ruth Nuñez:Nothing to Disclose, Valentina Ross:Nothing to Disclose, Jacinta Soza:Nothing to Disclose, Karla Pino:Nothing to Disclose, Francisco Fuster:Nothing to Disclose, Alejandro Soza Ried:Nothing to Disclose.

★ 4042 | ◆ POORER HEPATOCELLULAR CARCINOMA (HCC) SURVIVAL FOLLOWING SPONTANEOUS BUT NOT NUCLEOS(T)IDE ANALOGUE (NA)-INDUCED HEPATITIS B SURFACE ANTIGEN (HBSAG) LOSS IN CHRONIC HEPATITIS B (CHB)

Terry Cheuk-Fung Yip[1] Jimmy Che-To Lai[1] Mandy Lai[1] Vincent Wong[1] Henry Lik-Yuen Chan[2] Grace Wong[1],

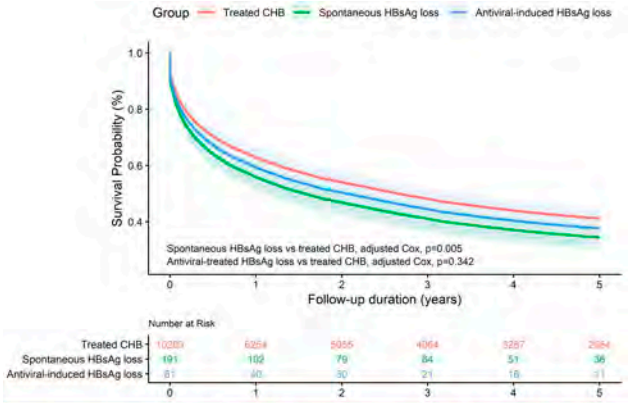
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Background: Current European and American guidelines provide limited guidance on HCC surveillance after HBsAg loss, and surveillance may be less standardized, particularly after spontaneous HBsAg loss. We compared survival in patients with HCC diagnosed after spontaneous HBsAg loss, after NA-induced HBsAg loss, and during NA therapy in patients with CHB. **Methods:** We identified two territory-wide retrospective cohorts from Hong Kong: adults with CHB who developed HCC after HBsAg loss between 2005 and 2024, and adults with CHB who developed HCC during entecavir/tenofovir therapy in the same period. Patients with HBsAg loss after liver transplantation (LT), or patients with CHB who had LT before entecavir/tenofovir therapy, were excluded. Patients were followed from HCC diagnosis until death, Dec 31, 2024, or 5 years from HCC diagnosis, whichever came first. Mortality risk was compared using multivariable Cox regression and propensity score weighting (PSW), adjusting for age, sex, cirrhosis, calendar year of HCC diagnosis, and HCC treatment. **Results:** We included 10,203 patients with HCC during NA therapy, 191 with HCC after spontaneous HBsAg loss, and 81 with HCC after NA-induced HBsAg loss. Patients with HCC after spontaneous HBsAg loss, HCC after NA-induced HBsAg loss, and HCC during NA therapy had mean ages of 69 ± 10, 68 ± 11, and 65 ± 11 years, respectively. The proportions of men were 80%, 78%, and 82%, and the prevalence of cirrhosis was 46%, 65%, and 56%, respectively. Compared with HCC during NA therapy, HCC treatment distribution differed modestly for HCC after spontaneous HBsAg loss (p = 0.027), with curative therapy in 33.0% vs 35.7%, locoregional therapy in 25.1% vs 22.4%, and best supportive care in 41.4% vs 37.3%, respectively. Treatment distribution was similar for HCC after NA-induced HBsAg loss compared with HCC during NA therapy (p = 0.796). At a median follow-up of 1.9 (0.3-5.0) years, death occurred in 5,576 (54.7%) patients with HCC during NA therapy, 110 (57.6%) with HCC after spontaneous HBsAg loss, and 47 (58.0%) with HCC after NA-induced HBsAg loss. Compared with HCC occurring during NA therapy, HCC after spontaneous HBsAg loss was associated with higher mortality (adjusted hazard ratio [aHR] 1.31, 95% CI 1.09-1.58, p = 0.005), while HCC after NA-induced HBsAg loss was not associated with increased mortality (aHR 1.15, 95% CI 0.86-1.53; p = 0.342) (Figure). Similar findings were observed after PSW: weighted aHR 1.35 (95% CI 1.10-1.66), p = 0.004 for spontaneous HBsAg loss, and weighted aHR 1.17 (95% CI 0.88-1.57), p = 0.286 for NA-induced HBsAg loss. **Conclusion:** HCC diagnosed after spontaneous HBsAg loss was associated with poorer survival than HCC diagnosed during NA

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therapy, whereas survival after NA-induced HBsAg loss was comparable. These findings suggest a potential surveillance gap after spontaneous HBsAg loss and support risk-based continuation of HCC surveillance post HBsAg loss.



Parameters	Univariate analysis		Multivariable analysis	
	HR (95% CI)	p value	aHR (95% CI)	p value
Treated chronic hepatitis B	Reference		Reference	
Spontaneous HBsAg loss	1.19 (0.99-1.44)	0.064	1.31 (1.09-1.58)	0.005
Antiviral-induced HBsAg loss	1.22 (0.92-1.63)	0.175	1.15 (0.86-1.53)	0.342
HCC treatment				
➢ Resection/LT	Reference		Reference	
➢ Local ablative therapy	1.30 (1.14-1.50)	<0.001	1.25 (1.09-1.43)	0.002
➢ Locoregional therapy	3.50 (3.16-3.87)	<0.001	3.29 (2.97-3.65)	<0.001
➢ Systemic therapy	7.78 (6.82-8.88)	<0.001	8.21 (7.18-9.38)	<0.001
➢ Best supportive care	8.78 (7.98-9.65)	<0.001	8.48 (7.71-9.33)	<0.001
Age at HCC	1.02 (1.01-1.02)	<0.001	1.01 (1.01-1.01)	<0.001
Male sex	1.21 (1.13-1.30)	<0.001	1.20 (1.12-1.29)	<0.001
Cirrhosis at HCC	1.16 (1.10-1.22)	<0.001	1.16 (1.10-1.22)	<0.001
Calendar year of HCC	1.00 (0.99-1.00)	0.424	0.98 (0.97-0.99)	<0.001

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4043 | ◆ RESIDUAL HBV DNA DURING NUCLEOS(T)IDE ANALOGUE THERAPY FOR CHRONIC HEPATITIS B: PREVALENCE AND ASSOCIATION WITH HCC RISK

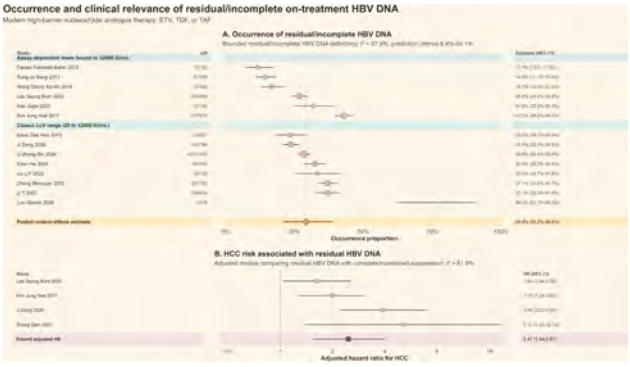
Ali Hemade[1] Ashwin Balagopal[1] Bryan Lau[1] Chloe Thio[1] David Thomas[1], [1]Johns Hopkins University

Background: HBV DNA that is detectable during nucleos(t)ide therapy is often referred to as low-level viremia, incomplete suppression, or residual viremia. Its frequency and clinical relevance as compared to complete viral response remain uncertain due to heterogeneity in construct definition and assay differences. **Methods:** We conducted a systematic review and meta-analysis of papers on residual viremia in chronic hepatitis B patients treated with first-line nucleos(t)ide analogue therapy. We only included papers that defined residual HBV DNA as quantitatively bounded to avoid construct drift. Data were extracted on complete viral response HBV DNA threshold, assay limits, timing/persistence, regimen context, denominators, outcomes, model adjustment domains, and risk of bias. We used random-effects to pool the estimated prevalence of residual HBV DNA and adjusted hepatocellular carcinoma (HCC) hazard ratios (HR) where appropriate. **Results:** Across PubMed, Embase, Scopus, citation chasing, and other sources, 7,653 potentially relevant records were identified. After deduplication, 4,076 were screened. After dual independent title/abstract screening, 94 full texts were assessed, 34 studies were included, and 21 contributed to quantitative analysis. In 14 studies with 7,338 patients, residual HBV DNA was characterized during treatment as 20–≤2,000 IU/mL or from an assay-dependent lower bound to ≤2,000 IU/mL. Pooled estimate of HBV DNA prevalence was 29.3% (95% CI, 21.2% - 38.9%; prediction interval, 8.4% - 65.1%). Between-study heterogeneity was high (I^2 = 97.8%) due to differences in assay lower limits of detection/quantification, upper thresholds, and persistence definitions. We included 4 suitable adjusted models comparing low level residual HBV DNA to complete viral response/suppression for HCC risk. Residual HBV DNA was associated with higher HCC risk (pooled adjusted HR, 2.47; 95% CI, 1.54–3.97; I^2 = 61.9%). Non-HCC outcomes were too heterogeneous to pool meaningfully, but residual HBV DNA was also associated consistently with measures of liver fibrosis progression. **Conclusion:** Residual HBV DNA during first-line NA therapy is common and associated with higher adjusted HCC risk as compared

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to complete suppression, findings that strongly support development of more potent antiviral regimens. However, since pretreatment HBV DNA is associated with both residual HBV DNA and HCC risk, confounding may have biased or pooled HR away from the null.



Disclosures: Ali Hemade:Nothing to Disclose, Ashwin Balagopal:Nothing to Disclose, Bryan Lau:Nothing to Disclose, Chloe Thio:Nothing to Disclose, David Thomas:Merck: DSMB, Rho: DSMB, Excision Bio: Advisor.

4044 | ◆ INTEGRATED EMERGENCY DEPARTMENT-BASED SCREENING FOR HEPATITIS B AND HEPATOCELLULAR CARCINOMA IN TANZANIA: A PROSPECTIVE MULTICENTER STUDY

James Ford[1] Erin Mann[2] James Ford[3] Muhanuzi Biita[4] Jenny Wagner[5] Francis Sakita[3] Johnstone Kayandabila[4] Juma Mfinanga[4] Seraphine Mrosso[4] Kalipa Gedion[6] Akash Desai[1] Julian Hertz[6] Hendry Sawe[3] Jose Debes[2], [1]University of California, San Diego, [2]University of Minnesota, [3]Kilimanjaro Christian Medical Center, [4]Muhimbili National Hospital, [5]California State University, [6]Duke University School of Medicine

Background: Hepatitis B (HBV) is a leading cause of hepatocellular carcinoma (HCC) worldwide and early detection is critical for improving survival. We evaluated implementation and clinical outcomes of a combined HBV and HCC screening program integrated into emergency departments (ED) workflows in Tanzania. **Methods:** We conducted a multicenter, prospective, implementation study between July 2023 and March 2025 at two tertiary referral centers in Dar es Salaam and Moshi, Tanzania, respectively. Prior to launch, we engaged key stakeholders including emergency physicians, hepatologists, oncologists, hospital administrators, and laboratory personnel to adapt screening workflows, define referral pathways, and ensure operational feasibility. Patients and accompanying visitors presenting to the ED were recruited and provided informed consent. Patients were screened for HBV using rapid, point-of-care hepatitis B surface antigen test kits. Those who tested positive underwent additional laboratory testing, HCC screening via point-of-care ultrasound (POCUS) and were referred to hepatology clinic. Data were analyzed using descriptive statistics and between group comparisons were made using tests of proportions. **Results:** Among 6,246 total enrolled patients, 54% (n = 3,337) were female with a median age was 39 years (IQR 27-54). Overall HBV prevalence was 6.6% (408/6,246). Prevalence was significantly higher in Dar es Salaam (7.8%, 253/3,256) compared with Moshi (5.2%, 159/2,990), with an absolute difference of 2.6% (95% CI 1.3% to 3.8%). Among HBV-positive patients, linkage to follow-up care occurred in 72% (292/408) and 57% (53/93) of treatment-eligible patients initiated started on antiviral therapy. Nearly all HBV-positive participants (97%, 395/408) underwent same-visit HCC screening via POCUS, of whom 5% (19/395) had concerning lesions. Confirmatory, triple-phase contrasted topography of the liver was successfully completed in 78% (15/19) of individuals with concerning POCUS lesions. HCC was diagnosed in 93% of these cases (14/15), and oncological treatment was initiated in 67% (10/15) of cases. **Conclusion:** ED–based HBV screening paired with integrated ultrasound evaluation for HCC is feasible and yields high rates of linkage-to-care and treatment initiation in a resource-limited setting. Emergency departments represent a promising and underutilized setting for combined infectious disease and cancer screening in regions with high HBV burden.

Disclosures: James Ford:Nothing to Disclose, Nothing to Disclose, Erin Mann:Nothing to Disclose, James Ford:Nothing to Disclose, Nothing to Disclose, Muhanuzi Biita:Nothing to Disclose, Jenny Wagner:Nothing to Disclose, Francis Sakita:Nothing to Disclose, Johnstone Kayandabila:Nothing to Disclose, Juma Mfinanga:Nothing to Disclose, Seraphine Mrosso:Nothing to Disclose, Kalipa Gedion:Nothing to Disclose, Akash Desai:Nothing to Disclose, Julian Hertz:Nothing to Disclose, Hendry Sawe:Nothing to Disclose, Jose Debes:Nothing to Disclose.

4045 | LOW HBSAG LEVELS AND HBSAG LOSS ARE ASSOCIATED WITH REDUCED RISK OF LONG-TERM ADVERSE CLINICAL OUTCOMES IN A LARGE COHORT OF CHRONIC HEPATITIS B INDIVIDUALS IN CHINA

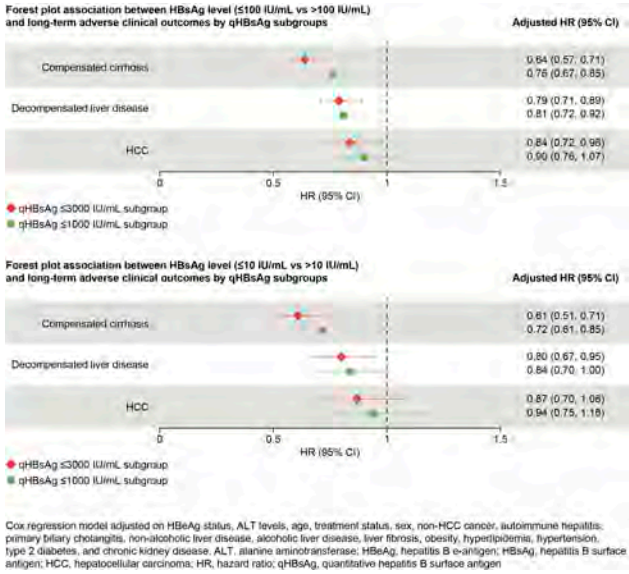
Myriam Drysdale[1] Jidong Jia[2] Mei Yang[3] Ying Shen[4] Sida Wei[4] Xin Li[4] Xin He[5] Lydia Demetriou[6] Menchi

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Background: Chronic hepatitis B virus (HBV) infection remains a major global public health challenge contributing to cirrhosis and liver cancer worldwide (~1.1 million deaths per year). In China, ~75 million people are chronically infected with HBV (~5.9% hepatitis B surface antigen [HBsAg] prevalence). Although HBsAg levels can predict treatment response and favorable virological outcomes, quantitative HBsAg (qHBsAg) testing is scarcely performed, limiting real-world evidence. This study assessed the associations between low HBsAg levels, subsequent HBsAg loss, and long-term adverse clinical outcomes such as compensated cirrhosis, decompensated liver disease, and hepatocellular carcinoma (HCC) during follow-up, in mainland China. **Methods:** We conducted a retrospective cohort study using regional electronic health records from Tianjin, China, including 82 hospitals (2016–2023). Adult patients (pts) with chronic HBV infection and a detectable qHBsAg test were included; the index date was the first recorded detectable qHBsAg test. Multivariable Cox regression analyses were performed among pts with HBsAg $\leq$3000 IU/mL and $\leq$1000 IU/mL, with no severe liver disease (i.e. cirrhosis, hepatic decompensation, or liver transplantation) at baseline (BL). **Results:** Among 33,826 pts with chronic HBV infection and detectable qHBsAg (mean [SD] age: 43.3 [13.4] years; 57.8% male), 15,529 had HBsAg $\leq$3000 IU/mL and no clinical evidence of severe liver disease at BL; 3238 (20.9%) of this subgroup received anti-HBV therapy at BL. HBsAg loss (N = 454; median time from index: 1589 days) was associated with substantially lower risks of clinical progression: 66% lower risk of compensated cirrhosis (adjusted hazard ratio [aHR]: 0.34, 95% CI: 0.24, 0.50), 95% lower risk of decompensated liver disease (aHR: 0.05, 95% CI: 0.02, 0.13), and 88% lower risk of HCC (aHR: 0.12, 95% CI: 0.04, 0.31) compared with no loss. HBsAg $\leq$100 IU/mL (N = 3932) was associated with 36%, 21%, and 16% reduced risks of compensated cirrhosis (aHR: 0.64, 95% CI: 0.57, 0.71), decompensated liver disease (aHR: 0.79, 95% CI: 0.71, 0.89), and HCC (aHR: 0.84, 95% CI: 0.72, 0.98), respectively. HBsAg $\leq$10 IU/mL (N = 1531) reduced the risk of compensated cirrhosis by 39% (aHR: 0.61, 95% CI: 0.51, 0.71) and decompensated liver disease by 20% (aHR: 0.80, 95% CI: 0.67, 0.95); the reduction in HCC risk did not reach statistical significance. Similar results were observed for the subgroup with HBsAg $\leq$1000 IU/mL (N = 9837) (**Figure**). **Conclusion:** Among a mixed treated and untreated cohort of chronic HBV pts with HBsAg levels $\leq$3000 IU/mL and $\leq$1000 IU/mL, both low HBsAg level and HBsAg loss were strongly associated with reduced risk of clinical progression. These findings support the clinical value of qHBsAg measurement for risk stratification and highlight low HBsAg levels and HBsAg loss as meaningful markers of favorable long-term outcomes in a real-world setting. **Funding** : GSK (219254)



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4046 | IDENTIFICATION OF VITAMIN D3 AS A POTENTIAL PREVENTIVE AGENT FOR TAMOXIFEN-INDUCED STEATOHEPATITIS: AN INTEGRATED APPROACH USING VIGIBASE AND IN VITRO VALIDATION

Yutaka Kawano[1] Mitshihiro Goda[2] Tomohiro Kubo[1] Naoki Okamoto[3] Shimon Takahashi[3] Atsushi Miyata[3] Keisuke Ishizawa[3] Yohei Arihara[4] Kohichi Takada[4], [1]Sapporo Medical University School of Medicine, [2]Hiroshima University, [3]Tokushima University, [4]Sapporo Medical University School of Medicine

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Background: Tamoxifen (TAM), a gold standard for breast cancer treatment, frequently induces tamoxifen-induced steatohepatitis (TASH) as a side effect. Severe cases often require treatment discontinuation, potentially worsening oncological outcomes. Despite its clinical significance, effective preventive or therapeutic strategies for TASH remain unestablished. This study aimed to identify candidate agents that suppress TASH using the WHO global database of individual case safety reports (VigiBase) and to validate their efficacy through cellular experiments. **Methods:** We analyzed 9,778 cases involving TAM from VigiBase. Hepatic adverse events were identified using 54 MedDRA/J ver.28.0 terms related to fatty liver and hepatitis. Disproportionality analysis was performed by calculating the Reporting Odds Ratio (ROR) to screen for concomitant medications associated with a significantly lower frequency of hepatic adverse events. For in vitro validation, HepG2 cells were exposed to TAM to induce intracellular triglyceride (TG) accumulation. The effects of 1α,25-dihydroxyvitamin D3 (VD3) on TG accumulation and the expression of lipid metabolism-related genes were evaluated using Oil Red O staining and RT-qPCR. **Results:** The disproportionality analysis revealed a significantly lower reporting frequency of TAM-induced hepatic injury in patients receiving concomitant Vitamin D3 compared to those without it. In HepG2 cells, TAM exposure markedly increased intracellular TG accumulation, which was suppressed by VD3 in a concentration-dependent manner. Gene expression analysis demonstrated that VD3 significantly attenuated the TAM-induced upregulation of *SREBP-1c* and *PPARγ*, both of which are master regulators of lipogenesis. **Conclusion:** By integrating large-scale real-world data with mechanistic experiments, we demonstrated that VD3 potentially prevents TASH. Since VD3 is an established drug with a well-known safety profile, it holds promise as a novel supportive therapy to ensure the continuity of breast cancer treatment. Further validation using multicenter clinical data is warranted to confirm these real-world benefits.

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4047 | HEPATITIS B/HEPATITIS D SCREENING AND LINKAGE-TO-CARE IN HIGHLY MARGINALIZED URBAN POPULATIONS IN SPAIN: THE DESCRIBE STUDY

Pablo Ryan[1] Antonio Madejon[2] Sabela Lens[3] Mario delHoyo[4] Marina Camblor Murube[5] Jorge Valencia[4] Xavier Forns[3] Francisco Javier Garcia-Samaniego[6], [1]Infectious Diseases Unit. Hospital Universitario Infanta Leonor/Universidad Complutense/CIBER.Madrid, [2]Liver Unit. Hospital Universitario La Paz. Madrid, [3]Liver Unit. Hospital Clinic/CIBER/IDIBAPS/Universitat de Barcelona. Barcelona, [4]Infectious Diseases Unit. Hospital Universitario Infanta Leonor. Madrid, [5]Faculty of Medine. Universidad Autónoma de Madrid (UAM). Madrid, [6]Liver Unit. Hospital Universitario La Paz/ IdiPAZ/Universidad Autónoma de Madrid (UAM). Madrid

Background: Socially marginalized urban (MU) populations remain disproportionately affected by viral hepatitis and frequently limited experience access to linkage-to-care services. Data on HBV and HDV infections in highly vulnerable populations reached through outreach and harm-reduction programs remain limited. **Methods:** Cross-sectional study of MU recruited through mobile outreach and harm-reduction programs in the two biggest Spanish cities (Madrid and Barcelona). Sociodemographic characteristics, healthcare access, substance use, and HIV/HBV-HDV/HCV screening data were collected. Participants underwent positive hepatitis rapid testing and liver disease staging, and were referred to specialized care if positive. **Results:** A total of 2,138 participants were included. Median age 40 years (IQR 28–51), and 67.2% male. Most participants were Caucasian (65%), Hispanic (20%), or African (7%). Housing and healthcare vulnerability were substantial, with 71% reporting unstable housing (shelters; 32.7%, refugee centers: 2.6%, and street homelessness: 7.2%), 38.7% lacking stable social support and 58.3% reporting barriers to healthcare access. Sexual risk behaviors were frequent, including inconsistent condom use (69.5%) and multiple condomless partners (33.8%). Drug use was reported by 51% of participants; among them, 89% reported use in the previous year, mainly cocaine (42.8%) and heroin (30.1%). Injection drug use was also frequent, with 49.7% reporting lifetime injection and of them, 74.6% active injection during the previous year; 33.8% received opioid substitution therapy. A high burden of viral hepatitis was observed, particularly HCV infection, while HBV and HDV were less frequent but clinically relevant (Table 1). Among the 687 participants with positive hepatitis rapid testing (HCV and/or HBV), 55.5% were linked to specialized care. Liver disease assessment was available in 355: F3 in 10.1% and F4 (liver cirrhosis) in 7.9%. Most participants with available Child-Pugh staging had compensated liver disease. **Conclusion:** Community-based hepatitis screening and harm-reduction programs identified highly MU populations with a high burden of viral hepatitis and significant liver disease. These outreach-based HBV/HDV screening strategies may improve access to specialized care and support hepatitis elimination

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efforts in underserved urban populations. **Funding Sources:** Proyect HDV-DESCRIBE funded by Gilead Sciences and Project PI22/00849, funded by Instituto de Salud Carlos III (ISCIII) and co-funded by the European Union.

Table 1. Viral hepatitis and HIV screening results

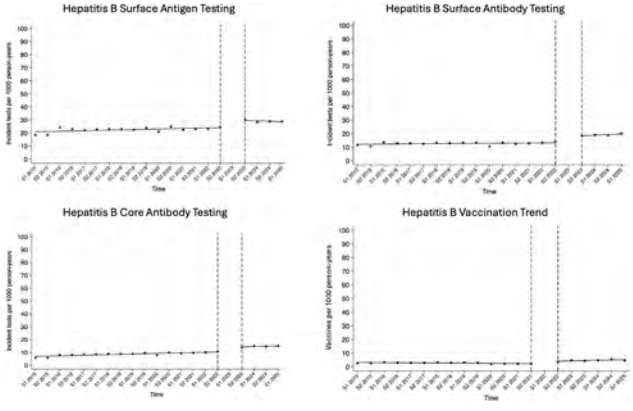
Variable	n/N (%)
HIV rapid test positive	138/2,126 (6.5%)
New HIV diagnoses	3/138 (2.2%)
Anti-HCV positive	623/2,130 (29.2%)
Detectable HCV RNA among total	266/2,138 (12.4%)
Detectable HCV RNA among PCR-tested	266/360 (73.9%)
HCV reinfection	99/181 (54.7%)
HBV rapid test positive	91/2,129 (4.3%)
Confirmed HBsAg positive	42/2,138 (2.0%)
Anti-HDV positive	2/32 (6.3%)
Detectable HDV RNA	1/2 tested

Disclosures: Pablo Ryan:Nothing to Disclose, Antonio Madejon:Nothing to Disclose, Sabela Lens:Nothing to Disclose, Mario delHoyo:Nothing to Disclose, Marina Camblor Murube:Nothing to Disclose, Jorge Valencia: Nothing to Disclose, Xavier Forns:Nothing to Disclose, Francisco Javier Garcia-Samaniego:Nothing to Disclose.

4048 | IMPACT OF UNIVERSAL GUIDELINE CHANGES ON NATIONAL HEPATITIS B VIRUS SCREENING AND VACCINATION RATES

Allen Luo[1] Rene Nichols[1] Christopher Wong[1] Kali Zhou[1], [1]Keck School of Medicine of USC

Background: Recent guideline changes have shifted Hepatitis B virus (HBV) screening and vaccination from risk-based to a universal approach. The ACIP recommended universal HBV vaccination for adults aged 19-59 in 2022, followed by 2023 CDC guidelines for universal one-time adult screening with a triple panel test. We evaluated temporal trends in HBV screening and vaccination in the United States (US) before and after guideline release. **Methods:** We utilized TriNetX, a multicenter research network of 66 US healthcare organizations, representing over 90 million patients across academic and non-academic centers. Two cohorts were identified for multiple-group interrupted time series analyses: (1) Cohort A: adults $\geq$18 years with no prior HBV screening and (2) Cohort B: adults aged 19-59 years with no prior HBV vaccination. Those with pre-existing HBV were excluded for both. In Cohort A, we compared incident HBV screening rates per 1000 person-years for HBsAg, anti-HBs, and anti-HBc in 6-month intervals before (March 2015-Feburary 2023) and after (September 2023-August 2025) the CDC guideline release. In Cohort B, we similarly compared rates of initiation of HBV vaccine before (March 2015-February 2022) and after (September 2022-August 2025) the ACIP guideline release. A 6-month washout period was included for both. Parallel trends were assessed with F-tests and autocorrelation with Newey-West standard errors. Incident HIV screening served as a negative control. **Results:** All HBV screening tests and vaccination rates showed significant immediate increases following guideline implementation (see Figure). HbsAg testing rates increased from 24.5 to 30.3 screenings per 1000 person-years ($\beta = 5.30$, 95% CI 3.19-7.41; $p < 0.001$). Anti-HBs testing rates increased from 13.9 to 18.3 per 1000 person-years ($\beta = 4.95$, 95% CI 4.01-5.88; $p < 0.001$), while anti-HBc testing rates increased from 10.6 to 13.9 per 1,000 person-years ($\beta = 3.63$, 95% CI 2.70-4.56; $p < 0.001$. HBV vaccination also increased from 2.6 to 4.0 per 1000 person-years ($\beta = 1.195$, 95% CI 0.118–2.273; $p = 0.03$). Sustained post-intervention increases were seen for anti-HBs ($\beta = 0.511$, 95% CI 0.249-0.773; $p < 0.001$), anti-HBc ($\beta = 0.292$, 95% CI 0.062-0.522; $p = 0.013$), and HBV vaccination ($\beta = 0.438$, 95% CI 0.293-0.583; $p < 0.001$). The HIV negative control showed a significant increase following intervention ($\beta = 4.43$, 95% CI 1.53-7.32; $p = 0.003$), but no significant post-intervention trend increase. **Conclusion:** Implementation of universal HBV screening and vaccination guidelines was associated with significant and immediate increases in testing and immunization rates in the US. However, anti-HBs/HBc testing rates lagged behind HBsAg despite triple panel recommendation. Longer follow-up is needed to determine if these increases are sustained and lead to meaningful improvement in HBV transmission and clinical outcomes at the population-level.



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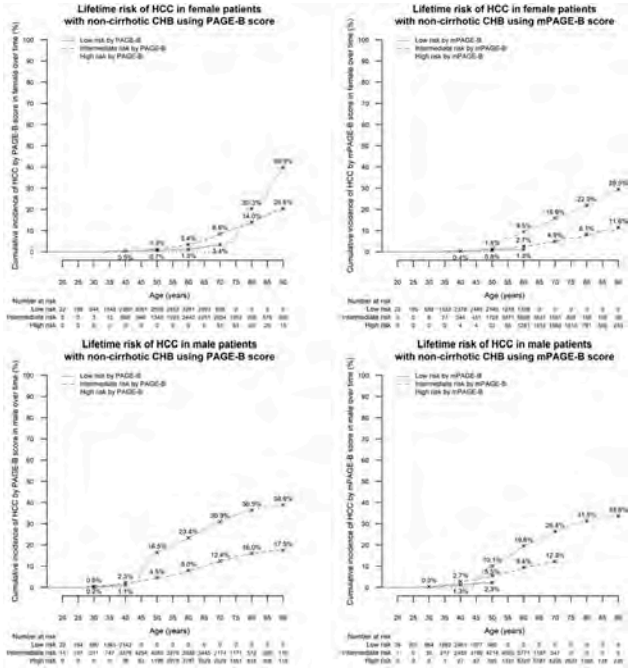
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Disclosures: Allen Luo:Nothing to Disclose, Rene Nichols:Nothing to Disclose, Christopher Wong:Nothing to Disclose, Kali Zhou:Gilead Sciences Inc: Grant/Research Support, Merck: Grant/Research Support.

4049 | LOW PAGE-B AND MODIFIED PAGE-B (MPAGE-B) SCORES MAY UNDERESTIMATE LIFETIME HEPATOCELLULAR CARCINOMA (HCC) RISK IN OLDER PATIENTS WITH NON-CIRRHOTIC CHRONIC HEPATITIS B (CHB): IMPLICATIONS FOR HCC SURVEILLANCE

Iris Tsz-Yau Chow[1] Cheuk Fung Yip[1] Wai Sun Vincent Wong[1] Mandy Lai[1] Jimmy Che-To Lai[1] Vicki Wing-Ki Hui[1] Lilian Yan Liang[1] Yee-Kit Tse[1] Henry Lik-Yuen Chan[1] Grace Wong[1], [1]the Chinese University of Hong Kong

Background: International guidelines recommend HCC surveillance starting at age 40 in men and 50 in women among patients with non-cirrhotic CHB, as well as in patients with PAGE-B ≥ 10 or mPAGE-B ≥ 9. However, some patients classified as low risk by PAGE-B or mPAGE-B scores are older than the recommended surveillance thresholds. We evaluated the predictive performance of PAGE-B and mPAGE-B scores and the annual HCC incidence in patients classified as low risk. **Methods:** This retrospective cohort study included adult patients with CHB who received treatment with entecavir (ETV), tenofovir disoproxil fumarate (TDF), or tenofovir alafenamide (TAF) between 2005 and 2022 in Hong Kong. Lifetime HCC risk and annual HCC incidence were estimated using age as the time scale (Figure). Patients were followed from their age at ETV/TDF/TAF treatment initiation and were censored at cirrhosis development. Inverse probability of censoring weighting was applied to account for informative censoring. Non-HCC death was treated as a competing risk. PAGE-B and mPAGE-B scores were analyzed as time-updating covariates, and their predictive performance was evaluated using integrated time-dependent areas under the receiver operating characteristic curves (itAUROCs). **Results:** Of 64,952 patients with non-cirrhotic CHB receiving ETV/TDF/TAF treatment, 36,364 (56.0%) were male, with a mean age at treatment initiation of 55.9 ± 13.6 years. During a median follow-up of 5.6 (IQR 3.2-9.0) years, 2,639 (4.1%) developed HCC. The itAUROC of the PAGE-B score reduced from 0.71 (95% CI 0.67-0.76) at age 50 to 0.68 (0.65-0.71) at age 60 and 0.64 (0.61-0.68) at age 70. Similarly, the itAUROC of the mPAGE-B score reduced from 0.70 (95% CI 0.65-0.76) at age 50 to 0.67 (0.64-0.71) at age 60 and 0.65 (0.62-0.69) at age 70. Among women aged 50-60 years, annual HCC incidence was 0.06% in those with low PAGE-B and 0.05% in those with low mPAGE-B; the corresponding incidence among women aged 60-70 years using PAGE-B score was 0.21%. Among women without cirrhosis who had intermediate-to-high PAGE-B scores, the annual HCC incidence exceeded 0.2%, except for those aged 50-60 years classified as intermediate risk by mPAGE-B. Among men without cirrhosis, the annual HCC incidence was 0.1% in those aged 40-50 years with a low mPAGE-B; below the recommended threshold for HCC surveillance. The annual HCC incidence exceeded 0.2% among men without cirrhosis who had intermediate-to-high PAGE-B or mPAGE-B scores, except for those aged 30-40 years classified as intermediate risk by PAGE-B. **Conclusion:** PAGE-B score may underestimate HCC risk in women older than 60 years, as their annual HCC risk is above 0.2% even when the score classifies them as low risk; hence, HCC surveillance remains necessary. On the other hand, women aged 50-60 years with a low PAGE-B or mPAGE-B score, and men aged 40-50 years with a low mPAGE-B score, have an annual HCC risk of $< 0.2\%$; therefore, routine HCC surveillance may not be required.



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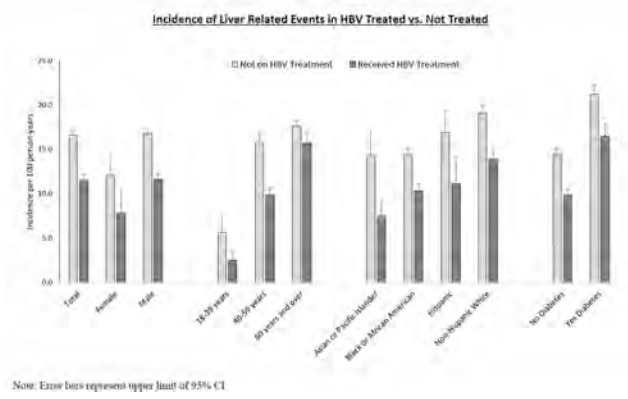
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Precision BioSciences: Advisor, Grace Wong:Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens, Fe: Speaking and Teaching, AstraZeneca, Barinthus, Gilead Sciences, GlaxoSmithKline, IntegerBio, Janssen and Virion: Advisor, Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens: Speaking and Teaching, Ferring, Gilead Sciences, GlaxoSmithKline, Janssen, Otsuka, Roche and Virion: Speaking and Teaching, Gilead Sciences: Grant/Research Support.

4050 | GAPS IN THE CHRONIC HEPATITIS B CASCADE OF CARE AND ANTIVIRAL TREATMENT LEADS TO SIGNIFICANTLY GREATER RISK OF LIVER-RELATED COMPLICATIONS

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Background: Gaps in the chronic hepatitis B (CHB) cascade of care contribute to delays in linkage to care, assessment for treatment eligibility, and initiation of antiviral therapy. These delays contribute to continued disease progression in patients with CHB. We aim to evaluate the clinical impact of gaps and delays in the CHB cascade of care among a national cohort of U.S. Veterans. **Methods:** Longitudinal national Veterans Affairs data were queried to identify adults with laboratory confirmed CHB from 1/1/2010-12/31/2025. Cascade of care assessed included GI/liver clinic (≥1 visit annually), laboratory monitoring (ALT and HBV DNA), assessment of treatment eligibility (AASLD criteria), receipt of antiviral therapy, and incidence of liver-related event (LRE) (ie. decompensated cirrhosis, hepatocellular carcinoma, death). Adjusted multivariable Cox proportional hazards models evaluated the impact of lack of treatment (among treatment-eligible) on risk of LRE. **Results:** Among 25,845 adults with CHB (mean age 57.2y, 92% men, 83% non-Asian ethnicity, 6.3% cirrhosis), 50.2% had annual GI/liver clinic follow up and 47.8% had ALT and HBV DNA testing within 12 months of diagnosis. At baseline, 17.9% were treatment eligible, among whom only 32.8% were treated. During a median follow up of 7.7 years (IQR 4.6-11.8), 28.6% of patients who were initially ineligible became eligible. Among all treatment-eligible patients, only 37.8% received antiviral therapy, which was higher in men vs. women (38% vs. 33%, OR 1.68, 95% CI 1.29-2.19), higher in Asians vs. non-Hisapnic whites (67% vs. 38%, OR 2.32, 95% CI 1.83-2.93). Higher treatment was observed in patients who had annual GI/Liver follow up (OR 4.71, 95% CI 4.28-5.21) or close laboratory monitoring (OR 1.82, 95% CI 1.65-2.02). Receiving antiviral therapy was associated with significantly lower incidence of LRE (11.5 vs. 16.6 per 100 person-years, HR 0.80, $p < 0.01$), which was seen across sex, age, race/ethnicity (Figure). Presence of diabetes mellitus (HR 1.40, $p < 0.01$) or cirrhosis (HR 6.90, $p < 0.01$) were also associated with greater risk or LRE. **Conclusion:** Among a predominantly non-Asian cohort of Veterans with CHB, major gaps in the CHB cascade of care were observed, including inconsistent GI/Liver clinic and laboratory monitoring, which led to only 37.8% of treatment eligible patients receiving antiviral therapy. These findings are alarming, given that timely receipt of treatment was associated with a 20% reduction in LRE.



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4052 | EFFECTIVENESS OF NUCLEOS(T)IDE ANALOGUES IN LIVER FAILURE WITH CHRONIC HEPATITIS B VIRUS INFECTION: A MULTICENTER, RETROSPECTIVE STUDY BASED ON A LARGE-SCALE REAL-WORLD DATABASE

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Background: In clinical practice, chronic hepatitis B (CHB) virus infection patients exhibit marked heterogeneity in treatment response among different populations, particularly those with comorbidities. Large-scale real-world data on nucleos(t)ide analogues (NAs) anti-hepatitis B virus (HBV) therapy remain limited, especially for newer agents like tenofovir amibufenamide (TMF) . **Methods:** This study used data from the Chronic Hepatitis B Specialty Cohort Database ("CHUANSHUO Project") of the National Center for Infectious Diseases. Patients with chronic HBV infection treated with TMF or other oral NAs between January 2023 and December 2024 were included. Effectiveness and safety were analyzed in the overall population and different cohorts. Main inclusion criteria were a diagnosis of CHB, chronic HBV infection, hepatitis B surface antigen (HBsAg) carrier, HBV carrier, or persistent HBsAg (+) $\geq$6 months. We evaluated the effectiveness of NAs in the liver failure cohort (defined by medical history) via assessment of changes in virological, biochemical, and coagulation parameters at 4 weeks. **Results:** A total of 366 liver failure patients were included (mean age 49.98 ± 12.17 years, 77.60% male), of whom 45 received TMF. For virological responses, median HBV DNA change from baseline to week 4 was -2.55 (IQR: -3.51, -1.39) $\log_{10}$ IU/mL. HBsAg also showed a median change of -0.23 (-0.66, 0.13) $\log_{10}$ IU/mL (P = 0.0002). The median change in alanine transaminase (ALT) was -176.20 (-582.80, -28.00) U/L (P < 0.0001), the ALT normalization rate was 44.41% (135/304) by local laboratory criteria and 28.00% (91/325) by AASLD criteria. The median change in aspartate transaminase (AST) was -126.10 (-421.50, -24.00) U/L (P < 0.0001). Total bilirubin (TBIL) showed a median change of -31.55 (-120.90, 5.10) μmol/L (P < 0.0001). For coagulation function, the median changes were 9.00% (-1.92%, 19.80%) for prothrombin activity (PTA) and -0.16 (-0.39, 0.06) for international normalized ratio (INR) (both P < 0.0001). Only four deaths were recorded in patients received NAs. In the TMF subgroup, rapid viral load declined within 4 weeks: HBV DNA decreased by -2.98 (-4.32, -1.99) $\log_{10}$ IU/mL (baseline: 6.37 [5.40, 7.76] $\log_{10}$ IU/mL vs. 4-week: 3.32 [2.75, 3.64] $\log_{10}$ IU/mL, P < 0.0001), and ALT dropped sharply by -297.50 (-732.40, -52.30) U/L. **Conclusion:** In this multicenter, retrospective real-world study, NAs therapy significantly improved virological, biochemical and coagulation parameters from baseline to week 4 in liver failure patient with chronic HBV infection. TMF also achieved rapid viral load reduction. These findings provide real-world evidence for short-term effectiveness of NAs in this critical population.

Table 1 Four-Week Virological, Biochemical and Coagulation Responses to NAs in Liver Failure Patients with Chronic Hepatitis B Virus Infection (N=366).

Variables	Baseline	Four week	Change from baseline	P
HBV DNA, log10IU/mL, median (IQR)	6.14 (4.53, 7.10)	3.23 (2.68, 3.83)	-2.55 (-3.51, -1.39)	<.0001
HBsAg, log10IU/mL, median (IQR)	3.23 (2.60, 3.81)	2.95 (2.40, 3.40)	-0.23 (-0.66, 0.13)	0.0002
ALT, U/L, median (IQR)	237.00 (69.00, 653.00)	46.60 (27.80, 77.00)	-176.20 (-582.80, -28.00)	<.0001
AST, U/L, median (IQR)	212.55 (90.70, 505.20)	61.00 (42.00, 103.50)	-126.10 (-421.50, -24.00)	<.0001
TBIL, μmol/L, median (IQR)	144.15 (60.70, 268.75)	74.95 (42.60, 160.00)	-31.55 (-120.90, 5.10)	<.0001
PTA, %, median (IQR)	46.50 (30.00, 62.20)	57.00 (42.62, 75.80)	9.00 (-1.92, 19.80)	<.0001
INR, median (IQR)	1.65 (1.38, 1.95)	1.44 (1.19, 1.76)	-0.16 (-0.39, 0.06)	<.0001

Note: NAs, nucleos(t)ide analogues; HBV, Hepatitis B Virus; HBsAg, Hepatitis B Surface Antigen; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; TBIL, Total Bilirubin; PTA, Prothrombin Time Activity; INR, International Normalized Ratio; IQR, Interquartile Range.

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4053 | CARDIOVASCULAR, RENAL, AND MORTALITY OUTCOMES IN PATIENTS WITH MET-HBV COMPARED TO PATIENTS WITH HBV AND MASLD ALONE: A REAL-WORLD PROPENSITY-MATCHED ANALYSIS

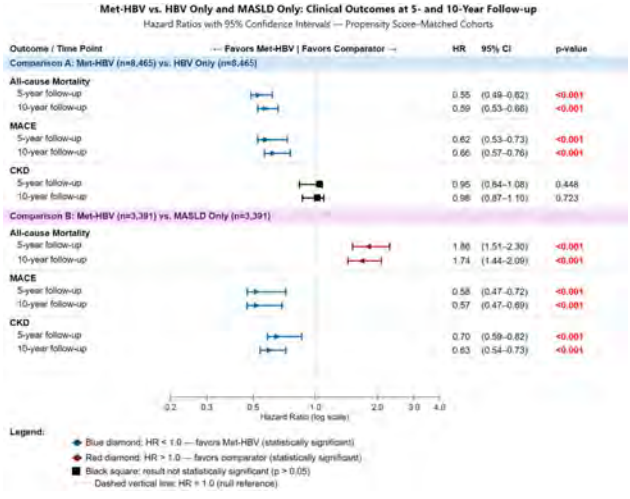
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Background: Met-HBV represents an emerging entity characterized by the coexistence of MASLD and HBV. Evidence suggests that patients with Met-HBV experience accelerated fibrosis progression, even with effective viral suppression. However, the extent to which metabolic and viral factors interact and influence long-term mortality, cardiovascular and renal outcomes remains unclear. We aimed to compare clinical outcomes in patients with Met-HBV versus those with HBV and those with MASLD alone. **Methods:** We conducted a retrospective cohort study using the TriNetX database. We included patients >18 years old. We identified three mutually exclusive cohorts: (1) Patients with a diagnosis of MASLD and HBV and at least one metabolic risk factor were classified as Met-HBV. (2) patients with MASLD and metabolic risk factor without HBV (3) patients with HBV without metabolic risk factors and MASLD. We excluded individuals with prior organ transplants, HCV, pregnancy, and malignancy. We then conducted two propensity score–matched (PSM) comparisons: Met-HBV vs. HBV and Met-HBV vs. MASLD. Outcomes included all-cause mortality, Major Adverse Cardiovascular Events

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(MACE), and chronic kidney disease (CKD), assessed at 5 and 10 years. Kaplan–Meier survival analysis and Cox proportional hazards regression were used for time-to-event analyses. A statistically significant result was defined as $p < 0.05$. **Results:** After PSM, we included 8,465 patients per group in the Met-HBV vs. HBV comparison and 3,391 patients per group in the Met-HBV vs. MASLD comparison. Compared to patients with HBV only, Met-HBV was paradoxically associated with significantly lower mortality at 5 years (HR 0.55, 95% CI 0.49–0.62) and 10 years (HR 0.59, 95% CI 0.53–0.66) and lower MACE at 5 years (HR 0.62, 95% CI 0.53–0.73) and 10 years (HR 0.66, 95% CI 0.57–0.76), all $p < 0.001$. No significant difference in CKD risk was observed at either time point. Compared to patients with MASLD only, Met-HBV was associated with significantly higher mortality at 5 years (HR 1.86, 95% CI 1.51–2.30) and 10 years (HR 1.74, 95% CI 1.44–2.09), both $p < 0.001$. However, Met-HBV was associated with lower MACE at 5 years (HR 0.58, 95% CI 0.47–0.72) and 10 years (HR 0.57, 95% CI 0.47–0.69) and lower CKD at 5 years (HR 0.70, 95% CI 0.59–0.82) and 10 years (HR 0.63, 95% CI 0.54–0.73; all $p < 0.001$). **Conclusion:** Met-HBV is a unique entity with divergent outcome patterns. The lower mortality and MACE in Met-HBV versus HBV may reflect surveillance bias. Compared to MASLD, Met-HBV carries significantly higher mortality, likely driven by the additive burden of chronic viral hepatitis on liver-related outcomes. Overall, these findings underscore that Met-HBV is a clinically distinct entity whose outcomes cannot be predicted by simply summing the risks of its individual components, and they highlight the need for tailored risk stratification and management strategies.



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4054 | PREVALENCE OF HDV INFECTION AND LIVER DISEASE SEVERITY IN A LARGE COHORT OF PATIENTS IN TWO BIG URBAN ÁREAS IN SPAIN. FINAL RESULTS OF HDV-DESCRIBE STUDY

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Background: The prevalence of hepatitis delta virus (HDV) infection among patients with chronic hepatitis B virus (HBV) infection varies across studies. This study aimed to assess the prevalence of HDV infection and evaluate the impact of HDV viremia on liver disease severity. **Methods:** A retrospective multicenter study was conducted in three hospitals in Madrid and Barcelona, Spain. Sociodemographic and clinical data from HBsAg-positive patients were collected through medical records review using REDCap. HDV prevalence was calculated and HDV-positive patients were descriptively analyzed. **Results:** A total of 2,667 HBsAg-positive patients were included. Overall, 1,620/2,667 (60%) underwent HDV testing. Screening rates were higher in Liver Units than others in-hospital Units. The serologic prevalence of HDV coinfection was 5.2% (138/2,667), and 39.9% of HDV-positive individuals had detectable HDV-RNA, with a mean viral load of 1.5 × 10^5 copies/mL (overall prevalence of viremic HDV infection: 2%). The median age of HDV-positive patients was 52.8 years; 58% were male and 35% were non-native individuals.Based on transient elastography or liver biopsy, cirrhosis (F4) was identified in 7.6% of the overall cohort compared with 46.8% of HDV-positive patients. Liver-related clinical events were more frequent in patients with HDV infection than in those without evidence of HDV infection (45% *vs*. 1.4%). Among HDV-positive patients, 18% were on the waiting list for liver transplantation and 10% had hepatocellular carcinoma.Ten patients (7.2%) had previously received pegylated interferon therapy,

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although 7 of them remained HDV-RNA positive. In multivariate analysis, detectable HDV-RNA was independently associated with cirrhosis (OR 8.1; 95% CI 2.9–22.7; p < 0.001). **Conclusion:** In this large urban Spanish cohort of HBsAg-positive patients, HDV serologic prevalence was 5.2%. Cirrhosis and liver-related events were highly prevalent, particularly among patients with detectable HDV-RNA. Exposure to interferon-based therapies was uncommon. In addition, the HDV cascade of care was suboptimal in patients managed off liver units. **Funding Sources:** Proyect HDV-DESCRIBE funded by Gilead Sciences and Project PI22/00849, funded by Instituto de Salud Carlos III (ISCIII) and co-funded by the European Union.

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4055 | FACTORS AFFECTING THE MANAGEMENT OF IMMUNOTOLERANT CHRONIC HBV PATIENTS: RESULTS FROM A WORLDWIDE SURVEY OF CLINICAL PRACTICE

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Background: Variation in HBV treatment practice may hinder viral hepatitis elimination, particularly for immunotolerant patients (HBeAg-positive with HBV DNA >20,000 IU/mL and normal ALT). We assessed clinician management patterns for immunotolerant patients and factors affecting treatment decisions. **Methods:** An international expert panel from the Global Liver Council developed and distributed a 37-item anonymous online survey from June-September 2025 to evaluate providers' knowledge and clinical practice patterns in HBV/HDV management. Immunotolerant patients were defined as HBeAg-positive cases with HBV DNA > 20,000 IU/mL and normal ALT. Multivariable logistic regression analysis was performed using $P < 0.05$ significance threshold. Potential predictive factors included: sex, age, medical degree, years in practice, specialty, practice setting, percentage of HBV patients in practice, HBV knowledge, comfort treating HBV, monthly and total HBV patient encounters and treatment frequencies, guidelines followed, and geographic region. **Results:** The survey was completed by 611 clinicians (hepatologists/gastroenterologists: 68%; infectious disease: 11.5%; other specialties: 20.5%) from seven global regions. EASL guidelines were most frequently followed (46%), followed by AASLD (21%), WHO (12.6%), APASL (10.1%), and other guidelines (10%). Of 540 responders regarding immunotolerant patient treatment, 25.9% treated routinely, 47.8% treated occasionally (patients with certain characteristics), and 26.2% treated based on patient preference (18.1%) or not at all (8.1%). Factors associated with each management pattern are shown in Table.In multivariate analysis, factor independently associated with "treat routinely" was having treated ≤50 HBsAg-positive patients (25.4% of sample) [OR (95% CI): 2.15 (1.40–3.29), $P = 0.0005$]. Factors associated with "treat occasionally" (versus patient preference or no treatment) included hepatology [OR: 3.00 (1.67–5.38), $P < 0.001$], gastroenterology [OR: 1.94 (1.10–3.42), $P = 0.023$], European practice location [OR: 2.22 (1.24–3.99), $P = 0.007$], urban setting [OR: 2.00 (1.00–3.99), $P = 0.049$], and female sex [OR: 1.92 (1.20–3.12), $P = 0.006$].Among 258 participants reporting occasional therapy, treatment criteria included: age ≥30 years (17.2%) or >40 years (52%); liver stiffness ≥8 kPa (50%) or >12 kPa (72.7%); Asian or African origin (15–16%); and family history of HBV cirrhosis/hepatocellular carcinoma (87.5%). **Conclusion:** Management of immunotolerant patients varies widely globally. Approximately 50% of physicians treat selectively based on patient characteristics, 25% treat routinely, and 25% treat based on patient preference or withhold therapy. Provider experience, specialty, geographic location, and demographics significantly affect treatment decisions in this clinically uncertain patient group.

Table. Factors affecting clinician management patterns for immunotolerant chronic HBV patients.

		Treat routinely N=140	Treat occasionally N=258	Treat none N=142	P value
Sex	Male	74 (53.2%)	146 (56.8%)	94 (66.7%)	0.06
	Female	65 (46.8%)	111 (43.2%)	47 (33.3%)	
Age	18-34 years	35 (25.0%)	53 (20.5%)	30 (21.1%)	0.57
	35-54 years	73 (52.1%)	141 (54.7%)	86 (60.6%)	0.33
	≥55 years	32 (22.9%)	64 (24.8%)	26 (18.3%)	0.33
Medical degree	Medical Doctor	127 (90.7%)	243 (94.2%)	130 (92.9%)	0.43
	Advanced Practice Provider /Trainee	12 (8.6%)	14 (5.4%)	9 (6.4%)	
Years of practice after training	≤10 years	61 (43.6%)	100 (38.8%)	67 (47.2%)	0.25
	>10 years	79 (56.4%)	158 (61.2%)	75 (52.8%)	
Specialty	Hepatology	42 (30.0%)	113 (43.8%)	44 (31.0%)	0.006
	Gastroenterology	51 (36.4%)	92 (35.7%)	50 (35.2%)	0.98
	Infectious Disease	19 (13.6%)	24 (9.3%)	17 (12.0%)	0.40
	Other	28 (20.0%)	29 (11.2%)	31 (21.8%)	0.009
Practice setting	Academic institution	82 (58.6%)	180 (69.8%)	95 (66.9%)	0.08
	Private Practice	22 (15.7%)	25 (9.7%)	16 (11.3%)	0.20
	Other	36 (25.7%)	53 (20.5%)	31 (21.8%)	0.49
Area of practice setting	Rural setting	17 (12.1%)	18 (7.0%)	25 (17.6%)	0.0048
	Urban setting	123 (87.9%)	240 (93.0%)	117 (82.4%)	
% practice with chronic HBV	≤50%	123 (87.9%)	228 (88.4%)	128 (90.1%)	0.81
	>50%	17 (12.1%)	30 (11.6%)	14 (9.9%)	
Level of knowledge on HBV	None/Basic	24 (17.3%)	22 (8.5%)	20 (14.1%)	0.03
	Adequate/Superior	115 (82.7%)	236 (91.5%)	122 (85.9%)	
Comfort treating chronic HBV pts	No/Some comfort	37 (26.6%)	37 (14.3%)	26 (18.3%)	0.011
	(Very) Comfortable	102 (73.4%)	221 (85.7%)	116 (81.7%)	
# HBsAg+ pts seen in 1 month	≤50	117 (84.8%)	206 (79.8%)	114 (80.9%)	0.48
	>50	21 (15.2%)	52 (20.2%)	27 (19.1%)	
# HBsAg+ pts ever seen	≤100	49 (35.5%)	60 (23.3%)	29 (20.4%)	0.007
	>100	89 (64.5%)	198 (76.7%)	113 (79.6%)	
# HBsAg+ pts treated in 1 month	≤10	87 (63.0%)	159 (62.6%)	83 (58.9%)	0.71
	>10	51 (37.0%)	95 (37.4%)	58 (41.1%)	
# HBsAg+ pts ever treated	≤50	51 (37.0%)	54 (21.2%)	31 (21.8%)	0.001
	>50	87 (63.0%)	201 (78.8%)	111 (78.2%)	
Preferred guidelines for HBV treatment	AASLD	31 (22.3%)	51 (19.8%)	30 (21.4%)	0.82
	EASL	64 (46.0%)	123 (47.7%)	61 (43.6%)	0.73
	APASL	14 (10.1%)	25 (9.7%)	16 (11.4%)	0.86
	Others	30 (21.6%)	59 (22.9%)	33 (23.6%)	0.92
Region of practice	USA	10 (7.1%)	19 (7.4%)	13 (9.2%)	0.77
	Europe	36 (25.7%)	66 (25.6%)	23 (16.2%)	0.07
	Latin America	9 (6.4%)	26 (10.1%)	8 (5.6%)	0.21
	MENA	27 (19.3%)	54 (20.9%)	28 (19.7%)	0.91
	South Asia	18 (12.9%)	17 (6.6%)	19 (13.4%)	0.041
	SE Asia	35 (25.0%)	67 (26.0%)	47 (33.1%)	0.23
	Africa	5 (3.6%)	9 (3.5%)	4 (2.8%)	0.92

Disclosures: George Papatheodoridis:Abbvie: Advisor, Abbvie: Grant/Research Support, Astra Zeneca: Advisor, Genesis: Advisor, Gilead: Advisor, GlaxoSmithKline: Advisor, Ipsen: Advisor, Novo Nordisk: Advisor, Roche: Advisor, Takeda: Advisor, Albireo: Advisor, Amgen: Advisor, BioArs: Advisor, Elpen: Advisor, Janssen: Advisor, Merck Sharp & Dohme: Advisor, Vir Biotechnology: Advisor, Gilead: Grant/Research Support, Takeda: Grant/Research Support, Vianex: Grant/Research Support, Maria Buti:Roche Pharma/Diagnostics: Consultant, Gilead Sciences: Consultant, GSK: Consultant, Abbvie: Consultant, Janssen: Consultant, Roche Pharma/Diagnostics: Speaking and Teaching, Gilead Sciences: Speaking and Teaching, GSK: Speaking and Teaching, Abbvie: Speaking and Teaching, Janssen: Speaking and Teaching, Bepirovirsen – GSK: Referral to unlabelled/unapproved products, Margarita Papatheodoridi:Nothing to Disclose, Phunchai Charatcharoenwitthaya:Nothing to Disclose, Ajeet Bhadoria:Nothing to Disclose, Jian-Gao Fan:Nothing

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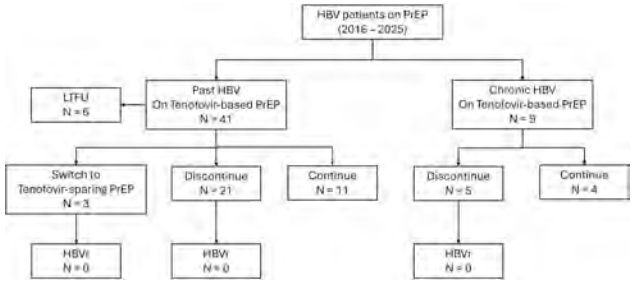
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4056 | HEPATITIS B TESTING PATTERNS IN INDIVIDUALS RECEIVING HIV PRE-EXPOSURE PROPHYLAXIS (PREP) AND PREP USE AMONG INDIVIDUALS WITH HBV INFECTION

Chia-Yu Chiu[1] Steven Mudroch[1] Samantha Kaplan[1] Sara Scherrer[1] Hillary Dunlevy[1] Michael Kriss[1] Lisa Forman[1] James Burton[1] Katherine Frasca[1], [1]University of Colorado

Background: Pre-exposure prophylaxis (PrEP) can be classified as tenofovir-based or tenofovir-sparing. Discontinuation of tenofovir-based PrEP or transition to a tenofovir-sparing PrEP may increase the risk of HBV reactivation. In addition, HBV screening among individuals receiving PrEP has not been systematically reported. **Methods:** We conducted a retrospective review of patients prescribed PrEP within UCHealth between 2016 and 2025. HBV serologic screening included hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc), and hepatitis B surface antibody (anti-HBs). Based on the 2018 AASLD guideline, HBV infection included past (HBsAg –/Anti-HBc+) and chronic HBV infection (HBsAg+/Anti-HBc+). HBV reactivation is defined according to 2018 AASLD criteria. We reported the rate of HBV screening in the PrEP population and HBV reactivation among the PrEP population with HBV infection. **Results:** During the study period, 1,854 patients were prescribed PrEP, of whom 3% (n = 50) had HBV infection (41 past HBV, 9 chronic HBV). PrEP was prescribed by infectious disease (ID) (52%), primary care physicians (PCP) (45%), and hepatologists (HEP) (3%). Testing rates differed significantly among PrEP prescribers. HBsAg testing was performed in 79%, 58%, and 90% of individuals by ID, PCP, and HEP ($p < 0.01$). Anti-HBc testing was performed in 41%, 40%, and 65% of individuals, respectively ($p < 0.01$). Anti-HBs testing was performed in 82%, 50%, and 89% of individuals, respectively ($p < 0.01$). Among the 50 patients with HBV infection, 56% were diagnosed at the time of PrEP initiation. Although no standardized HBV monitoring protocol was implemented, none developed HBV reactivation, including three patients who transitioned to tenofovir-sparing PrEP (Figure). **Conclusion:** There is a significant gap in HBV screening among individuals receiving PrEP. Although absence of HBV testing should not be a barrier to PrEP initiation or continuation, clinicians should recognize that discontinuation of tenofovir-based PrEP or transition to tenofovir-sparing regimens poses the risk of HBV reactivation and de novo HBV infection. PrEP programs also provide an important opportunity to identify and prevent HBV infection through tenofovir-based PrEP, and HBV vaccination.



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to Disclose, Sara Scherrer:Nothing to Disclose, Hillary Dunlevy:Nothing to Disclose, Michael Kriss:Nothing to Disclose, Lisa Forman:Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, James Burton:Nothing to Disclose, Katherine Frasca:Nothing to Disclose.

4057 | HIGH HBV SEROPREVALENCE AND HOST GENETIC LANDSCAPES (IFNL3) IN HAITIAN MIGRANTS: A CROSS-SECTIONAL STUDY IN CHILE

Javier Perez-Valenzuela[1] Patricio Astudillo[1] Javier Uribe[1] José Ignacio Vargas[1] Carlos Benitez[1] Marcelo López-Lastra[1] Ruth Nuñez[1] Valentina Ross[1] Jacinta Soza[1] Karla Pino[1] Francisco Fuster[2] Alejandro Soza Ried[1], [1]Pontificia Universidad Católica de Chile, [2]Hospital Gustavo Fricke

Background: Hepatitis B virus (HBV) affects 240 million people, increasing the risk of cirrhosis and hepatocellular carcinoma. Recent migration has expanded the Haitian population in Chile. Haiti has high HBV endemicity, but health assessments in this vulnerable group are scarce. Genetic polymorphisms, specifically IFNL3 variants, are linked to infection susceptibility and treatment response. Prior studies focused on Asian and non-African cohorts, leaving African ancestry populations underrepresented. We aimed to estimate the seroprevalence of HBV exposure, chronic HBV infection, HCV, and HIV in Haitian migrants in Chile and evaluated demographic, clinical, and genetic factors associated with the risk of the chronic infection among HBV-exposed participants. **Methods:** In this cross-sectional study of adult Haitian migrants in Santiago, clinical and demographic data were collected and serological assays performed for HBsAg, anti-HBs, anti-HBc, anti-HCV, and HIV. Among HBV-exposed participants (anti-HBc positive), subjects were categorized as chronic vs. resolved infection based on HBsAg status. Host IFNL3 single nucleotide polymorphisms (SNPs) rs12979860 and rs8099917 were genotyped by real-time PCR. Genotype distributions were evaluated for Hardy-Weinberg equilibrium (HWE). Associations in exposed subjects were analyzed using Fisher's exact and Mann-Whitney U tests. **Results:** Of 381 enrolled participants (median age 37, 52% female), seroprevalence was: anti-HBc 31% (116/371), anti-HBs 29% (107/370), HBsAg 2.4% (9/368), anti-HCV 0.5% (2/369), and HIV 0.8% (3/366). Among 116 HBV-exposed, 9 (7.8%) had chronic and 107 (92.2%) resolved infection. In the genotyped population (n = 102), the favorable rs12979860 CC genotype was absent in HBsAg-positive patients and present in 14.9% of resolved participants (0/8 vs 14/94; p = 0.59), without HWE deviation (p = 0.82). For rs8099917, distribution was TT 97.1% (99/102), TG 1.9% (2/102), and GG 1.0% (1/102), showing a HWE deviation (p = 0.03) due to low minor allele frequency. No significant differences were found between chronic and resolved patients regarding age, sex, body mass index, obesity, diabetes, hypertension, or smoking status or *IFNL3* genotype distribution. **Conclusion:** Haitian migrants in Chile show high HBV exposure (31%) and chronic infection (2.4%), vastly exceeding local figures (0.15%). Most exposed individuals (92.2%) resolved infection. The host IFNL3 polymorphisms did not reach statistical significance regarding chronic infection vs clearance, potentially limited by small number of cases, though the favorable rs12979860 CC genotype was exclusively observed in individuals who resolved the infection. These findings underscore the need for targeted public health policies, such as screening and vaccination programs, to mitigate HBV burden and support healthcare integration for this vulnerable community.

Characteristic	Exposed (n=116)	Chronic Infection (n=9)	Resolved (n=107)	p-value
Female sex, n (%)	45/116 (38.8)	4/9 (44.4)	41/107 (38.3)	0.73
Age, years (median, Q1-Q3)	40 (34-46)	36 (33-44)	40 (34-46)	0.60
Body Mass Index, kg/m² (median, Q1-Q3)	26.4 (23.4-30.1)	29.1 (22.3-31.7)	26.2 (23.6-30.0)	0.32
Obesity, n (%)	26/96 (27.1)	3/6 (50.0)	23/90 (25.6)	0.34
Hypertension, n (%)	39/103 (37.9)	4/7 (57.1)	35/96 (36.5)	0.42
Diabetes Mellitus, n (%)	5/111 (4.5)	0/9 (0)	5/102 (4.9)	> 0.9
Smoking, n (%)	1/114 (0.9)	0/9 (0)	1/105 (1.0)	> 0.9
SNP *rs12979860*, n (%)				0.59
CC	14/102 (13.7)	0/8 (0)	14/94 (14.9)	
CT/TT	88/102 (86.3)	8/8 (100)	80/94 (85.1)	
SNP *rs8099917*, n (%)				> 0.9
TT	99/102 (97.1)	8/8 (100)	91/94 (96.8)	
TG/GG	3/102 (2.9)	0/8 (0)	3/94 (3.2)	
HIV, n (%)	2/115 (1.7)	1/8 (12.5)	1/107 (0.9)	0.13
HCV, n (%)	1/114 (0.9)	0/9 (0)	1/105 (1.0)	> 0.9

Table 1. Characteristics of HBV-Exposed Haitian Migrants. Patients with Chronic Infection and Resolved Infection.

Disclosures: Javier Perez-Valenzuela:Nothing to Disclose, Patricio Astudillo:Nothing to Disclose, Javier Uribe:Nothing to Disclose, José Ignacio Vargas:Nothing to Disclose, Carlos Benitez:Nothing to Disclose, Marcelo López-Lastra:Nothing to Disclose, Ruth Nuñez:Nothing to Disclose, Valentina Ross:Nothing to Disclose, Jacinta Soza:Nothing to Disclose, Karla Pino:Nothing to Disclose, Francisco Fuster:Nothing to Disclose, Alejandro Soza Ried:Nothing to Disclose.

4058 | SIGNIFICANCE OF METABOLIC SYNDROME PARAMETERS IN PATIENTS WITH CHRONIC HEPATITIS B VIRUS (HBV) INFECTION

Spyros Siakavellas[1] Nicolaos Tsiamperas[2] Ioanna Tsiara[2] Charikleia Kranidioti[2] Christodoulos Sapounas[2] Alexandros Pelekanos[2] Maria

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Manolakopoulou[2] Pinelopi Antonakaki[2] Maria Tampaki[2] Maria Melanie Deutsch[2] Spilios Manolakopoulos[2], [1]Hepatogastroenterology Unit, [2]Hepatogastroenterology Unit, Hippocration General Hospital of Athens

Background: Chronic HBV infection remains a significant public health problem globally known to lead to cirrhosis,and hepatocellular carcinoma. In recent years there has also been a continuous increase in cases of metabolic syndrome (MetS) in the general population, with or without metabolic-associated steatotic liver disease (MASLD), which may aggravate pre-existing liver disease. The impact of the coexistence of MetS with chronic hepatitis B (CHB),(MET-HBV) has not been sufficiently investigated. The aim of this study is to describe the characteristics of patients with MET-HBV followed up at our tertiary centre. **Methods:** All HBsAg-positive patients with available data followed up between 2015 and 2025 at our Unit were identified. These patients either presented with a recent diagnosis for specialized management or were initially diagnosed at our centre. Clinical, laboratory, and demographic data was retrieved from medical records. Cirrhosis was diagnosed based on clinical and laboratory findings and/or liver stiffness values >12 kPa on elastography. A history of arterial hypertension was defined as use of antihypertensive medication at first visit. Type 2 diabetes mellitus was defined as fasting glucose >126 mg/dl at the first visit and/or use of antidiabetic treatment. Dyslipidemia was defined as use of lipid lowering therapy at first visit. Patients consuming >30 g of alcohol daily were excluded. **Results:** We present data from 747 patients; median age was 49.9 years (range 17–83), 55.7% (n = 416) were male. 50.9% were of Greek origin, 49.1% came from other countries. At presentation 42.6% had normal BMI, 36.7% were overweight (25–30 kg/m²) and 20.7% were obese (>30 kg/m²). Men had higher BMI than women (26.83 vs 26.12 kg/m²,p = 0.046). Type 2 diabetes was found in 9.5%, hypertension in 22.6% and dyslipidemia in 21.8% of patients. A total of 388 patients (52%) underwent elastography and 54 (7.2%) had liver biopsy performed at diagnosis/first visit. Among them 68.6% had no or mild fibrosis, 13.1% had moderate fibrosis and 8.8% had advanced fibrosis. Multivariate analysis showed that diabetes mellitus (p = 0.028), BMI >30 kg/m² (p = 0.077) and history of antiviral treatment (p = 0.001) were associated with advanced fibrosis/cirrhosis (defined as liver stiffness values >9 kPa). When analysis was restricted in treated patients high BMI (>30 kg/m²) remained associated with advanced fibrosis. On the other hand, in untreated patients (inactive carriers): diabetes (p = 0.008), high BMI (p = 0.016), and dyslipidemia (p = 0.017) were significantly associated with advanced fibrosis. 2.7% of patients developed HCC and 7.3% of patients passed away during follow-up. **Conclusion:** A significant proportion of patients with CHB in Greece are overweight or present with features of metabolic syndrome. BMI >30 kg/m² appears to worsen liver injury and contribute to devlopment of advanced liver fibrosis, regardless of of HBV infection .

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4059 | ASSESSING CHRONIC HEPATITIS B LIVER FIBROSIS STAGING AND ANTIVIRAL TREATMENT PATTERNS AT A COMMUNITY HEALTH CENTER IN NORTHERN CALIFORNIA

Zinnia Dong[1] Morgan Manter[1] Amy Tang[1], [1]North East Medical Services

Background: Liver elastography is recommended for people with chronic hepatitis B virus (HBV) infection, with chronic HBV guidelines using a fibrosis stage of F2 or greater as a treatment indicator. Community health centers (CHCs) care for over 50,000 people with HBV in the United States and are high-impact settings for HBV management. North East Medical Services (NEMS) is a large, federally funded CHC in the San Francisco Bay Area with an HBV registry-based care management program of over 3,500 active patients that began offering on-site vibration controlled transient elastography (VCTE) in 2021. We aimed to summarize findings and characteristics of NEMS patients with HBV who completed VCTE. **Methods:** We retrospectively analyzed electronic health record data of NEMS patients with chronic HBV and VCTE results between 1/1/21 to 4/30/26. If multiple VCTE assessments were completed, results from the first assessment were analyzed. Chart review was performed for patients with F4 stage without HBV antiviral treatment prescribed. **Results:** We identified 1,685 patients with HBV who completed VCTE with a median age of 58 years and fibrosis stage distribution of 1453 (86%) F0-1, 136 (8%) F2, 57 (3%) F3, and 39 (2%) F4. F2 staging or greater was significantly associated with male compared to female sex ($\chi^2 = 22.8$, $p < 0.01$; OR = 2.0, 95% CI [1.5,2.7]). HBV antiviral treatment prescription rate was 38% (639/1685) overall and 69% (161/232) among patients with ≥F2 staging. For the 5 patients with F4

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stage without HBV treatment prescribed, most were referred to hepatology for further evaluation and treatment (80%, 4/5). **Conclusion:** At a large CHC, on-site VCTE identified clinically significant fibrosis in 14% of patients with chronic HBV, including 6% with advanced fibrosis or cirrhosis. HBV antiviral treatment prescription was higher among patients with F2 or greater fibrosis with increased treatment prescription rates as fibrosis scores increased. These findings support VCTE integration at a CHC and its potential impact in timely HBV antiviral treatment and primary care-based HBV management.

Table 1. Characteristics of Patients with Chronic Hepatitis B by Fibrosis Stage (N=1,685)

Fibrosis Stage[1]	F0-1 (%)[2]	F2 (%)[2]	F3 (%)[2]	F4 (%)[2]	Total (%)[3]
Fibrosis Stage Total[3]	**1453** (86%)	**136** (8%)	**57** (3%)	**39** (2%)	**1685** (100%)
Sex					
Female	**740** (51%)	**43** (32%)	**19** (33%)	**17** (44%)	**819** (49%)
Male	**713** (49%)	**93** (68%)	**38** (67%)	**22** (56%)	**866** (51%)
Age					
<18	**1** (<1%)	-	-	-	**1** (<1%)
18-29	**23** (2%)	-	**1** (2%)	-	**24** (1%)
30-39	**110** (8%)	**12** (9%)	**3** (5%)	**1** (3%)	**126** (7%)
40-49	**281** (19%)	**24** (18%)	**2** (4%)	**5** (13%)	**312** (19%)
50-59	**366** (25%)	**29** (21%)	**15** (26%)	**11** (28%)	**421** (25%)
60-69	**368** (25%)	**39** (29%)	**19** (33%)	**10** (26%)	**436** (26%)
70-79	**259** (18%)	**26** (19%)	**15** (26%)	**11** (28%)	**311** (18%)
80+	**45** (3%)	**6** (4%)	**2** (4%)	**1** (3%)	**54** (3%)
Insurance					
Medicaid[4]	**991** (68%)	**101** (74%)	**40** (70%)	**25** (64%)	**1157** (69%)
Medicare	**198** (14%)	**17** (13%)	**11** (19%)	**5** (13%)	**231** (14%)
Private	**108** (7%)	**10** (7%)	**4** (7%)	**2** (5%)	**124** (7%)
Public Option	**34** (2%)	-	-	-	**34** (2%)
Self-Pay / Uninsured	**100** (7%)	**7** (5%)	**2** (4%)	**5** (13%)	**114** (7%)
Other	**22** (2%)	**1** (1%)	-	**2** (5%)	**25** (1%)
Comorbidities					
MASLD	**817** (56%)	**89** (65%)	**33** (58%)	**25** (64%)	**964** (57%)
Diabetes Mellitus	**260** (18%)	**42** (31%)	**21** (37%)	**17** (44%)	**340** (20%)
HBV Antiviral Treatment Prescribed	**478** (33%)	**81** (60%)	**46** (81%)	**34** (87%)	**639** (38%)
No HBV Antiviral Treatment Prescription	**975** (67%)	**55** (40%)	**11** (19%)	**5** (13%)	**1046** (62%)
HBV DNA <2000 IU/mL & ALT <ULN[5,6]	**497** (51%)	**24** (44%)	**5** (45%)	**3** (60%)	**529** (51%)
HBV DNA ≥2000 IU/mL & ALT (≥ULN)[6]	**7** (1%)	**1** (2%)	-	-	**8** (1%)

[1]F0-1: <7.2 kPa; F2: 7.2-9.3 kPa; F3: 9.4-12.1 kPa; F4: ≥12.2 kPa from Li, AP&T (2015)
[2]Proportion of fibrosis stage total
[3]Proportion of total patients
[4]Includes Medicaid/Medicare dual-eligible
[5]Upper Limit of Normal: >35 male | >25 female
[6]Proportion patients with no HBV antiviral treatment prescription
HBV: Hepatitis B Virus
MASLD: Metabolic Dysfunction-Associated Steatotic Liver Disease

Disclosures: Zinnia Dong:Nothing to Disclose, Morgan Manter:Nothing to Disclose, Amy Tang:Nothing to Disclose, Nothing to Disclose.

4060 | TEMPORAL TRENDS IN HEPATITIS B-RELATED MORTALITY IN THE UNITED STATES, 1999–2020

Albert Gyato[1] Mahader Wossene[2] Estherla Twene[3] Tsegaye Gebreamlak[2] Priyanka Dudani[2] Aditi Puri[2], [1]Loyola Medicine- MacNeal Hospital, [2]Loyola Medicine-MacNeal Hospital, [3]Bursky Public Health, Washington University in St. Louis

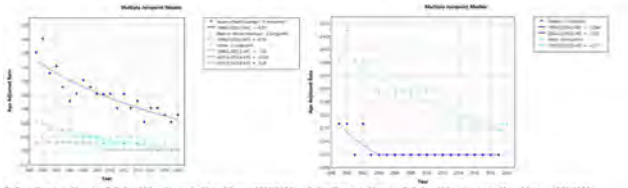
Background: Hepatitis B virus (HBV) infection is a leading cause of severe acute and chronic liver disease worldwide. In the United States, there has been a general decline in HBV incidence and prevalence. While universal childhood vaccination has contributed to a significant reduction in HBV incidence among younger populations, chronic HBV infection remains prevalent in adults, contributing to severe complications such as liver cirrhosis and hepatocellular carcinoma. In the era of prevention through screening, antiviral therapy and expanded vaccination, we aim to understand the current trends in HBV-related mortality and identify remaining gaps. **Methods:** This study used a retrospective, serial cross-sectional analysis of the national death certificate data from the CDC WONDER datasets from 1999 to 2020. Adults 18 years and older with Hepatitis B listed as the underlying cause of death were included. The primary outcome was the age-adjusted hepatitis B mortality rate (AAMR) calculated per 100,000 population. Mortality was stratified by sex, race (White, Black or African American, and Asian or Pacific Islander), and census region (large central metropolitan, smaller metropolitan, and rural). Temporal trends were assessed with Joinpoint regression expressed as average annual percent change (AAPC) and 95% confidence intervals (CI). Statistical significance was defined as $p < 0.05$. **Results:** From 1999 to 2020, 13,549 hepatitis B-related deaths occurred among U.S. adults, with an overall AAMR of 0.2 per 100,000 (95% CI: 0.2-0.2). Males accounted for 69% of deaths versus 31% among females. White individuals accounted for 63.0% of mortality, followed by Asian or Pacific Islanders (20.2%) and Black or African Americans (16.1%). HBV-related mortality declined significantly across all populations. AAMR was higher in males than females (0.4 to 0.2 vs 0.2 to 0.1; AAPC -4.2% vs -3.4%). Asian or Pacific Islanders had the highest mortality burden (AAMR 1.5 to 0.6; AAPC -4.4%), while Black or African Americans showed the steepest decline (AAMR 0.5 to 0.1; AAPC -6.7%). Large central metropolitan areas had the highest AAMR (0.5) and greatest decline (AAPC -5.0%). Smaller metropolitan areas declined from 0.3 to 0.1 (AAPC -4.7%, $p < 0.05$), while rural areas declined from 0.2 to 0.1 (AAPC -3.5%, $p < 0.05$). **Conclusion:** These findings revealed a sustained decline in HBV-related mortality from 1999 to 2020, likely due to advances made in HBV vaccinations and medical treatment. Despite this, there remained racial and sex disparities. Asian or Pacific Islanders had disproportionately higher mortality, possibly due to the higher prevalence of chronic HBV and a high proportion of individuals born in endemic countries or regions. Sex disparities are suspected to be due to increased opportunities for women to be identified and vaccinated during pregnancy. There is a need for continued targeted interventions to eliminate persistent racial and sex disparities.

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POPULATION	AAMR (1999)	AAMR (2020)	AAPC
SEX			
Males	0.4	0.2	−4.2%
Females	0.2	0.1	−3.4%
RACE			
Asian or Pacific Islander	1.5	0.6	−4.4%
Black or African American	0.5	0.1	−6.7%
White	0.2	0.1	−3.7%
CENSUS REGION			
Large central metropolitan areas	0.5	0.1	−5.0%
Smaller metropolitan areas	0.3	0.1	−4.7%
Rural areas	0.2	0.1	−3.5%

A: Table of various populations with associated AAMR (1999 and 2020) and AAPC. All AAPC values were statistically significant.



B: Race Trends in Hepatitis B-Related Mortality in the United States, 1999-2020 C: Sex Trends in Hepatitis B-Related Mortality in the United States, 1999-2020

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4061 | FACTORS ASSOCIATED WITH INCOMPLETE HBV DNA SUPPRESSION AMONG ADULTS IN NORTH AMERICA WITH HBV-HIV CO-INFECTION TREATED WITH TENOFOVIR

Jenny Oh[1] Marc Ghany[2] Wendy King[3] Mark Anderson[4] Raymond Chung[5] Gavin Cloherty[6] Richard Sterling[7], [1]NIH, [2]NIH/NIDDK, [3]Cleveland Clinic, [4]Abbott Laboratories, [5]Massachusetts General Hospital, [6]Abbott, [7]Virginia Commonwealth University

Background: Human immunodeficiency virus (HIV) commonly co-exists with hepatitis B virus (HBV). Both HBV and HIV are susceptible to nucleos(t)ide analogue therapy, allowing dual treatment with a single regimen. However, ~15% of HBV–HIV co-infected individuals fail to achieve complete HBV suppression despite effective HIV control. The reason is unclear. We aimed to identify factors associated with HBV incomplete viral suppression (IVS; HBV DNA ≥1,000 IU/mL) during tenofovir disoproxil fumarate (TDF) therapy and to interrogate the HBV genome for novel mutations associated with TDF resistance. **Methods:** Data and serum samples from HBV–HIV co-infected adults on TDF participating in the HBV–HIV Co-infection Ancillary Study of the Hepatitis B Research Network were evaluated. Among those with suppressed HIV RNA (<400 copies/mL), logistic regression was used to identify demographic, clinical, and virologic factors associated with HBV IVS. Whole HBV genome sequencing was performed by next-generation sequencing (NGS) among participants with IVS, with and without HIV RNA suppression. Phylogenetic analysis was conducted using GenBank reference sequences. Mutational analysis was focused on the reverse transcriptase (RT) domain of the HBV polymerase. **Results:** 91/114 participants had suppressed HIV RNA (<400 copies/mL). Among the 91, median duration of HBV-HIV infection was 20 years; 7.2% had CD4 <200 cells/mm³ and 13 (14%) had HBV IVS. In univariable analyses, higher BMI, higher ALT, low CD4 count (<200 cells/mm^3), higher qHBeAg, higher HBsAg, higher HBV RNA and higher HBcrAg were associated with HBV IVS (Table 1). In multivariable analysis, only HBV RNA was significant. Whole HBV genome sequencing was performed on 26 participants with IVS, 13 participants with and 13 without HIV RNA suppression. Multiple polymorphisms were identified in the RT domain but no mutational hotspots or known TDF resistance mutations (rtA194T, rtR192P, or MLVV) were identified. **Conclusion:** These findings indicate incomplete HBV DNA suppression among co-infected adults with HIV control on TDF is not due to TDF resistance, but rather a result of high covalently closed circular DNA transcriptional activity (reflected by elevated HBV RNA), suggesting this population may require more potent antiviral therapy to achieve HBV suppression.

Table 1: Associations between demographic, clinical, and viral factors and incomplete HBV DNA suppression among adults on TDF with HBV-HIV co-infection

	Total n = 91	HBV DNA <1000 n = 78	HBV DNA ≥1000 n = 13	Unadjusted OR, 95% CI	p-value
Age, years: Median (Q1, Q3)	49 (44, 54)	49 (45, 55)	50 (43, 48)	per 5 years 0.73 (0.50, 1.01)	0.05
Sex, n (%)					
Female	7 (7.7)	5 (6.4)	2 (15.4)	2.66 (0.46, 15.40)	0.28
Male	84 (92.3)	73 (93.6)	11 (84.6)	Ref	
Race, n (%)	n = 89	n = 78	n = 11		
Non-Hispanic Black	43 (48.3)	34 (44.7)	9 (69.2)	2.78 (0.79, 9.81)	0.11
Non-Hispanic White	30 (33.7)	27 (35.5)	3 (23.1)	Ref	
Non-Hispanic Asian	5 (5.6)	5 (6.6)	0 (0.0)		
Other	11 (12.4)	10 (13.2)	1 (7.7)		
Body mass index, kg/m^2 Median (Q1, Q3)	n = 88 25.8 (22.4, 30.3)	n = 75 25.8 (22.3, 29.3)	n = 13 31.3 (27.3, 36.4)	per 5 kg/m^2 1.99 (1.31, 3.29)	0.007
ALT, ULN Median (Q1, Q3)	n = 88 0.9 (0.6, 1.4)	n = 75 0.9 (0.6, 1.2)	n = 13 1.3 (1.1, 2.1)	per ULN 2.39 (1.17, 4.87)	0.02
HBeAg, n (%) Positive	57 (62.6)	44 (56.4)	13 (100.0)	Incalculable	0.002[b]
HBeAg, $\log_{10}$ IU/mL Median (Q1, Q3)	n = 88 0.1 (-0.6, 1.4)	n = 75 0.0 (-0.8, 0.9)	n = 13 2.8 (2.1, 2.9)	per $\log_{10}$ IU/mL 6.65 (2.61, 16.95)	< 0.0001
HBsAg, $\log_{10}$ IU/mL Median (Q1, Q3)	n = 88 3.2 (2.8, 3.8)	n = 75 3.1 (2.6, 3.4)	n = 13 4.0 (4.2, 5.0)	per $\log_{10}$ IU/mL 9.02 (3.13, 26.06)	< 0.0001
HBV RNA, $\log_{10}$ U/mL Median (Q1, Q3)	n = 87 5.0 (2.0, 5.6)	n = 75 5.4 (1.0, 5.0)	n = 12 7.7 (7.1, 8.2)	per $\log_{10}$ IU/mL 49.68 (2.07, >999.99)	0.02
HBcrAg, $\log_{10}$ U/mL Median (Q1, Q3)	n = 87 5.5 (3.7, 6.9)	n = 75 5.2 (3.7, 6.3)	n = 12 7.6 (6.8, 9.4)	per $\log_{10}$ IU/mL 1.76 (1.28, 2.47)	0.001

Abbreviations: ALT, alanine aminotransferase; DNA, deoxyribonucleic acid; HBcrAg, hepatitis B core-related antigen; HBV, hepatitis B virus; HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface antigen; RNA, ribonucleic acid; ULN, upper limit of normal.
Simple logistic regression unless otherwise noted.
[b] Fisher exact test.

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4062 | ARE TWO DOSES OF HEPB-CPG SUFFICIENT TO PROVIDE IMMUNITY IN PEOPLE WITH HIV AND PRIOR HEPATITIS B VACCINE NONRESPONSE? A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: People with HIV (PWH) are less likely to develop protective serologic responses to conventional hepatitis B vaccines. Recent recommendations suggest that nonresponders to the initial vaccination series should be reimmunized with two or three doses of HepB-CpG (Heplisav-B). However, large pooled data assessing the efficacy of two-doses of HepB-CpG compared with three doses of HepB-Alum vaccines (Engerix-B or Recombivax HB) among PWH remain limited. While two prior studies independently demonstrated the superiority of two-dose HepB-CpG compared to three-dose HepB-alum in separate study populations, they were limited by modest sample sizes and incomplete follow-up in both treatment arms. By pooling data across these trials,this meta-analysis aimed to provide more evidence regarding the comparative effectiveness of the two-dose HepB-CpG versus three-dose HepB-alum vaccination strategy. **Methods:** A systematic review and meta-analysis following PRISMA guidelines was conducted. PubMed, Embase, Web of Science, and CENTRAL were searched through 01/24/2026. The random-effects model was used to estimate the pooled risk ratios and seroconversion rates with 95% confidence intervals using the Comprehensive Meta-Analysis software (version 4.0; BIOSTAT, Englewood, NJ, USA). Heterogeneity was assessed using the I^2 statistic. **Results:** A total of 493 participants were included (248 HepB-CpG, 245 HepB-Alum). Mean age was 45 years; most were male. The cohort included White (46%), Black (37%), Asian (12%), and Hispanic (29%) participants. Individual studies showed higher seroconversion with HepB-CpG. Reilly-Evans et al. reported RR 1.62 (93.4% vs 57.6%), and Marks et al. reported RR 1.16 (93.1% vs 80.6%). However, pooled analysis showed no statistically significant difference, and did not confirm clear superiority of the two-dose HepB-CpG regimen (RR 1.35; 95% CI 0.97, 1.87; $p = 0.079$), with high heterogeneity ($I^2 = 86.5\%$). Subgroup analysis showed reduced seroprotection in diabetes (70.2%) and smokers (84%), both below the 90% optimal threshold. **Conclusion:** Although individual studies suggested higher seroconversion with HepB-CpG, pooled data did not show statistically significant superiority, and do not confirm that two-dose HepB-CpG alone is sufficient over HepB-Alum in prior nonresponders. Evidence suggests outcomes are influenced by heterogeneity and host factors. Current findings support consideration of additional third booster dose of HeB-CPG to achieve desirable seroconversion compared with three doses of HepB-Alum in PWH who had previously failed hepatitis B vaccination . Additional measures remain optimizing CD4+ levels to enhance immune response in diabetics and smokers.

Table 1. Baseline Characteristics of Participants by Vaccine Type and Pooled Sample

Variable	Reilly-Evans et al., 2023	Marks et al., 2025	Pooled
HepB-CpG n	61	187	248
HepB-Alum n	59	186	245
Sex assigned at birth, % male	NA	64	64
Sex assigned at birth, % female	NA	36	36
Gender identity, % male/cis	80.3	98	94
Gender identity, % female/trans	19.7	2	6
Age, mean ± SD	42±11	46±15	45.0±14.2
Race/ethnicity, % White	81.9	34	45.6
Race/ethnicity, % Black	13.1	45	37.1
Race/ethnicity, % Asian	0	16	11.7
Race/ethnicity, % AI/AN	0	1	0.4
Race/ethnicity, % NH/PI	1.6	0	0.4
Ethnicity, % Hispanic	49	21	28.6
Ethnicity, % Not Hispanic	51	79	71.4

Footnotes: NA, not available; SD, standard deviation; AI/AN, American Indian or Alaska Native; NH/PI, Native Hawaiian or Other Pacific Islander; HepB-CpG, hepatitis B vaccine with CpG adjuvant; HepB-Alum, hepatitis B vaccine with Alum adjuvant.



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4063 | OLDER AGE AS A KEY PREDICTOR OF SUSTAINED VIROLOGICAL RESPONSE IN HEPATITIS B PATIENTS RECEIVING LONG-TERM TENOFOVIR AMIBUFENAMIDE THERAPY

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Background: In a previously reported long-term cohort treated with tenofovir amibufenamide (TMF), 94.5% of patients achieved HBV DNA < 20 IU/mL after 5 years. In this high-response setting, the small subset of patients with low level viremia or virological fluctuation remains clinically important. It is unclear whether these events occur randomly or cluster within identifiable subgroups. **Methods:** This study used a combined phase III–IV clinical cohort of TMF with prospective follow-up. A total of 589 patients from the evaluable population were included based on predefined criteria. An endpoint event was defined as either failure to achieve HBV DNA < 20 IU/mL or any case of virological rebound (> 1 $\log_{10}$ IU/mL increase from nadir). Baseline factors associated with endpoint were assessed using logistic regression analysis. The analysis was designed to identify patterns of risk enrichment and a constrained classification and regression tree (CART) was established to enable clinically interpretable risk stratification. For continuous predictors, optimal cut-offs were determined by maximizing node purity (information gain) across all candidate thresholds. **Results:** Among 589 patients, 31 (5.3%) reached endpoint during 5 years of follow-up, indicating a low overall event rate. Events were not randomly distributed but showed concentration within specific baseline subgroups. In a univariable analysis, younger age and higher baseline HBV DNA level were associated with increased risk of endpoint events (Figure 1). In a multivariable analysis, age remained the only independent predictor (adjusted OR 0.95 per year, 95% CI 0.91–1.00, P = 0.030). In the CART analysis, age was consistently selected as the primary splitting variable, with 35 years as the optimal cut-off. Patients aged > 35 years had a low event rate (2.9%), while those ≤ 35 years had a higher rate (8.0%). Among patients aged ≤ 35-year, baseline HBV DNA > 7.7 $\log_{10}$ IU/mL further enriched risk, with an event rate of 12.2%, compared with 3.1% in the

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remaining patients. Other factors (e.g., cirrhosis and HBeAg positivity) provided limited additional stratification. **Conclusion:** In this high response TMF cohort, low level viremia or virological fluctuation was infrequent and non-randomly distributed, with higher risk in younger patients and those with high baseline HBV DNA. Age is a key predictor of sustained virological response during long-term TMF therapy.

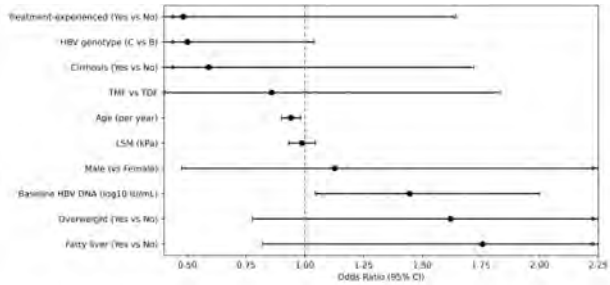


Figure 1. Baseline factors associated with endpoint events

Forest plot of univariable logistic regression analyses showing baseline factors associated with endpoint events. Odds ratios (ORs) and 95% confidence intervals (CIs) are displayed. Variables with unstable estimates due to sparse events (e.g., HBeAg status and abnormal ALT) were excluded from the plot.

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4064 | DIFFERENTIAL EFFECT OF ANTIVIRAL THERAPY ON HEPATOCELLULAR CARCINOMA RISK ACCORDING TO HBV DNA TRAJECTORIES IN HBEAG-NEGATIVE CHRONIC HEPATITIS B: A MULTINATIONAL STUDY

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Background: Prognostic significance of HBV DNA trajectories in HBeAg-negative chronic hepatitis B (CHB) remains unclear. We assessed whether the effect of antiviral therapy (AVT) on hepatocellular carcinoma (HCC) risk differs according to the duration of moderate-to-high viremia and its association with fibrosis progression. **Methods:** This multinational study recruited 9,336 treatment-naïve, non-cirrhotic HBeAg-negative CHB patients from South Korea, Hong Kong, and Taiwan (2007–2022). HBV DNA levels during the initial 3-year follow-up defined four groups: Group 1, persistent $<10{,}000$ IU/mL; Groups 2 and 3, moderate-to-high viremia ($\geq 10{,}000$ IU/mL) for <18 and ≥ 18 months, respectively; Group 4, AVT initiation within 3 years. **Results:** During a median follow-up of 10.0 (interquartile range, 7.0–12.2) years, 111 patients developed HCC (0.13/100 person-years). The annual HCC incidence was 0.08%, 0.20%, 0.36%, and 0.13% in Groups 1–4, respectively. Compared with Group 1, HCC risk increased with longer moderate-to-high viremia duration (Group 2: adjusted sub-distribution hazard ratio [aSHR] = 2.23; Group 3: aSHR = 4.02; all $P < 0.05$), whereas Group 4 showed a comparable risk. In propensity score analyses, the cumulative HCC incidence remained significantly higher in Group 3 than in Group 4 (all $P < 0.05$), but not in Group 2, even in patients with significant fibrosis or elevated alanine aminotransferase. Fibrosis progression also increased with longer moderate-to-high viremia duration, with the highest risk in Group 3 (P for trend < 0.001). **Conclusion:** Prolonged moderate-to-high viremia increased HCC and fibrosis progression risks in non-cirrhotic HBeAg-negative CHB, and the benefit of AVT appeared to differ by viremia duration, with benefit mainly in prolonged exposure.

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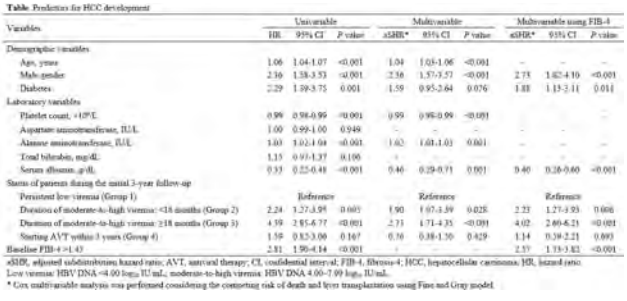


Table. Predictors for HCC development

Variables	Univariable			Multivariable			Multivariable using FIB-4		
	HR	95% CI	*P* value	aSHR*	95% CI	*P* value	aSHR*	95% CI	*P* value
Demographic variables									
Age, years	1.06	1.04-1.07	<0.001	1.04	1.03-1.06	<0.001	–	–	–
Male gender	2.36	1.38-3.53	<0.001	2.36	1.37-3.57	<0.001	2.75	1.62-4.10	<0.001
Diabetes	2.29	1.39-3.75	0.001	1.59	0.95-2.64	0.076	1.88	1.13-3.11	0.011
Laboratory variables									
Platelet count, ×10⁹/L	0.99	0.98-0.99	<0.001	0.99	0.98-0.99	<0.001	–	–	–
Aspartate aminotransferase, IU/L	1.00	0.99-1.00	0.949	–	–	–	–	–	–
Alanine aminotransferase, IU/L	1.03	1.02-1.04	<0.001	1.02	1.01-1.03	0.001	–	–	–
Total bilirubin, mg/dL	1.15	0.97-1.37	0.106	–	–	–	–	–	–
Serum albumin, g/dL	0.33	0.25-0.48	<0.001	0.46	0.29-0.71	0.001	0.40	0.26-0.60	<0.001
Status of patients during the initial 3-year follow-up									
Persistent low viremia (Group 1)	Reference			Reference			Reference		
Duration of moderate-to-high viremia: <18 months (Group 2)	2.24	1.27-3.95	0.005	1.90	1.07-3.39	0.028	2.23	1.27-3.93	0.006
Duration of moderate-to-high viremia: ≥18 months (Group 3)	4.59	2.85-7.37	<0.001	2.71	1.71-4.35	<0.001	4.02	2.60-6.21	<0.001
Starting AVT within 3 years (Group 4)	1.59	0.83-3.00	0.167	0.76	0.38-1.50	0.429	1.14	0.59-2.21	0.693
Baseline FIB-4 >1.43	2.81	1.90-4.14	<0.001	–	–	–	2.57	1.73-3.82	<0.001

aSHR, adjusted subdistribution hazard ratio; AVT, antiviral therapy; CI, confidential interval; FIB-4, fibrosis-4; HCC, hepatocellular carcinoma; HR, hazard ratio; Low viremia: HBV DNA <4.00 $\log_{10}$ IU/mL; moderate-to-high viremia: HBV DNA 4.00–7.99 $\log_{10}$ IU/mL.
* Cox multivariable analysis was performed considering the competing risk of death and liver transplantation using Fine and Gray model.

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4065 | HBV DNA-BASED TREATMENT THRESHOLDS FAIL TO REFLECT FIBROSIS BURDEN AND LONG-TERM OUTCOMES IN INDETERMINATE-PHASE CHRONIC HEPATITIS B

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Background: Management of patients with indeterminate-phase chronic hepatitis B (CHB) remains challenging because current decisions are largely based on serum HBV DNA thresholds, which may not adequately reflect underlying liver fibrosis burden or long-term prognosis. We investigated the clinical limitations of HBV DNA-based treatment stratification and evaluated whether fibrosis burden better predicts liver-related outcomes in patients with indeterminate-phase CHB. **Methods:** We retrospectively analyzed 497 patients with indeterminate-phase CHB who underwent liver biopsy. Histologic fibrosis stage, inflammation grade, and steatosis were assessed at baseline, and patients were categorized according to HBV DNA levels and treatment eligibility based on current guideline thresholds. Long-term outcomes included hepatocellular carcinoma (HCC), cirrhosis progression, hepatic decompensation, and composite liver-related events. **Results:** During a median follow-up of 148.0 months (total 5,740.7 person-years), 50 patients developed HCC, 68 showed cirrhosis progression, 26 experienced hepatic decompensation, [KSG1] and 109 developed composite liver-related events. In multivariable Cox analysis, fibrosis stage independently predicted liver-related outcomes (hazard ratio [HR] per 1-stage increase, 1.41; 95% confidence interval [CI], 1.15–1.72; $P = 0.0009$), whereas HBV DNA level was not independently associated with outcomes (HR, 0.90; 95% CI, 0.82–1.00; $P = 0.051$). Substantial discordance was observed between HBV DNA category and histologic fibrosis burden. Among patients with low-to-moderate HBV DNA levels (< 7 log IU/mL), 72.1% had significant fibrosis ($\geq$F2), while 35.5% of patients with high HBV DNA levels (> 7 log IU/mL) had minimal fibrosis (F0–1). Among patients with significant fibrosis ($\geq$F2), 80.3% had low-to-moderate HBV DNA levels, while among patients with HBV DNA levels within conventional treatment thresholds (4-8 log IU/mL), 20% showed no histologic indication for treatment. Noninvasive fibrosis markers showed good diagnostic performance for predicting significant fibrosis. Fibroscan demonstrated the highest accuracy for $\geq$F2 fibrosis (AUROC 0.818), $\geq$F3 fibrosis (AUROC 0.877), and cirrhosis (AUROC 0.870), outperforming FIB-4 and APRI. **Conclusion:** Current HBV DNA-based thresholds may misclassify a substantial proportion of patients with indeterminate-phase CHB, leading to both undertreatment of high-risk patients and overtreatment of low-risk patients. Risk stratification incorporating fibrosis burden, supported by noninvasive fibrosis markers, may improve individualized treatment decisions beyond HBV DNA-based approaches alone.
Disclosures: Seung Up Kim:Nothing to Disclose, Hanah Lee:Nothing to Disclose, Tae Hyung Kim: Nothing to Disclose, Yeon Seok Seo:Nothing to Disclose, Dae Won Jun:Nothing to Disclose, Soo Young Park:Nothing to Disclose, Hyun Woong Lee: Nothing to Disclose, Sang Gyune Kim:Nothing to Disclose.

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4066 | PREVALENCE OF HEPATITIS A TO E VIRUSES AMONG THE UNITED STATES POPULATION, 2011-2023

Zhiwei Chen[1] Jing Tang[2] Yan Han[3] Zhao Li[4], [1]The second affiliated hospital of CQMU, [2]Second Affiliated Hospital, Chongqing Medical University, [3]The Second Affiliated Hospital of Chongqing Medical University, [4]The Seventh People's Hospital of Chongqing

Background: With the 2030 WHO target for the elimination of viral hepatitis threat approaching, updated epidemiological data on hepatitis A–E in the United States is essential to optimize public health policies and facilitate progress toward this goal. **Methods:** This cross-sectional study included data of nationally representative participants aged ≥6 years in the National Health and Nutrition Examination Survey from 2011 to 2023. National trends in prevalence of hepatitis A to E were analyzed, and stratified by sex, age, and ethnicity and race. **Results:** A total of 39,753, 39,874, 39,644 and 39,879 eligible participants were included for analyses of hepatitis A, B, C and E, respectively. For HBV, the prevalence of current HBV infection (HBsAg and anti-HBc positivity) was 0.3% (95% CI: 0.2%–0.4%), remaining stable from 2011 to 2023. The prevalence of HBV susceptibility (HBsAg, anti-HBc and anti-HBs negativity) was 71.4% (95% CI: 70.4%–72.2%), with no obvious fluctuation across the study period. HBV vaccination coverage with at least one dose decreased from 50.4% (95% CI: 47.8%–53.1%) in 2011 to 48.4% (95% CI: 46.2%–50.7%) in 2020. A prominent declining trend was observed among individuals born after 1991, with coverage dropping from 90.0% (95% CI: 86.9%–92.4%) to 83.6% (95% CI: 81.3%–85.7%) (P for trend = 0.001). Notably, 57.0% (95% CI: 55.6%–58.4%) of HBV-vaccinated participants still remained susceptible to HBV. Among patients with current HBV infection, the seroprevalence of anti-HDV, retested using an updated laboratory assay, was 1.3% (95% CI: 0.3%–6.1%). For HCV, the seroprevalence of anti-HCV was 1.6% (95% CI: 1.4%–1.8%), and the prevalence of current HCV infection confirmed by positive HCV-RNA was 0.7% (95% CI: 0.6%–0.9%). Although anti-HCV seropositivity stayed stable over time, current HCV infection decreased from 0.8% (95% CI: 0.4%–1.4%) in 2011 to 0.4% (95% CI: 0.3%–0.7%) in 2023, with the most remarkable reduction seen in the population aged ≥50 years. The proportion of active infection among anti-HCV-positive individuals also declined significantly from 65.5% (95% CI: 46.4%–80.6%) to 31.3% (95% CI: 23.3%–40.7%) (P for trend = 0.005). For HAV, anti-HAV seroprevalence rose steadily from 41.6% (95% CI: 38.7%–44.6%) to 48.0% (95% CI: 44.7%–51.4%) (P for trend < 0.001), whereas HAV vaccination coverage maintained a relatively steady level throughout the years. For HEV, the prevalence of anti-HEV IgM positivity remained stable from 1.6% (95% CI: 1.2%–2.2%) in 2011 to 1.7% (95% CI: 1.2%–2.3%) in 2023. **Conclusion:** The sustained decline of current HCV infection reflects encouraging progress in hepatitis C prevention and treatment. However, the falling HBV vaccination coverage and rising anti-HAV seroprevalence might become emerging public health challenges. Targeted and strengthened interventions are urgently required to address these issues and advance the global agenda of viral hepatitis elimination. **Disclosures:** Zhiwei Chen:Nothing to Disclose, Jing Tang:Nothing to Disclose, Yan Han:Nothing to Disclose, Zhao Li:Nothing to Disclose.

4067 | SEX DIFFERENCES IN DISEASE PROGRESSION AMONG PATIENTS WITH CHRONIC HBV INFECTION

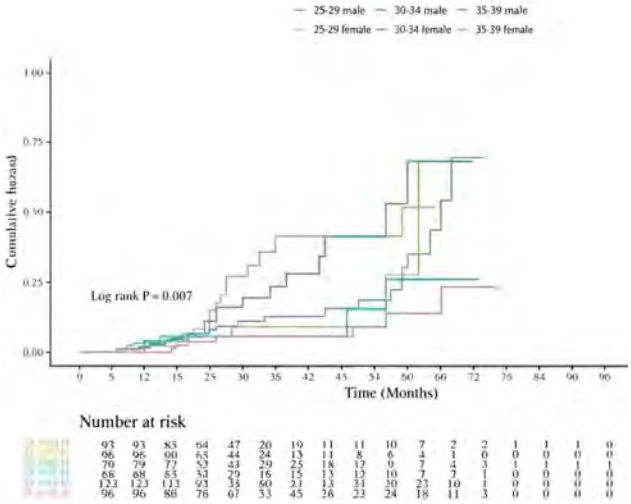
Dachuan Cai[1] Yiting Dai[1], [1]The Second Affiliated Hospital of Chongqing Medical University

Background: Chronic hepatitis B virus (HBV) infection shows sex disparities in progression, with males carrying higher risks for cirrhosis and hepatocellular carcinoma (HCC). However, current antiviral guidelines do not incorporate sex-related factors. We aim to investigate sex differences in chronic HBV progression and evaluate whether sex should guide antiviral therapy initiation for risk stratification. **Methods:** This retrospective cohort enrolled 555 treatment-naïve chronic hepatitis B patients (Jan 2016–Dec 2025). Patients were stratified by sex and age and followed longitudinally. The primary endpoint was overall liver disease progression (OLDP: hepatitis exacerbation, cirrhosis, or HCC). Kaplan–Meier, log-rank tests, and Cox models identified progression risk factors. Subgroup analyses targeted untreated patients. Propensity score matching (PSM) balanced baselines to evaluate antiviral impacts, while linear mixed-effects models assessed sex-specific virological responses. **Results:** A total of 555 patients were included, comprising 295 males and 260 females, with a cumulative follow-up of 16,722 person-months. During follow-up, 74 patients developed OLDP, corresponding to an incidence density of 5.31 per 100 person-years. The incidence density was significantly higher in males than in females (7.27 vs. 2.98 per 100 person-years, P < 0.001).The overall 5-year cumulative incidence of OLDP was 11.90%, which was significantly higher in males (P = 0.001). After age stratification, significant differences in cumulative incidence were observed across subgroups (P = 0.007). Multivariable Cox regression identified female sex as an independent protective factor for disease progression (HR = 0.47, 95% CI 0.27–0.80). This protective effect was more pronounced in untreated patients (HR

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= 0.33, 95% CI 0.14–0.75).After PSM, antiviral therapy was not significantly associated with reduced progression risk (HR = 0.94, P > 0.05), whereas female sex remained independently protective (HR = 0.32, 95% CI 0.10–0.96). Antiviral therapy significantly reduced HBV DNA levels (P < 0.001), although differences in the rate of virological response were observed among sex–age subgroups (P < 0.001). **Conclusion:** Significant sex differences exist in disease progression among patients with chronic hepatitis B, with females exhibiting a substantially lower risk than males. This protective effect is more evident in untreated populations, suggesting that the disparity mainly reflects differences in the natural history of the disease. A potential interaction between sex and age was observed. Incorporating sex and age into risk stratification models may help optimize individualized decisions regarding the initiation of antiviral therapy and facilitate more precise clinical management.

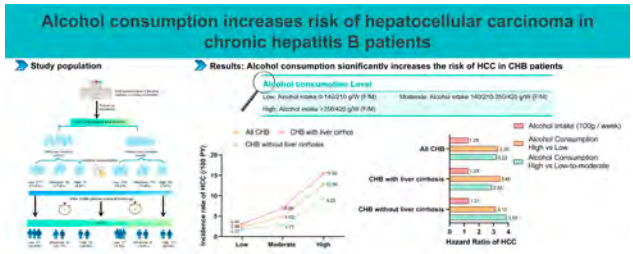


Disclosures: DACHUAN CAI:Nothing to Disclose, Yiting Dai:Nothing to Disclose.

4068 | ALCOHOL CONSUMPTION INCREASES RISK OF HEPATOCELLULAR CARCINOMA IN CHRONIC HEPATITIS B PATIENTS

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Background: Both chronic hepatitis B (CHB) and alcohol consumption are risk factors for hepatocellular carcinoma (HCC). However, their synergistic effect on HCC development is not fully elucidated. Therefore, we evaluated the association between alcohol consumption and HCC development in CHB patients. **Methods:** Patients with CHB were enrolled between March 1, 2005 and December 30, 2025 at two medical centers in China. COX proportional hazards regression model and Kaplan-Meier curves were used to evaluate the association between alcohol consumption and HCC risk in CHB patients. **Results:** A total of 1,010 CHB patients were included, among whom 129 (12.77%) developed HCC during 3,684 person-years of follow-up. Compared to those without HCC, CHB patients with HCC had higher alcohol intake levels (2.00 vs. 0.00×100 g/week, $P<0.001$). Multivariable Cox regression showed that each 100 g/week increase in alcohol intake was associated with a higher risk of HCC (adjusted hazard ratio [aHR] 1.29, $P<0.001$) in CHB patients. Compared with low (<140/210 g/week) and low-to-moderate (≤350/420 g/week) alcohol intake, high alcohol intake (>350/420 g/week) was associated with an increased risk of HCC (aHR 3.30 and 3.22, respectively; both $P<0.001$). In stratified analyses, similar associations were observed in both cirrhotic (aHR 1.29, 3.45, and 2.88) and non-cirrhotic CHB patients (aHR 1.31, 3.15, and 3.88). **Conclusion:** Alcohol consumption independently increases HCC risk among CHB patients, regardless of cirrhosis status. These findings highlight the importance of systematic assessment and control of alcohol intake to reduce HCC risk in CHB patients.



Disclosures: yukai chen:Nothing to Disclose, Fajuan Rui:Nothing to Disclose, Jie Li:Nothing to Disclose, Yuemin Nan:Nothing to Disclose.

4069 | MULTISTATE TRAJECTORIES PREDICT RECOMPENSATION AFTER FIRST HEPATITIS B VIRUS (HBV)-RELATED DECOMPENSATED CIRRHOSIS

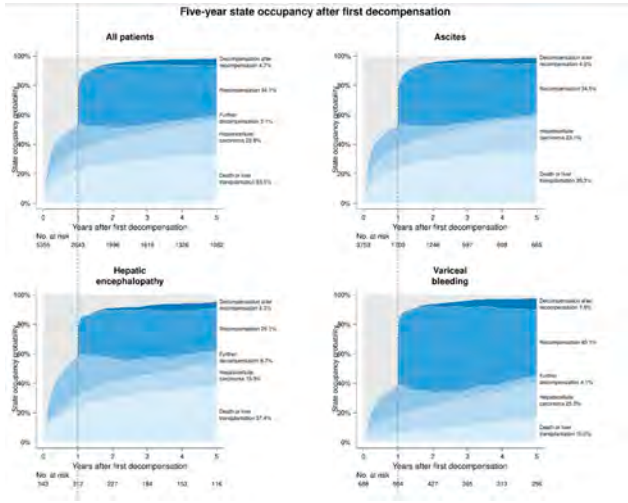
Vicki Wing-Ki Hui[1] Grace Wong[1] Wai Sun Vincent Wong[1] Jimmy Che-To Lai[1] Cheuk Fung Yip[1], [1]The Chinese University of Hong Kong

Background: Chronic HBV infection-related hepatic decompensation may improve after antiviral therapy, but the chance of recompensation varies across patients. We characterized multistate trajectories after first decompensation and assessed whether the presenting event identifies different probabilities of

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recompensation, further decompensation, hepatocellular carcinoma (HCC), and death or liver transplantation (LT). **Methods:** We conducted a territory-wide retrospective cohort study of adults with HBV-related decompensated cirrhosis receiving first-line antiviral therapy in Hong Kong between 2000 and 2023. First decompensation was classified according to Baveno VII criteria as ascites, hepatic encephalopathy (HE), variceal bleeding, or multiple complications, and patients were followed across subsequent states of further decompensation, recompensation, decompensation after recompensation, HCC, and death/LT. Disease trajectories were evaluated using transition probabilities and state occupancy at 1, 3, and 5 years. **Results:** Among 5,355 patients, first decompensation was ascites (n = 3,753), HE (n = 543), variceal bleeding (n = 688), or a combination of these events (n = 371). Baseline severity differed by the presenting event. Patients with variceal bleeding were younger and had less severe liver dysfunction (age 57.4 ± 11.1 years; Child-Pugh 9 [9–10]; MELD 10.7 ± 3.0), while patients with HE were older and had more advanced liver disease (age 61.0 ± 14.0 years; Child-Pugh 10 [10–12]; MELD 16.3 ± 8.1). Patients with ascites were aged 62.4 ± 12.4 years, had Child-Pugh 10 [9–11] and MELD 13.2 ± 5.5. From first decompensation, the most common next transition was recompensation (39%), followed by further decompensation (33%), death/LT (16%), and HCC (12%). Patient outcomes changed markedly over time: at 1 year, 27.3% remained in first decompensation, 19.7% achieved recompensation, 17.6% progressed to further decompensation, 13.0% developed HCC, and 22.4% died/received LT. By 5 years, only 1.8% remained in first decompensation, while 34.1% achieved recompensation, 33.5% died/underwent LT, and 22.9% developed HCC. Patients presenting with HE had lower 5-year recompensation occupancy (26.0%) and higher death/LT occupancy (42.6%), whereas variceal bleeding had higher recompensation occupancy (39.4%) and lower death/LT occupancy (20.4%). Ascites showed an intermediate pattern, with 34.5% occupying recompensation and 35.3% death/LT at 5 years. **Conclusion:** The chances of recompensation differ according to the presenting event. Variceal bleeding is followed by a greater potential for recompensation, whereas HE marks limited reversibility and higher risk of death/LT. Early reassessment may guide monitoring and timely transplant referral and assessment.



Disclosures: Vicki Wing-Ki Hui:Nothing to Disclose, Grace Wong:Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens, Fe: Speaking and Teaching, AstraZeneca, Barinthus, Gilead Sciences, GlaxoSmithKline, IntegerBio, Janssen and Virion: Advisor, Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens: Speaking and Teaching, Ferring, Gilead Sciences, GlaxoSmithKline, Janssen, Otsuka, Roche and Virion: Speaking and Teaching, Gilead Sciences: Grant/Research Support, Wai Sun Vincent Wong:Nothing to Disclose, Jimmy Che-To Lai:Nothing to Disclose, Cheuk Fung Yip:Nothing to Disclose.

4070 | EFFECT OF BASELINE HBSAG LEVEL AND HBEAG STATUS ON HBSAG SEROCLEARANCE AND TIME TO CLEARANCE FOLLOWING PEG-IFNα THERAPY

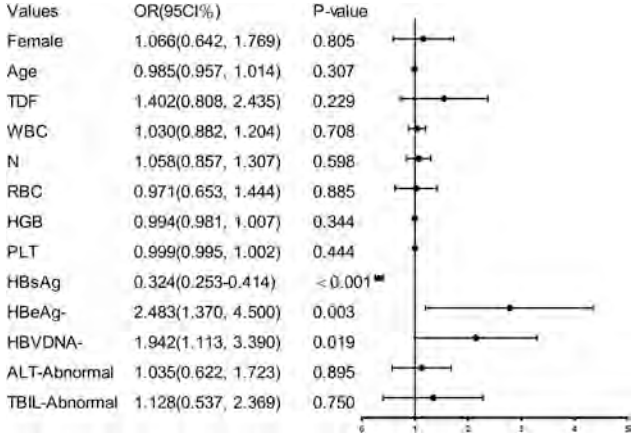
Wen Deng[1] Minghui Li[2] Yao Xie[2], [1]Beijing Ditan Hospital, Capital medical university, [2]Department of Hepatology Division 2, Beijing Ditan Hospital, Capital Medical University

Background: To analyze the factors influencing the achievement of HBsAg seroconversion in chronic hepatitis B virus (HBV) infection patients undergoing pegylated interferon α (Peg-IFNα) therapy and compare the differences in seroconversion time between different subgroups. **Methods:** A retrospective study was conducted including 411 chronic HBV infected patients who received Peg-IFNα therapy (≥ 6 months or < 6 months but achieved HBsAg seroconversion) at Beijing Ditan Hospital, Capital Medical University from September 2019 to January 2024. Demographic, treatment, clinical biochemical, blood routine, and HBV serological/virological baseline and follow-up data were collected. Binary logistic regression was used to analyze the factors influencing HBsAg seroconversion, and

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the Log-rank test and Cox regression were employed to compare the seroconversion times between subgroups. **Results:** The median follow-up time was 18.00 months. A total of 74 patients (18.00%) achieved HBsAg seroconversion. The baseline HBeAg-negative rate (78.38% vs. 59.35%) and HBV DNA-negative rate (72.97% vs. 58.16%) in the seroconversion group were significantly higher than in the non-seroconversion group. The baseline HBsAg (median: 1.09 vs. 3.33 log10 IU/ml) and HBV DNA (median: 1.00 vs. 1.00 log10 IU/ml) levels were significantly lower in the seroconversion group ($P < 0.05$). Univariate analysis indicated that lower baseline HBsAg, HBV DNA levels, and negative HBeAg and HBV DNA status were associated with HBsAg seroconversion ($P < 0.05$). Multivariate analysis showed that only lower baseline HBsAg level was an independent predictor of HBsAg seroconversion (OR = 0.306, 95% CI: 0.233–0.402, $P < 0.001$). Among seroconverted patients, those with baseline HBeAg-negative status were more likely to achieve early seroconversion within 48 weeks of treatment compared to those with positive HBeAg status [HR = 2.685 (1.143, 6.307), $P = 0.023$]. **Conclusion:** In chronic HBV patients undergoing Peg-IFNα therapy, lower baseline HBsAg levels are an independent predictor of HBsAg seroconversion, and baseline HBeAg-negative status may suggest an earlier occurrence of HBsAg seroconversion.



Disclosures: Wen Deng:Nothing to Disclose, Minghui Li:Nothing to Disclose, Yao Xie:Nothing to Disclose.

4071 | COMMUNITY-BASED SCREENING FOR HBV, HCV AND HDV AMONG THE MONGOLIAN POPULATION LIVING IN FRANCE: PRELIMINARY RESULTS OF THE MONDELTA STUDY

Francois Bailly[1] Francois Villeret[1] Fabien Zoulim[1] Enkhtuul Batbold[2] Birke Bartosch[3] Armand Abergel[4] Paule Letertre-Gibert[5] Frédéric Heluwaert[6] Caroline Jezequel[7] Antonio Saviano[8] Marjorie Viallon[1], [1]Lyon Hepatology Institute, IHU EVEREST; Croix Rousse Hospital; Hospices Civils de Lyon, [2]Lyon Hepatology Institute, IHU EVEREST, [3]Lyon Hepatology Institute, IHU EVEREST, [4]CHU Clermont Ferrand, [5]Service d'hépatogastro-entérologie, CH Alpes-Leman, Contamine-sur-Arve, France, [6]Service d'hépatogastro-entérologie, CH Annecy-Genevois; Epagny; France, [7]Service des Maladies du foie CHU de Rennes, Hôpital Pontchaillou, CHU de Rennes, Rennes; France, [8]Service d'hépatogastro-entérologie, CHU de Strasbourg; Strasbourg; France

Background: In Mongolia, the prevalence of hepatitis B virus (HBV) and hepatitis D virus (HDV) is the highest in the world. In 2018, a study of the Mongolian community living in California found an HBV prevalence of 9.7% with 42% testing positive for HDV. The Mongolian community living in France is estimated to number between 5,000 and 6,000 people. **Methods:** The MonDelta study (NCT: 07038863) is a French national multicenter study focusing on Mongolian population living in France who are 15 years of age or older; it began in September 2025. Community screening days are organized in several cities, featuring Rapid Diagnostic Orientation Test (RDOT) for HBV and HCV. In the event of a positive RDOT, additional serological testing and elastography are performed. For any positive HBV RDOT, a HDV serology is performed. During these screening days, sessions are performed to raise awareness of viral hepatitis and promote the prevention of liver disease. **Results:** 126 patients were screened at four French centers over the course of six screening days. Median age at screening was 47 years (IQR: 37–54), with majority of female (59.5%). Three HBV RDOT were positive (prevalence of 2.4%), all confirmed by a positive HBsAg and quantifiable serum HBV DNA. One HDV serology result was positive with undetectable serum HDV RNA. Among these 3 HBsAg-positive patients, only one was a new case of chronic HBV infection. One patient resumed treatment with Tenofovir (which had been discontinued due to loss to follow-up) and one patient started treatment with Entecavir. Eight HCV RDOT were positive (representing a prevalence of 6.3%): only one patient had quantifiable HCV RNA and antiviral treatment was initiated. Median elasticity was 6.55 kPa (IQR: 4.6–7.6); one case of cirrhosis secondary to HCV was diagnosed. **Conclusion:** These preliminary data confirm a higher prevalence of HBV and HCV in Mongolian population than in the general French population, but lower than the prevalence rates reported in other studies of the Mongolian population. The study is continuing, with several centers set to open in the coming weeks.

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Disclosures: Francois Bailly:Nothing to Disclose, Francois Villeret:Nothing to Disclose, Fabien Zoulim: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Enkhtuul Batbold:Nothing to Disclose, Birke BARTOSCH:Nothing to Disclose, Armand Abergel:Nothing to Disclose, Paule LETERTRE-GIBERT:Nothing to Disclose, Frédéric HELUWAERT:Nothing to Disclose, Caroline JEZEQUEL:Nothing to Disclose, Antonio Saviano:Nothing to Disclose, Marjorie Viallon:Nothing to Disclose.

4072 | FAMILY-LEVEL CLUSTERING OF HEPATITIS B VIRUS INFECTION AMONG US-BOUND REFUGEES, 2018–2023

Erin Mann[1] Kelly Searle[1] Jose Debes[1], [1]University of Minnesota

Background: Hepatitis B virus (HBV) clusters within households in endemic regions, with infection in children thought to be shaped by maternal or paternal status. Most prior evidence comes from clinic-based studies in unvaccinated populations; family-level HBV epidemiology among US-bound refugees has not been examined. **Methods:** We analyzed HBsAg screening data from refugees undergoing overseas health assessments through the United States Refugee Admissions Program, October 2018–September 2023. Family clusters were defined as fully screened nuclear families (mother, father, and ≥1 child) with ≥2 HBV-positive members. Among children <12 years, generalized estimating equations (GEE) logistic regression estimated adjusted odds ratios (aOR) for child HBV infection by family member HBV status, adjusted for region, sex, age, year, family size, and pre-resettlement vaccine doses. **Results:** Among 19,469 fully screened nuclear families (102,509 individuals), 1,341 (6.9%) had ≥1 HBV-positive member. Of these, 116 (8.7%) had ≥2 HBV-positive members (family clusters). The most common HBV+ cluster types were mother-offspring (41.4%), both parents only (20.7%), and siblings only (18.1%). Clustering was more common in families with an HBV-positive mother (18.0% vs. 4.1%), with the largest contrasts in Asia (24.7% vs. 3.0%) and the Eastern Mediterranean (12.2% vs. 1.5%). Among 34,919 children <12 years in 13,714 nuclear families, 59 children across 40 families tested HBV-positive. Having an HBV-positive mother (aOR 29.55, 95% CI 14.79–59.06) and HBV-positive sibling (aOR 42.37, 95% CI 19.23–93.36) were each strongly and independently associated with child HBV infection; paternal infection was weaker and not significant (aOR 2.29, 95% CI 0.96–5.51). Predicted probability of child infection rose from 0.03% (95% CI 0.01–0.05) when no family member was infected to 22.94% (95% CI 12.64–33.24) with mother and sibling infected and 37.73% (95% CI 17.89–57.58) with mother, father, and sibling all infected. **Conclusion:** HBV clustering in refugee families is driven primarily by maternal infection, with risk to children rising sharply when multiple family members are infected. The strong sibling effect and regional gradient may reflect underlying maternal HBeAg status, a key driver of perinatal transmissibility. These findings can help understand HBV family dynamics for targeted testing and care.

Disclosures: Erin Mann:Nothing to Disclose, Kelly Searle:Nothing to Disclose, Jose Debes:Nothing to Disclose.

4073 | DEVELOPMENT AND VALIDATION OF A MODEL OF INCORPORATING SERUM N-TERMINAL PROPEPTIDE OF TYPE III COLLAGEN AND PLATELET COUNT TO PREDICT ADVANCED FIBROSIS IN CHRONIC HEPATITIS B

Xue Bai[1] Qianqian Chen[1] Jie Li[1], [1]Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University

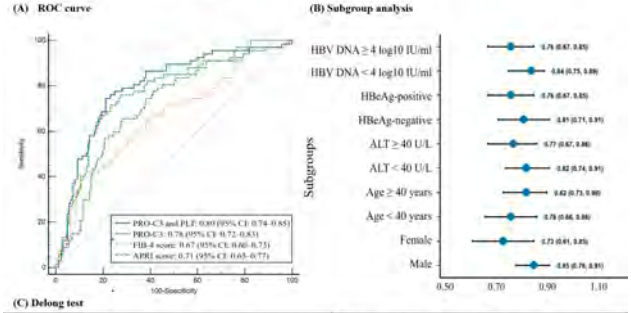
Background: Accurate non-invasive identification of advanced fibrosis (≥S3) is crucial for improving outcomes in chronic hepatitis B (CHB) patients. Serum PRO-C3, a marker of collagen synthesis, has shown promise. This study aimed to develop and validate a novel serum-based model incorporating PRO-C3 and routine clinical parameters for diagnosing CHB-related advanced fibrosis and cirrhosis (≥S3). **Methods:** This retrospective study enrolled 324 treatment-naïve CHB patients who underwent liver biopsy from two centers. Patients from center 1 (n = 227) formed the training cohort, and those from center 2 (n = 97) formed the validation cohort. Baseline clinical characteristics, serum Pro-C3 (ELISA), liver stiffness measurement (LSM), APRI, and FIB-4 were collected. Histological fibrosis staging used the Scheuer system (S0-S4), with ≥S3 defined as advanced fibrosis. Univariate and multivariate logistic regression were performed to identify independent predictors and construct a predictive model. The model's diagnostic performance was evaluated using the area under the receiver operating characteristic curve (AUC), sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), decision curve analysis (DCA), and calibration curves. Its robustness was tested across various patient subgroups. **Results:** In the overall cohort

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(n = 324), 83 patients (25.6%) had ≥ S3 fibrosis. In multivariate analysis, PRO-C3 (OR: 1.04, 95% CI: 1.02-1.05, P < 0.01) and platelet count (PLT) (OR: 0.99, 95% CI: 0.98-1.00, *P* = 0.04) were independent predictors. The derived model was: Logit(P) = −1.190 + 0.038 × (PRO-C3) − 0.007 × (PLT). In the training cohort, this Pro-C3 and PLT model achieved an AUC of 0.80 (95% CI: 0.74-0.85) for diagnosing ≥ S3 fibrosis, with a PPV of 59.5% and NPV of 88.1%. Its performance was superior to FIB-4 (AUC: 0.67, *P* < 0.01) and APRI (AUC: 0.71, P = 0.02), and comparable to Pro-C3 alone (AUC: 0.78, *P* = 0.17). The model was validated in the external cohort with an AUC of 0.84 (95% CI: 0.75-0.91). DCA indicated greater net clinical benefit, and calibration curves showed good agreement between predicted and observed probabilities. The model maintained diagnostic efficacy (AUCs > 0.70) across all tested subgroups, including different genders, ages, ALT levels, HBeAg statuses, and HBV DNA levels. **Conclusion:** The novel serum model combining Pro-C3 and platelet count demonstrates good and robust diagnostic performance for identifying CHB-related advanced fibrosis and cirrhosis (≥ S3), offering a convenient and accurate non-invasive tool for clinical decision-making.

Figure. Diagnostic performance of the combined PRO-C3 and PLT model for advanced liver fibrosis in patients with chronic hepatitis B.



(C) Delong test

Model	Cut-off	Sensitivity	Accuracy	Delong test (*P*)*	Model	Cut-off	Sensitivity	Accuracy	Delong test (*P*)*
PRO-C3 and PLT	0.30	74.63%	78.75%	-	FIB-4	1.89	41.79%	87.50%	<0.01
PRO-C3	35.70	76.12%	72.50%	0.17	APRI	0.47	65.67%	71.87%	0.02

Disclosures: Xue Bai:Nothing to Disclose, Qianqian Chen:Nothing to Disclose, Jie Li:Nothing to Disclose.

4074 | PATIENT AND PHYSICIAN PERSPECTIVES ON UNMET NEEDS IN CHRONIC HEPATITIS B VIRUS (HBV) MANAGEMENT IN CHINA

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Background: Clinical guidelines recommend functional cure (FC), defined as ≥ 24 weeks of sustained HBV DNA < lower limit of quantification and hepatitis B surface antigen (HBsAg) loss after finite therapy, as the optimal treatment (tx) endpoint for chronic hepatitis B virus (HBV) infection. Yet, FC is rarely achieved with current therapies, nucleos(t)ide analogs (NAs) and pegylated interferon (Peg-IFN). This study assessed physicians' and patients' (pts) tx goals, perceptions of FC, unmet clinical needs relating to NAs and Peg-IFN, and expectations for new therapies across China. **Methods:** Pts with chronic HBV infection receiving stable tx and physicians who are experienced in HBV management were enrolled. Eligible physicians were associate chief physicians or above in tertiary hospitals located in Tier 1 or 2 cities. Eligible pts had a self-reported diagnosis of chronic HBV infection for ≥ 1 year and received stable NA therapy for ≥ 1 year. At least half of pts had to have had prior Peg-IFN therapy. A 60-minute, one-to-one interview was conducted with eligible physicians and pts. **Results:** In total, 25 physicians and 20 pts were enrolled. Pt and physician characteristics are shown in the table. All physicians and pts expressed an acceptance of or desire to achieve FC. NAs were reported as the main tx with 17/20 (85%) pts starting on them within 3 months of diagnosis. The median proportion of pts with chronic HBV receiving Peg-IFN treatment, as reported by physicians, was 12.5%. Physicians (n = 25) reported that, among pts using Peg-IFN, the majority (median: 90%) received it in combination with NAs. Physicians cited limited FC (23/25 [92%]), long-term use (22/25 [88%]), and high relapse rates (18/25 [72%]) as the top three unmet needs of NA therapy. Most pts (19/20 [95%]) hoped to discontinue NAs; the most cited reasons included long treatment duration (14/19 [74%]) and side effect concerns (10/19 [53%]). The two most common unmet needs of Peg-IFN identified by physicians were pronounced adverse events (22/24 [92%]) and limited eligible population (21/24 [88%]). For pts achieving HBsAg clearance, most (24/25 [96%]) physicians reported the need for Peg-IFN consolidation therapy. 19/25 (76%) physicians reported that all pts would continue NA therapy after Peg-IFN discontinuation. For future therapies, physicians and pts expressed their expectation regarding treatment with higher HBsAg clearance rate/better efficacy (physicians: 22/22 [100%]; pts: 20/20 [100%]), improved safety/fewer side effects (physicians: 18/22 [82%]; pts: 16/20 [80%]), and shorter tx duration (physicians: 14/22 [64%]; pts: 14/20 [70%]) being the highest priorities. **Conclusion:** FC is recognized as the tx goal for chronic HBV infection in China. Substantial unmet needs remain associated with current chronic HBV tx, NAs and Peg-IFN, and there is a strong demand for innovative FC therapy with higher HBsAg clearance,

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finite tx, and improved safety. **Funding:** GSK (223175)

Table. Patient and physician characteristics

Physician sociodemographic and professional characteristics (n=25)	Total
Professional title, n (%)	
Associate chief physician	8 (32%)
Chief physician	17 (68%)
Practicing in chronic HBV clinical cure outpatient settings, n (%)	
Yes	14 (56%)
No	11 (44%)
Patient sociodemographic and clinical characteristics (n=20)	
Age (years)	
Mean ± SD	42.3 ± 9.6
Median (IQR)	42.0 (33.75–51)
Level of education, n (%)	
Primary school or below	0 (0%)
Junior high school	2 (10%)
Technical secondary school or high school	1 (5%)
Bachelor's degree	17 (85%)
Master's degree or above	0 (0%)
Current treatment received, n (%)	
NAs only	10 (50%)
Peg-IFN	0 (0%)
NAs + Peg-IFN	10 (50%)
Physicians' acceptance of functional cure (n=25)	
Fully agree	15 (60%)
Partially agree	10 (40%)
Disagree	0
Patients' desire to achieve functional cure (n=20)	
Strongly hope to	14 (70%)
Somewhat hope to	6 (30%)

HBV, hepatitis B virus; IQR, interquartile range; n, number; NA, nucleos(t)ide analog; Peg-IFN, pegylated interferon; SD, standard deviation.

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4075 | DEVELOPMENT OF A HEPATITIS B SHARED-DECISION MAKING TOOL (BSMART) FOR TREATMENT INITIATION TO SUPPORT NEW AASLD/IDSA HEPATITIS B PRACTICE GUIDELINE

Su Wang[1] Laziza Khodjaeva[2] Ruth Brogden[1] Jaymie Yango[1] Xu-Wuih Chai[3] Maggie Wang[3] Alexandrina Itile[3] Patrick Hilden[1] Mindy Houng[3] Elaine Zhai[3], [1]Cooperman Barnabas Medical Center, [2]Rutgers University, [3]Barnabas Health Medical Group

Background: The AASLD/IDSA Hepatitis B Practice Guidelines, updated November 2025, expands treatment eligibility utilizing a shared decision making (SDM) framework for hepatitis B (HBV) patients in 3 groups–the indeterminate and immune tolerant stages and for prevention of horizontal transmission. In December 2025, the HBV Primary Care Guidance was released, and simplify treatment guideline and include patient preference as one of 4 indicators to treat. Tools are needed to support clinicians to assess patient reported outcome (PRO), and to guide the shared decision making process. **Methods:** We developed the Hepatitis B Shared Management and Action Resource Tool (BSMART) to ascertain the HBV impact on patients, concerns and priorities in their HBV care, and to guide patients and physicians through a shared decision making process. Two surveys were piloted, the B-SMART for patients not on antiviral therapy, and the Hepatitis B On-Treatment Adherence Survey for those on therapy. Descriptive analysis were done examining treated and untreated patients and AASLD HBV phase categories. **Results:** From November 2025 to May 2026, 90 patients were enrolled from an internal medicine clinic in New Jersey, of whom 42 (52.5%) were male and the mean age was 55.2 years (range 27–83). Of the 89 who completed surveys, 37 (41%) were not on antiviral therapy (BSMART group) and 52 (58%) were on treatment. Of the BSMART patients phased per 2025 AASLD/IDSA guidelines, 41% (14) were in the indeterminate phase and 59% (20) were in the inactive phase. There were 1 immune tolerant and 2 active phase patients not included due to small numbers. The vast majority of patients reported little to no impact on their daily life from HBV (95% BSMART vs. 85% on treatment, $p = 0.471$). "Liver cancer/cirrhosis" was the top concern across all groups ($p = 0.776$). "Transmission to family" was the 2nd most reported concern across all groups with those untreasted higher at 73% vs. 52% on-treatment ($p = 0.051$)."Tired or low energy" was reported by 16% BSMART, 15% on-treatment ($p = 1.000$), and "stigma or being treated differently" was reported by 11% BSMART, 13% on-treatment ($p = 0.757$), both equally distributed between groups. Only 4–15% of all groups reported being "not very concerned." **Conclusion:** Despite the vast majority of all patients reporting "feeling fine with no symptoms," fatigue and worry were common for all patients, and most patients had a number of concerns. Concern over transmission was reported more in people not treated than in those treated. This is especially relevant because "prevention of high risk horizontal transmission" is a new treatment indication in the AASLD/IDSA guidelines. The B-SMART survey tool elicited patient reported outcomes and patient preferences and values, and such tools are important to assist in the HBV shared decision making process.

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Characteristic	Overall (n=89)	Survey Group		p-value	Test Used
		BSMART Survey (Untreated) n=37	On-Treatment Survey (On Antivirals) n=52	p-value	Test
S1Q1 — How are you feeling in regards to hepatitis B? (Check all that apply)					
Feeling fine / no symptoms	73 / 89 (82%)	31 / 37 (84%)	42 / 52 (81%)	p = 0.932	Chi-square
Worried or stressed	24 / 89 (27%)	8 / 37 (22%)	16 / 52 (31%)	p = 0.474	Chi-square
Embarrassed or ashamed	13 / 89 (15%)	3 / 37 (8%)	10 / 52 (19%)	p = 0.246	Chi-square
Tired or low energy	14 / 89 (16%)	6 / 37 (16%)	8 / 52 (15%)	p = 1.000	Chi-square
S1Q2 — How much does hepatitis B affect your life? (Fisher's exact test)					
Not at all	44 / 89 (49%)	20 / 37 (54%)	24 / 52 (46%)	p = 0.471	Fisher's exact
A little	35 / 89 (39%)	15 / 37 (41%)	20 / 52 (38%)	—	—
Sometimes	7 / 89 (8%)	1 / 37 (3%)	6 / 52 (12%)	—	—
A lot	3 / 89 (3%)	1 / 37 (3%)	2 / 52 (4%)	—	—
Little/No effect (combined)	79/89 (89%)	**35/37 (95%)**	**44/52 (85%)**	—	—
S1Q3 — Biggest concerns about hepatitis B (Select up to 3)					
Liver cancer / cirrhosis	74 / 89 (83%)	**30 / 37 (81%)**	**44 / 52 (85%)**	p = 0.776	Fisher's exact
Transmission to family	54 / 89 (61%)	**27 / 37 (73%)**	**27 / 52 (52%)**	p = 0.051	Fisher's exact
Lifelong medication	34 / 89 (38%)	**14 / 37 (38%)**	**20 / 52 (38%)**	p = 1.000	Fisher's exact
Side effects of medication	27 / 89 (30%)	8 / 37 (22%)	19 / 52 (37%)	p = 0.164	Fisher's exact
Stigma / treated differently	11 / 89 (12%)	4 / 37 (11%)	7 / 52 (13%)	p = 0.757	Fisher's exact
Not very concerned	6 / 89 (7%)	4 / 37 (11%)	2 / 52 (4%)	p = 0.229	Fisher's exact

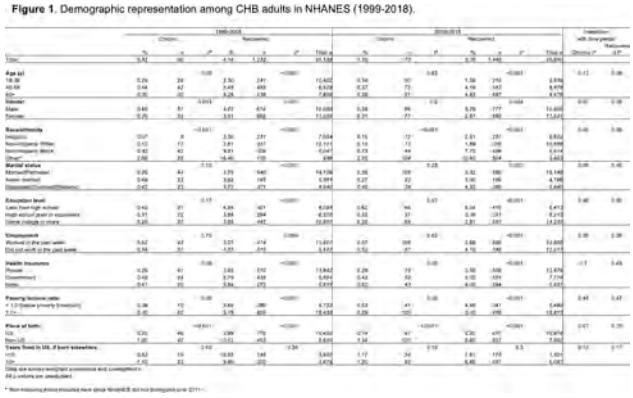
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4076 | TRENDS IN DIETARY AND LIFESTYLE PATTERNS IN HEPATITIS B VIRUS AND LIVER-RELATED OUTCOMES: LIMITATIONS OF NHANES 1999–2018

Kimberly Ho[1] Christina Raker[1] Hanna Abuhay[2] Man-Fung Yuen[3] Lung Yi Mak[3] Paige McLean Diaz[4], [1]Brown University, [2]Weill Cornell Medicine, [3]The University of Hong Kong, [4]Brown Medicine/Brown University Health

Background: Chronic hepatitis B virus (CHB) infection affects an estimated 880,000 persons in the United States, with significant variation in demographic representation. This study examined HBV seroprevalence trends, dietary and lifestyle characteristics, and liver-related outcomes using the National Health and Nutrition Examination Survey (NHANES). **Methods:** We analyzed data from 52,028 adults aged ≥18 years with HBV serology using NHANES in two survey periods (1999-2008 and 2009-2018). CHB was defined as HBsAg-positive and recovered HBV as HBsAg-negative. Data were analyzed by logistic or linear regression for complex survey data. **Results:** CHB prevalence was highest among non-US-born adults (1.00% and 1.34%), non-Hispanic Black adults (0.92% and 0.73%), and non-Hispanic Asians (2.56% and 2.20%). Between 1999 and 2018, CHB prevalence did not significantly change, and demographic representation remained stable. Regarding dietary data, CHB carriers consumed significantly less total fat (63 vs 83 g, p = 0.003) and saturated fat (18 vs 28 g, p < 0.001) in 1999-2008 compared to the general population. In 2009-2018, total and saturated fat intake along with total dietary energy, carbohydrates, and protein in CHB carriers all approached levels seen in the general population. Inverse trends for oils and added sugars were observed in CHB carriers in both survey periods. No significant associations were found between alcohol consumption or late-night snacking and CHB in either period. CHB was associated with markedly elevated odds of self-reported current liver conditions compared to no infection in both periods (adjusted OR 19.5 in 1999-2008; OR 7.8 in 2009-2018; interaction p = 0.04). **Conclusion:** Dietary and lifestyle differences observed in CHB in the US more likely reflect the immigrant and ethnic composition of the affected population (predominantly Asian and sub-Saharan African origin) rather than causal dietary effects or HBV-driven behavioral changes. Furthermore, the small sample of CHB in NHANES limited the extent to which robust comparative analyses can be performed to determine how lifestyle factors influence liver-related outcomes in CHB. Thus, while there were decreased odds of current liver conditions in CHB seen over time (adjusted OR 19.5 [1999-2008] vs 7.8 [2009-2018]), this may be secondary to improved disease management, shifts in population composition, or survival bias.

Figure 1. Demographic representation among CHB adults in NHANES (1999-2018).



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4077 | CHARACTERISTICS OF PERSONS ON TREATMENT FOR HEPATITIS B WITH HUMAN IMMUNODEFICIENCY VIRUS INFECTION IN THE UNITED STATES, 2014–2025

Ademola Osinubi[1] Yuna Zhong[1] Julian Grass[1] Hasan Symum[1] Eyasu Teshale[1], [1]CDC

Background: Despite advances in hepatitis B virus (HBV) and human immunodeficiency virus (HIV) treatment, coinfection with HBV and HIV remain associated with substantial morbidity and mortality. We described persons on treatment for hepatitis B coinfected with HIV and compared characteristics by HIV infection status using national pharmacy claims data from the United States. **Methods:** Using IQVIA's longitudinal prescription claims data, we identified persons receiving HBV antivirals with a hepatitis B ICD-10-CM diagnosis code during 2014–2025. Among this hepatitis B treated cohort, we defined HIV coinfection as the presence of ≥1 HIV ICD-10-CM diagnosis codes. We calculated chi-square tests to compare the demographic, payer, and prescriber characteristics of persons on HBV treatment with and without HIV coinfection. Statistical significance was defined as $p < .05$. **Results:** Of the 283,834 persons receiving HBV treatment, 9,836 (3.5%) were coinfected with HIV. Among those on HBV treatment with HIV coinfection, the majority were male (79.6%) and aged ≥ 60 years (55.3%); most hepatitis B treatment claims were paid by Medicare (47.2%) and commercial insurers (31.3%). Approximately half of prescribers were specialists; the proportion of persons treated by specialists decreased from 2014 (53.9%) to 2025 (47.1%). During the same period, the proportion of prescriptions written by nurse practitioners increased from 11.5% in 2014 to 20.0% in 2025. The largest proportion (41.9%) of coinfected persons resided in the Southern U.S Census region. Compared to persons on HBV treatment without HIV, persons on HBV treatment with HIV coinfection were more likely to be male (79.6% vs 58.6%), ≥60 years (55.3% vs 49.2%), have hepatitis B treatment paid by Medicare (47.2% vs 31.0%), and reside in the Southern region (41.9% vs 28.5%) ($p < .001$). **Conclusion:** Using a longitudinal prescription claims dataset with national-level coverage we found 3.5% of persons receiving HBV treatment were living with HIV infection. These findings highlight the ongoing health care needs of persons with HBV/HIV coinfection and the importance of targeted public health interventions.

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4078 | NATURAL HISTORY OF UNTREATED HBV-RELATED ADVANCED FIBROSIS: REASSESSING HCC RISK IN THE CONTEXT OF THE 2025 EASL GUIDELINES

Seung Up Kim[1] Beom Kyung Kim[1] Cheuk Fung Yip[2] Sang Hoon Ahn[3] Vincent Wong[4], [1]Yonsei University, [2]State Key Laboratory of Digestive Disease, The Chinese University of Hong Kong, Hong Kong, [3]Yonsei University College of Medicine, [4]The Chinese University of Hong Kong

Background: The 2025 EASL HBV guidelines recommend antiviral therapy (AVT) for advanced fibrosis (AdvF) with detectable HBV-DNA, which is regarded to be a routine AVT criterion for liver cirrhosis (LC). This study assessed HCC risk among patients with untreated viremic AdvF to determine whether the observed risk supported earlier initiation of AVT. **Methods:** South Korean patients with untreated viremic AdvF, who did not fulfill conventional AVT criteria (n = 302), and those with AVT-treated Child–Pugh A LC (n = 1694), were enrolled. LC was defined by imaging or liver stiffness (LS) on vibration-controlled transient elastography >11 kPa. AdvF was defined as LS of 8–11 kPa without LC on imaging. Multivariate Cox regression and propensity score matching (PSM; 2:1) were used to compare HCC risk. **Results:** Multivariable analyses revealed that patients with untreated viremic AdvF [A1] exhibited HCC risk comparable with that of

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[E2] AVT-treated LC (adjusted hazard ratio [aHR] 0.667 [95% confidence interval (CI) 0.432–1.602]; $p = 0.089$). Male sex and higher Fibrosis-4 index score were independently associated with HCC risk (all $p < 0.05$). In an external validation Hong Kong cohort (n = 302), patients with untreated viremic AdvF exhibited an HCC risk comparable with that of AVT-treated LC (aHR 0.926 [95% CI 0.512–1.678]; $p = 0.797$). Male sex and higher albumin–bilirubin (i.e., "ALBI") score were independently associated with HCC risk (all $p < 0.05$). PSM in both cohorts also confirmed comparable risk for HCC between the groups (all $p > 0.05$). **Conclusion:** Across 2 independent East Asian cohorts, the risk for HCC in those with untreated viremic AdvF was not negligible and at a level that may warrant the reconsideration of conventional AVT thresholds, supporting the rationale of the 2025 EASL HBV guidelines. **Disclosures:** Seung Up Kim:Nothing to Disclose, Beom Kyung Kim:Nothing to Disclose, Cheuk Fung Yip:Nothing to Disclose, Sang Hoon Ahn:Nothing to Disclose, Vincent Wong:Abbott: Speaking and Teaching, AbbVie: Advisor, AbbVie: Speaking and Teaching, Boehringer Ingelheim: Advisor, Echosens: Advisor, Echosens: Speaking and Teaching, Gilead Sciences: Advisor, Gilead Sciences: Speaking and Teaching, Gilead Sciences: Grant/Research Support, Novo Nordisk: Advisor, Pfizer: Advisor, TARGET PharmaSolutions: Advisor, Illuminatio Medical Technology: Stock – privately held company, Eli Lilly: Consultant, Merck: Consultant, Altimmune: Consultant, AstraZeneca: Consultant, Roche Diagnostics: Consultant, Furui: Consultant.

4079 | VIRAL HEPATITIS PREVALENCE AMONG MIGRANTS LIVING IN CATALONIA, SPAIN: RESULTS FROM COMMUNITY-BASED SCREENING ACTIONS

Adriana Palom[1] Jordi Gomez i Prat[2] Ariadna Rando-Segura[3] Helena Ortin i Berga[2] Tahir Rafi[4] Sumaira Malik[4] Alícia Garcia-Circuns[4] Hakima Ouaarab[2] Chia Ning Chung Huang[4] Juan Arenas Ruiz-Tapiador[5] Javier Garcia-Samaniego[6] Maria Buti[1], [1]Liver Unit, Hospital Universitari Vall d'Hebron, CIBERehd, Barcelona, Spain, [2]Department of Infectious Diseases, Hospital Universitari Vall d'Hebron, Barcelona, Spain, [3]Microbiology Department, Hospital Universitari Vall d'Hebron, Barcelona, Spain, [4]Vall d'Hebron Research Institute (VHIR), Public Health and Community Team (eSPiC), Barcelona, Spain, [5]Policlínica Gipuzkoa-Quiron Salud, CIBERehd, San Sebastian, Spain, [6]Liver Unit, Hospital Universitario La Paz, IdiPAZ, Madrid, Spain

Background: WHO hepatitis screening strategies prioritize migrants from highly endemic countries, assuming that prevalences in migrant communities are the same of their countries of origin. We aimed to compare the prevalence of hepatitis B virus (HBV), hepatitis C virus (HCV), and hepatitis D virus (HDV) among migrants living in Catalonia with published estimates from their countries of origin. **Methods:** We analyzed data from 4 community-based screening programs that were conducted among migrants from Pakistan, Mongolia, Romania and China in Catalonia. Screening activities were performed in community settings to facilitate population access and better approximate the real prevalence in migrant communities. Point-of-care HBV and HCV screening was performed, with confirmatory serological and virological testing when required. Observed prevalences were compared with Polaris Observatory epidemiological estimates from the respective countries of origin. **Results:** A total of 1,813 individuals were screened between April 2022 and April 2026. Among 1,003 participants from Pakistan, the prevalence of HBsAg was 0.8% and anti-HCV was 1.8%, both lower than the estimated prevalences in the country of origin (1.6% and 7.5%, respectively). In the cohort from Mongolia (n = 222), HBsAg prevalence was 3.6%, anti-HCV prevalence was 5.8% (with detectable HCV-RNA in 0.5%), and HDV was present in 0.9%. These values were lower than reported national prevalences, where HBV and HCV exceed 8-11% and HDV remains highly endemic (approximately 60% among HBsAg+). Among 330 participants from Romania, anti-HCV prevalence was 1.5% (with detectable HCV-RNA in 0.3%) and HBsAg prevalence was 1.5%, in comparison with national prevalences of approximately 3-4% for HCV and 3% for HBV. No subjects with HDV were identified. In the cohort from China (n = 258), HBsAg prevalence was 5.8%, anti-HCV prevalence was 0.4%, and no HDV infections were identified. These findings were similar to expected estimates for China (HBsAg 5.6%, anti-HCV 0.91%, anti-HDV 1%). **Conclusion:** Migrants from highly endemic countries living in Catalonia had substantially lower prevalences of HBV, HCV, and HDV than those reported in their countries of origin. Since these estimates come from community-based screening actions, they likely better reflect the true epidemiological burden in migrants living in Catalonia. These findings suggest that migratory flows are not directly comparable to the epidemiological reality of countries of origin, as each migration process is shaped by specific contextual factors that influence health outcomes.

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to Disclose, Chia Ning Chung Huang:Nothing to Disclose, Juan Arenas Ruiz-Tapiador:Nothing to Disclose, Javier Garcia-Samaniego:Nothing to Disclose, Maria Buti:Roche Pharma/Diagnostics: Consultant, Gilead Sciences: Consultant, GSK: Consultant, Abbvie: Consultant, Janssen: Consultant, Roche Pharma/Diagnostics: Speaking and Teaching, Gilead Sciences: Speaking and Teaching, GSK: Speaking and Teaching, Abbvie: Speaking and Teaching, Janssen: Speaking and Teaching, Bepirovirsen – GSK: Referral to unlabelled/unapproved products.

4080 | HEPATITIS DELTA TESTING RATES REMAIN LOW AMONG INDIVIDUALS WITH CHRONIC HEPATITIS B: A US ADMINISTRATIVE CLAIMS ANALYSIS

Alice Stead[1] Amanda Singer[2] Sundaresan Murugesan[1] Laura Telep[1] Kyle Hammond[2] Celine Der-Torossian[1] Craig Meyer[1] David Wyles[1] Robert Gish[3], [1]Gilead Sciences, [2]Gilead Sciences, Inc., [3]Robert G Gish Consultants LLC

Background: Hepatitis delta virus (HDV) infection remains underdiagnosed in the United States (US) due to previously limited diagnostic assays, low clinician awareness, inconsistent guidelines and lack of approved therapies. Prior studies, limited to select populations, show low testing rates in the chronic Hepatitis B virus (CHB) population. This study evaluated HDV testing trends and predictors among individuals with CHB in US administrative claims data. **Methods:** This retrospective study used Optum's de-identified ClinFormatics® Data Mart (2015-2025). CHB was identified by ≥ 1 inpatient or ≥ 2 outpatient international classification of disease (ICD) codes, laboratory evidence (positive hepatitis B DNA or hepatitis B surface antigen [HBsAg]), or CHB treatment with supporting ICD and/or laboratory codes. Individuals were required to have ≥ 365 days of continuous enrollment before the CHB index date and no prior HDV infection. Subgroups included HBsAg-positive individuals and those with HDV risk factors (HIV or hepatitis C co-infection, or history of injection drug use). HDV testing was identified by procedure codes on or after index. The proportion of individuals tested and annual testing rates were estimated; temporal trends were evaluated using a Mann-Kendall (MK) test. Cox proportional hazards models identified predictors of testing, reported as hazard ratios (HRs) and 95% confidence intervals (CIs). **Results:** Among 39,245 individuals with CHB, 1,386 (3.5%) received an HDV test during follow-up. Testing remained low, with 1.0% of individuals with CHB tested in 2025 (rate 1.13 per 100 person-years), compared to 0.6-1.1% annually from 2015 to 2024. The overall proportion tested was modestly higher among those with HBsAg positivity (508/10711, 4.7%) and those with HBsAg positivity plus HDV risk factors (43/732, 5.9%). The proportion tested in these subgroups increased slightly from 2020-2025. The MK test indicated an upward trend in testing among the HBsAg-positive with risk factors group but remained low overall (3.4% tested in 2025). In the full CHB cohort, individuals more likely to be tested were older (age group > 34 years), male sex, Asian, Black, or Other race, located in the Southern or Eastern US, HBsAg positive, treated for CHB, or had hepatic decompensation. Contrary to clinical guidelines, those with hepatitis C infection were less likely to be tested for HDV (aHR: 0.52, 95% CI: 0.39-0.70), and HIV infection and injection drug use were not associated with increased likelihood of testing. **Conclusion:** In this US claims-based study, HDV testing among those with CHB was persistently low over the last decade, even in those with recognized risk factors. These data highlight a large gap between guideline recommendations and clinical practice. The approval of bulevirtide in the US provides a treatment option for individuals with HDV infection, but efforts are needed to address the unmet need of routine testing and linkage to care.

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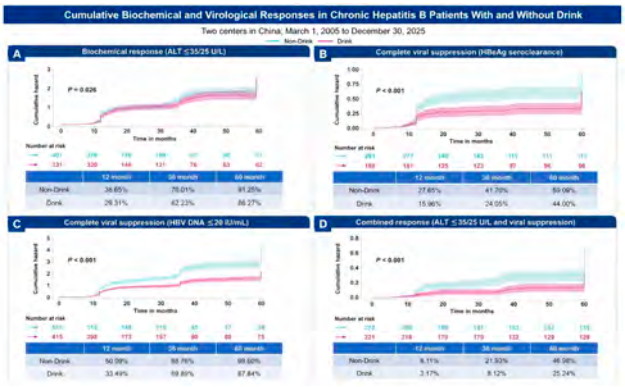
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4081 | ALCOHOL USE IMPAIRS VIROLOGICAL AND BIOCHEMICAL RESPONSES IN CHRONIC HEPATITIS B

Yukai Chen[1] Yuemin Nan[2] Jie Li[3] Fajuan Rui[3] Shaoya Li[2] Jiawei Cui[2] Zhandong Lin[2] Yaoyao Mao[2], [1]The Third Hospital of Hebei Medical University, [2]Hebei Medical University Third Hospital, [3]Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School

Background: Background:Both chronic hepatitis B (CHB) and alcohol consumption are established risk factors for adverse hepatic outcomes. However, the impact of alcohol use on treatment responses during long-term antiviral therapy in CHB remains unclear. We therefore examined the association between alcohol consumption and virological and biochemical responses in a longitudinal cohort. **Methods:** Methods:In this longitudinal cohort study, patients with CHB were consecutively enrolled from two tertiary centers in China between March 1, 2005 and December 30, 2025. Patients were stratified according to alcohol consumption status (Drink vs. Non-Drink). Endpoints included biochemical response (ALT < 35/25 U/L), HBeAg seroclearance, complete viral suppression (HBV DNA < 20 IU/mL), and a composite endpoint of biochemical and virological response. Cumulative incidences were estimated using the Kaplan–Meier method and compared using the log-rank test. **Results:** Results:During a follow-up of up to 60 months, non-drinkers consistently exhibited higher cumulative incidences of virological and biochemical responses compared with drinkers. For biochemical response (ALT < 35/25 U/L), cumulative rates at 12, 36, and 60 months were 38.65%, 70.01%, and 91.25% in non-drinkers, compared with 29.31%, 62.23%, and 86.27% in drinkers (P = 0.026). Similarly, HBeAg seroclearance rates were 27.65%, 41.70%, and 59.09% in non-drinkers versus 15.96%, 24.05%, and 44.00% in drinkers (P < 0.001). For complete viral suppression (HBV DNA < 20 IU/mL), corresponding rates were 50.09%, 88.76%, and 98.60% in non-drinkers, compared with 33.49%, 69.89%, and 87.84% in drinkers (P < 0.001). Consistently, the composite endpoint of biochemical and virological response was achieved in 8.11%, 21.93%, and 46.98% of non-drinkers, as compared with 3.17%, 8.12%, and 25.24% of drinkers (P < 0.001). Overall, response rates increased over time in both groups, with persistently lower probabilities observed among drinkers throughout follow-up. **Conclusion:** Conclusions:Alcohol consumption is significantly associated with poorer virological and biochemical responses in patients with chronic hepatitis B receiving long-term antiviral therapy. These findings indicate that alcohol use is a clinically relevant and potentially modifiable factor that influences treatment efficacy, underscoring the importance of its systematic assessment and management in the clinical care of CHB patients.



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4082 | TEMPORAL CHANGES IN HBSAG LOSS RATES BEFORE AND AFTER COVID-19 VACCINATION: AN INTERRUPTED TIME SERIES ANALYSIS

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Background: Hepatitis B surface antigen (HBsAg) loss, a functional cure in chronic hepatitis (CHB), is rare. We evaluated temporal changes in HBsAg loss rates in relation to the COVID-19 vaccination rollout. **Methods:** We performed an interrupted time series (ITS) analysis using electronic health records from 59,946 adults with CHB at a tertiary referral center in South Korea (2002–2025). Monthly HBsAg loss incidence rates were estimated using a competing risk framework. National COVID-19 vaccination coverage was used as a surrogate measure of population-level exposure. A three-phase segmental regression model was assessed changes in HBsAg loss rates before vaccination, during a predefined vaccination effect period (18 months following ≥80% of two-dose coverage), and after this period. Hepatocellular carcinoma (HCC) incidence was analyzed as a negative control outcome. **Results:** Over 382,509 person-years of follow-up, 2,291 HBsAg loss events occurred. Pre-vaccination HBsAg loss rates were stable. At the

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vaccination rollout (November 2021), HBsAg loss rates increased significantly (incidence rate ratio 1.56; 95% confidence interval 1.26–1.93; p < 0.001), followed by a plateau. A significant decline in slope was observed in the post-vaccination period (p = 0.003), suggesting attenuation over time. Results were consistent across multiple sensitivity analyses and subgroups. In contrast, HCC incidence showed no significant changes across phases. **Conclusion:** The COVID-19 vaccination rollout was temporally associated with a transient increase in HBsAg loss rates in CHB, followed by gradual attenuation. These findings suggest a potential population-level immunomodulatory effect of vaccination on HBV dynamics, warranting further investigation using individual-level data.

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4083 | CLINICAL OUTCOMES OF GRAY-ZONE CHRONIC HEPATITIS B COMPARED WITH INACTIVE CHRONIC HEPATITIS B

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Background: Current guidelines recommend treatment of chronic hepatitis B virus (CHB) based on abnormal serum aminotransferase or significant liver fibrosis. However, the decision to initiate antiviral treatment remains less clear in "gray zone" (GZ) patients. The objective of this study was to describe the natural history of GZ patients not receiving antiviral treatment, to determine the rates of clinical flares, subsequent treatment initiation and major adverse liver outcomes (MALO), and to compare their trajectory to that of inactive carriers. **Methods:** This is a single-center retrospective study of mono-infected adults with CHB, defined as having two positive HBsAg six months apart between July 1, 2005 and June 30, 2025, who were not receiving antiviral therapy. Eligible patients were identified through the Center for Data, Outcomes and Team Science (CDOTS) registry (Serper M, et al.). The upper limit of normal (ULN) of ALT was defined as < 35 U/L for men and < 25 U/L for women per AASLD. GZ CHB was defined by ALT ≤ 1x ULN with HBV DNA between 2,000 and 20,000 IU/mL, or ALT 1-2x ULN with HBV DNA < 2,000 IU/mL. Inactive CHB was defined as ALT ≤ 1x ULN and HBV DNA < 2000 IU/mL. The index date was the first date when both HBV DNA and ALT values were available. Outcomes included HBV flare (ALT ≥ 3 times baseline ALT and > 100 U/L), antiviral initiation, cirrhosis, hepatocellular carcinoma (HCC), and death. **Results:** A total of 33 patients were included, of whom 14 met the definition of GZ. Patients in the GZ tended to be younger than inactive carriers. Over a median follow-up of 12.1 years, two GZ patients developed HBV flare and one developed HCC. The GZ patient who ultimately developed HCC manifested ALT flare and elevated HBV DNA six months after the index date prompting treatment initiation, but was then lost to follow-up for 2 years before presenting with multifocal HCC at age 57. Three other GZ patients were started on antivirals for increased HBV DNA, during pregnancy, and for a clinical trial, respectively. The remaining 10 GZ patients required no therapy and developed no clinical events. Overall, the rates of flare, cirrhosis, HCC, and death were similar between GZ and inactive carriers. Kaplan-Meier analysis showed no significant difference in time to antiviral initiation (log-rank p = 0.64). **Conclusion:** Treatment initiation for CHB remains complex, especially for patients who do not fit into the classic disease stages. GZ patients exhibit relatively low rates of progression to HBV flare or clinical outcomes. Most did clinically well in the absence of antiviral therapy during 12.1 years of follow-up or received antiviral therapy when appropriate indications involved. Under standard clinical observation, a conservative approach to treatment initiation among young patients with GZ features may be reasonable.

Table 1: Comparison of clinical characteristics and outcomes between gray zone and inactive chronic hepatitis B

		Inactive CHB	Gray-zone CHB	p-value
N		19	14	
Age (median, [IQR])		45 [31, 57]	33 [29, 47]	0.19
Sex (N, %)				
	Men	8 (42)	4 (28)	
	Women	11 (58)	10 (72)	
Race (N, %)				
	Asian	10 (52)	10 (71)	
	White	5 (26)	1 (7)	
	Black	2 (11)	2 (14)	
	Others	2 (11)	1 (7)	
ALT group (N, %)				
	<1x ULN	19 (100)	6 (43)	
	1-2x ULN	0	8 (57)	
Baseline ALT (U/L)		19 [15, 23]	26 [20, 41]	0.0145*
HBVDNA group (N, %)				
	<2000	19 (100)	8 (57)	
	2000-20000	0	6 (43)	
Baseline HBV DNA (IU/ml)		109 [27, 824]	1117 [52, 10322]	0.0485*
History of MASLD (N, %)		2(11)	2 (14)	
Hepatitis B Flare (N, %)		0	2 (14)	0.172
Initiation of antiviral therapy (N, %)		7(37)	4 (29)	0.719
Cirrhosis (N, %)		0	0	
HCC (N, %)		0	1(7)	0.424
Death (N, %)		0	0	

Abbreviation: CHB= chronic hepatitis B, MASLD= metabolic-associated steatotic liver disease, HCC=hepatocellular carcinoma. *denotes statistical significance with p<0.05

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4084 | ◆ STOPPING NUCLEOSIDE ANALOUGUES IN HBEAG NEGATIVE CHRONIC HEPATITIS B WITH HBSAG < 100 IU/ML LEADS TO HIGH RATES OF HBSAG LOSS BUT RISK OF ALT FLARES: HALT NUC RANDOMISED CONTROL TRIAL

Seng Gee Lim[1] Wei Lyn yang[2] Rajneesh Kumar[3] Jessica Tan[4] Yin Mei Lee[1] Guan Huei Lee[1] Yock Young Dan[1] Daniel Huang[5] How Cheng Low[6] Gladys Tan[6] Htet Htet Toe Wai Khine[1] Amy Tay[1] Tiffany Fortney[7] Mark Anderson[7] Gavin Cloherty[8] Liang Shen[9], [1]National University Health System, [2]Tan Tock Seng Hospital, [3]Singapore General Hospital, [4]Changi General Hosptial, [5]National University Hospital, Singapore, [6]National University Hospital, [7]Abbott Laboratories, [8]Abbott, [9]Singapore Clinical Research Institute

Background: Despite multiple studies and clinical trials there is still controversy with regards to stopping nucleos(t)ide analogue (NA) therapy in HBeAg negative Chronic Hepatitis B(CHB) reflected in differences in guideline recommendations. A meta-analysis with metaregression identified the level of HBsAg, namely HBsAg < 100 IU/ml as an optimal threshold to stop NA therapy but this has not been tested in clinical trials. **Methods:** We conducted an investigator initiated randomised control trial of HBeAg negative CHB patients on NA > 12months with HBsAg < 100 IU/ml randomised to 2:1 stop NA or continue NA stratified by HBsAg < 10 or ≥ 10 IU/ml with the primary endpoint of HBsAg loss 144 weeks after randomisation in a multicentre randomised clinical trial of four tertiary hospitals in Singapore (clinicaltrials.gov NCT0410217). Safety of special interest were ALT flares ≥ 2x upper limit of normal (ULN), 5xULN and 10xULN. Analysis was by intention-to-treat and SPSS was used to analyse the results. **Results:** A total of 120 (HALT 81, continue 39) patients were randomized. The mITT population included 117 (HALT 78, continue 39) patients. One patient withdrew at baseline and two patients whose HBsAg were negative at baseline visit. The primary mITT endpoint of HBsAg loss at 144 weeks was achieved in 24/78 (30.4%) HALT and 3/39 (7.7%) continue (p = 0.005). HBsAg seroconversion was seen in 15/24 (62.5%) and 2/3 (66.6%) patients with HBsAg loss in HALT and continue arms respectively (p = 0.052). Apriori subgroup analysis of HBsAg < 10 IU/ml showed HBsAg loss at 144 weeks in 13/21 (61.9%) HALT versus 3/12 (25%) continue arm (p = 0.071). ALT ≥ 10xULN was seen in 8.7% versus 8.2% of HALT and continue for patients with HBsAg < 10 IU/ml. NA treatment > 10years and prior interferon was associated with higher rates of HBsAg loss (p < 0.05). ALT flares of ≥ 2x ULN, 5xULN and 10xULN were seen in 36.2% vs 7.7%, 22.5% vs 2.6% and 15% vs 2.6% of HALT and continue patients respectively (p < 0.001, p = 0.006, and p = 0.058 respectively). Bilirubin ≥ 1.5xULN occurred in 6.2% of HALT and 2.6% of continue arms (p = 0.662). HBeAg seroreversion occurred in 11.2% of HALT and 2.6% of continue patients (p = 0.163). Hospitalisations due to severe ALT flare occurred in 4.17% of HALT and none in continue patients. One patient in continue arm stopped NA as he ran out of study medication during COVID. HBV RNA at baseline was predictive of ALT flares (AUROC = 0.683, 95% CI 0.516 – 0.851, p = 0.032). At the cut-off value of ≥ 1.70254, the sensitivity, specificity, PPV and NPV of predicting severe ALT flare (ALT > 10xULN) are 100%, 51.1%, 15.4% and 100% respectively. **Conclusion:** While stopping NA in HBeAg negative CHB patients with HBsAg < 100 IU/ml comes with high rates of HBsAg loss, they carry a significant risk of severe ALT flares, HBeAg seroreversion, and hospitalisation.



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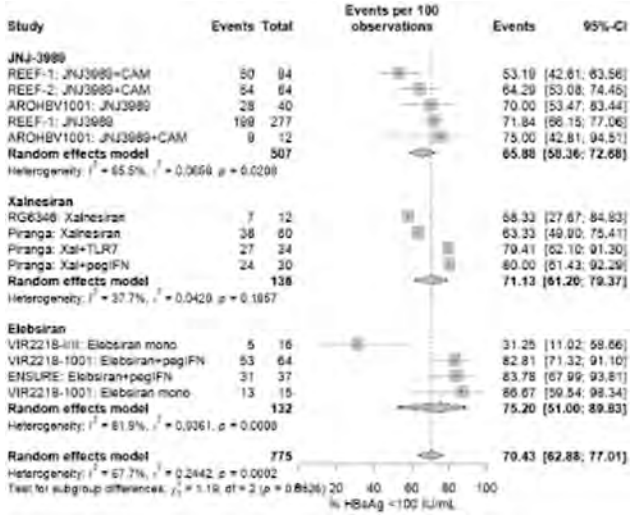
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to Disclose, Tiffany Fortney:Nothing to Disclose, Mark Anderson:Nothing to Disclose, Gavin Cloherty:Nothing to Disclose, Liang Shen:Nothing to Disclose.

4085 | EFFICACY AND SAFETY OF SMALL INTERFERING RNA AGENTS FOR CHRONIC HEPATITIS B: A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS

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Background: BackgroundSmall interfering RNA (siRNA) agents represent a promising therapeutic class for chronic hepatitis B virus (HBV) infection designed to silence viral transcripts and achieve a functional cure. However, a comprehensive evaluation of the comparative efficacy and safety of advanced siRNA pipelines remains lacking. **Methods:** MethodsMEDLINE, Embase, Cochrane CENTRAL, and ClinicalTrials.gov were searched through January 2026 for Phase I–III clinical trials evaluating siRNA agents (monotherapy or combination regimens) on background nucleos(t)ide analogue (NA) therapy. Frequentist random-effects network meta-analysis (NMA) and pairwise pooling were applied. The primary endpoint was the proportion of patients achieving hepatitis B surface antigen (HBsAg) levels < 100 IU/mL at the end of treatment (EOT). **Results:** ResultsEight clinical trials enrolling a total of 1,012 participants evaluating three distinct siRNA agents JNJ-73763989 (JNJ-3989), xalnesiran, or elebsiran were identified. In the NA-controlled NMA (5 studies, 7 nodes, I^2 = 0%), all active siRNA combinations demonstrated significant superiority over NA alone for achieving HBsAg < 100 IU/mL except elebsiran monotherapy (OR 2.39, p = 0.399). The highest odds of response were seen with JNJ-3989+NA (OR 140.68, 95% CI 31.53–627.67, p < 0.0001, NNT = 2) and JNJ-3989+capsid assembly modulator (CAM) +NA (OR 62.17, 95% CI 14.63–264.28, p < 0.0001, NNT = 2), followed by xalnesiran+pegylated interferon (pegIFN)+NA (OR 15.25, 95% CI 4.76-48.82) and xalnesiran+TLR7+NA (OR 14.83, 95% CI 4.83–45.54).For continuous continuous HBsAg change, siRNA regimens led to a significantly greater reduction vs. controls (weighted mean difference [WMD] −1.78 $\log_{10}$ IU/mL, 95% CI −1.89 to −1.66, I^2 = 24%). Single-arm synthesis of all 13 active arms yielded an overall response rate of 70.43% (95% CI 62.88–77.01%), peaking with pegIFN co-administration at 82.44%. Risks for Grade 3/4 adverse events (RR 1.30, 95% CI 0.49–3.44) and serious adverse events (RR 0.84, 95% CI 0.31–2.31) were comparable to controls, while ALT elevations were numerically higher (RR 3.11, 95% CI 0.62–15.56), heavily driven by pegIFN co-administration. **Conclusion:** Conclusion-siRNA agents induce profound, clinically meaningful reductions in surface antigen titers. Regimens incorporating JNJ-3989 demonstrate the highest relative probability of short-term response. Co-administration with pegIFN maximizes absolute surface antigen suppression but warrants close monitoring for immunomodulatory ALT flares.



Disclosures: Rahul Falodia:Nothing to Disclose, Ubaid Ahmed:Nothing to Disclose.

4086 | HEPATOCELLULAR CARCINOMA RISK AND ITS PREDICTORS IN CHRONIC HEPATITIS B PATIENTS RECEIVING DIFFERENT ANTIVIRAL STRATEGIES: EVIDENCE FROM MULTIPLE LARGE-SCALE REAL-WORLD DATABASES

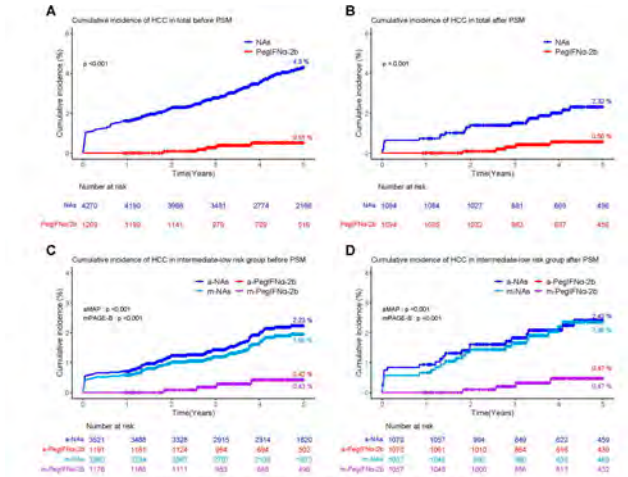
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Background: Hepatitis B virus (HBV) infection constitutes a leading etiology of hepatocellular carcinoma (HCC), contributing to over 50% of incident cases worldwide and up to 70% in China. While antiviral treatment substantially lowers HCC risk in chronic hepatitis B (CHB) patients, prior research indicates that peginterferon alpha (PegIFNα)-based therapy yields an additional 80%-90% risk reduction over nucleos(t)ide analogues (NAs) monotherapy. This study aimed to evaluate the real-world HCC risk and predictors in CHB patients receiving different antiviral strategies, leveraging a large-scale real-world database. **Methods:** This study utilized data from the databases of Xiamen Health and Medical Big Data Center (2016-2025) and People's Insurance Company of China (PICC; 2020-2025). The cohort enrolled 1,209 CHB patients completing ≥48 weeks of PegIFNα-2b (Pegbing®) therapy and 4,270 treated with NAs monotherapy. Median follow-up durations were 236 weeks and 269 weeks, respectively. Propensity score matching (PSM) was applied to minimize baseline differences, and multivariate Logistic regression analysis was used to identify the risk factors for HCC. **Results:** 165 patients developed HCC during follow-up. The cumulative HCC incidence at 5 years was significantly lower in the PegIFNα-2b group than NAs group (0.51% vs. 4.3%, HR = 0.11, P < 0.001; fig. A). Similar results were obtained in the PSM cohort (0.56% vs. 2.32%, HR = 0.23, P = 0.001; fig. B).Patients were stratified by HCC risk utilizing the aMAP and mPAGE-B scores. Subgroup analysis demonstrated that PegIFNα-2b significantly reduced the incidence of HCC, even among patients at intermediate to low risk. Before PSM, the cumulative HCC incidence at 5 years was significantly lower in PegIFNα-2b group defined by aMAP (0.42% vs. 2.23%, HR = 0.18, P < 0.001) and mPAGE-B (0.43% vs. 1.95%, HR = 0.21, P < 0.001; fig. C). These findings were replicated in the PSM cohort (aMAP: 0.47% vs. 2.42%, HR = 0.17, P < 0.001; mPAGE-B: 0.47% vs. 2.36%, HR = 0.18, P < 0.001; fig. D).Multivariate analysis showed that NAs therapy (vs. PegIFNα-2b therapy, HR = 7.33, P < 0.001), male gender (HR = 2.18, P < 0.001), age ≥ 50 years (HR = 2.53, P < 0.001), HBV DNA positive (HR = 2.10, P = 0.014), high HBsAg levels (HR = 1.47, P < 0.001), high ALT levels (HR = 1.00, P = 0.010), FIB-4 ≥ 3.25 (HR = 1.02, P = 0.031), high albumin levels (HR = 1.04, P = 0.002), cirrhosis (HR = 1.73, P = 0.004), and family history of HCC (HR = 2.33, P < 0.001) were independently associated with an increased risk of HCC. **Conclusion:** This analysis from Large-scale real-world databases demonstrate that PegIFNα-based therapy is associated with an approximate 80% reduction in HCC development compared to NAs monotherapy, even among patients at intermediate to low risk. In addition, sex, age, HBV DNA status, HBsAg, ALT, albumin levels, FIB-4 scores, cirrhosis, and family history of HCC were also associated with HCC development.



The cumulative HCC incidence between the PegIFNα and NAs group
(A, B) The Kaplan-Meier (KM) curves for the entire cohort before (A) and after (B) PSM.
(C, D) The KM curves for intermediate to low HCC risk patients stratified by aMAP/mPAGE-B scores before (C) and after (D) PSM.

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4087 | CLINICAL IMPACT OF ANTIVIRAL THERAPY ON REDUCING HCC AND CIRRHOSIS RISKS IN THE INDETERMINATE PHASE OF CHRONIC HEPATITIS B

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Background: Many patients in the indeterminate phase chronic hepatitis B (CHB) remain untreated due to rigid criteria. We aimed to evaluate whether untreated indeterminate patients have higher risks of hepatocellular carcinoma (HCC) and liver cirrhosis (LC) compared to treated active phase patients, and to evaluate the clinical benefits of antiviral therapy (AVT) in indeterminate phase

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subgroups. **Methods:** A total of 15,684 patients with HBV were analyzed from the VLINK HBV cohort, a multi-center database including data from seven tertiary-level hospitals. Patients with indeterminate phase was sub-stratified: Low-ALT (ALT U/L), moderate-level viremia (ALT 40–80 IU/L, DNA 2,000–8log), and low-level viremia (DNA2,000, ALT > 40 IU/L) groups. We calculated incidence rates (IR) per 100 person-years (PY) and adjusted hazard ratios (aHR) using Cox proportional hazards models. **Results:** In the HBeAg-positive group, untreated indeterminate patients showed a higher HCC IR (**0.938**) and LC IR (**1.84**) compared to treated active patients, who had an IR of **0** for both outcomes (**aHR = 1.85**, 95% CI 1.24–2.76 for HCC; **aHR = 2.12**, 95% CI 1.45–3.10 for LC). Similarly, untreated HBeAg-negative indeterminate patients had a higher HCC IR (**0.532**) than treated active patients (IR = **0.218**), representing a significantly elevated risk (**aHR = 1.42**, 95% CI 1.08–1.87). Within the indeterminate phase, AVT significantly reduced the LC IR from **2.888** to **1.521** (**aHR = 0.52**, 95% CI 0.38–0.71) and the HCC IR from **1.114** to **0.899** (**aHR = 0.68**, 95% CI 0.45–0.92) in moderate-level viremia group. Furthermore, in the low-level viremia **group,** the AVT-treated group showed a significantly lower HCC IR (**0.656**) compared to the untreated group (**0.947**; **aHR = 0.58**, 95% CI 0.35–0.96). **Conclusion:** Untreated indeterminate phase patients have higher risk of HCC and LC development than patients receiving AVT in the active phase. A more proactive antiviral strategy for indeterminate phase patients is essential to overcome the current treatment gap.

Disclosures: Hanah Lee:Nothing to Disclose, Sang Gyune Kim:Nothing to Disclose, Soo Young Park: Nothing to Disclose, Young Youn Cho:Nothing to Disclose, Hyung Joon Kim:Nothing to Disclose, Yeon Seok Seo:Nothing to Disclose, Sung Hwan Yoo: Nothing to Disclose, Seung Up Kim:Nothing to Disclose, Dae Won Jun:Nothing to Disclose.

4088 | RETREATMENT WITH SHORT-COURSE PEGINTERFERON ALPHA-2B LEADS TO HIGH HBSAG LOSS IN INTERFERON-EXPERIENCED CHRONIC HEPATITIS B PATIENTS WITH FAVORABLE INITIAL RESPONSE

Haiguang Xin[1] Xiaoyu Hu[2] Hong Tang[3] Chengrun Xu[4] Hongliang He[5] Li Zhu[6] Chuanwu Zhu[7] Feng Liu[8] Yufeng Gao[9] Jia Shang[10] Qingfa Ruan[11] Liang Chen[12] Xuehua Sun[13] Jing Feng[14] Liguan Liu[15] Haidong Zhao[16] Xiangyong Li[17] Lei Wang[18] Yumin Xu[1] Shaowen Jiang[1] Qing Guo[19] Qing Xie[1], [1]Ruijin Hospital, Shanghai Jiaotong University School of Medicine, [2]Disease at Hospital of Chengdu University of TCM, [3]West China Hospital of Sichuan University, [4]The 909th Hospital of the PLA Joint Logistic Support Force, [5]The First Affiliated Hospital of USTC (Anhui Provincial Hospital), [6]Public Hearth Clinical Center of Chengdu, [7]The Affiliated Infectious Diseases Hospital of Soochow University, [8]Tianjin Second People's Hospital, [9]The First Affiliated Hospital of Anhui Medical University, [10]Henan Provincial People's Hospital, [11]Xiamen Hospital of T.C,M., [12]Shanghai Public Health Clinical Center, [13]Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, [14]Weifang People's Hospital, [15]The 910th Hospital of the People's Liberation Army Joint Logistics Support Force, [16]Xiamen Chang Gung Hospital, [17]The Third Affiliated Hospital of Sun Yat-sen University, [18]The Second Qilu Hospital of Shandong University, [19]Ruijin Hospital,Shanghai Jiaotong University School of Medicine

Background: Data on retreatment for chronic hepatitis B (CHB) are limited. We aimed to evaluate the efficacy of peginterferon alpha-2b (PegIFNα-2b) retreatment in interferon-experienced CHB patients with favorable initial response. **Methods:** This prospective, real-world study (NCT06323681) recruited participants who had previously received interferon therapy (discontinued ≥ 3 months) and demonstrated a post-treatment HBsAg decline of ≥ 80%, had HBsAg ≤ 500 IU/mL at the current screening and experienced an HBsAg rebound of ≤ 50% of the initial treatment baseline. Patients were assigned to receive either PegIFNα-2b (Pegbing®, Xiamen Amoytop Biotech Co., Ltd.) with or without nucleos(t)ide analogues (NAs) (Group A), or NAs alone (Group B). Following a 48-week treatment course, the primary endpoint was HBsAg loss rate at week 48. The efficacy of the subgroup of patients who experienced relapses after achieving HBsAg loss with initial interferon therapy was also analyzed. **Results:** A total of 1,000 and 325 patients were included in groups A and B, respectively. Prior to the initial interferon therapy, the mean HBsAg levels were 2600.6 IU/mL in Group A and 1304.2 IU/mL in Group B. By the end of the first round of treatment, these levels had declined to 69.3 and 128.6 IU/mL, representing average reductions of 95.0% and 91.3%, respectively. At the start of the current study, the mean HBsAg levels were 64.3 IU/mL in Group A and 110.1 IU/mL in Group B. Among population with available data, the HBsAg loss rate in Group A increased from 30.5% at week 24 to 42.0% at week 48, whereas that in Group B changed from 3.9% to 5.8%, with Group A being significantly higher (all p values < 0.001). Similarly, among the total population reaching each timepoint, Group A maintained significantly higher HBsAg loss rates than Group B, at 27.4% vs. 1.5% at week 24 ($p < 0.001$) and 38.2% vs. 2.4% at week 48 ($p < 0.001$) (Fig. 1). Within Group A, 79 patients experienced HBsAg relapse after achieving HBsAg loss with initial interferon therapy. Of these, 96.2% had an HBsAg level < 100 IU/mL at the start of current treatment, with a median level of 0.36

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(0.16–1.78) IU/mL. Following 48 weeks of PegIFNα-2b retreatment, the HBsAg loss rates in this relapsed subgroup were 73.5% in the data-available population and 68.5% in the total population reaching the treatment point. Among the 334 patients in Group A who obtained HBsAg loss, the mean duration of PegIFNα-2b retreatment to achieve HBsAg loss was 21.13 ± 9.77 weeks. **Conclusion:** Interferon-experienced CHB patients with good initial HBsAg responses achieved high HBsAg loss rates after PegIFNα-2b retreatment. For patients who relapsed after achieving HBsAg loss with initial treatment, the HBsAg loss rate reached approximately 70%. The PegIFNα-2b retreatment course to achieve HBsAg loss was short. Consequently, these patients are suggested with PegIFNα-2b retreatment to achieve functional cure as early as possible.

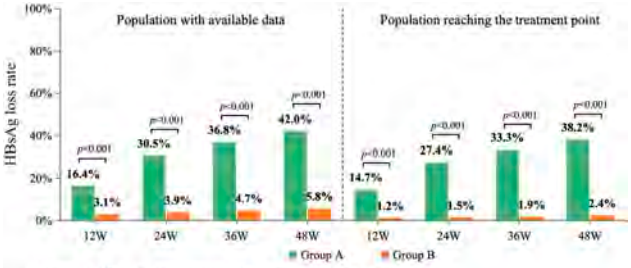


Figure 1. HBsAg loss rates of different groups among all patients.

Disclosures: Haiguang Xin:Nothing to Disclose, Xiaoyu Hu:Nothing to Disclose, Hong Tang:Nothing to Disclose, Chengrun Xu:Nothing to Disclose, Hongliang He:Nothing to Disclose, Li Zhu:Nothing to Disclose, Chuanwu Zhu:Nothing to Disclose, Feng Liu:Nothing to Disclose, Yufeng Gao:Nothing to Disclose, Jia Shang:Nothing to Disclose, Qingfa Ruan:Nothing to Disclose, Liang Chen:Nothing to Disclose, Xuehua Sun:Nothing to Disclose, Jing Feng:Nothing to Disclose, Liguan Liu:Nothing to Disclose, Haidong Zhao:Nothing to Disclose, Xiangyong Li:Nothing to Disclose, Lei Wang:Nothing to Disclose, Yumin Xu:Nothing to Disclose, shaowen jiang:Nothing to Disclose, Qing Guo:Nothing to Disclose, QING XIE:Nothing to Disclose.

4089 | COMBINING PAGE-B SCORE WITH FIBROTEST IMPROVES HCC RISK STRATIFICATION IN PATIENTS TREATED WITH TENOFOVIR-BASED TREATMENT

Milan Sonneveld[1] Grace Wong[2] Wai-Kay Seto[3] Kosh Agarwal[4] Jinlin Hou[5] Ming-Lung Yu[6] Hiroshi Yatsuhashi[7] Frida Abramov[8] Hongyuan Wang[8] Leland Yee[8] Maria Buti[9] Young Suk Lim[10] Harry Janssen[11], [1]Erasmus University Medical Center, Rotterdam, the Netherlands, [2]The Chinese University of Hong Kong, Shatin, Hong Kong, [3]The University of Hong Kong, Pok Fu Lam, Hong Kong, [4]King's College Hospital NHS Foundation Trust, London, UK, [5]Nanfang Hospital, Southern Medical University, Guangzhou, China, [6]Kaohsiung Medical University Hospital; Kaohsiung Medical University, Kaohsiung, Taiwan, [7]National Hospital Organization Nagasaki Medical Center, Nagasaki, Japan, [8]Gilead Sciences, Inc., Foster City, CA, USA, [9]Hospital Universitario Vall d'Hebron, Barcelona; CIBEREHD del Instituto Carlos III, Madrid, Spain, [10]Asan Medical Centre, University of Ulsan College of Medicine, Seoul, South Korea, [11]Erasmus University Medical Center, Rotterdam, the Netherlands; University Health Network, ON, Canada

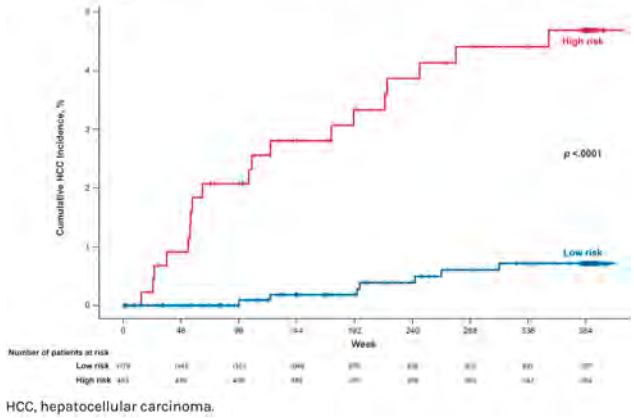
Background: Nucleos(t)ide analogue (NA) therapy reduces but does not eliminate the risk of hepatocellular carcinoma (HCC) in patients with chronic hepatitis B (CHB). The PAGE-B score is widely used to stratify HCC risk, but it identifies only a limited proportion of patients at low risk of developing HCC during long-term NA therapy. We aimed to evaluate whether FibroTest values can be used to optimize HCC risk stratification. **Methods:** In 2 similarly designed studies (GS-US-320-0108 and -0110), hepatitis B e antigen (HBeAg)-negative and -positive patients with CHB with hepatitis B virus DNA ≥20,000 IU/mL and alanine aminotransferase >60 U/L (males) or >38 U/L (females) were randomized (2:1) to tenofovir alafenamide (TAF) 25 mg or tenofovir disoproxil fumarate 300 mg given once daily in a double-blind phase for up to 3 years, followed by open-label TAF through year 8 (Y8). The PAGE-B score was calculated for all patients with available data; patients were assigned to low (≤9), intermediate (10–17 points), and high (≥18 points) risk groups based on previously reported cutoffs. Patients also underwent FibroTest (BioPredictive, Paris, France) assessment and were classified as having no to mild fibrosis (≤0.48), moderate to severe fibrosis (0.49–0.74), or cirrhosis (≥0.75) based on previously reported cutoffs. The Kaplan–Meier method was used to estimate cumulative HCC incidence at Y8. **Results:** Of the 1632 patients included, 1354 (83%) were Asian, 1063 (65%) were male, and 1039 (64%) were HBeAg positive, with a median (Q1, Q3) baseline age of 39 (31, 49) years. Through up to 8 years of treatment, 26 (1.6%) patients developed HCC. At baseline, PAGE-B scores (assessed in 1631 patients) were low, intermediate, and high in 642 (39%), 830 (51%), and 159 (10%) patients, respectively. Among patients with a low PAGE-B score, 4 (0.6%) developed HCC through Y8 (negative predictive value [NPV] for HCC at Y8 = 99.4%).At baseline, FibroTest values (available for 1594 patients) were ≤0.48, 0.49–0.74, and ≥0.75 in 1103 (69%), 336 (21%), and 155 (10%) patients, respectively. Among patients with FibroTest values ≤0.48, 6 (0.5%) developed HCC (NPV for HCC at Y8 = 99.5%). A combined strategy defining low risk as

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either a PAGE-B score ≤9 and/or a FibroTest value ≤0.48 expanded the low-risk population to 72% while maintaining a very high NPV for HCC at Y8 (NPV = 99.4%). The cumulative incidence of HCC development differed between low- and high-risk groups for the combined strategy (0.7% vs 4.7% at Y8; 0.87 vs 6.23 per 1000 person-years; $p < .0001$; **Figure**). **Conclusion:** A FibroTest value ≤0.48 is associated with a low risk of HCC in patients treated with tenofovir-based therapy. Combining PAGE-B with FibroTest better identified a low-risk population, as reflected by the increased proportion of patients classified as low risk (72%) vs with PAGE-B alone (39%), while maintaining a high NPV for HCC risk. These findings support refined HCC risk stratification in treated CHB populations.

Figure. Cumulative Incidence of HCC Development Over 8 Years (Combined PAGE-B and FibroTest Strategy)



HCC, hepatocellular carcinoma.

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4090 | 48-WEEK HBSAG SEROCLEARANCE AND PREDICTORS IN CHB PATIENTS WITH HBSAG <100 IU/ML RECEIVING PEGIFNα THERAPY

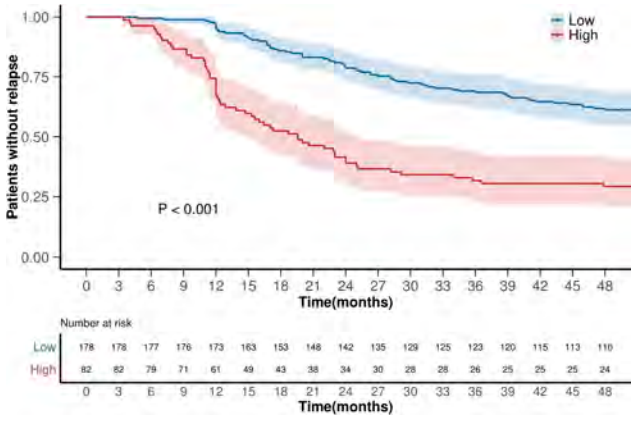
Yiwen Zhang[1] Qin Du[2] Jingzhe Zhang[1] Jiayin Wang[3] Jun Li[1] Yuchen Bao[4] Qing Ye[3] Huiling Xiang[3], [1]The Third Central Clinical College of Tianjin Medical University, [2]Nankai University Affinity the Third Central Hospital, [3]Central Hospital, Tianjin University /Tianjin Third Central Hospital, [4]Tianjin University,Tianjin University Central Hospital (Tianjin Third Central Hospital)

Background: HBsAg seroclearance is the optimal endpoint for functional cure in chronic hepatitis B (CHB). Although patients with HBsAg <100 IU/mL are considered favorable candidates for cure, spontaneous clearance remains rare and risks of hepatitis flare, cirrhosis, and hepatocellular carcinoma persist. Pegylated interferon alpha (PegIFNα) can improve functional cure rates, but data regarding its efficacy and predictive markers in this population remain limited. This study aimed to evaluate the efficacy of PegIFNα therapy and the predictive value of the ALT/HBsAg ratio

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for 48-week HBsAg seroclearance in CHB patients with HBsAg < 100 IU/mL. **Methods:** This retrospective study enrolled 277 CHB patients with baseline HBsAg < 100 IU/mL who received pegylated interferon alpha-2b (PEG-IFN α-2b), alone or combined with nucleos(t)ide analogues (NAs), at Tianjin Third Central Hospital between October 2018 and January 2026. The primary endpoint was HBsAg seroclearance within 48 weeks. Cox proportional hazards regression was used to evaluate the association between log10(ALT/HBsAg) and HBsAg seroclearance. Multivariable models adjusted for potential confounders. Subgroup analyses assessed result robustness. Receiver operating characteristic analysis identified the optimal cutoff value, and Kaplan–Meier analysis compared cumulative HBsAg seroclearance rates between groups. **Results:** The cumulative 48-week HBsAg seroclearance and seroconversion rates were 49.8% and 36.1%, respectively. Compared with the non-seroclearance group, patients achieving HBsAg seroclearance were younger, had lower baseline HBsAg levels,lower prevalence of family history of hepatitis B, milder fibrosis, and higher log10(ALT/HBsAg) levels.In univariable Cox analysis, each one-unit increase in log10(ALT/HBsAg) was associated with a 77% higher likelihood of HBsAg seroclearance (HR = 1.77, 95% CI:1.48~2.13 , P < 0.001). After multivariable adjustment, log10(ALT/HBsAg) remained an independent predictor of HBsAg seroclearance (HR = 1.51, 95% CI: 1.19~1.92, P < 0.001). Kaplan–Meier analysis showed significantly different cumulative HBsAg seroclearance rates among log10(ALT/HBsAg) subgroups (log-rank P < 0.001). **Conclusion:** CHB patients with HBsAg < 100 IU/mL achieved favorable 48-week HBsAg seroclearance and seroconversion rates following PegIFNα therapy, supporting the benefit of active antiviral intervention in this population. The ALT/HBsAg ratio was independently associated with HBsAg seroclearance and may help identify patients most likely to achieve functional cure with PegIFNα therapy.



Disclosures: Yiwen Zhang:Nothing to Disclose, qin du:Nothing to Disclose, jingzhe zhang:Nothing to Disclose, jiayin wang:Nothing to Disclose, jun Li:Nothing to Disclose, Yuchen Bao:Nothing to Disclose, Qing Ye:Nothing to Disclose, Huiling Xiang:Nothing to Disclose.

4091 | FIVE-YEAR DURABILITY OF FUNCTIONAL CURE FOLLOWING PEGINTERFERON ALPHA-2B THERAPY IN CHRONIC HEPATITIS B: A SINGLE-CENTER ANALYSIS FROM REAL-WORLD STUDIES

Shiji Xu[1] Weiqiang Gan[1] Na Gao[1] Zhishuo Mo[1] BingLiang Lin[1] Zhiliang Gao[1], [1]The Third Affiliated Hospital of Sun Yat-sen University

Background: Functional cure of chronic hepatitis B (CHB) is the optimal endpoint for significantly reducing hepatocellular carcinoma (HCC) risk. Our real-world Everest Project demonstrated substantial success in achieving functional cure using peginterferon alpha (PegIFNα). However, data on long-term off-treatment durability in large cohorts remain scarce. Furthermore, while emerging novel therapeutics (e.g., ASO) exhibit potent on-treatment viral suppression, their off-treatment durability remains largely suboptimal. Thus, we evaluated the up to 5-year durability, relapse patterns, and clinical outcomes in a large cohort of PegIFNα-treated patients who achieved functional cure. **Methods:** This single-center observational study included CHB patients who achieved functional cure following PegIFNα-2b (Pegbing®, Xiamen Amoytop Biotech Co., Ltd.) therapy. The cohort comprised patients from the Third Affiliated Hospital of Sun Yat-sen University, originally enrolled in multicenter projects (Everest [NCT04035837], E-cure [NCT05182463], STARHB [ChiCTR2200061541]). Patients were monitored for functional cure sustainability and HCC incidence. HBV markers (HBsAg, HBV DNA) were dynamically recorded upon relapse. **Results:** A total of 829 patients achieving functional cure were included. During the study, 509, 365, 235, 154, and 74 patients completed 1-, 2-, 3-, 4-, and 5-year follow-ups, respectively. Maintenance rates remained highly stable: 97.1% (494/509), 93.7% (342/365), 92.8% (218/235), 92.2% (142/154), and 93.2% (69/74) at years 1 through 5 (Figure 1). During the follow-up, 32 patients experienced relapse, comprising isolated HBsAg relapse in 17 (53.1%), isolated HBV DNA relapse in 2 (6.3%), and concurrent relapse in 13 (40.6%) patients. Viral levels at relapse were extremely low: median HBsAg was 0.34 (0.09–6.25) IU/mL, and HBV DNA was 38.0 (30.0–62.5) IU/mL. Only one patient developed HCC during the up to 5-year follow-up. **Conclusion:** The 5-year maintenance rate of PegIFNα-2b-induced functional cure in CHB patients exceeds 90%, demonstrating robust off-treatment durability that offers a distinct

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advantage over the high relapse rates of current emerging therapies. Relapses are rare and characterized by marginal virological rebounds. The low HCC incidence in this large cohort substantiates the long-term clinical benefits of PegIFNα-driven functional cure.

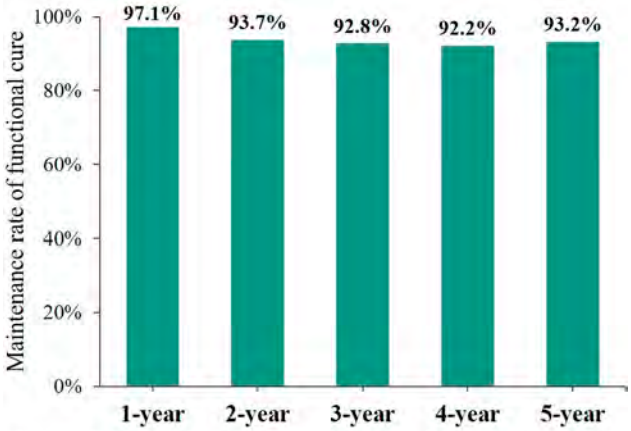


Figure 1. Up to 5 years maintenance rate of functional cure.

Disclosures: Shiji Xu:Nothing to Disclose, Weiqiang Gan:Nothing to Disclose, Na Gao:Nothing to Disclose, Zhishuo Mo:Nothing to Disclose, BingLiang Lin:Nothing to Disclose, Zhiliang Gao:Nothing to Disclose.

4093 | MODELING HDV RNA, HBSAG AND ALT KINETICS IN PATIENTS TREATED WITH BULEVIRTIDE AND PEGYLATED INTERFERON-ALPHA FOR 96 WEEKS IN THE SEE-D TRIAL

Adquate Mhlanga[1] Emmanuel Zavalis[2] Scott Cotler[1] Karin Lindahl[2] Susanne Cederberg[2] Annika Olsson[2] Niklas Bjorkstrom[2] Pietro Lampertico[3] Heiner Wedemeyer[4] Harel Dahari[1] Soo Aleman[2], [1]Loyola University Chicago, [2]Karolinska University Hospital, [3]University of Milan, [4]Hannover Medical School

Background: Bulevirtide (BLV) was recently approved by the FDA. In the MYR 204 trial, 48 week combination therapy with BLV and pegylated Interferon-alpha (peg-IFN) showed higher rates of on-treatment undetectable HDV RNA compared to either drug as monotherapy. SEE-D investigates the effect of 96 weeks combination therapy. We aim to explain HDV-host dynamics during BLV and peg-IFN therapy using mathematical modeling. **Methods:** 31 patients with chronic hepatitis D were enrolled at Karolinska University Hospital, Sweden (EU no. 2023-504414-29-00). They received 96-weeks of combination treatment with BLV (2 mg/day) and peg-IFN. One early dropout and one participant without quantifiable HDV RNA values were excluded. We used our recent mathematical model (http://dx.doi.org/10.2139/ssrn.6809660) accounting for both blocking of viral production (peg-IFN efficacy, ε) and blocking of infection (BLV efficacy; η), with total efficacy of ε_{tot}. Due to parameter identifiability issues, BLV efficacy was fixed at 80% as recently estimated under BLV monotherapy (http://dx.doi.org/10.2139/ssrn.6809660). The critical drug efficacy (CDE) was estimated, such that for ε_{tot} > CDE, HDV is ultimately cleared (i.e., cure), while ε_{tot} < CDE results in a new lower viral plateau or viral breakthrough. **Results:** The 29 participants initially showed a rapid first-phase HDV RNA decline (-0.91 $\log_{10}$ IU/mL/month), followed by undetectability (n = 26; Fig.1A), or a plateau close to LLoQ (n = 3; Fig. 1B) followed by viral breakthrough (VB, Fig.1C). The model reproduced the observed HDV kinetics and estimated ε_{tot} of 96% (95% CI 95 – 98), which exceeded CDE in 90% of the participants (Fig. 1A) but was below the CDE in the three participants who reached a lower plateau (Fig 1B), and a VB (Fig. 1C). Modeling explained VB by an increase of HDV-free hepatocytes. ALT normalization (Fig. 1) was explained by a decline in HDV-infected cells. HBsAg kinetics were explained by a constant number of HBsAg-producing hepatocytes during treatment (Fig. 1), except for in 3 participants who exhibited a >1 log HBsAg decline from baseline, which may reflect loss of HBsAg-producing cells and/or interferon-mediated inhibition of HBsAg production. **Conclusion:** The high rates of undetectable HDV RNA, with the finding that most patients who achieved TND had total efficacy exceeding the critical drug efficacy threshold, suggest that prolonged combination therapy substantially improves antiviral activity and increases the likelihood of sustained viral suppression.

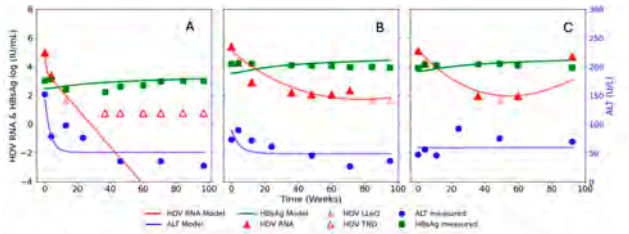


Figure 1. Measured kinetics (symbols) and modeling best curve fits (lines) in representative responder patients with a rapid sustained HDV RNA clearance (**A**), decline that becomes flat-partial at LLoQ (**B**), viral breakthrough (**C**). Estimated peg-IFN efficacy in blocking production in A, B and C was ε= 96%,ε= 57%, and ε = 5%, with BLV efficacy in blocking infection fixed at η=80% for all patients, corresponding to total ε_{tot} of 99%, 91%, and 81%, respectively. HDV RNA was measured using Robogene 2.0 (lower limit of detection, LLD = 6 IU/mL).

Disclosures: Adquate Mhlanga:Nothing to Disclose, Emmanuel Zavalis:Nothing to Disclose, Scott Cotler: Nothing to Disclose, Karin Lindahl:Nothing to Disclose, Susanne Cederberg:Nothing to Disclose, Annika Olsson: Nothing to Disclose, Niklas Bjorkstrom:Nothing to Disclose, Pietro Lampertico:ROCHE PHARMA/DIAGNOSTICS, GILEAD SCIENCES, GSK, ABBVIE, JANS: Advisor, Heiner Wedemeyer:Gilead Sciences GmbH & Gilead Sciences Ltd.: Grant/Research Support, Madrigal Pharmaceuticals, Inc.: Grant/Research Support, Biotest AG: Grant/Research Support, Gilead Sciences GmbH & Gilead Sciences Ltd.: Clinical Trials / Investigator, Madrigal Pharmaceuticals, Inc.: Clinical Trials / Investigator, Dr. Falk Pharma GmbH: Clinical Trials / Investigator,

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4094 | PEGYLATED INTERFERON α PLUS TENOFOVIR ALAFENAMIDE ACHIEVED A HIGHER HBSAG SEROCLEARANCE RATE THAN TENOFOVIR ALAFENAMIDE MONOTHERAPY IN TREATMENT-NAÏVE INDETERMINATE-PHASE CHRONIC HEPATITIS B PATIENTS WITH NEGATIVE HBEAG (FORESIGHT PROJECT)

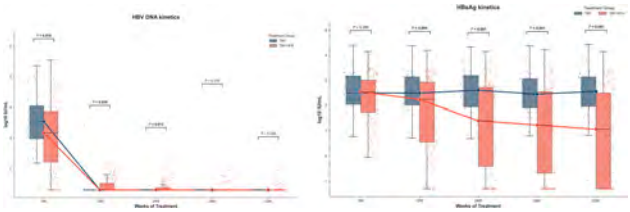
Mengya Liu[1] Huan Liu[1] Jiayi Wang[1] Juan Liao[1] Min He[1] Libo Yan[1] Lingyao Du[1] Lang Bai[1] Dongbo Wu[1] Juan Wang[2] Xia Zhu[2] Dong-Mei Zhang[2] Xing Cheng[2] Hong Li[2] Hong Tang[2], [1]Center of Infectious Diseases, West China Hospital of Sichuan University, Chengdu 610041, China;, [2]Center of Infectious Diseases, West China Hospital of Sichuan University, Chengdu 610041, China

Background: The indeterminate phase comprises chronic HBV-infected patients who do not fit into the four phases defined by current guidelines based on ALT, HBeAg, and HBV DNA levels. HBeAg-negative patients account for 70%–85% of this population. Although previous guidelines did not recommend antiviral therapy for these patients, they remain at risk of cirrhosis and hepatocellular carcinoma, warranting early antiviral treatment. However, the efficacy of different therapies in this population remains unclear. This study compared the clinical efficacy of nucleos(t)ide analogues (NAs) monotherapy versus NAs plus pegylated interferon alpha (Peg-IFNα) in treatment-naïve, HBeAg-negative, indeterminate-phase CHB patients with normal ALT. **Methods:** This prospective cohort enrolled treatment-naïve CHB patients with normal ALT ($\leq$40 U/L), negative HBeAg, and detectable HBV DNA ($\geq$20 IU/mL). Patients received TAF monotherapy or TAF plus Peg-IFN-α for 52 weeks according to patient preference. HBV DNA, HBV seromarkers, liver biochemistry, and blood cell counts were assessed every 12 weeks. The primary endpoint was undetectable HBV DNA (HBV DNA $<$20 IU/mL) at Week 52. The secondary endpoint was HBsAg seroclearance (HBsAg $<$0.05 IU/mL) at Week 52 (ChiCTR2200063868). **Results:** Among 183 enrolled patients, 42 received TAF monotherapy and 141 received TAF plus Peg-IFNα. Overall, the median age was 37.0 years (IQR: 34.0–44.0), and 49.2% were male. HBV DNA levels declined significantly at all follow-up time points ($p < 0.05$). At Week 52, 88.0% (161/183) achieved undetectable HBV DNA. In the TAF monotherapy group, median HBV DNA decline was 2.2 $\log_{10}$ IU/mL, and 92.9% (39/42) achieved undetectable HBV DNA. In the combination group, median HBV DNA decline was 1.9 $\log_{10}$ IU/mL, and 86.5% (122/141) achieved undetectable HBV DNA. The rate of undetectable HBV DNA was comparable between the two groups ($p = 0.402$). Overall, 20.8% (38/183) patients achieved HBsAg seroclearance at Week 52. Median HBsAg titer remained unchanged in the monotherapy group [2.5 (2.0-3.2) vs. 2.6 (2.0-3.1) log10 IU/mL, $p = 0.07$], and no patient achieved HBsAg seroclearance. Notably, median HBsAg titer in the combination group decreased from 2.5 to 1.1 $\log_{10}$ IU/mL at Week 52 ($p < 0.05$), with 27.0% (38/141) achieved HBsAg seroclearance, significantly higher than that in the monotherapy group ($p < 0.05$). Among patients achieved HBsAg seroclearance, 78.9% (30/38) further achieved HBsAg seroconversion, with a median anti-HBs titer of 132.5 mIU/mL (IQR: 76.4–208.5) at

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Week 52. **Conclusion:** Both TAF monotherapy and TAF plus Peg-IFNα effectively reduced HBV DNA levels, whereas combination therapy yielded superior HBsAg seroclearance in treatment-naïve, HBeAg-negative, indeterminate-phase CHB patients. These findings support active intervention with TAF plus Peg-IFNα to achieve HBsAg loss in this historically untreated population.

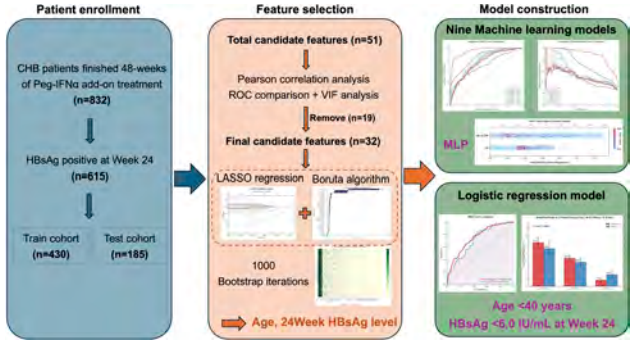


Disclosures: Mengya Liu:Nothing to Disclose, Huan Liu:Nothing to Disclose, Jiayi Wang:Nothing to Disclose, Juan Liao:Nothing to Disclose, Min He:Nothing to Disclose, Libo Yan:Nothing to Disclose, Lingyao Du:Nothing to Disclose, Lang Bai:Nothing to Disclose, Dongbo Wu:Nothing to Disclose, Juan Wang:Nothing to Disclose, xia zhu:Nothing to Disclose, Dong-Mei Zhang:Nothing to Disclose, Xing Cheng:Nothing to Disclose, Hong Li:Nothing to Disclose, Hong Tang:Nothing to Disclose.

4095 | IDENTIFYING CHRONIC HEPATITIS B PATIENTS WHO BENEFIT FROM CONTINUING PEG-IFNα BEYOND WEEK 24: A MACHINE LEARNING AND CLINICAL MODEL APPROAC

Jiayi Wang[1] Chen Zhou[1] Mengya Liu[1] Ning Han[1] Huan Liu[1] Hong Li[1] Lang Bai[1] Lingyao Du[1] Yilan Zeng[2] Hong Zhang[3] Juan Liao[1] Min He[1] Xuebing Chen[4] Jiahong Yang[5] Xing Cheng[1] Libo Yan[1] Hong Tang[1], [1]West China Hospital, [2]ublic Health Clinical Center of Chengdu, [3]Public Health Clinical Center of Chengdu, [4]epartment of Infectious Diseases, People's Hospital of Deyang City, [5]Department of Infectious Diseases, People's Hospital of Deyang City

Background: Chronic hepatitis B (CHB) remains a major global health burden and a leading cause of cirrhosis and hepatocellular carcinoma. Sustained HBsAg decline, particularly HBsAg loss, is critical in improving long-term clinical outcomes. Compared with nucleos(t)ide analogs (NAs), pegylated interferon-alpha (Peg-IFNα) more effectively promotes HBsAg reduction through combined antiviral and immunomodulatory effects. However, administration of Peg-IFNα beyond Week 24 provides limited benefit for many patients while increasing treatment burden. Therefore, a tool to identify patients likely to benefit from continued therapy is needed. We aimed to develop a simple model to guide individualized treatment decisions beyond Week 24. **Methods:** We analyzed a multicenter, prospective cohort of 832 NAs-experienced, HBeAg-negative CHB patients receiving Peg-IFNα add-on therapy for ≥ 48 weeks (NCT04035837). Among patients without HBsAg clearance at Week 24, treatment benefit from continued therapy was defined as HBsAg clearance at Week 48 or a >1 log10 IU/mL HBsAg decline from Weeks 24-48. Variables with a Pearson correlation coefficient >0.8 or variance inflation factor >5 were excluded to minimize multicollinearity. Predictors were selected using LASSO regression, the Boruta algorithm, and 1,000 bootstrap resamples. Nine machine learning (ML) models and a logistic regression (LR) model were developed and validated. **Results:** Overall, 615 (73.9%) patients remained HBsAg-positive at Week 24, among whom 159 (25.9%) achieved treatment benefit by Week 48. Age and Week 24 HBsAg level were identified as the most robust predictors. Among all ML models, the multilayer perceptron (MLP) demonstrated the best balance of discrimination and stability (AUC 0.721, 95% CI: 0.640–0.794). Stratification according to MLP-probabilities yielded distinct benefit rates in the test cohort (6.5% vs. 27.2% vs. 42.6% for low-, intermediate-, and high-probability groups, respectively; $p < 0.001$). The LR model showed comparable performance (AUC 0.716, 95% CI: 0.634-0.791, $p = 0.185$ *vs.* MLP) while offering greater clinical interpretability. Optimal cut-offs were 40 years for age and 0.772 log10 IU/mL (5.92 IU/mL) for Week 24 HBsAg. Based on these thresholds, patients were classified into a high-probability group (age <40 years and HBsAg <6.0 IU/mL), a low-probability group (age ≥40 years and HBsAg ≥6.0 IU/mL), and an intermediate-probability group (all remaining patients). Corresponding benefit rates were 50.0%, 9.4%, and 32.2%, respectively ($p < 0.001$). **Conclusion:** The MLP-based model identified patients unlikely to benefit from continued Peg-IFNα therapy, whereas patients aged <40 years with HBsAg <6.0 IU/mL at Week 24 are more likely to benefit from treatment continuation beyond Week 24.



Disclosures: Jiayi Wang:Nothing to Disclose, Chen Zhou:Nothing to Disclose, Mengya Liu:Nothing to Disclose, Ning Han:Nothing to Disclose, Huan Liu:

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Nothing to Disclose, Hong Li:Nothing to Disclose, Lang Bai:Nothing to Disclose, Lingyao Du:Nothing to Disclose, Yilan Zeng:Nothing to Disclose, Hong Zhang: Nothing to Disclose, Juan Liao:Nothing to Disclose, Min He:Nothing to Disclose, Xuebing Chen:Nothing to Disclose, Jiahong Yang:Nothing to Disclose, Xing Cheng:Nothing to Disclose, Libo Yan:Nothing to Disclose, Hong Tang:Nothing to Disclose.

4096 | PREGNANCY-INITIATED ANTIVIRAL THERAPY REDUCES THE RISK OF POSTPARTUM HEPATIC FLARES IN HIGHLY VIREMIC HBV-INFECTED WOMEN

Wan-Hsin Wen[1] Jin-Chung Shih[2] Chun Jen Liu[3] Yu Chun Chen[4] Mei-Hwei Chang[5] Huey-Ling Chen[5], [1]Cardinal Tien Hospital, [2]Department of Obstetrics and Gynecology, National Taiwan University College of Medicine and Hospital, [3]Department of Internal Medicine, National Taiwan University College of Medicine and Hospital, [4]Department of Pediatrics, National Taiwan University Hospital, [5]National Taiwan University

Background: Short-term antiviral therapy during late pregnancy is a standard strategy to prevent mother-to-child transmission (MTCT) among highly viremic HBV-infected women. However, the impact of maternal antiviral treatment on postpartum alanine aminotransferase (ALT) flares remains unclear. Previous studies have often defined hepatic flares using single-point measurements, which may fail to capture the dynamic nature of peripartum ALT fluctuation. This study aimed to identify independent predictors of postpartum hepatic flares by leveraging a trajectory-based approach. **Methods:** A prospective cohort of 333 highly viremic (HBV DNA > 200,000 IU/mL) mothers was followed from late pregnancy through 6 months postpartum, with protocol-driven ALT monitoring at baseline, 1 month post-baseline, delivery, and 1, 2, 4, 6 months postpartum. Pregnancy-treated women (n = 232) received tenofovir disoproxil fumarate or tenofovir alafenamide from the third trimester until 2–4 weeks postpartum. Based on a previously validated group-based trajectory model, four distinct peripartum ALT trajectories were identified: Pattern 1 (stable ALT throughout; 86.8%), Pattern 2 (moderate postpartum ALT elevation; 8.1%), Pattern 3 (marked postpartum ALT flares; 2.7%), and Pattern 4 (elevated ALT before delivery; 2.4%). Women with moderate and marked postpartum ALT elevations (Patterns 2 and 3) were combined into a composite postpartum flare group (n = 36), while those with stable ALT trajectories (Pattern 1) served as the reference group (n = 289). Multivariate logistic regression was performed to identify independent predictors of the postpartum flare trajectory. **Results:** In multivariate binary logistic regression adjusting for age, HBV genotype, and baseline viral load, antiviral therapy during pregnancy was identified as a powerful independent protective factor against postpartum ALT flares (adjusted odds ratio [aOR] = 0.35, 95% confidence interval [CI]: 0.15–0.80, p = 0.013). Conversely, higher baseline ALT was independently associated with an increased risk of subsequent postpartum flares (aOR = 1.08 per 1 U/L increase, 95% CI: 1.05–1.11, p < 0.001). Age (aOR = 1.10, p = 0.088), HBV genotype C (aOR = 1.51, p = 0.321), and baseline log10 viral load (aOR = 1.83, p = 0.131) were not significantly associated with the development of postpartum ALT flares. **Conclusion:** Among highly viremic HBV-infected women, approximately 10% exhibit peripartum ALT trajectories characterized by postpartum elevations or flares. Late-pregnancy antiviral therapy confers a protective effect against these flares, whereas higher baseline ALT increases the risk of subsequent flares. These findings underscore the benefit of maternal antiviral intervention in safeguarding postpartum hepatic stability. Additionally, our results highlight the need for vigilant monitoring, particularly in those with elevated baseline ALT.
Disclosures: Wan-Hsin Wen:Nothing to Disclose, Jin-Chung Shih:Nothing to Disclose, Chun Jen Liu:Nothing to Disclose, YU CHUN CHEN:Nothing to Disclose, Mei-Hwei Chang:Nothing to Disclose, Huey-Ling Chen: Nothing to Disclose.

4097 | TENOFOVIR ALAFENAMIDE FOR HBV PROPHYLAXIS AFTER LIVER TRANSPLANTATION: A 36-MONTH LONGITUDINAL REAL WORLD STUDY

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Background: HBV prophylaxis after liver transplantation requires durable viral suppression with favorable hepatic and renal safety. Data on long-term outcomes of tenofovir alafenamide (TAF) in this setting remain limited. **Methods:** This retrospective single-center cohort study included liver transplant recipients with HBV infection who received TAF 25 mg daily with tacrolimus-based immunosuppression. Clinical,

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virological, biochemical, and renal parameters were assessed at baseline and 6, 12, 24, and 36 months. HBV reactivation was defined as recurrent detectable HBV DNA after prior suppression **Results:** A total of 51 recipients were included. At baseline, median age was 49 (27-65) years, 47/51 (92.2%) were male, median BMI was 23.6 (17.6-32.1) kg/m², median HBsAg was 2.30 (0.00-3.95) log10 IU/mL, median ALT was 38 (8-2601) U/L, and median creatinine was 66 (38-111) µmol/L; baseline HBV DNA suppression was observed in 13/22 (59.1%) tested patients. HBsAg loss occurred in 32/39 (82.1%) at 6 months, 32/42 (76.2%) at 12 months, 31/35 (88.6%) at 24 months, and 16/17 (94.1%) at 36 months. HBV reactivation occurred in 1/45 (2.2%) patients at 12 months, with no new reactivation thereafter. Median ALT declined from 38 (8-2601) U/L at baseline to 24 (6-575) at 6 months, 20 (7-238) at 12 months, 16 (5-64) at 24 months, and 18 (6-98) U/L at 36 months; ALT normalization rates were 40/51 (78.4%), 43/51 (84.3%), 37/44 (84.1%), and 17/19 (89.5%) across follow-up, respectively. Median creatinine changed from 66 (38-111) µmol/L at baseline to 72 (38-208), 78 (45-197), 78 (35-176), and 65 (38-137) µmol/L, suggesting overall renal stability during long-term treatment. **Conclusion:** In liver transplant recipients with HBV infection, TAF provided durable prophylactic efficacy with a low HBV reactivation rate, progressive HBsAg clearance, improved ALT profiles, and stable renal function over 36 months, supporting both its antiviral effectiveness and long-term safety in this population.

Table 1. Baseline Characteristics of Liver Transplant Recipients (N=51)

Variable	Overall (N=51)
Demographics	
Age, years	49 (27-65)
Male, n (%)	47 (92.2)
BMI, kg/m²	23.6 (17.6-32.1)
Comorbidities, n (%)	
None	35 (68.6)
Hypertension	9 (17.6)
Diabetes mellitus	6 (11.8)
Biochemical Parameters	
ALT, U/L	38 (8-2601)
AST, U/L	50 (21-4314)
Albumin, g/L	32.4 (21.6-48.4)
Total bilirubin, µmol/L	51.5 (6.7-622.8)
Creatinine, µmol/L	66 (38-111)
Baseline Virological Markers	
HBV DNA undetectable (<100 IU/mL), n (%)	13 (25.5)
HBV DNA in detectable cases, log_{10} IU/mL	3.2 (3.1-4.2)
HBsAg, log_{10}IU/mL	2.3 (0.0-3.9)

Disclosures: Yuanmei Che:Nothing to Disclose, Jiaqi Zhang:Nothing to Disclose, Biao Wang:Nothing to Disclose, Xinyu Yang:Nothing to Disclose, Qinglin Ma: Nothing to Disclose.

4098 | VIROLOGICAL AND BIOCHEMICAL RESPONSES OF PROLONGED COMBINATION THERAPY WITH BULEVIRTIDE AND PEGYLATED INTERFERON FOR 120 WEEKS IN CHRONIC HEPATITIS D PATIENTS WITH ADVANCED FIBROSIS/CIRRHOSIS: INTERIM RESULTS FROM SEE-D TRIAL AT 120 WEEKS

Soo Aleman[1] Habiba Kamal Khodir Habiba Kamal[1] Katarina Århem[1] Emmanuel Zavalis[1] Annika Olsson[1] Niklas Björkström[2] Karin Lindahl[3], [1]1Dept of Infectious Diseases, Karolinska University Hospital/Karolinska Institutet, Stockholm, Swede, [2]4Dept of Clinical Microbiology, Karolinska University Hospital/Karolinska Institutet, Stockholm, Swe, [3]1Dept of Infectious Diseases, Karolinska University Hospital/Karolinska Institutet, Stockholm

Background: In MYR301 with BLV monotherapy, 90% of patients who achieved continuously undetectable HDV RNA for at least 72 weeks at w144 maintained undetectable HDV RNA off-therapy, this supports continuously undetectable HDV RNA duration as a surrogate for durable virological response. However, clinical trial data on extended combination therapy beyond 96 weeks remain limited. The SEE-D study evaluates the efficacy of a 96-week combination regimen of BLV and pegIFN followed by BLV monotherapy, here we present interim results at w120. **Methods:** Thirty-one patients with chronic hepatitis D and advanced fibrosis or cirrhosis were treated in the SEE-D clinical trial at Karolinska University Hospital, Sweden. Therapy consisted of BLV 2 mg and pegIFN alfa-2a 180 µg for the first 48 weeks followed by 135 µg for the subsequent 48 weeks, together with nucleos(t)ide analogues. HDV RNA was quantified using the RoboGene HDV RNA Quantification Kit 2.0 (lower limit of detection 6 IU/mL). HBsAg responses were classified as: responder ($\geq$2 log decrease or $<$200 IU/mL), partial responder ($\geq$1 to $<$2 log decrease), and non-responder ($<$1 log decrease). **Results:** Baseline characteristics were mean age 44.6 ($\pm$8.6) years, 58.1% men, 87.1% Asian, 70.9% IFN-experienced; median liver stiffness 12.8 kPa (IQR 4.4), median HDV RNA 5.1 log_{10} IU/mL (IQR 1.4), and median HBsAg 3.9 log_{10} IU/mL (IQR 0.4). In the intention-to-treat (ITT) analysis, undetectable HDV RNA was achieved in 76.0% (19/25) at w84, 75.9% (22/29) at w96 and 85.7% (12/14) at w120. In the per-protocol (PP) analysis (excluding two patients who were lost to follow-up), undetectable HDV RNA was achieved in 82.6% (19/23) at w84, in 81.5% (22/27) at w96 and in 100% (12/12) at w120. By w96, the median duration of sustained undetectable HDV RNA was 60 weeks (IQR 51–72),

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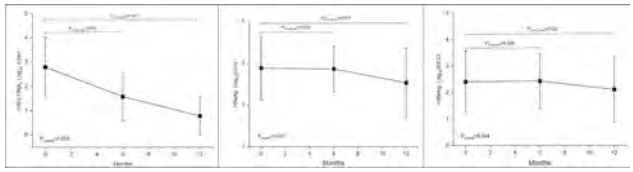
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with 72.4% (21/29) maintaining undetectable levels for ≥48 weeks. In PP analysis, abnormal ALT decreased from 77.4% (24/31) at baseline to 21.4% (6/28) at w72, 28.6% (8/28) at w96 and 7.7% (1/13) at w120. In PP analysis of HBsAg, 14.8% (4/27) were responders and 3.7% (1/27) were partial responders at w96; corresponding figures at w120 were 15.4% (2/13) and none (0/13), respectively. The median HBsAg decline was 0.2 $\log_{10}$ (IQR 0.5) IU/mL at w96 with three (11.1%) achieving HBsAg level <20 IU/mL at this time point, and one patient achieved HBsAg loss. **Conclusion:** In the SEE-D trial, BLV plus prolonged pegIFN combination therapy resulted in high rates of continuously undetectable HDV RNA for ≥60 weeks by w120. These findings support the use of extended pegIFN in combination with BLV when aiming for finite therapy.
Disclosures: Soo Aleman:Nothing to Disclose, Habiba Kamal Khodir Habiba Kamal:Nothing to Disclose, Katarina Århem:Nothing to Disclose, Emmanuel Zavalis:Nothing to Disclose, Annika Olsson:Nothing to Disclose, Niklas Björkström:Nothing to Disclose, Karin Lindahl:Nothing to Disclose.

4099 | REDUCTION OF SERUM HBV DNA BY TENOFOVIR ALAFENAMIDE IN PAEDIATRIC CHRONIC HEPATITIS B PATIENTS SWITCHED FROM ENTECAVIR: AN EXPLORATORY STUDY

Jie Zheng[1] Jia Wang[2] Yage Zhu[3] Lei Shi[3] Tianyan Chen[3], [1]First Affiliated Hospital of Xi'an Jiaotong University, [2]The Eighth Hospital of Xi'an, [3]The First Affiliated Hospital of Xi'an Jiaotong University

Background: Globally, an estimated 46.5 million children and adolescents suffered from chronic hepatitis B (CHB) as of 2019. Current clinical guidelines recommend potent antiviral agents with high genetic barrier to resistance for pediatric CHB, including entecavir (ETV), tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide fumarate (TAF). Previous research showed that the 12-month HBV DNA undetectable rate was about 78% with ETV monotherapy, indicating that around 20% of these patients still had detectable serum HBV DNA after treatment. Studies in adult CHB patients have demonstrated that switching from ETV to TAF remained effective in terms of HBV suppression. Limited data were reported for switching from ETV to TAF in children and adolescents. The study was to explore whether TAF could significantly reduce serum HBV DNA in pediatric CHB patients switched from ETV. **Methods:** This is a retrospective cohort study. Twelve CHB children switched from ETV to TAF monotherapy were enrolled between 2019 and 2025. All of the children were between 12 and 18 years old at the baseline (time of switching to TAF) and had been on ETV for at least 12 months. Serum HBV DNA, HBsAg and HBeAg were log transformed prior to the analysis. Means+/-standard deviations were reported for the continuous variables and the count numbers (percentages) were reported for the categorical variables. The change in serum HBV DNA, HBsAg, HBeAg and ALT were tested by using Repeated Measures Analysis of Variance (ANOVA). **Results:** Twelve CHB children switched from ETV to TAF monotherapy were analyzed with the average age at TAF treatment 13.1+/-1.4 years old. Five (41.7%) out of the 12 CHB children were female. Ten of the 12 patients switched from ETV to TAF due to inadequate therapeutic response to ETV, and their serum HBV DNA were all positive at baseline (the time of TAF treatment). The median time on ETV was 27.2 (Interquartile range [IQR]: 18.0, 39.3) months. The median time patients received TAF treatment was 16.8 (IQR: 8.0, 28.8) months. Baseline virological biomarkers were 2.79+/-1.23 Log10 IU/ml for serum HBV DNA, 3.88+/-0.76 Log10 IU/ml for HBsAg and 2.41 +/-1.16 Log10 S/CO for HBeAg. Baseline ALT was 34.6 +/-33.8 U/L, two children had ALT greater than 40 U/L at baseline. After switching to TAF, serum HBV DNA decreased significantly over time (baseline: 2.79 +/-1.23, 6 months:1.58+/-0.99, 12 months: 0.78+/-0.78 Log10 IU/ml, overall P value = 0.003). HBsAg (baseline: 3.88+/-0.76, 6 months:3.86+/-0.55, 12 months: 3.53 +/-0.83 Log10 IU/ml,overall P value = 0.023) and HBeAg (baseline:2.41+/-1.16, 6 months: 2.44+/-1.03, 12 months: 2.12+/-1.24 Log10 S/CO,overall P value = 0.004) decreased significantly as well. ALT was not found significantly changed over time. **Conclusion:** Switching from ETV to TAF monotherapy could reduce serum HBV DNA significantly among children with CHB. TAF could be a promising alternative particularly for those with inadequate response to ETV.



Disclosures: Jie Zheng:Nothing to Disclose, Jia Wang: Nothing to Disclose, Yage Zhu:Nothing to Disclose, Lei Shi:Nothing to Disclose, Tianyan Chen:Nothing to Disclose.

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4100 | RESMETIROM IN PATIENTS WITH MASH AND CHRONIC HEPATITIS B VIRUS INFECTION: REAL-WORLD SAFETY AND HEPATIC BIOMARKER RESPONSE

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Background: Data on resmetirom use in patients with concomitant metabolic dysfunction-associated steatohepatitis (MASH) and chronic hepatitis B virus infection (CHB) are limited because chronic viral hepatitis was excluded from phase 3 resmetirom trials. We evaluated hepatic biomarker trajectories and safety after resmetirom initiation in MASH patients with EHR-defined CHB versus HBV-negative controls. **Methods:** Adults with MASH initiating resmetirom were identified in the TriNetX Research Network of 109 healthcare organizations. CHB was defined by chronic HBV diagnosis and/or HBV serologic evidence, including HBsAg positivity; HBV-negative controls required HBsAg negativity and no HBV diagnosis. Exclusions included acute HBV, hepatitis C, autoimmune, cholestatic, alcohol-related liver disease, baseline cirrhosis or hepatic decompensation, hepatocellular carcinoma, and liver transplant. Index was first resmetirom exposure. Laboratory values were assessed at baseline (-183 to -1 days) and days 1-90, 91-180, and 181-365. Outcomes through 365 days were compared before and after 1:1 propensity-score matching on demographics, comorbidities, medications, and laboratory values. TriNetX-generated p values were used for comparisons. **Results:** The unmatched cohort included 36 CHB+ and 592 HBV-negative patients; 31 per group remained after matching. Before matching, CHB+ patients had slightly higher mean age but the same median age versus HBV-negative patients (60.4 ± 9.8 vs 57.4 ± 14.1 years; median 59 vs 59) and were more often male (63.9% vs 40.4%). Baseline ALT (69.6 ± 67.3 vs 66.9 ± 68.6 U/L) and AST (51.0 ± 49.8 vs 51.0 ± 53.3 U/L) were similar. In CHB+, ALT/AST were 68.2 ± 68.0/46.8 ± 41.7 at days 1-90, 69.5 ± 56.5/54.3 ± 37.3 at days 91-180, and 38.1 ± 22.8/32.1 ± 13.0 U/L at days 181-365; albumin and platelets remained stable. Across days 1-365, ALT and AST did not differ between CHB+ and HBV-negative patients (ALT 47.0 ± 30.8 vs 50.8 ± 42.3, $p = 0.637$; AST 36.5 ± 16.3 vs 40.6 ± 30.6, $p = 0.480$). ALT normalization (≤ 30 U/L) occurred in 30.6% versus 26.0% ($p = 0.548$), and ALT ≤ 46 U/L occurred in 55.6% versus 46.6% ($p = 0.297$). After matching, ALT normalization was 35.5% in both groups, and ALT ≤ 46 U/L was 58.1% versus 64.5% ($p = 0.602$). In CHB+, no coded drug-induced liver injury/toxic liver disease, pancreatitis, acute kidney injury, atrial fibrillation/flutter, hepatic decompensation, or death occurred through 365 days. **Conclusion:** In this small real-world cohort, resmetirom-treated MASH patients with EHR-defined CHB had late aminotransferase improvement, stable hepatic synthetic markers, and outcomes comparable to HBV− controls. Missing HBV virologic, serologic, and treatment data limit interpretation and support prospective validation in confirmed CHB populations.

Disclosures: Mohammad Alabbas:Nothing to Disclose, Kenan Abou Chaer:Nothing to Disclose, Omar Sims:Nothing to Disclose, Walaa Mahmoud:Nothing to Disclose, Naim Alkhouri:Madrigal: Speaking and Teaching, Novo Nordisk: Consulting, Novo Nordisk: Grant/Research Support, Corcept: Grant/Research Support, Echosens: Speaking and Teaching, Perspectum: Consultant, Cima: Consultant, Fibronostics: Consultant, 89Bio: Grant/Research Support, Inventiva: Grant/Research Support, Merck: Grant/Research Support, Pfizer: Grant/Research Support, Ipsen: Speaking and Teaching, Intercept: Speaking and Teaching, Madrigal: Consulting, Research Funding, Novo Nordisk: Consulting, Research Funding, Inventiva: Research Funding, Boehringer Ingelheim: Consulting, Research Funding, Corcept: Research Funding, Ipsen: Consulting, Research Funding, Gliead: Consulting, Research Funding, Speaking, Perspectum: Consulting, Research Funding, Cima: Advisor, 89Bio: Consulting, Research Funding, Arbutus: Grant/Research Support, GSK: Grant/Research Support, Regeneron: Grant/Research Support, AstraZeneka: Grant/Research Support, Madrigal: Grant/Research Support, Akero: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Eli Lilly: Grant/Research Support, Gilead: Grant/Research Support, Galectin: Grant/Research Support, Boston Pharma: Grant/Research Support.

4101 | END-OF-TREATMENT HBCRAG OUTPERFORMS QHBSAG IN PREDICTING CLINICAL RELAPSE AFTER NUCLEOS(T)IDE ANALOGUE CESSATION IN HBEAG-POSITIVE CHRONIC HEPATITIS B

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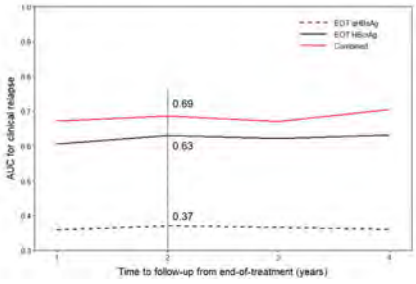
Background: Most studies of HBV viral biomarkers for predicting outcomes after nucleos(t)ide analogue cessation have included mixed pretreatment HBeAg-positive and HBeAg-negative populations. Data remain limited for patients with pretreatment HBeAg-positive chronic hepatitis B. We therefore evaluated the relative

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predictive value of end-of-treatment quantitative HBsAg and hepatitis B core-related antigen for off-therapy clinical relapse after Nuc cessation in this population. **Methods:** HBeAg-positive patients who stopped Nuc therapy per APASL criteria (HBV DNA undetectable ≥1 year; HBeAg loss for ≥1 year) with available EOT qHBsAg and HBcrAg data were analyzed. were analyzed. Clinical relapse (CR) was defined as ALT ≥2 times upper limit of normal and HBV DNA ≥2000 IU/mL. Time-dependent AUCs, cumulative incidence functions, Fine-Gray regression, and smoothed hazard functions evaluated predictive performance and biomarker-outcome associations; retreatment was treated as a competing risk. **Results:** Among 159 HBeAg-positive CHB patients who discontinued Nuc therapy, the mean age was 45 years, 74% were male, 22% had cirrhosis, and the median follow-up was 5.4 years. Median EOT qHBsAg and HBcrAg levels were 2.9 $\log_{10}$ IU/mL and 4.6 $\log_{10}$ U/mL, respectively. EOT HBcrAg outperformed qHBsAg for 2-year CR prediction, with AUCs of 0.63 versus 0.37, respectively; $p<0.001$. Adding qHBsAg to HBcrAg did not significantly improve discrimination beyond HBcrAg alone. In multivariable Fine-Gray analysis, EOT HBcrAg ≥4.5 $\log_{10}$ U/mL independently predicted CR, with an adjusted SHR of 2.71; 95% CI, 1.59–4.63; $p<0.001$, whereas EOT qHBsAg ≥3 $\log_{10}$ IU/mL did not. Patients with EOT HBcrAg ≥4.5 $\log_{10}$ U/mL had higher 2-year cumulative CR incidence than those with HBcrAg <4.5 $\log_{10}$ U/mL: 73% versus 48%; Gray's $p=0.004$. Smoothed hazard curves showed sustained late CR hazard beyond 6 months in patients with HBcrAg ≥4.5 $\log_{10}$ U/mL, and HBeAg seroreversion further identified the highest-risk subgroup. **Conclusion:** In HBeAg-positive CHB patients stopping Nuc therapy, EOT HBcrAg outperformed qHBsAg in predicting off-therapy clinical relapse and identified sustained late relapse risk beyond 6 months. Patients with EOT HBcrAg ≥4.5 $\log_{10}$ U/mL may warrant intensified off-therapy surveillance, particularly if HBeAg seroreversion occurs during follow-up.

Figure. Time dependent Area Under the ROC Curve (AUC) for clinical relapse in HBcrAg and qHBsAg at end-of-treatment (EOT)



Disclosures: Yen-Chun Liu:Nothing to Disclose, CHIEN-WEI PENG:Nothing to Disclose, Rachel Wen-Juei Jeng: GSK: Advisor, Gilead: Advisor, BMS: Speaking and Teaching, Roche: Advisor, Rong-Nan Chien:Nothing to Disclose, Yun-Fan Liaw:Nothing to Disclose.

4102 | CONTINUOUS OR CYCLICAL PEGINTERFERON ALFA-2B TREATMENT INDUCES COMPARABLE HBSAG LOSS IN INACTIVE HEPATITIS B VIRUS CARRIERS

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Background: Inactive hepatitis B virus (HBV) carriers (IHCs) exist a higher risk of hepatocellular carcinoma and liver-related mortality compared to individuals without chronic HBV infection. Peginterferon alfa (PegIFNα) therapy enables a significant proportion of IHCs to clear HBsAg, thereby reducing the risk of long-term adverse events. This study aimed to compare the efficacy of continuous versus cyclical PegIFNα-2b regimens in IHCs. **Methods:** In this randomized controlled trial, IHCs (defined as chronic HBV-infected individuals with HBV DNA < 2000 IU/mL, HBeAg negativity, HBsAg < 1000 IU/mL, and normal alanine aminotransferase levels) aged 18 to 65 years were randomly assigned to receive either continuous or cyclical PegIFNα-2b (Pegbing®, Xiamen Amoytop Biotech Co., Ltd.) therapy. The continuous group received PegIFNα-2b 180 μg weekly throughout the study, whereas the cyclical group received PegIFNα-2b 180 μg weekly for 8 weeks, followed by a 4-week pause, repeated in 12-week cycles. The treatment period for both groups did not exceed 96 weeks. **Results:** A total of 77 IHCs were included, comprising 37 in the PegIFNα-2b continuous group and 40 in the PegIFNα-2b cyclical group. At baseline, there were no significant differences between the two groups in median age (39 [36, 46] vs. 42 [37, 50] years, $p=0.211$), proportion of males (54.1% vs. 62.5%, $p=0.603$), HBsAg levels (1.85 [1.06, 2.37] vs. 1.94 [1.21, 2.53] $\log_{10}$ IU/mL, $p=0.456$), proportion of patients with HBsAg ≤ 100 IU/mL (56.8% vs. 55.0%, $p=1.000$), HBV DNA negativity rate (54.1% vs. 40%, $p=0.314$), and ALT levels (23.4 [16.5, 33.3] vs. 22.4 [17.9, 30.7] U/L, $p=0.456$). Sixty-two IHCs completed 24 weeks of treatment. By week 24, the continuous and cyclical groups showed comparable HBsAg loss rates (32.1% [9/28] vs. 20.6% [7/34], $p=0.457$), HBsAg seroconversion rates (18.2% [4/22] vs. 13.8% [4/29], $p=0.970$), and HBV DNA undetectable rates (80% [12/15] vs. 100% [21/21], $p=0.126$), although the median HBsAg decline was higher in the continuous group (1.39 [1.04, 2.25] vs. 0.58 [0.15, 1.39] $\log_{10}$ IU/mL,

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$p = 0.005$). Stratified analysis by baseline HBsAg levels revealed that the continuous group had numerically higher, but not statistically significant, HBsAg loss rates than the cyclical group (baseline HBsAg ≤100 IU/mL: 43.8% vs. 33.3%, $p = 0.787$; >100 IU/mL: 16.7% vs. 6.2%, $p = 0.791$). At week 24, the median ALT and AST levels in the cyclical group were 33.9 (22.4, 47.0) and 29.3 (23.2, 40.2) U/L, respectively, which were significantly lower than those in the continuous group (58.6 [42.5, 94.9] and 43 [39.6, 74.7] U/L, respectively, all $p < 0.001$). **Conclusion:** In IHCs, cyclical administration of PegIFNα-2b produced comparable efficacy and fewer hepatic biochemical abnormalities than continuous administration, supporting its potential as a valuable strategy for wider clinical implementation.

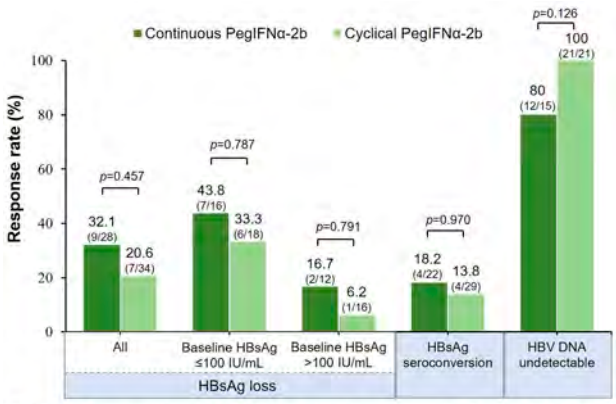


Figure 1. Response rate at week 24 following continuous or cyclical PegIFNα-2b treatment.

Disclosures: huibin ning:Nothing to Disclose, Jia Shang:Nothing to Disclose, Huiming Jin:Nothing to Disclose, Kuan Li:Nothing to Disclose, Zhen Peng: Nothing to Disclose.

4103 | TENOFOVIR ALAFENAMIDE IMPROVES ALT AND HCC RISK STRATIFICATION IN CHRONIC HEPATITIS B WITH NORMAL OR MILDLY ELEVATED ALT

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Background: Guidelines for antiviral treatment initiation in non-cirrhotic chronic hepatitis B (CHB) patients with HBV DNA level > 2,000 IU/mL, but with normal or mildly elevated alanine aminotransferase (ALT) remain controversial. We evaluated whether tenofovir alafenamide (TAF) improves ALT normalization and attenuates hepatocellular carcinoma (HCC) risk scores in this population. **Methods:** This interim analysis of an ongoing prospective single-center cohort study included non-cirrhotic CHB patients with HBV DNA level > 2,000 IU/mL, but with normal or mildly elevated ALT. Patients were classified into those who initiated TAF (antiviral treatment [AVT] group, n = 106) and those under untreated observation (control group, n = 32). At 1-year of follow-up, we assessed longitudinal ALT changes, ALT normalization rates by AASLD, EASL and KASL criteria, and HCC risk score transitions using HCC risk models including REACH-B and CU-HCC. **Results:** Over 1 year, the AVT group achieved a significant ALT reduction (median 24.5→21.0 U/L), while controls remained unchanged (26.0→26.5 U/L; interaction $p = 0.003$). AVT significantly improved ALT normalization rates by AASLD (64.2%→80.2%, $p = 0.002$) and KASL (71.7%→85.8%, $p = 0.003$), exhibiting divergent trends compared to the unchanged controls (Group×Time $p = 0.007$ and $p = 0.001$). For HCC risk stratification, category improvements were more frequent in AVT versus controls by REACH-B (14.2% vs. 3.1%) and CU-HCC (14.2% vs. 6.2%). Furthermore, continuous risk scores declined significantly faster in AVT for both models (interaction $p = 0.004$ and $p = 0.022$), whereas PAGE-B and aMAP showed no between-group differences ($p > 0.05$). **Conclusion:** TAF initiation in grey-zone non-cirrhotic CHB patients significantly improved ALT levels and achieved greater attenuation in HCC risk stratification compared to untreated controls, supporting the beneficial efficacy of early initiation of AVT in this population.

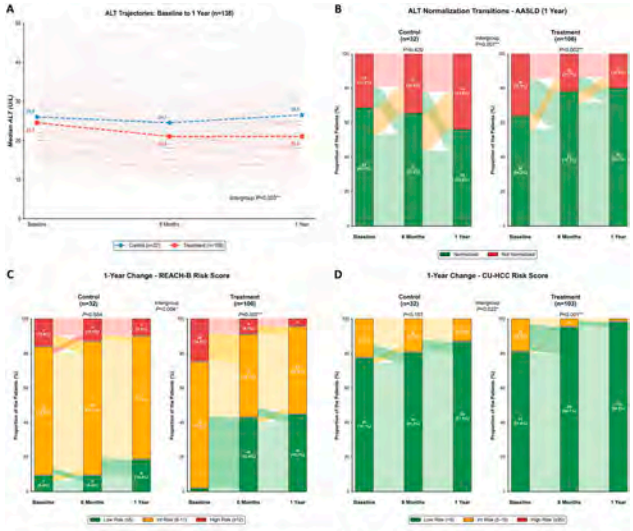


Figure 1. Longitudinal changes in ALT levels and HCC risk scores over 1 year in CHB patients with normal or mildly elevated ALT. (A) Individual patient ALT trajectories from baseline to 1 year in the antiviral treatment (AVT) and untreated control groups. (B) Transitions in ALT normalization status evaluated according to the AASLD criteria. Changes in HCC risk stratification categories (Improved, Stable, or Worsened) over 1 year assessed by the (C) REACH-B and (D) CU-HCC models. The AVT group exhibited significantly higher rates of ALT normalization and HCC risk category improvement compared to the control group.

Disclosures: Jaehong Jeong:Nothing to Disclose, Dong Yun Kim:Nothing to Disclose, Jae Seung Lee: Nothing to Disclose, Mi Na Kim:Nothing to Disclose, Hye Won Lee:Nothing to Disclose, Beom Kyung Kim: Nothing to Disclose, Jun Yong Park:Nothing to

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4104 | EFFECT OF NUCLEOS(T)IDE ANALOGUES WITH OR WITHOUT PEGINTERFERON ALFA-2B ON 48-WEEK OUTCOMES IN CHRONIC HEPATITIS B PATIENTS WITH HIGH HBSAG LEVEL: PRELIMINARY RESULTS FROM A MULTICENTER, PROSPECTIVE STUDY IN CHINA

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Background: Achieving hepatitis B surface antigen (HBsAg) loss and functional cure in patients with chronic hepatitis B (CHB) remains a significant challenge, particularly in those with high baseline HBsAg > 1500 IU/mL. This study provides evidence on the clinical benefit of a phased strategy by evaluating different antiviral therapies in patients with baseline HBsAg < 5000 IU/mL, particularly those > 1500 IU/mL. **Methods:** This multicenter, prospective, real-world study (the Glocure Project) enrolled CHB patients aged 18–65 years who were nucleos(t)ide analogues (NAs)-experienced or treatment-naïve, with HBsAg ≤ 5000 IU/mL from 12 medical centers in China. Patients were assigned to the NAs monotherapy group or the peginterferon α-2b (PegIFNα-2b) plus NAs group. This preliminary analysis evaluated the dynamic changes in HBsAg levels in both groups after 48 weeks of treatment, focusing on baseline HBsAg 1500 ~ 5000 IU/mL. **Results:** A total of 1230 patients in the PegIFNα-2b +NAs group and 597 patients in the NAs monotherapy group who had completed 48 weeks of treatment. At baseline, the combination group had higher proportion of males (69.9% vs. 64.0%, p = 0.0108), while the mean age (42.4 vs. 45.3 years, p < 0.05), HBsAg levels (3.12 vs. 3.20 $\log_{10}$ IU/mL, p < 0.05), and HBeAg positivity rate (25.45% vs. 32.83%, p = 0.005) were all lower, the HBV DNA levels were comparable (6.18 vs. 6.03 $\log_{10}$ IU/mL, p > 0.05). The proportions of patients with baseline HBsAg < 100, 100~ < 1500, and 1500~5000 IU/mL were 21.5% vs. 13.0%, 44.8% vs. 44.3%, and 33.7% vs. 42.7% respectively. After treatment, the PegIFNα-2b+NAs group showed significantly greater HBsAg reductions from baseline at both week 24 (-0.755 vs. -0.101 $\log_{10}$ IU/mL, p < 0.05) and week 48 (-0.938 vs. -0.167 $\log_{10}$ IU/mL, p < 0.05). In addition, the proportion of patients with HBsAg < 100 IU/mL was significantly higher in the combination group at week 24 (38.3% vs. 14.5%, p < 0.05) and week 48(43.1% vs. 15.3%, p < 0.05). Notably, subgroup analysis with baseline HBsAg 1500 ~ 5000 IU/mL. The baseline HBsAg levels were comparable (3.46 vs. 3.47 $\log_{10}$ IU/mL, p = 0.196). After treatment, the combination group showed greater HBsAg reductions from baseline at week 24 (-0.480 vs. -0.127 $\log_{10}$ IU/mL, p < 0.05) and week 48 (-0.715 vs. -0.196 $\log_{10}$ IU/mL, p < 0.05). At week 48, the combination group had a higher proportion achieving HBsAg < 1500 IU/mL (60.0% vs. 22.4%, p < 0.0001). **Conclusion:** In CHB patients with baseline HBsAg < 5000 IU/mL, PegIFNα-2b+NAs therapy induced greater and faster HBsAg reductions than NAs monotherapy, and more patients reached HBsAg < 1500 IU/mL and HBsAg < 100 IU/mL. These findings support PegIFNα-2b+NAs as a more effective treatment strategy for patients with high HBsAg levels, and may serve as a promising strategy for chronic hepatitis B patients with high HBsAg levels into advantageous populations eligible for clinical cure.

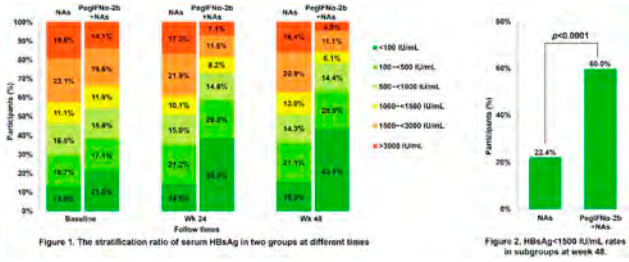


Figure 1. The stratification ratio of serum HBsAg in two groups at different times

Figure 2. HBsAg<1500 IU/mL rates in subgroups at week 48.

Disclosures: Yuemin Nan:Nothing to Disclose, suxian Zhao:Nothing to Disclose, Qing Ye:Nothing to Disclose, Jia Li:Nothing to Disclose, Aihua Gao:Nothing to Disclose, Haifang Cao:Nothing to Disclose, Lijun Chang:Nothing to Disclose, Musong Li:Nothing to Disclose, Qingge Zhang:Nothing to Disclose, Haiyan Kang:Nothing to Disclose, Ying Guo:Nothing to Disclose, Fenxiang Li:Nothing to Disclose, Suling Chen: Nothing to Disclose.

4105 | INCIDENCE AND RISK STRATIFICATION OF HEPATITIS B REACTIVATION IN PATIENTS RECEIVING ANTI-CD38 MONOCLONAL ANTIBODY THERAPY

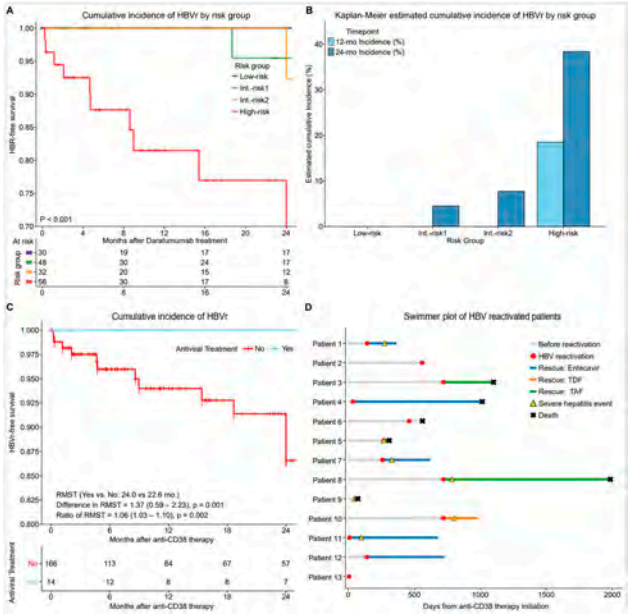
Pil Soo Sung[1], [1]Seoul St Mary's Hospital

Background: The human anti-CD38 monoclonal antibody daratumumab, used for multiple myeloma,

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induces substantial immunosuppression and may increase susceptibility to hepatitis B virus reactivation (HBVr). While reactivation has been documented in anti-HBc–positive individuals, real-world data evaluating the efficacy of prophylactic antiviral therapy and risk-stratification models are limited. **Methods:** We retrospectively analyzed a cohort of 180 anti-HBc–positive, HBsAg-negative patients among 709 multiple myeloma patients treated with daratumumab between 2015 and 2025. Clinical outcomes were compared between patients receiving prophylactic nucleos(t)ide analogue (NA) therapy (n = 14) and those who did not (n = 166). Independent predictors of HBVr were identified using multivariate Cox regression analysis to develop a risk-stratification model. **Results:** The overall incidence of HBVr in the untreated cohort was 7.8% (13/166), categorizing daratumumab as a moderate-risk agent (1–10%) according to the EASL framework. Baseline anti-HBs titers < 100 IU/L and the use of daratumumab as later-line (relapsed/refractory) therapy were identified as independent risk factors. In the high-risk subgroup (possessing both factors), the crude incidence of HBVr was 19.6% (11/56), while the estimated 24-month cumulative incidence approached 40%. No reactivation events were observed in the prophylactic NA group. Severe hepatitis (n = 7) and liver-related mortality (n = 3) occurred exclusively in the untreated group, predominantly among high-risk patients. **Conclusion:** Anti-CD38 therapy is associated with a significant and preventable risk of HBVr, particularly in a high-risk phenotype characterized by low baseline anti-HBs and later-line treatment. Routine NA prophylaxis should be prioritized for this high-risk group to prevent life-threatening liver complications, while intensified monitoring may be considered for intermediate-risk patients.



Disclosures: Pil Soo Sung:Nothing to Disclose.

4106 | RETREATMENT EFFICACY AND OVERALL OUTCOMES IN PATIENTS WITH CHRONIC HEPATITIS B WHO RELAPSED AFTER CLINICAL CURE

Huiling Xiang[1] Jun Li[2] Fei Yan[2] Jing Liang[1] Qing Ye[1], [1]Tianjin University Central Hospital (Tianjin Third Central Hospital), [2]The Third Central Clinical College of Tianjin Medical University

Background: To investigate the clinical efficacy of retreatment in patients with chronic hepatitis B (CHB) who have relapsed after achieving clinical cure; to compare the hepatitis B surface antigen (HBsAg) re-clearance rates among different retreatment regimens; and to analyze the natural course of the disease in patients with multiple relapses and those who have not received treatment. **Methods:** This single-center retrospective cohort study included CHB patients who achieved clinical cure (defined as HBsAg < 0.05 IU/mL, HBV DNA < 20 IU/mL, and normal liver function for ≥ 12 weeks after stopping therapy) and subsequently experienced confirmed relapse (HBsAg and/or HBV DNA re-positivity, with follow-up tests remaining positive 4–12 weeks later) at Tianjin University Central Hospital between January 2017 and June 2025. The relapse rate, relapse patterns, and HBsAg re-clearance after retreatment were analyzed. Retreatment regimens included pegylated interferon alpha-2b (Peg-IFNα-2b) monotherapy or combined with nucleos(t)ide analogs (NAs), and NAs monotherapy. HBsAg re-clearance rates were compared among regimens. Outcomes of patients with multiple relapses or no retreatment were also described. **Results:** A total of 322 clinically cured patients were enrolled; 41 experienced relapse, resulting in a relapse rate of 12.73%, with a median time to relapse of 30.86 weeks after discontinuation of treatment. The predominant type of relapse was HBsAg-positive and HBV DNA-negative (38 cases, accounting for 92.68%). Among the 41 patients who relapsed, 37 received retreatment, while 4 did not. The overall HBsAg re-clearance rate following retreatment was 48.65% (18/37). Among these, the HBsAg re-clearance rate in the Peg-IFNα-2b-based treatment group (27 patients) was 55.56% (15/27), which was significantly higher than the 30.00% (3/10) observed in the NAs monotherapy group (10 patients). Among the 18 patients who achieved HBsAg re-clearance, 83.3% (15/18) were from the Peg-IFNα-2b-based treatment group. Among these 18 patients, 4 subsequently experienced a third relapse, and only 1 achieved re-

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clearance after another round of retreatment. Among the 4 untreated patients, with a median follow-up of 177 weeks, none achieved HBsAg re-clearance, and all maintained low levels of HBsAg and HBV DNA. **Conclusion:** After clinical cure of CHB, the relapse rate was 12.73%. Re-treatment after relapse can still achieve a high rate of HBsAg re-clearance. Regimens based on Peg-IFNα-2b demonstrated a significantly higher rate of HBsAg re-clearance compared to NAs monotherapy, and 83.3% of re-clearance achievers received this regimen. Untreated patients failed to clear HBsAg over a median 3.4-year follow-up, suggesting that clinical cure is unlikely without antiviral therapy. Thus, Peg-IFNα-2b-based retreatment is recommended.

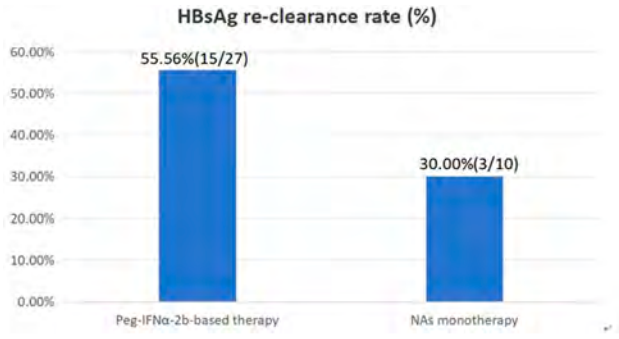


Figure 1. HBsAg Re-clearance Rates in Relapsed CHB Patients by Retreatment Regimen.

Disclosures: Huiling Xiang:Nothing to Disclose, jun Li:Nothing to Disclose, Fei Yan:Nothing to Disclose, Jing Liang:Nothing to Disclose, Qing Ye:Nothing to Disclose.

4107 | IMPACT OF CHRONIC HEPATITIS B COMORBID WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE ON HBSAG RESPONSE AND DISEASE PROGNOSIS

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Background: To investigate the virological and fibrotic characteristics of chronic hepatitis B (CHB) patients with concurrent metabolic dysfunction-associated steatotic liver disease (MASLD), and to analyze the impact of metabolic dysfunction-associated steatohepatitis (MASH) risk stratification on virological and fibrotic indicators, as well as HBsAg response. **Methods:** A total of 1356 CHB patients were retrospectively enrolled, including 889 in the CHB-only group and 467 in the CHB+MASLD group. The CHB+MASLD group was further stratified into no-MASH, suspected-MASH, and high-risk MASH subgroups based on the FibroScan-AST (FAST) scores. Among all patients, 626 (383 in the CHB-only group and 243 in the CHB +MASLD group) had follow-up data and were included in the HBsAg response analysis. Antiviral therapies during follow-up included nucleos(t)ide analogues (NAs) monotherapy, peginterferon alpha-2b (PegIFNα-2b, Pegbing®, Xiamen Amoytop Biotech Co., Ltd.) monotherapy, PegIFNα-2b plus NAs therapy, and no therapy. Data on virology, liver function, complete blood count, transient elastography, and noninvasive fibrosis markers were collected. Inverse probability of treatment weighting (IPTW) was applied to balance baseline differences between groups, and a Spearman correlation analysis was performed to assess correlations. A Cox proportional hazards regression model was used to analyze the predictors of HBsAg response. **Results:** After adjustment by IPTW, patients in the CHB+MASLD group exhibited a higher BMI (25.83 vs. 24.73 kg/m², P = 0.026) and lower HBsAg (3.27 vs. 3.42 $\log_{10}$ IU/mL, P = 0.009), HBeAg (-0.94 vs. -0.80 $\log_{10}$ S/CO, P < 0.001), and pgRNA (1.94 vs. 2.60 $\log_{10}$ copies/mL, P = 0.009) levels compared to the CHB-only group. Regarding fibrotic characteristics, patients in the CHB+MASLD group had higher liver stiffness measurement (LSM), fibrosis-4 (FIB-4), and AST-to-platelet ratio index (APRI) values than those in the CHB-only group (all P < 0.05). In the CHB+MASLD group, an increased MASH risk was associated with elevated liver injury and fibrosis markers, as well as lower HBsAg levels (P < 0.001). The FAST score showed a weak negative correlation with HBsAg levels (r = –0.176, P < 0.001). Follow-up analysis revealed that HBsAg response rates at all time points were higher in the high-risk MASH subgroup than in the CHB-only group and the no-MASH subgroup (P < 0.001). Multivariate Cox regression analysis identified lower baseline HBsAg levels (HR = 0.697, P < 0.001) and higher MASH risk stratification (HR = 3.930, P < 0.001) as independent predictors of higher HBsAg response rates (Table 1). **Conclusion:** Patients with CHB combined with MASLD exhibit lower virological markers but a heavier fibrotic burden. An increased risk of MASH is associated with liver injury and fibrosis progression. Baseline HBsAg level and MASH risk stratification are independent predictors of HBsAg response.

Table 1. Univariate and multivariate Cox regression analyses of HBsAg response.

Variable	Univariate analysis			Multivariate analysis		
	HR	95%CI	*P* value	HR	95%CI	*P* value
Age, years	0.997	0.983–1.010	0.638			
Male, %	1.191	0.851–1.666	0.309			
BMI, kg/m²	1.041	0.991–1.094	0.112			
Baseline HBsAg, $\log_{10}$ IU/mL	0.751	0.671–0.841	<0.001***	0.697	0.595–0.818	<0.001***
Baseline HBeAg, $\log_{10}$ S/CO	0.904	0.800–1.021	0.104			
Baseline HBV DNA, $\log_{10}$ IU/mL	1.047	0.990–1.107	0.107			
Baseline pgRNA, $\log_{10}$ copies/mL	0.921	0.869–0.976	0.006**	0.936	0.860–1.018	0.121
Baseline ALT, U/L	1.001	1.000–1.002	0.011*	1.001	0.995–1.008	0.663
Baseline AST, U/L	1.001	1.000–1.003	0.036*	0.999	0.994–1.007	0.780
Patient Group						
CHB-only	1	-	-	1	-	-
No-MASH	0.851	0.560–1.293	0.449			
Suspected-MASH	2.169	1.443–3.260	<0.001***	3.399	1.909–6.050	<0.001***
High-risk MASH	2.979	1.917–4.628	<0.001***	3.930	1.758–8.782	<0.001***
LSM, kPa	0.999	0.978–1.021	0.939			

Note: HR, hazard ratio; 95% CI, 95% confidence interval. *P<0.05, **P<0.01, ***P<0.001.

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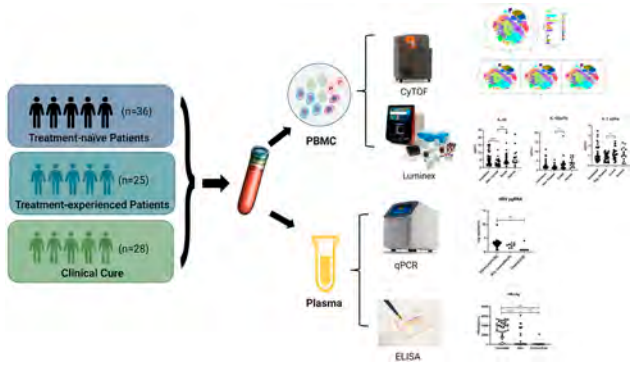
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Disclosures: Guiqun Huang:Nothing to Disclose, Guanghui Ren:Nothing to Disclose, Shi Yin:Nothing to Disclose, Ying Zhu:Nothing to Disclose.

4108 | CHARACTERISTICS OF CIRCULATING IMMUNE CELLS AND CYTOKINE PROFILES IN PEDIATRIC PATIENTS WITH CHRONIC HEPATITIS B UNDERGOING ANTIVIRAL THERAPY

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Background: Hepatitis B surface antigen (HBsAg) loss, or functional cure (FC), is the optimal therapeutic goal for chronic hepatitis B (CHB). However, the immunological landscape associated with FC in pediatric patients remain poorly defined. This study aimed to comprehensively characterize the circulating immune cell states, serum cytokine profiles, and viral markers in pediatric CHB patients to elucidate the mechanisms underlying FC. **Methods:** We performed high-dimensional mass cytometry (CyTOF) on PBMCs from 89 pediatric CHB patients (aged 3–18 years), categorized into: treatment-naïve (n = 36), NAs-treated (n = 25), and FC patients (n = 28, treated with NAs + peginterferon alpha-2b [PegIFNα-2b, Pegbing®, Xiamen Amoytop Biotech Co., Ltd.]). Serum cytokines/chemokines were measured via multiplex assays. Viral activity was assessed by quantifying HBVcrAg and HBVpgRNA levels using ELISA and qPCR, respectively. **Results:** Unsupervised analysis revealed a reconfigured circulating immune landscape in pediatric CHB patients who achieved FC, distinct from both treatment-naïve and NAs-treated patients without achieving FC. Viral marker analysis confirmed that FC patients achieved superior viral suppression compared to the other groups: HBcrAg levels were significantly lower in the FC group (123.6 ± 79.03 U/L) compared to NAs-treated (1341 ± 375.2 U/L) and treatment-naïve patients (3450 ± 263.1 U/L). Similarly, HBV pgRNA levels were significantly lower in FC patients (1.846 ± 0.3573 copies/μL) compared to those in the NAs-treated (198.3 ± 98.91 copies/μL) and treatment-naïve groups (1874 ± 468.9 copies/μL). Immunologically, FC patients exhibited a unique signature characterized by the expansion of NKT and TCRγδ+ T cells and a distinct chemokine receptor profile. Furthermore, systemic cytokine analysis showed that FC patients displayed a coordinated regulatory network, with significantly modulated pro-inflammatory cytokines and upregulated anti-inflammatory/regulatory factors (IL-10, IL-1Ra, IL-7, IL-12p70) compared to the untreated or NAs-treated groups. **Conclusion:** Pediatric CHB patients achieving FC exhibit profound viral suppression alongside a unique circulating immune profile, defined by T-cell functional reconstitution and a balanced regulatory cytokine network. These findings suggest that the synergistic effect of PegIFNα-2b and NAs facilitates both deep viral clearance and immune restoration, providing a strong rationale for immunotherapeutic strategies in pediatric CHB.



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4109 | SAFETY AND EFFICACY OF TENOFOVIR DISOPROXIL FUMARATE REGIMEN FROM PRECONCEPTION ON PREGNANT WOMEN WITH CHRONIC HEPATITIS B: A PROSPECTIVE COHORT STUDY

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Background: Antiviral prophylaxis in late pregnancy reduces hepatitis B virus (HBV) mother-to-child transmission (MTCT), but data on preconception-initiated tenofovir disoproxil fumarate (TDF) throughout pregnancy for chronic hepatitis B (CHB) relatively remain limited. This study evaluated the safety and efficacy of this strategy in well-matched cohorts. **Methods:** This prospective cohort study enrolled 153 pregnant women with chronic hepatitis B infection (2017–2020). Eight-six received TDF from preconception because of CHB and throughout pregnancy (the treatment group). Sixty-seven untreated controls had normal alanine transaminase (ALT) and HBV DNA $< 2\times10^5$ IU/mL during

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pregnancy (the control group). Groups were baseline-balanced in age and ALT. All infants received standard immunoprophylaxis and were followed ≥7 months postpartum. Primary outcomes included maternal virologic/biochemical control, pregnancy complications, and infant safety and HBV infection status. **Results:** Maternal age and ALT levels were comparable at baseline between groups. Antiviral treatment was well-tolerated in all mothers of the treatment group. Maternal HBV DNA levels were significantly lower in the treatment group both at delivery and 3 months postpartum ($P = 0.001$), compared with that of the control group. Maternal ALT was slightly higher in the treatment group at delivery ($P = 0.010$) but comparable between groups at 3 months postpartum ($P = 0.185$). There was no a statistically significant difference in pregnancy complications, gestational age, or delivery mode between the two groups, respectively ($P > 0.05$). Birth weight, birth length, and congenital anomaly rates were similar between the two groups ($P > 0.05$), respectively. None of infants in the two groups was positive for HBsAg at 7 months of age. **Conclusion:** It was safe and effective for pregnant women with CHB and their infants to take TDF from pre-conception to the entire pregnancy.

Maternal characteristics.

	Antiviral therapy group n=86	Control group n=67	χ^2 or t or Z value	P value
Maternal characteristics				
Age (years), mean ± SD	31.0±3.9	30.8±4.0	0.297	0.767
HBV DNA, log10 IU/mL	2.38±0.91	2.67±0.77	2.342	0.019
HBV DNA level < 10^5 IU/ml, n (%)	73(93.6)	45(100)	3.007	0.098
HBV DNA level < 10^2 IU/ml, n (%)	52(66.7)	16(35.6)	11.173	0.001
Normal ALT levels, n (%)	80(98.8)	61(96.8)	0.654	0.581

IVF-ET, in vitro fertilization and embryo transfer

Disclosures: Liyang Zhou:Nothing to Disclose, Xueting Ou:Nothing to Disclose, Panpan Zhai:Nothing to Disclose, Yinxing Lin:Nothing to Disclose, Bing Situ: Nothing to Disclose, Jun Huang:Nothing to Disclose, Xing-Fei Pan:Nothing to Disclose.

4110 | OUTCOME OF CHRONIC HEPATITIS B PATIENTS WITH HIGH HBSAG LEVEL AT 52 WEEKS AFTER PEGINTERFERON ALPHA-2B AND NUCLEOS(T)IDE ANALOGS COMBINATION THERAPY

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Background: Chronic hepatitis B (CHB) patients with HBV DNA < LLOQ, HBeAg negative and HBsAg < 1500 IU/mL after prior nucleos(t)ide analogs (NAs) treatment were the preferred population for clinical cure (PPCC). Nucleotides with add-on interferon treatment (NUC-IFN) provide significantly higher rates of HBsAg loss in CHB patients. The purpose of this study aims to observe the efficacy of NAs combined with PegIFNα-2b in treating CHB patients with HBsAg > 1500 IU/mL (Non-preferred population for clinical cure, NPPCC). **Methods:** The CREATED EXCELLENT study (ChiCTR2400081073) is a multi-center, prospective, non-randomized, open-label, positive-controlled study. CHB patients with NAs treated for ≥3 months and HBsAg > 1500 IU/mL were enrolled and divided into two groups. The NAs monotherapy group continued to receive their original NAs (ETV/TDF/TAF/TMF) treatment, while the PegIFNα-2b+NAs group received PegIFNα-2b (180 μg/week, Pegbing®, Xiamen Amoytop Biotech Co., Ltd.) subcutaneously in addition to NAs. The total treatment period was 52 weeks, and all participants were followed up for 24 weeks after the end of treatment (EOT). Primary efficacy outcome 1) the proportion of patients with HBsAg < 1500 IU/mL; 2) the reduction in HBsAg levels from baseline. **Results:** 682 patients were screened, 308 patients failed to meet enrollment criteria, and 373 were enrolled. Among the enrolled patients, 187 patients received NAs monotherapy;186 patients received PegIFNα-2b+NAs therapy. In PegIFNα-2b+NAs treated group, there are 9 patients reached HBsAg loss at EOT, 4 patents HBsAg seroconversion; In NAs monotherapy group, there are 2 patients reached HBsAg loss, 1 patients HBsAg seroconversion at EOT. The baseline average HBsAg level was 18767.23 ± 5623.33 IU/mL in NAs group and was 17346.91IU/mL ($P > 0.05$) in PegIFNα-2b+NAs group. At EOT, there are 6963.92 ± 1127.89 IU/mL in NAs group and 3589.40 ± 1223.47 IU/mL in PegIFNα-2b+NAs group ($P < 0.001$); the stratification ratio of patients with HBsAg < 1500, 1500 < HBsAg < 3000, 3000 < HBsAg < 9000, and more than 9000 IU/mL were 50.51%, 14.11%, 31.06%, and 9.32%, respectively, in the PegIFNα-2b+NAs group; the rates were 16.00%, 27.15%, 30.63%, and 26.22 % in the NAs group, respectively. **Conclusion:** Compared with NAs monotherapy, PegIFNα-2b combined with NAs therapy for the treatment of NPPCC (HBsAg > 1500 IU/mL) rapidly reduced HBsAg levels, and increased the number of PPCC (HBsAg < 1500 IU/mL), thereby providing a new

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treatment strategy for CHB patients with high-level HBsAg to achieve clinical cure.

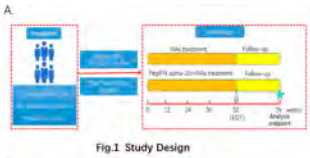


Fig.1 Study Design

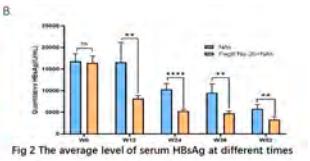


Fig 2 The average level of serum HBsAg at different times

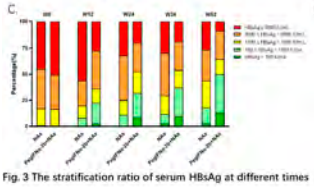


Fig. 3 The stratification ratio of serum HBsAg at different times



Fig. 4 Schematic diagram of PegIFNα+NAs therapy for CHB patients with high HBsAg levels

Disclosures: Wenhua Zhang:Nothing to Disclose, Haitao Tang:Nothing to Disclose, Qinghua Lu:Nothing to Disclose, Haifang Cao:Nothing to Disclose, Tingxia Chao:Nothing to Disclose, Fengmei Wang:Nothing to Disclose, Wenling Jia:Nothing to Disclose, Chunhui Liang:Nothing to Disclose, Feng Ren:Nothing to Disclose, Hongfei Zhang:Nothing to Disclose.

4111 | SUSTAINED FUNCTIONAL CURE AND ITS PREDICTORS WITH PEGINTERFERON ALPHA-2B COMBINATION THERAPY AT 156 WEEKS EXTENDED FOLLOW-UP AFTER A PHASE 3 TRIAL

Fengqin Hou[1] Jia Shang[2] Qing Xie[3] Chunliang Lei[4] Jianmei Lin[5] Guoxin Hu[6] Zhiliang Gao[7] Yilan Zeng[8] Jiabin Li[9] Qianguo Mao[10] Liying Zhu[11] Jun Chen[12] Xiaozhong Wang[13] Zuxiong Huang[14] Jiming Zhang[15] Ping An[16] Xiulan Xue[17] Yan Huang[18] Tianyan Chen[19] Jianqi Lian[20] Yueyong Zhu[21] Huiling Xiang[22] Xinyue Chen[23] Hui Guo[24] Ruoyi He[25] Yalin Yin[25] Li Sun[25] Guiqiang Wang[26], [1]Peking University First Hospital, Beijing, 100034, China, [2]Henan Provincial People's Hospital, Zhengzhou, 450000, China, [3]Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, 200000, China, [4]Guangzhou Eighth People's Hospital, Guangzhou Medical University, Guangzhou, 510000, China, [5]Sichuan Provincial People's Hospital·Sichuan Academy of Medical Sciences, Chengdu, 610000, China, [6]Peking University Shenzhen Hospital, Shenzhen, 518000, China, [7]The Third Affiliated Hospital, Sum Yat-Sen University, Guangzhou, 510000, China, [8]Public Health Clinical Center of Chengdu, Chengdu, 610000, China, [9]The First Affiliated Hospital of Anhui Medical University, Hefei, 230000, China, [10]Xiamen Hospital of Traditional Chinese Medicine, Xiamen, 361000, China, [11]The Fourth Affiliated Hospital of Harbin Medical University, Harbin, 150001, China, [12]Shenzhen Third People's Hospital, Shenzhen, 518000, China, [13]Xinjiang Uygur Autonomous Region Hospital of Traditional Chinese Medicine, Urumqi, 830000, China, [14]Mengchao Hepatobiliary Hospital of Fujian Medical University, Fuzhou, 350000, China, [15]Huashan Hospital, Fudan University, Shanghai, 200040, China, [16]The Sixth People's Hospital of Shenyang, Shenyang, 110000, China, [17]The First Affiliated Hospital of Xiamen University, Xiamen, 361000, China, [18]Xiangya Hospital Central South University, Changsha, 410000, China, [19]The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, 710061, China, [20]The Second Affiliated Hospital of the Air Force Military Medical University of CPLA, Xi'an, 710038, China, [21]The First Affiliated Hospital of Fujian Medical University, Fuzhou, 350000, China, [22]Tianjin Third Central Hospital, Tianjin, 300170, China, [23]Beijing Youan Hospital, Capital Medical University, Beijing, 100000, China, [24]First Teaching Hospital of Tianjin University of Traditional Chinese Medicine, Tianjin, 300170, China, [25]Xiamen Amoytop Biotech Co. Ltd, Xiamen, 361028, China, [26]Peking University First Hospital, Beijing, 100034, China; Peking University International Hospital, Beijing, 102206, China

Background: Functional cure, the ideal therapeutic goal in chronic hepatitis B (CHB), can be achieved through peginterferon alpha (PegIFNα) treatment. This study aimed to evaluate the long-term durability of PegIFNα-2b-induced functional cure and its predictors. **Methods:** Patients who achieved functional cure (maintain HBsAg loss and HBV DNA undetectable for 24 weeks follow-up after all drugs discontinuation) at the end of a phase 3 trial (NCT04846491) were enrolled in cohort 1 of this long-term follow-up study (NCT06707922) and observed for 5 years. In the preliminary phase 3 trial, nucleos(t)ide analogue (NA)-experienced patients were randomized to receive tenofovir disoproxil fumarate (TDF) monotherapy (group 1), TDF combined with PegIFNα-2b 180 μg/week (group 2) or 90 μg/week (group 3); after 48 weeks of TDF treatment, patients in group 1 either continue TDF monotherapy (group 1a) or add PegIFNα-2b 180 μg/week (group 1b). Treatment-naïve patients were also included to receive TDF combined with PegIFNα-2b 180 μg/week (group 4). The treatment period was 144 weeks and the follow-up was 24 weeks. PegIFNα-2b (Pegbing®, Xiamen Amoytop Biotech Co., Ltd.) were given intermittently in cycles. **Results:** A total of 88 patients who achieved functional cure were enrolled in cohort 1 of this follow-up study, comprising 32, 23, 29 and 4 patients from groups 2, 1b, 3 and 4 of the preliminary phase 3 trial, respectively, with no patients from group 1a. Among NA-experienced patients (groups 2, 1b, and 3), the mean age ranged from 36.1 to 41.5 years, with 58.6%–82.6% being male and 86.2%–91.3% being HBsAb positive. For treatment-naïve patients (group 4), the mean age was 30.5 years,

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25% were male, and 100% were HBsAb positive. By 156 weeks of follow-up, 87.5% (28/32), 82.6% (19/23), 86.2% (25/29), and 100% (4/4) of patients maintained functional cure in groups 2, 1b, 3 and 4, respectively. Among the 12 patients who experienced relapse, 10 had only HBsAg relapse, with a mean HBsAg level of 0.129 ± 0.106 IU/mL at the time of relapse, while 2 had only HBV DNA relapse (≥20 IU/mL). Multivariate analysis revealed that the HBsAb level at the time of functional cure (OR 1.032, 95%CI 1.007-1.077, $p = 0.034$) served as an independent predictor of the durability of functional cure. **Conclusion:** PegIFNα-2b combination therapy induced durable functional cure, with maintenance rates exceeding 80% in NA-experienced patients and being 100% in treatment-naïve patients at 156 weeks of extended follow-up. Patients who relapsed after functional cure had extremely low HBsAg levels at the time of relapse, and higher HBsAb levels were associated with better durability of functional cure. These findings strongly support the proactive use of PegIFNα-based regimens to achieve sustained functional cure and safe treatment discontinuation in patients with CHB.

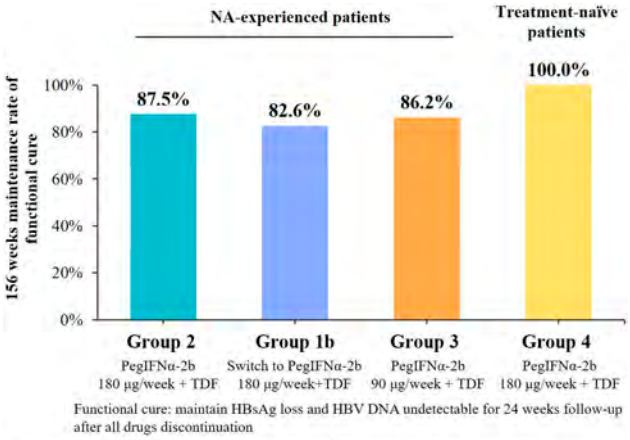


Figure 1. 156 weeks maintenance rate of functional cure in each group.

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4112 | FUNCTIONAL CURE OF PEGINTERFERON ALFA-2B RETREATMENT IN CHRONIC HEPATITIS B PATIENTS WITH LOW HBSAG LEVELS AFTER INITIAL THERAPY IN A PHASE 3 STUDY

Fengqin Hou[1] Jia Shang[2] Qing Xie[3] Chunliang Lei[4] Jianmei Lin[5] Guoxin Hu[6] Zhiliang Gao[7] Yilan Zeng[8] Jiabin Li[9] Qianguo Mao[10] Liying Zhu[11] Jun Chen[12] Xiaozhong Wang[13] Zuxiong Huang[14] Jiming Zhang[15] Ping An[16] Xiulan Xue[17] Yan Huang[18] Tianyan Chen[19] Jianqi Lian[20] Yueyong Zhu[21] Huiling Xiang[22] Xinyue Chen[23] Hui Guo[24] Ruoyi He[25] Yalin Yin[25] Li Sun[25] Guiqiang Wang[26], [1]Peking University First Hospital, Beijing, 100034, China, [2]Henan Provincial People's Hospital, Zhengzhou, 450000, China, [3]Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, 200000, China, [4]Guangzhou Eighth People's Hospital, Guangzhou Medical University, Guangzhou, 510000, China, [5]Sichuan Provincial People's Hospital·Sichuan Academy of Medical Sciences, Chengdu, 610000, China, [6]Peking University Shenzhen Hospital, Shenzhen, 518000, China, [7]The Third Affiliated Hospital, Sum Yat-Sen University, Guangzhou, 510000, China, [8]Public Health Clinical Center of Chengdu, Chengdu, 610000, China, [9]The First Affiliated Hospital of Anhui Medical University, Hefei, 230000, China, [10]Xiamen Hospital of Traditional Chinese Medicine, Xiamen, 361000, China, [11]The Fourth Affiliated Hospital of Harbin Medical University, Harbin, 150001, China, [12]Shenzhen Third People's Hospital, Shenzhen, 518000, China, [13]Xinjiang Uygur Autonomous Region Hospital of Traditional Chinese Medicine, Urumqi, 830000, China, [14]Mengchao Hepatobiliary Hospital of Fujian Medical University, Fuzhou, 350000, China, [15]Huashan Hospital, Fudan University, Shanghai, 200040, China, [16]The Sixth People's Hospital of Shenyang, Shenyang, 110000, China, [17]The First Affiliated Hospital of Xiamen University, Xiamen, 361000, China, [18]Xiangya Hospital Central South University, Changsha, 410000, China, [19]The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, 710061, China, [20]The Second Affiliated Hospital of the Air Force Military Medical University of CPLA, Xi'an, 710038, China, [21]The First Affiliated Hospital of Fujian Medical University, Fuzhou, 350000, China, [22]Tianjin Third Central Hospital, Tianjin, 300170, China, [23]Beijing Youan Hospital, Capital Medical University, Beijing, 100000, China, [24]First Teaching Hospital of Tianjin University of Traditional Chinese Medicine, Tianjin, 300170, China, [25]Xiamen Amoytop Biotech Co. Ltd, Xiamen, 361028, China, [26]Peking University First Hospital, Beijing, 100034, China; Peking University International Hospital, Beijing, 102206, China

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Background: Peginterferon alpha (PegIFNα) treatment induces functional cure in a considerable proportion of chronic hepatitis B (CHB) patients. However, still many patients fail to achieve this endpoint after initial therapy, and data on the efficacy of PegIFNα retreatment remain limited. This study investigated the efficacy of PegIFNα retreatment for patients who initially responded well but did not attain functional cure in a phase 3 study. **Methods:** This is a long-term follow-up study (NCT06707922) of a randomized controlled phase 3 trial (NCT04846491). At the end of the phase 3 trial, nucleos(t)ide analogue (NA)-experienced patients with HBsAg decline $\geq$ 1 $\log_{10}$ IU/mL and HBsAg level < 100 IU/mL, as well as treatment-naïve patients with HBsAg decline $\geq$ 1.5 $\log_{10}$ IU/mL and HBsAg level < 1500 IU/mL were enrolled in cohort 2. All patients initially received treatment with PegIFNα-2b (Pegbing®, Xiamen Amoytop Biotech Co., Ltd.) 180 μg/week combined with tenofovir alafenamide fumarate (TAF) for 72 weeks, after which the drugs were discontinued and patients were followed up to 5 years. PegIFNα-2b was given intermittently in cycles (8 weeks of treatment + 4 weeks of interval, repeating every 12 weeks). The 24-week post-treatment follow-up was completed, and the data were analyzed here. **Results:** A total of 47 NA-experienced patients and 15 treatment-naïve patients were enrolled in cohort 2. The mean ages of the two populations were 42.5 ± 7.2 and 34.5 ± 7.9 years, and 85.1% and 66.7% were male. Among NA-experienced patients, the mean baseline HBsAg level was 13.0 ± 17.8 IU/mL, and all patients were negative for HBeAg and HBV DNA. Among treatment-naïve patients, the mean baseline HBsAg level was 272.8 ± 328.5 IU/mL, 73.3% were HBeAg negative and 100% were HBV DNA undetectable. During treatment, HBsAg levels in both NA-experienced and treatment-naïve patients gradually decreased with the extension of treatment duration. Among NA-experienced patients, the proportions achieving HBsAg loss with undetectable HBV DNA were 42.6% at week 48 and 46.8% at week 72. Furthermore, 36.2% of patients achieved functional cure at 24 weeks follow-up after discontinuation both TAF and PegIFNα-2b. The proportions of treatment-naïve patients who attained HBsAg loss with undetectable HBV DNA at weeks 48 and 72 were 26.7% and 40%, respectively, and the functional cure rate was 33.3%. **Conclusion:** The functional cure rate of PegIFNα-2b retreatment in both NA-experienced and treatment-naïve patients exceeded 30%. Patients who respond well initially to PegIFNα should be considered for PegIFNα retreatment to better pursue functional cure.

Disclosures: Fengqin Hou:Nothing to Disclose, Jia Shang:Nothing to Disclose, QING XIE:Nothing to Disclose, Chunliang Lei:Nothing to Disclose, Jianmei Lin:Nothing to Disclose, Guoxin Hu:Nothing to Disclose, Zhiliang Gao:Nothing to Disclose, Yilan Zeng:Nothing to Disclose, Jiabin Li:Nothing to Disclose, Qianguo Mao:Nothing to Disclose, Liying Zhu:Nothing to Disclose, Jun Chen:Nothing to Disclose, Xiaozhong Wang:Nothing to Disclose, Zuxiong Huang:Nothing to Disclose, Jiming Zhang:Nothing to Disclose, Ping An:Nothing to Disclose, Xiulan Xue:Nothing to Disclose, Yan Huang:Nothing to Disclose, Tianyan Chen:Nothing to Disclose, Jianqi Lian:Nothing to Disclose, Yueyong Zhu:Nothing to Disclose, Huiling Xiang:Nothing to Disclose, Xinyue Chen:Nothing to Disclose, Hui Guo:Nothing to Disclose, Ruoyi He:Nothing to Disclose, Yalin Yin:Nothing to Disclose, Li Sun:Nothing to Disclose, Guiqiang Wang:Nothing to Disclose.

4113 | PROGNOSIS OF ENTECAVIR VERSUS TENOFOVIR IN HBV-RELATED HEPATOCELLULAR CARCINOMA: EVIDENCE FROM A NATIONWIDE COHORT

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Background: While some reports suggest differential prognostic impacts of antiviral agents in hepatitis B virus (HBV)-related hepatocellular carcinoma (HCC), these findings often lack generalizability due to their single-center nature. We investigated the association between antiviral agent type and overall survival in patients with HBV-related HCC using a nationwide real-world cohort. **Methods:** Using the Korean Liver Cancer Registry database from 2014 to 2021, we identified patients with HBV-related HCC who received entecavir or tenofovir disoproxil fumarate as initial antiviral therapy. Overall survival was compared between groups using multivariable Cox regression analyses. To minimize potential confounding and selection bias, propensity score matching was additionally performed. **Results:** The ETV and TDF groups comprised 1,796 and 2,409 patients, respectively. The mean age was significantly lower in the TDF group than in the ETV group (57.1 vs. 58.8 years, $p < 0.001$). The proportion of male patients (80.6% vs. 76.7%, $p = 0.002$), those with Child–Pugh class B or C (22.8% vs. 21.4%, $p = 0.002$), and those with distant metastasis (13.3% vs. 10.7%) was significantly higher in the TDF group than in the ETV group. The proportion of patients who received curative treatment was 42.2% in the ETV group and 39.0% in the TDF group.During a mean follow-up of 50 months in the overall cohort, 2,175 deaths were observed. In multivariable Cox regression analysis of the overall cohort, TDF was independently associated with improved overall survival compared with ETV (HR

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0.89, 95% CI 0.81–0.98; p = 0.023). This association remained significant in multivariable Cox regression analysis after propensity score matching (HR 0.88, 95% CI 0.79–0.98; p = 0.017). However, in stabilized inverse probability of treatment weighting analyses, TDF did not showed demonstrated a consistent favorable trend for overall survival compared with ETV (HR 0.90, 95% CI 0.79–1.03; p = 0.115). **Conclusion:** In this nationwide cohort of patients with HBV-related HCC, TDF was independently associated with modest improvement of overall survival compared with ETV after multivariable and propensity score-based adjustments.
Disclosures: Chang Wook Park:Nothing to Disclose, Jin-Wook Kim:Nothing to Disclose, Sook-Hyang Jung: Nothing to Disclose, Min Kyung Park:Nothing to Disclose, Gwang Hyeon Choi:Nothing to Disclose, Eun Sun Jang:Nothing to Disclose.

4114 | HIGH TREATMENT ADHERENCE IS ASSOCIATED WITH LOWER HCC RISK IN CIRRHOSIS, AND TENOFOVIR ALAFENAMIDE IS ASSOCIATED WITH FAVORABLE OUTCOMES

Young Seok Kim[1], [1]Soon Chun Hyang University

Background: Adherence to antiviral therapy is essential for viral suppression in chronic hepatitis B (CHB), yet its effect on hepatocellular carcinoma (HCC) remains uncertain. We examined the association between nucleos(t)ide analogue (NA) adherence and HCC risk, focusing on tenofovir alafenamide (TAF) versus entecavir (ETV). **Methods:** Treatment-naïve adults with CHB initiating TAF or ETV were identified from the Korean National Health Insurance Service database. Adherence was measured using the medication possession ratio, with high adherence defined as ≥ 90%. The primary outcome was HCC incidence. **Results:** A total of 28,448 patients were included, of whom 19,001 (66.8%) showed high adherence and 9,447 (33.2%) low adherence. In the overall cohort, HCC incidence was comparable between high- and low-adherence groups (14.89 vs. 13.76 per 1,000 person-years; IRR 1.08, 95% CI 0.95–1.24). Among cirrhotic patients, however, high adherence was associated with substantially lower HCC incidence (32.92 vs. 49.59 per 1,000 person-years; IRR 0.66, 95% CI 0.57–0.78). Multivariable analysis confirmed high adherence as an independent protective factor (HR 0.77, 95% CI 0.66–0.90). Notably, within the high-adherence group, TAF was linked to a significantly lower HCC risk than ETV (HR 0.54 vs. 0.89; log-rank p < 0.001), whereas low adherence to either agent conferred no protection. Logistic regression further identified ETV use as a strong predictor of poor adherence (OR 2.80, 95% CI 2.65–2.96). **Conclusion:** High adherence to antiviral therapy reduces HCC risk in cirrhotic CHB patients. TAF was associated with higher adherence and lower HCC incidence than ETV, although causal inference beyond adherence is limited in this observational study.
Disclosures: Young Seok Kim:Nothing to Disclose.

4115 | IMPACT OF FAMILY HISTORY OF HEPATOCELLULAR CARCINOMA ON THE EFFICACY OF COMBINED PEG-IFN α-2B ANTIVIRAL THERAPY IN PATIENTS WITH CHRONIC HEPATITIS B

Huimin Liu[1] Lijian Ran[1] Siwei Miao[1] Li Jiang[1] Yan Zhu[1] Guohong Deng[1], [1]The First Affiliated Hospital of Army Medical University

Background: Although family history (FH)-positive hepatocellular carcinoma (HCC) is a recognized risk factor for disease progress in chronic hepatitis B (CHB), its effect on hepatitis B surface antigen (HBsAg) seroclearance during pegylated interferon α-2b (PEG-IFN α-2b) plus nucleos(t)ide analogues (NAs) therapy is unknown. This study aimed to explore the correlation between FH of HCC and HBsAg seroclearance in CHB patients treated with PEG-IFN α-2b plus NAs, and to identify independent risk factors associated with HBsAg seroclearance. **Methods:** Clinical data were retrospectively collected from 2108 CHB patients who received > 24 weeks of PEG-IFN α-2b plus NAs therapy at Southwest Hospital from May 2019 to February 2026. Patients were aged 5–67 years with baseline HBsAg ≤ 124925 IU/mL. All patients were divided into the FH group (n = 313) and non-FH group (n = 1795) based on whether they had FH of HCC. A 1:2 propensity score matching (PSM) was performed to balance baseline confounders, including demographic, hematological, biochemical, immunological, virological and adverse reaction-related indicators. The endpoint was HBsAg seroclearance (≤ 0.05 IU/mL). Logistic regression was used to find independent factors, and a nomogram was constructed. Receiver operating characteristic (ROC) curves, calibration curves, and decision curve analysis (DCA) were used to evaluate the discrimination, calibration and clinical utility of the model. **Results:** After PSM, 918 patients were enrolled, including 308 in the FH group and 610 in the non-FH group, with balanced baseline characteristics between the two groups (all P > 0.05) **(Tab.1)** . At the end of treatment, the FH group exhibited a significantly lower HBsAg seroclearance rate than the non-FH group (20.1% vs 26.1%, $\chi^2 = 3.95$, P = 0.047) **(Tab.2)** . Univariate logistic regression identified FH-positive HCC as a significant factor for HBsAg seroclearance, while multivariate regression further demonstrated that baseline HBsAg

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(log10 level) (OR = 1.68, 95%CI: 1.55–1.83, P < 0.001) and treatment duration (OR = 0.96, 95%CI: 0.95–0.97, P < 0.001) were independent predictors **(Tab.3)** . A nomogram was established **(Fig.1A)** and showed superior discriminative performance compared with single baseline HBsAg or HCC FH alone(Fig.2). The model presented good agreement and clinical applicability, as verified by calibration curves **(Fig.1B)** and DCA **(Fig.1C)** . **Conclusion:** FH of HCC is not an independent risk factor for reduced HBsAg seroclearance in CHB patients treated with PEG-IFN α-2b plus NAs. Elevated baseline HBsAg level and shorter treatment duration are key factors contributing to lower HBsAg seroclearance rates.Therefore, clinical attention should be paid to baseline HBsAg levels in CHB patients with an FH-positive HCC. Sufficient courses of PEG-IFN α-2b plus NAs antiviral therapy are recommended for patients with high baseline HBsAg to improve the probability of HBsAg seroclearance.

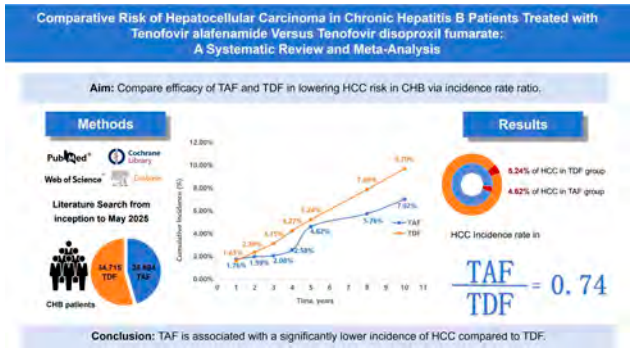


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4116 | COMPARATIVE RISK OF HEPATOCELLULAR CARCINOMA IN CHRONIC HEPATITIS B PATIENTS TREATED WITH TENOFOVIR ALAFENAMIDE VERSUS TENOFOVIR DISOPROXIL FUMARATE: A SYSTEMATIC REVIEW AND META-ANALYSIS

Xue Bai[1] Nan Geng[1] Jie Li[1], [1]Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University

Background: Tenofovir alafenamide (TAF) and tenofovir disoproxil fumarate (TDF) are widely used antiviral therapies for chronic hepatitis B (CHB). However, their relative efficacy in reducing hepatocellular carcinoma (HCC) remains uncertain. This meta-analysis aimed to compare HCC incidence rate ratios (IRRs) between CHB patients treated with TAF and TDF. **Methods:** PubMed, Embase, Web of Science, and the Cochrane Library were searched from inception to May 2025 for studies reporting HCC outcomes in TAF- vs. TDF-treated CHB patients. IRRs and cumulative incidence proportions (%) across different follow-up years were pooled using inverse-variance weighted meta-analysis and logit-transformed proportions, respectively, under common- and random-effects models. Heterogeneity was assessed by the I^2 statistic. This study was registered with PROSPERO (CRD42024618942). **Results:** Of 2,596 records screened, 11 studies comprising 63,409 CHB patients (TAF: 28,694; TDF: 34,715) were included. Over a median follow-up of 4,619 PYs, the TAF group showed a lower 5-year cumulative incidence (3.37% vs. 5.07%) of HCC compared to the TDF group. The pooled IRR was 0.74 (95% CI, 0.68, 0.81; P < 0.01), with no significant heterogeneity (I^2 = 0%; P = 0.76). The results of subgroup analyses by cohort type (whole vs. treatment-naive), follow-up years (≥5 vs. <5), continent (non-Asia vs. Asia), person year (accurate vs. estimated), sample size (≥1000 vs. <1000), and mean or median age (≥50 vs. <50) all favoured TAF. **Conclusion:** TAF is associated with a significantly lower incidence of HCC compared to TDF, which may provide insights for the clinical medication of CHB.



Disclosures: Xue Bai:Nothing to Disclose, Nan Geng:Nothing to Disclose, Jie Li:Nothing to Disclose.

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4117 | CLINICAL IMPACT OF COEXISTING MASLD ON LONG-TERM OUTCOMES AFTER SWITCHING TO TENOFOVIR ALAFENAMIDE IN PATIENTS WITH CHRONIC HEPATITIS B: A MULTICENTER COHORT STUDY

Eiichi Ogawa[1] Motoyuki Kohjima[2] Toshimasa Koyanagi[3] Kazufumi Dohmen[4] Aritsune Ooho[5] Akira Kawano[6] Norihiro Furusyo[7] Eiji Kajiwara[8] Takeaki Satoh[9] Kazuhiro Takahashi[10] Koichi Azuma[11] Rie Sugimoto[12] Yasunori Ichiki[13] Hiromasa Amagase[14] Masatake Tanaka[15] Hideyuki Nomura[16] Jun Hayashi[17], [1]Kyushu University Hospital, [2]NHO Kyushu Medical Center, [3]Fukuoka City Hospital, [4]Chihaya Hospital, [5]Steel Memorial Yawata Hospital, [6]Kitakyushu Municipal Medical Center, [7]Taihaku Avenue Clinic, [8]Kajiwara Clinic, [9]NHO Kokura Medical Center, [10]Hamanomachi Hospital, [11]Kyushu Central Hospital, [12]NHO Kyushu Cancer Center, [13]JCHO Kyushu Hospital, [14]Amagase Clinic, [15]Graduate School of Medical Sciences, Kyushu University, [16]Haradoi Hospital, [17]Kyushu University

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is increasingly recognized in patients with chronic hepatitis B (CHB) and may contribute to fibrosis progression and liver-related complications. However, long-term data on the clinical impact of MASLD in CHB patients receiving tenofovir alafenamide (TAF) remain limited. We aimed to evaluate the long-term virological, biochemical, and renal outcomes of CHB patients switched from prior nucleos(t)ide analogues to TAF according to the presence or absence of coexisting MASLD. **Methods:** This multicenter study used a TAF treatment database and included 419 adult CHB patients without a history of hepatocellular carcinoma who were followed for 5 years after switching to TAF. Patients were stratified by MASLD status at baseline, defined at the time of TAF switch. Virological outcomes included the rate of HBV DNA suppression (< 10 IU/mL) and decline in hepatitis B surface antigen (HBsAg) level. Biochemical response was assessed by alanine aminotransferase (ALT) normalization. Renal safety was evaluated by changes in estimated glomerular filtration rate (eGFR). **Results:** At baseline, the mean age was 57.5 ± 12.6 years, 254 patients (61.4%) were male, 301 (72.7%) had normal ALT, 54 (13.0%) had cirrhosis, and 154 (36.8%) had MASLD. Prior antiviral therapy consisted of entecavir in 177 patients, tenofovir disoproxil fumarate in 122, and combination therapy in 115. At 5 years after switching to TAF, the rate of HBV DNA suppression increased significantly in both groups, from 88.3% to 100% in the MASLD group and from 87.2% to 99.6% in the non-MASLD group (both $P < 0.01$). Over 5 years of TAF therapy, the decline in HBsAg was comparable between the groups: 0.39 ± 0.43 logIU/mL in the MASLD group (annual decline, 0.078 logIU/mL) versus 0.35 ± 0.42 logIU/mL in the non-MASLD group (annual decline, 0.070 logIU/mL). ALT normalization improved in both groups, from 54.5% to 71.4% in the MASLD group and from 89.8% to 94.7% in the non-MASLD group; however, the ALT normalization rate remained significantly lower in patients with MASLD ($P < 0.01$). Change in eGFR over 5 years was similar between the groups (-4.53 ± 8.35 vs. -4.09 ± 10.9, respectively). **Conclusion:** Coexisting MASLD did not compromise long-term antiviral efficacy or renal safety after switching to TAF. However, patients with MASLD showed persistently lower biochemical response, suggesting that residual liver injury may be driven in part by metabolic dysfunction rather than insufficient viral control. Integrated metabolic management should therefore be considered alongside antiviral therapy in CHB patients with MASLD.

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4118 | TENOFOVIR AMIBUFENAMIDE (TMF) IMPROVES LIVER FIBROSIS, RENAL FUNCTION, AND SKELETAL HEALTH IN A RAT MODEL OF CHRONIC IMMUNE-MEDIATED LIVER FIBROSIS

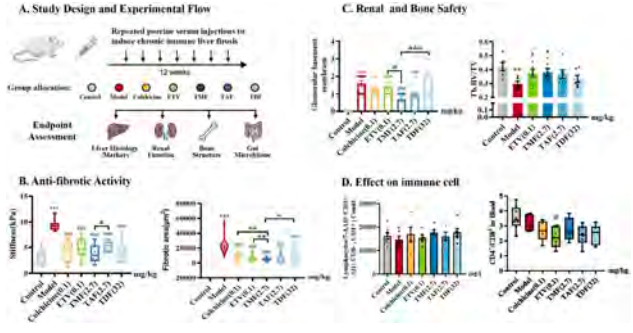
Zhizhen Hu[1] Yan Huo[1] Fanru Nie[1], [1]Jiangsu Hansoh Pharmaceutical Group Co., Ltd.

Background: Long-term anti-HBV therapy may adversely affect bone and renal function. Tenofovir amibufenamide (TMF) is a novel second-generation tenofovir prodrug with antiviral efficacy comparable to tenofovir disoproxil fumarate (TDF) and a more favourable safety profile in phase III trials. The underlying mechanisms remain incompletely understood. This study compared antifibrotic, renal, skeletal, and immunological effects of TMF with other nucleos(t)ide analogues in a rat model of chronic immune-mediated

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liver fibrosis. **Methods:** Rats were randomized by body weight into 7 groups (n = 16 per group): control, model, colchicine, entecavir (ETV), TMF, tenofovir alafenamide (TAF), and TDF. Chronic immune-mediated liver fibrosis was induced by repeated porcine serum injections. Control and model groups received 0.5% CMC-Na solution; others received corresponding medications at clinically equivalent doses once daily, 6 days weekly for 12 weeks. Liver fibrosis was evaluated by ultrasound elastography, histopathology, serum fibrosis markers, and hepatic hydroxyproline content. Renal function was assessed using renal injury biomarkers and renal histopathological analysis. Skeletal parameters were determined by dual-energy X-ray absorptiometry and micro-computed tomography. Hematologic parameters and immune cell profiles were analyzed by automated hematology analysis and flow cytometry (Figure 1A). **Results:** TMF significantly reduced liver stiffness compared with the model group (3.82 ± 1.82 vs 9.35 ± 1.07 kPa; $P < 0.001$) and showed greater reduction than TAF ($P < 0.05$). TMF improved hepatocellular necrosis and portal inflammation, reduced lesion area (0.01 ± 0.00 vs 0.18 ± 0.05 μm²; $P < 0.001$) and decreased fibrotic area (5015.91 vs 23257.86 μm²; $P < 0.001$) versus model, ETV($P < 0.01$) and TDF ($P < 0.05$) (Figure 1B). Despite similar routine renal parameters, TMF lowered cystatin C and improved renal protection versus model (3.10 ± 1.37 vs 8.50 ± 2.42; $P < 0.001$), ETV ($P < 0.05$) and TDF ($P < 0.001$) (Figure 1C). TMF preserved bone mineral density (BMD) and significantly increased bone volume fraction (BV/TV: 0.381 ± 0.064 vs 0.297 ± 0.045; $P < 0.05$) versus model, whereas TDF showed lower BMD and weaker skeletal benefits than TMF. TMF also numerically elevated immune cells versus the model group with no statistical significance (Figure 1D). **Conclusion:** In a rat model of chronic immune-mediated liver fibrosis, TMF provides superior antifibrotic, renal and skeletal protection with potential immunomodulatory benefits. These findings support further investigation of TMF as an anti-HBV therapy with benefits beyond viral suppression.



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4119 | EARLY HBSAG DECLINE WITH PRADEFOVIR MESYLATE-BASED STRATEGIES IN CHRONIC HEPATITIS B: A REAL-WORLD EXPLORATORY STUDY

Yingying Zhang[1] Jinghan Zhu[1] Yiling Chen[2] Heqing Huang[1] Hong Lu[1] Zutao Chen[1], [1]The Fourth Affiliated Hospital of Soochow University, [2]Medical College of Soochow University

Background: HBsAg clearance remains difficult to achieve with long-term nucleos(t)ide analogue therapy in chronic hepatitis B. Pradefovir mesylate (PDF) is a novel anti-HBV agent, but its early serological effect in patients with different treatment backgrounds remains insufficiently characterized. We evaluated HBsAg kinetics and safety during PDF-based therapy in patients with chronic hepatitis B. **Methods:** This exploratory real-world study included 113 patients with chronic hepatitis B receiving PDF-based treatment. Patients were categorized into four groups: switch from nucleos(t)ide analogues to PDF without recent pegylated interferon-α (PegIFN-α) exposure; PDF monotherapy after prior nucleos(t)ide analogue plus PegIFN-α therapy; treatment-naïve PDF monotherapy; and treatment-naïve PDF plus PegIFN-α. HBsAg changes at weeks 12 and 24 were assessed, together with the proportions of patients achieving HBsAg reductions > 0.5 and > 1 log10 IU/mL. Safety was evaluated using liver and renal function, platelet count, uric acid, and lipid parameters. **Results:** Baseline characteristics differed across groups, reflecting distinct treatment backgrounds. At week 12, early HBsAg decline was already observed in selected patients, particularly among treatment-naïve patients receiving PDF plus PegIFN-α, although the magnitude of decline became more evident by week 24. At week 24, the greatest HBsAg decline was observed in this group, with a median reduction of 0.50 log10 IU/mL from baseline (P = 0.049). In this group, 50.0% and 33.3% of patients achieved HBsAg reductions > 0.5 and > 1 log10 IU/mL, respectively. Patients receiving PDF monotherapy after prior nucleos(t)ide analogue plus PegIFN-α therapy also showed notable serological responses, with 39.3% and 28.6% achieving HBsAg reductions > 0.5 and > 1 log10 IU/mL at week 24, respectively. No clear signal of renal impairment or lipid deterioration was observed. Isolated fluctuations in liver function and platelet-related parameters did not show a consistent pattern attributable to PDF treatment. **Conclusion:** PDF-based therapy was associated with early HBsAg decline in selected patients with chronic hepatitis B, particularly when combined with PegIFN-α in treatment-naïve

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patients or used after prior PegIFN-α-based therapy. These findings suggest that PDF may be a promising component of treatment strategies aimed at enhancing HBsAg reduction. Larger prospective studies are warranted to confirm the optimal patient population and therapeutic strategy.

Disclosures: Yingying Zhang:Nothing to Disclose, Jinghan Zhu:Nothing to Disclose, Yiling Chen:Nothing to Disclose, Heqing Huang:Nothing to Disclose, Hong Lu:Nothing to Disclose, Zutao Chen:Nothing to Disclose.

4120 | KINETIC CHARACTERIZATION OF HBV DNA, HBSAG AND ALT AFTER DISCONTINUATION OF NA TREATMENT IN PATIENTS WITH CHRONIC HEPATITIS B

Leeor Hershkovich[1] Gustaf Rydell[2] Johan Ringlander[2] Scott Cotler[1] Harel Dahari[1] Magnus Lindh[2], [1]Loyola University Chicago, [2]University of Gothenburg

Background: Detailed HBV kinetic characterization after nucleos(t)ide analog (NA) discontinuation is lacking. We aim to characterize the kinetics of HBV DNA, HBsAg, and ALT during the first ~1 year post NA treatment cessation. **Methods:** 26 patients with chronic HBV who were receiving NA and were candidates for discontinuation of NA therapy were prospectively enrolled at 3 medical centers in Sweden. After NA stopped, blood samples were collected frequently (Fig.1). NA treatment was resumed in 8 patients in the first year (6 due to severe flare, 2 due to unsatisfactory outcome) were excluded in this analysis. **Results:** For the 18 participants who did not restart NA, median baseline HBsAg was 3.1 log IU/mL (IQR 2.2-3.4) and median baseline ALT was 22.4 U/L (IQR 18.4-38.1). While baseline HBV DNA was at or below LLoQ for 16/18 participants, 2 patients had baseline viral load of 2.8 and 3.0 log IU/mL. 6 participants experienced a decline (>0.59 log) in HBsAg (Fig.1A, B), while the remaining 12 had stable HBsAg (Fig.1C, D) after NA was stopped. Among the 6 participants with a HBsAg decline, the median reduction from baseline was 1.4 log (IQR 0.8-2.6) by the end of 60 weeks, including one who achieved undetectable HBsAg (Fig.1A). The HBsAg decline group had significantly lower (p = 0.001) median baseline HBsAg (2.1 log IU/mL, IQR 2.0-2.2) compared to the stable HBsAg group (3.3 log IU/mL, IQR 3.1-3.5).All patients (except for one, with baseline viral load at 2.8 log IU/mL) had a rise in virus after NA was stopped, which peaked at median week 8.1 (IQR 8.0-8.9) with median magnitude 4.3 log IU/mL (IQR 3.9-5.0). The increase in viral load was similar between the HBsAg stable and decline groups. Interestingly, 2 participants in the HBsAg stable group had a very slow rise in viral load (Fig.1D), which peaked at median week 22, followed by a plateau. Following a peak, all those with HBsAg decline (n = 6/6) also experienced an immediate decline in viral load to <2 log IU/mL by week 20 (Fig.1A, B). Only 2/12 (17%) participants with stable HBsAg experienced a similar viral decline; the rest (n = 10/12) had a viral decline after the peak which did not fall below 2 log IU/mL and then plateaued (Fig.1C, D).Three participants had transient ALT increases with peaks above 5x upper the limit of normal (ULN), of whom one was in the stable HBsAg group (>7x ULN), and two were in the HBsAg decline group, with peak values 9x ULN (Fig.1A) and 23x ULN. **Conclusion:** The combination of baseline HBsAg below 2.5 log IU/mL, and a viral pattern characterized by a rise in viral load followed by a return to <2 log IU/mL by week 20 post treatment cessation were predictive of HBsAg decline (>0.5 log) within the first year, with 100% PPV and 92% NPV for HBsAg decline.

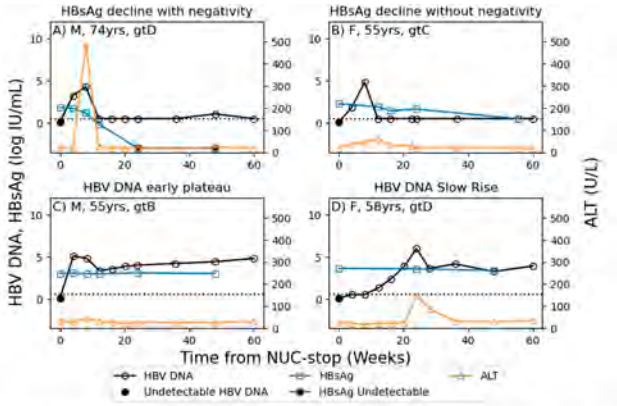


Figure 1: Representative kinetics in the first 60 weeks after stopping NA therapy, including ALT, HBV DNA (Cobas 6800, Roche; LLoQ 10 IU/mL), and HBsAg (Alinity, Abbott; LLoQ 0.05 IU/mL). **(A)** Shows the one participant with HBsAg decline that reaches TND, and **(B)** shows an example of HBsAg decline (>0.5 log) without reaching negativity. **(C)** Shows an example of stable HBsAg with an early HBV DNA plateau, while **(D)** shows an example of stable HBsAg with a slow HBV DNA rise. Dotted horizontal line shows HBV DNA LLoQ, filled markers represent undetectable HBV DNA or HBsAg. Each figure includes the sex (M or F), age, and HBV genotype of the displayed participant. Normal ALT was defined as 45 U/L for male and 30 U/L for female participants.

Disclosures: Leeor Hershkovich:Nothing to Disclose, Gustaf Rydell:Nothing to Disclose, Johan Ringlander: Nothing to Disclose, Scott Cotler:Nothing to Disclose, Harel Dahari:VIR: Advisor, Magnus Lindh:Nothing to Disclose.

4121 | NATIONWIDE UNDERUTILIZATION OF ANTIVIRAL THERAPY IN PREVENTING HEPATITIS B VIRUS-RELATED HEPATOCELLULAR CARCINOMA IN TAIWAN, 2016–2023

Chia-Ching Wu[1] Cheng-Hao Tseng[2] Jia-Ling Wu[1] Ying-Nan Tsai[2] Mindie Nguyen[3] Chun-Ying Wu[4] Yao-Chun Hsu[5], [1]E-Da Hospital, [2]E-Da Cancer Hospital, [3]Stanford University Medical Center, [4]National Yang

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MIng Chiao Tung University, Taiwan, [5]I-Shou University

Background: Antiviral therapy for chronic hepatitis B (CHB) reduces the risk of hepatocellular carcinoma (HCC), but its real-world uptake before HCC development remains poorly characterized at the population level. There is a paucity of nationwide data to clarify the magnitude of this care gap and to characterize patients who missed the opportunities of using antiviral therapy to prevent HCC. We aimed to quantify, at the national level, the proportion of patients with CHB who developed HCC without prior antiviral therapy, and to compare clinical and healthcare-utilization profiles between treated and untreated patients. **Methods:** We conducted a nationwide retrospective cohort study using the National Health Insurance Laboratory Databases (NHILD) in Taiwan. All adults with CHB who developed incident HCC between January 1, 2016, and December 31, 2023, were included. Antiviral exposure prior to HCC was ascertained from prescription records. Laboratory values within ±90 days of HCC diagnosis were extracted, with the most recent measurement per patient retained. We compared characteristics of patients with and without antiviral treatment prior to HCC diagnosis. **Results:** We identified a total of 34,550 patients with HBV-related HCC (median age 63.44 years; 78.81% male; 29.46% with cirrhosis, at the diagnosis of HCC), and 68.74% (23,751/34,550) had not received antiviral therapy before HCC diagnosis. Compared with treated patients, untreated patients had higher serum ALT (median 43 vs 30 U/L, $p < .0001$), AST (56 vs 34 U/L, $p < .0001$), and HBV DNA (4.51 vs 0 $\log_{10}$ IU/mL, $p < .0001$). Notably, the platelet counts were significantly higher in untreated patients (188 vs 148 $\times 10^9$/L, $p < .0001$), indicating less pronounced liver fibrosis. Prior to HCC development, untreated patients had significantly fewer ALT measurements (1.01 vs 2.59 per year, $p < .0001$), HBV DNA tests (0 vs 0.28 per year, $p < .0001$), and abdominal ultrasounds (0.30 vs 1.22 per year, $p < .0001$). Pre-HCC antiviral coverage rose from 24.28% in 2016 to 39.40% in year 2023. **Conclusion:** Approximately 68.74% of patients who developed HBV-related HCC in Taiwan had not received antiviral therapy before HCC diagnosis. Our findings indicate persistent gaps in the CHB care cascade in Taiwan despite universal health insurance coverage, highlighting the need to strengthen linkage to care and expand treatment eligibility.

Disclosures: Chia-Ching Wu:Nothing to Disclose, Cheng-Hao Tseng:Nothing to Disclose, Jia-Ling Wu: Nothing to Disclose, Ying-Nan Tsai:Nothing to Disclose, Mindie Nguyen:Pfizer, Astra Zeneca, Aligos, GSK, Delfi, Innogen, Exact Sci: Grant/Research Support, GSK: Advisor, Chun-Ying Wu:Nothing to Disclose, Yao-Chun Hsu:Gilead Sciences: Grant/Research Support, Gilead Sciences: Advisor, Sysmex: Advisor, Abbvie: Speaking and Teaching, Bristol Myers Squibb: Speaking and Teaching, Gilead Sciences: Speaking and Teaching, Roch: Speaking and Teaching, Grifols: Speaking and Teaching, GlaxoSmithKline: Consultant, AusperBio: Consultant.

4122 | TENOFOVIR ALAFENAMIDE IN DECOMPENSATED HEPATITIS B CIRRHOSIS: MULTICENTER REAL-WORLD OUTCOMES THROUGH 48-96 WEEKS

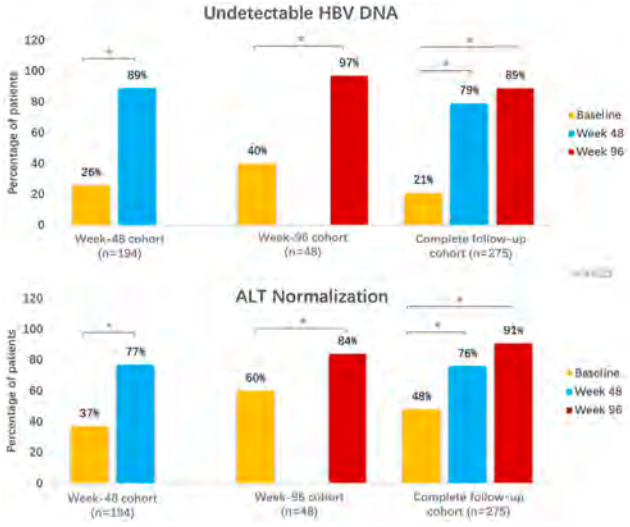
Hu Li[1] Li Liu[2] Huagang Xiong[3] Xiaozhong Wang[4] Songsong Xie[5] Li Shi[6] Wenjuan Shi[7] Guicheng Wu[8] Shujun Zhang[9] Quan Zhang[10] Basa Zhuoga[11] Guangying Shi[12] Yongping Zhang[13] Huiyan Zhang[14] Zhengjie Chen[1] Lu Zhang[1] Dachuan Cai[1] Peng Hu[1] Hong Ren[1], [1]The Second Affiliated Hospital of Chongqing Medical University, Chongqing, China, [2]Kunming Third People's Hospital, Yunnan, China, [3]Guiyang Public Health Clinical Center, Guizhou, China, [4]Traditional Chinese Medical Hospital Affiliated to Xinjiang Medical University, Xinjiang, China, [5]The First Affiliated Hospital of Shihezi University, Xinjiang, China, [6]People's Hospital of Tibet Autonomous Region, Tibet, China, [7]The No.2 People's Hospital of Lanzhou, Gansu, China, [8]Chongqing University Three Gorges Hospital, Chongqing, China, [9]The First Affiliated Hospital of Chongqing Medical University, Chongqing, China, [10]The Affiliated Hospital of Guizhou Medical University, Guizhou, China, [11]The Third People's Hospital of Tibet Autonomous Region, Tibet, China, [12]Hospital of Xinjiang Production and Construction Corps, Xinjiang, China, [13]People's Hospital of Xinjiang Uyghur Autonomous Region, Xinjiang, China, [14]The Third Affiliated Hospital of Chongqing Medical University, Chongqing, China

Background: Evidence for tenofovir alafenamide (TAF) in decompensated hepatitis B (HBV) cirrhosis is limited. We assessed real-world antiviral effectiveness and safety of TAF in this population. **Methods:** We performed a multicenter retrospective study across 14 hospitals (April 2017–March 2026). Adults with decompensated HBV cirrhosis treated with TAF were followed for 48 or 96 weeks. The primary efficacy indicator was hepatitis B virus (HBV) DNA seronegative conversion rate at 48 and 96-weeks, and the secondary efficacy indicator was alanine aminotransferase (ALT) normalization rate at 48 and 96-weeks. Safety assessments included renal function, lipid parameters, and adverse drug reactions. **Results:** A total of 517 cases from 14 hospitals were included. Of these, 340 were males, with a median age of 52 years (range 21–81). Follow-up comprised three non-overlapping cohorts: 194 patients

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had data through week 48, 48 through week 96 (without week 48), and 275 had complete assessments at baseline, week 48, and week 96. In the week-48 cohort (n = 194), the proportion with undetectable HBV DNA increased from 26.09% (49/184) at baseline to 88.55% (147/166) at week 48 ($p < 0.05$), and ALT normalization increased from 39.69% (77/194) to 77.32% (150/194) ($p < 0.05$). In the week-96 cohort(n = 48), undetectable HBV DNA improved from 39.53% (17/43) to 86.05% (37/43) at week 96 ($p < 0.05$), and ALT normalization rose from 59.57% (28/47) to 84.44% (38/45) ($p < 0.05$). In the complete follow-up cohort(n = 275), undetectable HBV DNA increased from 21.05% (56/266) at baseline to 79.10% (212/268) at week 48 and 88.85% (239/269) at week 96 (both $p < 0.05$); ALT normalization increased from 47.64% (131/275) to 75.75% (203/268) at week 48 and 91.39% (244/267) at week 96 (both $p < 0.05$). For safety profile, renal function and lipid parameters remained stable after 48 or 96 weeks versus baseline (all $p > 0.05$), with no new safety signals. **Conclusion:** In this large multicenter real-world cohort of decompensated HBV cirrhosis, TAF was associated with robust viral suppression and improved ALT normalization through 96 weeks, with stable renal and lipid safety profiles.



Disclosures: Hu Li:Nothing to Disclose, Li Liu:Nothing to Disclose, Huagang Xiong:Nothing to Disclose, Xiaozhong Wang:Nothing to Disclose, Songsong Xie: Nothing to Disclose, Li Shi:Nothing to Disclose, Wenjuan Shi:Nothing to Disclose, Guicheng Wu:Nothing to Disclose, Shujun Zhang:Nothing to Disclose, Quan Zhang:Nothing to Disclose, Basa Zhuoga:Nothing to Disclose, Guangying Shi:Nothing to Disclose, Yongping Zhang:Nothing to Disclose, Huiyan Zhang: Nothing to Disclose, Zhengjie Chen:Nothing to Disclose, Lu Zhang:Nothing to Disclose, DACHUAN CAI: Nothing to Disclose, Peng Hu:Nothing to Disclose, Hong Ren:Nothing to Disclose.

4123 | COST-EFFECTIVENESS ANALYSIS OF CHRONIC HEPATITIS B TREATMENT EXPANSION GUIDELINE RECOMMENDATIONS IN THE TOP NINE COUNTRIES WITH MAJOR GLOBAL BURDEN

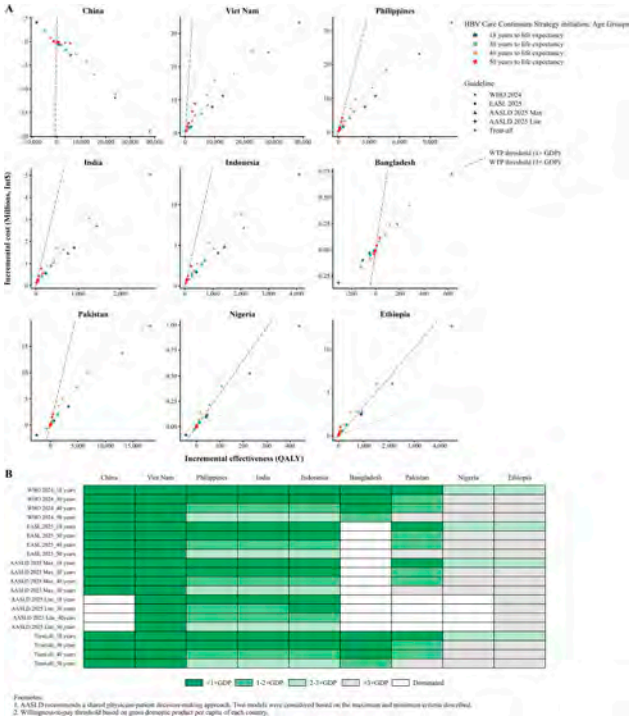
Hanting Li[1] Jiandong Zhou[2] Dijing You[2] Polin Chan[3] Hong You[4] Jie Li[5] Ajeet Bhadoria[6] Amit Goel[7] Cosmas Rinaldi Lesmana[8] Andri Sanityoso Sulaiman[8] Solomon Obekpa[9] Danjuma Adda[10] Hailemichael Desalegn[11] Shahinul Alam[12] Vo Thong[13] Minh Khuê Pham[14] Pham Chi Tran[15] Janus Ong[16] Ian Homer Cua[17] Saeed Hamid[18] Lung Yi Mak[2] Man-Fung Yuen[2] Mindie Nguyen[19] Lei Zhang[20] William Cw Wong[2] Wai-Kay Seto[2], [1]School of Public Health, Sun Yat-sen University, Guangzhou, China, [2]The University of Hong Kong, [3]World Health Organization South-east Asia Regional Office, [4]Capital Medical University, Beijing, China, [5]Nanjing Drum Tower Hospital, Nanjing University, Nanjing, China, [6]All India Institute of Medical Sciences (AIIMS), Uttarakhand, India, [7]Sanjay Gandhi Postgraduate Institute of Medical Sciences, India, [8]Dr. Cipto Mangunkusumo National General Hospital, Medical Faculty Universitas Indonesia, [9]National Postgraduate Medical College of Nigeria, Lagos, Nigeria, [10]Centre For Initiative and Development, Taraba, Nigeria, [11]St Paul's Hospital, Millennium Medical College, Addis Ababa, Ethiopia, [12]Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh, [13]University of Medicine and Pharmacy, [14]Faculty of Public Health , Haiphong University of Medicine and Pharmacy, Vietnam, [15]Hue Central Hospital, Vietnam, [16]University of the Philippines, Manila, Philippines, [17]St. Luke's Medical Center, [18]Aga Khan University, Karachi, Pakistan, [19]Stanford University Medical Center, [20]Monash University, Melbourne, Australia

Background: Recent international chronic hepatitis B (CHB) guidelines, including updated recommendations from the World Health Organization (WHO), European Association for the Study of the Liver (EASL), & American Association for the Study of Liver Diseases (AASLD), have substantially expanded and simplified eligibility criteria for antiviral treatment. The cost-effectiveness of implementing these strategies across endemic countries remains uncertain. We evaluated the cost-effectiveness of major international CHB treatment expansion recommendations in nine countries: China, India, Indonesia, Nigeria, Ethiopia, Bangladesh, Vietnam, Philippines & Pakistan, which together account for more than two-thirds of the global hepatitis B virus infected population. **Methods:** A state-transition Markov model was developed to simulate the natural history and management of CHB in the nine countries. Treatment expansion recommendations based on WHO 2024, EASL 2025, two models of AASLD 2025 ("Max" & "Lite" based on shared decision-making), & "Treat-all" were compared. Analyses were conducted across multiple CHB care continuum strategies (diagnosis to

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disease monitoring to treatment) initiation ages, from 18, 30, 40, & 50 years, over a lifetime horizon from a healthcare payer perspective. Quality-adjusted life years (QALYs) & incremental cost-effectiveness ratios (ICERs) were assessed against country-specific willingness-to-pay (WTP) thresholds based on gross domestic product per capita. **Results:** When comparing WHO, EASL and AASLD guidelines (Figure 1), China demonstrated cost-saving outcomes across nearly all strategies initiation ages, with negative ICERs (USD $-497 to $-46/QALY) observed. The expanded strategy strategies were cost-effective in Vietnam, Philippines, India & Indonesia with WHO_18 being the most cost-effective (ICERs $864/QALY, $2919/QALY, $1881/QALY & $3369/QALY respectively). EASL & AASLD remained cost-effective but at greater costs with fewer QALYs averted. ICERs increased incrementally with older age of strategy initiation; Pakistan ($1052/QALY for WHO_18) loses cost-effectiveness for all strategies with initiation at 50 years. Only WHO was cost-effective in Bangladesh ($1357/QALY at 18 yrs), while cost-effectiveness in Nigeria and Ethiopia was limited to initiation at 18 years ($2313/QALY & $2853/QALY for WHO_18). Treat-all approaches generally produced the lowest ICERs across initiation ages. **Conclusion:** Expanded antiviral treatment eligibility strategies for CHB were generally cost-effective in countries with the highest global HBV burden, particularly when strategy was initiated at an earlier age. WHO 2024 and Treat-all consistently produced the lowest ICERs, supporting the potential economic value of broader treatment expansion. Cost-effectiveness varied substantially across settings & was more limited in lower-income countries with lower WTP thresholds.



Disclosures: Hanting Li:Nothing to Disclose, Jiandong Zhou:Nothing to Disclose, Dijing You:Nothing to Disclose, Polin Chan:Nothing to Disclose, Hong You:Nothing to Disclose, Jie Li:Nothing to Disclose, Ajeet Bhadoria:Nothing to Disclose, Amit Goel:Nothing to Disclose, Cosmas Rinaldi Lesmana:Nothing to Disclose, Andri Sanityoso Sulaiman:Nothing to Disclose, Solomon Obekpa:Roche: Employee, Danjuma Adda: Gilead Sciences: Grant/Research Support, Hailemichael Desalegn:Nothing to Disclose, Shahinul Alam:Nothing to Disclose, Vo Thong:Nothing to Disclose, Minh Khuê PHAM:Nothing to Disclose, Pham Chi TRAN:Nothing to Disclose, Janus Ong:Nothing to Disclose, Ian Homer Cua:Nothing to Disclose, Saeed Hamid:Nothing to Disclose, Lung Yi Mak:Gilead Sciences: Grant/Research Support, Roche Diagnostics: Grant/Research Support, Gilead Sciences: Grant/Research Support, Roche Diagnostics: Grant/Research Support, Gilead Sciences: Advisor, Roche Diagnostics: Advisor, GSK: Speaker fee, Man-Fung Yuen:AbbVie, Abbott Diagnotics, Aligos Therapeutics: Consultant, Arbutus Biopharma, Arrowhead Pharmaceuticals, Assembly Biosc: Consultant, Clear B Therapeutics, Dicerna Pharmaceuticals, Immuncore: Consultant, Fujirebio Incorporation, GSK, Gilead Sciences: Consultant, Immunocore, Janssen, Precision BioSciences: Consultant, Roche, Sysmex Corporation, Tune Therapeutics: Consultant, Vir Biotechnology and Visirna Therapeutics: Consultant, AbbVie, Assembly Biosciences, Arrowhead Pharmaceuticals, Aligos Therapeutics, Arbutus Biopharma: Grant/Research Support, Fujirebio Incorporation, Gilead Sciences, Immunocore, Clear B Therapeutics, GSK, Janssen: Grant/Research Support, Sysmex Corporation and Roche: Grant/Research Support, Fujirebio Incorporation, Gilead Sciences, Roche, Sysmex Corp, Aligos Therapeutics, Arbutus Biopharma: Speaking and Teaching, Precision BioSciences: consultancy, Ausperbio: consultancy, IntergerBio: consultancy, Tune Therapeutics: consultancy, Clear B Therapeutics, GSK, Immuncore, Janssen, Vir Biotechnology: Speaking and Teaching, Mindie Nguyen:Pfizer, Astra Zeneca, Aligos, GSK, Delfi, Innogen, Exact Sci: Grant/Research Support, GSK: Advisor, Lei Zhang:Nothing to Disclose, William Cw Wong:Nothing to Disclose, Wai-Kay Seto:MSD: Speaking and Teaching, Echosens: Speaking and Teaching, Pfizer: Grant/Research Support, 89Bio: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Ribo Life Science: Grant/Research Support, AstraZeneca: Grant/Research Support, Gilead: Grant/Research Support, Gilead: Speaking and Teaching, Gilead: Consultant, Abbott: Consultant, Abbott: Speaking and Teaching.

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4124 | EFFICACY AND SAFETY OF TENOFOVIR ALAFENAMIDE FOR CHRONIC HEPATITIS B PATIENTS WITH ADVANCED FIBROSIS AND PARTIAL VIROLOGIC RESPONSES TO ORAL NUCLEOS(T)IDE ANALOGUES

Ming-Lun Yeh[1], [1]Kaohsiung Medical University Hospital

Background: On-treatment low-level viremia (LLV) is associated with an increased risk of hepatocellular carcinoma (HCC) compared to maintained virological response. However, management strategies for chronic hepatitis B (CHB) patients with a partial response to nucleot(s)ide analogues (NUCs) remain poorly defined. This study evaluated the efficacy and safety of switching to tenofovir alafenamide (TAF) in CHB patients with advanced fibrosis and a partial response to prior NUC therapy. **Methods:** This prospective study enrolled CHB patients with advanced fibrosis who had received non-TAF NUC therapy for >52 weeks but remained DNA-detectable. All participants were switched to TAF 25 mg/day for 96 weeks. Efficacy was measured by virological response (HBV DNA <20 IU/mL), biochemical response (ALT normalization per AASLD criteria), and changes in liver stiffness and HBsAg titers. **Results:** Sixty-eight patients were enrolled (median age 56 years; 51.5% male; 47.1% HBeAg-positive); 60 patients completed 96 weeks of treatment. Prior therapies included entecavir (75.0%) and TDF (19.7%). The virological response rate increased significantly over time, reaching 75.0% (45/60) at week 96. Combined virological and biochemical response was achieved by 53.3% of patients at week 96. Among HBeAg-positive patients, HBeAg loss and seroconversion occurred in 13.3% and 10.0%, respectively. Median HBsAg titers significantly declined from 1803 IU/mL at baseline to 1135 IU/mL at week 96 ($P < 0.05$). Furthermore, median liver stiffness improved from 7.7 kPa to 6.0 kPa, with the proportion of patients achieving liver stiffness <9.5 kPa increasing from 57.4% to 80.0%. Renal function (eGFR/creatinine) and body weight remained stable. Eight patients discontinued early, including two unrelated deaths. Four cases of new-onset HCC were identified during study period. **Conclusion:** In CHB patients with advanced fibrosis and a partial response to prior NUCs, switching to TAF effectively suppresses viral replication, promotes HBsAg decline, and leads to a significant reduction in liver stiffness.

Disclosures: Ming-Lun Yeh:Nothing to Disclose.

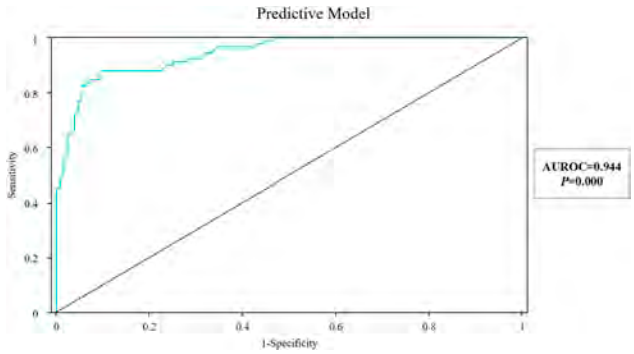
4125 | IDENTIFICATION OF NEW EARLY PREDICTIVE MARKERS FOR HBSAG LOSS IN PATIENTS WITH CHRONIC HEPATITIS B UNDERGOING 24-WEEK PEGYLATED INTERFERON α-2B TREATMENT

Min Qiu[1] Jiaqi Pan[1] Ka Zhang[1], [1]the Third Affiliated Hospital of Sun Yat-Sen University

Background: The loss of hepatitis B surface antigen (HBsAg) is considered an optimal outcome in the treatment of chronic hepatitis B (CHB) with pegylated interferon α-2b (Peg-IFN α-2b). However, the availability of reliable early predictive markers remains limited. **Methods:** CHB patients who underwent 24 weeks of Peg-IFN α-2b therapy were categorized into two cohorts: HBsAg loss and non-loss groups. Analyses were conducted to find predictors of HBsAg loss and evaluate the early predictive value of on-treatment HBsAg levels and CBC-derived inflammatory indices for HBsAg loss at week 24. **Results:** HBsAg loss was observed in 91 of the 242 participants (37.6%) following a 24-week regimen of Peg-IFN α-2b therapy. Participants with HBsAg loss had much lower initial HBsAg levels (15.1IU/mL) than those without loss (313IU/mL, $P = 0.01$). Independent predictors of HBsAg loss at week 24 included age (OR = 0.912, $P = 0.003$), sex (OR = 0.103, $P = 0.005$), HBsAg level at week 12 (OR = 0.075, $P < 0.001$), neutrophil to lymphocyte ratio (NMLR) at week12 (OR = 0.222, $P = 0.005$), systemic immune inflammation response index (SIRI) at week 12 (OR = 11.48, $P = 0.001$), and hemoglobin (HGB) decline at week 12 (OR = 0, $P = 0.019$). A predictive model using these variables showed high accuracy for forecasting HBsAg loss at week 24, with an ROC AUC of 0.944 (95% CI: 0.916-0.972), indicating early predictive value in clinical practice. **Conclusion:** At week 12, on-treatment HBsAg levels and CBC-derived inflammatory indices (NMLR, SIRI, and HGB decline) are useful early indicators for predicting HBsAg loss in CHB patients undergoing 24 weeks of Peg-IFN α-2b therapy. Baseline age and sex also independently predict outcomes.

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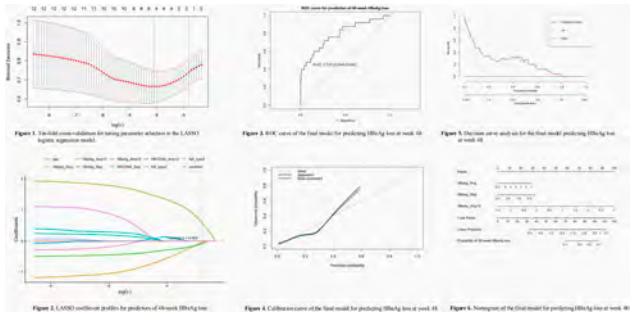


Disclosures: Min Qiu:Nothing to Disclose, Jiaqi Pan: Nothing to Disclose, Ka Zhang:Nothing to Disclose.

4126 | PREDICTORS OF HBEAG LOSS AND NOMOGRAM DEVELOPMENT IN PATIENTS WITH CHRONIC HEPATITIS B TREATED WITH PEGINTERFERON α-2B

Shiyu Wang[1] Wen Deng[1] Weihua Cao[1] Yaqin Zhang[1] Xin Wei[1] Zixuan Gao[1] Linmei Yao[1] Shuojie Wang[1] Yao Xie[1] Minghui Li[1], [1]Department of Hepatology Division 2, Beijing Ditan Hospital, Capital Medical University, Beijing

Background: To develop a predictive model using LASSO regression based on serological and clinical indicators for achieving hepatitis B e antigen (HBeAg) seroconversion at week 48 of pegylated interferon alpha-2b therapy in patients with chronic hepatitis B, and to evaluate its predictive performance. **Methods:** A total of 192 patients with chronic hepatitis B who received PEG-IFNα-2b therapy and completed 48 weeks of follow-up were enrolled. Clinical and laboratory data were collected at baseline and week 12. Patients were classified into HBeAg seroconversion and non-seroconversion groups according to week-48 HBeAg status. Between-group comparisons were performed using t-test, Wilcoxon rank-sum test, or chi-square test, as appropriate. Candidate predictors were screened by univariate analysis and LASSO regression, followed by multivariate logistic regression to establish a predictive model. A nomogram was constructed, and model performance was assessed using ROC analysis, bootstrap validation, calibration curves, decision curve analysis, and clinical impact curves. **Results:** Among 192 patients with chronic hepatitis B, 25 achieved HBeAg seroconversion at week 48 of treatment. Eleven variables—age, sex, NA_type, HBsAg_0log, HBeAg_0log, HBVDNA_0log, HBsAg_drop12, HBeAg_drop12, HBVDNA_drop, ALT_change12, and PLT_drop12—were included in the LASSO regression. After LASSO regression selection, HBsAg_0log, HBeAg_0log, and HBeAg_drop12 were incorporated into multivariate logistic regression analysis. Multivariate analysis showed that HBsAg_0log (OR = 0.67, 95% CI: 0.42–0.69), HBeAg_0log (OR = 0.45, 95% CI: 0.24–0.83), and HBeAg_drop12 (OR = 7.22, 95% CI: 2.90–17.90) were independent predictors of HBeAg seroconversion at week 48. A nomogram prediction model was constructed based on these variables, yielding an area under the ROC curve (AUC) of 0.791. After 1,000 bootstrap internal validations, the model demonstrated good discriminative ability and stability. The calibration curve showed good agreement between predicted probabilities and actual observations, and decision curve analysis indicated favorable clinical net benefit across a wide range of threshold probabilities. **Conclusion:** A nomogram based on HBsAg_0log, HBeAg_0log, and HBeAg_drop12 was developed using LASSO regression incorporating patient baseline characteristics and serological indicators. This model can predict the probability of HBeAg seroconversion in CHB patients treated with PEG-IFNα-2b, and may serve as a valuable reference for clinical decision-making.



Disclosures: Shiyu Wang:Nothing to Disclose, Wen Deng:Nothing to Disclose, Weihua Cao:Nothing to Disclose, Yaqin Zhang:Nothing to Disclose, Xin Wei: Nothing to Disclose, Zixuan Gao:Nothing to Disclose, Linmei Yao:Nothing to Disclose, Shuojie Wang:Nothing to Disclose, Yao Xie:Nothing to Disclose, Minghui Li: Nothing to Disclose.

4127 | CLINICAL OUTCOMES OF ANTIVIRAL THERAPY IN HBEAG-NEGATIVE CHB PATIENTS WITH LOW HBSAG LEVELS

Jian Wang[1] Taotao Yan[2] Zhiyi Zhang[3] Li Zhu[4] Shaoqiu Zhang[1] Xiaonan Wu[5] Juan Xia[1] Xiaomin Yan[1] Jie Qin[2] Huali Wang[6] Xingxiang Liu[7] Qun Zhang[8] Chuanwu Zhu[4] Yingren Zhao[2] Chao Wu[1] Rui Huang[1], [1]Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University, [2]The First Affiliated Hospital of Xi'an Jiaotong University, [3]The Affiliated

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Background: Low serum hepatitis B surface antigen (HBsAg) levels (< 100 IU/mL) was associated with a reduced risk of adverse outcomes in patients with chronic hepatitis B (CHB). The long-term benefit of antiviral therapy in CHB patients with low HBsAg levels is not clear. This study compared the clinical outcomes between untreated and treated HBeAg-negative CHB patients with low HBsAg. **Methods:** A total of 949 HBeAg-negative CHB patients with HBsAg < 100 IU/mL, detectable HBV DNA, ALT < 2 times of upper limit of normal (40 U/L) and without liver cirrhosis were enrolled from six medical centers in China. Inverse probability of treatment weighting (IPTW) and propensity score matching (PSM) were performed to balance the baseline characteristics between groups. The clinical outcomes of this study were liver-related events (LREs, including hepatocellular carcinoma and cirrhosis) and HBsAg seroclearance. **Results:** During a median follow-up of 2.9 years, 26 patients developed LREs and 51 achieved HBsAg seroclearance. 41.3% of patients received nucleos(t)ide analogues (NAs) treatment. After IPTW, untreated group had a significantly higher 6-year cumulative incidence of LREs than NA-treated group (10.5% vs. 2.4%, P = 0.004). In the multivariable Cox regression, NA treatment was associated with low risk of LREs (adjusted hazard ratio [aHR]: 0.26, 95% confidence interval [CI]: 0.09-0.77, *P* = 0.015), while family history of of HCC or cirrhosis (aHR: 5.43, 95% CI: 1.68-17.51, *P* = 0.005) and mildly elevated ALT (1-2×ULN) (aHR: 2.85, 95% CI: 1.22-6.68, *P* = 0.016) were associated with higher risk of LREs. Results remained consistent after excluding patients with significant liver fibrosis at baseline. However, NA treatment was not significantly associated with HBsAg seroclearance. Similar findings were observed in the PSM cohort. **Conclusion:** HBeAg-negative CHB patients with low HBsAg levels, detectable HBV DNA, and mildly elevated ALT may still benefit from NA treatment, with a reduced risk of LREs.

Disclosures: Jian Wang:Nothing to Disclose, Taotao Yan:Nothing to Disclose, Zhiyi Zhang:Nothing to Disclose, Li Zhu:Nothing to Disclose, Shaoqiu Zhang: Nothing to Disclose, Xiaonan Wu:Nothing to Disclose, Juan Xia:Nothing to Disclose, Xiaomin Yan:Nothing to Disclose, Jie Qin:Nothing to Disclose, Huali Wang: Nothing to Disclose, Xingxiang Liu:Nothing to Disclose, Qun Zhang:Nothing to Disclose, Chuanwu Zhu:Nothing to Disclose, Yingren Zhao:Nothing to Disclose, Chao Wu:Nothing to Disclose, Rui Huang:Nothing to Disclose.

4128 | PREDICTIVE VALUE OF FAMILY HISTORY OF HEPATITIS B FOR HBSAG CLEARANCE AFTER PEGYLATED INTERFERON ALPHA-2B TREATMENT AND SUBGROUP ANALYSIS

Jun Li[1] Yiwen Zhang[1] Qin Du[2] Yanchao Fu[3] Jiayin Wang[3] Chao Yang[3] Jing Liang[3] Qing Ye[3] Huiling Xiang[3], [1]The Third Central Clinical College of Tianjin Medical University, [2]Nankai University Affiliated Third Central Hospital, [3]Tianjin University Central Hospital (Tianjin Third Central Hospital)

Background: To investigate whether a family history of hepatitis B virus (HBV) infection independently predicts hepatitis B surface antigen (HBsAg) clearance in patients with chronic hepatitis B (CHB) receiving pegylated interferon alpha-2b (Peg-IFNα-2b) and to identify the patient subgroups in which this association is most pronounced. **Methods:** This single-center, retrospective cohort study consecutively enrolled 1384 CHB patients who received Peg-IFNα-2b for ≥ 12 weeks between December 2021 and September 2025 at Tianjin University Central Hospital. Patients were categorized according to the presence or absence of a family history of HBV infection. Multivariable logistic regression was used to adjust for baseline confounders and evaluate the independent effect of family history on HBsAg clearance. Pre-specified subgroup analyses were performed stratified by sex, age, HBV DNA level, HBsAg level, hepatitis B e antigen (HBeAg) status, cirrhosis, and metabolic dysfunction-associated steatotic liver disease (MASLD) to explore potential heterogeneity. **Results:** Of the 1384 patients, 713 (51.52%) had a family history of HBV infection. The HBsAg clearance rate was significantly lower in the family history-positive group than in the family history-negative group (10.80% vs. 16.24%, P = 0.003). At baseline, the family history-positive group exhibited a higher virologic burden: the proportions of patients with HBV DNA > 2000 IU/mL (16.71% vs. 12.27%, P = 0.021), HBsAg > 1500 IU/mL (46.62% vs. 38.37%, P = 0.002), and positive HBeAg (23.26% vs. 16.27%, P = 0.005) were all significantly greater than those in the family history-negative group. After adjusting for baseline confounders, a family history of HBV infection remained an independent risk factor for lower HBsAg clearance [odds ratio (OR) = 0.631, 95% confidence interval (CI): 0.417-0.955, P = 0.029]. In subgroup analyses, the inverse association between family history and HBsAg clearance persisted in women (OR = 0.397, P = 0.002), younger patients (OR = 0.483, P = 0.013), those with lower HBV DNA levels (OR = 0.682, P = 0.022), lower HBsAg levels (OR = 0.701, P = 0.050), HBeAg-negative patients (OR = 0.646, P = 0.019), patients without cirrhosis (OR = 0.611, P = 0.005), and those with MASLD (OR = 0.404, P = 0.002). **Conclusion:** A family history of HBV infection is an independent risk factor for failure to achieve HBsAg clearance during Peg-IFNα-2b therapy in CHB patients. This

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association remains significant among women, younger patients, HBeAg-negative patients, those without cirrhosis, those with MASLD, and patients with lower levels of HBV DNA and HBsAg. These findings suggest that CHB patients with a positive family history may require more potent or prolonged antiviral strategies to improve HBsAg clearance rates.

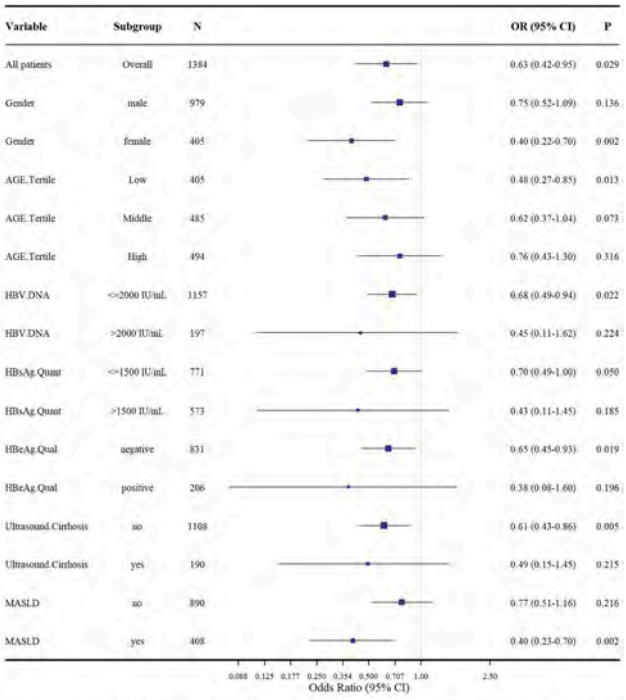


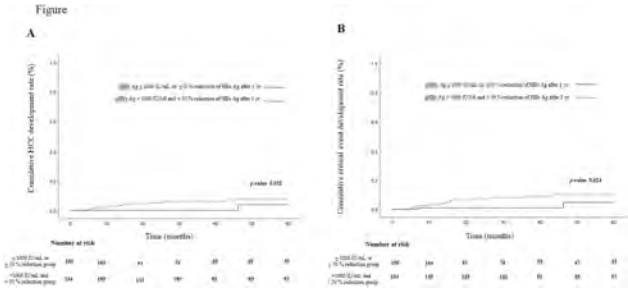
Figure 1. Forest plot of subgroup analyses for the association between family history of hepatitis B and HBsAg clearance.

Disclosures: jun Li:Nothing to Disclose, Yiwen Zhang: Nothing to Disclose, qin du:Nothing to Disclose, Yanchao Fu:Nothing to Disclose, jiayin wang:Nothing to Disclose, Chao Yang:Nothing to Disclose, Jing Liang:Nothing to Disclose, Qing Ye:Nothing to Disclose, Huiling Xiang:Nothing to Disclose.

4129 | QUANTITATIVE HEPATITIS B SURFACE ANTIGEN (QHBSAG) DYNAMICS IN PATIENTS WITH CHRONIC HEPATITIS B UNDERGOING ANTIVIRAL THERAPY: ASSOCIATION WITH THE RISK OF HCC

Jung Hwan Yu[1] Jin-Woo Lee[2] Yunmi Ko[2], [1]Inha university, [2]Inha university hospital

Background: This study evaluated the clinical implications of hepatitis B surface antigen quantification (qHBsAg) in patients with chronic hepatitis B (CHB) treated with entecavir (ETV), tenofovir disoproxil fumarate (TDF), or tenofovir alafenamide (TAF). We specifically aimed to identify the association between qHBsAg levels and the risk of developing hepatocellular carcinoma (HCC). **Methods:** Between January 2009 and December 2023, clinical data and qHBsAg levels were analyzed for 279 patients (ETV: n = 65, TDF: n = 164, TAF: n = 50) who initiated antiviral therapy.The method of measuring the HBs Ag quantitative value in all patients was the Architect HBsAg QT (Abbott Diagnostic, Wiesbaden, Germany). All of them had been HBs Ag-positive for longer than six months and had undergone antiviral therapy for a CHB infection according to the guidelines published by the American Association for the Study of Liver Diseases (AASLD). **Results:** During a mean follow-up period of 43.2 months, 105 patients (44.8%) achieved either a > 50% reduction in qHBsAg or a qHBsAg level < 1,000 IU/mL after one year of treatment. Patients meeting these criteria showed a significantly lower incidence of HCC ($p < 0.032$) and decompensated cirrhosis ($p < 0.023$) compared to those who did not. There were no significant differences in HCC development ($p = 0.290$) or qHBsAg reduction rates ($p = 0.204$) among the ETV, TDF, and TAF groups. Multivariate analysis identified the present of cirrhosis ($p = 0.043$) as an independent predictor of critical event development. **Conclusion:** A significant reduction in qHBsAg (> 50% decrease or level < 1,000 IU/mL) at one year of antiviral therapy is associated with a lower risk of HCC and decompensated cirrhosis. Monitoring qHBsAg levels can serve as a valuable predictive marker for long-term clinical outcomes in CHB patients treated with ETV, TDF, or TAF.



Disclosures: Jung Hwan Yu:Nothing to Disclose, Jin-Woo Lee:Nothing to Disclose, Yunmi Ko:Nothing to Disclose.

4130 | TENOFOVIR ALAFENAMIDE ADD-ON THERAPY DURING PEGYLATED INTERFERON ALFA-2B TREATMENT IS LINKED TO GREATER HBSAG LOSS IN NA-EXPERIENCED CHRONIC HEPATITIS B: A REAL-WORLD COHORT STUDY WITH INTERNAL VALIDATION OF A 48-WEEK PREDICTION MODEL

Xueping Yu[1] Huatang Zhang[2] Kaimin Song[2], [1]The First Hospital of Quanzhou affiliated to Fujian Medical, [2]The First Hospital of Quanzhou affiliated to Fujian Medical University

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Background: This study aimed to compare the clinical outcomes of different pegylated interferon alfa-2b (Peg-IFNα-2b)-based treatment strategies in nucleos(t)ide analogue (NA) -experienced patients with chronic hepatitis B (CHB), and to develop internally validated models for predicting hepatitis B surface antigen (HBsAg) loss at week 48. **Methods:** In this single-center retrospective real-world cohort, 865 NA-experienced patients with CHB were initially screened, and 765 eligible patients were included in the final analysis. According to the treatment regimen, patients were classified into four groups: Peg-IFNα-2b monotherapy, Peg-IFNα-2b plus entecavir (ETV), Peg-IFNα-2b plus tenofovir disoproxil fumarate (TDF), and Peg-IFNα-2b plus tenofovir alafenamide (TAF). Longitudinal changes in four binary outcomes, including HBsAg loss, hepatitis B e antigen (HBeAg) loss, undetectable hepatitis B virus DNA (HBV DNA), and alanine aminotransferase (ALT) normalization, were examined using generalized estimating equation (GEE) logistic models, with particular attention to treatment-by-time interactions. Adjusted multivariable logistic regression was then used to compare week-48 outcomes across treatment groups. Missing data were handled through complete-case analysis, multiple imputation, and inverse probability weighting as sensitivity analyses. Baseline and simplified week-12 dynamic models were constructed to predict HBsAg loss at week 48. Model performance was assessed using the area under the receiver operating characteristic curve (AUC), Brier score, bootstrap correction, and 10-fold cross-validation. **Results:** Across follow-up, all four groups showed overall improvements in HBsAg loss, HBeAg loss, HBV DNA suppression, and ALT normalization. After adjustment for baseline covariates, the Peg-IFNα-2b plus TAF group showed the highest estimated probability of HBsAg loss at week 48 (46.6%), compared with Peg-IFNα-2b monotherapy (25.7%), Peg-IFNα-2b plus TDF (33.3%), and Peg-IFNα-2b plus ETV (28.9%). For HBeAg loss, HBV DNA negativity, and ALT normalization, no consistent or robust between-group differences were observed at week 48. The baseline prediction model achieved an apparent AUC of 0.853 and a bootstrap-corrected AUC of 0.842. The simplified week-12 dynamic model yielded an apparent AUC of 0.842 and a bootstrap-corrected AUC of 0.841. Among patients with available week-12 HBsAg data, the simplified week-12 model reached an AUC of 0.850, which was comparable to the predictive value of week-12 HBsAg alone. **Conclusion:** Different Peg-IFNα-2b treatment strategies were associated with virological and biochemical improvements, and the TAF combination regimen was associated with a higher probability of HBsAg loss. Lower baseline HBsAg level, younger age, and TAF combination therapy were associated with 48-week HBsAg loss.

Disclosures: Xueping Yu:Nothing to Disclose, Huatang Zhang:Nothing to Disclose, Kaimin Song:Nothing to Disclose.

4131 | FUNCTIONAL CURE IN DIFFERENT STRATIFIED ANALYSES OF CHRONIC HEPATITIS B PATIENTS TREATED WITH PEGINTERFERON ALPHA-2B: A POST-HOC ANALYSIS OF A PHASE 3 TRIAL

Guiqiang Wang[1] Fengqin Hou[2] Qing Xie[3] Chunliang Lei[4] Zhiliang Gao[5] Jia Shang[6] Jianmei Lin[7] Guoxin Hu[8] Xiaozhong Wang[9] Yilan Zeng[10] Jiabin Li[11] Jun Chen[12] Zuxiong Huang[13] Liying Zhu[14] Yan Huang[15] Qianguo Mao[16] Guozhong Gong[17] Jiming Zhang[18] Hongxin Piao[19] Ye Gu[20] Ping An[20] Xiaolu Wu[21] Xiulan Xue[21] Liaoyun Zhang[22] Yueyong Zhu[23] Yingren Zhao[24] Fusheng Wang[25] Jianqi Lian[26] Xinyue Chen[27] Chao Wu[28] Hui Guo[29] Huiling Xiang[30] Yao Xie[31] Dongliang Li[32] Qin Ning[33] Xiaobo Lu[34] Ruoyi He[35] Yalin Yin[35] Li Sun[35], [1]Peking University First Hospital, Beijing, 100034, China; Peking University International Hospital, Beijing, 102206, China, [2]Peking University First Hospital, Beijing, 100034, China, [3]Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, 200000, China, [4]Guangzhou Eighth People's Hospital, Guangzhou Medical University, Guangzhou, 510000, China, [5]The Third Affiliated Hospital, Sum Yat-Sen University, Guangzhou, 510000, China, [6]Henan Provincial People's Hospital, Zhengzhou, 450000, China, [7]Sichuan Provincial People's Hospital · Sichuan Academy of Medical Sciences, Chengdu, 610000, China, [8]Peking University Shenzhen Hospital, Shenzhen, 518000, China, [9]Xinjiang Uygur Autonomous Region Hospital of Traditional Chinese Medicine, Urumqi, 830000, China, [10]Public Health Clinical Center of Chengdu, Chengdu, 610000, China, [11]The First Affiliated Hospital of Anhui Medical University, Hefei, 230000, China, [12]Shenzhen Third People's Hospital, Shenzhen, 518000, China, [13]Mengchao Hepatobiliary Hospital of Fujian Medical University, Fuzhou, 350000, China, [14]The Fourth Affiliated Hospital of Harbin Medical University, Harbin, 150001, China, [15]Xiangya Hospital Central South University, Changsha, 410000, China, [16]Xiamen Hospital of Traditional Chinese Medicine, Xiamen, 361000, China, [17]The Second Xiangya Hospital of Central South University, Changsha, 410000, China, [18]Huashan Hospital, Fudan University, Shanghai, 200040, China, [19]Yanbian University Hospital (Yanbian Hospital), Yanji, 133000, China, [20]The Sixth People's Hospital of Shenyang, Shenyang, 110000, China, [21]The First Affiliated Hospital of Xiamen University, Xiamen, 361000, China, [22]The First Hospital of Shanxi

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Background: In a randomized controlled phase 3 trial, treatment with peginterferon alfa-2b (PegIFNα-2b, Pegbing®, Xiamen Amoytop Biotech Co., Ltd.) at 180 μg/week resulted in HBsAg loss and HBV DNA undetectable at 24 weeks after discontinuation of all drugs—that is functional cure—in 31.4% of nucleos(t)ide analogue (NA)-experienced chronic hepatitis B patients. Here, we analyzed the impact of baseline characteristics on the achievement of functional cure. **Methods:** NA-experienced patients with HBsAg < 1,500 IU/mL, HBeAg < 10 COI, and HBV DNA < 100 IU/mL were enrolled in a phase 3 trial (NCT04846491) and randomly assigned to receive tenofovir disoproxil fumarate (TDF) monotherapy (group 1), TDF plus PegIFNα-2b 180 μg/week (group 2) or 90 μg/week (group 3). The treatment period was 144 weeks and the follow-up was 24 weeks. PegIFNα-2b was administered intermittently in cycles. This post-hoc analysis evaluated the impact of baseline HBsAg levels, HBeAg and HBV DNA statuses on functional cure in the PegIFNα-2b 180 μg/week group (group 2). **Results:** Among NA-experienced patients receiving PegIFNα-2b 180 μg/week combination therapy (group 2), the overall functional cure rate was 31.4%. In the HBeAg-negative subgroup, the functional cure rates for patients with baseline HBsAg ≤ 100 and >100 −≤1000 IU/mL were 66.7% (18/27) and 30.4% (17/56), respectively (Figure 1). Among HBeAg-negative patients with undetectable HBV DNA, the functional cure rates were 65.4% (17/26) for patients with baseline HBsAg ≤ 100 IU/mL and 27.8% (15/54) for patients with >100 −≤1000 IU/mL, respectively. **Conclusion:** A finite regimen of PegIFNα-2b resulted in functional cure in over 30% of NA-experienced patients. Lower baseline HBsAg levels were associated with higher functional cure rates. Notably, even in the subgroup with baseline HBsAg levels >100−≤1000 IU/mL and HBeAg-negative, a robust functional cure rate of 30% was observed.

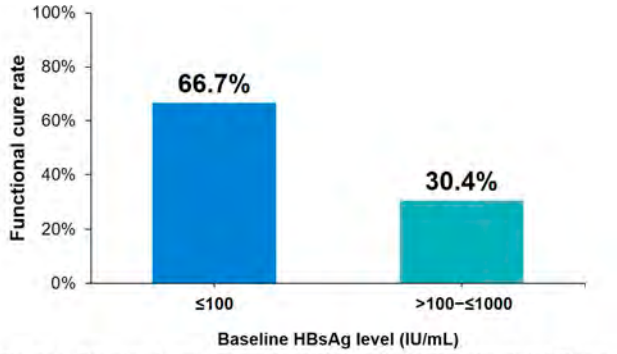


Figure 1. Functional cure rates stratified by baseline HBsAg levels in HBeAg-negative patients in the PegIFNα-2b 180 μg/week combination group.

Disclosures: Guiqiang Wang:Nothing to Disclose, Fengqin Hou:Nothing to Disclose, QING XIE:Nothing to Disclose, Chunliang Lei:Nothing to Disclose, Zhiliang Gao:Nothing to Disclose, Jia Shang:Nothing to Disclose, Jianmei Lin:Nothing to Disclose, Guoxin Hu:Nothing to Disclose, Xiaozhong Wang:Nothing to Disclose, Yilan Zeng:Nothing to Disclose, Jiabin Li:Nothing to Disclose, Jun Chen:Nothing to Disclose, Zuxiong Huang:Nothing to Disclose, Liying Zhu:Nothing to Disclose, Yan Huang:Nothing to Disclose, Qianguo Mao:Nothing to Disclose, Guozhong Gong:Nothing to Disclose, Jiming Zhang:Nothing to Disclose, Hongxin Piao:Nothing to Disclose, Ye Gu:Nothing to Disclose, Ping An:Nothing to Disclose, Xiaolu Wu:Nothing to Disclose, Xiulan Xue:Nothing to Disclose, Liaoyun Zhang:Nothing to Disclose, Yueyong Zhu:Nothing to Disclose, Yingren Zhao:Nothing to Disclose, Fusheng Wang:Nothing to Disclose, Jianqi Lian:Nothing to Disclose, Xinyue Chen:Nothing to Disclose, Chao Wu:Nothing to Disclose, Hui Guo:Nothing to Disclose, Huiling Xiang:Nothing to Disclose, Yao Xie:Nothing to Disclose, Dongliang Li:Nothing to Disclose, Qin Ning:Nothing to Disclose, Xiaobo Lu:Nothing to Disclose, Ruoyi He:Nothing to Disclose, Yalin Yin:Nothing to Disclose, Li Sun:Nothing to Disclose.

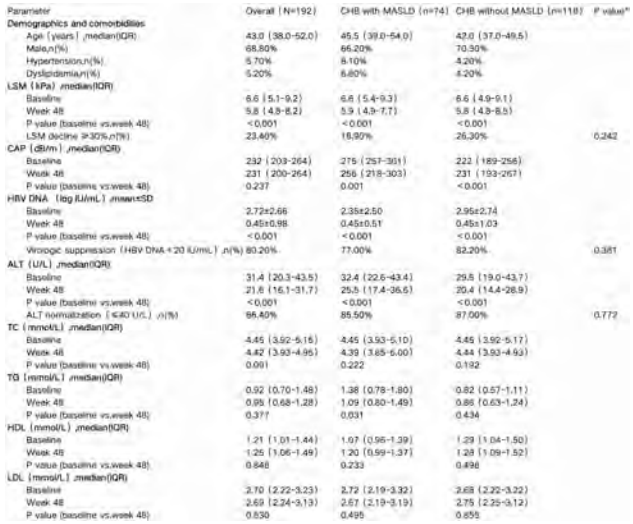
4132 | IMPACT OF TENOFOVIR AMIBUFENAMIDE ON LIVER STIFFNESS MEASUREMENT IN CHRONIC HEPATITIS B PATIENTS WITH CONCOMITANT MASLD: A REAL-WORLD STUDY

Wen Xie[1] Jingjing Wang[1] Wenya Chen[1] Qi Wang[1] Hong Zhao[1] Liugai Liu[1], [1]Beijing Ditan Hospital, Capital Medical University

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Background: Tenofovir amibufenamide (TMF) is a Chinese original first-line antiviral agent for the treatment of chronic hepatitis B (CHB). Metabolic dysfunction-associated steatotic liver disease (MASLD) is a common comorbidity in CHB patients and may influence the improvement of liver stiffness measurementf (LSM) following antiviral therapy. However, more evidence is needed regarding the efficacy of TMF in CHB patients with concomitant MASLD. **Methods:** This retrospective real-world study enrolled 192 CHB patients who received TMF monotherapy for at least 48 weeks, including 74 (38.5%) with baseline MASLD. All patients underwent transient elastography (FibroScan) at baseline and week 48 to record LSM and controlled attenuation parameter (CAP). According to the device operating instructions, the upper limit of normal LSM was 7.0 kPa, and the upper limit of normal CAP was 238 dB/m. The primary endpoint was the proportion of patients with a $\geq$30% decline in LSM from baseline. Changes in LSM decline, virologic suppression (HBV DNA < 20 IU/mL), ALT normalization ($\leq$40 U/L), and lipid profiles were compared between the two groups. **Results:** At baseline, median LSM was within the normal range in both groups (6.6 kPa for both). After 48 weeks of treatment, the proportion of patients with a $\geq$30% decline in LSM was 18.9% in the MASLD group and 26.3% in the non-MASLD group, with no statistically significant difference between the two groups (P = 0.242). Virologic suppression rates (77.0% vs. 82.2%, P = 0.381) and ALT normalization rates (85.5% vs. 87.0%, P = 0.772) were also similar between the two groups. Within the MASLD group, patients with a $\geq$30 dB/m decline in CAP (n = 28, 43.8%) had a higher proportion of $\geq$30% LSM decline compared to those without CAP improvement (28.6% vs. 8.3%, P = 0.047). Lipid profile analysis showed a decrease in triglyceride levels in the MASLD group (1.38 vs. 1.09 mmol/L, P = 0.031), while total cholesterol, HDL, and LDL remained stable (all P > 0.05). **Conclusion:** This study yields three main findings. First, in CHB patients with baseline LSM within the normal range, the presence of MASLD did not affect the efficacy of TMF in achieving LSM decline, virologic suppression, or ALT normalization after 48 weeks of treatment. Second, improvement in hepatic steatosis was associated with a higher proportion of LSM decline, suggesting that metabolic control may enhance anti-fibrotic efficacy. Third, lipid profiles remained stable during TMF treatment, with a trend toward decreased triglycerides and no adverse metabolic effects. In summary, TMF, as a Chinese original first-line antiviral agent, offers both consistent antiviral efficacy and favorable metabolic safety in CHB patients with concomitant MASLD.



Parameter	Overall (N=192)	CHB with MASLD (n=74)	CHB without MASLD (n=118)	P value*
Demographics and comorbidities				
Age (years) ,median(IQR)	43.0 (38.0-52.0)	45.5 (39.0-54.0)	42.0 (37.0-49.5)	
Male,n(%)	68.80%	66.20%	70.30%	
Hypertension,n(%)	5.70%	8.10%	4.20%	
Dyslipidemia,n(%)	5.20%	5.80%	4.20%	
LSM (kPa) ,median(IQR)				
Baseline	6.6 (5.1-9.2)	6.6 (5.4-9.3)	6.6 (4.9-9.1)	
Week 48	5.8 (4.9-8.2)	5.9 (4.9-7.7)	5.8 (4.9-8.5)	
P value (baseline vs.week 48)	<0.001	<0.001	<0.001	
LSM decline ≥30%,n(%)	23.40%	18.90%	26.30%	0.242
CAP (dB/m) ,median(IQR)				
Baseline	232 (203-264)	275 (257-301)	222 (189-256)	
Week 48	231 (200-264)	256 (218-303)	231 (193-267)	
P value (baseline vs.week 48)	0.237	0.001	<0.001	
HBV DNA (log IU/mL) ,mean±SD				
Baseline	2.72±2.66	2.35±2.50	2.95±2.74	
Week 48	0.45±0.98	0.45±0.51	0.45±1.03	
P value (baseline vs.week 48)	<0.001	<0.001	<0.001	
Virologic suppression (HBV DNA < 20 IU/mL) ,n(%)	80.20%	77.00%	82.20%	0.381
ALT (U/L) ,median(IQR)				
Baseline	31.4 (20.3-43.5)	32.4 (22.6-43.4)	29.5 (19.0-43.7)	
Week 48	21.6 (16.1-31.7)	25.5 (17.4-36.5)	20.4 (14.4-28.9)	
P value (baseline vs.week 48)	<0.001	<0.001	<0.001	
ALT normalization (≤40 U/L) ,n(%)	86.40%	85.50%	87.00%	0.772
TC (mmol/L) ,median(IQR)				
Baseline	4.45 (3.92-5.16)	4.45 (3.93-5.10)	4.45 (3.92-5.17)	
Week 48	4.42 (3.93-4.95)	4.39 (3.85-5.00)	4.44 (3.93-4.93)	
P value (baseline vs.week 48)	0.091	0.222	0.192	
TG (mmol/L) ,median(IQR)				
Baseline	0.92 (0.70-1.48)	1.38 (0.78-1.80)	0.82 (0.57-1.11)	
Week 48	0.95 (0.68-1.28)	1.09 (0.80-1.49)	0.86 (0.63-1.24)	
P value (baseline vs.week 48)	0.377	0.031	0.434	
HDL (mmol/L) ,median(IQR)				
Baseline	1.21 (1.01-1.44)	1.07 (0.96-1.39)	1.29 (1.04-1.50)	
Week 48	1.25 (1.06-1.49)	1.20 (0.99-1.37)	1.28 (1.09-1.52)	
P value (baseline vs.week 48)	0.848	0.233	0.498	
LDL (mmol/L) ,median(IQR)				
Baseline	2.70 (2.22-3.23)	2.72 (2.19-3.32)	2.68 (2.22-3.22)	
Week 48	2.69 (2.24-3.13)	2.67 (2.19-3.19)	2.75 (2.25-3.12)	
P value (baseline vs.week 48)	0.830	0.495	0.655	

Disclosures: wen Xie:Nothing to Disclose, Jingjing Wang:Nothing to Disclose, Wenya Chen:Nothing to Disclose, Qi Wang:Nothing to Disclose, Hong Zhao: Nothing to Disclose, Liugai Liu:Nothing to Disclose.

4133 | ANALYSIS OF THE EFFICACY AND SAFETY OF PRADEFOVIR MESYLATE TABLETS IN THE TREATMENT OF CHRONIC HEPATITIS B: A REAL-WORLD STUDY OF 81 PATIENTS

Yuemin Nan[1] Yukai Chen[2] Yaoyao Mao[2] Rongqi Wang[2] Suxian Zhao[2] Na Fu[2], [1]Third hosptial of Hebei medical university, [2]Hebei Medical University Third Hospital

Background: Chronic Hepatitis B (CHB) is caused by persistent infection with the Hepatitis B virus (HBV). Globally, there are approximately 254 million chronic carriers, with 1,100,000 annual deaths. In China, the HBsAg prevalence rate is 5%-6%, equating to about 75 million patients, representing a significant disease burden. Pradefovir Mesylate Tablets (PDF), a liver-targeting prodrug launched in 2024, was confirmed in Phase III clinical trials to effectively suppress HBV DNA replication and rapidly and potently reduce Hepatitis B surface antigen (HBsAg) levels, laying the foundation for clinical cure of CHB. However, due to its recent market entry, there is an urgent need for real-world clinical treatment data to provide strategies for individualized treatment optimization. **Methods:** This retrospective study analyzed the complete medical records of 81 NAs-experienced CHB patients nationwide who received PDF treatment. Data collected and analyzed included baseline levels and levels at 12 and 24 weeks post-treatment for HBV DNA, HBsAg, HBeAg, serum

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ALT, as well as the occurrence of adverse events during treatment, to evaluate the efficacy and safety of Pradefovir Mesylate Tablets. **Results:** After PDF treatment, the 81 CHB patients showed significant improvements in virological and serological markers. Specifically: The HBV DNA undetectable rate reached 63.04% (29/46) at week 12 and 73.91% (34/46) at week 24; Among patients with baseline HBV DNA levels between the lower limit of detection and 2000 IU/mL (n = 19), 12 patients (63.0%) achieved HBV DNA undetectability at week 12, and 14 patients (73.68%) at week 24; Among 6 patients with high viral load (HBV DNA $\geq 10^7$ IU/mL), the HBV DNA undetectable rates were 33.33% (n = 2) at week 24; The HBsAg loss rate was 3.75% (n = 3) at week 12 and 5% (n = 4) at week 24; The proportion of patients with HBsAg $\leq$ 1000 IU/mL increased from 30.86% (n = 25) at baseline to 35.80% (n = 29) at week 12 and 40.74% (n = 33) at week 24; The HBeAg seroconversion rate was 3.85% (n = 1) at week 12 and 11.54% (n = 3) at week 24; The ALT normalization rate was 72.73% (n = 16) at week 12; No significant changes were observed in liver function, kidney function, or blood lipid levels before and after treatment, and no significant adverse events were identified. **Conclusion:** In real-world clinical practice, PDF effectively suppresses HBV DNA replication and rapidly promotes HBsAg clearance, demonstrating good clinical efficacy and safety. Its clinical application value warrants further exploration in the future.

Disclosures: Yuemin Nan:Nothing to Disclose, yukai chen:Nothing to Disclose, Yaoyao Mao:Nothing to Disclose, Rongqi Wang:Nothing to Disclose, suxian Zhao:Nothing to Disclose, Na Fu:Nothing to Disclose.

4134 | MACHINE LEARNING-BASED MODEL FOR PREDICTING HBSAG SEROCLEARANCE IN CHRONIC HEPATITIS B PATIENTS RECEIVING PEG-IFN COMBINED WITH TAF/TDF

Tianyu Ma[1] Minghui Li[1], [1]Beijing Ditan Hospital, Capital Medical University

Background: Functional cure is the ideal treatment goal for chronic hepatitis B (CHB). Pegylated interferon (Peg-IFN) combined with tenofovir alafenamide (TAF) or tenofovir disoproxil fumarate (TDF) is a commonly used regimen. However, early and accurate prediction of which patients will achieve HBsAg loss remains challenging. This study aimed to develop and validate a machine learning model for early prediction of functional cure in CHB patients receiving Peg-IFN combined with TAF/TDF. **Methods:** We retrospectively included 302 CHB patients from a single center as the training cohort, and 142 patients from a subsequent time period as the internal temporal validation cohort. Functional cure was defined as achieving HBsAg < 0.05 IU/mL within 18 months or less after treatment initiation. A total of 68 clinical and laboratory variables at baseline and at 3 months were collected. Feature selection was performed using the Boruta algorithm and least absolute shrinkage and selection operator (LASSO) regression, and collinear variables were removed from the pooled set of selected variables. Eleven machine learning algorithms were constructed, including Random Forest (RF), Support Vector Machine (SVM), Logistic Regression (LR), K-Nearest Neighbors (KNN), Partial Least Squares (PLS), Gradient Boosting Machine (GBM), Neural Network (NN), Naïve Bayes (NB), Linear Discriminant Analysis (LDA), LASSO (glmnet), and Adaptive Boosting (AdaBoost). Model performance was evaluated using the area under the receiver operating characteristic curve (AUC), accuracy, sensitivity, specificity, F1 score, and decision curve analysis (DCA). The optimal model was interpreted using SHapley Additive exPlanations (SHAP). **Results:** Functional cure was achieved in 46 of 302 patients (15.2%) in the training cohort and in 33 of 142 patients (23.2%) in the validation cohort. Six variables were ultimately selected: baseline HBsAg (log10), 3-month HBsAg decline (log10), 3-month red blood cell count (RBC_3), age, 3-month change in ALT (log10), and 3-month HBeAg (log10). Among all models, the GBM model exhibited good discriminative ability, with an AUC of 0.839 (95% CI: 0.766–0.913) in the validation set, and showed the highest net benefit in decision curve analysis within the clinically relevant threshold range (0.1–0.4), suggesting superior clinical utility. SHAP analysis revealed that 3-month HBsAg decline and baseline HBsAg were the most important predictors. **Conclusion:** The GBM-based prediction model accurately identifies CHB patients likely to achieve functional cure following treatment with Peg-IFN combined with TAF/TDF. This model offers favorable clinical net benefit and can assist clinicians in individualized treatment decisions, although external validation in multicenter cohorts remains necessary.

Models	Sensitivity	Specificity	Accuracy	PPV	NPV	F1	Youden's index
RandomForest	0.6363636	0.8532110	0.8028169	0.5675676	0.8857143	0.6000000	0.4895746
SVM_Kernel	0.6363636	0.8348624	0.7887324	0.5384615	0.8834951	0.5833333	0.4712260
LogisticModel	0.7272727	0.7798165	0.7676056	0.5000000	0.9042553	0.5925926	0.5070892
NeighborMethod	0.8181818	0.7889908	0.7957746	0.5400000	0.9347826	0.6506024	0.6071726
PLSModel	0.7272727	0.7706422	0.7605634	0.4897959	0.9032258	0.5853659	0.4979149
BoostingMethod	0.7272727	0.7981651	0.7816901	0.5217391	0.9062500	0.6075949	0.5254379
NeuralNet	0.6969697	0.7798165	0.7605634	0.4893617	0.8947368	0.5750000	0.4767862
BayesMethod	0.8181818	0.6972477	0.7253521	0.4500000	0.9268293	0.5806452	0.5154295
DiscriminantModel	0.7272727	0.7706422	0.7605634	0.4897959	0.9032258	0.5853659	0.4979149
Lasso	0.7272727	0.7798165	0.7676056	0.5000000	0.9042553	0.5925926	0.5070892
AdaptiveBoosting	0.6363636	0.8532110	0.8028169	0.5675676	0.8857143	0.6000000	0.4895746

Disclosures: Tianyu Ma:Nothing to Disclose, Minghui Li:Nothing to Disclose.

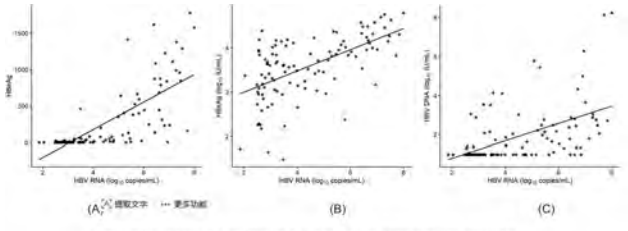
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4135 | DYNAMIC CHANGES AND VIROLOGICAL CORRELATIONS OF HBV RNA DURING PEGIFN ADD-ON THERAPY IN NUCLEOS(T)IDE ANALOGUE-EXPERIENCED PATIENTS WITH CHRONIC HEPATITIS B

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Background: HBV RNA is considered to originate from intrahepatic covalently closed circular DNA (cccDNA) transcriptional products and may reflect HBV transcriptional activity. In chronic hepatitis B (CHB) patients receiving long-term nucleos(t)ide analogue (NA) therapy, HBV DNA is often effectively suppressed, whereas the dynamic changes and clinical significance of HBV RNA remain unclear. This study aimed to characterize HBV RNA dynamics during PegIFN-α add-on therapy in NA-experienced patients with CHB and to evaluate its correlations with virological and clinical parameters. **Methods:** A total of 295 patients with CHB who had received NA therapy for more than 24 weeks and subsequently received PegIFN-α 180 μg add-on therapy were enrolled. HBV RNA, HBV DNA, HBsAg, HBeAg, and liver function parameters were collected at baseline and at weeks 12, 24, and 48. Spearman correlation analysis was performed to assess correlations between HBV RNA and other clinical parameters. Baseline characteristics were also compared between HBV RNA-positive and HBV RNA-negative patients. **Results:** At baseline, 36.61% (108/295) of patients were HBV RNA-positive. Compared with HBV RNA-negative patients, HBV RNA-positive patients had significantly higher levels of HBsAg, HBV DNA, and HBeAg (all $P < 0.001$), as well as higher ALT and AST levels (both $P < 0.001$).Among HBV RNA-positive patients, HBV RNA levels showed a strong positive correlation with HBeAg ($r = 0.792$, $P < 0.001$) and moderate positive correlations with HBsAg ($r = 0.597$, $P < 0.001$) and HBV DNA ($r = 0.590$, $P < 0.001$). No significant correlations were observed between HBV RNA and liver function parameters, including ALT, AST, TBIL, and ALB (all $P > 0.05$).During PegIFN-α add-on therapy, HBV RNA levels gradually declined over time. Median HBV RNA levels decreased from 1.40 (1.40, 3.07) log10 copies/mL at baseline to 1.40 (1.40, 2.12) log10 copies/mL at week 48 ($P < 0.001$). Meanwhile, HBsAg levels continuously declined, whereas HBV DNA remained suppressed from the early treatment phase onward. **Conclusion:** In NA-experienced patients with CHB, HBV RNA was well correlated with HBsAg, HBV DNA, and HBeAg, suggesting that it may reflect HBV transcriptional activity. HBV RNA showed an overall declining trend during PegIFN-α add-on therapy but demonstrated limited correlation with liver function parameters, indicating that HBV RNA mainly reflects virological activity rather than host immune-mediated liver injury.



A: HBV RNA and HBeAg; B: HBV RNA and HBsAg; C: HBV RNA and HBV DNA

Figure 4. Correlations between HBV RNA and other parameters in patients with positive HBV RNA at baseline.

Disclosures: Ziyu Zhang:Nothing to Disclose, Minghui Li:Nothing to Disclose.

4136 | SHORT-TERM EFFICACY AND SAFETY ANALYSIS OF PDF MONOTHERAPY VERSUS PDF COMBINED WITH INTERFERON FOR CHRONIC HEPATITIS B

Wenwen Ren[1] Ying Wang[1] Xiaolan Shi[1] Chi Lv[1] Juan Li[1], [1]the First Affiliated Hospital of Zhengzhou University

Background: Pradefovir mesylate (PDF), a novel liver-targeting adefovir prodrug developed using the HepDirect™ prodrug technology, has become an important treatment option for adult patients with chronic hepatitis B (CHB). However, real-world clinical evidence regarding its short-term efficacy and safety remains insufficient. Therefore, this study aimed to evaluate the short-term efficacy of PDF monotherapy versus PDF combined with interferon in a real-world setting, and to observe their impact on liver and kidney function. **Methods:** This study retrospectively analyzed the efficacy and safety of 12-week short-term treatment with PDF monotherapy (PDF, $n = 78$) or PDF combined with interferon (PDF+IFN, $n = 29$) in 107 CHB patients. The primary efficacy endpoints included the HBV DNA negative conversion rate and reduction magnitude, changes in HBsAg levels and HBsAg negative conversion rate, and the ALT normalization rate. Safety indicators covered liver function, kidney function, lipids, and others. **Results:** At the end of 12 weeks of treatment, the HBV DNA negative conversion rate in the PDF group was 52.50%, which was significantly higher than that in the PDF+IFN group (18.75%, $P = 0.021$). In the PDF group, the quantitative HBV DNA level decreased from a baseline of 2.50 ± 1.97 $\log_{10}$ IU/mL to 1.97 ± 1.15 $\log_{10}$ IU/mL at week 12, with a mean decline of -0.53 ± 1.42 $\log_{10}$ IU/mL ($P = 0.044$). In the PDF+IFN group, the HBV DNA level decreased from

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2.88 ± 2.20 log_{10} IU/mL at baseline to 2.07 ± 0.94 log_{10} IU/mL at week 12, with a mean decline of –0.81 ± 1.52 log_{10} IU/mL (P = 0.075). No HBsAg seroclearance occurred in either group; however, the PDF+IFN group showed a significantly greater reduction in HBsAg level than the PDF group (–0.35 ± 0.42 vs. –0.08 ± 0.20, P = 0.0023). During the treatment period, no statistically significant difference was observed in ALT levels between the two groups (P > 0.05), and no other serious adverse events occurred. **Conclusion:** PDF monotherapy for 12 weeks effectively suppresses HBV DNA with a favorable safety profile; the addition of interferon further reduces HBsAg, offering added value in strategies aiming for HBsAg decline.

Disclosures: Wenwen Ren:Nothing to Disclose, Ying Wang:Nothing to Disclose, Xiaolan Shi:Nothing to Disclose, Chi Lv:Nothing to Disclose, Juan Li:Nothing to Disclose.

4137 | LIVER FUNCTION ABNORMALITIES AND ANTIVIRAL TREATMENT PATTERNS IN HBV-INFECTED PREGNANT WOMEN FOLLOWING IVF-ET: A SINGLE-CENTER RETROSPECTIVE STUDY

Xueting Ou[1] Liyang Zhou[1] Panpan Zhai[1] Sichen Li[1] Shiyun Wu[1] Xing-Fei Pan[1], [1]The Third Affiliated Hospital, Guangzhou Medical University

Background: It remains unclear that whether hepatitis flare during pregnancy could affect the maternal and neonatal outcomes of HBV-infected patients who had undergone in vitro fertilization-embryo transfer (IVF-ET). In the present study, we compared the clinical characteristics, pregnancy complications, and antiviral treatment strategies between HBV-infected patients with and without abnormal liver function after IVF-ET, in order to provide evidence for the management of liver disease during the pregnancy period. **Methods:** A retrospective study was conducted on HBV-infected patients who underwent IVF-ET at the Third Affiliated Hospital of Guangzhou Medical University between 2022 and 2023. Patients were divided into two groups based on liver function during pregnancy: abnormal liver function group (n = 23) and normal liver function group (n = 78). Demographic characteristics, virological parameters, medical history, pregnancy complications, features of liver dysfunction, and treatment regimens were collected, respectively. Non-parametric tests and chi-square tests were used for intergroup comparisons. **Results:** There were no statistically significant differences in age, HBeAg positivity rate, underlying diseases, or pregnancy complications between the two groups, respectively (P > 0.05). The abnormal liver function group showed a trend toward higher HBV DNA levels compared to the normal liver function group (median 6.09 vs. 3.37 log IU/mL, P = 0.054).The first onset of liver dysfunction was often at gestational week 6, with median ALT and AST levels of 69.80 U/L and 48.60 U/L, respectively. The rate of taking antiviral drug was similar between the two groups (69.57% vs. 73.08%, P = 0.741). However, the proportion of patients initiating antiviral therapy before pregnancy was significantly higher in the abnormal liver function group (26.09% vs. 7.69%, P = 0.017), and the median gestational week of initiating antiviral therapy was earlier (22.00 vs. 28.00 weeks, P = 0.012) compared to the normal liver function group. There was no a statistically significant difference in the choice of TDF or TAF regimen between the two groups. Liver-protecting therapy was administered to 69.57% of patients with abnormal liver function. **Conclusion:** In HBV-infected pregnant women who had undergone IVF-ET, abnormal liver function during pregnancy may be associated with higher HBV DNA levels and need initiating antiviral therapy in the early-to-mid pregnancy. Hepatitis flare often occurs in the first trimester in patients with high viral loads, highlighting the importance of monitoring liver function during early pregnancy. Due to the retrospective nature and limited sample size of this study, further prospective studies with larger cohorts need doing to validate these findings.

Table 1. Baseline characteristics, obstetric complications, and treatment strategies of HBV-infected patients with or without abnormal liver function after IVF-ET

Characteristic	Abnormal LF group (n=23)	Normal LF group (n=78)	*P* value
Demographics and virology			
Age (years)	33.00 (30.00, 36.50)	31.00 (34.00, 37.00)	0.274
HBeAg positive, n (%)	12 (52.17)	32 (41.03)	0.343
HBV DNA (log IU/mL)	6.09 (2.82, 8.06)	3.37 (0.00, 7.12)	0.054
Medical history, n (%)			
Alcohol intake	0 (0.00)	5 (6.41)	0.213
Raw food consumption	2 (8.70)	9 (11.54)	0.701
Fatty liver	0 (0.00)	4 (5.13)	0.268
Hypertension	1 (4.35)	1 (1.28)	0.354
Diabetes	1 (4.35)	1 (1.28)	0.354
Obstetric complications, n (%)			
Gestational hypertension	1 (4.35)	4 (5.13)	0.879
Preeclampsia	2 (8.70)	1 (1.28)	0.066
Gestational diabetes	3 (13.04)	11 (14.10)	0.897
Intrahepatic cholestasis of pregnancy	1 (4.35)	2 (2.56)	0.658
Multiple pregnancy	4 (17.39)	16 (20.51)	0.741
Liver function abnormalities			
Gestational week at onset	6.00 (4.00, 14.00)	–	–
ALT (U/L)	69.80 (57.30, 95.40)	–	–
AST (U/L)	48.60 (37.10, 58.20)	–	–
Therapy			
Liver-protecting medicine, n (%)	16 (69.57)	–	–
Gestational week at initiation	7.00 (4.00, 16.50)	–	–
Antiviral drug use, n (%)	16 (69.57)	57 (73.08)	0.741
TDF, n (%)	12 (52.17)	38 (48.72)	0.771
TAF, n (%)	4 (17.39)	19 (24.36)	0.484
Antiviral treatment initiation time			
Before pregnancy, n (%)	6 (26.09)	6 (7.69)	0.017
After pregnancy, n (%)	10 (43.48)	51 (65.38)	0.059
Gestational week at initiation	22.00 (7.25, 26.50)	28.00 (26.00, 30.00)	0.012

Data are presented as median (IQR) or n (%). P values were calculated using Mann-Whitney U test for continuous variables and chi-square or Fisher's exact test for categorical variables.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBV, hepatitis B virus; HBeAg, hepatitis B e antigen; IQR, interquartile range; IVF-ET, in vitro fertilization and embryo transfer; LF, liver function; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Disclosures: Xueting Ou:Nothing to Disclose, Liyang Zhou:Nothing to Disclose, Panpan Zhai:Nothing to Disclose, Sichen Li:Nothing to Disclose, Shiyun Wu:Nothing to Disclose, Xing-Fei Pan:Nothing to Disclose.

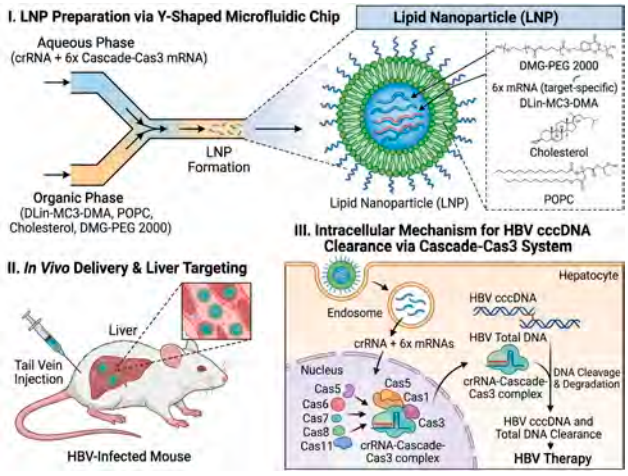
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4138 | ◆ LIPID-BASED CRISPR/CAS3 NANODRUG VIA MICROFLUIDIC TECHNOLOGY FOR HBV GENOME EDITING AND TREATMENT

Li Li[1] Xiangru Shan[1] Xinyue Guo[1] Yibei Xiao[2] Chuanlong Zhu[1], [1]The First Affiliated Hospital of Nanjing Medical University, [2]China Pharmaceutical University

Background: Hepatitis B virus (HBV) infection is a major etiological driver of chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma. Although current antiviral therapies effectively suppress HBV replication, they fail to eradicate intracellular HBV DNA, leaving patients vulnerable to viral rebound and disease recurrence after treatment discontinuation. The CRISPR/Cas3 system, characterized by sequencespecific target recognition and processive degradation of DNA, offers a promising therapeutic strategy for the precise targeting and clearance of HBV DNA. **Methods:** Based on conserved functional regions of the HBV genome, a crRNA targeting genes within the C region was rationally screened and designed. mRNAs encoding the Cascade–Cas3 system were generated by in vitro transcription, and a stable, uniform liposome-based nanodrug was constructed using microfluidic technology. The HBV DNA editing efficiency and potential off-target effects of the Cascade–Cas3 system were assessed by targeted capture sequencing. Furthermore, the antiviral efficacy of this system was systematically evaluated both in vitro and in vivo using multiple complementary approaches, including qPCR, ELISA, and WB. **Results:** The targeted capture sequencing verified the sequence-specific targeting of the HBV genome by the designed crRNA. The characterization experiments by DLS and TEM confirmed that nanodrug is an electrically neutral sphere with a particle size of approximately 80 nm and uniform distribution. Moreover, the encapsulation rate of LNP is 90%, demonstrating excellent stability and biocompatibility. Functionally, qPCR analysis showed that the lipid-based therapeutic formulation reduced HBV cccDNA and total HBV DNA by approximately 70% in HepG2.2.15 cells. In parallel, the expression of HBsAg and HBeAg was significantly suppressed, with reductions of 54.64% and 64.14% in HepG2.2.15 cells. The important point is that in the modelmice infected with hepatitis B virus, systemic administration reduced the HBV DNA in the liver by approximately 90%. The WB and immunohistochemical staining of liver tissue further corroborated the potent inhibitory effect of this nanodrug on HBsAg production in vivo. **Conclusion:** This study established a lipid-based CRISPR/Cas3 nanodrug and systematically evaluated it across multiple dimensions, including crRNA design, nanodrug fabrication, and both in vitro and in vivo efficacy assessments. The nanodrug demonstrated potent anti-HBV activity while maintaining favorable biocompatibility, providing compelling experimental evidence for the application of CRISPR/Cas3 in HBV-targeted nucleic acid therapy.



Disclosures: Li Li:Nothing to Disclose, Xiangru Shan:Nothing to Disclose, Xinyue Guo:Nothing to Disclose, Yibei Xiao:Nothing to Disclose, Chuanlong Zhu:Nothing to Disclose.

4139 | ◆ IMMUNE-MODULATORY EFFECTS OF PEVIFOSCORVIR SODIUM IN HBEAG-POSITIVE PATIENTS WITH CHRONIC HEPATITIS B INFECTION

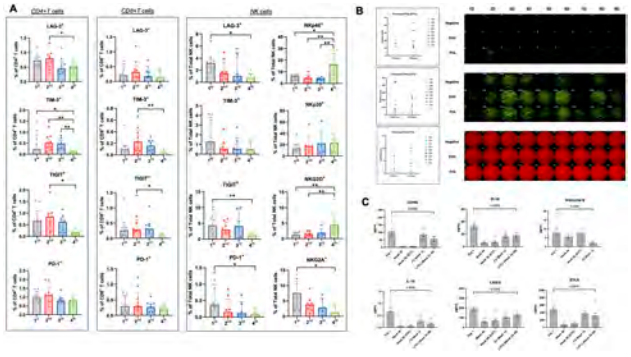
Lung Yi Mak[1] Andreas Jekle[2] Liqiong Yang[1] Sushmita Chanda[2] Lilian Adame[2] Heleen Roose[3] Lawrence Blatt[4] Min Wu[2] Kha Le[2] Tse-I Lin[5] Man-Fung Yuen[1], [1]The University of Hong Kong, [2]Aligos Therapeutics, Inc., San Francisco, United States, [3]Aligos Belgium BV, [4]Aligos Therapeutics, Inc., [5]Aligos Belgium, Leuven, Belgium

Background: Pevifoscorvir sodium (pevy, ALG-000184) is a novel Type E Capsid Assembly Modulator which demonstrated potent on-treatment viral antigen suppression in the Phase 1 study ALG-000184-201 (NCT04536337) in participants with chronic hepatitis B infection who received oral, once daily 300 mg pevy for 96 weeks. After the end of the pevy treatment (EOT), these antiviral effects were sustained up to 48 weeks of follow-up (FU) while on entecavir (ETV) alone (Mak LY et al. EASL 2026 #Wed-588). Here, we report the immunomodulatory effects during and after PEVY treatment. **Methods:** 9 of 10 HBeAg-positive participants form study ALG-000184-201 were recruited for $\geq$ 24 weeks (wk) of ETV-only FU. Peripheral blood was

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collected at baseline, wks 48 and 96 of PEVY, and FU 24-48 wks after EOT. Plasma cytokine levels were determined by ProcartaPlex™ multiplex kits. PBMCs were evaluated ex vivo by multicolor flow cytometry for CD4+, CD8+, regulatory T cells (Tregs), NK cells, and coinhibitory markers. HBV-specific T cell function was assessed by Fluorospot assay for IFN-g, TNF-a, and IL-2 after co-culturing synthetic HBV peptide (envelope [env] and polymerase [pol]) using the ImmunoSpot® Software. **Results:** Expression of co-inhibitory markers ($\geq$ 2 among LAG-3, TIM-3, TIGIT, PD-1) on CD4+T, CD8+T and NK cells, and proportion of Treg were significantly reduced at 24-48 wks after EOT compared to earlier timepoints. Expression of activating NK receptors (NKG2D, NKp46) increased over time, while expression of inhibitory NK receptor (NKG2A) was reduced on NK cells (Fig.A). There was no apparent correlation of baseline qHBsAg levels with the PBMC phenotypes, but baseline TIGIT expression on CD4+T was positively correlated with wk 96 HBsAg level and HBsAg change at wk 48, wk 96, and at FU. Baseline TIGIT expression on CD8+T cells was positively correlated with wk 96 HBsAg level. Fluorospot analysis showed presence of HBV-specific T cells [env or pol] producing IFN-g, TNF-a, and IL-2 (Fig.B). The frequency of IL-2 producing HBV-specific T cells (pol) were negatively correlated with TIM-3 on CD4+T and TIGIT on CD8+T at FU. IFN-g-producing HBV-specific T cells [pol] were also negatively correlated with LAG-3 on CD4+T cells at FU. Interestingly, IFN-g-producing T cells were positively correlated with LAG-3 and TIGIT on NK cells, suggestive of involvement of NK cells in modulating HBV-specific T cell function. Plasma cytokine analysis revealed significant reduction of both pro-inflammatory cytokines (CD40L, IP-10, granzyme B) and inhibitory cytokines (IL-10, LAG-3, BTLA) with time plateauing during PEVY treatment (Fig.C), suggestive of complex immunomodulatory effect associated with PEVY which persisted partially after EOT. **Conclusion:** Potent suppression of HBsAg during and after PEVY treatment was associated with robust immunomodulatory changes in the peripheral compartment, favoring enhancement of immune control of HBV infection.



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4140 | ◆ UP TO 15 MONTHS DURABILITY OF FUNCTIONAL CURE IN RESPONSE TO BEPIROVIRSEN THERAPY IN B-WELL RESPONDERS ENROLLED INTO B-SURE

Edward Gane[1] Maria Buti[2] Monica Gomes da Silva[3] Maria Hlebowicz[4] Jinlin Hou[5] Rachel Wen-Juei Jeng[6] Pietro Lampertico[7] Seng Gee Lim[8] Jianmei Lin[9] Rajiv Mehta[10] Anca Streinu Cercel[11] Qing Xie[12] Hyung Joon Yim[13] Man-Fung Yuen[14] Alexandra Walker[15] Yi Cui[16] Tamara Lukic[17] Lauren Maynard[16] Helene Plein[15] Geoffrey Quinn[16] Isabelle Santhiapillai[15] Michael Willis[16] Melanie Paff[18] Dickens Theodore[19] Rob Elston[16], [1]University of Auckland, Auckland, New Zealand, [2]Hospital Universitario Vall D´Hebron, CIBEREHD del Instituto Carlos III, Barcelona, Spain, [3]Hospital de Clinicas, Federal University of Paraná, Curitiba, Brazil, [4]University of Warmia and Mazury in Olsztyn, Olsztyn, Poland, [5]Nanfang Hospital, Southern Medical University, Guangzhou, China, [6]Chang Gung

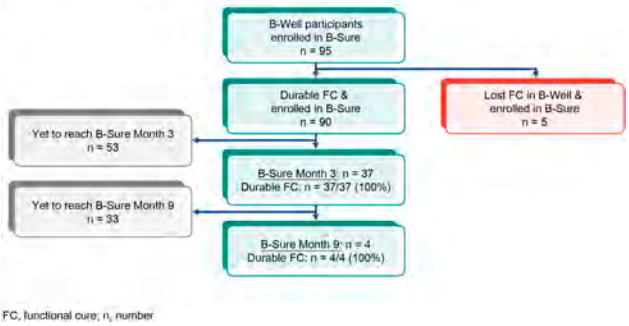
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Background: Functional cure (FC) is defined as ≥24 weeks of sustained hepatitis B surface antigen (HBsAg) not detected (<0.05 IU/mL) and hepatitis B virus (HBV) DNA < lower limit of quantification (LLOQ [20 IU/mL]) off all HBV treatment with or without hepatitis B surface antibody. FC is the optimal treatment endpoint for chronic HBV infection but is rarely achieved with currently available antiviral therapies. Bepirovirsen, an unconjugated antisense oligonucleotide, is an investigational medicine in development for the treatment of chronic HBV infection. In the Phase 3 B-Well 1 & 2 studies (NCT05630807, NCT05630820), a subset of participants achieved FC 24 weeks post nucleos(t)ide analog (NA) and bepirovirsen cessation (B-Well Week 72). Eligible participants who reached the end of B-Well 1 & 2 (Week 96) were enrolled into the long-term durability of efficacy study, B-Sure (NCT04954859; ongoing), to further assess the durability of FC. Here we present data from the first interim analysis of B-Well NA-cessated participants enrolled into B-Sure. **Methods:** Participants who discontinued NAs and achieved FC or had HBsAg <1 IU/mL and HBV DNA <LLOQ at B-Well Week 96 were eligible for enrollment into B-Sure. Participants were enrolled into B-Sure up to 3 months after the end of B-Well. As both studies were ongoing at the data cut-off date (DCO), not all participants had reached the end of B-Well 1 & 2 studies. Maintenance of FC was defined as sustained HBsAg not detected and HBV DNA <LLOQ off all HBV treatment without the use of rescue medication. Loss of FC was defined as the first occurrence of either confirmed HBsAg reversion or HBV DNA reversion, or use of any rescue medication. Durability of FC is reported for participants who achieved FC in B-Well. **Results:** In total, 95 participants who achieved FC in B-Well 1 & 2 were enrolled into the ongoing B-Sure study at the DCO. Of these, 5/95 (5%) participants had lost FC in B-Well and 90/95 (95%) were maintaining FC at enrollment to B-Sure. Among these 90 participants, 37/37 (100%) participants who had reached the B-Sure Month 3 visit at the DCO maintained FC; and 4/4 (100%) who had reached Month 9 visit were maintaining FC, demonstrating at least 15 months durability of FC (i.e. 6 months of FC durability in B-Well 1 & 2, up to 3 months before enrollment into B-Sure, and 9 months in B-Sure) (**Figure**). **Conclusion:** Once achieved, FC remains durable in participants who achieved and maintained FC to B-Well Week 96, up to their latest available data in B-Sure, which is at least 15 months for some participants. Ongoing follow-up of B-Well participants enrolled into B-Sure will be important to confirm the durability of FC in a larger subset of patients. **Funding:** GSK (206882).

Figure. Participant flow diagram: Participants from B-Well 1 & 2 enrolled into B-Sure



FC, functional cure; n, number

Disclosures: Edward Gane:Nothing to Disclose, Maria Buti:Roche Pharma/Diagnostics: Consultant, Gilead Sciences: Consultant, GSK: Consultant, Abbvie: Consultant, Janssen: Consultant, Roche Pharma/Diagnostics: Speaking and Teaching, Gilead Sciences: Speaking and Teaching, GSK: Speaking and Teaching, Abbvie: Speaking and Teaching, Janssen: Speaking and Teaching, Bepirovirsen – GSK: Referral to unlabelled/unapproved products, Monica Gomes da Silva: Nothing to Disclose, Maria Hlebowicz:Nothing to Disclose, Jinlin Hou:Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Rachel Wen-Juei Jeng:GSK: Advisor, Gilead: Advisor, BMS: Speaking and Teaching, Roche: Advisor, Pietro Lampertico:ROCHE PHARMA/DIAGNOSTICS, GILEAD SCIENCES, GSK, ABBVIE, JANS: Advisor, Seng Gee Lim:GSK: Grant, speaker bureau, AusperBio Therapeutics: Advisor, Abbott Laboratories: Grant support, Aligos: Advisor, Sysmex: grant support, IRnovate: Stock – privately held company, Jianmei Lin:Nothing to Disclose, Rajiv Mehta:Nothing to Disclose, Anca Streinu Cercel:Nothing to Disclose, Qing Xie:Nothing to Disclose, Hyung Joon Yim:Nothing to Disclose, Man-Fung Yuen:AbbVie, Abbott Diagnotics, Aligos Therapeutics: Consultant, Arbutus Biopharma, Arrowhead Pharmaceuticals, Assembly Biosc: Consultant, Clear B Therapeutics, Dicerna Pharmaceuticals, Immuncore: Consultant, Fujirebio Incorporation, GSK, Gilead Sciences: Consultant, Immunocore, Janssen, Precision BioSciences: Consultant, Roche, Sysmex Corporation, Tune

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4141 | SAFETY, PHARMACOKINETICS AND PHARMACODYNAMICS OF THE DUAL-TARGET HBV/PD-L1 SIRNA SA1211: PHASE 1 INTERIM RESULTS DEMONSTRATING ROBUST HBSAG SUPPRESSION AND IMMUNE RESTORATION IN CHB PARTICIPANTS

Yanhua Ding[1] Yue Hu[1] Junqi Niu[1] Nan Liu[2] Hui Chen[2] Wenbo Zheng[1] Hong Zhang[1] Xiaojiao Li[1] Feifei Zhao[2] Hongli Zhang[2] Zhiwei Yang[2], [1]The First Hospital of Jilin University, [2]Suzhou Siran Biotechnology Co.,Ltd.

Background: SA1211 is a dual-target siRNA designed to silence HBV and PD-L1 mRNA, aiming to reduce HBsAg and relieve PD-L1-mediated immune suppression. This Phase 1 study evaluated the safety, pharmacokinetics (PK), pharmacodynamics (PD) and immunomodulatory effects in healthy volunteers and CHB participants. Interim blinded data are reported. **Methods:** This study consists of single-ascending dose (SAD) in healthy volunteers and multiple-ascending dose (MAD) in CHB participants. SAD planned doses ranged from 50 mg to 600 mg with follow-up to Day 85; interim safety and PK were analyzed for 50–450 mg. MAD enroll CHB participants with baseline HBsAg $\leq$1000 IU/mL, who will receive subcutaneous SA1211 at 150 mg, 300 mg and 450 mg on Day 1/15/29. Interim data were available for 150 mg up to Day 57 and 300 mg up to Day 15. Evaluations covered safety, plasma/urinary PK, HBsAg level, HBV-specific T cell phenotypes and peripheral PD-L1 expression. **Results: Safety**: SA1211 was well tolerated across 50–450 mg. The most common adverse events were Grade 1 injection-site pain/erythema and transient abnormalities in laboratory tests (e.g., elevated C-reactive protein (CRP), elevated liver enzymes etc.) and all resolved spontaneously. No SAE or treatment discontinuation occurred. **PK**: Plasma exposure increased more than dose-proportionally from 50–450 mg (nonlinear). Mean 0-24h urinary excretion < 11%, indicating renal elimination is minor. Similar PK profiles were observed for both siRNA strands and across healthy volunteers and CHB participants. **PD-HBsAg**: In the 150 mg cohort (n = 10), mean $\log_{10}$ HBsAg declined by 0.73 at Week 8. One participant achieved sustained clearance (< 0.05 IU/mL) from Week 4, and one participant achieved HBsAg decline from 136.1 to 2.75 IU/mL. In the 300 mg cohort (n = 9, Week 2 only), mean $\log_{10}$ HBsAg dropped by 0.38; one participant showed a > 1.9 $\log_{10}$ decline (75.77→0.945 IU/mL) approaching clearance. These blinded interim PD data demonstrate potent, rapid and durable HBsAg suppression, supporting the dual-target siRNA strategy for functional cure. **Immunomodulation**: On Day 29 in the 150 mg dose group, HBV-specific effector $CD8^+$ T cells increased ~76% from baseline; exhausted $PD\text{-}1^+$, $TIM3^+$ and $LAG3^+$ $CD8^+$ subsets decreased by 37%, 70% and 55%, respectively. Peripheral PD-L1 expression was downregulated by 15%, confirming dual-target engagement and reversal of T cell exhaustion. **Conclusion:** Interim blinded data show that SA1211 has favorable safety, nonlinear PK, robust HBsAg reduction and immune restoration in CHB participants. These results support further clinical development for functional cure. **Disclosures:** Yanhua Ding:Nothing to Disclose, Yue Hu:Nothing to Disclose, Junqi Niu:Nothing to Disclose, Nan Liu:Nothing to Disclose, Hui Chen:Nothing to Disclose, Wenbo Zheng:Nothing to Disclose, Hong Zhang:Nothing to Disclose, Xiaojiao Li:Nothing to Disclose, Feifei Zhao:Nothing to Disclose, Hongli Zhang:Nothing to Disclose, Zhiwei Yang:Nothing to Disclose.

4142 | PEVIFOSCOVIR SODIUM REDUCES HBSAG LEVELS TO < 3000 IU/ML IN HBEAG POSITIVE SUBJECTS WITH CHRONIC HBV INFECTION FOLLOWING LONG-TERM ON-STUDY TREATMENT

Man-Fung Yuen[1] Edward Gane[2] Kosh Agarwal[3] Junqi Niu[4] Hong Ren[5] Yanhua Ding[6] Alina Juzov[7] Xier Liang[8] Lung Yi Mak[1] Min Wu[9] Kha Le[9] Andreas Jekle[9] Lawrence Blatt[9] Sushmita Chanda[9] Tse-I Lin[10] Jinlin

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Background: Pevifoscorvir sodium (PEVY, ALG-000184) is a novel Type E Capsid Assembly Modulator (CAM-E). In the Phase 1 study ALG-000184-201 (NCT04536337), 96 weeks of 300 mg PEVY ± the nucleoside analog entecavir (ETV) have demonstrated potent on-treatment suppression of HBV DNA, RNA, and viral antigens in participants with chronic HBV infection. Here, we describe in detail the HBsAg reductions observed in HBeAg+ participants during 96 weeks of PEVY ± ETV treatment (ALG-000184-201) as well as during post-PEVY long-term follow-up (LTFU) treatment with ETV in an investigator-initiated study (REG26-1185). **Methods:** A total of 20 HBeAg+ participants with baseline HBsAg > 3000 (3.5 $\log_{10}$) IU/mL were evaluated for HBsAg during 96 weeks of 300 mg PEVY monotherapy (n = 10, P4CB) or PEVY + ETV (n = 10, P4C2) combination therapy and during up to 8 weeks of ETV-only Follow-Up (FU). Additionally, a subset of 9 HBeAg+ participants with PEVY monotherapy completed ETV LTFU of 24-48 weeks in an investigator-initiated study. **Results:** The mean HBsAg levels at baseline, Week 48 and 96 were 4.4, 3.5 and 3.5 $\log_{10}$ IU/mL, respectively. Substantially greater reductions were observed in participants with high baseline HBsAg (> 10000 IU/mL, n = 15) compared to those with low baseline HBsAg (3000-10000 IU/mL, n = 5). At Week 48 and 96, 60% (9 of 15) and 50% (6 of 12) of participants with high baseline HBsAg level achieved HBsAg < 3000 IU/mL. The mean baseline HBsAg level of the subset of 9 participants, that completed 24-48 weeks of ETV LTFU were 4.26 $\log_{10}$ IU/mL. Of these, 57% (4/7) of participants with high baseline HBsAg achieved HBsAg < 3000 IU/mL at both Week 48 and 96, further increased to 83% (5/6) at the last LTFU visit as of data cutoff date. In contrast, of the 3 participants with baseline HBsAg levels < 10000 IU/mL, none reached HBsAg levels < 3000 IU/mL at weeks 48 and 96, and only one at LTFU. **Conclusion:** The extent in HBsAg reduction during PEVY mono and combination therapy was dependent on baseline HBsAg levels with substantially higher reductions in participants with baseline HBsAg levels > 10000 IU/mL. Of these participants, 9/15 (60 %) achieved HBsAg < 3000 IU/mL at Week 48, suggesting potential eligibility for a functional cure combination regimen, that might include an antisense oligonucleotide agent (Table 1).

Table 1: HBeAg+ participants achieving HBsAg < 3000 IU/mL after 96 weeks of PEVY ± ETV and up to 24-48 weeks of ETV LTFU

Baseline HBsAg Level	N	Participants with HBsAg <3000 IU/mL (%)		
		At 48 weeks of PEVY ± ETV	At 96 weeks of PEVY ± ETV	At 24-48 weeks of ETV LTFU after 96 weeks of PEVY
3000-10000 IU/mL	5	0/5 (0%)	0/5 (0%)	1/3 (33%)
> 10000 IU/mL	15	9/15 (60%)	6/12 (50%)	5/6 (83%)
All	20	9/20 (45%)	6/17 (35%)	6/9 (67%)

Disclosures: Man-Fung Yuen:AbbVie, Abbott Diagnotics, Aligos Therapeutics: Consultant, Arbutus Biopharma, Arrowhead Pharmaceuticals, Assembly Biosc: Consultant, Clear B Therapeutics, Dicerna Pharmaceuticals, Immuncore: Consultant, Fujirebio Incorporation, GSK, Gilead Sciences: Consultant, Immunocore, Janssen, Precision BioSciences: Consultant, Roche, Sysmex Corporation, Tune Therapeutics: Consultant, Vir Biotechnology and Visirna Therapeutics: Consultant, AbbVie, Assembly Biosciences, Arrowhead Pharmaceuticals, Aligos Therapeutics, Arbutus Biopharma: Grant/Research Support, Fujirebio Incorporation, Gilead Sciences, Immunocore, Clear B Therapeutics, GSK, Janssen: Grant/Research Support, Sysmex Corporation and Roche: Grant/Research Support, Fujirebio Incorporation, Gilead Sciences, Roche, Sysmex Corp, Aligos Therapeutics, Arbutus Biopharma: Speaking and Teaching, Precision BioSciences: consultancy, Ausperbio: consultancy, IntergerBio: consultancy, Tune Therapeutics: consultancy, Clear B Therapeutics, GSK, Immuncore, Janssen, Vir Biotechnology: Speaking and Teaching, Edward Gane:Nothing to Disclose, Kosh Agarwal:Nothing to Disclose, Junqi Niu:Nothing to Disclose, Hong Ren: Nothing to Disclose, Yanhua Ding:Nothing to Disclose, Alina Juzov:Nothing to Disclose, Xier Liang:Nothing to Disclose, Lung Yi Mak:Gilead Sciences: Grant/Research Support, Roche Diagnostics: Grant/Research Support, Gilead Sciences: Grant/Research Support, Roche Diagnostics: Grant/Research Support, Gilead Sciences: Advisor, Roche Diagnostics: Advisor, GSK: Speaker fee, Min Wu:Nothing to Disclose, Kha Le:Nothing to Disclose, Andreas Jekle:Aligos Therapeutics: Employee, Aligos Therapeutics: Stock - publicly traded company, Lawrence Blatt:Nothing to Disclose, Sushmita Chanda:Nothing to Disclose, Tse-I Lin: Nothing to Disclose, Jinlin Hou:Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose.

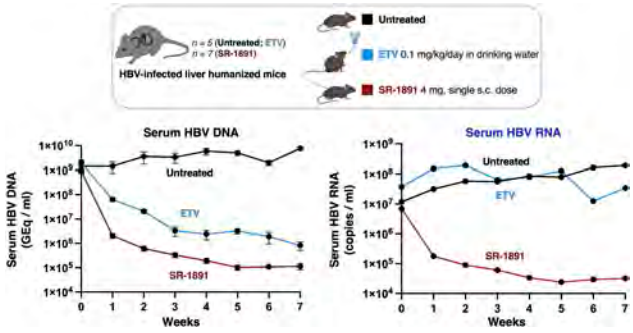
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4143 | A SINGLE SUBCUTANEOUS DOSE OF THE LONG-ACTING CAPSID ASSEMBLY MODULATOR SR-1891 PRODUCES DURABLE, SUPERIOR SUPPRESSION OF SERUM HBV DNA AND RNA COMPARED WITH DAILY ENTECAVIR FOR ≥7 WEEKS IN HUMANIZED AND TRANSGENIC MOUSE MODELS OF CHB

Romano Di Fabio[1] Marco Manenti[1] Alessandro Grillo[1] Pietro Di Lucia[1] Elisa Bono[2] Leonardo Giustini[2] Lorena Donnici[3] Marika Longo Minnolo[3] Katherine Squires[4] Gaston Picchio[2] Raffaele De Francesco[5] Matteo Iannacone[6] Micol Rava'[1] Luca Guidotti[6], [1]Vita-Salute San Raffaele University, [2]IRCCS San Raffaele Scientific Institute, [3]INGM, National Institute of Molecular Genetics, [4]Former Antios Therapeutics, [5]INGM, National Institute of Molecular Genetics & Università degli Studi di Milano, [6]Vita-Salute San Raffaele University & IRCCS San Raffaele Scientific Institute

Background: Chronic HBV infection remains a major global health burden, underscoring the need for novel suppressive therapies with improved antiviral potency and adherence versus current nucleos(t)ide analogues. We report the discovery and preclinical characterization of SR-1891, an ultrapotent (sub-nM) capsid assembly modulator (CAM) that provides long-acting antiviral activity after a single subcutaneous (s.c.) administration. **Methods:** SR-1891 was evaluated for in vitro anti-HBV activity, ADME and PK properties. Antiviral efficacy was assessed following a single s.c. dose of SR-1891 (4 mg/mouse) in HBV-infected immunodeficient liver-humanized mice (HBV Hu; baseline viremia 4×10^8–2×10^9 copies/mL) monitored longitudinally for human serum albumin (HSA), or in immunocompetent HBV-transgenic mice (HBV Tg; 10^7–10^8 copies/mL). This dose is comparable to that used during preclinical development of lenacapavir, a long-acting CAM approved for HIV treatment. At abstract submission, both cohorts remained alive and under follow-up through week 7. Control animals received continuous oral entecavir (ETV; 0.1 mg/kg/day in drinking water). Serum HBV DNA, RNA, HBeAg, HBsAg, and ALT were measured longitudinally. In selected HBV Tg, liver histopathology and hepatocellular capsid distribution were evaluated at week 4. **Results:** A single s.c. administration of SR-1891 demonstrated ADME and PK characteristics consistent with long-acting potential, including low intrinsic clearance and high metabolic stability across species, and liver exposure 34-fold above the 10× protein-adjusted EC90 at the last measurement (day 28). Daily ETV treatment produced progressive multi-$\log_{10}$ reductions in serum HBV DNA through week 7 (reaching −3.3 $\log_{10}$ in HBV Hu and the limit of detection [LOD; ~−4.0 $\log_{10}$] in HBV Tg), without affecting serum HBV RNA or viral antigens. In contrast, a single SR-1891 injection induced faster, deeper and more durable DNA reductions , reaching ≥4 $\log_{10}$ declines by week 5 onward in HBV Hu and by week 2 onward in HBV Tg. Unlike ETV, SR-1891 also reduced serum HBV RNA, with declines ≥-2.5 $\log_{10}$ by week 2 in HBV Hu and to the LOD (≥-2.5 $\log_{10}$) from week 1 in HBV Tg. SR-1891 also produced ~50% reductions in HBeAg and HBsAg beginning at week 5 in cccDNA-bearing HBV Hu, whereas no antigen reductions were observed in cccDNA-deficient HBV Tg. Both ETV and SR-1891 were well tolerated, with stable HSA levels, no ALT elevations, and no histologic evidence of liver injury or aberrant empty capsid accumulation. **Conclusion:** A single dose of SR-1891 produced potent, durable antiviral activity exceeding continuous daily ETV, with efficacy maintained for at least 7 weeks after dosing. Selective reductions in viral antigens in HBV Hu further suggest a potential effect on cccDNA, biogenesis, maintenance and/or function. Ongoing studies evaluating the antiviral activity beyond week 7 and effects on hepatic cccDNA will be presented at the meeting.



Disclosures: Romano Di Fabio:Nothing to Disclose, Marco Manenti:Nothing to Disclose, Alessandro Grillo: Nothing to Disclose, Pietro Di Lucia:Nothing to Disclose, Elisa Bono:Nothing to Disclose, Leonardo Giustini:Nothing to Disclose, Lorena Donnici:Nothing to Disclose, Marika Longo Minnolo:Nothing to Disclose, Katherine Squires:Nothing to Disclose, Gaston Picchio: Nothing to Disclose, Raffaele De Francesco:Nothing to Disclose, Matteo Iannacone:Nothing to Disclose, Micol Rava':Nothing to Disclose, Luca Guidotti:nChroma Bio: Consultant, Ananda Immunotherapies: Consultant, Genenta Science: Stock - publicly traded company.

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4144 | NEW CLINICAL CARE PATHWAY IN ERA OF HBV FUNCTIONAL CURE: A US MULTIDISCIPLINARY EXPERT CONSENSUS

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Background: Current care pathways for chronic hepatitis B (CHB) relying on long-term viral suppression deliver minimal functional cure (FC) rates. As therapies achieving higher FC rates emerge, care pathways need to be updated. In 2025, a group of global hepatology experts proposed a 9-step FC care pathway with limited consensus due to heterogeneity in health care systems across countries.[1] We aimed to develop an updated US-focused CHB care pathway for the implementation of FC therapies. **Methods:** A nominal group technique was used to achieve consensus on a US pathway. US stakeholders from multiple disciplines reviewed evidence and guidance relevant to FC care pathways from a targeted literature review and completed a silent brainstorm on the global pathway[1] considering US-specific adaptations. Two consensus meetings were held in 2026. In the first meeting, 8 stakeholders, mainly nonspecialists, discussed changes to the global pathway and voted on an updated pathway. In the second meeting, 11 stakeholders, mainly specialists, discussed the global pathway as well as the amended US pathway and voted on a revised pathway. In each meeting, revisions continued until consensus was achieved for every step. **Results:** In the first meeting, a new US pathway with 6 steps was developed with 100% consensus. Key modifications focused on patient characterization and education, establishment of treatment eligibility, treatment initiation, and care plan development. In the second meeting, the pathway was expanded into 8 steps with 100% consensus (Figure), separating shared decision making processes at the start/end of treatment and adding nuances to monitoring steps. Across both meetings, stakeholders identified several key implementation areas, including quantitative hepatitis B surface antigen testing, access to FC treatment, tools and systems for supporting patient engagement/adherence, provider resources/education, and specific FC treatment algorithms. The role of care coordinators, as well as the need for community engagement and awareness building, were emphasized for successful adoption of FC therapies. **Conclusion:** The new 8-step US FC pathway and implementation priorities may help guide the paradigm shift in CHB management from chronic viral suppression to finite FC therapy.

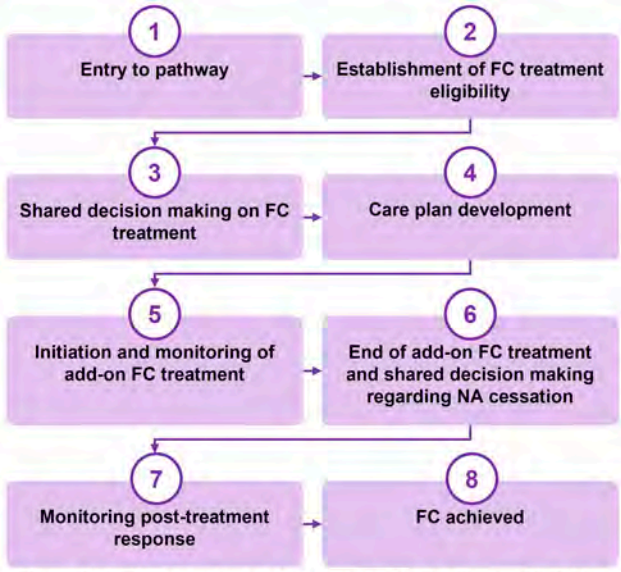


Figure: New FC care pathway in CHB developed by the diverse stakeholders representing different specialties (eg, primary care, advanced practice providers, public health and advocacy representatives, pharmacists, hepatologists, gastroenterologists, infectious disease specialists) and healthcare delivery models in the US (eg, academia and community health centers). The FC care pathway included 8 steps: (1) Entry to pathway: Characterization of patient with CHB (including assessment of qHBsAg, fibrosis stage, HCC risk); patient education (discussion of disease and treatment options); HCC surveillance. (2) Establishment of FC treatment eligibility: Evaluation of patient eligibility (including initiation of NA therapy). (3) Shared decision making on FC treatment: Consideration of risks, benefits, and logistics. (4) Care plan development: Determination of insurance coverage and laboratory costs; arrangement of transportation; coordination with care team members (eg, family, pharmacist, care coordinator). (5) Initiation and monitoring of add-on FC treatment: Adherence to medication and laboratory testing; side effect management; response-guided therapy. (6) End of add-on FC treatment and shared decision making regarding NA cessation. (7) Monitoring post-treatment response: Adherence to clinical and laboratory monitoring; NA retreatment (if needed). (8) FC achieved: Long-term monitoring (reactivation, risk-based HCC surveillance). CHB, chronic hepatitis B; FC, functional cure; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; NA, nucleos(t)ide analog; qHBsAg, quantitative hepatitis B surface antigen.

Disclosures: Joseph Ahn:Ipsen: Speaking and Teaching, Madrigal: Speaking and Teaching, GSK: Speaking and Teaching, Gilead: Speaking and Teaching, Andrea Caracostis:Nothing to Disclose, Chloe Choi:Nothing to

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Disclose, Dawn Drazek:Cymabay: participated on an advisory board for seladelpar, Gilead: participated in an advisory board for seladelpar, Ipsen: participated in a elafibranor advisory board, Madrigal: participated in a resmetirom advisory board, Intercept: participated in an obetacholic acid advisory board, GSK: participated in advisory board, Pedestal Health: Employee, Jane Giang:Nothing to Disclose, Robert Gish:Genlantis, HepQuant, HepaTx, Virion: Stock – privately held company, Gilead Sciences, GlaxoSmithKline, HHHbio, Helio, HepQuant, Intercept, Ipsen, Madrigal,: Consultant, Mirum, Precision BioSciences, Prodigy, Topography Health, Tune Therapeutics, Virion, Quest: Consultant, AbbVie, AstraZeneca, BlueJay Therapeutics, Brii Bio, EIT Pharma, Genlantis, Gerson Lehrman Group: Consultant, Gilead Sciences Inc., Intercept, Ipsen Biopharmaceuticals, Madrigal, Mallinckrodt, Mirum: Speaking and Teaching, Syneos Health: Data Safety Monitoring Board, Genlantis, Gilead, HepaTX, HepQuant, Intercept, Prodigy: Leadership in Related Society, Board, Journal, Loc Le:Nothing to Disclose, Mindie Nguyen:Pfizer, Astra Zeneca, Aligos, GSK, Delfi, Innogen, Exact Sci: Grant/Research Support, GSK: Advisor, Amanda Noska:Nothing to Disclose, Nancy Reau:Gilead: Grant/Research Support, Gilead: Grant/Research Support, Arbutus: Consultant, Arbutus: Consultant, Gilead: Consultant, Gilead: Consultant, VIR: Consultant, VIR: Consultant, Salix: Consultant, Salix: Consultant, Salix: Grant/Research Support, Salix: Grant/Research Support, AbbVie: Grant/Research Support, AbbVie: Grant/Research Support, VIR: Grant/Research Support, VIR: Grant/Research Support, mirum: Grant/Research Support, mirum: Consultant, GSK: Consultant, IPSEN: Consultant, Gilead: Grant/Research Support, Gilead: Grant/Research Support, Arbutus: Consultant, Arbutus: Consultant, Gilead: Consultant, Gilead: Consultant, VIR: Consultant, VIR: Consultant, Salix: Consultant, Salix: Consultant, Salix: Grant/Research Support, Salix: Grant/Research Support, AbbVie: Grant/Research Support, AbbVie: Grant/Research Support, VIR: Grant/Research Support, VIR: Grant/Research Support, mirum: Grant/Research Support, mirum: Consultant, GSK: Consultant, IPSEN: Consultant, Jimyeong Son:Nothing to Disclose, Mark Sulkowski:AbbVie: Advisor, Arbutus: Advisor, Aligos: Advisor, Gilead: DSMB member, Precision Biosciences: Advisor, Vir: Advisor, Vir: Grant/Research Support, GSK: Advisor, GSK: Grant/Research Support, Virion: Advisor, ImmunoCore: DSMB member, Pfizer: Advisor, Yee Hui Yeo: Nothing to Disclose, Julie Yoshimachi:GSK: Advisor, Chari Cohen:Vio Biotechnology: grant funds renumerated to Hepatitis B Foundation, Dynavax Technologies: grant funds renumerated to Hepatitis B Foundation, Gilead Sciences: grant funds renumerated to Hepatitis B Foundation, GSK: grant funds renumerated to Hepatitis B Foundation, Roche: grant funds renumerated to Hepatitis B Foundation, Gilead Sciences: funds renumerated to Hepatitis B Foundation, GSK: funds renumerated to Hepatitis B Foundation, Calvin Pan:Gilead: Grant/Research Support, GSK: Advisor, Norah Terrault:Nothing to Disclose.

4145 | TREATMENTS REDUCING HBX SHAPE THE HEPATITIS B VIRUS RESERVOIR TOWARDS A MORE REPRESSIVE CHROMATIN STATE IN VIVO

Maura Dandri[1] Johannes Bächer[1] Moritz Calaminus[1] Andrea Pirosu[1] Tassilo Volz[2] Katja Giersch[1] Marc Lütgehetmann[1] Lena Allweiss[1], [1]University Medical Center Hamburg-Eppendorf, [2]University Medical Centre Hamburg-Eppendorf

Background: Therapeutic interventions that suppress the activity of the HBV reservoir, the cccDNA minichromosome, are urgently needed, as cccDNA silencing may promote functional HBV cure. The structural maintenance of chromosomes 5/6 complex (SMC5/6) is a host restriction factor degraded by HBx. We previously showed that siRNA targeting all HBV transcripts or interferon alpha (pegIFNα) reduced HBV transcripts and proteins, including HBx, in HBV-infected humanized mice, enabling reappearance of SMC5/6 in approximately 40% of human hepatocytes and its association with the cccDNA (Allweiss, Gut 2022). Moreover, SMC5/6-mediated cccDNA silencing persisted after treatment withdrawal when the entry inhibitor bulevirtide was administered to protect hepatocytes from new infections. Herein, we aimed to investigate the epigenetic landscape of SMC5/6-associated cccDNA molecules in mice that received either siRNA, pegIFNα or pegIFNβ, which acts on the same cellular receptor. **Methods:** Post-translational modifications (PTMs) of cccDNA-bound histones, total H3 levels, and SMC5/6 occupancy (via its subunit NSE4) were analyzed by chromatin immunoprecipitation-qPCR (ChIP-qPCR) in livers of HBV-infected humanized mice treated either with siRNA (4 weeks), pegIFNα, or pegIFNβ (25ng/gr, twice/week for 6 weeks). To improve sensitivity, we established sequential ChIP protocols (Re-ChIP) to assess epigenetic marks specifically on NSE4-bound cccDNA molecules. HBV markers were measured by qPCR, WB, and IF. Correlation analyses evaluated associations between intrahepatic viral parameters and cccDNA epigenetic marks. **Results:** pegIFNβ had a stronger antiviral effect than pegIFNα in reducing viremia (-2.6Log vs -1.2Log) and intrahepatic HBV RNA (-1.6Log vs -0.6Log). Both IFN treatments reduced HBx (determined by WB) and promoted the association of SMC5/6 to the cccDNA. However, pegIFNβ significantly increased the levels of

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the heterochromatin mark H3K9me3 and total H3 levels on cccDNA, while the ratio of active marks (H3K27ac, H3K4me3) to H3 decreased. Re-ChIP enabled assessment of SMC5/6-bound cccDNA molecules in mice receiving siRNA or peg-IFNα. In NSE4-occupied cccDNA, H3K9me3 levels exceeded those of active histone PTMs H3K27ac and H3K4me3, thus confirming the repressive pattern observed by peg-IFNβ. Moreover, the levels of repressive mark H3K9me3, NSE4 and H3 negatively correlated with HBV DNA and transcription levels across mice and antiviral treatment regimens. **Conclusion:** Treatment with pegIFNβ exerted the strongest antiviral effect in immunodeficient humanized mice, resulting in potent SMC5/6-mediated cccDNA silencing. Our data suggest that cccDNA silencing following HBx reduction shifts the epigenetic landscape of the minichromosome toward a more repressed state, highlighting the potential of HBx-targeting therapies to induce sustained silencing of the HBV reservoir.

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4146 | INTRAHEPATIC HBSAG REDUCTION BY IMDUSIRAN IS ASSOCIATED WITH REMODELING OF EXHAUSTED T-CELL PHENOTYPES IN CHRONIC HEPATITIS B

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Background: Chronic hepatitis B (CHB) accounts for a substantial proportion of primary hepatocellular carcinoma worldwide and remains a major cause of liver-related mortality. Functional cure, defined by sustained hepatitis B surface antigen (HBsAg) loss with or without anti-HBs seroconversion off all therapy, occurs in approximately 1% of individuals receiving current antiviral therapy. While nucleos(t)ide analogues (NUC) effectively suppress hepatitis B virus (HBV) replication, they rarely lead to HBsAg clearance. Loss of HBsAg is associated with recovery of HBV-specific immunity, suggesting that therapeutic reduction of HBsAg may facilitate immune restoration. Small interfering RNAs (siRNAs) that target HBV transcripts and reduce HBsAg expression are under development; however, their effects on intrahepatic immune cell phenotypes remain poorly defined. This study evaluated the impact of the *N*-acetylgalactosamine–conjugated, pangenotypic siRNA imdusiran (AB-729) on intrahepatic T-cell phenotypes in CHB. **Methods:** Starting July 2024, adults with CHB virally suppressed on NUC without liver fibrosis were enrolled at the Institute of Human Virology, University of Maryland School of Medicine. Participants received imdusiran 60 mg subcutaneously every 8 weeks for 4 doses. Paired liver biopsies were obtained within 24 hours after the first dose and 8 weeks after the final dose. Fresh liver samples were analyzed by flow cytometry to assess intrahepatic immune phenotypes. Viral markers and clinical laboratory parameters, including alanine aminotransferase (ALT), direct bilirubin, and complete blood counts, were monitored. **Results:** Five participants were enrolled. Transient ALT elevations ($\leq$5× the upper limit of normal, without concurrent increases in direct bilirubin) were observed in 4 participants, while the fifth exhibited no ALT changes. HBsAg levels decreased in all participants; in 3 participants with available data, HBsAg change from baseline at week 24 ranged from -1.2 to -2.8 $\log_{10}$ IU/mL. Paired liver biopsy data is available for 4 participants. Markers of T-cell exhaustion were reduced: PD-1 decreased in $CD4^+$ but not $CD8^+$ T cells (mean reduction from 64% to 52%). 2B4 and TIGIT declined in both $CD4^+$ (2B4: 15% to 3%; TIGIT: 32% to 24%) and $CD8^+$ T cells (2B4: 62% to 39%; TIGIT: 44% to 40%). $CCR7^-$ effector memory T cells decreased within the $CD4^+$ population (mean reduction from 95.5% to 79.7%) but not in $CD8^+$. CD38 and HLA-DR expression were markedly reduced on both $CD4^+$ and $CD8^+$ T cells. **Conclusion:** Reduction of intrahepatic HBsAg via siRNA therapy was associated with remodeling of dysfunctional intrahepatic T-cell phenotypes, characterized by decreased expression of exhaustion markers and contraction of effector memory populations. These findings support intrahepatic antigen reduction as a strategy for restoring liver immune dysfunction in CHB.

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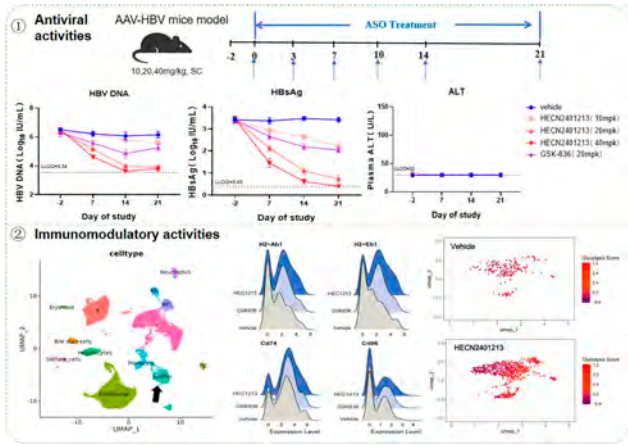
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4147 | ANTIVIRAL AND IMMUNE PROFILING OF HECN2401213, A POTENTIAL BEST-IN-CLASS HBV ANTISENSE OLIGONUCLEOTIDE

Pu Wang[1] Yong Xie[1] Chujun Liu[1] Yuzhuang Li[2] YingLin Zuo[1] Baohua Gu[1] Jing Li[1] Yunfu Chen[1], [1]Sunshine Lake Pharma Co., Ltd., [2]Dongguan HEC Biopharmaceuticals R&D Co., Ltd.

Background: Functional cure in chronic hepatitis B (CHB) remains a significant challenge. While most novel anti-HBV agents fail to achieve meaningful HBsAg loss, HBV antisense oligonucleotides (ASOs) such as bepirovirsen (GSK-836) and AHB-137 have demonstrated unique activity as monotherapy, owing to their dual mechanism of RNase H-mediated viral RNA degradation and immunomodulatory effects. Here we characterize HECN2401213, a next-generation HBV ASO engineered for superior antiviral potency, and evaluate its immunomodulatory profiles across multiple pre-clinical models. **Methods:** Antiviral activities were assessed in HepG2.2.15 cells, HBV-infected primary human hepatocytes (PHH), adeno-associated virus (AAV)-HBV and HBV-transgenic mouse models. Immunomodulatory activities were evaluated in human peripheral blood mononuclear cells (PBMCs), a toll-like receptor 8 (TLR8) reporter cell line and hTLR8 knock-in mice. Further hepatic immune profiling was done via flow cytometry and single-cell RNA sequencing (scRNA-seq) in wild-type C57BL/6 mice. **Results:** In the PHH-HBV model, HECN2401213 demonstrated approximately 4-fold higher antiviral potency than GSK-836, with EC_{50} values ranging from 1.1 to 2.3 nM across various viral markers. In AAV-HBV mice, HECN2401213 produced a 2.68 $\log_{10}$ IU/mL reduction in plasma HBsAg versus 1.38 $\log_{10}$ IU/mL for GSK-836 at an identical dose/regimen ($p < 0.001$, n = 5/group). *In vitro*, HECN2401213 and GSK-836 induced comparable level of cytokines (e.g. IL-6) in human PBMC and exhibited similar TLR8 agonism in reporter cell lines. In hTLR8 knock-in mice, both ASOs triggered significant IL-12 elevation in serum and liver. In C57BL/6 mice, both agents markedly expanded intrahepatic immune cell populations, consistent with robust hepatic innate immune activation. Notably, HECN2401213 significantly upregulated MHC class II-related gene (e.g., H2-Ab1, H2-Eb1, Cd74, and Cd86) and increased glycolysis towards antiviral states in Kupffer cells, which are pivotal for effective intrahepatic T-cell priming during chronic HBV infection. **Conclusion:** HECN2401213 exhibits best-in-class potential, characterized by significantly superior antiviral efficacy and balanced, finely-tuned immunomodulatory activities. These data strongly support its advancement into clinical development, either as monotherapy or in combination regimens, to accelerate functional cure rates in CHB. IND-enabling studies are ongoing.



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4148 | LONG-TERM EFFICACY AND SAFETY OF TENOFOVIR AMIBUFENAMIDE IN CHRONIC HEPATITIS B VIRUS-INFECTED PATIENTS WITH NORMAL ALANINE AMINOTRANSFERASE: 144-WEEK RESULTS FROM THE PROMOTE STUDY

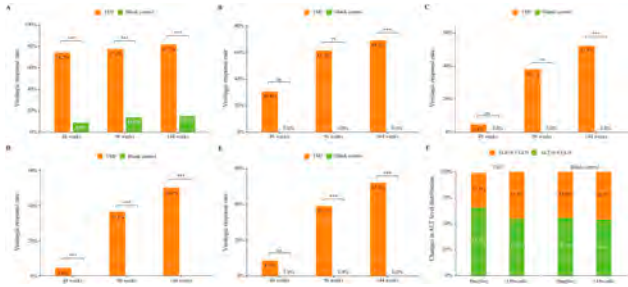
Honglian Gui[1] Qing Xie[2] Lihong Qu[3] Zhili Tan[3] Lin Tan[4] Piao Hu[5] Feng Qian[6] Xiaoping Wu[7] Yuanwang Qiu[8] Sujun Zheng[9] Jiaojian Lv[10] Yunzhen Shi[11] Jun Li[12] Yongfang Jiang[13] Zhizhen Hu[14] Yan Huo[14] Fanru Nie[14], [1]Ruijin Hospital, Shanghai Jiao Tong University School of Med, [2]Ruijin Hospital, [3]Department of infectious diseases, East Hospital Affiliated To Tongji University, [4]Department of infectious diseases, The Second People's Hospital of Fuyang, [5]Department of infectious diseases, Hangzhou Xiaoshan First People's Hospital, [6]Department of infectious diseases, The Fifth People's Hospital of Suzhou, [7]Department of infectious diseases, The First Affiliated Hospital of Nanchang University, [8]Department of infectious diseases, Wuxi Fifth People's Hospital, [9]Beijing Youan Hospital, [10]Department of infectious diseases, Lishui People's Hospital, [11]Department of infectious diseases, Dongyang People's Hospital, [12]Department of infectious diseases, Jiangsu Provincial People's Hospital,

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Background: The PROMOTE study has demonstrated significant efficacy of tenofovir amibufenamide (TMF) at weeks 48 and 96 in chronic HBV-infected patients with normal alanine aminotransferase (ALT) levels, with favorable bone, renal and lipid safety profiles. Here, we reported the 144-week long-term results of the PROMOTE study. **Methods:** In this multicenter, randomized, open-label, blank-controlled trial conducted in China, eligible patients aged 18-65 years with chronic HBV-infection (serum HBV DNA >20 IU/mL) and normal ALT levels ($\leq$1×ULN [40 IU/L]) were enrolled. Patients were randomly assigned (1:1) to receive once-daily TMF for 240 weeks or blank control group. The efficacy endpoints included the proportion of patients achieving HBV DNA <20 IU/mL, the changes in HBsAg and ALT levels. **Results:** A total of 193 patients were included in the full analysis set (93 in the TMF group and 100 in the blank control group). Baseline characteristics were well-balanced between groups. The proportion of patients achieving HBV DNA <20 IU/mL in the TMF group increased steadily, from 74.2% at week 48 to 77.4% at week 96 and 81.7% at week 144, with significant differences versus the blank control group (all $p<0.001$). Patients with baseline HBV DNA $\geq$8 $\log_{10}$ IU/mL showed a steady increase in virologic response rate, reaching 4.8% at week 48, 38.1% at week 96 and 52.4% at week 144. Similar trends were observed in other difficult-to-treat subgroups, including patients aged $\leq$30 years, baseline HBV DNA $\geq$7 $\log_{10}$ IU/mL, or HBeAg-positive. Moreover, among patients with baseline HBV DNA $\geq$8 $\log_{10}$ IU/mL who did not achieve virologic response, HBV DNA levels decreased significantly by 6.23 $\log_{10}$ IU/mL from baseline as early as week 48. In the TMF group, the proportion of patients achieving ALT <0.5×ULN increased significantly by week 48 and remained stable, whereas it showed little change in the blank control group. One patient in the TMF group achieved HBsAg loss with seroconversion at week 48, sustained through week 144. In the blank control group, 9 patients who experienced disease progression met the treatment criteria per current Chinese guidelines and subsequently initiated TMF treatment during the 144-week follow-up period. No antiviral resistance was observed in the TMF group through 144 weeks, including two patients who experienced virologic breakthrough. In the blank control group, one patient experienced an ALT flare (ALT >5×ULN). Changes from baseline in estimated glomerular filtration rate, creatinine clearance, serum creatinine, calcium, phosphorus, and lipid parameters (including triglyceride, high-density lipoprotein cholesterol and TC/HDL) during the 144 weeks were similar between groups (all $p>0.05$). **Conclusion:** Long-term treatment with TMF provided sustained virologic benefits in patients with CHB and normal ALT, with a favorable renal, bone, and lipid safety profile at week 144.



Disclosures: Honglian Gui:Nothing to Disclose, Qing Xie:Nothing to Disclose, Lihong Qu:Nothing to Disclose, Zhili Tan:Nothing to Disclose, Lin Tan:Nothing to Disclose, Piao Hu:Nothing to Disclose, Feng Qian:Nothing to Disclose, Xiaoping Wu:Nothing to Disclose, Yuanwang Qiu:Nothing to Disclose, Sujun Zheng:Nothing to Disclose, Jiaojian Lv:Nothing to Disclose, Yunzhen Shi:Nothing to Disclose, JUN LI:Nothing to Disclose, Yongfang Jiang:Nothing to Disclose, Zhizhen Hu:Nothing to Disclose, Yan Huo:Nothing to Disclose, Fanru Nie:Nothing to Disclose.

4149 | EFFICACY AND SAFETY OF TENOFOVIR ALAFENAMIDE VERSUS TENOFOVIR AMIBUFENAMIDE IN CHRONIC HEPATITIS B PATIENTS WITH LOW-LEVEL VIREMIA

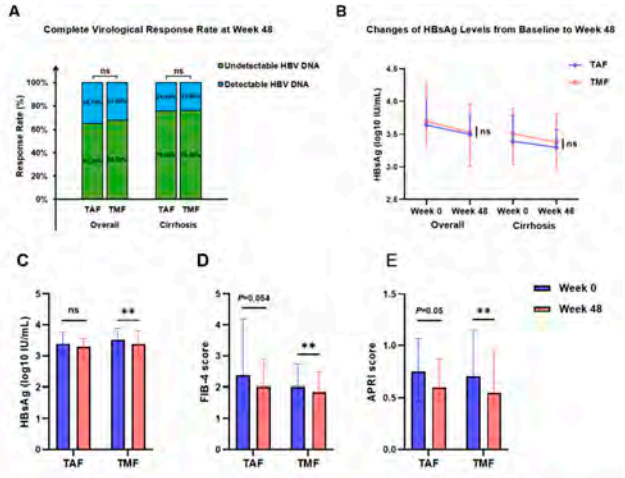
Wenting Peng[1] Lei Fu[2] Chuan Jiang[2], [1]Xiangya Hospital Central South University, [2]Xiangya Hospital CSU

Background: Low-level viremia (LLV) during nucleos(t)ide analogue (NA) therapy remains a challenging issue in chronic hepatitis B (CHB), as LLV is associated with fibrosis progression, hepatocellular carcinoma (HCC), and virological breakthrough. Tenofovir alafenamide (TAF) and tenofovir amibufenamide (TMF) are both potent first-line agents with favorable safety profiles; however, real-world data in NA-treated LLV patients are limited, especially in those with cirrhosis. This study compares the efficacy and safety of TAF and TMF in this population, with a focused analysis on the compensated cirrhosis subgroup. **Methods:** This retrospective study enrolled NA-treated CHB patients with LLV (HBV DNA: 10-2000 IU/mL) who switched to TAF or TMF between November 2018 and December 2024. The primary endpoint was the rate of complete virological response (CVR; defined as undetectable HBV DNA) at week 48. Secondary endpoints included HBsAg decline, HBeAg loss, ALT normalization, lipid profile changes, and non-invasive fibrosis indices (FIB-4, APRI). For the cirrhosis subgroup, changes in

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portal vein diameter and spleen thickness were additionally evaluated. **Results: Overall Cohort (N = 359):** The week-48 CVR was 65.3% (130/199) in the TAF group and 68.1% (109/160) in the TMF group ($P > 0.05$). HBeAg-negative patients showed significantly higher CVR rates than HBeAg-positive patients ($P < 0.05$). Inter-group comparisons revealed no significant differences in HBsAg decline or lipid profile alterations at week 48 ($P > 0.05$). **Cirrhosis Subgroup (N = 101):** Week-48 CVR rates were comparable between the TAF (75.6%, 44/59) and TMF (76.2%, 32/42) groups ($P > 0.05$), with higher CVR again observed in HBeAg-negative patients ($P < 0.05$). No significant differences were found between the two groups in HBsAg decline, FIB-4, or APRI scores ($P > 0.05$). Within-group analysis showed that in the TMF group, HBsAg decline, FIB-4, and APRI scores decreased significantly from baseline ($P < 0.05$), whereas the TAF group did not show statistically significant decreases in these parameters. No cirrhosis progression or HCC was observed during the 48-week follow-up in either group. **Conclusion:** In NA-treated CHB patients with LLV, TMF, and TAF demonstrated comparable virological suppression and lipid stability at week 48. In the cirrhosis subgroup, both agents also showed comparable CVR rates and similar effects on non-invasive fibrosis indices. Although within-group analyses revealed significant improvements in HBsAg levels and non-invasive fibrosis indices with TMF in cirrhotic patients, its potential superiority over TAF warrants further investigation.



(A) Complete virological response (CVR) rates at week 48: Comparison of CVR (defined as undetectable HBV DNA) at week 48 between the TAF and TMF groups in the overall cohort and the cirrhosis subgroup.

(B) Changes in HBsAg levels from baseline to week 48: Trends of HBsAg level changes from baseline (Week 0) to week 48 in the TAF and TMF groups within the overall cohort and the cirrhosis subgroup.

(C-E) Within-group changes of clinical indices in the cirrhosis subgroup: Within-group analysis showing the changes in (C) HBsAg levels, (D) FIB-4 scores, and (E) APRI scores from baseline (0W) to week 48 (48W) in the cirrhosis subgroup.

*(Note: ns indicates no significant difference, P > 0.05; * P < 0.05; ** P < 0.001.)*

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4150 | BASELINE PREDICTORS OF FUNCTIONAL CURE IN CHRONIC HEPATITIS B PATIENTS TREATED WITH BEPIROVIRSEN: B-WELL PHASE 3 TRIALS

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Background: Bepirovirsen (BPV), an antisense oligonucleotide, is the first anti-hepatitis B virus (HBV) therapy in global Phase 3 trials with functional cure (FC) as the primary outcome. Baseline predictors of response analyses may be helpful in assessing whether there is heterogeneity in the treatment effect. This exploratory analysis investigated the baseline predictors of FC following BPV treatment in the B-Well 1 and 2 trials. **Methods:** B-Well 1 and 2 are global double-blind Phase 3 trials, including non-cirrhotic adults with nucleos(t)ide analog (NA)-suppressed chronic HBV infection (HBV DNA < 90 IU/mL) and hepatitis B surface antigen (HBsAg) > 100– ≤ 3000 IU/mL. Participants (pts) were randomized 2:1 to BPV 300 mg or placebo (PBO) weekly for 24 weeks (wks), and discontinued NAs at Wk48, if eligible. FC is defined as HBV DNA < lower limit of quantification and HBsAg loss 24 wks after cessation of all HBV treatment. Baseline variables examined in this analysis included age, alanine aminotransferase, aspartate aminotransferase to platelet ratio index, baseline NA type, body mass index, estimated glomerular filtration rate, hepatitis B core-related antigen (log10), hepatitis B e-antigen (HBeAg) status, platelet, quantitative HBsAg (log10), quantitative HBV DNA (log10), race, sex, study, time on current NA, treatment, and HBV genotype, which was assessed using a multimethod approach since pts were virally suppressed on NA. Logistic regression analysis using backward elimination based on Akaike information criterion (AIC) was used to identify baseline predictors of FC, and a multivariable model was constructed which included study, treatment, and HBsAg strata irrespective of their impact on AIC. **Results:** In this multivariable analysis, 944 pts from B-Well 1 and 832 pts from B-Well 2 were included. Among BPV-treated pts, 19% (227/1182) achieved FC whereas no PBO pts achieved FC (0/594). Lower baseline HBsAg (log10) was strongly associated with higher FC rates (odds ratio [OR]: 0.12, 95% CI: 0.067, 0.218; p < 0.0001). Younger age (OR: 0.95, 95% CI: 0.931, 0.962; p < 0.0001), female sex (OR: 1.63, 95% CI: 1.144, 2.314; p = 0.0067), and HBeAg negative status (OR: 0.42, 95% CI: 0.193, 0.930; p = 0.0323) were also significantly associated with FC. HBV genotype was significantly associated with FC (p = 0.0013), with the highest FC rates observed in genotype A, followed by B, D, and C (**Table**). **Conclusion:** A lower baseline HBsAg (log10) was a strong predictor of FC after 24 wks of BPV treatment. As the B-Well studies collected samples for novel biomarkers, future analyses may incorporate novel biomarkers as potential baseline predictors of response to develop a more comprehensive multivariable model that could serve as a reference to evaluate simpler models meant for clinical use. **Funding:** GSK (202009/NCT05630807; 219288/NCT05630820)[For the B-Well Study Group]

Table. Statistical analysis of baseline variables significantly associated with FC success

Baseline variable	OR	95% CI	Overall p-value
qHBsAg (log10)	0.12	(0.067, 0.218)	<0.0001
Age	0.95	(0.931, 0.962)	<0.0001
HBV genotype			0.0013
A (reference)			
B	0.38	(0.214, 0.669)	
C	0.32	(0.182, 0.565)	
D	0.51	(0.299, 0.867)	
Missing	0.59	(0.074, 4.742)	
Other	0.20	(0.079, 0.518)	
Sex			0.0067
Male (reference)			
Female	1.63	(1.144, 2.314)	
HBeAg status			0.0323
Negative (reference)			
Positive	0.42	(0.193, 0.930)	

CI, confidence interval; FC, functional cure; HBeAg, hepatitis B e-antigen; HBV, hepatitis B virus; OR, odds ratio; qHBsAg, quantitative hepatitis B surface antigen.

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4151 | HEPATITIS B SURFACE ANTIGEN DYNAMICS IN PARTICIPANTS TREATED WITH BEPIROVIRSEN WHO DID NOT ACHIEVE FUNCTIONAL CURE: B-WELL PHASE 3 TRIALS

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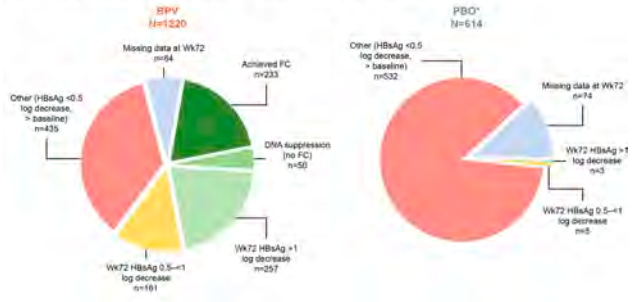
Background: Bepirovirsen (BPV) is an antisense oligonucleotide and is the first anti-hepatitis B virus (HBV) therapy in global Phase 3 trials with functional cure (FC) as the primary outcome. The aim of this post-hoc analysis is to describe the hepatitis B surface antigen (HBsAg) dynamics in participants (pts) who did not achieve FC. **Methods:** B-Well 1 and 2 are global double-blind Phase 3 trials. Non-cirrhotic adults with nucleos(t)ide analog (NA)-suppressed chronic HBV infection (HBV DNA <90 IU/mL) and HBsAg $>100–\leq3000$ IU/mL were randomized 2:1 to BPV 300 mg or placebo (PBO) weekly for 24 weeks (wks).

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Pts discontinued NAs at Wk48, if eligible. HBsAg and HBV DNA levels were monitored throughout the study. FC was defined as ≥24 wks of sustained HBV DNA < lower limit of quantification (LLOQ) and HBsAg loss (<0.05 IU/mL) after finite therapy (i.e. off all HBV therapy including NAs), with or without hepatitis B surface antibody. DNA suppression was defined as ≥24 wks of sustained HBV DNA **Results:** Among pooled B-Well 1 and 2 BPV pts, 24% (295/1220) pts stopped NAs at Wk48. At Wk72, 19.1% (233/1220) achieved FC and an additional 4.1% (50/1220) achieved DNA suppression without FC (**Figure**), of which 49 pts maintained HBsAg <10 IU/mL (one pt had missing quantitative HBsAg); no PBO pts stopped NAs or achieved FC. Of 12 pts who stopped NAs and failed to achieve either FC or DNA suppression at Wk72, 5 had confirmed HBV DNA elevation (HBV DNA >20 IU/mL but <2000 IU/mL) and the remaining 7 pts could not be evaluated (e.g. due to withdrawal from study, missing data, or reinitiation of NAs not for the purpose of DNA control). Of the pts who did not achieve FC or DNA suppression at Wk72, 44.6% (418/937) BPV pts versus 1.3% (8/614) PBO pts had a >0.5 log decrease in HBsAg from baseline and 27.4% (257/937) BPV pts versus 0.5% (3/614) PBO pts also had a >1 log decrease in HBsAg from baseline. This included 23 BPV pts and one PBO pt who continued NAs at Wk48 and consequently were not assessed for FC but had HBsAg loss at Wk72. **Conclusion:** At Wk72, approximately 1 year after the end of BPV treatment, 19.1% of BPV pts had FC, and an additional 4.1% of BPV pts had DNA suppression with low, but detectable HBsAg. Of remaining pts, 27.4% of BPV pts had a >1 log decrease in HBsAg from baseline. By comparison, no PBO pts achieved FC and 0.5% of PBO pts experienced the same level of HBsAg reduction relative to baseline at Wk72. Long-term follow-up will determine the clinical significance of observed reductions in HBsAg from baseline in the absence of FC. **Funding:** GSK (202009/NCT05630807; 219288/NCT05630820) [For the B-Well Study Group]

Figure. HBsAg response at Wk72 in pooled B-Well 1 and B-Well 2 pts on BPV versus PBO



*No PBO pts achieved FC or DNA suppression without FC.
BPV, bepirovirsen; FC, functional cure; HBsAg, hepatitis B surface antigen; PBO, placebo; pts, participants; Wk72, Week 72.

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publicly traded company, GSK: Employee, Dickens Theodore:Nothing to Disclose, Rob Elston:Nothing to Disclose.

4152 | FREQUENCY OF BASELINE BEPIROVIRSEN BINDING SITE NUCLEOTIDE POLYMORPHISMS AND IMPACT ON TREATMENT RESPONSE TO BEPIROVIRSEN (PHASE 3 B-WELL 1 AND 2 STUDIES)

Christopher Sampson[1] Jerome Bouquet[2] Maria Agostini[2] William Jordan[3] Scott Speer[2] Sonia Maciejewski[3] Michael Maguire[1] Phillip Yates[4] Alexander Koenig[3] Michael Savarese[3] Christine Livingston[3] Shihyun You[3] Yu Tao[3] Sai Vinusha Kosaraju[5] Michael Willis[1] Geoffrey Quinn[1] Jennifer Cremer[6] Dickens Theodore[6] Melanie Paff[3] Rob Elston[1] Jill Walker[2], [1]GSK, Stevenage, Hertfordshire, UK, [2]GSK, South San Francisco, CA, USA, [3]GSK,

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Collegeville, PA, USA, [4]GSK, Stevenage, Hertfordshire, UK (at time of study conduct), [5]GSK, Upper Providence, NJ, USA, [6]GSK, Durham, NC, USA

Background: Bepirovirsen (BPV) is an antisense oligonucleotide that targets a conserved 20-nucleotide sequence within hepatitis B virus (HBV) pregenomic RNA and mRNAs. B-Well 1 and 2 are global, randomized, double-blind, Phase 3 trials assessing the efficacy and safety of weekly BPV 300 mg or placebo (PBO) for 24 weeks in participants (pts) with nucleos(t)ide analog (NA)-suppressed chronic HBV infection, with functional cure (FC) as the primary outcome. This analysis assessed the association of BPV binding site single nucleotide polymorphisms (SNPs) detected at baseline with FC rate (Week 72) and end of treatment (EOT; Week 24) hepatitis B surface antigen (HBsAg) serum level reduction. **Methods:** Next-generation sequencing was used to sequence HBV DNA/RNA at baseline for all pts. A SNP was reported in any nucleotide polymorphism (substitution, deletion or insertion) with allelic frequency $\geq$5%. FC was defined as $\geq$24 weeks of sustained HBV DNA **Results:** In a pooled analysis of B-Well 1 and 2, baseline sequence information was only available for 19% (n = 227/1223) of BPV pts and 20% (n = 120/611) of PBO pts as pts were on NAs. BPV binding site SNPs presented with low prevalence in both BPV (n = 14/227; 6%) and PBO (n = 15/120; 13%) treatment groups; 20 unique binding site SNPs were identified at baseline. BPV binding site SNP C1589A was most commonly observed and was present in 1 PBO- and 4 BPV-treated pts. FC was achieved for 14% (n = 2/14) of pts on BPV with baseline binding site SNPs versus 10% (n = 22/211) of pts on BPV without baseline binding site SNPs. Baseline binding site SNPs G1588T and C1589A were identified in pts who achieved FC. In pts treated with BPV, numerically lower reductions in change from baseline EOT HBsAg levels were observed in pts with baseline BPV binding site SNPs versus those with wild-type binding sites; this was consistent in both studies (mean change from baseline: −2.21 vs −2.94 $\log_{10}$ IU/mL [n = 7 vs n = 108; B-Well 1]; −2.78 vs −2.99 $\log_{10}$ IU/mL [n = 5 vs n = 90; B-Well 2]). **Conclusion:** Baseline SNPs within the BPV binding site were infrequent, with low prevalence across studies and treatment groups; C1589A was the most frequently observed SNP at baseline. Pts with baseline BPV binding site SNPs had reductions in HBsAg levels at EOT, albeit numerically lower when compared with those with wild-type BPV binding site sequences. The clinical impact of BPV binding site baseline SNPs on BPV treatment cannot be determined at this stage and will be subject to further evaluation. **Funding:** GSK (202009/NCT05630807; 219288/NCT05630820)[for the B-Well Study Group]

Disclosures: Christopher Sampson:GSK: Employee, GSK: Stock - publicly traded company, Jerome Bouquet:GSK: Employee, GSK: Stock - publicly traded company, Maria Agostini:Nothing to Disclose, William Jordan:Nothing to Disclose, Scott Speer:Nothing to Disclose, Sonia Maciejewski:Nothing to Disclose, Michael Maguire:Nothing to Disclose, Phillip Yates: GSK: Consultant, Alexander Koenig:Nothing to Disclose, Michael Savarese:Nothing to Disclose, Christine Livingston:Nothing to Disclose, Shihyun You:Nothing to Disclose, Yu Tao:Nothing to Disclose, Sai Vinusha Kosaraju:Nothing to Disclose, Michael Willis:Nothing to Disclose, Geoffrey Quinn:Nothing to Disclose, Jennifer Cremer:Nothing to Disclose, Dickens Theodore:Nothing to Disclose, Melanie Paff:GSK: Stock - publicly traded company, GSK: Employee, Rob Elston:Nothing to Disclose, Jill Walker:Nothing to Disclose.

4153 | SERUM BIOMARKERS ASSOCIATED WITH AND MEDIATING THERAPEUTIC ALANINE AMINOTRANSFERASE (ALT) INCREASES DURING BEPIROVIRSEN TREATMENT IN B-WELL 1 AND B-WELL 2

Jenn Singh[1] Johannes Freudenberg[1] Sorcha O'Byrne[2] Jared Delahaye[1] Kai Fu[1] Puneet Dhawan[1] Luca Pagliaroli[1] Sohil Joshi[1] Kristen Consalvo[1] Corey Poveda-Rogers[1] Rob Elston[2] Melanie Paff[1] Dickens Theodore[3] Jill Walker[4], [1]GSK, Collegeville, PA, USA, [2]GSK, Stevenage, UK, [3]GSK, Durham, NC, USA, [4]GSK, San Francisco, CA, USA

Background: Bepirovirsen (BPV) is an antisense oligonucleotide that targets a conserved 20-nucleotide sequence within hepatitis B virus (HBV) pregenomic RNA and mRNAs. B-Well 1 and 2 are global, randomized, double-blind, Phase 3 trials assessing the efficacy and safety of weekly BPV 300 mg or placebo (PBO) for 24 weeks (wks) in participants (pts) with nucleos(t)ide analog (NA)-suppressed chronic HBV infection, with functional cure (FC) as the primary outcome. Approximately 25% of pts treated with BPV in B-Well experienced transient ALT increases ($\geq$3x upper limit of normal). Here, we investigated serum biomarkers and their association with ALT increase in pts on BPV in the B-Well studies. **Methods:** The Olink Explore 1536 platform was used to perform proteomic analysis on serum samples longitudinally. Pt serum was used to measure roughly 1400 individual proteins. A multipronged post hoc analysis was performed. First, a targeted assessment of ALT dynamics and longitudinal profiles of 83 prespecified cytokines, chemokines, and other proteins (associated with ALT in the B-Together study,[1] HBV, and/or liver heath) were compared across increasing ALT changes from

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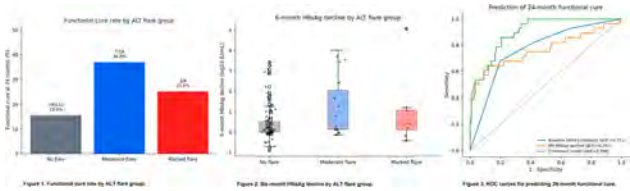
baseline (CFB). This was followed by a mediation analysis in all proteins to computationally model the cause of ALT increase and quantify the effect of BPV on ALT. FC was defined as ≥ 24 wks of sustained HBV DNA < lower limit of quantification and hepatitis B surface antigen (HBsAg) loss after finite therapy. **Results:** In pts on BPV, ALT increase was associated with greater and earlier HBsAg reduction; most, but not all, FC responders had an ALT increase (≥ 3-fold CFB). The targeted analysis revealed six protein expression profiles; some protein levels increased before and during ALT increase (e.g. TNF and IL-10) and others solely corresponded with ALT temporal dynamics (e.g. KRT18 and AIFM1). Mediation analysis identified a subset of proteins where higher expression at Wk4 subsequently led to higher ALT increases later in the treatment phase. Proteins associated with T cells (PD-1, 4-1BB, LAG3) and B cells (FCER2, FCRL2, CD22) had significant mediating effects on ALT increases during BPV treatment. Proteins associated with other cell types such as macrophages and dendritic cells (TIMD4, MARCO) also had significant mediating effects of BPV on ALT. **Conclusion:** In the B-Well trials, ALT increase was associated with greater and earlier HBsAg decline, and most, but not all, FC responders on BPV had ALT increase (≥ 3-fold CFB). ALT increase accentuates some protein induction associated with BPV treatment while others corresponded with ALT temporal dynamics. Mediation analysis highlighted that B- and T-cell activation are key immune processes leading to ALT increase. **Funding:** GSK (202009/NCT05630807; 219288/NCT05630820)[for the B-Well Study Group]1. Buti M, et al. *J Hepatol* 2025;82 (2):222–234

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4154 | ALT FLARE AND HBSAG DYNAMICS IN FUNCTIONAL CURE OF HBEAG-NEGATIVE CHRONIC HEPATITIS B

Yaqin Zhang[1] Minghui Li[1], [1]Beijing Ditan Hospital, Capital Medical University

Background: ALT flare during pegylated interferon-based therapy may reflect immune activation in chronic hepatitis B. This study evaluated the association between ALT flare, HBsAg dynamics, and 24-month functional cure in HBeAg-negative patients receiving pegylated interferon plus nucleos(t)ide analogues. **Methods:** This retrospective study included 149 HBeAg-negative chronic hepatitis B patients treated with pegylated interferon plus nucleos(t)ide analogues. Patients were classified as no flare, moderate flare, or marked flare. Moderate flare was defined as ALT ≥ 1.5× the upper limit of normal and ≥ 2× baseline ALT, but < 3× the upper limit of normal; marked flare was defined as ALT ≥ 3× the upper limit of normal. Functional cure at 24 months was defined as HBsAg ≤ 0.05 IU/mL. HBsAg dynamics and functional cure rates were compared among groups. Logistic regression was used to identify factors associated with functional cure. **Results:** Among 149 patients, 122 had no flare, 19 had moderate flare, and 8 had marked flare. Overall, 28 patients achieved 24-month functional cure, with a cure rate of 18.8%. Functional cure rates were 15.6%, 36.8%, and 25.0% in the no-flare, moderate-flare, and marked-flare groups, respectively (P = 0.079). Moderate flare showed a higher cure rate than no flare in exploratory pairwise comparison (36.8% vs. 15.6%, P = 0.050), but this was not significant after multiple-comparison adjustment. Patients with functional cure had lower baseline HBsAg levels and greater 6-month HBsAg decline. Moderate/marked ALT flare was associated with functional cure in univariate analysis (OR = 2.71, 95%CI: 1.06–6.92, P = 0.037), but this association was attenuated after adjustment. Six-month HBsAg decline remained the strongest predictor of functional cure (OR = 4.76, 95% CI: 2.28–9.96, P < 0.001). The combined model of baseline HBsAg category and 6-month HBsAg decline showed good predictive performance, with an AUC of 0.898. **Conclusion:** In HBeAg-negative chronic hepatitis B, moderate ALT flare was associated with a higher trend of functional cure, but was not an independent predictor after accounting for HBsAg-related factors. Baseline HBsAg category and 6-month HBsAg decline may better predict functional cure.



Disclosures: Yaqin Zhang:Nothing to Disclose, Minghui Li:Nothing to Disclose.

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4155 | ORAL DELIVERY OF EGCG VIA A DUAL-SHELL FERRITIN NANOPLATFORM RESTORES LYSOSOMAL FUNCTION AND SUPPRESSES HBV REPLICATION

Yixin Dong[1], [1]The First Affiliated Hospital with Nanjing Medical University

Background: Hepatitis B virus (HBV) disrupts lysosomal maturation and acidification, resulting in incomplete autophagy that supports viral persistence. Restoration of lysosomal function has emerged as a promising host-directed therapeutic strategy against HBV. Epigallocatechin gallate (EGCG) has been reported to enhance lysosomal acidification and suppress HBV replication; however, its application is limited by poor stability and low intestinal permeability. We developed a dual-shell chitosan/ferritin nanoplatform (CHE) to improve oral delivery and antiviral efficacy of EGCG. **Methods:** EGCG was encapsulated within recombinant human H-chain ferritin nanocages using a pH-triggered disassembly/reassembly strategy, followed by chitosan coating to generate CHE nanoparticles. Nanoparticle stability and gastrointestinal release behavior were evaluated in simulated digestive conditions. Intestinal transport was assessed using differentiated Caco-2 monolayers and Transwell co-culture systems containing Caco-2 and HepG2.2.15 or HepAD38. Lysosomal acidification, cathepsin B maturation, and autophagic flux were analyzed by acridine orange staining and Western blotting. Antiviral activity was determined by measuring intracellular HBV DNA, pgRNA, HBsAg, and HBeAg levels. **Results:** CHE markedly improved EGCG stability and delayed gastrointestinal release compared with free EGCG and ferritin-loaded EGCG (HE). In differentiated Caco-2 monolayers, CHE significantly enhanced transepithelial transport while maintaining epithelial barrier integrity. In HepG2.2.15 and HepAD38 cells, CHE restored lysosomal acidification and increased mature-cathepsin B expression, indicating recovery of lysosomal function. CHE further promoted autophagic flux, as evidenced by enhanced degradation of p62 and increased LC3 turnover. These effects translated into significantly greater inhibition of HBV DNA and pgRNA synthesis, accompanied by reduced HBsAg and HBeAg secretion. Importantly, CHE retained superior antiviral activity following transport across intestinal epithelial monolayers in co-culture models. **Conclusion:** A dual-shell ferritin-based oral nanoplatform effectively overcomes the stability and intestinal delivery limitations of EGCG and significantly enhances its anti-HBV activity. Restoration of lysosomal acidification and autophagic flux represents a key mechanism underlying viral suppression. These findings support lysosomal restoration as a novel host-directed therapeutic approach for chronic HBV infection and establish CHE as a promising oral nano-therapy for antiviral intervention.

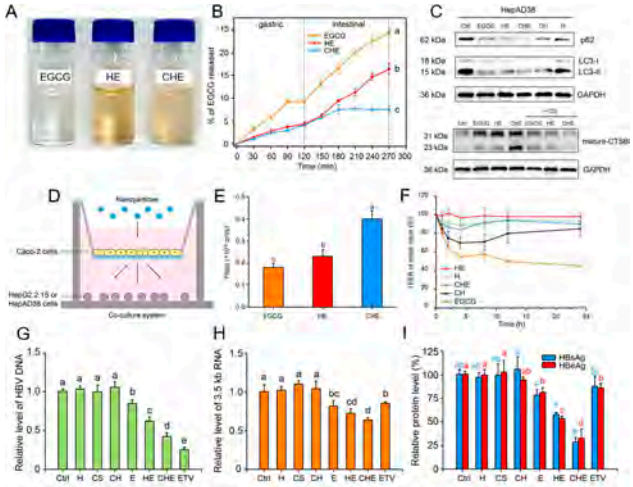


Figure. (A) Representative images of different samples, including EGCG, HE, and CHE. (B) In vitro simulated gastrointestinal digestion analysis. (C) Western blot analysis of p62, LC3, and mature-cathepsin B (mature-CTSB) expression. (D) Schematic illustration of the Transwell model with a differentiated Caco-2 monolayer established over 21 days. (E) P_{app} of free EGCG and EGCG encapsulated within HE and CHE nanoparticles after 24 h of incubation with Caco-2 monolayers in Transwell inserts. (F) Effects of different formulations on TEER values of Caco-2 monolayers over a 24 h exposure period. Inhibitory effects on HBV DNA (G), pgRNA (3.5 kb RNA) (H), HBsAg and HBeAg (I) secretion in HepAD38 cells. Different letters indicate statistically significant differences ($p < 0.05$), as determined by Duncan's multiple range test.

Disclosures: Yixin Dong:Nothing to Disclose.

4156 | THE POTENTIALLY BEST-IN-CLASS HBV ASO ALG-170675 DEMONSTRATES A FAVOURABLE PRECLINICAL PROFILE: EFFICACY IN AN AAV-HBV MOUSE MODEL, PHARMACOKINETICS AND SAFETY IN MOUSE AND MONKEY

Jin Hong[1] Dinah Misner[1] Kusum Gupta[1] Vivek Rajwanshi[1] Jimmy Lu[2] Sandra Chang[1] Hyunsoon Kang[1] Min Luo[1] Antitsa Stoycheva[1] Dana Cho[1] John Cortez[1] Kellan Passow[1] Jacquelyn Sousa[1] Shane Daguison[1] Jieun Song[1] Lillian Adame[1] Cheng Liu[1] Sarah Stevens[1] Aneerban Bhattacharya[1] Lawrence Blatt[3] Leonid Beigelman[4] David Smith[1] Sushmita Chanda[1] Li Sun[2] Julian Symons[1], [1]Aligos Therapeutics, [2]Amoytop Biotech., [3]Aligos Therapeutics, Inc., [4]Former employee of Aligos Therapeutics

Background: ALG-170675 is a next generation HBV ASO with dual RNase H and human TLR8 agonist activities and is currently in late-stage preclinical development. ALG-170675 demonstrated better efficacy and liver PK than GSK-836 when dosed at 40 mg/kg x 6 in AAV-HBV mice. No liver toxicity was observed when ALG-170675 was dosed at 50 mg/kg x 7 in either uninfected or HBV-infected PXB mice with humanized livers (Publication 1155, AASLD 2025). Here, ALG-170675 was dosed in an AAV-HBV mouse model in

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combination with a close analog of ALG-000184 (HBV CAM-E). ALG-170675 combinations with the nucleos(t)ide analog entecavir (ETV), HBV siRNA ALG-125903 (parent drug of ALG-125755) and ALG-001075 (parent drug of ALG-000184) were also studied in vitro. Pharmacodynamics (PD), pharmaco-/toxicokinetics (PK/TK) and toxicology of ALG-170675 were evaluated in mouse and monkey. **Methods:** HBV cell models, such as HepG2.2.15 and HepG2.117, were used for combination studies in vitro to assess reduction in HBsAg and HBV DNA, respectively. In vivo ALG-170675 dose response and combination studies were performed in the AAV-HBV mouse model. PK, PD and toxicity/TK evaluations in mouse and monkey were conducted at Wuxi AppTec. **Results:** When dosed at 10, 20 and 40 mg/kg x 6 in AAV-HBV mice, ALG-170675 showed dose response related reductions in HBsAg levels with up to a 0.66 $\log_{10}$ IU/mL additional maximum HBsAg reduction compared to GSK-836. Elevated liver exposures compared to GSK-836 were observed. When close analogs of ALG-170675 and ALG-000184 were combined in AAV-HBV mice, both plasma HBsAg and HBV DNA showed additive to synergistic effects. Further, in vitro combination studies showed additive effects when ALG-170675 was combined with ETV, or CAM-E ALG-001075, or HBV siRNA ALG-125903. ALG-170675 was absorbed and distributed rapidly following a single subcutaneous (SC) dose in CD-1 mice. ALG-170675 was stable in plasma as the intact ASO was the major circulating entity (>99%). Liver concentrations were measurable through 28 days, with a half-life of ~7 days. Following repeat SC administrations over 28 days, the exposures increased proportionally from 10 to 100 mg/kg/dose in mice and monkeys. No sex difference or accumulation of systemic exposures was observed in monkeys. Monkey PD markers IL-1RA, MCP-1, and CRP were elevated. ALG-170675 was well tolerated in 1-month repeat-dose range-finding toxicity studies in mice and monkeys and NOAELs were determined to be 30 mg/kg/dose in both species. Adverse effects at the higher dose of 100 mg/kg/dose included hepatocellular necrosis in mice accompanied by increases in liver enzymes and thymic lymphocytic hypocellularity in monkeys. **Conclusion:** ALG-170675 showed potential to be a best-in-class HBV ASO based on preclinical studies conducted to date. Preclinical development is underway, with ALG-170675 expected to enter the clinic in late 2026.

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4157 | ALT TRAJECTORY PATTERNS ARE ASSOCIATED WITH VIROLOGICAL RESPONSE STABILITY IN CHB PATIENTS RECEIVING PEG-IFN COMBINATION THERAPY

Dianya Qiu[1] Minghui Li[1], [1]Capital Medical University Affiliated Beijing Ditan Hospital

Background: Alanine aminotransferase (ALT) dynamics may reflect hepatic inflammation and immune activity during antiviral therapy for chronic hepatitis B (CHB). However, the relationship between longitudinal ALT trajectory patterns and the stability of virologic response (VR) during pegylated interferon (PEG-IFN)-based combination therapy remains unclear. **Methods:** A total of 255 CHB patients receiving PEG-IFN combined with tenofovir alafenamide (TAF) or tenofovir disoproxil fumarate (TDF) with 24-month follow-up were enrolled. ALT normalization was defined as ALT $\leq$40 U/L, and VR as HBV DNA $\leq$20 IU/mL. Sustained virologic response (SVR) was defined as VR maintained at months 12, 18, and 24. Group-based trajectory modeling (GBTM) was used to identify dynamic ALT patterns, and associations between ALT trajectories and virologic outcomes were evaluated. **Results:** ALT normalization increased from 62.4% at baseline to 74.9% at month 24, while the VR rate increased from 63.9% to 91.0%. Three ALT trajectories were identified: low-stable ALT (86.3%), persistent abnormal/fluctuating elevated ALT (5.5%), and high ALT with rapid decline (8.2%). The persistent abnormal/fluctuating elevated ALT group showed the lowest SVR rate (50.0%) compared with the low-stable ALT group (79.5%) and the high ALT with rapid decline group (81.0%) ($P = 0.033$). At month 24, VR rates were 95.2%, 91.4%, and 78.6%, respectively, with no significant difference among groups ($P > 0.05$). Among patients without VR at baseline, time to VR did not differ significantly across ALT trajectory groups (log-rank $P = 0.15$). Agreement between ALT flare and HBV DNA flare was low (Kappa = 0.068). **Conclusion:** CHB patients receiving PEG-IFN combination therapy exhibit distinct dynamic ALT trajectories. Persistent abnormal or fluctuating ALT elevation is associated with reduced

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SVR stability, suggesting that longitudinal ALT trajectory analysis may help identify patients at risk for unstable virologic suppression during treatment. Given the small sample sizes in some trajectory subgroups, these findings should be considered exploratory, and the independent predictive value of ALT trajectories requires validation in larger cohorts.

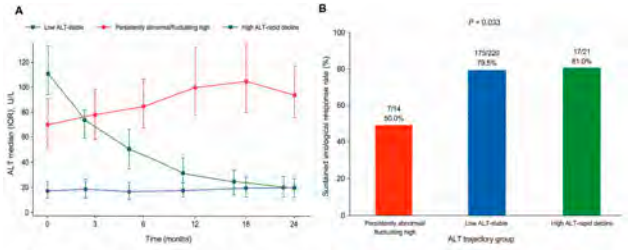


Figure 1. Association between ALT trajectory patterns and sustained virological response stability during PEG-IFN combination therapy. (A)Distinct ALT trajectory groups during treatment follow-up. (B)Sustained virological response by ALT trajectory group.

Disclosures: Dianya Qiu:Nothing to Disclose, Minghui Li:Nothing to Disclose.

4158 | PEVIFOSCORVIR SODIUM (CAM-E) IS SUPERIOR TO NUCLEOS(T)IDE ANALOGS IN SUPPRESSING HEPATITIS B VIRUS DOUBLE-STRANDED LINEAR DNA IN VITRO

Yannick Debing[1] Antonios Kountouratzis[1] Hannah Vanrusselt[1] Jordi Verheyen[1] Julian Symons[2] Lawrence Blatt[3] Tse-I Lin[1] Andreas Jekle[3], [1]Aligos Belgium BV, [2]Aligos Therapeutics, [3]Aligos Therapeutics, Inc.

Background: Circulating hepatitis B virus (HBV) DNA consists mostly of relaxed circular DNA (rcDNA) and double-stranded linear DNA (dslDNA). dslDNA is the precursor form for HBV DNA integration into the host genome, which contributes to disease progression and development of hepatocellular carcinoma. It remains unclear to what extent nucleos(t)ide analogs (NAs), such as tenofovir disoproxil fumarate (TDF) and entecavir (ETV), affect rcDNA vs. dslDNA production. Additionally, the HBV capsid assembly process has emerged as a key target for the treatment of chronic HBV infection. The capsid assembly modulator (CAM) pevifoscorvir sodium (pevy) has demonstrated best-in-class reductions of HBV DNA, RNA, HBsAg, HBeAg and HBcrAg in participants with chronic HBV infection. Here, we investigated the effects of NAs and CAMs on production and secretion of HBV rcDNA and dslDNA in vitro. **Methods:** HBV rcDNA and dslDNA were quantified by a specifically developed multiplex digital PCR (dPCR) procedure that allows to distinguish and quantify each form in a way that is not possible with conventional quantitative PCR. The effects of NAs TDF and ETV and CAM ALG-001075 (pevy active parent) on intracellular and secreted HBV rcDNA and dslDNA were assessed in HepG2.117, HepAD38, HBV-infected HepG2-NTCP cells and primary human hepatocytes. **Results:** The specificity of the dPCR protocol was confirmed with selective nuclease digestions of either rcDNA or dslDNA before analysis. In all tested cellular systems, NAs and CAM ALG-001075 inhibited the production of both rcDNA and dslDNA in a dose-dependent fashion. Interestingly, NAs TDF and ETV showed a clear difference in inhibiting rcDNA vs. dslDNA, with consistently lower EC_{50} values for rcDNA than for dslDNA, again in all tested cellular systems. Conversely, CAM ALG-001075 showed similar EC_{50} values for both forms, in line with its mechanism of action, blocking pgRNA encapsidation, which precedes the reverse transcription to rcDNA and dslDNA. Intriguingly, relative ratios of rcDNA vs. dslDNA differed between cellular systems and between intracellular and secreted fractions of HBV DNA. Quantification of dslDNA and rcDNA in patient samples will be presented at the conference as well. **Conclusion:** CAM ALG-001075 demonstrated pronounced and equipotent inhibition of HBV rcDNA and dslDNA production in vitro, whereas NAs were less effective at inhibiting dslDNA than rcDNA production. These results suggest that CAMs could be superior to NAs in preventing HBV DNA integration, not only through deeper suppression of HBV DNA levels, but also by more effective suppression of dslDNA, the precursor to integration.

Disclosures: Yannick Debing:Aligos Therapeutics, Inc.: Employee, Aligos Therapeutics, Inc.: Stock - publicly traded company, Antonios Kountouratzis:Nothing to Disclose, Hannah Vanrusselt:Aligos Belgium: Employee, Jordi Verheyen: Nothing to Disclose, Julian Symons:Aligos Therapeutics Inc.: Employee, Lawrence Blatt:Nothing to Disclose, Tse-I Lin:Nothing to Disclose, Andreas Jekle:Aligos Therapeutics: Employee, Aligos Therapeutics: Stock - publicly traded company.

4159 | THERAPEUTIC VACCINATION WITH TLR9-ADJUVANTED HBSAG IN CHRONIC HEPATITIS B: A PHASE 1 PROOF-OF-CONCEPT STUDY

Gaayathri Krishnan[1] Tetiana Pozniak[2] Alip Ghosh[2] Salma Sharaf[2] Shyamasundaram Kottilil[2] Lydia Tang[2], [1]University of Maryland, [2]Institute of Human Virology

Background: Chronic hepatitis B (CHB) infection results from inadequate host immune control of the hepatitis B virus (HBV). Although nucleos(t)ide analogs (NUCs) effectively suppress viral replication, they rarely achieve a functional cure, defined as sustained loss of hepatitis B surface antigen (HBsAg) and undetectable

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HBV DNA following treatment discontinuation. We investigated if achieving HBsAb production lead to sustained HBsAg loss in CHBToll-like receptor 9 (TLR9) is central to activating innate immunity and is a promising immunomodulatory target in CHB. Expressed on dendritic cells and B cells, TLR9 recognizes HBV DNA and promotes downstream antiviral and humoral immune responses. In CHB, TLR9 expression is reduced and signaling is impaired. Preclinical studies demonstrate that TLR9 agonists, particularly in combination with NUCs, increase antiviral cytokine production and reduce surface antigen levels, supporting their therapeutic potential. The BOOST-9 study evaluated HEPLISAV-B (Dynavax Technologies Corporation), an FDA-approved prophylactic HBV vaccine containing HBsAg adjuvanted with a TLR-9 agonist, as a therapeutic vaccination strategy to assess safety, tolerability, and immunological and virological efficacy in patients with CHB. **Methods:** BOOST-9 was a single-site, pilot phase 1 proof-of-concept study evaluating safety and humoral and virologic responses to toll-like receptor 9 adjuvanted HBV vaccination. Ten adults with CHB on NUCs, without liver fibrosis, received two 0.5 mL intramuscular injections of HEPLISAV-B (day 0 and week 4), with follow-up at weeks 8 and 24, and at 12 months. Clinical (HBV DNA, renal and liver function tests, complete blood count, and quantitative HBsAb) and research labs (B cell ELISpots, flow cytometry, and pregenomic RNA [pgRNA]) were collected throughout. **Results:** All 10 subjects (ages 31-71) completed vaccination and 8 weeks of follow-up. No grade 3 or above adverse events (AE) occurred. The most common AE was injection site reactions (50%). At week 8, HBsAg levels remained stable or declined, with 8 participants demonstrating modest reductions ranging from 0.1 to 0.5 log10. HBsAb titers increased in two participants, including one with a significant rise to 452 IU/mL. pgRNA levels were below the lower limit of quantification (25 copies/mL) throughout the study. **Conclusion:** HEPLISAV vaccination was safe and well-tolerated in patients with CHB. Induction of HBV-specific humoral response was observed in a subset of participants. There was a trend toward reduced HBsAg levels, suggesting a potential early immunologic effect. These fundings support further investigation of TLR9-mediated therapeutic vaccination as a strategy to restore HBV-specific immunity particularly in combination with antiviral agents and advance toward a functional cure. **Disclosures:** Gaayathri Krishnan:Nothing to Disclose, Tetiana Pozniak:Nothing to Disclose, Alip Ghosh: Nothing to Disclose, Salma Sharaf:Nothing to Disclose, Shyamasundaram Kottilil:Nothing to Disclose, Lydia Tang:Arbutus: Grant/Research Support, Gilead Sciences: Grant/Research Support, Moderna: Grant/Research Support, Ausperbio: Grant/Research Support.

4160 | ANALYSIS OF HEPATITIS B VIRUS (HBV) GENOTYPE ASSOCIATION TO BEPIROVIRSEN TREATMENT RESPONSE IN PATIENTS WITH CHRONIC HBV INFECTION: PHASE 3 B-WELL 1 AND 2 STUDIES

Jerome Bouquet[1] Christopher Sampson[2] Maria Agostini[1] William Jordan[3] Scott Speer[1] Sonia Maciejewski[3] Michael Maguire[2] Phillip Yates[2] Yu Tao[3] Sai Vinusha Kosaraju[3] Ritesh Dhimmar[3] Michael Willis[2] Geoffrey Quinn[2] Jennifer Cremer[4] Amir Youssef[3] Ahmed Nader[3] Tamara Lukic[5] Lin-Ming Shen[6] Dickens Theodore[4] Melanie Paff[3] Rob Elston[2] Jill Walker[1], [1]GSK, South San Francisco, CA, USA, [2]GSK, Stevenage, UK, [3]GSK, Collegeville, PA, USA, [4]GSK, Durham, NC, USA, [5]GSK, Dubai, United Arab Emirates, [6]GSK, Waltham, MA, USA

Background: Bepirovirsen (BPV) is an antisense oligonucleotide that targets a conserved 20 nucleotide sequence within HBV pregenomic RNA and mRNAs. B-Well 1 and 2 are global randomized, double-blind, Phase 3 trials assessing the efficacy and safety of weekly 300 mg BPV or placebo (PBO) for 24 weeks (wks) in participants (pts) with nucleos(t)ide analog-suppressed chronic HBV infection. Functional cure (FC) was the primary outcome. Comprehensive HBV genotype (GT) information is useful to better understand heterogeneity in clinical trials for HBV but difficult to obtain in virally suppressed pts. Here, we present pooled GT distribution and hepatitis B surface antigen (HBsAg) reduction at Wk24 and FC rate at Wk72 by viral GT from the B-Well studies. **Methods:** GT was assigned in this order based on availability: (1) medical history, (2) baseline next generation sequencing of HBV RNA, and (3) baseline serology assay targeting HBsAg GT-specific epitopes (IMMUNIS HBV Genotype EIA). FC (primary outcome) was defined as $\geq$24 wks of sustained HBV DNA < lower limit of quantification and HBsAg loss after finite therapy, with or without hepatitis B surface antibody. **Results:** HBV genotype information was available for 975/978 (99.7%) B-Well 1 and 843/856 (98.5%) B-Well 2 pts. In pts treated with BPV across both B-Well studies (B-Well 1 [N = 650] and 2 [N = 570]), all 10 GTs (A–J) were observed. GT distribution across pooled studies was comparable between BPV and PBO treatment groups; most pts treated with BPV were GTs C (31%; n = 376), D (26%; n = 318), B (25%; n = 308), and A (10%; n = 126). A significant reduction in HBsAg levels from baseline to Wk24 was observed in all GTs with more than 1 pt. The mean maximal log decline in HBsAg levels from baseline to Wk24 was similar across GTs A–D (−2.90 log10 IU/mL to −3.59 log10 IU/mL). FC response rates at Wk72 were similar across GTs, with GT A exhibiting

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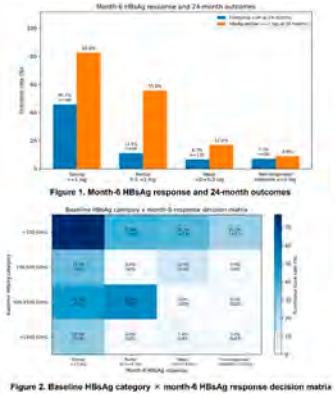
the highest FC rate in the HBsAg ≤3000 IU/mL and ≤1000 IU/mL populations (HBsAg ≤3000 IU/mL: 28%; ≤1000 IU/mL: 39%), followed by GTs B (21%; 27%), D (20%; 27%), and C (15%; 23%). **Conclusion:** The multi-tiered approach allowed for determination of HBV GTs in ≥99% of pts enrolled in the B-Well studies that were virally suppressed. The strengths of the B-Well studies were size and global reach reflected in the broad range of HBV GTs. Though subgroups with low representation (GTs F–J) were not fully evaluable, the treatment effect of BPV on FC rate was favorable across HBV GTs and greatest among GT A. **Funding:** GSK (202009/NCT05630807; 219288/NCT05630820) [for the B-Well Study Group]

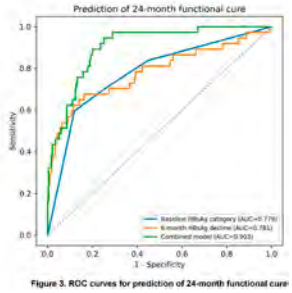
Disclosures: Jerome Bouquet:GSK: Employee, GSK: Stock - publicly traded company, Christopher Sampson:GSK: Employee, GSK: Stock - publicly traded company, Maria Agostini:Nothing to Disclose, William Jordan:Nothing to Disclose, Scott Speer:Nothing to Disclose, Sonia Maciejewski:Nothing to Disclose, Michael Maguire:Nothing to Disclose, Phillip Yates:GSK: Consultant, Yu Tao:Nothing to Disclose, Sai Vinusha Kosaraju:Nothing to Disclose, Ritesh Dhimmar:Nothing to Disclose, Michael Willis:Nothing to Disclose, Geoffrey Quinn:Nothing to Disclose, Jennifer Cremer:Nothing to Disclose, Amir Youssef:Nothing to Disclose, Ahmed Nader:GSK: Employee, Tamara Lukic:GSK: Employee, Lin-Ming Shen:GSK: Employee, Voyager Therapeutics: Stock - publicly traded company, GSK: Stock - publicly traded company, Dickens Theodore:Nothing to Disclose, Melanie Paff:GSK: Stock - publicly traded company, GSK: Employee, Rob Elston:Nothing to Disclose, Jill Walker:Nothing to Disclose.

4161 | INTEGRATING BASELINE HBSAG CATEGORY AND MONTH-6 HBSAG DECLINE TO PREDICT FUNCTIONAL CURE IN CHRONIC HEPATITIS B

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Background: Early on-treatment decline in hepatitis B surface antigen (HBsAg) may help identify patients with chronic hepatitis B who are more likely to benefit from pegylated interferon (Peg-IFN)-based therapy. This study aimed to develop a month-6 HBsAg response-based framework for predicting 24-month outcomes across HBeAg status. **Methods:** This retrospective real-world study included 273 patients with chronic hepatitis B receiving Peg-IFN plus nucleos(t)ide analogues. According to HBsAg decline at month 6, patients were categorized as strong responders (≥1 log), partial responders (0.5–1 log), weak responders (0–0.5 log), and non-responders/rebounders (≤0 log). The primary endpoint was functional cure at month 24, defined as HBsAg ≤0.05 IU/mL. The secondary endpoint was HBsAg decline ≥1 log at month 24. Logistic regression was used to evaluate factors associated with functional cure. **Results:** Among 273 patients, 38 achieved functional cure at month 24, with an overall rate of 13.9%. HBsAg decline ≥1 log at month 24 was observed in 86 patients (31.5%). The month-6 strong, partial, weak, and non-response/rebound groups included 46, 36, 135, and 56 patients, respectively. Functional cure rates differed significantly across month-6 response categories, reaching 45.7% in strong responders, compared with 11.1%, 6.7%, and 7.1% in partial, weak, and non-response/rebound groups, respectively (P < 0.001). In multivariable analysis, month-6 HBsAg decline remained independently associated with 24-month functional cure (OR = 4.01, 95%CI: 2.22–7.24, P < 0.001). The combined model integrating baseline HBsAg category and month-6 HBsAg decline showed the best predictive performance, with an AUC of 0.903, compared with baseline HBsAg category alone and month-6 HBsAg decline alone. **Conclusion:** Month-6 HBsAg decline provides clinically meaningful stratification for 24-month functional cure in patients receiving Peg-IFN-based combination therapy. A response-adapted framework integrating baseline HBsAg category and early HBsAg kinetics may help identify patients with a higher probability of sustained antigenic benefit and guide individualized continuation of Peg-IFN-based treatment.





Disclosures: Yaqin Zhang:Nothing to Disclose, Shiyu Wang:Nothing to Disclose, Zixuan Gao:Nothing to Disclose, Minghui Li:Nothing to Disclose.

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4162 | QUALITY OF LIFE IMPROVEMENTS OBSERVED IN B-CLEAR COMPLETE RESPONDERS FOLLOWING BEPIROVIRSEN TREATMENT: OFF-TREATMENT FOLLOW-UP IN THE B-SURE STUDY

Shannon Keith[1] Afisi Ismaila[2] Lauren Maynard[3] Geoffrey Quinn[3] Alexandra Walker[4] Jane Dong[5] Isabelle Santhiapillai[3] Yi Cui[3] Melanie Paff[2] Dickens Theodore[6] Rob Elston[3] Marjan Hezareh[4], [1]GSK, Wilmington, DE, USA, [2]GSK, Collegeville, PA, USA, [3]GSK, Stevenage, UK, [4]GSK, London, UK, [5]GSK, Shanghai, China, [6]GSK, Durham, NC, USA

Background: Patients (pts) with chronic hepatitis B virus (HBV) infection can experience stigma, anxiety and other impacts on their health-related quality of life (HRQoL). Bepirovirsen is an unconjugated antisense oligonucleotide in Phase 3 clinical trials for the treatment of chronic HBV infection. Complete (CR) or partial (PR) responders at the end of the Phase 2b B-Clear study (NCT04449029) were eligible for the long-term durability B-Sure study (NCT04954859). Here we present Hepatitis B Quality of Life (HBQoL) scores of B-Clear pts on nucleos(t)ide analogue (NA) therapy (On-NA) who were CR at the end of B-Clear and entered B-Sure. **Methods:** CR was defined as hepatitis B surface antigen (HBsAg) < 0.05IU/mL and HBV DNA < lower limit of quantification (LLOQ). If eligible, pts discontinued NA treatment 3 months (mo) into B-Sure (≥ 9 mo from their last bepirovirsen dose) and were followed further to determine achievement of functional cure (FC) and durability of response off all HBV therapy. Participants completed the HBQoL v1.0 questionnaire at B-Clear baseline (BL) and throughout the B-Sure study (mo 0, 3, 9, 21 and 33). Mean scores for each of the six subdomains and overall HBQoL scores at B-Clear BL and B-Sure mo 33 (i.e. 24 mo post-FC achievement) are reported. Data are descriptive; a higher HBQoL score indicates worse HRQoL. **Results:** In total, 14 CRs were enrolled into B-Sure; 10/14 CRs discontinued NAs 3 mo into B-Sure. 8/10 pts maintained CR at Month 9 and achieved FC; 8/8 had maintained FC for 24 mo and 7/7 for 30 mo (follow-up ongoing). At B-Clear BL, psychological well-being, anticipation anxiety, vitality, stigma, vulnerability and transmissibility subdomain scores were 38.0, 41.7, 22.3, 23.7, 35.3 and 44.9, respectively. Corresponding subdomain scores were 18.4, 27.3, 15.6, 15.3, 22.2 and 25.0, at B-Sure mo 33, for CRs who discontinued NAs at 3 mo, respectively. For CRs who did not discontinue NAs, subdomain scores were 45.4, 33.4, 40.0, 33.3, 33.4 and 20.9 at B-Sure mo 33, respectively. At B-Clear BL, the overall HBQoL score was 33.8 for CR participants (n = 13). At mo 33 of B-Sure, overall HBQoL score was 20.1 for CRs who discontinued NAs at 3 mo (n = 9), and 36.3 for CRs who did not discontinue NAs at 3 mo (n = 2). **Conclusion:** Following discontinuation of NA treatment in B-Sure, improvements in all HBQoL domains and overall HBQoL scores were observed in On-NA CRs enrolled in B-Sure. Improvements were also seen for some HBQoL subdomains in CRs who did not discontinue NA treatment. **Funding:** GSK (206882; NCT04954859).
Disclosures: Shannon Keith:GSK: Employee, GSK: Employee, GSK: Stock - publicly traded company, Afisi Ismaila:Nothing to Disclose, Lauren Maynard:Nothing to Disclose, Geoffrey Quinn:Nothing to Disclose, Alexandra Walker:Nothing to Disclose, Jane Dong: Nothing to Disclose, Isabelle Santhiapillai:Nothing to Disclose, Yi Cui:GlaxoSmithKline: Employee, Melanie Paff:GSK: Stock - publicly traded company, GSK: Employee, Dickens Theodore:Nothing to Disclose, Rob Elston:Nothing to Disclose, Marjan Hezareh: GSK: Employee, GSK: Stock - publicly traded company.

4163 | PREDICTING THE EFFECTS OF BEPIROVIRSEN DOSING IN PATIENTS WHO RELAPSE AFTER AN INITIAL COURSE OF TREATMENT

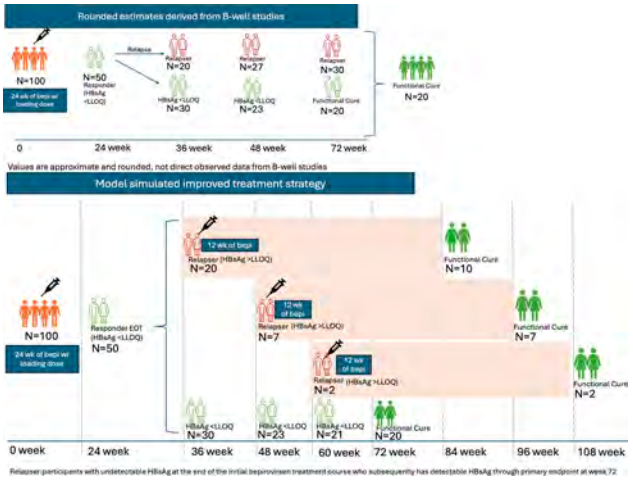
Qianwen Wang[1] Melanie Paff[2] Andrew Skingsley[3] Dickens Theodore[4] Attila Mihalyi[5] Ahmed Nader[6], [1]Clinical Pharmacology and Quantitative Medicine, GSK, UK, [2]Specialty Product Development, GSK, US, [3]Vx Clinical Sc. Flu/Covid/Pandemic/Exploratory, GSK, UK, [4]Hepatology Clinical Development, GSK, US, [5]Global Medical Affairs - Specialty Care, GSK, Belgium, [6]Clinical Pharmacology and Quantitative Medicine, GSK, US

Background: Achieving functional cure (FC) in chronic hepatitis B (CHB) remains a major unmet need, with a substantial proportion of patients failing to sustain response after finite therapy. Clinical experience with peginterferon suggests retreatment may benefit selected patients, but there is limited evidence to guide similar strategies for novel agents. Bepirovirsen, an antisense oligonucleotide targeting HBV, has demonstrated clinical benefit in recent Phase 3 studies; with approximately 44% treated patients achieving undetectable HBsAg and HBV DNA. **Methods:** A previously developed mechanistic PKPD model describing bepirovirsen treatment effect and HBsAg dynamics was extended to conduct an *in-silico* evaluation of retreatment scenarios. Virtual populations were generated using resampling techniques and stratified into clinically relevant subgroups based on Phase 3 studies (Figure 1), assuming that response parameters following the initial course of treatment were unchanged for the second course.

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Simulations evaluated HBsAg trajectories and FC outcomes under different treatment regimens and in different patient subgroups. **Results:** Simulations suggest that a second course of 12-week treatment of bepirovirsen may result in FC in a majority of relapsers. In contrast, no benefit was predicted for null responders (< 0.5 log drop of HBsAg with detectable HBsAg at end of the first course of bepirovirsen). Limited benefit was predicted in partial responders (> 0.5 log HBsAg reduction but still detectable HBsAg at the end of the first course), mainly driven by a subgroup with HBsAg levels between 0.05 and 1 IU/mL at the end of first course. Earlier treatment in relapsers was associated with higher predicted FC compared with delayed treatment. Based on simulated treatment strategies, initiation of second course of treatment for relapsers within the week 36–72 window is proposed for evaluation in future studies (Figure 1). Limited benefit was predicted for alternative dosing strategies such as regimen of 24 weeks or the inclusion of a loading dose. **Conclusion:** Model simulated results demonstrated a substantial increment in FC for initial responders who relapse when treated with 12 additional weeks of weekly bepirovirsen. This quantitative framework can be used to inform additional treatment strategies and offers key insights to guide a more efficient clinical development program. **Funding:** GSK (202009/NCT05630807; 219288/NCT05630820)Figure 1: Patient journey: B-well studies (rounded estimates from data using quantitative HBsAg assay, upper panel), simulated treatment in relapsers after initial course of bepirovirsen (lower panel).



Disclosures: Qianwen Wang:Nothing to Disclose, Melanie Paff:GSK: Stock - publicly traded company, GSK: Employee, Andrew Skingsley:GSK: Also stock holder, Dickens Theodore:Nothing to Disclose, Attila Mihalyi:GSK: Employee and stock holder, Ahmed Nader:GSK: Employee.

4164 | A SECOND-GENERATION HBV SIRNA EXHIBITS BEST-IN-CLASS POTENTIAL IN TREATING CHRONIC HEPATITIS B AND D IN PRECLINICAL STUDIES

Jin Hong[1] Vivek Rajwanshi[1] Kellan Passow[1] Hyunsoon Kang[1] Min Luo[1] Shane Daguison[1] Jacquelyn Sousa[1] Kusum Gupta[1] Cheng Liu[1] Antitsa Stoycheva[1] Aneerban Bhattacharya[1] Jieun Song[1] Lillian Adame[1] Alexander Leung[1] Dana Cho[1] John Cortez[1] Dinah Misner[1] Lawrence Blatt[2] Leonid Beigelman[3] David Smith[1] Julian Symons[1], [1]Aligos Therapeutics, [2]Aligos Therapeutics, Inc., [3]Former Employee of Aligos Therapeutics

Background: HBV siRNAs such as AB-729, VIR-2218, RG6346 and JNJ-3989 can effectively reduce HBsAg in chronic hepatitis B (CHB) subjects. However, to achieve functional cure, siRNAs need to be combined with immunomodulatory agents such as interferon. HBV siRNA is also being evaluated as a lead-in therapy to improve the functional cure rate of HBV ASO. In HBV/HDV coinfected patients, HBV siRNA appears to significantly improve the time to HDV RNA undetectability when combined with an anti-HBsAg monoclonal antibody. The potential first/best in class CAM-E, pevifoscorvir sodium (pevy, ALG-000184) and potential best in class HBV ASO ALG-170675 could potentially benefit from the addition of an HBV siRNA in treating CHB and CHD. A Phase 1 study of the HBV siRNA, ALG-125755 found that it was well tolerated with a favorable PK profile and HBsAg lowering at all dose levels evaluated. In this new preclinical study, a multi-pronged approach was taken to further improve the potency, stability, hepatocyte-specific delivery and safety of ALG-125755 with the aim of developing a best-in-class HBV siRNA. **Methods:** In vitro inhibition of HBsAg release by siRNA was performed in the HepG2.2.15 cell line after transfection. The stability of HBV siRNAs was determined in mouse liver homogenates. Off target activity was evaluated by RNAseq in HepG2.2.15. The binding of different GalNAc moieties to the asialoglycoprotein receptor (ASGR) was measured in human and mouse liver microsomes. In the AAV-HBV mouse model, HBV siRNAs conjugated with GalNAc were administered subcutaneously with serial blood collections for HBsAg and ALT assessment. **Results:** ALG-127563 emerged as one of the lead 2nd generation HBV siRNAs. It showed an EC_{50} of 4.5 pM in inhibiting HBsAg release while ALG-125755 and 3 Phase 2/3 competitor siRNAs exhibited double-digit pM EC_{50} values. After a 96 hour incubation in mouse liver homogenate, 92% of the antisense strand (AS) of ALG-127563 remained intact, exhibiting superior stability relative to the AS of ALG-125755 or Phase 2/3 siRNAs with intact AS remaining at 60 to 70%. The GalNAc

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moiety used in ALG-125755 was also optimized, resulting in a 4X improvement in binding to human liver microsome ASGR. In an HBV-infected 3-D human liver chip study with no transfection, siRNA with a 2nd gen GalNAc demonstrated improvement with up to an 84% additional HBsAg knock down. ALG-127563 RNASeq and human PBMC assays demonstrated a clean in vitro safety profile. In a 35-day AAV-HBV mouse study, a single dose of 5 mg/kg ALG-127563 showed a maximum HBsAg knock down of 2.43 $\log_{10}$ IU/mL while dosing of clinical stage compounds showed a 1.8-1.9 $\log_{10}$ IU/mL maximum reduction. The durability of HBsAg reduction by ALG-127563 was also enhanced compared to that of clinical benchmarks. **Conclusion:** ALG-127563 demonstrated improved in vitro and in vivo potency when compared with ALG-125755 and Ph2/3 siRNAs. Further studies are ongoing.

Disclosures: Jin Hong:Nothing to Disclose, Vivek Rajwanshi:Nothing to Disclose, Kellan Passow:Nothing to Disclose, Hyunsoon Kang:Nothing to Disclose, Min Luo:Nothing to Disclose, Shane Daguison:Nothing to Disclose, Jacquelyn Sousa:Nothing to Disclose, Kusum Gupta:Nothing to Disclose, Cheng Liu:Nothing to Disclose, Antitsa Stoycheva:Nothing to Disclose, Aneerban Bhattacharya:Nothing to Disclose, Jieun Song:Aligos Therapeutics: Employee, Lillian Adame: Nothing to Disclose, Alexander Leung:Nothing to Disclose, Dana Cho:Nothing to Disclose, John Cortez: Nothing to Disclose, Dinah Misner:Nothing to Disclose, Lawrence Blatt:Nothing to Disclose, Leonid Beigelman: Nothing to Disclose, David Smith:Nothing to Disclose, Julian Symons:Aligos Therapeutics Inc.: Employee.

4165 | SG12, A NOVEL HBV-TARGETING ANTISENSE OLIGONUCLEOTIDE (ASO) WITH DUAL MECHANISMS, DEMONSTRATES SUPERIOR EFFICACY AND FAVORABLE PK/SAFETY IN PRECLINICAL STUDIES

Yue Huang[1] Xiaohua Yu[1] Yuhang Wang[1] Haisheng Wang[1], [1]SicaGene BioScience Co., Ltd.

Background: Achieving functional cure for chronic hepatitis B (CHB) remains a high medical need with promising potential pursued by innovative therapeutics. SG12 is a novel HBV-targeting ASO with a unique dual antiviral mechanism. This study evaluated its preclinical efficacy, pharmacokinetics, safety, and mechanism of action. **Methods:** Anti-HBV activity was assessed in HepG2.2.15 cells, HBV transgenic mice, and rAAV8-1.3HBV mice, with bepirovirsen as control. Mechanistic studies examined SG12 colocalization with Kupffer cells. PK and safety were evaluated in CD-1 mice and cynomolgus monkeys following single or repeated doses. **Results:** SG12 significantly inhibited HBV activity in vitro and in vivo, showing superior efficacy versus bepirovirsen with approximately greater than 1-log improvement in HBsAg reduction at the same dose level. SG12 efficiently colocalized with Kupffer cells, confirming a dual mechanism of gene silencing and innate immune activation. PK results showed rapid absorption, slow elimination (notably in monkeys), high liver enrichment, high protein binding, and good metabolic stability. In a 28-day repeat-dose toxicity study, the maximum tolerated dose (MTD) in cynomolgus monkeys was 20 mg/kg. In 29-day dosing with 28-day recovery studies, the non-observed adverse effect level (NOAEL) was 20 mg/kg in CD-1 mice and 15 mg/kg in cynomolgus monkeys. No genotoxicity, hemolysis, or systemic allergic reactions were observed, and immunogenicity was low. **Conclusion:** SG12 exhibits superior anti-HBV efficacy, favorable liver-targeting PK, and a reliable safety profile in preclinical studies. Its dual mechanism supports further clinical development for CHB functional cure. It is currently being evaluated in Phase 1 clinical study.

Disclosures: YUE HUANG:Nothing to Disclose, Xiaohua Yu:Nothing to Disclose, Yuhang Wang:Nothing to Disclose, Haisheng Wang:Nothing to Disclose.

4166 | PERSPECTIVES AND PREFERENCES ON POTENTIAL LONG-ACTING ANTIVIRAL TREATMENT MODALITIES AMONG PEOPLE LIVING WITH HEPATITIS B: A GLOBAL QUALITATIVE STUDY

Yasmin Ibrahim[1] David Thomas[2] Karine Dubé[3] Chari Cohen[1], [1]Hepatitis B Foundation, [2]Johns Hopkins School of Medicine, [3]Perelman School of Medicine, University of Pennsylvania

Background: Long-acting antiviral (LAA) therapies are emerging as potential promising future alternatives to daily oral treatment for chronic hepatitis B. However, patient perspectives on different LAA modalities remain poorly understood. This study aimed to explore perceptions, preferences, and acceptability of potential LAA treatment modalities among people living with hepatitis B (PLWHB) globally. **Methods:** This IRB-approved qualitative focus group study was conducted as part of a larger mixed-methods investigation among PLWHB. An initial focus group was conducted with six participants representing Africa, Asia, North America, and Europe. Discussions explored experiences with current hepatitis B treatment and perspectives on hypothetical LAA modalities, including injectables, microneedle patches, and implants. The focus group guide was aligned with survey questions to support

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thematic triangulation across qualitative and quantitative data. Data were analyzed thematically. **Results:** Participants described several challenges associated with current daily oral treatment, including the burden of medication access and approval processes, and fear of committing to a daily pill for life. Overall, participants expressed openness toward the concept of LAA therapies; however, acceptability differed across proposed modalities (injection vs microneedle patch vs implant). Although a long-acting pill was not among the proposed modalities, some participants identified oral treatment as their preferred option as it allowed them to maintain a sense of control over their treatment journey. Preferences were shaped by multiple considerations beyond modality alone, including perceived effectiveness, safety, convenience (ease of use, needing cold chain, non-invasive), duration, reversibility, and accessibility. Through discussions, participants highlighted the importance of clear communication and adequate information regarding potential benefits and risks to support treatment acceptability and informed decision-making. **Conclusion:** PLWHB expressed interest in LAA therapies as alternatives to daily oral treatment, although preferences varied across modalities. These initial findings underscore the importance of incorporating patient perspectives early in the development of future LAAs and highlight the need for transparent communication regarding treatment risks, benefits, and practical considerations.

Disclosures: Yasmin Ibrahim:Roche/ Genentech: Speaking and Teaching, Vir Biotechnology: Speaking Honorarium paid to the Hepatitis B Foundation, David Thomas:Merck: DSMB, Rho: DSMB, Excision Bio: Advisor, Karine Dubé:Gilead Sciences, Inc.: Consultant, Merck & Co., Inc.: Grant/Research Support, Chari Cohen:Vio Biotechnology: grant funds renumerated to Hepatitis B Foundation, Dynavax Technologies: grant funds renumerated to Hepatitis B Foundation, Gilead Sciences: grant funds renumerated to Hepatitis B Foundation, GSK: grant funds renumerated to Hepatitis B Foundation, Roche: grant funds renumerated to Hepatitis B Foundation, Gilead Sciences: funds renumerated to Hepatitis B Foundation, GSK: funds renumerated to Hepatitis B Foundation.

4167 | EARLY ON-TREATMENT HBSAG DECLINE PREDICTS FUNCTIONAL CURE IN CHB PATIENTS RECEIVING PEG-IFN-BASED THERAPY

Zixuan Gao[1] Minghui Li[1], [1]Capital Medical University Affiliated Beijing Ditan Hospital

Background: Functional cure remains an important therapeutic goal in chronic hepatitis B (CHB). Early on-treatment biomarkers predicting hepatitis B surface antigen (HBsAg) loss during pegylated interferon (PEG-IFN)-based therapy remain incompletely defined. **Methods:** We retrospectively analyzed 328 CHB patients receiving PEG-IFN-based therapy in a real-world cohort. Functional cure was defined as sustained HBsAg loss confirmed on two separate occasions at least 6 months apart. Baseline and on-treatment HBsAg levels were collected at weeks 12, 24, and 48. Early HBsAg decline was calculated as the reduction in log10 HBsAg relative to baseline. Cox regression, ROC analysis, and Kaplan–Meier analyses were performed to evaluate predictors of functional cure. **Results:** Forty-one patients (12.5%) achieved functional cure. Patients achieving functional cure had significantly lower baseline HBsAg levels compared with non-responders (0.87 vs. 2.98 log10 IU/mL, $P < 0.001$). Multivariable Cox analysis demonstrated that lower baseline HBsAg (HR 0.217, 95% CI 0.147–0.321, $P < 0.001$), greater week 24 HBsAg decline (HR 1.481, 95% CI 1.046–2.098, $P = 0.027$), and greater week 48 HBsAg decline (HR 2.917, 95% CI 1.941–4.385, $P < 0.001$) were independently associated with functional cure. ROC analysis showed that week 24 HBsAg decline predicted functional cure with an AUC of 0.780 and an optimal cutoff value of 0.65 log10 IU/mL. Week 48 HBsAg decline demonstrated an AUC of 0.817 with an optimal cutoff value of 0.33 log10 IU/mL. Kaplan–Meier analysis demonstrated significantly lower functional cure-free probability among patients with rapid early HBsAg decline (log-rank $P < 0.001$). **Conclusion:** Early on-treatment HBsAg decline is strongly associated with long-term functional cure in CHB patients receiving PEG-IFN-based therapy. Dynamic monitoring of HBsAg kinetics may help identify patients most likely to achieve functional cure.

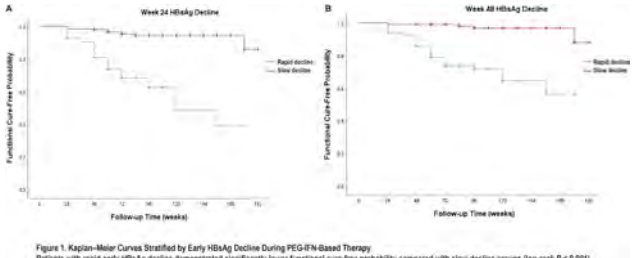


Figure 1. Kaplan–Meier Curves Stratified by Early HBsAg Decline During PEG-IFN-Based Therapy
Patients with rapid early HBsAg decline demonstrated significantly lower functional cure-free probability compared with slow decline groups (log-rank $P < 0.001$).

Disclosures: Zixuan Gao:Nothing to Disclose, Minghui Li:Nothing to Disclose.

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4168 | IN VITRO AND IN VIVO POTENCY, PHARMACOKINETIC PROFILE IN MICE AND MONKEYS, AND COMPREHENSIVE GLP SAFETY EVALUATION OF ACT201 (ALG-170675), A NOVEL ASO FOR CHRONIC HEPATITIS B

Yuejin Yu[1] Jingyi Xu[1] Jimmy Lu[1] Jinjia Zhang[1] Zhiyu Luo[1] Yatin Zhuo[1] Xiaorong Chen[1] Yanlan Lin[1] Guangqiang Pei[1] Yuejun Li[1] Yuanyuan Chen[1] Dinah Misner[2] Kusum Gupta[2] Vivek K. Rajwanshi[2] Hyunsoon Kang[2] Jin Hong[2] Li Huang[1] Li Sun[1] Yalin Yin[1] Huihuang Lin[1] Xuejing Li[1], [1]Amoytop Biotech Co., No. 330 Wengjiao Road, Haicang, Xiamen, Fujian, P.R. China, [2]Aligos Therapeutics, Inc., 1 Corporate Drive, South San Francisco, CA 94080, USA

Background: HBsAg loss is central to the functional cure of chronic hepatitis B (CHB). Antisense oligonucleotides (ASOs) represent a highly promising class of investigational therapies for CHB, with the potential to advance the achievement of functional cure. Based on sequence design and screening, ACT201 (ALG-170675) is a next-generation hepatitis B virus (HBV) ASO in late stage pre-clinical development. We have validated the drug's antiviral activity and fully characterized its pharmacokinetic and comprehensive GLP safety profile in mice and monkeys. **Methods:** Analysis of in vitro antiviral activity in HepG2.2.15 was conducted by Aligos Therapeutics. Antiviral potency assay in HepG2 cells transfected with HBV genotype A-J plasmids was conducted by WuXi AppTec. PK, tissue distribution and toxicity/TK evaluations in mice and monkeys were conducted at WuXi AppTec and Joinn Laboratories. **Results:** In HepG2.2.15 cells, ACT201 strongly inhibited HBsAg release with a mean EC_{50} of 10.33 nM. ACT201 also demonstrated significant release of HBsAg inhibition without cytotoxicity in HepG2 cells transfected with HBV A-J plasmids.In the AAV-HBV mouse model, ACT201 showed a better therapeutic index than GSK-836 (bepirovirsen). ACT201 showed higher levels of HBsAg and HBeAg reduction than GSK-836 at corresponding 40, 20, and 10 mg/kg dose levels, with as high as 0.66 $\log_{10}$ IU/mL additional mean HBsAg reduction on Day 28. Furthermore, ACT201 did not show a positive ALT signal during the treatment period, while the GSK-836 40 mg/kg group showed a positive ALT signal on Day 21 and 28, indicating a superior safety profile for ACT201. Following a single subcutaneous injection in mice (10, 20, 40 mg/kg) and monkeys (2, 4, 8 mg/kg), the plasma exposure increased in a dose-dependent manner. In monkeys, the systemic exposure levels in the liver increased with increasing dose, with the rate of increase closely matching the theoretical dose ratio, and liver exposure levels were significantly higher than those in plasma.In a 4-week study administering ACT201 via subcutaneous injection to mice and monkeys at a maximum dose of 50 mg/kg, all animals tolerated the treatment well, and NOAELs were determined to be 50 mg/kg in both species. The primary effects observed were typical ASO-related effects, such as macrophage vacuolization and/or basophilic granules; following an 8-week recovery period, these histopathologic changes were either completely resolved or showed a trend toward resolution. ACT201 exhibited no abnormal effects in safety pharmacology, genotoxicity, hemolysis and sensitization tests, and irritation was reversible, demonstrating its favorable safety profile. **Conclusion:** ACT201 has potent antiviral activity, favorable liver-targeted PK and a robust safety profile. Its balanced efficacy and safety profile in vivo suggests a potential best-in-class potential for CHB therapy. Clinical development is anticipated to begin in late 2026.

Disclosures: Yuejin Yu:Nothing to Disclose, Jingyi Xu:Nothing to Disclose, Jimmy Lu:Nothing to Disclose, Jinjia Zhang:Nothing to Disclose, Zhiyu Luo:Nothing to Disclose, Yatin Zhuo:Nothing to Disclose, Xiaorong Chen:Nothing to Disclose, Yanlan Lin:Nothing to Disclose, Guangqiang Pei:Nothing to Disclose, Yuejun Li:Nothing to Disclose, Yuanyuan Chen:Nothing to Disclose, Dinah Misner:Nothing to Disclose, Kusum Gupta:Nothing to Disclose, Vivek K. Rajwanshi:Nothing to Disclose, Hyunsoon Kang:Nothing to Disclose, Jin Hong:Nothing to Disclose, Li Huang:Nothing to Disclose, Li Sun:Nothing to Disclose, Yalin Yin:Nothing to Disclose, Huihuang Lin:Nothing to Disclose, Xuejing Li:Nothing to Disclose.

4169 | ◆ EXPANSION OF IGG$^+$ CLASSICAL MEMORY B CELLS CONSTITUTES THE CELLULAR BASIS FOR ANTI-HBC MAINTENANCE IN PATIENTS WITH CHRONIC HEPATITIS B

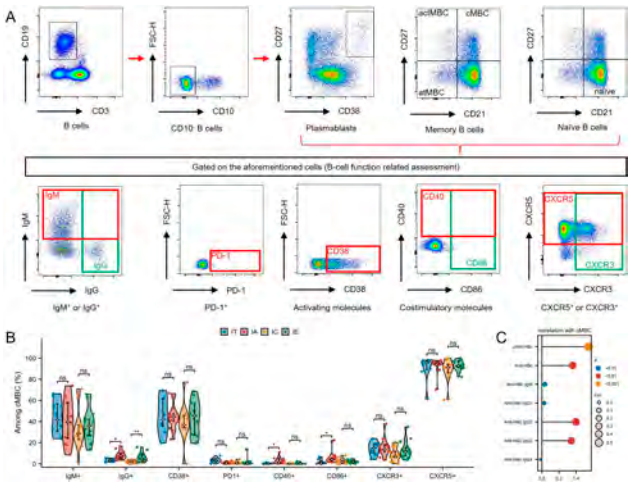
Yanjie Lin[1] Chi Zhang[1] Hong Zhao[1] Juan Du[2] Yao Xie[2] Minghui Li[2] Guiqiang Wang[1], [1]Peking University First Hospital, [2]Beijing Ditan Hospital, Capital Medical University

Background: Chronic hepatitis B virus (HBV) infection affects more than 254 million people worldwide, and accurate assessment of hepatic inflammatory activity is critical for disease management. Quantitative hepatitis B core antibody (qAnti-HBc) has been shown to correlate closely with histological liver inflammation and may serve as a potential non-invasive inflammatory biomarker. However, the cellular immunological basis underlying its dynamic changes remains unclear, particularly the identity of the B cell subset responsible

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for anti-HBc production and maintenance. **Methods:** 48 patients with untreated chronic HBV infection stratified by natural history phase and 10 healthy controls were prospectively enrolled. Peripheral blood mononuclear cells (PBMCs) were isolated, and multiparameter flow cytometry was used to systematically analyze B cell subset across disease phases. qAnti-HBc levels were quantified and correlated with immunological findings. **Results:** In patients at the immune clearance and immune reactivation phase, the proportion of circulating IgG^+ classical memory B cells (cMBCs) was significantly higher than that in the immune-tolerant and immune control phases, accompanied by upregulation of CD40 and CD86 and downregulation of PD-1. Among all B cell subsets examined, IgG^+ cMBCs showed the strongest positive correlation with qAnti-HBc ($r = 0.548$, $P < 0.001$). **Conclusion:** The expansion of IgG^+ cMBCs closely parallels hepatic inflammatory activity and qAnti-HBc levels, suggesting that IgG^+ cMBC expansion represents the core cellular basis for Anti-HBc production and long-term maintenance in CHB patients, providing direct cellular immunological support for the clinical utility of qAnti-HBc.



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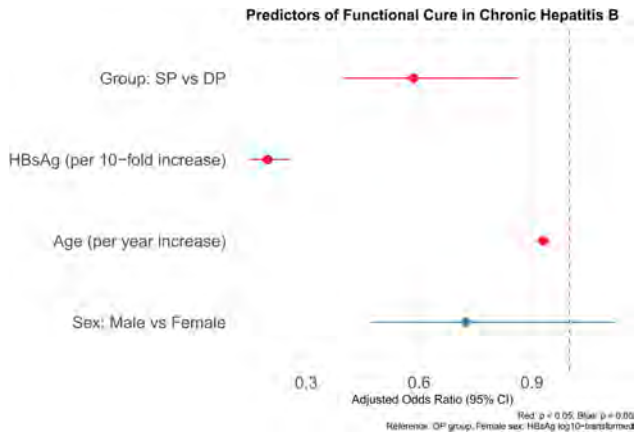
4170 | ◆ THE COEXISTENCE OF HBSAG AND ANTI-HBS FACILITATES FUNCTIONAL CURE OF CHRONIC HEPATITIS B WITH INTERFERON TREATMENT

Huiying Yu[1] Zhiliang Gao[1], [1]The Third Affiliated Hospital of Sun Yat-sen University

Background: The coexistence of HBsAg and anti-HBs (HBsAg+/Anti-HBs+) represents a unique serological profile associated with distinct immune states, hepatic inflammation, and fibrosis. This study aimed to investigate the impact of serum HBsAg+/anti-HBs+ profile on functional cure outcomes in chronic hepatitis B (CHB) patients treated with pegylated interferon alpha (pegIFN-alpha). **Methods:** We retrospectively analyzed clinical data from 945 CHB patients enrolled in the “Everest Project”, a clincial project for functional cure of CHB patients. These patients whose HBsAg < 1500 IU/mL, HBV DNA < 100 IU/mL, HBeAg were negative at baseline, were treated with pegIFN-alpha with or without nucleos(t)ide analogues for at least 48 weeks.The prevalence of baseline HBsAg+/anti-HBs+ status, clinical cure rates following pegIFN-alpha therapy, and post-cure HBsAg reversion rates were evaluated. **Results:** Among 945 patients, 52 (5.5%) exhibited baseline HBsAg+/anti-HBs+ , and 112 developed this double positive pattern during pegIFN-alpha therapy. Double positive patients showed a significantly higher functional cure rate than single positive (HBsAg+/anti-HBs-) patients (51.83% vs 36.88%, OR: 1.842, 95% CI: 1.305–2.567, p = 0.0004), but also a higher risk of HBsAg reversion after cure (29.41% vs 14.93%, OR: 2.374, 95% CI: 1.334–4.207, p = 0.0038). Multivariate logistic regression identified HBsAg+/anti-HBs+ status, lower baseline HBsAg levels, and younger age as independent predictors of functional cure. What’s more, Double positive status and lower peak anti-HBs titers after HBsAg loss independently predicted HBsAg reversion. Notably, cured single positive patients more frequently achieved anti-HBs titers > 100 U/L, and especially > 1000 U/L, compared to double positive patients. In both groups, cured patients exhibited greater aminotransferase elevations at week 12 of therapy than uncured patients. In the cured group, the elevation of aminotransferase in the double positive subgroup showed a trend of being greater than that in the single positive subgroup. Survival curve analysis showed, single positive cured patients achieved functional cure fastest and had the lowest reversion risk, whereas the median time to cure was longest in the group double positive after interferon therapy and the risk of HBsAg reversion was highest in the group double positive before interferon therapy. **Conclusion:** HBsAg +/anti-HBs+ CHB patients exhibit higher functional cure rates but also greater HBsAg reversion risks following pegIFN-alpha therapy, with double positive status serving as an independent predictor for both outcomes.

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Disclosures: Huiying Yu:Nothing to Disclose, Zhiliang Gao:Nothing to Disclose.

4171 | ◆ PD-1 EXPRESSION STRATIFIES TERMINAL/ EXHAUSTION-ASSOCIATED AND INFLAMMATORY ATYPICAL MEMORY B-CELL STATES IN CHRONIC HEPATITIS B

Thi Kim Duyen Nguyen[1] Yen-Chun Liu[2] Hsiang-Wei Huang[3] Chia-Wei Lin[3] Jian He Fan[3] Wei-Ting Ku[3] Rachel Wen-Juei Jeng[3] Chun-Yen Lin[3], [1]Chang Gung University, [2]Chang Gung Memorial Hospital, Linkou main branch, [3]Chang Gung Memorial Hospital, Linkou Medical Center

Background: Atypical memory B cells (atMBCs) are expanded in chronic hepatitis B (CHB) and are generally regarded as a dysfunctional or exhausted B-cell population. However, whether atMBCs represent a homogeneous dysfunctional population or contain divergent immunopathological states remains unclear. We examined whether PD-1 expression stratifies atMBC subsets linked to hepatic inflammation, bystander CD8 T-cell activation, and immunoregulatory crosstalk. **Methods:** scRNA-seq/CITE-seq was performed on peripheral B cells from 17 HBeAg-negative CHB patients. Unsupervised clustering, pseudotime trajectory analysis, and pathway enrichment characterized atMBC states. Flow cytometry quantified PD-1 $^{+}$/PD-1 $^{-}$ atMBCs, PD-1^{+} Tregs, and CD38^{+}HLA-DR^{+} CD8 T cells (bystander-activated, hepatotoxic-like) in validation cohorts. Intracellular cytokine staining evaluated IL-6, TNF-α, and IL-10 production by PD-1-defined atMBC subsets. Correlations were assessed using Spearman rank analysis, with $p < 0.05$ considered significant. **Results:** Unsupervised analysis resolved two transcriptionally distinct atMBC subsets. One occupied a terminal differentiation state with high PD-1 at RNA and protein levels, elevated FCRL5 and T-bet (TBX21), and suppressed BCR signaling (NES = -1.89, $p = 0.001$), consistent with an exhaustion-associated phenotype. Flow cytometry showed that PD-1^{+} atMBC frequency correlated positively with ALT ($r = 0.509$, $p = 0.003$) and CD38^{+}HLA-DR^{+} CD8 T-cell expansion ($r = 0.605$, $p = 0.003$; $n = 22$), while the frequency of PD-1^{-} atMBCs among B cells showed no correlation with ALT levels. Total atMBC frequency showed no ALT association, revealing clinically relevant heterogeneity not captured by total atMBC abundance. Functionally, PD-1^{+} atMBCs produced significantly less IL-6 and TNF-α than PD-1^{-} atMBCs ($n = 19$, $p < 0.001$), while IL-10 production remained comparable across PD-1^{+} atMBCs, PD-1^{-} atMBCs, and cMBCs. Notably, IL-10^{+}/PD-1^{+} atMBCs correlated with PD-1^{+} Tregs ($r = 0.575$, $p = 0.025$), whereas IL-6^{+} and TNF-α^{+}/PD-1^{-} atMBCs correlated with CD38^{+}HLA-DR^{+} CD8 T cells ($r = 0.702$, $p = 0.0035$ and $r = 0.529$, $p = 0.0428$ respectively) and showed a trend toward correlation with ALT levels ($r = 0.524$, $p = 0.054$ and $r = 0.538$, $p = 0.047$ respectively), identifying the PD-1^{-} compartment as the active source of B-cell-derived inflammatory cytokines associated with hepatic inflammation. **Conclusion:** PD-1 stratifies atMBCs into two functionally opposing states in CHB: PD-1^{-} atMBCs harbor cytokine-producing effectors linked to hepatic inflammation, while PD-1^{+} atMBCs represent a terminal/exhaustion-associated state that possibly reflects a shared cytokine niche, co-expanding with PD-1^{+} Tregs and bystander-activated CD8^{+} T cells. PD-1 thus acts not as a simple exhaustion marker but as a stratifying axis distinguishing active B-cell inflammatory effectors from passive niche-coupled exhaustion in CHB.

Disclosures: Thi Kim Duyen Nguyen:Nothing to Disclose, Yen-Chun Liu:Nothing to Disclose, Hsiang-Wei Huang:Nothing to Disclose, Chia-Wei Lin:Nothing to Disclose, Jian He Fan:Nothing to Disclose, Wei-Ting Ku:Nothing to Disclose, Rachel Wen-Juei Jeng: GSK: Advisor, Gilead: Advisor, BMS: Speaking and Teaching, Roche: Advisor, Chun-Yen Lin:Nothing to Disclose.

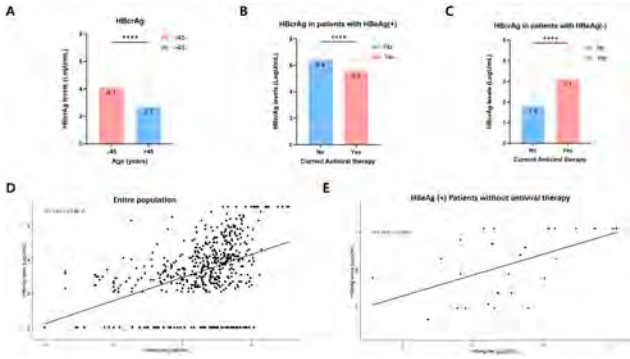
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4172 | ◆ HBV CORE-RELATED ANTIGEN LEVELS CORRELATE WITH QUANTITATIVE HBSAG LEVELS REGARDLESS OF HBEAG STATUS AND ANTIVIRAL THERAPY

Hee Sun Cho[1] Soon Kyu Lee[1] Soon Woo Nam[1] Jung Hyun Kwon[1], [1]The Catholic University of Korea

Background: Hepatitis B core-related antigen (HBcrAg), which reflects the combined levels of HBcAg, HBeAg, and the p22 core-related protein, has been shown to correlate strongly with serum HBV DNA and intrahepatic covalently closed circular DNA (cccDNA) levels. In this study, we aimed to evaluate HBcrAg levels according to several clinical factors and to assess the correlation between HBcrAg and quantitative HBsAg levels. **Methods:** We prospectively enrolled 876 consecutive patients with chronic HBV infection who underwent HBcrAg testing between March 2025 and February 2026. HBcrAg levels were compared according to age, HBeAg status, and antiviral therapy. In addition, correlation analyses were performed to evaluate the relationship between HBcrAg and quantitative HBsAg levels across HBeAg status and antiviral therapy. **Results:** The median age of the study population was 57.9 years, and 56.7% (n = 497) were male. Approximately half of the patients (n = 433, 49.4%) were receiving antiviral therapy. The mean HBcrAg level was 2.9 LogU/mL and was significantly higher in younger patients (< 45 years) than in older patients (4.1 vs. 2.7 LogU/mL; p < 0.0001; Figure A) and in HBeAg-positive patients compared with HBeAg-negative patients (5.9 vs. 2.4 LogU/mL; p < 0.0001). Among HBeAg-positive patients, HBcrAg levels were significantly higher in those not receiving antiviral therapy (p < 0.0001; Figure B). In contrast, among HBeAg-negative patients, HBcrAg levels were significantly lower in those receiving antiviral therapy (p < 0.0001; Figure C). HBcrAg levels showed a significant positive correlation with quantitative HBsAg levels (R = 0.44, p < 0.0001; Figure D). This correlation was consistently observed across HBeAg status and antiviral therapy, with the strongest correlation found in HBeAg-positive patients not receiving antiviral therapy (R = 0.53, p = 0.0053; Figure E). HBcrAg levels were also positively correlated with HBV DNA levels in both HBeAg-positive and HBeAg-negative patients (p < 0.05). Notably, among 67 patients who achieved HBsAg loss, approximately 25% (17/67) still had detectable HBcrAg levels. **Conclusion:** Our findings suggest that HBcrAg levels were lower in older patients and in those with negative HBeAg status. HBcrAg levels were significantly correlated with quantitative HBsAg levels regardless of HBeAg status or antiviral therapy, suggesting that HBcrAg may serve as a useful surrogate marker of viral activity across different clinical settings.



Disclosures: Hee Sun Cho:Nothing to Disclose, Soon Kyu Lee:Nothing to Disclose, SOON WOO NAM: Nothing to Disclose, Jung Hyun Kwon:Nothing to Disclose.

4173 | INTEGRATED MODEL WITH BASELINE T-CELL AND DNT CELL PROPORTIONS ACCURATELY IDENTIFIES CANDIDATES FOR PEG-IFNα-2B-INDUCED HBSAG SEROCLEARANCE

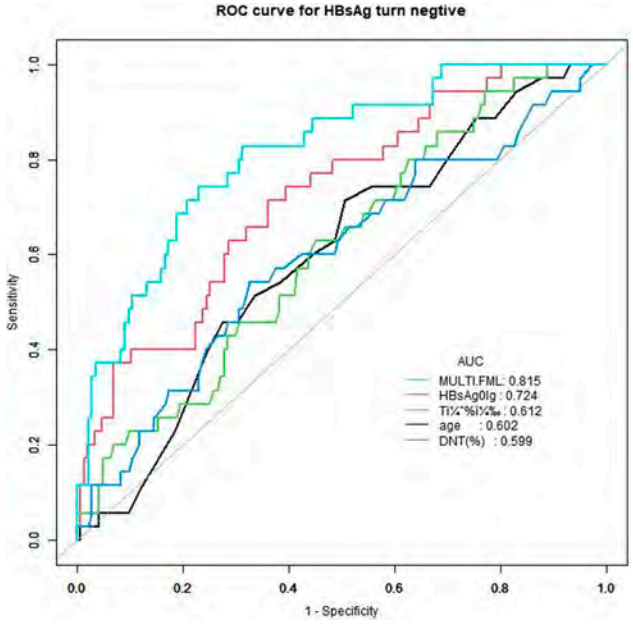
Jing Chen[1] Qin Du[1] Peng Wang[1] Jianyin Wang[1] Yanchao Fu[1] Huiling Xiang[1], [1]Central Hospital, Tianjin University; Tianjin Institute of Hepatobiliary Disease, Tianjin, China

Background: Clinical cure of chronic hepatitis B (CHB) is defined as hepatitis B surface antigen (HBsAg) seroclearance. Interferon (IFN) efficacy is highly dependent on host immune status. However, most existing prediction models rely on conventional virological parameters and lack direct, quantifiable baseline immunological markers, limiting accurate identification of patients most likely to benefit from IFN therapy. This study aimed to evaluate the predictive value of baseline T-cell proportion and double-negative T (DNT) cell proportion for pegylated interferon-α-2b (peg-IFNα-2b)-induced HBsAg seroclearance and to develop an optimized predictive model integrating clinical and immunological parameters. **Methods:** A total of 182 patients with CHB or compensated cirrhosis receiving initial peg-IFNα-2b therapy were retrospectively enrolled. Least Absolute Shrinkage and Selection Operator (LASSO) regression was used for variable selection, and Cox regression was applied to identify independent predictors, with a focus on baseline T-cell and DNT cell proportions. A predictive model was constructed and internally validated via bootstrap resampling. Model performance was assessed using receiver operating

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characteristic (ROC) curves, calibration curves, and decision curve analysis. A risk-stratification system was established based on model scores, and HBsAg seroclearance rates were compared across strata. **Results:** The overall HBsAg seroclearance rate was 19.23% (35/182). Multivariate Cox regression identified baseline T-cell proportion (HR = 1.087, P = 0.00724) and DNT cell proportion (HR = 1.060, P = 0.03519) as independent protective factors for HBsAg seroclearance, while age and baseline HBsAg level were independent risk factors. The integrated model demonstrated good calibration and stability, with an AUC of 0.838 in the training set and 0.760 in the validation set, significantly outperforming models based solely on conventional clinical or virological parameters. Three-tier risk stratification revealed that the immune-favorable group (high T-cell and DNT cell proportions) achieved a 48-week HBsAg seroclearance rate of 46.34%, substantially higher than the intermediate (19.67%) and poor-prognosis (5.20%) groups (P < 0.0001). **Conclusion:** Baseline T-cell and DNT cell proportions are key, independent immunological markers for predicting peg-IFNα-2b-induced HBsAg seroclearance, significantly improving the predictive performance of conventional clinical/virological indicators. This integrated model accurately identifies optimal candidates for IFN therapy and provides a critical basis for individualized immunotherapy in CHB.



Disclosures: Jing Chen:Nothing to Disclose, qin du: Nothing to Disclose, Peng Wang:Nothing to Disclose, Jianyin Wang:Nothing to Disclose, Yanchao Fu:Nothing to Disclose, Huiling Xiang:Nothing to Disclose.

4174 | SINGLE-CELL TRANSCRIPTOMIC ANALYSIS REVEALS DYNAMIC HBV EXPRESSION STATES IN HBV-ASSOCIATED HEPATOCELLULAR CARCINOM

Zhi Chen Yan[1] PeiChing Chang[1] Chun-Ying Wu[2], [1]National Yang Ming Chiao Tung University, [2]National Yang MIng Chiao Tung University, Taiwan

Background: Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death, with 55%-80% of cases arising in the context of chronic hepatitis B virus (HBV) infection. Although HBV vaccination programs have reduced new infections, chronic HBV remains affecting approximately 350 million people worldwide. Single-cell analysis has been widely applied to investigate the TME of HCC, with primary focus on elucidating the immune landscape. Interaction analyses have also primarily highlighted immune-immune crosstalk; however, the single-cell characteristics of HBV-infected HCC cell interactions have yet to be elucidated. **Methods:** Using single-cell RNA sequencing, we identified HBV-infected HCC cells at single-cell resolution and stratified tumor cell populations according to HBV transcript abundance. Trajectory analysis combined with inferCNV revealed a progressive evolutionary pattern originating from tumor cells with intermediate HBV transcript levels (HCC-c4), advancing toward high HBV transcript expression (HCC-c1 and HCC-c2), followed by bifurcation into distinct branches that either maintained intermediate viral transcript levels (HCC-c3 and HCC-c5) or potentially underwent viral transcript silencing (HCC-c6). **Results:** Gene ontology analysis identified eight major functional categories enriched among HCC subpopulations. Notably, HCC-c4, defined as the trajectory origin population, exhibited activation of proliferation, survival, cellular movement, and cancer-associated pathways. As HBV transcript levels increased, HCC-c2 became predominantly associated with cellular movement-related pathways, whereas HCC-c1 demonstrated enrichment of apoptosis-related pathways and cellular responses to therapeutics. These findings suggest that progressive HBV activation may initially enhance tumor aggressiveness and migratory potential, followed by induction of stress-response and apoptotic programs. Then, the trajectory diverges into two distinct branches. One branch, enriched for intermediate HBV transcript levels, included HCC-c3 and HCC-c5, which displayed functional profiles similar to HCC-c1. The second branch contained HCC-c6, a rare subpopulation with minimal HBV transcript expression. **Conclusion:** Collectively, these findings indicate the emergence of heterogeneous tumor evolutionary states originating from intermediate and progressing toward peak HBV

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transcription, followed by bifurcation into distinct cellular fates. One branch maintained HBV transcription, whereas the other exhibited loss of HBV transcription. **Disclosures:** ZHI CHEN YAN:Nothing to Disclose, PeiChing Chang:Nothing to Disclose, Chun-Ying Wu: Nothing to Disclose.

4175 | HBX EXPLOITS GLUCOSE TO PROMOTE HEPATOCELLULAR CARCINOMA DEVELOPMENT VIA ITS PHOSPHORYLATION AND ENHANCEMENT OF THE TCA CYCLE

Xiaoyun Huang[1] Ying Lin[1] Fenglin Chen[1], [1]Fujian Medical University Union Hospital

Background: Type 2 diabetes and chronic hepatitis B virus (HBV) infection are both established drivers of hepatocellular carcinoma (HCC), yet the interplay between hyperglycemia and HBV oncogenic activity remains poorly defined. The HBV X protein (HBx) is a classic oncoprotein capable of simultaneously reprogramming multiple signaling pathways and elevates blood glucose as well, but whether—and how—hyperglycemia modulates HBx function is largely unknown. We aimed to investigate how glucose availability influences HBx function. **Methods:** As HBx is low in patient tissue, human hepatoma lines stably expressing low or high HBx (plus vector controls) were generated by lentiviral infection to exclude overexpression artifacts. $^{13}C_6$-glucose was used to trace flux through TCA cycle intermediates (measured by GC-MS) in cells cultured in high glucose (30 mM). Proteomic profiling was performed on hepatoma cells expressing no, low, or high HBx under high-glucose conditions. Murine hepatoma cells stably expressing luciferase with no, low, or high HBx were injected via tail vein into db/db mice, and tumor dissemination was tracked by in vivo bioluminescence imaging. Single-cell transcriptomics was performed on three regions of one diabetic-HBV HCC tumor. Finally, HBx phosphorylation was assessed by immunoprecipitation in cells cultured in 5.5 mM versus 30 mM glucose. **Results:** Under high glucose, HBx significantly increased labeled TCA cycle intermediates (citrate, α-ketoglutarate, succinate, fumarate, malate) at both low and high expression levels ($P < 0.05$). Proteomic analysis showed differentially expressed proteins enriched in carbohydrate, oxoacid, and nucleobase-containing small-molecule metabolism; KEGG analysis implicated metabolic pathways (purine metabolism, pentose phosphate pathway, cysteine/methionine metabolism) and tumor-associated pathways (HIF-1, TNF, cell adhesion/cytoskeletal regulation). In db/db mice, HBx-expressing hepatoma cells produced more tumor foci and higher bioluminescence than vector controls ($n = 5$, $P < 0.05$). Single-cell profiling of the diabetic-HBV HCC tumor (~29,700 cells) resolved malignant hepatocytes into region-biased subpopulations co-expressing a pro-invasive program (SPP1, FN1, CD24, AKR1B10), consistent with the proteomic pathways and the metastatic phenotype in vivo. HBx phosphorylation was ~35% higher in 30 mM than 5.5 mM glucose. **Conclusion:** Concurrent diabetes and HBx enhance hepatoma cell metastasis. HBx exploits excess glucose to fuel the TCA cycle and reprogram metabolic and migration-associated pathways. Elevated HBx phosphorylation may underlie this glucose-adaptive behavior. These findings reveal how HBx leverages glucose to potentiate HCC metastatic potential, offering new insight into glucose-regulated oncoprotein biology.
Disclosures: Xiaoyun Huang:Nothing to Disclose, Ying Lin:Nothing to Disclose, Fenglin Chen:Nothing to Disclose.

4176 | T CELL DEFICIENCY ENHANCES HUMORAL IMMUNITY BUT FAILS TO CONTROL HBV: EVIDENCE FOR DUAL PATHWAYS OF ANTI-HBC PRODUCTION

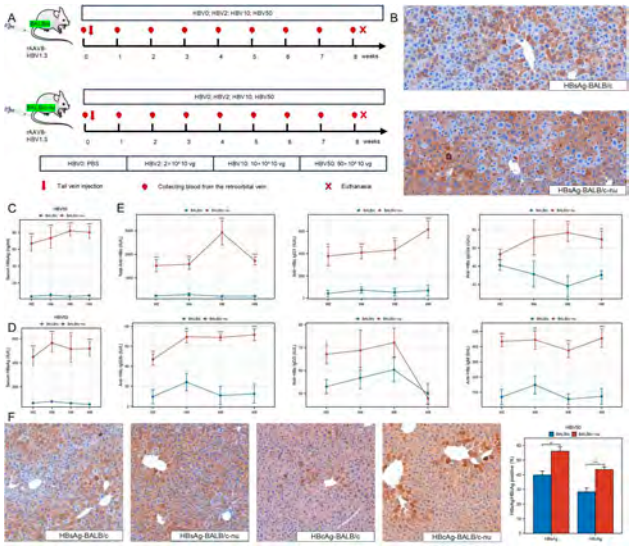
Yanjie Lin[1] Chi Zhang[1] Hong Zhao[1] Juan Du[2] Yao Xie[2] Guiqiang Wang[1] Minghui Li[2], [1]Peking University First Hospital, [2]Beijing Ditan Hospital, Capital Medical University

Background: Chronic hepatitis B virus (HBV) infection affects approximately 250 million people worldwide and is a major cause of cirrhosis and hepatocellular carcinoma. Accurate assessment of hepatic inflammatory activity is essential for disease staging and antiviral treatment decisions. Quantitative hepatitis B core antibody (qAnti-HBc) has been shown to correlate closely with liver inflammation and host immune activation, supporting its potential as a non-invasive biomarker. However, the cellular immunological mechanisms underlying anti-HBc production and maintenance remain unclear, particularly whether it depends on T cell involvement. **Methods:** AAV8-HBV1.3 infection model was established in wild-type BALB/c mice and T cell-deficient BALB/c-nu mice to induce persistent HBV antigen expression. Serum HBsAg, HBeAg, total anti-HBc, and its isotypes were dynamically measured. Hepatic HBsAg and HBcAg expression was assessed by immunohistochemistry, and liver transcriptomic sequencing was performed to analyze immune-related pathways. **Results:** Sustained HBV antigen expression was successfully established in both groups. HBV-BALB/c-nu mice exhibited significantly higher levels of HBsAg and HBeAg than HBV-BALB/c mice. Anti-HBc was detectable in both groups. However, HBV-BALB/c-nu mice showed delayed peak timing and markedly

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elevated levels, suggesting that anti-HBc production involves both T cell-dependent and T cell-independent pathways. Enhanced humoral immunity was observed in HBV-BALB/c-nu mice, characterized by increased IgM and multiple IgG subclasses. Transcriptomic analysis revealed upregulation of B cell-related genes (Cd19, Ms4a1, Cd79a/b) and enrichment of pathways related to humoral immunity, immunoglobulin-mediated responses, and complement activation, along with activation of macrophage and natural killer cell pathways. Despite this compensatory response, viral control remained ineffective, as hepatic HBsAg and HBcAg levels were significantly higher in HBV-BALB/c-nu mice. **Conclusion:** Anti-HBc can be generated through both T cell-dependent and T cell-independent pathways. T cell deficiency induces compensatory enhancement of humoral immunity centered on B cells but fails to achieve effective viral clearance, highlighting the critical role of T cells in HBV-specific immune regulation.



Disclosures: Yanjie Lin:Nothing to Disclose, Chi Zhang:Nothing to Disclose, Hong Zhao:Nothing to Disclose, Juan Du:Nothing to Disclose, Yao Xie: Nothing to Disclose, Guiqiang Wang:Nothing to Disclose, Minghui Li:Nothing to Disclose.

4177 | DUAL MODALITY MARKERS FOR PERIPHERAL BLOOD MONONUCLEAR CELL SUBTYPING IN CHRONIC HEPATITIS B VIRUS INFECTION

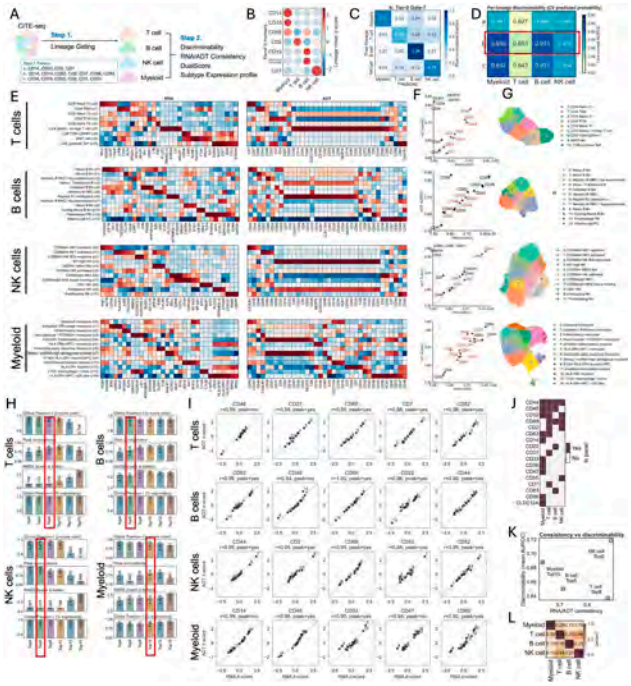
Fengge Zhu[1] Man-Fung Yuen[1] Lung Yi Mak[1], [1]The University of Hong Kong

Background: We aim to identify a set of markers for peripheral blood mononuclear cell (PBMC) subtyping that are applicable for both scRNA-seq and flow cytometry, based on a CITE-seq dataset of human PBMCs. **Methods:** We analyzed a CITE-seq dataset (GSE291286) containing 153 PBMC samples from 24 patients with chronic hepatitis B infection. A Weighted Nearest Neighbour (WNN) proxy method was applied by concatenating RNA and antibody derived tags (ADT) principal components and Leiden clustering on the joint kNN graph. Modality-specific discrimination for markers was quantified by the area under the receiver operating characteristic curve (AUROC) with *sklearn.metrics.roc_auc_score*. A custom dual-modality score (DualScore) was defined to rank markers according to their cross-modality performance. **Results:** Three lineage panels (Panel a, b and c, Figure 1A, B) were tested to assign cells to the 4 major compartments (myeloid, T, B, and NK) using stratified five-fold cross-validation of standardized multinomial logistic regression. Panel b (CD14, CD19, CD22, CD2, CD7, CD55, CD33) provided the strongest cross-validated lineage discrimination (one-vs-rest AUROC 0.853-0.935), with excellent recovery of B cells (row-normalized recall 0.95) and myeloid cells (0.81) (Figure 1C, D).For each purified lineage (Myeloid, T, B, NK) (Figure 1E, G), lineage-specific Top-N ADT panels were selected from DualScore-ranked, ADT-mapped shared RNA/ADT markers by evaluating candidate sizes (N = 4, 5, 8, 10, 12, 15) on within-lineage WNN clusters and choosing the list with the highest balanced score (Global Pearson r, Peak concordance, normalized RMSE (Root mean square error)) among candidates with Pearson r $\geq$ 0.75, yielding T cell Top8 (*CD48, CD27, CD69, CD7, CD52, CD2, CD63, CD44*), B cell Top5 (*CD83, CD48, CD69, CD22, CD44*), NK cell Top5 (*CD44, CD2, CD69, CD55, CD52*), and Myeloid Top10 (*CD14, CD48, CD33, CD47, CD86, CD36, CD44, CD63, CD52, CLEC12A*) (Figure 1F, H).We plotted cluster-level z-scored mean expression (RNA versus ADT) of the candidate markers for each lineage (Figure 1H, Top 5 highlighted in red). Most markers showed strong cross-modality alignment ($r > 0.90$), including CD48 ($r = 0.99$) and CD27 ($r = 0.98$) in T cells, CD83 ($r = 0.99$) and CD48 ($r = 0.94$) in B cells, CD44 ($r = 0.99$) and CD2 ($r = 0.99$) in NK cells, CD36 ($r = 1.00$) and CD14 ($r = 0.99$) in myeloid cells, supporting their use as a dual-modality marker set (Figure 1I).Across the 4 major lineages, Top-N marker panels share only CD44 universally, while most markers are lineage-restricted (Figure 1J). Top-N marker panel for NK cells showed the strongest combined performance (Figure 1K), lineage-specific marker composition and limited cross-lineage overlap (Jaccard < 0.44, Figure 1L). **Conclusion:** We curated a set of marker panels for PBMC subtyping suitable

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for both scRNA-seq and flow cytometry data. Experimental evidence is needed to further consolidate the findings.



Disclosures: Fengge Zhu:Nothing to Disclose, Man-Fung Yuen:AbbVie, Abbott Diagnotics, Aligos Therapeutics: Consultant, Arbutus Biopharma, Arrowhead Pharmaceuticals, Assembly Biosc: Consultant, Clear B Therapeutics, Dicerna Pharmaceuticals, Immuncore: Consultant, Fujirebio Incorporation, GSK, Gilead Sciences: Consultant, Immunocore, Janssen, Precision BioSciences: Consultant, Roche, Sysmex Corporation, Tune Therapeutics: Consultant, Vir Biotechnology and Visirna Therapeutics: Consultant, AbbVie, Assembly Biosciences, Arrowhead Pharmaceuticals, Aligos Therapeutics, Arbutus Biopharma: Grant/Research Support, Fujirebio Incorporation, Gilead Sciences, Immunocore, Clear B Therapeutics, GSK, Janssen: Grant/Research Support, Sysmex Corporation and Roche: Grant/Research Support, Fujirebio Incorporation, Gilead Sciences, Roche, Sysmex Corp, Aligos Therapeutics, Arbutus Biopharma: Speaking and Teaching, Precision BioSciences: consultancy, Ausperbio: consultancy, IntergerBio: consultancy, Tune Therapeutics: consultancy, Clear B Therapeutics, GSK, Immuncore, Janssen, Vir Biotechnology: Speaking and Teaching, Lung Yi Mak:Gilead Sciences: Grant/Research Support, Roche Diagnostics: Grant/Research Support, Gilead Sciences: Grant/Research Support, Roche Diagnostics: Grant/Research Support, Gilead Sciences: Advisor, Roche Diagnostics: Advisor, GSK: Speaker fee.

4178 | HEPATIC STEATOSIS ALONE IS INSUFFICIENT TO DRIVE HBSAG LOSS IN EXPERIMENTAL MODELS OF CHRONIC HEPATITIS B WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

Xupeng Hong[1] Yichen Zhou[2] Kaicheng U[1] Alireza Ramandi[2] Leon Seifert[1] Chenhui Zou[1] Corrine Quirk[1] Luis Chiriboga[3] Charles Rice[1] Ype De Jong[2],
[1]Laboratory of Virology and Infectious Disease, The Rockefeller University, New York, NY, USA., [2]Division of Gastroenterology and Hepatology, Weill Cornell Medicine, New York, NY, USA., [3]Department of Pathology, NYU Langone New York University Langone Medical Center, New York, NY, USA

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) and its progressive inflammatory form, metabolic dysfunction-associated steatohepatitis, are increasingly common chronic liver diseases. Clinical studies suggest that concurrent MASLD in patients with chronic hepatitis B virus (HBV) infection is associated with higher rates of HBsAg seroclearance, but the underlying mechanism remains unclear. Here, we used multiple experimental models of chronic HBV infection to investigate the bidirectional interactions between hepatic steatosis and HBV infection, assessing both the effects of steatosis on HBV antigen expression and viral replication and the impact of HBV infection on steatosis development. **Methods:** We performed a meta-analysis of patient studies to assess the relationship between chronic HBV infection and liver steatosis, as well as the association between hepatic steatosis and spontaneous HBsAg clearance. We then examined the effects of oleic acid and palmitic acid treatment, which induces lipid accumulation, in HBV-infected primary human hepatocytes in vitro. To model MASLD in vivo, we fed HBV-transgenic mice a western diet and fed HBV-infected human liver chimeric mice 10% high-fructose corn syrup. Finally, we used an adeno-associated virus (AAV)-HBV mouse model to further assess the effects of hepatic steatosis on HBV antigen expression. **Results:** Meta-analysis showed that HBV infection was negatively associated with liver steatosis (OR, 0.71; 95% CI, 0.67-0.75; I^2 = 0%), whereas hepatic

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steatosis was associated with spontaneous HBsAg clearance (OR, 1.40; 95% CI, 1.17-1.67; I^2 = 0%). In HBV-infected primary human hepatocytes, oleic acid and palmitic acid treatment induced lipid accumulation but did not reduce secreted HBV antigens, and decreased HBV antigen was observed only after the onset of cell death. In HBV-transgenic mice, western diet feeding induced hepatic steatosis, but serum HBsAg and HBeAg levels remained unchanged. Notably, HBV-transgenic mice gained body weight more slowly and developed less severe steatosis than wild-type littermates, suggesting that HBV may attenuate MASLD progression. Similarly, HBV-infected human liver chimeric mice fed 10% high-fructose corn syrup developed less hepatic steatosis than non-infected controls, while HBsAg and HBV DNA levels were not reduced compared with HBV-infected human liver chimeric mice on a normal diet. Finally, in the AAV-HBV mouse model, induction of hepatic steatosis alone did not alter serum HBsAg levels. **Conclusion:** Across complementary in vitro and in vivo models, our results suggest that hepatic steatosis does not directly reduce HBV antigen levels or viral replication. Instead, adaptive immune responses and hepatocyte injury may be required for HBsAg loss in the setting of MASLD/steatotic liver disease.

Disclosures: Xupeng Hong:Nothing to Disclose, Yichen Zhou:Nothing to Disclose, Kaicheng U:Nothing to Disclose, Alireza Ramandi:Nothing to Disclose, Leon Seifert:Nothing to Disclose, Chenhui Zou:Nothing to Disclose, Corrine Quirk:Nothing to Disclose, Luis Chiriboga:Nothing to Disclose, Charles Rice:Vir: Grant/Research Support, Vir: Advisor, Vir: Options, non-excersized will expire in August 2024, Invisishield: Advisor, Invisishield: Stock – privately held company, Apath LLC: Manager, GSK: Grant/Research Support, AstraZeneca: Advisor, Ype De Jong:Nothing to Disclose.

4179 | DOCK11 PROMOTES HBV CCCDNA FORMATION BY REGULATING PARP1 RECRUITMENT TO RCDNA

Hideo Takayama[1] Kouki Nio[1] Taro Yamashita[1],
[1]Kanazawa University

Background: Chronic hepatitis B virus (HBV) infection is a major cause of liver fibrosis and hepatocarcinogenesis. Current antiviral therapies cannot eliminate covalently closed circular DNA (cccDNA), a stable nuclear viral reservoir. We previously identified Dedicator of Cytokinesis 11 (DOCK11) as a host factor required for HBV replication. Poly (ADP-ribose) polymerase 1 (PARP1) has been reported to bind relaxed circular DNA (rcDNA) and facilitate cccDNA formation. However, the mechanisms governing PARP1 recruitment to rcDNA remain unclear. Here, we investigated the role of DOCK11 in cccDNA formation and its underlying mechanism. **Methods:** To assess the role of DOCK11 in cccDNA maintenance, we measured luciferase activity over time in hepatoma cell lines transfected with minicircle HBV cccDNA with a Gaussia Luciferase reporter (mcHBV-GLuc cccDNA). To evaluate its role in cccDNA formation, we established an in vitro assay in which rcDNA isolated from culture supernatants was incubated with nuclear extracts. DOCK11-associated HBV DNA-interacting proteins were identified by immunoprecipitation followed by LC-MS/MS. Protein interactions and localization were analyzed by immunoprecipitation and super-resolution microscopy. **Results:** DOCK11 depletion in Huh7 and HepG2 cells led to a marked, time-dependent reduction in luciferase activity after mcHBV-GLuc cccDNA transfection, indicating impaired cccDNA maintenance, with a potential contribution to cccDNA stability. In the in vitro assay, DOCK11 overexpression significantly enhanced cccDNA formation, whereas DOCK11 knockout markedly suppressed it. LC-MS/MS revealed PARP1 as a central component of the DOCK11–HBV DNA complex. DOCK11 and PARP1 co-localized in hepatoma cells and human liver tissue. Notably, DOCK11 did not affect PARP1 protein expression or enzymatic activity, but was essential for its recruitment to DNA damage sites and HBV DNA. This was demonstrated by UV-induced damage assays and PARP1 immunoprecipitation. Collectively, these findings indicate that DOCK11 facilitates cccDNA formation by promoting PARP1 recruitment to rcDNA. **Conclusion:** DOCK11 controls PARP1 recruitment to rcDNA without altering its expression or activity, thereby promoting HBV cccDNA formation and persistence. Targeting the DOCK11–PARP1 axis may represent a novel therapeutic strategy for eliminating HBV cccDNA.

Disclosures: Hideo Takayama:Nothing to Disclose, Kouki Nio:Nothing to Disclose, Taro Yamashita:Nothing to Disclose.

★ 4180 | A NOVEL MECHANISM OF INFLAMMATION-INDUCED HEPATOCARCINOGENESIS IN HBV INFECTION

Daichi Onomura[1] Yuki Nakaya[1] Kazumoto Murata[1],
[1]Jichi Medical University

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Background: Chronic hepatitis B virus (HBV) infection is a major risk factor for hepatocellular carcinoma (HCC), but its precise mechanisms remain incompletely understood. Yes-associated protein (YAP), a transcriptional coactivator of the Hippo pathway, plays important roles in liver regeneration and HCC. Therefore, we investigated whether HBV contributed to YAP-related hepatocarcinogenesis. **Methods:** HBV-mediated YAP activation was examined in HBV-infected HepG2-NTCP, Huh-7-NTCP cells, and primary hepatocytes from human chimeric mice by quantitative RT-PCR, Western blots, immunofluorescence staining, and a luciferase reporter system in which the YAP promoter region was inserted upstream of the luciferase gene. SK-HEP-1 cells, which express tumor necrosis factor (TNF) receptor-2, were treated with recombinant human TNF-alpha, and YAP activation was evaluated. Human CD14-positive monocyte-derived macrophages were exposed to purified HBV particles, and cytokine production was examined at the mRNA and protein levels. SK-HEP-1 cells were treated with the culture supernatants from HBV-exposed macrophages, and YAP reporter activity was measured with or without neutralizing antibodies against several cytokines. **Results:** In contrast to previous reports suggesting a direct link between HBV and YAP activation, HBV infection did not induce apparent YAP activation in HepG2-NTCP cells or primary human hepatocytes. Meanwhile, we found that recombinant TNF-alpha induced YAP dephosphorylation, nuclear translocation, and upregulation of YAP target genes in SK-HEP-1 cells and primary human hepatocytes. High copy numbers of HBV induced human macrophages to produce TNF-alpha in a time- and HBV dose-dependent manner. Furthermore, the culture supernatants from HBV-exposed macrophages activated YAP in SK-HEP-1 cells. HBV induced several other inflammatory cytokines, such as interleukin (IL)-1beta, IL-6, and IL-12, from macrophages, but only neutralization of TNF-alpha abolished YAP activation, whereas neutralization of other cytokines had no effect. Cell proliferation, cell cycle-related proteins, and proliferation-related signaling in SKHEP-1 cells were inhibited by YAP knockdown and enhanced by recombinant TNF-alpha. **Conclusion:** HBV does not directly activate YAP in hepatocytes, but indirectly activates YAP through macrophage-derived TNF-alpha, which subsequently promotes tumor-associated signaling in HCC cells. These findings identify a macrophage–TNF-alpha–YAP axis as a novel indirect mechanism of HBV-related hepatocarcinogenesis, which partially explains why HBV-related HCC occurs even in a non-cirrhotic liver.

Disclosures: Daichi Onomura:Nothing to Disclose, Yuki Nakaya:Nothing to Disclose, Kazumoto Murata: Nothing to Disclose.

4181 | PROTEOMIC IDENTIFICATION OF THE COP9 SIGNALOSOME AS A DRUGGABLE REGULATOR OF HBV CCCDNA TRANSCRIPTION THROUGH HBX DEGRADATION

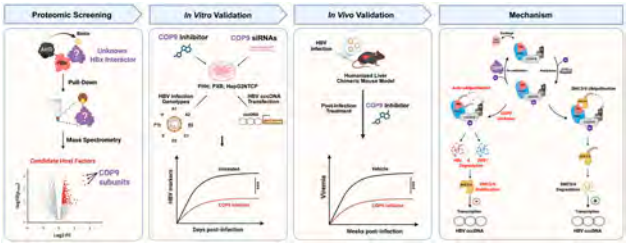
Karim Mouzannar[1] Anne Schauer[1] Susannah Stephenson-Tsoris[1] Zhensheng Zhang[1] Min Zhang[1] Seung Bum Park[1] D. Eric Anderson[1] T. Jake Liang[1], [1]Liver Diseases Branch, NIDDK, NIH, Bethesda, Maryland, USA

Background: Hepatitis B virus X protein (HBx) is essential for viral replication by activating cccDNA transcription and antagonizing host restriction factors. Its most well-established mechanism is the degradation of the SMC5/6 complex via the DDB1–Cullin 4 (CRL4) E3 ubiquitin ligase. However, additional HBx-host interactions likely exist and remain poorly defined, limiting our understanding of cccDNA regulation and development of HBx-targeted antiviral strategies. **Methods:** We performed AirID-based proximity labeling coupled with mass spectrometry to identify novel HBx-interacting proteins in live cells. AirID enables high-specificity detection of transient and weak protein interactions, outperforming co-immunoprecipitation and conventional biotinylation approaches. COP9 function was disrupted using (i) siRNA knockdown of multiple subunits and (ii) pharmacological inhibition of CSN5 (COP9i), the catalytic deneddylase subunit regulating CRL activity and an emerging therapeutic target in oncology. **Results:** Our proteomic screen identified multiple COP9 signalosome subunits as HBx interactors, with CSN5 as the top hit. Knockdown of COP9 subunits (CSN5, CSN6, CSN7A, CSN8) significantly reduced HBV markers in HBV-infected primary human hepatocytes (PHH) and HepG2-NTCP cells.Pharmacological inhibition with COP9i showed potent antiviral activity with a favorable therapeutic window (EC_{50}: 50–100 nM; EC_{90}: 150–300 nM; CC_{50} > 10 μM) and a broad pan-genotypic efficacy (A1, A2, B2, C1, D3, E, F1b, H). *In vivo*, post-infection oral administration of COP9i in HBV-infected FRG humanized mice significantly reduced serum HBV DNA levels.Mechanistically, COP9 inhibition selectively suppressed cccDNA transcription as demonstrated using a cccDNA reporter system (mcHBV-Luc). COP9i induced robust HBx degradation. Inhibition of COP9 locks CRL4 in a hyper-neddylated state,

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promoting auto-ubiquitination and degradation of HBx and DDB1, leading to stabilization of SMC5/6 and sustained repression of cccDNA transcription. **Conclusion:** The COP9 signalosome is a previously unrecognized and druggable regulator of HBV cccDNA transcription. Targeting COP9 induces HBx degradation and restores SMC5/6-mediated restriction, providing a mechanistically defined and translational antiviral strategy.

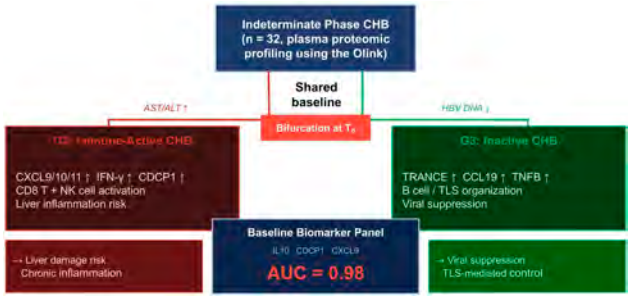


Disclosures: Karim Mouzannar:Nothing to Disclose, Anne Schauer:Nothing to Disclose, Susannah Stephenson-Tsoris:Nothing to Disclose, Zhensheng Zhang:Nothing to Disclose, Min Zhang:Hepanova Inc.: Employee, Seung Bum Park:Nothing to Disclose, D. Eric Anderson:Nothing to Disclose, T. Jake Liang: Nothing to Disclose.

4182 | PRE-ENCODED PLASMA PROTEOMIC SIGNATURE PREDICTS IMMUNE-ACTIVE TRANSITION IN INDETERMINATE-PHASE CHRONIC HEPATITIS B

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Background: Patients with indeterminate-phase chronic hepatitis B (CHB), particularly those with high viremia (HBV DNA >2,000 IU/mL) and persistently normal or mildly elevated alanine aminotransferase (ALT), remain poorly characterized regarding their immunological profiles and heterogeneous clinical trajectories. We investigated whether plasma proteomic signatures could predict immune trajectory in CHB and whether transition to the immune-active phase occurs as an acute switch-like event rather than gradual immunological drift. **Methods:** Longitudinal plasma proteomic profiling using the Olink Target 96 Inflammation panel was performed in 32 CHB patients from the observational arm of the ATTENTION study (NCT03753074), a multicenter randomized trial in non-cirrhotic patients with high viremia and normal or mildly elevated ALT. Patients were classified into persistently indeterminate CHB (G1, n = 11), transition to immune-active CHB (G2, n = 12), and spontaneous transition to inactive CHB (G3, n = 9). Differential abundance, longitudinal mixed-effects, and changepoint analyses centered on clinical event timing (T_0) were performed. A baseline multi-protein biomarker model predicting immune-active transition was subsequently developed. **Results:** Baseline global plasma proteomes overlapped substantially across groups. However, longitudinal analyses demonstrated that G2 represented the only proteomically distinct trajectory, whereas G3 remained indistinguishable from G1 despite viral suppression. G2 acutely diverged from both G1 and G3 at the time of clinical event, with 83–89% of proteomic transitions clustering within $T_0 \pm 1$ timepoint. The G2 program was characterized by IFN-γ/CD8/NK-cell activation signatures, including CXCL9, CXCL10, CXCL11, CDCP1, IL-18, and TNFRSF9. IL-10 showed a context-dependent dual role, with baseline elevation preceding immune-active transition and transient surge at T_0 correlating with IFN-γ and ALT recovery. A baseline inflammatory panel comprising IL-10, CDCP1, and CXCL9 accurately predicted future G2 patients (AUC = 0.98). **Conclusion:** In indeterminate-phase CHB, immune trajectory appears pre-encoded within the baseline plasma proteome and diverges through an acute switch-like event. Baseline plasma biomarkers may enable prospective identification of patients at risk for immune-active transition.



Disclosures: Won-Mook Choi:Gilead Sciences: Speaking and Teaching, AbbVie: Speaking and Teaching, Roche: Consultant, Boehringer Ingelheim: Advisor, GSK: Consultant, Eisai: Speaking and Teaching, AstraZeneka: Speaking and Teaching, Heeju Ryu: Nothing to Disclose, Young Suk Lim:Gilead Sciences: Grant/Research Support.

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4183 | SYNERGISTIC EFFECTS OF GUIZHI JIA HUANGQI DECOCTION COMBINED WITH NUCLEOS(T)IDE ANALOGUES AND PEGYLATED INTERFERON ON FUNCTIONAL CURE OF CHRONIC HEPATITIS B: A 48-WEEK IMMUNOVIROLOGICAL ANALYSIS

Xiaoyu Hu[1], [1]Hospital of Chengdu University of Traditional Chinese Medici

Background: The clearance rate of hepatitis B surface antigen (HBsAg) remains limited in patients with chronic hepatitis B (CHB) receiving nucleos(t)ide analogue (NA) combined with pegylated interferon (Peg-IFN) therapy. Traditional Chinese medicine (TCM) possesses immunomodulatory properties; however, its efficacy and underlying mechanisms when combined with NAs and Peg-IFN remain unclear. **Methods:** A total of 111 patients with CHB were enrolled and assigned to either a dual-therapy group (NA + Peg-IFN, n = 55) or a triple-therapy group (TCM + NA + Peg-IFN, n = 56) for 48 weeks. Virological, hematological, biochemical, and immunological parameters were evaluated. Immunological indices were analyzed at baseline and week 24 using flow cytometry. **Results:** The triple therapy group (TCM + NA + Peg-IFN) exhibited significantly higher HBsAg clearance rates (44.6% vs. 20.0%, P = 0.006) and seroconversion rates (33.9% vs. 16.4%, P = 0.033) compared with the dual therapy group. Immunologically, treatment in the triple therapy group led to a marked reduction in PD-1 expression on B cells (11.1% → 4.7%, P = 0.002) and $CD8^+$ T cells (23.5% → 16.9%, P = 0.02), accompanied by a significant increase in $CD8^+$ T cell counts (P = 0.04). Additionally, serum IL-8 levels were significantly elevated (P = 0.041). Regarding safety, white blood cell (WBC) and neutrophil (NEUT) counts at weeks 4, 8, and 12 were significantly better in the triple therapy group compared with the dual therapy group (P < 0.05). During the 24-week follow-up, no serious adverse events were observed in either group, and patients who achieved HBsAg clearance did not experience HBsAg recurrence. **Conclusion:** The triple therapy regimen combining TCM, NA, and Peg-IFN enhances the functional cure rate in chronic hepatitis B (CHB) and mitigates Peg-IFN-induced reductions in WBC and NEUT counts. Mechanistically, these effects are likely mediated through reversal of B cell and $CD8^+$ T cell exhaustion, promotion of $CD8^+$ T cell expansion, and induction of controlled IL-8–mediated immune activation.

Synergistic Effects of Guizhi Jia Huangqi Decoction Combined with Nucleos(t)ide Analogues and Pegylated Interferon on Functional Cure of Chronic Hepatitis B: A 48-Week Immunovirological Analysis

Xiaoyu Hu

Department of Infectious Diseases, Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu, People's Republic of China

Abstract

Background: The clearance rate of hepatitis B surface antigen (HBsAg) remains limited in patients with chronic hepatitis B (CHB) receiving nucleos(t)ide analogue (NA) combined with pegylated interferon (Peg-IFN) therapy. Traditional Chinese medicine (TCM) possesses immunomodulatory properties; however, its efficacy and underlying mechanisms when combined with NAs and Peg-IFN remain unclear.

Methods: A total of 111 patients with CHB were enrolled and assigned to either a dual-therapy group (NA + Peg-IFN, n = 55) or a triple-therapy group (TCM + NA + Peg-IFN, n = 56) for 48 weeks. Virological, hematological, biochemical, and immunological parameters were evaluated. Immunological indices were analyzed at baseline and week 24 using flow cytometry.

Results: The triple therapy group (TCM + NA + Peg-IFN) exhibited significantly higher HBsAg clearance rates (44.6% vs. 20.0%, P = 0.006) and seroconversion rates (33.9% vs. 16.4%, P = 0.033) compared with the dual therapy group. Immunologically, treatment in the triple therapy group led to a marked reduction in PD-1 expression on B cells (11.1% → 4.7%, P = 0.002) and $CD8^+$ T cells (23.5% → 16.9%, P = 0.02), accompanied by a significant increase in $CD8^+$ T cell counts (P = 0.04). Additionally, serum IL-8 levels were significantly elevated (P = 0.041). Regarding safety, white blood cell (WBC) and neutrophil (NEUT) counts at weeks 4, 8, and 12 were significantly better in the triple therapy group compared with the dual therapy group (P < 0.05). During the 24-week follow-up, no serious adverse events were observed in either group, and patients who achieved HBsAg clearance did not experience HBsAg recurrence.

Conclusions: The triple therapy regimen combining TCM, NA, and Peg-IFN enhances the functional cure rate in chronic hepatitis B (CHB) and mitigates Peg-IFN-induced reductions in WBC and NEUT counts. Mechanistically, these effects are likely mediated through reversal of B cell and $CD8^+$ T cell exhaustion, promotion of $CD8^+$ T cell expansion, and induction of controlled IL-8–mediated immune activation.

1.Background

Currently, nucleos(t)ide analogue (NA) combined with pegylated interferon (Peg-IFN) therapy represents a major strategy for achieving functional cure in chronic hepatitis B (CHB); however, the rate of hepatitis B surface antigen (HBsAg) clearance remains suboptimal (1). Traditional Chinese medicine (TCM) has been reported to possess immunomodulatory and anti-inflammatory properties (2), yet its efficacy and underlying mechanisms when combined with NAs and Peg-IFN remain unclear. Therefore, this study aimed to evaluate the 48-week clinical cure rate of a TCM + NA + Peg-IFN triple regimen and to systematically characterize treatment-related changes in virological responses, peripheral immune cell profiles—including T cells, B cells, natural killer (NK) cells, and their PD-1 expression—and selected serum inflammatory cytokines.

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2. Materials and Methods

2.1 Study Design

This was a prospective, single-center, exploratory cohort study that enrolled 111 patients with CHB between January 2024 and December 2025. Eligibility criteria included baseline HBsAg levels < 1500 IU/mL and hepatitis B virus (HBV) DNA levels below the lower limit of detection (< 100 IU/mL). Patients were assigned to either the dual-therapy group (Dual), which received NA + Peg-IFN treatment (n = 55), or the triple-therapy group (Combination), which received TCM + NA + Peg-IFN treatment (n = 56).

2.2 Interventions

Patients in the dual-therapy group received NA combined with pegylated interferon α-2b (Peg-IFNα-2b, 180 μg/week) for 48 weeks. Patients in the triple-therapy group received the same regimen supplemented with Guizhi Jia Huangqi Decoction granules (one dose daily, administered three times per day) for 48 weeks.

2.3 Study Endpoints

The primary endpoint was the HBsAg clearance rate at week 48. Secondary endpoints included HBsAg seroconversion rate, HBeAg seroconversion rate (in patients who were HBeAg-positive at baseline), incidence of alanine aminotransferase (ALT) flare, and safety outcomes. ALT flare was defined as ALT > 2 × the upper limit of normal (ULN) with a peak value > 80 U/L during the 48-week treatment period. Functional cure was defined as HBsAg clearance at week 48 that remained negative 24 weeks after treatment discontinuation. Seroconversion was defined as HBsAg clearance accompanied by HBsAb positivity (≥ 10 mIU/mL).

2.4 Definition of Response Status

According to HBsAg clearance status at week 48, patients were categorized into a responder group (patients achieving HBsAg clearance) and a non-responder group (patients without HBsAg clearance) for subsequent analysis of ALT flare incidence.

2.5 Laboratory Assessments

Peripheral venous blood samples were collected at weeks 0, 2, 4, 8, 12, 24, 36, and 48 during treatment. The following parameters were assessed: Virological parameters: Serum HBsAg, HBeAg, and HBV DNA levels were measured at baseline, weeks 4, 8, 12, 24, 36, and 48, as well as at the 24-week post-treatment follow-up. Hematological and biochemical parameters: White blood cell count (WBC), neutrophil count (NEUT), platelet count (PLT), thyroid function panel (six parameters), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) were assessed at baseline, weeks 4, 8, 12, 24, 36, 48, and at the 24-week post-treatment follow-up. Immunological parameters: Peripheral blood collected at baseline and week 24 was analyzed by flow cytometry for PD-1 expression on CD8+ T cells, B-cell counts, PD-1 expression on B cells, NK cell counts, and CD4/CD8 ratio. Inflammatory mediators: Serum IL-8 levels were measured using enzyme-linked immunosorbent assay (ELISA).

2.6 Statistical Analysis

Within-group comparisons were performed using the paired t-test or Wilcoxon signed-rank test, as appropriate. Between-group comparisons were conducted using the independent-samples t-test, Mann–Whitney U test, or chi-square test. A two-sided P value < 0.05 was considered statistically significant.

2.7 Ethical Approval

This study was approved by the Ethics Committee of the Hospital of Chengdu University of Traditional Chinese Medicine. Written informed consent was obtained from all participants prior to enrollment.

3. Results

3.1 Baseline Demographic and Clinical Characteristics

A total of 111 patients with CHB were enrolled in this study, including 55 patients in the dual-therapy group (NA + Peg-IFNα-2b) and 56 patients in the triple-therapy group (TCM + NA + Peg-IFNα-2b). As shown in Table 1, no significant differences were observed between the two groups with respect to age, sex distribution, HBeAg positivity rate, baseline HBsAg levels, or baseline ALT levels (all $P > 0.05$), indicating comparable baseline characteristics. All enrolled patients had HBV DNA levels below the lower limit of detection (< 100 IU/mL) at baseline, and thyroid function parameters were within the normal range.

Table 1. Baseline Demographic and Clinical Characteristics

Variable	Dual-Therapy Group (n = 55)	Dual-Therapy Group(n = 56)	*P* value
Age (years)	47±9	44.5±9	0.145
Sex (male/female)	39/16	45/11	0.246
HBeAg positivity, *n* (%)	4（7.3%）	5（8.9%）	0.749
Baseline HBsAg	62.45（13.22，130.53）	106.36（26.58，150）	0.105
(IU/mL)			
Baseline ALT (U/L)	23（17，37）	26（18.75，38.25）	0.637

3.2 Virological Response and ALT Flare

At week 24, the HBsAg clearance rates were 26.8% in the triple-therapy group and 14.5% in the dual-therapy group ($P = 0.112$), while HBsAg seroconversion rates were 19.6% and 10.9% ($P = 0.201$), respectively. By week 48, the triple-therapy group achieved significantly higher HBsAg clearance (44.6% vs. 20.0%, $P = 0.006$) (Figure 1A) and HBsAg seroconversion rates (33.9% vs. 16.4%, $P = 0.033$) (Figure 1B) compared with the dual-therapy group. Regarding ALT flare, patients who achieved HBsAg clearance (responders) had a significantly higher incidence than non-responders (50.0% vs. 30.7%, $P = 0.048$) (Figure 1C).

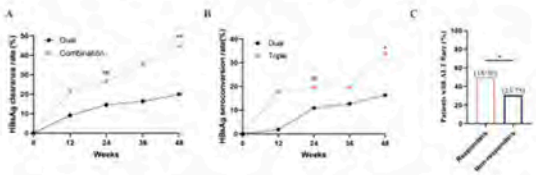


Figure 1. Week 48 efficacy endpoints and incidence of ALT flare. (A) HBsAg clearance rate. (B) HBsAg seroconversion rate. (C) Incidence of ALT flare. ALT flare was defined as ALT > 2 × the upper limit of normal (ULN) with a peak value > 80 U/L during the 48-week treatment period. Responders were defined as patients who achieved HBsAg clearance at week 48. Data are presented as percentages. Between-group comparisons were performed using the chi-square test. *$P < 0.05$, **$P < 0.01$.

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3.3 Immune and Inflammatory Responses

3.3.1 Dynamic Changes in T Cells

At 24 weeks of treatment, PD-1 expression on $CD8^+$ T cells was significantly reduced from baseline in both groups: from 21.8% to 16.0% in the dual therapy group ($P = 0.013$) and from 23.5% to 16.9% in the triple therapy group ($P = 0.02$) (Figure 2A). $CD8^+$ T cell counts exhibited divergent trends: they increased significantly in the triple therapy group ($P = 0.04$) but decreased significantly in the dual therapy group ($P < 0.01$) (Figure 2B). In contrast, the CD4/CD8 ratios showed no notable changes from baseline in either group (Figure 2C).

3.3.2 Dynamic Changes in NK Cells

At 24 weeks of treatment, total NK cell counts decreased significantly from baseline in both groups: from 231.9×10^6/L to 174.3×10^6/L in the dual therapy group ($P = 0.027$) and from 227.2×10^6/L to 180.0×10^6/L in the triple therapy group ($P = 0.029$) (Figure 2D). The CD4/CD8 ratio remained largely unchanged in both groups (Figure 2C). Additionally, no significant differences were observed in NK cell PD-1 expression before and after treatment in either group (Figure 2E).

3.3.3 B-Cell Responses

With respect to total B-cell counts, a significant reduction was observed in the dual-therapy group at week 24 compared with baseline ($P = 0.007$) (Figure 2E). Although a similar decreasing trend was observed in the triple-therapy group, the difference did not reach statistical significance (Figure 2F).

Notably, the proportion of PD-1–expressing B cells was significantly reduced in the triple-therapy group at week 24 compared with baseline ($P = 0.002$), whereas only a non-significant downward trend was observed in the dual-therapy group.

3.3.4 Inflammatory Mediators

IL-8 is a pro-inflammatory and pro-fibrotic cytokine, and persistently elevated IL-8 levels may indicate uncontrolled hepatic inflammation and progression toward fibrosis or hepatocellular carcinoma. Compared with the dual-therapy group, the triple-therapy group exhibited significantly higher serum IL-8 levels at week 24 ($P = 0.041$), suggesting that the addition of TCM to interferon-based therapy may induce a stronger immune activation state (Figure 2G). This finding is consistent with the higher HBsAg clearance rate observed in the triple-therapy group and supports enhanced immune activation as an important driver of functional cure. Importantly, the increase in IL-8 was not accompanied by severe adverse events, indicating that this immune response was well tolerated.

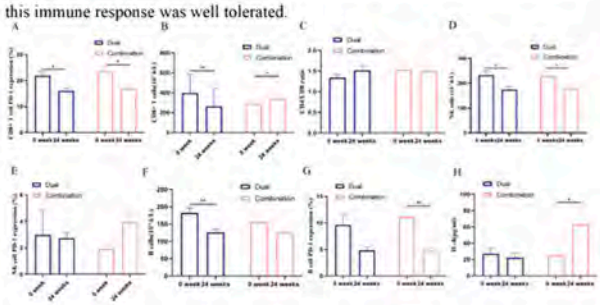


Figure 2 Changes in immunological and inflammatory response indicators (week 0 vs. week 24). (A) CD8+ T cell PD-1 expression rate; (B) CD8+ T cell count; (C) CD4/CD8 ratio; (D) Total NK cell count; (E) NK cell PD-1 expression rate; (F) B cell count; (G) B cell PD-1 expression rate; (H) Serum IL-8 level. Data are presented as mean ± standard deviation. Paired t-tests were used for within-group comparisons. $^*P < 0.05$, $^{**}P < 0.01$.

4. Safety Evaluation

During the treatment period, WBC, NEUT, and PLT levels in both groups exhibited a declining trend between weeks 4 and 12. WBC and NEUT reached their lowest values at week 4, whereas PLT levels were lowest at week 8. At weeks 4 and 8, the triple therapy group had significantly higher WBC and NEUT levels compared with the dual therapy group ($P < 0.05$), while PLT levels did not differ significantly between groups at any time point (Figures 3A–C). After week 12, WBC, NEUT, and PLT levels gradually recovered toward normal ranges in both groups. No patients experienced grade 3/4 neutropenia or clinically significant thrombocytopenia requiring intervention.

Regarding hepatic safety, no significant difference was observed in the incidence of ALT flare—defined as ALT > 2 × the ULN with a peak value > 80 U/L during the 48-week treatment period—between the dual-therapy and triple-therapy groups (29.1% vs. 32.1%, respectively) (Figure 3D).
In addition, no clinically meaningful abnormalities in thyroid function were detected in either group throughout treatment. During the subsequent 24-week follow-up period, no serious adverse events were observed in either group, and no HBsAg reversion occurred among patients who had achieved HBsAg clearance.

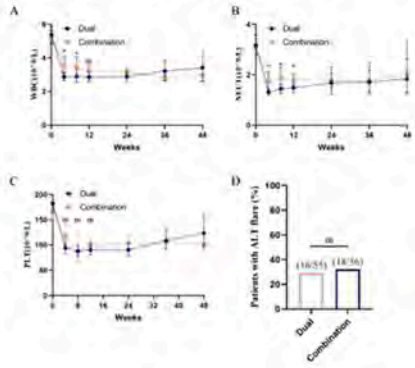


Figure 3 Hematological and hepatic safety parameters during treatment. (A) White blood cell (WBC) count; (B) Neutrophil (NEUT) count; (C) Platelet (PLT) count; (D) Incidence of ALT flare. ALT flare was defined as ALT > 2×ULN with a peak value > 80 U/L within the 48-week treatment period. Data are presented as mean ± standard deviation. Paired t-tests were used for within-group comparisons of continuous variables, and chi-square tests were used for between-group comparisons of categorical variables. $^*P < 0.05$, $^{**}P < 0.01$.

4.Discussion

The present study found that the triple therapy (TCM + NA + Peg-IFN) significantly improved HBsAg clearance rate (44.6% vs. 20.0%) and seroconversion rate (33.9% vs. 16.4%) compared to the dual therapy. Furthermore, in the triple group, B-cell PD-1 expression significantly decreased from baseline (11.1% to 4.7%, $P = 0.002$), CD8+ T-cell PD-1 expression also significantly decreased (23.5% to 16.9%, $P = 0.02$), and CD8+ T-cell count significantly increased ($P = 0.04$). These findings suggest that the Chinese herbal medicine may enhance both humoral and cellular immune functions by simultaneously reversing B-cell and CD8+ T-cell exhaustion and promoting CD8+ T-cell expansion, thereby facilitating HBsAg clearance and seroconversion.

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Notably, our previous studies demonstrated that Guizhi Jia Huangqi Decoction can inhibit HBV entry into hepatocytes through blockade of the NTCP receptor, thereby preventing new infection events. In addition, this formula can directly suppress cccDNA transcription, reducing HBsAg production at its source (3). This direct antiviral activity may create a more favorable environment for immune-mediated viral clearance. On the one hand, by reducing newly infected hepatocytes, the persistent production and release of viral antigens—including HBsAg—are diminished, thereby alleviating immune exhaustion caused by chronic high antigen exposure. On the other hand, stabilization and gradual reduction of the infected hepatocyte pool may establish a more permissive microenvironment for subsequent interferon-mediated immune clearance.

From an immunomodulatory perspective, serum IL-8 levels were significantly elevated in the triple-therapy group without an accompanying increase in severe adverse events. Although IL-8 is generally considered a pro-inflammatory and pro-fibrotic cytokine, and persistently elevated IL-8 levels are often associated with uncontrolled hepatic inflammation, the increase observed in this study was consistent with the higher HBsAg clearance rate. Mechanistic studies have shown that interferon can induce IL-8 expression, while upregulated IL-8 may directly suppress HBsAg production and release in hepatocytes by enhancing the expression of bone marrow stromal antigen 2 (BST2) (4). These findings support the concept that an early and moderate increase in inflammatory cytokines during interferon therapy may reflect effective immune reactivation (5).

Taken together, we propose a "dual-mode synergistic" model through which TCM combined with interferon promotes functional cure in CHB. Specifically, TCM exerts direct antiviral effects through NTCP blockade, thereby interrupting new infection events at the upstream level and reducing the immunological burden on the host. Simultaneously, the combination of TCM and interferon may reverse PD-1–mediated B-cell exhaustion and induce controlled IL-8–associated immune activation at the downstream level, thereby enhancing immune-mediated viral clearance. This synergistic strategy of "source blockade" and "terminal clearance" may represent the central mechanism underlying the superior HBsAg clearance achieved by the triple regimen and provides a theoretical basis for optimizing integrative therapeutic strategies for CHB. It should be noted that during the study period, 9 and 7 patients in the dual and triple groups, respectively, discontinued treatment prematurely, while 23 and 9 patients did not reach the treatment endpoint. Although the dropout rates were generally manageable in both groups and may introduce some bias into the efficacy assessment, the overall completion rate remained acceptable. Future studies with larger sample sizes and optimized follow-up management are needed to further validate the findings of this study.

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Disclosures: Xiaoyu Hu:Nothing to Disclose.

4184 | THE LANDSCAPE OF HBV INTEGRATION BURDEN ACROSS CHRONIC HEPATITIS B, CIRRHOSIS, AND HEPATOCELLULAR CARCINOMA

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Background: Chronic hepatitis B (CHB) remains a major global public health burden, which can progress into liver cirrhosis (LC) and eventually hepatocellular carcinoma (HCC). Accumulating evidence has established that HBV integration into the host genome is a critical oncogenic event in HCC pathogenesis, driving genomic instability, aberrant gene expression, and malignant transformation. However, the distinct characteristics of HBV integration across the three progressive disease stages—CHB, LC, and HCC—remain poorly understood. **Methods:** We collected liver tissues from patients with CHB, HBV-related LC, and HBV-related HCC at the Second Affiliated Hospital of Chongqing Medical University. Viral capture sequencing precisely detected genome-wide HBV integration breakpoints to analyze integration patterns, distribution, and clonal expansion of HBV-integrated hepatocytes across stages. RNA sequencing profiled host gene expression, with integrative bioinformatics exploring the relationship between clonal expansion of HBV-integrated hepatocytes and immune infiltration. **Results:** This cross-sectional study enrolled 103 patients: 45 with CHB, 22 with LC, 35 with HCC. The number of unique integration types was significantly higher in CHB than in LC/HCC (123 vs 42.5, 123 vs 71, both $P < 0.01$), reflecting early heterogeneous integration and reduced integration diversity. Clonal expansion of HBV-integrated hepatocytes was markedly elevated in HCC (18.70 vs 5.02, 18.70 vs 4.73, both $P < 0.001$), indicating monoclonal dominance during malignancy. Integration diversity correlated positively with HBsAg and ALT; clonal expansion of HBV-integrated hepatocytes correlated positively with AFP and age. The peak of HBV genomic breakpoints was located in the X gene, gradually shifting toward the DR2 region from CHB to HCC. A total of 44 shared genes were identified. Among these, integration frequencies of LOC100507412 and TERT progressively increased, while those of PCDH15 and CTNNA2 gradually decreased. These integration patterns may facilitate

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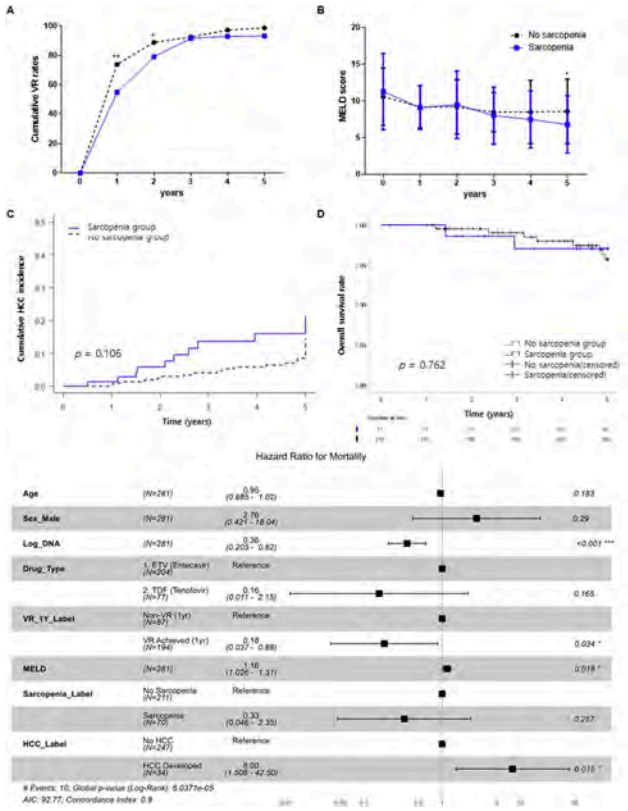
disease progression from CHB to LC and ultimately to HCC. Genes positively associated with clonal expansion of HBV-integrated hepatocytes were enriched in cell cycle and proliferation pathways, while negatively associated genes in immune-metabolic pathways. Clonal expansion of HBV-integrated hepatocytes positively correlated with intrahepatic M2 macrophages, suggesting immunosuppression. **Conclusion:** This study systematically delineates the HBV integration features across CHB-LC-HCC, showing decreasing diversity and increasing clonality from early infection to HCC, providing new insights into disease progression.

Disclosures: Xingyue Yi:Nothing to Disclose, Na Wu: Nothing to Disclose, Fang Wei:Nothing to Disclose, Zhiwei Chen:Nothing to Disclose, Hong Ren:Nothing to Disclose.

4185 | SARCOPENIA DELAYS EARLY VIROLOGICAL RESPONSE BUT DOES NOT AFFECT LONG-TERM PROGNOSIS IN PATIENTS WITH CHRONIC HEPATITIS B AND LIVER CIRRHOSIS

Yeonwoo Cha[1] In Hee Kim[1] Chang Hun Lee[1] Byung Chul Jin[1] Yun Chae Lee[1] Seung Young Seo[1] Seong Hun Kim[1] Seung Ok Lee[1], [1]Jeonbuk National University Hospital

Background: This study aimed to investigate the clinical significance of sarcopenia in virological response (VR) and long-term prognosis among treatment-naïve chronic hepatitis B (CHB) patients with liver cirrhosis (LC). **Methods:** We retrospectively reviewed the data of treatment-naïve CHB patients who initiated antiviral therapy between 2007 and 2018 at Jeonbuk National University Hospital. Eligible patients were those diagnosed with LC who had maintained antiviral therapy for more than a year. L3 skeletal muscle index (L3SMI) was calculated using computed tomography, and sarcopenia was defined using the gender quartile method (cut-off: <46.0 cm^2 /m^2 for males and <35.37 cm^2 /m^2 for females). **Results:** A total of 283 patients (71 in the sarcopenic group and 212 in the non-sarcopenic group) were enrolled. The sarcopenic group was significantly older and had a higher frequency of alcohol consumption history compared to the non-sarcopenic group. Mean baseline HBV DNA levels and MELD scores did not differ significantly between the groups. The cumulative VR rates were significantly lower in the sarcopenic group at 1 and 2 years, indicating a delay in viral suppression. However, VR rates became comparable after 3 years of continuous therapy. There were no significant differences in serial MELD scores, cumulative HCC incidence, or overall survival rates between the two groups. Consistent trends were observed in subgroup analyses of patients with sarcopenic obesity and those aged ≥ 60 years. In multivariate analysis for 5-year overall survival, baseline log HBV DNA, VR at 1 year, MELD score, and HCC development were independent prognostic factors, whereas sarcopenia was not. **Conclusion:** Sarcopenia in patients with CHB-related LC tends to delay the achievement of an early virological response, but it does not affect serial MELD scores, HCC incidence, or long-term survival. Consequently, preserving liver function and achieving early viral suppression are more critical for prognosis than maintaining muscle mass in this population.



Disclosures: Yeonwoo Cha:Nothing to Disclose, In Hee Kim:Nothing to Disclose, Chang Hun Lee:Nothing to Disclose, Byung Chul Jin:Nothing to Disclose, Yun Chae Lee:Nothing to Disclose, Seung Young Seo: Nothing to Disclose, Seong Hun Kim:Nothing to Disclose, Seung Ok Lee:Nothing to Disclose.

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4186 | UPREGULATING B CELL POPULATION AND MATURATION WITH INCREASING CD4 TO CD8 RATIO IN HEPATITIS B E ANTIGEN-NEGATIVE HEPATITIS B VIRUS CARRIERS WITH CRYOGLOBULINEMIA

Ming-Ling Chang[1], [1]Department of Gastroenterology and Hepatology

Background: The immunological basis for lower hepatitis B surface antigen (HBsAg) levels in hepatitis B e antigen (HBeAg)-negative hepatitis B virus (HBV) carriers with than those without cryoglobulinemia remains elusive. We aim to elucidate it. **Methods:** A prospective cohort of 75 HBeAg-negative HBV carriers with normal alanine aminotransferase levels without any anti-HBV therapy who had been surveyed for cryoglobulinemia was conducted. The serum and peripheral blood mononuclear cells (PBMCs) were assessed for biochemistry and flowcytometry, respectively. **Results:** Of 75 patients (mean age: 56.7 years), 40 (53.3%) were males. More frequently female (57.8%, $p = 0.018$), higher proportions of peripheral total B cell (4.54+/-2.91 vs. 2.67+/-1.47%, $p = 0.015$), mature B cell (CD19+CD10-/CD19) 97.3+/-1.12 vs. 95.4+/-1.69%, $p = 0.013$) and helper T cells (Th) (59.0 +/-10.9 vs. 50.9+/-11.8%, $p = 0.028$), but lower proportions of cytotoxic T cells (Tc) (28.8 +/-10.2 vs. 37.3 +/-11.4%, $p = 0.017$) (namely, higher Th/Tc ratio, 2.42 +/-1.16 vs. 1.50 +/-0.7 3, $p = 0.019$) and immature B cell (CD19+CD10+/CD19)(2.42+/-1.05 vs. 4.26+/-1.64%, $p = 0.014$) were noted in patients with than those without cryoglobulinemia. All the proportions of other investigated T and B cell subpopulations including HBsAg-specific B cells, early (7-AAD-Annexin V+ CD19) or late apoptotic B cells (7-AAD+Annexin V+ CD19) and serum human B cell activation factor (BAFF) levels (1139.4 +/-294 vs. 1165.3+/-361 pg/mL, $p = 0.796$) were comparable between patients with and without mixed cryoglobulinemia. Among the PBMCs, low titer HBV DNA (32-69 IU/ml) were mainly found in B cells, regardless of mixed cryoglobulinemia, and in CD8 cells (47 IU/ml) of patients with cryoglobulinemia. **Conclusion:** Through infecting PBMCs, cryoglobulinemia is associated with upregulating total B cell and Th cell populations, accelerating B cell maturation, but downregulating Tc cell populations in HBeAg-negative HBV carriers.

Disclosures: Ming-Ling Chang:Nothing to Disclose.

4187 | COMPARISONS OF INTEGRATED HBV DNA (IDNA) PROFILES BETWEEN MATCHED LIVER AND PLASMA SAMPLES FROM PATIENTS WITH HBEAG (+) AND HBEAG(-) CHRONIC HEPATITIS B

Daryl Lau[1] Hsin-Ni Liu[2] Zhili Wang[3] Zach Heimer[3] Selena Lin[3] Fwu-Shan Shieh[3] Haitao Guo[4] Ying-Hsiu Su[5], [1]Beth Israel Deaconess Medical Center, Harvard Medical School, [2]The Baruch S. Blumberg Institute, [3]JBS Science Inc. Lansdale, PA, [4]University of Pittsburgh, [5]Baruch S. Blumberg Institute

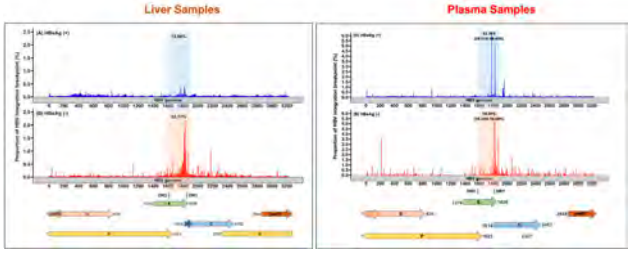
Background: HBsAg can be derived from intrahepatic cccDNA and integrated HBV DNA (iDNA). We previously analyzed the iDNA patterns from liver tissues of 24 HBeAg(+) and 32 HBeAg(-) treatment-naive CHB patients and correlated them with other virological biomarkers. Since liquid biopsies are more conveniently accessible than liver biopsies, we compared the hepatic and plasma iDNA profiles of these patients to evaluate if they can yield similar results. **Methods:** For iDNA detection, total DNA from liver and plasma samples was subjected to HBV hybridization-targeted next generation sequencing (HBV-NGS) assay for identification of the HBV-host junction sequences (HBV-JS). The ChimericSeq bioinformatics pipeline determined % HBV-JS of all HBV reads and their breakpoint coordinates. **Results:** Intrahepatic cccDNA, serum HBV DNA, HBV RNA, HBcrAg and qHBsAg were higher in HBeAg(+) CHB. The quantity of HBV DNA templates detected in both liver and plasma showed a significant correlation with serum viral load (Liver: Spearman's rho = 0.72, Plasma: rho = 0.74; $p < 0.001$ for both). HBeAg(+) participants generally had lower % iDNA in total HBV DNA from both liver and plasma compared to the HBeAg(-) ones. Only 4 HBeAg(+) subject had > 60% iDNA in liver and none in plasma. In contrast, 22(69%) and 7(22%) of HBeAg(-) participants had > 60% iDNA in the liver and plasma, respectively. For HBeAg(+) CHB, the iDNA integration sites were more random with 15.9% and 33.8% from liver and plasma localized to the DR2-DR1 region, respectively. [Figure] For HBeAg(-) CHB, > 50% of the iDNA integrations in both liver and plasma were clustered at the DR2-DR1 'HCC hot spot' region. [Figure] **Conclusion:** Plasma HBV DNA represents apoptotic DNA fragments released from the entire liver, with preferential survival of nucleosome-protected or transcription factor–associated regions following nuclease degradation. In contrast, liver biopsy tissue reflects the total HBV DNA content present within a very small sampled tissue. In both liver and plasma, HBeAg(-) CHB was associated with higher iDNA concentrations and frequency of DR2-DR1 iDNA distributions. The

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striking enrichment peaks in plasma iDNA at DR2-DR1 for both HBeAg(+) and (-) patients likely represented the dense histone and/or transcription factor association around the nt 1800 region. Liquid biopsy has the potential to detect changes in iDNA profiles during therapy and to monitor functional cure. In addition, iDNA distribution likely can serve as a HCC biomarker.

Figure: Comparison of the distribution of junction breakpoints in the HBV genome between liver and plasma samples in HBeAg(+) and HBeAg(-) CHB

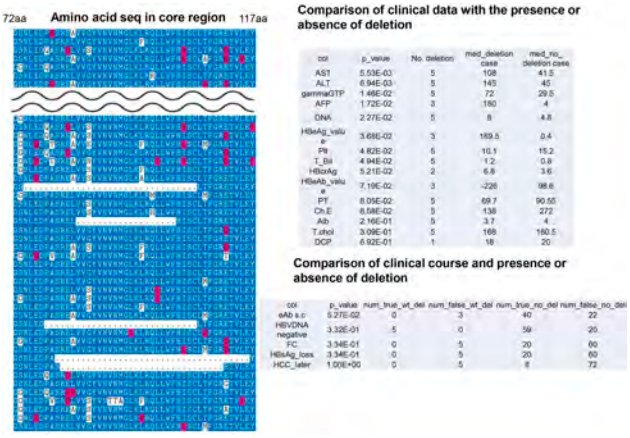


Disclosures: Daryl Lau:Gilead: Grant/Research Support, GSK: Consultant, Abbott Laboratories: Consultant, Hsin-Ni Liu:Nothing to Disclose, Zhili Wang:Nothing to Disclose, Zach Heimer:Nothing to Disclose, Selena Lin: JBS Science Inc.: Stock – privately held company, Fwu-Shan Shieh:Nothing to Disclose, Haitao Guo:Arbutus Biopharma: Stock - publicly traded company, Jericho Sciences: Advisor, Genentech: Consultant, Arbutus Biopharma: Stock - publicly traded company, Ying-Hsiu Su:JBS Science Inc.: Stock – privately held company.

4188 | THE RELATIONSHIP BETWEEN HBV DELETION MUTATIONS AND DISEASE PROGRESSION BASED ON WHOLE-GENOME ANALYSIS

Takashi Honda[1] Yoji Ishizu[1] Norihiro Imai[1] Takanori Ito[1] Kena Yamamoto[1] Shinya Yokoyama[1] ITO Kimihito[2] Yoshiki Murakami[3] Hiroki Kawashima[1], [1]Nagoya University Graduate School of Medicine, [2]Division of Bioinformatics, Hokkaido University, [3]Department of Molecular Pathology, Tokyo Medical University

Background: Deletions and mutations in HBV-DNA are associated with the progression of hepatitis. In particular, hepatitis B virus (HBV) is prone to genetic mutations during replication, and the emergence of viruses with deletions or mutations in specific regions is known to significantly alter the disease state. This study analyzed the association between deletions in various ORF regions of HBV and clinical features using whole-genome analysis with long-read sequencing. **Methods:** 78 patients with chronic hepatitis B who visited the outpatient clinic of Nagoya University Hospital were included in the analysis. HBV DNA was extracted from serum, and the HBV DNA sequence was analyzed using long-read sequencing. A consensus sequence was determined based on the HBV genome database (https://hbvdb.lyon.inserm.fr/HBVdb/HBVdbIndex), and the amino acid sequence was determined for each ORF. Clinical data (liver injury markers, HBV virus markers, tumor markers) were grouped according to the presence or absence of deletions in each HBV ORF, and differences were examined using the Wilcox test. Furthermore, for HBeAg seroconversion, HBV DNA negativity, functional remission, liver cancer development during disease progression, and HBsAg seroconversion, each HBV protein was grouped based on the presence or absence of deletion, and differences were examined using Fisher's test. **Results:** Of the 78 cases analyzed, deletions were found in 8 cases in the preS1 region, 7 in the preS2 region, 0 in the S region, 2 in the X region, 2 in the precore region, 5 in the core region, and 17 in the polymerase (pol) region. Significant differences were observed in total bilirubin (T.Bil), prothrombin time (PT), albumin (Alb), and platelet count (Plt) depending on the presence or absence of deletion in the preS1 region. In the precore region, differences were observed in Plt and ALT. Furthermore, significant differences were observed between the two groups in AST, ALT, GGTP, AFP, HBVDNA, HBeAg, platelet count, and total bilirubin in the core region, and in Alb in the pol region. On the other hand, no differences were observed between the presence or absence of deletions in sAg and eAg seroconversion, HBV DNA negativity, functional cure, or hepatocellular carcinoma development. Whole-genome analysis of HBV using long-read sequencing enabled comprehensive analysis of HBV genome deletions that were difficult to detect with conventional methods. The appearance of deletions in the core region was suggested to be associated with hepatitis activity and disease progression, while deletions in preS1 and the core region were associated with the progression of liver fibrosis. **Conclusion:** These findings suggest that differences in the deletion site in the HBV genome may have different effects on pathological conditions such as inflammation and fibrosis progression.



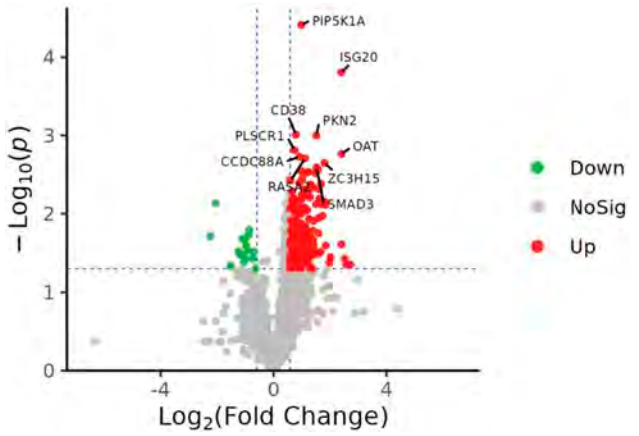
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Disclosures: Takashi Honda:Nothing to Disclose, yoji ishizu:Nothing to Disclose, Norihiro Imai:Nothing to Disclose, Takanori Ito:Nothing to Disclose, Kena Yamamoto:Nothing to Disclose, Shinya Yokoyama: Nothing to Disclose, ITO Kimihito:Nothing to Disclose, Yoshiki Murakami:Nothing to Disclose, Hiroki Kawashima:Nothing to Disclose.

4189 | PLSCR1 ASSOCIATES WITH INTERFERON RESPONSE IN CHB PATIENTS ACHIEVING HBSAG SEROCLEARANCE

Huiling Xiang[1] Qin Du[2] Jingzhe Zhang[3] Jun Li[3] Jiayin Wang[4] Qing Ye[5], [1]Tianjin University Central Hospital (Tianjin Third Central Ho, [2]Nankai University Affiliated Third Central Hospital, Tianjin University Central Hospital (Tianjin Third, [3]The Third Central Clinical College of Tianjin Medical University, Tianjin University Central Hospita, [4]Department of Gastroenterology and Hepatology, Tianjin University Central Hospital (Tianjin Third Cen, [5]Tianjin University Central Hospital (Tianjin Third Central Hospital)

Background: Pegylated interferon-alpha (peg-IFNα) induces HBsAg seroclearance in a subset of chronic hepatitis B (CHB) patients, but the key molecular drivers remain unclear. This study aimed to identify proteins linked to IFN response, immune landscape, and metabolic profiles associated with HBsAg loss. **Methods:** Forty-five CHB patients treated with 48-week peg-IFNα were enrolled: 29 with persistent HBsAg positive (D1) and 16 with HBsAg seroclearance (D2). Proteomics, immune infiltration (CIBERSORT/TIMER2.0), KEGG enrichment, PPI network, K-means clustering, and proteome-metabolome correlation were performed. PLSCR1 expression was validated in HPA database. **Results:** A total of 220 differentially expressed proteins were identified in D2 vs D1, with PLSCR1 as the most significantly upregulated. PLSCR1 correlated positively with B cells, T cells, monocytes, and macrophage infiltration. It clustered with antiviral ISGs (MX1, IFIT3, IFITM3, ISG20) and was central in PPI networks linking interferon signaling and metabolic pathways. Proteome-metabolome analysis showed PLSCR1 correlated with purine and glycolytic metabolites, supporting energy metabolism rewiring. HPA confirmed predominant PLSCR1 expression in macrophages. **Conclusion:** PLSCR1 is strongly associated with peg-IFNα-induced HBsAg seroclearance, correlating with enhanced interferon response, immune cell infiltration, and macrophage metabolic reprogramming. PLSCR1 may serve as a potential biomarker for IFN response in CHB.



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4190 | SAFETY AND REAL WORLD OUTCOMES OF HBV NAT POSITIVE, RECIPIENT NEGATIVE KIDNEY TRANSPLANTATION

Sara Gaines[1] Benyam Addissie[2] Sandeep Khurana[1] Alberto Unzueta[1] Clifford Akateh[1] Anil Kotru[1] Michael Marvin[1], [1]Geisinger Medical Center, [2]University of Rochester

Background: The use of hepatitis B virus (HBV) nucleic acid test (NAT) positive donor organs has emerged as a strategy to expand the donor pool. Data describing real world outcomes in HBV NAT positive, recipient negative kidney transplantation remain limited. We evaluated HBV serologic outcomes, antiviral prophylaxis requirements, and the impact of perioperative hepatitis B immune globulin (HBIG) and pre transplant immunity in this population. **Methods:** This retrospective cohort study included adult recipients of HBV NAT positive kidney transplants between October 2023 through November 2025. Patients were monitored for HBV serologies pre and post transplant. Antiviral prophylaxis with entecavir was initiated perioperatively per institutional protocol. Outcomes included development and persistence of hepatitis B core antibody (HBcAb) positivity, durability of immunity, and need for lifelong antiviral therapy. **Results:** Eighteen HBV NAT positive kidney transplants were performed. One patient had baseline HBcAb positivity and will remain on lifelong antiviral prophylaxis. Ten patients reached ≥12 months of follow up. Seven maintained immunity and remained HBcAb negative at 12 months, allowing

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discontinuation of antiviral therapy. Three patients developed persistent HBcAb positivity and remain on lifelong prophylaxis; two received intraoperative HBIG, and two lacked documented pre transplant immunity, defined as hepatitis B surface antibody < 100 mIU/mL. Five of ten patients at ≥ 12 months received intraoperative HBIG; three developed HBcAb positivity, including one transient case which resolved by month 9. Eight patients had < 12 months of follow up; four developed or maintained HBcAb positivity at 3 months, three of whom received HBIG, and 1 lacked immunity pre transplant. Overall, nine patients received HBIG; six demonstrated HBcAb positivity at 3 months, one of which spontaneously resolved. Two patients with immunity who did not receive HBIG developed HBcAb positivity at 3 months; one of which remained at 12 months while the other continues to demonstrate positivity at 6 months of follow-up. Three patients received an HBV/HCV co infected organ and had pre existing immunity; one developed persistent HBcAb positivity. No patient developed hepatitis B surface antigen positivity or HBV viremia. **Conclusion:** HBV NAT positive kidney transplantation appears safe with appropriate antiviral prophylaxis. Development of HBcAb positivity occurred but acute infection did not. Lack of pre transplant immunity and administration of HBIG were associated with HBcAb seroconversion. These findings support consideration of expanding the use of HBV NAT positive donor organs.

Table 1: Patient Demographics & Serology

Age	Sex	HCV +	HBg	Pre sAg	Pre sAb	Pre cAb	3 mo sAg	3 mo sAb	3 mo cAb	6 mo sAg	6 mo sAb	6 mo cAb	9 mo sAg	9 mo sAb	9 mo cAb	12 mo sAg	12 mo sAb	12 mo cAb
68	F	No	Yes	Neg	<3.5	Neg	Neg	30.2	Pos	Neg	<3.5	Pos	Neg	<3.5	Pos	Neg	<3.5	Pos
57	F	No	Yes	Neg	34.2	Neg	Neg	356	n/a	Neg	98.2	Neg	Neg	139	Neg	Neg	82.5	Neg
70	M	No	Yes	Neg	45.6	Neg	Neg	>1000	Pos	Neg	973	Pos	Neg	214	Neg	Neg	97.7	Neg
67	M	No	Yes	Neg	103	Neg	Neg	193	Neg	Neg	118	Neg	Neg	85.4	Neg	Neg	867	Neg
54	F	No	No	Neg	915	Neg	Neg	589	Neg	Neg	525	Neg	Neg	573	Neg	Neg	308	Neg
58	M	No	No	Neg	>1000	Neg	Neg	>1000	Neg	Neg	>1000	Neg	Neg	>1000	Neg	Neg	>1000	Neg
61	M	Yes	No	Neg	>1000	Neg	Neg	>1000	Pos	Neg	972	Pos	Neg	871	Pos	Neg	982	Pos
77	M	Yes	No	Neg	322	Neg	Neg	248	Neg	Neg	231	Neg	Neg	219	Neg	Neg	196	Neg
64	M	Yes	No	Neg	112	Neg	Neg	61.8	Neg	n/a	882.86	n/a	Neg	328.38	Neg	Neg	429	Neg
45	M	No	Yes	Neg	30.3	Neg	Neg	>1000	Pos	Neg	179	Pos	Neg	49.6	Pos	Neg	>1000	Pos
79	F	No	Yes	Neg	176	Neg	Neg	>1000	Neg	Neg	683	Neg	Neg	377	Neg	-	-	-
74	M	No	No	Neg	>1000	Neg	Neg	795	Neg	Neg	685	Neg	-	-	-	-	-	-
73	M	No	No	Neg	413	Neg	Neg	269	Pos	Neg	216	Pos	-	-	-	-	-	-
71	M	No	Yes	Neg	79.7	Neg	Neg	197	Pos	Neg	103	Pos	-	-	-	-	-	-
51	F	No	No	Neg	>1000	Neg	Neg	>1000	Neg	Neg	>1000	Neg	-	-	-	-	-	-
42	M	No	No	Neg	>1000	Neg	Neg	>1000	Neg	Neg	>1000	Neg	-	-	-	-	-	-
73	F	No	Yes	Neg	164	Neg	Neg	815	Pos	Neg	283	Pos	-	-	-	-	-	-
75	M	No	Yes	Neg	136	Pos	Neg	>1000	Pos	Neg	>1000	Pos	-	-	-	-	-	-

Disclosures: Sara Gaines:Gilead: I served on their PharmD PBC Advisory Panel, Benyam Addissie:Nothing to Disclose, Sandeep Khurana:Nothing to Disclose, Alberto Unzueta:Nothing to Disclose, Clifford Akateh: Nothing to Disclose, Anil Kotru:Nothing to Disclose, Michael Marvin:Nothing to Disclose.

4191 | FACTORS ASSOCIATED WITH HEPATITIS B SURFACE ANTIGEN SERO-CLEARANCE IN HEMODIALYSIS PATIENTS

Raja Khan[1] Nasir Hasan Luck[2] Abbas Ali Tasneem[2] Kiran Bajaj[2], [1]Bahrain Specialist hospital, [2]Sindh Institute of Urology and Transplantation

Background: The data regarding the factors predicting hepatitis B surface antigen (HBsAg) sero-clearance in hemodialysis patients with chronic hepatitis B is scarce. Therefore, our aim was to determine the HBsAg sero-clearance rates in the hemodialysis population and to identify the factors predictive of HBsAg sero-clearance in this population. **Methods:** It was prospective observational study including all the patients with HBsAg reactive chronic hepatitis B undergoing hemodialysis from January 2019 to December 2020. While, those patients with HBV and hepatitis D co-infection or those with HBV and hepatitis C co-infection or HBV and HIV co-infection were excluded from the study. Patients were then followed for two years for HBsAg loss which was repeated yearly for the clearance. Significant factors on univariate analysis underwent multivariate logistic regression analysis to ascertain the independent predictors of HBsAg loss in hemodialysis population. **Results:** A total of 213 patients with chronic HBV undergoing hemodialysis patients were enrolled in this study. After two years of hemodialysis, HBsAg loss was observed in 26(12%) patients. On univariate analysis, HBsAg levels < 1000IU/ml, HBV DNA levels < 5000IU/ml, HBeAg negative disease and multiple sessions of hemodialysis was associated with increased HBsAg loss while on multivariate analysis, HBV DNA levels < 5000 IU/ml at baseline and multiple sessions of hemodialysis were the independent predictors of loss of HBsAg in hemodialysis patients. **Conclusion:** The rate of HBsAg clearance is high in hemodialysis population especially those with decreased HBV DNA levels at baseline and undergoing multiple sessions of hemodialysis per week.

Disclosures: Raja Khan:Nothing to Disclose, Nasir Hasan Luck:Nothing to Disclose, Abbas Ali Tasneem: Nothing to Disclose, Kiran Bajaj:Nothing to Disclose.

4192 | HIV CO-INFECTION EXACERBATES HBV-INDUCED METABOLIC REPROGRAMMING AND LIVER FIBROGENESIS THROUGH A PYRUVATE-PPARα-DEPENDENT PATHWAY

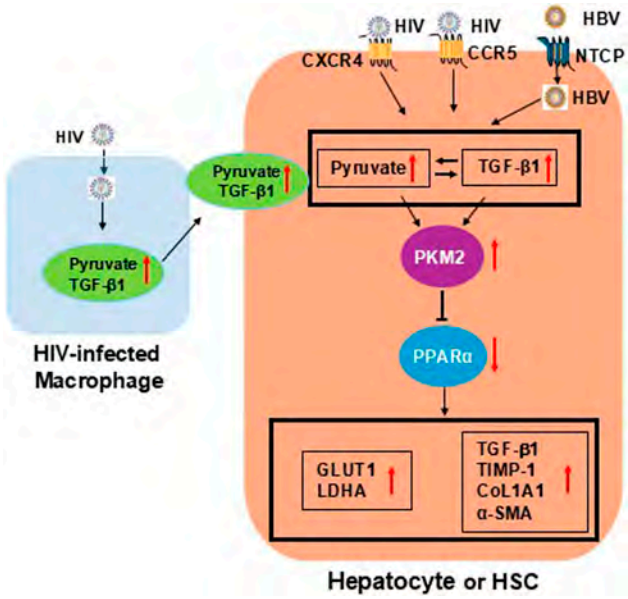
Thien Nguyen[1] Olivia Mezzetti[1] Xiaoqiong Duan[2] Shasha Li[3] Yongtao Wang[1] Zeinab Heidariyan[1] Swastika Tripathi[1] Shadi Salloum[1] Min Xu[1] Raymond Chung[1] Wenyu Lin[1], [1]Massachusetts General Hospital, Harvard Medical School, [2]Chinese Academy of Medical Sciences and Peking Union Medical College, [3]The Second People's Hospital of Fuyang City

Background: Chronic hepatitis B virus (HBV) and HIV co-infect approximately 4 million individuals worldwide, yet the mechanisms underlying the accelerated liver fibrosis observed in co-infected patients remain poorly

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understood. Based on our previous findings that HIV/HBV co-infection results in stronger fibrogenic signaling than HBV mono-infection through increased TGF-β1 levels, and that HBV infection drives fibrogenesis through increased pyruvate production and reduced PPARα expression, we investigate whether HIV-induced dysregulation of the TGF-β1–PKM2–PPARα axis contributes to fibrogenesis in hepatocytes and hepatic stellate cells. **Methods:** Hepatocytes (NTCP-HepG2, HepAD38) and hepatic stellate cells (LX2) were exposed to supernatants from HepAD38 cells (HBVsup) and/or HIV-infected U937 macrophages or CEMT4 T-cell lines (HIVsup). Fibrotic and metabolic gene expression were assessed by qPCR, and extracellular pyruvate levels were quantified using a colorimetric assay. Combination treatments with pyruvate, TGF-β1, and HIV gp120 protein were performed to evaluate synergistic effects on metabolic and fibrotic responses in NTCP-HepG2 and LX2 cells. TGF-β1 inhibition experiments were performed to evaluate its role in HIV-associated metabolic reprogramming. **Results:** Exposure to HIV-derived supernatants, HIV gp120, or pyruvate each induced expression of glycolytic (GLUT1, PKM2, and LDHA) and profibrotic genes (TGFB1, TIMP1, and COL1A1) and suppressed PPARα expression in NTCP-HepG2 and LX2 cells. HBV/HIV co-infection induced higher expression of these genes than HBV or HIV infection or exposure alone. Combination treatments involving pyruvate, TGF-β1, and HIV gp120 synergistically amplified metabolic and fibrotic responses compared to dual-combination or single-factor treatments. Extracellular pyruvate accumulation increased in cell supernatants under HIV-associated conditions and was further amplified during HBV/HIV co-infection and combination treatments. Treatment with a PPARα agonist reduced glycolytic and profibrotic responses induced by HIV-associated factors, implicating TGF-β1 as a mediator of HIV-associated metabolic reprogramming. **Conclusion:** HIV co-infection exacerbates HBV-induced liver fibrogenesis through TGF-β1-mediated metabolic reprogramming characterized by glycolytic activation, extracellular pyruvate accumulation, and suppression of PPARα signaling. Synergistic interactions between extracellular pyruvate and HIV-associated factors further amplified metabolic and profibrotic responses in NTCP-HepG2 and LX2 cells. These findings suggest that HIV infection enhances HBV-induced metabolic reprogramming and fibrogenesis through a TGF-β1-PKM2-PPARα axis, identifying this pathway as a promising therapeutic target of HBV/HIV-associated liver fibrosis.



Disclosures: Thien Nguyen:Nothing to Disclose, Olivia Mezzetti:Nothing to Disclose, Xiaoqiong Duan:Nothing to Disclose, Shasha Li:Nothing to Disclose, Yongtao Wang:Nothing to Disclose, Zeinab Heidariyan:Nothing to Disclose, Swastika Tripathi:Nothing to Disclose, Shadi Salloum:Nothing to Disclose, Min Xu:Nothing to Disclose, Raymond Chung:Nothing to Disclose, Wenyu Lin:Nothing to Disclose.

4193 | MATHEMATICAL MODELING SUGGESTS HEPLISAV-B INDUCES BLOCKAGE OF INTRACELLULAR HBSAG SYNTHESIS ALONGSIDE REDUCTION OF AAV-HBV

Aarim Khan[1] Louis Shekhtman[2] Adquate Mhlanga[1] Ashish Goyal[1] Jiapeng Wu[3] Lishan Su[3] Harel Dahari[1] James Ahodantin[4], [1]Loyola University Chicago, [2]Loyola University Chicago & Bar Ilan University, [3]Institute of Human Virology, University of Maryland School of Medicine, [4]University of Nebraska Medical Center

Background: Heplisav-B is a newly FDA approved prophylactic 2-dose hepatitis B vaccine with a CpG adjuvant. We recently demonstrated the therapeutic benefits of Heplisav-B in an AAV-HBV mouse model and aim herein to understand the kinetics of serum HBV DNA, HBsAg, HBeAg, and anti-HBs IgG (IgG) using mathematical modeling. **Methods:** Ten AAV-HBV infected mice were included. Heplisav-B was administered to 6 mice at weeks 4 and 8. Blood samples were collected every 2-4 weeks until the end

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of the experiment (EOE) at week 25 as described in (PMID: 41889877). The modes of action (MOA) of Heplisav-B were modelled by a reduction in virus template AAV-HBV levels (MOA 1), an increase in IgG synthesis (MOA 2), and a reduction in intracellular HBsAg synthesis (MOA 3). **Results:** In the unvaccinated agglomerate mouse, the model recapitulated the observed increase and plateau in serum HBV-DNA, HBeAg, and HBsAg as well as the observation that IgG remained undetectable (Fig.1A). In the vaccinated agglomerate mouse, observed kinetics were similar to the unvaccinated agglomerate mouse up until vaccination, after which there was a 2.4 log(ge/ml) decrease in serum HBV-DNA by week 8 followed by a subsequent 2.5 log(ge/ml) increase until EOE, a 2.6 log(ng/ml) decline in serum HBsAg by week 8 to below detection that remained until EOE, a 0.3 log(PEIU/ml) decline in serum HBeAg by EOE, and a gradual 3.0 log (U/ml) increase and plateau in IgG until EOE (Fig.1B). Additionally, intracellular HBV-RNA, HBV-DNA, and AAV-HBV were approximately 0.6 log, 1.0 log, and 0.6 log lower, respectively, than in unvaccinated mice at EOE. Modeling predicted that an 80% reduction in AAV-HBV levels (MOA 1) and a 2.5-fold increase in IgG production (MOA 2) were sufficient to capture the kinetics of HBeAg and IgG, as well as the relative decline in intracellular AAV-HBV, HBV-RNA and HBV-DNA, but were insufficient to explain serum HBV DNA and/or HBsAg kinetics without including an initial 99.9% blocking of HBsAg synthesis which gradually decays to 98.5% by EOE (MOA 3). **Conclusion:** Modeling suggests that reduction of AAV-HBV and enhanced anti-HBs IgG production are insufficient to explain the therapeutic effects of Heplisav-B in AAV-HBV–infected mice without assuming potent suppression of intracellular HBsAg synthesis. These findings support a mechanism in which Heplisav-B exerts both antiviral and immunomodulatory effects, leading to sustained HBsAg suppression and partial control of viral replication.

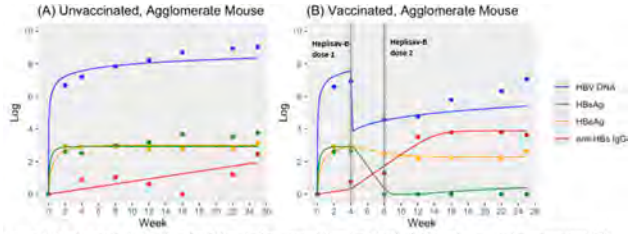


Figure 1. Mathematical modeling (solid lines) of measured kinetics (dots) of the agglomerated unvaccinated **(A)** and vaccinated **(B)** mice. Gray vertical lines indicate 1st and 2nd dose of Heplisav-B vaccine. *HBsAg detection limit is represented by horizontal dotted line.* We assumed in the model that the number of HBV-infected hepatocytes is fixed from infection to EOE. In each infected hepatocyte, three products are produced from AAV-HBV: intracellular HBV RNA, HBsAg, and HBeAg. Within the cell, HBV RNA is converted to HBV DNA, and HBsAg is either converted to HBsAg subviral particles or incorporated into virus-like particles containing HBV RNA or HBV DNA during secretion. Anti-HBs IgG follows a logistic growth model and is cleared when it forms a complex with serum HBsAg, HBV RNA, or HBV DNA. The late rebound in serum HBV DNA despite persistent HBsAg suppression may reflect increased production of naked HBV DNA or defective viral particles, warranting further investigation.

Disclosures: Aarim Khan:Nothing to Disclose, Louis Shekhtman:Nothing to Disclose, Adquate Mhlanga: Nothing to Disclose, Ashish Goyal:Nothing to Disclose, Jiapeng Wu:Nothing to Disclose, Lishan Su:Nothing to Disclose, Harel Dahari:VIR: Advisor, James Ahodantin: Nothing to Disclose.

4194 | ◆ NEOADJUVANT TRIPLE IMMUNE CHECKPOINT BLOCKADE PREVENTS POST-RESECTION RECURRENCE IN MURINE HEPATOCELLULAR CARCINOMA

Lea Lemaitre[1] Siya Agrawal[2] Venika Kakarla[2] Dawiyat Massoudi[2] Ankit Srivastava[2] Renumathy Dhanasekaran[2], [1]Stanford University, [2]Stanford

Background: Recurrence following surgical resection remains the dominant driver of HCC mortality, yet adjuvant immunotherapy benefits only a minority of patients. We hypothesized that residual tumor cells exploit multiple co-occurring immune evasion pathways beyond CTLA4/PD-L1, and that targeting these mechanisms at the right time relative to surgery could prevent recurrence. **Methods:** We established a syngeneic orthotopic immunocompetent mouse model of HCC by implanting Hep53.4 cells directly into the liver, followed by surgical resection of the tumor-bearing lobe to recapitulate post-hepatectomy recurrence. This model enabled head-to-head evaluation of neoadjuvant (pre-resection) and adjuvant (post-resection) ICI delivery in the context of an intact immune system. Xenium spatial transcriptomics profiled 1.4 million liver cells from treated tissues (n = 12; 1.4 million cells). CODEX multiplexed spatial proteomics (54 markers) was applied to HCC patients with post-surgical recurrence (n = 124, n = 1,065,284 cells). Findings were validated in patient-derived organoid co-cultures with autologous $CD8^+$ T cells and monocyte-derived macrophages. **Results:** Standard dual ICI (aPD-L1 + aCTLA-4) failed to reduce post-resection murine HCC recurrence adjuvantly (56% vs. 100%, p = 0.10) or neoadjuvantly (50% vs. 100%, p = 0.18). Xenium analysis revealed that $Havcr2^+$ cells comprised 15.4% of exhausted $CD8^+$ T cells, with 56–77% maintaining Tim-3^+ exhausted $CD8^+$ neighbors expressing Lgals9 within 30µm, in both control and dual-therapy treated groups, identifying Tim-3/Galectin-9 signaling as a persistent resistance mechanism. CODEX confirmed high Tim-3 expression on $CD8^+$ T cells and Tregs in patients with post-surgical recurrence (both pAdj < 0.05). We therefore targeted Tim-3 directly: adjuvant tri-therapy (aPD-L1 + aCTLA-4 + aTim-3) failed to reduce recurrence (89% vs. 100%), whereas neoadjuvant tri-therapy dramatically reduced liver recurrence (38% vs. 100%, p = 0.007), liver metastasis count (mean 1.1 vs. 5.0, p = 0.001), lung metastasis incidence (23% vs. 100%, p = 0.001), and lung

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metastasis count (mean 0.5 vs. 8.6, $p < 0.001$). while preserving functional intratumoral $CD8^+$ T cells. In PDO co-cultures, robust tumor killing required both $CD8^+$ T cells and macrophages, confirming that T cell reinvigoration and macrophage reprogramming cooperate to drive the therapeutic effect. **Conclusion:** We demonstrate that Tim-3/Galectin-9-mediated crosstalk between exhausted $CD8^+$ T cells and pro-tumoral macrophages establishes a critical immunosuppressive niche that standard checkpoint blockade fails to dismantle. By targeting this axis neoadjuvantly, triple checkpoint blockade reshapes the tumor immune microenvironment prior to resection and dramatically reduces recurrence establishing Tim-3 inclusion and treatment timing as co-equal determinants of immunotherapy efficacy in resectable HCC.

Disclosures: Lea Lemaitre:Nothing to Disclose, Siya Agrawal:Nothing to Disclose, Venika Kakarla:Nothing to Disclose, Dawiyat Massoudi:Nothing to Disclose, Ankit Srivastava:Nothing to Disclose, Renumathy Dhanasekaran:Nothing to Disclose.

4195 | ◆ THERAPEUTIC ATTRITION CREATES APPARENT SURVIVAL ADVANTAGES IN DELAYED SYSTEMIC THERAPY FOR HEPATOCELLULAR CARCINOMA

Francisco Vargas-Navarro[1] Wagner Ramirez[1] María Fernanda Lynch Mejía[1] Daniel Pérez-Muñoz[2] Fiorella Ajún-Ulate[2] Andrés Solera-Vega[2] Silvia Alfaro Cartín[3] Karen Melissa Rodríguez Masís[3] Dennis Brenes Redondo[4] Pablo Coste[5], [1]Liver Unit, Hospital R.A. Calderón Guardia / LiverLab CR, [2]Liver Unit, Hospital R.A. Calderón Guardia, [3]Department of Oncology, Hospital Dr. Rafael Ángel Calderón Guardia, [4]Department of Oncology, Hospital Dr. Max Peralta Jiménez, [5]Liver Unit, Hospital Dr. Rafael Ángel Calderón Guardia / LiverLab CR

Background: Delayed transition from locoregional to systemic therapy is common in hepatocellular carcinoma (HCC), yet its clinical implications remain controversial due to survivor and time-zero biases. We evaluated therapeutic attrition, timing of systemic therapy initiation, and survival outcomes in a real-world HCC cohort from Central America. **Methods:** We conducted a multicenter real-world longitudinal cohort study including consecutive adults with confirmed HCC managed across two tertiary referral centers between 2018 and 2024. Therapeutic trajectories were reconstructed longitudinally. Transition to systemic therapy (sorafenib or atezolizumab-bevacizumab) was classified as early (first or second treatment) or delayed (≥ 2 prior treatments). Overall survival (OS) was analyzed both from HCC diagnosis and from systemic therapy initiation using Kaplan-Meier and Cox proportional hazards models adjusted for ALBI grade, ECOG performance status, and BCLC stage. **Results:** Among 260 patients with HCC, 184 (70.8%) received active treatment, 111 (42.7%) underwent multiple therapeutic interventions, but only 50 (19.2%) ultimately reached systemic therapy, demonstrating substantial therapeutic attrition. Thirty-five patients (70%) transitioned early and 15 (30%) underwent delayed transition. When OS was measured from systemic therapy initiation, survival did not differ between groups (log-rank $p = 0.77$). However, when OS was measured from HCC diagnosis, delayed transition was associated with longer survival (log-rank $p = 0.003$; adjusted HR 0.40, $p = 0.019$), consistent with survival time-zero and survivor selection biases. **Conclusion:** Therapeutic attrition substantially limits access to systemic therapy in real-world HCC care. Apparent survival advantages associated with delayed transition primarily reflect survival time-zero and survivor biases, cautioning against naïve interpretation of survival analyses in treatment sequencing studies.

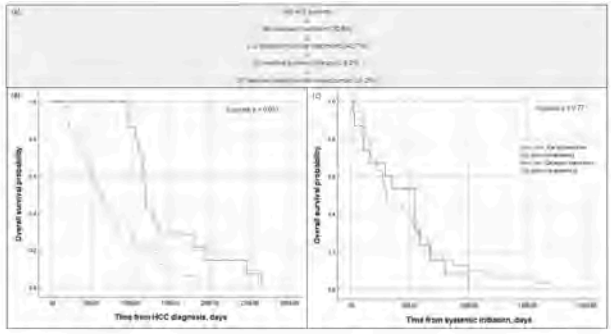


Figure 1. Therapeutic attrition and survival time-zero definition bias in real-world hepatocellular carcinoma. (A) Therapeutic attrition cascade across the HCC care pathway. Among 260 patients with HCC, 184 (70.8%) received active treatment, 111 (42.7%) underwent multiple therapeutic interventions, 50 (19.2%) ultimately reached systemic therapy, and 37 (14.2%) received atezolizumab-bevacizumab. (B) Kaplan-Meier estimates of overall survival from HCC diagnosis according to timing of transition to systemic therapy. Patients undergoing delayed transition (≥2 prior treatments) appeared to have longer survival than those initiating systemic therapy early (≤1 prior treatment) (log-rank p = 0.003). (C) Kaplan-Meier estimates of overall survival from systemic therapy initiation according to timing of transition. No significant survival differences were observed between early and delayed transition groups (log-rank p = 0.77). Together, these findings illustrate the impact of therapeutic attrition and survival time-zero bias in real-world HCC analyses

Disclosures: Francisco Vargas-Navarro:Nothing to Disclose, Wagner Ramirez:Nothing to Disclose, María Fernanda Lynch Mejía:Nothing to Disclose, Daniel Pérez-Muñoz:Nothing to Disclose, Fiorella Ajún-Ulate:Nothing to Disclose, Andrés Solera-Vega:Nothing to Disclose, Silvia Alfaro Cartín:Nothing to Disclose, Karen Melissa Rodríguez Masís:Nothing to Disclose, Dennis Brenes Redondo:Nothing to Disclose, Pablo Coste:Nothing to Disclose.

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4196 | ◆ SPATIAL INTERACTION BETWEEN PD-L1(+) TUMOR-ASSOCIATED MACROPHAGES AND CD8(+) T CELLS INFLUENCES RESPONSE TO ATEZOLIZUMAB PLUS BEVACIZUMAB IN HEPATOCELLULAR CARCINOMA

Takuto Nosaka[1] Tatsushi Naito[2] Junki Yamashita[1] Yosuke Murata[1] Yu Akazawa[1] Tomoko Tanaka[1] Kazuto Takahashi[1] Yasunari Nakamoto[1], [1]University of Fukui, [2]University of Fuku

Background: Intercellular interactions among immune cells play an important role in combination immunotherapy for hepatocellular carcinoma (HCC). We previously reported that PD-L1(+) tumor-associated macrophages (TAMs) regulate antitumor immune responses (Neoplasm 2025). In this study, we analyzed the spatial proximity between PD-L1(+) TAMs and CD8(+) T cells in pretreatment liver tumor biopsy specimens from patients with HCC and examined its association with the therapeutic efficacy of systemic treatments, including atezolizumab plus bevacizumab (Atezo+Bev) and lenvatinib. In addition, we evaluated the underlying molecular and cellular pathology using next-generation sequencing (NGS) analysis. **Methods:** Multiplex immunohistochemistry was performed on biopsies from patients treated with Atezo+Bev (n = 23) or lenvatinib (n = 20). An interaction variable was defined via nearest-neighbor analysis as CD8(+) T cells within 25 μm of PD-L1(+) TAMs, normalized to cell counts. Associations with tumor shrinkage and progression-free survival (PFS) were examined. CD8(+) T cell phenotypes were evaluated via GZMB and TIM3. Transcriptomic profiling of resected HCCs was conducted using next-generation sequencing and gene set enrichment analysis (GSEA). Predictive performance was assessed using ROC analysis. Internal validation of the predictive model was performed using bootstrap resampling to estimate optimism-corrected discriminatory performance. **Results:** In Atezo+Bev-treated patients, multivariate analysis identified the PD-L1(+) TAM–CD8(+) T cell interaction variable as an independent factor associated with PFS (HR = 0.8373; 95% CI, 0.6870–0.9773; $p < 0.05$), together with vascular invasion (HR = 4.252). The median nearest-neighbor distance from PD-L1(+) TAMs to CD8(+) T cells was shorter in tumors with shrinkage than in those with progression (14 μm vs. 24 μm). ROC analysis for discriminating PFS > 1 year showed an apparent AUC of 0.881 for the interaction variable. This association was absent in the lenvatinib cohort. High-interaction tumors showed increased proportions of GZMB(+) and TIM3(+) CD8(+) T cells. Transcriptomic analysis revealed upregulation of inflammatory, cytotoxic, chemotactic, and immunoregulatory genes (TIGIT and LAG3), with enrichment of chemokine (CXCL9), IFN-gamma, and IL-10 signaling pathways. **Conclusion:** Spatial proximity between PD-L1(+) TAMs and CD8(+) T cells defines an immune niche characterized by coexisting immune activation and regulatory programs and is strongly associated with Atezo+Bev responsiveness in HCC. These findings suggest that this spatial proximity reflects the immune pathobiology of HCC and may serve as a promising tissue biomarker for predicting responses to combination immunotherapy. **Disclosures:** Takuto Nosaka:Nothing to Disclose, Tatsushi Naito:Nothing to Disclose, Junki Yamashita:Nothing to Disclose, Yosuke Murata:Nothing to Disclose, Yu Akazawa:Nothing to Disclose, Tomoko Tanaka:Nothing to Disclose, Kazuto Takahashi:Nothing to Disclose, Yasunari Nakamoto:Nothing to Disclose.

4197 | ◆ PRE-TREATMENT PERIPHERAL BLOOD MONONUCLEAR CELL ANGIOGENESIS-RELATED SIGNATURE IS ASSOCIATED WITH SPP1-POSITIVE MACROPHAGES IN HEPATOCELLULAR CARCINOMA

Satoshi Narahara[1] Hiromitsu Ohbo[1] Takahiro Mizuta[1] Toshinori Toyota[1] Daiki Maeda[1] Kentaro Tanaka[1] Hiroki Inada[1] Sotaro Kurano[1] Yoko Yoshimaru[1] Takehisa Watanabe[1] Katsuya Nagaoka[1] Hiroko Setoyama[1] Haruki Uojima[1] Yasuhito Tanaka[1], [1]Department of Gastroenterology and Hepatology, Faculty of Life Sciences, Kumamoto University

Background: Atezolizumab plus bevacizumab (Atezo+Bev) is widely used for advanced hepatocellular carcinoma (HCC); however, reliable biomarkers predicting treatment response before therapy initiation remain unclear. We investigated pre-treatment peripheral blood mononuclear cells (PBMCs), paired liver tumor biopsy samples, and surgical specimens to identify biomarkers associated with response to Atezo+Bev. **Methods:** Among 119 patients with advanced HCC who received Atezo+Bev as first-line therapy between November 2018 and December 2025, 30 patients with available pre-treatment PBMC samples and adequate follow-up were enrolled. Initial therapeutic response was assessed by mRECIST and patients were classified into responders (complete response [CR]/partial response [PR]) and non-responders (stable disease [SD]/progressive disease [PD]). RNA sequencing of pre-treatment PBMCs was performed. To evaluate intratumoral localization of gene expression, spatial transcriptomic analysis using the Visium platform was additionally conducted on liver tumor specimens. **Results:** Gene set enrichment analysis of pre-treatment PBMCs demonstrated significant enrichment

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of angiogenesis-related gene sets in non-responders compared with responders (NES = 1.63, FDR q < 0.05). Leading-edge analysis further identified a coordinated gene program associated with angiogenesis, extracellular matrix remodeling, and myeloid cell biology, with SPP1 emerging as a central component of this resistance-associated signature. Spatial transcriptomic analysis of HCC tissues revealed heterogeneous intratumoral distribution of angiogenesis-related signatures, with prominent enrichment at the tumor margin. Importantly, regions with high angiogenesis-related signatures showed spatial overlap with macrophage-enriched areas. SPP1 expression was spatially co-localized with CD68-positive macrophage-rich regions, indicating the accumulation of SPP1-positive TAM-like myeloid populations within pro-angiogenic tumor niches. These findings suggest that the angiogenesis-related PBMC signature observed in non-responders reflects, at least in part, a systemic myeloid program linked to pro-angiogenic and immunosuppressive tumor microenvironments. **Conclusion:** Pre-treatment PBMCs from non-responders exhibited an SPP1-centered angiogenesis-associated myeloid program that was spatially linked to intratumoral accumulation of SPP1-positive TAM-like cells at the tumor margin. These findings identify a previously unrecognized blood–tumor axis associated with resistance to atezolizumab plus bevacizumab in HCC.

Disclosures: Satoshi Narahara:Nothing to Disclose, Hiromitsu Ohbo:Nothing to Disclose, Takahiro Mizuta: Nothing to Disclose, Toshinori Toyota:Nothing to Disclose, Daiki Maeda:Nothing to Disclose, Kentaro Tanaka:Nothing to Disclose, Hiroki Inada:Nothing to Disclose, Sotaro Kurano:Nothing to Disclose, Yoko Yoshimaru:Nothing to Disclose, Takehisa Watanabe: Nothing to Disclose, Katsuya Nagaoka:Nothing to Disclose, Hiroko Setoyama:Nothing to Disclose, Haruki Uojima:Nothing to Disclose, Yasuhito Tanaka:Nothing to Disclose.

4198 | ◆ COMPOSITE SCORE FROM A MULTI-TARGET HCC BLOOD TEST REFLECTS TUMOR SIZE AND STAGE IN THE ALTUS STUDY

Binu John[1] Mark Camardo[2] Amit Singal[3] Neehar Parikh[4] Ju Dong Yang[5] Lewis Roberts[6] Natasha Kureshi[2] Paul Elias[2] Elle Kielar-Grevstad[2] Paul Limburg[2], [1]University of Miami and Miami VA, [2]Abbott, Madison, WI, [3]Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, [4]University of Michigan Medical Center, [5]Cedars-Sinai Medical Center, [6]Mayo Clinic Rochester

Background: A multi-target hepatocellular carcinoma (HCC) blood test (mt-HBT) generates a continuous composite score from methylated DNA, AFP, and patient sex to aid in HCC detection in adults with cirrhosis or chronic HBV, with a score ranging from 0 to 1 and a 0.2255 positivity cutoff. While mt-HBT binary performance has been reported, associations between composite score and tumor burden, LI-RADS category, and liver disease etiology and severity have not been characterized. **Methods:** ALTUS was a prospective, multicenter U.S. study in which 2,463 adults underwent HCC surveillance and concurrent mt-HBT testing. Participants were classified by central CT/MRI review as HCC (LR-5, LR-TIV), indeterminate (LR-3, LR-4, LR-M), or non-HCC (LR-neg, LR-1, LR-2). Associations between composite score and tumor size, number, and stage (Milan, BCLC) were assessed for HCCs via Spearman correlation, tertile analysis, and interaction regression. Composite score was modeled against LI-RADS category for the full cohort (40 HCC, 157 indeterminate, 2,266 non-HCC) and against disease severity (ALBI) and etiology among non-HCCs. **Results:** Composite score was strongly correlated with tumor size ($\rho = 0.63$) but not tumor number. Scores in the largest tumor size tertile (median 4.25 cm) were significantly higher ($p = 0.002$, Fig 1a) than those in the lowest tertile (median 1.54 cm). Scores were significantly higher for HCCs outside Milan versus within Milan ($p = 0.003$, Fig 1b), while the effect of BCLC stage was not significant ($p = 0.06$). Milan status modified the tumor size effect, with each 1-cm increase within Milan associated with a score increase of 0.24 (95% CI, 0.12–0.37), compared to 0.02 (-0.07–0.11) per cm outside Milan. Scores increased stepwise with LI-RADS category (Fig 1c, $p < 0.001$), with LR-3s and LR-4s having higher mean scores than non-HCCs and lower mean scores than LR-Ms, LR-5s, and LR-TIVs. ALBI score correlated weakly ($\rho = 0.11$) with composite score among non-HCCs (Fig 1d). Scores were marginally higher in non-viral etiology versus viral etiology (0.02 difference; 95% CI, 0.0005–0.03; $p = 0.04$). **Conclusion:** mt-HBT composite score correlated with tumor size, Milan status, and LI-RADS category, while disease etiology and severity had little impact on score variability. Indeterminate observations had scores between non-HCCs and LR-5s, likely reflecting some prevalent HCCs. These data support interpretation of the composite score as a quantitative measure of tumor-related factors rather than background liver disease.

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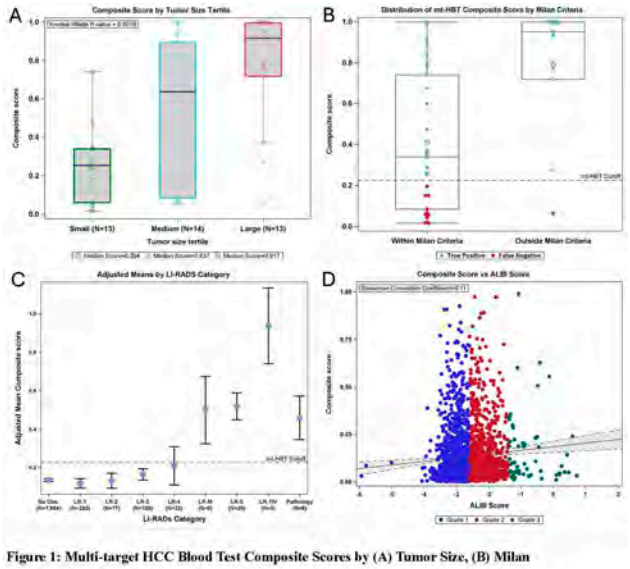


Figure 1: Multi-target HCC Blood Test Composite Scores by (A) Tumor Size, (B) Milan Status, (C) LI-RADS Category, and (D) ALBI Score.

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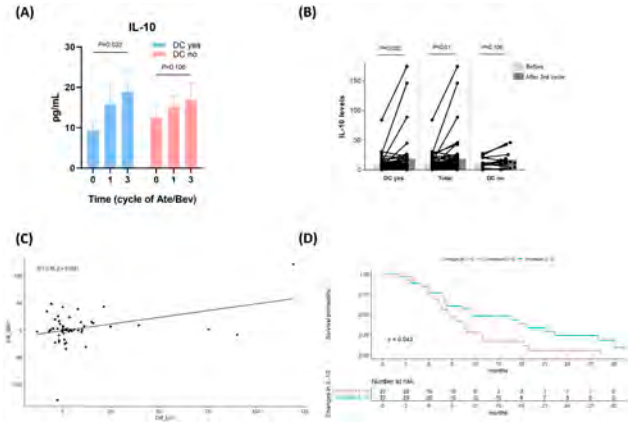
4199 | ◆ LONGITUDINAL ELEVATION OF IL-10 FOLLOWING ATEZOLIZUMAB PLUS BEVACIZUMAB IS ASSOCIATED WITH FAVORABLE RESPONSE AND SURVIVAL IN ADVANCED HEPATOCELLULAR CARCINOM

Hee Sun Cho[1] Soon Kyu Lee[1] Soon Woo Nam[1] Jung Hyun Kwon[1], [1]The Catholic University of Korea

Background: We previously reported that early increases in interleukin-10 (IL-10) and tumor necrosis factor-α (TNF-α) levels following atezolizumab plus bevacizumab (Ate/Bev) therapy predict survival in patients with advanced hepatocellular carcinoma (HCC). In this study, we aimed to longitudinally assess serial cytokine changes and evaluate their association with outcome in advanced HCC patients receiving Ate/Bev. **Methods:** We prospectively enrolled 154 consecutive patients with advanced HCC who were treated with Ate/Bev between July 2022 and June 2025. Of these, 54 patients who provided blood samples at three time points—before initiation of Ate/Bev, prior to the second cycle, and prior to the fourth cycle—were included in the cytokine analysis. Serum levels of IL-2, IL-6, IL-10, IL-12, IL-17, interferon-γ (IFN-γ), and TNF-α were measured at each time point, and temporal changes in cytokine levels were examined. The primary endpoint was overall survival, while secondary endpoints included treatment response. **Results:** During a mean follow-up of 11.4 months, 42 patients (77.7%) died. The median age was 66.0 years, with most patients being male (92.6%), and the predominant etiology was viral-related HCC (85.2%). Serial changes in IL-2, IL-6, IL-12, IL-17, IFN-γ, and TNF-α levels were not significantly associated with overall survival. In contrast, IL-10 levels significantly increased following

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Ate/Bev treatment (p = 0.01), particularly among patients who achieved disease control (p = 0.022) (Figure A, B). Changes in IL-10 levels were positively correlated with changes in the CRP levels (r = 0.38, p = 0.004) (Figure C). Notably, patients exhibiting an increase in IL-10 levels demonstrated significantly better survival compared with those showing a decrease (p = 0.042) (Figure D). In multivariable analysis, an increase in IL-10 levels and CRP levels remained an independent predictor of overall survival in advanced HCC patients treated with Ate/Bev. **Conclusion:** Our findings suggest that serial changes in cytokine levels—particularly IL-10—following Ate/Bev therapy may serve as a useful biomarker for monitoring treatment response and predicting clinical outcomes in patients with advanced HCC.

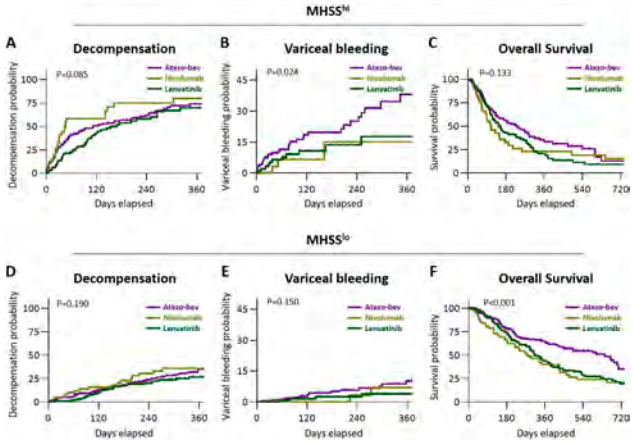


Disclosures: Hee Sun Cho:Nothing to Disclose, Soon Kyu Lee:Nothing to Disclose, SOON WOO NAM: Nothing to Disclose, Jung Hyun Kwon:Nothing to Disclose.

4200 | ◆ MACHINE LEARNING BASED HEPATIC SAFETY SCORE PREDICTS DECOMPENSATION IN HEPATOCELLULAR CARCINOMA SYSTEMIC THERAPY

Ji Won Han[1] Jaejun Lee[2] Keungmo Yang[2] Kwon Yong Tak[2] Hyun Yang[2] Si Hyun Bae[2] Hee Sun Cho[2] Heechul Nam[2] Chang Wook Kim[3] Haelim Lee[2] Hee Yeon Kim[2] Sung Won Lee[2] Ahlim Lee[2] Do Seon Song[2] Seok-Hwan Kim[2] Myeong Jun Song[2] Soon Woo Nam[2] Soon Kyu Lee[2] Soon Kyu Lee[2] Jung Hyun Kwon[2] Pil Soo Sung[2] Jeong Won Jang[2], [1]The Catholic University of Korea, Seoul St. Mary's Hospital, [2]The Catholic University of Korea, [3]Uijeongbu St. Mary's Hospital

Background: Hepatocellular carcinoma (HCC) frequently coexists with portal hypertension, significantly increasing the risk of hepatic decompensation (HD) and variceal bleeding during systemic therapy. **Methods:** We developed a machine learning based hepatic safety score (MHSS) using data from 2,026 patients with unresectable HCC to predict clinically significant portal hypertension (CSPH) and prognosis. A random forest model was trained in a derivation cohort (n = 1,262) and validated in an independent cohort (n = 764). **Results:** The MHSS demonstrated robust performance (AUROC 0.840) in CSPH and predicting HD. Stratification revealed that high MHSS patients faced significantly elevated risks of HD (HR 3.25), variceal bleeding (VB, HR 4.90), and mortality (HR 2.21). Crucially, while atezolizumab-bevacizumab offered a survival advantage in low MHSS patients, it was associated with high bleeding risk and no survival benefit in the high MHSS group compared to other regimens. A simulation of MHSS guided treatment selection demonstrated a 24% reduction in HD, a 40% reduction in VB, and a 26% reduction in mortality. **Conclusion:** In conclusion, the MHSS effectively predicts CSPH, decompensation, and survival in patients with HCC prior to systemic therapy. By enabling individualized risk stratification, the MHSS may guide personalized treatment selection between bevacizumab-containing and alternative regimens, ultimately improving patient outcomes.



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★ 4201 | ◆ WNT/β-CATENIN–MUTATED HCC: PATHWAY-LEVEL PROFILE AND GENE-LEVEL HETEROGENEITY DEFINING DISTINCT SUBTYPES

Pegah Farrokhi[1] David Stenehjem[1], [1]University of Minnesota

Background: WNT/β-catenin pathway mutations occur in 25–40% of hepatocellular carcinoma (HCC) and are associated with an immune-excluded phenotype and variable response to immune checkpoint inhibitors (ICI), though the magnitude and consistency of this association across patient subgroups remain debated. Clinical characteristics, co-mutation architecture, and biological heterogeneity within the WNT pathway lack comprehensive characterization at a multi-cohort level. **Methods:** We performed integrated clinicogenomic analysis of 1,785 advanced or metastatic HCC patients from the AACR Project GENIE registry across 8 institutional cohorts. WNT alterations were defined as somatic mutations in *CTNNB1, AXIN1, APC, CREBBP, or GSK3B*. TMB-high was defined as ≥10 mut/Mb. Fractional genome alteration (FGA) and somatic mutation count distinguished mutation-load vs. copy-number-driven TMB differences. **Results:** WNT mutations occurred in 40.8% of patients (*CTNNB1* 27.9%, *AXIN1* 8.4%, *APC* 4.7%). *CREBBP* and *GSK3B* sample sizes were too small to analyze. At the pathway level, WNT-mutated patients were significantly older (median 63 vs. 59 years), predominantly male (85.6% vs. 74.8%), with lower serum AFP ($p = 0.04$); viral etiology and cirrhosis were similar. Tumors were microsatellite stable.WNT-mutated HCC showed significant negative co-occurrence with *TP53* (OR = 0.63) and positive with *TERT* (OR = 1.57), *ARID1A* (OR = 1.80), and *CDKN2A* (OR = 2.38). They had significantly higher mutation counts (median 82 vs.62) and higher TMB-high rates (5.8% vs.1.5%) without an FGA increase (0.21 vs. 0.22), reflecting increased somatic mutation load over chromosomal instability.Gene-level analysis revealed pronounced heterogeneity within the pathway. *CTNNB1* and *AXIN1* rarely co-mutated (OR = 0.29; FDR < 0.01).*CTNNB1* mutation was the main driver of the pathway-level phenotype: low AFP, better differentiation (71.1% vs. 44.2%, $p < 0.01$), *TP53* negative co-occurrence (OR = 0.48, $p < 0.01$), *TERT* and *CDKN2A* co-occurrence, and TMB-high enrichment (6.0% vs. 2.2%, $p < 0.01$).*AXIN1*-mutated HCC had significantly higher AFP (≥400 ng/mL: 37.5% vs. 19.6%), elevated PIVKA-II, higher FGA (0.3 vs. 0.2) indicating instability, *ARID1A* co-occurrence, and no TMB elevation ($p = 0.20$).*APC*-mutated tumors had the highest mutation burden (median 108 vs. 70; $p < 0.01$), highest TMB-high rate (10.8% vs. 2.9%; $p < 0.01$), and *PTEN* co-occurrence. **Conclusion:** WNT/β-catenin–mutated HCC is a distinct subset; older age, male predominance, low AFP, *TP53* mutual exclusivity, and mutation-load–driven TMB elevation without chromosomal instability. Whether this elevated TMB translates to clinical immunogenicity warrants prospective evaluation given conflicting ICI response data. Importantly, the pathway is internally heterogeneous: *CTNNB1* drives the TMB-elevated, well-differentiated phenotype, while *AXIN1* defines a chromosomal-instability–driven, high-AFP subtype.

Disclosures: Pegah Farrokhi:AstraZeneca: Grant/Research Support, David Stenehjem:Nothing to Disclose.

4202 | ◆ PERI-TREATMENT ANTIBIOTIC EXPOSURE AND SURVIVAL IN HEPATOCELLULAR CARCINOMA PATIENTS RECEIVING IMMUNE CHECKPOINT INHIBITORS: A LARGE REAL-WORLD PROPENSITY-MATCHED COHORT STUDY

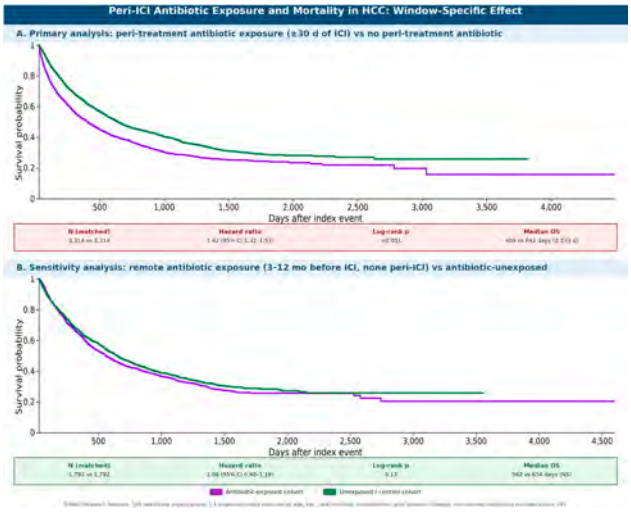
Mazen Elsheikh[1] Hamza Salim[2] Osamah Salim[3] Sherry Fares[1] Karim Adhem[1] Mohamad Ali Ibrahim[1] Chandni Bhagtaney[1] Angela Aguilar[1] Ximena Ramirez Morales[1] Prasun Jalal[1], [1]Baylor College of Medicine, [2]Department of Gastroenterology and Hepatology, University of Texas Medical Branch, Galveston, TX, [3]Sam Houston State University College of Osteopathic Medicine

Background: Immune checkpoint inhibitors (ICIs) are standard of care for advanced hepatocellular carcinoma (HCC), yet only a minority of patients derive durable benefit. Antibiotics disrupt the gut microbiome and have been linked to reduced ICI efficacy across malignancies, but prior HCC studies produced conflicting results and were underpowered. We examined whether antibiotic exposure within ±30 days of ICI initiation is associated with mortality in HCC patients. To test the gut-microbiome hypothesis, we also assessed whether remote antibiotic exposure, long before ICI, carried the same risk. **Methods:** We conducted a propensity-score-matched retrospective cohort study using the TriNetX Research Network (109 healthcare organizations). Adults with HCC (ICD-10 C22.0) who received any ICI (nivolumab, pembrolizumab, ipilimumab, atezolizumab, durvalumab, tremelimumab, tislelizumab, or toripalimab) on or after HCC diagnosis were included, with first ICI as the index event. Exposed patients received at least one systemic antibiotic (10 drug classes) within ±30 days of index; unexposed patients received none. Groups were matched 1:1 on demographics,

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cirrhosis, comorbidities (diabetes, COPD, alcohol-related disorders), prior systemic therapy (sorafenib, lenvatinib, regorafenib, cabozantinib), microbiome-modulating co-medications (rifaximin, proton pump inhibitors), and alpha-fetoprotein ≥400 ng/mL. Outcomes were counted from 30 days after index to avoid immortal-time bias. To confirm any harm was specific to the peri-treatment window, a pre-specified sensitivity analysis compared patients who received antibiotics 3 to 12 months before ICI, but none within ±30 days, against patients with no recent antibiotics. The primary outcome was all-cause mortality (Kaplan-Meier, Cox proportional hazards). **Results:** After matching, 3,314 exposed patients were compared with 3,314 unexposed controls (all standardized differences <0.05). Peri-treatment antibiotic exposure was associated with significantly increased mortality (HR 1.42, 95% CI 1.32–1.53; log-rank p<0.001); median overall survival was 409 versus 642 days (Δ 233 days). In the sensitivity analysis (1,792 vs 1,792 matched), remote antibiotic exposure showed no significant survival difference versus antibiotic-unexposed controls (HR 1.08, 95% CI 0.98–1.19; log-rank p=0.13). The 95% CIs of the two analyses did not overlap. **Conclusion:** In the largest real-world HCC ICI cohort to date (6,628 matched), antibiotic exposure at ICI initiation was associated with a 42% increased hazard of death, whereas exposure 3 to 12 months earlier was not. This window-specific harm argues against confounding by patient frailty and supports a microbiome-mediated interaction with ICI efficacy, favoring antibiotic stewardship at ICI initiation in HCC.



Disclosures: Mazen Elsheikh:Nothing to Disclose, Hamza Salim:Nothing to Disclose, Osamah Salim: Nothing to Disclose, Sherry Fares:Nothing to Disclose, Karim Adhem:Nothing to Disclose, Mohamad Ali Ibrahim:Nothing to Disclose, Chandni Bhagtaney:Nothing to Disclose, Angela Aguilar:Nothing to Disclose, Ximena Ramirez Morales:Nothing to Disclose, Prasun Jalal:Mallinckrodt Pharmaceuticals: Advisor, Madrigal: Grant/Research Support, Ipsen: Grant/Research Support, mirum: Advisor.

★ 4203 | ◆ SERIAL MONITORING OF CIRCULATING TUMOR CELLS REFLECTS TREATMENT RESPONSE ACROSS SYSTEMIC THERAPIES IN UNRESECTABLE HEPATOCELLULAR CARCINOMA

Yosuke Murata[1] Takuto Nosaka[1] Yu Akazawa[1] Tomoko Tanaka[1] Tatsushi Naito[1] Kazuto Takahashi[1] Yasunari Nakamoto[1], [1]University of FUKUI

Background: The strategy of systemic therapy for hepatocellular carcinoma (HCC) has changed with the introduction of immune checkpoint inhibitors. However, clinically useful biomarkers for treatment response remain limited and mechanisms of disease progression have not been fully elucidated. Circulating tumor cells (CTCs) are a form of liquid biopsy that offers a noninvasive approach and is expected to serve as a biomarker for treatment response and to reveal mechanisms of disease progression. We serially collected CTCs from patients with HCC undergoing Atezolizumab plus Bevacizumab (AB), Durvalumab plus Tremelimumab (DT) and Lenvatinib (LEN). Changes in molecular profiles of CTCs were analyzed to assess clinical utility of CTCs for treatment response and investigate mechanisms of disease progression. **Methods:** We obtained 5 mL of peripheral blood from 63 patients with HCC treated by systemic therapy. CTCs were isolated with RosetteSep Human CD45 Depletion Cocktail and enriched cells were stained with monoclonal antibodies targeting Pan-CK and CD45. CD45(-) and Pan-CK(+) cells were defined as CTCs by flow cytometry with FACSAria II. CTC-derived RNA of patients (AB/DT/LEN:16/7/10) was analyzed by 373-gene targeted RNA sequencing with next-generation sequencing (NGS). Gene set enrichment analysis was also performed. **Results:** Baseline CTC counts were higher in patients with advanced-stage disease, including elevated DCP, multiple tumors, vascular invasion, and distant metastasis. At response evaluation, CTC counts decreased in responders in each treatment group (p<0.05). ROC analysis showed that CTC count changes had a higher predictive value for treatment response (AUC=0.837) than AFP and DCP. In 373-gene NGS analysis, baseline CTCs of patients with aggressive tumor features, including vascular invasion or high CTC counts, showed increased expression of cancer progression-related genes, CDKN2B and BCL2L1 (p<0.05). Unsupervised hierarchical clustering classified patients into responders and non-responders in each treatment group, and responders showed longer PFS (p<0.05). Pathway analysis revealed that TGF-β signaling was upregulated in non-responders to AB and LEN during the clinical course, whereas interferon signaling was

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upregulated in non-responders to DT ($p < 0.05$). Furthermore, baseline expression of TGF-β signaling-related genes, CRABP2 and PDGFRB was higher in non-responders to AB treatment ($p < 0.05$). **Conclusion:** In systemic therapy for HCC, CTC counts more accurately and sensitively reflect changes in tumor burden than existing biomarkers. Gene expression analysis suggested that different pathways, such as TGF-β and interferon signaling, are associated with treatment resistance depending on the therapy. Molecular profiling of CTCs may serve as a useful biomarker for monitoring treatment response and elucidating the underlying mechanisms of disease progression in systemic therapy for HCC.

Disclosures: Yosuke Murata:Nothing to Disclose, Takuto Nosaka:Nothing to Disclose, Yu Akazawa: Nothing to Disclose, Tomoko Tanaka:Nothing to Disclose, Tatsushi Naito:Nothing to Disclose, Kazuto Takahashi:Nothing to Disclose, Yasunari Nakamoto: Nothing to Disclose.

4204 | ◆ NECROSIS-BIOLOGY DISCORDANCE IN HEPATOCELLULAR CARCINOMA LOCOREGIONAL THERAPY PRIOR TO LIVER TRANSPLANTATION

Keri Zhou[1] Devi Veeramgari[1] Yonatan Kaplan[1] Madeline Chiang[1] Aashrith Madagiri[1] Sami Ali[1] Daisuke Imai[2] Yuzuru Sambommatsu[2] Vinay Kumaran[2] Muhammad Saeed[2] Aamir Khan[2] Amit Sharma[2] Adrian Cotterell[2] Hannah Lee[3] David Bruno[2] Seung Lee[2], [1]Virginia Commonwealth University School of Medicine, [2]Virginia Commonwealth University Hume-Lee Transplant Center, [3]Virginia Commonwealth University

Background: Pathologic tumor necrosis after locoregional therapy (LRT) is commonly used to estimate prognosis in hepatocellular carcinoma (HCC) prior to liver transplantation. High necrosis is traditionally interpreted as a favorable prognostic sign, reassuring clinicians and guiding post-transplant surveillance. However, whether favorable necrosis can be overridden by adverse tumor biology remains poorly understood. **Methods:** This retrospective cohort study included 243 patients with HCC who underwent LRT prior to liver transplantation. Patients were stratified into four groups based on concordance between pathologic tumor necrosis on explant and tumor biology: Group 1 (Concordant Low Risk; high necrosis/good biology), Group 2 (Hidden High Risk; high necrosis/adverse biology), Group 3 (Biology-Reassured; low necrosis/good biology), and Group 4 (Concordant High Risk; low necrosis/adverse biology). High necrosis was defined as $>= 90\%$ on explant pathology. Adverse biology was defined by the presence of any of the following: AFP non-response after LRT, post-LRT AFP > 20 ng/mL, MVI on explant pathology, or poor tumor grade (Grade 3 or 4). The primary outcome was recurrence-free survival (RFS), defined as time to recurrence or death. Secondary outcomes included early RFS failure ($<= 24$ months) and extrahepatic involvement at first recurrence. Between-group differences were assessed using chi-square tests. Multivariable Cox proportional hazards and binary logistic regression modeled outcomes, adjusting for tumor diameter, MVI, and AFP response. An additive biology score (0-4) tested dose-response relationships. Kaplan-Meier curves were compared by log-rank test. **Results:** RFS event rates differed significantly across discordance groups ($\chi^2 = 13.48$, $p = 0.004$). Group 2 demonstrated a 31.7% event rate versus 17.6% in Group 1. This held after adjusting for other risk factors including tumor size and MVI. Early failure within 24 months occurred in 15.0% of Group 2 patients versus 8.2% in Group 1 (OR 2.41, 95% CI 1.09–5.32, $p = 0.030$). Group 2 had higher odds of extrahepatic spread at first recurrence compared to Group 1 (OR 3.55, 95% CI 1.02–12.3, $p = 0.046$). Survival curves separated significantly ($p = 0.012$): median RFS was not reached in Group 1, 68.4 months for Group 2, and 18.2 months for Group 4. **Conclusion:** Adverse tumor biology significantly mitigates the protective signal of necrosis. Patients with discordant high necrosis but poor biology are misclassified as low-risk under necrosis-based criteria alone and experience recurrence at twice the expected rate. These findings support integrating biological markers alongside necrosis assessment to improve post-transplant surveillance stratification in HCC.

Table: Comparison of Post-Transplant Outcomes by Necrosis-Biology Discordance Group

Outcome Measure	Group 1: Concordant Low Risk (High Necrosis/Good Biology)	Group 2: Hidden High Risk (High Necrosis/Adverse Biology)	Statistical Comparison (Group 2 vs. Group 1)
RFS Event Rate (Recurrence/Death)	17.6%	31.7%	chi-sq = 13.48; p = 0.004
Early RFS Failure (<=24 mo)	8.2%	15.0%	OR 2.41 (1.09–5.32); p = 0.030
Extrahepatic Spread at Recurrence	Reference	3.4x higher odds	OR 3.55 (1.02–12.3); p = 0.046
Median RFS (Months)	Not Reached	68.4	Log-rank p = 0.012
Biology Dose-Response	–	–	Biology Score (0-4) significant

Disclosures: Keri Zhou:Nothing to Disclose, Devi Veeramgari:Nothing to Disclose, Yonatan Kaplan:Nothing to Disclose, Madeline Chiang:Nothing to Disclose, Aashrith Madagiri:Nothing to Disclose, Sami Ali:Nothing to Disclose, Daisuke Imai:Nothing to Disclose, Yuzuru Sambommatsu:Nothing to Disclose, Vinay

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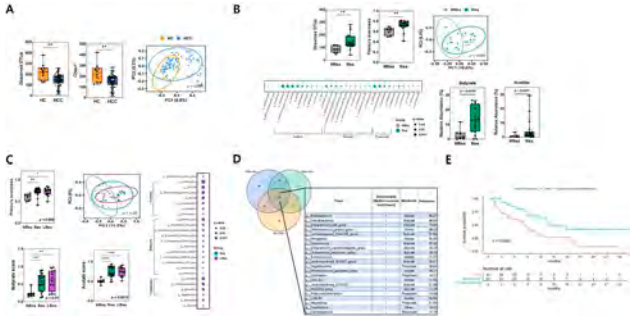
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Kumaran:Nothing to Disclose, Muhammad Saeed: Nothing to Disclose, Aamir Khan:Nothing to Disclose, Amit Sharma:Nothing to Disclose, Adrian Cotterell: Nothing to Disclose, Hannah Lee:Nothing to Disclose, David Bruno:Nothing to Disclose, Seung Lee:Nothing to Disclose.

4205 | ◆ SUSTAINED ENRICHMENT OF BUTYRATE- AND ACETATE-PRODUCING MICROBES IS ASSOCIATED WITH BETTER OUTCOMES TO ATEZOLIZUMAB PLUS BEVACIZUMAB IN ADVANCED HEPATOCELLULAR CARCINOMA

Soon Kyu Lee[1] Juhyeong Ko[2] Joo Yeon Jhun[1] Jung Hyun Kwon[3] Soon Woo Nam[1] Mi-La Cho[1] Yunju Jeong[2] Hye Won Lee[4], [1]College of Medicine, The Catholic University of Korea, [2]Kyung Hee University, [3]The Catholic University of Korea, [4]Yonsei University College of Medicine

Background: We conducted a prospective, multicenter study to identify functional microbial signatures and metabolite profiles associated with treatment response and to evaluate their potential as predictive biomarkers of clinical outcomes following atezolizumab plus bevacizumab (Ate/Bev) therapy in advanced hepatocellular carcinoma (HCC). **Methods:** We prospectively enrolled 71 patients (discovery cohort) with advanced HCC who received Ate/Bev as first-line systemic therapy between 2022 and 2024 at two tertiary university hospitals. Baseline (pre-treatment) fecal microbiome samples and follow-up samples obtained at the time of the first radiologic response assessment were serially collected to evaluate treatment response–associated changes in the gut microbiome and metabolite profiles. Age-matched healthy controls (HC; n = 10) were included for comparison of baseline fecal microbiome composition. For validation, fecal microbiome samples were obtained from patients with long-term response (LRes; n = 12) treated with Ate/Bev at an independent hospital. LRes was defined as a sustained treatment response for more than 12 cycles of therapy. In vitro experiments using PBMCs from patients with HCC were performed to assess the effects of microbial metabolites on exhausted $CD8^+$ T cells. **Results:** At baseline, patients with advanced HCC exhibited significantly reduced gut microbial diversity compared with healthy controls (HC) (Fig. A). Only subtle differences were observed between responders (Res) and non-responders (NRes) at baseline. However, post-treatment microbiome analysis revealed that the Res group demonstrated a significant increase in gut microbial diversity along with distinct compositional changes. Notably, responders were enriched in bacterial taxa with short-chain fatty acid (SCFA)–producing potential (Fig. B). The increased microbial diversity with enrichment of key acetate- and butyrate-producing genera were further enhanced in the LRes group (Fig. C). *In vitro* experiments demonstrated that treatment with acetate or butyrate significantly reduced the expression of $TIGIT^+$ and $PD\text{-}1^+$ $CD8^+$ T cells. Venn diagram analysis across NRes, Res, and LRes groups identified a consensus set of 22 bacterial taxa associated with favorable response, including enrichment of 20 SCFA-producing taxa and depletion of *[Ruminococcus]_gnavus_group* (Fig. D). Microbial signature–based stratification using the top 40% most prevalent taxa derived from these 22 taxa consistently discriminated overall survival outcomes (Fig. E), which were consistently significant in the multivariable Cox analysis. **Conclusion:** Our findings indicate that a responder-specific microbial signature, marked by enrichment of SCFA-producing taxa and depletion of dysbiosis-associated markers, is associated with improved treatment response and may represent a potential predictive biomarker for survival in advanced HCC.



Disclosures: Soon Kyu Lee:Nothing to Disclose, Juhyeong Ko:Nothing to Disclose, Joo Yeon Jhun: Nothing to Disclose, Jung Hyun Kwon:Nothing to Disclose, SOON WOO NAM:Nothing to Disclose, Mi-La Cho:Nothing to Disclose, Yunju Jeong:Nothing to Disclose, Hye Won Lee:Nothing to Disclose.

4206 | ◆ USING HISTOTRIPSY TO TREAT LIVER TUMORS IN THE OUTPATIENT SETTING

Roukaya Hassanein[1] Deanna Oliver[2] Anna Hefner[2] Mikaela Banuelos[1] Fatma Barakat[3] Tarek Hassanein[2], [1]Southern California Abdominal Cancer Group, [2]Southern California Liver Centers, [3]SCTI Research Foundation

Background: Liver tumors continue to pose a major health and economic burden. Despite advancements in therapeutic options liver transplantation remains the only curative option, which poses eligibility and

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availability challenges. Histotripsy is a novel, non-invasive, focused ultrasound pulses designed to mechanically liquify tumors. It is a sonic beam therapy platform that can destroy targeted liver tumors at a subcellular level. It received FDA approval in 2023 and has been mainly used in hospital-based/academic settings. We report on our outpatient center's experience **Methods:** Between November 2024 and May 2026, 34 patients (pts) diagnosed with liver tumors were treated with Histotripsy. Each Histotripsy consisted of at least 1 session. Each session treated a unique liver lesion. Actual number of treatments per session and duration of each treatment was tailored to each pt's disease burden and need. Histotripsy eligibility work-up was done. Histotripsy was performed mainly by a Hepatologist or Surgeon. **Results:** 50% male. 35.3% Hispanic, 94.1% white. Mean age was 66.4 ± 13.9 years. All were Child-Pugh A or B. 50% had Hepatocellular Carcinoma, 14.8% Cholangiocarcinoma, 17.6% Colorectal, and 17.6% metastasis. Prior to Histotripsy: 64.8% had 1 lesion, 17.6% had 2 lesions, 17.6 had 3 or more lesions. 14.7% of pts received at least one cycle of Immune Checkpoint Inhibitors (ICI), 26.5% had chemotherapy, and 5.9% had both ICI and Chemotherapy. Histotripsy: 50% had 1 treatment/session, 38.2% 2-3 treatments/session, and 11.8% 4-6 treatments. Each treatment treated a different lesion. Longest session duration was 142 minutes. Median duration of a single treatment was 25 minutes (3-90 minutes). Safety and Outcomes: No significant complications during Histotripsy were observed. 73.5% of pts are alive. No changes in liver enzymes, inflammation markers, coagulation, and MELD score post Histotripsy. 28% experienced mild adverse reactions such as skin erythema on treatment site. 2 pts had acute renal injury that resolved within a week of supportive care/hydration. **Conclusion:** Histotripsy is a novel form of focused ultrasound that uses high amplitude, very short pulses to create a "bubble cloud" designed to mechanically destroy and liquefy targeted liver tumors. As the first outpatient, community-based Hepatology medical practice to implement Histotripsy, it proved to be doable to implement in a non-hospital setting. Patients were able to have multiple treatments in a single session. No pts needed overnight observation. Histotripsy is tolerable and a highly effective non-invasive therapy for treating different kinds of liver tumors in the outpatient setting. Analysis of combining Histotripsy with ICI and/or LRT is underway. Histotripsy protocol continues to be implemented as standard of care with the goal of prolonging disease-free survival in patients with liver tumors, especially Hepatocellular Carcinoma.

Disclosures: Roukaya Hassanein:Nothing to Disclose, Deanna Oliver:Nothing to Disclose, Anna Hefner: Nothing to Disclose, Mikaela Banuelos:Nothing to Disclose, Fatma Barakat:Nothing to Disclose, Tarek Hassanein:AbbVie: Speaker and Research Support, Gilead: Speaker and Research Support, HepQuant Shunt: Advisor, Madrigal: Advisor and Research Support, Amgen: Grant/Research Support, Astra Zeneca: Grant/Research Support, Boehringer- Ingelheim: Grant/Research Support, COUR: Grant/Research Support, Escient: Grant/Research Support, Galectin: Grant/Research Support, Grifols: Grant/Research Support, Intercept: Grant/Research Support, Janssen: Grant/Research Support, Merck: Grant/Research Support, Mirum: Grant/Research Support, NeuroBo: Grant/Research Support, Novartis: Grant/Research Support, Novo Nordisk: Grant/Research Support, Pfizer: Grant/Research Support, Regeneron: Grant/Research Support, Salix Pharmaceuticals: Grant/Research Support, Takeda: Grant/Research Support, Akero: Grant/Research Support, Ipsen: Grant/Research Support, Kowa: Grant/Research Support, Bristol-Myers Squibb: Grant/Research Support, DURECT: Grant/Research Support, HepQuant: Grant/Research Support, Terns Pharmaceuticals: Grant/Research Support, Mallinckrodt: Speaker and Research Support, Eli Lilly: Grant/Research Support, PharmaIn: Grant/Research Support, Sonic incytes: Grant/Research Support, Tensor Bio: Grant/Research Support, 89Bio: Grant/Research Support, Terns Pharmaceuticals: Grant/Research Support, Nterica: Consultant, Atea: Grant/Research Support, Harbinger: Grant/Research Support, Sanofi-Aventis: Grant/Research Support, CurveBio: Grant/Research Support, AbbVie: Speaker and Research Support, Gilead: Speaker and Research Support, HepQuant Shunt: Advisor, Madrigal: Advisor and Research Support, Amgen: Grant/Research Support, Astra Zeneca: Grant/Research Support, Boehringer- Ingelheim: Grant/Research Support, COUR: Grant/Research Support, Escient: Grant/Research Support, Galectin: Grant/Research Support, Grifols: Grant/Research Support, Intercept: Grant/Research Support, Janssen: Grant/Research Support, Merck: Grant/Research Support, Mirum: Grant/Research Support, NeuroBo: Grant/Research Support, Novartis: Grant/Research Support, Novo Nordisk: Grant/Research Support, Pfizer: Grant/Research Support, Regeneron: Grant/Research Support, Salix Pharmaceuticals: Grant/Research Support, Takeda: Grant/Research Support, Akero: Grant/Research Support, Ipsen: Grant/Research Support, Kowa: Grant/Research Support, Bristol-Myers Squibb: Grant/Research Support, DURECT: Grant/Research Support, HepQuant: Grant/Research Support, Terns Pharmaceuticals: Grant/Research Support, Mallinckrodt: Speaker and Research Support, Eli Lilly: Grant/Research Support, PharmaIn: Grant/Research Support, Sonic incytes: Grant/Research Support, Tensor Bio: Grant/Research Support, 89Bio: Grant/Research Support, Terns Pharmaceuticals: Grant/Research Support, Nterica: Consultant, Atea: Grant/Research Support, Harbinger: Grant/

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4207 | ◆ MULTICENTER PROPENSITY-WEIGHTED COMPARISON OF HEPATIC ARTERIAL INFUSION CHEMOTHERAPY AND TYROSINE KINASE INHIBITORS IN PATIENTS WITH ADVANCED HEPATOCELLULAR CARCINOMA PREVIOUSLY TREATED WITH ATEZOLIZUMAB–BEVACIZUMAB

Kwon Yong Tak[1] Pil Soo Sung[2], [1]Seoul St. Mary's Hospital, [2]Seoul St Mary's Hospital

Background: Following the failure of first-line atezolizumab–bevacizumab (AB), the optimal second-line strategy for advanced hepatocellular carcinoma (HCC) remains undefined. The 2025 BCLC recommendations emphasize individualized decision-making under the CUSE framework. This study aimed to compare the clinical outcomes of hepatic arterial infusion chemotherapy (HAIC) and tyrosine kinase inhibitors (TKIs) in this setting. **Methods:** This multicenter retrospective study included 90 patients (HAIC, n = 51; TKIs, n = 39) from four tertiary centers who experienced disease progression after AB. Baseline characteristics, including higher tumor burden and portal vein tumor thrombosis (PVTT) in the HAIC group, were adjusted using inverse probability of treatment weighting (IPTW). Tumor response was assessed via mRECIST by blinded radiologists. Primary endpoints were progression-free survival (PFS) and overall survival (OS). **Results:** HAIC yielded significantly higher objective response rates (35.3% vs. 5.1%, $P = .002$) and disease control rates (66.7% vs. 25.6%, $P < .001$) compared to TKIs. In the IPTW-weighted analysis, HAIC was associated with significantly longer PFS (7.1 vs. 3.4 months; $P < .001$), although OS did not differ significantly between the groups (10.5 vs. 6.3 months; $P = .31$). Notably, the TKI group had a substantially higher rate of treatment discontinuation due to toxicity compared to the HAIC group (53.8% vs. 15.7%). **Conclusion:** As a second-line treatment after AB failure, HAIC provides superior radiologic response and longer PFS compared to TKIs. While no definitive OS benefit was observed, these findings support HAIC as an effective investigational salvage option, particularly for patients with liver-dominant disease requiring robust intrahepatic control.

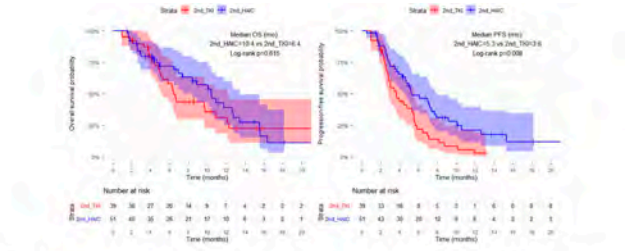


Fig 3. Overall survival comparison and B. Progression free survival between patients treated with second-line HAIC and second-line TKIs using the Kaplan-Meier curve. HAIC, hepatic arterial infusion chemotherapy; TKI, tyrosine kinase inhibitor; OS, overall survival, PFS, progression-free survivial.

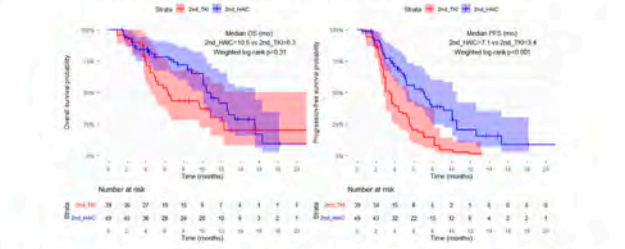


Fig 4. IPTW-weighted Kaplan–Meier curves for OS and PFS in patients treated with HAIC versus TKIs following AB therapy failure. Weighted Cox proportional hazards regression was applied with IPTW to adjust for baseline differences. OS and PFS were compared between treatment groups using weighted log-rank tests. OS, overall survival; PFS, progression-free survival; IPTW, inverse probability of treatment weighting; HAIC, hepatic arterial infusion chemotherapy; TKI, tyrosine kinase inhibitor; AB, atezolizumab–bevacizumab.

Disclosures: Kwon Yong Tak:Nothing to Disclose, Pil Soo Sung:Nothing to Disclose.

4208 | ◆ TRANSARTERIAL CHEMOEMBOLIZATION COMBINED WITH RALOX-HAIC VERSUS FOLFOX-HAIC FOR UNRESECTABLE HEPATOCELLULAR CARCINOMA: A RETROSPECTIVE IPTW-ADJUSTED STUDY

Yusi Ding[1] Yuanyi Chen[1] Wenjun Wang[1] Yaping Li[1] Guoying Pan[1] Xiaoli Jia[1], [1]The Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China

Background: Transarterial chemoembolization (TACE) and hepatic arterial infusion chemotherapy (HAIC) are widely used for unresectable hepatocellular carcinoma (uHCC), especially in China. FOLFOX (oxaliplatin, fluorouracil, leucovorin) is the most common HAIC regimen, but its prolonged 46-hour infusion limits convenience. Raltitrexed, a thymidylate synthase inhibitor with a longer half-life, allows shorter infusion and may be a more convenient alternative. This study compared the efficacy and safety of TACE combined with RALOX-HAIC (oxaliplatin plus raltitrexed) versus TACE combined with FOLFOX-HAIC in uHCC patients. **Methods:** This retrospective study included 108 patients with uHCC treated between January 2023 and December 2025. Among them, 66 patients received TACE plus FOLFOX-HAIC and 42 received TACE plus RALOX-HAIC. Treatment efficacy was assessed using objective response rate (ORR), disease control rate (DCR), and progression-free survival (PFS). Treatment-related adverse

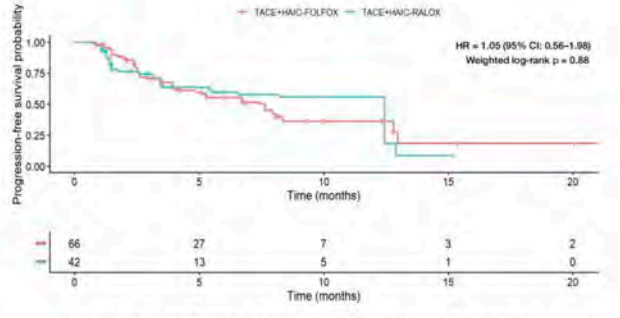
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events were also compared between groups. Inverse probability of treatment weighting (IPTW) was applied to balance baseline demographic and clinical characteristics. Multivariable Cox regression analysis was performed to identify factors associated with PFS. **Results:** After IPTW adjustment, tumor response was comparable between the TACE–RALOX-HAIC and TACE–FOLFOX-HAIC groups. ORR was identical in both groups (48.2% vs. 60.8%, *P* = 0.270, while DCR did not differ significantly between groups (69.5% vs. 78.1%, *P* = 0.336). Median PFS was 12.43 months in the TACE–RALOX-HAIC group and 7.30 months in the TACE–FOLFOX-HAIC group, with no statistically significant difference observed between treatments (hazard ratio, 1.05; 95% confidence interval, 0.56-1.98; *P* = 0.880). In multivariable analysis, extrahepatic metastasis and poor performance status were independently associated with shorter PFS. The overall incidence of grade 3/4 treatment-related adverse events was similar between groups. Fever occurred more frequently in the TACE–RALOX-HAIC group than in the TACE–FOLFOX-HAIC group (40.5% vs. 19.7%, *P* = 0.027). **Conclusion:** In this IPTW-adjusted retrospective study, TACE combined with RALOX-HAIC demonstrated comparable efficacy and safety to TACE combined with FOLFOX-HAIC in patients with uHCC. Given its shorter infusion duration, RALOX-HAIC may provide a more convenient alternative to FOLFOX-HAIC without compromising antitumor activity. Prospective studies are warranted to validate these findings.

Table. Tumor Response by mRECIST after IPTW.

Treatment / Response	TACE+HAIC-FOLFOX n=66	TACE+HAIC-RALOX n=42	*P* value
CR	3 (4.2%)	4 (8.9%)	0.481
PR	37 (56.6%)	16 (39.3%)	
SD	11 (17.3%)	9 (20.4%)	
PD	14 (21.9%)	13 (31.3%)	
ORR	40 (60.8%)	20 (48.2%)	0.270
DCR	51 (78.1%)	29 (69.5%)	0.336



Disclosures: Yusi Ding:Nothing to Disclose, Yuanyi Chen:Nothing to Disclose, Wenjun Wang:Nothing to Disclose, Yaping Li:Nothing to Disclose, Guoying Pan: Nothing to Disclose, Xiaoli Jia:Nothing to Disclose.

4210 | THE RISING BURDEN OF MASLD-ASSOCIATED NON-CIRRHOTIC HEPATOCELLULAR CARCINOMA: A NATIONAL STUDY OF U.S. VETERANS

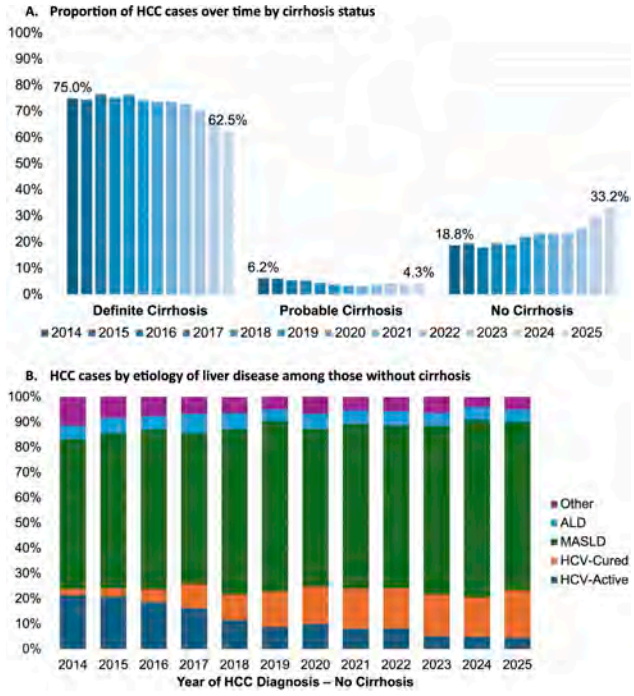
Nicole Kim[1] Philip Vutien[1] Bret Mecham[2] Vyshnika Sriskantharajah[2] Elliott Lowy[2] Kristin Berry[2] George Ioannou[2], [1]University of Washington, [2]Veterans Affairs Puget Sound Health Care System

Background: Hepatocellular carcinoma (HCC) can occur in patients without liver cirrhosis. We aimed to examine the trends in HCC diagnoses by cirrhosis status and etiology of liver disease among U.S. Veterans over time. **Methods:** We identified U.S. Veterans diagnosed with incident HCC between 1/1/2014 and 10/26/2025. Cirrhosis status was categorized as "definite" based on ICD-codes for cirrhosis and/or related complications within 1 year of the HCC diagnosis date, "probable" based on not meeting criteria for definite cirrhosis but having a FIB-4 score >3.25 or a transient elastography liver stiffness measurement >12.5 kPa within 2 years before or 6 months after the HCC diagnosis date, and "no cirrhosis" based on not meeting criteria for definite and probable cirrhosis. Descriptive statistics were performed to stratify HCC diagnoses by cirrhosis status, etiology of liver disease, and diagnosis year. **Results:** There were 33,628 U.S. Veterans diagnosed with new HCC during 2014-2025, with 73%, 4.6%, and 22.4% of cases occurring in the setting of definite, probable, and no cirrhosis respectively. The mean age at HCC diagnosis was 68 years (SD 8.2) and majority were male (98.5%), White (70.2%), with leading liver disease etiologies of hepatitis C (HCV; 47.4%), metabolic dysfunction-associated steatotic liver disease (MASLD; 33.9%) and alcohol-related liver disease (ALD; 13.3%). From 2014 to 2025, the proportion of HCC cases with definite and probable cirrhosis decreased by 12.5% and 1.9% respectively, while HCC cases without cirrhosis increased by 14.4% (18.8% to 33.2%, Figure A). While most patients with HCV- and ALD-related HCC had definite cirrhosis (>85%), 43% of patients with MASLD-related HCC did not have cirrhosis. In 2025, 66.8% of non-cirrhotic HCC cases were due to MASLD (Figure B). Patients with non-cirrhotic HCC were also more likely to be female (2.4% vs. 1.3%; p<0.001), older (median age 71 vs. 67 years; p<0.001), and have MASLD (64.7% vs. 23.4%; p<0.001) than those with definite cirrhosis. **Conclusion:** In the last decade, the proportion of HCC cases without liver cirrhosis increased from 18.8% to

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33.2%, with the majority (66.8% in 2025) due to MASLD. These findings emphasize the need to develop rational strategies and recommendations for surveillance and early detection of MASLD-associated non-cirrhotic HCC.

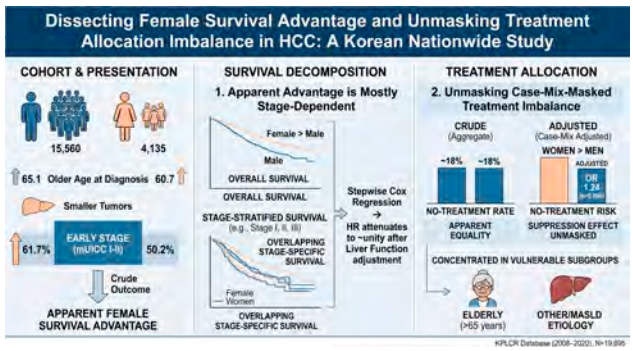


Disclosures: Nicole Kim:Madrigal: Grant/Research Support, Madrigal Pharmaceuticals: Clinical trial (to institution), Madrigal: Grant/Research Support, Philip Vutien:Nothing to Disclose, Bret Mecham:Nothing to Disclose, Vyshnika Sriskantharajah:Nothing to Disclose, Elliott Lowy:Nothing to Disclose, Kristin Berry: Nothing to Disclose, George Ioannou:Nothing to Disclose.

4211 | DISSECTING FEMALE SURVIVAL ADVANTAGE AND TREATMENT ALLOCATION IMBALANCE IN HEPATOCELLULAR CARCINOMA: A KOREAN NATIONWIDE REGISTRY STUDY

Ji Won Han[1] Do Seon Song[2], [1]The Catholic University of Korea, Seoul St. Mary's Hospital, [2]The Catholic University of Korea

Background: Female patients with hepatocellular carcinoma (HCC) often present with more favorable tumor characteristics and better survival than male patients. However, whether this apparent advantage reflects a residual within-stage survival benefit or favorable stage distribution remains unclear. We aimed to decompose sex-based survival differences and evaluate treatment non-receipt after accounting for tumor case mix. **Methods:** We analyzed 19,695 patients with newly diagnosed HCC from the Korean Primary Liver Cancer Registry between 2008 and 2020. Stage-stratified Kaplan–Meier analysis and stepwise Cox regression were used to assess the female survival advantage. Multivariable logistic regression evaluated the association between female sex and treatment non-receipt after adjustment for age, stage, liver function, performance status, tumor size, and macrovascular invasion. Subgroup analyses were performed by age and etiology. **Results:** Among 19,695 patients, 4,135 (21.0%) were female. Women were older but had smaller tumors, less macrovascular invasion, and more early-stage disease than men (mUICC Stage I–II: 61.7% vs 50.2%, p < 0.001). Despite this favorable stage distribution, overall treatment non-receipt was similar between women and men (18.1% vs 18.4%, p = 0.508). Stage-stratified survival curves overlapped across all mUICC stages. In stepwise Cox regression, the unadjusted female survival advantage (HR 0.829) attenuated after adjustment for stage and liver function and remained modest after full adjustment (HR 0.910), suggesting a predominantly stage-distribution–mediated advantage. In logistic regression, female sex was not associated with treatment non-receipt in crude analysis (OR 1.056, p = 0.403), but became independently associated after full adjustment (OR 1.237, p = 0.006). This imbalance was most apparent in the Other/MASLD subgroup (OR 1.624, p = 0.001) and patients aged >65 years (OR 1.321, p = 0.006). **Conclusion:** The apparent female survival advantage in HCC was largely explained by favorable stage distribution. Case-mix adjustment revealed treatment allocation imbalance, particularly among elderly women and patients with non-viral, non-alcohol-related etiologies.



Disclosures: Ji Won Han:Nothing to Disclose, Do Seon Song:Nothing to Disclose.

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4212 | TACE IN THE SETTING OF PORTAL VEIN THROMBOSIS: EVALUATING RISKS AND OUTCOMES IN HCC AND CIRRHOSIS

Het Patel[1] Erik Dehkes[1] Barbara Halicki[1] Hammad Liaquat[1], [1]St. Luke's University Healthcare Network

Background: Transarterial chemoembolization (TACE) is a standard locoregional therapy for hepatocellular carcinoma (HCC) in patients with cirrhosis. The presence of portal vein thrombosis (PVT) is common in advanced disease and may impact hepatic perfusion, procedural safety, and clinical outcomes following TACE. This study evaluates differences in patient characteristics and inpatient outcomes among patients with cirrhosis and HCC undergoing TACE with and without PVT. **Methods:** We conducted a retrospective cohort study using the National Inpatient Sample (NIS) database to identify adults with cirrhosis and HCC who underwent TACE between 2019 and 2022. Patients were stratified based on the presence or absence of PVT. Demographics, comorbidities, hospital characteristics, and inpatient complications were compared between groups. Statistical analyses were performed using STATA software, with significance defined as $p < 0.05$. **Results:** Of the 3,660 patients who met inclusion criteria, 76.6% were male and mean age was similar between groups (64.9 versus 65.8 years, $p \geq 0.05$). Demographics, including gender and race, were otherwise comparable between groups ($p \geq 0.05$). Charlson Comorbidity Index (CCI) was similar between groups (≥ 0.05), except for CCI score 6, which was higher in the PVT group ($p < 0.05$). Although patients with PVT had lower rates of alcohol use ($p < 0.05$), there were no significant differences in COPD, CHF, diabetes, hypertension, malnutrition, or smoking ($p \geq 0.05$). Patients with PVT undergoing TACE had higher odds of variceal bleeding (OR 2.933, 95% CI 1.255–6.857), acute kidney injury (OR 2.478, 95% CI 1.451–4.232), and acute liver failure (OR 2.422, 95% CI 1.212–4.842). No significant differences were observed in spontaneous bacterial peritonitis, sepsis, liver transplantation, ICU admission, mechanical ventilation, vasopressor use, and inpatient mortality ($p \geq 0.05$). Length of stay was longer in the PVT group (7.8 versus 5.2 days, $p < 0.05$), while total hospitalization charges were similar between groups ($p \geq 0.05$). **Conclusion:** In patients with cirrhosis undergoing TACE for HCC, patients with alcohol use were less likely to have PVT. We found higher rates of variceal bleeding, acute kidney injury, acute liver failure, and overall length of stay in patients with PVT consistent with guideline recommendations favoring alternative systemic therapies in PVT. We recommend monitoring for these complications and further prospective studies to identify risk factors and safety of TACE in the setting of PVT.

Table 1: Demographics

	With PVT (n = 340)	Without PVT (n = 3,320)	p value	Odds Ratio (95% CI)
Mean Age, years	64.9	65.8	0.436	-
Gender, n				
Male	250 (73.5%)	2555 (77.0%)	0.514	0.832(0.478-1.447)
Female	90 (26.5%)	765 (23.0%)	0.514	1.202(0.691-2.092)
Race, n				
White	175 (51.5%)	1570 (47.3%)	0.529	1.182(0.702-1.991)
Black	30 (8.8%)	395 (11.9%)	0.460	0.717(0.296-1.734)
Hispanic	80 (23.5%)	835 (25.2%)	0.787	0.916(0.484-1.734)
Asian	25 (7.4%)	265 (8.0%)	0.853	0.915(0.357-2.347)
Native American	0 (0.0%)	55 (1.7%)	-	-
Other	5 (1.5%)	95 (2.9%)	0.511	0.507(0.067-3.846)
Alcohol Use, n	105 (30.9%)	1465 (44.1%)	0.029	0.566(0.339-0.943)
COPD, n	40 (11.8%)	365 (11.0%)	0.847	1.079(0.497-2.344)
Congestive Health Failure (CHF), n	25 (7.4%)	330 (9.9%)	0.561	0.719(0.237-2.183)
Diabetes, n	130 (38.2%)	1280 (38.6%)	0.957	0.987(0.606-1.607)
Hypertension, n	115 (33.8%)	1530 (46.1%)	0.055	0.598(0.353-1.012)
Malnutrition, n	40 (11.8%)	190 (5.7%)	0.058	2.196(0.973-4.957)
Smoking, n	130 (38.2%)	1645 (49.5%)	0.100	0.630(0.364-1.093)
Charlson Comorbidity Index, n				
≤3	45 (13.2%)	680 (20.5%)	0.158	0.592(0.286-1.225)
4	35 (10.3%)	525 (15.8%)	0.230	0.611(0.273-1.367)
5	85 (25.0%)	730 (22.0%)	0.572	1.183(0.661-2.117)
6	80 (23.5%)	450 (13.6%)	0.021	1.962(1.106-3.482)
≥7	95 (27.9%)	935 (28.2%)	0.968	0.989(0.579-1.690)

Table 2: Hospitalization Co-illnesses, Level of Care, Length of Stay, and Cost

	With PVT (n = 340)	Without PVT (n = 3,320)	p value	Odds Ratio (95% CI)
Variceal Bleed, n	35 (10.3%)	125 (3.8%)	0.013	2.933(1.255-6.857)
Spontaneous Bacterial Peritonitis (SBP), n	15 (4.4%)	120 (3.6%)	0.739	1.231(0.363-4.179)
Acute Kidney Injury (AKI), n	175 (51.5%)	995 (30.0%)	0.001	2.478(1.451-4.232)
Sepsis, n	30 (8.8%)	290 (8.7%)	0.981	1.011(0.414-2.469)
Acute Liver Failure (ALF), n	55 (16.2%)	245 (7.4%)	0.012	2.422(1.212-4.842)
Liver Transplant, n	5 (1.5%)	20 (0.6%)	0.424	2.463(0.271-22.409)
ICU, n	45 (13.2%)	355 (10.7%)	0.524	1.274(0.604-2.686)
Mechanical Ventilation, n	40 (11.8%)	295 (8.9%)	0.435	1.367(0.623-3.001)
Vasopressors, n	10 (2.9%)	145 (4.4%)	0.578	0.664(0.156-2.816)
Mortality, n	45 (13.2%)	285 (8.6%)	0.207	1.624(0.765-3.452)
Length Of Stay, days	7.8	5.2	0.002	-
Total Charge, dollars	$176,447.80	$134,669.70	0.067	-

Disclosures: Het Patel:Nothing to Disclose, Erik Dehkes:Nothing to Disclose, Barbara Halicki:Nothing to Disclose, Hammad Liaquat:Nothing to Disclose.

4213 | NON-INVASIVE RISK STRATIFICATION TO GUIDE PRE-TREATMENT ENDOSCOPIC SCREENING AND PREDICT HEPATIC DECOMPENSATION IN HEPATOCELLULAR CARCINOMA PATIENTS RECEIVING SYSTEMIC THERAPY: A PROSPECTIVE COHORT STUDY

Laia Aceituno Sierra[1] Giselle Caballero[2] Shiva Babakhani[2] Ahmed Elsheaita[3] Farah Albader[3] Elena Valenzi[3] Ann Ma[3] Roxana Bucur[2] Arndt Vogel[4], [1]Toronto General Hospital, University Health Network, [2]University Health Network, HPB Surgical Oncology, Toronto, Ontario, Canada., [3]Division of Gastroenterology and Hepatology, Toronto General Hospital, Toronto, Canada., [4]University of Toronto

Background: Atezolizumab–bevacizumab (AB) is the first-line standard-of-care therapy for advanced hepatocellular carcinoma (HCC). Concerns regarding bevacizumab-associated variceal bleeding have led to

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recommendations for routine pre-treatment esophagogastroduodenoscopy (EGD) in all patients, potentially increasing procedural burden and delaying treatment initiation. Baveno VII criteria use liver stiffness measurement (LSM) and platelet count to identify cirrhosis patients at low risk of varices who may safely avoid screening EGD, although their applicability in advanced HCC remains unclear. We evaluated whether non-invasive liver assessment tools could safely guide pre-treatment EGD strategies and predict hepatic decompensation. **Methods:** This prospective observational single-centre study included adult HCC patients initiating systemic therapy at Princess Margaret Cancer Centre, Toronto. Patients were stratified using Baveno VII criteria into low-risk (LR: LSM <15 kPa and platelets $\geq 150\times10^9$/L) or high-risk (HR: LSM ≥ 15 kPa and/or platelets $<150\times10^9$/L). HR patients underwent pre-treatment EGD, while LR patients proceeded directly to therapy. Primary endpoints were variceal bleeding and hepatic decompensation during follow-up. **Results:** 50 patients were included, 37 patients (70%) were classified as HR and 13 (30%) as LR according to Baveno VII criteria. Baseline HR patients had significantly higher LSM values and lower platelet counts compared with LR patients (27.0 vs. 9.0 kPa, $p<0.001$; 155 vs. 217 $\times10^9$/L, $p=0.013$). Portal vein thrombosis was more frequent in the HR group (51% vs. 15%, $p=0.053$). Varices were identified in 11/35 HR patients (35%), including 5 patients with high-risk stigmata. One HR patient (2%) developed post-AB variceal bleeding. No bleeding events occurred in the LR group. During follow-up, seven patients (14%) developed hepatic decompensation. Patients who decompensated had higher baseline bilirubin and MELD-Na scores and more frequently had prior decompensation and pre-existing varices. CP score did not significantly differ between groups, whereas ALBI grade 2 was associated with increased risk of decompensation (OR 6.25, 95% CI 1.06–36.74). MELD-Na demonstrated the highest discriminative performance for predicting decompensation (AUC 0.81, 95% CI 0.70–0.93). **Conclusion:** Baveno VII–based non-invasive stratification safely identified HCC patients receiving AB who could avoid pre-treatment EGD without bleeding complications, while MELD-Na outperformed other liver assessment tools for predicting hepatic decompensation. These findings support incorporation of non-invasive liver assessment into pre-treatment evaluation pathways for HCC systemic therapy.

Disclosures: Laia Aceituno Sierra:Nothing to Disclose, Giselle Caballero:Nothing to Disclose, Shiva Babakhani:Nothing to Disclose, Ahmed Elsheaita:Nothing to Disclose, Farah Albader:Nothing to Disclose, Elena Valenzi:Nothing to Disclose, Ann Ma:Nothing to Disclose, Roxana Bucur:Nothing to Disclose, Arndt Vogel: Roche: Advisor.

4214 | MAPPING REAL WORLD TREATMENT JOURNEYS OF HEPATOCELLULAR CARCINOMA IN THE IMMUNOTHERAPY ERA

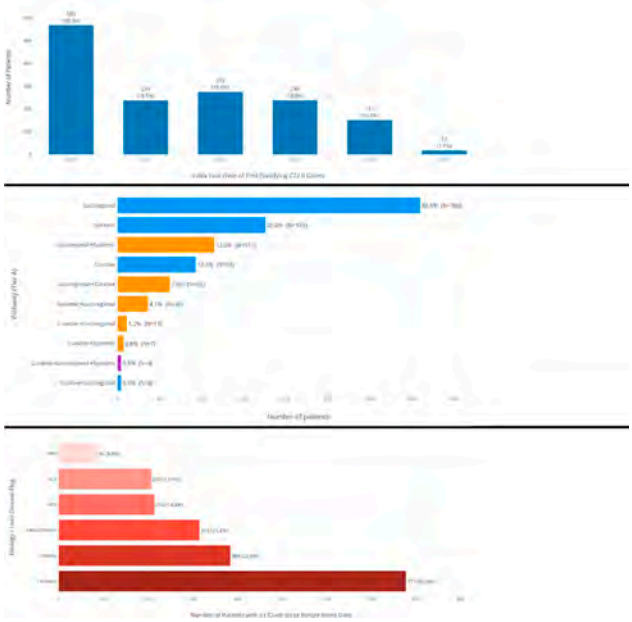
Kavana Madhiraju Sanjay[1] Renu Dhanasekaran[1],
[1]Stanford University School of Medicine

Background: Hepatocellular carcinoma (HCC) systemic therapy has been transformed by the approvals of multiple immunotherapies as first line treatment, but the structure of real-world treatment journeys and how immunotherapy adoption has reshaped sequencing across curative, locoregional, and systemic modalities has not been quantified at scale. **Methods:** We conducted a retrospective cohort study of US adults with hepatocellular carcinoma (≥ 2 ICD-10 C22.0 claims ≥ 30 days apart) in the HealthVerity claims database (Jan 2020-Mar 2025), requiring ≥ 90 days continuous pre-index enrollment. Modality-anchored treatment journeys were constructed from procedure and pharmacy claims, with contamination control for non-liver-specific codes. We quantified pathway heterogeneity at three nested levels- Tier A (3 treatment classes), Tier B (7 modalities), Tier C (drug-level systemic) using normalized Shannon entropy with patient-level bootstrap 95% CIs (2,000 resamples). Temporal trends in first-line systemic agent use and immunotherapy positioning within the journey were tested with Cochran-Armitage and Kaplan-Meier methods. **Results:** Among 1,487 patients (median age 66 years; 74% male; 41% Medicare), 59% received ≥ 1 HCC-directed treatment. TACE was the most prevalent modality (32.5%), followed by systemic therapy (22.7%) and TARE (17.4%). Systemic therapy as the first treatment modality increased from 56% of systemic-treated patients in 2020 to 73% in 2023 ($z = +2.04$, $p = 0.041$). Durvalumab-based regimens rose from 0% of first-line systemic use in 2020-2021 to 42% by 2024 (Cochran-Armitage $z = +7.83$, $p<0.0001$), and sorafenib fell from 14% in 2020 to 0% from 2023 onward ($z = -4.52$, $p<0.0001$), while atezolizumab +bevacizumab maintained an overall share of approximately 31% with a modest rising trend ($z = +1.77$, one-sided $p = 0.038$). Nivolumab fell from 27% in 2020 to near-zero by 2024. Oral TKIs were infrequent across the dual-enrolled subset, with lenvatinib (4.4%) the most common, followed by cabozantinib (1.7%), sorafenib (1.4%), and regorafenib (0.9%). **Conclusion:** Real-world HCC treatment heterogeneity is concentrated at the drug-choice layer rather than in macro-sequencing, and the IO era has produced consolidation around dominant immunotherapy combinations, while shifting systemic therapy earlier in the patient journey. These findings reframe the post-immunotherapy treatment landscape and provide a quantitative baseline against which future sequencing trials and access

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analyses can be benchmarked.

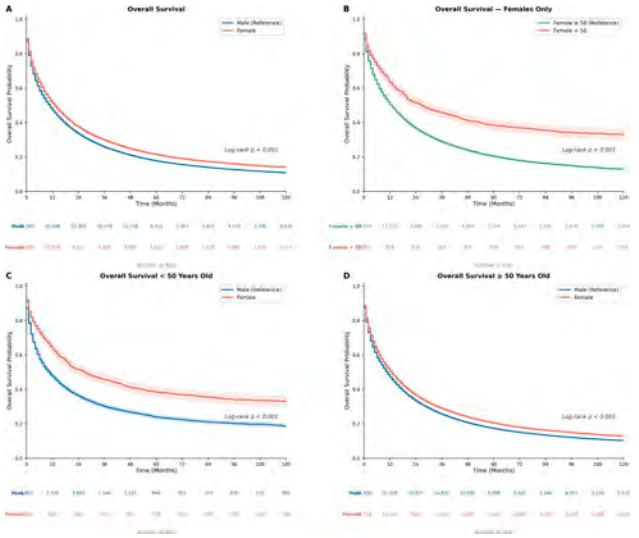


Disclosures: Kavana Madhiraju Sanjay:Nothing to Disclose, Renu Dhanasekaran:Nothing to Disclose.

4215 | AGE-DEPENDENT SEX DIFFERENCES IN SURVIVAL AMONG PATIENTS WITH HEPATOCELLULAR CARCINOMA: A POPULATION-BASED ANALYSIS FROM THE TEXAS AND CALIFORNIA CANCER REGISTRIES

Mohammad Jarrah[1] Mohammed Al-Hasan[1] Zachary Whitham[1] Lauren Matevish[1] Ju Dong Yang[2] Fasiha Kanwal[3] Adam Yopp[1] Amit Singal[1] Nicole Rich[1], [1]University of Texas Southwestern Medical Center, [2]Cedars-Sinai Medical Center, [3]Michael E. DeBakey VA Medical Center

Background: Hepatocellular carcinoma (HCC) predominantly affects men, yet mechanisms underlying sex differences in HCC outcomes remain incompletely understood. Experimental models and observational studies suggest estrogen may protect against HCC progression. Prior population-based studies have largely relied on SEER datasets, which historically underrepresented patients from Texas and portions of California – states accounting for a substantial proportion of the U.S. HCC burden. Herein, we evaluated sex differences in overall survival (OS) among patients with HCC using population-based data from the Texas Cancer Registry (TCR) and California Cancer Registry (CCR). **Methods:** Patients diagnosed with HCC between 2004 and 2022 were identified from the TCR and CCR, using ICD code C22.0 and morphology codes 8170–8175. Patients diagnosed before age 18 years, non-HCC histology codes, or identified by death certificate or autopsy only were excluded. Associations between sex and OS were evaluated using Kaplan-Meier analysis and multivariable Cox proportional hazards models adjusting for age, race/ethnicity, SEER stage (localized, regional, distant), and treatment modality (surgical, locoregional, systemic). Age <50 was used as a surrogate for pre-menopausal status, and interaction between sex and age was assessed in multivariable models. **Results:** Among 95,237 patients with HCC (median age 64 years; 75.3% men), 44.4% were from TCR and 55.6% from CCR. The cohort was racially and ethnically diverse, including 40.8% White, 33.9% Hispanic, 14.1% Asian and 10.1% Black patients. Despite major changes in HCC epidemiology over time, including increasing MASLD-associated HCC, women consistently represented a minority of HCC cases across eras. Women more frequently presented with localized disease (54.4% vs 47.5%; $p<0.001$) and received surgery more often than men (8.0% vs 7.6%; $p<0.001$). Median OS was longer among women than men (13 vs. 11 months; $p<0.001$). After multivariable adjustment, female sex remained independently associated with lower mortality (aHR 0.88, 95% CI 0.87–0.90) (**Figure 1A**); this finding persisted across all stages ($p<0.001$ for all). Among women, those aged <50 years had substantially longer OS compared to women aged ≥ 50 years (27 vs. 13 months), corresponding to lower adjusted mortality (aHR 0.74, 95% CI 0.68–0.80) (**Figure 1B**). The survival advantage associated with female sex was greatest among women aged <50 years and attenuated with increasing age (**Figure 1C-D;** interaction $p<0.001$). **Conclusion:** In this large cohort, women with HCC demonstrated a survival advantage compared with men, particularly among younger women. The attenuation of this effect after age 50, together with the stable underrepresentation of women across eras, supports the presence of sex-related biologic differences in HCC susceptibility and progression.



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4216 | OVERALL SURVIVAL AMONG PATIENTS UNDERGOING DIRECT LIVER TRANSPLANTATION VERSUS BRIDGING LOCOREGIONAL THERAPY BEFORE TRANSPLANT FOR HEPATOCELLULAR CARCINOMA

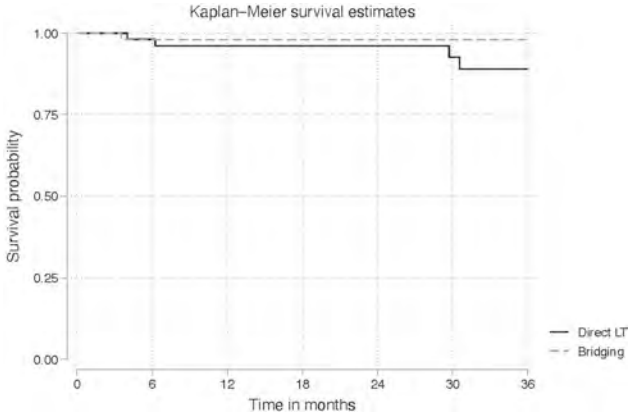
Saleh Alqahtani[1] Saleh Alessy[2] Layan Alsubki[2] Amwaj Alanazi[2] Basmah Khoja[2] Habeeb Ibrahim Abdul Razack[3] Alwaleed Almojel[2] Fahad AlMugbel[2] Ali Alqahtani[2] Waleed Alomaim[2] Mohammed Alsager[4] Fuat Saner[2] May Alzahrani[5] Khalid AlNaamani[6] Dimitri Raptis[2] Dieter Broering[2] Saad Alghamdi[7] Faisal Abaalkhail[2], [1]King Faisal Specialist Hospital & Research Center, [2]King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia, [3]King Saud University, Riyadh, Saudi Arabia, [4]King Saud Medical City, Riyadh, Saudi Arabia, [5]King Faisal Specialist Hospital and Research Center, Jeddah, Saudi Arabia, [6]The Medical City for Military and Security Services, Muscat, Oman, [7]King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia

Background: Locoregional therapy is commonly used as a bridging strategy before liver transplantation in patients with hepatocellular carcinoma to maintain transplant eligibility and reduce tumor progression while awaiting transplantation. We aimed to compare patients undergoing direct liver transplantation with those receiving bridging transarterial chemoembolization (TACE) or transarterial radioembolization (TARE) using real-world outcome data. **Methods:** We used data from the HCC registry, a large prospectively maintained registry established in 2020 at King Faisal Specialist Hospital & Research Center, a major tertiary referral center in Saudi Arabia. Adult patients with HCC who underwent liver transplantation were included. Patients were categorized into those who underwent direct liver transplantation without prior locoregional therapy and those who received bridging locoregional therapy with transarterial chemoembolization (TACE) or transarterial radioembolization (TARE) before transplantation. Baseline demographic, clinical, and tumor characteristics, including BCLC stage, Milan criteria, Child-Pugh class, and albumin-bilirubin (ALBI) grade, and the median time to transplant were compared between groups. Overall survival was assessed using Kaplan–Meier analysis and Cox proportional hazards models. **Results:** Among 696 patients with HCC, 138 (19.8%) underwent liver transplantation. Transplant recipients were younger at diagnosis than non-transplant patients (60.0 vs. 66.0 years, $p < 0.001$), while the sex distribution was comparable. The prevalence of MASLD/MASH was comparable between transplant and non-transplant patients (35.5% vs. 35.8%) and represented the leading etiology in both groups. Among the transplanted patients, 78 (56.5%) underwent direct transplantation and 60 (43.5%) received bridging locoregional therapy before transplantation. Age and sex distribution were similar between groups. BCLC stage and Milan criteria status were also similar. The median time from diagnosis to transplantation was longer among patients receiving bridging therapy (224.0 vs. 130.5 days; $P = 0.018$). Bridged patients had more favorable liver reserve by Child-Pugh class (Child-Pugh A: 71.7% vs. 44.9%; $P = 0.002$) and ALBI grade ($P = 0.012$). In Cox regression adjusted for age and sex, bridging therapy was not associated with a higher risk of death following transplantation (adjusted HR 0.23, 95% CI 0.02–2.19). **Conclusion:** Bridging locoregional therapy before liver transplantation was not associated with an increased risk of post-transplant mortality after adjusting for age and sex. However, the wide confidence interval and baseline differences in liver reserve highlight limited precision and potential

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residual confounding.

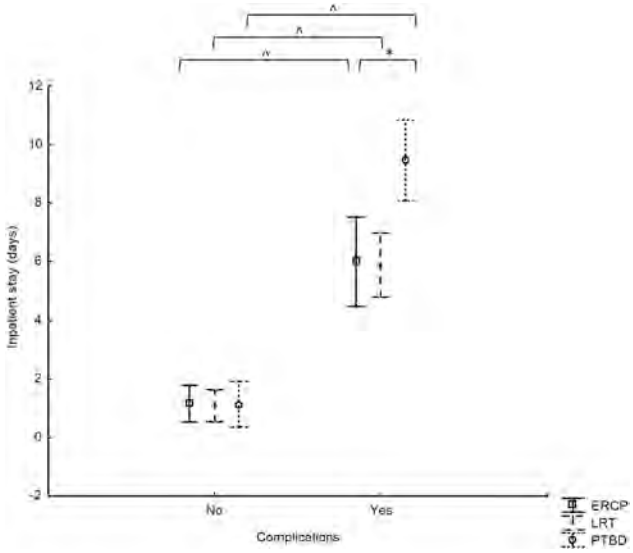


Disclosures: Saleh Alqahtani:Nothing to Disclose, Saleh Alessy:Nothing to Disclose, Layan Alsubki: Nothing to Disclose, Amwaj Alanazi:Nothing to Disclose, Basmah Khoja:Nothing to Disclose, Habeeb Ibrahim Abdul Razack:Nothing to Disclose, Alwaleed Almojel:Nothing to Disclose, Fahad AlMugbel:Nothing to Disclose, Ali Alqahtani:Nothing to Disclose, Waleed Alomaim:Nothing to Disclose, Mohammed Alsager: Nothing to Disclose, Fuat Saner:Nothing to Disclose, May Alzahrani:Nothing to Disclose, Khalid AlNaamani: Nothing to Disclose, Dimitri Raptis:Nothing to Disclose, Dieter Broering:Nothing to Disclose, Saad Alghamdi: Nothing to Disclose, Faisal Abaalkhail:Nothing to Disclose.

4217 | MEDICAL MANAGEMENT OF PATIENTS UNDERGOING ELECTIVE, LIVER-RELATED INVASIVE PROCEDURES – A NOVEL COLLABORATION MODEL BETWEEN HEPATOBILIARY SURGEONS AND HEPATOLOGISTS

Chiara Mangini[1] Federica Giunta[1] Cecilia Busato[1] Domenico Bassi[1] Riccardo Boetto[1] Carmine Gabriele Gambino[1] Riccardo Carandina[1] Matteo Ghisa[1] Caterina Soldà[2] Sabrina Cervesato[3] Michele Tessarin[4] Umberto Cillo[1] Sara Montagnese[1], [1]University of Padova, [2]Veneto Institute of Oncology IOV-IRCCS, Padova, Italy, [3]Universty of Padova, [4]Medical Management, Padova University Hospital

Background: To describe and evaluate a novel, joint surgical-hepatological management model for patients undergoing elective hepatobiliary procedures within the setting of a short medical hospitalization. **Methods:** Elective admissions to the Internal Medicine Ward 5 - Hepatology of Padova University Hospital for the above purpose between Feb 2023 (when the new system was implemented) and Dec 2025 were jointly scheduled and prioritized by a designated hepatologist and hepato-biliary surgeon, and managed by a specialist nurse. Outcomes of interest included length of the inpatient stay, complications and their management, plus estimated health costs. **Results:** 462 procedures (records of 74% male patients, 67 ± 12 years) were performed over the observation period, including 125 (27%) endoscopic retrograde cholangiopancreatographies (ERCP), 178 (39%) locoregional treatments (LRT) for liver lesions, 89 (19%) percutaneous transhepatic biliary drainages (PTBD), and 70 (15%) "other". 336 (73%) were first admissions and 126 (27%) were repeated admissions for scheduled multistep protocols. Most common underlying conditions were cirrhosis (33%), a history of liver transplantation (23%), and hepatobiliary malignancies (59%). Average inpatient stay was 2.4 ± 6.1 days, with 85% discharged within 72 hours. Complications occurred in 88 patients (19%), with significantly longer hospitalizations (6.7 ± 12.5 days vs 1.2 ± 0.6, $p < 0.001$), especially for PTBD (Figure). By way of comparison, 201 of the 3 most common procedures had been performed in the hepatobiliary surgery ward over the year 2022. Admissions were 16.8 per month in surgery and 13.2 in medicine, with pertinent, adjusted costs being € 18,085 in medicine and € 47,500 in surgery. **Conclusion:** Hepatological-surgical co-management of patients undergoing hepatobiliary procedures within the setting of an elective medical hospitalization is feasible, cost-effective and most likely scalable.



Disclosures: Chiara Mangini:Nothing to Disclose, Federica Giunta:Nothing to Disclose, Cecilia Busato: Nothing to Disclose, Domenico Bassi:Nothing to Disclose, Riccardo Boetto:Nothing to Disclose, Carmine Gabriele Gambino:Nothing to Disclose, Riccardo

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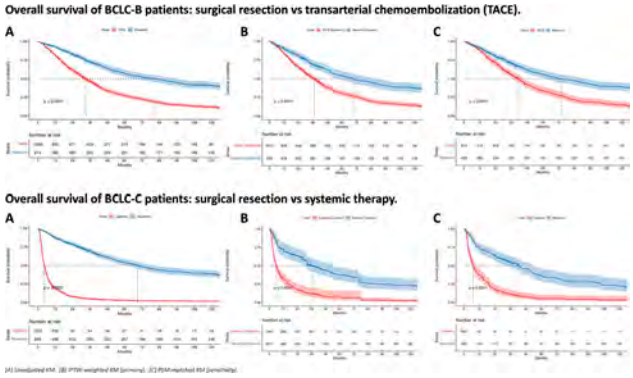
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Carandina:Nothing to Disclose, Matteo Ghisa:Nothing to Disclose, Caterina Soldà:Nothing to Disclose, Sabrina Cervesato:Nothing to Disclose, Michele Tessarin: Nothing to Disclose, Umberto Cillo:Nothing to Disclose, Sara Montagnese:Nothing to Disclose.

4218 | POPULATION-LEVEL OUTCOMES OF CUSE-GUIDED TREATMENT STAGE MIGRATION TO SURGICAL RESECTION IN BCLC-B AND BCLC-C HCC: A NATIONWIDE KOREAN REGISTRY ANALYSIS

Minseob Kim[1] Youngrok Choi[1] Suk Kyun Hong[1] Su Young Hong[1] Hye-Sung Jo[1] Kwang-Woong Lee[1] Eun-Woo Choi[2], [1]Seoul National University, College of Medicine, [2]Department of Surgery, Seoul National University College of Medicine, Seoul, Korea

Background: Surgical resection is the recommended curative option for hepatocellular carcinoma (HCC) at Barcelona Clinic Liver Cancer (BCLC) stage 0/A, whereas transarterial chemoembolization (TACE) and systemic therapy are recommended for intermediate (BCLC-B) and advanced (BCLC-C) disease, respectively. Whether selected BCLC-B or BCLC-C patients benefit from resection remains uncertain. Therefore, we investigated this in a nationwide Korean cohort. **Methods:** From 21,178 patients in the Korean Primary Liver Cancer Registry (2008–2021), we identified 1,713 with BCLC-B HCC (resection vs TACE) and 2,031 with BCLC-C HCC (resection vs systemic therapy). Inverse probability of treatment weighting (IPTW) was the primary analysis; propensity score matching (PSM), cause-specific Cox regression, restricted mean survival time (RMST), and era-stratified analysis were sensitivity analyses. **Results:** Pre-weighting imbalances across baseline covariates — most pronounced for tumor multifocality and (in BCLC-C) macrovascular invasion and distant metastasis — were balanced after IPTW (all standardized mean differences <0.1). Resection was associated with substantially better overall survival: hazard ratio (HR) 0.528 (95% CI 0.446–0.626) for BCLC-B and 0.327 (0.241–0.442) for BCLC-C. RMST gains in the matched cohort were 7.0 (4.3–9.7) and 22.3 (18.2–26.4) months, respectively. Cause-specific HRs for cancer death (0.506 [BCLC-B] and 0.332 [BCLC-C]) mirrored overall estimates. The benefit was preserved in the post-IMbrave era (HR 0.203, 0.105–0.392). **Conclusion:** In carefully selected BCLC-B and BCLC-C patients in this Korean nationwide cohort, surgical resection was associated with substantially better survival than the standard first-line option, supporting CUSE-guided multidisciplinary evaluation of surgical candidacy. The magnitude of effect likely reflects both real biological benefit in resectable patients and residual selection by unmeasured operability factors; prospective definition of resectability criteria is warrante



Disclosures: MINSEOB KIM:Nothing to Disclose, Youngrok Choi:Nothing to Disclose, Suk Kyun Hong: Nothing to Disclose, Su Young Hong:Nothing to Disclose, Hye-Sung Jo:Nothing to Disclose, Kwang-Woong Lee:Nothing to Disclose, Eun-Woo Choi:Nothing to Disclose.

4219 | STEROTACTIC BODY RADIATION THERAPY VERSUS YTTRIUM-90 TRANSARTERIAL RADIOEMBOLIZATION FOR HEPATOCELLULAR CARCINOMA: A SYSTEMATIC REVIEW AND META-ANALYSIS

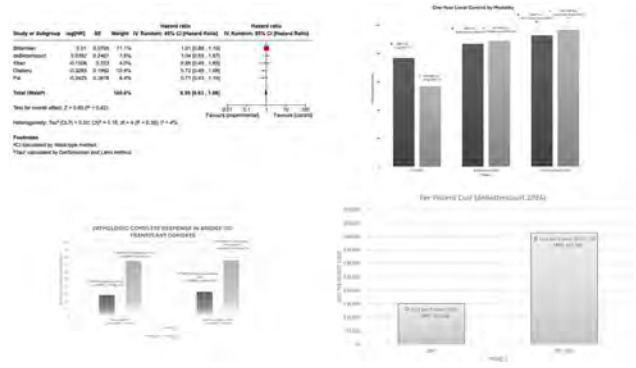
Bilind Ismail[1] Hasan Al-Obaidi[2] Hayder Alamily[2] Abdulkareem Jomaa[3] Muhammad Tausif[4] Zoha Khan[5] Hrishikesh Samant[6], [1]Willis Knighton Health, [2]University of Toledo, [3]University of Duhok College of Medicine, [4]Willis-Knighton Health, [5]Rawalpindi Medical University, [6]Ochsner Clinic Foundation

Background: Hepatocellular carcinoma (HCC) is the most common primary liver cancer. Considering the recent advances, locoregional therapy in the management of liver-confined disease is increasing. Among the various options, stereotactic body radiation therapy (SBRT) and yttrium-90 (Y90) transarterial radioembolization (TARE) are becoming popular for disease control and bridging to transplant. **Methods:** We performed a PRISMA 2020-compliant systematic review and meta-analysis of PubMed, EMBASE, MEDLINE, and Cochrane CENTRAL from 2010 to May 2026. Eligible studies directly compared SBRT and Y90 TARE for HCC at any BCLC stage. Primary outcomes were overall survival (OS) and local control. Secondary outcomes were progression-free survival (PFS), complete response in bridge-to-liver-transplant cohorts, grade ≥ 3 toxicity, and per-patient cost when reported. Pooled

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estimates were calculated in RevMan. Risk of bias was assessed by ROBINS-I and certainty by GRADE. **Results:** Nine studies were included (N ≈ 12,747). Patient and disease characteristics differed widely across studies, which limits comparability. Five studies reported adjusted HRs for OS were Pai 2025 (n = 247), 0.71 (95% CI 0.43-1.20); Oladeru 2016 (n = 189), 0.72 (0.49-1.07); Khan 2026 (n = 9,084, indirect), 0.86 (0.45-1.66); Bitterman 2019 (n = 2,685), 1.01 (0.88-1.16); and deBettencourt 2024 (n = 84), 1.04 (0.65-1.67). The pooled random-effects HR for OS was 0.95 (95% CI 0.83-1.08, $I^2 = 4\%$), with no statistically significant difference between modalities. Local control varied widely (57-97%) without a consistent modality advantage after adjustment. PFS was similarly neutral (HR 0.96, 0.61-1.50). In bridge-to-transplant cohorts, Y90 TARE produced higher rates of complete tumor necrosis at explant, 75% vs. 28.5% (Mohamed 2016) and 76% vs. 33% (De la Garza-Ramos 2025). Grade ≥3 toxicity was uncommon and similar where it was reported. One institutional cost analysis suggested lower per-patient costs with SBRT ($15,148 vs. $41,360 for Y90), though downstream costs were not evaluated. Risk of bias was serious across all studies. GRADE certainty was very low for all outcomes. **Conclusion:** Across available comparative studies, SBRT and Y90 TARE showed no statistically significant differences in adjusted or pooled OS, local control, or PFS. The most consistent finding was in bridge-to-transplant populations, where Y90 TARE produced higher rates of complete tumor necrosis in both series that reported it. Limited cost data favored SBRT per patient, though downstream costs were not captured. In the absence of randomized evidence, treatment selection should be individualized based on transplant strategy, tumor burden, liver reserve, and multidisciplinary expertise. Ongoing trials including BIIRTH (NCT07293468) and NCT07530172 are actively enrolling and will provide the first randomized comparative data.



Disclosures: BILIND ISMAIL:Nothing to Disclose, Hasan Al-Obaidi:Nothing to Disclose, Hayder Alamily: Nothing to Disclose, Abdulkareem Jomaa:Nothing to Disclose, Muhammad Tausif:Nothing to Disclose, Zoha Khan:Nothing to Disclose, Hrishikesh Samant:Nothing to Disclose.

4220 | MULTIDIMENSIONAL PROGNOSTIC STRATIFICATION INTEGRATING NUTRITION, FIBROSIS, STEATOSIS, AND CARDIOMETABOLIC BURDEN FOR HEPATOCELLULAR CARCINOMA PATIENTS UNDERGOING CURATIVE RESECTION

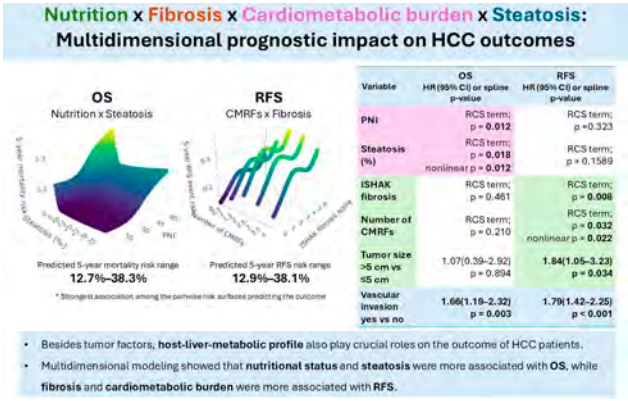
Chun-Ting Ho[1] Shin-Yu Tsai[2] Chia-Jung Ho[3] Yi-Hsiang Huang[2] Ming-Chih Hou[2] Jaw-Ching Wu[4] Chien-Wei Su[2], [1]Taipei Veterans General Hospital/NYCU, [2]Taipei Veterans General Hospital, [3]Taichung Veterans General Hospital, [4]National Yang Ming Chiao Tung University

Background: Besides tumor factors, the prognosis of hepatocellular carcinoma (HCC) patients after curative resection can also be influenced by host factors, including nutritional reserve, fibrosis severity, hepatic steatosis, and cardiometabolic risk factors (CMRFs). However, their joint prognostic impact has not been well evaluated. We aim to comprehensively evaluate the joint prognostic impact of nutrition, fibrosis, steatosis, and cardiometabolic burden on HCC patients undergoing surgical resection. **Methods:** 1004 HCC patients undergoing curative resection at a tertiary center in Taiwan were analyzed. Four host–liver–metabolic domains were evaluated: nutritional status using the prognostic nutritional index (PNI), fibrosis severity using the ISHAK fibrosis grade, hepatic steatosis using histologic steatosis percentage, and cardiometabolic burden using the number of comorbid CMRFs. Multivariable Cox proportional (COX PH) hazardous models adjusted for age, gender, tumor size, tumor number, vascular invasion, Child–Pugh class, and viral etiology were performed to identify independent prognostic factors. Restricted cubic splines (RCS) were used to model potential nonlinear associations. Pairwise 3D risk surfaces/bands of the four domains were generated to visualize the 5-year outcome risks. **Results:** After a median follow-up of 55 months, 210 patients had died. The 5-year overall survival (OS) was 71.4%, and the 5-year recurrence-free survival (RFS) was 48.9%. The COX PH models for OS and RFS including the four domains were both statistically significant with good discrimination (likelihood ratio χ^2 = 103.64 and 106.44, both $p < 0.001$; approximate C-index = 0.716 and 0.673). Among the four domains, nutritional status was significantly associated with OS (χ^2 = 10.88, p = 0.012), and steatosis demonstrated a significant nonlinear association with OS (χ^2 = 10.10, p = 0.018; nonlinear p = 0.012). Vascular invasion was also associated with worse OS. Regarding RFS, Ishak fibrosis grade was identified as an independent risk factor (χ^2 = 11.72, p = 0.008), as well as

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cardiometabolic burden (χ^2 = 6.88, p = 0.032), tumor size, and vascular invasion. In adjusted risk-surface visualization, the PNI and steatosis surface demonstrated the greatest discriminability for 5-year OS, whereas the fibrosis and CMRF surface showed the most prominent gradients for 5-year RFS event risk. **Conclusion:** Nutrition, fibrosis, steatosis, and cardiometabolic burden play important roles in the prognosis of HCC patients. While nutrition and steatosis were more closely associated with OS, fibrosis and cardiometabolic burden were more relevant to RFS. Adjusted 3D risk-surface visualization demonstrated a clinically interpretable and heterogeneous multi-dimensional prognostic landscape. These findings revealed the diverse impact of host-liver-metabolic factors on the outcome of HCC patients undergoing curative resection.

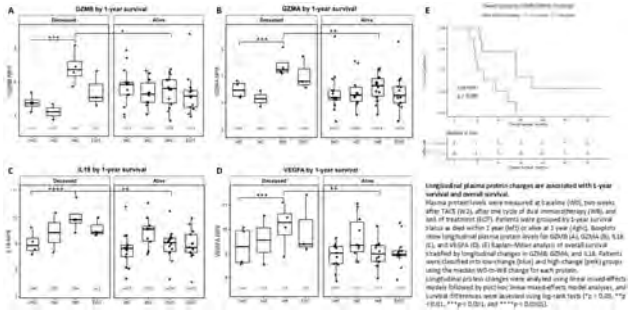


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4221 | LONGITUDINAL PLASMA PROTEIN DYNAMICS ASSOCIATED WITH SURVIVAL IN INTERMEDIATE-STAGE HEPATOCELLULAR CARCINOMA TREATED WITH TACE FOLLOWED BY DURVALUMAB AND TREMELIMUMAB

Boqun Zhu[1] Harry Luu[1] Leya Chambo[1] Aida Kamalian[1] Abhay Moghekar[1] Hong Kelvin[1] Ana De Jesus-Acosta[1] Amy Kim[1], [1]Johns Hopkins University School of Medicine

Background: Combining transarterial chemoembolization with immune checkpoint blockade is an emerging strategy for intermediate-stage hepatocellular carcinoma (HCC), but biomarkers that guide patient selection and predict clinical outcomes remain limited. We evaluated longitudinal plasma protein changes to identify candidate biomarkers associated with 1-year survival and overall survival (OS) in patients with Barcelona Clinic Liver Cancer (BCLC) stage B disease treated with TACE followed by dual immunotherapy. **Methods:** In a phase II trial (NCT03638141), 20 patients with unresectable, transplant-ineligible BCLC stage B HCC were enrolled, and included in this analysis. Patients received TACE followed by durvalumab and tremelimumab. Plasma samples were collected at baseline (W0, pre-treatment), Week 2 after TACE (W2), Week 8 after 1 cycle of immunotherapy (W8), and end of treatment (EOT). Samples were profiled for 92 immune-oncology proteins (Olink's proximity extension assay). Protein abundance was reported as normalized protein expression (NPX) values. Plasma protein dynamics were evaluated according to 1-year survival status and overall survival (OS). For survival analyses, protein change was defined as W8 minus W0 NPX values. Patients were stratified into high- and low-change groups using the median change value for each marker. **Results:** Among 20 patients, four patients had died by 1 year after TACE. Compared with 1-year survivors, patients who died within 1 year had higher W8 plasma levels of GZMB, GZMA, IL18, and VEGFA. These patients also demonstrated greater increases in GZMB, GZMA, IL18, and VEGFA from W0 to W8 compared to1-year survivors (Fig 1). Patients were further stratified into high- and low-GZMB/GZMA/IL18 groups using their median W0-to-W8 change. High increases in GZMB, GZMA, or IL18 were each associated with significantly worse overall survival compared with low-change groups. **Conclusion:** Early increases in GZMB, GZMA, and IL18 from W0 to W8 identified a high-risk group with higher 1-year mortality and worse overall survival. These findings may indicate robust but ineffective immune activation rather than effective tumor control early after treatment and may enable early risk stratification for poor outcomes.



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Disclose, Ana De Jesus-Acosta:Nothing to Disclose, Amy Kim:AstraZeneca: Speaking and Teaching.

4222 | TRANSARTERIAL CHEMO- VERSUS RADIO-EMBOLIZATION FOR EARLY AND INTERMEDIATE STAGE HEPATOCELLULAR CARCINOMA (HCC): A CLINICAL AND COST COMPARISON ANALYSIS IN A NATIONAL COHORT

Meena Tadros[1] Courtney Williamson[2] Shalini Bansal[3] David Kaplan[1], [1]University of Pennsylvania, [2]Corporal Michael J Crescenz Philadelphia VA Medical Center, [3]The Mount Sinai Hospital

Background: Trans-arterial chemo- and radioembolization (TACE and TARE) are primary treatment modalities for early- and intermediate-stage hepatocellular carcinoma (HCC). Prior studies, primarily from tertiary academic centers, comparing outcomes and cost for TACE and TARE have shown mixed results. We aimed to directly compare TACE and TARE clinical and cost effectiveness in a non-tertiary setting in a national Veterans Affairs (VA) cohort. **Methods:** We reviewed patients with HCC diagnosed from 1/1/2021 to 4/1/2021 who underwent first-line (1L) TACE or TARE for HCC within the VA system. Severity of liver disease, tumor characteristics including Barcelona Clinic Liver Cancer (BCLC) staging, ECOG performance status, treatment history/response (LI-RADs), clinical outcomes and costs (VA HERC and DSS) were collected. Survival was evaluated by Kaplan-Meier methodology, with adjustment for unbalanced baseline covariates. **Results:** We identified 121 patients who received 1L TACE (n = 94) or TARE (n = 27). Median age was 69.4, 99.2% were male, 59.5% were White, 19.8% Black and 12.4% Hispanic. Predominant underlying liver disease was ALD ± HCV with 22% MASH. Child-Pugh A5/A6/B7/B8+ status was 58/19/12/11%. There was no statistical difference in BCLC Stage between TACE and TARE patients, with similar median tumor number. Patients selected for TARE had larger size of the largest tumor (4.0 vs. 2.7 cm, p = 0.0009, and total tumor diameter (4.6 vs. 2.9 cm, p = 0.0055). ALBI grade was more likely to be 2A among TARE patients (p = 0.04). Pre-treatment AFP was also higher for patients undergoing TARE (44.5 vs.10.0 p = 0.0049). During follow-up, response rates by LI-RADs were similar among TACE and TARE patients, with LR-TR nonviable status achieved in 46.2%. The median total number of treatments received did not differ, p = 0.84. Median survival was 960d (95% CI 810-1650) for TACE and 570d (95% CI 360-NA) for TARE, p = 0.44. In unadjusted Cox analysis and analyses adjusted for tumor size, AFP, and ALBI grade, there was no significant difference in the risk of mortality between TACE and TARE. There was no significant difference in the likelihood of worsening Child-Pugh or ALBI score during 1 year of follow-up. Median cost of healthcare in the first year of follow-up did not differ between TACE and TARE, $136K vs. $141K, however there was trend towards higher inpatient cost for TACE patients $24.9K vs. $8.5K, p = 0.07 (Table 1). **Conclusion:** In this preliminary cohort with ongoing data collection, there were no significant differences in survival, liver function, or total healthcare costs when TACE or TARE was first line therapy for early or intermediate stage HCC. Further analysis with propensity matching, stage stratification, and generalized linear modeling for cost to assess the average marginal cost of treatment choice is planned.

Table 1. Baseline Characteristics of Patients Receiving Locoregional Therapy for HCC and Subsequent Costs (n=121)

Variable		Overall	TACE	TARE	p-value
n		121	94	27	
Age at Treatment (years) (median [IQR])		69.40 [65.60, 73.90]	69.00 [65.67, 73.80]	70.30 [65.90, 74.10]	0.70
Sex (%)	M	120 (99.2)	94 (100.0)	26 (96.3)	0.50
	F	1 (0.8)	0 (0.0)	1 (3.7)	
Race/Ethnicity (%)	White	72 (59.5)	53 (56.4)	19 (70.4)	0.51
	Black	24 (19.8)	19 (20.2)	5 (18.5)	
	Hispanic	15 (12.4)	13 (13.8)	2 (7.4)	
	Other/Unknown	10 (8.3)	9 (9.6)	1 (3.7)	
Liver Disease Etiology (%)	ALD	27 (22.3)	25 (26.6)	2 (7.4)	0.07
	ALD + HCV	33 (27.3)	25 (26.6)	8 (29.6)	
	HCV	32 (26.4)	21 (22.3)	11 (40.7)	
	MASH	27 (22.3)	22 (23.4)	5 (18.5)	
	HBV	1 (0.8)	0 (0.0)	1 (3.7)	
	Other	1 (0.8)	1 (1.1)	0 (0.0)	
Child-Turcotte-Pugh Class (%)	A	93 (76.9)	71 (75.5)	22 (81.5)	0.53
	B	24 (19.8)	19 (20.2)	5 (18.5)	
	C	4 (3.3)	4 (4.3)	0 (0.0)	
Largest Tumor (median [IQR])		2.90 [2.1, 4.4]	2.70 [1.9, 3.8]	4.00 [3.0, 6.1]	**0.0009**
Total Tumor Diameter (median [IQR])		3.4 [2.3, 5.8]	2.90 [2.1, 5.1]	4.6 [3.4, 8.5]	**0.0055**
BCLC Stage (%)	0	12 (10.0)	10 (10.8)	2 (7.4)	0.30
	A	81 (67.5)	65 (69.9)	16 (59.3)	
	B	21 (17.5)	15 (16.1)	6 (22.2)	
	C	6 (5.0)	3 (3.2)	3 (11.1)	
Size of treated treated (median [IQR])		3.5 [2.4, 5.8]	2.9 [2.3, 5.3]	4.9 [3.4, 8.4]	**0.0078**
RECIST Response (%)	LR-TR Nonviable	55 (46.2)	42 (45.7)	13 (48.1)	0.71
	LR-TR Equivocal	17 (14.3)	12 (13.0)	5 (18.5)	
	LR-TR Viable	37 (31.1)	29 (31.5)	8 (29.6)	
	LR-TR Not Evaluable	10 (8.4)	9 (9.8)	1 (3.7)	
Total Locoregional Treatments Received (median [IQR])		2.0 [1.0, 2.0]	2.0 [1.0, 2.0]	2.0 [1.0, 2.0]	0.84
Pretreatment AFP (ng/ml) (median [IQR])		12.7 [4.6, 126.3]	9.9 [3.8, 69.7]	44.50 [10.9, 704.1]	**0.0049**
Baseline modified ALBI Class (%)	1	55 (45.5)	46 (48.9)	9 (33.3)	**0.0362**
	2A	22 (18.2)	12 (12.8)	10 (37.0)	
	2B	36 (29.8)	29 (30.9)	7 (25.9)	
	3	8 (6.6)	7 (7.4)	1 (3.7)	
Year 1 Cost (median US$ [IQR])		138.3K [56.7,206.9]	136.6K [54.6, 198.3]	141.4K [61.1, 305.2]	0.58
Year 2 Cost (median US$ [IQR])		15.7K [0.0, 63.3]	17.0 [0.0, 70.2]	5.8 [0.0, 50.2]	0.42
Year 1 Inpatient Cost (median [IQR])		22.4K [7.4, 53.8]	24.9 [7.4, 52.9]	8.5 [0.0, 54.1]	0.07
Year 2 Inpatient Cost (median [IQR])		0.0 [0.0, 7.9]	0.0 [0.0, 14.6]	0.0 [0.0, 0.0]	0.06

Disclosures: Meena Tadros:Nothing to Disclose, Courtney Williamson:Nothing to Disclose, Shalini Bansal:Nothing to Disclose, David Kaplan:AstraZeneca Inc: Grant/Research Support, Roche Genentech: Independent Contractor, Exact Sciences: Grant/Research Support, Glycotest: Grant/Research Support, Exelixis: Advisor, AstraZeneca: Advisor, Gilead: Grant/Research

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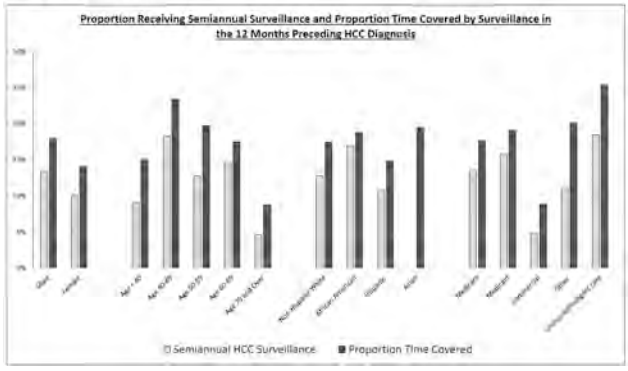
Support, Bausch Healthcare: Grant/Research Support, Mirumn: Grant/Research Support, Bausch: Grant/Research Support, Exact Sciences: Grant/Research Support, AstraZeneca: Grant/Research Support, Mirum: Grant/Research Support.

4223 | CONSISTENT GASTROENTEROLOGY/LIVER CLINIC FOLLOW-UP IS THE STRONGEST PREDICTOR OF HEPATOCELLULAR CARCINOMA SURVEILLANCE AMONG ADULTS WITH CIRRHOSIS

Robert Wong[1] Bolin Niu[2] Mandana Khalili[3] Paulo Pinheiro[4] Mae Thamer[5] Onkar Kshirsagar[5] Yi Zhang[5] Ronnie Fass[2] Jasmine Davis[4] Lisa Quirk[6] George Therapondos[7] Amit Singal[6] Patricia Jones[8], [1]Stanford/VA Palo Alto Healthcare System, [2]MetroHealth Medical Center, [3]University of California, San Francisco, [4]University of Miami, [5]Medical Technology and Practice Patterns Institute, [6]University of Texas Southwestern, [7]Ochsner Health System, [8]University of North Carolina at Chapel Hill

Background: Guideline-concordant surveillance for hepatocellular carcinoma (HCC) in patients with cirrhosis improves HCC detection at an earlier stage. However, HCC surveillance remains underutilized in real-world settings, contributing to a more advanced tumor stage at diagnosis. We evaluated gaps in HCC surveillance prior to HCC diagnosis, and whether modifiable factors could be identified to improve surveillance. **Methods:** Adults with cirrhosis who were diagnosed with HCC from 3/1/2018 – 2/29/2024 across four U.S. safety-net health systems were evaluated. HCC surveillance in the 12 months prior to HCC diagnosis was assessed by the 1) proportion having semiannual surveillance imaging and 2) proportion of time covered (PTC), estimated by dividing the number of covered months (6 months of coverage applied to each completed surveillance exam) that fell within this 12- month period by 12. Adjusted multivariable logistic regression and linear regression models evaluated predictors of semiannual surveillance and PTC, respectively. **Results:** A total of 622 adults with HCC were identified (mean age 61.8y, 74.6% men, 46.0% Hispanic, 28.8% non-Hispanic white, 16.1% African American, 1.0% Asian, 33.3% Medicare, 25.4% Medicaid, 12.2% uninsured/indigent care). At HCC diagnosis, 14% had very early BCLC stage 0 and 62.9% within Milan criteria. In the 12 months prior to HCC diagnosis, 12.5% received semiannual surveillance, which was higher in men (vs. women), highest in adults age 40-49y, and highest in those with Medicaid or uninsured/indigent care (Figure). Overall, mean PTC was 16.9% (mean 2.03 months), which was higher in men vs. women, highest in adults age 40-49y, highest in Asians, and highest in those with indigent care or uninsured (Figure). On multivariable regression, only linkage to GI/Liver clinic ($\geq$1 visit within past 12 months) was significantly associated with semiannual HCC surveillance. Compared to patients who did not have GI/Liver visit, those who did had significantly greater odds of semiannual surveillance (aOR 7.08, 95% CI 3.94-12.70) and significantly greater PTC (3.80 vs. 1.80 months in those without GI/Liver clinic follow up, $p < 0.01$) prior to HCC diagnosis. **Conclusion:** Among a multi-center safety-net cohort of cirrhosis patients who developed HCC, major gaps in surveillance were observed. Patients who were engaged into GI/Liver care were significantly more likely to have had HCC surveillance prior to HCC diagnosis, emphasizing the importance of improved engagement with primary care and ensuring consistent GI/Liver follow-up in those with access to liver care.

Figure. Proportion Receiving Semiannual Surveillance and Proportion Time Covered by Surveillance in the 12 Months Preceding HCC Diagnosis



Disclosures: Robert Wong:Theratechnologies: Grant/Research Support, Theratechnologies: Grant/Research Support, Durect: Grant/Research Support, Durect: Grant/Research Support, Gilead Sciences: Grant/Research Support, Gilead Sciences: Grant/Research Support, Exact Sciences: Grant/Research Support, Exact Sciences: Grant/Research Support, Madrigal Pharmaceuticals: Grant/Research Support, Theratechnologies: Grant/Research Support, Theratechnologies: Grant/Research Support, Durect: Grant/Research Support, Durect: Grant/Research Support, Gilead Sciences: Grant/Research Support, Gilead Sciences: Grant/Research Support, Exact Sciences: Grant/Research Support, Exact Sciences: Grant/Research Support, Madrigal Pharmaceuticals: Grant/Research Support, Bolin Niu:Nothing to Disclose, Mandana Khalili:gilead sciences: Grant/Research Support, GSK pharmaceuticals: Consultant, Intercept pharmaceuticals: Grant/Research Support, Gilead Sciences Inc: Consultant, Resolution Therapeutics: Consultant, Paulo Pinheiro:Nothing to Disclose, Mae Thamer:

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Nothing to Disclose, Onkar Kshirsagar:Nothing to Disclose, Yi Zhang:Nothing to Disclose, Ronnie Fass: Nothing to Disclose, Jasmine Davis:Nothing to Disclose, Lisa Quirk:Nothing to Disclose, George Therapondos:Novo Nordisk: Consultant, Intercept: Speaking and Teaching, Madrigal: Speaking and Teaching, Ipsen: Speaking and Teaching, Gilead: Speaking and Teaching, Amit Singal:Genentech: Consultant, AstraZeneca: Consultant, Bayer: Consultant, Eisai: Consultant, Exelixis: Consultant, Merck: Consultant, Elevar: Consultant, FujiFilm Medical Sciences: Consultant, Exact Sciences: Consultant, Glycotest: Consultant, Boston Scientific: Consultant, Sirtex: Consultant, HelioGenomics: Consultant, ImCare: Consultant, DELFI: Consultant, Curve Biosciences: Consultant, Catalym: Consultant, Verve: Consultant, Patricia Jones:Nothing to Disclose.

4224 | CLINICAL PREDICTORS OF IMMUNE CHECKPOINT INHIBITOR RESPONSE IN ADVANCED CHOLANGIOCARCINOMA: ANALYSIS FROM A MULTI-SITE TERTIARY CARE CENTER

Sarah Khan[1] Diana Segovia[1] Jessie Hohenstein[1] Qian Shi[1] Chen Wang[1] Lewis Roberts[2], [1]Mayo Clinic-Rochester, [2]Mayo Clinic Rochester

Background: Cholangiocarcinoma (CCA) is a highly lethal malignancy whose prognosis remains dismal, partly due to unpredictable response to systemic therapies including first-line immune checkpoint inhibitors (ICI). This analysis aims to characterize predictors of ICI response in advanced CCA. **Methods:** Patients with CCA treated across the tri-site Mayo Clinic from 2018-2025 were evaluated. Clinical variables were investigated, including patient characteristics, tumor molecular data and oncologic course. ICI response was classified per RECIST criteria using 3–6-month surveillance imaging scans, with development of a disease-controlled cohort (DC) (stable disease, partial or complete response) and non-responder cohort (progressive disease). **Results:** Our final cohorts included 60 ICI responders (DC; 65.9%) and 31 non-responders (NR; 34.1%). The cohort was predominantly Caucasian (96.7%), of median age 65.6 years and with slight female predominance (56.0%). Median overall survival from diagnosis was 4.3 years in DC versus 1.4 years in NR ($p = 0.05$), with 43.3% of DC versus 96.8% of NR dying during follow-up ($p < 0.001$; figure 1A). Median progression-free survival was 2.5 years for DC vs 0.9 years for NR ($p < 0.001$, figure 1B). CCA subtypes included intrahepatic ($n = 55$), perihilar ($n = 28$), and distal CCA ($n = 8$), without significant difference between groups. The dominant first-line regimen was durvalumab-based (76.7% DC vs. 77.4% NR), followed by pembrolizumab (16.7% DC vs 16.1% NR), and no significant difference in regimens between cohorts ($p = 0.896$). Compared to metastatic disease (M1), patients with M0 disease were more likely to be DC (75.5% vs 24.5%, $p = 0.04$). DC patients more frequently had surgical resection (79.4% vs 20.6%, $p = 0.04$, figure 1C) and second-line immunotherapy (21.1% vs. 0%, $p = 0.006$). Survival difference persists between DC and NR when comparing non-surgical canidates. No differences were present in microsatellite instability or histologic grade. Patients with IDH1 mutations were less likely to respond to ICI, while those with CDKN2A mutations were more likely (OR 0.20, $p = 0.04$ for IDH1 and OR 7.20, $p = 0.072$ for CDKN2A). Multivariable regression identified M1 disease as a predictor of non-response (M1 OR 0.26, $p = 0.02$). Models adjusting for pre-treatment tumor size, multifocal disease, M1, tumor mutation burden and serum CA19-9 achieved AUC 0.73 (95% CI 0.51-0.95) and 0.79 (95% CI 0.65-0.94) for extrahepatic and intrahepatic ICI response prediction (figure 1D). **Conclusion:** Our analysis identifies important predictors of ICI response including M1 status and IDH1 mutations. Models revealed these characteristics were more predictive than most molecular tumoral characteristics, though sample size is a limitation. These findings are critical for improving precise prognostication of CCA patients.

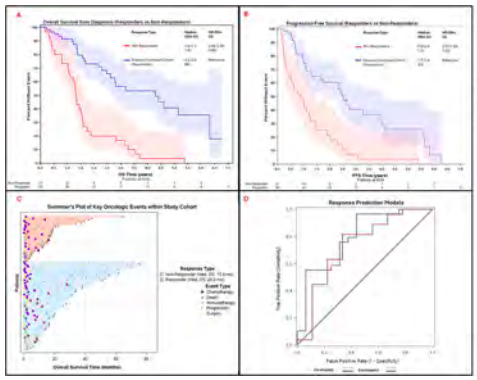


Figure 1:
A. Overall survival comparison by immune checkpoint inhibitor response type between disease-controlled cohort (DC, i.e., responders) vs non-responders (NR).
B. Progression-free survival comparison of DC vs NR.
C. Swimmer's plot detailing oncologic courses of DC and NR.
D. Areas under the curve for clinical models predicting ICI response for intrahepatic and extrahepatic (perihilar and distal) CCA.

Disclosures: Sarah Khan:Nothing to Disclose, Diana Segovia:Nothing to Disclose, Jessie Hohenstein:Nothing to Disclose, Qian Shi:Nothing to Disclose, Chen Wang:Nothing to Disclose, Lewis Roberts:Nothing to Disclose.

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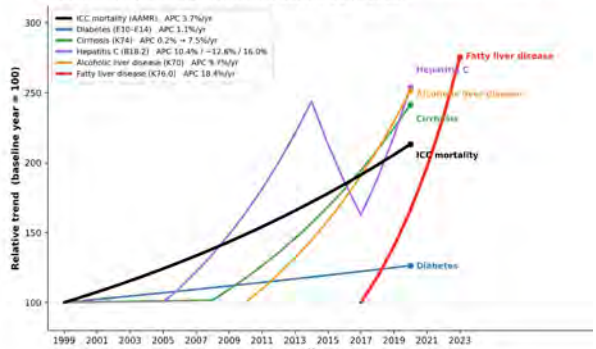
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4225 | TRENDS IN INTRAHEPATIC CHOLANGIOCARCINOMA MORTALITY AND SHIFTING COMORBIDITY PROFILE IN THE UNITED STATES, 1999–2020: A POPULATION-BASED MULTIPLE CAUSE OF DEATH ANALYSIS

Kanachai Boonpiraks[1] Kyle Yuquimpo[1] Nizar Talaat[1], [1]University of Kansas Medical Center

Background: Intrahepatic cholangiocarcinoma (ICC) is the second most common primary liver malignancy, with rising US incidence and mortality. The comorbidity profile of ICC decedents has not been systematically characterized, despite growing concern that metabolic dysfunction-associated steatotic liver disease (MASLD) may be an emerging risk factor for liver cancer. Hence, we aim to evaluate liver-related co-lisitng deaths to gain proper population-level insight. **Methods:** We conducted a retrospective, population-based mortality study using the CDC WONDER Multiple Cause of Death databases (1999–2020 finalized and 2018–2023 expanded for fatty liver). We identified all decedents with ICC (ICD-10 C22.1) as underlying cause. Age-adjusted mortality rates (AAMR) per 100,000 (2000 US standard population) were calculated and stratified by sex, race, and Hispanic origin. Joinpoint regression model was used to estimate annual percent change (APC) with 95% confidence interval (CI). We identified ICC deaths co-listing diabetes (E10–E14), cirrhosis (K74), chronic hepatitis C (B18.2), alcoholic liver disease (K70), or fatty liver disease (K76.0), and assessed temporal trends in proportions. **Results:** A total of 107,149 ICC deaths occurred from 1999–2020. AAMR rose from 0.9 to 1.9 per 100,000 (APC 3.67%, 95% CI 3.29–4.00, $p < 0.001$), with no joinpoints. African American individuals had the steepest racial increase (APC 4.08%), while Asian/Pacific Islanders maintained the highest absolute AAMR. Males had consistently higher absolute mortality rates than females. The comorbidity profile shifted markedly throughout the following period as shown in Figure 1. Cirrhosis co-listing nearly tripled (0.98% to 2.89%) with acceleration after 2008 (APC 7.48%, $p = 0.011$). Alcoholic liver disease grew at 9.66%/year ($p = 0.015$). Hepatitis C showed an interesting trend of significant rise through 2014 then a decline from 2014-2017, followed by a rebound. Diabetes increased modestly (APC 1.12%, $p < 0.001$). Fatty liver disease data was absent before 2017. However, it rose from 14 to 42 annual ICC deaths during 2017–2023 putting it as the steepest comorbidity trend observed in the study (APC 18.40%, 95% CI 12.63–26.47, $p < 0.001$). **Conclusion:** ICC mortality continues to rise in the US with significant racial disparities. The comorbidity profile of ICC decedents is shifting toward metabolic and alcohol-associated liver disease, most strikingly with fatty liver disease. This could reflect the growing population burden of MASLD. These findings support heightened clinical awareness of MASLD-related liver cancer risk and may inform surveillance strategies.

Figure 1. Relative trends in intrahepatic cholangiocarcinoma (ICC) mortality and co-listed comorbidities, United States, 1999–2023



Each line is the joinpoint-modeled trend, indexed to 100 at that series' first analyzed year (ICC mortality, diabetes & cirrhosis 1999; hepatitis C 2003; alcoholic liver disease 2010; fatty liver disease 2017). Comorbidity lines show the proportion of ICC deaths co-listing each condition (1999–2020); fatty liver shows the crude ICC death rate co-listing K76.0 (2011–2023, provisional). Indexing places all series on one scale so relative change is directly comparable.

Disclosures: Kanachai Boonpiraks:Nothing to Disclose, Kyle Yuquimpo:Nothing to Disclose, Nizar Talaat:Madrigal: Speaking and Teaching.

4226 | CYTOKERATIN 19 EXPRESSION STRATIFIES OUTCOMES WITH HEPATIC ARTERIAL INFUSION CHEMOTHERAPY BUT NOT ATEZOLIZUMAB PLUS BEVACIZUMAB IN ADVANCED HEPATOCELLULAR CARCINOMA

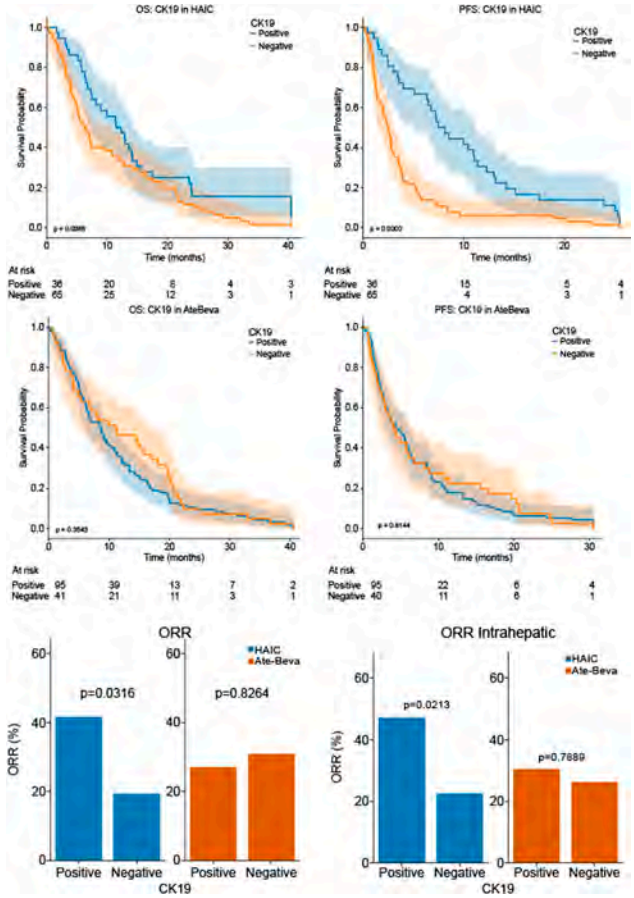
Pil Soo Sung[1], [1]Seoul St Mary's Hospital

Background: Cytokeratin 19 (CK19)-positive hepatocellular carcinoma (HCC) exhibits biliary/progenitor features and aggressive biology, raising uncertainty regarding the optimal therapeutic strategy for this subgroup. We evaluated the prognostic and predictive value of CK19 expression according to treatment modality in patients with advanced HCC treated with hepatic arterial infusion chemotherapy (HAIC) or atezolizumab plus bevacizumab. **Methods:** We retrospectively analysed consecutive patients with advanced HCC who received atezolizumab plus bevacizumab or HAIC between January 2020 and July 2025. Only patients with available tumour biopsy and immunohistochemical assessment of CK19 were included. Overall survival (OS) and progression-free survival (PFS) were compared by CK19 status within each treatment group using Kaplan-Meier analysis and log-rank testing. Objective response rate (ORR), including overall and intrahepatic responses, was evaluated by radiologic assessment, excluding non-evaluable cases. Categorical variables were compared using chi-square tests. **Results:** We included 136

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patients treated with atezolizumab plus bevacizumab (CK19-positive n = 95; CK19-negative n = 41; median follow-up 8.7 months) and 101 treated with HAIC (CK19-positive n = 36; CK19-negative n = 65; median follow-up 7.4 months). In the atezolizumab plus bevacizumab group, OS and PFS did not differ by CK19 status (OS p = 0.3643; PFS p = 0.8144), and ORR was similar for both overall (p = 0.8264) and intrahepatic responses (p = 0.7889). In contrast, in the HAIC group, CK19-positive tumours showed improved OS and PFS compared with CK19-negative tumours (OS p = 0.0365; PFS p < 0.0001). ORR was higher in CK19-positive than CK19-negative tumours after HAIC for both overall response (41.7% vs 19.4%, p = 0.0316) and intrahepatic response (47.2% vs 22.6%, p = 0.0213). **Conclusion:** CK19 expression identifies a subgroup of advanced HCC with differential outcomes following HAIC, whereas outcomes with atezolizumab plus bevacizumab were not stratified by CK19 status. CK19 assessment may support biomarker-informed selection of HAIC in advanced HCC, warranting prospective validation.



Disclosures: Pil Soo Sung:Nothing to Disclose.

4227 | COST-EFFECTIVE AGE THRESHOLDS FOR HEPATOCELLULAR CARCINOMA SURVEILLANCE IN PATIENTS WITH CIRRHOSIS ACROSS ETIOLOGIES AND COMORBIDITIES

Szu-Yu Kao[1] David Hutton[2] Neehar Parikh[3] Amit Singal, [1]Siemens Medical Solutions, [2]University of Michigan, [3]University of Michigan Medical Center

Background: The net benefit of hepatocellular carcinoma (HCC) surveillance likely varies by liver disease etiology, liver disease severity, and burden of non-liver comorbidity. However, in contrast to other cancer screening programs, stopping rules based on age and comorbiditity have not been defined. We aimed to determine ages to start and stop HCC surveillance in Child-Pugh A cirrhosis, including any variation in thresholds across etiology and comorbidity, through cost-effectiveness analysis. **Methods:** We developed a microsimulation model for cirrhosis, following 1 million patients with Child-Pugh A cirrhosis in semiannual cycles over their lifetimes. The population was stratified into 12 subgroups based on cirrhosis etiology (viral, MASLD, alcohol with active use) crossed with Charlson Comorbidity Index (CCI) categories (0, 1-2, 3-4, ≥5). Etiology affected HCC incidence and all-cause mortality, and higher CCI increased all-cause mortality. We compared 15 semiannual surveillance strategies across starting ages of 50-70 and stopping ages of 60-80, with a minimum 10-year duration. From a healthcare-sector perspective, we estimated lifetime direct medical costs and quality-adjusted life-years (QALYs) in each subgroup vs. no surveillance as the comparator. A strategy was cost-effective if it produced the most QALYs while keeping the incremental cost-effectiveness ratio (ICER) below a willingness-to-pay threshold of $150,000 per QALY gained. **Results:** Surveillance strategies with earlier starting ages and longer durations detected more HCC cases than those with later starting ages and shorter durations. Early-stage HCC detection rose from 12-13% without surveillance to as high as 66% with surveillance. However, early-stage detection was lower among patients with high comorbidity (CCI ≥3) than those with lower comorbidity (CCI 0 or 1-2), particularly for strategies with later starting ages and shorter durations. Surveillance was cost-effective for patients with low comorbidity. The cost-effective durations of surveillance differed by etiology. Specifically, across low comorbidity subgroups, the cost-effective starting age was 50 and the stopping age ranged from 70 to 80, with

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ICERs varying between $137,653 and $149,929 per QALY gained (**Table**). Surveillance was not cost-effective for patients with high comorbidity, regardless of etiology. **Conclusion:** Cost-effective HCC surveillance age thresholds in Child-Pugh A cirrhosis depend on liver disease etiology and comorbidity. Surveillance was cost-effective for patients with low comorbidity, with varying starting and stopping ages by etiology, but not for those with high comorbidity, in whom competing mortality outweighed the benefit. These findings support risk-stratified rather than one-size-fits-all HCC surveillance recommendations based on patient comorbidity and age.



Disclosures: Szu-Yu Kao:Siemens Healthineers: Employee, David Hutton:Nothing to Disclose, Neehar Parikh:Genentech: Grant/Research Support, Genentech: Grant/Research Support, Exelixis: Grant/Research Support, Exelixis: Grant/Research Support, Exelixis: Consultant, Exelixis: Consultant, AstraZeneca: Consultant, AstraZeneca: Consultant, Exact Sciences: Grant/Research Support, Exact Sciences: Grant/Research Support, Exact Sciences: Consultant, Exact Sciences: Consultant, Fujifilm Medical: Advisor, Fujifilm Medical: Advisor, Sirtex: Advisor, Genentech: Grant/Research Support, Genentech: Grant/Research Support, Exelixis: Grant/Research Support, Exelixis: Grant/Research Support, Exelixis: Consultant, Exelixis: Consultant, AstraZeneca: Consultant, AstraZeneca: Consultant, Exact Sciences: Grant/Research Support, Exact Sciences: Grant/Research Support, Exact Sciences: Consultant, Exact Sciences: Consultant, Fujifilm Medical: Advisor, Fujifilm Medical: Advisor, Sirtex: Advisor, Amit Singal:Genentech: Consultant, AstraZeneca: Consultant, Bayer: Consultant, Eisai: Consultant, Exelixis: Consultant, Merck: Consultant, Elevar: Consultant, FujiFilm Medical Sciences: Consultant, Exact Sciences: Consultant, Glycotest: Consultant, Boston Scientific: Consultant, Sirtex: Consultant, HelioGenomics: Consultant, ImCare: Consultant, DELFI: Consultant, Curve Biosciences: Consultant, Catalym: Consultant, Verve: Consultant.

4228 | SYSTEM-LEVEL BOTTLENECKS ACROSS THE HCC CARE CASCADE IN LATIN AMERICA

Pablo Coste[1] Luis Díaz[2] Marco Arrese[2] Wagner Ramirez[1] Francisco Vargas Navarro[3] Maria Fernanda Lynch-Mejia[1] Federico Piñero[4] Manuel Mendizabal[5] Maria Reig[6] Jeffrey Lazarus[7] Margarita Anders[8] Josemaría MenendezDutra[9] Juan Pablo Arab[10], [1]Liver Unit, Hospital Rafael Ángel Calderón Guardia, LiverLab CR, San José, Costa Rica, [2]Pontificia Universidad Católica de Chile, Santiago, Chile, [3]Hospital RA Calcderón Guardia, [4]Hepatology and Liver Transplant Unit, Hospital Universitario Austral, Buenos Aires, Argentina, [5]Hospital Universitario Austral, [6]Director, Liver Cancer Unit, Consultant Liver Unit - Hospital Clínic Barcelona, [7]University of Barcelona, [8]Hepatology and Liver Transplantation Unit. Alemán Hospital, Buenos Aires, Argentina., [9]Liver Transplantation National Program, Hospital Militar, Montevideo, Uruguay., [10]Virginia Commonwealth University

Background: Hepatocellular carcinoma (HCC) outcomes depend on healthcare system performance across the care cascade, yet operational assessments of system-level capacity remain scarce in Latin America. **Methods:** We conducted a multinational cross-sectional analysis including 20 Latin American countries. Twenty variables were operationalized into six predefined domains: fibrosis detection, surveillance, diagnosis, multidisciplinary care (MDT), curative treatment, and non-curative treatment. Data were compiled through expert-based country validation and publicly available healthcare system indicators. Variables were coded using a predefined ordinal scale reflecting implementation and accessibility, and normalized into 0–100 domain scores. System-level bottlenecks across the HCC care cascade were evaluated descriptively. **Results:** Marked heterogeneity in HCC care capacity was observed across the region, with total scores ranging from 0 to 85.4. Higher-performing systems demonstrated preserved diagnostic and treatment capacity, whereas lower-performing countries exhibited widespread deficiencies across all domains. Upstream deficiencies in fibrosis detection and linkage to care persisted even among higher-performing systems with otherwise preserved downstream therapeutic capacity. In contrast, curative treatment access, particularly liver transplantation, represented the principal limitation among intermediate-performing systems. A progressive gradient of healthcare system capacity was observed across the HCC care cascade. **Conclusion:** HCC care capacity across Latin America appears constrained primarily by upstream deficiencies in fibrosis detection and surveillance, even in systems with preserved downstream therapeutic capacity. These findings support integrated system-level strengthening strategies centered on early detection and structured HCC care pathways.

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Country	Fibrosis detection (16.7%)	Surveillance (16.7%)	Diagnosis (16.7%)	MDT (16.7%)	Curative (16.7%)	Noncurative (16.7%)	Total_score (100%)	Bottleneck
Chile	66.7	87.5	100	100	75	83.3	85.4	Fibrosis detection
Uruguay	66.7	87.5	100	100	75	83.3	85.4	Fibrosis detection
Argentina	66.7	75	83.3	83.3	87.5	83.3	79.9	Fibrosis detection
Brazil	66.7	75	83.3	83.3	87.5	83.3	79.9	Fibrosis detection
Colombia	66.7	75	83.3	83.3	75	83.3	77.8	Fibrosis detection
Mexico	66.7	75	83.3	83.3	75	83.3	77.8	Fibrosis detection
Costa Rica	66.7	62.5	66.7	83.3	75	66.7	70.1	Surveillance
Perú	66.7	75	83.3	83.3	37.5	66.7	68.8	Curative
Panamá	66.7	75	66.7	83.3	37.5	66.7	66	Curative
Cuba	50	87.5	50.0	50	12.5	16.7	44.4	Curative
Ecuador	16.7	37.5	33.3	33.3	25	50	32.6	Fibrosis detection
Dom. Rep.	16.7	37.5	33.3	33.3	25	50	32.6	Fibrosis detection
Paraguay	16.7	25	33.3	33.3	25	50	30.6	Fibrosis detection
Venezuela	16.7	25	33.3	33.3	12.5	16.7	22.9	Curative
El Salvador	16.7	25	16.7	33.3	12.5	16.7	20.1	Curative
Guatemala	16.7	25	16.7	33.3	12.5	16.7	20.1	Curative
Honduras	16.7	25	16.7	33.3	12.5	16.7	20.1	Curative
Bolivia	16.7	25	16.7	0.0	12.5	16.7	14.6	MDT
Nicaragua	0	25	16.7	0	12.5	16.7	11.8	Fibrosis detection
Haiti	0	0	0	0	0	0	0	All domains

Figure 1. HCC care cascade performance across Latin America. Domain-specific scores (0–100) are shown for each country across six domains: fibrosis detection, surveillance, diagnosis, multidisciplinary care (MDT), curative treatment, and non-curative treatment. Countries are ordered by overall performance (total score). Colors represent level of system capacity (red: low [0–39]; yellow: intermediate [40–69]; green: high [≥70]). The primary bottleneck for each country is defined as the lowest-scoring domain, in case of ties, the most upstream domain was selected. A clear gradient of system performance is observed, ranging from countries with preserved downstream capacity but persistent upstream deficiencies to those with widespread limitations across all domains.

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4229 | IMPACT OF PRIOR AND CURRENT TREATMENT RESPONSES ON SURVIVAL OUTCOMES DURING SEQUENTIAL SYSTEMIC THERAPY AFTER ATEZOLIZUMAB PLUS BEVACIZUMAB IN UNRESECTABLE HEPATOCELLULAR CARCINOMA

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Background: As survival outcomes improve, sequential systemic therapies after atezolizumab plus bevacizumab (Atezo/Bev) failure are increasingly performed in patients with unresectable hepatocellular carcinoma (uHCC). However, real-world treatment patterns and prognostic factors during subsequent systemic treatment lines remain unclear. We evaluated sequential treatment patterns and prognostic factors associated with survival outcomes during subsequent systemic therapies following Atezo/Bev failure in patients with uHCC. **Methods:** In this retrospective cohort study, we evaluated second- and third-line treatment patterns and survival outcomes in patients with uHCC who received at least one dose of Atezo/Bev (May 2022–December 2023) and subsequent systemic therapies. Overall survival (OS) and progression-free survival (PFS) were compared according to prior and current treatment responses (PD vs. non-PD) among patients who underwent at least one response evaluation during each treatment line. Prognostic factors associated with survival outcomes after subsequent systemic therapies were analyzed using Cox proportional hazards models. **Results:** Among 466 patients who received subsequent treatment after first-line Atezo/Bev, 388 and 148 patients were included in the second- and third-line systemic therapy cohorts, respectively. In the second-line setting, Lenvatinib was the most used systemic therapy (> 50%) and showed significantly longer PFS than sorafenib, while OS was comparable between two groups. Second-line non-PD group showed significantly longer OS and PFS than PD group (mOS: 9.6 vs. 3.9 months; mPFS: 5.3 vs. 1.4 months; *Ps* < 0.001). In the third-line settings, tyrosine kinase inhibitors (TKIs) predominated and showed comparable survival outcomes with immune checkpoint inhibitors (ICIs) (mOS: 6.1 vs. 4.0 months; mPFS: 1.6 vs. 1.7 months; *Ps=NS*). Furthermore, third-line non-PD group also showed significantly higher survival outcomes (mOS: 9.0 vs. 4.5 months; mPFS: 4.8 vs. 1.4 months; *Ps* < 0.001). In Cox proportional models, survival outcomes during sequential systemic therapy were more strongly associated with response to the current treatment line than with prior treatment response. **Conclusion:** In this Korean real-world study, TKIs remained the predominant subsequent systemic therapies after first-line Atezo/Bev for uHCC. Subsequent systemic therapies may be more strongly influenced by response to the current treatment line than with prior treatment response. Active sequential systemic therapy may

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therefore provide a survival benefit, irrespective of the initial response of first-line Atezo/Bev.

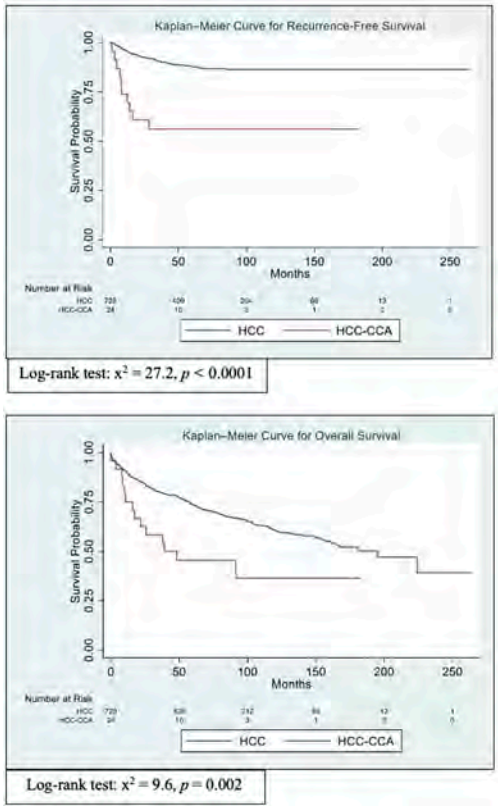
Disclosures: Ji won Yang:Nothing to Disclose, SUNG WON CHUNG:Nothing to Disclose, JEAYEON PARK: Nothing to Disclose, Byeong Geun Song:Nothing to Disclose, Jihyun An:Nothing to Disclose, Eun Sun Jang:Nothing to Disclose, Su Jong Yu:Nothing to Disclose, Ju Hyun Shim:Nothing to Disclose.

4230 | RISK FACTORS AND OUTCOMES ASSOCIATED WITH MIXED HEPATOCELLULAR-CHOLANGIOCARCINOMA (HCC-CCA) IDENTIFIED AT TIME OF LIVER TRANSPLANT

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Background: Frequently misdiagnosed on imaging, mixed hepatocellular-cholangiocarcinoma (HCC-CCA) cases are heterogeneous and rare. HCC-CCAs often exhibit intermediate outcomes, though such findings are confounded by diagnostic delays and a lack of standardized management. The purpose of this study was to investigate the prevalence, risk factors, and outcomes associated with HCC-CCA. **Methods:** A retrospective analysis of patients with HCC or HCC-CCA confirmed on explant at a large academic medical center from 1998 – 2025 was conducted. Via chart review, data pertaining to patient characteristics, pre-liver transplant (LT) diagnostics, tumor characteristics, and post-LT outcomes were collected. **Results:** On explant, there were 728 patients with HCC and 24 patients with HCC-CCA. 21 of the HCC-CCA patients were pre-operatively diagnosed with HCC; the others were transplanted for cirrhosis without a tumor diagnosis. HCC and HCC-CCA patients were similar with respect to demographics, MELD score, time on the waitlist, and rates of pre-LT locoregional therapy. The mean maximum CA 19-9 level among HCC-CCA patients was low at 17; the mean AFP level was 254 among HCC-CCA patients versus 388 among HCC patients (p = 0.47). Among those ultimately found to have HCC-CCA, 4 patients (17%) had pre-LT lesional biopsy consistent with HCC alone. MRI was the final imaging modality pre-LT for 80% of HCC patients and 76% of HCC-CCA patients (p = 0.52). On explant, 41% of HCC-CCA cases met Milan criteria versus 70% of HCC cases (p = 0.003). A significantly higher proportion of HCC-CCA tumors were moderately or poorly differentiated (p = 0.002), and HCC-CCA tumors exhibited higher rates of microvascular (p = 0.02) and lymphatic (p < 0.001) invasion. In Kaplan Meier analyses, recurrence-free survival (p < 0.0001) and overall survival (p = 0.002) were significantly shorter in the HCC-CCA cohort than the HCC cohort (Figure 1). **Conclusion:** Over nearly 3 decades, approximately 3% of patients transplanted for HCC were incidentally found to have HCC-CCA. Despite high rates of MRI imaging and even lesional biopsy, in some cases, no patients were diagnosed with HCC-CCA prior to LT. Current diagnostic methods are suboptimal in identifying HCC-CCA, which is associated with worse post-LT outcomes.

Figure 1. Kaplan-Meier analyses comparing recurrence-free survival and overall survival between HCC (hepatocellular carcinoma) and HCC-CCA (mixed hepatocellular-cholangiocarcinoma) patients



Disclosures: Mahip Grewal:Nothing to Disclose, Yuan Zhang:Nothing to Disclose, Meaghan Phipps:AstraZeneca: Advisor, AstraZeneca: Advisor, AstraZeneca: Advisor, AstraZeneca: Advisor.

4231 | PREDICTING MULTIDISCIPLINARY LIVER TUMOR BOARD TREATMENT RECOMMENDATIONS FOR HEPATOCELLULAR CARCINOMA USING MACHINE LEARNING

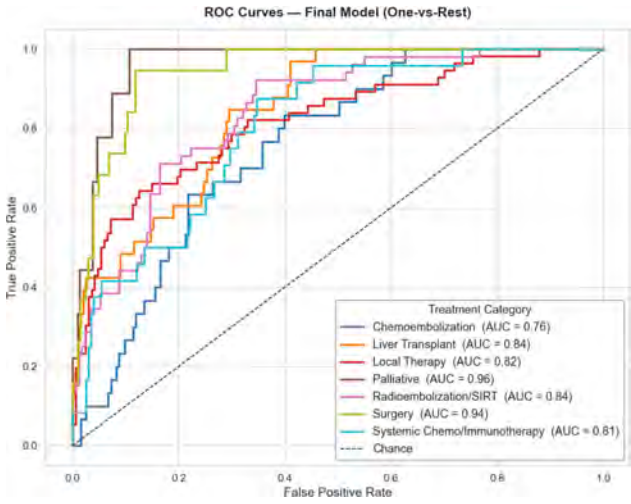
Madelaine Hack[1] Phillip Jenkins[1] W. Gaya Shivega[1] Steven Bedrick[1] Alexandra Bolognese[1] Christopher

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Connelly[1] Pushpa Neppala[1] Oren Shaked[1] Flavio Rocha[1] Skye Mayo[1] Nima Nabavizadeh[1] Adel Kardosh[1] Parmede Vakil[1] Ruchi Thanawala[1] Julie Doberne[1] Willscott Naugler[1] Erin Maynard[1] C. Kristian Enestvedt[1], [1]Oregon Health & Science University

Background: Multidisciplinary tumor boards (MDTBs) guide treatment for hepatocellular carcinoma (HCC). Few prior studies have attempted to computationally model these complex evaluations and treatment recommendations. **Methods:** We analyzed 1,115 individual HCC cases presented in MDTB at our NCI designated comprehensive cancer center between 2016-2024. Seven consolidated treatment categories were predicted (liver transplant, resection, chemoembolization, radioembolization, systemic therapy, combined local therapy—encompassing locoregional treatments with consolidative treatment of external beam radiation or ablation—and palliative care). Multinomial logistic regression and XGBoost (gradient boosted trees) statistical modeling were compared. Clinician-expressed decisional confidence in the MDTB recommendation was graded and incorporated as a variable in the models. Performance was assessed with overall accuracy, area under the receiver operator curve (AUC), and per-class Brier Scores. Shapley Additive Explanations (SHAP) analysis was used to identify key variables contributing to model performance. All analyses were performed in Python 3.13. **Results:** The 1,115 patients were predominantly male (70.5%) with a median age of 65 years. Most patients were BCLC Stage A (53.5%). The most common primary recommendations were radioembolization (23.4%), combined local therapy (22.8%), and liver transplant (15.1%). Multinomial logistic regression modeling achieved 28.7% accuracy in predicting treatment recommendations. The XGBoost model improved accuracy to 51.1% with strong discriminative performance across treatment classes (one-vs-rest AUC 0.76–0.96; Fig. 1), compared to a theoretical chance performance for seven-class prediction of 14.3%. Per-class Brier scores were lowest for palliative care (0.029) and surgery (0.057), reflecting high specificity for these classes, and highest for radioembolization (0.147) and combined local therapy (0.138), the two largest and most overlapping categories. SHAP analysis showed that the size of the dominant lesion, BCLC stage, MELD score, and platelet count were among the most influential variables. **Conclusion:** Complex MDTB treatment recommendations for patients with HCC can be modeled by machine learning with reasonable accuracy and strong discriminative performance. Incorporating these tools into clinical practice may allow for more efficient and consistent MDTB discussions but will require careful refinement and validation.



Disclosures: Madelaine Hack:Nothing to Disclose, Phillip Jenkins:Nothing to Disclose, W. Gaya Shivega: Nothing to Disclose, Steven Bedrick:Nothing to Disclose, Alexandra Bolognese:Nothing to Disclose, Christopher Connelly:Nothing to Disclose, Pushpa Neppala:Nothing to Disclose, Oren Shaked:Nothing to Disclose, Flavio Rocha:Nothing to Disclose, Skye Mayo:Nothing to Disclose, Nima Nabavizadeh:Nothing to Disclose, Adel Kardosh:genentech: Advisor, cardiff oncology: Advisor, Eisai: Advisor, jazz pharmaceuticals: Advisor, Parmede Vakil:Nothing to Disclose, Ruchi Thanawala:Nothing to Disclose, Julie Doberne:Nothing to Disclose, Willscott Naugler:Nothing to Disclose, Erin Maynard:Nothing to Disclose, C. Kristian Enestvedt:Nothing to Disclose.

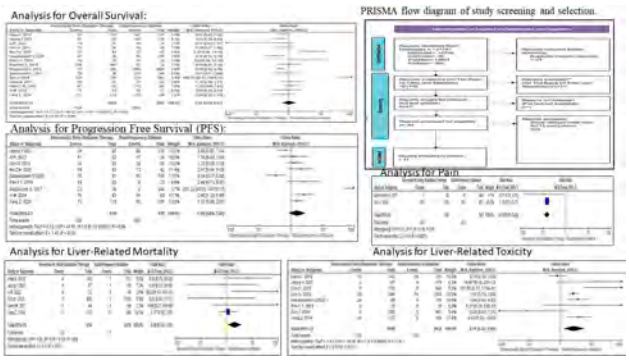
4232 | SAFETY AND EFFICACY OF STEREOTACTIC BODY RADIATION THERAPY VS RADIOFREQUENCY ABLATION IN PATIENTS WITH HEPATOCELLULAR CARCINOMA. A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Hepatocellular carcinoma (HCC) remains a leading cause of cancer mortality worldwide. While radiofrequency ablation (RFA) is the standard local

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therapy for early-stage HCC, stereotactic body radiation therapy (SBRT) has emerged as a non-invasive alternative, particularly for tumors in anatomically challenging locations. Comparative evidence on the efficacy and safety of SBRT versus RFA remains inconclusive. This systematic review and meta-analysis aimed to compare both modalities in terms of survival, local control, and treatment-related toxicity. **Methods:** Following PRISMA guidelines, PubMed, Embase, MEDLINE, and Cochrane databases were searched up to 2025. Randomized controlled trials and cohort studies directly comparing SBRT and RFA in HCC patients were included. Pooled odds ratios (OR) or mean differences (MD) with 95% confidence intervals (CI) were calculated using Review Manager (RevMan). Heterogeneity was assessed using the I^2 statistic, and study quality was evaluated using the ROB-2 tool and Newcastle–Ottawa Scale. **Results:** Seventeen studies (one RCT, sixteen cohorts) involving 10182 HCC patients were included. The SBRT group has 2468 patients, and the RFA group has 7714 patients. Pooled analysis showed no significant difference in overall survival (OR = 1.02, 95% CI 0.62–1.67) or progression-free survival (OR = 1.58, 95% CI 0.84–3.01). Local control and recurrence rates were comparable. SBRT demonstrated significantly lower liver-related mortality (OR = 2.08, p = 0.02) and reduced post-procedural pain (OR = 0.15, p < 0.0001), whereas RFA showed higher complete response rates (OR = 0.21, p = 0.02) but increased liver-related toxicity (OR = 2.74, p = 0.01). Overall treatment-related complications did not differ significantly between modalities. **Conclusion:** SBRT and RFA yield comparable long-term oncologic outcomes in HCC. SBRT offers advantages in pain reduction and lower liver-related mortality, while RFA may achieve higher complete response in small, peripherally located tumors. Both modalities remain effective and safe; treatment selection should be individualized based on tumor characteristics, liver function, and anatomical feasibility. Further randomized trials with standardized protocols are warranted.



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4233 | GLP-1 RECEPTOR AGONIST EXPOSURE AND OUTCOMES IN HEPATOCELLULAR CARCINOMA ACROSS THE LIVER TRANSPLANT CONTINUUM: A SINGLE-CENTER, EXPLORATORY ANALYSIS

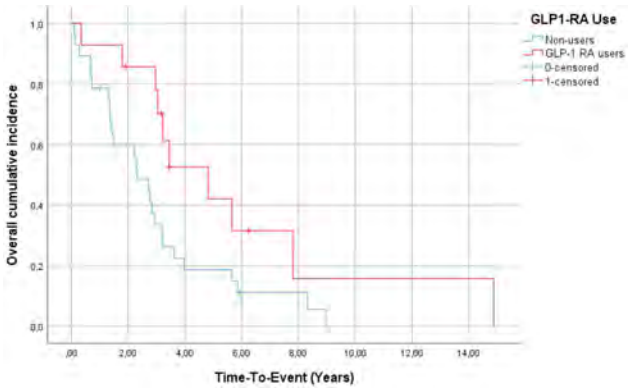
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Background: GLP-1 receptor agonists (GLP-1 RAs) have shown favorable metabolic and liver-related effects in type 2 diabetes mellitus with potential to reduce hepatocellular carcinoma (HCC) risk. However, their impact on outcomes in patients with HCC, particularly across the liver transplant (LT) spectrum, are not fully elucidated. We evaluated the association between GLP-1 RA exposure and clinical outcomes in patients with HCC and T2DM before and after LT. **Methods:** We conducted a retrospective, matched cohort of adults with HCC and T2DM, comparing GLP-1 RA users with non-users in a 1:2 ratio. Two separate analyses were performed. In the pre-LT cohort, GLP-1 RA users were matched to non-users to evaluate outcomes since HCC diagnosis, accounting for liver transplant, death, and loss to follow-up as competing events. In the post-LT cohort, LT recipients with prior GLP-1 RA exposure were matched to non-exposed controls to assess HCC recurrence following LT. Demographic, clinical, tumor, treatment, and outcomes-related data were extracted from electronic medical records. Time-to-event analyses and non-parametric tests were used as appropriate. **Results:** Overall, 84 patients were included, comprising 14 GLP-1 RA-exposed patients matched to 28 controls across the two settings. In the pre-LT setting, age, sex, and tumor burden were comparable between groups. MASLD was the predominant underlying liver disease in both groups (43%). Primary HCC treatment modalities among GLP-1 RA users included ablation (57%)

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and transarterial chemoembolization (TACE) (38%), compared with 43% and 50% in controls, respectively. Complete response rates were 50% in the GLP-1 RA group and 65% in controls, while progression occurred in 29% and 12%, respectively. Despite similar LT rates (21% vs 21%), GLP-1 RA exposure was associated with lower mortality in time-to-event analyses (50% vs. 83%; log-ran p = 0.033) (Figure 1). In the post-LT cohort, patients were again similar in baseline characteristics. Only two cases of recurrent HCC were observed, both occurring within 5 years post-LT and exclusively among the non-exposed group. **Conclusion:** In this exploratory, single-center, matched cohort study, GLP-1 RA exposure in patients with HCC and T2DM was not associated with worse oncologic outcomes and may have been associated with lower pre-transplant mortality. Post-LT recurrence was rare and occurred only among non-exposed patients. Larger, multicenter studies are needed to confirm these findings and further define the implications of GLP-1 RA use in HCC.



Disclosures: Talal Alhejaili:Nothing to Disclose, Lameyaa Alsheekh:Nothing to Disclose, Lujain Alrabghi:Nothing to Disclose, Xin Tong Ma:Nothing to Disclose, Chiara Becchetti:Nothing to Disclose, Mohammad Qasim Khan:Nothing to Disclose.

4234 | HEPATOCELLULAR CARCINOMA IN WOMEN: DISTINCT ETIOLOGIC PATTERNS AND AGE-RELATED SURVIVAL OUTCOMES COMPARED WITH MEN

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Background: Hepatocellular carcinoma (HCC) in women may differ from that in men in disease characteristics, with potential age-related effects on presentation and survival. However, female-specific HCC patterns remain incompletely explored in Saudi Arabia. We aimed to characterize the clinical features, etiologies, and survival outcomes of female patients with HCC across different age groups and compare outcomes between female and male patients. **Methods:** Data were obtained from a comprehensive institutional database of all patients diagnosed with HCC between January 2020 and April 2026 at two major tertiary referral centers in Saudi Arabia. Demographic, etiologic, and clinical data were analyzed using descriptive statistical methods. Female patients were categorized into three age groups (< 55, 55–64, and ≥ 65 years). Overall survival was estimated using the Kaplan-Meier method, with mortality data supplemented by the National Death Registry maintained by the Ministry of Health. **Results:** Among 693 patients with HCC, 205 (29.6%) were female, with a median age at diagnosis of 65 years, comparable to males. Smoking history (current or former) was uncommon among females (3.0% vs 22.3% of males, P < 0.001). Etiologic distribution differed by sex (P < 0.001): hepatitis C virus was most frequent among females (38.5%), whereas metabolic dysfunction-associated steatotic liver disease/steatohepatitis was most frequent among males (35.9%); hepatitis B virus etiology was less common in females than males (10.2% vs. 27.5%). Liver cirrhosis was more frequent in females than males (91.7% vs. 85.9%, P = 0.033), while Child-Pugh class distribution was similar (Child–Pugh A: 56.1% vs. 60.0%, P = 0.281). Tumor stage at presentation was similar between females and males (early-stage BCLC 0–A: 41.0% in both groups, P = 0.865), as was first-line locoregional therapy use (48.8% vs. 43.2%, P = 0.616) in females and males. Survival analysis showed that females had higher overall survival probabilities than males (at 36 months: 0.53; 95% CI 0.42 - 0.62 vs 0.50; 95% CI 0.44-0.56), with the most favorable estimated outcomes observed among the female patients aged < 55 years (< 55 years) compared with older age groups (55–64 and ≥ 65 years). **Conclusion:** Female patients with HCC in Saudi Arabia demonstrate distinct etiologic patterns and broadly similar stage and treatment characteristics compared with males. Females had higher overall survival, particularly among those aged < 55 years, highlighting

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a potential age-related survival advantage that warrants further investigation.



Figure 1: Stage at diagnosis by gender

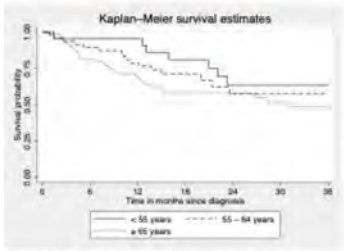
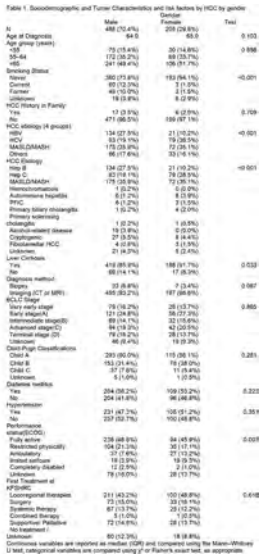


Figure 2: Kaplan–Meier Survival Probability Among Females by Age Group



Disclosures: Saleh Alqahtani:Nothing to Disclose, Duna Barakeh:Nothing to Disclose, Saleh Alessy:Nothing to Disclose, Amwaj Alanazi:Nothing to Disclose, Mussadique Jhatial:Nothing to Disclose, Mehwish Hussain:Nothing to Disclose, Layan Alsubki:Nothing to Disclose, Ahad Alseraihi: Nothing to Disclose, Fahad AlMugbel:Nothing to Disclose, Ali Alqahtani:Nothing to Disclose, Habeeb Ibrahim Abdul Razack:Nothing to Disclose, Mohammed Shouki Bazarbashi:mERCK: Advisor, Merck Sharp and Dohm: Advisor, Bayer: Speaking and Teaching, AstraZeneca: Advisor, Astellas: Advisor, Servier: Speaking and Teaching, Beone: Speaking and Teaching, Biologix: Advisor, Adnan Alzanbagi:Nothing to Disclose, Khalid AlNaamani:Nothing to Disclose, Waleed Alomaim:Nothing to Disclose, Tatyana Kushner:Gilead: Grant/Research Support, Gilead: Advisor, GSK: Advisor, Eiger: Advisor, GSK: Consultant, Madrigal: Advisor, Ipsen: Advisor, Mirum: Advisor, Mirum: Grant/Research Support, Ipsen: Grant/Research Support, Dieter Broering:Nothing to Disclose, Saad Alghamdi:Nothing to Disclose, Faisal Abaalkhail:Nothing to Disclose.

4235 | RADIOTHERAPY COMBINED WITH ATEZOLIZUMAB PLUS BEVACIZUMAB IN HEPATOCELLULAR CARCINOMA WITH MAIN PORTAL VEIN TUMOR THROMBOSIS: REFINED ANALYSIS WITH IPTW ADJUSTMENT IN A MULTICENTER REAL-WORLD COHORT

Hyun Young Woo[1] Young Joo Park[2] Ki Youn Yi[2] Junsik Yoon[3] Yeowool Kang[4] Woo Sun Rou[5] Jeongeun Song[6] Joonho Jeong[7] Yu Rim Lee[8] Jae hyun Yoon[9] Young Mi Hong[10] Sangyoun Hwang[11] Hyun Jin Cho[12] Yang Hyun Baek[4] Soo Young Park[8] Won Young Tak[13] Sung Bum Cho[14] Jeong Heo[15], [1]College of Medicine, Pusan National University and Pusan National University Hospital, [2]Pusan National University Hospital, [3]Busan Paik Hospital, Inje University College of Medicine, [4]Dong-A University College of Medicine, [5]Chungnam National University College of Medicine, [6]Daegu Catholic University Medical Center, Catholic University of Daegu School of Medicine, [7]Ulsan University Hospital, University of Ulsan College of Medicine, [8]School of Medicine, Kyungpook National University, Kyungpook National University Hospital, [9]Chonnam National University Hospital, School of Medicine, [10]College of Medicine, Pusan National University, Pusan National University Yangsan Hospital, [11]Dongnam Institute of Radiologic & Medical Sciences, [12]Gyeongsang National University, [13]School of Medicine, Kyungpook National University, [14]Chonnam National University Hwasun Hospital and Chonnam National University Medical School, [15]Pusan National University College of Medicine, Busan, Republic of Korea

Background: Our previous study demonstrated that RT combined with atezolizumab plus bevacizumab (Ate/bev) improved OS in high-risk HCC patients including Vp4 PVTT. However, that analysis included heterogeneous high-risk features without accounting for RT timing or baseline confounders. Here, we performed a refined analysis in HCC patients with main PVTT (MPVTT), incorporating RT timing classification and inverse probability of treatment weighting (IPTW). **Methods:** This multicenter retrospective cohort study included 183 HCC patients with MPVTT who received Ate/bev across five tertiary hospitals in Korea (July 2020–December 2023). Patients receiving RT before or after Ate/bev completion (n = 14) were excluded, yielding 169 patients: RT group (n = 95) and Ate/bev-only group (n = 74). Median RT dose was 35 Gy in 12 fractions. Tumor response was assessed per mRECIST. Primary endpoint was OS; secondary endpoints were TTP, ORR, and DCR. IPTW was applied to adjust for selection bias. Subgroup analysis was performed in patients without extrahepatic spread (EHS). **Results:** The RT group had younger age (62 vs. 66 years), better ECOG PS 0 (60% vs. 46%), higher Child-Pugh A (94% vs. 78%), and lower EHS rate (45% vs. 54%). The RT group showed significantly higher DCR (82.2% vs. 53.3%, p < 0.001) and numerically higher ORR (32.2% vs. 18.3%, p = 0.09). Median TTP (6.1 vs. 2.5 months, p < 0.001) and OS (9.9 vs. 6.0 months, p < 0.001) were significantly longer in the RT group. On univariate Cox analysis, RT significantly improved OS (HR 0.638, 95% CI 0.453–0.898, p = 0.010) and TTP (HR 0.598, 0.412–0.869, p = 0.007). After IPTW adjustment, RT

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independently predicted prolonged TTP (HR 0.672, 0.512–0.883, p = 0.004) with a trend toward improved OS (HR 0.787, p = 0.10). In the no-EHS subgroup (RT n = 52, No-RT n = 34), RT independently predicted OS (HR 0.505, 0.294–0.868, p = 0.013; median 11.0 vs. 6.7 months, p = 0.010) and TTP (6.9 vs. 3.0 months, p = 0.035). **Conclusion:** RT combined with Ate/bev independently predicted prolonged TTP after IPTW adjustment and improved OS in MPVTT patients without EHS. These results extend our previous findings and support RT as a meaningful adjunct to Ate/bev, particularly in locoregionally confined MPVTT. Prospective trials are warranted.

Disclosures: Hyun Young Woo:Nothing to Disclose, Young Joo Park:Nothing to Disclose, Ki Youn Yi: Nothing to Disclose, Junsik Yoon:Nothing to Disclose, Yeowool Kang:Nothing to Disclose, Woo Sun Rou: Nothing to Disclose, Jeongeun Song:Nothing to Disclose, Joonho Jeong:Nothing to Disclose, Yu Rim Lee: Nothing to Disclose, Jae hyun Yoon:Nothing to Disclose, Young Mi Hong:Nothing to Disclose, SANGYOUN HWANG:Nothing to Disclose, Hyun Jin Cho: Nothing to Disclose, Yang Hyun Baek:Nothing to Disclose, Soo Young Park:Nothing to Disclose, Won Young Tak:Nothing to Disclose, Sung Bum Cho: Nothing to Disclose, Jeong Heo:Gilead: Grant/ Research Support, Roche: Speaking and Teaching, Yuhan: Speaking and Teaching, Abbvie: Speaking and Teaching, AstraZeneca: Advisor, Oncolys Japan: Grant/Research Support, Surrozen: Advisor, MedVir: Advisor.

★ 4236 | MACHINE PERFUSION AND HEPATOCELLULAR CARCINOMA RECURRENCE AFTER LIVER TRANSPLANTATION: A SYSTEMATIC REVIEW AND META-ANALYSIS

Patricia Viana[1] Gabriel Chiacchio[2] João Vitor Carneiro[3] Paulo Martins[1], [1]University of Oklahoma, [2]Centro Universitário Tocantinense Presidente Antônio Carlos, [3]Pontifical Catholic University of Paraná

Background: Hepatocellular carcinoma (HCC) recurrence following liver transplantation (LT) remains a significant clinical challenge, affecting 10–20% of recipients. Ischemia-reperfusion injury (IRI) has been implicated as a modifiable risk factor for tumor recurrence, and machine perfusion (MP) strategies have emerged as a potential means of mitigating IRI. We conducted a systematic review and meta-analysis to compare tumor recurrence outcomes in patients undergoing LT for HCC with and without MP. **Methods:** MEDLINE, Embase, and the Cochrane databases were searched for studies comparing any modality of MP (hypothermic oxygenated perfusion and normothermic machine perfusion with static cold storage in adult LT recipients with HCC were eligible for inclusion. Binary outcomes were synthesized using odds ratios (OR) and time-to-event outcomes using hazard ratios (HR), both calculated with random-effects models. Statistical analyses were performed using R (version 4.3.1). The study protocol was prospectively registered on PROSPERO. **Results:** Four observational cohort studies (spanning from 2020 to 2025) met inclusion criteria, encompassing 1,525 patients, of whom 621 (40.7%) received MP. Median follow-up ranged from 12 to 64 months. Reconstructed Kaplan–Meier analysis demonstrated superior recurrence-free survival in the MP group, with an estimated 5-year RFS of approximately 90% versus 65–70% in the SCS group. On pooled time-to-event analysis, MP was independently associated with a significant reduction in recurrence risk (HR 0.26; 95% CI 0.18–0.38; p = 0.001). Moreover, MP was associated with a significantly lower risk of HCC recurrence compared with SCS (OR 0.30; 95% CI 0.10–0.92; p = 0.007). **Conclusion:** This first meta-analysis evaluating the association between MP and HCC recurrence after LT demonstrates that MP is associated with significantly lower recurrence rates and improved recurrence-free survival. As MP adoption expands globally, prospective randomized trials are warranted to confirm these findings and define optimal perfusion strategies for oncologic benefit in LT.

Figure 1. Recurrence-free survival: machine perfusion was associated with a significantly lower risk of HCC recurrence compared with SCS

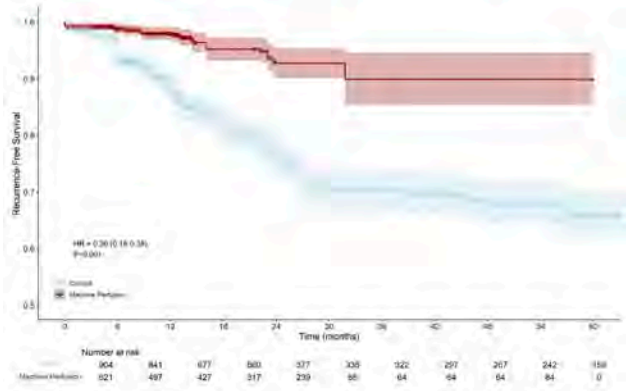
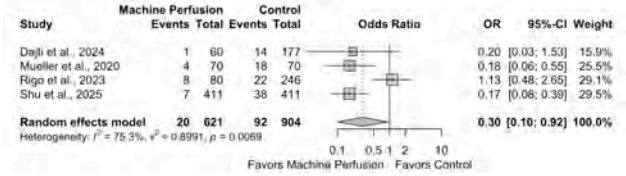


Figure 2. Recurrence rate: machine perfusion was associated with a significantly lower risk of HCC recurrence compared with SCS



Disclosures: Patricia Viana:Nothing to Disclose, Gabriel Chiacchio:Nothing to Disclose, João Vitor

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Carneiro:Nothing to Disclose, Paulo Martins:Nothing to Disclose.

★ 4237 | MIP-3α AND IP-10 AS PROMISING BIOMARKERS FOR HEPATOCELLULAR CARCINOMA IN HIV AND VIRAL HEPATITIS COINFECTED PATIENTS: A PILOT AND VALIDATION COHORT STUDY

Johana Acuña[1] Casper Rokx[2] Ângelo Zambam de Mattos[3] Anthonie Groothuismink[2] Ibrahim Irfanullah[4] Andre Boonstra[5] Jose Debes[6], [1]Universidade Federal de Ciências da Saúde de Porto Alegre, [2]Erasmus MC, Erasmus University, Rotterdam, the Netherlands, [3]Federal University of Health Sciences of Porto Alegre, [4]University of Minnesota, Minneapolis, USA, [5]Erasmus University Medical Center, [6]University of Minnesota

Background: Hepatocellular carcinoma (HCC) has higher mortality in individuals co-infected with HIV and HCV or HBV, presenting additional complexities for screening and surveillance. There is a lack of data across the globe related to surveillance of HCC in this population. **Methods:** We evaluated a pilot cohort of 129 patients from Latin America (Brazil) and a validation cohort of 80 from Europe (the Netherlands) each divided into three groups: HCC + viral hepatitis + HIV; viral hepatitis + HIV; and HIV only. Thirteen immunological markers-TNFα, IL-6, IP-10, IL-10, VEGF-A, BCA-1, IFN-γ, MIP-3α, MDC, MCP-4, TECK, MIG, and HGF- were measured in serum samples. Values below the lower limit of quantification (LLOQ) replaced by LLOQ/2 and false discovery rate (FDR) correction applied. **Results:** In both cohorts, male sex predominated in HCC and coinfected groups (Latin America: 60% and 62%; Europe: 93% and 100%, respectively); HCC group had higher prevalence of cirrhosis than coinfected group (Latin America: 80% vs. 9%; Europe: 86% vs. 16%). In the pilot cohort, IP-10 was the marker with the greatest differentiation, with a median of 113.1 pg/mL in the HCC group — approximately 33-fold higher than coinfected (3.4 pg/mL) and HIV groups (3.3 pg/mL)— reaching statistical significance ($q = 0.049$ for both comparisons). MIP-3α also showed consistently elevated levels in HCC patients, with a median of 20.9 pg/mL, representing a 5.2-fold increase over the coinfected (4.0 pg/mL; $q = 0.039$) and a 4.1-fold increase over HIV groups (5.2 pg/mL; $q = 0.049$). BCA-1 showed the strongest statistical separation ($q = 0.001$ for both comparisons), with a median of 33.3 pg/mL in the HCC group — approximately 10-fold higher than in both control groups (3.35 pg/mL each), where values equivalent to LLOQ/2 indicated that the vast majority of patients without HCC had undetectable levels of this marker.In the validation cohort, MIP-3α was the only marker to reach statistical significance, with HCC group median levels 2.8-fold higher than the coinfected group (49.9 vs 18.1 pg/mL) and 3.5-fold higher than the HIV group (14.4 pg/mL; $q = 0.050$). IP-10 levels in HCC group were also consistently higher than in both control groups, showing the same directional trend observed in the pilot cohort, although without reaching post-FDR significance. BCA-1 did not show a consistent trend in this cohort. Cirrhotic and non-cirrhotic patients showed no significant differences in any marker in either cohort. **Conclusion:** MIP-3α was the only marker to reach statistical significance in both cohorts, emerging as the most robust discriminator of HCC in this cohort. IP-10 and BCA-1 present relevant findings that deserve further exploration. Overall, immune markers could play an important role in surveillance for HCC in individuals with HIV.

Disclosures: Johana Acuña:Nothing to Disclose, Casper Rokx:ViIV Healthcare: Grant/Research Support, Gilead Sciences: Grant/Research Support, MSD: Advisor, Ângelo Zambam de Mattos:Nothing to Disclose, Anthonie Groothuismink:Nothing to Disclose, Ibrahim Irfanullah:Nothing to Disclose, Andre Boonstra:Gilead: Grant/Research Support, GSK: Grant/Research Support, Fujirebio: Grant/Research Support, Jose Debes:Nothing to Disclose.

4238 | SUBMILLIMETRE SPATIALLY FRACTIONATED RADIOTHERAPY (μSFRT) PROMOTES REGENERATIVE RESPONSES AND PRESERVES LIVER ARCHITECTURE FOLLOWING HIGH-DOSE IRRADIATION

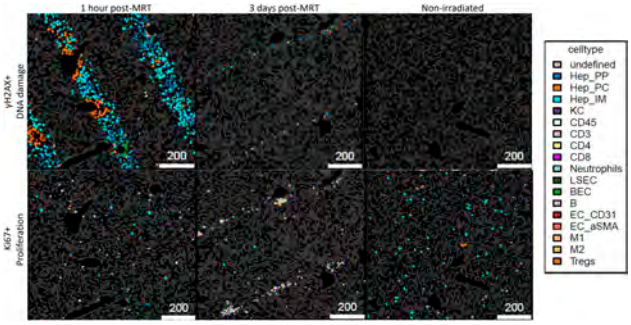
Cheuk Ting Wu[1] Nahoko Shintani[2] Tural Yarahmadov[3] Verdiana Trappetti[2] Cristian Fernandez-Palomo[2] Deborah Keogh-Stroka[3] Valentin Djonov[2], [1]Institute of Anatomy, [2]Insitute of Anatomy, University of Bern, [3]DBMR, University of Bern

Background: Radiation-induced liver disease (RILD) limits radiotherapy efficacy in hepatocellular carcinoma (HCC). Submillimetre spatially fractionated radiotherapy (μSFRT), including microbeam (MRT) and minibeam (MBRT) modalities, delivers highly heterogeneous dose distributions that spare normal tissue despite ablative peak doses. Early clinical MBRT in palliative patients has demonstrated tumour response and symptom relief with favourable normal tissue tolerability, supporting further investigation in liver

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malignancies. The mechanisms underlying normal tissue sparing and absence of RILD following µSFRT remain undefined. **Methods:** C57BL/6 mice received synchrotron-generated MRT (50 µm beam width, 400 µm spacing, ~400 Gy peak dose). Liver tissue and serum were collected 1 hour to 6 days post-irradiation for assessment of DNA damage, cell death pathways, proliferation, and liver injury markers. Imaging Mass Cytometry (IMC) with a custom hepatic-immune panel characterized spatial cellular dynamics. Long-term histological analyses were performed up to 6 months post-irradiation. Comparative studies using MBRT (~50 Gy peak, 200 µm beams/800 µm spacing) and conventional broadbeam radiotherapy (CONV-RT) via a CIX FLASH orthovoltage irradiator are ongoing. **Results:** MRT induced highly localized DNA damage confined to beam paths with minimal systemic liver injury. Classical apoptosis, necroptosis, ferroptosis, and pyroptosis were minimally activated; instead, poly (ADP-ribose) accumulation and apoptosis-inducing factor (AIF) upregulation, consistent with a parthanatos-like cell death mechanism. IMC revealed transient reductions in periportal and intermediate hepatocyte populations with localized immune cell enrichment at peak-dose regions, largely resolving within 6 days. Long-term analyses demonstrated preserved hepatic architecture without fibrosis at 6 months following MRT. Preliminary Masson's Goldner staining revealed markedly reduced fibrosis in MBRT-treated livers (50 Gy peak) compared to CONV-RT at matched (50 Gy) and lower (25 Gy) doses, with the difference most pronounced at equivalent doses. **Conclusion:** µSFRT induces spatially compartmentalised cell death and coordinated immune-regenerative responses that restore liver homeostasis without chronic injury. Parthanatos-like signalling may represent a mechanistically distinct, tissue-protective death pathway activated by extreme dose heterogeneity. Preliminary histological evidence of reduced fibrosis across both MRT and MBRT versus CONV-RT supports a potential µSFRT class effect on long-term liver protection, implicating regenerative reprogramming as central to RILD prevention. Ongoing orthotopic HCC studies will define the relationship between normal tissue preservation and tumour control.



Disclosures: Cheuk Ting Wu:Nothing to Disclose, Nahoko Shintani:Nothing to Disclose, Tural Yarahmadov:Nothing to Disclose, Verdiana Trappetti:Nothing to Disclose, Cristian Fernandez-Palomo:Nothing to Disclose, Deborah Keogh-Stroka:Nothing to Disclose, Valentin Djonov:Nothing to Disclose.

4239 | REAL-WORLD OUTCOMES OF ATEZOLIZUMAB PLUS BEVACIZUMAB ACCORDING TO ETIOLOGY IN UNRESECTABLE HEPATOCELLULAR CARCINOMA

Yeowool Kang[1] Jun Sik Yoon[2] Jung Eun Song[3] Joonho Jeong[4] Yu Rim Lee[5] Jae hyun Yoon[6] Young Mi Hong[7] Sang Youn Hwang[8] Hyun Young Woo[9] Soo Young Park[5] Sung-Bum Cho[10] Yanghyun Baek[11],
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Background: Atezolizumab plus bevacizumab is the preferred first-line systemic therapy for unresectable hepatocellular carcinoma (uHCC). Because HCC exhibits substantial etiologic and immunologic heterogeneity, treatment responsiveness to immune checkpoint inhibitors may differ according to underlying liver disease. However, vascular endothelial growth factor inhibition may attenuate these biologic differences. We evaluated survival outcomes and treatment-related adverse events according to HCC etiology in a large real-world multicenter cohort treated with atezolizumab plus bevacizumab. **Methods:** We conducted a multicenter retrospective cohort study including patients with uHCC who received first-line atezolizumab plus bevacizumab between January 2022 and December 2024 across participating tertiary referral centers in Korea. Patients were classified into viral HCC (HBV or HCV infection) and non-viral HCC groups, including alcohol-

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related liver disease, metabolic dysfunction-associated steatotic liver disease, and cryptogenic liver disease. Overall survival (OS), progression-free survival (PFS), treatment response, and immune-related adverse events (irAEs) were compared between groups using Kaplan–Meier and multivariable Cox regression analyses. **Results:** A total of 1,020 patients were included, comprising 743 patients with viral HCC and 277 with non-viral HCC. Patients with non-viral HCC were older and had higher rates of obesity, hypertension, and diabetes mellitus, whereas viral HCC had a higher proportion of Child-Pugh class B disease. Median OS was comparable between viral and non-viral HCC (11.9 vs. 12.7 months; p = 0.83), as was median PFS (5.9 vs. 6.3 months; p = 0.088). In multivariable Cox regression analyses, viral etiology was not independently associated with OS (HR 1.15, 95% CI 0.97–1.37; p = 0.11) or PFS (HR 1.16, 95% CI 0.99–1.35; p = 0.067), showing no statistically significant difference between the two groups. Objective response rates were comparable between viral and non-viral HCC (23% vs. 29%; p = 0.086). Impaired liver function, poor performance status, macrovascular invasion, and elevated AFP were the strongest predictors of survival. The incidence of irAEs was generally comparable between groups (18.4% vs. 13.7%, p = 0.10). **Conclusion:** In this large real-world multicenter cohort, atezolizumab plus bevacizumab demonstrated broadly similar efficacy and safety across viral and non-viral etiologies of uHCC. Treatment outcomes were primarily determined by liver function, performance status, and tumor burden rather than underlying disease etiology. These findings suggest that atezolizumab plus bevacizumab may provide consistent clinical benefit across diverse HCC etiologies.

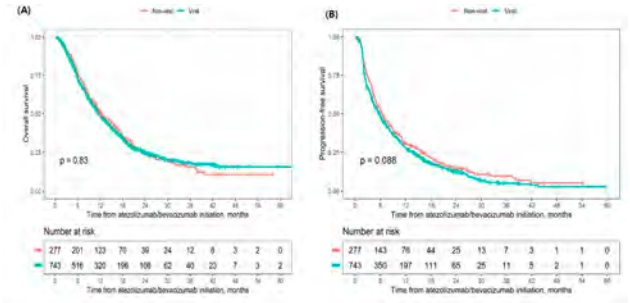


Figure. Kaplan–Meier curves for overall survival (A) and progression-free survival (B) according to HCC etiology (viral vs non-viral) in the overall cohort.

Disclosures: Yeowool Kang:Nothing to Disclose, Jun Sik Yoon:Nothing to Disclose, Jung Eun Song:Nothing to Disclose, Joonho Jeong:Nothing to Disclose, Yu Rim Lee:Nothing to Disclose, Jae hyun Yoon:Nothing to Disclose, Young Mi Hong:Nothing to Disclose, Sang Youn Hwang:Nothing to Disclose, Hyun Young Woo: Nothing to Disclose, Soo Young Park:Nothing to Disclose, Sung-Bum Cho:Nothing to Disclose, Yanghyun Baek:Nothing to Disclose.

4240 | DOCUMENTED VARICEAL PROPHYLAXIS AND BLEEDING AFTER ATEZOLIZUMAB-BEVACIZUMAB: A MARKER OF PORTAL HYPERTENSION SEVERITY, NOT PROPHYLAXIS FAILURE

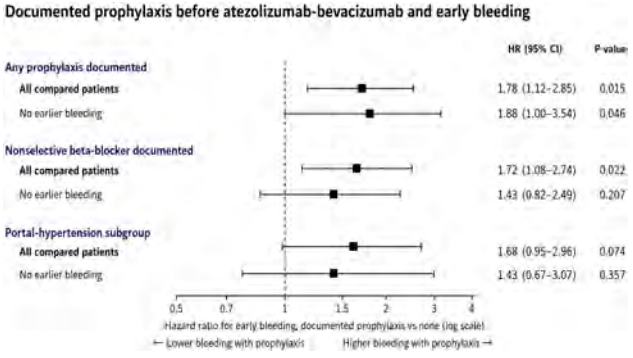
EzzElDien A. Ibrahim[1] Mahmoud Majed Mansour[1] Akram Alnounou[2] Yazan Alnairah[3] Abdallah Al Ghnaimat[4] Fouad Jaber[5] Islam Mohamed[1] Ahmad Hassan Ali[1] Nikki Duong[6] Khulood T Ahmed[1], [1]University of Missouri, Columbia, Missouri, USA, [2]Western Michigan University Homer Stryker M.D. School of Medicine,, [3]Jordanian Royal Medical Services,Amman, Jordan, [4]Hashemite University, Jordan, [5]Baylor College of Medicine, [6]Stanford University, Palo Alto, CA

Background: Portal hypertension assessment is integral to treatment planning before atezolizumab-bevacizumab for unresectable hepatocellular carcinoma (HCC), given bevacizumab-associated hemorrhagic risk. In electronic health record (EHR) data, documented variceal prophylaxis may reflect clinician-recognized high-risk portal hypertension rather than adequate risk mitigation. We evaluated the association between documented variceal prophylaxis and early bleeding after treatment initiation. **Methods:** We identified adults in the TriNetX Global Collaborative Network initiating first-line atezolizumab-bevacizumab for HCC, classified by documented variceal prophylaxis status, defined as nonselective beta-blocker (NSBB) prescription or endoscopic intervention in the 180 days preceding treatment initiation. Propensity score matching (1:1) was performed on 30 covariates encompassing demographics, liver function, portal hypertension indicators, oncologic characteristics, medications, and laboratory values. Primary outcomes over days 1–180 were variceal-only bleeding and a composite of variceal and upper gastrointestinal (GI) bleeding. Sensitivity analyses restricted the exposure to NSBBs alone, excluded prior bleeders, and enriched both arms for documented portal hypertension. **Results:** Among 3,095 patients initiating first-line atezolizumab-bevacizumab, 326 (10.5%) had documented prophylaxis and 2,769 (89.5%) did not; 280 matched pairs were formed. Variceal-only bleeding was numerically higher in the prophylaxis group before matching, though post-match event counts were small. For the composite variceal/upper-GI bleeding endpoint after matching, events occurred in 47 of 280 (16.8%) vs 28 of 280 (10.0%) patients (risk ratio [RR] 1.68, 95% CI 1.08–2.60; hazard ratio [HR] 1.78, 95% CI 1.12–2.85). After excluding patients with prior bleeding, estimates remained elevated but borderline: 27 of 233 (11.6%) vs 15 of 229 (6.6%) (RR 1.77, 95% CI 0.97–3.24; HR 1.88, 95% CI 1.00–3.53; log-rank P = 0.046). In the NSBB-only

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sensitivity analysis, the inclusive HR was 1.72 (95% CI 1.08–2.74), attenuating to 1.43 (95% CI 0.82–2.49) when restricted to incident events. Portal-hypertension-enriched estimates remained directionally consistent but imprecise (HR 1.68, 95% CI 0.95–2.96; incident HR 1.43, 95% CI 0.67–3.07). **Conclusion:** Patients with documented variceal prophylaxis before atezolizumab-bevacizumab experienced higher rates of early bleeding, likely reflecting underlying portal hypertension severity rather than prophylaxis failure. This signal persisted after excluding prior bleeders and adjusting for portal hypertension markers, suggesting that documented prophylaxis may identify a subgroup with incompletely mitigated hemorrhagic risk. Prospective studies integrating portal hemodynamics and variceal grading are needed to refine patient selection and monitoring.



Disclosures: EzzElDien A. Ibrahim:Nothing to Disclose, Mahmoud Majed Mansour:Nothing to Disclose, Akram Alnounou:Nothing to Disclose, Yazan Alnairah: Nothing to Disclose, Abdallah Al Ghnaimat:Nothing to Disclose, Fouad Jaber:Nothing to Disclose, Islam Mohamed:Nothing to Disclose, Ahmad Hassan Ali: Nothing to Disclose, Nikki Duong:Nothing to Disclose, Khulood T Ahmed:Nothing to Disclose.

4241 | RACIAL AND ETHNIC DIFFERENCES IN STAGE AT PRESENTATION, PRIMARY-SITE SURGERY, AND SURVIVAL FOR HEPATOCELLULAR CARCINOMA: A SEER ANALYSIS, 2000–2022

Kesava Manikanta Achuta[1] Vatsal Khanna[2] Abhishek Vadher[3] Sujata Kambhatla[3], [1]Garden city hospital, Michigan State University, [2]HFH, Providence, [3]Garden City Hospital, MSUCOM

Background: Hepatocellular carcinoma (HCC) is a leading cause of cancer death in the United States, and surgery remains central to curative-intent management. Racial and ethnic disparities in HCC survival have been reported, but whether these differences are driven by later presentation, lower treatment receipt, or both has not been fully characterized. We evaluated racial/ethnic differences in stage at presentation, surgery, survival in adults with HCC using population-based data. **Methods:** Adults with primary liver HCC diagnosed 2000–2022 were identified from SEER Research Data. Race/ethnicity was categorized as White (n = 61,374), Black (n = 14,739), API (n = 20,056), AI/AN (n = 1,616), and Hispanic (n = 25,849). Advanced-stage analysis was limited to 80,961 patients with known summary stage. Recorded primary-site surgery was defined using SEER RX Summ–Surg Prim Site codes. Multivariable logistic regression evaluated advanced-stage presentation and surgery receipt. Stepwise Cox regression assessed survival using three sequential models: demographic-adjusted (age, sex, year), tumor-adjusted (stage, grade, tumor size, histology), and treatment-adjusted (surgery, chemotherapy, radiation). **Results:** Among 123,934 patients, advanced-stage disease was more common in Black than White patients (50.6% vs 46.0%; adjusted OR 1.20, 95% CI 1.15–1.26). Recorded surgery was lower in Black (19.0%), AI/AN (20.4%), and Hispanic (19.8%) versus White patients (24.2%). Adjusted odds of surgery were lower for Black (OR 0.72, 95% CI 0.69–0.76), AI/AN (OR 0.77, 95% CI 0.67–0.88), and Hispanic patients (OR 0.73, 95% CI 0.70–0.76), but higher for API patients (OR 1.39, 95% CI 1.34–1.45). Surgery gaps persisted among localized/regional disease (stage-by-race interaction $p < 0.001$). In stepwise survival models, Black-White mortality attenuated from HR 1.17 (95% CI 1.14–1.19) to HR 1.08 after tumor adjustment and HR 1.01 after treatment adjustment, indicating approximately half of excess mortality was explained by tumor factors and the remainder by treatment receipt. **Conclusion:** Black patients had higher odds of advanced-stage presentation and lower odds of surgery. The Black–White mortality disparity attenuated from HR 1.17 to HR 1.01 after sequential adjustment for tumor factors and treatment, suggesting later presentation and lower treatment receipt may largely explain the survival gap. Lower surgery among Black, Hispanic, and AI/AN patients persisted among localized/regional disease, a treatment-access signal not explained by stage alone. API patients had higher surgery odds and lower mortality, supporting system-level rather than biological factors. SEER lacks data on insurance, liver disease severity, and transplant evaluation; findings represent

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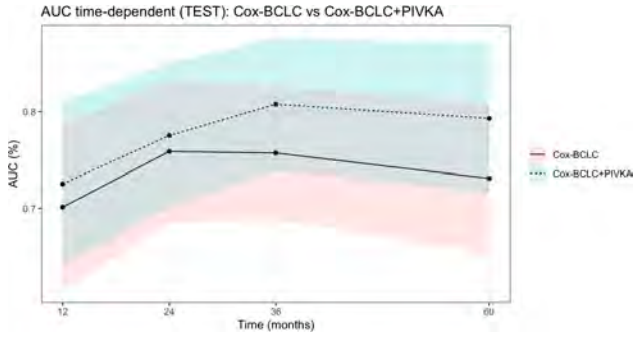
potential care-pathway disparities, not causal proof. Studies using access-linked datasets are needed to identify modifiable targets for reducing HCC outcome inequities.

Disclosures: Kesava Manikanta Achuta:Nothing to Disclose, vatsal khanna:Nothing to Disclose, Abhishek Vadher:Nothing to Disclose, sujata kambhatla:Nothing to Disclose.

4242 | PIVKA-II SERUM LEVELS ENHANCE PROGNOSTIC STRATIFICATION BEYOND BCLC STAGING IN NEWLY DIAGNOSED HEPATOCELLULAR CARCINOMA: A MULTICENTRE COHORT STUDY

Francesco Damone[1] Gian Paolo Caviglia[2] Francesco Faita[3] Piero Colombatto[1] Filippo Oliveri[1] Marta Guariglia[2] Gabriele Ricco[4] Silvia Gaia[5] Daniela Cavallone[1] Veronica Romagnoli[1] Emanuela Rolle[6] Patrizia Carucci[6] Ferruccio Bonino[3] Maurizia Brunetto[7], [1]Hepatology Unit, Pisa University Hospital, Italy, [2]Department of Medical Sciences, University of Turin, Turin, Italy, [3]Biostructure and Bio-imaging Institute of National Research Council of Italy, [4]Hepatology Unit, Pisa University Hospital, Italy;, [5]Unit of Gastroenterology, Città della Salute e della Scienza - Molinette Hospital, Turin, Italy, [6]Unit of Gastroenterology, Città della Salute e della Scienza - Molinette Hospital, Turin, Italy;, [7]Department of Clinical and Experimental Medicine, Pisa University and Hepatology Unit, Pisa Universi

Background: Current prognostic tools for Hepatocellular Carcinoma (HCC), including the Barcelona Clinic Liver Cancer (BCLC) staging system, rely on liver function, tumour burden and performance status, yet fail to capture tumour biological heterogeneity and aggressiveness. This multicentre cohort study investigated whether baseline serum Protein induced by Vitamin K Absence-II (PIVKA-II) levels could complement BCLC staging to enhance prognostic accuracy. **Methods:** A cohort of 605 consecutive patients with newly diagnosed HCC, enrolled between 2010 and 2024 at two Italian tertiary referral centres, was analysed. PIVKA-II was incorporated as a continuous variable. The primary endpoint was Overall Survival (OS). Prognostic performance was evaluated by comparing two Cox proportional hazards models: one based on BCLC stage alone and the other additionally incorporating baseline PIVKA-II. Discrimination and calibration were assessed using time-dependent AUC, Brier score, and C-index at 24, 36, and 60 months. Internal validation was performed through a 70/30 train–test split approach. **Results:** BCLC stage distribution was as follows: 83 patients BCLC-0, 284 BCLC-A, 151 BCLC-B, and 87 BCLC-C. Median OS for the overall cohort was 29.0 months, with stage-specific medians ranging from 47.9 months (BCLC-0) to 10.7 months (BCLC-C) ($p < 0.001$). Adding PIVKA-II to the BCLC model substantially improved prognostic discrimination at mid- and long-term timepoints: time-dependent AUC at 36 months was 80.8% versus 75.7% ($p = 0.006$), rising to 79.3% versus 73.1% at 60 months ($p = 0.002$). Calibration also marginally improved with PIVKA-II integration, as evidenced by lower Brier scores at 36 months (18.9% vs 19.2%) and 60 months (19.8% vs 20.1%). Overall discriminative ability favoured the integrated model (C-index: 0.71 vs 0.68). **Conclusion:** Baseline PIVKA-II serum levels offer meaningful prognostic value beyond BCLC staging in patients with newly diagnosed HCC, significantly enhancing mid- and long-term survival prediction. These results support the design of prospective studies aimed at incorporating tumour biomarkers into established staging frameworks, in line with a precision medicine approach to HCC management.



Disclosures: Francesco Damone:Nothing to Disclose, Gian Paolo Caviglia:Nothing to Disclose, Francesco Faita:Nothing to Disclose, Piero Colombatto:Nothing to Disclose, Filippo Oliveri:Nothing to Disclose, Marta Guariglia:Nothing to Disclose, Gabriele Ricco:Nothing to Disclose, Silvia Gaia:Nothing to Disclose, DANIELA CAVALLONE:Nothing to Disclose, Veronica Romagnoli:Nothing to Disclose, Emanuela Rolle:Nothing to Disclose, Patrizia Carucci:Nothing to Disclose, Ferruccio Bonino:Nothing to Disclose, Maurizia Brunetto: Nothing to Disclose.

4243 | OUTCOMES OF HEPATOCELLULAR CARCINOMA IN PATIENTS WITH METABOLIC SYNDROME VERSUS VIRAL HEPATITIS: A COMPARATIVE EFFECTIVENESS STUDY

Eunice Aregbesola[1] Ibukunoluwa Oshobu[2] Abisola Ajayi[3] Bright Nwatamole[4] Eunice Omeludike[5],

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Background: Metabolic syndrome–associated hepatocellular carcinoma (HCC) is increasingly recognized as a major etiologic subtype of liver cancer, yet comparative outcomes relative to viral hepatitis– associated HCC remain unclear. We evaluated clinical outcomes among HCC patients with metabolic syndrome versus viral hepatitis using a multicenter electronic health record database. **Methods:** We performed a retrospective propensity score–matched comparative effectiveness study using the TriNetX Research Network. Adult patients with HCC and metabolic syndrome were matched1:1 to patients with HCC associated with chronic viral hepatitis (HBV/HCV) based on demographics, cirrhosis status, obesity, diabetes mellitus, smoking history, and cardiovascular comorbidities. Primary outcome was all-cause mortality. Secondary outcomes included hepatic decompensation, portal hypertension, liver-related hospitalization, metastatic disease, liver transplantation, and systemic therapy utilization. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using Cox proportional hazards models. **Results:** After propensity matching, 41,882 patients were included in each cohort. During a median follow-up of 5.8 years, metabolic syndrome–associated HCC demonstrated significantly higher all-cause mortality compared with viral hepatitis–associated HCC (38.6% vs 32.4%; HR 1.29, 95% CI 1.23–1.35; $p < 0.001$), with progressive divergence in overall survival over time (log-rank $p < 0.001$) (Fig. 1). Patients with metabolic syndrome–associated HCC additionally demonstrated increased risks of hepatic decompensation (22.1% vs 18.4%; HR 1.24, 95% CI 1.18–1.31), portal hypertension (27.8% vs 23.3%; HR 1.21, 95% CI 1.15–1.27), liver-related hospitalization (41.2% vs 35.9%; HR 1.26, 95% CI 1.21–1.32), and metastatic disease at presentation (18.7% vs 14.1%; HR 1.38, 95% CI 1.29–1.47) (Fig. 2). Conversely, these patients were less likely to undergo liver transplantation (4.9% vs 8.7%; HR 0.58, 95% CI 0.52–0.65) or receive systemic therapy (21.4% vs 25.9%; HR 0.81, 95% CI 0.76–0.86). Increased mortality persisted among patients with obesity (HR 1.33), diabetes mellitus (HR 1.27), and non-cirrhotic disease (HR 1.41) (all $p < 0.001$). Sensitivity analyses excluding alcohol-associated liver disease continued to demonstrate worse survival in the metabolic syndrome cohort (HR 1.22, 95% CI 1.16–1.29; $p < 0.001$). **Conclusion:** Metabolic syndrome–associated HCC was associated with worse survival, increased hepatic complications, and lower transplantation utilization compared with viral hepatitis–associated HCC. These findings highlight important etiologic differences in HCC presentation and outcomes and support the need for improved surveillance and risk stratification strategies.

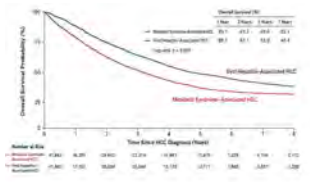


Fig. 1: Kaplan-Meier Overall Survival Curve Metabolic Syndrome-Associated HCC vs. Viral Hepatitis-Associated HCC

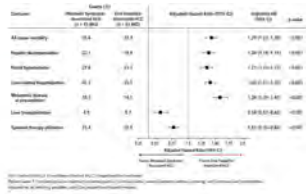


Fig. 2: Forest Plot of Adjusted Hazard Ratios for Clinical Outcomes Metabolic Syndrome-Associated HCC vs. Viral Hepatitis-Associated HCC

Disclosures: Eunice Aregbesola:Nothing to Disclose, Ibukunoluwa Oshobu:Nothing to Disclose, Abisola Ajayi:Nothing to Disclose, Bright Nwatamole:Nothing to Disclose, Eunice Omeludike:Nothing to Disclose.

4244 | HEPATOCELLULAR CARCINOMA IN A LARGE CORRECTIONAL HEALTHCARE SYSTEM: BURDEN, MANAGEMENT, AND OUTCOMES

Raakhi Menon[1] Mahnur Haider[2] Hari Movva[1] Hisham Alsharif[1] Muhammad Mushtaq[1] Biai Digbeu[1] Gwen Baillargeon[1] Jessica Khan[1] Olugbenga Ojo[1] Owen Murray[1] Sreeram Parupudi[1], [1]University of Texas Medical Branch, [2]Georgetown University

Background: Incarcerated populations have a high prevalence of hepatocellular carcinoma (HCC) risk factors, particularly chronic hepatitis C virus (HCV) infection, yet data on HCC characteristics, management, and outcomes in correctional settings remain limited. We describe the burden of HCC within the Texas Department of Criminal Justice (TDCJ). **Methods:** Retrospective study of individuals, 18 years or older, incarcerated in TDCJ (January 2015–December 2023). HCC was identified via ICD-9/10 codes and confirmed by chart review using standardized imaging criteria (LI-RADS) and/or histopathology. Stage classified as early (solitary ≤ 3 cm, no vascular invasion or metastasis), intermediate (multifocal or > 3 cm, no vascular invasion or metastasis), or advanced (vascular invasion and/or metastasis). Clinical characteristics were compared by HCV viral clearance status (undetectable HCV RNA). **Results:** 408 HCC cases were confirmed; 395 (96.8%) diagnosed during incarceration. Cohort was predominantly male (97.8%); 45.1% incarcerated 3–5 years, 35.2% > 5 years. Cirrhosis present in 88.7%, mostly viral hepatitis (93.4%). At diagnosis, median MELD-Na was 9.0 (IQR 8–12), 51.9% were ALBI grade 2, and 30.4% had decompensated cirrhosis. Stage: early 18.1%, intermediate 32.4%, advanced 22.5%; 27.0% unstaged. HCC-directed therapy received by 71.3%: 54.2% chemoembolization, 20.9% ablation,10.8% systemic therapy and 10.0% surgical resection. Median time to first treatment

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was 61 days (IQR 34–108). Mortality was 49.8%; median time from diagnosis to death was 365 days (IQR 152–831). Of 331 patients with HCV testing, 312 (94.3%) had chronic HCV; 111 (27.2%) received antiviral therapy, of whom 84 (75.6%) achieved HCV viral clearance. One-third (31.5%) initiated HCV treatment after HCC diagnosis. Most prescribed regimens: sofosbuvir/velpatasvir (45%), glecaprevir/pibrentasvir (30%), ledipasvir/sofosbuvir (18%). Compared to those without HCV viral clearance, patients with viral clearance were more often incarcerated >5 years (63.3% vs. 29.7%; $p < 0.001$), had lower hepatic fibrosis by APRI ($p = 0.002$), and trended toward earlier HCC stage (25.6% vs. 17.1%) and lower mortality (41.1% vs. 50.9%), although these did not reach statistical significance (Table 1). **Conclusion:** Correctional healthcare systems face substantial barriers to care and remain understudied. Chronic HCV was the predominant etiology of liver disease, highlighting the high burden of HCV mediated HCC among incarcerated individuals. Despite patients receiving HCC-directed therapy, nearly half died, many presenting with intermediate or advanced-stage disease. Patients achieving HCV viral clearance had significantly less hepatic fibrosis and longer incarceration duration. Correctional healthcare systems represent critical opportunities for HCV treatment, cirrhosis care, and HCC surveillance, and require dedicated resources to address this burden.

Table 1. Clinical characteristics by HCV viral clearance status among individuals with documented chronic HCV and available HCV RNA testing (n=312)

Variable	Achieved viral clearance (n=90)	No viral clearance (n=222)	P-value
Age, median (IQR)	60 (56.25-63)	58 (53.5-61)	0.268
Male sex, n (%)	87 (96.7%)	216 (97.3%)	0.7207
Race, n (%)			0.7466
White	38 (42.2%)	86 (38.7%)	
Black	24 (26.7%)	54 (24.3%)	
Hispanic	28 (31.1%)	81 (36.5%)	
Asian	0 (0.0%)	1 (0.5%)	
Years incarcerated n (%)			0.0005
≤2 years	2 (2.2%)	44 (19.8%)	
3-5 years	31 (34.4%)	112 (50.5%)	
> 5 years	57 (63.3%)	66 (29.7%)	
MELD-Na, median (IQR)	10.0 (8.0-13.5)	9.0 (7.0-12.0)	0.202
ALBI grade, n (%)			0.1299
Grade 1	35 (38.9%)	62 (27.9%)	
Grade 2	43 (47.8%)	113 (50.9%)	
Grade 3	8 (8.9%)	33 (14.9%)	
APRI category, n (%)			0.0020
> 1	45 (50.0%)	148 (66.7%)	
0.5-1	24 (26.7%)	48 (21.6%)	
< 0.5	15 (16.7%)	10 (4.5%)	
Decompensated cirrhosis, n (%)	33 (36.7%)	60 (27.0%)	0.2206
HCC Stage n (%)			0.334
Early	23 (25.6%)	38 (17.1%)	
Intermediate	32 (35.6%)	73 (32.9%)	
Advanced	17 (18.9%)	48 (21.6%)	
Received treatment for HCC	52 (57.8%)	126 (56.8%)	0.7701
Surgery, n (%)	2 (2.2%)	4 (1.8%)	
TACE, n (%)	44 (48.9%)	126 (56.8%)	
Ablation, n (%)	18 (20.0%)	20 (9.0%)	
Systemic therapy, n (%)	6 (6.7%)	25 (11.3%)	
Received HCV treatment	84 (93.3%)	25 (11.3%)	p<0.001
Timing of HCV treatment			0.3280
Before HCC Diagnosis	60 (66.7%)	15 (6.8%)	
After HCC Diagnosis	24 (26.7%)	10 (4.5%)	
Death	37 (41.1%)	113 (50.9%)	0.149

† Categorical variables compared using Fisher's Exact test where expected cell counts were <5. Continuous variables compared using Mann-Whitney U tests. A two-sided p-value <0.05 was considered statistically significant. Percentages may not sum to 100% due to missing data. HCC stage analysis restricted to patients with known stage (n=236).

Disclosures: Raakhi Menon:Nothing to Disclose, Mahnur Haider:Nothing to Disclose, Hari Movva:Nothing to Disclose, Hisham Alsharif:Nothing to Disclose, Muhammad Mushtaq:Nothing to Disclose, Biai Digbeu:Nothing to Disclose, Gwen Baillargeon:Nothing to Disclose, Jessica Khan:Nothing to Disclose, OLUGBENGA OJO:Nothing to Disclose, Owen Murray:Nothing to Disclose, Sreeram Parupudi:Nothing to Disclose.

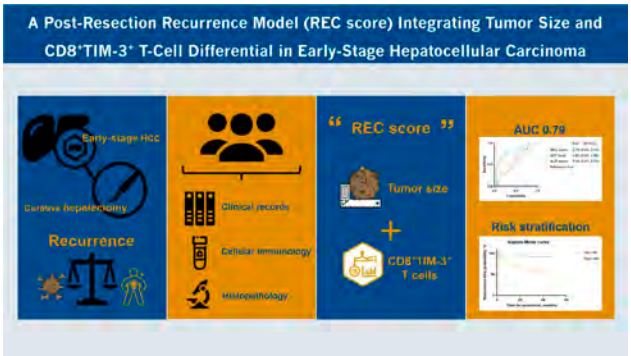
4245 | A POST-RESECTION RECURRENCE MODEL (REC SCORE) INTEGRATING TUMOR SIZE AND CD8⁺TIM-3⁺ T-CELL DIFFERENTIAL IN EARLY-STAGE HEPATOCELLULAR CARCINOMA

Qing Zhao[1] Jie Wang[2] Wei Wu[2] Qi Xia[2], [1]Zhejiang University, [2]The First Affiliated Hospital, Zhejiang University School of Medicine

Background: Early-stage hepatocellular carcinoma (HCC) frequently recurs after curative resection, yet individualized prediction tools remain limited. **Methods:** We retrospectively enrolled 59 patients with early-stage HCC who underwent hepatectomy and completed ≥ 3-year follow-up. Clinical-pathological parameters, peripheral immune profiling by flow cytometry and tumor tissue immunofluorescence were compared between recurrent and non-recurrent patients. Independent predictors from multivariable Cox regression were integrated into the Recurrence Estimation after Curative resection (REC) score. Discrimination and risk stratification were evaluated by area under the receiver operating characteristic (ROC) curve and Kaplan-Meier (KM) analysis. **Results:** Recurrent patients exhibited higher levels of alpha-fetoprotein (AFP) and protein induced by vitamin K absence or antagonist-II (PIVKA-II), larger tumor size, poorer differentiation, and a greater pre-post change in the proportion of CD8⁺TIM-3⁺ T-cell (all $p < 0.05$) compared to non-recurrent patients. Tumor size (HR 1.17, 95%CI 1.02-1.30) and pre-post change of CD8⁺TIM-3⁺ T-cell proportion (HR 1.55, 95%CI 1.03-2.21) were independently associated with recurrence and constructed the predictive REC score. The REC score achieved an AUC of 0.79, outperforming AFP (AUC 0.65) and albumin-bilirubin (ALBI) (AUC 0.58). With the optimal cutoff (0.533), REC stratified patients into low-risk (n = 37, 3-year RFS > 91.90%) and high-risk (n = 22, 3-year RFS < 50.00%) groups (log-rank $p < 0.01$). **Conclusion:** This exploratory study suggests that integrating tumor burden with dynamic T-cell dysfunction may provide promising insights into predicting post-resection recurrence in early-stage HCC. However, theses preliminary findings require validation in larger, more diverse cohorts due to the small sample size and statistical limitations.

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4246 | MULTIMODAL SEQUENCING IDENTIFIES SYNERGISTIC MECHANISMS DRIVING RESISTANCE TO NEOADJUVANT NIVOLUMAB TREATMENT IN HCC

Irene Ng[1] Fanhong Zeng[2] Jiax Guo[1] Zheng Zeng[1] Vanilla Zhang[2] Daniel Ho[2], [1]The University of Hong Kong, [2]University of Hong Kong

Background: The tumor immune microenvironment (TIME) critically modulates therapeutic responses to immune checkpoint inhibitors (ICIs) in hepatocellular carcinoma (HCC). Relative to the other solid tumors, HCC is characterized by more pronounced intratumoral heterogeneity and has comparatively poorer responsiveness to ICI blockade treatment. Importantly, the correlation of the underlying mechanism of TIME and the molecular underpinnings of immunotherapy resistance in HCC remains elusive. **Methods:** We employed an integrative multi-omics approach, including spatially resolved transcriptomics, single-cell and bulk RNA sequencing, and lipidomics to delineate the spatiotemporal dynamics and mechanistic basis of resistance to anti-PD-1 therapy in patient HCC tumors. **Results:** Our analyses revealed a profoundly immunosuppressive TIME in non-responsive patients, marked by sparse immune cell infiltration within the tumor niche, in contrast to the immune-inflamed TIME observed in the responders. Multidimensional profiling further uncovered dysregulated and enhanced lipogenesis and aberrant lipid accumulation in tumor cells of the non-responder cases. Notably, tumor-associated macrophages (TAMs), exhausted CD8 T cells, and lipid-enriched tumor cells co-localize at the tumor-immune interface, forming a physical and functional barrier that precludes effective immune cell infiltration into the tumor niche. We also identified a pivotal TAM-tumor cell crosstalk via ADM-RAMP1-EBP signaling axis, orchestrating lipid metabolism reprogramming and contributing to the attenuated PD-1 therapeutic efficacy. To evaluate the therapeutic potential of the combined actions of EBP inhibition and anti-PD1 immune checkpoint blockade, we utilized an orthotopic liver injection HCC mouse model. While anti-PD1 or EBP inhibitor monotherapy effectively suppressed tumor growth, the combination of both agents showed a robust synergistic effect in further abrogating the tumor growth. **Conclusion:** Collectively, these findings provide a comprehensive mechanistic framework for anti-PD1 resistance, unveiling actionable biomarkers and a translational vulnerability to enhance precision therapeutics in HCC.

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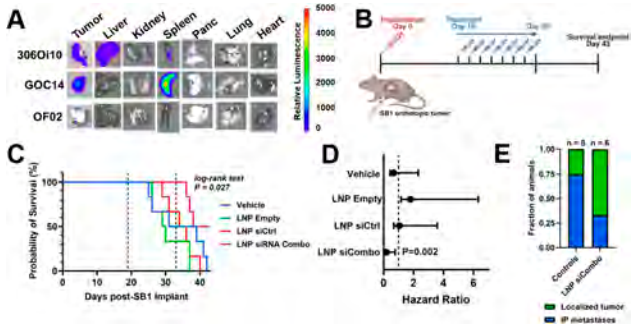
4247 | LIPID NANOPARTICLE-TARGETED SIRNA THERAPEUTICS FOR CHOLANGIOCARCINOMA

Brandon Wilbanks[1] Danielle Carlson[1] Jayla Millender[1] Shelby Yee[1] Hidemi Nishi[1] Enis Ozmert[1] Emily Siegler[1] Leonard Di Filippo[1] Gregory Gores[1] Sai Yerneni[1] Rory Smoot[1], [1]Mayo Clinic

Background: Cholangiocarcinoma (CCA) is a highly lethal primary hepatic malignancy arising from the biliary epithelium. Resection is curative for some patients, though most are not eligible due to advanced disease at the time of presentation. Current treatment strategies rely on systemic treatment with chemotherapeutics or small molecule inhibitors, leaving many potential therapeutic targets unexplored due to the systemic toxicity of their inhibitors. No approach for tumor-selective inhibition is available. **Methods:** We performed an in vitro screen with unique 96 lipid nanoparticles (LNPs) composed of varied combinations of ionizable lipids and phospholipids to discover an LNP with selective cholangiocarcinoma delivery properties. This screen and subsequent in vivo validation with mice bearing orthotopically implanted tumors (panel A) identified an LNP that delivers nucleic acid payloads to tumors without off-target deposition in all other tissues except for spleen. We then used this LNP for delivery of siRNAs targeting Mcl-1 and Bcl-xL to selectively induce apoptosis in tumors. After implanting CCA cells and allowing 19 days of orthotopic tumor development, mice were treated 3X weekly for two weeks and then observed to humane endpoint. **Results:** LNP-targeted siRNA treatment with anti-Mcl-

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1 and Bcl-xL knockdown ("siCombo") extended survival in CCA-bearing mice (panels B-D), slowed tumor growth rates, and reduced intraperitoneal metastatic burden (panel E). We observed no long-term damage in spleen as a result of off-target delivery. All mice in control groups met humane endpoint criteria (20% body weight loss or 15% weight gain with visible ascites) before study termination (43 days post-implant) while half of siRNA-treated animals survived. **Conclusion:** LNP-targeted siRNA therapies represent a promising new modality for CCA treatment. Importantly, this platform enables knockdown of target genes that are otherwise undruggable due to systemic toxicity of small molecule inhibitors. We are exploring additional therapeutic targets and methods for extended target knockdown with chemically modified siRNAs.



Disclosures: Brandon Wilbanks:Nothing to Disclose, Danielle Carlson:Nothing to Disclose, Jayla Millender: Nothing to Disclose, Shelby Yee:Nothing to Disclose, Hidemi Nishi:Nothing to Disclose, Enis Ozmert:Nothing to Disclose, Emily Siegler:Nothing to Disclose, Leonard Di Filippo:Nothing to Disclose, Gregory Gores:Nothing to Disclose, Sai Yerneni:Nothing to Disclose, Rory Smoot:Nothing to Disclose.

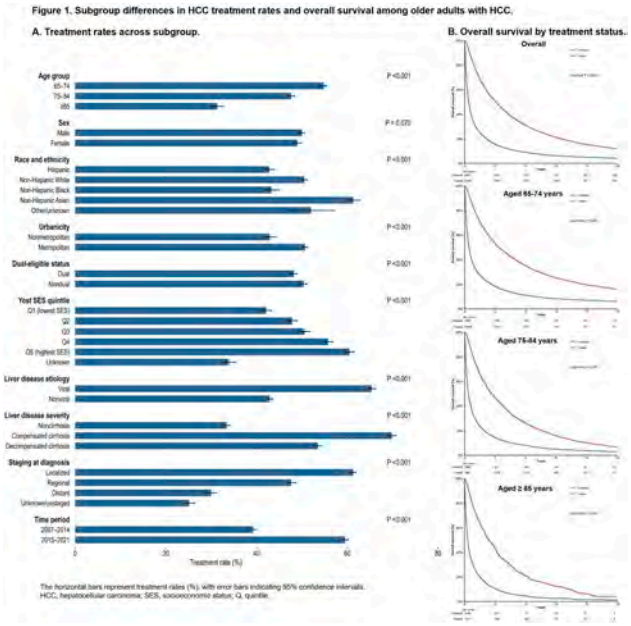
4248 | UNDERTREATMENT AND DISPARITIES IN HCC TREATMENT AMONG OLDER PATIENTS WITH HEPATOCELLULAR CARCINOMA (HCC): A U.S. POPULATION-BASED STUDY

Danfeng Ren[1] Taotao Yan[1] Joanne Kimiko Liu[2] Nicholas Chien[2] Bowu Chen[3] Hong Fan[2] Xiaonan Su[4] Ramsey Cheung[2] Mindie Nguyen[2], [1]The First Affiliated Hospital of Xi'an Jiaotong University, [2]Stanford University Medical Center, [3]Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, [4]Zhejiang Provincial Clinical Research Center for Digestive Diseases, The First Affiliated Hospital

Background: HCC disproportionately affects older adults who may have more barriers to treatment, which may lead to poorer survival outcomes. However, population-based data on treatment utilization, disparities and its evolution over time in this population remain limited. The current study evaluated changes by HCC diagnosis year in the overall treatment rates, treatment types and overall survival (OS) of older patients with HCC using a U.S. national population-based database. **Methods:** We conducted a retrospective cohort study of 40,996 adults aged ≥65 years who were diagnosed with HCC from 2007 to 2021 using the Surveillance, Epidemiology, and End Results (SEER)-Medicare database. Temporal trends in treatment utilization were assessed using Joinpoint regression to estimate average annual percentage change (AAPC). **Results:** Only 49.7% of the study cohort received HCC treatment of any type. Initial treatments were surgery in 9.6%, local ablation in 6.0%, other locoregional therapy in 26.7%, and systemic therapy in 7.4%. Treatment rates declined with increasing age (54.8%, 47.6%, and 31.1% for ages 65-74, 75-84, and ≥85 years) and more advanced HCC stage (61.3%, 47.6%, and 30.0% for localized, regional, and distant HCC), respectively, with significant disparities across sociodemographic and clinical subgroups (Figure 1A). However, treatment rates increased over time (32.4% in 2007 to 64.2% in 2021; AAPC 4.84%, 95% CI 4.14%–5.31%) but mostly in nonsurgical treatments (AAPC: 5.34% for local ablation, 5.85% for other locoregional therapy and 7.45% for systemic therapy, $P<0.001$ for all), with consistent increase across major subgroups, especially in patients aged ≥85 years (18.0% in 2007 to 49.3% in 2021; AAPC 8.85%, 95% CI 6.24%–11.50%) though they remained the least treated in 2021. Multivariable analysis adjusting for age, sex, race and ethnicity, urbanicity, insurance status, socioeconomic status (SES), liver disease etiology and severity, Charlson Comorbidity Index, tumor stage at diagnosis and diagnosis period showed lower odds of treatment with age ≥85 vs 65–74 (aOR 0.41, 95% CI 0.37–0.44), distant vs localized stage (aOR 0.27, 95% CI 0.25–0.28), and non-Hispanic Black vs White (aOR 0.63, 95% CI 0.58–0.69), while higher odds were observed with compensated cirrhosis vs noncirrhosis (aOR 2.76, 95% CI 2.60–2.93), viral vs nonviral etiology (aOR 1.81, 95% CI 1.71–1.91), highest vs lowest SES quintile (aOR 1.78, 95% CI 1.65–1.93). Treated (vs untreated) patients had longer median OS overall (24.0 vs 3.0 months, $P<0.001$) and in each age subgroup including those older than 85 (all $P<0.001$) (Figure 1B). **Conclusion:** Among older adults with HCC, though treatment rates have increased over time, these gains were mainly with nonsurgical palliative treatment and nearly half still untreated, with substantial age, racial and ethnic, geographic, and socioeconomic disparities.

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4249 | TRANSCRIPTOMIC SHANNON DIVERSITY STRATIFIES PROGNOSIS AND MARKS AN ONCOFETAL SUBTYPE IN GRADE 1 HEPATOCELLULAR CARCINOMA

Haley Arbore[1] Jia-Jun Liu[1] Silvia Liu[1] Panayiotis Benos[2] Juliane Beier[1] Gavin Arteel[1], [1]University of Pittsburgh, [2]University of Florida

Background: Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality worldwide, yet histologic grading does not fully capture molecular heterogeneity, particularly in well-differentiated tumors. Transcriptomic Shannon diversity is a per-sample measure of transcript abundance evenness that has been proposed as a pan-cancer index of tumor heterogeneity. Its prognostic relevance in HCC and its relationship to tumor biology have not been established. This study examines whether Shannon diversity predicts survival in a grade-dependent manner and whether it relates to oncofetal dedifferentiation in well-differentiated HCC. **Methods:** Shannon diversity indices were computed from TCGA-LIHC bulk RNA-seq data across all tumors (n = 374), and quartile boundaries (Q1-Q4) were established from this full cohort distribution. Differential gene expression analysis was performed using DESeq2 (Q4 vs Q1, Q2, and Q3). Ingenuity Pathway Analysis was applied to Q4 vs Q1 DEGs. Overall survival was evaluated by Kaplan-Meier and Cox regression across all tumor grades. A hepatocyte differentiation score was computed as the mean log2(CPM+1) expression of 24 mature hepatocyte marker genes. Spearman correlation was used to assess the relationship between Shannon diversity and hepatocyte differentiation across tumor grades. **Results:** Shannon diversity independently predicted mortality after adjusting for T stage and tumor grade (OR = 1.16 per unit, $p < 0.001$). Grade 1 was the only grade at which Shannon diversity significantly stratified survival; Q4/G1 tumors had 62.5% mortality compared to 15.8% in Q1/G1. High Shannon diversity (Q4) was associated with significantly worse overall survival compared to Q1 in Grade 1 tumors (log-rank $p < 0.001$). No significant survival association was found in Grade 2 ($p = 0.489$) or Grade 3/4 ($p = 0.823$). DEG analysis identified 944 significant genes in Q4 vs Q1, the majority downregulated. IPA showed suppression of mature hepatocyte programs including the urea cycle, LXR/RXR activation, metallothionein signaling, and acute phase response, with concurrent activation of ID3 and SPINK1 pathways. Q4 tumors had significantly lower hepatocyte differentiation scores than Q1 ($p = 3.6 \times 10^{-6}$), and Shannon diversity was inversely correlated with hepatocyte differentiation in Grade 1 ($r = -0.516$, $p = 5.5 \times 10^{-5}$), Grade 2 ($r = -0.447$, $p = 4.2 \times 10^{-10}$), and Grade 3/4 ($r = -0.403$, $p = 1.2 \times 10^{-6}$). **Conclusion:** High Shannon diversity in Grade 1 HCC identifies a clinically aggressive subgroup with loss of hepatocyte identity and oncofetal transcriptional activation. The prognostic value of Shannon diversity is restricted to well-differentiated HCC, where it captures molecular heterogeneity not reflected by histologic grade alone, and points to oncofetal reprogramming as a driver of poor outcomes in early-stage disease.

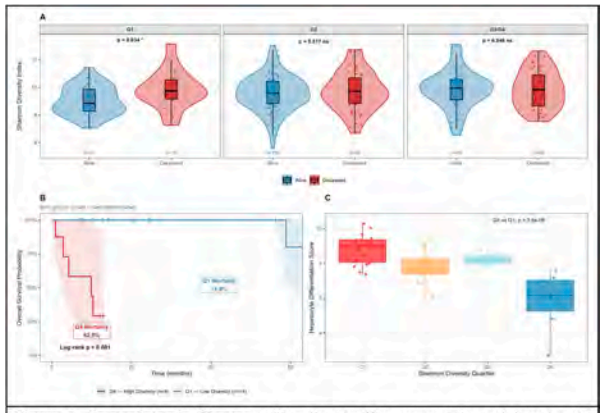


Figure 1. Transcriptomic Shannon diversity stratifies prognosis and hepatocyte identity in Grade 1 HCC. (A) Shannon diversity compared between deceased and surviving patients by tumor grade (TCGA-LIHC, n=364). Grade 1 is the only grade with a significant dead/alive difference (9.93 vs. 9.52, Mann-Whitney p=0.034); no significant difference was observed in Grade 2 (p=0.517) or Grade 3/4 (p=0.946). **(B)** Kaplan-Meier survival curves for Grade 1 tumors stratified by Shannon quartile (Q4 vs. Q1). Despite identical histologic grade, Q4 tumors exhibit 62.5% mortality vs. 15.8% in Q1 (log-rank p<0.001). Tick marks indicate censored observations. **(C)** Hepatocyte differentiation score (mean log2(CPM+1) of 24 mature hepatocyte marker genes) by Shannon quartile in Grade 1 tumors. Q4 tumors show a stepwise reduction compared to Q1 (Wilcoxon $p = 3.6 \times 10^{-6}$), indicating progressive loss of hepatocyte gene expression with increasing transcriptomic diversity.

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4250 | HEPATIC ADENOMATOSIS: A SYSTEMATIC REVIEW OF DEFINITIONS, DIAGNOSTIC EVALUATION, MANAGEMENT, AND OUTCOMES

Thomas Stirrat[1] Shankar Thiru[2] Stella Kim[2] Soham Apte[3] Deeptha Bejugam[2] Michael Flatley[4] Amol Rangnekar[5] Rachel Redfield[6], [1]University of California Los Angeles (UCLA), [2]Georgetown University School of Medicine, [3]Kentucky College of Osteopathic Medicine, [4]University of Colorado Internal Medicine Residency Program, [5]Georgetown University Hospital, [6]MedStar Georgetown University Hospital

Background: Hepatic adenomatosis (HA), the multifocal phenotype of hepatocellular adenoma, is inconsistently defined and managed. We performed a systematic review to synthesize definitions, imaging use, pathology reporting, management strategies, and outcomes. **Methods:** MEDLINE/PubMed, Embase, Web of Science, and CINAHL were searched from inception through August 25, 2025. Human case reports/series with original clinical data and diagnostic confirmation by imaging and/or histopathology were included. Data were abstracted using standardized fields and synthesized descriptively. **Results:** Fifty-four reports describing 55 patients were included; 53/54 studies (98.1%) were single-case reports. Most patients were female (45/55, 81.8%), with median age 34 years. Definitions most often used a $\geq$10-lesion threshold (37/54, 68.5%). Among cases with quantifiable lesion burden, the median lesion count was 15; median largest-lesion diameter was 80 mm (range 13-170), and 37/46 (80.4%) measured $\geq$5 cm. MRI was reported in 34/51 (66.7%), but hepatobiliary-phase MRI was reported in only 2/51 (3.9%). Histologic/molecular subtype reporting was sparse. Management included observation (34/53, 64.2%), resection (32/53, 60.4%), transplantation (6/53, 11.3%), embolization (4/53, 7.5%), and ablation (1/53, 1.9%). Indications for active intervention included size $\geq$5 cm (21/41, 51.2%), malignancy/diagnostic concern (17/41, 41.5%), hemorrhage/risk (11/41, 26.8%), and symptoms (10/41, 24.4%). Follow-up documented hemorrhage in 5/55 (9.1%) and malignant transformation in 6/55 (10.9%), likely reflecting publication/severity bias. **Conclusion:** HA literature remains fragmented by variable definitions, incomplete imaging protocols, limited molecular profiling, and sparse follow-up. A pragmatic research framework should standardize HA as $\geq$10 adenomas in a non-cirrhotic liver while emphasizing hepatobiliary-contrast MRI, targeted biopsy/molecular profiling of index lesions, hormone withdrawal, and risk-adapted intervention.

Hepatic adenomatosis: key abstract outcomes

Variable	Value
Reports / patients included	54 / 55
Female patients	45/55 (81.8%)
Median age	34 years
≥10-lesion definition used	37/54 (68.5%)
Median lesion count	15
Median largest-lesion diameter	80 mm
Largest lesion ≥5 cm	37/46 (80.4%)
MRI reported	34/51 (66.7%)
Hepatobiliary-phase MRI reported	2/51 (3.9%)
Hemorrhage / malignant transformation	5/55 (9.1%) / 6/55 (10.9%)

Disclosures: Thomas Stirrat:Nothing to Disclose, Shankar Thiru:Nothing to Disclose, Stella Kim:Nothing to Disclose, Soham Apte:Nothing to Disclose, Deeptha Bejugam:Nothing to Disclose, Michael Flatley:Nothing to Disclose, Amol Rangnekar:Nothing to Disclose, Rachel Redfield:Nothing to Disclose.

4251 | DIAGNOSTIC PERFORMANCE OF MRI VS. CONTRAST ENHANCED ULTRASOUND FOR DETECTION OF HCC IN PATIENTS WITH INDETERMINATE LIVER NODULES

Amit Singal[1] Guruveer Bhamra[1] Emma Jones[1] David Fetzer[1] Sruthi Yekkaluri[1] Takeshi Yokoo[1] So Yeon Kim[1] Lisa Quirk[1] Kayleen Sorto[1] Nicole Rich[2], [1]UT Southwestern Medical Center, [2]University of Texas Southwestern Medical Center

Background: Patients with indeterminate liver nodules (ILNs), i.e., LI-RADS 3 and 4 observations, have a 35-70% risk of developing hepatocellular carcinoma (HCC) and require close surveillance. Multi-phase CT or MRI are the most common surveillance modalities, and the role of contrast-enhanced ultrasound (CEUS) is unknown. **Methods:** We conducted an interim analysis of a prospective cohort of patients with cirrhosis and LR-3 or LR-4 observations to compare the performance of MRI and CEUS for diagnosing HCC (NCT06184152).

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Patients were enrolled from 2 large health systems in Dallas, TX between November 2023 and April 2026. We excluded patients with a history of liver cancer, liver transplant, or extra-hepatic malignancy. Patients underwent both contrast MRI and CEUS every 3-6 months. Exams were performed within one month of each other and interpreted per LI-RADS v2018 criteria, blinded to the other exam results. Patients were followed until HCC diagnosis, death, transplant, ILNs resolving on both studies, or 2 years of stability. Cases with discordant findings were resolved by multi-phase CT, biopsy, or clinical diagnosis per tumor board. The primary outcome was patient-level sensitivity for HCC detection, and a secondary outcome was specificity. **Results:** Of 135 enrolled patients, 89 completed follow-up and were included in this analysis. Median age was 61 years (IQR 50-67), and 56.2% were male. Patients were diverse regarding race/ethnicity (47% Hispanic, 38% non-Hispanic White, 9% Black, 6% Asian/other) and cirrhosis etiology (38%, ALD, 28% MASLD, 15% post-SVR HCV). Most patients (83%) had Child Pugh A cirrhosis. There were 48 patients with LR-3 (median 1.2 cm (IQR 0.8-1.8) and 41 with LR-4 (median 1.7 cm (IQR 1.2-2.4). Most (66.3%) had a unifocal ILN, 21.4% had 2 ILNs, and the rest had 3 or more ILNs. During a median follow-up of 7 months (IQR 2.9-12), 31 patients (34.8%) developed HCC. Among these, 83.9% were early stage (BCLC stage A), 9.7% BCLC stage B, and 6.5% BCLC stage C. 54.8% of HCC were detected by MRI alone, 19.4% by both CEUS and MRI, and 9.7% by CEUS alone. Compared to MRI, CEUS had a significantly lower sensitivity (74% [95%CI 55-88] vs. 29% [95%CI 14-48], $p = 0.01$) but comparable specificity (97% [95%CI 89-100] vs 95% [95%CI 86-99]), yielding a higher diagnostic odds ratio (84.8 vs. 7.9). Findings were similar in the subset of patients with early-stage HCC. Of 18 ILNs that resolved prior to 2 years, 6 first resolved on CEUS, 6 on MRI, and 6 on both simultaneously. **Conclusion:** In a prospective cohort of patients with ILNs, MRI had superior sensitivity than CEUS for HCC detection, although CEUS may be complementary in some cases.

Disclosures: Amit Singal:Genentech: Consultant, AstraZeneca: Consultant, Bayer: Consultant, Eisai: Consultant, Exelixis: Consultant, Merck: Consultant, Elevar: Consultant, FujiFilm Medical Sciences: Consultant, Exact Sciences: Consultant, Glycotest: Consultant, Boston Scientific: Consultant, Sirtex: Consultant, HelioGenomics: Consultant, ImCare: Consultant, DELFI: Consultant, Curve Biosciences: Consultant, Catalym: Consultant, Verve: Consultant, Guruveer Bhamra:Nothing to Disclose, Emma Jones:Nothing to Disclose, David Fetzer:Nothing to Disclose, Sruthi Yekkaluri:Nothing to Disclose, Takeshi Yokoo:Ascelia Pharma: Advisor, Bayer: Advisor, Siemens Healthineers: Grant/Research Support, So Yeon Kim:Nothing to Disclose, Lisa Quirk:Nothing to Disclose, Kayleen Sorto:Nothing to Disclose, Nicole Rich:AstraZeneca: Advisor, AstraZeneca: Advisor, Genentech: Consulting, Genentech: Consulting, Exelixis: Advisor, Exelixis: Advisor, Eisai: Advisor, Eisai: Advisor, Madrigal: Advisor, Madrigal: Advisor, AstraZeneca: Advisor, AstraZeneca: Advisor, Genentech: Consulting, Genentech: Consulting, Exelixis: Advisor, Exelixis: Advisor, Eisai: Advisor, Eisai: Advisor, Madrigal: Advisor, Madrigal: Advisor.

4252 | COMPARABLE LONG-TERM ONCOLOGICAL OUTCOMES AFTER CONVERSION THERAPY FOLLOWED BY RESECTION VERSUS UPFRONT RESECTION IN INTERMEDIATE-STAGE HEPATOCELLULAR CARCINOMA

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Background: Hepatocellular carcinoma (HCC) at Barcelona Clinic Liver Cancer (BCLC) stage B poses a therapeutic challenge, as current guidelines generally recommend surgical resection for early-stage disease, while selected patients with intermediate-stage HCC may also be considered for curative-intent surgery. Recent advances in therapies have enabled conversion to curative-intent resection in intermediate-stage patients. We therefore compared long-term oncological outcomes between patients who underwent upfront resection and those who underwent curative-intent resection following conversion therapy. **Methods:** Between January 2004 and December 2025, 2,455 patients with clinically diagnosed HCC who underwent surgical resection were retrospectively screened. Patients presenting with initial BCLC stage B disease on pre-treatment imaging were included. Conversion therapy consisted of locoregional treatment, systemic therapy, or their combination before resection. Propensity score matching (PSM) was performed based on age, sex, initial tumor size and count, etiology, and albumin-bilirubin grade. Recurrence-free survival (RFS) and hazard ratios (HRs) were estimated using Kaplan-Meier and Cox regression. **Results:** Of 176 patients with initial BCLC stage B, 114 underwent upfront surgical resection and 62 underwent curative-intent resection following conversion therapy. In the entire cohort, 7-year RFS did not differ significantly between groups (HR 1.41, 95% confidence interval [CI] 0.98–2.04, $p = 0.066$). After 1:1 PSM, 90 patients were included in the matched cohort, and RFS was comparable between the two treatment groups (HR 0.97, 95% CI 0.59–1.59, $p = 0.904$). On multivariable analysis, pre-operative alpha-fetoprotein non-response (HR 1.56, 95% CI 1.01–2.41, $p = 0.046$), tumor number

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≥3 (HR 1.83, 95% CI 1.22–2.73, p = 0.003), and prothrombin time–international normalized ratio (HR 1.42, 95% CI 1.13–1.79, p = 0.003) were associated with worse RFS. **Conclusion:** In selected patients with intermediate-stage HCC who ultimately underwent curative-intent resection, conversion therapy followed by resection showed long-term recurrence-free survival comparable to upfront resection. These findings support further evaluation of conversion therapy as a strategy to expand curative surgical opportunities in this population.

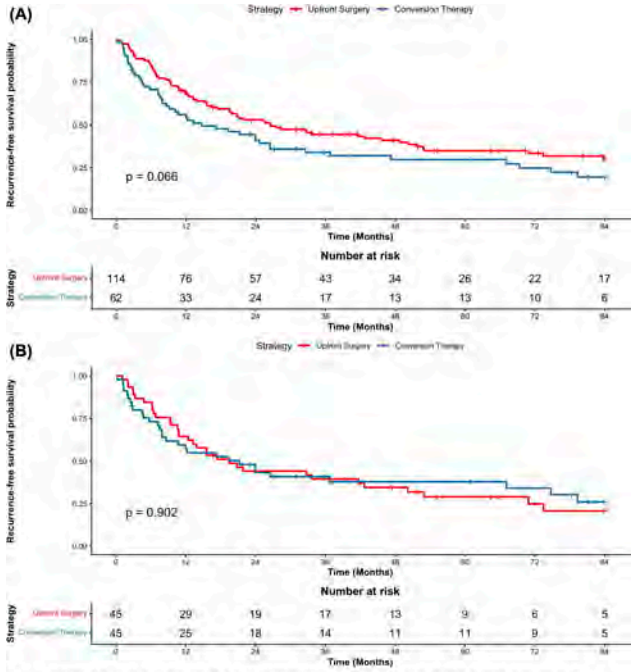


Fig 1. Kaplan-Meier curves for (A) 7-year recurrence-free survival in the entire cohort and (B) propensity score-matched 7-year recurrence-free survival in patients with intermediate-stage hepatocellular carcinoma.

Disclosures: Seohyun Ryu:Nothing to Disclose, Jaehong Jeong:Nothing to Disclose, Hye Won Lee:Nothing to Disclose.

4253 | CLINICAL CHARACTERISTICS OF PATIENTS MAINTAINING ATEZOLIZUMAB PLUS BEVACIZUMAB TREATMENT BEYOND TWO YEARS IN HEPATOCELLULAR CARCINOMA: A MULTICENTER RETROSPECTIVE COHORT STUDY

Young Mi Hong[1] Junsik Yoon[2] Yu Rim Lee[3] Jae hyun Yoon[4] Hyun Young Woo[5] Sangyoun Hwang[6] Yeowool Kang[7] Joonho Jeong[8] Sung Bum Cho[9] Jeongeun Song[10], [1]Pusan National University School of Medicine, [2]Department of Internal Medicine, Busan Paik Hospital, Inje University College of Medicine, [3]Department of Internal Medicine, School of Medicine, Kyungpook National University, [4]Department of gastroenterology and hepatology, Chonnam National University Hospital, [5]Department of Internal Medicine, College of Medicine, Pusan National University, [6]Department of Internal Medicine, Dongnam Institute of Radiologic & Medical Sciences, [7]Department of Internal Medicine, Dong-A University College of Medicine, [8]Department of Internal Medicine, Ulsan University Hospital, University of Ulsan College of Medicine, [9]Department of gastroenterology and hepatology, Chonnam National University, [10]Department of Internal Medicine, Daegu Catholic University Medical Center

Background: Atezolizumab plus bevacizumab (Atezo/Bev) has become a standard first-line treatment for unresectable hepatocellular carcinoma (HCC). While durable responses and long-term survival have been increasingly reported, the clinical characteristics of patients maintaining long-term Atezo/Bev treatment remain poorly understood. We aimed to investigate the characteristics and treatment outcomes of patients who maintained Atezo/Bev therapy beyond two years. **Methods:** We retrospectively analyzed patients with unresectable HCC treated with Atezo/Bev across multicenter cohorts. Patients who maintained Atezo/Bev treatment for ≥ 2 years were identified and compared with those who did not. Baseline liver function, tumor burden, inflammatory biomarkers, and treatment response were analyzed. **Results:** Among 943 patients treated with Atezo/Bev, 73 patients (7.7%) maintained treatment beyond two years. Patients maintaining long-term treatment showed more favorable baseline characteristics, including lower intrahepatic tumor extent (< 50%), lower ALBI grade, lower neutrophil-to-lymphocyte ratio (NLR), and lower AFP and PIVKA-II levels. Tumor response was strongly associated with long-term treatment maintenance. In the ≥ 2-year treatment group, complete response was observed in 17.8%, partial response in 43.8%, and stable disease in 38.4% of patients, indicating that durable disease control was observed even in patients without complete response. **Conclusion:** A subset of patients with HCC can maintain Atezo/Bev treatment beyond two years in real-world practice. Favorable liver function, lower inflammatory status, and lower intrahepatic tumor burden were associated with prolonged treatment maintenance. Importantly, durable disease control, including prolonged stable disease without complete response, may represent a key feature associated with long-term clinical benefit during Atezo/Bev treatment.

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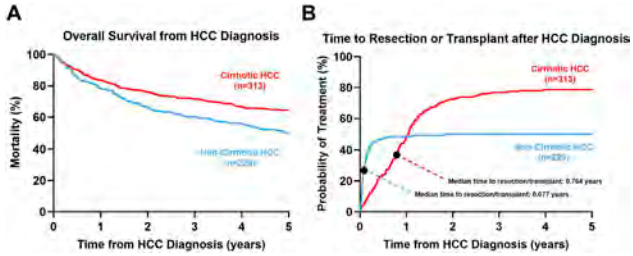
Characteristics	≥ 2 years (n= 73)	< 2 years (n= 870)	P value
Age, yrs	65.64 (±9.34)	65.70 (±9.81)	0.965
Sex, male	60 (82.2)	750 (86.2)	0.344
Etiology			0.740
Viral	55 (75.3)	640 (73.6)	
Non-viral	18 (24.7)	230 (26.4)	
Underlying cirrhosis	47 (83.9)	607 (85.5)	0.750
CP score			0.119
A	72 (98.6)	821 (94.4)	
B	1 (1.4)	49 (5.6)	
ALBI grade*			< 0.001
1	48 (85.7)	365 (51.4)	
2	8 (14.3)	345 (48.6)	
BCLC			0.192
A	0 (0.0)	2 (0.2)	
B	13 (17.8)	95 (10.9)	
C	60 (82.2)	773 (88.9)	
Tumor extent			0.040
< 50 %	67 (93.1)	677 (79.0)	
≥ 50 %	5 (6.9)	180 (21.0)	
Vascular invasion			0.032
Absent	50 (68.5)	482 (55.5)	
Present	23 (31.5)	386 (44.5)	
Extrahepatic metastasis			0.694
Absent	31 (42.5)	349 (40.1)	
Present	42 (57.5)	521 (59.9)	
NLR	2.47 (±1.49)	3.61 (±3.25)	0.003
AFP*, ng/mL	3253.84 (± 9392.86)	16381.37 (± 111837.44)	0.001
PIVKA-II*, mAU/L	3935.07 (± 11022.46)	12397.40 (± 40704.72)	< 0.001
Previous therapy	48 (65.8)	480 (55.2)	0.080
Combined RT	21 (28.8)	307 (35.3)	0.637

Disclosures: Young Mi Hong:Nothing to Disclose, Junsik Yoon:Nothing to Disclose, Yu Rim Lee:Nothing to Disclose, Jae hyun Yoon:Nothing to Disclose, Hyun Young Woo:Nothing to Disclose, SANGYOUN HWANG:Nothing to Disclose, Yeowool Kang:Nothing to Disclose, Joonho Jeong:Nothing to Disclose, Sung Bum Cho:Nothing to Disclose, Jeongeun Song:Nothing to Disclose.

4254 | CLINICAL FEATURES AND SURVIVAL RATE OF PATIENTS WITH NON-CIRRHOTIC HEPATOCELLULAR CARCINOMA

Hunter Miller[1] Adrienne Gefre[1] Robert Vierkant[1] Perapa Chotiprasidhi[1] Karina Sato Espinoza[1] Lewis Roberts[1] Kirk Wangensteen[1], [1]Mayo Clinic

Background: Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related deaths worldwide. Non-cirrhotic HCC (NC-HCC) accounts for nearly 15-20% of HCC cases. However, there remains a gap in understanding the clinicopathologic characteristics, treatment patterns, and outcomes of NC-HCC in rigorously phenotyped patient cohorts. This study analyzed the electronic health records (EHR) of 539 patients with HCC to compare the clinical characteristics, treatment patterns, and outcomes of patients with NC-HCC and cirrhotic HCC (C-HCC). **Methods:** Initially, 1,400 patients were identified through the Mayo Clinic Hepatobiliary Cancer Registry. Following EHR abstraction, 226 were classified as NC-HCC and 313 as C-HCC for comparison. 72 cases were excluded due to mixed HCC-cholangiocarcinoma, fibrolamellar HCC, F3 fibrosis, or insufficient clinical data. Demographic, etiologic, laboratory, tumor, treatment, and survival characteristics were compared between cohorts. Mann-Whitney U, chi-squared or Fisher exact testing were used for respective continuous and categorical variables. Survival was analyzed using Kaplan-Meier methodology with log-rank and Gehan-Breslow-Wilcoxon testing. **Results:** A total of 226 patients with NC-HCC and 313 patients with C-HCC were included. Compared to C-HCC, patients with NC-HCC demonstrated lower median Fib-4 scores (1.90 vs 6.40), higher platelet counts (256.5 vs 95.5 $\times 10^9$/L), and lower MRI elastography stiffness (2.7 vs 5.9 kPa) (all $P < 0.0001$). NC-HCC patients had lower rates of hepatitis C (5.8% vs 37.4%), steatohepatitis (16.4% vs 34.5%), and alcohol-associated liver disease (7.1% vs 32.9%), while idiopathic HCC was more common in NC-HCC (23.5% vs 2.9%)(all $P < 0.0001$).Patients with NC-HCC more frequently presented with solitary tumors (67.7% vs 48.6%), whereas multifocal disease (>5 tumors) was more common in C-HCC patients (1.3% vs 8.0%). NC-HCC had higher rates of Grade 3 tumors (20.8% vs 8.9%), greater T3 tumor stage (22.1% vs 4.2%), and less T1 stage (15.3% vs 23.6%). Nodal and metastatic staging did not significantly differ.With regards to initial treatment, NC-HCC patients were more likely to undergo resection (44.2% vs 6.7%), whereas baseline liver transplantation (0.4% vs 8.3%) and chemoembolization (12.4% vs 38.3%) were more common in C-HCC patients (all $P < 0.0001$). Ultimately, liver transplantation occurred much more frequently in C-HCC patients (1.8% vs 51.1%, $P < 0.0001$). 5-year overall survival was significantly lower in NC-HCC compared to C-HCC patients (50.1% vs 64.5%, $P = 0.0013$). **Conclusion:** Non-cirrhotic HCC is a distinct clinical subtype characterized by minimal fibrosis, more advanced tumors at presentation, different treatment patterns, and worse survival. The genetic and environmental factors underlying NC-HCC remain unclear. This study establishes a well-characterized NC-HCC cohort for future genomic and risk stratification studies.



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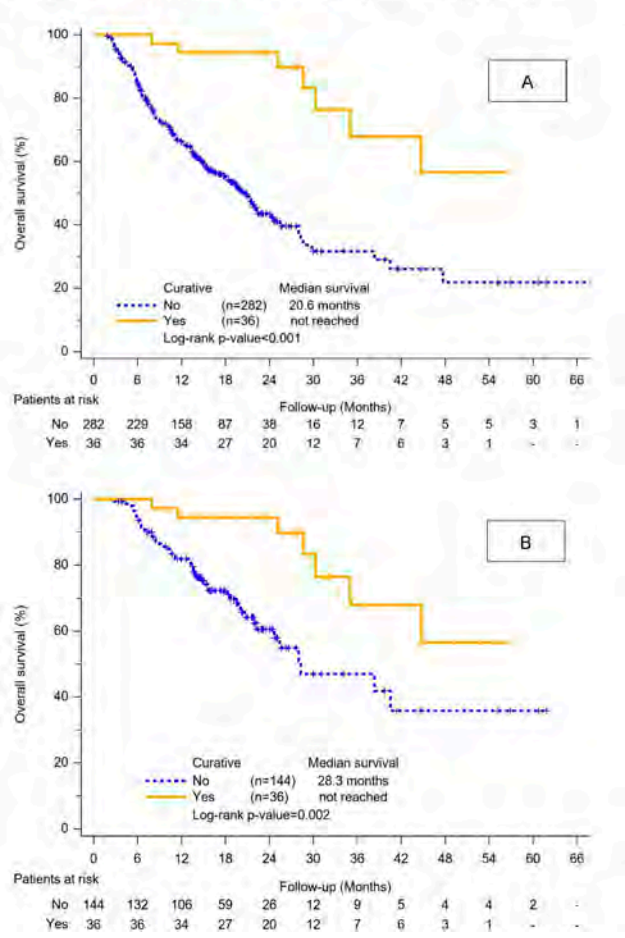
Disclosures: Hunter Miller:Nothing to Disclose, Adrienne Gefre:Nothing to Disclose, Robert Vierkant: Nothing to Disclose, Perapa Chotiprasidhi:Nothing to Disclose, Karina Sato Espinoza:Nothing to Disclose, Lewis Roberts:Nothing to Disclose, Kirk Wangensteen: Nothing to Disclose.

4255 | SURVIVAL OUTCOMES OF CONVERSION CURATIVE THERAPY FOLLOWING ATEZOLIZUMAB–BEVACIZUMAB IN ADVANCED HEPATOCELLULAR CARCINOMA

Chao-Hung Hung[1] Ying-Hsin Chen[1] Wei-Feng Li[1] Yen-Hao Chen[1] Jing-Houng Wang[1], [1]Kaohsiung Chang Gung Memorial Hospital

Background: The prognostic value of curative therapies—including liver transplantation, hepatectomy, and local ablation—in patients with advanced hepatocellular carcinoma (HCC) following atezolizumab plus bevacizumab treatment remains unclear. This study evaluated the feasibility of curative therapy and compared survival outcomes between patients who did and did not undergo curative interventions following atezolizumab plus bevacizumab, using a propensity score–matched analysis. **Methods:** We retrospectively analyzed 318 consecutive patients with advanced HCC who received atezolizumab plus bevacizumab between 2020 and 2024. Overall survival (OS) and progression-free survival (PFS) were defined as the primary and secondary endpoints, respectively, and were estimated using the Kaplan–Meier method and assessed with multivariate Cox proportional hazards regression. **Results:** The objective response rate to atezolizumab plus bevacizumab was 34.6%. Thirty-six patients (11%) subsequently underwent curative therapy, including liver transplantation (n = 8, 2.5%), hepatectomy (n = 11, 3.5%), and local ablation (n = 17, 5.3%). Patients receiving curative therapy demonstrated significantly improved OS ($p < 0.001$) and PFS ($p < 0.001$) compared with those who did not, with benefits persisting after propensity score matching. Multivariate Cox regression identified curative therapy as an independent predictor of OS (hazard ratio [HR] 0.204; 95% confidence interval [CI] 0.094–0.444; $p < 0.001$). **Conclusion:** Curative therapy following atezolizumab plus bevacizumab confers substantial survival benefits in selected patients with advanced HCC.

Overall survivals in patients who received conversion curative therapy compared with those who did not (A) Entire cohort (B) Propensity score matching cohort



Disclosures: Chao-Hung Hung:Nothing to Disclose, Ying-Hsin Chen:Nothing to Disclose, Wei-Feng Li: Nothing to Disclose, Yen-Hao Chen:Nothing to Disclose, Jing-Houng Wang:Nothing to Disclose.

4256 | CLINICAL CHARACTERISTICS AND DIAGNOSIS OF DOUBLE-NEGATIVE HEPATOCELLULAR CARCINOMA WITH AFP AND PIVKA-II

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Background: This study elucidates the clinical and imaging features of double-negative hepatocellular carcinoma (HCC), identify independent hazard factors for double-negative tumor markers in HCC patients, construct a risk prediction model, and analyze the challenges and countermeasures in the current diagnostic paradigm centered on serum biomarkers and imaging. **Methods:** A total of 535 patients diagnosed with HCC between January 2019 and June 2024 were consecutively enrolled and randomized into a training (n = 361) and a testing cohort (n = 174) at a 7:3 ratio. Based on serum AFP and PIVKA-II levels, patients were categorized into double-negative and non-double-negative groups. Demographic, clinical, laboratory (including liver and coagulation functions), and contrast-enhanced CT/MRI features were systematically collected and compared between the two groups. Statistical analyses were performed using SPSS 26.0 and R 4.1.0. A risk prediction model was constructed and validated using receiver operating characteristic (ROC) curves, while decision curve analysis (DCA) was utilized to assess its clinical net benefit. **Results:** In the training set, double-negative HCC accounted for 29.4% (106/361) of cases. The univariate analysis revealed that the two tumor markers negative group was diagnosed at a younger age than the non-double-negative group, a meaningly lower prevalence of cirrhosis (83.0% vs. 94.1%, P < 0.001) and a greater percentage of younger patients (42.5% vs. 18.4%, P < 0.001). Etiologically, metabolic-associated fatty liver disease (MAFLD) was much more common in the double-negative group (17.0% vs. 2.8%, P < 0.001). Imaging features indicated that the double-negative group had smaller tumor diameters (2.3 [1.6, 3.8] cm vs. 5.3 [2.8, 10.2] cm, P < 0.001) and a greater prevalence of solitary tumors (72.6% vs. 48.6%, P < 0.001). Binary logistic regression study identified younger age, MAFLD etiology, and smaller tumor diameter as independent predictors of double-negative status. A nomogram-based risk prediction model was established using these factors, attaining a training set region beneath the ROC curve (AUC) of 0.812 and a validation set AUC of 0.798. DCA showed that the model had great clinical applicability, and calibration curves (CC) showed good consistency between anticipated and observed values. **Conclusion:** "Young age, metabolic association, and small tumor size" are independent hazard factors for AFP and PIVKA-II double-negative HCC. The anticipated outcome model based on these factors demonstrates good discriminative ability and clinical applicability. For high-risk young populations with metabolic risk factors or non-viral backgrounds, it is recommended to optimize imaging screening strategies and enhance the role of high-resolution multimodal imaging in clinical diagnostic pathways to compensate for the limitations of traditional serological markers in this subgroup.

Disclosures: yanhui shi:Nothing to Disclose, wenjun du:Nothing to Disclose, Shiyu Wang:Nothing to Disclose, Weihua Cao:Nothing to Disclose, Wen Deng: Nothing to Disclose, Minghui Li:Nothing to Disclose.

4257 | ETIOLOGY AS A BIOMARKER CONTEXT RATHER THAN A DRIVER-MUTATION CLASSIFIER IN HEPATOCELLULAR CARCINOMA

Motoyuki Otsuka[1], [1]Okayama University

Background: Hepatocellular carcinoma (HCC) develops through diverse etiologic backgrounds, including HBV, HCV, and nonviral liver diseases. However, whether etiology should be used to define distinct molecular subtypes or to contextualize genomic biomarker interpretation remains unclear. We reappraised nationwide comprehensive genomic profiling data to determine whether viral and nonviral backgrounds primarily shape core oncogenic drivers, biomarker phenotypes, or the clinical utility of tissue- and liquid-based genomic testing. **Methods:** We analyzed 551 patients with HCC registered in the Japanese C-CAT database, a nationwide repository of clinical cancer gene panel testing/comprehensive genomic profiling data. Patients were classified into HBV-related, HCV-related, and nonviral/noncholestatic HCC. Pathogenic or likely pathogenic alterations detected by clinical comprehensive genomic profiling were evaluated across three interpretive layers: recurrent driver alterations, biomarker-associated phenotypes including tumor mutation burden (TMB) and homologous recombination repair (HRR)-related alterations, and the detection of druggable alterations by tissue- versus liquid-based profiling. **Results:** Etiology had limited impact on the core driver framework of HCC. TERT splice-site alterations represented the dominant genomic event across etiologic groups, and major drivers such as TP53 and CTNNB1 showed broadly comparable distributions. Only modest etiology-associated signals were observed, including enrichment of AXIN1 alterations in HCV-related HCC and DDR2 alterations in HBV-related HCC. In contrast, etiology was more informative for biomarker interpretation. TMB was generally low in HCC, but nonviral/noncholestatic HCC showed significantly lower TMB than HCV-related HCC, suggesting a less mutation-burdened biomarker phenotype in nonviral tumors. HRR-related alterations, including ATM, BRCA2, CHEK2, and BRCA1, were not associated with

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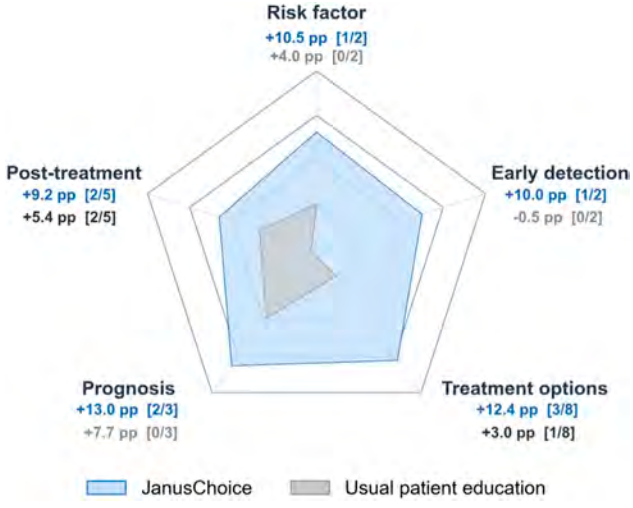
increased TMB, indicating that HRR alteration status should not be used as a surrogate for hypermutation in HCC. Tissue-based profiling detected more oncogenic alterations overall, whereas liquid biopsy retained a comparable yield for druggable alterations. Despite the identification of druggable genomic findings, matched therapy was implemented in only a minority of patients. **Conclusion:** HCC etiology does not appear to define fundamentally separate driver-mutational diseases. Rather, etiology functions as a clinically relevant context for interpreting genomic biomarkers, particularly TMB, HRR-related alterations, and liquid biopsy results. These findings support an etiology-aware precision oncology framework in HCC, in which treatment strategies may remain broadly unified across etiologies, while biomarker interpretation and clinical trial stratification should account for the underlying liver disease background.

Disclosures: Motoyuki Otsuka:Nothing to Disclose.

4258 | A RETRIEVAL-AUGMENTED AI CHATBOT IMPROVES HEALTH LITERACY IN NEWLY DIAGNOSED EARLY-STAGE HEPATOCELLULAR CARCINOMA: A MULTICENTRE RANDOMISED CONTROLLED TRIAL

Chun-Ying Wu[1] Li-Lin Liang[1] Che-Lun Hung[1], [1]National Yang MIng Chiao Tung University, Taiwan

Background: Patients with newly diagnosed early-stage hepatocellular carcinoma (HCC) face complex curative-intent treatment decisions under time pressure, with limited health literacy a prevalent unmet need. Whether AI chatbots can address this gap, particularly for socioeconomically vulnerable patients, remains untested. **Methods:** In a multicentre randomised controlled trial across five tertiary hospitals in Taiwan (NCT06384950), 150 patients with BCLC stage 0/A HCC were randomly assigned to usual patient education or usual education plus JanusChoice, a retrieval-augmented chatbot delivered through the LINE messaging platform. **Results:** JanusChoice produced a 7.1-percentage-point net gain in liver cancer literacy (P = .016), with concentrated improvements in treatment-options and prognosis domains. Two of five consultation-quality dimensions improved significantly. User experience exceeded the scale midpoint (P = .008). Lower-income, retired or unemployed, and AI-naive participants derived the largest benefits. **Conclusion:** Messaging-platform-delivered RAG chatbots can improve patient literacy in early-stage HCC, with benefits concentrated in populations typically underserved by digital health interventions.



Disclosures: Chun-Ying Wu:Nothing to Disclose, Li-Lin Liang:Nothing to Disclose, Che-Lun Hung:Nothing to Disclose.

4259 | SPATIALLY RESOLVED PHENOTYPIC AND FUNCTIONAL CHARACTERIZATION OF THE IMMUNE MICROENVIRONMENT IN MASH- AND FONTAN-ASSOCIATED HEPATOCELLULAR CARCINOMA

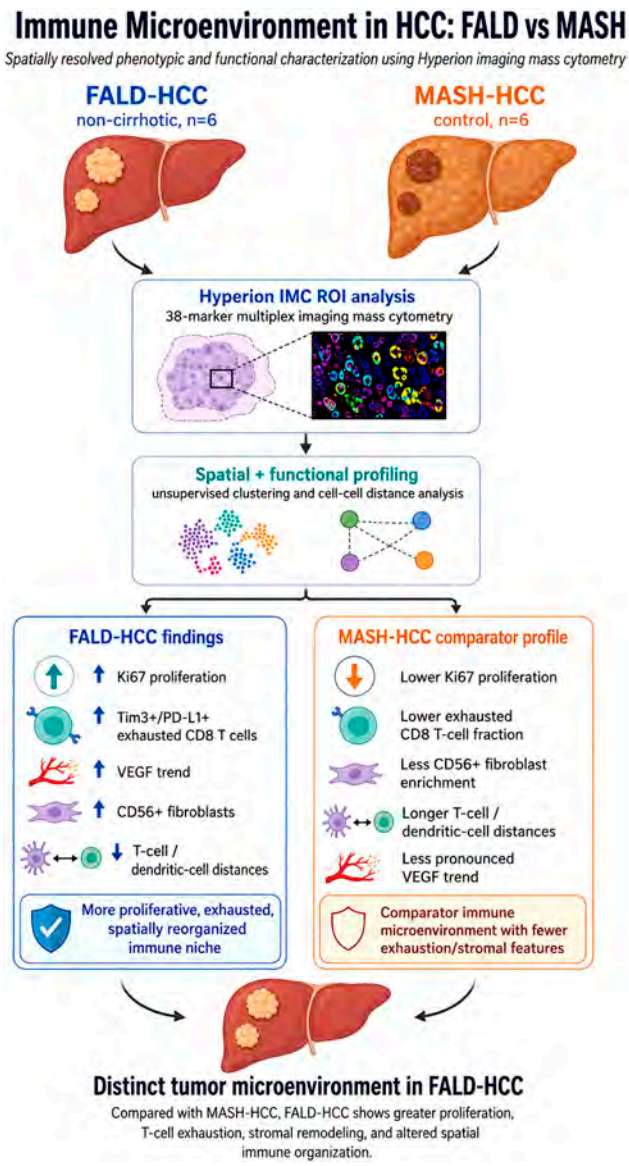
Papawee Sutthirat[1] Christine Nguyen[2] Brenna Novotny[1] Chen Wang[1] Timucin Taner[1] Nidhi Jalan-Sakrikar[1] Vijay Shah[1] Moira Hilscher[1] Maarouf Hoteit[3] Yuli Kim[4], [1]Mayo Clinic Rochester, [2]Mayo Clinic Rocheste, [3]Penn Medicine, [4]Divisions of Cardiology at Penn and Children's Hospital of Philadelphia

Background: Fontan associated liver disease (FALD) is associated with an increased risk of hepatocellular carcinoma (HCC). Approximately half of HCC in FALD occurs in the absence of cirrhosis. The occurrence of HCC in the absence of cirrhosis or overt inflammatory activity suggests a unique pathophysiology. In this study, we characterized

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the immune microenvironment of HCC in FALD and metabolic-dysfunction associated steatohepatitis (MASH). **Methods:** Multiplex imaging mass cytometry (Hyperion) was performed on tumor and adjacent non-tumor regions from non-cirrhotic FALD-HCC (n = 6) and MASH-HCC (n = 6). A 38-marker panel captured parenchymal, epithelial, stromal, endothelial, and immune cells, with functional markers of proliferation, angiogenesis, cytotoxicity, and exhaustion. Two-step unsupervised clustering was used to define major lineages and then functional states, with T-cell phenotyping focused on CD4+ and CD8+ subsets. ROI-level data were aggregated by patients to avoid pseudo-replication. Cell proportions, Ki67+, VEGF+, T-cell phenotypes, and nearest-neighbor distances were compared across tumor ROIs. **Results:** FALD-HCC demonstrated increased multiple cells proliferation compared with MASH-HCC. Ki67 expression was significantly higher in macrophages ($p = 0.041$), dendritic cells ($p = 0.011$), T cells($p = 0.014$), and endothelial cells($p = 0.013$), while B cells and hepatocyte/tumor cell did not significantly differ. Exhausted $CD8^+$ T cells, defined by Tim3, HLA-DR, or PD-L1 expression, were increased in FALD-HCC compared with MASH-HCC, whereas central memory, naïve, and terminal effector $CD8^+$ T-cell proportions are not significantly differ. $VEGF^+$ cell frequency show non-significant upward trends in FALD-HCC, most notably in endothelial cells($p = 0.065$), with additional non-significant trends in macrophage and hepatocyte/tumor cells. FALD-HCC also show enrichment of $CD56^+$ fibroblasts, suggesting a stromal population may contribute to fibrosis–tumor crosstalk. Spatial nearest-neighbor analysis reveal alter tumor immune architecture in FALD-HCC, with $CD8^+$ T cells positione closer to tumor cells by ~20.2 µm and closer to dendritic cells by ~24.5 µm compare with MASH-HCC. $CD4^+$ T cells were also position closer to dendritic cells in FALD-HCC by ~42.8 µm. **Conclusion:** FALD-HCC exhibits a distinct tumor microenvironment compare with MASH-HCC, characterize by increase immune and endothelial proliferation, greater $CD8^+$ T-cell exhaustion, $CD56^+$ fibroblast enrichment, pro-angiogenic VEGF trends, and closer T-cell proximity to dendritic cells and tumor cells. These spatial findings provide insight beyond cell proportions alone and suggest that FALD-HCC may harbor a permissive, spatially organize immune niche that promotes persistent T-cell stimulation and exhaustion. Further studies are warrant to define how Fontan-associated hepatic immune remodeling contributes to HCC pathophysiology.



Disclosures: Papawee Sutthirat:Nothing to Disclose, Christine Nguyen:Nothing to Disclose, Brenna Novotny: Nothing to Disclose, Chen Wang:Nothing to Disclose, Timucin Taner:Nothing to Disclose, Nidhi Jalan-Sakrikar:Nothing to Disclose, Vijay Shah:Boehringer Ingelheim: Consultant, GSK: Consultant, GENFIT SA: Consultant, Intercept Pharmaceuticals, Inc.: Advisor, Korro Bio, Inc.: Consultant, Novo Nordisk A/S: Consultant, Resolution Therapeutics, Ltd.: Advisor, Seal Rock Therapeutics, Ltd.: Consultant, Surrozen: Advisor, Dexcel Pharma Technologies, Ltd.: Consultant, Dimension Inx.: Advisor, Enveda: Consultant, Ochre Bio: Consultant, Satellite Biosciences, Inc.: Consultant, Moira Hilscher:Orphalan: Consultant, Maarouf Hoteit: Nothing to Disclose, Yuli Kim:Nothing to Disclose.

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4260 | YTTRIUM-90 SIRT CLINICAL DECISION-MAKING AND OUTCOMES IN UNRESECTABLE HEPATOCELLULAR CARCINOMA PATIENTS WITH ELEVATED LUNG SHUNT FRACTION

Jingqin Ma[1] Minjie Yang[1] Wen Zhang[1] Yaozu Liu[1] Jianjun Luo[1] Zhiping Yan[1], [1]Department of Interventional Radiology, Zhongshan Hospital, Fudan University

Background: Yttrium-90 selective internal radiation therapy (SIRT) provides potent local control and downstaging for unresectable hepatocellular carcinoma (uHCC). However, elevated lung shunt fraction (LSF) in Chinese patients poses severe radiation pneumonitis risks, potentially exacerbated by immunotherapy. This study evaluated multidisciplinary team (MDT)-guided triage, dosimetry, and outcomes in uHCC patients with high LSF ($\geq$10%) assessed via ^{99} Tc-MAA MAPPING. **Methods:** Clinical data of 45 uHCC patients with baseline LSF$\geq$10% between June 2024 and December 2025 were reviewed. Based on MDT consensus, patients were triaged into three pathways: direct SIRT (N = 14), conversion SIRT (SIRT preceded by 2 cycles of HAIC plus lenvatinib, N = 8), and conventional TACE (N = 23). Baseline anatomy, parameter evolution, and 6-month outcomes were compared. **Results:** The overall baseline mean LSF was 17.89% (range: 10.06%-43.40%). The direct SIRT group had a significantly lower baseline LSF than the conversion SIRT and TACE groups (12.49% vs 22.33% vs 20.32%, P < 0.05). In the conversion group, upfront HAIC plus Lenvatinib significantly reduced the mean LSF from 22.33% to 7.75% (P < 0.001), enabling safe SIRT for all 8 patients. The overall mean tumor volume was 846.07 ml, with the direct SIRT group showing a significantly lower tumor burden than the conversion SIRT and TACE groups (381.74 ml vs 1109.13 ml vs 1037.21 ml, P < 0.05). No significant difference was found in mean tumor absorbed dose between direct and conversion SIRT (239.29 Gy vs 224.29 Gy, P = 0.8799), though the conversion group required a significantly higher mean prescribed activity (4.70 GBq vs 3.43 GBq, P < 0.05). At 6 months, the objective response rates (ORR) of direct and conversion SIRT were comparable, both being significantly superior to TACE (71.4% vs 75.0% vs 60.9%, P < 0.05). Notably, 2 conversion patients (25.0%) successfully achieved radical surgical resection. **Conclusion:** For uHCC with high tumor burden and baseline LSF, upfront HAIC plus lenvatinib effectively remodels microvasculature and minimizes lung shunting. This conditioning strategy ensures lung safety and allows higher prescribed activity, yielding excellent ORR and surgical conversion opportunities.

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4262 | REAL-WORLD IMPACT OF HEPATOCELLULAR CARCINOMA SURVEILLANCE ON SURVIVAL: A PROSPECTIVE BRAZILIAN COHORT

Diego Vieira[1] Rodrigo Cambraia[1] Geraldo Pereira[1] Lucy Ana Fonseca[1] Marcelo Chaves França[1] Rosangela Teixeira[1], [1]Hospital das Clínicas (EBSERH/UFMG), School of Medicine, Federal University of Minas Gerais

Background: Hepatocellular carcinoma (HCC) surveillance is recommended for patients with cirrhosis and selected high-risk populations, playing a pivotal role in early tumor detection and improved outcomes. However, evidence regarding the real-world impact of surveillance on tumor burden, hepatic reserve, and overall survival (OS) remains limited. This study evaluated the effect of structured HCC surveillance on tumor stage, hepatic reserve, and OS in cirrhosis-associated HCC patients. **Methods:** Patients from a tertiary HCC referral center were prospectively enrolled between 2019 and 2024. HCC diagnosis was established by contrast-enhanced CT or MRI according to LI-RADS criteria. Patients were stratified into: (1) HCC detected through structured surveillance with biannual ultrasound plus alpha-fetoprotein (AFP), and (2) HCC diagnosed outside surveillance protocols. The primary outcome was HCC-related mortality. OS was estimated using the Kaplan–Meier method and compared with the log-rank test. For intergroup comparisons were employed chi-square, Fisher's exact, Student's t, or Mann–Whitney U tests, as appropriate. The study was approved by the local Ethics Committee, and all participants provided written informed consent. **Results:** A total of 206 patients were prospectively included, of whom 73 (35.4%) were diagnosed under surveillance and 133 (64.6%) outside surveillance protocol. Patients undergoing surveillance had lower baseline AFP levels (7.8 vs. 59.0 ng/mL; p = 0.002), lower prevalence of AFP > 20 ng/mL (41.1% vs. 56.9%; p = 0.03), and higher frequency of early-stage HCC (BCLC 0/A) (71.0% vs. 35.5%; p < 0.001). Surveillance was also associated with smaller tumors (31.5 vs. 54.0 mm; p < 0.001), higher prevalence of ALBI grade I (70.4% vs. 32.5%; p < 0.001), compensated cirrhosis (91.0% vs. 68.8%; p < 0.001), lower HCC-related mortality (20.5% vs. 45.4%; p < 0.001), and longer OS (48.1 vs. 29.7 months; p < 0.001). **Conclusion:** HCC surveillance was associated with earlier-stage diagnosis, lower tumor burden, better hepatic reserve, and

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longer OS. These findings support surveillance as an effective strategy to improve eligibility for curative-intent therapies and optimize long-term outcomes in real-world practice.

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4263 | A HOSPITAL-INTEGRATED ONCOLOGY PLATFORM FOR RISK-ADAPTED MULTIDISCIPLINARY REVIEW OF HEPATOCELLULAR CARCINOMA

Cheng Huang[1] Jiabin Cai[1] Dian Wang[2] Cunying Pu[3] Jitthye Kee[4] Qiang Gao[1] Jian Zhou[1] Jia Fan[1] Huichuan Sun[1], [1]Department of Hepatobiliary Surgery and Liver Transplantation Zhongshan Hospital, Fudan University, [2]Roche Diagnostics (Shanghai) Ltd, Shanghai, China, [3]Roche Diagnostics (Shanghai) Ltd., Shanghai, China, [4]Roche Diagnostics (Shanghai) Ltd., Shanghai , China

Background: Risk-adapted management of hepatocellular carcinoma (HCC) depends on multidisciplinary review of tumor status, liver reserve, prior treatment, pathology, genomic findings and longitudinal outcomes. In routine care, these data are often dispersed across hospital systems and external reports, delaying review and making recurrence risk assessment less consistent. We assessed whether a hospital-integrated oncology platform could assemble structured longitudinal patient summaries and support recurrence risk assessment in an HCC multidisciplinary team (MDT) setting. **Methods:** This retrospective implementation study included 2,465 patients with HCC treated at Zhongshan Hospital, Fudan University from January 2020 to December 2022 who had follow-up data available. The Oncology Hub (OH, provided by Roche Diagnostics China), a commercially available integrated oncology platform, connected HIS/EMR, LIS, PACS, pathology and genomics systems, and external reports through FHIR/RESTful APIs, ETL, OCR and LLM-assisted semantic parsing. Outcomes included MDT operation logs recorded from March 25, 2025 to May 5, 2026, timed workflow samples, quality review of system-generated summaries, patient-like-me retrieval and internal validation of a recurrence risk model. **Results:** Over 13.3 months, 316 patients were discussed in 58 MDT sessions (5.45 cases/session). Mean case-preparation time was 24 min 55 s. Data aggregation through the platform, including OCR processing and timeline generation, averaged 9 min 55 s and had a median of 7 min 37 s (IQR, 4 min 42 s), compared with a manual review benchmark of approximately 15 min per case; MDT recording required 5-10 min per case. System-generated summaries were produced in 1 min 18 s. Quality review showed physician modification and key-information omission rates of 6.92% and 6.47%, respectively. Patient-like-me analytics aligned 2,281 evaluable patients and displayed top-matched cases with similarity scores, CNLC stage, treatment history, disease-free survival, overall survival and recurrence status. In 630 patients used for internal validation, the recurrence risk model achieved an AUC of 0.742 and accuracy of 0.70; for recurrent cases, precision, recall and F1-score were 0.63, 0.59 and 0.61. **Conclusion:** In a tertiary HCC MDT program, implementation of the Oncology Hub platform organized fragmented clinical data into longitudinal profiles and comparable outcome trajectories for risk-adapted review. Further multicenter evaluation should determine whether this approach improves MDT recommendation consistency, follow-up planning and patient outcomes.

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4264 | HEPATOCYTE FGF21 DICTATES OPPOSING FATES OF BREAST CANCER LIVER METASTASIS IN A STEATOSIS-SEVERITY-DEPENDENT MANNER

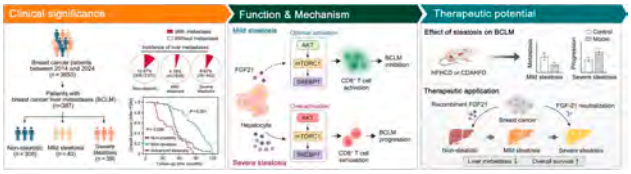
Junli Liu[1] Qiyue Hong[2] Jiaxing Yin[1] Yihui Yu[3] Wenchao Li[2] Xiaowen Wang[2] Keke Zhang[1] Xinya Yu[3] Kunpeng Hu[2] Hengdong Qu[1], [1]State Key Laboratory of Bioactive Molecules and Druggability Assessment, Jinan University, [2]The Third Affiliated Hospital of Sun Yat-Sen University, [3]Jiangxi Ganbei Integrated Traditional Chinese and Western Medicine Hospital

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is highly prevalent in patients with breast cancer; however, whether pre-existing hepatic steatosis differentially modulates breast cancer liver metastasis (BCLM) remains undefined. **Methods:** We retrospectively analyzed 3,653 breast cancer patients diagnosed across multiple centers in China (2014–2024), of whom 387 (11%) developed liver metastasis. Steatosis severity was determined by biopsy or imaging and graded as mild (5–33% fat) versus severe ($\geq$34% fat). To validate the causal effect of MASLD on BCLM, mice were fed a high-fat high-cholesterol diet (HFHCD) or a choline-deficient, L-amino acid-defined, high-fat diet (CDAHFD), followed by intra-splenic or left ventricular

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injection of syngeneic E0771 or 4T1 breast cancer cells. Single-cell transcriptomics, hepatocyte secretomics, and FGF21 supplementation or neutralization were employed to dissect the underlying mechanisms and therapeutic potential. **Results:** MASLD was independently associated with a lower overall risk of liver metastasis ($p < 0.001$), with mild steatosis conferred stronger protection against BCLM than severe steatosis. Survival analyses showed that mild steatosis prolonged both liver metastasis-free survival (LMFS) and overall survival (OS) (both $p < 0.01$), whereas severe steatosis markedly shortened LMFS and post-metastasis OS (OSLM), leading to significantly worse OS ($p < 0.05$ for LMFS; $p < 0.01$ for OSLM and OS). These findings remained robust after 1:1 propensity score matching (all $p < 0.01$). In murine models, MASLD markedly reduced liver metastatic colonization; however, only mild steatosis prolonged mouse survival, while severe steatosis showed the opposite trend, faithfully recapitulating the clinical observations. Mechanistically, single-cell transcriptomics and secretomics identified hepatocyte-derived FGF21 as a steatosis-severity-dependent effector. Compared with normal livers, FGF21 secretion was moderately elevated (2.5-fold) in mild steatosis but markedly increased (7.8-fold) in severe steatosis. Functionally, moderately elevated FGF21 activated optimal AKT/mTORC1/SREBP1 signaling, which enhanced infiltration of IFN-γ^+/granzyme B^+ $CD8^+$ T cells and suppressed tumor cell engraftment. In contrast, pathologically high FGF21 drove sustained AKT/mTORC1/SREBP1 activation, induced $CD8^+$ T-cell cholesterol overload and exhaustion and consequently promoted BCLM progression. Therapeutically, low-dose recombinant FGF21 administration to non-steatotic mice reduced BCLM, whereas FGF21 neutralization in mice with severe steatosis markedly prolonged survival in BCLM-bearing mice. **Conclusion:** FGF21 exerts a dual, dose-dependent role in BCLM depending on steatosis severity. Modulating FGF21 levels may represent a promising therapeutic strategy for concurrently managing MASLD and BCLM.



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4265 | FECAL MICROBIOTA TRANSPLANTATION IN ADDITION TO LENVATINIB IN ADVANCED HEPATOCELLULAR CARCINOMA: A DOUBLE-BLIND, PLACEBO-CONTROLLED PILOT RANDOMIZED TRIAL

Ayush Agarwal[1] Arnav Aggarwal[1] Vishal Chauhan[1] Shubham Jain[1] Sarthak Saxena[2] Sejal Kotwani[1] Shubham Garg[1] Sanchita Gupta[1] Shivanand Gamanagatti[1] Ankur Goyal[1] Raju Sharma[1] Bipin Tiwari[1] Samagra Agarwal[1] Sagnik Biswas[1] Shalimar[1], [1]All India Institute of Medical Sciences, New Delhi, [2]All India Institute of Medical Sciences, Delhi

Background: Objective response rates to systemic therapies in advanced hepatocellular carcinoma (HCC) remain low. Adjunctive faecal microbiota transplantation (FMT) has been reported to improve immunotherapy response in malignant melanoma. We aimed to assess the safety and efficacy of FMT in combination with lenvatinib in advanced HCC. **Methods:** In this double-blind placebo-controlled pilot randomised trial, treatment naïve adult patients with advanced HCC (Barcelona Clinic Liver Cancer Stage C) were randomly assigned (1:1) to receive either FMT or placebo (equal volume of normal saline), along with systemic therapy with oral weight-based lenvatinib. FMT/placebo instillation in duodenum was done via endoscopy 1 week prior to starting lenvatinib. FMT was sourced from 2 healthy donors and processed by independent research staff. Radiological, serological and questionnaire-based assessments were performed at 3 and 6 months. Outcomes included response (RECIST1.1), overall survival (OS), progression-free survival (PFS), adverse events and quality of life (EORTC QLQ-C30 and QLQ-HCC18). **Results:** 20 patients were randomised; 19 were included in analysis (9 in FMT arm, 10 in placebo arm). Baseline characteristics were comparable (mean age: 56.0 ± 9.5 years; 85% males; median AFP 6692 [IQR 1667-25904], mean ALBI score −2.3 ± 0.1). Major etiologies of liver disease were hepatitis C (42.1%) and hepatitis B (36.8%). Cirrhosis was present in 84.2% patients. Extrahepatic metastases were present in 8 (42.1%) patients and portal venous thrombosis in 15 (78.9%) patients. Of 12 patients with radiological assessment at 3 months, 6 (50%) had stable disease (3 per group); the remainder had progressive disease. At 6 months, 2 FMT patients had stable disease and 2 control arm patients had progressive disease ($p = 0.33$). The OS (104 [IQR 84-176] vs 134 [IQR 19-180] days, $p = 0.51$) and PFS (100 [IQR 84-167] vs 90 [IQR 90-91] days, $p = 0.63$) were similar in FMT and control arms. Adverse events, including ascites (26.3%) and hand foot syndrome (15.8%), were similar in both arms. Serious adverse events occurred in 7 patients in FMT

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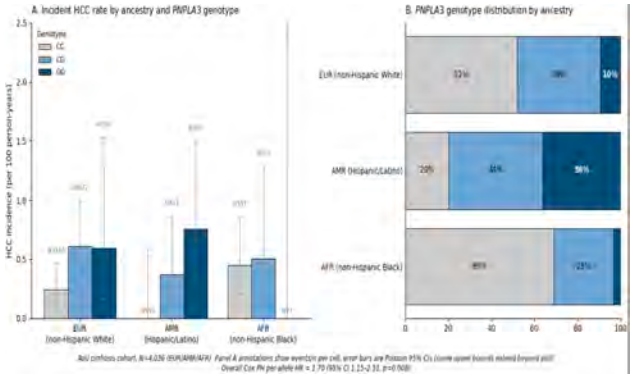
arm vs 6 patients in placebo arm (77.7% vs 60%, p = 0.6). Nutritional issues and pain symptom scales were lower in FMT arm at 1 week (p = 0.016 and 0.029 respectively), while global health and functional scale scores were similar in both arms. **Conclusion:** Fecal microbiota transplantation in addition to lenvatinib is safe in advanced hepatocellular carcinoma.

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4266 | MULTI-ANCESTRY ASSOCIATION OF *PNPLA3* RS738409 WITH INCIDENT HEPATOCELLULAR CARCINOMA IN CIRRHOTIC PARTICIPANTS OF THE ALL OF US RESEARCH PROGRAM

Hyunseok Kim[1] Walid Ayoub[1] Alexander Kuo[2] Paul Martin[2] Aarshi Vipani[2] Yun Wang[2] Yee Hui Yeo[2] Stephen Pandol[2] Debiao Li[2] David Cohen[2] Shelly Lu[2] Suthat Liangpunsakul[3] Juan Pablo Arab[4] JuDong Yang[2], [1]Cedars-Sinai Medical Center, [2]Cedars Sinai Medical Center, [3]Indiana University Medical Center, [4]Virginal Commonwealth University Medical Center

Background: *PNPLA3* rs738409 G-allele is an established hepatocellular carcinoma (HCC) risk factor in predominantly European (EUR)-ancestry cohorts. The variant exhibits striking allele frequency variation across populations, yet validation in multi-ancestry US cirrhosis cohorts remains limited. **Methods:** We identified All of Us cohort participants with whole-genome sequencing and ICD-coded cirrhosis at EHR consent (baseline), excluding pre-existing HCC. Genetic ancestry was inferred from WGS; EUR, AFR, and AMR labels correspond predominantly to participants self-identifying as non-Hispanic White, non-Hispanic Black, and Hispanic/Latino, respectively. Incident HCC required ≥ 2 diagnosis codes ≥ 30 days apart, with a 6-month landmark exclusion to remove likely prevalent disease. Cox proportional hazards regression was adjusted for age, sex, hierarchical primary etiology (HCV/HBV/Alcohol/MASLD/Other), genetic ancestry, and first three principal components. Pre-specified secondary analyses tested *PNPLA3* × ancestry and *PNPLA3* × etiology interactions; sensitivity analyses examined severity-restricted subsets. **Results:** Among 4,098 cirrhotic participants (EUR 2,269; AMR 960; AFR 807; other 62), 56 incident HCC events occurred over median 3.8 years (crude incidence 0.43/100 person-years; 1.51/100 in decompensated HCV-cirrhosis). *PNPLA3* GG homozygote frequency differed markedly by ancestry (AMR 36%, EUR 10%, AFR 3%). Each G-allele was associated with a 70% increase in HCC hazard (HR 1.70, 95% CI 1.15-2.51, p = 0.008). Within AMR cirrhotics, HCC incidence increased monotonically with genotype (CC 0.00, CG 0.37, GG 0.76/100 person-years). The association was directionally consistent across etiologies (HCV: HR 1.35; alcohol: HR 1.45; MASLD: HR 1.44) without interaction (p = 0.83) and persisted in severity-restricted sensitivity analyses (decompensated HR 1.38, p = 0.077; FIB-4 high or decompensated HR 1.41, p = 0.030). The effect was attenuated in AFR participants (interaction p = 0.24), consistent with recent reports of weakened *PNPLA3*-HCC association in AFR. Addition of *PNPLA3* improved discrimination (c-statistic 0.74 -> 0.76, p-value < 0.01). *MBOAT7* (HR 1.38, p = 0.09) and *MARC1* (HR 0.63, p = 0.10) showed directionally consistent but non-significant associations. **Conclusion:** In a US multi-ancestry cirrhosis cohort, *PNPLA3* rs738409 G-allele dosage was associated with incident HCC, with effect consistent across EUR and AMR ancestries, major cirrhosis etiologies, and disease severity strata. The substantially higher GG homozygote frequency in AMR participants, combined with monotonic genotype-stratified incidence in this group, suggests *PNPLA3* genotyping may have clinical utility for risk stratification in Hispanic/Latino cirrhotic populations. Validation in larger cohorts and assessment of incremental utility beyond established clinical risk scores are warranted.



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4267 | AN ARTIFICIAL INTELLIGENCE MODEL FOR PREDICTING RESPONSE TO ATEZOLIZUMAB–BEVACIZUMAB IN HCC: MULTICENTER REAL-WORLD

Yu Rim Lee[1] Sung-Bum Cho[2] Hyun Young Woo[3] Jae Hyun Yoon[4] Jun Sik Yoon[5] Yeowool Kang[6] Jeong Eun Song[7] Young Mi Hong[8] Sang Youn Hwang[9] Joonho Jeong[10] Jeong Heo[3] Yang Hyun Baek[6] Young Oh Kweon[1] Soo Young Park[1] Won Young Tak[11], [1]Kyungpook National University, [2]Chonnam National University, [3]Pusan National University, [4]Chonnam National University Hospital, [5]Busan Paik Hospital, [6]Dong-A University Hospital, [7]Daegu Catholic University School of Medicine, [8]Pusan National University School of Medicine, [9]Dongnam Institute of Radiologic & Medical Sciences, [10]University of Ulsan College of Medicine, [11]School of Medicine, Kyungpook National University

Background: Atezolizumab plus bevacizumab (atezo/bev) has been established as an effective first-line treatment for unresectable hepatocellular carcinoma (HCC). Although various prognostic markers and prediction models have been proposed to estimate treatment outcomes in patients with HCC, clinically validated biomarkers remain limited. Therefore, we aimed to develop a machine learning–based model to predict treatment outcomes following atezo/bev therapy using demographic, laboratory, and imaging data from a large, multicenter real-world population. **Methods:** From May 2020 to October 2025, this retrospective cohort study included 1,114 patients with HCC from 10 tertiary hospitals who were treated with atezo/bev. Machine learning models, including random forest, were developed using baseline and follow-up parameters obtained after treatment initiation. **Results:** Among a total of 1,114 patients, 773 (69.4%) died at a median of 8.4 months during the study period (median 10.7 months). Age, modified ALBI grade, tumor size, CRP level, and main portal vein invasion at baseline were identified as significant predictors based on SHAP (SHapley Additive exPlanations) values. A random forest model trained using these five baseline factors and longitudinal variables, including follow-up NLR, AFP, and PIVKA-II levels, demonstrated superior performance compared with other machine learning models (AUROC, 0.765 [95% CI, 0.739–0.795]). Furthermore, compared with existing models, including the CRAFITY score, CRAFITY plus early AFP response model, and mALBI-based prognostic model, the proposed model demonstrated markedly improved discriminatory performance (AUROCs: 0.616 [0.580–0.650], 0.592 [0.554–0.629], and 0.627 [0.595–0.659], respectively). **Conclusion:** This model may serve as an adjunctive tool in clinical practice by assisting physicians in predicting treatment response and helping patients better understand their prognosis.

Table. Prognostic accuracy of prediction models to predict the survival of HCC patients : Comparison with existing models

Model	Key variables	Performance
Random Forest	Key5 = NL3 + AFP3 + PIVKA3	0.765 (0.739–0.795)
CRAFITY score	CRP ≥1 mg/dL, AFP ≥100 ng/mL	0.616 (0.580-0.650)
CRAFITY + Early AFP response	CRAFITY score + AFP response (≥75% decrease at 6–8 weeks)	0.592 (0.554-0.629)
mALBI-based prognostic model	mALBI (1 / 2a / 2b) + AFP, NLR	0.627 (0.595-0.659)

Disclosures: Yu Rim Lee:Nothing to Disclose, Sung-Bum Cho:Nothing to Disclose, Hyun Young Woo:Nothing to Disclose, Jae Hyun Yoon:Nothing to Disclose, Jun Sik Yoon:Nothing to Disclose, Yeowool Kang:Nothing to Disclose, Jeong Eun Song:Nothing to Disclose, Young Mi Hong:Nothing to Disclose, Sang Youn Hwang:Nothing to Disclose, Joonho Jeong:Nothing to Disclose, Jeong Heo:Gilead: Grant/Research Support, Roche: Speaking and Teaching, Yuhan: Speaking and Teaching, Abbvie: Speaking and Teaching, AstraZeneca: Advisor, Oncolys Japan: Grant/Research Support, Surrozen: Advisor, MedVir: Advisor, Yang Hyun Baek:Nothing to Disclose, Young Oh Kweon:Nothing to Disclose, Soo Young Park: Nothing to Disclose, Won Young Tak:Nothing to Disclose.

4268 | SARCOMATOID DIFFERENTIATION AND SURVIVAL OUTCOMES IN HEPATOCELLULAR CARCINOMA: A POPULATION-BASED SEER ANALYSIS

Kesava Manikanta Achuta[1] Rutwik Pradeep Sharma[2] Tharun Gopannagari[1] Narissa Nursjamsi[1] Hari Conjeevaram[3] Sujata Kambhatla[1], [1]Garden city hospital, Michigan State University, [2]Sparrow Hospital, U of M, [3]University of Michigan Medical Center

Background: Sarcomatoid hepatocellular carcinoma is a rare histologic variant with poor outcomes. It

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remains unclear whether its survival disadvantage is explained by advanced presentation or persists after adjustment for tumor and treatment factors. We used contemporary SEER data to evaluate whether sarcomatoid histology identifies an aggressive phenotype and independently predicts mortality. **Methods:** Adults with primary liver hepatocellular carcinoma diagnosed from 2000-2022 were identified using SEER Research Data (17 registries, November 2024 submission). Conventional and sarcomatoid hepatocellular carcinoma were defined by ICD-O-3 codes 8170/3 and 8173/3. Overall survival was assessed using Kaplan-Meier analysis and Cox regression. Sensitivity analyses included cancer-specific survival, Fine-Gray competing-risk analysis, restricted mean survival time, and inverse probability of treatment weighting (IPTW). **Results:** Among 126,290 patients, 126,190 (99.92%) had conventional HCC and 100 (0.08%) had sarcomatoid HCC. Median overall survival was 11 months versus 3 months respectively. Sarcomatoid histology was associated with worse overall survival in unadjusted analysis (HR 2.01, 95% CI 1.64-2.46), core-adjusted analysis (HR 1.72, 95% CI 1.41-2.10), and fully adjusted analysis (HR 1.49, 95% CI 1.22-1.83). It was also associated with cancer-specific mortality (HR 1.58, 95% CI 1.28-1.96) and competing-risk-adjusted cancer death (sub distribution HR 1.50, 95% CI 1.26-1.78). Sarcomatoid hepatocellular carcinoma was associated with advanced stage, poor or undifferentiated grade, larger tumor size, and an aggressive phenotype (OR 7.19, 95% CI 3.42-18.49). Restricted mean survival time showed 12.4 fewer months alive over 60 months. Propensity-weighted analysis supported worse survival (HR 1.88, 95% CI 1.49-2.39), although residual imbalance remained. **Conclusion:** Stage, grade, and tumor size explained part of the survival disadvantage, but excess mortality persisted after adjustment. SEER lacks liver disease severity data, including Child-Pugh class, MELD score, portal hypertension, cirrhosis etiology, viral hepatitis status, and baseline liver function tests. This supports sarcomatoid differentiation as a clinically meaningful marker of aggressive tumor biology rather than a finding explained only by later-stage presentation. Given the rarity of this subtype, population-level analyses may define prognosis, support careful histologic reporting, and guide future studies evaluating treatment response and risk stratification in contemporary cohorts. **Conclusion:** Sarcomatoid hepatocellular carcinoma is rare but associated with aggressive clinicopathologic features and substantially worse survival. Recognizing sarcomatoid differentiation may improve prognostic counseling and support focused study in modern treatment-era cohorts.

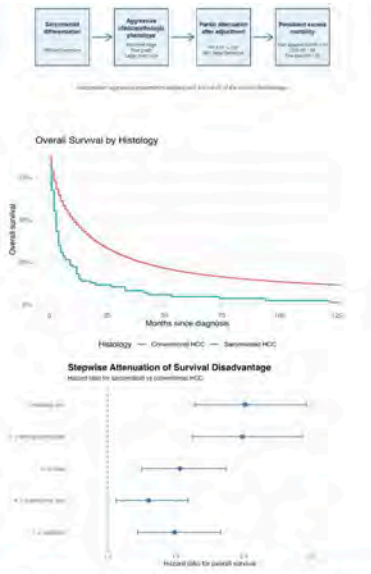


Table 1. Primary survival models for sarcomatoid versus conventional HCC.

Outcome	Adjustment	HR	95% CI	P value
Overall survival	Unadjusted	2.01	1.64-2.46	<0.001
Overall survival	Core adjusted	1.72	1.41-2.10	<0.001
Overall survival	Fully adjusted	1.49	1.22-1.83	<0.001
Cancer-specific survival	Fully adjusted	1.58	1.28-1.96	<0.001

Hazard ratios above 1 indicate higher mortality for sarcomatoid HCC compared with conventional HCC. Full covariate results are provided in Supplementary Table 9.

Disclosures: Kesava Manikanta Achuta:Nothing to Disclose, Rutwik Pradeep Sharma:Nothing to Disclose, Tharun Gopannagari:Nothing to Disclose, narissa nursjamsi:Nothing to Disclose, Hari Conjeevaram: Nothing to Disclose, sujata kambhatla:Nothing to Disclose.

4269 | COMPARISON OF EFFICACY AND SAFETY OF PD-1/PD-L1 INHIBITORS COMBINED WITH TARGETED THERAPY IN HEPATOCELLULAR CARCINOMA: A NETWORK META-ANALYSIS

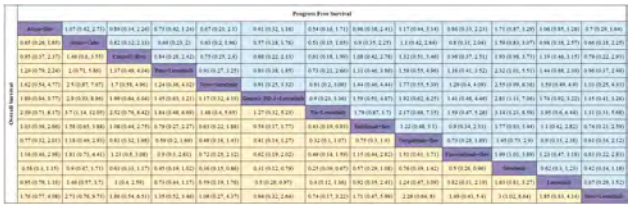
Tianyu Ma[1] Ruyu Liu[1], [1]Beijing Ditan Hospital, Capital Medical University

Background: Hepatocellular carcinoma (HCC) is a leading cause of cancer-related death worldwide, with most patients diagnosed at advanced stages where systemic therapy is the mainstay. Immune checkpoint inhibitors (ICIs) combined with targeted therapy have significantly improved outcomes in advanced HCC; however, whether PD-1 inhibitors and PD-L1 inhibitors differ in efficacy and safety when paired with targeted agents remains unclear due to the lack of head-to-head comparisons. This network meta-analysis aims to comprehensively compare the efficacy and safety of

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PD-1-based versus PD-L1-based combination regimens for advanced HCC, providing evidence to guide clinical decision-making. **Methods:** We performed a network meta-analysis of 28 studies (13 regimens). PubMed, Embase, Cochrane Central, and Web of Science were searched. Outcomes included overall survival (OS), progression free survival (PFS), objective response rate (ORR), disease control rate (DCR), and adverse events. Pooled hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using Bayesian models. **Results:** Among all included studies, tislelizumab plus lenvatinib showed the potential for the best OS (P = 44.7%). PD-1 plus lenvatinib was significantly superior to atezolizumab plus bevacizumab for ORR (HR 0.17, 0.06 0.41) and DCR (HR 0.19, 0.06 0.49). No significant differences in OS or PFS were observed between PD-1 based and PD-L1 based combinations. PD-1 plus lenvatinib ranked among the top two regimens in most subgroups (AFP > 400 ng/mL, BCLC C, ECOG 0, female). Sintilimab plus bevacizumab ranked first for OS in BCLC B patients (P = 41.2%). Most regimens increased the risk of hypothyroidism and proteinuria versus sorafenib. **Conclusion:** PD-1 plus lenvatinib may benefit patients with high AFP or female sex. PD-1 inhibitor plus lenvatinib significantly improved ORR and DCR versus atezolizumab plus bevacizumab in first line advanced HCC, with tislelizumab plus lenvatinib ranking best for OS. No significant differences in OS or PFS were observed between PD-1 based and PD-L1 based regimens.



Disclosures: Tianyu Ma:Nothing to Disclose, Ruyu Liu: Nothing to Disclose.

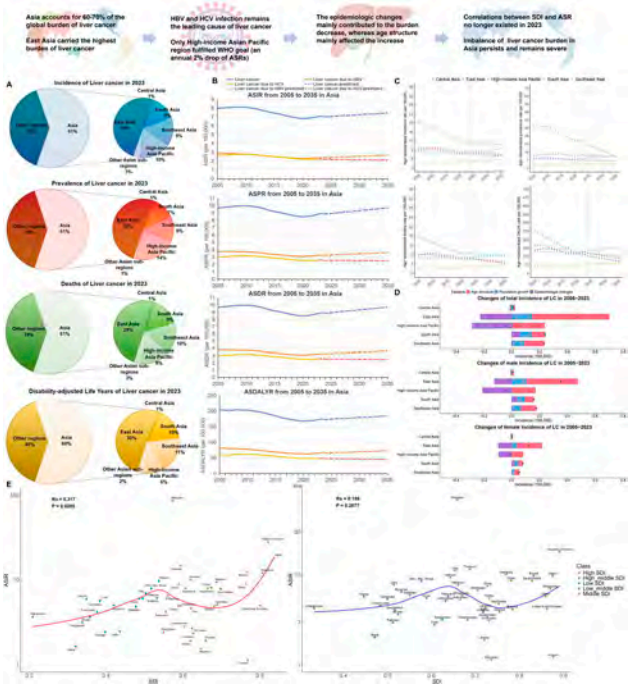
4270 | BURDEN, TRENDS, AND PREDICTIONS OF LIVER CANCER IN ASIA: ESTIMATES OF 2005-2023 AND PROJECTIONS TO 2035

Yujiao Deng[1] Yixin Guo[1] Qiaoman Fei[1] Xiao Yuan[1] Xubing Zhou[1] Chongyu Zhang[1] Dou Qu[1] Qian Wang[1] Huan Deng[1] Gaixia He[1] Meijuan Han[1] Qi Shang[1] Yuan Wang[1] Fanpu Ji[1], [1]The Second Affiliated Hospital of Xi'an Jiaotong University

Background: Asia bears the heaviest burden of liver cancer (LC) globally. Analysis of its disease burden, variation and predictions of future trends is crucial for reducing its burden. **Methods:** Using GBD 2023 study, we calculated age-standardized incidence (ASIR), prevalence (ASPR), death (ASDR), disability-adjusted life years (DALYs) rates (ASDALYR) and their average annual percent change (AAPC) in Asia and ite subregions and countries. We conducted a Prophet model to predict ASRs between 2024 to 2035 based on the data from 2005 to 2023. Temporal and spatial trends, Das Gupta's standardization, spearman correlation, decomposition method and predictive analysis was used to decompose and explain the regional difference. **Results:** From 2005 to 2023, East Asia carried the highest burden of LC and kept decreasing (Figure 1). High-income Asian Pacific (HIAP) always had the highest ASIR, ASPR, ASDR of LC, with the fastest decrease. South Asia always had the lowest ASRs. ASIR decreased in all Asian areas but increased in South Asia. ASDR, ASPR, ASDALYR decreased in HIAP, Central and East Asia, but increased in South and Southeast Asia. ASRs is projected to increase in South and Southeast Asia in 2035. Mongolia had the highest ASRs. China always carried the highest ASPR of LC in East Asia. In HIAP and Southeast Asia, the countries with the highest ASR are South Korea and Thailand respectively. ASRs of LC due to hepatitis B (LCB) kept the highest in East Asia, ASRs of LC due to hepatitis C (LCC) was the highest in HIAP. ASR (except for ASPR) of LCC and LCB decreased the fastest in Central Asia and increased only in South Asia, while ASPR decreased the fastest in HIAP. Notably, only HIAP successfully achieved the WHO-targeted declining trend in LC ASIR. The peak age for the LC and LCB burden of male is earlier than that for females. The epidemiologic changes mainly contributed to the burden decrease, whereas age structure mainly affected the increase. In 2005, ASIR, ASPR, and ASDR of LC, ASPR of LCB in Asian countries were positively correlated with sociodemographic index (SDI). However, by 2023, these correlations no longer existed. **Conclusion:** The imbalance in the burden of LC in the Asian region persists and remains severe. East Asia always carried the highest disease burden of LC and LCB. HIAP always had the highest ASRs of LC, with the fastest decrease. China always carried the highest ASPR of LC. ASRs of LC is no longer correlated with SDI in Asian countries.

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4271 | CLINICAL OUTCOMES FOR CONTEMPORARY COHORT OF PATIENTS WITH HCC LISTED FOR LIVER TRANSPLANTATION

Manasa Narasimman[1] Neil Mehta[2] Parissa Tabrizian[3] Ju Dong Yang[4] Neehar Parikh[5] Ang Gao[1] Lisa Quirk[1] Naomy Kim[6] Madeline Smith[7] Rashmita Raghunathan[7] Willis Tang[2] Zoe Berman[2] Jasmine Gamez[2] Amit Singal[1], [1]UT Southwestern Medical Center, [2]University of California, San Francisco, [3]Mount Sinai, [4]Cedars-Sinai Medical Center, [5]University of Michigan Medical Center, [6]Cedars Sinai, [7]University of Michigan

Background: Liver transplantation (LT) is a preferred curative option for patients with early-stage hepatocellular carcinoma (HCC). Changes in eligibility (e.g., downstaging), waitlist priority policies, and types of bridging therapy (e.g., use of immune checkpoint inhibitors), can lead to changes in risk of waitlist dropout and recurrence. We characterized clinical outcomes in a contemporary multi-center cohort of patients with HCC listed for LT in the U.S. **Methods:** We conducted a multi-center retrospective cohort study to characterize patterns and outcomes among patients with HCC listed for LT between January 2019 and July 2023 across 5 sites in the HCC-Live Consortium. We excluded patients with patients with cholangiocarcinoma (including known mixed HCC-CCA) and unknown treatment history prior to listing. We used Fine and Gray competing risk analysis to characterize time to waitlist dropout and time to post-LT recurrence, with death as a competing risk for both models; for waitlist dropout analysis, patients were censored at LT. **Results:** We identified 900 eligible patients, with median age 63 (IQR 57.6 – 67.0), 73.6% male, and 51.3% non-Hispanic White. Liver disease etiology included 27.0% post-SVR, 12.6% viremic HCV, 22.9% MASLD, 18.4% ALD, 12.1% HBV. At diagnosis, most patients (68.6%) had unifocal HCC, 20.7% had 2 lesions, and remainder had 3+ lesions. Median HCC diameter was 2.7 (IQR 2.0 – 3.8) cm, with 24 (2.7%) having vascular invasion. Waitlist dropout occurred in 308 (34.2%) patients, with 102 (33.1%) due to tumor progression. Median time to dropout was 32.5 months, with 6-, 12-, and 18-month dropout probabilities of 0.06 (95%CI 0.04 – 0.08), 0.15 (0.12 – 0.17), and 0.24 (0.20 – 0.28). Waitlist dropout was associated with older age (HR 1.03, 95%CI, 1.00 – 1.06) and presence of ascites (HR 1.81, 95%CI 1.18 – 2.79). Waitlist dropout did not differ by tumor burden at diagnosis (number of HCC: HR 1.02, 95%CI 0.88 – 1.18 and maximum diameter: HR 1.02, 95%CI 0.95 – 1.10), AFP at diagnosis (continuous: HR 1.00, 95%CI 1.00 – 1.00), or bridging modality (vs. TACE: ablation (HR 0.97, 95%CI 0.64 – 1.46); resection (HR 0.81, 95%CI 0.50 – 1.29); TARE/SBRT (HR 0.89, 95%CI 0.62 – 1.27). Of 550 patients who underwent LT, 56 (10.1%) experienced HCC recurrence, with 12- and 24-month probabilities of 0.03 (95%CI 0.02 – 0.05) and 0.07 (95%CI 0.05 – 0.09). Recurrence was associated with male sex (HR 2.38, 95%CI 1.08 – 5.22), microvascular invasion on explant (HR 7.99, 95%CI 4.27 - 15.0), and AFP at transplant (HR 1.01, 95%CI 1.01 – 1.02). Rejection was observed in 77 (14.0%) patients, with no significantly associated factors. **Conclusion:** In contemporary patients with HCC listed for LT, waitlist dropout occurs in over one-third of patients, often due to tumor progression, while post-LT recurrence rates remain acceptably low.

Disclosures: Manasa Narasimman:Nothing to Disclose, Neil Mehta:Merck: Consultant, FujiFilm WAKO: Consultant, Merck: Consultant, FujiFilm WAKO: Consultant, Boston Scientific: Consultant, FujiFilm: Grant/ Research Support, FujiFilm: Consultant, Merck: Consultant, FujiFilm WAKO: Consultant, Merck: Consultant, FujiFilm WAKO: Consultant, Boston Scientific:

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4272 | DEVELOPMENT AND EXTERNAL VALIDATION OF A SIMPLIFIED PREDICTION MODEL FOR EARLY HCC RECURRENCE: THE SPARE SCORE

Jaehong Jeong[1] Dai Hoon Han[1] Hye Won Lee[1],
[1]Yonsei University College of Medicine, Seoul, Korea

Background: Early HCC recurrence after curative resection significantly limits survival. Existing predictive models are often limited by inflexible categorical systems, complex variables, or insufficient external validation. We aimed to develop and externally validate the SPARE (Simplified Prediction model for Advanced Recurrence Evaluation) score to provide continuous probabilities for predicting 2-year HCC recurrence. **Methods:** The development cohort included patients undergoing first-line surgical resection for HCC at Severance Hospital (Jan 2004–Jan 2025). An independent validation cohort was collected from Gangnam Severance Hospital (Dec 2004–Aug 2024). A logistic regression nomogram, the SPARE score, was developed using multivariable analysis. Its predictive performance was externally validated and compared to ERASL-pre and ERASL-post models. **Results:** The development and external validation cohorts included 2,099 and 372 patients, respectively. The final simplified model consisted of five core variables: age, sex, log (alpha-feto protein), tumor diameter, and microvascular invasion. In the external validation cohort, the SPARE score achieved an AUC of 0.663, demonstrating statistically non-inferior and numerically comparable performance to the highly complex ERASL-post (AUC 0.633, $P = 0.222$) and ERASL-pre (AUC 0.629, $P = 0.276$) models. Applying predefined statistical tertiles calculated from the SPARE score (low risk: $\leq 21.1\%$, intermediate risk: 21.1–38.4%, high risk: $> 38.4\%$) successfully stratified the external cohort into distinct risk groups with perfectly separated recurrence-free survival curves (log-rank $P < 0.001$). **Conclusion:** The SPARE score predicts 2-year HCC recurrence using only five clinical variables while achieving non-inferior predictive performance compared to complex existing models. It provides robust continuous probabilities, enabling simple and intuitive clinical risk stratification.

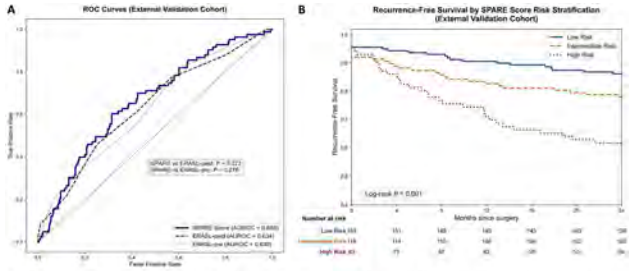


Figure 1. Predictive Performance and Risk Stratification of the SPARE Score. (A) Receiver-operating-characteristic (ROC) curves predicting 2-year early HCC recurrence, comparing the SPARE score to existing ERASL models. (B) Kaplan-Meier recurrence-free survival curves demonstrating successful risk stratification using predefined SPARE score tertiles. Abbreviations: ERASL, Early Recurrence After Surgery for Liver cancer; HCC, hepatocellular carcinoma; SPARE, Simplified Prediction model for Advanced Recurrence Evaluation.

Disclosures: Jaehong Jeong:Nothing to Disclose, Dai Hoon Han:Nothing to Disclose, Hye Won Lee:Nothing to Disclose.

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4273 | HIGH RISK OF HCC PERSISTS BEYOND 2 YEARS IN PATIENTS WITH INDETERMINATE LIVER NODULES

Janvi Patel[1] Sruthi Yekkaluri[1] So Yeon Kim[1] Nicole Rich[2] Amit Singal[1], [1]UT Southwestern Medical Center, [2]University of Texas Southwestern Medical Center

Background: Patients with indeterminate liver nodules (ILNs, i.e., LR-3 and LR-4) have a high risk of developing hepatocellular carcinoma (HCC). However, LI-RADS recommends that these lesions are downgraded after 2 years of stability, so patients can then return to ultrasound-based surveillance. However, clinical outcomes, including the risk of HCC, after the 2-year landmark have not been well described. **Methods:** We conducted a retrospective cohort study of patients with ILNs diagnosed at two academic medical centers between August 2013 and December 2021. We included those patients who had a newly diagnosed LR-3 or LR-4 lesion with 2 years of stability; we excluded patients who developed HCC, had the ILN resolve, or were transplanted within the 2-year period. We collected all subsequent imaging receipt and results. We used Fine-Gray subdistribution hazard models to characterize time to HCC after the 2-year landmark, with liver transplantation and death as competing events. Fine-Gray multivariable regression, with backward selection, was used to identify factors associated with incident HCC. **Results:** Of 53 eligible patients (44 with LR-3 and 9 with LR-4 lesions), median age was 59 years and 56.6% were male. Patients were diverse regarding race (18.9% White, 56.6% Hispanic, 22.6% Black) and liver etiology (24.5% hepatitis C, 34.0% MASLD, 18.9% alcohol-associated). The median size of the ILN was 1.0 cm (IQR 0.9 – 1.2) at diagnosis, which was similar median (1.0 cm, IQR 0.9 – 1.5) at the 2-year landmark. Despite stability, radiologists only downgraded the ILN in 10 (18.9%) cases. During a median follow-up of 37.7 months after the 2-year landmark, 15 developed HCC, 2 underwent transplant, and 5 died. The overall HCC incidence after the 2-year landmark was 9.3 per 100 person-years, with a cumulative incidence of 10.3% (95%CI 3.7 – 20.7) during year 2-3, 14.8% (95%CI 6.4 – 26.4) during year 3-4, and 19.5% (95%CI 9.5 – 32.2) during year 4-5. Stratified by ILN, the cumulative incidence was 9.9% (95%CI 3.1 – 21.5) during year 2-3 and 12.6% (95CI 4.5 – 25.1) during years 3-4 for patients with LR-3 lesions and 12.5% (95%CI 0.5 – 44.5) during year 2-3 and 25.0% (95CI 3.0 – 57.9) during years 3-4 for patients with LR-4 lesions. The only factor associated with HCC in multivariable analysis was Child Pugh B cirrhosis at diagnosis (sHR 16.8, 95%CI 2.1 – 137.0). Male sex was associated with increased HCC risk but this did not achieve statistical significance (sHR 4.76, 95%CI 0.99 – 25.0). **Conclusion:** Patients with ILNs have a persistent high risk of HCC beyond 2 years after initial diagnosis, arguing against current recommendations to downgrade these lesions. Our data suggest a need for continued surveillance using multi-phase CT or MRI beyond 2 years.

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4274 | BEYOND TACE REFRACTORINESS: HEPATIC RESERVE AS THE DECISION ANCHOR FOR TRANSITION TO ATEZOLIZUMAB-BEVACIZUMAB IN UNRESECTABLE HEPATOCELLULAR CARCINOMA

Hyo Jin Nam[1] Soe Thiha Maung[2] Sung Won Chung[1] Ji won Yang[3] Won-Mook Choi[1] Jonggi Choi[4] Roongruedee Chaiteerakij[5] Danbi Lee[1] Ju Hyun Shim[1] Kang Mo Kim[1] Young Suk Lim[1] Han Chu Lee[1], [1]Asan Medical Center, [2]Faculty of Medicine, Chulalongkorn University, [3]Asan Medical Center, University of Ulsan College of Medicine, [4]University of Ulsan, Asan Medical Center, [5]Chulalongkorn University

Background: In unresectable hepatocellular carcinoma (HCC), repeated transarterial chemoembolization (TACE) may impair hepatic reserve before formal TACE refractoriness is recognized. We evaluated whether hepatic reserve at the pre-final-TACE better identifies the optimal transition window to atezolizumab-bevacizumab (Atezo/Bev) than refractoriness alone. **Methods:** This retrospective single-center cohort included 154 patients with unresectable HCC who received sequential TACE followed by Atezo/Bev. TACE refractoriness was defined according to Japan

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Society of Hepatology criteria and assessed at Atezo/Bev initiation. Overall survival (OS) and radiologic progression-free survival (PFS) were measured from Atezo/Bev initiation. Pre-final-TACE ALBI grade/score, INR, cumulative TACE count, and integrated decision models were evaluated. **Results:** Patients underwent a median of 4 TACE sessions, and 117 (76.0%) met refractoriness criteria at Atezo/Bev initiation. Among 148 patients with paired pre-final-TACE ALBI data, 121 (81.8%) already had ALBI grade 2/3 at the last TACE. A refractoriness-only model yielded a C-index of 0.535 for PFS and 0.536 for OS in the complete-case subset. In the key cross-classification analysis, non-refractory patients with pre-final-TACE ALBI grade 2/3 had worse PFS than refractory patients with preserved ALBI grade 1 (adjusted hazard ratio 2.75, 95% confidence interval 1.35–5.64; $p = 0.006$). In exploratory analyses, pre-final-TACE ALBI > -2.36 and INR values entering the 1.10–1.20 range as clinically relevant warning signals. A composite rule incorporating ALBI > -2.36, INR category, and TACE > 4 yielded a higher C-index than refractoriness alone (C-index 0.619 for PFS and 0.698 for OS). **Conclusion:** TACE refractoriness alone is an insufficient anchor for transition timing. Dynamic hepatic reserve assessment at the last TACE, particularly ALBI and INR, should be incorporated to identify patients who may benefit from timely transition to Atezo/Bev before irreversible reserve loss.

Disclosures: Hyo Jin Nam:Nothing to Disclose, Soe Thiha Maung:Nothing to Disclose, SUNG WON CHUNG:Nothing to Disclose, Ji won Yang:Nothing to Disclose, Won-Mook Choi:Gilead Sciences: Speaking and Teaching, AbbVie: Speaking and Teaching, Roche: Consultant, Boehringer Ingelheim: Advisor, GSK: Consultant, Eisai: Speaking and Teaching, AstraZeneka: Speaking and Teaching, Jonggi Choi:Nothing to Disclose, Nothing to Disclose, Roongruedee Chaiteerakij: Nothing to Disclose, Danbi Lee:Nothing to Disclose, Ju Hyun Shim:Nothing to Disclose, Kang Mo Kim:Nothing to Disclose, Young Suk Lim:Gilead Sciences: Grant/Research Support, Han Chu Lee:Roche: Grant/Research Support, BMS: Grant/Research Support, Astrazeneca: Grant/Research Support, Merck: Grant/Research Support.

4275 | METABOLIC DYSFUNCTION–ASSOCIATED STEATOTIC LIVER DISEASE AND RISK OF HEPATOCELLULAR CARCINOMA IN NON-CIRRHOTIC PATIENTS: A PROPENSITY-MATCHED COHORT STUDY

Eunice Aregbesola[1] Ibukunoluwa Oshobu[2] Eunice Omeludike[3] Abisola Ajayi[4] Winifred Iklaki[5], [1]University of Missouri, Columbia, [2]University of Missouri-Columbia Hospital, [3]Piedmont Athens Regional Medical Center, [4]Moorehouse School of Medicine, [5]University of Missouri - Columbia

Background: Metabolic dysfunction–associated steatotic liver disease (MASLD) is increasingly linked to hepatocellular carcinoma (HCC), including in patients without cirrhosis. We evaluated the association between MASLD and incident HCC in non-cirrhotic patients using a multicenter electronic health record database. **Methods:** We performed a retrospective propensity score–matched cohort study using the TriNetX Research Network. Adult patients with MASLD without prior cirrhosis, viral hepatitis, alcoholic liver disease, hepatic decompensation, or pre-existing HCC were matched 1:1 to controls without MASLD based on demographics and metabolic comorbidities. The primary outcome was incident HCC. Secondary outcomes included progression to cirrhosis, hepatic decompensation, liver-related hospitalization, and all-cause mortality. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using Cox proportional hazards models. **Results:** After propensity matching, 84,216 patients were included in each cohort with balanced baseline characteristics. During a median follow-up of 6.2 years, MASLD patients demonstrated significantly higher incidence of HCC compared with controls (1.12% vs 0.41%; HR 2.41, 95%CI 2.08–2.79; $p < 0.001$), with progressive divergence in cumulative HCC incidence over time (log-rank $p < 0.001$) (Fig. 1). MASLD was additionally associated with increased risks of progression to cirrhosis (6.84% vs 1.91%; HR 3.87, 95% CI 3.61–4.15), hepatic decompensation (2.16% vs 0.74%; HR 2.98, 95% CI 2.63–3.37), portal hypertension (HR 2.76, 95% CI 2.41– 3.15), liver-related hospitalization (8.92% vs 4.63%; HR 1.94, 95% CI 1.82–2.07), and all-cause mortality (12.7% vs 10.9%; HR 1.18, 95% CI 1.11–1.25) (Table 1). Elevated HCC risk persisted across patients with obesity (HR 2.27), diabetes mellitus (HR 2.61), and metabolic syndrome (HR 2.48) (all $p < 0.001$), and remained significant even among MASLD patients without obesity or diabetes (HR 1.89, 95% CI 1.42–2.51). Sensitivity analyses excluding patients who developed cirrhosis during follow-up continued to demonstrate increased HCC risk in the MASLD cohort (HR 1.76, 95% CI 1.39–2.24; $p < 0.001$). **Conclusion:** MASLD was independently associated with significantly increased risk of HCC in non-cirrhotic patients. These findings suggest hepatocarcinogenesis may occur prior to cirrhosis in MASLD and highlight the need for improved risk stratification and surveillance strategies.

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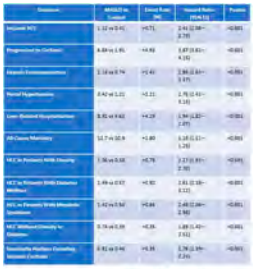


Table 1: Association of MASLD With Hepatic Outcomes and Hepatocellular Carcinoma in Non-Cirrhotic Patients

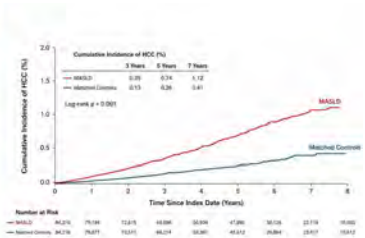


Fig. 1: Kaplan-Meier Curve for Cumulative Incidence of Hepatocellular Carcinoma (HCC) in MASLD vs. Matched Controls

Disclosures: Eunice Aregbesola:Nothing to Disclose, Ibukunoluwa Oshobu:Nothing to Disclose, Eunice Omeludike:Nothing to Disclose, Abisola Ajayi:Nothing to Disclose, Winifred Iklaki:Nothing to Disclose.

4276 | AGE-STRATIFIED INCIDENCE, TUMOR CHARACTERISTICS, TREATMENT PATTERNS, AND SURVIVAL IN FIBROLAMELLAR CARCINOMA: A POPULATION-BASED ANALYSIS OF SEER DATA (2000–2023)

Nicholas Thomas[1] Krishna Chandrasekhara[1] Chandni Bhagtaney[1] Prasun Jalal[1], [1]Baylor College of Medicine

Background: Fibrolamellar Carcinoma (FLC) is a rare tumor believed to account for 1-5% of all liver cancers. Uniquely, FLC is not associated with liver disease and is typically found in non-cirrhotic parenchyma. As a result, FLC characteristically affects younger patients with a bimodal age distribution, exhibiting peaks at 15-19 and 65-75 years of age. No previous literature has looked at the differences in FLC presentation, treatment, and prognosis between these age groups. **Methods:** 366 cases of FLC were identified between 2000–2023 from the Surveillance, Epidemiology, and End Results (SEER) database using ICD-O-3 histology code 8171/3. Groups were compared based on sex, year of diagnosis, tumor size, histologic grade, stage at diagnosis, surgical resection (any hepatic resection vs. no surgery), receipt of chemotherapy, and cancer-specific survival (CSS). The chi-squared test was applied for categorical variables, and the Kruskal-Wallis Test was applied for non-normally distributed continuous variables. For comparisons of CSS, the log-rank test was used to evaluate differences between Kaplan-Meier curves. **Results:** Consistent with existing literature, a bimodal age distribution was found, with a large and small incidence peak at 15-19 and 65-69 years of age, respectively. Likelihood of metastasis (regional or distant) at diagnosis was highest for patients < 20 years old (66% of cases), compared to only 46% for patients > 60. However, tumor size did not differ significantly across age groups ($p = 0.14$), indicating that it was not a primary contributor to the observed differences in cancer staging. Treatment approaches differed significantly by age group ($p < 0.001$), with the highest rates of surgical resection seen in patients 15-19 years old (74%) before declining to 20% of patients > 80 years old. Chemotherapy rates followed a similar decline, with 71% of patients < 15 receiving chemotherapy, compared to 24% of patients 70-79 years old. CSS was significantly different across age groups ($p = 0.00036$), with patients diagnosed at an older age having a worse prognosis, even after multivariate analysis. **Conclusion:** Younger FLC patients demonstrated better rates of cancer-specific survival despite higher rates of metastasis at diagnosis. This is likely reflected in the treatment approach (greater rates of surgical resection and chemotherapy in this population) rather than tumor burden, as tumor size did not differ across age groups. Differences in treatment might be explained by the higher prevalence of comorbidities and functional decline among older patients.

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4277 | COMPREHENSIVE SAFETY AND EFFICACY EVALUATION OF IMMUNOTHERAPY COMBINATION APPROACHES VERSUS TYROSINE-KINASE INHIBITOR MONOTHERAPY AS FIRST-LINE TREATMENT OF HEPATOCELLULAR CARCINOMA: A NETWORK AND INDIVIDUAL PATIENT DATA (IPD) META-ANALYSIS

Maen Abdelrahim[1] Abdullah Esmail[2] Yazan Hamdaneh[2] Zaid Al-Abed[2] Ebtesam Al-najjar[2] Nour Mustafa[2], [1]Houston Methodist Neal Cancer Center, Houston, Tx, [2]Section of GI Oncology, Department of Medicine, Houston Methodist Cancer Center, Houston, TX 77030

Background: Hepatocellular carcinoma (HCC) represents the most common primary liver cancer and a significant cause of global cancer-related mortality, with a lot of patients diagnosed at advanced or unresectable stages. Historically, tyrosine-kinase inhibitor (TKI) monotherapies such as sorafenib and lenvatinib served as the primary systemic standard of care. However, the emergence of immune checkpoint inhibitor (ICPI)-based combinations has significantly transformed the

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treatment landscape. We aim to perform a comparative analysis of ICPI-based combination treatment versus TKI monotherapy among advanced HCC patients. **Methods:** This study utilized a reconstructed individual patient data (IPD) pooled analysis derived from nine phase 3 randomized clinical trials, adhering to PRISMA-IPD reporting guidelines. A total of 6,161 patients were included in the analysis, which categorized treatment into five primary strategies: ICPI monotherapy, ICPI plus bevacizumab, dual ICPI (duplet), ICPI plus TKI, and TKI monotherapy as the control group. The primary endpoint was overall survival (OS), with secondary endpoints including progression-free survival (PFS) and the incidence of grade 3 or higher adverse events (AEs). **Results:** The analysis demonstrated that ICPI-based combinations provided a significant survival advantage over TKI monotherapy. Key hazard ratios (HR) for OS compared to TKIs were 0.76 (95% CI: 0.67–0.85, $p < 0.001$) for dual ICPI, 0.76 (95% CI: 0.68–0.85, $p < 0.001$) for ICPI plus TKI, and 0.70 (95% CI: 0.61–0.81, $p < 0.001$) for ICPI plus bevacizumab. Median OS was numerically highest for ICPI plus TKI at 19.68 months and dual ICPI at 19.58 months, compared to 14.84 months for the TKI group. Among FDA-approved regimens, Nivolumab plus Ipilimumab (NivoIpi) achieved the longest median OS of 24.08 months. From a safety standpoint, the ICPI plus TKI group had the highest incidence of grade 3/4 AEs at 69.1%. Conversely, TKI monotherapy showed a 50.1% incidence, while dual ICPI therapy exhibited the most favorable safety profile at 32.7%. **Conclusion:** ICPI-containing combination therapies are superior to TKI monotherapy for the first-line treatment of advanced HCC, providing marked improvements in survival outcomes. Dual ICPI therapy represents the most balanced approach between efficacy and safety, achieving high survival with the lowest rates of severe toxicity. Among approved options, NivoIpi demonstrated the strongest survival signal, while DurvaTreme offered the highest tolerability, supporting a personalized treatment approach based on individual patient risk factors and hepatic reserve.

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4278 | COMPARISON OF TUMOR CONTROL AND TOXICITY ASSOCIATED WITH SBRT AND TARE THERAPY FOR HCC

Alisa Likhitsup[1] Neehar Parikh[2], [1]University of Michigan, [2]University of Michigan Medical Center

Background: Treatment of hepatocellular carcinoma (HCC) with Stereotactic Body Radiation Therapy (SBRT) vs Transarterial radioembolization (TARE) has been shown to be effective for tumor control; however, the comparative safety and efficacy of the approaches are not well described. We aimed to compare tumor control and risk of hepatic decompensation following SBRT or TARE. **Methods:** We included patients from single institution with diagnosis of HCC, based on AASLD guidelines, who underwent SBRT or TARE between July 2018 and June 2023. Records were reviewed for demographics, Barcelona Clinic Liver Cancer (BCLC) tumor stage/ tumor burden, laboratory, and symptoms of hepatic decompensation. Radiation side effects were evaluated by changes in Albumin-Bilirubin (ALBI) grades and Child-Pugh (CP) progression at 3-month, 6-month, and 12-month intervals from index radiation treatment compared to baseline (before index treatment). **Results:** We included 59 patients were included, 42 treated with SBRT and 17 treated with ARE, with a median age 68 (64,72) years, 71% male, 95% White, 93% with cirrhosis (39% viral hepatitis, 31% MASLD, 14% alcohol, and 5% others), average tumor burden (n) 1.6 (1.1) lesions, average tumoral size 3.8 (2.9) cm, average follow up time 30 (range 4, 88) months. Tumor numbers, tumor size, and BCLC stages were more advanced, and AFP level was higher among patients who received TARE compared with SBRT. Age, sex, race, and cirrhosis etiologies were similar. MELD scores, CP scores, and ALBI grades were comparable at baseline (Table 1). Compared to CP score and ALBI grades at baseline, at 3 months, CP progression developed 24%, and ALBI grades increased in 14% among SBRT group, whereas CP progression was 29% and ALBI grades increased in 18% among TARE group ($p = 0.65$ for CP and $p = 0.75$ for ALBI). At 6 months, 29% had CP progression and 12% had ALBI grades increased, and were similar among the groups ($p = 0.95$ for CP and 0.99 for ALBI). At 12 months, the SBRT group had 10% CP progression, and 21% increased ALBI grades, whereas 12% and 18% of TARE group had CP progression and ALBI grades increased, respectively ($p = 0.80$ for CP and 0.75 for ALBI). Tumor control rates at 3 months was similar (83% SBRT and 82% TARE, $p = 0.70$). HCC recurrence rates were 12% at 6 months and 14% at 12 months among SBRT group, and 47% at 6 months and 18% at 12 months among TARE group. Death occurred 45% among SBRT (10% HCC progression and 12% liver-related death) and 59% among TARE (29% HCC progression and 35% liver-related death). Overall, 12% received liver transplantation. Median survival 31(19, 57) months among SBRT and 20(9, 38) months among TARE ($p = 0.09$). **Conclusion:** A significant proportion of patients with HCC developed CP and ALBI progression within 3-6 months of treatment with SBRT/TARE, with

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similar rates of tumor control. Strategies to mitigate radiation related liver toxicity are needed to improve patient outcomes.

Table 1: Clinical Characteristics of HCC cohorts by radiation treatment received.

Variables	SBRT (n=42)	TARE (n=17)	p-value
Age (years, se)	67 (8)	68 (10)	0.72
Male (%)	30 (71%)	12 (71%)	0.95
White (%)	40 (95%)	15 (88%)	0.33
BMI (kg/m2, mean, se)	31 (2.17)	31 (2.07)	0.46
Etiologies (%)			0.95
Viral hepatitis	16 (38%)	6 (35%)	
MASLD	12 (29%)	6 (35%)	
Alcohol	6 (14%)	2 (12%)	
Others	6 (14%)	3 (18%)	
Tumor numbers (mean, se)	1.38 (0.12)	2.12 (0.37)	0.02
Tumor sizes (mean, se)	3.47 (2.42)	4.54 (3.68)	0.19
BCLC stage A/B/C (%)	24 (57%)/16 (38%)/2 (5%)	7(41%)/8 (47%)/2(12%)	0.43
AFP (mean, se)	110.65 (73.8)	844.59 (635.88)	0.09
Varices needed band ligations (%)	13 (31%)	6 (31%)	0.75
Ascites required diuretics/para (%)	9(21%)/2 (5%)	4 (24%)/1 (6%)	0.97
HE grade 1-2/3-4 (%)	13 (31%)/0	2 (12%)/0	0.13
ECOG 0/1/2/3	28(67%)/12(29%)/2(5%)/0	11(65%)/6(35%)/0/0	0.61
At baseline			
MELD Na (mean, se)	9.64 (0.52)	8.41 (0.44)	0.16
CP A/B/C (%)	28 (67%)/12 (29%)/2 (5%)	13 (76%)/4(24%)/0	0.58
ALBI score 0/1/2/3 (%)	23 (67%)/19 (29%)/0	9 (53%)/8 (47%)/0	0.90
At 3 months			
MELD Na (mean)	10.5 (0.61)	13.53 (1.92)	0.97
CP progression (%)	10 (24%)	5 (29%)	0.65
ALBI score increased (%)	6 (14%)	3 (18%)	0.75
At 6 months			
MELD Na (mean, se)	13.10 (1.16)	16 (1.94)	0.90
CP progression (%)	12 (29%)	5 (29%)	0.95
ALBI score increased (%)	5 (12%)	2 (12%)	0.99
At 12 months			
MELD Na (mean, se)	10.10 (0.75)	10.67 (4.70)	0.64
CP progression (%)	4 (10%)	2 (12%)	0.80
ALBI score increased (%)	9 (21%)	3 (18%)	0.75
Tumor control at 3 months	35 (83%)	14 (82%)	0.70
Second treatment for HCC	5 (10%) SBRT, 2 (5%) MWA	1 (6%) SBRT, 1 (6%) TARE, 1 (6%) Systemic Rx	0.08
HCC recurrence at 6 months	5 (12%)	8 (47%)	0.08
HCC recurrence at 12 months	6 (14%)	3 (18%)	<0.001
Median survival (months)	31 (19, 57)	20 (9, 38)	0.09
Death	19 (45%)	10 (59%)	0.34
HCC progression	4(10%)	5 (29%)	0.14
Liver-related	5 (12%))	6 (35%)	0.10
Liver transplant	5 (12%)	2 (12%)	0.95

Disclosures: Alisa Likhitsup:Meridian Bioscience: Grant/Research Support, Neehar Parikh:Genentech: Grant/Research Support, Genentech: Grant/Research Support, Exelixis: Grant/Research Support, Exelixis: Grant/Research Support, Exelixis: Consultant, Exelixis: Consultant, AstraZeneca: Consultant, AstraZeneca: Consultant, Exact Sciences: Grant/Research Support, Exact Sciences: Grant/Research Support, Exact Sciences: Consultant, Exact Sciences: Consultant, Fujifilm Medical: Advisor, Fujifilm Medical: Advisor, Sirtex: Advisor, Genentech: Grant/Research Support, Genentech: Grant/Research Support, Exelixis: Grant/Research Support, Exelixis: Grant/Research Support, Exelixis: Consultant, Exelixis: Consultant, AstraZeneca: Consultant, AstraZeneca: Consultant, Exact Sciences: Grant/Research Support, Exact Sciences: Grant/Research Support, Exact Sciences: Consultant, Exact Sciences: Consultant, Fujifilm Medical: Advisor, Fujifilm Medical: Advisor, Sirtex: Advisor.

4279 | FROM LIVER RESERVE TO LIVER RESPONSE: HEPATIC ADAPTATION PHENOTYPES FOLLOWING TACE AND THEIR ASSOCIATION WITH MRECIST RESPONSE IN HEPATOCELLULAR

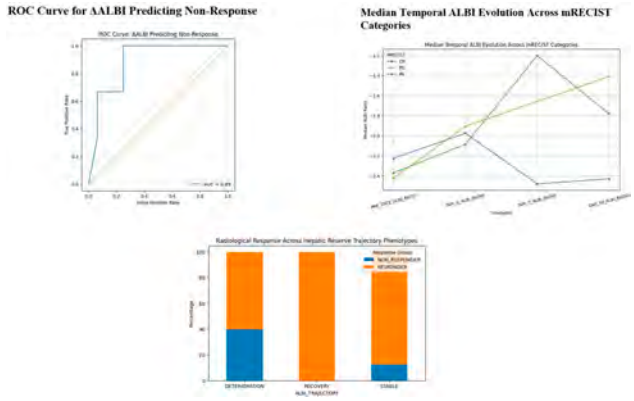
Anthieya Jude[1] Mrinalni J[1], [1]Sree balaji medical college and hospital

Background: Transarterial chemoembolization is the standard locoregional therapy for intermediate-stage hepatocellular carcinoma, with treatment response assessed only on follow-up imaging. Baseline ALBI and MELD scores reflect pre-treatment hepatic reserve, while dynamic post-TACE changes in these markers may carry prognostic information beyond baseline values. This study evaluated whether post-TACE ALBI and MELD trajectories correlate with mRECIST response and whether hepatic adaptation phenotyping enables earlier outcome stratification. **Methods:** This preliminary analysis includes 96 patients from an ongoing retrospective cohort study with an anticipated final enrollment of 250 patients. Adult HCC patients undergoing TACE with complete pre- and post-procedural laboratory data were included. ALBI and MELD scores were calculated at baseline, Day 7, and Day 30 post-TACE, with laboratory assessments accepted within a ±2 day window. Dynamic changes in ALBI and MELD at Day 30 were derived and used as the primary exposure variables. Patients were subsequently classified into three hepatic adaptation phenotypes — Recovery, Stable, and Deterioration — based on their post-TACE ALBI trajectories. A Hepatic Recovery Score was additionally derived from persistent worsening of both ALBI and MELD at Day 30. Radiological response was assessed per mRECIST criteria **Results:** In this preliminary cohort of 96 patients, change in ALBI at Day 30 was significantly associated with radiological response ($p = 0.044$) and demonstrated strong discrimination for non-response (AUC = 0.89). Change in MELD showed a directional trend ($p = 0.068$; AUC = 0.77). Response rates declined progressively across adaptation phenotypes from 100% in Recovery to 60% in Deterioration, with the Hepatic Recovery Score demonstrating a consistent dose-response gradient across non-response rates of 14.1%, 27.3%, and 37.5%. Traditional tumour biomarkers showed no meaningful association — AFP ($p = 0.092$) and PIVKA-II ($p = 0.608$) were uninformative. Baseline ALBI similarly showed no significant association ($p = 0.376$), confirming the limited utility of static pre-procedural assessment. Early stress markers at 24 hours showed limited value (AUC = 0.54), reflecting transient ischaemic injury rather than sustained treatment response biology. These findings will be validated in the complete cohort. **Conclusion:** The liver's adaptive response to TACE carries significantly

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more prognostic information than its baseline state. Dynamic ALBI and MELD trajectories outperformed static scores and tumour biomarkers in predicting mRECIST response, and hepatic adaptation phenotyping identified clinically meaningful response gradients using data already routinely collected. Validation in the complete cohort is ongoing.

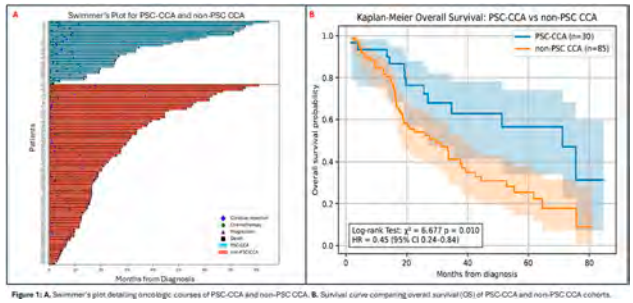


Disclosures: Anthieya Jude:Nothing to Disclose, Mrinalni J:Nothing to Disclose.

4280 | PSC-ASSOCIATED CHOLANGIOCARCINOMA IS DIAGNOSED WITH EARLIER-STAGE DISEASE AND IMPROVED SURVIVAL COMPARED TO NON-PSC CHOLANGIOCARCINOMA

Sarah Khan[1] Niharika Bhattacharjee[2] Mosbah Aouad[2] Diana Segovia[1] Jessie Hohenstein[1] Qian Shi[1] Chen Wang[1] Ravishankar Iyer[2] Lewis Roberts[3], [1]Mayo Clinic- Rochester, [2]University of Illinois- Urbana Champagne, [3]Mayo Clinic Rochester

Background: Primary sclerosing cholangitis (PSC) is a well-established risk factor for cholangiocarcinoma (CCA), but outcomes may differ compared to de novo CCA due to surveillance, referral patterns, and access to transplantation. We compared clinicopathologic features, treatment, recurrence, and survival in PSC-associated versus non-PSC CCA at a multi-site tertiary referral center. **Methods:** We performed a retrospective analysis of 115 CCA patients diagnosed from 2015 to 2025 (PSC-CCA n = 30, non-PSC CCA n = 85), who consented to participate within our registry and biorepository. Clinical, pathologic, treatment, and overall survival data were compared using Mann-Whitney U, Fisher's exact, and chi-square tests with Benjamini-Hochberg correction. **Results:** Compared to non-PSC patients with CCA, PSC-CCA patients were predominantly male (73.3% vs. 43.5%, p = 0.009), younger (median age 55.9 vs 65.6, p < 0.0005), and had higher rates of cirrhosis (56.7% vs. 7.1%, p < 0.0001) and ulcerative colitis (63.3% vs. 4.7%, p < 0.0001). PSC-CCA was more frequently perihilar in subtype (perihilar PSC-CCA vs non-PSC CCA 76.7% vs. 29.4%, p < 0.0001). PSC-CCA tumors were smaller at diagnosis (median 2.0 vs. 5.2 cm, p < 0.0001) with earlier T stage (T1a/T1b: 46.7% vs. 13.0%, p = 0.003), less nodal involvement (N0: 66.7% vs. 37.6%, p = 0.023), and lower rates of distant metastasis (M1: 13.3% vs. 48.2%, p = 0.002). PSC-CCA patients had better ECOG performance status (ECOG 0: 76.7% vs. 47.6%, p = 0.011) and more frequently underwent curative surgery (73.3% vs 36.5% p = 0.001; figure 1A). Within this cohort, liver transplantation was performed exclusively in PSC-CCA cases (43.3% vs. 0%, p < 0.0001), and post-surgical recurrnce was significantly lower in PSC-CCA (38.1% vs. 76.9%, p = 0.003). Among patients with PSC, 29.0% of patients underwent non-transplant hepatectomy, with recurrence occurring in 88.0% of this population. Of PSC-CCA cases, 36.7% were detected due to screening, 36.7% due to symptoms, and 23.3% were diagnosed with PSC at CCA diagnosis. Most PSC cases were referrals for liver transplant evaluation (70.0%). The median overall survival was significantly longer in PSC-CCA relative to de novo counterparts (31.5 vs. 18.7 months, p = 0.005; figure 1B). **Conclusion:** PSC-associated CCA presents and is detected at an earlier stage with smaller tumors, fewer metastases, and greater eligibility for curative-intent therapy including transplantation. This results in markedly improved survival and lower post-surgical recurrence compared to non-PSC counterparts. Our experience strongly supports maintaining a high degree of suspicion for CCA in IBD patients, rigorous structured CCA surveillance in PSC and expedient transplantation evaluation in this population.



Disclosures: Sarah Khan:Nothing to Disclose, Niharika Bhattacharjee:Nothing to Disclose, Mosbah Aouad: Nothing to Disclose, Diana Segovia:Nothing to Disclose, Jessie Hohenstein:Nothing to Disclose, Qian Shi: Nothing to Disclose, Chen Wang:Nothing to Disclose, Ravishankar Iyer:Nothing to Disclose, Lewis Roberts: Nothing to Disclose.

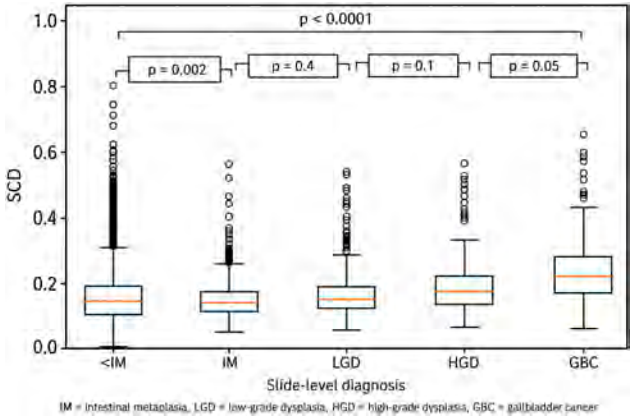
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4281 | DEVELOPMENT OF A GALLBLADDER STROMAL CELLULAR DENSITY ALGORITHM AND ASSOCIATION WITH THE SPECTRUM OF DISEASE

Jill Koshiol[1] Ilona Argirion[2] Karun Mutreja[3] Scott Lawrence[3] Petra Lenz[3] Rime Jebai[3] Allan Hildesheim[4] Ruth Pfeiffer[3] Catterina Ferreccio[5] Juan Araya[6], [1]1Division of Cancer Epidemiology and Genetics, NCI, NIH, [2]Georgetown University Medical Center, [3]Division of Cancer Epidemiology and Genetics, NCI, NIH, [4]Agencia Costarricense de Investigaciones Biomedicas, San Jose, Costa Rica, [5]Instituto de Salud Pública de Chile, [6]Hospital Dr. Hernan Henríquez Aravena, Temuco, Chile

Background: Gallbladder cancer (GBC) incidence is high in Chile. Gallstones are a major risk factor, but most people with gallstones never develop GBC. In a cohort designed to evaluate the determinants of progression from gallstones to cancer, we developed a stromal cellular density (SCD) algorithm to help characterize non-epithelial tissue composition on digital H&E slide images and assess SCD across the spectrum of disease. **Methods:** Using digital H&E slide images from the Chile Biliary Longitudinal Study (BiLS), we created an algorithm with 5 steps (tissue detection, QC to identify good tissue, liver detection and removal, epithelia and non-epithelia detection, account cells in non-epithelia) in HALO (Indica Labs, Arizona) to estimate SCD as the area of cells in non-epithelial region/area of non-epithelia. The training set included 41 images with 204 annotated regions and the test set 349 images with 2025 annotated regions (1060 non-epithelial, 965 epithelial). After evaluating precision (positive predictive value), recall (sensitivity), and the F1 Score [2*(precision*recall/(precision + recall)], we ran the algorithm on 37,553 independent images with pathologist-determined slide-level worst diagnosis from Chile BiLS. We excluded images with >50% artifact area and <30mm^2 usable tissue, leaving 33,544 images for analysis. We fit linear regression models to log(SCD) with slide level outcome as the independent variable, with independence working correlation and robust standard errors to account for repeated observations adjusted for age at cholecystectomy, waist-to-height ratio, and ethnicity. **Results:** The precision, recall, and F1-score were 0.94, 0.92, and 0.92 overall; 0.91, 0.84, and 0.87 for epithelial tissue; and 0.97, 0.99, and 0.98 for stromal tissue. A pathologist qualitatively confirmed performance on 600 of the 37,553 independent images from Chile. Compared to images with a slide-level diagnosis <intestinal metaplasia (IM), the betas were 0.07 (95% confidence interval [CI]: 0.03-0.11) for IM, 0.10 (0.04-0.16) for low-grade dysplasia (LGD), 0.18 (0.085-0.28) for high-grade dysplasia (HGD), and 0.33 (0.21-0.46) for GBC ($p < 0.001$). Making pairwise comparisons across the spectrum of disease, the p-values were 0.002 for IM vs. <IM, 0.4 for LGD vs. IM, 0.1 for HGD vs. LGD, and 0.05 for GBC vs. HGD. **Conclusion:** The SCD algorithm showed robust performance on gallbladder H&E slide images from Chile. The increase in SCD across the spectrum of gallbladder disease suggests that SCD could help characterize micro-environmental changes across disease progression and support investigation of associations with GBC risk factors.



Disclosures: Jill Koshiol:Nothing to Disclose, Ilona Argirion:Nothing to Disclose, Karun Mutreja:Nothing to Disclose, Scott Lawrence:Nothing to Disclose, Petra Lenz:Nothing to Disclose, Rime Jebai:Nothing to Disclose, Allan Hildesheim:Nothing to Disclose, Ruth Pfeiffer:Nothing to Disclose, Catterina Ferreccio:Nothing to Disclose, Juan Araya:Nothing to Disclose.

4282 | METABOLIC DYSFUNCTION–ASSOCIATED STEATOTIC LIVER DISEASE IS ASSOCIATED WITH HIGHER MORTALITY AND HEPATIC DECOMPENSATION IN HEPATOCELLULAR CARCINOMA PATIENTS TREATED WITH IMMUNE CHECKPOINT INHIBITORS: A PROPENSITY-MATCHED ANALYSIS OF A FEDERATED HEALTH NETWORK

Mazen Elsheikh[1] Osamah Salim[2] Hamza Salim[3] Sherry Fares[1] Karim Adhem[1] Mohamad Ali Ibrahim[1] Youseph Karouni[1] Nicholas Thomas[1] Krishna Chandrasekhara[1] Prasun Jalal[1], [1]Baylor College of Medicine, [2]Sam Houston State University College of Osteopathic

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Background: Immune checkpoint inhibitors (ICIs) are standard care for advanced hepatocellular carcinoma (HCC), but emerging evidence suggests that HCC arising from metabolic dysfunction-associated steatotic liver disease (MASLD) responds poorly to ICIs, owing to a dysbiosis-shaped, pre-exhausted immune microenvironment. Large real-world comparative data remain limited. We compared mortality and hepatic decompensation in MASLD-HCC versus non-MASLD HCC. **Methods:** We conducted a retrospective cohort study using the TriNetX Research Network (112 healthcare organizations). Adults with HCC who initiated an ICI (atezolizumab, durvalumab, tremelimumab, nivolumab, pembrolizumab, or ipilimumab) after HCC diagnosis were identified. The MASLD-HCC cohort required ICD-10 diagnostic codes for nonalcoholic steatohepatitis (K75.81) or hepatic steatosis (K76.0) and excluded viral, alcohol-related, autoimmune, cholestatic, and hereditary liver disease; the comparator was ICI-treated HCC without these steatotic codes. Patients receiving chemotherapy, tyrosine kinase inhibitors, or radiotherapy after ICI initiation were excluded to isolate ICI-based treatment. Cohorts were 1:1 propensity score-matched on demographics, cardiometabolic/hepatic comorbidities, and portal vein thrombosis. Follow-up began one day after first ICI administration, and all-cause mortality and hepatic decompensation (ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, bleeding esophageal varices, or hepatorenal syndrome) were assessed using risk ratios (RR) and Kaplan-Meier hazard ratios (HR). **Results:** Of 4,879 ICI-treated HCC patients, 578 had MASLD-HCC and 4,301 had non-MASLD HCC. After matching, 541 patients per cohort were balanced (all standardized differences <0.1; similar median follow-up, 213 vs 204 days). MASLD-HCC patients had significantly higher all-cause mortality (59.1% vs 48.1%; RR 1.23, 95% CI 1.10-1.38; $p<0.001$) and shorter median survival (241 vs 360 days; HR 1.25, 95% CI 1.06-1.47; log-rank $p=0.007$). Hepatic decompensation was also more frequent in MASLD-HCC (51.8% vs 43.8%; RR 1.18, 95% CI 1.04-1.34; $p=0.009$), with shorter median time to decompensation (168 vs 326 days; HR 1.24, 95% CI 1.05-1.48; log-rank $p=0.013$). **Conclusion:** In this large, propensity-matched real-world cohort, MASLD-HCC patients treated with ICIs had significantly higher mortality and more frequent, earlier hepatic decompensation than non-MASLD HCC patients. These findings support the hypothesis that the MASLD immunometabolic milieu limits ICI efficacy and underscore the need for etiology-specific strategies, including microbiome-targeted approaches.

Table 1. Propensity-matched cohort characteristics and clinical outcomes: MASLD-HCC vs non-MASLD HCC treated with immune checkpoint inhibitors

TriNetX Research Network (112 healthcare organizations). 1:1 propensity score matching: 541 patients per cohort. Median follow-up after matching: 213 days (MASLD-HCC) vs 204 days (non-MASLD HCC).

A. Selected baseline characteristics after 1:1 propensity score matching

Characteristic	MASLD-HCC (n=541)	Non-MASLD HCC (n=541)	P value	Std. diff.
Age at index, mean (SD), years	68.7 (10.2)	68.8 (9.9)	0.869	0.010
Male sex	68.6%	68.2%	0.896	0.008
White race	77.6%	77.3%	0.884	0.009
Type 2 diabetes mellitus	66.0%	66.9%	0.746	0.020
Overweight / obesity	47.5%	47.7%	0.951	0.004
Dyslipidemia	60.6%	59.3%	0.619	0.030
Essential hypertension	82.8%	81.0%	0.478	0.047
Hepatic fibrosis / cirrhosis	88.0%	89.5%	0.468	0.032
Portal vein thrombosis	22.7%	21.3%	0.557	0.036
Chronic ischemic heart disease	43.3%	42.1%	0.712	0.022
Acute myocardial infarction	7.9%	7.0%	0.564	0.035
Heart failure	17.9%	17.6%	0.936	0.005
Cardiomyopathy	5.0%	4.8%	0.888	0.009
Hypertensive heart disease	13.1%	14.0%	0.657	0.021
Hypertensive chronic kidney disease	14.6%	13.5%	0.602	0.022
Atherosclerosis	17.9%	17.8%	0.974	0.010
Cerebral infarction	3.3%	3.5%	1.000	<0.001
Occlusion / stenosis of cerebral arteries	3.3%	3.8%	1.000	<0.001

B. Clinical outcomes after propensity score matching (time window: 1 day post-index onward)

Outcome / metric	MASLD-HCC (n=541)	Non-MASLD HCC (n=541)	Effect estimate (95% CI), P value
All-cause mortality			
Patients with event, n (risk)	320 (59.1%)	260 (48.1%)	Risk difference 11.1% (5.2-17.0)
Risk ratio			1.23 (1.10-1.38); P < 0.001
Odds ratio			1.57 (1.23-1.99)
Median survival, days	241	360	
Hazard ratio (Kaplan-Meier)			1.25 (1.06-1.47); log-rank P = 0.007
Hepatic decompensation (composite)			
Patients with event, n (risk)	280 (51.8%)	237 (43.8%)	Risk difference 7.9% (2.0-13.5)
Risk ratio			1.18 (1.04-1.34); P = 0.009
Odds ratio			1.38 (1.08-1.75)
Median time to event, days	168	326	
Hazard ratio (Kaplan-Meier)			1.24 (1.05-1.48); log-rank P = 0.013

HCC, hepatocellular carcinoma; MASLD, metabolic dysfunction-associated steatotic liver disease; ICI, immune checkpoint inhibitor; PSM, propensity score matching; SD, standard deviation; CI, confidence interval; RR, risk ratio; HR, hazard ratio; OR, odds ratio; ascites, hepatic encephalopathy, hepatorenal syndrome, spontaneous bacterial peritonitis, bleeding esophageal varices, or hepatorenal syndrome. ICI initiation were excluded. The composite outcome comprises ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, bleeding esophageal varices, or hepatorenal syndrome. All standardized differences after matching were <0.1, indicating adequate covariate balance.

Disclosures: Mazen Elsheikh:Nothing to Disclose, Osamah Salim:Nothing to Disclose, Hamza Salim: Nothing to Disclose, Sherry Fares:Nothing to Disclose, Karim Adhem:Nothing to Disclose, Mohamad Ali Ibrahim:Nothing to Disclose, Youseph Karouni:Nothing to Disclose, Nicholas Thomas:Nothing to Disclose, Krishna Chandrasekhara:Nothing to Disclose, Prasun Jalal:Mallinckrodt Pharmaceuticals: Advisor, Madrigal: Grant/Research Support, Ipsen: Grant/Research Support, mirum: Advisor.

4283 | SEX DIFFERENCES IN ALL-CAUSE, LIVER-RELATED AND NONLIVER-RELATED MORTALITY AMONG PATIENTS WITH HEPATOCELLULAR CARCINOMA: A POPULATION-BASED LONGITUDINAL STUDY

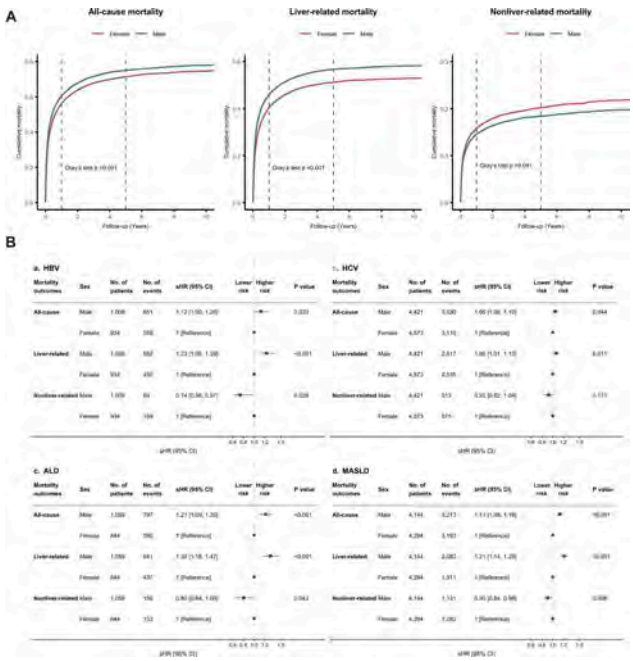
Bowu Chen[1] Xiaonan Su[2] Danfeng Ren[3] Ramsey Cheung[4] Mindie Nguyen[4], [1]Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, [2]The First Affiliated Hospital, Zhejiang University School of Medicine, [3]The First Affiliated Hospital of Xi'an Jiaotong University, [4]Stanford University Medical Center

Background: Males generally have higher HCC risk across most chronic liver diseases. However, sex differences in clinical outcomes after HCC diagnosis

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are less well characterized. This study aimed to fill in this gap by comparing long-term all-cause, liver-related, and nonliver-related mortality between male and female patients with HCC. **Methods:** We conducted a population-based retrospective cohort study of patients with HCC who had at least one hospitalization for any cause from the California Department of Health Care Access and Information database from 1/2005 to 12/2019 using 1:1 propensity score matching (PSM, caliper 0.1) to balance background differences between the male and female study groups. We evaluated long-term mortality obtained from California State Death Statistical Master File records which included deaths occurring in both inpatient and outpatient settings. Associations between sex and mortality were evaluated using Fine-Gray competing risk models (competing events: liver transplantation (LT) or alternate cause of death as applicable). Robustness was assessed with demographic (age, race, ethnicity) and clinical (etiology, comorbidity, cirrhosis, liver decompensation) subgroup analyses and multiple sensitivity analyses including stricter-caliper (0.01) PSM, inverse probability of treatment weighting (IPTW) as alternate matching method, exclusion of deaths within 3 months, and analyses without treating LT as a competing event. **Results:** We analyzed a total of 44,340 adult patients with HCC (29.1% female) after excluding HIV infection, LT before HCC, or residence outside California. PSM yielded 12,569 female-male pairs with balanced baseline characteristics (standardized mean difference [SMD] $\leq$ 0.1). Compared with females, males had higher 5-year cumulative all-cause (75.1%, 95% CI 74.3–75.9 vs. 71.4%, 95% CI 70.5–72.2) and liver-related (56.7%, 95% CI 55.8–57.6 vs. 51.2%, 95% CI 50.3–52.1) mortality, but lower nonliver-related mortality (18.4%, 95% CI 17.7–19.1 vs. 20.2%, 95% CI 19.5–20.9) (Figure 1A). In Fine-Gray models, male sex was associated with higher risks of all-cause (subdistribution hazard ratio [sHR] 1.12, 95% CI 1.09–1.15) and liver-related mortality (sHR 1.18, 95% CI 1.14–1.22), but lower risk of nonliver-related mortality (sHR 0.89, 95% CI 0.85–0.95), all $P < 0.001$. Findings were consistent across sensitivity and subgroup analyses. Additionally, disparities varied by etiology with the higher sHR for liver-related mortality in males with ALD (sHR 1.30), HBV (sHR 1.23), and MASLD (sHR 1.21) and lowest with HCV (sHR 1.06) (Figure 1B). **Conclusion:** Among patients with HCC, male patients had higher all-cause and liver-related mortality while females had higher nonliver-related mortality. Sex disparities should be taken into consideration in future disease monitoring and treatment decision-making for patients with HCC.



Disclosures: Bowu Chen:Nothing to Disclose, Xiaonan Su:Nothing to Disclose, Danfeng Ren:Nothing to Disclose, Ramsey Cheung:Nothing to Disclose, Mindie Nguyen:Pfizer, Astra Zeneca, Aligos, GSK, Delfi, Innogen, Exact Sci: Grant/Research Support, GSK: Advisor.

4284 | ASSOCIATION OF LEAN MASLD WITH CLINICAL PROGNOSIS IN HEPATOCELLULAR CARCINOMA AFTER CURATIVE RESECTION IN MASLD AND/OR HEPATITIS B VIRUS PATIENTS

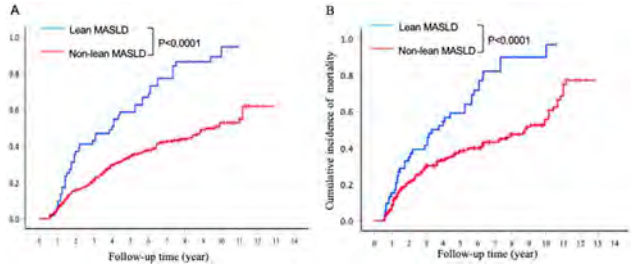
Chih Wen Lin[1] Yaw-Sen Chen[2] Yu-Wei Huang[2] Steven Lin[3] James Lin[4] Yao-Chun Hsu[2] Chih-Che Lin[5] Ming-Lung Yu[6], [1]Lin Da Clinic and E-Da Hospital, I-Shou University, [2]E-Da Hospital, I-Shou University, [3]New York University, [4]Wentworth institute of technology, [5]Kaohsiung Chang Gung Memorial Hospital, [6]Kaohsiung Medical University

Background: The prevalence of metabolic dysfunction–associated steatotic liver disease (MASLD) is increasing in worldwide. The prevalence of concomitant MASLD and hepatitis B virus (HBV)-related hepatocellular carcinoma (HCC) is also increasing. Our previous study showed patients with concomitant MASLD and HBV are at a significantly greater risk of HCC recurrence and mortality after curative hepatectomy than those with MASLD or HBV alone. Patients with MASLD are at increased risk of both hepatic and extrahepatic adverse outcomes.

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However, the evidence regarding lean MASLD and hepatic prognosis remains controversial. This study explored the effect of lean MASLD on clinicopathological features and long-term clinical prognoses in patients with MASLD-related and/or HBV-related HCC after curative hepatectomy. **Methods:** The study retrospectively collected the data of 653 patients with HCC who had undergone curative hepatectomy between 2011 and 2022. We assessed the association of histologically confirmed MASLD. The endpoint is HCC recurrence and mortality after curative resection. Lean MASLD was defined as body mass index (BMI) < 23 kg/m². **Results:** Of 653 patients, 320 (49.0%), 103 (15.8%), and 230 (35.2%) had concomitant MASLD and HBV, MASLD only, and HBV only, respectively. The median follow-up period was 5.1 years. Patients with concomitant MASLD and HBV were at a significantly increased risk of HCC recurrence (P = 0.013 and P = 0.041) and mortality (P = 0.044 and P = 0.026) than those with MASLD or HBV alone. Fifth-three patients (12.5%) were lean MASLD. In multivariable analyses, lean MASLD, GOT > 40 serum aspartate aminotransferase ≥ 40 U/L, tumor size ≥ 5 cm, Lymph node invasion, and cirrhosis were significantly associated with increased HCC recurrence. Furthermore, lean MASLD, type 2 diabetes mellitus, tumor size ≥ 5 cm, Lymph node invasion, microvascular invasion, AJCC stage III-IV and tumor recurrence were significantly associated with increased mortality. Patients with lean MASLD were at a significantly increased risk of HCC recurrence (P < 0.0001) and mortality (P < 0.0001) than those with non-lean MASLD. **Conclusion:** Patients with lean MASLD were at a significantly increased risk of HCC recurrence and mortality than those with non-lean MASLD in MASLD and/or HBV related HCC patients after curative hepatectomy.



Disclosures: Chih Wen Lin:Nothing to Disclose, Yaw-Sen Chen:Nothing to Disclose, Yu-Wei Huang:Nothing to Disclose, Steven Lin:Nothing to Disclose, James Lin: Nothing to Disclose, Yao-Chun Hsu:Gilead Sciences: Grant/Research Support, Gilead Sciences: Advisor, Sysmex: Advisor, Abbvie: Speaking and Teaching, Bristol Myers Squibb: Speaking and Teaching, Gilead Sciences: Speaking and Teaching, Roch: Speaking and Teaching, Grifols: Speaking and Teaching, GlaxoSmithKline: Consultant, AusperBio: Consultant, Chih-Che Lin:Nothing to Disclose, Ming-Lung Yu:Abbvie, Gilead and Roche diagnostics.: Grant/Research Support, Abbott, Abbvie, Gilead, Roche and Roche diagnostics: Consultant, Abbvie, BMS, Gilead, Roche and Roche diagnostics: Speaking and Teaching.

4285 | ENDOTHELIAL REMODELING AND A CORE9 VASCULAR-IMMUNE SIGNATURE DURING THE CIRRHOSIS-TO-HCC TRANSITION

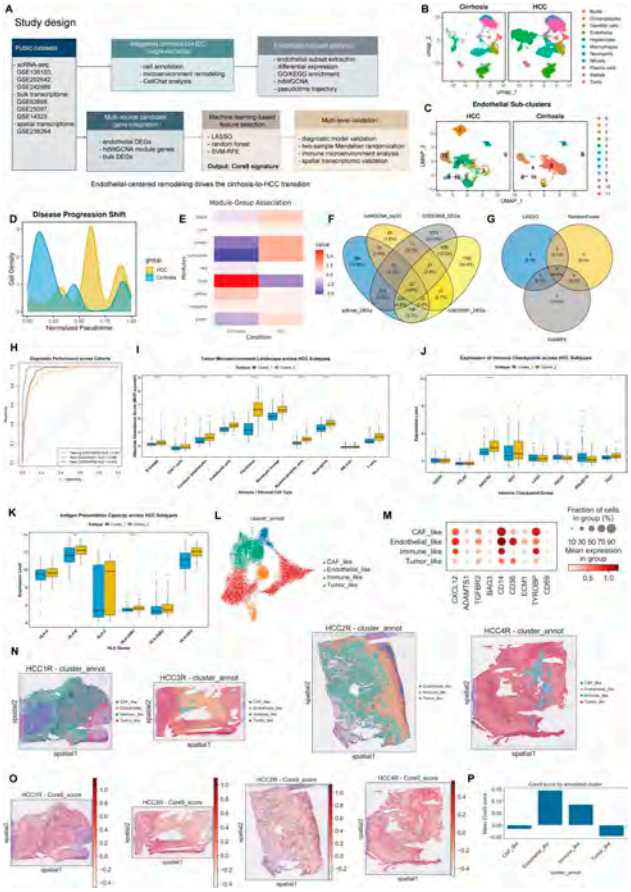
Jiahao Yuan[1] Min Cong[1], [1]Liver Research Center, Beijing Friendship Hospital, Capital Medical University

Background: Hepatocellular carcinoma (HCC) commonly develops in cirrhotic liver, but endothelial programs accompanying malignant transition remain poorly defined. We aimed to characterize endothelial remodeling across the cirrhosis-to-HCC continuum and identify an endothelial-associated signature with diagnostic and microenvironmental relevance. **Methods:** Three public human liver single-cell RNA-seq datasets were integrated to build a cirrhosis-to-HCC atlas. Endothelial cells were extracted for subclustering, differential expression, cell-cell communication, hdWGCNA, and pseudotime analyses. Candidate genes were prioritized by integrating endothelial single-cell signals, co-expression modules, and two bulk transcriptomic cohorts, followed by LASSO, random forest, and SVM-RFE feature selection. Spatial localization, Mendelian randomization (MR)-based prioritization, diagnostic performance, and tumor microenvironment associations were evaluated in independent datasets. **Results:** The integrated atlas revealed marked remodeling of the cirrhosis-to-HCC microenvironment, with endothelial cells showing compositional expansion and transcriptional displacement. Endothelial reclustering resolved inflammatory, sinusoidal, lymphatic-like, metabolic, and proliferative states. hdWGCNA and pseudotime analyses indicated disease-biased co-expression modules and progressive endothelial state transitions. Multi-source integration and machine-learning convergence identified a nine-gene endothelial-associated Core9 signature comprising CXCL12, ADAMTS1, TGFBR2, BAG3, CD14, CD36, ECM1, TYROBP, and CD69. MR-based prioritization highlighted CD36 and CD69 as dynamic candidates with genetic support. Spatial transcriptomic validation localized the Core9 program preferentially to endothelial-like niches in HCC tissues. The Core9

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model showed strong diagnostic performance across cohorts, with AUCs of 0.927, 0.989, and 0.953. Core9-defined HCC subtypes differed in immune infiltration, immune checkpoint expression, and HLA-related antigen-presentation profiles. **Conclusion:** Endothelial remodeling is a consistent feature of cirrhosis-to-HCC progression. The Core9 signature captures a spatially enriched vascular-immune remodeling program with diagnostic value and potential utility for microenvironmental stratification in HCC.



Disclosures: Jiahao Yuan:Nothing to Disclose, Min Cong:Nothing to Disclose.

4286 | COMBINED RAS, TP53, AND SMAD4 MUTATIONS AS A PROGNOSTIC MODEL FOR PATIENTS UNDERGOING RESECTION OF COLORECTAL LIVER METASTASES: A SYSTEMATIC REVIEW AND META-ANALYSIS

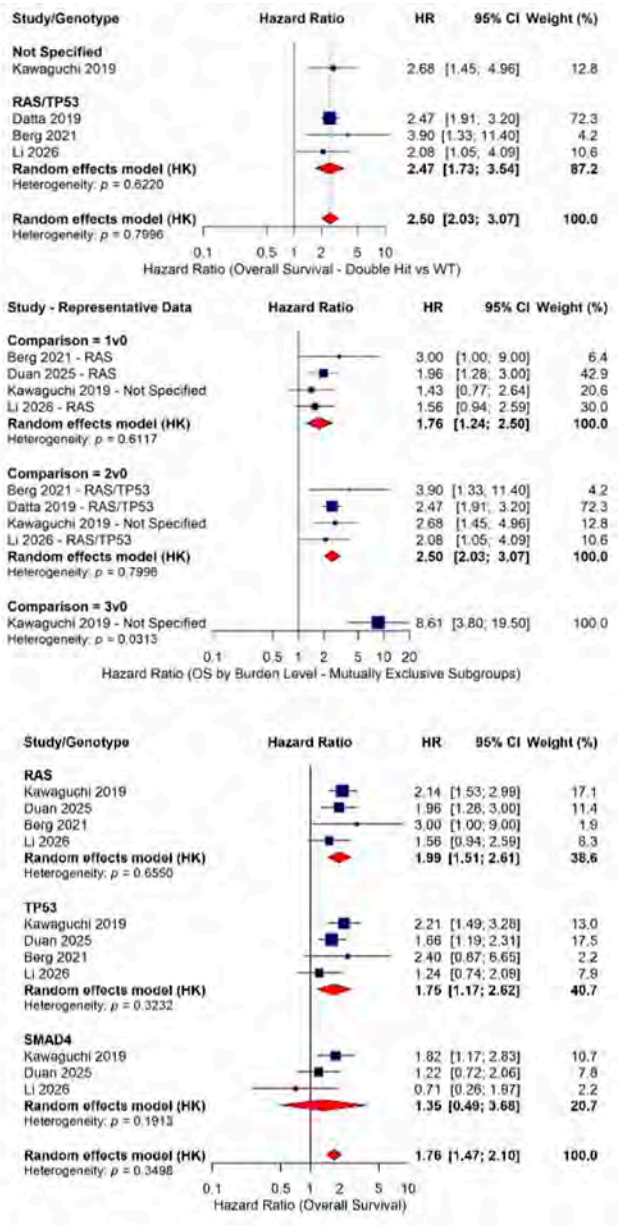
Ahmed Sayed Ahmed[1] Abdullah Ahmed[2] Mariam Ismail[3] Asmaa Soliman[4] Sanaa Farahat[3] Sapana Verma[1] Reham Zayed[5] Elise Hokr[1] Erlind Erlind[1] Kyungran Justina Cho[6] Chase Wehrle[1] Khalil Mazhar[1] Kim Jaekeun[1] Federico Aucejo[1], [1]Department of Surgery Transplantation Center, The Cleveland Clinic Foundation, OH, USA, [2]Hameed Latif Teaching Hospital, Lahore, Pakistan, [3]Faculty of Medicine, Delta University for Science and technology, Gamasa, Egypt, [4]Faculty of Medicine, Zagazig University, Sharqia, Egypt, [5]Department of Gastroenterology, Hepatology and Nutrition, The Cleveland Clinic Foundation, OH, USA, [6]Department of Gastroenterology, The Cleveland Clinic Foundation, OH, USA

Background: Predicting outcomes after resection of colorectal liver metastases (CRLM) remains difficult, and existing prognostic tools do not adequately account for combined mutational burden. RAS, TP53, and SMAD4 mutations each carry prognostic weight individually, but their cumulative effect has not been systematically quantified. This meta-analysis aimed to define the prognostic impact of combined RAS, TP53, and SMAD4 mutations in patients undergoing curative-intent CRLM resection. **Methods:** A systematic review and meta-analysis were conducted in accordance with PRISMA guidelines, with searches performed across PubMed, Scopus, and Embase. Studies were eligible if they reported hazard ratios (HR) for overall survival (OS) or recurrence-free survival (RFS) according to somatic mutational status of RAS, TP53, and/or SMAD4 in patients undergoing curative-intent CRLM resection. Patients were categorized by mutational burden: single-hit (1 mutation vs. wild-type), double-hit (2 mutations vs. wild-type), or triple-hit (3 mutations vs. wild-type). Pooled HRs were derived using a random-effects model with Hartung-Knapp adjustment. Heterogeneity was quantified using the I^2 statistic. **Results:** Five studies met inclusion criteria. A stepwise increase in mortality risk with rising mutational burden was observed across all analyses ($p < 0.0001$). For OS, the pooled HR for single-hit mutations was 1.56 (95% CI 1.28–1.91, $I^2 = 0\%$), rising to 2.50 for double-hit genotypes (95% CI 2.03–3.07, $I^2 = 0\%$), and peaking in the triple-hit group (HR 8.61, 95% CI 3.80–19.50; Kawaguchi et al.). In genotype-specific analysis of single-hit mutations, RAS (HR 1.99, 95% CI 1.51–2.61) and TP53 (HR 1.75, 95% CI 1.17–2.62) were independent predictors of worse OS, while isolated SMAD4 mutation did not reach significance (HR 1.35, 95% CI 0.49–3.68). A parallel escalating pattern was seen for RFS in the Kawaguchi cohort, with HRs of 1.18, 1.81, and 3.72 for 1-hit, 2-hit, and 3-hit genotypes, respectively. Heterogeneity was low across the primary burden analyses ($I^2 = 0\%$). **Conclusion:** Combined RAS, TP53, and SMAD4 mutational burden shows a consistent, stepwise relationship with survival after CRLM resection. The strength of this dose-response pattern across studies supports incorporating multi-gene mutational profiling into clinical prognostic models, with potential implications for patient

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selection and treatment planning.



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4287 | GENOMIC DETERMINANTS OF RECURRENCE AFTER CURATIVE-INTENT THERAPY FOR HEPATOCELLULAR CARCINOM

Laia Aceituno Sierra[1] Javier Ruiz Ramirez[2] Elena Valenzi[3] Giselle Caballero[4] Giselle Caballero[4] Shiva Babakhani[4] Roxana Bucur[4] Trevor Pugh[2] Anand Ghanekar[4] Arndt Vogel[5], [1]Toronto General Hospital, University Health Network, [2]Princess Margaret Cancer Centre, University Health Network, Toronto, Ontario, Canada, [3]Division of Gastroenterology and Hepatology, Toronto General Hospital, Toronto, Canada, [4]University Health Network, HPB Surgical Oncology, Toronto, Ontario, Canada, [5]University of Toronto

Background: Recurrence after curative-intent therapy for hepatocellular carcinoma (HCC) remains a major challenge, and current risk stratification is largely clinicopathologic. We aimed to define genomic predictors of recurrence and characterize biological differences between resection and transplantation using an integrated gene- and pathway-level framework. **Methods:** We analyzed 158 patients with HCC undergoing resection (87) or liver transplantation (71) with tumor genomic profiling. Gene-level associations with recurrence were assessed using Fisher's exact test with Benjamini–Hochberg correction. Recurrence-free survival (RFS) was evaluated using Kaplan–Meier and Cox proportional hazards models. Pathway-level analyses were performed using curated oncogenic pathways. **Results:** Among the included patients, the median age was 63.7 years, and 83.2% were male. Recurrence occurred in 27.2% of cases and was more frequent following resection than transplantation (36.8% vs. 15.5%, $p = 0.004$). The most commonly observed genomic alterations were TERT (46.8%), TP53 (43.0%), and MAP2K4 (29.1%). Distinct genomic differences by treatment modality were evident, with *TP53*, *FLCN*, and *MAP2K4* alterations enriched in resection specimens. At the pathway level, RTK/growth factor, RAS/MAPK, Hippo, and PI3K/AKT/mTOR signaling were significantly enriched in resection (FDR $q < 0.1$), although no pathway independently predicted recurrence after multiple testing correction. TP53 alterations (43%) were associated with worse RFS (log-rank $p = 0.042$), with a particularly strong effect observed in the transplant subgroup ($p = 0.014$). In multivariable analysis, a combined TP53 + ARID1B model provided the best prediction of recurrence (HR 2.13, 95% CI 1.07–4.21, $p = 0.03$; model concordance 0.66). **Conclusion:** Preliminary results show that

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TP53-driven biology, particularly when co-occurring with ARID1B alterations, might help to identify patients at increased risk of recurrence. Further analysis needs to be completed.

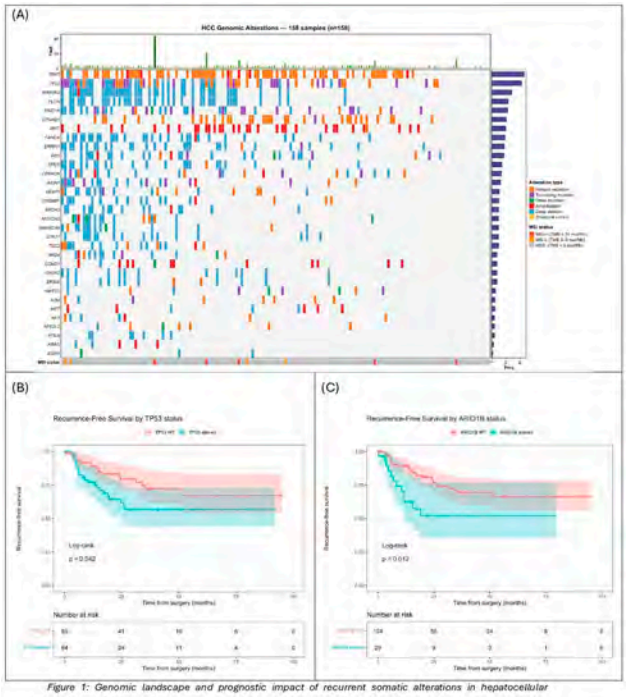


Figure 1: Genomic landscape and prognostic impact of recurrent somatic alterations in hepatocellular carcinoma. (A) Oncoprint representation of the most frequently altered showing mutation types, copy number alterations, tumor mutational burden, and microsatellite instability status.(B) Kaplan–Meier analysis of recurrence-free survival according to TP53 alteration status. (C) Kaplan–Meier of recurrence-free survival according to ARID1B alteration status.

Disclosures: Laia Aceituno Sierra:Nothing to Disclose, Javier Ruiz Ramirez:Nothing to Disclose, Elena Valenzi:Nothing to Disclose, Giselle Caballero:Nothing to Disclose, Nothing to Disclose, Giselle Caballero: Nothing to Disclose, Nothing to Disclose, Shiva Babakhani:Nothing to Disclose, Roxana Bucur:Nothing to Disclose, Trevor Pugh:Nothing to Disclose, Anand Ghanekar:Nothing to Disclose, Arndt Vogel:Roche: Advisor.

4288 | CLINICAL IMPACT OF TP53 MUTATIONS AND TUMOR-INFILTRATING LYMPHOCYTES IN UNRESECTABLE INTRAHEPATIC CHOLANGIOCARCINOMA

Hiroki Inada[1] Daiki Maeda[1] Fumiya Otsuka[1] Satoshi Narahara[1] Hideaki Miyamoto[1] Takehisa Watanabe[1] Katsuya Nagaoka[1] Hiroko Setoyama[1] Haruki Uojima[1] Yasuhito Tanaka[1], [1]Kumamoto University

Background: The clinical utility of predictive biomarkers for immune checkpoint inhibitor (ICI)-based combination therapy in unresectable intrahepatic cholangiocarcinoma (ICC) remains unclear. We previously reported that TP53 mutations influence the tumor immune microenvironment and serve as a prognostic factor in ICC patients treated with ICIs. In this study, we investigated the tumor cell characteristics driven by TP53 mutations and evaluated tumor-infiltrating lymphocytes (TILs). **Methods:** We retrospectively analyzed 41 patients with ICC who received gemcitabine, cisplatin, and durvalumab (GCD) or GC plus pembrolizumab (GCP) at our institution and affiliated hospitals between December 2022 and March 2026. TILs were evaluated using hematoxylin and eosin staining and classified into three groups: High (>40%), Intermediate (11–40%), and Low (<10%). Spatial transcriptomic analysis using Xenium was performed to characterize TP53-mutant tumor cells. **Results:** The median age was 72 years (range, 44–83 years). Treatment regimens included GCD in 35 patients and GCP in 6 patients, and 29 patients (64%) received first-line therapy. Comprehensive genomic profiling was performed in 37 patients (90%). TIL classification was High in 3 patients (7%), Intermediate in 8 (20%), Low in 26 (63%), and unevaluable in 4 (10%). Median progression-free survival (PFS) was 21.2 months in the High group, 3.5 months in the Intermediate group, and 5.4 months in the Low group, demonstrating favorable PFS in the TIL-High group. Median PFS in TP53-mutant ICC was 4.1 months (95% CI, 2.5–6.3), which was significantly shorter than that in TP53 wild-type ICC (6.9 months; 95% CI, 4.4–10.7; $p = 0.021$). Spatial transcriptomic analysis revealed enrichment of cell cycle-related pathways, including HALLMARK_G2M_CHECKPOINT and HALLMARK_E2F_TARGETS, whereas inflammatory response pathways were suppressed in TP53-mutant ICC. Furthermore, SOX2 expression was significantly elevated in TP53-mutant tumor cells ($p < 0.001$), suggesting activation of cancer stem cell programs. **Conclusion:** TIL-High ICC cases demonstrated favorable PFS following ICI-based combination therapy. TP53-mutant ICC showed activation of cell cycle- and cancer stem cell-related pathways along with suppression of inflammatory response-related genes, suggesting that these tumor cell characteristics may contribute to impaired antitumor immunity and resistance to ICI therapy.

Disclosures: Hiroki Inada:Nothing to Disclose, Daiki Maeda:Nothing to Disclose, Fumiya Otsuka:Nothing to

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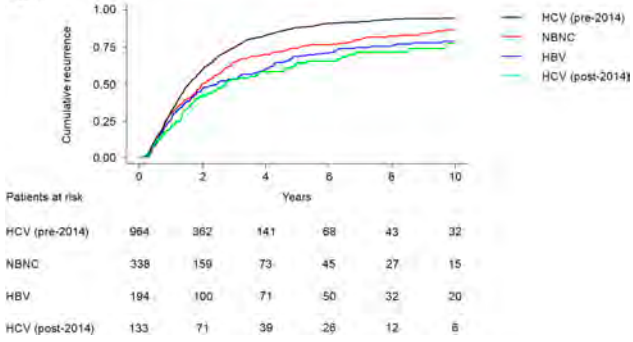
Disclose, Satoshi Narahara:Nothing to Disclose, Hideaki Miyamoto:Nothing to Disclose, Takehisa Watanabe: Nothing to Disclose, Katsuya Nagaoka:Nothing to Disclose, Hiroko Setoyama:Nothing to Disclose, Haruki Uojima:Nothing to Disclose, Yasuhito Tanaka:Nothing to Disclose.

4289 | EVOLVING LANDSCAPE OF HEPATOCELLULAR CARCINOMA RECURRENCE AFTER CURATIVE RADIOFREQUENCY ABLATION IN THE ANTIVIRAL ERA: AN ETIOLOGY- AND ERA-STRATIFIED HAZARD ANALYSIS

Makoto Moriyama[1] Naoto Fujiwara[2] Takuma Nakatsuka[1] Tatsuya Minami[1] Mitsuhiro Fujishiro[1] Ryosuke Tateishi[1], [1]The University of Tokyo, [2]Mie university

Background: Following the introduction of direct-acting antivirals (DAAs) and the widespread use of nucleos(t)ide analogues (NAs), the etiologic landscape of hepatocellular carcinoma (HCC) has shifted toward non-viral etiologies. However, comparative long-term recurrence patterns among non-B, non-C (NBNC), hepatitis B virus (HBV), and hepatitis C virus (HCV)-related HCC in the DAA era remain poorly defined. **Methods:** In this single-center, retrospective study, consecutive patients who underwent radiofrequency ablation (RFA) as initial curative treatment for HCC (complete response on imaging) between January 2000 and December 2023 were enrolled. Patients were stratified into four groups: NBNC, HBV (the majority of whom were on NA therapy either before or after initial HCC treatment), pre-2014 HCV, and post-2014 HCV (the era of approved interferon-free DAA regimens in Japan). Cumulative recurrence rates were estimated using the Kaplan-Meier method and compared by pairwise log-rank tests with Bonferroni adjustment, using NBNC as the reference group. Annualized recurrence hazard rates were estimated using natural cubic splines weighted by the number at risk. **Results:** Among 1,629 patients who underwent curative RFA (NBNC n = 338; HBV n = 194; pre-2014 HCV n = 964; post-2014 HCV n = 133), 1,340 recurrences were observed over a median follow-up of 1.67 years. Cumulative recurrence rates at 5/10 years were: 88.1%/94.3% in pre-2014 HCV, 74.2%/86.6% in NBNC, 68.4%/78.6% in HBV, and 62.8%/77.0% in post-2014 HCV. Compared with NBNC, pre-2014 HCV had higher recurrence ($p = 1.3 \times 10^{-5}$), whereas post-2014 HCV had lower recurrence ($p = 0.026$); HBV showed no significant difference ($p = 0.066$). Within the HCV cohort, the post-2014 cohort had substantially lower cumulative recurrence than the pre-2014 cohort ($p = 2.0 \times 10^{-8}$). Annualized hazard analysis showed that the pre-2014 HCV cohort displayed a biphasic trajectory, with an initial peak of 64.7%/year at 2.5 years and a secondary rise to 23.8%/year at 7 years. NBNC exhibited a similar biphasic pattern, with an early peak of 42.1%/year at 2.2 years and a late rise to 16.2%/year at 7 years. In contrast, the post-2014 HCV (peak 34.9%/year at 1.8 years; 5-year hazard 12.7%/year) and HBV (peak 27.3%/year at 1.6 years; 5-year hazard 14.1%/year) cohorts showed attenuated, unimodal trajectories with progressive decline. **Conclusion:** The introduction of DAAs has significantly reduced the cumulative recurrence of HCV-related HCC. In the DAA era, however, NBNC-related HCC now exhibits a higher cumulative recurrence rate than DAA-era HCV-related HCC. Annualized hazard analysis further revealed that NBNC-related HCC displays a bimodal recurrence pattern resembling that of pre-DAA HCV-related HCC, underscoring the need for sustained long-term surveillance even in patients without early recurrence.

Figure



Disclosures: Makoto Moriyama:ASKA Pharmaceutical Co., Ltd.: Speaking and Teaching, Lilly: Speaking and Teaching, AstraZeneca: Speaking and Teaching, Mitsubishi Tanabe Pharma: Speaking and Teaching, Novo Nordisk Pharma: Speaking and Teaching, Naoto Fujiwara: Nothing to Disclose, Takuma Nakatsuka:Nothing to Disclose, Tatsuya Minami:Asahi Kasei Pharma Corporation: Speaking and Teaching, AstraZeneca K.K.: Speaking and Teaching, Mitsuhiro Fujishiro:Nothing to Disclose, Ryosuke Tateishi:Bristol Myers Squibb: Speaking and Teaching, AstraZeneca: Speaking and Teaching, Abbvie: Speaking and Teaching, Eisai: Speaking and Teaching, Canon: Speaking and Teaching, Gilead: Speaking and Teaching, Medtronic: Speaking and Teaching, Novo Nordisk Pharma: Speaking and Teaching, Ono Pharmaceutical: Speaking and Teaching, Chugai: Speaking and

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Teaching, Japan Lifeline: Speaking and Teaching, Fujirebio: Speaking and Teaching, STARmed: Speaking and Teaching, Daiichi-Sankyo: Speaking and Teaching, Sawai: Speaking and Teaching.

4290 | DIVERGENT AGE-STRATIFIED TRENDS IN HEPATOCELLULAR CARCINOMA MORTALITY IN THE UNITED STATES, 1999–2024

Moksha Prasoona Avvaru[1] Shashank Trivedi[2] Mythily Rao Ponaganti[3] Sri Ram Charan Gundapaneni[4] Suhas Kataveni[5] Gaurav Sharma[6], [1]Harnett Health, [2]Rochester General Hospital, NY, [3]SBH health system, [4]UCF/HCA Florida Ocala Hospital, [5]HCA Citrus, Florida, [6]JNU Medical School, Jaipur

Background: The epidemiology of hepatocellular carcinoma (HCC) in the United States has evolved substantially over the past two decades amid changing hepatitis C virus prevalence, advances in antiviral therapy, and increasing metabolic liver disease burden. However, contemporary age-stratified national mortality trends remain incompletely characterized. **Methods:** We performed a retrospective serial cross-sectional analysis using the CDC WONDER Multiple Cause of Death database from 1999–2024. Deaths with HCC listed as the underlying cause of death were identified using ICD-10 code C22.0. Age-adjusted mortality rates (AAMRs) per 100,000 population were analyzed for adults aged <55 (25-54) years and ≥ 55 years. Temporal trends were evaluated using Joinpoint regression analysis with calculation of annual percent changes (APCs) and corresponding 95% confidence intervals. **Results:** HCC mortality trajectories diverged substantially by age beginning around 2010. Among adults aged <55 years, mortality initially increased from 1999–2004 (APC +4.20%, $p=0.017$), followed by a sustained decline from 2010–2024 (APC −5.97%, $p<0.001$). Age-adjusted mortality rates in this group decreased from a peak of 1.18 per 100,000 in 2005 to 0.48 per 100,000 in 2024. In contrast, adults aged ≥ 55 years demonstrated persistent increases in HCC mortality throughout the study period, including continued growth after 2014. Mortality rates in this cohort increased from 6.72 per 100,000 in 1999 to 12.47 per 100,000 in 2024, with ongoing significant increases observed from 2017–2024 (APC +0.91%, $p=0.002$). **Conclusion:** HCC mortality trends in the United States have diverged markedly by age over the past two decades. While adults aged <55 years experienced sustained mortality declines after 2010, adults aged ≥ 55 years continued to demonstrate progressive increases in HCC mortality. These findings suggest an increasing concentration of HCC burden among aging populations and highlight the evolving epidemiology of chronic liver disease in the United States.

Disclosures: Moksha Prasoona Avvaru:Nothing to Disclose, Shashank Trivedi:Nothing to Disclose, Mythily Rao Ponaganti:Nothing to Disclose, Sri Ram Charan Gundapaneni:Nothing to Disclose, Suhas Kataveni:Nothing to Disclose, Gaurav Sharma:Nothing to Disclose.

4291 | ETIOLOGY-SPECIFIC CONTRIBUTIONS TO ADVANCED CHRONIC LIVER DISEASE IN HEPATOCELLULAR CARCINOMA PATIENTS WITH CONCURRENT METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

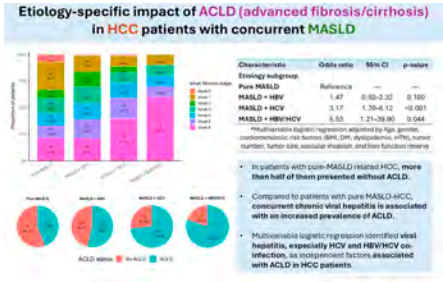
Chun-Ting Ho[1] Shin-Yu Tsai[2] Yi-Hsiang Huang[2] Ming-Chih Hou[2] Jaw-Ching Wu[3] Chien-Wei Su[2], [1]Taipei Veterans General Hospital/NYCU, [2]Taipei Veterans General Hospital, [3]National Yang Ming Chiao Tung University

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a rising etiology for hepatocellular carcinoma (HCC), with heterogeneous pathophysiology related to or independent from advanced chronic liver disease (ACLD). Also, other etiologies including viral hepatitis can also lead to liver fibrosis and carcinogenesis. Our study aimed to investigate the burden and etiological impact on ACLD among HCC patients with concurrent MASLD. **Methods:** 478 treatment-naïve HCC patients with concurrent MASLD who underwent curative resection at a tertiary center in Taiwan with available pathological specimens and complete clinical data were included. Patients were divided into ACLD and non-ACLD groups according to their ISHAK fibrosis grade from the surgical specimen using a cut-off of four. Subgroup analysis was performed in patients with pure-MASLD without viral hepatitis, concurrent MASLD and chronic hepatitis B (CHB), MASLD and chronic hepatitis C (CHC), and finally MASLD with CHB and CHC co-infection. Multivariable logistic regression was performed to determine factors associated with the presence of ACLD. **Results:** Among all patients, 257 (53.8%) had ACLD. The prevalence of ACLD differed significantly across etiology-specific

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subgroups and increased progressively with concomitant chronic viral hepatitis: 43.9% in pure MASLD-related HCC, 53.6% in MASLD and CHB, 73.2% in MASLD and CHC, and 80.0% in MASLD and CHB/CHC co-infection. In multivariable logistic regression adjusted by age, gender, tumor factors and cardiometabolic risk factors (CMRFs), presence of viral hepatitis, especially CHC and CHB/CHC co-infection, were identified as independent factors associated with ACLD in HCC patients, along with female gender and smaller tumor size. Individual CMRFs, such as diabetes, obesity, dyslipidemia, and hypertension, were not independently associated with ACLD. **Conclusion:** The burden of ACLD among HCC patients with concurrent MASLD varies significantly by etiology. While chronic viral hepatitis was independently associated with a higher prevalence of ACLD in HCC patients with MASLD, more than half of pure MASLD-related HCC patients presented without ACLD, indicating distinct pathophysiology features.



Disclosures: Chun-Ting Ho:Nothing to Disclose, Shin-Yu Tsai:Nothing to Disclose, Yi-Hsiang Huang:Nothing to Disclose, Ming-Chih Hou:Nothing to Disclose, Jaw-Ching Wu:Nothing to Disclose, Chien-Wei Su:Gilead Sciences: Speaking and Teaching, Gilead Sciences: Grant/Research Support.

4292 | MIXED SARCOMATOID HEPATOCELLULAR CARCINOMA/ CHOLANGIOCARCINOMA: A CONCERNING COMBINATION

Martin Sharpe[1] Jason Eng[2], [1]Ohio State University Medical Scientist Training Program, [2]The Ohio State University College of Medicine

Background: Mixed sarcomatoid hepatocellular carcinomas/cholangiocarcinomas (sHCC/ICC) are an exceptionally rare, primary malignant cancer of the liver. Although their pathogenesis remains largely unknown, cases of sHCC/ICC often appear in patients that have been treated with locoregional therapies such as radiofrequency ablation or transarterial chemoembolization. sHCC/ICC carries a very poor prognosis due to its late presentation, lack of effective treatments, and high potential for metastases. Here, we report the case of a 54-year-old female referred to our clinic for decompensated MASH cirrhosis management. **Methods:** N/A **Results:** Standard HCC screening diagnostics, including RUQ ultrasound and serum AFP, both failed to suggest the presence of a malignancy. However, abdominal MRI ordered for transplant evaluation revealed a small focus initially suggestive of a LR-5 lesion (HCC) in segment 7. Surprisingly, serial imaging demonstrated radiographic changes that eventually suggested evolution to an LR-M (metastatic) lesion which led to a subsequent biopsy. Pathology demonstrating hallmark histopathological findings such as mixed epithelial and spindle cell features, with both components showing variable cytokeratin expression confirmed the diagnosis of a mixed sarcomatoid hepatocellular/cholangiocarcinoma. The patient underwent ablation of the lesion followed by imaging which demonstrated adequate treatment response. **Conclusion:** While exceedingly rare, *de novo* sarcomatoid carcinomas can develop in patients with cirrhosis. This case highlights a unique instance in which a patient with no prior risk factors associated with this type of cancer developed a mixed cell-type variant which was identified early in its formation, providing an opportunity for aggressive treatment.

Disclosures: Martin Sharpe:Nothing to Disclose, Jason Eng:Nothing to Disclose.

4293 | TEMPORAL TRENDS IN INCIDENCE, TREATMENT, AND SURVIVAL IN FIBROLAMELLAR CARCINOMA: IMPACT OF THE DNAJB1–PRKACA FUSION DISCOVERY ERA USING SURVEILLANCE, EPIDEMIOLOGY, AND END RESULTS (SEER) 2000–2023 DATABASE

Krishna Chandrasekhara[1] Nicholas Thomas[1] Chandni Bhagtaney[1] Prasun Jalal[1], [1]Baylor College of Medicine

Background: Fibrolamellar carcinoma (FLC) is a rare, aggressive liver cancer predominantly affecting adolescents and young adults without underlying liver disease or cirrhosis. Historically misclassified as "HCC with fibrolamellar features," FLC's classification

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was transformed in 2014 by the discovery of the DNAJB1–PRKACA fusion protein, arising from a chromosome 19 deletion juxtaposing DNAJB1 and PRKACA. Dysregulated PKA activity drives oncogenesis; the fusion is detected in essentially 100% of cases. This established FLC as molecularly distinct, prompted WHO criteria updates in 2019, and is an active clinical trial target, though no FDA-approved therapy exists. True incidence may be 5–8 times higher than reported. Prior SEER studies characterize survival without analyzing treatment trends or contextualizing within the fusion discovery era. **Methods:** SEER identified FLC cases (ICD-O-3 code 9173/3) from 2000–2023 (n = 366). Cases were classified pre-2014 (n = 191) or post-2014 (n = 175). Annual incidence was plotted through 2022 with segmented regression. Stage proportions used 3-year rolling means; surgical and chemotherapy rates used LOESS smoothers. CSS was time to FLC-attributable death per SEER. Kaplan–Meier curves compared eras by log-rank test; 5-year CSS computed for 2000–2018. A Cox model adjusted for age and stage isolated the independent era effect. Chi-square tests compared categorical variables; $p < 0.05$ was significant. **Results:** 366 FLC cases were identified (range 5–21/year) with a modest upward trend and no step-change at 2014. Stage was stable across eras ($p = 0.72$). Surgical resection (49% vs 57%, $p = 0.11$) and chemotherapy (51% vs 48%, $p = 0.60$) did not differ. Five-year CSS was 44.0% (95% CI 37.4–51.7%) pre-2014 and 48.9% (95% CI 40.7–58.7%) post-2014; the difference was not significant ($p = 0.27$). After age and stage adjustment, era HR was 0.92 (95% CI 0.67–1.27, $p = 0.626$); age (HR 1.22/decade) and advanced stage were independent adverse predictors (both $p < 0.001$). **Conclusion:** Incidence did not increase post-2014, possibly reflecting incomplete adoption of molecular testing or challenges disseminating advocated diagnostic criteria, meaning true FLC may be misclassified as HCC and distort incidence given FLC's rarity. The unadjusted survival difference (44.0% vs 48.9% at 5 years) was attenuated to null after age and stage adjustment (HR 0.92, $p = 0.626$), suggesting apparent improvements reflect a more favorable case mix rather than a true era effect. Age and stage remain the primary CSS determinants. Longitudinal monitoring following broader molecular testing adoption will be important to assess whether current rates underestimate true disease burden, and whether DNAJB1–PRKACA-targeted therapies under development, given the inherent lag from discovery to clinical maturity, ultimately translate into measurable survival gains.

Disclosures: Krishna Chandrasekhara:Nothing to Disclose, Nicholas Thomas:Nothing to Disclose, Chandni Bhagtaney:Nothing to Disclose, Prasun Jalal:Madrigal, GSK, Mirum, Ipsen, Gilead, Genentech, Zydus: Grant/Research Support, Intercept, Genfit: Grant/Research Support.

4294 | TRENDS IN INCIDENCE, TREATMENT PATTERNS, AND OVERALL SURVIVAL OF INTRAHEPATIC CHOLANGIOCARCINOMA IN THE UNITED STATES, 2000-2022

Fadhil Jamil[1] Hyunseok Kim[2] Michael Luu[2] Paul Martin[2] Alexander Kuo[3] Walid Ayoub[3] Yun Wang[2] Aarshi Vipani[3] Nicole Rich[4] Neehar Parikh[5] Kambiz Kosari[2] Nicholas Nissen[2] Cristina Ferrone[6] Amit Singal[4] Ju Dong Yang[3], [1]American University of Antigua College of Medicine, [2]Cedars Sinai Medical Center, [3]Cedars-Sinai Medical Center, [4]University of Texas Southwestern Medical Center, [5]University of Michigan Medical Center, [6]Cedar Sinai Medical Center

Background: Intrahepatic cholangiocarcinoma (iCCA) represents the second most common primary liver cancer worldwide after hepatocellular carcinoma (HCC). With evolving epidemiology and treatment strategies, recent trends in iCCA incidence, tumor burden, treatment patterns, and overall survival in the United States warrant investigation. **Methods:** The Surveillance, Epidemiology, and End Results (SEER) database, including the SEER-21 and SEER-17 registries, was used to evaluate patients with iCCA. Using the SEER-21 registry, we calculated annual percent change (APC) and average annual percent change (AAPC) with Joinpoint regression analysis. Patient-level analyses were performed using the SEER-17 registry to evaluate tumor characteristics, treatment patterns, and overall survival (OS) among 17,833 patients diagnosed with iCCA between 2000 to 2022. Multivariable logistic regression identified factors associated with receipt of surgical treatment, while Cox regression analysis identified factors associated with OS. **Results:** iCCA incidence increased significantly from 2000 to 2022 (AAPC: 6.64%, 95% CI: 6.18% - 7.12%, $p < 0.001$) with a similar pattern between females (AAPC: 6.99%, 95% CI: 6.45% - 7.54%, $p < 0.001$) and males (AAPC: 6.32%, 95% CI: 5.65% - 6.99%, $p < 0.001$). Joinpoint analysis analyis identified an inflection point with a rapid increase in the incidence rates among individual younger than 50 years between 2020 and 2022 (APC: 21.13%, 95% CI: 1.56% - 35.93%, $p = 0.010$). Compared with 2000-2010, diagnosis during 2011-2019 was associated with higher odds of receiving surgical treatment (aOR: 1.29, 95% CI: 1.16-1.44, $p < 0.001$) (**Table**). Compared with non-Hispanic White patients, Hispanic (aOR: 0.69, 95% CI: 0.61-0.78, $p < 0.001$) and non-Hispanic Black patients (aOR: 0.70, 95% CI: 0.59-0.83, $p < 0.001$) had significantly lower odds of receiving surgical treatment. In multivariable analyses, recent diagnosis was independently associated with improved OS, with better survival among patients diagnosed in 2020-2022 (aHR: 0.76, 95% CI: 0.72-0.79, $p < 0.001$) compared to 2000-

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2010. Hispanic ethnicity (aHR: 1.10, 95% CI: 1.05-1.16, p < 0.001), non-Hispanic Black race (aHR: 1.08, 95% CI: 1.01-1.15, p = 0.017) and non-Hispanic American Indian/Alaska Native race (aHR: 1.22, 95% CI: 1.03-1.46, p = 0.024) were associated with worse OS after adjusting for diagnosis year, sex, age group, race/ethnicity, household income, rural-urban classification, tumor size, stage, and grade. **Conclusion:** iCCA incidence continues to rise in the United States with marked increase among patients younger than 50 years in recent years. Although survival has improved in recent years, disparities in treatment receipt and outcomes persist among racial and ethnic minority groups. Addressing these gaps is essential to improving equitable access to treatment and optimizing outcomes for patients with iCCA.

Table 1 - Factors associated with receipt of surgical treatment among all iCCA patients in SEER 17 database.

	Univariate Analysis			Multivariable Analysis		
Characteristic	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Diagnosis Year						
2000-2010	—	—		—	—	
2011-2019	1.14	1.03, 1.25	**0.008**	1.29	1.16, 1.44	**<0.001**
2020-2022	0.98	0.88, 1.09	0.7	1.13	1.00, 1.28	0.052
Sex						
Female	—	—		—	—	
Male	0.93	0.86, 1.00	0.053	0.91	0.84, 1.0	**0.038**
Age Group						
<50	—	—		—	—	
50-64	0.74	0.65, 0.85	**<0.001**	0.61	0.52, 0.72	**<0.001**
>=65	0.52	0.46, 0.59	**<0.001**	0.32	0.28, 0.38	**<0.001**
Race/Ethnicity						
Non-Hispanic White	—	—		—	—	
Hispanic (All Races)	0.78	0.70, 0.87	**<0.001**	0.69	0.61, 0.78	**<0.001**
Non-Hispanic Black	0.76	0.65, 0.88	**<0.001**	0.70	0.59, 0.83	**<0.001**
Non-Hispanic Asian or Pacific Islander	0.94	0.83, 1.05	0.2	0.89	0.78, 1.02	0.091
Non-Hispanic American Indian/Alaska Native	0.92	0.59, 1.38	0.7	0.96	0.60, 1.52	0.9
Household Income						
<$40,000	—	—		—	—	
$40,000-59,999	0.96	0.61, 1.58	0.9	1.03	0.61, 1.75	>0.9
$60,000-99,999	1.00	0.70, 1.77	0.7	1.11	0.65, 1.88	0.7
>= $100,000	1.19	0.76, 1.94	0.5	1.24	0.73, 2.13	0.4
Rural-Urban Continuum						
Metro <250,000	—	—		—	—	
Metro >1 million	1.14	0.98, 1.33	0.085	1.21	1.01, 1.45	**0.036**
Metro 250,000–1 million	1.12	0.95, 1.32	0.2	1.20	0.99, 1.44	0.062
Nonmetro/rural	0.97	0.80, 1.17	0.8	0.95	0.77, 1.18	0.7
Tumor Size						
≤2 cm	—	—		—	—	
2–5 cm	0.94	0.80, 1.10	0.4	1.02	0.87, 1.19	0.9
>5 cm	0.46	0.39, 0.53	**<0.001**	0.64	0.54, 0.74	**<0.001**
Tumor Grade						
G1	—	—		—	—	
G2	0.94	0.79, 1.11	0.5	1.21	1.13, 1.52	**<0.001**
G3	0.45	0.38, 0.54	**<0.001**	0.71	0.60, 0.83	**<0.001**
G4	0.51	0.28, 0.89	**0.020**	1.09	0.59, 2.02	0.8
Stage at Diagnosis						
Localized	—	—		—	—	
Regional	0.52	0.47, 0.57	**<0.001**	0.53	0.48, 0.58	**<0.001**
Distant	0.08	0.07, 0.09	**<0.001**	0.08	0.07, 0.09	**<0.001**

Abbreviations: CI = Confidence Interval, OR = Odds Ratio

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4295 | PROGNOSTIC IMPACT OF NUTRITIONAL STATUS AND IMMUNE-RELATED ADVERSE EVENTS IN HEPATOCELLULAR CARCINOMA PATIENTS TREATED WITH ATEZOLIZUMAB PLUS BEVACIZUMAB

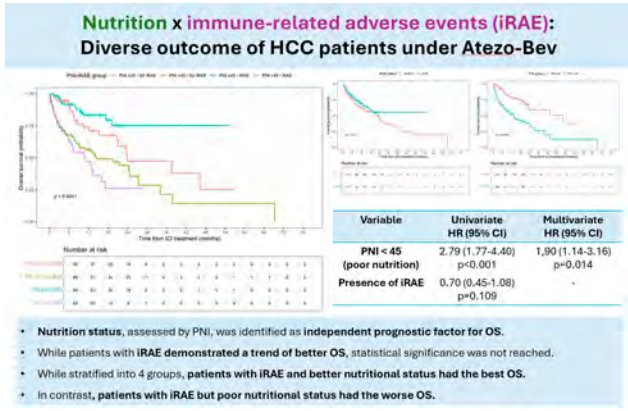
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Background: Both host nutritional status and immune-related adverse events (iRAEs) may influence outcomes in patients with hepatocellular carcinoma (HCC) receiving immunotherapy. However, the interaction between these two factors is not well studied. We aimed to evaluate the combined prognostic effects of baseline nutritional status and iRAE development on overall survival (OS) in HCC patients treated with atezolizumab plus bevacizumab. **Methods:** This multicenter retrospective study included 248 HCC patients treated with atezolizumab plus bevacizumab in Taiwan. Baseline nutritional status was assessed using the prognostic nutritional index (PNI), with poor nutrition defined as PNI < 45. Patients were further categorized according to the occurrence of iRAEs during treatment. Multivariable Cox proportional hazards models adjusted for age, sex, tumor stage, macrovascular invasion, and viral etiology were used to identify independent predictors of OS. Survival outcomes were analyzed using Kaplan-Meier methods and compared by log-rank tests. **Results:** After a median follow-up of 16.3 months, 102 deaths occurred, with an overall 5-year OS rate of 25.2% (95% confidence interval, CI: 14.3%–44.5%). On multivariable Cox PH analysis, poor nutritional status (PNI < 45) was identified as a significant, independent adverse prognostic factor for OS (hazard ratio, HR: 1.90; 95% CI: 1.14–3.16; p = 0.014), alongside macrovascular invasion, elevated alpha-fetoprotein (AFP) levels, and higher ALBI grade. Although the development of iRAEs was associated with a trend toward improved survival on univariable analysis (HR, 0.70; 95% CI, 0.45–1.08; p = 0.109), it was not independently associated with OS after adjustment. Notably, significant survival differences emerged when patients were stratified according to both nutritional status and iRAE occurrence (p < 0.001). Patients with preserved nutritional status who developed iRAEs achieved the best survival outcomes. In contrast, patients with poor baseline nutrition who developed iRAEs exhibited the worst OS among all subgroups. **Conclusion:** Baseline nutritional status is a critical determinant of survival in HCC patients receiving atezolizumab plus bevacizumab. Moreover, the prognostic implication of iRAEs appears to be highly dependent on host nutritional reserve. While iRAEs may reflect effective antitumor immune activation in well-nourished patients, their occurrence in malnourished patients is associated with markedly poor outcomes. These findings highlight the importance of nutritional assessment and optimization in patients undergoing combination immunotherapy for HCC.



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4296 | MODEL TO PREDICT EARLY HEPATIC DECOMPENSATION DURING IMMUNE CHECKPOINT INHIBITOR THERAPY FOR HEPATOCELLULAR CARCINOMA

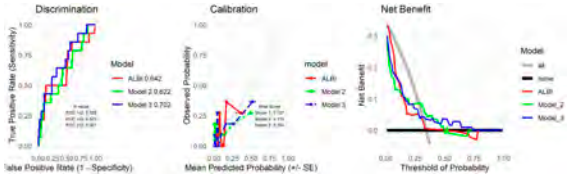
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Background: Immune checkpoint inhibitors (ICI) have significantly improved survival outcome for patients with unresectable hepatocellular (uHCC). However, due to high prevalence of pre-existing advanced liver dysfunction, a significant fraction of ICI-treated uHCC patients will experience early hepatic decompensation and liver-related death. The objective of this study was develop and internally validate a clinical prediction tool for early death or new/worsening decompensation under ICI therapy for uHCC. **Methods:** All U.S. Veteran patients who received first-line (1L) ICI therapies were identified in the U.S. Veterans Administration CDW between 10/2020 and 2/2024. Manual chart abstraction confirmed uHCC diagnosis, immediate pre-1L tumor characteristics (number, tumor diameters, macrovascular invasion, extrahepatic spread, prior LRT or resection), evidence of portal hypertension (ascites, endoscopy, imaging), spleen size, prior hepatic decompensations (ascites, variceal hemorrhage, encephalopathy), Child-Pugh, ALBI score, ECOG performance status, and baseline labs. Chart abstraction further

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identified time to death and post-treatment decompensations including new/worsening ascites (clinical/imaging), variceal hemorrhage, hepatic encephalopathy, SBP (lab confirmed), and HRS. After 70%:30% random sampling, generalized linear models to predict 30-day death or decompensation were trained and internally validated for AUROC, calibration and decision-curve analysis to compare net benefit using ALBI score as a reference. **Results:** 367 patients undergoing 1L atezolizumab/bevacizumab (n = 245), STRIDE (n = 101), atezolizumab (n = 16) or durvulamab (n = 5) monotherapy were abstracted. Median age was 70 (IQR 66-74); 98.9% were male; 211 (57.5%) were white; etiology of liver disease was ALD/ALD+HCV/HCV/MASH/HBV in 16.3%/25.6%/33.5%/21.0%/1.1%; baseline CTP A/B/C 76.0%/23.4%/0.5%; median tumor number was 4 [IQR 1-5], largest tumor size 5.5cm [2.7 - 11.1cm], TTD 11.5cm [5.3 - >20cm] , 127 had MVI (34.6%, 13% VP4) and 84 extrahepatic spread (22.9%); and BCLC 0/A/B/C/D stage was 1.4%/7.1%/30.0%/59.9%/ 1.6%. 39 (10.6%) died or developed worsening decompensation within 30 days (9 variceal hemorrhage, 10 new/worsening ascites, 3 SBP, 0 HRS, 9 hepatic encephalopathy, with 25 deaths). After training, compared to ALBI, Model 3 based on age, MELD3.0, tumor number, largest tumor size, VP3/4 MVI, AST and splenomegaly showed superior discrimination, calibration and net-benefit for prediction 30-day outcomes (Figure 1). **Conclusion:** Death and worsening decompensation within 30 days of initiation of ICI therapy for uHCC is relatively frequent and can be reasonably predicted with a parsimonious set of readily available clinical and laboratory values. After external validation, such predictive models may be utilized to identify patients for whom poor liver reserve may mitigate benefits of ICI.



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4297 | REVISITING THE BURDEN OF LIVER CANCER IN THE EASTERN MEDITERRANEAN REGION AND ITS PROJECTIONS TO 2050

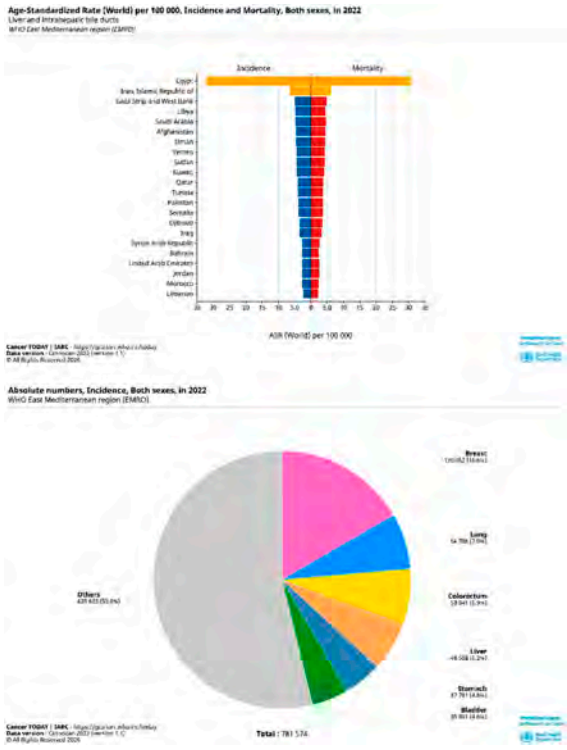
Saleh Alessy[1] Mariam Zahwe[2] Basmah Khoja[1] Habeeb Razack[3] Ghadeer Jamjoum[4] Aldanah Althwanay[5] Lolwa Alobaid[6] Nouf Al-Turki[7] Mohammad Mawardi[8] May Alzahrani[8] Khalid AlNaamani[9] Isabelle Soerjomataram[2] Saleh Alqahtani[10], [1]King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia, [2]The International Agency for Research on Cancer, Lyon, France, [3]King Saud University, Riyadh, Saudi Arabia, [4]King Abdulaziz University Hospital, Jeddah, Saudi Arabia, [5]Washington University at St.Louis, St.Louis, USA, [6]King Abdulaziz Medical City, Riyadh, Saudi Arabia, [7]King Abdulaziz University, Jeddah, Saudi Arabia, [8]King Faisal Specialist Hospital and Research Centre-Jeddah, Jeddah, Saudi Arabia, [9]The Medical City for Military and Security Services, Muscat, Oman, [10]King Faisal Specialist Hospital & Research Center

Background: Liver cancer remains a major cause of cancer-related mortality, despite being largely linked to modifiable risk factors, including viral hepatitis and metabolic liver disease. For the World Health Organization (WHO) Eastern Mediterranean Region (EMR), updated country-level burden estimates and projections to 2050 are needed to guide regional cancer-control planning. We aimed to assess the current burden and project future liver cancer incidence in the EMR through 2050 to inform regional cancer control efforts. **Methods:** We used cancer estimates from the International Agency for Research on Cancer GLOBOCAN 2022 dataset to assess liver cancer incidence and mortality across all 22 EMR countries. Cases, deaths, and age-standardized incidence rates (ASIRs) were summarized by country and sex. Future incidence projections to 2050 accounted for projected population growth and aging, and the annual incidence reduction required to maintain 2022 case counts was estimated. **Results:** In 2022, an estimated 48,568 new liver cancer cases occurred across the EMR, representing 6.2% of all regional cancer cases. Liver cancer ranked fourth overall and among males, and third among females. Egypt accounted for almost two-thirds (57.5%) of the estimated cases, followed by Pakistan (12.6%) and Iran (12.0%). The ASIR for liver cancer in Egypt was 32.0 per 100,000, a 5-fold higher rate than Iran, the second-highest-ranking country (ASIR, 6.4 per 100,000 persons). Liver cancer was the second leading cause of cancer-related death in males and females and third overall, accounting for 46,820 deaths (9.6% of all cancer deaths). A 3% annual reduction in incidence would be required across the region to maintain the same number of cases in 2050 as in 2022. **Conclusion:** Liver cancer remains a major and projected growing burden in the EMR, with most cases in Egypt, likely reflecting the historically high prevalence of hepatitis

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C. Maintaining 2022 case counts by 2050 would require sustained incidence reductions, supporting integrated strategies for viral hepatitis elimination, prevention and management of metabolic dysfunction-associated steatotic liver disease, and regional cancer-control planning. Interpretation should consider variability in cancer-registry completeness, reliance on modeled GLOBOCAN estimates, and uncertainty in long-term demographic projections.



Disclosures: Saleh Alessy:Nothing to Disclose, Mariam Zahwe:Nothing to Disclose, Basmah Khoja: Nothing to Disclose, Habeeb Razack:Nothing to Disclose, Ghadeer Jamjoum:Nothing to Disclose, Aldanah Althwanay:Nothing to Disclose, Lolwa Alobaid:Nothing to Disclose, Nouf Al-Turki:Nothing to Disclose, Mohammad Mawardi:Nothing to Disclose, May Alzahrani: Nothing to Disclose, Khalid AlNaamani:Nothing to Disclose, Isabelle Soerjomataram:Nothing to Disclose, Saleh Alqahtani:Nothing to Disclose.

4298 | EARLY-ONSET HEPATOCELLULAR CARCINOMA IN A SAUDI TERTIARY REFERRAL-CENTER REGISTRY: PREVALENCE, ETIOLOGIES, STAGE DISTRIBUTION, AND SURVIVAL OUTCOMES

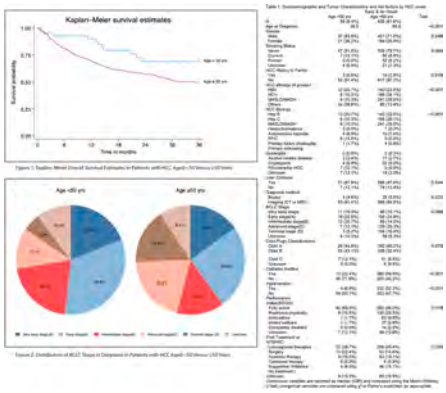
Saleh Alqahtani[1] Waleed Al Hamoudi[1] Lolwa Alobaid[2] Duna Barakeh[1] Amwaj Alanazi[1] Mussadique Jhatial[1] Mehwish Shahzadi[1] Ahmed Alyahya[3] Fahad AlMugbel[1] Ali Alqahtani[1] Hadi Kuriry[4] Hamdan Alghamdi[5] Khalid Alswat[6] Khalid AlNaamani[7] Waleed Alomaim[1] Dieter Broering[1] Saad Alghamdi[8] Faisal Abaalkhail[1] Saleh Alessy[1], [1]King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia, [2]King Abdulaziz Medical City, Riyadh, Saudi Arabia, [3]Ministry of Health, Riyadh, Saudi Arabia, [4]King Fahad Specialist Hospital, Dammam, Saudi Arabia, [5]King Abdulaziz Medical City of National Guard Hospital, [6]King Saud University/KKUH, [7]The Medical City for Military and Security Services, Muscat, Oman, [8]King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia

Background: Trends in early-onset hepatocellular carcinoma (HCC) vary globally, and data from Saudi Arabia remain limited. Shifting global HCC etiologies highlight the need to characterize disease patterns in younger populations. We aimed to describe prevalence, etiologies, and survival outcomes of HCC in patients younger than 50 years in Saudi Arabia. **Methods:** Data were extracted from the King Faisal Specialist Hospital and Research Center HCC Registry, a tertiary referral-center registry receiving patients from across Saudi Arabia, for patients diagnosed between Jan 2020 and Apr 2026. Patients aged <50 years (younger group) were compared with those aged ≥ 50 years (older group). Demographic, etiologic, and clinical characteristics were analyzed descriptively. Overall survival up to 36 months was estimated using the Kaplan-Meier method, with mortality data supplemented through the National Death Registry. **Results:** Among 693 patients with HCC, 8.4% (n = 58) were <50 years. The median age at diagnosis was 36.5 years and 65.0 years in the two groups, respectively. Males were predominant in both groups. Family history of HCC was more frequent in younger patients (8.6% vs. 2.8%; P = 0.019). Metabolic dysfunction-associated steatotic liver disease and steatohepatitis (MASLD/MASH) were less common in the younger group (10.3% vs. 38.0%). Hepatitis B virus (HBV) prevalence was comparable between groups (20.7% vs. 22.5%), while hepatitis C virus (HCV) was less prevalent among younger patients (10.3% vs. 26.1%). Other etiologic categories were more frequent in younger patients (58.6% vs. 13.4%; $P < 0.001$), including progressive familial intrahepatic cholestasis (PFIC, 15.5%), autoimmune hepatitis (6.9%), cryptogenic disease (6.9%), and unknown etiology (12.1%). Cirrhosis prevalence was high and comparable between groups (87% in both). Younger patients showed a trend towards early-stage disease (BCLC 0-A; 51.8% vs. 40.0%; p = 0.086). Overall survival at 12 and 36 months was higher in the younger group (0.90 and 0.68) compared with the older group (0.69 and 0.49). Child-Pugh B/C was more frequent in younger patients, although not

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statistically significant (55.2% vs. 38.9%; P = 0.075). **Conclusion:** Early-onset HCC accounted for 8.4% of registry cases and showed distinct etiologic and clinical characteristics, with reduced contribution from MASLD/MASH and HCV and a disproportionate burden of other etiologic categories, including PFIC, fibrolamellar HCC, autoimmune hepatitis, and cryptogenic disease. Younger patients demonstrated higher estimated survival despite comparable cirrhosis burden, supporting the need for age-specific surveillance and management strategies.



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4299 | INCIDENCE AND ASSOCIATED RISK FACTORS OF HEPATOCELLULAR CARCINOMA IN PEOPLE WITH HIV: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: The epidemiology of hepatocellular carcinoma (HCC) in people with HIV (PWH) has evolved in the era of antiretroviral therapy (ART) and direct-acting antivirals for hepatitis C virus (HCV). HCC incidence estimates remain heterogeneous, and the contribution of distinct liver disease phenotypes to HCC in PWH is incompletely characterized. **Methods:** We conducted a PRISMA-guided systematic review and meta-analysis reporting HCC incidence among adults with HIV. PubMed, EMBASE, Cochrane Library, Web of Science, and Scopus were searched from January 1996 through December 2025. The primary outcome was pooled HCC incidence per 1,000 person-years (PY). Random-effects models were used to estimate pooled incidence rates overall. Study quality was assessed using the Newcastle-Ottawa Scale. **Results:** We included 13 studies comprising 153,071 PWH and 855 HCC cases over 957,920 PY of follow-up. The pooled HCC incidence was 1.18 per 1,000 PY (95% CI: 0.64-2.17), with high between-study heterogeneity (I^2 = 97.2%). Incidence was lower in African and Asian cohorts. HCC incidence was lowest with HIV mono-infection (0.12 per 1,000 PY; 95% CI: 0.05-0.29), increased in HCV coinfection (1.72 per 1,000 PY; 95% CI: 1.25-2.36), HBV coinfection (2.01 per 1,000 PY; 95% CI: 1.69-2.40), and triple infection (4.52 per 1,000 PY; 95% CI: 3.29-6.22). HCV-related cirrhosis conferred the highest risk overall (15.40 per 1,000 PY; 95% CI: 6.42-37.08). MASLD was also associated with elevated HCC incidence (1.97 per 1,000 PY; 95% CI: 1.17-3.11). CD4 cell count demonstrated a non-significant inverse association (β = -0.015 per cell/µL increase, p = 0.21), suggesting a possible contribution of immune dysfunction to hepatocarcinogenesis. Era-stratified analysis did not demonstrate a significant reduction in HCC incidence in contemporary compared to historical cohorts. **Conclusion:** Among PWH, HCC risk appears to be driven by underlying liver disease phenotype rather than HIV infection itself. Viral hepatitis coinfections, cirrhosis, alcohol-related liver disease, and MASLD were associated with markedly increased HCC incidence. These findings support phenotype-based HCC surveillance strategies in HIV care, with increasing consideration for MASLD.

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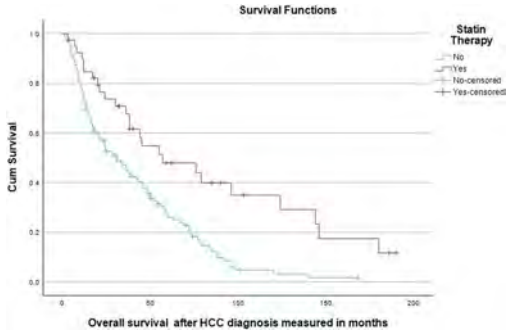
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4300 | THE EFFECT OF STATIN THERAPY ON THE OVERALL SURVIVAL OF PATIENTS WITH HEPATOCELLULAR CARCINOMA: A SINGLE-CENTER EXPERIENCE

Christos Triantos[1] Konstantinos Papantoniou[1] Vasileios Lekakis[2] Efthymios Tsounis[1] Evangelia Bourdalou[1] Nikitas Kimiskidis[1] Georgios Geramoutsos[1] Ploutarchos Pastras[1] Ioanna Aggeletopoulou[1] Odyssefs Ampazis[1] Georgia Diamantopoulou[1] Tryfon Spyridonidis[3] Konstantinos Katsanos[4] Konstantinos Thomopoulos[1], [1]Division of Gastroenterology, Department of Internal Medicine, University of Patras, 26504, Patras, [2]First Academic Department of Gastroenterology, Medical School of National and Kapodistrian Universit, [3]Nuclear Medicine Department, University Hospital of Patras, Rio, Greece, [4]Department of Interventional Radiology, University Hospital of Patras, Rio, Greece

Background: Statins exert pleiotropic anti-inflammatory, antifibrotic, and potential antineoplastic effects beyond lipid lowering. Although previous studies have suggested a protective role against hepatocellular carcinoma (HCC) development, their impact on survival after HCC diagnosis remains unclear. **Methods:** To evaluate the association between statin use and overall survival in patients with HCC, we conducted a retrospective single-center study including consecutive patients with HCC managed at a tertiary referral center from January 2000 onward. Demographic, clinical, laboratory, tumor-related, and treatment data were collected. Patients were classified according to statin use prior to HCC diagnosis. Overall survival (OS) was assessed using Kaplan–Meier analysis and compared with the log-rank test. Cox proportional hazards regression models were used to identify independent predictors of survival. **Results:** A total of 190 patients were included (90.5% male; median age 67 years), of whom 137 (72.1%) had cirrhosis. Among cirrhotic patients, 48 (35%) had hepatic decompensation at diagnosis. Statins were administered in 42 patients (22.1%). Baseline liver function, AFP levels, and treatment allocation were comparable between statin users and non-users, although statin users more frequently had diabetes mellitus and arterial hypertension. During follow-up, statin therapy was associated with significantly improved survival. Mean OS was 82.5 months in statin users versus 41.7 months in non-users, while median OS was 57 versus 31 months, respectively (log-rank $p < 0.001$). In univariate Cox analysis, statin use was associated with reduced mortality risk (HR 0.45, 95%CI 0.28–0.70, $p < 0.001$). Other adverse prognostic factors included hepatic decompensation, ascites, portal vein thrombosis, and extrahepatic metastases. In multivariate models adjusting for liver function, tumor burden, and therapeutic interventions, statin therapy remained independently associated with improved survival, with hazard ratios ranging from 0.19 to 0.44 across models (all $p < 0.05$). Advanced liver dysfunction and tumor stage also independently predicted worse outcomes. **Conclusion:** Statin therapy prior to HCC diagnosis was independently associated with significantly improved overall survival in a real-world cohort of HCC patients. These findings support a potential beneficial role of statins as adjunctive therapy in HCC and warrant prospective multicenter studies to further clarify their impact on prognosis and disease progression.



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4301 | Y90 VS. SBRT AS HCC BRIDGING THERAPY TO LIVER TRANSPLANTATION: A REAL-WORLD COMPARATIVE ANALYSIS

Tarek Aridi[1] Luke Ghabril[1] Pedro Escobedo[1] Adel Hajj Ali[1] Patrick Ryan[1] Amna Yaqub[1] Naushair Hussain[1] Olivia Carlton[1] Lauren Nephew[1] Marco Lacerda[1] Chandrashekhar Kubal[1] John Holden[1], [1]Indiana University

Background: Hepatocellular carcinoma (HCC) bridging therapy aims to prevent tumor progression in patients awaiting orthotopic liver transplantation (OLT). Yttrium-90 radioembolization (Y90) and stereotactic body radiation therapy (SBRT) are well-established locoregional therapies used for bridging, yet comparative data on pre- and post-OLT outcomes remains limited. **Methods:** We conducted a single-center retrospective study of consecutive patients referred between January 1, 2008 and December 31, 2023 with a single HCC lesion (< 4cm in size) and no prior bridging therapy who received either Y90 or SBRT as initial bridging therapy to OLT. Outcomes were assessed through April 30, 2026.The primary study outcomes were pre-OLT time to progression (TTP). Secondary outcomes for the study included post-OLT tumor-free survival (TFS). Multivariable Cox regression, stratified by treatment arm and adjusted for age, sex, race, ethnicity, viral hepatitis, Child-Pugh score, AFP, tumor size, and ECOG performance status, was used to compare TTP and Pre-OLT survival. Kaplan-Meier analysis with log-rank testing was performed for primary and secondary outcomes. **Results:** A total of 119 patients met inclusion criteria: 71 patients received Y90 and 48 patients received SBRT. The treatment groups were well-matched at baseline. Among Y90 patients, mean dosimetry was 57.3 mCi. Among SBRT patients, 18 (38.3%) received 3 fractions and 29 (61.7%) received 5 fractions, with a mean total of 45.0 Gy. HCC size at time of evaluation was significantly greater in Y90 as compared to SBRT (28 vs 23 mm, p = 0.034). Pre-OLT deaths were similar between groups, 28/71 in Y90 (39.4%) and 22/48 in SBRT (45.8%) groups (p = 0.567). Pre-OLT progression occurred in 15/71 Y90 (21.1%) and 14/48 SBRT (29.2%) patients (log-rank p = 0.385). The median follow-up overall was 307 and 481 days in the Y90 and SBRT groups respectively (p = 0.090). In those who progressed, median TTP was significantly higher in the SBRT group (621 days) as compared to the Y90 group (257 days, p = 0.026). On multivariable analysis, treatment modality was not independently associated with TTP (adjusted HR 1.24 95% CI (0.51–3.01), p = 0.631). Among 58 transplanted patients (Y90 n = 38, SBRT n = 20), post-OLT recurrence was 5.3% versus 0.0% (p = 0.548), with no difference in tumor-free survival (log-rank p = 0.345). Multivariable Cox regression for post-OLT recurrence was not feasible because no recurrence events occurred in the SBRT group. **Conclusion:** Y90 and SBRT were associated with similar pre- and post-OLT outcomes as bridging therapies to transplant for HCC, with no significant difference in pre-OLT time to progression, pre-OLT survival, or post-OLT tumor-free survival seen after multivariable adjustment. Our findings suggest both modalities remain reasonable bridging approaches for carefully selected patients.

Variable	Y90 (n = 71) Median (IQR) or n(%)	SBRT (n = 48) Median (IQR) or n(%)	p-value
Age at OLT evaluation, yr	64.8 (59.6–67.8)	62.8 (58.6–67.1)	0.373
Male sex	52 (73.2%)	34 (70.8%)	0.774
Race			0.378
White	54 (76.1%)	42 (87.5%)	
Ethnicity			0.937
Non-Hispanic	64 (90.1%)	44 (91.7%)	
Child-Pugh score	6 (5–8)	6 (5–7)	0.860
Child-Pugh class			0.252
A	41 (57.7%)	27 (58.7%)	
B	26 (36.6%)	19 (41.3%)	
C	4 (5.6%)	0 (0.0%)	
MELD-Na at evaluation	11 (9–14)	9 (8–12)	0.062
Viral etiology (HCV, ETOH+HCV, HBV)	33 (46.5%)	31 (64.6%)	0.052
AFP at evaluation, ng/mL	7.5 (4.5–22.0)	6.0 (3.7–14.0)	0.254
AFP range			0.186
<400	69	45	
400-1000	1	3	
>1000	2	0	
Largest HCC size, mm	28 (21–34)	23 (20–29)	**0.034**
ECOG performance status			0.645
0	38 (53.5%)	27 (56.2%)	
1	27 (38.0%)	15 (31.3%)	
2	6 (8.5%)	6 (12.5%)	
Listed for transplant	42 (59.2%)	23 (47.9%)	0.227
Pre-OLT death	28 (39.4%)	22 (45.8%)	0.567
Received OLT	38 (53.5%)	20 (41.7%)	0.204
Within Milan criteria on imaging at OLT	36 (94.7%)	20 (100.0%)	0.309
Explant nodules, n	1 (0–2)	1 (0–2)	0.845
Largest explant nodule, mm	15 (0–25)	12 (0–32)	0.952
Retreat score	1 (0–2)	1 (0–2)	0.723
Post-OLT HCC recurrence	2 (5.3%)	0 (0.0%)	0.548
Pre-OLT time to progression (TTP)			
Total N / events (progression)	71 / 15 (21.1%)	48 / 14 (29.2%)	0.385
Median follow-up overall, days *	307 (207–452)	481 (199–814)	0.090
Median TTP in those who progressed, days	257 (109-452)	621 (380-847)	**0.026**
SBRT vs Y90 — adjusted HR †	*Adjusted Hazard Ratio* 1.24 (0.51–3.01)		0.631
Post-OLT tumor-free survival (TFS) ‡			
Total N / events (deaths)	38 / 2 (5.3%)	20 / 0 (0.0%)	0.345

Abbreviations: AFP, alpha-fetoprotein; CI, confidence interval; CP, Child-Pugh; ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; HR, hazard ratio; IQR, interquartile range; MELD, Model for End-Stage Liver Disease; NR, not reached; OLT, orthotopic liver transplantation; SBRT, stereotactic body radiation therapy; TFS, tumor-free survival; TTP, time to progression; Y90, yttrium-90 radioembolization.

* Timed to progression, death, loss to follow-up, and OLT

† Adjusted Cox for pre-OLT TTP stratified by treatment arm and adjusted for: age, sex, race, ethnicity, Child-Pugh score, AFP, largest HCC size, viral cirrhosis etiology, and ECOG performance status. The primary treatment comparison (SBRT vs Y90) is the only covariate shown; all adjustment variables were non-significant (p=0.788).

‡ Cox non-estimable — information matrix singular since SBRT has zero events

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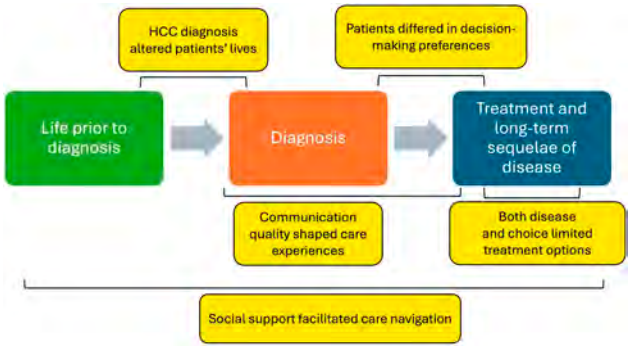
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4302 | PATIENT EXPERIENCES WITH HEPATOCELLULAR CARCINOMA CARE: A QUALITATIVE STUDY

Zoe Zimmerman[1] Kyra Chism[2] Forough Heidarzad Pahlaviani[1] Mario Strazzabosco[1] Leah Ferrucci[3] Bubu Banini[1], [1]Yale School of Medicine, [2]Morehouse School of Medicine, [3]Yale School of Public Health, Yale Cancer Center

Background: Hepatocellular carcinoma (HCC) remains a highly lethal malignancy, with a 5-year survival rate of approximately 20%. Thus, understanding patients' experiences with HCC care may provide important insights for improving the quality and equity of care delivery. At present, significant differences exist in HCC incidence, treatment, and mortality, with racial and ethnic minority populations and individuals of lower socioeconomic status experiencing higher disease burden and poorer clinical outcomes. The purpose of this study is to explore the experiences of patients with HCC and identify barriers to and facilitators of high-quality, patient-centered care. **Methods:** We conducted a qualitative study involving semi-structured interviews of patients with HCC. Participants were recruited from HCC-specific and general GI oncology clinics across the Yale Cancer Center Smilow Network (YCCSN) from July 2025 to April 2026. Interviews were recorded and transcribed. We applied thematic analysis using an inductive approach. Three members of the study team independently coded a subset of transcripts and came to a consensus on the codebook, which was then iteratively refined as additional transcripts were coded. Finally, codes were grouped into themes. **Results:** We interviewed 22 patients with HCC. Participants were predominantly male (86%) and non-Hispanic/Latino (95%); 59% identified as white and 36% identified as black. Insurance coverage types included employer-based (9%), Medicare only (32%), Medicaid only (13%), private and public (36%), more than one public (5%), and no insurance (5%). Income distribution for <$20,000, $20,000-$34,999, $35,000-$49,999, $50,000-$74,999, $75,000-$100,000, and >$100,000 were 41%, 5%, 5%, 5%, 18%, and 27%, of the cohort, respectively. Five major themes were identified: 1) HCC diagnosis altered patients' lives; 2) communication quality shaped care experiences; 3) patients differed in decision-making preferences; 4) both disease and choice limited treatment options; and 5) social support facilitated care navigation. The impact of each theme (yellow boxes) along the care continuum is demonstrated by the figure. The study identified opportunities to improve patient-centered HCC care, including the need for transparency regarding diagnosis and treatment options; early assessment of patient preferences for involvement; prompt follow-up to explain test results; involvement of family members in care; and tailored education and navigation support for individuals with limited health literacy. **Conclusion:** Patients with HCC generally reported positive care experiences. Insurance coverage and care coordination were largely adequate, although financial challenges persisted for some patients. Areas for improvement included communication about HCC diagnosis and treatment and additional support for patients navigating HCC care.



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4303 | ADDING ALPHA-FETOPROTEIN TO ALBI GRADE OR MELD 3.0 DOES NOT IMPROVE 6-MONTH HEPATIC DECOMPENSATION PREDICTION FOR CIRRHOTIC PATIENT WITH HEPATOCELLULAR CARCINOMA UNDERGOING TACE PROCEDURE

Rabia Afzaal[1] Hasan Bualbanat[1] David Hudson[1] Tamoor Afzaal[1], [1]Western University

Background: Post-transarterial chemoembolization (TACE) hepatic decompensation remains a critical consideration in patients with cirrhosis and hepatocellular carcinoma (HCC). Alpha-fetoprotein (AFP) reflects tumor biology and disease burden, but limited data exist on whether baseline AFP improves prediction of post-TACE decompensation beyond established liver reserve models. **Methods:** We conducted a retrospective analysis of an anonymized cohort of 280 patients with cirrhosis and HCC undergoing TACE. The primary outcome was any decompensating event within 6 months, including hepatic encephalopathy, spontaneous bacterial peritonitis, variceal bleeding, or ascites. Logistic regression models incorporating ALBI grade and MELD 3.0, each with and without log-transformed AFP, were compared. Model discrimination was

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assessed using area under the receiver operating characteristic curve (AUROC) with DeLong testing. Reclassification performance was evaluated using continuous net reclassification improvement (NRI) and integrated discrimination improvement (IDI). **Results:** Decompensation occurred in 84/280 patients (30.0%) within 6 months of TACE. MELD 3.0 alone demonstrated the strongest discrimination for post-TACE decompensation (AUROC 0.81). Addition of AFP did not significantly improve discrimination for either ALBI grade (DeLong $p = 0.30$) or MELD 3.0 (DeLong $p = 0.64$). Reclassification analyses similarly demonstrated no clinically meaningful improvement with AFP incorporation. **Conclusion:** In this cohort of cirrhosis and HCC patients undergoing TACE, addition of baseline AFP to either ALBI grade or MELD 3.0 did not improve prediction of 6-month hepatic decompensation. MELD 3.0 alone provided the strongest discriminatory performance for post-TACE decompensation.

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4304 | ANA AND SMA POSITIVITY ARE NOT ASSOCIATED WITH IMMUNE-RELATED ADVERSE EVENTS OR TREATMENT OUTCOMES IN ICI-TREATED HEPATOCELLULAR CARCINOMA

Pin-Jung Chen[1] Manaf Alsudaney[2] Ashley Kim[2] Priyanshi Shah[3] Hyunseok Kim[2] Paul Martin[2] Alexander Kuo[2] Walid Ayoub[2] Yun Wang[2] Aarshi Vipani[2] Emily Kaymen[1] Cristina Ferrone[4] Neil Mehta[5] Nguyen Tran[3] Paul Thevenot[6] Michael Li[5] Ju Dong Yang[2], [1]Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, [2]Karsh Division of Gastroenterology and Hepatology, Cedars-Sinai Medical Center, [3]Department of Medical Oncology, Mayo Clinic, Rochester, [4]Department of Surgery, Cedars-Sinai Medical Center, [5]Division of Gastroenterology and Hepatology, University of California, San Francisco, [6]Institute of Translational Research, Ochsner Clinic Foundation

Background: Immune checkpoint inhibitors (ICI) are standard-of-care for advanced hepatocellular carcinoma (HCC), yet immune-related adverse events (irAE) cause significant morbidity. Whether baseline antinuclear antibody (ANA) and smooth muscle antibody (SMA) predict irAE risk or treatment response in ICI-treated HCC has not been rigorously evaluated. **Methods:** We conducted a multi-institutional retrospective cohort study. Baseline ANA titer and SMA (positive defined as any reported positive or numeric value ≥ 20) were abstracted. Primary outcomes include any irAE and time to first irAE. Secondary outcomes include grade ≥ 3 irAE, hepatic irAE, objective response rate (ORR) [partial response (PR) + complete response (CR)], disease control rate (DCR), progression-free survival (PFS), and overall survival (OS). Site-adjusted and clinically adjusted logistic and Cox models were used to assess the association between autoantibodies and clinical outcomes. Site-adjusted models included institution as a covariate; clinically adjusted models additionally adjusted for age, sex, Child-Pugh score, and BCLC stage. **Results:** A total of 233 patients enrolled; median age 72 years, 75% male, 90% cirrhotic, 86% BCLC B/C. There was 183 patients (ANA-positive 69/183 [37.7%]) in the ANA-evaluable cohort. SMA-evaluable cohort incldued 189 patients (SMA-positive 57/189 [30.2%]). Baseline characteristics were balanced between ANA and SMA groups (all $p > 0.05$). ANA positivity was not associated with higher irAE rates (26.1% vs 34.2%; site-adj OR 0.59 [0.28–1.21], $p = 0.151$), grade ≥ 3 irAE (OR 0.85 [0.35–2.11], $p = 0.732$), or time to first irAE (HR 0.68 [0.38–1.22], $p = 0.198$). SMA positivity similarly showed no association with any irAE (36.8% vs 36.4%; OR 1.01 [0.51–1.96], $p = 0.988$), grade ≥ 3 irAE (OR 1.26 [0.49–3.22], $p = 0.626$), or hepatic irAE (OR 1.12 [0.41–3.05], $p = 0.829$). ORR was numerically lower with ANA positivity (23.4% vs 33.7%; fully adjusted OR 0.59 [0.27–1.32], $p = 0.200$) and SMA positivity (29.4% vs 35.4%; OR 0.59 [0.27–1.27], $p = 0.176$), but neither reached statistical significance. DCR, PFS, and OS were also non-significant for both antibodies (**Table**). In exploratory combined ANA/SMA phenotype analysis ($n = 139$), no phenotype group showed significantly different irAE rates vs the ANA−/SMA− reference (global χ^2 $p = 0.561$). **Conclusion:** In this multi-institutional study of 233 ICI-treated HCC patients, baseline ANA and SMA positivity did not independently predict irAE risk, severity, ORR, DCR, or survival. These null findings were consistent across primary, sensitivity, and combined phenotype analyses. Routine autoantibody screening does not guide irAE risk stratification or ICI candidacy decisions in HCC.

Autoantibody Status and Outcomes in ICI-Treated HCC (N = 233)

Outcome	ANA+ (n=69)	ANA− (n=114)	OR or HR (95% CI), p	SMA+ (n=57)	SMA− (n=132)	OR or HR (95% CI), p
TOXICITY						
Any irAE	18/69 (26.1%)	39/114 (34.2%)	OR 0.59 (0.28–1.21), p=0.151	21/57 (36.8%)	48/132 (36.4%)	OR 1.01 (0.51–1.96), p=0.988
Grade ≥3 irAE	9/69 (13.0%)	21/114 (18.4%)	OR 0.85 (0.35–2.11), p=0.732	8/51 (15.7%)	23/122 (17.2%)	OR 1.26 (0.49–3.22), p=0.626
Time to first irAE	NR	NR	HR 0.68 (0.38–1.22), p=0.198	NR	NR	HR 0.84 (0.55–1.30), p=0.425
TREATMENT RESPONSE						
ORR (PR + CR)	15/64 (23.4%)	32/95 (33.7%)	OR 0.59 (0.27–1.32), p=0.200	15/51 (29.4%)	40/113 (35.4%)	OR 0.59 (0.27–1.27), p=0.176
DCR (SD + PR + CR)	33/64 (51.6%)	50/95 (52.6%)	OR 0.95 (0.50–1.80), p=0.873	27/51 (52.9%)	64/113 (56.6%)	OR 0.85 (0.45–1.61), p=0.619
SURVIVAL						
Progression-free survival	Med 4.2 mo	Med 4.9 mo	HR 1.06 (0.75–1.49), p=0.756	Med 4.9 mo	Med 4.2 mo	HR 0.94 (0.70–1.26), p=0.705
Overall survival	Med 6.5 mo	Med 11.5 mo	HR 1.14 (0.79–1.66), p=0.488	Med 12.4 mo	Med 8.7 mo	HR 0.98 (0.67–1.43), p=0.917

HRs/ORs shown as fully adjusted estimates (site + age + sex + CTP/MELD + BCLC C/D) given comparable precision with adjusted p=0.063; all other differences are non-significant. NR = median not reached; ORR/DCR denominators exclude unevaluable/missing responses. All 95% CIs cross 1.0.

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4305 | COMPARATIVE EFFICACY AND SAFETY OF FIRST-LINE SYSTEMIC THERAPIES IN ADVANCED BILIARY TRACT CANCER: A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS

Rahul Falodia[1] Maheen Afzal[2] Ubaid Ahmed[3], [1]All India Institute of Medical Sciences Jodhpur, [2]University of Alabama at Birmingham, Montgomery, [3]Dow University of Health Sciences, Karachi, Pakistan

Background: The standard of care for first-line treatment of advanced biliary tract cancer (BTC) has rapidly evolved with the introduction of immune checkpoint inhibitors and triplet chemotherapy regimens. In the absence of head-to-head randomized controlled trials (RCTs), we conducted a network meta-analysis (NMA) to evaluate the comparative efficacy and safety of these novel regimens. **Methods:** A systematic literature search identified Phase II/III RCTs evaluating first-line systemic therapies for advanced BTC. A Bayesian NMA was performed to synthesize indirect comparisons. The primary outcome was overall survival (OS). Secondary outcomes included progression-free survival (PFS), objective response rate (ORR), and grade ≥ 3 adverse events (AEs). Treatment ranking was assessed using the surface under the cumulative ranking curve (SUCRA). **Results:** Ten RCTs encompassing over 3,000 patients and 10 distinct treatment regimens were included. Compared with standard gemcitabine plus cisplatin (GemCis), the addition of durvalumab (HR 0.74, 95% CrI 0.63–0.87) and pembrolizumab (HR 0.83, 95% CrI 0.72–0.95) significantly improved OS. Triplet chemotherapy regimens, including GemCis plus nab-paclitaxel (HR 0.93) and GemCis plus S-1 (HR 0.79), did not show a statistically significant OS benefit over GemCis. For ORR, triplet regimens ranked highest, with GemCis plus S-1 and GemCis plus nab-paclitaxel showing greater response rates than immuno-oncology doublet regimens. Grade ≥ 3 adverse events were highest with mFOLFIRINOX and nab-paclitaxel–based regimens, while immuno-oncology doublet regimens maintained a safety profile comparable to standard GemCis. **Conclusion:** Chemo–immunotherapy combinations (durvalumab plus GemCis and pembrolizumab plus GemCis) represent the optimal first-line systemic options for improving overall survival in advanced BTC. However, for patients requiring rapid tumor downstaging, triplet chemotherapy regimens achieve higher objective response rates, albeit with increased toxicity.

Disclosures: Rahul Falodia:Nothing to Disclose, Maheen Afzal:Nothing to Disclose, Ubaid Ahmed: Nothing to Disclose.

4306 | CIRCULATING TUMOR DNA AS A BIOMARKER FOR RECURRENCE DETECTION IN CURATIVELY TREATED CHOLANGIOCARCINOMA, A SYSTEMATIC REVIEW

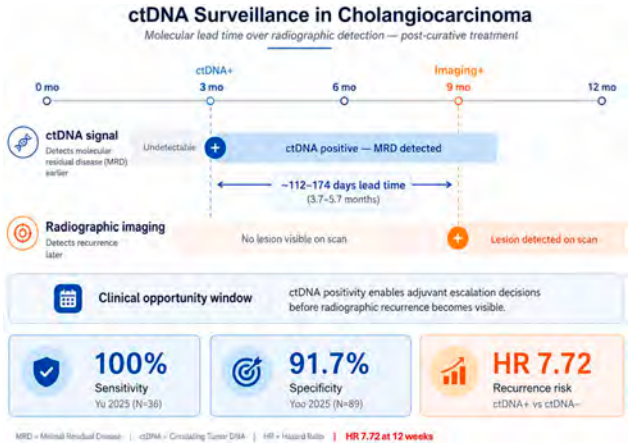
Ahmed Sayed Ahmed[1] Abdullah Ahmad[2] Sanna Farahat[3] Asmaa Soliman[4] Erlind Allkushi[1] Elise Hokr[1] Mariam Ismail[3] Sapana Verma[1] Kyungran Justina Cho[5] Chase Wehrle[1] Kim Jaekeum[1] Khalil Mazhar[1] Federico Aucejo[1], [1]Department of Surgery Transplantation Center, The Cleveland Clinic Foundation, OH, USA, [2]Hameed Latif Teaching Hospital, Lahore, Pakistan, [3]Faculty of Medicine, Delta University for Science and Technology, Gamasa, Egypt, [4]Faculty of Medicine, Zagazig University, Sharqia, Egypt, [5]Department of Gastroenterology, The Cleveland Clinic Foundation, OH, USA

Background: Cholangiocarcinoma (CCA) carries a dismal prognosis, with 5-year recurrence rates exceeding 60% following curative-intent treatment. Conventional surveillance including cross-sectional imaging and serum CA19-9 demonstrates insufficient sensitivity for early relapse detection. Circulating tumor DNA (ctDNA) as a surrogate for molecular residual disease (MRD) represents a promising paradigm shift for post-surgical risk stratification and treatment response monitoring

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Methods: Following a pre-registered PROSPERO protocol (CRD42026129755), PubMed, Embase, Scopus, and CENTRAL were systematically searched. Eligible studies enrolled adults with curatively treated CCA (resection or transplantation) who underwent post-treatment cell-free ctDNA analysis. Hazard ratios (HR) for survival outcomes and diagnostic accuracy metrics were extracted and narratively synthesized. **Results:** Three longitudinal cohort studies met inclusion criteria from 1,296 screened records. In the STAMP trial cohort (Yoo 2025, N = 89), post-operative ctDNA positivity independently predicted significantly worse recurrence-free survival at the pre-adjuvant chemotherapy baseline (HR 1.80, 95% CI 1.06–3.07; p = 0.029), 12 weeks into adjuvant therapy (HR 7.72, 95% CI 4.09–14.56; p < 0.001), and 24 weeks into adjuvant therapy (HR 5.24, 95% CI 2.75–9.97; p < 0.001). Diagnostically, Yu 2025 (N = 36) demonstrated a surveillance sensitivity of 100%, specificity of 84%, PPV of 73.3%, and NPV of 100%, with a median molecular lead time of 112.6 days preceding radiographic detection. Yoo 2025 yielded a sensitivity of 69.2%, specificity of 91.7%, PPV of 95.7%, and NPV of 52.4%, with a mean lead time of 174 days. In a small liver transplantation cohort (Abdelrahim 2025, N = 4), all diagnostic metrics reached 100% in the CCA subpopulation, though this finding requires cautious interpretation given the limited sample size **Conclusion:** Post-treatment ctDNA dynamics constitute highly sensitive and specific biomarkers for predicting relapse in curatively treated cholangiocarcinoma, consistently anticipating radiographic recurrence by three to six months. While the current evidence base remains limited to three cohort studies, these findings support prospective integration of ctDNA surveillance into post-treatment monitoring frameworks and future trials evaluating ctDNA-guided adjuvant escalation strategies.



Disclosures: Ahmed Sayed Ahmed:Nothing to Disclose, Abdullah Ahmad:Nothing to Disclose, Sanna Farahat:Nothing to Disclose, Asmaa Soliman:Nothing to Disclose, Erlind Allkushi:Nothing to Disclose, Elise Hokr:Nothing to Disclose, Mariam Ismail:Nothing to Disclose, Sapana Verma:Nothing to Disclose, Kyungran Justina Cho:Nothing to Disclose, Chase Wehrle:Nothing to Disclose, Kim Jaekeum:Nothing to Disclose, Khalil Mazhar:Nothing to Disclose, Federico Aucejo:Nothing to Disclose.

4307 | DISTINCT ALPHA-FETOPROTEIN TRAJECTORIES DURING THE FIVE YEARS PRECEDING HEPATOCELLULAR CARCINOMA DIAGNOSIS: A LATENT CLASS MIXED-MODEL ANALYSIS

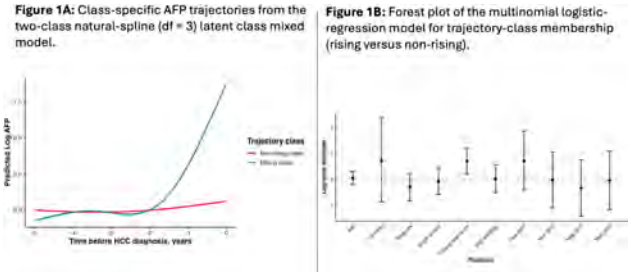
Apichat Kaewdech[1] Chanavee Toh[2] Pimsiri Sripongpun[1] Naichaya Chamroonkul[1] Pisit Tangkijvanich[3] Teerha Piratvisuth[1] Suthat Liangpunsakul[4] Thammasin Ingviya[5] Paramee Thongsuksai[1], [1]Prince of Songkla University, [2]Faculty of Medicine, Prince of Songkla University, [3]Chulalongkorn University, [4]Indiana University School of Medicine, [5]Baylor College of Medicine

Background: Hepatocellular carcinoma (HCC) is frequently diagnosed at an advanced stage, and serum alpha-fetoprotein (AFP), the most widely used biomarker for HCC surveillance, exhibits substantial interpatient variability. We characterized longitudinal AFP trajectories during the five years preceding HCC diagnosis and identified clinical features associated with rising versus non-rising AFP patterns. **Methods:** We analyzed 529 patients with newly diagnosed HCC at Songklanagarind Hospital, each with at least three serum AFP measurements obtained within five years before diagnosis. Log-transformed AFP values were modeled using latent class mixed models (LCMMs) with natural cubic splines (degrees of freedom 3–5) and linear fixed and random effects for time. Optimal model complexity was selected based on Bayesian Information Criterion (BIC), entropy, and clinical interpretability. Multinomial logistic regression and Cox proportional hazards models were used to evaluate associations between AFP trajectory class, baseline characteristics, and overall survival. **Results:** A two-class natural spline model (df = 3) provided the most parsimonious and clinically interpretable solution (BIC = 9003). Class 1 ("non-rising," n = 440; 83.2%) demonstrated a near-flat AFP trajectory throughout the observation period, whereas Class 2 ("rising," n = 89; 16.8%) exhibited an exponential increase beginning approximately 18–24 months before diagnosis. Compared with the non-rising group, patients in the rising group were significantly more likely to present with tumors > 2 cm (78% vs 62%; p = 0.009). The rising trajectory group was also associated with shorter overall survival on log-rank analysis (p = 0.03), although this association attenuated after adjustment for Barcelona Clinic Liver Cancer (BCLC) stage. **Conclusion:** Two distinct AFP

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trajectories were identified during the five years preceding HCC diagnosis. Most patients (approximately 83%) did not demonstrate meaningful AFP elevation, underscoring the need for complementary surveillance biomarkers. In contrast, the minority with a rising AFP trajectory may benefit from risk-stratified intensification of imaging surveillance.



Disclosures: Apichat Kaewdech:Nothing to Disclose, Chanavee Toh:Nothing to Disclose, Pimsiri Sripongpun:Novo Nordisk: Speaking and Teaching, Takeda: Speaking and Teaching, Nestle: Speaking and Teaching, Zuellig Pharma: Speaking and Teaching, Thai Meiji: Speaking and Teaching, Thai Otsuka: Speaking and Teaching, Naichaya Chamroonkul:Nothing to Disclose, PISIT TANGKIJVANICH:Nothing to Disclose, Teerha Piratvisuth:Nothing to Disclose, Suthat Liangpunsakul:Durect Corporation: Consultant, Surrozen: Consultant, Korro Bio: Consultant, Durect Corporation: Consultant, Dimension Bio: Consultant, Thammasin Ingviya:Nothing to Disclose, Paramee Thongsuksai:Nothing to Disclose.

4308 | CONDITIONAL SURVIVAL AFTER ABLATION FOR LOCALIZED HEPATOCELLULAR CARCINOMA AND THE ASSOCIATION OF TUMOR SIZE WITH PROGNOSIS

Henry Souto[1] George Ashji[1] Dustin Roberts[1], [1]Rutgers New Jersey Medical School

Background: Tumor size is an important prognostic factor in localized hepatocellular carcinoma and is routinely utilized in framing expectations for survival and treatment planning. However, survival estimates calculated at diagnosis may become less informative for patients who have already survived beyond the early high-risk period. This study uses a conditional survival approach to examine how baseline tumor size and other factors are associated with prognosis over time. **Methods:** Using SEER 2004-2017, we identified 6,088 adults with localized hepatocellular carcinoma treated with ablation only (transplant recipients were excluded), with known tumor size (≤ 2, 2.1-3, 3.1-5, >5 cm). Conditional survival was assessed at 1-, 2-, 3-, and 5-year landmarks, with time-to-event recalculated at each landmark. Cancer-specific mortality and overall mortality were analyzed. Cumulative incidence functions were estimated nonparametrically and stratified by tumor size, and multivariable Fine-Gray and Cox regression models were performed at each landmark, adjusting for tumor size, age, sex, race/ethnicity, diagnosis year, and grade. Analyses were performed in R version 4.2.2. **Results:** Five-year post-landmark conditional all-cause survival improved with longer survivorship, and differences by tumor size narrowed over time (Figure 1). Among tumors >5 cm, 5-year conditional survival increased from 26% at the 1-year landmark to 48% at the 5-year landmark; among tumors ≤ 2 cm, it increased from 48% to 56%. For overall mortality, the hazard ratio for >5 cm versus ≤ 2 cm tumors attenuated from 1.54 (95% CI 1.26-1.88, $p<0.001$) at the 1-year landmark to 1.16 (95% CI 0.88-1.53, $p=0.293$) at the 3-year landmark, remaining insignificant at the 5-year landmark. A similar pattern was shown in adjusted Fine-Gray subdistribution hazards for cancer-specific mortality. Older age was associated with higher mortality at all landmarks (HR per additional year 1.02-1.04, $p < 0.001$), while later diagnosis year was a significant predictor of decreased overall mortality across all landmarks (HR per additional year 0.94-0.97, $p < 0.001$). **Conclusion:** Conditional survival estimates capture the dynamic prognosis in HCC ablation patients over time, providing a more clinically meaningful foundation for survivorship counseling than risk stratification at the time of diagnosis. These findings are relevant to improving post-ablation surveillance strategies.

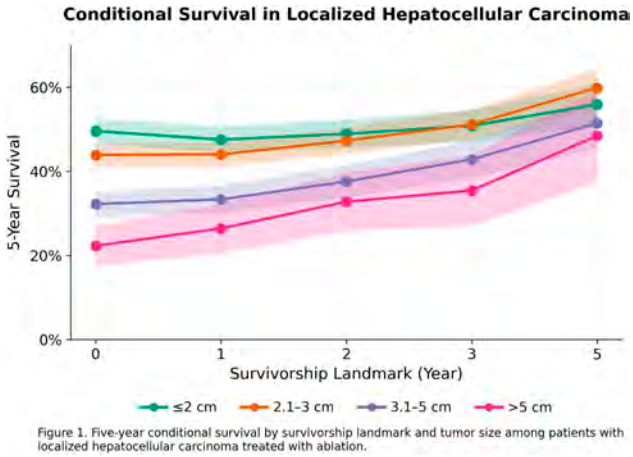


Figure 1. Five-year conditional survival by survivorship landmark and tumor size among patients with localized hepatocellular carcinoma treated with ablation.

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4309 | PALLIATIVE MEDICINE UTILIZATION FOR OLDER ADULTS WITH HEPATOCELLULAR CARCINOMA REFERRED FOR LIVER TRANSPLANTATION

Gavisha Waidyaratne[1] Jason Benedict[1] Leanna Perez Eiterman[2] Laura Rush[2] Sean Kelly[1] Jessica Merlin[1] Ann McAlearney[2] Brittany Waterman[3], [1]The Ohio State University Wexner Medical Center, [2]The Ohio State College of Medicine, [3]The Ohio State Wexner Medical Center

Background: The incidence and prevalence of chronic liver disease and hepatocellular carcinoma (HCC) for older adults ($\geq$ 65 years) have continued to increase worldwide, with a subsequent increase in the proportion of older adults referred for liver transplantation (LT) evaluation. Evidence suggests that long term outcomes for older adults are similar to younger cohorts when stratified by stage and treatment, including LT. However, older adults with HCC often have more advanced disease at diagnosis and have been shown to receive less disease-directed treatment, including locoregional therapies, surgical resection, and LT, as compared with younger cohorts. Older adults with HCC referral for LT have considerable and often unmet palliative care (PC) needs related to prognostic uncertainty, high rates of LT deferral, morbidity, and mortality. Existing PC patterns and association with outcomes for these patients have not yet been fully described, which is an important step in developing the evidence base needed to guide PC integration for this high-need group. **Methods:** We conducted a retrospective chart review to describe PC utilization and health outcomes for older adults with ESLD referred for LT evaluation between 7/1/2015 and 6/30/2021. Outcomes were followed through 6/30/22. This project represents a subgroup analysis examining patients with HCC within the larger cohort. **Results:** Within the HCC subgroup (N = 102; 24% of total cohort of N = 421), formal LT evaluation was initiated for 76% of patients (N = 78), while in comparison, LT evaluation was initiated for 66% of the non-HCC cohort (N = 209) (p = 0.04). LT deferral occurred in 42% (N = 33) of the HCC group while in only 32% (N = 100) of the non-HCC group (p = 0.10). Of those approved for LT, successful completion of LT occurred in 41% (N = 32) of the HCC group and 47% (N = 130) of the non-HCC group (p = 0.37). Finally, death in the study period occurred in 48% of both the HCC (N = 49) and the non-HCC (N = 152) groups (p > 0.95). Within HCC patients, PC encounters occurred for 31 patients (30% vs. N = 77, 24% in the non-HCC group, p = 0.24). Those without PC referrals had higher rates of LT referral (80% vs 68%), higher rates of LT completion (75% vs 56%), and lower rates of LT deferral (37% vs 57%) as compared with those who had PC encounters. A larger proportion of patients died in the group who received PC (84% vs. 32%). **Conclusion:** As compared with the non-HCC cohort, the subgroup of older adults with HCC had higher rates of LT referral, lower rates of LT deferral, and lower rates of LT completion. Patients with HCC who encountered PC had lower rates of LT referral and completion, as well as higher rates of LT deferral. This finding suggests that PC referrals may be more commonly pursued for patients unable to complete the LT process. However, the temporal relationship between these LT outcomes and PC encounters is not defined in this dataset but will be examined in future studies.

Disclosures: Gavisha Waidyaratne:Nothing to Disclose, Jason Benedict:Nothing to Disclose, Leanna Perez Eiterman:Nothing to Disclose, Laura Rush:Nothing to Disclose, Sean Kelly:Nothing to Disclose, Jessica Merlin:Nothing to Disclose, Ann McAlearney:Nothing to Disclose, Brittany Waterman:Nothing to Disclose.

4310 | VISION-LANGUAGE MODEL–DERIVED COMPUTED TOMOGRAPHY PHENOTYPES ARE ASSOCIATED WITH SURVIVAL AFTER TRANSARTERIAL CHEMOEMBOLIZATION

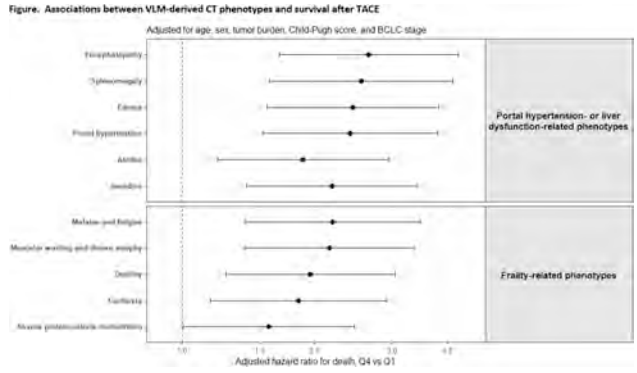
Philip Vutien[1] George Ioannou[2] Amilcare Gentili[3] Chunnan Hsu[3], [1]University of Washington Medical Center, [2]University of Washington, [3]Veterans Affairs San Diego Healthcare System

Background: Accurate risk stratification of HCC patients after transarterial chemoembolization (TACE) remains challenging, as conventional staging systems incompletely capture liver function, portal hypertension, and patient frailty. Vision–language models (VLMs) such as Merlin can generate interpretable Computed Tomography (CT)-derived phenotypes aligned with clinically meaningful concepts. We evaluated whether VLM-derived CT phenotypes reflecting portal hypertension, liver dysfunction, and frailty are independently associated with overall survival after TACE. **Methods:** Using the publicly available WAW-TACE dataset, we analyzed 233 patients with hepatocellular carcinoma (HCC) with multiphase CT imaging $\leq$ 90 days before initial TACE, excluding those with metastatic disease, vascular invasion, or Child–Pugh class C. A pretrained VLM (Merlin) was applied to baseline CT imaging to generate probabilistic imaging-derived phenotypes that are associated with clinical diagnoses. Phenotype probabilities were stratified into quartiles and each phenotype was evaluated in separate Cox proportional hazards models for associations with overall survival adjusting for age, sex, tumor burden (number and

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largest lesion diameter), Child–Pugh score, and Barcelona Clinic Liver Cancer stage. **Results:** Median age was 66 years, 48 (21%) were women, 149 (64%) had unifocal disease, and the median largest tumor diameter was 4.5 cm (IQR 3–6.2). During a median follow-up of 871 days (IQR 332–1,386), 170 (73%) patients died. VLM-derived CT phenotypes demonstrated strong, graded associations with overall survival. In multivariable analyses, the highest versus lowest quartile of portal hypertension–or liver-dysfunction related phenotypes - including splenomegaly (aHR 2.55, 95% CI 1.58–4.12), ascites (aHR 1.88, 95% CI 1.20–2.94), CT-correlates of encephalopathy (aHR 2.69, 95% CI 1.66–4.23), and jaundice (aHR 2.19, 95% CI 1.40–3.43) - was associated with increased mortality. Similarly, frailty-related features including cachexia (aHR 1.84, 95% CI 1.16–2.91) and muscular wasting (aHR 2.16, 95% CI 1.39–3.36), were independently associated with worse survival. **Conclusion:** VLM-derived CT phenotypes captured imaging signatures of portal hypertension, liver dysfunction, and frailty that were independently associated with overall survival after TACE. These findings suggest that VLM-based imaging phenotypes may provide complementary, noninvasive risk stratification and warrant further validation in larger multi-center cohorts.



Disclosures: Philip Vutien:Nothing to Disclose, George Ioannou:GlaxoSmithKline(GSK): Grant/Research Support, Amilcare Gentili:Nothing to Disclose, Chunnan Hsu:Nothing to Disclose.

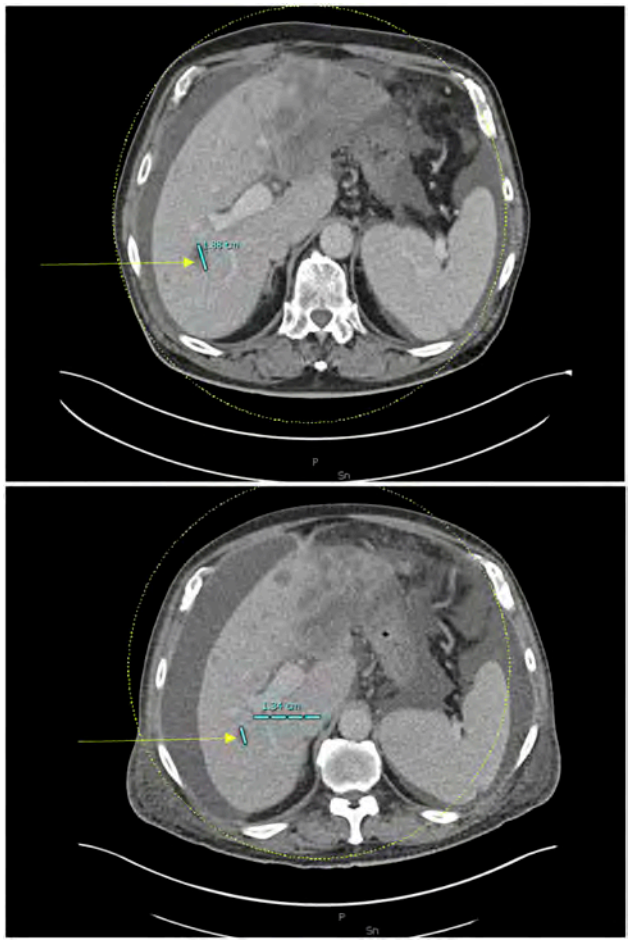
4311 | WHEN TUMOR RESPONSE FAILS THE PATIENT: REAL-WORLD LIMITATIONS OF FUTIBATINIB IN FGFR2-REARRANGED INTRAHEPATIC CHOLANGIOCARCINOMA

Joshika Agarwal[1] Abul Hasan Shadali Abdul Khader[2] Jaison Lawrence Alexander Santhi[2] Rajesh Thirumaran[2], [1]Mercy Catholic Medical Center, [2]Mercy Catholic Medical Center, Darby, PA

Background: Biliary tumors, including intrahepatic cholangiocarcinoma (ICC), are rare tumors with a poor median survival of around one year. Patients are often asymptomatic, resulting in advanced-stage presentation, making tumor detection and treatment difficult. We present the case of an advanced ICC harboring fibroblast growth factor receptor (FGFR2 fusion), managed on a targeted therapy, Futibatinib, commonly known as Lytgobi. This case highlights the diverse real-world outcomes of the drug in comparison to results obtained in the clinical trial in 2022, which resulted in the drug's accelerated approval in the US. **Methods:** A 74-year-old male presented with one week of severe abdominal pain, fatigue, and weight loss. Vitals and labs, including AFP and CEA, were unremarkable. MRI abdomen revealed a 9.4 cm left hepatic lobe mass with intrahepatic bile duct dilation and lymphadenopathy. A liver biopsy was consistent with advanced cholangiocarcinoma. The patient was started on combination chemotherapy with gemcitabine, cisplatin, and pembrolizumab. Subsequent next-generation sequencing identified a fibroblast growth factor receptor (FGFR2) fusion, and therapy was switched to futibatinib, an irreversible FGFR 2 inhibitor. Over the course of treatment, the patient developed recurrent ascites requiring paracentesis with albumin replacement. He was still maintained on the escalating doses of futibatinib based on follow-up imaging displaying some response to the drug. However, due to progressive clinical decline, he was transitioned to hospice care despite the first four months of tolerance on futibatinib therapy. **Results:** The FOENIX-CCA2 trial, under its Phase 2, demonstrated an objective response rate of 42%, a median response duration of 9.7 months, and a median time to response of 2.5 months, along with a manageable adverse effect, including hyperphosphatemia, in patients with unresectable or metastatic ICC treated with futibatinib. In this case, the patient tolerated the medication well with mild side effects of nausea, vomiting, and constipation. However, ascitic fluid analysis that revealed an elevated serum–ascites albumin gradient (SAAG) > 1.1, indicating portal hypertension due to underlying cirrhosis and hepatic metastasis causing portal vein occlusion, further worsened by hypoalbuminemia, was the likely culprit for refractory ascites, rather than direct drug-related effects indicative of disease progression. **Conclusion:** Initial response to targeted molecular therapies does not preclude challenges, including hepatic decompensation that can outpace tumor response, limiting overall clinical benefit. The ongoing FOENIX-CCA3 trial is anticipated to emphasize such limitations for optimizing therapeutic outcomes.

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Disclosures: Joshika Agarwal:Nothing to Disclose, Abul Hasan Shadali Abdul Khader:Nothing to Disclose, Jaison Lawrence Alexander Santhi:Nothing to Disclose, Rajesh Thirumaran:Nothing to Disclose.

4312 | CONSTRUCTION AND VALIDATION OF A NOMOGRAM FOR PREDICTING PROGRESSION-FREE SURVIVAL IN AFP-NEGATIVE HEPATOCELLULAR CARCINOMA PATIENTS BASED ON AGE, VASCULAR INVASION, PIVKA-II, AND GGT

Yanhui Shi[1] Wenjun Du[2] Shiyu Wang[3] Weihua Cao[3] Wen Deng[3] Xulong Zhang[4] Minghui Li[3], [1]Department of Hepatology Division 2, Beijing Ditan Hospital,Capital Medical University, Beijing, [2]Department of Liver Diseases, Shandong Public Health Clinical Center, Shandong University, Jinan, [3]Department of Hepatology Division 2, Beijing Ditan Hospital, Capital Medical University, Beijing, [4]HBV Infection, Clinical Cure and Immunology Joint Laboratory for Clinical Medicine, Capital Medical

Background: Alpha-fetoprotein (AFP) serves as a crucial prognostic indicator for individuals diagnosed with hepatocellular carcinoma (HCC). Drawing upon real-world clinical evidence, our research sought to develop and verify a progression-free survival (PFS) prediction model for AFP-negative HCC via LASSO-Cox regression, and to explore the risk factors for early progression in this population receiving standard treatment. **Methods:** Clinical data from 72 AFP-negative HCC patients receiving various standardized treatments (including curative and non-curative modalities) were retrospectively analyzed. LASSO and multivariable Cox regression identified prognostic factors to construct the nomogram. Model performance was evaluated via C-index, ROC, calibration, and decision curve analysis (DCA). Internal validation was conducted using bootstrap resampling, and external validation was performed in The Cancer Genome Atlas (TCGA) cohort. **Results:** Among the 72 patients, 65 experienced disease progression or death (62 progressions and 3 deaths), all of which were early endpoint events ($\leq$2 years). Among them, 36 patients experienced very early progression ($\leq$1 year). The median PFS for this cohort was 6.28 months. Subsequent multivariable Cox regression assessment identified Age (HR : 1.037, P = 0.035), PIVKA-II (HR : 2.326, P = 0.002), Vascular invasion (HR : 1.909, P = 0.024), and GGT (HR : 1.006, P = 0.003) as independent risk factors for early progression in AFP-negative HCC. An individualized nomogram was subsequently developed incorporating these independent risk factors. The model's C-index was 0.705 (95% CI: 0.644 - 0.767) in the training set. After internal validation and correction using the Bootstrap method, yielding an optimism-adjusted C-index of 0.688 (95% CI: 0.627–0.750) alongside a minimal optimism of 0.017. External validation results showed a model C-index of 0.622 (95% CI: 0.475–0.768). Time-dependent ROC curve assessments exposed that the areas under the curve (AUC) for predicting half-year and 12-month PFS in the internally corrected training dataset were 0.723 and 0.738, respectively. The calibration curve demonstrated good fit. DCA indicated that the nomogram provided a good net clinical benefit across a wide range of threshold probabilities. After grouping patients based on the nomogram risk scores, the disparity in PFS between the high and low-risk groups reached statistical significance, suggesting that the model has good risk stratification capability. **Conclusion:** The nomogram model based on Age, Vascular invasion, PIVKA-II and GGT can effectively predict PFS in AFP-negative HCC patients. It provides a strategy for clinicians to optimize treatment plans earlier, adjust follow-up strategies and enhance the prognosis of patients with AFP-negative HCC.

Disclosures: yanhui shi:Nothing to Disclose, Wenjun Du:Nothing to Disclose, Shiyu Wang:Nothing to

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4313 | INTRAVENOUS AT-101 DEMONSTRATES FAVORABLE TOLERABILITY AND DIRECTIONAL TUMOR-GROWTH SUPPRESSION IN AN SK-HEP-1 MURINE XENOGRAFT MODEL OF HEPATOCELLULAR CARCINOMA

Stanley Lewis[1], [1]A28 Therapeutics, Inc

Background: Hepatocellular carcinoma (HCC) remains a major cause of global cancer mortality, necessitating continued development of novel therapeutic approaches. AT-101, a lytic peptide that targets the gonadotropin-releasing hormone receptor, was evaluated for anti-tumor efficacy in a murine SK-Hep-1 xenograft model of HCC. This study aimed to determine whether repeated intravenous dosing of AT-101 suppresses tumor growth compared with vehicle and the reference standard sorafenib. **Methods:** Male Nu/J mice (n = 31) were implanted subcutaneously with 3×10^6 SK-Hep-1 cells. When mean tumor volume reached approximately 75 mm³, animals were randomized into three treatment groups: AT-101 (n = 11, twice-weekly IV), vehicle control (n = 10, twice-weekly IV), and sorafenib (n = 10, daily oral gavage). Treatments were administered for three weeks. Tumor volumes were measured three times weekly. Body weight and detailed clinical observations were recorded at baseline, early study time points, and weekly thereafter. At study completion, animals were euthanized, and gross necropsy evaluations were performed. Terminal tumor weights were collected, and tumors were flash-frozen for potential future analyses. **Results:** AT-101–treated mice demonstrated lower mean terminal tumor volumes (124.12 mm^3) relative to both vehicle- (182.18 mm^3) and sorafenib-treated (145.39 mm^3) groups throughout the treatment period, although these differences did not reach statistical significance. Mean terminal tumor weights were likewise reduced in the AT-101 (0.069g) and sorafenib groups (0.084g) compared with vehicle (0.104g). Body weights remained stable across all treatment arms, with no evidence of systemic toxicity or treatment-related clinical abnormalities. Necropsy revealed two isolated liver findings—one AT-101–treated mouse with a small hard hepatic deposit and one vehicle-treated mouse with a pale mottled liver—both considered incidental and unrelated to treatment due to lack of recurrence or dose response. No adverse events or unscheduled deaths occurred. **Conclusion:** Repeated intravenous dosing of AT-101 was well tolerated and associated with a consistent trend toward reduced tumor growth in this SK-Hep-1 xenograft model of HCC. Although statistical significance was not achieved, the directionality of tumor reduction and favorable safety profile support further evaluation of AT-101 in dose-optimization, mechanistic, or combination-therapy studies.
Disclosures: Stanley Lewis:Nothing to Disclose.

4314 | CLINICAL FEATURES, TREATMENT PATTERNS, AND OUTCOMES OF YOUNG-ONSET HEPATOCELLULAR CARCINOMA: A TERTIARY COHORT ANALYSIS WITH A NATIONWIDE POPULATION-BASED STUDY

Eunju Kim[1] Jina Park[2] Sung Won Chung[2] Won-Mook Choi[2] Danbi Lee[2] Ju Hyun Shim[2] Kang Mo Kim[2] Young Suk Lim[2] Han Chu Lee[2] Jonggi Choi[3], [1]Chung-Ang University, [2]Asan Medical Center, [3]University of Ulsan, Asan Medical Center

Background: Hepatocellular carcinoma (HCC) in younger patients is uncommon, and its clinical characteristics and prognosis remain uncertain. We aimed to evaluate the clinical features, treatment patterns, and outcomes of young-onset HCC using large-scale datasets. **Methods:** This study included two cohorts: the Asan Medical Center (AMC) HCC registry (2009–2023) and the nationwide Korean Liver Cancer Association (KLCA) registry. Young-onset HCC was defined as age ≤ 40 years. Outcomes were compared between young (≤ 40 years) and non-young (> 40 years) patients, with additional analyses across three age groups (≤ 40, 41–65, > 65 years). Propensity score matching (PSM) was performed to adjust for baseline differences. Overall survival (OS), recurrence-free survival (RFS), treatment patterns, and treatment intensity were evaluated. In the KLCA cohort, survival analyses were limited to patients diagnosed between 2015 and 2021. **Results:** A total of 21,699 patients in the AMC cohort and 21,178 in the KLCA cohort were included. Young-onset HCC accounted for 955 (4.4%) and 627 (3.0%) cases, respectively. Before matching, younger patients had larger tumors, higher alpha-fetoprotein levels, and more advanced disease. After PSM, OS was comparable between groups in the AMC cohort (median 3.8 vs. 4.0 years; p = 0.890) and the KLCA cohort (median 3.7 vs. 2.9 years; p = 0.053). Stage-stratified analyses showed no significant differences in OS. RFS was also similar between groups in the AMC cohort. Initial treatment distribution and longitudinal treatment intensity were comparable, whereas patients aged > 65 years were less likely to receive curative treatments. **Conclusion:** Young-onset HCC shows more aggressive tumor features but comparable outcomes

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after adjustment. Age alone may not be an independent determinant of prognosis.

Disclosures: Eunju Kim:Nothing to Disclose, Jina Park:Nothing to Disclose, SUNG WON CHUNG:Nothing to Disclose, Won-Mook Choi:Gilead Sciences: Speaking and Teaching, AbbVie: Speaking and Teaching, Roche: Consultant, Boehringer Ingelheim: Advisor, GSK: Consultant, Eisai: Speaking and Teaching, AstraZeneka: Speaking and Teaching, Danbi Lee: Nothing to Disclose, Ju Hyun Shim:Nothing to Disclose, Kang Mo Kim:Nothing to Disclose, Young Suk Lim: Gilead Sciences: Grant/Research Support, Han Chu Lee:Roche: Grant/Research Support, BMS: Grant/Research Support, Astrazeneca: Grant/Research Support, Merck: Grant/Research Support, Jonggi Choi: Nothing to Disclose, Nothing to Disclose.

4315 | REAL-WORLD OUTCOMES AND PREDICTORS OF RESPONSE TO FIRST-LINE STRIDE IN UNRESECTABLE HEPATOCELLULAR CARCINOMA: FOCUS ON VP4 PORTAL VEIN TUMOR THROMBUS

Chi-Jung Wu[1] Ming-Chieh Hsieh[1] Pei-Chang Lee[1] Chen-Ta Chi[1] I-Cheng Lee[1] Chieh-Ju Lee[1] Ming-Chih Hou[1] Yi-Hsiang Huang[1], [1]Taipei Veterans General Hospital

Background: While the STRIDE regimen (tremelimumab plus durvalumab) is a standard first-line treatment for unresectable hepatocellular carcinoma (uHCC), patients with Vp4 portal vein tumor thrombus (PVTT) remain severely underrepresented in landmark clinical trials. As a result, real-world evidence guiding the use of STRIDE in this ultra-high-risk cohort is highly limited. This study evaluated the real-world efficacy and safety of first-line STRIDE therapy in uHCC and sought to identify key clinical predictors of objective response. **Methods:** Between December 2023 and February 2026, 90 consecutive patients with advanced HCC receiving first-line STRIDE therapy at Taipe Veterans General Hospital were prospectively enrolled. Tumor response was assessed by RECIST v1.1; AEs were graded using CTCAE v5.0. Survival curves were calculated via the Kaplan–Meier method. Predictors of objective response were determined using multivariable logistic regression. **Results:** Of the 90 patients enrolled, 85.6% (n = 77) had Child–Pugh class A liver function, 90.0% (n = 81) had BCLC stage C disease, and 22.2% (n = 20) presented with Vp4 PVTT. Over a median follow-up of 6.6 months (ranged: 0.7-27.4), the median progression-free survival (PFS) was 3.7 months (95% CI: 1.5–5.9), while median overall survival was not reached. Survival outcomes did not differ significantly between patients with and without Vp4 PVTT. Notably, robust antitumor activity was preserved in the Vp4 PVTT subgroup, which achieved an objective response rate (ORR) of 40.0% and a disease control rate (DCR) of 65.0%. Multivariable analysis identified infiltrative tumor morphology (OR:6.42, 95% CI:1.66-24.80; p = 0.007) and a lower tumor burden score (within up-to-11 criteria) (OR:3.76, 95% CI:1.22-11.57; p = 0.021) as independent predictors of objective response. Grade $\geq$ 3 treatment-related AEs (TRAEs) reported in 20.0%. High-dose corticosteroids were required in 18.9% of patients, and 8.9% discontinued treatment due to toxicity. **Conclusion:** This real-world study confirms the favorable therapeutic index of first-line STRIDE in uHCC, extending its clinical utility to high-risk patients with Vp4 PVTT. Furthermore, the unexpected link between infiltrative morphology and improved objective response implies a unique immune susceptibility in this aggressive subgroup, offering a potential clinical selection tool for optimizing dual immunotherapy.

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4316 | PALLIATIVE CARE IN THE MANAGEMENT OF HEPATOCELLULAR CARCINOMA

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Background: Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer, and patients often present with advanced stage disease and poor overall survival despite surveillance recommendations. Patients with HCC experience substantial impairments in quality of life, including significant physical and emotional distress arising from the combined burden of malignancy and underlying chronic liver disease. However, the incorporation of palliative and hospice care in the management of HCC is limited, and the existing literature within this realm represents an opportunity for further optimization of care. **Methods:** This scoping review followed the PRISMA guidelines (PROSPERO protocol CRD42019123398). Our study focused on articles investigating attitudes towards, experiences with, and clinical outcomes related to palliative care (PC) or hospice care in patients with HCC. Studies indexed in Pubmed, Embase, and Cochrane Library and published between January 1, 1965 until January 24, 2026 that met inclusion criteria were analyzed. These studies were subsequently assessed for risk of bias with the Joanna Briggs Institute Critical Appraisal tools. **Results:** The 22 included studies consisted of 3 qualitative studies and 19

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quantitative studies; the quantitative evidence was predominantly retrospective observational in design (14 cohort studies, 4 cross-sectional analyses, and 1 case series), with only 1 pilot randomized controlled trial. Most articles were at moderate to serious risk of bias. Outcomes were classified by five distinct categories: current practice trends, caregiver and patient perspectives; end-of-life outcomes and hospice; resource utilization and cost; and health disparities. Clinician accounts revealed infrequent and delayed specialty PC and hospice referrals for patients and limited training in PC among hepatologists, despite recognizing the importance of multidisciplinary supportive care. Patients expressed negative misconceptions about PC, but education on PC improved patient perceptions and referral to PC improved quality of life and decreased physical symptom burden, such as pain and pruritus. Notable disparities in access to palliative care and hospice were observed around insurance coverage and racial and ethnic background, such as Black and Hispanic patients having less frequent hospice utilization compared to White patients. Palliative and hospice care reduced inpatient expenditures overall and invasive interventions in terminal hospitalizations. **Conclusion:** The care of patients with HCC requires a standardized, multidisciplinary approach that individualizes palliative and hospice care for patients. Future research and integrated care models that focus on clinician education, patient-reported outcomes, and equity are essential to provide high quality care to this patient population.

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4317 | PROGNOSTIC ROLE OF ABSOLUTE EOSINOPHIL COUNT IN PATIENTS WITH HEPATOCELLULAR CARCINOMA TREATED WITH ATEZOLIZUMAB PLUS BEVACIZUMAB

Jung Pyo Hong[1] Yeo Wool Kang[2] Jun Sik Yoon[3] Jeong Eun Song[4] Joon Ho Jeong[5] Yu Rim Lee[6] Jae Hyun Yoon[7] Young Mi Hong[8] Sang Youn Hwang[9] Hyun Young Woo[10] Yang Hyun Baek[2] Soo Young Park[6] Sung Bum Cho[11] Hyun Chin Cho[1], [1]Gyeongsang National University College of Medicine, [2]Dong-A University College of Medicine, [3]Inje University College of Medicine, [4]Catholic University of Daegu School of Medicine, [5]University of Ulsan College of Medicine, [6]School of Medicine, Kyungpook National University, [7]Chonnam National University Hospital, School of Medicine, [8]College of Medicine, Pusan National University, [9]Dongnam Institute of Radiologic & Medical Sciences, [10]College of Medicine, Pusan National University and Biomedical Research Institute, [11]Chonnam National University Medical School

Background: Atezolizumab plus bevacizumab is the standard first-line treatment for advanced hepatocellular carcinoma (HCC). However, predictive biomarkers for survival remain scarce. We investigated the prognostic value of baseline and early kinetic changes in absolute eosinophil count (AEC) in patients receiving this combination therapy. **Methods:** We analyzed a multicenter, retrospective cohort of 1,153 patients with HCC treated with atezolizumab plus bevacizumab. The optimal baseline AEC cut-off was determined as 54 /μL (equivalent to 0.95% of the median white blood cell count). We assessed overall survival (OS) and progression-free survival (PFS) using Kaplan-Meier methods and multivariable Cox proportional hazards models. Inverse probability of treatment weighting (IPTW) mitigated baseline confounding. A 3-week landmark analysis evaluated the impact of AEC kinetics ($\geq$ 86 /μL). **Results:** High baseline AEC ($\geq$ 54 /μL) was present in 920 patients (79.8%). Patients with high AEC demonstrated significantly improved OS (HR 0.63; 95% CI 0.52–0.75; $P < 0.001$) and PFS (HR 0.77; 95% CI 0.65–0.91; $P = 0.002$) in multivariable analysis compared to the low AEC group ($n = 233$). This survival benefit persisted after IPTW adjustment for OS (HR 0.70; 95% CI 0.54–0.91; $P = 0.007$). The prognostic advantage of high baseline AEC remained consistent across patients with preserved liver function (Child-Pugh A). In the landmark analysis ($n = 900$), maintaining or achieving an AEC $\geq$ 86 /μL at 3 weeks was significantly associated with superior OS ($P = 0.002$) and PFS ($P < 0.001$). **Conclusion:** Baseline AEC and its early kinetics serve as simple, universally accessible prognostic biomarkers for patients with HCC receiving atezolizumab plus bevacizumab.

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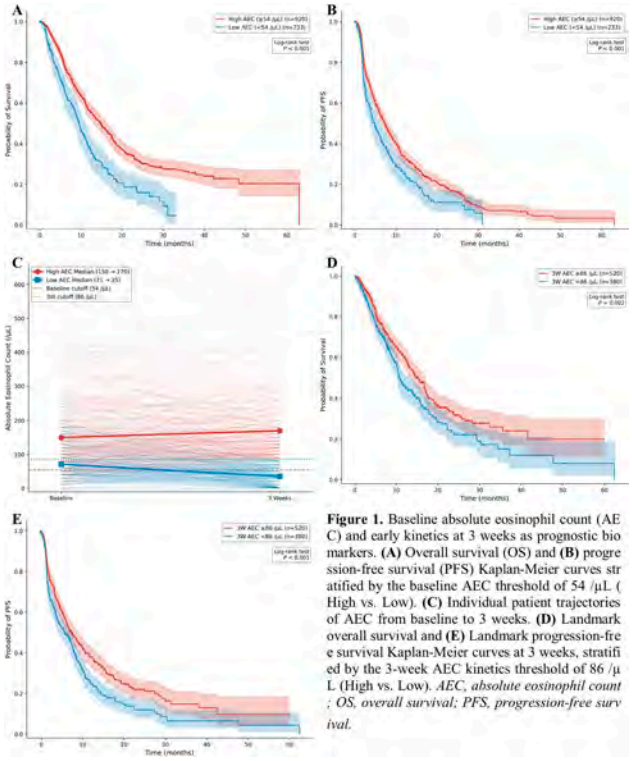


Figure 1. Baseline absolute eosinophil count (AEC) and early kinetics at 3 weeks as prognostic biomarkers. **(A)** Overall survival (OS) and **(B)** progression-free survival (PFS) Kaplan-Meier curves stratified by the baseline AEC threshold of 54 /μL (High vs. Low). **(C)** Individual patient trajectories of AEC from baseline to 3 weeks. **(D)** Landmark overall survival and **(E)** Landmark progression-free survival Kaplan-Meier curves at 3 weeks, stratified by the 3-week AEC kinetics threshold of 86 /μL (High vs. Low). *AEC, absolute eosinophil count; OS, overall survival; PFS, progression-free survival.*

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4318 | ASSESSING PATIENT SYMPTOMS AND QUALITY OF LIFE AFTER LOCOREGIONAL THERAPY FOR HEPATOCELLULAR CARCINOMA

Garren Montgomery[1] Maria Krantz[1] Arsheya Patel[2] Kelly Durkin[1] Stacey Culp[1] Vivek Mendiratta[1] Lindsay Sobotka[1], [1]The Ohio State University Medical Center, [2]Gastro Health

Background: Locoregional therapies (LRT) including transarterial chemoembolization (TACE), radiofrequency ablation (RFA), stereotactic body radiation therapy (SBRT), and transarterial radioembolization (TARE) are often utilized in the management of hepatocellular carcinoma (HCC). While the efficacy of LRT is well-supported, there is limited data concerning the effect of LRT on patients' well-being. The aim of this study was to assess feasibility of collecting longitudinal health-related quality of life (HRQoL) measures in patients undergoing LRT using the Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep) questionnaire, and to describe early HRQoL patterns among these patients. **Methods:** Adult patients diagnosed with HCC who were recommended for LRT were eligible for enrollment. Patient demographics and details regarding liver disease history and HCC were collected by chart review. HRQoL was assessed using the FACT-Hep questionnaire at baseline (pre-LRT), 1 week post-LRT, and 1 month post-LRT. Feasibility outcomes included enrollment rate and FACT-Hep completion at each time point. FACT-Hep subscores were compared between patients receiving TARE or SBRT (Group 1) and those receiving TACE or ablation (Group 2) using a descriptive analysis. **Results:** Of 58 eligible patients, 21 were enrolled (36.2%). Eight patients did not complete the baseline or follow-up surveys (6 unable to be contacted and 2 canceled LRT due to illness). Thirteen patients completed the baseline survey and at least one of the post-LRT surveys. Of these, 85% completed the 1 week post-LRT survey and 92% completed the 1 month post-LRT survey. Ten patients were in Group 1 (6 TARE and 4 SBRT) and 3 were in Group 2 (2 TACE and 1 ablation). Median age was higher in Group 1 (62.5) compared to Group 2 (51). At baseline, Group 1 had lower mean physical well-being, emotional well-being, functional well-being, and hepatobiliary cancer subscores. At 1 week, Group 2 experienced larger declines in all FACT-Hep subscores compared to Group 1 (Table 1). By 1 month post-treatment, this difference was not as apparent, and individual trajectories in both groups trended towards improvements in each subscore (Figure 1). These observations were not powered for statistical comparison. **Conclusion:** Prospective longitudinal HRQoL assessment using the FACT-Hep questionnaire before and after LRT appears feasible. While enrollment is modest, for those who enroll survey completion rates at 1 week and 1 month are reasonable. Early descriptive trends suggest differing HRQoL trajectories between patients treated with TARE or SBRT (Group 1) and Ablation or TACE (Group 2), particularly at 1 week post treatment. A larger, adequately powered study is needed to assess if these differences are statistically significant.

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Table 1: Comparisons of mean FACT-Hep scores and its subscores pre- and post-LRT between Groups 1 and 2

		FACT-Hep Score/Subscore						
		PWB	SWB	EWB	FWB	HCS	FACT-G	FACT-Hep Total
Group 1 (TARE/SBRT)	Baseline	21.6	23.5	16.1	20.7	52.8	80.8	133.6
	1 week post LRT	20.9	24.2	19.8	19.6	54.5	84.7	139.3
	1 month post LRT	23.1	23.8	16.2	19.4	56.9	84.3	141.4
	Mean difference at 1 week (from baseline)	-0.7	0.7	4.7	-0.9	1.7	3.9	5.7
	Mean difference at 1 month (from baseline)	2.2	0.3	3.1	-1.3	4.1	3.7	7.8
Group 2 (TACE/ablation)	Baseline	24.3	19.6	16.5	26.8	58	87.3	145.3
	1 week post LRT	12	14.5	11	19.2	46	56.7	102.8
	1 month post LRT	25	23.5	20	23.6	66.5	92.1	158.6
	Mean difference at 1 week (from baseline)	-12.3	-5.1	-5.5	-7.6	-12	-30.6	-42.5
	Mean difference at 1 month (from baseline)	0.7	3.9	3.5	-3.2	8.5	4.8	13.3

FACT-Hep, Functional Assessment of Cancer Therapy-Hepatobiliary; LRT, locoregional therapy; TAFE, transarterial radioembolization; SBRT, stereotactic body radiation therapy; TACE, transarterial chemoembolization; PWB, physical well-being; SWB, social well-being; EWB, emotional well-being; FWB, functional well-being; HCS, hepatobiliary cancer subscale; FACT-G, FACT-General.

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4319 | SELECTION OF POSTOPERATIVE ADJUVANT THERAPY REGIMENS AND EFFICACY ASSESSMENT IN INTRAHEPATIC CHOLANGIOCARCINOMA

Zhongquan Sun[1] Weilin Wang[2] Yang Huang[2] Haotian Fu[2] Hongfan Ding[2], [1]Zhejiang University, [2]The Second Affiliated Hospital Zhejiang University School of Medicine

Background: Intrahepatic cholangiocarcinoma (iCCA) is a highly aggressive and heterogeneous malignancy, accounting for approximately 10%–15% of primary liver cancers. Radical surgical resection remains the only potentially curative treatment; however, prognosis remains poor even after curative resection owing to its aggressive biological behavior. Immune checkpoint inhibitors (ICIs) have demonstrated significant efficacy across various malignancies, whereas their role in the adjuvant setting for iCCA remains to be fully elucidated. This study aimed to evaluate the efficacy and safety of different postoperative adjuvant treatment strategies in patients with iCCA and to identify prognostic risk factors, thereby providing evidence to inform clinical decision-making. **Methods:** Clinical and pathological data of patients with iCCA who underwent curative resection between January 1, 2018 and June 30, 2025 were retrospectively collected from 10 tertiary hospitals in China, including The Second Affiliated Hospital, Zhejiang University School of Medicine. A total of 513 patients met the inclusion criteria. Patients were categorized into a non-adjuvant group and an adjuvant group according to whether postoperative adjuvant therapy was administered. Based on treatment regimens, the adjuvant group was further stratified into an oral chemotherapy group, a gemcitabine-based intravenous chemotherapy group, and an ICIs plus intravenous chemotherapy group. The primary endpoints were recurrence-free survival (RFS) and overall survival (OS). Independent prognostic factors were identified, and treatment-related adverse events were assessed. **Results:** Multifocal intrahepatic lesions, tumor diameter >5 cm, concomitant biliary stones, lymph node metastasis, vascular invasion, perineural invasion, and a narrow surgical margin (defined as a tumor-free margin <1 cm) were identified as independent risk factors for postoperative recurrence in patients with iCCA. Based on these factors, patients were stratified into recurrence risk groups.Patients with low recurrence risk derived greater survival benefits from oral chemotherapy with capecitabine or S-1, with improvements observed in both RFS and OS. In contrast, for patients with high recurrence risk, neither oral chemotherapy nor intravenous chemotherapy alone conferred significant survival benefits. However, ICIs combined with intravenous chemotherapy significantly improved RFS, indicating improved disease control, with an overall manageable safety profile. **Conclusion:** Postoperative adjuvant treatment strategies for patients with iCCA should be individualized. Oral chemotherapy with capecitabine or S-1 may provide greater survival benefits in patients with low recurrence risk, whereas ICIs combined with intravenous chemotherapy represents an effective and tolerable adjuvant treatment option for those with high recurrence risk.

Disclosures: zhongquan Sun:Nothing to Disclose, Weilin Wang:Nothing to Disclose, Yang Huang:Nothing to Disclose, Haotian Fu:Nothing to Disclose, Hongfan Ding:Nothing to Disclose.

4320 | GEMCITABINE-BASED CHEMOTHERAPY PLUS PD-1/PD-L1 INHIBITORS AND TYROSINE KINASE INHIBITORS FOR INITIALLY UNRESECTABLE INTRAHEPATIC CHOLANGIOCARCINOMA: A MULTICENTER, RETROSPECTIVE COHORT STUDY

Zhongquan Sun[1] Yuan Ding[2] Xin Han[2] Hongfan Ding[2] Haotian Fu[2], [1]Zhejiang University, [2]The Second Affiliated Hospital Zhejiang University School of Medicine

Background: Patients with initially unresectable intrahepatic cholangiocarcinoma have poor prognoses and the current first-line standard treatments remain unsatisfactory. Our study aimed to evaluate gemcitabine-based chemotherapy plus PD-1/PD-L1 inhibitors

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and tyrosine kinase inhibitors (TKIs) for previous untreated unresectable intrahepatic cholangiocarcinoma. **Methods:** In this multicenter retrospective cohort study, 392 patients were included in the full cohort analysis. For the primary analysis, 88 patients received gemcitabine-based chemotherapy (GEMCIS or GEMOX), and 177 patients received the same chemotherapy backbones combined with PD-1/PD-L1 inhibitors and TKIs. The primary outcome was to evaluate overall survival (OS). The propensity score matching (PSM) method was utilized to reduce potential confounders. **Results:** Overall, 392 patients were included from 12 hospitals across China, with data from January 2016 to December 2024. In the full cohort analysis, the combination of GEMCIS/GEMOX with PD-1/PD-L1 inhibitors and TKIs significantly prolonged median OS compared to GEMCIS/GEMOX alone (26.7 vs. 15.3 months; hazard ratio [HR] 0.47, 95% CI: 0.35-0.63, $P < 0.001$). In the primary analysis, the combination strategy was associated with a median OS of 24.8 months (95% CI: 20.8-28.8) and median progression-free survival (PFS) of 11.0 months (95% CI: 8.5-13.5), with corresponding HRs of 0.56 (95% CI: 0.38-0.83, $P = 0.004$) for OS and 0.46 (95% CI: 0.32-0.66, $P < 0.001$) for PFS after PSM. Furthermore, in the combination cohort, the incidence of grade 3-4 hematological adverse events was 30%, compared with 27% in the chemotherapy cohort, with no significant difference observed ($P = 0.604$). Importantly, our treatment strategy increased the rate of conversion surgery to 42% for locally advanced disease, ultimately resulting in significantly improved overall outcomes (HR for OS: 0.17 [95% CI: 0.05-0.61]). **Conclusion:** Combining gemcitabine-based chemotherapy with PD-1/PD-L1 inhibitors and TKIs may provide a promising new first-line treatment option for patients with initially unresectable intrahepatic cholangiocarcinoma.

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4321 | ASSOCIATION BETWEEN PNPLA3 I148M GENOTYPE AND TUMOR CHARACTERISTICS AND DISEASE SEVERITY IN PATIENTS WITH HEPATOCELLULAR CARCINOMA

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Background: The I148M (rs738409) polymorphism in the patatin-like phospholipase domain-containing protein 3 (PNPLA3) gene is a well-established genetic variant associated with disease progression, cirrhosis, and HCC. However, its role in HCC biology remains unclear. The aim of this study was to evaluate the association between the PNPLA3 rs738409 variant and tumor biology and clinical outcomes in patients with HCC. **Methods:** This single-center retrospective cohort study included patients diagnosed with HCC. Under a recessive genetic model, the PNPLA3 rs738409 variant was considered the risk genotype. Patients with HCC were categorized into two etiological groups: steatotic liver disease (SLD)–related HCC and viral hepatitis–related HCC. **Results:** A total of 105 patients were included. The mean age was 64.7 ± 7.9 years, and 78% were male. Viral hepatitis–related HCC was the most common etiology (57%), followed by SLD-related HCC (36%) in this HCC cohort. At diagnosis, cirrhosis was present in 94% of patients. Overall, 42% of patients had early-stage disease (BCLC 0–A). A single lesion was identified in 55% of patients, while portal vein invasion and extrahepatic involvement were observed in 12% and 9% of cases, respectively. Patients with SLD–related HCC were significantly older than those with viral-related HCC (median age 66.7 vs. 63.9 years, $p = 0.031$). In multivariable Cox regression analysis, SLD–related HCC was associated with a higher risk of mortality compared with viral hepatitis-related HCC (HR 0.45, 95% CI 0.24–0.85, $p = 0.014$). The frequency of the PNPLA3 rs738409 variant was significantly higher in patients with SLD-related HCC than in those with viral-etiology-related HCC (47.2% vs. 25.4%, respectively; $p = 0.016$). Patients carrying the PNPLA3 rs738409 variant had more advanced liver disease ($p = 0.025$), more advanced-stage HCC ($p = 0.013$), and higher ALBI scores ($p = 0.009$). Portal vein invasion was more frequent among PNPLA3 rs738409 variant carriers ($p = 0.028$), suggesting more aggressive tumor behavior. Additionally, carriers exhibited numerically greater tumor burden, including a slightly larger median total tumor diameter ($p = 0.30$), higher rates of multifocality ($p = 0.63$), and elevated serum AFP levels ($p = 0.39$). Kaplan–Meier analysis showed significant differences in overall survival among genotype groups (log-rank $p = 0.048$). **Conclusion:** In this cohort of patients with HCC, the epidemiological landscape of HCC risk factors has shifted from virus-related to steatotic liver disease. The PNPLA3 I148M GG genotype was more frequently observed in SLD-related HCC and was associated with more advanced liver disease, as well as tumor features consistent with a more aggressive

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biological phenotype. These findings suggest that PNPLA3 may influence HCC biology and disease severity rather than acting as the sole independent prognostic marker.
Disclosures: Dilara Turan Gokce:Nothing to Disclose, Halil Tuğrul Akarca:Nothing to Disclose, Rifat Furkan Aydın:Nothing to Disclose, Esra Tunç:Nothing to Disclose, Volkan Yılmaz:Nothing to Disclose, Özge Koç:Nothing to Disclose, Zeynep Melekoglu Ellik: Nothing to Disclose, Mesut Gümüssoy:Nothing to Disclose, ramazan erdem er:Nothing to Disclose, Hale Gökcan:Nothing to Disclose, Ramazan İdilman:Nothing to Disclose.

4322 | INTERDEPENDENCE ACROSS THE HCC CARE CASCADE IN LATIN AMERICA: A MULTINATIONAL SYSTEM-LEVEL ANALYSIS

Pablo Coste[1] Luis Antonio Diaz[2] Marco Arrese[3] Francisco Vargas Navarro[1] Maria Fernanda Lynch-Mejia[4] Wagner Ramirez[1] Federico Piñero[5] Manuel Mendizabal[6] Maria Reig[7] Jeffrey Lazarus[8] Margarita Anders[9] Josemaría MenendezDutra[10] Juan Pablo Arab[11], [1]Liver Unit, Hospital Rafael Ángel Calderón Guardia, Liver Lab CR, San José, Costa Rica, [2]Pontificia Universidad Católica de Chile, [3]Pontificia Universidad Católica de Chile, Santiago, Chile., [4]Caja Costarricense de Seguro Social, [5]Hepatology and Liver Transplant Unit, Hospital Universitario Austral, Buenos Aires, Argentina, [6]Hospital Universitario Austral, [7]Liver Cancer Unit, Hospital Clínic Barcelona, Barcelona, España, [8]University of Barcelona, [9]Hepatology and Liver Transplant Unit, Hospital Alemán, Buenos Aires, Argentina, [10]Liver Transplant National Program, Hospital Militar, Montevideo, Uruguay, [11]Virginia Commonwealth University

Background: Hepatocellular carcinoma (HCC) outcomes depend on the integrity of the care cascade, yet structural relationships between healthcare system components remain poorly characterized in Latin America. **Methods:** We conducted a multinational cross-sectional analysis including 20 Latin American countries. Twenty variables were operationalized into six predefined domains: fibrosis detection, surveillance, diagnosis, multidisciplinary care (MDT), curative treatment, and non-curative treatment. Domain scores were normalized to a 0–100 scale. Correlations across domains were assessed using Spearman coefficients, and hierarchical clustering analysis was performed to identify system-level performance patterns across the HCC care cascade. **Results:** Substantial heterogeneity in HCC care capacity was observed across countries, with total scores ranging from 0 to 85.4. Strong correlations were identified across all domains ($\rho = 0.73–0.98$; $p < 0.001$), indicating marked interdependence throughout the care cascade. Fibrosis detection demonstrated strong associations with diagnosis ($\rho = 0.92$) and MDT performance ($\rho = 0.95$), while curative and non-curative treatment domains were highly correlated ($\rho = 0.98$). Hierarchical clustering revealed a continuum of healthcare system capacity rather than discrete categories. Higher-performing systems clustered with preserved downstream therapeutic capacity, whereas lower-performing systems demonstrated widespread limitations across multiple domains. Across all settings, deficiencies in fibrosis detection and linkage to care emerged as the most consistent limitation. **Conclusion:** HCC care performance in Latin America appears to reflect integrated healthcare system capacity rather than isolated domain-specific factors. These findings support system-level strengthening strategies centered on early detection and structured HCC care pathways.

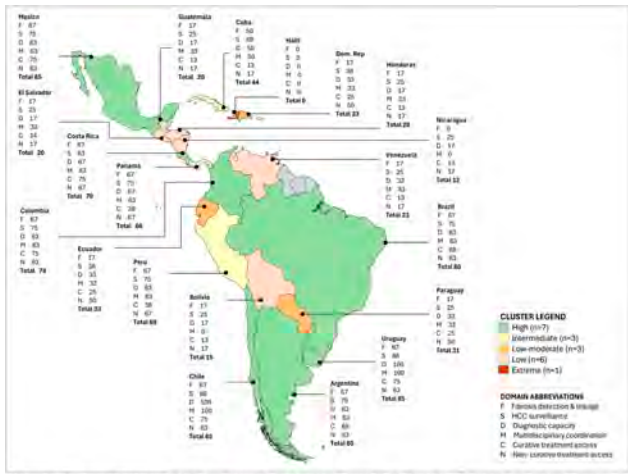


Figure 1. Clustered heatmap of HCC care cascade performance across Latin America. Countries are ordered according to hierarchical clustering based on six domain-level scores. Colors represent relative healthcare system capacity (red: low; yellow: intermediate; green: high). Clusters reflect progressive gradients of system-level performance across the HCC care cascade.

Disclosures: Pablo Coste:Nothing to Disclose, Luis Antonio Diaz:Novo Nordisk: Consultant, Marco Arrese:Nothing to Disclose, Nothing to Disclose, Francisco Vargas Navarro:Nothing to Disclose, Maria Fernanda Lynch-Mejia:Roche Pharmaceuticals: Travel support, Wagner Ramirez:Nothing to Disclose, FEDERICO PIÑERO:Nothing to Disclose, Manuel Mendizabal:Gilead: Speaking and Teaching, Biosidus: Speaking and Teaching, Gador: Speaking and Teaching, Knight: Speaking and Teaching, Novo Nordisk: Advisor, Maria Reig:AstraZeneca, Bayer, BMS, Eli Lilly, Geneos, Ipsen, Merck: Advisor, AstraZeneca, Bayer, BMS, Eli Lilly, Gilead Sciences, Roc: Speaking and Teaching, Abbvie, BMS, Sanofi, Adaptimmune,

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4323 | THE EASTERN MEDITERRANEAN LANDSCAPE OF LIVER CANCER CLINICAL TRIALS (1999–2022): EVIDENCE FROM THE WHO CLINICAL TRIALS DATABASE

Saleh Alessy[1] Atheer Almutairi[2] Maryam Alalawi[3] Basmah Khoja[4] Aldanah Althwanay[5] Ghadeer Jamjoum[6] Adnan Alzanbagi[7] Khalid AlNaamani[8] Saad Alghamdi[9] Saleh Alqahtani[10], [1]Saudi Electronic University, Riyadh, Saudi Arabia, [2]King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia, [3]Columbia University, New York, USA, [4]King Faisal Specialist Hospital & Research Hospital, Riyadh, Saudi Arabia, [5]Washington University at St.Louis -Barnes Jewish Hospital, [6]King Abdulaziz University Hospital, Jeddah, Saudi Arabia, [7]King Abdullah Medical City, Makkah, Saudi Arabia, [8]The Medical City of Military and Security Services, Muscat, Oman, [9]King Faisal Specialist Hospital and Research Center, [10]King Faisal Specialist Hospital & Research Center

Background: Liver cancer clinical trials are critical for providing timely access to innovative prevention and treatment strategies and generating evidence to improve liver cancer control. The World Health Organization (WHO) Eastern Mediterranean Region (EMR) includes countries with a substantial liver cancer burden, yet regional participation in liver cancer clinical research has not been well characterized. We aimed to assess the liver cancer clinical trial landscape in the WHO EMR from 1999 to 2022 and benchmark regional trial activity against global patterns. **Methods:** We analyzed data from the WHO landscape of clinical trials on cancer, published in September 2025. This dataset includes information from the WHO International Clinical Trials Registry Platform and cancer prevalence, incidence, and mortality estimates from the International Agency for Research on Cancer GLOBOCAN 2022 database. Characteristics of liver cancer trials were summarized globally and for EMR countries by registration year, recruitment country, trial phase, and sponsor category. **Results:** Between 1999 and 2022, 4,199 liver cancer clinical trials were registered globally, with the cumulative count increasing from 11 trials in 1999. China had the highest number of trials (n = 1,860), followed by the United States (n = 752), and Japan (n = 698). Globally, most trials were sponsored by academic or research institutions (79%), whereas pharmaceutical and biotechnology sponsors accounted for only 7%. Overall, liver cancer trials represented 4.68% of all oncology clinical trials worldwide, despite liver cancer contributing to 9.02% of global cancer-related deaths in 2020. Within the WHO EMR, only 59 trials were registered by 2022, with trial activity increasing from a single trial in 2002, with Egypt contributing the largest share (n = 45), followed by Saudi Arabia (n = 12). Phase III studies represented the largest proportion of EMR trials (35.6%, n = 21), highlighting limited early-phase trial activity across the region. In contrast, industry sponsorship was proportionally higher in the EMR (20% vs 7% globally), although academic institutions remained the predominant sponsors (56% vs 79% globally). **Conclusion:** Despite the substantial global expansion of liver cancer clinical trials, the EMR contributed only 1.4% of global liver cancer trials, despite serving a population of nearly 745 million people. These findings highlight substantial geographic disparities in liver cancer clinical research, with trial activity concentrated in few countries and limited early-phase activity across the region. Targeted investment in regional trial networks, early-phase research capacity, and academic engagement may help address this gap. Interpretation should consider potential underregistration, incomplete registry updates, disease-classification uncertainty, and multicountry trial counting in the WHO database.

Disclosures: Saleh Alessy:Nothing to Disclose, Atheer Almutairi:Nothing to Disclose, Maryam Alalawi:Nothing to Disclose, Basmah Khoja:Nothing to Disclose, Aldanah Althwanay:Nothing to Disclose, Ghadeer Jamjoum:Nothing to Disclose, Adnan Alzanbagi:Nothing to Disclose, Khalid AlNaamani:Nothing to Disclose, Saad Alghamdi:Nothing to Disclose, Saleh Alqahtani:Nothing to Disclose.

4324 | *ABCB4*-RELATED HEPATOCELLULAR CARCINOMA IN ADULT PATIENTS: A SERIOUS COMPLICATION WITH IMPORTANT SURVEILLANCE IMPLICATIONS

Saad Alghamdi[1] Saleh Alessy[1] Faisal Abaalkhail[1] Waleed Al Hamoudi[1] Fahad AlMugbel[1] Layan Alsubki[1] Sateesh Maddirevula[1] Ali Alqahtani[1] Mohammed Shagrani[1] Dieter Broering[1] Saleh Alqahtani[2], [1]King Faisal Specialist Hospital & Research Center, Riyadh,

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Saudi Arabia, [2]King Faisal Specialist Hospital & Research Center

Background: *ABCB4*-related diseases are exceedingly rare causes of liver cirrhosis in adults and can be associated with serious complications that require liver transplantation, such as hepatocellular carcinoma (HCC). Data on the outcomes of HCC in adults with *ABCB4*-related liver disease remain scarce because of the rarity of this condition. Here, we characterized the clinical presentation, tumor features, and management of patients with HCC arising in the setting of *ABCB4*-related liver disease. **Methods:** We retrospectively collected clinical, biochemical, radiological, and genetic data of adult patients (n = 5) with HCC arising in genetically confirmed *ABCB4*-related liver disease. Patients were identified from a large HCC registry at the King Faisal Specialist Hospital and Research Center in Saudi Arabia. **Results:** Five patients with ABCB4-related liver disease and HCC were identified. The median age at ABCB4-related liver disease diagnosis was 19 years, while the median age at HCC diagnosis was 23.0 years, and 60% were male. All patients had underlying cirrhosis, and none had a family history of HCC. Jaundice was present in all patients during the disease course, whereas ascites and prior variceal bleeding were observed in 2 patients (40%) and 1 patient (20%), respectively. Most patients had decompensated liver disease, with 3 patients (60%) classified as Child-Pugh B and 1 patient (20%) as Child-Pugh C. MRI identified hepatic lesions in all patients. At diagnosis, 2 patients (40%) had early-stage disease (BCLC A), 1 patient (20%) had intermediate-stage disease (BCLC B), and 2 patients (40%) had advanced-stage disease (BCLC C). Vascular invasion was observed in one patient (20%). Three patients (60%) were within Milan criteria. Initial treatment strategies included liver transplantation in two patients (40%), locoregional therapy in one (20%), best supportive care in one (20%), and one patient awaiting liver transplantation. **Conclusion:** HCC can develop at a remarkably young age in patients with ABCB4-related liver disease, frequently in the setting of cirrhosis and significant hepatic dysfunction. Despite the young age of the cohort, 2 of 5 patients presented with advanced HCC at diagnosis. These findings highlight the need for further awareness in ABCB4-related liver disease and the importance of careful HCC surveillance guidelines in patients with this rare condition.

Table 1: Sociodemographic Characteristics, and Hepatocellular Carcinoma characteristics related ABCB4 related liver disease

Patients (N)	5
Age at Diagnosis	23.000 (7.280)
Gender	
Male	3 (60.0%)
Female	2 (40.0%)
BMI	
Normal	4 (80.0%)
Overweight	1 (20.0%)
Child-Pugh Classifications	
Child A	1 (20.0%)
Child B	3 (60.0%)
Child C	1 (20.0%)
Family history of HCC	
No	5 (100.0%)
Imaging modality	
CT	4 (80.0%)
MRI	5 (100.0%)
Liver cirrhosis	
Yes	5 (100.0%)
No	0
BCLC Stage	
Early stage(A)	2 (40.0%)
Intermediate stage(B)	1 (20.0%)
Advanced stage(C)	2 (40.0%)
Ascites	
Yes	2 (40.0%)
No	3 (60.0%)
Variceal bleeding	
Yes	1 (20.0%)
No	4 (80.0%)
Jaundice	
Yes	5 (100.0%)
No	0
Vascular invasion	
Yes	1 (20.0%)
No	4 (80.0%)
Within Milan criteria	
Yes	3 (60.0%)
No	2 (40.0%)
First Treatment modality	
Locoregional therapies	1 (20.0%)
Liver transplantation	2 (40.0%)
Best supportive care	1 (20.0%)
No treatment	1 (20.0%)

Disclosures: Saad Alghamdi:Nothing to Disclose, Saleh Alessy:Nothing to Disclose, Faisal Abaalkhail: Nothing to Disclose, Waleed Al Hamoudi:Nothing to Disclose, Fahad AlMugbel:Nothing to Disclose, Layan Alsubki:Nothing to Disclose, Sateesh Maddirevula: Nothing to Disclose, Ali Alqahtani:Nothing to Disclose, Mohammed Shagrani:Nothing to Disclose, Dieter Broering:Nothing to Disclose, Saleh Alqahtani:Nothing to Disclose.

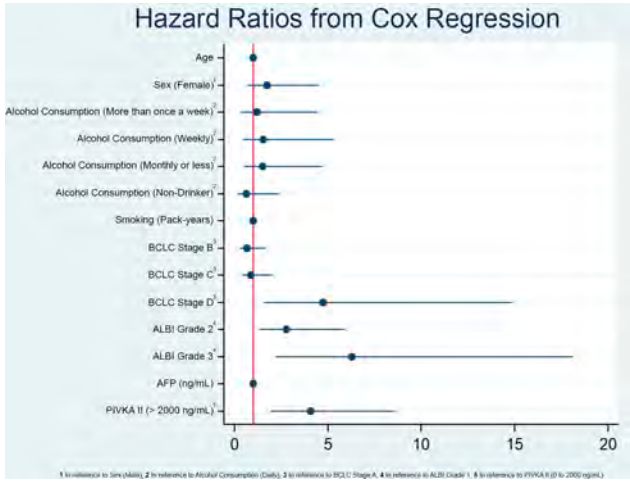
4325 | INITIAL EVALUATION OF PROGNOSTIC FACTORS IN HEPATOCELLULAR CARCINOMA THROUGH COX REGRESSION IN A PHILIPPINE COHORT

Leann Mariella Sala[1] Angela Salvaña[2] Janus Ong[3] John Carlo Reyes[3] Geraldine Arevalo[1] Mathew Timothy Manuel[1], [1]National Institutes of Health, University of the Philippines Manila, [2]University of the Philippines, [3]University of the Philippines Manila

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Background: Hepatocellular carcinoma (HCC) is the fourth most common cancer in the Philippines. Despite established risk factors and advancements in treatment management, prognosis remains poor. Comprehensive analysis of factors will allow for optimized diagnosis and patient care. We present an initial evaluation of selected prognostic factors applied to a small cohort of HCC patients from the Philippines through Cox regression modeling. **Methods:** Baseline records from 120 newly diagnosed, treatment-naive HCC patients from six study sites across the Philippines were obtained. These include patient demographics, clinical data, and laboratory (hepatitis and hematological markers) parameters evaluated for overall survival. A subgroup of 52 patients was also evaluated for TP53 gene mutation. Univariate and multivariate Cox proportional hazards regression models were constructed. Continuous variables were transformed into categorical variables based on Martingale residual plots. Events of interest include death and TP53 gene mutation presence, respectively. Statistical analyses were all performed using STATA version 13.0. **Results:** The cohort is predominantly male (76%) aged 62 ± 10 years. Notable cohort characteristics include large BCLC Stage C (39.17%) and ALBI Grade 2 (45%) classifications, with wide ranged and high-valued AFP (23331.10 ± 71102.6) and PIVKA II (2302.83 ± 5020.84) ng/mL results. Univariate and multivariate analysis revealed HCC patients categorized as BCLC Stage D (HR 4.55; 95% CI 1.46 - 14.22; p = 0.009), assessed as ALBI Grade 2 (HR 2.65; 95% CI 1.24 - 5.65; p = 0.012) and Grade 3 (HR 6.00; 95% CI 2.10 - 17.13; p = 0.001), and patients with PIVKA II results > 2000 ng/mL (HR 3.48; 95% 1.64 - 7.38; p = 0.001) have an increased risk of death compared to their references, while holding other factors in the model constant. Subgroup analysis revealed that Hepatitis B positive HCC patients have an increased risk of TP53 gene mutation compared to Hepatitis B negative HCC patients (HR 5.60; 95% CI 1.16 - 27.09; p = 0.032). **Conclusion:** Our preliminary results are consistent with literature and further highlights the need to evaluate potential prognostic factors in HCC, warranting further exploration in a larger Philippine cohort. Strengthened screening and surveillance efforts, especially in high-risk populations, are highly recommended to detect early stages of HCC and reduce mortality rates.



Disclosures: Leann Mariella Sala:Nothing to Disclose, Angela Salvaña:Nothing to Disclose, Janus Ong:Nothing to Disclose, John Carlo Reyes:Nothing to Disclose, Geraldine Arevalo:Nothing to Disclose, Mathew Timothy Manuel:Nothing to Disclose.

4326 | COMPARISON OF TEMPORAL MORTALITY TRENDS IN YOUNG PATIENTS (2544) WITH COLORECTAL CANCER AND HEPATOCELLULAR CARCINOMA IN THE UNITED STATES, 1999-2024

Abigail Jacobs[1] Kate Backes[1], [1]Kansas City University

Background: Hepatocellular Carcinoma (HCC) is one of the leading causes of cancer-related mortality worldwide, with incidence and mortality rates continuing to rise, particularly in the United States.[1] In comparison, Colorectal Cancer (CRC) remains the third most diagnosed cancer globally and the second leading cause of cancer-related death.[2] Additionally, these numbers are increasingly rising in young people.[3] Currently, there has been limited studies to investigate the regional differences associated with these changing trends in the United States. The aim of this study was to compare the mortality trends of CRC and HCC in young people ages 25-45 across different geographical regions within the United States. **Methods:** Data from the Centers for Disease Control and Prevention (CDC) WONDER database were aggregated across multiple years at the regional level by sex, age group, and underlying cause of death. Descriptive statistics were used to summarize CRC and HCC mortality by sex,

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region, and age group. Statistical analysis was performed using aligned rank transformation (ART) ANOVA to compare differences in CRC and HCC mortality rates over time. ART ANOVA was selected because the data were not normally distributed. **Results:** From 1999-2024, overall mortality rates among adults ages 25-44 were higher in CRC compared to HCC. Colon cancer mortality rose in the 35–44 age group (2.34 to 2.52). This result differed from liver cancer mortality, where there was a decline seen in the 35–44 age group (0.93 to 0.81). Both HCC and CRC in the 25–34 group remained stable. Males had higher mortality for both cancers, though the male-female liver cancer gap is narrowing. Regionally, the South maintained the highest CRC burden while the West was the only region with a sustained upward colon cancer mortality trend. HCC rates are narrower across all regions (0.4 to 0.65). From 1999-2024, there was a significant difference in overall mortality rates among young adults between CRC and HCC ($p < 0.001$). However, there was not significant difference in the rates of CRC and HCC across years ($p > 0.05$). The interaction between cancer type and year was also not significant, indicating the differences in mortality rates between CRC and HCC remained consistent over time ($p > 0.05$). **Conclusion:** Our findings proved that there is a difference in mortality rates of HCC and CRC in young patients ages 25-44, but the differences have remained stable over time (1999-2024). The differences in mortality rates among regions warrants further investigation into underlying behavioral and demographic factors. Overall, these findings suggest that while CRC mortality is generally more common in younger patients, the relative mortality rates of HCC and CRC remain stable over time and highlights the need for prevention strategies in young adults.

Disclosures: Abigail Jacobs:Nothing to Disclose, Kate Backes:Nothing to Disclose.

4327 | A NOVEL INJECTABLE SMART-POLYMER CHEMOEMBOLIC PLATFORM AS A SAFER ALTERNATIVE TO LIPIODOL FOR TRANSARTERIAL CHEMO EMBOLIZATION IN HEPATOCELLULAR CARCINOMA

Riham Soliman[1] Mitsuhiro Ebara[2] Ayman Hassan[3] Talal Amer[4] Ahmed Nabil[2] Gamal Shiha[5], [1]Egyptian Liver Research Institute and Hospital (ELRIAH), Sherbin, El Mansoura, Egypt., [2]National Institute for Materials Science (NIMS), Tsukuba, Ibaraki 305-0044, Japan, [3]Higher Technological Institute of Applied Health Sciences, Sherbin, Mansoura, Egypt, [4]Interventional radiology Department, Faculty of Medicine, Mansoura, Egypt, [5]Internal Medicine Department, Faculty of Medicine, Mansoura University, Egypt.

Background: Lipiodol remains the standard carrier for transarterial chemoembolization (TACE) in hepatocellular carcinoma (HCC), despite recognized limitations including persistent vascular occlusion, hepatic ischemic injury, and chronic inflammatory changes. We evaluated a novel injectable smart-polymer embolic platform as a potential next-generation alternative to Lipiodol for locoregional doxorubicin delivery **Methods:** In this controlled preclinical proof-of-concept study, 140 rats underwent portal venous administration of saline control, Lipiodol alone, polymer alone, Lipiodol–doxorubicin mixture, polymer–doxorubicin mixture, or doxorubicin control. Animals were sacrificed serially on days 1, 2, 7, and 14. Outcomes included serial doppler ultrasonography , serum biochemistry, and blinded histopathologic assessment using a semiquantitative injury score evaluating necrosis, lipid droplets, leukocyte infiltration, edema, fibrosis, and portal congestion. **Results:** No significant systemic biochemical toxicity signals were identified across treatment groups (all $p > 0.05$). However, marked differences emerged on imaging and histopathology. Lipiodol-containing formulations demonstrated the greatest hepatic injury, characterized by extensive sinusoidal lipid entrapment, coagulative necrosis, inflammatory infiltration, portal congestion, and persistent portal vein thrombosis. Peak injury occurred at day 2 in the Lipiodol-alone group (necrosis score 3; leukocyte infiltration score 3), with persistent vascular compromise through day 14. The Lipiodol–doxorubicin group demonstrated the most sustained chronic injury pattern, including persistent lipid deposition, edema, fibrosis, and vascular congestion.In contrast, the smart-polymer–doxorubicin formulation demonstrated substantially milder early hepatic injury, with minimal necrosis and reduced inflammatory changes. Although transient portal venous thrombosis was observed at day 7, restoration of portal vein patency and near-normal hepatic architecture occurred by day 14. Polymer-alone and saline groups maintained largely preserved hepatic architecture throughout the study period. Doxorubicin alone preserved portal venous patency but was associated with early systemic illness and ascites. **Conclusion:** This injectable smart-polymer embolic platform demonstrated significantly lower hepatotoxicity and improved vascular reversibility compared with Lipiodol-based formulations. Unlike Lipiodol, which induced persistent thrombosis and sustained hepatic injury, the smart-polymer formulation enabled restoration of portal venous patency with reduced histologic damage. These findings identify injectable smart-polymer embolization as a promising next-generation chemoembolic platform warranting

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further translational evaluation in arterial HCC models.

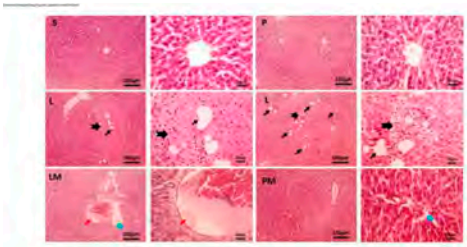


Fig1: Microscopic examination of hematoxylin and eosin (H&E)-stained liver sections one day post-injection demonstrated preserved hepatic architecture in the Polymer-only (P) group, comparable to the Saline (S) group, with normal hepatocytes, central veins, sinusoids, and portal tracts. In contrast, sections from the Lipiodol (L) group revealed multiple lipid droplets (thin black arrows) entrapped within the sinusoids, associated with focal areas of coagulative necrosis infiltrated by neutrophils (thick black arrows). In the Lipiodol Mix (LM) group, liver sections showed portal congestion (red arrows) and edema (thick blue arrows). Meanwhile, the Polymer Mix (PM) group exhibited only very mild portal edema (thick blue arrows). Magnifications: ×100 (scale bar = 100 μm) and ×400 (scale bar = 50 μm).

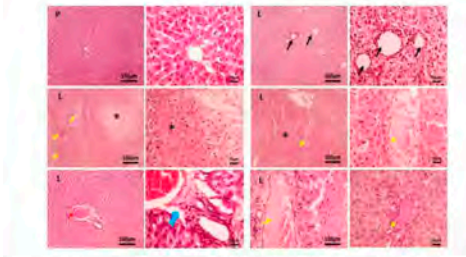


Figure 2: Microscopic examination of hematoxylin and eosin (H&E)-stained liver sections in the Polymer (P) group, two days post-injection, demonstrated preserved hepatic architecture with normal hepatocytes, central veins, sinusoids, and portal tracts. In contrast, liver sections from the Lipiodol (L) group at the same time point revealed multiple lipid droplets (thin black arrows) within the sinusoids, surrounded by leukocytic infiltration, along with fresh portal thrombi (yellow arrows). Additionally, extensive areas of coagulative necrosis infiltrated by neutrophils (*), portal congestion (red arrows), and edema (thick blue arrows) were observed. Magnifications: ×100 (scale bar = 100 μm) and ×400 (scale bar = 50 μm).

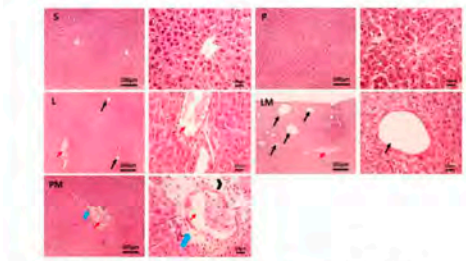


Fig 3: Microscopic examination of hematoxylin and eosin (H&E)-stained liver sections 7 days post-injection demonstrated preserved hepatic architecture in the Polymer (P) group, comparable to the Saline (S) group, with normal hepatocytes, central veins, sinusoids, and portal tracts. In the Lipiodol (L) group, multiple lipid droplets (thin black arrows) were observed within the sinusoids, accompanied by portal congestion (red arrows). Similarly, the Lipiodol Mix (LM) group showed large lipid droplets (thin black arrows) entrapped within the sinusoids, along with vascular congestion (red arrows). In the Polymer Mix (PM) group, liver sections exhibited portal congestion (red arrows), edema (thick blue arrows), and leukocytic infiltration (arrowheads). Magnifications: ×100 (scale bar = 100 μm) and ×400 (scale bar = 50 μm).

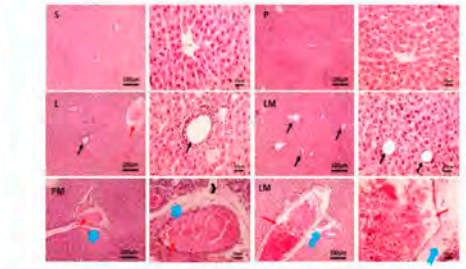


Figure 4: Microscopic examination of hematoxylin and eosin (H&E)-stained liver sections 14 days post-injection demonstrated preserved hepatic architecture in the Polymer (P) group, comparable to the Saline (S) group, with normal hepatocytes, central veins, sinusoids, and portal tracts. In the Lipiodol (L) group, multiple lipid droplets (thin black arrows) were observed within the sinusoids, surrounded by leukocytes, along with portal congestion (red arrows). In the Lipiodol Mix (LM) group, liver sections revealed multiple lipid droplets (thin black arrows) entrapped within the sinusoids, accompanied by portal congestion (red arrows) and edema (thick blue arrows). Similarly, the Polymer Mix (PM) group exhibited portal congestion (red arrows) and edema (thick blue arrows). Magnifications: ×100 (scale bar = 100 μm) and ×400 (scale bar = 50 μm).

Disclosures: Riham Soliman:Nothing to Disclose, Mitsuhiro Ebara:Nothing to Disclose, Ayman Hassan: Nothing to Disclose, Talal Amer:Nothing to Disclose, Ahmed Nabil:Nothing to Disclose, Gamal Shiha:Nothing to Disclose.

4328 | EXPRESSION AND CLINICAL SIGNIFICANCE OF CDKN3 IN HEPATITIS B-RELATED HEPATOCELLULAR CARCINOMA

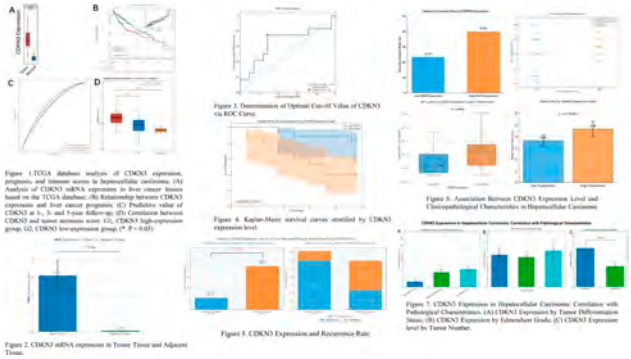
Ning Lin[1] Guangming Li[2] Gongming Zhang[2] Yifan Han[1] Qingya Wang[1] Haiyang Zhou[3] Ying Liu[3] Mengqi Li[4] Yanyan Yu[1] Xiaoyuan Xu[1], [1]Peking University First Hospital, [2]Beijing YouAn Hospital, Capital Medical University, [3]Beijing iGandan Foundation, [4]Beijing Ditan Hospital, Capital Medical University

Background: Hepatocellular carcinoma (HCC) has a persistently high incidence in China, with hepatitis B virus (HBV) infection serving as the primary risk factor. Cell cycle dysregulation is involved in the progression of HCC. As a cell cycle regulatory molecule, cyclin-dependent kinase inhibitor 3 (CDKN3) plays a role in a variety of malignant tumors. This study aimed to investigate the expression pattern and clinical prognostic significance of the cell cycle regulator CDKN3 in hepatitis B-related HCC. **Methods:** Transcriptomic and clinical data of 371 HCC samples were retrieved from The Cancer Genome Atlas (TCGA) database to analyze the relationship between CDKN3 expression and patient prognosis. Additionally, 33 patients with hepatitis B-related HCC who received radical resection were enrolled from Beijing You'an Hospital were enrolled (Ethics Approval No.: LL-2024-127-K). CDKN3 expression in paired tumor and adjacent nontumor tissues was detected, and the optimal cut-off value of CDKN3 expression was determined using receiver operating characteristic (ROC) curves. Chi-square test, Kaplan-Meier survival analysis, and multivariate logistic regression were applied to evaluate the correlations of CDKN3 expression with clinicopathological characteristics and postoperative recurrence. **Results:** Both TCGA data analysis and clinical sample validation verified that CDKN3 was significantly upregulated in hepatitis B-related HCC tissues ($P < 0.05$). High CDKN3 expression was closely associated with aggressive pathological phenotypes, including poor tumor differentiation, advanced Edmondson grade, and vascular invasion. Multivariate analysis identified CDKN3 as an independent risk factor for 2-year postoperative recurrence in hepatitis B-related HCC patients ($P < 0.01$), with an AUC value of 0.659 for recurrence prediction. The optimal cut-off value of CDKN3 expression was determined as 3.85 based on the ROC curve. Accordingly, patients were stratified into the low-expression group (n = 18) and high-expression group (n = 15). Patients with elevated CDKN3 expression had a markedly higher 2-year recurrence rate and shorter

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recurrence-free survival (P < 0.05). **Conclusion:** CDKN3 is abnormally overexpressed in hepatitis B-related HCC. It serves as a reliable indicator for evaluating postoperative recurrence risk and clinical prognosis, which has great potential to be a novel prognostic biomarker and therapeutic target for hepatitis B-related HCC.



Disclosures: Ning Lin:Nothing to Disclose, Guangming Li:Nothing to Disclose, Gongming Zhang:Nothing to Disclose, Yifan Han:Nothing to Disclose, Qingya Wang: Nothing to Disclose, Haiyang Zhou:Nothing to Disclose, Ying Liu:Nothing to Disclose, Mengqi Li:Nothing to Disclose, yanyan yu:Nothing to Disclose, Xiaoyuan Xu: Nothing to Disclose.

4329 | SOCIOECONOMIC DISPARITIES IN TREATMENT PATTERNS AND SURVIVAL OUTCOMES AMONG PATIENTS WITH HEPATOCELLULAR CARCINOMA: A NATIONWIDE POPULATION-BASED COHORT

Heejoon Jang[1] Yookyoung Lim[2], [1]SMG-SNU Boramae Medical Center, [2]Boramae Medical Center

Background: While overall survival of hepatocellular carcinoma (HCC) has improved with advances in treatment, whether survival gains have been distributed equitably across socioeconomic strata remains unknown. We aimed to evaluate income-based disparities in treatment patterns and survival outcomes in a nationwide population-based cohort of patients with HCC. **Methods:** Using the Korean National Health Insurance Service database, we identified 35,050 adult patients newly diagnosed with HCC between January 2009 and December 2024. Income level was categorized into quintiles based on insurance premium–derived household income. The primary outcome was overall survival. Inverse probability of treatment weighting (IPTW) was applied to balance baseline covariates across income groups, and weighted Cox proportional hazards models were used to estimate adjusted hazard ratios (HRs) for mortality. **Results:** Lower-income patients were less likely to receive early-stage treatments — including surgical resection, liver transplantation, and radiofrequency ablation (Q1: 29.3% vs. Q5: 33.9%) — and more likely to receive chemotherapy (Q1: 8.9% vs. Q5: 6.7%), suggesting later-stage presentation at diagnosis among lower-income patients. The proportion of untreated patients was highest in Q1 (19.8%). Compared with Q1, patients in Q5 had significantly lower all-cause mortality, with a dose-response relationship observed across quintiles (adjusted HR 0.74, 95% CI 0.70–0.78). Additionally, income levels tended to decline following HCC diagnosis, suggesting that the disease itself may further widen pre-existing socioeconomic disparities. **Conclusion:** Despite universal health insurance coverage in Korea, lower-income patients with HCC were less likely to receive curative-intent treatment and experienced significantly higher mortality. Income levels further declined following diagnosis, potentially creating a vicious cycle that widens existing disparities. Although HCC surveillance programs are established, strengthening their outreach and utilization among low-income populations is essential to improve early detection and access to curative treatment.

Figure 1. Overall survival stratified by income quintile in patients with hepatocellular carcinoma.

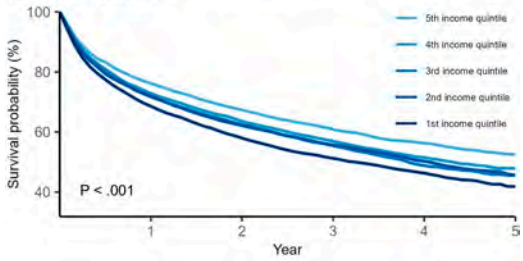
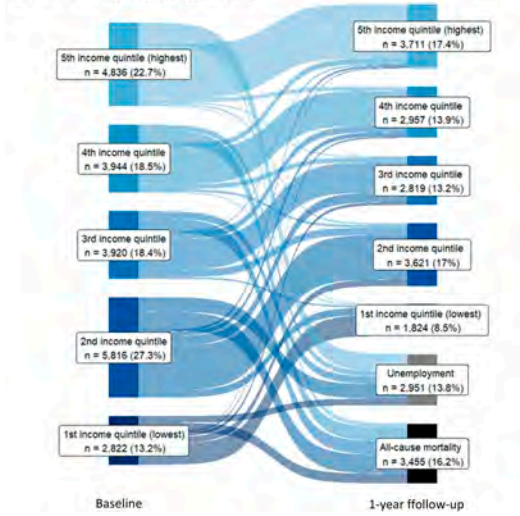


Figure 2. Income quintile distribution at baseline and 1-year follow-up among patients with hepatocellular carcinoma.



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Disclosures: Heejoon Jang:Nothing to Disclose, Yookyoung Lim:Nothing to Disclose.

4330 | NEUTROPHIL-TO-LYMPHOCYTE RATIO AND EXTRAHEPATIC SPREAD PREDICT RESPONSE AND SURVIVAL IN UNRESECTABLE HEPATOCELLULAR CARCINOMA

Sung Won Lee[1] Dong Yun Kim[2] Heechul Nam[1] Do Young Kim[2], [1]The Catholic University of Korea, [2]Yonsei University

Background: Identifying patients unlikely to respond to atezolizumab plus bevacizumab (AB) remains a critical challenge in unresectable hepatocellular carcinoma (uHCC). We aimed to develop and externally validate a simple risk scoring system using baseline neutrophil-to-lymphocyte ratio (NLR) and extrahepatic spread (EHS) to predict treatment outcomes. **Methods:** We included 304 patients with uHCC receiving first-line AB from multiple Korean centers, forming discovery (n = 220) and validation (n = 84) cohorts. Study outcomes included objective response rate (ORR) assessed by modified Response Evaluation Criteria in Solid Tumors , overall survival (OS), and progression-free survival (PFS). Multivariable analysis identified high NLR (> 4.575) and EHS as independent predictors of nonresponse. The NLR-EHS score assigned 2 points for high NLR and 1 point for EHS (range, 0–3). **Results:** In the discovery cohort, the score achieved an area under the receiver operating characteristic curve (AUC) of 0.749 (95% CI, 0.688–0.810) for predicting nonresponse, with ORR decreasing progressively: 67.3%, 47.7%, and 8.2% for low- (0), moderate- (1-2), and high- (3) risk groups, respectively ($p < 0.001$). External validation confirmed comparable discrimination (AUC, 0.705; 95% CI, 0.603–0.806), with a consistent ORR gradient of 77.8%, 54.2%, and 22.2% across risk groups ($p < 0.001$). The score maintained prognostic value for OS in both discovery (HR 1.28; $p = 0.003$) and validation cohorts (HR 1.45; $p = 0.007$). High-risk patients had notably inferior median OS (6.9 vs. 17.1 months in validation). **Conclusion:** The NLR-EHS score is a simple, practical tool for stratifying nonresponse risk and survival in uHCC patients receiving AB, facilitating early identification of high-risk patients who may benefit from alternative strategies.

Disclosures: Sung Won Lee:Nothing to Disclose, Dong Yun Kim:Nothing to Disclose, Heechul Nam:Nothing to Disclose, Do Young Kim:Nothing to Disclose.

4331 | OVERALL SURVIVAL AMONG PATIENTS WITH HEPATOCELLULAR CARCINOMA RECEIVING SYSTEMIC THERAPY BY UNDERLYING ETIOLOGY: VIRAL VERSUS MASLD/MASH-RELATED DISEASE

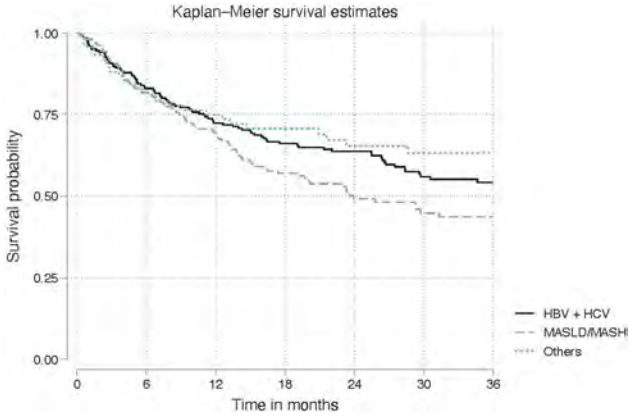
Saleh Alqahtani[1] Saleh Alessy[2] Layan Alsubki[2] Amwaj Alanazi[2] Basmah Khoja[2] Alwaleed Almojel[2] Fahad AlMugbel[2] Waleed Alomaim[2] Mona Ismail[3] Marwan AlHajeli[4] Mohammed Alsager[5] Dimitri Raptis[2] Dieter Broering[2] Saad Alghamdi[6] Faisal Abaalkhail[2] Ali Alqahtani[2], [1]King Faisal Specialist Hospital & Research Center, [2]King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia, [3]Imam Abdulrahman bin Faisal University, Dammam, Saudi Arabia, [4]King Abdulaziz University, Jeddah, Saudi Arabia, [5]King Saud University, Riyadh, Saudi Arabia, [6]King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia

Background: In recent years, systemic therapy options for hepatocellular carcinoma (HCC) have expanded substantially. However, treatment response and outcomes may vary according to the underlying etiology of liver disease, particularly between metabolic dysfunction–associated steatotic liver disease or its progressive form (MASLD/MASH)-related and viral-related HCC. We aimed to characterize the allocation of systemic therapy among patients with HCC and assess overall survival by etiology, including viral-related, MASLD/MASH-related, and other etiologies. **Methods:** We used data from the HCC registry, a large prospectively maintained registry established in 2020 at King Faisal Specialist Hospital & Research Centre, a major tertiary referral center in Saudi Arabia. Adult patients diagnosed with HCC between January 2020 and December 2025 were included. Systemic therapy exposure was defined as receipt of systemic therapy at baseline or within the first year after diagnosis. Descriptive statistics were used to summarize patient characteristics and treatment allocation. Overall survival among patients receiving systemic therapy was assessed using Kaplan–Meier analysis and Cox proportional hazards models to compare etiology groups. **Results:** Of the 696 patients in the cohort, 18.0% (n = 125) received systemic therapy either as first-line treatment or during another treatment episode within their first year after diagnosis. Most treated patients had intermediate-to-terminal-stage disease, with 60% classified as BCLC stages B, C, or D . The distribution of HCC etiologies was comparable between patients who received systemic therapy and those who did not, with MASLD/MASH being the most common etiology in both groups (35.2% vs. 35.9%), followed by HCV (26.4% vs. 25.2%) and HBV (23.2% vs. 21.7%) (p = 0.939). Patients who received systemic therapy were more likely to

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present with advanced tumor burden, including tumors outside the Milan criteria (60.0% vs 34.3%, p < 0.001) and metastatic disease at diagnosis (24.8% vs 9.3%, p < 0.001), compared with patients who did not receive systemic therapy. After adjusting for sex and BCLC stage, patients with MASLD/MASH-related HCC had a higher risk of mortality than those with viral-related HCC (adjusted HR 1.43, 95% CI 1.05–1.95). **Conclusion:** Among patients receiving systemic therapy for HCC, MASLD/MASH was the major underlying etiology and was associated with worse overall survival compared with viral-related HCC after adjusting for sex and BCLC stage. These findings highlight potential etiologic differences in outcomes among patients treated with contemporary systemic therapies.

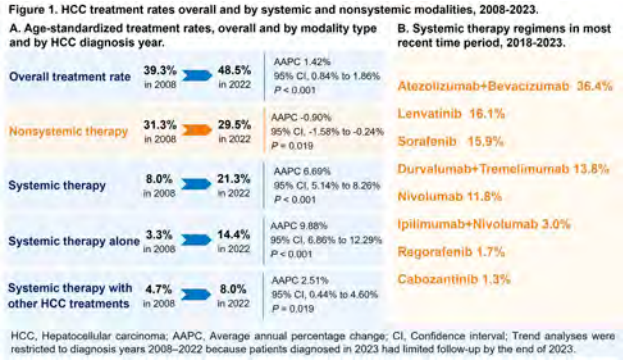


Disclosures: Saleh Alqahtani:Nothing to Disclose, Saleh Alessy:Nothing to Disclose, Layan Alsubki:Nothing to Disclose, Amwaj Alanazi:Nothing to Disclose, Basmah Khoja:Nothing to Disclose, Alwaleed Almojel:Nothing to Disclose, Fahad AlMugbel:Nothing to Disclose, Waleed Alomaim:Nothing to Disclose, Mona Ismail:Nothing to Disclose, Marwan AlHajeli:Nothing to Disclose, Mohammed Alsager:Nothing to Disclose, Dimitri Raptis: Nothing to Disclose, Dieter Broering:Nothing to Disclose, Saad Alghamdi:Nothing to Disclose, Faisal Abaalkhail: Nothing to Disclose, Ali Alqahtani:Nothing to Disclose.

4332 | CHANGING LANDSCAPE OF SYSTEMIC THERAPY IN PATIENTS WITH HEPATOCELLULAR CARCINOMA

Danfeng Ren[1] Taotao Yan[1] Xianhua Mao[2] Bowu Chen[3] Hong Fan[2] Ramsey Cheung[2] Mindie Nguyen[2], [1]The First Affiliated Hospital of Xi'an Jiaotong University, [2]Stanford University Medical Center, [3]Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine

Background: The landscape of systemic therapy utilization for hepatocellular carcinoma (HCC) has changed substantially in recent years, but real-world data on its evolving role is limited. **Methods:** We conducted a retrospective cohort study using the Merative™ MarketScan Research Database to identify adults aged 18 to 90 years with HCC diagnosed from 2008 to 2023. We estimated age-standardized HCC treatment rates by year of HCC diagnosis, overall and by treatment type (systemic and nonsystemic) and their average annual percentage changes (AAPCs) using Joinpoint regression. Among patients who received systemic therapy, treatment patterns were categorized as systemic therapy alone or systemic therapy with other HCC treatments, whether before or after systemic therapy. **Results:** We analysed a total of 45,047 patients with HCC; of these, 5,557 patients (12.3%) received systemic therapy. The use of systemic therapy increased from 8.0% in 2008 to 21.3% in 2022 (AAPC 6.69%, 95% CI 5.14%–8.26%), especially when used alone (AAPC 9.88%, 95% CI 6.86%–12.29%) (Figure 1A). Meanwhile, there was also an increase in the overall treatment rate for HCC from 39.3% in 2008 to 48.5% in 2022 (AAPC 1.42%, 95% CI 0.84%–1.86%) while there was a small decline in nonsystemic treatment (AAPC -0.90%, 95% CI -1.58% to -0.24%) (Figure 1A). Early on (2008–2012), sorafenib was the dominant systemic therapy (98.3%), but the landscape became more diverse afterwards, with atezolizumab+bevacizumab as the most common regimen (36.4%) (Figure 1B). Among patients who received both systemic therapy and other HCC treatments, the majority (70.0% [1,923/2,746]) received other HCC treatments only before systemic therapy initiation, with most of the remaining only after systemic therapy initiation (22.9% [628/2,746]) and transarterial chemoembolization (TACE) as the predominant nonsystemic treatment modality (65.7% [1,264/1,923] and 86.9% [546/628] of patients, respectively). Only 7.1% (195/2,746) received other HCC treatment both before and after systemic therapy initiation. **Conclusion:** HCC treatment rates increased over time, driven largely by increasing use of systemic therapy, especially as stand-alone therapy. When used in combination with other HCC treatment, the most commonly used modality was TACE, regardless of timing. The findings highlight recent therapeutic advances in HCC care and underscore the importance of multimodal HCC management.



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4333 | ARTIFICIAL INTELLIGENCE IN HEPATOCELLULAR CARCINOMA ABLATION: A PILOT ANALYSIS OF STUDIES ON CLINICALTRIALS.GOV

Vikram Sivakumar[1] Mohammad Salman[1] Gianluca Ramirez[1] Kat Light[1] Adam Webb[2], [1]Medical College of Georgia, [2]Memorial Health System

Background: Artificial intelligence (AI) applications have played an important role in diagnostic radiology and oncology; however, their integration into interventional oncology (IO) is still maturing. Hepatocellular carcinoma (HCC), as the primary indication for percutaneous ablation, offers an avenue for AI to play a greater role in procedural planning, guidance, and treatment response, expanding beyond diagnostic measures. Understanding the current landscape of AI-integrated clinical studies focusing on HCC ablation is essential to identify translational barriers and opportunities for growth in IO. **Methods:** We systematically searched ClinicalTrials.gov using Boolean operators combining AI-related terms (artificial intelligence, machine learning, deep learning, radiomics) with IO procedural terms (ablation, microwave ablation, cryoablation, radiofrequency ablation). Inclusion criteria required explicit integration of AI technologies in HCC ablation studies. We extracted and analyzed trial characteristics including ablation modality, AI application type, primary endpoints, study design, sponsorship, enrollment targets, imaging platforms, and geographic distribution. **Results:** Eight studies met inclusion criteria; all were observational, single-center, and academically sponsored. Median planned enrollment was 250 (mean: 489). Geographic distribution showed concentration in China (n = 6, 75%), with single studies in France and the Netherlands. Ablation modalities varied: microwave and radiofrequency (25% each), irreversible electroporation (13%), multiple modalities (13%), and unspecified thermoablation (25%). AI applications included treatment simulation (50%), outcome prediction (25%), and radiomics-based biomarker development (25%). Primary endpoints lacked standardization: local tumor control (38%), algorithm performance metrics (25%), and overall survival, progression-free survival, and imaging response (mRECIST) each at 13%. Imaging platforms included multimodal approaches (38%), CT (25%), with MRI and ultrasound each at 13%. **Conclusion:** The clinical study landscape shows important translational gaps. Despite extensive preclinical literature, clinical trial activity remains limited. The concentration of studies in one region limits generalizability and highlights low industry engagement in AI for IO. Studies prioritize prognostic modeling over intraprocedural guidance. Most AI tools remain investigational, emphasizing the need for long-term prospective studies with standardized endpoints and regulatory alignment to advance implementation in HCC ablation. **Disclosures:** Vikram Sivakumar:Nothing to Disclose, Mohammad Salman:Nothing to Disclose, Gianluca Ramirez:Nothing to Disclose, Kat Light:Nothing to Disclose, Adam Webb:Nothing to Disclose.

4334 | THE MAGNITUDE OF HEPATOCELLULAR CARCINOMA IN SAUDI ARABIA: RESULTS FROM A COMPREHENSIVE CLINICAL REGISTRY

Saleh Alessy[1] Waleed Al Hamoudi[1] Lolwa Alobaid[2] Maram Alotaiby[3] Ahmed Alyahya[3] Duna Barakeh[1] Amwaj Alanazi[1] Mussadique Jhatial[1] Mehwish Hussain[1] Fahad AlMugbel[1] Ali Alqahtani[1] Malak Abedalthagafi[4] Marwan AlHajeili[5] Waleed Alomaim[1] Mohammad Mawardi[6] Dieter Broering[1] Saad Alghamdi[7] Faisal Abaalkhail[1] Saleh Alqahtani[1], [1]King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia, [2]King Abdulaziz Medical City, Riyadh, Saudi Arabia, [3]Ministry of Health, Riyadh, Saudi Arabia, [4]Tufts Medical Center and Tufts University School of Medicine, Massachusetts, MA, United States, [5]King Abdulaziz University, Jeddah, Saudi Arabia, [6]King Faisal Specialist Hospital & Research Center, Jeddah, Saudi Arabia, [7]King Faisal Specialist Hospital and Research Center

Background: Hepatocellular carcinoma (HCC) is a leading cause of cancer-related morbidity and mortality worldwide, with substantial regional variations in its epidemiology, etiology, clinical presentation, and outcomes. Understanding the patterns and underlying causes of HCC in Saudi Arabia is critical for developing targeted prevention and management strategies. This study aimed to describe the prevalence, clinical characteristics, and survival outcomes of HCC in Saudi Arabia using a large clinical registry. **Methods:** Data were collected from the HCC registry, at King Faisal Specialist Hospital and Research Center (KFSHRC), a tertiary referral center estimated to manage about 30% of HCC cases in the country. Cases diagnosed between 2020 and 2026 were identified from oncology services and multidisciplinary tumor boards. Data collected included demographics, etiologies, and clinical presentations, as well as mortality data linked

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through the National Death Registry at the Ministry of Health. **Results:** Our analysis included 693 cases, of which 70% were male (2.3:1 male-to-female ratio), and the median age at diagnosis was 64.0 years. Metabolic dysfunction-associated steatotic liver disease and steatohepatitis (MASLD/MASH) were the most common etiologic category, accounting for 35.6% of cases, followed by hepatitis C virus (24.8%) and hepatitis B virus (22.4%). A history of smoking (current or former) was reported in 16.6% of patients, diabetes in 56.7%, and hypertension in 48.5%. Most patients (94.2%) were diagnosed by imaging. Early-stage disease (BCLC stage 0 or A) was observed in 40.9%, while 12.4% had no underlying cirrhosis[BAN1] [SAA2] . Locoregional therapy was the most common first treatment at KFSHRC (44.9%), followed by surgery (15.3%) and systemic therapy (13.3%). Overall survival at 12 and 36 months was 71.4% and 51.0%, respectively. **Conclusion:** The KFSHRC registry provides valuable insights into the epidemiology and survival outcomes of HCC in Saudi Arabia. MASLD/MASH were the leading etiologic category of HCC, surpassing both HBV and HCV, reflecting a major etiological transition in Saudi Arabia. The relatively high proportion of early-stage HCC in this registry may reflect referral bias, as KFSHRC is the country's largest transplant center, leading to an over-representation of patients suitable for curative interventions.

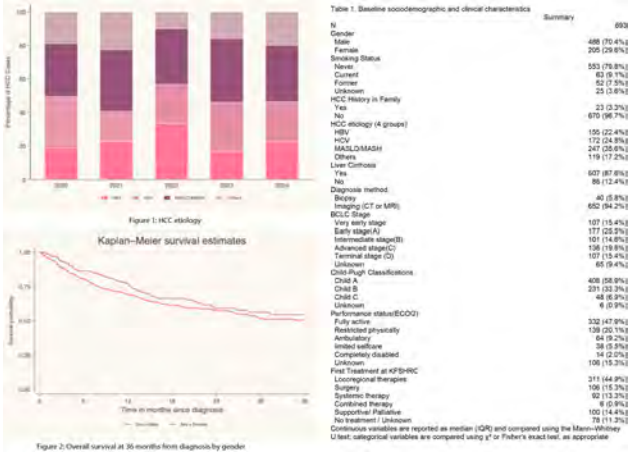


Table 1. Baseline sociodemographic and clinical characteristics

	Summary
N	693
Gender	
Male	488 (70.4%)
Female	205 (29.6%)
Smoking Status	
Never	553 (79.8%)
Current	63 (9.1%)
Former	52 (7.5%)
Unknown	25 (3.6%)
HCC History in Family	
Yes	23 (3.3%)
No	670 (96.7%)
HCC etiology (4 groups)	
HBV	155 (22.4%)
HCV	172 (24.8%)
MASLD/MASH	247 (35.6%)
Others	119 (17.2%)
Liver Cirrhosis	
Yes	607 (87.6%)
No	86 (12.4%)
Diagnosis method	
Biopsy	40 (5.8%)
Imaging (CT or MRI)	652 (94.2%)
BCLC Stage	
Very early stage	107 (15.4%)
Early stage(A)	177 (25.5%)
Intermediate stage(B)	101 (14.6%)
Advanced stage(C)	136 (19.6%)
Terminal stage (D)	107 (15.4%)
Unknown	65 (9.4%)
Child-Pugh Classifications	
Child A	408 (58.9%)
Child B	231 (33.3%)
Child C	48 (6.9%)
Unknown	6 (0.9%)
Performance status(ECOG)	
Fully active	332 (47.9%)
Restricted physically	139 (20.1%)
Ambulatory	64 (9.2%)
limited selfcare	38 (5.5%)
Completely disabled	14 (2.0%)
Unknown	106 (15.3%)
First Treatment at KFSHRC	
Locoregional therapies	311 (44.9%)
Surgery	106 (15.3%)
Systemic therapy	92 (13.3%)
Combined therapy	6 (0.9%)
Supportive/ Palliative	100 (14.4%)
No treatment / Unknown	78 (11.3%)

Continuous variables are reported as median (IQR) and compared using the Mann–Whitney U test; categorical variables are compared using χ^2 or Fisher's exact test, as appropriate

Disclosures: Saleh Alessy:Nothing to Disclose, Waleed Al Hamoudi:Nothing to Disclose, Lolwa Alobaid:Nothing to Disclose, Maram Alotaiby:Nothing to Disclose, Ahmed Alyahya:Nothing to Disclose, Duna Barakeh:Nothing to Disclose, Amwaj Alanazi: Nothing to Disclose, Mussadique Jhatial:Nothing to Disclose, Mehwish Hussain:Nothing to Disclose, Fahad AlMugbel:Nothing to Disclose, Ali Alqahtani: Nothing to Disclose, Malak Abedalthagafi:Nothing to Disclose, Marwan AlHajeili:Nothing to Disclose, Waleed Alomaim:Nothing to Disclose, Mohammad Mawardi:Nothing to Disclose, Dieter Broering:Nothing to Disclose, Saad Alghamdi:Nothing to Disclose, Faisal Abaalkhail:Nothing to Disclose, Saleh Alqahtani:Nothing to Disclose.

4335 | ESTABLISHMENT OF A PATIENT-DERIVED RAT MODEL OF HEPATOCELLULAR CARCINOMA FOR ENDOVASCULAR LOCOREGIONAL THERAPY AND SYSTEMIC THERAPY

Austin Zhang[1] Yohan Kim[1] Eleanna Kaffe[2] Ariful Islam[2] George McClung[2] Kelley Weinfurtner[2] David Tischfield[2] Terence Gade[2], [1]Perelman School of Medicine, University of Pennsylvania, [2]University of Pennsylvania

Background: Locoregional therapies (LRT), such as transarterial chemoembolization, and systemic therapies, such as immune checkpoint inhibitors, represent major treatment modalities for hepatocellular carcinoma (HCC), yet animal models that enable the study of these approaches in combination are lacking. Although patient-derived xenograft models of HCC exist in mice, their vasculature is too small to accomodate LRT. The rat is the smallest animal in which clinically relevant LRT techniques can be performed, while also being more practical than larger animals for studying treatments at scale. This study aims to establish a patient-derived orthotopic xenograft (PDOX) rat model of HCC for the preclinical study of combination LRT and systemic therapies. **Methods:** First, rat HCC PDOXs were generated by orthotopic implantation of tumor fragments from human HCC biopsy-derived PDX tumors, initially expanded in immunodeficient mice, into immunodeficient SRG rats (Rag2/Il2rg 2xKO). Tumor size was monitored weekly via T2 MRI. Rats with tumors $\geq 180mm^3$ were randomized into treatment groups including transarterial embolization (TAE), performed in an angio suite using a Siemens Artis Pheno robotic C-arm, 1.7Fr microcatheter, and 40-120µm particle embolic, with post-procedure MRI follow-up. Second, rats with humanized livers and immune system chimerism were generated in immunodeficient RRGS rats (Rag1/Il2rg 2xKO, hSIRPα). Conditioning with retrorsine (30mg/kg) was performed at age 4 weeks. At 8 weeks, myeloablation via irradiation (4Gy) was followed by 80% partial hepatectomy and intrasplenic injection of 3×10^6 human hepatocytes and 3×10^5 human CD34+ hematopoietic stem cells. Human liver and immune chimerism were assessed at 14 weeks via proteomics and flow cytometry, respectively. **Results:** Engraftment rates across 4 patient lines reached 70-100%. Growth curves showed variable kinetics reflecting inter-patient tumor heterogeneity. TAE was reproducibly performed, with embolized tumors showing reduced growth compared to controls. Liver chimerism assessment across

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174 rat-only or human-only proteins showed equal abundance of each, demonstrating ~50% chimerism. Flow cytometry revealed ~25% abundance of hCD45 cells, confirming partial immune chimerism. **Conclusion:** This novel rat HCC PDOX model enables endovascular locoregional intervention and longitudinal imaging, while partial humanization of the liver and immune system provide a foundation for evaluating combination locoregional and systemic therapies. As such, it represents a promising preclinical platform for translational studies of HCC treatment. Given the importance of endothelial and immune microenvironments in HCC, this work lays the foundation for a translational model that better recapitulates the heterogeneity of human disease encountered in clinical practice, thereby enabling preclinical study of combination LRT and systemic therapy.

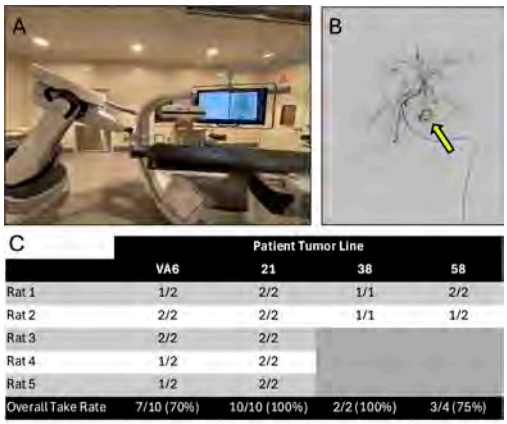


Fig. HCC PDOX Data: embolization procedure, tumor engraftment, growth kinetics, post-embolization response.
(A) Angio suite and C-arm used for embolization procedure. (B) Digital subtraction angiography performed during embolization procedure with tumor location denoted by arrow. (C) Take rates for tumors of 4 different patient lines implanted into SRG rats to generate HCC PDOX, numerator denoting successfully engrafted tumors and denominator denoting how many tumors were implanted into each rat. (D) Tumor growth curves based on MRI volumetric segmentation. (E) Growth rates of embolized (n=5) vs non-embolized tumors (n=2).

Disclosures: Austin Zhang:Nothing to Disclose, Yohan Kim:Nothing to Disclose, Eleanna Kaffe:Nothing to Disclose, Ariful Islam:Nothing to Disclose, George McClung:Nothing to Disclose, Kelley Weinfurtner:Nothing to Disclose, David Tischfield:Nothing to Disclose, Terence Gade:Nothing to Disclose.

4336 | HIGH SERUM ALPHA-FETOPROTEIN VALUES (≥500 NG/ML) ARE MORE COMMON AT DIAGNOSIS IN NON-CIRRHOTIC THAN CIRRHOTIC HEPATOCELLULAR CARCINOMA

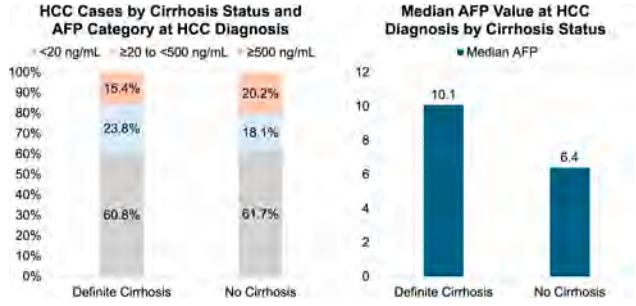
Nicole Kim[1] Philip Vutien[1] Bret Mecham[2] Vyshnika Sriskantharajah[2] Elliott Lowy[2] Kristin Berry[2] George Ioannou[2], [1]University of Washington, [2]Veterans Affairs Puget Sound Health Care System

Background: Elevated serum alpha-fetoprotein (AFP) values correlate with more advanced stage hepatocellular carcinoma (HCC) and poor prognosis. We aimed to examine serum AFP values at HCC diagnosis by cirrhosis status and etiology of liver disease. **Methods:** We identified U.S. Veterans diagnosed with incident HCC between 1/1/2014 and 10/26/2025. Cirrhosis status was categorized as “definite” based on ICD-codes for cirrhosis and/or related complications within 1 year of the HCC diagnosis date, “probable” based on not meeting criteria for definite cirrhosis but having a FIB-4 score >3.25 or a transient elastography liver stiffness measurement >12.5 kPa within 2 years before or 6 months after the HCC diagnosis date, and “no cirrhosis” based on not meeting criteria for definite and probable cirrhosis. Serum AFP values obtained on or within 6 months before or after the date of HCC diagnosis were reviewed. Descriptive statistics were used to compare median and categories of AFP values by cirrhosis status and etiology of liver disease. **Results:** A total of 25,625 U.S. Veterans diagnosed with HCC during 2014-2025 had an AFP value around the time of their HCC diagnosis. Of these patients, 81%, 3.7%, and 15.6% had definite, probable, and no cirrhosis respectively. Patients without cirrhosis had a lower median AFP value at HCC diagnosis than those with definite or probable cirrhosis (6.4 vs. 10.1 vs. 35.1 ng/mL; $p<0.001$, Figure), and a similar proportion of patients with definite and no cirrhosis had an AFP value <20 ng/mL at the time of HCC diagnosis (61% vs. 62%). However, a greater proportion of patients with non-cirrhotic HCC than those with definite cirrhosis and HCC had an AFP value ≥500 ng/mL at the time of HCC diagnosis (20.2% vs. 15.4%; $p<0.001$, Figure). These findings persisted across liver disease etiologies, including hepatitis C, metabolic-dysfunction associated steatotic liver disease, and alcohol-related liver disease ($p<0.001$). **Conclusion:** A very high proportion (20.2%) of patients with non-cirrhotic HCC have

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very high AFP values ≥500 ng/mL at the time of diagnosis. This suggests late diagnosis at advanced stages of HCC and is associated with poor prognosis. These findings support the need to develop rational HCC surveillance strategies to enhance early detection of non-cirrhotic HCC.



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4337 | HEPATOCELLULAR CARCINOMA IN AUTOIMMUNE LIVER DISEASES: A SINGLE-CENTRE CASE SERIES

Shubham Jain[1] Arnav Aggarwal[2] Ayush Agarwal[2] Sarthak Saxena[3] Sudipta Nandi[2] Ankush Garg[2] Vishal Singh Chauhan[2] Samagra Agarwal[2] Sagnik Biswas[4] . Shalimar[2], [1]All India Institute of Medical Sciences, New Delhi, [2]All India Institute of Medical Sciences , New Delhi, [3]All India Institute of Medical Sciences, Delhi, [4]All India Institute of Medical Sciences New Delhi

Background: Hepatocellular carcinoma (HCC) is a rare but increasingly recognised complication of autoimmune liver diseases (AILD). Despite growing recognition of AILD-associated HCC, data regarding its clinical presentation, tumour characteristics, treatment outcomes, and survival remain limited. We aimed to evaluate the clinicopathological profile and overall survival outcomes of patients with AILD-associated HCC in a tertiary care centre. **Methods:** We conducted a retrospective observational study of 13 patients with AILD-related HCC treated at a tertiary care centre. We analysed demographic, biochemical, radiological, staging, treatment, and outcome data. The Barcelona Clinic Liver Cancer (BCLC) staging system was used to assess tumour burden. Overall survival (OS) was calculated from the date of HCC diagnosis until death or the last follow-up. **Results:** Among the 13 patients, underlying aetiologies included autoimmune hepatitis (AIH) in 9 (69.2%), primary biliary cholangitis (PBC) in 2 (15.4%), AIH-PBC overlap syndrome in 1 (7.7%), and AIH-primary sclerosing cholangitis overlap syndrome in 1 patient (7.7%). Six patients (46.2%) had HCC at the time of initial AILD diagnosis, while 7 (53.8%) developed HCC during follow-up. The median duration from AILD diagnosis to HCC development was 66 months [interquartile range (IQR) 51.5–126.5]. BCLC stage A was the most common stage at presentation. The median tumour size was 3.05 cm [IQR 2.3–6.5] while one had an infiltrative lesion. Portal vein thrombosis and extrahepatic metastases were infrequent. Treatment modalities included transarterial chemoembolization (TACE) in 4 patients (30.8%), transarterial radioembolization (TARE) in 1 (7.7%),microwave ablation (MWA) in 2 (15.4%), percutaneous acetic acid injection (PAI) in 2 (15.4 %), stereotactic body radiation therapy (SBRT) in 1 (7.7 %), lenvatinib-based systemic therapy in 2 (15.4%) and immunotherapy in 2 (15.4%) according to tumour stage and hepatic function with median Child–Turcotte–Pugh (CTP) score at HCC diagnosis being 7 [IQR 6–9] . No patient received a transplant during the follow-up. Kaplan–Meier survival analysis demonstrated poor overall survival following HCC diagnosis. Median overall survival was 4.5 months [IQR 2–12], with an estimated survival probability of approximately 54% at 6 months, declining to 31% at 12 months. **Conclusion:** In our cohort, AILD-related HCC was linked to poor survival after diagnosis, even with locoregional and systemic therapies. This aligns with findings from earlier case series of AIH and overlap syndrome related HCC and highlights the need for regular surveillance and better risk assessment in patients with AILD for earlier HCC detection.

Disclosures: Shubham Jain:Nothing to Disclose, Arnav Aggarwal:Nothing to Disclose, Ayush Agarwal:Nothing to Disclose, Sarthak Saxena:Nothing to Disclose, Sudipta Nandi:Nothing to Disclose, Ankush Garg:Nothing to Disclose, Vishal Singh Chauhan:Nothing to Disclose, Samagra Agarwal:Nothing to Disclose, Sagnik Biswas: Nothing to Disclose, . Shalimar:Nothing to Disclose.

4338 | BASELINE ALPHA-FETOPROTEIN PREDICTS SURVIVAL IN PATIENTS WITH HEPATOCELLULAR CARCINOMA: A PROSPECTIVE BRAZILIAN COHORT STUDY

Rodrigo Cambraia[1] Diego Vieira[1] Geraldo Pereira[1] Osvaldo Flávio Couto[1] Lincoln Cordeiro da Mata[1] Antônio Orlando Neto[1] Rosangela Teixeira[2], [1]Hospital das Clínicas (EBSERH/UFMG), School of Medicine, Federal University of Minas Gerais, [2]Federal University of Minas Gerais

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Background: Although alpha-fetoprotein (AFP) is widely used for hepatocellular carcinoma (HCC) surveillance and diagnosis, the prognostic significance of lower AFP thresholds remains insufficiently validated in real-world cohorts. This study evaluated the prognostic value of baseline AFP levels in patients with HCC. **Methods:** Patients with HCC were prospectively enrolled between 2019 and 2024. Diagnosis and staging were established according to LI-RADS and Barcelona Clinic Liver Cancer (BCLC) classification. Clinical and imaging data were collected at baseline and reassessed every 3–4 months or as clinically indicated. Overall survival (OS) was estimated using the Kaplan–Meier method and compared by log-rank test. Variables with $p \leq 0.20$ in univariate analyses were included in multivariable Cox proportional hazards models. The study was approved by the local Ethics Committee, and all participants provided written informed consent. **Results:** A total of 206 patients were included (mean age: 67.4 ± 9.6 years; 76.7% male), with a median follow-up of 16.0 months (IQR: 8.0–30.0). Baseline AFP levels were ≤20 ng/mL in 102 patients (49.5%) and >20 ng/mL in 104 (50.5%). During follow-up, 74 HCC-related deaths (35.9%) occurred. Estimated mean OS for the entire cohort was 38.3 months (95% CI: 34.5–42.0). Early-stage HCC (BCLC 0/A) was more frequent among patients with AFP ≤20 ng/mL (60.2% vs. 36.5%). AFP >20 ng/mL was associated with higher HCC-related mortality (67.6% vs. 40.9%; $p < 0.001$) and shorter OS (30.3 vs. 46.3 months; $p < 0.001$). Additional predictors of worse survival included advanced BCLC stage ($p < 0.001$) and ALBI grade II/III ($p = 0.001$). In univariate analyses, AFP >20 ng/mL was associated with impaired liver function (Child-Pugh B/C: 29.7% vs. 15.9%; $p = 0.03$), larger tumors (55.5 mm vs. 41.5 mm; $p = 0.02$), and higher prevalence of portal vein tumor thrombosis (14.1% vs. 2.1%; $p = 0.003$). In multivariable analysis, AFP >20 ng/mL remained independently associated with HCC-related mortality (adjusted hazard ratio [aHR]: 2.07; 95% CI: 1.21–3.50; $p = 0.008$). Likewise, BCLC stage B (aHR: 2.06; 95% CI: 1.10–3.86; $p = 0.02$), BCLC stage C/D (aHR: 2.69; 95% CI: 1.35–5.33; $p = 0.005$), and ALBI grade II/III (aHR: 1.89; 95% CI: 1.09–3.27; $p = 0.02$) were independently associated with poorer survival. **Conclusion:** Baseline AFP >20 ng/mL was independently associated with worse survival in HCC, conferring mortality risk comparable to advanced tumor stage and impaired liver function. These findings suggest that relatively low AFP thresholds may improve prognostic stratification and identify patients with more aggressive tumor biology.

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4339 | NONINVASIVE PREDICTION OF CLINICALLY SIGNIFICANT PORTAL HYPERTENSION IN HEPATOCELLULAR CARCINOMA: A TUMOR-ADJUSTED MODEL

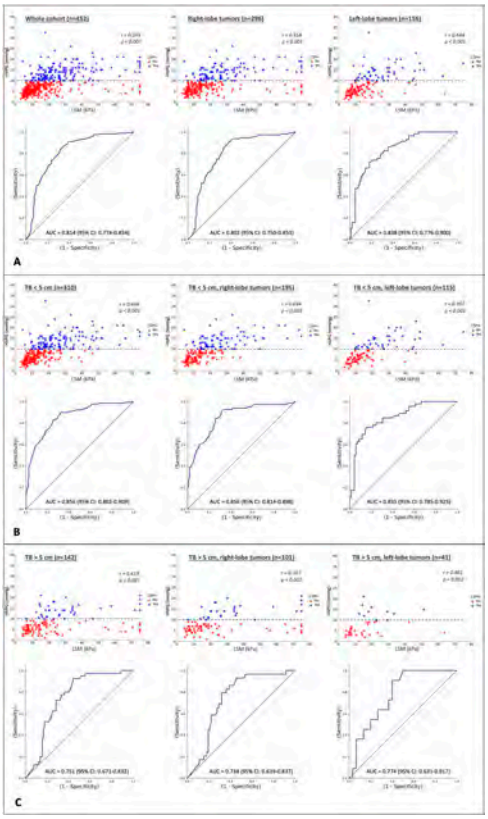
Coskun Demirtas[1] Catherine Mezzacappa[2] Riccardo Sartoris[3] Pierre-Emmanuel Rautou[4] Mario Romero-Cristóbal[5] Rafael Banares Canizares[5] Cosmina Sutac[6] Bogdan Procopet[6] Manon Allaire[7] Dominique Thabut[7] Elba Llop[8] Juan Carlos Garcia-Pagan[9] Muthukumarassamy Rajakannu[10] Eric Vibert[10] Tamar Taddei[11] Guadalupe Garcia-Tsao[11], [1]Marmara University School of Medicine, [2]Yale School of Medicine, [3]AP-HP, University Hospitals Paris Nord Val-de-Seine, [4]Université Paris-Cité, Inserm, Centre de recherche sur l'inflammation, [5]Liver Unit, Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria, [6]"Prof. Dr. Octavian Fodor" Regional Institute of Gastroenterolog, [7]AP-HP Sorbonne Université, Hôpital Universitaire Pitié-Salpêtrière, [8]Hospital Universitario Puerta de Hierro Majadahonda, [9]Hospital Clinic, [10]Centre Hépato-Biliaire, AP-HP Hôpital Paul Brousse, [11]Yale University

Background: Noninvasive assessment of clinically significant portal hypertension (CSPH) using liver stiffness measurement (LSM) and platelet count (per Baveno VII criteria) may be influenced by tumor-related factors in patients with hepatocellular carcinoma (HCC). We evaluated the relationship between LSM and hepatic venous pressure gradient (HVPG) and developed a tumor-adjusted model for CSPH prediction in HCC. **Methods:** In this multicenter study, 452 patients with compensated cirrhosis and HCC who underwent LSM by vibration-controlled transient elastography (VCTE) and HVPG measurement within three months across six tertiary centers were retrospectively analyzed. The correlation between LSM and HVPG was assessed using Spearman correlation analyses, including stratification by tumor characteristics. CSPH was defined as HVPG ≥10 mmHg. A tumor-adjusted predictive model (Baveno-HCC) was developed in a derivation cohort (n = 316) and validated in an independent cohort (n = 136). Model discrimination, calibration, and clinical utility were evaluated using AUROC analysis, calibration plots, Hosmer-Lemeshow testing, and decision curve analysis. **Results:** LSM correlated moderately with HVPG overall ($r = 0.593$, $p < 0.001$; AUC = 0.814), with substantially reduced performance in patients with tumor burden >5 cm, particularly with right-lobe involvement ($r = 0.357$; AUC = 0.738). Baveno

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VII criteria maintained high rule-out performance (negative predictive value >90%, sensitivity >87%) across subgroups but showed limited rule-in accuracy in patients with tumor burden >5 cm (positive predictive value [PPV] 50.0% and specificity 70.4%). The Baveno-HCC model, incorporating LSM, platelet count, spleen size, and tumor burden, improved rule-in performance of CSPH, with higher PPV and specificity while preserving rule-out accuracy. Improvements were most pronounced in patients with tumor burden >5 cm, with PPV increasing from 46.2% to 84.6% in the derivation cohort and from 56.3% to 100.0% in the validation cohort, and with specificity improving from 72.6% to 95.8% in the derivation cohort and from 65% to 100.0% in the validation cohort. Indeterminate classifications were also reduced (41.8% to 38.7%). The Baveno-HCC model demonstrated strong discrimination (AUROC = 0.884 in the derivation cohort; 0.860 in the validation cohort) with improved calibration and net benefit on decision curve analysis. **Conclusion:** Tumor burden and location affect LSM-based CSPH assessment in HCC. The proposed Baveno-HCC model, incorporating readily available clinical variables, improves CSPH prediction and supports more accurate risk stratification and clinical decision-making in patients with HCC.



Disclosures: Coskun Demirtas:Nothing to Disclose, Catherine Mezzacappa:Nothing to Disclose, Riccardo Sartoris:Nothing to Disclose, Pierre-Emmanuel Rautou:Cook: Consultant, Genfit: Consultant, Jazz: Consultant, Astra Zeneca: Consultant, Leo Pharma: Speaking and Teaching, Mario Romero-Cristóbal: Nothing to Disclose, RAFAEL BANARES CANIZARES:Nothing to Disclose, Cosmina Sutac:Nothing to Disclose, Bogdan Procopet:Nothing to Disclose, Manon Allaire:Nothing to Disclose, Dominique Thabut: Nothing to Disclose, Elba Llop:Nothing to Disclose, Juan Carlos Garcia-Pagan:Mallinckrodt: Grants or contracts, COOK Medical: Honoraria for lectures, presentations, speakers bureaus, GORE Medical: Honoraria for lectures, presentations, speakers bureaus, AstraZeneca: Grants or contracts, MUTHU KUMARASSAMY RAJAKANNU:Nothing to Disclose, Eric Vibert:Nothing to Disclose, Tamar Taddei:Nothing to Disclose, Guadalupe Garcia-Tsao:Nothing to Disclose.

4340 | AN EDGE-DEPLOYABLE REPVIT FRAMEWORK FOR ZERO-SHOT SEGMENTATION AND AUTOMATED CLASSIFICATION OF FOCAL LIVER LESIONS ON B-MODE ULTRASOUND

Elangovan Krishnan[1] Kavin Elangovan[2] Nayanika Tummala[3] Jansi Sethuraj[4] Ramya Elangovan[5] Namratha Cherukuru[3] Gautam Maddineni[6] Giulio Quarta[3] Tarun Sharma[3] Mushtaq Jaghuri[2], [1]Indian Institute of Technology Bombay, [2]AIM, [3]NYMC ST Mary's General Hospital St Clares, [4]The University of Texas Health Science Center at Houston, [5]Johns Hopkins University, [6]Creighton University

Background: Hepatocellular carcinoma (HCC) is the most prevalent primary liver malignancy, accounting for over 900,000 new cases annually worldwide. B-mode ultrasound remains the frontline screening modality, yet radiological differentiation from benign hemangioma is unreliable, particularly in cirrhotic liver parenchyma. Contemporary deep learning classifiers achieve high benchmark accuracy but rely on computationally intensive architectures, including multi-branch attention networks and vision transformers, that are impractical for point-of-care or resource-limited deployment. Lightweight, edge-deployable models that preserve diagnostic fidelity without GPU dependency represent an unmet clinical need. **Methods:** We developed a two-stage diagnostic pipeline employing Re-parameterised Vision Transformer (RepViT) architectures. Stage 1 used LiteMedSAM, a promptable foundation segmentation model, to isolate focal liver lesions and eliminate background parenchymal confounders. Stage 2 applied a RepViT classifier to the segmented lesion masks to distinguish HCC from hemangioma. Models were trained and internally validated on SMC-LUD, a high-quality

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public dataset of 5,385 histopathologically and radiologically confirmed B-mode ultrasound images from 1,021 patients (Samsung Medical Centre, 2015–2024), with patient-level train/validation/test partitioning (70:20:10). External validation was conducted on the TCIA B-mode liver dataset. Performance was assessed by AUROC, sensitivity, specificity, F1, and F2 scores. **Results:** Stage 1 segmentation yielded a Dice Similarity Coefficient of 0·89. On internal validation, the RepViT classifier achieved an accuracy of 95%, sensitivity 94%, specificity 96%, AUROC 0·98, F1-score 95%, and F2-score 95%, while requiring less than 1 second per image on a standard CPU without GPU acceleration. **Conclusion:** A lightweight, two-stage RepViT pipeline achieves clinically competitive HCC-versus-hemangioma classification on B-mode ultrasound with edge device deployability, offering a practical solution for real-time liver lesion triage in resource-limited settings. Limitations include single-centre training data and a binary classification scope; prospective multicentre validation and extension to additional focal liver lesion subtypes are warranted.

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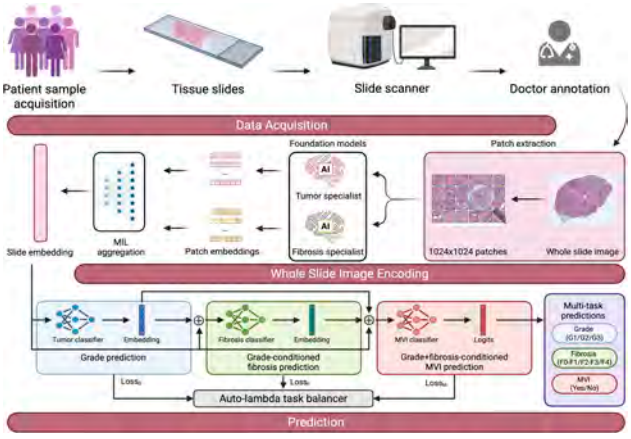
4341 | A CASCADED MULTI-TASK AI MODEL FOR TUMOR GRADE, FIBROSIS STAGE, AND MICROVASCULAR INVASION ASSESSMENT IN HEPATOCELLULAR CARCINOMA WHOLE SLIDE IMAGE

Yan Miao[1] Philip Yu[2] Tak-Siu Wong[3] Regina Lo[1] Rex Wan-Hin Hui[1] Ho-Ming Cheng[1] Lung Yi Mak[1] Man-Fung Yuen[1] Wai-Kay Seto[1], [1]The University of Hong Kong, [2]Education University of Hong Kong, [3]Pamela Youde Nethersole Eastern Hospital

Background: Hepatocellular carcinoma (HCC) pathology reports usually include tumor grading, background fibrosis staging, and microvascular invasion (MVI). All of them facilitate postoperative risk assessment and clinical management. Most artificial intelligence models for liver pathology predict these findings separately, although pathologists assess tumor morphology, fibrosis and vascular invasion simultaneously during the same slide review. We developed CIPHER, a cascaded multi-task model that predicts these three HCC characteristics from hematoxylin and eosin (H&E) whole slide images (WSIs) in a single workflow. **Methods:** The present study included 2,246 H&E WSIs from 319 surgically resected HCC patients at Queen Mary Hospital, Hong Kong. Two board-certified pathologists with more than 10 years of experience annotated tumor grade as G1, G2, or G3, fibrosis as F0-F1, F2-F3, or F4, and MVI as present or absent. Each WSI was divided into tissue-containing patches after color-based quality filtering, and each retained patch received annotation-based labels while preserving its slide coordinates. Up to 1,000 patches per slide were sampled with class-aware weights to reduce dominance by common tissue regions. CIPHER used a pretrained pathology foundation model, UNI, with task-adapted tumor and fibrosis encoders, followed by a transformer-based slide aggregator. Three prediction classifiers at the end of the pipeline were arranged as a clinical cascade: grade first, then fibrosis informed by the grade probabilities, and MVI informed by both grade and fibrosis probabilities. Task masks were used during training so that each slide contributed only to prediction tasks with available reference labels. **Results:** Experiments were performed on a held-out test set. Microvascular invasion was present in 26.1% (n = 586) of slides. For tumor grading, Area Under the Curve (AUC) was 0.967 (95% CI 0.931-0.992), sensitivity was 0.887 (0.746-0.977), specificity was 0.930 (0.870-0.979), positive predictive value (PPV) was 0.870 (0.714-0.962), and negative predictive value (NPV) was 0.918 (0.857-0.967). For fibrosis stage, AUC was 0.985 (0.966-0.997), sensitivity was 0.891 (0.785-0.983), specificity was 0.974 (0.943-0.999), PPV was 0.903 (0.794-0.993), and NPV was 0.983 (0.957-0.997). For MVI status, AUC was 0.982 (0.965-0.995), sensitivity was 0.946 (0.885-0.988), specificity was 0.944 (0.906-0.976), PPV was 0.886 (0.812-0.949), and NPV was 0.974 (0.945-0.994). **Conclusion:** CIPHER predicted three slide-level HCC findings in a single workflow that follows how a pathologist interprets liver histology in a real-world setting, with strong diagnostic performances for tumor grading, fibrosis staging, and MVI. A cascaded multi-task design that respects the clinical reading order may help bring AI assistance closer to routine HCC sign-out.

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Disclosures: Yan Miao:Nothing to Disclose, Philip Yu: Nothing to Disclose, Tak-Siu Wong:Nothing to Disclose, Regina Lo:Nothing to Disclose, Rex Wan-Hin Hui:Nothing to Disclose, Ho-Ming Cheng:Nothing to Disclose, Lung Yi Mak:Gilead Sciences: Grant/Research Support, Roche Diagnostics: Grant/Research Support, Gilead Sciences: Grant/Research Support, Roche Diagnostics: Grant/Research Support, Gilead Sciences: Advisor, Roche Diagnostics: Advisor, GSK: Speaker fee, Man-Fung Yuen:AbbVie, Abbott Diagnotics, Aligos Therapeutics: Consultant, Arbutus Biopharma, Arrowhead Pharmaceuticals, Assembly Biosc: Consultant, Clear B Therapeutics, Dicerna Pharmaceuticals, Immuncore: Consultant, Fujirebio Incorporation, GSK, Gilead Sciences: Consultant, Immunocore, Janssen, Precision BioSciences: Consultant, Roche, Sysmex Corporation, Tune Therapeutics: Consultant, Vir Biotechnology and Visirna Therapeutics: Consultant, AbbVie, Assembly Biosciences, Arrowhead Pharmaceuticals, Aligos Therapeutics, Arbutus Biopharma: Grant/Research Support, Fujirebio Incorporation, Gilead Sciences, Immunocore, Clear B Therapeutics, GSK, Janssen: Grant/Research Support, Sysmex Corporation and Roche: Grant/Research Support, Fujirebio Incorporation, Gilead Sciences, Roche, Sysmex Corp, Aligos Therapeutics, Arbutus Biopharma: Speaking and Teaching, Precision BioSciences: consultancy, Ausperbio: consultancy, IntergerBio: consultancy, Tune Therapeutics: consultancy, Clear B Therapeutics, GSK, Immuncore, Janssen, Vir Biotechnology: Speaking and Teaching, Wai-Kay Seto:MSD: Speaking and Teaching, Echosens: Speaking and Teaching, Pfizer: Grant/Research Support, 89Bio: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Ribo Life Science: Grant/Research Support, AstraZeneca: Grant/Research Support, Gilead: Grant/Research Support, Gilead: Speaking and Teaching, Gilead: Consultant, Abbott: Consultant, Abbott: Speaking and Teaching.

4342 | LIVER AND PREGNANCY OUTCOMES ASSOCIATED WITH HEPATIC ADENOMAS IN PREGNANCY: A SINGLE-CENTER RETROSPECTIVE COHORT STUDY

Clara McNatt[1] Maria Anzola-Schnell[2] Scarlet Yang[2] Tatyana Kushner[2], [1]Weill Cornell Medicine - Division of GI and Hepatology, [2]Weill Cornell Medicine

Background: Hepatocellular adenomas (HCAs) are at risk of growth, bleeding, and rupture in the context of pregnancy. Current guidelines recommend resection or embolization of HCAs > 5cm prior to conception, yet risks of adverse pregnancy outcomes (APOs) in this population remain poorly understood. **Methods:** We performed a single-center retrospective cohort study of HCAs diagnosed before or during pregnancy since 2010. Medical records were reviewed for demographics, HCA characteristics, treatment, and pregnancy outcomes. **Results:** We identified a total of 24 patients with HCAs diagnosed before or during pregnancy. Median age at diagnosis was 29.5 years, median BMI was 23.9, 21% were Hispanic, 54% white, 16% Black, and 21% Other. HCAs ranged in size from 0.6cm-14.8cm (median 4.0cm) (Table). Ten (42%) patients underwent surgery (partial hepatectomy or sectionectomy) or embolization, which was performed a median of 3.5 years prior to pregnancy. Among HCAs resected, median size was 6.8cm. Thirteen (54%) patients had HCAs that were not treated surgically; of those, median size was 2.6cm (Table). Four (31%) of these patients experienced growth during pregnancy, including two who developed new HCAs; 3 of these 4 patients had at least one lesion measuring over 5cm at baseline, and 2 had multiple lesions. Two patients experienced hemorrhagic complications: one was a case of intratumoral hemorrhage, which was monitored until delivery, and one was a rupture at 26 weeks requiring prompt surgical removal. Both patients delivered at term without complication. Rates of APOs were similar between patients who had pre-pregnancy resection and those who did not. Among those post-resection, 6 had APOs: 2 had GDM, 2 had ICP, 1 had gHTN, and 1 had PEC with severe features. Among those without pre-pregnancy resection, 2 had GDM and 2 had PEC, 1 with severe features. **Conclusion:** Our real-world retrospective cohort showed that 69% of HCAs did not show intra-pregnancy growth, and only 31% did. Patients with larger (>5cm) or multiple HCAs at baseline were more likely to exhibit growth during pregnancy. Pregnancy outcomes were similar between patients with remaining HCAs and those post-resection. Hemorrhage occurred in only two cases, perhaps suggesting a lower risk of complication than previously thought. This study reinforces current guidelines to resect adenomas greater than 5cm prior to pregnancy

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and indicates that large or multiple HCAs may post greater risk.

Table 1. Cohort Characteristics

	Overall (N=24)	HCA Not Resected (n=14)	HCA Resected (n=10)
Demographics			
Median age, years (IQR)	29.5 (25.6–32)		
Median BMI (IQR)	23.9 (21.2–32.5)		
Median parity*	1 (range 0-9)		
Aspirin 81mg	9 (38%)		
Race / Ethnicity			
White	13 (54%)		
Black	4 (16%)		
Other	5 (21%)		
Declined	2 (8%)		
Hispanic ethnicity	5 (21%)		
HCA Characteristics			
Median HCA size, cm (IQR)	4.0 (2.0–8.1)	2.8 (1.7–4.0)	6.8 (5.0–10.3)
HCA > 5cm	11 (46%)	3 (21%)	8 (80%)
Median years from resection	—	N/A	3.5 (2.2–6.6)
Adverse Pregnancy Outcomes			
Any APO	9 (38%)	4 (29%)	6 (60%)
Gestational diabetes		2	2
Intrahepatic cholestasis of		0	2
Gestational hypertension		0	1
Preeclampsia		2	1
HCA-Related Complications			
Growth during pregnancy		3 (21%)	1
New lesion(s) developed		2	1
Intratumoral hemorrhage		1	0
Rupture		1	0

*Parity at most recent visit in health system when HCA was seen.

Disclosures: Clara McNatt:Nothing to Disclose, Maria Anzola-Schnell:Nothing to Disclose, Scarlet Yang: Nothing to Disclose, Tatyana Kushner:Gilead: Grant/Research Support, Gilead: Advisor, GSK: Advisor, Eiger: Advisor, GSK: Consultant, Madrigal: Advisor, Ipsen: Advisor, Mirum: Advisor, Mirum: Grant/Research Support, Ipsen: Grant/Research Support.

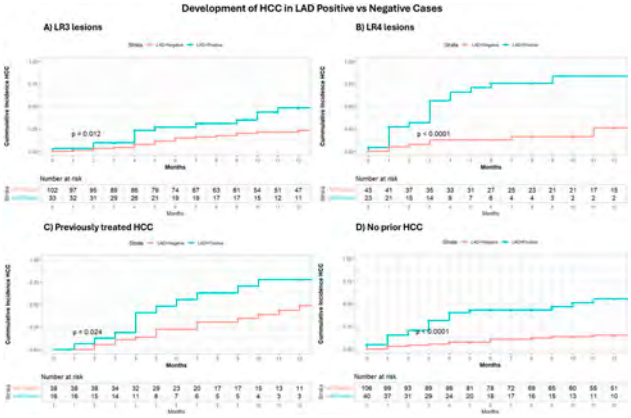
4343 | VALIDATION OF A BIOMARKER-DERIVED INDEX IN PREDICTING HCC DEVELOPMENT IN PATIENTS WITH LI-RADS 3 OR 4 LESIONS

Jeff Liang[1] Ashley Kim[1] Mai Abdusamad[1] Naomy Kim[1] Zoe Berman[2] Jasmine Gamez[2] Lixia Wang[1] Hyunseok Kim[1] Yun Wang[1] Aarshi Vipani[1] Walid Ayoub[1] Paul Martin[1] Alexander Kuo[1] Tsuyoshi Todo[1] Irene Kim[1] Georgios Voidonikolas[1] Todd Brennan[1] Steven Wisel[1] Justin Steggerda[1] Kambiz Kosari[1] Nicholas Nissen[1] Tyler Sandow[3] Rola Saouaf[1] Paul Thevenot[3] Neil Mehta[2] Ju Dong Yang[1], [1]Cedars-Sinai Medical Center, [2]University of California, San Francisco, [3]Ochsner Medical Center

Background: LI-RADS 3 (LR3) and LI-RADS 4 (LR4) lesions pose a diagnostic dilemma and management often requires a multidisciplinary discussion. In a prior study, we developed an index based on the biomarkers, AFP- **L** 3%, **A** FP, and **D** CP—termed the LAD score—that had good performance for detecting viable hepatocellular carcinoma (HCC) after HCC treatment. In this study, we aim to evaluate the accuracy of the LAD score in predicting the progression of LR3 and LR4 lesions to HCC. **Methods:** We identified patients with cirrhosis or chronic hepatitis B infection who had the biomarkers AFP, AFP-L3%, and DCP measured between January 2020–January 2026. We analyzed patients with CT or MRI features of LR3 or 4. The LAD score, obtained within 3 months from imaging, is calculated from the following formula:-0.3695 + 0.6915×log(AFP) + 0.0414×AFP-L3% + 1.180×log(DCP)Positivity is defined as a score $\geq$ 0.927. Diagnosis of HCC was determined by characteristic imaging findings (LR-5) on subsequent imaging or histology. Patients taking Coumadin and those with existing HCC were excluded, although patients who achieved remission after HCC treatment were included. Multivariate Cox regression and AUROC of the LAD score in predicting progression to HCC were calculated, and a Kaplan-Meier plot was used to estimate the incidence of HCC diagnosis over time. **Results:** A total of 201 patients were included. The mean age was 62 years, and 59% were male. HCV and alcohol were the predominant etiologies of HCC (57%). 67% and 33% had LR3 and LR 4 lesions, respectively. Roughly one-quarter of the patients had a history of previously treated HCC with no residual tumor at the time of imaging and blood collection.A total of 56 (28%) patients had a positive LAD score and 66 (33%) patients developed HCC with a median follow-up of 5.0 months. After adjusting for demographic covariates, patients with a positive LAD score were significantly more likely to develop HCC than those with a negative LAD score (HR 3.65, 95% CI 2.18-6.12, $P < 0.01$). The LAD score predicted HCC development in the subset of patients with LR3 (HR 2.24, 95% CI 1.12-4.48, $P = 0.02$), LR4 (HR 9.42, 95% CI 3.15-28.1, $P < 0.01$), and with (HR 2.41, 95% CI 1.10-5.27, $P < 0.01$)/without (HR 5.61, 95% CI 2.84-11.1, $P < 0.01$) prior history of HCC (Figure). The AUROC of the LAD score for predicting HCC development was 0.69 (95% CI: 0.59-0.79) and 0.79 (95% CI: 0.67-0.92) for patients with LR3 and LR4 lesions, and 0.75 (95% CI: 0.62-0.88) and 0.76 (95% CI: 0.66-0.86) for patients with, without prior history of HCC, respectively. **Conclusion:** We found that a positive LAD score is associated with HCC development in patients with LR3 and LR4 lesions. These findings suggest that the LAD score may be a useful adjunct in predicting HCC among patients with indeterminate liver lesions (LR-3/4).

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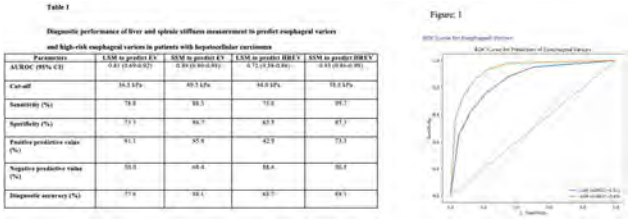
★ 4344 | SPLENIC STIFFNESS MEASUREMENT TO PREDICT THE ESOPHAGEAL VARICES IN PATIENTS WITH HEPATOCELLULAR CARCINOMA

Sayan Malakar[1] Mayank Agarwal[2] Virendra Singh[1] Sumit Rungta[3] Tushar Kundu[2] Amandeep Singh[4] Jahnvi Dhar[1] Nitesh Bassi[5] Upasna Rajput[1] Anmol Anmol[1], [1]Punjab Institute of Liver and Biliary Sciences, [2]King George Medical University, [3]KGMU, [4]Punjab Institute of Liver and Billiary Sciences, [5]Punjab Institute of Liver and Bilary Sciences

Background: The presence of clinically significant portal hypertension (CSPH) and its complications pose significant challenges in hepatocellular carcinoma (HCC) management. Presence of high risk esophageal varices (HREV) can be associated with bleeding following immune-check-point inhibitor therapy. Liver resection is contraindicated the presence of CSPH in patients with HCC. Hence, non-invasive tests to detect CSPH in HCC is worth exploring. Hepatic venous pressure gradient (HVPG) measurement is the gold standard; however, it is an invasive test and requires expertise. Hence, we aimed to explore the role of splenic stiffness measurement (SSM) to predict EV in patients with HCC. **Methods:** This cross-sectional study included 220 patients with HCC who underwent transient elastography evaluation for SSM and liver stiffness measurement (LSM). Patients with ascites, overt hepatic encephalopathy, history of variceal bleeding and splenic space occupying lesions were excluded. Patients were categorised according to the presence or absence of EV and high-risk EV (HREV). Receiver operating characteristic (ROC) curve analysis was performed to determine the diagnostic accuracy of LSM and SSM for predicting EV and HREV. **Results:** The age at presentation was 53.9 ± 11.5 years [male: 181 (82.3%]. The most common etiology of HCC was chronic hepatitis C [83 (37.7%)]. Among 220 patients with HCC, 167 (75.9%) had EV, and 18 (8.2%) had HREV. Patients with EV had significantly higher LSM [48.59 ± 19.84 kPa vs 26.33 ± 11.80 kPa; $p < 0.001$] and SSM [57.50 ± 16.03 kPa vs 42.87 ± 13.50 kPa; $p < 0.001$]. SSM demonstrated superior diagnostic performance compared with LSM for predicting EV [area under the receiver operating curve (AUROC): 0.89 and 0.8] and HREV [AUROC: 0.93 and 0.72], respectively (Table 1 and figure 1). An SSM cut-off of 49.5 kPa has a sensitivity of 88.5% and a specificity of 86.7% for predicting EV in patients with HCC. **Conclusion:** SSM is a better tool to predict EV and HREV in patients with HCC.

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Disclosures: Sayan Malakar:Nothing to Disclose, Mayank Agarwal:Nothing to Disclose, Virendra Singh: Nothing to Disclose, SUMIT RUNGTA:Nothing to Disclose, Tushar Kundu:Nothing to Disclose, Amandeep Singh:Nothing to Disclose, Jahnvi Dhar:Nothing to Disclose, Nitesh Bassi:Nothing to Disclose, Upasna Rajput:Nothing to Disclose, Anmol Anmol:Nothing to Disclose.

4345 | TARGETING HYPOGLYCOSYLATED MUC1 USING SCFV TO DEVELOP NOVEL RADIOTHERANOSTIC AGENTS FOR CHOLANGIOCARCINOMA

Piyushkumar Gondaliya[1] Dylan Zinn[2] Irene Yan[2] Julia Driscoll[2] Christian Ogaugwu[2] Vijayalakshmi Kancharla[2] Wenhui Fu[2] Joshua Knight[2] Adinarayana Kunamneni[2] Hancheng Cai[2] Tushar Patel[2], [1]Mayo Clinic, [2]Mayo Clinic Florida

Background: Cholangiocarcinoma (CCA) is an aggressive malignancy that is challenging to diagnose and to treat. Hypoglycosylated mucin-1 (MUC1) is highly expressed on CCA cells and exposes tumor-specific epitopes that can be selectively targeted. We developed novel single-chain variable fragment antibodies (scFvs) against hypoglycosylated MUC1 and evaluated their therapeutic and radiodiagnostic potential in CCA **Methods:** BALB/c mice were immunized with a MUC1 variable number tandem repeat (VNTR) peptide, and a high-diversity scFv library was generated from splenocyte RNA. Ribosome display technology was used to isolate high-affinity MUC1-binding scFvs. Binding specificity was assessed by ELISA, flow cytometry, and immunocytochemistry in human CCA cell lines (HuCCT1, SNU1079, and KMCH). Functional effects on tumor cell viability were evaluated using MTS assays. Biodistribution and tumor tropism were assessed in orthotopic xenograft mouse models using fluorescently labeled scFvs. scFv-8 was radiochemically conjugated with Gallium-68 (68Ga), and its diagnostic potential was evaluated in orthotopic CCA-bearing mice by ex vivo tissue radioactivity analysis. **Results:** Two novel lead candidates (scFv-8 and scFv-10) were identified by ribosome display and demonstrated selective binding to hypoglycosylated MUC1-positive CCA cells with negligible binding to MUC1-negative controls. Both scFvs reduced CCA cell viability in vitro and suppressed tumor growth in orthotopic xenograft models. Biodistribution studies demonstrate detectable tumor localization with limited off-target tissue retention. Based on its favorable binding and in vivo distribution profile, scFv-8 was selected for further development as a radiodiagnostic and was successfully conjugated with 68Ga. 68Ga-labeled scFv-8 retained MUC1-binding activity following radiolabeling. Ex vivo tissue radioactivity analysis demonstrated localization of radiolabel within orthotopic tumors. **Conclusion:** These findings demonstrate the feasibility and utility of hypoglycosylated MUC1-targeted molecular imaging and the potential for developing precision-targeted therapy. They established a foundation for the development of novel theranostic agents using humanized scFv to hypoglycosylated MUC1 for the diagnosis and treatment of CCA.

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4346 | PERFORMANCE OF ASAP, LG2M, AND GP73 FOR HCC DETECTION IN PATIENTS WITH CIRRHOSIS

Mohammad Jarrah[1] Mohammed Al-Hasan[1] Mariadelcarmen Yanez[1] Maria Yow[1] Fouzia Ahmed[1] Nicole Rich[1] Sneha Deodhar[1] Amit Singal[1], [1]University of Texas Southwestern Medical Center

Background: The sensitivity of ultrasound plus alpha-fetoprotein (AFP) for early-stage hepatocellular carcinoma (HCC) detection remains suboptimal, prompting growing interest in blood-based biomarkers as an alternative strategy. The ASAP [age, sex, AFP, PIVKA-II] score has shown promising performance in prior studies, although further validation in contemporary Western populations is needed. **Methods:** We conducted a case-control study with cases defined as patients with HCC and controls as patients with cirrhosis but without HCC. Blood specimens were collected within 6 months following HCC diagnosis (cases) and during routine visits for cirrhosis (controls). AFP, PIVKA-II, LG2m, and GP73 were measured using the Abbott Alinity platform, and ASAP scores were calculated. The diagnostic performance

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of each individual biomarker and ASAP was assessed by ROC curves and AUROC values. Sensitivity and specificity for detection of early-stage HCC (BCLC stage 0 or A) were compared between ASAP and ultrasound plus AFP using McNemar's Chi-square test, with a positive ultrasound defined as a liver lesion ≥ 1 cm within 6 months of blood collection. **Results:** Among 294 patients (median age 61 years, 67.7% men), 50.7% had HCC (69.1% BCLC 0/A). Liver disease etiology in our cohort included HCV (29.9% viremic HCV; 15.3% post-SVR), ALD (24.5%), and MASLD (16.0%). The diagnostic performance of individual biomarkers for early-stage HCC was moderate to poor (AUROC: AFP 0.76, PIVKA-II 0.79, LG2m 0.53, and GP73 0.57), while ASAP had an AUROC of 0.82. ASAP, at a cutoff of ≥ 0.526, demonstrated a sensitivity of 88.3% for early-stage HCC, with specificity of 54.5%. Sensitivity was higher in men (94.7% vs. 71.4%) and viremic HCV (97.4% vs. 76.9%), whereas specificity was higher in younger individuals (58.5% vs. 37.0%), women (65.6% vs. 46.4%), and those with Child Pugh A cirrhosis (67.5% vs. 37.1%). ASAP, at a cutoff of ≥ 0.804 per Youden's index, demonstrated a sensitivity of 68.0% for early-stage HCC and specificity of 83.4%. In a paired analysis ($n = 178$), ASAP had comparable sensitivity to ultrasound plus AFP (85.5% vs. 90.3%; $p = 0.51$) but lower specificity (53.4% vs. 93.1%; $p < 0.001$). Paired analysis results were consistent across subgroups by age, sex, etiology, and Child-Pugh. **Conclusion:** ASAP demonstrated high sensitivity but suboptimal specificity for early-stage HCC detection. Optimization of ASAP's threshold in Western populations may be needed to better balance sensitivity and specificity.

Disclosures: Mohammad Jarrah:Nothing to Disclose, Mohammed Al-Hasan:Nothing to Disclose, Mariadelcarmen Yanez:Nothing to Disclose, Maria Yow:Nothing to Disclose, Fouzia Ahmed:Nothing to Disclose, Nicole Rich:AstraZeneca: Advisor, AstraZeneca: Advisor, Genentech: Consulting, Genentech: Consulting, Exelixis: Advisor, Exelixis: Advisor, Eisai: Advisor, Eisai: Advisor, Madrigal: Advisor, Madrigal: Advisor, AstraZeneca: Advisor, AstraZeneca: Advisor, Genentech: Consulting, Genentech: Consulting, Exelixis: Advisor, Exelixis: Advisor, Eisai: Advisor, Eisai: Advisor, Madrigal: Advisor, Madrigal: Advisor, Sneha Deodhar:Nothing to Disclose, Amit Singal:Genentech: Consultant, AstraZeneca: Consultant, Bayer: Consultant, Eisai: Consultant, Exelixis: Consultant, Merck: Consultant, Elevar: Consultant, FujiFilm Medical Sciences: Consultant, Exact Sciences: Consultant, Glycotest: Consultant, Boston Scientific: Consultant, Sirtex: Consultant, HelioGenomics: Consultant, ImCare: Consultant, DELFI: Consultant, Curve Biosciences: Consultant, Catalym: Consultant, Verve: Consultant.

4347 | SERUM GLYCAN PROFILING AUGMENTS THE GAAD SCORE FOR EARLY-STAGE HEPATOCELLULAR CARCINOMA DETECTION

Yujie Feng[1] Ming Chen[2] Rui Ma[2] Ziqiang Li[3] Haiguang Xin[3] Qing Guo[3] Honglian Gui[3] Qing Xie[4], [1]Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, [2]Shanghai Jiao Tong University School of Medicine, [3]Department of Infectious Diseases, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, [4]Ruijin Hospital

Background: In China, hepatocellular carcinoma (HCC) is a major public health burden, with chronic viral hepatitis as the leading cause. Curative therapy yields over 90% 5-year survival for early-stage HCC, yet timely detection remains an unmet clinical challenge. Conventional diagnostics have clear limitations: nearly 40% of HCC lesions show atypical imaging features, while AFP and PIVKA-II/DCP exhibit insufficient sensitivity, especially for early-stage HCC. The GAAD score, integrating gender, age, AFP and DCP, improves diagnostic performance but still exhibits suboptimal sensitivity. While dysregulated serum glycoprotein glycosylation participates in HCC progression, robust clinical validation is currently lacking. This study aimed to evaluate whether fluorescence-labeled capillary electrophoresis-based Glycan Test (GT) could augment the performance of GAAD and conventional biomarkers. **Methods:** This cross-sectional study enrolled patients from Shanghai Ruijin Hospital, stratified into an HCC group and a high-risk cohort with chronic hepatitis or liver cirrhosis. HCC cases were further stratified by CNLC and BCLC staging, with diagnoses confirmed pathologically or clinically. Serum AFP and DCP were tested; the Elecsys GAAD score was calculated via logistic regression at a validated cutoff of 2.57. All samples underwent parallel GT profiling. ROC analysis, Cohen's kappa, DCA and stage-stratified analysis compared performance of standalone GT, standalone GAAD and the GAAD-GT combination. **Results:** A total of 171 participants were enrolled (median age 58.1 years; 65.5% male), including 59 chronic hepatitis (34.5%), 48 liver cirrhosis (28.1%) and 64 HCC patients (37.4%). As a standalone biomarker, GT outperformed AFP, DCP and GAAD, with sensitivity 81.25%, accuracy 91.23% and kappa 0.807. AFP, DCP and GAAD showed lower sensitivity (59.38%, 62.50%, 75.00%), accuracy (79.53%, 82.46%, 88.89%) and kappa consistency (0.538, 0.603, 0.753). GT specificity reached 97.20%, comparable to GAAD. AUC values were 0.844 (AFP), 0.861 (GAAD), 0.892 (GT), 0.913 (DCP). The GAAD-GT combination increased AUC to 0.94. DCA confirmed favorable clinical utility of the combined model across wide threshold probabilities. Subgroup analysis showed standalone GT

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achieved sensitivities of 80.49% and 78.43% for BCLC and CNLC early-stage HCC, while standalone GAAD reached 70.73% and 68.63%. The GAAD-GT combination increased the sensitivity to 90.24% and 88.24%. For advanced HCC, the model yielded sensitivities of 91.30% and 100% under BCLC and CNLC criteria. **Conclusion:** GT presents reliable diagnostic performance for HCC across clinical stages, superior to standalone AFP, DCP and GAAD. Combining GT with GAAD further improves accuracy, with the greatest advantage in early detection of HCC. This novel cost-effective serological strategy warrants prospective validation for early HCC detection in high-risk populations.

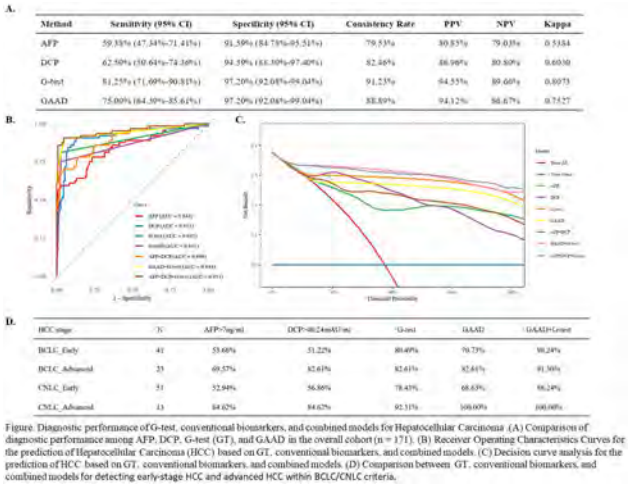


Figure. Diagnostic performance of G-test, conventional biomarkers, and combined models for Hepatocellular Carcinoma. (A) Comparison of diagnostic performance among AFP, DCP, G-test (GT), and GAAD in the overall cohort (n = 171). (B) Receiver Operating Characteristics Curves for the prediction of Hepatocellular Carcinoma (HCC) based on GT, conventional biomarkers, and combined models. (C) Decision curve analysis for the prediction of HCC based on GT, conventional biomarkers, and combined models. (D) Comparison between GT, conventional biomarkers, and combined models for detecting early-stage HCC and advanced HCC within BCLC/CNLC criteria.

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4348 | MRI-TRAINED SELF-SUPERVISED LEARNING TO IMPROVE RECURRENCE PREDICTION IN HEPATOCELLULAR CARCINOMA POST-TRANSPLANTATION

Shreeja Patel[1] Conor Conor Donnelly[2] Lars Chen[3] Dorry Segev[4] Michal Mankowski[3] Karim Halazun[5], [1]NYU Langone Health, [2]NYU Langone Department of Surgery, [3]NYU Center for Surgical and Transplant Applied Research, [4]NYU Center for Surgical and Transplant Applied Resarch, [5]NYU Langone Transplant Institue

Background: Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality worldwide, with increasing incidence in Western populations. Current criteria for selecting patients with HCC for liver transplantation relies on absolute tumor size and number of lesions. However, this approach simplifies the extent and heterogeneity of HCC burden. Given demand for organs continues to outpace supply, optimization of candidate selection for transplantation in the setting of HCC to ensure maximum organ utility is critical. This study aimed to compare the performance of a trained and untrained imaging-based artificial intelligence in HCC recurrence prediction after liver transplantation. **Methods:** We assembled an MRI-specific dataset comprising approximately 330,000 unlabeled abdominal scans drawn from LLD-MMRI4, AMOS5, CHAOS6, and LiverHccSeg. A DINOv2 model was pre-trained using these specific images. We then identified all patients who underwent liver transplantation for HCC between 2014 and 2024 at a single academic health system as our experimental population. An untrained general-purpose DINOv2 model (trained only on ImageNet) and the pre-trained DINOv2 model were independently asked to evaluate the final pre-transplant MRI of our experimental population and predict recurrence. Model performance was evaluated using survival-specific metrics, including the concordance index (C-index) for time-to-event analysis, and area under the receiver operating characteristic curve (AUC-ROC), precision, recall, and specificity for binary classification. **Results:** In 109 patients who underwent transplantation for HCC at this single center, there were 9 recurrences. For survival analysis, the concordance index (C-index) of the general-purpose model was 0.6815 ± 0.1988 (mean ± SD), compared with the MRI-pretrained model 0.7558 ± 0.2556. In classification-based evaluation, the general-purpose model yielded an AUC-ROC of 0.5559 ± 0.0406, precision of 0.0640 ± 0.0175, and recall of 0.5286 ± 0.2124. By contrast, the MRI-pretrained model was slightly improved to AUC-ROC (0.5766 ± 0.1038) and recall (0.5571 ± 0.1623), although not statistically significant [Table 1]. **Conclusion:** We demonstrate that an abdominal MRI–trained self-supervised learning (SSL) model, which learns image representations from large collections of unlabeled abdominal MRI and relies solely on routine pre-transplant imaging, achieves higher discrimination for post-transplant HCC recurrence than a general-purpose image-recognition model. This proof-of-concept suggests that MRI-specific SSL may provide a practical approach to improving recurrence risk stratification among liver transplant candidates with HCC. Our findings demonstrate the potential of leveraging transformers like DINOv2 to adapt artificial intelligence to aid imaging-guided clinical decision making in transplant hepatology.

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Table 1. Comparison of our MRI-Trained model to a general-purpose model (trained on generic ImageNet images) in the prediction of time to event, as well as binary recurrence vs no recurrence.

Model (Survival)	C-index
General Purpose	0.6815 ± 0.1988
MRI-Trained	0.7558 ± 0.2556

Model (Binary)	AUC	AUC-PR	Precision	Recall	F1	Accuracy
General Purpose	0.5559 ± 0.0406	0.1236 ± 0.0550	0.0640 ± 0.0175	0.5286 ± 0.2124	0.1135 ± 0.0325	0.4836 ± 0.1008
MRI-Trained	0.5766 ± 0.1038	0.1389 ± 0.0916	0.0735 ± 0.0186	0.5571 ± 0.1623	0.1295 ± 0.0326	0.5255 ± 0.0734

Disclosures: Shreeja Patel:Nothing to Disclose, Conor Conor Donnelly:Nothing to Disclose, Lars Chen:Nothing to Disclose, Dorry Segev:Nothing to Disclose, Michal Mankowski:Nothing to Disclose, Karim Halazun:Nothing to Disclose.

4350 | DEVELOPMENT AND INDEPENDENT VALIDATION OF AN ARTIFICIAL INTELLIGENCE MODEL FOR HEPATOCELLULAR CARCINOMA DETECTION USING PORTAL VEIN DOPPLER ULTRASOUND WAVEFORMS

Ibrahim Irfanullah[1] Wenjie Zhang[2] Angelo Mattos[3] Fernanda Branco[3] Giovanna Dumoncel[3] Ju Sun[2] Jose Debes[2], [1]Carle Illinois College of Medicine, [2]University of Minnesota, [3]Universidade Federal de Ciências da Saúde de Porto Alegre

Background: Hepatocellular carcinoma (HCC) surveillance relies on ultrasonography, a modality that is operator-dependent and demonstrates suboptimal sensitivity for early-stage disease. These limitations are particularly relevant in resource-limited settings, where HCC burden is high and access to specialized expertise may be restricted. We developed an artificial intelligence (AI)-based approach utilizing Doppler ultrasound waveforms to identify physiologic vascular changes associated with HCC and sought to validate this approach in an independent patient cohort. **Methods:** We analyzed Doppler ultrasound examinations from a U.S.-based development cohort of 228 patients (85 HCC, 143 cirrhotic controls) and an independent Brazilian validation cohort of 116 patients (18 HCC, 98 cirrhotic controls). HCC diagnoses were confirmed by cross-sectional imaging and/or histopathology. Doppler waveforms from the main portal vein (MPV), hepatic artery, and inferior vena cava were analyzed using deep learning models based on a VGG16 architecture. These vessels are routinely assessed during liver ultrasonography and can be identified with minimal additional operator training. Model performance was evaluated using area under the receiver operating characteristic curve (AUROC). **Results:** The development and validation cohorts had median ages of 60 and 67 years, respectively, and included 60% and 58% male participants. Among evaluated vessels, the MPV demonstrated the strongest individual performance for HCC detection. In the development cohort, MPV alone achieved an AUROC of 0.77, increasing to 0.84 when combined with AFP. Most models demonstrated improved performance when analyses were restricted to tumors < 5 cm, with the MPV-only model achieving an AUROC of 0.82. In the independent validation cohort, MPV alone achieved an AUROC of 0.65, while the highest-performing model combined MPV and age, achieving an AUROC of 0.70. **Conclusion:** AI analysis of routine MPV Doppler ultrasound waveforms can differentiate patients with HCC from cirrhotic controls and retained discriminatory ability in an independent Brazilian validation cohort. Performance improved further when combined with AFP and in patients with tumors < 5 cm. This approach leverages routinely acquired ultrasound data and may provide a scalable, low-cost adjunct to current HCC surveillance strategies. Larger multicenter studies are warranted to assess generalizability and clinical implementation.

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4351 | MINIMUM-FOOTPRINT LIVER LESION CLASSIFICATION WITH MOBILENETV4 AND LITEMEDSAM: CLOSING THE DEPLOYMENT GAP FOR ULTRASOUND-BASED HCC TRIAGE IN RESOURCE-CONSTRAINED SETTINGS

Ramya Elangovan[1] Elangovan Krishnan[2] Nayanika Tummala[3] Kavin Elangovan[4] Jansi Sethuraj[5] Namratha Cherukuru[3] Jeril Lasington[6] Anas Al Mardini[3] Gautam Maddineni[7] Tarun Sharma[8] Giulio Quarta[6] Mushtaq Jaghuri[4], [1]Johns Hopkins University, [2]Indian Institute of Technology Bombay, [3]NYMC St Marys St Clares, [4]AIM, [5]The University of Texas Health Science Center at Houston, [6]NYMC St Marys, [7]Creighton University, [8]NYMC St Clares

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Background: A fundamental and underappreciated tension persists in applied medical artificial intelligence: the settings where automated hepatocellular carcinoma (HCC) triage is most urgently needed, communities where B-mode ultrasound constitutes the sole accessible imaging modality and specialist radiological expertise is absent, are precisely those least equipped to run prevailing deep learning classifiers. Architectures optimised for benchmark accuracy impose GPU requirements that render them inoperable on edge or mobile hardware, concentrating diagnostic benefits in well-resourced health systems. **Methods:** We developed a two-stage minimum-footprint pipeline: LiteMedSAM, operating from bounding-box prompts, segmented focal liver lesions and generated perilesional crops (10–20% margin), which a fine-tuned MobileNetV4-Conv-Small network then classified as HCC or hemangioma. Internal validation used SMC-LUD, 5,385 B-mode images from 1,021 patients (Samsung Medical Center, 2015–2024), all HCC cases histopathologically confirmed and hemangioma cases radiologically verified by two independent board-certified radiologists, with strict patient-level partitioning (70:20:10) , and external validation used the TCIA liver dataset. Outcomes included AUROC, sensitivity, specificity, F1-score, F2-score, and Dice Similarity Coefficient. **Results:** LiteMedSAM yielded a Dice Similarity Coefficient of 0·87 at zero-shot inference, improving to 0·89 after fine-tuning. MobileNetV4-Conv-Small achieved 91·0% accuracy and 92·0% F1-score on standard lesion crops; perilesional-margin cropping improved both metrics to 93·0%, with AUROC 0·958. Complete two-stage inference required under one second on edge devices, with a total model footprint under 20 MB, a deliberate accuracy–efficiency trade-off quantifiably justified by the deployment context. **Conclusion:** LiteMedSAM yielded a Dice Similarity Coefficient of 0·87 at zero-shot inference, improving to 0·89 after fine-tuning. MobileNetV4-Conv-Small achieved 91·0% accuracy and 92·0% F1-score on standard lesion crops; perilesional-margin cropping improved both metrics to 93·0%, with AUROC 0·958. Complete two-stage inference required under one second on edge devices, with a total model footprint under 20 MB, a deliberate accuracy–efficiency trade-off quantifiably justified by the deployment context.

Disclosures: Ramya Elangovan:Nothing to Disclose, Elangovan Krishnan:Nothing to Disclose, Nayanika Tummala:Nothing to Disclose, Kavin Elangovan:Nothing to Disclose, Jansi Sethuraj:Nothing to Disclose, Namratha Cherukuru:Nothing to Disclose, Jeril Lasington:Nothing to Disclose, Anas Al Mardini:Nothing to Disclose, Gautam Maddineni:Nothing to Disclose, Tarun Sharma:Nothing to Disclose, Giulio Quarta:Nothing to Disclose, Mushtaq Jaghuri:Nothing to Disclose.

4352 | FASTVIT-SA12 AND SA24 WITH LITEMEDSAM FOR SEGMENTATION-ASSISTED, EDGE-DEPLOYABLE CLASSIFICATION OF HEPATOCELLULAR CARCINOMA ON B-MODE ULTRASOUND

Kavin Elangovan[1] Nayanika Tummala[2] Elangovan Krishnan[3] Ramya Elangovan[4] Jansi Sethuraj[5], [1]AIM, [2]NYMC St Marys St Clares, [3]Indian Institute of Technology Bombay, [4]Johns Hopkins University, [5]The University of Texas Health Science Center at Houston

Background: Hepatocellular carcinoma (HCC) is diagnosed in approximately 905,000 individuals annually, with a 5-year survival below 20% in most regions. B-mode ultrasound is widely accessible for surveillance, yet focal liver lesion characterisation without specialist input remains unreliable. Contemporary deep learning classifiers demonstrate high diagnostic accuracy but depend on GPU-intensive architectures incompatible with mobile or edge deployment. Hybrid vision transformers engineered specifically for on-device inference represent a structurally distinct and underexplored solution to this constraint. **Methods:** A two-stage pipeline was constructed pairing LiteMedSAM, prompted with bounding boxes to segment liver lesions and extract perilesional crops (10–20% margin), with independently fine-tuned FastViT-SA12 and FastViT-SA24 classifiers (Apple). Both models were trained and internally validated on SMC-LUD: 5,385 B-mode images from 1,021 patients, all HCC cases histopathologically confirmed and hemangioma cases radiologically verified by two independent board-certified abdominal radiologists, patient-level split 70:20:10. External validation used the TCIA liver dataset. Primary outcomes: AUROC, sensitivity, specificity, F1-score, F2-score, and Dice Similarity Coefficient (DSC). **Results:** LiteMedSAM segmentation yielded a DSC of 0·90 (zero-shot) and 0·93 (fine-tuned). FastViT-SA12 achieved 93·0% accuracy and F1-score on standard crops, improving to 95·0% with perilesional-margin cropping; AUROC was 0·96. FastViT-SA24 reached 96·0% accuracy and AUROC 0·98, performance commensurate with heavier architectures benchmarked on SMC-LUD, while both variants completed inference in under one second per image on edge devices. **Conclusion:** FastViT-SA24, guided by LiteMedSAM segmentation, achieves excellent HCC classification with full edge deployability; FastViT-SA12 provides a leaner alternative for settings where model footprint is the primary constraint. Both variants deliver lesion-level spatial interpretability. Limitations include single-centre training data and binary classification scope; prospective multicentre validation is required before clinical adoption.

Disclosures: Kavin Elangovan:Nothing to Disclose, Nayanika Tummala:Nothing to Disclose, Elangovan

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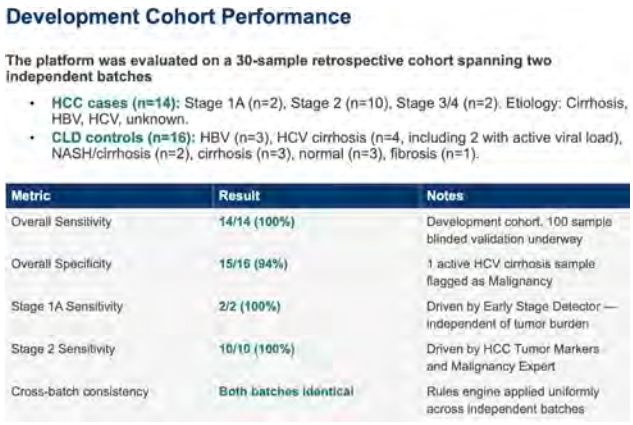
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Krishnan:Nothing to Disclose, Ramya Elangovan:Nothing to Disclose, Jansi Sethuraj:Nothing to Disclose.

4353 | EARLY HCC DETECTION USING MULTI-EXPERT MACHINE LEARNING ON CELL-FREE WHOLE GENOME BISULFITE SEQUENCING DATA

Mythili Subharam[1] Ryan Koehler[2], [1]OmicXHealth, [2]VerdAscend Sciences

Background: Standard HCC surveillance with AFP/Ultrasound has limited sensitivity for early-stage disease and targeted, narrow panel liquid biopsy approaches also fall short in detecting BCLC 0/A stage HCC, where it is treatable. Early-stage HCC is characterized by low tumor-derived cfDNA fraction, where tumor-shedding-dependent markers are unreliable. We developed a multi-expert machine learning (ML) platform employing cell-free whole genome bisulfite sequencing (cfWGBS) with six independently trained ML classifiers integrated through a biologically informed rules engine with etiology-aware adjudication. **Methods:** Six ML classifiers were independently trained on domain-specific published datasets in a Mixture of Experts (MoE) architecture, ensuring orthogonal signals. Five methylation-based classifiers target distinct biomarker sets: (1) Sensitivity Expert for HCC signal gating (2) Malignancy Expert targeting pan-GI malignancy biomarkers (3) HCC Tumor Markers for focal HCC promoter silencing detectable at low tumor fraction (4) Early Stage Detector targeting liver cell death-associated loci (5) Tumor Burden Hypomethylation for HBV-specific hypomethylated blocks. A sixth classifier interrogates cfDNA fragmentation, a structurally orthogonal modality. Both signal types are extracted from plasma moderate-depth whole genome bisulfite sequencing (WGBS) and integrated through a hierarchical rules engine with multi-signal corroboration and etiology-aware adjudication. Thresholds are biologically grounded, not ROC-optimized. Evaluated in a 30-plasma biosample cohort (14 HCC: Stage1A n = 2, Stage2 n = 10, Stage3/4 n = 2; 16 CLD(14 Cirrhosis/HBV, and 2 normal). **Results:** Sensitivity 14/14 (100%); Specificity 15/16 (94%). One HCV/Cirrhosis sample generated a false malignancy signal attributed to active viral hepatitis. Stage1A detection (2/2) was driven by the Early Stage Detector, operating independently of tumor-derived cfDNA. Low-shedding HCC was identified via HCC Tumor Markers where tumor burden signal was absent. No single-expert dependency was identified, each HCC call required corroboration from at least two experts.**Conclusion:** This MoE WGBS platform demonstrates proof-of-concept in a challenging cohort inclusive of active viral hepatitis (HCV), NASH, HBV and Cirrhosis. Orthogonal detection mechanisms address biological heterogeneity limiting single-mechanism approaches. Biologically grounded thresholds and etiology-aware adjudication reduce cohort-specific calibration dependence. Current cohort size is small but independent blinded validation (n = 100, major academic medical center) is underway to confirm if the results hold in a larger validation cohort. This approach may offer a clinically translatable path toward blood-based HCC surveillance that maintains specificity while improving early-stage detection across etiologically diverse high-risk populations.



Disclosures: Mythili Subharam:OmicXHealth: Executive role, Ryan Koehler:Nothing to Disclose.

4354 | NON-CONTRAST MAGNETIC RESONANCE IMAGING FOR HEPATOCELLULAR CARCINOMA SURVEILLANCE IN PATIENTS WITH CIRRHOSIS: A COST-UTILITY ANALYSIS

Dong Ho Lee[1] Seokyung Hahn[2] Yeonggyeong Jang[2], [1]Seoul national university hospital, [2]Seoul National University College of Medicine

Background: Ultrasound (US) is the standard surveillance modality for hepatocellular carcinoma (HCC) in at-risk populations, but its sensitivity for early-stage detection is limited. Non-contrast abbreviated MRI (NC-MRI) offers higher sensitivity; however, its cost-effectiveness remains uncertain. We aimed to

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evaluate the cost-effectiveness of biannual NC-MRI and an alternating NC-MRI/US strategy compared with US in patients with cirrhosis, identifying specific HCC incidence thresholds for clinical benefit. **Methods:** A Markov model simulated a cohort of 10,000 patients with cirrhosis (age 50 years) over a 30-year horizon. Three strategies were compared: (1) biannual US, (2) biannual NC-MRI, and (3) alternating NC-MRI and US at 6-month intervals. Model inputs, including sensitivity for detecting very early and early-stage HCC (NC-MRI 86%, US 47%, alternating 83.9%) and transition probabilities, were derived from the literature. Outcomes were expressed as incremental cost-effectiveness ratios (ICERs) per quality-adjusted life-year (QALY). Deterministic and probabilistic sensitivity analyses were performed. **Results:** At a base-case annual HCC incidence of 3%, biannual NC-MRI and the alternating strategy yielded higher QALYs (8.60 and 8.58, respectively) than US (8.22). The corresponding ICERs were $9,625/QALY for biannual NC-MRI and $3,467/QALY for the alternating strategy. At a willingness-to-pay threshold of $20,000/QALY, biannual NC-MRI was cost-effective when the annual HCC incidence exceeded 1.57%, whereas the alternating strategy was cost-effective when incidence exceeded 0.70%. Probabilistic sensitivity analysis indicated an >80% probability of cost-effectiveness for both NC-MRI-based strategies at a WTP of $50,000/QALY. **Conclusion:** NC-MRI–based surveillance is cost-effective for HCC in patients with cirrhosis, particularly at annual incidence rates ≥1.57% at a $20,000/QALY threshold. An alternating NC-MRI/US strategy offers a more efficient option at lower risk thresholds (≥0.70%), supporting its incorporation into risk-stratified surveillance strategies.

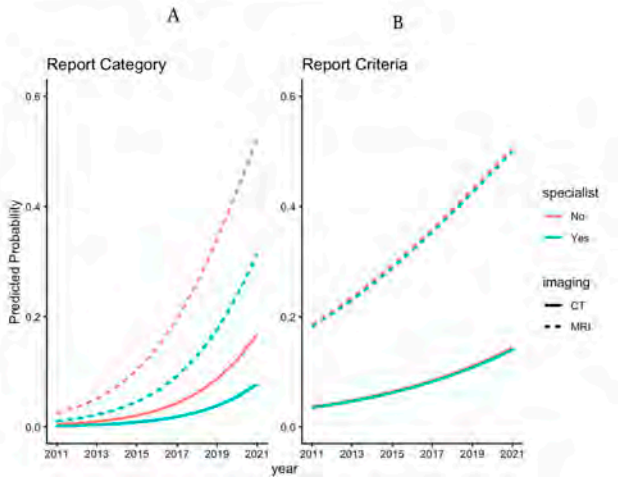
Disclosures: Dong Ho Lee:Nothing to Disclose, Seokyung Hahn:Nothing to Disclose, Yeonggyeong Jang:Nothing to Disclose.

4355 | PATTERN OF ADHERENCE TO LI-RADS REPORTING STANDARDS IN A CANADIAN PROVINCE; RETROSPECTIVE STUDY

Miray Eskandar[1] Sayli Devdikar[2] Robert Balshaw[3] Signy Holmes[1] Maged Nashed[4], [1]University of Manitoba, [2]CancerCare Manitoba, [3]George and Fay Yee Centre for Healthcare Innovation; University of Manitoba, [4]CancerCare Manitoba; University of Manitoba

Background: The radiological diagnostic algorithm, Liver Imaging Reporting & Data System (LI-RADS) is a comprehensive system for standardizing reporting of liver imaging. The lack of adherence to its standards may lead to delayed diagnoses of hepatocellular carcinoma (HCC). **Methods:** In this retrospective study, we aimed to determine whether diagnostic radiologists were compliant in reporting on the four LI-RADS criteria and final category score. We also sought to identify factors that might influence the pattern of LI-RADS reporting. We collected demographic and diagnostic radiological details of patients diagnosed with HCC in Manitoba, by either CT or MRI, between January 2011 and December 2021. **Results:** 725 patients were identified with a median age at diagnosis of 67 years. 10% of scans reported a LI-RADS category and 25% reported all four criteria. There has been a significant increase in reporting both category and criteria over time (P = < 0.001 for both). MRI-based reporting of category and criteria was significantly more frequent than CT-based reporting (P = < 0.001 for both). Specialist radiologists were less likely [OR 0.42; CI 0.22, 0.79] to report category compared to non-specialists but there was no difference in the frequency of reporting criteria between specialist and non-specialist radiologists. **Conclusion:** Compliance with the standardized LI-RADS reporting system in Manitoba has been improving over the years. Nevertheless, it is still suboptimal, and efforts should be made to enhance diagnostic radiologists' compliance with the recommended standards.

Figure 2. Predicted probability of LI-RADS category (A) and criteria (B) reporting over time (2011-2021) by specialist vs non-specialist radiologists when MRI or CT is used for diagnosis. N.b. The logistic regression models included the main effects of year, specialist and imaging.



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4356 | DEEP LEARNING-ASSISTED IMAGE ANALYSIS FOR MORPHOLOGIC PHENOTYPING AND TREATMENT MONITORING OF CIRCULATING TUMOR CELLS IN HEPATOCELLULAR CARCINOMA

Hirotaka Nomiya[1] Takuto Nosaka[1] Yosuke Murata[1] Yu Akazawa[1] Tomoko Tanaka[1] Tatsushi Naito[1] Kazuto Takahashi[1] Yasunari Nakamoto[1], [1]University of Fukui

Background: Circulating tumor cells (CTCs) are promising liquid biopsy biomarkers in hepatocellular carcinoma (HCC). We previously showed that dynamic changes in CD90-positive CTCs were associated with tumor shrinkage and survival (Cancers 2025). However, morphologic evaluation of HCC CTCs has not been established. We quantified CTC morphology using deep learning–based detection and segmentation and examined its association with tumor burden and treatment-related change. **Methods:** Peripheral blood was collected before treatment and at 8–12 weeks after treatment initiation from 18 patients with unresectable HCC receiving atezolizumab plus bevacizumab (n = 14) or durvalumab plus tremelimumab (n = 4); BCLC stage B/C was 12/6. Paired pre/post samples were available in 8 patients. After CD45-positive leukocyte depletion, samples were stained with DAPI/CD45/PanCK and images were acquired by confocal microscopy (FV1200) and whole-slide microscopy (VS200). TruAI (Olympus) was trained on spike-in and HCC samples and used for CTC detection and segmentation. CTCs were defined as DAPI-positive, CD45-negative, PanCK-positive cells with preserved nuclear morphology. Area, circularity, solidity, and aspect ratio were extracted. Each CTC was classified as solitary or non-solitary, and the non-solitary CTC fraction was calculated. Morphologic phenotypes were defined by principal component analysis and Ward clustering. **Results:** The workflow showed linearity in spike-in experiments and agreement with flow cytometry ($R^2 = 0.71$, $P < 0.01$). A total of 714 CTCs from 30 objects were analyzed. Unsupervised clustering identified two morphologic phenotypes. Phenotype 1 showed a large, elongated cells with irregular contour, whereas Phenotype 2 showed a smaller, rounder cells with smoother contour. Phenotype 1 had a larger area than Phenotype 2 (573.83 vs 472.80, $P < 0.05$), with differences in circularity, solidity, and aspect ratio (all $P < 0.01$). In the baseline cohort, Phenotype 1 (n = 8) tended to show larger maximal tumor size (88.21 vs 27.98 mm), higher AFP (25.05 vs 5.90 ng/mL), and higher DCP (898.50 vs 173.50 mAU/mL) than Phenotype 2 (n = 10). In paired samples, CTC count decreased after treatment ($P < 0.05$), the non-solitary CTC fraction showed a decreasing trend ($P = 0.055$), and the PC1 score derived from non-solitary CTC morphology shifted from 0.2 to -1.0, indicating reduced morphologic irregularity after treatment. **Conclusion:** Deep learning–assisted image analysis enabled morphologic phenotyping of HCC CTCs. A large, elongated, irregular phenotype was associated with higher tumor burden and serum tumor markers, and treatment was accompanied by reductions in CTC count and non-solitary morphologic irregularity. Complementing subset-based and molecular profiling, this morphology-based approach may extend multimodal liquid biopsy for characterizing tumor aggressiveness and monitoring treatment-associated change in HCC.

Disclosures: Hirotaka Nomiya:Nothing to Disclose, Takuto Nosaka:Nothing to Disclose, Yosuke Murata: Nothing to Disclose, Yu Akazawa:Nothing to Disclose, Tomoko Tanaka:Nothing to Disclose, Tatsushi Naito: Nothing to Disclose, Kazuto Takahashi:Nothing to Disclose, Yasunari Nakamoto:Nothing to Disclose.

4357 | LITEMEDSAM AND EFFICIENTNETV2-B0: A SEGMENTATION-GUIDED, EDGE-DEPLOYABLE PIPELINE FOR SONOGRAPHIC CLASSIFICATION OF HEPATOCELLULAR CARCINOMA AND HEMANGIOMA

Nayanika Tummala[1] Elangovan Krishnan[2] Kavin Elangovan[3] Jansi Sethuraj[4] Ramya Elangovan[5] Namratha Cherukuru[1] Gautam Maddineni[6] Giulio Quarta[1] Mushtaq Jaghuri[3], [1]NYMC ST Mary's General Hospital St Clares, [2]Indian Institute of Technology Bombay, [3]AIM, [4]The University of Texas Health Science Center at Houston, [5]Johns Hopkins University, [6]Creighton University

Background: Hepatocellular carcinoma (HCC) accounts for approximately 830,000 deaths annually and is routinely detected during B-mode ultrasound surveillance. Reliably distinguishing HCC from benign hepatic hemangioma on ultrasound remains diagnostically challenging, particularly in the setting of cirrhotic parenchymal heterogeneity. Contemporary deep learning classifiers achieve high benchmark accuracy but depend on computationally intensive, GPU-reliant architectures impractical for point-of-care or resource-limited deployment. Lightweight, lesion-focused models combining automated segmentation with efficient classification, operable on standard CPU hardware, represent an unmet clinical priority. **Methods:** A two-stage diagnostic pipeline was developed. In Stage 1, LiteMedSAM received bounding-box prompts to generate lesion segmentation masks, from which lesion-centered crops with a 10–20% perilesional margin were extracted. In Stage 2, an ImageNet-pretrained EfficientNetV2-B0 classifier was fine-tuned on cropped lesion images. The model was trained and internally validated on SMC-LUD, a publicly available dataset of 5,385 B-mode

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ultrasound images from 1,021 patients (Samsung Medical Center, 2015–2024), all HCC cases histopathologically confirmed and hemangioma cases radiologically verified by two independent board-certified abdominal radiologists, with strict patient-level partitioning (70:20:10). External validation was conducted on the TCIA B-mode liver dataset. Primary outcomes were AUROC, sensitivity, specificity, F1-score, F2-score, and Dice Similarity Coefficient (DSC). **Results:** Zero-shot LiteMedSAM segmentation yielded a DSC of 0·89; fine-tuned segmentation improved to 0·91 model performance on ultrasound. EfficientNetV2-B0 on standard lesion crops achieved 92% accuracy and F1-score; the perilesional-margin strategy attained 95% accuracy. HCC sensitivity was 93%, hemangioma sensitivity 94%, and AUROC 0·95. These results are commensurate with heavier architectures benchmarked on SMC-LUD while requiring less than 1 second per image on standard edge devices.**Conclusion:** A two-stage LiteMedSAM–EfficientNetV2-B0 pipeline achieves clinically competitive HCC classification, lesion-level spatial interpretability, and edge deployability. This framework offers a reproducible, resource-efficient tool for real-time liver lesion triage in resource-limited settings. Limitations include single-centre training data and binary classification scope; prospective multicentre validation across heterogeneous ultrasound platforms is required before clinical translation.

Disclosures: Nayanika Tummala:Nothing to Disclose, Elangovan Krishnan:Nothing to Disclose, Kavin Elangovan:Nothing to Disclose, Jansi Sethuraj:Nothing to Disclose, Ramya Elangovan:Nothing to Disclose, Namratha Cherukuru:Nothing to Disclose, Gautam Maddineni:Nothing to Disclose, Giulio Quarta:Nothing to Disclose, Mushtaq Jaghuri:Nothing to Disclose.

4358 | LARGE LANGUAGE MODEL EXTRACTION OF TRANSPLANT-RELEVANT IMAGING FEATURES FROM MULTIPHASE MRI RADIOLOGY REPORTS IN HEPATOCELLULAR CARCINOMA

Usamah Chaudhary[1] Farzad Tahmasebi Arashloo[1] Nicole Rich[2] Amit Singal[1], [1]UT Southwestern, [2]University of Texas Southwestern Medical Center

Background: Accurate characterization of hepatocellular carcinoma (HCC) on multiphase MRI is critical for diagnosis, staging, transplant eligibility, and longitudinal monitoring. However, extracting structured features from free-text radiology reports remains labor-intensive and limits large-scale retrospective research. Large language models (LLMs) show strong performance in medical text interpretation, but their ability to extract granular HCC imaging features and determine transplant-relevant criteria remains incompletely characterized. We evaluated GPT-5.5 for extracting clinically relevant HCC imaging features from multiphase MRI reports. **Methods:** We performed a retrospective study of patients with HCC who underwent multiphase liver MRI. Free-text radiology reports were provided to GPT-5.5 using a standardized structured extraction prompt without fine-tuning. The model extracted predefined features, including number of hepatic lesions and LR-3/LR-4/LR-5 observations, lesion size, arterial phase hyperenhancement (APHE), washout, capsule appearance, tumor in vein, cirrhosis, portal hypertension, ascites, and Milan criteria eligibility. Ground-truth labels were established by manual physician review. **Results:** A total of 348 lesions (132 LR3, 62 LR4, 154 LR5) across 152 MRI reports from 112 unique patients were analyzed. Compared to manual physician review, GPT-5.5 demonstrated high overall extraction performance. The model correctly identified and classified 344 of 348 lesions as LR-3, LR-4, or LR-5, yielding lesion-level classification accuracy of 98.9%. Two lesions, one LR-5 and one LR-3, were missed; one LR-5 was mislabeled LR-4, and one LR-4 was mislabeled LR-5. Among correctly identified lesions, diameter was extracted accurately in all cases. Lesion-level feature extraction was strong, with high accuracy for APHE (98.9%), washout appearance (99.4%), capsule appearance (100%), and vascular invasion (100%). Milan criteria were assessed with 93.4% accuracy. The model also performed well in identifying advanced liver disease features, including portal hypertension (100%), ascites (100%), and extrahepatic metastatic disease or lymph node involvement (94.1%). When stratified by our internal structured report format, lesion classification improved to 99.4%, with all lesion APHE, washout, and capsule appearance correctly identified. Milan criteria accuracy improved to 97.6%. Average processing time per report was 2.59 seconds. **Conclusion:** A GPT-5.5 large language model demonstrated excellent performance extracting clinically meaningful and transplant-relevant imaging features from free-text multiphase MRI radiology reports in patients with HCC. These findings suggest LLM-assisted extraction may enable scalable structured HCC imaging datasets for clinical research, transplant evaluation, and longitudinal outcome studies.

Disclosures: Usamah Chaudhary:Nothing to Disclose, Farzad Tahmasebi Arashloo:Nothing to Disclose, Nicole Rich:AstraZeneca: Advisor, AstraZeneca: Advisor, Genentech: Consulting, Genentech: Consulting, Exelixis: Advisor, Exelixis: Advisor, Eisai: Advisor, Eisai: Advisor, Madrigal: Advisor, Madrigal: Advisor, AstraZeneca: Advisor, AstraZeneca: Advisor, Genentech: Consulting, Genentech: Consulting, Exelixis: Advisor, Exelixis: Advisor, Eisai: Advisor, Eisai: Advisor, Madrigal: Advisor,

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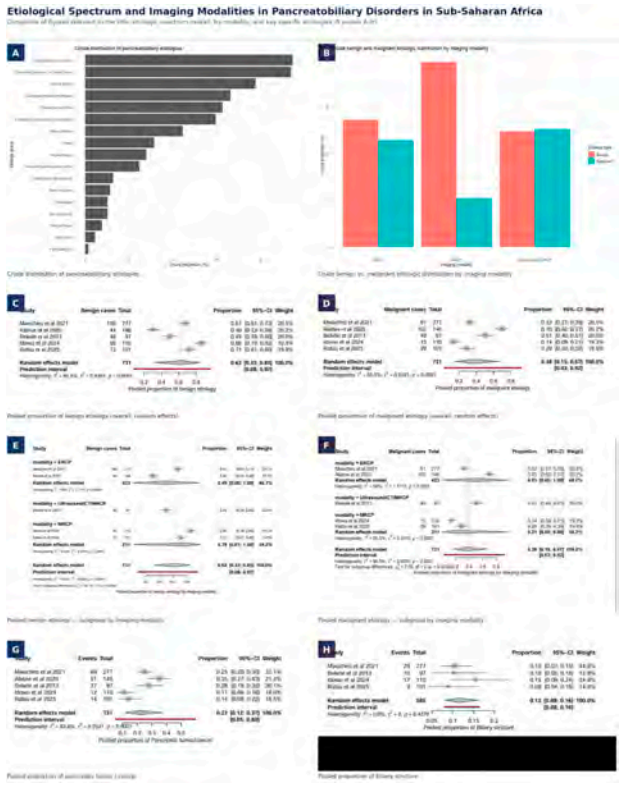
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4359 | ETIOLOGICAL SPECTRUM AND IMAGING MODALITIES IN PANCREATOBILIARY DISORDERS IN SUB-SAHARAN AFRICA (SSA): A SYSTEMATIC REVIEW AND META-ANALYSIS (SRMA)

Emeka Stanley Obi[1] Joshua Kalu[2] Olamide Asifat[3] Chimezirim Ezeano[4] Ihunanya Kanu[5] Uwakmfonabasi Umoudoh[6] Adedeji Adenusi[7] Anthony Ude[8] Nneoma Abajue[9] Onyinyechukwu Onyewuchi[10], [1]Brookdale University Hospital and Medical Center, [2]Suny Downstate Medical Center, [3]Georgia Southern University, [4]Advocate Aurora Healthcare, [5]Baptist Memorial Hospital- Golden Triangle, [6]NYCHHC/Lincoln Medical Center, [7]One Brooklyn Health-Interfaith Medical Center, Brooklyn, NY., [8]Department of Radiology CHUKWUEMEKA ODUMEGWU OJUKWU UNIVERSITY (COOU), [9]Regions Healthcare, Mgbirichi, Imo State, [10]Department of Clinical Services, Clinix Healthcare Diagnostics, Awka, Nigeria

Background: Pancreatobiliary disorders contribute substantially to gastrointestinal morbidity, but their etiologic distribution and diagnostic imaging patterns remain poorly characterized in SSA, worsened by limited access to advanced imaging which further influence diagnostic pathways and reported disease patterns. This systematic review and meta-analysis synthesized available evidence on imaging-diagnosed pancreatobiliary etiologies in SSA settings. **Methods:** We conducted a systematic review and random-effects meta-analysis of proportions. Eight databases were searched from January 2010 for studies of adults evaluated for obstructive jaundice in sub-Saharan Africa by ultrasound, CT, MRCP, or ERCP. 472 of 487 results were excluded, and of 15 screened, 5 studies (731 patients; Kenya, Nigeria, Ethiopia) met eligibility; risk of bias was assessed with QUADAS-2. Extracted data included country, sub-region, imaging modality, sample size, benign and malignant etiologies, and specific pancreatobiliary diagnoses. Pooled proportions were estimated using logit-transformed random-effects models with REML. Heterogeneity was quantified by I^2 and τ^2. Exploratory subgroup analyses by sub-region and imaging modality where conducted where data permitted, and sequential leave-one-out sensitivity analyses for primary and diagnosis-specific outcomes reported in ≥ 3 studies, were performed. **Results:** Benign and malignant etiologies were identified in 445 and 286 cases, respectively. The pooled proportion of benign etiologies was 62.3% (95% CI: 32.5%-85.1%; I^2 = 95.5%) and 37.7% malignant (95% CI: 14.9%-67.5%). Diagnosis-specific pooling showed pancreatic tumor/cancer at 22.0% of cases (95% CI: 11.8%-37.1%; I^2 = 83.8%), biliary stricture at 11.5% of cases (95% CI: 8.1%-16.2%; I^2 = 0%), and gallbladder cancer at 3.4% of cases (95% CI: 0.3%-27.7%). Subgroup analyses showed no statistically significant East–West African difference. By imaging modality, MRCP-based studies yielded higher benign etiology proportions than ERCP (79.3% vs. 48.6%), while ERCP yielded higher malignant proportions (51.4% vs. 20.7%). **Conclusion:** Benign etiologies appeared to predominate among imaging-detected pancreatobiliary disorders although malignant causes remained substantial. Pancreatic tumor/cancer and biliary stricture were important diagnosis-specific findings. Modality-based subgroup analyses suggested different etiologic distributions across imaging pathways, but these patterns likely reflect clinical indication, referral pathway, and disease severity rather than comparative diagnostic superiority. Substantial heterogeneity highlights the need for standardized, prospective, multicenter studies with complete diagnostic accuracy data to guide imaging strategies, procurement, training, and region-specific clinical decision-making



Disclosures: Emeka Stanley Obi:Nothing to Disclose, Joshua Kalu:Nothing to Disclose, Nothing to Disclose,

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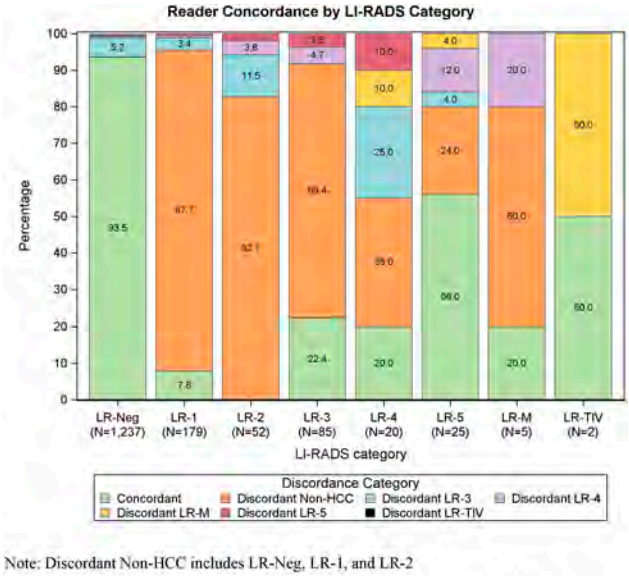
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4360 | CENTRAL MRI LI-RADS INTER-READER AGREEMENT IN ALTUS, A PROSPECTIVE MULTICENTER HCC SURVEILLANCE STUDY

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Background: CT/MRI LI-RADS standardizes imaging diagnosis of hepatocellular carcinoma (HCC); however, most inter-reader agreement studies have been retrospective and performed using curated datasets. We report the first inter-reader reproducibility study of LI-RADS v2018 from a large, prospective, multicenter HCC surveillance study utilizing consecutive cross-sectional imaging examinations. **Methods:** ALTUS (NCT05064553) was a multi-center U.S. study of 2,463 adults with cirrhosis or chronic HBV evaluating the performance of a multi-target HCC blood test with central CT/MRI LI-RADS v2018 assessment as reference. Two blinded, fellowship-trained abdominal radiologists—randomly paired from a pool of six—independently assigned LI-RADS categories to 1,605 MRI exams, with a single, experienced fellowship-trained radiologist adjudicating any discrepancies. Inter-reader concordance was evaluated for overall LI-RADS classification, individual major features, and observation number and size using percent agreement, Gwet's AC2, and intraclass correlation coefficient (ICC). **Results:** Overall LI-RADS concordance was 75.4% (95% CI, 73.2-77.4) with AC2 of 0.90 (0.89-0.92), driven largely by high agreement (93.5%, 92.0-94.8) on LR-Neg (n = 1237) images (Fig. 1). LR-3 (n = 85) and LR-4 (n = 20) concordance was 22.4% (14.8-32.3) and 20.0% (8.1-41.6), respectively. A majority (89.4%, 59/66) of LR-3 discrepancies were LR-Neg, LR-1, or LR-2, whereas 31.3% (5/16) of LR-4 discrepancies were LR-3, and 25.0% (4/16) were malignant (2 LR-5, 2 LR-M). LR-5 (n = 25) concordance was 56.0% (33.6-66.4), with 9.1% (1/11) of discrepancies being LR-3, 27.3% (3/11) LR-4, and 9.1% (1/11) LR-M. LR-5 major feature concordance for arterial phase hyperenhancement, enhancing capsule, and non-peripheral washout were 68.0%, 60.0%, and 48.0%, respectively. Concordance on observation count was 15.8% (12.4-19.8). For index observation size, ICC was 0.79, with a median absolute difference between paired readers of 0.3 cm (median observation size 1.5 vs 1.2 cm). **Conclusion:** In this large prospective multicenter cohort, LI-RADS classification demonstrated high agreement in negative examinations, with lower concordance across indeterminate categories where imaging assessment is inherently challenging. Differences in categorization in these settings reflect the complexity of real-world surveillance imaging and may have management implications, underscoring the importance of reader calibration and adjudicated central review in clinical and research settings.



Note: Discordant Non-HCC includes LR-Neg, LR-1, and LR-2

Figure 1. Summary of inter-reader concordance and discordance by LI-RADS category.

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4361 | LONGITUDINAL UPDATING OF THE HEPATOCELLULAR CARCINOMA RISK SCORES IMPROVES THE PREDICTION OF HCC DEVELOPMENT IN PATIENTS WITH CHRONIC HEPATITIS B

Volkan Yilmaz[1] Ali Eren Turkan[2] Beyza Doganay[3] Dilara Turan Gokce[4] Fatih Karakaya[5] Özge Koç[4] Mesut Gümüssoy[6] Zeynep Melekoglu Ellik[6] Hale Gokcan[6] Atilla Halil Elhan[3] Ramazan Idilman[7]

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Background: Hepatitis B virus-related disease remains the most common cause of liver-related morbidity and mortality. The present study aimed to develop and validate an accurate risk score for predicting hepatocellular carcinoma (HCC) in patients with chronic hepatitis B (CHB) who were treated with nucles(t)ide analogs. **Methods:** This was a single-center, observational study that included cirrhotic Caucasian patients with CHB. All patients received nucles(t)ide analogs at the physician's discretion and achieved sustained virological suppression. Most of the Turkish patients with HBV are infected with genotype D. The aMAP, PAGE-B, and ALBI scores were utilized to predict the development of HCC. Baseline risk scores were categorized into clinically interpretable risk groups according to predefined cutoffs. For aMAP, patients were classified as low risk (<50), medium risk (50–60), and high risk (>60). For PAGE-B, categories were defined as low risk (<9), medium risk (10–17), and high risk (≥ 18). ALBI categories were defined as low risk (<-2.6), medium risk (-2.6 to -1.39), and high risk (>-1.39). **Results:** A total of 340 cirrhotic patients were included in the analysis. The median age was 54.0 years, and the majority were male (79%). At admission, nearly half of the patients exhibited decompensation, and 43 patients had been diagnosed with HCC. The median aMAP, PAGE-B, and ALBI scores of these 43 patients with HCC were 64.9 (interquartile range [IQR], 8.2), 19.0 (IQR, 4.0), and -2.0 (IQR: -0.84), respectively. During the median follow-up period of 60 months (IQR: 24-118 months), de novo HCC was developed in 52 patients. Patients who developed HCC were older and more frequently male than those who did not develop HCC. Baseline mean aMAP (67 ± 5 vs 60 ± 8), PAGE-B (19.9 ± 2.7 vs 16.2 ± 4.9), and ALBI scores (-1.84 ± 0.61 vs -2.24 ± 0.66) were all significantly higher in the HCC group than in the non-HCC group (all $p < 0.001$), indicating a higher baseline risk profile among patients who subsequently developed HCC. In Cox regression analyses, all three scores were significantly associated with HCC development. PAGE-B showed the highest hazard ratio, whereas aMAP demonstrated the highest discriminative performance. Longitudinal, time-dependent Cox regression analyses incorporating repeated measurements showed that all three scores remained significantly associated with HCC development over time (all $p < 0.001$). Time-dependent models also demonstrated consistently higher discriminative performance compared with baseline-only models. **Conclusion:** In conclusion, the aMAP, PAGE-B, and ALBI scores are objective, straightforward, and reliable in accurately predicting HCC development in patients with cirrhosis due to CHB. We suggest that longitudinal updating of these risk scores improves HCC prediction compared with a single baseline assessment.

Table 1 -Baseline Cox regression analyses

Score	HR(%95 CI)	C-index	AIC	P value
Baseline aMAP	3.38 (2.14–5.34)	0.765	351	<0.001
Baseline PAGE-B	3.46 (2.04–5.86)	0.752	354	<0.001
Baseline ALBI	1.92 (1.42–2.61)	0.711	387	<0.001
Baseline ALBI*	1.92 (1.38–2.67)	0.776	[illegible]	<0.001

*: adjusted for age and sex

Table 2- Time-dependent Cox regression analyses

Score	HR(%95 CI)	C-index	AIC	P value
aMAP	3.67 (2.56–5.25)	0.808	430.3	<0.001
PAGE-B	4.07 (2.60–6.38)	0.775	435.3	<0.001
ALBI	2.37 (1.73–3.26)	0.754	448.1	<0.001
ALBI*	2.32 (1.65–3.27)	0.809	444.1	<0.001

*: adjusted for age and sex

Disclosures: Volkan YILMAZ:Nothing to Disclose, Ali Eren TURKAN:Nothing to Disclose, Beyza DOGANAY: Nothing to Disclose, Dilara Turan Gokce:Nothing to Disclose, Fatih Karakaya:Nothing to Disclose, Özge Koç:Nothing to Disclose, Mesut Gümüssoy:Nothing to

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4362 | ◆ CLINICAL RISK SIGNATURE-GUIDED REVERSE-ENGINEERING APPROACH TO IDENTIFY REPURPOSED DRUGS FOR HCC CHEMOPREVENTION

Hiroaki Kanzaki[1] Nevena Slovic[2] Courtney Katz[1] Hiroyuki Suzuki[1] Ece Janet Dinc[3] Hai-Cheng Huang[1] Sheza Siddiqui[1] Jingxuan Chen[1] Purva Gopal[1] Adam Yopp[1] Amit Singal[1] Joachim Lupberger[4] Emilie Crouchet[2] Thomas Baumert[5] Yujin Hoshida[1], [1]University of Texas Southwestern Medical Center, [2]University of Strasbourg, [3]UT Southwestern Medical Center, [4]Inserm U748, [5]INSERM

Background: Despite promising preclinical data, the clinical translation of experimental HCC chemoprevention strategies has been unsuccessful, as evidenced by a series of failed clinical trials. This gap suggests that biological hypotheses derived from experimental models may not be clinically relevant. Clinically well-validated HCC risk biomarkers may serve as clues to identify therapies that can elicit clinically meaningful chemopreventive effects. We previously identified and validated a hepatic transcriptome-based biomarker (prognostic liver signature [PLS]) predictive of incident HCC in multiple cohorts of chronic liver disease patients. We utilized the PLS as a probe to computationally and experimentally screen compounds that likely elicit clinically meaningful chemopreventive effects. **Methods:** We conducted an in silico primary screen of 13,945 FDA-approved drugs and bioactive compounds to identify those that favorably modulate the high-risk PLS. Selected compounds underwent an in vitro secondary screen in a PLS-inducible cell culture model (cPLS system). The prioritized compounds from this 2-step screen were subsequently evaluated in the choline-deficient, L-amino acid-defined, high-fat diet (CDA/HFD) rat model of MASH fibrosis-driven HCC development. The clinical relevance of the selected compounds was assessed using organotypic ex vivo culture of precision-cut liver slices (PCLS) from patients with various liver diseases. **Results:** The PLS-guided in silico primary screen identified 159 compounds that favorably modulate the high-risk PLS, of which 52 compounds were selected for the in vitro secondary screen based on their potential for clinical translation. In the secondary screen using the cPLS system, 12 compounds were prioritized for their shared favorable effects on HCV- and free fatty acid-induced high-risk PLS. Among them, aripiprazole, chloroquine, and minoxidil were selected as repurposed drugs for subsequent in vivo validation in CDA/HFD rats. These drugs were well tolerated, without recognizable hepatic or systemic adverse effects. As predicted, the number of liver tumor nodules was reduced to varying degrees, preferentially in male rats, accompanied by a relative reduction in liver fibrosis and a favorable modulation of the PLS and our previously reported Fibrosis Progression Signature (FPS). Hepatic transcriptome profiling revealed varying degrees of suppression of inflammatory, fibrogenic, and oncogenic pathways among the drugs. Clinical PCLS culture showed improved PLS in 50%–75% of the patients, suggesting the proportion of patients who might benefit from these therapies, and warranting the exploration of predictive biomarkers of response. **Conclusion:** The clinical HCC risk signature-guided reverse-engineering strategy identified multiple repurposed drugs as promising candidate HCC chemoprevention therapies for subsequent clinical evaluation.

Disclosures: Hiroaki Kanzaki:Nothing to Disclose, Nevena Slovic:Nothing to Disclose, Courtney Katz: Nothing to Disclose, Hiroyuki Suzuki:Nothing to Disclose, Ece Janet Dinc:Nothing to Disclose, Hai-Cheng Huang:Nothing to Disclose, Sheza Siddiqui: Nothing to Disclose, Jingxuan Chen:Nothing to Disclose, Purva Gopal:Nothing to Disclose, Adam Yopp: Nothing to Disclose, Amit Singal:Genentech: Consultant, AstraZeneca: Consultant, Bayer: Consultant, Eisai: Consultant, Exelixis: Consultant, Merck: Consultant, Elevar: Consultant, FujiFilm Medical Sciences: Consultant, Exact Sciences: Consultant, Glycotest: Consultant, Boston Scientific: Consultant, Sirtex: Consultant, HelioGenomics: Consultant, ImCare: Consultant, DELFI: Consultant, Curve Biosciences: Consultant, Catalym: Consultant, Verve: Consultant, Joachim Lupberger:Nothing to Disclose, Emilie Crouchet:Nothing to Disclose, Thomas Baumert:Nothing to Disclose, Yujin Hoshida:Helio Genomics: Advisor, Alentis Therapeutics: Stock – privately held company, Espervita Therapeutics: Stock – privately held company, Espervita Therapeutics: Advisor, Helio Genomics: Advisor, Alentis Therapeutics: Stock – privately held company, Espervita Therapeutics: Stock – privately held company, Espervita Therapeutics: Advisor, Helio Genomics: Advisor, Alentis Therapeutics: Stock – privately held company, Espervita Therapeutics: Stock – privately held company, Espervita Therapeutics: Advisor, Helio Genomics: Advisor, Alentis Therapeutics: Stock – privately held company, Espervita Therapeutics: Stock – privately held company, Espervita Therapeutics: Advisor.

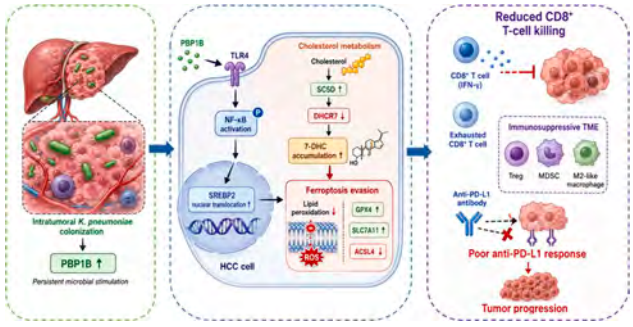
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★ 4363 | ◆ INTRATUMORAL *KLEBSIELLA PNEUMONIAE* DRIVES ANTI-PD-L1 RESISTANCE IN HEPATOCELLULAR CARCINOMA BY PROMOTING 7-DEHYDROCHOLESTEROL-MEDIATED FERROPTOSIS EVASION

Liqiu Li[1] Hongli Liu[2] Xuying Xu[1] Wenjuan Yang[1] Yongxiang Yi[3], [1]Kunshan Hospital of Traditional Chinese Medicine, [2]The Second Hospital of Nanjing, [3]Nanjing Drum Tower Hospital

Background: Immune checkpoint blockade targeting the PD-1/PD-L1 axis has expanded therapeutic options for hepatocellular carcinoma (HCC), although limited response rates and treatment resistance remain major barriers. Ferroptosis is an iron-dependent form of regulated cell death characterized by lipid peroxidation and closely linked to antitumor immunity. The contribution of intratumoral microbiota to ferroptosis regulation and anti-PD-L1 efficacy in HCC remains insufficiently defined. Here, we examined whether tumor-resident *Klebsiella pneumoniae* (*K. pneumoniae*) promotes anti-PD-L1 resistance by reprogramming cholesterol metabolism and suppressing ferroptosis. **Methods:** Intratumoral *K. pneumoniae* colonization was evaluated in human HCC specimens and immunocompetent mouse HCC models. The therapeutic response to anti-PD-L1 antibody was assessed in K. pneumoniae-colonized Hepa1-6 tumors. Bacterial PBP1B-deficient *K. pneumoniae*, recombinant PBP1B, TLR4/NF-κB and SREBP2 inhibition, SC5D/DHCR7 manipulation, and 7-dehydrocholesterol supplementation were used to dissect the mechanistic pathway. Ferroptosis was examined by lipid peroxidation, 4-HNE, MDA, C11-BODIPY, GPX4, SLC7A11, and ACSL4 analyses. CD8⁺ T-cell function, IFN-γ-dependent cytotoxicity, and tumor immune infiltration were assessed by flow cytometry, immunostaining, and T cell–tumor cell co-culture assays. **Results:** Intratumoral *K. pneumoniae* was enriched in HCC tissues and was associated with reduced ferroptotic activity and an immunosuppressive tumor microenvironment. In immunocompetent HCC models, *K. pneumoniae* colonization markedly impaired the antitumor efficacy of anti-PD-L1 therapy. Mechanistically, *K. pneumoniae*-derived PBP1B persistently activated TLR4/NF-κB signaling in HCC cells, promoted SREBP2 nuclear translocation, upregulated SC5D, suppressed DHCR7, and drove the accumulation of 7-dehydrocholesterol. This metabolic rewiring attenuated membrane lipid peroxidation, increased GPX4 and SLC7A11 expression, reduced ACSL4 expression, and conferred ferroptosis evasion. Disruption of PBP1B, TLR4/SREBP2 signaling, or 7-dehydrocholesterol accumulation restored ferroptosis, enhanced CD8⁺ T cell/IFN-γ-mediated tumor cell killing, and resensitized *K. pneumoniae*-colonized tumors to anti-PD-L1 therapy. **Conclusion:** Our findings reveal tumor-resident K. pneumoniae as a microbial determinant of anti-PD-L1 resistance in HCC. *K. pneumoniae*-derived PBP1B rewires cholesterol metabolism through TLR4/NF-κB–SREBP2 signaling, resulting in 7-dehydrocholesterol accumulation, ferroptosis evasion, and weakened CD8⁺ T-cell immunity. This bacteria–metabolism–ferroptosis circuit may represent a targetable vulnerability for improving immune checkpoint blockade in HCC.



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4364 | ◆ CD4⁺ T CELLS MEDIATE ANTITUMOR IMMUNITY IN NOVEL PD1-RESITANT PSC-ASSOCIATED CHOLANGIOCARCINOMA MODEL

Pinzhu Huang[1] Zaur Abilov[1] Chandra Sekar Shankar[1] Yoshiko Nanki[1] Jered Garrison[1] Victor Turkowski[1] Yury Popov[1], [1]Beth Israel Deaconess Medical Center, Harvard Medical School

Background: Patients with primary sclerosing cholangitis (PSC) are at high risk to develop cholangiocarcinoma (CCA), yet the underlying immune mechanism remain obscure. We established a novel syngeneic, immunocompetent murine CCA model arising in PSC-like fibroinflammatory microenvironment (SB CCA.*Mdr2-/-)* that recapitulates high susceptibility to CCA in human PSC. Here, we interrogated the relative contributions of T cell subsets in PSC-CCA antitumor immunity. **Methods:** Intrahepatic CCA was induced in PSC-like *Mdr2-/-* mice via hydrodynamic tail vein injection of sleeping beauty transposon-transposase system with activated forms of AKT (myr-AKT) and Yap (YapS127A). PD1, PD-L1, CD4, and CD8 cells were quantified in CK7+ CCA stroma. Role of adaptive immunity in tumor

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progression was interrogated in *Mdr2-/-;Rag1-/-* and via selective CD4 and CD8 antibody-mediated cell depletion in vivo. TGFb receptor 1 inhibitor (ALK5i) and therapeutic antibody against PD-1 or integrin β8 (C6D4 mAb) were administered 1-4 weeks post transduction (n = 5-12/group). **Results:** In our SB CCA.*Mdr2-/-* model, all CCA tumors expressed PD-L1 + and were immunologically "hot" with robust stromal PD-1+, CD8+ and CD4+ immune infiltration. Introduction of CCA in immunodeficient *Mdr2-/-;Rag1-/-* mice (lacking T and B cells) demonstrated dramatically accelerated tumor growth and shortened survival, suggesting adaptive immunity restrains tumorigenesis in our system. Intriguingly, in the immunocompetent SB CCA.*Mdr2-/-* model selective depletion of $CD4^+$, but not $CD8^+$, T cells markedly accelerated tumors. Administration of anti-PD-1 mAB therapy resulted in increased stromal CD8+, but not CD4+ cells, but had no impact on tumor growth. Likewise, significant increase in tumor-infiltrating CD4+, but not CD8+ lymphocytes was associated with therapeutic anti-tumor response to both pan-TGFb (ALK5i) or selective TGF inhibition via integrin β8. **Conclusion:** We generated immunocompetent, PD1-resistant PSC-associated CCA model that recapitulate predisposition to biliary cancer in human PSC. CD4+, rather than CD8+ T cells play indispensable role in antitumor immunity in the settings of chronic sclerosing cholangitis in SB CCA.*Mdr2-/-* model. Therapeutic strategies enhancing $CD4^+$ T-cell responses may represent a promising approach for PSC-associated CCA.

Disclosures: Pinzhu Huang:Nothing to Disclose, Zaur Abilov:Nothing to Disclose, Chandra Sekar Shankar: Nothing to Disclose, Yoshiko Nanki:Nothing to Disclose, Jered Garrison:Nothing to Disclose, Victor Turkowski:Nothing to Disclose, Yury Popov:Nothing to Disclose.

4365 | ◆ P38 MAPK-DEPENDENT YAP ACTIVATION PROMOTES SPONTANEOUS LIVER FIBROSIS AND HEPATOCARCINOGENESIS IN HEPATOCYTE-SPECIFIC TAK1-DEFICIENT MICE

Tiantian Chang[1] Jieun Kim[1] Takashi Tsuchiya[1] Michael Pimienta[2] Ekihiro Seki[1], [1]Cedars-Sinai Medical Center, [2]PIH Health Good Samaritan Hospital

Background: Transforming growth factor (TGF)-β-activated kinase 1 (TAK1) activates nuclear factor-κB (NF-κB), p38, and c-Jun N-terminal kinase (JNK), which regulate cell death, proliferation, and carcinogenesis. Hepatocyte-specific deletion of TAK1 results in spontaneous development of hepatocellular carcinoma (HCC), accompanied by liver inflammation and fibrosis. Yes-associated protein (YAP), a key effector of the Hippo signaling pathway that regulates cell proliferation and apoptosis, also functions as a major oncogenic driver in HCC. Previous studies have suggested that p38 can regulate YAP expression and activity. However, it remains unclear whether hepatocyte p38 signaling promotes HCC and fibrosis through YAP activation. **Methods:** We generated hepatocyte-specific TAK1 knockout mice ($TAK1^{\Delta Hep}$) and hepatocyte-specific TAK1/p38 double-knockout mice ($TAK1/p38^{\Delta Hep}$). $TAK1^{flox/flox}$ and $p38^{\Delta Hep}$ mice were used as controls, respectively. A YAP inhibitor (VT-103) was administered intraperitoneally to 9-month-old $TAK1^{flox/flox}$ and $TAK1^{\Delta Hep}$ mice. Liver injury, inflammation, fibrosis, and HCC development were assessed. In vitro, the p38 inhibitor SB203580 and the YAP inhibitor VT-103 were applied to the liver cancer cell lines, Hep3B and Huh7. **Results:** Levels of phospho-p38 and YAP were markedly increased in the livers from 9-month-old $TAK1^{\Delta Hep}$ mice, which developed severe liver fibrosis and HCC. In contrast, $TAK1/p38^{\Delta Hep}$ mice were protected from these pathological changes, exhibiting reduced liver fibrosis and diminished tumor development. Moreover, immunohistochemical staining suggested that total and nuclear YAP expression was reduced in the livers from $TAK1/p38^{\Delta Hep}$ mice, supporting YAP as a downstream effector of p38 signaling. For in vitro studies, Hep3B and Huh7 cells were treated with either the p38 inhibitor SB203580 or the YAP inhibitor VT-103. Western blot and immunohistochemical analyses demonstrated that treatment with SB203580 reduced YAP expression and activity in both liver cancer cell lines, further supporting YAP as a downstream effector of p38 signaling. In addition, YAP inhibition with VT-103 reduced the expression of the downstream target genes, CTGF and CYR61, and suppressed cancer cell proliferation, migration, and invasion. Finally, $TAK1^{\Delta Hep}$ mice were treated with the YAP inhibitor VT-103, and YAP blockade significantly attenuated spontaneous HCC development and hepatic fibrosis. **Conclusion:** Hepatocyte-specific p38 ablation mitigates spontaneous liver injury, inflammation, fibrosis, and hepatocarcinogenesis in hepatocyte-specific TAK1-deficient mice through suppression of YAP expression and activity. These findings highlight the p38–YAP signaling axis as a potential therapeutic target for HCC and liver fibrosis.

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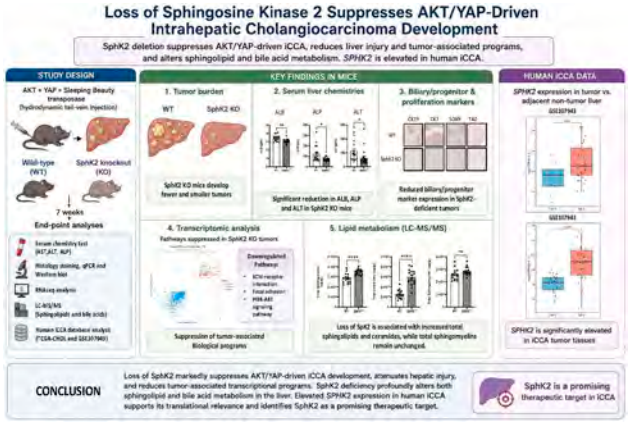
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4366 | LOSS OF SPHINGOSINE KINASE 2 SUPPRESSES AKT/YAP-DRIVEN INTRAHEPATIC CHOLANGIOCARCINOMA DEVELOPMENT

Yun-Ling Tai[1] Nan Wu[1] Grayson Way[1] Meiyi Song[1] Derrick Zhao[1] Sareh Bayatpour[1] Chen Chen[1] Hongkun Lu[1] Lianyong Su[1] Xuan Wang[1] Phillip Hylemon[1] Emily Gurley[1] Huiping Zhou[1], [1]Virginia Commonwealth University

Background: Intrahepatic cholangiocarcinoma (iCCA) is an aggressive primary liver malignancy with a poor prognosis and limited therapeutic options. Sphingosine kinase 2 (SphK2), a key regulator of sphingolipid metabolism, has been implicated in cancer progression; however, its role in iCCA remains unclear. We assessed whether SphK2 loss suppresses AKT/YAP-driven iCCA and its relevance in human datasets. **Methods:** Wild-type (WT) and SphK2 knockout (KO) mice (both sexes,n = 6-10) underwent hydrodynamic tail-vein injection of AKT, YAP, and Sleeping Beauty transposase to induce iCCA. Mice were sacrificed 7 weeks post-injection, and tumor burden alongside serum liver chemistries were assessed. Immunohistochemistry and qPCR were used to evaluate biliary/progenitor and proliferation-associated markers. Transcriptomic profiling was performed by RNAseq with pathway enrichment analysis. Targeted sphingolipid and bile acid profiling were performed by LC-MS/MS. Public human iCCA transcriptomic datasets were analyzed for *SPHK2* expression. **Results:** Loss of SphK2 significantly reduced tumor burden, with KO mice developing fewer and smaller tumors compared with WT across both male and female cohorts. Serum AST, ALT, ALP, and total bilirubin levels were significantly reduced in KO mice. Histologic and molecular analyses demonstrated reduced expression of biliary/progenitor markers (CK19, EpCAM, CK7, and SOX9) and the proliferation marker Ki67 in KO mice. Transcriptomic analysis revealed suppression of tumor-associated pathways, specifically ECM-receptor interaction, focal adhesion, and PI3K-AKT signaling. Targeted LC-MS/MS demonstrated significantly elevated total ceramides, long-chain ceramide species, and conjugated bile acids with altered 12α-hydroxylation ratios in WT tumor-bearing mice, whereas SphK2 KO mice maintained both sphingolipid and bile acid profiles markedly closer to non-tumor baseline. Analysis of public human iCCA datasets (TCGA-CHOL and GSE107943) demonstrated significantly elevated SPHK2 expression in tumor tissues compared with adjacent non-tumor liver. **Conclusion:** Loss of SphK2 markedly suppresses AKT/YAP-driven iCCA development, attenuates hepatic injury, and disrupts tumor-associated transcriptional and metabolic reprogramming. Consistently elevated SPHK2 expression in human iCCA cohorts supports its translational relevance and identifies SphK2 as a promising therapeutic target.



Disclosures: Yun-Ling Tai:Nothing to Disclose, NAN WU:Nothing to Disclose, Grayson Way:Nothing to Disclose, Meiyi Song:Nothing to Disclose, Derrick Zhao:Nothing to Disclose, Sareh Bayatpour:Nothing to Disclose, Chen Chen:Nothing to Disclose, Hongkun Lu: Nothing to Disclose, Lianyong Su:Nothing to Disclose, Xuan Wang:Nothing to Disclose, Phillip Hylemon: Nothing to Disclose, Emily Gurley:Nothing to Disclose, Huiping Zhou:Nothing to Disclose

★ 4367 | CHILDHOOD OBESITY–INDUCED KUPFFER CELL DYSFUNCTION PROMOTES LIVER CANCER SUSCEPTIBILITY LATER IN LIFE

Yuta Myojin[1] Chi Ma[2] Kylynda Bauer[2] Gabriel Prata[2] Mohamed-Reda Benmebarek[2] Patrick Huang[2] Kohei Kamizono[3] Lorenz Kocheise[2] Rajiv Trehan[2] Hayato Hikita[3] Takahiro Kodama[3] Firouzeh Korangy[2] Tim Greten[2], [1]The University of Osaka, National Cancer Institute, [2]National Cancer Institute, [3]The University of Osaka

Background: Childhood obesity has been epidemiologically associated with an increased risk of hepatocellular carcinoma (HCC) later in life; however, the underlying biological mechanism remains poorly understood. **Methods:** C57BL/6 mice were fed a short-term Western diet (SWD) after weaning and then returned to standard chow to model transient juvenile obesity. Liver tumor susceptibility was evaluated using three models: orthotopic liver tumor implantation, intravenous metastasis to the liver, and DEN-induced hepatocarcinogenesis. Bone marrow chimera experiments and Kupffer cell depletion were used. Immune remodeling

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was characterized by flow cytometry, single-cell RNA sequencing, and in vivo SIINFEKL-specific cytotoxic T-cell assays. Spatial immune organization and cell-cell relationships were analyzed using CosMx spatial molecular imaging. **Results:** Although body weight and hepatic steatosis improved after the dietary intervention, mice exposed to SWD during the juvenile period showed significantly increased tumor burden in orthotopic liver tumor, liver metastasis, and DEN-induced carcinogenesis models. In contrast, subcutaneous tumor growth was not increased, indicating that transient juvenile obesity enhanced hepatic tumor susceptibility. Bone marrow chimera and depletion experiments suggested that this phenotype was driven predominantly by persistent alterations in liver-resident immune cells. SWD induced durable remodeling of Kupffer cell states, including altered inflammatory and antigen-presenting programs, and impaired liver antigen-dependent $CD8^+$ T-cell cytotoxicity in vivo. Spatial analysis further demonstrated that, in SWD livers, $CD8^+$ T-cell cytotoxic programs were attenuated in proximity to Kupffer cells, whereas in regular diet controls, $CD8^+$ T cells located near Kupffer cells exhibited increased cytotoxicity. **Conclusion:** Transient obesity during the juvenile period leaves a long-lasting hepatic immune imprint characterized by altered Kupffer cell states and impaired local $CD8^+$ T-cell effector function. This persistent liver-specific immune remodeling promotes HCC susceptibility. These findings provide a mechanistic link between childhood obesity and adult liver cancer risk and highlight liver-resident immune reprogramming as a potential target for prevention and therapeutic intervention.

Disclosures: Yuta Myojin:Nothing to Disclose, Chi Ma:Nothing to Disclose, Kylynda Bauer:Nothing to Disclose, Gabriel Prata:Nothing to Disclose, Mohamed-Reda Benmebarek:Nothing to Disclose, Patrick Huang:Nothing to Disclose, Kohei Kamizono:Nothing to Disclose, Lorenz Kocheise:Nothing to Disclose, Rajiv Trehan:Nothing to Disclose, Hayato Hikita:Gilead Sciences, Inc.: Grant/Research Support, Gilead Sciences, Inc.: Speaking and Teaching, AbbVie GK: Speaking and Teaching, Nobelpharma Co., Ltd.: Speaking and Teaching, Kowa Co., Ltd.: Speaking and Teaching, AstraZeneca K.K.: Speaking and Teaching, Japan Lifeline Co., Ltd.: Speaking and Teaching, CHUGAI PHARMACEUTICAL CO., LTD.: Speaking and Teaching, Nippon Boehringer Ingelheim Co., Ltd: Speaking and Teaching, Bristol Myers Squibb: Speaking and Teaching, Eisai Co., Ltd.: Speaking and Teaching, NIPRO CORPORATION: Speaking and Teaching, Otsuka Pharmaceutical Co., Ltd.: Speaking and Teaching, Mochida Pharmaceutical Co., Ltd.: Grant/Research Support, GlaxoSmithKline K.K.: Grant/Research Support, Takahiro Kodama:Nothing to Disclose, Firouzeh Korangy:Nothing to Disclose, Tim Greten:Nothing to Disclose.

4368 | FENOFIBRATE OVERCOMES FIBROINFLAMMATION-DRIVEN RESISTANCE TO PD-1 BLOCKADE IN HEPATOCELLULAR CARCINOMA

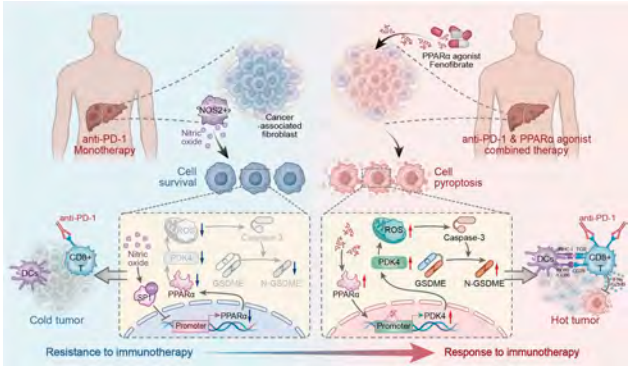
Peng Chen[1] Zheyu Dong[1] Yuanbo Zhao[2] Huajin Pang[3], [1]Nanfang Hospital, Southern Medical University, [2]Zhujiang Hospital: Zhujiang Hospital of Southern Medical University, [3]Interventional Treatment Center, Zhujiang Hospital, Southern Medical University

Background: Resistance to immune checkpoint blockade remains a major challenge in hepatocellular carcinoma (HCC). Because most HCCs arise in chronically inflamed and fibrotic livers, we investigated whether the fibroinflammatory liver microenvironment (FILM) promotes immune resistance and explored therapeutic strategies to restore anti-tumor immunity. **Methods:** Human HCC cohorts, anti-PD-1-treated specimens, bulk RNA-seq, single-cell RNA-seq, spatial transcriptomics, orthotopic and spontaneous HCC models, and humanized patient-derived xenograft models were integrated to define mechanisms of FILM-associated immunotherapy resistance and evaluate therapeutic interventions. **Results:** FILM was associated with inferior survival and reduced responsiveness to anti-PD-1 therapy in HCC patients. Consistently, HCC established in independent FILM models exhibited profound resistance to PD-1 blockade and markedly reduced GSDME cleavage despite preserved total GSDME expression. Restoration of cleaved GSDME re-sensitized FILM tumors to anti-PD-1 therapy and enhanced dendritic-cell activation and cytotoxic $CD8^+$ T-cell responses. Multi-omics analyses identified tumor-intrinsic PPARα suppression as a central feature of FILM-associated immune resistance. Mechanistically, FILM-associated $NOS2^+$ macrophages induced SP1 S-nitrosylation and transcriptional repression of PPARα, thereby suppressing the PDK4–ROS–caspase-3 pathway and disabling GSDME-dependent pyroptotic immunogenic cell death. Conversely, pharmacologic activation of PPARα restored pyroptosis and anti-tumor immunity. Both the selective PPARα agonist GW7647 and the FDA-approved agonist fenofibrate significantly enhanced anti-PD-1 efficacy in orthotopic and spontaneous HCC models. In humanized immune-system PDX models, fenofibrate potentiated anti-PD-1 responses selectively in PPARα-positive tumors. Importantly, concomitant fenofibrate use was associated with prolonged progression-free survival and greater tumor shrinkage in an exploratory cohort of anti-PD-1-treated HCC patients. **Conclusion:** FILM drives anti-PD-1 resistance through suppression of a tumor-intrinsic NOS2–SP1–PPARα–PDK4 axis that restrains GSDME-dependent pyroptotic immunogenicity. Pharmacologic activation of PPARα with fenofibrate

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restores pyroptosis, enhances anti-tumor immunity, and sensitizes HCC to PD-1 blockade, supporting biomarker-guided repurposing of fenofibrate for fibroinflammatory HCC.



Disclosures: Peng Chen:Nothing to Disclose, Zheyu Dong:Nothing to Disclose, Yuanbo Zhao:Nothing to Disclose, Huajin Pang:Nothing to Disclose.

4369 | DUAL INHIBITION OF INOS AND COX2 REMODELS MYELOID PROGRAMS TO IMPROVE RESPONSE TO PD-L1 BLOCKADE IN HEPATOCELLULAR CARCINOMA

Qianru Wu[1] Yuzhen Li[1] Timothy Billiar[1], [1]University of Pittsburgh

Background: Immune evasion in hepatocellular carcinoma (HCC) is driven in part by a suppressive tumor microenvironment shaped by tumor-infiltrating monocytes and macrophages. We investigated whether combined pharmacologic inhibition of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX2) could remodel the HCC immune microenvironment and enhance antitumor response to PD-L1 blockade. **Methods:** An orthotopic murine HCC model was established by intrahepatic injection of 6×10^5 RIL-175 cells into mice. Mice received vehicle control, anti-PD-L1 antibody, the selective iNOS inhibitor 1400W plus the COX2 inhibitor celecoxib, or 1400W plus celecoxib combined with anti-PD-L1. After three weeks, tumors and plasma samples were collected for downstream analyses. Tumor response was evaluated by gross liver morphology, H&E histology, and survival. Flow cytometry was used to assess T-cell exhaustion-associated markers and intracellular cytokine production. Single-cell RNA sequencing was performed to characterize tumor-infiltrating immune populations, with focused reanalysis of monocyte/macrophage-lineage cells and treatment-associated functional programs. CODEX multiplex imaging with HALO spatial analysis was used to evaluate immune-cell localization and cellular proximity within tumor and stromal regions. **Results:** Triple therapy with 1400W, celecoxib, and anti-PD-L1 induced marked tumor regression and significantly improved survival compared with vehicle control, anti-PD-L1 alone, or 1400W plus celecoxib. Flow cytometry showed improved T-cell function, with reduced exhaustion markers and increased CD4+ IL-2 and CD8+ IFNγ production. Focused scRNA-seq analysis suggested that 1400W/celecoxib-based treatment remodeled tumor-infiltrating monocyte/macrophage programs, shifting away from SPP1/TAM-like states toward antigen-presenting and IFN-responsive states. Plasma cytokine profiling revealed increased IFNγ, IP-10/CXCL10, and other immune-activating cytokines following treatment. CODEX spatial analysis demonstrated increased proximity and clustering of inflammatory macrophages with CD4+ and CD8+ T cells in tumor and stromal regions, supporting improved myeloid–T-cell organization within the TME. **Conclusion:** Combined inhibition of iNOS and COX2 remodels the HCC tumor immune microenvironment and enhances antitumor response to PD-L1 blockade. Triple therapy with 1400W, celecoxib, and anti-PD-L1 induced tumor regression, significantly improved survival, enhanced T-cell effector function, increased systemic immune-activating cytokines, and shifted monocyte/macrophage programs away from SPP1/TAM-like states toward antigen-presenting, IFN-responsive states. Together, these data support a model in which iNOS/COX2 inhibition reshapes the myeloid compartment and promotes a T-cell-supportive immune microenvironment in HCC.

Disclosures: Qianru Wu:Nothing to Disclose, Yuzhen Li:Nothing to Disclose, Timothy Billiar:Nothing to Disclose.

4370 | SILIBININ INHIBIT THE METASTASIS OF HCC BY INTERFERING WITH THIOREDOXIN-INDUCED GLYCOLYSIS

Jin Shang[1], [1]Sichuan Cancer Hospital

Background: Metastasis is the main cause of high morality of hepatocellular carcinoma (HCC). We previously found that RNA-binding protein Thioredoxin(Trx) regulates alternative splicing and promotes metastasis of HCC via interacting with LINC00152. It's worth noticing that Trx could be up-regulated by glycolysis to maitain NADP/NADPH homeostasis. Aerobic glycolysis is an emerging hallmark of many human cancers. The aim of this study was to explore whether interfering of Trx-induced glycolysis could inhibit the metastasis of HCC. **Methods:** Trx-related metabolism reprograming was first analyzed by Whole transcriptome sequencing between HCC with metastasis and HCC without metastasis. Next, bioinformatic analysis was conducted

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based on the single-cell transcriptome data derived from HCC patients in different stages to explore the metabolism reprograming in HCC cell sutsets. Finally, the impact of 79 glycolysis inhibition drugs approved by the FDA drug repository on Trx expression was screened by Western blot. The effect of glycolysis inhibitor on the metastasis ability of hepatocellular carcinoma cells was observed by transwell experiment. Lactate dehydrogenase (LDH) and NADPH were detected to verify the metabolism reprogramby glycolysis inhibitor. **Results:** We screen glycolysis inhibition drugs approved by the FDA drug repository, we found that among 79 drugs, a total of 54 kinds of drugs could decrease the expression of Trx more than half, in which we found that the hepatitis treatment commonly used drug silibinin could significantly reduce the expression of Trx, The inhibition of Trx expression by silibinin was further verified by Western method, and Transwell method showed that the metastatic ability of MHCC97L-Trx was decreased under silibinin treatment. Experiments on glucose metabolism showed that silibinin could significantly reduce LDH production and NADPH level, and the level of glycolysis could be significantly reduced by silibinin. Finally, under the treatment of silibinin, the expression levels of ALDOB, a glucose metabolic enzyme that inhibits the pentose phosphate pathway, were significantly increased, suggesting that silymarin mainly inhibits the expression of Trx by inhibiting the pentose phosphate pathway of glycolysis. As a potential inhibitor of Trx, the clinical application of silibinin in targeted therapy or combination therapy in the future is worth further exploration. **Conclusion:** Silibinin showed promising suppressive effects on HCC metastasis via inhibting Trx-induced glycolysis, indicating that glycolysis inhibitors are potential targeted drugs for Trx, the clinical application of silibininin future targeted therapy and combination therapy for hepatocellular carcinoma is worthy of further exploration.

Disclosures: Jin Shang:Nothing to Disclose.

4371 | ATTENUATED BACTERIAL THERAPY SUPPRESSES HEPATOCELLULAR CARCINOMA AND RESHAPES THE INTRATUMORAL IMMUNE LANDSCAPE

Xinlei Guo[1] Lujie Liu[1] Weiqi Ai[1] Duminduni Angappulige[1] Shan Xu[1] Jianxun Song[1], [1]Texas A&M University Health Science Center

Background: Hepatocellular carcinoma (HCC) is characterized by a profoundly immunosuppressive tumor microenvironment that limits the efficacy of current immunotherapies. Strategies capable of reprogramming intratumoral immunity and restoring effective anti-tumor responses are urgently needed. **Methods:** A spontaneous murine HCC model was established by hydrodynamic tail vein injection of oncogenic plasmids (MYC, sgTrp53, and sgPten) using the Sleeping Beauty transposase system. Mice were treated with attenuated *Brucella*-derived bacterial strain lacking virulent genes (1×10^8 CFU) or PBS control on day 5 after tumor induction. Tumor burden was monitored longitudinally by bioluminescence imaging (BLI) on day 5, 10 and 15. Tumors were harvested on day 15 for comprehensive immune profiling by flow cytometry, including cytotoxic $CD8^+$ T cells, macrophage subsets, regulatory T cells (Tregs), and T cell exhaustion markers. **Results:** Attenuated bacterial therapy significantly suppressed tumor progression compared with controls, as demonstrated by reduced tumor-associated bioluminescence. Immune profiling revealed marked remodeling of the intratumoral immune landscape. Treatment increased cytotoxic $CD8^+$ T cell activity, as indicated by elevated IFN-γ and TNF-α production, and expanded M1-like macrophage populations ($CD11b^+F4/80^+CD80^+CD86^+$), consistent with a pro-inflammatory and anti-tumor phenotype. Conversely, immunosuppressive components were reduced, including intratumoral Tregs ($CD4^+CD25^+FOXP3^+$). In addition, bacterial therapy alleviated T cell exhaustion, with decreased PD-1 and CTLA-4 expression on both $CD8^+$ and $CD4^+$ T cells, indicating improved effector function within the tumor microenvironment. **Conclusion:** Attenuated bacterial therapy suppresses HCC progression and promotes coordinated reprogramming of intratumoral immunity. These findings highlight microbial-based immunotherapy as a promising strategy to overcome immune suppression in HCC and support further translational investigation of this approach in liver cancer. **Keywords** : Hepatocellular carcinoma (HCC); Bacterial immunotherapy; Tumor microenvironment; Antitumor immunity

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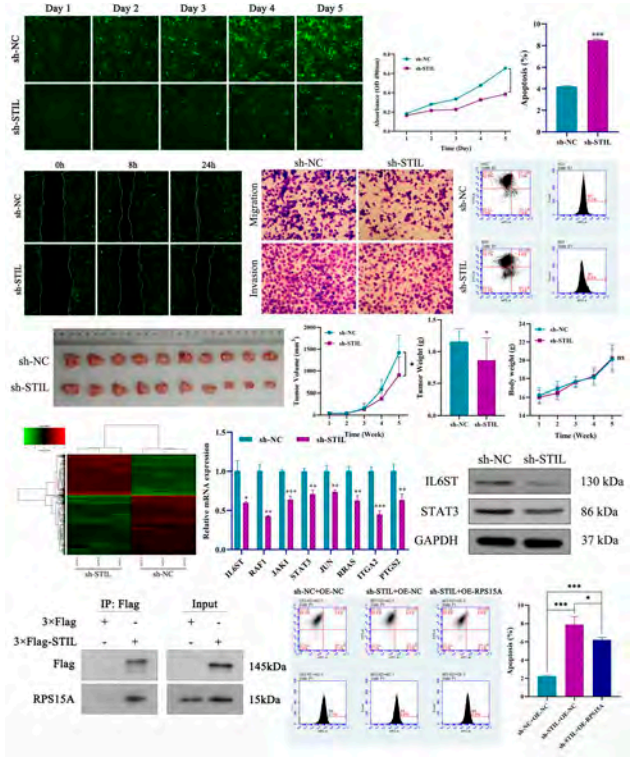
4372 | STIL ACTIVATES HGF/C-MET/STAT3 PATHWAY AND COOPERATES WITH RPS15A TO PROMOTE HEPATOCELLULAR CARCINOMA PROGRESSION

Lin Mei[1] Han Lin[2], [1]Xi'an Jiaotong University, [2]School of Gongli Hospital Medical Technology, University of Shanghai for Science and Technology

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Background: STIL (SCL/TAL1 interrupting locus) is a key regulator of centrosome duplication and mitosis. Although its overexpression is associated with the progression of multiple tumors, its biological functions and molecular mechanisms in hepatocellular carcinoma (HCC) remain to be systematically elucidated. This study aims to characterize the expression profile, functional roles, and downstream pathways of STIL in HCC, and to explore its potential as a novel target for precision therapy. **Methods:** STIL expression and clinical relevance in HCC were analyzed using GEPIA, GEO, and UALCAN. PPI networks were built with STRING and GeneMANIA, and GSEA was performed on the TCGA-LIHC cohort. STIL was knocked down in Hep3B and SK-HEP-1 cells via shRNA lentivirus. Cell proliferation, apoptosis, migration, and invasion were assessed by MTT, Celigo, flow cytometry, wound healing, and Transwell assays. In vivo tumorigenicity was evaluated using a subcutaneous xenograft nude mouse model. Microarray profiling combined with IPA identified downstream pathways, validated by qPCR and Western blot. STIL-interacting proteins were identified by Co-IP coupled with LC-MS/MS, followed by rescue experiments to clarify their functional roles. **Results:** TCGA analysis showed STIL was significantly overexpressed in 25 cancers including HCC, validated by GEO datasets and tissue microarray immunohistochemistry. High STIL expression correlated with advanced stage, lymph node metastasis, poor differentiation, TP53 mutation, and poor prognosis (OS: HR = 1.6, P = 0.013; DFS: HR = 1.5, P = 0.007), particularly in males. GSEA revealed enrichment of ribosomal and protein synthesis pathways in the STIL-high group. STIL knockdown inhibited proliferation ($P < 0.01$), migration and invasion ($P < 0.05$), and promoted apoptosis (4.2% vs 8.5%, $P < 0.001$). In vivo, sh-STIL tumors showed reduced volume and weight (0.864 ± 0.35 g vs 1.158 ± 0.20 g, P = 0.034). Mechanistically, IPA identified the HGF/c-MET axis as the most significantly inhibited pathway upon STIL knockdown (Z-score = −2.496), with downstream molecules (IL6ST, RAF1, JAK1, STAT3, JUN, RRAS, ITGA2, PTGS2) downregulated at the mRNA level, and IL6ST and STAT3 concordantly decreased at the protein level. Co-IP/MS identified 174 candidate STIL-interacting proteins and confirmed specific binding between STIL and ribosomal protein RPS15A. RPS15A overexpression partially rescued STIL knockdown-induced apoptosis (8.9% to 5.9%, $P < 0.05$), indicating STIL regulates HCC apoptosis via RPS15A interaction. **Conclusion:** STIL is highly expressed in HCC and correlates with poor prognosis. It promotes HCC progression via a dual mechanism: activating the HGF/c-MET/STAT3 pathway to drive proliferation and invasion, while binding RPS15A to suppress apoptosis. STIL represents a promising prognostic biomarker and therapeutic target for HCC.



Disclosures: Lin Mei:Nothing to Disclose, Han Lin: Nothing to Disclose.

4373 | FAM17 LIMITS SENESCENCE-ASSOCIATED TRANSCRIPTIONAL ELONGATION TO PROMOTE HEPATOCELLULAR CARCINOMA

Taofei Zeng[1] Hao He[1] Jiuxiang Chang[1] Weiqiao Chen[1] Jiayi Geng[1] Yabin Huang[1] Dalong Yin[1], [1]The First Affiliated Hospital of USTC

Background: Cellular senescence is accompanied by extensive transcriptional remodeling, including altered RNA polymerase II elongation. However, whether Pol II pause release actively instructs senescence-associated transcription in hepatocellular carcinoma remains unresolved. **Methods:** Candidate regulators of senescence-associated transcription were identified by integrating public HCC RNA-seq and ATAC-seq datasets with transcriptomic profiles from senescence models. ATAC-seq and CUT&Tag were used to map chromatin accessibility, Pol II occupancy, Pol II Ser2/Ser5 phosphorylation and histone modifications. FAM17-interacting proteins were identified by IP–MS and validated by co-immunoprecipitation. The in vivo function of FAM17 was assessed using *Alb-Cre; Fam17$^{fl/fl}$* mice, followed by single-cell RNA sequencing and flow

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cytometry to characterize tumor immune microenvironment remodeling. **Results:** Integrative multiomic screening identified FAM17 as a candidate regulator of senescence-associated transcription in HCC. FAM17 was induced during senescence but functionally restrained senescence execution, as its depletion triggered cellular senescence and SASP activation. Loss of FAM17 increased chromatin accessibility at TP53, CDKN1A and CDKN1B, promoted Pol II pause release and enhanced elongating Pol II accumulation at these loci, together with H3K4me3 enrichment at adjacent super-enhancers. Mechanistically, FAM17 interacted with PHF and promoted PHF degradation, thereby restraining PHF-dependent Pol II pause release and transcriptional elongation through the PHD1 domain. Consistently, hepatocyte-specific FAM17 loss in *Alb-Cre;Fam17$^{fl/fl}$* mice enhanced senescence-associated transcription and secretory programs, suppressed liver tumorigenesis, and remodeled the tumor immune microenvironment, characterized by increased NK-cell infiltration and reduced myeloid-cell abundance. Therapeutically, GalNAc-conjugated siFAM17 recapitulated the antitumor effects of genetic FAM17 loss, promoting tumor senescence, reducing liver tumor burden and prolonging survival. **Conclusion:** FAM17 functions as a suppressor of senescence-associated transcription by coupling PHF degradation to Pol II pause-release control. Targeting FAM17 reactivates tumor senescence and suppresses HCC progression, providing a liver-directed therapeutic strategy for HCC.

Disclosures: Taofei Zeng:Nothing to Disclose, Hao He:Nothing to Disclose, Jiuxiang Chang:Nothing to Disclose, Weiqiao Chen:Nothing to Disclose, Jiayi Geng:Nothing to Disclose, Yabin Huang:Nothing to Disclose, Dalong Yin:Nothing to Disclose.

4374 | LIPIDOMIC SIGNATURE OF HEPATOCELLULAR CARCINOMA

Héloïse Giudicelli[1] Valérie-Ann Raymond[2] Caroline Daneault[3] Isabelle Robillard[3] Simon Turcotte[2] Matthieu Ruiz[3] Marc Bilodeau[2], [1]Université de Montréal, Sorbonne Université, [2]Université de Montréal, [3]Université de Montréal, Institut de cardiologie de Montréal

Background: Hepatocellular carcinoma (HCC) is a leading cause of cancer-related death. In the liver, disrupted lipid homeostasis can lead to steatosis and Metabolic Dysfunction–Associated SteatoHepatitis (MASH), a preneoplastic condition to HCC. Metabolic reprogramming is a cancer hallmark and lipid metabolism may play a key role in hepatocarcinogenesis, especially in steatotic liver disease. This study aimed to characterize lipidomic differences across HCC, adjacent cirrhotic tissue, steatotic liver and healthy liver. **Methods:** We analyzed HCC arising from MASH (n = 10) and non-MASH cirrhosis (n = 10), along with matched adjacent non-tumoral liver (MASH n = 10; non-MASH cirrhosis n = 10). Non-cirrhotic samples included steatotic (> 20% steatosis, n = 10) and healthy liver (n = 10) from resections for benign tumors or colorectal metastases. Lipidomic profiling was performed using high-performance liquid chromatography–mass spectrometry (HPLC). Linear regression (adjusted for age and sex, without multiple testing correction) or paired t-tests (for the comparisons of tissues from the same individual) identified significant changes ($p < 0.05$; FC > 1.25 or < 0.8). Gene expression was assessed by qPCR. **Results:** Compared with healthy liver, HCC showed 698 lipid features significantly altered, of which, for now, we annotated 192 features across 5 lipid categories: fatty acyls (FA), glycerophospholipids (GP), sphingolipids, sterol lipids, and glycerolipids. More precisely, in terms of major subclasses, HCC displayed increased acylcarnitines (CAR), triacylglycerols (TG) enriched in very-long-chain unsaturated FA and steryl esters (SE), but reduced diacylglycerophoscholines (PC) and ceramides (CER). Beyond elevated CAR, used as surrogates of impaired fatty acid β-oxidation (FAO), we observed in HCC a downregulation of specific markers of FAO: ACAA2($p < 0{,}001$), ACSL1 ($p = 0{,}002$), ECH($p < 0{,}001$), CPT2 ($p = 0{,}006$). The same trend was observed in HADHA and ACSS2 expression. MASH-HCC exhibited increased CAR and mono-(LPC) and di-acylglycerophosphocholines (PC) while TG are down-regulated compared to MASH adjacent liver. Non-MASH-HCC exhibited increased CAR, TG enriched in very-long-chain unsaturated FA and SE compared to adjacent cirrhotic liver. Compared to non-MASH-HCC, MASH-HCC had lower CAR, SE, and CER. Steatotic liver versus healthy liver showed 1267 altered lipid features, and particularly decreased CAR, CER and major subclasses of GP but increased TG enriched in long-chain saturated FA. **Conclusion:** In conclusion, these findings highlight a survival-driven metabolic reprogramming in HCC, where suppressed fatty acid oxidation—evidenced by acylcarnitine accumulation—potentially limits reactive oxygen species production. Additionally, the distinct remodeling of acylcarnitines, ceramides, and sterols in MASH-HCC underscores a clear metabolic continuum spanning from steatosis to tumorigenesis.

Disclosures: Héloïse Giudicelli:Nothing to Disclose, Valérie-Ann Raymond:Nothing to Disclose, Caroline Daneault:Nothing to Disclose, Isabelle Robillard:Nothing to Disclose, Simon Turcotte:Nothing to Disclose, Matthieu Ruiz:Nothing to Disclose, Marc Bilodeau: Mirum Pharmaceuticals: Speaking and Teaching.

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4375 | TEAD INHIBITION BY IAG933 AS A FERROPTOSIS-SENSITIZING THERAPEUTIC STRATEGY IN CHOLANGIOCARCINOMA

Hidemi Nishi[1] Brandon Wilbanks[1] Erik Jessen[1] Shelby Yee[1] Meina Cai[1] J. Pedro Fincatto Safi[1] Danielle Carlson[1] Amro Abdelrahman[1] Enis Hikmet Ozmert[1] Jack Sample[1] Nathan Werneburg[1] Rory Smoot[1], [1]Mayo Clinic Rochester

Background: Cholangiocarcinoma (CCA) is an aggressive biliary tract malignancy with limited therapeutic options and poor prognosis. Dysregulation of the Hippo–YAP/TAZ–TEAD pathway contributes to tumor progression and therapeutic resistance. IAG933 is a novel pan-TEAD inhibitor that suppresses YAP/TAZ–TEAD transcriptional activity. Previously, we demonstrated that IAG933 exhibits synergistic effects with Gemcitabine/Cisplatin (GemCis) and the pan-RAS inhibitor RMC6236. Recent chromatin profiling studies further suggested that TEAD inhibition induces tumor-selective enhancer remodeling and ferroptosis-associated transcriptional priming. We therefore investigated whether combination therapy with the GPX4 inhibitor RSL3 enhances ferroptosis-mediated anti-tumor effects in CCA. **Methods:** Human CCA cell lines (HuCCT1 and RBE) and murine CCA cell lines (SB1 and FAC) were treated with IAG933 alone or in combination with GemCis, RMC6236, or RSL3. Cell viability assays were used to determine IC_{50} values and calculate Combination Index (CI) scores. TEAD activity was evaluated using luciferase reporter assays and qRT-PCR of canonical target genes. RNA-seq, CUT&RUN, and chromatin accessibility analyses were integrated to evaluate enhancer remodeling, YAP chromatin occupancy, and ferroptosis-associated transcriptional responses following TEAD inhibition. **Results:** IAG933 significantly suppressed TEAD-dependent transcription and reduced expression of canonical YAP/TEAD target genes. IC_{50} values ranged from approximately 500–1400 nM across CCA cell lines. Combination treatment with GemCis or RMC6236 demonstrated synergistic effects (CI < 1). Integrated chromatin analyses revealed marked loss of H3K27ac at tumor-specific enhancer loci in CCA cells, whereas normal cholangiocyte chromatin architecture remained relatively preserved. Transcriptomic analyses demonstrated induction of ferroptosis-associated genes, including SOD2, ACSL4, SLC7A11, and NFE2L2, suggesting that TEAD inhibition primes CCA cells for ferroptosis. MitoSOX staining demonstrated increased mitochondrial ROS levels following IAG933 treatment. Sequential combination treatment with IAG933 and RSL3 demonstrated concentration-dependent synergistic effects in HuCCT1 cells, particularly within intermediate-dose ranges where CI values were consistently below 1. Pretreatment with IAG933 followed by RSL3 exposure reduced viability compared with either agent alone. **Conclusion:** IAG933 induces tumor-selective chromatin remodeling and ferroptosis-associated transcriptional priming in cholangiocarcinoma. Combination treatment with GemCis, RMC6236, and the ferroptosis inducer RSL3 demonstrated synergistic effects across multiple CCA models. These findings support TEAD inhibition-based ferroptosis combination therapy as a promising therapeutic strategy for YAP/TEAD-dependent cholangiocarcinoma.

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4376 | WNT RECEPTOR FZD10 MARKS CAR-INDUCED TUMOR-ASSOCIATED HEPATOCYTE POPULATION WITH CANCER STEM CELL-LIKE FEATURES

Elena (Yu) Sun[1] Maxim Pyatkov[1] David Waxman[1], [1]Boston University

Background: Constitutive androstane receptor (CAR, *Nr1i3*) is a hepatocyte-expressed nuclear receptor that mediates widespread transcriptional responses to xenobiotics, promotes steatosis, and with prolonged exposure, induces mouse hepatic tumorigenesis. Mice were treated with TCPOBOP, a selective CAR agonist xenobiotic, to identify early CAR-induced gene responses that drive liver tumor formation, with the goal of interdicting liver disease progression at an early stage. **Methods:** snRNA-seq, ChIP-seq and ATAC-seq datasets were analyzed for male CD1 mouse livers exposed to TCPOBOP persistently, with liver tumors first detected at 14 wk and becoming extensive by 20-22 wk. smFISH validated localization and co-expression. Human HCC data were analyzed using UALCAN. DAVID and Ingenuity Pathway Analysis (IPA) identified enriched pathways and upstream regulators. **Results:** *Fzd10* was rapidly (within 3 hr) and strongly (>90-fold) induced by TCPOBOP in mouse liver. ATAC-seq sites proximal to *Fzd10* responded to TCPOBOP by chromatin opening, were linked to *Fzd10* expression by multiomic analysis, and acquired enhancer histone marks (H3K27ac, H3K4me1). A subset of these *Fzd10*-proximal enhancers showed strong CAR binding, indicating that *Fzd10* is a direct CAR target gene.

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Fzd10 and Sox4 RNAs co-localize within an snRNA-seq pericentral hepatocyte subcluster where CAR is enriched, in both high and low Fzd10- and Sox4-expressing subpopulations. The Sox4 locus was increasingly accessible (snATAC-seq) in Fzd10+ cells, suggesting that Fzd10 and Sox4 define a common cancer stem cell-like population. smFISH validated the expression and co-localization of both gene transcripts. DAVID analysis indicated cancer-associated pathway enrichment, and IPA identified Tbx3, a Wnt/β-catenin target that maintains cancer stemness, as an activated upstream regulator in Fzd10+ and Sox4+ hepatocytes. Hepatocyte re-clustering using 433 tumor-specific gene features, including 32 well-defined liver cancer markers representing distinct tumorigenic programs, revealed high- and low-expression patterns aligned with Fzd10-high and Fzd10-low subclusters, suggesting shared tumor-related transcriptional programs. Human HCC data showed FZD10 overexpression and association with aggressive tumor features. **Conclusion:** CAR induces both Fzd10-high and Fzd10-low pericentral hepatocytes, which may represent distinct tumor-associated reprogramming events. Fzd10+ hepatocytes are proposed to acquire cancer stem cell-like and tumor-associated features through increased Wnt/β-catenin signaling. These findings support Fzd10 as an early marker and a potential therapeutic target for CAR-driven HCC.

Disclosures: Elena (Yu) Sun:Nothing to Disclose, Maxim Pyatkov:Nothing to Disclose, David Waxman: Nothing to Disclose.

4377 | EEF1E1 DRIVES IMMUNE EVASION IN HEPATOCELLULAR CARCINOMA BY SUSTAINING EGFR SIGNALING

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Background: Although immune checkpoint inhibitors have recently achieved promising advances, their clinical benefits in hepatocellular carcinoma (HCC) remain limited. Therefore, it is urgent to identify novel biomarkers that can predict which patients are more likely to benefit from immunotherapy and guide rational combination treatment strategies. Our previous studies identified EEF1E1 as a recurrence-associated gene in HCC. However, its role in the tumor immune microenvironment (TIME) remains unclear. **Methods:** Immunohistochemistry (tissue microarray, n = 141), RNA sequencing, and spatial transcriptomic analyses were performed to evaluate the expression pattern and prognostic significance of EEF1E1 in HCC tissues. In vitro and in vivo functional assays were conducted to investigate the oncogenic function role of EEF1E1. Single-cell RNA sequencing combined with multiparameter flow cytometry was used to analyze the impact of EEF1E1 on the TIME. Co-immunoprecipitation and signaling pathway–related experiments were performed to validate the interaction between EEF1E1 and epidermal growth factor receptor (EGFR). **Results:** EEF1E1 was significantly upregulated in HCC tissues and identified as an independent risk factor for poor prognosis in HCC patients. Functional experiments demonstrated that EEF1E1 promoted HCC cell invasion, migration, and epithelial–mesenchymal transition (EMT) both in vitro and in vivo, while remodeling the TIME toward an immunosuppressive phenotype characterized by increased infiltration of $PD\text{-}1^{+}$ $CD8^{+}$ T cells. Mechanistically, EEF1E1 interacted with EGFR at the protein level and prevented EGFR degradation through the endosome–lysosome pathway, thereby promoting EGFR accumulation and sustained activation of the EGFR–STAT signaling pathway. Consistent with this mechanism, treatment with the EGFR inhibitor osimertinib reduced $PD\text{-}1^{+}$ $CD8^{+}$ T-cell infiltration in mouse models. Moreover, the combination of osimertinib and anti–PD-1 antibody exhibited significantly superior antitumor efficacy compared with either monotherapy alone. Notably, tumors with high EEF1E1 expression derived the greatest benefit from the combination therapy. **Conclusion:** EEF1E1 drives aggressive biological behaviors and mediates immune evasion in HCC by sustaining EGFR signaling activity. Furthermore, EEF1E1 may serve as both a prognostic and predictive biomarker, providing a theoretical basis for combination therapy with PD-1 inhibitors and EGFR inhibitors in HCC.

Disclosures: Dongbo Chen:Nothing to Disclose, Liying Ren:Nothing to Disclose, Hongsong Chen:Nothing to Disclose.

4378 | DEFINING THE ROLE OF A DISTINCT CANCER-ASSOCIATED FIBROBLAST IN HUMAN HEPATOCELLULAR CARCINOMA

Angela Ferguson[1] Felix Marsh-Wakefield[2] Positha Santhakumar[3] Lily Rodgers[4] Colista Tsao[4] Joo-Shik Shin[5] Ruta Gupta[5] Ken Liu[6] Geoffrey McCaughan[7] Umaimainthan Palendira[4], [1]Centenary Institute, The University of Sydney,, [2]Centenary Institute, The University of Sydney, Sydney, New South Wales, Australia, [3]The University of Sydney, Sydney, New South Wales, Australia, [4]School of Medical Sciences, Faculty of Medicine and Health, The University of

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Background: In 2020, Hepatocellular carcinoma (HCC) was the sixth most frequent cancer and third leading cause of cancer-related deaths worldwide. Technological advances provide insight into the human tumour microenvironment (TME) and its influence on clinical outcomes. These studies have advanced our knowledge considerably, however, cancers with unique TMEs such as HCC do not adhere to these classifications for immune cells or Cancer-associated Fibroblasts (CAFs). **Methods:** A total of 39 patients undergoing liver resection for HCC at a single tertiary hospital from 2021 to 2024 were included. We interrogated the HCC TME in tumour and adjacent non-tumour (NT) regions using multi-omic technologies including single-cell RNA sequencing (scRNAseq, n = 10), high-dimensional imaging (IMC (n = 16) & Lunaphore COMET) and spatial transcriptomics (Xenium, n = 35). **Results:** scRNAseq analysis of dissociated HCC tumour identified a new CAF phenotype with attributes of fibroblasts (ACTA2/aSMA, COL3A1/type I/II collagens) and endothelial cells (ECs) (CD31/PECAM1, CDH5/VE-cadherin, PLVAP, CD34). Due to this unique profile, we designated these cells "*endothelial-like*-CAFs" or ***'el-CAF'***. Using multiple high-dimensional tissue imaging platforms we confirmed the presence of *el*-CAFs in the HCC TME. Interestingly, this data showed *el*-CAFs present in higher proportions in tumour compared to adjacent NT tissue. Ligand-receptor (L-R) analysis revealed *el*-CAFs may interact with myeloid cells, CD4 Tregs, B cells, CD8 T cells and ECs. Amongst these, the greatest potential interaction was with ECs through multiple L-R pairs such as, CX3CL1/ITGAV, ENG/CDH5, TGFb3/TGFbR2 or ENG, and COL4A1-2/ITGA1. These interactions suggest *el*-CAFs have multiple roles within the TME including promotion of leukocyte adhesion and activation, facilitating tumour cell adhesion and spread, supporting angiogenesis and endothelial mesenchymal transition (endMT). Spatial transcriptomics confirmed cell proximity and L-R communication between *el*-CAFs and ECs independent of cell densities. Moreover, quantitation of *el*-CAF showed higher numbers in HCC tumours containing vessels-encapsulating tumour clusters (VETC) compared to VETC-negative tumour tissue or VETC+ adjacent NT tissue. **Conclusion:** We have identified a novel CAF, *el*-CAF, with attributes of both fibroblasts and ECs, suggesting these cells result from endMT within highly vascularised HCC tumours. In particular, *el*-CAFs were most abundant in tumours with abnormal vascular pathology, VETC, suggesting *el*-CAFs are associated with abnormal and dysfunctional vasculature that has a unique role in metastasis and poor patient outcomes in HCC. These findings challenge existing dogma by redefining stromal cell archetypes in HCC and advancing a new, tumour type-specific framework for understanding TME organisation and function.

Disclosures: Angela Ferguson:Nothing to Disclose, Felix Marsh-Wakefield:Nothing to Disclose, Positha Santhakumar:Nothing to Disclose, Lily Rodgers:Nothing to Disclose, Colista Tsao:Nothing to Disclose, Joo-Shik Shin:Nothing to Disclose, Ruta Gupta:Nothing to Disclose, Ken Liu:Nothing to Disclose, Geoffrey McCaughan:Nothing to Disclose, Umaimainthan Palendira:Nothing to Disclose.

4379 | CD8⁺ T CELL EXHAUSTION DRIVEN BY SUSTAINED JAK/STAT–IFN-Γ SIGNALING DEFINES RESISTANCE TO ATEZOLIZUMAB PLUS BEVACIZUMAB IN HEPATOCELLULAR CARCINOMA: A XENIUM SPATIAL TRANSCRIPTOMIC STUDY

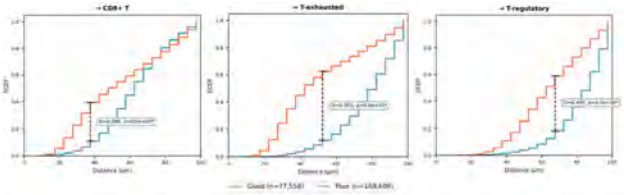
Young-Sun Lee[1] Sungjun Jang[2] Eunho Choi[2] Yang Jae Yoo[2] Seong Hee Kang[2] Sun Young Yim[2] Taehyung Kim[2] Young Kul Jung[2] Ji Hoon Kim[2] Yeon Seok Seo[2] Hyung Joon Yim[2] Jong Eun Yeon[2], [1]Korea University College of Medicine, [2]Korea university

Background: Atezolizumab plus bevacizumab is the standard first-line systemic therapy for advanced hepatocellular carcinoma (HCC), but objective responses are achieved in only a minority of patients, and the spatial features of the tumor microenvironment (TME) that govern response remain incompletely defined. We applied in situ spatial transcriptomics to dissect the cellular architecture and signaling programs distinguishing responders from non-responders. **Methods:** We retrospectively assembled tissue microarrays from primary resected HCC specimens of 14 patients who subsequently received atezolizumab plus bevacizumab for post-operative recurrence, and stratified them by RECIST v1.1 best response: responders (complete or partial response; n = 5) and non-responders (stable or progressive disease; n = 9). Spatial transcriptomic profiling was performed on the 10× Genomics Xenium platform, followed by unsupervised clustering and annotation of 15 cell populations, differential expression and pathway enrichment analyses, and nearest-neighbor distance analysis between malignant hepatocytes and immune subsets. **Results:** Responder tumors retained well-differentiated hepatocyte identity, with preserved cytochrome P450 expression (CYP17A1, CYP1A2) and enrichment of androgen

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and xenobiotic metabolism pathways. Non-responder tumors exhibited loss of metabolic hepatocyte programs, upregulation of the invasion-associated laminin LAMC2, and POSTN-high cancer-associated fibroblast–driven stromal remodeling. Despite robust expression of the T cell–recruiting chemokines CXCL9 and CXCL10, $CD4^+$ and $CD8^+$ T cells in non-responders displayed high LAG3, consistent with a terminally exhausted phenotype, and tumor-associated macrophages expressed MARCO, indicating immunosuppressive polarization. Pathway analysis demonstrated concurrent activation of E2F targets, VEGF signaling, and—most prominently—sustained JAK/STAT and interferon-γ signaling, a configuration mechanistically linked to terminal T cell exhaustion. Nearest-neighbor analysis revealed that exhausted T cells, regulatory T cells, and total $CD8^+$ T cells were positioned significantly closer to malignant hepatocytes in non-responders than in responders (Kolmogorov–Smirnov test, $p < 0.001$; KS statistic $D = 0.505$, 0.405, and 0.286, respectively). **Conclusion:** These findings nominate sustained type II interferon signaling and tumor-proximal exhausted-cell niches as candidate biomarkers and therapeutic targets—via LAG3 blockade, intensified anti-angiogenic pressure, or JAK inhibition—for overcoming primary resistance to atezolizumab plus bevacizumab.



Empirical Cumulative Distribution Function (ECDF) of Nearest-Neighbor Distances from Malignant Hepatocytes to $CD8^+$ T, T Exhausted, and T Regulatory Cells (within 100 μm)

Disclosures: Young-Sun Lee:Nothing to Disclose, Sungjun Jang:Nothing to Disclose, Eunho Choi:Nothing to Disclose, Yang Jae Yoo:Nothing to Disclose, Seong Hee Kang:Nothing to Disclose, Sun Young Yim:Nothing to Disclose, Taehyung Kim:Nothing to Disclose, Young Kul Jung:Nothing to Disclose, Ji Hoon Kim:Nothing to Disclose, Yeon Seok Seo:Nothing to Disclose, Hyung Joon Yim:Nothing to Disclose, Jong Eun Yeon:Nothing to Disclose.

4380 | UNCOVERING THE ROLE OF VISCOELASTICITY IN LIVER CANCER COLLECTIVE INVASION IN THE CIRRHOTIC LIVER

Vidushi Bansal[1], [1]*Stanford University*

Background: Hepatocellular carcinoma (HCC) is highly invasive and carries a poor prognosis. While increased bulk stiffness during cirrhosis is a well-established driver of tumor progression, the cirrhotic liver microenvironment is highly architectural and mechanically heterogeneous. We showed that regenerative areas—where dysplastic nodules arise—exhibit increased viscoelasticity characterized by fast stress relaxation, independent of bulk stiffness change. How these localized viscoelastic matrix properties impact early collective HCC cell invasion remains poorly defined. This study characterizes how matrix stress relaxation drives collective invasion modes and identifies key downstream mechanosensitive transcriptomic regulators. **Methods:** We used a 3D collagen-alginate interpenetrating network (CAiPN) to decouple stiffness from viscoelasticity. Epithelial (Huh7) and mesenchymal (SNU449) spheroids were embedded in CAiPNs (~2.5 kPa) tuned for fast/slow stress relaxation. Tracks were captured via live-imaging. Patient-derived organoids (PDOs) with stroma were established via air-liquid interface, embedded in CAiPNs , and profiled via spatial transcriptomics across the invasive front. Blockades against integrin β1, Rac1, RhoA, and CK666 validated mechanisms. **Results:** Both Huh7 and SNU449 spheroids exhibited significantly enhanced invasion in fast stress-relaxing CAiPNs compared to slow stress-relaxing counterparts at equal stiffness. Huh7 spheroids invaded through cohesive, multicellular protrusions, whereas SNU449 spheroids migrated via rapid cell streaming. While matrix metalloproteinase (MMP) inhibition showed minimal impact, blocking integrin β1 and Arp2/3 (CK666) completely abrogated viscoelasticity-induced invasion. Crucially, spatial transcriptomic profiling of patient-derived organoids identified transgelin-2 (TAGLN2) as a highly significant mechanosensitive hit, demonstrating intense upregulation specifically at the leading edge of collectively invading cells in fast stress-relaxing matrices. The invading cells in the organoids expressed a metabolic shift toward aerobic glycolysis, whereas there were elevated glycolytic gene patterns in mouse RNA-seq data and increased lactic acid production observed under high viscoelastic conditions. **Conclusion:** Matrix viscoelasticity, rather than stiffness alone, determines early collective HCC invasion. The integrin β1 axis upregulates cytoskeletal TAGLN2 and coordinates localized metabolic reprogramming at the invasive margin. Targeting viscoelastic mechanosensing or downstream effectors like TAGLN2 provides a compelling framework to impede collective invasion.

Disclosures: Vidushi Bansal:Nothing to Disclose.

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4381 | MELK INHIBITION ACTIVATES THE NLRP3 INFLAMMASOME AND PYROPTOSIS TO INDUCE RADIOFREQUENCY ABLATION MEDIATED IMMUNOGENIC CELL DEATH IN THE HCC

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Background: Residual hepatocellular carcinoma cells after radiofrequency ablation (RFA) often create an immunosuppressive microenvironment that promotes tumor recurrence. This study aimed to develop a pH-responsive superparamagnetic iron oxide nanoparticle platform, SPIO/OTS167@cRGD-phSiNPs, for targeted delivery of the MELK inhibitor OTS167 to residual tumor regions, and to use real-time MRI monitoring to evaluate its combined effects with RFA in inducing immunogenic cell death (ICD) and reversing immunosuppression. **Methods:** cRGD-modified pH-sensitive nanoparticles (SPIO/OTS167@cRGD-phSiNPs) were constructed and characterized by transmission electron microscopy, dynamic light scattering, and in vitro release assays. In vitro, HCC-LM3 and SK-HEP1 cell lines were used, and in vivo, mouse subcutaneous and orthotopic liver cancer models based on Hepa1-6 cells were established to evaluate the nanoparticles' targeting ability, biodistribution, antitumor efficacy in combination with RFA, and immunoregulatory mechanisms. Western blotting, flow cytometry, immunofluorescence, and single-cell RNA sequencing were employed to analyze MELK expression, ROS levels, NLRP3 inflammasome activation, dendritic cell maturation, and $CD8^+$ T-cell infiltration. **Results:** SPIO/OTS167@cRGD-phSiNPs had a particle size of approximately 100 nm, exhibited favorable pH-responsive drug release properties, and showed strong tumor-targeting capability. In vitro, the nanoparticles combined with hyperthermia significantly suppressed MELK expression, increased ROS levels, activated the NLRP3/GSDMD pathway to induce pyroptosis, and promoted CRT exposure and HMGB1 release, thereby enhancing dendritic cell maturation and $CD8^+$ T-cell cytotoxicity. In tumor-bearing mice, treatment with RFA combined with the nanoparticles significantly inhibited tumor growth and prolonged survival, and further synergized with PD-L1 blockade to strengthen the antitumor immune response. **Conclusion:** This study developed a theranostic nanoparticle platform that combines diagnostic and therapeutic functions. By targeting and inhibiting MELK, it enhances pyroptosis and immunogenic cell death in residual tumors after RFA, reverses the immunosuppressive microenvironment, and provides a new strategy for combined local and systemic immunotherapy of liver cancer.

Disclosures: Bufu Tang:Nothing to Disclose, Xiaojie Zhang:Nothing to Disclose, Jinhua Luo:Nothing to Disclose.

4382 | SPATIAL TRANSCRIPTOMIC PROFILING OF RESPONSE TO EGFR INHIBITION WITH ERLOTINIB FOR HCC CHEMOPREVENTION

Hai-Cheng Huang[1] Hiroaki Kanzaki[1] Jingxuan Chen[1] Kenneth Tanabe[2] Yujin Hoshida[1], [1]University of Texas Southwestern Medical Center, [2]Massachusetts General Hospital and Harvard Medical School

Background: Our previous preclinical study showed that EGFR inhibition in myofibroblasts attenuates liver fibrosis and reduces HCC nodules in rodent models of cirrhosis-driven hepatocarcinogenesis. Building on these findings, a recent phase I clinical trial of a 7-day erlotinib treatment in patients with cirrhosis confirmed target engagement, evidenced by reduced phospho-EGFR (p-EGFR) staining, at 25 mg/day (Gastro Hep Adv, 3;426, 2024). Furthermore, our clinically validated hepatic transcriptomic signature predictive of long-term HCC risk (Prognostic Liver Signature [PLS]) was favorably modulated at 50 mg/day. Identifying clinical and molecular correlates of this therapeutic response will provide mechanistic insights and inform the design of subsequent clinical trials and translation. **Methods:** Using paired pre- and post-treatment FFPE liver tissues from a p-EGFR/PLS responder and a non-responder in the phase I trial, we performed spatial transcriptome profiling with the Visium HD assay. We assessed therapeutic changes in cell-type proportions, EGFR signaling, related genes, and relevant molecular pathways, and compared these changes between the responder and non-responder. These molecular modulations were also compared with bulk tissue-based transcriptome profiles. **Results:** The paired biopsy and surgical tissues were successfully assayed to generate high-quality spatial transcriptome data. In the responder, the proportion of myofibroblasts decreased from 5.58% to 0.06% with erlotinib treatment, whereas the proportion of myofibroblasts in the non-responder was low (0.65%) and unchanged with treatment (0.62%). This result suggests that erlotinib reduced myofibroblasts in the responder, and the pre-treatment proportion of myofibroblasts may be associated with the p-EGFR/PLS response. The fibrotic area in the tissue decreased in the responder (39.7% to 30.2%), whereas minimal change was observed in the non-responder (53.0% to 50.3%), suggesting that underlying fibrogenic activity is associated with the erlotinib response. The

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EGFR pathway gene set was suppressed in myofibroblasts in the responder, whereas such an effect was not observed in the non-responder. These results collectively support our hypothesis that erlotinib elicits a p-EGFR/PLS-improving effect via EGFR inhibition in myofibroblasts. Modest suppression of the EGFR pathway gene set was also observed in macrophages in the responder, suggesting the involvement of this cell type in the response. **Conclusion:** Spatially resolved, cell type-specific transcriptome profiling provides insights into the mechanism of action and identifies correlates of response to erlotinib in patients with cirrhosis.

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4383 | DOWNREGULATION OF MICRORNA-1297 MEDIATES HYPOXIA-INDUCED LENVATINIB RESISTANCE IN HEPATOCELLULAR CARCINOMA BY TARGETING THYMOSIN-β10

Takayuki Kogure[1] Mari Satoh[1] Kennichi Satoh[1], [1]Tohoku Medical and Pharmaceutical University

Background: Hypoxia in the tumor microenvironment is a key driver of acquired drug resistance. Consistently, VEGF inhibition by lenvatinib induces significant intratumoral hypoxia. This study investigated the mechanisms underlying lenvatinib resistance, focusing on the role of microRNAs (miRNAs) in hepatocellular carcinoma (HCC) under hypoxic conditions. **Methods:** Human HCC cell lines (PLC/PRF/5, HepG2, and Huh7) were cultured under hypoxia (1% O_2, 5% CO_2, 94% N_2) or normoxia (95% air, 5% CO_2). Cell proliferation was assessed via metabolic assays, and apoptosis was evaluated morphologically and by caspase-3/7 activity. Genome-wide miRNA profiling was performed to identify resistance-associated miRNA alterations. An Argonaute2-based RNA-binding protein immunoprecipitation (RIP) assay combined with mRNA profiling was used to identify miRNA targets, which were further validated using a 3'-UTR luciferase reporter assay. **Results:** Lenvatinib inhibited HCC cell proliferation dose-dependently; however, its IC_{50} increased significantly under hypoxia. Lenvatinib-induced apoptosis was reduced by 22.4% and 19.6% in PLC/PRF/5 and HepG2 cells, respectively, under hypoxia, and caspase-3/7 activation was suppressed. Genome-wide profiling identified 42 upregulated miRNAs in PLC/PRF/5 cells treated with lenvatinib under normoxia, 28 of which were downregulated under hypoxia. We focused on miR-1297, which showed the most significant change. Under hypoxia, forced expression of miR-1297 significantly sensitized cells to lenvatinib, reducing viability (PLC/PRF/5: 76.6%, HepG2: 67.1%) compared with negative controls (88.3%, 75.3%). RIP assays and TargetScan analysis identified *TMSB10* mRNA as a target containing complementary sequences to the seed region of miR-1297. Forced expression of miR-1297 reduced thymosin-β10 protein levels by 46.3% and 33.4% in PLC/PRF/5 and HepG2 cells, respectively. Silencing *TMSB10* mRNA partially restored lenvatinib cytotoxicity under hypoxia, reducing cell viability by 14.7% and 13.5%. A 3'-UTR reporter assay confirmed that co-transfection of miR-1297 with a firefly luciferase vector containing the 3'-UTR of *TMSB10* mRNA decreased luciferase activity by 64.4% compared to the negative control. **Conclusion:** Downregulation of miR-1297 may contribute to hypoxia-induced lenvatinib resistance by upregulating thymosin-β10, a protein associated with cell survival and proliferation. These observations suggest that the miR-1297/thymosin-β10 axis could be a potential therapeutic target for overcoming lenvatinib resistance.

Disclosures: Takayuki Kogure:Nothing to Disclose, MARI SATOH:Nothing to Disclose, Kennichi Satoh: Nothing to Disclose.

4384 | CD147 AS A CANCER BIOMARKER: THE DIAGNOSTIC UTILITY OF CIRCULATING EXTRACELLULAR VESICLES IN HCC

Maria De Los Angeles Rojas[1] Rocío Muñoz Hernández[2] Antonio Gil-Gómez[3] Sheila Gato-Zambrano[2] Vanessa Garcia-Fernandez[4] Rocio Gallego-Duran[5] Douglas Maya-Miles[2] Paloma Carrillo-Fernández[2] Irene Parra Gonzalez[2] Maria Teresa Ferrer Rios[6] Javier Ampuero Herrojo[6] Manuel Romero-Gómez[7], [1]Dpto. de Farmacia y Tecnología Farmacéutica, Investigación y Desarrollo Tecnológico en Nanomedicina., [2]Seliver Group. Instituto De Biomedicina De Sevilla (IBiS), Hospital Universitario Virgen Del Rocío, [3]Seliver Group. Instituto De Biomedicina De Sevilla (IBiS), Hospital Universitario

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Background: CD147 is a transmembrane glycoprotein that has been linked to liver cancer. It is well known that extracellular vesicles (EVs) are nano-sized, membranous structures secreted into the extracellular space to mediate intercellular communication and carry markers derived from their cell of origin. The lack of reliable biomarkers for HCC management makes them excellent candidates for study in this context. **Aims:** To explore CD147 expression in liver cancer and to evaluate the clinical utility of circulating CD147-positive extracellular vesicles as a non-invasive diagnostic tool for hepatocellular carcinoma (HCC) management. **Methods:** A) CD147 gene expression was evaluated in liver cancer cell lines and CD147+ EVs release was confirmed in vitro studies. B) *CD147* mRNA expression was analysed in a cohort of 25 HCC patients undergoing transplantation or resection (6 cirrhotic patients, 12 non-cirrhotic patients who developed HCC, and 7 cirrhotic patients with HCC). Total mRNA was isolated from tumoral and non-tumoral tissue, and gene expression was determined by qPCR. In addition, CD147 protein expression was analysed by immunohistochemistry. C) CD147-EVs were quantified in cohort of 96 patients.; non-cirrhotic liver disease (8), 38 patients with cirrhosis (F4) and 50 with HCC.EVs were characterized by size (0.2-1µm) and CD147 expression and phosphatidylserine cell surface by flow cytometry in plasma heparin samples. **Results:** *CD147* gene expression was upregulated in HepG2 cells compared to Huh7.5 (fold change: 2.06 ± 0.15: p = 0,.002) and CD147+EVs constituted around 70% of the total EVs released by HepG2. Gene expression levels were significantly higher in tumor tissue compared to non-tumor tissue, regardless of fibrosis stage (HCC vs. non-F4: fold-change 3.74 ± 0.53; p < 0.001 and HCC vs. F4: 2.08 ± 0.32; p = 0.004). This upregulation were also observed at protein levels in HCC compared to cirrhosis and non-cirrhotic tissue. C) In our cohort, 90.6% were men, with a mean age of 64.6 ± 9.5 years. Main etiologies were alcohol consumption and HCV infection. AFP, ALT, and GGT levels were significantly increased in HCC group vs. F4 (p < 0.001, p = 0.05 and p = 0.02 respectively). The level of EVs AV+-CD147+ U/µl was significantly increased in HCC patients vs cirrhotic patients (1096 ± 211 vs. 6374 ± 1294 U/µl; p = 0.002), demonstrating an AUC of 0.82 (0.715-0.915; p < 0.0001) for HCC diagnosis (spec: 80%; sens: 70.8%, NPV 83.3% and PPV 74.3% (cut off: 1111.21U/µl)). In the multivariate analysis, age, AFP serum levels and AV+CD147+ EVs (OR: 12.7 (2.06-78.81) p = 0.006) were independently associated with HCC diagnosis. **Conclusion:** CD147 expression levels are increased in liver cancer cell lines and HCC tumor tissue, (independently of the liver fibrosis stage). HepG2 cells release CD147+EVs, confirming their origin. Additionally, circulating levels of AV-CD147 EVs represent a promising non-invasive diagnostic tool for HCC.

Disclosures: Maria De Los Angeles Rojas:Nothing to Disclose, Rocío Muñoz Hernández:Nothing to Disclose, Antonio Gil-Gómez:Nothing to Disclose, Sheila Gato-Zambrano:Nothing to Disclose, Vanessa Garcia-Fernandez:Nothing to Disclose, Rocio Gallego-Duran: Nothing to Disclose, Douglas Maya-Miles:Nothing to Disclose, Paloma Carrillo-Fernández:Nothing to Disclose, Irene Parra Gonzalez:Nothing to Disclose, MARIA TERESA Ferrer Rios:Nothing to Disclose, Javier Ampuero Herrojo:Nothing to Disclose, Manuel Romero-Gómez:Nothing to Disclose.

4385 | TARGETING DICKKOPF-1 UNLOCKS SYNERGISTIC ANTITUMOR IMMUNITY WITH PD-L1 BLOCKADE IN HEPATOCELLULAR CARCINOMA

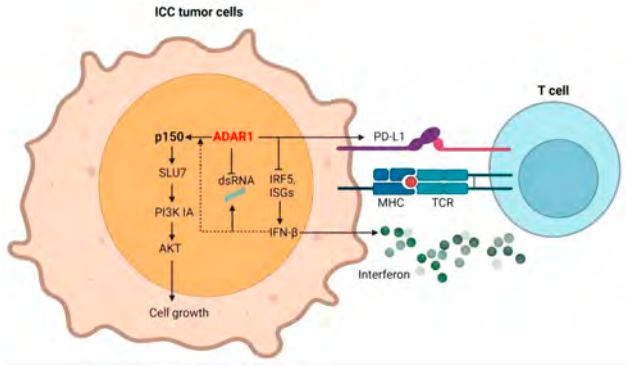
Seung Up Kim[1] Yuri Cho[2], [1]Yonsei University, [2]National Cancer Center, Goyang, Korea

Background: Dickkopf-1 (DKK1), a secreted Wnt antagonist, is frequently overexpressed in hepatocellular carcinoma (HCC) and has been implicated in tumor progression. However, its role in immune regulation and therapeutic response remains unclear. We investigated the immunomodulatory function of DKK1, its association with programmed death-ligand 1 (PD-L1), and the potential benefit of DKK1 inhibition combined with anti–PD-L1 therapy. **Methods:** We employed patient samples, human HCC cell lines with DKK1 knock-out (KO) or overexpression, and a syngeneic murine HCC model. PD-L1 expression was assessed by immunohistochemistry, western blotting, and qRT-PCR. T-cell activity was evaluated through Jurkat co-culture assays and cytokine secretion. The pharmacologic DKK1 inhibitor WAY-262611 was tested alone or in combination with anti–PD-L1 *in vitro* and *in vivo*. **Results:** High DKK1 expression correlated with increased PD-L1 levels in human HCC tissues and cell lines, while DKK1 KO reduced PD-L1 expression. Co-culture experiments revealed that DKK1 suppressed Jurkat T-cell viability and IFN-γ production. Treatment with WAY-262611 downregulated PD-L1 expression and reduced tumor cell migration. *In vivo*, Hepa1-6 DKK1 tumors displayed enhanced growth suppression when treated with combined DKK1 inhibition and anti–

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PD-L1, compared with either agent alone ($P < 0.05$). Dual blockade significantly increased $CD8^+$ T-cell infiltration and reduced immune evasion. **Conclusion:** DKK1 promotes immune escape in HCC by upregulating PD-L1 and impairing T-cell function. Pharmacologic inhibition of DKK1 augments the antitumor efficacy of PD-L1 blockade, suggesting that DKK1 is a promising therapeutic target and biomarker for immunotherapy combinations in HCC.

Disclosures: Seung Up Kim:Nothing to Disclose, Yuri Cho:Nothing to Disclose.



4386 | THE ROLE OF ADAR1 IN THE PROGRESSION OF INTRAHEPATIC CHOLANGIOCARCINOMA

Yi Tong[1] Guoteng Qiu[2] Zeyuan Qiang[1] Haichuan Wang[1], [1]West China Hospital, Sichuan University, [2]Sichuan Provincial People's Hospital, University of Electronic Science and Technology of China

Background: Intrahepatic cholangiocarcinoma (ICC) is an aggressive malignancy with limited treatment options. The role of ADAR1-mediated RNA editing in ICC progression remains unclear. **Methods:** ADAR1 expression and A-to-I RNA editing levels were evaluated in ICC tissues and cell lines. Functional assays and orthotopic murine models were used to assess tumor progression. RNA sequencing was performed to identify downstream pathways associated with ADAR1 signaling. **Results:** ADAR1 was significantly upregulated in ICC and positively correlated with A-to-I editing activity. ADAR1 overexpression enhanced ICC proliferation and tumor growth in vitro and in vivo. Transcriptomic analyses demonstrated suppression of interferon-related pathways, including IRF5 and interferon-stimulated genes. Increased ADAR1 expression was additionally associated with reduced CD8+ T-cell infiltration and elevated PD-L1 expression, suggesting an immune-evasive tumor phenotype.SLU7 expression was also markedly elevated in ICC models and positively correlated with ADAR1 expression. **Conclusion:** ADAR1 promotes ICC progression and is associated with immune modulation and altered expression of interferon-related pathways. The positive correlation between ADAR1 and SLU7 suggests a potential link between RNA editing and tumor-intrinsic signaling in ICC. Targeting ADAR1 may represent a promising therapeutic strategy for ICC.

Disclosures: Yi Tong:Nothing to Disclose, Guoteng Qiu:Nothing to Disclose, Zeyuan Qiang:Nothing to Disclose, Haichuan Wang:Nothing to Disclose.

4387 | TRANSCRIPTOMIC PROFILING REVEALS INTRINSIC MULTI-MECHANISM PD-1 RESISTANCE IN VINYL CHLORIDE-ASSOCIATED HCC

Haley Arbore[1] Pooja Muddasani[1] Olivia Bannister[1] Jiang Li[1] Tyler Yasaka[1] Silvia Liu[1] Gavin Arteel[1] Junyan Tao[1] Satdarshan (Paul) Monga[1] Juliane Beier[1], [1]University of Pittsburgh

Background: Vinyl chloride (VC) is an established hepatic carcinogen associated with HCC. Beyond high-dose occupational exposure, sub-OSHA level VC exposure enhances CLD progression and accelerates HCC development in our mouse models. This VC-driven HCC exhibits a unique transcriptomic signature that clusters a subset of human TCGA-LIHC tumors with disproportionately poor survival despite lower pathologic burden, suggesting an aggressive, etiology-driven phenotype. Whether VC exposure shapes the tumor transcriptome to confer intrinsic immunotherapy resistance is unknown. **Methods:** RNA sequencing was performed on tumors from a VC-exposed Met/β-catenin mouse model. Concordantly upregulated genes were identified by cross-referencing mouse DEGs with TCGA-LIHC tumor DEGs (DESeq2, $\log_2FC > 0.5$, $p < 0.05$, $n = 512$). These were intersected with genes trending toward non-responders in an independent human HCC immunotherapy cohort (GSE202069; $n = 17$, 8 responders and 9 non-responders, anti-PD-1 therapy, Illumina NovaSeq 6000), yielding a 63-gene resistance signature. Prognostic validation used TCGA-LIHC ($n = 338$, 116 events) as a completely independent cohort with Cox models adjusted for age and stage. Immune infiltration was

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assessed using CIBERSORT and quanTIseq deconvolution. **Results:** The signature was enriched for VC-specific genes (59% VC-specific, 25% VC-amplified, 14% tumor-general). High signature expression independently predicted worse overall survival in external validation (HR = 1.705, 95% CI 1.163-2.498, Cox p = 0.006, log-rank p = 0.0008). Sixteen of 63 genes were individually prognostic after multiple testing correction, dominated by mitotic kinases and chromosomal instability markers including PBK (HR = 1.530), TROAP (HR = 1.444), and ESPL1 (HR = 1.402). The prognostic effect was directionally consistent across tumor grades G1-G3 and reached significance in G3 (HR = 2.26, p = 0.033). Immune deconvolution revealed Treg enrichment ($\rho = 0.310$, adj.p < 0.001), M0 macrophage enrichment ($\rho = 0.239$), and neutrophil enrichment ($\rho = 0.255$) in high-signature tumors without significant cytotoxic immune depletion, indicating active immunosuppression rather than immune desert. Comparison with the immunotherapy cohort confirmed non-responder genes were enriched among VC-downregulated DEGs (OR = 2.42, p < 0.001), and VC mouse tumors scored deeply negative on a net PD-1 response prediction score. **Conclusion:** A 63-gene VC-associated transcriptomic signature predicts worse survival and implicates Treg-mediated immunosuppression and tumor-intrinsic proliferative resistance as co-drivers of anti-PD-1 resistance in VC-exposed HCC. This signature may improve patient stratification in immunotherapy trials and inform treatment selection in a disease where PD-1 checkpoint inhibitors represent the current standard of care.

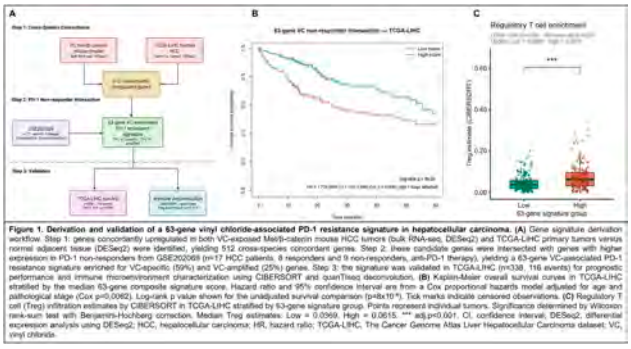


Figure 1. Derivation and validation of a 63-gene vinyl chloride-associated PD-1 resistance signature in hepatocellular carcinoma. (A) Gene signature derivation workflow. Step 1: genes concordantly upregulated in both VC-exposed Met/β-catenin mouse HCC tumors (bulk RNA-seq, DESeq2) and TCGA-LIHC primary tumors versus normal adjacent tissue (DESeq2) were identified, yielding 512 cross-species concordant genes. Step 2: these candidate genes were intersected with genes with higher expression in PD-1 non-responders from GSE202069 (n=17 HCC patients, 8 responders and 9 non-responders, anti-PD-1 therapy), yielding a 63-gene VC-associated PD-1 resistance signature enriched for VC-specific (59%) and VC-amplified (25%) genes. Step 3: the signature was validated in TCGA-LIHC (n=338, 116 events) for prognostic performance and immune microenvironment characterization using CIBERSORT and quanTIseq deconvolution. **(B)** Kaplan-Meier overall survival curves in TCGA-LIHC stratified by the median 63-gene composite signature score. Hazard ratio and 95% confidence interval are from a Cox proportional hazards model adjusted for age and pathological stage (Cox p=0.0062). Log-rank p value shown for the unadjusted survival comparison (p=8x10⁻⁴). Tick marks indicate censored observations. **(C)** Regulatory T cell (Treg) infiltration estimates by CIBERSORT in TCGA-LIHC stratified by 63-gene signature group. Points represent individual tumors. Significance determined by Wilcoxon rank-sum test with Benjamini-Hochberg correction. Median Treg estimates: Low = 0.0369, High = 0.0615. *** adj.p=0.001. CI, confidence interval; DESeq2, differential expression analysis using DESeq2; HCC, hepatocellular carcinoma; HR, hazard ratio; TCGA-LIHC, The Cancer Genome Atlas Liver Hepatocellular Carcinoma dataset; VC, vinyl chloride.

Disclosures: Haley Arbore:Nothing to Disclose, Pooja Muddasani:Nothing to Disclose, Olivia Bannister:Nothing to Disclose, Jiang Li:Nothing to Disclose, Tyler Yasaka:Nothing to Disclose, Silvia Liu:Nothing to Disclose, Gavin Arteel:Nothing to Disclose, Junyan Tao:Nothing to Disclose, Satdarshan (Paul) Monga: Vicero Inc.: Advisor, Alnylam: Grant/Research Support, Alnylam: Consultant, Vicero: Advisor, UbiquiTx: Consultant, Alnylam: Grant/Research Support, Alnylam: Consultant, UbiquiTx: Consultant, Revolution Medicines: Grant/Research Support, Antlera: Advisor, Vicero Inc.: Advisor, Alnylam: Grant/Research Support, Alnylam: Consultant, Vicero: Advisor, UbiquiTx: Consultant, Alnylam: Grant/Research Support, Alnylam: Consultant, UbiquiTx: Consultant, Revolution Medicines: Grant/Research Support, Antlera: Advisor, Juliane Beier:Nothing to Disclose.

4388 | FIVE HEPATOCELLULAR CARCINOMA CELL LINES WITH DISTINCT LIPID METABOLIC PROFILES DURING HEPATOCARCINOGENESIS

Héloïse Giudicelli[1] Valérie-Ann Raymond[2] Laure Voisin[2] Sylvain Meloche[2] Marc Bilodeau[2], [1]Université de Montréal, Sorbonne Université, [2]Université de Montréal

Background: Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality worldwide. Impaired liver lipid homeostasis can lead to Metabolic dysfunction–Associated SteatoHepatitis (MASH), a preneoplastic condition for HCC. This study aimed to (i) characterize lipid metabolism alterations in five human HCC cells lines; (ii) identify specific lipid transporters that modulate fatty acid (FA) flux in HCC cells, as future therapeutic target. **Methods:** Cells were cultured in high-glucose DMEM with 10% FBS (complete medium) or in nutrient free DMEM (blank medium) supplemented with linoleic acid (LA) at 400µM. Gene expression was analyzed by quantitative PCR. Cell viability was assessed by MTT assay. Intracellular triglyceride (TG) content was measured with Cobas system or Oil Red O staining. Mitochondrial respiratory function was assessed using a high-resolution respirometer (Seahorse). Cultured primary human hepatocytes (PH) were used as controls. Among 20 human HCC cell lines, we selected five cell lines using principal component analysis: (i) HepaRG as the main alternative to PH, (ii) JHH2 and SNU-387, which displayed β-oxidative genes expression similar to PH, (iii) PLC-PRF5 (PP5) and Huh7, which exhibited lower β-oxidative profile. Data are presented as mean ± standard error and multifactorial ANOVA was used for statistics (p < 0.05). **Results:** LA treatment increased TG storage in HuH7 and PP5 compared to HepaRG and SNU-387 (p < 0.05). In blank medium, cell viability was reduced in HuH7 (p < 0.05) and not restored by LA supplementation, in contrast to glucose or glutamine. In complete medium, LA reduced viability at 48 hours in Huh7 (p < 0.05), suggesting lipotoxicity, but not in PP5/HepaRG/SNU-387. Metabolic effects peaked at 48 hours. In Huh7 and PP5, expression of β-oxidation genes (ACSL1, CPT2, LCAD, ECH, ACAA1/2) was decreased compared to PH (p < 0.05). In SNU-387 and JHH-2, expression of ACLS1, ACSS2, CPT1/2, ECH and HADAH genes was similar as PH. In Huh7, genes

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involved in FA desaturation (SCD1, FADS1) and elongation (ELOVL6) were upregulated compared with PH ($p < 0.05$). PLIN2 was overexpressed in JHH2 and SNU-387 and repressed in Huh7 and PP5 compared to PH. Transcriptional regulation showed increased SREBP (Huh7) and PPARγ (all) while ChREBP decreased (all) ($p < 0.05$). FA synthesis (ACAC, ACLY, FASN) was not altered (all). Basal and maximal respiration rate were increased in JHH2 and Huh7, moderate in SNU 387 and decreased in HepaRG and PP5 ($p < 0,001$). Transporters FATP2/5, FABP4, and CD36 were decreased in all cell lines compared to PH, while FABP1 expression was maintained in Huh7 and PP5. **Conclusion:** HCC cell lines display distinct lipid metabolic reprogramming, without following a uniform pattern. Impaired FA transport and utilization underscore the need for stratified therapeutic approaches targeting lipid metabolism in HCC

Disclosures: Héloïse Giudicelli:Nothing to Disclose, Valérie-Ann Raymond:Nothing to Disclose, Laure Voisin:Nothing to Disclose, Sylvain Meloche:Nothing to Disclose, Marc Bilodeau:Mirum Pharmaceuticals: Speaking and Teaching.

4389 | SMP30/POLA1 DOWNREGULATION IN MALE MEDIATES GENDER DIFFERENCES IN LIVER INJURY AND TUMORIGENESIS OF HEPATOCELLULAR CARCINOMA

Tae-Un Kim[1] Jin-Kyu Park[1], [1]Kyungpook National University

Background: Hepatocellular carcinoma (HCC) exhibits well-established gender disparity, with higher incidence and poorer prognosis in males compared with female. However, the underlying molecular mechanisms remain incompletely understood. Senescence marker protein-30 (SMP30), a calcium-binding protein known to decline with aging, has been reported to regulate hepatocellular homeostasis and carcinogenesis. In this study, we investigated the role of SMP30 in gender disparities of HCC progression through regulation of DNA replication process. **Methods:** Male and female mouse HCC tissues were analyzed to identify potential genes associated with gender disparities in HCC progression, with particular focus on X chromosome–linked candidates independent of hormonal effects. SMP30 and DNA polymerase alpha (Pola1) expression were selected via gene chip profiling and analyzed in both HCC tissues and HEPG2 cell line with quantitative PCR and western blotting. Cycloheximide chase assay and polysome profiling were conducted to evaluate protein stability and translational regulation. SMP30 mice HCC tissues were analyzed to further confirm regulatory effects of SMP30 on Pola1 expression. **Results:** HCC liver tissues of male mice showed elevated liver injury and tumorigenesis compared with female mice. Gene chip assay showed marked elevation of oxidoreductase activity and DNA repair gene expression, especially Pola1. Relationship between SMP30 and Pola1 was investigated. SMP30 knockdown significantly reduced Pola protein expression without marked changes in total Pola1 mRNA levels, suggesting post-transcriptional regulation. Cycloheximide chase assays demonstrated no significant difference in POLA degradation between control and SMP30-deficient cells, indicating that enhanced proteolysis was unlikely to account for the observed reduction. Polysome profiling revealed decreased association of Pola1 mRNA with polysomes following SMP30 knockdown, consistent with selective translational suppression rather than global translational inhibition. HCC liver tissue of SMP30 KO mice showed severe tumorigenesis and decreased Pola expression compared with wild-type HCC mice. **Conclusion:** The present study suggests SMP30 as a potential mediator of sex disparity in HCC through selective translational regulation of Pola1. Reduced SMP30 expression may impair DNA replication homeostasis by suppressing Pola1 translation, thereby promoting replication stress and hepatocarcinogenesis. This study provides a novel mechanistic framework connecting aging-related proteins, translational regulation, and gender-associated differences in liver cancer biology.

Disclosures: Tae-Un Kim:Nothing to Disclose, Jin-Kyu Park:Nothing to Disclose.

4390 | STUDY ON BIOMARKERS OF IMMUNE CHECKPOINT INHIBITOR COMBINATION THERAPY-RELATED ADVERSE EVENTS IN HEPATOCELLULAR CARCINOMA PATIENTS BASED ON MULTI-OMICS INTEGRATION

Dachuan Cai[1] Yiheng Tang[1], [1]The Second Affiliated Hospital of Chongqing Medical University

Background: Immune checkpoint inhibitors (ICIs) combined with targeted drug therapy have played a pivotal role in the treatment of advanced hepatocellular carcinoma (HCC). However, beyond their antitumor effects, traditional chemotherapeutic agents, macromolecular or small-molecule targeted drugs, and ICIs can all induce off-target adverse reactions, known as treatment-related adverse events (trAEs). Hepatocellular carcinoma typically arises in the context of chronic liver disease, where underlying liver conditions may cause symptoms overlapping with AEs or exacerbate their severity. By analyzing proteomic and

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metabolomic data, we aimed to screen for biomarkers capable of early identification of trAEs in these patients. **Methods:** This study employed a nested case-control design. Plasma samples were collected from patients who met the inclusion and exclusion criteria. Proteomics and metabolomics technologies were utilized to profile proteins and metabolites. Candidate biomarkers were selected through an integrative analysis of proteomic and metabolomic data, taking into account fold changes, P-value rankings, and correlations within common biological pathways. **Results:** Integrated analysis of proteomics and metabolomics data revealed eight common pathways, including thyroid hormone synthesis, central carbon metabolism in cancer, and protein digestion and absorption. Seven differentially expressed proteins and six differentially expressed metabolites were annotated to these shared pathways. Based on a combination of fold change, P-value ranking, and correlations within the common pathways, the following proteins were selected: TTR, APOL1, ICAM1, CNDP1, COL12A1, and PON1, EPB42, EXT2, LAMP2, along with metabolites: glutathione, urocanic acid, and citric acid. **Conclusion:** Through integrated proteomic and metabolomic analysis, this study demonstrated that candidates possess diagnostic value for treatment-related adverse events in patients with primary liver cancer undergoing immune checkpoint inhibitor (ICIs) combination therapy. However, further validation in large-scale cohorts is required to confirm their clinical utility.

Disclosures: DACHUAN CAI:Nothing to Disclose, YIHENG TANG:Nothing to Disclose.

4391 | IRAK4 IS A POTENTIAL THERAPEUTIC TARGET IN BILIARY TRACT CANCER

Vivian Ortiz[1] Huaping Li[2] Richard Kurupi[2] Kian-Huat Lim[2], [1]Washington University in St. Louis, [2]Division of Oncology, Department of Medicine, Washington University in St. Louis

Background: Biliary tract cancer (BTC) is the second most common hepatic malignancy after hepatocellular carcinoma that arises from biliary epithelia with 5-year survival ranging from 2–23%. Despite the addition of immunotherapy to the backbone treatment of gemcitabine and cisplatin, the increase in survival and progression-free survival is only modest. New therapies are needed to prolong survival in patients with this malignancy. Interleukin-1 receptor–associated kinase 4 (IRAK4) is a pivotal serine/threonine kinase in the NF-κB and MAPK pathway whose inhibition has shown sensitization to immune checkpoint inhibitors in mice with pancreatic adenocarcinoma. Thus, we hypothesize that IRAK4 is upregulated in response to gemcitabine and cisplatin treatment, and its inhibition leads to anti-tumor response. **Methods:** Human and mouse BTC cell lines were incubated with gemcitabine and cisplatin (GC). Transcriptomic analysis and protein expression were assessed by bulk RNA sequencing, Western Blot and reverse phase protein array were done. Synergy analysis between gemcitabine, cisplatin and IRAK4 inhibitor CA-4948 was employed using Alamar blue and Incucyte. **Results:** Incubation of GC leads to protein activation of activated IRAK4 and NF-κB as well as transcriptional activation of NF-kB. Preliminary RPPA analysis also show upregulation of p-p38 and HSP27 in addition to p- NF-kB. Addition of CA-4948 to gemcitabine and cisplatin in human and mouse BTC cell lines increases apoptosis activation. **Conclusion:** IRAK4 is a potential additive therapeutic target for treatment of BTC. Further in vivo studies are underway to evaluate efficacy of CA-4948 effect in combination with GC and unveil its cytotoxic mechanism in BTC.

Disclosures: Vivian Ortiz:Nothing to Disclose, Huaping Li:Nothing to Disclose, Richard Kurupi:Nothing to Disclose, Kian-Huat Lim:Nothing to Disclose.

4392 | IMPACT OF ACSM5 ON FATTY ACID METABOLISM IN HEPATOCELLULAR CARCINOMA

Lei Yang[1] Shaoning Jiang[1] Kien Pham[1] Chen Liu[1], [1]Yale University

Background: Hepatocellular carcinoma (HCC) is characterized by dysregulated lipid metabolism, which plays a critical role in tumor progression and prognosis. We and others have reported that Acyl-CoA synthetase medium-chain family member 5 (ACSM5) is down-regulated in HCC and is closely associated with poor prognosis; however, the underlying mechanisms remain unclear. In this study, we investigated the role of ACSM5 in fatty acid metabolism and its potential impact on HCC progression. **Methods:** Stable ACSM5-overexpressing Huh7 cells (Huh7-ACSM5) were established to evaluate alterations in fatty acid metabolism. Cell pellets were collected and subjected to mass spectrometry-based fatty acid analysis. Huh7 and Huh7-ACSM5 cells were further treated with different fatty acids, including palmitic acid (PA), linoelaidic acid (LA), arachidonic acid (AA), and oleic acid (OA), to assess lipid accumulation. In addition, the expression levels of STAT3 activation and TGFB were analyzed. **Results:** Huh7-ACSM5 cells exhibited lower total fatty acid levels compared with Huh7 control cells. Mass spectrometry analysis demonstrated an overall reduction in fatty acid content in ACSM5-overexpressing cells. Saturated fatty acids were markedly decreased, whereas unsaturated fatty acids remained relatively stable. Specifically, levels of C14:0, C16:0, C16:1n7, C18:2n6t, and C20:4n6 were reduced in Huh7-ACSM5

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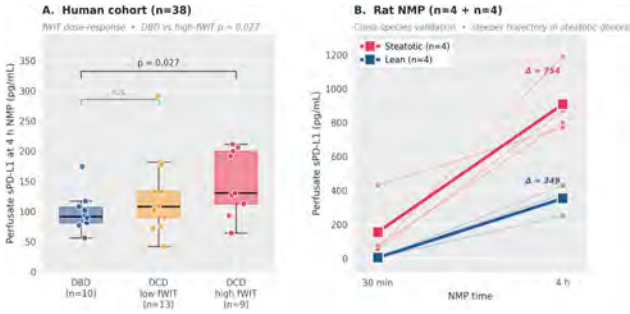
cells, while C18:1n9 levels were increased. These alterations resulted in a lower proportion of saturated fatty acids in ACSM5-overexpressing cells. Among the fatty acid treatments, LA treatment induced the most significant lipid accumulation, accompanied by increased STAT3 activation and elevated TGFB expression, suggesting a potential mechanism contributing to HCC progression and poor prognosis. **Conclusion:** Our findings demonstrate that ACSM5 plays an important role in regulating fatty acid metabolism in HCC. Reduced ACSM5 expression in cancer cells promotes lipid accumulation and STAT3 activation, thereby contributing to HCC progression. In contrast, restoration of ACSM5 significantly reduced lipid accumulation, particularly under LA treatment conditions, and modulated signaling pathways associated with tumor progression. These results provide new insights into the molecular mechanisms underlying HCC pathogenesis and suggest ACSM5 as a potential therapeutic target for HCC treatment.

Disclosures: Lei Yang:Nothing to Disclose, Shaoning Jiang:Nothing to Disclose, Kien Pham:Nothing to Disclose, Chen Liu:Nothing to Disclose.

4393 | ◆ PERFUSATE SOLUBLE PD-L1 TRACKS ISCHAEMIC INJURY BURDEN DURING LIVER NORMOTHERMIC MACHINE PERFUSION: AN INTEGRATED HUMAN, RAT, AND COMPUTATIONAL ANALYSIS

Sally Campbell[1] Fangyu Zhou[1] Omar Alomar[1] Cliona O'Farrelly[2] William Chapman[1], [1]Washington University, St Louis, [2]Trinity College Dublin

Background: Soluble PD-L1 (sPD-L1) is detectable in human liver perfusate during normothermic machine perfusion (NMP), but its upstream drivers and functional role remain undefined. CD274 (encodes PD-L1) has been identified as the strongest gene-level predictor of NMP graft quality, and PD-1/PD-L1 signalling limits ischaemia-reperfusion injury (IRI) in murine models. We asked whether perfusate sPD-L1 reflects an active, injury-proportional response that scales with donor ischaemic burden. **Methods:** Three complementary analyses were performed. First, sPD-L1 was measured by ELISA on serial perfusate from 38 human donor livers undergoing NMP, linked to donor type, functional warm ischaemia time [fWIT; SBP < 50 mmHg → NRP (normothermic regional perfusion) start], cold ischaemia time (CIT), NRP modality, viability criteria, and early allograft dysfunction (EAD). Second, sPD-L1 was measured on rat NMP perfusate from lean (n = 4) and steatotic (n = 4) donor livers, sampled at 30 min and 4 h of perfusion, following 15 min in-situ hepatic ischaemia. Third, an integrated transcriptomic analysis across six published datasets spanning healthy human liver, steatosis, human NMP, human IRI, and rat orthotopic liver transplantation (OLT) was used to define cellular sources and regulators of CD274. **Results:** Human cohort (38 grafts): perfusate sPD-L1 rose progressively from a median 15 pg/mL at 0–30 min to 403 pg/mL at 10–13 h. Within DCDs (n = 22), longer fWIT was associated with higher 4-h sPD-L1: DBD 91, DCD-low-fWIT 108, DCD-high-fWIT 131 pg/mL (p = 0.027 for DBD vs high-fWIT). The signal was strongest with the pure asystolic window (declaration to NRP start, p = 0.003). After adjusting for CIT, age, BMI and sex (n = 32), high-fWIT vs DBD remained significant (β = +0.39, p = 0.044). sPD-L1 did not discriminate viability or binary EAD on time-adjusted endpoints. Rat NMP: sPD-L1 rose in all livers from 30 min to 4 h with a steeper trajectory in steatotic versus lean donors, paralleling the human ischaemic-burden gradient. Computational analysis: hepatocytes, macrophages and neutrophils showed increased CD274 at end-NMP; CD274, ADAM17 (PD-L1 sheddase) and PD-1 were each upregulated in IRI+ versus IRI− tissue (p = 0.025, 0.045, 0.009). Rat OLT showed coordinated CD274 + ADAM17 induction alongside broad injury-response signalling (Type I/II IFN, TNF/NF-κB, IL-1, TLR/DAMP), all normalising in long-term survivors. **Conclusion:** Perfusate sPD-L1 during liver NMP is a kinetic, injury-proportional response. Transcriptomic data reveal coordinated CD274 / ADAM17 induction alongside broad injury-response signalling, a programme normalising in long-term survivors. Higher trajectories in DCDs (especially long-fWIT) and in steatotic rat livers identify ischaemic burden as the dominant driver, framing sPD-L1 as a candidate dynamic biomarker of graft injury during NMP and post-transplant, with the PD-L1 axis as a potential therapeutic target.



Disclosures: Sally Campbell:Nothing to Disclose, Fangyu Zhou:Nothing to Disclose, Omar Alomar:Nothing to Disclose, Cliona O'Farrelly:Nothing to Disclose, William Chapman:OrganOx Limited: Advisor.

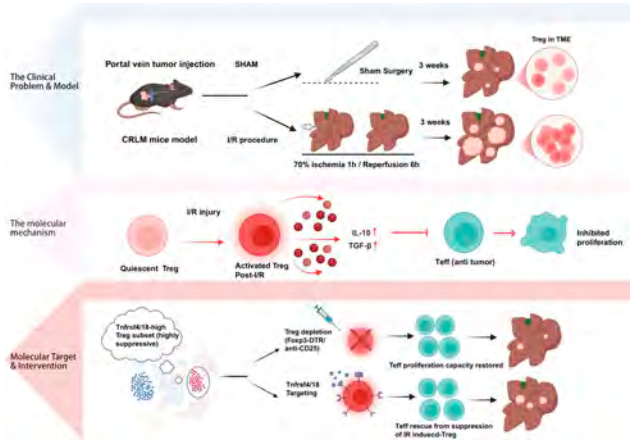
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4394 | ◆ SURGICAL STRESS-INDUCED HEPATIC REGULATORY T CELLS PROMOTE THE DEVELOPMENT OF COLORECTAL LIVER METASTASES

Ti Yang[1] Grace Wu[1] Xingping Huang[1] Xiaorong Guo[1] Preethi Jayakumar[1] Ameilia solan[1] Ephraim Ansa-Addo[2] Hai Huang[3], [1]The Feinstein Institute for Medical Research, [2]The Ohio State University Wexner Medical Center, [3]Feinstein Institutes for Medical Research

Background: Complete surgical resection remains central to curative treatment of colorectal liver metastases (CRLM), yet up to 50-60% of patients undergoing liver resection subsequently recur within five years. One of the mechanisms that drives recurrence is the reshaping of the hepatic immune microenvironment during surgical stress or ischemia-reperfusion (I/R) injury. Regulatory T cells (Tregs) promote wound healing and repair in injured tissues but are also known to restrain antitumor immunity. Moreover, whether I/R-induced alterations in Tregs contribute to subsequent tumor metastatic growth has not yet been elucidated. **Methods:** In this study, Wild-type mice (8-12 weeks) were injected with murine MC38 colon carcinoma cells expressing firefly luciferase. 70% hepatic I/R was performed with 60 minutes of ischemia time. CD25 antibody injections were used to deplete Tregs. Foxp3^{DTR} mice, followed by diphtheria toxin -mediated ablation of Treg cells. Treg numbers were confirmed by flow cytometry (percentage of Foxp3^{+} /CD4^{+}). Tumor growth was quantified by bioluminescence, tumor-to-body weight ratio, and number of macroscopic nodules. Single-cell RNA sequencing (scRNA-seq) was performed to identify transcriptomic changes in Tregs from I/R vs. sham livers. **Results:** Compared to sham mice, greater tumor growth was observed after I/R at 1- to 3-weeks post-surgery on bioluminescence. The number of hepatic Tregs was greater in tumor-bearing mice subjected to I/R versus sham surgery. After depletion of Tregs, reduced tumor growth was observed by bioluminescence at 1, 2, and 3 weeks post-surgery. Analysis of the top differentially expressed genes in I/R Tregs yielded significant upregulation of genes implicated in an immunosuppressive microenvironment, as confirmed by experiments; moreover, we identified that the OX40^{high} GITR^{high} Treg subpopulation was significantly enriched in the I/R group. After we neutralized the two markers *in vitro*, the Teff proliferation capacity recovered. **Conclusion:** Hepatic I/R drives the expansion of immunosuppressive hepatic Tregs, thereby promoting CRLM outgrowth. Treg depletion before I/R and during tumorigenesis attenuates this effect. Single-cell profiling further revealed an expanded OX40^{high} GITR^{high} effector Treg subset after I/R, and functional blockade of these molecules restored effector T-cell proliferation, supporting this population as a promising therapeutic target in postoperative CRLM.



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4395 | ◆ LIVER ABO RE-ENDOTHELIALIZATION FOLLOWING TRANSPLANTATION – FACT OR FICTION?

Anna Beck[1] Byoung Uk Park[1] Oyedele Adeyi[2] Srinath Chinnakotla[1] Claudia Cohn[1], [1]University of Minnesota, [2]Univ of Alabama, Birmingham

Background: Transplant patients may receive organs with major and minor ABO-mismatches. Endothelial cells of the transplanted organ express ABO antigens, making them a potential target for attack from the patient's isohemagglutinins. It has been hypothesized that transplanted organs undergo a process of re-endothelialization to protect the transplant. Re-endothelialization replaces the organ's native endothelial cells with new cells of patient origin, thus, the ABO of the organ's vascular lining would transform from native-type to patient-type over time. We sought to characterize this process by staining serial biopsies from patients who received ABO-mismatched organs. This study will allow us to better understand the timing and extent of re-endothelialization post-transplant. **Methods:** We analyzed the ABO endothelial status of 6 pediatric liver transplant patients, with surgery occurring from December 2010 to April 2023. All transplants were from whole livers except patient 6, who received a split liver. Biopsy follow-up time ranged from 4 months to 129 months. The number of biopsies taken per patient ranged from

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one to six. They were evaluated with immunohistochemical stains using anti-A and anti-B antibodies with appropriate control slides. Native hepatectomy specimens were also evaluated and served as additional controls. Stained slides were read for ABO status, as well as scored for intensity of staining and percent of each vascular compartment staining (hepatic artery, portal vein, central vein, and sinusoids). **Results:** Results are summarized in Table A. Native explants showed ABO staining consistent with that of the recipient's blood type, while all follow-up allograft biopsies demonstrated staining consistent with the donor's blood type. This pattern was observed in all follow-up biopsies for each patient, with the strongest and most reliable staining seen in the hepatic artery and portal vein compartments, while staining of the central vein and sinusoidal compartments was more variable. **Conclusion:** Post-transplant endothelial ABO antigen expression reflects donor ABO type, with the strongest and most reliable staining seen in the portal vascular endothelium. Sinusoidal and central venous expression is more variable and may show reduced staining over time or by compartment. Re-endothelialization of donor endothelium to recipient ABO type was not observed in our population.

Table A. Summary of ABO Staining in Liver Explants and Transplant Biopsies

	Blood Type	Donor Type	Explant / Control	Transplant Bx	Re-endothelialized ?	Time from transplant to latest biopsy
Patient 1	O+	A	O	A	No	34 months
Patient 2	O+	B	O	B	No	12 months
Patient 3	A-	B	A	B	No	22 months
Patient 4	A-	A1B	A	AB	No	129 months
Patient 5	AB+	AB	AB	AB	No	4 months
Patient 6	O+	B	O	B	No	11 months

Disclosures: Anna Beck:Nothing to Disclose, Byoung Uk Park:Nothing to Disclose, Oyedele Adeyi:Nothing to Disclose, Srinath Chinnakotla:Nothing to Disclose, Claudia Cohn:Fresenius Kabi: Advisor, CellPhire: Advisor, Hemerus: Advisor, American Association for the Advancement of Blood & B (AABB): Executive role.

4396 | ◆ SLC6A8-MEDIATED CREATINE TRANSPORT IN HEPATIC STELLATE CELLS IS ESSENTIAL FOR LIVER REGENERATION AND POST-SURGICAL HEPATIC RECOVERY

Thi Linh Nguyen[1] Ning Wang[2] Jieun Lee[1] Alfin Mohammad Abdillah[1] Ji Sun Moon[1] Ho Yeop Lee[1] Hyo Ju Jang[1] Aulia Reski Widyaningrum[1] Hyon-Seung Yi[1], [1]Chungnam National University School of Medicine, [2]Zhejiang University School of Medicine

Background: This study investigated the role of creatine metabolism and the impact of its deficiency on liver regeneration. The liver's ability to restore mass and function following injury or surgical resection is essential for recovery in patients with liver disease. Although multiple metabolic pathways have been implicated, the contribution of creatine metabolism remains poorly understood. **Methods:** A two-thirds partial hepatectomy (PH) model in mice was used to evaluate the role of creatine in hepatic regeneration. Creatine deficiency was induced by administering β-guanidinopropionic acid (β-GPA), a creatine analogue, while controls received standard drinking water. Liver regeneration was assessed by measuring the expression of proliferation markers and metabolic genes. Single-cell RNA sequencing was performed to identify key cell populations involved in creatine transport. To further examine the effects of creatine deficiency in a clinically relevant setting, a liver transplantation model was established in Sprague–Dawley rats. The relationship between creatine levels and post-surgical liver recovery in recipients was evaluated using CT-based imaging. **Results:** Expression of the creatine transporter gene Slc6a8 increased during the S and G2/M phases of liver regeneration, paralleling the induction of proliferation markers such as PCNA and Ki67. Inhibition of creatine uptake by β-GPA treatment significantly suppressed hepatocyte proliferation, as evidenced by decreased PCNA and Ki67 expression. Single-cell RNA sequencing revealed that Slc6a8 is predominantly expressed in hepatic stellate cells (HSCs) and is upregulated upon their activation. Conditional knockdown of the creatine transporter in HSCs using the Cre-loxP system markedly impaired regenerative capacity compared with floxed controls. Furthermore, β-GPA treatment induced upregulation of oxidative phosphorylation genes, indicating a metabolic shift toward mitochondrial energy utilization under creatine-deficient conditions. Consistent with these findings, β-GPA administration substantially delayed liver regeneration in a reduced-size rat liver transplantation model. Notably, creatine levels were strongly and positively correlated with regenerative capacity across all post-surgical time points. **Conclusion:** Creatine deficiency impairs hepatic regenerative processes and alters hepatic energy metabolism. Genetic disruption of creatine transport in HSCs further compromises the liver's ability to restore its mass and function. Clinical data demonstrated a strong positive correlation between creatine levels and regenerative potential following liver surgery. Collectively, these findings establish creatine metabolism as an underrecognized determinant of hepatic recovery and highlight its potential as a therapeutic target for improving outcomes after liver injury or transplantation.

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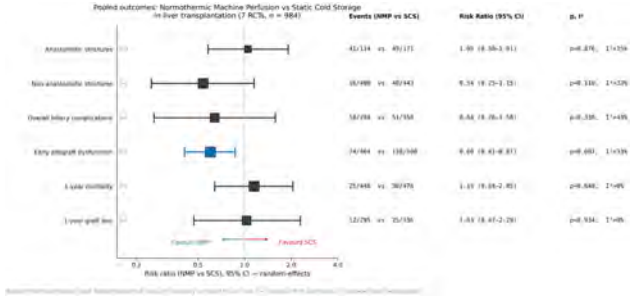
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Aulia Reski Widyaningrum:Nothing to Disclose, Hyon-Seung Yi:Nothing to Disclose.

4397 | NORMOTHERMIC MACHINE PERFUSION (NMP) VERSUS STATIC COLD STORAGE (SCS) IN LIVER TRANSPLANTATION: AN UPDATED SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

Paramveer Love[1] Alexander Moersch[1] Rabia Afzaal[1] David Hudson[1] Karim Qumosani[1] Mohammad Khan[1] Anouar Teriaky[2] Tamoor Afzaal[1], [1]Western University, [2]London Health Sciences Centre

Background: Donor organ shortage in liver transplantation has driven increased use of higher-risk grafts and extended-criteria donors. Normothermic machine perfusion (NMP) maintains the graft at physiological temperature with oxygenated perfusion and may reduce early allograft dysfunction (EAD), biliary complications, and hospital resource use compared with static cold storage (SCS). We performed an updated systematic review and meta-analysis of all available randomized control trials (RCT). **Methods:** MEDLINE, Embase and CENTRAL were searched from inception to March 2026 (PROSPERO CRD420261330445). Search strategy was developed in conjunction with a medical librarian. Eligible studies were RCTs of adult deceased-donor liver transplantation comparing any normothermic preservation strategy (ex situ NMP, ischemia-free liver transplantation, or controlled oxygenated rewarming) with SCS. Two reviewers independently performed screening, extraction and Cochrane RoB 2 assessment. Continuous data was analyzed using mean difference with random-effects model. Dichotomous outcomes were pooled as risk ratios (RR) using DerSimonian–Laird random-effects models and continuous outcomes as mean differences (MD). Heterogeneity was quantified using I^2. **Results:** Seven RCTs (2018–2026) enrolling 984 recipients (476 NMP, 508 SCS) were included. NMP significantly reduced EAD (15.9% vs 25.6%; RR 0.60, 95% CI 0.41–0.87; p = 0.007; I^2 = 33%; k = 7). Non-anastomotic strictures (4.0% vs 9.0%; RR 0.54, 95% CI 0.25–1.15; p = 0.110; k = 5) and overall biliary complications (6.1% vs 14.6%; RR 0.64, 95% CI 0.26–1.58; p = 0.330; k = 4) were numerically lower with NMP but did not reach significance. Anastomotic strictures (RR 1.05, 95% CI 0.58–1.91; k = 3), 1-year mortality (RR 1.15, 95% CI 0.64–2.05; k = 5) and 1-year graft loss (RR 1.03, 95% CI 0.47–2.29; k = 4) were comparable. ICU length of stay favoured NMP (MD −0.55 days, 95% CI −0.84 to −0.26; p < 0.001; k = 3); hospital length of stay did not differ (MD +1.06 days, 95% CI −1.24 to +3.37; p = 0.366; k = 5). **Conclusion:** NMP reduces early allograft dysfunction by approximately 40% and is associated with shorter ICU stay compared with SCS, with consistent point-estimate reductions in biliary complications and comparable 1-year survival.



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★ 4398 | IMPACT OF NORMOTHERMIC MACHINE PERFUSION IN DONATION AFTER BRAIN DEATH LIVER TRANSPLANTATION

Mohammad Almokdad[1] Atsushi Nishimagi[1] Rikako Oki[1] Jack Avedikian[2] Mohamed Adhnan[2] Abbas Al-Kurd[2] Ahmed Nassar[2] Atsushi Yoshida[2] Marwan Abouljoud[2] Shunji Nagai[2], [1]Henry Ford Hospital, [2]Henry Ford Hospital Transplant Institute

Background: Normothermic machine perfusion (NMP) has shown clear benefits in donation after circulatory death (DCD) liver transplantation, particularly in reducing early allograft dysfunction (EAD). However, its role in donation after brain death (DBD) liver transplantation remains limited and inconsistent. In this study, we aimed to evaluate the impact of NMP on early outcomes and to characterize its role in DBD liver transplantation (LT). **Methods:** First, a retrospective single centered study was performed including a total of 230 DBD liver transplantations performed between January 2022 and December 2025. Patients were divided based on preservation technique into static cold storage (Non-NMP) (N = 177) and NMP(N = 53) groups. The primary outcome was EAD. Secondary outcomes were peak ALT/AST, ICU stay, hospital stay, and 180-day graft and patient survival. Multivariable logistic regression was used to identify independent factors of EAD. Second, historical comparison analysis was conducted to evaluate the impact of NMP introduction in transplant practice, in which waiting time, donor and procedural characteristics

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in the NMP era (2022-2025) were compared with a pre-NMP cohort (2017-2021; N = 339). **Results:** Recipient characteristics were comparable between both groups, with NMP group having a lower MELD score (22 vs 28.5, p = 0.002). Donor age was higher in the NMP group (57 vs 48, p = 0.001), while cold ischemia time was significantly shorter (117 vs 404 minutes, p < 0.001). Total operation time was higher in the NMP group (416 vs 387 minutes, p = 0.04). There was no significant difference in the rate of EAD between NMP and non-NMP group (20.8% vs 14.1%, p = 0.24), and NMP was not independently associated with EAD on multivariable analysis (odds ratio, 0.23 [95% confidence interval, 0.03-2.08], p = 0.29). As for the second historical comparison analysis, the NMP era showed a higher proportion of donors aged > 70 years old (8.3% vs 1.5%, p < 0.001), a greater frequency of multiple same-day transplants (16% vs 5.3%, p < 0.001) and a significantly shorter waitlist time (median days, 20 vs 85, p < 0.001). Although non-NMP group had a higher MELD score (median, 27 vs 21, p = 0.002), the NMP group showed a significantly shorter waitlist time. **Conclusion:** In conclusion, NMP did not reduce EAD or 180-day survival in standard DBD transplantation, however it enabled the acceptance of higher-risk grafts, including older donors, and expansion of access for those who needed retransplantation. Notably, waiting time significantly reduced by approximately 76% in the NMP era. These findings support the use of NMP in DBD liver transplant as a tool for donor pool expansion and improved transplant access especially for challenging surgical cases, contributing to a marked reduction in waitlist time in the NMP era, without compromising post-transplant outcome.

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4399 | PHARMACOLOGIC MODULATION OF CELL METABOLISM AND HIBERNATION AS A STRATEGY TO REDUCE ISCHEMIA DURING ORGAN PRESERVATION

Dylan Zinn[1] Piyushkumar Gondaliya[1] Irene Yan[1] Julia Driscoll[1] Christine Mehner[1] Tushar Patel[1], [1]Mayo Clinic Florida

Background: Hepatic ischemia and reperfusion injury (IRI) is a significant concern during liver surgery and transplantation. Preservation strategies such as cold storage are typically used to reduce the metabolic activity of organs, thereby protecting them from IRI. However, prolonged cold storage can result in cold-induced injury, which is exacerbated during organ rewarming. Hibernation in mammals is characterized by a shift to use of glycerol as an energy substrate. To explore whether modulation of metabolism under normothermic conditions could be used to mimic the preservation effects of cold storage, we developed CellNap, a metabolic modulator that uses glycerol as an alternative energy source to glucose. **Methods:** The effects of CellNap on metabolic activity, nutrient homeostasis and metabolic phenotype were assessed in primary human hepatocytes. Cell viability, proliferation, metabolic activity, glucose consumption, and protein translation were assessed using trypan blue exclusion, MTS assay, glucose monitoring, and L-AHA incorporation click chemistry respectively. Studies were performed at 4°C, 21°C, or 37°C to mimic hypothermia, room temperature, and normothermia respectively. Metabolic activity was assessed using Seahorse XF analysis after 24 or 48 hrs to measure OCR, ECAR, glycoPER, metabolic phenotype, and mitoOCR/glycoPER ratios. The effects of systemic pre-administration of CellNap were evaluated using a murine hepatic IRI model after 90 mins of partial ischemia followed by 3 or 6 hrs reperfusion in C57BL/6J mice. Liver injury was assessed by serum markers, histology, necrotic area, and immunohistochemistry. **Results:** CellNap decreased metabolic activity, glucose consumption, and protein translation, indicating reduced nutrient demand and suppression of biosynthetic processes. Whilst cell proliferation was significantly reduced, CellNap preserved hepatocyte viability at 4°C, 21°C, and 37°C. Compared with controls at 21°C, Cell Nap treated hepatocytes had improved viability whilst proliferation and metabolic activity were stable across conditions. Metabolic activity analysis confirmed reduced basal and compensatory glycolysis, lower OCR and ECAR, and an increased mitoOCR/glycoPER ratio, suggesting a less energetic phenotype with a shift toward oxidative phosphorylation. In vivo, CellNap reduced ALT and AST levels, reduced the area of necrosis, and decreased cleaved caspase-3 staining at 3 and 6 hrs after reperfusion, consistent with a reduction of hepatic IRI. **Conclusion:** CellNap leads to a suppression of metabolism whilst preserving cell viability and thereby promotes a hibernation-like state in hepatocytes. These data support the use of pharmacological modulation of cell metabolism to reduce hepatic ischemia-reperfusion injury and improve liver preservation during surgery and transplantation.

Disclosures: Dylan Zinn:Nothing to Disclose, Piyushkumar Gondaliya:Nothing to Disclose, Irene Yan: Nothing to Disclose, Julia Driscoll:Nothing to Disclose,

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Christine Mehner:Nothing to Disclose, Tushar Patel: Nothing to Disclose.

4400 | ◆ ROLE OF SARCOPENIA AND FRAILTY MEASURES IN IMPROVING WAITLIST MORTALITY PREDICTION IN LIVER-TRANSPLANT CANDIDATES: A RETROSPECTIVE COHORT STUDY

Michael Garas[1] Shivangi Gupta[2] Robin van de Meeberg[3] Ben Bull[4] May Kang[5] Christopher Welman[6] Leon Adams[1] George Garas[1] Gerry MacQuillan[7] Michael Wallace[8] Briohny Smith[8] Luc Delriviere[7] Angus Jeffrey[8] Chloe Attree[7] Gary Jeffrey[7], [1]University of Western Australia, [2]Sir Charles Gairdner Hospital, Western Australia, [3]The Kids Research Institute Australia, 15 Hospital Ave, Nedlands, 6009, WA, Australia, [4]Department of Physiotherapy, Sir Charles Gairdner Hospital, Western Australia, [5]Dietetics and Nutrition, Sir Charles Gairdner Hospital, Western Australia, [6]Department of Medical Imaging, Fiona Stanley Hospitals Group, Murdoch, Australia, [7]Western Australian Liver Transplant Service, Sir Charles Gairdner Hospital, Western Australia, [8]Sir Charles Gairdner Hospital

Background: Sarcopenia and frailty are common in Liver Transplant (LT) candidates and associated with adverse events. Skeletal Muscle Index (SMI) and Intramuscular Adipose Tissue (IMAT) are CT measures of sarcopenia assessing muscle quantity and quality, whereas frailty is assessed using the Liver Frailty Index (LFI). While frailty has been shown to improve prognostic ability of MELD 3.0, the additional benefit of sarcopenia measures remains unclear, particularly in cohorts with hepatocellular carcinoma (HCC). This project evaluated the utility of frailty and sarcopenia measures in improving prediction of waitlist mortality in LT candidates. **Methods:** Patients waitlisted for LT from a single centre between 2018-2025 were retrospectively identified. Baseline biochemistry, CT and physiotherapy assessment for LFI were obtained ±4 weeks from LT evaluation. SMI and IMAT were calculated at the L3 vertebral level. Primary outcome was waitlist mortality defined by death on waitlist or within 30 days of delisting. Models with MELD 3.0 and risk factors were developed using cox proportional hazards models, then assessed and internally validated using optimism corrected concordance indices and Net Reclassification Indices (NRI). **Results:** Among 215 patients evaluated for LT, 160 (76%) were listed. Median age was 55 years; 108 (67.5%) were male. Median MELD 3.0 score was 18 , LFI 3.86, SMI 44 cm²/m², and IMAT 6.7%. After a median follow up of 110 days, 14 (8.75%) experienced waitlist mortality. Addition of LFI to MELD 3.0 improved discrimination (c-index 0.82 to 0.90). NRI showed an 11.4% improvement at 3 months. Frailty and MELD 3.0 remained statistically significant when accounting for aetiology and HCC status. The addition of SMI or IMAT had no further benefit. **Conclusion:** In LT candidates, including those with HCC, LFI improved prediction of waitlist mortality beyond MELD 3.0 alone. Further addition of SMI or IMAT provided no significant benefit.

Model	Original Concordance -Index	Corrected Concordance-index	Akaike Information Criterion	Net Reclassification Index
MELD 3.0	0.84	0.82	151.35	-
MELD 3.0 + LFI	0.91	0.90	104.54	0.114 (-0.152 – 0.401)
MELD 3.0 + Sarcopenia	0.86	0.82	121.88	0.095 (-0.034 – 0.274)
MELD 3.0 + SMI	0.84	0.82	150.42	0.035 (-0.057 – 0.176)
MELD 3.0 + IMAT	0.84	0.81	153.04	-0.016 (-0.039 – 0.000)
MELD 3.0 + LFI + Sarcopenia	0.92	0.90	97.02	0.114 (-0.152 – 0.411)
MELD 3.0 + LFI + SMI	0.92	0.90	104.56	0.217 (0.033 – 0.431)
MELD 3.0 + LFT + IMAT	0.91	0.89	106.50	0.113 (-0.146 – 0.361)

Table 1: Model comparison of additional variables vs MELD 3.0 alone for the prediction of waitlist mortality in liver transplant candidates. LFI = Liver Frailty Index; SMI = Skeletal Muscle Index; IMAT = Intramuscular Adipose Tissue.

Disclosures: Michael Garas:Nothing to Disclose, Shivangi Gupta:Nothing to Disclose, Robin van de Meeberg:Nothing to Disclose, Ben Bull:Nothing to Disclose, May Kang:Nothing to Disclose, Christopher Welman:Nothing to Disclose, Leon Adams:Novo Nordisk: Advisor, SCL Behring: Advisor, Dr Falk: Speaking and Teaching, Novo Nordisk: Grant/Research Support, Boehringer Ingelheim: Speaking and Teaching, George Garas:Nothing to Disclose, Gerry MacQuillan:Nothing to Disclose, Michael Wallace:Nothing to Disclose, Briohny Smith:Nothing to Disclose, Luc Delriviere: Nothing to Disclose, Angus Jeffrey:Nothing to Disclose, Chloe Attree:Nothing to Disclose, Gary Jeffrey:Nothing to Disclose.

4401 | ◆ VARIATION IN CONTROLLED SUBSTANCE ABSTINENCE POLICIES ACROSS US LIVER TRANSPLANT CENTERS

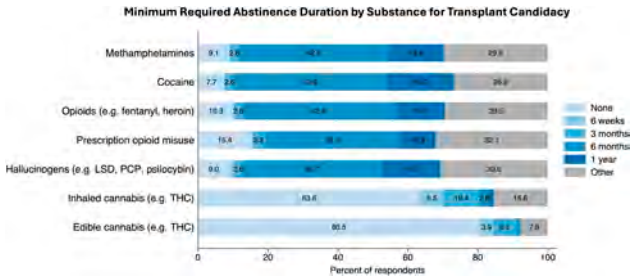
Chelsea Pan[1] Debra Yen[2] Po-Hung (Victor) Chen[3] FNU Baimaji[3] Nicholas Lim[4] Allison Kwong[5] Alexander Yang[6] Neil Mehta[1] Gene Im[7] Courtney Sherman[1], [1]University of California, San Francisco, [2]California Pacific Medical Center, [3]Johns Hopkins University, [4]University of Rochester Medicine, [5]Stanford University Medical Center, [6]University of California San Diego, [7]Center for Liver Disease and Transplantation, Division of Digestive and Liver Diseases Columbia Univ

Background: Substance use assessment is a key component of liver transplant (LT) psychosocial

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evaluation. Current 2025 AASLD/AST guidance considers active intravenous drug use a contraindication to LT and discourages inhaled substance use but allows centers to establish their own substance-specific policies, resulting in substantial practice variation. This study provides an updated national survey of LT center policies on controlled substances during transplant candidacy evaluation. **Methods:** We distributed a structured survey on alcohol-associated transplant protocols to one hepatologist at each active adult LT center in the United States, selecting medical directors or transplant hepatologists with expertise in their center practices. Respondents were asked the minimum abstinence duration of non-alcohol substances required for transplant candidacy. We defined federally controlled substances to include stimulants, non-prescription opioids, misused prescription opioids, and hallucinogens. We separately considered inhaled/edible cannabis, which is controlled state-by-state. Frequencies were averaged across all federally controlled substances and separately across cannabis. Responses were further analyzed by US census geographic region, center volume, and median MELD at transplant (MMaT) as characterized by the SRTR database. **Results:** Among 117 centers, 78 with representation from all 11 UNOS regions responded (67% response rate). For stimulants, opioids, and hallucinogens, 42% required 6 months of abstinence, 15% required 1 year, and 10% required no minimum. Among centers selecting "Other" (30%), most reported case-by-case decisions or reliance on psychosocial or addiction medicine evaluation. In contrast, most reported no minimum requirement for inhaled (64%) or edible cannabis (81%), with no statistical difference when stratified by cannabis legality. Regional analysis showed the Northeast (N = 18) had the most stringent centers, with > 70% requiring at least 6 months of abstinence for non-cannabis substances. Centers with 150+ annual transplants (N = 23) were most permissive, with 12% requiring no abstinence period and none requiring ≥ 1 year; however, centers with higher MMaT (MELD 30-34, N = 47) tended to require longer abstinence, with 33% requiring 6 months to 1 year versus 22% for lower MMaT (MELD 25-29, N = 31). **Conclusion:** LT centers across the United States demonstrate substantial variation in controlled substance abstinence requirements during candidacy evaluation, with differing policies when stratified by region, center volume, and MMaT. These center characteristics may play a multifactorial role in determining center-specific practices. Further work evaluating how these policies influence patient perceptions, psychosocial interventions, and transplant outcomes can help shape future LT selection guidance.



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4402 | ◆ EXPANDING THE DCD LIVER DONOR POOL: THE IMPACT OF NORMOTHERMIC MACHINE PERFUSION ON BILIARY INTERVENTIONS AND RESOURCE SAVINGS

Mingyi Zhang[1] Nicole Loo[2] Andrew Keaveny[2] Liu Yang[2] Denise Harnois[2] Kristopher Croome[2] Omar Mousa[2], [1]Mayo Clinic, [2]Mayo Clinic Florida

Background: Donation after circulatory death (DCD) liver grafts have historically been underutilized because of concerns for early allograft dysfunction, ischemic cholangiopathy, and graft loss after static cold storage (SCS). Normothermic machine perfusion (NMP) may mitigate these risks, safely expanding the marginal graft pool while demonstrating early perioperative resource savings. However, delayed biliary complications after NMP may impose a downstream resource burden that is not captured by index-admission outcomes. This study aims to compare early perioperative resource utilization against biliary intervention burden in DCD liver transplantation using NMP versus SCS. **Methods:** This is a retrospective review of 333 DCD liver transplants preserved with either SCS (n = 167) or NMP (n = 166). Donor, graft, recipient

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demographics, intraoperative characteristics, resource utilization, 1-year clinical and biliary outcomes were compared between groups. Early resource utilization outcomes included operative time, index length of stay, ICU admission, and blood product transfusion. Clinical and biliary outcomes through 1 year included primary nonfunction, graft loss, patient survival, biliary complications, anastomotic strictures, ERCP utilization, and biliary stent placement. **Results:** Compared to SCS, NMP was used for significantly higher-risk DCD grafts, including older donors (59.5 vs 39.0 yrs), higher BMI (29.6 vs 26.6), longer warm ischemia (14.0 vs 9.0 min), higher DRI (3.89 vs 2.98), and greater steatosis (24.1% vs 6.0%) [all $p < 0.001$]. Despite this higher-risk graft profile, NMP improved early outcomes: lower PNF (0.0% vs 3.6%), less post-reperfusion syndrome, lower ICU admission (30.7% vs 44.9%), and fewer transfusions [all $p < 0.05$]. Index LOS ($p = 0.66$) and operative time ($p = 0.31$) were similar. However, NMP required fewer pRBCs (3.7 ± 2.8 vs 6.5 ± 6.0), FFP (2.8 ± 3.0 vs 5.5 ± 5.3), and platelets (0.9 ± 1.1 vs 1.7 ± 2.0) [all $p \leq 0.05$]. Total blood products were 8.7 ± 6.7 vs 15.5 ± 13.2 units/transplant ($p < 0.001$), saving 680 units per 100 transplants. However, NMP had higher rates of anastomotic strictures (32.5% vs 18.6%, $p < 0.001$), ERCP need (35.5% vs 26.9%, $p < 0.001$), and stenting (34.9% vs 20.4%, $p < 0.05$). Non-anastomotic strictures were low (5.4% vs 9.0%, $p = 0.31$). One-year graft loss (4.2% vs 7.7%, $p = 0.17$) and survival (96.9% vs 95.2%, $p = 0.40$) were comparable. **Conclusion:** NMP enabled using older, higher-risk DCD grafts while improving early outcomes and reducing transfusions, without compromising operative time, LOS, graft loss, or survival. However, these early benefits were accompanied by significantly higher rates of anastomotic strictures, ERCP, and stenting. Economic evaluations of NMP must extend beyond index-admission metrics to include delayed biliary interventions to reveal the true cost of expanding the donor pool.

Outcome Metric	SCS (n=167)	NMP (n=166)	P value
CORE OUTCOME			
RBC transfusion (units)	6.5±6.0	3.7±2.8	<0.001
FFP transfusion (units)	5.5±5.3	2.8±3.0	<0.001
Platelet transfusion (units)	1.7±2.0	0.9±1.1	<0.05
UKDCD score	3.00 (3.0–6.0)	5.00 (3.0–8.0)	<0.001
Postreperfusion syndrome (n,%)	25 (14.9%)	11 (6.6%)	<0.05
Primary Non-Function (n,%)	6 (3.6%)	0 (0.0%)	<0.05
Hepatic Artery Thrombosis (n,%)	2 (1.2%)	0 (0.0%)	0.16
Unplanned return to OR (n,%)	28 (16.8%)	21 (12.7%)	0.29
Post-Op ICU Admission Required (n,%)	75 (44.9%)	51 (30.7%)	<0.05
Index Hospital Length of Stay (days)	5.00 (5.0–8.0)	5.00 (5.0–9.0)	0.66
30-Day Readmission rate (n,%)	31/159 (19.4%)	40/166 (24.4%)	0.31
1 year graft loss rate (n,%)	13 (7.7%)	7 (4.2%)	0.17
1 year patient survival rate (n,%)	159 (95.2%)	161 (96.9%)	0.40
BILIARY COMPLICATIONS			
Overall Biliary Complication Rate (n,%)	49 (29.3%)	63 (37.9%)	0.10
Transplant to initial diagnosis (days)	29 (20, 129)	49 (22,137.5)	0.36
Onset within 1 year (n,%)	38 (22.8%)	55 (33.1%)	<0.05
Biliary Leak (n,%)	16 (9.6%)	14 (8.4%)	0.70
Anastomotic Stricture (n,%)	31 (18.6%)	54 (32.5%)	<0.001
Ischemic Cholangiopathy (IC)(n,%)	15 (9.0%)	9 (5.4%)	0.31
IC SUB-TYPES			
- Minor Form	6	6	0.77
- Confluence Dominant	5	2	0.26
- Multifocal Progressive	3	1	0.66
- Diffuse Necrosis	1	0	0.31
ERCP (n,%)	45 (26.9%)	59 (35.5%)	<0.001
Total Cumulative ERCPs per Patient	5 (4,7)	5 (4,7)	0.54
Managed with Stent Placement (n,%)	34 (20.4%)	58 (34.9%)	<0.05

Disclosures: MINGYI ZHANG:Nothing to Disclose, Nicole Loo:Ipsen: Advisor, Andrew Keaveny:River 2 Renal Corporation: Grant/Research Support, Liu Yang: Nothing to Disclose, Denise Harnois:Nothing to Disclose, Kristopher Croome:Nothing to Disclose, Omar Mousa:Nothing to Disclose, Nothing to Disclose.

4403 | ◆ PROSPECTIVE SILENT TRIAL OF A MULTI-AGENTIC AI LIVER TRANSPLANT COMMITTEE FOR OBJECTIVE DECISION-MAKING IN TRANSPLANT CANDIDACY

Yingji Sun[1] Ghazal Azafar[1] Peter Maksymowksy[1] Peregrina Peralta[1] Irene Chen[2] Jin Ge[2] Divya Sharma[3] Elmar Jaeckel[1] Mamatha Bhat[4], [1]University Health Network, [2]University of California, San Francisco, [3]York University, [4]Toronto General Hospital

Background: Liver transplant (LT) selection committee decisions are complex and may be influenced by subjectivity despite their significant impact on patient outcomes. We previously demonstrated that a multi-agent artificial intelligence (AI) system composed of large language models (LLMs) simulating LT committee specialists could accurately identify patients likely to benefit from transplantation. We developed a dashboard and conducted a prospective silent trial to evaluate the feasibility of implementing this AI Selection Committee (AI-SC) in clinical practice. **Methods:** We included adult LT candidates discussed at weekly University Health Network Liver Transplant Program listing meetings. Cohort 1 comprised patients reviewed retrospectively between June 2022 and May 2025, while Cohort 2 included candidates evaluated prospectively between August and December 2025. In the multi-agentic sysmtem, an agent was first prompted as an AI medical scribe to generate standardized clinical vignettes from electronic health records. For the prospective silent trial, we developed an interactive dashboard that ingested the PowerPoint slides presented during committee meetings as input to the medical scribe agent. The AI-SC consisted of six large language model agents representing a hepatologist, surgeon, cardiologist, social worker, anesthesiologist, and psychiatrist. Institutional transplant guidelines were incorporated through retrieval-augmented generation. For each candidate, the AI-SC generated a listing recommendation (list vs. decline), specialty-specific rationales, and cosine similarity analyses. Cohort 1 vignettes were reviewed for accuracy and hallucinations. AI-SC recommendations in both cohorts were compared with those of the clinical transplant selection committee. **Results:** Fewer than 10% of AI-generated vignettes in cohort 1 ($n = 500$) contained hallucinated information, primarily due to missing or incomplete source data. 88 vignettes were eligible for analysis after excluding cases with insufficient written clinical information. The AI-SC accurately identified

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contraindications to liver transplant and effectively assessed transplant candidacy with an accuracy of 86.4% (95% CI, 79.0–93.8%), sensitivity of 91.0% (95% CI, 84.0–97.0%), and specificity of 58.0% (95% CI, 30.0–87.0%). Across the prospective cohort (n = 89), the AI-SC demonstrated an accuracy of 85.4%, sensitivity of 88.0%, and specificity of 71.4%. Discordant decisions were predominantly attributable to incomplete clinical documentation and abbreviations not recognized by the system. **Conclusion:** A multi-agent LLM framework can simulate LT selection committee deliberations and generate listing recommendations with high concordance to clinical decisions. These findings support the feasibility of AI-assisted decision support for improving the objectivity, consistency, and equity of LT candidate assessment.

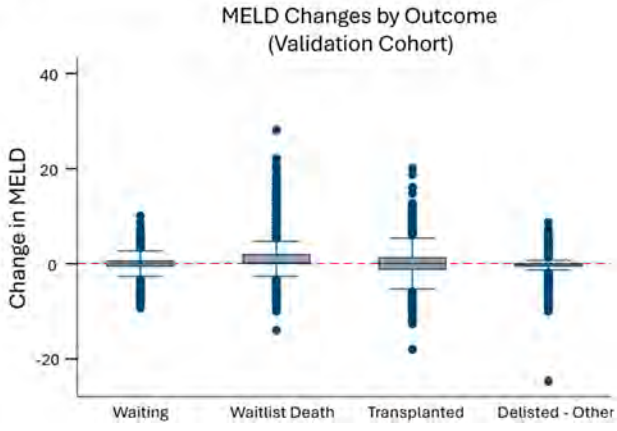
Disclosures: Yingji Sun:Nothing to Disclose, Ghazal Azafar:Nothing to Disclose, Peter Maksymowksy:Nothing to Disclose, Peregrina Peralta:Nothing to Disclose, Irene Chen:Nothing to Disclose, Jin Ge:Merck and Co: Grant/Research Support, Iota Biosciences/Astellas Pharmaceuticals: Consultant, Madrigal Pharamaceuticals: Consultant, Gilead Sciences: Consultant, Divya Sharma:Nothing to Disclose, Elmar Jaeckel:Nothing to Disclose, Mamatha Bhat:Novo Nordisk: Grant/Research Support, Natera: Grant/Research Support, Oncoustics: Grant/Research Support, KNIGHT THERAPEUTICS: Grant/Research Support, Astra Zeneca: Consultant, Merck: Grant/Research Support, AFFLO: Grant/Research Support, MERCK: Grant/Research Support, CAREDX: Grant/Research Support, THERMOFISHER: Grant/Research Support.

4404 | ◆ MELD-RISE (RISK OF INCREMENTAL SCORE ELEVATION): QUANTIFYING INCREASES IN MORTALITY RISK CONFERRED BY CHANGES IN MELD

Xiaohan Ying[1] Russell Rosenblatt[2], [1]NewYork Presbyterian/Weill Cornell, [2]Weill Cornell Medicine

Background: The Model for End-Stage Liver Disease (MELD) score has guided liver transplantation (LT) allocation since 2002, prioritizing candidates based on estimated short-term mortality risk. Despite its widespread adoption and iterative refinements, MELD remains a static, cross-sectional measure that captures disease severity at a single point without accounting for trajectory. In this study, we developed and validated a novel trajectory-based scoring system (MELD-RISE) that incorporates MELD changes to improve prediction of 90-day WL mortality in the contemporary allocation era. **Methods:** We used the UNOS STAR file and included adult LT candidates listed from 2/4/20-12/31/25 with at least 3 MELD assessments. We excluded candidates listed with status 1A, multiorgan, exception points, prior LT, and initial MELD > 23 (median MELD of our cohort). The cohort was split randomly 70:30 into derivation and validation groups. Competing-risk regression including *a priori* covariates (age, sex, diagnosis, function according to performance status, region) estimated waitlist (WL) mortality and LT. The primary outcome was 90-day WL mortality. A score incorporating change in MELD was created. Discrimination was assessed using the area under the curve (AUC). **Results:** Of the 20,738 patients included in the derivation cohort, 55.5% were transplanted, 16.2% remained on the WL, and 10.2% died. The characteristics of the validation cohort (8,685) were similar to the derivation cohort. After competing risk regression, change in MELD over the last 3 measurements was associated with a significant increase in WL mortality (sHR 1.08, 95% CI: 1.06-1.09). A MELD-RISE score was created: MELD-RISE = last MELD + 0.94 * [MELD change over last 3 measurements]. Essentially, for each point of MELD score change over 3 checks, the risk of WL mortality was equal to an extra MELD point (**Figure 1**). Using the validation cohort, however, AUC was lower than using the last MELD score itself (0.81 vs 0.82, p < 0.001). **Conclusion:** In this study, we developed and validated a novel trajectory-based score integrating both the most recent MELD and the magnitude of MELD changes. Each one-point increase in MELD conferred a mortality hazard equivalent to nearly one additional point to the most recent MELD score. This suggests that the rate and direction of MELD changes carry independent prognostic weight not captured by a static, cross-sectional score. Additionally, this further quantifies the impact of a rise in MELD – a clinical situation that is known to result in increased mortality above the score itself. The incorporation of this trajectory-based approach may be warranted to better identify and prioritize patients whose true mortality risk is underestimated by the current scoring system.

Figure 1. MELD-RISE: Visualization of the Mortality Contribution of Longitudinal MELD Changes Across Three Sequential Assessments



Disclosures: Xiaohan Ying:Nothing to Disclose, Russell Rosenblatt:Gilead: Grant/Research Support.

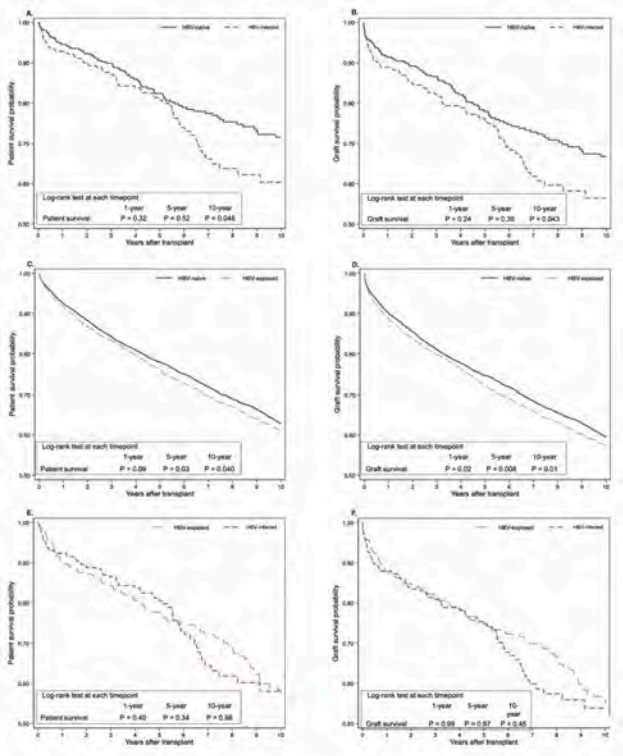
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4405 | ◆ PROPENSITY-MATCHED ANALYSIS OF 10-YEAR GRAFT AND PATIENT SURVIVAL AFTER LIVER TRANSPLANTATION WITH HEPATITIS B VIRUS-POSITIVE DONOR ORGANS

Rachael Mahle[1] Leandro Sierra[2] Katherine Cooper[1] Karin Andersson[1] Daniel Sikavi[1] Doan Dao[1] Eric Przybyszewski[1] Xing Li[1] Irun Bhan[1] Deepika Devuni[3] Raymond Chung[1] Arthur Kim[1] Camille Kotton[1] Heidi Yeh[1] Shimul Shah[1] Emily Bethea[1], [1]Massachusetts General Hospital, [2]Cleveland Clinic Foundation, [3]UMass Memorial Health

Background: Hepatitis B virus (HBV)-positive donor grafts represent an important opportunity to expand the liver donor pool to increase access to transplantation. However, data on long-term outcomes across the spectrum of donor HBV serologic profiles remain limited. We evaluated short- and long-term graft and recipient outcomes across HBV-infected (HBsAg+ and/or NAT+), HBV-exposed (HBcAb+; HBsAg-, NAT-), and HBV-naïve (HBcAb-, HBsAg-, NAT-) donor grafts. **Methods:** We conducted a retrospective cohort study using the United Network for Organ Sharing/Organ Procurement and Transplantation Network (UNOS/OPTN) national registry (2000-2025). Three pairwise propensity-matched comparisons across donor HBV serologic profiles were performed. Patient and graft survival at 1, 5, and 10 years were assessed by Kaplan-Meier estimation. Sensitivity analyses included Cox proportional hazards regression, Royston-Parmar flexible parametric models, restricted mean survival time, 30-day landmark analysis, and Fine-Gray competing-risk models. **Results:** Among 138,485 recipients, 130,684 (94.4%) received HBV-naïve, 7,404 (5.2%) HBV-exposed, and 397 (0.3%) HBV-infected donor grafts. After propensity matching, recipients of HBV-naïve and HBV-infected donor grafts showed comparable graft and patient survival at 1 and 5 years. However, at 10 years, HBV-infected donor grafts were associated with lower graft survival (66.8% vs 56.5%; P = 0.043) and patient survival (71.6% vs 60.4%; P = 0.046). Recipients of HBV-exposed donor grafts demonstrated statistically significant lower graft and patient survival compared with HBV-naïve donor graft recipients at all time points; however, the absolute differences between groups ranged from 1.3% to 2.3%. No significant differences were observed between recipients of HBV-exposed and HBV-infected grafts. **Conclusion:** In this national propensity-matched analysis, HBV-infected donor grafts showed comparable short- and intermediate-term outcomes compared to HBV-naïve donor grafts, with differences emerging only at long-term follow-up. While HBV-exposed donor grafts were associated with a reduction in graft and patient survival compared with HBV-naïve donor grafts, the absolute differences were small and may have limited clinical significance. These findings support ongoing expansion of HBV-positive donor utilization and highlight the need for long-term post-transplant monitoring.



Disclosures: Rachael Mahle:Nothing to Disclose, Leandro Sierra:Nothing to Disclose, Katherine Cooper:Nothing to Disclose, Karin Andersson:Nothing to Disclose, Daniel Sikavi:Nothing to Disclose, Doan Dao:Roche: Grant/Research Support, Gilead Sciences: Grant/Research Support, IVQIA: Consultant, BMJ: Independent Contractor, Fujifilm Medical System: Grant/Research Support, DELFI Diagnostics Inc.: Grant/Research Support, Ludwig Institute for Cancer Research: Grant/Research Support, Abbott Diagnostics: Grant/Research Support, Eric Przybyszewski: Nothing to Disclose, Xing Li:Nothing to Disclose, Irun Bhan:Nothing to Disclose, Deepika Devuni:Nothing to Disclose, Raymond Chung:Nothing to Disclose, Arthur Kim:Shionogi, Inc.: Consultant, Camille Kotton:Nothing to Disclose, Heidi Yeh:Nothing to Disclose, Shimul Shah:Nothing to Disclose, Emily Bethea:Nothing to Disclose.

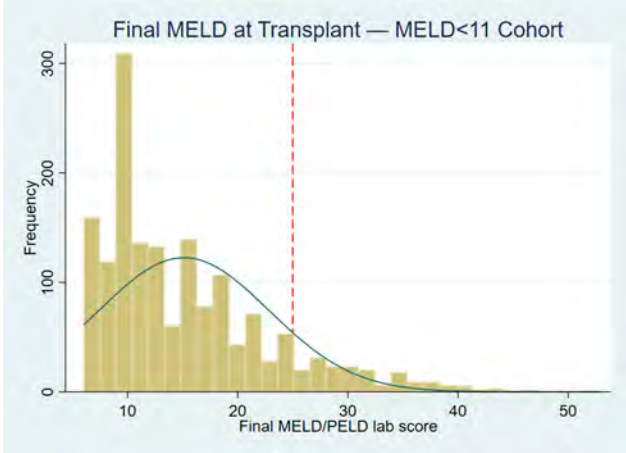
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4406 | VERY LOW MELD SCORES ON THE WAITLIST: HIGHER WAITLIST MORTALITY

Hanna Abuhay[1] Alexander Zhao[2] Russell Rosenblatt[1], [1]Weill Cornell Medicine, [2]Joan and Sanford I. Weill Medical College of Cornell University

Background: Patients with low MELD scores are often perceived to have favorable prognosis and may not be considered for liver transplantation (LT) at many centers. However, outcomes among patients listed with very low MELD scores remain poorly defined. We evaluated outcomes in patients listed for LT with MELD ≤ 10 without access to MELD exception points or living donation. **Methods:** Adults listed for LT between 2015–2025 with MELD ≤ 10 in the UNOS STAR file were identified. In order to isolate patients with poor access to LT, patients with hepatocellular carcinoma, MELD exception points, multi-organ transplant listing, or LDLT were excluded. Competing risk regression models were used to evaluate predictors of waitlist (WL) mortality, LT, and delisting due to clinical improvement, with covariates selected a priori. **Results:** Among 6,120 patients, mean age was 57 years and mean MELD at listing was 9. Alcohol-associated liver disease (ALD) (32.2%) was the most common etiology. Despite low MELD scores, 69.4% had ascites and 53.6% had hepatic encephalopathy (HE). Mean WL time was 677 days. During follow-up, 14.7% died on the WL, 28.3% underwent LT, 23.4% were delisted due to clinical improvement, 19.3% were delisted for other reasons, and 14.3% remained listed. At WL removal, mean MELD at LT was 13, 14 at mortality, and 9 at delisting/still waiting. On competing risk regression, older age was associated with increased WL mortality (SHR 1.03, 95% CI 1.03–1.04, $p < 0.001$), while ALD was associated with lower WL mortality (SHR 0.62, 95% CI 0.49–0.78, $p < 0.001$) and higher likelihood of clinical improvement (SHR 1.72, 95% CI 1.43–2.08, $p < 0.001$). Male sex, higher MELD, and HE were associated with lower likelihood of improvement. Older age, male sex, higher MELD, ascites, and HE were associated with LT. **Conclusion:** Patients listed for LT with MELD ≤ 10 without access to living donation or MELD exception points represent a clinically heterogeneous cohort with substantial underlying hepatic decompensation and surprisingly high WL mortality despite low laboratory MELD scores. Although nearly 1 in 4 improved sufficiently for delisting, particularly in ALD, over 1 in 4 underwent LT and nearly 1 in 6 died on the WL, highlighting the fact that MELD incompletely captures disease burden in this population.



Disclosures: Hanna Abuhay:Nothing to Disclose, Alexander Zhao:Nothing to Disclose, Russell Rosenblatt:Gilead: Grant/Research Support.

4407 | THE SAFETY AND EFFICACY OF COMBINED LIVER TRANSPLANT AND SLEEVE GASTRECTOMY: A SYSTEMATIC REVIEW AND META-ANALYSIS

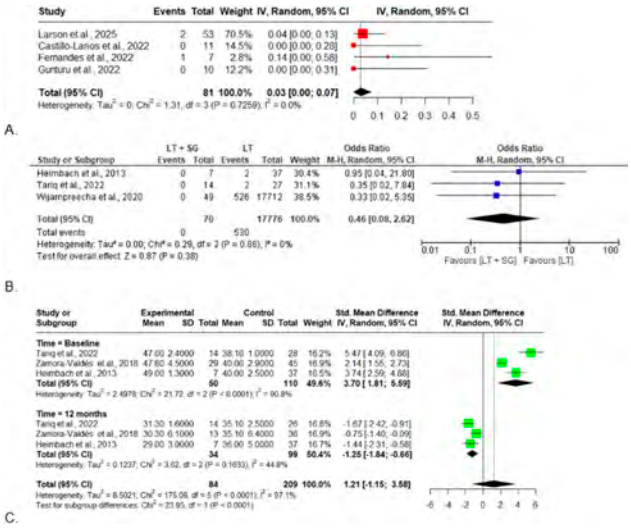
Muaaz Masood[1] Amita Kasar[1] Mala Jain[2] Richard Kozarek[1] Asma Siddique[1], [1]Virginia Mason Franciscan Health, [2]Westchester Medical Center

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is currently the most common etiology of chronic liver disease and the most common indication for liver transplantation (LT) in the United States. The rate of obesity in patients undergoing LT has increased. Additionally, there is a risk for recurrent and de novo MASLD following LT. Several studies have revealed that a combined LT and sleeve gastrectomy (SG) may be effective. This is the first systematic review and meta-analysis to our knowledge to evaluate the safety and efficacy of combined LT and SG. **Methods:** We performed a comprehensive search from four databases including PubMed, Scopus, Google Scholar and ScienceDirect. All analyses were performed using a random-effects model. Statistical analysis was conducted using R version 4.5.1 and Review Manager (RevMan) 5.4. For comparative outcomes, pooled effect sizes were calculated using standardized mean differences (SMDs). The odds ratio was calculated for mortality. Statistical significance was defined as $p < 0.05$. Between-study heterogeneity was assessed using the I2 statistic, characterized as low (25%), moderate (50%), or high (75%) heterogeneity.

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Results: Four studies with a total of 81 patients were included in the meta-analysis of perioperative mortality following LT + SG (A). The pooled mortality rate was 3% (95% CI 0–7%), with no heterogeneity (I2 = 0%). Three studies with 17,846 patients compared post-operative complications between LT + SG and LT alone. In the LT + SG group, no complications were reported (0/70), whereas in the LT only group, 530 events occurred (B). The pooled odds ratio was 0.46 (95% CI 0.08–2.62), which indicated no significant difference between groups (p = 0.38). The pooled mean body mass index (BMI) was determined at baseline and at 12 months (C). The pooled mean BMI decreased from 45.54 (95% CI 43.14–47.95; I2 = 93%) at baseline to 30.57 at 12 months following LT + SG (95% CI 29.41–31.72; I2 = 43.3%). Subgroup differences between the time points were statistically significant (Chi2 = 128.43, p < 0.0001), which suggested sustained improvements in BMI. **Conclusion:** Our study demonstrated that combined LT + SG is safe and is not associated with increased perioperative mortality compared to LT alone. There was no significant differences in reported complications among LT + SG patients which suggests that the addition of SG does not affect postoperative outcomes in select patients. Subgroup analysis revealed sustained improvements in BMI which were statistically significant. Studies also revealed a trend towards improvement in metabolic comorbidities. LT + SG remains an option for patients who are not able to take medications for obesity due to barriers, e.g. medication side effects, cost, insurance coverage, and patients with inadequate response to medical therapy. Additional studies are warranted to explore outcomes with LT + SG.



Disclosures: Muaaz Masood:Nothing to Disclose, Amita Kasar:Nothing to Disclose, Mala Jain:Nothing to Disclose, Richard Kozarek:Nothing to Disclose, Asma Siddique:Nothing to Disclose.

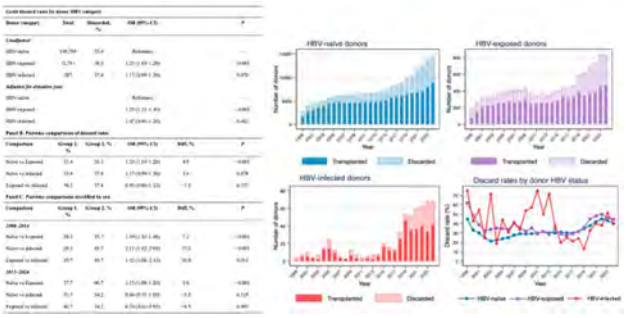
4408 | UTILIZATION TRENDS IN HEPATITIS B VIRUS POSITIVE DONORS FROM 2000-2024

Rachael Mahle[1] Leandro Sierra[2] Katherine Cooper[1] Karin Andersson[1] Daniel Sikavi[1] Doan Dao[1] Eric Przybyszewski[1] Xing Li[1] Irun Bhan[1] Deepika Devuni[3] Raymond Chung[1] Arthur Kim[1] Camille Kotton[1] Heidi Yeh[1] Shimul Shah[1] Emily Bethea[1], [1]Massachusetts General Hospital, [2]Cleveland Clinic Foundation, [3]UMass Memorial Health

Background: The global burden of liver disease is driving a growing demand for liver transplantation, which remains a resource-limited field. HBV-positive donor grafts have been used to expand access to suitable organs. In this study, we evaluated HBV-positive donor graft utilization patterns, stratified by HBV-naïve (HBcAb-, HBsAg-, NAT-), HBV-exposed (HBcAb+; HBsAg- and NAT-), and HBV-infected donors (HBsAg+ or NAT+). **Methods:** This retrospective cohort study (2000-2024) used the United Network for Organ Sharing/Organ Procurement and Transplantation Network (UNOS/OPTN) registry. Transplanted grafts were identified by linkage to recipient records, while donors without a matched liver transplant recipient were classified as discarded. Pearson's chi-square test was used to compare discard rates across donor groups, and logistic regression was used to estimate odds ratios (ORs) for graft discard using HBV-naïve donors as the reference group. Era-stratified analyses (2000-2014 vs 2015-2024) were used to assess temporal trends in utilization. **Results:** Among 208,087 deceased donors with classifiable HBV serologic profiles, discard rates were similar across donor categories: 33.4% for HBV-naïve, 38.3% for HBV-exposed, and 37.0% for HBV-infected donors. After adjusting for donation year, HBV-exposed donors had modestly increased odds of discard compared with HBV-naïve donors (OR 1.25, 95% CI 1.21-1.30; P < 0.001), while the difference for HBV-infected donors was not significantly different (OR 1.07, 95% CI 0.90-1.26; P = 0.463). Era-stratified analyses showed that from 2000-2014, HBV-infected donors had substantially higher discard rates than HBV-naïve donors (45.7% vs 28.5%; OR 2.12, P < 0.001). However, in 2015-2024, discard rates became similar between groups (34.2% vs 37.7%; OR 0.86, P = 0.13). There was significant regional variation in HBV-positive donor utilization, with the highest transplant rates in OPTN Regions 7 and 11 and the lowest in Regions 5 and 6. **Conclusion:** Utilization of HBV-positive liver grafts has increased substantially in the US. In the last decade, HBV-infected donors had similar discard rates to HBV-naïve donors. These findings may suggest growing national acceptance of HBV-positive donor grafts. Ongoing regional differences in utilization represents an opportunity to improve equitable use of HBV-positive donor organs.

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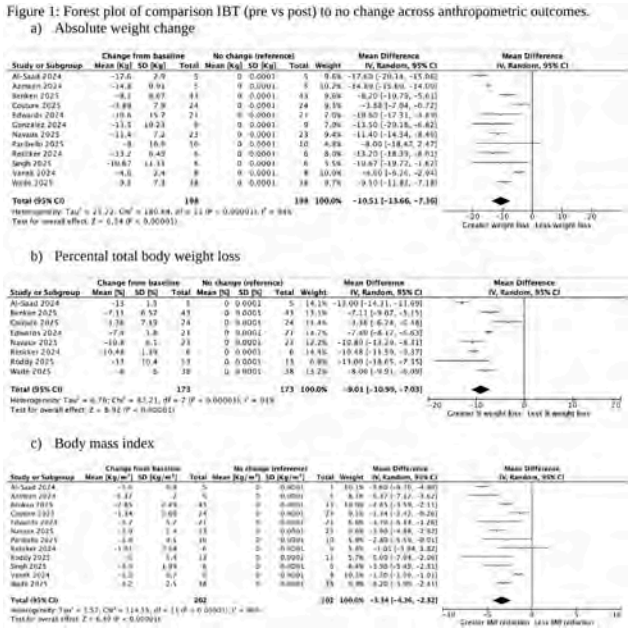
4409 | INCRETIN-BASED THERAPIES AS A BRIDGE TO LIVER AND OTHER SOLID ORGAN TRANSPLANTATION: A SYSTEMATIC REVIEW AND META-ANALYSIS

Ahmed Mohammad[1] Noor Mawaz-Khan[2] Areej Hasan[3] Shreya Narayanamoorrthy[2] Mohammad Qasim Khan[4], [1]Department of Medicine, Western University, [2]Faculty of Health Sciences, Western University, [3]Faculty of Science, McMaster University, [4]Department of Epidemiology, Department of Medicine, Division of Gastroenterology, Western University

Background: Obesity is a major barrier to solid organ transplantation (SOT), limiting transplant candidacy, waitlist activation, and access to transplantation. Incretin-based therapies (IBTs), including GLP-1 receptor agonists (GLP-1 RAs) and GIP/GLP-1 RAs are effective weight-loss therapies, but their effectiveness as a bridge-to-transplant remains uncertain. We evaluated the effectiveness of IBTs on anthropometric and transplant-related outcomes among adults undergoing evaluation for SOT. **Methods:** We conducted a systematic review and meta-analysis of studies evaluating IBTs in adult SOT candidates with obesity-related barriers to transplantation. Outcomes included absolute weight change, percentage total body weight loss (%TBWL), body mass index (BMI) change, waitlist activation, and receipt of transplantation, and exposure characteristics describing how IBTs were used. Random-effects meta-analyses were performed for continuous anthropometric outcomes. Sensitivity analyses explored treatment duration, transplanted organ type, and study-level heterogeneity. **Results:** Nineteen studies across liver, kidney, heart, lung, and combined-organ transplant populations were included. Semaglutide was the most reported agent followed by tirzepatide, liraglutide, and dulaglutide. Treatment duration ranged from approximately 3 to 15 months. In single-arm pooled analyses, IBTs were associated with significant reductions in absolute body weight across 12 studies (mean change −10.51 kg, 95% CI: −13.66 to −7.36 kg), BMI across 12 studies (mean change −3.34 kg/m², 95% CI −4.36 to −2.32 kg/m²), and %TBWL across 8 studies (mean change −9.01%, 95% CI −10.99 to −7.03%). Despite substantial heterogeneity across anthropometric outcomes, treatment effects were directionally consistent across sensitivity analyses. Transplant-related outcomes were synthesized narratively. Across studies, IBTs were associated with improved transplant candidacy, increased waitlist activation, and progression to transplantation. Comparative studies demonstrated higher likelihood of waitlisting (aHR 1.66, 95% CI 1.28 to 2.13) and transplantation (aOR 2.51, 95% CI 1.72 to 3.67) among IBT users versus non-users. Multiple single-arm cohorts further demonstrated that clinically meaningful proportions of previously ineligible candidates subsequently achieved waitlisting or transplantation following IBT-associated weight loss. **Conclusion:** IBTs are associated with clinically meaningful reductions in weight and BMI among transplant candidates with obesity-related barriers. These therapies may improve access to transplantation by facilitating waitlist activation and progression to transplant. Prospective controlled studies are needed to define optimal implementation strategies and long-term post-transplant outcomes.

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4410 | LIVING LIVER DONATION IS FINANCIALLY AND OCCUPATIONALLY SAFE: NATIONAL EVIDENCE REASSURING DONORS ON INSURANCE AND EMPLOYMENT OUTCOMES

Sri Harsha Boppana[1] Subhash Gurappa[2] Sachin Sravan Kumar Komati[2] Gautam Maddineni[3] Raja Chandra Chakinala[4] Venkata Sunkesula[5] Pradeep Yarra[6] Kamran Qureshi[7], [1]Nassau University Medical Center, [2]Florida International University, [3]Creighton university, [4]Guthrie Robert Packer Hospital, [5]Case Western Reserve University, [6]UT Health San Antonio, [7]Saint Louis University

Background: Living liver donation saves lives and expands transplant access, yet unfounded concerns about financial harm — including insurance loss and income disruption — continue to deter potential donors. Robust national data are needed to reassure candidates that donation does not jeopardize their financial security or occupational stability. We aimed to comprehensively characterize insurance, employment, and disability outcomes after living liver donation in a contemporary national cohort and identify modifiable risk factors for work disruption. **Methods:** Retrospective cohort study using OPTN/UNOS STAR data (2014–2024). Adult living liver donors aged 18–65 were assessed for donation-attributed health insurance loss, life insurance loss, work disruption (employed at donation, not employed at follow-up), and transition to disability status. Multivariable logistic regression identified independent predictors of work disruption, adjusting for donor demographics, donation type, liver complications, and hospital readmission. **Results:** Among 5,159 adult living liver donors (median age 36; 56.3% female), donors were young, healthy, and economically active: 86.1% were employed and 94.6% were insured at donation. Donation-attributed insurance loss was exceedingly rare: only 34 of 5,050 donors (0.67%) lost any coverage — health insurance in 25 and life insurance in 12. Although liver complications occurred in 738 donors (14.3%) and hospital readmissions in 621 (12.0%), nearly 9 in 10 employed donors successfully maintained employment after donation. Work disruption occurred in 504 of 4,461 baseline-employed donors (11.3%). On multivariable analysis, readmission — not hepatic complications — was the primary independent predictor of work disruption (OR 1.79, 95% CI 1.36–2.36; hepatic complications OR 1.02, p = 0.92). Donor sex, age, and graft type were not significant predictors. Long-term transition to disability status remained low across the cohort. **Conclusion:** This large national study provides compelling reassurance that living liver donation is financially and occupationally safe for the overwhelming majority of donors. Insurance loss affected fewer than 1 in 150 donors, employment was preserved in nearly 9 of 10 working donors, and transition to disability was uncommon. The principal driver of work disruption was readmission rather than hepatobiliary complications, identifying a specific and preventable target for perioperative support. These findings should be actively shared with prospective donors and their families during evaluation to address financial concerns, reduce donation hesitancy, and promote broader expansion of living liver donation.

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4411 | EARLIER MESO-REX BYPASS ACHIEVES GREATER PHYSIOLOGIC PORTAL FLOW RESTORATION IN CHILDREN WITH

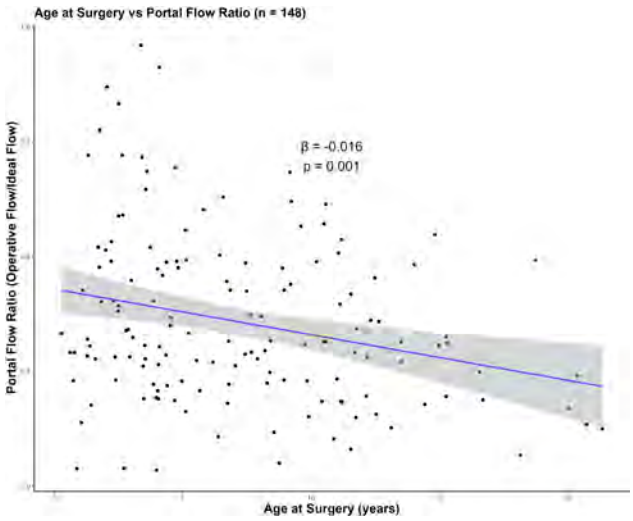
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EXTRAHEPATIC PORTAL VEIN OBSTRUCTION

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Background: Meso-Rex bypass (MRB) is the preferred physiologic treatment for extrahepatic portal vein obstruction (EHPVO) in children. Despite increasing acceptance of MRB, many patients with EHPVO experience significant delays in surgical referral possibly due to a concern for technical feasibility in younger children with smaller vessels. We sought to determine whether age at operation influences the degree of physiologic portal venous inflow restoration achieved following MRB. **Methods:** We analyzed a prospectively maintained cohort of children undergoing primary MRB for EHPVO between 1997 and 2026 at a quaternary pediatric referral center. Intraoperative shunt flow was measured using a vascular flow probe and normalized to patient-specific predicted physiologic portal venous inflow derived from body surface area and cardiac output. This calculation generates a Meso-Rex Flow Ratio (measured flow/ideal portal flow). Linear regression was used to evaluate the relationship between age at surgery and achieved flow ratio. Previously established associations between flow ratio and bypass durability were used to contextualize clinical significance. **Results:** A total of 148 children underwent primary MRB and met inclusion criteria. Median age at operation was 6.3 years (IQR 3.4–10.6 years). Age at surgery demonstrated a significant inverse association with achieved Meso-Rex Flow Ratio (β = -0.016, p = 0.001), with younger children consistently achieving higher normalized portal venous inflow following reconstruction. Children undergoing MRB at younger ages frequently achieved portal inflow approaching or exceeding predicted physiologic requirements, whereas older children demonstrated progressively lower flow ratios. Prior analyses within this cohort demonstrated that higher flow ratios are associated with improved primary bypass patency and reduced need for postoperative intervention. These findings suggest that earlier intervention may confer a physiologic advantage by maximizing restoration of hepatopetal portal flow. **Conclusion:** Younger age at MRB is associated with superior restoration of physiologic portal venous inflow. These data directly challenge the perception that younger children are technically disadvantaged candidates for MRB and instead support earlier evaluation and referral before prolonged portal venous deprivation occurs.



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4412 | LIVER TRANSPLANTATION IN RECIPIENTS AGED 75 YEARS AND OLDER IN THE ACUITY-CIRCLE ALLOCATION ERA

Irena Helenowski[1] Eyad Razzak[2] Kush Patel[2] Scott Cotler[2] Eric Kallwitz[2], [1]Loyola University Chicago, [2]Loyola University Health System

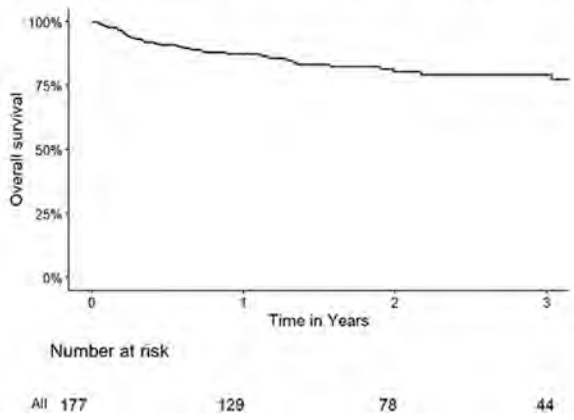
Background: Liver transplantation (LT) is increasingly considered in older individuals, especially those with MASLD and hepatocellular carcinoma (HCC). There is no established recipient age threshold which serves as a contraindication to LT. The purpose of this study was to perform a descriptive analysis of LT recipients aged 75 and older. **Methods:** Liver transplant recipients aged ≥75 years in the UNOS database from Feb 2020–December 2024 were included in this analysis. Descriptive data were included and patient and graft survival was estimated using Kaplan-Meier survival curves. **Results:** In the era included, there were 177 LT recipients aged ≥75 years. The annual number increased from 18 transplants in 2020 to 51 transplants in 2024. Fifty-five transplant centers transplanted at least one patient aged 75 and older. Recipients 75 and older were largely non-Hispanic, white (n = 127, 71.8%) and male (n = 118, 66.7%). The most common transplant

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indications were HCC (n = 74, 41.1%) and MASLD (n = 40, 22.6%). The Karnofsky score was < 40% in 61 recipients (34.5%) and 67 (37.9%) recipients had a BMI < 25 kg/m2. Fifty-one recipients were in an ICU (28.8%) at time of transplant, and 11 (6.2%) had a history of grade 3-4 encephalopathy. Only 16 recipients (9%) received dialysis within one week of registration and 24 recipients (14%) received dialysis within one week of transplant. The distribution of recipient MELD scores was 25.4% MELD 6-11, 10.7% MELD 12-14, 11.9% MELD 15-17, 10.2% MELD 18-21, 13.6% MELD 22-25, 9.6% MELD 26-29, 10.7% MELD 30-34 and 7.9% MELD 35-40. Livers from donors aged 70 and older were used in 13.1% of recipients, whereas roughly 25% (n = 44) received a donor aged 18-39 years. Donation after cardiac death livers were utilized in 25.4% of cases. Donor location was 39.6% local, 29.4% regional and 31.1% national. Median cold ischemic time in donors was 6.6 hours. Overall patient survival is shown in the Figure. Notably patient survival at one year was 87.31%; 95% CI 82.49, 92.41 and at 3 years was 79.33; 95% CI 72.85,86.39. Five-year patient survival data were limited by a small sample size, but was 60.23; 95% CI 43.67,83.07. Graft survival was fairly similar to patient survival at 1 year (86.30; 95% CI 81.36, 91.55) and 3 years (78.42, 95% CI 71.91, 85.52). **Conclusion:** Selected recipients aged 75 and older had acceptable 1 year (87.3%) and 3 year (79.3%) survival. While LT in recipients aged 75 and older was uncommon, 55 centers performed at least one transplant in this age group. These data suggest that chronological age alone should not serve as an absolute contraindication to LT. Further data are needed to identify optimal selection criteria in this group and additional long term survival data are needed.

Figure. 1 and 3 year overall survival in transplant recipients aged 75 and older



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4413 | REGIONAL IMPACT OF NEW LIVER TRANSPLANT CENTER ENTRY: A NATURAL EXPERIMENT

Holly Huang[1] John Roberts[1] Hillary Braun[1] Garrett Roll[1] Jennifer Lai[1] Jin Ge[1], [1]University of California, San Francisco

Background: Prior studies of liver transplant competition identified associations between competitive states and transplant outcomes but could not establish how programs respond to competition changes. In this retrospective cohort study, we used a quasi-experimental approach to evaluate the impact of a single new center opening on regional transplant volume, transplant efficiency, market share, donor utilization, and recipient case-mix. **Methods:** Using United Network for Organ Sharing (UNOS) registry data (February 14, 2022–December 31, 2024), we identified competing centers as those drawing ≥80% of transplanted livers from the same organ procurement organization (OPO) network as the new center. We analyzed transplant volume, efficiency (transplants per OPO deceased donor), and market share (transplants per OPO-recovered liver) in the regional cohort (competing plus new center; n = 8) and competing cohort (n = 7) in equal 526-day pre- and post-entry windows using Poisson regression and differences-in-differences (DiD) analysis, with UNOS Region 5 centers as external control. We compared regional donor and recipient characteristics pre- and post-entry using Mann-Whitney U and chi-square tests. **Results:** Regional transplant volume increased by 14% (931 pre vs. 1,058 post; rate ratio [RR] 1.14, 95% CI 1.04–1.24, p = 0.004; table 1), comparable to that of the external control (RR 1.10, p < 0.01); DiD confirmed no significant difference from control trends (incidence rate ratio [IRR] 1.02, 95% CI 0.92–1.14, p = 0.71). Among competing centers, volume did not change significantly (RR 1.07, 95% CI 0.98–1.17, p = 0.12; table 1), and DiD found no significant growth displacement (IRR 0.96, 95% CI 0.86–1.08, p = 0.52). Competing centers maintained transplant efficiency (RR 0.96, p = 0.37) but lost market share (RR 0.91, 95% CI 0.83–1.00, p = 0.042) while regional and external control shares remained stable; despite this, they increased absolute procurement from shared OPOs by 64 livers (compared to only +4 from other OPOs). Across regional cohort, donor profiles shifted markedly post-entry: the Donor Risk Index (DRI) increased (median 2.26 vs. 2.51, p < 0.01), cold ischemia time lengthened (6.75 vs. 7.57 h, p < 0.01), deceased cardiac donor (DCD) use nearly doubled (8.6% vs. 15.6%, p < 0.01), and machine perfusion use more than doubled (12.9% vs. 26.9%, p < 0.01). Recipient Model for End-Stage Liver Disease (MELD) scores at listing and transplant were unchanged, and the overall recipient case-mix was stable. **Conclusion:**

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New liver transplant center entry did not significantly suppress incumbent transplant volume. The region adapted by accepting higher-risk donors while maintaining recipient acuity, and the adoption of machine perfusion may reflect a structural response to this shift. These findings suggest a new transplant center does not harm existing programs when donor supply is sufficient or organ utilization can be improved.

Table 1. Transplant volume: Poisson regression, transplants per 526-day period

Analysis	Pre N	Post N	Pre Rate*	Post Rate*	Rate Ratio	95% CI	P value
Competing centers (n=7)	931	999	1.77	1.90	1.073	0.981–1.173	0.122
Competing centers + new entrant (n=8)	931	1058	1.77	2.01	1.136	1.041–1.241	0.004
UNOS Region 5 centers (excluding competing and new centers; n=17)	2461	2716	4.68	5.16	1.104	1.045–1.165	<0.01
National cohort (n=144 pre, n=143 post)	14410	16212	27.40	30.82	1.125	1.100–1.151	<0.01

*Rate expressed as number of transplants per day × 100. Rate ratios compare post- to pre-entry periods.

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4414 | MELD-CYSC: A DE NOVO 90-DAY WAITLIST MORTALITY SCORE INCORPORATING CYSTATIN C IMPROVES RISK PREDICTION BY CAPTURING FRAILTY IN A 14-CENTER US LIVER TRANSPLANT CONSORTIUM

Giuseppe Cullaro[1] Taryn Liu[1] Jennifer Lai[2] Benjamin Cho[2] Brian Lee[3] Sean Lee[4] Sydney Whittaker[5] Stevan Gonzalez[6] Daniel Woodfin[7] Zachary Fricker[8] Todd Frederick[9] Hugo Vargas[10] Sharon Lechtig-Wasserman[11] Douglas Simonetto[12] Miguel Gomez[12] Hani Wadei[13] Ibrahim Alhayani[13] Clara Tow[14] Yixuan Du[14] Justin Belcher[15] Kavish Patidar[16] R. Mark Ghobrial[17] Eric Orman[18] Andres Duarte-Rojo[19] Seong Park[20] Elizabeth Verna[21] Andrew Allegretti[5], [1]Columbia University, [2]UCSF, [3]Keck School of Medicine, [4]USC, [5]MGH, [6]Baylor Scott and White All Saints Medical Center Fort Worth, [7]Burnett School of Medicine at TCU, [8]Beth Israel Deaconess Medical Center, [9]CPMC, [10]Mayo Clinic Arizona, [11]Mayo Arizona, [12]Mayo Clinic Rochester, [13]Mayo, [14]Albert Einstein College of Medicine, [15]Yale, [16]Houston Methodist, [17]Houston Methodist JC Walter Transplant Center, [18]Indiana University, [19]Northwestern Medicine, [20]Northwestern University, [21]Columbia University Medical Center

Background: Serum creatinine (sCr)–based scores, including MELD 3.0, underestimate waitlist mortality in sarcopenic and frail liver transplant candidates. Cystatin C (cysC) is a muscle-independent glomerular filtration marker. We hypothesized that incorporating cysC into MELD 3.0 would improve risk prediction. **Methods:** This substudy of the HRS-HARMONY consortium assembled 14 US LT centers that protocolized the measurement of cysC at the time of LT evaluation. 2,592 candidates with paired cysC and sCr at listing were randomly split 80:20 (stratified by site and 90-day outcome) into derivation (n = 2,083) and held-out validation (n = 509) cohorts. In the derivation cohort, we newly derived MELD-CYSC for 90-day waitlist mortality using multivariable Cox regression with stepwise selection. Candidate predictors were female sex, bilirubin, INR, albumin, sodium, sCr, cysC, and the cysC − sCr difference [Δ(cysC−sCr)]. Transformations and bounds were data-driven (penalized splines, log- vs. linear-fit), with sCr and cysC capped at their upper bounds on renal replacement therapy. MELD-CYSC was compared to MELD 3.0 by Harrell's C, calibration slope, and net reclassification (NRI). In candidates with Liver Frailty Index (LFI), we tested Spearman correlation with Δ(cysC−sCr) and ran a Cox mediation analysis testing whether adding LFI attenuated Δ(cysC−sCr)'s coefficient for 90-day mortality. **Results:** Derivation 2,083 (69 90-day events); validation 509 (13 90-day events). Median age 57y; 40% women; 8% RRT at listing; 72% ascites; 58% HE; alcohol 44%, MASLD 32%. Median (IQR): sCr 0.98 (0.7–1.5), cysC 1.5 (1.1–2.2), Δ(cysC−sCr) 0.5 (0.2–0.7), total bilirubin 2.4 (1.2–5.1), INR 1.50 (1.2–1.8), albumin 3.3 (2.8–3.8), sodium 136 (133–139); MELD 3.0 19 (14–25); MELD-CYSC 18 (13–24). The final MELD-CYSC included bilirubin, INR, sCr, and Δ(cysC−sCr) **(Panel 1a).** In validation, MELD-CYSC discriminated 90-day waitlist mortality numerically better than MELD 3.0 (ΔC +0.03, p = 0.04). MELD-CYSC was substantially better calibrated than MELD 3.0 (calibration slope 1.06 vs 0.18, p < 0.001); MELD-CYSC correctly reclassified 22% of candidates (p < 0.001) driven by appropriate downward reclassification of survivors **(Panel 1b).** Among 1,299 candidates with measured LFI, Δ(cysC−sCr) correlated significantly with LFI (r 0.22, p < 0.001). When LFI was added to the MELD-CYSC variable set, Δ(cysC−sCr)'s hazard ratio fell from 1.58 to 1.20 while LFI itself emerged as the strongest predictor (HR 2.28 per unit, p = 0.002), consistent with LFI-measured frailty mediating the delta's prognostic signal. **Conclusion:** MELD-CYSC improves discrimination, calibration, and reclassification of 90-day waitlist mortality compared with MELD 3.0. The contribution of Δ(cysC−sCr) to WLM prediction is partially explained by LFI, suggesting muscle impairment as a biological mechanism through which cysC improves risk stratification beyond

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creatinine-based scores.

Panel 1a. Derived MELD-CYSC model (n = 2,083 candidates)

Variable	β (SE)	HR (95% CI)	p-value
log(Tot. Bilirubin)	0.75 (0.13)	2.12 (1.64–2.75)	<0.001
log(INR)	1.51 (0.38)	4.50 (2.15–9.41)	<0.001
log(sCr)	1.80 (0.27)	6.06 (3.54–10.35)	<0.001
Δ(cysC−sCr)	0.47 (0.25)	1.60 (1.02–2.70)	0.047

Panel 1b. MELD-CYS performance in validation cohort (n = 509 candidates)

Metric	MELD 3.0	MELD-CYSC	p-value
Median score (IQR)	19 (14–25)	18 (13–24)	—
Harrell's C (95% CI)	0.84 (0.77–0.92)	0.87 (0.80–0.94)	p=0.04
Calibration slope	0.18	1.06	p<0.001
NRI (95% CI)	reference	+22% (5–47%)	p<0.001

Disclosures: Giuseppe Cullaro:Ocelot Bio: Consultant, Retro Sciences: Consultant, Ipsen: Consultant, Taryn Liu:Nothing to Disclose, Jennifer Lai:Nestle Nutrition Institute: Grant/Research Support, Novo Nordisk: Consultant, Genfit: Consultant, Boehringer Ingelheim: Advisor, Lipocine: Site PI, Gilead: Site PI, Insmed: Consultant, Cosmo: Advisor, Benjamin Cho:Nothing to Disclose, Brian Lee:NIAAA: Grant/Research Support, Novo Nordisk: Advisor, GSK: Advisor, HepaTx: Advisor, Siemens Healthineers: Grant/Research Support, AltImmune: Advisor, Assertio: Consultant, Sean Lee: Nothing to Disclose, Sydney Whittaker:Nothing to Disclose, Stevan Gonzalez:Mallinckrodt Pharmaceuticals: Speaking and Teaching, Mallinckrodt Pharmaceuticals: Consultant, Madrigal Pharmaceuticals: Advisor, HEPQuant: Advisor, Daniel Woodfin:Nothing to Disclose, Zachary Fricker:Lipocine, Inc: Grant/Research Support, Pick Research: Consultant, River2-Renal Corp: Grant/Research Support, Bausch, Inc.: Grant/Research Support, Guidepoint Global, LLC: Consultant, WL Gore: Speaking and Teaching, Todd Frederick:Madrigal: Consultant, Mallinckrodt: Consultant, Salix: Grant/Research Support, Astra Zeneca: Grant/Research Support, River2Renal: Grant/Research Support, Ipsen: Consultant, HepQuant: Consultant, Miromatrix: Consultant, HepQuant: Consultant, Hugo Vargas:Sequana Medical: Consultant, Mallinckrodt: Consultant, Ocelot: Grant/Research Support, Arrowhead Phama: Grant/Research Support, Takeda: Grant/Research Support, Durect: Grant/Research Support, Durect: Grant/Research Support, River2Renal: Grant/Research Support, Genfit: Grant/Research Support, Kezar Pharmaceuticals: Grant/Research Support, Kezar Pharmaceuticals: Grant/Research Support, Bausch: Grant/Research Support, Sharon Lechtig-Wasserman:Nothing to Disclose, Douglas Simonetto: Mallinckrodt: Consultant, BioVie: Consultant, Resolution Therapeutics: Consultant, Evive: Consultant, Iota: Consultant, Novo Nordisk: Consultant, Astra Zeneca: Consultant, Miguel Gomez:Nothing to Disclose, Hani Wadei:Nothing to Disclose, Ibrahim Alhayani:Nothing to Disclose, Clara Tow:Madrigal: Advisor, Yixuan Du: Nothing to Disclose, Justin Belcher:Mallinckrodt Pharmaceuticals: Advisor, Kavish Patidar:Madrigal Pharmaceuticals: Medical Advisory Board, Mallincrodt Pharmaceuticals: Consultant, HepQaunt: Consultant, Mallinckrodt Pharmaceuticals: Medical Advisory Board, OrganOx: Advisor, Madrigal Pharmaceuticals: Advisor, Keenova Therapeutics: Advisor and Consultant., Keenova Therapeuatics: Advisor and Consultant, Novo Nordisk: Advisor, HepQaunt: Consultant, Keenova Therapeutics: Advisor and Consultant, HepQuant: Consultant, R. Mark Ghobrial:Nothing to Disclose, Eric Orman:Sitero: Consultant, Biovie: Advisor, Bausch Health: Consultant, Vertex: Consultant, Zydus: Consultant, Eccogene: Consultant, Zealand: Consultant, Andres Duarte-Rojo:Echosens: Grant/Research Support, Echosens: Grant/Research Support, CIMA Sciences: Consultant, HepQuant: Advisor, Merz: Advisor, CIMA Sciences: Grant/Research Support, Merz Therapeutics: Advisor, Seong Park:Nothing to Disclose, Elizabeth Verna:Nothing to Disclose, Andrew Allegretti: Nothing to Disclose.

4416 | XENOPAX PLUS INTRAOPERATIVE STEROID IMMUNOSUPPRESSION IN PEDIATRIC LIVER TRANSPLANTATION: A SINGLE-CENTER RETROSPECTIVE STUDY

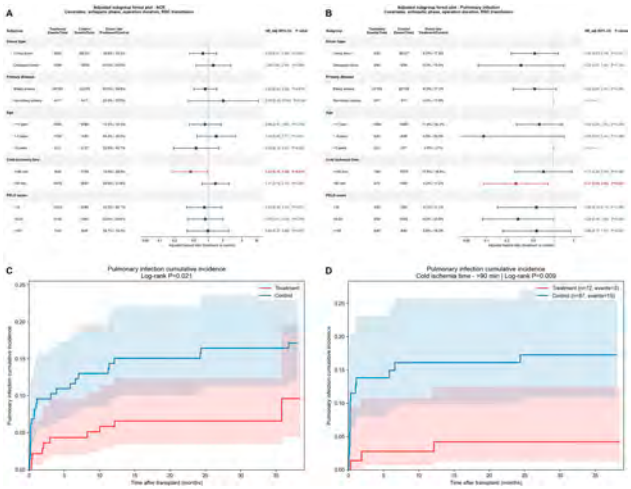
Shunqi Cao[1] Chong Dong[1], [1]Tianjin First Central Hospital

Background: Pediatric liver transplantation (LT) requires balanced immunosuppression to prevent acute cellular rejection (ACR) while limiting infections. Anti-CD25 induction improves outcomes; we evaluated xenopax, a novel humanized IL-2 receptor antagonist, combined with intraoperative methylprednisolone for early ACR and complication prevention. **Methods:** Single-center retrospective study of 283 consecutive pediatric LT recipients (age $\leq$6 years) undergoing first ABO-compatible LT between September 2021 and September 2023. All received intraoperative methylprednisolone (10mg/kg) and postoperative tacrolimus monotherapy.Xenopax group (n = 137): 1mg/kg on days 0 and +14. Basiliximab group (n = 146): 10mg (< 35kg) or 20mg($\geq$35kg) on days 0 and +4. Baseline characteristics were well balanced. Primary observation outcome : the incidence of ACR.Secondary outcome: infection. Analyses: Cox regression, Kaplan–Meier. **Results:** Median follow-up was 36.57 months (range 4.9–51.13 months). One-year ACR rates were similar (20.4% vs 25.3%, P = 0.402). However, in patients with cold ischemia time (CIT) $\leq$90 minutes, xenopax had a significantly decreased ACR risk trend (HR = 0.43, 95% CI: 0.19-0.99, P = 0.046). Xenopax also significantly reduced pulmonary infection (7.3% vs 17.1%, P = 0.020; Log-rank P = 0.021), with pronounced benefit in the CIT > 90 minutes subgroup (HR = 0.27, 95% CI 0.09–0.83, P = 0.022; Log-rank P = 0.009). **Conclusion:** Xenopax plus intraoperative steroids provides non-inferior ACR prophylaxis relative to basiliximab in pediatric LT, with a

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favorable safety profile marked by lower pulmonary infection risk—especially in patients with CIT >90 minutes. Patients with CIT ≤90 minutes may derive particular benefit for rejection prevention. This regimen is a promising induction strategy for pediatric liver transplantation.



Disclosures: Shunqi Cao:Nothing to Disclose, Chong dong:Nothing to Disclose.

4417 | COMPREHENSIVE OR EXCLUSIVE: A 10-YEAR EXAMINATION OF AGE-RELATED OUTCOMES AND DISPARITIES IN LIVING LIVER DONATION

Lindsay Beaman[1] Claire Cywes[2] Audrey Bankes[2] Alyssa Abbott[1] Robert Daniels[2] Ali Hamandi[2] Frank Lee[3] Weslyn Bunn[3] Tayyab Diwan[3], [1]Mayo Clinic Biomedical Ethics Research Program, [2]Mayo Clinic Alix School of Medicine, [3]Mayo Clinic

Background: Young adults (YAs, ages 18-25) are recognized as a vulnerable population in living donation due to age-related psychosocial concerns—such as perceived maturity, financial instability, and risk for later onset of psychiatric disorders. Thus, many transplant centers have adopted age-specific donation policies, including requiring additional psychosocial evaluations for YA donor candidates. This study aimed to examine the relationship between age and liver donor (LD) evaluation outcome and identify antecedent factors associated with denial for LD. **Methods:** All adult living LD candidates from 2014-2023 at a single institution were included. Groups were created based on age (18-25 versus greater than 25). Chi-square and Kruskall-Wallis were used to determine demographic differences and multivariable logistic regression was employed to assess the association between age group and LD. Covariables included the presence of medical or psychiatric comorbidities, area deprivation index (ADI), and presence of social issues. **Results:** There were 401 adults evaluated for living LD; 43 (10.7%) were YA. Overall, YA were denied at similar rates to older candidates (58.1% vs 61.5%, $p=0.674$). However, older candidates experienced more medical comorbidities (28.6% vs 51.1%, $p=0.012$) yet were denied at similar rates for this reason (18.6% vs 24.9%, $p=0.365$). Meanwhile, YA experienced significantly more psychosocial comorbidities (96.9% vs 79.3%, $p=0.016$) and were denied more often for this reason (9.3% vs 1.7%, $p=0.002$). On multivariable analysis, only the presence of medical comorbidities was associated with decreased likelihood of living LD (OR 0.423, 95% CI 0.259-0.690, $p=0.001$). Age, ADI, psychiatric comorbidities, and presence of social issues were not independently associated with LD. **Conclusion:** Our results indicate that despite greater rates of medical suitability, YAs experience similar rates of approval as older adults. This finding suggests that YAs may face unique barriers that are unaddressed by current age-specific selection practices, given that YAs were denied more often for psychosocial reasons. As such, concerns arise about the utilization of certain psychosocial measures—such as relationship status as a proxy for social support—and whether current evaluation practices may systematically disadvantage YAs whose support networks may be equally as robust but fail to be captured by the nature of the assessment. This poses critical questions about whether current practice truly ensures age-related assumptions do not lead to unnecessary denials and how we can best support this unique group of LD candidates.

Disclosures: Lindsay Beaman:Nothing to Disclose, Claire Cywes:Nothing to Disclose, Audrey Bankes:Nothing to Disclose, Alyssa Abbott:Nothing to Disclose, Robert Daniels:Nothing to Disclose, Ali Hamandi:Nothing to Disclose, Frank Lee:Nothing to Disclose, Weslyn Bunn:Nothing to Disclose, Tayyab Diwan:Nothing to Disclose.

4418 | NONLINEAR ASSOCIATION BETWEEN DONOR VASOACTIVE BURDEN AND GRAFT FAILURE AFTER LIVER TRANSPLANTATION: A NATIONAL UNOS REGISTRY ANALYSIS

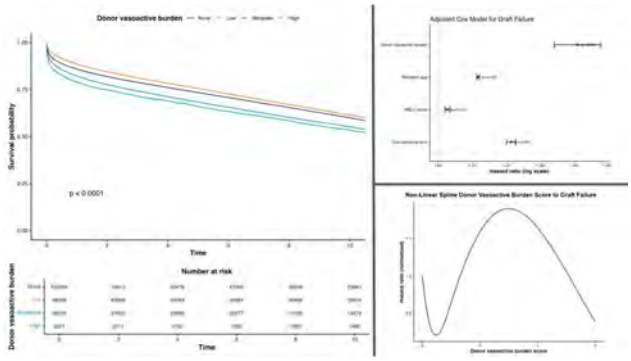
Narissa Nursjamsi[1] Elsa Sasongko[2] Kesava Manikanta Achuta[1] Abed Dabaja[1] Bashar Hmoud[1], [1]garden city hospital/msucom, [2]Faculty of Medicine, Universitas Padjadjaran

Background: Liver transplant numbers have increased yearly in the USA with up to 10% of grafts being non-functional at 1 year post transplant. While both donor and recipient factors contribute to outcomes, the impact of

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donor hemodynamic instability prior to procurement remains poorly characterized as a determinant of graft outcomes. **Methods:** This retrospective cohort study utilized the UNOS STAR 2010-2025 database. Adult liver transplant recipients were identified, excluding those ≤ 18 years old and transplanted before 2010. Variables collected include recipient demographics, MELD score, graft status, time to graft failure, recipient status, donor vasoactive exposure, and cold ischemia time. Donor vasoactive exposure are categorized as burden scores were classified into none (no exposure), low (1 agent), moderate (2-3 agents), and high (> 4 agents). Cold ischemia time was grouped as < 6 hours, 6-10 hours, and > 10 hours. The primary outcome was graft failure after liver transplantation. Graft survival was evaluated using Kaplan-Meier (KM) analysis with group comparisons using log-rank testing. Multivariable Cox models adjusted for recipient age, MELD score, and ischemic time. Restricted cubic spline analysis was performed to evaluate non-linear association between donor vasoactive burden score and graft failure. **Results:** Using UNOS STAR 2010-2025 data, 234,981 adult liver transplant recipients met the inclusion criteria (Mean age 53 years old, MELD score 21, and ischemic time 6.6 hours). KM analysis showed distinct separation in graft survival across donor vasoactive burden groups, with highest burden showed the worst outcomes and low burden showed most favorfable survival (log-rank p < 0.0001). On multivariable Cox analysis, donor vasoactive burden remained independently associated with graft failure (HR 1.04, p < 0.001) and showed the strongest predictor compared with age, MELD score, and ischemia time. Restricted cubic spline analysis confirmed a significant non-linear association between donor vasoactive burden and graft failure, with lowest risk at low burden followed by a progressive increase at higher levels. **Conclusion:** Donor vasoactive burden is an underrecognized,independent prognostic marker with a non-linear association with graft failure. As an immediate available donor metric, it may improve risk stratification and guide recipient selection and perioperative planning.



Disclosures: narissa nursjamsi:Nothing to Disclose, elsa sasongko:Nothing to Disclose, Kesava Manikanta Achuta:Nothing to Disclose, abed dabaja:Nothing to Disclose, bashar hmoud:Nothing to Disclose.

4419 | EARLY NATIONAL EXPERIENCE WITH LIVER TRANSPLANTATION FOR COLORECTAL LIVER METASTASES FOLLOWING NATIONAL LIVER REVIEW BOARD GUIDANCE

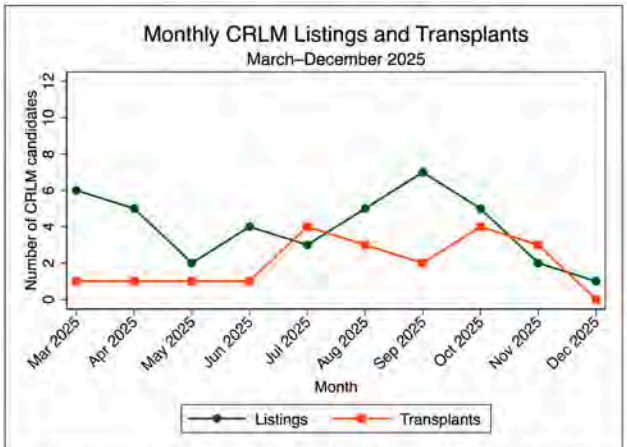
Benjamin Rosenthal[1] Therese Bittermann[1] Peter Abt[1] Samir Abu-Gazala[1] Maarouf Hoteit[1], [1]University of Pennsylvania

Background: Selected patients with unresectable colorectal liver metastases (CRLM) may achieve favorable outcomes after liver transplantation (LT). Candidates with unresectable or recurrent CRLM may be considered for LT if they have disease stability and no extrahepatic disease or local recurrence. The National Liver Review Board (NLRB) recommended CRLM exception scores of the center's median MELD at transplant (MMAT) minus 20, with a minimum score of 15. We hypothesize that utilization and outcomes vary across listing centers. **Methods:** This is a retrospective cohort study using UNOS/OPTN registry data to identify CRLM patients following implementation of NLRB guidance on February 27, 2025, through December 31, 2025. The primary exposure was center MMAT, calculated from all adult LT during study period, categorized into tertiles. Candidate-level variables included exception application status and waitlist outcome. Center level variables include number of CRLM listings and transplant yield, calculated as CRLM transplants divided by CRLM listings. Comparisons were performed using chi-squared, Fisher's exact and Kruskal-Wallis tests. **Results:** We identified 91 CRLM exception applications for 50 patients, two of whom applied for exception points at two centers. Patients were 76.9% White, had median ages of 48 (IQR 43-54), were 32.7% female and had median laboratory MELD of 7 (IQR 6-9). Twenty of 26 centers listed ≤2 candidates and only 2 centers listed >4 candidates. 57% of initial applications were approved, and 85% of patients submitted ≤2 applications. At the time of analysis, 25 candidates (48%) remained on the waitlist and 20 (39%) underwent LT at 10 centers. Among the 20 transplanted, 3 (15%) received living donor transplants, 17 (85%) received deceased donor transplants, 6 (35%) of which were from donors after circulatory death (DCD). Transplantation varied across MMAT tertiles: 67% of candidates at low-MMAT centers underwent transplant, compared to 21% and 18% at intermediate- and high-MMAT centers (p = 0.003). In center level analysis, mean center transplant yield was 84% per listing at low MMAT centers, compared to 33% and 8% among intermediate- and high-MMAT centers (p = 0.006). There was no association

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between donor age and use of DCD donors between MMAT tertiles. **Conclusion:** We identify variable access to transplant for CRLM depending on the listing center MMAT. These early findings suggest that assigning CRLM exception priority at a fixed MELD score may create geography-dependent access to transplantation. Longer follow-up is needed, but these data raise concern that current policy may not achieve equitable access.



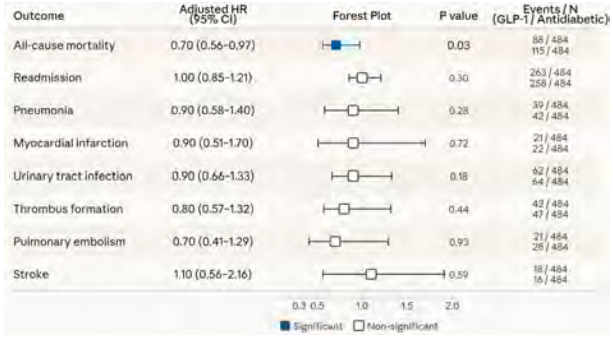
	Low MELD center MMAT 18-21, N=5 centers	Intermediate MELD center MMAT 22-25, N=9 centers	High MELD center MMAT 26.5-30, N=12 centers	Total N=26 centers	p-value
Patients, N (%)	21 (40)	14 (27)	17 (33)	52	-
Transplanted, N (%)	14 (67)	3 (21)	3 (18)	20	0.003
CRLM application approval	71%	86%	77%	76.9%	0.616
Centers with ≤2 CRLM listings, N (%)	2 (40)	7 (78)	11 (92)	20 (77)	0.048
Median waitlist days (IQR)	29 (12-126)	134.5 (31-190)	126 (56-247)	98 (29-177)	0.035
Mean center-level CRLM transplant yield, % (SD)	84 (29) %	33 (50) %	8 (19) %	32 (44) %	0.006

Disclosures: Benjamin Rosenthal:Nothing to Disclose, Therese Bittermann:Nothing to Disclose, Peter Abt: Nothing to Disclose, Samir Abu-Gazala:Nothing to Disclose, Maarouf Hoteit:Nothing to Disclose.

4420 | GLP-1 RECEPTOR AGONISTS ARE ASSOCIATED WITH LOWER 1-YEAR MORTALITY FOLLOWING HEPATECTOMY IN PATIENTS WITH TYPE 2 DIABETES: A PROPENSITY-MATCHED TRINETX COHORT STUDY

Shahzaib Zindani[1] Muhammad Qasim Chaudhry[1] Huzaifa Ansari[2] Zayed Rashid[3] Faiz Jajja[1] Syed Naqvi[1], [1]New York Medical College/Landmark Medical Center, [2]Dow University of Health Sciences, [3]Conemaugh Memorial Medical Center

Background: GLP-1 receptor agonists (GLP-1 RAs) have demonstrated cardioprotective, anti-inflammatory, and hepatoprotective properties beyond glycemic control. Hepatectomy carries substantial perioperative risk in patients with type 2 diabetes mellitus (T2DM), yet the impact of preoperative GLP-1 RA use on postoperative survival remains unknown. We evaluated postoperative outcomes in T2DM patients on GLP-1 RAs versus other antidiabetic agents undergoing hepatectomy. **Methods:** Using the TriNetX Research Network (111 healthcare organizations), adults with T2DM undergoing hepatectomy (January 2018–December 2024) with antidiabetic exposure within one year prior were identified. GLP-1 RA users (semaglutide, liraglutide, exenatide, dulaglutide, lixisenatide; GLP-1 RA-only) were compared to users of metformin, sulfonylureas, SGLT2 inhibitors, or DPP-4 inhibitors (GLP-1 RA-naive). Propensity score matching (1:1) on age, sex, race, ethnicity, BMI, ischemic heart disease, obesity, CKD, and nicotine dependence yielded 484 patients per cohort. Outcomes assessed at 1 year included all-cause mortality, readmission, surgical complications, pneumonia, MI, stroke, thrombus, pulmonary embolism, and UTI. **Results:** A total of 7,912 patients were identified pre-matching (GLP-1 RA: n = 484; other antidiabetics: n = 7,428). The GLP-1 RA cohort was younger (mean age 59.0 vs. 64.4 years), predominantly female (60.7% vs. 42.5%), and more commonly White (70.0% vs. 49.2%), with higher rates of obesity (43.0% vs. 18.6%) and CKD (36.4% vs. 22.5%) at baseline. After 1:1 propensity score matching (n = 484 per cohort), cohorts were well-balanced (mean age 59.0 vs. 59.6 years; female 60.7% vs. 60.5%; White 70.0% vs. 72.7%). GLP-1 RA use was associated with significantly lower 1-year all-cause mortality (18.2% vs. 23.8%; risk difference −5.6%, 95% CI −10.7 to −0.5; RR 0.77, 95% CI 0.60–0.98; OR 0.71, 95% CI 0.52–0.97; p = 0.033). Kaplan-Meier analysis confirmed superior 1-year survival (81.1% vs. 74.9%; log-rank p = 0.033; HR 0.74, 95% CI 0.56–0.98). Rates of readmission, surgical complications, pneumonia, MI, stroke, thrombus, pulmonary embolism, and UTI were similar between groups (all p > 0.05). **Conclusion:** In a propensity-matched real-world cohort, preoperative GLP-1 RA use was associated with a 26% reduction in 1-year all-cause mortality following hepatectomy in T2DM patients, without differences in major surgical or cardiorenal complications. These findings highlight a potentially important perioperative survival benefit of GLP-1 RAs in patients undergoing major hepatic resection, and support the need for prospective trials to validate these results.



Disclosures: Shahzaib Zindani:Nothing to Disclose, muhammad qasim chaudhry:Nothing to Disclose,

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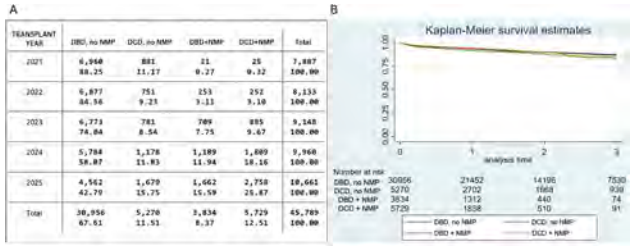
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Huzaifa Ansari:Nothing to Disclose, Zayed Rashid: Nothing to Disclose, Faiz Jajja:Nothing to Disclose, Syed Naqvi:Nothing to Disclose.

4421 | UNOS-BASED TRENDS IN NMP UTILIZATION AND OUTCOMES FOR DCD AND DBD LIVER TRANSPLANTATION BETWEEN 2021-2025

Ozge Ozgur[1] Shanmukh Lingamsetty[2] Umnia Shnawa[2] Malak Elsawy[2] Ahmet Gurakar[3] Behnam Saberi[4], [1]University of Pittsburgh Medical Center, [2]BIDMC, Harvard Medical School, [3]Johns Hopkins University, [4]BIDMC Harvard Medical School

Background: Liver transplantation increasingly relies on extended criteria donors, including donation after circulatory death (DCD) grafts, to expand the donor pool and meet rising organ demand. This has driven the need for advanced preservation strategies to mitigate ischemia–reperfusion injury. Normothermic machine perfusion (NMP) has emerged as a transformative platform to assess, resuscitate, and optimize donor liver quality prior to transplantation. **Methods:** We performed a retrospective cohort study of adult liver transplant recipients using deceased donor grafts from the UNOS database (2021–2025). Grafts were stratified into four groups: DBD without NMP, DCD without NMP, DBD + NMP, and DCD + NMP. The primary outcome was recipient survival up to 3 years, analyzed using Kaplan–Meier methods with log-rank testing and pairwise comparisons. **Results:** A total of 45,789 liver transplants were included. Over time, there was a marked shift in practice toward increased use of both DCD grafts and NMP. DBD without NMP remained the largest group (67.6%) but declined from 88.3% in 2021 to 42.8% in 2025. In contrast, DCD + NMP increased from 0.3% to 25.9%, and DBD + NMP from 0.3% to 15.6%. DCD without NMP also increased modestly from 11.2% to 15.8% (Figure 1A). Kaplan–Meier analysis demonstrated significant differences in recipient survival across groups (log-rank $p < 0.001$), with modest separation of survival curves. Pairwise comparisons showed that DBD + NMP differed significantly from DBD without NMP ($p < 0.001$), DCD without NMP ($p = 0.005$), and DCD + NMP ($p < 0.001$). No significant differences were observed between DBD without NMP and DCD without NMP ($p = 0.21$), DBD without NMP and DCD + NMP ($p = 0.34$), or DCD without NMP and DCD + NMP ($p = 0.51$) (Figure 1B). **Conclusion:** The use of normothermic machine perfusion increased rapidly across both DBD and DCD liver transplantation, alongside a concurrent rise in DCD graft utilization. Although overall survival differed across groups, this was primarily driven by outcomes in the DBD + NMP cohort, while survival among DBD without NMP, DCD without NMP, and DCD + NMP remained comparable. These findings suggest that expanding use of DCD grafts and NMP has not been associated with a uniform survival benefit or harm in early post-transplant outcomes. However, interpretation of long-term survival is limited by the recent adoption of NMP and shorter follow-up in later cohorts. Continued longitudinal assessment is needed to define durable outcomes of these evolving preservation strategies.



Disclosures: Ozge Ozgur:Nothing to Disclose, Shanmukh Lingamsetty:Nothing to Disclose, Umnia Shnawa:Nothing to Disclose, Malak Elsawy:Nothing to Disclose, Ahmet Gurakar:DURECT: Grant/Research Support, Orphalan: Advisor, ETON: Advisor, Behnam Saberi:Nothing to Disclose.

4422 | EVOLVING ACCESS AND OUTCOMES AMONG HIGH-MELD LIVER TRANSPLANT CANDIDATES IN THE UNITED STATES

Elias Rady[1] Ahmad Anouti[1] Lauren Matevish[1] Pojsakorn Danpanichkul[2] Sarah Lieber[1] Lisa VanWagner[1] Arjmand Mufti[1] Parsia Vagefi[1] Madhukar Patel[1], [1]University of Texas Southwestern Medical Center, [2]Texas Tech University Health Sciences Center

Background: Liver transplant allocation in the U.S. has increasingly prioritized medical urgency, yet the contemporary impact of these policy shifts on access to transplantation, donor-quality, and post-transplant outcomes among patients with high MELD scores (≥ 30) remains poorly understood. **Methods:** We analyzed United Network for Organ Sharing (UNOS) adult deceased donor liver transplant data across three eras (2010–2015, 2016–2020, 2021–2025), stratified by listing MELD score category (30–35, 36–40, >40). Outcomes included waitlist transplant rate and mortality (Fine-Gray competing risk models), transplant by 30 days, allocation distance and high-risk donor receipt (multivariable logistic regression), delta-MELD trajectory, and post-transplant survival (Kaplan-Meier and adjusted Cox models). **Results:** Among 102,419 adult liver transplants, the proportion of high-MELD recipients increased from 26.9%

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(N = 7,429/27,641) in 2010–2015 to 31.7% (N = 13,128/41,364) in 2021–2025. Etiology shifted substantially, with alcohol-related liver disease rising from 24.3% to 55.0% and viral hepatitis declining from 22.6% to 3.2% (both $p < 0.001$). Among MELD 30–35 candidates, 30-day transplantation increased from 56.8% to 78.7%, while 90-day waitlist mortality declined from 19.6% to 6.6%. Comparable improvements were seen among MELD 36–40 (30-day transplantation: 65.5% to 83.6%; 90-day mortality: 22.7% to 9.1%) and MELD > 40 candidates (30-day transplantation: 61.6% to 78.5%; 90-day mortality: 31.1% to 13.3%). Among MELD ≥ 30, multivariable analyses demonstrated increased likelihood of waitlist transplantation in 2016–2020 (sHR 1.29, 95% CI 1.25–1.33) and 2021–2025 (sHR 1.66, 95% CI 1.61–1.71) compared with 2010–2015, alongside substantially lower waitlist death (HR 0.61, 95% CI 0.57–0.65 and HR 0.51, 95% CI 0.48–0.54, respectively; all $p < 0.001$). In the 30 days before transplant, median ΔMELD declined by 2 points between 2010-2015 and 2020-2025 across all MELD categories. Median allocation distance for MELD > 40 recipients increased from 106 to 222 nautical miles, while allocation ≥ 250 nautical miles became significantly more common in 2021–2025 (OR 2.44, 95% CI 2.29–2.60). High-risk donor utilization was also more likely in the contemporary era (OR 1.34, 95% CI 1.22–1.47). One-year post-transplant survival improved from 89.2% to 94.2%, 88.5% to 92.7%, and 87.0% to 90.5% in MELD 30–35, 36–40, and > 40, respectively. However, adjusted interaction modeling demonstrated attenuation of survival gains among MELD > 40 recipients in the modern era (interaction HR 1.54, 95% CI 1.30–1.81, $p < 0.001$). **Conclusion:** High-MELD LT has expanded with marked reductions in waitlist mortality and improved post-transplant survival, but improved access was accompanied by broader geographic sharing, and significant waitlist mortality persists, particularly among MELD > 40 candidates.

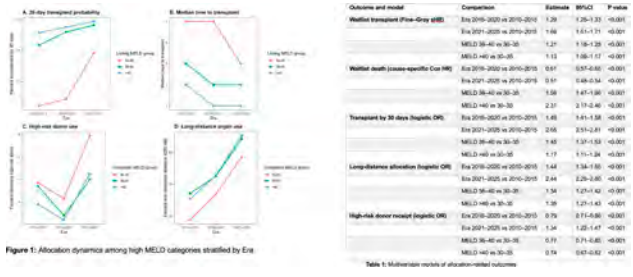


Figure 1: Allocation dynamics among high MELD categories stratified by Era

Table 1: Multivariable models of allocation-related outcomes

Disclosures: Elias Rady:Nothing to Disclose, Ahmad Anouti:Nothing to Disclose, Lauren Matevish:Nothing to Disclose, Pojsakorn Danpanichkul:Nothing to Disclose, Sarah Lieber:Nothing to Disclose, Lisa VanWagner:W.L. Gore & Associates: Grant/Research Support, Akero: Grant/Research Support, Madrigal: Grant/Research Support, Gerson Lehrman Group: Consultant, Madrigal: Advisor, Slingshot Insights: Consultant, Antheneum Partners: Consultant, Gerson Lehrman Group: Consultant, Alpha Insights: Consultant, Slingshot Insights: Consultant, Madrigal Pharmaceuticals: Grant/Research Support, W.L. Gore & Associates: Grant/Research Support, BD: Grant/Research Support, Medicolegal consulting: Consultant, Arjmand Mufti:Nothing to Disclose, Parsia Vagefi:Nothing to Disclose, Madhukar Patel:Nothing to Disclose.

★ 4423 | EXAMINING TOPICS, SENTIMENT, AND MEETING DYNAMICS IN LIVER TRANSPLANT CANDIDATE SELECTION PRACTICES: AN LLM-POWERED ANALYSIS

Sue Hyon Kim[1] Sy Hwang[1] Jacqueline Theroux[1] Abbie Jin[1] Douglas Schaubel[1] Megan Saucke[2] Brian Fisher[2] Esra Alagoz[2] Michael Lucey[2] Ethan Weinberg[1] Brian Lee[3] Danielle Mowery[1] Marina Serper[4], [1]University of Pennsylvania, [2]University of Wisconsin, [3]Keck School of Medicine, [4]University of Pennsylvania Health System

Background: Although prior studies have raised concerns about inconsistent liver transplant (LT) selection practices, we lack understanding whether the nature of discussion during liver transplant selection committee (LTSC) meetings influences listing decisions. Our study aim was to evaluate LTSC practices including topics, sentiments, and meeting dynamics, and link them to waitlist decisions. **Methods:** We analyzed transcripts of 27 LTSC meetings at two centers (> 1,000 pages of ~50 hours of discussion), using a large language model (LLM) to extract features for downstream statistical analysis. We included patient discussions that resulted in a decision, excluding re-evaluations of waitlisted patients and those with predetermined decisions pending preoperative clearance. Human experts annotated a representative 30% subset to establish the reference standard for LLM training and evaluation. Iterative prompt engineering was conducted using GPT-OSS-120b hosted on Microsoft Azure Databricks, a HIPAA-compliant cloud-based environment. Multivariable logistic regression was used to evaluate associations between patient characteristics, topics, sentiments, and meeting dynamics with waitlist decisions as the outcome; results with $p < 0.05$ are reported. **Results:** We included 175 LT candidate evaluations (58.3% male; mean age 54 years; 74.3% White). The mean MELD score was 20 ± 9. Alcohol-associated liver disease (ALD) was the most common primary indication for LT (58.3%), followed by viral or autoimmune hepatitis (26.3%) and metabolic dysfunction-related liver disease (15.4%); 40.0% of evaluations resulted in waitlist acceptance, 38.3% in deferral, and 21.7% in decline.There were variations in key topics discussed across etiology-decision groups (**Figure 1**). Initial introduction sentiments were mostly neutral across etiologies (67.4 - 74.1%) with a notable negative shift for 40.2% of discussions for patients with ALD. Most

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discussions were collegial (90.9%) with occasional tangential conversations (27.4%). Stigmatizing language was identified more often in ALD (23.5%) than non-ALD discussions (11%). We dichotomized waitlist outcomes (accept vs. defer or decline) and prioritized clinical features and meeting dynamics for logistic regression. Patients with concurrent hepatocellular carcinoma diagnosis were more likely to be accepted for LT (OR = 4.60). ALD etiology (vs. non-ALD, OR = 0.30) and discussions focused on chronic comorbidities (OR = 0.25) were associated with lower odds of acceptance. While initial introduction sentiments did not influence the final decision, negative overall sentiment was strongly associated with reduced odds of listing (OR = 0.02); discussions with tangential conversations were more likely to result in acceptance (OR = 4.10). **Conclusion:** Findings suggest that LT selection is an inconsistent process, influenced by biases toward certain etiologies and interpersonal dynamics.

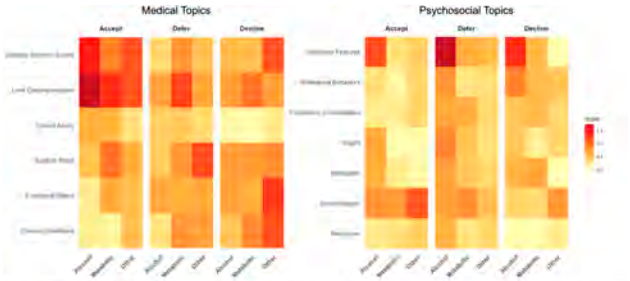


Figure 1. The LLM validated against human-annotated gold standards assigned decision weights to discussion topics (Low=0, Moderate=1, High=2). The heatmap shows greater variation in cases where decisions were to defer or decline. Medical topics predominated discussions of patients with metabolic dysfunction-related, viral, or autoimmune liver disease, whereas psychosocial topics carried more weight for patients with alcohol-associated liver disease who were deferred or declined.

Disclosures: Sue Hyon Kim:Nothing to Disclose, Sy Hwang:Nothing to Disclose, Jacqueline Theroux:Nothing to Disclose, Abbie Jin:Nothing to Disclose, Douglas Schaubel:Nothing to Disclose, Megan Saucke:Nothing to Disclose, Brian Fisher:Nothing to Disclose, Esra Alagoz:Nothing to Disclose, Michael Lucey:Nothing to Disclose, Ethan Weinberg:Nothing to Disclose, Brian Lee: NIAAA: Grant/Research Support, Novo Nordisk: Advisor, GSK: Advisor, HepaTx: Advisor, Siemens Healthineers: Grant/Research Support, AltImmune: Advisor, Assertio: Consultant, Danielle Mowery:Roche: Grant/Research Support, Marina Serper:Transplant Genomics: Grant/Research Support, Grifols: Grant/Research Support.

4424 | OUTCOMES OF LIVER TRANSPLANTATION USING DONORS AGED 70 YEARS AND OLDER: A

Michael Friedman[1] Dylan Russell[2] Navpreet Kaur[2] Linda Sher[3], [1]Keck School of Medicine of USC, [2]Keck Medicine of USC, [3]Keck Medical Center of USC

Background: Donor age is an established risk factor for inferior liver transplant outcomes, yet a persistent organ shortage has increased utilization of older donors in the US over the last decade. We examined patient and graft survival following liver transplantation from donors aged ≥ 70 years using a contemporary national registry to review the outcomes from this growing trend. **Methods:** We analyzed 72,120 adult recipients of whole deceased-donor liver transplants from the OPTN/UNOS STAR database from January 2015–December 2025 with multiorgan, living donor, pediatric, and those with previous transplants excluded. Recipients of organs from donors ≥ 70 years (n = 3,373) were compared with those from donors aged 18–69 years (n = 68,747). Primary outcomes were graft survival and patient survival. Death was a censoring event ensuring that it was not double counted in graft and patient survival. Unadjusted comparisons used Kaplan-Meier curves with the log-rank test. Adjusted analyses used multivariate Cox proportional hazards regression with 17 covariates. Fine-Gray subdistribution hazard regression addressed the competing risk of death in graft failure analyses. Propensity score matching (1:1 nearest-neighbor) served as a sensitivity analysis. **Results:** Donors aged ≥ 70 years represented 4.7% of the cohort. Five-year patient survival was 77.8% for donor-age ≥ 70 versus 81.7% for donors aged 18–69 (log-rank $p < 0.001$). Five-year graft survival was 74.7% versus 79.8% (log-rank $p < 0.001$). On multivariate analysis, receipt of an organ from a donor ≥ 70 was associated with a higher hazard of death (HR 1.17, 95% CI 1.07–1.28, $p < 0.001$) and graft failure (HR 1.30, 95% CI 1.20–1.41, $p < 0.001$). After propensity score matching, the excess graft failure risk persisted (HR 1.17, 95% CI 1.05–1.31, $p = 0.006$), whereas the patient survival difference was attenuated and non-significant (HR 1.08, 95% CI 0.96–1.22, $p = 0.195$). **Conclusion:** In a contemporary national cohort, liver transplantation from donors ≥ 70 years is associated with significantly reduced graft survival after accounting for recipient characteristics, transplant factors, and era. However, patient survival is not significantly reduced in donors ≥ 70 years in matched cohorts, which suggests that these organs should be reserved for recipients who would benefit most from more accessible organs with a higher failure rate.

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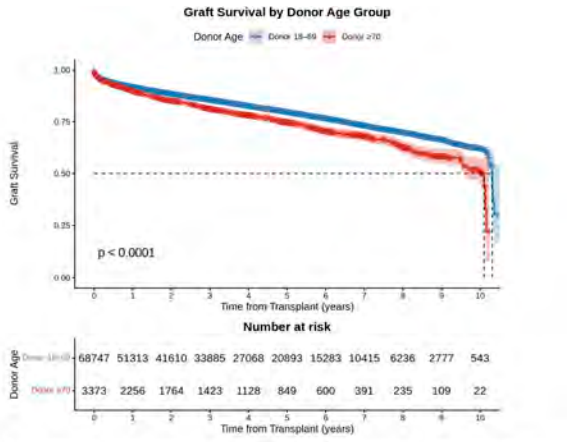


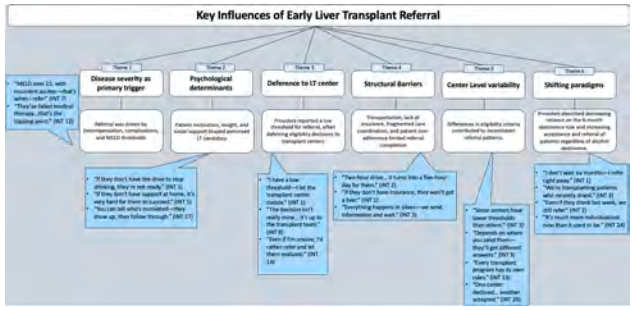
Figure 2: Kaplan-Meier curves for graft survival by donor age group (log-rank $p=2.92\times10^{-11}$). Number at risk shown below the panel. Shaded areas represent 95% confidence intervals.

Disclosures: Michael Friedman:Nothing to Disclose, Dylan Russell:Nothing to Disclose, Navpreet Kaur: Nothing to Disclose, Linda Sher:Nothing to Disclose.

4425 | BARRIERS AND FACILITATORS TO EARLY LIVER TRANSPLANT REFERRAL IN ALCOHOL-ASSOCIATED LIVER DISEASE: A MULTI-SITE QUALITATIVE STUDY WITHIN THE INTEGRATE COLLABORATIVE

Natasha Schaefer Solle[1] Sarah Lieber[2] Avesh Thuluvath[3] Aida vanMossel[1] Hemangi Dhole[2] Anne Fernandez[4] Jessica Mellinger[5] David Goldberg[1] Elizabeth Verna[6] Lisa VanWagner[2], [1]University of Miami, [2]University of Texas Southwestern, [3]Columbia Univesity, [4]Rutgers University, [5]Henry Ford Health-Michigan State University, [6]Columbia University

Background: Alcohol-associated liver disease (ALD) is the leading indication for liver transplantation (LT) in the United States. Although evidence supports early LT (eLT), defined as LT with <6 months of abstinence, many eligible patients are not referred for LT, resulting in potentially preventable mortality. As part of the INTEGRATE cohort, a multi-site, multidisciplinary research collaborative examining eLT across the care continuum, this study identifies barriers and facilitators influencing referral for eLT in ALD. **Methods:** Semi-structured qualitative interviews were conducted with healthcare providers across four INTEGRATE sites (Florida, Texas, New York, and Michigan). Eligible participants included physicians and advanced practice providers (APPs) providing ALD care, including referring patients to transplant centers for LT evaluation. Interviews were conducted virtually by an experienced qualitative researcher, audio recorded, and transcribed verbatim. Data were analyzed using constant comparative methods with an inductive thematic approach. Recruitment continued until thematic saturation was achieved. **Results:** Twenty-four providers participated with a mean age of 49 years (range 28–73) with a mean of 17 years of clinical experience (range 1- 40). A majority were physicians (83%), with APPs comprising 17% of the cohort. Participants were predominantly male (67%) and practiced across private and academic settings. Six themes emerged as key influences of eLT referral. (1) Disease severity as the primary trigger: Referral was driven by decompensation, complications, and MELD thresholds. (2) Psychosocial determinants: Patient motivation, insight, and social support shaped perceived LT candidacy. (3) Deference to LT center: Providers reported a low threshold for referral, often deferring eligibility decisions to transplant centers. (4) Structural barriers: Transportation, lack of insurance, fragmented care coordination, and patient non-adherence limited referral completion. (5) Center-level variability: Differences in eligibility criteria contributed to inconsistent referral patterns. (6) Shifting paradigms: Providers described decreasing reliance on the 6-month abstinence rule and increasing acceptance and referral of patients regardless of alcohol abstinence. **Conclusion:** Early LT referral for ALD is shaped by a complex interplay of clinical severity, psychosocial judgments, and structural determinants. While providers increasingly support early referral, significant barriers persist at patient and system levels, contributing to heterogeneity in referring practices. Interventions targeting care coordination, behavioral health integration, and structural barriers are needed to optimize timely referral and improve outcomes.



Disclosures: Natasha Schaefer Solle:Nothing to Disclose, Sarah Lieber:Nothing to Disclose, Avesh Thuluvath:Nothing to Disclose, Aida vanMossel:Nothing to Disclose, Hemangi Dhole:Nothing to Disclose, Anne Fernandez:Nothing to Disclose, Jessica Mellinger:GlaxoSmithKline: Advisor, GlaxoSmithKline: Consultant, Novo Nordisk: Consultant, GlaxoSmithKline: Advisor, Boehringer Ingelheim: Consultant, GlaxoSmithKline: Consultant, Novo Nordisk: Consultant, Boehringer Ingelheim: Consultant, GlaxoSmithKline:

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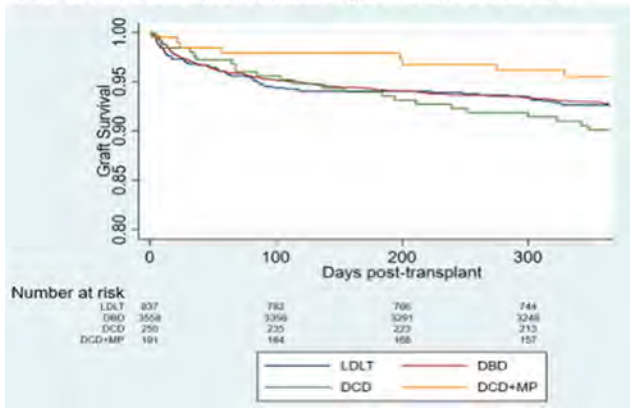
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4426 | DOES ALLOGRAFT TYPE IMPACT OUTCOMES IN PATIENTS WHO UNDERGO TRANSPLANT FOR PSC?

Yael Nobel[1] Russell Rosenblatt[2], [1]Columbia University Irving Medical Center, [2]Weill Cornell Medicine

Background: Graft selection for liver transplant (LT) in primary sclerosing cholangitis (PSC) is complicated by the high risk of biliary strictures, arising from conditions ranging from recurrent disease to a graft-related processes like ischemic cholangiopathy (IC). DCD allografts are associated with IC and have traditionally been used with caution in PSC. While machine perfusion has reduced non-anastomotic biliary stricture rates after DCD in LT broadly, its impact in PSC, and the impact of allograft type more generally, remain unknown. Therefore, we analyzed the association of allograft type with clinical outcomes after LT for PSC. **Methods:** The UNOS STAR file was queried for adults listed for LT from 2010–2024 with PSC. Graft types were living donor (LD), donation after brain death (DBD), DCD alone, or DCD with machine perfusion (DCD+MP). Three analyses were performed comparing outcomes based on graft type: 1. Patient survival from time of listing, 2. Short-term (1 year) patient and graft survival following LT, and 3. Long-term (after 1 year) patient and graft survival following LT. Cox proportional hazards regressions were performed with DBD as the reference group, adjusting for *a priori* selected covariates including recipient age, sex, MELD, exception points, and cholangiocarcinoma. A sensitivity analysis was performed using patients with primary biliary cholangitis (PBC) to assess if cholestatic diseases had similar outcomes. **Results:** 7,003 patients with PSC were included: 838 (12.0%) LD, 3,571 (51.0%) DBD, 251 (3.6%) DCD alone, 191 (2.7%) DCD+MP, and 2,152 (30.7%) who were not transplanted. LD recipients were younger with lower MELD scores and less severe disease at listing. In Analysis 1, from time of listing, receipt of any LT was associated with markedly improved survival compared to no LT (HR 144, 95%CI 78–269). The unadjusted survival advantage of LD compared to deceased donor LT did not persist after multivariable adjustment. In Analysis 2, after LT pairwise unadjusted log rank testing between graft types showed improved graft survival with DCD+MP vs. DCD alone ($p = 0.04$; Figure 1). However, there were no significant differences in graft or patient survival after adjusting for covariates. Finally, in Analysis 3, starting from 1 year post-LT, the unadjusted patient survival advantage of LD over DBD ($p = 0.01$) was again not significant after adjustment. Of note, only 60% of patients who received DCD+MP were included in the landmark analysis due to the recency of use. Findings were similar in the PBC sensitivity analysis. **Conclusion:** In this large national registry cohort, receiving a transplant by any means, not the allograft type, was independently associated with improved patient survival after LT for PSC. These findings do not support exclusion of DCD allografts in PSC recipients. Machine perfusion may improve early graft survival in DCD recipients, warranting further study.

Figure 1. Graft survival within one year post-transplant based on allograft type (Analysis 2). LDLT: living donor liver transplant. DBD: Donation after brain death organ. DCD: Donation after cardiac death organ. DCD+MP: Donation after cardiac death organ with machine perfusion.



Disclosures: Yael Nobel:Mirum Pharmaceuticals: Consultant, Russell Rosenblatt:Gilead: Grant/Research Support.

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4427 | COMPARATIVE OUTCOMES OF OPEN, HYBRID, LAPAROSCOPIC, AND ROBOTIC HEPATECTOMY FOR LIVING LIVER DONORS: A NETWORK META-ANALYSIS

Puneet Bansal[1] Mohammed Quazi[2] Eric Welwin[3] Abdul Awan[4] Muhammad Ahmad Nadeem[5] Chase Wehrle[5] Federico Aucejo[5] Jaekeun Kim[5] Choon Kwon[5] Mazhar Khalil[5], [1]Cleveland Clinic Foundation, [2]Department of Family and Community Health, West Virginia University, [3]City College of New York School of Medicine, [4]Nishtar Medical University, [5]Digestive Disease and Surgery Institute, Cleveland Clinic

Background: Living donor hepatectomy is essential to expanding the donor pool in liver transplantation but exposes otherwise healthy individuals to the risks of major hepatic resection, making donor safety paramount. Minimally invasive techniques have been increasingly adopted to reduce surgical morbidity, yet a comprehensive comparison across all available approaches is lacking, as existing data are largely derived from pairwise studies. We aimed to evaluate perioperative and postoperative outcomes across open, hybrid, laparoscopic, and robotic donor hepatectomy. **Methods:** Four databases were searched from inception to December 2025 for studies comparing open, laparoscopic, and robotic hepatic donor resections. A Bayesian network meta-analysis assessed differences in perioperative outcomes, post-operative complications, and hospital stay. **Results:** Thirty-one studies were included. Robotic hepatectomy was associated with longer operative time compared with open, hybrid, and laparoscopic approaches. Laparoscopic hepatectomy demonstrated higher conversion rates to open surgery than robotic surgery (OR [95% CrI]: 5.47 [1.19-52.89]). Estimated intraoperative blood loss was lower with robotic hepatectomy compared with open surgery, though no significant differences were observed relative to laparoscopic or hybrid approaches. Hospital stay was significantly longer after open hepatectomy compared with laparoscopic, with no differences compared to hybrid or robotic approaches. Robotic hepatectomy had lower odds of overall postoperative complications compared with open (OR [95% CrI]: 0.34 [0.18-0.65]), with no significant differences compared with hybrid or laparoscopic approaches. No significant differences were observed in bile leak, wound complications, Clavien-Dindo grade ≥ III complications, or reoperation rates amongst all modalities. **Conclusion:** Minimally invasive donor hepatectomy demonstrated favorable perioperative and postoperative outcomes compared with open surgery. Despite longer operative times, robotic approaches were associated with lower blood loss and fewer complications, supporting their selective use with appropriate patient selection and institutional expertise. These findings can help inform surgical approach selection while preserving donor safety as the foremost priority, though prospective and randomized studies are warranted to confirm these comparative benefits given the observational nature of the included evidence.

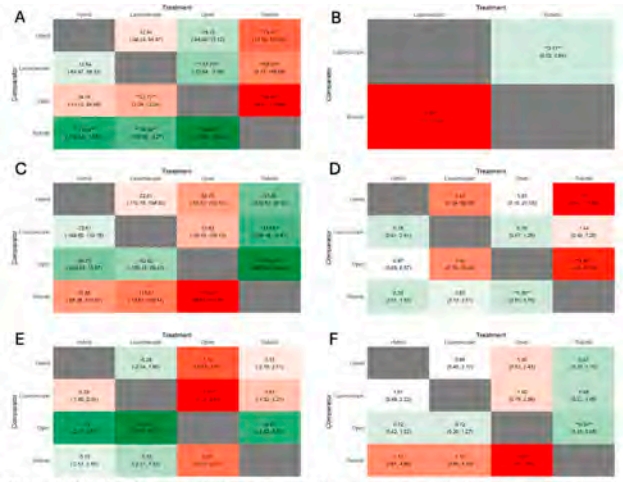


Figure 1. Pairwise Bayesian network meta-analysis comparing donor outcomes across surgical approaches for living donor hepatectomy. Heatmaps display pooled effect estimates with 95% credible intervals for each pairwise comparison, with the column-defined treatment compared against the row-defined comparator. Double asterisks indicate significance. Panels depict operative time **(A)**, conversion **(B)**, estimated blood loss **(C)**, bleeding events **(D)**, length of stay **(E)**, and overall complications **(F)**.

Disclosures: Puneet Bansal:Nothing to Disclose, Mohammed Quazi:Nothing to Disclose, Eric Welwin:Nothing to Disclose, Abdul Awan:Nothing to Disclose, MUHAMMAD AHMAD NADEEM:Nothing to Disclose, Chase Wehrle:Nothing to Disclose, Federico Aucejo:Nothing to Disclose, Jaekeun Kim:Nothing to Disclose, Choon Kwon:Nothing to Disclose, Mazhar Khalil:Nothing to Disclose.

4428 | PREHABILITATION IN HPB SURGERY: HEPATECTOMY OUTCOMES FROM A SYSTEMATIC REVIEW AND META-ANALYSIS

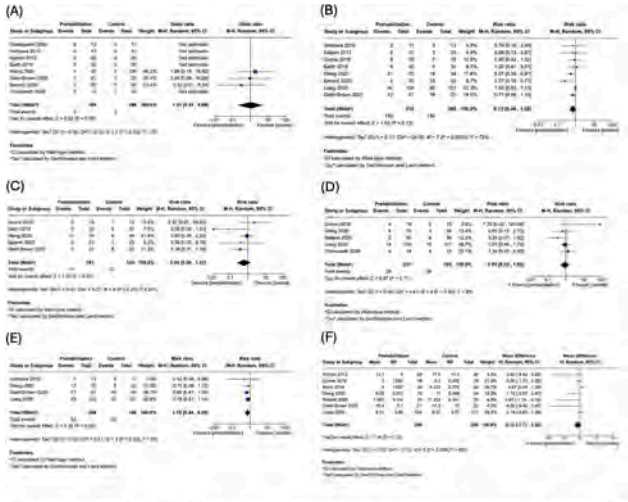
Eitan Dines[1] Danhui Heo[2] Agata Grochowska[3] Mariana Del Col[4] Affan Asim[5] Ahmad Mahamid[1], [1]Technion Israel Institute of Technology, Rappaport Faculty of Medicine, Haifa, Israel, [2]Doctoral School of Experimental and Preventive Medicine, Albert Szent-Györgyi Medical School, Univer, [3]Norbert Barlicki Memorial Teaching Hospital No. 1 of the Medical University of Lodz, [4]Nacional University of Mar del

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Background: Hepatectomy remains associated with significant postoperative morbidity and mortality. Modifiable factors have emerged as critical predictors of adverse outcomes. Prehabilitation aims to enhance physiological reserve to withstand surgical stress. Despite growing application, its specific impact on outcome after hepatectomy remains to be fully synthesized. **Methods:** A systematic review and meta-analysis of prehabilitation in HPB surgery was conducted following PROSPERO and PRISMA guidelines using PubMed, EMBASE, and Cochrane CENTRAL. Eligible interventions required ≥ 1 week of preoperative unimodal or multimodal prehabilitation. Outcomes included mortality, overall complications, major complications (Clavien-Dindo ≥ 3), global pulmonary morbidity, readmission, and length of stay. Random-effects meta-analyses were performed using Mantel-Haenszel and inverse variance methods. Effect estimates were expressed as Risk Ratio (RR), Odds Ratio (OR) for rare events such as mortality, and Mean Difference (MD) with 95% confidence intervals (CI). Heterogeneity was assessed via I^2. Here, we only report the hepatectomy subgroup analysis. **Results:** Eleven studies on prehabilitation for hepatectomy were included. Extractable data from 8 studies demonstrated that 197 of 263 patients completed the program (compliance 74.9%). Diet and exercise were the most frequent unimodal interventions; most programs were predominantly home-based. Prehabilitation significantly reduced pulmonary morbidity (RR 0.72; 95% CI 0.54–0.95; $P = 0.02$; $I^2 = 0\%$). No significant differences were observed in overall complications (RR 0.73; 95%CI 0.49–1.09; $P = 0.13$; $I^2 = 72\%$), major complications (RR 0.59; 95%CI 0.26–1.37; $P = 0.22$; $I^2 = 24\%$), readmission (RR 0.90; 95%CI 0.52–1.56; $P = 0.71$; $I^2 = 9\%$), or LOS (MD -0.72 days; 95%CI -1.77–0.34; $P = 0.18$; $I^2 = 65\%$). Mortality was a rare event across studies, with no significant difference observed between groups (OR 1.01; 95%CI 0.21–4.86; $P = 0.99$; $I^2 = 0\%$). **Conclusion:** Prehabilitation prior to hepatectomy is safe, shows strong compliance, and significantly reduces postoperative pulmonary morbidity. A protective trend toward fewer overall and major complications was observed, though it did not reach statistical significance. Limitations include the high heterogeneity of prehabilitation programs and the lack of consistent outcome reporting across studies. Larger, standardized RCTs are warranted to firmly establish its broader impact on surgical outcomes.



Forest plots comparing prehabilitation versus control in patients undergoing liver surgery. (A) Mortality, (B) Overall complications, (C) Major complications (Clavien-Dindo grade ≥ 3), (D) Readmission, (E) Global pulmonary morbidity, and (F) Length of hospital stay

Disclosures: EITAN DINES:Nothing to Disclose, Danhui Heo:Nothing to Disclose, Agata Grochowska: Nothing to Disclose, Mariana Del Col:Nothing to Disclose, Affan Asim:Nothing to Disclose, Ahmad Mahamid:Nothing to Disclose.

4429 | FOLEY CATHETER-BASED INTRAPERITONEAL VERSUS TOURNIQUET-STYLE EXTRAPERITONEAL PRINGLE MANEUVERS IN LAPAROSCOPIC HEPATECTOMY: PERIOPERATIVE OUTCOMES AND EARLY POSTOPERATIVE LIVER FUNCTION RECOVERY

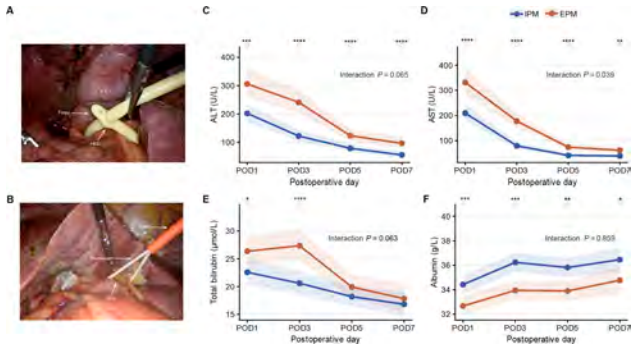
Shenao Zhang[1] Lei Wu[2] Zhihong Chen[3] Haosheng Jin[4] Shi Ning[4] Shunan Zhou[4], [1]School of Medicine South China University of Technology, [2]Guangdong Cardiovascular Institute, [3]Department of Liver Surgery, Peking Union Medical College Hospital, [4]Department of Hepatobiliary Surgery, Guangdong Provincial People's Hospital

Background: Effective bleeding control during parenchymal transection is critical for laparoscopic liver resection (LLR). Intermittent Pringle occlusion is widely used for inflow control, but whether different occlusion configurations influence early postoperative hepatocellular injury remains unclear. This study compared Foley catheter–based intraperitoneal Pringle maneuver (IPM) with tourniquet-style extraperitoneal Pringle maneuver (EPM) in terms of perioperative outcomes,

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and early postoperative liver function recovery. **Methods:** In this retrospective cohort study (October 2024–February 2026), 110 patients undergoing LLR were classified by predominant inflow occlusion technique: Foley catheter-based IPM or tourniquet-style EPM, with 55 patients in each group.Intraoperative outcomes, postoperative recovery, 30-day complications, and post-hepatectomy liver failure (PHLF) were compared. Postoperative alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBil), and albumin (ALB) levels on postoperative days (POD) 1, 3, 5, and 7 were analyzed using propensity score-weighted linear mixed-effects models (LMMs). Overlap weighting (OW) was the primary analysis, and inverse probability of treatment weighting was used as a sensitivity analysis. **Results: Results:** : Occlusion frequency, cumulative occlusion time, operative time, and blood loss were similar between groups. IPM was associated with a lower postoperative drainage volume than EPM (688.0 vs. 1093.0 mL, $P < 0.001$) and a shorter drainage duration ($P = 0.032$). Within the OW cohort, the IPM group exhibited lower AST and ALT levels at POD1, 3, 5, and 7 (all $P < 0.01$), alongside consistently higher ALB levels throughout the observation period (all $P < 0.05$). TBil levels in the IPM group were lower on POD 1 and 3 ($P < 0.05$) , but no statistical differences were observed on POD 5 and 7. In OW, the group-by-time interaction was significant for AST ($P = 0.039$). Major complications (1.82% vs. 0%) and PHLF (14.55% vs. 18.18%) did not differ significantly. **Conclusion:** Compared with EPM, Foley catheter-based IPM was associated with a more favorable early postoperative biochemical profile, with the most prominent statistical evidence observed for AST. These findings support Foley catheter-based IPM as an advantageous and feasible inflow occlusion technique in LLR.



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4430 | LIVER TRANSPLANTATION IN THE ELDERLY: OUTCOMES AND EXPANDING TRANSPLANT CANDIDACY IN PATIENTS AGED 75 AND OLDER

Kevin Harris[1] Mohammed Abusuliman[1] Nirajan Budhathoki[1] Dilip Moonka[1], [1]Henry Ford Health

Background: Liver transplantation (LT) is an effective treatment for patients with end stage liver disease. In recent years, there has been an increase in organ availability in part due to normothermic machine perfusion and improved therapy for hepatitis C. We looked at LT outcomes in patients 75 years and older, using the United Network for Organ Sharing (UNOS) registry to determine if this is a potential population for expansion. **Methods:** The UNOS database was queried for patients ≥ 18 y/o undergoing initial, liver alone, deceased donor LT from 1/1/2015 to 6/30/2025. Patients were grouped by age: 18–49, 50–59, 60–69, 70–74, and 75+ years. Groups were compared for patient and donor characteristics and for graft survival using Kaplan-Meier analysis with log-rank test and multivariate analysis. **Results:** A total of 96,218 LT were performed between 1/1/2015 and 6/30/2015. 73,521 patients met criteria. Of these patients, 332 were ≥ 75 y/o (0.45%) and six patients were 80 or older. There has been consistent growth in LT in patients ≥ 75 y/o over the years of the analysis from 16.7 LT per year from 2015-2018 to 52.3 from 2023-2025. When compared to younger patients, patients ≥ 75 y/o were less likely to be black (3.3% vs 9.7%), less likely to have alcoholic cirrhosis (11% vs. 43%) and more likely to have MASH (25% vs 7.3%) and HCC (51% vs 5.9%). Patients ≥ 75 y/o were more likely to have a Karnofsky score of 70-100% (41% vs 25%) and had a lower laboratory MELD at transplant (17 vs 30). Patients ≥ 75 y/o were more likely to have cold ischemia time of ≥ 8 hours (30% vs 23%) and to have received a donation after circulatory death liver (20% vs. 12%). All differences were significant at $P < 0.001$. In patients ≥ 75 y/o, one year graft survival was 85.2% (95% CI: 81.2 - 89.4), three-year graft survival was 76.2% (95% CI: 71.1 - 81.7) and five-year graft survival was 70.1 (95% CI: 64.0 – 76.8) (Table 1). On multivariate analysis, there was no statistically significant difference in survival between patients ≥ 75 y/o and those 70-74 with a hazard ratio of 0.87 (95% CI: 0.69 – 1.10: $P = 0.238$) but there were significant differences with all other age groups: 60-69 y/o (HR 0.76: 95% CI: 0.60 – 0.96: $P = 0.022$) ages 50-59 (HR 0.62: 95% CI:0.49 – 0.79: $P < 0.001$), ages 18-49 (HR 0.61: 95% CI 0.48 – 0.78: $P < 0.001$). On univariate and multivariate analysis, no one patient or donor variable was associated with worse outcomes in patients ≥ 75 y/o presumably because of low numbers. **Conclusion:**

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Liver transplantation in patients over the age of 75 is feasible with acceptable one- and three-year graft survival. Patients in this age group had favorable patient characteristics but not donor characteristics. Despite the acceptable graft survival, liver transplantation in patients over the age of 75 is rare. With increasing organ availability, liver transplantation should be considered a viable treatment option in select patients above the age of 75.

	Age Group				
Survival, % (95% CI)	18-49	50-59	60-69	70-74	75+
1-year	93.2 (92.8 – 93.5)	92.3 (92.0 – 92.7)	90.6 (90.3 – 91.0)	89.3 (88.3 – 90.3)	85.2 (81.2 – 89.4)
3-year	87.7 (87.1 – 88.2)	86.8 (86.3 – 87.3)	83.3 (82.8 – 83.8)	79.4 (77.9 – 80.9)	76.2 (71.1 – 81.7)
5-year	82.5 (81.8 – 83.2)	81.2 (80.6 – 81.8)	76.2 (75.6 – 76.9)	71.7 (69.9 – 73.6)	70.1 (64.0 – 76.8)
10-year	64.8 (62.0 – 67.9)	61.9 (59.9 – 63.9)	51.7 (49.6 – 53.9)	37.9 (30.8 – 46.7)	insufficient data

Table 1. Graft survival estimates from Kaplan-Meier method

Disclosures: Kevin Harris:Nothing to Disclose, Mohammed Abusuliman:Nothing to Disclose, Nirajan Budhathoki:Nothing to Disclose, Dilip Moonka:Gilead: Speaking and Teaching, Madrigal: Speaking and Teaching.

4431 | LIVER TRANSPLANT ALLOCATION BY MILAN CRITERIA EXCLUDES ELIGIBLE HCC PATIENTS WITHOUT SURVIVAL BENEFIT – A POST-HOC ANALYSIS OF THE SILVER STUDY

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Background: Selection criteria for liver transplant allocation are crucial for benefit-risk assessment of every patient evaluated for liver transplantation (LTx). Currently, Milan criteria are the key decision tool in several countries to assess whether a patient with hepatocellular carcinoma (HCC) is eligible for LTx. In this post-hoc analysis of the SiLVER Study, we analysed the performance of Milan criteria compared to the broader criteria UCSF, Up-to-7 and MT 2.0 to assess whether there is need to reform the selection process of HCC patients evaluated for LTx. **Methods:** Outcomes of 485 patients of the multicentre and randomized SiLVER Study were analysed determined by recurrence-free survival (RFS), overall survival (OS) and freedom of tumor (FoT). **Results:** All three more broadly inclusive criteria outperformed Milan in all three analysed outcome categories in terms of classification accuracy. Up-to-7 classified patients with the highest accuracy, especially regarding FoT with a correct classification of 78.8%, versus Milan at 67.4%. Simultaneously, categorizing patients inside the broader defined scores did not result in worse outcomes, compared to patients classified inside Milan. **Conclusion:** Our data suggest that Milan criteria exclude patients with HCC evaluated for LTx too strictly without an oncological or survival benefit, questioning Milan criteria as sole selection tool in many regions doing liver transplants.

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4432 | ANALYZING GROUP DYNAMICS OF TUMOR BOARD DISCUSSION DURING MULTIDISCIPLINARY MANAGEMENT OF HEPATOCELLULAR CARCINOMA

Norine Chan[1] Whitney Welsh[1] Allison Martin[1] Michela Fabricius[1] Andrew Muir[2] Peter Allen[1] Lisa McElroy[1], [1]Duke University Hospital, [2]Duke University

Background: Consensus management is the standard of care for hepatocellular carcinoma (HCC) and occurs through multidisciplinary tumor board conferences (MDC), which are associated with improved patient survival. Despite known impacts of group discourse, team composition, and interpersonal dynamics on decision-making, there has been limited exploration of group interactions during MDC-based HCC discussions. This study aims to characterize patterns of group dynamics during MDC discussions of HCC. **Methods:** We performed a prospective, single-center qualitative study of HCC cases during virtual weekly hepatopancreatobiliary (HPB) MDCs, which were recorded from January to April 2026. Team-based coding of all transcripts was performed with three analysts simultaneously and content analysis was used to identify dominant themes. **Results:** Across 14 MDCs, a total of 226 patients were discussed, of which 63 (27.9%) were HCC cases. 90 clinical team members participated during the study period, consisting of gastroenterologists/hepatologists (26.7%), advanced practice providers (16.7%), transplant/HPB surgeons (14.4%), medical oncologists (12.2%), fellows/residents (10%), diagnostic radiologists (8.9%), interventional radiologists (IRs) (6.7%), radiation oncologists (3.3%), and pathologists (1.1%). Three main interaction patterns were identified: clinician deference, direct naming, and group priming. Clinician deference occurred in settings

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of treatment decision-making, additional imaging requests, and subject expertise. Deference was typically observed across specialties with hepatologists being the most common initiators (50%). Surgeons were deferred to most often (50%) followed by medical oncologists (25%). Direct clinician naming was a mechanism of engagement for treatment discussion, clinical expertise, attendance confirmation, and referral to colleagues. IRs were named most often (37.5%); in contrast, hepatologists named others in 31% of cases but were only named in 6.9% of cases. Surgeons exhibited comparable frequencies of being named (31.9%) and naming others (39.4%). During complex discussions, group priming was used by hepatologists and diagnostic radiologists to convey clinical ambiguity. Surgeons used priming less often but were more likely to declaratively communicate their assessments. **Conclusion:** Surgeons, interventional radiologists, and medical oncologists were found to be dominant influences during tumor board discussion of HCC. Hepatologists, despite being highly represented in MDC participation, were infrequently engaged directly and more likely to introduce uncertainty and deference in their clinical assessments. Understanding group dynamics among professional roles can inform development of standardized MDC guidelines and practices that mitigate potential bias, ensure balanced participation, and promote a culture of engagement across specialties.

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4433 | WHAT PATIENTS ARE SAYING: AN ANALYSIS OF LIVER TRANSPLANT DISCUSSIONS ON REDDIT

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Background: Liver transplant patients, donors, and caregivers face significant informational and emotional burdens across all stages of the transplant journey, with prior studies documenting persistent unmet informational and psychosocial needs extending well into the post-transplant period. Despite this, gaps remain in understanding patient and caregiver experiences beyond formal clinical interactions. Social media platforms such as Reddit host unsolicited, real-world narratives that may capture these unmet needs at scale. Understanding how these communities engage online may inform targeted improvements in transplant education and care delivery. **Methods:** Reddit posts were scraped from three liver transplant-related subreddits (r/Transplant, r/LiverDisease, r/FattyLiver-NAFLD). Of 16,912 posts collected, the top 3,000 by engagement score were retained, then filtered to 983 posts containing substantive liver transplant discussion (January 2023–May 2025). Each post was classified across ten dimensions using Claude (Anthropic), including: author perspective, transplant stage, sentiment, emotional tone, presence of care gaps, and medical team sentiment. **Results:** Of 983 posts, 55.3% were authored by transplant recipients and 12.3% by caregivers, and 73.1% were pre-transplant. Nearly half (45.0%) of posts were negative in sentiment, while only 17.4% were positive. Sentiment shifted significantly ($p < 0.05$) across stages: pre-transplant posts were predominantly negative, peri-transplant posts showed a reversal with positive sentiment prevailing, and post-transplant posts demonstrated equalization of positive and negative sentiment (Fig 1A). Anxiety was the dominant emotional tone (61.4%, Fig 1B), with pre-transplant anxiety significantly higher (70.2%, Fig 1C) than peri- or post-transplant stages (~28% each, $p < 0.05$). Among negative posts, fear of the unknown was the leading driver (54%, Fig 1D), followed by emotional/psychological distress (16%) and healthcare system frustration (12%). Care gaps were identified in one in four posts overall (25.8%), with higher prevalence in the post-transplant period (29.1%, $p < 0.05$, Fig 1E). **Conclusion:** Social media data represents an underutilized resource for identifying gaps in transplant care. Our findings corroborate prior reports of persistent unmet informational and psychosocial needs in the liver transplant population, and extend them by demonstrating that these gaps are detectable at scale in unsolicited social media data. Fear of the unknown was the dominant driver of negative sentiment, suggesting that proactive patient education, particularly pre-transplant, represents the highest-yield intervention target. The persistence of care gaps into the post-transplant period, despite emotional recovery, points to a specific window where follow-up care is inadequate.

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4434 | LIVER TRANSPLANTATION RESTORES PRODUCTIVE LIFE: WORKING-FOR-INCOME AT ONE YEAR REFLECTS FIRST-YEAR SUCCESS AND HERALDS SUPERIOR LONG-TERM SURVIVAL

Sri Harsha Boppana[1] Subhash Gurappa[2] Sachin Sravan Kumar Komati[3] Gautam Maddineni[4] Raja Chandra Chakinala[5] Venkata Sunkesula[6] Pradeep Yarra[7] Kamran Qureshi[8], [1]Nassau University Medical Center, [2]sg001@fiu.edu, [3]sachinkomati23@gmail.com, [4]Creighton university, [5]Guthrie Robert Packer Hospital, [6]Case Western Reserve University, [7]UT Health San Antonio, [8]Saint Louis University

Background: Liver transplantation (LT) offers recipients not only survival but the prospect of returning to productive, working life. Whether working-for-income at 1 year independently drives improved long-term survival or reflects the success of the first post-transplant year is an important distinction for counseling recipients and directing rehabilitation efforts. We aimed to characterize national employment trajectories after LT and examine the clinical determinants and long-term prognostic significance of working at 1 year. **Methods:** Retrospective cohort study of working-age adult LT recipients (18–64) using OPTN/UNOS STAR data (2014–2024). Recipients with documented 1-year employment status were included. Employment trajectories were characterized using transition matrices from listing to 1 year. Multivariable logistic regression identified predictors of working at 1 year with emphasis on first-year recovery. Landmark Cox regression from 1 year assessed associations with subsequent patient and graft survival. **Results:** Of 59,493 eligible working-age recipients, 44,959 had observed 1-year employment status; 32.5% were working for 1 year versus 31.8% at listing. Encouragingly, 64.5% (9,373/14,543) of baseline-employed recipients successfully retained employment, and 17.0% (5,094/29,978) of those not working at listing returned to work after transplant. The strongest predictors of working at 1 year were pre-transplant employment (OR 6.59, 95% CI 5.67–7.66) and functional independence at follow-up (OR 4.07, 95% CI 2.70–6.13) — both markers of robust recovery. First-year hospitalization reduced odds of employment (OR 0.72, 95% CI 0.66–0.78). Government insurance (Medicaid OR 0.34; Medicare OR 0.22 vs. private) and older age (OR 0.96/year) also predicted non-employment. In landmark analysis, working at 1 year was associated with markedly superior patient survival (HR 0.67, 95% CI 0.63–0.72) and graft survival (HR 0.67, 95% CI 0.62–0.71), both $p < 0.001$. **Conclusion:** LT restores productive life for a meaningful proportion of working-age recipients, and those who return to work by 1 year demonstrate substantially improved long-term survival. This association reflects the success of first-year recovery — functional independence and freedom from rehospitalization — rather than employment as a direct cause of survival benefit. Return to work is a powerful composite indicator of transplant success and recipient resilience. Optimizing first-year recovery through readmission reduction, functional rehabilitation, and targeted socioeconomic support represents a high-yield opportunity to expand productive recovery and improve long-term outcomes after LT.

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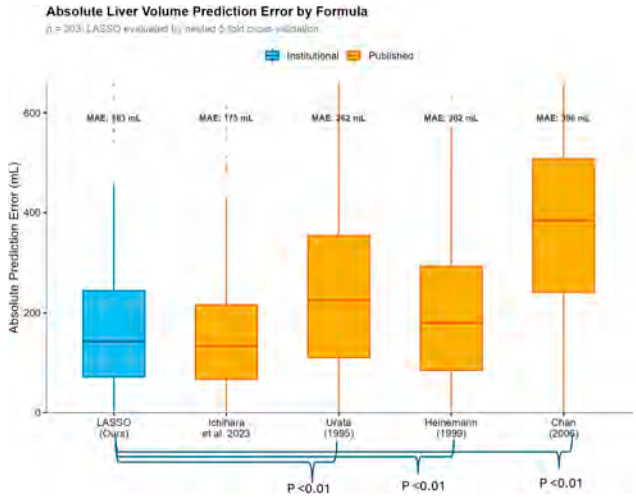
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4435 | PERFORMANCE OF ANTHROPOMETRIC STANDARD LIVER VOLUME EQUATIONS IN CONTEMPORARY MRI-BASED LIVING LIVER DONOR EVALUATION

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Background: Liver volume estimation is essential to optimize appropriate graft selection and donor safety in living donor liver transplantation (LDLT). Urata (1995), Heinemann (1999), Ichihara (PLOS 2023), and Chan (2006) formulas are anthropometric standard liver volume (SLV) equations historically used for this purpose. Despite widespread use, the external validity of these equations in a midwestern, modern cohort has not been established especially as rates of obesity and hepatic steatosis increase. **Methods:** Adult living liver donor candidates (N = 202) underwent preoperative MRI volumetry between 2017-2025 were included. Predicted liver volumes were calculated using Urata (1995), Heinemann (1999), Ichihara (PLOS 2023), and Chan (2006) equations and compared to MRI-derived liver volumes. LASSO regularized linear regression with five fold cross validation was used to train a linear model to predict SLV from clinical data. Primary outcomes included mean absolute error (MAE), root mean square error (RMSE), and correlation. Donors were quantitatively grouped by hepatic steatosis using MRI proton density fat fraction (PDFF) $\geq 5\%$ or $< 5\%$, and subgroup differences in MAE were evaluated using two-sample t-tests. Association of BMI, steatosis, and equation prediction error was determined using multivariable linear regression. **Results:** Baseline donor characteristics include mean age of 39 years, BMI 27.2 kg/m^2, with mean MRI-derived total liver volume 1606 ± 318 mL. Among published models, the Ichihara formula had the lowest bias (-68 mL) and MAE (175 mL). Urata and Chan both systemically underestimated liver volumes, with Chan demonstrating the largest overall error MAE (396 mL). Bland-Altman analysis revealed increasing disagreement at large liver volumes for both Urata and Chan formulas. On univariate and multivariate analyses PDFF $\geq 5\%$ but not BMI was associated with worsening error for both Urata (362 vs 235 mL, $p < 0.01$) and Chan (478 vs 373 mL, $p < 0.01$) but not Heinemann (216 vs 199 mL, $p = 0.85$). Our LASSO derived model (TLV (mL) = 347.3 + 10.61 × weight (kg) + 2.44 × height (cm)) had significantly lower MAE than Urata, Chan, and Heineman formulas ($p < 0.01$). Our model had a lower bias compared to the Ichihara model with lower bias (+4 vs -68, $p < 0.001$). (Figure). **Conclusion:** Among the evaluated anthropometric equations, our LASSO derived model and the Ichihara model were superior to historic SLV predictive models which demonstrated increasing error as steatosis increased. Future research should validate our findings to improve accuracy of donor selection.



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4436 | LESSONS LEARNED FROM IMPLEMENTING A STANDARDIZED CURRICULUM ON DECEASED DONOR PROCUREMENT AND TRANSPLANT SURGERY CURRICULUM FOR PRECLINICAL MEDICAL STUDENTS

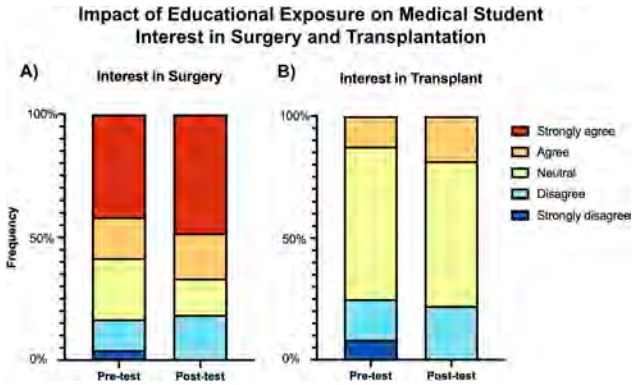
Morgan Miovski[1] Darin Mak[1] Anirudh Koneru[1] Joseph Torkieh[2] Vrindda Atrii[2] Shareef Syed[2] Danielle Krinsky[2] Keri Lunsford[1] Flavio Paterno[1] Jay Graham[1] William Boyan[2] Matthew Rosenzweig[3] Matthew Hanlon[3] Valeria Ripa[3] Advaith Bongu[2] Harry Sun[3] Arpit Amin[1], [1]Rutgers New Jersey Medical School, [2]Rutgers Robert Wood Johnson Medical School, [3]Cooperman Barnabas Medical Center

Background: The current American College of Surgeons medical student preclinical curriculum strives to provide medical students with foundational surgical knowledge. One of the limitations of this curriculum is the lack of information about organ donation and transplant surgery. **Methods:** We implemented a formal standardized curriculum for preclinical medical students from October 18, 2025, to April 30, 2026, focused on deceased donor organ procurement and abdominal transplant surgery at Rutgers-affiliated medical schools. Students' baseline knowledge about organ donation and abdominal transplant surgery was

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assessed using a 10-point questionnaire. Thereafter, students participated in a didactic session and observed deceased donor procurement and/or abdominal transplant surgery through a 24-hour call. **Results:** 119 out of 195 [61%] 24-hour call shifts were filled by students. 28 students observed either a donor procurement or an abdominal transplant surgery during their assigned shift. Pretest questionnaire revealed that 60% of the cohort were interested in surgery and 10% of the cohort were interested in transplant surgery. Post-test questionnaire revealed that 67% of the participating students were interested in surgery and 15% were interested in transplant surgery. Participating students' feedback revealed that the curriculum was awe-inspiring and simultaneously improved their knowledge on surgical technique, donor procurement process, and anatomy. Competing mandatory school sessions, increasing difficulty of course load through the academic year, and unpredictability of procurement/transplant surgery schedule were the main barriers faced by students in completing the curriculum successfully. **Conclusion:** A standardized curriculum on deceased donor procurement and abdominal transplant surgery provides an excellent opportunity for preclinical medical students to increase their knowledge on surgical anatomy and may act as a gateway to students pursuing surgery as their eventual career choice.



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4437 | LIVING DONOR LIVER TRANSPLANTATION IN ALCOHOL-ASSOCIATED HEPATITIS: UNOS ANALYSIS

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Background: Over the last 10-15 years, there has been a growing interest in early liver transplantation (LT) in patients with severe alcohol-associated hepatitis (AH). Since these patients are very sick with a high MELD score, living donor liver transplantation (LDLT) remains controversial and has been performed less frequently. The data on the efficacy and safety of LDLT in patients with AH are limited. We sought to assess patient and graft survival at 1 year, comparing LDLT and deceased donor liver transplantation (DDLT) in patients undergoing LT for AH using the United Network for Organ Sharing (UNOS) database. **Methods:** First-time LT (1/1/2004 to 3/31/2026) in adults at the UNOS database were analyzed. A cohort of LT performed for AH using LDLT was extracted and propensity score-matched on recipient age, sex, obesity, MELD score, and donor risk index (DRI). Outcomes were patient and graft survival rates at 1 year. Chi-square and Student t-tests were used to compare categorical and continuous variables, respectively. Kaplan-Meier survival curves were generated comparing LDLT vs. DDLT, and the log-rank test was used to analyze the statistical significance. Cox proportional hazards regression models were fitted to assess the independent effect of LDLT vs. DDLT on graft and patient survival at 1 year. **Results:** Of 163,658 total LT, there were 7,225 (4.5%) LDLT. 3,915 LTs (2.4%) were performed for AH, including only 33 by LDLT. Of the 33 LDLTs in AH, 29 were performed after 2021. Regional distribution showed 12, 6, and 4 LDLT in UNOS regions 2, 4, and 5, respectively. In LT for AH, compared to DDLT, recipients with LDLT were older, more frequently female, had poorer performance status, and were less obese. Interestingly, LDLT recipients had lower median MELD scores at listing (18 [range 7–29] vs. 36 [range 7–69]; $p < 0.001$) and transplantation (18 [range 7–29] vs. 36 [range 6–69]; $p < 0.001$), with a longer waitlist time and lower DRI than DDLT recipients (**Table**). After propensity score matching, patient and graft survival rates were similar comparing LDLT vs. DDLT: 100% vs. 99.0%, $p = 0.543$, and 100% vs. 94.7%, $p = 0.183$. Obesity, performance status 80-100 vs. 10-30, MELD score, and DRI were associated with graft and patient survival, with respective hazard ratios (95% confidence interval) of 1.39 (1.02-1.88, $p = 0.035$), 2.55 (1.46-4.47,

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p = 0.001), 1.03 (1.01-1.05, p = 0.011), and 1.39 (1.05-1.85, p = 0.022). **Conclusion:** LDLT is used in fewer than 1% of LT procedures performed in AH patients, with a high concentration in regions 2, 4, and 5. In the select population, patient and graft survival after LDLT are similar to those after DDLT. With very low MELD scores at listing and LT, longer wait times, and limited data on LDLT use, multicenter prospective studies are needed to assess the utility and optimal timing of LDLT in patients with severe AH.

Table 1 Baseline characteristics comparing unmatched and matched cohorts using living donor liver transplantation (LDLT) vs. deceased donor liver transplantation (DDLT) in patients with alcohol-associated hepatitis (AH)

	Before propensity score matching			After propensity score matching		
	DDLT (N=3882)	LDLT (N=33)	p	DDLT (N=95)	LDLT (N=32)	p
Age at listing (years, mean ± SD)	44.7 ± 10.9	50 ± 10.2	0.005	50.1 ± 10.3	49.8 ± 10.3	0.874
Females (%)	35	58	0.006	53.7	56.3	0.801
Ethnicity (NHW, AA, H, O %)	73, 5, 14, 9	88, 0, 9, 3	0.223	69, 3, 19, 9	88, 0, 9, 3	0.380
Obesity (%)	42	21	0.017	21	21.9	0.922
DM (%)	9.9	15.1	0.312	19	15.6	0.673
Insurance (Medicare, Medicaid, Pvt %)	7, 27, 66	9, 18, 73	0.511	19, 25, 56	9, 16, 75	0.153
Listing MELD score (mean ± SD)	33.7 ± 8.7	18.2 ± 5.6	<0.001	19.3 ± 8.1	18.4 ± 5.5	0.534
TX MELD score (mean ± SD)	34 ± 8.8	17.9 ± 5.8	<0.001	17.7 ± 8.7	18.1 ± 5.7	0.757
Wait time on the list (days, mean ± SD)	31 ± 112	137 ± 145	<0.001	142 ± 304	129 ± 147	0.953
KPSS (10-30, 40-70, 80-100 %)	20, 24, 56	55, 42, 3	<0.001	52, 39, 9	56, 41, 3	0.690
Donor risk index (mean ± SD)	2.48 ± 0.55	2.10 ± 0.33	<0.001	2.13 ± 0.35	2.11 ± 0.32	0.749

NHW, Non-Hispanic White; AA, African American; H, Hispanic; O, Other; DM, Diabetes mellitus; Pvt, Private insurance; MELD, Model for End-Stage Liver Disease; TX, Transplantation; KPSS, Karnofsky Performance Status Scale; DRI, Donor risk index; SD, Standard deviation.

Disclosures: Chencheng Xie:Nothing to Disclose, Suvisesh Pothuraju:Nothing to Disclose, David Maundu: Nothing to Disclose, Fatima Elmustafa:Nothing to Disclose, Mangesh Pagadala:Nothing to Disclose, Nimish Thakral:Nothing to Disclose, Faris Abdulaziz:Nothing to Disclose, Steven Flamm:Nothing to Disclose, Ashwani Singal:Madrigal: Speaking and Teaching, Pleiogenix: Stock – privately held company, Pleiogenix: Consultant, CLD Foundation: Advisor, Medical Speaker's Network: Speaking and Teaching, Up-to-Date: Royalties or patent beneficiary, Medscape: Speaking and Teaching, University of Louisville School of Medicine: Employee, NIAAA: Grant/Research Support, Gastro Endo News: Executive role, Durect: Advisor, University of Louisville Health: Other.

4438 | STRUCTURED REFERRAL PATHWAYS IMPROVE GEOGRAPHIC REPRESENTATION AND TRANSPLANT ACCESS IN A CENTRALIZED NATIONAL LIVER TRANSPLANT SYSTEM: A REAL-WORLD STUDY FROM COSTA RICA

Maria Fernanda Lynch-Mejia[1] Daniel Pérez-Muñoz[2] Francisco Vargas Navarro[1] Wagner Ramirez[1] Vanessa López-Jara[2] Pablo Coste[1], [1]Liver Lab CR / Liver Unit, Hospital R.A. Calderón Guardia, [2]Liver Unit, Hospital R.A. Calderón Guardia

Background: Geographic inequities may substantially limit access to liver transplantation (LT) in centralized healthcare systems, particularly in middle-income countries where transplant services are concentrated in metropolitan regions. This study aimed to evaluate the impact of implementing a structured referral pathway on geographic representation and transplant outcomes within the national LT waiting list in Costa Rica. **Methods:** A retrospective quasi-experimental cohort study was conducted including consecutive adults incorporated into the national liver transplant waiting list between 2020 and 2024 at a tertiary referral center in San José, Costa Rica. Eligible patients were ≥ 18 years old and formally accepted onto the LT waiting list, regardless of liver disease etiology or transplant indication. Patients were categorized according to referral pathway period: pre- versus post-algorithm implementation (March 13, 2023). Geographic burden was evaluated using rurality, travel distance, and travel time to the transplant center. Clinical severity, waitlist outcomes, Kaplan-Meier time-to-transplant analyses, and multivariable logistic regression for LT within 12 months were performed. **Results:** A total of 93 patients were included. Following pathway implementation, rural patient representation increased from 31.1% to 60.4% (p = 0.005). Median travel burden significantly increased, including travel time (p = 0.002) and distance to the transplant center (p = 0.020). Despite greater travel burden, post-algorithm patients were referred at earlier stages of liver disease severity, including fewer Child-Pugh C presentations (10.4% vs. 26.7%, p = 0.006) and lower median MELD 3.0 scores (15 vs 18 points, p = 0.034). LT within 12 months increased from 33.3% to 70.8% (p < 0.001), while mortality decreased from 40.0% to 20.8% (p = 0.044). In multivariable analysis, pathway implementation independently predicted LT within 12 months (OR 5.47, 95%CI 1.94–15.42; p = 0.001). **Conclusion:** Structured referral pathways may reduce geographic inequities in centralized LT systems by improving rural representation and access to transplantation despite greater travel burden. These findings support coordinated referral networks as scalable strategies to optimize equitable and timely access to LT in middle-income countries and other regions with centralized high-complexity care systems.

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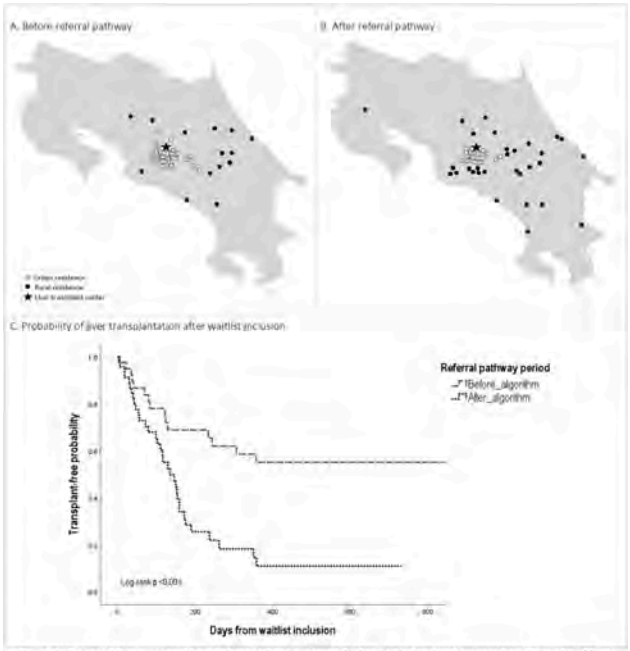


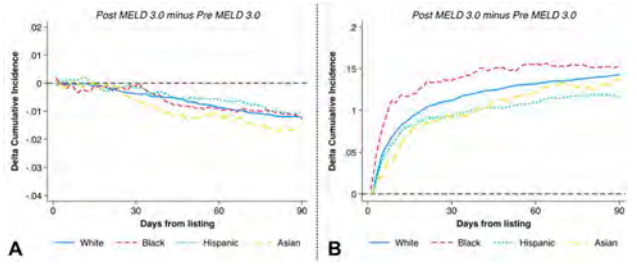
Figure 1. Geographic representation and transplant outcomes before and after implementation of a national liver transplant referral pathway in Costa Rica. (A) Geographic distribution of patients included in the national liver transplant waiting list during the pre-pathway period. (B) Geographic distribution after implementation of the referral pathway, demonstrating broader national and rural representation. (C) Kaplan-Meier analysis of probability of liver transplantation according to referral pathway period. Squares represent urban residence, circles represent rural residence, and the star indicates the national liver transplant center.

Disclosures: Maria Fernanda Lynch-Mejia:Roche Pharmaceuticals: Travel support, Daniel Pérez-Muñoz:Nothing to Disclose, Francisco Vargas Navarro:Nothing to Disclose, Wagner Ramirez:Nothing to Disclose, Vanessa López-Jara:Nothing to Disclose, Pablo Coste:Nothing to Disclose.

4439 | MELD 3.0 IS ASSOCIATED WITH LOWER WAITLIST MORTALITY AND HIGHER TRANSPLANT INCIDENCE ACROSS RACE AND ETHNICITY GROUPS

Farinaz Ghodrati[1] Ashley Bo Zhang[2] Nadim Mahmud[2], [1]University of Pennsylvania, [2]Hospital of the University of Pennsylvania

Background: MELD 3.0 was implemented to address known limitations of MELD-Na, particularly sex-related disparities. While studies have since found MELD 3.0 to have narrowed sex-based disparities, less is known about how it performs across racial and ethnic groups, a critical dimension of evaluation for prediction models. Our study aimed to evaluate changes in 90-day waitlist death/dropout and transplant incidence following MELD 3.0 implementation. **Methods:** This was a retrospective cohort study using United Network for Organ Sharing registry data. We included adult liver transplant candidates listed between 2016 and the most recent available follow-up. The primary policy exposure was listing era, defined as pre-MELD 3.0 versus post-MELD 3.0 implementation, defined by listing date on or after July 13, 2023. Crude cumulative incidence functions were estimated for (1) waitlist death/dropout and (2) transplantation, accounting for the alternative event as a competing risk. Post-MELD 3.0 minus pre-MELD 3.0 differences in cumulative incidence over 90 days were calculated within racial/ethnic groups, yielding "delta cumulative incidence" curves. Adjusted analyses were performed using Fine-Gray competing-risk regression. Separate models were fit for waitlist death/dropout, treating transplantation as the competing event, and vice versa. Models included post-MELD 3.0 era, race/ethnicity, a post-MELD 3.0 × race/ethnicity interaction term, age, and sex. Subhazard ratios (sHRs) and 95% confidence intervals were reported. **Results:** Our study included 108, 044 adult liver transplant waitlist candidates, of whom 82,402 were listed in the MELD-Na era and 25,642 in the MELD 3.0 era. The MELD 3.0 era had slightly younger candidates (median age 56 vs. 58 years, $P < 0.001$) and a higher proportion of females (40.8% vs. 36.6%, $P < 0.001$). Race/ethnicity distributions also differed between eras ($P < 0.001$), with a lower proportion of White candidates and a higher proportion of Hispanic and Other candidates in the MELD 3.0 era. Delta cumulative incidence curves demonstrated lower 90-day post-MELD 3.0 waitlist death (**Figure panel A**) and higher transplant incidence (**Figure panel B**) across all for all race/ethnicity groups in the post vs. pre-MELD 3.0 era. In adjusted analyses, there was no significant interaction between era and race/ethnicity in waitlist mortality ($p = 0.77$) or transplant models (0.06). **Conclusion:** MELD 3.0 implementation was associated with lower waitlist mortality and higher transplant incidence across all racial/ethnic groups. These findings suggest MELD 3.0 improved short-term allocation outcomes without clear evidence of worsening racial/ethnic inequities. Our findings broaden the current MELD 3.0 literature beyond sex disparities and highlight the importance of post-implementation surveillance to monitor long-term equity and subgroup-specific allocation effects.



Disclosures: Farinaz Ghodrati:Nothing to Disclose, Ashley Bo Zhang:Nothing to Disclose, Nadim Mahmud: Nothing to Disclose.

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4440 | OUTCOMES OF PORTAL VEIN RECANALIZATION VARY BY INDICATION

Christopher Danford[1] Kendon Holdaway[2] James Trotter[1] Suaka Kagbo-Kue[1], [1]Intermountain Medical Center, [2]University of Utah

Background: Portal vein recanalization with/without transjugular intrahepatic portosystemic shunting (PVR-TIPS) is a relatively novel procedure with a high technical success rate of 95% and a 12-monthPV patency of 79% 1 . Despite high rates of technical success, there is limited literature on clinicaloutcomes of patients post-PVR-TIPS outside of transplant. This study aims to describe clinicaloutcomes PVR-TIPS performed for transplant and other indications and identify predictors ofsuccess to aid in future patient selection. **Methods:** We performed a retrospective chart review of electronic medical records on 69 consecutivePVR/PVR-TIPS procedures performed at Intermountain Health from 2018 to 2024. Four caseswere excluded due to procedures other than PVR/PVR-TIPS performed, and/or lack ofthrombosis found upon procedural examination. Nine cases were repeat procedures on the sameindividuals and ultimately 56 unique individuals were included. Primary outcomes includedtechnical and clinical success, with technical success determined primarily by patency onimaging at 12 months. Subjective clinical success was determined via consensus panel review ofthree hepatologists, with consideration of factors including vascular patency, resolution oforiginal symptoms/indication, and successful liver transplantation (when applicable) balancedwith adverse events such as bleeding, infection, need for repeat procedures, and mortality **Results:** Most patients were male (68.4%) and Caucasian (80.7%), with an average age of 51.7 ± 14.6years. Approximately half (52.6%) had cirrhosis, with the most common cirrhotic etiologies ofalcohol consumption (29.8%) and metabolic-dysfunction associated steatohepatitis (17.5%).Portal hypertensive bleeding (43.9%), to enable liver transplantation (26.3%), and abdominalpain (21.1%) were the most common indications.While 83% of these PVR/PVR-TIPS procedures were deemed technically successful, only 48%(n = 27) were deemed clinically successful. Most patients who underwent TIPS-PVR to enabletransplantation (92.3%) were successful whereas those whose initial indication was abdominalpain or had underlying JAK2 mutation or malignancy were unlikely to be successful, 28.6% and12.5% respectively. **Conclusion:** These findings underscore the importance of careful selection of PVR/PVR-TIPS candidates.Indications such as bridge to transplantation showed highest rates of clinical success whereasprocedural indications of abdominal pain or underlying malignancy and JAK2 mutation wereunlikely to be clinically successful.

Disclosures: Christopher Danford:Ipsen Pharmaceuticals: Advisor, Miromatrix: Consultant, Kendon Holdaway:Nothing to Disclose, James Trotter:Nothing to Disclose, Suaka Kagbo-Kue:Nothing to Disclose.

4441 | COMPARATIVE OUTCOMES OF OPEN, LAPAROSCOPIC, AND ROBOTIC LIVER RESECTION FOR INTRAHEPATIC CHOLANGIOCARCINOMA: A NETWORK META-ANALYSIS

Muhammad Ahmad Nadeem[1] Puneet Bansal[1] Mohammed Quazi[2] Abdul Awan[3] Mohanad Baroudi[1] Beren Berber[1] Jaekeun Kim[1] Chase Wehrle[1] Federico Aucejo[1] Mazhar Khalil[1], [1]Digestive Disease and Surgery Institute, Cleveland Clinic, [2]Department of Family and Community Health, West Virginia University, [3]Nishtar Medical University

Background: Intrahepatic cholangiocarcinoma (ICC) is an aggressive hepatobiliary malignancy for which surgical resection remains the only potentially curative treatment. Minimally invasive liver resection is increasingly used in this setting, but comparative evidence across open, laparoscopic, and robotic approaches remains fragmented and largely confined to pairwise studies. We aimed to evaluate perioperative outcomes and mortality across open, laparoscopic, and robotic hepatic resection for ICC. **Methods:** Four databases were searched from inception to September 2025 for studies comparing open, laparoscopic, and robotic hepatic resections in adults with ICC. A Bayesian network meta-analysis assessed differences in mortality, complications, readmissions, and hospital stay. Surgical intensity and complexity were incorporated as covariates within MCMC-based random-effects. **Results:** Eighteen studies (10,010 patients) were included. Open surgery was associated with significantly higher 30-day mortality compared with laparoscopic resection (OR [95% CI]: 7.47 [1.07-78.37]). Clavien-Dindo $\geq$ 3 complications were significantly more frequent after open surgery than laparoscopic surgery (OR [95% CI]: 2.01 [1.16-3.71]). Open resection was also associated with significantly longer hospital stay compared with laparoscopic surgery (MD [95% CI]: 3.76 days [1.32-6.33]) and greater estimated blood loss (MD [95% CI]: 178 mL [72-301]). After adjustment for morbidity, these differences were attenuated and no longer statistically significant, although open surgery consistently ranked highest for risk. No significant differences were observed for 90-day mortality, operative time, readmission, or R0

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resection, while robotic surgery consistently ranked most favorable across several outcomes. **Conclusion:** Minimally invasive approaches, particularly robotic surgery, demonstrated more favorable perioperative profiles than open surgery for ICC resection, while achieving comparable R0 resection rates. Although differences in mortality and major complications were attenuated after adjustment for surgical morbidity, robotic and laparoscopic techniques consistently ranked more favorably across multiple endpoints. These findings support broader adoption of minimally invasive techniques in appropriately selected patients at centers with sufficient expertise, and highlight the need for prospective comparative studies to refine modality selection across varying degrees of surgical complexity and to confirm long-term oncologic equivalence.

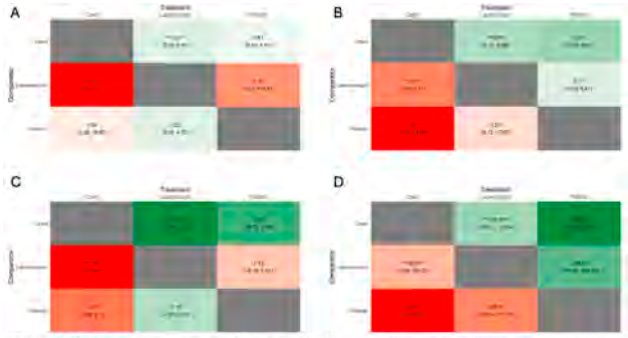


Figure 1. Pairwise Bayesian network meta-analysis comparing perioperative outcomes across open, laparoscopic, and robotic liver resection for intrahepatic cholangiocarcinoma. Heatmaps display pooled unadjusted effect estimates with 95% credible intervals for each pairwise comparison, with the column-defined treatment compared against the row-defined comparator. Effect measures are odds ratios for binary outcomes and mean differences for continuous outcomes. Double asterisks indicate statistical significance. Panels depict 30-day mortality (A), Clavien-Dindo grade ≥3 complications (B), hospital length of stay in days (C), and estimated blood loss in mL (D).

Disclosures: MUHAMMAD AHMAD NADEEM:Nothing to Disclose, Puneet Bansal:Nothing to Disclose, Mohammed Quazi:Nothing to Disclose, Abdul Awan: Nothing to Disclose, Mohanad Baroudi:Nothing to Disclose, Beren Berber:Nothing to Disclose, Jaekeun Kim:Nothing to Disclose, Chase Wehrle:Nothing to Disclose, Federico Aucejo:Nothing to Disclose, Mazhar Khalil:Nothing to Disclose.

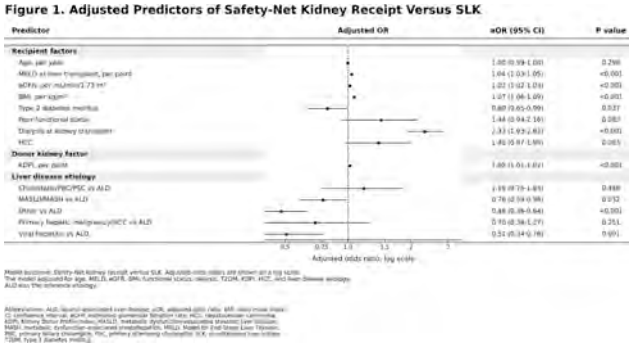
4442 | CLINICAL PHENOTYPES AND CORRELATES OF SAFETY-NET VERSUS SIMULTANEOUS LIVER–KIDNEY TRANSPLANTATION

Abhijith Atkuru[1] Sidart Pradeep[2] Eugenia Tsai[2],
[1]Tulane University School of Medicine, [2]Texas Liver Institute; UT Health San Antonio

Background: The 2017 Organ Procurement and Transplantation Network (OPTN) simultaneous liver–kidney (SLK) allocation policy introduced standardized SLK criteria and a Safety-Net pathway prioritizing kidney allocation for liver-alone recipients with persistent renal dysfunction. Yet independent correlates of kidney pathway have not been examined in a national registry analysis. This study compared recipient and donor profiles associated with Safety-Net versus SLK pathways using the largest post-policy cohort to date. **Methods:** Using OPTN/Scientific Registry of Transplant Recipients (SRTR) Standard Transplant Analysis and Research (STAR) data (2018–2024), adults who underwent SLK or received a Safety-Net kidney 60–365 days after liver-alone transplantation were identified. Recipient demographics, illness severity, functional status, diabetes, liver disease etiology, estimated glomerular filtration rate (eGFR), and Kidney Donor Profile Index (KDPI) were compared using Wilcoxon and chi-square tests. Multivariable logistic regression identified factors associated with Safety-Net kidney receipt versus SLK, adjusting for age, Model for End-Stage Liver Disease (MELD), eGFR, body mass index (BMI), functional status, dialysis, type 2 diabetes mellitus (T2DM), Kidney Donor Profile Index (KDPI), hepatocellular carcinoma (HCC), and liver disease etiology. **Results:** Among 4,197 recipients, 3,506 (83.6%) underwent SLK and 691 (16.4%) received a Safety-Net kidney. Compared with SLK, Safety-Net recipients were younger (55 vs 58 years), had higher MELD score at liver transplant (34 vs 28), higher eGFR (33.1 vs 18.1 mL/min/1.73 m²), and higher body mass index (BMI; 29.9 vs 27.5 kg/m²; all $p < 0.001$). Higher MELD among Safety-Net recipients likely reflects urgent liver transplantation before 90-day chronic kidney disease criteria for SLK eligibility could be met. Alcohol-associated liver disease and metabolic dysfunction-associated steatohepatitis were the leading etiologies in SLK (33.4% and 25.6%, respectively) and Safety-Net recipients (51.1% and 24.5%, respectively; overall $p < 0.001$). In adjusted analyses, higher MELD, eGFR, BMI, dialysis, and KDPI were associated with Safety-Net receipt (all $p < 0.001$; Figure 1). T2DM was associated with lower odds of Safety-Net receipt (aOR 0.80, 95% CI 0.65–0.99; $p = 0.037$; Figure 1), likely reflecting confounding by indication, with severe chronic kidney disease preferentially selected for upfront SLK. **Conclusion:** SLK and Safety-Net recipients represent clinically distinct populations. Despite higher eGFR at liver transplantation, Safety-Net recipients carried higher illness severity and worse functional status, suggesting eGFR alone inadequately captures renal risk trajectory at listing. These findings support early post-transplant renal surveillance in patients with high MELD, functional impairment, or elevated BMI at the time of liver transplantation.

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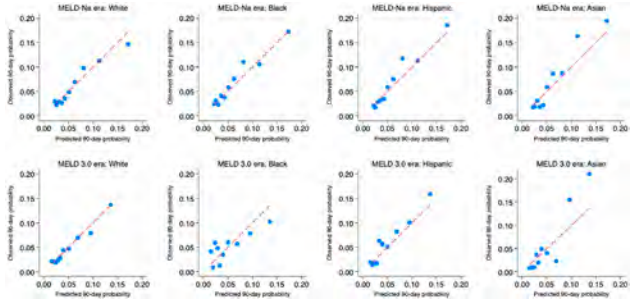


Disclosures: Abhijith Atkuru:Nothing to Disclose, Sidart Pradeep:Nothing to Disclose, Eugenia Tsai: Nothing to Disclose.

4443 | MELD 3.0 DEMONSTRATES PRESERVED PREDICTIVE PERFORMANCE ACROSS RACIAL AND ETHNIC GROUPS WITH MODEST CALIBRATION VARIABILITY

Ashley Zhang[1] Farinaz Ghodrati[1] Nadim Mahmud[1], [1]Hospital of the University of Pennsylvania

Background: The implementation of MELD 3.0 addressed known limitations of MELD-Na, namely sex-related disparities and suboptimal calibration. MELD 3.0 has been shown to more accurately predict waitlist mortality with equity across sex; however, its predictive performance across racial and ethnic groups remains largely unexplored. Our study aimed to evaluate the predictive performance of MELD 3.0 across race and ethnicity for waitlist mortality. **Methods:** This was a retrospective cohort study using United Network for Organ Sharing registry data. Adult candidates listed for a single liver transplant between 2016 and the most recent available follow-up were identified. Listing era was defined as pre-MELD 3.0 versus post-MELD 3.0 implementation (listing date on or after 7/13/2023). Within each era, an era-specific logistic regression model was fit with 90-day waitlist death/dropout as the outcome and the corresponding score as the predictor. Predicted probabilities and linear predictors from these models were used to evaluate discrimination and calibration. Discrimination was assessed using the area under the receiver operating characteristic curve. Calibration was assessed using calibration slope, calibration intercept, and observed-to-expected ratios. Calibration plots were generated by grouping candidates into score deciles and plotting observed versus predicted event probabilities by race/ethnicity and era. **Results:** Of the total 108,044 waitlist candidates included in our study, 25,642 were listed in the MELD 3.0 era, which had younger candidates (median age 56 vs. 58 years, $P < 0.001$) and a higher percentage of females (40.8% vs. 36.6%, $P < 0.001$). The distribution of race/ethnicity also varied ($P < 0.001$) with the MELD 3.0 era have a higher proportion who self-reported as Hispanic and Other compared to White. Predictive performance metrics stratified by race/ethnicity and allocation showed that overall discrimination for 90-day waitlist mortality was similar across eras. The overall AUC was 0.699 (95% CI 0.692-0.707) in the MELD-Na era and 0.700 (95% CI 0.685-0.715) in the MELD 3.0 era. Overall calibration was preserved across eras, but there was modest subgroup heterogeneity by race/ethnicity (**Figure 1**). In the MELD 3.0 era, Black candidates demonstrated a calibration slope < 1 (0.569, 95% CI 0.262-0.877), whereas Asian candidates demonstrated a calibration slope > 1 (1.538, 85% CI 1.088-1.988) (**Figure 1**). **Conclusion:** In this national cohort, MELD 3.0 demonstrated preserved predictive performance across racial and ethnic groups, with comparable discrimination to the MELD-Na era and modest subgroup variability in calibration. Although overall performance was preserved, the observed subgroup calibration differences warrant continued evaluation of allocation equity across racial and ethnic groups.



Disclosures: Ashley Zhang:Nothing to Disclose, Farinaz Ghodrati:Nothing to Disclose, Nadim Mahmud: Nothing to Disclose.

4444 | NOVEL PERFUSION SOLUTION ADDRESSING REVERSE ELECTRON TRANSPORT, FERROPTOSIS, AND MITOCHONDRIAL DYSFUNCTION IMPROVES HEPATIC VIABILITY DURING HYPOTHERMIC OXYGENATED MACHINE PERFUSION

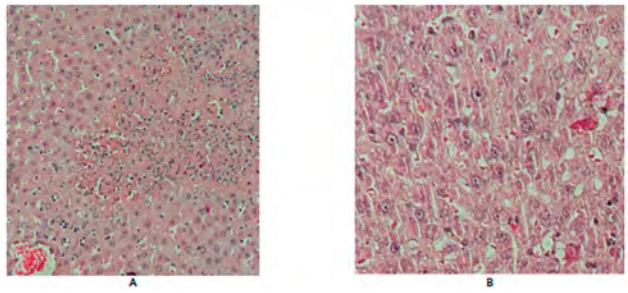
Boris Yaremin[1] Bakhtiyar Kazymov[2] Catherine Anosova[3] Aslan Balkarov[4] Murad Novruzbekov[2], [1]NV Sklifosovsky Research Institute of Emergency Medicine, [2]Sklifosovsky Institute Of Emergency

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Background: Available preservation solutions were developed for static cold storage and fail to address reperfusion-specific mechanisms operative during HOPE. Mitochondrial reverse electron transport (RET) driven by succinate reoxidation and ferroptosis-mediated lipid peroxidation are major drivers of hepatocellular and cholangiocellular injury after donation after circulatory death (DCD). We developed an 18-component extracellular-type solution with simultaneous pharmacologic action on RET, ferroptosis, mPTP opening, endothelial dysfunction, and ATP depletion. **Methods:** 18 male Wistar rats underwent 30-min warm ischemia (DCD), 2-hr HOPE at 8–10°C with HTK/Custodiol (control) or experimental solution, then 60-min normothermic reperfusion. Endpoints: ALT, AST, LDH, lactate, ATP recovery, bile production, 4-HNE, MDA, GPX4 activity, mitochondrial swelling, sinusoidal endothelial detachment, Suzuki score, zonal necrosis area, apoptotic index (TUNEL). Stability confirmed 7 days at 4°C. Statistics: ANOVA, Tukey, Holm-Bonferroni. **Results:** Hepatocellular injury markers were markedly reduced: ALT −76% (169 ± 91 vs. 694 ± 247 U/L; $p < 0.05$), AST −71% (243 ± 118 vs. 836 ± 301 U/L; $p < 0.05$), LDH −68% (412 ± 154 vs. 1289 ± 436 U/L; $p < 0.05$). Lactate after reperfusion fell from 5.8 ± 1.7 to 2.1 ± 0.9 mmol/L ($p < 0.05$); tissue ATP recovered to 81 ± 14% of baseline vs. 43 ± 16% in controls, confirming effective metabolic rescue. Bile production increased 2.4-fold (0.74 ± 0.24 vs. 0.31 ± 0.15 µL/min/g; $p < 0.05$), directly reflecting cholangiocyte viability. Ferroptosis was effectively suppressed: 4-HNE −58%, MDA −49%, GPX4 activity +1.9-fold. Mitochondrial swelling score improved from 2.8 ± 0.6 to 1.1 ± 0.5. Sinusoidal endothelial detachment was observed in 67% of control specimens vs. 17% in the experimental group. Histologically, controls demonstrated confluent centrilobular necrosis involving 34 ± 11% of lobular area with severe sinusoidal congestion and ballooning extending into zone II; the experimental group showed only focal pericentral degeneration affecting 8 ± 4% of tissue ($p < 0.05$). Suzuki score: 1[1–2] vs. 3[2–4]. Apoptotic index decreased from 18.6 ± 5.2% to 6.1 ± 2.7% ($p < 0.05$). **Conclusion:** Simultaneous targeting of RET, ferroptosis, mPTP opening, energy depletion, and endothelial dysfunction during HOPE produced substantial, mechanistically verified hepatoprotection in a model. Marked reduction of centrilobular necrosis combined with 2.4-fold improvement in bile production directly addresses the 20–30% ischemic cholangiopathy burden — the principal unresolved complication of DCD liver transplantation. These findings establish that HOPE requires pharmacologic strategies fundamentally distinct from static cold storage solutions. Patent application pending (2025). A prospective clinical study at a high-volume DCD transplant center is in preparation, with biliary complication rate as primary endpoint.



Disclosures: Boris Yaremin:Nothing to Disclose, Bakhtiyar Kazymov:Nothing to Disclose, Catherine Anosova:Nothing to Disclose, Aslan Balkarov:Nothing to Disclose, Murad Novruzbekov:Nothing to Disclose.

4445 | PERFORMANCE OF A STRATIFIED CARDIAC SCREENING PROTOCOL FOR CORONARY ARTERY DISEASE IN LIVER TRANSPLANT CANDIDATES

Sanjaya Satapathy[1] David Stern[1] Tapan Buch[2] Fariha Ilyas[2] Sohil Khurana[2] Reanay Berezovskiy[2] Shahidul Islam[2] Cristina Sison[2] Nabil Dagher[2] James Park[2], [1]Northshore University Hospital/Northwell Health, [2]Northwell Health

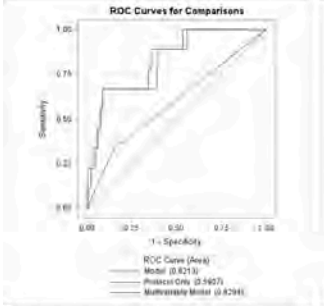
Background: Cardiovascular disease—particularly coronary artery disease (CAD)—is a leading cause of morbidity and mortality among liver transplant candidates. To improve pre-transplant cardiac evaluation, we implemented a stratified screening protocol based on the presence of high-risk features and the total number of cardiovascular risk factors. This study evaluates the diagnostic performance of the protocol in detecting asymptomatic CAD, including both clinically significant and obstructive disease. **Methods:** We retrospectively evaluated liver transplant candidates categorized into high-risk (≥ 1 high-risk feature or ≥ 3 total risk factors) and low-risk groups. The protocol directed patients to dobutamine stress echocardiography (DSE), coronary CT angiography (CCTA), or invasive coronary angiography based on their risk stratification and noninvasive test results. We assessed protocol performance in predicting three outcomes: any CAD, clinically significant CAD, and obstructive CAD. Diagnostic accuracy was evaluated using sensitivity, specificity, positive and negative predictive values (PPV and NPV). Discrimination was assessed using the area under the receiver operating characteristic curve (AUC) derived from both standard logistic and Firth-penalized logistic regression as appropriate. **Results:** Among 254 patients, the

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protocol demonstrated strong discrimination for clinically significant CAD (AUC: 0.83 overall; 0.80 in high-risk vs. 0.59 in low-risk patients). In the high-risk group, the protocol alone outperformed multivariable models. For obstructive CAD, Firth-penalized regression showed modest discrimination (AUC: 0.59–0.83), with higher performance in high-risk patients. Sensitivity and NPV were highest in the low-risk group, supporting its utility for ruling out disease. PPV remained limited, particularly in the low-risk strata, reflecting the low prevalence of CAD in this population. **Conclusion:** A stratified cardiac screening protocol demonstrates robust performance for detecting clinically significant CAD in high-risk liver transplant candidates, outperforming traditional risk models. Its high negative predictive value in low-risk patients supports its role in guiding safe transplant listing decisions and reducing unnecessary testing.

Figure 1. ROC Curves Comparing Predictive Models for Obstructive CAD in High-Risk Liver Transplant Candidates.

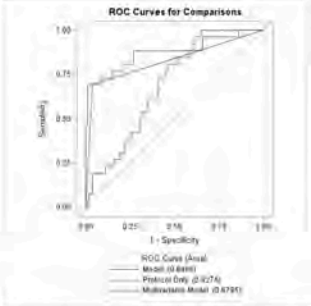


Receiver operating characteristic (ROC) curves comparing the diagnostic performance of three Firth logistic regression models for predicting obstructive coronary artery disease (CAD) in the high-risk group:

- **Protocol Only Model** (AUC = 0.591, 95% CI: 0.424–0.757)
- **Multivariable Model** (AUC = 0.828, 95% CI: 0.698–0.959), adjusted for age, BMI, diabetes, MASH, hypertension, dyslipidemia, and family history of CAD.
- **Full Model** including protocol status and covariates (AUC = 0.821, 95% CI: 0.679–0.963).

The multivariable model outperformed the protocol-only model, indicating improved discrimination when clinical variables were incorporated.

Figure 2. ROC Curves Comparing Predictive Models for Clinically Significant CAD in High-Risk Liver Transplant Candidates.



Receiver operating characteristic (ROC) curves comparing the diagnostic performance of three logistic regression models for predicting clinically significant coronary artery disease (CAD) in the high-risk group:

- **Protocol Only Model** (AUC = 0.828, 95% CI: 0.735–0.920)
- **Multivariable Model** (AUC = 0.680, 95% CI: 0.576–0.783), adjusted for age, BMI, diabetes, MASH, hypertension, dyslipidemia, and family history of CAD
- **Full Model including protocol status and covariates** (AUC = 0.889, 95% CI: 0.807–0.970)

The cardiac protocol demonstrated strong discrimination for clinically significant CAD, which was further improved when combined with clinical risk factors. The multivariable model without protocol status showed substantially lower discriminatory performance.

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4446 | TEMPORAL TRENDS AND POST-TRANSPLANT OUTCOMES OF COVID-POSITIVE LIVER DONORS: A UNOS ANALYSIS

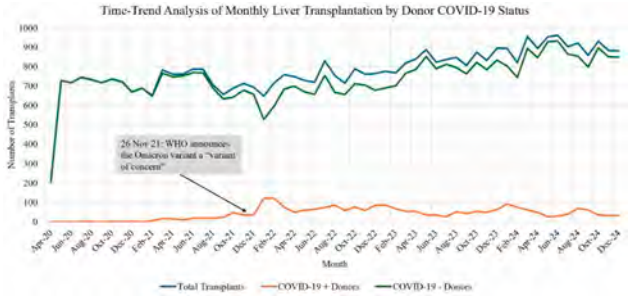
Oliver Liu[1] Nandini Sriram[1] Jewel Ng[1] Arthi Venkatesan[1] Daisuke Imai[1], [1]Virginia Commonwealth University School of Medicine

Background: The COVID-19 pandemic introduced unprecedented volatility into the organ donor pool, raising concerns regarding transplantation of COVID positive organs. No prior study has evaluated liver transplant outcomes across the full COVID-era UNOS dataset. Here, we aimed to characterize temporal trends in donor utilization and the impact of donor COVID status on post-transplant outcomes. **Methods:** We analyzed all COVID positive (n = 2,381) and COVID negative (n = 42,038) liver donors recorded in UNOS from 2020–2024 to characterize temporal trends in COVID positive donor usage. Transplant outcomes were assessed using a 1:3 propensity-matched cohort of COVID-positive (n = 1,026) and COVID negative (n = 3,068) donors based on donor BMI, DCD status, cold ischemia time, diabetes/steatosis/HCV status, and recipient MELD, age, primary diagnosis, sodium, and first vs. re-transplant. Kaplan-Meier analyses were used to assess effects on patient mortality/graft failure. A Cox proportional hazards model with fixed, baseline covariates (COVID status, Age, MELD, cold ischemia time, and DCD status) was used to assess the associated HRs. Logistic regression was used to assess effects on biliary complications, primary rejection, and diffuse cholangiopathy. **Results:** Time-trend analysis revealed a breakpoint at Dec 2021-Jan 2022, where COVID positive donor utilization rates increased from 5.06% to 18.7%. The Kaplan-Meier curves indicated that COVID status did not impact graft failure ($p = 0.0608$) or mortality ($p = 0.0698$). Cox modeling confirmed no association (mortality $p = 0.8453$, graft failure $p = 0.0948$). Among covariates, mortality risk was increased by age (HR 1.0110 per year, 95%, $p = 0.0009$), MELD score (HR 1.0126 per point, $p = 0.0137$), and cold ischemia time (HR 1.0215 per hour, $p = 0.0437$), but decreased by DCD status (HR 0.5492, $p = 0.0036$). Graft failure risk was increased by age (HR 1.0120 per year, $p < 0.0001$), MELD score (HR 1.0093 per point, $p = 0.0490$), and cold ischemia time (HR 1.0189 per hour, $p = 0.0473$). DCD status did not impact graft outcomes ($p = 0.1135$). Logistic regression showed that COVID status was not

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associated with acute rejection (p = 0.662) or primary non-function (p = 0.804), though a trend toward diffuse cholangiopathy (p = 0.0674) was observed. **Conclusion:** The breakpoint of COVID positive donor utilization in Dec 2021 coincides with the emergence of Omicron. Additionally, we found that carefully selected COVID positive donors did not have worse outcomes than COVID negative donors. However, COVID status may still impact biliary complications, though lack of reliable UNOS data regarding anastomotic strictures and non-anastomotic biliary strictures limits further biliary outcome analysis. Notably, given the highly selective use of COVID positive grafts early in the pandemic, residual selection bias remains a concern.



Disclosures: Oliver Liu:Nothing to Disclose, Nandini Sriram:Nothing to Disclose, Jewel Ng:Nothing to Disclose, Arthi Venkatesan:Nothing to Disclose, Daisuke Imai:Nothing to Disclose.

4447 | HEPATIC ARTERIAL INFUSION PUMP THERAPY BEFORE LIVER TRANSPLANTATION FOR COLORECTAL LIVER METASTASES IS ASSOCIATED WITH SUPERIOR PATHOLOGIC DOWNSTAGING

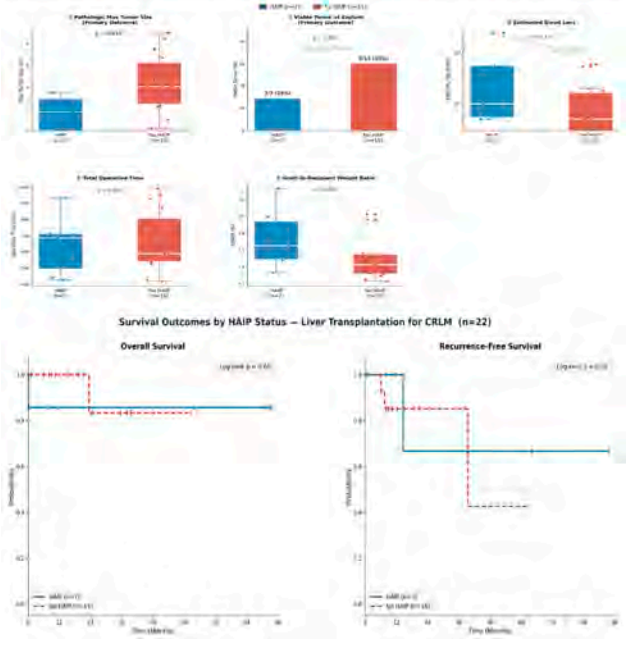
Ahmed Sayed Ahmed[1] Chase Wehrle[1] Sami Shoucair[1] Muhammad Ahmad Nadeem[1] Kyungran Justina Cho[2] Kim Jaekeun[1] Federico Aucejo[1] Koji Hashimoto[1] Mazhar Khalil[1], [1]Department of Surgery Transplantation Center, The Cleveland Clinic Foundation, OH, USA, [2]Department of Gastroenterology, The Cleveland Clinic Foundation, OH, USA

Background: Liver transplantation (LT) for unresectable colorectal liver metastases (CRLM) has gained traction as a treatment strategy in carefully selected patients. Hepatic arterial infusion pump (HAIP) therapy delivers high-dose regional chemotherapy directly to the liver and may achieve deeper locoregional tumor response than systemic chemotherapy alone. Whether pre-LT HAIP therapy translates into superior pathologic response at explant remains unknown. **Methods:** We reviewed 22 patients who underwent LT for CRLM at a single center. Patients were grouped by pre-LT HAIP therapy (n = 7) vs. systemic chemotherapy and locoregional therapy (LRT) (n = 15). Primary outcomes were viable tumor at explant and maximum pathologic tumor size. Secondary outcomes included recurrence-free survival (RFS), overall survival (OS), portal hilar lymph node yield and status, estimated blood loss (EBL), Roux-en-Y biliary reconstruction rate, and operative time. **Results:** Baseline characteristics were comparable. Mean age was 43.1 ± 4.2 vs. 50.4 ± 9.6 years (p = 0.072). Bilobar disease was present in 5/7 (71.4%) vs. 13/15 (86.7%) (p = 0.57), synchronous CRLM in 2/7 (28.6%) vs. 6/15 (40.0%) (p = 1.00), and median CEA was 3.3 (IQR 1.4–4.1) vs. 3.6 (IQR 1.9–5.5) ng/mL (p = 0.53). HAIP patients received more chemotherapy cycles [median 27.5 vs. 15.0, p = 0.41] and had a significantly longer interval from CRLM diagnosis to transplantation [mean 60.9 ± 20.8 vs. 34.5 ± 14.1 months, p = 0.002]. Portal hilar lymph nodes were sampled in 15/22 patients (68%); zero had nodal involvement. Operative outcomes were similar: operative time 637 ± 178 vs. 671 ± 189 min (p = 0.70) and median EBL 1,000 vs. 501 mL (p = 0.18). Of 22 patients, 12 (54.5%) received Y-90 radioembolization pre-LT. Viable tumor was present in 5/12 (41.7%) Y-90-treated vs. 6/10 (60.0%) untreated patients (p = 0.67). Patients receiving both HAIP and Y-90 (n = 2) had 0% viable tumor vs. 80.0% (4/5) receiving neither (p = 0.17), suggesting a potential additive downstaging effect. On explant analysis, HAIP patients had a significantly smaller mean maximum pathologic tumor size [1.6 ± 1.6 vs. 4.4 ± 2.7 cm, p = 0.019]. Viable tumor was present in 2/7 (28.6%) vs. 9/15 (60.0%) explants (p = 0.36).Recurrence occurred in 1/7 (14.3%) vs. 3/15 (20.0%) (p = 1.00). Median OS was 11.4 (IQR 4.1–77.9) vs. 19.1 (IQR 9.6–30.0) months (log-rank p = 0.60) and median RFS 11.4 (IQR 4.1–39.2) vs. 12.2 (IQR 7.7–22.7) months (log-rank p = 0.70). Shorter OS in the HAIP group reflects one intraoperative death and shorter follow-up. **Conclusion:** Pre-LT HAIP was associated with significantly smaller residual tumor at explant and a trend toward viable tumor elimination, supporting superior locoregional downstaging vs. systemic chemotherapy and LRT. Universal portal lymph node negativity across all 22 patients supports oncologic safety of LT for CRLM. Larger prospective studies are needed to validate findings and optimize patient selection.

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Variable	HAIP (n=7)	No HAIP (n=15)	p-value
BASELINE CHARACTERISTICS			
Age at LT, mean ± SD (years)	43.1 ± 4.2	50.4 ± 9.6	0.07
Male sex, n (%)	5/7 (71.4%)	8/15 (53.3%)	0.65
Biledact disease, n (%)	5/7 (71.4%)	13/15 (86.7%)	0.57
Synchronous CRLM, n (%)	2/7 (28.6%)	6/15 (40.0%)	1.00
CEA at listing, median (IQR), ng/mL	3.3 (1.4–4.1)	3.6 (1.9–5.5)	0.53
Oslo score, median (IQR)	1.0 (0.0–1.0)	0.0 (0.0–1.5)	0.88
Living donor (LDLT), n (%)	3/7 (42.9%)	10/15 (66.7%)	0.38
PRE-TRANSPLANT TREATMENT			
Chemotherapy cycles, median (IQR)	27.5 (16.0–39.0)	15.0 (12.0–29.5)	0.41
CRLM diagnosis to LT, mean ± SD (months)	60.9 ± 20.8	34.5 ± 14.1	**0.002**
Prior hepatic resection, n (%)	6/7 (85.7%)	4/15 (26.7%)	**0.020**
INTRAOPERATIVE VARIABLES			
Operative time, mean ± SD (min)	636.9 ± 178.1	670.7 ± 188.8	0.69
EBL, median (IQR) (mL)	1000.0 (550.0–5500.0)	501.0 (300.0–1650.0)	0.18
pRBC transfused, median (IQR) (units)	4.0 (2.0–12.5)	3.0 (0.0–4.5)	0.25
Transfusion required, n (%)	6/7 (85.7%)	8/15 (53.3%)	0.19
Roux-en-Y biliary reconstruction, n (%)	2/7 (28.6%)	3/15 (20.0%)	1.00
PORTAL LYMPH NODE STATUS			
Patients with ≥1 LN sampled, n (%)	6/7 (85.7%)	9/15 (60.0%)	0.35
Portal LN yield, median (IQR)	1.0 (1.0–1.5)	1.0 (0.0–2.0)	0.71
Portal LN positive for carcinoma, n (%)	0/7 (0.0%)	0/15 (0.0%)	N/A
EXPLANT PATHOLOGY — PRIMARY OUTCOMES			
Max pathologic tumor size, mean ± SD (cm)	1.6 ± 1.6	4.4 ± 2.7	**0.019**
Viable tumor at explant, n (%)	2/7 (28.6%)	9/15 (60.0%)	0.36
Pathologic tumor count, median (IQR)	1.5 (1.0–3.5)	3.0 (1.0–3.0)	0.53
Y-90 RADIOEMBOLIZATION (n=12; Y-90 vs. n=10 No-Y-90)			
Y-90 received, n (%)	2/7 (28.6%)	10/15 (66.7%)	0.17
Viable tumor, Y-90 vs. No-Y-90, n (%)	5/12 (41.7%)	6/10 (60.0%)	0.67
Max tumor size, Y-90 vs. No-Y-90, mean±SD (cm)	4.3 ± 2.2	2.3 ± 3.0	0.05
HAIP+Y-90, viable tumor vs. No-HAIP+No-Y-90, n (%)	0/2 (0.0%)	4/5 (80.0%)	0.17
ONCOLOGIC OUTCOMES			
Disease recurrence, n (%)	1/7 (14.3%)	3/15 (20.0%)	1.00
Median OS, months (IQR)	11.4 (4.1–77.9)	19.1 (9.6–30.0)	0.60
Median RFS, months (IQR)	11.4 (4.1–39.2)	12.2 (7.7–22.7)	0.70



Disclosures: Ahmed Sayed Ahmed:Nothing to Disclose, Chase Wehrle:Nothing to Disclose, Sami Shoucair:Nothing to Disclose, MUHAMMAD AHMAD NADEEM:Nothing to Disclose, Kyungran Justina Cho: Nothing to Disclose, Kim Jaekeun:Nothing to Disclose, Federico Aucejo:Nothing to Disclose, Koji Hashimoto:OrganOx: Advisor, Mazhar Khalil:Nothing to Disclose.

4448 | EARLY POST-OPERATIVE OUTCOMES IN PEDIATRIC LIVER RECIPIENTS OF WHOLE, REDUCED AND SPLIT LIVER GRAFTS FOLLOWING NORMOTHERMIC MACHINE PERFUSION

Varvara Kirchner[1] Tyler York[1] Sidra Yang Xu[1] Sue Fu[1] Jacquelyn Yu[1] Kamil Hanna[1] Noelle Ebel[2] Leina Alrabadi[3] Carlos Esquivel[4] Kliment Bozhilov[1] Stephan Busque[1] Kazunari Sasaki[1] Marc Melcher[1] Thomas Pham[1] Gregory Tiao[1], [1]Stanford University, [2]Stanford, [3]Stanford/Lucile Packard Childrens Hospital, [4]Stanford University Medical Center

Background: Limited availability of size-matched organs and higher complication risk remain major challenges in pediatric liver transplantation (LT). Normothermic machine perfusion (NMP) may expand access to life-saving organs for children by enabling prolonged preservation during transport, graft assessment/rehabilitation, and ex vivo graft reduction/splitting prior to implantation. Although NMP is widely used in adult LT, early outcomes in pediatric LT using whole and technical-variant grafts are not well defined. We report early outcomes of NMP for grafts intended for pediatric recipients. **Methods:** We retrospectively evaluated outcomes of liver grafts initially allocated to pediatric recipients that were preserved with NMP and transplanted as whole or technical-variant grafts, with a minimum follow-up of 30 days. Livers were transported on NMP and transplanted either as whole grafts or after ex vivo reduction/splitting at the recipient center. Donor/recipient characteristics, 30-day graft survival, and early allograft function were assessed. **Results:** Twenty-three livers underwent NMP. Eleven were transplanted as whole grafts into pediatric recipients, including one simultaneous heart–liver and one lung–liver transplant. Seven grafts were reduced after NMP and transplanted as left or extended-left segments into pediatric recipients. Five grafts were split into extended-right segments (ERS) and left-lateral segments (LLS); 4 ERS were transplanted into adults and 1 into a teenage recipient (simultaneous liver–kidney), and all 5 LLS were transplanted into infants. Pediatric recipient age ranged from 6 months to 17 years for whole grafts and 6 months to14 years for technical variant grafts. All grafts were from donors following donation after brain death with age range 2–53 years old. NMP duration was 8–31 hours and transport distance to recipient hospital was 250–2,300 nautical miles. Thirty-day graft survival was 91% for whole grafts, 100% for reduced grafts, 80% for LLS, and 80% for ERS. Causes of graft loss within 30 days: primary nonfunction (1 whole graft from a pediatric donor; 1 ERS in an adult recipient) and 1 portal vein

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thrombosis (LLS). Postoperative laboratory trajectories for grafts surviving ≥30 days are summarized in Table 1. **Conclusion:** NMP for pediatric recipients increases access to high quality livers by enabling extended-distance transport and optimizing transplant logistics with acceptable short-term graft survival for whole and reduced grafts. The outcomes after split/reduced graft transplantation following NMP warrant further evaluation and technical optimization, particularly for small-volume grafts that demonstrate pronounced early transaminitis.

Table 1: Post-Operative Lab Trajectory of Grafts with >30-Day Survival

	Median Peak Lactate (mmol/L)	Post-op Day Normal Lactate	Median Peak ALT (IU/L)	Post-op Day ALT<200	Median Peak AST (IU/L)	Post-op Day AST <200	Peak T Bili (mg/dL)	Post-op Day T Bili <2.5	Peak INR	Post-op Day INR≤2
Whole Graft (n=10)	4.7 (1.5-9.4)	1 (0-4)	610 (215-2773)	5 (0-6)	1219 (460-6460)	9 (1-7)	3.2 (1.5-9.4)	1 (0-8)	1 (1.4-1.7)	0 (0-1)
Reduced Left or Extended Left Segments (V, VIII) (n=7)	2.9 (1.5-6.7)	1 (0-5)	1520 (1021-7000)	9 (7-11)	1255 (1263-7000)	6 (4-8)	3.8 (0.5-10.8)	7 (0-19)	2.8 (2.6-6.1)	3 (0-7)
Split Left Lateral Segment (n=4)	2.35 (1.5-9)	0 (0-5)	2389 (210-7000)	8 (0-12)	4845 (162-7000)	0 (4-8)	9 (4.7-9.4)	11 (1-11)	4.2 (2.5-6.8)	1 (0-4)
Split Extended Right Segment (4)	3.4 (2.2-9.1)	0 (0-1)	1252 (634-1420)	0 (4-7)	1913 (1166-2756)	5 (0-8)	3.1 (1.9-15.3)	1 (0-41)	2.2 (1.9-2.4)	1 (0-2)

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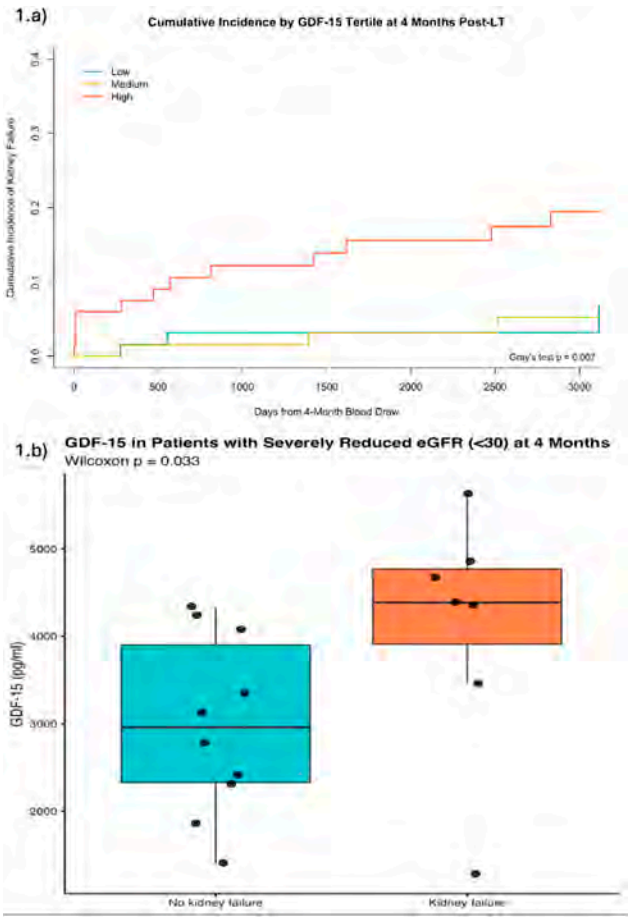
4449 | GDF-15 AT 4 MONTHS POST-LIVER TRANSPLANTATION PREDICTS KIDNEY FAILURE AND ENHANCES RISK STRATIFICATION IN PATIENTS WITH SEVERELY REDUCED EGFR

Kai-Philipp Seeger[1] Zhihao Li[2] Julie Heimbach[1], [1]Mayo Clinic Rochester, [2]Mayo Clinic

Background: 5-year-incidence of post-transplant kidney failure in liver transplant (LTx) patients is 29%, carrying significant morbidity and mortality. Growth differentiation factor 15 (GDF-15), a stress-responsive cytokine released under tissue injury and metabolic stress, correlates with chronic kidney disease (CKD) progression in both diabetic and non-diabetic populations. We assessed GDF-15 as a novel biomarker for post-transplant kidney failure. **Methods:** Adults undergoing orthotopic LTx for metabolic dysfunction-associated liver disease at Mayo Clinic Rochester (2010–2024), who had frozen plasma samples drawn pre-transplant (t0) and at 4 months post-transplant (t4) stored in the institutional biobank, were included. GDF-15 was assessed using enzyme-linked immunosorbent assay. Kidney failure was defined as sustained estimated glomerular filtration rate (eGFR) <15 mL/min/1.73m² or dialysis dependency over 30 days. GDF-15 was log-transformed prior to regression analyses. Time-to-event analyses used Fine-Gray models for competing risks regression, with death as a competing event. **Results:** 213 patients with a median age of 59.4 years [IQR: 54.4–64.6] were included. 26 (12%) patients developed kidney failure and 65 (31%) died over a median follow-up of 7.3 years. The median model for end-stage liver disease (MELD) score at LTx was 23 [IQR:15-32] and 59% of patients were diabetic. Median GDF-15 declined significantly from 3,834 pg/mL at t0 [IQR: 2,591–5,742] to 2,161 pg/mL at t4 [IQR: 1,411–3,546] (paired t-test, $p = 0.013$). Pre-transplant GDF-15 correlated with MELD score ($R^2 = 0.40$, $p = 0.013$) and was independently associated with diabetes (OR: 2.06, 95% CI 1.22–3.64, $p = 0.008$). GDF-15 at t4 independently predicted kidney failure (HR: 2.59, 95% CI 1.03–6.55, $p = 0.04$), with the strongest effect in the first post-transplant year (HR: 11.6, 95% CI 1.4–94.68, $p = 0.028$). Competing risks regression confirmed this association accounting for the high competing risk of death (sub-distribution HR: 1.66, 95% CI 1.06–2.58, $p = 0.025$, *figure 1.a*). Discrimination tended to be superior to concurrent eGFR (C-statistic 0.760 vs. 0.733), failing to reach significant superiority. In the subgroup of patients with severely reduced eGFR at 4 months (<30 mL/min/1.73m², n = 23), GDF-15 significantly discriminated between progressors to kidney failure and non-progressors (median 4,387 vs 2,961 pg/mL, $p = 0.033$, *figure 1.b*). This suggests additive value in the highest-risk stratum, although these findings should be interpreted cautiously given the small subgroup size. **Conclusion:** GDF-15 at 4 months post-LTx independently predicts kidney failure across multiple analytical frameworks and adds risk stratification beyond eGFR in the highest-risk patients, with implications for early identification of candidates who may benefit from calcineurin inhibitor minimization or subsequent kidney transplantation referral.

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Disclosures: Kai-Philipp Seeger:Nothing to Disclose, Zhihao Li:Nothing to Disclose, Julie Heimbach:Nothing to Disclose.

4450 | IMPACT OF DONOR-LIVER ENZYMES FLUCTUATIONS ON LIVER TRANSPLANTATION OUTCOME

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Background: Organ shortage remains a critical issue in liver transplantation (LT). While multiple strategies aim to expand the donor pool, the impact of pre-procurement fluctuations in donor liver enzymes on post-LT outcomes is unclear. We evaluated whether LTs from donors with marked variations in donor alanine aminotransferase (ALT) were associated with poorer outcomes and should influence graft acceptance. **Methods:** Donor ALT variation within 7 days before procurement was quantified using a linear regression coefficient. Patients were classified as "Stable ALT" (patients whose donor had stable ALT, eg. regression coefficient [-10, 10) IU/day) or "Disturbed ALT (D-ALT)" (patients whose donor had either ascending or declining ALT, eg. regression coefficient < -10 or ≥ 10 IU/day). The primary endpoint was arterial and biliary complication (ABC)-free interval. Secondary endpoints included 60-month ABC-free survival (ABCFS), 60-month transplant survival, early allograft dysfunction and acute kidney injury. First analysis included LTs performed at our center (2012–2020); Second analysis included all eligible adult LTs performed in all other French LT centers (2008–2020). Survival analyses were adjusted using propensity scores. **Results:** In the derivation cohort (n = 565), 361 patients were in the « Stable ALT » group and 204 in the « D-ALT » group. « Stable ALT » donors were older (p < 0,001), more frequently hypertensive (p < 0,001) and less likely to have experienced cardiac arrest prior organ procurement (p < 0,001). Graft-to-recipient weight ratio was lower (p < 0,01) and Euro-Transplant Donor Risk Index higher (p < 0,01) in the « Stable ALT » group. Recipient variables were comparable between the two groups. Following compensation with the propensity score, at 60 months, at least one ABC event occurred more often in « Stable ALT » group (31.4% vs. 21.1%; p = 0.02). At multivariate analysis « D-ALT » was associated with longer ABC-free interval (0.80 vs 0.65; p < 0.01) and higher ABCFS (0.65 vs 0.51; p < 0.01). At univariate analysis, 60-month post LT survival was also better in « D-ALT » group (p = 0.02). Other post operative complications were comparable. The French cohort (n = 7621) confirmed similar donor and recipient characteristics. A trend toward improved transplant survival was observed in « D-ALT » group (p = 0.21). **Conclusion:** Fluctuations in donor ALT-whether increasing or decreasing- within 7 days before procurement were not associated with worse post-LT outcomes and were even linked to improved ABC-free interval which could lead to a beneficial effect on transplant survival. These findings suggest that marked fluctuations in donor ALT levels alone should not justify discarding liver grafts.

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4451 | SEX DISPARITIES IN LIVER TRANSPLANT PRIORITIZATION ACROSS SCORING SYSTEMS: A KOREAN MULTICENTER COHORT STUDY

Jeayeon Park[1], [1]Ajou University Hospital

Background: Given the scarcity of donor organs, equitable allocation in deceased donor liver

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transplantation (DDLT) is crucial. The Model for End-Stage Liver Disease (MELD) score was developed to prioritize patients with the highest mortality risk. Although it has significantly improved organ allocation, the MELD score has been associated with sex disparities, leading to the introduction of MELD 3.0. However, validation of these revised models in Asian populations remains limited. Thus, using a Korean multicenter cohort, this study aims to validate whether these improved scoring systems mitigate sex disparities in liver transplant allocation within an Asian population. **Methods:** We retrospectively analyzed consecutive patients aged ≥19 years listed for DDLT between 2010 and 2024 using multicenter cohorts from Seoul National University Hospital (SNUH) and the Catholic Medical Center (CMC). To account for the transition in South Korea's organ allocation system from the Child-Pugh Score (CPS) to the MELD score during the study period, analyses were stratified into the CPS era and the MELD era. The primary outcome was DDLT within 90 days. Death without transplantation was treated as a competing event, and the outcomes were assessed using cumulative incidence functions and Fine–Gray subdistribution hazard models. The secondary outcomes were transplantation-free survival (TFS) and 90-day waitlist mortality. **Results:** A total of 1,390 patients were included (1,034 from SNUH and 356 from CMC). During the Child-Pugh Score (CPS) era, the cumulative incidence of DDLT within 90 days was significantly higher in females (subdistribution hazard ratio 1.37, 95% CI 1.06–1.78, P = 0.02, Figure 1). However, this sex disparity was resolved in the MELD era (P = 0.36). Waitlist mortality showed no significant sex differences in either the CPS (P = 0.95) or MELD (P = 0.38) eras. Transplantation-free survival (TFS) was significantly reduced in females during the CPS era (hazard ratio 1.32, 95% CI 1.07–1.63, P = 0.01), likely driven by their higher transplantation rate, whereas no significant difference was observed in the MELD era (P = 0.85) (Figure 2). Furthermore, in the CPS era, the sex-based difference in 90-day waitlist mortality risk increased sharply within the high-risk group. In the MELD era, the Gender-Equity Model for Liver Allocation corrected by serum sodium (GEMA-Na) model demonstrated the lowest and most stable sex disparity (Figure 3). **Conclusion:** While the transition of DDLT allocation criteria from CPS to the MELD score has partially alleviated sex disparities, our findings suggest that GEMA-Na could serve as a more optimal scoring system for the Asian population.

Figure 1

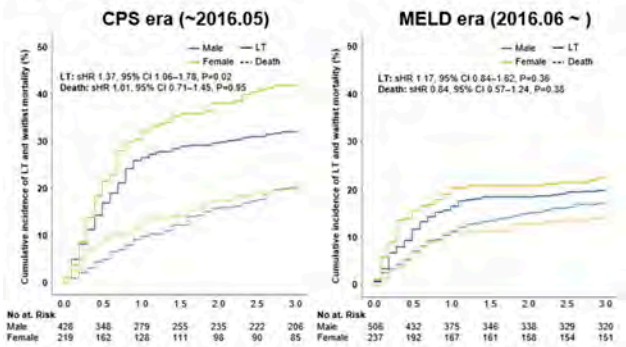


Figure 2

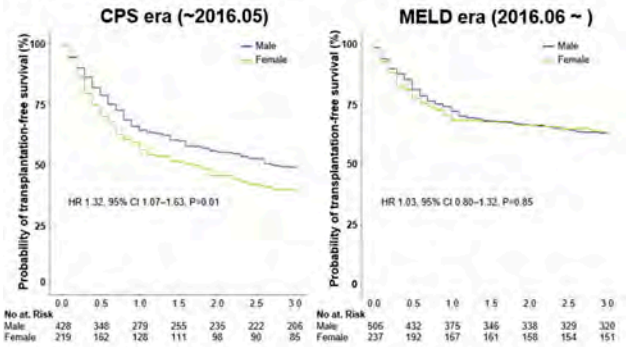
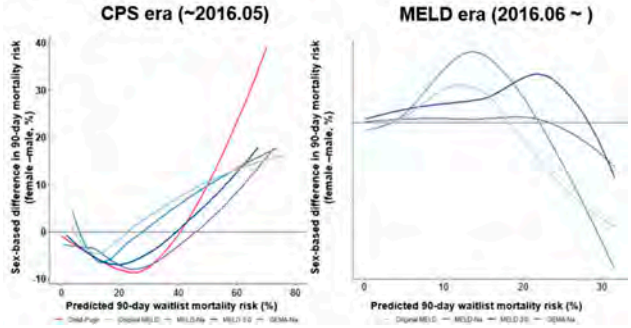


Figure 3



Disclosures: Jeayeon Park:Nothing to Disclose.

4452 | MELD 3.0 AND GENDER DISPARITY IN SIMULTANEOUS LIVER KIDNEY TRANSPLANTATION IN THE UNITED STATES - ANALYSIS OF SRTR DATA

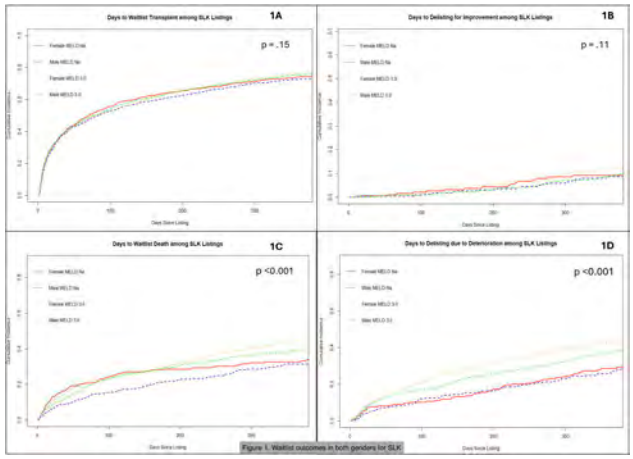
Ragesh Thandassery[1] Allison Wells[1] Drew Castleberry[1] Urveesh Sharma[2] Tamar Taddei[3], [1]University of Arkansas for medical Sciences, Little Rock, AR, [2]University of Arkansas for Medical Sciences, Little Rock,AR, [3]Yale University, New Haven

Background: Gender disparities in liver transplantation (LT) and simultaneous liver-kidney

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transplantation (SLK) in the United States are a significant concern. MELD 3.0 was designed to address gender disparity in LT; its real-world impact on SLK has not been studied. We analyzed Scientific Registry of Transplant Recipients data from January 2018 to June 2023 (T1-pre-MELD 3.0) and July 2023 to March 2026 (T2-post-MELD 3.0) to assess these effects. **Methods:** We analyzed primary outcomes including days to transplant, waitlist mortality, delisting due to clinical deterioration and delisting due to improvement. Bivariate analysis by gender were done for each era. Cause specific cumulative incidence functions for each outcome stratified by gender and era were built. Differences between groups were evaluated with Gray's test. **Results:** A total of 6,102 candidates in T1 and 2,123 candidates in T2 were listed for SLK. Age at listing was higher for women in both eras. The ethnic distribution was similar between genders in both eras. The etiology of cirrhosis was different, predominantly alcohol related in men and metabolic dysfunction associated steatotic liver disease in women, in both eras. Women had lower serum creatinine levels (at listing) in both eras (T1- 2.67 [IQR 1.79-4.09] vs 3.41 [IQR 2.21-5.41], $p < 0.001$ and T2- 2.61 [1.83-4.10] vs 3.50 [2.30-5.39], $p < 0.001$). The median MELD at listing was higher for women in T2 (24 [20-30] vs 23 [20-29], $p = 0.035$), but the same in T1 (24 for both), $p = 0.27$. The distribution of SLK listings across UNOS regions did not reveal gender disparity in either era. The median waiting time for SLK was similar for both genders in both eras, however it was lower for both genders in T2. Most importantly, persistence on the wait list was lower for women in T2 (11.3% vs 14.3%, $p = 0.043$). During the follow-up period, the number of patients receiving SLK was comparable in both genders in both eras (M/F 62.1%/61.2% in T1 and 62.2%/60.6% in T2), Fig.1A. Similarly, the rates of delisting for improvement on the waitlist were comparable between both genders in both eras, Fig.1B. There were more deaths on the waitlist in both genders in T2 (Fig.1C) and more delisting due to deterioration in both genders in Group T2 (Fig.1D). **Conclusion:** Following the implementation of MELD 3.0, the median MELD at listing for SLK became higher for women, and a lower percentage of women remained on the waitlist for SLK. No significant gender disparity was observed in SLK rates or delisting due to clinical improvement or deterioration before or after implementation of MELD 3.0. Long-term follow-up is required to understand further the impact of MELD 3.0 on addressing gender disparity in the receipt of SLK.



Disclosures: Ragesh Thandassery:Nothing to Disclose, Allison Wells:Nothing to Disclose, Drew Castleberry:Nothing to Disclose, Urveesh Sharma:Nothing to Disclose, Tamar Taddei:Nothing to Disclose.

4453 | WAITLIST OUTCOMES ARE BETTER, AND POST-TRANSPLANT OUTCOMES ARE SIMILAR IN ALCOHOL ASSOCIATED HEPATITIS VS. ALCOHOL ASSOCIATED CIRRHOSIS: A UNOS ANALYSIS

Bipneet Singh[1] Mangesh Pagadala[2] Yong-Fang Kuo[3] Umang Arora[4] Anil Arora[5] Robert Wong[6] Winston Dunn[7] Brian Lee[8] Norah Terrault[9] Ashwani Singal[10], [1]University of Kentucky, [2]Liver Institute Methodist Dallas, Irving, United States,, [3]University of Texas Medical Branch, Galveston, United States, [4]Mayo Clinic, Rochester, [5]Sir Ganga Ram Hospital, [6]Stanford/ VA Palo Alto Healthcare System, [7]University of Kansas Medical Center, [8]Keck School of Medicine, University of South California, United States, [9]University of Southern California, [10]University of Louisville

Background: Alcohol-associated liver disease, which includes alcohol-associated cirrhosis (AC) and alcohol-associated hepatitis (AH) forms the leading indication of liver transplantation. Post-LT results in AH were similar to those of LT recipients for AC in our earlier study (UNOS database). However, information regarding waiting outcomes and long-term post-transplant outcomes comparing AH and AC is scarce. **Methods:** UNOS codes were used to stratify adult LT listings for ALD in the UNOS database (01/2004-03/2025) to AH and AC as indications. Living donor LT was not

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included. AH and AC were compared in the following analyses: a) trends on listings and LT; b) 90-day cumulative waitlist (WL) mortality and receipt of LT using competing risk analysis; and c) 10-yr. post-LT graft and patient survival. Propensity score matching (PSM) was performed to balance baseline demographic, clinical, and disease severity variables at listing. Sub-hazard ratios (SHR) and 95% confidence intervals (95% CI) were reported for WL outcomes using Fine and Gray models, and HR (95% CI) reported outcomes using Cox proportional models. **Results:** Of 63,025 listings [4168 (6.6%) AH], listings for AH increased from 3.1% in 2004 to 16.1% in 2025. Candidates from AH were younger (45 vs. 53 years) and more female (35 vs. 29%), $P < 0.001$. Further, AH candidates were more likely to be obese, on life support, and, despite a higher MELD score, have a better functional status. 90-day cumulative waitlist mortality was lower in AH (13.9 vs. 24.5%) with HR (95% CI) of 0.88 (0.78-0.98), $P = 0.019$. Concurrently, 90-d LT probability was higher in AH (76.9% vs 60.3%), 2.53 (2.43–2.63), $P < 0.001$. In the PSM cohort after matching for demographics and MELD score, 90-d WL mortality was similar comparing AH vs. AC, 0.916 (0.801–1.046), $P = 0.195$. However, AH candidates had a slightly higher probability of 90-d LT, 1.050 (1.003–1.100), $P = 0.037$. Age, MELD score, hepatic encephalopathy, and being on life support were other predictors of WL mortality. Between 2004 and 2025, LT for AH rose from 2.3% to 16.1% of 40,902 LT [3233 (7.9%) AH]. AH and AC on graft had comparable 10-year post-LT results in the PSM cohort [88 vs. 82%, Log Rank $P = 0.329$, 1.09 (0.96-1.24), $P = 0.177$] and patient survival [90 vs. 84%, $P = 0.988$, 1.01 (0.88-1.16), $P = 0.873$] **Conclusion:** Compared to AC, AH had a higher probability of LT, with similar adjusted 90-day waitlist mortality and long-term post-LT graft and patient survival as AC. These results underline the need to assess organ access equity for a wider range of patients with alcohol-related liver disease, while also supporting the continued LT for AH.

Disclosures: Bipneet Singh:Nothing to Disclose, Mangesh Pagadala:Nothing to Disclose, Yong-Fang Kuo: Nothing to Disclose, Umang Arora:Nothing to Disclose, Anil Arora:Nothing to Disclose, Robert Wong:Theratechnologies: Grant/Research Support, Theratechnologies: Grant/Research Support, Durect: Grant/Research Support, Durect: Grant/Research Support, Gilead Sciences: Grant/Research Support, Gilead Sciences: Grant/Research Support, Exact Sciences: Grant/Research Support, Exact Sciences: Grant/Research Support, Madrigal Pharmaceuticals: Grant/Research Support, Theratechnologies: Grant/Research Support, Theratechnologies: Grant/Research Support, Durect: Grant/Research Support, Durect: Grant/Research Support, Gilead Sciences: Grant/Research Support, Gilead Sciences: Grant/Research Support, Exact Sciences: Grant/Research Support, Exact Sciences: Grant/Research Support, Madrigal Pharmaceuticals: Grant/Research Support, Winston Dunn:Nothing to Disclose, Brian Lee:Nothing to Disclose, Norah Terrault:Elseiver: Royalties or patent beneficiary, GSK: Grant/Research Support, Elseiver: Royalties or patent beneficiary, Elseiver: Royalties or patent beneficiary, Eiger Pharmaceuticals: Grant/Research Support, GSK: Grant/Research Support, GSK: Grant/Research Support, Helio Health: Grant/Research Support, Eiger Pharmaceuticals: Grant/Research Support, Eiger Pharmaceuticals: Grant/Research Support, Durect Corp: Grant/Research Support, Helio Health: Grant/Research Support, ImmunoCore: Grant/Research Support, Helio Health: Grant/Research Support, Durect Corp: Grant/Research Support, HBV Foundation: Board member, Durect Corp: Grant/Research Support, AASLD: Executive role, ImmunoCore: Grant/Research Support, ImmunoCore: Grant/Research Support, Genentech-Roche: Grant/Research Support, HBV Foundation: Board member, HBV Foundation: Board member, Hepatitis B Foundation: Executive role, AASLD: Executive role, AASLD: Executive role, Genentech-Roche: Grant/Research Support, Genentech-Roche: Grant/Research Support, Hepatitis B Foundation: Executive role, Hepatitis B Foundation: Executive role, Elseiver: Royalties or patent beneficiary, GSK: Grant/Research Support, Elseiver: Royalties or patent beneficiary, Elseiver: Royalties or patent beneficiary, Eiger Pharmaceuticals: Grant/Research Support, GSK: Grant/Research Support, GSK: Grant/Research Support, Helio Health: Grant/Research Support, Eiger Pharmaceuticals: Grant/Research Support, Eiger Pharmaceuticals: Grant/Research Support, Durect Corp: Grant/Research Support, Helio Health: Grant/Research Support, ImmunoCore: Grant/Research Support, Helio Health: Grant/Research Support, Durect Corp: Grant/Research Support, HBV Foundation: Board member, Durect Corp: Grant/Research Support, AASLD: Executive role, ImmunoCore: Grant/Research Support, ImmunoCore: Grant/Research Support, Genentech-Roche: Grant/Research Support, HBV Foundation: Board member, HBV Foundation: Board member, Hepatitis B Foundation: Executive role, AASLD: Executive role, AASLD: Executive role, Genentech-Roche: Grant/Research Support, Genentech-Roche: Grant/Research Support, Hepatitis B Foundation: Executive role, Hepatitis B Foundation: Executive role, Elseiver: Royalties or patent beneficiary, GSK: Grant/Research Support, Elseiver: Royalties or patent beneficiary, Elseiver: Royalties or patent beneficiary, Eiger Pharmaceuticals: Grant/Research Support, GSK: Grant/Research Support, GSK: Grant/Research Support, Helio Health: Grant/Research Support, Eiger Pharmaceuticals: Grant/Research Support, Eiger Pharmaceuticals: Grant/Research Support, Durect Corp: Grant/Research Support, Helio Health: Grant/Research

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Support, ImmunoCore: Grant/Research Support, Helio Health: Grant/Research Support, Durect Corp: Grant/Research Support, HBV Foundation: Board member, Durect Corp: Grant/Research Support, AASLD: Executive role, ImmunoCore: Grant/Research Support, ImmunoCore: Grant/Research Support, Genentech-Roche: Grant/Research Support, HBV Foundation: Board member, HBV Foundation: Board member, Hepatitis B Foundation: Executive role, AASLD: Executive role, AASLD: Executive role, Genentech-Roche: Grant/Research Support, Genentech-Roche: Grant/Research Support, Hepatitis B Foundation: Executive role, Hepatitis B Foundation: Executive role, Ashwani Singal:Madrigal: Speaking and Teaching, Pleiogenix: Stock – privately held company, Pleiogenix: Consultant, CLD Foundation: Advisor, Medical Speaker's Network: Speaking and Teaching, Up-to-Date: Royalties or patent beneficiary, Medscape: Speaking and Teaching, University of Louisville School of Medicine: Employee, NIAAA: Grant/Research Support, Gastro Endo News: Executive role, Durect: Advisor, University of Louisville Health: Other.

4454 | TWO-DECADE TRENDS AND OUTCOMES OF LIVER TRANSPLANTATION FOR AUTOIMMUNE HEPATITIS IN THE UNITED STATES AND EUROPE

Maria Stepanova[1] Giacomo Germani[1] Ana Lleo[1] Vincent Karam[1] René Adam[1] Saleh Alqahtani[1] Linda Henry[1] Patrizia Burra[1] Zobair Younossi[1], [1]The Global NASH/MASH Council

Background: Autoimmune hepatitis (AIH) is an immune-mediated liver disease that may progress to liver failure requiring liver transplantation (LT). We assessed demographics, clinical features, and outcomes of LT recipients with AIH in the US and Europe. **Methods:** Adult (≥18) LT recipients with AIH were identified from the European Liver Transplant Registry (ELTR) and U.S. Scientific Registry of Transplant Recipients (SRTR) (2000–2022) using their primary listing diagnoses. **Results:** Over 22 years, a total of 6,925 LT recipients with AIH were included (ELTR n = 3,069; SRTR n = 3,856). The AIH recipients in SRTR were older (mean ± SD : 48 ± 15 vs. 46 ± 15 years, p < 0.0001), had higher BMI (28.2 ± 6.4 vs. 25.6 ± 5.0, p < 0.0001), and were more likely to have ascites (82% vs. 60%) and hepatic encephalopathy (66% vs. 32%) than those from ELTR (all p < 0.0001). MELD scores were also higher in SRTR (24 ± 10 vs. 18 ± 8, p < 0.0001). Overall, 29% of recipients were male, more common in ELTR (31% vs. 28%, p = 0.01). HCC was present in 6.8% of LT recipients with AIH (increased from 2-4% in 2000-2006 to 11% in 2022, p < 0.0001), while cholangiocarcinoma was rare (< 0.1%). AIH as a proportion of all LTs for a chronic liver disease increased in ELTR from 2.8% (2000) to 3.8% (2022) (p < 0.0001), while remaining stable in SRTR (pooled 3.2%, p > 0.05). Post-transplant mortality was 11% at 1 year, 17% at 3 years, 22% at 5 years, and 35% at 10 years. In multivariable survival analyses of patients with AIH, higher post-transplant mortality was independently associated with earlier calendar year (aHR (95% CI) = 0.982 (0.972-0.992) per year), older age (1.014 (1.010-1.018) per year), higher MELD score (1.013 (1.007-1.019) per point), severe hepatic encephalopathy (1.44 (1.21-1.72)), transplantation in a small transplant center (< 15/year; aHR = 1.56 (1.13-2.16)), and older donor age (1.007 (1.004-1.010) per year) (all p < 0.05). There was no significant difference in post-transplant mortality between ELTR and SRTR (aHR = 1.05 (0.92-1.20), p = 0.51), and recipient-donor sex matching was also not associated with post-transplant survival (aHR = 1.00 (0.90-1.11), p = 0.97). **Conclusion:** Liver transplantations for AIH remained stable in the US but increased in Europe over time. Despite regional differences in recipient characteristics, post-transplant survival was similar between ELTR and SRTR cohorts. Post-transplant survival exceeded 75% at 5 years in both registries and continued to improve over time.

Disclosures: Maria Stepanova:Nothing to Disclose, Giacomo Germani:Nothing to Disclose, Ana Lleo: Advanz Pharma: Advisor, Ipsen: Advisor, GSK: Advisor, AstraZeneca: Advisor, Gilead: Speaking and Teaching, Abbvie: Speaking and Teaching, MSD: Speaking and Teaching, Advanz Pharma: Speaking and Teaching, AlfaSigma: Speaking and Teaching, GSK: Speaking and Teaching, Gilead: Consultant, Mirum: Consultant, Mirum: Speaking and Teaching, Ipsen: Speaking and Teaching, Vincent Karam:Nothing to Disclose, René Adam:Nothing to Disclose, Saleh Alqahtani:Nothing to Disclose, Linda Henry:Nothing to Disclose, Patrizia Burra:Nothing to Disclose, Zobair Younossi:Zobair M. Younossi is a consultant or has received research: Consultant, madrigal: Grant/Research Support, Siemens: Research funding, GSK: Consultant, BI: Consultant, Sanofi: Research funding.

4455 | CONTROLLED ATTENUATED PARAMETER (CAP) IS AN ACCURATE METHOD TO SCREEN LIVING LIVER DONOR (LLD) CANDIDATES IRRESPECTIVE OF OBESITY

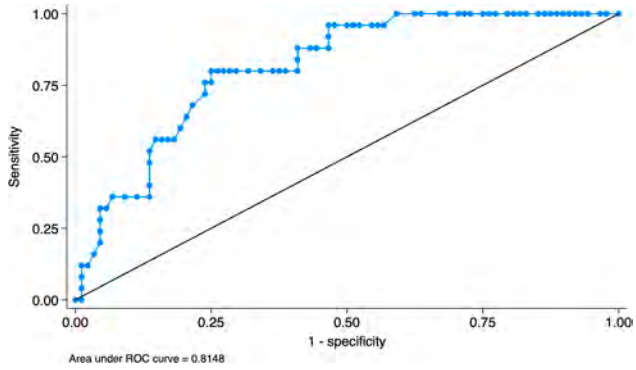
Lane Herbert[1] Jacob Liskh[1] Daniel Borja-Cacho[2] Justin Boike[3] Juan Carlos Caicedo[1] Daniel Ganger[4] Zachary Dietch[1] Daniela Ladner[5] Amir Borhani[1] Sarang Thaker[2]

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Christopher Moore[1] Andres Duarte-Rojo[1], [1]Northwestern Medicine, [2]Northwestern, [3]Northwestern Memorial Hospital/Northwestern University, [4]Northwestern Memorial Hospital, [5]Northwestern University

Background: Steatosis assessment with CAP from vibration-controlled transient elastography (VCTE) has been proposed as an alternative to proton density fat fraction (PDFF) from magnetic resonance in LLD. In November 2025, we incorporated VCTE (Fibroscan 430, Echosens, Paris) to the standard of care of our LLD evaluations. Herein, we report our comparative experience against PDFF and liver biopsy. **Methods:** This was a prospective quality improvement project. Apart from baseline characteristics and steatosis metrics, transplant outcomes were collected. We used the following PDFF thresholds for steatosis grading: < 6.4%, 6.4 to < 17.4%, 17.4 to < 22.1%, and 22.1% for grades 0-3, respectively. ROC curves were constructed to assess CAP accuracy to identify any degree of steatosis. When available, steatosis grading was compared against biopsy. **Results:** A total of 124 donors were evaluated (71 [57%] female; 39 ± 10 years; White 77%; obese 30%). VCTE was done in 123, and PDFF in 115. Forty-eight LLD candidates were approved for donation and 27 ultimately donated. Main reasons for decline were surgical 30%, consent withdrawn 13%, having a deceased donor offer 10%, medical and alternate LLD candidate 8% for either. Both CAP (248 dB/m [212-305] vs 223 [192-256]; p < 0.002) and PDFF (4.1% [2.7-6.5] vs 2.8 [2.1-4.8]; p = 0.034) were higher among nonapproved vs approved donors, and there was a trend for BMI (28.4 ± 4.5 kg/m^2 vs 26.9 ± 3.5; p = 0.051). However, there were no differences in liver stiffness (4.8 [4.2-6.7] vs 5.0 [4.1-5.9]; p = 0.68). Steatosis (any degree) by PDFF was found in 22%. The CAP AUROC showed excellent accuracy to identify any degree of steatosis (**Figure**) and 255 dB/m was the threshold with best sensitivity (80%), specificity (75%), and positive/negative predictive values (93% and 48%); the AUROC for moderate-to-severe steatosis was 0.808. Using the recommended threshold of 300 dB/m for moderate-to-severe steatosis, CAP overestimated steatosis in 19 LLD who had no or mild steatosis per PDFF. Sensitivity analysis limiting donors to those with BMI ≤ 30 or ≤ 35 kg/m^2 did not change results. Among 17 donors with liver biopsy, 3 had mild steatosis and there was similar agreement with either CAP (82.4%, kappa = 0.564, p = 0.004) or PDFF (82.3%, kappa = 0.463, p = 0.02). **Conclusion:** Our results support the use of CAP in LLD given its excellent accuracy. CAP offers a practical alternative to rule out steatosis with a high negative predictive value. This strategy can be particularly applied to rapidly screen for LLD in outreach or peripheral clinics where PDFF is not available.



Disclosures: Lane Herbert:Nothing to Disclose, Jacob Liskh:Nothing to Disclose, Daniel Borja-Cacho:Nothing to Disclose, Justin Boike:W. L. Gore and Associates: Grant/Research Support, Echosens: Consultant, W. L. Gore and Associates, Inc.: Consultant, Novo Nordisk: Speaking and Teaching, Juan Carlos Caicedo:Nothing to Disclose, Daniel Ganger: WCG: Consultant, Zachary Dietch:Nothing to Disclose, Daniela Ladner:Nothing to Disclose, Amir Borhani:Nothing to Disclose, Sarang Thaker:Nothing to Disclose, Christopher Moore:Nothing to Disclose, Andres Duarte-Rojo:Echosens: Grant/Research Support, Echosens: Grant/Research Support, CIMA Sciences: Consultant, HepQuant: Advisor, Merz: Advisor, CIMA Sciences: Grant/Research Support, Merz Therapeutics: Advisor.

4456 | OUTCOMES OF LIVER RETRANSPLANTATION IN THE UNITED STATES: A 25-YEAR ANALYSIS OF THE UNOS STAR REGISTRY (2000–2024)

Kevin Nhieu[1] Oliver Liu[1] Megan Castle[1] Anjelica Alfonso[1] Sonal Rajpal[1] Jacob Hallesy[1] Shashank Nadimpalli[1] Daisuke Imai[1], [1]Virginia Commonwealth University School of Medicine

Background: Liver retransplantation remains the only curative option for organ/graft failure (GF) following primary liver transplant. However, the risk factors for poor outcomes after liver retransplantation remain incompletely defined. In this study, we aimed to identify predictors of post-retransplant GF and produce an associated risk stratification model. **Methods:** We analyzed adult deceased-donor liver transplants in the UNOS STAR registry from 2000 through 2024, identifying a group of retransplants (n = 9,615) and primary transplants (n = 150,320). Survival analyses

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were applied to a propensity-matched group of subjects (using BMI, sex, age, Karnofsky performance status (KPS), transplant era, center volume, MELD, deceased donor status) with known 1-year mortality outcomes (n = 16,330). Using a multivariable Cox model, we identified predictors of both overall and death-censored GF. **Results:** Kaplan-Meier analysis indicated that retransplantation had significantly worse survival outcomes than primary transplantation, both for graft failure ($p < 0.001$) and patient mortality ($p < 0.001$). On logistic regression, prior graft failure due to biliary complication (OR 4.42; $p < 0.001$), infection (OR 4.99; $p < 0.001$), and hepatic arterial thrombosis (OR 2.52; $p = 0.004$) were the strongest graft-loss predictors. Later transplant era markedly reduced risk (2016–2020 vs 2000–2005: OR 0.50; $p < 0.001$). Cox modeling identified recipient age, MELD, donor age, KPS, cause of prior failure, and transplant era as significant predictors of GF. **Conclusion:** Retransplant recipients face substantially lower graft survival than primary recipients, even after propensity adjustment. Prior graft failure due to biliary complication or infection confers the greatest graft-loss risk, while era-level improvements reflect advances in perioperative care. Recipient age, MELD, donor age, KPS, cause of prior failure, and transplant era are significant predictors of post-retransplant GF and should inform patient selection and risk counseling.

Table 3. *Multivariable logistic regression for 1-year graft loss: overall graft survival (death = event) and death-censored graft survival (death = censored).*

Covariate	Overall Graft Survival OR (95% CI)	p	Death-Censored Graft Survival OR (95% CI)	p
Recipient Factors				
Recipient age (per year)	1.02 (1.02–1.03)	<0.001	1.01 (1.00–1.02)	0.011
MELD at retransplant (per point)	1.01 (1.01–1.02)	0.001	1.01 (1.00–1.02)	0.204
Karnofsky performance status (per point)	0.99 (0.99–1.00)	<0.001	0.99 (0.98–1.00)	0.003
Hospitalized (floor/ward) vs outpatient at transplant	0.81 (0.66–0.99)	0.037	0.90 (0.64–1.26)	0.537
ICU vs outpatient at transplant	0.92 (0.70–1.21)	0.559	1.27 (0.81–1.99)	0.304
Donor Factors				
Donor age (per year)	1.01 (1.00–1.01)	0.033	1.00 (0.99–1.01)	0.712
DCD donor	1.08 (0.51–2.30)	0.846	1.74 (0.51–6.00)	0.379
Cause of Prior Graft Failure				
Biliary complication	4.42 (2.37–8.25)	<0.001	4.97 (2.63–9.37)	<0.001
Hepatic artery thrombosis	2.52 (1.34–4.75)	0.004	2.70 (1.39–5.26)	0.004
Infection	4.99 (2.95–8.44)	<0.001	5.16 (3.03–8.79)	<0.001
Era and Center Effects				
Era 2011–2015 vs 2000–2005	0.61 (0.48–0.77)	<0.001	0.50 (0.33–0.74)	<0.001
Era 2016–2020 vs 2000–2005	0.50 (0.39–0.65)	<0.001	0.32 (0.20–0.52)	<0.001
Center volume Q4 vs Q1	1.07 (0.86–1.33)	0.530	0.92 (0.64–1.34)	0.669

Note: *ORs > 1 indicate higher odds of graft loss within 1 year. Overall graft survival (OGS) counts patient death as a graft failure; death-censored graft survival (DCGS) censors patients who die with a functioning graft, isolating allograft-specific failure. Reference categories: cause of prior failure = Acute Rejection; medical condition at transplant = not hospitalized/outpatient; era = 2000–05; center-volume quartile: Q1 = lowest-volume centers, Q4 = highest-volume centers.*

Disclosures: Kevin Nhieu:Nothing to Disclose, Oliver Liu:Nothing to Disclose, Megan Castle:Nothing to Disclose, Anjelica Alfonso:Nothing to Disclose, Sonal Rajpal:Nothing to Disclose, Jacob Hallesy:Nothing to Disclose, Shashank Nadimpalli:Nothing to Disclose, Daisuke Imai:Nothing to Disclose.

4457 | OUTCOMES OF DIFFERING SUTURING TECHNIQUES ON BILIARY ANASTOMOTIC COMPLICATIONS AFTER LIVER TRANSPLANT

Adina Shrestha[1] Sophia Cury[1] Megan Lee[1] Ritika Kanapareddy[1] Hannah Alex[1] Daisuke Imai[1] Yuzuru Sambommatsu[1] Vinay Kumaran[1] Muhammad Saeed[1] Amit Sharma[1] Adrian Cotterell[1] David Bruno[1] Seung Lee[1] Aamir Khan[1], [1]Virginia Commonwealth University School of Medicine

Background: Biliary anastomotic complications, including strictures, leaks, and post-transplant cholangitis, remain common after liver transplantation and may impact graft and patient survival. Anastomosis technique is a potentially modifiable factor, but comparative evidence between continuous and mixed (continuous-posterior/interrupted-anterior) techniques is limited. **Methods:** The retrospective study cohort included 373 adult liver transplant recipients between July 2022 to December 2024 (continuous n = 295; mixed n = 55; interrupted n = 23). Primary outcomes were anastomotic biliary stricture, bile leak, and post-transplant cholangitis. Propensity score matching (PSM, 1:1, n = 96) was performed on 8 clinically selected covariates (recipient age, sex, BMI, MELD, warm and cold ischemia times, NMP use, biliary duct size mismatch) with priority weighting for key confounders. Outcomes were compared using chi-square/Fisher's exact tests, Mann-Whitney U test, logistic regression (adjusted for residual imbalance), and time-to-event analyses with Kaplan-Meier curves and Cox proportional hazards models. **Results:** Baseline characteristics were well balanced after PSM (⅞ covariates with |SMD| < 0.10; biliary mismatch slightly imbalanced, |SMD| ~ 0.12, adjusted in regression). Unadjusted and adjusted analysis showed no statistically significant differences in primary outcomes between continuous and mixed techniques: anastomotic stricture (18.4% vs. 20.0%; adjusted OR 0.98, 95% CI 0.44-2.18), bile leak (7.1% vs. 5.5%; adjusted OR 0.90, 95% CI 0.23-3.49), post-transplant cholangitis (16.3% vs. 20.0%; adjusted OR 1.25, 95% CI 0.55-2.80). Time-to-event analysis confirmed these findings, with 1-year stricture-free survival rates of 83.1% (continuous) vs. 84.3% (mixed, log-rank p = 0.946) and bile leak-free survival rates of 93.3% vs. 96.2% (log-rank p = 0.393). Similarly, patient and graft survival showed no significant differences (adjusted HR range 0.67-0.90). **Conclusion:** Continuous and mixed sutures techniques demonstrated comparable rates of biliary

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anastomotic complications and survival outcomes after liver transplantation. Limitations included modest sample size, organ specific factors, and potential surgeon-specific technical confounders. Despite these constraints, the findings suggest similar safety profiles for continuous and mixed biliary anastomotic techniques. Prospective studies are needed to confirm these results and guide optimal surgical practice.

Disclosures: Adina Shrestha:Nothing to Disclose, Sophia Cury:Nothing to Disclose, Megan Lee:Nothing to Disclose, Ritika Kanapareddy:Nothing to Disclose, Hannah Alex:Nothing to Disclose, Daisuke Imai: Nothing to Disclose, Yuzuru Sambommatsu:Nothing to Disclose, Vinay Kumaran:Nothing to Disclose, Muhammad Saeed:Nothing to Disclose, Amit Sharma:Nothing to Disclose, Adrian Cotterell:Nothing to Disclose, David Bruno:Nothing to Disclose, Seung Lee:Nothing to Disclose, Aamir Khan:Nothing to Disclose.

4458 | TRACKING LIVING DONOR-CANDIDATE DYADS: EHR INFRASTRUCTURE CHALLENGES

Ursula Rogers[1] Tyler Schappe[1] Anthony Dreher[2] Jacqueline Henson[1] Elisa Gordon[2] Neehar Parikh[3] Peter Reese[2], [1]Duke University, [2]Vanderbilt University Medical Center, [3]University of Michigan Medical Center

Background: Living donor liver transplantation (LDLT) offers superior outcomes compared to deceased donor transplantation, including improved survival and reduced waitlist time. Yet over the past decade, growth in living donation has stagnated. An underexplored barrier to LDLT access is the health system–level data infrastructure to support the study and improvement of the living donor pipeline. **Methods:** We assembled a retrospective cohort of adults (age $\geq$18) referred for LT evaluation or living liver donation between November 1, 2016, and December 31, 2022, at Duke University Medical Center and Vanderbilt University Medical Center. Investigators extracted data directly from the EHRs of each institution. We linked potential living donors with their intended recipients to examine interactions between the donor and candidate experiences. Potential living donors with a linked potential liver transpalnt recipient were considered dyads. **Results:** Among 603 donor referrals during the study period, 20 linked dyads were ultimately deemed implausible: 19 because the donor referral date occurred prior to the candidate referral date and 1 because the donor was linked to the wrong referral episode in a candidate with 3 referrals during the study period. In addition, 25 unique donor study IDs were present in the donor cohort file but did not appear in the dyad file. Of these, 15 were referred after the recipient's administrative censor date or prior to the recipient referral date, 2 were incorrectly labeled as donating an organ not needed by their intended recipient, 1 was linked to a recipient who was incorrectly listed, and 6 donors were excluded due to the donor referral date occurring prior to the recipient referral date. **Conclusion:** The current EHR data infrastructure lacks the capability to allow reliable donor-recipient dyad linkages for patients with multiple transplant referrals. This shortcoming risks implausible dyads in analytic datasets, ultimately reducing the ability to identify where in the pipeline potential donors are lost or evaluate the impact of interventions aimed at converting potential donors to actual donors. These limitations have direct consequences for health system–based research and quality improvement, as the current data environment reduces the living donor process to an incomplete and potentially misleading narrative. Addressing these challenges requires a coordinated approach that spans EHR design, data capture at the point of care, and alignment with national data systems.

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4459 | PUMPING UP THE VOLUME: NORMOTHERMIC MACHINE PERFUSION DRIVES PROGRAM EXPANSION WITHOUT SACRIFICING PATIENT OUTCOMES

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Background: The growing demand for liver transplantation (LT) has driven the adoption of advanced preservation techniques such as normothermic machine perfusion (NMP), enabling expanded utilization of donation after circulatory death (DCD) grafts. DCD donors were associated with higher rates of ischemic cholangiopathy and inferior outcomes compared with donation after brain death (DBD). Recent data suggests that outcomes and survival between DCD and DBD donors are comparable, likely due to improved donor and recipient selection, rapid procurement techniques, and the implementation of machine perfusion technologies. We aim to compare the donor and recipient characteristics, LT outcomes, and discuss real-world experience using NMP at an urban liver transplant center. **Methods:** A retrospective analysis of 165 liver transplant, including simultaneous liver-kidney transplants, preformed from 1/1/2023 to 12/31/2025. Outcomes between NMP and standard static cold storage (SCS) were compared using standard two-sided t-test and chi squared analysis and fisher's exact test for subgroups. **Results:** 165 liver transplants occured during the study period; 97 NMP and 68 SCS LTs (Table 1). Donor characteristics were compared between NMP and SCS groups with significant differences in miles to hospital (202.6 vs 294.3), DCD donors (89 vs 5) and CIT (1011.8 vs 409.3). No difference was found in donor age, BMI, donor risk criteria, or HCV. Recipients' characteristics were compared, showing significant differences in age (55.9 vs 52.4), MELD (22.8 vs 27.9), hospitalized at transplant (23.7% vs 41.2%) and portal vein thrombosis (21.6% vs 8.8%). No difference found in recipient BMI, gender, alcohol associated liver disease, simultaneous liver-kidney transplant or retransplant status. Transplant outcomes were compared among NMP and SCS groups with significant differences in nighttime OR (16.5% vs 52.9%), PRBC transfusion intraoperatively (4.7 vs 7.3), use of cell saver (71.1% vs 50%), and hospital length of stay (11.0 vs 14.2). No differences were found for early allograft dysfunction, allograft rejection, AKI, severe postop thrombocytopenia, washout for bleeding, or hospital readmission. **Conclusion:** Our program has grown from 26 LTs in 2023 to 74 LTs in 2025. This was largely due to the use of NMP and extended donor criteria. The use of NMP has facilitated transplantation for patients with lower MELD scores, older age, not hospitalized at transplant, without compromising quality of care including rejection and early allograft dysfunction. Additionally, the use of NMP has allowed us to have non-urgent OR start times when ancillary staff and resources are abundant. There is a decreased need for blood transfusions and shorter hospital length of stay with use of NMP. As transplant rates and NMP use increase across the world, continued data and understanding of risks and benefits of NMP need to be collected and published.

Table 1. Donor and Recipient Characteristics by NMP Use

	NMP (n=97)	SCS (n=68)	*P* value
Donor characteristics			
Age (y)	48.6	49.0	NS
BMI	28.9	29.9	NS
Distance to recipient hospital (mi)	**202.6**	**294.3**	**0.003**
DCD	**89**	**5**	**<0.00001**
CIT (h)	**1011.8**	**409.3**	**<0.00001**
Increased risk criteria	20	14	NS
Hepatitis C virus positive (%)	8	9	NS
Recipient characteristics			
Age (y)	**55.9**	**52.4**	**0.046**
BMI	30.18	29.81	NS
Male (%)	56.7%	57.4%	NS
MELD	**22.8**	**27.9**	**<0.00001**
Alcoholic liver disease	46.4%	55.9%	NS
Hospitalized at transplant (%)	**23.7%**	**41.2%**	**0.017**
Portal vein thrombosis (%)	**21.6%**	**8.8%**	**0.028**
Liver/kidney transplant (%)	9.3%	14.7%	NS
Retransplant (%)	2.1%	1.5%	NS
Transplant Outcomes			
Nighttime OR start (18:00-04:59)	**16.5%**	**52.9%**	**<0.001**
PRBC transfusions at Tx (units)	**4.7**	**7.3**	**<0.001**
Cell Saver Use (%)	**71.1%**	**50.0%**	**0.006**
Early allograft dysfunction (%)	10.0%	16.2%	NS
Rejection (%)	14.4%	14.7%	NS
Methylprednisolone Prescription (%)	17.5%	13.2%	NS
AKI	39.2%	33.8%	NS
Severe Thrombocytopenia POD7	19.6%	16.2%	NS
OR Washout for Bleeding	10.3%	8.8%	NS
Hospital LOS (days)	**11.0**	**14.2**	**0.013**
Readmissions < 30 days (%)	22.7%	13.2%	NS

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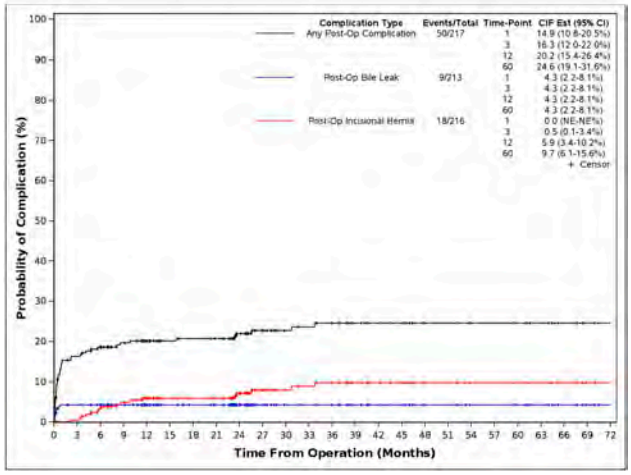
4460 | CT BODY COMPOSITION CONTRIBUTES TO RISK ASSESSMENT IN LIVING LIVER DONOR EVALUATION

Saurav Panda[1] Tyler Zemla[1] Sara Daleiden[1] Timucin Taner[2] Kymberly Watt[1], [1]Mayo Clinic Rochester, MN, [2]Mayo Clinic Rochester

Background: Body Mass Index (BMI) is a suboptimal metric for evaluation of living donor candidacy as it fails to accurately reflect visceral adiposity distribution and is affected by muscle and bone mass. Computed Tomography (CT) imaging obtained at the time of live donor evaluations can provide a solution to quantify fat distribution, which can aid in identifying donors at risk of complications. **Methods:** This single center study included 219 living liver donors between 2010-2025, with anthropometric, pre-operative radiological, and procedural data collected during donation and follow-up data for complications and clinical course. The routine pre-operative CT scan for assessment of living donors, was processed through a validated fully automated deep learning body composition analysis pipeline selecting the slice with maximum visceral adipose tissue (VAT) area, subcutaneous adipose tissue (SAT) area and intermuscular adipose tissue (IMAT) area. Visceral-to-subcutaneous adipose tissue area ratio (VSR) was derived by dividing VAT by SAT. Waist circumference was estimated from the same slice, by calculating the contour around the segmented subcutaneous adipose tissue. Cox regression models were designed around these body composition variables to determine predictive potential for post-operative complications following donation. **Results:** Of these 219 donors, mean age was 39.3 years (SD 10.2), with 49% male, a mean BMI of 25.5 (SD 2.9), mean VAT of 84.2 cm^2 (SD 68.8), mean SAT of 187.6 cm^2 (SD 81.2), and mean VSR of 0.46 (SD 0.38). 50 donors had post-operative complications noted in the follow up period. The most common postoperative complications were incisional hernias (n = 18) and bile leaks (n = 9). Unadjusted probabilities for post-operative complications, incisional hernia, and bile leak were reported at 1 month, 3 months, 1 year, and 5 years in figure. Univariate cox regression model fitted to potential predictors of a first post-operative complication of any type showed VSR (per 0.25 increase) as the sole significant association [HR: 1.17 (1.01, 1.37), p = 0.006] (table). A univariate cox regression model and multivariable logistic regression model for the most common post-operative complication i.e. incisional hernia, are shown in table. The multivariable model for incisional hernia indicated BMI [HR 2.67 (1.09, 6.56), P = 0.03] and VSR [HR 1.40 (1.10, 1.78), P = 0.006] as significant predictors. **Conclusion:** CT-derived body composition markers can add to risk evaluation for post-operative complications, particularly post-operative incisional hernia for living liver donors.

Outcome	Factor	Univariate HR (95% CI)	Univariate P-value	Multivariable HR (95% CI)	Multivariable P-value
Any Post-Operative Complications	Age (per 10-year increase)	1.06 (0.83–1.42)	0.5612	–	–
	Female vs Male	0.67 (0.38–1.17)	0.1615	–	–
	BMI (per 5-unit increase)	1.16 (0.72–1.87)	0.3627	–	–
	Visceral adiposity (per 50-unit increase)	1.11 (0.92–1.33)	0.2937	–	–
	Subcutaneous adiposity (per 50-unit increase)	0.89 (0.74–1.07)	0.2095	–	–
	Intermuscular adiposity (per 5-unit increase)	1.41 (0.89–1.46)	0.3012	–	–
	Visceral-to-subcutaneous ratio (VSR) (per 0.25 increase)	**1.17 (1.01–1.37)**	**0.0060**	–	–
	Waist circumference (per 10-unit increase)	1.03 (0.88–1.20)	0.7315	–	–
Incisional Hernia	Age (per 10-year increase)	1.52 (0.94–2.44)	0.0849	–	–
	Female vs Male	0.36 (0.12–1.01)	0.0512	–	–
	BMI (per 5-unit increase)	**3.67 (1.61–8.35)**	**0.0020**	**2.67 (1.09–6.56)**	**0.0325**
	Visceral adiposity (per 50-unit increase)	**1.58 (1.21–2.07)**	**0.0009**	–	–
	Subcutaneous adiposity (per 50-unit increase)	0.96 (0.71–1.30)	0.7987	–	–
	Intermuscular adiposity (per 5-unit increase)	**1.59 (1.12–2.26)**	**0.0092**	–	–
	Visceral-to-subcutaneous ratio (VSR) (per 0.25 increase)	**1.54 (1.23–1.93)**	**0.0092**	**1.40 (1.10–1.78)**	**0.0064**
	Waist circumference (per 10-unit increase)	**1.25 (1.06–1.48)**	**0.0091**	–	–
Bile Leak	Age (per 10-year increase)	0.80 (0.47–1.72)	0.7562	–	–
	Female vs Male	1.15 (0.31–4.30)	0.8312	–	–
	BMI (per 5-unit increase)	1.02 (0.33–3.10)	0.9796	–	–
	Visceral adiposity (per 50-unit increase)	0.80 (0.45–1.40)	0.4304	–	–
	Subcutaneous adiposity (per 50-unit increase)	1.03 (0.69–1.54)	0.8796	–	–
	Intermuscular adiposity (per 5-unit increase)	1.49 (0.90–2.45)	0.1215	–	–
	Visceral-to-subcutaneous ratio (VSR) (per 0.25 increase)	0.77 (0.44–1.35)	0.3364	–	–
	Waist circumference (per 10-unit increase)	0.89 (0.55–1.44)	0.6261	–	–

HR = Hazard Ratio, CI = Confidence Interval, VSR = Visceral-to-Subcutaneous Ratio
Bold indicates P-value < 0.05



Disclosures: Saurav Panda:Nothing to Disclose, Tyler Zemla:Nothing to Disclose, Sara Daleiden: Nothing to Disclose, Timucin Taner:Nothing to Disclose, Kymberly Watt:Madrigal: Stock - publicly traded company, Viking: Stock - publicly traded company, Novo Nordisk: Speaking and Teaching.

4461 | LIVER TRANSPLANTATION TRENDS AND DONOR UTILIZATION IN THE AMERICAS: A COMPARATIVE ANALYSIS OF USA, BRAZIL, CANADA, ARGENTINA, COLOMBIA, AND MEXICO (2020–2024)

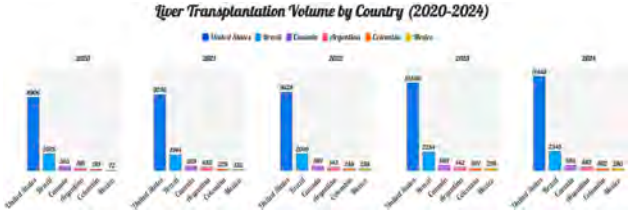
Luis Bogran Perdomo[1] Karla Carias Martinez[2] Pablo Garcia[3] Juan Pineda Paz[4], [1]National Autonomous University of Honduras, [2]Renal Medicine Associates, [3]University Of New Mexico, [4]Centro Endoscopico Hondureno, Honduras

Background: Liver transplantation (LT) is the definitive treatment for end-stage liver disease, yet

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infrastructure varies across the Americas. While high-income nations expand donor pools via advanced protocols, many Latin American countries face persistent procurement challenges. Understanding regional disparities in donor types: Donation after Brain Death (DBD) versus Donation after Circulatory Death (DCD), is critical for hemispheric health equity. This study analyzes the post-pandemic recovery of the six highest-volume transplant nations in the Americas to identify systemic barriers and opportunities for collaboration. **Methods:** A retrospective analysis was conducted using annual transplant activity data (2020–2024) from the Global Observatory on Donation and Transplantation (GODT). Total LT volumes (deceased/living donors) were evaluated for the USA, Brazil, Canada, Argentina, Colombia, and Mexico. Primary metrics included annual absolute volumes and growth rates. We analyzed DBD and DCD utilization to assess the impact of procurement protocols on regional output. **Results:** The six nations demonstrated a resilient upward trend, with a 49% average volume increase since 2021. The USA achieved a record 11,458 procedures in 2024, driven by aggressive DCD expansion. Brazil leads Latin America in absolute volume (2,345), followed by Canada (655) and Argentina (483). Colombia (302) and Mexico (280) reported steady growth but maintain lower transplant rates per million population relative to disease burdens. **Conclusion:** Regional LT activity has recovered robustly, yet a structural "protocol gap" persists. North American growth is increasingly fueled by DCD and machine perfusion, while Latin American programs remain dependent on DBD. To enhance equity, Mexico and Colombia require legal and technical frameworks supporting DCD expansion. A Pan-American framework is advocated to standardize donor management and share procurement technologies.



Disclosures: Luis Bogran Perdomo:Nothing to Disclose, Karla Carias Martinez:Nothing to Disclose, Pablo Garcia:Nothing to Disclose, Juan Pineda Paz:Nothing to Disclose.

4462 | THE INFLUENCE OF DONOR BMI ON POST-TRANSPLANT OUTCOMES IN OLDER VERSUS YOUNGER MARGINAL LIVER RECIPIENTS

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Background: Increasing liver transplant waitlist registrations have prompted greater utilization of marginal liver donors. As obesity prevalence rises, high-BMI donors will be encountered with increasing frequency, yet the interaction between donor BMI and recipient age on post-transplant outcomes remains poorly characterized. We sought to examine whether donor BMI impacts graft and patient survival differently in older versus younger marginal liver recipients. **Methods:** A retrospective cohort study was conducted of adult marginal liver transplant recipients at the University of Florida between January 2019 and September 2024. Donors were classified as marginal if they met at least one of the following criteria: age >65 years, BMI >30 kg/m², ICU stay >4 days, serum sodium >160 mmol/L, ALT >105 U/L, AST >90 U/L, bilirubin >3 mg/dL, substance use history, extrahepatic malignancy, donation after circulatory death, cold ischemic time >12 hours, or viral hepatitis seropositivity. Recipients were stratified by age at transplant (<60 vs. ≥ 60 years) and donor BMI (<30 vs. ≥ 30 kg/m²). Primary outcome was all-cause mortality; secondary outcomes included 1- and 3-year graft survival. Survival was estimated using the Kaplan-Meier method and compared between groups using the log-rank test, with $p<0.05$ considered statistically significant. **Results:** Of 542 marginal liver transplant recipients, 352 (64.9%) were younger than 60 years and 190 (35.1%) were 60 years or older. Donor BMI was less than 30 kg/m² in 351 recipients (64.8%) and 30 kg/m² or greater in 191 (35.2%). Forty-five deaths occurred over the follow-up period. Donor BMI did not significantly impact all-cause survival overall (log-rank $p=0.279$) or within either age stratum (younger: $p=0.752$; older: $p=0.176$), though older recipients receiving livers from BMI ≥ 30 donors had numerically lower survival than those receiving BMI <30 donors (77.3% vs. 88.6%). One-year graft survival did not differ by donor BMI in younger recipients (97.3% vs. 97.5%, $p=0.909$); however, among older recipients, donor BMI ≥ 30 was associated with significantly lower 1-year graft survival compared to BMI <30 (95.4% vs. 100%, $p=0.017$), but this finding should be interpreted with caution given the small number of events. Three-year graft survival did not differ significantly by donor BMI in either age group (younger: $p=0.788$; older:

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p = 0.355). **Conclusion:** Donor BMI ≥ 30 kg/m² was significantly associated with lower 1-year graft survival in marginal liver recipients aged 60 years or older (95.4% vs. 100%, p = 0.017), with no significant effect observed in younger recipients. While overall survival and 3-year graft survival did not differ significantly by donor BMI in either age group, older recipients receiving high-BMI donor livers demonstrated consistently lower survival estimates across all outcomes. This difference suggests further study with multi-center data is warranted.

Table 1: Log Rank Summary - donor BMI <30 vs ≥30

Outcome	Stratum	n	Events	Final surv BMI <30	Final surv BMI ≥30	χ^2	p-value
All-cause mortality	Overall	542	45	88.0%	83.3%	1.17	0.279
	Younger (< 60 years)	352	28	87.6%	86.3%	0.10	0.752
	Older (≥60 years)	190	17	88.6%	77.3%	1.83	0.176
1-yr graft survival	Overall	541	12	98.2%	96.8%	1.20	0.274
	Younger (< 60 years)	352	9	97.3%	97.5%	0.01	0.909
	Older (≥60 years)	189	3	100%	95.4%	5.69	0.017
3-yr graft survival	Overall	288	46	84.0%	81.4%	0.53	0.466
	Younger (< 60 years)	195	30	84.0%	83.0%	0.07	0.788
	Older (≥60 years)	93	16	83.9%	78.1%	0.86	0.355

Disclosures: Natalie Rosseau:Nothing to Disclose, Yasmeen Saker:Nothing to Disclose, Andreas Zori: Nothing to Disclose.

4463 | INTERVENTIONS TO PREVENT RELAPSE IN PATIENTS WITH ALCOHOL ASSOCIATED LIVER DISEASE UNDERGOING LIVER TRANSPLANT ASSESSMENT: A SYSTEMATIC REVIEW AND META-ANALYSES

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Background: Alcohol associated liver disease (ALD) is one of the leading indications for liver transplantation in Canada. How to best assess and support these patients to prevent relapse pre and post transplant remains a top research priority. The aim of this review was to determine what interventions or programs should be offered to transplant recipients with ALD to help prevent alcohol relapse in the pre and post transplant period. **Methods:** We performed a systematic review and meta-analysis. Medline, Embase and Cochrane databases were searched from inception to October 2025 to identify prospective cohort studies and randomized controlled trials (RCTs). Title/abstract, full-text, risk of bias (ROB) assessment and data extraction were performed in duplicate. A meta-analysis with fixed and random effects models were performed using RevMan version 5.3. Certainty of evidence was assessed using GRADE. **Results:** A total of 9765 citations were identified, and 16 studies were included in the meta-analysis. The majority of studies were of high ROB. Multidisciplinary team approach and addictions counselling did result in a reduced rate of harmful drinking relapse (RR 0.55, 95% CI 0.32, 0.94) and improved all-cause mortality (RR 0.28, 95%CI0.13, 0.64). Harm reduction strategies and pharmacotherapy had an uncertain effect on rate of relapse (RR 0.95, 95%CI 0.48-1.87). The overall certainty of evidence was low. **Conclusion:** The use of multidisciplinary teams and addiction counsellings can be beneficial to prevent relapse in patients with ALD and improve overall mortality.

Disclosures: Dorota Borovsky:Nothing to Disclose, Simon Oczkowksi:VitalAire: Consultant, Muhammad Usman Ali:Nothing to Disclose, Susan Abbey:Nothing to Disclose, Jennifer Chandler:Nothing to Disclose, Vanessa Gruben:Nothing to Disclose, Vladimir Marquez:Nothing to Disclose, Marie Chantal Fortin:Nothing to Disclose, Sylvia Carbert:Nothing to Disclose, Theodore Christou:Nothing to Disclose, Susan Gilmour:Mirum Pharma: Consultant, Medison Pharma: Consultant, Intercept Pharma: Grant/Research Support, Novo Nordisc: Site PI, Fatima Dharsee:Nothing to Disclose, Marilyn Swinton:Nothing to Disclose, Prosanto Chaudhury:Nothing to Disclose, Nazia Selzner:Nothing to Disclose, Joanna Dionne:Nothing to Disclose.

4464 | PERSISTENT SEX-BASED INEQUITIES IN LIVER TRANSPLANTATION FOR HEPATOCELLULAR CARCINOMA DESPITE MEDIAN MELD AT TRANSPLANT MINUS THREE (MMAT-3) EXCEPTION POLICY REFORM

Shirley Eng[1] Ahmed Aboseria[1] Sanjaya Satapathy[2], [1]Zucker School of Medicine/Northwell Health, [2]North Shore University Hospital/Northwell Health

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Background: The median MELD at transplant minus 3 (MMaT-3) policy was implemented to reduce geographic inequities in liver allocation among hepatocellular carcinoma (HCC) candidates however whether this policy change differentially affects candidates by sex remains unclear. **Methods:** We performed a retrospective cohort study using UNOS/OPTN data including adult HCC exception candidates listed in the pre–MMaT-3 (August 2017–November 2018) and post–MMaT-3 (June 2019–August 2020) eras. The primary outcome was waitlist mortality, analyzed using cause-specific Cox proportional hazards models with transplantation treated as a competing event. Fine–Gray models evaluated transplant probability and waitlist dropout. Models adjusted for age, MELD score, serum sodium, and diabetes. Sex-by-era interaction analyses assessed differential policy effects. **Results:** Among 6,467 candidates (23.2% female), post-MMaT-3 era was associated with lower waitlist mortality (HR 0.87, 95% CI 0.77–0.98, p = 0.028) and female sex with reduced mortality (HR 0.83, 95% CI 0.71–1.00, p = 0.038) (Figure 1). However, no significant sex-by-era interaction was observed (p = 0.54), indicating that MMaT-3 did not differentially affect outcomes by sex. Stratified analyses demonstrated lower female mortality in the pre-policy era (HR 0.84, p = 0.048), which attenuated after MMaT-3 implementation (HR 0.91, p = 0.32). Post–MMaT-3 mortality reduction was significant among males only. No significant differences were observed in transplant probability or waitlist dropout by sex or sex-by-era interaction, and non-death dropout consistently exceeded waitlist mortality across all subgroups. **Conclusion:** MMaT-3 implementation was associated with modest improvement in overall waitlist mortality among HCC candidates, but this improvement appeared to be primarily driven by male candidates, whereas outcomes among females remained largely unchanged. Despite this, there was no significant interaction between era and sex on transplant dropout or mortality. Transplant probability remained largely unchanged across eras and between sexes, as demonstrated in cumulative incidence curves (Figure 2). This indicates that the observed reduction in mortality was not driven by increased transplant access but may instead reflect more nuanced changes in allocation timing, prioritization, or candidate selection. Thus, while allocation reforms may improve overall outcomes, additional targeted strategies may be needed to address persistent sex-related inequities in liver transplantation.

Figure 1. Cumulative incidence of waitlist death among HCC candidates stratified by gender and MMaT-3 era
Cumulative incidence functions were estimated using Fine-Gray competing risks methodology with liver transplantation treated as a competing event. Prior to MMaT-3, female candidates demonstrated a higher cumulative incidence of waitlist death compared to males. Following MMaT-3, this pattern reversed, with females exhibiting lower mortality than males, suggesting a shift in gender disparities under the revised allocation policy.

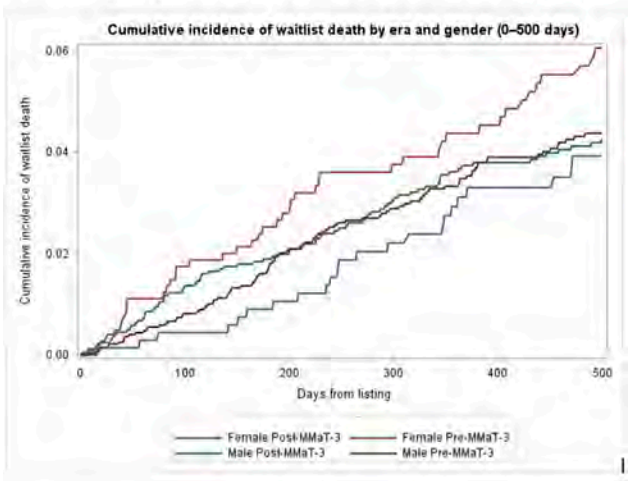
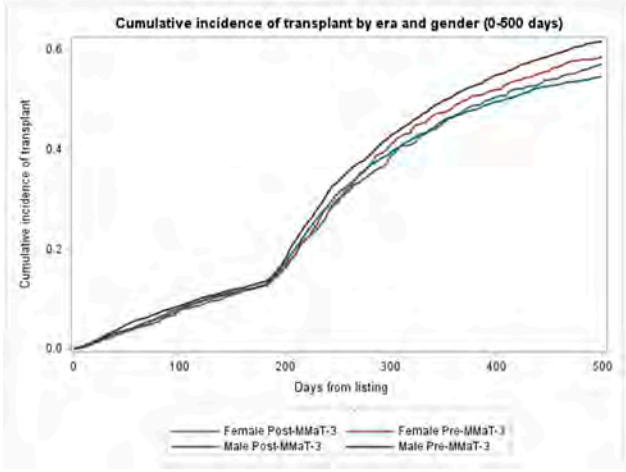


Figure 2. Cumulative incidence of transplant among hepatocellular carcinoma candidates by gender and MMaT-3 era
Cumulative incidence functions were estimated with waitlist dropout treated as a competing event. Curves were broadly similar across gender and era groups, consistent with adjusted Fine-Gray analyses showing no significant interaction between gender and MMaT-3 era for transplant probability.



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4465 | COMPARISON OF EARLY VERSUS LATE COMPLICATIONS AFTER LIVING DONOR LIVER TRANSPLANTATION

James Mo[1] Nemie Beltran[1] Maria Zanini[1] Deepak Venkat[1] Syed-Mohammed Jafri[1], [1]Henry Ford Health System

Background: Due to the limited availability of deceased donor livers, living donor liver transplantation (LDLT) has emerged as an important alternative. However, post-operative outcomes after LDLT remain incompletely characterized. We aimed to compare the complications occurring within 3 months versus beyond 3 months of receiving an LDLT. **Methods:** We retrospectively reviewed all adult LDLT recipients at a single tertiary center from 2015 to 2025. Patient characteristics and post-transplant outcomes were collected through manual chart review. **Results:** A total of 76 patients received an LDLT. Of these, 57.9% were male and 90.8% were Caucasian, with a mean age of transplantation of 56 years (range 18 to 75). Etiologies of cirrhosis included alcohol (17.1%), MASH (40.8%), PSC (23.7%), PBC (7.9%), hepatitis C (5.3%), and other causes (5.3%); 7.9% of patients also had hepatocellular carcinoma. Regarding vascular complications, portal vein thrombosis/stenosis was diagnosed in 9 patients (11.8%) within 3 months of LDLT and in 5 (6.6%) beyond 3 months. None developed hepatic vein stenosis within 3 months, whereas 4 (5.3%) were beyond 3 months. Hepatic artery thrombosis/stenosis occurred in 5 patients (6.6%) within 3 months and in 3 (3.9%) beyond 3 months. Among biliary complications, bile leaks occurred in 18 patients (23.7%) within 3 months compared to 8 (10.5%) beyond 3 months. Biliary strictures were diagnosed in 18 patients (23.7%) within 3 months versus 22 (28.9%) beyond 3 months. Incisional hernias were seen in 2 patients (2.6%) within 3 months and in 10 (13.2%) beyond 3 months. Re-operative interventions were required in 13 patients (17.1%) within 3 months, including exploratory surgeries, re-do transplantations, and hepaticojejunostomies. Six patients (7.9%) required additional surgical intervention beyond 3 months. Only 1 patient required dialysis, which occurred within 3 months post-transplant. No patients experienced primary nonfunction or underwent re-transplantation. Four patients (5.3%) died within 3 months of LDLT. **Conclusion:** In this single-center cohort of LDLT recipients, complication patterns differed by timing after transplantation. Early complications within 3 months were predominantly vascular, bile leaks, and the need for re-operative interventions, whereas later complications were more frequently related to biliary strictures and incisional hernias. Understanding the timing of complications after LDLT may help inform post-transplant management strategies and patient counseling.

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4466 | MAPPING THE GLOBAL LIVER TRANSPLANT LANDSCAPE

Rym Yousfi[1] Hanna Blaney[2] Juan Pablo Arab[2], [1]Virginia Commonwealth University School of Medicine, [2]Virginia Commonwealth University

Background: Liver transplantation (LT) is life-saving for select patients with advanced chronic liver disease and acute liver failure, but global access depends on transplant infrastructure, donor availability, and health system capacity. Alcohol-associated liver disease (ALD) is a major indication for LT worldwide, and severe alcohol-associated hepatitis (AH) carries high short-term mortality. This study aimed to characterize global and regional variation in LT availability and reported transplant activity, with attention to the availability of LT for AH. **Methods:** We performed a descriptive country-level analysis of LT availability and activity across 193 countries using publicly available transplant registry and country-level sources. Variables included LT availability, donor type distribution, and annual LT volume from 2011–2024. Transplant indications across regions were also examined, with particular attention to AH. Countries were grouped by geographic region to compare access and reported transplant activity. **Results:** LT availability data were available for 188 countries; 89 offered LT (47.3%). Availability varied substantially by region: Europe 34/42 (81.0%), North America 8/23 (34.8%), South America 8/10 (80.0%), Asia 33/48 (68.8%), Australia/Oceania 2/14 (14.3%), and Africa 5/54 (9.3%). Within the North America region, availability was concentrated in Canada, the United States and Mexico, with more limited availability across Central America and the Caribbean. (Figure 1A). Among the 62 total countries with donor-type data, deceased donor LT (DDLT) predominated, with a median of 93% of LTs DDLT versus 7% living donor LT (LDLT), with marked country and regional variation (Figure 1B). In 2024, 64 countries reported 43,310 LTs globally. Reported volume was highest in Asia (18,103), North America (12,113), and Europe (10,238), and lowest in Africa (65). Reported annual LT volume generally increased over time in regions with available longitudinal data, though interpretation is limited by variable reporting. Etiology-specific reporting was limited, with no publicly available country-level data identifying LTs performed for AH. **Conclusion:** LT availability varies markedly globally, with limited access across many countries in Africa,

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Oceania, and the Caribbean. Access for AH is likely even more limited, but remains difficult to assess with publicly available data due to sparse etiology-specific reporting. These findings support expanded transplant infrastructure, standardized reporting, and international collaboration to improve access for patients with all forms of liver disease, including AH.



Figure 1A: Global liver transplantation availability.

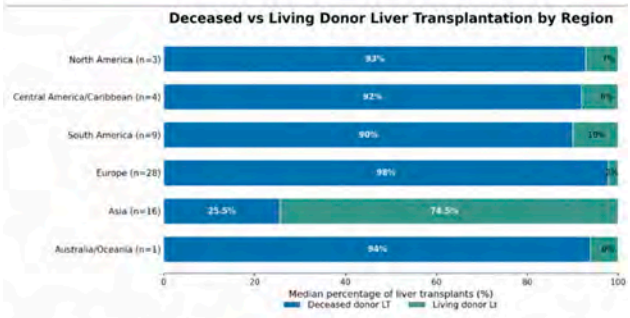


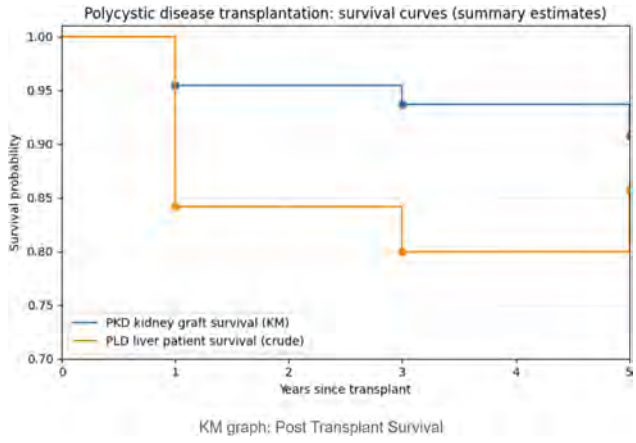
Figure 1B: Median proportion of deceased donor LT and living donor LT by region among countries with available donor-type data.

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4467 | POLYCYSTIC DISEASE ACROSS ORGANS: ERA-LINKED SHIFTS IN ACCESS, TIMING, AND OUTCOMES IN SINGLE-CENTER KIDNEY(PKD) AND LIVER (PLD) TRANSPLANTATION

Nishtha Singh[1] Emily Schonfeld[2] Russell Rosenblatt[3] Rebecca Craig-Schapiro[3] Juan Rocca[2] Danielle Brandman[3] Benjamin Samstein[3] Sandip Kapur[3] Dustin Carpenter[3], [1]NewYork-Presbyterian/Weill Cornell Medical College, [2]NewYork-Presbyterian/Weill Cornell Medical Center, [3]Weill Cornell Medicine

Background: Polycystic disease spans kidney and liver failure pathways yet faces distinct allocation challenges:PKD timing is often framed by dialysis exposure,while PLD symptom burden may be underestimated by laboratory MELD.We evaluated how major U.S.allocation-era transitions aligned with access,logistics,and outcomes in PKD kidney and PLD liver transplantation at a high-volume center. **Methods:** Retrospective OPTN/UNOS donor–recipient export(1990–present).PKD kidney transplants were identified by primary diagnosis at transplant and/or listing;PLD liver transplants by primary diagnosis at transplant("Benign tumor:polycystic liver disease").Eras by transplant date:Pre-MELD(< 2/27/2002),MELD(2/27/2002–1/10/2016),MELD-Na(1/11/2016–2/3/2020), MMaT/Acuity Circles(≥ 2/4/2020).Era comparisons used Kruskal–Wallis/chi-square. PKD graft survival was Kaplan–Meier;multivariable logistic regression modeled dialysis at transplant(yes/no).PLD survival was summarized as crude survival among recipients with ≥ 1-,3-,5-year follow-up. **Results:** PKD:591 kidney transplants(Pre-MELD81;MELD269;MELD-Na102; MMaT/Acuity142).Recipient age increased (50.0→57.0y;$p < 0.001$) while dialysis at transplant declined(85.2%Pre-MELD vs44–56%later;$p < 0.001$). Living donation increased($p < 0.001$) and DCD use rose to18.3% in MMaT/Acuity($p < 0.001$);LOS decreased (6→4d;$p < 0.001$).Kaplan–Meier graft survival was95.5%(1y),93.7%(3y),90.8%(5y).Adjusted odds of dialysis were lower vs Pre-MELD:MELD aOR0.23, MELD-Na0.17,MMaT/Acuity0.09(all $p < 0.001$);living donation was protective(aOR0.23;$p < 0.001$) and longer wait increased odds(aOR1.27 per log-day;$p < 0.001$). PLD:25 liver transplants(MMaT/Acuity18;MELD-Na6; MELD1) with low lab MELD overall(median12.0 [9.0–20.0]).Waitlist time was shorter in MMaT/Acuity (32.5[20.5–113.0]d) vs MELD-Na(247.0[127.5–327.5]d; $p = 0.034$) with greater national sharing in MMaT/Acuity (77.8% vs83.3% local in MELD-Na;$p = 0.014$).Crude survival was84.2%(1y),80.0%(3y),85.7%(5y). **Conclusion:** Across allocation eras,polycystic disease transplantation demonstrated measurable gains in timely access—reduced dialysis dependence for PKD and shorter wait time with broader sharing for PLD—while maintaining strong medium-term outcomes;PLD findings are hypothesis-generating given small numbers.



KM graph: Post Transplant Survival

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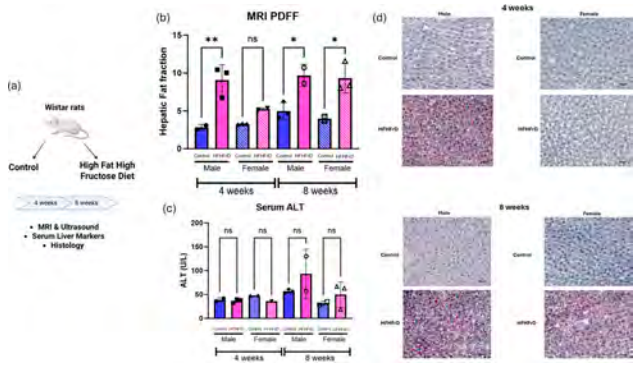
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4468 | A NON-INFLAMMATORY DIET-INDUCED MODEL OF DONOR HEPATIC STEATOSIS

Mobin Ibne Mokbul[1] Jack R. Cahill[2] Hidemi Nishi[2] Usman Yaqoob[2] Caixin Qiu[2] Jayla T. Millender[2] Purnima Tyagi[2] Meng Yin[1] Nidhi Jalan-Sakrikar[2] Timucin Taner[2] Robert Huebert[2], [1]Mayo Clinic, [2]Mayo Clinic Rochester

Background: Bland hepatic steatosis without accompanying inflammation or fibrosis in donor livers represents a common but important clinical challenge in transplantation, given the high discard rate of steatotic donor livers. However, robust and reproducible preclinical models that accurately represent this phenotype remain limited. We aimed to establish a diet-induced rat model of isolated hepatic steatosis to resemble discarded human donor livers. **Methods:** Forty Wistar rats (20 male, 20 female) were assigned to control or high-fat diet groups and studied across 4-week and 8-week feeding cohorts. The high-fat and high-fructose diet (HFHFrD) consisted of 45% kcal from fat (predominantly oleic acid to reduce hepatic inflammation) with 10% fructose supplementation in drinking water. Ultrasound and magnetic resonance imaging–proton density fat fraction (MRI-PDFF) was performed prior to tissue collection. Animals were further evaluated using serum liver injury markers and histology (oil red O, H&E, picrosirius red, and Mason's trichome). **Results:** Ultrasound and MRI-PDFF confirmed progressive hepatic fat accumulation in the high-fat diet group (4 weeks: 3.08 vs. 7.53, $p = 0.002$, 8 weeks: 4.57 vs. 9.47, $p = 0.008$), with significantly greater and more rapid steatosis observed in male rats compared to females. Serum ALT ($p = 0.48$) and AST ($p = 0.11$) levels did not differ significantly between high-fat and control groups, indicating the absence of hepatocellular injury. Histological analysis with hematoxylin and eosin staining demonstrated prominent micro- and macrovesicular steatosis in the HFHFrD group, without evidence of steatohepatitis or fibrosis. Oil Red O staining on liver tissues revealed significant effects of diet, sex, and time on lipid accumulation across groups. In line with the MRI data, at 4 weeks, the HFHFrD markedly increased lipid deposition in males (0.95 vs. 16.02, $p = 0.02$), but not in females (0.03 vs. 0.07, $p = 0.99$). However, at 8 weeks, both male and female groups showed significant steatosis. Interestingly, there was no further increase in steatosis between males at 4 or 8 weeks after the HFHFrD ($p = 0.98$). The absence of fibrosis in all rats was further confirmed by both picrosirius red and Mason's trichome staining. Therefore, we propose that male rats fed for 4 weeks with the HFHFrD represents the most rapid non-inflammatory steatosis model for transplant research applications. **Conclusion:** We report a rapid and reproducible dietary model of bland hepatic steatosis in rodents. The model is characterized by significant lipid accumulation in the absence of steatohepatitis or fibrosis. This model closely resembles human donor liver steatosis and may serve as a valuable platform for transplantation research and the development of therapeutics for deployment during normothermic machine perfusion.



Disclosures: Mobin Ibne Mokbul:Nothing to Disclose, Jack R. Cahill:Nothing to Disclose, Hidemi Nishi: Nothing to Disclose, Usman Yaqoob:Nothing to Disclose, Caixin Qiu:Nothing to Disclose, Jayla T. Millender:Nothing to Disclose, Purnima Tyagi:Nothing to Disclose, Meng Yin:Resoundant, Inc.: Stock – privately

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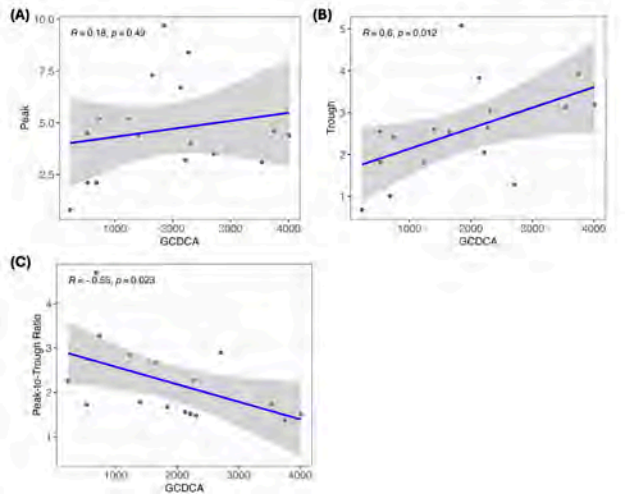
held company, Nidhi Jalan-Sakrikar:Nothing to Disclose, Timucin Taner:Nothing to Disclose, Robert Huebert:Nothing to Disclose.

4469 | ◆ ASSOCIATION BETWEEN MICROBIAL METABOLITES AND TACROLIMUS PHARMACOKINETICS AFTER LIVER TRANSPLANT

Yael Nobel[1] Rebecca Yeh[1] Serge Cremers[1] Anne-Catrin Uhlemann[1] Elizabeth Verna[1], [1]Columbia University Irving Medical Center

Background: Tacrolimus (TAC) is the cornerstone of immunosuppression after liver transplant (LT). Individual dose-response (drug levels following a given dose of TAC) varies widely between patients, which can lead to under- or over-dosing and risk of allograft rejection or drug toxicity. Microbial metabolites, including bile acids (BA) and short-chain fatty acids (SCFA), are plausible modifiers of TAC pharmacokinetics via effects on host enzymatic (CYP3A) and efflux pump (P-glycoprotein) activity. **Methods:** LT recipients receiving TAC underwent two timed whole blood collections at one month post-LT: approximately 1.5 hours (peak) and 12 hours (trough) after TAC dose. A pharmacokinetic modeling approach was applied to calculate true simulated peak and trough TAC concentration accounting for sample timing variation. Plasma microbial metabolites, including BA and SCFA, were measured. Dietary questionnaires, clinical data, and use of CYP inhibiting- or inducing-drugs at time of sample were collected. Correlations were assessed between microbial metabolite concentrations and dose-normalized TAC trough level, peak level, and peak-to-trough ratio. **Results:** In this pilot study, 17 participants have been analyzed. 53% were male and median age was 49 years (IQR 45-62). CYP inhibitors were used by 41% of patients and median dietary fat intake was 33% of calories (IQR 31-38%). Median peak and trough TAC levels were 9.3 (7.0-15.3) and 5.1 (3.9-6.1) ng/mL, respectively. Glycochenodeoxycholic acid (GCDCA) was the most abundant BA (median 1,841 [IQR 734-2,310] ng/mL). GCDCA was positively correlated with dose normalized TAC trough level (Spearman $r = 0.60$, $p = 0.01$) and negatively correlated with peak-to-trough ratio ($r = -0.55$, $p = 0.02$) (Figure). Ursodeoxycholic acid (UDCA) ($r = 0.60$, $p = 0.01$) and its taurine-conjugated metabolite (TUDCA) ($r = 0.48$, $p = 0.05$) were also positively correlated with trough level. In multivariable linear regression adjusting for age, sex, and use of CYP inhibitors or inducers, GCDCA remained positively associated with TAC trough level ($p = 0.05$) and inversely associated with peak-to-trough ratio ($p = 0.02$). No significant associations were identified between SCFA and TAC parameters. **Conclusion:** Plasma concentration of GCDCA was associated with increased TAC trough levels and, correspondingly, inversely associated with peak-to-trough ratio. This finding is consistent with preclinical models in which GCDCA competitively inhibits CYP3A activity and inhibits P-glycoprotein efflux pump. The microbiome may contribute to inter-patient variability in TAC dose-response after LT via BAs, and BA levels could offer a future target to help guide personalized dose selection.

Figure. Spearman correlations of plasma GCDCA concentration (ng/mL) with **(A)** dose-normalized peak tacrolimus concentration (ng/mL), **(B)** dose-normalized trough tacrolimus concentration (ng/mL), and **(C)** ratio of tacrolimus peak level to tacrolimus trough level.



Disclosures: Yael Nobel:Mirum Pharmaceuticals: Consultant, Rebecca Yeh:Nothing to Disclose, Serge Cremers:Nothing to Disclose, Anne-Catrin Uhlemann: Nothing to Disclose, Elizabeth Verna:Nothing to Disclose.

4470 | ◆ EPIDEMIOLOGY, MICROBIOLOGY, AND RISK FACTORS FOR MULTIDRUG-RESISTANT BACTERIAL INFECTIONS AFTER LIVER TRANSPLANTATION

Konstantinos Ouranos[1] Tilemachos Koutouratsas[1] Mark Michael[1] Siddharth Das[1] Poojasree Pasupuleti[1] Evangelia Mylona[1] Fadi Shehadeh[1] Diana Avila[1] Sudha Kodali[1] Tamneet Basra[1] Michelle Jones-Pauley[1] David Victor[1] Mazen Noureddin[1] Markos Kalligeros[2] Luma Succar[3] Payal Gurnani[1] Ashish Saharia[3] Yee Lee Cheah[3] Caroline Simon[1] Constance Mobley[1] Ashton Connor[1] Mark Ghobrial[1] Eleftherios Mylonakis[1] Kavish Patidar[1], [1]Houston Methodist

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Background: Early bacterial infections (BI) following liver transplantation (LT) remain a major cause of morbidity and mortality; however, the epidemiology and determinants of multidrug-resistant bacterial infections (MDRBIs) in the immediate post-LT period remain poorly characterized. We aimed to define the incidence, microbiologic spectrum, and risk factors associated with MBRBIs within 90 days after LT. **Methods:** This was a single-center retrospective cohort study of adult LT recipients (1/2016–4/2025). Patients with at least one culture-positive BI within 90 days were included. MDRBI was defined as resistance to ≥3 antimicrobial classes. Culture sources included blood, urine, respiratory tract specimens, cerebrospinal fluid, fluid from organized collections or abscesses, and bile. The primary outcome was incidence of MDRBI. Multivariable logistic regression was performed to identify independent risk factors associated with MDRBI, with candidate variables selected based on clinical relevance and significance in univariable analyses. **Results:** Of 1,787 LT recipients, 524 (29%) developed at least one culture-positive BI within 90 days; 392 met MDRBI criteria, yielding an overall incidence of 22%. There were no significant differences in age, race, MELD 3.0 scores or cirrhosis etiology between patients who developed MDRBI and those who did not. However, patients with MDRBI were more likely exposed to ciprofloxacin within 3 months pre-LT (13% vs 4%, p = 0.007). Among 515 MDRBI episodes (576 pathogens, 45 polymicrobial), the most common infection sites were urinary tract (n = 176), pulmonary (n = 161), blood (n = 104), skin/soft tissue (n = 98), and intra-abdominal (n = 34). Gram-negative organisms predominated: *Klebsiella pneumoniae* (n = 148), *Escherichia coli* (n = 83), and *Pseudomonas aeruginosa* (n = 40). Key gram-positive organisms included *Enterococcus faecium* (n = 84), coagulase-negative Staphylococci (n = 30), and *Staphylococcus aureus* (n = 23). On multivariable analysis, pre-LT ciprofloxacin exposure (OR 3.48, 95% CI 1.31–9.23, p = 0.01) and MELD-3.0 score (OR 1.03/point increase, 95% CI 1.00–1.06, p = 0.03) were independently associated with MDRBI development (**Table 1**). **Conclusion:** MDBRIs occur frequently within the first 90 days after LT and are predominantly driven by gram-negative pathogens from pulmonary and urinary sources. Pre-LT ciprofloxacin exposure was independently associated with subsequent MDRBI development, highlighting a potentially modifiable risk factor. These findings support reassessment of current spontaneous bacterial peritonitis prophylaxis strategies and highlight the importance of antimicrobial stewardship approaches among high-risk LT candidates and recipients.

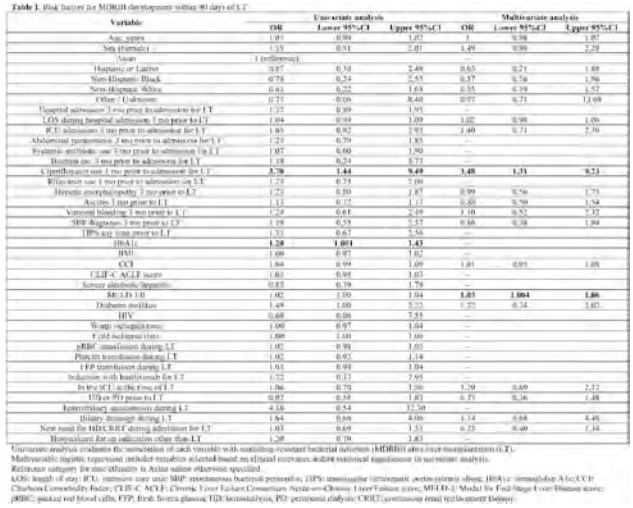


Table 1. Risk factors for MDRBI development within 90 days of LT

Variable	Univariate analysis			Multivariate analysis		
	OR	Lower 95%CI	Upper 95%CI	OR	Lower 95%CI	Upper 95%CI
Age, years	1.01	0.99	1.03	1	0.98	1.02
Sex (female)	1.35	0.91	2.01	1.49	0.99	2.28
Race	1 (reference)					
Hispanic or Latino	0.87	0.39	2.49	0.63	0.27	1.48
Non-Hispanic Black	0.78	0.24	2.55	0.57	0.16	1.76
Non-Hispanic White	0.61	0.22	1.68	0.35	0.12	1.52
Other / Unknown	0.77	0.09	8.40	0.97	0.11	13.69
Hospital admission 7 mo prior to admission for LT	1.23	0.89	1.95	–	–	–
LOS during hospital admission 7 mo prior to LT	1.04	0.99	1.09	1.02	0.98	1.06
ICU admission 3 mo prior to admission for LT	1.63	0.92	2.93	1.40	0.71	2.76
Abdominal paracentesis 7 mo prior to admission for LT	1.23	0.79	1.85	–	–	–
Systemic antibiotic use 3 mo prior to admission for LT	1.07	0.60	1.90	–	–	–
Rifaximin use 3 mo prior to admission for LT	1.18	0.24	5.73	–	–	–
Ciprofloxacin use 3 mo prior to admission for LT	**3.70**	**1.44**	**9.49**	**3.48**	**1.31**	**9.23**
Rifaximin use 3 mo prior to admission for LT	1.25	0.78	2.00	–	–	–
Hepatic encephalopathy 3 mo prior to LT	1.23	0.80	1.87	0.99	0.56	1.73
Ascites 3 mo prior to LT	1.13	0.75	1.71	0.88	0.50	1.54
Variceal bleeding 3 mo prior to LT	1.24	0.61	2.49	1.16	0.52	2.52
SBP diagnosis 3 mo prior to LT	1.28	0.55	2.92	0.86	0.28	1.99
TIPS any time prior to LT	1.33	0.67	2.56	–	–	–
HbA1c	**1.20**	**1.001**	**1.43**	–	–	–
BMI	1.00	0.97	1.02	–	–	–
CCI	1.04	0.99	1.09	1.01	0.95	1.08
CLIF-C ACLF score	1.02	0.99	1.05	–	–	–
Severe alcoholic hepatitis	0.83	0.39	1.78	–	–	–
MELD 3.0	1.02	1.00	1.04	**1.03**	**1.004**	**1.06**
Diabetes mellitus	1.49	1.00	2.23	1.23	0.74	2.05
HIV	0.68	0.06	7.55	–	–	–
Weight reduplication	1.00	0.97	1.04	–	–	–
Cold ischemia time	1.00	1.00	1.00	–	–	–
pRBC transfusion during LT	1.02	0.98	1.05	–	–	–
Platelet transfusion during LT	1.02	0.92	1.14	–	–	–
FFP transfusion during LT	1.01	0.98	1.04	–	–	–
Induction with basiliximab for LT	1.72	0.87	3.95	–	–	–
Is the CCI score from the LT	1.06	0.70	1.66	1.20	0.69	2.12
HD or PD prior to LT	0.97	0.59	1.63	0.73	0.36	1.48
Gastrointestinal anastomosis during LT	4.16	0.54	32.10	–	–	–
Biliary drainage during LT	1.84	0.96	4.08	1.74	0.88	4.48
New renal for HD/CRRT during admission for LT	1.03	0.69	1.53	0.73	0.40	1.34
Hospitalized for an indication other than LT	1.20	0.79	1.83	–	–	–

Univariate analysis evaluates the association of each variable with multidrug-resistant bacterial infection (MDRBI) after liver transplantation (LT).
Multivariable logistic regression included variables selected based on clinical relevance and/or statistical significance in univariate analysis.
Reference category for race/ethnicity is Asian unless otherwise specified.
LOS: length of stay; ICU: intensive care unit; SBP: spontaneous bacterial peritonitis; TIPS: transjugular intrahepatic portosystemic shunt; HbA1c: hemoglobin A1c; CCI: Charlson Comorbidity Index; CLIF-C ACLF: Chronic Liver Failure Consortium Acute-on-Chronic Liver Failure score; MELD-3: Model for End-Stage Liver Disease score; pRBC: packed red blood cells; FFP: fresh frozen plasma; HD: hemodialysis; PD: peritoneal dialysis; CRRT: continuous renal replacement therapy.

Disclosures: Konstantinos Ouranos:Nothing to Disclose, Tilemachos Koutouratsas:Nothing to Disclose, Mark Michael:Nothing to Disclose, Siddharth Das: Nothing to Disclose, Poojasree Pasupuleti:Nothing to Disclose, Evangelia Mylona:Nothing to Disclose, Fadi Shehadeh:Nothing to Disclose, Diana Avila:Nothing to Disclose, Sudha Kodali:Nothing to Disclose, Tamneet Basra:Nothing to Disclose, Michelle Jones-Pauley: Nothing to Disclose, David Victor:Intercept: Speaker, and Advisor, Gilead: Speaking and Teaching, Madrigal: Speaker, BMS: Stock - publicly traded company, Pfizer: Stock - publicly traded company, Mazen Noureddin:Akero: Advisor, Alligos: Advisor, Altimmune: Advisor, AstraZeneca: Advisor, Boehringer Ingelheim: Advisor, Boston Pharma: Advisor, Cytodyn: Advisor, GSK: Advisor, Lilly: Advisor, Madrigal: Advisor, Merck: Advisor, Novo Nordisk: Advisor, Sagimet: Advisor, Terns: Advisor, Takeda: Advisor, Akero: Principal Investigator, Allergan: Principal Investigator, Altimmune: Principal Investigator, Boehringer Ingelheim: Principal Investigator, Bristol Myers Squibb: Principal Investigator, Boston Pharma: Principal Investigator, Conatus: Principal Investigator, Corcept: Principal Investigator, Galectin: Principal Investigator, Genfit: Principal Investigator, GSK: Principal Investigator, Kowa: Principal Investigator, Enanta: Principal Investigator, Madrigal: Principal Investigator, Lilly: Principal Investigator, Merck: Principal Investigator, Novartis: Principal Investigator, Novo Nordisk: Principal Investigator, Rivus: Principal Investigator, Shire: Principal Investigator, Takeda: Principal Investigator, Terns: Principal Investigator, Viking: Principal Investigator, Zydus: Principal Investigator, Rivus: Stock – privately held company, Cytodyn: Stock - publicly traded company, ChronWell: Stock – privately held company, Madrigal: Speakers bureau, Gilead Sciences: Principal Investigator, Akero: Consultant, Altimmune: Consultant, Alligos:

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4471 | ◆ EXTERNAL VALIDATION OF POST-LIVER TRANSPLANT RISK SCORES FOR HEPATOCELLULAR CARCINOMA RECURRENCE IN LIVER TRANSPLANT RECIPIENTS

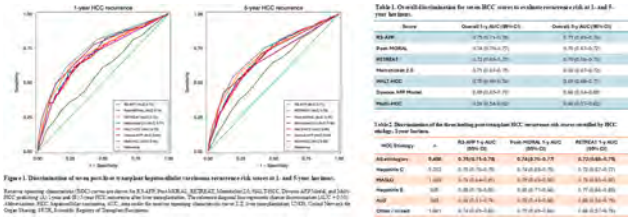
Leandro Sierra[1] Butros Fakhoury[2] Na Bo[3] Juan Pablo Arab[2] Neil Mehta[4] Amit Singal[5], [1]Cleveland Clinic Foundation, [2]Virginia Commonwealth University School of Medicine, Richmond, VA, USA, [3]Virginia Commonwealth University, Richmond, VA, USA., [4]University of California San Francisco, San Francisco, CA, USA, [5]The University of Texas Southwestern Medical Center, Dallas, TX, USA

Background: Multiple risk scores have been proposed to predict hepatocellular carcinoma (HCC) recurrence after liver transplant (LT). However, head-to-head comparisons in a national cohort are lacking. We assessed the performance of post-LT HCC recurrence risk scores stratified by median MELD at Transplant minus three points (MMaT-3 era) and HCC etiology. **Methods:** Using the United Network for Organ Sharing/Scientific Registry of Transplant Recipients (UNOS/SRTR) database, we performed an external validation of 7 prognostic scores: HALT-HCC, Multi-HCC, the Duvoux AFP Model, Metroticket 2.0, RETREAT, R3-AFP, and Post-MORAL. We included adult recipients transplanted for HCC and excluded those with prior LT, fibrolamellar HCC, mixed HCC-cholangiocarcinoma, multiorgan transplantation, and missing explant data. Scores were calculated from variables at transplant and/or explant pathology. Primary outcomes were HCC recurrence at 1 and 5 years post-LT. Discrimination was assessed by area under the ROC (AUC) curve with pairwise DeLong comparisons. Risk stratification was evaluated across score quartiles using Fine-Gray competing risk models, treating death as a competing event. Subgroup analyses were performed by allocation policy era (pre- vs post-MMaT-3) and HCC etiology. **Results:** Among 9,450 LT recipients with HCC, recurrence developed in 3.0% at 1 year and 8.1% at 5 years. Diagnostic performance of each model is detailed in **Table 1** . R3-AFP achieved the highest 1-year discrimination (AUC 0.75), which was comparable to Post-MORAL (AUC 0.74; $p = 0.10$) and significantly higher than RETREAT (AUC 0.72; head-to-head $p = 0.02$). Metroticket 2.0 (AUC 0.71), HALT-HCC (AUC 0.70), Duvoux AFP (AUC 0.69), and Multi-HCC (AUC 0.58) (global $p < 0.001$). The same pattern was observed at 5 years. From Q1 to Q4, the 5-year cumulative recurrence rate rose from 9% to 18% with R3-AFP (subhazard ratio [SHR] 5.79, 95%CI 4.77–7.02), from 9% to 20% with Post-MORAL (SHR 6.04), and from 9% to 23% with RETREAT (SHR 7.27) (all p-trend < 0.001). In subgroup analyses, 1-year discrimination improved in the post-MMaT-3 era for R3-AFP (AUC 0.85 vs 0.74; $p = 0.004$) and Post-MORAL (AUC 0.87 vs 0.72; $p = 0.001$) but not

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RETREAT (p = 0.61); performance of these scores at 1 year remained consistent across most liver disease etiologies (AUC 0.74–0.85) but was attenuated in alcohol-associated liver disease (R3-AFP AUC 0.62; Post-MORAL AUC 0.55) (**Table 2**). **Conclusion:** In a representative U.S. cohort, R3-AFP and Post-MORAL achieved the highest discrimination for post-LT HCC recurrence at both 1- and 5-year horizons, including improved diagnostic performance in the MMaT-3 allocation era. These risk scores can be adopted to guide post-LT HCC surveillance and future tertiary prevention strategies.



Disclosures: Leandro Sierra:Nothing to Disclose, Butros Fakhoury:Nothing to Disclose, Na Bo:Nothing to Disclose, Juan Pablo Arab:Nothing to Disclose, Neil Mehta:Merck: Consultant, FujiFilm WAKO: Consultant, Merck: Consultant, FujiFilm WAKO: Consultant, Boston Scientific: Consultant, FujiFilm: Grant/Research Support, FujiFilm: Consultant, Merck: Consultant, FujiFilm WAKO: Consultant, Merck: Consultant, FujiFilm WAKO: Consultant, Boston Scientific: Consultant, FujiFilm: Grant/Research Support, FujiFilm: Consultant, Amit Singal:Genentech: Consultant, AstraZeneca: Consultant, Bayer: Consultant, Eisai: Consultant, Exelixis: Consultant, Merck: Consultant, Elevar: Consultant, FujiFilm Medical Sciences: Consultant, Exact Sciences: Consultant, Glycotest: Consultant, Boston Scientific: Consultant, Sirtex: Consultant, HelioGenomics: Consultant, ImCare: Consultant, DELFI: Consultant, Curve Biosciences: Consultant, Catalym: Consultant, Verve: Consultant.

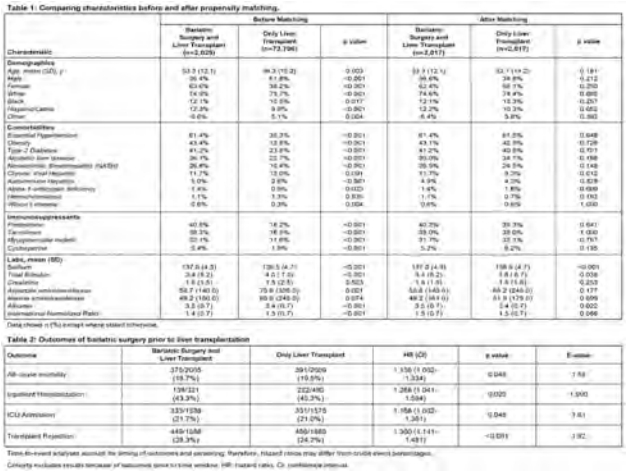
4473 | ◆ IMPACT OF PRIOR BARIATRIC SURGERY ON MORTALITY, HOSPITAL UTILIZATION, AND GRAFT OUTCOMES AFTER LIVER TRANSPLANTATION: A TRINETX RETROSPECTIVE PROPENSITY-MATCHED COHORT STUDY

Peter Mounas[1] Mikaela Nikkola Jara-Tantoco[1] Abiodun Idowu[1] Maria Lagarde Mussa[1], [1]Jefferson Einstein Philadelphia Hospital

Background: Obesity is a major driver of metabolic dysfunction-associated steatotic liver disease (MASLD), putting patients at risk of complications including cirrhosis and hepatocellular carcinoma. Bariatric surgery has shown to improve outcomes in obese patients, which may improve transplant candidacy. There have been studies positing that bariatric surgery can lead to increased mortality and rejection due to malnutrition and malabsorption. Data is limited regarding long-term outcomes such as mortality, transplant graft rejection, and hospital utilization in patients with prior bariatric surgery. **Methods:** This retrospective cohort study used the TriNetX US Collaborative Network, encompassing 67 healthcare organizations. Adult liver transplant patients (> 18 years) were identified using CPT, ICD-10, and procedural transplant codes. Patients with a history of bariatric surgery prior to transplant were identified using CPT codes and ICD-10 codes for sleeve gastrectomy, Roux-en-Y gastric bypass, adjustable gastric banding, and biliopancreatic diversion procedures. Propensity score matching (1:1) adjusted for demographics, metabolic disease, liver disease etiology, MELD score, and immunosuppressive medication exposure (see table 1). After matching, outcomes of mortality, transplant graft rejection, and hospital utilization were compared using Kaplan-Meier survival analysis and hazard ratios. E-value was measured for each outcome to determine the effect of unmeasured confounders. **Results:** After propensity score matching, 2,006 patients remained in each cohort for analysis. There was significantly increased hazard of all-cause mortality (HR 1.156 CI 1.002-1.334), inpatient hospitalization (HR 1.288 CI 1.041-1.594), ICU admission (1.168 CI 1.002-1.361), and graft outcomes (1.300 CI 1.141-1.481) in patients with prior bariatric surgery compared to liver transplant recipients alone (all p < 0.05). Moreover, when E-values were computed for these outcomes, HR and their CI were found below their respective E values (see table 2). **Conclusion:** In this propensity-matched, multi-institutional cohort, bariatric surgery prior to liver transplant was associated with an increased hazard in mortality, hospital utilization and transplant graft rejection, highlighting its less favorable outcomes. Factors such as malnutrition can contribute to worsening outcomes in bariatric surgery patients. Some limitations of the study include TriNetX reliance on ICD coding, which may introduce coding inaccuracies and bias. Future studies can be beneficial in understanding the effects of nutritional status, bariatric surgery timing, and surgical subtypes.

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4474 | ◆ BEYOND REJECTION DETECTION: PRECISION IMMUNOSUPPRESSION UTILIZING DONOR-DERIVED CELL-FREE DNA AS A DYNAMIC BIOMARKER AFTER LIVER TRANSPLANTATION

Alexander Frangenberg[1] Kinnari Modi[1] Kyle Schneider[1] Khushbu Tejani[2] Kanish Mohib[2] Parvez Mantry[1], [1]Methodist Dallas Medical Center, Dallas, Texas, USA, [2]CareDx,Inc., California, USA

Background: Immunosuppression (IS) management in liver transplant recipients requires balancing rejection prevention with risks of renal toxicity, infection, and malignancy to improve survival and morbidity. Current IS adjustment strategies rely primarily on liver enzyme monitoring, which may result in late detection of allograft rejection. This study evaluates the utility of donor-derived cell-free DNA (dd-cfDNA) as a serum marker to guide IS titration in liver transplant recipients. **Methods:** We retrospectively analyzed 154 liver transplant recipients with stable liver function tests (LFTs) who underwent dd-cfDNA testing (AlloSure, CareDx Inc) between August 2021 and January 2026 at a single medical center. Based on dd-cfDNA levels, patients were categorized into three IS management cohorts: Stable (no IS change), decreased IS (DIS), and increased IS (IIS). Statistical analyses included Kruskal Wallis, Mann Whitney U, and Wilcoxon signed rank tests. **Results:** Of 134 patients, dd-cfDNA levels guided categorization into: Stable (n = 84), DIS (n = 37), and IIS (n = 13). Age and LFTs were comparable across groups. The DIS group showed significantly lower median pre-adjustment dd-cfDNA levels compared to the IIS group (1.8%; IQR 1.0-3.4% vs. 9.8%; 5.3-15.5%, p = < 0.0001). Post-adjustment, DIS group dd-cfDNA levels remained stable (2.6%; 1.5-3.8% vs. 1.8%; 1.0-3.4%, p = 0.32). In the IIS group, dd-cfDNA levels decreased in 75% of patients, achieving levels comparable to stable patients (3.2%; 2.8-13% vs. 2.9%; 1.8-5.0%, p = 0.035). Based on dd-cfDNA results, 93% of patients underwent any class medication down titration adjustment of therapy, with 78% down titrating CNI levels. Of the patients, 95% maintained stable AST and ALT post-titration. Eight post-titration biopsies showed no rejection. **Conclusion:** Donor-derived cell-free DNA testing appears to be an effective biomarker for guiding immunosuppression management in stable liver transplant recipients. The successful medication adjustments in down titration of 93% of patients, with maintained stability post-titration, suggests dd-cfDNA monitoring enables more precise immunosuppression optimization compared to traditional liver enzyme monitoring alone. These findings support incorporating dd-cfDNA testing into post-transplant monitoring protocols for identifying candidates suitable for IS reduction thus reducing risk of systemic toxicity, though further prospective studies are needed to validate these results.

Table 1: Clinical Characteristics, Medication Adjustments, and Outcomes

Parameter	Stable (n=84)	Augmented IS (n=13)	Decreased IS (n=37)
Laboratory Values			
Prior to IS Adjustment, AST (u/L), median (IQR)	19 (19-28)	59.5 (31-102)	21 (16-25)
Prior to IS Adjustment, ALT (u/L), median (IQR)	22 (15-28)	67 (35-128)	17 (13-27)
Following IS Adjustment, AST (u/L), median (IQR)	-	53 (25-87) p-value=0.27	19 (16-28) p-value=0.11
Following IS Adjustment, ALT (u/L), median (IQR)	-	47 (26-61) p-value=0.1	20.5 (14-26) p-value=0.98
dd-cfDNA Values*			
Prior to IS Adjustment (%), median (IQR)	2.9 (1.8-5.0)	9.75 (5.3-15.5)	1.8 (1-3.4)
Following IS Adjustment (%), median (IQR)	-	3.2 (2.8-13)	2.6 (1.5-3.8)
p-value	-	**p-value=0.01	p-value=0.32
CNI Adjustments, n (%)		(n=11)	(n=34)
No change	-	2 (18%)	2 (6%)
≤25% change	-	5 (46%)	6 (18%)
25-≤75%	-	4 (36%)	25 (73%)
Discontinued	-	-	1 (3%)
mTOR Adjustments, n (%)		(n=1)	(n=2)
No change	-	1 (100%)	-
25-≤50% change	-		2 (100%)
Discontinued	-	-	-
MMF Adjustments, n (%)		(n=10)	(n=20)
No change	-	4 (40%)	15 (75%)
Adjusted by ≤50%	-	6 (60%)	4 (20%)
Discontinued	-	-	1 (5%)
Steroid Adjustments, n (%)		(n=9)	(n=19)
No change	-	5 (56%)	8 (42%)
Increased	-	3 (33%)	
Decreased		1 (11%)	1 (5%)
Discontinued	-	-	10 (53%)

*Note: 1st AlloSure draw utilized for calculation of median dd-cfDNA for stable cohort

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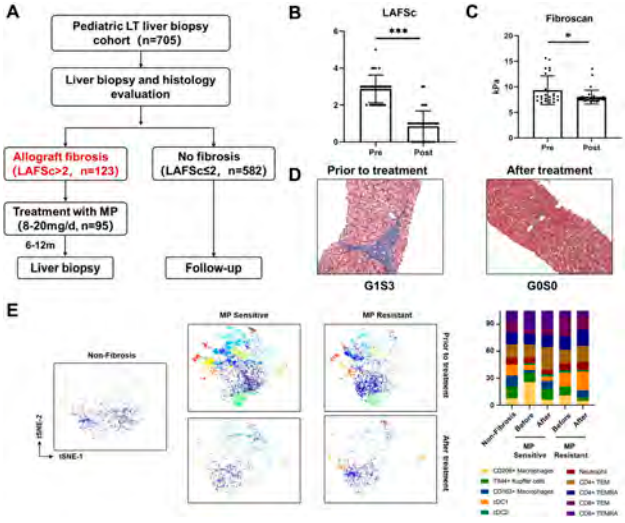
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★ 4475 | ◆ LOW-DOSE ORAL METHYLPREDNISOLONE REVERSES INTRAHEPATIC FIBROSIS AFTER PEDIATRIC LIVER TRANSPLANTATION BY ELIMINATING CD206⁺HLA-DR⁺CD14⁺ MACROPHAGE

Yuan Liu[1] Bingran Wang[2] Qiang Xia[2], [1]Renji Hospital affiliated to Shanghai Jiao Tong University, [2]Renji Hospital affiliated to Shanghai Jiao Tong University School of Medicine

Background: Liver transplantation is the most effective treatment for pediatric patients with end-stage liver diseases, with 10-year survival rate exceeded 90%. However, intrahepatic fibrosis has emerged as a significant long-term threat to graft survival. Nearly 30% of recipients were found fibrosis within the first year after LT, and this proportion increases to over 70% at 10 years. Currently, no therapy has been established for the treatment of graft fibrosis after LT. Methylprednisolone (MP) has been widely used in the treatment of autoimmune hepatitis. However, its role in reversing graft fibrosis after LT remains largely unexplored. **Methods:** We conducted a prospective clinical study involving pediatric LT recipients who were diagnosed with intrahepatic fibrosis during protocol liver biopsy. Rcipients with LAFSc >2 were enrolled for oral MP treatment. Depending on fibrosis severity, the initial dosage of MP was 8-20 mg/day and was gradually tapered every 2 weeks, after which maintained at 4 mg/day for 6–12 months. Follow-up liver biopsies were subsequently performed to evaluate fibrosis progression or regression. In parallel, mass cytometry (CyTOF) was performed to analyze changes in the intrahepatic immune microenvironment before and after treatment. **Results:** Between June 2023 and March 2026, 705 pediatric LT recipients underwent protocol liver biopsy at Renji Hospital. Among them, 141 recipients (20.0%) were found to have intrahepatic fibrosis, with a mean follow-up duration of 48.3 months. Of these patients, 123 recipients were classified as LAFSc >2, and 95 recipients received MP treatment. The average treatment duration was 12.9 months. Among all treated participants, 65 recipients (68.4%) demonstrated fibrosis improvement or complete resolution. After treatment, the average LAFSc decreased from 3.449 to 0.849, with inflammation grade was reduced from 1.688 to 0.182. In addition, the average FibroScan decreased from 9.71 to 6.96 kPa. No significant metabolic adverse effects were observed during treatment. CyTOF analysis revealed that CD206⁺HLA-DR⁺CD14⁺ macrophages accumulated predominantly in the peripheral regions surrounding fibrotic scars, and MP treatment markedly reduced this macrophage subset. *In vitro* analyses indicated intrahepatic CD206⁺HLA-DR⁺CD14⁺ macrophages could secrete pro-inflammatory cytokines following stimulation. Interestingly, recipients who were resistant to MP treatment exhibited lower levels of CD206⁺HLA-DR⁺CD14⁺ macrophage infiltration. Instead, a distinct CD11c⁺HLA-DR⁺ DC subset was enriched within the fibrotic core regions of these recipients. The abundance of CD11c⁺HLA-DR⁺ DC increased progressively with worsening graft fibrosis, even after MP treatment. **Conclusion:** Low-dose oral MP may effectively reverse intrahepatic fibrosis after pediatric LT by inhibiting the function of CD206⁺HLA-DR⁺CD14⁺ macrophages.



Disclosures: Yuan Liu:Nothing to Disclose, Bingran Wang:Nothing to Disclose, Qiang Xia:Nothing to Disclose.

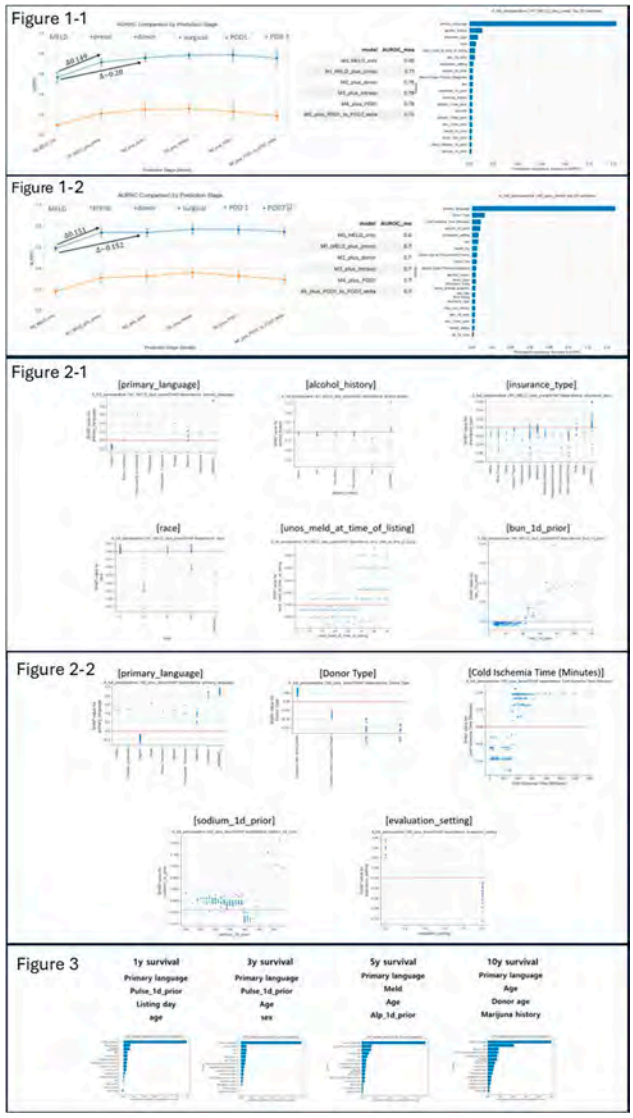
4476 | ◆ MACHINE LEARNING OUTPERFORMS MELD AND IDENTIFIES SOCIAL DETERMINANTS AS KEY PREDICTORS OF POST-TRANSPLANT SURVIVAL

Chiwoo Song[1] Myna Lim[2] Jaekyoung Kim[2] Raza Malik[3], [1]Roger Williams Medical Center, [2]KAIST, South Korea, [3]Lahey Hospital & Medical Center

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Background: The Model for End-Stage Liver Disease (MELD) score was introduced as an organ allocation system to reduce waitlist mortality and has become the most widely used tool. However, it does not reliably predict post-transplant survival. Originally derived using linear regression, MELD may oversimplify complex, non-linear interactions among recipient, donor, and perioperative factors. Certain machine learning algorithms offer the ability to model such interactions while addressing the "black box" limitation. This study aimed to develop an improved and interpretable prediction model for post-transplant outcomes and to identify key influential factors. **Methods:** We retrospectively analyzed adult patients who underwent liver transplant at a single academic center from 2000 to 2024, collecting >200 variables across five domains: MELD score, preoperative, donor, surgical, and postoperative. Post-transplant survival predictions at 90 days, 1 year, and long-term (>1 year) were modeled using CatBoost for short-term and Random Survival Forest (RSF) for long-term, evaluated by the area under the receiver operating characteristic curve (AUROC). To assess the incremental value of clinically available data over time, sequential models were constructed using progressively added data domains: MELD-only, preoperative, donor, surgical, and postoperative variables. Shapley Additive Explanations (SHAP) values quantified each variable's contribution to model predictions. **Results:** A total of 1,655 recipients were included. Sequential CatBoost models outperformed MELD alone, with AUROC improving from 0.567 to 0.786 for 90-day and 0.587 to 0.770 for 1-year mortality (Figures 1-1, 1-2). SHAP analysis identified "primary language" as the most influential predictor at all timepoints, with non-English primary language predicting poorer outcomes independent of clinical severity. Insurance type and race were additional SDOH predictors in preoperative models. Adverse clinical predictors included MELD >30, BUN >40 mg/dL, cold ischemia time >300 minutes, and serum sodium <130 mmol/L one day prior LT. In contrast, favorable predictors included English primary language, private insurance, outpatient evaluation, and living donor grafts (Figures 2-1, 2-2). RSF analysis confirmed primary language as a significant predictor beyond 1 year, with predictor importance varying dynamically across 1-, 3-, 5-, and 10-year timepoints (Figure 3). **Conclusion:** Our models outperformed MELD alone in predicting post-transplant mortality. They consistently identified "primary language," likely reflecting underlying SDOH, as a significant prognostic factor across all prediction timepoints, highlighting the importance of incorporating SDOH into risk stratification.



Disclosures: Chiwoo Song:Nothing to Disclose, Myna Lim:Nothing to Disclose, Jaekyoung Kim:Nothing to Disclose, Raza Malik:Nothing to Disclose.

4477 | ◆ A MULTIMODAL MACHINE LEARNING BIOMARKER FOR NON-INVASIVE, CAUSE-SPECIFIC DIAGNOSIS OF LIVER GRAFT INJURY

Soumita Ghosh[1] Cristina Baciu[1] Elisa Pasini[1] Chris Shi[1] Sara Naimimohasses[1] Sandra Fischer[2] Sandra Holdsworth[1] Bima Hasjim[3] Michael Brudno[4] Daniel De Carvalho[5] Björn Hartleben[6] Bastian Engel[7] Richard Taubert[7] Mamatha Bhat[8], [1]Ajmera Transplant Centre, University Health Network, Toronto, ON, Canada.,

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Background: Liver graft dysfunction affects more than 30% of liver transplant recipients (LTRs). Current non-invasive assays detect graft injury but have limited ability to distinguish clinically competing causes such as T cell-mediated rejection (TCMR) and post-transplant metabolic dysfunction-associated steatohepatitis (MASH-LT), often leaving biopsy as the diagnostic standard. This is critical because TCMR and MASH-LT require different immunosuppression strategies. We developed a multimodal AI biomarker integrating circulating cell-free DNA (cfDNA) methylation signatures with clinical variables to enable non-invasive, cause-specific diagnostic support. **Methods:** Plasma-derived genome-wide cfDNA methylation profiles from 125 biopsy-confirmed LTRs across 2 transplant centres, UHN and Hannover Medical School, were integrated with matched clinical variables. The cohort was partitioned into training and held-out test sets while preserving class balance. Boruta feature selection identified 201 informative methylation windows. We developed a dual-branch attention-gated neural network (dbAGNN), which learned separate methylation and clinical representations to classify TCMR, MASH-LT, and Controls. Attention-gate weights and SHAP were used to quantify modality contributions and feature importance. Model performance was assessed on the test set using 101 stratified bootstrap iterations. Tissue-of-origin deconvolution was used to localize the cfDNA injury signal. **Results:** The multimodal dbAGNN achieved a mean weighted AUROC of 0.974 (95% CI 0.969-0.978) on the held-out test set, outperforming methylation-only and clinical-only models. Bootstrap metrics confirmed robust performance: accuracy 0.883 (95% CI 0.872–0.895), macro-F1 0.872 (95% CI 0.859–0.885), and negative predictive value (NPV) 0.944 (95% CI 0.939–0.950). Attention-gate weights varied significantly across classes (Kruskal-Wallis $H = 26.42$, $p < 0.001$). TCMR predictions relied predominantly on methylation (mean weight: 0.924 ± 0.101), while MASH-LT also relied strongly on methylation (0.844 ± 0.089). CTRL-LT showed greater clinical contribution (clinical weight 0.566 ± 0.225), indicating pathology-appropriate modality prioritization. SHAP identified relevant methylation loci (RUNX1, NOTCH1, WNT5A) and clinical factors (AST, BMI). Tissue-of-origin deconvolution localized injury-associated cfDNA to immune- and hepatocyte-derived fragments. Immune-enriched cfDNA was elevated in TCMR versus CTRL-LT (AUROC 0.721), and hepatocyte-enriched cfDNA was elevated in MASH-LT versus TCMR (AUROC 0.665), concordant with liver tissue methylation ($R = 0.56$-0.71). **Conclusion:** This multimodal AI biomarker shows diagnostic potential for non-invasive transplant monitoring. The framework adds interpretability through attention-gate attribution, patient-level feature importance, and tissue-of-origin deconvolution.

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4478 | ◆ LONG-TERM OUTCOMES OF BASILIXIMAB INDUCTION THERAPY IN ADULT LIVER TRANSPLANT RECIPIENTS: A PROPENSITY SCORE–MATCHED, LARGE-SCALE REAL-WORLD EVIDENCE STUDY

Mythily Rao Ponaganti[1] Moksha Prasoona Avvaru[2] Erick Phocco[1] Suresh Kumar Nayudu[1] Naga Praneeth Vakkalagadda[3], [1]SBH Health System, [2]Harnett Health, [3]University of Alabama at Birmingham

Background: Basiliximab(BSX), a renal protective interleukin-2 receptor antagonist, for induction immunosuppression in liver transplantation (LT) to delay calcineurin inhibitor (CNI) use. Though short-term benefits are well known, limited data available on long-term outcomes. We aimed to evaluate the association between BSX induction and acute kidney injury (AKI) as the primary outcome, and the cardiovascular events and mortality as secondary outcomes in adult LT recipients over a 5-year follow-up period. **Methods:** We conducted a retrospective propensity score–matched cohort study using the Global Collaborative Network. Adult ($\geq$18 years) LT recipients were divided into BSX and control cohorts who received BSX and tacrolimus respectively. Propensity score matching (1:1) was performed on characteristics including demographics, comorbidities and laboratory values. The primary outcome was AKI and secondary outcomes

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included MI, stroke, CKD and all-cause mortality over a period of 5 years. Measures of association and Kaplan-Meier (KM) survival analyses with log-rank tests and hazard ratios [HR] were calculated. Patients with the outcome prior to the time window were excluded from each respective analysis. **Results:** After propensity score matching, a total of 5260 patients were included in each cohort with mean age of 55.2 years at index and 66% were male. AKI risk was significantly lower in the BSX group at 30 and 90 days, but the difference attenuated later with no difference at 5 years, though KM analysis showed a higher AKI-free survival in the BSX group (table 1). MI rates were low but did not differ significantly between groups at any time point, whereas Stroke was significantly lower in the BSX group at 30 days but not at subsequent time points. All-Cause Mortality was significantly lower in the BSX group at 5 years [table2] although benefit was not apparent at earlier time points, with a trend emerging at 3 years. Notably, CKD was significantly higher in the BSX group from 90 days onward. **Conclusion:** BSX induction in adult LT recipients resulted in lower incidence of AKI at early time points and improved 5-year survival. However, BSX induction showed higher rates of CKD, likely reflecting residual confounding by indication, as BSX is preferentially used in high-risk patients with history of CKD. These findings support the short-term renal-protective role of BSX induction with a potential long-term survival benefit, while highlighting the need for prospective studies with comprehensive adjustment for disease severity to establish the development of CKD.

Table 1: Significant Values for AKI (Basiliximab vs. Control)

Time Point	Analysis Type	Basiliximab Risk/Survival	Control Risk/Survival	Effect Estimate (95% CI)	P-value
30 days	Risk analysis	5.6%	7.7%	RR 0.736 (0.592, 0.914); OR 0.720 (0.571, 0.908)	**0.005**
30 days	Survival analysis	94.30%	92.19%	HR 0.712 (0.569, 0.891)	**0.003**
90 days	Risk analysis	9.9%	12.1%	RR 0.820 (0.697, 0.965); OR 0.801 (0.667, 0.961)	**0.017**
90 days	Survival analysis	89.89%	87.50%	HR 0.782 (0.659, 0.929)	**0.005**
5 years	Survival analysis	70.40%	66.88%	HR 0.879 (0.786, 0.983)	**0.024**

Table 2: Significant Values for Mortality (Basiliximab vs. Control)

Time Point	Analysis Type	Basiliximab Risk/Survival	Control Risk/Survival	Effect Estimate (95% CI)	P-value
5 years	Risk analysis	12.2%	14.1%	RR 0.865 (0.783, 0.956); OR 0.846 (0.754, 0.950)	**0.004**
5 years	Survival analysis	84.46%	81.13%	HR 0.851 (0.765, 0.948)	**0.003**

Disclosures: Mythily Rao Ponaganti:Nothing to Disclose, Moksha Prasoona Avvaru:Nothing to Disclose, Erick Phocco:Nothing to Disclose, Suresh Kumar Nayudu:Nothing to Disclose, Naga Praneeth Vakkalagadda:Nothing to Disclose.

4479 | ◆ FIBROSIS PROGRESSION AFTER BIOPSY-CONFIRMED POST-TRANSPLANT MASH: A 35-YEAR LONGITUDINAL HISTOLOGY COHORT STUDY

Sobia Laique[1] Muhammad Ahmad Nadeem[1] Puneet Bansal[1] Chase Wehrle[1] Jacob Sweeney[1] Xuefeng Zhang[1] Mohamed El Hag[1] Pablo Bejarano[2] Rhea Abraham[1] Sapana Verma[1] Erlind Allkushi[1] Alejandro Pita[1] Mazhar Khalil[1] Masato Fujiki[1] Federico Aucejo[1] Jaekeun Kim[1] Andrea Schlegel[1] Koji Hashimoto[1] Jamak Modaresi Esfeh[3] Daniela Allende[1], [1]Cleveland Clinic, [2]Cleveland Clinic, Florida, [3]Cleveland Clinic Foundation

Background: Post-transplant metabolic dysfunction-associated steatohepatitis (MASH) is increasingly recognized, but its fibrotic trajectory remains poorly characterized. Because non-invasive fibrosis tests (NITs) are not validated after liver transplant (LT), histology remains essential. We evaluated fibrosis progression and predictors among LT recipients with biopsy-confirmed post-LT MASH and serial biopsies. **Methods:** Of 3,912 adult LT recipients at Cleveland Clinic (Ohio and Florida) between 1985-2020, 2,577 had post-transplant biopsy data. Among these, 134 patients with biopsy-confirmed post-transplant MASH comprised the analytic cohort. The longitudinal cohort included 64 patients with ≥ 1 biopsy after index MASH (19 recurrent, 45 de novo). Fibrosis was staged using NASH-CRN criteria. Progression was defined as ≥ 1-stage increase from index to last biopsy. Annualized progression rate was calculated as fibrosis stage change divided by inter-biopsy interval. Groups were compared using Fisher exact or Wilcoxon rank-sum tests. Cumulative progression was assessed using Kaplan-Meier estimates with censoring at last biopsy. Given limited events, multivariable analysis was not performed. **Results:** Median time from transplant to index MASH biopsy was 1.63 years (IQR 0.51–4.03); 3.37 years for recurrent and 1.10 years for de novo MASH ($P = 0.041$). Patients had a median of 3 biopsies (IQR 2–4) over a median index-to-last-biopsy interval of 2.66 years (IQR 0.74–5.21). At index biopsy, fibrosis was F0–F1 in 48 (75.0%), F2 in 13 (20.3%), and F3 in 3 (4.7%); none had F4. Fibrosis progression occurred in 31 patients (48.4%): 7/19 recurrent (36.8%) and 24/45 de novo (53.3%; $P = 0.228$). Progression to advanced fibrosis ($\geq$F3) occurred in 12 (18.8%) and to cirrhosis in 4 (6.3%), with no difference by MASH type. Among progressors, median annualized rate was 0.38 stages/

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year (IQR 0.19–0.91), corresponding to an estimated F0-to-F4 interval of approximately 10 years. Kaplan-Meier analysis showed no significant difference in cumulative progression between recurrent and de novo MASH (log-rank P = 0.205). On univariable analysis, no baseline variable, including MASH type, age, BMI, diabetes, NAS score, or fibrosis stage, was significantly associated with progression; index ballooning grade showed a non-significant trend (P = 0.070). **Conclusion:** In this 35-year multicenter longitudinal histology cohort, nearly half of patients with post-transplant MASH experienced fibrosis progression, with an estimated decade-long trajectory from no fibrosis to cirrhosis. Progression rates were similar regardless of whether MASH was recurrent or de novo, and no baseline feature reliably predicted progression. These findings establish that post-transplant MASH carries meaningful fibrotic potential regardless of indication, and highlight the need for validation of NITs against histology to enable scalable post-LT surveillance.

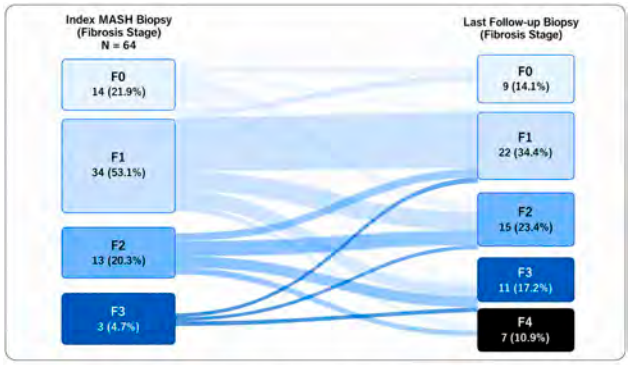


Figure 1. Fibrosis Stage Transitions From Index to Last Follow-Up Biopsy After Post-Transplant MASH

64 recipients with post-transplant MASH and ≥1 follow-up biopsy (19 recurrent, 45 de novo). Band width is proportional to patient count. Median inter-biopsy interval: 2.66 years (IQR 0.74–5.21). Trajectory was defined by change in fibrosis stage from index MASH biopsy to last follow-up biopsy. MASH, metabolic dysfunction-associated steatohepatitis; F, fibrosis stage.

Disclosures: Sobia Laique:Madrigal Pharmaceuticals Inc: Advisor, Madrigal Pharmaceutical: Consultant, Novo Nordisk: MASH Curriculum Steering Committee, MUHAMMAD AHMAD NADEEM:Nothing to Disclose, Puneet Bansal:Nothing to Disclose, Chase Wehrle: Nothing to Disclose, Jacob Sweeney:Nothing to Disclose, Xuefeng Zhang:Nothing to Disclose, Mohamed El Hag:Nothing to Disclose, Pablo Bejarano:Nothing to Disclose, Rhea Abraham:Nothing to Disclose, Sapana Verma:Nothing to Disclose, Erlind Allkushi:Nothing to Disclose, Alejandro Pita:Nothing to Disclose, Mazhar Khalil:Nothing to Disclose, Masato Fujiki:Nothing to Disclose, Federico Aucejo:Nothing to Disclose, Jaekeun Kim:Nothing to Disclose, Andrea Schlegel:Nothing to Disclose, Koji Hashimoto:OrganOx: Advisor, Jamak Modaresi Esfeh:Nothing to Disclose, Daniela Allende: Gilead: Advisory board member, Elsevier: Royalties on book, Educational Symposia: Speaking and Teaching.

4480 | ◆ LONGITUDINAL INTELLIGENT FORECAST FOR EXPECTED OUTCOMES POST-LIVER TRANSPLANT (LIFE-LT) – AN ARTIFICIAL INTELLIGENCE PREDICTION MODEL

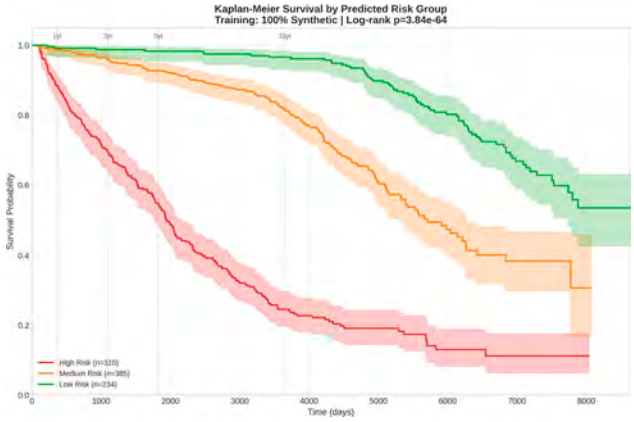
Omar Mousa[1] Aadarsh Barot[1] Andrew Keaveny[1] Rohan Goswami[1], [1]Mayo Clinic Florida

Background: Predicting long-term survival after liver transplantation (LT) is critical for patient counseling and organ allocation optimization. Post-LT prediction tools are lacking, and the Model for End-Stage Liver Disease (MELD) has limited post-transplant prognostic utility (C-index 0.60-0.65). A key barrier to clinical AI tools is the tension between data access and privacy. We hypothesized that training an AI model exclusively on synthetic patients could overcome this barrier while achieving clinically meaningful accuracy. **Methods:** This retrospective study included adult LT recipients at a high volume transplant center from 1/1/2002 to 12/31/2016. The original cohort (N = 1896) was randomly divided in two groups: 51% source cohort (n = 967) and 49% held-out test cohort (n = 929). A conditional tabular generative adversarial network was trained exclusively on the source cohort to learn statistical relationships among donor, recipient and transplant variables, and subsequently generated 5,138 synthetic patients without containing identifiable patient data. Statistical fidelity was confirmed through distribution matching and correlation preservation. An 18-model stacking ensemble with isotonic calibration was trained exclusively on synthetic data using 105 donor-recipient-transplant features. The model was tested on the source and held-out cohorts. Performance was assessed via C-index, time-dependent AUC, net reclassification improvement (NRI), and integrated discrimination improvement (IDI) versus MELD. **Results:** In the test cohort (929 patients, 462 events), the model achieved a C-index of 0.825 (95% CI: 0.806-0.843), compared with 0.802 in the source cohort for predicting post-LT survival up to 15 years, supporting good generalization. Time-dependent AUC was stable: 1-year 0.866, 3-year 0.884, 5-year 0.886, 10-year 0.885. The model outperformed MELD (NRI = 0.560, IDI = 0.355; $p < 0.001$), even when applied across multiple clinical subgroups. Risk stratification yielded three prognostic groups with markedly different outcomes and median survivals of 5.3, 11.5, and 17.2 years ($p < 0.001$) (Figure 1). Preliminary analysis of a MASLD subgroup (n = 81) showed promising discrimination (C-index 0.88, 95% CI: 0.83-0.92), warranting confirmation in larger cohorts. SHAP identified hepatocellular carcinoma status, recipient sodium, and donor-recipient interactions as top predictors. **Conclusion:** An AI

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model trained exclusively on synthetic data achieved excellent discrimination for post-LT survival without real patient exposure during development, substantially outperforming MELD. This privacy-preserving paradigm eliminates data-sharing barriers in transplant AI, enables individualized survival counseling and may inform allocation policy. Preliminary data concerning recipients transplanted for MASLDs merit investigation in larger cohorts of this rapidly expanding transplant population.

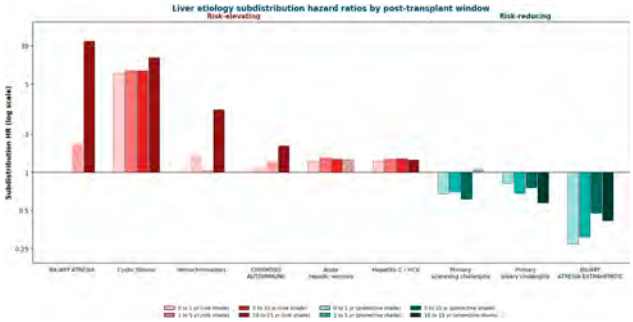


Disclosures: Omar Mousa:Nothing to Disclose, Aadarsh Barot:Nothing to Disclose, Andrew Keaveny: River 2 Renal Corporation: Grant/Research Support, Rohan Goswami:Nothing to Disclose.

4481 | ETIOLOGY-SPECIFIC AND INSULIN-DEPENDENCE-STRATIFIED RISK OF NEW-ONSET DIABETES POST-LIVER TRANSPLANTATION

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Background: New-onset diabetes after transplant (NODAT) is a recognized driver of post-liver-transplant mortality, but the risk profile is widely assumed to be temporally uniform. Whether NODAT risk and its insulin-dependence phenotype vary by pre-transplant liver disease etiology, and whether these signals change across the post-transplant timeline, is not well characterized. **Methods:** We assembled all adult liver-only transplants in OPTN/SRTR 1987–2021 with complete baseline diabetes status. Of 111,783 non-diabetic recipients at transplant, 102,201 remained at risk at the 1-year landmark (declining to 82,525, 47,836, and 24,351 at 5, 10, and 15 yr, respectively, after accounting for NODAT events and competing deaths). For each of the pre-transplant etiologies, we fit Fine-Gray subdistribution hazard models with death-without-NODAT as the competing event, adjusted for age, sex, BMI, and transplant era, separately within four landmark windows (0–1, 1–5, 5–10, 10–15 yr). Insulin-dependent (IDDM) and non-insulin-dependent (NIDDM) NODAT were modeled as cause-specific subtypes within the same Fine-Gray framework, using the OPTN INSULIN_DEPENDENT field at each NODAT onset visit to define the phenotype; events with unknown insulin status were excluded from the stratified sub-analysis. **Results:** Of 39 unique pre-transplant etiologies analyzed, two showed elevated NODAT risk consistently across all four landmark windows: cystic fibrosis (combined sHRs 6.09–8.09, the strongest etiology-NODAT association in the cohort) and chronic HCV infection (sHR 1.23–1.29, modest). Acute hepatic necrosis showed near-consistent elevation (sHR 1.23, 1.30, and 1.28 at 0–1, 1–5, and 5–10 yr, respectively). Three additional etiologies came up significant as late-onset risks at 10–15 yr: hemochromatosis (sHR 3.14 [1.42–6.94]), autoimmune cirrhosis (sHR 1.62 [1.09–2.42]), and biliary atresia (sHR 10.95 [2.54–47.17], n = 2 events). Three cholestatic and biliary etiologies were associated with consistently reduced NODAT risk across windows: biliary atresia, extrahepatic (sHR 0.27–0.48), primary sclerosing cholangitis (sHR 0.62–0.71 through 10 yr), and primary biliary cholangitis (sHR 0.58–0.82). All cited associations were significant at $p < 0.05$ (most at $p < 0.001$).The insulin-stratified analysis showed etiology-specific phenotype divergence concentrated in the first post-transplant decade: cystic fibrosis and HCV showed insulin-dependent (IDDM)-predominant patterns (CF IDDM sHRs 7.74, 8.06, and 7.63 across 0–1, 1–5, and 5–10 yr). **Conclusion:** Post-liver-transplant NODAT risk varies strongly by pre-transplant etiology. Cystic fibrosis, HCV, hemochromatosis, and autoimmune cirrhosis represent high-risk subgroups; the IDDM phenotype captures most etiology-specific signal and warrants targeted glycemic surveillance.



Disclosures: Mishal Ali:Eli Lilly and Company: Employee, Raghavendra Mirmira:Nothing to Disclose, Mary Rinella:akero: Consultant, akero: Consultant, 89Bio: Consultant, 89Bio: Consultant, Boehringer

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4482 | HEPATIC IRON DEPOSITION IN LIVER EXPLANTS: PATTERNS, ETIOLOGIES, AND CLINICAL ASSOCIATIONS

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Background: Hepatic iron loading is common in alcohol-associated liver disease (ALD) and metabolic dysfunction-associated steatotic liver disease (MASLD) and may worsen liver injury through ferroptosis. However, its prevalence, distribution, and clinical significance in decompensated cirrhosis are not well defined. We aimed to characterize hepatic iron deposition in liver explants and assess its associations with liver disease etiology and severity. **Methods:** We retrospectively analyzed adult liver transplant recipients at a single liver transplant center from 2013-2023. Explant pathology reports were reviewed for the presence and pattern of hepatic iron. Total and hepatocellular(HC) iron were evaluated in relation to pre-transplant MELD-Na, liver disease etiology, hepatocellular carcinoma (HCC), and metabolic risk factors using chi-square testing and multivariable logistic regression adjusted for age, sex, body mass index, and diabetes. The analyses were further assessed by exclusion of advanced chronic kidney disease (CKD stage 4-5) or simultaneous liver-kidney transplantation (SLK). **Results:** Among 1,345 liver transplant recipients, hepatic iron deposition was present in 49.9% of explants, including 30.7% hepatocellular (HC), 6.1% mixed pattern, and 12.0% reticular (RE) pattern. Total iron deposition prevalence varied by etiology (Figure 1) and was highest in viral hepatitis (64.2%) and ALD (63.3%), followed by MASLD (54.4%) and cryptogenic liver disease (53.9%). Lower prevalence was observed in autoimmune hepatitis (39.1%), PBC (31.3%), and PSC (9.8%). As HC iron is considered pathognomonic and is the most common pattern in explants, we further evaluated associations with MELD-Na severity. HC iron prevalence increased across MELD-Na categories. In adjusted analyses, MELD 25-29 (OR 1.53, 95% CI 1.10-2.13; $p = 0.011$) and MELD 30-34 (OR 2.09, 95% CI 1.42-3.08; $p < 0.001$) were associated with higher odds of HC iron (Table 1). Diabetes (OR 0.67, 95% CI 0.51-0.88; $p = 0.004$) and HCC (OR 0.71, 95% CI 0.53-0.97; $p = 0.029$) were associated with lower odds, whereas age, sex, and body mass index were not independently associated. Associations with MELD severity, diabetes, and HCC remained significant after exclusion of recipients with advanced CKD or SLK. **Conclusion:** Hepatic iron deposition in liver transplant explants is highly prevalent in ALD, MASLD, and viral hepatitis, with a predominantly HC pattern. Iron deposition was associated with higher MELD-Na scores, suggesting a link with more advanced liver dysfunction. In contrast, HCC and diabetes were associated with lower odds of HC iron deposition. Whether hepatic iron accumulation contributes to portal hypertension and clinical decompensation warrants further investigation.

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Figure 1. Distribution of hepatic iron pattern in chronic liver diseases.

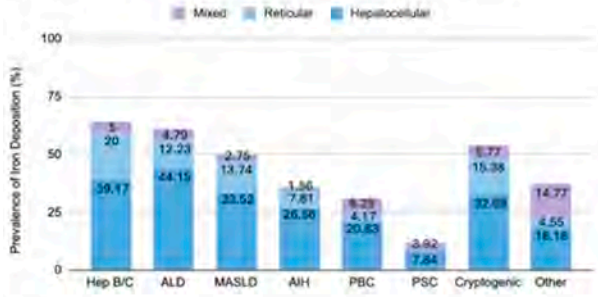


Table 1. Association of clinical factors with hepatocellular iron deposition.

Variable	Adjusted OR	95% CI	p value
Age (per year)	1.01	0.99–1.02	0.327
Male sex	1.18	0.89–1.56	0.246
Body mass index	0.99	0.97–1.02	0.602
Diabetes	0.67	0.51–0.88	0.004
HCC	0.71	0.53-0.97	0.029
MELD-Na 20–24	1.22	0.84–1.76	0.295
MELD-Na 25–29	1.53	1.10–2.13	0.011
MELD-Na 30–34	2.09	1.42–3.08	<0.001

Disclosures: Roxanna Sharifi:Nothing to Disclose, Yinan Su:Nothing to Disclose, Daanyaal Kumar:Nothing to Disclose, Paul Paik:Nothing to Disclose, Andrew John Cruz:Nothing to Disclose, Kalpana Gopalkrishnan:Nothing to Disclose, Niveda Balemurughan:Nothing to Disclose, Juan Carlos Delgado:Nothing to Disclose, Alejandro Delgado:Nothing to Disclose, Scott Jun:Nothing to Disclose, Derek Samson:Nothing to Disclose, Jeffrey Kahn:Nothing to Disclose, Norah Terrault:Elseiver: Royalties or patent beneficiary, GSK: Grant/Research Support, Elseiver: Royalties or patent beneficiary, Elseiver: Royalties or patent beneficiary, Eiger Pharmaceuticals: Grant/Research Support, GSK: Grant/Research Support, GSK: Grant/Research Support, Helio Health: Grant/Research Support, Eiger Pharmaceuticals: Grant/Research Support, Eiger Pharmaceuticals: Grant/Research Support, Durect Corp: Grant/Research Support, Helio Health: Grant/Research Support, ImmunoCore: Grant/Research Support, Helio Health: Grant/Research Support, Durect Corp: Grant/Research Support, HBV Foundation: Board member, Durect Corp: Grant/Research Support, AASLD: Executive role, ImmunoCore: Grant/Research Support, ImmunoCore: Grant/Research Support, Genentech-Roche: Grant/Research Support, HBV Foundation: Board member, HBV Foundation: Board member, Hepatitis B Foundation: Executive role, AASLD: Executive role, AASLD: Executive role, Genentech-Roche: Grant/Research Support, Genentech-Roche: Grant/Research Support, Hepatitis B Foundation: Executive role, Hepatitis B Foundation: Executive role, Elseiver: Royalties or patent beneficiary, GSK: Grant/Research Support, Elseiver: Royalties or patent beneficiary, Elseiver: Royalties or patent beneficiary, Eiger Pharmaceuticals: Grant/Research Support, GSK: Grant/Research Support, GSK: Grant/Research Support, Helio Health: Grant/Research Support, Eiger Pharmaceuticals: Grant/Research Support, Eiger Pharmaceuticals: Grant/Research Support, Durect Corp: Grant/Research Support, Helio Health: Grant/Research Support, ImmunoCore: Grant/Research Support, Helio Health: Grant/Research Support, Durect Corp: Grant/Research Support, HBV Foundation: Board member, Durect Corp: Grant/Research Support, AASLD: Executive role, ImmunoCore: Grant/Research Support, ImmunoCore: Grant/Research Support, Genentech-Roche: Grant/Research Support, HBV Foundation: Board member, HBV Foundation: Board member, Hepatitis B Foundation: Executive role, AASLD: Executive role, AASLD: Executive role, Genentech-Roche: Grant/Research Support, Genentech-Roche: Grant/Research Support, Hepatitis B Foundation: Executive role, Hepatitis B Foundation: Executive role, Liyun Yuan:Nothing to Disclose.

4483 | CENTER-LEVEL VARIATION IN MARGINAL LIVER TRANSPLANT OUTCOMES

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Background: With the advent of novel organ preservation strategies, transplant centers (TCs) are increasingly using livers from historically marginal donors, however center-level variation in outcomes with these donors is not well characterized. We aimed to quantify TC-level variation in marginal liver transplant outcomes and assess performance changes over time. **Methods:** We analyzed OPTN STAR data for adult deceased-

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donor liver transplants performed from 2010–2024, restricted to centers performing ≥10 transplants per year. Marginal organs were defined as those above the 75th percentile of the Donor Risk Index (DRI). The primary outcome was 1-year graft failure. Center performance was estimated using mixed-effects logistic regression with empirical Bayes random-effects centering, adjusting for donor and recipient characteristics via backward elimination. Centers were classified as Better, Expected, or Worse based on whether their 95% CI for risk-adjusted log-odds excluded or included zero. Inter-center variability was compared across two eras (2015–2019 vs. 2020–2024) using Levene's test. **Results:** The cohort included 104,201 liver transplants across 95 TCs (78,147 standard, 26,054 marginal). Marginal liver transplants were more concentrated among select TCs compared to standard organs. Risk-adjusted center performance varied widely, ranging from −1.7 to +0.9 in the relative log-odds of graft failure. Performance on standard and marginal organs was only moderately correlated ($R^2 = 0.309$), suggesting that outcomes with standard livers do not reliably predict success with marginal organs. Median graft failure rates for marginal transplants declined from 12.8% in 2015 to 7.6% in 2024 (rho = -0.76, p = 0.011), while standard rates fell from 9.1% to 7.5% (rho = -0.20, p = 0.580). Between-TC variability in marginal transplant outcomes decreased significantly in the more recent era (Levene's p < 0.001). Marginal transplants had significantly higher failure rates than standard organs overall (Wilcoxon p < 0.001), though this gap narrowed over time with weak significance (rho = -0.60, p = 0.067). **Conclusion:** TCs' outcomes vary substantially when utilizing marginal livers. Performance with standard organs is only moderately predictive of marginal organ success. While outcomes have improved and between-center variability has narrowed, a performance gap persists between standard and marginal organs. Standardized strategies are necessary to optimize marginal liver utilization and expand the effective donor pool.

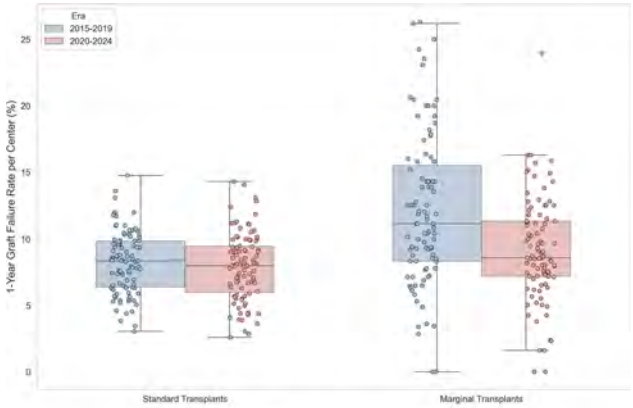


Figure 1: TC-level 1-year graft failure rates for standard (DRI ≤ 75th percentile) vs. marginal (DRI > 75th) percentile) organs, by era. Each point represents a single TC.

Disclosures: Billy Block:Nothing to Disclose, Amirhossein Moosavi:Nothing to Disclose, David Hutton:Nothing to Disclose, Mariel Lavieri:Nothing to Disclose, Neehar Parikh:Genentech: Grant/Research Support, Genentech: Grant/Research Support, Exelixis: Grant/Research Support, Exelixis: Grant/Research Support, Exelixis: Consultant, Exelixis: Consultant, AstraZeneca: Consultant, AstraZeneca: Consultant, Exact Sciences: Grant/Research Support, Exact Sciences: Grant/Research Support, Exact Sciences: Consultant, Exact Sciences: Consultant, Fujifilm Medical: Advisor, Fujifilm Medical: Advisor, Sirtex: Advisor, Genentech: Grant/Research Support, Genentech: Grant/Research Support, Exelixis: Grant/Research Support, Exelixis: Grant/Research Support, Exelixis: Consultant, Exelixis: Consultant, AstraZeneca: Consultant, AstraZeneca: Consultant, Exact Sciences: Grant/Research Support, Exact Sciences: Grant/Research Support, Exact Sciences: Consultant, Exact Sciences: Consultant, Fujifilm Medical: Advisor, Fujifilm Medical: Advisor, Sirtex: Advisor.

4484 | SINGLE-CELL AND BULK RNA SEQUENCING REVEAL MCL1 AS A KEY REGULATOR OF MITOCHONDRIAL FUNCTION IN LIVER ISCHEMIA-REPERFUSION INJURY

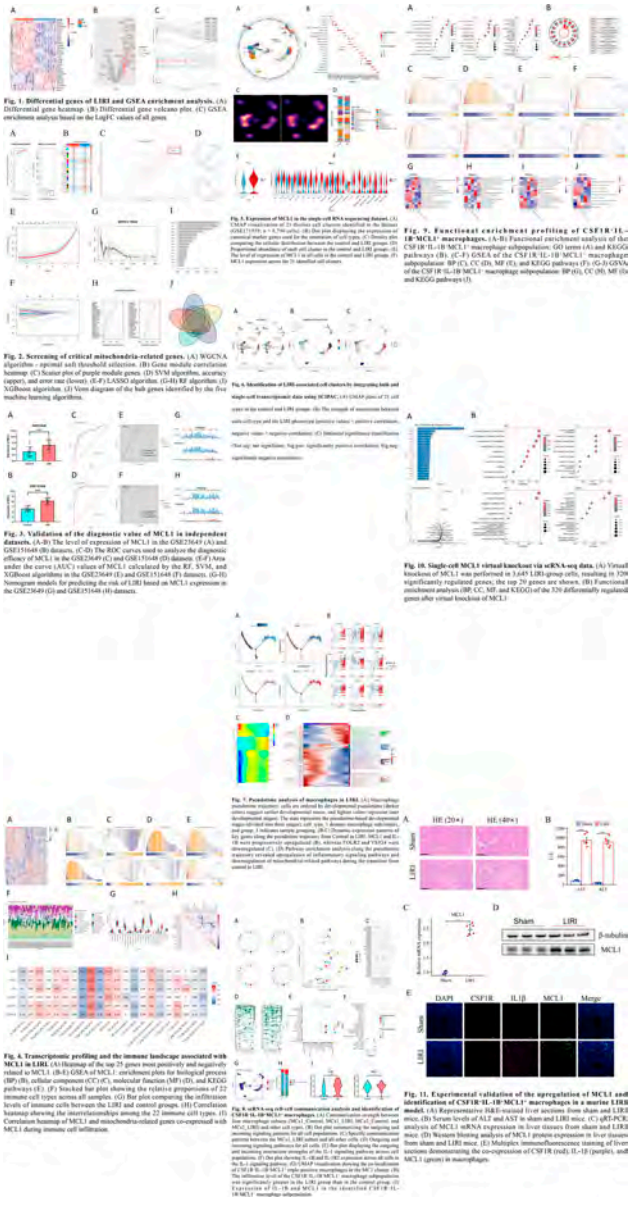
Xianxiang Chen[1], [1]The First Affiliated Hospital of Guangxi Medical University

Background: Liver ischemia-reperfusion injury (LIRI) may occur after liver transplantation or surgery, and few treatments are available to overcome this problem. The pathogenesis of LIRI is closely related to maladaptive immune responses and mitochondrial dysfunction; however, key regulators that link the above processes are still not known. **Methods:** Several microarray datasets (GSE12720, GSE112713, GSE23649, and GSE151648) were used in combination with single-cell RNA sequencing data (GSE171539). Additionally, hub genes were identified through differential analysis (WGCNA) and using four machine learning algorithms (SVM, LASSO, RF, and XGBoost). The results were validated with additional datasets using the murine LIRI model by in silico perturbation. **Results:** Our findings revealed that MCL1 is a hub gene related to mitochondria, whose expression is considerably increased in LIRI, and it has satisfactory diagnostic accuracy. Additionally, single-cell analysis revealed that MCL1 was specifically enriched in endothelial cells and macrophages. Moreover, the new macrophage subset CSF1R+IL-1B+MCL1+, which has a dual pro-inflammatory and pro-survival phenotype, was detected in

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LIRI patients. This process results in increased intercellular crosstalk and is related to important pathways such as the NF-κB, apoptosis, and cytokine signaling pathways. Moreover, knocking out MCL1 in silico dramatically altered immune-related gene networks. MCL1 was experimentally confirmed to be upregulated, and the macrophage subset was validated to exist in the LIRI mouse model. **Conclusion:** Through bulk and single-cell RNA sequencing analysis, we identified that MCL1 is the key factor for LIRI, which links immune inflammation and mitochondrial function through a new subset of macrophages. MCL1 is a candidate diagnostic biomarker and therapeutic target for treating LIRI.



Disclosures: Xianxiang Chen:Nothing to Disclose.

4485 | CLINICAL OUTCOMES OF GLP-1 RECEPTOR AGONIST USE IN LIVER TRANSPLANT RECIPIENTS WITH DIABETES: A MULTICENTER STUDY

Azhar Hussain[1] Avleen Kaur[2] Prerna Kherajani[2] Kalsoom Khalil[3] Ahmad Nawaz[2] Bishnu Sapkota[2] Savio John[4], [1]SUNY Upstate Medical University, NY, [2]SUNY Upstate Medical University, NY, USA, [3]Ameer-ud-Din Medical College, Lahore, Pakistan, [4]SUNY Upstate Medical University

Background: While GLP-1 receptor agonists (GLP-1 RAs) have demonstrated substantial efficacy in the general population for glycemic control and weight loss, data regarding their safety and clinical impact specifically within the liver transplant population remain limited. This study aims to compare clinical outcomes between LT recipients with T2DM who are treated with GLP-1 RAs versus standard anti-diabetic regimen. **Methods:** This was a retrospective propensity-matched cohort study using deidentified data from the U.S. population-based TriNetX Research Network. Adult patients (18-89 years) with a confirmed history of liver transplantation who had existing T2DM or developed PTDM (defined as HbA1c >6.5% or fasting glucose >126 mg/dL diagnosed >3 months post-transplant when stable on immunosuppression) were identified. Exclusion criteria included T1DM and multi-organ transplant status. After matching for demographics, comorbidities, and laboratory parameters, two cohorts were established: 983 patients initiated on GLP-1 RAs (semaglutide, liraglutide, dulaglutide, or tirzepatide), and a 983-matched non-GLP-1 RAs cohort with standard anti-diabetic regimen cohort or (all-antidiabetic agents except GLP-1 RAs). The primary outcome of the study was the all-cause mortality at 1, 3, and 5 years after the index event. Secondary outcomes included systemic complications (sepsis, septic shock), improvements in HbA1c, weight loss (mean difference in BMI), acute liver graft failure within 6 months after LT, Major Adverse Cardiovascular Events (MACE), and Major Adverse Kidney Events (MAKE). MACE is defined as a composite outcome of myocardial infarction, stroke, or death after index event. MAKE is defined as a composite outcome of initiation of new dialysis or kidney replacement therapy, decline of cGFR >50% from baseline or death after index event. **Results:** Over a mean follow-up of 25.5 ± 18.3 months, the LT recipients in the GLP-1 RA cohort had a significantly lower incidence of all-cause mortality at 1, 3, and 5 years after the index event (OR 0.266; 95% CI, 0.191-0.369 for the 5th year) compared to the non-GLP-1 RAs cohort (Figure 1). LT recipients who received GLP-1 RA had lower HbA1c and BMI at 1-year with a mean difference of 1.5 ± 0.9%, and 1.7 ± 0.9 kg/m2, (p < 0.05

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for both). LT recipients in the GLP-1 RA cohort had a lower risk of sepsis, septic shock, MACE, MAKE, mechanical ventilation, need for ICU admission, acute liver graft failure/rejection, and lower ER visits/all-cause hospitalizations, compared to those in the non-GLP-1 RA cohort ($P < 0.001$ for all) at 3-years (Table 1). **Conclusion:** GLP-1 RAs use in LT recipients with preexisting T2DM or PTDM was associated with a lower risk of all-cause mortality, improved metabolic and overall clinical outcomes, and lower healthcare utilization.

Table 1: Primary and secondary outcomes among GLP-1 RA cohort vs. non-GLP-1 RAs cohort

Outcome	GLP-1 RAs cohort (n=983)	SGLT2i cohort (n=983)	Odds Ratio (95% CI)	p-value
Primary Outcome				
All-Cause Mortality at 1-Year	31 (3.1%)	69 (7.0%)	0.426 (0.283–0.678)	0.004
All-Cause Mortality at 3-Year	46 (4.8%)	132 (13.4%)	0.331 (0.235–0.466)	<0.001
All-Cause Mortality at 5-Year	51 (5.1%)	167 (16.9%)	0.266 (0.191–0.369)	<0.001
Secondary Outcomes at 3 Years				
MACE	100 (10.1%)	195 (19.8%)	0.458 (0.353–0.593)	<0.001
MAKE	98 (10.2%)	128 (12.9%)	0.911 (0.699–0.917)	0.042
Sepsis	58 (5.9%)	150 (15.2%)	0.348 (0.254–0.478)	<0.001
Septic Shock	15 (1.5%)	75 (7.6%)	0.188 (0.107–0.329)	<0.001
Mechanical Ventilation	23 (2.3%)	69 (7.0%)	0.317 (0.196–0.513)	<0.001
ICU Admission	49 (4.8%)	119 (12.0%)	0.376 (0.2669–0.533)	<0.001
ED Visit/All-Cause Hospitalization	199 (20.2%)	257 (26.1%)	0.717 (0.581–0.885)	0.001
Acute liver graft failure/rejection at 6 months	60 (6.1%)	172 (17.4%)	0.307 (0.225–0.417)	<0.001

Abbreviations: MACE: Major Adverse Cardiovascular Events, MAKE: Major Adverse Kidney Events, ICU: Intensive Care Unit, ED: Emergency Department

Disclosures: Azhar Hussain:Nothing to Disclose, Avleen Kaur:Nothing to Disclose, Prerna Kherajani: Nothing to Disclose, Kalsoom Khalil:Nothing to Disclose, Ahmad Nawaz:Nothing to Disclose, Bishnu Sapkota:Nothing to Disclose, Savio John:Nothing to Disclose.

4486 | EXTERNAL VALIDATION OF PRE-LIVER TRANSPLANT RISK SCORES FOR WAITLIST OUTCOMES IN LIVER TRANSPLANT CANDIDATES WITH HEPATOCELLULAR CARCINOMA

Leandro Sierra[1] Butros Fakhoury[2] Na Bo[3] Juan Pablo Arab[2] Neil Mehta[4] Amit Singal[5], [1]Cleveland Clinic Foundation, [2]Virginia Commonwealth University School of Medicine, Richmond, VA, USA, [3]Virginia Commonwealth University, Richmond, VA, USA., [4]University of California San Francisco, San Francisco, CA, United States, [5]The University of Texas Southwestern Medical Center, Dallas, TX, USA

Background: Multiple risk scores have been proposed to predict adverse waitlist (WL) outcomes in liver transplant (LT) candidates with hepatocellular carcinoma (HCC), yet head-to-head comparisons in a national cohort are lacking. We aimed to assess the discrimination and risk stratification of five HCC risk scores for 1-year WL dropout and mortality. **Methods:** Using the United Network for Organ Sharing/Scientific Registry of Transplant Recipients (UNOS/SRTR) database, we performed an external validation of five prognostic scores: HALT-HCC, Multi-HCC, the Duvoux AFP Model, the Mehta Dropout Score, and Metroticket 2.0. We included adult candidates listed with HCC between 2000 and 2025 and excluded those who had prior liver transplant, incident HCC after listing, listing for multiorgan transplant, and fibrolamellar HCC. All scores were calculated from variables at listing. Primary outcomes of interest were waitlist dropout and waitlist mortality at 1 year. Discrimination was quantified by area under the receiver operating characteristic (AUC) curve with pairwise DeLong comparisons. Risk stratification was evaluated across score quartiles using Fine-Gray competing risk models treating LT as a competing event, censored at 1 year. **Results:** Among 19,285 LT candidates with HCC (median WL time 161 days), 13,820 (71.6%) underwent LT at a median of 121 days from listing. 1-year WD occurred in 2,345 (12.2%) and 1-year WM in 832 (4.3%) patients. For 1-year dropout, Multi-HCC (AUC 0.75, 95% CI 0.74–0.77) and Mehta (AUC 0.75, 95% CI 0.73–0.76) significantly outperformed HALT-HCC (AUC 0.64, 95 %CI 0.63–0.66), Metroticket 2.0 (AUC 0.60, 95% CI 0.58–0.62), and Duvoux AFP (AUC 0.58, 95% CI 0.56–0.59) (global $p < 0.001$), with no significant difference between Multi-HCC and Mehta ($p = 0.11$). For 1-year mortality, Multi-HCC achieved the highest discrimination (AUC 0.81, 95% CI 0.79–0.83), exceeding Mehta (AUC 0.79, 95% CI 0.77–0.81; head-to-head $p < 0.001$) and the remaining scores (HALT-HCC, Metroticket 2.0, Duvoux AFP; all AUC ≤ 0.62, global $p < 0.001$). Multi-HCC and Mehta had steep risk gradients across quartiles. From Q1 to Q4, 1-year WD rose from 11% to 50% (Multi-HCC HR 4.71, 95% CI 4.13–5.37; Mehta HR 4.84, 95% CI 4.15–5.65), and 1-year WM rose from 2% to 25% (Multi-HCC HR 10.8, 95% CI 8.1–14.2 ; Mehta HR 9.75, 95% CI 7.06–13.5) (all p-trend < 0.001). **Conclusion:** Multi-HCC and the Mehta Dropout Score reliably identified HCC candidates at high risk for 1-year waitlist dropout and mortality, outperforming other prognostic models. These scores may help prioritize candidates for access to LT, closer monitoring, and more aggressive bridging therapy.

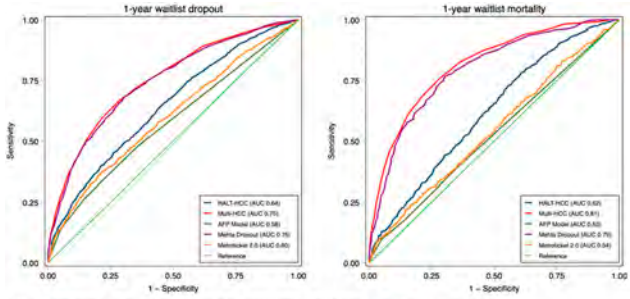


Figure 1. Discrimination of five pre-transplant risk scores for 1-year waitlist outcomes in liver transplant candidates with hepatocellular carcinoma.

Receiver operating characteristic (ROC) curves for 1-year waitlist dropout (left panel) and 1-year waitlist mortality (right panel). Areas under the curve (AUC) with 95% confidence intervals are shown for each score. Multi-HCC and the Mehta Dropout Score demonstrated the strongest discrimination for both outcomes. Multi-HCC was the single best discriminator for 1-year waitlist mortality (head-to-head DeLong $p < 0.001$ vs Mehta).

Disclosures: Leandro Sierra:Nothing to Disclose, Butros Fakhoury:Nothing to Disclose, Na Bo:Nothing to Disclose, Juan Pablo Arab:Nothing to Disclose, Neil

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4487 | GLP-1 RECEPTOR AGONISTS VERSUS BARIATRIC SURGERY AND UNTREATED CONTROLS IN PATIENTS WITH OBESITY AND CIRRHOSIS: A PROPENSITY-MATCHED MULTICENTER COHORT STUDY

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Background: Obesity affects over 40% of patients with cirrhosis, accelerates hepatic decompensation, and represents a barrier to transplant listing for eligible candidates, yet optimal weight management strategies in this population remain undefined. Bariatric surgery carries elevated perioperative risk in cirrhosis, while GLP-1 receptor agonists (GLP-1 RAs) demonstrate hepatoprotective properties beyond weight loss. Real-world comparative evidence in established cirrhosis is lacking. **Methods:** Propensity score-matched (PSM) cohort study using the TriNetX multicenter network of adults with obesity and all-cause cirrhosis: (1) GLP-1 receptor agonist (GLP-1 RA) therapy vs bariatric surgery (n = 1,080/group); (2) GLP-1 RA vs untreated controls (n = 14,816/group). Post-PSM cohorts were balanced for age, sex, diabetes, and body mass index (BMI); albumin and bilirubin remained imbalanced. Outcomes assessed by Kaplan-Meier survival analysis at 1 and 5 years included all-cause mortality, ascites, paracentesis, hepatic encephalopathy (HE), hepatorenal syndrome (HRS), spontaneous bacterial peritonitis (SBP), malnutrition, hospitalization, liver transplant, and hepatocellular carcinoma (HCC). **Results:** Comparison 1 (bariatric surgery vs GLP-1 RA): Bariatric surgery was associated with higher hazards of mortality (HR 4.41 at 1yr; 2.76 at 5yr), ascites (HR 2.42; 1.48), paracentesis (HR 4.75; 2.18), HRS (HR 1.82 at 5yr), SBP (HR 2.29 at 5yr), and malnutrition (HR 5.11 at 5yr); all $p < 0.05$ vs GLP-1 RA. Liver transplant did not differ (HR 1.87 at 5yr, $p = 0.062$). Bariatric surgery achieved greater BMI reduction (32.6 vs 35.3 kg/m2 at 5yr). Estimated MELD-Na was higher in the bariatric cohort at baseline (17 vs 8), 1 year (23 vs 11), and 5 years (25 vs 12), indicating residual severity imbalance limiting causal inference. Comparison 2 (untreated controls vs GLP-1 RA): Controls had higher hazards of mortality (HR 2.73 at 1yr; 2.07 at 5yr), ascites, paracentesis, SBP, HRS, HE, and hospitalization at both time points (all $p < 0.001$ vs GLP-1 RA), and higher liver transplant rates at 1 year (HR 1.71) and 5 years (HR 1.29, $p = 0.003$). HCC did not differ in either comparison. **Conclusion:** GLP-1 RA therapy was associated with lower risks of hepatic decompensation and mortality vs both bariatric surgery and untreated controls, and with reduced liver transplant utilization vs untreated controls, suggesting a hepatoprotective effect beyond weight loss alone. HCC rates were unaffected. Residual confounding by disease severity and the observational design limit causal inference; MELD imbalance in the surgical comparison warrants particular caution. Prospective randomized trials are needed to confirm these findings and define optimal obesity management strategies in patients with established cirrhosis.

Disclosures: Aldanah Althwanay:Nothing to Disclose, Muhammad Haris Latif:Nothing to Disclose, Imran Khokhar:Nothing to Disclose, Maya Mahmoud:Nothing to Disclose.

4488 | HEPATOCYTE CIRCFADS2 MODULATES TCMR IN PEDIATRIC LIVER TRANSPLANTATION

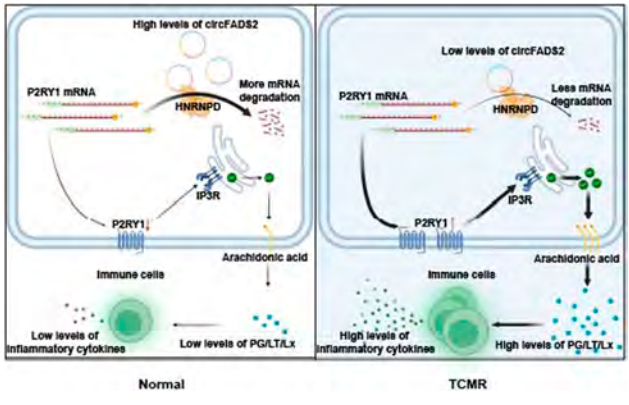
Qi Pan[1] Aiwei Zhou[1] Yuan Liu[1] Yongbo Liu[1] Qiang Xia[1], [1]Renji Hospital

Background: T cell-mediated rejection (TCMR) remains a major immune complication after pediatric liver transplantation, compromising graft function and long-term survival. Sensitive and tissue-specific early warning markers are still lacking, and graft-intrinsic susceptibility remains insufficiently understood. **Methods:** Graft biopsy specimens from pediatric liver transplant recipients were analyzed by circRNA microarray. Candidate circRNAs were validated by RT-qPCR in an independent cohort, and cellular origin was determined by fluorescence-activated cell sorting. Mechanistic studies were performed in THLE2 hepatocytes using overexpression, post-transcriptional interaction assays, and signaling analyses. A hepatocyte-conditioned medium system was used to assess effects on primary human CD4+ T cells. In vivo

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relevance was examined by pharmacological targeting of P2RY1 in an allogeneic mouse liver transplantation model. **Results:** CircRNA profiling showed a distinct expression pattern between TCMR and non-rejection grafts. CircFADS2, a hepatocyte-enriched circRNA derived from exons 2-5 of FADS2, was significantly downregulated in pediatric TCMR. In an independent diagnostic cohort, circFADS2 discriminated TCMR from non-rejection with an AUC of 0.86. Mechanistically, circFADS2 promoted HNRNPD-dependent degradation of P2RY1 mRNA, reduced P2RY1 expression, and suppressed the P2RY1-related Ca2+/cPLA2 pathway, leading to decreased release of arachidonic acid and lipid mediators. Conditioned medium from circFADS2-overexpressing hepatocytes inhibited the proliferation, activation, and effector cytokine production of primary human CD4+ T cells, and these effects were reversed by arachidonic acid add-back. In the allogeneic mouse liver transplantation model, P2RY1 activation aggravated graft injury and immune responses, whereas P2RY1 antagonism alleviated graft damage and inflammation-related indices. **Conclusion:** Hepatocyte-enriched circFADS2 is closely associated with pediatric TCMR and may serve as a tissue biomarker of rejection. Mechanistically, circFADS2 restrains graft injury by promoting HNRNPD-mediated degradation of P2RY1 mRNA, suppressing P2RY1-Ca2+/cPLA2 signaling, limiting arachidonic acid release, and weakening the graft microenvironment's support for CD4+ T cell effector responses. The circFADS2-HNRNPD-P2RY1-arachidonic acid axis suggests a potential target for early diagnosis and precision intervention in pediatric liver transplant rejection.



Disclosures: Qi Pan:Nothing to Disclose, Aiwei Zhou: Nothing to Disclose, Yuan Liu:Nothing to Disclose, Yongbo Liu:Nothing to Disclose, Qiang Xia:Nothing to Disclose.

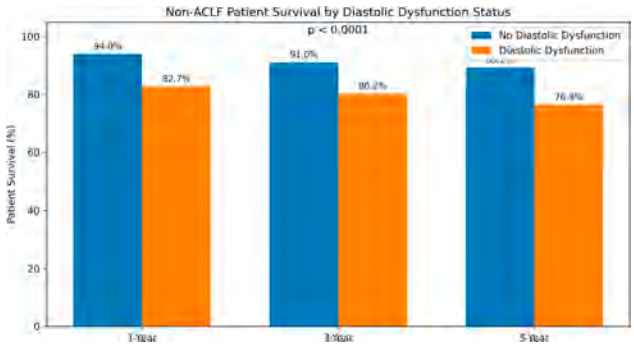
4489 | DIASTOLIC DYSFUNCTION INCREASES POST-TRANSPLANT MORTALITY IN NON-ACLF PATIENTS

Nishita Sunkara[1] Kathryn Thompson[1] Jake MacDonald[1] Naveena Murugan[1] Vignesh Jayaraman Muralidharan[1] Hima Veeramachaneni[1] Andrew Yu[1] Ram Subramanian[2] Nader Dbouk[3], [1]Emory University School of Medicine, [2]Emory University, [3]Emory Universirty School of Medicine

Background: Diastolic dysfunction is a hallmark of cirrhotic cardiomyopathy, a condition affecting up to 50% of patients with cirrhosis, particularly those with decompensated liver disease. Cardiovascular disease is a major contributor to both short- and long-term mortality after liver transplantation (LT), although the impact of diastolic dysfunction on post-LT outcomes remains controversial. We evaluated the association between diastolic dysfunction and post-LT outcomes in patients without acute-on-chronic liver failure (ACLF). **Methods:** We conducted a retrospective study of 816 liver transplant recipients between 2014 and 2025, including 572 patients without ACLF. Primary outcomes included 1-, 3-, and 5-year patient and graft survival. We evaluated the impact of diastolic dysfunction on these outcomes. ChatGPT (OpenAI) was used solely to assist with language refinement and improve readability of the abstract. **Results:** Diastolic dysfunction was a significant predictor of both patient and graft survival in the overall cohort ($p = 0.002$ and $p = 0.004$, respectively) and emerged as the strongest predictor of outcomes among non-ACLF patients (both $p < 0.0001$). In non-ACLF patients, those with diastolic dysfunction had significantly worse 1-, 3-, and 5-year patient survival compared to those without diastolic dysfunction (82.7% vs 94.0%, 80.2% vs 91.0%, and 76.4% vs 89.2%, respectively; $p < 0.0001$). Graft survival demonstrated a similar pattern, with significantly lower 1-, 3-, and 5-year graft survival in patients with diastolic dysfunction compared to those without (82.7% vs 94.5%, 80.2% vs 91.7%, and 77.1% vs 89.9%, respectively; $p < 0.0001$). A history of coronary artery disease (CAD) was associated with consistently 3–4% lower patient and graft survival across all time points; however, CAD was not a significant predictor of outcomes in the overall cohort (all $p = 0.159$). **Conclusion:** In this retrospective study, diastolic dysfunction emerged as the strongest predictor of both short- and long-term mortality among non-ACLF patients. These findings highlight the importance of careful screening for diastolic dysfunction in liver transplant candidates, including evaluation of more granular echocardiographic markers such as left ventricular longitudinal strain to better assess preoperative cardiac function.

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4490 | BURDEN OF PRE-TRANSPLANT CARDIOMETABOLIC RISK FACTORS PREDICT MAJOR ADVERSE CARDIOVASCULAR EVENTS AFTER LIVER TRANSPLANT

Andrew John Cruz[1] Paul Paik[2] Juan Carlos Delgado[3] Kalpana Gopalkrishnan[4] Niveda Balemurughan[2] Yinan Su[2] Roxanna Sharifi[2] Daanyaal Kumar[5] Scott Jun[5] Alejandro Delgado[5] Derek Samson[6] Navpreet Kaur[2] Jeffrey Kahn[2] Norah Terrault[2] Liyun Yuan[2], [1]USC/ LA General Medical Center Internal Medicine Training Program, [2]University of Southern California, [3]The Kaiser Permanente Los Angeles Medical Center, [4]University of Southern Calironia, [5]USC/Los Angeles General Medical Center Internal Medicine Residency Program, [6]Transplant Institute, Keck medical center of USC

Background: Cardiometabolic risk factors (CMRFs) including diabetes, hypertension, dyslipidemia, and elevated BMI are increasingly prevalent among liver transplant (LT) candidates across all indications. Despite pre-transplant cardiovascular screening, major adverse cardiovascular events (MACE) remain a leading cause of post-LT morbidity. Whether cumulative pre-LT CMRF burden predicts MACE across all LT indications has not been evaluated. **Methods:** Adult LT recipients (2013-2023) at a single large LT center were studied at 1-year (n = 1,000), 3-year (n = 724), and 5-year (n = 481) follow-up. The number of pre-LT CMRFs (0-4) was determined using AACE metabolic syndrome criteria: diabetes, hypertension, dyslipidemia, and BMI ≥ 25 kg/m. The primary outcome was MACE (MI, CVA, unstable angina hospitalization). Cox proportional hazards regression adjusted for age, sex, MELD-Na, HCC, indication, and pre-LT CAD was used to estimate the independent effect of CMRF burden. Multivariable logistic regression with the same covariates was performed at each timepoint. Cochran-Armitage trend tests assessed the association between CMRF burden and MACE at each timepoint. Univariate logistic regression evaluated each individual CMRF as a predictor of MACE. **Results:** Among 1,172 LT recipients (59% male, 50% Latinx, median age 57 [IQR 48-63], median MELD-Na 20 [IQR 14-27], 177 [15%] LDLT), etiologies included ALD (33%), viral (23%), MASLD (22%), autoimmune/cholestatic (12%), and other (10%). Overall MACE incidence at 1, 3, and 5 years was 0.5%, 1.2%, and 4.6% (22 events at 5 years), with increasing CMRF burden associated with higher MACE at 5 years: 0.9%, 2.9%, 6.5%, 13.7%, and 10.0% for 0-4 CMRFs (trend p = 0.0002) (Figure 1, Table 1). On univariate analysis, HTN (OR 3.35, p = 0.006), DM (OR 3.24, p = 0.008), BMI ≥ 25 (OR 2.55, p = 0.10), and dyslipidemia (OR 2.18, p = 0.23) were assessed; DM and HTN were significant predictors. On Cox regression, each additional CMRF was associated with a 75% increase in the hazard of MACE (HR 1.75, 95% CI 1.16-2.66, p = 0.008). On logistic regression at 5 years, each additional CMRF had an OR of 1.84 (95% CI 1.18-2.85, p = 0.007). By etiology, 68% of 5-year MACE events occurred in non-MASLD recipients (ALD 27%, viral 18%, autoimmune/cholestatic 18%, other 5%), with MASLD accounting for 32%. **Conclusion:** Pre-LT CMRF burden shows a dose-dependent association with MACE after LT across all indications. DM and HTN are the strongest individual predictors. The majority of MACE events occurred in non-MASLD recipients. These findings support cardiometabolic risk stratification and optimization at the pre-transplant phase for all LT indications.

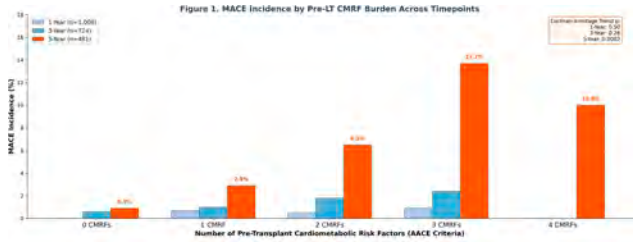


Table 1. 5-Year MACE by Pre-LT CMRF Burden (0-4), n=481

Events	0 CMRFs (n=106)	1 CMRF (n=207)	2 CMRFs (n=107)	3 CMRFs (n=51)	4 CMRFs (n=10)	p-value
MACE (any)	1/111 (0.9%)	6/207 (2.9%)	7/107 (6.5%)	7/51 (13.7%)	1/10 (10.0%)	0.0002
MI	0/106 (0%)	2/207 (1.0%)	4/107 (3.7%)	2/51 (3.9%)	1/10 (10.0%)	0.0001
CVA/stroke	0/106 (0%)	2/207 (1.0%)	2/107 (1.9%)	2/51 (3.9%)	0/10 (0%)	0.17
Unstable angina hospitalization	1/106 (0.9%)	2/207 (1.0%)	1/107 (0.9%)	3/51 (5.9%)	0/10 (0%)	0.08

Disclosures: Andrew John Cruz:Nothing to Disclose, Paul Paik:Nothing to Disclose, Juan Carlos Delgado:

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4491 | DYNAMIC LIVER FRAILTY INDEX PREDICTS ADVERSE WAITLIST OUTCOMES IN LIVER TRANSPLANT CANDIDATES: A MULTI-STATE SURVIVAL ANALYSIS

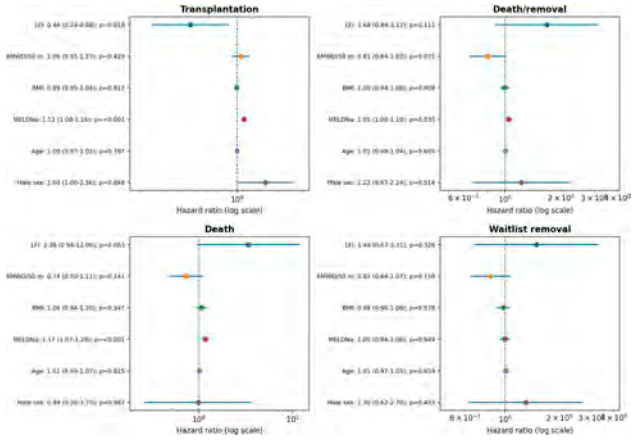
Rakan Alqahtani[1] Ibrahim Alomar[1] Erica Lo[2] Tracy Fuller[2] Kristin Morris[2] Tania Larsen[2] Anouar Teriaky[1] David Hudson[1] Karim Qumosani[1] Tamoor Afzaal[1], [1]Western University, [2]London Health Sciences Centre

Background: Frailty is a key determinant of outcomes in liver transplant candidates (LTCs). However, the prognostic significance of longitudinal changes in Liver Frailty Index (LFI) and six-minute walk distance (6MWD) while awaiting transplant remains uncertain. We evaluated whether dynamic frailty and physical function trajectories predict waitlist outcomes including transplantation, death on the waitlist, and waitlist removal. **Methods:** We conducted a retrospective cohort study of adult LTCs waitlisted in London, ON, Canada between January 2020 and December 2022, who underwent serial physiotherapy assessments. Patients were followed from waitlisting until transplantation, death on the waitlist, waitlist removal, or censoring (June 30, 2024). Baseline characteristics were compared using χ^2 or Fisher's exact tests for categorical variables, and ANOVA or Kruskal-Wallis tests for continuous variables. Missing data were addressed using multiple imputation by chained equations. Multi-state survival analyses were performed using Aalen-Johansen estimators. Cause-specific Cox proportional hazards models evaluated associations of time-varying LFI, 6MWD, BMI, age, sex, and MELDNa with transplantation and waitlist death, and removal. Secondary exploratory analyses evaluated LFI and

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6MWD cutoffs, concordant-discordant frailty / physical function phenotypes, and longitudinal changes (ΔLFI, Δ6MWD). **Results:** Among 164 LTCs, 103 (62.8%) underwent transplantation, 14 (8.5%) died on the waitlist, 43 (26.2%) were removed, and 4 (2.4%) were censored. Median baseline MELDNa and LFI differed significantly across outcome categories (MELDNa: 23.0 in deaths vs 17.6 in transplanted patients; p = 0.018; LFI: 3.9 in deaths/removals vs 3.5 in transplanted patients; p = 0.009). Baseline 6MWD was lowest among patients who died on the waitlist (336 m, p = 0.060). One-year cumulative incidences of death, waitlist removal, and transplantation were 7.9%, 21.3%, and 54.3%, respectively. In multivariable multi-state Cox models, higher time-varying LFI independently reduced transplantation likelihood (HR 0.46, 95%CI 0.24–0.88; p = 0.018), while higher MELDNa increased transplantation likelihood (HR 1.12, 95%CI 1.08–1.16; p < 0.001). Higher LFI showed a trend towards increased risk of waitlist death/removal (HR 1.68, 95%CI 0.89–3.17; p = 0.111). Each 50m increase in 6MWD trended toward lower risk of waitlist death/removal (HR 0.81, 95%CI 0.64–1.02; p = 0.071) (Figure). Worsening ΔLFI and declining Δ6MWD trajectories were associated with higher waitlist death/removal and lower transplantation probabilities. **Conclusion:** Dynamic frailty assessment via LFI provides useful prognostic information beyond static measures, predicting liver transplantation likelihood. Serial monitoring of frailty and physical function trajectories may mprove waitlist risk stratification and identify targets for prehabilitation.



Disclosures: RAKAN ALQAHTANI:Nothing to Disclose, Ibrahim Alomar:Nothing to Disclose, Erica Lo: Nothing to Disclose, Tracy Fuller:Nothing to Disclose, Kristin Morris:Nothing to Disclose, Tania Larsen:Nothing to Disclose, Anouar Teriaky:Nothing to Disclose, David Hudson:Nothing to Disclose, Karim Qumosani: Nothing to Disclose, Tamoor Afzaal:Nothing to Disclose.

4492 | WEIGHT TRAJECTORIES AFTER LIVER TRANSPLANTATION PREDICT MORTALITY AND CARDIOVASCULAR RISK

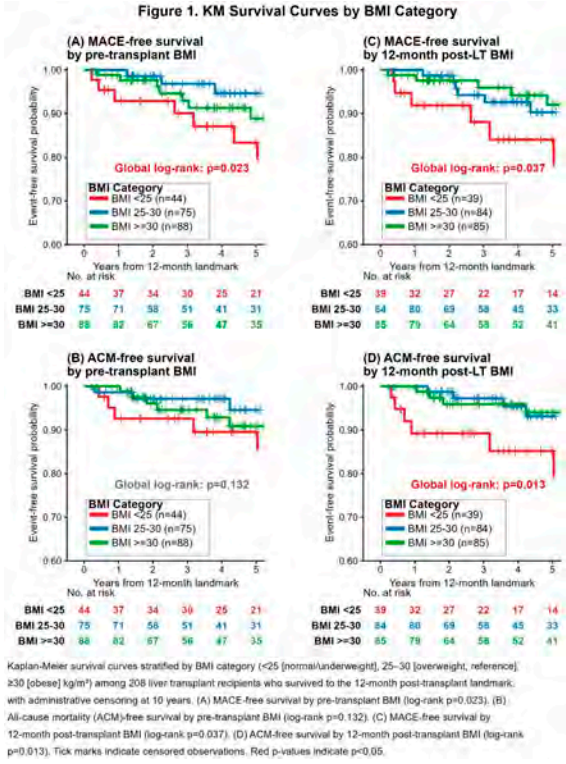
Isra Taha[1] Khang Nguyen[2] Barbara Okeke[3] Kelly Fan[3] Rusdha Mansuri[2] Spencer Hobbs[2] Ava Delonais-Parker[2] Sneha Manikandan[2] Sahita Gandra[2] Mina Benjamin[3] Uchenna Agbim[4], [1]SSM Saint Louis University Hospital, [2]Saint Louis University School of Medicine, [3]SSM Health Saint Louis University Hospital, [4]SSM Health Saint Louis University Hosptial

Background: Weight change after liver transplantation (LT) is common and may reflect physiologic recovery, yet its relationship with outcomes remains unclear. We evaluated associations between pre-LT and 12-month post-LT BMI with major adverse cardiovascular events (MACE) and all-cause mortality (ACM) in LT recipients. **Methods:** We conducted a single-center retrospective cohort study of adult LT recipients from January 2014 to January 2024. BMI was categorized as < 25 kg/m² (normal/underweight), 25–30 kg/m² (overweight), or ≥ 30 kg/m² (obese). Mixed-effects models assessed BMI trajectories pre-LT through 12 months post-LT across BMI categories. A 12-month landmark analysis was applied to Cox proportional hazard and Kaplan-Meier (KM) models: patients who died or were lost to follow-up within 12 months were excluded and survival was measured from the 12-month post-LT landmark. Cox and KM analyses evaluated associations between pre- and post-LT BMI and MACE or ACM, and Cox model was adjusted for age, sex, diabetes, hypertension, and MELD. Outcomes were capped to 10 years post-LT. **Results:** In 208 patients, 26 MACE and 22 ACM events were recorded over 10 years. Mixed effects model showed normal/underweight patients gained BMI more rapidly during the first 12 months post-LT compared to overweight patients (2.79 vs. +1.25 kg/m²/yr; interaction β = 0.128/month, p = 0.028) but remained normal/underweight at 12 months. Obese patients remained weight stable (0.02 kg/m²/year; interaction β = −0.102/month, p = 0.035). KM analysis showed significant between-group differences in MACE-free survival by pre-LT BMI (p = 0.023) and in ACM-free survival (p = 0.013) by 12-month post-LT BMI; pairwise comparisons of KM analysis showed statistically significant worse MACE-free survival in pre-LT BMI < 25 kg/m² vs. BMI 25-30 (p = 0.006) and ACM-free survival by 12-month post-LT BMI < 25 kg/m² vs. BMI 25-30 (p = 0.014). Adjusted Cox models found pre-LT BMI < 25 kg/m² was associated with higher MACE risk compared to BMI 25-30 (HR 6.34, 95% CI 1.63–24.63; p = 0.008) and 12-month post-LT BMI < 25 kg/m² was associated with higher ACM risk (HR 9.20, 95% CI 1.86–45.51; p = 0.006) compared to BMI 25-30 kg/m². **Conclusion:** Normal/underweight BMI (< 25 kg/m²) both pre- and post-LT predicted adverse outcomes,

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with pre-LT BMI < 25 kg/m² predicting post-LT MACE and 12-month post-LT BMI < 25 kg/m² predicting ACM. These findings suggest that peri-LT BMI is associated with post-LT outcomes, highlighting the importance of nutritional status in transplant recipients.



Kaplan-Meier survival curves stratified by BMI category (<25 [normal/underweight], 25–30 [overweight, reference], ≥30 [obese] kg/m²) among 208 liver transplant recipients who survived to the 12-month post-transplant landmark, with administrative censoring at 10 years. (A) MACE-free survival by pre-transplant BMI (log-rank p=0.023). (B) All-cause mortality (ACM)-free survival by pre-transplant BMI (log-rank p=0.132). (C) MACE-free survival by 12-month post-transplant BMI (log-rank p=0.037). (D) ACM-free survival by 12-month post-transplant BMI (log-rank p=0.013). Tick marks indicate censored observations. Red p-values indicate p<0.05.

Disclosures: Isra Taha:Nothing to Disclose, Khang Nguyen:Nothing to Disclose, Barbara Okeke:Nothing to Disclose, Kelly Fan:Nothing to Disclose, Rusdha Mansuri:Nothing to Disclose, Spencer Hobbs:Nothing to Disclose, Ava Delonais-Parker:Nothing to Disclose, Sneha Manikandan:Nothing to Disclose, Sahita Gandra:Nothing to Disclose, Mina Benjamin:Nothing to Disclose, Uchenna Agbim:Nothing to Disclose.

4493 | ANGIOTENSIN II TYPE I RECEPTOR ANTIBODIES ARE ASSOCIATED WITH RETRANSPLANTATION IN LIVER ALLOGRAFTS

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Background: The clinical significance of antibodies to non-HLA targets such as Angiotensin II Type 1 Receptor (AT1R-Abs) is not well known in liver transplantation (LT) despite their association with rejection and graft loss in renal transplantation. **Aim:** To study the prevalence of AT1R-Abs and their association with LT complications including antibody mediated rejection (ABMR), hepatic artery complications and re-LT. **Methods:** This prospective study included primary LT recipients, from the South Australian Liver Transplant Unit between 2015-2023, with at least 12 months follow-up. AT1R-Abs from pre- and post-LT serum samples were tested and the clinical course was reviewed. **Results:** 105 patients (58% male) with a median age 62 years (IQR 13) were studied for a median period of 4 years. The prevalence of AT1R-Abs pre-LT was as follows: negative (< 10 U/mL) -18%, at risk (10-17 U/mL) - 44%, positive (> 17 U/mL) - 38%. There was no significant association between their prevalence and age, gender or liver disease etiology. Post-LT, the prevalence of negative AT1R-Abs increased to 45% whereas that of risk and positive AT1R-Abs decreased to 30% and 25% respectively. More women than men (61 VS 39%) were positive for AT1R-Abs post-LT. Four patients underwent re-LT– three for vascular complications and one for ABMR. They demonstrated significantly higher pre-LT AT1R-Abs than patients without re-LT. Four patients had ABMR and their post- LT AT1R-Abs were significantly higher than those without ABMR. Five patients developed de novo detection of AT1R-Abs, with one developing ABMR. One of these patients also required a third LT for ABMR. The antibody levels and their association with complications is demonstrated in Table 1. **Conclusion:** In our study cohort, high AT1R-Abs were associated with ABMR and with re-LT. Further studies are required to confirm their role as a predictive biomarker for LT complications and intervention with AT1R blocking drugs

Table 1: Comparison of ATR1-Ab levels in patients with and without post LT complications

Complication	Occurrence	Pre-LT AT1R-Ab U/mL Median (IQR)	Post-LT AT1R-Ab U/mL Median (IQR)
T-Cell mediated rejection	Yes (n=39)	14(30)	Yes–11(11)
	No (n=66)	13(12)	No--10(5)
	p value	0.248	0.663
Antibody mediated rejection	Yes (n=4)	64(284)	100(303)
	No (n=101)	13(15)	11(9)
	p value	0.231	**0.049**
Re transplantation	Yes (n=4)	29(265)	25(265)
	No (n=101)	13(15)	11(8)
	p value	**p=0.028** HR1.009(95% CI 1.001-1.017)	P=0.103
Hepatic artery complications	Yes (n=5)	16(109)	13(105)
	No (n=100)	13(15)	10(8)
	p value	P=0.507	P=0.078

Disclosures: Jeyamani Ramachandran:Nothing to Disclose, Kathleen Davy:Nothing to Disclose, Sarah Mikowski:Nothing to Disclose, Adrian Fleet:Nothing to Disclose, Tim Emery:Nothing to Disclose, Kate Muller: CSL Behring: Advisor, NovoNordisk: Advisor, AstraZeneca: Advisor, Chiesi: Advisor, Eisai: Speaking and

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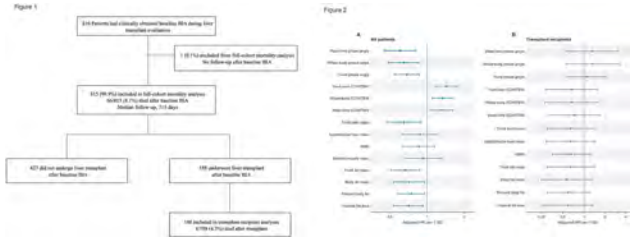
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Teaching, Ipsen: Speaking and Teaching, John Chen: Nothing to Disclose, Alan Wigg:Nothing to Disclose, Robert Carroll:Nothing to Disclose, Alexander Rodgers: Nothing to Disclose.

4494 | BIOELECTRICAL IMPEDANCE PHASE ANGLE AND FLUID DISTRIBUTION DURING LIVER TRANSPLANT EVALUATION: A PROSPECTIVE OBSERVATIONAL COHORT STUD

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Background: Patients with advanced liver disease often have malnutrition, extracellular volume expansion, and frailty incompletely captured by body-mass index or muscle-size metrics. Bioelectrical impedance analysis (BIA) quantifies phase angle and fluid distribution at the point of care. In this largest cohort of BIA during liver transplant evaluation to date, We evaluated whether BIA-derived measures were associated with mortality, post-transplant outcomes, and clinical benchmarks during liver transplant evaluation. **Methods:** We prospectively collected baseline BIA assessments in 816 patients undergoing liver transplant evaluation, 188 later underwent transplantation. Cox models for mortality treated transplantation after BIA as a time-varying covariate, and post-transplant outcomes were modeled among recipients (Figure 1). **Results:** During a median 315-day follow-up, 66 of 815 patients died. Higher whole-body phase angle was associated with lower mortality (hazard ratio per 1-SD [0.9-degree] increase, 0.65; 95% CI, 0.49-0.86), whereas higher whole-body extracellular water-to-total body water ratio was associated with higher mortality (hazard ratio per 1-SD [0.017] increase, 1.34; 95% CI, 1.10-1.63) (Figure 2). Appendicular skeletal muscle index was not associated with mortality. MELD and MELD-Na provided the largest incremental mortality prediction, but selected BIA measures added more prognostic value than body-mass index, appendicular skeletal muscle index, documented sarcopenia, documented reduced grip strength, and 6-minute walk distance. Whole-body BIA associations attenuated after direct MELD/MELD-Na adjustment. Post-transplant mortality was infrequent; other post-transplant analyses were exploratory. **Conclusion:** BIA-derived phase angle and extracellular water-to-total body water ratio outperform conventional size-based and functional benchmarks for prognostic vulnerability during liver transplant evaluation. BIA complements MELD-based severity assessment and warrants external validation as a scalable risk-phenotyping tool.



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4495 | EARLY POSTOPERATIVE RESUSCITATION PHENOTYPES ARE ASSOCIATED WITH RENAL DYSFUNCTION AND CLINICAL OUTCOMES FOLLOWING LIVER TRANSPLANTATION

Rohit Khullar[1] Ki Jung Lee[1] Mohammad Almeqdadi[1], [1]Tufts Medical Center

Background: Optimal postoperative fluid management following liver transplantation remains poorly defined. Albumin, blood products, and isotonic fluids are frequently administered during the immediate postoperative period, yet the relationship between distinct resuscitation strategies and post-transplant outcomes remains unclear. We sought to characterize early postoperative resuscitation phenotypes and evaluate their association with graft function, renal dysfunction, and clinical outcomes following liver transplantation. **Methods:** We performed a retrospective cohort study of adult liver transplant recipients at a single academic transplant center. Patients were classified into albumin-, blood product-, or isotonic fluid-predominant phenotypes based on the largest proportion of total intravenous fluid resuscitation administered during the first 24 postoperative hours. Patients without a predominant phenotype were excluded from comparative analyses. Outcomes included early allograft dysfunction (EAD) defined by Olthoff criteria, acute kidney injury (AKI), renal replacement therapy (RRT), postoperative laboratory values, and healthcare utilization. Continuous variables were compared using analysis of variance and categorical variables using chi-square testing. **Results:** Among 287 transplant recipients, 25 (8.7%) were albumin-predominant, 175 (61.0%) blood product-predominant, and 87 (30.3%) isotonic fluid-predominant. Total resuscitation volume differed

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significantly among phenotypes ($p < 0.001$), with blood product-predominant patients receiving the greatest fluid administration. Rates of EAD were similar across groups (36.0% vs. 32.6% vs. 24.1%, $p = 0.31$). Compared with albumin- and isotonic fluid-predominant patients, blood product-predominant patients were more likely to develop MELD ≥ 18 by postoperative day 5 (60.0% vs. 32.0% vs. 37.9%, $p < 0.001$), require RRT (25.7% vs. 12.0% vs. 13.8%, $p = 0.044$), mechanical ventilation (47.4% vs. 28.0% vs. 29.9%, $p = 0.011$), and prolonged hospitalization ≥ 10 days (79.4% vs. 60.0% vs. 51.7%, $p < 0.001$). Blood product-predominant patients also demonstrated higher bilirubin levels on postoperative days 1 and 5 ($p = 0.02$ and $p < 0.001$, respectively). AKI occurred more frequently in blood product-predominant patients, although this difference did not reach statistical significance (26.9% vs. 8.0% vs. 21.8%, $p = 0.11$). **Conclusion:** Although EAD rates were similar across phenotypes, blood product-predominant resuscitation was associated with greater postoperative morbidity, including increased RRT utilization, higher bilirubin levels, and prolonged hospitalization. Early postoperative resuscitation phenotypes may provide a practical framework for identifying liver transplant recipients at increased risk for postoperative renal dysfunction and adverse clinical outcomes.

Table 1. Baseline Characteristics and Post-Transplant Outcomes Stratified by Early Postoperative Resuscitation Phenotype

	Fluid Resuscitation Predominant Phenotype			p-value[b]
	Albumin	Blood Product	Isotonic Fluid	
n	25	175	87	-
Total IV Fluid Resuscitation, mL (Mean)	1236	3995	1847	< 0.001
Albumin	633	238	157	< 0.001
Blood Products	207	2993	336	< 0.001
Isotonic Fluids	396	764	1354	< 0.001
Demographics				
Age (mean)	59.8	55.8	55.5	<0.18
Gender (% Female)	20.0	27.4	28.7	< 0.69
Race/Ethnicity				< 0.14
White	52.0	69.7	56.3	-
Black	16.0	6.3	16.1	-
Hispanic	4.0	6.9	8.0	-
Asian	12.0	4.0	4.6	-
Other/Unknown	16.0	13.1	14.9	-
Post-Transplant Outcomes, % of Total				
Early Allograft Dysfunction[a]	36.0	32.6	24.1	< 0.31
MELD ≥ 18 Day 5	32.0	60.0	37.9	< 0.001
Acute Kidney Injury by Day 5	8.0	26.9	21.8	< 0.11
Requires Renal Replacement Therapy	12.0	25.7	13.8	< 0.044
Need for Vasopressors	44.0	33.1	11.5	< 0.001
Need for Mechanical Ventilation	28.0	47.4	29.9	<0.011
30-Day Mortality	0.0	1.7	2.3	< 0.74
90-Day Mortality	0.0	2.9	2.3	< 0.68
Length-of-Stay ≥ 10 Days	60.0	79.4	51.7	< 0.001
Laboratory Values, Day 1 and 5 Post-Transplant				
Creatinine, Day 1	1.6	1.7	1.5	< 0.19
Creatinine, Day 5	1.3	1.7	1.6	< 0.16
Bilirubin, Day 1	3.7	7.2	5.9	< 0.02
Bilirubin, Day 5	2.3	4.6	2.3	< 0.001
INR, Day 1	1.8	1.7	1.6	< 0.32
INR, Day 5	1.2	1.4	1.3	< 0.41

[a]Early Allograft Dysfunction defined as binary variable by Olthoff Criteria: AST or ALT ≥ 2000 in first 7 days post-transplant, Day 7 Total Bilirubin ≥ 10, or Day 7 INR ≥ 1.6
[b]Statistical significance measured by chi-squared contingency test for categorical variables and by one-way ANOVA with Tukey-Kramer Post Hoc Test for intergroup assessment of differences

Disclosures: Rohit Khullar:Nothing to Disclose, Ki Jung Lee:Nothing to Disclose, Mohammad Almeqdadi:Nothing to Disclose.

4496 | MACHINE LEARNING OUTPERFORMS BMI FOR PREDICTING WAITLIST MORTALITY IN MASH-SPECTRUM LIVER TRANSPLANT CANDIDATES

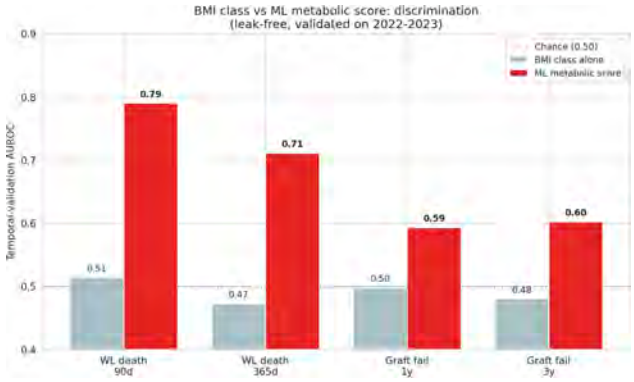
Sri Harsha Boppana[1] Subhash Gurappa[2] Sachin Sravan Kumar Komati[2] Gautam Maddineni[3] Raja Chandra Chakinala[4] Venkata Sunkesula[5] Pradeep Yarra[6] Christina Awad[6], [1]Nassau University Medical Center, [2]Florida International University, [3]Creighton university school of medicine, [4]Guthrie Robert Packer Hospital, [5]Case Western Reserve University, [6]UT health San Antonio

Background: Body mass index (BMI) remains a highly visible factor in liver transplant (LT) evaluation for metabolic dysfunction-associated steatohepatitis (MASH), yet its prognostic value relative to integrated clinical risk modeling is uncertain. We developed and temporally validated machine-learning (ML) models to determine whether listing BMI class meaningfully predicts waitlist mortality and post-LT graft failure in MASH-spectrum LT candidates. **Methods:** Adult, single-organ LT candidates listed from 2018-2023 with MASH or cryptogenic cirrhosis were identified from a national registry cohort. Candidates listed in 2018-2021 formed the training cohort and those listed in 2022-2023 formed a temporal validation cohort. Outcomes were waitlist death within 90 and 365 days and graft failure within 1 and 3 years after LT. BMI class was compared with ML models using XGBoost, random forest, and elastic net. Discrimination was assessed by validation AUROC; model improvement over BMI was quantified using AUROC gain, net reclassification improvement (NRI), and integrated discrimination improvement (IDI). SHAP values identified dominant predictors. **Results:** Among 5,063 listed candidates, 3,152 underwent LT and 1,911 were never transplanted; 994 waitlist deaths occurred, including 399 within 90 days and 718 within 365 days. The 90- and 365-day cumulative incidence of waitlist death was 8.0% and 14.9%, respectively, with 365-day transplant as a competing event in 54.6%. Waitlist death at 365 days was similar across BMI strata: non-obese 14.7%, class I 14.4%, class II 15.0%, and class III 19.2% ($p = 0.125$). BMI alone performed at chance for waitlist death (AUROC 0.514 at 90 days; 0.472 at 365 days) and graft failure (0.498 at 1 year; 0.480 at 3 years). In temporal validation, leak-free ML models improved discrimination for waitlist death (AUROC 0.771 at 90 days; 0.711 at 365 days), with AUROC gains of 0.257 and 0.239 over BMI alone. The full-feature ML model achieved AUROC 0.860 for 90-day and 0.779 for 365-day waitlist death, with NRI 1.130/0.833 and IDI 0.184/0.157. De-leaked SHAP analysis ranked age, MELD-Na, bilirubin, albumin, and

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creatinine above BMI, which ranked sixth of 12 predictors. (Figure1) **Conclusion:** In a contemporary national MASH-spectrum LT cohort, BMI class did not meaningfully stratify waitlist mortality and BMI alone predicted death or graft failure no better than chance. Temporally validated ML models substantially improved short-term waitlist mortality prediction by integrating liver disease severity, renal function, age, and BMI. These data challenge BMI-centered listing decisions and support AI-enabled risk stratification to individualize LT evaluation in MASH.

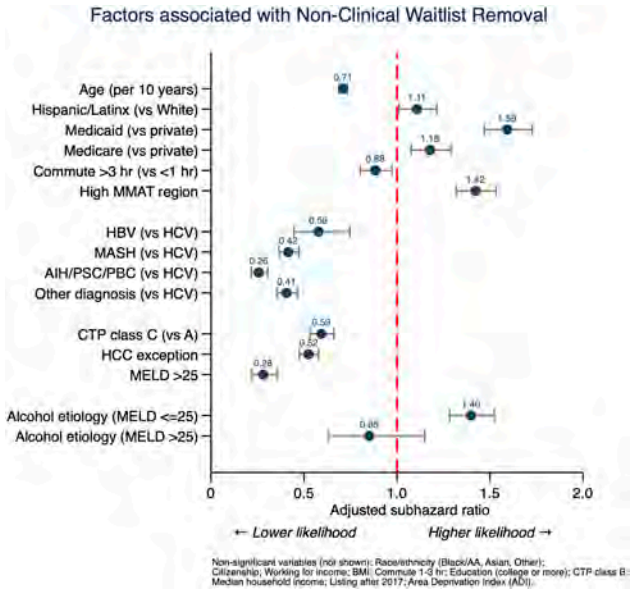


Disclosures: Sri Harsha Boppana:Nothing to Disclose, Subhash Gurappa:Nothing to Disclose, Sachin Sravan Kumar Komati:Nothing to Disclose, Gautam Maddineni: Nothing to Disclose, Raja Chandra Chakinala:Nothing to Disclose, Venkata Sunkesula:Nothing to Disclose, Pradeep Yarra:Nothing to Disclose, Christina Awad: Nothing to Disclose.

4497 | FACTORS INFLUENCING LIVER TRANSPLANT WAITLIST REMOVAL FOR NON-CLINICAL REASONS: A NATIONAL RETROSPECTIVE COHORT ANALYSIS

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Background: Liver transplant (LT) waitlist removal for non-clinical reasons has had limited exploration despite the high likelihood of subsequent morbidity and mortality. Unlike clinical reasons such as medical/surgical contraindications or being too early for transplant, non-clinical reasons including psychosocial barriers and loss to follow-up are potentially modifiable. This retrospective cohort analysis seeks to identify factors that influence non-clinical reasons for waitlist removal. **Methods:** We analyzed waitlist removal data from the Scientific Registry of Transplant Recipients database on adults listed for LT from 2005-2022. Reasons for waitlist removal were categorized as non-clinical, clinical, death, and transplant. Removals classified as "Other" (N = 5473) were manually re-categorized. Non-clinical reasons were grouped into (1) psychosocial barriers, (2) lost to follow-up, and (3) patient choice/refusal. The patient choice group was excluded from analysis as they represented a different population. Multivariable competing risk Cox regression analysis was used to examine factors at time of waitlisting associated with non-clinical removal, with transplant as the competing risk and other reasons censored at time of waitlist removal. **Results:** Among 82,895 waitlist removals, 54,709 (66.0%) were transplanted and 17,617 (21.3%) died. 5,324 (6.4%) were removed for non-clinical reasons and 5,245 (6.3%) were removed for clinical reasons. Of non-clinical removals, 55.5% were due to psychosocial reasons, 16.8% were lost to follow-up, and 27.6% for patient choice/transplant refusal. Among psychosocial removals, 50.3% were for alcohol/substance use and 30.1% for non-adherence, with the remaining for insufficient social support/transportation/finances. Factors associated with non-clinical waitlist removals included Hispanic race/ethnicity (vs White; SHR: 1.11 [1.01-1.21]), living in a higher median MELD at transplant (MMAT) region (vs lower MMAT; SHR: 1.42 [1.32-1.53]), non-private insurance (vs private), and alcohol etiology (vs HCV, SHR: 1.40 [1.28-1.52]) (Figure). Protective factors included older age, CTP category C, higher MELD and HCC MELD exception. There was a significant interaction between alcohol etiology and MELD at listing ($p < 0.01$): the likelihood of non-clinical removal was higher for alcohol compared to non-alcohol etiologies with MELD scores < 25 (SHR MELD < 25: 1.40 [1.28–1.52], SHR MELD ≥ 25: 0.85 [0.63–1.15]). **Conclusion:** Psychosocial concerns account for most non-clinical LT waitlist removals. Higher urgency based on clinical factors protected against removal for non-clinical reasons, while sociodemographic factors and higher organ competition heightened risk. Interventions are needed to address psychosocial barriers while on the waitlist to ensure equitable LT access for socially vulnerable individuals.



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Disclosures: Nikhilesh Kumar:Nothing to Disclose, Shayana Seneviratne:Nothing to Disclose, Kali Zhou: Gilead Sciences Inc: Grant/Research Support, Merck: Grant/Research Support.

4498 | KIDNEY ALLOGRAFT OUTCOMES AFTER SIMULTANEOUS LIVER–KIDNEY VS SAFETY-NET TRANSPLANTATION

Abhijith Atkuru[1] Sidart Pradeep[2] Eugenia Tsai[2], [1]Tulane University School of Medicine, [2]Texas Liver Institute; UT Health San Antonio

Background: Following the 2017 Organ Procurement and Transplantation Network (OPTN) policy, short-term kidney allograft outcomes between simultaneous liver–kidney (SLK) and Safety-Net pathways have been described, yet longer-term graft survival, patient survival, and early graft function metrics remain uncharacterized in a national cohort. Kidney allograft outcomes were compared between SLK and Safety-Net recipients in the largest post-policy national cohort to date. **Methods:** Using OPTN/Scientific Registry of Transplant Recipients (SRTR) Standard Transplant Analysis and Research (STAR) data (2018–2024), adults who underwent SLK or received a Safety-Net kidney 60-365 days after liver-alone transplantation were identified. Outcomes included delayed graft function (DGF), kidney graft failure by follow-up graft status, creatinine at kidney transplant, 6 and 12 months, and Kaplan-Meier (KM) patient survival. Kidney graft failure was defined as failed graft status; deaths without graft-status failure and return to maintenance dialysis alone were not counted. Comparisons used chi-square, Wilcoxon rank-sum, log-rank, and linear models. **Results:** Among 4,197 recipients, 3,506 underwent SLK and 691 received a Safety-Net kidney. Safety-Net recipients had higher Model for End-Stage Liver Disease score (34 vs 28), dialysis use (66.3% vs 46.3%), and kidney-transplant creatinine (4.00 vs 3.20 mg/dL; all $p < 0.001$). DGF was more frequent after SLK (30.8% vs 18.6%, $p < 0.001$), whereas kidney graft failure by follow-up graft status was similar (4.5% vs 4.4%, $p = 0.978$). Safety-Net recipients also had higher creatinine at 6 months (1.40 vs 1.23 mg/dL) and 12 months (1.41 vs 1.25 mg/dL; both $p < 0.001$). KM patient survival was lower after SLK at 1 year (90.4% vs 95.7%), 3 years (82.8% vs 90.5%), and 5 years (75.0% vs 82.6%; all $p < 0.001$) (Table 1). **Conclusion:** Despite greater pre-transplant renal dysfunction and higher post-transplant creatinine through 12 months, Safety-Net recipients had lower DGF and superior 1-, 3-, and 5-year patient survival compared to SLK. These findings suggest that chronic kidney disease burden at liver transplantation, rather than acute renal dysfunction, is the dominant driver of long-term mortality in this population and support early Safety-Net listing planning.

Table 1. Kidney Allograft and Patient Survival Outcomes
SLK versus Safety-Net kidney transplantation, OPTN/SRTR STAR data 2018-2024

Outcome	SLK	Safety-Net	P value
Pre-Kidney Transplant Clinical Profile			
Model for End-Stage Liver Disease score, (median)	28	34	<0.001
Dialysis use at kidney transplant	46.3%	66.3%	<0.001
Kidney-transplant creatinine, median [IQR], mg/dL	3.20 [2.08-4.87]	4.00 [2.90-5.62]	<0.001
Early Kidney Allograft Events, n/N (%)			
Delayed graft function	1,043/3,390 (30.8%)	128/689 (18.6%)	<0.001
Kidney graft failure by follow-up graft status	147/3,249 (4.5%)	30/680 (4.4%)	0.978
Post-Kidney Transplant Renal Function, median [IQR], mg/dL			
At kidney transplant	3.20 [2.08-4.87]	4.00 [2.90-5.62]	<0.001
6 months	1.23 [1.00-1.53]	1.40 [1.12-1.74]	<0.001
12 months	1.25 [1.03-1.53]	1.41 [1.13-1.70]	<0.001
Kaplan-Meier Patient Survival			
1 year	90.4%	95.7%	<0.001
3 years	82.8%	90.5%	<0.001
5 years	75.0%	82.6%	<0.001
Pathway-by-Etiology Interaction for Creatinine			
At kidney transplant			0.012
6 months			0.852
12 months			0.863

Note: Kidney graft failure was defined as failed follow-up graft status, deaths without graft-status failure and return to maintenance dialysis alone were not counted. Patient survival was estimated using Kaplan-Meier analysis.

Abbreviations: DGF, delayed graft function; IQR, interquartile range; KM, Kaplan-Meier; MELD, Model for End-Stage Liver Disease; OPTN, Organ Procurement and Transplantation Network; SLK, simultaneous liver-kidney; SRTR, Scientific Registry of Transplant Recipients; STAR, Standard Transplant Analysis and Research.

Disclosures: Abhijith Atkuru:Nothing to Disclose, Sidart Pradeep:Nothing to Disclose, Eugenia Tsai: Nothing to Disclose.

4499 | BRIDGING OBESE LIVER TRANSPLANT CANDIDATES TO LISTING: SAFETY AND EFFICACY OF VLCD COMBINED WITH PHARMACOTHERAPY IN DECOMPENSATED CIRRHOSIS

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Background: Liver transplant candidates with BMI > = 40 kg/m2 face a 29% lower adjusted transplant rate and decreased post-transplant survival. When rapid pre-transplant weight reduction is required, pharmacotherapy alone may take months for meaningful BMI reduction, and endoscopic bariatric procedures, while promising for sustained weight loss, have not been well studied in patients with decompensated cirrhosis. Very low-calorie diets (VLCD, < 900 kcal/day) offer a rapid bridging strategy, yet safety data in decompensated cirrhosis requiring urgent listing remain limited. **Methods:** Prospective single-center case series (09/2023-03/2025) of 13 patients whose obesity precluded transplant eligibility. Ten initiated VLCD (< 900 kcal/day) with phentermine (n = 9) and GLP-1 receptor agonists (n = 8; tirzepatide, semaglutide, liraglutide, or dulaglutide). Three received pharmacotherapy alone as a pragmatic comparison. All underwent multidisciplinary transplant evaluation with weekly electrolyte and

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acid-base monitoring. **Results:** Mean age 62 years; 54% male. Etiologies: MASH (54%), HCV (15%), AIH/PBC (15%), Met-ALD (8%), SSC (8%). 77% had decompensated cirrhosis. Mean initial BMI 46 kg/m2 (range 36-58); median initial MELD 21 (range 18-30). VLCD patients achieved mean weight loss of 45 lbs (range 13-106) over 61 days (range 32-119), reducing mean BMI to 40 kg/m2 with median listing MELD of 24 (range 16-27). No patient required discontinuation for metabolic complications; weekly monitoring showed no electrolyte derangements or metabolic acidosis, including in advanced decompensation. Nine of 10 VLCD patients (90%) achieved transplant approval; 6 were transplanted (one simultaneous liver-kidney) with 5 alive and well. Two early deaths (gastrointestinal bleed day 3, subdural hematoma day 11) were not attributed to VLCD. None of the 3 pharmacotherapy-only patients achieved eligibility. **Conclusion:** To our knowledge, this is the largest prospective case series evaluating VLCD for rapid pre-transplant weight reduction in decompensated cirrhosis. VLCD (< 900 kcal/day) was safe, metabolically well-tolerated, and achieved transplant eligibility in 90% of patients under multidisciplinary oversight. When urgency demands rapid BMI reduction, this approach should be considered as a safe and efficacious strategy. The small sample, single-center design, and limited follow-up constrain generalizability; larger multicenter studies with longer-term outcomes are warranted.



Table 1. Patient Characteristics, Interventions, and Clinical Outcomes (N=13)

Patient Characteristics	Time on VLCD (Days)	GLP-1 RA (Generic / Brand)	Oral Weight Loss Medication	Outcomes
64F MASH Ascites + HE	36	Tirzepatide (Mounjaro)	Phentermine	Transplanted BMI 41.3 → 37.5 (−9.8) No complications
73M Met-ALD Ascites + HCC	N/AT	Semaglutide (Ozempic / Wegovy)	None	Approved for transplant Removed from list 07/2025 (patient request) HCC: non-viable >12 months; viable synthetic function
65F MASH HE	97	Tirzepatide (Mounjaro) Semaglutide (Ozempic) Liraglutide (Victoza)	Phentermine	SLK transplanted 12/2025 BMI 49.0 → 38.0 (−10.0) No complications
39M MASH Ascites + HE	37	Tirzepatide (Mounjaro) Dulaglutide (Trulicity)	Phentermine	Approved; 30 lb weight loss achieved Died of presumed septic shock 2 months post-approval (prior to waitlist outcome)
42M MASH Ascites + HE Prior GIB	118	None	Phentermine	Transplanted BMI 46.3 → 44.3 (−2.0) RTCP +1 for hematoma washout Currently doing well
63F MASH Ascites + HE	47	Tirzepatide (Mounjaro)	None	Transplanted BMI 58.0 → 38.6 (−19.4) Acalculous cholitis requiring biliary stenosis (cross site) Currently doing well
65M HCV Ascites + HE Prior HTN + HCC	32	Semaglutide (Ozempic)	Phentermine	Transplanted BMI 40.7 → 36.6 (−4.1) Delayed CMV viremia Currently doing well
51M MASH Ascites + HE Prior GIB	55	Semaglutide (Ozempic)	Phentermine	Died intraoperatively BMI 52.3 → 45.3 (−7.0) Cardiac collapse after reperfusion
68F AIH / PBC Overlap	115	None	Phentermine	Died during admission Spontaneous SDH + seizures (11 days after VLCD initiation) Never listed
65F AIH / PBC Overlap Ascites + HE + HRS	33	Dulaglutide (Trulicity)	None	Admitted for UGI bleed (likely before VLCD initiation) Discharged to hospice; died shortly after Never listed
73F MASH Ascites + HCC	53	None	Phentermine	Transplanted BMI 43.8 → 34.3 (−9.5) Recurrent IV paracentesis Currently doing well
58M HCV HCC	N/AT	None	Topiramate-phentermine (Qsymia, stopped 1W)	Approved for transplant Removed from list (patient request) HCC non-viable
40F SSC	N/AT	None	None	Not listed; followed in clinic (Pharmacotherapy only comparison group)

Abbreviations: HE = hepatic encephalopathy; HCC = hepatocellular carcinoma; GIB = gastrointestinal bleeding; HRS = hepatorenal syndrome; SLK = simultaneous liver-kidney transplant; SDH = subdural hematoma; RTCP = return to operating room; SE = side effects; SAC = secondary autoimmune cholangitis; CMV = cytomegalovirus; Pulm HTN = pulmonary hypertension; AIH = autoimmune hepatitis; PBC = primary biliary cholangitis; Met-ALD = metabolic dysfunction–associated steatotic liver disease; HCV = hepatitis C virus; VLCD = very low-calorie diet (<900 kcal/day); SLP 1 RA = glucagon-like peptide-1 receptor agonist.
† Did not tolerate VLCD; managed with pharmacotherapy alone (weight loss comparison group).
‡ Early deaths not attributed to VLCD; day 3 (upper GI bleed, likely within VLCD initiation) and day 11 (unwitnessed SDH).

Disclosures: Aldanah Althwanay:Nothing to Disclose, Scott McHenry:Nothing to Disclose, Megan White: Nothing to Disclose.

4500 | IRON CHELATION MODULATES THE TRANSCRIPTOME TO ATTENUATE FERROPTOSIS IN HUMAN MARGINAL DONOR LIVERS

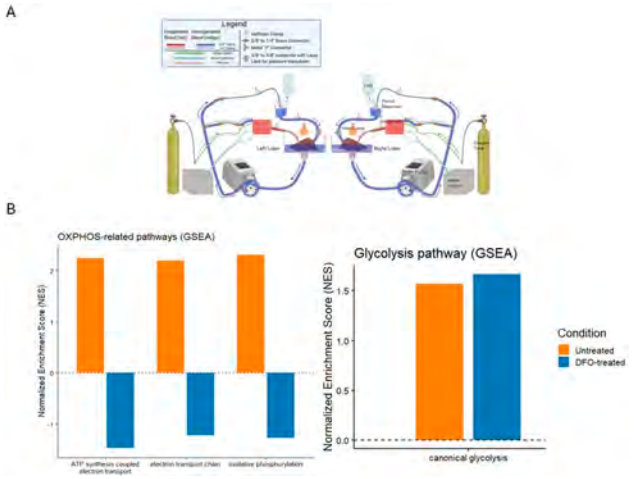
Shun Onishi[1] Takahiro Okura[1] Chandrashekhara Manithody[1] Mustafa Nazzal[1] Ajay Jain[1], [1]Saint Louis University

Background: Marginal donor livers (MDLs) expand the transplant pool but are vulnerable to ischemia–reperfusion injury (IRI). Ferroptosis, an iron-dependent lipid peroxidation cell death pathway, mediates IRI. Deferoxamine (DFO), an iron chelator, may attenuate ferroptosis, but its transcriptomic effects during ex vivo human liver perfusion are undefined. We tested impact of DFO in paired human MDLs using PROTECT. **Methods:** Six discarded human MDLs were split into paired lobes and perfused using our patent pending PROTECT (Perfusion Regulated Organ Therapeutics with Enhanced Controlled Testing). One lobe received DFO, with single or dual dosing, while the contralateral lobe served as control. Biopsies were obtained at baseline and 5 hours. Bulk RNA-seq was analyzed by Time × Treatment interaction modeling; significant genes, padj < 0.1, underwent GSEA, GO, and Reactome enrichment. Validation included tissue iron, ferroptosis markers, HIF-1α, TUNEL, MDA, and injury markers. **Results:** Baseline transcriptomes were concordant between paired lobes, validating PROTECT. By 5 hours, DFO induced metabolic-redox changes. GSEA showed oxidative phosphorylation and mitochondrial respiratory enrichment in controls, while DFO suppressed mitochondrial oxidative signatures. DFO downregulated electron transport chain genes across Complexes I–V while preserving glycolytic enrichment, including PFKP, PFKFB1, FOXK1, and ENO2 upregulation, and modulated iron-handling, ROS, and inflammasome pathways. Transcriptomic changes aligned with chelation and reduced injury. DFO achieved ≥ 20% tissue iron reduction and downregulated ferroptosis genes, including HIF-1α, IREB2, RPL8, FTH1, ACSF2, and ATP5G3, with multiple targets $p < 0.0001$. HIF-1α protein decreased, $p = 0.0040$. Injury was attenuated, with fewer TUNEL-positive cells, $p = 0.0283$, decreased MDA, and a trend toward lower AST, $p = 0.0727$. Non-chelated lobes showed persistent iron accumulation, ferroptosis activation, oxidative stress, and apoptosis. Iron reduction associated with ferroptosis gene suppression, $p = 0.0040$–0.0485, and lower injury markers. Dual dosing improved chelation efficacy, 2/2 dual-dose versus 2/4 single-dose;

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protection was observed in steatotic livers. **Conclusion:** DFO induces transcriptomic programming during ex vivo perfusion of human MDLs, suppressing mitochondrial oxidative phosphorylation while preserving glycolytic metabolism and attenuating iron-, ROS-, inflammasome-, and ferroptosis-associated pathways. These changes were accompanied by reduced iron burden, lipid peroxidation, apoptosis, and early hepatocellular injury providing evidence of therapeutic optimization in donor livers.



Disclosures: Shun Onishi:Nothing to Disclose, Takahiro Okura:Nothing to Disclose, Chandrashekhara Manithody:Nothing to Disclose, Mustafa Nazzal:Nothing to Disclose, Ajay Jain:Nothing to Disclose.

4501 | FXR AGONIST IN POST LIVER TRANSPLANTATION PATIENTS: FINAL RESULTS FROM A RANDOMIZED OPEN-LABEL STUDY (CTRI/2021/11/038218)

Anila Kutty Narayanan[1] Saraswathy S Nair[1] Arun Valsan[1] Anandakrishnan Nandakumar[2] Sudhindran S[1], [1]Amrita Institute of Medical Sciences and Research Centre, Kochi, Amrita Vishwa Vidyapeetham, India, [2]Amrita Institute of Medical Sciences & Research Centre, Kochi, Amrita Vishwa Vidyapeetham, India

Background: Post-liver transplant cholestasis remains a common complication following living-donor liver transplantation (LDLT), contributing to delayed graft recovery, increased morbidity, and greater healthcare burden. Ursodeoxycholic acid (UDCA) is widely used in this setting; however, it does not directly target bile acid regulatory pathways. Obeticholic acid (OCA), a potent farnesoid X receptor agonist, may therefore offer a mechanism-based therapeutic alternative. This study aimed to compare the efficacy and safety of OCA versus UDCA in ameliorating cholestasis following LDLT. **Methods:** In this prospective, open-label trial, conducted between 2021 and 2025, 287 adult LDLT recipients were randomized to OCA or UDCA using a computer-generated sequence. The primary endpoint was the proportion achieving ≥15% reduction in alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT) at 3, 6, and 12 months from the 1-month post-transplant baseline. Secondary outcomes included absolute values of liver biochemistry, molecular markers (Fibroblast Growth Factor-19, cytokeratin-18, Bile Salt Export Pump serum autotaxin, and Transforming Growth Factor-β), rejection, biliary complications, survival, adverse events, and quality of life (by Chronic Liver Disease Questionnaire). Modified intention-to-treat analysis excluded patients who did not survive beyond one month(N = 44). Baseline-adjusted analyses used logistic regression, ANCOVA, and repeated-measures models. **Results:** Of 287 randomized patients, 225 were included in the primary efficacy analysis (OCA n = 109; UDCA n = 116). Baseline characteristics were broadly comparable, although early cholestatic enzyme levels were higher in the OCA group. Although in unadjusted analyses, OCA showed higher ALP responder rates at 3 months (50% vs 35%, p = 0.018) and 6 months (50% vs 33%, p = 0.010), and higher GGT response at 12 months (83% vs 69%, p = 0.022) compared to UDCA, after baseline imbalance adjustment, no clear longitudinal superiority was observed. OCA demonstrated greater early reduction in plasma bile acids [OCA 250 (133, 332) vs UDCA 326 (245, 337), p < 0.001]. CRP levels were significantly higher in the OCA group at 6 months (p = 0.019) and 12 months (p = 0.011), while LDL levels were also higher at baseline (p = 0.014), 3 months (p = 0.015), and 6 months (p < 0.001), becoming comparable by 12- months. Rates of rejection, EAD, pruritic, biliary complications, hospital stay, and mortality was similar. Quality of life was largely comparable, though abdominal symptoms and worry domains favored UDCA. There were no major adverse effects in liver function in the postoperative period attributable to OCA **Conclusion:** Although OCA demonstrated FXR-mediated biochemical activity, it was not superior to UDCA in longitudinal biochemical, molecular, or clinical outcome analyses. Its safety profile appeared comparable to that of UDCA in post-liver transplant patients.

Table 1: Number of patients with 15% reduction in Alkaline Phosphatase (ALP) & Gamma Glutamyl Transferase (GGT) - Primary Endpoints.

Biomarker/Time points	Overall, N = 225[1]	OCA, N = 109[1]	UDCA, N = 116[1]	p-value[2]
ALP (month to month)				
1 to 3	95 (42%)	55 (50%)	40 (35%)	0.018
3 to 6	68 (31%)	32 (31%)	36 (32%)	0.9
1 to 6	89 (41%)	52 (50%)	37 (33%)	0.010
6 to 12	71 (36%)	39 (39%)	32 (32%)	0.3
1 to 12	89 (45%)	51 (52%)	38 (38%)	0.063
GGT (month to month)				
1 to 3	164 (74%)	81 (75%)	83 (72%)	0.6
3 to 6	117 (54%)	61 (59%)	56 (50%)	0.3
1 to 6	154 (72%)	78 (76%)	76 (68%)	0.2
1 to 12	149 (76%)	81 (83%)	68 (69%)	0.022
6 to 12	80 (41%)	39 (40%)	41 (42%)	0.8

[1]n (%)
[2]Pearson's Chi-squared test

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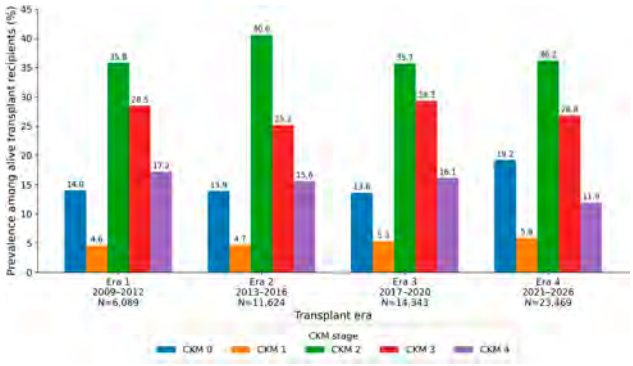
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4502 | POST-LIVER TRANSPLANT CARDIOVASCULAR-KIDNEY-METABOLIC SYNDROME STAGING PREVALENCE AND TEMPORAL PROGRESSION

Joseph Gunderson[1] Ludovic Saba[2] Saket Girotra[1] Sarah Lieber[1] Arjmand Mufti[1] Madhukar Patel[1] Lisa VanWagner[1], [1]University of Texas Southwestern Medical Center, [2]UT Southwestern Medical Center

Background: Cardiovascular disease (CVD) is the leading cause of non-graft-related death after liver transplantation (LT), yet risk assessment remains fragmented across metabolic, renal, and cardiovascular domains. The American Heart Association cardiovascular-kidney-metabolic (CKM) framework integrates these interrelated conditions, highlighting shared pathophysiology, overlapping risk factors, and common therapeutic approaches. The CKM staging continuum - from ideal health (stage 0), excess adiposity (Stage 1), metabolic risk factors or chronic kidney disease (CKD) (Stage 2), subclinical or high predicted CVD risk (Stage 3), to clinical CVD (Stage 4) - captures escalating risk and emphasizes prevention. However, the burden and progression of CKM disease after LT are unknown. **Methods:** We conducted a retrospective cohort study using the TriNetX Global Collaborative Network, a federated health research network that provides deidentified electronic health record data from 171 healthcare organizations. We identified living adult LT recipients (2009-2026) and excluded multi-organ transplants. CKM stage was defined using ICD-10-CM, LOINC, and CPT codes and assessed across four transplant eras (Figure). **Results:** Among 55,525 living LT recipients (mean age 60 years, 61.6% male, 61.3% White, 8.2% Hispanic), 83.9% met criteria for CKM stage $\geq$1. Stage 2 was most prevalent (36.9%), followed by stage 3 (27.3%) and stage 4 (14.3%), with 41.6% classified as stage 3-4. Stage 1 was uncommon (5.3%). CKM severity varied across transplant eras, demonstrating a gradient consistent with time-dependent progression (Figure). Stage 4 prevalence increased with longer post-transplant follow-up (11.9% for patients transplanted in 2021-26 vs 17.2% in 2009-12), while stage 0 was most common in the most recent era (19.2%). Notably, advanced CKM stages (3-4) were already prevalent in recent cohorts. **Conclusion:** CKM syndrome affects the vast majority of LT recipients, with a substantial burden of advanced disease and evidence of progressive stage advancement over time. The presence of advanced CKM even in recent cohorts suggests that cardiovascular risk emerges early after LT, representing a critical window for intervention. Stage 2 predominance highlights metabolic-renal disease as a key, modifiable target before progression to overt CVD. These findings support integration of CKM staging into routine post-transplant care and early, multidisciplinary risk management to mitigate long-term adverse cardiovascular outcomes in this high-risk population.



Disclosures: Joseph Gunderson:Nothing to Disclose, Ludovic Saba:Nothing to Disclose, Saket Girotra:Nothing to Disclose, Sarah Lieber:Nothing to Disclose, Arjmand Mufti:Nothing to Disclose, Madhukar Patel:Nothing to Disclose, Lisa VanWagner:W.L. Gore & Associates: Grant/Research Support, Akero: Grant/Research Support, Madrigal: Grant/Research Support, Gerson Lehrman Group: Consultant, Madrigal: Advisor, Slingshot Insights: Consultant, Antheneum Partners: Consultant, Gerson Lehrman Group: Consultant, Alpha Insights: Consultant, Slingshot Insights: Consultant, Madrigal Pharmaceuticals: Grant/Research Support, W.L. Gore & Associates: Grant/Research Support, BD: Grant/Research Support, Medicolegal consulting: Consultant.

4503 | EVALUATION OF A BLOOD-BASED MICRORNA CLINICAL ASSAY FOR GUIDING IMMUNOSUPPRESSIVE MANAGEMENT IN LIVER TRANSPLANT RECIPIENTS

Yipeng Wang[1] Haleigh Parker[1] Chang Han[1] Byung-In Lee[1] Gordon Vansant[1] Shuguang Huang[1] Bao-Li Loza[2] Brendan Keating[3] Kim Olthoff[4] Abraham Shaked[2], [1]LuminoDx Inc., [2]University of Pennsylvania, [3]New York University, [4]Hospital of the University of Pennsylvania

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Background: Liver transplant recipients require lifelong immunosuppression, which is associated with infection, malignancy, nephrotoxicity, metabolic complications, and reduced quality of life. Current monitoring relies on liver enzymes and biopsy, which typically detect rejection only after liver injury has occurred. HepatoTrack is a circulating microRNA assay previously shown to have strong clinical performance for detection of acute cellular rejection (ACR) in liver transplant recipients and may identify rejection-associated molecular signals before clinical injury becomes apparent. This study evaluated the utility of HepatoTrack for guiding immunosuppression minimization and identifying patients at risk for rejection during withdrawal. **Methods:** HepatoTrack uses 200 µL serum or plasma for RT-qPCR analysis of four microRNAs: miR-122, miR-885, miR-23a, and cel-miR-39. HepatoTrack prediction scores (HPS) for acute cellular rejection (ACR) were generated using a predefined proprietary algorithm. Two liver transplant cohorts undergoing immunosuppression withdrawal were analyzed. Cohort 1 included samples from the A-WISH study (ITN030ST), and Cohort 2 included samples from the OPTIMAL study (ITN056ST; NCT02533180). Biopsy-confirmed ACR served as the reference standard when available. HepatoTrack performance was assessed using ROC analysis and compared with alanine aminotransferase (ALT). **Results:** In Cohort 1, 22 samples had paired liver biopsy results, including 16 biopsy-confirmed ACR and 6 non-ACR samples. HepatoTrack demonstrated strong diagnostic performance for ACR detection with an AUC of 0.896, compared with 0.51 for ALT alone ($p < 0.05$). In Cohort 2, 404 samples from 62 patients undergoing immunosuppression withdrawal were analyzed. Positive HepatoTrack scores (HPS > 2) were infrequent in tolerant patients (6.2%) but more common in non-tolerant by biopsy (30.4%), failed after withdrawal (26.8%), and failed withdrawal (28.4%) groups. Among biopsy-confirmed non-tolerant patients, HPS became elevated 180–240 days after enrollment indicating ACR while ALT remained within normal range. Detectable baseline miR-885 was associated with subsequent withdrawal failure, suggesting potential utility for identifying patients less likely to tolerate immunosuppression minimization. **Conclusion:** HepatoTrack demonstrated strong performance for detecting acute cellular rejection and identified molecular evidence of alloimmune activation during immunosuppression withdrawal before biochemical injury or biopsy-proven rejection became apparent. These findings support HepatoTrack as a promising noninvasive tool for guiding immunosuppression minimization and personalized post-transplant management, with the potential to identify high-risk patients earlier and reduce reliance on liver biopsy.

Disclosures: Yipeng Wang:LuminoDx Inc.: Executive role, Haleigh Parker:Nothing to Disclose, Chang Han: Nothing to Disclose, Byung-In Lee:Nothing to Disclose, Gordon Vansant:Nothing to Disclose, Shuguang Huang:Nothing to Disclose, Bao-Li Loza:Nothing to Disclose, Brendan Keating:Nothing to Disclose, Kim Olthoff:OrganOx: Advisor, OrganOx: Advisor, OrganOx: Advisor, OrganOx: Advisor, Abraham Shaked: Nothing to Disclose.

4504 | ASSOCIATION OF PRE-TRANSPLANT FRAILTY WITH MAJOR ADVERSE CARDIOVASCULAR EVENTS AFTER LIVER TRANSPLANTATION

Isra Taha[1] Yanqing Lyu[2] Sneha Manikandan[3] Barbara Okeke[2] Kelly Fan[2] Spencer Hobbs[3] Ava Delonais-Parker[3] Sahita Gandra[3] Mina Benjamin[2] Uchenna Agbim[2], [1]SSM Saint Louis University Hospital, [2]SSM Health Saint Louis University Hospital, [3]Saint Louis University School of Medicine

Background: Frailty is an established predictor of adverse outcomes in liver transplantation (LT), including higher waitlist mortality, post-transplant mortality, healthcare utilization, and acute rejection. The relationship between frailty and post-transplant major adverse cardiovascular events (MACE) remains unclear. We evaluated whether pre-transplant frailty is associated with post-transplant MACE in LT recipients. **Methods:** We conducted a single-center retrospective cohort study of adult LT recipients from January 2014 to January 2024. Frailty was defined using Liver Function Index (LFI) score: frailty as LFI 4.5, pre-frailty as LFI 3.2 – 4.4, and non-frailty as LFI 3.1. Univariate and multivariable logistic and Cox regression analyses evaluated associations between frailty status and post-LT outcomes. Frail/pre-frail patients were grouped for multivariable analysis due to limited event numbers. **Results:** Among 126 LT recipients, cardiovascular comorbidities were largely similar across frailty groups, although diabetes mellitus and MASLD differed significantly by frailty status ($p = 0.025$ and $p = 0.030$, respectively).Overall MACE incidence was 22.2%. MACE incidence was highest in non-frail patients (37.5%) compared with pre-frail (19.7%) and frail (13.8%) patients ($p = 0.1098$). In multivariate analysis, frailty/pre-frailty was associated with lower odds of MACE (OR 0.39, 95% CI

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0.15–0.99, p = 0.0496). Findings were consistent in time-to-event analysis (HR 0.44, 95% CI 0.20–0.96, p = 0.0397). Overall all-cause mortality incidence was 14.3%. Mortality rates were 23.3% in frail, 7.4% in pre-frail, and 21.4% in non-frail patients (p = 0.043). Frailty status was not independently associated with all-cause mortality in multivariable analysis. Kaplan-Meier analysis demonstrated significantly worse survival among frail patients (p = 0.049). **Conclusion:** Pre-LT frailty was **associated with higher all-cause mortality risk but paradoxically lower post-LT MACE risk.** This association may reflect competing mortality risk or transplant candidacy selection bias. Differences in baseline metabolic risk factors, including diabetes and MASLD prevalence across frailty groups, may have also contributed to this paradoxical association. Limited sample size and low cardiovascular event rates limit statistical power. Overall, while frailty shows associations with post-transplant mortality risk, frailty alone may not be a reliable predictor of post-transplant cardiovascular risk and warrants further evaluation in larger cohorts.

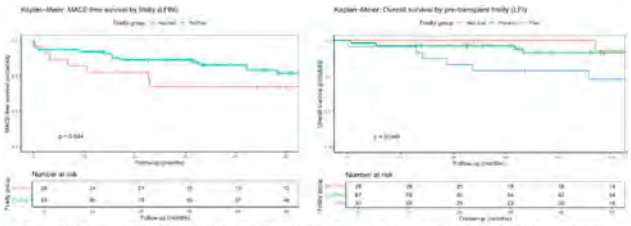


Figure 1: Kaplan Meier survival curves demonstrating worse MACE-free survival among non-frail patients compared to pre-frail/frail patients (p = 0.034) and worse all-cause mortality in frail patients compared to pre-frail or non-frail patients (p = 0.049).

Disclosures: Isra Taha:Nothing to Disclose, Yanqing Lyu:Nothing to Disclose, Sneha Manikandan:Nothing to Disclose, Barbara Okeke:Nothing to Disclose, Kelly Fan: Nothing to Disclose, Spencer Hobbs:Nothing to Disclose, Ava Delonais-Parker:Nothing to Disclose, Sahita Gandra:Nothing to Disclose, Mina Benjamin:Nothing to Disclose, Uchenna Agbim:Nothing to Disclose.

4505 | FRAILTY IS ASSOCIATED WITH INCREASED HEPATIC DECOMPENSATION AND ADVERSE WAITLIST OUTCOMES IN LIVER TRANSPLANT CANDIDATES

Lily Johnsky[1] Amanda Van Jacobs[1] Quyen Diep[1] Sarah Peterson[1], [1]Rush University Medical Center

Background: The Liver Frailty Index (LFI) is a validated frailty tool developed for patients with cirrhosis that objectively quantifies physiologic reserve. A score ≥4.5 has been associated with increased waitlist mortality and adverse post-transplant outcomes. Although multicenter studies reinforced the prognostic value of the LFI, many included patients from the original University of California San Francisco (UCSF) FraILT cohort. The aim of this study was to independently evaluate the predictive value of the LFI in an urban setting outside of the FraILT cohort. Notably, the majority of our cohort had alcohol-associated liver disease (AUD) (45%) and metabolic dysfunction-associated steatotic liver disease (MASLD) (25%), two populations at higher risk for malnutrition and frailty. **Methods:** A retrospective cohort study of adult patients undergoing liver transplant evaluation at a single tertiary care center from January 2020-August 2024 was conducted. Frailty assessment was completed at the patient's initial outpatient transplant evaluation appointment by a registered dietitian. Patients with an LFI ≥4.5 were classified as frail. Demographic characteristics, disease severity, cirrhosis complications, and waitlist outcomes were compared between frail and non-frail patients. **Results:** A total of 428 patients were included, of whom 164 (38.3%) met criteria for frailty. Frail patients were older, more likely to be female, and more likely to have diabetes mellitus. Frail patients had significantly higher MELD scores compared with non-frail patients (18 vs 15, p < 0.001). Frailty was associated with higher rates of hepatic encephalopathy (65.9% vs 48.5%, p < 0.001), ascites (83.5% vs 64%, p < 0.001), and more frequent paracentesis requirements (p < 0.001). Frail patients also experienced longer hospital length of stay (6.8 vs 4.4 days, p = 0.045), higher waitlist mortality (4.9% vs 1.1%, p = 0.038), and higher rates of delisting due to being too high risk (21% vs 13%) or noncompliance (12% vs 7.4%). Frail patients were less likely to undergo transplantation (30.5% vs 36.4%). No significant differences were observed in BMI category or spontaneous bacterial peritonitis rates. **Conclusion:** Frailty was common at this urban transplant center and demonstrated similar predictive utility to prior FraILT studies, including increased risk of waitlist mortality. Additionally, frail patients were more likely to experience hepatic decompensation, particularly hepatic encephalopathy, potentially reflecting the impact of malnutrition and sarcopenia commonly seen in patients with AUD and MASLD. These findings further validate the prognostic utility of the LFI when evaluating patients for liver transplant and suggest that frailty assessment may provide prognostic value beyond MELD 3.0, helping guide early intervention and risk stratification.

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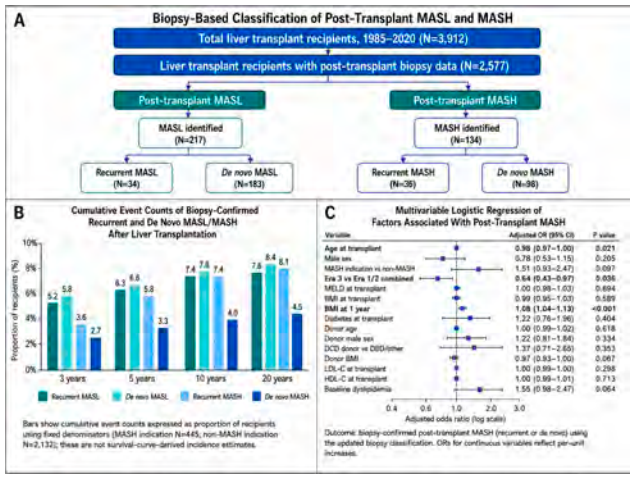
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Disclosures: Lily Johnsky:Nothing to Disclose, Amanda Van Jacobs:Nothing to Disclose, Quyen Diep:Nothing to Disclose, Sarah Peterson:Nothing to Disclose.

4506 | INCIDENCE, TIMING, AND PREDICTORS OF RECURRENT AND DE NOVO MASLD AFTER LIVER TRANSPLANTATION: A 35-YEAR MULTICENTER HISTOLOGY-BASED COHORT STUDY

Sobia Laique[1] Muhammad Ahmad Nadeem[1] Puneet Bansal[1] Chase Wehrle[1] Jacob Sweeney[1] Mohamed El Hag[1] Xuefeng Zhang[1] Pablo Bejarano[2] Rhea Abraham[1] Awwab Hammad[1] Erlind Allkushi[1] Mazhar Khalil[1] Jaekeun Kim[1] Alejandro Pita[1] Federico Aucejo[1] Shilpa Junna[1] Masato Fujiki[1] Andrea Schlegel[1] Koji Hashimoto[1] Daniela Allende[1] Jamak Modaresi Esfeh[3], [1]Cleveland Clinic, [2]Cleveland Clinic, Florida, [3]Cleveland Clinic Foundation

Background: MASLD is the fastest-growing indication for liver transplantation (LT), yet the natural history of post-transplant MASLD remains poorly defined. Prior studies have been limited by small sample sizes, heterogeneous diagnostic criteria, and inconsistent distinction between recurrent and de novo disease. We aimed to characterize biopsy-confirmed post-transplant MASLD in a large LT cohort. **Methods:** We evaluated 2,577 adult LT recipients with clinically indicated post-transplant liver biopsy data from 3,912 patients transplanted at Cleveland Clinic Ohio and Florida between 1985 and 2020. All biopsies underwent centralized histologic re-review using NASH-CRN criteria. Post-transplant MASLD was classified as recurrent (MASH transplant indication; n = 445) or de novo (non-MASH transplant indication; n = 2,132). Transplant eras were defined as Era 1 (1985–1999), Era 2 (2000–2009), and Era 3 (2010–2020). Cumulative event rates were assessed at 3, 5, 10, and 20 years post-transplant using fixed denominators. Multivariable logistic regression incorporating recipient, donor, and metabolic covariates, with multiple imputation for missing data, was used to identify independent predictors of post-transplant MASH. **Results:** Post-transplant MASL occurred in 217 recipients (34 recurrent [7.6%], 183 de novo [8.6%]); MASH occurred in 134 (36 recurrent [8.1%], 98 de novo [4.6%]). De novo disease accounted for most MASL (84.3%) and MASH (73.1%) cases. Median time to disease was early: 1.42 and 1.01 years for recurrent and de novo MASL, and 3.43 and 1.81 years for recurrent and de novo MASH, respectively. Cumulative rates are shown in Figure, Panel B; notably, the majority of events accrued within the first 5 years, with 20-year rates reaching 8.4% and 7.6% for de novo and recurrent MASL, and 4.5% and 8.1% for de novo and recurrent MASH. On multivariable analysis (Figure, Panel C), BMI at 1 year post-LT was independently associated with MASH (aOR 1.08/kg/m²; 95% CI 1.04–1.13; P < 0.001), whereas BMI at transplant was not (P = 0.589). Younger age at transplant (aOR 0.98/year; P = 0.021) and Era 3 transplantation (aOR 0.64 vs Era 1/2; P = 0.036) were also significant. **Conclusion:** In this largest histology-based post-transplant MASLD cohort, MASL and MASH were common, developed early, and predominantly occurred de novo, underscoring that all LT recipients require metabolic surveillance regardless of indication. BMI at 1 year, not at transplant, was the key modifiable predictor, identifying a critical early window for weight-focused interventions. Lower Era 3 MASH odds may reflect evolving immunosuppression practices, while younger recipients warrant intensified monitoring given their longer at-risk period. These findings support integrating structured metabolic protocols into post-transplant care.



Disclosures: Sobia Laique:Madrigal Pharmaceuticals Inc: Advisor, Madrigal Pharmaceutical: Consultant, Novo Nordisk: MASH Curriculum Steering Committee, MUHAMMAD AHMAD NADEEM:Nothing to Disclose, Puneet Bansal:Nothing to Disclose, Chase Wehrle:Nothing to Disclose, Jacob Sweeney:Nothing to Disclose, Mohamed El Hag:Nothing to Disclose, Xuefeng Zhang:Nothing to Disclose, Pablo Bejarano:Nothing to Disclose, Rhea Abraham:Nothing to Disclose, Awwab Hammad:Nothing to Disclose, Erlind Allkushi:Nothing to Disclose, Mazhar Khalil:Nothing to Disclose, Jaekeun Kim:Nothing to Disclose, Alejandro Pita:Nothing to Disclose, Federico Aucejo:Nothing to Disclose, Shilpa Junna:Nothing to Disclose, Masato Fujiki:Nothing to Disclose, Andrea Schlegel:Nothing to Disclose, Koji Hashimoto:OrganOx: Advisor, Daniela Allende: Gilead: Advisory board member, Elsevier: Royalties

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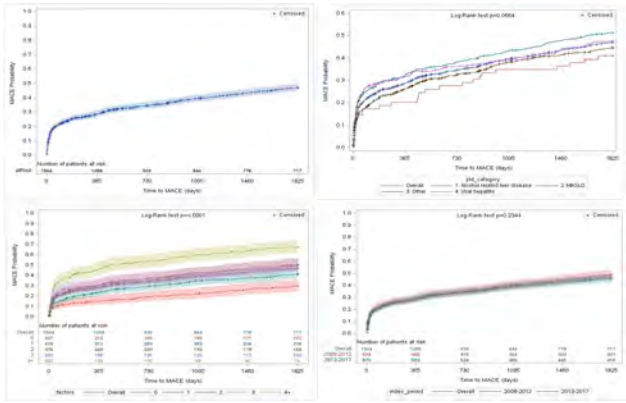
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on book, Educational Symposia: Speaking and Teaching, Jamak Modaresi Esfeh:Nothing to Disclose.

4507 | INCIDENCE, DISTRIBUTION, AND DETERMINANTS OF MAJOR ADVERSE CARDIOVASCULAR EVENTS FOLLOWING LIVER TRANSPLANTATION IN A CONTEMPORARY POPULATION-BASED COHORT

Mohammad Qasim Khan[1] Juan Pablo Arab[2] Melody Lam[3] Brooke Carter[3] Kristin Clemens[1], [1]University of Western Ontario, [2]Virginia Commonwealth University, [3]ICES Western, London Health Sciences Centre Research Institute

Background: Cardiovascular disease is a major contributor to mortality following liver transplantation (LT), yet contemporary population-based data evaluating major adverse cardiovascular events (MACE) beyond the early post-LT period remain limited. Considering the changing epidemiological landscape in liver transplantation, with older recepients and increasing burden of steatotic liver disease, we evaluated the incidence, distribution, and determinants of MACE among adult liver transplant recipients (LTRs) across Ontario, Canada. **Methods:** We conducted a population-based, retrospective cohort study using linked healthcare administrative databases housed at ICES. Adult patients undergoing primary liver-only transplantation between January 1, 2008 and December 31, 2017 were included and followed for up to 5 years post-LT. The primary outcome was MACE, defined as cardiovascular death or hospitalization for myocardial infarction (MI), atrial fibrillation (AF), heart failure (HF), revascularization, pulmonary embolism (PE), cardiac arrest, transient ischemic attack (TIA), or stroke. Kaplan-Meier analyses estimated cumulative incidence and event rates, while Cox proportional hazards models identified predictors of post-LT MACE. Era-based analyses compared pre-direct acting antiviral (DAA) (2008–2012) and post-DAA (2013–2017) periods. **Results:** Among 1,564 LTRs, median age was 57 years (IQR 50–62), 69.4% were male, and MASLD represented the most common liver disease (63.5%). Over a median follow-up of 4 years, 44.9% developed MACE (incidence rate: 15.3 events per 100 person-years). AF was the most common MACE subtype (5.7 events per 100 person-years). Development of MACE was associated with significantly reduced survival post-LT (log-rank $p < 0.001$). Although overall MACE incidence did not differ between pre- and post-DAA eras (16.1 vs. 14.6 events per 100 person-years; $p = 0.207$), the phenotype evolved, with lower MI rates (7.7 vs. 3.8 events per 100 person-years; $p < 0.0001$) and higher cerebrovascular event rates (1.7 vs. 2.5 events per 100 person-years; $p = 0.042$) in the contemporary era. A strong graded relationship was observed between cumulative baseline cardiovascular risk burden and MACE incidence (log-rank $p < 0.0001$). In adjusted analyses, older age (aHR 1.02, 95%CI 1.01–1.03), AF (aHR 1.69, 95%CI 1.34–2.12), HF (aHR 2.41, 95%CI 1.86–3.11), and prior cerebrovascular accident (aHR 1.44, 95%CI 1.05–1.97) independently predicted post-LT MACE. **Conclusion:** Nearly half of LTRs developed MACE within 5 years post-LT, highlighting a worrisome long-term cardiovascular burden in the contemporary era. MACE risk was strongly associated with pre-existing cardiovascular disease and cumulative baseline risk rather than isolated atherosclerotic risk factors alone, underscoring the need for improved risk stratification and integrated cardiometabolic care pathways post-LT.



Disclosures: Mohammad Qasim Khan:Nothing to Disclose, Juan Pablo Arab:Nothing to Disclose, Melody Lam:Nothing to Disclose, Brooke Carter:Nothing to Disclose, Kristin Clemens:DSM: Grant/Research Support, Celltrion: Grant/Research Support.

4508 | LIVER TRANSPLANTATION FOR STEATOTIC LIVER DISEASE IN THE UNITED STATES: TRENDS AND OUTCOMES FROM 2000–2025

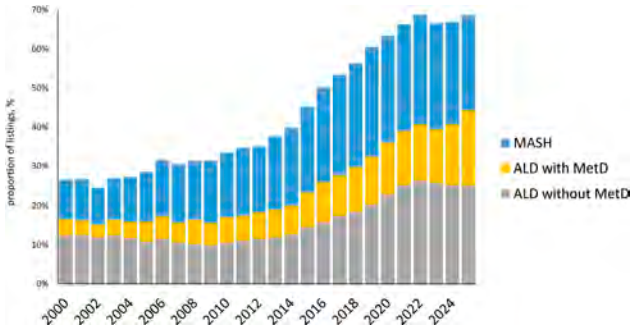
Zobair Younossi[1] Giacomo Germani[1] Adrián Gadano[1] Patrizia Burra[1] Linda Henry[1] Khalid AlNaamani[1] Waleed Al-hazzani[2] Shadan AlMuhaidib[2] Basmah Khoja[3] Saleh Alqahtani[4] Maria Stepanova[1], [1]The Global NASH/MASH Council, [2]Research and Innovation Institute, Ministry of Defense Health Services, Riyadh, Saudi Arabia, [3]King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia,

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Background: Steatotic liver disease (SLD) is the most common indication for liver transplantation (LT) in the United States. Metabolic-associated steatotic liver disease (MASH) cirrhosis is inherently accompanied by metabolic dysfunction (MetD), whereas alcohol-related liver disease (ALD) may present without (ALD-1) or with (ALD-2) overt metabolic dysfunction including diabetes and/or obesity. We assessed temporal trends and waitlist and post-transplant outcomes in SLD patients stratified by metabolic status. **Methods:** Adult LT candidates and recipients with SLD-related cirrhosis as primary listing diagnosis (2000–2025) were identified from the Scientific Registry of Transplant Recipients (SRTR). SLD subtypes included MASH, ALD-1 (ALD without overt metabolic dysfunction), and ALD-2 (ALD with overt metabolic dysfunction). **Results:** Among 274,868 LT candidates with chronic liver disease, SLD cirrhosis increased substantially from 27% (2000) to 69% (2025). MASH rose from 10% (2000) to peak at 28% (2019–2022), declining to 24% (2025). ALD-1 increased from 12% to 27% (2022), declining to 25% (2025). ALD-2 demonstrated the most pronounced increase: 4% (2000) → 9% (2015) → 13% (2020) → 19% (2025). Among recent candidates (2021–2025), MASH patients were significantly older (60 ± 9 years) compared to ALD-1 (52 ± 11 years) and ALD-2 (54 ± 10 years). MELD scores were higher in both ALD subtypes (22.5 ± 10.1 and 22.7 ± 9.9) than MASH (20.3 ± 9.0). Hepatocellular carcinoma (HCC) prevalence was highest in MASH (15.5%) versus ALD-1 (5.4%) and ALD-2 (12.5%).Transplant rates were similar across groups (70%). Cumulative waitlist mortality was highest in MASH (13.5%) compared to ALD-1 (8.4%) and ALD-2 (9.9%). ALD-1 demonstrated the highest clinical improvement rate (6.6% vs. 2.5% MASH, 3.9% ALD-2).In multivariable competing-risk analysis, ALD-2 (ALD-Met) was not independently associated with increased waitlist mortality versus ALD-1 (aHR = 1.03 [0.94–1.13]), whereas MASH demonstrated significantly higher risk (aHR = 1.21 [1.11–1.33]). Five-year post-transplant mortality: MASH 19.9%, ALD-1 15.2% and ALD-2 17.6%. After adjustment for other predictors, neither SLD etiology (MASH or ALD-2 vs. ALD-1) was independently associated with post-transplant mortality (all $p > 0.05$). Older age, poorer pre-LT functional status, public insurance, pre-LT diabetes, more advanced liver disease (higher MELD, decompensation, life support, HCC) were independently associated with higher waitlist and post-LT mortality in SLD. **Conclusion:** ALD with MetD has become a major indication for liver transplantation in the U.S. Despite greater metabolic burden, these patients demonstrated waitlist and post-transplant mortality comparable to ALD without MetD and MASH.



Disclosures: Zobair Younossi:Zobair M. Younossi is a consultant or has received research: Consultant, madrigal: Grant/Research Support, Siemens: Research funding, GSK: Consultant, BI: Consultant, Sanofi: Research funding, Giacomo Germani:Nothing to Disclose, Adrián Gadano:Nothing to Disclose, Patrizia Burra:Nothing to Disclose, Linda Henry:Nothing to Disclose, Khalid AlNaamani:Nothing to Disclose, Waleed Al-hazzani:Nothing to Disclose, Shadan AlMuhaidib:Nothing to Disclose, Basmah Khoja:Nothing to Disclose, Saleh Alqahtani:Nothing to Disclose, Maria Stepanova:Nothing to Disclose

4509 | HEPATIC ARTERY DISSECTION DURING ENDOVASCULAR TREATMENT OF HEPATIC ARTERY STENOSIS AFTER LIVER TRANSPLANTATION

Ricardo Paz-Fumagalli[1] Miguel Cadenas[1] Ali Montazeri[1] Kristopher Croome[2], [1]Mayo Clinic, [2]Mayo Clinic Florida

Background: Hepatic artery stenosis (HAS) following orthotopic liver transplantation is a risk factor for hepatic artery thrombosis, graft ischemia, biliary injury, and graft loss. Endovascular therapy is the first-line treatment but can be complicated by arterial dissection. Hepatic artery dissection (HAD) remains a poorly characterized procedural complication. This study evaluates the incidence, and outcomes of HAD during endovascular treatment of HAS. **Methods:** A retrospective review was performed of 4569 liver transplants conducted between January 1999 and April 2026 that had endovascular intervention for hepatic artery stenosis. Data collected included imaging findings (CT scan, MRI, color Doppler with

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spectral analysis), alkaline phosphatase levels, vessel tortuosity, timing of intervention relative to transplantation (< 60 vs ≥ 60 days), main versus branch hepatic artery involvement, flow-limiting versus non-flow-limiting dissection, hepatic artery thrombosis, and biliary complications. Outcomes included technical success, primary patency, assisted primary patency, secondary patency, graft survival, and retransplantation. **Results:** HAS was treated in 175/4569 grafts (3.8%). HAD occurred in 23/175 (13.1%). Features common in HAD included tortuous vessels, early post-transplant interventions, and branch artery stenoses. Flow-limiting dissections demonstrated higher rates of thrombosis, reintervention, and biliary injury than non-flow-limiting dissections. Dissection involving hepatic artery branches correlated with increased risk of arterial occlusion. Non-flow-limiting dissections frequently remained clinically stable and were successfully managed conservatively. One patient with severe biliary injury after arterial dissection received retransplantation (1/23, 4.3 %). At 6, 12 and 36 months, the primary patency rates were 61, 47, and 47%, primary-assisted 77, 73, and 73%, and secondary patency rates were 77, 73 and 73%. Biliary injury occurred in 2 patients who suffered flow limiting dissection, one required retransplantation and the other chronic biliary drain management. Despite having variable degrees of arterial flow alteration 21/23 did not develop biliary injury, often because of development of hilar and capsular hepatic artery collaterals. **Conclusion:** HAD during endovascular treatment of HAS is uncommon and can lead to biliary injury and graft loss. Tortuosity, branch vessel intervention, and early post-transplant timing appear to increase procedural risk. Non-flow-limiting dissections are well tolerated and can heal completely. Arterial occlusion from HAD is associated with inferior patency and increased graft-related morbidity. Angioplasty and stent placement, repeated as needed, can achieve long-term arterial patency in about 70% of grafts despite procedure-related arterial dissection.

Disclosures: Ricardo Paz-Fumagalli:Nothing to Disclose, Miguel Cadenas:Nothing to Disclose, Ali Montazeri:Nothing to Disclose, Kristopher Croome:Nothing to Disclose.

4510 | A SURVEY OF TRANSPLANT CENTER EVALUATION AND MANAGEMENT OF PATENT FORAMEN OVALE

Puja Brahmbhatt[1] Burcin Ekser[2] Yucel Yankol[1] Scott Cotler[1] Eric Kallwitz[1], [1]Loyola University Health System, [2]Loyola University Chicago

Background: A patent foramen ovale (PFO) presents a potential risk for paradoxical embolism and stroke during liver transplantation. Retrospective studies have not shown a definitive benefit to prophylactic PFO closure prior to liver transplant. The theoretic risk of paradoxical embolism must be balanced against the potential risk of delaying liver transplant for PFO closure. There are no current guidelines or consensus for managing PFOs in liver transplant. The purpose of this study was to survey management of PFOs at US liver transplant centers. Methods: A survey was sent out to medical and surgical directors **Methods:** A survey was sent out to medical and surgical directors at US transplant centers to query management of PFOs. The survey contained questions regarding evaluation, diagnosis and management of PFOs in liver transplant candidates. There were additional questions regarding any potential observed complications. One response was included per center **Results:** Twenty eight centers responded with 20 centers reporting a volume greater than 100 liver transplants per year. All centers use an echocardiogram with bubble study during evaluation. Most centers use a threshold number of cardiac cycles to distinguish intra-cardiac versus intrapulmonary shunting (21 centers used cardiac cycles, 6 did not). Only 5 of the 28 centers routinely perform a transesophageal echocardiogram (TEE) for a positive bubble study. However, most centers (n = 20) routinely have anesthesia use TEE during liver transplant. Seventeen centers selectively close PFOs, while 11 centers report not closing any PFOs. For centers that selectively close PFOs, a history of prior stroke was the most common indication for closure. When a PFO is discovered, 15 of 28 centers reported rarely closing PFOs and 3 of 28 centers reported never closing PFOs. Three of 28 centers reported closing most PFOs and 2 of 28 centers reported closing all. If a PFO is closed, most centers immediately active for transplant (n = 17), while some centers wait one month (n = 9). Seven centers reported at least one patient complication attributed to a PFO, all of which consisted of stroke. Two centers reported a complication attributed to the PFO closure. Twenty-two centers thought that PFO management should be addressed formally in liver transplant guidelines. **Conclusion:** A majority of transplant centers selectively close PFOs, particularly in patients with a history of stroke. Overall, relatively few adverse events attributed to a PFO were reported. Society recommendations would be useful to provide a more uniform approach to PFOs. Finally, multi-center prospective data would be helpful in developing guidance.

Disclosures: Puja Brahmbhatt:Nothing to Disclose, Burcin Ekser:Nothing to Disclose, Yucel Yankol:Nothing to Disclose, Scott Cotler:Nothing to Disclose, Eric Kallwitz:Nothing to Disclose.

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4511 | COGNITIVE IMPAIRMENT AND ALCOHOL ASSOCIATED LIVER DISEASE INDEPENDENTLY PREDICT LOWER SCORES ON THE LIVER TRANSPLANT KNOWLEDGE QUESTIONNAIRE: RESULTS FROM LIVCOG, A PROSPECTIVE COHORT STUDY

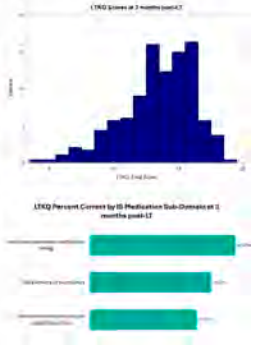
Abbie Jin[1] Douglas Schaubel[1] Ann Tierney[1] Nianfu Song[1] Serena Sohmen[1] Anna Gurian[2] Julia Benavente[3] Sumeet Asrani[4] Michael Wolf[3] Marina Serper[5], [1]University of Pennsylvania Perelman School of Medicine, [2]University of Colorado Anschutz School of Medicine, [3]Northwestern University Feinberg School of Medicine, [4]Liver Consultants of Texas, [5]University of Pennsylvania Health System

Background: Cognitive impairment is prevalent among liver transplant recipients (LTRs) and may negatively affect self-management skills and health behaviors following liver transplantation (LT). Our study aim was to evaluate associations between post-LT cognition and transplant-related knowledge using the novel Liver Transplant Knowledge Questionnaire (LTKQ). **Methods:** LivCog is an NIDDK-funded prospective, multicenter cohort study which longitudinally follows LTRs to study cognition, health behaviors, and health outcomes. At 1-, 3-, 12-, and 24-months post-LT, cognition was assessed using the Animal Naming Test (ANT) and Montreal Cognitive Assessment (MoCA). Transplant knowledge was assessed using the LTKQ, a performance-based instrument measuring knowledge and skills required for post-LT self-management that includes immunosuppression timing, drug interactions, medication safety, and health behaviors. The LTKQ items which pertained to immunosuppression (IS) medication knowledge were categorized into three subdomains: medication timing, side effects of tacrolimus, and medications that may cause drug interactions. Using the GEE version of linear regression, we fitted (separate) models for total LTKQ score and each of the afore-listed LTKQ subdomains. **Results:** Among 447 LTRs, the median age is 56 (IQR 48-64); 82% are white; 63% are male; 42% have < = high school education. At 3-months post-LT, 186 participants (50.7%) had a MoCA score < 26 consistent with mild cognitive impairment; 32 (8.7%) had ANT < 15. The median LTKQ score was 14/19 (74% correct). As shown in **Figure 1**, participants scored highest on the IS medication timing subdomain (84.6%), followed by tacrolimus side effects (70.1%) and lowest on drug interactions (61.9%).Adjusted for demographic and baseline clinical characteristics, longer time post-LT ($\beta = 0.04$; $p < 0.001$) was associated with higher LTKQ scores. Older age ($\beta = -0.10$; $p = 0.025$), education level at high school or less ($\beta = -1.23$; $p < 0.001$), and alcohol-associated liver disease ($\beta = -0.62$; $p = 0.038$) were associated with significantly lower LTKQ scores, as were low MoCA ($\beta = -0.69$; $p = 0.007$) and ANT ($\beta = -0.86$; $p = 0.048$) scores. Pre-LT hepatic encephalopathy ($\beta = -0.21$) was associated with lower LTKQ only in univariable analysis.In adjusted models for IS medication subdomains (medication timing, tacrolimus side effects, and drug interactions), lower scores were independently associated with worse cognitive performance on the MoCA ($\beta = -0.03$, $\beta = -0.01$, and $\beta = -0.04$, respectively). Medication timing and drug interactions scores were also independently associated with lower ANT scores ($\beta = -0.04$ and $\beta = -0.05$). **Conclusion:** LTRs demonstrate gaps in post-LT knowledge that are significantly associated with cognitive impairment, age, and alcohol-associated liver disease. The LTKQ questionnaire can help identify knowledge deficits post-LT, tailor interventions, and improve health outcomes.

Figure 1. Predictors of LTKQ Score and Distribution at 3 months post-LT

Table 1. Predictors of Liver Transplant Knowledge Questionnaire (LTKQ) Score: covariate-adjusted

Predictor	β	p value
Month	0.044	<0.001
Age (per 5 yrs)	-0.105	0.025
Female	0.261	0.299
Education: shigh school	-1.226	<0.001
Pre-LT hepatic encephalopathy	-0.206	0.416
Liver disease: Alcohol-related	-0.619	0.038
Liver disease: HCC	1.058	0.006
MoCA <26	-0.600	0.007
ANT <15	-0.857	0.048



Disclosures: Abbie Jin:Nothing to Disclose, Douglas Schaubel:Nothing to Disclose, Ann Tierney:Nothing to Disclose, Nianfu Song:Nothing to Disclose, Serena Sohmen:Nothing to Disclose, Anna Gurian:Nothing to Disclose, Julia Benavente:Nothing to Disclose, Sumeet Asrani:Nothing to Disclose, Michael Wolf: Nothing to Disclose, Marina Serper:Transplant Genomics: Grant/Research Support, Grifols: Grant/ Research Support.

4512 | VALIDATION OF A NATURAL LANGUAGE PROCESSING ALGORITHM FOR IDENTIFYING KERATINOCYTE CARCINOMA IN SOLID ORGAN TRANSPLANT RECIPIENTS

Danelle Antelo[1] Carolina Carvajalino[1] David Goldberg[1] David Kaplan[2] Cindy Delgado[1] Therese Bittermann[3] Catherine Blandon[1], [1]University of Miami, [2]University of Pennsylvania, [3]Royal Brisbane & Women's Hospital

Background: Keratinocyte carcinoma (KC), encompassing squamous cell carcinoma (SCC) and basal cell

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carcinoma (BCC), is the most common malignancy following solid organ transplantation. Administrative coding algorithms for identifying clinical diagnoses have known limitations, underscoring the need for validated approaches using electronic health records. We developed and validated a natural language processing (NLP) algorithm to identify KC in Veterans Health Administration (VHA) transplant recipients. **Methods:** We conducted a cross-sectional study using linked VHA and Organ Procurement and Transplantation Network (OPTN) data including kidney and liver transplant recipients (January 2005–December 2021) with pre- and post-transplant VHA engagement. Potential KC cases required either an ICD-O-3 code or a combination of ICD-9/10 and CPT code (Mohs, destruction, or excision) plus an NLP-confirmed pathology report within 7 days. The NLP algorithm, developed with transplant physicians, dermatologists, and a dermato-pathologist, classified pathology reports as KC-positive based on: (1) KC-related keywords; (2) active diagnosis language; and (3) skin-relevant anatomical site. We evaluated positive predictive value (PPV) via independent review of 100 randomly selected NLP-positive pathology reports, calculating a point estimate and 95% binomial confidence interval. We also reviewed medical charts for 100 patients with KC-related administrative codes who lacked a corresponding NLP-identified pathology report. **Results:** Among 176 reviewed patients, median age at transplant was 62.0 years (IQR 58.0–66.0); 98.3% were male, 86.9% were White, and 42.0% were liver-transplant recipients. Of 100 pathology reports classified as KC-positive by the NLP algorithm, 95 (95%) were validated as true KC diagnoses by human reviewers, yielding a PPV of 95% (95% CI 88.7%–98.4%). The 5 unconfirmed reports reflected patients with a known prior history of KC, suggesting the algorithm captured historical cases. Among patients with KC-related administrative codes but no supporting pathology report or NLP-identified case, KC was confirmed via chart review in 95 of 100 cases (95%). **Conclusion:** A combined administrative code and NLP algorithm demonstrated high accuracy (PPV 95%) for identifying KC among VHA solid organ transplant recipients. Among patients with KC-related administrative codes but no NLP-captured pathology report, KC was confirmed via chart review in 95% of cases, further strengthening confidence in the overall algorithm performance. Given the elevated KC burden in this high-risk population, this validated tool addresses a critical methodological gap and enables future large-scale studies examining risk factors, treatment patterns, and outcomes of post-transplant KC. Accurate identification of KC can inform post-transplant skin cancer surveillance guidelines for transplant recipients.

Disclosures: Danelle Antelo:Nothing to Disclose, Carolina Carvajalino:Nothing to Disclose, David Goldberg:Nothing to Disclose, David Kaplan:AstraZeneca Inc: Grant/Research Support, Roche Genentech: Independent Contractor, Exact Sciences: Grant/Research Support, Glycotest: Grant/Research Support, Exelixis: Advisor, AstraZeneca: Advisor, Gilead: Grant/Research Support, Bausch Healthcare: Grant/Research Support, Mirumn: Grant/Research Support, Bausch: Grant/Research Support, Exact Sciences: Grant/Research Support, AstraZeneca: Grant/Research Support, Mirum: Grant/Research Support, Cindy Delgado:Nothing to Disclose, Therese Bittermann:Nothing to Disclose, Catherine Blandon:Bluebird Bio: Stock - publicly traded company, Intellia Therapeutics: Stock - publicly traded company, Editas Medicine: Stock - publicly traded company.

4513 | POST TRANSPLANT SURVIVAL BY AGE GROUP AND DONOR TYPE (DCD VS DBD) IN DECEASED DONOR LIVER TRANSPLANT OVER THE PAST 5 YEARS: A NATIONAL ANALYSIS

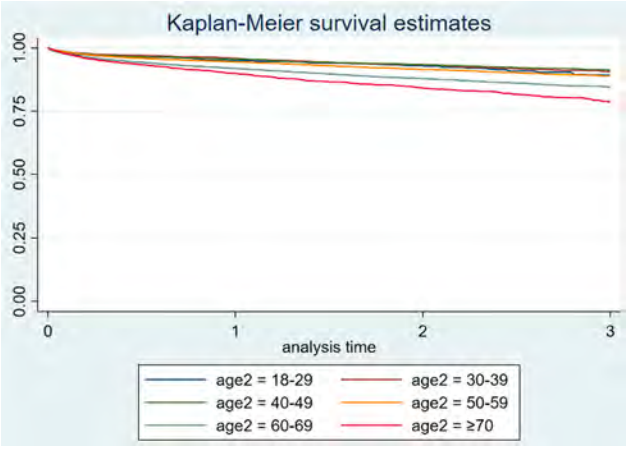
Maria Diaz Soto[1] Behnam Saberi[2] Alan Bonder[1] Sebastian Niezen[1], [1]Beth Israel Deaconess Medical Center, [2]BIDMC Harvard Medical School

Background: Both the proportion of elderly liver transplant recipients as well as the use of DCD grafts (donation after circulatory death) have been increasing over the past decade. In the United States there were 207 liver transplant recipients 70 years or older in 2015 and over 700 in 2025. There is mixed data in terms of survival outcomes for the elderly population . Similarly the use of DCD grafts has significantly increased specially over the last 5 years after the widespread adoption of normothermic machine perfusion (NMP). 11.6% of the total transplants were DCD in 2020 vs 42.7% in 2025. We examined post transplant survival across recipient age groups and compared survival between DCD and DBD donor types. **Methods:** Using the UNOS database we identified adults (³ 18yrs) deceased donor liver transplant recipients from January 2021 to December 2025 (N = 41,346). Simultaneous liver kidney, other multiorgan, living donors, partial liver/split grafts and prior liver transplants were excluded. Recipients were classified into 6 age groups (18-29, 30-39, 40-49, 50-59, 60-69 and ³ 70 years). Patient survival was estimated by Kaplan Meier and compared across age groups with log rank test. Multivariable Cox proportional hazard regression was used to identify independent factors associated with mortality. Candidate variables included age category, race, sex, etiology of disease, dialysis, MELD, donor type, age, BMI. Figures were generated with Claude AI, data

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analysis was done with STATA. **Results:** Among 41,346 recipients there were 3,706 deaths (9%). In the Kaplan Meier curve survival declined with increasing age group (log-rank $\chi^2 = 315.4$, df = 5, $p < 0.001$). The age group effect remained independently significant in the multivariate analysis with higher risk of mortality for age group ³ 70 years HR 2.42 (95% CI 2.12–2.77), age group 60–69 = HR of 1.86 and for age group HR 50–59 = 1.29: all $p < 0.001$. Other Independent predictors of mortality included pre transplant dialysis HR 1.6, black race HR 1.2 $p < 0.001$. 1 year mortality was comparable between DCD and DBD recipients HR 1.04 (0.93–1.16) $p = 0.53$. **Conclusion:** In a contemporary US cohort, increasing recipient age was independently associated with worse post transplant survival with the highest mortality risk for patients ³ 70 years. Despite rapid expansion of DCD grafts use over the past 5 years, 1 year mortality was comparable between the DCD and DBD recipients which can support the continued use of DCDs.



Disclosures: Maria Diaz Soto:Nothing to Disclose, Behnam Saberi:Nothing to Disclose, Alan Bonder: Nothing to Disclose, Sebastian Niezen:Nothing to Disclose.

4514 | METABOLIC BURDEN AND WAITLIST OUTCOMES IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS: A NATIONAL REGISTRY ANALYSIS

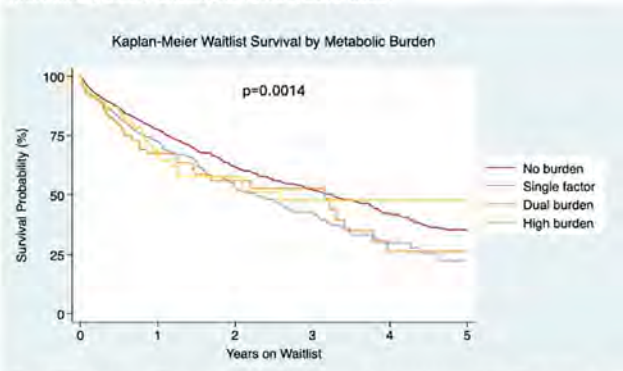
Giuliana Arevalo[1] Ana Marenco-Flores[2] Romelia Barba[3] Victoria Abadi-Ron[2] Natalia Rojas-Amaris[2] Fernando Munguia[2] Alan Bonder[2], [1]University Of Miami Miller School of Medicine, [2]Beth Israel Deaconess Medical center, [3]Texas Tech University

Background: Metabolic comorbidities are increasingly prevalent in patients with primary biliary cholangitis (PBC), yet their combined impact on transplant outcomes remains undefined. We evaluated the effect of a composite metabolic burden score on waitlist and post-transplant survival in PBC using a national registry. **Methods:** We analyzed adults with PBC listed for liver transplantation in the UNOS database (2013–2025). Multi-organ transplants were excluded. A metabolic burden score was constructed: 0 = no diabetes and BMI < 30; 1 = diabetes alone or BMI 30–34.9; 2 = diabetes + BMI 30–34.9; 3 = diabetes + BMI ≥ 35 kg/m². The primary waitlist outcome was a composite of death or removal for clinical deterioration. Kaplan-Meier methods, log-rank tests, and multivariable Cox regression adjusted for age, sex, and MELD were used. Statistical significance was defined as $p < 0.05$. **Results:** Among 4,240 adults with PBC, 60.3% had no metabolic burden, 24.3% had single-factor burden (score 1), 4.0% had dual burden (score 2), and 2.9% had high burden (score 3). Higher metabolic burden was associated with older recipient age ($p = 0.002$), higher MELD ($p = 0.024$), and significant differences in racial/ethnic distribution ($p = 0.007$). A composite waitlist event occurred in 22.1% of patients overall, with rates of 20.9%, 23.4%, 29.8%, and 25.8% across burden groups ($p = 0.019$). Kaplan-Meier analysis demonstrated significantly worse waitlist survival with increasing metabolic burden (log-rank $p = 0.0014$). On multivariable Cox regression adjusted for age, sex, and MELD score, single-factor burden (HR 1.22, 95% CI 1.05–1.43, $p = 0.010$) and dual burden (HR 1.73, 95% CI 1.29–2.30, $p < 0.001$) were independently associated with waitlist mortality. Post-transplant survival analyses demonstrated persistently lower long-term survival among metabolically burdened recipients, with disparities most pronounced among White and Hispanic patients. **Conclusion:** In a contemporary national cohort of PBC patients, a composite metabolic burden score independently predicted waitlist mortality. These findings highlight the growing impact of metabolic dysfunction on liver transplant outcomes in a traditionally non-metabolic indication and support the integration of metabolic risk stratification into PBC listing and management decisions. This composite metabolic burden score represents a hypothesis-generating risk stratification framework and requires prospective validation in independent cohorts.

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Figure 1. Kaplan-Meier Waitlist Survival by Metabolic Burden Score in Patients with Primary Biliary Cholangitis (UNOS, 2013–2025)



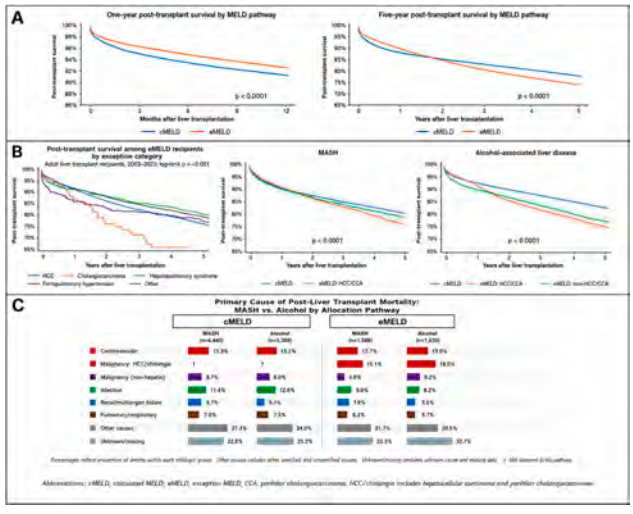
Legend: Kaplan-Meier curves depicting time-to-waitlist death or removal for clinical deterioration, stratified by composite metabolic burden score. Metabolic burden was categorized as: No Burden (no diabetes, BMI <30 kg/m²); Single Factor (diabetes alone OR BMI 30–34.9 kg/m²); Dual Burden (diabetes + BMI 30–34.9 kg/m²); and High Burden (diabetes + BMI ≥35 kg/m²). Log-rank p=0.0014. Analysis restricted to adult patients listed for isolated liver transplantation. Multi-organ transplants excluded.

Disclosures: Giuliana Arevalo:Nothing to Disclose, Ana Marenco-Flores:Nothing to Disclose, Romelia Barba:Nothing to Disclose, Victoria Abadi-Ron:Nothing to Disclose, Natalia Rojas-Amaris:Nothing to Disclose, Fernando Munguia:Nothing to Disclose, Alan Bonder:Nothing to Disclose.

4515 | NOT ALL EXCEPTIONS ARE EQUAL: DISEASE-SPECIFIC CAUSE OF DEATH PATTERNS AFTER MELD-EXCEPTION LIVER TRANSPLANTATION IN MASH AND ALCOHOL-ASSOCIATED LIVER DISEASE

Jonathan Smith[1] Shiv Patel[1] Brian Wentworth[1] Zachary Henry[1] Curtis Argo[1] Nicolas Intagliata[1] Neeral Shah[1] Stephen Caldwell[1] Anya Mezina[1] Yazan Al-Adwan[1] Shawn Pelletier[1] Stephanie Silpe[1] Juan Guerra[1] Mohammad Siddiqui[1] Anh Bui[1], [1]University of Virginia

Background: MELD-based allocation prioritizes waitlist candidates by mortality risk; however, over one-third of liver transplants (LT) in the US now occur through MELD-exception (eMELD) pathways that bypass conventional MELD (cMELD) scoring for select disease states. Whether eMELD allocation translates into durable post-LT survival, and how outcomes differ by exception indication and cause of death, remains poorly characterized. This study addresses this critical gap using the UNOS/SRTR database. **Methods:** This SRTR/UNOS analysis, focused on adults undergoing deceased donor LT between 2003-2023, classified as eMELD or cMELD based on approved exception status. Kaplan-Meier analyses estimated survival by pathway and exception indication. Cause-specific mortality was compared across disease etiology (MASH vs. ALD) by allocation pathway. Multivariable Cox regression evaluated pathway-associated post-LT mortality. **Results:** Among 113,334 adult LT recipients, 37,263 (32.9%) were transplanted via eMELD. eMELD recipients demonstrated superior 1-year survival; however, this advantage attenuated over time **(Panel A)** . Survival trajectories diverged strikingly by exception indication: recipients transplanted for hepatic cancers (HCC or cholangiocarcinoma) experienced profound early post-LT attrition followed by stabilization, while non-oncologic eMELD recipients followed a distinct survival pattern **(Panel B)** . Disease-specific cause-of-death profiling revealed that HCC/cholangiocarcinoma was absent in both cMELD groups yet accounted for 15.1% and 18.0% of deaths in MASH-eMELD and ALD-eMELD respectively **(Panel C)** . Within eMELD, non-hepatic malignancy mortality was lower in MASH (4.0%) than ALD (6.2%), while both remained below their cMELD counterparts (~8%), suggesting reduced de novo oncologic risk in MASH-eMELD. Conversely, renal/multiorgan failure was substantially higher in MASH-cMELD (9.7%) versus ALD-cMELD (5.1%), whereas cardiovascular mortality was consistent across all four groups (~13%). eMELD was independently associated with increased post-LT mortality overall (aHR 1.11, 95% CI 1.08–1.14), in MASH (aHR 1.15), and ALD (aHR 1.16; all $P < 0.001$). **Conclusion:** eMELD pathways confer early survival advantages, but long-term benefit is eroded by hepatic cancer recurrence. Disease-specific profiling reveals divergent oncologic and renal mortality patterns across allocation pathways, supporting individualized post-LT surveillance and reappraisal of exception criteria.



Disclosures: Jonathan Smith:Nothing to Disclose, Shiv Patel:Nothing to Disclose, Brian Wentworth:Ipsen: Consultant, Ipsen: Speaking and Teaching, GSK:

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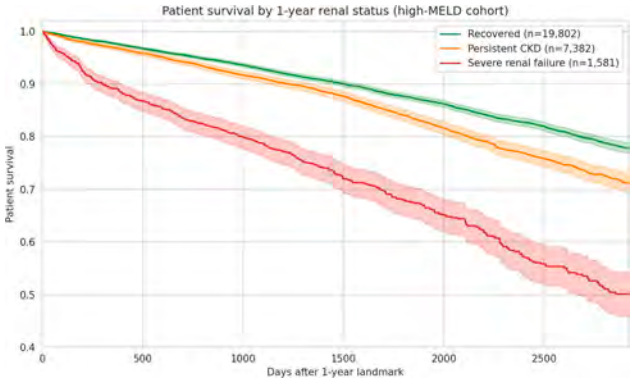
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Consultant, Luna Labs USA: Consultant, Zachary Henry:Nothing to Disclose, Curtis Argo:Nothing to Disclose, Nicolas Intagliata:Nothing to Disclose, Neeral Shah:McGraw Hill Publishing: Royalties or patent beneficiary, UptoDate: Royalties or patent beneficiary, Stephen Caldwell:Nothing to Disclose, Anya Mezina: Nothing to Disclose, Yazan Al-Adwan:Nothing to Disclose, Shawn Pelletier:Nothing to Disclose, Stephanie Silpe:Nothing to Disclose, Juan Guerra:Nothing to Disclose, Mohammad Siddiqui:NovoNordisk: Grant/Research Support, 89Bio: Consultant, Sagimet: DSMB, Anh Bui:Zydus: Consultant.

4516 | MACHINE LEARNING PREDICTION OF RENAL FAILURE AT ONE YEAR AFTER LIVER TRANSPLANTATION IN HIGH-MELD RECIPIENTS USING NATIONAL OPTN/UNOS DATA

Sri Harsha Boppana[1] Subhash Gurappa[2] Sachin Sravan Kumar Komati[2] Gautam Maddineni[3] Raja Chandra Chakinala[4] Venkata Sunkesula[5] Pradeep Yarra[6] Kamran Qureshi[7], [1]Nassau University Medical Center, [2]Florida International University, [3]Creighton university, [4]Guthrie Robert Packer Hospital, [5]Case Western Reserve University, [6]UT Health San Antonio, [7]Saint Louis University

Background: High-MELD liver transplant (LT) recipients are vulnerable to post-LT renal failure, yet national-scale prediction using pre-LT renal trajectory and machine learning remains limited. Many established risk factors for persistent renal failure after LT have been identified. We aimed to identify predictors of severe renal impairment (SRI) at 1 year after LT, compare conventional and machine-learning prediction models, and evaluate machine learning models for the prediction of safety-net renal transplantation (SNRT) after LT. **Methods:** We performed a retrospective OPTN/UNOS STAR cohort study of adult primary single-organ LT recipients transplanted from 2014–2024 with MELD $\geq$25 who survived $\geq$30 days. The primary outcome was SRI at 1 year, defined as creatinine $\geq$2.5 mg/dL using the closest follow-up value within 9–18 months post-LT. Multivariable logistic regression estimated adjusted odds ratios (ORs). Logistic regression, gradient boosting, XGBoost, and neural network models were compared using 5-fold cross-validated area under the receiver operating characteristic curve (AUC) and additionally evaluated for SNRT prediction. Post–1-year mortality was assessed using landmark Cox regression. **Results:** Among 33,864 recipients, median MELD was 33 and median transplant creatinine was 1.4 mg/dL; 2,058 (6.1%) received donation-after-circulatory-death (DCD) grafts. One-year creatinine follow-up was available in 30,904 (91.3%): 21,224 (68.7%) recovered (creatinine $<$1.5 mg/dL), 7,910 (25.6%) had persistent CKD (creatinine 1.5–2.5 mg/dL), and 1,770 (5.7%) had SRI (creatinine $\geq$2.5 mg/dL). DCD was not independently associated with SRI after adjustment (OR 0.84, 95% CI 0.64–1.09; p = 0.19). Independent SRI predictors included Black race vs. White race (OR 1.71, 95% CI 1.45–2.02), male sex (OR 1.52, 95% CI 1.36–1.70), alcohol-related disease vs. HCV (OR 1.30, 95% CI 1.11–1.53), age (OR 1.025/year), cold ischemia time (OR 1.04/hour), pre-LT dialysis days (OR 1.05/day), initial creatinine (OR 1.17/mg/dL), and waitlist dialysis (OR 2.64; all p $\leq$ 0.049). Gradient boosting performed best (AUC 0.771), followed by XGBoost (0.769), logistic regression (0.746), and neural network (0.740). XGBoost identified pre-LT dialysis days as the dominant feature (importance 0.22, $>$3-fold the next feature). One-year renal status strongly predicted mortality: persistent CKD HR 1.22 (95% CI 1.14–1.31) and SRI HR 2.67 (95% CI 2.41–2.96). (Figure 1) **Conclusion:** SRI at 1 year is uncommon but prognostically powerful in high-MELD LT. Pre-LT dialysis burden outperformed donor type as a risk signal. Tree-based machine learning modestly improved discrimination over logistic regression; neural networks added no benefit, supporting interpretable renal-trajectory models for SLK evaluation, post-LT nephroprotection, and SNRT risk stratification.



Disclosures: Sri Harsha Boppana:Nothing to Disclose, Subhash Gurappa:Nothing to Disclose, Sachin Sravan Kumar Komati:Nothing to Disclose, Gautam Maddineni: Nothing to Disclose, Raja Chandra Chakinala:Nothing to Disclose, Venkata Sunkesula:Nothing to Disclose, Pradeep Yarra:Nothing to Disclose, Kamran Qureshi: Nothing to Disclose.

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4517 | RULING OUT CAD: DIAGNOSTIC UTILITY OF CCTA IN LIVER TRANSPLANT CANDIDATES

Lauren Callans[1] Sandeep Sikerwar[2] Jacky Choi[1] Himel Mallick[1] Elizabeth Verna[2] Danielle Brandman[1], [1]Weill Cornell Medicine, [2]Columbia University Medical Center

Background: Major Adverse Cardiac Events (MACE) are a significant cause of post-liver transplant (LT) morbidity, underscoring the need for preoperative cardiac risk stratification. Coronary computed tomography angiography (cCTA) has emerged as a noninvasive alternative to coronary angiography in this setting, yet its diagnostic performance and prognostic value in LT candidates remain undefined. This study evaluated 1) the diagnostic performance of cCTA in detecting coronary artery disease (CAD) and 2) the association between CAD identified on cCTA and post-LT MACE. **Methods:** Adult patients who underwent LT evaluation at Weill Cornell and Columbia University (2021-2024) were included. cCTA findings were categorized as no CAD, non-obstructive CAD, or obstructive CAD, and dichotomized (any CAD vs. none) for diagnostic performance analyses. Sensitivity, specificity, Cohen's kappa, and AUC were calculated, using left heart catheterization (LHC) as the reference standard. MACE events were classified as a composite of acute coronary syndrome, new heart failure, tachyarrhythmia, cardiac arrest, cardiac death, and revascularization. MACE-free survival was estimated using Kaplan-Meier with log-rank tests, and hazard ratios were obtained from univariate unadjusted Cox proportional hazards regression. **Results:** Of 548 patients evaluated for LT, 133 (24%) underwent cCTA; these patients were older and had higher rates of diabetes, hypertension, hyperlipidemia, and smoking history compared with patients who underwent alternative imaging modalities ($p < 0.01$ for all comparisons). On cCTA, 60% of patients had non-obstructive CAD, 21% had obstructive CAD, and 19% showed no CAD.Among 42 patients who underwent both cCTA and LHC, cCTA demonstrated 100% sensitivity for detecting both any CAD and obstructive CAD, with specificity of 40 and 60%, respectively. Cohen's kappa demonstrated moderate agreement between cCTA and LHC, with the strongest agreement for identifying any CAD (κ = 0.54), and ROC analysis demonstrated good discriminative ability for obstructive CAD (AUC 0.80, 95% CI 0.71-0.89) (Figure 1).Among 80 patients with cCTA who underwent LT, 14 MACE occurred. Post-LT MACE-free survival did not differ across CAD categories, and no clear predictive relationship between cCTA findings and MACE was identified. **Conclusion:** cCTA demonstrated excellent sensitivity for detecting CAD. However, the modest specificity of cCTA may have resulted in overestimation of obstructive CAD, and cCTA findings did not predict post-LT MACE, likely reflecting limited event rates and false-positive disease classification. These findings support the utility of cCTA for ruling out obstructive CAD in LT candidates, potentially reducing the need for invasive angiography among patients with no or non-obstructive CAD on cCTA. Larger prospective studies are needed to clarify the role of cCTA in post-LT cardiac outcomes.

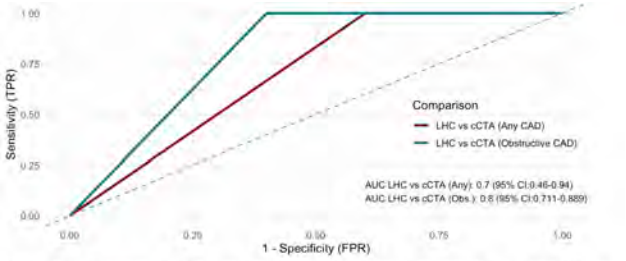


Figure 1. ROC curves for cCTA in detecting any CAD and obstructive CAD, with LHC as the reference gold standard.

Disclosures: Lauren Callans:Nothing to Disclose, Sandeep Sikerwar:Nothing to Disclose, Jacky Choi: Nothing to Disclose, Himel Mallick:Nothing to Disclose, Elizabeth Verna:Nothing to Disclose, Danielle Brandman:Novo Nordisk: Consultant, Madrigal: Consultant.

4518 | IMPACT OF PRE-TRANSPLANT PORTAL VEIN THROMBOSIS ON LIVER TRANSPLANTATION OUTCOMES: A RETROSPECTIVE COHORT STUDY FROM A TERTIARY CARE CENTER IN MEXICO CITY

Paola Cáceres-Moreno[1] Sergio Escalante Gutiérrez[1] Berenice Monserrat Román Calleja[1] Nayelli Cointa Flores García[1] José González-Regueiro[1], [1]Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán"

Background: Portal vein thrombosis (PVT) affects up to 26% of candidates awaiting liver transplantation (LT). Extensive PVT was considered a contraindication for LT and nowadays remains as a major technical challenge for LT, contributing to increased morbidity and mortality despite surgical advancements. We aimed to evaluate the impact of pre-transplant PVT on clinical outcomes during and after LT. **Methods:** A retrospective cohort study was conducted at the Instituto de Nutrición y Ciencias Médicas "Salvador Zubirán" in Mexico City. We included all adult LT recipients from 2018 to 2024. Patients were stratified by presence or absence of pre-LT PVT diagnosis on imaging studies. Data was recorded from electronic medical records. Perioperative

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and postoperative clinical outcomes were compared between both groups. Normality was assessed using Kolmogorov-Smirnov test. Continuous variables were compared using Student's t test or Mann-Whitney U test, and categorical variables using Chi-square or Fisher's exact test. Multivariable logistic regression was performed to identify independent predictors of vascular complications. **Results:** A total of 275 patients were analyzed and included 222 patients (80.72%) without PVT and 53 patients (19.28%) with PVT who underwent LT. There were no significant differences between groups regarding demographic characteristics, LT indication, comorbidities, cirrhosis etiology and severity of liver disease. Perioperatively clinical outcomes: PVT was associated with significant higher anhepatic time (61 vs. 56 min; p = 0.033), intraoperative bleeding (3500 vs. 2000 mL; p < 0.001), increased blood units requirements (5 vs. 3 units; p < 0.001), and peak lactate value (5.9 vs 4.9 mmol/L; p = 0.018). Postoperatively clinical outcomes: PVT was associated with longer hospital stay (12 vs. 8 days; p = 0.002), and more frequent vascular complications (17% vs 9.5%; p = 0.039). Mortality (11.8% vs. 12.2%; p = 0.886) was not significantly different between groups. Multivariate analysis identified pretransplant PVT as an independent predictor factor of postoperative vascular complications (OR 2.65; CI 95% 1.07-6.55; p = 0.035). **Conclusion:** Pre-transplant PVT significantly increases perioperative blood loss and surgical complexity and is an independent predictor factor for postoperative vascular complications. Despite this, long-term patient survival remains comparable to recipients without PVT, supporting the feasibility of LT for this population in specialized centers.

Table 1. Perioperative and postoperative clinical outcomes of liver transplantation stratified by presence or absence or portal vein thrombosis.

Table 1A. Perioperative clinical outcomes of liver transplantation stratified by presence or absence of portal vein thrombosis.

	Total (n=275)	PVT (n=53)	Non-PVT (n=222)	P Value
Surgical time (min)	386 (330-450)	405 (349-480)	385 (327-439)	0.050
Cold ischemia time (min)	417 (351-505)	389 (356-540)	419 (349-499)	0.749
Warm ischemia time (min)	50 (38-57)	50 (41-58)	49 (38-56)	0.636
Anhepatic time (min)	57 (47-64)	61 (53-69)	56 (46-63)	**0.033**
Bleeding (mL)	2000 (1275-3350)	3500 (2000-4750)	2000 (1200-3000)	**<0.001**
Red blood cells (units)	3 (1-5)	5 (3-7)	3 (1-4)	**<0.001**
Peak norepinephrine dose (mcg/Kg/min)	0.40 (0.25-0.70)	0.43 (0.25-0.70)	0.40 (0.25-0.70)	0.680
Peak lactate (mmol/L)	5.0 (3.5-6.4)	5.9 (4.4-7.7)	4.9 (3.4-6.2)	**0.018**

Table 1B. Postoperative clinical outcomes of liver transplantation stratified by presence or absence of portal vein thrombosis.

	Total (n=275)	PVT (n=53)	Non-PVT (n=222)	P Value
Length of stay (days)	9 (7-14)	12 (8-17)	8 (7-12)	**0.002**
Length of ICU stay (days)	3 (2-4)	3 (2-4)	2 (2-4)	0.291
Vascular complications	30 (10.9)	9 (17.0)	21 (9.5)	**0.039**
Biliary complications	37 (13.5)	9 (17.0)	28 (12.7)	0.381
Immune-mediated complications	55 (20.1)	9 (17.0)	46 (20.9)	0.574
Retrasplant	3 (1.1)	0	3 (1.1)	0.395
Mortality	33 (12.4)	6 (11.8)	27 (12.2)	0.886

Table 1C. Multivariate logistic regression analysis for predictors of vascular complications after liver transplantation.

Variable	Adjusted OR	CI 95%	P Value
PVT	2.65	1.07–6.55	**0.035**
MELD 3.0 score	0.97	0.90–1.05	0.456
Age at LT	0.97	0.94–1.00	0.050

Disclosures: Paola Cáceres-Moreno:Nothing to Disclose, Sergio Escalante Gutiérrez:Nothing to Disclose, Berenice Monserrat Román Calleja:Nothing to Disclose, Nayelli Cointa Flores García:Nothing to Disclose, José González-Regueiro:Nothing to Disclose.

4519 | CARDIOVASCULAR DEATH DRIVES INCREASED MORTALITY IN OLDER PATIENTS UNDERGOING LIVER TRANSPLANTATION FOR MASH CIRRHOSIS

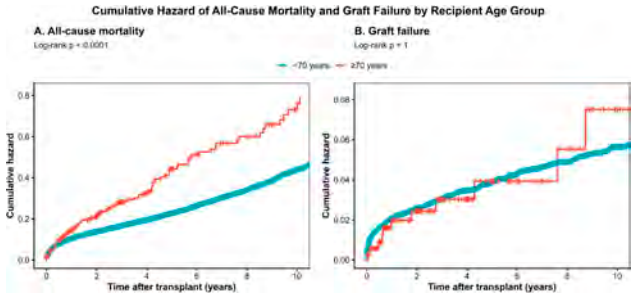
Wyatt Nice[1] David Lee[1] Neha Jakhete[1], [1]University of Maryland School of Medicine

Background: It is well established that older patients undergoing liver transplantation (LT) for metabolic dysfunction-associated steatohepatitis (MASH) have increased post-transplant mortality. However, it remains unclear whether the increased mortality observed in older recipients is driven by specific causes of death or by increased graft failure. We aimed to evaluate age-stratified post-transplant outcomes in patients undergoing LT for MASH cirrhosis, with a focus on cause-specific mortality and graft survival. **Methods:** We performed a retrospective cohort study using the United Network for Organ Sharing Standard Transplant Analysis and Research (UNOS-STAR) registry from 2005 to 2019 of adult patients undergoing primary LT for MASH cirrhosis. Recipients were stratified by age < 70 versus ≥ 70 years at the time of transplantation. The primary outcomes were all-cause mortality and graft failure following LT. Secondary outcomes included cause-specific mortality. Prognostic survival curves were generated and compared using the log-rank test. Multivariable Cox proportional hazards models adjusted for recipient demographic and clinical covariates were used to evaluate post-transplant outcomes. **Results:** A total of 9,797 recipients age < 70 years and 366 recipients age ≥ 70 years underwent LT for MASH cirrhosis and were included in the analysis. Recipients ≥ 70 years had a significantly increased risk of all-cause mortality compared to recipients < 70 years (HR 1.60, 95% CI 1.33–1.93; p < 0.001). In contrast, there was no significant difference in graft failure between the groups (HR 0.98, 95% CI 0.54–1.80; p = 0.95). The increased mortality observed among recipients ≥ 70 years was primarily driven by a higher risk of cardiac mortality (HR 1.67, 95% CI 1.08–2.57; p = 0.020). Older recipients also demonstrated a significantly increased risk of mortality related to renal causes (HR 2.83, 95% CI 1.51–5.31; p < 0.001). **Conclusion:** Older recipients undergoing LT for MASH cirrhosis experience significantly increased post-transplant mortality despite similar graft survival compared to younger recipients. This increased mortality appears to be driven primarily by cardiovascular death and, to a lesser extent, renal mortality. These findings highlight the importance of

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cardiovascular risk stratification prior to LT and aggressive management of cardiometabolic risk factors in older patients with MASH cirrhosis.

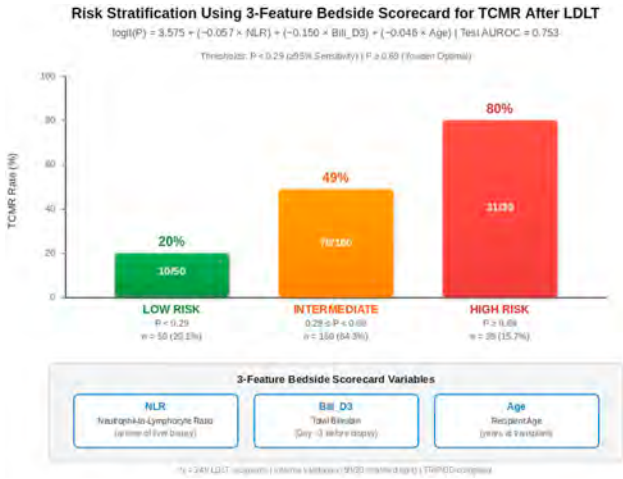


Disclosures: Wyatt Nice:Nothing to Disclose, David Lee:Nothing to Disclose, Neha Jakhete:Gilead: Advisor, Ipsen: Advisor.

4520 | DEVELOPMENT AND INTERNAL VALIDATION OF A NOVEL MACHINE LEARNING-BASED CLINICAL DECISION SUPPORT SYSTEM FOR PREDICTING T-CELL MEDIATED REJECTION AFTER LIVING DONOR LIVER TRANSPLANTATION

Neeraj Saraf[1] Swapnil Dhampalwar[1] Narendra Choudhary[1] Kunwar Singh[1] Nischal Modak[1] Prashant Bhangui[2] Arvinder Soin[1], [1]Medanta The Medicity, [2]Medanta - The Medicty

Background: T-cell mediated rejection (TCMR) may occur in 20-30% of living donor liver transplantation (LDLT) recipients in the early post-operative period which requires an invasive liver biopsy to rule out other causes of graft dysfunction. However, a liver biopsy may get delayed and often difficult to perform because of ascites and/or coagulopathy. Early risk stratification for likelihood of TCMR may allow pre-emptive immunosuppressive optimization, but validated bedside prediction tools for TCMR after LDLT are unavailable. We aimed to analyze performance of different Machine Learning (ML) models and develop a simple, interpretable clinical scorecard for TCMR prediction using machine learning. **Methods:** We have a prospectively maintained database of 4703 LT recipients from August 2004. LT recipients with graft dysfunction underwent liver biopsy after ruling out biliovascular complications by imaging. 249 such patients who underwent liver biopsy within 1st month of LT from January 2015 to August 2023 were included in this study to see the performance of 12 different ML models. Each patient's data instance consisted of demographic parameters, perioperative variables (i.e. operative time, GRWR), and biochemical parameters at the time of biopsy including trends in LFTs. Data were split 80/20 with stratification. Performance was evaluated using AUROC with 95% CI, calibration, and decision curve analysis. TRIPOD guidelines were followed. **Results:** Two hundred and forty-nine patients were included for analysis. TCMR occurred in 113/249 patients (45.4%). Amongst, the comprehensive 12-model comparison, Linear SVM achieved the highest test AUROC of 0.798 (95% CI 0.691-0.905). Forward selection identified a simple 3-feature logistic regression scorecard (test AUROC 0.753, 95% CI 0.638-0.868) using: Neutrophil-to-Lymphocyte Ratio at biopsy (NLR), Day-3 pre-biopsy bilirubin (Bili D-3), and recipient age (*Figure 1*). The formula is: logit(P) = 3.575 + (−0.057 × NLR) + (−0.150 × Bili D-3) + (−0.046 × Age). All coefficients were negative, reflecting biologically coherent protective mechanisms: elevated NLR indicates neutrophilic rather than T-cell inflammation, high bilirubin reflects cholestasis/ischemia-reperfusion injury, and older age confers immune-senescence. This risk stratification model classified patients into Low (n = 50, TCMR 20%), Intermediate (n = 160, TCMR 49%), and High risk (n = 39, TCMR 80%) categories. **Conclusion:** Among 12 ML models, Linear SVM had best performance (AUROC 0.798) for likelihood of TCMR. A simple 3-feature bedside scorecard using routinely available peri-biopsy parameters can serve as Clinical Decision Support tool by stratifying risk of TCMR risk after LDLT. External multi-center validation is warranted for optimal use of these ML models in improving graft and patient survival.



Disclosures: Neeraj Saraf:Nothing to Disclose, Swapnil Dhampalwar:Nothing to Disclose, Narendra Choudhary:Nothing to Disclose, Kunwar Singh:Nothing to Disclose, Nischal Modak:Nothing to Disclose, Prashant Bhangui:Nothing to Disclose, Arvinder Soin: Nothing to Disclose.

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4521 | GLP1RA USE AND CLINICAL OUTCOMES AMONGST LIVER TRANSPLANT CANDIDATES

Sara Naimimohasses[1] Tomohiro Tanaka[1], [1]University of Iowa Hospitals and Clinics

Background: Obesity in liver transplant (LT) candidates often prompts the need for weight loss pre LT. The safety and clinical utility of glucagon-like peptide 1 receptor agonists (GLP1RA) amongst individuals on the LT waitlist remains understudied. This study aimed to evaluate the clinical impact of GLP1RA initiation amongst patients with decompensated liver disease awaiting LT. **Methods:** A retrospective cohort design based on a linked dataset comprising the Scientific Registry of Transplant Recipients (SRTR) and Medicare administrative claims were used to compare outcomes between LT candidates initiated on GLP1RA therapy during their waitlist tenure and a matched cohort of non-users. Adults, newly listed for LT between 1/ 2021 and 12/ 2022 were included. A 1:3 propensity score matching without replacement was implemented. The propensity score was estimated via logistic regression using a prespecified set of covariates including age, sex, race, BMI, initial MELD score, MELD exception status, and metabolic dysfunction associated steatotic liver disease (MASLD) diagnosis, DM, KPS at listing, and transplant center volume tercile. Matching incorporated exact matching on index date (GLP1RA initiation date for treated patients). The primary outcomes for this study were the cumulative incidence of LT and waitlist mortality (defined as death or removal due to clinical deterioration), which were treated as competing risks to each other. **Results:** Following propensity score matching, data was analyzed from 540 patients listed for LT; 135 were treated with GLP1RA and 405 were non-users on the index date. MASLD was listed as the indication for LT in (n = 189, 46.7%) vs. (n = 59 43.7%), p = 0.62. Mean initial MELD was 12.7 vs. 12.5, p = 0.76. Mean BMI was 32.4 vs 32.7, p = 0.94, most patients had a diagnosis of DM (n = 352, 86.9%) vs. (n = 118, 87.4%), p = 1.00. At 120 days, patients treated with GLP1RA demonstrated a significantly lower risk of death compared with those who were untreated (risk difference -7.6%, 95% CI -14.6 to -0.6, p = 0.034). [TT1] However, no significant difference in mortality was observed beyond 120 days. There was no significant difference in the probability of LT between the two groups at any evaluated time interval. **Conclusion:** Amongst patients listed for LT, GLP1RA use was associated with increased shot-term survival at 120 days following listing, suggesting potential benefit in this population, although this effect was not consistently observed over time, nor for LT access.

Disclosures: Sara Naimimohasses:Nothing to Disclose, Tomohiro Tanaka:Nothing to Disclose.

4522 | DONOR-RECIPIENT SEX PAIRING MODIFIES THE ASSOCIATION BETWEEN DONOR HEPATITIS B VIRUS STATUS AND POST–LIVER TRANSPLANT MORTALITY

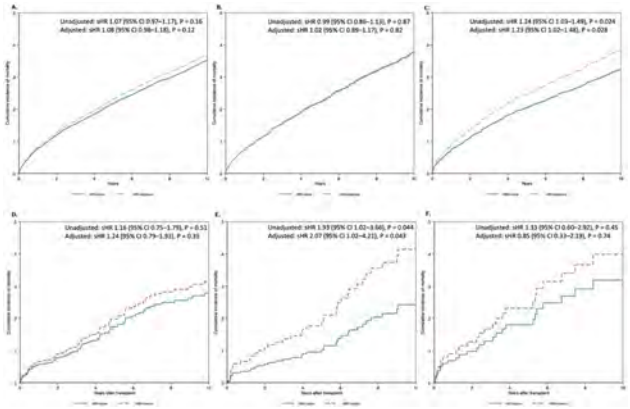
Katherine Cooper[1] Leandro Sierra[2] Rachael Mahle[3] Deepika Devuni[4] Emily Bethea[3] Karin Andersson[3], [1]Massachusetts General Hospital, Harvard Medical School, [2]Cleveland Clinic Foundation, [3]Massachusetts General Hospital, [4]UMass Chan Medical School

Background: Donor hepatitis B virus (HBV) exposure and infection are increasingly relevant in liver transplant (LT) as donor organ availability expands. Whether the association between donor HBV status and recipient outcomes differs by donor–recipient sex pairing remains unclear. We evaluated post-LT mortality associated with donor HBV category, stratified by donor-recipient sex pairing. **Methods:** We performed a retrospective cohort study of adult liver transplant recipients using propensity score-matched donor HBV cohorts. Recipients of HBV-naïve donor grafts were compared with recipients of HBV-exposed donor grafts and, separately, HBV-infected donor grafts. Donor-recipient sex pairing was categorized as sex-matched, female donor to male recipient, or male donor to female recipient. The primary outcome was all-cause mortality within 10 years after LT. Cumulative incidence functions were estimated using Fine–Gray competing risks models, with retransplantation before death treated as a competing event. Subdistribution hazard ratios (sHR) were estimated before and after adjustment for recipient, donor, and transplant-specific characteristics. **Results:** In the HBV-naïve versus HBV-exposed donor cohort, 6,087 recipients were matched in each group. Among sex-matched donor–recipient pairs, HBV-exposed donor grafts were not associated with increased mortality after adjustment compared with HBV-naïve grafts (adjusted sHR 1.08, 95% CI 0.98–1.18). No mortality difference was observed among female donor to male recipient pairs (adjusted sHR 1.02, 95% CI 0.89–1.17). In contrast, among male donor to female recipient pairs, HBV-exposed donor grafts were associated with higher mortality (adjusted sHR 1.23, 95% CI 1.02–1.48). In the HBV-naïve versus HBV-infected donor cohort, 377 recipients were matched in each group. HBV-infected donor grafts were not significantly associated with mortality among sex-matched pairs (adjusted sHR 1.24, 95% CI 0.79–1.93) or male donor to female recipient pairs (adjusted sHR 1.95, 95% CI 0.33–2.19). However, HBV-infected donor grafts were associated with higher mortality among female donor to male recipient pairs (adjusted sHR 2.07, 95% CI 1.02–4.21). **Conclusion:** The association between donor HBV status and post-

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LT mortality may vary by donor-recipient sex pairing. HBV-exposed donor grafts were associated with higher mortality specifically among male donor to female recipient pairs, while HBV-infected donor grafts showed a signal for increased mortality among female donor to male recipient pairs. These findings suggest that donor-recipient sex pairing may modify risk associated with HBV-positive LT grafts, although results should be interpreted cautiously due to low sample size. Further studies are needed to validate these findings and clarify whether sex-specific immunologic or graft-related mechanisms contribute to differential post-LT outcomes.



Disclosures: Katherine Cooper:Nothing to Disclose, Leandro Sierra:Nothing to Disclose, Rachael Mahle: Nothing to Disclose, Deepika Devuni:Nothing to Disclose, Emily Bethea:Nothing to Disclose, Karin Andersson:Nothing to Disclose.

4523 | PERIOPERATIVE RENAL DYSFUNCTION, NOT METABOLIC BURDEN, DRIVES LONG-TERM MORTALITY AFTER MASLD/MASH LIVER TRANSPLANTATION

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD/MASH) is a rapidly growing indication for liver transplantation. Although MASLD/MASH recipients frequently carry substantial metabolic burden, the relative contribution of obesity versus perioperative renal dysfunction to long-term survival remains unclear. We evaluated predictors of long-term mortality after liver transplantation for MASLD/MASH, focusing on early post-transplant hemodialysis and body mass index. **Methods:** We retrospectively analyzed 100 consecutive adult recipients undergoing liver transplantation for MASLD/MASH between 2008 and 2025 at a tertiary transplant center. Overall survival was assessed using Kaplan-Meier analysis and Cox proportional hazards models. To mitigate immortal time bias, a predefined 30-day landmark analysis evaluated the impact of early post-transplant hemodialysis (HD-30d) on subsequent mortality. **Results:** Median follow-up was 4.9 years (IQR 2.6–8.8). Overall survival at 1, 3, 5, and 10 years was 92.9%, 89.4%, 80.4%, and 75.0%, respectively. HD-30d occurred in 20% of recipients and was associated with markedly inferior long-term survival (10-year survival: 47.9% vs 83.6%; log-rank $p = 0.004$). In landmark multivariable Cox analysis excluding deaths within 30 days, HD-30d was the strongest independent predictor of mortality (HR 5.07, 95%CI 1.63–15.74, $p = 0.005$), independent of age, MELD-Na, and baseline creatinine.In contrast, obesity was not associated with worse survival. Recipients with BMI ≥ 30 had numerically higher survival than those with BMI < 30 at both 5 years (87.3% vs 72.3%) and 10 years (84.3% vs 57.8%), suggesting that BMI alone may poorly capture biological vulnerability in cirrhotic MASLD/MASH candidates. **Conclusion:** In MASLD/MASH liver transplantation, early renal dysfunction requiring hemodialysis, rather than obesity or baseline metabolic burden, is the dominant predictor of long-term mortality. The unexpectedly poorer outcomes among non-obese recipients may reflect hidden sarcopenia or reduced physiologic reserve, supporting integrated assessment of renal vulnerability and body composition in this population.

Disclosures: Patricia Almeida:Nothing to Disclose, Giovana Fernandes:Nothing to Disclose, Maria Pilz: Nothing to Disclose, Andre Souza:Nothing to Disclose, Lilian Curvelo:Nothing to Disclose, Celso Matielo: Nothing to Disclose.

4524 | CLOSING THE ADVANCE CARE PLANNING GAP IN LIVER TRANSPLANT EVALUATION: A QUALITY IMPROVEMENT PILOT

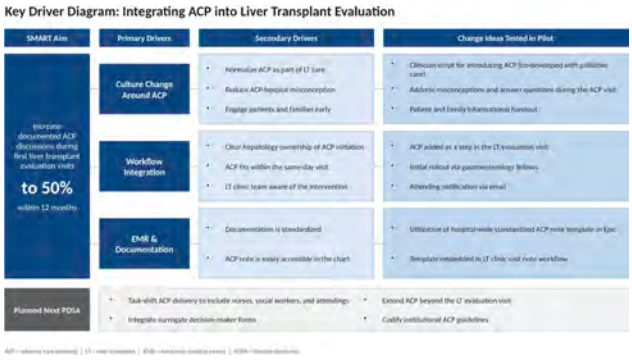
Mayowa Adefuye[1] Swathi Krishnan[2] Michelle Hughes[2] Vandana Khungar[2], [1]Yale New Haven Health System, CT, USA, [2]Section of Digestive Diseases, Yale School of Medicine, New Haven, CT, USA

Background: Patients with end-stage liver disease face high mortality and risk of delisting from the transplant waitlist due to serious illness or death, yet advance care planning (ACP) is poorly integrated into liver transplant (LT) evaluation. Nationally, fewer than half of LT centers require advance directive discussions during evaluation, and only 9% of LT candidates complete ACP beforehand, despite most reporting

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readiness. We piloted a quality improvement (QI) intervention as proof of concept to embed a structured ACP into the initial LT evaluation visit. **Methods:** This single-center QI pilot was conducted at Yale New Haven Hospital between Jan 23 and May 15, 2026, per SQUIRE 2.0. Our SMART aim was to increase documented ACP during first LT evaluation visits to 50% within 12 months. We mapped the clinic workflow and built a key driver diagram targeting culture change, workflow, and EMR optimization. Core change ideas included a clinician script co-developed with palliative care, a patient handout, and a structured ACP note template embedded in the LT visit note, implemented by gastroenterology fellows. We compared documentation between the pilot and an equal 16-week pre-intervention period via chart review. Co-primary outcomes: overall ACP documentation rate and capture rate among patients without prior ACP. Acceptability was assessed via post-visit patient survey. **Results:** Pre-intervention, 6 of 31 patients (19%) had documented ACP. During the pilot, documentation rose to 27 of 37 (73%), exceeding the SMART aim. Among 32 patients without prior ACP, the intervention captured 22 (69%). Median age was 58 years (IQR 46–66), 64% were male; 68% White (non-Hispanic), 14% Hispanic, 5% Black; median MELD 3.0: 14 (IQR 9–19); Child-Pugh B in 59%. Leading etiologies were alcohol-related liver disease (59%), MASH (18%), hepatitis C-related (14%). All ACP discussions (100%) were documented on the same-day, and a healthcare proxy was identified in every encounter; a support person was present at 77% of visits. All patients completed the survey, 100% found it helpful, 92% felt the topic was important, and 83% reported no anxiety or discomfort **Conclusion:** A structured, workflow-integrated ACP intervention is feasible, highly acceptable to patients and providers, and produced a near-fourfold increase in documentation (19% → 73%) in a 16-week pilot. Coordinated change across culture, workflow, and EMR enabled rapid measurable improvement without added visit burden. Next steps include integrating other healthcare professionals into ACP delivery and codifying institutional ACP guidelines to support scale.



Disclosures: Mayowa Adefuye:Nothing to Disclose, Swathi Krishnan:Nothing to Disclose, Michelle Hughes: Nothing to Disclose, Vandana Khungar:Nothing to Disclose.

4525 | BEYOND LIVER TRANSPLANTATION: LONG-TERM SURVIVAL AND CAUSES OF MORTALITY IN HEPATIC SARCOIDOSIS

Alexis Kim[1] Anh Bui[2] Siddhant Nair[1] Shilpa Jasti[3] Aamer Syed[1] Thomas Iden[1] Jessica McLaughlin[1] Dana Alderson[1] Jordana Kron[1] Huzaefah Syed[1] Neha Gupta[1] Ryan Canissario[1] Duaa AbdelHameid[1] Mohammad Siddiqui[4] Vaishali Patel[2], [1]Virginia Commonwealth University Health System, [2]Virginia Commonwealth University, [3]Virginia Commonwealth University Medical School, [4]University of Virginia

Background: Hepatic sarcoidosis (HS) is a rare indication for liver transplantation (LT), and its long-term outcomes remain poorly characterized compared to other immune-mediated liver diseases. This study aimed to evaluate post-LT survival and cause-specific mortality in patients with HS compared to those with primary sclerosing cholangitis (PSC), primary biliary cholangitis (PBC), and autoimmune hepatitis (AIH). **Methods:** Using the OPTN/UNOS database (2002-2022), we identified 872 adult deceased-donor LT recipients with HS and compared their outcomes to those with PSC (n = 4705), PBC (n = 3166), and AIH (n = 2960). Patients with prior LT or concurrent hepatocellular carcinoma were excluded. Survival was analyzed using Kaplan-Meier (KM) curves and Cox proportional hazards regression, while Fine-Gray subdistribution hazards models were applied to assess cardiovascular disease (CVD)-specific mortality. **Results:** HS LT recipients demonstrated significantly lower 5- and 10-year survival (75.8%, 62.7%) compared to PSC (85.8%, 75.2%, $p < 0.0001$), PBC (83.5%, 71.0%, $p < 0.0001$), and AIH (80.2%, 67.2%, $p = 0.0063$) (Figure 1A). On multivariate analysis adjusting for age, sex, race, MELD score, transplant year, obesity, and pre-existing diabetes, HS remained an independent predictor of worse 10-year survival compared to PSC (HR 1.47, $p < 0.001$) and PBC (HR 1.22, $p = 0.03$), though survival differences compared to AIH were not statistically significant (HR 1.06, $p = 0.51$). CVD (23.5%) was the leading cause of death in HS (23.5%), followed by infection (15.2%) and malignancy (11.3%). Cumulative incidence analysis further revealed significantly higher CVD-specific mortality in HS patients, with a three-fold increased risk compared to PSC (HR 3.33, $p < 0.001$) and approximately two-fold increased risk compared to

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both PBC (HR 1.85, p = 0.013) and AIH (HR 1.86, p = 0.004) (Figure 1B). **Conclusion:** Patients receiving an LT for HS demonstrate worse long-term survival when compared to PSC and PBC patients. CVD-related mortality accounts for this increase in mortality in HS compared to other cholestatic and autoimmune liver diseases, underscoring the need for targeted strategies to mitigate cardiovascular risk following LT in HS.

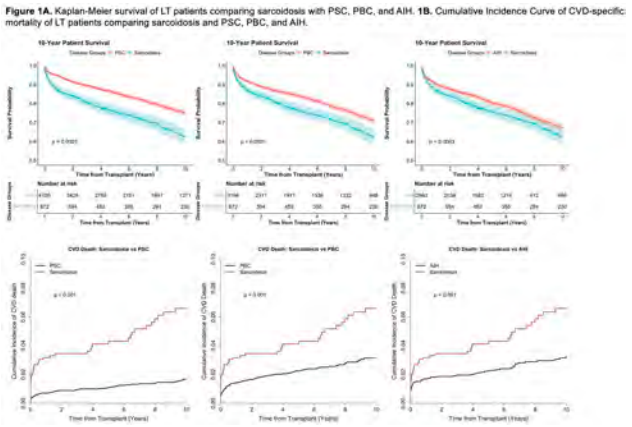


Figure 1A. Kaplan-Meier survival of LT patients comparing sarcoidosis with PSC, PBC, and AIH. 1B. Cumulative Incidence Curve of CVD-specific mortality of LT patients comparing sarcoidosis and PSC, PBC, and AIH.

Disclosures: Alexis Kim:Nothing to Disclose, Anh Bui: Zydus: Consultant, Siddhant Nair:Nothing to Disclose, Shilpa Jasti:Nothing to Disclose, Aamer Syed:Nothing to Disclose, Thomas Iden:Nothing to Disclose, Jessica McLaughlin:Nothing to Disclose, Dana Alderson:Nothing to Disclose, Jordana Kron:Nothing to Disclose, Huzaefah Syed:Nothing to Disclose, Neha Gupta: Nothing to Disclose, Ryan Canissario:Nothing to Disclose, Duaa AbdelHameid:Nothing to Disclose, Mohammad Siddiqui:NovoNordisk: Grant/Research Support, 89Bio: Consultant, Sagimet: DSMB, Vaishali Patel:Nothing to Disclose.

4526 | INCIDENCE AND RISK FACTORS FOR ANASTOMOTIC BILIARY STRICTURES FOLLOWING LIVER TRANSPLANTATION USING MACHINE PERFUSION

Caroline Olson[1] Andrew Keaveny[1] Nicole Loo[1] Liu Yang[1] Surakit Pungpapong[1] Kristopher Croome[1] Omar Mousa[1], [1]Mayo Clinic Florida

Background: Biliary strictures are the most common complication following donation-after-circulatory-death (DCD) liver transplantation (LT), occurring in 5-30% of cases. Machine perfusion (MP) technologies including in situ normothermic regional perfusion (NRP) and ex situ normothermic machine perfusion (NMP) perfuse donor organs with oxygenated blood at body temperature, prolong viability and expand the DCD donor pool. Their impact on biliary strictures is not well studied. The aim of our study was to determine the incidence of biliary strictures by MP modality and identify factors associated with stricture development after DCD-LT. **Methods:** This was a retrospective review of 437 DCD-LT recipients at a single center between 2/2017 - 10/2025. Patients were included if they had an endoscopic retrograde cholangiopancreatography procedure (ERCP) post-LT. Donor/recipient demographics, NMP time, anastomosis type, transplant year, bile leak, and vascular complications were compared by χ^2 and Kruskal–Wallis tests. Univariate and multivariable logistic regression identified factors associated with the presence of stricture. **Results:** Recipients were grouped by perfusion modality: NMP (n = 166), NRP (n = 75), combined NRP+NMP (n = 29) and no MP (n = 167). Anastomotic biliary strictures occurred in 22.8% recipients. The overall incidence was highest in NMP (56/166, 33.7%) vs NRP (14/75, 18.7%) vs NRP/NMP (4/29, 13.8%) and no MP (26/167, 15.6%; p < 0.001). Anastomotic stricture rates improved year-over-year in the NMP group (46% in 2023, 35% in 2024, 24.5% in 2025). NMP recipients had longer NMP time (median 16.2 vs 6.2 vs 6.3 h; p < 0.001), older donor age (59.5 vs 57.0 vs 39.0 y; p < 0.001), and higher donor BMI (p < 0.001). On univariate analysis, NMP (OR 2.30, p < 0.001), and biliary leak (OR ~8.0, p < 0.001) were associated with increased odds of biliary stricture. Recipient age, recipient BMI, donor age, and donor BMI were not significantly associated with stricture risk. On multivariate analysis adjusting for recipient and donor factors as well as perioperative variables, biliary leak remained the only independent predictor of biliary stricture (OR ~8.0, p < 0.001), and NMP was not significantly associated with stricture development. The use of perfusion modality did not impact survival (log-rank p $\asymp$ 0.18). **Conclusion:** Anastomotic biliary stricture rates were higher in NMP-preserved DCD-LT recipients but improved over the years likely due to refinements in surgical and organ perfusion techniques. The unadjusted NMP-stricture association attenuated after adjustment for era, donor characteristics, and NMP time, suggesting that donor selection and perioperative complexity, rather than perfusion modality alone, may drive risk. Bile leak was the strongest independent predictor of ABS. These findings inform donor allocation, peri- and post-operative management, and risk stratification in DCD-LT programs using machine perfusion.

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Table 1 Patient and donor characteristics by perfusion modality

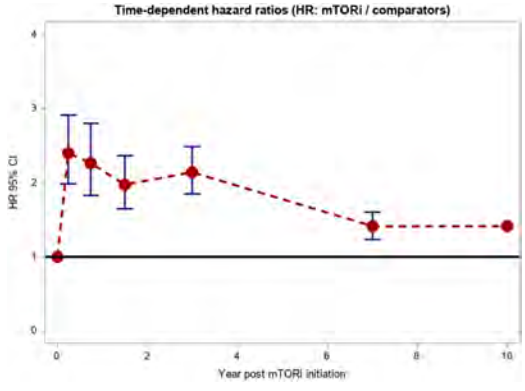
	Any Machine Perfusion modality N = 270	No machine perfusion N = 167	p value
Gender male	187/270 (69.3%)	107/167 (64.1%)	0.294
Age (years), median [IQR]	61.0 [53.0–66.8]	61.0 [54.0–66.0]	0.600
BMI at transplant, Kg/m2	28.7 [25.1–33.0]	27.8 [24.8–32.4]	0.425
Donor Age (years), median [IQR]	58 [45–66]	39 [32–52]	<0.001
Donor BMI, Kg/m2	29.4 [25.4–35.0]	26.6 [23.8–32.0]	<0.001
Distance from transplant center	146 [75–426.8]	131 [64.5–221]	0.001
Biliary leak	20/270 (7.4%)	15/167 (9.0%)	0.589
Anastomotic stricture	74/270 (27.4%)	26/167 (15.6%)	0.005
Anastomotic stricture by year			
2023	19/55 (34.5%)	1/8 (12.5%)	
2024	33/108 (30.5%)	0/1 (0%)	
2025	21/91 (23%)	0/0	
1 year survival post LT (95% CI)	96.5% (93.1%–98.2%)	96.8% (92.6%–98.7%)	0.741

Disclosures: Caroline Olson:Nothing to Disclose, Andrew Keaveny:River 2 Renal Corporation: Grant/Research Support, Nicole Loo:Ipsen: Advisor, Liu Yang:Nothing to Disclose, Surakit Pungpapong:Nothing to Disclose, Kristopher Croome:Nothing to Disclose, Omar Mousa:Nothing to Disclose, Nothing to Disclose.

4528 | MTOR INHIBITOR-BASED IMMUNOSUPPRESSION IS ASSOCIATED WITH INCREASED MORTALITY IN LIVER TRANSPLANT RECIPIENTS WITH MEDICARE

Therese Bittermann[1] Douglas Schaubel[2] Charles Leonard[2] Qufei Wu[2] David Goldberg[3] David Kaplan[4], [1]University of Pennsylvania Perelman School of Medicine, [2]Department of Biostatistics, Epidemiology and informatics; University of Pennsylvania, [3]University of Miami, [4]University of Pennsylvania

Background: Mechanistic target of rapamycin inhibitors (mTORi) are used off-label in liver transplantation (LT) based on clinical trial and single center data suggesting benefits in selected recipients. Using a large retrospective cohort of Medicare LT beneficiaries, we previously demonstrated that mTORi use is highly variable among centers and most often occurs in patients with high comorbidity burden. To date, U.S. population-based studies on the association of mTORi with outcomes using real-world data are lacking. **Methods:** This study used an existing data linkage of Medicare claims and data from the Organ Procurement and Transplantation Network. The study population (n = 17,239) included adult recipients of first-LT-alone between 1/1/2007-12/31/2019. For each patient a risk score for mTORi initiation was derived using a stratified Cox model based on a large number baseline and time-updating demographic, clinical and socio-economic covariates. Each mTOR inhibitor treated patient was matched at the time of mTORi initiation to 1-3 comparators within the same transplant center, +/- 5 years of age and +/- 0.05 of prognostic score. The association of mTORi initiation on survival was then evaluated using the sequential stratification version of Cox regression. Sub-analyses included examining interactions between mTORi and each of pre and/or post-LT cancer and post-LT end-stage renal disease (ESRD) or chronic kidney disease (CKD). Models were also fit allowing for non-proportional hazards. **Results:** Median follow-up time was 3.8 (IQR: 1.2-7.1) years. A total of 3,537 (20.5%) unique patients ever initiated mTORi. From this group, 2,944 (83.2%) were matched to 1-3 comparators (64.2% to 3 comparators), resulting in 7,204 matched comparators. mTORi initiation occurred at a median 5.0 months (IQR: 2.0-14.6) from LT and median follow-up time post-matching was 4.11 years (IQR: 1.74-7.58). In total, 3,043 (30.0%) deaths were observed. mTORi initiation was associated with an increased risk of mortality: HR = 1.92 (95% CI 1.78-2.07; p < 0.001) averaged across follow-up. The magnitude of this effect persisted for at least 4 years after mTORi-initiation and was still present, albeit considerably diminished, for up to 10 years (Figure). Significant interactions by cancer status and renal function were detected. Mortality risk with mTORi initiation was higher for patients with cancer (HR = 2.02; p < 0.001) vs without (HR = 1.47; p < 0.001). However, for patients the mTORi hazard ratio was decreased for patients with ESRD (HR = 1.45; p = 0.001) or CKD (HR = 1.50; p < 0.001) relative to patients with neither (HR = 2.53; p < 0.001). **Conclusion:** We previously found that post-transplant comorbidity incidence is associated with increased mTORi initiation rates. Despite employing methodology that matches on time-dependent risk factors, mortality risk remains significantly elevated after mTORi initiation.



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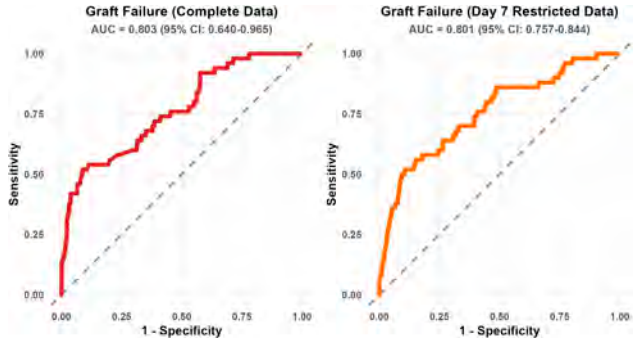
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4529 | TACROLIMUS VARIABILITY AND DAY 7 LABORATORY TRAJECTORIES PREDICT GRAFT FAILURE AFTER LIVER TRANSPLANTATION

Kevin Korenblat[1], [1]Washington University School of Medicine

Background: Post-liver transplant graft failure occurs in 5-10% of recipients within the first year. While risk scores such as L-GrAFT and EASE incorporate perioperative laboratory data to predict post-transplant outcomes, these models have not achieved widespread clinical adoption. A model for early risk stratification using accessible electronic health record data could enable targeted interventions during index hospitalization when most patients remain admitted. Gradient boosting models using 528,000 laboratory measurements across 28 unique analytes were developed to predict 90-day graft failure, comparing models using complete hospitalization data versus data restricted to postoperative day 7, when 70% of patients remain hospitalized and accessible to interventions. **Methods:** This retrospective analysis included 922 adult liver transplant recipients at a single center (August 2019-August 2025). Graft failure was defined as retransplantation or death within 90 days. Laboratory data were aggregated into time windows with calculation of trajectory features (mean, maximum, variability, peak timing). Derived features included MELD scores, tacrolimus coefficient of variation (CV), and interaction terms. Gradient-boosted decision trees were trained using 5-fold stratified cross-validation. **Results:** Among 922 transplant recipients, 50 (5.4%) experienced graft failure within 90 days. The complete model achieved mean cross-validation AUC 0.803 (SD 0.131, 95% CI 0.640-0.965). The day 7 restricted model achieved AUC 0.801 (SD 0.035, 95% CI 0.757-0.844), representing only 0.2% performance loss. Feature importance analysis identified AST peak timing (12.3%), lactate trajectory (7.1%), and tacrolimus CV × creatinine interaction (6.2%) as dominant predictors in the day 7 restricted model. Calibration analysis demonstrated good agreement between predicted and observed outcomes (Brier score 0.161 in the day 7 restricted model). **Conclusion:** Machine learning models using day 7 laboratory trajectories predict 90-day graft failure after liver transplantation with excellent discrimination (AUC 0.81). The tacrolimus variability × creatinine interaction emerged as a novel predictor, identifying modifiable risk factors for early intervention. Minimal performance loss with day 7 implementation enables early risk stratification while most patients remain hospitalized, establishing targets for intensive monitoring to reduce graft failure risk.



Disclosures: Kevin Korenblat:Nothing to Disclose.

4530 | COMBINED HEART–LIVER TRANSPLANTATION: CURRENT EVIDENCE AND EVOLVING PRACTICES

Fatima Elmustafa,[1] Shahzad Ashraf[2] Faris Abdulaziz[1] Sajid Jalil[3] Mangesh Pagadala[4] Akash Shukla[5] Binu John[6] Patrizia Burra[7] Winston Dunn[8] Ashwani Singal[9], [1]Henry Ford Warren, [2]Eastridge PrimeCare Hospital, [3]Stanford University, [4]Methodist Transplant Specialists, [5]Seth GS Medical College & KEM Hospital, [6]University of Miami and Miami VA, [7]University of Padova, [8]University of Kansas Medical Center, [9]University of Louisville

Background: Data on combined heart–liver transplantation (CHLT) are limited. We aimed to examine trends, indications, and outcomes of CHLT. **Methods:** Adult (≥18 years) CHLT recipients in the United Network for Organ Sharing (UNOS) database (1987-2025) were included. Prior LT recipients were excluded. Survival was analyzed using Kaplan–Meier and Cox regression methods. **Results:** Among 805 CHLT recipients, simultaneous heart–liver transplants (sHLT) accounted for most cases (n = 660, 82.0%), followed by heart-before-liver (HBL) transplants (HBL; n = 116, 14.4%),

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and heart-after-liver (HAL) transplants (n = 29, 3.6%). Trends (1987-1995 to 2016-2025) varied: HBL 93.4% to 4.4%, sHLT 3.9% to 95.3%, (P < 0.001). HAL remained relatively stable, 2.5% to 7.1%. Diabetes mellitus, MELD-XI score, ventilator support, and dialysis use differed (Table). Congenital heart disease and cardiomyopathy accounted for 39% and 32% for sHLT, whereas cardiomyopathy was the commonest cardiac cause in HAL (79%) and HBL (35%) transplants. Coronary artery disease and valvular heart disease accounted for 2.1%, 0%, 4.3% and 0.9%, 6.9%, 2.6% in sHLT, HAL, HBL respectively. MASH or cryptogenic was the liver diagnosis in 75%, 55%, 32% in sHLT, HAL, HBL transplants respectively. Alcohol-associated liver disease and hepatocellular carcinoma were other common causes, with respective figures of 4.5%, 10.3%, 2.6% and 3.6%, 24.1%, 6.9%. Over a median (25th – 75th percentile) follow-up of 3 (1-7.3) yrs., 224 (30.6%) recipients lost cardiac graft, with only four rejection episodes, one ACR in HAL, and three chronic rejection (1 SLH and 2 HBL). Patient survival at 1 yr. was 96.7%, 84.6%, and 75.9% in HBL, sHLT, and HAL, respectively. However, this was similar at 3 yrs. P = 0.495 and at 5 yrs. P = 0.403. Adjusted Cox regression models showed that compared to HBL, recipients with HAL had an over 11-fold hazard of dying within a year. (HR 11.59, 95% CI 1.36–98.97, P = 0.025). The survival was like that of sHLT. Being on dialysis was associated with a hazard ratio of over 2, and recipient age with a 2% mortality reduction for every unit increase in age. There was no effect of year of transplant (Table). **Conclusion:** sHLT has become the predominant CHLT approach over time, reflecting evolving transplant practices. In this UNOS cohort selected for CHLT, HBL demonstrated the best 1-yr. survival, with similar long-term survival highlights the need for diligent candidate selection for CHLT.

Table: Baseline Characteristics of Adult Combined Heart–Liver Transplant Recipients by Transplant Sequence

Parameter	SLH (n=660)	HAL (n=29)	HBL (n=116)	P	HR (95% CI)
sHLT as CHLT type					6.92 (0.92-52.0), p=0.060
HAL as CHLT type					11.59 (1.36-99.0), p=0.025
HBL as CHLT type					Ref.
Calendar yr					1.02 (0.98-1.06), p=0.314
Age, years	46 (33–57)	57 (46–63)	50 (37–58)	0.399	0.98 (0.96-0.99), p=0.002
Female sex, %	32	38	29	0.559	0.87 (0.55-1.37), p=0.539
Obesity, %	18	21	19	0.883	1.47 (0.92-2.36), p=0.111
Diabetes mellitus, %	16	28	34	<0.001	1.33 (0.79-2.25), p=0.284
MELD-XI score	11.5 (7–15.7)	9.5 (4.6–18.8)	15.2 (8.7–25.2)	<0.001	1.01 (0.98-1.04), p=0.533
Graft LVEF, %	61 (58–65)	60 (57–65)	65 (55–70)	0.582	0.97 (0.94-1.00), p=0.076
Ventilator support, %	4.2	13.8	12.9	<0.001	1.17 (0.52-.263), p=0.701
ECMO use, %	3.2	3.5	0	0.365	1.35 (0.56-3.30), p=0.507
Inotrope use, %	43	38	49	0.644	0.91 (0.60-1.36), p=0.634
Dialysis, %	6.7	6.9	21.6	<0.001	2.20 (1.16-4.17), p=0.016

SLH: Simultaneous liver heart; HAL: Heart after liver, HBL: Heart before liver; LVEF: Left ventricular ejection fraction; HR: Hazard ratio; CI: Confidence interval.

Disclosures: Fatima Elmustafa,:Nothing to Disclose, Shahzad Ashraf:Nothing to Disclose, Faris Abdulaziz: Nothing to Disclose, Sajid Jalil:Nothing to Disclose, Mangesh Pagadala:Nothing to Disclose, Akash Shukla: Nothing to Disclose, Binu John:Exact Sciences: Grant/Research Support, Genentech: Grant/Research Support, Glycotest, Inc: Grant/Research Support, Gilead: Grant/Research Support, Takeda: Grant/Research Support, Exelixis: Consultant, Exact Sciences: Received institutional research funding, Genentech: Received institutional research funding, Takeda: Received institutional research funding, Madrigal: Advisor, Ipsen: Advisor, Patrizia Burra:Nothing to Disclose, Winston Dunn:Nothing to Disclose, Ashwani Singal:Madrigal: Speaking and Teaching, Pleiogenix: Stock – privately held company, Pleiogenix: Consultant, CLD Foundation: Advisor, Medical Speaker's Network: Speaking and Teaching, Up-to-Date: Royalties or patent beneficiary, Medscape: Speaking and Teaching, University of Louisville School of Medicine: Employee, NIAAA: Grant/Research Support, Gastro Endo News: Executive role, Durect: Advisor, University of Louisville Health: Other.

4531 | ALLOGRAFT STEATOSIS REFLECTS PRE-TRANSPLANT METABOLIC RISK RATHER THAN AN INDEPENDENT DRIVER OF OUTCOMES IN ADULT LIVER TRANSPLANT RECIPIENTS

Yinan Su[1] Roxanna Sharifi[1] Daanyaal Kumar[2] Paul Paik[3] Andrew John Cruz[2] Kalpana Gopalkrishnan[4] Niveda Balemurughan[4] Juan Carlos Delgado[5] Alejandro Delgado[2] Scott Jun[2] Derek Samson[6] Jeffrey Kahn[7] Norah Terrault[8] Liyun Yuan[8], [1]Keck Medicine of USC, University of Southern California, [2]USC/Los Angeles General Medical Center Internal Medicine Residency Program, [3]Keck School of Medicine, University of Southern California. Los Angeles, California, [4]Keck School of Medicine, University of Southern California, [5]The Kaiser Permanente Los Angeles Medical Center, [6]Transplant Institute, Keck Medicine of USC, University of Southern California,, [7]Keck School of Medicine, University of Southern Cal, [8]University of Southern California

Background: Allograft steatosis is commonly identified on liver biopsy among liver transplant (LT) recipients. The natural history of allograft steatosis and associated fibrosis has been reported with a wide range of outcomes, ranging from slow indolent courses to rapid progression. These discrepancies may derive from heterogeneity in patient populations, metabolic risk burden, and differences in fibrosis assessment methodology. In this study, we investigated i) the prevalence and the associated risk factors for allograft steatosis and ii) evaluate graft fibrosis and post-transplant mortality in patients with allograft steatosis. **Methods:** We conducted a retrospective,

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single-center study of adult liver transplant recipients transplanted 2015-2023 who underwent post-transplant liver biopsy for abnormal liver tests at any point from 3 months to 5 years post-LT. Hepatic steatosis was defined as ≥5% macrovesicular steatosis. Fibrosis was assessed histologically and graded as F1, F2/F3, F4, or indeterminate. Multivariable logistic regression adjusted for age and sex assessed factors associated with allograft steatosis. **Results:** Among the subgroup of 489 patients who underwent post-LT biopsy (median age 57, 45.4% female), 158 (32.3%) had allograft steatosis at any point between 3 months and 5 years post-LT. The cumulative number of patients identified with allograft steatosis increased over time post-LT. Pre-LT metabolic syndrome (aOR 2.59, 95% CI 1.59-4.21; p < 0.001), diabetes (aOR 1.62, 95% CI 1.06-2.47; p = 0.02), and obesity (aOR 1.59, 95% CI 1.04-2.41; p = 0.03) were associated with allograft steatosis, while post-LT development of de novo metabolic risk factors was not after adjustment for age and sex. Hepatic fibrosis was uncommon and predominantly mild in patients with allograft steatosis. Among patients with allograft steatosis biopsied up to 5 years post-LT, 3.8% (n = 6) had F1 fibrosis, 1.3% (n = 2) had F2 or F3, and no patients had F4 or allograft cirrhosis. **Conclusion:** Allograft steatosis is a common finding among individuals receiving post-LT biopsy. It is linked to pre-transplant metabolic risk factors including metabolic syndrome, type 2 diabetes and obesity, whereas de novo post-LT diabetes and obesity were not independently associated. Yet, the progression to advanced fibrosis was rare within 5 years, and no patients developed allograft cirrhosis at up to 5 years post-LT. However, longer-term follow-up may identify additional patients with advanced fibrosis. Additionally, patients with allograft steatosis did not present with worse outcomes in comparison to those without allograft steatosis. These findings suggest that allograft steatosis may primarily reflect pre-transplant metabolic risk rather than serving as an independent driver of adverse outcomes.

Table1. Outcomes counted at each time interval among individuals with allograft steatosis

	3 month	6 month	1year	3 year	5 year
Cumulative allograft steatosis(n)	55	77	108	143	157
Fibrosis at this visit	5 (9.1%)	5 (6.5%)	13 (12%)	19 (13.3%)	9 (5.7%)
F1	4 (7.3%)	4 (5.2%)	11(10.2%)	13 (9.1%)	6 (3.8%)
F2/F3	1 (1.8%)	0 (0.0%)	1 (0.9%)	1 (0.7%)	2 (1.3%)
F4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Indeterminate score	0 (0.0%)	1 (1.3%)	1 (0.9%)	5 (3.5%)	1 (0.6%)

Table 2. Associated risk factors with the presence of allograft steatosis.

	aOR (95% CI)	P
Pre-LT metabolic syndrome	2.59 (1.59-4.21)	<.001
Pre-LT diabetes	1.62 (1.06-2.47)	.02
Pre-LT obesity	1.59 (1.04-2.41)	.03
Post-LT new diabetes	1.51 (0.92-2.50)	.11
Post-LT obesity	1.68 (0.88-3.21)	.12

Multivariable logistic regression, with presence of allograft steatosis found on biopsy at any point from 3 months to 5 years post-LT as the outcome, adjusted for age and sex.

Disclosures: Yinan Su:Nothing to Disclose, Roxanna Sharifi:Nothing to Disclose, Daanyaal Kumar:Nothing to Disclose, Paul Paik:Nothing to Disclose, Andrew John Cruz:Nothing to Disclose, Kalpana Gopalkrishnan:Nothing to Disclose, Niveda Balemurughan:Nothing to Disclose, Juan Carlos Delgado:Nothing to Disclose, Alejandro Delgado:Nothing to Disclose, Scott Jun:Nothing to Disclose, Derek Samson:Nothing to Disclose, Jeffrey Kahn:Nothing to Disclose, Norah Terrault:Elseiver: Royalties or patent beneficiary, GSK: Grant/Research Support, Elseiver: Royalties or patent beneficiary, Elseiver: Royalties or patent beneficiary, Eiger Pharmaceuticals: Grant/Research Support, GSK: Grant/Research Support, GSK: Grant/Research Support, Helio Health: Grant/Research Support, Eiger Pharmaceuticals: Grant/Research Support, Eiger Pharmaceuticals: Grant/Research Support, Durect Corp: Grant/Research Support, Helio Health: Grant/Research Support, ImmunoCore: Grant/Research Support, Helio Health: Grant/Research Support, Durect Corp: Grant/Research Support, HBV Foundation: Board member, Durect Corp: Grant/Research Support, AASLD: Executive role, ImmunoCore: Grant/Research Support, ImmunoCore: Grant/Research Support, Genentech-Roche: Grant/Research Support, HBV Foundation: Board member, HBV Foundation: Board member, Hepatitis B Foundation: Executive role, AASLD: Executive role, AASLD: Executive role, Genentech-Roche: Grant/Research Support, Genentech-Roche: Grant/Research Support, Hepatitis B Foundation: Executive role, Hepatitis B Foundation: Executive role, Elseiver: Royalties or patent beneficiary, GSK: Grant/Research Support, Elseiver: Royalties or patent beneficiary, Elseiver: Royalties or patent beneficiary, Eiger Pharmaceuticals: Grant/Research Support, GSK: Grant/Research Support, GSK: Grant/Research Support, Helio Health: Grant/Research Support, Eiger Pharmaceuticals: Grant/Research Support, Eiger Pharmaceuticals: Grant/Research Support, Durect Corp: Grant/Research Support, Helio Health: Grant/Research Support, ImmunoCore: Grant/Research Support, Helio Health: Grant/Research Support, Durect Corp: Grant/Research Support, HBV Foundation: Board member, Durect Corp: Grant/Research Support, AASLD: Executive role, ImmunoCore: Grant/Research Support, ImmunoCore: Grant/Research Support, Genentech-Roche: Grant/Research Support, HBV Foundation: Board member, HBV Foundation: Board member, Hepatitis B Foundation: Executive role, AASLD: Executive role, AASLD: Executive role, Genentech-Roche: Grant/Research Support, Genentech-Roche: Grant/Research Support, Hepatitis B Foundation: Executive role, Hepatitis B Foundation: Executive role, Elseiver: Royalties or patent beneficiary, GSK: Grant/Research Support, Elseiver: Royalties or patent beneficiary, Elseiver: Royalties or

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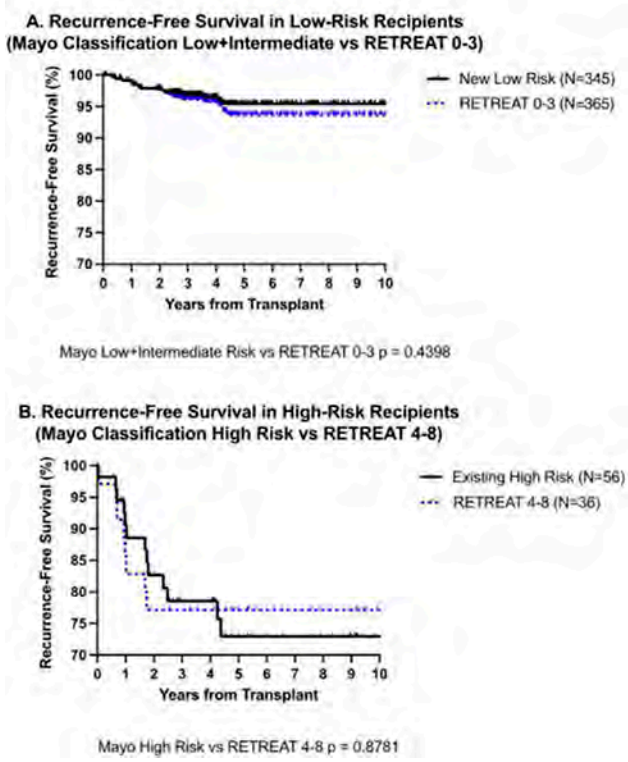
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4532 | A SIMPLIFIED STRATEGY TO STRATIFY HEPATOCELLULAR CARCINOMA RECURRENCE RISK AFTER LIVER TRANSPLANTATION

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Background: Hepatocellular carcinoma (HCC) recurrence risk after liver transplantation (LT) necessitates imaging-based surveillance in most patients. Among several risk-prediction models, the Risk Estimation of Tumor REcurrence After Transplant (RETREAT) score is a well-validated 0-8 scale derived from the alfa-fetoprotein level at LT, and number of viable tumors, largest viable tumor size and microvascular invasion status in the explant, to direct the frequency and duration of surveillance. Our institution utilizes an alternative, consensus-derived, low (LR), intermediate (IR), and high risk (HR) classification based on tumor burden, vascular invasion, and grade of differentiation that obviates the need to compute a discrete score. Whereas a RETREAT of 5-8 proposes 12-14 chest and abdomen scans over 5 years, our HR category requires 6 chest and abdomen scans over 3 years. We investigated how our institutional scale performs against the RETREAT score in predicting HCC recurrence. **Methods:** We conducted a survival analysis, stratified by RETREAT and Mayo Clinic risk scores, of all patients who underwent LT for HCC or were incidentally found to have HCC at LT at Mayo Clinic Arizona between 1/2015-12/2023, followed through May 2026. We categorized RETREAT 0-3, 4-5, and 6-8 as risk groups that may correspond to LR, IR, and HR, respectively. **Results:** In 401 LT recipients, median follow up was 4.3 years (IQR 2.8-7.3) and overall HCC recurrence rate was 6.4%, with only 1.2% recurring beyond 3 years. Recurrence rate was 4.2%, 5.8% and 27.1% in LR, IR, and HR groups respectively, and 4.9%, 19.3%, and 40% by RETREAT scores 0-3, 4-5, and 6-8 respectively. LR and IR recurrence rates were comparable to RETREAT 0-3, allowing LR+IR to be collapsed into a single New Low Risk category ($p = 0.44$) (Fig. 1A). HR outcomes were comparable to RETREAT 4-5 and 6-8, allowing RETREAT 4-8 to be collapsed as a single high-risk category ($p = 0.88$) (Fig. 1B). C-index for predicting recurrence with RETREAT was 0.631 and 0.691 with the Mayo score. **Conclusion:** In this retrospective single-center analysis, a simplified risk stratification based on tumor burden differentiated patients at lower and higher HCC recurrence risk, comparable to the four-variable, 9-point RETREAT score. HCC recurrence rate beyond 3 years was low. If further validated, this simplified paradigm may adequately identify patients who need more intensive post-LT HCC recurrence surveillance, and necessitate fewer scans and shorter surveillance duration than proposed in the RETREAT guidelines.

Figure 1



Disclosures: Akarshi Brar:Nothing to Disclose, Michele Barnhill:Nothing to Disclose, Fares Jamal:Nothing to Disclose, Abdullah Alsulaiman:Nothing to Disclose, W. Ray Kim:Nothing to Disclose, Bashar

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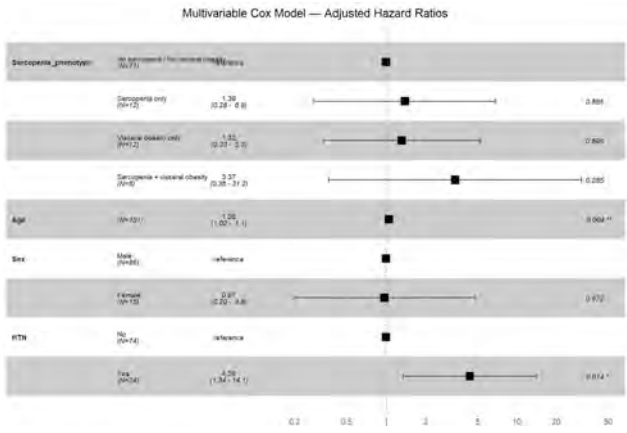
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Aqel:Nothing to Disclose, Channa Jayasekera:Nothing to Disclose.

4533 | COMPUTED TOMOGRAPHY–DEFINED SARCOPENIA AND VISCERAL OBESITY PHENOTYPES ARE NOT INDEPENDENTLY ASSOCIATED WITH POST-LIVER TRANSPLANT MAJOR ADVERSE CARDIOVASCULAR EVENTS

Poojitha Pai[1] Tamoor Afzaal[2] Sangmin Lee[1] Lujain Alrabghi[1] Saleh Alobaid[1] Carly Burow[1] Anya Sarma[3] Daniel Picard[4] Milad Hamwi[4] Harry Marshall[5], [1]Department of Medicine, Western University, [2]Department of Medicine, Division of Gastroenterology, Western University, [3]Western University, [4]Department of Radiology, London Health Sciences Centre, [5]Department of Radiology, Vanderbilt University Medical Center

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a leading indication for liver transplantation (LT) and is closely linked to sarcopenia and visceral obesity (VO). Sarcopenic visceral obesity (SVO) is associated with poor post-LT outcomes, however, its relationship with post-LT major adverse cardiovascular events (MACE) is ill-defined. We evaluated the association between CT-defined sarcopenia/VO phenotypes and post-LT MACE. **Methods:** We performed a retrospective cohort study of adult LT recipients (LTR) in London, Canada (2005-2019) with available pre-LT abdominal CT imaging and longitudinal follow-up. Patients with multi-organ transplantation, previous transplant, severe allograft dysfunction, re-transplantation within 1 year, and living donors, were excluded. Cross-sectional body composition analysis at the L3 vertebral level quantified skeletal muscle index (SMI) and visceral-to-subcutaneous adipose tissue ratio (VSR). Sarcopenia was defined as SMI < 50 cm²/m² in men and < 39 cm²/m² in women. VO was defined using sex-specific VSR thresholds. LTRs were categorized into 4 phenotypes: no sarcopenia/no VO, sarcopenia only, VO only, and combined SVO. Primary outcome was post-LT MACE, defined as cardiovascular death or hospitalization for myocardial infarction, revascularization, heart failure, atrial fibrillation, stroke/TIA, pulmonary embolism, or cardiac arrest. Cox proportional hazards (PH) models identified risk factors for post-LT MACE. **Results:** Among 566 LTRs, 419 met exclusion criteria. In the analyzed 147 LTRs (mean age 61.0 ± 16.4 years; 82.3% male), sarcopenia only, VO only, and SVO phenotypes were present in 17.7%, 10.9%, and 5.4%, respectively. Post-LT MACE incidence was 26.7%. MACE rates differed across phenotypes but not statistically significant (no sarcopenia/no VO 26.0% vs sarcopenia only 14.3% vs VO only 55.6% vs SVO 20.0%; $p = 0.168$). In multivariable Cox PH analysis, sarcopenia only (aHR 1.39, 95%CI 0.28–6.87), VO only (aHR 1.32, 95%CI 0.33–5.27), and SVO (aHR 3.37, 95%CI 0.36–31.2) were not associated with post-LT MACE. Older age (aHR 1.05/year, 95%CI 1.02–1.09; $p = 0.004$) and hypertension (aHR 4.36, 95%CI 1.34–14.1; $p = 0.014$) were significantly associated with post-LT MACE. Longitudinal analyses revealed concerning metabolic trajectories among VO phenotypes, persistently higher HbA1c levels 5 years post-LT (7.0% in VO only vs 6.2% in no sarcopenia/no VO; $p = 0.055$), while sarcopenic phenotypes trended towards worsening renal function. **Conclusion:** Sarcopenia and VO phenotypes were not independently associated with post-LT MACE after adjusting for traditional cardiovascular risk factors. However, VO demonstrated higher MACE rates and concerning metabolic trajectories, suggesting a potential signal warranting larger, adequately-powered studies. Older age and hypertension, remain significantly associated with post-LT MACE



Disclosures: Poojitha Pai:Nothing to Disclose, Tamoor Afzaal:Nothing to Disclose, Sangmin Lee: Nothing to Disclose, Lujain Alrabghi:Nothing to Disclose, Saleh Alobaid:Nothing to Disclose, Carly Burow:Nothing to Disclose, Anya Sarma:Nothing to Disclose, Daniel Picard:Nothing to Disclose, Milad Hamwi:Nothing to Disclose, Harry Marshall:Nothing to Disclose.

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4534 | OLDER LIVING DONORS: NOT THE BEST, BUT DEFINITELY WORTH WAITING FOR

Lauren Callans[1] Russell Rosenblatt[1], [1]Weill Cornell Medicine

Background: Living donor liver transplantation (LDLT) is associated with improved post-transplant survival, but a recent study suggested that older LDLT grafts have worse outcomes. This study aims to evaluate the survival differences in patients on the waitlist by graft type, with a focus on older LDLT donors. **Methods:** Adults listed for LT in the UNOS STAR file from 2015-2025 were included. Patients were excluded if they were listed for multiple organs, had prior liver transplants, had exception points, or had acute liver failure. Graft types were classified as LDLT old (donor age ≥ 45), LDLT young (donor age < 45), donation after brain death (DBD), donation after circulatory death (DCD), DCD with machine perfusion (DCD+M), and not transplanted. The primary outcomes were graft and overall survival. We performed two analyses: 1. As-treated (AT), starting at time of LT and 2. Intention-to-treat (ITT), starting at time of waitlisting. Survival analysis was performed and, to counteract immortal time bias, time-varying covariates were utilized. A flexible parametric survival model was fitted using the Royston-Parmar approach and predicted survival curves were generated. The multivariable model included liver disease etiology, age, MELD, and sex. Finally, LDLT old were compared to all patients awaiting deceased donor to evaluate whether this was superior to waiting. **Results:** 82,216 were included in the AT analysis – 3.9% LDLT young, 1.5% LDLT old, 82% DBD, 8.7% DCD, and 4.2% DCD+M. An additional 129,769 were included in the ITT analysis who were not transplanted. LDLT recipients were younger with lower MELD scores than deceased donor LT recipients.In the AT analysis, survival was excellent across all donor types. LDLT young had the best, while DCD had the worst graft/overall survival (Figure 1A). In multivariable models, compared to LDLT old, only LDLT young was significantly different, showing improved survival (HR 0.79, 95% CI 0.66–0.95). Time-varying analyses demonstrated these differences remained stable over time.In the ITT analysis, compared to LDLT old, LDLT young maintained a survival advantage across all timepoints, DBD and DCD+M showed an early survival advantage that attenuated over time, and DCD showed no difference compared with LDLT old. Remaining on the waitlist was associated with significantly higher mortality that increased over time.Finally, LDLT old was compared to all patients awaiting deceased donor. LDLT old showed improved survival across all time points (HR 0.45, 95% CI 0.39-0.52) (Figure 1B). **Conclusion:** LDLT old achieved survival rates that were comparable to patients receiving deceased donor transplants but worse than LDLT young. However, LDLT old maintained significantly better survival compared to those awaiting deceased donor transplant on the waitlist, demonstrating its overall benefit on survival.

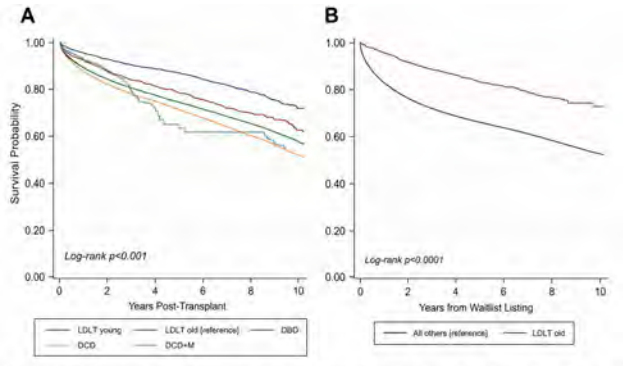


Figure 1A. Observed overall survival post-transplant grouped by transplant donor type in AT analysis starting at time of transplant. **B.** Observed overall survival post-listing comparing LDLT old vs. All others (excluding LDLT young) in ITT analysis starting at time of waitlisting.

Disclosures: Lauren Callans:Nothing to Disclose, Russell Rosenblatt:Gilead: Grant/Research Support.

4535 | AGE ABOVE 65 YEARS OLD AND FRAILTY ARE ADVERSE PREDICTORS OF LIVING-DONOR LIVER TRANSPLANT RECIPIENTS' GRAFT FAILURE, MORTALITY, AND LENGTH OF HOSPITALIZATION

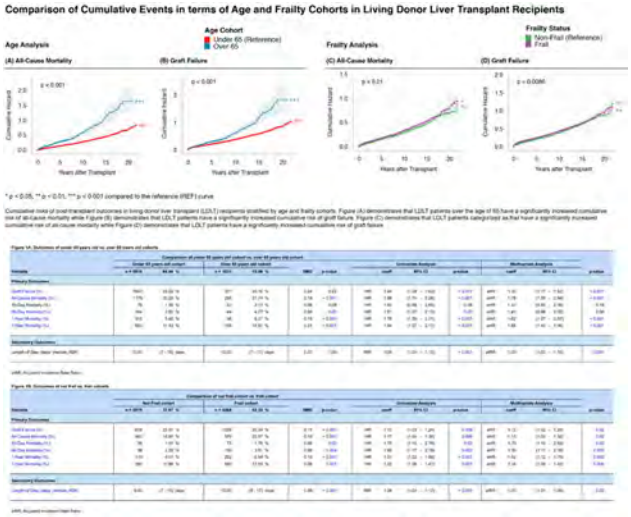
Christina Lee[1] Gregory Fan[1] Ki Jung Lee[1] Raffi Karagozian[1], [1]Tufts medical center

Background: Frailty is a well-known predictor of adverse outcomes in liver transplant recipients and living-donor liver transplantation (LDLT) is widely known to provide excellent post-transplant outcomes. However, there exists a knowledge gap for predictors of LDLT outcomes. Our study is aimed to understand the survival outcomes of elderly and frail patients undergoing LDLT. **Methods:** A total of 6,847 LDLT patients were selected from the 2002-2024 UNOS-STAR database and stratified by age (1031 over 65 years old and 5816 under 65 years old) and by frailty (4268 frail and 2579 non-frail). Demographics were the following in the cohort for the elderly patients: race (white, 81%), mean age 68 years old, sex (male, 50%), BMI (27 kg/m2). Demographics were the following in the cohort for the frail patients: race (white, 79%), mean age 56 years old, sex (male, 51%), BMI (26 kg/m2). Elderly age was defined as > 65 years old and non-elderly age was defined between 18-64 years old. Frailty was defined using the following clinical findings: presence of dialysis, Karnofsky's functional status < 70%, BMI < 18 kg/m2,

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presence of hepatic encephalopathy, albumin < 2.5 g/L. A cumulative total score of 3 or greater defined frailty. Primary outcomes were the following: graft failure, all-cause mortality, 30-day, 90-day mortality, 1-year, 5-year mortality. Length of hospital stay was investigated as our secondary outcome. For both graft failure and all-cause mortality, follow-up time was 8 years. All outcomes were analyzed using cause-specific Cox regression while accounting for competing risks. **Results:** After LDLT, elderly patients overall had significantly higher graft failure and all-cause mortality within 8-years ($p < 0.001$). Elderly patients demonstrated higher mortality at 90 days ($p = 0.02$) in the univariate analysis, higher mortality at both 1-year and 5-year status-post LDLT ($p = < 0.001$). Secondarily, length of hospital stay was longer in the elderly patients ($p = 0.001$). **Figure 1A.** Frail patients exhibited significantly higher rates of the following after LDLT: graft failure ($p = 0.02$), all-cause mortality ($p = 0.02$), 30-day mortality ($p = 0.02$), 90-day mortality ($p = 0.010$), 1-year mortality ($p = 0.003$), 5-year mortality ($p = 0.006$), and length of hospital stay ($p = 0.02$). **Figure 1B. Conclusion:** Both elderly age and frailty served as strong adverse predictors of higher graft failure, all-cause mortality, as well as increased length of hospitalization status post LDLT. Our results help guide future liver transplant recipient selection processes, as well as heightens awareness about the potential higher complications which can occur in this specific population of patients undergoing a LDLT.



Disclosures: Christina Lee:Nothing to Disclose, Gregory Fan:Nothing to Disclose, Ki Jung Lee:Nothing to Disclose, Raffi Karagozian:Nothing to Disclose.

4536 | ANALYSIS OF CIRCADIAN DYSFUNCTION IN NON-DIABETIC INDIVIDUALS WITH CIRRHOSIS

Sofia Alikhan[1], [1]University of Chicago

Background: Circadian rhythms are the internal clocks which regulate sleep, eating patterns, physical activity, and metabolism. The liver plays a central role in maintaining metabolic stability, and many of its functions are synchronized with these circadian rhythms. In cirrhosis, this metabolic stability is disrupted, which impacts these rhythms. We aim to determine how these disruptions occur across sleep and eating patterns in non-diabetic individuals with cirrhosis. **Methods:** This study used activity monitoring and continuous glucose monitoring (CGM) to characterize sleep and eating patterns in non-diabetic individuals with cirrhosis undergoing liver transplant evaluation. Fifty-one subjects with cirrhosis without diabetes completed sleep monitoring using a Fitbit Inspire 3 and 34 subjects completed glucose monitoring using blinded Abbott Libre Pro CGMs, which were then compared against surveys completed by each of the patients including the Morningness-Eveningness Questionnaire (MEQ), Pittsburgh Sleep Quality Index (PSQI), and PRAPARE socioeconomic questionnaire. **Results:** Overall, the subjects objectively woke consistently between 3 - 4 AM regardless of preferred wake timing on the MEQ ($p = 0.94$, Fig. A). Subjects went to bed significantly later than their self-reported ideal bedtime by an average of 1.54 hours ($p < 0.0005$, Fig. B). Objective sleep duration averaged approximately 5 - 7 hours nightly and did not significantly differ across PSQI self-reported sleep-duration categories ($p = 0.35$, Fig. C), indicating a disconnect between perceived and objective sleep. Sleep, wake, and sleep duration misalignment were not significantly associated with socioeconomic factors, sleep quality, glucose spikes, MELD 3.0 score, or CTP score ($p > 0.05$ for all confounders). Average CGM eating analyses showed that timing of glucose-spike events and low-glucose events did not significantly predict altered sleep timing, wake timing, or sleep-duration discrepancy ($p > 0.05$ for all). Time of first eating and eating schedules differed significantly between individuals ($p < 0.0001$). However, meal timing remained stable across days of the week for each individual ($p = 0.34$, Fig. D), indicating individuals had distinct patterns of eating and CGM spikes. **Conclusion:** These findings demonstrate circadian disruption in non-diabetic individuals with cirrhosis undergoing transplant evaluation that is not explained by common social, or disease-severity confounders. In the future, we will continue to research the underlying mechanisms of these irregularities, as well as possible interventions to restore circadian

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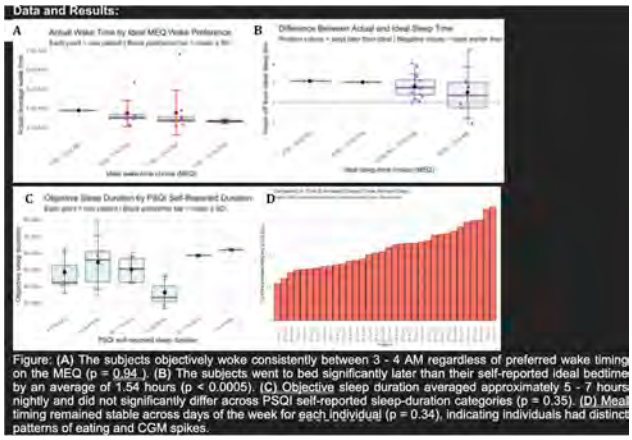


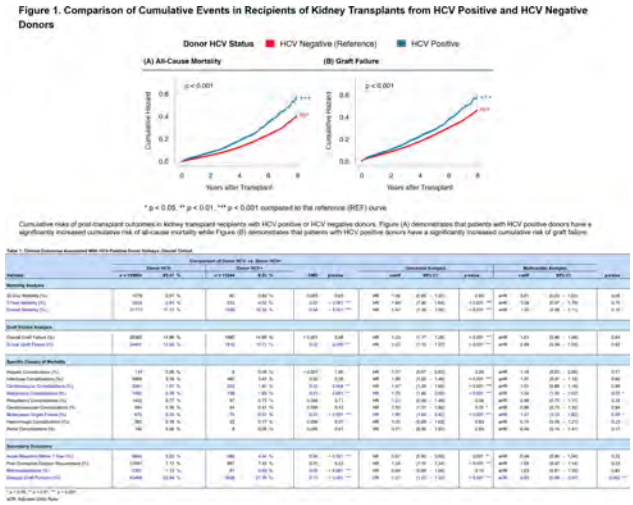
Figure: **(A)** The subjects objectively woke consistently between 3 - 4 AM regardless of preferred wake timing on the MEQ ($p = 0.94$). **(B)** The subjects went to bed significantly later than their self-reported ideal bedtime by an average of 1.54 hours ($p < 0.0005$). **(C)** Objective sleep duration averaged approximately 5 - 7 hours nightly and did not significantly differ across PSQI self-reported sleep-duration categories ($p = 0.35$). **(D)** Meal timing remained stable across days of the week for each individual ($p = 0.34$), indicating individuals had distinct patterns of eating and CGM spikes.

Disclosures: Sofia Alikhan:Nothing to Disclose.

4537 | CONTEMPORARY OUTCOMES FOLLOWING KIDNEY TRANSPLANTATION FROM HCV-POSITIVE DONORS: A NATIONAL UNOS REGISTRY ANALYSIS

Ki Jung Lee[1] Gregory Fan[1], [1]Tufts Medicine

Background: The utilization of hepatitis C virus (HCV)-positive donor kidneys has increased substantially in the direct-acting antiviral era to expand the donor pool and reduce waitlist times. However, concerns remain regarding graft survival and post-transplant outcomes among recipients of HCV-positive donor organs. **Methods:** We performed a retrospective cohort study using the United Network for Organ Sharing (UNOS) registry from 2016-2024 evaluating adult kidney transplant recipients stratified by donor HCV status. Baseline recipient and donor characteristics were compared between groups. Multivariable logistic regression and Cox proportional hazards models were used to evaluate delayed graft function (DGF), graft failure, mortality, and post-transplant complications after adjustment for recipient demographics, comorbidities, dialysis duration, donor characteristics, HLA mismatch, and ischemic time. **Results:** A total of 202,798 kidney transplant recipients were included, of whom 13,244 (6.5%) received kidneys from HCV-positive donors. Recipients of HCV-positive donor kidneys exhibited a greater comorbidity burden and longer cold ischemic times, while HCV-positive donors were more frequently male and had higher rates of cocaine exposure. In unadjusted analyses, transplantation from HCV-positive donors was associated with increased delayed graft function (OR 1.27, 95% CI 1.22-1.32), 5-year graft failure (HR 1.22, 95% CI 1.16-1.27), 1-year mortality (HR 1.49, 95% CI 1.36-1.64), and overall mortality (HR 1.47, 95% CI 1.39-1.55). However, these associations were largely attenuated after multivariable adjustment. HCV-positive donor status was not independently associated with increased 5-year graft failure (aHR 0.99, 95% CI 0.94-1.05), overall mortality (aHR 1.05, 95% CI 0.99-1.11), cardiovascular complications (aHR 1.01, 95% CI 0.88-1.16), or infectious complications (aHR 1.01, 95% CI 0.91-1.13). Adjusted analyses demonstrated lower odds of delayed graft function among recipients of HCV-positive donor kidneys (aOR 0.93, 95% CI 0.89-0.97). Although most associations were attenuated after adjustment, increased risks of malignancy complications (aHR 1.24, 95% CI 1.02-1.52) and multisystem organ failure complications (aHR 1.37, 95% CI 1.03-1.82) persisted. **Conclusion:** Recipients of HCV-positive donor kidneys demonstrated worse unadjusted graft and mortality outcomes, reflecting substantial baseline differences in recipient and donor risk profiles. However, these associations were largely attenuated after multivariable adjustment, with no independent increase in long-term graft failure or overall mortality observed. These findings suggest that HCV-positive donor kidneys can be utilized without compromising long-term graft or patient survival and support continued use of these organs to expand the donor pool.



Disclosures: Ki Jung Lee:Nothing to Disclose, Gregory Fan:Nothing to Disclose.

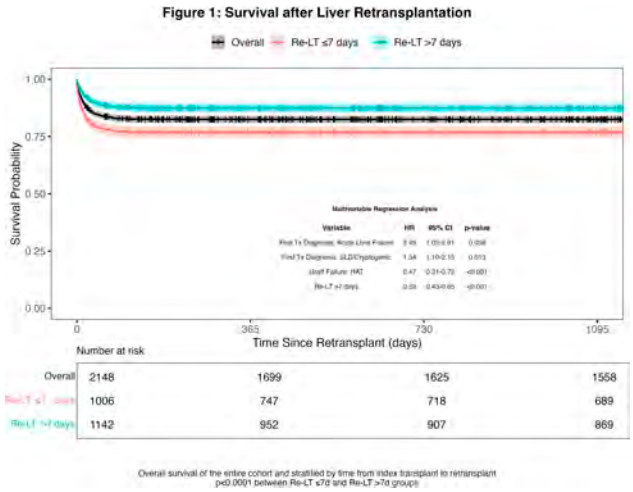
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4538 | TIMING OF LIVER RETRANSPLANTATION FOR EARLY GRAFT FAILURE: A NATIONAL REGISTRY ANALYSIS

Eytan Palte[1] Elizabeth Verna[2] Jason Hawksworth[1] Tomoaki Kato[3] Giuseppe Cullaro[1], [1]Columbia University Irving Medical Center, [2]Columbia University Medical Center, [3]Columbia University

Background: Early graft failure within 30 days of liver transplantation (LT) is a rare but devastating complication requiring urgent decisions about retransplantation (re-LT). The optimal timing of re-LT in this setting is poorly characterized. **Methods:** We conducted a retrospective cohort study using the Scientific Registry of Transplant Recipients (SRTR) including all adult (≥ 18 years) liver transplant recipients who underwent re-LT within 30 days of their index transplant during the MELD era (2002-2025). The primary outcome was post-re-LT survival censored at 5 years. An optimal timing threshold was identified using maximally selected rank statistics with bootstrap validation. Multivariable Cox proportional hazards models assessed associations between re-LT timing and survival, adjusting for recipient, donor, and transplant-level covariates. **Results:** Among 2,161 patients who underwent re-LT within 30 days, median time to re-LT was 8 days (IQR 4-15). Overall 1-year survival after re-LT was 82.5%. 7 days was the optimal timing threshold (bootstrap stability 78%, 95% CI 2-8 days). In the multivariable analysis, patients retransplanted > 7 days after index LT had 47% lower hazard of death compared to those retransplanted within 7 days (adjusted HR 0.53, 95% CI 0.43-0.65). Hepatic artery thrombosis (HAT) as the cause of graft failure was independently associated with improved post-re-LT survival (adjusted HR 0.47, 95% CI 0.31-0.72). These findings persisted in a contemporary cohort (2016-2025) isolated to account for decreases in HCV recurrence (n = 785; adjusted HR 0.54, 95% CI 0.36-0.81). Among those who underwent re-LT within 7 days, each one-point increase in donor risk index (DRI) was associated with a 20% increased hazard of death (HR 1.20, 95% CI 1.00-1.44, p = 0.045). There was no statistically significant interaction between cause of graft failure and time to retransplant. **Conclusion:** Among patients undergoing re-LT for early graft failure, survival beyond 7 days from the index transplant identifies a subgroup with substantially better post-re-LT outcomes, likely reflecting survivor selection rather than a causal benefit of delay. Within 7 days, donor quality (DRI) is a key determinant of survival. These findings cannot guide allocation policy but can inform clinician–patient discussions of risk in early re-LT.



Overall survival of the entire cohort and stratified by time from index transplant to retransplant p<0.0001 between Re-LT ≤7d and Re-LT >7d groups

Disclosures: Eytan Palte:Nothing to Disclose, Elizabeth Verna:Nothing to Disclose, Jason Hawksworth: Nothing to Disclose, Tomoaki Kato:Nothing to Disclose, Giuseppe Cullaro:Ocelot Bio: Consultant, Retro Sciences: Consultant, Ipsen: Consultant.

4539 | IMPACT OF DONOR AND RECIPIENT DIABETES STATUS ON CAUSE-SPECIFIC POST-TRANSPLANT MORTALITY IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS

Kai-Lou Yue[1] Katherine Cooper[2] Ami Patel[1] Deepika Devuni[3], [1]UMass Chan Medical School, Worcester, MA, [2]Massachusetts General Hospital, Boston, MA, [3]UMass Memorial Medical Center, Worcester, MA

Background: Pre-transplant type 2 diabetes mellitus (T2DM) in liver transplant (LT) recipients is associated with increased post-LT mortality, particularly in those transplanted for metabolic dysfunction-associated steatotic liver disease (MASLD). However, the impact of donor diabetes on mortality remains unclear. **Methods:** This study used United Network for Organ Sharing (UNOS) Standard Transplant Analysis and Research (STAR) data from 1/1/05-12/31/25. Adult deceased donor LT recipients transplanted for metabolic dysfunction-associated steatohepatitis (MASH) with known donor and recipient diabetes status were included, excluding those listed for status 1A or multi-organ transplant. Diabetes status was categorized as: no diabetes, recipient-only (RO) diabetes, donor-only (DO) diabetes, and combined donor and recipient (D+R) diabetes. All-cause mortality rates were compared across diabetes groups using chi-squared analyses. Causes of death were grouped per UNOS categorizations. Cox regression models adjusted by sex, MELD score, age, BMI, and donor hypertension were used to

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evaluate cause-specific mortality in combined D+R diabetes vs RO diabetes. Secondary analyses examined the impact of DO diabetes on cause-specific mortality in recipients without pre-transplant diabetes. **Results:** A total of 4319 individuals were included, of whom 1931 died within the study period. All-cause mortality differed across diabetes groups ($p < 0.01$): 40.9% no diabetes (722/1767), 48.3% RO (943/1952), 39.6% DO (108/273), and 48.3% R+D (158/327). Among those with recipient diabetes, use of a donor with diabetes was not associated with increased mortality ($p = 1.00$). Similarly, among those without recipient diabetes, donor diabetes did not increase mortality ($p = 0.68$). The three most common reported causes of death across diabetes groups were infection (n = 276, 14.3%), cardiovascular disease (CVD; n = 263, 13.6%), and malignancy (n = 211, 10.9%). There were no significant differences in cause-specific mortality between R+D and RO; however, there was a trend toward increased CVD-related (HR 1.29, 95% CI 0.81-2.06) and decreased malignancy-related (HR 0.67, 95% CI 0.35-1.30) mortality in the R+D group. Similarly, there were no significant associations between DO and cause-specific mortality compared to no diabetes. **Conclusion:** In this cohort of LT recipients transplanted for MASH, D+R diabetes did not confer significant additional cause-specific mortality risk beyond that of RO diabetes across the three leading identified causes of post-transplant death. DO diabetes also did not increase mortality risk in those without T2DM. These findings suggest that donor diabetes status alone should not preclude utilization of an otherwise suitable organ in this population, which may have implications for organ allocation.

Table 1: Association between diabetes status and cause-specific post-transplant mortality in MASH

Cause of death	Comparison diabetes group	Reference diabetes group	Hazard Ratio (95% confidence interval)
Infection	Donor + recipient	Recipient only	0.99 (0.61-1.61)
	Donor-only	No diabetes	1.08 (0.65-1.78)
Cardiovascular disease	Donor + recipient	Recipient only	1.29 (0.81-2.06)
	Donor-only	No diabetes	1.21 (0.68-2.17)
Malignancy	Donor + recipient	Recipient only	0.67 (0.35-1.30)
	Donor-only	No diabetes	0.56 (0.27-1.17)

Disclosures: Kai-Lou Yue:Nothing to Disclose, Katherine Cooper:Nothing to Disclose, Ami Patel:Nothing to Disclose, Deepika Devuni:Nothing to Disclose.

4540 | NEW SUBMISSIONWAITLIST OUTCOMES AND LIVER TRANSPLANT ACCESS IN THE MELD 3.0 ERA: A UNOS ANALYSIS

Mangesh Pagadala[1] Jamil Abdo[2] David Maundu[3] Chencheng Xie[4] Sajid Jalil[5] Winston Dunn[6] Yong-Fang Kuo[7] Ashwani Singal[2], [1]Liver Institute Methodist Dallas, [2]University of Louisville, [3]KUMC, [4]University of Iowa, [5]Stanford University, [6]University of Kansas Medical Center, [7]UTMB

Background: MELD 3.0 was implemented on July 13, 2023, to reduce inequity in liver transplant (LT) allocation among women by incorporating sex into the algorithm. We evaluated the impact of MELD 3.0 on access to LT and waitlist (WL) mortality. **Methods:** A retrospective cohort (01/01/21 to 12/31/25) using the UNOS database of adult candidates listed for first deceased-donor LT was stratified into pre- (01/01/21 to 07/12/23) and post- (07/13/23 to 12/31/25) MELD 3.0 eras. We excluded status 1A/1B listings, pediatric candidates, living donor recipients, and multi-organ transplants. The primary outcome was the 90-day cumulative probability of WL mortality comparing males and females in the two MELD eras, with LT as the competing event. Fine and Gray regression models in the two eras were fitted to examine the sex-based impact on 90-day WL mortality after adjusting for other variables. **Results:** 52,208 adult LT listings (19,439 females), with 25,102 in the post–MELD 3.0 era (9578 females), were analyzed. Comparing pre- and post- MELD 3.0 eras, there was an increase in females (38 to 41.2%), alcohol-associated liver disease etiology (50 to 62%), and alcohol-associated hepatitis (16.1 to 34.7%), and a decrease in MASH (25 to 13%) < $P < 0.001$ for all. The crude rate of LT within 90 days increased for women (44.3% to 52.2%) and men (45.3% to 52.8%). WL mortality at 90 days declined, with a greater absolute reduction in women (6.6% to 5.5%) than men (5.4% to 4.9%). The unadjusted sub-hazard ratio (sHR) with 95% CI comparing 90-day WL mortality in women vs. men declined from 1.23 (1.11-1.36) in the pre- MELD 3.0 era to 1.12 (1.00-1.25) in the post- MELD 3.0 era. Similar figures, after adjusting for demographics, comorbidities, MELD score at listing, blood group, insurance, and performance status, were 0.97 (0.86–1.10, $P = 0.661$) and 0.97 (0.84–1.12, $P = 0.655$), respectively. In the post-MELD 3.0 era, a higher MELD score, poorer functional status, and older age predicted WL mortality, whereas ALD etiology was associated with lower WL mortality. **Conclusion:** MELD 3.0 implementation is associated with a greater reduction in waitlist mortality in women. Studies are needed to assess the role of factors beyond those in MELD 3.0, such as liver disease etiology, in determining the optimal use of liver transplantation

Disclosures: Mangesh Pagadala:Nothing to Disclose, Jamil Abdo:Nothing to Disclose, David Maundu:Nothing to Disclose, Chencheng Xie:Nothing to Disclose, Sajid Jalil:Nothing to Disclose, Winston Dunn:Nothing to Disclose, Yong-Fang Kuo:Nothing to Disclose, Ashwani Singal:Madrigal: Speaking and Teaching, Pleiogenix: Stock – privately held company, Pleiogenix: Consultant, CLD Foundation: Advisor, Medical Speaker's Network: Speaking and Teaching, Up-to-Date: Royalties or patent beneficiary, Medscape: Speaking and Teaching,

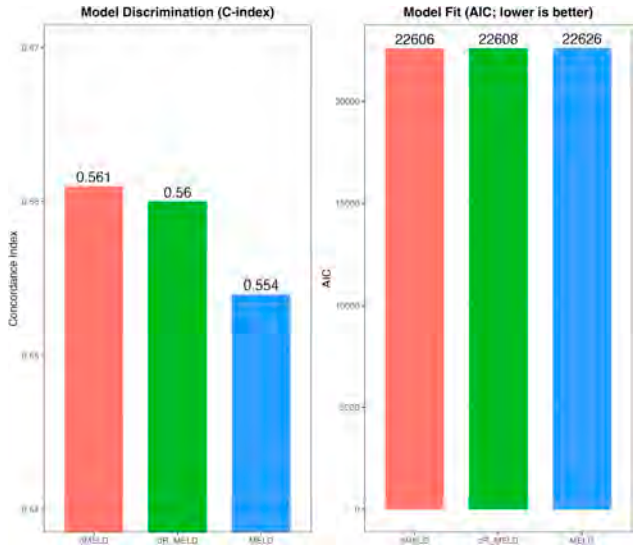
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University of Louisville School of Medicine: Employee, NIAAA: Grant/Research Support, Gastro Endo News: Executive role, Durect: Advisor, University of Louisville Health: Other.

4541 | CLINICAL UTILITY OF DONOR-RECIPIENT INTERACTION METRICS IN LIVER TRANSPLANTATION: A UNOS REGISTRY ANALYSIS

Shashank Varma Nadimpalli[1] Zyannah Malick[1] Tanisha Roy[1] Jacob Hallesy[1] Yuzuru Sambommatsu[1] David Bruno[1] Seung Duk Lee[1] Amit Sharma[1] Aamir Khan[1] Muhammad Saeed[1] Vinay Kumaran[1] Adrian Cotterell[1] Daisuke Imai[1], [1]Virginia Commonwealth University

Background: The Model for End-Stage Liver Disease (MELD) is widely used for liver transplant allocation but does not incorporate donor–recipient interaction effects or capture heterogeneity in donor age and recipient age relationships that may influence post-transplant outcomes. We evaluated whether interaction-based metrics, DMELD (donor age × MELD) and DRMELD (donor age × recipient age × MELD), provide incremental prognostic value over MELD alone across clinical eras and recipient subgroups. **Methods:** We performed a retrospective cohort study of adult liver transplant recipients from a national registry, assessing time to graft failure (graft loss or death). Exclusion criteria included age < 18 years, retransplantation, acute liver failure, HIV positivity, combined or split organ transplantation, in-vivo or non-heart-beating donation, metastatic disease, and incomplete records. Separate multivariable Cox proportional hazards models were constructed for MELD, DMELD, and DRMELD, adjusting for recipient age, BMI, creatinine, INR, donor characteristics, and ischemia times. Analyses were stratified by transplant era (2002–2014 vs 2015–present) and HCV serostatus. Model performance was assessed using Akaike Information Criterion (AIC) and Harrell's C-index. **Results:** Overall, all three models demonstrated similar discrimination. DMELD showed the lowest AIC (22,606) and highest C-index (0.561), compared with MELD (22,626; 0.554) and DRMELD (22,608; 0.560), although absolute differences were small. In multivariable analysis, recipient age (HR 1.011, $p < 0.001$), cold ischemia time (HR 1.029, $p < 0.001$), and warm ischemia time (HR 1.007, $p = 0.003$) were consistent independent predictors across models. Serum creatinine was significant only in the MELD model. Both DMELD (HR 1.0003, $p < 0.001$) and DRMELD (HR 1.000005, $p < 0.001$) were statistically significant but had minimal effect size per unit increase. Stratified analyses showed modest variation across subgroups. In the historical era (2002–2014), interaction-based metrics modestly outperformed MELD (DMELD C-index 0.566 vs 0.557), while in the modern era MELD performed similarly or slightly better (0.561 vs 0.554). In HCV-stratified analyses, patterns were comparable. DRMELD showed slightly improved visual separation in higher-risk strata despite near-identical global discrimination metrics. **Conclusion:** Interaction-based donor–recipient metrics are associated with graft survival and demonstrate statistically significant but small improvements in model performance compared with MELD. DMELD showed the most consistent incremental improvement; however, differences in discrimination were minimal across eras and subgroups. Overall, donor–recipient interaction effects appear biologically relevant but provide limited additional prognostic value beyond MELD in contemporary liver transplantation.



Disclosures: Shashank varma Nadimpalli:Nothing to Disclose, Zyannah Malick:Nothing to Disclose, Tanisha Roy:Nothing to Disclose, Jacob Hallesy:Nothing to Disclose, Yuzuru Sambommatsu:Nothing to Disclose, David Bruno:Nothing to Disclose, Seung Duk Lee: Intuitive: Consultant, Amit Sharma:Nothing to Disclose, Aamir Khan:Nothing to Disclose, Muhammad Saeed: Nothing to Disclose, Vinay Kumaran:Nothing to Disclose, Adrian Cotterell:Nothing to Disclose, Daisuke Imai:Nothing to Disclose.

4542 | RISK FACTORS FOR DEATH OR WAITLIST REMOVAL FOR DETERIORATION AMONG LIVER TRANSPLANT CANDIDATES AGED 70–74 YEARS: A COMPETING-RISK ANALYSIS

Kush Patel[1] Eyad Abdulrazzak[1] Irena Helenowski[1] Eric Kallwitz[1] Scott Cotler[1], [1]Loyola University Health System

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Background: Liver transplantation is increasingly considered for carefully selected older patients, but waitlist outcomes in candidates aged 70–74 are not well defined. We compared waitlist outcomes in candidates aged 70–74 with those of younger candidates and identified factors associated with death or waitlist removal for deterioration within the 70–74 cohort. **Methods:** The study population consisted of liver transplant candidates younger than 75 years placed on the UNOS liver transplant waiting list from 2/2020 to 12/2024. The primary endpoint was death or removal from the waitlist for deterioration. Fine-Gray competing-risk models were performed, with candidates aged 40–59 serving as the reference group. A full-cohort multivariable model adjusted for race/ethnicity, sex, diagnosis, ABO blood type, BMI < 25, diabetes, MELD, TIPS, bacterial peritonitis, hepatic encephalopathy grade 3–4, and Karnofsky score < 40% at registration. A separate multivariable model was performed within the 70–74 cohort. **Results:** The study population included 59,000 liver transplant candidates, of whom 3,448 were aged 70–74. Compared with younger candidates, those aged 70–74 more frequently had MASH, HCC, and diabetes, and had lower frequencies of hepatic encephalopathy grade 3–4, Karnofsky score < 40%, dialysis, bacterial peritonitis, and high MELD categories (all $p < 0.05$). In univariable Fine-Gray analysis, candidates aged 70–74 had increased risk of death or removal for deterioration compared with candidates aged 40–59 (sHR 2.09, 95% CI 1.86–2.34). In the full-cohort multivariable model, age 70–74 remained associated with increased risk (sHR 2.13, 95% CI 1.87–2.42). In the 70–74 cohort, factors independently associated with death or waitlist removal for deterioration included higher MELD categories, including MELD 30–34 (sHR 1.88, 95% CI 1.13–3.15) and MELD 35–40 (sHR 4.26, 95% CI 2.33–7.79), non-HCC cancer (sHR 1.98, 95% CI 1.06–3.69), BMI < 25 (sHR 1.53, 95% CI 1.19–1.96), and diabetes (sHR 1.44, 95% CI 1.12–1.85) (Figure). Female sex was associated with lower risk (sHR 0.73, 95% CI 0.56–0.95). **Conclusion:** During the acuity-circle allocation era, liver transplant candidates aged 70–74 had increased risk of death or waitlist removal for deterioration compared with younger candidates. Within the 70–74 cohort, adverse waitlist outcomes were associated with higher MELD, non-HCC cancer, BMI < 25, and diabetes, while female sex was associated with lower risk. These findings may help refine risk stratification among older liver transplant candidates.

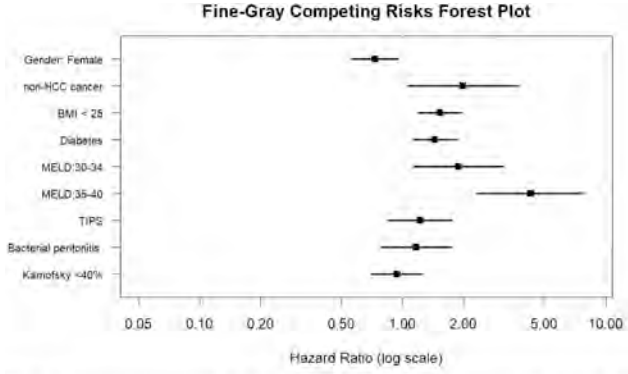


Figure. Factors associated with death or waitlist removal for deterioration in the aged 70-74 cohort.

Disclosures: Kush Patel:Nothing to Disclose, Eyad Abdulrazzak:Nothing to Disclose, Irena Helenowski: Nothing to Disclose, Eric Kallwitz:Nothing to Disclose, Scott Cotler:Nothing to Disclose.

4543 | INCIDENCE OF CHYLOUS COMPLICATIONS AFTER PEDIATRIC LIVER TRANSPLANTATION: A SINGLE-CENTER RETROSPECTIVE ANALYSIS

Richa Gupta[1] Rachel Smith[1], [1]UPMC Children's Hospital of Pittsburgh

Background: Chyle leaks are a recognized and relatively common complication following liver transplantation (LT); however, data specific to post-operative chylous effusion (CE) in the pediatric population is scarce. We aimed to evaluate the incidence of CE among recent liver recipients at our institution, and to identify potential medical risk factors for development of CE after transplant. **Methods:** This retrospective pilot study examined the frequency of chylous effusion and chylous ascites (CA) in a large, single-center pediatric LT cohort. The study comprised 81 patients undergoing first time isolated liver transplant between January 2023 and April 2026, with a median age at transplant of 2.5 years. Data including diagnosis, graft type, abdominal wall closure, initiation of enteral nutrition or TPN/lipids within 72 hours of transplant, and length of stay were collected and stratified based on the presence of CE and/or CA, with a focus on CE given the scarcity of data on this complication. **Results:** The incidence of CE in our study population (16%) was higher than values of chylous leak that have been reported in other mixed pediatric and adult

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studies. Almost a third (32%) of our cohort were transplanted for a diagnosis of maple syrup urine disease (MSUD) which is much higher than national averages. Patients with MSUD had a lower incidence of CE compared to other diagnoses, as did patients with biliary atresia, despite an increased risk of chylous leak due to extensive perihepatic dissection during transplant. 61.5% of patients who developed CE did have full abdominal wall closure at the time of transplant, compared to 51.5% of patients who did not develop CE. The average length of stay for patients with CE was 8.8 days longer compared to those without CE. A binomial logistical regression analysis was performed for patients with any chylous complication (effusion or ascites), chylous effusion alone, and chylous ascites alone. For any chylous complication, there was a statistically significant association with graft type, with an odds ratio of 0.064 (CI 0.003-0.675, p = 0.041) for whole organ vs LLS. For chylous effusion alone, there was a statistically significant association with those who had TPN initiation within 72 hours, with an odds ratio of 0.172 (CI 0.027 – 0.941, p = 0.047). There were no statistically significant findings for the group with chylous ascites alone. **Conclusion:** This study highlights that chylous leaks continue to be a challenging post-transplant complication, occuring with relative frequency and associated with suboptimal outcomes including length of stay. Larger, multicenter studies are needed to better define patient- and procedure-specific risk factors for CE, clarify the role of perioperative nutritional management, and evaluate strategies for prevention and early intervention aimed at reducing morbidity and length of stay after pediatric liver transplantation.

Table 1: Patient Characteristics With and Without Postoperative Chylous Leak

	Postoperative CE (n = 13)	No postoperative CE (n = 68)	Postoperative CA (n = 27)	No postoperative CA (n = 54)
Age at LT, years	2.50	2.55	2.29	2.70
Sex, male	7 (53.8%)	34 (50.0%)	13 (48.1%)	28 (51.9%)
Diagnosis				
Biliary Atresia	1 (7.7 %)	10 (14.7%)	4 (14.8%)	7 (13.0%)
MSUD	3 (23.1%)	23 (33.8%)	8 (29.6%)	18 (33.3%)
Other	9 (69.2%)	35 (51.5%)	15 (55.6%)	29 (53.7%)
Graft Type				
Whole	1 (7.7%)	18 (26.5%)	3 (11.1%)	16 (29.6%)
LLS (living or deceased)	11 (84.6%)	37 (54.4%)	20 (74.1%)	28 (51.9%)
Other reduced	1 (7.7%)	13 (19.1%)	4 (14.8%)	10 (18.5%)
Abdominal Wall Closure				
Full	8 (61.5%)	35 (51.5%)	16 (59.3%)	27 (50.0%)
Other	5 (38.4%)	33 (48.5%)	11 (40.7%)	27 (50.0%)
Enteral Feeds Within 72H				
Yes	3 (23.1%)	20 (29.4%)	7 (25.9%)	16 (29.6%)
No	10 (76.9%)	48 (70.6%)	20 (74.1%)	38 (70.4%)
TPN/Lipids Within 72H				
Yes	7 (53.8%)	49 (72.1%)	19 (70.4%)	37 (68.5%)
No	6 (46.2%)	19 (27.9%)	8 (29.6%)	17 (31.5%)
LOS, days	43.7	34.9	31.1	39.0

NOTE: Age shown as median, LOS shown as mean, all other data shown as n (%).
CE, chylous effusion; CA, chylous ascites; LT, liver transplant; MSUD, maple syrup urine disease; LLS, left lateral segment; TPN, total parenteral nutrition; LOS, length of stay

Disclosures: Richa Gupta:Nothing to Disclose, Rachel Smith:Nothing to Disclose.

4544 | PSYCHOSOCIAL BURDENS IN LIVER TRANSPLANT SURVIVORSHIP: PREVALENCE OF LONELINESS AND SOCIAL ISOLATION

Nicole Lulkin[1] Shilpa Jasti[1] Alexis Kim[2] Amon Asgharpour[2] Anh Bui[2] Zachary Henry[3] Nicolas Intagliata[4] Juan Guerra[3] Stephanie Silpe[3] Vaishali Patel[2] Idris Yakubu[2] Mohammad Siddiqui[3], [1]Virginia Commonwealth University School of Medicine, [2]Virginia Commonwealth University, [3]UVA Health, [4]University of Virginia

Background: Social isolation and lack of social support have been linked to poorer clinical outcomes across various organ transplant populations. Loneliness, in particular, has been associated with delayed recovery and increased complications in both chronic disease and post-transplant settings. Despite its growing recognition as a factor of health, the prevalence and clinical relevance of loneliness in liver transplant (LT) recipients remain understudied. This study investigates the frequency of loneliness among LT recipients and examines its relationship to health-related quality of life (HRQoL), symptom burden, and self-perceived health. **Methods:** We completed a cross-sectional study of adult LT recipients at a large academic medical center. Patients completed the De Jong Gierveld Loneliness Scale, Lubben Social Network Scale, and Patient-Reported Outcomes Measurement Information System (PROMIS) scale to assess physical, emotional, and social elements of HRQoL. Clinical and demographic data were used from the electronic health record. Associations between loneliness and quality of life domains were analyzed using multivariable linear and logistic regression analyses adjusted for age, sex, time since transplant, and comorbidities. **Results:** Seventeen participants (16.5%) were at risk for loneliness, and 19 (18.4%) were at risk for social isolation. Only four participants met the criteria for both conditions, suggesting limited overlap between loneliness and social isolation. Loneliness prevalence was highest among patients transplanted for metabolic dysfunction-associated steatotic liver disease. Patients at risk for social isolation were more likely to be unemployed or disabled (63.2% vs 35.7%, p = 0.039). No other significant demographic or clinical differences were identified, and no independent predictors remained significant on multivariable analysis. **Conclusion:** Approximately one in six LT recipients were at risk for loneliness or social isolation despite many reporting established social support systems. Loneliness and social isolation demonstrated limited overlap, suggesting they represent distinct psychosocial constructs. These findings highlight the need for targeted psychosocial screening and interventions in LT survivorship care.

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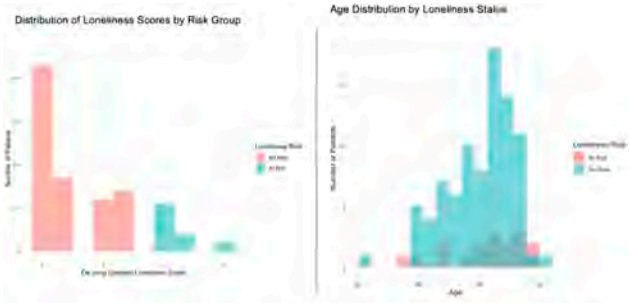


Figure 1: Distribution of Loneliness Scores. Right: Age distribution of participants stratified by loneliness risk status. Average age for patients a risk for loneliness is 62 compared to 60.5 for patients no at risk (p=0.61). Left: Histogram showing distribution of DJG-6 Scale scores by risk group. 17 patients (16.5%) were at risk for loneliness with DJG-6 ≥3.

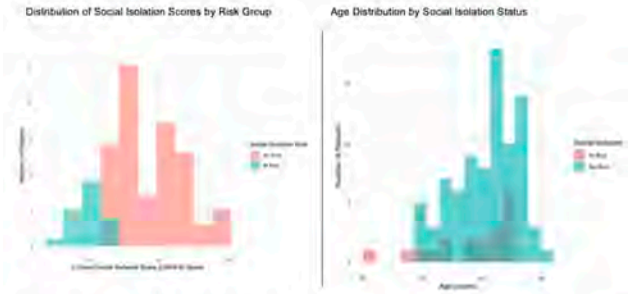


Figure 2: Distribution of Social Isolation Scores. Right: Age distribution of participants stratified by social isolation risk status. Most liver transplant recipients were not socially isolated, with similar age distributions observed between risk groups. Left: Histogram showing distribution of LSNS-6 scores categorized by risk group. 19 patients (18.4%) were at risk for social isolation with LSNS scores ≤12.

Disclosures: Nicole Lulkin:Nothing to Disclose, Shilpa Jasti:Nothing to Disclose, Alexis Kim:Nothing to Disclose, Amon Asgharpour:Galectin: Clinical Endpoint Committee, NovoNordisk: Advisor, Madrigal: Advisor, Chronic Liver Disease Foundation: Speaking and Teaching, Intercept: Consultant, Anh Bui:Zydus: Consultant, Zachary Henry:Nothing to Disclose, Nicolas Intagliata:Nothing to Disclose, Juan Guerra: Nothing to Disclose, Stephanie Silpe:Nothing to Disclose, Vaishali Patel:Nothing to Disclose, Idris Yakubu:Nothing to Disclose, Mohammad Siddiqui: NovoNordisk: Grant/Research Support, 89Bio: Consultant, Sagimet: DSMB.

4545 | RADIATION EXPOSURE FROM CT AND FLUOROSCOPICALLY-GUIDED PROCEDURES IN LIVER TRANSPLANT PATIENTS

Pavel Trunecka[1] Denisa Kyselova[1] Irena Mikova[2] Tomas Hucl[1] Lucie Sukupova[3], [1]Institute for Clinical and Experimental Medicine, [2]Institute for Clinical and Experimetal Medicine, [3]Institute for Clinical and Experimebtal Medicine

Background: Liver transplant (LT) candidates typically undergo long-term medical management requiring imaging that utilizes ionizing radiation. Numerous examinations are required both prior to waitlisting and post-TX follow-up. With the prolonged survival of LT recipients, concerns have arisen regarding the stochastic effects of radiation from repeated imaging, specifically computed tomography (CT) scans and fluoroscopically guided interventions. We aimed to evaluate the cumulative radiation dose accrued from medical imaging in a cohort of 1,000 consecutive LT pts treated at our institution between December 2017 and June 2025. **Methods:** Data on radiation doses were collected for each patient for every high-exposure procedure (CT scans and fluoroscopy) using the institutional dose monitoring system and converted to cumulative effective dose (CED) using standard protocols. The study cohort comprised 383 females and 617 males, with a median age at LT of 59 years (IQR: 47–67). We analyzed the CED incurred by the type of examination and evaluated the impact of the LT indication on the CED. Pts with a CED exceeding 100 mSv were identified, and relative rates for each diagnostic entity were calculated. Differences between groups were assessed using non-parametric methods (the Kruskal-Wallis test). **Results:** Abdominal CT was the most frequently performed examination (2,754 exams), followed by fluoroscopically guided abdominal procedures (1,974 procedures); together, these contributed substantially to cumulative radiation exposure. The mean number of examinations and radiation dose per exam were as follows: brain CT: 0.6 exams (1.1 mSv); chest CT: 0.9 exams (8.5 mSv); abdominal CT: 2.8 exams (20.3 mSv); cardiac CT: 0.1 exams (20.3 mSv); fluoroscopically guided abdominal procedures: 2.0 procedures (8.4 mSv); and fluoroscopically guided cardiac procedures: 0.4 procedures (6.6 mSv). Overall, 278 pts received a CED > 100 mSv. Among these, 184 patients received 100–200 mSv, 65 received 200–300 mSv, 20 received 300–400 mSv, 8 received 400–500 mSv, and 1 patient received > 500 mSv. The maximum CED was 601 mSv. On average, pts accumulated a mean total effective dose of 85 mSv, with a median cumulative dose of 58 mSv. The highest CED was received by pts transplanted for cholangiocarcinoma and hepatocellular carcinoma, whereas the lowest exposures were noted in pts with acute conditions and liver cirrhosis without carcinoma (Table 1). **Conclusion:** A substantial proportion of patients received cumulative effective doses well above 100 mSv—a level generally considered to increase long-term radiation risks—with major differences observed between diagnostic groups. Especially in patients with a long post-transplantation life expectancy, strict clinical justification and a preference for alternative imaging modalities with limited or no ionizing radiation must be prioritized.

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Table 1. Cumulative effective doses accrued during the management of liver transplant patients and differences between major diagnostic groups.

Diagnostic group	N	CED Median (IQR) (mSv)	Proportion of subjects with CED >100 mSv (%)
Alcoholic liver disease	189	49 (32–76)	16.9
ACLF	21	39 (13–66)	4.8
Acute liver failure	40	28 (12–53)	5.0
Autoimmune cirrhosis	23	39 (23–87)	13.0
Cholangiocarcinoma	12	123 (65–178)	58.0
Hepatocellular carcinoma	233	103 (64–179)	57.9
Viral hepatitis B	15	53 (33–75)	6.7
Viral hepatitis C	21	61 (29–92)	9.5
MASLD	71	50 (37–117)	29.6
Cryptogenic cirrhosis	42	49 (23–74)	11.9
Polycystic disease	48	47 (25–82)	22.9
Primary sclerosing cholangitis	78	37 (19–55)	9.0
Primary biliary cholangitis	37	36 (33–164)	5.4
Retransplanted recipients	82	78 (47–147)	31.0

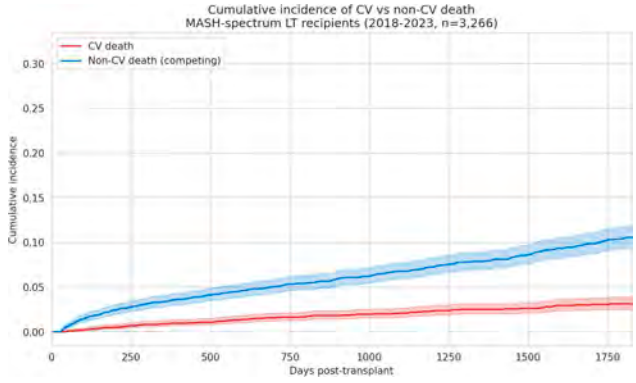
Footnote & Legend:
CED, cumulative effective dose; ACLF, acute-on-chronic liver failure; MASLD, metabolic dysfunction-associated steatotic liver disease; IQR, interquartile range. Differences between groups were assessed using the Kruskal-Wallis test and were significant ($p < 0.0001$).

Disclosures: Pavel Trunecka:Nothing to Disclose, Denisa Kyselova:Nothing to Disclose, Irena Mikova: Nothing to Disclose, Tomas Hucl:Nothing to Disclose, Lucie Sukupova:Nothing to Disclose.

4546 | COMPETING-RISKS PREDICTION OF CARDIOVASCULAR DEATH AFTER LIVER TRANSPLANTATION FOR MASH-SPECTRUM DISEASE

Sri Harsha Boppana[1] Subhash Gurappa[2] Sachin Sravan Kumar Komati[2] Gautam Maddineni[3] Raja Chandra Chakinala[4] Meghana Kakarla[5] Venkata Sunkesula[6] Christina Awad[7] Pradeep Yarra[7], [1]Nassau University Medical Center, [2]Florida International University, [3]Creighton university, [4]Guthrie Robert Packer Hospital, [5]infirmary health, [6]Case Western Reserve University, [7]UT Health San Antonio

Background: Cardiovascular (CV) death is often presumed to be a dominant post-transplant threat in metabolic dysfunction-associated steatohepatitis (MASH), yet conventional binary models may obscure competing non-CV mortality. We aimed to define the incidence and predictors of CV death after liver transplantation (LT) for MASH-spectrum disease using a competing-risks predictive framework. **Methods:** We performed a retrospective cohort study of adult, primary, single-organ LT recipients in the OPTN/UNOS STAR file with MASH-spectrum diagnoses (MASH, cryptogenic cirrhosis, or unspecified MASH-spectrum codes), transplanted from 2018-2023 and alive at 30 days. CV death was defined by cause-of-death codes 4800-4899; non-CV death was modeled as the competing event. Cumulative incidence functions were estimated by Aalen-Johansen methods and compared across body mass index (BMI) classes. Cause-specific Cox models evaluated recipient, donor, metabolic, liver disease, and functional predictors. A 1-year landmark model tested post-LT mean creatinine and new-onset diabetes as longitudinal predictors of subsequent CV death. **Results:** Among 3,266 recipients, median age was 58 years and 1,528 (46.8%) were male. Diagnoses included MASH (n = 1,551), cryptogenic cirrhosis (n = 1,120), and unspecified MASH-spectrum disease (n = 595). During follow-up, 424 deaths occurred: 95 CV and 329 non-CV. CV death cumulative incidence was 0.9% at 1 year, 2.1% at 3 years, and 3.1% at 5 years, versus 3.4%, 6.8%, and 10.6% for non-CV death. BMI class did not discriminate CV death risk (3-year incidence: non-obese 2.0%, class I 2.5%, class II 2.7%, class III 0.9%; Gray/cause-specific $p = 0.41$). In CV death models, age was the only significant predictor (HR 1.013/year, 95% CI 1.002-1.024; $p = 0.025$), whereas diabetes (HR 0.93, 95% CI 0.70-1.24; $p = 0.62$), BMI (HR 1.00, 95% CI 0.98-1.02; $p = 0.91$), and MELD ($p = 0.72$) were not predictive; concordance was 0.637. In contrast, diabetes predicted non-CV death (HR 1.44, 95% CI 1.18-1.76; $p < 0.001$). Among 3,051 1-year survivors, post-LT mean creatinine (HR 1.02, 95% CI 0.86-1.21; $p = 0.82$) and new-onset diabetes (HR 0.93, 95% CI 0.62-1.39; $p = 0.72$) did not improve CV death prediction. **Conclusion:** In contemporary MASH-spectrum liver transplant recipients, CV death was uncommon and substantially outnumbered by competing non-CV mortality. BMI, diabetes, MELD score, renal trajectory, and new-onset post-transplant diabetes did not independently predict cardiovascular death, though the study was likely underpowered to detect clinically meaningful predictors. Competing-risks modeling materially reframes post-transplant risk stratification: metabolic risk factors - diabetes in particular - mapped more strongly to non-CV than CV mortality, underscoring the importance of accounting for competing causes when interpreting outcomes in this population.



Disclosures: Sri Harsha Boppana:Nothing to Disclose, Subhash Gurappa:Nothing to Disclose, Sachin Sravan

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Kumar Komati:Nothing to Disclose, Gautam Maddineni: Nothing to Disclose, Raja Chandra Chakinala:Nothing to Disclose, meghana kakarla:Nothing to Disclose, Venkata Sunkesula:Nothing to Disclose, Christina Awad:Nothing to Disclose, Pradeep Yarra:Nothing to Disclose.

4547 | PREVALENCE AND EVALUATION OF CORONARY ARTERY DISEASE IN LIVER TRANSPLANT CANDIDATES

Tasmia Promi[1] Shirley Eng[1] Anwesha Satapathy[1] James Park[1] Nabil Dagher[1] Tapan Buch[1] David Stern[1] Amgad Makaryus[1] Sanjaya Satapathy[2], [1]Northwell Health, [2]Northshore University Hospital/ Northwell Health

Background: Coronary artery disease (CAD) is a major determinant of perioperative morbidity and mortality in liver transplant candidates and remains a critical component of pre-transplant cardiovascular risk assessment. The increasing prevalence of diabetes, obesity, and metabolic dysfunction-associated steatotic liver disease has heightened concern for underlying coronary atherosclerosis in this population. However, reported CAD prevalence varies widely across studies, reflecting differences in patient characteristics, disease definitions, and diagnostic modalities used for detection. **Methods:** We conducted a systematic review and meta-analysis of studies reporting CAD prevalence in adult liver transplant candidates. Databases were searched through 2025. Random-effects models were used to pool prevalence of any CAD and obstructive CAD, with subgroup analyses by diagnostic modality. **Results:** Twenty-one studies (n = 37–17,482 participants) published between 1995 and 2024 were included. Reported prevalence of any CAD varied widely (approximately 9% to >80%), with consistently higher estimates in CT-based imaging cohorts. Obstructive CAD prevalence was lower, generally ranging from 2% to 18%. Pooled analyses demonstrated substantial heterogeneity (I^2 >75%). CT-based strategies identified significantly higher prevalence of any CAD, driven primarily by nonobstructive atherosclerosis, whereas estimates of obstructive CAD were more consistent across modalities. Sensitivity analyses confirmed that modality-driven differences accounted for most heterogeneity. **Conclusion:** CAD is highly prevalent among liver transplant candidates, but estimates are strongly influenced by diagnostic modality. CT-based imaging reveals a substantial burden of nonobstructive coronary atherosclerosis that is not captured by invasive angiography alone. These findings demonstrate the need to distinguish total atherosclerotic burden from obstructive disease in pre-transplant cardiovascular risk assessment.

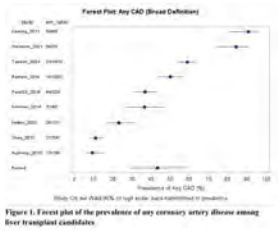


Figure 1. Forest plot of the prevalence of any coronary artery disease among liver transplant candidates

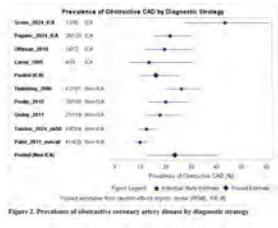


Figure 2. Prevalence of obstructive coronary artery disease by diagnostic strategy

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4548 | LIVER TRANSPLANT INTRAOPERATIVE TRANSFUSION VOLUME AND HEPATOCELLULAR CARCINOMA RECURRENCE

William Vroom[1] Devi Veeramgari[1] Yonatan Kaplan[1] Keri Zhou[1] Sami Ali[1] Daisuke Imai[1] Yuzuru Sambommatsu[1] Vinay Kumaran[1] Muhammad Saeed[1] Aamir Khan[1] Amit Sharma[1] Adrian Cotterell[1] Hannah Lee[1] David Bruno[1] Seung Duk Lee[1], [1]VCU School of Medicine

Background: Intraoperative PRBC transfusion has been associated with increased and earlier recurrence in a variety of cancers, including in hepatocellular carcinoma (HCC) following liver resection. However, there is limited evidence regarding transfusion in liver transplants. This study will analyze whether intraoperative PRBC transfusion affects HCC recurrence following transplant and if it does so in a dose dependent manner. **Methods:** A total of 75 patients with HCC who underwent liver transplantation were analyzed. Intraoperative PRBC transfusion was standardized to units (1 unit = 300 mL) and modeled continuously and categorically (0, 1–2, ≥3 units). Cox proportional hazards regression evaluated associations with time to recurrence; binary logistic regression assessed early recurrence (<24 months). Preoperative neutrophil-to-

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lymphocyte ratio (NLR) was evaluated as an independent predictor in both models. **Results:** Seventy five recurrence events were available for analysis. When modeled continuously, intraoperative PRBC units did not significantly predict time to recurrence ((HR 1.047, 95% CI 0.991–1.106, p = 0.103)) or early recurrence (OR 1.058, 95% CI 0.967–1.159, p = 0.218). However, categorical analysis showed that transfusion of 3+ units was associated with significantly increased risk of recurrence compared to no transfusion (HR 2.339, 95% CI 1.008–5.429, p = 0.048) and of early recurrence (OR 3.141, 95% CI 1.049–9.401, p = 0.041). The 1-2 unit category was not significant in either model. Preoperative NLR was independently associated with both time to recurrence (HR 1.129, p = 0.009) and early recurrence. (OR 1.185, p = 0.010). The Cox model demonstrated significant overall fit (LLR p = 0.0036), and the logistic model showed no evidence of poor calibration (Hosmer-Lemeshow p = 0.451). **Conclusion:** Intraoperative PRBC transfusion of 3+ units was associated with earlier and increased risk of HCC recurrence following liver transplant, though it did not predict faster time to recurrence or early recurrence in a dose-dependent manner. These findings likely reflect a variety of factors related to PRBC transfusion which worsen liver transplant outcomes, such as immunosuppressive effects and greater operative difficulty, and indicate the value of minimizing intraoperative blood loss and transfusion volume. However, missing registry data limited analysis on certain covariates, namely cell-saver use, underscoring the need for larger studies to fully understand the effects of intraoperative PRBC transfusion.

Disclosures: William Vroom:Nothing to Disclose, Devi Veeramgari:Nothing to Disclose, Yonatan Kaplan:Nothing to Disclose, Keri Zhou:Nothing to Disclose, Sami Ali:Nothing to Disclose, Daisuke Imai:Nothing to Disclose, Yuzuru Sambommatsu:Nothing to Disclose, Vinay Kumaran:Nothing to Disclose, Muhammad Saeed:Nothing to Disclose, Aamir Khan:Nothing to Disclose, Amit Sharma:Nothing to Disclose, Adrian Cotterell:Nothing to Disclose, Hannah Lee:Nothing to Disclose, David Bruno:Nothing to Disclose, Seung Duk Lee:Intuitive: Speaking and Teaching.

4549 | IMPACT OF CYTOMEGALOVIRUS DISEASE ON INPATIENT OUTCOMES AND RESOURCE UTILIZATION AFTER LIVER TRANSPLANTATION

Serena Brosten[1] Spencer Goble[2] Timothy Davie[1] Jesse Fletcher[1] Kartik Dapke[3] Anna Strauss[1] Giovanni Roldan[2] Supavit Chesdachai[4] Prowpanga Udompap[5],

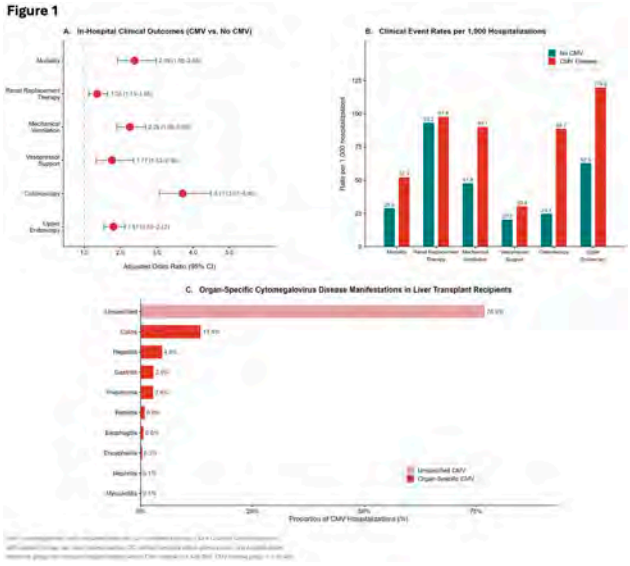
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Background: Cytomegalovirus (CMV) is the most common opportunistic viral infection after liver transplantation, with the highest disease risk occurring in donor-seropositive and recipient-seronegative pairs. CMV disease negatively impacts liver transplant outcomes through direct organ involvement and indirect immune dysregulation. Nationally representative data on inpatient outcomes and resource utilization attributed to CMV disease in liver transplantation remains limited. **Methods:** A retrospective analysis was conducted on data from the National Inpatient Sample (NIS). Hospitalizations for liver transplant recipients with concurrent CMV diseasea between 2016 and 2023 were identified using ICD-10 codes. The clinical and economic outcomes were evaluated and compared between recipients admitted with and without CMV disease. Primary outcomes of interest included mortality, length of stay, and total hospitalization costs. Secondary outcomes assessed included mechanical ventilation, renal replacement therapy, vasopressor support, and endoscopic evaluation. Weighted multivariable analyses were performed to identify independent predictors of the specified outcomes. **Results:** Among 437,190 liver transplant hospitalizations, 10,430 presented with CMV disease. Compared to liver transplant receipients without CMV disease, recipients with CMV were slightly younger (median: 58 vs. 62 years; p < 0.01) and had a lower comorbidity burden (median Charlson Comorbidity Index: 3 vs. 4; p < 0.01). While sex was not associated with CMV disease (p = 0.46), significant differences were observed across race/ethnicity, hospital region, and primary payer strata (all p < 0.01). Regarding organ manifestation, most CMV cases (76.9%) had no organ-specific codes, followed by CMV colitis at 13.4%, with the remaining manifestations detailed in Figure 1C. The presence of CMV disease significantly increased the adjusted risk for severe clinical outcomes, including in-hospital mortality (52.3 vs. 28.9 per 1,000 hospitalizations; adjusted odd ratio (aOR) 2.39, p < 0.01), requirement for mechanical ventilation (90.1 vs. 47.8 per 1,000 hospitalizations; aOR 2.26, p < 0.01), and need for vasopressor support (30.4 vs. 20.3 per 1,000 hospitalizations; aOR 1.77, p < 0.01) (Figures 1A and 1B). Furthermore, CMV hospitalizations incurred a significantly longer median length of stay (7 vs. 4 days; aRR 2.21, p < 0.01) and higher median healthcare costs ($19,846 vs. $11,820; aRR 2.40, P < 0.01). **Conclusion:** In this retrospective study, CMV disease following

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liver transplantation was associated with significantly worse inpatient outcomes and greater healthcare resource utilization despite having a slightly younger demographic with fewer comorbidities. These findings reinforce the importance of early detection and intervention of CMV disease.



Disclosures: Serena Brosten:Nothing to Disclose, Spencer Goble:Nothing to Disclose, Timothy Davie:Nothing to Disclose, Jesse Fletcher:Nothing to Disclose, Kartik Dapke:Nothing to Disclose, Anna Strauss:Nothing to Disclose, Giovanni Roldan:Nothing to Disclose, Supavit Chesdachai:Nothing to Disclose, Prowpanga Udompap:Nothing to Disclose.

4550 | PATIENT SELECTION, SURVIVAL, AND REJECTION OUTCOMES IN DUAL LIVER–LUNG TRANSPLANT RECIPIENTS

Piotr Babinski[1] Janae Gonzales[1] Amanda Kamar[1] Mrinalini Venkata Subramani[1] Krishnan Warrior[1] Alan Betensley[1] Anthony Joudi[1] Bradford Bemiss[1] Catherine Myers[1] Andres Duarte-Rojo[1] Ambalavanan Arunachalam[1], [1]Northwestern University

Background: Liver transplantation is a life-saving procedure that can often be performed simultaneously with another organ, most commonly seen with the kidney because of the high prevalence of renal insufficiency in patients with end-stage liver disease. As a result, there is more robust data regarding general outcomes, organ dysfunction, and rejection with kidney's compared to simultaneous liver-lung transplantations. We report our experience with 14 simultaneous lung-liver organ transplants at our institution and general associated outcomes. **Methods:** All patients consented to our IRB approved general lung transplant biorepository. Data was collected as a retrospective analysis using data from the biorepository and chart review. **Results:** From 8/1/2022 - 5/1/2026, our institution performed 14 simultaneous lung-liver transplants on adult patients, with the indications for lung and liver transplantation listed below (Table 1). Most of the transplants performed were bilateral lung transplants (11/14) and were completed on cardiopulmonary bypass or ECMO (10/14). Patients on average had a MELD-NA score of 11 and a CAS score of 29.795. Two patients were considered highly sensitized (PRAs of 88/0 and 85/46) with a positive T/B cell crossmatch and received our institution's lung transplant desensitization protocol. All patients had uneventful immediate post-operative hospital courses and had an average 18-day post-operative length of stay. None of our 14 patients required treatment for AMR following dual organ transplant and or had persistent DSA on outpatient follow-up. Two of our highly sensitized patients had positive DSAs post-transplant that were no longer detected on follow-up without targeted treatments. There was one case of pulmonary grade A1 acute cellular rejection that was treated within the first year. Literature suggests that following lung transplantation patients typically have an 88% 1-year survival: Our cohort showed a 90.91% 1-year survival (10/11, 3 patients have not reached one year). One patient passed away less than a year from transplant during a hospitalization for hepatic ACR, hemorrhagic shock, and possible hemophagocytic lymphohistiocytosis. **Conclusion:** Our simultaneous lung-liver transplant data showed 1-year survival rates comparable to overall national lung transplant data with minimal signs of rejection following transplant, despite being an overall sicker cohort of patients. This suggests that simultaneous liver-lung transplant is feasible in this carefully selected patient population.



Disclosures: Piotr Babinski:Nothing to Disclose, Janae Gonzales:Nothing to Disclose, Amanda Kamar:Nothing to Disclose, Mrinalini Venkata Subramani:Nothing to Disclose, Krishnan Warrior:Nothing to Disclose, Alan Betensley:Nothing to Disclose, Anthony Joudi:Nothing to Disclose, Bradford Bemiss:Nothing to Disclose, Catherine Myers:Nothing to Disclose, Andres Duarte-Rojo:Echosens: Grant/Research Support, Echosens: Grant/Research Support, CIMA Sciences: Consultant, HepQuant: Advisor, Merz: Advisor, CIMA Sciences: Grant/Research Support, Merz Therapeutics: Advisor, Ambalavanan Arunachalam:Nothing to Disclose.

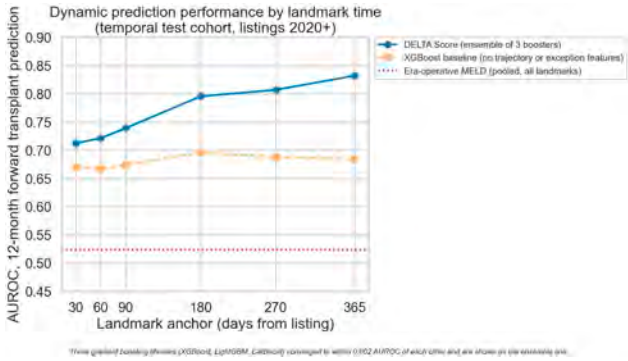
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4551 | LONGITUDINAL WAITLIST TRAJECTORY IMPROVES LIVER TRANSPLANTATION DISCRIMINATION OVER STATIC MELD: A NATIONAL REGISTRY PROOF-OF-CONCEPT

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Background: The Model for End Stage Liver Disease score predicts 90-day waitlist mortality but performs poorly for transplant access, an outcome shaped not only by biological severity, but by blood type, geographic organ availability, and transplant center behavior. Among patients with equivalent MELD scores, those whose laboratory values are actively worsening face meaningfully different prognoses than those who are stable, yet current allocation treats them identically. The DELTA Score was developed to address this limitation by integrating serial laboratory trajectories and exception data to predict 12-month transplant probability across the US national waitlist. **Methods:** In this retrospective cohort study using UNOS/OPTN STAR data of all (n = 223,941) newly listed adult liver transplant patients between 2002–2024, trajectory features (laboratory slopes, variability, recency) and exception variables (exception MELD, HCC burden, locoregional therapy, AFP) were derived exclusively from pre-landmark data at six timepoints (1, 2, 3, 6, 9, 12 months post-listing). Of 206,422 patients reaching at least one landmark timepoint, a gradient boosting ensemble (XGBoost, LightGBM, CatBoost) was trained on pre-2020 listings (n = 166,424) and temporally validated on 2020–2024 listings (n = 39,998). Comparators were era-appropriate MELD and a trajectory-naïve snapshot model using identical features without trajectory or exception data. **Results:** DELTA achieved AUROC 0.771 (95% CI 0.762–0.780) in temporal validation versus 0.704 (95% CI 0.694–0.714) for the snapshot model and 0.524 (95% CI 0.513–0.535) for era-appropriate MELD. The 0.067 AUROC gain represents the isolated contribution of trajectory and exception data. Discrimination increased with follow-up: 0.712 (95% CI 0.706–0.718) at 1 month to 0.833 (95% CI 0.826–0.840) at 12 months. High-risk patients had three-fold higher 1-year transplant cumulative incidence (56.2% vs. 18.8%, , $p < 0.001$), with equivalent waitlist death and deterioration across strata, confirming DELTA captures transplant access rather than biological urgency. Performance was consistent across cirrhosis etiologies (AUROC > 0.75 in all groups) and lower in HCC (0.716–0.654), which was expected given tumor-driven allocation policy. **Conclusion:** Integrating serial laboratory trajectories and exception data improves discrimination of liver transplantation over static MELD across the national waitlist, with consistent performance across all cirrhosis etiologies. These findings establish proof of concept for trajectory-aware modeling as a complement to static MELD for waitlist risk stratification in the US. Whether trajectory-based prediction identifies patients who would benefit from earlier intervention, beyond what serial MELD monitoring already informs requires further prospective validation.



Disclosures: Sri Harsha Boppana:Nothing to Disclose, Pradeep Yarra:Nothing to Disclose, Eugenia Tsai: Nothing to Disclose.

4552 | INCREASED RISK OF ACUTE CORONARY SYNDROME AFTER LIVER TRANSPLANT IN MASLD VS ALCOHOL-ASSOCIATED CIRRHOSIS: A PROPENSITY-MATCHED ANALYSIS

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Background: Liver transplantation (LT) is an established treatment for end-stage liver disease, with metabolic dysfunction-associated steatotic liver disease (MASLD) and alcohol-associated liver disease (ALD) serving as leading indications. Post-transplant cardiovascular complications represent a significant cause of morbidity. This study utilizes a large-scale federated health research network to compare the three-year risk of acute coronary syndrome (ACS) and all-cause mortality between LT recipients with ALD and those with MASLD. **Methods:** A retrospective cohort study was conducted using the TriNetX platform, which provided access to electronic medical records across 107 healthcare organizations. Two

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cohorts were identified: patients with ALD who underwent a liver transplant (n = 7,966) and patients with MASLD cirrhosis who underwent a liver transplant (n = 3,776). Propensity score matching (PSM) was performed to balance 23 baseline characteristics, including demographics, cardiometabolic risk factors and comorbidities (e.g., hypertension, chronic kidney disease), medications, and laboratory values. Outcomes were evaluated within 3 years after transplant. **Results:** Following PSM, 2,817 patients were included in each cohort. The analysis revealed a significantly higher risk of ACS in the MASLD cohort compared to the ALD cohort (4.9% vs. 3.5%; risk ratio 1.39, 95% CI 1.07–1.80, p = 0.013). There was no statistically significant difference in 3-year all-cause mortality between the two groups (MASLD 13.5%, vs. ALD 13.6%; Risk Ratio 0.988, 95% CI 0.865–1.127, p = 0.855). **Conclusion:** Liver transplant recipients with MASLD face a significantly higher risk of developing acute coronary syndrome within the first three years post-transplant compared to those transplanted for ALD, even after matching for traditional cardiovascular risk factors. Despite this increased cardiovascular risk, three-year all-cause mortality remained comparable between the two etiologies. These findings support early, structured cardiovascular risk assessment and aggressive risk factor modification in MASLD transplant candidates and recipients, even when traditional risk factors appear balanced.

Outcome	MASLD + Transplant	ALD + Transplant	Risk Ratio (95% CI)*	P-value
Acute Coronary Syndrome	4.9%	3.5%	1.389 (1.070, 1.802)	0.013
All-Cause Mortality	13.5%	13.6%	0.988 (0.865, 1.127)	0.855

Disclosures: Nadera Altork:Nothing to Disclose, Omar Abureesh:Nothing to Disclose, Ismail Elkhattib:Nothing to Disclose, Nathalie Khoury:Nothing to Disclose, Marco Olivera-Martinez:Nothing to Disclose.

4553 | ISCHEMIC CHOLANGIOPATHY AFTER DCD LIVER TRANSPLANTATION IN THE NMP ERA: A SINGLE-CENTER CASE SERIES

Saleh Al-Juburi[1] Almokdad Mohammad[1] Jack Avedikian[1] Adhnan Mohamed[1] Ahmed Nassar[1] Atsushi Yoshida[1] Marwan Abouljoud[1] Shunji Nagai[1], [1]Henry Ford Hospital

Background: Ischemic cholangiopathy (IC) is a serious complication after liver transplantation (LT) and may lead to graft loss or retransplantation. Although normothermic machine perfusion (NMP) may reduce ischemia-reperfusion injury, IC still occurs. Therefore, this study aimed to describe the clinical characteristics and outcomes of IC cases after DCD liver transplantation at our center. **Methods:** A single-center retrospective analysis was conducted of all recipients who underwent LT from DCD donors between January 2018 and December 2025. LT from DBD donors, living donor liver transplantation, simultaneous multi-organ liver transplantation, and retransplantation were excluded. Among 268 DCD LTs, NMP was used in 191 cases. **Results:** IC developed in 11 of 268 DCD LT recipients (4.1%): 5 cases occurred in the NMP group and 6 occurred in the non-NMP group (2.6% vs. 7.8%, p = 0.08). Among recipients who developed IC, donor BMI was significantly higher in the NMP group than in the non-NMP group (35.8 vs. 23.8 kg/m², p = 0.02). In the NMP group, patients who developed IC had a higher donor BMI than those without IC (35.8 vs. 27.6, p = 0.04) and a longer agonal phase time (31 vs. 18 min, p = 0.03). Ten cases were diagnosed by ERCP at a median of 90 days after LT [51–177], and one case was diagnosed by MRCP. IC was classified as confluence-dominant in 5 cases, multifocal progressive in 4 cases, and minor in 2 cases. Most patients were managed with ERCP stenting, while one patient was successfully treated with percutaneous transhepatic cholangiography catheter placement. Two patients underwent retransplantation due to IC: one with the multifocal progressive type at 160 days after LT and the other with the confluence-dominant type at 181 days after LT. Both patients were in the NMP group. The median follow-up duration was 1.7 years [0.8–5.7]. At the last follow-up, 7 patients were alive, including the 2 patients who underwent retransplantation, whereas 4 patients had died. Among the 4 patients who died, the median patient survival was 3.8 years (range, 1.7–5.9 years), and the causes of death were cerebral hemorrhage, infection, respiratory failure, and unknown; none of the deaths were attributed to IC. **Conclusion:** IC tended to be less frequent in the NMP group than in the non-NMP group, although the difference was not statistically significant. IC remained clinically relevant, with two patients requiring retransplantation; however, both were alive at the last follow-up, and no deaths were directly attributed to IC.

Disclosures: Saleh Al-Juburi:Nothing to Disclose, Almokdad Mohammad:Nothing to Disclose, Jack Avedikian:Nothing to Disclose, Adhnan Mohamed:Nothing to Disclose, Ahmed Nassar:Nothing to Disclose, Atsushi Yoshida:Nothing to Disclose, Marwan Abouljoud:Nothing to Disclose, Shunji Nagai:Nothing to Disclose.

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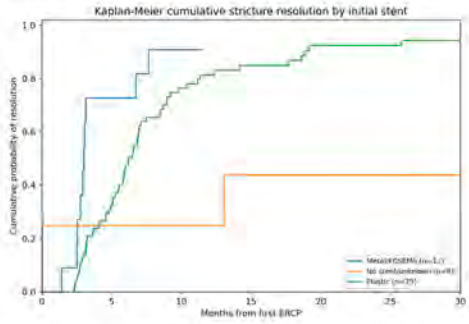
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4554 | FULLY COVERED METAL STENTS REDUCE ERCP BURDEN AND ACCELERATE RESOLUTION OF ANASTOMOTIC BILIARY STRICTURES AFTER MACHINE PERFUSION-PRESERVED DCD LIVER TRANSPLANTATION

Caroline Olson[1] Andrew Keaveny[1] Nicole Loo[1] Frank Lukens[1] Liu Yang[1] Kristopher Croome[1] Omar Mousa[1], [1]Mayo Clinic Florida

Background: Anastomotic biliary strictures (ABS) are a major cause of morbidity after donation-after-circulatory-death (DCD) liver transplantation (LT). Machine perfusion (MP), including ex-situ normothermic oxygenated perfusion via normothermic machine perfusion (NMP) and in-situ normothermic regional perfusion (NRP), mitigates biliary ischemic injury and has expanded safe use of DCD grafts, but its impact on ABS incidence, endoscopic burden, and stent-specific outcomes in DCD-LT is less well defined. We characterized ABS rates, ERCP burden, stent type, and time to resolution across perfusion modalities. **Methods:** Retrospective cohort of 414 adult DCD-LT recipients at a single center (2/2017–10/2025), stratified by modality: no MP/static cold storage (SCS, n = 157), NMP alone (n = 154), NRP alone (n = 74), and NRP+NMP (n = 29). ABS was defined as ERCP confirmed anastomotic stricture. ERCP count, initial stent (plastic vs fully covered self-expandable metal stent [FCSEMS]), stent strategy, time to resolution, and complications were assessed. Logistic regression adjusted for transplant year, recipient age/sex/BMI, MELD, donor age, and cold ischemia plus perfusion time. Time-to-resolution was modeled with Kaplan-Meier and Cox regression; ERCP count with Poisson regression. **Results:** The rates of ABS and biliary leaks were 22.9% and 7.0% in this cohort, respectively. ABS incidence differed by modality: NMP alone 33.1% (95% CI 26.2–40.9), NRP alone 18.9%, NRP+NMP 13.8%, SCS 16.6% (p = 0.002). Among 95 ABS cases, the initial stent was plastic in 78.9%, FCSEMS in 12.6%, and no stent placed in 8.5%. Cases using plastic stents had a complication rate of 10.9% (pancreatitis, cholangitis, stent migration, bleeding) compared with 28.6% in FCSEMS. The observed resolution rate was similar (plastic 84.0% vs FCSEMS 83.3%; p = 1.000), but FCSEMS required fewer ERCPs (median 2 vs 3, p = 0.014) and achieved faster resolution (KM median 3.0 vs 6.2 months; log-rank p = 0.018) (Figure). In adjusted models, FCSEMS independently predicted faster resolution (HR 2.10, 95% CI 1.06–4.18, p = 0.034) and 27% fewer ERCPs (IRR 0.73, 95% CI 0.56–0.93, p = 0.013). These results were similar across the perfusion modalities; within the NMP subgroup, KM median time to resolution was 2.7 months for FCSEMS vs 5.8 months for plastic. **Conclusion:** In this large DCD-LT cohort spanning the contemporary machine perfusion era, ABS incidence varied across preservation modalities. Among recipients who developed ABS, FCSEMS when used initially achieved equivalent resolution with significantly fewer ERCPs and faster time to resolution than plastic stents. This benefit was observed consistently across perfusion strategies, including NMP-preserved grafts. These data support FCSEMS as the preferred first-line endoscopic strategy to promote stricture resolution, reduce procedural burden and accelerate recovery in DCD-LT recipients with ABS, regardless of preservation modality.

Figure: Kaplan-Meier cumulative stricture resolution by initial stent type.



Initial stent comparison: Plastic vs Metal/FCSEMS had similar observed resolution proportions (84.0% vs 83.3%; Fisher p=1.000), but Metal/FCSEMS required fewer ERCPs (median 2.0 vs 3.0; Wilcoxon p=0.014) and had faster time to resolution/censor (p=0.013).

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4555 | SIX-MINUTE WALK TEST AND THE LIVER FRAILTY INDEX ARE COMPARABLE IN PREDICTION OF PRE- AND POST-TRANSPLANT OUTCOMES IN LIVER TRANSPLANT CANDIDATES

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Background: Assessing functional status in liver transplant candidates is an integral part of any liver transplant evaluation given its prognostic value. Although multiple assessment tools exist, comparative studies are lacking, leaving uncertainty about the optimal method to use in clinical practice. The AASLD guidance does not specify a preferred frailty tool, allowing centers to choose based on practice. Our institution utilizes both the Six Minute Walk Distance (6MWD) and Liver Frailty Index (LFI) to evaluate candidates, enabling a direct comparison of their prognostic value in predicting pre- and post-transplant

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outcomes among liver transplant candidates. **Methods:** This was a single center retrospective cohort study including 287 adults who underwent liver transplant evaluation. LFI and 6MWD were obtained in each patient as part of the evaluation. Pre-transplant outcomes including transplant denial, transplant approval/waitlist and clinical deterioration or death while waitlisted. Post transplant outcomes were also explored including re-admission rates within 6 months of transplant, intensive care unit duration and hospital length of stay. Logistic regression models with categorical and continuous frailty measures were developed for each outcome with and without adjustment for MELD 3.0. Discrimination was assessed using the area under the receiver operating characteristic curve. **Results:** For transplant denial, LFI-defined frailty was associated with higher odds compared to 6MWD (adjusted OR 10.89 vs. 4.53). For transplant approval, frailty by LFI was strongly associated with lower likelihood of approval (adjusted OR 0.19, $p < 0.001$). 6MWD-defined frailty was also significantly associated with reduced odds after adjustment (adjusted OR 0.33, $p = 0.002$). Nine patients experienced waitlist mortality or clinical deterioration; given the limited sample size, neither tool reached statistical significance (AUC 0.531–0.571 for both). In post-transplant outcomes, 6MWD frailty categories significantly predicted longer hospital stays (Kruskal-Wallis $p = 0.044$; frail median 8.0 vs.5.0–6.0 days for robust and pre-frail respectively), while LFI did not ($p = 0.786$). **Conclusion:** Frailty is a crucial factor to consider when evaluating patients for liver transplantation. Our study aimed to compare the 6MWD and the LFI to determine which tool is more predictive of complications before and after transplantation. Based on our results, either tool may be used interchangeably in pretransplant evaluation, depending on availability and patient tolerance. In post-transplant outcomes, pretransplant 6MWD was shown to be more predictive of hospital length of stay in comparison to LFI; however, larger prospective studies are required to validate these findings.

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4556 | GLP-1 RECEPTOR AGONISTS ARE ASSOCIATED WITH LOWER RATES OF REJECTION, GRAFT FAILURE, AND MORTALITY AFTER LIVER TRANSPLANTATION COMPARED TO DPP-4 INHIBITORS: A PROPENSITY-MATCHED ANALYSIS

Ethan Chivi[1] Blesscamal Nadeak[1] Ishan Antony[2] Ashali Jain[2] Mary Beth Hodge[2] Jagriti Upadhyay[2] Ming Lin[2],

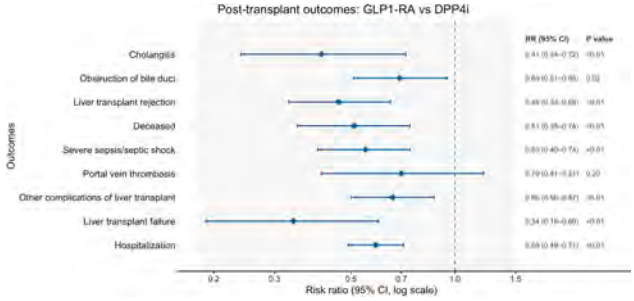
[1]UMass Chan Medical School, [2]Lahey Hospital and Medical Center

Background: GLP-1 receptor agonists (GLP-1 RAs) have demonstrated anti-inflammatory properties, including reductions in IL-6, IL-17 and TNF-a which may provide benefits in immunocompromised populations. In solid organ transplant recipients, GLP-1 RAs are associated with low rejection rates and reduced cardiovascular mortality. However, comparative data on broader post-liver transplant (LT) complications between GLP-1 RAs and DPP4-inhibitors (DPP-4i) is limited. This study aims to compare rates of these post-LT complications in adults with type 2 diabetes mellitus (T2DM) receiving GLP-1 RAs vs DPP-4is using an active comparator new-user design. **Methods:** Data were derived from the TriNetX Global Collaborative Network (55 healthcare organizations, 2007 – 2025). Adults ≥ 18 years with T2DM and a history of LT were identified. New users of GLP-1 RAs without prior DPP-4i exposure were compared with new users of DPP-4is without prior GLP-1 RA exposure, both initiated 3–24 months post-LT. Propensity score matching (1:1) was performed to balance demographics, immunosuppression and comorbidities. We identified nine commonly encountered post-LT complications/outcomes and these include cholangitis, bile duct obstruction, liver graft rejection, sepsis, portal vein thrombosis (PVT), other LT complications, LT failure, all-cause mortality, and unplanned inpatient/observation admission. These outcomes were compared over a five-year time window after initiation of incretin-based therapy. Risk ratios (RR), risk differences (RD), 95% confidence intervals, and p-values were obtained for each outcome. **Results:** After matching, 545 patients remained in each group with no significant differences in baseline characteristics. GLP-1 RAs were associated with significantly lower risk of cholangitis (3.2% vs 7.8%; RR 0.41 [95% CI 0.24 – 0.72]), bile duct obstruction (10.8% vs 15.6%; RR 0.71 [95% CI 0.51 – 0.95]), graft rejection (7.8% vs 16.9%; RR 0.46 [95% CI 0.32 – 0.65]), graft failure (2.9% vs 8.4%; RR 0.34, [95% CI 0.19 – 0.61]), all-cause mortality (6.8% vs 13.5%; RR 0.51 [95% CI 0.35 – 0.74]), severe infection (10.3% vs 18.8%; RR 0.55 [95% CI 0.40 – 0.74]), rate of hospitalization (23.8% vs 40.1%; RR 0.59 [95% CI 0.49 – 0.71]), and other complications of LT (13.7% vs 20.7%; RR 0.66 [95% CI 0.50 – 0.87]). PVT rates were comparable (4.0% vs 5.7%; RR 0.70 [95% CI 0.41 – 1.21]). **Conclusion:** This study demonstrated the use of GLP-1 RAs were associated with significant reduction in mortality, graft rejection, graft failure, cholangitis, bile duct obstruction, severe infections and hospitalization when compared to DPP-4is, with portal vein thrombosis being the only outcome without a significant difference. These findings suggest that GLP-1 RAs anti-inflammatory properties may confer a favorable safety profile in liver transplant recipients and warrants further

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prospective studies.



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4557 | BETA-BLOCKER MANAGEMENT GAPS AND SUBMAXIMAL DOBUTAMINE STRESS ECHOCARDIOGRAPHY IN LIVER TRANSPLANT CANDIDATES: BASELINE FINDINGS FOR A QUALITY IMPROVEMENT INITIATIVE

Yusuf Yalcin[1] Carmi Punzalan[2] Amir Qamar[2] Ming Lin[3] Raza Malik[1] Sarah Meade[3], [1]Lahey Hospital & Medical Center, [2]Lahey Clinic Medical Center, [3]Lahey Hospital and Medical Center

Background: Submaximal dobutamine stress echocardiography (DSE) can lead to additional cardiac testing and delays during liver transplant evaluation. Inconsistent pre-test beta-blocker instructions and documentation may contribute to potentially avoidable nondiagnostic studies. **Methods:** We performed a retrospective quality review of liver transplant candidates undergoing DSE at a tertiary transplant center from March 2015 through July 2025. Outside studies were excluded. Submaximal DSE was defined as failure to achieve adequate target heart rate; symptom-limited studies were excluded from the primary outpatient comparison. The primary analysis compared outpatient submaximal versus adequate DSEs after excluding inpatient evaluations. Chart review assessed prescribed beta-blocker use and documentation of medication-hold status. **Results:** Among 1,321 DSEs performed at the center, the primary outpatient cohort included 205 submaximal and 942 adequate studies. Excluded from the primary comparison were 34 symptom-limited submaximal studies, 39 inpatient submaximal studies, and 101 inpatient adequate studies. Prescribed beta-blocker use was more common among submaximal than adequate outpatient DSEs: 72.2% versus 42.9%, respectively. Beta-blocker use was associated with higher odds of submaximal DSE, with an OR of 3.46, 95% CI 2.51–4.78; $p < 0.001$. Among submaximal outpatients prescribed beta-blockers, $n = 148$, only 2 patients, 1.4%, had documented appropriate medication holding; 55, 37.2%, did not hold medications appropriately; and 91, 61.5%, lacked documentation of hold status. **Conclusion:** In liver transplant candidates undergoing outpatient DSE, prescribed beta-blocker use was strongly associated with submaximal studies. Medication holding was rarely documented as appropriate and was often either not performed or not documented, identifying a modifiable systems gap. These baseline findings support a targeted quality improvement intervention using standardized medication-hold instructions, pre-test reminders, and routine documentation of beta-blocker hold status, with planned reassessment of submaximal DSE rates and documentation compliance after implementation.

Figure 2. Association Between Beta-Blocker Use and DSE Adequacy in Outpatient Liver Transplant Candidates

DSE outcome	On beta-blocker	Not on beta-blocker	Total
Submaximal DSE	148 (72.2%)	57 (27.8%)	205
Adequate DSE	404 (42.9%)	538 (57.1%)	942
Odds ratio	OR 3.46 (95% CI 2.51–4.78), p < 0.001		

Key result
Beta-blocker use was significantly more common in submaximal than adequate outpatient DSEs.

Disclosures: Yusuf Yalcin:Nothing to Disclose, Carmi Punzalan:Madrigal: Advisor, Salix: Advisor, Ipsen: Advisor, Amir Qamar:Nothing to Disclose, Ming Lin: Nothing to Disclose, Raza Malik:Nothing to Disclose, Sarah Meade:Nothing to Disclose.

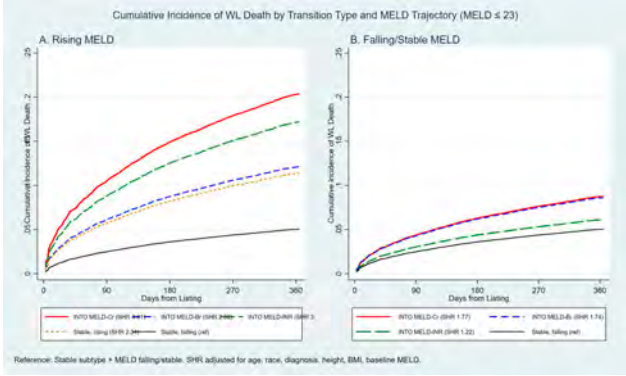
4558 | TRANSITIONS BETWEEN MELD SUBTYPES PREDICT WAITLIST MORTALITY IN LOW-MELD LIVER TRANSPLANT CANDIDATES

Nicholas Kosinski[1] Russell Rosenblatt[2] Giuseppe Cullaro[3], [1]NewYork-Presbyterian / Weill Cornell Medical Center, [2]Division of Gastroenterology and Hepatology, Weill Cornell Medicine, New York, NY, [3]Center for Liver Disease and Transplantation, Vagelos College of Physicians & Surgeons

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Background: Despite changes in MELD score calculation, mortality risk remains underestimated in certain liver transplant (LT) candidates, especially those with low MELD scores. Prior studies demonstrated that MELD subtyping by creatinine (MELD-Cr), bilirubin (MELD-Br), and INR (MELD-INR) dominance may improve mortality risk stratification. We investigated whether transitions between MELD subtypes further predicted waitlist (WL) mortality among low-MELD liver transplant candidates. **Methods:** Adult LT candidates from the UNOS STAR file from 2020–2025 were analyzed. Patients with acute liver failure, MELD exception points, hepatocellular carcinoma, or multi-organ transplantation were excluded. To isolate patients listed by lab MELD and allow time for subtype transitions, analysis was limited to patients at or below median MELD (≤ 23) of the cohort. MELD subtypes were defined using K-means clustering. Multi-state models were used to evaluate transitions between MELD subtypes, stratified by rising versus stable/falling MELD trajectories. The primary outcome was WL mortality, analyzed using time-dependent competing risk regression adjusted for age, race/ethnicity, disease etiology, height, and BMI and accounting for LT. Patients without subtype transition and with stable/falling MELD were the reference. **Results:** A total of 28,265 patients were included after applying all exclusion criteria. Patients were grouped into three MELD subtypes at baseline: MELD-Cr (n = 2,055, 7.3%), MELD-Br (n = 17,416, 61.6%), and MELD-INR (n = 8,794, 31.1%). Of the 28,265 patients at listing, 3,037 (10.7%) died on the waitlist, 16,265 (57.5%) underwent liver transplantation, 5,236 (18.5%) were delisted, and 3,727 (13.2%) remained waiting at censoring. Transitions into a new MELD-dominant state with rising MELD score were associated with increased waitlist mortality – most prominently in transition to MELD-Cr (SHR 4.41, 95% CI [3.66-5.31]), MELD-INR (SHR 3.65, 95% CI [3.12-4.26]) and MELD-Br (SHR 2.50, 95% CI [2.03-3.07]). Transitions occurring with falling MELD scores were associated with comparatively lower risk, but still increased WL mortality (SHR 1.77 for MELD-Cr, 1.74 for MELD-Br, and 1.22 for MELD-INR; all $p < 0.001$). A rising MELD score without subtype transition was independently associated with increased waitlist mortality (SHR 2.34). **Conclusion:** Dynamic transitions into different MELD subtypes are associated with differential WL mortality risks compared with MELD score changes alone. Even when MELD is static or falling, transitions into different subtypes still increase the risk of mortality. This study supports the concept that changes in the physiologic drivers of MELD score provide prognostic information that is missing from a static MELD score.



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4559 | POST-LIVER TRANSPLANT MASLD PREVALENCE INCREASES OVER TIME AND IS ASSOCIATED WITH HIGHER MACE BUT SIMILAR SURVIVAL

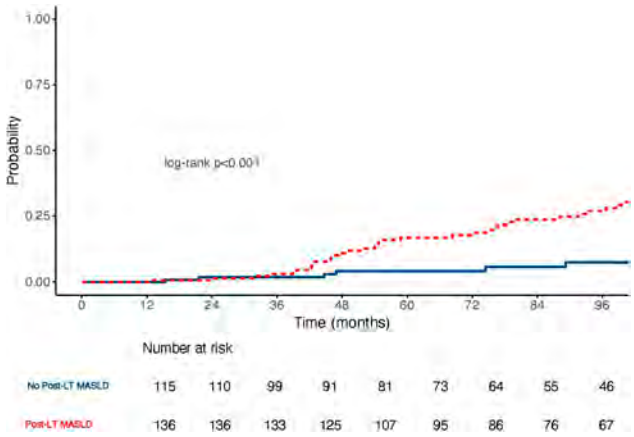
Gupse Adali[1] Osman Karatas[1] Baver Ordu[1],
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Background: Post-liver transplant metabolic dysfunction-associated steatotic liver disease (MASLD) is increasingly recognized after liver transplantation (LT); however, its long-term clinical impact remains unclear. We aimed to evaluate the prevalence, predictors, and clinical outcomes of post-LT MASLD in a longitudinal LT cohort. **Methods:** This retrospective cohort study included 251 adult LT recipients. Baseline demographic, metabolic, and laboratory characteristics were analyzed. Post-LT steatosis was assessed using either transient elastography or MRI. Logistic regression analyses were performed to identify the predictors of post-LT MASLD, and survival analyses were conducted using Kaplan–Meier and Cox regression analyses. **Results:** The mean age was 56.8 ± 12.5 years, and 64.1% of the patients were male. Living donor liver transplantation accounted for 82.5% of the cases, with a median follow-up duration of 88.1 months (IQR 48.2–125.5). Viral liver disease was the most common indication for transplantation (53.8%), whereas MASLD-related liver disease accounted for 16.3% of cases. Pre-LT MASLD was present in 24.7% of the patients. Overall, post-LT MASLD was identified in 54.2% of recipients, with a median time to diagnosis of 52.3 months (IQR, 28.4–84.6). The cumulative prevalence of post-LT

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MASLD increased over time, from 3.2% at 1 year, 19.9% at 3 years, 30.9% at 5 years, and 54.0% beyond 5 years after LT (Figure 1). In the multivariable analysis, post-LT diabetes (aOR 4.7, 95% confidence interval [CI] 2.42–9.13, p < 0.001), hypertension (aOR 3.6, 95% CI 1.92–6.73, p < 0.001), and post-LT BMI (aOR 1.16, 95% CI 1.07–1.26, p < 0.001) were independently associated with post-LT MASLD. Overall survival was similar between patients with and without post-LT MASLD (HR 1.12, 95% CI 0.61–2.06, p = 0.713) (Figure 2). However, post-LT MASLD was associated with a significantly higher risk of major adverse cardiovascular events (MACE) (HR 3.47, 95% CI 1.85–6.51, p < 0.001)(Figure 3). No significant difference in post-LT malignancy rates was observed between patients with and without post-LT MASLD (p = 0.141). **Conclusion:** Post-LT MASLD increases over time and affects more than half of liver transplant recipients during long-term follow-up. Post-LT diabetes, hypertension, and increased BMI were independent predictors of post-LT MASLD development. Although the overall survival was comparable between patients with and without post-LT MASLD, it was associated with a significantly higher risk of MACE. These findings highlight the importance of long-term metabolic surveillance and cardiovascular risk management following LT.



Disclosures: Gupse Adali:Nothing to Disclose, Osman Karatas:Nothing to Disclose, Baver Ordu:Nothing to Disclose.

4560 | PROTOCOLED CA 19-9 TESTING FOR LIVER TRANSPLANT EVALUATION IN A SOUTHWEST COHORT

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Background: Carbohydrate antigen 19-9 (CA 19-9) is commonly used as a tumor marker for cholangiocarcinoma (CCA) but may also be elevated in cholestasis and chronic liver disease. Although CA 19-9 is incorporated into liver transplant (LT) evaluation at many centers, this practice is not universal, and its utility in this setting remains unclear. We aim to determine the prevalence of elevated CA 19-9 among patients undergoing LT evaluation and identify clinical factors associated with these elevations. **Methods:** This single-center, retrospective cohort study included patients undergoing LT evaluation from January 1, 2020, to April 1, 2025. Inclusion criteria included age ≥ 18 and ICD-10 codes consistent with liver transplant status. Only patients with electronically available CA 19-9 values were included. Patients were stratified into elevated (> 37 U/ml) and normal CA 19-9 groups. The primary outcome was the frequency of elevated CA 19-9 levels during LT evaluation and identifying clinical associations, including CCA, liver disease etiology, and total bilirubin elevation. Univariate and multivariable logistic regression analyses were performed to identify predictors of CA 19-9 elevations. **Results:** In this cohort, among all patients who underwent LT evaluation, 373 had electronically available CA 19-9 values; 180 had elevated values. No association was observed between CA 19-9 levels and CCA on explant (p = 0.68). Total bilirubin was strongly associated with CA 19-9 status (p < 0.001). Alcohol-associated liver disease (ALD) was most associated with elevated CA 19-9 (p = 0.01). Patients with hepatocellular carcinoma had reduced odds of elevated CA 19-9 compared to ALD (p = 0.002). Primary sclerosing cholangitis showed no association with CA 19-9 (p = 0.35). Comorbidities such as diabetes (DM) (p = 0.007), hyperlipidemia (HLD) (p = 0.03), and hypertension (HTN) (p = 0.003) were inversely associated with elevated CA 19-9. In univariable logistic regression analysis, ethnicity, total bilirubin, liver disease etiology, DM, HLD, and HTN were all significant predictors of elevated CA 19-9. In multivariable analysis, only ethnicity and total bilirubin remained significant predictors: Non-Hispanic/Latino patients (OR 1.85, 95% CI 1.16–2.95; p = 0.01) and elevated total bilirubin (OR 2.05, 95% CI 1.24–3.43; p = 0.005). **Conclusion:** While several clinical factors were associated with elevated CA 19-9 in univariable analysis, only ethnicity and total bilirubin remained independent predictors after multivariable adjustment. CA 19-9 elevation was not associated with CCA on explant, suggesting that CA 19-9 elevations in this population may primarily reflect underlying cholestasis and liver dysfunction rather than malignancy. These

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findings question the utility of routine CA 19-9 screening during pre-transplant evaluation and warrant further prospective multicenter studies to better define its role in the transplant process.

Table 1: Multivariable Logistic Regression Predicting Elevated CA 19-9

Characteristic	No. (%) Normal (N=193)	Elevated (N=180)	multivariable OR(CI95)†	
Ethnicity—no. (%)				
Hispanic/Latino	82 (42.49)	53 (29.44)	Ref	
Not Hispanic/Latino	111 (57.51)	127 (70.56)	1.85(1.1638933 - 2.952057)	0.01
Elevated total Bilirubin—no. (%)				
No	87 (45.08)	44 (24.44)	Ref	
Yes	106 (54.92)	136 (75.56)	2.05(1.2390317 - 3.425052)	0.005

CI, Confidence interval; N, number; OR, odds ratio; Ref, reference group.
*P<0.05. Odds ratios that are statistically significant are in **BOLD**
†, when controlling for Hypertension, Hyperlipidemia,Diabetes, Etiology
Normal was used as the reference group for the CA 19-9 groups

Disclosures: Diwanshu Soni:Nothing to Disclose, Bianca Arellano:Nothing to Disclose, Abdullah Niyas: Nothing to Disclose, Kevin Mesinas:Nothing to Disclose, Pooja Rangan:Nothing to Disclose, Rohit Nathan:Nothing to Disclose.

4561 | A RARE CASE OF PERSISTENT HEPATOPULMONARY SYNDROME POST LIVER TRANSPLANT

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Background: Congenital extrahepatic portosystemic shunts are rare and responsible for complications like hyperammonemia, encephalopathy, pulmonary arterial hypertension, and hepatopulmonary syndrome even in the absence of liver cirrhosis. Generally, these occur in conjunction with other anomalies like polysplenia or biliary atresia, but isolated instances have been reported.Hepatopulmonary syndrome is caused by intrapulmonary right-to-left shunting, which leads to insufficient oxygenation. It is diagnosed with the contrast echocardiogram. It occurs due to portocaval shunting, with or without portal hypertension, bypassing hepatic metabolism of vasoactive ET-1, a potent vasodilator. **Methods:** A 42-year-old male with alcohol-associated cirrhosis and hepatopulmonary syndrome (HPS) underwent orthotopic liver transplantation, but his post-transplant course was complicated by persistent hypoxemic respiratory failure. CT imaging demonstrated a large right colic vein to IVC shunt, leading to portosystemic shunting even in the absence of portal hypertension, possibly leading to persistent HPS. The patient underwent an echocardiogram, which demonstrated a co-existing intracardiac and hepatopulmonary shunt. The patient subsequently underwent portosystemic shunt embolization with improvement in oxygen requirement from 15L/min of intranasal oxygen to 3L/min which was noticable within the first few weeks post procedure. Patient continued to show improvement with towards the end of 3 months with concomitant pulmonary rehabilitation. **Results:** At least 20% people have persistent hepatopulmonary syndrome post liver transplant, but the presence of a portosystemic shunt allowed for persistent hepatopulmonary physiology in the patient. The right colic vein is a tributary of the superior mesenteric vein, and its connection to the inferior vena cava allows for portosystemic shunting even in the absence of portal hypertension. Interestingly, the patient did not have features of portal hypertension. However, the presence of a persistnet portosystemic shunt post transplant allowed for the continuation of the disease physiology **Conclusion:** HPS is a persistent complication from cirrhosis and takes months after transplant to improve. Persistent or worsening HPS should warrant factors that might lead to persistent symptoms.

Disclosures: Bipneet Singh:Nothing to Disclose, Vivek Jasti:Nothing to Disclose, Nimish Thakral:Nothing to Disclose.

4562 | IMPACT OF PRE-TRANSPLANT WAITLIST DURATION ON WAITLIST AND POST-TRANSPLANT OUTCOMES IN ALCOHOL-RELATED LIVER DISEASE: A NATIONAL UNOS ANALYSIS

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Background: Alcohol-related liver disease (ALD) remains a leading indication for liver transplantation (LT), yet the impact of pre-transplant waitlist duration on waitlist outcomes and long-term post-transplant survival remains poorly characterized. We aimed to evaluate the association between waitlist duration and both waitlist and post-transplant outcomes among LT candidates with ALD using a national United Network for Organ Sharing (UNOS) cohort. **Methods:** Adult LT candidates with ALD listed in the UNOS database were identified and categorized according to pre-transplant waitlist duration: <30 days, 30–89 days, 90–179 days, and ≥ 180 days. Competing-risk regression models were used to evaluate waitlist mortality or removal for being too sick, accounting for transplantation as a competing event. Kaplan-Meier and multivariable Cox proportional hazards models were used to assess post-transplant patient and graft survival. Analyses were adjusted for demographic, clinical, and transplant-related variables. **Results:** Among 49,613 ALD waitlist candidates, 6,451 experienced waitlist death or removal for clinical deterioration. In competing-risk

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analysis, prolonged waitlist duration was associated with increased adverse waitlist outcomes. In adjusted post-transplant analyses of 31,887 LT recipients, recipients transplanted after prolonged waitlist duration ($\geq$180 days) demonstrated significantly worse patient survival (adjusted hazard ratio [aHR] 1.11, 95% confidence interval [CI] 1.02–1.22) and graft survival (aHR 1.11, 95% CI 1.02–1.22) compared with recipients transplanted within <30 days. Alcohol-associated liver disease with concomitant hepatitis C virus infection was independently associated with inferior patient survival (aHR 1.27, 95% CI 1.16–1.39) and graft survival (aHR 1.21, 95% CI 1.11–1.33). Kaplan-Meier analyses demonstrated significantly lower long-term patient and graft survival among recipients with prolonged waitlist duration (log-rank $p < 0.0001$ for both). **Conclusion:** Among LT candidates with ALD, prolonged pre-transplant waitlist duration was associated with worse waitlist outcomes and inferior long-term post-transplant patient and graft survival. These findings highlight the importance of timely transplantation and may inform future strategies for risk stratification and allocation in ALD transplantation.

Table 1. Competing-Risk Regression Analysis for Waitlist Dropout Among Adult Patients With Alcohol-Related Liver Disease.

Variable	Subdistribution Hazard Ratio (SHR)	95% CI	p-value
Age at listing (per year)	1.041	1.038–1.044	<0.001
Female sex	1.090	1.032–1.151	0.002
MELD at listing (per point)	1.026	1.023–1.029	<0.001
HCC absent (vs HCC present)	0.798	0.742–0.859	<0.001
ALD subtype			
Alcohol cirrhosis	Reference	—	—
Acute alcohol hepatitis	0.884	0.784–0.997	0.045
Alcohol + HCV	1.120	1.025–1.223	0.012
MetALD	0.431	0.262–0.709	0.001
Waitlist registration era			
Pre-2014	Reference	—	—
2014–2019	10.44	8.01–13.61	<0.001
2020–2022	7.42	5.68–9.69	<0.001
2023–present	4.95	3.77–6.49	<0.001

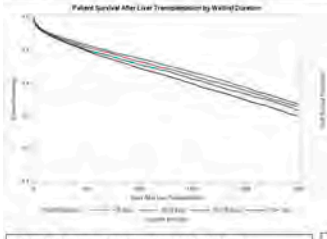


Figure 2. Kaplan-Meier patient survival after liver transplantation stratified by pre-transplant waitlist duration. Kaplan-Meier analysis demonstrating post-transplant patient survival among adult liver transplant recipients with alcohol-related liver disease according to duration of waitlist time prior to transplantation. Recipients transplanted after prolonged waitlist duration (≥180 days) demonstrated the lowest long-term survival, whereas recipients transplanted within <30 days had the most favorable post-transplant survival. Differences between groups were statistically significant by log-rank testing (p<0.0001). Waitlist duration categories were defined as <30 days, 30–89 days, 90–179 days, and ≥180 days prior to transplantation.

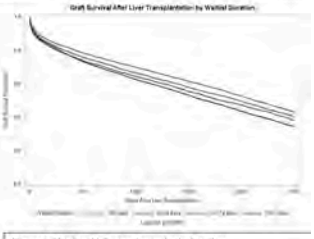


Figure 3. Kaplan-Meier graft survival after liver transplantation stratified by pre-transplant waitlist duration. Kaplan-Meier curves demonstrating post-transplant graft survival among adult liver transplant recipients with alcohol-related liver disease according to pre-transplant waitlist duration. Recipients transplanted after prolonged waitlist duration (≥180 days) demonstrated the lowest long-term graft survival, whereas recipients transplanted within <30 days had the most favorable graft survival outcomes. Intermediate graft survival patterns were observed among recipients waiting 30–89 days and 90–179 days prior to transplantation. Differences between groups were statistically significant by log-rank testing (p<0.0001). Waitlist duration categories were defined as <30 days, 30–89 days, 90–179 days, and ≥180 days prior to liver transplantation.

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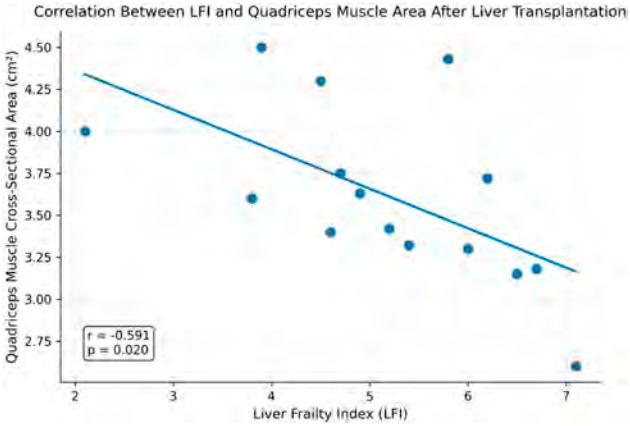
4563 | POINT-OF-CARE MUSCLE ULTRASOUND REFLECTS FUNCTIONAL IMPAIRMENT AFTER LIVER TRANSPLANTATION

Patricia Almeida[1] Thiago Carvalho[1] Samia Sousa[1] Angelica Cruz[1] Fernanda Rezende[1] Fernanda Oliveira[1], [1]Einstein Hospital Israelita

Background: Frailty and sarcopenia are increasingly recognized as major determinants of outcomes in liver transplantation. Although the Liver Frailty Index (LFI) is a validated tool for functional assessment in patients with advanced liver disease, data correlating functional frailty with objective muscle ultrasound parameters in the immediate post-transplant setting remain scarce. This study aimed to evaluate the association between LFI and quadriceps muscle cross-sectional area measured by point-of-care ultrasonography in hospitalized patients after liver transplantation. **Methods:** This cross-sectional observational study included adult patients admitted to the solid organ transplant ward of a tertiary hospital in Brazil after discharge from the intensive care unit following liver transplantation. Data from the first physiotherapy assessment after ward admission were analyzed, including LFI and quadriceps muscle cross-sectional area assessed by bedside ultrasonography. Patients with severe cognitive impairment, permanent motor limitations, or death before evaluation were excluded. Quantitative variables were expressed as mean ± standard deviation. Normality was assessed using the Ryan-Joiner test, and correlations were analyzed using Pearson's correlation coefficient, with a significance level of 5%. **Results:** Fifteen patients were included. Mean LFI was 5.17 ± 1.31, while mean quadriceps muscle cross-sectional area was 3.63 ± 0.53 cm². A significant moderate negative correlation was observed between LFI and muscle cross-sectional area ($r = -0.591$; $p = 0.020$), demonstrating that greater frailty was associated with lower muscle mass in the early post-transplant period. **Conclusion:** Functional frailty was significantly associated with lower quadriceps muscle cross-sectional area in the early post-transplant period. These findings support point-of-care peripheral muscle ultrasonography as a promising bedside biomarker of frailty in liver transplant recipients, providing an objective and readily applicable tool for early risk stratification and individualized rehabilitation planning after transplantation.

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Disclosures: Patricia Almeida:Nothing to Disclose, Thiago Carvalho:Nothing to Disclose, Samia Sousa: Nothing to Disclose, Angelica Cruz:Nothing to Disclose, Fernanda Rezende:Nothing to Disclose, Fernanda Oliveira:Nothing to Disclose.

4564 | TOWARDS PATIENT-LED ACUTE REJECTION SURVEILLANCE IN LIVER TRANSPLANTATION: EXPLORING ACCEPTABILITY AND ATTITUDINAL DOMAINS IN A NATIONAL CROSS-SECTIONAL STUDY

Omar Quidwai[1] Linda Kelly[1] Grace Buckley[2] Stephanie Bollard[1] Audrey Dillon[1] Zita Galvin[1] Masood Iqbal[1] Fiona Hand[1] Emir Hoti[1] John Hammond[1] Andrew Malone[1] Aurelie Fabre[1] Helen Heneghan[3] Henk Giele[4] Omar Elsherif[1] Roisin Dolan[1], [1]St Vincent's University Hospital, [2]UCD School of Medicine & Medical Sciences, [3]University College Dublin, [4]Oxford University Hospitals NHS Foundation Trust

Background: Invasive protocol biopsy remains the diagnostic gold standard for rejection surveillance after liver transplantation, despite procedural risks and the absence of reliable early predictive biomarkers. Co-transplanted sentinel skin flaps (SSF) have been proposed as a visible, minimally invasive adjunct to conventional monitoring; however, patient acceptability data in liver transplant populations are lacking. Exploratory data in simultaneous pancreas-kidney (SPK) recipients, in whom the SSF concept has existing clinical precedent, are similarly absent. **Methods:** We conducted a cross-sectional acceptability study of 100 liver transplant candidates and recipients at a national transplant centre, with a convenience sample of 22 SPK candidates and recipients enrolled for exploratory comparison. Following a standardised explanation of the SSF concept, participants rated willingness to adopt, perceived benefits, concerns, and confidence in self-monitoring using five-point Likert scales. Exploratory factor analysis (EFA) identified underlying attitudinal domains and free-text responses underwent inductive thematic analysis. **Results:** Acceptability was high among liver participants, with 89% reporting definite or likely willingness to adopt an SSF. Perceived reassurance (93%), patient empowerment (84%), and confidence in self-monitoring (91%) were the principal drivers of acceptability. Cosmetic (29%) and social stigma (19%) concerns were common but did not substantially reduce willingness, with 76-93% of concerned participants remaining willing to proceed. EFA identified three domains: perceived benefit and reassurance, acceptance and willingness to adopt, and confidence in self-monitoring. Cosmetic concern was the only independent predictor of reduced willingness on multivariate analysis ($\beta = -0.65$, $p = 0.004$). Thematic analysis confirmed reassurance and early rejection detection as dominant themes, with visibility and body image as the principal concerns. In the exploratory SPK cohort, comparable acceptability was observed, with candidates awaiting transplantation reporting greater anticipated benefit than established recipients. **Conclusion:** Liver transplant candidates and recipients demonstrate high acceptability of forearm SSF monitoring, with three attitudinal domains identified and cosmetic concern representing the primary modifiable barrier. Exploratory findings in SPK recipients support comparable acceptability and warrant dedicated evaluation in larger cohorts. These findings support progression to early-phase feasibility evaluation, with structured pre-operative counselling addressing cosmetic and visibility concerns during implementation.

Disclosures: Omar Quidwai:Nothing to Disclose, Linda Kelly:Nothing to Disclose, Grace Buckley: Nothing to Disclose, Stephanie Bollard:Nothing to Disclose, Audrey Dillon:Nothing to Disclose, Zita Galvin:Nothing to Disclose, Masood Iqbal:Nothing to Disclose, Fiona Hand:Nothing to Disclose, Emir Hoti: Nothing to Disclose, John Hammond:Nothing to Disclose, Andrew Malone:Nothing to Disclose, Aurelie Fabre:Nothing to Disclose, Helen Heneghan:Nothing to Disclose, Henk Giele:Nothing to Disclose, Omar Elsherif:Nothing to Disclose, Roisin Dolan:Nothing to Disclose.

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4565 | ENDOSCOPIC ULTRASOUND-GUIDED VERSUS STANDARD LIVER BIOPSY IN LIVER TRANSPLANT RECIPIENTS: A PROPENSITY SCORE MATCHED STUDY

Pauline Bozon-Rivière[1] Philippe Willems[1] Eya Hamdani[2] Meziane Silhadi[2] Catherine Vincent[3] Julien Bissonnette[4] Julian Hercun[5], [1]CHUM, Montréal, Québec, Canada, [2]Université de Montréal, Québec, Canada, [3]University of Montreal, Canada, [4]University of Montreal Hospital Center, [5]Centre hospitalier de l'Universite de Montreal

Background: Liver biopsy (LB) remains the gold standard for diagnosing graft-related complications after liver transplantation (LT). However, percutaneous biopsy (PC-LB) may be limited by ascites, split LT or antiplatelet therapy, whereas transjugular biopsy (TJ-LB) can be challenging in cases of difficult venous access. Endoscopic ultrasound-guided liver biopsy (EUS-LB) has emerged as an alternative that also allows direct presinusoidal portal pressure assessment, but data in liver transplant recipients remain limited. Our study aimed to assess the diagnostic adequacy and safety of EUS-LB and to compare it with standard biopsy approaches in LT recipients. **Methods:** We conducted a retrospective single-center study including all consecutive LT recipients who underwent EUS-guided LB between January 2023 and December 2025. To reduce the risk of selection bias related to the choice of biopsy technique, we compared EUS-LB to a cohort of LT patients who underwent LB between January 2021 and December 2022, before the introduction of EUS-LB at our institution. Propensity score matching including age, sex, BMI, presence of ascites, anticoagulation, antiplatelet therapy, platelet count, international normalized ratio, creatinine level, and type of caval anastomosis was performed in a 1:1 ratio. Primary endpoints were diagnostic adequacy and safety. Secondary endpoints included specimen quality and recovery time. **Results:** A total of 19 EUS-LB were included. The majority were male (78.9%), with a median age of 54 ± 18 years. At the time of biopsy, 31.6% of patients were on anticoagulation, 42.1% on antiplatelet therapy and 10.5% had ascites. EUS-LB was preferred over conventional techniques because of either the need for concomitant EGD or biliary assessment (68.4%), prior difficult transjugular access or anatomical constraints (21.1%), or patient preference (10.5%).The historical cohort included 62 consecutive patients. Propensity score matching was performed, resulting in 19 matched biopsies. Diagnostic adequacy was high in both groups, with a numerically higher rate in the EUS-LB group (100% vs. 89.5%; p = 0.486). Overall histological quality was comparable between groups (p = 0.31). The number of biopsy passes was significantly lower in the EUS-LB group compared with the standard biopsy group (SBG) (1.26 ± 0.56 vs. 2.42 ± 1.17; p < 0.001). Two inadvertent renal tissue samples were obtained in the SBG, without clinical consequence. Post-procedural pain occurred in 15.8% of patients in both groups. One case of bleeding (subcapsular hematoma) occurred in the SBG while one case of biliary infection requiring hospitalization occurred in both groups. Recovery time was significantly shorter after EUS-LB (120 vs. 240 minutes; p < 0.001). **Conclusion:** In liver transplant recipients, EUS-guided LB appears to be a feasible and safe alternative to standard biopsy techniques.

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4566 | ASSOCIATION OF ACUITY CIRCLES IMPLEMENTATION WITH TIME TO LIVER TRANSPLANTATION IN PATIENTS WITH MASLD

Navin Prasad[1] David Twitchell[2], [1]Presbyterian Hospital, [2]Banner University Medical Group

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the fastest growing indication for liver transplantation in the United States. With an aim to minimize geographic disparities in liver transplant,, the Organ Procurement and Transplantation Network (OPTN) implemented the acuity circles allocation policy in February 2020. This model prioritizes the highest acuity patients per MELD score and expands the donor pool region to concentric circles in miles from the donor center, opposed to allocating only within rigid regions. The association between this policy change and transplantation patterns among patients with MASLD remains incompletely understood. **Methods:** We performed a retrospective analysis of adult liver transplant recipients with a primary diagnosis of MASLD (NASH/MASH) identified within the OPTN database from 2016–2023. Adult liver transplant recipients with a primary diagnosis of MASLD (NASH/MASH) were stratified into pre–acuity circles (before February 4, 2020) and post–acuity circles cohorts. The primary outcome was time from listing to transplantation. Secondary outcomes included demographic and clinical characteristics, including MELD scores at listing and transplantation. **Results:** A total of 10,519 MASLD transplant recipients were included (pre-acuity cohort: 5,186; post-acuity cohort: 5,333). Median time to

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transplantation decreased significantly from 86 days (IQR 21–286) in the pre-policy era to 56 days (IQR 10–159) following implementation of acuity circles ($p < 0.001$).Baseline characteristics were largely similar between groups. Median age (61 vs 61 years, $p = 0.165$), diabetes prevalence (44.1% vs 43.5%, $p = 0.563$), and MELD at listing (20 vs 20, $p = 0.341$) were unchanged. The proportion of female recipients increased modestly following policy implementation (47.5% vs 49.5%, $p = 0.041$). BMI was slightly lower in the post-policy cohort (31.6 vs 32.0 kg/m², $p = 0.004$). Median MELD at transplantation was similar between groups (24 vs 24), although a small statistically significant distributional difference was observed ($p = 0.003$). **Conclusion:** Implementation of acuity circles in liver transplant allocation is associated with significantly shorter time from listing to transplantation among patients with MASLD, without meaningful differences in disease severity at listing. These findings suggest that the acuity circle model improves efficiency of liver transplant in the MASLD cirrhosis population.

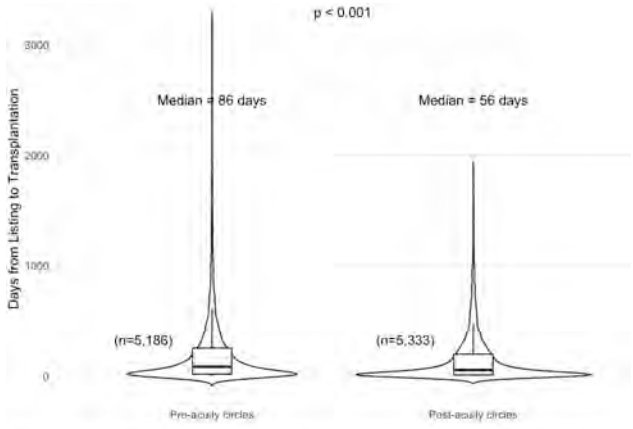


Figure 1. Time to Liver Transplant Among MASLD Patients Before and After Acuity Circles

Disclosures: Navin Prasad:Nothing to Disclose, David Twitchell:Nothing to Disclose.

4567 | COMPARATIVE WAITLIST AND EARLY POST-TRANSPLANT OUTCOMES IN ASIAN VS. NON-ASIAN LIVER TRANSPLANT CANDIDATES: A PROPENSITY-MATCHED UNOS STUDY (2002-2025)

Amukta Palakurthi[1] Mangesh Pagadala[2] Suvisesh Pothuraju[3] Sajid Jalil[4] Chencheng Xie[5] Nimish Thakral[6] Yong-Fang Kuo[7] Winston Dunn[8] Robert Wong[9] Paul Kwo[10] Ashwani Singal[11], [1]Appalachian Regional Healthcare, [2]Liver Institute, Methodist Dallas Medical Center, [3]University of Louisville School of Medicine, [4]Stanford University School of Medicine, [5]University of Iowa, [6]University of Kentucky Medical Center, [7]University of Texas Medical Branch, [8]University of Kansas Medical Center, [9]Stanford/VA Palo Alto Healthcare System, [10]Stanford University Medical Center, [11]University of Louisville

Background: Data on waitlist and post-transplant outcomes after liver transplant (LT) in Asians compared to other racial/ethnic groups in the US are limited. **Methods:** Using the United Network for Organ Sharing (UNOS) database (2002 to 2025), we identified adult LT candidates and recipients, excluding pediatric and multi-organ transplants except for liver and kidney. Propensity score matching was conducted to compare Asians with Non-Hispanic Whites (NHW), African Americans (AA), Hispanics (HW), and Native Americans (NA) based on demographics, comorbidities, liver disease etiology, and MELD score. Primary outcomes were 90-day waitlist mortality and post-transplant patient/ liver graft survival at 1 year. **Results:** Among 194,535 listings, 7,568 (3.9%) were for Asians. In unadjusted analyses, Asians had lower waitlist mortality than AA (HR 0.80; 95% CI 0.71–0.89), HW (HR 0.81; 95% CI 0.73–0.90), and NA (HR 0.78; 95% CI 0.64–0.94). After PSM, waitlist mortality in Asians remained lower than in NA (HR 0.74; 95% CI 0.56–0.97), but was like NHW (0.90; 0.76–1.05), AA (0.89; 0.76–1.05), and HW (0.85; 0.73–1.00). A total of 4533 LTs were performed in Asians, with better graft and patient survival rates than AA: 90.1 vs. 86.7%, 0.84 (0.71–0.98, $p < 0.001$) and 92.7 vs. 89.4%, 0.80 (0.67–0.97) respectively, $p < 0.001$ for both. These rates were similar for Asians compared with NHW, HW, or NA ($p > 0.20$ for all). HBV accounted for 40% of listings and LT in Asians, compared with approximately 1–8% in other groups. Within the HBV subgroup, compared to Asians, NA had a higher hazard of 90-day waitlist mortality, 1.91 (1.11-3.31, $p = 0.020$), and NHW had a higher hazard of graft/patient loss: 1.340 (1.05-1.85, $p = 0.021$) and 1.55 (1.10-2.16, $p = 0.01$), respectively. **Conclusion:** These findings highlight population-specific ethnic differences in waitlist and post-transplant outcomes among liver transplant candidates and recipients, which require further investigation.

Disclosures: Amukta Palakurthi:Nothing to Disclose, Mangesh Pagadala:Nothing to Disclose, Suvisesh Pothuraju:Nothing to Disclose, Sajid Jalil:Nothing to Disclose, Chencheng Xie:Nothing to Disclose, Nimish Thakral:Nothing to Disclose, Yong-Fang Kuo:Nothing to Disclose, Winston Dunn:Nothing to Disclose, Robert Wong:Theratechnologies: Grant/Research Support, Theratechnologies: Grant/Research Support, Durect: Grant/Research Support, Durect: Grant/Research Support, Gilead Sciences: Grant/Research Support, Gilead Sciences: Grant/Research Support,

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4568 | CAD-LT AND THE BURDEN OF FUTILE CORONARY ANGIOGRAPHY

Bandar Aljudaibi[1] Saleh Alqahtani[2] Khalid Bzeizi[3] Manhal Izzy[4] Saad Alghamdi[5] Ehab Abufarhaneh[3] Fuat Saner[6] Maryam Abdulla[7], [1]King Faisal Specialist Hospital and Research Centre, [2]King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia, [3]King Faisal Specialists Hospital and Research Centre, [4]Vanderbilt University Medical Center, [5]King Faisal Specialist Hospital and Research Center, [6]King Faisal Specilaists Hospital and Research Centre, [7]Alfaisal Univeristy

Background: Cardiovascular disease remains a major source of morbidity after liver transplantation (LT). The CAD-LT score was developed to identify LT candidates at increased risk for coronary artery disease (CAD), but its performance in Middle Eastern populations in living-donor LT programs is uncertain. This study evaluated the association between CAD-LT risk stratification, invasive coronary angiography findings, preoperative coronary intervention, and post-transplant cardiovascular outcomes in a Middle Eastern LT cohort. **Methods:** This retrospective single-center study included 353 adult LT recipients who underwent preoperative cardiac catheterization between 2020 and 2024. Patients were stratified into low–intermediate and high-risk groups according to the CAD-LT score. Baseline characteristics, angiographic findings, coronary interventions, and post-transplant cardiovascular outcomes were analyzed. **Results:** Of the 353 patients, 244 (69.1%) were classified as high risk and 109 (30.9%) as low–intermediate risk. High-risk patients were older and had significantly higher rates of diabetes mellitus, hypertension, hypercholesterolemia, and prior CAD. Obstructive CAD ($\geq$50% stenosis) was identified in 37 patients (10.48%) overall and was more common in the high-risk group (12.30% vs. 6.42%, p = 0.096). Percutaneous coronary intervention (PCI) was performed in 10.06% of patients, predominantly in the high-risk group (11.93% vs. 5.71%, p = 0.077). Despite a higher cardiovascular risk profile and more frequent invasive interventions, post-transplant cardiac outcomes were comparable between groups. Cardiac-related mortality was low (2.04%) and did not differ significantly between low–intermediate and high-risk patients (1.87% vs. 2.12%, p = 0.89). Rates of cardiac arrest, atrial arrhythmias, acute coronary syndrome, and post-transplant dialysis were also similar between groups. **Conclusion:** In this Middle Eastern LT cohort, the CAD-LT score identified patients with a higher cardiovascular risk profile and greater likelihood of coronary intervention. However, the prevalence of obstructive CAD requiring PCI remained low, with nearly 90% of invasive coronary angiograms demonstrating non-obstructive disease. CAD-LT ability to predict clinically significant obstructive CAD requiring intervention is modest in this population.

Disclosures: Bandar Aljudaibi:Nothing to Disclose, Saleh Alqahtani:Nothing to Disclose, Khalid Bzeizi: Nothing to Disclose, Manhal Izzy:Mallinckrodt: Speaking and Teaching, Madrigal: Advisor, Natera: Advisor, Mirum: Advisor, Saad Alghamdi:Nothing to Disclose, Ehab Abufarhaneh:Nothing to Disclose, Fuat Saner: Nothing to Disclose, Maryam Abdulla:Nothing to Disclose.

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4569 | POST-TRANSPLANT CARDIAC OUTCOMES AND SURVIVAL ACCORDING TO CAD-LT RISK CLASSIFICATION

Bandar Aljudaibi[1] Maryam Abdulla[2] Saad Alghamdi[3] Manhal Izzy[4] Saleh Alqahtani[5] Ehab Abu-Farhaneh[6] Khalid Bzeizi[7] Fuat Saner[7], [1]King Faisal Specialist Hospital and Research Centre, [2]Alfaisal Univeristy, [3]King Faisal Specialist Hospital and Research Center, [4]Vanderbilt University Medical Center, [5]King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia, [6]University of Toronto, [7]KFSH

Background: Cardiac complication post liver transplantation (LT) are a leading cause of morbidity and mortality. CAD-LT score was designed to stratify the risk of obstructive coronary artery disease (CAD) in LT candidates; however, its association with post-transplant cardiac outcomes and survival in Saudi and Arabian Gulf population LT recipients has not been well described. We evaluated whether CAD-LT risk classification predicts post-LT cardiac events, patient survival, and graft survival in our cohort. **Methods:** We conducted a retrospective single-center analysis 353 LT candidates evaluated at King Faisal Specialist Hospital and Research Centre (KFSHRC), Riyadh, Saudi Arabia, between 2020 -2024**.** All patients underwent coronary angiography as part of pre-transplant workup and were stratified by CAD-LT risk classification into low/intermediate-risk and high-risk groups. Post-LT cardiac outcomes included cardiac death, cardiac arrest, atrial fibrillation/flutter, ventricular arrhythmia, myocardial infarction, and need of post-transplant dialysis. Patient and graft survival were compared between CAD-LT risk groups using Kaplan-Meier analysis with log-rank testing. Multivariable Cox proportional hazards regression was performed to assess predictors of patient survival. **Results:** Of 353 patients, 109 were classified as low/intermediate risk and 244 as high risk. Overall, post-LT cardiac events occurred in 35 patients (9.9%). Cardiac events were more frequent in the high-risk group compared with the low/intermediate-risk group (12.3% vs 4.6%). Cardiac death occurred in 7 patients, cardiac arrest in 17, atrial fibrillation in 5, atrial flutter in 2, ventricular arrhythmia in 1, and myocardial infarction in 12. Dialysis after transplant occurred in 25 patients overall and was more common in the high-risk group (8.6% vs 3.7%). Despite the higher burden of post-LT cardiac events in the high-risk group, patient survival did not differ significantly between CAD-LT risk categories. Death occurred in 42 patients overall, with similar rates in low/intermediate-risk and high-risk groups (11.9% vs 11.9%). Graft failure also occurred in 42 patients, with identical rates between groups. Kaplan-Meier curves demonstrated no significant difference in patient or graft survival between risk categories (log-rank $p = 0.937$ for both endpoints). On multivariable Cox regression, CAD-related variables were not independently associated with patient survival. **Conclusion:** In this large LT cohort, CAD-LT high-risk classification was associated with a higher observed rate of post-transplant cardiac events, but not with inferior patient or graft survival. These findings suggest that while CAD-LT may help identify patients requiring closer perioperative cardiac monitoring, its prognostic value for long-term survival appears limited in this population

Disclosures: Bandar Aljudaibi:Nothing to Disclose, Maryam Abdulla:Nothing to Disclose, Saad Alghamdi: Nothing to Disclose, Manhal Izzy:Mallinckrodt: Speaking and Teaching, Madrigal: Advisor, Natera: Advisor, Mirum: Advisor, Saleh Alqahtani:Nothing to Disclose, Ehab Abu-Farhaneh:Nothing to Disclose, Khalid Bzeizi: Nothing to Disclose, Fuat Saner:Nothing to Disclose.

4570 | EPSTEIN BARR VIRUS VIREMIA ASSOCIATED WITH INCREASED POST TRANSPLANT LYMPHOPROLIFERATIVE DISORDERS AND OVERALL MORTALITY IN ADULT LIVER TRANSPLANT RECIPIENTS

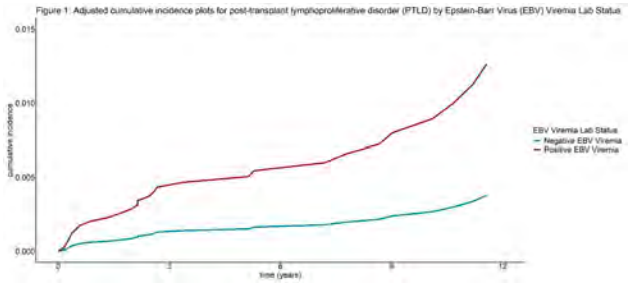
Carter Chapman[1] Deena Brosi[2] Jesse Schold[2] Michael Kriss[3] Jon Rice[3] Cassandra Duarte[4] Bradley Haverkos[5], [1]University of Colorado Anschutz Internal Medicine Residency, [2]University of Colorado School of Medicine, Division of Transplant Surgery, [3]University of Colorado School of Medicine, Division of Gastroenterology and Hepatology, [4]University of Colorado School of Medicine, Division of Hematology and Oncology, [5]Unviersity of Colorado School of Medicine, Division of Hematology and Oncology

Background: Post-Transplant Lymphoproliferative Disorders (PTLD) represent a spectrum of lymphoid neoplasms that occur following solid-organ and hematopoietic stem cell transplant and are strongly associated with the Epstein-Barr Virus (EBV). Although uncommon, they are the leading cause of cancer-related mortality in solid-organ transplant recipients. Despite this, there is limited adult liver transplant recipient specific data confirming the relationship between EBV viral load and future risk of PTLD development. Therefore, this study seeks to further investigate the relationship between EBV viremia and the development of PTLD in adult liver transplant recipients. **Methods:** We used our internal organ transplant registry at the University of Colorado Health Transplant Center to identify first-time adult

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liver transplant (LT) recipients from 1/1/2012 – 9/8/2025. Our sample includes 1,237 LT recipients, 27.6% (n = 342) of which had a detectable EBV PCR (either whole blood or plasma) taken after LT. The remaining patients – those with either negative EBV testing or those that had never been tested – formed the negative EBV viremia group. Our primary outcomes of interest were diagnosis of PTLD and all-cause mortality. We estimated sub-distribution hazard ratios (sHRs) using Fine & Gray's competing risks analysis, which considered retransplant and loss-to follow up as competing events for both outcomes and all-cause mortality as an additional competing event for risk of PTLD. Sub-distribution hazard ratios were adjusted for primary liver diagnosis prior to transplant, immunosuppressive regimens, treatment of rejection, baseline demographics, EBV serostatus, and history of cytomegalovirus viremia. **Results:** The unadjusted sHR of PTLD was 4.17 (95% confidence interval [CI]: 1.92 – 8.05; p-value < 0.001) higher among LT recipients in the positive EBV viremia group compared with those in the negative EBV viremia group. The adjusted sHR of PTLD was 3.61 (95% confidence interval [CI]: 1.55 – 8.41; p-value = 0.003) higher among LT recipients in the positive EBV viremia group. Adjusted cumulative incidence of PTLD was also found to be higher in the positive EBV viremia group compared to the negative EBV viremia group (Figure 1). LT recipients in the positive EBV viremia group had significantly higher risk of mortality with an adjusted sHR of 2.35 (95% CI: 1.62 – 3.40; p-value < 0.001). **Conclusion:** Our study demonstrates a significant association between a history of detected EBV viremia and the development of PTLD in adult liver transplant recipients, as well as a significant association between EBV viremia and all-cause mortality in this population. Future directions of our study involve evaluating the relationship between quantitative EBV viral load and immune suppression and the development of PTLD in order to establish viral load cutoffs that identify high risk patients.



Disclosures: Carter Chapman:Nothing to Disclose, Deena Brosi:Nothing to Disclose, Jesse Schold: Nothing to Disclose, Michael Kriss:Nothing to Disclose, Jon Rice:Nothing to Disclose, Nothing to Disclose, Cassandra Duarte:Cogent Biosciences: Consultant, Blueprint Medicine: Advisor, EMD Serono: Advisor, Bradley Haverkos:Nothing to Disclose.

4571 | OPHTHALMIC MANIFESTATIONS FOLLOWING LIVER TRANSPLANTATION IN THE EPIC COSMOS DATABASE

Miles Richman[1] Reagan McGinley[1] Sidart Pradeep[2] Jan Petrasek[3] Masih Ahmed[4], [1]School of Medicine, Baylor College of Medicine, Houston, Texas, USA, [2]UT Health San Antonio, [3]Texas Liver Institute, San Antonio, TX, USA, [4]Department of Ophthalmology, Cullen Eye Institute, Baylor College of Medicine, Houston, Texas, USA

Background: The purpose of this study was to report the incidence of ophthalmic manifestations in liver transplant recipients. **Methods:** This is a retrospective cohort study of the Epic Cosmos database where we looked at patients who received a liver transplant between October 01, 2017, to September 30, 2023. Patients were only included if they had a baseline eye exam in the year preceding liver transplant. We then searched for predefined ophthalmic conditions using ICD-10 codes in the two years following transplant, recorded the average time to diagnosis, and identified incident manifestations by comparison with the baseline eye exam. We categorized the pathologies into eyelid, corneal, conjunctival, lens, retina, optic disc, and ocular surface conditions, as well as viral infections. **Results:** We retrieved 5,051 liver transplant recipients from the database. The mean age of patients was 55.7 ± 11.5. Overall, 516 (10.22%) had any incident ocular pathology. The most common categories of incident pathologies were retina (4.59%), lens (2.87%), conjunctival (2.65%), and ocular surface (1.76%). The most common manifestations were diabetic retinopathy (2.79%), nuclear sclerosis (2.55%), dry eye (1.76%), conjunctivitis (1.90%), and age-related macular degeneration (1.41%). The average time to diagnosis following transplant ranged from 22 to 433 days. **Conclusion:** Ophthalmic manifestations were seen in a substantial portion of liver transplant recipients. It is important for providers to understand the incidence of these conditions following liver transplants and to recommend that patients undergo ocular exams to diagnose early and avoid treatment delays.

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Table 1: Demographic Characteristics

	Demographic	Patients
Age	Mean	55.7 (11.5)
	Median	58 (49-64)
Race/Ethnicity	NH White	3367
	NH Black	254
	NH Asian	102
	NH American/Alaskan Native	33
	Multiracial/Other	509
	Hispanic	573
	Unknown/Missing	213
Sex	Male	3173
	Female	1877
	Unknown	1

Table 2: Ophthalmic Pathology Categories

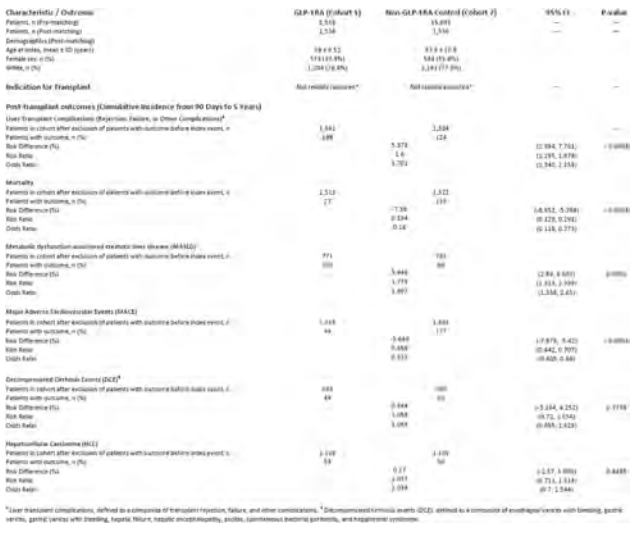
Pathology Category	Patients Affected
Eyelid pathology	16 (0.32%)
Corneal pathology	6 (0.12%)
Conjunctival pathology	134 (2.65%)
Lens pathology	145 (2.87%)
Retina pathology	232 (4.59%)
Optic disc pathology	11 (0.22%)
Ocular surface pathology	89 (1.76%)
Viral infections	12 (0.24%)

Disclosures: Miles Richman:Nothing to Disclose, Reagan McGinley:Nothing to Disclose, Sidart Pradeep:Nothing to Disclose, JAN PETRASEK:Nothing to Disclose, Masih Ahmed:Nothing to Disclose.

4572 | METABOLIC, CARDIOVASCULAR, AND HEPATIC OUTCOMES ASSOCIATED WITH GLP-1 RECEPTOR AGONIST USE IN LIVER TRANSPLANT RECIPIENTS WITH TYPE 2 DIABETES MELLITUS: A PROPENSITY-MATCHED COHORT STUDY

Allan Zhang[1] Mohamad Ali Ibrahim[2] Kimberly Taing[1] Prasun Jalal[2], [1]University of Texas Southwestern Medical Center, [2]Baylor College of Medicine

Background: As survival after liver transplantation improves, long-term metabolic and cardiovascular complications have emerged as important determinants of post-transplant outcomes. While GLP-1 receptor agonists (GLP-1RAs) grant cardiometabolic benefits in the general population, evidence supporting their use after liver transplantation remains limited. As such, this study evaluated the association of GLP-1RA use with metabolic, hepatic, and cardiovascular outcomes among liver transplant recipients with type 2 diabetes mellitus (T2DM). **Methods:** Using the TriNetX Research Network, we identified adult liver transplant recipients with T2DM who initiated a GLP-1RA (semaglutide, exenatide, liraglutide, dulaglutide, or tirzepatide) within 3 months of transplant. These patients were compared against non-GLP-1RA controls in a retrospective cohort design. Patients with kidney, lung, or heart transplantation were excluded. Outcomes assessed as 5-year cumulative incidence beginning 90 days after index (date of transplant) included mortality, major adverse cardiovascular events (MACE), liver transplant complications, metabolic dysfunction-associated steatotic liver disease (MASLD), decompensated cirrhosis events (DCE), and hepatocellular carcinoma (HCC). Transplant complications were defined as a composite of liver transplant rejection, liver transplant failure, and other complications of liver transplant. Cohorts were propensity score matched 1:1 for demographics, metabolic and cardiovascular comorbidities, liver disease etiologies, immunosuppressive therapy, and laboratory markers. **Results:** Among 16,593 eligible liver transplant recipients, 1,558 patients receiving GLP-1RAs and 15,035 controls were identified. After matching, 1,536 patients remained in each cohort. GLP-1RA use was associated with significantly reduced risk of mortality (RR 0.19, 95% CI 0.13-0.29; $p < 0.0001$) and MACE (RR 0.56, 95% CI 0.44-0.71; $p < 0.0001$). No significant differences were observed in HCC or DCE. Interestingly, GLP-1RA exposure was associated with increased 5-year cumulative rates of MASLD (RR 1.78, 95% CI 1.31-2.40; $p = 0.0001$) and transplant complications (RR 1.6, 95% CI 1.30-1.98; $p < 0.0001$). **Conclusion:** In liver transplant recipients with T2DM, GLP-1RA use was linked to lower mortality and cardiovascular risk. Higher MASLD rates could reflect confounding by indication, as GLP-1RAs may be initiated in patients who are more likely to develop de novo graft steatosis. Furthermore, observed elevations in transplant complications may reflect claims-data limitations and surveillance bias. As such, prospective studies with graft biopsies and drug monitoring are needed to clarify post-transplant GLP-1RA safety.



Disclosures: Allan Zhang:Nothing to Disclose, Mohamad Ali Ibrahim:Nothing to Disclose, Kimberly Taing:Nothing to Disclose, Prasun Jalal:Madrigal, GSK, Mirum, Ipsen, Gilead, Genentech, Zydus: Grant/Research Support, Intercept, Genfit: Grant/Research Support.

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4573 | ANTI-CD25 ANTIBODY INDUCTION COMBINED WITH REDUCED-DOSE CORTICOSTEROIDS IN LIVER TRANSPLANTATION: A REAL-WORLD COMPARISON OF SHORT- AND LONG-INTERVAL DOSING REGIMENS

Xuguang Hu[1] Zhidan Xu[2] Laibang Luo[2] Zehong Fang[2] Xuyang Wang[2] Gang Liu[2], [1]Jiangxi Provincial People's Hospital, [2]Jiangxi Provincial People's Hospital, Nanchang, China

Background: Humanized anti-CD25 monoclonal antibodies (mAbs) are commonly used for induction therapy in liver transplantation (LT) to prevent early acute cellular rejection (ACR). Nevertheless, real-world data regarding their clinical efficacy and optimal dosing interval remain limited. This study assessed clinical outcomes of anti-CD25 mAb induction paired with a reduced-dose corticosteroid protocol, and compared short- and long-interval dosing strategies. **Methods:** This single-center retrospective cohort study enrolled 140 LT recipients treated between September 2022 and December 2024. All patients received anti-CD25 mAb (two 50-mg doses) and a 50% reduced corticosteroid protocol (initial daily dose < 120 mg). Patients were stratified according to the timing of the second dose: short-interval group (7–10d, n = 98) and long-interval group (14d, n = 42). Baseline characteristics were well balanced between groups. The primary endpoint was clinically confirmed ACR. Secondary endpoints comprised infection rates, and both graft and patient survival.Continuous and categorical variables were compared using t-test/Mann-Whitney U test and χ^2/Fisher's exact test, respectively; survival was analyzed via Kaplan-Meier method. **Results:** Clinically confirmed ACR developed in 13.6%. All episodes responded to corticosteroid, and no steroid-resistant rejection occurred. Six- and 12-month graft survival rates were 100% and 99.3%; patient survival rates were 95.9% and 90.1%. Median IV steroid discontinuation was 6 days (87.0% success rate), and 85% of patients achieved target TAC troughs by month 1.Pre-second-dose immune monitoring revealed a trend toward lower absolute T-cell counts (356 ± 259 vs. 501 ± 329, P = 0.109) and CD4+ T-cell counts (212 ± 160 vs. 309 ± 213, P = 0.108) in the short-interval group, suggesting more sustained perioperative T-cell suppression. Consistently, TAC trough levels were lower in the short-interval group on postoperative day7 (7.3 ± 3.6 vs. 9.4 ± 18.3 ng/mL, P = 0.019) and on day14 (8.5 ± 8.3 vs. 11.1 ± 30.3 ng/mL, P = 0.060). The short-interval group also had a trend toward a lower ACR rate (10.2% vs. 21.4%, P = 0.075), while overall infection rates were similar between the two groups (22.2% vs. 26.2%, P = 0.45). Cohort infection rate was 22.1% , including 3.6% requiring ICU admission. AKI occurred in 12.9% ; none required renal replacement. No drug-related adverse events were observed. **Conclusion:** Induction therapy with humanized anti-CD25 mAb plus reduced-dose corticosteroids yields favorable anti-rejection efficacy and safety among LT recipients. The 7–10 day short-interval dosing schedule optimizes perioperative immune control, with a trend toward reduced ACR without elevating infection risk. These real-world data provide valuable evidence for timing optimization of induction regimens, and support the adoption of individualized, precision immunosuppression in clinical liver transplantation.

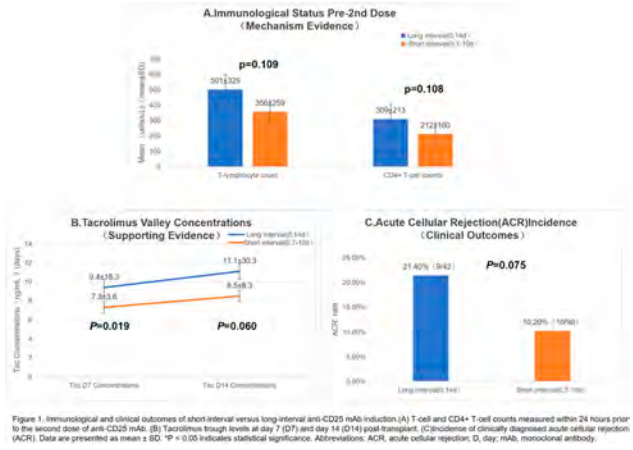


Figure 1. Immunological and clinical outcomes of short-interval versus long-interval anti-CD25 mAb induction.(A) T-cell and CD4+ T-cell counts measured within 24 hours prior to the second dose of anti-CD25 mAb. (B) Tacrolimus trough levels at day 7 (D7) and day 14 (D14) post-transplant. (C)Incidence of clinically diagnosed acute cellular rejection (ACR). Data are presented as mean ± SD. *P < 0.05 indicates statistical significance. Abbreviations: ACR, acute cellular rejection; D, day; mAb, monoclonal antibody.

Disclosures: Xuguang Hu:Nothing to Disclose, Zhidan Xu:Nothing to Disclose, Laibang Luo:Nothing to Disclose, Zehong Fang:Nothing to Disclose, Xuyang Wang:Nothing to Disclose, Gang Liu:Nothing to Disclose.

4574 | TUMOR BIOLOGY MODIFIES THE ASSOCIATION BETWEEN SURGICAL MARGIN WIDTH AND RECURRENCE FOLLOWING CURATIVE-INTENT RESECTION FOR HEPATOCELLULAR CARCINOMA

Matthew Kim[1] Devi Veeramgari[1] Yonatan Kaplan[1] Adina Shrestha[1] Aashrith Madagiri[1] Daisuke Imai[1] Yuzuru Sambommatsu[1] Vinay Kumaran[1] Muhammad Saeed[1] Aamir Khan[1] Amit Sharma[1] Adrian Cotterell[1] Hannah Lee[1] David Bruno[1] Seung Lee[1], [1]Virginia Commonwealth University School of Medicine

Background: For patients with hepatocellular carcinoma (HCC), recurrence following liver resection remains high. While surgical margin width and

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biological factors have been shown to independently predict recurrence, whether these adverse risk factors modify the relationship between surgical margin width and recurrence is poorly understood. We aimed to determine if margin width modified recurrence risk differently based on tumor biology (tumor grade, alpha fetoprotein [AFP], and microvascular invasion [MVI]) for curative-intent HCC resection. **Methods:** A retrospective analysis of patients from an institutional HCC registry from 2010 to 2020 was performed. Patients were categorized into a no risk (0 risk factors), intermediate risk (1 risk factor), or high risk group (2+ risk factors) based on AFP levels (<20 vs ≥ 20 ng/mL), tumor grade (low grade = G1/G2, high grade = G3/G4), and MVI (negative or positive), with an AFP $\geq$ 20 ng/mL, high grade, or positive MVI being considered a risk factor. Stratified multivariable cox proportional hazards model analyzed independent predictors of recurrence free survival (RFS), and fine gray analysis accounted for death without recurrence. A pooled cox model was used to assess effect modification. Sensitivity analysis on AFP thresholds was conducted. Models were adjusted for age, sex, tumor number, resection type, and cirrhosis. **Results:** 49 patients were included in this analysis (margin $<$1cm: n = 23, margin $\geq$ 1cm: n = 16, positive margin: n = 10). In multivariable cox analysis, intermediate and high risk group were independent predictors of RFS in the margin $<$1cm ($p = .04$ and $p < .001$, respectively) and positive margin group ($p = .03$ and $p < .001$, respectively). Pooled interaction analysis found a significant interaction between margin width and risk status ($p = .03$), with the interaction remaining significant across all tested AFP cutoffs (AFP $\geq$ 20 ng/mL, AFP $\geq$ 200 ng/mL, AFP $\geq$ 400 ng/mL) in the high risk margin width $<$1cm group (HR 5.12, $p = .03$; HR 4.88, $p = .03$; HR 4.72, $p = .04$, respectively). Fine gray analysis found worse RFS in the high risk group compared to no/intermediate risk in the margin $<$1cm group (sHR 3.84, 95% CI 1.92 - 7.68, $p < .001$) and positive margin group (sHR 5.62, 95% CI 2.41 - 13.09, $p < .001$). **Conclusion:** These findings suggest that achieving a surgical margin width $\geq$ 1cm may be crucial to improve survival, and for individuals with a surgical margin width $<$1cm or with positive margins, poor tumor characteristics may significantly worsen prognosis.

Disclosures: Matthew Kim:Nothing to Disclose, Devi Veeramgari:Nothing to Disclose, Yonatan Kaplan:Nothing to Disclose, Adina Shrestha:Nothing to Disclose, Aashrith Madagiri:Nothing to Disclose, Daisuke Imai: Nothing to Disclose, Yuzuru Sambommatsu:Nothing to Disclose, Vinay Kumaran:Nothing to Disclose, Muhammad Saeed:Nothing to Disclose, Aamir Khan:Nothing to Disclose, Amit Sharma:Nothing to Disclose, Adrian Cotterell:Nothing to Disclose, Hannah Lee:Nothing to Disclose, David Bruno:Nothing to Disclose, Seung Lee: Nothing to Disclose.

4575 | POST LIVER TRANSPLANT OUTCOMES IN CONTEMPORARY RECIPIENTS AGED 70–74 YEARS: A NATIONAL COHORT ANALYSIS

Iyiad Alabdul Razzak[1] Kush Patel[1] Irena Helenowski[2] Eric Kallwitz[3] Scott Cotler[3], [1]Loyola University Medical Center, [2]Loyola University, [3]Loyola University Health System

Background: Liver transplantation (LT) has increased in older patients. While age is not a contraindication to LT, it is associated with comorbidities and reduced functional status. We aimed to compare post-LT patient and graft survival between contemporary recipients aged 70–74 years and younger recipients and to identify factors associated with post-transplant outcomes in the age 70-74 cohort. **Methods:** This retrospective cohort study used United Network for Organ Sharing (UNOS) data from adult LT recipients aged $<$75 years transplanted between Feb 2020 and Dec 2024. Recipients aged 70–74 years were compared with younger age cohorts (see Fig 1 for cohorts) with the 40-59 age cohort serving as the reference group. Primary outcomes included post-LT patient and graft survival. Kaplan Meier curves were compared by log-rank tests and Cox proportional hazards models were adjusted for recipient, donor, and transplant related characteristics. **Results:** Among 33,889 adult LT recipients, 2,164 (6.4%) were aged 70–74. Compared with younger recipients, recipients aged 70-74 more frequently had HCC (34.1% vs 13.8%), MASH (29.2% vs 18.8%), diabetes (44.4% vs 28.5%), received donors aged $\geq$70 years (10.9% vs 3.9%) and had lower rates of Karnofsky score $<$40% at transplant (30.7% vs 41.1%) and ICU hospitalization at transplant (22.5% vs 38.0%) (all $p < 0.05$). In unadjusted Cox analysis, age 70–74 was associated with worse patient survival (HR 2.33, 95% CI 2.08–2.61, $p < 0.001$) and graft survival (HR 1.85, 95% CI 1.66–2.07, $p < 0.001$) compared with recipients aged 40–59 (Figures 1A, B). In adjusted models, recipient age 70–74 remained associated with worse patient survival (HR 3.22, 95% CI 2.00–5.17) and graft survival (HR 3.00, 95% CI 1.90–4.74). Within the 70–74 cohort, factors associated with reduced patient survival included non-HCC malignancy (HR 2.41, 95% CI 1.33–4.39), diabetes (HR 1.57, 95% CI 1.24–1.97), BMI $<$25 (HR 1.55, 95% CI 1.22–1.98), ICU hospitalization at transplant (HR 1.51, 95% CI 1.09–2.08) and portal vein thrombosis (HR 1.31, 95% CI 1.00–1.72). Similarly, within the 70–74 cohort, worse graft survival was associated with non-HCC malignancy (HR 2.24, 95% CI 1.22–4.13), diabetes (HR 1.59, 95% CI 1.26–1.99), BMI $<$25 (HR 1.46, 95% CI 1.15–1.85), and ICU hospitalization at transplant (HR 1.56, 95% CI 1.14–2.14). **Conclusion:** Contemporary LT recipients

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aged 70–74 years had reduced patient and graft survival compared with younger recipients. In the age 70-74 cohort, adverse outcomes were associated with comorbidities, low BMI, perioperative acuity, and portal vein thrombosis, supporting individualized candidate selection and development of risk stratification tools to better identify older LT candidates most likely to achieve favorable outcomes.

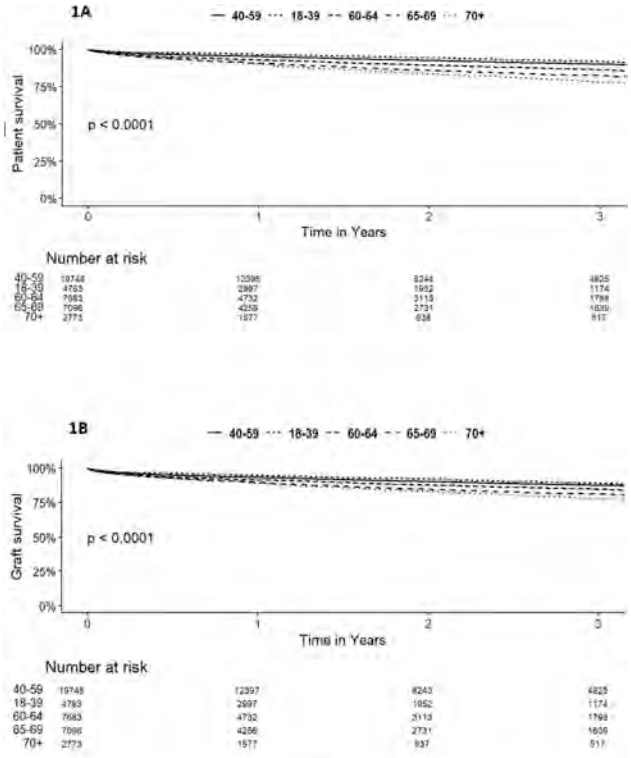


Figure 1: Post liver transplant patient survival (1A) and graft survival (1B) stratified by age cohort. P-values represent overall comparisons across groups.

Disclosures: Iyiad Alabdul Razzak:Nothing to Disclose, Kush Patel:Nothing to Disclose, Irena Helenowski:Nothing to Disclose, Eric Kallwitz:Nothing to Disclose, Scott Cotler:Nothing to Disclose.

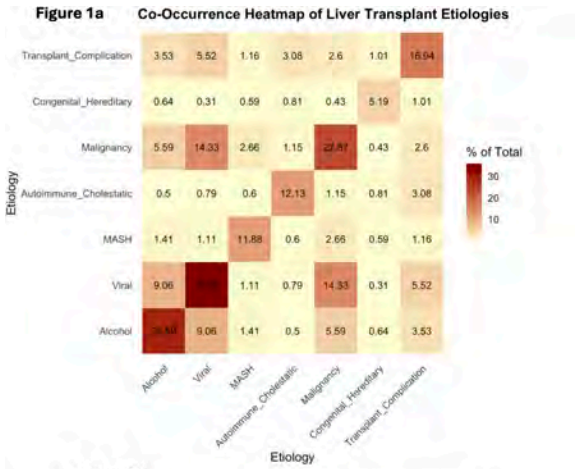
4576 | LIVER DISEASE ETIOLOGY CO-OCCURRENCE, DUAL-ORGAN TRANSPLANTATION, AND PERSISTENT RACIAL/ETHNIC DISPARITIES IN OUTCOMES: A 25-YEAR NATIONAL ANALYSIS OF U.S. LIVER TRANSPLANTATION

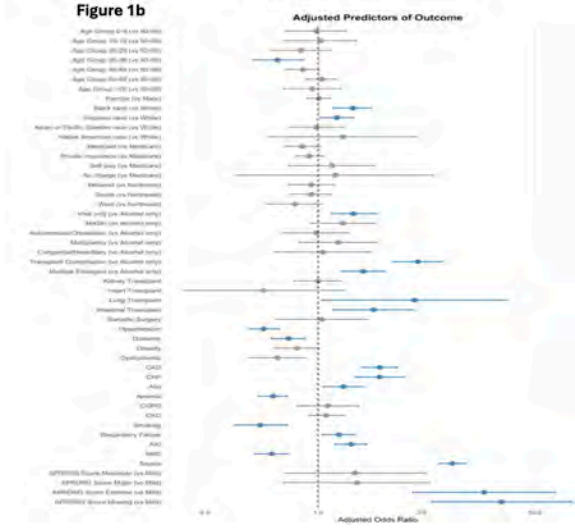
Monica Tincopa[1] Mohammed Abu Rumaileh[2] Bisher Sawaf[2] Hamzeh Abugharbieh[2] Marwan Joma[2] Umberto Battistin[2] Yusuf Hallak[2] Mohannad Qwaider[2] Kyrillos Gerges[3] Leena Alnsour[4] Naser Gharaibeh[5] Abdallah Kheshman[6], [1]University of California, San Diego, [2]University of Toledo, [3]Sohag University,, [4]South Tyneside and Sunderland NHS Foundation Trust,, [5]Icahn School of Medicine at Mount Sinai, [6]Wayne State University

Background: Long-term national trends in liver transplantation (LT) integrating etiology co-occurrence, recipient complexity, and outcomes across distinct epidemiologic eras remain incompletely characterized. This study aimed to: 1) characterize shifts in LT indications including co-occurring liver disease across three epidemiologic eras; 2) describe changes in recipient complexity, length of stay (LOS), and hospital charges; and 3) identify predictors of in-hospital mortality including racial/ethnic disparities. **Methods:** We conducted an analysis of LT hospitalizations in the National Inpatient Sample (NIS) over 25 years (1998–2022). LT hospitalizations were identified using procedure codes. Liver disease etiologies were classified as non-mutually exclusive to characterize co-occurring etiologies. Temporal trends in recipient complexity, comorbidities, dual-organ transplantation, LOS, hospital charges, and in-hospital mortality were assessed. Multivariable logistic regression identified independent predictors of mortality. **Results:** Among 31,454 LT hospitalizations, ALD (29.2% to 43.8%) and MASH (1.8% to 24.7%) increased while viral hepatitis declined (47.7% to 12.6%) across three epidemiologic eras. Etiology co-occurrence was common: viral hepatitis with malignancy (14.3%), viral hepatitis with ALD (9.1%), and ALD with malignancy (5.6%) (**Figure 1a**). Recipient complexity increased including older age (47.1 to 52.0 years), rising metabolic comorbidities, and liver-kidney transplantation (2% to 8%). Despite this, in-hospital mortality declined from 8.0% to 2.5%, with the most rapid declines in viral hepatitis and ALD recipients; malignancy showed no significant decline in mortality. Longer LOS and highest costs were observed with transplant related complications, Medicaid insurance and Hispanic ethnicity ($638,555 vs. $470,560 for White recipients). Independent predictors of higher mortality included transplant complications (OR 2.89), co-occurring etiologies (OR 1.61), viral hepatitis (OR 1.46), lung-liver (OR 2.79) and liver-intestinal transplantation (OR 1.80), Black race (OR 1.45) and Hispanic ethnicity (OR 1.22)(**Figure 1b**). **Conclusion:** Despite increasing complexity including rising age, dual liver disease etiology, increased comorbidity burden and multiorgan transplant, early post-LT mortality improved substantially over 25 years. Systematic characterization of etiology co-occurrence reveals the multifactorial nature of modern LT indications with direct clinical implications. Persistent racial/ethnic disparities in mortality, cost and LOS, including a hypothesis-generating signal among Hispanic recipients, underscore the need for targeted interventions and dedicated disparities research.

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Disclosures: Monica Tincopa:Nothing to Disclose, Nothing to Disclose, Mohammed Abu Rumaileh:Nothing to Disclose, Bisher Sawaf:Nothing to Disclose, Hamzeh Abugharbieh:Nothing to Disclose, Marwan Joma:Nothing to Disclose, Umberto Battistin:Nothing to Disclose, Yusuf Hallak:Nothing to Disclose, Mohannad Qwaider:Nothing to Disclose, Kyrillos Gerges:Nothing to Disclose, Leena Alnsour:Nothing to Disclose, Naser Gharaibeh:Nothing to Disclose, Abdallah Kheshman:Nothing to Disclose.

4577 | INADEQUATE EMPIRICAL ANTIBIOTICS IN POST-TRANSPLANT PNEUMONIA ARE ASSOCIATED WITH LONGER TREATMENT AND HIGHER TREATMENT FAILURE RATES

Zehra Karabal[1] Muhammad Ebrahim Ferozie[2] Nihad Jamalli[2] Narmin Dadashova[2] Laman Karimli[2] Elshad Yagubzade[2] Irem Yasa[2] Tonguc Utku Yilmaz[3] Iftihar Koksal[3], [1]Acibadem University, [2]Acibadem University Medicine Faculty, [3]Acibadem Atakent Hospital

Background: Pneumonia following liver transplantation represents a life threatening infectious complication in an already immunocompromised host. When a liver transplant recipient develops pneumonia, the treating clinician must choose empirical antibiotics before cultures return, a high stakes decision with guidance extrapolated from non-transplant populations. Causative pathogens include multidrug-resistant and opportunistic organisms more prevalent than in the general population, and immunosuppression blunts the clinical deterioration that normally signals treatment failure. Despite this complexity, the clinical consequences of empirical regimen inadequacy have never been quantified specifically in liver transplant recipients. **Methods:** All 118 liver transplant recipients with pneumonia were identified retrospectively from a single-center cohort (2015-2025). Regimen change was defined as any modification to the initial empirical regimen made in response to culture results demonstrating resistance to the prescribed antibiotics or lack of clinical improvement within 72 hours as assessed by the treating physician. Patients with missing antibiotic regimen data (n = 7) were excluded from the primary analysis. The primary endpoints were treatment duration (days) and treatment failure, defined as no clinical response at the end of the full treatment course. Pneumonia specific hospital LOS was a secondary outcome. Mann-Whitney U and Fisher's exact tests were used. **Results:** Regimen change occurred in 45 of 111 analyzable patients (40.5%); 66 (59.5%) completed treatment without modification. Regimen-change patients had significantly longer treatment duration (median 14 days, IQR 9-29 vs. 8 days, IQR 6-12; p = 0.0002) and longer hospital LOS (median 1 day, IQR 0-7 vs. 0 days, IQR 0-0; the vast majority of patients in the unchanged group required no additional inpatient days; p < 0.001). Treatment failure occurred in 17 of 44 evaluable patients (38.6%) in the regimen-change group vs. 8 of 65 (12.3%) in the unchanged group (one missing outcome per group); OR 4.49 (95% CI 1.72-11.68; p = 0.002). **Conclusion:** Empirical regimen change occurred in 40.5% of evaluable cases and was associated with a 75% longer treatment course and a significantly higher treatment failure rate (OR 4.49; p = 0.002). When the initial regimen proved adequate, 87.7% of patients achieved resolution without modification. To our knowledge, this is the first such quantification in liver transplant recipients. These findings support transplant-specific empirical protocols informed by local resistance surveillance rather than general community-acquired or hospital-acquired pneumonia guidelines, and early microbiological sampling to enable prompt culture-guided therapy.

Disclosures: Zehra Karabal:Nothing to Disclose, Muhammad Ebrahim Ferozie:Nothing to Disclose, Nihad Jamalli:Nothing to Disclose, Narmin Dadashova:Nothing to Disclose, Laman Karimli:Nothing to Disclose, Elshad Yagubzade:Nothing to Disclose, Irem

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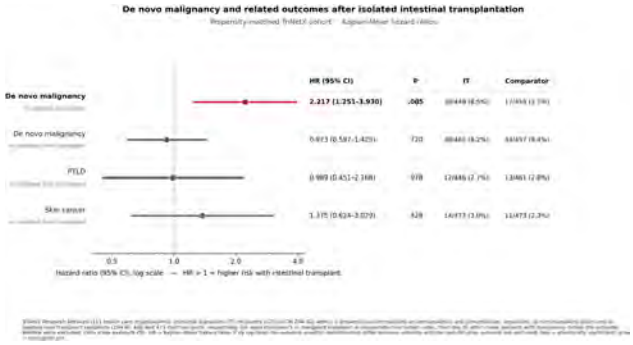
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Yasa:Nothing to Disclose, Tonguc Utku Yilmaz:Nothing to Disclose, Iftihar Koksal:Nothing to Disclose.

4578 | DE NOVO MALIGNANCY AFTER ISOLATED INTESTINAL TRANSPLANTATION: HIGHER THAN THE GENERAL POPULATION BUT COMPARABLE TO LIVER TRANSPLANTATION IN A PROPENSITY-MATCHED COHORT

Akram Alnounou[1] Mohammad Alabbas[2] Ezzeldien Ibrahim[3] Syed-Mohammed Jafri[4] Faruq Pradhan[5], [1]Western Michigan University Homer Stryker MD SOM, [2]Cleveland Clinic Foundation, [3]University of Missouri-Columbia, [4]Henry Ford Health System, [5]University of Nebraska Medical Center

Background: De novo malignancy is a recognized complication of solid-organ transplantation, but its risk after isolated intestinal transplantation, and relative to other transplant populations, is poorly defined in multicenter data. We compared de novo malignancy among adults with isolated intestinal transplant status, matched non-transplant adults, and matched isolated liver transplant recipients. **Methods:** Using the TriNetX Research Network (111 health care organizations), we identified adults aged ≥18 years with intestinal transplant status (ICD-10-CM Z94.82); isolated status required no other transplant-status code before or within 1 month after index. Patients with malignancy before the outcome window were excluded. The primary outcome was de novo malignancy (malignant neoplasm or neuroendocrine tumor codes) from day 31 after index; post-transplant lymphoproliferative disorder (PTLD) and skin cancer were also assessed against liver transplant. Recipients were separately 1:1 propensity-score matched, on demographics and comorbidities, to non-transplant controls and to isolated liver transplant recipients (Z94.4). Kaplan–Meier hazard ratios (HRs) with 95% CIs were estimated and groups compared by log-rank test. **Results:** Of 486 identified isolated intestinal transplant recipients, 460 were matched to non-transplant adults and 473 to liver transplant recipients. Versus non-transplant adults, intestinal transplant status was associated with higher de novo malignancy (38/449 [8.5%] vs 17/458 [3.7%]; HR 2.217, 95% CI 1.251–3.930; risk difference 4.8%, 95% CI 1.6–7.9; P = .005). Versus liver transplant recipients, risk did not differ for de novo malignancy (38/462 [8.2%] vs 43/457 [9.4%]; HR 0.923, 95% CI 0.597–1.429; P = .720), PTLD (12/446 [2.7%] vs 13/461 [2.8%]; HR 0.989, 95% CI 0.451–2.168; P = .978), or skin cancer (14/473 [3.0%] vs 11/473 [2.3%]; HR 1.375, 95% CI 0.624–3.029; P = .428). **Conclusion:** In this matched EHR cohort, isolated intestinal transplant status was associated with more than twofold higher de novo malignancy risk than non-transplant adults but comparable to liver transplant recipients across malignancy, PTLD, and skin cancer. Because cohorts were matched on demographics and comorbidities but not on immunosuppression, time since transplant, or transplant indication, and outcomes were code-based, prospective studies incorporating these measures are warranted.



Disclosures: Akram Alnounou:Nothing to Disclose, Mohammad Alabbas:Nothing to Disclose, Ezzeldien Ibrahim:Nothing to Disclose, Syed-Mohammed Jafri: Takeda: Speaking and Teaching, Gilead: Speaking and Teaching, Abbvie: Speaking and Teaching, Ironwood: Advisor, Intercept: Speaking and Teaching, Faruq Pradhan:Madrigal Pharmaceuticals: Advisor, Ipsen Biopharmaceuticals: Advisor.

4579 | SYSTEMIC IMMUNE-INFLAMMATION INDEX (SII) AND TUMOR DIFFERENTIATION GRADE

William Vroom[1] Devi Veeramgari[1] Yonatan Kaplan[1] Sophia Cury[1] Matthew Kim[1] Daisuke Imai[1] Yuzuru Sambommatsu[1] Vinay Kumaran[1] Muhammad Saeed[1] Aamir Khan[1] Amit Sharma[1] Adrian Cotterell[1] Hannah Lee[1] David Bruno[1] Seung Duk Lee[1], [1]VCU School of Medicine

Background: Validated models have been developed to predict post-transplant recurrence in hepatocellular carcinoma (HCC) patients and included markers such as neutrophil-lymphocyte ratio (NLR) and alpha-fetoprotein (AFP). The systemic immune-inflammation Index (SII) is an additional composite biomarker that may serve as a useful tool to identify recurrence. We aimed to determine if a higher SII correlated with poorly differentiated HCC could predict recurrence. **Methods:** 58 patients with HCC who underwent curative resection or liver transplantation between 2005-2011 were included. Preoperative SII was calculated as neutrophil count × platelet count / lymphocyte count. Log-transformed SII and AFP were evaluated for associations with tumor grade (n = 39 with complete pathologic data), time to first recurrence, and early recurrence (≤24 months) using ordinal logistic

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regression, Cox proportional hazards, and binary logistic regression, respectively. Covariates included surgery type, microvessel invasion, and maximum tumor diameter. **Results:** 58 patients were reviewed, of which 19 had recurrence events and 39 had tumor grade data available for analysis. SII predicted increased tumor grade on ordinal logistic regression (β = 1.428, SE = 0.612, p = 0.020), reduced time to recurrence on Cox proportional hazards (HR = 2.65, 95% CI 1.38 - 5.09, p = 0.003), and increased early recurrence on binary logistic regression (OR = 3.12, 95% CI 1.45 - 6.71, p = 0.004). AFP did not display significant predictive value on tumor grade (β = 0.115, SE = 0.185, p = 0.534), time to recurrence (HR = 1.08, 95% CI 0.88 - 1.33, p = 0.451), or early recurrence (OR = 1.12, 95% CI 0.75 - 1.68, p = 0.582). The predictive values of surgery type (OTL vs resection), microvascular invasion, and max tumor diameter were also assessed, with the latter being associated with reduced time to recurrence (HR = 1.14, 95% CI 1.06 - 1.22, p < 0.001) and increased early recurrence (OR = 1.18, 95% CI 1.07 - 1.31, p = 0.001). **Conclusion:** Elevated SII was independently associated with worse tumor differentiation, shorter time to recurrence, and increased odds of early recurrence in HCC, even after adjustment for AFP and key clinical factors. AFP was not a significant predictor in our models, suggesting that SII provides additional prognostic value beyond traditional biomarkers. Overall, our results support SII as an effective biomarker that may inform post-operative surveillance strategies in HCC.

Disclosures: William Vroom:Nothing to Disclose, Devi Veeramgari:Nothing to Disclose, Yonatan Kaplan:Nothing to Disclose, Sophia Cury:Nothing to Disclose, Matthew Kim:Nothing to Disclose, Daisuke Imai:Nothing to Disclose, Yuzuru Sambommatsu:Nothing to Disclose, Vinay Kumaran:Nothing to Disclose, Muhammad Saeed:Nothing to Disclose, Aamir Khan:Nothing to Disclose, Amit Sharma:Nothing to Disclose, Adrian Cotterell:Nothing to Disclose, Hannah Lee:Nothing to Disclose, David Bruno:Nothing to Disclose, Seung Duk Lee:Intuitive: Speaking and Teaching.

4580 | ONE-YEAR PATIENT AND GRAFT SURVIVAL AFTER LIVER TRANSPLANTATION FOR ACUTE-ON-CHRONIC LIVER FAILURE: A COMPARATIVE ANALYSIS OF MASH AND NON-MASH RECIPIENTS

Sanjaya Satapathy[1] Jiten Kothadia[2] Fariha Ilyas[3],
[1]Northshore University Hospital/Northwell Health,
[2]University of Tennessee, [3]Northwell Health

Background: Metabolic dysfunction–associated steatohepatitis (MASH) has become one of the leading indications for liver transplantation (LT). However, post-transplant outcomes among recipients transplanted for acute-on-chronic liver failure (ACLF) remain incompletely characterized. We evaluated 1-year patient and graft survival, organ failure patterns, and causes of death following LT for ACLF in recipients with MASH compared with non-MASH etiologies. **Methods:** We performed a retrospective cohort study of 29,820 adult LT recipients with ACLF, including 3,907 (13.1%) with MASH and 25,913 (86.9%) with non-MASH liver disease. Recipient demographics, organ failure profiles, post-transplant outcomes, and causes of death were compared. Kaplan–Meier methods and Cox proportional hazards models were used to assess patient and graft survival. **Results:** Compared with non-MASH recipients, patients with MASH were older (56 ± 10 vs. 48 ± 12 years) and had higher body mass index (32.6 ± 6.8 vs. 28.2 ± 6.1 kg/m²), with a substantially higher prevalence of diabetes mellitus (47.0% vs. 12.3%; all p < 0.001). Organ failure profiles differed significantly between groups; kidney failure was more common among MASH recipients (56.6% vs. 43.0%, p < 0.001), whereas liver and circulatory failure occurred more frequently in non-MASH recipients (both p < 0.001).At 1 year after LT, overall mortality was 8.3% (n = 2,488) and graft loss occurred in 10.3% (n = 3,081). Kaplan–Meier analysis demonstrated comparable 1-year patient survival (log-rank p = 0.21) and graft survival (log-rank p = 0.57) between MASH and non-MASH recipients. In unadjusted analysis, MASH was not associated with graft loss (HR 0.97, 95% CI 0.87–1.08; p = 0.58). After adjustment for recipient, donor, and transplant characteristics, MASH was independently associated with a reduced risk of 1-year graft loss (adjusted HR 0.84, 95% CI 0.75–0.95; p = 0.004).Among recipients who died within 1 year, infection was the leading cause of death (48.6%), followed by malignancy (22.2%) and cardiovascular events (6.0%). The distribution of causes of death did not differ significantly between MASH and non-MASH recipients (p = 0.23). **Conclusion:** Among LT recipients transplanted for ACLF, 1-year patient and graft survival were similar between MASH and non-MASH etiologies. Despite a distinct metabolic phenotype and higher burden of kidney failure, MASH was independently associated with improved adjusted graft survival. Infection remains the predominant cause of early post-transplant mortality irrespective of underlying liver disease. These findings support equitable transplant access for patients with MASH-related ACLF and underscore the importance of tailored peri-transplant management strategies in this rapidly growing population.

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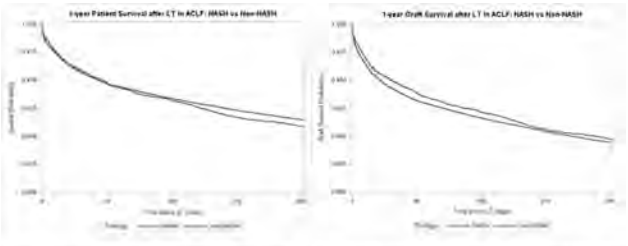


Figure 1. Kaplan–Meier estimates of 1-year patient survival after liver transplantation (LT) among recipients transplanted with acute-on-chronic liver failure (ACLF), stratified by etiology (NASH vs non-NASH). Survival curves were compared using the log-rank test (χ^2=1.5536, df=1; P=0.2126). Wilcoxon test: χ^2=1.2952 (df=1; P=0.2551). Likelihood ratio test: −2Log(LR)=1.1514 (df=1; P=0.2833).

Figure 2. Kaplan–Meier estimates of 1-year graft survival after liver transplantation (LT) among recipients transplanted with acute-on-chronic liver failure (ACLF), stratified by etiology (NASH vs non-NASH). Survival distributions were compared using the log-rank test (χ^2=0.3177, df=1; P=0.5730). Wilcoxon test: χ^2=0.4456 (df=1; P=0.5044). Likelihood ratio test: −2Log(LR)=0.5644 (df=1; P=0.4525).

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4581 | NEW SUBMISSION BEYOND BIOPSY: NON-INVASIVE AND MOLECULAR DIAGNOSTICS FOR ACUTE REJECTION IN LIVER TRANSPLANTATION - A SYSTEMATIC REVIEW

Helena Paran[1] Omar Quidwai[2] Sinead Sullivan[3] Fiona Hand[2] John Hammond[2] Emir Hoti[4] Stephanie Bollard[4] Zita Galvin[4] Audrey Dillon[4] Masood Iqbal[4] Omar El Sherif[4] Roisin Dolan[4], [1]University College Dublin School of Medicine, [2]St. Vincent's University Hospital, Dublin, Ireland, [3]University of Limerick, [4]St. Vincent's University Hospital, Dublin, Ireland.

Background: Timely detection of acute rejection remains central to preserving graft function after liver transplantation. Although liver biopsy is considered the diagnostic reference standard, it is invasive, carries procedural risk, and is limited by sampling error and inter-observer variability. In response, a new generation of minimally invasive and non-invasive diagnostic approaches has emerged, including donor-derived cell-free DNA assays, gene expression profiling, immune monitoring platforms, and advanced imaging modalities. These technologies offer the potential to detect early alloimmune activity before overt graft dysfunction, reducing reliance on invasive biopsy. However, the diagnostic performance of these emerging modalities relative to biopsy-proven acute cellular rejection has not been comprehensively synthesised. This systematic review aimed to evaluate the diagnostic accuracy of minimally invasive and non-invasive diagnostic modalities for detecting biopsy-proven acute cellular rejection following liver transplantation. **Methods:** A systematic review was conducted in accordance with PRISMA-DTA guidelines and registered with PROSPERO. MEDLINE (Ovid), Embase, and CENTRAL were searched using controlled-vocabulary and free-text terms without restrictions. Of 2,266 records identified, 478 duplicates were removed, leaving 1,788 for screening. Studies evaluating minimally-invasive or non-invasive tests for detecting biopsy-proven acute rejection in LT were included. Screening, data extraction, and risk-of-bias assessment (QUADAS-2) were performed independently by two reviewers, with conflicts resolved by a third reviewer. **Results:** Twenty studies (2,612 recipients) were included. Diagnostic approaches included donor-derived cell-free DNA, gene-expression profiling, immune-monitoring platforms, and imaging. Molecular biomarkers demonstrated the most consistent performance, with some studies identifying subclinical alloimmune activity preceding graft-dysfunction. However, heterogeneity in study design, sampling, thresholds, and definitions of rejection was substantial. Bias (QUADAS-2) related to patient selection and index-test interpretation. **Conclusion:** Minimally invasive and non-invasive modalities, particularly molecular biomarkers, show promise for detecting ACR and may reduce reliance on biopsy. However, heterogeneity and methodological limitations necessitate standardisation and further validation before routine clinical use.

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4582 | LIVER TRANSPLANTATION IN METABOLIC DISEASES: A 17-YEARS SINGLE CENTER EXPERIENCE

Andrea Pietrobattista[1] Silvio Veraldi[1] Gionata Spagnoletti[1] Alberto Fratti[2] Riccardo Cirelli[2] Marta Maistri[2] Gian Luigi Natali[2] Lidia Monti[2] Simone Reali[2]

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Paola Francalanci[2] Luca Della Volpe[2] Daniela Liccardo[2] Diego Martinelli[2] Barbara Siri[2] Carlo Dionisi Vici[2] Rosanna Pariante[2] Marco Spada[2], [1]Bambino Gesù Children Hospital, IRCCS, Rome, Italy, [2]Bambino Gesù Children's Hospital, IRCCS, Rome, Italy

Background: Metabolic diseases (MD) represent the second most common indication for liver transplantation (LT) in children. Indications include prevention of metabolic decompensation, treatment of the liver disease and improvement of neurological outcomes and organ damage. **Methods:** We retrospectively reviewed the clinical records of patients who underwent LT for MD at the Bambino Gesù Children's Hospital from January 2008 to December 2025. **Results:** 92 out of 422 (21.8 %) (age: 90.5 months, IQR: 72) children underwent a LT for MD. Weight and height z-scorewere -0.855 (IQR: 2.2) and -0.887 (IQR: 2.45). 18 had a MD with structural liver disease (ALF, HCC or ESLD) with amedian MELD/PELD of 28 (IQR: 15): tyrosinemia type 1 [n:8, 8.7%], Wilson's disease [n: 5, 5.4%], bile acid synthesis disorders [n: 3, 3.3%], DGUOK deficiency and cholesteryl ester storage disease [n: 1 (1%) for each]. 74 underwent LT without structural severe liver disease: organic acidemias [n: 24, 26%], urea cycle disorders [n: 16, 17.4%], maple syrupurine disease [n: 13, 14%], primary hyperoxaluria type 1 [n: 13, 14%], glycogen storage disease type Ia [n: 4, 4.3%], others [n: 4 (4.3%)] (Fig. 1). Heterozygous living donor LTs were performed in 16 (17.4%); deceased donor whole and split livers transplantation in 25 (27.2%) and 47 (51%). 8 had a combined or sequential liver-kidney transplant. A patient with MSUD who underwent LT provided a whole liver for a child with biliary cirrhosis. After 63.9 months (IQR: 72)(median follow-up) patient and survivals were 96.7% and 94.6%: 2 died because of perioperative complications, 1 of cardiorespiratory failure with normal liver function. 2 pts were retx because of EGD. In the 1-year after LT, 8 (9%) required relaparotomy; 12 (13%) and 13 (14%) developed vascular and biliary complications successfully treated with interventional radiology and/or endoscopy. 27 had an acute liver rejection (29%). CMV viremia was seen in 41 (44.5%) with pre-emptive treatment needed in 21 (22.8%). EBV viremia was reported in 60 (65.2%) with 45 already positive before LT. Throughout the follow-up period, 4 patients (4.4%) were diagnosed with PTLD/lymphoma. 14 (15.2%) experienced either acute or chronic neurological complications (i.e.PRESS, seizures, or tremors) with 4 attributed to CNI toxicity. With the exception of one patient (propionic acidemia), no metabolic decompensation was observed after LT. All children resumed a normal protein intake within 4 weeks. 1-yearafter LT, patients presented a median increase in height and weight z-scores of 0.389 (IQR: 2.15) and 0.181 (IQR:1.74). **Conclusion:** LT in MD had excellent outcomes with a significant regression of the risk of metabolic decompensation and an improvement in QoL. Long-term data are needed to evaluate the role on neurological and organ damage. Multidisciplinary follow-up and timely transplantation are key factors in the management of these patients.

Disclosures: Andrea Pietrobattista:Nothing to Disclose, silvio veraldi:Nothing to Disclose, Gionata Spagnoletti:Nothing to Disclose, Alberto Fratti:Nothing to Disclose, Riccardo Cirelli:Nothing to Disclose, Marta Maistri:Nothing to Disclose, Gian Luigi Natali:Nothing to Disclose, Lidia Monti:Nothing to Disclose, Simone Reali:Nothing to Disclose, Paola Francalanci:Nothing to Disclose, Luca Della Volpe:Nothing to Disclose, Daniela Liccardo:Nothing to Disclose, Diego Martinelli: Nothing to Disclose, Barbara Siri:Nothing to Disclose, Carlo Dionisi Vici:Nothing to Disclose, Rosanna Pariante:Nothing to Disclose, Marco Spada:Nothing to Disclose.

4583 | PRE-LIVER TRANSPLANT USE OF IMMUNE CHECKPOINT INHIBITORS FOR HEPATOCELLULAR CARCINOMA: A SINGLE CENTER EXPERIENCE

Kaitlyn Legg[1] Ian Booth[1] Neha Jakhete[2] Kenneth Saunders[1] Christine Wolesensky[1], [1]University of Maryland Medical Center, [2]University of Maryland

Background: Immune checkpoint inhibitors (ICIs) are increasingly used in patients with hepatocellular carcinoma (HCC). ICI's have changed the landscape of HCC treatment in recent years but are associated with rejection post-transplant; optimal timing for discontinuation prior to liver transplantation (LT) has not been standardized. Little information is known regarding optimal immunosuppression (IS) management in this population. We aimed to characterize patient survival, rejection outcomes, and describe IS practices post-LT in the ICI treatment population at our center. **Methods:** We reviewed all LT recipients, including multi-organ transplants, with a pretransplant diagnosis of HCC transplanted at our center from 1/1/2019 through 12/31/2025. Those identified as receiving an ICI prior to LT were followed for 2 years post-LT as this period is the highest risk for HCC recurrence. The primary endpoint was patient survival at 2 years. Secondary endpoints included biopsy proven acute rejection (BPAR), infectious complications, IS management, renal function, and HCC recurrence. **Results:** Six patients were identified as receiving ICI prior to transplant, with a median age of 66 years. One patient received simultaneous liver kidney; the remaining 5 were liver only. Pre-LT imaging showed 4 patients (66%) had a single tumor and 3 patients (50%) with a tumor larger than 5 cm. Three patients

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received durvalumab/tremelimumab, 2 received atezolizumab/bevacizumab, and 1 received durvalumab alone with a median of 10.5 doses (IQR 7.3-13) prior to LT. Median duration of ICI pre-LT was 271 days (IQR 169.5-331.3) with the last dose prior to LT being 120.5 days (range 72-164 days). At time of abstract submission, 3 patients (50%) have reached 2 years post-LT with 100% survival. BPAR occurred in 1 patient, 23 months post-LT. Four infections occurred in 2 patients, with bacteremia accounting for 75%. Median eGFR at day 7 was 74 mL/min/1.73 m2 (IQR 72-113) and by 2 years was 53 mL/min/1.73 m2 (IQR 46-79.5). At 2 years, one patient remained on tacrolimus, while two patients had been converted to mTOR inhibitors. At 2 years, all three patients remained on mycophenolate with a median total daily dose of 500 mg (IQR 250-500, n = 3), and prednisone use was 33% (n = 1). No recurrence of HCC was seen at 2 years, though 2 patients had recurrence after 2 years. **Conclusion:** All patients who received an ICI pre-LT survived until 2 years post-LT or until last follow up with a functioning graft. No patients had rejection early post-LT, which is consistent with current literature that suggests holding ICI dose at least 50 days prior to LT. One incidence of rejection was seen at almost 2 years post-transplant, which was unlikely to be related to ICI use pre-LT. Future studies should focus on identifying the optimal time to perform a LT after the last dose of an ICI and finding the optimal IS balance to mitigate the increased risk of rejection with ICIs and long-term risk of HCC recurrence.

Baseline Characteristics	
Age at transplant (y), median (IQR)	66.04 (62-69)
Transplant type, n (%)	
Liver only	5 (83)
Liver and Kidney	1 (17)
ICI received pre-transplant, n (%)	
Durvalumab	1 (17)
Durvalumab/Tremelimumab	3 (50)
Atezolizumab/Bevacizumab	2 (33)
Time from last dose of ICI to transplant (d), median (range)	120.5 (72-164)
Tumor number, n (%)	
Single	4 (67)
Multiple	2 (33)
Tumor size, n (%)	
Greater than 5 cm	3 (50)
Less than 5 cm	3 (50)
Tumor necrosis on explant, n (%)	2 (33)
Post-Transplant Outcomes	
Rejection at 6-months post-transplant, n (%)	0 (0%), n=6
Rejection at 2-year post-transplant, n (%)	1 (33), n=3
Time post-transplant (d)	688
Infection incidences within 2 years post-transplant, n (%)	4
Bacteremia	3 (75%)
CMV viremia	1 (25%)
HCC recurrence at 6-months post-transplant, n (%)	0 (0%), n=6
HCC recurrence at 2-years post-transplant, n (%)	0 (0%), n=3
Retransplant at 6-months post-transplant, n (%)	0 (0%), n=6
Retransplant at 2-years post-transplant, n (%)	0 (0%), n=3
Survival to 6-months post-transplant, n (%)	6 (100), n=6
Survival to 2-years post-transplant, n (%)	3 (100), n=3

Disclosures: Kaitlyn Legg:Nothing to Disclose, Ian Booth:Nothing to Disclose, Neha Jakhete:Gilead: Advisor, Ipsen: Advisor, Kenneth Saunders:Nothing to Disclose, Christine Wolesensky:Nothing to Disclose.

4584 | ◆ CLINICAL VALIDATION OF A NOVEL CELL-FREE DNA-BASED ASSAY FOR DETECTION OF REJECTION IN LIVER TRANSPLANT

Phil Gauthier[1] Mamatha Bhat[2] Ali Zarrinpar[3] Daniel Maluf[4] D. Giovanni Biagini[1] Nina Verstraete[1] Andrew Doud[1] Yen-An Chen[1] Navchetan Kaur[1] Felipe Acosta[1] Ebad Ahmed[1] Amy Baer[1] Mita Banik[1] Naoshin Haque[1] Sarah McCormick[1] Kate Woodruff[1] Jing Xie[1] Nour Al Haj Baddar[1] Niraja suresh[1] Zachary Demko[1] Adam Prewett[1] Hossein Tabriziani[1] Sangeeta Bhorade[1] Juliet Emamaullee[5], [1]Natera, Inc., [2]University Health Network / University of Toronto, [3]University of Florida, [4]University of Maryland School of Medicine, [5]Keck School of Medicine of USC

Background: Liver transplantation (LTx) is the definitive treatment for end-stage liver disease. Donor-derived cell-free DNA (dd-cfDNA) is a noninvasive biomarker for allograft rejection. We present a clinical validation study to evaluate dd-cfDNA performance characteristics for detecting active rejection (AR) in LTx recipients and assess clinical factors associated with dd-cfDNA elevation. **Methods:** Adult LTx patients with blood samples collected ≥ 14 days post LTx were included. Rejection was defined as a treated clinical rejection or biopsy-proven acute rejection. dd-cfDNA performance metrics (sensitivity, specificity, negative predictive value [NPV], positive predictive value [PPV], and area under curve [AUC]) were calculated. Random forest classifiers were applied to identify association between several clinical variables (liver function tests [LFTs; aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase], graft type (whole or partial), rejection diagnosis, donor-recipient sex mismatch, donor type (living or deceased), donor relatedness)- and positivity of dd-cfDNA (dd-cfDNA% ≥10.0%). **Results:** A total of 199 LTx patients with 209 dd-cfDNA samples were included. Among the cohort, 32 patients experienced a total of 33 rejection episodes, including 29 episodes of acute cellular mediated rejection (ACMR) and 4 episodes of treated clinical rejections; the remaining 167 patients had no rejection (NR). Median dd-cfDNA levels were significantly higher in AR (21.1%) vs NR (3.6%; p < 0.001; **Fig 1A**). Median dd-cfDNA levels were significantly higher in mild (grade 3-4) or moderate (grade 6-7) rejection activity index scores compared to none (20.8% and 25.0%, vs. 3.7%, respectively; p < 0.001 for both). A 10.0% dd-cfDNA threshold showed a sensitivity of 87.9%, specificity of 87.5%, PPV of 56.9%, and NPV of 97.5%. ROC yielded an AUC of 0.90; **Fig 1B**). Elevated LFTs, rejection, and donor-recipient sex mismatch were associated with elevated dd-cfDNA; **Fig 1C**). **Conclusion:** This validation established that dd-cfDNA ≥10.0% is associated with increased risk of allograft rejection and that it accurately distinguishes AR from NR with high sensitivity and

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specificity and correlates with liver allograft histological rejection activity. dd-cfDNA elevation association with the immune related clinical factors supports its utility as a noninvasive biomarker for liver allograft injury.

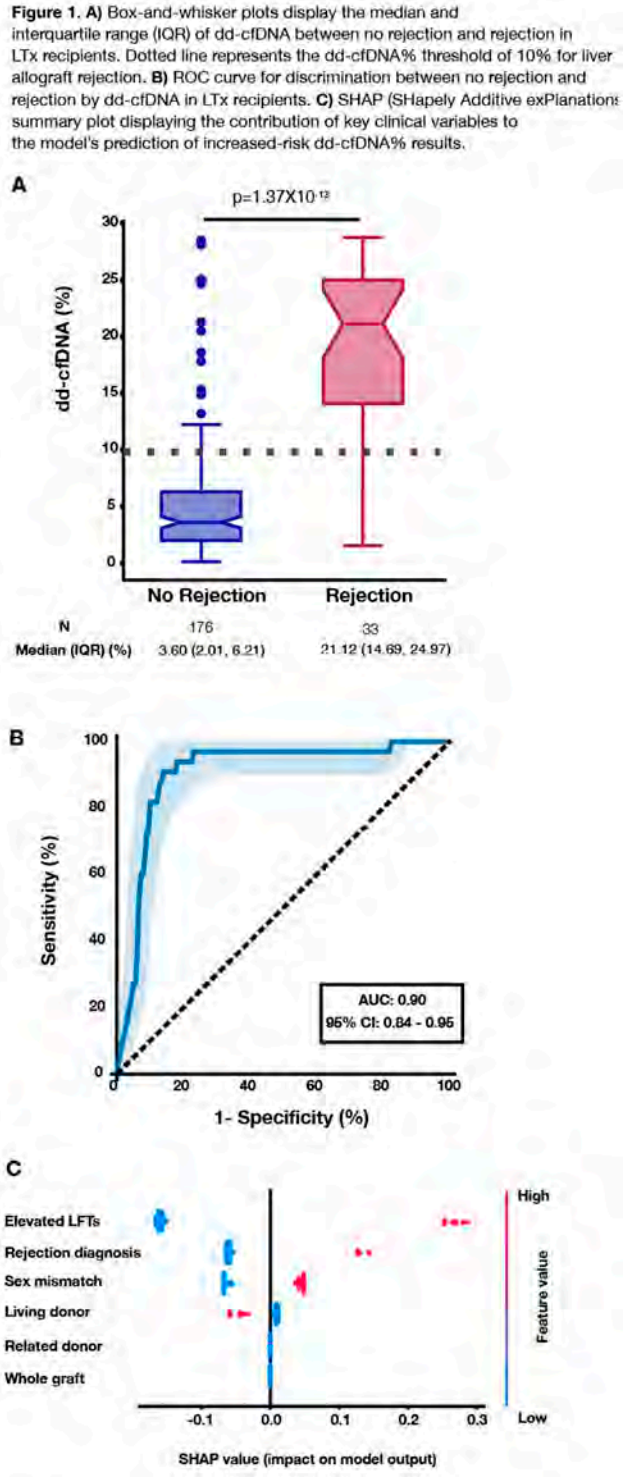


Figure 1. A) Box-and-whisker plots display the median and interquartile range (IQR) of dd-cfDNA between no rejection and rejection in LTx recipients. Dotted line represents the dd-cfDNA% threshold of 10% for liver allograft rejection. **B)** ROC curve for discrimination between no rejection and rejection by dd-cfDNA in LTx recipients. **C)** SHAP (SHapely Additive exPlanations summary plot displaying the contribution of key clinical variables to the model's prediction of increased-risk dd-cfDNA% results.

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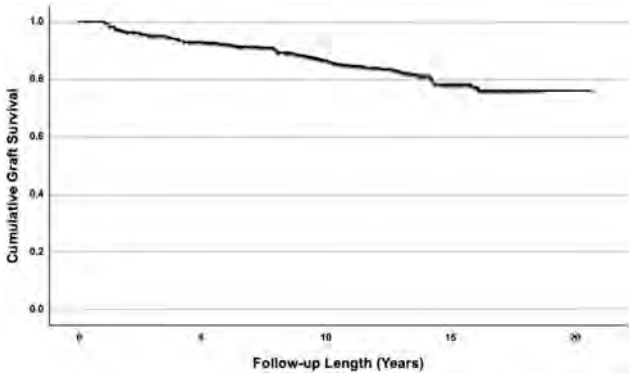
4585 | EXCELLENT LONG-LERM GRAFT SURVIVAL USING 3RD GENERATION NUCLEOS(T)IDE ANALOGS WITHOUT HEPATITIS B IMMUNE-GLOBULIN AFTER LIVER TRANSPLANTATION FOR CHRONIC HEPATITIS B

James Fung[1] Tiffany Wong[2] Kevin Ng[2] Wing Chiu Dai[1] Kin Pan Au[1] Sui-Ling Sin[1] Miu Yee Chan[1] Kwan-Lung Ko[1] Loey Mak[2] Man-Fung Yuen[2] Albert Chan[2], [1]Queen Mary Hospital, [2]The University of Hong Kong

Background: Despite efficacy of 3rd-generation nucleos(t)ide analogs (NUCs) as prophylaxis after liver transplantation (LT) for chronic hepatitis B (CHB), hepatitis B immune globulin (HBIG) continues to be routinely used despite incurring high costs. **Methods:** This is a large retrospective cohort study of consecutive CHB patients positive for hepatitis B surface antigen (HBsAg) undergoing LT from October 2005 to December 2024, using 3rd-generation NUCs including entecavir (ETV), tenofovir disoproxil fumarate (TDF), or tenofovir alafenamide (TAF) as initial antiviral prophylaxis after LT. No HBIG was administered at any stage, representing a completely HBIG-free regimen. The primary outcome was graft survival. **Results:** A total of 546 patients was included. After exclusion of those with less than 1 year follow-up, 499 were included in final analysis with a median follow up

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of 123 months. The median age at LT was 54 years, of which 82% were male, and 22%, 33% and 45% were transplanted for decompensated cirrhosis (DC), severe flares, and hepatocellular carcinoma (HCC) respectively. After LT, 85%, 9%, 3% and 3% were treated with ETV, TDF, TAF, and ETV + TDF respectively. At the last follow-up, 68%, 1%, 30% and 1% were on ETV, TDF, TAF, and ETV + TDF respectively, with increasing use of TAF. The cumulative graft survival at 5, 10, 15, and 20 years was 93%, 86%, 78%, and 76% respectively for those who survived beyond the first year. Importantly, no patients had graft loss secondary to HBV reactivation. Over half (52%) had detectable HBV DNA at the time of LT, with a median level of 5320 IU/mL for those with quantifiable HBV DNA. HBsAg loss was observed in 95%, and was maintained in 86% at time of last follow up. There was no survival difference observed between those that was HBsAg-negative vs. positive at last follow-up ($p = 0.116$). Of the 71 patients with positive HBsAg at last follow-up, 68 (96%) had undetectable or unquantifiable HBV DNA. The remaining 3 patients achieved undetectable HBV DNA, and HBV DNA became detectable only after HCC recurrence. The cumulative incidence of HCC in the entire cohort at 5, 10 and 15 years after LT was 4%, 6%, and 6% respectively, without any de novo HCC observed. The HCC recurrence rate for those with HCC at time of LT was 10%, 13%, and 14% at 5, 10 and 15 years respectively. Patients transplanted for severe flares had better long-term survival compared to those for DC or HCC (88% vs. 76% vs. 71% respectively at 15 years, $p = 0.01$). **Conclusion:** These long-term results demonstrate definitively that completely HBIG-free regimens using 3rd generation NUCs alone are safe and effective in preventing hepatitis B reactivation, with excellent long-term survival, and should become the standard of care in CHB patients undergoing LT in the era of highly effective NUCs.



Disclosures: James Fung:Nothing to Disclose, Tiffany Wong:Nothing to Disclose, Kevin Ng:Nothing to Disclose, Wing Chiu Dai:Nothing to Disclose, Kin Pan Au:Nothing to Disclose, Sui-Ling Sin:Nothing to Disclose, Miu Yee Chan:Nothing to Disclose, Kwan-Lung Ko:Nothing to Disclose, Loey Mak:Nothing to Disclose, Man-Fung Yuen:AbbVie, Abbott Diagnotics, Aligos Therapeutics: Consultant, Arbutus Biopharma, Arrowhead Pharmaceuticals, Assembly Biosc: Consultant, Clear B Therapeutics, Dicerna Pharmaceuticals, Immuncore: Consultant, Fujirebio Incorporation, GSK, Gilead Sciences: Consultant, Immunocore, Janssen, Precision BioSciences: Consultant, Roche, Sysmex Corporation, Tune Therapeutics: Consultant, Vir Biotechnology and Visirna Therapeutics: Consultant, AbbVie, Assembly Biosciences, Arrowhead Pharmaceuticals, Aligos Therapeutics, Arbutus Biopharma: Grant/Research Support, Fujirebio Incorporation, Gilead Sciences, Immunocore, Clear B Therapeutics, GSK, Janssen: Grant/Research Support, Sysmex Corporation and Roche: Grant/Research Support, Fujirebio Incorporation, Gilead Sciences, Roche, Sysmex Corp, Aligos Therapeutics, Arbutus Biopharma: Speaking and Teaching, Precision BioSciences: consultancy, Ausperbio: consultancy, IntergerBio: consultancy, Tune Therapeutics: consultancy, Clear B Therapeutics, GSK, Immuncore, Janssen, Vir Biotechnology: Speaking and Teaching, Albert Chan: Nothing to Disclose.

4586 | NALTREXONE USE IN EARLY POST-LIVER TRANSPLANT CARE FOR ALCOHOL-ASSOCIATED LIVER DISEASE

Fayez Jabboure[1] FNU Baimaji[1] Bill Zhang[1] Adeline Vo[2] Mayan Teles[3] Lauren Boyer[1] Daniel Warren[1] James Hamilton[2] Andrew Cameron[1] Po-Hung (Victor) Chen[2], [1]Johns Hopkins Medicine, [2]Johns Hopkins University, [3]Johns Hopkins University School of Medicine

Background: Alcohol-associated liver disease (ALD) is the leading indication for liver transplant (LT) in the US. Alcohol use disorder (AUD) is a chronically relapsing condition. Post-LT alcohol relapse is common and can adversely affect graft function and survival. Although naltrexone and other medications for AUD (MAUD) have demonstrated benefit in patients with ALD, their use in LT recipients remains poorly studied. We evaluated naltrexone use, hepatic safety, and alcohol relapse during the first post-LT year. **Methods:** We conducted a single-center study of adults who underwent LT for severe ALD between January 2021 and May 2024. For all patients who received naltrexone after LT, hepatic safety was assessed using alanine aminotransferase (ALT), alkaline phosphatase (ALP), and total bilirubin (Tbili) values from 1 month before through 2 months after naltrexone initiation. Clinically significant elevations were defined as ALT > 40 U/L in males and > 30 U/L

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in females with a ≥1.5-fold increase, ALP >120 U/L with a ≥2-fold increase, and Tbili >1.2 mg/dL with a ≥1.5-fold increase from baseline. A separate landmark analysis evaluated alcohol relapse among patients who survived 100 alcohol-free days post-LT hospital discharge. Patients with early naltrexone start within 100 days of discharge were designated as the treatment group and analyzed using an intention-to-treat approach. Age, sex, other MAUD use, incretin therapy, and psychosocial interventions (PSI) were included as fixed covariates. Fine-Gray competing-risk regression evaluated time to first alcohol relapse (PEth >20 ng/mL), with death treated as a competing event. **Results:** We identified 186 participants. Among them, 83 (45%) received naltrexone after LT, including 37 (20%) within 100 days of discharge. Clinically significant laboratory elevations occurred in 5 patients (6%) (Figure 1). Chart review identified alternative explanations in all cases, including graft rejection in 3 (2 biopsy-proven) and obstructive biliary pathology in 2 patients. Compared to the control group, those with early naltrexone start were younger (47.6 vs. 53.7 years, p = 0.035) and had fewer days of pre-LT abstinence (105 vs. 274.5 days, p = 0.002). Early naltrexone start was associated with higher PSI engagement (57% vs. 35%, p = 0.025) and transplant clinic follow-up rates (75% vs. 70%, p = 0.039). Early naltrexone start was associated with an adjusted subhazard ratio of 0.97 (95% CI 0.37-2.56) for alcohol relapse. One-year post-LT survival was non-significantly higher among patients who started naltrexone early (100% vs. 96%, p = 0.58). **Conclusion:** Naltrexone use after LT was not associated with hepatotoxicity. Early initiation of naltrexone was associated with higher PSI engagement and clinic follow-up rates. These findings support the hepatic safety and potential benefit of naltrexone in early post-LT AUD care.

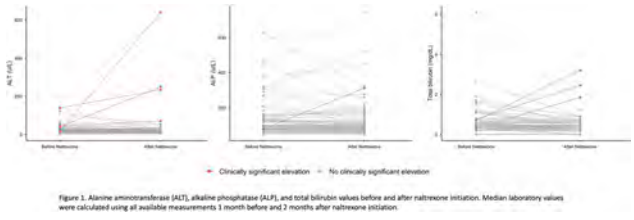


Figure 1. Alanine aminotransferase (ALT), alkaline phosphatase (ALP), and total bilirubin values before and after naltrexone initiation. Median laboratory values were calculated using all available measurements 1 month before and 2 months after naltrexone initiation.

Disclosures: Fayez Jabboure:Nothing to Disclose, FNU Baimaji:Nothing to Disclose, Bill Zhang:Nothing to Disclose, Adeline Vo:Nothing to Disclose, Mayan Teles:Nothing to Disclose, Lauren Boyer:Nothing to Disclose, Daniel Warren:Nothing to Disclose, James Hamilton:orphalan pharmaceuticals: Advisor, mirum pharmacueticals: Advisor, Andrew Cameron:Nothing to Disclose, Po-Hung (Victor) Chen:Gilead Sciences Research Scholars Program: Grant/Research Support, Gilead Sciences: Grant/Research Support.

4587 | NATIONAL SURVEY ON MANAGEMENT OF ALCOHOL USE DISORDER POST-LIVER TRANSPLANT FOR PATIENTS WITH ALCOHOL-ASSOCIATED LIVER DISEASE

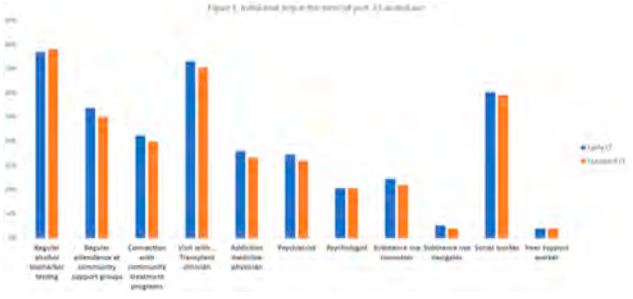
Debra Yen[1] Po-Hung (Victor) Chen[2] Nicholas Lim[3] Alexander Yang[4] Holly Huang[5] Chelsea Pan[6] Allison Kwong[7] Neil Mehta[6] Gene Im[8] Courtney Sherman[9], [1]California Pacific Medical Center, [2]Johns Hopkins University, [3]University of Rochester, [4]University of California San Diego, [5]University of California, San Francisco (UCSF), [6]University of California, San Francisco, [7]Stanford University Medical Center, [8]Center for Liver Disease and Transplantation, Division of Digestive and Liver Diseases Columbia Univ, [9]University of California San Francisco

Background: Alcohol-associated liver disease (ALD) is the leading indication for liver transplantation (LT) in the United States (US). However, post-LT alcohol use increases risks of graft failure and mortality. Therefore, policies to mitigate alcohol use after transplant are paramount but can vary widely between centers. We sought to examine the spectrum of post-LT strategies employed nationally to manage alcohol use disorder (AUD) in patients transplanted for ALD. **Methods:** We disseminated a web-based survey to one hepatologist at each active adult LT center in the US from November 2025 to April 2026. Medical directors or transplant hepatologists knowledgable of their center practices were selected, and only one response was accepted per center. Early liver transplant (ELT) was defined as LT for individuals with ALD with less than 6 months of alcohol abstinence. Standard LT (SLT) referred to those transplanted after at least 6 months of abstinence. **Results:** Out of 117 LT centers in the US, we received 80 responses (68.4%) representing all 11 UNOS regions. All responding centers perform ELT. Most centers (79%) require psychosocial AUD interventions after ELT, compared with 33% for SLT. Only 29% have a post-LT AUD pharmacotherapy protocol. After ELT, 96% require regular alcohol biomarker testing, and 61% require support group attendance. For routine post-ELT care, 62% require follow-up with addiction providers, 54% with mental health providers, and 47% with social workers. Over half (54%) had different follow-up requirements for ELT compared to SLT, mostly related to increased

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frequency of alcohol biomarker testing and visits with addiction providers and/or social work.Nearly all centers routinely test for alcohol biomarkers: 27% for all transplant recipients regardless of indication, 51% for all ALD recipients, and 15% for ELT recipients only. All centers use serum phosphatidylethanol (PEth) for alcohol biomarker testing. In the event of post-LT alcohol use, 76% recommend visits with at least 2 provider specialties that can include the transplant clinician, addiction providers, mental health providers, or social worker (Figure 1). Respondents perceived that center AUD resources are more often utilized than community resources. **Conclusion:** After LT for ALD, routine alcohol biomarker testing is heavily relied upon, with near universal adoption for ELT. Psychosocial intervention requirements are more common in ELT than in SLT, and most centers lack an AUD pharmacotherapy protocol. Similar care plans are utilized for ELT and SLT in the event of post-LT alcohol use, which typically involve a multimodal approach including visits with different team members and connection with community AUD resources. Future work determining the impact of post-LT AUD policies on clinical outcomes can guide recommendations for optimal AUD management and resource allocation priorities in this unique population.



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4588 | THE IDEAL POST-TRANSPLANT PROGRAM: PATIENT AND CAREGIVER PERSPECTIVES FROM A LARGE LONGITUDINAL LIVER TRANSPLANT SURVIVORSHIP COHORT

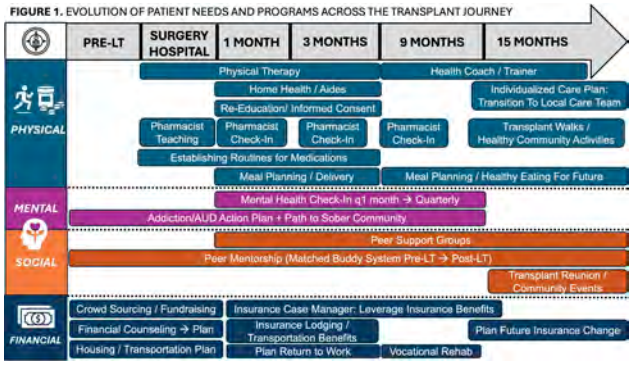
Sarah Lieber[1] Gi Giamarqo[2] Alvaro Noriega Ramirez[2] Dyanna Gregory[2] Arjmand Mufti[2] Madhukar Patel[2] Jeremy Louissaint[2] Shannan Tujios[2] Cheri Goldstein[2] Samantha Kimbrough[2] Brandy Brasfield[2] Melissa Fogg[2] Derek Bartlett[2] Lisa VanWagner[2] Amit Singal[2] Simon Craddock Lee[3] Donna Evon[4], [1]UT Southwestern Division of Digestive and Liver Diseases, [2]University of Texas Southwestern Medical Center, [3]The University of Kansas Medical Center, [4]University of North Carolina

Background: Liver transplantation (LT) is lifesaving but can pose major challenges to patients and caregivers. How their needs evolve over time remains poorly understood. LT programs differ in structure, available resources, and approaches to long-term support. We characterized longitudinal needs of LT recipients (LTRs) and their caregivers, to identify the programs and resources considered most effective in promoting successful post-LT recovery. **Methods:** This longitudinal mixed-methods study enrolled adult LTRs and their caregivers at a large transplant center. Participants completed 3 interviews at ~3, 9, and 15 months post-LT, alongside surveys assessing clinical and patient-reported outcomes (PROs). Interviews focused on post-LT physical, emotional, psychological, social, and financial challenges, as well as resources/programmatic needs to optimize LT care. De-identified transcripts were analyzed using deductive thematic content analysis (NVivo). Sequential analyses examined theme evolution over time. PRO measures evaluated health literacy (Newest Vital Sign), financial toxicity (COST-FACIT), physical and psychological symptoms, support, and quality of life (PROMIS). **Results:** Among 178 LTRs enrolled (40% female; mean age 52 years [SD 12]), 121 completed 6-month post-LT surveys. LT indication included ALD (50%) and MASLD (29%); 16% had HCC. A total of 108 qualitative interviews were analyzed—31% included caregivers and 30 LTRs completed the 3 interviews at ~3, 9, and 15-months post-LT. LTRs and caregivers emphasized the need for “proactive” not “reactive” post-LT care. Key elements included 24/7 access to the transplant team, strong coordination with local providers, and efficient communication. Suggested interventions included case managers, in-home phlebotomy, transplant “advocates”, visual care plans, and integrated clinics. Desired programs included: 1) re-orientation/ongoing education (28% had limited health literacy), 2) physical and medication support, 3) psychological and social support

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(mean PROMIS anxiety 48 [SD 10]; depression 47 [SD 9]), 4) financial counseling (21% reported high financial toxicity and 9% had transportation challenges), and 5) caregiver training. **Figure 1** highlights shifting temporal needs: early physical and financial support, later mental health, social, and community support. Programmatic needs also varied by acuity and indication: LTRs with ALD wanted destigmatizing support beyond structured sobriety programs to build sober communities. Those undergoing inpatient LT evaluation requested substantial post-LT re-orientation due to inability to fully engage in the pre-transplant process. **Conclusion:** In a large prospective survivorship cohort, we identified key features of the ideal post-transplant program. Evolving LTR and caregiver needs demand a shift from reactive to proactive, longitudinal care models in post-LT program design.



Disclosures: Sarah Lieber:Nothing to Disclose, Gi Giamarqo:Nothing to Disclose, Alvaro Noriega Ramirez:Nothing to Disclose, Dyanna Gregory:Nothing to Disclose, Arjmand Mufti:Nothing to Disclose, Madhukar Patel:Nothing to Disclose, Jeremy Louissaint:Nothing to Disclose, Shannan Tujios:Nothing to Disclose, Cheri Goldstein:Nothing to Disclose, Samantha Kimbrough: Nothing to Disclose, Brandy Brasfield:Nothing to Disclose, Melissa Fogg:Nothing to Disclose, Derek Bartlett:Nothing to Disclose, Lisa VanWagner:W.L. Gore & Associates: Grant/Research Support, Akero: Grant/Research Support, Madrigal: Grant/Research Support, Gerson Lehrman Group: Consultant, Madrigal: Advisor, Slingshot Insights: Consultant, Antheneum Partners: Consultant, Gerson Lehrman Group: Consultant, Alpha Insights: Consultant, Slingshot Insights: Consultant, Madrigal Pharmaceuticals: Grant/Research Support, W.L. Gore & Associates: Grant/Research Support, BD: Grant/Research Support, Medicolegal consulting: Consultant, Amit Singal:Genentech: Consultant, AstraZeneca: Consultant, Bayer: Consultant, Eisai: Consultant, Exelixis: Consultant, Merck: Consultant, Elevar: Consultant, FujiFilm Medical Sciences: Consultant, Exact Sciences: Consultant, Glycotest: Consultant, Boston Scientific: Consultant, Sirtex: Consultant, HelioGenomics: Consultant, ImCare: Consultant, DELFI: Consultant, Curve Biosciences: Consultant, Catalym: Consultant, Verve: Consultant, Simon Craddock Lee:Nothing to Disclose, Donna Evon:Nothing to Disclose.

4589 | INVESTIGATING HEPATITIS B VIRUS RECURRENCE IN LIVER TRANSPLANT RECIPIENTS: A SINGLE-CENTER RETROSPECTIVE COHORT STUDY

Tonguç Utku Yılmaz[1] Iftihar Koksal[1] Alara Apa[2] Serhat Özfıstıkçı[2] Ece Cılli[2] İman Cihan[2] Zehra Karabal[2] Ömer Şaka[2] Dença Silahlı[2] Ufuk Canözer[2] Sevan Dağlıyan[2], [1]Acıbadem Atakent Hospital, [2]Acıbadem Mehmet Ali Aydınlar University School of Medicine

Background: Hepatitis B virus (HBV) infection is a primary indication for liver transplantation globally and in Türkiye. Despite effective post-transplant prophylaxis (Hepatitis B immunoglobulin and nucleos(t)ide analogues), HBV recurrence still affects approximately 10% of recipients. High pre-transplant viral load, HBeAg positivity, and poor adherence to immunosuppression are known recurrence determinants. A comprehensive assessment of recurrence risk factors is essential to optimize post-transplant prophylaxis and improve long-term outcomes in high-risk patients. The present study aims to investigate the incidence and associated risk factors of HBV recurrence among Turkish patients who underwent living donor liver transplantation (LDLT) for HBV-related disease at Acıbadem Atakent Hospital in Türkiye, a large transplant center at a university hospital. **Methods:** This retrospective, single-center cohort study included records of 150 adult Turkish patients who underwent LDLT for HBV-related disease at our center between 2014 and 2025. Collected data consist of demographic, clinical, biochemical, virological, and pre-transplant tumor parameters, alongside specific HBV prophylactic and immunosuppressive protocols. Patient characteristics and HBV recurrence incidence were summarized using descriptive statistics. Continuous variables were presented as mean ± standard deviation or median (interquartile range (IQR)), and categorical variables as n (%). Patients with and without HBV recurrence were compared using Mann Whitney U and Fisher's exact test. The distribution of HBV recurrence after LDLT over time was assessed with Kaplan-Meier survival analysis, groups were compared with the log-rank test. A p-value of <0.05 was considered statistically significant. **Results:** Among 150 patients (76.0% male, mean age 54.17 ± 9.65) included in the study, HBV recurrence was observed in 2.7% (n = 4). Median follow-up time was 42.7 months (IQR 17.1-69.9), and median time to HBV recurrence was 12 months (IQR

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9.3-15.0). Only one of the 53 patients with hepatocellular carcinoma (HCC) had HCC recurrence. Death occurred in 21 patients (14%), and 1 patient (0.7%) required retransplantation. Hepatitis D virus coinfection was present in 23.3% of the patients, while 4.0% had Hepatitis C virus (HCV) coinfection. Positive HBV DNA and HCC presence at the time of LDLT were not significant for HBV recurrence ($p = 1.000$ and $p = 0.614$, respectively). Sex differed significantly between two groups ($p = 0.043$). Kaplan-Meier analysis showed a significant difference in HBV recurrence-free survival according to HCV coinfection (log-rank $p = 0.022$). **Conclusion:** The results of this study support the effectiveness of a structured post-LDLT prophylaxis and follow-up protocol in prevention of the recurrence of HBV infection. HCV coinfection was associated with a poorer HBV recurrence-free survival, suggesting a potential prognostic relevance.

Variable	No HBV Recurrence (n = 146)	HBV Recurrence (n = 4)	p value
Age, years	55.00 (49.00-61.00)	50.00 (44.00-54.80)	0.241
Sex, n (%)			0.043
Male	113 (77.4%)	1 (25.0%)	
Female	33 (22.6%)	3 (75.0%)	
BMI, kg/m²	26.20 ± 4.13	28.30 ± 3.92	0.330
HBV DNA positive, n (%)	59 (40.4%)	2 (50.0%)	1.000
Etiology, n (%)			1.000
HBV alone	97 (66.4%)	3 (75.0%)	
HBV + other	49 (33.6%)	1 (25.0%)	
Pre-op AFP	4.35 (2.00-13.30)	4.00 (2.72-26.20)	0.764
HCC presence, n (%)	51 (34.9%)	2 (50.0%)	0.614
Outside Milan, n (%) (N = 46)	25 (56.8%)	1 (50.0%)	1.000
HDV coinfection, n (%)	35 (24.0%)	0 (0.0%)	0.573
HCV coinfection, n (%)	5 (3.4%)	1 (25.0%)	0.152
MELD score	17.00 (14.00-21.00)	21.00 (17.80-24.50)	0.126
Disease duration, months	96.00 (48.00-192.00)	60.00 (51.00-105.00)	0.668
Graft/recipient weight ratio, %	1.10 (0.96-1.23)	1.45 (1.08-1.80)	0.246
Portal vein thrombosis, n (%) (N = 136)	15 (11.2%)	0 (0.0%)	1.000
Steatosis, n (%)			1.000
0%	65 (46.1%)	2 (50.0%)	
0-10%	66 (46.8%)	2 (50.0%)	
10-20%	10 (7.1%)	0 (0.0%)	
Post-op immunosuppression regimens			1.000
Tacrolimus	107 (81.7%)	4 (100%)	
Cyclosporine	16 (12.2%)	0 (0.0%)	
Everolimus	8 (6.1%)	0 (0.0%)	

Disclosures: Tonguç Utku Yılmaz:Nothing to Disclose, Iftihar Koksal:Nothing to Disclose, Alara Apa: Nothing to Disclose, Serhat Özfıstıkçı:Nothing to Disclose, Ece Cıllı:Nothing to Disclose, İman Cihan: Nothing to Disclose, Zehra Karabal:Nothing to Disclose, Ömer Şaka:Nothing to Disclose, Dença Silahlı: Nothing to Disclose, Ufuk Canözer:Nothing to Disclose, Sevan Dağlıyan:Nothing to Disclose.

4590 | INCREMENTAL INCREASE IN DONOR-DERIVED CELL-FREE DNA AND RISK OF REJECTION IN LIVER TRANSPLANT RECIPIENTS

Phil Gauthier[1] Mamatha Bhat[2] Ali Zarrinpar[3] Daniel Maluf[4] D. Giovanni Biagini[1] Nina Verstraete[1] Andrew Doud[1] Yen-An Chen[1] Navchetan Kaur[1] Felipe Acosta[1] Ebad Ahmed[1] Amy Baer[1] Mita Banik[1] Naoshin Haque[1] Sarah McCormick[1] Kate Woodruff[1] Jing Xie[1] Nour Al Haj Baddar[1] Niraja suresh[1] Zachary Demko[1] Adam Prewett[1] Hossein Tabriziani[1] Sangeeta Bhorade[1] Juliet Emamaullee[5], [1]Natera, Inc., [2]University Health Network / University of Toronto, [3]University of Florida, [4]University of Maryland School of Medicine, [5]Keck School of Medicine of USC

Background: Donor-derived cell-free DNA (dd-cfDNA) is a validated biomarker that is often used as a binary discriminator for rejection in patients with solid organ transplants. Whether there is a more nuanced application to dd-cfDNA utility as a continuous biomarker to assess allograft status is not well-known. Here, we utilized a cross-sectional study of liver transplant (LTx) patients to investigate the effect of time post transplant on dd-cfDNA levels and test if incremental increases in dd-cfDNA correlate with higher probability of rejection. **Methods:** Adult LTx patients were included in this study. Blood samples (drawn ≥ 14 days post LTx) were collected. dd-cfDNA fraction (%) levels were measured using the Prospera™ test. Linear generalized additive model (GAM) was fit to understand the effect of time since transplant on dd-cfDNA in stable patients (defined by lack of rejection and normal liver function tests [LFTs]). A univariate logistic regression was performed to assess the risk of each doubling of dd-cfDNA% with rejection diagnosis, defined as either biopsy-proven rejection activity index ≥ 3) or treated clinical rejection. Statistical differences were assessed using a log-likelihood ratio test. **Results:** 199 LTx patients with 209 dd-cfDNA samples were included; 32 experienced a total of 33 rejection episodes; the remaining 167 had no rejection. Out of the 199 patients, 135 (67.8%) were identified as stable. The GAM model showed no effect of time since transplant on dd-cfDNA% in stable LTx patients; **Fig 1A**). Logistic regression modelling revealed that each two-fold increase in dd-cfDNA% conferred a 4.75x higher odds of rejection (95% CI: 2.89-7.82; $p = 6.82 \times 10^{-18}$; **Fig 1B**). **Conclusion:** While standard clinical practice uses dd-cfDNA% as a binary discriminator for rejection, we found that when used as a continuous variable, the rejection risk increases monotonically with higher dd-cfDNA% levels in LTx patients. As no effect of time since transplant was observed on dd-cfDNA% levels, the increase in dd-cfDNA% is more likely associated with rejection rather than post-transplant temporal changes.

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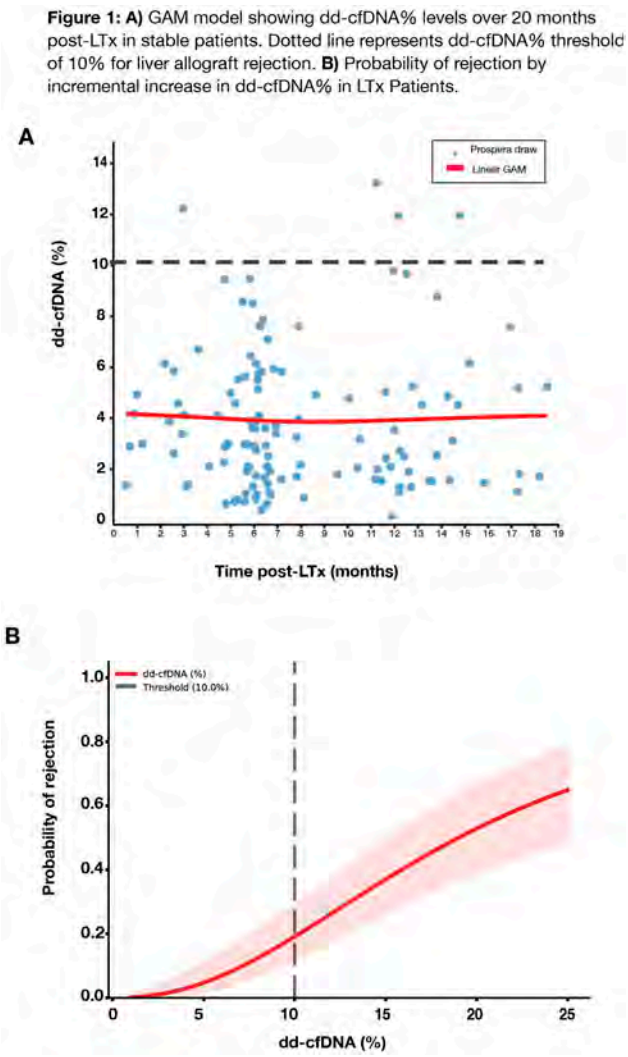


Figure 1: A) GAM model showing dd-cfDNA% levels over 20 months post-LTx in stable patients. Dotted line represents dd-cfDNA% threshold of 10% for liver allograft rejection. **B)** Probability of rejection by incremental increase in dd-cfDNA% in LTx Patients.

Disclosures: Phil Gauthier:Natera, Inc.: and equity, Mamatha Bhat:Novo Nordisk: Grant/Research Support, Natera: Grant/Research Support, Oncoustics: Grant/Research Support, KNIGHT THERAPEUTICS: Grant/Research Support, Astra Zeneca: Consultant, Merck: Grant/Research Support, AFFLO: Grant/Research Support, MERCK: Grant/Research Support, CAREDX: Grant/Research Support, THERMOFISHER: Grant/Research Support, Ali Zarrinpar:Nothing to Disclose, Daniel Maluf:Nothing to Disclose, D. Giovanni Biagini:Natera: Employee, Nina Verstraete: Nothing to Disclose, Andrew Doud:Nothing to Disclose, Yen-An Chen:Nothing to Disclose, Navchetan Kaur:Nothing to Disclose, Felipe Acosta:Natera: Employee, Ebad Ahmed:Nothing to Disclose, Amy Baer:Nothing to Disclose, Mita Banik:Natera: An employee of Natera and may own stock and/or stock option, Natera Inc: Employee of Natera and may own stock and/or stock options, Naoshin Haque:Nothing to Disclose, Sarah McCormick:Nothing to Disclose, Kate Woodruff:Nothing to Disclose, Jing Xie:Natera: Stock holder, Nour Al Haj Baddar:Natera, Inc.: Employee, Natera, Inc.: Stock – privately held company, Niraja suresh:Natera, Inc.: Salary, Natera, Inc.: Stock – privately held company, Natera, Inc.: Stock – privately held company, Zachary Demko:Nothing to Disclose, Adam Prewett:Natera: Employee, Hossein Tabriziani: Nothing to Disclose, Sangeeta Bhorade:Nothing to Disclose, Juliet Emamaullee:Nothing to Disclose.

4591 | LOWER EPICARDIAL FAT THICKNESS IS ASSOCIATED WITH DIASTOLIC DYSFUNCTION AND PULMONARY HEMODYNAMIC ABNORMALITIES IN CIRRHOSIS

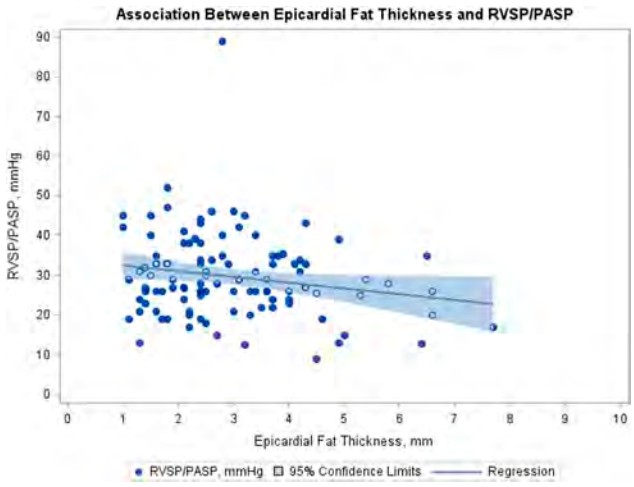
Anwesha Satapathy[1] Benjamin Seifer[2] Tasmia Promi[2] Manahil Muneeb[2] James Park[2] Amgad Makaryus[2] Sanjaya Satapathy[1], [1]Northshore University Hospital/ Northwell Health, [2]Northwell Health

Background: Cirrhotic cardiomyopathy (CCM) is characterized by impaired cardiac reserve, diastolic dysfunction, and pulmonary hemodynamic abnormalities in patients with advanced liver disease. Epicardial adipose tissue is a metabolically active cardiac fat depot implicated in myocardial remodeling and cardiovascular dysfunction; however, its role in CCM remains poorly understood. We aimed to evaluate the association between epicardial fat thickness (EFT) and the presence of diastolic dysfunction, as well as its individual echocardiographic components, in liver transplant candidates with cirrhosis. **Methods:** We conducted a retrospective study of adult patients with cirrhosis undergoing liver transplant evaluation at a tertiary transplant center who underwent pre-transplant transthoracic echocardiography. EFT was measured on echocardiography and analyzed both continuously and by quartile distribution. The primary outcome was the presence or absence of diastolic dysfunction on echocardiography. Individual echocardiographic components of diastolic dysfunction including medial E/e' and left atrial volume index (LAVI), as well as other parameters of right ventricular systolic pressure/pulmonary artery systolic pressure (RVSP/PASP) were also evaluated separately. Multivariable logistic and linear regression analyses were performed adjusting for age, body mass index (BMI), diabetes mellitus, and sex. **Results:** A total of 202 patients with available EFT measurements were included. Patients with higher EFT were older and had higher BMI, while MELD score and liver frailty index were similar across EFT quartiles. Lower EFT was independently associated with the presence of diastolic dysfunction on multivariable logistic regression analysis (odds ratio [OR] 0.59, 95% confidence

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interval [CI] 0.38–0.91, p = 0.017). Among individual components, lower EFT was independently associated with higher pulmonary pressures, with an inverse relationship observed between EFT and RVSP/PASP on adjusted linear regression analysis (β = −2.09, 95% CI −3.93 to −0.26, p = 0.026). Although continuous associations between EFT and medial E/e' were modest, patients with lower EFT demonstrated broader distributions and clustering of elevated filling-pressure abnormalities. No independent association was observed between EFT and elevated LAVI after adjustment. **Conclusion:** Lower epicardial fat thickness was independently associated with diastolic dysfunction and elevated pulmonary pressures in cirrhosis. These findings suggest that reduced EFT may identify a distinct frailty-associated cardiocirculatory phenotype in advanced liver disease rather than a traditional obesity-mediated cardiometabolic process. EFT may serve as a novel non-invasive imaging biomarker of advanced cirrhotic cardiomyopathy in liver transplant candidates.



Disclosures: Anwesha Satapathy:Nothing to Disclose, Benjamin Seifer:Nothing to Disclose, Tasmia Promi:Nothing to Disclose, Manahil Muneeb:Nothing to Disclose, James Park:Nothing to Disclose, Amgad Makaryus:Nothing to Disclose, Sanjaya Satapathy: Gilead Sciences: Grant/Research Support, Durect Pharma: Grant/Research Support, Fibronostics: Grant/Research Support, Novartis: Grant/Research Support, Zydus Pharma: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Intercept Pharma: Grant/Research Support, AKERO: Grant/Research Support, Altimmune: Grant/Research Support, IPSEN: Grant/Research Support, Madrigal: Grant/Research Support.

4592 | PULMONARY HEMODYNAMIC ABNORMALITIES AND FRAILTY IN LIVER TRANSPLANT CANDIDATES: ASSOCIATION BETWEEN ECHOCARDIOGRAPHIC MARKERS OF CIRRHOTIC CARDIOMYOPATHY AND FRAILTY

Manahil Muneeb[1] Tasmia Promi[1] Anwesha Satapathy[1] Benjamin Seifer[1] James Park[1] Amgad Makaryus[1] Nabil Dagher[1] Sanjaya Satapathy[1], [1]Northwell Health

Background: Frailty is an important predictor of adverse outcomes in patients with cirrhosis awaiting liver transplantation. Cirrhotic cardiomyopathy (CCM), characterized by structural and functional cardiac abnormalities, may contribute to impaired physiologic reserve and frailty; however, the relationship between echocardiographic manifestations of CCM and frailty remains poorly defined. We aimed to evaluate the association between echocardiographic markers of CCM and frailty among liver transplant candidates. **Methods:** We performed a retrospective cohort study of adult liver transplant candidates who underwent pre-transplant transthoracic echocardiography and frailty assessment at a tertiary transplant center between 2014 and 2023. Echocardiographic markers of CCM included medial E/e', left atrial volume index (LAVI), right ventricular systolic pressure/pulmonary artery systolic pressure (RVSP/PASP), and right atrial (RA) pressure. A composite CCM burden score was constructed based on abnormal echocardiographic parameters. Frailty was assessed using the Liver Frailty Index (LFI), Karnofsky Performance Status (KPS), and binary frailty definitions including LFI ≥ 4.5. Multivariable linear and logistic regression models adjusted for age, sex, body mass index, diabetes mellitus, and MELD score. **Results:** Among 288 liver transplant candidates with available echocardiographic data, 267 had sufficient data for CCM burden assessment and 227 had available frailty assessment. Elevated RVSP/PASP (≥ 35 mmHg) demonstrated the strongest association with frailty outcomes. In adjusted logistic regression analysis, elevated RVSP/PASP was independently associated with increased odds of LFI-defined frailty (OR 6.07, 95% CI 1.73–21.27, p = 0.0048). Continuous RVSP/PASP demonstrated a borderline association with frailty risk (OR 1.05 per mmHg increase, 95% CI 0.997–1.114, p = 0.0657). In contrast, composite CCM burden score was not independently associated with continuous LFI, KPS at listing, KPS at transplant, or frailty status after multivariable adjustment. Correlation analyses demonstrated

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moderate inter-correlation among echocardiographic CCM markers but weak correlations between most markers and frailty measures. **Conclusion:** Pulmonary hemodynamic abnormalities, particularly elevated RVSP/PASP, were independently associated with frailty in liver transplant candidates, whereas composite echocardiographic CCM burden was not. These findings suggest that pulmonary vascular and hemodynamic dysfunction may contribute more substantially to impaired physiologic reserve than traditional structural echocardiographic markers of CCM. Further prospective studies are needed to determine whether targeted cardiopulmonary assessment may improve frailty risk stratification in patients with advanced liver disease.

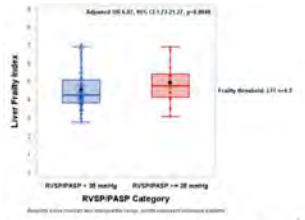


Figure 1. Liver Frailty Index Across RVSP/PASP Categories

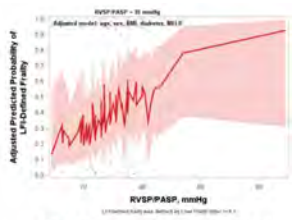


Figure 2. Adjusted Probability of Frailty by RVSP/PASP

Disclosures: Manahil Muneeb:Nothing to Disclose, Tasmia Promi:Nothing to Disclose, Anwesha Satapathy:Nothing to Disclose, Benjamin Seifer:Nothing to Disclose, James Park:Nothing to Disclose, Amgad Makaryus:Nothing to Disclose, Nabil Dagher:Nothing to Disclose, Sanjaya Satapathy:Gilead Sciences: Grant/Research Support, Durect Pharma: Grant/Research Support, Fibronostics: Grant/Research Support, Novartis: Grant/Research Support, Zydus Pharma: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Intercept Pharma: Grant/Research Support, AKERO: Grant/Research Support, Altimmune: Grant/Research Support, IPSEN: Grant/Research Support, Madrigal: Grant/Research Support.

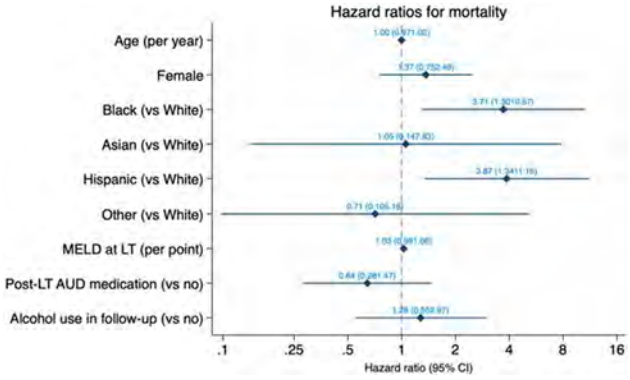
4593 | REAL-WORLD USE, TOLERABILITY, AND MORTALITY ASSOCIATIONS OF PHARMACOTHERAPY FOR ALCOHOL USE DISORDER AFTER LIVER TRANSPLANTATION IN THE UNITED STATES

Wei Zhang[1] Luis Díaz[2] Kelly Hsu[3] Cassidy Sun[1] Stephanie Mrowczynski[4] Peng-Sheng Ting[4] Ami Patel[5] Deepika Devuni[6] Christina Leyson[7] Ellen Green[8] Sasha Deutsch-Link[9] Giuseppe Joseph Morelli[4] Ana Ivkovic[1] Russell Goodman[1] Esperance Schaefer[10] Jay Luther[1] Heidi Yeh[1] Emily Bethea[1], [1]Massachusetts General Hospital, [2]University of California San Diego, [3]Tuft University School of Medicine, [4]Tulane University School of Medicine, [5]Univeristy of Massachusetts, [6]University of Massachusetts, [7]University of Kentucky, [8]University of North Carolina, Chapel Hill, NC, USA, [9]UNC Chapel Hill, [10]Brigham and Women's Hospital

Background: Liver transplantation (LT) is increasingly performed for alcohol-associated liver disease (ALD), including in patients with active alcohol use, making ongoing management of alcohol use disorder (AUD) after LT a growing priority. Several pharmacotherapies reduce drinking in the general AUD population, but their uptake, tolerability, and clinical associations after LT are poorly characterized. We examined real-world prescribing patterns and outcomes across a multinational transplant consortium. **Methods:** We conducted a multicenter (5 centers) retrospective cohort study of adults who underwent LT (2016–2025) with documented AUD/alcohol-associated liver disease in the United States. We characterized pre- and post-LT AUD pharmacotherapy and non-pharmacological management, reasons for discontinuation, and modeled all-cause mortality using Cox proportional-hazards regression adjusted for age, sex, race/ethnicity, Model for End-Stage Liver Disease (MELD) at LT, post-LT AUD pharmacotherapy, and post-LT alcohol use. **Results:** We included 445 recipients with a mean age of 55.4 years, 70.2% male, and 89.4% White; 39.8% had active alcohol use at baseline. Before LT, only 15.1% had received any AUD pharmacotherapy (naltrexone 7.4%, acamprosate 6.5%), while approximately half (49.9%) had received non-pharmacological treatment. After LT, 25.5% received at least one AUD medication, most commonly naltrexone (20.0%), followed by acamprosate (6.3%), gabapentin (4.4%), and topiramate (1.2%); disulfiram and varenicline were rarely used. Over 1,713 person-years (62 deaths; maximum follow-up 9.4 years), discontinuation attributable to side effects was uncommon—patient choice and perceived lack of efficacy were the leading reasons—supporting overall tolerability. In adjusted models, post-LT AUD pharmacotherapy was associated with a numerically lower but non-significant hazard of all-cause mortality (HR 0.64, 95% CI 0.28–1.47; p = 0.295). Black and Hispanic race/ethnicity were associated with higher mortality, though small subgroup sizes warrant caution (**Figure**). **Conclusion:** In this multinational cohort, AUD pharmacotherapy remained underutilized after LT—used in only about one in four recipients and dominated by naltrexone—yet appeared well tolerated, with side effects rarely prompting discontinuation. A consistent but statistically non-significant signal toward lower mortality supports the safety and feasibility of post-LT AUD pharmacotherapy and underscores the need for adequately powered prospective studies, which the expanding LICOP-AUD consortium aims to address.

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4594 | WAITLIST AND POST-TRANSPLANT OUTCOMES OF ACUTE ALCOHOL-ASSOCIATED HEPATITIS COMPARED WITH NON-AH ALCOHOL-ASSOCIATED LIVER DISEASE: A CONTEMPORARY NATIONAL ANALYSIS

Sanjaya Satapathy[1] James Park[2] Nabil Dagher[2] Nishi Joshi[2], [1]Northshore University Hospital/Northwell Health, [2]Northwell Health

Background: Liver transplantation (LT) for acute alcohol-associated hepatitis (AH) has increased substantially in recent years; however, concerns regarding waitlist prioritization and long-term post-transplant outcomes persist. We aimed to compare waitlist and post-transplant outcomes between patients with AH and non-AH alcohol-associated liver disease (ALD) using a contemporary national cohort. **Methods:** Adult ALD candidates listed for LT in the United States were identified from the United Network for Organ Sharing (UNOS) database. Patients were categorized as AH or non-AH ALD. Waitlist outcomes included waitlist death, removal for clinical deterioration, and transplantation. Post-transplant outcomes included patient survival and graft survival. Kaplan–Meier analyses and multivariable Cox proportional hazards models adjusted for demographic, clinical, and donor characteristics were performed. Sensitivity analyses included granular ALD subgroup comparisons and interaction analyses by transplant era and MELD strata. **Results:** Among 96,372 waitlisted ALD candidates, 4,098 (4.3%) had AH. The proportion of AH listings increased markedly across transplant eras, rising from < 1% before 2014 to approximately 15% in the contemporary era. AH candidates were more likely to undergo transplantation (75.3% vs 54.9%) and less likely to experience waitlist death (6.2% vs 13.1%) or removal for clinical deterioration (3.4% vs 7.6%) compared with non-AH ALD candidates.In adjusted competing-risk analyses, AH was not independently associated with waitlist death (HR 0.98, 95% CI 0.84–1.14, p = 0.79). However, patients with combined alcohol-associated liver disease and HCV demonstrated significantly higher waitlist dropout risk compared with alcohol-associated cirrhosis without AH (HR 1.36, 95% CI 1.24–1.48, p < 0.001).Among 53,245 LT recipients, unadjusted Kaplan–Meier analyses demonstrated superior patient and graft survival in AH recipients (log-rank p < 0.001 for both). However, after multivariable adjustment, AH was not independently associated with post-transplant mortality (adjusted HR 1.08, 95% CI 0.94–1.24, p = 0.26) or graft failure (adjusted HR 1.11, 95% CI 0.99–1.26, p = 0.09). Findings remained consistent in donor-adjusted sensitivity analyses and across MELD strata. A borderline interaction between AH and transplant era was observed for patient survival (interaction p = 0.051), suggesting potential temporal variation in outcomes. **Conclusion:** Liver transplantation for AH has expanded rapidly in the United States. Despite favorable unadjusted waitlist and post-transplant outcomes, adjusted analyses demonstrated post-transplant patient and graft survival comparable to traditional ALD recipients. These findings support the continued use of LT in carefully selected patients with AH.

Table 1. Adjusted Cox Proportional Hazards Models, Interaction Analyses, and Sensitivity Analyses for Post-Transplant Outcomes

Analysis Category	Comparison / Model	Adjusted Hazard Ratio (95% CI)	p-value
Primary adjusted models			
	Primary patient survival model	1.09 (0.95–1.25)	0.214
	Primary graft survival model	1.11 (0.99–1.26)	0.086
	Donor-adjusted graft survival sensitivity model	1.11 (0.98–1.26)	0.094
Interaction analyses			
	AH × MELD group interaction	—	0.863
	AH × transplant era interaction	—	0.051
Granular ALD phenotype sensitivity analyses			
	AH vs alcohol-associated cirrhosis without AH	1.09 (0.95–1.25)	0.214
	Alcohol + HCV vs alcohol-associated cirrhosis without AH	1.25 (1.14–1.37)	<0.001

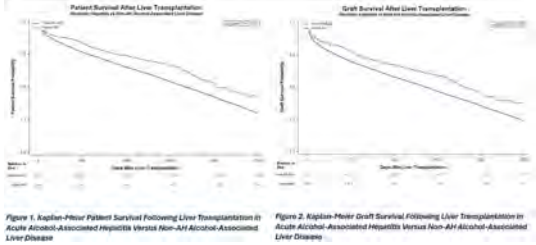


Figure 1. Kaplan–Meier Patient Survival Following Liver Transplantation in Acute Alcohol-Associated Hepatitis Versus Non-AH Alcohol-Associated Liver Disease

Figure 2. Kaplan–Meier Graft Survival Following Liver Transplantation in Acute Alcohol-Associated Hepatitis Versus Non-AH Alcohol-Associated Liver Disease

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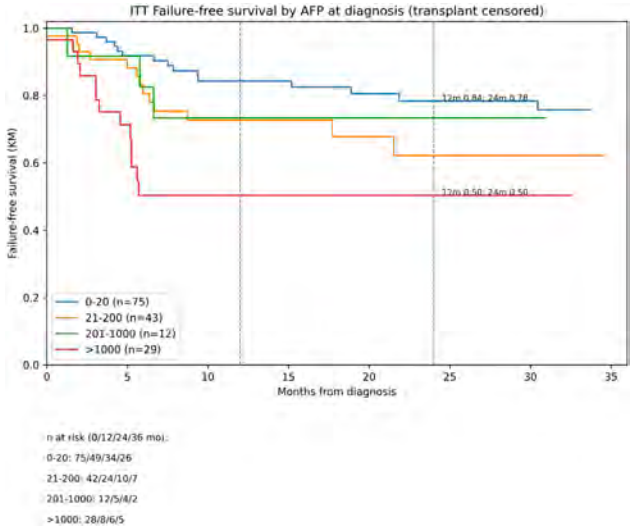
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4595 | AFP KINETICS AS A BIOLOGY GATEKEEPER DURING DOWNSTAGING BEYOND T2: AN INTENTION-TO-TREAT ANALYSIS

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Background: In HCC treated beyond OPTN T2, the real clinical question is often not "who can be transplanted," but "who can stay stable long enough to reach the waitlist." We tested whether temporal AFP kinetics capture this biologic bottleneck across the downstaging timeline. **Methods:** We analyzed 167 consecutive HCC patients treated outside OPTN T2 criteria (2015–2025), grouped as UNOS downstaging-eligible (DS, n = 65) versus all-comers beyond DS (AC, n = 102). AFP was recorded at routine clinical anchors (diagnosis and subsequent treatment/listing milestones). Biology was summarized by diagnostic AFP strata (0–20, 21–200, 201–1000, > 1000 ng/mL) and a dynamic peak-to-last pre-decision AFP response metric (peak AFP prior to the decision window vs last available pre-decision anchor AFP; response ≥ 50% decline). Primary endpoint was intention-to-treat (ITT) pathway failure (progression and/or waitlist dropout) from diagnosis, censoring at transplant. Secondary endpoints were listing and transplant rates. **Results:** AC entered with substantially higher-risk AFP biology than DS (median AFP 58.7 vs 12.8 ng/mL; AFP > 1000: 24.5% vs 7.7%) and retained a larger high-risk tail at the last anchor (AFP > 1000: 15.7% vs 3.1%). Clinically, this translated into early ITT attrition: pathway failure occurred in 50.0% of AC (51/102) versus 18.5% of DS (12/65). Failure-free survival declined in a graded, clinically intuitive manner by AFP at diagnosis: AFP 0–20, 84.3%/78.4% vs AFP > 1000, 50.4%/50.4% at 12/24 months (KM N = 166; 51 events). Listing was achieved in 43.1% of DS vs 23.5% of AC; among listed patients, transplant rates were similar (85.7% vs 79.2%). **Conclusion:** AFP kinetics operationalize tumor biology during downstaging beyond T2. High diagnostic AFP—particularly > 1000—marks early pathway attrition before listing, while access after listing appears comparable. Integrating dynamic AFP response with tumor burden may improve counseling, triage, and timing of downstaging escalation.



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4596 | POST LIVER TRANSPLANT ALCOHOL RELAPSE RATE – A SINGLE CENTER EXPERIENCE

Jordan Holliday[1] Lydia Aye[1] Vikrant Rachakonda[1], [1]University of California Davis

Background: Alcohol associated liver disease (ALD) is the most common indication for liver transplant in the United States. Relapse rates for alcohol use post liver transplant (LT) have been reported to be 8-20%. We defined relapse in our patients as any patient that had a positive PETH result. Our aim is to characterize patients who relapsed with alcohol use post-LT and to identify potential risk factors and interventions to help decrease the risk of relapse in post liver transplant patients. **Methods:** Method: Retrospective chart review of post-LT patients from July 15, 2023 to July 31, 2025 at a single liver transplant center in the United States. **Results:** Results: Ninety-four patients underwent liver transplant, 79 patients were transplanted for ALD (n = 67) or alcohol associated hepatitis (AH) (n = 12).

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Eleven (13.9%) patients relapsed post-LT, 9 (13.4%) ALD and 2 (16.7%) AH. There was no difference in rate of relapse between ALD and AH patients (p = 0.528). Time to relapse from last alcohol use for ALD (333 days) and AH (267) was not significantly different (p = 0.727). SIPAT score pre-LT for ALD (25) and AH (25) was not significantly different (p = 0.781). MELD at time of LT was significantly higher for those who relapsed (35) compared to those who did not (25), p = 0.009. **Conclusion:** Conclusions: Our single center experience in post-LT alcohol relapse rate is consistent with prior studies. There have been several studies that have examined factors that influence post-LT relapse. Most of these studies examine risk factors pre-LT. There was no difference in relapse rates and time to relapse from last alcohol use between those transplanted for ALD and for AH. Time of sobriety should not be used alone in determining transplant candidacy. Our patients were found to be minimally acceptable candidates by the SIPAT score and there was no significant difference in SIPAT scores between patients who did or did not relapse post-LT. Future studies should focus on early prediction for relapse in our post-LT patients and developing early interventions for these patients.

Disclosures: Jordan Holliday:Nothing to Disclose, Lydia Aye:Nothing to Disclose, Vikrant Rachakonda: Nothing to Disclose.

4597 | COMPARISON OF TRANSARTERIAL RADIOEMBOLIZATION VERSUS TRANSARTERIAL CHEMOEMBOLIZATION AS BRIDGING THERAPY TO LIVER TRANSPLANTATION IN PATIENTS WITH HEPATOCELLULAR CARCINOMA

Arpit Amin[1] Lucia Romero Socorro[1] Paul Gaglio[2] Abhishek Kumar[1] Pratik Shukla[1] Keri Lunsford[3] Mumtaz Niazi[1] Vivek Lingiah[1] Zaid Tafesh[1] Flavio Paterno[3], [1]Rutgers New Jersey Medical School, [2]Rutgers NJ Medical School, [3]Rutgers University - New Jersey Medical School

Background: There is scant data in the literature about the optimal bridging locoregional treatment (LRT) option for hepatocellular carcinoma (HCC) in patients on the liver transplant (LT) waitlist. LRT resulting in complete pathologic necrosis of HCC on liver explant has been shown to improve HCC recurrence free survival in LT recipients. The main objective of this study is to evaluate the effectiveness of trans-arterial radioembolization (TARE) based LRT protocol versus trans-arterial chemoembolization (TACE) based LRT protocol in achieving complete pathologic necrosis of HCC on liver explant specimens of patients, who underwent LT. **Methods:** This is a single-center retrospective study of 80 consecutive HCC patients, who underwent LT between January 1, 2010, and August 31, 2025. Patients with HCC were primarily treated with TACE based LRT protocol between January 1, 2010, till December 31, 2019. Subsequently, patients with HCC were primarily treated with TARE based LRT protocol between January 1, 2020 till August 31, 2025. Patients were excluded if there was any crossover between TACE and TARE treatment arms. We compared pathologic necrosis, microvascular invasion, recurrence rate, and overall survival between two study groups. **Results:** Out of 80 HCC LT recipients, 64 patients (with total of 97 HCC lesions) underwent TACE based LRT and 16 patients (with total of 23 HCC lesions) underwent TARE based LRT. There was a longer interval between last TARE based LRT to LT compared to last TACE based LRT to LT (456 days vs 238 days, p 0.003) suggestive of more durable radiologic treatment response with TARE on LT waitlist. Mean number of LRT sessions were similar between TACE based LRT and TARE based LRT (1.28 vs 1.39, p 0.387). Complete pathologic necrosis was identified in 19/23 (83%) TARE treated HCC lesions compared to 51/97 (53%) TACE treated HCC lesions (p 0.01). Microvascular invasion was identified in 1/16 (6%) of TARE treated HCC patients compared to 8/97 (8%) of TACE treated HCC patients (p 0.479). There was no statistically significant difference in 2-year HCC recurrence rates between two groups (0% in TARE group vs 11% in TACE group, p 0.334). There was no statistically significant difference in overall 2-year survival rates between two groups (88% in TARE group vs 92% in TACE group, p 0.281). **Conclusion:** TARE based LRT is more effective in achieving complete pathologic necrosis of HCC lesions compared to TACE based LRT.

Table 1 – Clinical and HCC tumor characteristics

	TACE group (n=97)	TARE (Y-90) group (n=23)	p-value
Age (years)	60 ± 8	64 ± 7	0.04
MELD 3.0 score at LT	15 ± 8	13 ± 6	0.29
Time on waitlist	304 ± 408	371 ± 164	0.52
Time from last LRT to LT	238 ± 242	456 ± 286	0.003
Tumor size	2.2 ± 0.9	2.5 ± 1.5	0.21
AFP at diagnosis	37 ± 62	25 ± 61	0.50
AFP prior to LT	15 ± 28	22 ± 50	0.45
Pathologic response			0.01
Complete	51 (53%)	19 (83%)	
Incomplete	45 (47%)	4 (17%)	
2-year HCC recurrence rates	7 (10.9%)	0 (0%)	0.334

Disclosures: Arpit Amin:Nothing to Disclose, Lucia Romero Socorro:Nothing to Disclose, Paul Gaglio:Nothing to Disclose, Abhishek Kumar:Boston Scientific: Consultant, Medtronic: Consultant, Trisaylus: Consultant, Sirtex: Consultant, Pratik Shukla:Varian: Consultant, Balt: Consultant, Boston Scientific: Consultant, Keri Lunsford: ROM Tech: Stock – privately held company, Johnson and

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4598 | SIX-MINUTE WALK DISTANCE VERSUS LIVER FRAILTY INDEX IN PREDICTING POST-TRANSPLANT OUTCOMES IN HEPATOPULMONARY SYNDROME

Amani Elshaer[1] Fares Jamal[2] Elizabeth Carey[1], [1]Mayo Clinic Arizona, [2]Mayo Clinic

Background: In patients with hepatopulmonary syndrome (HPS), impaired oxygenation and exercise intolerance may limit the reliability of walk-based assessments such as the 6-minute walk distance (6MWD), raising concern about its use in this population. Alternatively, the Liver Frailty Index (LFI) is less dependent on cardiopulmonary reserve may be preferred as the initial frailty assessment; however, the comparative superiority of either test remains uncertain. Our aim was to compare the predictive validity of pretransplant 6MWD and LFI analyzed as continuous variables for post-transplant ICU length of stay (LOS), hospital LOS, and 30-day readmission in patients with HPS undergoing LT. **Methods:** This is a retrospective single-center case series of all HPS patients undergoing LT at our institution. Pretransplant 6MWD (meters) and LFI were entered as unmodified continuous predictors. Post-transplant outcomes, ICU LOS, hospital LOS, and 30-day readmission, were analyzed as continuous variables. Pearson correlation coefficients and simple linear regression were used between each frailty measure and each outcome. **Results:** Nine HPS patients (67% female; mean age 54.9 ± 15.3 years; mean BMI 30.8 kg/m²; mean MELD 3.0 = 12.2) underwent LT; no patients were denied or died on the waitlist. Mean 6MWD was 337.9 ± 170.7 m (range: 40–495 m) and mean LFI was 3.64 ± 1.07 (range: 2.25–5.50). Mean ICU LOS was 2.7 ± 3.1 days and mean hospital LOS was 19.7 ± 27.4 days; 30-day readmission occurred in 6 of 9 patients (67%). As continuous predictors, 6MWD demonstrated statistically significant correlations with all three post-transplant outcomes: ICU LOS ($r = -0.78$, $p = 0.014$, $R^2 = 0.604$), hospital LOS ($r = -0.83$, $p = 0.005$, $R^2 = 0.694$), and 30-day readmission ($r = 0.69$, $p = 0.038$). On linear regression, each 100-meter reduction in 6MWD corresponded to approximately 1.4 additional ICU days ($\beta = -0.014$/m) and 13.4 additional hospital days ($\beta = -0.134$/m). Results remained significant when adjusted for MELD 3.0. In contrast, LFI did not reach statistical significance for any post-transplant outcome: ICU LOS ($r = 0.54$, $R^2 = 0.291$, $p = 0.134$), hospital LOS ($r = 0.65$, $R^2 = 0.428$, $p = 0.056$), and 30-day readmission ($r = -0.46$, $p = 0.219$). Neither 6MWD nor LFI significantly predicted waitlist duration. **Conclusion:** Pretransplant 6MWD was statistically significant predictor of all measured post-transplants substantially outperforming LFI, which did not reach significance for any outcome. These findings are likely reflective of the underlying physiology of HPS. The oxygen-dependent impairment of ambulation makes 6MWD more predictive of the cardiopulmonary reserve, unlike the LFI which reflects the musculoskeletal frailty with the grip strength and chair-stand components. The linear regression estimates, approximately 13 additional hospital days per 100-meter decrement in 6MWD, offer a clinically actionable threshold for risk counseling and resource planning.

Disclosures: Amani Elshaer:Nothing to Disclose, Fares Jamal:Nothing to Disclose, Elizabeth Carey: Nothing to Disclose.

4599 | INTERACTION BETWEEN LIPOPROTEINS AND BODY COMPARTMENTS IN LIVER TRANSPLANT RECIPIENTS

Tsola Efejuku[1] Olivia Reszczynski[1] Alexis Kim[2] Mohammad Siddiqui[1], [1]University of Virginia, [2]Virginia Commonwealth University

Background: Cardiovascular disease (CVD) is a leading cause of morbidity and mortality following liver transplantation (LT), with atherosclerotic cardiovascular disease (ASCVD) representing a major contributor to adverse long-term outcomes. Sarcopenic obesity and altered lipoprotein metabolism are increasingly recognized as important drivers of cardiometabolic risk in LT recipients; however, the relationship between body composition and advanced lipoprotein profiles remains poorly defined. Our goal was to evaluate the associations between MRI-derived body composition parameters, metabolomic markers, and NMR-derived lipoprotein subclasses in LT recipients. **Methods:** Adult LT recipients followed at a tertiary transplant center from 03/2013–10/2023 underwent MRI-based body composition analysis and nuclear magnetic resonance (NMR)-based metabolomic and lipoprotein profiling. Body composition variables included fat-free muscle volume (FFMV), muscle fat infiltration (MFI), and visceral adipose tissue index (VATi). Lipoprotein outcomes included LDL particle concentration (LDL-P), small LDL-P, HDL particle concentration (HDL-P), and HDL subclasses. Additional analyses evaluated inflammatory markers (GlycA), gut metabolites, and branched-chain amino acids (BCAA). Linear regression models were performed in unadjusted analyses and adjusted for age, sex, and BMI. Independent-samples t-tests compared normal versus abnormal body

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composition groups. Statistical significance was defined as $p < 0.05$. **Results:** A total of 48 LT recipients were included. Higher MFI was independently associated with lower LDL-P (β −40.64, $p = 0.008$) and higher HDL-P (β 2.28, $p < 0.001$). Greater VATi was associated with increased HDL-P (β 3.29, $p = 0.008$) and large HDL-P (β 3.16, $p = 0.003$). Inflammatory profiling demonstrated inverse associations between GlycA and HDL subclasses, including small HDL-P (β −0.018, $p = 0.002$). BCAA metabolites were strongly associated with atherogenic lipoprotein phenotypes, including higher LDL-P (β 0.36, $p < 0.001$) and small LDL-P (β 0.38, $p < 0.001$). Patients with abnormal MFI demonstrated significantly lower LDL-P and higher large HDL-P concentrations compared to patients with normal MFI ($p = 0.008$). **Conclusion:** Skeletal muscle composition, visceral adiposity, inflammatory markers, and amino acid metabolism are strongly associated with lipoprotein remodeling following LT. MFI and BCAA metabolism demonstrated the strongest relationships with atherogenic lipoprotein subclasses, supporting the role of the muscle–liver metabolic axis in post-transplant cardiovascular risk. Integration of MRI-derived body composition analysis with advanced lipoprotein profiling may improve cardiometabolic risk stratification in LT recipients.

Table — Muscle Fat Infiltration and Lipoproteins

Outcome	β unadjusted	p-value	β adjusted	p-value
LDL-P	-54.81	<0.001	-40.64	0.008
Small LDL-P	-25.90	0.005	-20.99	0.067
HDL-P	2.64	<0.001	2.28	<0.001
Large HDL-P	2.68	<0.001	2.09	<0.001

Disclosures: Tsola Efejuku:Nothing to Disclose, Olivia Reszczynski:Nothing to Disclose, Alexis Kim:Nothing to Disclose, Mohammad Siddiqui:NovoNordisk: Grant to institution, 89 Bio: Consulting.

4600 | THE EFFECT OF WEIGHT LOSS ON INSULIN RESISTANCE AND INFLAMMATION IN LIVER TRANSPLANT RECIPIENTS

Danielle Kirkman[1] Maksim Piazza[1] Domenico Chavez[1] Geneva Roache[1] Margery Connelly[2] Susan Wolver[1] Mohammad Siddiqui[3], [1]Virginia Commonwealth University, [2]Labcorp, [3]University of Virginia

Background: Clinically meaningful weight gain following a liver transplant (LT) is highly prevalent, increasing the risk of developing *de novo* steatotic liver disease and cardiovascular disease. The biological mechanisms linking post-transplant weight gain to metabolic dysfunction, however, are under-researched and complex. The purpose was to investigate whether weight loss improves key metabolic biomarkers implicated in metabolic disease development and progression, specifically insulin resistance and systemic inflammation, in LT recipients. **Methods:** This was a retrospective analysis of a randomized controlled clinical trial investigating dietary strategies for weight loss in obese LT recipients. Thirty participants (mean ± SD; Age, 56.4 ± 11.8 years; 17 female; 7 Black) were grouped based on weight change over six months into a weight-loss group (WL; ≥ 4 kg loss) and a non–weight-loss group (NWL; < 4 kg loss or weight gain). Metabolic outcomes were assessed at baseline and at six months. Venous blood samples were analyzed by nuclear magnetic resonance (NMR) spectroscopy for branched chain amino acids, lipoprotein particle concentrations and subclass sizes, and GlycA, a composite NMR-derived marker of systemic inflammation. Laboratory derived indices of insulain rsistance and inflammation were calculated including the Lipoprotein Insulin Resistance Score (LP-IR), which quantifies insulin resistance based on lipoprotein particle characteristics, and an inflammation index derived from the GlycA signal. A mixed model repeated-measures ANOVA was used to analyze changes over time and between groups, with significant interactions followed up by simple effects analyses. **Results:** By design, weight loss was significantly greater in the WL group compared to the NWL group (D –14.7 ± 20.9 *vs*. +1.6 ± 4.4 kg; interaction $p < 0.01$). Nutrition-induced weight loss resulted in significant reductions in insulin resistance as measured by LP-IR (*WL vs NWL;* D –23.5 ± 14.2 *vs*. –1.0 ± 11.2 %; interaction $p = 0.01$), and significant decreases in systemic inflammation, reflected by reductions in GlycA (D –42.0 ± 42 *vs*. –10.9 ± 33.2 mmol/L; interaction $p = 0.04$) and the inflammation index (D –7.3 ± 7.6 *vs*. + 0.3 ± 5.9 AU; interaction $p = 0.02$). **Conclusion:** These findings suggest that weight loss directly improves physiological mechanisms that contribute to the risk *de novo* steatotic liver disease and the post-transplant cardiovascular burden. This reinforces the need for effective weight management strategies after transplant.

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4601 | THE IMPACT OF AREA DEPRIVATION ON EARLY CLINICAL OUTCOMES IN LIVER TRANSPLANTATION FOR ALCOHOL-RELATED LIVER DISEASE

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Background: Social determinants of health are associated with poorer outcomes in liver disease and liver transplantation. Patients with alcohol-related liver disease (ALD) routinely experience psychosocial barriers to care. Therefore, the aim of this study was to determine whether socioeconomic disadvantage measured by area deprivation index (ADI) impacts clinical outcomes in liver transplantation for alcohol-related liver disease. **Methods:** This was a single-center, retrospective chart review of patients of 79 patients with alcohol-related liver diseases including cirrhosis due to ALD (N = 58), metabolic and alcohol-related steatotic liver disease (Met-ALD, N = 9), and alcohol-associated hepatitis (N = 12) transplanted between June 2023 and July 2025. National ADI scores were obtained using the University of Wisconsin Neighborhood Atlas based on patient addresses to identify census blocks. **Results:** The median ADI was 30 (IQR 19 – 42), and patients were stratified into low risk (ADI $\leq$ 30, N = 40) and high risk (ADI > 30, N = 39) cohorts. The median age was 46.0 (IQR 39.8 – 54.5 years, and there was no difference between low and high ADI groups. There were no differences in liver disease etiology across ADI cohorts, and more women (34.2%) had lower ADI. Overall, pre-transplant substance use navigation (SUN) services were provided to 32.9% of patients, but no differences were noted between ADI cohorts. However, low ADI patients had higher rates of pre-transplant addiction medicine consultation (22.5% vs 7.7% p = 0.065) and psychiatric services (52.5% vs 33.3%, p = 0.013) than high ADI groups. SIPAT scores did not differ between groups, but there was a trend towards lower median MELD 3.0 in high ADI patients [25 (IQR 20 – 31) vs 31 (23 – 39), p = 0.060], and there was negative correlation between MELD and ADI (Spearman rho -0.2019, p = 0.0745). After transplant, eleven patients (13.9%) experienced relapse, and all cases were detected by positive blood phosphatidylethanol (PETH) tests. Post transplant addiction medicine consultation was provided to 41.8% of patients, and 12.7% received medications for alcohol use disorder (MAUD) after transplant. There were no differences between rates of relapse, addiction medicine consults, acute cellular rejection (ACR), or MAUD between high and low-risk ADI cohorts. **Conclusion:** Among patients transplanted for alcohol-related liver disease, patients with high ADI received few pre-transplant addiction medicine and psychiatric services, but this did not result in increased return to drinking or ACR after liver transplant. Future studies are planned to study targeted pre-transplant AUD treatment in high-risk cohorts.

Disclosures: Jordan Holliday:Nothing to Disclose, Samuel Ji:Nothing to Disclose, Vikrant Rachakonda: Nothing to Disclose, Sophoclis Alexopoulos:Nothing to Disclose, Lea Matsuoka:Nothing to Disclose, Yvonne Kelly:Nothing to Disclose, Lydia Aye:Nothing to Disclose.

4602 | SECULAR TRENDS OF PHOSPHATIDYLETHANOL (PETH) TESTING IN THE PERI-LIVER TRANSPLANT PERIOD: A US REGISTRY-BASED ANALYSIS

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Background: Phosphatidylethanol (PEth) is a sensitive and specific biomarker of alcohol use with growing clinical utility in liver transplantation (LT). Real-world data on temporal trends in post-LT PEth surveillance and clinical outcomes stratified by alcohol use disorder (AUD) history remain scarce. We evaluated post-transplant PEth patterns, graft rejection, and mortality among adult LT recipients stratified by AUD history. **Methods:** Using the Apollo Atropos Health real-world database, adult LT recipients (January 2015–October 2025) were stratified by AUD history: No AUD, Prior AUD (pre-LT diagnosis), and post-transplant AUD (post-LT diagnosis only). AUD was defined using Elixhauser ICD-10 criteria. Positive PEth was defined as $\geq$ 20 ng/mL. Outcomes included PEth testing rates, time to first positive test, graft rejection, and all-cause mortality. **Results:** Among 21,536 LT recipients (no AUD n = 14,591; prior AUD n = 5,492; post-transplant AUD n = 1,453), post-LT PEth testing occurred in 0.19%, 3.46%, and 0.62%, respectively. Testing frequency increased markedly over time in the prior AUD group, rising from 0% in 2015–2016 to 8.3% within 1 year post-LT in 2025. Positive PEth values occurred exclusively in the prior AUD cohort (0.95% anytime post-LT; mean 32.0 ng/mL vs. 2.96 ng/mL, 1.11 ng/mL in no AUD and post-transplant AUD, respectively), with a median time to first positive test of 587 days post-LT (IQR: 203–1,030 days; max 2,194 days). Graft rejection rates were approximately double in prior AUD (14.4%) and post-transplant AUD (14.2%) vs. no AUD (7.1%). The post-transplant AUD cohort had a low PEth testing rate (0.62%) with zero positive tests identified, yet

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carried the highest all-cause mortality, 24.2% (post-transplant AUD) vs. 16.8% (no AUD) vs. 14.1% (prior AUD). **Conclusion:** Post-transplant PEth testing is increasing, reflecting growing clinical awareness, yet overall uptake remains low across all groups. The wide variability in time to first positive PEth among prior AUD patients supports the need for long-term PEth surveillance in this group. Graft rejection risk doubled with any AUD history, highlighting the clinical importance of adequate post-transplant monitoring. The post-transplant AUD group had the highest mortality, yet a low PEth testing rate with no positive tests detected. The post-transplant AUD cohort may represent individuals diagnosed purely via clinical/behavioral presentation or billing codes after a severe relapse event, and thus missing the window of PEth biomarker detection. The lack of routine surveillance raises concern for underdiagnosis of harmful alcohol use post-transplant and underscores the need for targeted, longitudinal PEth protocols in this high-risk population.

Figure 1: Post-transplant PEth testing frequency increased over time



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4603 | CARDIOMETABOLIC VS NON-CARDIOMETABOLIC CIRRHOSIS PHENOTYPES AND THEIR ASSOCIATION WITH CIRRHOTIC CARDIOMYOPATHY IN LIVER TRANSPLANT RECIPIENTS

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Background: Cirrhotic cardiomyopathy (CCM) is a subclinical cardiac dysfunction that arises during physiologic stress, such as liver transplantation, and may be associated with worse transplant outcomes. However, the influence of underlying cirrhosis phenotype on CCM is not well-studied. One area of increasing interest is the impact of cardiometabolic factors in the interplay between hepatic and cardiac disease processes. Our study aimed to assess whether cardiometabolic cirrhosis (CMC) is associated with higher prevalence and severity of CCM compared to non-alcoholic non-cardiometabolic cirrhosis (non-CMC). **Methods:** This retrospective cohort included 115 adult liver transplant recipients with complete pre-transplant echocardiographic data. CMC (n = 95) included cirrhosis of any etiology with cardiometabolic factors (BMI $\geq$ 30, type 2 diabetes, or metabolic syndrome). Non-CMC (n = 20) included non-alcoholic cirrhosis without any cardiometabolic factors. CCM was defined as the presence of $\geq$ 2 abnormal echocardiographic markers per the 2020 Cirrhotic Cardiomyopathy Consortium guidelines: left ventricular ejection fraction $\leq$ 50%, global longitudinal strain > -18%, left atrial volume index > 34 mL/m^2, septal e' < 7 cm/s, tricuspid regurgitation velocity > 2.8 m/s, and E/e' > 15. Logistic regression was used to assess associations, adjusting for age, MELD score, and sex. **Results:** CCM was present in 34.8% of patients, with similar prevalence in CMC (34.7%) and non-CMC (35.0%; p = 0.98). The mean number of abnormal criteria was also comparable (1.18 vs. 1.25). Individual echocardiographic parameters, as described by the 2020 guidelines, did not differ significantly between phenotypes (Table 1). In adjusted models, CMC was not independently associated with CCM (Odds Ratio 0.89, 95% Confidence Interval 0.31 – 2.53; p = 0.82). **Conclusion:** Our study shows that the cardiometabolic cirrhosis phenotype is not associated with CCM. This finding underscores the importance of routine pre-transplant cardiac evaluation across all etiologies of cirrhosis because no specific phenotype has been disproportionately linked to CCM. Future studies are warranted to

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identify alternative drivers of CCM to better evaluate transplant candidates.

Table 1. CCM Component Comparison by Phenotype

CCM Component	CMC (n=95)	Non-CMC (n=20)	p-value
Left Ventricular Ejection Fraction ≤ 50%	4.2%	5%	0.89
Global Longitudinal Strain > -18%	29.5%	25%	0.67
Left Atrial Volume Index >34 mL/m²	60%	55%	0.72
Septal e' <7 cm/s	52.6%	50%	0.84
Tricuspid Regurgitation velocity >2.8 m/s	18.9%	15%	0.77
E/e' >15	20%	10%	0.21

Disclosures: Jade Pace:Nothing to Disclose, Manahil Muneeb:Nothing to Disclose, Tasmia Promi:Nothing to Disclose, Ahmed Aboseria:Nothing to Disclose, Michael Attanasi:Nothing to Disclose, Anwesha Satapathy:Nothing to Disclose, Andrew Park:Nothing to Disclose, Benjamin Seifer:Nothing to Disclose, Justin Lin:Nothing to Disclose, Nabil Dagher:Nothing to Disclose, David Stern:Alnylam: Consultant, AstraZeneca: Consultant, BridgeBio: Consultant, Pfizer: Consultant, Amgad Makaryus:Nothing to Disclose, Sanjaya Satapathy:Gilead Sciences: Grant/Research Support, Durect Pharma: Grant/Research Support, Fibronostics: Grant/Research Support, Novartis: Grant/Research Support, Zydus Pharma: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Intercept Pharma: Grant/Research Support, AKERO: Grant/Research Support, Altimmune: Grant/Research Support, IPSEN: Grant/Research Support, Madrigal: Grant/Research Support.

4604 | NEW SUBMISSION

Diana Coman[1] Aaron Hass[1] Chaimaa Ouizzane[1] Jeanne-Marie Giard[1] Philippe Willems[1] Julian Hercun[1], [1]Montreal University Health Center

Background: Screening for obstructive coronary artery disease (CAD) prior to liver transplantation is crucial in improving post-transplant survival. However, cardiovascular risk assessment lacks standardization across centers. Coronary computed tomography angiography (CCTA) is a non-invasive modality commonly incorporated into screening algorithms, with a high negative predictive value for excluding obstructive CAD. However, it lacks functional assessment of coronary blood flow and myocardial ischemia, which may overestimate cardiovascular risk and lead to potentially unnecessary invasive angiography. Its optimal role in pre-transplant screening remains uncertain. **Methods:** We conducted a retrospective study on patients who underwent liver transplantation between 2023 and 2025 at a quaternary center. The primary endpoint was the rate of major adverse cardiovascular events (MACE) within 30 days of liver transplantation. High-risk CAD lesions on CCTA were evaluated as a secondary endpoint, including rates of downstream invasive coronary angiography, PCI yield, and perioperative MACE. **Results:** A total of 149 patients who underwent liver transplantation were included in the analysis; 68 underwent CCTA and 81 did not. One 30-day post-transplant MACE occurred in the CCTA group and none in the non-CCTA group. In the CCTA group, 32 (47%) patients had subsequent invasive coronary angiography. The cohort was predominantly male (75%), with a mean age of 60 ± 4.83 years, and 46% had a component of metabolic-related cirrhosis. Cardiovascular risk factors were common, including diabetes (50%), hypertension (59%), hyperlipidemia (46%), obesity (35%), and active smoking (26%). 9% had known CAD. In the CCTA group, 14 patients (21%) were reported to have high-risk coronary stenosis, prompting invasive coronary angiography. Of these, 3 patients (4%) had significant stenosis confirmed and underwent percutaneous coronary intervention (PCI), while 11/14 (79%) lesions were reclassified as non-severe on coronary angiography and did not require coronary intervention before transplantation. Seven (11%) patients underwent coronary angiography despite no significant stenosis on CCTA, and none required PCI. Four CCTA studies were inconclusive, of which one patient had significant coronary stenosis on angiography and benefited from a PCI. No false-negative CCTA results were observed. For detecting severe stenosis ($\geq$70% obstruction), CCTA demonstrated 100% sensitivity and negative predictive value, 56% specificity, and 21.4% positive predictive value. **Conclusion:** In this cohort of liver transplant candidates, the rate of MACE was low irrespective of CCTA screening. High-risk CAD lesions identified on CCTA were associated with a high rate of invasive coronary angiography without subsequent PCI, suggesting that CCTA may yield false-positive results in this population and that its role warrants further evaluation.

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4605 | AFP, TUMOR NECROSIS, PATHOLOGIC GRADE, VASCULAR INVASION, AND TUMOR SIZE AS PREDICTORS OF INTRAHEPATIC, OLIGOMETASTATIC, AND POLYMETASTATIC RECURRENCE PATTERNS IN HEPATOCELLULAR CARCINOMA

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Background: Recurrence site of hepatocellular carcinoma (HCC) affects prognosis. Existing models for predicting HCC recurrence do not account for recurrence patterns of spread. This study assesses whether pre-treatment AFP, tumor necrosis, pathologic grade, vascular invasion, and tumor size are associated with intrahepatic-only, oligometastatic, or polymetastatic recurrence patterns. **Methods:** This retrospective study included 55 patients with HCC who underwent resection or liver transplantation and developed recurrence. Patients were stratified into three groups: Intrahepatic-only (n = 31) was defined as recurrence confined to the liver. Oligometastatic (n = 12) was defined as a single extrahepatic organ site only or one intrahepatic plus one extrahepatic site. Polymetastatic (n = 12) was defined as multiple extrahepatic sites and/or intrahepatic recurrence with multiple extrahepatic sites. Baseline characteristics were compared using Kruskal-Wallis and Fisher's exact tests. Ordinal logistic regression was used with recurrence pattern modeled as an ordinal outcome (intrahepatic-only < oligometastatic < polymetastatic). Log-transformed AFP and microvascular invasion were selected a priori for multivariable analysis. Tumor size, tumor necrosis, and pathologic grade were assessed in exploratory univariable analyses. **Results:** Mean pre-treatment AFP increased across groups (12.4, 65.4, 184.6 ng/mL; $p < 0.001$), as did tumor size (2.5, 4.6, 6.2 cm; $p = 0.004$). Microvascular invasion (39%, 42%, 50%; $p = 0.007$) and high-grade pathology (23%, 42%, 67%; $p = 0.015$) also increased across groups. Tumor necrosis and multifocal disease were not significantly different. In multivariable ordinal logistic regression, log10 AFP (OR 2.41, 95% CI 1.38–4.22, $p = 0.002$) and microvascular invasion (OR 3.85, 95% CI 1.21–12.35, $p = 0.023$) were independently associated with advanced recurrence patterns. Treatment type and multifocal disease were not significant. In exploratory univariable analyses, tumor size (OR 1.18, 95% CI 1.05–1.34, $p = 0.007$) and pathologic grade (OR 4.12, 95% CI 1.55–11.02, $p = 0.004$) were significant. Tumor necrosis was not significant. **Conclusion:** Pretreatment log-transformed AFP and microvascular invasion were independently associated with advanced recurrence patterns. In exploratory analyses, larger tumor size and higher pathologic grade were also associated with advanced recurrence patterns. Tumor necrosis, multifocal disease, and treatment type were not significant predictors.

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4606 | A POST-LIVER TRANSPLANT PSYCHOLOGICAL CLINIC FOR MODERATE- AND HIGH-RISK PATIENTS FOR RELAPSE ON ALCOHOL: A NOVEL INTEGRATED APPROACH

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Background: Routine follow-up of post-LT patients can help identify and mitigate risk factors that influence surgical outcomes such as alcohol relapses, psychiatric variables and non-adherence to treatment plans. Prior work has identified characteristics of individuals at risk for post-LT alcohol relapse, including a psychiatric diagnosis, abstinence of less than 1.5 years at time of transplant and history of alcohol relapse prior to LT. Moderate-risk patients were considered to have two of these variables and high-risk patients were considered to have all three. Psychologists are uniquely equipped to address the multitude of factors that impact patients' risk for poor surgical outcomes. The objective of the study was to investigate outcomes following the implementation of a post-LT psychological clinic to assess patients at moderate- and high-risk for alcohol relapse. **Methods:** Retrospective chart reviews were conducted for all patients who underwent LT from January 2022 to December 2023 (N = 223). Data were extracted from the evaluations conducted by transplant psychology staff pre-LT and the recommended one-and six-month post-LT visits. **Results:** Of the 223 patients, 29.1% fell into the moderate/high-risk category and were recommended for post-LT follow-up. Of the patients who were recommended to have follow-up, 96.9% completed the one-month visit and 93.8% completed the six-month visit. At the one-month visit, 86.1% had an alcohol-related etiology and at the six-month visit, 92.8%. At the one-month visit, 9% of patients had elevated depression and anxiety scores, and at the six-month visit, 11.6% had elevated depression scores and 8.6% had elevated anxiety scores. At the one- and six-month follow-ups, patients were given a variety of recommendations to optimize post-LT outcomes including continuing with prescribed psychotropic medications, establishing care with a behavioral health providers, completing relapse prevention, utilizing cognitive behavioral skills (i.e., relaxation), and quitting tobacco and cannabis use. **Conclusion:** Finding suggests it is feasible for moderate- and high-risk patients to attend a post-LT psychological clinic and may be an appropriate

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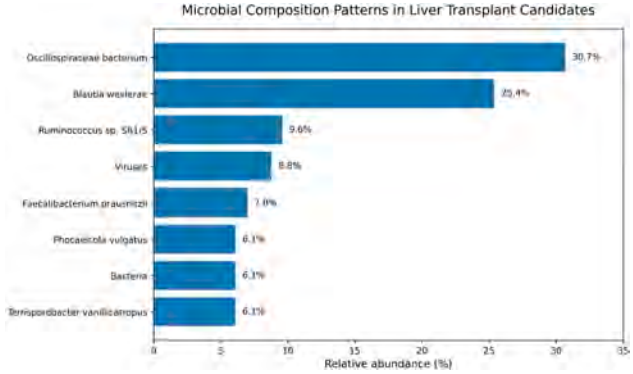
method for identifying individuals who develop post-LT psychiatric symptoms. Imbedding the post-LT psychological clinic within the post-transplant hepatology clinic is imperative for success while optimizing interdisciplinary teamwork. This information could be used by other behavioral health professionals who are considering expanding the breath of psychosocial care provided to post-LT patients for individualized treatment. Future work will examine long-term benefits of this integrated clinic.

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4607 | GUT MICROBIAL DYSBIOSIS IN LIVER TRANSPLANT CANDIDATES: AN EXPLORATORY METAGENOMIC ANALYSIS

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Background: Gut microbiota dysbiosis has been increasingly implicated in the progression of advanced liver disease and cirrhosis-related complications. Alterations in microbial diversity and expansion of opportunistic taxa may contribute to systemic inflammation, immune dysfunction, and worsening hepatic status. This study aimed to explore gut microbial composition patterns in liver transplant candidates using publicly available metagenomic sequencing data **Methods:** Ten paired-end fecal metagenomic samples from liver transplant candidates included in the PRJNA1039781 dataset were analyzed. Raw sequencing reads underwent quality control and taxonomic classification through a standardized metagenomic workflow. Relative microbial abundance profiles were generated, and dominant taxa across samples were evaluated to identify microbial patterns associated with advanced liver disease. **Results:** The microbial landscape demonstrated marked inter-individual heterogeneity, consistent with variable degrees of gut dysbiosis in end-stage liver disease. Several samples showed relative preservation of beneficial commensal taxa, including Faecalibacterium prausnitzii, whereas others demonstrated enrichment of opportunistic microorganisms and dysbiosis-associated taxa. Oscillospiraceae-related species and Blautia wexlerae represented dominant components of the microbial ecosystem, while the presence of potentially pathogenic and inflammation-associated taxa suggested disruption of intestinal microbial homeostasis. These findings are consistent with previously reported microbiome alterations in cirrhosis and advanced hepatic disease. **Conclusion:** This exploratory metagenomic analysis supports the emerging role of gut microbial dysbiosis in liver transplant candidates. The observed microbial composition patterns reinforce the potential relevance of microbiome profiling in advanced liver disease and highlight the need for further studies investigating microbiota-derived biomarkers for disease stratification and prognostic assessment in liver transplantation.



Disclosures: Rosa Ragozzino:Nothing to Disclose.

4608 | REAL-WORLD TESTING OF MULTI-AGENT AI FOR LIVER TRANSPLANT SELECTION REVEALS GAPS IN CLINICAL REASONING

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Background: Multi-agentic AI systems have been proposed to simulate liver transplant selection committees, potentially mitigating biases. Prior work, however, relied on SRTR-derived synthetic cases, leaving real-world performance unknown. Building on work by collaborators at the University Health Network (UHN), we developed a novel institution-specific system incorporating local policies via retrieval-augmented generation (RAG). We then conducted the first large-scale retrospective validation of a multi-agentic AI selection committee using actual clinical and psychosocial documentation to test whether these systems can replicate real-world transplant decision-making. **Methods:** We identified 3,458 patients evaluated for liver transplantation at University of California, San Francisco (UCSF) between 2003-2024, extracting case presentation and psychosocial evaluation notes. We modified the multi-agentic

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system pioneered by UHN to better reflect UCSF's committee composition by adding a nurse transplant coordinator agent to the existing transplant hepatologists, transplant surgeon, and social worker agents. In this system: 1. The surgeon, hepatologist, and social worker agents independently analyze data. 2. The transplant coordinator agent then generates questions informed by institutional policies implemented as a RAG database. 3. Committee agents engage in up to five deliberation rounds before rendering a consensus list/defer/decline decision. For comparison, we also replicated the previously published UHN multi-agentic AI architecture, which uses a binary list/decline framework. **Results:** The UCSF system achieved 61.1% accuracy, 34.4% sensitivity, 91.9% specificity, 82.3% PPV, and 56.1% NPV. The replicated UHN system performed similarly, with 63.5% accuracy and 49.7% sensitivity. The UCSF system generated more defer decisions (N = 2,313 vs. actual N = 1,323), suggesting the AI recognized clinical complexity but could not resolve it, defaulting to indecision. When the UCSF system committed to listing, it was correct 82.3% of the time. Neither system achieved sensitivity acceptable for clinical decision support, with both missing 50-66% of historically listed candidates. **Conclusion:** In the first real-world test of multi-agentic AI for liver transplant selection, we demonstrate that current multi-agentic AI cannot reliably replicate committee judgment, even with institution-specific calibration. While high PPV (82.3%) suggests potential as a confirmatory tool for clear-cut listing candidates, the systems failed to navigate the nuanced, often implicit reasoning that drives real committee decisions. These findings establish that transplant selection involves dimensions of reasoning beyond current AI models, and that substantially more work is needed before such tools can be incorporated into clinical decision-making.

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4609 | INTEGRATED MITOCHONDRIAL STRESS AND DYNAMIC HEPATOBILIARY FUNCTION DURING NORMOTHERMIC PERFUSION PREDICT POST-TRANSPLANTATION ANASTOMOTIC BILIARY COMPLICATIONS: A PROSPECTIVE COHORT STUDY

Xiaojun Cai[1] Sori Lundin[1] Dana Perry[1] Isabel Yang[1] Cemal Taner[1] Omar Mousa[1] Kristopher Croome[1] Liu Yang[1], [1]Mayo Clinic Florida

Background: Anastomotic biliary complications (ABCs), including bile leak and anastomotic stricture, remain a major source of morbidity after liver transplantation. The pathogenesis of ABCs is thought to involve surgical technical factors, microcirculatory impairment at the anastomotic site, and graft dysfunction, and is mechanistically distinct from ischemic cholangiopathy (IC). Despite the widespread adoption of normothermic machine perfusion (NMP), which has significantly reduced the incidence of IC, the risk of ABCs persists. Currently, there is no reliable method to predict ABC risk. We hypothesized that integrating mitochondrial injury biomarkers with dynamic hepatobiliary functional assessment during perfusion would identify grafts at risk for post-transplant ABCs. **Methods:** In this prospective cohort study of 132 donor livers undergoing NMP, normothermic regional perfusion (NRP), or sequential NRP+NMP, we quantified perfusate and biliary flavin mononucleotide (FMN), bile production, perfusate indocyanine green (ICG) clearance, and biliary ICG excretion. The primary endpoint was post-transplant ABC. Logistic regression and receiver operating characteristic (ROC) analyses were used to evaluate predictive performance. **Results:** ABCs occurred in 22%–30% of transplanted grafts across perfusion strategies. Early hepatocellular function, as assessed by perfusate ICG clearance, was not associated with ABC. In contrast, grafts that developed ABC demonstrated: (1) elevated perfusate FMN during NMP ($p = 0.028$), (2) reduced bile output at 60 and 120 minutes ($p = 0.005$ and $p = 0.011$, respectively), (3) impaired late-phase biliary ICG excretion at 120 minutes ($p = 0.044$), and (4) shorter transport distance, which was independently associated with ABC. A composite model integrating mitochondrial stress (FMN), biliary function (bile output and ICG excretion), and transport distance showed better discrimination than any individual biomarker alone (AUC 0.7834). **Conclusion:** A biologically integrated signature linking mitochondrial

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injury with impaired hepatobiliary excretory and transport function during normothermic perfusion predicts post-transplant ABCs. These findings provide new mechanistic insight into the development of ABCs and may help clinicians identify high-risk grafts earlier. **Disclosures:** Xiaojun Cai:Nothing to Disclose, Sori Lundin:Nothing to Disclose, Dana Perry:Nothing to Disclose, Isabel Yang:Nothing to Disclose, Cemal Taner:Nothing to Disclose, Omar Mousa:Nothing to Disclose, Nothing to Disclose, Kristopher Croome:Nothing to Disclose, Liu Yang:Nothing to Disclose.

★ 4610 | KINETIC BREAKPOINT ANALYSIS IDENTIFIES IMMUNE REMODELING DURING QHBSAG DECLINE IN CHRONIC HEPATITIS B

Sung Won Chung[1] Hyunjae Shin[2] Hyejung Lee[3] Changyeon Kim[2] Moon Haeng Hur[2] Yun Bin Lee[4] Eun Ju Cho[5] Su Jong Yu[2] Yoon Jun Kim[2] Jung-Hwan Yoon[2] Joo-Young Park[3] Jeong-Hoon Lee[5], [1]Department of Gastroenterology, Liver Center, Asan Medical C, [2]Seoul National University College of Medicine, [3]Seoul National University School of Dentistry, Seoul National University Dental Hospital, [4]Seoul National University, [5]Seoul National University Hospital

Background: Hepatitis B surface antigen (HBsAg) seroclearance represents functional cure in chronic hepatitis B (CHB). The immunological mechanisms underlying quantitative HBsAg (qHBsAg) decline remain incompletely understood, as prior studies have largely contrasted persistent and resolved states rather than the transitional decline phase. This study aimed to characterize longitudinal qHBsAg kinetic patterns and identify immune cell phenotypes associated with qHBsAg decline. **Methods:** This ambidirectional cohort study enrolled 71 prospectively consented CHB patients (n = 67 in final analysis). Patients were stratified as maintained (n = 27) or declining (n = 40) qHBsAg groups according to the annualized $\log_{10}$ qHBsAg slope over the preceding year (threshold: −0.25 $\log_{10}$ IU/mL/year). Candidate qHBsAg kinetic breakpoints were algorithmically detected and validated via bootstrap resempling (B = 2,000). Flow cytometry was performed to characterize 84 immune cell markers across T, B, NK, and myeloid cell populations. Single-cell RNA sequencing combined with T cell receptor V(D)J profiling was conducted to define clonal immune architecture associated with qHBsAg decline in a subset (n = 12;6 per group). **Results:** Bootstrap validation confirmed 37 of 67 (55%) candidate qHBsAg kinetic breakpoints at $P \leq 0.05$. Unsupported candidates were characterized by gradual kinetic patterns (73%) or high-noise trajectories (70%) and exhibited a smaller dynamic range (median $\log_{10}$ range 1.12 versus 3.38). Compared to patients with maintaned qHBsAg levels, patients with declining demonstrated significantly reduced innate-like effector populations, including perforin$^+$ CD4/CD8 double-negative (DN) T cells (7.6% versus 32.5%, P = 0.009), MAIT cells (0.34% versus 1.30%, P = 0.02), CD3$^+$ DN T cells (4.0% versus 6.9%, P = 0.03), and NKG2A$^+$ cells (22% versus 30%, P = 0.04). Single-cell transcriptomic and V(D)J profiling demonstrated enrichment of NK cells and clonal expansion of CD8$^+$ effector-memory T cells in patients with qHBsAg decline, without evidence of generalized cytotoxic activation. Among patients with validated kinetic breakpoints (n = 38; median interval 1.84 years), PD-1$^+$ memory T cell markers positively correlated with time since breakpoint transition (PD-1$^+$ memory CD8$^+$ T cell: $\rho = 0.54$, P = 0.03), suggesting progressive accumulation of exhaustion associated immune phenotypes following the onset of qHBsAg decline. **Conclusion:** Algorithmically defined qHBsAg kinetic breakpoints were validated in a substantial subset of patients with CHB, providing a structured framework for analyzing dynamics for antigen decline. Within this framework, qHBsAg decline was associated with reduced innate-like effector populations and subsequent PD-1$^+$ memory T-cell phenotypes. These findings support the presence of coordinated immune remodeling during the transition toward functional cure in CHB.

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★ 4611 | ANTIVIRAL THERAPY REDUCES LIVER-RELATED EVENTS IN HBEAG-NEGATIVE CHRONIC HEPATITIS B PATIENTS WITH LOW HBV DNA LEVELS AND NO SIGNIFICANT ALT ELEVATION

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Background: Antiviral treatment is generally not recommended for non-cirrhotic chronic hepatitis B (CHB) patients with low-level viremia and no significant ALT elevation according to the AASLD 2025 hepatitis B guidelines. The clinical benefit of antiviral therapy in CHB patients with low-level viremia and without significant alanine aminotransferase (ALT) elevation remains unclear. To address this gap, we compared the long-term risk of liver-related events (LREs) between treated and untreated HBeAg-negative, non-cirrhotic CHB patients with low HBV DNA levels and no significant ALT elevation. **Methods:** This was a muli-center cohort study which included HBeAg-negative patients without liver cirrhosis but with low HBV DNA (20-2000 IU/mL) and non-significant elevated ALT (< 80 U/L) from five medical centers in China. Inverse probability of treatment weighting (IPTW) and propensity score matching (PSM) were used to balance the baseline characteristics between groups. The development of LREs which included hepatocellular carcinoma and cirrhosis was compared between the treated and untreated patients. **Results:** A total of 2,129 CHB patients were enrolled, of whom 43.0% were treated with nucleos(t)ide analogues (NAs). During a median follow-up of 2.9 years, 41 patients (1.9%) developed LREs, including 33 patients in the untreated group and 8 patients in the treated group. In the IPTW cohort, the untreated group had a significantly higher 6-year cumulative incidence of LRE than the treated group (5.8% vs. 1.6%, $P = 0.004$). In the multivariate Cox regression, NA treatment was associated with a reduced risk of LRE development (adjusted hazard ratio[aHR]: 0.27, 95% confidence interval [CI]: 0.12-0.61, P=0.002). These findings remained consistent in the sensitivity analyses by excluding patients with significant liver fibrosis at baseline. Consistent results were also obtained in the PSM cohort. **Conclusion:** Antiviral therapy was associated with a significant reduction in the risk of LREs among HBeAg-negative, non-cirrhotic CHB patients with low-level viremia and without significantly elevated ALT, supporting expanded treatment indications for these patients.

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4612 | GENETICALLY PREDICTED HEPATIC STEATOSIS INCREASES HEPATOCELLULAR CARCINOMA RISK IN PATIENTS WITH CHRONIC HEPATITIS B: A MENDELIAN RANDOMIZATION STUDY STRATIFIED BY DIABETES MELLITUS

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Background: Whether hepatic steatosis causally increases hepatocellular carcinoma (HCC) risk among patients with chronic hepatitis B (CHB) remains contested, with existing literature frequently confounded by shared metabolic risk factors. We applied Mendelian Randomization (MR) to estimate the effect of genetically predicted hepatic steatosis on HCC risk in CHB patients and examined effect modification by diabetes mellitus (DM). **Methods:** From the Taiwan Precision Medicine Initiative (TPMI), we identified 17,857 adults with CHB defined by HBsAg positivity, excluding individuals with hepatitis C, alcohol-related liver disease, or drug-induced hepatitis (54.9% male; median age 51.6 years at entry of TPMI). The presence of liver steatosis was ascertained by ultrasound reports and HCC was defined by ICD-10 C22.0/C22.9 with confirmatory imaging or pathology. Candidate steatosis-associated single nucleotide polymorphisms (SNPs) in GCKR, TM6SF2, MBOAT7, and PNPLA3 were evaluated as instruments. In the primary MR analysis, 3,688 patients with liver steatosis were matched 1:3 to controls by age at diagnosis using incidence density sampling, and causal hazard differences were estimated by additive hazards G-estimation under dominant and recessive models. Effect modification by DM was examined in the full unmatched cohort using semiparametric additive hazards regression stratified by DM, with follow-up from first TPMI visit to HCC diagnosis or administrative censoring. **Results:** Among SNPs in the four candidate genes, only PNPLA3 p.Ile148Met met instrument strength criteria, with F statistics of 10.14 under the dominant model and 23.01 under the recessive model. MR G-estimation showed a significantly increased hazard of liver steatosis on HCC under the recessive model (hazard difference [HD] = 0.066, 95% CI 0.012–0.120, p = 0.017). Sensitivity analysis using additional PNPLA3-region SNPs confirmed directionally consistent estimates, with 57 of 60 strong-instrument SNPs reaching nominal statistical significance (p < 0.05). In DM-stratified analysis, PNPLA3 p.Ile148Met was significantly associated with HCC in individuals with DM (HD =

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0.0059, 95% CI 0.0006–0.0113, p = 0.030) but not among those without DM (HD = 0.0009, p = 0.108). Among PNPLA3-region variants, 56 of 60 SNPs were significant in the DM stratum versus 1 of 60 in the non-DM stratum. **Conclusion:** Genetically predicted hepatic steatosis was associated with an increased HCC risk in patients with CHB, with the association markedly enriched in individuals with concurrent DM. These findings support a causal role of hepatic steatosis in HCC development and suggest that diabetes-associated metabolic dysfunction may potentiate PNPLA3-driven hepatocarcinogenesis, supporting DM-stratified HCC risk surveillance among CHB patients.

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